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Lipid-lowering treatment and LDL-C goal attainment in high and very high cardiovascular risk patients: Evidence from the SANTORINI study-The Italian experience

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ABSTRACT

The SANTORINI study is an observational study that enrolled 9602 adult individuals at high or very high cardiovascular (CV) risk across Europe, aimed at providing information on the current status of the management of dyslipidaemias, in light of the most recent 2019 ESC/EAS guidelines.
Italy participated in the study with 1977 patients, 1531 (77.4%) of whom were classified at very high CV risk and 446 (22.6%) at high CV risk. Overall, in the Italian population, 79.31% of the patients had a history of atherosclerotic cardiovascular disease (ASCVD). At enrolment, the mean level of LDL-C in the total population was 98.4 mg/dL. LDL-C levels were lower in the very high-risk group (94.6 mg/dL) than in the high-risk group (111.4 mg/dL). Considering the therapeutic goals recommended by the most recent 2019 ESC/EAS guidelines (LDL-C <55 mg/dL or <70 mg/dL in very high or high-risk patients, respectively), only 20.3% of the overall study population achieved such goals (19.9% of very high-risk patients and 21.8% of high-risk patients). About one-third of the patients included in the study (32.6%) were not prescribed any therapy, one-third received statin monotherapy (34.4%), and only one-third (33%) were taking combination therapy; these percentages were comparable in the two risk subgroups.
Based on the most recent 2019 ESC/EAS guidelines, the use of cholesterol-lowering therapies is not always optimal to achieve the therapeutic goals even in patients with very high CV risk. This means that about 80% of patients are far from the recommended therapeutic goals for their risk category.

Keywords
Atherosclerotic cardiovascular disease; Lipid lowering therapy; LDL-cholesterol; Cardiovascular risk assessment; Guidelines

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Introduction

The causal role of low-density lipoprotein cholesterol (LDL-C) in atherosclerotic-related cardiovascular diseases (ASCVD) has been unequivocally established and a vast amount of studies have indisputably shown that reducing LDL-C levels reduces the risk of ASCVD (1, 2). Treating with statins has been for long the best approach for primary and secondary prevention of CVD, and, based on the considerable evidence, guidelines for the treatment of dyslipidaemias recommend statins as the first-line approach (3, 4). However, several new hypolipidaemic drugs have been developed and approved in the

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last few years, thus expanding the pharmacological armamentarium available for efficient control of circulating LDL-C levels.

It is also clear that the reduction of CV risk is proportional to the magnitude of LDL-C level reduction, independently of the drug used to achieve such a reduction (1). These last observations imply that combination therapy may represent an excellent chance to safely achieve larger LDL-C reductions, taking advantage of complementary mechanisms of action of different drugs.

Based on these considerations, it is expected that patients may also take advantage of this opportunity in everyday clinical practice. Nevertheless, several studies have shown that this is not the case. The most recent DA VINCI study reported relevant gaps in Europe between clinical practice and 2016 ESC/EAS guidelines, with only 54% of enrolled patients achieving the LDL-C goal, a percentage even lower (39%) among those at very high-risk (5). This observation validates the results of previous observational studies reporting less-than-optimal management of LDL-C levels in patients at high CV risk (6-8). Since the last 2019 ESC/EAS guidelines have introduced substantial downward adjustments to the LDL-C goals (3), the gap between recommendations and clinical practice is bound to grow.

The SANTORINI study is an observational study that enrolled patients at high and very high CV risk to evaluate the management of dyslipidaemia in a real-world setting and assess the gaps in clinical practice (9). In this paper we have analysed the data deriving from the Italian patients recruited in the SANTORINI study.

Methods

Study design

The Treatment of high and very high-risk dyslipidemic pAtients for the preveNTion of cardiovascular events in Europe - a multInatioNal observatIonal (SANTORINI) study is a multinational, multicentre, prospective observational, non-interventional study that enrolled 9602 patients (9044 with complete data) at high and very high CV risk requiring lipid-lowering therapies from 14 European countries between March 2020 to February 2021 (NCT04271280) (9, 10). The methodology and rationale for this study have been described previously (10). Italy participates in the study with 1977 patients; data were obtained from each patient at enrolment and included baseline biochemical parameters, current lipid-lowering therapies, and medical history.

Eligibility criteria

Patients were eligible if they were ≥18 years old, had high or very high CV risk and required lipid-lowering therapy. The CV risk was defined at enrolment by the investigators; the Systematic Coronary Risk Estimation (SCORE) system was used centrally to assess CV risk in the primary prevention population. All participants provided written informed consent. No specific exclusion criteria were defined.

Data source

As an observational descriptive study, the sample size of the whole study was based on the assumption that data from approximately 8000 patients would provide sufficient precision (95% confidence interval) to show the rates of CV events during one-year follow-up. Therefore, all adult patients deemed by the physician as being at high or very high CV risk, and who would be eligible for lipid-lowering therapy (LLT) as per 2019 ESC/EAS guidelines were included in this study. CV risk was assigned by physicians at enrolment, and the basis for risk category was documented. CV risk was also assessed centrally based on the information present in the study database according to SMART, Framingham or Systematic Coronary Risk Estimation [SCORE] risk score systems per 2019 ESC/EAS guideline criteria (11). When inconsistencies were found between the CV risk as assessed by the physician and the CV risk category recalculated centrally, a medical query was raised and the physicians were given the possibility to confirm their classification. The results presented here are from the Baseline Analysis Set, which consisted of all patients from the All-Documented Patients Set with adequate baseline information, including completing a medical review of all open queries.

Objectives of the study

This study's primary objectives were to evaluate the use of lipid-lowering therapies and the effectiveness of these treatment approaches in achieving the recommended goals in high and very high-risk patients requiring lipid-lowering therapies in a real-world setting. Furthermore, a comparative analysis has been performed between Italy and the rest of Europe enrolled patients.

Statistical analysis

Baseline characteristics are presented as means (standard deviation [SD]) or median (interquartile range [IQR]) of continuous variables and as percentages of categorical variables. Results are reported by CV risk classification as assessed by physicians (high-risk, and very high-risk), ASCVD status (with ASCVD, and without ASCVD), LLT received, and proportion of patients achieving LDL-C goals.

