

Editorial

High-Density Lipoprotein and Cardiovascular Risk Reduction: Promises and Realities

Lipoproteínas de alta densidad y reducción de riesgo cardiovascular: ¿promesas o realidades?

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In a recent article in the *Revista Española de Cardiología*, Cordero et al.¹ reported a study of the concentrations of high-density lipoprotein cholesterol (HDL-C) in 959 unselected consecutive patients who were admitted for chest pain. The authors found that low levels of HDL-C (<40 mg/dL) were independently associated with diagnosis of acute coronary syndrome (ACS), that is, the lower the level of HDL-C, the greater the prevalence of ACS.

This article appears at a time when the assumed protective role of HDL-C against arteriosclerotic cardiovascular disease (CVD) has been called into question after the publication of the ACCORD clinical trial² and the premature discontinuation of the AIM-HIGH study. In view of this, it is worth asking ourselves about the actual role of HDL-C in CVD.

IMPORTANCE OF HIGH CONCENTRATIONS OF HIGH-DENSITY LIPOPROTEINS

Primary and Secondary Prevention

First, we should remember that numerous epidemiological studies have shown an inverse correlation between HDL-C levels and cardiovascular risk (CVR), both in primary and secondary prevention (Table).

Interventional Trials With Drugs

Likewise, several clinical trials have shown the benefits of increasing high-density lipoprotein (HDL) levels by pharmacological means (for a review of these interventional studies, we refer the reader to Badimón et al.¹²). These classic studies have been confirmed recently in a retrospective analysis of 30 067 “real-life” patients that showed that, for every 5 mg/dL increase of HDL-C in the initial determination, the risk of hospitalization for cardiovascular

(CV) reasons decreased 6%.¹³ In addition, if the levels of HDL-C increased 6.5 mg/dL between the first and second determinations, CVR decreased 8%, whereas if HDL-C decreased 6.5 mg/dL, CVR increased 11%.

Patients With Acute Coronary Syndrome

By analogy with the risk associated with low levels of HDL in patients with chronic CVD, low concentrations of HDL-C are an indicator of poor prognosis in patients with ACS. The most conspicuous (but not the only) example is the MIRACL clinical trial (Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering), which randomized 3086 patients with ACS to 16 weeks of treatment with atorvastatin or placebo. In a treatment-adjusted analysis, the levels of HDL-C at the time of diagnosis of ACS predicted the risk of death, repeat infarction, or recurrent angina at 16 weeks.¹⁴ In fact, while low-density lipoprotein cholesterol (LDL-C) levels did not predict CVR, the risk in patients in the upper quartile of HDL-C (>53 mg/dL) was 62% lower than in patients in the lower quartile (≤38 mg/dL). In a single-center observational study of 1032 patients with ACS who underwent percutaneous coronary intervention (PCI) and were treated with statins, multivariate analysis showed that the risk of death or a CV event was greater in patients with low HDL-C, both at 1 month and at 1 year of follow-up.¹⁵ Another study with 320 patients recruited at the point of ACS diagnosis showed that high levels of HDL-C were associated with a lower cardiovascular risk.¹⁶ The study by Cordero et al.¹ reinforces the evidence for the protective role of HDL-C in patients with chest pain in general.

After Percutaneous Coronary Intervention

Several studies provide evidence that low concentrations of HDL-C are a risk factor for major CV events after PCI. Concentrations of HDL-C prior to PCI were an independent predictor of restenosis of the stent and 1-year mortality.^{17–19} Concentrations of HDL-C even predict stent patency at 1 year in the case of the carotid artery.²⁰ The beneficial role of HDL-C is also maintained with very low concentrations of LDL-C. In a registry of 2693 patients who underwent PCI with stenting and mean LDL-C of 70 mg/dL (the recommended level according to the guidelines), low levels of HDL-C were independently associated with the need for repeat

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Table

Summary of the Main Epidemiological Studies That Demonstrate the Inverse Relationship Between High-Density Lipoprotein Cholesterol Concentrations and Cardiovascular Risk.

