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Current lipid lowering treatment and attainment of LDL targets recommended by ESC/EAS guidelines in very high-risk patients with established atherosclerotic cardiovascular disease: Insights from the START registry

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ABSTRACT

Background: Current European Society of Cardiology (ESC)/European Atherosclerosis Society (EAS) guidelines for the management of dyslipidemias have further reduced low density lipoprotein-cholesterol (LDL-C) targets, as compared to the guidelines released in 2016. These targets are particularly restraining for patients at very high risk (VHR).

Methods: Using the data from a nationwide, prospective registry on patients with established atherosclerotic cardiovascular disease (ASCVD), we sought to assess: 1) the contemporary use of conventional cholesterol-lowering therapies and the achievement of LDL-C goals according to previous and current ESC guidelines in subjects at VHR; 2) the proportion of VHR patients potentially eligible for proprotein convertase subtilisin/kexin type 9 inhibitor (PCSK9i) treatment.

Results: Among the 5053 patients with data available, 4751 (94.0%) were deemed as VHR. Among these patients, the mean LDL-C levels were 62.4 ± 47.7 mg/dl at enrollment. A high dose of statin was used in 54.9%, while the association of high dose statin and ezetimibe was prescribed in 4.8% of VHR patients. A target level of LDL-C < 70 mg/dl recommended by 2016 ESC guidelines was reached by 58.1%, while a target of <55 mg/dl and LDL-C reduction ≥50% recommended by 2019 ESC guidelines, would be reached by 3.2% of patients at VHR. Accordingly, 9.4% and 1.4% of VHR patients would be eligible for PCSK9i according to ESC guidelines and Italian regulations, respectively.

Conclusions: In VHR patients enrolled in this large cohort of established ASCVD managed by cardiologists, the lipid management and LDL-C targets attainment is largely suboptimal.

1. Introduction

Current European Society of Cardiology (ESC)/European Atherosclerosis Society (EAS) Guidelines on the management of dyslipidemias that have recently been released have further reduced low density lipoprotein-cholesterol (LDL-C) targets [1] as compared to the previous edition of ESC/EAS guidelines released in 2016 [2]. Indeed, current

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guidelines recommended to reach a goal of LDL-C <55 mg/dl together with a minimum 50% LDL-C reduction in very high risk (VHR) patients [1]. This approach is based on evidence from multiple meta-analyses and randomized controlled trials, which show a consistent and graded reduction in ischemic risk in response to absolute reductions in LDL-C levels [3–6]. Moreover, several recent placebo-controlled clinical studies have shown that further reduction of LDL-C down to very low levels obtained by the addition of either ezetimibe or proprotein convertase subtilisin/kexin type 9 inhibitor (PCSK9i) to statin therapy provides a further reduction in ASCVD risk, which is directly and positively correlated with the incrementally achieved absolute LDL-C reduction [7–9].

Nevertheless, the new LDL-C targets appear to be particularly challenging in terms of LDL-C lowering regimens to be used and patients' adherence. In addition, the use of PCSK9i, that need a background of intensive cholesterol lowering therapies, have been approved for use with restrictions by national regulatory agencies, in dealing with the potential financial impact of these expensive drugs on health care systems. Therefore, the reachability in the real-word clinical practice of newly recommended LDL-C goals in VHR patients remains to be established.

Using the data from the STable Coronary Artery Diseases RegisTry (START) study [10,11], an Italian nationwide registry on patients with established atherosclerotic cardiovascular disease (ASCVD) presenting to cardiologists, we sought to assess 1) the contemporary use of conventional cholesterol-lowering therapies and the achievement of LDL-C goals according to previous and current ESC/EAS guidelines in subjects at VHR; 2) the proportion of VHR patients potentially eligible for third-line PCSK9i treatment according to guidelines criteria and Italian regulations.

