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Remnant Cholesterol, Not LDL Cholesterol, Is Associated With Incident Cardiovascular Disease

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ABSTRACT

BACKGROUND Genetic, observational, and clinical intervention studies indicate that circulating levels of triglycerides and cholesterol transported in triglyceride-rich lipoproteins (remnant cholesterol) can predict cardiovascular events.

OBJECTIVES This study evaluated the association of triglycerides and remnant cholesterol (remnant-C) with major cardiovascular events in a cohort of older individuals at high cardiovascular risk.

METHODS This study determined the baseline lipid profile and searched for major adverse cardiovascular events (MACEs) in the high-risk primary prevention PREDIMED (Prevención con Dieta Mediterránea) trial population (mean age: 67 years; body mass index: 30 kg/m^2; 43% men; 48% with diabetes) after a median follow-up of 4.8 years. Unadjusted and adjusted Cox proportional hazard models were used to assess the association between lipid concentrations (either as continuous or categorical variables) and incident MACEs (N = 6,901; n cases = 263).

RESULTS In multivariable-adjusted analyses, triglycerides (hazard ratio [HR]: 1.04; 95% confidence interval [CI]: 1.02 to 1.06, per 10 mg/dl [0.11 mmol/l]; p < 0.001), non–high-density lipoprotein cholesterol (HDL-C) (HR: 1.05; 95% CI: 1.01 to 1.10, per 10 mg/dl [0.26 mmol/l]; p = 0.026), and remnant-C (HR: 1.21; 95% CI: 1.10 to 1.33, per 10 mg/dl [0.26 mmol/l]; p < 0.001), but not low-density lipoprotein cholesterol (LDL-C) or HDL-C, were associated with MACEs. Atherogenic dyslipidemia (triglycerides >150 mg/dl [1.69 mmol/l] and HDL-C <40 mg/dl [1.03 mmol/l] in men or <50 mg/dl [1.29 mmol/l] in women) was also associated with MACEs (HR: 1.44; 95% CI: 1.04 to 2.00; p = 0.030). Remnant-C ≥30 mg/dl (0.78 mmol/l) differentiated subjects at a higher risk of MACEs compared with those at lower concentrations, regardless of whether LDL-C levels were on target at ≤100 mg/dl (2.59 mmol/l).

CONCLUSIONS In overweight or obese subjects at high cardiovascular risk, levels of triglycerides and remnant-C, but not LDL-C, were associated with cardiovascular outcomes independent of other risk factors.
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Atherogenic dyslipidemia, characterized by high circulating triglycerides and low concentrations of high-density lipoprotein cholesterol (HDL-C) with normal concentrations of low-density lipoprotein cholesterol (LDL-C), is a common lipid disorder associated with increased cardiovascular disease (CVD) risk. It is considered one of the main causes of lipid-dependent residual risk, regardless of LDL-C concentration (1–4). Atherogenic dyslipidemia is present in a wide range of chronic cardio-metabolic disorders within the scope of diabetes (pre-diabetes, type 2 diabetes, and poorly controlled diabetes), overweight and obesity, metabolic syndrome, and renal failure. The prevalence of atherogenic dyslipidemia is currently increasing, mirroring the trend of these coexisting diseases, which are influenced by an unhealthy lifestyle (5,6). The lipid profile of atherogenic dyslipidemia is characterized by: 1) an excess of serum triglycerides (contained in very–low-density lipoproteins, intermediate-density lipoproteins, and their remnants; all of them are known as triglyceride-rich lipoproteins (TRLs); 2) low concentrations of HDL-C; and 3) high concentrations of small dense LDLs. All these traits have been associated with increased CVD risk, despite optimal concentrations of LDL-C (7–9).

SEE PAGE 2736

Triglycerides, but not cholesterol, can be easily metabolized in most cells. Therefore, it has been hypothesized that cholesterol, not triglycerides, is the harmful component in TRLs (10). TRLs and the remnant cholesterol (remnant-C) carried in these particles have the capacity to cross the arterial wall and are taken up by macrophages and smooth muscle cells. Because human cells can generally degrade triglycerides but not cholesterol, accumulation in the arterial wall of the remnant-C may play a causal role in atherosclerosis development, similar to LDL-C (11). In addition, in atherogenic dyslipidemia, TRLs are more abundant and larger and carry more cholesterol (in absolute terms) than LDL; thus, it is not surprising that their remnant-C content has been associated with cardiovascular events and total mortality (8,11,12) in both observational and genetic studies (8,11–15). However, scarce information is available from populations in which TRLs and remnant-C are more often present (overweight, obesity, and diabetes), as well as from Mediterranean cohorts, because studies on the association between triglycerides and remnant-C with CVD have been mainly conducted in north European and U.S. population samples (3,11–15).

The PREDIMED (Prevención con Dieta Mediterránea) study was a randomized controlled trial conducted in Spain that examined the effects of the Mediterranean diet (MedDiet) compared with a low-fat diet for the primary prevention of CVD in high-risk subjects (16). PREDIMED trial participants had a high prevalence of diabetes, obesity, and metabolic syndrome, conditions that are associated with insulin resistance, hypertriglyceridemia, and atherogenic dyslipidemia (17). Thus, this cohort of subjects at high cardiovascular risk was well suited to investigate the association of triglycerides and TRLs with cardiovascular outcomes (18).

ABBREVIATIONS AND ACRONYMS

BMI = body mass index

CVD = cardiovascular disease

HDL-C = high-density lipoprotein cholesterol

LDL-C = low-density lipoprotein cholesterol

MACE = major adverse cardiovascular event

MedDiet = Mediterranean diet

Remnant-C = remnant cholesterol

TRL = triglyceride-rich lipoproteins

METHODS

STUDY DESIGN. The PREDIMED study was a multicenter, randomized clinical trial that tested the efficacy of MedDiets enriched with extra-virgin olive oil or mixed nuts against a control diet for the primary prevention of CVD in older subjects at high cardiovascular risk (16,19,20). Results on the main outcome were published (16). For the present study, we used data from the PREDIMED trial, which was considered an observational cohort study. The institutional ethics committees of each recruiting center approved the protocol, and the participants gave written informed consent before the beginning of the study. This trial was registered in Current Controlled Trials, London (ISRCTN35739639, funded by Instituto de Salud Carlos III, Spanish Government). The detailed protocol is described elsewhere (16,19,20).

