

Association of Apolipoprotein B-Containing Lipoproteins and Risk of Myocardial Infarction in Individuals With and Without Atherosclerosis

Distinguishing Between Particle Concentration, Type, and Content

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IMPORTANCE Lipid management typically focuses on levels of low-density lipoprotein cholesterol (LDL-C) and, to a lesser extent, triglycerides (TG). However, animal models and genetic studies suggest that the atherogenic particle subpopulations (LDL and very-low-density lipoprotein [VLDL]) are both important and that the number of particles is more predictive of cardiac events than their lipid content.

OBJECTIVE To determine whether common measures of cholesterol concentration, TG concentration, or their ratio are associated with cardiovascular risk beyond the number of apolipoprotein B (apoB)-containing lipoproteins.

DESIGN, SETTING, AND PARTICIPANTS This prospective cohort analysis included individuals from the population-based UK Biobank and from 2 large international clinical trials, FOURIER and IMPROVE-IT. The median (IQR) follow-up was 11.1 (10.4-11.8) years in UK Biobank and 2.5 (2.0-4.7) years in the clinical trials. Two populations were studied in this analysis: 389 529 individuals in the primary prevention group who were not taking lipid-lowering therapy and 40 430 patients with established atherosclerosis who were receiving statin treatment.

EXPOSURES ApoB, non-high-density lipoprotein cholesterol (HDL-C), LDL-C, and TG.

MAIN OUTCOME AND MEASURES The primary study outcome was incident myocardial infarction (MI).

RESULTS Of the 389 529 individuals in the primary prevention group, 224 097 (58%) were female, and the median (IQR) age was 56.0 (49.5-62.5) years. Of the 40 430 patients with established atherosclerosis, 9647 (24%) were female, and the median (IQR) age was 63 (56.2-69.0) years. In the primary prevention cohort, apoB, non-HDL-C, and TG each individually were associated with incident MI. However, when assessed together, only apoB was associated (adjusted hazard ratio [aHR] per 1 SD, 1.27; 95% CI, 1.15-1.40; $P < .001$). Similarly, only apoB was associated with MI in the secondary prevention cohort. Adjusting for apoB, there was no association between the ratio of TG to LDL-C (a surrogate for the ratio of TG-rich lipoproteins to LDL) and risk of MI, implying that for a given concentration of apoB-containing lipoproteins, the relative proportions of particle subpopulations may no longer be a predictor of risk.

CONCLUSIONS AND RELEVANCE In this cohort study, risk of MI was best captured by the number of apoB-containing lipoproteins, independent from lipid content (cholesterol or TG) or type of lipoprotein (LDL or TG-rich). This suggests that apoB may be the primary driver of atherosclerosis and that lowering the concentration of all apoB-containing lipoproteins should be the focus of therapeutic strategies.

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Historically, epidemiological studies have demonstrated an association between circulating levels of serum total cholesterol and cardiovascular risk.¹ Investigation of lipoprotein subfractions pointed to the atherogenic potential for apolipoprotein B-100 (apoB-100)-containing lipoproteins (low-density lipoproteins [LDL], intermediate-density lipoproteins [IDL], and very-low-density lipoproteins [VLDL]), and guidelines have historically focused on LDL-cholesterol (LDL-C). Such a focus was not unreasonable, given that the foundational lipid-modifying therapy is statin based and that statins can cause upregulation of the LDL receptor, clearance of LDL particles, and a reduction in serum LDL-C levels. Indeed, development of additional therapies that further reduce LDL-C and cardiovascular risk, such as ezetimibe and proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors, has given clinicians additional tools that, when used in combination, can reduce LDL-C by approximately 85%.

Attention has now turned to the residual risk associated with other lipoproteins, and therapies are being developed that can preferentially target these lipoproteins. To that end, recent studies have attempted to tease apart the relative clinical importance of circulating concentrations of LDL-C, so-called remnant cholesterol (eg, the cholesterol on IDL and VLDL), and triglycerides (TG).^{2,3} These studies have suggested that TG and remnant cholesterol may be more potent risk factors for myocardial infarction (MI) than LDL-C is.^{2,3}

