Low high-density lipoprotein predicts death in patients with mild left ventricular dysfunction regardless of coronary atherosclerosis

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Objective Low plasma high-density lipoprotein (HDL)-cholesterol is a major risk factor for cardiovascular diseases. We investigated whether HDL-cholesterol levels had a prognostic value in patients with mild left ventricular dysfunction, irrespective of the presence of coronary disease.

Methods The study included 686 consecutive patients hospitalized between January 2002 and December 2006 because of left ventricular dysfunction. All patients completed lipid profile and underwent coronary angiography. Patients were followed for a mean period of 23 months, during which major events were recorded.

Results Seventy-three percent patients were New York Heart Association (NYHA) class I-II, with the mean values of left ventricular ejection fraction and left ventricular end-diastolic diameter being respectively 36.3 ± 8.6% and 58.3 ± 7.9 mm. Half of the patients (52%) had HDL values less than 40 mg/dl, 28% presented with HDL less than 35 mg/dl. In multivariable analysis, patients with HDL-cholesterol concentration less than 40 mg/dl showed higher risk for cumulative mortality (HR 1.77, \( P < 0.05 \)) and for cardiac death (HR 2.06, \( P < 0.05 \)). This higher risk was also observed in patients with low HDL-cholesterol levels but without significant coronary stenosis. The inclusion of the CRP inflammation marker into the model highly improved the power of death prediction.

Conclusion In patients with left ventricular dysfunction, regardless of the presence of coronary atherosclerosis, lower HDL-cholesterol was a strong and independent predictor of both cardiac and all cause death.

Keywords: atherosclerosis, coronary artery disease, C-reactive protein, high-density lipoprotein, left ventricular dysfunction

Introduction Already 40 years ago, the Framingham study indicated low plasma HDL-cholesterol (HDL) as a major risk factor for cardiovascular diseases [1]. Further studies showed HDL ability to predict death among the general population as well as in specific groups [2]. It has been proposed that low HDL levels are unable to remove and transport cholesterol efficiently from peripheral tissues to the liver (reverse cholesterol transport), thus favoring cholesterol accumulation in the vascular wall [3] and therefore coronary artery disease (CAD).

On the contrary, the number of coronary arteries affected by significant coronary stenosis at angiography is a well known powerful predictor of cardiac death, this variable being largely used for risk stratification of hard cardiac events [4].

Several studies have highlighted the complex relationships between plasma concentration of HDL lipoproteins and arterial wall homeostasis. In addition to acting in the reverse cholesterol transport, HDLs preserve endothelial functions and inhibit the inflammatory processes associated with cholesterol accumulation inside the vascular wall [5,6]. Moreover, they increase endothelial bioavailability of nitric oxide by binding to scavenger receptor class B type 1 thus activating endothelial nitric oxide synthase [7,8], which altogether might explain the improved endothelium-dependent vasodilatation after infusion of reconstituted HDLs [9]. It has also been demonstrated that HDLs modulate other key control mechanisms of microcirculation such as prostacyclin [10], endothelium depolarizing factor [11] and endothelin secretion [12], platelet activation [13] and cell proliferation [14]. Low levels of HDL can adversely affect the vascular wall by activation of pro-inflammatory mechanisms, either nonspecific, such as the increase of C reactive protein (CRP) [15], or specific of endothelium activation such as expression of adhesion molecules [16] and even cardiac function, according to both the experimental evidence of HDLs’ myocardial protection from ischemia reperfusion injury [17]. More recent research focuses on...
the potential direct HDLs role on idiopathic dilated cardiomyopathy [18].

Considering the putative direct protective effect of HDLs on coronary macro and micro-vessels, even beyond the cholesterol pathway regulation, the aim of the study was to investigate in a large cohort of patients with left ventricular dysfunction, and with and without coronary obstructive disease, the predictive value of plasma HDLs concentration. In the same cohort, we also investigated the potential additional role of inflammatory markers, such as CRP, in risk stratification.

**Methods**

**Study design and objective**

This was a prospective cohort study aimed at evaluating the prognostic value of low HDL lipoprotein in patients with LVDys and angiographically documented coronary anatomy. Study participants gave their written informed consent and the study protocol gained ethical approval.

**Patients and follow-up**

From a total population of 1169 individuals with LVDys, NYHA (New York Heart Association Classification) class I-IV admitted to our cardiology department from January 2002 to December 2006, 686 consecutive patients (546 males), were considered.

