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A Meta-Analysis of Low-Density Lipoprotein Cholesterol, Non-High-Density Lipoprotein Cholesterol, and Apolipoprotein B as Markers of Cardiovascular Risk

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Background—Whether apolipoprotein B (apoB) or non-high-density lipoprotein cholesterol (HDL-C) adds to the predictive power of low-density lipoprotein cholesterol (LDL-C) for cardiovascular risk remains controversial.

Methods and Results—This meta-analysis is based on all the published epidemiological studies that contained estimates of the relative risks of non-HDL-C and apoB of fatal or nonfatal ischemic cardiovascular events. Twelve independent reports, including 233 455 subjects and 22 950 events, were analyzed. All published risk estimates were converted to standardized relative risk ratios (RRRs) and analyzed by quantitative meta-analysis using a random-effects model. Whether analyzed individually or in head-to-head comparisons, apoB was the most potent marker of cardiovascular risk (RRR, 1.43; 95% CI, 1.35 to 1.51), LDL-C was the least (RRR, 1.25; 95% CI, 1.18 to 1.33), and non-HDL-C was intermediate (RRR, 1.34; 95% CI, 1.24 to 1.44). The overall comparisons of the within-study differences showed that apoB RRR was 5.7%>non-HDL-C ($P<0.001$) and 12.0%>LDL-C ($P<0.0001$) and that non-HDL-C RRR was 5.0%>LDL-C ($P=0.017$). Only HDL-C accounted for any substantial portion of the variance of the results among the studies. We calculated the number of clinical events prevented by a high-risk treatment regimen of all those >70th percentile of the US adult population using each of the 3 markers. Over a 10-year period, a non-HDL-C strategy would prevent 300 000 more events than an LDL-C strategy, whereas an apoB strategy would prevent 500 000 more events than a non-HDL-C strategy.

Conclusions—These results further validate the value of apoB in clinical care. **(*Circ Cardiovasc Qual Outcomes*. 2011;4:00-00.)**

Key Words: cholesterol LDL ■ cholesterol HDL ■ apolipoproteins B ■ cardiovascular diseases ■ risk ■ meta-analysis

Low-density lipoprotein cholesterol (LDL-C) is now so firmly entrenched in the professional and public consciousness that few remember the intense debate that attended its introduction into routine clinical care. On the one hand, total cholesterol (TC) was the accepted standard and could be measured accurately and inexpensively. On the other hand, LDL-C offered greater accuracy in the assessment of risk, particularly in the small number of individuals in whom TC would be misleading because of extreme values for high-density lipoprotein cholesterol (HDL-C). Moreover, LDL-C was a conceptual advance in that it identified more precisely the pathogenic mechanism that produced arterial injury. These advantages had to be balanced against the disadvantages of a more-complex and expensive technology that was not standardized, was not free of significant error, necessitated fasting, and required reeducation of the profession and the public. Notwithstanding that TC and LDL-C were highly correlated and that there was no evidence of a major increase in predictive accuracy in groups, LDL-C won out, although overall risk continued to be expressed as the TC/HDL-C ratio.

History repeats itself: There is now a similar debate about whether non-HDL-C and apolipoprotein B (apoB) should supplant LDL-C. Non-HDL-C is the sum of the masses of cholesterol in the atherogenic apoB lipoprotein particles. On average, approximately one quarter of this cholesterol is in very-low-density lipoprotein (VLDL) and three quarters in

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LDL, although the actual proportion is highly variable.[1] ApoB is the number of atherogenic apoB lipoprotein particles because each of these contains 1 molecule of apoB. LDL particles account for 90% of the total apoB particles and VLDL the other 10%, with little change in this relation except for unusual conditions, such as familial dyslipoproteinemia.[2] Thus, apoB may be usefully considered a measure of LDL particle number (LDL-P) and is closely correlated to concentrations of LDL-P derived by NMR spectroscopy.[3]

Both non-HDL-C and apoB have been shown to be superior to LDL-C in a number of prospective epidemiological studies. The conventional explanation for the superiority of non-HDL-C over LDL-C is that it includes the cholesterol in VLDL. We tested this hypothesis and demonstrated that because there is almost always very much more cholesterol in LDL than in VLDL, the relative risk of VLDL cholesterol versus LDL-C would have to be unrealistically high for this to be the explanation.[4] Rather, non-HDL-C appears to be a more accurate index of vascular risk than LDL-C because it is a better surrogate for LDL-P assessed by either apoB or NMR measurement.[4,5] Given their very high degree of correlation, it is not surprising that in large groups the overall relations of non-HDL-C and apoB to ischemic risk are very similar.

WHAT IS KNOWN

- Both non-high-density lipoprotein cholesterol (Non-HDL-C) (the total mass of cholesterol within the very-low-density lipoprotein [LDL] and LDL particles) and apolipoprotein B (apoB) (the total number of atherogenic apoB lipoprotein particles) have been suggested to be more accurate markers than LDL cholesterol (LDL-C) of the risk of vascular disease.
- The results of individual published studies have not yielded a consistent result, particularly with regard to the relative predictive powers of non-HDL-C and apoB.

WHAT THE STUDY ADDS

- The present study is a meta-analysis of all the published studies reporting estimates of the relative risks of non-HDL-C and apoB of fatal and nonfatal ischemic vascular events.
- Whether analyzed individually or head to head, apoB was the most potent marker of risk, LDL-C was the least, and non-HDL-C was intermediate.
- This study indicates that apoB is superior to LDL-C and non-HDL-C as a predictor of cardiovascular risk.

