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Achievement of low density lipoprotein (LDL) cholesterol targets in primary and secondary prevention: Analysis of a large real practice database in Italy

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HIGHLIGHTS

- Target and intensity of low-density lipoprotein cholesterol (LDL-C) lowering therapy should be tailored according to the individual global cardiovascular (CV) risk.
- Despite recommendations from international guidelines and recent evidence in favour of the beneficial effects derived from even intensive LDL-C reductions in very high risk patients, several observational studies and clinical surveys reported poor control rates of LDL-C in different clinical settings.
- We aimed at retrospectively evaluating real-life LDL-C goal attainment and predictive factors for predefined LDL-C therapeutic goals in adult outpatients in primary or secondary prevention.
- We observed relatively poor control rates of LDL-C in high or very high SCORE risk individuals in primary prevention and in very high risk outpatients with comorbidities in secondary prevention.

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ABSTRACT

Background and aims: Target and intensity of low-density lipoprotein cholesterol (LDL-C) lowering therapy should be tailored according to the individual global cardiovascular (CV) risk. We aimed at retrospectively evaluating real-life LDL-C goal attainment and predictive factors for predefined LDL-C therapeutic goals both in

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Therapeutic targets

primary and secondary prevention.
Methods: We collected data from a large cohort of outpatients aged 40–65 years, followed by general practitioners, cardiologists and diabetologists in Italy. All data were centrally analysed for global CV risk assessment and rates of control of major CV risk factors, including LDL-C. Study population was stratified according to the presence or absence of previous CV events, including coronary artery disease (CAD), peripheral artery disease (PAD) or stroke/TIA. CV risk profile characterization was based on the European SCORE. Predefined therapeutic goals were set according to the European guidelines on dyslipidaemia: LDL-C levels < 70 mg/dl for very high CV risk patients in primary prevention and for those in secondary prevention; < 100 mg/dl LDL-C levels for high CV risk patients in primary prevention. Logistic regression analysis with clinical covariates was used to identify predictive factors for achieving these goals; lipid lowering therapy entered in the analysis as continuous (model 1) or categorical variable (model 2).
Results: We included 4,142 outpatients (43,7% female, age 58.0 ± 5.2 years, BMI 28.5 ± 5.0 kg/m^2) among whom 2,964 (71.6%) in primary and 1,178 (28.4%) in secondary prevention. In primary prevention, none of the patients at very high CV risk had LDL-C < 70 mg/dl and 8.9% of patients at high CV risk showed LDL-C < 100 mg/dl. Only 5.8% of patients in secondary prevention had LDL-C levels < 70 mg/dl, specifically 6.5% of patients with CAD, 2.6% of patients with PAD and 4.7% of patients with CVD ($p < 0.001$). Beyond diabetes and lipid lowering therapy, high risk SCORE estimation resulted a strong and independent predictor for the lack of achieving all predefined therapeutic targets, including LDL-C < 100 mg/dl [OR: 0.806 (0.751–0.865)); $p < 0.001$], and LDL-C < 70 mg/dl [OR: 0.712 (0-576-0.880); $p = 0.002$], in primary prevention.
Conclusions: Despite high or very high SCORE risk and use of lipid lowering therapies, we observed poor achievement of LDL-C targets in this large cohort of outpatients followed in a setting of real practice in Italy.

1. Introduction

Dyslipidaemia is one of the most common modifiable risk factors for cardiovascular (CV) disease in Western countries, including Italy. A large number of randomized clinical trials and meta-analyses demonstrated that lipid-lowering therapies, mostly based on statins, are able to reduce the incidence of major CV events in both primary and secondary prevention, as well as in both genders and all age groups [1]. The Cholesterol Treatment Trialists (CTT), which included more than 170,000 participants and 26 randomized controlled trials performed with statins, showed a 10% reduction in all-cause mortality and 20% reduction in CV death per 1.0 mmol/L (40 mg/dl) of low-density lipoprotein cholesterol (LDL-C) reduction [2]. In the same analysis, the risk of coronary events was also reduced by 23% and the risk of stroke was reduced by 17% per the same LDL-C reduction [2].

Over the last few years, different sets of guidelines have consistently recommended that lipid-lowering therapy intensity and therapeutic goals should be tailored according to individual global CV risk profile, thus suggesting more ambitious therapeutic goals in high or very high-risk individuals. Despite these recommendations and recent evidence in favour of the beneficial effects derived even from intensive LDL-C reductions in very high risk patients, several observational studies and clinical surveys reported poor control rates of LDL-C in different clinical settings. As an example, in the EURIKA study, which examined the achievement of different lipoprotein treatment goals in patients at high CV risk in Europe, only 1.3% of patients at very high risk and 4.9% of patients at high risk reached all three LDL-C, non-high density lipoprotein cholesterol (HDL-C) and apolipoprotein B level goals [3]. More recently, the IV EUROASPIRE survey confirmed that a large majority of patients with previous coronary artery disease (CAD) do not achieve the recommended therapeutic targets for secondary prevention, thus reporting that about 80% of patients had LDL-C ≥70 mg/dl (≥1.8 mmol/l) [4]. Similar findings have been also observed in several surveys performed in Italy, although limited to diabetic individuals [5–7], or very high risk patients with previous CAD [8].

The Evaluation of Final Feasible Effect of Control Training and Ultra Sensitisation (EFFECTUS) was a nation-wide clinical survey, which reported high prevalence and poor control rates of different risk factors, including hypercholesterolemia, in a very large cohort of outpatients at various CV risk profiles, who were followed by physicians with different professional skills (mostly general practitioners), in a setting of real practice in Italy [9]. Further analyses from the same database were performed to detect potentially different approaches to CV disease management and control in high-risk subsets of outpatients, such as those with diabetes or hypertension [10,11]. A very recent analysis of the same database showed that despite low prevalence and optimal medical therapy, high-to-very-high SCORE risk individuals did not achieved the recommended therapeutic targets for multiple concomitant CV risk factors in a setting of real practice [12]. However, specific analysis evaluating the achievement of different LDL-C targets in predefined subgroups of outpatients stratified according to European risk SCORE equation was not conducted.

