Original Article

High Density Lipoprotein Cholesterol in Coronary Artery Disease: When Higher Means Later

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***Aim*: Although high-density lipoprotein cholesterol (HDL-C) levels are inversely associated with cardiovascular risk, patients with elevated HDL-C also develop coronary artery disease (CAD) and cardiac events. We aimed to draw the clinical profile of CAD patients with elevated HDL-C and to assess the prognostic impact of elevated HDL-C.**

***Methods*: We prospectively examined 2322 patients (age 67 ± 10 years, 79% male) with chronic CAD, defined by >50% coronary stenosis and/or previous myocardial infarction.**

***Results*: HDL-C levels were low (<35 mg/dL) in 736 patients (32%), normal (35-60 mg/dL) in 1464 (63%), and high (>60 mg/dL) in 122 (5%). Patients with elevated HDL-C were less frequently male ($p<0.0001$), smokers ($p<0.0001$), diabetic ($p<0.0001$), and obese ($p<0.0015$) than those with low or normal HDL-C, but were 3 and 5 years older, respectively ($p<0.0001$). During follow-up (median, 46 months) 143 patients died from cardiac causes and 80 developed a non-fatal infarction. Cardiac event-free survival was lower in patients with low compared to normal HDL-C ($p<0.0001$), but was not significantly different from that of patients with elevated HDL-C. The prognostic impact of low HDL-C was independent of age, sex, diabetes, LV function, extent of coronary stenoses, low density lipoprotein cholesterol, triglycerides, complete blood count, thyroid and renal function ($p<0.0001$). Conversely, the prognostic impact of elevated HDL-C disappeared ($p>0.10$) after adjustment for age.**

***Conclusion*: Patients with elevated HDL-C develop CAD and cardiac events as do those with low or normal HDL, but at a more advanced age.**

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Key words; High-density lipoprotein cholesterol, Coronary artery disease, Prognosis, Age, Atherosclerosis

Introduction

Among the general population without prior cardiovascular disease, plasma concentrations of high density lipoprotein cholesterol (HDL-C) are inversely related to coronary events and ischemic stroke, even after adjustment for lipid and non-lipid risk factors[1, 2]. Specifically, the analysis of 68 studies of 302,430 participants showed that each unit of standard deviation increase in HDL-C concentration (0.38 mmol/L or 15 mg/dL) is associated with 22% reduction in coronary artery disease (CAD) risk[3]; however, it is acknowledged that the data are not clear for very low or very high HDL-C levels[3, 4].

The evidence of HDL-C as an independent risk factor is further strengthened in high-risk patients treated by statins. In a post hoc analysis of the Treating to New Targets (TNT) study, HDL-C levels were predictive of major cardiovascular events in 9,770 patients with clinically evident CAD treated with statins[5]. A recent meta-analysis of 170,000 subjects in 26 statin trials showed that irrespective of the low-density lipoprotein cholesterol (LDL-C) level achieved or the intensity of statin therapy, cardiovascular risk is

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always lower at higher levels of achieved HDL-C[6]. The protective effect of high vs low HDL-C has also been demonstrated in patients achieving LDL-C targets with statins after percutaneous coronary interventions[7]. Very recently, HDL-C levels have been shown to be most closely associated with the presence of CAD assessed by multi-detector row computed tomography, irrespective of statin treatment[8]. Finally, in patients with acute coronary syndrome, HDL-C but not LDL-C was shown to be an independent predictor of short-term prognosis[9]. Based on the above evidence, several attempts have been made to increase HDL-C concentration for therapeutic purposes[10].

Despite the above considerations, patients with elevated values of HDL-C also present with CAD and encounter cardiac events during follow-up. In addition, the inverse relationship between HDL-C levels and the incidence of CAD is not homogeneous in different patient populations. A significant U-shaped relationship between HDL-C levels and the incidence of ischemic changes in electrocardiograms has been shown in Japanese patients. In this population, marked hyperalphalipoproteinemia appears to be caused by genetic cholesteril ester transfer protein (CEPT) deficiency[11-13]. Mutations of the CEPT gene have also been documented in Italian subjects with hyperalphalipoproteinemia and in other populations[14, 15]. Thus, elevated HDL-C does not obviously represent longevity insurance.