Diagnostic criterion for LVDys was left ventricular ejection fraction (LVEF) less than 45% at 2D-echocardiography. Exclusion criteria were: myocardial infarction within the previous 6 months, congenital heart disease, myocarditis, pericarditis, use of cardiac implantable devices, severe renal insufficiency (<35 ml/min according to Cockroft–Gault formula [19]), cancer or other organ or systemic diseases able to affect prognosis, coronary angiography not available. No exclusion criteria were applied to traditional cardiovascular risk factors including age. All patients underwent a lipid profile and the HDL cut-off was set at 40 mg/dl in accordance with NCEP (ATP III) guidelines [20] irrespective of sex.

Patients were followed up for a mean period of 23 months. Follow-up data were obtained from review of the patient’s record, personal communication from the patient’s physician, telephone interview conducted by trained personnel, or medical examination at the outpatient clinic.

The documented outcome events were death for all causes, cardiac death, nonfatal myocardial infarction (MI) and revascularization procedure, as coronary artery bypass grafting (CABG) or percutaneous coronary interventions (PCI). The cause of death was obtained from medical records or death certificates. The classification of cardiac death required the documentation of life-threatening arrhythmias, or cardiac arrest, or acute MI, or acute left ventricular insufficiency or progressive congestive heart failure. During the follow up, a total of 85 deaths were recorded, 52 were classified as cardiovascular death, eight patients died for sudden death and in eight cases the cause of death was unknown.

With the exception of the high prevalence of males in our population (80%), biases related to patient’s recruitment and care can be assumed to be negligible; they were admitted in the same period of time, in the same hospital department and underwent the same diagnostic and therapeutic procedures by the same medical staff.

**Laboratory analyses and medical examinations**

Information about anthropometric measures, arterial pressure, glycemic state, lipid profile and smoke habit was obtained. Hypertension was defined as sampling systolic blood pressure at least 140 mmHg or a diastolic at least 90 mmHg, or with patients on antihypertensive drugs. Diabetes was diagnosed in presence of fasting glucose levels higher than 126 mg/dl in at least two determinations or with patients on insulin/hypoglycemic drugs. Patients were classified as affected by mild to moderate renal failure when the estimated glomerular filtration rate (eGFR), calculated according to Cockroft–Gault formula [19], was at least 35 or at least 89 ml/min [21].

Total cholesterol, HDL and triglycerides were measured in duplicate by standard enzymatic techniques (Synchro CX9 Pro, Beckman Coulter, Inc., Fullerton USA). Low-density lipoprotein (LDL) cholesterol was calculated according to Friedewald formula. High-sensitivity CRP was assayed by rate nephelometry (Behring BN 100, DADE Behring, Italy).

Coronary angiography was performed in all patients; coronary stenosis was defined as at least 50% lumen diameter reduction of large epicardial vessels (corresponding to 75% reduction in cross-section area). Diagnosis of coronary artery disease (CAD) was based on the presence of at least one-vessel disease or previous coronary revascularization procedures.

**Statistical analysis**

Data were expressed as mean ± SD, percentage or logarithmic transformation was used when appropriate. We performed Zeta test to evaluate the prevalence differences of variables categorized according to HDL quartiles or HDL NCEP-ATPIII cut-off (40 mg/dl). We used ANOVA test for comparison of means, Mann–Whitney test for comparison between nonnormal distributed variables, whereas, for categorical variables we employed the Chi-square or Fischer’s exact test. The relationship between HDL and coronary atherosclerosis was adjusted for covariates such as age, sex, BMI, smoking, diabetes, hypertension, renal failure, NYHA class,
LVEF and medications (statins, β-blockers, ACE-inhibitor); the relationship was evaluated by Poisson regression models. Because of the high correlation between HDL and triglycerides levels that can affect the regression model by colinearity, triglycerides were not included among confounding variables. Furthermore, to evaluate the combined risk for cardiac or all cause deaths during the follow-up, we performed a multivariate survival analysis with the Cox proportional hazard ratio (HR) model adjusted for the following cardiovascular risk factors: age, sex, BMI, smoking, hypertension, diabetes, renal failure, NYHA class, LVEF, medications (statin, β-blockers, ACE-inhibitor) and CAD. In a subgroup of 546 patients, the role of CRP in HDL mortality prediction was also studied.