2. Methods

The design and main results of the START registry have been published previously [10]. Briefly, the START was a prospective, observational, nationwide study aimed to evaluate the current presentation, management, treatment and quality of life of patients with established ASCVD as seen by cardiologists in clinical practice in Italy, during a 3-month period [10]. Enrolment was made at the end of outpatient or day-hospital visit or at hospital discharge. Data on baseline characteristics, including demographics, risk factors and medical history, were collected. Information on the use of diagnostic cardiac procedures, type and timing of revascularization therapy (if performed) and use of pharmacological or non-pharmacological therapies were recorded on an electronic case report form (CRF) at hospital discharge or the end of outpatient visit.

The Italian Association of Hospital Cardiologists (ANMCO) invited to participate all Italian cardiology wards, including university teaching hospitals, general and regional hospitals, and private clinics receiving patients with established ASCVD. No specific protocols or recommendations for evaluation, management, and/or treatment have been put forth during this observational study. However, current guidelines for the management of patients with ASCVD have been discussed during the investigator meetings [10].

All patients were informed of the nature and aims of the study and asked to sign an informed consent for the anonymous management of their individual data. Local Institutional Review Boards (IRB) approved the study protocol according to the current Italian rules.

One-hundred eighty-three cardiology centers included consecutive patients in the survey in different periods of 3 months between March 2016 and February 2017 [10].

To estimate the pre-treatment LDL-C levels, we multiplied the on-treatment LDL-C level by a correction factor based on the potency of their LDL-C lowering regimen as suggested before [12]. In brief, we determined the estimated LDL-C lowering potency of a specific lipid-lowering drug and dose. We multiplied the on-treatment LDL-C level with that treatment potency, yielding an estimated pre-treatment LDL-C level. In case of concomitant use of ezetimibe, we increased the relative LDL-C reduction by 15% [12].

All patients included into the analysis were evaluated for being at VHR according to the ESC/EAS clinical guidelines for the management of dyslipidemias [e.g. documented ASCVD including previous acute coronary syndromes (ACS), coronary revascularization, stable angina, stroke or transient ischemic attack, peripheral artery disease (PAD), diabetes mellitus (DM) with target organ damage or type 1 DM of long duration, severe chronic kidney disease (CKD), a SCORE ≥ 10% for 10-year risk of fatal cardiovascular disease or familiar hypercholesterolemia with ASCVD or another major risk factor] [1,2].

Patients at VHR were evaluated for PCSK9 inhibitor eligibility using the criteria suggested by current ESC/EAS guidelines and those released by the Italian regulatory agency (Agenzia Italiana del Farmaco; AIFA). In particular, ESC/EAS guidelines proposed a treatment algorithm for pharmacological LDL-C lowering where, in case of persistent high LDL-C despite treatment with a maximally tolerated statin, combination with ezetimibe is recommended and, if still not at goal, the addition of a PCSK9i is suggested [1]. According to the AIFA criteria, VHR patients aged ≤80 years, estimated creatinine clearance ≥30 ml/min (according to the Cockroff-Gault equation) and LDL-C > 100 mg/dl despite treatment with high potency statins (20–40 mg rosuvastatin, 40–80 mg atorvastatin) plus ezetimibe or ezetimibe alone in the presence of a well-documented condition of statin intolerance, were considered eligible for PCSK9 inhibitor therapy (http://www.agenziafarmaco.gov.it). As it was not possible to estimate the presence of statin intolerance, we have considered the use of ezetimibe alone as a proxy for statin intolerance.

2.1. Statistical analysis

Categorical variables are presented as number and percentages while continuous variables are presented as mean and standard deviation (SD). Analyses were performed with IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY.

3. Results

From the 5070 consecutive patients with established ASCVD enrolled in the registry, 17 (0.3%) were excluded from the analysis because of missing data, 302 (6.0%) resulted as not-VHR and the remaining 4751 (94.0%) were classified as VHR, according to ESC/EAS Guidelines definitions [1,2].

Baseline characteristics of VHR patients are shown in Table 1. As expected, patients at VHR presented a high rate of major risk factors and suboptimal hemodynamic and laboratory parameters at baseline (Table 1).

