# Treatment gaps in the implementation of LDL cholesterol control among high- and very high-risk patients in Europe between 2020 and 2021: the multinational observational SANTORINI study

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The Lancet Regional Health - Europe 2023;29: 100624

Published Online xxx https://doi.org/10.1016/j.lanepe.2023.100624

## Summary

**Background** European data pre-2019 suggest statin monotherapy is the most common approach to lipid management for preventing cardiovascular (CV) events, resulting in only one-fifth of high- and very high-risk patients achieving the 2019 ESC/EAS recommended low-density lipoprotein cholesterol (LDL-C) goals. Whether the treatment landscape has evolved, or gaps persist remains of interest.

**Methods** Baseline data are presented from SANTORINI, an observational, prospective study that documents the use of lipid-lowering therapies (LLTs) in patients ≥18 years at high or very high CV risk between 2020 and 2021 across primary and secondary care settings in 14 European countries.

**Findings** Of 9602 enrolled patients, 9044 with complete data were included (mean age: 65.3 ± 10.9 years; 72.6% male). Physicians reported using 2019 ESC/EAS guidelines as a basis for CV risk classification in 52.0% (4706/9044) of patients (overall: high risk 29.2%; very high risk 70.8%). However, centrally re-assessed CV risk based on 2019 ESC/EAS guidelines suggested 6.5% (308/4706) and 91.0% (4284/4706) were high- and very high-risk patients, respectively. Overall, 21.8% of patients had no documented LLTs, 54.2% were receiving monotherapy and 24.0% combination LLT. Median (interquartile range [IQR]) LDL-C was 2.1 (1.6, 3.0) mmol/L (82 [60, 117] mg/dL), with 20.1% of patients achieving risk-based LDL-C goals as per the 2019 ESC/EAS guidelines.

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**Interpretation** At the time of study enrolment, 80% of high- and very high-risk patients failed to achieve 2019 ESC/EAS guidelines LDL-C goals. Contributory factors may include CV risk underestimation and underutilization of combination therapies. Further efforts are needed to achieve current guideline-recommended LDL-C goals.

**Trial registration** ClinicalTrials.gov Identifier: NCT04271280.

**Funding** This study is funded by Daiichi Sankyo Europe GmbH, Munich, Germany.



**Keywords:** Cardiovascular disease; LDL cholesterol; High cardiovascular risk; Lipid-lowering therapy; Real-world evidence; Cohort study

### Research in context

#### Evidence before this study

Lowering low-density lipoprotein cholesterol (LDL-C) is recognised as a key therapeutic strategy to reduce the risk of cardiovascular disease (CVD); nevertheless, over the past decade, registries and retrospective cohort data have shown that the majority of patients at higher cardiovascular (CV) risk remain below guideline-recommended LDL-C goals.

#### Added value of this study

The SANTORINI study provides data on lipid management (2020–2021) in the years following the 2019 update of the ESC/EAS guidelines for dyslipidemias and documents the effectiveness of current treatment practice in managing LDL-C levels for those in the higher CV risk categories (high and very high risk). Therefore, this study provides a contemporary picture of the evolving lipid management landscape, quantifying current gaps in treatment implementation, and potentially informing future approaches to improve care.

#### Implications of all the available evidence

Findings from the baseline data of SANTORINI study across 14 countries remain consistent with previous European studies conducted in various health care settings and indicating that LDL-C goal attainment remains poor. Although several lipid-lowering therapies are available as adjunct to statins, the impact of lowering the 2019 ESC/EAS LDL-C goals means that as baseline starting cholesterol levels remain largely unchanged, as does the potency of first line therapy namely statins, the impact of lowering the cholesterol goals means that a greater use of combination therapies will be required to fully implement the guidelines.

## Introduction

Cardiovascular disease (CVD) causes more than 4 million deaths annually in Europe, accounting for 45% of all deaths.[1] Low-density lipoprotein cholesterol (LDL-C) not only plays a direct causal role in the development of atherosclerotic cardiovascular disease (ASCVD),[2–4] but lowering LDL-C is recognised as a key therapeutic option to reduce the risk of CVD, particularly amongst those at highest risk of future events.[5,6] In this regard, the 2019 update from the European Society of Cardiology/European Atherosclerosis Society (ESC/EAS) guidelines for lipid management recommended more stringent cholesterol goals. For patients at high cardiovascular (CV) risk an LDL-C reduction of ≥50% plus a goal of <1.8 mmol/L (<70 mg/dL) is now recommended, and for very high risk ≥50% reduction plus a goal of <1.4 mmol/L (<55 mg/dL).[5]

For well over a decade, registries and retrospective cohort data have shown that many patients at highest CV risk fail to achieve the prior, less stringent LDL-C goals of <1.8 mmol/L (<70 mg/dL).[7–9] The EU-Wide Cross-Sectional Observational Study of Lipid-Modifying Therapy Use in Secondary and Primary Care (DA VINCI) study (2017–2018) showed that the majority of lipid-lowering therapies (LLTs) in Europe is statin-based monotherapy (84%), while only 10% is combination therapies. This approach resulted in 55% of patients achieving the 2016 ESC/EAS guidelines risk-based goals, and only 33% likely to achieve the more stringent 2019 guidelines goals.[8,10] Furthermore, the DA VINCI study suggested that even when high-intensity statins are used in very high CV risk patients, only 22% of them achieved LDL-C levels <1.4 mmol/L (<55 mg/dL).[8] Given that statins and ezetimibe are generic and that several LLTs are available and the 2019 updated ESC/EAS guidelines in dyslipidemias recommend intensification of treatment through use of combination therapies, we conducted the Treatment of high and very high riSk dyslipidemic pAtients for the preveNTion of cardiOvasculaR events in Europe–a multInatioNal observatIonal (SANTORINI) study to describe the approaches to lipid management in patients with

higher CV risk (high and very high risk) across 14 European countries. The primary objective of this manuscript is to report baseline patient characteristics from the SANTORINI study and document approaches to lipid management used in clinical practice and to what extent at the time of study enrolment these might result in achievement of the 2019 guidelines, or whether changes in our approach are needed.

