

# Role of the Apolipoprotein B–Apolipoprotein A-I Ratio in Cardiovascular Risk Assessment: A Case–Control Analysis in EPIC-Norfolk

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**Background:** An elevated apolipoprotein B–apolipoprotein A-I (apo B–apo A-I) ratio is a risk factor for future coronary artery disease (CAD). It is not known whether this ratio is better than traditional lipid values for risk assessment and prediction and whether it adds predictive value to the Framingham risk score.

**Objective:** To evaluate whether the apo B–apo A-I ratio is associated with future CAD events independent of traditional lipid measurements and the Framingham risk score and to evaluate the ability of this ratio to predict occurrence of future CAD.

**Design:** Prospective, nested case–control study.

**Setting:** Norfolk, United Kingdom.

**Participants:** Apparently healthy men and women (45 to 79 years of age) in the European Prospective Investigation into Cancer and Nutrition-Norfolk. Cases ( $n = 869$ ) were persons who developed fatal or nonfatal CAD. Controls ( $n = 1511$ ) were persons without CAD who were matched for age, sex, and enrollment period.

**Measurements:** Total cholesterol, high-density lipoprotein (HDL) cholesterol, triglyceride, apolipoprotein, and C-reactive protein levels were measured directly. Low-density lipoprotein (LDL) cholesterol values were calculated by using the Friedewald formula.

**Results:** The apo B–apo A-I ratio was associated with future CAD events, independent of traditional lipid values (adjusted odds ratio,

1.85 [95% CI, 1.15 to 2.98]), including the total cholesterol–HDL cholesterol ratio, and independent of the Framingham risk score (adjusted odds ratio, 1.77 [CI, 1.31 to 2.39]). However, it did no better than lipid values at discriminating between CAD cases and controls (area under the receiver-operating characteristic curve, 0.670 for total cholesterol–HDL cholesterol ratio vs. 0.673 for apo B–apo A-I ratio [ $P = 0.38$ ]) and added little to the predictive value of the Framingham risk score (area under the receiver-operating characteristic curve, 0.594 for Framingham risk score alone vs. 0.613 for Framingham risk score plus apo B–apo A-I ratio [ $P < 0.001$ ]). In addition, it incorrectly classified 41.1% of cases and 50.4% of controls.

**Limitations:** No participant was taking lipid-lowering medication, and diabetes was uncommon.

**Conclusions:** The apo B–apo A-I ratio is independently associated with, but adds little to, existing measures for CAD risk assessment and discrimination in the general population. Other characteristics of the test, such as the ability to perform it on nonfasting samples, may still make it useful in some settings.

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Low-density lipoprotein (LDL) cholesterol is a primary treatment target in coronary artery disease (CAD) prevention guidelines (1), but it is a poor predictor of future cardiovascular events (2). Similarly, the ratio of total cholesterol to high-density lipoprotein (HDL) cholesterol is a potent risk factor for CAD (3, 4), but it improves CAD risk prediction only modestly (5).

Apolipoprotein B and apolipoprotein A-I are the main structural proteins of atherogenic lipoproteins and HDL particles, respectively. In theory, the apolipoprotein B–apolipoprotein A-I (apo B–apo A-I) ratio could improve lipoprotein-related cardiovascular risk prediction. Apolipoprotein B levels reflect the entire spectrum of pro-atherogenic particles, including very-low-density, intermediate-density, and low-density lipoproteins, whereas LDL cholesterol levels do not (6). Apolipoprotein B levels also provide a good measure of the number of LDL particles, which reflects the atherogenicity of LDL (7, 8). In addition, apolipoprotein A-I is more important than HDL cholesterol content for biochemical pathways that make HDL anti-atherogenic, including adenosine triphosphate binding cas-

sette A1–mediated cellular cholesterol efflux (9), lecithin-cholesterol acyltransferase–mediated maturation of HDL particles (10), and several antioxidative processes (11). Besides these physiologic considerations, apolipoprotein assessment does not require fasting blood samples (6), a feature that facilitates logistics at outpatient clinics. Collectively, these considerations have led to recommendations to implement the apo B–apo A-I ratio in routine clinical care (12).

Studies before 1993 on the relationship between apolipoprotein levels and CAD incidence have reported incon-

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sistent results (13–17). These discrepancies are largely attributable to the lack of standardization of the laboratory tests at that time. Since the introduction of standardized reference materials by the International Federation of Clinical Chemistry (18, 19), large studies, such as Apolipoprotein-related Mortality RISK (AMORIS) (20) and INTERHEART (21), have unambiguously shown that the apo B–apo A-I ratio is a robust risk factor for future CAD events. However, these studies did not address the crucial question of whether the apo B–apo A-I ratio predicts those events better than traditional lipid values do.

We sought to evaluate whether the apo B–apo A-I ratio is associated with future CAD events, independent of traditional lipid-based variables and of the Framingham risk score (22), and to evaluate the ability of the ratio to predict CAD events.