Indeed, the Emerging Risk Factors Collaboration (ERFC) meta-analysis found the hazard ratios of apoB and non-HDL-C and of non-HDL-C and LDL-C to be indistinguishable.[6] The ERFC meta-analysis was based on patient-level data, which was one of its major strengths. Of the total of 68 studies included, apoB and non-HDL-C could be compared in 22. The authors' conclusion is that all 3 variables (LDL-C, non-HDL-C, and apoB) are interchangeable as markers of vascular risk, but this conclusion conflicts with the considerable published evidence (as discussed in this article) that apoB and non-HDL-C are superior to LDL-C for this purpose.

Of note, not all the published prospective studies were included in the ERFC meta-analysis, and 2 major case-control studies were specifically excluded. Accordingly, we have undertaken a meta-analysis of all published reports containing apoB and non-HDL-C cardiovascular relative risk ratios (RRRs). Our objectives were to determine the overall balance of the evidence comparing the standardized RRRs of all 3 markers and, if possible, to identify any factors associated with the variance among the studies.

Methods

Data Sources

We attempted to identify all published reports that reported risk estimates of non-HDL-C and apoB, relying on 4 sources: (1) the ERFC study,[6] (2) a literature search based on PubMed for articles published since 2005 containing both *apoB* and *non-HDL-C* as key words; (3) a meta-analysis by Thompson and Danesh[7] that included all published reports since 1997 containing apoB risk associations, and (4) narrative reviews by Sniderman et al[8] and the American Association for Clinical Chemistry Lipoproteins and Vascular Diseases Division Working Group on Best Practices.[9] From these sources, as shown in Figure 1, a total of 107 reports were identified. Of the 68 studies cited within the 56 reports noted in e-Appendix 1 of the ERFC study,[6] 45 lacked relevant data and are not included in either meta-analysis. One, the Framingham Offspring Study,[10] was cited by ERFC but, apparently, not included in the comparison of apoB with non-HDL-C and LDL-C. Thus, the ERFC comparison is based on 22 studies. On the other hand, the published versions of 19 studies included in the ERFC meta-analysis did not contain apoB and non-HDL-C risk associations, so they could not be included in the current meta-analysis. Three[11–13] of the original 56 reports cited in the ERFC and the Framingham Offspring Study[10] were included in the current meta-analysis. Of the 51 other reports identified either through PubMed or through the other reviews, 10 had published apoB and non-HDL-C RRRs. We used 2 of these reports[12,13] instead of ERFC-cited reports because the Copenhagen City Heart Study report cited by ERFC[14] did not contain the necessary risk associations, and the Women's Health Study report[15] excluded women taking hormone replacement therapy. The remaining 8 reports[16–23] with risk associations were included in the current analysis. Thus, 12 published reports containing both apoB and non-HDL-C vascular associations were identified for the present analysis.[10–13,16–23] Three studies[10,13,17] reported results stratified by sex, bringing the total number of analyses to 15 (Table).

Calculations

All published apoB, non-HDL-C, and LDL-C risk associations (odds ratios or hazard ratios) and 95% CIs were converted to RRRs per 1-SD increment in the study being examined. Accordingly, in all studies, risk was estimated as a continuous variable. If the risk associations were reported by quantiles, the increments were set equal to the difference between standard normal distribution mean values of the 2 quantiles compared (2.18 SDs for top versus bottom tertiles, 2.54 for quartiles, and 2.80 for quintiles). SEs for each log-RRR point estimate were calculated from the CIs. SEs for the difference between 2 measures were estimated using the reported correlation between the 2 measures or, if not reported, the correlation in the National Health and Nutrition Examination Survey 2005 to 2006 code book[24] (apoB correlation, $r=0.89$ with LDL-C and $r=0.95$ with non-HDL-C; non-HDL-C correlation with LDL-C, $r=0.94$). Estimates of the means and SDs of apoB, non-HDL-C, LDL-C, TC, HDL-C, and triglycerides were derived from reported statistics.