At the time of enrollment, the mean LDL-C levels were 62.4 ± 47.7 mg/dl, while, after adjustment for different statins and dosages, mean estimated pretreatment LDL-C values resulted as 164.7 ± 76.1 mg/dl.

At the time of discharge or at the end of the visit, a statin was prescribed in 4470 (94.1%) patients at VHR. Among these patients, a low dose of statin (atorvastatin ≤10 mg/day, fluvastatin ≤40 mg/day, lovastatin ≤20 mg/day, pravastatin ≤20 mg/day, rosuvastatin ≤5 mg/day or simvastatin ≤20 mg/day) was prescribed in 12,8%, while a high dose (atorvastatin≥40 mg or rosuvastatin≥20 mg) was used in 54.9% of patients at VHR. Atorvastatin was the most employed statin compound followed by simvastatin and rosuvastatin (Fig. 1). Mean dosages of statins prescribed in patients at VHR are shown in Table 2. The main reasons for the lack of statins prescription or for their low dose prescription are depicted in Fig. 2.

Concerning the other lipid-lowering agents, ezetimibe was used in 14.4%, omega-3 fatty acids in 14.1%, while fibrates in 0.5% of VHR patients. The association of high dose statin and ezetimibe was prescribed

Table 1
Clinical characteristics, hemodynamic parameters and laboratory variables at baseline.

	VHR $n = 4751$
Age, years (mean ± SD)	67.6 ± 10.5
Age > 75 years, *n* (%)	1272 (26.8%)
Females, n (%)	914 (19.2%)
BMI, kg/m^2 (mean ± SD)	27.98 ± 22.29
Active smokers, n (%)	821 (17.3%)
Hypercholesterolemia, *n* (%)	3594 (75.6%)
Diabetes mellitus, *n* (%)	1556 (32.8%)
Hypertension, *n* (%)	3789 (79.8%)
Chronic renal dysfunction, *n* (%)	587 (12.4%)
Peripheral artery disease, *n* (%)	451 (9.5%)
COPD, *n* (%)	571 (12.0%)
Sleep apnea, *n* (%)	156 (3.3%)
Malignancy, *n* (%)	311 (6.5%)
Depression, *n* (%)	515 (10.8%)
Previous stroke/TIA, *n* (%)	276 (5.8%)
History of major bleeding events, *n* (%)	92 (1.9%)
History of heart failure, *n* (%)	661 (13.9%)
NYHA class III-IV, *n* (%)	152 (3.2%)
Prior MI, *n* (%)	1828 (38.5%)
Previous coronary revascularization, *n* (%)	3966 (83.5%)
Ejection fraction (%), mean ± SD	53.7 ± 10.0
SBP (mmHg), mean ± SD	130 ± 16.5
HR (bpm), mean ± SD	65.8 ± 10.9
Hb (gr/dl), mean ± SD	12.6 ± 3.8
Creatinine (mg/dl), mean ± SD	1.01 ± 0.6
Total cholesterol (mg/dl), mean ± SD	127.1 ± 67.3
LDL cholesterol (mg/dl), mean ± SD	62.4 ± 47.7
Triglycerides (mg/dl), mean ± SD	101.2 ± 76.1
Glycemia (mg/dl), mean ± SD	97.4 ± 53.5

BMI: body mass index; CAD: coronary artery disease; COPD: chronic obstructive pulmonary disease; Hb: hemoglobin; HR: heart rate; LDL: low density lipoprotein; MI: myocardial infarction; MI: myocardial infarction; NYHA: New York Heart Association; SBP: systolic blood pressure; TIA: transient ischemic attack.

in 4.8% of patients and other associations of cholesterol lowering agents were not frequently employed (Fig. 3).

Among patients at VHR, a target level of LDL-C < 70 mg/dl recommended by 2016 guidelines [2] was reached by 58.1%, while a ≥ 50% reduction of LDL-C and target of <55 mg/dl, as recommended by 2019 guidelines [1], would be reached by 3.2% of patients at VHR (Fig. 4).