PARTICIPANTS AND RECRUITMENT. Eligible participants were community-dwelling men, 55 to 80 years of age, and women, 60 to 80 years of age,

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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the *JACC* author instructions page.

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TABLE 1 Baseline Characteristics of Study Subjects by Group

	All Participants (N = 6,901)	Controls (n = 2,251)	MedDiet+Nuts (n = 2,270)	MedDiet+EVOO (n = 2,380)
Men	2,937 (42.6)	907 (40.3)	1,045 (46.0)	985 (41.4)
Age, yrs	67.0 ± 6.17	67.4 ± 6.31	66.6 ± 6.03	67.0 ± 6.16
Diabetes	3,333 (48.3)	1,085 (48.2)	1,052 (46.3)	1,196 (50.3)
Body mass index, kg/m^2	30.0 ± 3.85	30.3 ± 4.03	29.7 ± 3.77	30.0 ± 3.72
Body mass index groups				
≤25 kg/m^2	519 (7.5)	154 (6.8)	186 (8.2)	179 (7.5)
25–30 kg/m^2	3,145 (45.6)	986 (43.8)	1,078 (47.5)	1,081 (45.4)
>30 kg/m^2	3,237 (46.9)	1,111 (49.4)	1006 (44.3)	1,120 (47.1)
Hypercholesterolemia	5,020 (72.7)	1,629 (72.4)	1,672 (73.7)	1,719 (72.2)
Hypertension	5,727 (83.0)	1,891 (84.0)	1,882 (82.9)	1,954 (82.1)
Smoking				
Never	4,243 (61.5)	1,410 (62.6)	1,360 (59.9)	1,473 (61.9)
Actual	961 (13.9)	306 (13.6)	324 (14.3)	331 (13.9)
Former	1,697 (24.6)	535 (23.8)	586 (25.8)	576 (24.2)
Statin treatment	2,802 (40.6)	914 (40.6)	903 (39.8)	985 (41.4)
Fibrates treatment	265 (3.84)	76 (3.38)	103 (4.54)	86 (3.61)
Waist circumference, cm	100 (10.3)	101 (10.4)	100 (10.3)	100 (10.0)
Waist-to-height ratio	0.63 (0.07)	0.63 (0.07)	0.63 (0.06)	0.63 (0.06)
Total physical activity, METs × min/day	233 (242)	216 (242)	250 (249)	233 (233)
14-point score of adherence to the Mediterranean diet	8.68 (1.90)	8.45 (1.89)	8.79 (1.90)	8.80 (1.91)
Alcohol consumption, g/day	8.48 (14.3)	7.55 (13.2)	9.27 (15.2)	8.61 (14.4)

Values are n (%) or mean ± SD.
MedDiet+EVOO = Mediterranean diet enriched with extra-virgin olive oil; MedDiet+Nuts = Mediterranean diet enriched with nuts.

who had a diagnosis of type 2 diabetes mellitus or disclosed ≥3 of the following CVD risk factors: current smoking; hypertension (blood pressure >140/90 mm Hg or treatment with antihypertensive drugs); LDL-C levels >4.14 mmol/l (>160 mg/dl) or treatment with hypolipidemic agents; HDL-C concentrations <1.29 mmol/l (50 mg/dl) for women or <1.03 mmol/l (40 mg/dl) for men; body mass index (BMI) >25 kg/m^2; or a family history of premature coronary heart disease. Exclusion criteria were history of CVD, any severe chronic illness, drug or alcohol addiction, history of allergy or intolerance to olive oil or nuts, or a low predicted likelihood of changing dietary habits (19). The date of the first recruited participant was June 2003, and the end of the follow-up was December 2010.

GENERAL AND LIFESTYLE INFORMATION. The baseline examination included the administration of a 14-item questionnaire of adherence to the Mediterranean diet (21), a 137-item validated food frequency questionnaire (22), the validated Spanish version of the Minnesota Leisure Time Physical Activity Questionnaire (23,24), and a 47-item questionnaire about education, lifestyle, history of illnesses, and medication use. Anthropometric and blood pressure measurements were performed, and samples of fasting blood and first morning spot urine were obtained from participants at baseline. The intervention did not target anti-atherosclerotic medication; pharmacological agents were prescribed by the family physicians of participants within the context of their usual medical care.

OUTCOME ASCERTAINMENT. The primary endpoint was a composite of major adverse cardiovascular events (MACEs)—myocardial infarction, stroke, or cardiovascular death. The sources of information to identify endpoints were contact with participants and family physicians, yearly revision of medical records, and consultation of the National Death Index. All medical records related to endpoints were evaluated by the endpoint adjudication committee, whose members were blinded to treatment assignment (16,19,20).

DETERMINATION OF LIPID PROFILE. Serum samples were collected after an overnight fast and stored at −80 °C until analysis. Biochemical analyses were performed in local laboratories. The clinical investigators and laboratory technicians were blinded to the interventions. Glucose was measured by the glucose-oxidase method, cholesterol by esterase-oxidase-peroxidase, triglycerides by glycerol-phosphate oxidase-peroxidase, and HDL-C by direct measurement after precipitation with phosphotungstic acid and magnesium chloride. All local