## METHODS

### Design

We performed a nested case–control study of participants in the European Prospective Investigation into Cancer and Nutrition (EPIC)-Norfolk. The EPIC-Norfolk was a prospective population study of 25 663 men and women 45 to 79 years of age residing in Norfolk, United Kingdom, who completed a baseline questionnaire survey and

### Context

The apolipoprotein B–apolipoprotein A-I (apo B–apo A-I) ratio is a strong risk factor for atherosclerotic cardiovascular disease.

### Contribution

The researchers found that the apo B–apo A-I ratio was a risk factor for atherosclerotic cardiovascular disease, but its ability to distinguish people who developed disease from those who did not was no better than that of the total cholesterol–high density lipoprotein ratio, and it did not add further to the Framingham risk score.

### Caution

Few people with diabetes and no one using lipid-lowering medication participated in the study.

### Implication

The apo B–apo A-I ratio is a risk factor for atherosclerotic cardiovascular disease, but it adds little to conventional measures of risk discrimination in a general population.

—The Editors

Table 1. Baseline Characteristics\*

Characteristic	Controls (n = 1511)	Cases (n = 869)	P Value†
Men, n (%)	942 (62.3)	553 (63.6)	Matched
Mean age (SD), y	65 (8)	6 (8)	Matched
Smoking status, n (%)			<0.001
Current	123 (8.2)	138 (16.1)	
Former	749 (50.2)	439 (51.1)	
Never	620 (41.6)	282 (32.8)	
Persons with diabetes, n (%)	25 (1.7)	53 (6.1)	<0.001
Mean body mass index (SD), kg/m <sup>2</sup>	26.2 (3.4)	27.3 (3.9)	<0.001
Mean systolic blood pressure (SD), mm Hg	139 (18)	144 (19)	<0.001
Mean diastolic blood pressure (SD), mm Hg	84 (11)	86 (12)	<0.001
Mean total cholesterol level (SD)			
mmol/L	6.2 (1.1)	6.4 (1.2)	
mg/dL	239.8 (42.5)	247.5 (46.4)	<0.001
Mean LDL cholesterol level (SD)			
mmol/L	4.1 (1.0)	4.3 (1.1)	
mg/dL	158.5 (38.7)	166.3 (42.5)	<0.001
Mean HDL cholesterol level (SD)			
mmol/L	1.35 (0.40)	1.26 (0.37)	
mg/dL	52.2 (15.5)	48.7 (14.3)	<0.001
Mean non-HDL cholesterol level (SD)			
mmol/L	4.9 (1.1)	5.2 (1.2)	
mg/dL	189.5 (42.5)	201.1 (46.4)	<0.001
Median triglyceride level (IQR)‡			
mmol/L	1.6 (1.1–2.2)	1.8 (1.3–2.6)	
mg/dL	141.6 (97.4–194.7)	159.3 (115.0–230.1)	<0.001
Mean apolipoprotein A-I level (SD), g/L	1.62 (0.30)	1.55 (0.30)	<0.001
Mean apolipoprotein B level (SD), g/L	1.29 (0.30)	1.37 (0.32)	<0.001
Mean apolipoprotein B–apolipoprotein A-I ratio	0.82 (0.23)	0.91 (0.26)	<0.001
Median C-reactive protein level (IQR), mg/L	1.5 (0.7–3.1)	2.3 (1.1–4.9)	<0.001

\* HDL = high-density lipoprotein; IQR = interquartile range; LDL = low-density lipoprotein.

† Case-patients and age- and sex-matched controls were compared by using conditional logistic regression for categorical variables and a mixed-effects model for continuous variables.

‡ Triglyceride levels were log-transformed before analysis.

**Table 2. Risk for Future Coronary Artery Disease, by Lipid Value Quartile\***

Variable	Men and Women				P Value†
	Quartile 1	Quartile 2	Quartile 3	Quartile 4	
<b>Total cholesterol level, mmol/L‡</b>					
Median	5.0	5.9	6.6	7.6	
Range	2.7–5.5	5.5–6.2	6.2–6.9	6.9–11.7	
Odds ratio (95% CI)	1.00	1.12 (0.88–1.42)	1.09 (0.84–1.41)	1.63 (1.27–2.10)	<0.001
<b>LDL cholesterol level, mmol/L‡</b>					
Median	3.0	3.7	4.3	5.3	
Range	1.1–3.4	3.4–4.0	4.0–4.7	4.7–8.7	
Odds ratio (95% CI)	1.00	1.31 (1.02–1.68)	1.30 (1.01–1.66)	1.68 (1.32–2.14)	<0.001
<b>HDL cholesterol level, mmol/L‡</b>					
Median	1.0	1.2	1.5	1.9	
Range	0.5–1.1	1.1–1.3	1.3–1.6	1.6–3.1	
Odds ratio (95% CI)	1.00	0.65 (0.52–0.83)	0.60 (0.47–0.76)	0.48 (0.36–0.63)	<0.001
<b>Non-HDL cholesterol level, mmol/L‡</b>					
Median	3.7	4.5	5.2	6.2	
Range	1.8–4.1	4.1–4.8	4.8–5.6	5.6–9.8	
Odds ratio (95% CI)	1.00	1.38 (1.06–1.79)	1.51 (1.18–1.94)	2.15 (1.69–2.76)	<0.001
<b>Total cholesterol–HDL cholesterol ratio</b>					
Median	3.3	4.3	5.3	6.8	
Range	1.9–3.9	3.9–4.7	4.7–5.8	5.8–12.8	
Odds ratio (95% CI)	1.00	1.32 (1.01–1.73)	1.91 (1.47–2.48)	2.57 (1.98–3.33)	<0.001
<b>Apo B–apo A-I ratio</b>					
Median	0.56	0.72	0.88	1.10	
Range	0.25–0.65	0.65–0.79	0.79–0.96	0.96–2.55	
Odds ratio (95% CI)	1.00	1.33 (1.01–1.77)	1.78 (1.37–2.32)	2.64 (2.04–3.42)	<0.001