CV risk was calculated using patient data and applying the CV risk classification of 2019 ESC/EAS guidelines (3, 12). ASCVD was considered present if any of the following was reported in the medical history: coronary ASCVD (myocardial infarction; unstable angina; angina pectoris; coronary artery bypass graft surgery; percutaneous transluminal coronary angioplasty; coronary artery disease [CAD]; CAD unequivocal on imaging); cerebral ASCVD (stroke; transient ischemic attack; cerebrovascular disease; cerebrovascular disease unequivocal on imaging; carotid artery disease); peripheral/other ASCVD (peripheral arterial disease [PAD]; lower extremity artery disease; PAD unequivocal on imaging; retinal vascular disease; abdominal aortic aneurysm; renovascular disease); polyvascular ASCVD (if affecting more than one vascular bed).

Ethics approval and consent to participate

The SANTORINI study has been performed in accordance with the Declaration of Helsinki and Good Clinical Practice. All patients provided written informed consent before participating in the study.

Results

Patient characteristics

A total of 1977 patients were enrolled in Italy from 125 sites (**Appendix 1**); 1531 (77.4%) were classified by the investigators as very high CV risk and 446 (22.6%) as high CV risk patients. The overall population included 73.5% men and 26.5% women; the percentage of women was much higher in the high-risk group than in the very high-risk group (44.8% and 21.1%, respectively) (**Table 1**). Baseline characteristics of the overall population and CV risk subgroups are presented in **Tables 1 and 2** and **Table S1**. Renal insufficiency was present in 15.1% of the enrolled individuals, most of whom showed mild-to-moderate renal insufficiency (**Table S1**).

The majority of enrolled patients had a previous diagnosis of dyslipidaemia (>4 weeks) (77.3%) (**Table 2**). The mean LDL-C level was 98.4±49.7 mg/dL; high-risk patients had higher LDL-C levels than very high-risk patients (111.4±55.3 mg/dL vs 94.6±47.3 mg/dL) (**Table 2**). ApoB and Lp(a) were measured in a very limited

Table 1 | Baseline characteristics of the overall population and cardiovascular risk subgroups at enrolment visit – Italy.

Baseline characteristic	Overall (N=1977)	Risk classification as reported by the investigators	
		Very high-risk (N=1531)	High-risk (N=446)
Gender Male, n (%) Female, n (%)	 1454 (73.5%) 523 (26.5%)	 1208 (78.9%) 323 (21.1%)	 246 (55.2%) 200 (44.8%)
Age, years, mean (SD)	64.5 (11.1)	65.3 (10.6)	61.9 (12.2)
Smoking history, n (%) Current Former Never	 393 (19.9%) 752 (38.0%) 832 (42.1%)	 332 (21.7%) 650 (42.5%) 549 (35.9%)	 61 (13.7%) 102 (22.9%) 283 (63.5%)
Hypertension, n (%)	1409 (71.3%)	1154 (75.4%)	255 (57.2%)
Familial hypercholesterolaemia, n (%)	254 (12.9%)	126 (8.2%)	128 (28.7%)
Diabetes, n (%) Diabetes with target organ damage, n (%)	569 (28.8%) 131 (6.6%)	457 (29.9%) 113 (7.4%)	112 (25.1%) 18 (4.0%)
BMI, kg/m², mean (SD)	27.4 (4.2)	27.5 (4.2)	26.9 (4.2)
BP systolic, mean (SD) *BP diastolic, mean (SD)*	129.5 (16.5) 76.6 (9.5)	129.5 (16.9) 76.3 (9.8)	129.4 (15.0) 77.8 (8.5)

SD: standard deviation; BMI: body mass index; BP: blood pressure.

Table 2 | Laboratory values in the overall population and cardiovascular risk subgroups at enrolment visit – Italy.

Baseline characteristic		Overall (N=1977)	Risk classification as reported by the investigators	
			Very high-risk (N=1531)	High-risk (N=446)
Newly diagnosed with dyslipidaemia, n (%) Newly diagnosed (<4 weeks) Previously diagnosed (> 4 weeks)		 448 (22.7%) 1529 (77.3%)	 373 (24.4%) 1158 (75.6%)	 75 (16.8%) 371 (83.2%)
LDL-C [mg/dL]	*n*	1964	1519	445
	Mean (SD)	98.4 (49.7)	94.6 (47.3)	111.4 (55.3)
HDL-C [mg/dL]	*n*	1963	1519	444
	Mean (SD)	47.9 (15.5)	46.0 (14.9)	46.0 (14.9)
non-HDL-C [mg/dL]	*n*	1962	1518	444
	Mean (SD)	120.2 (54.4)	116 (51.4)	134.6 (61.7)
TC [mg/dL]	*n*	1968	1522	446
	Mean (SD)	169.7 (57.6)	163.3 (54.5)	191.4 (62.4)
ApoB [g/L]	*n*	57	51	6
	Mean (SD)	0.9 (0.4)	0.9 (0.3)	1.1 (0.4)
TG [mg/dL]	*n*	1725	1351	374
	Mean (SD)	135.6 (91.9)	134.8 (92.4)	138.5 (90.1)
Lp(a) [mg/dL]	*n*	108	94	14
	Median (IQR)	31.0 (10.0, 79.1)	28.2 (10.0, 71.7)	60.8 (13.0, 102.0)
HbA1c [%]	*n*	567	457	110
	Mean (SD)	6.56 (1.30)	6.56 (1.33)	6.57 (1.13)
Fasting glucose [mmol/L]	*n*	1179	966	213
	Mean (SD)	6.35 (2.08)	6.41 (2.16)	6.07 (1.69)
Hs-CRP [mg/L]	*n*	223	195	28
	Median (IQR)	3.0 (0.7, 10.2)	3.30 (0.98, 12.2)	0.90 (0.35, 2.75)

LDL-C: low-density lipoprotein cholesterol; HDL-C: high-density lipoprotein cholesterol; TC: total cholesterol; apoB: apolipoprotein B; TG: triglycerides; Lp(a): lipoprotein(a); HbA1c: glycated haemoglobin; hs-CRP: high sensitivity C reactive protein.

number of patients (**Table 2**). Lp(a) levels were higher in the high-risk group than in the very high-risk group (median: 60.8 [13.0-102.0] mg/dl vs 28.2 [10.0-71.7] mg/dL). Overall, the high-risk patient subgroup exhibited a worse lipid profile than the very high-risk patient subgroup. Hs-CRP was much higher in the very high-risk subgroup (**Table 2**).

Cardiovascular risk assessment

Almost all individuals were enrolled from hospitals (97.7%), with cardiologists being the major specialty involved in the recruitment (64.2%) (particularly for very high-risk patients), followed by internists/internal medicine specialists (24.2%) (**Table 3**)**.** General practitioners only contributed with 10 out of 1977 enrolled patients.

