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# Lipid-lowering therapy in patients with coronary heart disease: an Italian real-life survey. Results from the Survey on Risk FactOrs and CardiovascuLar secondary prEvention and drug strategieS (SOFOCLES) in Italy

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**Abstract**

In patients at high cardiovascular risk, a low-density lipoprotein cholesterol (LDL-C) reduction of 50% from baseline and an LDL-C goal of <70 mg/dL (or <55 mg/dL in very high-risk patients) are recommended. Multiple registry and retrospective studies have shown that patients with high atherosclerotic cardiovascular risk often do not reach the targets defined by the European Society of Cardiology guidelines as a result of suboptimal management of LDL-C. Here, we report the data on lipid-lowering therapy and lipid targets from the Survey on Risk FactOrs and CardiovascuLar secondary prEvention and drug strategieS (SOFOCLES), an observational, prospective study designed to collect data on patients with ischemic heart disease treated at cardiac outpatient clinics across the Italian national territory. We included patients with known coronary heart disease (CHD) who underwent follow-up visits at various outpatient cardiology clinics. A total of 2532 patients were included (mean age: 67±17 years, 80% male). Among patients with available laboratory data (n=1712), 995 (58%) had LDL-C <70 mg/dL, 717 (42%) had LDL-C 70 mg/dL, and 470 (27%) had LDL-C <55 mg/dL. Patients who more frequently achieved the recommended LDL-C levels were male, had diabetes, had a higher educational level, and performed intense physical activity. Statins were used in 2339 (92%) patients, high-intensity statins (*e.g.*, rosuvastatin 20/40 mg or atorvastatin 40/80 mg) in 1547 patients (61% of the whole population and 66% of patients on statins), and ezetimibe in 891 patients (35%). Patients receiving high-intensity statins tended to be younger, not to have diabetes, and to have been included in a cardiac rehabilitation program. In a real-world sample of Italian patients with CHD, adherence to lipid-lowering therapy fell markedly short of optimal levels. Many patients did not achieve the LDL-C target of 70 mg/dL, and even fewer reached the LDL-C target of 55 mg/dL. Notably, patients with a lower educational level had a greater likelihood of being undertreated. Strategies aimed at improving preventive interventions for CHD and overcoming social disparities should be evaluated and optimized.

**Key words**: coronary heart disease, cholesterol, secondary prevention, statin.

Central illustration summarizing the results, clinical implications and future prospectives.

**CENTRAL ILLUSTRATION: Results, clinical implications and future prospectives**

The SOFOCLES survey involved 20 centers (selected based on availability) providing routine outpatient follow-up services, including cardiac rehabilitation (CR), acute cardiac care and outpatient cardiology services. From February 2016 to December 2021, 2532 patients were included (mean age 67±17 years; 80% male).

Statins were used in 2339 (92%) patients, high-intensity statins (e.g., rosuvastatin 20/40 mg or atorvastatin 40/80 mg) in 1547 patients (61% of the whole population and 66% of patients on statins), and ezetimibe in 891 patients (35%). Patients receiving high-intensity statins tended to be younger, not to have diabetes and to have been included in a cardiac rehabilitation program.

In a real-world sample of Italian patients with CHD, adherence to lipid-lowering therapy fell markedly short of optimal levels.


Strategies aimed at improving the implementation of preventive intervention in CHD (overcoming social disparities) should be evaluated and optimized.

## Introduction

Dyslipidemia, characterized by elevated levels of low-density lipoprotein cholesterol (LDL-C), is a major risk factor for Coronary artery disease (CAD) [1,2]. Lipid-lowering therapies play a crucial role in CAD management, aiming at decreasing LDL-C levels and improving cardiovascular outcomes [3]. Furthermore, no threshold is known below which lowering LDL-C is considered beneficial or harmful [4,5].

In the 2016 European Society of Cardiology/European Atherosclerosis Society (ESC/EAS) guidelines, an LDL-C reduction of 50% from baseline and an LDL-C goal <70 mg/dl are recommended [6], whereas in the 2019 ESC/EAS guidelines an LDL-C goal <55 mg/dl is suggested for very high-risk patients [7].