TABLE 2 Baseline Lipid Profile by Intervention Group

	All Participants (N = 6,901)	Controls (n = 2,251)	MedDiet+Nuts (n = 2,270)	MedDiet+EVOO (n = 2,380)
Total cholesterol, mg/dl	206 ± 36.0	205 ± 36.6	205 ± 35.6	209 ± 35.7
mmol/l	5.33 ± 0.92	5.30 ± 0.93	5.30 ± 0.91	5.40 ± 0.91
HDL-C, mg/dl	51.2 ± 11.5	51.2 ± 11.8	51.0 ± 11.5	51.3 ± 11.2
mmol/l	1.32 ± 0.03	1.32 ± 0.03	1.32 ± 0.29	1.33 ± 0.28
LDL-C, mg/dl	129 ± 32.2	128 ± 33.0	129 ± 32.0	131 ± 31.6
mmol/l	3.34 ± 0.82	3.31 ± 0.84	3.34 ± 0.8	3.39 ± 0.79
Triglycerides, mg/dl	128 ± 57.0	129 ± 56.7	128 ± 57.3	129 ± 57.1
mmol/l	1.45 ± 0.64	1.46 ± 0.64	1.45 ± 0.65	1.46 ± 0.65
Non–HDL-C, mg/dl	155 ± 34.1	154 ± 35.1	154 ± 33.5	157 ± 33.6
mmol/l	4.01 ± 0.87	3.98 ± 0.89	3.98 ± 0.85	4.06 ± 0.86
Remnant-C, mg/dl	25.7 ± 11.4)	25.8 ± 11.3	25.5 ± 11.5	25.8 ± 11.4
mmol/l	0.66 ± 0.29	0.67 ± 0.28	0.66 ± 0.29	0.67 ± 0.29
Triglycerides >150 mg/dl (1.69 mmol/l) + HDL-C <40/50 mg/dl (1.03/1.29 mmol/l) (in men/women)	963 (14.0)	325 (14.4)	307 (13.5)	331 (13.9)
LDL-C and remnant-C groups				
LDL-C ≤100 mg/dl (2.59 mmol/l) and remnant-C ≤30 mg/dl (0.78 mmol/l)	880 (12.8)	320 (14.2)	297 (13.1)	263 (11.1)
LDL-C ≤100 mg/dl (2.59 mmol/l) and remnant-C >30 mg/dl (0.78 mmol/l)	400 (5.8)	140 (6.2)	144 (6.3)	116 (4.9)
LDL-C >100 mg/dl (2.59 mmol/l) and remnant-C ≤30 mg/dl (0.78 mmol/l)	4,124 (59.8)	1,313 (58.3)	1,356 (59.7)	1,455 (61.1)
LDL-C >100 mg/dl (2.59 mmol/l) and remnant-C >30 mg/dl (0.78 mmol/l)	1,497 (21.7)	478 (21.2)	473 (20.8)	546 (22.9)

Values are mean ± SD or n (%).
HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; Remnant-C = remnant-cholesterol; other abbreviations as in Table 1.

facilities satisfied external quality control requirements and homogenized their results according to a concordance study (25). When triglycerides were <300 mg/dl, LDL-C was calculated by the Friedewald formula. Remnant-C was estimated as total cholesterol minus LDL-C minus HDL-C. Non–HDL-C was calculated as total cholesterol minus HDL-C. For this study, we had available data of baseline lipids standardized to the reference laboratory in 6,901 of 7,447 participants.

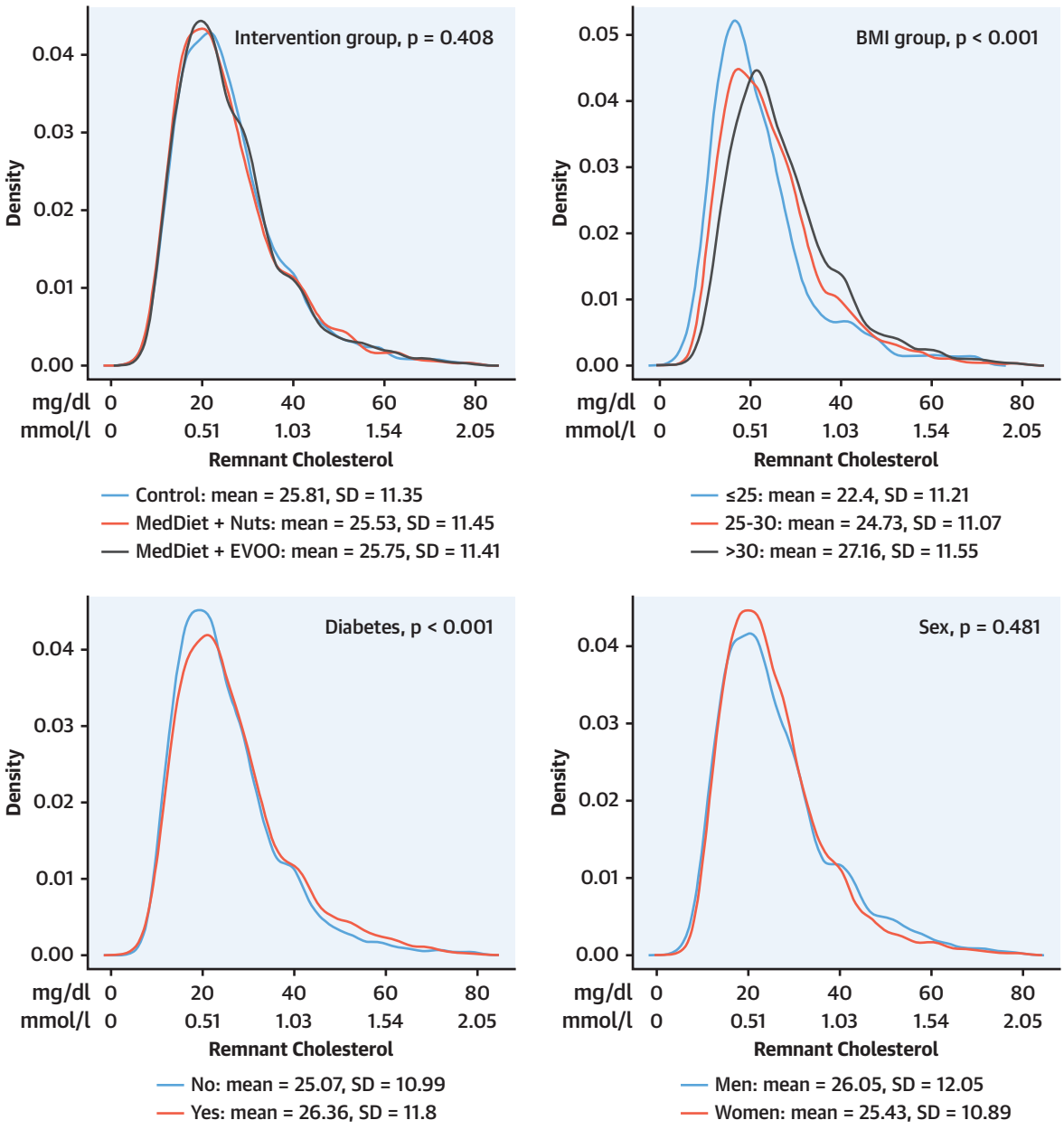
STATISTICAL ANALYSES. Normality of continuous variables was assessed by kurtosis and skewness measures and normal probability plots. Non-normally distributed variables were log-transformed to achieve normality before analyses. Differences in baseline characteristics of the volunteers by sex were evaluated by chi-square, analysis of variance, or Kruskal-Wallis tests, as appropriate.