Accordingly, 9.4% and 1.4% of VHR patients would be eligible for PCSK9i according to ESC/EAS guidelines and AIFA criteria, respectively.

Table 2
Mean dosages of statins prescribed at the time of discharge/end of the visit.

	VHR $n = 4751$
Atorvastatin	41.61 ± 20.7
Fluvastatin	70.0 ± 26.5
Lovastatin	29.3 ± 10.4
Pravastatin	33.8 ± 10.1
Rosuvastatin	14.5 ± 7.2
Simvastatin	25.8 ± 11.6

4. Discussion

The major results of present analysis including a large, nationwide, contemporary, real world cohort of established ASCVD patients were the following: 1) a target level of LDL-C is currently reached in approximately half, according to 2016 ESC/EAS guidelines recommendations, and 3% of VHR patients, according to current guidelines for the management of dyslipidemias; 2) less than 5% of subjects at VHR has been treated by cardiologists with a combination of high dose statin and ezetimibe at the time of discharge/end of the visit; 3) only a minority of ASCVD patients deemed at VHR would be eligible for PCSK9i.

Based on the best available evidence, ESC/EAS guidelines identified four categories of risk and corresponding LDL-C goals [1,2]. The features and the cut-off points that have been used to define the categories of risk were both arbitrary and based on the risk levels at which benefit is evident in clinical trials [1,2]. Patients at VHR are those with documented ASCVD and other major risk factors for CV events. The incidence of VHR features is around 35–40% in general populations with LDL-C measurements [1,13,14], but, as documented in our analysis, it raises to 95% of cases in a cohort of patients with established ASCVD managed by specialists. This finding implies that the vast majority of ASCVD patients should be intensively managed in term of pharmacological and non-pharmacological strategies in order to reduce their global CV risk.

To the best of our knowledge this is the first analysis assessing LDL-C goals attainment according to current guidelines in a real-world setting. Although the START registry was conducted in 2016–2017, long before the publication of current ESC/EAS guidelines, the LDL-C target would be reached in an absolute minority of VHR patients included in the analysis. Indeed, in our context, the ideal goal identified by current guidelines seems arduous to reach and unrealistic, especially if VHR

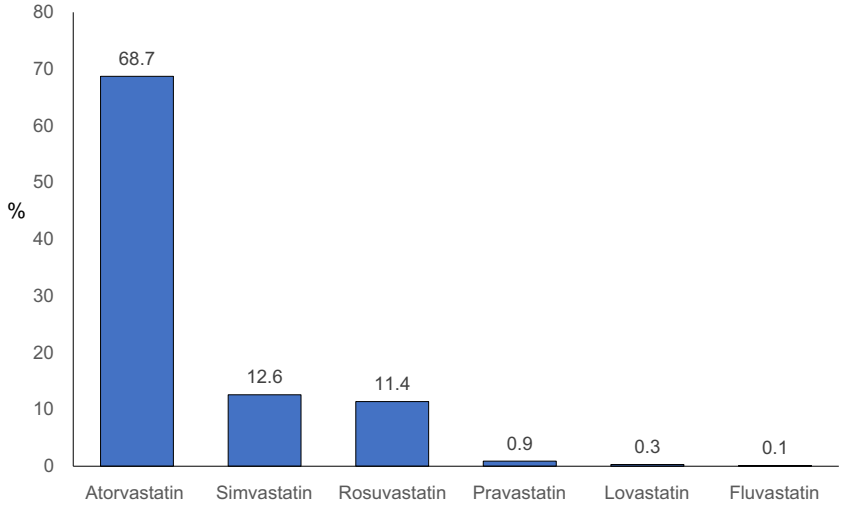

Fig. 1. Statin compounds prescribed at the time of discharge/end of the visit in patients at VHR.