However, measures of cholesterol and TG provide information on the lipids in the blood and thus only indirectly on the types of lipoproteins and their composition, and not on the number of lipoproteins. As there is exactly 1 apoB-100 on each of the atherogenic apoB-containing particles (ie, LDL, IDL, and VLDL), its measurement can be used as a surrogate for the concentration or number of atherogenic lipoprotein particles. Mendelian randomization studies have shown that apoB is a better predictor of coronary artery disease risk than serum LDL-C or TG concentration, suggesting that the number of atherogenic particles may be the driver of cardiovascular risk, rather than cholesterol or TG content per se.^{4,5} In this analysis, we investigated data from a large primary cohort and 2 secondary prevention cohorts to determine whether common measures of cholesterol concentration, TG concentration, or their ratio carry any predictive value for cardiovascular risk beyond the number of apoB-containing lipoproteins.

Methods

Study Design and Population

We performed a prospective cohort analysis in 2 types of patient populations. The primary prevention group included 389 529 individuals without lipid-lowering therapy from a general population in UK Biobank.^{6,7} All patients with CAD, prior stroke, peripheral artery disease, or receiving lipid-lowering therapy at the baseline visit were excluded. The second group included 40 430 patients with established atherosclerosis disease who were receiving lipid-lowering therapy and were enrolled in either Further Cardiovascular Outcomes Research with

Key Points

Question Are common measures of cholesterol concentration, triglyceride concentration, or their ratio associated with cardiovascular risk beyond the number of apolipoprotein B (apoB)-containing lipoproteins?

Findings In this cohort analysis, apoB was the only lipid parameter significantly associated with risk of myocardial infarction after adjustment. No association was found between the ratio of lipoprotein types and myocardial infarction, indicating that, for a given number of apoB-containing lipoproteins, one type may not be associated with increased risk.

Meaning Risk of myocardial infarction may best be captured by the number of apoB-containing lipoproteins, independent from lipid content (cholesterol or triglyceride) or type of lipoprotein (low-density lipoprotein or triglyceride-rich).

PCSK9 Inhibition in Subjects with Elevated Risk (FOURIER)^{8,9} or Improved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT).^{10,11} In FOURIER, patients were required to be receiving statin therapy and half of patients were randomized to the PCSK9-inhibitor evolocumab. In IMPROVE-IT, all patients were receiving statin therapy and half were randomized to ezetimibe in addition to statin therapy. To account for achieved lipid levels, the clinical trial analysis was landmarked at 3 months in FOURIER and 4 months in IMPROVE-IT, such that all randomized patients who reached this time point were included in the analysis.

All individuals from the parent clinical trial signed informed consent and had lipid panels, including apoB, performed at the beginning of the study period and throughout the trial, with LDL-C measured by Friedewald equation, except for those with LDL-C less than 40 mg/dL (to convert to millimoles per liter, multiply by 0.0259) in the FOURIER trial, in whom it was measured using ultracentrifugation. No patients were excluded from this analysis for TG values, although patients with TG of 400 mg/dL or greater in FOURIER and 350 mg/dL or greater in IMPROVE-IT were excluded from the trials (to convert to millimoles per liter, multiply by 0.0113). UK Biobank data are available to the public. The data from FOURIER and IMPROVE-IT will not be made publicly available but interested parties may contact the corresponding author. The institutional review board or ethics committee of each participating site approved each of the clinical trial protocols, and the clinical trials followed the New England Journal of Medicine reporting guidelines.

End Points

The end point of interest in both cohorts was fatal or nonfatal MI, a cardiovascular outcome that can be known with high precision and is strongly associated with dyslipidemia. In UK Biobank, this was defined by the general *International Classification of Diseases, Tenth Revision*, code I21 and its subcodes I210 to I214 and I219. In FOURIER and IMPROVE-IT, MI was a component of the trials' primary end points and was therefore adjudicated by the Thrombolysis in Myocardial Infarction (TIMI) central clinical end points committee. Adjudicators were blinded to lipid levels and treatment arm. A sensitivity