Aim

With these considerations in mind, we undertook this study to investigate the clinical profile of patients with chronic CAD and elevated HDL-C and to assess the role of elevated HDL-C in patient outcome.

Methods

Patients

We studied a group of 2,322 consecutive patients suffering from chronic CAD, admitted to our Institute for the first time between 2001 and 2007. Inclusion criteria were the documentation of previous myocardial infarction (MI) and/or angiographic evidence of coronary stenoses that reduced the lumen of one or more coronary arteries by at least 50%. During hospitalization, each patient underwent a diagnostic workup that included clinical evaluation, a 12-lead electrocardiogram, two-dimensional echocardiography, laboratory testing and coronary arteriography. The criteria used to define diabetes mellitus, arterial hypertension, hypercholesterolemia and obesity were consistent with international guidelines[16-19]. The left ventricular (LV) ejection fraction was measured by two-dimensional echocardiography using the single-plane or biplane Simpson rule. After coronary arteriography was performed, each patient was assigned an angiographic score whereby 1 = single vessel disease, 2 = two-vessel disease, 3 = three-vessel disease, 4 = disease of left main stem, 0.5 = disease of secondary vessels only, and 0 = absence of significant coronary stenoses[20]. If a vessel had more than one stenosis, the more severe stenosis was considered. We excluded patients with acute MI, valvular heart disease of at least moderate degree, overt hyperthyroidism (free triiodothyronine [fT3] > 420 pg/dL or free thyroxine [fT4] >1.85 ng/dL, with undetectable thyrotropin) and those on hemodialysis for chronic renal failure.

Of the entire group of 2,322 patients (median age 68 years, 79% male), 27% showed angina on effort, 18% angina at rest, and 29% mixed angina, while 26% were asymptomatic. A previous MI was documented in 54% of patients. The LV ejection fraction was 52 ± 11%; the ejection fraction was ≤ 35% in 13% of patients, and ranged between 36 and 50% in 24% of patients. A >50% coronary stenosis in at least one coronary artery was present in 95% of patients. The stenosis involved a single coronary vessel in 36% of patients, two vessels in 25%, three vessels in 17%, the left main stem in 10%, and secondary branches in only 7% of patients.

Laboratory Tests

On the first day of hospital admission, samples of peripheral venous blood were drawn from the antecubital vein after the patient had fasted overnight and were processed for a complete series of routine laboratory assays. The laboratory variables explored were hematocrit, white blood cell (WBC) count, platelet count, fasting glucose, serum creatinine, total cholesterol, high-density lipoprotein cholesterol (HDL-C), triglycerides, thyrotropin (TSH), free triiodothyronine (fT3), free thyroxine (fT4), and high-sensitivity C-reactive protein (CRP). Total and HDL-C and triglycerides were measured using a Synchron CX analyzer (Beckman Systems, Fullerton, CA, USA), and LDL-C concentration was calculated using the Friedewald equation[21]. All laboratory tests were analyzed as categorical variables based on the normal values in our laboratory or previous studies. Low T3 syndrome was defined as fT3 serum <2.1 pg/mL with TSH in the normal range; hypothyroidism was defined as TSH > 3.8 μIU/ml[22, 23].