## Methods

### Study design

The rationale, objectives, and methodology used in SANTORINI have been described in detail previously.[11] Briefly, this prospective, observational, non-interventional study (NCT04271280) enrolled patients with high and very high CV risk across Europe. The patient recruitment period lasted from 17th March 2020 to 11th February 2021. The primary objective of this report of the baseline characteristics was to assess how physicians assessed risk, how they then approached lipid lowering regimens and to what extent the current approaches would result in attainment of the latest 2019 ESC/EAS lipid goals. Baseline data were collected from the patient charts from all dyslipidaemia-related visits at which the patient has been seen by the physician, starting from date of diagnosis. Electronic data capture was used for the recording of the information. No formal visits, examinations, laboratory tests or procedures were mandated as part of this non-interventional observational study.

### Patient cohort and data

There were no specific exclusion criteria. Patients were eligible for enrolment if they were ≥18 years of age with high or very high risk of ASCVD, for whom LLT would likely be beneficial and had an anticipated life expectancy of more than one year. These patients were recruited from different care settings (primary and secondary care, and across different specialities); there was no specific criterion regarding physician selection.[11] The CV risk was assigned by the physician at enrolment, and the basis for risk classification was documented. CV risk was also assessed centrally based on the information present in the study database according to SMART, Framingham or SCORE risk score systems per 2019 ESC/EAS guideline criteria.[12–15] 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 original classification. In this manuscript, we present the baseline analysis dataset, which consisted of those patients from all documented patients (all patients with any electronic case report form) with adequate baseline information (see Supplementary Table S3 for a full list of parameters), including completing medical review of all open queries.

### Statistical analysis

As an observational descriptive study, the sample size was based on the assumption that data from approximately 8000 patients would provide sufficient precision (determined by the width of the 95% confidence interval) to show the rates of CV events during 1-year follow-up. Assuming an absolute reduction of LDL-C across all treatment modalities between baseline and 1-year follow-up in a real-life setting of 0.9 mmol/L, the sample size was selected to provide information for an expected change in the relative risk of major vascular events with an absolute precision of ±13% (relative precision ±16%).

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 by 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 (Supplementary Table S4).[5] 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). All statistical analyses were performed using Statistical Analysis System (SAS®) Version 9.4.

### Role of funding source

The funder, Daiichi Sankyo Europe GmbH, Munich, Germany, had a role in study design, data collection, data analysis, interpretation, and funded medical writing support in accordance with Good Publication Practice guidelines 3.

## Results

### Baseline demographics and patient characteristics

A total of 9602 patients were enrolled from 623 hospital and medical centres across 14 countries (Austria [n = 310], Belgium [n = 489], Denmark [n = 311], Finland [n = 337], France [n = 797], Germany [n = 2086], Italy [n = 1977], the Netherlands [n = 523], Portugal [n = 112], Republic of Ireland [n = 100], Spain [n = 990], Sweden [n = 190], Switzerland [n = 149] and the United Kingdom [n = 673]) (Supplementary Tables S2 and S5).

| Characteristic | Overall (n = 9044) | Risk classification as reported by physician | |
|---|---|---|---|
| | | High risk (n = 2637) | Very high risk (n = 6401) |
| **Male, n (%)** | 6563 (72.6) | 1639 (62.2) | 4920 (76.9) |
| **Age, years, mean (SD)** | 65.3 (10.9) | 63.5 (11.7) | 66.0 (10.5) |
| **Centre of recruitment, n (%)** | | | |
| Hospital | 5955 (65.8) | 1494 (56.7) | 4455 (69.6) |
| Medical practice | 3089 (34.2) | 1143 (43.3) | 1946 (30.4) |
| **Hypertension, n (%)** | 6372 (70.5) | 1740 (66.0) | 4629 (72.3) |
| **Diabetes, n (%)** | 3038 (33.6) | 882 (33.5) | 2154 (33.7) |
| **Familial hypercholesterolemia, n (%)** | 893 (9.9) | 413 (15.7) | 480 (7.5) |
| **Smoking history, n (%)** | | | |
| Current | 1493 (16.5) | 400 (15.2) | 1092 (17.1) |
| Former | 3856 (42.6) | 949 (36.0) | 2904 (45.4) |
| Never | 3544 (39.2) | 1256 (47.6) | 2287 (35.7) |
| **LDL-C, mmol/L, median (IQR)** | 2.1 (1.6, 3.0) | 2.4 (1.7, 3.4) | 2.0 (1.5, 2.8) |
| **HDL-C, mmol/L, mean (SD)** | 1.3 (0.4) | 1.4 (0.4) | 1.2 (0.4) |
| **Non-HDL-C, mmol/L, mean (SD)** | 3.0 (1.4) | 3.4 (1.4) | 2.9 (1.3) |
| **TC, mmol/L, mean (SD)** | 4.3 (1.4) | 4.7 (1.5) | 4.2 (1.3) |
| **apoB, g/L, median (IQR)** | 0.8 (0.6, 1.1) | 0.9 (0.7, 1.1) | 0.8 (0.6, 1.1) |
| **TG, mmol/L, median (IQR)** | 1.4 (1.0, 2.0) | 1.5 (1.0, 2.1) | 1.4 (1.0, 2.0) |
| **Lp(a), mg/dL, median (IQR)** | 24.3 (8.3, 80.4) | 18.7 (8.0, 61.8) | 27.4 (8.3, 83.0) |
| **BMI, kg/m$^2$, mean (SD)** | 28.3 (4.9) | 28.5 (5.2) | 28.2 (4.8) |
| **BP systolic, mmHg, mean (SD)** | 133.9 (18.1) | 133.5 (18.2) | 134.7 (17.8) |
| **BP diastolic, mmHg, mean (SD)** | 77.9 (10.5) | 77.6 (10.6) | 78.7 (10.3) |

Missing risk, n = 6. ApoB, apolipopretein B; BMI, body mass index; BP, blood pressure; HDL-C, high-density lipoprotein cholesterol; IQR, interquartile range; LDL-C, low-density lipoprotein cholesterol; Lp(a), lipoprotein(a); SD, standard deviation; TC, total cholesterol; TG, triglycerides.