All confidence intervals were estimated at the 95% level, a P-value less than 0.05 was considered statistically significant. The power-analysis test, performed to evaluate the reliability of the findings, was 80%. STATA 8 analysis software (Stata Corp LP, College Station, Texas, USA) was used.

Results
Descriptive analysis
Male individuals were 80% of the total population and were significantly younger than females (66 ± 11 vs. 70 ± 9 years, P < 0.0001). Table 1 reports anthropometric data, lipid profile, cardiac function parameters, CAD prevalence, hypertension, diabetes, obesity, arrhythmias, valvulopathies, mild or moderate renal failure, smoking and pharmacological therapy in the whole population, when patients were stratified by the HDLs cut-off and when patients were grouped according to CAD diagnosis.

In 31% of patients we observed an average LDL concentration above the guideline cut-off (LDL < 100 mg/dl) recommended for patients with CAD or coronary heart disease risk equivalents. In more than half of our population HDL levels were below 40 mg/dl; moreover, 28% of patients (a prevalence nearly threefold the general population) presented extremely reduced HDL concentrations (< 35 mg/dl).

As compared with patients with negative angiography (no CAD), those with significant coronary stenosis (CAD) had lower HDL levels (40.5 ± 12.2 vs. 46.1 ± 13.6 mg/dl, P < 0.0001), but lower prevalence of NYHA class III-IV (23.4% vs. 40.8% P < 0.0001). In our population, despite the high prevalence of CAD, less than half of patients with documented atherosclerosis were on statin treatment.

No significant correlation was found between HDL, NYHA class, and LVEF in the whole population; nevertheless, in no CAD group, patients with HDL less than 40 mg/dl showed a lower LVEF as compared with individuals with HDL at least 40 mg/dl (31.4 ± 7.1 vs. 35.5 ± 8.2, adjusted P < 0.005) in accordance with the higher prevalence of NYHA III-IV observed in those with HDL below 40 mg/dl.

Results on inflammation status showed that CRP concentration were significantly higher in LVDys patients with low HDL levels as compared with individuals with HDL at least 40 mg/dl (median 0.715, range 0.01–47.0 vs. 0.420, 0.02–16.5 mg/dl, P < 0.0005) and in LVDys patients with CAD as compared with individuals without CAD (median 0.620, range 0.01–47.0 vs.

Table 1 Baseline characteristics, lipid profiles, diseases and medications prevalence in the whole population and stratified according to the high-density lipoproteins cut-off or coronary artery disease