At enrolment, individuals' CV risk was assessed by investigators; 1531 patients (77.4%) were classified as very high CV risk and 446 (22.6%) were classified as high CV risk. The majority of patients were classified based on the 2019 ESC/EAS guidelines (72.8% in the overall population), 22.8% were classified based on the clinical experience of the investigators, and a small percentage were classified using other criteria (**Table 3**). Similar percentages were reported in the very high-risk and high-risk subgroups.

Patients whose risk was calculated by the investigators according to the 2019 ESC/EAS guidelines (N=1439, very high-risk 1164, high-risk 275) were further evaluated centrally, again according to the 2019 ESC/EAS guidelines. Among patients classified by the investigators as "very high-risk", the central determination of the CV risk confirmed this classification in 99% of individuals (only 9 out of 1164 were reclassified as "high-risk") (**Figure 1A**). On the contrary, among patients classified as "high-risk" by the investigators, the central assessment of the CV risk provided a reclassification as "very

Table 3 | Specialty of investigators by cardiovascular risk factors at enrolment visit-Italy.

	Overall (N=1977)	Risk classification as reported by the investigators	
		Very high-risk (N=1531)	High-risk (N=446)
Site setting, n (%)			
Hospital	1931 (97.7%)	1521 (99.4%)	410 (91.9%)
Medical practice	46 (2.3%)	10 (0.6%)	36 (8.1%)
Specialty, n (%)			
Cardiologist	1269 (64.2%)	1102 (72.0%)	167 (37.4%)
Diabetologist	125 (6.3%)	63 (4.1%)	62 (13.9%)
General practitioner	10 (0.5%)	5 (0.3%)	5 (1.1%)
Internal medicine specialist/ internist	479 (24.2%)	282 (18.4%)	197 (44.2%)
Lipidologist	135 (6.8%)	100 (6.5%)	35 (7.8%)
Basis for risk classification, n (%)			
Clinical experience	451 (22.8%)	327 (21.4%)	124 (27.8%)
Institutional practice and/or considerations	17 (0.9%)	10 (0.7%)	7 (1.6%)
Institutional guidelines	34 (1.7%)	13 (0.9%)	21 (4.7%)
Regional guidelines	0 (0.0%)	0 (0.0%)	0 (0.0%)
National guidelines	19 (1.0%)	14 (0.9%)	5 (1.1%)
ESC/EAS guidelines	1439 (72.8%)	1164 (76.0%)	275 (61.7%)
Other	17 (0.9%)	3 (0.2%)	14 (3.1%)

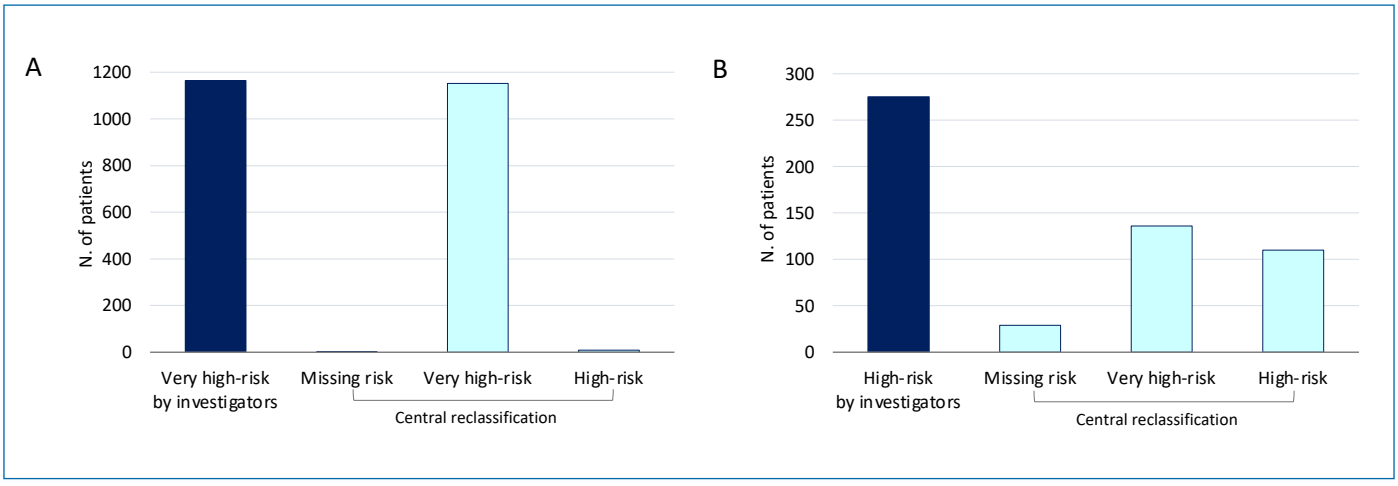

Figure 1 | Recalculated risk classification by ESC/EAS criteria. *Patients classified by investigators as very-high-risk (A) or high-risk (B) by ESC/EAS criteria were reclassified centrally by ESC/EAS criteria. Blue bars represent the number of patients classified as very-high-risk (A) or high-risk by investigators based on ESC/EAS criteria; grey bars represent the same patients whose risk was recalculated centrally based on ESC/EAS criteria.*