Table 1. Baseline Characteristics in Primary and Secondary Prevention Cohorts

Characteristic	Prevention, No. (%)	
	Primary (n = 389 529)	Secondary (n = 40 430)
Demographic characteristics		
Age, median (IQR), y	56.0 (49.5-62.5)	63.0 (56.2-69.0)
Female	224 097 (58)	9647 (24)
Male	165 432 (42)	30 782 (76)
BMI, median (IQR) ^a	26.4 (23.8-29.4)	28.4 (25.5-31.7)
Race and ethnicity^b		
Asian	7539 (1.9)	3216 (8.0)
Black	9128 (2.3)	912 (2.3)
White	366 114 (94.0)	34 360 (85.0)
Other/unknown ^c	6748 (1.7)	1942 (4.8)
Medical history		
Myocardial infarction	0 (0)	24225 (59.9)
Stroke	0 (0)	5577 (13.8)
Peripheral artery disease	0 (0)	4174 (10.3)
Diabetes	2702 (0.7)	13 205 (32.7)
CKD (eGFR < 60 mL/min/1.73 m ²)	5739 (1.6)	7445 (18.5)
Hypertension	21 930 (5.6)	29 533 (73.1)
Smoking	41 230 (10.6)	12 009 (29.7)
Lipid values, median (IQR), mg/dL		
Apolipoprotein B ^d	105 (90-121)	68 (46-86)
Cholesterol^e		
Total	226 (199-253)	134 (105-162)
LDL	142 (122-163)	61 (36-85)
HDL	55 (46-66)	46 (38-55)
Non-HDL	168 (143-196)	86 (56-114)
Triglycerides ^f	127 (90-184)	115 (84-163)
Statin use, %	0	99.95

Abbreviations: BMI, body mass index; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

^a Calculated as weight in kilograms divided by height in meters squared.

^b Race and ethnicity data were self-reported and collected as part of the protocol in each of the original cohorts.⁶⁻¹¹

^c In UK Biobank, other/unknown includes 0.6% of individuals whose data was not available or who preferred not to answer and 1.1% who reported mixed racial or ethnic background or other race or ethnicity that was not further defined. In the TIMI trials, 0.4% of individuals were American Indian or Alaskan Native, 0.1% were Native Hawaiian or Pacific Islander, 1.5% were of Spanish descent (option was only available in IMPROVE-IT), and 2.8% self reported as "other."

^d To convert to g/L, multiply by 0.01.

^e To convert to mmol/L, multiply by 0.0259.

^f To convert to mmol/L, multiply by 0.0113.

analysis using a broader composite atherosclerotic cardiovascular disease end point was performed in each cohort. The median (IQR) follow-up was 11.1 (10.4-11.8) years in UK Biobank and 2.5 (2.0-4.7) years in the combined clinical trial cohort.

Lipid Measurement

Lipid measurements in UK Biobank were performed on the Beckman Coulter AU5800 platform and run using an immune-

turbidimetric approach. Original measurements were in grams per liter with a normal reference range reported by the manufacturer of 0.4 to 2.0 g/L. Storage and processing of the samples have previously been described.¹²