*Table 1:* **Baseline characteristics by risk classification as reported by physician.**

The Baseline Analysis Set consisted of 9044 patients at the end of the enrolment period (cut-off date of 31$^{st}$ July 2021). Most of the patients (65.9%, n = 5955) were recruited from a hospital/specialist setting. Baseline demographics and patient characteristics are shown in Table 1. The mean (SD) age was 65.3 (10.9) years and 72.6% of the study population was male. Hypertension was the most frequently reported CV risk factor (70.5%), followed by diabetes (33.6%). Familial hypercholesterolemia (FH) as documented by physicians was reported in 893 (9.9%) patients.

### Risk classification and cardiovascular history

As reported by physicians, about one-third of patients (29.2%, n = 2637) were classified as high CV risk and two-thirds (70.8%, n = 6401) as very high risk. The relevant factors associated with this classification included documented ASCVD, diabetes, SCORE >5 and/or elevated laboratory parameters, as shown in Table 2. Overall, the 2019 ESC/EAS guidelines were cited as the most commonly used basis for risk classification (52.0%), followed by clinical experience (34.2%), and national guidelines (9.3%) (Table 2). Of note, the 2019 ESC/EAS guidelines were the main basis for risk classification in very high-risk patients (59.2%), whereas clinical experience was the most common basis when assessing the risk level of the high-risk group (43.8%). However, when the CV risk was re-assessed centrally for patients whose risk was classified based on the 2019 ESC/EAS guidelines, 6.5% (308/4706) and 91.0% (4284/4706) were deemed as high- and very high-risk patients, respectively (missing risk, n = 114).

Overall, 76.9% (6954/9044) of patients had a documented history of ASCVD at baseline, but 15.7% (1094/6954) of these were classified by physicians as high risk. The majority of patients with confirmed ASCVD were male (76.9%) and mean (SD) age was 66.1 (10.4) years. Baseline demographics and characteristics overall and by type of ASCVD (coronary, cerebral, peripheral, other or polyvascular) are shown in Table 3.

### LDL-C goal attainment and use of LLT

The majority of patients (73.3%) were not at 2019 ESC/EAS risk-based LDL-C goal, with the median LDL-C being 2.1 mmol/L (82 mg/dL) in the overall population, 2.4 mmol/L (93 mg/dL) in the high-risk patient group and 2.0 mmol/L (78 mg/dL) in the very high-risk patient group as evaluated by physicians (Fig. 1). Among patients with documented ASCVD, the median LDL-C was 2.0 mmol/L (78 mg/dL). As shown in Fig. 1, only 20.1% (n = 1821/9044) of the overall group of patients were at LDL-C goal. Among those receiving lipid-

| | Overall (n = 9044) | Risk classification as reported by physician[a] | |
|---|---|---|---|
| | | High risk (n = 2637) | Very high risk (n = 6401) |
| **ASCVD, n (%)** | 6954 (76.9) | 1094 (41.5) | 5856 (91.5) |
| **Diabetes with target organ damage, n (%)** | 610 (6.7) | 125 (4.7) | 485 (7.6) |
| **Diabetes with no target organ damage, n (%)** | 2428 (26.9) | 757 (28.7) | 1669 (26.1) |
| **HeFH with ASCVD** | 504 (5.6) | 92 (3.5) | 412 (6.4) |
| **eGFR, mL/min/1.73 m$^2$, mean (SD)** | 78.2 (24.0) | 81.4 (24.0) | 76.9 (23.9) |
| Severe (eGFR <30 mL/min/1.73 m$^2$) | 121 (1.3) | 15 (0.6) | 106 (1.7) |
| Moderate (eGFR 30–59 mL/min/1.73 m$^2$) | 933 (10.3) | 197 (7.5) | 736 (11.5) |
| **Primary prevention patients with SCORE reported, n (%)** | 2947 (32.6) | 1840 (69.8) | 1107 (17.3) |
| SCORE 5–9% | 1026 (34.8) | 573 (31.1) | 453 (40.9) |
| SCORE ≥10% | 240 (8.1) | 123 (6.7) | 117 (10.6) |
| **Patients with elevated TC >8 mmol/L or LDL-C >4.9 mmol/L or SBP >180 mmHg or DBP >110 mmHg** | 559 (6.2) | 222 (8.4) | 334 (5.2) |
| **Basis for risk classification, n (%)** | | | |
| Missing | 6 (0.1) | 0 | 0 |
| Clinical experience | 3089 (34.2) | 1154 (43.8) | 1935 (30.2) |
| Institutional practice and/or considerations | 111 (1.2) | 34 (1.3) | 77 (1.2) |
| Institutional guidelines | 109 (1.2) | 57 (2.2) | 52 (0.8) |
| Regional guidelines | 102 (1.1) | 73 (2.8) | 29 (0.5) |
| National guidelines | 844 (9.3) | 361 (13.7) | 483 (7.6) |
| ESC/EAS guidelines | 4706 (52.0) | 916 (34.7) | 3790 (59.2) |
| Other | 77 (0.9) | 42 (1.6) | 35 (0.6) |
| **Recalculated risk classification by ESC/EAS criteria, n (%)[b]** | 4706 (52.0) | 308 (6.5) | 4284 (91.0) |

Patients were either below high risk (based on available data and SCORE) or potentially high-risk patients (max 48) but without the evidence in the dataset to support this classification. ASCVD, atherosclerotic cardiovascular disease; CV, cardiovascular; DBP, diastolic blood pressure; HeFH, heterozygous familial hypercholesterolaemia; eGFR, estimated glomerular filtration rate; ESC/EAS, European Society of Cardiology/European Atherosclerosis Society; LDL-C, low-density lipoprotein cholesterol; SBP, systolic blood pressure; SD, standard deviation; SCORE, Systematic COronary Risk Evaluation; TC, total cholesterol. [a]Total missing risk, n = 6. [b]Missing risk, n = 110.