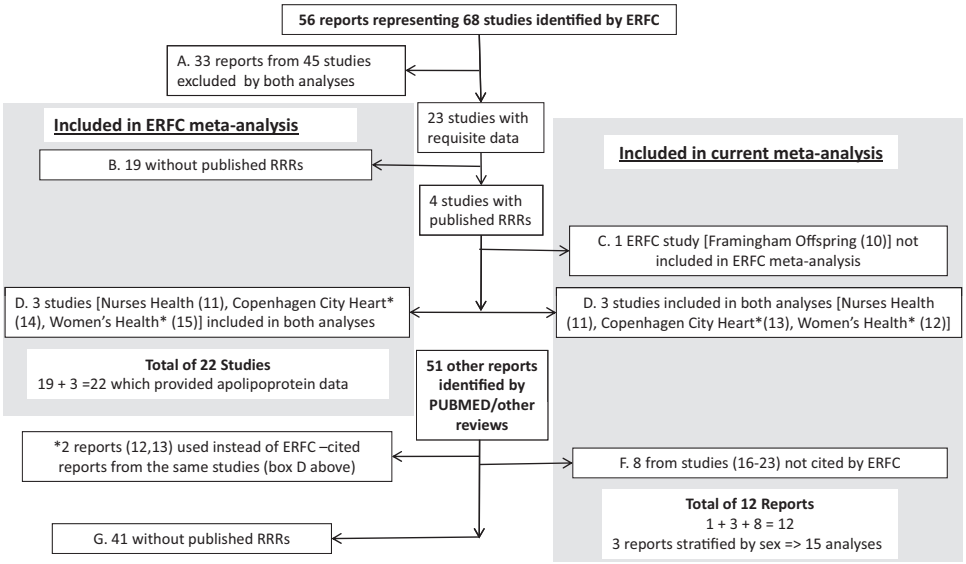

Figure 1. Comparison of reports and studies included in the current meta-analysis versus those included in the ERFC comparison of apoB and non-high-density lipoprotein cholesterol RRRs for cardiovascular events. The 107 candidate reports for the current meta-analysis are categorized A through E as indicated in the text and listed individually in online-only Data Supplement Table 1. The ERFC meta-analysis obtained patient-level data from all studies whether previously published or not, whereas the current meta-analysis was based on published statistics only. ERFC indicates Emerging Risk Factors Collaboration; RRR, relative risk ratio.

Meta-Analysis Model

Meta-analyses of these statistics were performed as recommended by Borenstein et al[25] with a random-effects model. We chose a random-effects rather than a fixed-effects model for a number of reasons, among which was the fact that not all studies had the same mixture of clinical ischemic events, as follows: The Casale Monferrato study[19] was based only on fatal ischemic events; the INTERHEART study[22] and International Studies of Infarct Survival (ISIS)[23] were based only on nonfatal ischemic events; and the remainder included both nonfatal and fatal events. By choosing a random-effects model, we do not assume that the atherogenic parameters being compared have exactly the same relation to fatal as to nonfatal ischemic events.

Subgroup analyses were conducted to assess the heterogeneity associated with the different attributes of the studies. Meta-regression also was performed using continuous measures. In addition, because this review was limited to published reports, we conducted analyses to assess the extent of publication bias.

Results

The 15 independent published analyses identified for this meta-analysis provided a total of 233 455 subjects and 22 950 events.

RRRs of Each Marker

The forest plots of the RRRs from these studies for each of the 3 indices (LDL-C, non-HDL-C, and apoB) are shown in Figure 2, and details are provided in online-only Data Supplement Figures 1 through 3.The overall geometric mean RRRs (95% CI) among these 15 analyses were as follows: apoB, 1.43 (1.35 to 1.51); non-HDL-C, 1.34 (1.24 to 1.44); and LDL-C, 1.25 (1.18 to 1.33) (all $P<0.001$). These results pointed to a hierarchy of accuracy among the 3 markers, with apoB having the highest RRR, LDL-C having the lowest RRR, and non-HDL-C an intermediate RRR. Each individual study RRRs were significantly ($P<0.05$) >1.0 except for non-HDL-C in the Casale Monferrato study ($P=0.22$)[19] and Copenhagen Heart women ($P=0.058$)[13] and for LDL-C in the health professionals with diabetes ($P=0.08$),[16] Casale Monferrato ($P=0.17$), Copenhagen Heart women ($P=0.13$), and Framingham Offspring ($P=0.13$ in men; $P=0.07$ in women; reported as significant when pooled, however) studies.

Percentage Differences Among RRRs

The meta-analysis of the percentage difference between the apoB and non-HDL-C RRRs is shown in Figure 3A. On average, across all studies, the apoB RRR was 5.7% higher than the non-HDL-C RRR (95% CI, 2.4% to 9.1%; $P<0.001$). Thus, apoB in head-to-head comparison was superior to non-HDL-C. The comparison of non-HDL-C to LDL-C is shown in Figure 3B. On average, the RRR of non-HDL-C was 5.0% greater than the LDL-C RRR (95% CI, 0.9% to 9.1%; $P=0.017$). Finally, Figure 3C shows the forest plot of the comparison of apoB and LDL-C. On average, the RRR of apoB was 12.0% greater than the RRR of LDL-C (95% CI, 8.5% to 15.4%; $P<0.0001$). These head-to-head analyses also rank order the 3 markers as follows: apoB>non-HDL-C>LDL-C. Additional details on the head-to-head comparisons are provided in online-only Data Supplement Figures 4 through 6. There was significant heterogeneity of each of these 3 comparisons across all the studies ($P<0.001$).

Heterogeneity and Meta-Regression Analysis

The studies comparing apoB to non-HDL-C can be divided into 2 groups: those that found the 2 markers to be equivalent and those that demonstrated apoB to be statistically superior. No study demonstrated non-HDL-C to be substantially better than apoB. To assess this heterogeneity in outcome, we conducted the subgroup analyses presented in online-only Data Supplement Figure 7. There was no evidence of any significant effect on the variance of within-study difference between the apoB RRR and the non-HDL-C RRR due to sex, age range, diabetes status, outcome measure, or documenta-

Table. Published Studies With Vascular Risk Associations for Both Apolipoprotein B and Non-HDL-C