\* Odds ratios were calculated by using conditional logistic regression that took into account matching for sex, age, and time of enrollment. No additional correction was done for other cardiovascular risk factors. Apo B–apo A-I = apolipoprotein B–apolipoprotein A-I; HDL = high-density lipoprotein; LDL = low-density lipoprotein.

† For linear trend.

‡ To convert values to mg/dL, divide by 0.0259.

attended a clinic visit (23). Participants were recruited from age and sex registers of general practices in Norfolk as part of the 10-country collaborative EPIC, which was designed to investigate dietary and other determinants of cancer. Additional data were obtained in EPIC-Norfolk so that determinants of other diseases could also be assessed.

The design and methods of EPIC-Norfolk are described in detail elsewhere (23). In short, eligible participants were recruited by mail. At the baseline survey between 1993 and 1997, participants completed a detailed

health and lifestyle questionnaire. Nonfasting blood samples were obtained by venipuncture into plain and citrate bottles. Blood samples were processed for assay at the Department of Clinical Biochemistry, University of Cambridge, or were stored at  $-80^{\circ}\text{C}$ . All participants were flagged for death certification at the United Kingdom Office of National Statistics, and vital status was ascertained for the entire cohort. In addition, hospitalized participants were identified by using their unique National Health Service number through data linkage with the East Norfolk

**Table 3. Risk for Future Coronary Artery Disease in Adjusted Models\***

Model	Men and Women				P Value
	Quartile 1	Quartile 2	Quartile 3	Quartile 4	
<b>Model 2†</b>					
Total cholesterol–HDL cholesterol ratio	1.00 (referent)	1.34 (0.99–1.80)	1.88 (1.41–2.52)	2.55 (1.90–3.42)	<0.001
Apo B–apo A-I ratio	1.00 (referent)	1.42 (1.04–1.93)	1.79 (1.33–2.40)	2.72 (2.04–3.63)	<0.001
<b>Model 3a: apo B–apo A-I ratio‡</b>					
	1.00 (referent)	1.27 (0.90–1.79)	1.49 (1.01–2.19)	2.08 (1.30–3.31)	0.001
<b>Model 3b: apo B–apo A-I ratio§</b>					
	1.00 (referent)	1.23 (0.87–1.74)	1.40 (0.95–2.07)	1.85 (1.15–2.98)	0.01

\* Odds ratios were calculated by using conditional logistic regression that took into account matching for sex, age, and time of enrollment. Apo B–apo A-I = apolipoprotein B–apolipoprotein A-I; HDL = high-density lipoprotein.

† Adjusted for age, sex, time of enrollment, diabetes (yes or no), body mass index, smoking status (yes or no), systolic blood pressure, and C-reactive protein level.

‡ Adjusted for all variables in model 2, low-density lipoprotein cholesterol level, and HDL cholesterol level.

§ Adjusted for all variables in models 2 and 3a and log-transformed triglyceride values.