*Table 2:* **Baseline CV risk factors and basis for risk classification by risk classification as reported by physician.**

| | No ASCVD (n = 2089) | Confirmed ASCVD (n = 6954) | | | | |
|---|---|---|---|---|---|---|
| | | Total (n = 6954) | Coronary ASCVD[a] (n = 4857) | Cerebral ASCVD[b] (n = 400) | Peripheral/Other ASCVD[c] (n = 150) | Polyvascular ASCVD[d] (n = 1547) |
| **Male, n (%)** | 1218 (58.3) | 5345 (76.9) | 3865 (79.6) | 223 (55.8) | 104 (69.3) | 1153 (74.5) |
| **Age, years, mean (SD)** | 62.5 (12.1) | 66.1 (10.4) | 65.1 (10.5) | 66.3 (10.6) | 67.3 (9.8) | 69.1 (9.3) |
| **Hypertension, n (%)** | 1346 (64.4) | 5026 (72.3) | 3336 (68.7) | 293 (73.3) | 100 (66.7) | 1297 (83.8) |
| **Familial hypercholesterolaemia, n (%)** | 389 (18.6) | 504 (7.3) | 321 (6.6) | 40 (10.0) | 9 (6.0) | 134 (8.7) |
| **Diabetes, n (%)** | 931 (44.6) | 2107 (30.3) | 1339 (27.6) | 108 (27.0) | 53 (35.3) | 607 (39.2) |
| Diabetes with target organ damage, n (%) | 160 (7.7) | 450 (6.5) | 223 (4.6) | 25 (6.3) | 14 (9.3) | 188 (12.2) |
| **BMI, kg/m$^2$, mean (SD)** | 29.0 (5.7) | 28.1 (4.6) | 28.2 (4.7) | 27.7 (5.3) | 27.7 (4.2) | 27.8 (4.5) |
| **LDL-C, mmol/L, median (IQR)** | 2.6 (1.8, 3.5) | 2.0 (1.5, 2.9) | 2.0 (1.5, 2.9) | 2.4 (1.7, 3.3) | 2.3 (1.6, 3.4) | 1.9 (1.4, 2.6) |
| **Very high-risk patients,[e] n (%)** | 544 (26.0) | 5856 (84.2) | 4160 (85.7) | 285 (71.3) | 105 (70.0) | 1306 (84.4) |
| **Centre of recruitment, n (%)** | | | | | | |
| Hospital | 1141 (54.6) | 4813 (69.2) | 3457 (71.2) | 225 (56.3) | 90 (60.0) | 1041 (67.3) |
| Medical practice | 948 (45.4) | 2141 (30.8) | 1400 (28.8) | 175 (43.8) | 60 (40.0) | 506 (32.7) |

ASCVD, atherosclerotic cardiovascular disease; BMI, body mass index; IQR, interquartile range; LDL-C, low-density lipoprotein cholesterol; SD, standard deviation. [a]Coronary ASCVD: myocardial infarction; unstable angina; angina pectoris; coronary artery bypass graft surgery; percutaneous transluminal coronary angioplasty; coronary artery disease; coronary artery disease unequivocal on imaging. [b]Cerebral ASCVD: stroke; transient ischemic attack; cerebrovascular disease; cerebrovascular disease unequivocal on imaging; carotid artery disease. [c]Peripheral/Other ASCVD: peripheral arterial disease (PAD); lower extremity artery disease; PAD unequivocal on imaging; retinal vascular disease; abdominal aortic aneurysm; renovascular disease. [d]Polyvascular ASCVD: if more than one is reported. [e]Risk classification as reported/deemed by physician.