<table>
<thead>
<tr>
<th>Total (n 686)</th>
<th>HDL &lt; 40 (n 354)</th>
<th>HDL ≥ 40 (n 332)</th>
<th>P*</th>
<th>CAD (n 534)</th>
<th>No CAD (n 152)</th>
<th>P**</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (range)</td>
<td>66 ± 10 (20–92)</td>
<td>66 ± 11 (34–90)</td>
<td>67 ± 10 (20–92)</td>
<td>&lt; 0.05</td>
<td>64 ± 11 (34–90)</td>
<td>67 ± 10 (20–92)</td>
</tr>
<tr>
<td>Sex (male/female)</td>
<td>546/140</td>
<td>304/90</td>
<td>242/90</td>
<td>&lt; 0.0001</td>
<td>443/91</td>
<td>103/49</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>26.9 ± 4.1</td>
<td>27.4 ± 4.1</td>
<td>26.4 ± 4.0</td>
<td>&lt; 0.005</td>
<td>27.8 ± 4.8</td>
<td>26.6 ± 3.8</td>
</tr>
<tr>
<td>Cholesterol (mg/dl)</td>
<td>183.5 ± 43.1</td>
<td>168.2 ± 35.8</td>
<td>199.5 ± 44.3</td>
<td>&lt; 0.0001</td>
<td>180.8 ± 41.5</td>
<td>192.7 ± 47.0</td>
</tr>
<tr>
<td>Triglycerides (mg/dl)</td>
<td>122.6 ± 89.3</td>
<td>131.10 ± 75.3</td>
<td>113.5 ± 101.4</td>
<td>&lt; 0.0001</td>
<td>122.1 ± 71.6</td>
<td>124.1 ± 134.3</td>
</tr>
<tr>
<td>HDL (mg/dl)</td>
<td>41.7 ± 12.7</td>
<td>33.0 ± 4.6</td>
<td>51.0 ± 12.1</td>
<td>&lt; 0.0001</td>
<td>116.3 ± 34.4</td>
<td>122.2 ± 38.1</td>
</tr>
<tr>
<td>LDL (mg/dl)</td>
<td>117.4 ± 35.4</td>
<td>108.8 ± 30.1</td>
<td>126.4 ± 38.2</td>
<td>&lt; 0.0001</td>
<td>122.2 ± 38.1</td>
<td>NS</td>
</tr>
<tr>
<td>BMI &gt; 30 kg/m² (%)</td>
<td>21</td>
<td>29</td>
<td>17</td>
<td>&lt; 0.01</td>
<td>17</td>
<td>25</td>
</tr>
<tr>
<td>Smoking (%)</td>
<td>50</td>
<td>53</td>
<td>45.5</td>
<td>&lt; 0.05</td>
<td>53</td>
<td>37.5</td>
</tr>
<tr>
<td>NYHA class II (%)</td>
<td>73</td>
<td>74</td>
<td>NS</td>
<td>77</td>
<td>59</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>36.7 ± 8.4</td>
<td>36.4 ± 8.7</td>
<td>37.0 ± 8.0</td>
<td>NS</td>
<td>37.5 ± 8.3</td>
<td>34.0 ± 8.0</td>
</tr>
<tr>
<td>LVEDD (mm)</td>
<td>57.9 ± 7.8</td>
<td>57.7 ± 7.6</td>
<td>59.8 ± 7.7</td>
<td>NS</td>
<td>56.7 ± 7.2</td>
<td>61.9 ± 7.8</td>
</tr>
<tr>
<td>CAD (%)</td>
<td>78</td>
<td>84.7</td>
<td>70.5</td>
<td>&lt; 0.0001</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Diabetes (%)</td>
<td>30</td>
<td>35.6</td>
<td>23.5</td>
<td>&lt; 0.0005</td>
<td>33</td>
<td>18.4</td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>43.1</td>
<td>42.7</td>
<td>43.7</td>
<td>NS</td>
<td>43.8</td>
<td>40.8</td>
</tr>
<tr>
<td>Arrhythmias (%)</td>
<td>24.3</td>
<td>24</td>
<td>24.7</td>
<td>NS</td>
<td>19.7</td>
<td>40.8</td>
</tr>
<tr>
<td>Valvulopathies (%)</td>
<td>13.8</td>
<td>12.4</td>
<td>15.4</td>
<td>NS</td>
<td>11.4</td>
<td>22.4</td>
</tr>
<tr>
<td>Renal failure (%)</td>
<td>7.6</td>
<td>7.3</td>
<td>7.8</td>
<td>NS</td>
<td>8.4</td>
<td>4.6</td>
</tr>
<tr>
<td>Statins (%)</td>
<td>37.8</td>
<td>35.3</td>
<td>40.6</td>
<td>NS</td>
<td>42.9</td>
<td>20.3</td>
</tr>
<tr>
<td>β-blockers (%)</td>
<td>64.1</td>
<td>66.4</td>
<td>61.7</td>
<td>NS</td>
<td>65.2</td>
<td>60.5</td>
</tr>
<tr>
<td>ACE-inhibitor (%)</td>
<td>53.1</td>
<td>53.4</td>
<td>52.7</td>
<td>NS</td>
<td>49.4</td>
<td>65.8</td>
</tr>
</tbody>
</table>

Reported P value is relative to (>) HDL < 40 vs. HDL ≥ 40 or (**) CAD vs. no-CAD comparison. Values are Mean ± SD. Conversion Factor mg/dl to mmol/l: LDL, HDL, CH = 0.02586; TG = 0.01129. BMI, body mass index; CAD, coronary artery disease; HDL, high density lipoprotein; LDL, low density lipoprotein; LVEDD, left ventricular end diastolic dimension; LVEF, left ventricular ejection fraction; NS, not significant; NYHA, New York Heart Association.
0.381, 0.01–11.2 mg/dl, \( P < 0.0001 \). If we compare the low-HDL/CAD group and the high-HDL/noCAD group, the difference on CRP levels is maximized, median value of the first group is more than double: 0.78 (0.01–4.70) vs. 0.35 (0.02–11.17) mg/dl \( P < 0.0001 \), suggesting that condition characterized by atherosclerosis and reduced HDL levels is associated with higher inflammatory response.