The entire patient population was divided into

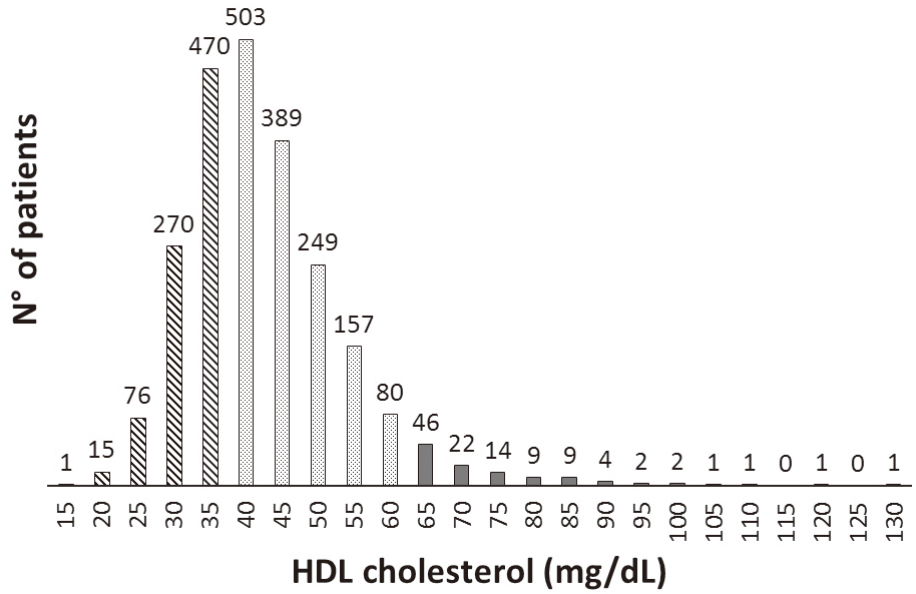

Fig. 1. Frequency distribution of HDL-C levels in the population studied.

three groups based on HDL-C levels: i.e., low (<35 mg/dL), normal (35-60 mg/dL), or elevated (>60 mg/dL). Although the accepted cut-off value of low HDL-C is 40 mg/dL in current guidelines[24], we used a cut-off value of 35 mg/dL[25] since HDL-C values below this threshold appeared more strictly associated with cardiac events in our patient population. In addition, although the reference cut-off point of elevated HDL-C is 60 mg/dL[18], we also evaluated a cut-off point of 55 mg/dL for high HDL-C.

Follow-Up

The entire group of patients was followed for up to 7 years (median, 46 months). Patients were followed up by periodic examinations in the outpatient setting. For patients who did not attend this program, follow-up data were obtained using a written telephone interview (administered to the patient or the patient's family by dedicated personnel) or mail questionnaires. In the case of negative answers, the local demographic registry was queried. Cardiac death was defined as death caused by acute MI, death caused by heart failure, or sudden and unexpected death not related to any known cause; non-fatal MI was documented by clinical records. The study protocol was approved by the local committee on human research. In addition, patients gave written informed consent to have their clinical data prospectively collected for research purposes.

Statistical Analysis

Continuous variables are expressed as the mean and standard deviation (SD), and categorical variables as percentages. The differences in demographic, clinical and laboratory variables among patients with low, normal and elevated HDL-C were tested by analysis of variance, a multiple comparison procedure. The impact of HDL-C levels on survival free from cardiac events (cardiac death or non-fatal MI) was tested using univariate analysis, performed using the Cox proportional hazards regression model. We explored the effect of demographic, clinical and laboratory variables on the ability of HDL-C levels to predict event-free survival by entering each of the above variables into the model together with HDL-C. Categorical variables were included in the model as dummy variables. The prognostic impact of the HDL-C level was considered to persist if the P-value remained <0.05 after adjustment for additional variables. The prognostic impact of HDL-C was considered to disappear if the P-value was >0.05 after adjusting for additional variables. All statistical tests were two-tailed. Statistical analysis was performed with the software program JMP 9 [SAS Institute Inc.] and R: A Programming Environment for Data Analysis and Graphics, version 2.7.1 [R Foundation for Statistical Computing].

Results

The frequency distribution of HDL-C levels in the population studied is illustrated in **Fig. 1**. HDL-C

Table 1. Characteristics of patients

	Low HDL-C $n=736$ (32%)	Normal HDL-C $n=1464$ (63%)	High HDL-C $n=122$ (5%)	*P*-value
Age (years)	65.2 ± 10.8	67.3 ± 9.5	70.4 ± 8.6	< 0.0001
Male sex, n° (%)	633 (86)	1129 (77)	67 (55)	< 0.0001
Family history, n° (%)	350 (48)	717 (49)	59 (48)	0.82
Smoking, n° (%)	411 (56)	689 (47)	44 (36)	< 0.0001
Diabetes, n° (%)	249 (34)	346 (24)	20 (16)	< 0.0001
Hypertension, n° (%)	433 (59)	895 (61)	82 (67)	0.18
Obesity, n° (%)	232 (32)	392 (27)	26 (21)	0.0151
Angina, n° (%)	504 (68)	1123 (77)	90 (74)	< 0.001
Previous infarction, n° (%)	460 (63)	739 (50)	49 (40)	< 0.0001
Previous CABG, n° (%)	85 (12)	183 (13)	11 (9)	0.45
Previous PCI, n° (%)	141 (19)	291 (20)	15 (12)	0.10
LVEF, (%)	50.3 ± 11.2	52.3 ± 10.9	50.8 ± 12.2	< 0.0001
Coronary lesions, (n°)	1.9 ± 1.1	1.8 ± 1.1	1.7 ± 1.2	0.0645