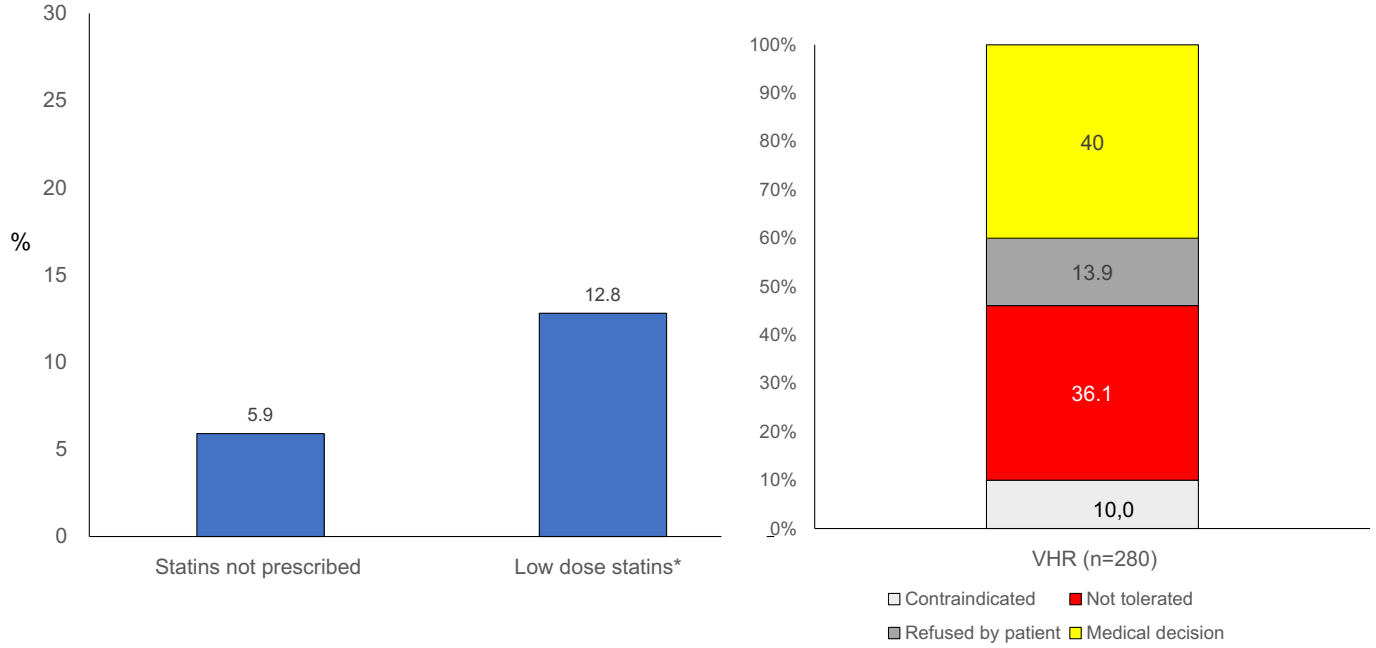

Fig. 2. Patients at VHR ($n = 280$) not receiving statins or receiving low dose statins (Atorvastatin ≤10 mg/day, Fluvastatin ≤40 mg/day, Lovastatin ≤20 mg/day, Pravastatin ≤20 mg/day, Rosuvastatin ≤5 mg/day, Simvastatin ≤20 mg/day) at the time of discharge/end of the visit (left panel). Reasons for lack of statins or low dose statins prescription (right panel).

patients continue to be undertreated, i.e. with low use of high intensity statins or, even better, with the combinations of lipid-lowering therapies. Specifically, in our series a high intensity statin was prescribed in 55% of VHR population and lipid lowering association therapies are unfrequently used being the combination statin plus ezetimibe prescribed in only 5% of VHR patients. These findings should stimulate the cardiological community to organize educational campaigns on the importance of LDL-C reduction and lipid-lowering therapies optimization.