Follow-up time was calculated as the interval between the date of randomization and the date of the incident MACE, the date of the last visit, or the last recorded clinical event of participants still alive, whichever came first. Unadjusted and adjusted Cox proportional hazard models were used to assess the association between baseline lipid concentrations (considered as both continuous and categorical variables) and incident MACEs. Adjustments were made for age, sex, dietary intervention, BMI, diabetes, physical activity, educational level, adherence to the MedDiet, hypertension, diabetes, alcohol intake, statin treatment, and fibrate use (Supplemental Table 1). We also tested the interaction between lipid parameters and the allocation to PREDIMED intervention groups. All models were adjusted by 3 propensity scores that estimated the probability of assignment to each intervention group on the basis of 30 baseline variables clustered by pairs (16). The 2-sided significance level was set at $p < 0.05$. All statistical analyses were performed with the SPSS 12.3 software (SPSS Inc., Chicago, Illinois) for Windows XP (Microsoft, Redmond, Washington) and R Software version 3.5.3 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

BASELINE CHARACTERISTICS. Table 1 depicts the baseline characteristics of the participants (N= 6,901) in the 3 intervention groups, which were evenly distributed among them. Participants' mean age was 67 years (57.4% women), mean BMI was 30.0 kg/m^2, 48.3% had diabetes, 40.6% were on statin treatment, and 3.8% were treated with fibrates. Table 2 presents the lipid profile at baseline. Remnant-C (mean ± SD) was 25.7 ± 11.4 mg/dl (0.66 ± 0.29 mmol/l), and there were no differences between intervention groups; its distribution was similar in men and women but differed by BMI categories (<25 kg/m^2: 22.4 ± 11.2 mg/dl [0.58 ± 0.29 mmol/l]); 25 to 30 kg/m^2: 24.1 ± 11.1 mg/dl [0.62 ± 0.29 mmol/l]); >30 kg/m^2: 27.2 ± 11.5 mg/dl

FIGURE 1 Remnant Cholesterol Distribution at Baseline by Intervention Group, Sex, BMI (kg/m^2) Categories, and Diabetes Status



Remnant cholesterol was distributed similarly between intervention groups and sex, but increased with increasing body mass index (BMI) and in participants with diabetes compared with those without diabetes. MedDiet+EVOO = Mediterranean diet enriched with extra-virgin olive oil; MedDiet+Nuts = Mediterranean diet enriched with nuts.

[0.7 ± 0.3 mmol/l]; $p < 0.001$) and diabetes status (no diabetes: 25.1 ± 10.9 mg/dl [0.65 ± 0.28 mmol/l]; diabetes: 26.3 ± 11.8 mg/dl [0.68 ± 0.31 mmol/l]; $p < 0.001$) (Figure 1).

BASELINE LIPID CONCENTRATIONS AND CARDIOVASCULAR EVENTS. As shown in Table 3, HDL-C and LDL-C levels were not associated with MACEs in our population. Conversely, the serum concentrations of triglycerides and non–HDL-C were associated with a 4% and 5% higher risk of MACEs per every 10 mg/dl increase, respectively, whereas remnant-C was associated with a 21% higher risk per 10 mg/dl increase. The lipid alterations characteristic of atherogenic dyslipidemia (triglycerides >150 mg/dl

TABLE 3 Association of Baseline Lipid Values With Cardiovascular Outcomes

	No Event (n = 6,638)	Event (n =263)	Hazard Ratio (95% CI)	p Value
HDL-C, mg/dl	51.3 ± 11.5	49.1 ± 11.2	+5 mg/dl: 0.97 (0.91–1.04)	0.427
mmol/l	1.33 ± 0.29	1.27 ± 0.28		
LDL-C, mg/dl	130 ± 32.2	129 ± 32.5	+10 mg/dl: 1.01 (0.97–1.07)	0.583
mmol/l	3.36 ± 0.82	3.34 ± 0.83		
Triglycerides, mg/dl	128 ± 56.6	142 ± 66.3	+10 mg/dl: 1.04 (1.02–1.06)	<0.001
mmol/l	1.45 ± 0.64	1.60 ± 0.75		
Non–HDL-C, mg/dl	155 ± 34.1	157 ± 34.2	+10 mg/dl: 1.05 (1.01–1.10)	0.026
mmol/l	4.01 ± 0.87	4.06 ± 0.87		
Remnant-C, mg/dl	25.6 ± 11.3	28.5 ± 13.3	+10 mg/dl: 1.21 (1.03–1.33)	<0.001
mmol/l	0.66 ± 0.28	0.742 ± 0.34		
Triglycerides >150 mg/dl (1.71 mmol/l) + HDL-C <40/50 mg/dl (1.02/1.28 mmol/l) (in men/women)	915 (13.8)	48 (18.3)	1.44 (1.04–2.00)	0.030

Values are mean ± SD or n (%), unless otherwise indicated. Hazard ratios (HRs) were estimated by Cox proportional hazards regression models adjusted for age, sex, dietary intervention, body mass index, physical activity, educational level, adherence to the Mediterranean diet, hypertension, diabetes, alcohol intake, statin treatment, and fibrate use.

CI = confidence interval; other abbreviations as in Table 2.

[1.69 mmol/l] and HDL-C <40 mg/dl [1.03 mmol/l] in men or <50 mg/dl [1.29 mmol/l] in women) were also associated with a 44% higher risk of MACEs. No significant interactions were observed between lipid variables and dietary intervention groups or sex.

We further examined the association between quartiles of triglycerides, non–HDL-C and remnant-C and CVD risk. The incidence of MACEs was particularly high in participants in the upper quartiles of the 3 lipid variables compared with the lowest quartiles (Figure 2).