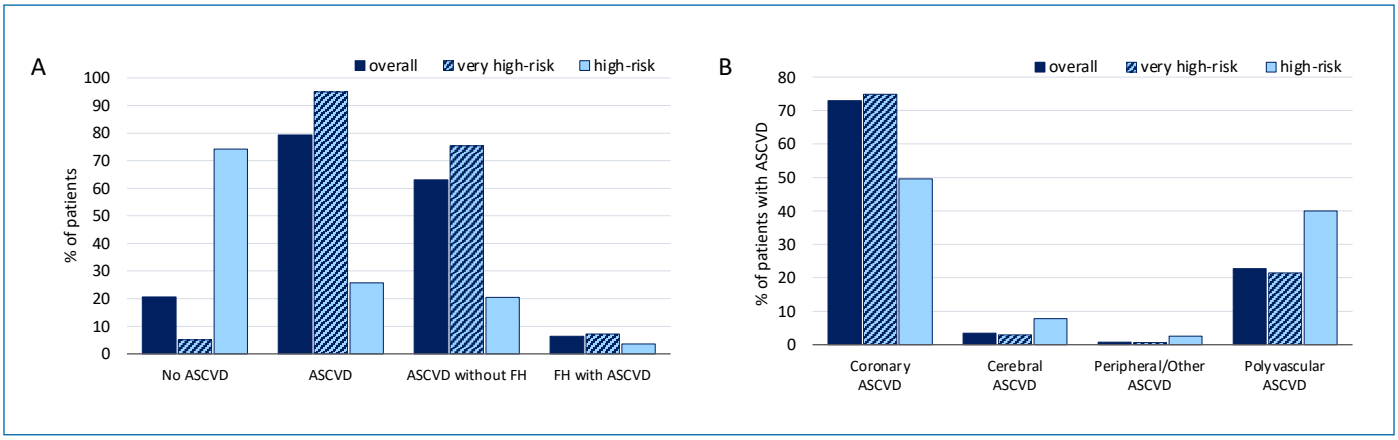

Figure 2 | ASCVD status at baseline. *(A) percentage of patients with or without ASCVD and with or without familial hypercholesterolemia. (B) ASCVD subtypes among patients with ASCVD.*

high-risk" in 136 out of 275 (49.5% of patients) (**Figure 1B**). Overall, the risk classification based on 2019 ESC/EAS criteria identified 1288 patients at very high-risk and 119 at high-risk.

Cardiovascular history at enrolment

Overall, 79.3% of the enrolled patients had ASCVD (**Figure 2A**); this percentage was higher in the very high-risk subgroup and much lower in the high-risk group (94.9% and 25.8%, respectively). Most patients had ASCVD without having FH. Coronary ASCVD was the most common type of ASCVD, representing 74.9% in the very high-risk subgroup and 49.6% in the high-risk subgroup; polyvascular ASCVD was more common among high-risk patients (**Figure 2B**).

About half of the enrolled patients had a history of myocardial infarction, most of whom were in the very high-risk subgroup (936 out of 978) (**Table 4**). Similarly, most of the patients having a history of angina pectoris and unstable angina were part of the very high-risk subgroup (**Table 4**). Overall, 58.6% of individuals (73.9% of those having ASCVD) have had a percutaneous transluminal coronary angioplasty (PTCA) procedure and 9.3% (11.7% of those with ASCVD) had undergone a coronary artery bypass graft (CABG) (**Table 4**). Coronary artery disease was identified in 70.2% of the enrolled patients (86.0% in the very high-risk subgroup); peripheral artery disease and carotid artery disease were present in 16.4% and 12.5% of enrolled patients, respectively (**Table 4**).

Table 4 | Relevant cardiovascular history by cardiovascular risk at enrolment visit.

	Overall (N=1977)	Risk classification as reported by the investigators	
		Very high-risk (N=1531)	High-risk (N=446)
ASCVD, n (%)			
MI	978 (49.5%)	936 (61.1%)	42 (9.4%)
Angina pectoris	461 (23.3%)	436 (28.5%)	25 (5.6%)
Unstable angina	216 (10.9%)	208 (13.6%)	8 (1.8%)
Cardiac arrhythmia	279 (14.1%)	227 (14.8%)	52 (11.7%)
PTCA	1158 (58.6%)	1110 (72.5%)	48 (10.8%)
CABG	183 (9.3%)	176 (11.5%)	7 (1.6%)
CAD	1388 (70.2%)	1316 (86.0%)	72 (16.1%)
CAD unequivocal on imaging	925 (46.8%)	889 (58.1%)	36 (8.1%)
Stroke	78 (3.9%)	72 (4.7%)	6 (1.4%)
TIA	72 (3.6%)	63 (4.1%)	9 (2.0%)
PAD	325 (16.4%)	279 (18.2%)	46 (10.3%)
PAD unequivocal on imaging	132 (6.7%)	114 (7.4%)	18 (4.0%)
Cerebrovascular disease	155 (7.8%)	137 (8.9%)	18 (4.0%)
Cerebrovascular disease unequivocal on imaging	67 (3.4%)	59 (3.8%)	8 (1.8%)
Carotid artery disease	247 (12.5%)	207 (13.5%)	40 (9.0 %)

ASCVD: atherosclerotic cardiovascular disease; MI: myocardial infarction; PTCA: percutaneous transluminal coronary angioplasty; CABG: coronary artery bypass graft; CAD: coronary artery disease; TIA: transient ischemic attack; PAD: peripheral artery disease.

Table 5 | Subgroups by cardiovascular risk factors.

	Overall (N=1977)	No ASCVD (N=409)	Confirmed ASCVD (N=1568)				
			Total (N=1568)	Coronary ASCVD (N=1145)	Cerebral ASCVD (N=53)	Peripheral/ Other ASCVD (N=12)	Polyvascular ASCVD (N=358)
Female, n (%)	523 (26.5%)	190 (46.5%)	333 (21.2%)	214 (18.7%)	23 (43.4%)	3 (25.0%)	93 (26.0%)
Age, years, mean (SD)	64.5 (11.1)	61.6 (13.0)	65.3 (10.4)	64.1 (10.5)	66.6 (9.0)	67.8 (12.9)	68.6 (9.5)
Hypertension, n (%)	1409 (71.3%)	237 (58.0%)	1172 (74.7%)	817 (71.4%)	44 (83.0%)	7 (58.3%)	304 (84.9%)
FH	254 (12.9%)	128 (31.3%)	126 (8.0%)	81 (7.1%)	1 (1.9%)	0 (0.0%)	44 (12.3%)
Diabetes, n (%)	569 (28.8%)	127 (31.1%)	442 (28.2%)	285 (24.9%)	18 (34.0%)	3 (25.0%)	136 (38.0%)
Diabetes with target organ damage, n (%)	131 (6.6%)	28 (6.9%)	103 (6.6%)	57 (5.0%)	3 (5.7%)	1 (8.3%)	42 (11.7%)
BMI, kg/m², mean (SD)	27.4 (4.2)	26.85 (4.3)	27.48 (4.2)	27.61 (4.37)	27.03 (4.1)	26.22 (2.73)	27.19 (3.83)
LDL-C, mg/dL, mean (SD)	98.2 (39.8)	114.5 (56.1)	94.4 (47.1)	96.7 (47.1)	107.9 (55.8)	83.1 (40.7)	85.1 (43.9)
Very high-risk patients, n (%)*	1531 (77.4%)	78 (19.1%)	1453 (92.7%)	1088 (95.0%)	44 (83.0%)	9 (75.0%)	312 (87.2%)

ASCVD: atherosclerotic cardiovascular disease; FH: familial hypercholesterolemia; BMI: body mass index; LDL-C: low-density lipoprotein cholesterol. *Risk classification as reported by the investigators.