								Relative Risk Reported		
Year	Study	Sex	Design	Assay*	Outcome	Adjust†	Per‡	ApoB	Non-HDL-C	LDL-C
2004	Health Professionals[16]	Male	Pros	Y Y Y	CVD	Demog	Quintile	2.31 (1.25–4.27)	2.25 (1.24–4.08)	1.63 (0.94–2.81)
2004	Nurses' Health[11]	Female	Pros CC	Y Y Y	CHD	+RFs	1 SD	1.80 (1.50–2.20)	1.60 (1.30–1.90)	1.40 (1.20–1.60)
2005	MONICA/KORA[17]	Male	Pros	N Y Y	CHD	+RFs	1 SD	1.49 (1.25–1.78)	1.49 (1.26–1.75)	Not reported
2005	MONICA/KORA[17]	Female	Pros	N Y Y	CHD	+RFs	1 SD	1.73 (1.32–2.27)	1.79 (1.40–2.30)	Not reported
2005	Health Professionals[18]	Male	Pros CC	Y Y Y	CHD	+RFs	Quintile	2.98 (1.76–5.06)	2.75 (1.62–4.67)	2.07 (1.24–3.45)
2005	Women's Health[15]	Female	Pros	Y Y Y	CVD	+RFs	Quintile	2.50 (1.68–3.72)	2.51 (1.69–3.72)	1.62 (1.17–2.25)
2006	Casale Monferrato[19]	Pooled	Pros	_ _ _	Fatal CVD	+RFs	Quartile	1.48 (1.02–2.14)	0.79 (0.54–1.15)	0.77 (0.53–1.12)
2007	Copenhagen Heart[13]	Female	Pros	N _ _	IHD	Demog	Tertile	1.51 (1.19–2.50)	1.28 (0.99–1.85)	1.27 (0.98–1.83)
2007	Copenhagen Heart[13]	Male	Pros	N _ _	IHD	Demog	Tertile	1.95 (1.49–2.55)	1.90 (1.45–2.50)	1.70 (1.24–2.24)
2007	Chin–Shan Cohort[20]	Pooled	Pros	Y Y Y	CHD	+RFs	Quintile	2.74 (1.45–5.19)	1.98 (1.00–3.92)	1.86 (1.00–3.46)
2007	Fram Offspring[10]	Female	Pros	Y Y Y	CHD	+RFs	1 SD	1.38 (1.15–1.67)	1.28 (1.06–1.56)	1.20 (0.99–1.46)
2007	Fram Offspring[10]	Male	Pros	Y Y Y	CHD	+RFs	1 SD	1.37 (1.20–1.57)	1.22 (1.06–1.40)	1.11 (0.97–1.27)
2008	AMORIS[21]	Pooled	Pros	Y Y Y	MI	Demog	1 SD	1.51 (1.47–1.55)	1.50 (1.46–1.53)	1.42 (1.36–1.45)
2008	INTERHEART[22]	Pooled	CC	Y Y Y	Nonfatal MI	Smoking	1 SD	1.32 (1.28–1.36)	1.21 (1.17–1.24)	1.28 (1.25–1.32)
2009	Women's Health[12]	Female	Pros	Y Y Y	CVD	+RFs	Quintile	2.57 (1.98–3.33)	2.52 (1.95–3.25)	1.74 (1.40–2.16)
2009	ISIS[23]	Pooled	CC	_ _ _	Nonfatal MI	Smoking	2 SDs	2.66 (2.37–2.99)	2.10 (1.89–2.33)	2.21 (1.96–2.48)

Data are presented as relative risk reduction (95% CI). AMORIS indicates Apolipoprotein Mortality Risk study; ApoB, apolipoprotein B; CC, case control; CHD, coronary heart disease; CVD, cardiovascular disease; Demog, demographics; Fram, Framingham; HDL-C, high-density lipoprotein cholesterol; IHD, ischemic heart disease; ISIS, International Studies of Infarct Survival; LDL-C, low-density lipoprotein cholesterol; MI, myocardial infarction; MONICA/KONA, Monitoring of Trends and Determinants in Cardiovascular Disease Augsburg project; Pros, prospective; RF, risk factor.

*Our consensus assessment of the assurances reported regarding apoB assay quality: Y indicates yes; N, no; _, unknown (not reported); first assessment, whether the assay used was World Health Organization-International Federation of Clinical Chemistry and Laboratory Medicine standardized; second assessment, whether the assay was robust (quality assay with documented performance); third assessment, whether sample integrity was maintained.

†Adjust indicates extent of adjustments as follows: demographics, age, sex, and ethnicity/region; smoking, demographics+smoking only; +RFs, demographics+conventional risk factors. A complete list of all covariates is provided in online-only Data Supplement Table 1.

‡Per indicates the increment for reported risk associations (highest vs lowest quantile).

tion of assay quality. However, heterogeneity was significant ($P<0.001$) by type of outcome as follows: the Casale Monferrato study[19] with an apoB RRR 28.0% (95% CI, 10.3% to 48.6%; $P<0.001$) higher than that for non-HDL-C, included only fatal outcomes; ISIS and INTERHEART combined (10.7%; 95% CI, 6.4% to 15.3%; $P<0.001$) included only nonfatal outcomes; and all the other studies that included both fatal and nonfatal outcomes favored apoB by 3.5% (95% CI, 1.1% to 5.9%; $P<0.01$). ISIS and INTERHEART, on the basis of their size, yielded the most precise estimates of effect size. However, even if both are excluded from the analysis, apoB remains superior to non-HDL-C as a marker of risk ($P<0.01$).

We used meta-regression to search for a potential explanation of the dispersion of the results. By the method of moments (appropriate given our assumption of random effects), no significant impact was observed for year of publication ($P=0.49$), mean age of subjects ($P=0.60$), or the range of apoB estimated as the SD divided by the mean ($P=0.48$). By contrast, as shown in Figure 4, the results of the meta-regression of mean HDL-C levels were of interest. Studies with higher mean HDL-C concentrations were associated with smaller differences between the RRR for non-HDL-C and apoB, whereas studies with lower HDL-C levels were associated with greater differences. Including all studies resulted in an overall association between HDL-C and the difference in RRR between apoB and non-HDL-C that almost reached statistical significance ($P=0.064$), and the R^2 of 0.565 indicated that the variance in HDL-C explained more than half of the overall variance in the differences in RRR between non-HDL-C and apoB. If the Casale Monferrato study[19] were to be excluded from the regression as an outlier (Figure 4), the association became significant with an even higher R^2 (0.613, $P=0.034$). It is noteworthy that the correlation between apoB and non-HDL-C in the Casale Monferrato study was substantially less than usual, and the point estimates of both non-HDL-C and LDL-C RRRs were <1.0.