**Table 2—Continued**

Men Only					Women Only				
Quartile 1	Quartile 2	Quartile 3	Quartile 4	P Value†	Quartile 1	Quartile 2	Quartile 3	Quartile 4	P Value†
4.9	5.8	6.6	7.5		5.1	5.9	6.7	7.7	
2.7–5.5	5.5–6.2	6.2–6.9	6.9–11.0		3.5–5.5	5.5–6.2	6.2–6.9	6.9–11.7	
1.00	1.14 (0.86–1.51)	1.11 (0.81–1.51)	1.80 (1.32–2.46)	0.001	1.00	1.02 (0.65–1.63)	1.00 (0.63–1.60)	1.36 (0.88–2.12)	0.09
3.0	3.7	4.3	5.2		3.0	3.7	4.3	5.4	
1.1–3.4	3.4–4.0	4.0–4.7	4.7–7.9		1.5–3.4	3.4–4.0	4.0–4.7	4.7–8.7	
1.00	1.43 (1.05–1.95)	1.44 (1.06–1.94)	1.72 (1.27–2.34)	0.001	1.00	1.09 (0.71–1.69)	1.05 (0.67–1.64)	1.51 (1.01–2.28)	0.03
1.0	1.2	1.5	1.8		1.0	1.3	1.5	1.9	
0.5–1.1	1.1–1.3	1.3–1.6	1.6–3.0		0.5–1.1	1.1–1.3	1.3–1.6	1.6–3.1	
1.00	0.69 (0.52–0.91)	0.57 (0.42–0.78)	0.52 (0.35–0.79)	<0.001	1.00	0.59 (0.38–0.91)	0.60 (0.40–0.89)	0.44 (0.29–0.66)	<0.001
3.6	4.5	5.2	6.2		3.7	4.5	5.2	6.3	
1.8–4.1	4.1–4.8	4.8–5.6	5.6–9.4		1.8–4.1	4.1–4.8	4.8–5.6	5.6–9.8	
1.00	1.27 (0.93–1.75)	1.44 (1.06–1.95)	2.08 (1.52–2.84)	<0.001	1.00	1.62 (1.03–2.56)	1.67 (1.08–2.59)	2.33 (1.54–3.55)	<0.001
3.4	4.3	5.3	6.8		3.3	4.3	5.2	6.8	
2.1–3.9	3.9–4.7	4.7–5.8	5.8–12.8		1.9–3.9	3.9–4.7	4.7–5.8	5.8–10.2	
1.00	1.63 (1.10–2.41)	2.28 (1.57–3.32)	2.78 (1.93–4.00)	<0.001	1.00	1.06 (0.72–1.56)	1.60 (1.09–2.32)	2.70 (1.81–4.02)	<0.001
0.57	0.72	0.88	1.10		0.55	0.72	0.87	1.10	
0.27–0.65	0.65–0.79	0.79–0.96	0.96–2.55		0.25–0.65	0.65–0.79	0.79–0.96	0.96–1.80	
1.00	1.36 (0.92–2.02)	1.83 (1.28–2.61)	2.58 (1.82–3.66)	<0.001	1.00	1.28 (0.86–1.93)	1.70 (1.14–2.53)	2.83 (1.89–4.24)	<0.001

Health Authority database, which identifies all hospital contacts throughout England and Wales for residents of Norfolk. Coronary artery disease was defined as codes 410 through 414 of the International Classification of Diseases, Ninth Revision. Participants were identified as having CAD during follow-up if they had a hospital admission or died with CAD as an underlying cause. Previous validation studies in our cohort indicate high specificity for such case ascertainment (24). The study was approved by the Norwich District Health Authority Ethics Committee, and all participants gave signed informed consent.

**Participants**

We describe elsewhere a similarly designed nested case-control study (24–26). Extension of follow-up has resulted in the identification of more CAD cases, allowing the current study to be considerably larger. We excluded all persons who reported a history of heart attack or stroke or use of lipid-lowering drugs at the baseline clinic visit. Cases were persons who developed fatal or nonfatal CAD during follow-up until November 2003 (mean follow-up, 6 years). Controls were study participants who remained free of any cardiovascular disease during follow-up. We matched 2

**Table 3—Continued**

Men Only					Women Only				
Quartile 1	Quartile 2	Quartile 3	Quartile 4	P Value	Quartile 1	Quartile 2	Quartile 3	Quartile 4	P Value
1.00 (referent)	1.54 (1.00–2.37)	2.19 (1.44–3.32)	2.65 (1.76–3.99)	<0.001	1.00 (referent)	1.20 (0.78–1.83)	1.62 (1.06–2.48)	2.91 (1.83–4.62)	<0.001
1.00 (referent)	1.40 (0.91–2.15)	1.81 (1.22–2.70)	2.56 (1.73–3.78)	<0.001	1.00 (referent)	1.42 (0.90–2.22)	1.72 (1.10–2.70)	3.18 (2.00–5.06)	<0.001
1.00 (referent)	1.25 (0.79–1.98)	1.48 (0.90–2.42)	1.88 (1.04–3.38)	0.03	1.00 (referent)	1.26 (0.74–2.15)	1.46 (0.77–2.76)	2.47 (1.10–5.57)	0.03
1.00 (referent)	1.23 (0.78–1.94)	1.41 (0.86–2.31)	1.70 (0.93–3.10)	0.08	1.00 (referent)	1.18 (0.68–2.03)	1.34 (0.70–2.56)	2.11 (0.92–4.82)	0.08

**Table 4. Risk for Future Coronary Artery Disease, by Lipid Ratio Quartile\***

Ratio	Quartile				P Value†
	1	2	3	4	
Total cholesterol–HDL cholesterol	1.00 (referent)	1.08 (0.75–1.56)	1.22 (0.78–1.93)	1.23 (0.72–2.11)	0.50
Apo B–apo A-I	1.00 (referent)	1.28 (0.88–1.86)	1.44 (0.93–2.24)	2.03 (1.23–3.36)	0.006

\* Odds ratios were calculated by using conditional logistic regression that took into account matching for sex, age, and time of enrollment and was adjusted for diabetes (yes or no), body mass index, smoking status (yes or no), systolic blood pressure, C-reactive protein level, and log-transformed triglyceride level. Apo B–apo A-I = apolipoprotein B–apolipoprotein A-I; HDL = high-density lipoprotein.

† For linear trend.

controls to each case by age (within 5 years), sex, and time of enrollment (within 3 months).