*Table 3:* **Baseline characteristics by ASCVD status.**

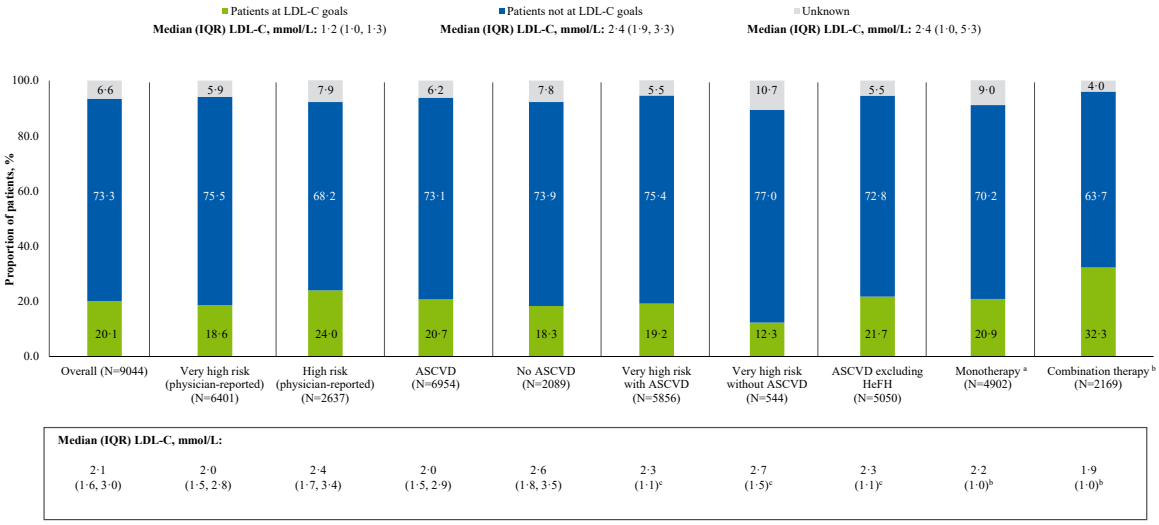


***Fig. 1:*** **LDL-C goal attainment by CV risk, ASCVD status and LLT.** LLT record was missing for patients n = 1. Patients receiving monotherapy, n = 1023/4902. Patients receiving combination therapy, n = 2169. [a]Monotherapy including: statin alone; ezetimibe alone; PCSK9i alone; bempedoic acid alone; any other oral LLT alone; [b]Combination therapy including: statin + ezetimibe; PCSK9i combination; bempedoic acid fixed-dose combination; any other oral combination therapy; [c]Data are presented as mean ± standard deviation. ASCVD, atherosclerotic cardiovascular disease; CV, cardiovascular; EZE, ezetimibe; FDC, fixed-dose combination; HeFH, familial hypercholesterolaemia, IQR, interquartile range; LLT, lipid-lowering therapy; PCSK9i, proprotein convertase subtilisin/kexin type 9 inhibitor; SD, standard deviation.

lowering monotherapy and combination LLT, 20.9% (1023/4902) and 32.3% (700/2169) were at goal, respectively. Of note, 5.0% (98/1972) were reported to be at goal despite not receiving any documented LLT at the time of enrolment (data not shown). Additional information on the type of LLT and the proportion of patients at LDL-C goals is shown in Supplementary Table S6 and Supplementary Fig. S1.

Overall, about one in five patients (21.8%) had no recorded LLT at baseline (Fig. 2A). The overall use of monotherapy (either statin, ezetimibe, proprotein convertase subtilisin/kexin type 9 [PCSK9] inhibitors alone or other oral LLT) was similar across high- and very high-risk patients (Fig. 2B and C), or patients with/without confirmed ASCVD (Fig. 2D and E). The most frequently documented LLT was statin monotherapy, used in 50.2% of all patients (54.5% and 48.4% of patients in the high- and very high-risk groups, respectively; Fig. 2B and C). Overall, moderate- and high-intensity statins were the preferred statin regimen (Supplementary Table S6 and Supplementary Fig. S1). The use of other lipid-lowering agents as monotherapies was low among all patients, including ezetimibe (1.8%), PCSK9 inhibitors (1.7%), and other oral LLT (0.6%) (Fig. 2A). Overall, combination therapy was used in 24.0% of all patients and was more frequently utilised in the very high-risk group (26.4%), compared with the high-risk group (18.1%). Combination therapy included 16.0% of patients who received statin plus ezetimibe, 4.5% who received a PCSK9 inhibitor plus oral LLT, and 3.5% receiving any other oral combination therapy (Fig. 2A). The pattern of LLT use was similar regardless of ASCVD status (Fig. 2D and E).

### Use of LLT across countries

Results from individual countries largely mirrored the trends observed overall. Monotherapy was the most commonly used LLT across all patient subgroups (Fig. 3), regardless of the ASCVD status. The UK, Republic of Ireland, and Finland had the highest rates of monotherapy treatment (>70%) among all enrolled patients per country, and some of the lowest rates of combination treatment (<13%) (Fig. 3). Italy, Spain, and Portugal recorded the highest use of combination therapy (33.0%, 40.0% and 45.5% respectively).

## Discussion

Baseline data from the SANTORINI study evaluating contemporary clinical practice between 2020 and 2021 show that control of LDL-C in patients at high or very high CV risk remains suboptimal across Central and Western Europe, with the vast majority far from achieving guideline recommendations at enrolment. Compared with earlier studies, the use of combination therapies has increased but overall remains low with less than one third receiving combination therapy.[8,9,16]

A potential contributor to the current picture of LLT use could be underestimation of the CV risk by some