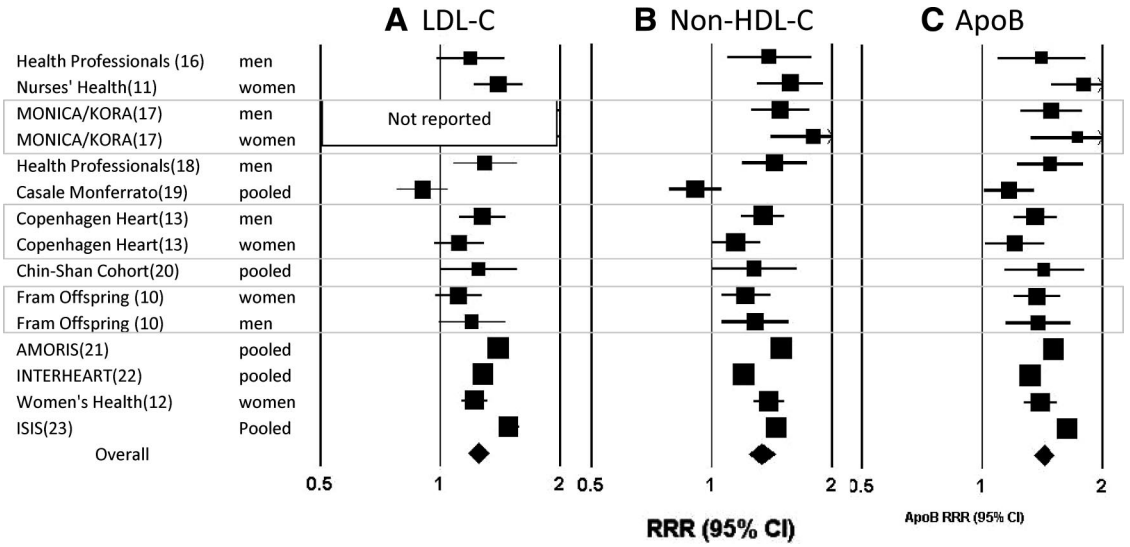

Figure 2. Forest plots of standardized vascular RRRs and 95% CIs for LDL-C (**A**), non-HDL-C (**B**), and apoB (**C**) from 12 independent epidemiological studies reporting RRRs for both apoB and non-HDL-C. The area of each marker is proportional to the weight (1/variance of the estimate) of the study in the meta-analysis. The diamond represents the estimated mean (95% CI) of all studies' effects as follows: apoB, 1.43 (1.35 to 1.51); non-HDL-C, 1.34 (1.24 to 1.44); and LDL-C, 1.25 (1.18 to 1.33). The overall effect and heterogeneity were highly significant ($P<0.001$) for each marker. An earlier Women's Health Study report[15] was excluded because its data were a subset of the data analyzed for the subsequent Women's Health Study report.[12] AMORIS indicates Apolipoprotein Mortality Risk study; ApoB, apolipoprotein B; Fram, Framingham; ISIS, International Studies of Infarct Survival; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; MONICA/KORA, Monitoring of Trends and Determinants in Cardiovascular Disease Augsburg project; RRR, relative risk ratio.

All are consistent with the non-HDL-C result in Casale Monferrato being an outlier.

Publication Bias

The analyses to assess the potential for publication bias[25] revealed no significant evidence that our principal findings herein would be significantly altered by the inclusion of other reports (online-only Data Supplement Figure 8).

Discussion

This meta-analysis indicates that apoB is a more accurate marker of cardiovascular risk than non-HDL-C and that non-HDL-C is a more accurate marker of cardiovascular risk than LDL-C. There is a hierarchy among the markers, with apoB as the best, LDL-C as the worst, and non-HDL-C as intermediate between apoB and LDL-C. Moreover, the advantage of apoB over LDL-C was much greater than the