Multiple lipid-lowering agents have shown efficacy in lowering LDL-C and improving outcomes in patients with CAD. Statins, the mainstay of lipid-lowering therapy, have shown consistent benefits in reducing the risk for cardiovascular events and mortality. Large-scale trials [8,9], have provided robust evidence supporting the use of statins in CAD management. Ezetimibe, in combination with statins, incrementally lowers LDL-C levels and improves cardiovascular outcomes [10]. However, in patients at high cardiovascular risk treated with statins and ezetimibe, residual risk remains [11].

The introduction of proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors, a newer class of lipid-lowering agents, has revolutionized the treatment landscape for patients with CAD with persistently high LDL-C levels despite maximal statin therapy [12,13]. Combination therapies, including statins with ezetimibe or PCSK9 inhibitors, have shown additional LDL-C-lowering effects, thus leading to a further decrease in risk.

Inclisiran, a small interfering RNA molecule, is a first-in-class medication that inhibits PCSK9 synthesis. Treatment with inclisiran has been shown to markedly decreases LDL-C [14] but its effects on cardiovascular outcomes have not been established yet.

Bempedoic acid is a novel lipid-lowering agent that acts upstream of statins by inhibiting the enzyme ATP citrate lyase [15]. Recently, treatment with bempedoic acid has been associated with a lower risk of major adverse cardiovascular events in statin-intolerant patients [16].

Despite this evidence, many studies based on registry or retrospective data have shown that patients with high atherosclerotic cardiovascular disease (ASCVD) risk often do not reach the LDL-C targets recommended by the ESC/EAS guidelines and have suboptimal management of LDL-C [17,18].

In the present study, we report the data on lipid-lowering therapies and LDL-C targets recorded in the SOFOCLES survey, an observational study designed to collect data on patients with coronary heart disease (CHD) treated at cardiac outpatient clinics across the Italian national territory.

**Materials and Methods**

The SOFOCLES survey involved 20 centers (selected based on availability) providing routine outpatient follow-up services, including cardiac rehabilitation (CR), acute cardiac care and outpatient cardiology services.

All patients with known CHD who underwent a follow-up visit at various outpatient cardiology clinics were included. The inclusion criteria were: (i) patients with clinical and instrumental evidence of previous acute coronary syndrome and (ii) patients with obstructive CAD with any of the following: (a) previous coronary artery bypass graft (CABG), (b) previous percutaneous coronary intervention ± stenting (bare metal stent, drug-eluting stent, or bio-active stent), or (c) (previous coronary angiography findings of significant stenosis or evidence of ischemia at provocative tests).

According to the 2016 ESC/EAS guidelines, these patients are classified as being at very high cardiovascular risk and should achieve an LDL-C treatment goal of <70 mg/dl and/or a reduction of LDL-C  50% from baseline.

Patients with one or more of the above clinical conditions were eligible for enrollment if the minimum length of time from the index event was  3 months, and the maximum length of time was <5 years from the index event or initial diagnosis.

All patients provided signed informed consent. The study was approved by the relevant ethics committees.

The following variables were recorded: sex, age, history of diabetes, hypertension, smoking status, obesity, physical activity (none, mild, or intense), educational level (none or primary school, secondary school, high school, or bachelor's degree), heart rate, systolic blood pressure, diastolic blood pressure, height, weight, waist circumference and medical therapy. Statin therapy was grouped into high-intensity (atorvastatin 40/80 mg or rosuvastatin 20/40 mg) or low-to-moderate intensity according to the 2013 American College of Cardiology/American Heart Association (ACC/AHA) guidelines [19].

Patients were asked to provide their most recent laboratory values of total cholesterol, LDL-C, high-density lipoprotein cholesterol, blood glucose and triglycerides; only laboratory results obtained in the previous 12 months were considered.

### *Statistical analysis*

Continuous variables are reported as mean and standard deviation, and categorical variables are reported as numbers and percentages. An unpaired *t*-test was used to compare differences in continuous variables, and a chi-squared test was used to compare differences in categorical variables. A p-value <0.05 was considered statistically significant.