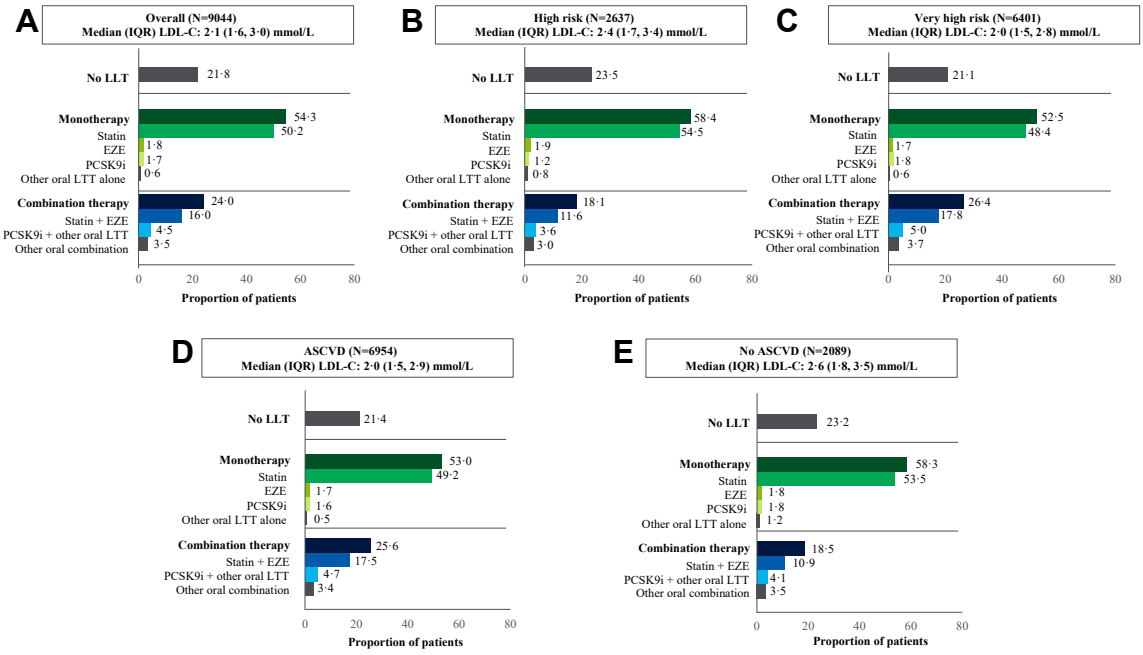


***Fig. 2:*** **Lipid-lowering treatment in A) overall; B) patients at high CV risk; C) patients at very high CV risk; D) patients with confirmed ASCVD; and E) patients without ASCVD.** Missing risk, n = 6. Percentages may not add up to 100% as they are rounded and there were unknown/missing data. Statin includes: high-intensity statins (atorvastatin 40–80 mg or rosuvastatin 20–40 mg), moderate-intensity statins (atorvastatin 10–20 mg, rosuvastatin 5–10 mg, simvastatin 20–40 mg, pravastatin 40–80 mg, lovastatin 40 mg, fluvastatin XL 80 mg, fluvastatin 40 mg BID, or pitavastatin 2–4 mg), and low-intensity statins (simvastatin 10 mg, pravastatin 1–20 mg, lovastatin 20 mg, fluvastatin 20–40 mg, or pitavastatin 1 mg). ASCVD, atherosclerotic cardiovascular disease; BID, twice-daily; CV, cardiovascular; EZE, ezetimibe; LDL-C, low-density lipoprotein cholesterol; LLT, lipid-lowering therapy; PCSK9i, proprotein convertase subtilisin kexin 9 inhibitor.

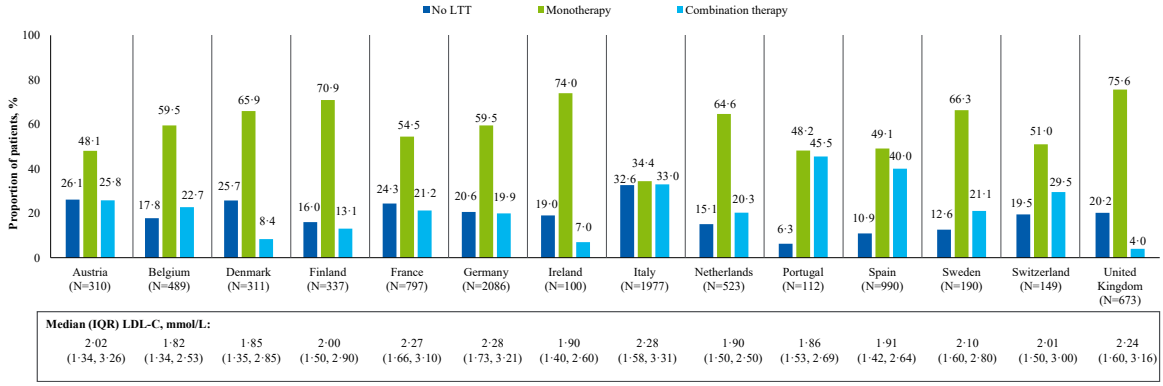


***Fig. 3:*** **Lipid-lowering treatment by country.** IQR, interquartile range; LDL-C, low-density lipoprotein cholesterol.

physicians. We observed that, although the 2019 ESC/EAS guidelines were the most frequently cited basis for classifying CV risk, the true risk was often underestimated: where physician assessment suggested 70.8% of patients were at very high CV risk, the centrally recalculated risk indicated that 91.0% were at very high risk. We acknowledge that clinical practice often lags behind guideline recommendations. The choice of LLT regimen (choice between high intensity treatment or combination of regimens) is likely influenced by physician perceptions of the CV risk; as in this study the patients' risk was underestimated, the need for treatment intensification may have been less obvious. Our data indicate a discordance between the assigned CV risk and lipid management, as a significant proportion of patients had either no documented LLT or were

receiving only monotherapy at enrolment. We assume that a proportion of these patients may have been newly diagnosed patients requiring LLT in combination with lifestyle or diet modification which may have occurred after the baseline data were captured. Furthermore, out of pocket expenses for medications, availability of therapies or a prior history of intolerance or unwillingness to use LLTs may have accounted for some of these cases. Of note, monotherapy-based approach and low utilisation of combination therapies was similar between those considered to be at high or very high risk. The individualised approach recommended by the 2021 ESC Prevention Guidelines[17] to assess global risk—and thus benefit—from different therapies may be of value, in particular the use of the SMART risk calculator for risk estimation in secondary prevention, as opposed to simply looking at the presence or absence of high risk traits to guide decision making. This approach has been assessed in trials[13] and general populations,[18] with an updated competing risks model validated in several geographical regions.[19]

The rationale behind the more stringent LDL-C goals recommended by the 2019 ESC/EAS guidelines is borne out of data showing that the addition of non-statin LLT, i.e., combination therapies, results in achieving lower LDL-C levels, and thus, a lower risk of CV events.[5] On this note, a key consideration is that for the vast majority of very high-risk patients, LDL-C goals cannot be achieved even with high-intensity statin monotherapy.[8] Therefore, the use of lower-intensity monotherapy regimens would result in lower rates of LDL-C goal achievement. In both the high- and very high-risk populations included in SANTORINI, the median LDL-C levels were well above the guideline-recommended goals: mean 2.4 mmol/L (93 mg/dL) and 2.0 mmol/L (78 mg/dL) in the high- and very high-risk patients, respectively, versus ESC/EAS goals of <1.8 mmol/L (<70 mg/dL) and <1.4 mmol/L (<55 mg/dL). Based on the Cholesterol Treatment Trialists' Collaboration regression line,[20] each risk category is, at a population level, 0.6 mmol/L above current recommended goals, potentially resulting in a 12–15% higher relative risk of CV events. If the present data reflect general European populations and clinical practice, then in a region such as Europe with an estimated population of 450 million people, a residual and potentially modifiable risk of 12–15% represents a considerable burden on CV health outcomes and financial burden on healthcare in the years to come.