On the basis of these considerations, and considering the very large and representative population sample of this database, the primary aim of the present analysis was to retrospectively evaluate real-life LDL-C goal attainment and predictive factors for predefined LDL-C therapeutic goals in adult outpatients in primary or secondary prevention.

2. Materials and methods

2.1. Methodology of the study

The methodology of this observational, retrospective, multicentre study has been previously described [9]. Briefly, the EFFECTUS survey was designed to evaluate prevalence and control rates of major CV risk factors, as well diagnostic opportunities and treatment habits of physicians in a setting of real practice in Italy. The program was addressed to physicians operating in both general practice and outpatient clinics across the whole national territory, and was aimed at improving quality standards for CV disease management and control. Physicians were invited to participate in an educational training program, aimed at evaluating the efficacy of a clinical problem-oriented learning approach for improving individual global CV risk management in their routine clinical practice. Acceptance of this initial invitation placed physicians under no obligation, and physicians were entitled to drop out of the survey at any stage.

Written invitations were forwarded in a sizable number to ensure a sufficient representative of the study population sample and to achieve this target within a period of approximately 3–4 weeks. For this purpose, each of the 20–24 regional referral centres invited 60 physicians per region (35 general practitioners, 15 cardiologists, and 10 diabetologists) to participate to this survey, for a total of 1.400 individual physicians, selected on the basis of the above-mentioned clinical habits and personal characteristics. Then, approximately 1.250 invitations were issued and physicians were asked to fill questionnaires featuring their characteristics and practice (age, gender, geographic location,

professional expertise, use of electronic database) and to reply anonymously to the administrative site of their regional referral centres.

Following their acceptance, involved physicians were asked to report clinical data extracted from their clinical records from the first 10 consecutive adult Caucasian outpatients aged more than 40 years, whatever the reason they referred to their own attending physicians. The entire data collection was completed by participants on-site and then delivered to the data collection centre by on-line access to remote database. At each study site, collection data was conducted during one week in May 2006. Physicians who completed the program did not receive any compensation for their participation.

2.2. Data collection

Data collection included full medical history and physical examination. Information was obtained on current therapy for hypertension, dyslipidaemia, diabetes and concomitant CV diseases and comorbidities, including CAD, stroke, and heart failure, as well as any concomitant medication. Based on anthropometric data, calculation was made of body mass index (BMI), that was expressed as body weight in kilograms divided by the square of height in meters (kg/mˆ2). Clinic systolic and diastolic blood pressure (BP) levels, serum levels of total cholesterol (TOT-C), HDL-C, LDL-C, triglycerides, glucose, glycosylated haemoglobin (Hbc1A), and creatinine were extracted from available clinical records and generally not exceeding 12 months. Information on electrocardiogram (ECG), echocardiogram, carotid or peripheral vascular ultrasound analysis, *fundus oculi* examination, and exercise stress test were also recorded by physicians, when available. Available data were centrally analysed for global CV risk evaluation and CV risk profile characterization.

The study conformed to the Declaration of Helsinki and its subsequent modifications, and was authorized by the reference Ethical Committee. The confidentiality of the data was carefully and strictly protected.

2.3. Definition of risk factors, markers of organ damage and comorbidities

Diagnosis of hypertension was defined in the presence of systolic BP levels ≥140 mmHg and/or diastolic BP levels ≥90 mmHg in untreated subjects or in the presence of stable (≥6 months) antihypertensive drug treatment [13]. Diagnosis of hypercholesterolemia was defined in the presence of TOT-C levels ≥190 mg/dl or LDL-C levels ≥130 mg/dl, while hypertriglyceridemia for triglyceride levels ≥150 mg/dl or stable lipid-lowering drug treatment in both conditions [14–16]. In addition, low levels of HDL-C levels were defined by ≤ 40 mg/dl in men and ≤50 mg/dl in women [14–16]. Obesity was defined in the presence of BMI ≥25 kg/m2 [17]. Finally, diabetes was defined in the presence of plasma glucose levels ≥200 mg/dl, or fasting plasma glucose levels ≥126 mg/dl [18–20].

Cardiac organ damage (OD) was defined by the presence of electrocardiographic left ventricular hypertrophy [13]. Vascular OD was defined by the presence of carotid atherosclerotic plaque, determined by b-mode ultrasonography for intima-media thickness values > 1,5 mm [13]. Finally, renal OD was assessed by measuring plasma creatinine concentration and defined by the presence of either estimated glomerular filtration rate (eGFR) less than 60 ml/min/1.73 m2, calculated according to the Cockcroft-Gault formula, or creatinine clearance (CrCl) less than 60 ml/min/1.73 m2 [13].

CAD was defined according to the presence of the two of the following three items: symptoms (e.g. chest pain) lasting longer than 15 min, transient increase in serum concentrations of enzymes indicating cardiac damage (more than twice the upper limit of normal) and electrocardiographic changes typical of myocardial ischemia (new persistent ST-segment elevation or pathological Q waves in two contiguous leads) [21,22]. However, the diagnosis of CAD may also include other coronary events, for example acute coronary syndrome, recurrent angina and coronary revascularization, which were distinguished in the case-report form [23]. Peripheral artery disease (PAD) was defined in the presence of atherosclerotic plaque or lesion in at least one artery from all vascular sites, including carotid, vertebral, mesenteric, renal, upper and lower extremity vessels, causing clinically evident signs or symptoms [24]. Finally, cerebrovascular disease (CVD), namely non-fatal stroke, was defined as a neurological deficit with sudden onset and persistence of symptoms for more than 24 h or leading to death with no apparent causes other than vascular ones [25]. Transient ischemic attack (TIA) was defined as a neurological event with the signs and symptoms of stroke, but which resolves within a short period of time (less than 24 h) [26].

Study population has been stratified into two groups, depending on absence (primary prevention) or presence (secondary prevention) of previous CV events, including either CAD, PAD or stroke/TIA.

2.4. Risk score models

CV risk was estimated by using European SCORE risk equation, which provides the 10-year risk evaluation of patients aged between 40 and 65 years [27]. Risk estimation for developing fatal coronary events is based on the following items for the equation: TOT-C, systolic BP, age, and smoking status [27]. Since study population was composed by adult Caucasian individuals born and living in Italy, the low-risk score charts have been applied [27].