## Results

### *Study population*

Only patients from centers that completed the study were evaluated. From February 2016 to December 2021, 2532 patients were included (mean age 67±17 years; 80% male). Patient characteristics are reported in Table 1. Among patients with available laboratory data (*n*=1712), 995 (58%) had LDL-C  70 mg/dl and 470 (27%) had LDL-C  55 mg/dl.

A comparison of clinical characteristics between patients who reached or did not reach the LDL-C target of <70 mg/dl is shown in Table 2. Patients who reached the LDL-C target were more frequently male, had diabetes and a higher educational level, and performed intense physical activity.

An LDL-C target of <70 mg/dl was used as recommended by the 2016 ESC/EAS guidelines available at the time when the study was carried out.

***Lipid-lowering therapy***

Statins were used in 2339 (92%) patients. Of 193 patients not on statins, 61 patients had intolerance, 3 patients had contraindications, and no reason was reported for 101 patients. Statin use was as follows : Pravastatin 10 pts (0,42%), Simvastatin 190 pts (8.12%), Atorvastatin 1551 pts (66.3%), Rosuvastatin 570 pts (24.3%), Other statin 18 pts (0.76%), No statin 165 pts (6.56%). High-intensity statins (e.g., rosuvastatin 20/40 mg or atorvastatin 40/80 mg) were used in 1547 patients (61% of the whole population and 66% of patients on statins).

Ezetimibe was used in 891 (35%) patients. Differences between patients with vs without high-intensity statin use are shown in Table 3. Patients on high-intensity statins tended to be younger, not to have diabetes and to have participated in a CR program.

A total of 26 (1.03%) patients were on a PCSK9 inhibitor.

**Discussion**

In the present study, in a large sample of Italian patients with CHD, the target LDL-C levels were achieved in slightly more than half of patients. A substantial proportion of patients (42%) had LDL-C  70 mg/dl. Furthermore, in this Italian cohort, drug treatment was far from optimal in many patients, with 40% of participants not receiving high-intensity treatment despite their high-risk level.

Patients who reached the LDL-C target, compared with those who did not, tended to be male, to have diabetes and no history of dyslipidemia, to perform intense physical activity, and to have a higher educational level.

Some of these data may be explained by the use of high-intensity statins, which were more frequently prescribed to patients with higher levels of physical activity. Furthermore, patients participating in CR programs showed a trend toward better LDL-C control and significantly higher use of high-intensity statins.

Unexpectedly, in patients taking high-intensity vs low/moderate intensity statins, no significant differences in LDL-C levels and number of patients meeting the LDL-C target were observed. This finding might be explained by differences in LD-C levels before therapy initiation: patients taking high-intensity statins might have had higher starting values, thus resulting in large relative decreases after therapy.

A previous report has shown that lipid-lowering treatment is far from optimal in several countries across Europe. In a real-world study from Germany in patients with ASCVD, 43.6% received statin therapy; their mean LDL-C was 117.8 mg/dl, and 8.5% achieved an LDL-C <70 mg/dl [20].

In the EUROASPIRE V study in 7824 hospitalized patients and healthy individuals in primary care at high risk of developing cardiovascular disease, an LDL-C <70 mg/dl was observed in 30% of the study population [17].

In the DA VINCI study, a 188 country cross-sectional observational study of patients treated for primary or secondary prevention across Europe, LDL-C <70 mg/dl was observed in 39% of patients [18]. In the same study, 54% of patients achieved their risk-based goal according to the 2016 ESC/EAS guidelines, and 33% achieved the goals according to the 2019 ESC/EAS guidelines. In secondary prevention, high-intensity statins were used in 38% of patients.

More recently, in the SANTORINI study in participants at high or very high risk of ASCVD treated in different care settings, a treatment gap in LDL-C control was observed between high and very high-risk patients in Europe between 2020 and 2021. The median LDL-C was 78 mg/dl among patients with ASCVD receiving monotherapy or combination therapy, with 20.9% and 32.3% reaching their goals, respectively [21].

In our cohort, the prevalence of patients meeting their target LDL-C levels was higher than previously reported; more frequent use of ezetimibe and the participation of more than half of the study population in CR programs might account for this difference.