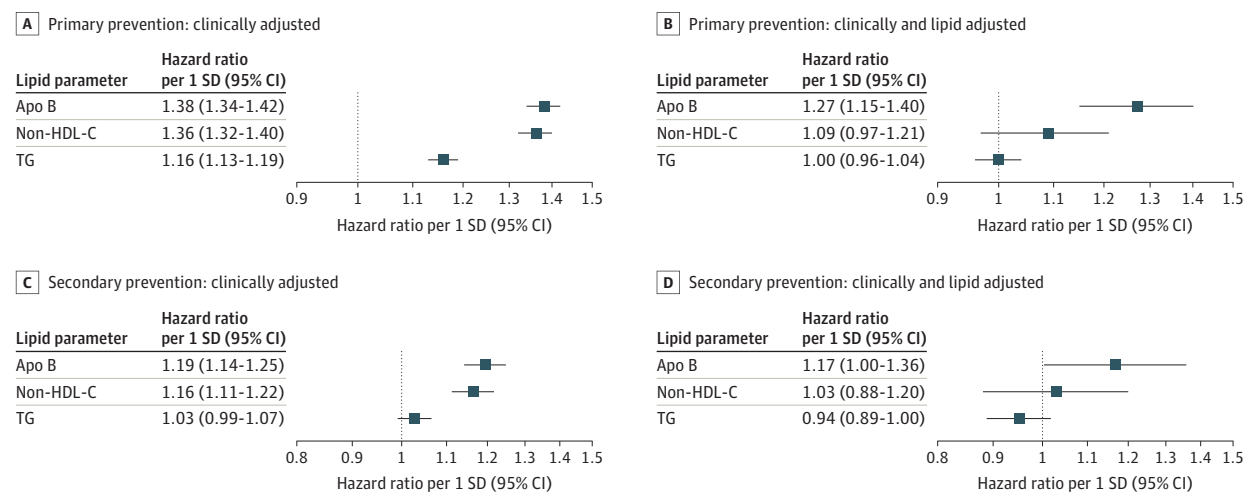
Statistical Analysis

In the primary prevention cohort from UK Biobank, baseline lipid panels from study entry were used for this analysis. In FOURIER and IMPROVE-IT, achieved lipid levels at 3 and 4 months, respectively, were used as the patient's new baseline, and analyses were landmarked from that time point forward. Correlation coefficients were calculated across lipid parameters. A Cox proportional hazards model was used to calculate adjusted hazard ratios (aHR) for MI per 1 SD-higher apoB, non-HDL-C, and TG. Clinical adjustment included age, sex, body mass index (calculated as weight in kilograms divided by height in meters squared), diabetes, hypertension, smoking status, race and ethnicity, kidney function (creatinine clearance in UK Biobank and estimated glomerular filtration rate in FOURIER and IMPROVE-IT), prior MI, prior stroke, and peripheral artery disease (the latter 3 for the secondary prevention cohort only), all assessed at baseline visit in UK Biobank and at study enrollment in the trial cohort. Further adjustment included the lipid parameters HDL-C, TG, non-HDL-C, and apoB. Intermediate models included partial lipid adjustment. *P* values were derived from testing the significance of the coefficient of each lipid market in the Cox proportional hazard models. Given the high level of correlation between many of the lipid parameters, we calculated the variant inflation factor for each lipid in every model to assess the presence of collinearity. To determine whether lipoprotein type could predict CV risk beyond lipoprotein concentration, the TG/LDL-C ratio was evaluated in both UK Biobank and the trials with adjustment for apoB. Statistical analyses were performed using SAS version 9.4 (SAS Institute) and R version 3.6 (the R Foundation). Two-sided *P* values were considered statistically significant at less than .05.

Results

The primary prevention cohort without lipid-lowering therapy was made up of 389 529 individuals (224 097 [58%] female) with a median (IQR) age of 56.0 (49.5-62.5) years. Race and ethnicity in this cohort were as follows: there were 7539 Asian individuals (1.9%), 9128 Black individuals (2.3%), 366 114 White individuals (94.0%), and 6748 individuals of other races or ethnicities (1.7%) that were consolidated owing to lack of data or to individuals preferring not to answer, not knowing how to answer, reporting a mixed racial or ethnic background, or reporting "other." The median (IQR) LDL-C was 142 (122-163) mg/dL, non-HDL-C was 168 (143-196) mg/dL (to convert to millimoles per liter, multiply by 0.0259), TG was 127 (90-184) mg/dL, and apoB was 105 (90-121) mg/dL (to convert to grams per liter, multiply by 0.01) (Table 1). The secondary prevention statin-treated cohort included 40 430 patients (9647 [24%] female) with a median (IQR) age of 63.0 (56.2-69.0) years. Race and ethnicity in this cohort were as follows: there were 3216

Figure 1. Lipid Parameters and Risk of Myocardial Infarction



All models were adjusted for age, sex, body mass index (calculated as weight in kilograms divided by height in meters squared), smoking status, hypertension, diabetes, ethnicity, and kidney function. The secondary prevention cohort was also adjusted for prior myocardial infarction, stroke, and peripheral artery disease. Clinically and lipid-adjusted models also included apolipoprotein B, non-high-density lipoprotein cholesterol, triglycerides, and high-density lipoprotein cholesterol in addition to the clinical variables.

Table 2. Baseline Lipid Parameters and Adjusted Hazard Ratios for Myocardial Infarction in the Primary Prevention Cohort Without Lipid-Lowering Therapy

Lipid parameter	Adjust hazard ratios (95% CI) ^a				
	Clinically adjusted models	Clinically + lipid-adjusted models			
		TG	Non-HDL-C	ApoB	All lipids ^b
ApoB	1.38 (1.34-1.42)	1.34 (1.30-1.38)	1.32 (1.20-1.44)	NA	1.27 (1.15-1.40)
Non-HDL-C	1.36 (1.32-1.40)	1.34 (1.30-1.38)	NA	1.05 (0.95-1.15)	1.09 (0.97-1.21)
TG	1.16 (1.13-1.19)	NA	1.04 (1.01-1.07)	1.07 (1.05-1.10)	1.00 (0.96-1.04)

Abbreviations: ApoB, apolipoprotein B; HDL-C, high-density lipoprotein cholesterol; NA, not applicable; TG, triglycerides.