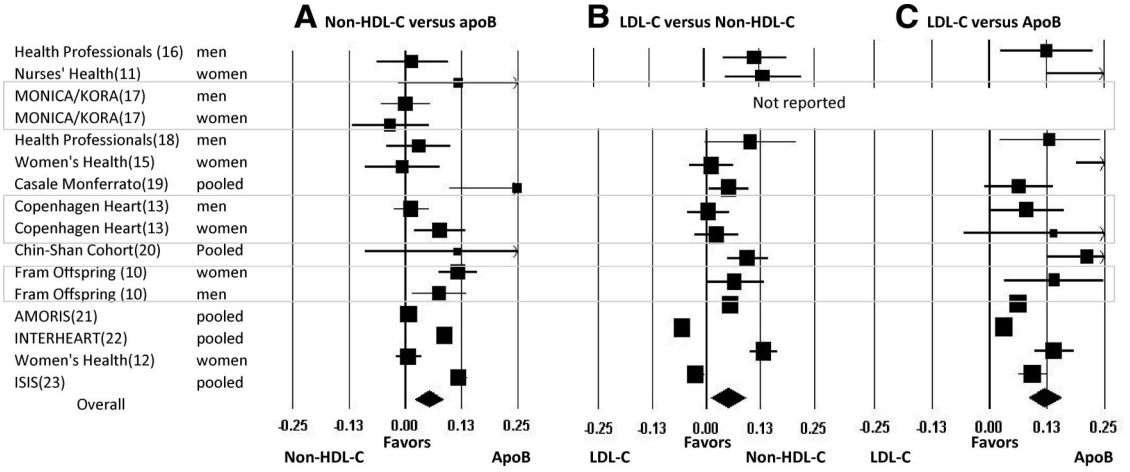

Figure 3. Forest plots of the differences between the logarithm of standardized RRRs of non-HDL-C (**A**), LDL-C (**B**), and apoB (**C**) from 12 independent epidemiological studies reporting RRRs for both apoB and non-HDL-C. The marker for each study represents the point estimate of the difference, and lines represent the 95% CIs. The area of each marker is proportional to the weight (1/variance of the estimate) of the study in the meta-analysis. The diamond represents the estimated mean difference (95% CI) across all studies. These differences were converted to percentages ($e^{\text{difference in log RRRs}}-1$) as follows: apoB RRR is 5.7% (2.4% to 9.1%) higher than non-HDL-C RRR ($P=0.001$) and 12.0% (8.5% to 15.4%) higher than LDL-C RRR ($P<0.001$) and non-HDL-C RRR is 5.0% (0.9% to 9.1%) higher than LDL-C RRR ($P=0.017$). AMORIS indicates Apolipoprotein Mortality Risk study; ApoB, apolipoprotein B; Fram, Framingham; ISIS, International Studies of Infarct Survival; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; MONICA/KORA, Monitoring of Trends and Determinants in Cardiovascular Disease Augsburg project; RRR, relative risk ratio.

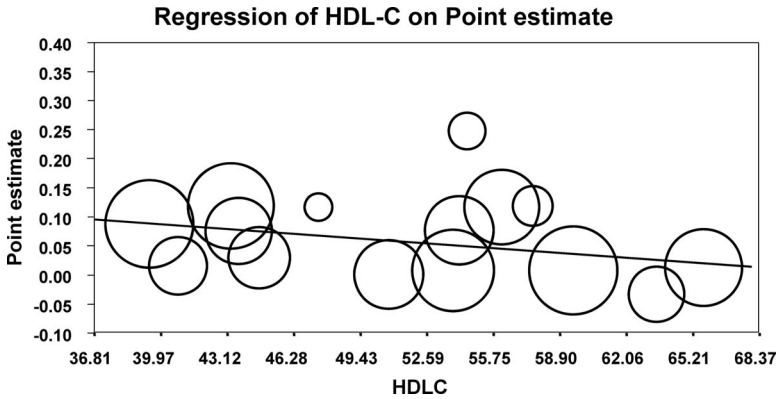

Figure 4. Plot of the meta-regression of the studies' mean HDL-C levels on the difference between apoB and non-HDL-C log-RRRs. The weight given each study by the method of moments is indicated by the area within each circle. The estimated slope of this curve represents a decrease in the difference of 0.0026 per milligram/deciliter increase in mean HDL-C ($P=0.064$). The R^2 index is 0.565, indicating more than half of the variance among studies may be explained by the variance in the studies' mean HDL-C level. If the Casale Monferrato study is excluded as an outlier, the method of moments estimate of the slope is −0.0028 ($R^2=0.613$, $P=0.034$). AMORIS indicates Apolipoprotein Mortality Risk study; ApoB, apolipoprotein B; Fram, Framingham; ISIS, International Studies of Infarct Survival; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; MONICA/KORA, Monitoring of Trends and Determinants in Cardiovascular Disease Augsburg project; RRR, relative risk ratio.

advantage of non-HDL-C over LDL-C. Our findings differ, therefore, from those of the ERFC, which found apoB, LDL-C, and non-HDL-C to be of equivalent value as markers of cardiovascular risk.[6]

Comparison of Present Study With the ERFC Study

A major strength of the ERFC study is that the analyses are patient based and not study based as in the present analysis. Moreover, ERFC included only prospective epidemiological studies, although many were not originally designed as such. The apoB versus non-HDL-C comparisons in the ERFC study are based on 22 studies that included 91 307 subjects and 4449 events, whereas the present results are based on 12 reports that included 233 455 subjects and 22 950 events. Because we have relied on published materials, only 3 of the 22 studies used in the ERFC could be incorporated in the present analysis. Conversely, 9 of the studies included in this analysis were not incorporated in the ERFC study.

ERFC specifically excluded 2 major case-control studies—INTERHEART[22] and ISIS[23]—whereas we included them in the present analysis. There are arguments on both sides. Correct matching of controls to cases and the possibility that consequences of the event might alter the risk profile of the cases are potential weaknesses of the case-control design. By contrast, the massive number of cases that can be compared to controls, a strength that is particularly relevant in the present instance where closely correlated variables are being compared, is an indisputable strength of the case-control design. It is noteworthy that the effect sizes of INTERHEART and ISIS fit within the range of the other studies that make up the present analysis. The very large number of events, however, does result in much greater precision in the estimate of the effect size. No evidence of bias due to sampling time or other relevant biases was found in either study. Finally, omitting these studies does not change the overall results. ERFC also omitted the AMORIS (Apolipoprotein Mortality Risk) study on the basis that HDL-C was calculated, not measured by conventional methods.[21] However, the investigators validated this approach. AMORIS,[21] unlike INTERHEART[22] and ISIS,[23] showed non-HDL-C and apoB to be virtually the same in predictive value.