The Poisson regression analysis indicated that atherosclerosis risk decreases by 1% \( (P < 0.01, \text{after adjustment for confounding variables}) \) for each 1 mg/dl HDL increase.

**Follow-up**

During the follow-up, 32.4% of patients underwent coronary revascularization (procedures performed at enrollment -134 cases- were excluded). Results of coronary angiography show: three or four partially occluded vessels in 136 individuals, one or two stenotic vessels in 248 individuals, and a negative angiography in 168 individuals. The mean time of revascularization after enrollment is 12.3 months.

Table 2 shows distribution of events and statistical significance according to HDL cut-off and to presence or absence of significant CAD. Total revascularization procedures were more frequent in patients with HDL less than 40 mg/dl than in patients with HDL at least 40 mg/dl (38 vs. 27%, \( P < 0.005 \)). Inferential analysis showed a significant association between HDL levels and total revascularization procedures: cumulative revascularization incidence rate increased by 62% in the subgroup with HDL less than 40 mg/dl as compared with the one with HDL at least 40 mg/dl \( (P < 0.005, \text{after adjustment}) \).

Five percentage of patients developed MI (n 34), with a higher-but not significant- incidence in the subgroup with low HDL (5.9 vs. 3.9%).

During follow up, a total of 85 deaths were recorded (the 15.2% in HDL<40 subgroup mg/dl and the 9.3% in HDL \( \geq 40 \) mg/dl subgroup, \( P < 0.05 \)). The Cox analysis showed an association between HDL levels and risk of cumulative death: total mortality rate increase by 77% \( (P < 0.05, \text{after adjustment}) \) in the group with HDL less than 40 mg/dl as compared with group with HDL at least 40 mg/dl (Fig. 1a). This result is well evident in Fig. 1b, where predicted survival curves are stratified according to HDL quartiles: moving from high to low HDL quartile the risk of total mortality increases of 34% at each step \( (P < 0.01, \text{after correction}) \). Also considering HDL as continuous variable, the incidence rate decreases by 2.1% \( (P = 0.08, \text{after adjustment}) \) for each 1 mg/dl increase in HDL.

Cardiac deaths were 61.2% of total deaths, this prevalence was more than double in HDL less than 40 mg/dl vs. HDL at least 40 mg/dl group \( (10.5 \text{ vs. } 4.5\%, \ P < 0.005) \); patients who died for cardiac causes had lower HDL levels than those deceased for noncardiac causes \( (36.0 \pm 8.9 \text{ vs. } 43.5 \pm 17.9, \ P < 0.01 \text{after correction}) \). We observe that patients with unclassified death (eight patients died for sudden death and for eight patients for unknown cause) show a prevalence of HDL less than 40 mg/dl (69%) very similar to cardiac death group (71%). Hence, supposing a casual distribution of these deaths, the relationship between HDL and cardiac death should not be influenced.

Inferential analysis indicated a very strong association between low HDL levels and risk for cardiac deaths: we postulated a risk reduction of 4.5% \( (P < 0.005, \text{after adjustment}) \) for every HDL increase of 1 mg/dl; moreover, individuals with HDL less than 40 mg/dl showed a 106% death risk increase \( (HR \ 2.06 \ P < 0.05, \text{after adjustment}) \) in the whole population Fig. 2a) as compared with the HDL at least 40 mg/dl group. In Fig. 2b the survival curves have been compared for each HDL quartiles. Cox analysis revealed that, moving from higher to lower HDL quartile, the risk of cardiac death progressively increase by 45% \( (HR \ 1.45 \ P < 0.01, \text{in the whole population after correction}) \).

Patient population was further split into two subgroups with or without CAD. In individuals with angiographically normal or near normal coronary arteries, HDL was a good predictor of cardiac and cumulative mortality. Accordingly, in the CAD negative group, patients with HDL less than 40 mg/dl had a 5.2-fold \( (P < 0.05, \text{adjusted}) \) and 11-fold \( (P < 0.05, \text{adjusted}) \) higher probability of all causes death and cardiac mortality respectively, as compared with those with high HDL (Fig. 3a and b).