Previous ESC/EAS guidelines on dyslipidemias that were in use at the time of the START registry recommended (Class I) for patients at VHR an LDL-C goal of <70 mg/dl or a reduction of at least 50% if the baseline LDL-C is between 70 and 135 mg/dl [2]. In our cohort this target was reached by only 58% of VHR patients. These findings are in accordance with data from international registries showing suboptimal attainments of LDL-C target in real world clinical settings [15–17]. Indeed, European and Asiatic retrospective studies reported that only 20–40% of ASCVD patients receiving statins attain recommended LDL-C goals [15–17]. Accordingly, in the international SUrvey of Risk Factors (SURF) clinical audit involving 79 centres from 11 countries, an LDL-C target of <70 mg/dl was reached by 15% of Asian, 33% of European and 35% of Middle Eastern patients [18]. In addition, in the EUROASPIRE IV, a cross-sectional study undertaken at 78 centres from 24 European countries less than 20% of enrolled patients reached levels of LDL-C < 70 mg/dl [19].

Notably, VHR individuals with recurrent events, extensive ASCVD or high global CV risk scores are likely to be key targets for the use of PCSK9i in clinical practice [1]. Indeed, according to current ESC/EAS guidelines, patients should be titrated to the maximally tolerated dose of efficacious statin (preferably atorvastatin or rosuvastatin); if LDL-C

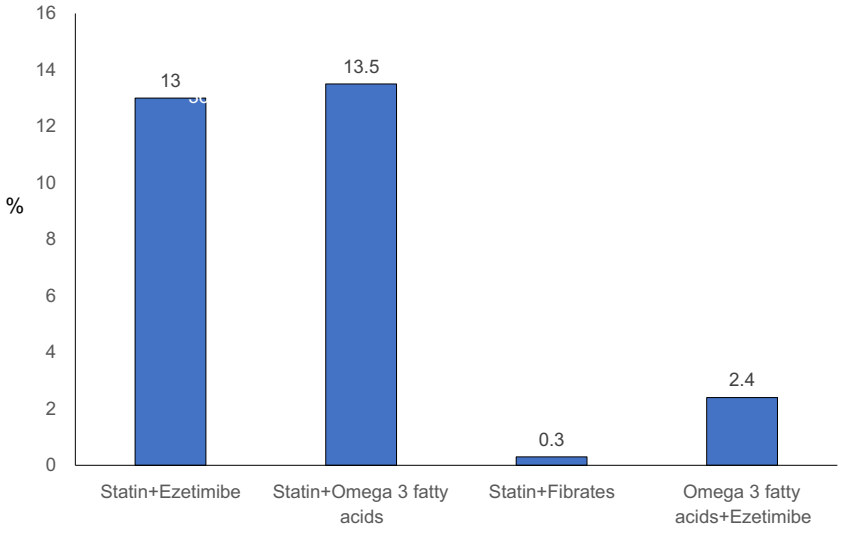

Fig. 3. Associations of lipid lowering strategies† in patients at VHR. † Other possible combinations not shown were used in less than 0.5% of cases.

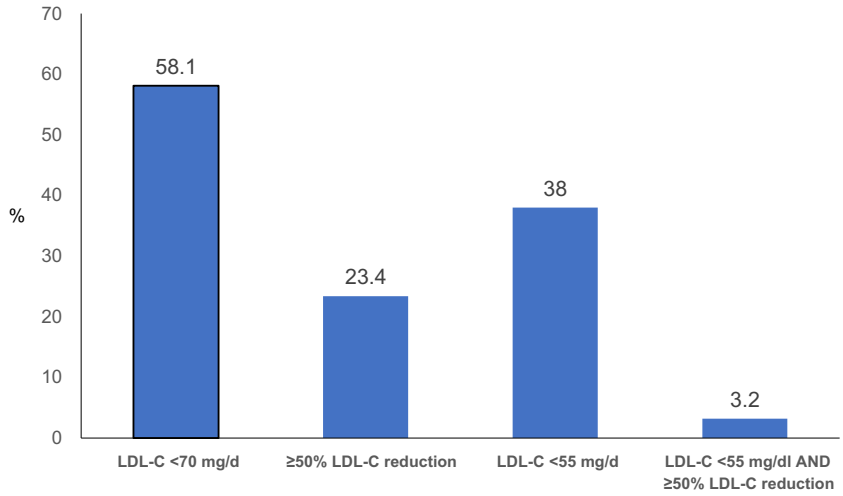

Fig. 4. Frequency of VHR patients reaching LDL-C goals recommended by 2016 and 2019 ESC/EAS guidelines.