In this study, mean LDL-C levels were consistently lower in the very high-risk group than in the high-risk group. The most reasonable explanations behind this data are a more intensive statin monotherapy treatment or a potentially better adherence to medications in patients with a prior history of ASCVD (who made up the majority of the cohort).[21] Additionally, more FH primary prevention patients were in the high-risk category, and, as these individuals tend to have higher LDL-C levels, their inclusion in this risk category may have been the driver for the difference observed, especially if they were patients who tend to have higher LDL-C levels even with conventional LLTs. It should be recognised that 5.0% of patients had LDL-C levels at goal, even though they were not on any documented LLT. There are several possible explanations for this, such as enrolment to the study before starting LLT (thus the prescribed treatment was not captured in this analysis), incorrect classification before recruitment or being at high or very high CV risk due to other risk factors which impact global risk without extremes of LDL-C elevation. These patients further underscore the multifactorial nature of CV risk and why LLT should not simply be considered on the basis of LDL-C levels, but rather on the basis of CV risk and LDL-C reduction as part of the strategy to reduce CV risk.[22]

The baseline data from the SANTORINI study provides contemporary European data and remains consistent with previous European studies conducted prior to the ESC/EAS guideline update in 2019. Sadly, the trend of implementation of guidelines in practice lags considerably behind evidence and guideline updates,[9,10,16] however, it would be of interest for future analyses to consider other relevant guidelines, such as national/regional guidelines, that may have an impact on physicians' decisions. Understandably, the timeframe between the 2019 ESC/EAS dyslipidaemia guidelines update and the data collection timing (2020–2021) might have been too short to allow for complete implementation of the recommendations in clinical practice. However, several previous observational studies, such as the Dyslipidemia International Study (DYSIS), DYSIS II and the EUROASPIRE surveys, which were conducted over several decades (1995–2018), have shown that despite sufficient time for them to be implemented, lipid management in patients with higher CV risk remains suboptimal, with failure to achieve historical guidelines a decade on, let alone to any new, more stringent set of guidelines.[7–9,16,23,24] More recently, the DA VINCI study (2017–2018) has shown that the majority of LLT in Europe is monotherapy, mainly comprising of moderate and high-intensity statin (51.8% and 27.6%, respectively), with only 33% of patients attaining the 2019 ESC/EAS guideline LDL-C goals.[8] Findings from the baseline data of the SANTORINI study were similar, suggesting that the gap between clinical guidelines and clinical practice for lipid management across Europe not only persists but widen with the new guidelines seemingly out of reach with monotherapy. Perhaps implementation would be better served through reducing barriers such as stepwise approaches and moving directly to recommending earlier use of combination therapies with both statins and generic non-statin LLTs, with newer, potentially more

expensive treatments reserved for those who do not achieve goal with dual therapy.

At a patient population level, the effect of lowering LDL-C goals inevitably places these out of the reach of monotherapy-based LLT. As doubling the dose of statins typically results in a further 6% LDL-C lowering, a greater use of combination therapy will be needed to achieve LDL-C levels <1.4 or 1.8 mmol/L (<55 or 70 mg/dL).[8] It may be appropriate, especially for patients with high and very high CV risk, to move from the concept of "high-intensity statin" to "high-intensity LLT", i.e., combination therapy.[25] Meta-analyses have shown that reductions in ASCVD risk with LDL-C-lowering agents are directly related to the absolute LDL-C reduction, irrespective of how this is achieved with currently available treatments.[5] Simulations have also shown that large numbers of CV events could be avoided through intensification of LLT in patients with ASCVD.[26] Although the personalised stepwise approach to LLT has its merits,[17] it may be practically harder to implement, and a simplified combination approach may be a pragmatic standard of care for initiating LLT.[27] The management of lipids is evolving with the greater availability of treatment options such as oral medication, including bempedoic acid[28,29] and ezetimibe which can reduce LDL-C by 38%, or injectable therapies, like inclisiran or monoclonal antibodies to PCSK9, which can reduce LDL-C by more than 50%. However, PCSK9i use is affected by local guideline recommendations and reimbursement constraints and may be restricted locally to those not reaching their LDL-C goals. For example, contemporary practice in Europe suggests that the average LDL-C at initiation is 4.0 mmol/L (154 mg/dL),[30] meaning that in the general population these treatments are being used for "outliers" with higher LDL-C levels, which often means they are not on oral agents, in order to be above the threshold for reimbursement. Thus, most patients will not be eligible for these treatments and will remain at increased CV risk.

The limitations of the present study merit consideration. Although the study was multicentre and conducted across diverse regions in Central and Western European countries, the sites participating in research (hospital or specialist centres) are often better at managing patients, and the present findings may reflect best-case scenarios; nevertheless, these were the main centres where high- and very high-risk patients were identified and thus enrolled. As Germany, Italy, and Spain are relatively among the larger countries in terms of population size, they had the greatest number of patients enrolled in the cohort which may have biased the overall results. Eastern and some Central European countries were not represented in this study, but it could be interesting to compare previous studies to SANTORINI. An underestimation of CV risk by the physicians was observed but potential driving factors of physician choices were not assessed in granularity as these were outside the scope of this study. This is an observational, non-interventional cross-sectional study, so adherence to medication, lifestyle and control of other risk factors were left to routine care and patient choices, and these aspects were not examined in this study. The planned 1-year of follow-up analysis of SANTORINI may help with answering outstanding questions, such as changes to LLT, adherence to treatment and what associations, if any, were between baseline characteristics and subsequent CV events.