Study	Population	Methods	Results
Tromsø Heart Study ³	6595 men; age 20–49 years	Population screening; follow-up, 2 years	HDL-C levels were inversely correlated with CVR. HDL-C was 3-fold stronger predictor of CVR than non-HDL cholesterol
MRFIT (Multiple Risk Factor-Intervention Trial) ⁴	5792 men with CVRF; age 35–57 years	Modification of CVRF vs no intervention, follow-up, 7 years	No change in HDL-C occurred. No differences in CV deaths
Lipid Research Clinics Coronary Primary Prevention Trial ⁵	1808 men with hyperlipidemia; age 30–69 years	Low-fat diet + placebo vs cholestyramine; follow-up, 7 years	In both groups, 1 mg/dL increase in HDL-C was associated with 3.4%–4.5% decrease in CV events
Framingham Heart Study ⁶	1605 patients; age 49–82 years	16 groups stratified according to HDL-C concentrations and TC; follow-up, 12 years	High levels of HDL-C were associated with lower incidences of CVD for all TC levels. Increase in HDL-C of 1 mg/dL correlated with 2%–3% decrease in CVR
Prospective Cardiovascular Munster (PROCAM) ⁷	19 698 volunteers (4559 men analyzed, 40–64 years)	Follow-up, 6 years	Subjects with HDL-C < 35 mg/dL have 4-fold higher CVR
Israeli Ischemic Heart Disease Study (Gouldbort) ⁸	8565 men; age > 42 years	4 groups stratified by HDL-C and TC levels, follow-up, 21 years	Subgroups with low HDL-C concentrations had 36% greater CVD mortality than subgroups with elevated HDL-C (even after adjusting for age and CVRF)
Atherosclerosis Risk in Communities (ARIC) Study ⁹	12 339 participants; age 45–64 years	Follow-up, 10 years	Inverse relationship between HDL-C and CVR. Predictive power of HDL-C for CVR seems to be higher in women than in men
Prospective Epidemiological Study of Myocardial Infarction (PRIME) ¹⁰	10 592 volunteers; age 50–59 years	Prospective cohort study; follow-up, 5 years	Significant linear relationship ($P < .0001$) between decrease in HDL-C and apoA-I and increase in CVR

CV, cardiovascular; CVD, cardiovascular disease; CVR, cardiovascular risk; CVRF, cardiovascular risk factors; HDL, high-density lipoprotein; HDL-C, high-density lipoprotein cholesterol; TC, total cholesterol.

Adapted from Santos-Gallego et al.¹¹ with the permission of Future Medicine Ltd.

revascularization of the culprit lesion and the culprit vessel.²¹ We wish to highlight that it was concentrations of HDL-C and not LDL-C that were associated with CVR in this study. Finally, a very interesting article showed that the risk of periprocedural acute myocardial infarction was inversely related to HDL-C concentrations.²² In fact, for every 5 mg/dL increase in HDL-C concentrations, the risk of periprocedural acute myocardial infarction decreased by 20%.

STRATEGIES FOR INCREASING HIGH-DENSITY LIPOPROTEIN CHOLESTEROL CONCENTRATIONS

The mechanisms by which HDL-C decreases CVR have been reviewed recently by our group,^{11,23} and we refer the reader to these articles for more detailed information. In short, HDL-C is responsible for the return of excess cholesterol from extrahepatic structures to the liver, where it is excreted in bile and feces. This process is called reverse cholesterol transport. Likewise, it should be highlighted that HDL-C shows antioxidant, antiapoptotic, anti-inflammatory, vasodilator, and antithrombotic activity as well as providing endothelial protection.¹¹

Once the atheroprotective effect has been demonstrated, the problem is to determine the appropriate means for increasing HDL-C concentrations. Unlike LDL-C (a lipoprotein with relatively simple metabolism, for which levels can be effectively modified with statins), HDL-C is a lipoprotein with a complex metabolism and truly effective therapies are lacking. Below, we briefly mention the main ones.^{11,12}