CONTRIBUTION OF REMNANT-C TO RESIDUAL LIPID RISK BY LDL-C LEVEL. A remnant-C ≥75th percentile of the cohort (~30 mg/dl) (0.78 mmol/l) was the cutoff to define abnormally high levels of remnant-C. For LDL-C, high levels were conventionally defined as >100 mg/dl (2.59 mmol/l) for this primary prevention cohort. Supplemental Table 2 depicts the characteristics of the subgroups resulting from the 4 possible combinations of LDL-C and remnant-C cutoff levels. Only 880 participants (12.8% of the cohort) were at target for both lipid values. The subgroups with high LDL-C had less men and a lower frequency of diabetes and statin treatment, whereas those with high remnant-C had higher BMI, triglycerides levels, and prevalence of hypertension, and lower physical activity and HDL-C. Of the 2,802 statin-treated participants, 728 (26%) had optimal levels of LDL-C of ≤100 mg/dl (2.59 mmol/l).

Residual lipid risk assessed by a remnant-C ≥30 mg/dl (0.78 mmol/l) recognized subjects at higher cardiovascular risk, regardless of LDL-C concentrations (Figure 3). Within each LDL-C subgroup (>100 or ≤100 mg/dl [2.59 mmol/l]), high baseline remnant-C identified subjects at a higher risk of MACEs compared with those at lower concentrations. MACE incidence was lowest in the low remnant-C groups, independently of LDL-C levels (Figure 4).

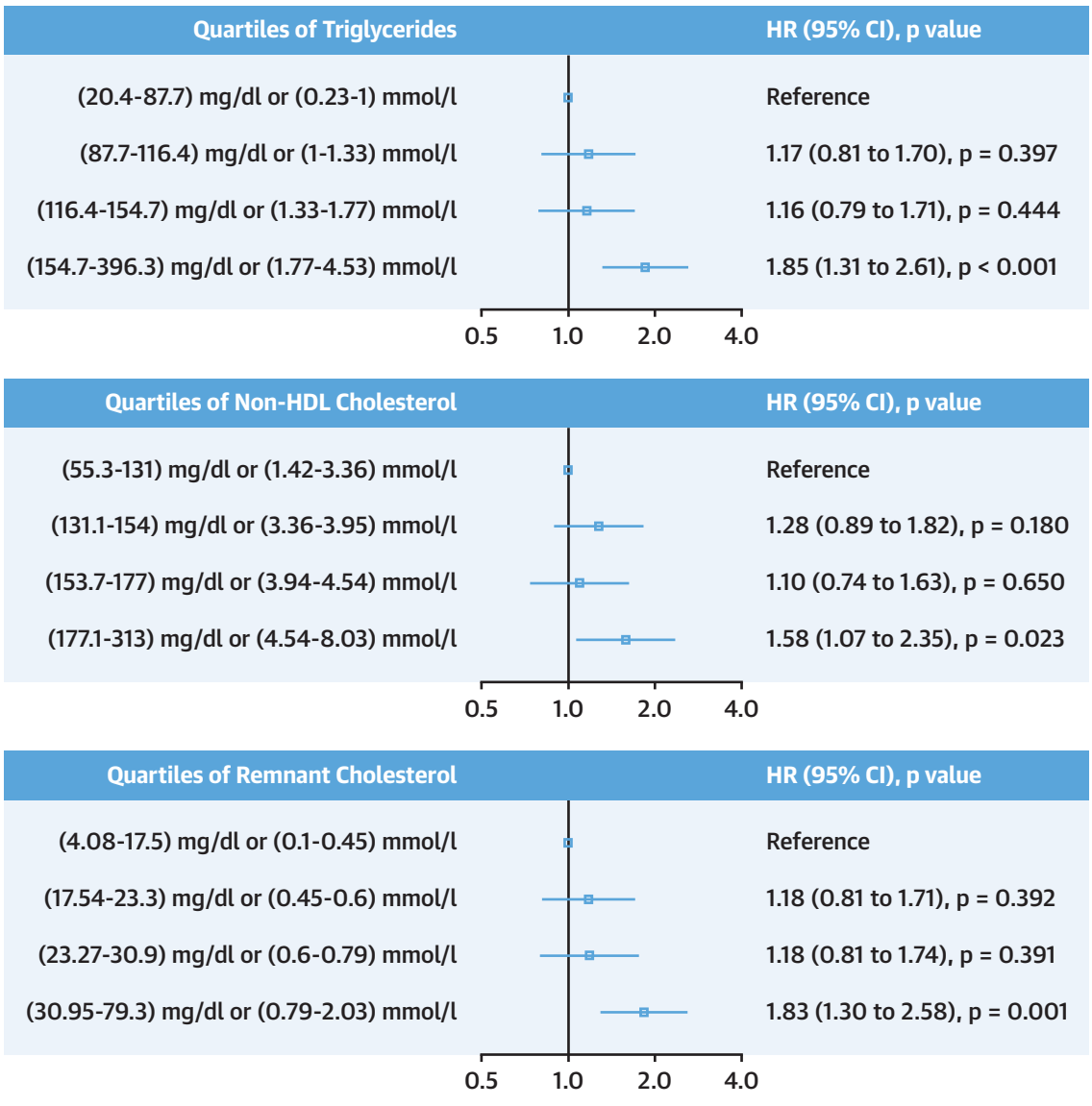
DISCUSSION

In a primary prevention cohort of participants at high cardiovascular risk in the PREDIMED trial, baseline triglycerides, estimated remnant-C and non–HDL-C, but not LDL-C or HDL-C, were associated with major CVD events, regardless of intervention group, other clinical phenotypes (obesity and diabetes), lifestyle confounders related to both lipid concentrations and cardiovascular risk, and lipid-lowering treatment.

Our results confirmed previous evidence on the causal role of triglycerides in CVD (7,8,10,26). They also expanded our knowledge on the atherogenicity of remnant-C derived from observational studies (11,12,14,27), post hoc data from the Treating to New Targets trial (28), and Mendelian randomization studies (15,29–32).