^a Models include no lipid adjustment, partial lipid adjustment, and all lipids adjustment. All models adjusted for age, sex, body mass index (calculated as

weight in kilograms divided by height in meters squared), smoking status, hypertension, diabetes, race and ethnicity, and creatinine clearance. Additional lipid adjustment shown as labeled.

^b Includes HDL-C, TG, non-HDL-C, and apoB.

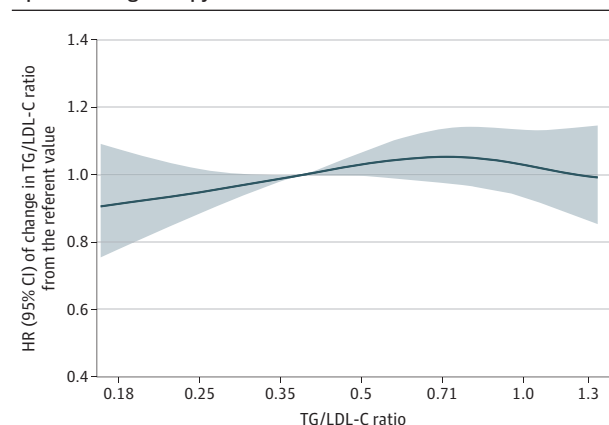
Asian individuals (8.0%), 912 Black individuals (2.3%), 34 360 White individuals (85.0%), and 1942 individuals of other races or ethnicities (4.8%) that were consolidated owing to low numbers, including American Indian or Alaskan Native, Native Hawaiian or Pacific Islander, of Spanish descent (IMPROVE-IT only), or self-reported "other." The median LDL-C was 61 (36-85) mg/dL, non-HDL-C was 86 (56-114) mg/dL, TG was 115 (84-163) mg/dL, and apoB was 68 (46-86) mg/dL. In addition to all having established atherosclerotic cardiovascular disease, the secondary prevention cohort had higher rates of diabetes, hypertension, and smoking (Table 1).

The Spearman correlation coefficients for key lipid parameters in primary prevention individuals without lipid-lowering therapy are shown in eTable 1 in the Supplement. ApoB, LDL-C, and non-HDL-C were correlated ($\rho \geq 0.95$). TG was positively correlated with these 3 parameters ($\rho = 0.38-0.52$). HDL-C was correlated with apoB, LDL-C, and non-HDL-C ($\rho \leq |0.12|$) and negatively correlated with TG ($\rho = -0.49$). Similar associations between lipid parameters were seen in the statin-treated secondary prevention cohort (eTable 2 in the Supplement).

The aHRs for MI per 1-SD increase in lipoprotein component for primary and secondary prevention populations are presented in Figure 1. In the primary prevention cohort, each 1 SD higher apoB was associated with a 38% increase in risk of MI (aHR, 1.38; 95% CI, 1.34-1.42; $P < .001$) (Figure 1A). This significant positive association was maintained after full adjustment for lipid parameters, including TG, non-HDL-C, and HDL-C (HR, 1.27; 95% CI, 1.15-1.40; $P < .001$) (Figure 1B). Non-HDL-C had similar MI association with clinical adjustment, and while this was maintained after adding TG to the model, non-HDL-C was no longer associated with MI when adjusted for apoB (Table 2). This same pattern was seen in secondary prevention (Figure 1C and D).

In the primary prevention cohort, with each 1-SD increase, TG was associated with a 16% greater risk of MI (aHR per 1 SD, 1.16; 95% CI, 1.13-1.19; $P < .001$) (Figure 1A). However, this association was no longer apparent when adjusting for all clinical and lipid parameters (aHR per 1 SD, 1.00; 95% CI, 0.96-1.04; $P = .71$) (Figure 1B). In the secondary prevention group of patients treated with statin, TG was not associated with risk of MI in either clinically adjusted (aHR per

Figure 2. Relative Importance of Lipoprotein Type After Adjusting for Apolipoprotein B Concentration in Individuals Not Receiving Lipid-Lowering Therapy



TG indicates triglyceride-rich lipoprotein; LDL-C, low-density lipoprotein cholesterol particles. The solid line represents the hazard at a given TG/LDL-C ratio compared with the hazard at the median TG/LDL-C ratio. Shaded area indicates 95% CIs. The slope of the line is not statistically different from 0 ($P = .12$). Adjusted for age, sex, ethnicity, body mass index (calculated as weight in kilograms divided by height in meters squared), smoking status, diabetes, creatine clearance, high-density lipoprotein, and apolipoprotein B.