**Table 2 Prevalence distribution of recorded events according to 40 mg/dl HDL cut-off and according to CAD diagnosis**

<table>
<thead>
<tr>
<th>Total</th>
<th>HDL&lt;40</th>
<th>HDL&gt;40</th>
<th>( P^{a} )</th>
<th>CAD</th>
<th>no-CAD</th>
<th>( P^{1} )</th>
</tr>
</thead>
<tbody>
<tr>
<td>PTCA ( ^{+} )</td>
<td>115</td>
<td>25.7%</td>
<td>18.0%</td>
<td>( P &lt; 0.005 )</td>
<td>29.5%</td>
<td>0%</td>
</tr>
<tr>
<td>CABG ( ^{+} ^{+} )</td>
<td>73</td>
<td>14.9%</td>
<td>11.6%</td>
<td>NS</td>
<td>18.2%</td>
<td>0%</td>
</tr>
<tr>
<td>Total coronary revasc ( ^{++} )</td>
<td>179</td>
<td>38.0%</td>
<td>26.9%</td>
<td>( P &lt; 0.005 )</td>
<td>45.5%</td>
<td>0%</td>
</tr>
<tr>
<td>Cumulative death</td>
<td>85</td>
<td>15.2%</td>
<td>9.3%</td>
<td>( P &lt; 0.05 )</td>
<td>13.3%</td>
<td>9.2%</td>
</tr>
<tr>
<td>Cardiac death</td>
<td>52</td>
<td>10.5%</td>
<td>4.5%</td>
<td>( P &lt; 0.005 )</td>
<td>8.6%</td>
<td>3.9%</td>
</tr>
</tbody>
</table>

\[\text{Reported } P \text{ value is relative to } (^{+}) \text{HDL}<40 \text{ vs. } \text{HDL}>40 \text{ or } (^{+}) \text{CAD vs. no-CAD comparison}, (^{+}) \text{Intra-procedure mortality 0.4%}, (^{++}) \text{intraprocedure mortality 1.3%}; (^{+++}) \text{patients (n 9) treated with both PTCA and CABG have been counted an only ones; procedures performed at enrollment 134 cases – were excluded. CABG, coronary artery bypass graft; CAD, coronary artery disease; HDL, high density lipoprotein; NS, not significant; PTCA, percutaneous transluminal coronary angioplasty.}\]
the relationship did not have statistic relevance.

In a subgroup of 546 patients we tested also the predictive role of the CRP, a sensitive but relatively nonspecific inflammatory marker for death prediction. When we added CRP (categorized by 0.30 mg/dl cut-off) to the Cox model (Table 3), it significantly predicted cumulative death (HR 2.45, \( P < 0.05 \) adjusted), whereas it resulted only borderline in respect to cardiovascular death (HR 2.39, \( P = 0.08 \) adjusted).

Moreover, in order to evaluate the HDL and CRP prognostic power as single or coupled variables, we implemented an additional Cox model that included four groups according to the generally accepted cut-off for this variables (HDL <40 mg/dl and CRP >0.30 mg/dl):

- low-HDL/low-CRP,
- low-HDL/high-CRP,
- high-HDL/low-CRP,
- high-HDL/high-CRP.

As far as cumulative mortality is concerned, both groups – high-HDL/high-CRP and low-HDL/low-CRP – had a significantly higher risk than the reference ‘normal’ group (high-HDL/low-CRP): the HR were respectively 5.0 (\( P < 0.05 \), adjusted) and 5.0 (\( P = 0.05 \), adjusted), thus with no significant difference between the two. However, when the values of both risk factors were abnormal (low-HDL/high-CRP), the predictive power of cumulative death in the whole population markedly increased to HR 7.8 (\( P < 0.005 \), adjusted; Fig. 4).

The analysis of cardiac mortality showed that the HDL and CRP predictive power barely reached a
borderline significance as compared with the high-HDL/low-CRP reference group: the HR was 5.5 for low-HDL/low-CRP group (\( P < 0.1 \), adjusted) and 6.7 for high-HDL/high-CRP group (\( P < 0.1 \), adjusted). Conversely, when patients showed abnormal values of both HDL and CRP, the predictive power for death widely increased up to HR 10.8 (\( P < 0.05 \), adjusted).

Thus, in LVDys patients, low HDL levels predicted both cardiac and cumulative deaths, whereas the predictive value of CRP was more striking for cumulative mortality.

Among the variables included in the Cox model, besides HDL and CRP, advanced age (highest age quartile included over 75 year patients), diabetes and renal impairment significantly predicted cumulative mortality. As far as cardiac death, the only additional significant variable over advanced age was renal failure (Table 3).