## Conclusion

The baseline data from the SANTORINI study shows that despite the 2019 ESC/EAS guidelines seemingly being used widely across Europe to classify patients according to their level of CV risk, the goals are not being sufficiently implemented, resulting in a substantial proportion of patients remaining at high CV risk. Factors contributing to this may be inadequate risk classification and underutilization of combination therapies.

### Contributors

All other authors contributed to the study investigation. K.K.R., A.L.C., I.H. and A.B. contributed to study conceptualization and methodology. In addition, K.K.R. wrote the first draft. All authors reviewed and edited the manuscript and approved the final version.

### Data sharing statement

De-identified individual participant data and applicable supporting clinical study documents are available on request, depending on circumstances, at https://vivli.org. In cases in which clinical study data and supporting documents are provided pursuant to the sponsor's policies and procedures, the sponsor will continue to protect the privacy of the clinical study participants. Details on data sharing criteria and the procedure for requesting access can be found at https://vivli.org/ourmember/daiichi-sankyo/.

### Declaration of interests

K.K.R. has received honoraria for consulting, lectures from Abbott Laboratories, Amgen, Astra Zeneca, Bayer Healthcare Pharmaceuticals, Boehringer Ingelheim, Cargene, CRISPR, Daiichi Sankyo, Eli Lilly Company, Esperion, Kowa, New Amsterdam Pharma, Novartis Corporation, Novo Nordisk, Pfizer, Regeneron, Sanofi, SCRIBE, Silence Therapeutics, and VAXXINITY. In addition, he has received research grant support to his institution from Amgen, Daiichi Sankyo, Sanofi and Regeneron. A.L.C. has received honoraria, lecture fees, or research grants from: Aegerion, Amgen, Amryt, AstraZeneca, Amarin, Daiichi Sankyo, Esperion, Ionis Pharmaceutical, Kowa, Medscape, Menarini, Merck, Mylan, Novartis, PeerVoice, Pfizer, Recordati, Regeneron, Sandoz, Sanofi, The Corpus. In addition, he has received research grants from Sanofi, Eli Lilly, Mylan, Sanofi Regeneron, Menarini, and Amgen. J.F. has received lecture fees from Akcea, Amgen, Lilly, Mylan, MSD, Sanofi and Servier. C.A. has received honoraria for consultancy and/or lectures fees from Abbott, Daiichi Sankyo, Novartis, Medinfar, and Tecnimede. In addition, he has received support from Tecnimede for attending meetings and/or travel. D.L.C. has received fees for advisory boards, research and lectures from, Daiichi Sankyo, and Novartis. T.S. has received consulting fees and research and educational grants from Amgen, Novartis, Orion Pharma, Pfizer, Sankyo, Sanofi and Servier. He has received payment or honoraria for lectures by profit and non-profit entities; support by the European Geriatric Medicine Society for attending

meetings; he chaired the committee behind the publication of the National Finnish guideline for dyslipidaemia; lastly, he declared to be a statin patient. H.T. has received consulting and lecture fees as well as grants from Daiichi Sankyo. M.A. has received consulting and lecture fees from Alfasigma, Amgen, Amryt, IONIS/Akcea Therapeutics, Daiichi Sankyo, Novartis, Regeneron and Sanofi. He has also received research grants from Amgen, Amryt, IONIS/Akcea Therapeutics, Daiichi Sankyo, Novartis, Pfizer, Regeneron and Sanofi and payments for advisory board participation from Alfasigma, Amgen, Amryt, Pfizer. E.R. has received honoraria for lectures from Daiichi Sankyo, Servier and Novartis; payments for attending meetings from Sanofi; and for attending advisory boards from Amarin and Novartis; all paid directly to Ghent University. He is also President of the Belgian Atherosclerosis Society and a member of the Superior Health Council of Belgium, all voluntary roles. D.N. is or has been an investigator in clinical studies sponsored by Amgen, Pfizer, Daiichi Sankyo and Novartis; he has not received any personal fees for this work. J.M.M. has received lecture fees from Amgen, Daiichi Sankyo, Ferrer, Novartis, Servier, Sanofi and Viatris; and consultancy fees from Amgen, Sanofi, Novartis, Daiichi Sankyo, Servier. He has also received support from Sanofi and Amgen for attending meetings. U.L. has received honoraria for lectures and participation in advisory boards from Amgen, Daiichi Sankyo, Novartis and Sanofi. He has also received research grants to Leipzig University from Daiichi Sankyo, Amgen and Novartis, and is a member of DACH, DGK and ESC. I.H., M.C.M. and Aikaterini Bilitou are employees of Daiichi Sankyo and Annie Burden is a contract employee of Daiichi Sankyo. F.L.J.V. and M.E. declare no conflicts of interest.

#### Acknowledgements

Kausik Ray acknowledges support from the National Institute of Health Research Imperial Biomedical Research Centre and from the National Institute for Health and Care Research Applied Research Collaboration Northwest London. Alberico L. Catapano acknowledges support from the Italian Ministry of Health—Ricerca Corrente—IRCCS MultiMedica.

The authors would like to thank Florence Mercier for her statistical support and input. Medical writing support was provided by Martina Klinger Sikora and Stefan Courtney of inScience Communications, Springer Healthcare Ltd, UK, and was funded by Daiichi Sankyo Europe GmbH, Munich, Germany in accordance with Good Publication Practice (GPP3) guidelines (http://www.ismpp.org/gpp3).

Funding information: This study is funded by Daiichi Sankyo Europe GmbH, Munich, Germany.

#### Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.lanepe.2023.100624.

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