According to current European Guidelines [28], adult outpatients without overt CV diseases (primary prevention) have been further stratified according to risk SCORE equation, as follows: 1) low CV risk (SCORE < 1%; group A); 2) moderate CV risk (SCORE ≥1% - < 5%; group B); 3) high CV risk (SCORE ≥5% - < 10%; group C); 4) very high CV risk (SCORE ≥10%; group D).

2.5. Definition of LDL-C goals and lipid lowering therapies

The following LDL goals were defined for patients in primary prevention: LDL-C levels < 70 mg/dl in very high; LDL-C levels < 100 mg/dl in high CV risk patients; LDL-C levels < 115mg/dl in low-to-intermediate CV risk patients. For those patients in secondary prevention LDL-C levels should be < 70 mg/dl. These therapeutic goals have been set according to the recommendations of European guidelines [28].

Lipid-lowering therapies may include the following drugs: 1) statins; 2) fibrates; 3) omega-3; 4) ezetimibe; 5) resins; 6) other compounds (e.g. nutraceuticals). Proportions of patients on therapy, as well as average number of lipid lowering drugs have been calculated in the overall population sample and in patients in either primary or secondary prevention. In view of the study design, these proportions, as well as those of patients having LDL-C within predefined therapeutic goals, have been calculated at the time of data collection. For the definition of in-treatment for lipid lowering therapies, the last prescriptions before the visit (not exceeding 12 months) in which LDL-C levels, as well as other lipid parameters, have been considered.

2.6. Statistical analysis

All data were entered into Microsoft Access for Windows (Microsoft Office, Microsoft Corp, Redmond, Wash). Baseline characteristics of patients are presented as number and percentage for dichotomous variables and mean ± standard deviation (SD) of the mean for continuous variables. Normal distribution of data was assessed using histograms and Kolmogorov-Smirnov test. Differences among continuous variables were assessed using ANOVA test, and adjusted for potential confounding factors, including age, gender, BMI, diabetes, hypertension, CAD, SCORE risk, and presence of lipid-lowering therapy, by adopting univariate general linear model with least square deviation for multiple comparisons. Categorical variables were compared among groups by the chi-square test. To evaluate the significance of predictors

of LDL-C control, odds ratios (OR) and 95% confidence intervals (CI) were derived from two logistic regression models (Model 1 and Model 2). Both multivariate models were fitted with baseline covariates associated with LDL-C control by univariate analysis at the 0.1 significance level. Lipid-lowering therapy entered as continuous variable (number of lipid lowering drugs) in Model 1 and as categorical variable (presence/absence of lipid lowering therapy) in Model 2. For this analysis the following definitions for LDL-C control (proportions of patients within predefined outcomes) have been applied: 1) LDL-C < 100 mg/dl in high CV risk individuals and < 70 mg/dl in very high CV risk individuals in primary prevention; 2) LDL-C < 70 mg/dl in patients in secondary prevention. Models were applied to those patients in primary prevention who had valid clinical data for calculating risk SCORE equation. All tests were two-sided, and a p value of less than 0.05 was considered statistically significant. All calculations were generated using SPSS, version 20.0 (SPSS Inc., Chicago, Illinois).

3. Results

3.1. Study population

From an overall sample of 16,645 individuals included in the original database, we selected 4,142 (24.9%) adult outpatients (43,7% female, age 58.0 ± 5.2 years, BMI 28.5 ± 5.0 kg/m^2) with valid C-LDL data and within predefined age criteria. Selection criteria and flowchart for the study population are illustrated in Supplementary Fig. 1. Included patients were stratified as follows: 2,964 (71.6%) patients in primary prevention (group 1) and 1,178 (28.4%) in secondary prevention (group 2). The vast majority of patients (about 70%) were followed by GPs. Proportions of patients followed by cardiologists were significantly higher in the setting of secondary compared to that of prevention ($p < 0.001$), whilst there was no significant difference between groups regarding number of patients followed by diabetologists.

All variables requested by the risk SCORE equation were available in 2,800 patients (94.5% of patients in primary prevention). In this setting, 645 (21.8%) outpatients were at low risk (group A), 753 (59.1%) at moderate risk (group B), 349 (11.8%) at high risk (group C) and 53 (1.8%) at very high risk (group D). In the setting of secondary prevention, 693 (58.8%) patients had CAD, 194 (16.5%) had PAD, and 86 (7.3%) had CVD, while the remaining proportion of patients (17.3%) had at least one of the predefined CV events.

General characteristics of the study population are reported in Table 1. Patients in secondary prevention were significantly older ($p < 0.001$) and more frequently male ($p < 0.001$) than those in primary prevention. With regard to clinical parameters, BMI ($p = 0.022$) and systolic BP levels ($p = 0.045$) resulted significantly higher in the former than in the latter group, whereas no significant differences were found for diastolic BP levels. Fasting glucose and HbA1c were significantly higher in patients in secondary compared to those in primary prevention ($p < 0.001$). As expected, all major CV risk factors, including smoking, hypertension, dyslipidaemia and diabetes, resulted significantly more frequent in secondary compared to primary prevention patients ($p < 0.001$). CKD showed a similar distribution between tested groups ($p = 0.076$).

Distribution of drug therapies between groups is also reported in Table 1. Patients in secondary prevention were more frequently treated with BP and glucose lowering drugs, as well as with antiplatelet agents compared to those in primary prevention ($p < 0.001$). They were also more frequently treated with lipid-lowering therapy ($p < 0.001$), mostly including statins ($p < 0.001$), omega3 ($p = 0.001$) and ezetimibe ($p = 0.001$) compared to those in primary prevention. In addition, they received significantly more lipid-lowering drugs compared to control group ($p < 0.001$). In particular, proportions of patients on monotherapy (36.1% vs 53.9%; $p < 0.001$) and on dual combination therapy (5.8% vs. 21.6%; $p < 0.001$) were significantly higher in patients in secondary prevention compared to those in primary prevention, whilst only a minority of the patients (0.3%) received triple combination therapy for lipid lowering strategy in both groups.