1 SD, 1.03; 95% CI, 0.99-1.07) or clinically and lipid-adjusted models (aHR per 1 SD, 0.94; 95% CI, 0.89-1.00) (Figure 1C, D). The patterns for apoB and TG were consistent in sensitivity analyses performed in the subset of individuals with TG greater than 200 mg/dL and in the placebo and additional lipid-lowering therapy arms separate from both clinical trials. The findings were all consistent when a broader atherosclerotic cardiovascular disease composite end point was evaluated (eTables 3 and 4 in the Supplement).

We obtained variant inflation factor values greater than 10 for apoB and non-HDL-C when the 2 lipids appeared in the same model and we addressed the issue by running a bootstrapped version of an adjusted Cox regression for the risk of MI, including all the lipids under examination (apoB, TG, non-HDL-C, and HDL). The distribution of the aHRs is reported in eFigure 1 in the Supplement where, despite an expected larger SD for apoB and non-HDL-C compared with TG, the mean estimates are consistent with our general findings.

To infer whether the type of apoB-containing lipoprotein (TG-rich lipoprotein vs LDL particle) has prognostic importance, we evaluated the TG/LDL-C ratio while adjusting for apoB and clinical risk factors. In individuals not receiving lipid-lowering therapy, the median (IQR) TG/LDL-C ratio was 0.39 (0.29-0.55). The association between the ratio of lipoprotein types and MI was flat (aHR per 1 SD, 1.04; 95% CI, 0.99-1.09; $P = .12$), indicating that, for a given number of apoB-containing lipoproteins, one type is not associated with significantly greater risk than the other (Figure 2). This flat association was seen up to TG/LDL-C ratios of 2 in the clinical trials, where LDL-C lowering therapies lowered LDL-C, resulting in much higher TG/LDL-C ratios (eFigure 2 in the Supplement). This flat association was also seen in sensitivity analyses in the subset of individuals with TG levels greater than 200 mg/dL.

Discussion

There are 3 components to consider when assessing the atherogenicity of apoB-containing lipoproteins. The first is the concentration of the lipoprotein particles, represented by apoB, given the 1:1 association between apoB and atherogenic lipoprotein particles. The second is the type of apoB-containing lipoprotein particle, such as TG-rich lipoproteins (ie, VLDL and IDL, estimated by TG) or LDL particle (estimated by LDL-C). The third is the amount of cholesterol (non-HDL-C) and TG contained carried by the particles. Standard measurements of TG and cholesterol can be misleading as they measure overall serum concentrations without directly addressing the number and type of particles. For example, 2 individuals can have the same LDL-C levels, but if one has twice the number of LDL particles but half the cholesterol content on each, our data suggest that that individual will have a higher risk of MI than the other. Conversely, 2 individuals can have the same apoB levels (and hence the same number of atherogenic lipoproteins). An individual with lower LDL-C, the metric on which the field currently focuses, may be perceived as being at lower risk, but that is not necessarily the case. ApoB allows for accurate assessment of particle concentration, and when it is held constant, the measurements of TG and LDL-C reflect particle type and content.

In this study, all lipid-adjusted analyses included adjustment for apoB, thereby accounting for lipoprotein particle concentration in the risk assessment. Using this approach, we had 3 key findings. First, apoB was the only independent driver of lipid-associated MI risk, confirming the importance of particle concentration. Second, the amount of lipid (cholesterol or TG) carried on the apoB-containing lipoprotein particles did not confer additional risk beyond apoB concentration. Third, the type of apoB-containing lipoprotein particle, either TG-rich lipoproteins or LDL particle, did not confer additional risk beyond particle concentration. Each of these findings was consistent across both primary and secondary populations and in those receiving and not receiving lipid lowering therapy.