Nineteen out of the 22 studies included in the ERFC[6] have not published their results, particularly their event rates and lipid and apoB values, which limits assessment of the completeness of the follow-up, definition of events, adequacy of sample preservation, and assay quality. The last points are of particular relevance because it is clear that a number of the reports included in the ERFC were not either initially designed as prospective studies or intended to measure apoB. Moreover, whereas the present study pointed to a hierarchy of efficacy among the major markers for the atherogenic lipoproteins, a result that is consistent with the results of individual published studies, ERFC, which had 5 times fewer events, reported no significant gradient of efficacy among the 3 markers, a finding that is at variance with the published literature. It is also noteworthy that in the ERFC analysis, triglycerides had no independent predictive power, whereas in a prior study[26] and subsequent meta-analysis[27] by some of the same investigators, triglycerides were independent significant predictors of risk.

The results of the published studies that make up the present meta-analysis fall into 2 categories: those that show non-HDL-C and apoB to be equivalent as markers of risk and those that show apoB to be superior. We could not identify any published study that showed non-HDL- C to be substantially superior to apoB, and there was no evidence of publication bias. It is worth noting that even if the risk of non-HDL-C and apoB were equal overall in predictive power within groups, this finding would not be the case for large numbers of individuals within those groups.[28] VLDL and LDL particles differ in composition on the basis of differences in cholesterol content. These compositional differences often produce differences in the concentration of non-HDL-C and apoB that are sufficiently different as to produce clinically significant differences in risk assessments.

It is worth noting that the INTERHEART study demonstrated that all the major modifiable risk factors, including apoB, had similar associations in all the major peoples of the world.[29] Accordingly, our choice of a random-effects model rather than a fixed-effects model represents a conservative approach to the analysis of the interactions.

Pathophysiological Basis for Non-HDL-C as a Marker of Vascular Risk

That non-HDL-C and apoB should be close in performance as markers of risk should not be surprising given the very high correlation (generally >0.9) that exists between them. Non-HDL-C includes all the cholesterol in the apoB lipoproteins, whereas apoB reflects the total number of apoB-containing particles, the great majority of which are LDL. The present analysis indicates that non-HDL-C is superior to LDL-C as a marker of cardiovascular risk. The conventional explanation would be that the gain in predictive power is due to the cholesterol in VLDL. However, as we have outlined here, this cannot be the case. The superiority of non-HDL-C over LDL-C is due to the fact that non-HDL-C is a better marker of LDL-P than LDL-C.[4,5] It is not surprising, therefore, that non-HDL-C falls intermediately between apoB or LDL-P and LDL-C as a marker of cardiovascular risk, whereas apoB and LDL-P appear to be equivalent as predictors of risk.

The Impact of HDL-C on the Relative Predictive Powers of Non-HDL-C and ApoB

With the exception of HDL-C, we were unable to identify any factor that could materially affect the variance in the comparisons of the predictive power between non-HDL-C and apoB among the studies. LDL-C and HDL-C are independent variables. By contrast, there is evidence of a significant inverse relation between HDL-C and apoB or LDL-P such that lower levels of HDL-C tend to be associated with higher levels of apoB.[30] The inverse relation between apoB and HDL-C likely relates to the fact that HDL, as well as LDL, can participate in cholesteryl ester transfer protein-mediated core lipid exchange with the VLDL or LDL, with cholesteryl ester moving to the apoB particles in exchange for triglyceride moving to the HDL particles. A higher HDL-C points to less core lipid exchange and, therefore, greater concordance between non-HDL-C and apoB. A lower HDL-C points to more core lipid exchange and, therefore, greater discordance between non-HDL-C and apoB. When apoB and non-HDL-C are concordant, they will predict risk equally, whereas when they are discordant, apoB will be superior. Thus, one explanation consistent with our meta-regression findings is that compositional changes from core lipid exchange explain much of the variance in the predictive power of non-HDL-C and apoB. As discussed in this article, however, the predictive power of non-HDL-C appears to be related more to LDL-P than to inclusion of VLDL cholesterol along with LDL-C.[4]

Our findings add to the urgency to better understand the relation of HDL to the risk of vascular disease. Is HDL as important as we previously thought, and if so, which marker of HDL is most appropriate: HDL-C or HDL particle number? Alternatively, is the risk associated with HDL related more directly to one of the very large molecules that are associated with it?

Population Implications

To help readers to assess the potential clinical significance of this report's statistical conclusions, we performed the calculations shown in Figure 4. These estimates of benefit are possible because the National Health and Nutrition Examination Survey 2005 to 2006 is designed to be representative of the entire nonpregnant, noninstitutionalized, civilian American population.[24] Targeting the different markers in the same National Cholesterol Education Program Adult Treatment Panel III-based preventive treatment strategy[31–33] reveals that selecting non-HDL-C rather than LDL-C could potentially reduce the number of incident cases among adult US residents by an additional 300 000 (1.8 million versus 1.5 million) over 10 years, whereas targeting apoB rather than non-HDL-C would prevent another 500 000 patients (2.3 million versus 1.8 million) from experiencing a coronary event. These differences in effectiveness result from the higher average absolute risk among patients eligible for treatment and the greater RRRs associated with the measures with higher RRRs. It must be noted that these calculations are principally intended to illustrate the clinical implications and should not be taken as advocating the particular strategy assumed for the comparisons. Comparing more-complex, and potentially more effective, strategies is beyond the scope of this article. However, comparisons of scenarios with different targets using the realistic strategy chosen demonstrate that the differences in overall average standardized relative risks are clearly clinically as well as statistically significant.