Table 5 lists the main baseline characteristics of patients according to the absence or presence of ASCVD (N=409 and N=1568, respectively) and the type of ASCVD.

Use of lipid-lowering therapy

Overall, 67.4% of the enrolled participants were taking a lipid-lowering therapy; half of them were taking a combination therapy (**Figure 3**). Among very high-risk patients, 34.2% were not under lipid-lowering treatment.

Of the patients taking LLT (N=1332), 44.7% were taking statin monotherapy, in most cases a moderate- or high-intensity statin (**Table 6, Figure 4A**). Ezetimibe alone or PCSK9 inhibitors alone were administered in only 2.6% and 3.1%, respectively. Patients treated with combination therapy mainly received a combination of statin and ezetimibe (23.6%), while a combination with a PCSK9 inhibitor was administered in 14% of patients (**Table 6, Figure 4B**). Interestingly, a higher percentage of the high-risk patients were treated with a PCSK9 inhibitor in combination with ezetimibe or ezetimibe+statin than the very high-risk patients (**Figure 4B**).

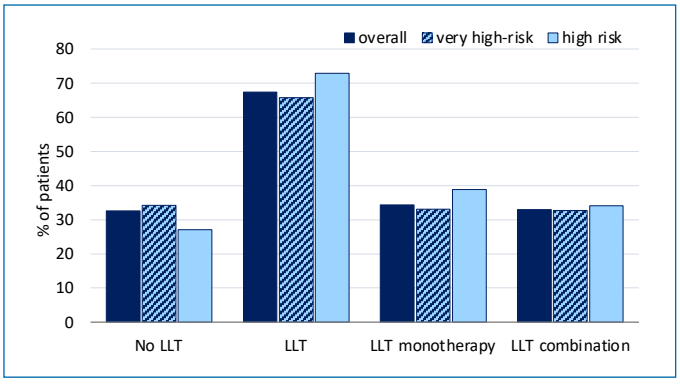

Figure 3 | Lipid-lowering therapy at baseline.

The analysis according to the ASCVD status showed that a high percentage of patients with ASCVD were not taking LLT (34.1% versus 27.1% in patients without ASCVD) (**Table 6**).

Attainment of 2019 ESC/EAS guideline LDL-C goals

Overall, 79% of study participants (1562 out of 1977) were not at goal; only 19.9% of the very high-risk patients and 21.8% of high-risk patients achieved LDL-C goals recommended by current 2019 ESC/EAS guidelines (**Table 7**). Among patients with ASCVD, 78.1% were not at LDL-C goal (**Table 7**), a percentage similar to that reported among patients without ASCVD (82.4%), very high-risk with ASCVD (79%), or very high-risk without ASCVD (84.6%). Only 4% of individuals not taking LLT were at LDL-C goal; among those taking a lipid-lowering therapy, 21.6% of patients taking a monotherapy and 35.1% of patients taking a combination therapy were at LDL-C goal (**Table 7**).

European (without Italy) and Italian data comparison (descriptive analysis)

Then, we compared the results obtained in the Italian subgroup with those obtained in the rest of the enrolled European patients ("Europe w/o Italy" group). Baseline characteristics of the "Europe

Table 6 | Lipid-modifying therapy in the overall population and according to cardiovascular risk or ASCVD status.

	Overall (N=1977)	Risk classification as reported by the investigators*		ASCVD status	
		Very high-risk (N=1531)	High-risk (N=446)	ASCVD (N=1568)	No ASCVD (N=409)
LLT, n (%)					
No LLT	645 (32.6%)	524 (34.2%)	121 (27.1%)	534 (34.1%)	111 (27.1%)
LLT	1332 (67.4%)	1007 (65.8%)	325 (65.8%)	1034 (65.8%)	298 (65.8%)
Monotherapies	680 (34.4%)	507 (33.1%)	173 (38.8%)	518 (33.0%)	162 (39.6%)
Statin alone	595 (30.1%)	446 (29.1%)	149 (33.4%)	458 (29.2%)	137 (33.5%)
Ezetimibe alone	34 (1.7%)	26 (1.7%)	8 (1.8%)	27 (1.7%)	7 (1.7%)
PCSK9i alone	43 (2.2%)	31 (2.0%)	12 (2.7%)	30 (1.9%)	13 (3.2%)
Any other oral LLT alone	8 (0.4%)	4 (0.3%)	4 (0.9%)	3 (0.2%)	5 (1.2%)
Combination therapies	652 (33.0)	500 (32.7%)	152 (34.1%)	516 (32.9%)	136 (33.3%)
Combination statin+ezetimibe	315 (15.9%)	256 (16.7%)	59 (13.2%)	267 (17.0%)	48 (11.7%)
PCSK9i combination	187 (9.5%)	128 (8.4%)	59 (13.2%)	134 (8.6%)	53 (13.0%)
Any other oral combination therapy	150 (7.6%)	116 (7.6%)	34 (7.6%)	115 (7.3%)	35 (8.6%)

ASCVD: atherosclerotic cardiovascular disease; LLT: lipid-lowering therapy; PCSK9i: proprotein convertase subtilisin/kexin 9 inhibitors.