HDL-C: high density lipoprotein cholesterol; CABG: coronary artery bypass graft; PCI: percutaneous coronary interventions

Table 2. Laboratory examinations

	Low HDL-C $n=736$ (32%)	Normal HDL-C $n=1464$ (63%)	High HDL-C $n=122$ (5%)	*P*-value
Hematocrit, (%)	40.6 ± 4.9	41.3 ± 4.6	41.2 ± 4.8	0.0018
WBC, (n°/mm^3)	7845 ± 2399	7374 ± 2157	7241 ± 2380	< 0.0001
Platelets, (n°/mm^3)	229 ± 73	225 ± 62	226 ± 80	0.49
Fasting glucose, (mg/dL)	111 ± 43	106 ± 33	104 ± 28	0.0077
Creatinine, (mg/dL)	1.2 ± .4	1.1 ± .3	1.0 ± .4	< 0.0001
Total cholesterol, (mg/dL)	160 ± 36	194 ± 40	217 ± 38	< 0.0001
LDL-C, (mg/dL)	103 ± 32	125 ± 36	127 ± 37	< 0.0001
Triglycerides, (mg/dL)	138 ± 77	128 ± 79	96 ± 53	< 0.0001
Hypothyroidism, n (%)	62 (9)	129 (9)	12 (11)	0.80
Low T3 syndrome, n (%)	197 (28)	347 (25)	32 (28)	0.31
CRP, (mg/dL)	1.4 ± 3.6	0.9 ± 2.5	0.7 ± 1.7	0.0005

HDL-C: high density lipoprotein cholesterol; WBC: white blood cells; LDL-C: low density lipoprotein cholesterol; CRP: C-reactive protein

levels were low in 736 patients (32%), normal in 1464 (63%), and elevated in 122 patients (5%). Patients with elevated HDL-C showed a more favorable cardiovascular risk profile than those with normal or low HDL-C, being less frequently male, smokers, diabetic, or obese; however, patients with elevated HDL-C were 3 years older than those with normal HDL-C and 5 years older than those with low HDL-C (**Table 1**). Regarding laboratory parameters, patients with elevated HDL-C showed less evidence of inflammation (CRP and WBC count) and lower creatinine levels than those with low or normal HDL-C (**Table 2**). As for medical treatment, patients with normal, low and elevated HDL-C received the same treatment with anti-platelet agents, anticoagulant agents, heparin, and nitrates; however, medical treatment differed as to beta blockers, calcium antagonists, ACE inhibitors and lipid-lowering agents (**Table 3**).

During follow-up (median 46 months), 143 patients died from cardiac causes and 80 developed a non-fatal MI. The 7-year rate of cardiac events (cardiac death and non-fatal MI) was 20%. As expected, cardiac event-free survival was lower in patients with low compared to normal HDL-C (hazard ratio [HR] 1.98, 95% confidence interval [CI] 1.5 to 2.6, $p < 0.0001$) (**Fig. 2**). Surprisingly, cardiac event-free survival was also lower in patients with high compared to normal HDL-C (HR 1.78, 95% CI 1.03 to 2.87, $p = 0.039$) (**Fig. 3**). The prognostic impact of low HDL-C persisted ($p < 0.0001$) after adjusting for age, sex, dia-

Table 3. Medical treatment

	Low HDL-C $n=736$ (32%)	Normal HDL-C $n=1464$ (63%)	High HDL-C $n=122$ (5%)	*P*-value
Antiplatelet agents, n° (%)	611 (83)	1225 (84)	96 (79)	0.38
Anticoagulant agents, n° (%)	53 (7)	74 (5)	10 (8)	0.07
Heparin, n° (%)	154 (21)	294 (20)	22 (18)	0.73
Beta blockers, n° (%)	498 (68)	855 (58)	64 (52)	<0.0001
Calcium antagonists, n° (%)	70 (10)	232 (16)	24 (20)	<0.0001
ACE inhibitors, n° (%)	357 (49)	610 (42)	52 (43)	<0.01
Nitrates, n° (%)	504 (68)	984 (67)	89 (73)	0.39
Lipid-lowering agents, n° (%)	526 (71)	1117 (76)	84 (69)	<0.05