3.2. Lipid levels and control

In primary prevention, 15.8% of patients had LDL-C below 100 mg/dl, whereas only 5.8% of patients in secondary prevention had LDL-C below 70 mg/dl (Table 2A). In the subgroup of patients in primary prevention (Table 2B), 8.9% of patients at high CV risk showed LDL-C below 100 mg/dl, and none of the patients at very high CV risk had LDL-C below 70 mg/dl ($p < 0.001$). In the subgroup of patients in secondary prevention (Table 2C), only 6.5% of patients with CAD, 2.6% of patients with PAD and 4.7% of patients with CVD had LDL-C on target ($p < 0.001$).

Similar distributions have been observed even after selecting those patients under lipid-lowering therapies (data not shown). In the setting of primary prevention, 10.1% and 3.6% of patients on monotherapy and 11.6% and 3.5% of patients on dual combination therapies achieved the LDL-C goals of less than 100 mg/dl and 70 mg/dl, respectively. In the setting of secondary prevention, 5.5% of patients on monotherapy and 9.0% of patients on dual combination therapies achieved the recommended LDL-C target of less than 70 mg/dl,

Table 1
General characteristics of the study population stratified in either primary or secondary prevention.

Parameters	Primary prevention	Secondary prevention	p value
Outpatients (%)	2,964 (71.6)	1,178 (28.4)	–
Female (%)	1451 (49.1)	361 (30.7)	< 0.001
Age (years)	57.6 ± 5.2	58.9 ± 4.9	< 0.001
BMI (kg/m^2)	28.4 ± 5.0	28.8 ± 4.9	0.022
Fx CVD	866 (29.2)	486 (41.3)	< 0.001
Smoking (%)	1,125 (38.0)	523 (44.4)	< 0.001
Hypertension (%)	1,860 (62.8)	906 (76.9)	< 0.001
Dyslipidaemia (%)	1,472 (49.7)	835 (70.9)	< 0.001
Diabetes (%)	957 (32.3)	539 (45.8)	< 0.001
Systolic BP (mmHg)	135.3 ± 14.0	136.3 ± 14.8	0.045
Diastolic BP (mmHg)	82.0 ± 8.0	81.7 ± 8.2	0.341
Glucose (mg/dl)	118.5 ± 40.9	130.0 ± 48.2	< 0.001
HbA1c (%)	7.0 ± 1.4	7.3 ± 1.6	< 0.001
Creatinine (mg/dl)	0.9 ± 0.2	1.0 ± 0.3	< 0.001
eGFR (mg/ml/1.73 m^2)	92.9 ± 43.0	90.1 ± 59.3	0.172
TOT-C (mg/dl)	215.3 ± 39.8	207.1 ± 42.8	< 0.001
LDL-C (mg/dl)	134.7 ± 38.8	128.3 ± 39.6	< 0.001
HDL-C (mg/dl)	51.7 ± 13.0	48.6 ± 12.5	< 0.001
Triglycerides (mg/dl)	158.1 ± 77.6	165.1 ± 92.8	0.021
GPs (%)	2,217 (74.8)	806 (68.4)	< 0.001
Cardiologists (%)	244 (8.6)	177 (15.0)	< 0.001
Diabetologists (%)			
BP lowering Tx (%)	1,968 (66.4)	1,074 (91.2)	< 0.001
Glucose lowering Tx (%)	898 (30.3)	483 (41.0)	< 0.001
Antiplatelet Tx (%)	727 (24.5)	919 (78.0)	< 0.001
Dyslipidaemia Tx (%)	1,248 (42.1)	897 (76.1)	< 0.001
Statins (%)	1,111 (37.5)	838 (71.1)	< 0.001
Ezetimibe (%)	48 (1.6)	39 (3.3)	0.001
Fibrates (%)	65 (2.2)	23 (2.0)	0.628
Omega3 (%)	199 (6.7)	258 (21.9)	< 0.001
Other drugs (%)	54 (1.8)	29 (2.5)	0.185
Average drugs (n)	0.48 ± 0.6	0.99 ± 0.7	< 0.001

BMI, body mass index; Fx CVD, family history for cardiovascular disease; BP, blood pressure; HbA1c, glycosylated haemoglobin; eGFR, estimated glomerular filtration rate; TOT-C, total cholesterol; LDL-C, low density lipoprotein cholesterol; HDL-C, high density lipoprotein cholesterol; GPs, general practitioners; Tx, therapy.

Table 2
Distribution of patients according to LDL-C therapeutic goals in the overall population (A), and in patients in either primary (B) or secondary prevention (C).

A

Parameters	Primary prevention	Secondary prevention	*p* value
LDL-C ≥115 mg/dl	2006 (67.7)	742 (63.0)	< 0.001
LDL-C < 115 mg/dl	489 (16.5)	181 (15.4)	
LDL-C < 100 mg/dl	385 (13.0)	187 (15.9)	
LDL-C < 70 mg/dl	84 (2.8)	68 (5.8)	

B

Parameters	SCORE < 1%	SCORE ≥1- < 5%	SCORE ≥5- < 10%	SCORE ≥10%	*p* value
LDL-C ≥115 mg/dl	348 (54.0)	1,216 (69.4)	271 (77.7)	49 (92.5)	< 0.001
LDL-C < 115 mg/dl	145 (22.5)	277 (15.8)	47 (13.5)	2 (3.8)	
LDL-C < 100 mg/dl	118 (18.3)	217 (12.4)	29 (8.3)	2 (3.8)	
LDL-C < 70 mg/dl	34 (5.3)	43 (2.5)	2 (0.6)	0 (0.0)	

C

Parameters	CAD	PAD	CVD	*p* value
LDL-C ≥115 mg/dl	422 (60.9)	136 (70.1)	60 (69.8)	< 0.001
LDL-C < 115 mg/dl	110 (15.9)	25 (12.9)	10 (11.6)	
LDL-C < 100 mg/dl	116 (16.7)	28 (14.4)	12 (14.0)	
LDL-C < 70 mg/dl	45 (6.5)	5 (2.6)	4 (4.7)	

LDL-C, low density lipoprotein cholesterol; CAD, coronary artery disease; PAD, peripheral artery disease; CVD, cerebrovascular disease.

respectively. In both conditions, only few patients were on triple combination therapy. In primary prevention, 9.8% of those patients with SCORE ≥5% - < 10% had LDL-C less than 100 mg/dl, whilst none of the treated patients with SCORE ≥10% had LDL-C less than 70 mg/dl. Of note, in secondary prevention none of the treated patients showed LDL-C less than 70 mg/dl and only 17.8% had LDL-C less than 100 mg/dl.