A central aspect for the success of secondary prevention programs is the opportunity for access to CR. In fact, a rehabilitation program may successfully improve adherence to evidence-based therapies, leading to a considerable reduction of the risk for cardiovascular events and recurrent infarction. Consequently, according to the AHA/ACC guidelines, comprehensive cardiovascular rehabilitation is a class 1 recommendation for all eligible patients with acute coronary syndrome, and patients immediately after CABG or PCI, either before hospital discharge or during the first follow-up office visit [22].

One hallmark of providing lipid-lowering therapy is matching the ASCVD status or risk to appropriate statin intensity. However, many patients are not treated with an appropriate statin intensity for their cardiovascular risk. Even patients on high-intensity statin therapy failed to reach the recommended LDL-C target, thus confirming the importance of larger implementation of lipid-lowering therapies with PCSK9 inhibitors or bempedoic acid.

Our data also demonstrated the existence of a gap associated with educational level: patients with higher levels of education more often received adequate treatment and more often reached their LDL-C targets.

The SOFOCLES survey, including CR, acute cardiac care and outpatient cardiology services, demonstrated that this gap is unfortunately evident at any level of intensity of care.

Thus, substantial effort should be made to eradicate this disparity in care.

The Effectus Study also demonstrated that exists eterogeity in lipid lowering treatment intensity and discrepancies in clinical management of CV risk in Italy, but its results are obtained only in patients involved in CR programmes [23].

### *Study limitations*

Several limitations should be acknowledged. This study was performed in outpatient offices in a cardiological setting. Our results cannot be generalized to other medical settings or to primary care or internal medicine practices. Laboratory tests were not centralized. Because the intent of the study was to provide a real-world view, patient data from other laboratories in the 12 months before each visit were recorded. The physical activity level was evaluated on an individual basis. Laboratory values were available for 1712/2532 patients; however, the lack of laboratory surveillance in patients at high cardiovascular risk (who did not present any laboratory results during the visit) is in itself an issue that should be addressed and a major limitation of many follow-up programs.

## Conclusions

In a real-world sample of Italian patients with CHD, we found that adherence to lipid-lowering therapy, as indicated by the ESC/EAS guidelines, falls markedly short of optimal levels. Many patients do not achieve the LDL-C target of 70 mg/dl, and even fewer reach the LDL-C target of 55 mg/dl. Consistent with previous reports, our study shows that attainment of the recommended LDL-C goals is unsatisfactory. Therefore, several adverse cardiovascular outcomes are preventable, and patients with lower educational level have greater likelihood of being undertreated. Lipid-lowering therapy plays a crucial role in CAD management by reducing LDL-C levels and improving cardiovascular outcomes. Statins continue to serve as the foundation of therapy, as supported by extensive evidence. Combination therapies and the emergence of PCSK9 inhibitors offer additional options for lowering LDL-C in high-risk patients with CAD. Strategies aimed at improving the implementation of preventive intervention in CHD (overcoming social disparities) should be evaluated and optimized.

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**Table 1. Patient characteristics.**

| | |
|---|---|
| Patients, *n* | 2532 |
| Age (years) | 67±17 |
| Male sex | 2026 (80%) |
| **Cardiovascular disease history** | |
| Stable angina | 313 (12.44%) |
| Unstable angina | 297 (11.80%) |
| STEMI | 984 (39.11%) |
| NSTEMI | 641 (25.48%) |
| CABG | 451 (17%) |
| PCI | 1972 (78%) |
| Unknown | 281 (11.17%) |
| **Medical history** | |
| Diabetes | 673 (26%) |
| Dyslipidemia | 1720 (68%) |
| Hypertension | 1806 (71%) |
| Obesity | 556 (22%) |
| Active smoker | 374 (14%) |
| Former smoker | 1175 (47%) |
| Physical activity (*n*=1749) | |
| None | 725 (41%) |
| Moderate | 860 (49%) |
| Intense | 164 (9%) |
| Cardiac rehabilitation | 1430 (56%) |
| **Clinical features** | |
| Heart rate (bpm) | 65±11 |
| SBP (mmHg) | 127±16 |
| DBP (mmHg) | 75±9 |
| Height (cm) | 168±10 |
| Weight (kg) | 79±15 |
| BMI (kg/m$^2$) | 28±13 |
| Waist circumference (cm) | 99±12 |
| **Laboratory (n=1712)** | |
| Total cholesterol (mg/dl) | 136.2±32 |
| LDL-C (mg/dl) | 70.7±26 |
| 70 mg/dl | 995 (58%) |
| <55 mg/dl | 470 (27%) |
| HDL-C (mg/dl) | 45.8±14 |
| Triglycerides (mg/dl) | 121.7±64 |
| Glycemia (mg/dl) | 111.6±33 |