Very-low-density lipoproteins, remodeled in the circulation, undergo hydrolysis by the lipoprotein lipase enzyme, becoming intermediate-density lipoproteins and LDLs. Remnant-C is the cholesterol content of the TRLs that consists of very-low and intermediate density lipoproteins in the fasting state and chylomicron remnants in the nonfasting state. These partially catabolized TRLs also become enriched in cholesterol due to a delayed metabolism and are highly atherogenic (Central Illustration). The increased risk of MACEs associated with remnant-C could be attributed to previously described mechanisms related not only to atherosclerotic plaque formation but also to local inflammation (33). High levels of remnant-C in serum would contribute to an increased penetration into the arterial wall, where

FIGURE 2 **Risk of MACEs Across Quartiles of Baseline Lipid Parameters**

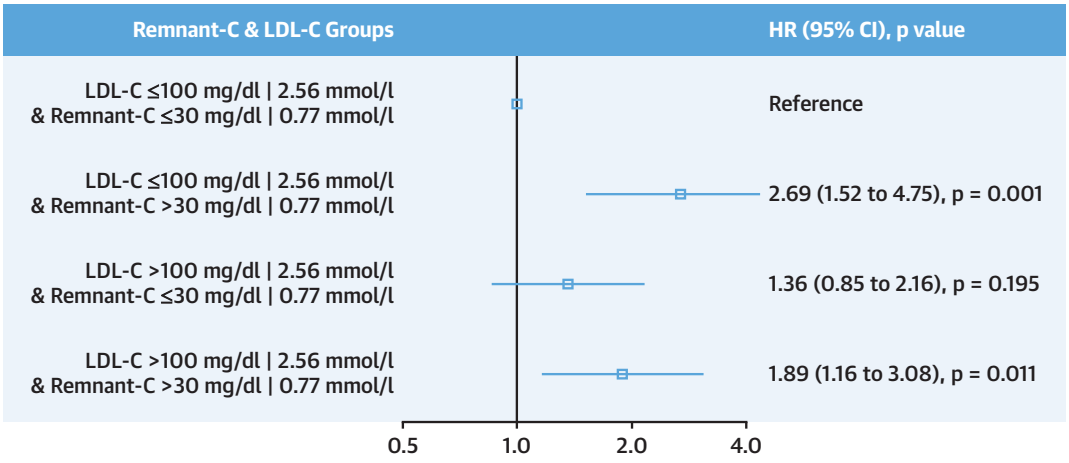


To assess the risk of major adverse cardiovascular events (MACEs) associated with the baseline lipid values of interest, we calculated hazard ratios (HR) for the second, third, and fourth quartiles (compared with the first quartile) of levels of **(A)** triglycerides, **(B)** non–high-density lipoprotein cholesterol (HDL-C), and **(C)** remnant cholesterol (remnant-C). Analyses were adjusted for age, sex, intervention group, body mass index, diabetes status, educational level, score of adherence to Mediterranean diet, alcohol consumption, physical activity, statin treatment, and fibrate use. The incidence of MACEs was significantly higher in participants in the upper quartiles of the 3 lipid variables. CI = confidence interval.

remnant-C is more easily trapped and taken up by macrophages than LDL, which leads to a faster formation of foam cells (34). Remnant-C from the hydrolysis of TRLs could also induce the production of cytokines (tumor necrosis factor-α), interleukins (IL) (IL-1, IL-6, IL-8), and pro-atherogenic adhesion molecules activating inflammation and the coagulation cascade through plasminogen activator inhibitor 1 (35,36). All these processes may lead to plaque rupture and, consequently, MACEs.

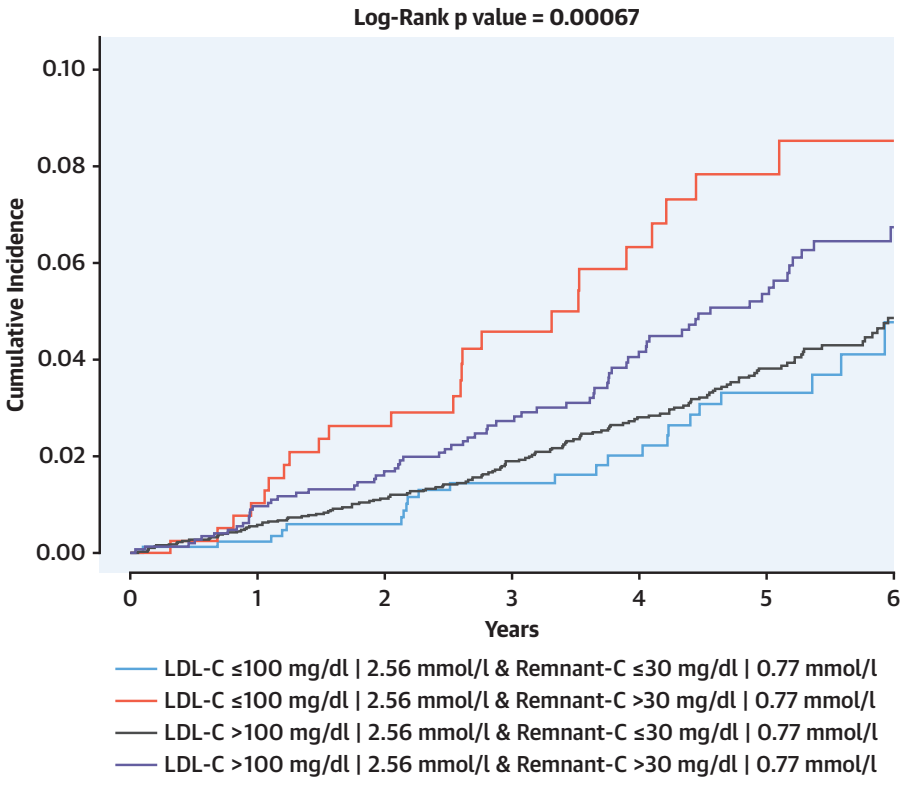
The present population sample differed from those assessed in previous studies that related triglycerides, TRLs, or remnant-C to CVD risk by at least 2 aspects. First, the PREDIMED cohort included subjects at high cardiovascular risk with obesity (47%) and diabetes (49%). Thus, a major