In the overall population, both TOT-C ($p < 0.001$) and LDL-C ($p < 0.001$) were significantly higher in patients in primary compared to those in secondary prevention, even after correction for potentially confounding factors, including age, gender, BMI, diabetes and lipid-lowering therapy. Conversely, triglycerides were significantly higher in secondary prevention compared to primary prevention ($p < 0.001$), even after corrections for the same covariates ($p = 0.032$). HDL-C were significantly higher in patients in primary prevention compared to those in secondary prevention ($p < 0.001$), though this difference was not statistically significant after correction for covariates ($p = 0.078$)

Average lipid levels are illustrated in Fig. 1 for patients in primary prevention, in Fig. 2 for patients in secondary prevention and in Fig. 3 for diabetic patients in both primary and secondary prevention. In the first group, TOT-C levels showed a significant trend toward reduction from group at very high SCORE risk to group at low SCORE risk ($p < 0.001$). Both LDL-C and triglycerides levels were significantly higher in groups D and C compared to groups A and B ($p < 0.001$), whereas opposite results were observed for HDL cholesterol levels ($p < 0.001$). In the second group, TOT-C ($p < 0.001$) and LDL-C ($p = 0.035$) were significantly lower in patients with CAD compared to other groups. Finally, in diabetic patients, TOT-C and LDL-C resulted significantly higher in patients in primary prevention compared to those in secondary prevention ($p < 0.001$), whilst significant

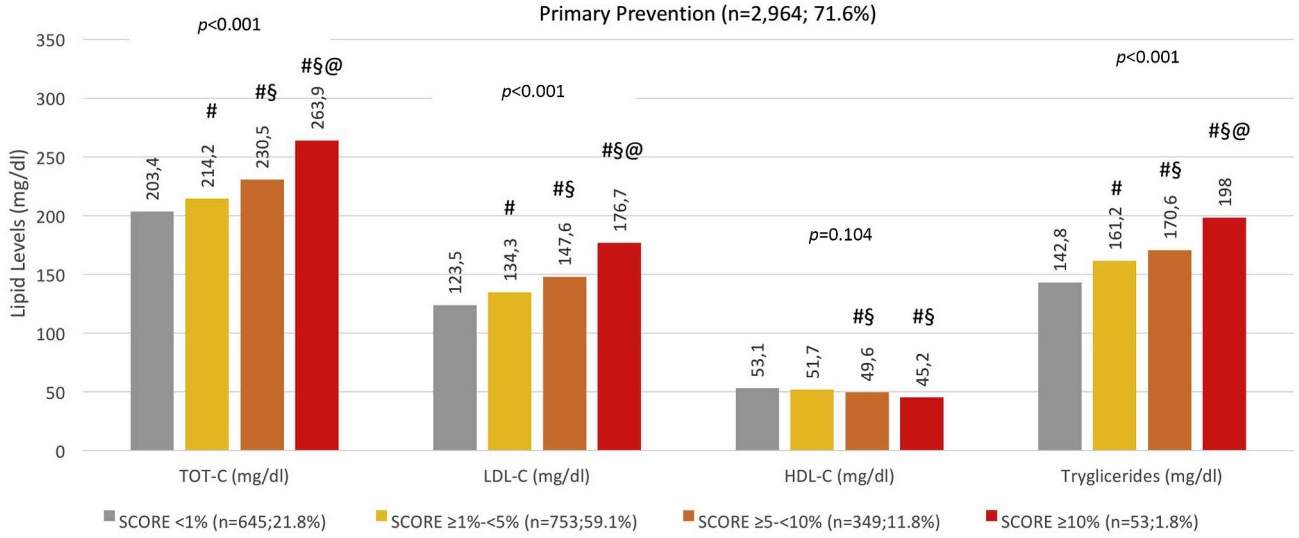

Fig. 1. Average levels of TOT-C, LDL-C, HDL-C and triglycerides among different risk SCORE strata in patients in primary prevention.
All variables requested by the risk SCORE equation were available in 2,800 patients (94.5% of patients in primary prevention). Significant differences among groups have been adjusted for age, gender, body mass index, diabetes, and lipid-lowering therapy. TOT-C, total cholesterol; LDL-C, low density lipoprotein cholesterol; HDL-C, high density lipoprotein cholesterol. #$p < 0.001$ *vs.* SCORE < 1%; §$p < 0.001$ *vs.* SCORE ≥1%- < 5%; @ $p < 0.001$ *vs.* SCORE ≥5%- < 10%.