In our population, the power-analysis showed a significant relationship between HDL and each of the considered endpoints (revascularization 93%, cardiac death 82% and total death 78%), supporting the hypothesis of predictive role of HDLs in LVDys mortality.

In spite of the fact that LDL was calculated indirectly, based on HDL, TC and triglycerides levels, and being aware that LDL is more sensitive than HDL to statin therapy, we performed an additional multivariate analysis replacing HDL with LDL in order to evaluate the possible LDL contribution to outcome. LDL did not show significant relationship with outcome, neither when LDL was considered a continuous variable, nor when patients were split into two subgroups, with LDL higher or lower than 100 mg/dl (data not shown).

**Discussion**

Previous studies have shown an inverse correlation between plasma HDL and death rate in an apparently
healthy population [2]. More recently, other studies have indicated a relationship between HDL levels and mortality in LVDys condition at univariate analysis. However, this association was not further confirmed after adjustment of confounding factors [22–23].

In a population of relatively young patients mainly with moderate LVDys (mean age 66 years, less than 9% of age at least 80 years; 73% in NYHA class I-II), we have shown that reduced HDL concentrations strongly predicted short and medium-term mortality, the average follow-up period being of approximately 2 years. HDLs resulted able to predict both cumulative and cardiac mortality; this was true irrespective of the presence of significant CAD. LVDys patients without significant CAD but with HDL less than 40 mg/dl had a worse prognosis in respect to the group with HDL at least 40 mg/dl (Fig. 3).

The major limitation of our study stays, of course, in the fact that it cannot establish a cause–effect relationship between low HDLs and LVDys. Nevertheless, the results of the present study solicit the hypothesis of a pathogenetic role of HDLs in LVDys, beyond its contribution to atherogenesis, which in turn prospects for new therapeutic approaches. Endothelial dysfunction is the common denominator of different vascular pathologies, in the very early stages as well as in the stabilized or complicated phases of the disease. It is well documented that the negative effects of low HDLs on endothelial function are induced by numerous mechanisms – some of which are still waiting elucidation – via vessel-wall cholesterol-deposition, inflammation-antinflammation unbalance, increased LDL oxidation, reduced nitric oxide bio-availability and impaired antithrombotic effects. Indeed, endothelial dysfunction is a conditio sine qua non for microvascular dysfunction, a disorder that appears to be involved in the progression of LVDys [24,25]. The recently reported direct effect of HDLs on cardiac function further supports the possible role of HDLs in the development of LVDys and its progression beyond the atherosclerotic burden [25,26].

Another limitation of this study is the lack of information regarding exact indication for coronary revascularization procedures and the incidence of hospitalization for LVDys during follow up.

This is the first study to report the strong and independent power of HDL in predicting cumulative/cardiac death among patients with left ventricular dysfunction. This data has its possible biologic basis on the recent evidence of a myocardial protection against ischemia-reperfusion injury [17] directly exerted by HDL, restoration of vasomotor response to acetylcholine or sodium nitroprusside [27], improved outcome following as much as 10% increase in HDL concentration [28,29], and reduction in the extension of atherosclerotic lesions [30]. All together, this evidence evokes a therapeutic potential for HDLs also in LVDys condition.

In LVDys prognostic assessment, a part from the other variables considered such as advanced age, diabetes and renal failure, CRP values less than 0.30 mg/dl were associated to a mortality risk five times higher as compared with patients with low CRP. The combination of HDL and CRP measurements improved death prediction of cumulative and cardiac mortality: in LVDys patients who had reduced levels of HDL and, at the same time, high values of CRP concentration, the risk of cumulative and cardiac deaths were 7.8 and 10.8 fold respectively higher than in patient with HDL at least 40 mg/dl and normal CRP levels. This finding could be explained by the fact that low HDL concentrations favors inflammation, as revealed by higher CRP expression levels observed both in idiopathic dilated cardiomyopathy [15] and in hypoalphalipoproteinemia condition [18].

Our study identifies HDL-cholesterol plasma levels as strong and independent predictor of mortality in patients’ whit left ventricular dysfunction being this or not of postischemic nature. Considering the elevated prevalence of low HDLC in LVDys patients (52% among our study population), the HDLs rise as a novel potential therapeutic target in the management of this pathological condition.

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Conflict of interest: The authors declare that: the paper is not under consideration elsewhere, none of the paper’s contents have been previously published, all authors have read and approved the manuscript, the authors do not have any potential conflict of interest.

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