BMI, body mass index; CABG, coronary artery bypass graft; DBP, diastolic blood pressure; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; NSTEMI, non-STE-elevation myocardial infarction; PCI, percutaneous coronary intervention; SBP, systolic blood pressure; STEMI, ST-elevation myocardial infarction.

**Table 2. Differences between patients who reached or did not reach the LDL-C target of 70 mg/dL.**

| | All | | LDL-C 70 mg/dl | | LDL-C <70 mg/dl | | p-value |
|---|---|---|---|---|---|---|---|
| | N | *n*=1712 | N | *n*=717 | N | *n*=995 | |
| Male sex | 1712 | 1398 (81.7%) | 717 | 553 (77.1%) | 995 | 845 (84.9%) | 0.000* |
| Age (years) | 1712 | 66±11 | 717 | 67±11 | 995 | 66±11 | 0.396§ |
| Diabetes | 1712 | 452 (26.4%) | 717 | 157 (21.9%) | 995 | 295 (29.6%) | 0.000* |
| Dyslipidemia | 1712 | 1217 (71.1%) | 717 | 559 (78.0%) | 995 | 658 (66.1%) | 0.000* |
| Hypertension | 1712 | 1235 (72.1%) | 717 | 525 (73.2%) | 995 | 710 (71.4%) | 0.396* |
| Obesity | 1712 | 415 (24.2%) | 717 | 167 (23.3%) | 995 | 248 (24.9%) | 0.437* |
| Active smoker | 1527 | 805 (52.7%) | 645 | 344 (53.3%) | 882 | 461 (52.3%) | 0.680* |
| Former smoker | 1527 | 262 (17.2%) | 645 | 115 (17.8%) | 882 | 147 (16.7%) | 0.552* |
| Moderate PA | 1229 | 583 (47.4%) | 515 | 230 (44.7%) | 714 | 353 (49.4%) | 0.098* |
| Intense PA | 1229 | 141 (11.5%) | 515 | 30 (5.8%) | 714 | 111 (15.5%) | 0.000* |
| Educational level | | | | | | | |
| None/primary school | 1211 | 246 (20.3%) | 511 | 124 (24.3%) | 700 | 122 (17.4%) | 0.003* |
| Secondary school | 1211 | 413 (34.1%) | 511 | 175 (34.2%) | 700 | 238 (34.0%) | 0.929* |
| High school | 1211 | 455 (37.6%) | 511 | 185 (36.2%) | 700 | 270 (38.6%) | 0.401* |
| Bachelor's degree | 1211 | 97 (8.0%) | 511 | 27 (5.3%) | 700 | 70 (10.0%) | 0.003* |
| Cardiac rehabilitation | 1492 | 997 (66.8%) | 621 | 399 (64.3%) | 871 | 598 (68.7%) | 0.075* |
| Heart rate (bpm) | 1678 | 65±11 | 699 | 66±12 | 979 | 65±11 | 0.198§ |
| SBP (mmHg) | 1678 | 128±16 | 704 | 128±16 | 974 | 127±16 | 0.372§ |
| DBP (mmHg) | 1678 | 76±9 | 704 | 76±9 | 974 | 76±9 | 0.437§ |
| Weight (kg) | 1535 | 80±14 | 634 | 79±14 | 901 | 80±14 | 0.360§ |
| Waist circumference (cm) | 738 | 100±12 | 260 | 100±12 | 478 | 100±12 | 0.685§ |
| BMI ($kg/m^2$) | 1498 | 27.7±4.3 | 614 | 27.8±4.3 | 884 | 27.7±4.4 | 0.503§ |

BMI, body mass index; DBP, diastolic blood pressure; LDL-C, low-density lipoprotein cholesterol; PA, physical activity; SBP, systolic blood pressure; *Chi-squared test; §ANOVA.