### Biochemical Analyses

Serum total cholesterol, HDL cholesterol, and triglycerides were measured in fresh samples by using the RA-1000 analyzer (Bayer Diagnostics, Basingstoke, United Kingdom). Low-density lipoprotein cholesterol levels were calculated by using the Friedewald formula (27) to closely approach current clinical procedures. Non-HDL cholesterol was calculated as total cholesterol minus HDL cholesterol. Serum apolipoprotein A-I and apolipoprotein B were measured by using rate immunonephelometry (Behring Nephelometer BNII, Marburg, Germany) with calibration traceable to the International Federation of Clinical Chemistry primary standards (28). The interassay coefficients of variation were 5% for apolipoprotein A-I and 3% for apolipoprotein B. Plasma C-reactive protein was measured by using a sandwich-type enzyme-linked immunosorbent assay, as described elsewhere (29). Samples were analyzed in random order to avoid systematic bias. Researchers and laboratory personnel were blinded to identifiable information and could identify samples by number only.

### Statistical Analysis

Statistical analyses were performed by using SPSS software, version 12.0.1 (SPSS, Inc., Chicago, Illinois). A *P* value less than 0.05 was considered statistically significant. Before being used as continuous variables in the analyses, triglyceride levels were log-transformed to approach a normal distribution more closely. Baseline characteristics were compared between cases and controls (Table 1), taking into account the matching. A mixed-effects model was used for continuous variables, and conditional logistic regression was used for categorical variables.

To evaluate the association between a risk factor and occurrence of CAD, odds ratios and 95% CIs were calculated by using conditional logistic regression analysis, taking into account matching for sex, age, and time of enrollment (30). Odds ratios were calculated per quartile of each risk factor, on the basis of the distribution among controls. The first quartile was used as the reference group (odds ratio, 1.00). *P* values represent significance for linearity across the odds ratios connected to the 4 quartiles of each risk factor. First, we calculated odds ratios per quartile of total cholesterol, LDL cholesterol, HDL cholesterol, and

non-HDL cholesterol levels and total cholesterol–HDL cholesterol and apo B–apo A-I ratios (model 1). We selected the 2 variables with the highest odds ratios in the fourth quartile (apo B–apo A-I ratio and total cholesterol–HDL cholesterol ratio), then we fit a model for each ratio that adjusted for diabetes (yes or no), body mass index, smoking (yes or no), systolic blood pressure, and C-reactive protein level (model 2). We then added variables for LDL cholesterol and HDL cholesterol levels (model 3a) and for triglyceride levels (model 3b). We then entered the apo B–apo A-I and total cholesterol–HDL cholesterol ratios simultaneously into a new model that adjusted for all major cardiovascular risk factors. Finally, to assess the association of the apo B–apo A-I ratio with CAD independent of the Framingham risk score, we categorized participants into 3 risk groups (low [ $<10\%$ ], intermediate [ $10\%$  to  $20\%$ ], or high [ $>20\%$ ]) based on the Framingham risk score algorithm (1, 22) and calculated odds ratios for future CAD by quartile of the apo B–apo A-I ratio, with adjustment for Framingham risk score category.

To evaluate the ability of the apo B–apo A-I ratio to predict CAD (that is, to discriminate between patients who will and will not develop a future CAD event), we constructed receiver-operating characteristic (ROC) curves (31, 32) and calculated the areas under the curves (AUCs) from regression models that included apo B–apo A-I or total cholesterol–HDL cholesterol ratio plus diabetes mellitus (yes or no), body mass index, smoking (yes or no), systolic blood pressure, and C-reactive protein level. We used bootstrapping of the ROC curves to calculate the statistical significance of the differences in AUCs (33, 34). Similarly, we evaluated differences in AUCs when the apo B–apo A-I ratio was added to a model that included the Framingham risk score (on a continuous scale).

To provide a clinical view of the value of the apo B–apo A-I ratio for risk prediction, we used logistic regression analysis to calculate the predicted probability of being a case or control in the study sample, comparing prediction models with the apo B–apo A-I ratio or total cholesterol–HDL cholesterol ratio and adjusting for diabetes mellitus (yes or no), body mass index, smoking (yes or no), systolic blood pressure, and C-reactive protein level. We categorized the predicted probability values into 4 subgroups (0 to 0.25, 0.25 to 0.50, 0.50 to 0.75, and 0.75 to 1.00) to assess the

number of participants who were reclassified by apo B–apo A-I ratio into a different category of probability.

### Role of the Funding Sources

The EPIC-Norfolk is supported by program grants from the Medical Research Council (United Kingdom) and Cancer Research UK and receives additional support from the European Union, Stroke Association, British Heart Foundation, United Kingdom Department of Health, Food Standards Agency, and the Wellcome Trust. Some of the lipid and apolipoprotein measurements described in this article were funded by an educational grant from the Future Forum. The funding sources had no role in the study design, conduct, or analysis or in the decision to submit the manuscript for publication.