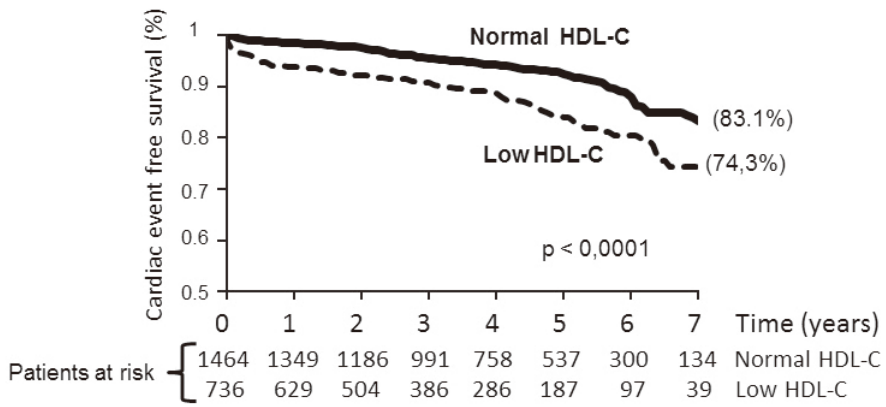

Fig. 2. Comparison between cardiac event-free survival in patients with normal and low HDL-C levels.

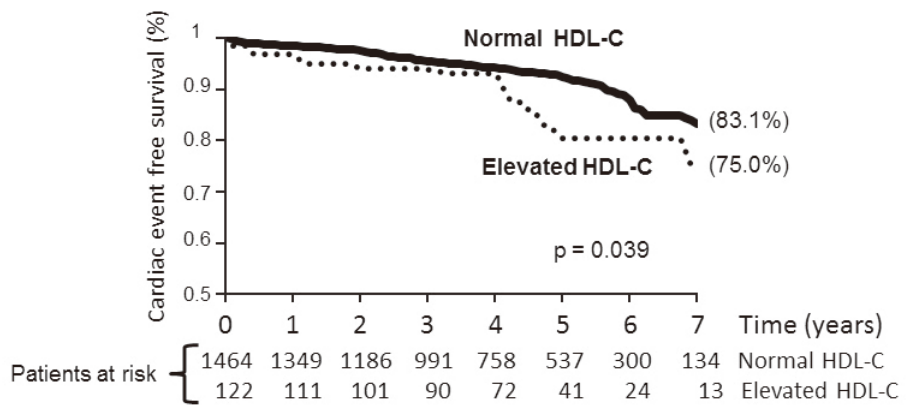

Fig. 3. Comparison between cardiac event-free survival in patients with normal and elevated HDL-C.

betes mellitus, LV ejection fraction, extent of coronary stenoses, LDL-C, triglycerides, complete blood count, thyroid and renal function. Conversely, the prognostic impact of elevated HDL-C disappeared ($p>0.10$) after adjusting for age. The impact of elevated HDL-C on cardiac event-free survival disappeared if the cut-off value was shifted from ≥ 60 to ≥ 55 mg/dL.

Considering cardiac death as the only end-point, survival was lower in patients with low compared to normal HDL-C (HR 2.21, 95% CI 1.56 to 3.12, $p<0.0001$). Survival was also lower in patients with high compared to normal HDL-C (HR 2.32, 95% CI 1.22

to 4.07, $p = 0.011$). Considering non-fatal MI as the only end-point, event-free survival was lower in patients with low compared to normal HDL-C (HR 1.63, 95% CI 1.01 to 2.59, $p < 0.0435$), while event-free survival was not significantly different in patients with high compared to normal HDL-C.

Discussion

This study shows that patients with elevated HDL-C develop CAD as do those with low or normal HDL-C, but at a more advanced age.

It is known from large prospective studies that LDL-C lowered by 25-40% following statin therapy is associated with a 9-38% reduction in cardiovascular disease risk[26-29]; however, while statin therapy is effective in reducing cardiovascular risk, treatment fails to prevent the majority of cardiovascular disease events[30]. As indicated by the INTERHEART study, dyslipidemia is not a single entity related to LDL-C and apolipoprotein B, and extensive evidence shows that low HDL cholesterol[31, 32] and elevated postprandial triglycerides[33, 34] are associated with increased cardiovascular risk.