FIGURE 3 Risk of MACEs Based on Categories of LDL-C and Remnant-C Levels



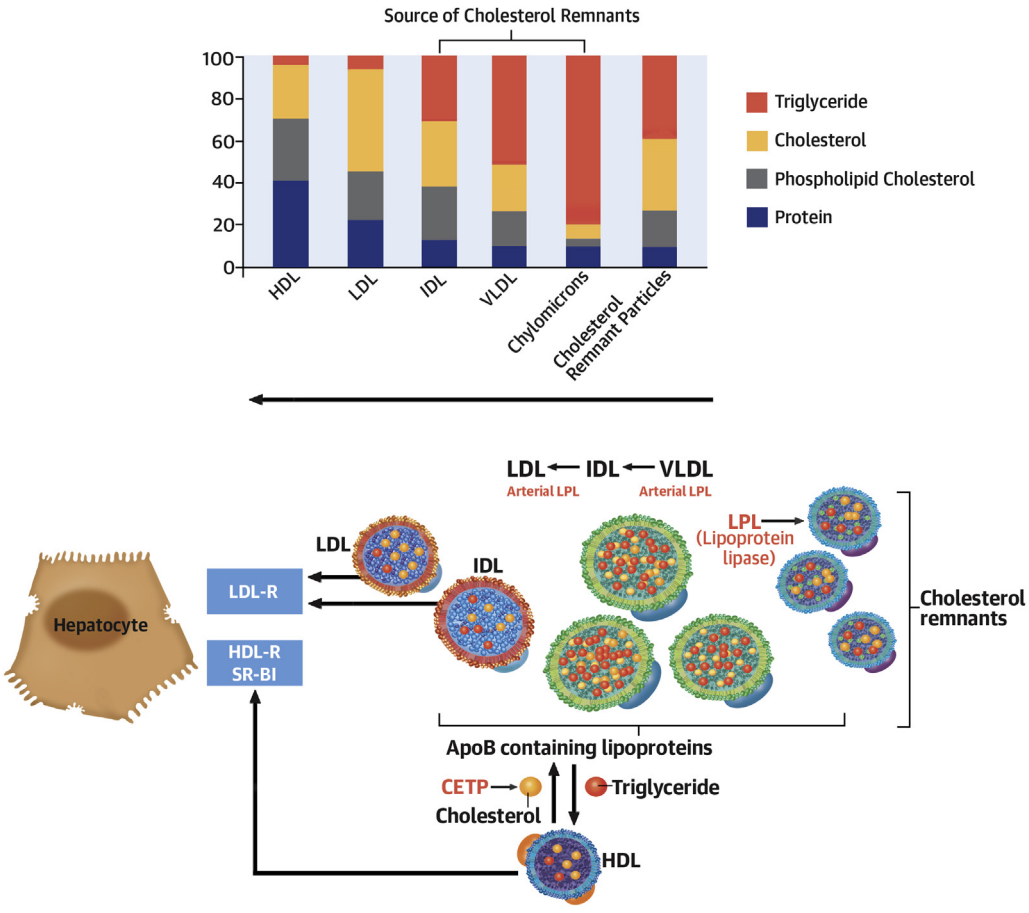
To assess the risk of MACEs by categories of low and high low-density lipoprotein-cholesterol (LDL-C) and remnant-C, HRs were plotted relative to the lowest risk category (LDL-C ≤100 mg/dl and remnant-C ≤30 mg/dl). Data were adjusted for age, sex, intervention group, body mass index, diabetes status, educational level, score of adherence to Mediterranean diet, alcohol consumption, physical activity, statin treatment, and fibrate use. High remnant-C was associated with MACEs, regardless of LDL-C values. Other abbreviations as in Figure 2.

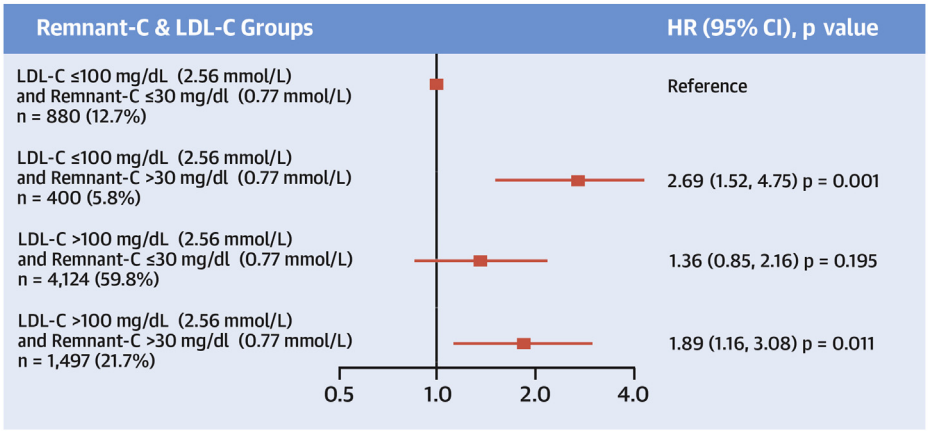
FIGURE 4 Incidence Curves of MACEs Based on Pre-defined Categories of LDL-C and Remnant-C Levels



Kaplan-Meier curves were constructed to assess the incidence of MACEs by categories of low and high LDL-C and remnant-C. MACE incidence was lowest in the low remnant-C groups, independently of LDL-C levels. Abbreviations as in Figures 2 and 3.

CENTRAL ILLUSTRATION **Remnant Cholesterol Metabolism and Cardiovascular Risk Derived From Low and High Remnant- And Low-Density Lipoprotein-Cholesterol at Baseline in the PREDIMED Cohort**





Castañer, O. et al. J Am Coll Cardiol. 2020;76(23):2712–24.

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contribution of remnant-C to residual risk could be expected in these participants. Second, previous studies that pointed to a causal association between remnant-C and CVD were mainly conducted in north European and U.S. population samples (3,11-15,27-32,37-39). There was scarce evidence for the role of remnant-C in CVD risk in Mediterranean areas, where a culturally driven dietary pattern was thought to explain part of the lower incidence of cardiovascular events compared with northern Europe or the United States (40). In addition, the analytical models used in this study addressed potential confounders of the association between remnant-C and CVD risk. Data were adjusted for potential modulators of TRL biology, such as obesity, diabetes, sex, and lifestyle factors (5,6). In addition, the results were independent of ongoing lipid-lowering treatment. Studies of cohorts in which participants were treated with statins indicated that elevated remnant-C also explained part of their residual CVD risk (15,28). Even when treated with statins, patients with high remnant-C levels had more coronary artery disease (41).