## RESULTS

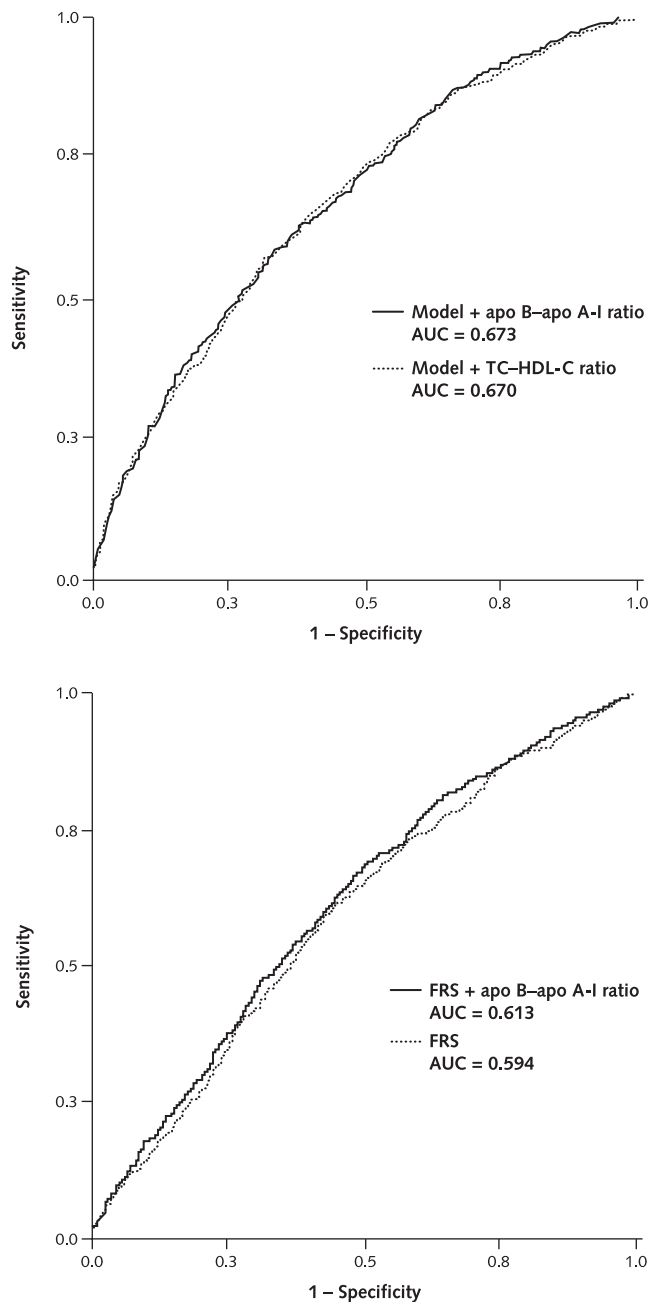
### Baseline Characteristics

We identified 869 persons who did not report a history of cardiovascular disease at the baseline visit but developed CAD during follow-up. Of these, 611 persons (70.3%) had nonfatal events and 258 (29.7%) had fatal events. We were able to match 642 cases to 2 controls and 227 cases to 1 control; thus, the control group comprised 1511 people. Because of matching, sex and age distribution were similar between cases and controls (Table 1). Cases were more likely than controls to smoke and to have diabetes. Body mass index; systolic and diastolic blood pressure; and total cholesterol, LDL cholesterol, non-HDL cholesterol, triglyceride, apolipoprotein B, and C-reactive protein values were statistically significantly higher in cases than in controls, whereas HDL cholesterol and apolipoprotein A-I values were significantly lower. The apo B–apo A-I ratio was statistically significantly higher in cases. The patterns for these differences were similar when cases were divided into fatal and nonfatal events and when men and women were analyzed separately (data not shown).

### Analysis of Association

In unadjusted analyses (Table 2), the odds ratio for future CAD increased per quartile of total cholesterol level, LDL cholesterol level, non-HDL cholesterol level, total cholesterol–HDL cholesterol ratio, and apo B–apo A-I ratio and decreased per quartile of HDL cholesterol level ( $P < 0.001$  for all). Similar patterns were observed when men and women were analyzed separately. Estimates of risk were highest for the total cholesterol–HDL cholesterol ratio (odds ratio for highest vs. lowest quartile, 2.57 [95% CI, 1.98 to 3.33];  $P < 0.001$  for linearity) and apo B–apo A-I ratio (odds ratio, 2.64 [CI, 2.04 to 3.42];  $P < 0.001$  for linearity). Adjustment for major cardiovascular risk factors (model 2 in Table 3) had little effect on the apo B–apo A-I ratio estimate, whereas adjustment for LDL and HDL cholesterol levels (model 3a in Table 3) and triglyceride level (model 3b in Table 3) reduced it slightly (odds ratio for apo B–apo A-I ratio and CAD, 1.85 [CI, 1.15 to

**Figure.** Receiver-operating characteristic curves for the prediction of coronary artery disease.



**Top.** Results of models that included apolipoprotein B–apolipoprotein A-I (*apo B–apo A-I*) ratio or total cholesterol–high-density lipoprotein cholesterol (*TC–HDL-C*) ratio plus diabetes, body mass index, smoking, systolic blood pressure, and C-reactive protein level. **Bottom.** Results of models that used the Framingham risk score (*FRS*) alone or in combination with the apo B–apo A-I ratio. AUC = area under the curve.