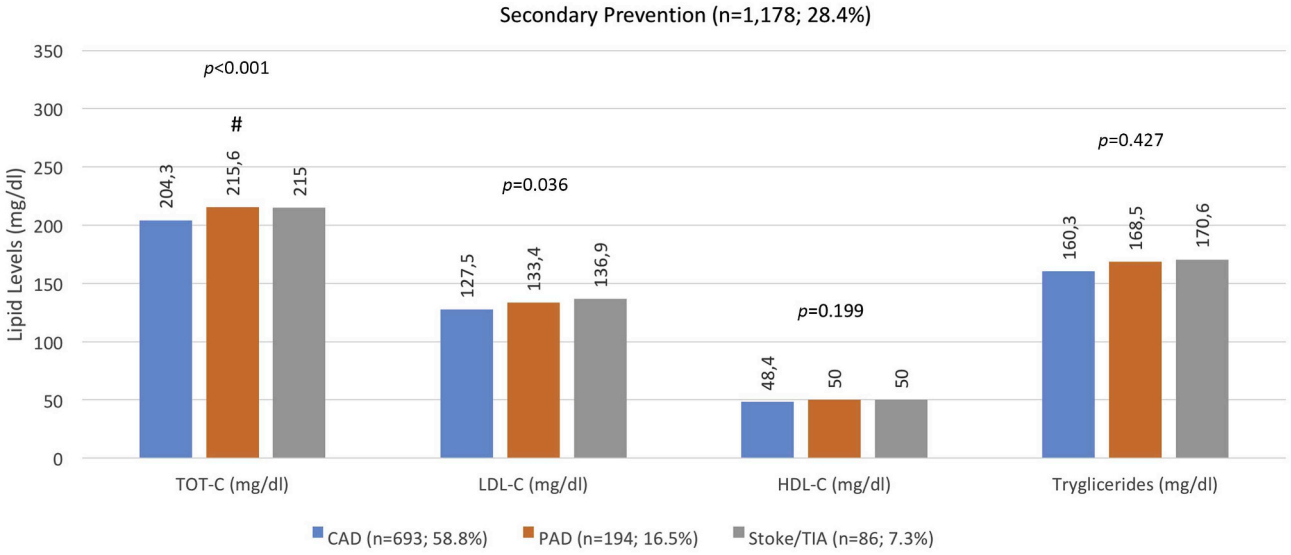

Fig. 2. Average levels of TOT-C, LDL-C, HDL-C and triglycerides among different subgroups of patients in secondary prevention.
Significant differences among groups have been adjusted for age, gender, body mass index, diabetes, and lipid-lowering therapy. TOT-C, total cholesterol; LDL-C, low density lipoprotein cholesterol; HDL-C, high density lipoprotein cholesterol.#$p < 0.001$ *vs.* CAD; §$p < 0.001$ *vs.* PAD; @ $p < 0.001$ *vs.* CVD.

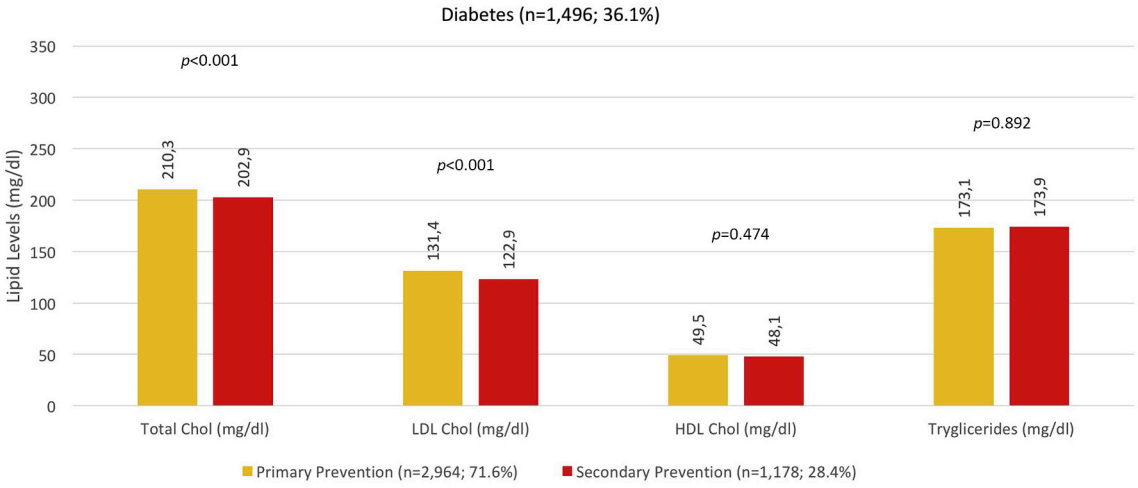

Fig. 3. Average levels of TOT-C, LDL-C, HDL-C and triglycerides among diabetic patients in either primary or secondary prevention.
Significant differences among groups have been adjusted for age, gender, body mass index, diabetes, and lipid-lowering therapy. TOT-C, total cholesterol; LDL-C, low density lipoprotein cholesterol; HDL-C, high density lipoprotein cholesterol.#$p < 0.001$ *vs.* CAD; §$p < 0.001$ *vs.* PAD; @ $p < 0.001$ *vs.* CVD.

differences were found for HDL-C and triglycerides levels in this group.

Correlations between European SCORE estimations and lipid levels are shown in Supplementary Fig. 2. In primary prevention patients, significant positive correlations were found with C-LDL ($r = 0.24$; $p < 0.001$), and triglycerides ($r = 0.14$; $p < 0.001$), whereas inverse significant correlation was found between European SCORE estimations and C-HDL ($r = -0.10$; $p < 0.001$). Similar findings have been observed after selecting diabetic patients in primary prevention for C-LDL ($r = 0.26$; $p < 0.001$), and triglycerides ($r = 0.07$; $p = 0.029$); no significant correlation was found for C-HDL ($r = -0.05$; $p = 0.134$) in this diabetic subgroup.

3.3. Univariate and multivariate analyses

These analyses for predicting the achievement of predefined LDL-C goals are reported in Table 3A (LDL-C below 100 mg/dl) and Table 3B (LDL-C below 70 mg/dl) for patients in primary prevention and in Table 3C (LDL-C below 70 mg/dl) in patients in secondary prevention. In the setting of primary prevention, presence of diabetes and hypertension resulted predictive factors for LDL-C < 100 mg/dl, although only diabetes maintained an independent role at multivariate analysis [OR 1.76 (95% CI: 1.42–2.19); $p < 0.001$]. Similar findings were observed for the LDL-C < 70 mg/dl, with diabetes having an independent predictive role for this LDL-C threshold [OR 2.36 (95% CI: 1.39–3.99); $p = 0.001$]. On the other hand, high risk SCORE estimation resulted a strong and independent predictor for the lack of achieving the predefined therapeutic targets, including LDL-C < 100 mg/dl [OR: 0.81 (95% CI: 0.75–0.86); $p < 0.001$], and LDL-C < 70 mg/dl [OR: 0.71 (95% CI: 0-58-0.88); $p < 0.002$]. Also lipid lowering therapy resulted an independent predictor for the lack of achieving the predefined therapeutic target of LDL-C < 100 mg/dl, in both models of multivariate analysis, although this was not observed for the therapeutic target of LDL-C < 70 mg/dl. In the setting of secondary prevention, diabetes, CAD and number of lipid lowering drugs resulted predictive factors for achieving LDL-C < 70 mg/dl, with diabetes having as the most powerful and independent role at multivariate analysis.