levels are still above recommended goals, addition of ezetimibe is recommended before consideration of a PCSK9i in order to ensure appropriate patient pre-treatment before prescription of new drugs [1]. In addition to the evidence, policymakers must balance economic, financial, ideological and other perspectives on single issue, especially in poorer countries. Indeed, in dealing with the potential financial impact of expensive PCSK9i on health care systems, national regulatory agencies have defined criteria for using these medications in clinical practice. In particular, the Italian regulatory agency recommended the prescription of PCSK9i in particular subsets and when LDL-C concentration remains above 100 mg/dL despite the use of maximally tolerated statin dose in combination with ezetimibe (http://www.agenziafarmaco.gov.it). Recent studies suggested that these criteria limit considerably the eligibility for PCSK9i even in patients after myocardial infarction who, among the VHR population, are those usually more aggressively treated with lipid-lowering therapies in clinical practice [20,21]. Accordingly, in our population of ASCVD subjects at VHR, including post-MI patients, the eligibility for PCSK9i according to current European guidelines or Italian agency criteria is poor, considering the suboptimal use of available intensive LDL lowering drugs.

4.1. Study limitations

Our study must be evaluated in the light of some limitations. First, data reported in the present analysis are limited to the time of enrolment and we do not have data on long-term persistence to prescribed therapies, their changes and relative outcomes. Nevertheless, a clinical follow-up at 1 year from enrolment in the START study showed a persistence to statin therapy higher than 90% [11]. Finally, even if the participating centers were asked to include in the registry all consecutive patients with established ASCVD, we were not able to verify the enrolment process, due to the absence of administrative auditing.

5. Conclusions

In patients at VHR enrolled in this large cohort of established ASCVD managed by cardiologists, the lipid management and LDL-C target attainment is suboptimal or scant, according to 2016 or 2019 ESC/EAS guidelines for the management of dyslipidemias, respectively. Accordingly, a large proportion of VHR patients would benefit from more aggressive treatment with conventional lipid lowering therapies, allowing to extend the eligibility to novel and more potent drugs and the achievement of LDL-C goals.

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Declaration of Competing Interest

All authors have reported that no potential conflicts of interest exist with any companies/organizations whose products or services may be discussed in this article.

Appendix A. Appendix

A.1. Steering committee

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Aprilia (M Pignalosa, D Lucchetti); Boscotrecase (F Di Palma, RA La Mastra); Galatina (AF Amico, M De Filippis); Gavardo (B Fontanella, G Zanini); Lido di Camaiore (G Casolo, J Del Meglio); San Benedetto del Tronto, Madonna del Soccorso (VM Parato, E Genovesi); Somma Lombardo (A D'Alimonte, A Miglioranza); Latina, Polo Ospedaliero Integrato (N Alessandri, F Moscariello); Napoli, AORN Cardarelli (C Mauro, A Sasso); Napoli, AORN Colli-Monaldi, UOC Cardiologia (P Caso, C Petrillo); Teramo (C Napoletano, SR Paparoni); Rieti (V Bernardo, R Serdoz); Roccadaspide (R Rotunno, I Oppo); Taranto, Casa di Cura Villa Verde (A Aloisio, A Aurelio); Augusta (G Licciardello, L Cassaniti); Catania, Garibaldi-Nesima (MM Gulizia, GM Francese); Veruno (C Marcassa, PL Temporelli); Vigevano, Civile (R Villani, F Zorzoli); Polistena (F Mileto, M De Vecchis); Copertino (AF Amico, D Scolozzi); Genova, Padre Antero Micone (G Lupi, D Caruso); Palermo, Casa di Cura Candela (E Rebulla, B La Fata); San Bonifacio (M Anselmi, P Girardi); 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