2.98];  $P = 0.01$  for linearity [model 3b]). Separate analyses for men and women yielded similar patterns. In a multivariable analysis that adjusted for total cholesterol–HDL cholesterol ratio and apo B–apo A-I ratio simultaneously,

**Table 5. Observed Number of Patients in Each Group of Predicted Probability of Coronary Artery Disease\***

Predicted Probability Based on Apo B–Apo A-I Ratio	Predicted Probability Based on Total Cholesterol–HDL Cholesterol Ratio			
	0–0.25	0.25–0.50	0.50–0.75	0.75–1.00
0–0.25	77/374	10/54	0/0	0/0
0.25–0.50	16/32	502/848	22/11	0/0
0.50–0.75	0/0	30/29	142/110	3/1
0.75–1.00	0/0	0/0	4/6	28/4

\* Probability of being considered a case-patient or control (*n/n*) in the study sample. Values were calculated by using a logistic regression model that included total cholesterol–HDL cholesterol ratio or apo B–apo A-I ratio plus diabetes (yes or no), body mass index, smoking status (yes or no), systolic blood pressure, and C-reactive protein level. Apo B–apo A-I = apolipoprotein B–apolipoprotein A-I; HDL = high-density lipoprotein.

the total cholesterol–HDL cholesterol ratio lost statistical significance (Table 4) but the apo B–apo A-I ratio remained significant (odds ratio for highest vs. lowest quartile, 2.03 [CI, 1.23 to 3.36];  $P = 0.006$  for linearity) (Table 4). The ratio also remained significant in an analysis that adjusted for the Framingham risk score (odds ratio, 1.77 [CI, 1.31 to 2.39];  $P < 0.001$  for linearity).

#### Analysis of Discriminative Ability

Areas under the ROC curves derived from models that adjusted for total cholesterol–HDL cholesterol ratio or apo B–apo A-I ratio plus several major cardiovascular risk factors (diabetes, body mass index, smoking, systolic blood pressure, and C-reactive protein level) did not statistically significantly differ (0.670 for total cholesterol–HDL cholesterol ratio vs. 0.673 for apo B–apo A-I ratio;  $P = 0.38$ ) (Figure). Areas under the ROC curves derived from adjustment for the Framingham risk score without and with the apo B–apo A-I ratio differed significantly in statistical but not clinical terms (0.594 for Framingham risk score alone vs. 0.613 for Framingham risk score plus apo B–apo A-I ratio;  $P < 0.001$ ) (Figure).

The models using apo B–apo A-I ratio or total cholesterol–HDL cholesterol ratio to predict the probability of being a case or control in the study sample categorized 749 of 834 cases (89.8%) and 1336 of 1469 controls (90.9%) similarly (Table 5). Eighty-five cases and 133 controls were reclassified by the apo B–apo A-I ratio. Of the 85 cases, 35 (41.1%) were reclassified into lower categories of probability. Of the 133 controls, 67 (50.4%) were reclassified into higher categories of probability.

## DISCUSSION

Recent studies have shown that the apo B–apo A-I ratio is strongly associated with future CAD (20, 21). This association and the ability to measure apolipoprotein in nonfasting blood samples have led to recommendations that the apo B–apo A-I ratio be used in routine clinical care (12). The recommendation cannot be fully justified, however, until the apo B–apo A-I ratio is shown to be associated with CAD independent of traditional lipid variables and to be better at predicting future CAD events.

The 2 largest studies in this field, AMORIS (20) and INTERHEART (21), did not report whether the associa-

tion between the apo B–apo A-I ratio and CAD was independent of traditional lipid variables. In the AMORIS study, LDL cholesterol and HDL cholesterol values were indirectly estimated from total cholesterol, triglyceride, and apolipoprotein A-I values, which precluded simultaneous use of these variables in 1 statistical model. In INTERHEART, LDL cholesterol and HDL cholesterol were measured directly, but they were not incorporated in the statistical analyses. Data from the Québec Cardiovascular Study showed that apolipoprotein B level was associated with CAD independent of LDL cholesterol level, but apolipoprotein A-I level was not associated with CAD independent of HDL cholesterol level (7). The Prospective Epidemiological Study of Myocardial Infarction reported that apolipoprotein A-I level was associated with CAD independent of HDL cholesterol level (35). Data from the Atherosclerosis Risk in Communities Study suggested that apolipoprotein A-I and B levels no longer contributed to CAD risk prediction when considered together with traditional lipid values (36); however, the apolipoproteins were quantified by using radial immunodiffusion, a technique that has well-known problems with linearity and reproducibility. The Caerphilly study (37) corroborated the lack of a lipid-independent association between apolipoprotein levels and CAD. Collectively, these studies provide conflicting results that may be attributable to differences in samples, limited statistical power, and poorly standardized methods for apolipoprotein measurement.