Table 3
Univariate and multivariate analyses for the risk of having predefined LDL-C therapeutic goals, including LDL-C < 100 mg/dl (A), and LDL-C < 70 mg/dl (B) for patients in primary prevention, and LDL-C < 70 mg/dl (C) for patients in secondary prevention. Presence of lipid-lowering therapy entered either as categorical variable (presence of lipid-lowering drugs) in Model 1, or as continuous variable (number of lipid-lowering drugs) in Model 2.

	Univariate analysis		Multivariate analysis			
	OR (95% CI)	*p* value	Model 1		Model 2	
			OR (95% CI)	*p* value	OR (95% CI)	*p* value
A						
Age	0.98 (0.96–1.00)	0.032	1.02 (0.99–1.04)	0.147	1.02 (0.99–1.04)	0.158
BMI	0.99 (0.97–1.02)	0.587	–	–	–	–
Female	0.95 (0.78–1.16)	0.647	–	–	–	–
Diabetes	1.55 (1.27–1.90)	< 0.001	1.76 (1.42–2.19)	< 0.001	1.76 (1.42–2.19)	< 0.001
Hypertension	0.74 (0.61–0.90)	0.003	0.84 (0.68–1.04)	0.115	0.82 (0.68–1.04)	0.106
SCORE	0.82 (0.78–0.87)	< 0.001	0.81 (0.75–0.86)	< 0.001	0.81 (0.75–0.86)	< 0.001
Dyslipidaemia Tx (Y/N)	0.77 (0.63–0.95)	0.013	0.77 (0.62–0.97)	0.023	–	–
Dyslipidaemia Tx (num)	0.82 (0.70–0.97)	0.023	–	–	0.82 (0.68–0.97)	0.025
B						
Age	0.94 (0.90–0.97)	0.001	1.00 (0.95–1.05)	0.913	1.00 (0.95–1.05)	0.925
BMI	1.05 (1.00–1.09)	0.030	1.03 (0.99–1.08)	0.177	1.03 (0.99–1.08)	0.150
Female	1.06 (0.69–1.64)	0.778	–	–	–	–
Diabetes	2.37 (1.53–3.66)	< 0.001	2.36 (1.39–3.99)	0.001	2.36 (1.41–4.06)	0.001
Hypertension	1.01 (0.65–1.59)	0.948	–	–	–	–
SCORE	0.70 (0.60–0.83)	< 0.001	0.71 (0-58-0.88)	0.002	0.71 (0-58-0.88)	0.002
Dyslipidaemia Tx (Y/N)	1.61 (1.04–2.48)	0.032	1.50 (0.90–2.52)	0.119	–	–
Dyslipidaemia Tx (num)	1.36 (0.98–1.88)	0.064	–	–	1.27 (0.87–1.86)	0.220
C						
Age	1.01 (0.96–1.06)	0.815	–	–	–	–
BMI	1.02 (0.97–1.07)	0.414	–	–	–	–
Female	1.35 (0.77–2.37)	0.298	–	–	–	–
Diabetes	3.05 (1.77–5.17)	< 0.001	3.26 (1.90–5.59)	< 0.001	3.38 (1.96–5.80)	< 0.001
Hypertension	1.06 (0.59–1.92)	0.835	–	–	–	–
CAD	2.38 (1.17–4.87)	0.017	2.73 (1.33–5.61)	0.006	2.49 (1.21–5.15)	0.014
CVD	1.02 (0.52–1.98)	0.960	–	–	–	–
PAD	0.72 (0.41–1.27)	0.721	–	–	–	–
Dyslipidaemia Tx (Y/N)	1.87 (0.94–3.72)	0.072	–	–	–	–
Dyslipidaemia Tx (num)	1.56 (1.09–2.22)	0.014	–	–	1.53 (1.06–2.21)	0.024

BMI, body mass index; CAD, coronary artery disease; PAD, peripheral artery disease; CVD, cerebrovascular disease; Tx, therapy.

4. Discussion

Dyslipidaemia is one of the most common CV risk factor at global level, heavily affecting the risk of developing major CV outcomes, mostly CAD and coronary procedures. Several independent observational studies and clinical surveys [3,4] have shown high prevalence and relatively poor control of lipid levels despite the large availability of effective and well-tolerated lipid lowering strategies. The same studies, however, included either patients in secondary prevention [4] or otherwise healthy individuals mostly followed by GPs [3].

Our analysis of a larger cohort of adult outpatients in a setting of both primary and secondary CV prevention confirmed that despite the use of lipid lowering drugs and recommendations for adopting favourable life-style measures, high or very high SCORE risk individuals had relatively poor control rates of LDL-C levels. In particular, in primary prevention, none of the patients at very high CV risk had LDL-C below 70 mg/dl and less than 9% of patients at high CV risk showed LDL-C below 100 mg/dl, as recommended by current European guidelines [28,29]. At the same time, only 6.5% of patients with CAD, 2.6% of patients with PAD and 4.7% of patients with CVD had LDL-C within the recommended therapeutic target of less than 70 mg/dl for secondary prevention outpatients.