Remnant-C was the major cholesterol fraction contributor to MACEs in our cohort of participants at high cardiovascular risk but who had no previous CVD; these subjects had moderately elevated triglyceride concentrations and a high frequency of statin treatment. Expectedly, total triglycerides, which were highly correlated with remnant-C, and non–HDL-C, a measure that includes all atherogenic lipoproteins and often has a higher predictive value of atherosclerotic CVD than LDL-C when triglycerides are elevated (42), were also independently associated with MACEs. Participants with remnant-C levels ≥30 mg/dl (75th percentile of the cohort) had a higher risk of MACEs, regardless of whether LDL-C was at optimal levels (≤100 mg/dl; 2.59 mmol/l). Concurring with the well-known increased cardiovascular risk of so-called atherogenic dyslipidemia (elevated triglycerides and low HDL-C) (5,6,42), this combination of lipid alterations, present in 14% of the cohort, was strongly associated with the risk of MACEs.

From the present data, it could be inferred that treatment of residual risk, measured as triglycerides or remnant-C, was probably more beneficial than further reducing LDL-C in high-risk subjects in primary prevention not eligible for statin treatment or already treated with moderate- or high-dose statins (8,15,28). Furthermore, it was recently reported that lowering remnant-C by 32 mg/dl (0.83 mmol/l) was estimated to reduce recurrent MACEs by 20% in secondary prevention (43).

Several therapeutic strategies are available to lower triglycerides and remnant-C levels (44). High-intensity statin treatment lowers triglycerides modestly (28), whereas fibrates have a more profound triglyceride-lowering effect while effectively reducing CVD risk in subjects with atherogenic dyslipidemia (45-47). PCSK9 inhibitors can be used when statin and/or ezetimibe doses have been optimized or there is intolerance to statins, but triglyceride lowering is also modest with these agents (48,49). In contrast, high-dose n-3 fatty acids, particularly icosapent ethyl (ethyl eicosapentaenoic acid) (48), and newer agents, such RNA-based antisense- oligonucleotide inhibitors of apolipoprotein C-III and angiopoietin-like 3 genes (49,50), markedly reduce TRLs. Nevertheless, it remains to be tested in randomized clinical trials whether this approach would be superior, in terms of CVD prevention, to a more intensive LDL-C lowering strategy, particularly in subjects at high CVD risk with elevated triglycerides, even when risk-specific LDL-C targets have been reached.

STUDY LIMITATIONS. First, our participants were older subjects at high cardiovascular risk, and we

CENTRAL ILLUSTRATION Continued

Very-low-density lipoproteins (VLDLs) are remodeled in the circulation by lipoprotein lipase (LPL), with ensuing reduction in size, thus becoming intermediate-density lipoproteins (IDLs) and low-density lipoproteins (LDLs), which are taken up by the liver. Remnant-cholesterol is the cholesterol contained in triglyceride-rich lipoproteins, made up of VLDL and IDL in the fasting state, plus chylomicron remnants after feeding. When sustained in time, the circulating remnant-cholesterol concentration (highly correlated with triglycerides) contributes to residual cardiovascular risk even when LDL-C levels are controlled. These partially catabolized triglyceride-rich lipoproteins become enriched in cholesterol in the circulation due to delayed metabolism and are highly atherogenic. Furthermore, in atherogenic dyslipidemia, triglyceride-rich lipoproteins are more abundant and larger and can carry more cholesterol than LDL. Because most cells can degrade triglycerides, and none can degrade cholesterol, the cholesterol remnants can be deposited in the arterial intima to a similar extent, even easier, than cholesterol from LDL. Baseline remnant cholesterol was associated with an increased risk of major cardiovascular events, regardless of high or low LDL-C levels in the primary prevention cohort of the PREDIMED trial study, which consisted of participants with overweight/obesity and diabetes who were prone to delayed triglyceride catabolism.

cannot generalize the results to other populations. In particular, subjects with prevalent CVD were excluded in our study; thus, those who reached recruitment age (55 to 80 years) without CVD were a population that could be considered as having protective factors against the pro-atherogenic effects of dyslipidemia. Second, our findings were observational, and the causal role of remnant-C on CVD risk should be verified in further studies. Third, some of the covariates used in multivariable adjustment, such as those related to dietary adherence, leisure time physical activity, and alcohol intake, were based on self-reports and might be biased and subject to residual confounding. Finally, indirect calculation of remnant-C in our study might have overestimated its value in comparison to direct measurement (12). However, the indirect calculation of remnant-C is an affordable and inexpensive method that could provide valuable data for clinical management. Similarly, the calculation of LDL-C or non–HDL-C, although implying some variability compared with direct measurements, are key indicators in standard clinical care. Nevertheless, in vulnerable patients more sophisticated and expensive remnant-C methodologies could be required for accurate results.

CONCLUSIONS

Our results showed that levels of triglycerides and estimated remnant-C, but not LDL-C or HDL-C, were associated with CVD outcomes independently of lifestyle characteristics and other cardiovascular risk factors in a cohort of Mediterranean subjects at high risk with a high prevalence of diabetes and obesity. Remnant-C should be considered a preferential treatment target in this population. Randomized controlled trials with hard CVD outcomes are warranted to compare the benefit of interventions directed at lowering remnant-C against standard cholesterol-lowering therapy, particularly when LDL-C target levels have been achieved.

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AUTHOR DISCLOSURES

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: In overweight or obese subjects at high cardiovascular risk, blood levels of triglycerides and remnant cholesterol, but not LDL-C, are independently associated with cardiovascular outcomes.

TRANSLATIONAL OUTLOOK: Future studies should seek to establish whether remnant-C level is a preferred treatment target in patients at high cardiovascular risk.

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APPENDIX For supplemental tables, please see the online version of this paper.