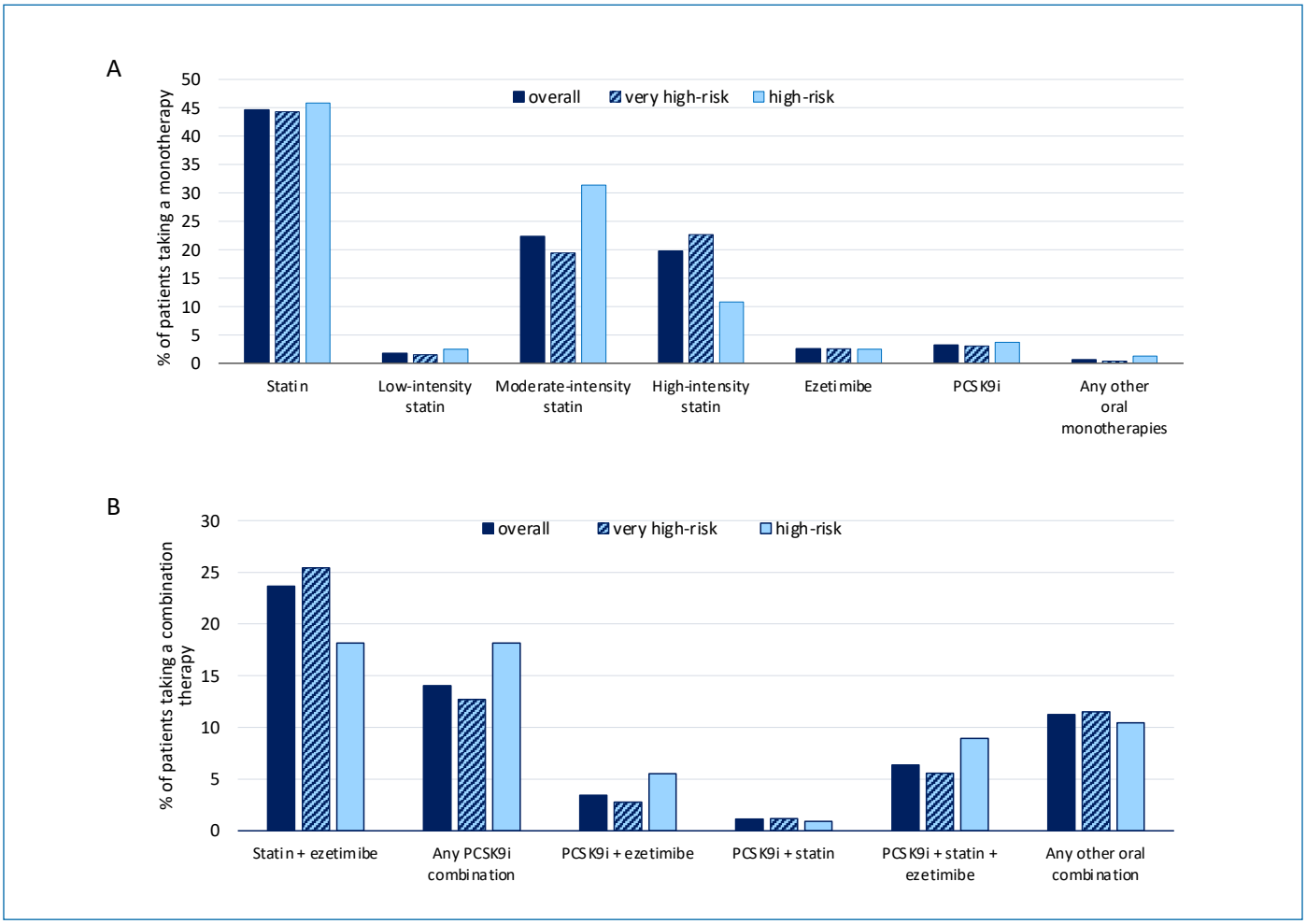

Figure 4 | Details on the lipid-lowering therapies used in Italy. *(A) Monotherapies, (B) combination therapies.*

without Italy" group are listed in **Tables S2** and **S3.** No major differences were observed compared with the Italy subgroup in most baseline characteristics. The prevalence of FH was lower than in the Italy group (9.0% vs 12.9%), whereas diabetes was more prevalent (34.9% vs 28.8%).

Over 90% of enrolled patients had a previous diagnosis of dyslipidaemia, compared with 77% in Italy (**Table S3**). LDL-C levels were 98.4 mg/dL and 91.7 mg/dL in Italy and Europe w/o Italy subgroups, with 79% and 71.7% of individuals not at goal, respectively. Median hs-CRP levels were comparable (**Tables 2 and S3**); interestingly, no differences were observed between very high-risk and high-risk subgroups in the "Europe w/o Italy" population (**Table S3**), contrarily to what observed in the Italian patients (3.30 mg/L [0.70-10.20] and 0.90 mg/L [0.35-2.75], respectively).

Hospitals represented the major centre for patient recruitment in Italy (97.7%), whereas in the group Europe w/o Italy medical practice contributed significantly (43.1%) (**Table S4**). Similarly, while in Italy the contribution of general practitioners is almost irrelevant (0.5%), in the Europe w/o Italy subgroup 16.5% of patients were enrolled by the general practitioners, who contributed more specifically to the recruitment of high-risk patients (27.9%) (**Table S4**). Clinical experience appears to be more relevant for the risk classification in the Europe w/o Italy group (37.3% vs 22.8% in Italy), whereas 2019 ESC/EAS guidelines were less applied (46.2% vs 72.8% in Italy) (**Table S4**).

Furthermore, the application of 2019 ESC/EAS guidelines for risk classification performed very well for the "very high-risk" subgroup in both Italy and the Europe w/o Italy groups, where 99% and 98.2% of patients received the same risk classification by investigators and centrally. However, among the patients classified as "high-risk" by investigators according to 2019 ESC/EAS guidelines, a larger percentage would have been reclassified as "very high-risk" by central assessment (65.1% in the Europe w/o Italy group compared with 49.5% in the Italy group) (**Figure 5**).

Overall, the incidence of ASCVD did not differ between Italy and the Europe w/o Italy groups (**Figure 6**). A higher percentage of high-

Table 7 | LDL-C goal attainment using investigator-reported risk.

	LDL-C (mg/dL) Mean (SD)	Patients at LDL-C goal, N (%)	Patients not at LDL-C goal, N (%)	Unknown, N (%)
Overall	98.2 (49.7)	402 (20.3%)	1562 (79.0%)	13 (0.7%)
Very high-risk (Investigator-reported)	94.7 (47.3)	305 (19.9%)	1214 (79.3%)	12 (0.8%)
High-risk (Investigator-reported)	111.4 (55.3)	97 (21.8%)	348 (78.0%)	1 (0.2%)
ASCVD	94.3 (47.0)	332 (21.2%)	1225 (78.1%)	11 (0.7%)
No ASCVD	114.5 (56.2)	70 (17.1%)	337 (82.4%)	2 (0.5%)
Very high-risk with ASCVD	94.0 (46.8)	294 (20.2%)	1148 (79.0%)	11 (0.8%)
Very high-risk without ASCVD	104.8 (54.6)	11 (14.1%)	66 (84.6%)	1 (1.3%)
ASCVD (excluding FH)	84.0 (45.6)	260 (20.9%)	978 (78.5%)	8 (0.6%)
No LLT	131.1 (45.9)	26 (4.0%)	615 (95.4%)	4 (0.6%)
Monotherapy	86.6 (39.8)	147 (21.6%)	527 (77.5%)	6 (0.9%)
Combination therapy	78.1 (46.1)	229 (35.1%)	420 (64.4%)	3 (0.5%)