**Table 3. Differences between patients on high vs low-to-moderate intensity statin.**

| | All | | High-intensity statin | | Low-to-moderate intensity statin | | p-value |
|---|---|---|---|---|---|---|---|
| | N | *n*=2339 | N | *n*=792 | N | *n*=1547 | |
| Male sex | 2339 | 1898 (81.1%) | 792 | 630 (79.5%) | 1547 | 1268 (82.0%) | 0.157* |
| Age | 2339 | 67±11 | 792 | 69±11 | 1547 | 66±11 | 0.000§ |
| Diabetes | 2339 | 623 (26.6%) | 792 | 239 (30.2%) | 1547 | 384 (24.8%) | 0.006* |
| Dyslipidemia | 2339 | 1609 (68.8%) | 792 | 551 (69.6%) | 1547 | 1058 (68.4%) | 0.560* |
| Hypertension | 2339 | 1690 (72.3%) | 792 | 603 (76.1%) | 1547 | 1087 (70.3%) | 0.003* |
| Obesity | 2339 | 523 (22.4%) | 792 | 174 (22.0%) | 1547 | 349 (22.6%) | 0.746* |
| Former smoker | 2040 | 348 (17.1%) | 670 | 73 (10.9%) | 1370 | 275 (20.1%) | 0.000* |
| Current smoker | 2040 | 1091 (53.5%) | 670 | 375 (56.0%) | 1370 | 716 (52.3%) | 0.115* |
| Moderate PA | 1631 | 830 (50.9%) | 528 | 273 (51.7%) | 1103 | 557 (50.5%) | 0.649* |
| Intense PA | 1631 | 161 (9.9%) | 528 | 38 (7.2%) | 1103 | 123 (11.2%) | 0.012* |
| Educational level | | | | | | | |
| None/primary school | 1626 | 373 (22.9%) | 534 | 133 (24.9%) | 1092 | 240 (22.0%) | 0.187* |
| Secondary school | 1626 | 557 (34.3%) | 534 | 174 (32.6%) | 1092 | 383 (35.1%) | 0.321* |
| High school | 1626 | 568 (34.9%) | 534 | 185 (34.6%) | 1092 | 383 (35.1%) | 0.865* |
| Bachelor's degree | 1626 | 128 (7.9%) | 534 | 42 (7.9%) | 1092 | 86 (7.9%) | 0.994* |
| Cardiac rehabilitation | 2000 | 1328 (66.4%) | 670 | 421 (62.8%) | 1330 | 907 (68.2%) | 0.017* |
| Heart rate (bpm) | 2262 | 65±11 | 764 | 66±12 | 1498 | 65±11 | 0.129§ |
| SBP (mmHg) | 2268 | 128±16 | 764 | 129±16 | 1504 | 127±16 | 0.029§ |
| DBP (mmHg) | 2268 | 75±9 | 764 | 76±9 | 1504 | 75±9 | 0.020§ |
| Weight (kg) | 2062 | 79±15 | 686 | 79±15 | 1376 | 79±14 | 0.493§ |
| Waist circumference (cm) | 993 | 100±12 | 297 | 100±12 | 696 | 100±12 | 0.842§ |
| BMI ($kg/m^2$) | 2009 | 27.5±4.3 | 676 | 27.5±4.4 | 1333 | 27.6±4.3 | 0.646§ |
| LDL-C (mg/dl) | 1592 | 69±25 | 548 | 71±26 | 1044 | 68±24 | 0.063§ |
| LDL-C <70 mg/dl | 1592 | 959 (60.2%) | 548 | 313 (57.1%) | 1044 | 646 (61.9%) | 0.065* |

BMI, body mass index; DBP, diastolic blood pressure; LDL-C, low-density lipoprotein cholesterol; PA, physical activity; SBP, systolic blood pressure; *Chi-squared test; §ANOVA.