Nonpharmacological Means

The first action for increasing HDL-C concentrations should always be the implementation of nonpharmacological measures

such as a healthier lifestyle including smoking cessation, weight loss, regular physical exercise (at least 3 days a week is recommended), and Mediterranean diet (rich in monosaturated and polyunsaturated fatty acids). Likewise, moderate alcohol intake can increase HDL-C concentrations by 10%, but in people who do not drink alcohol, the benefits should be weighed against the risks of recommending alcohol intake.¹¹

Niacin

This is the most effective drug. It increases HDL-C concentrations by 15% to 35% while reducing triglycerides by 30% to 50% and LDL-C by 20%. Several clinical trials and imaging studies provide support for its usefulness in reducing CVR. Nevertheless, its use is limited by adverse effects, mainly flushing. It is currently being studied in combination with laropirant, and this appears to reduce the incidence of flushing.¹²

Fibrates

These drugs increase HDL-C by 10% to 20%, and reduce LDL-C by 10% to 15% and triglycerides by 20% to 50%. Several clinical trials and imaging studies provide support for its usefulness in reducing CVR.¹¹

Thiazolidinediones

Both pioglitazone and rosiglitazone increase HDL-C concentrations by 10%. However, use of these compounds has decreased drastically in recent years as rosiglitazone has been linked to an increased risk of congestive heart failure and acute myocardial infarction, whereas pioglitazone causes water retention.¹²

Cholesterol Ester Transporter Protein Inhibitors

The first drug of this type, torcetrapib, was very disappointing, as it was shown that it increased CV mortality even though it increased HDL-C concentrations by 72%.²⁴ These events seem to be due to effects on adrenal function and activation of the rennin-angiotensin-aldosterone system specific to torcetrapib (in fact, the molecule induced an increase in blood pressure in some patients of up to 15 mmHg, and increased sodium, bicarbonate, and aldosterone concentrations). Nevertheless, 2 new drugs of the same kind have been developed, anacetrapib and dalcetrapib. These increase HDL-C concentrations without apparently affecting adrenal function; in fact, clinical trials have recently been published with both compounds which demonstrate their safety (no increase in blood pressure) and efficacy (HDL-C is increased and atheromatous plaques were decreased in imaging tests).^{25,26} The results of ongoing clinical trials with the 2 drugs with clinical endpoints (CV events) are awaited with interest (DAL-Outcomes for dalcetrapib and REVEAL for anacetrapib).

CONTROVERSY SURROUNDING HIGH-DENSITY LIPOPROTEIN CHOLESTEROL? THE ACCORD AND AIM-HIGH TRIALS

Now that the atheroprotective role of HDL-C has been put in perspective, we return to the question posed at the beginning of this editorial, namely, how to explain the results of the ACCORD and AIM-HIGH trials. The lipids arm of the ACCORD trial²¹ investigated whether the fibrate plus statins strategy was superior to statin monotherapy in 5518 patients with diabetes. The results show no statistically significant differences between the 2 strategies in terms of the primary outcome measure (CV events) or secondary outcome measures. However, an in-depth analysis showed that the differences in the lipid profile attained at the end of the study were minimal despite the use of fibrates (LDL-C concentrations only decreased by 1.1 mg/dL and HDL-C only increased by 0.7 mg/dL), and so this is not an appropriate trial for studying the effects of increasing HDL-C concentrations. In addition, although the study included patients with diabetes, surprisingly only 17% of the population had diabetic dyslipidemia (hypertriglyceridemia and low HDL-C); in fact, a subanalysis showed that the subgroup with low HDL-C and triglycerides >200 mg/dL benefited from fibrate therapy, without showing an excess risk of myopathy or hepatotoxicity. The principal investigator of the ACCORD trial, Henry Ginsberg, actually supported the use of fibrates in this population with low HDL-C and hypertriglyceridemia.²⁷