We have overcome most of these potential problems by evaluating a large number of cases and by using carefully standardized methods for measurement of apolipoprotein and lipid levels. The apo B–apo A-I ratio was associated with future CAD events independent of standard cardiovascular risk factors (diabetes, body mass index, smoking, systolic blood pressure, and C-reactive protein level) and lipid values (LDL cholesterol, HDL cholesterol, and triglyceride levels and, in a separate model, total cholesterol–HDL cholesterol ratio). This may be because the apolipoprotein B level reflects the presence of small LDL particles, which may be more atherogenic, more accurately than do cholesterol values (7, 8). The adjusted odds ratio of 1.85 (CI, 1.15 to 2.98) for the highest quartile of apo B–apo A-I ratio (model 3b in Table 3) approximates that

of classic (38, 39) and some newer risk factors (such as C-reactive protein level [21, 40]). Inclusion of the apo B–apo A-I ratio and total cholesterol–HDL cholesterol ratio in a single multivariable model suggested that the apo B–apo A-I ratio retains CAD risk information, whereas the total cholesterol–HDL cholesterol ratio does not (Table 4). Moreover, the apo B–apo A-I ratio remained a significant risk factor independent of the Framingham risk score. These findings suggest that the apo B–apo A-I ratio may be a valuable alternative to traditional lipid-based variables for assessing risk for CAD.

However, when we used ROC analysis to evaluate whether and to what extent this apparent advantage of the apo B–apo A-I ratio translates into improved CAD risk prediction (32), we found that the apo B–apo A-I ratio did not contribute to the total cholesterol–HDL cholesterol ratio and added only marginally to the Framingham risk score. These findings suggest that the apo B–apo A-I ratio is no better than the total cholesterol–HDL cholesterol ratio at discriminating individual risk. This conclusion was strengthened by the model suggesting that many cases and controls were incorrectly reclassified and that the net proportion of cases who were correctly reclassified is modest and not clinically relevant (Table 5).

Our study has several limitations. First, case ascertainment is an issue in the design of every prospective study. However, a validation study indicated that case ascertainment in our study was at least equivalent to that of other large prospective cohort studies (24).

Second, our conclusions apply only to apparently healthy people who are not receiving lipid-lowering medication. Lipid-based variables lose their association with future CAD in persons receiving lipid-lowering therapy with 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (statins) (41, 42). The relation between apolipoprotein B level, apolipoprotein A-I level, or apo B–apo A-I ratio and future CAD in this subgroup could differ (41, 42). In addition, apolipoprotein values are of particular relevance in detecting atherogenic dyslipidemias in persons with low or normal LDL cholesterol levels but an increased LDL particle number (43–45). These persons, comprising those with diabetes or the metabolic syndrome, are at very high risk for CAD. Our cohort contained only few diabetic participants, and information was insufficient to determine the presence of the metabolic syndrome. Therefore, our findings do not apply to these patients.

In conclusion, in a case–control cohort of apparently healthy persons not receiving lipid-lowering therapy, we showed that the apo B–apo A-I ratio was more closely associated with future CAD events than was the total cholesterol–HDL cholesterol ratio but that the 2 measures were equivalent in their ability to discriminate between persons with and those without cardiovascular events. Thus, our data suggest that replacement of traditional lipid values with the apo B–apo A-I ratio adds little to CAD risk assessment in the general population. However, other char-

acteristics of the test, such as the ability to perform it on nonfasting samples, may make it useful in some settings.

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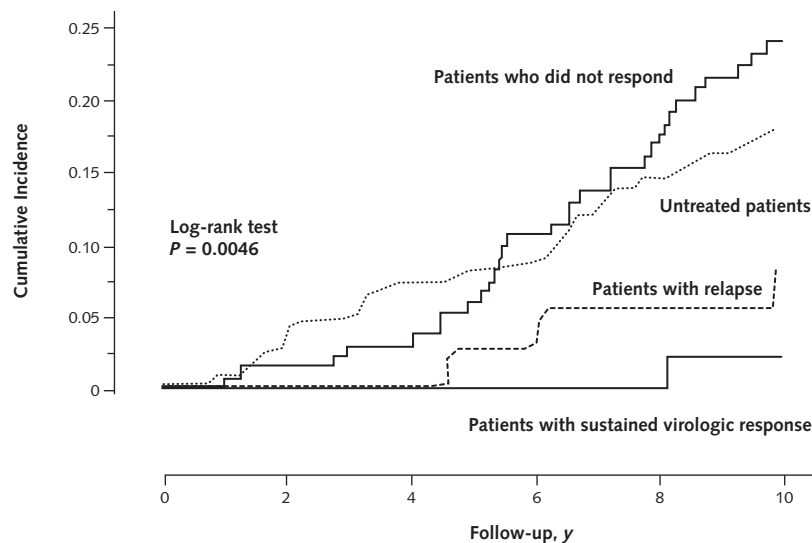
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**Appendix Figure. Cumulative incidence of hepatocellular carcinoma among patients with hepatitis treated with interferon and untreated patients.**



Patients at risk, <i>n</i>	0	2	4	6	8	10
Untreated patients	353	335	304	273	248	227
Interferon-treated patients						
Patients who did not respond	132	130	126	111	103	92
Patients with relapse	38	38	37	33	32	31
Patients with sustained virologic response	53	52	49	45	44	43