ASCVD: atherosclerotic cardiovascular disease; LDL-C: low-density lipoprotein cholesterol; FH: familial hypercholesterolemia; LLT: lipid-lowering therapy,

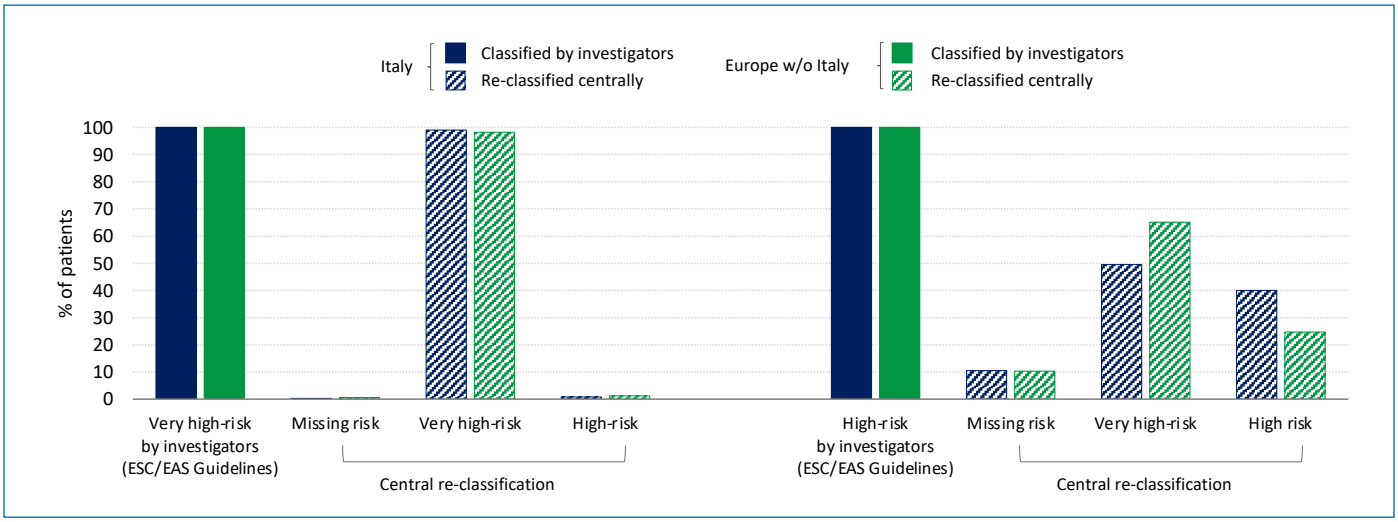

Figure 5 | Risk classification details: comparison between Italy and Europe w/o Italy groups.

risk individuals in the Europe w/o Italy group had coronary ASCVD (29% vs 12.8%) and had a previous myocardial infarction (17.7% vs 9.4), but overall a lower percentage of patients had experienced an MI. Overall, high-risk patients in the Europe w/o Italy group have a greater history of cardiovascular disease compared with the Italy group (**Figure 6**), which can at least in part explain the higher percentage of patients that would have been reclassified as very high-risk patients when re-evaluated centrally (**Figure 5**).

More individuals were taking an LLT (81.2% vs 67.4%), but most were treated with monotherapy (59.7% vs 34.4% in Italy), with statin

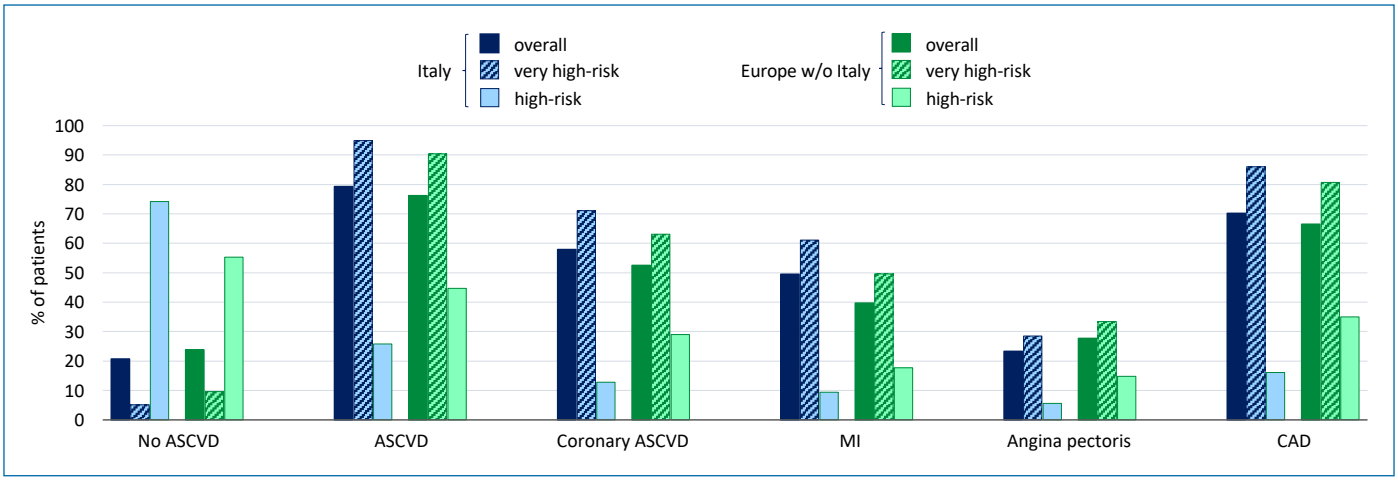

Figure 6 | Detailed cardiovascular history at baseline: comparison between Italy and Europe w/o Italy.