On the other hand, AIM-HIGH studied whether the combination of long-acting niacin and statins was superior to statin monotherapy in 3414 patients with chronic CVD. The early termination of the study (after an interim futility analysis) has created many doubts about the benefits of increasing HDL-C. First, we must await publication of the trial results before we know the details of the findings. Here, however, we will emphasize the study design, as one of the inclusion criteria was LDL-C concentrations of 40 mg/dL to 80 mg/dL, which would place these patients in a very low risk group. Given that the greater the baseline risk, the easier it is to demonstrate the benefits of an intervention, it is doubtful whether the chosen study population was the most appropriate. Likewise, the sample size might have been too small to demonstrate an improvement in the clinical outcomes; ie the REVEAL clinical trial (in which anacetrapib is studied) will randomize more than 30 000 patients and the HPS2-THRIVE clinical trial (Treatment of HDL to Reduce the Incidence of Vascular Events) will randomize more than 25 000 patients (this trial will investigate whether the combination of statins and niacin with laropiprant is superior to statin monotherapy).

We should highlight that the inverse relationship between CVR and HDL-C is maintained even when LDL-C is very low. A post-hoc analysis of the Treating New Targets trial (9779 patients with a mean LDL-C of 62 mg/dL) confirmed that HDL-C was a predictor of CV events in statin-treated patients; this relationship was confirmed even in patients with LDL-C <70 mg/dL, as the patients in the highest HDL-C quintile had a lower CVR than those in the lowest quintile.²⁸ In addition, in a prospective secondary prevention study, 4188 patients with LDL-C <60 mg/dL (mean, 48 mg/dL) were in follow-up for 1 year²⁹; for every 10 mg/dL decrease in HDL-C, an increase of 10% was observed in the primary outcome measure of ACS or hospitalization for CV causes, regardless of statin use.

LOW LEVELS OF HIGH-DENSITY LIPOPROTEIN CHOLESTEROL IN ACUTE CORONARY SYNDROME IN CLINICAL PRACTICE

It is worrying that low concentrations of HDL-C are increasingly common in patients with ACS. Classic studies indicate that more than 50% of patients who present with ACS have suboptimal concentrations of HDL-C.³⁰ More recent data indicate a very strong trend towards a decrease in HDL-C in patients with ACS. In an analysis of 136 094 hospitalizations occurring between 2000 and 2006 in the United States, mean concentrations of HDL-C were 40 mg/dL; however, in an analysis by year of presentation, it was observed that the concentration of HDL-C showed a statistically significant decrease of 10% in this brief period (from 43 mg/dL in 2000-2001 to 38 mg/dL in 2005-2006).³¹ During the same period, there was a decrease of only 5% in the concentrations of LDL-C. As the prevalence of obesity and metabolic syndrome in modern societies continues to increase (to what some would describe as epidemic proportions), it does not seem unreasonable to assume that HDL-C concentrations will continue to decrease in all patients in general and in patients with ACS in particular. The lack of effective therapies for raising HDL-C is another fundamental factor in explaining this epidemic of low HDL-C.

Although the Mediterranean population has a lipid profile with higher concentrations of HDL-C, in Spain itself the situation does not appear to be particularly flattering. In a recent study that included 648 patients admitted for ACS, recruited from 6 tertiary hospitals in Spain, it was observed that the prevalence of low concentrations of HDL-C was 57%.³² An additional worrying finding was that history of CVD was the factor most strongly associated with low HDL-C concentrations³²; that is, patients with greater CVR (those with symptomatic CVD) were those with lowest concentrations of HDL-C. The study by Cordero et al.¹ also shows a similar percentage of patients (54.6%) with ACS and low HDL-C. Both studies are cause for concern, given that Spain is considered in general to have a healthier lifestyle (Mediterranean diet, etc.).

CONCLUSIONS

The study by Cordero et al.¹ echoes the inverse association between HDL concentrations and CVR and also reflects the high incidence of low HDL concentrations in the Spanish population. Likewise, it serves as a wake-up call for the need to manage CVR in an integrated fashion, with statin use to reduce elevated LDL-C, and to pay attention to HDL-C concentrations. Despite the apparently contradictory results of the ACCORD and AIM-HIGH studies, we should not forget the evidence from epidemiological studies and interventional studies that supports the inverse relationship between CVR and concentrations of HDL-C. In addition, we need to pay close attention to the promising results with new cholesterol ester transfer protein inhibitors.

CONFLICTS OF INTEREST

None declared.

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