This study builds on prior work showing that apoB concentration is the most predictive parameter of CV risk,¹³⁻¹⁵ and further advances our understanding by demonstrating that LDL-C and TG levels do not have predictive value beyond apoB. These findings are of increased relevance as recent publications have reported that TG, rather than LDL-C, most strongly predict CV risk.² However, these studies have limitations that include incomplete model adjustment, residual confounding, and not accounting for the concentration of lipoprotein particles as measured by apoB. Of note, though, both these prior studies and our work suggest that a TG-rich lipoprotein is just as important a risk factor for MI as an LDL particle.

For institutions that have apoB assays available, this would be the preferred lipid measure for assessing CV risk and response to lipid-lowering therapy. Indeed, measuring apoB is now recommended in the most recent lipid guidelines.¹⁶ That is not to say that conventional lipid profiles do not still have clinical utility. LDL-C and non-HDL-C are correlated with apoB,

and therefore can be used to approximate lipoprotein particle concentration and CV risk when apoB is not available. They can also serve as additional parameters more easily understood by patients and patient advocate organizations. However, it should be recognized that these measures do not identify the number of apoB-containing lipoprotein particles as reliably and have been shown to not always accurately predict CV risk.¹⁷ When necessary, non-HDL-C in particular is the preferred surrogate for apoB, as it incorporates TG-rich lipoproteins in addition to LDL.

There is also still value in the traditional lipid panel in understanding what is driving a high concentration of apoB-containing lipoproteins. For example, very high LDL-C but normal TGs could suggest familial hypercholesterolemia, whereas very high TGs and normal LDL-C are more consistent with a primary hypertriglyceridemia. This knowledge could impact the clinical diagnosis, choice of lipid-lowering therapy, and need for genetic testing and family screening. Therefore, apoB should not replace the standard lipid panel, but rather be added to it when possible.

Prior studies in UK Biobank and other cohorts have examined the predictive value of different lipid measurements.^{18,19} However, our study differs in a number of important ways. First, we have not only the largest, to our knowledge, primary prevention cohort from the latest UK Biobank data, but also a large secondary prevention cohort from 2 large clinical trials, providing much more data on patients receiving statin therapy. Second, in addition to adjustment for clinical risk factors, we adjusted simultaneously for other lipid parameters, which is critical for the interpretation of any one lipid measurement. Other studies have typically compared the magnitude of the risk ratios of individual different lipid measurements. In contrast, our approach allowed us to assess whether it is lipoprotein concentration, content, or type that drives CHD risk. Third, the inclusion of 2 prospective clinical trials provides data down to very low levels of LDL-C, non-HDL-C, and apoB only recently encountered in clinical practice.

It should be noted that there is some debate as to whether apoB should be better standardized prior to more widespread

use. The National Lipid Association has raised this issue in a scientific statement,²⁰ but the American Association of Clinical Chemistry has stated that apoB is standardized and can be measured with more accuracy than LDL-C and non-HDL-C.²¹ Indeed, LDL-C is often calculated by laboratories rather than directly measured, which may contribute to less accurate measurements compared with those for apoB and support more widespread use of apoB.

Limitations

This study has limitations. Lipid values in these cohorts were measured using conventional lipid profiles rather than nuclear magnetic resonance spectroscopy. While such an approach can specifically measure the number and particle size of lipoprotein particles, prior studies have shown that they are not superior to conventional lipid profiles.²² Nonetheless, nuclear magnetic resonance spectroscopy would offer a more accurate method for determining the VLDL-to-LDL ratio compared with the surrogate of TG to LDL-C used in this study. Additionally, lipid values and lipid-lowering therapy data were collected at baseline in UK Biobank, but may have changed in some individuals during the follow-up period. Because individuals with higher lipid values would be most likely to start lipid-lowering therapy, we anticipate this may have attenuated the association for each lipid parameter. Moreover, our study was not enriched for patients with severe hypertriglyceridemia, so we cannot comment on risk associations in such individuals.

Conclusions

In this cohort study, association with MI was best captured by the number of apoB-containing lipoproteins, independent from lipid content (cholesterol or TG) or type of lipoprotein (LDL or TG-rich). This suggests that apoB may be the primary driver of atherosclerosis and that lowering the overall concentration of all apoB-containing lipoproteins should be the focus of therapeutic strategies.

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