Individual Patient Implications

We believe that the present results add to the already strong case that apoB be monitored routinely in the care of individual patients. We would note 4 points in particular. First, measurement of apoB identifies major abnormalities in LDL that are not evident when LDL-C is relied on, including in many patients with type 2 diabetes and the metabolic syndrome in whom LDL-C level is normal but apoB level is elevated.[8] Importantly, not all hypertriglyceridemic patients have elevated apoB, and not all normotriglyceridemic normocholesterolemic patients have a normal apoB.[8] As well, a substantially increased LDL-P will not be recognized in other patients who present with low HDL-C and otherwise normal lipids if apoB level is not measured.[34,35] On the other hand, apoB also allows a more accurate assessment of risk in individuals with elevated LDL-C but normal apoB levels.[36]

Second, measurement of apoB along with TC and triglyceride levels makes diagnosis of all the atherogenic dyslipoproteinemias possible in individual patients.[37] This includes identification of familial combined hyperlipidemia, the most common familial dyslipoproteinemia associated with vascular disease, and familial dysbetalipoproteinemia, an unusual but not rare dyslipoproteinemia associated with major vascular risk that cannot be diagnosed accurately at the present time in most lipid clinics.

Third, successful diagnosis and therapy in individual patients demands that the diagnostic biomarker be measured

accurately and precisely. When LDL-C was introduced into clinical practice, great effort was expended to ensure that the laboratory determination was as reliable as possible. Particular attention was paid to the measurement of HDL-C, a component of the Friedewald equation. Although never fully standardized, the chemical precipitation methods were reasonably reliable and robust. Unfortunately, that is less true with newer, homogeneous HDL-C methods, and errors in the measurement of HDL-C can affect the accuracy of non-HDL-C measurement. The clinical assays for apoB, on the other hand, have become reliable and robust, and apoB can be measured on nonfasting samples at low cost.[9] Accordingly, apoB is superior to LDL-C and non-HDL-C as a laboratory analyte, and reducing laboratory error will reduce clinical error in individual patient care.

Fourth, although within statin trials non-HDL-C and apoB are generally equivalent risk markers,[8] apoB is a better marker of the individual who can benefit from an increased dose of statins in that apoB level identifies more individuals with LDL-P that remain elevated above reasonable percentile target levels of the population.[38]

The Canadian guidelines determined that levels of apoB $\geq$120 mg/dL identify patients at high risk of vascular disease due to atherogenic lipoproteins and selected a single target of $<$80 mg/dL.[39] No very-high-risk target was selected, but based on the most recent statin clinical trials, we would suggest that it be $<$70 mg/dL. Thus, 120 mg/dL, 80 mg/dL, and 70 mg/dL for apoB would correspond to values of 160 mg/dL, 100 mg/dL, and 70 mg/dL for LDL-C and 190 mg/dL, 130 mg/dL, and 100 mg/dL for non-HDL-C.

Summary

The present meta-analysis indicates that apoB is superior to non-HDL-C and that non-HDL-C is superior to LDL-C as a predictor of cardiovascular risk. Moreover, we have shown that if apoB measurement is introduced into routine care, many more events would be prevented than if diagnosis and therapy were based on either LDL-C or non-HDL-C levels. Thus, at a population level, apoB is a superior analytic tool to LDL-C or non-HDL-C. The issue is complicated, however, because the advantage of apoB is not constant. In patients in whom LDL composition is normal, the cholesterol markers and apoB are equivalent markers of risk.[5,8] The critical difference is when the markers are discordant, that is, when LDL-C is normal but LDL-P is high or, alternatively, when LDL-C is high but LDL-P is normal. Here, the evidence-indicated risk follows apoB and LDL-P, not LDL-C.[5,8,38]

Significant discordance in LDL composition is common. Hypertriglyceridemic hyperapoB is characterized by increased cholesterol-depleted LDL-P.[5] Hypertriglyceridemic hyperapoB is the hallmark dyslipoproteinemia associated with diabetes mellitus and the metabolic syndrome[40] and the most common dyslipoproteinemia associated with premature coronary artery disease.[8] Indeed, it is only because discordant LDL is so common in the general population that apoB becomes a more accurate overall marker of cardiovascular risk than LDL-C or non-HDL-C.

Entry and trapping of apoB lipoprotein particles within the arterial wall is the prime cause of atherosclerosis, the signal event that initiates, sustains, and collaborates in completing the long complex cycle that results in the acute arterial injury that produces a clinical event. Given this fundamental pathophysiological reality, it makes clinical sense to measure the parameter that matters most to this process—the number of atherogenic apoB particles in plasma, apoB—rather than the concentration of a constituent of these atherogenic particles—cholesterol.

This dispute about markers is a dispute with consequence. If measures of atherogenic particle number are not introduced into clinical care and if the apoB model is valid, we have shown that the price in terms of lives lost that could have been saved and infarcts that occurred that could have been prevented would be substantial. Accordingly, not introducing the apoB model into clinical care demands a high degree of certainty that the evidence in favor of apoB is not correct, a degree of certainty we submit is not reasonable given the array of available evidence.

We believe that history does repeat itself. LDL-C allowed us to move from plasma lipids to lipoprotein lipids, a change that at the time was hotly disputed, but a change that with time led to improvement in diagnosis and therapy. Similarly, apoB will allow us to move from lipoprotein lipids to lipoprotein particles, and this will lead to further improvement in diagnosis, therapy, and prevention of cardiovascular events.

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Disclosures

None.

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