Figure 7 | Lipid-lowering therapy at baseline: comparison between Italy and Europe w/o Italy. *(A) percentage of patients without therapy or taking a lipid-lowering therapy (monotherapy or combination) overall and by CV risk in Italy and Europe w/o Italy groups. (B) Details on the type of lipid-lowering therapies used in Italy and Europe w/o Italy.*

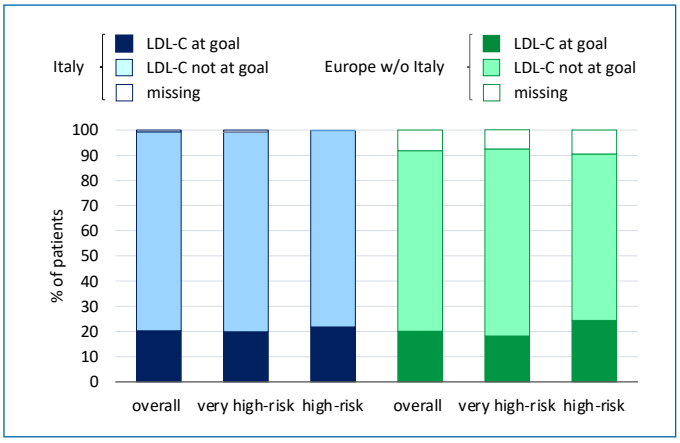

Figure 8 | LDL-C goal attainment in Italy and Europe w/o Italy.

being used in almost twice as many patients in the Europe w/o Italy subgroup than in Italy (moderate- or high-intensity) (**Figure 7A and 7B**). Combination therapy with PCSK9i was more frequently used in Italy.

Overall, 79% and 71.7% of enrolled patients were not at LDL-C goal in Italy and Europe w/o Italy, respectively; a major difference was observed between the high-risk groups, with 78% and 66.1% of patients being not at LDL-C goal, respectively (**Figure 8**).

Discussion

Recognizing that LDL-C has a causal role in ASCVD has greatly pushed research in developing new and more efficient lipid-lowering drugs so that physicians have adequate pharmacological tools to manage efficiently hypercholesterolemia and reduce the CV risk. Based on the observation that reducing LDL-C reduces the CV risk proportionally to the absolute reduction in LDL-C, even at the very low LDL-C levels that can be achieved by combining the most effective cholesterol-lowering drugs, the 2019 ESC/EAS guidelines have further reduced the LDL-C goals, particularly for high-risk and very high-risk patients (3).

Indeed, several observational studies have unequivocally shown that, in clinical practice, patients with high and very high CV risk are substantially undertreated, far from the recommended goals, and thus retain an elevated risk of experiencing a CV event. Relevant gaps were reported between observational studies in real-world settings and the recommendations contained in 2016 ESC/EAS guidelines (5-8); due to the tightening of LDL-C goals contained in 2019 ESC/EAS guidelines (3), it is expected that these gaps may further make things worse. The SANTORINI study was thus set to answer this question (10), and the present study provides information about the management of high and very high CV risk patients in clinical practice in Italy, assessing the quality of the treatment and the attainment of LDL-C goals according to the 2019 ESC/EAS guidelines.

The majority of patients enrolled in this observational study were classified as very high-risk patients. Guidelines recommend that these patients have an LDL-C <55 mg/dL together with an LDL-C reduction of ≥50% from baseline when treated; here we found that very high-risk patients had an LDL-C level very far from optimal and only one-fifth of them were at goal. Analysing the lipid-lowering treatment status, we observed that not all patients had a prescribed therapy, and only half of those taking an LLT were given combination therapy. These represent relevant issues. Moreover, if on the one hand, there is a too high percentage of patients at very high-risk who are not treated, on the other hand, there is a substantial underutilization of combination therapies. Combination therapy represents the most effective approach to reduce substantially LDL-C levels and CV risk in these patients (13). Such an inadequate pharmacological approach implies that a large proportion of individuals at high or very high CV risk are not able to meet the goals recommended by current guidelines. As highlighted in this analysis, only an irrelevant percentage of untreated patients were at goal, and, among those taking an LLT, those treated with combination therapy had more chance to be at LDL-C goal.

We must also underline that, in the Italian setting, the contribution of general practitioners in the recruitment of patients at high or very high CV risk is neglectable while being more relevant in the rest of Europe. This represents a major gap that needs to be filled shortly.

An interesting observation is that overall 2019 ESC/EAS guidelines drive the risk classification by investigators; however, in Italy 2019 ESC/EAS guidelines are followed by a higher percentage of investigators compared with the Europe w/o Italy subgroup. This might, at least in part, explain a higher use of combination therapy in Italy in both high-risk and very high-risk; despite that, LDL-C level is far from optimal in both settings.

The analysis of baseline characteristics of patients involved in the Santorini study, and specifically those recruited in Italy, suggest that high and very high CV risk patients are still undertreated, with LDL-C levels much higher than guidelines recommended goals and underutilization of effective lipid-lowering combination therapies.

Although the guidelines provide clear evidence that treating dyslipidaemias is crucial for the prevention of cardiovascular disease, several observational studies have unequivocally demonstrated that, in real-world clinical practice, individuals at high/very high CV risk are generally not adequately treated. Underestimation of risk and underutilisation of combination therapies are major factors contributing to this. In most cases, monotherapies are insufficient to achieve the recommended goals in these patients, but they are still widely prescribed. Clinicians should bear in mind that high-intensity statin monotherapies can provide an average 50% reduction in LDL-C; oral combination therapies and, where appropriate, treatment with monoclonal antibodies against PCSK9 allow to achieve ≥80% reduction in LDL-C (13). The current availability of cholesterol-lowering therapies with different mechanisms of action should help physicians to personalize treatment based on individual needs. A tailored therapy might represent the right tool to reduce side effects while increasing adherence and compliance, resulting in a higher chance of achieving LDL-C goals and consequently reducing CV risk.

The therapy algorithm of the ESC/EAS guidelines suggests a stepwise therapy strategy in which combination therapy is the second step of intervention. While this approach may be useful for patients at moderate CV risk or with LDL-C levels not far from the goal, patients at very high CV risk who are distant from the goal need therapies that can substantially lower their LDL-C levels regardless of their baseline. Lowering LDL-C log-linearly reduces the risk of CV events without reaching a plateau, suggesting that patients at very high-risk may benefit greatly from an early intervention based on combination therapy. It is expected that a maximised therapy strategy with a combination of high-intensity statin therapy, ezetimibe, a PCSK9 inhibitor (and possibly bempedoic acid) could effectively lower LDL-C levels, increase adherence and consequently reduce CV risk in very high-risk patients.

Conflict of interest

MA Arca has received payments for the provision of grants and consulting services from Akcea/Ionis, Alfasigma, Amgen, Amryt, Amarin, Daiichi-Sankyo, Pfizer, Regeneron, Sanofi, SOBI, Viatris

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Authorship and Author Contributions

MA, PC, AS, RG, KR, and ALC contributed to the study conceptualization and methodology; all authors contributed to the design and writing of the manuscript, and revising it critically.

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