Several explanations might be proposed to try to explain these findings, among which probably the most appropriate one is the relatively insufficient use of lipid lowering drugs applied in our population sample, both in monotherapy and in combination therapies (average drug number of 0.5 in primary prevention and 1.0 in secondary prevention), as well as in other clinical studies [30]. Furthermore, at the time of collection data most of the fixed combination therapies were not available. In this regard, evidence from recent randomized clinical trials have consistently demonstrated the beneficial effects of integrated lipid lowering therapies based on the concomitant use of statins plus either ezetimibe [31,32] or the PCSK9 inhibitors alirocumab [33] or evolocumab [34]. Of note, these beneficial effects have been observed also in the presence of more intensive LDL-C reductions in very high risk patients who were effectively treated with statin therapy. In the Improved Reduction of Outcomes: Vytorin Efficacy-International Trial (IMPROVE-IT) [32] combination therapy of ezetimibe 10 mg plus simvastatin 40 mg significantly reduced the incidence of the primary composite CV outcome compared with monotherapy based on simvastatin 40 mg in very high risk patients who were hospitalized for an acute coronary syndrome and had LDL-C within the recommended therapeutic targets of 50–100 mg/dl (1.3–2.6 mmol/lt). More recently, the Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk (FOURIER) trial [34] demonstrated that the addition of the PCSK9 inhibitor evolocumab to statin therapy significantly reduced CV morbidity and mortality by reducing LDL-C from a median of 92 to 30 mg/dl. On the basis of these results, both Italian [35] and European [28,29] guidelines have strongly supported the use of combination therapies for effective clinical management of adult outpatients with hypercholesterolemia, particularly in the presence of high or very high SCORE risk profile or comorbidities. Another aspect that should be taken in consideration is the potential impact on adherence to prescribed drug therapies, mostly lipid lowering therapies. A recent observational study has demonstrated a notable improvement in LDL-C control when considering some adherence measure, like the so-called proportion of days covered [36], as described also in other reports [37–39]. At the same time, reasons for explaining the significantly different values of both TOT-C and LDL-C levels between primary and secondary prevention might be related to other, non-pharmacological

interventions that can be applied in these very high CV risk patients, such as dietary attention, physical activities, and balanced diet. Finally, other potential explanation of the poor control of LDL-C observed in our analysis may be the fact that data collection has been ruled out about ten years ago. Even if therapeutic thresholds for LDL-C have had minor changes over time along different sets of guidelines [40,41], it cannot be excluded that at the time of the observation enrolled physicians were not aware of the most recent evidence from the above mentioned randomized controlled clinical trials supporting the achievement of more ambitious LDL-C targets.

Whatever the case, our findings reinforce the recommendations from current guidelines [28,29] for adopting proper global CV risk stratification and tailoring lipid-lowering therapies to individual characteristics, in order to improve the overall rates of control of LDL-C and reduce the burden of CV diseases related to treated uncontrolled dyslipidaemia. In fact, one of the most relevant aspect of our analysis was the observation that the presence of diabetes and CAD had a highly significant and independent predictive role for the achievement of the recommended LDL-C therapeutic goals, whereas the use of lipid lowering therapy seems to have limited role, probably due to undertreatment. Diabetes has generally been considered a “CV risk equivalent”, since diabetic patients without CAD events showed a similar coronary mortality as non-diabetic patients who had a previous coronary event. These arguments led European guidelines to recommend patients with diabetes to be treated as a separate high-risk category, with no need for stratification [27]. Indeed, we observed significantly higher LDL-C levels in diabetic patients in primary prevention compared to those in secondary prevention, even after correction for lipid-lowering therapies. This may support an independent role for diabetes in CAD risk, which is not similar to the risk of patients with prior CV disease.

On the other hand, high risk SCORE estimations showed a strong and independent negative predictor role for the achievement of all predefined therapeutic targets in the setting of primary prevention. This may suggest at least, in part, that Italian physicians paid more attention to achieve the recommended therapeutic goals in adult outpatients with clinically evident atherosclerotic diseases (namely in secondary prevention), whereas they do not use adequate lipid-lowering therapies in high or very high CV risk patients according to risk SCORE equation in the setting of primary prevention.

Several studies have demonstrated that treating otherwise healthy individuals with dyslipidaemia is a cost-effectiveness approach for reducing the persistently high burden of disease related to uncontrolled dyslipidaemia. Indeed, the benefits of combined lipid-lowering therapies were further enhanced in high or very high risk patients with or without diabetes, thus suggesting the importance of personalized therapeutic strategy for achieving the recommended therapeutic goals. Novel treatment options have been also explored and are now available for the clinical management of hypercholesteraemic patients with favourable efficacy and safety profile [42].

4.1. Potential limitations

The present study has some potential limitations that should be acknowledged. First of all, it is based on a large, descriptive survey performed in 2006. During recent years, the approach to cholesterol management in the contest of CV prevention has profoundly changed and new drugs, as well as new combination therapies have been made available for treating patients with dyslipidaemia. Despite these therapeutic improvements, however, recent studies confirmed the poor achievement of the recommended lipid goals in the setting of clinical practice [43], as observed in our survey. Secondly, SCORE risk stratification was available in 2,800 individuals without overt CV diseases, which represented 94.5% of patients in primary prevention. The correlations between lipid factors and SCORE should be considered in the light of the fact that TOT-C is one of the determinants of the risk algorithm. We cannot provide a specific analysis based on the intensity (low/moderate/high potency), as well as on changes of lipid lowering therapies over time, since these data were not available in the database. In addition, recommendations for adopting healthier life style measures were recorded among physicians’ prescriptions, but not among in-use treatment. One of the main limitation is that the data are relatively old, and during recent years the approach to cholesterol management in the contest of CV prevention is probably profoundly changed. Indeed, patients included in the present analysis were consecutively enrolled in 2006. During this period, several sets of guidelines and recommendations from national and international societies for CV prevention have been produced [28,29], often proposing contrasting diagnostic thresholds and therapeutic targets for very high risk patients with comorbidities. However, recent studies confirmed the poor achievement of the lipid goals due to low adherence to guidelines recommendations.

4.2. Conclusions

Data emerged from this analysis of a large cohort of adult outpatients followed in a setting of real practice in Italy showed that, despite the use of lipid lowering drugs and recommendations for adopting favourable life-style measures, poor control rates of LDL-C were observed in high or very high SCORE risk individuals in primary prevention and in very high risk outpatients with comorbidities in secondary prevention. These findings highlight the need of adopting integrated therapeutic approach and improve adherence to a lipid-lowering therapy for ameliorating lipid control and reducing the burden of CV disease in our Country. Further investigations should be performed to confirm the therapeutic gap and to better identify potential causes of poor control rates of LDL-C in Italy.

Conflicts of interest

The authors declared they do not have anything to disclose regarding conflict of interest with respect to this manuscript.

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Appendix A. Supplementary data

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