Considering the inverse relationship between HDL-C concentration and cardiovascular risk, it might be surprising that our patients with elevated HDL-C developed CAD and cardiac events in a similar way to those with low HDL-C. A possible explanation is that our data paradoxically confirm the protective role of HDL-C, because patients with elevated HDL-C and CAD were 3 and 5 years older than those with normal or low HDL-C, respectively. Thus, elevated HDL-C prolongs the time to the appearance of CAD due to its protective effects.

An alternative interpretation of the observation made in this study is that very high levels of HDL-C can be associated with increased cardiovascular risk in some patient populations. It is acknowledged that the data on the impact of HDL-C concentration on mortality are not clear for very elevated HDL-C levels (> 85-100 mg/dL)[3, 4]. Furthermore, in the context of an aggressive LDL-C target for patients with CAD[24], a U-shaped relationship between HDL-C and all-cause mortality has been recently shown, mortality being higher for patients with both low and very elevated HDL-C[35]. This relationship was initially described in Japanese patients, where marked hyperalphalipoproteinemia, associated with juvenile corneal opacification, is frequently caused by genetic CEPT deficiency[11-13]. Since CEPT is a key protein in reverse cholesterol transport, its deficiency could favor coronary atherosclerosis and increase cardiovascular risk[36]. Mutations of the CEPT gene have also been documented in Italian subjects with hyperalphalipoproteinemia[14]; however, genetic analysis was not performed in this study.

Finally, in non-diabetic post-infarction patients with hypercholesterolemia and inflammation, elevated HDL-C is a risk factor for recurrent coronary events[37], as recently shown in patients with type 1 diabetes[38]. The above effects of HDL-C are believed to arise from inflammation-induced alterations in HDL particles by displacement and/or modification of multiple constituents of HDL-C (including apolipoprotein A1, lecithin: cholesterol acyl-transferase, paraoxonase, and lipoprotein-associated phospholipase A_2)[39]. These changes are thought to affect anti-atherogenic HDL-C function regarding reverse cholesterol transport[40] and HDL-mediated inhibition of oxidative degradation of LDL-C[39]. Furthermore, many studies have documented that the protective nature of HDL-C can be altered in the presence of glucose intolerance or diabetes and under conditions of inflammation where HDL-C can be modified by oxidative processes and replacement or modification of its protein and lipid components[41].

Surprisingly, in our patients, LDL-C concentration was not associated with cardiac events during follow-up, probably due to the effects of pharmacological treatment, mainly statins, which reduce LDL-C levels but have little effect on HDL-C levels, differing according to the types and doses of statins[42]. Regarding low HDL-C concentrations, we found values < 35 mg/dL to be more closely associated with cardiac events than those below the more commonly accepted cut-off value of < 40 mg/dL. In this respect, our data appear to indicate that very low levels of HDL-C must be given particular attention in order to risk-stratify CAD patients[25]. Because the prognostic impact of elevated HDL-C on cardiac event-free survival disappeared if the cut-off value was shifted from ≥ 60 to ≥ 55 mg/dL, our data also suggest that very high levels of HDL-C must also be paid particular attention[18].

This study is affected by several limitations. First of all, the number of patients examined was high for an observational cohort study performed in a single center, but limited if compared with that of large pharmaceutical trials. The patient population was heterogeneous and patient enrollment was lengthy. Thus, the medical treatment of our patients does not reflect current optimal medical treatment, but rather routine clinical practice in 2001-2007. We cannot rule out that these differences in medical treatment could have affected our results. Another limitation was the lack of information on laboratory parameters after hospital

discharge. Furthermore, Apolipoprotein A1 and Apolipoprotein B were not routinely determined in our Center[43]. Genetic analysis was not performed to address the issue of possible genetic mutations in the CEPT gene[11, 15]. No information was available regarding patient lifestyle, including alcohol intake, and adherence to medical treatment. On the other end, this study shows that even a single determination of HDL-C, performed at hospital admission, provides prognostic information on patients with chronic CAD.

Conclusion

Patients with elevated HDL-C and CAD have a more favorable risk profile than patients with low or normal HDL-C; the protective effect of elevated HDL-C and the more favorable risk profile delays the appearance of CAD by 3 to 5 years. Once affected by CAD, patients with elevated HDL-C develop cardiac events as do others.

Conflicts of Interest

None.

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