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FULL RESEARCH PAPER
Cardiovascular disease

Use of combination therapy is associated with improved LDL cholesterol management: 1-year follow-up results from the European observational SANTORINI study

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Aims To assess whether implementation of the 2019 European Society of Cardiology (ESC)/European Atherosclerosis Society (EAS) dyslipidaemia guidelines observed between 2020 and 2021 improved between 2021 and 2022 in the SANTORINI study.

Methods and results Patients with high or very high cardiovascular (CV) risk were recruited across 14 European countries from March 2020 to February 2021, with 1-year prospective follow-up until May 2022. Lipid-lowering therapy (LLT) and 2019 ESC/EAS risk-based low-density lipoprotein (LDL) cholesterol (LDL-C) goal attainment (defined as <1.4 mmol/L for patients at very high CV risk and <1.8 mmol/L for patients at high CV risk) at 1-year follow-up were compared with baseline. Of 9559 patients enrolled, 9136 (2626 high risk and 6504 very high risk) had any available follow-up data, and 7210 (2033 high risk and 5173 very high risk) had baseline and follow-up LDL-C data. Lipid-lowering therapy was escalated in one-third of patients and unchanged in two-thirds. Monotherapy and combination therapy usage rose from 53.6 and 25.6% to 57.1 and 37.9%, respectively. Mean LDL-C levels decreased from 2.4 to 2.0 mmol/L. Goal attainment improved from 21.2 to 30.9%, largely driven by LLT use among those not on LLT at baseline. Goal attainment was greater with combination therapy compared with monotherapy at follow-up (39.4 vs. 25.5%).

Conclusion Lipid-lowering therapy use and achievement of risk-based lipid goals increased over 1-year follow-up particularly when combination LLT was used. Nonetheless, most patients remained above goal; hence, strategies are needed to improve the implementation of combination LLT.

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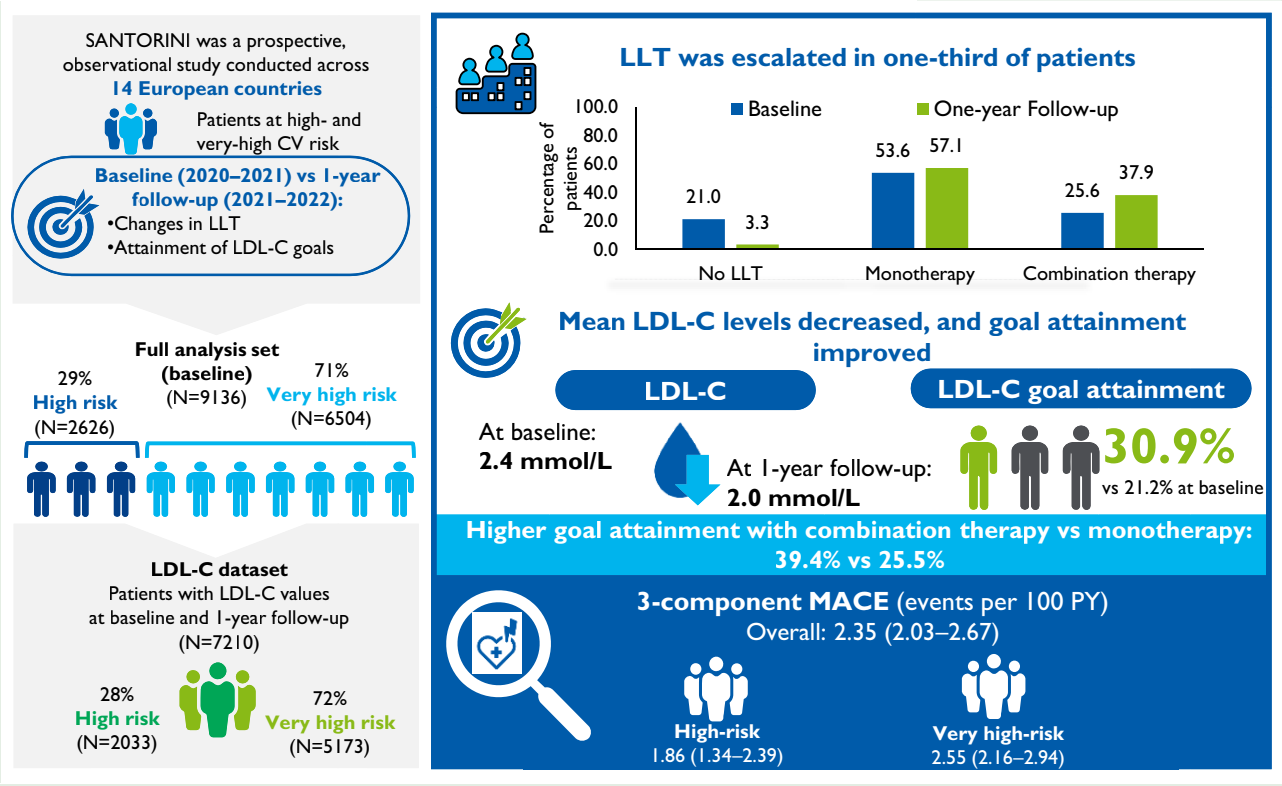
Lay summary

- Cardiovascular (CV) diseases, a group of disorders of the heart and blood vessels, are the most common cause of death worldwide. Lowering LDL cholesterol (LDL-C) in the bloodstream reduces the risk of the development of CV diseases such as heart attacks and strokes. Guidelines recommend that those at the highest risk of CV disease should achieve the lowest levels of LDL-C. Several medications are available that help lower LDL-C levels and prevent CV events; however, recent studies have shown that the majority of patients continue to have LDL-C levels above optimal value in part due to a suboptimal use of these medications.
- In this study, we report the results after 1 year of follow-up of the SANTORINI study (started in 2020), which aimed to document the management of LDL-C in clinical practice across 14 countries in Europe.
- We found that a better control of LDL-C occurred when more than one drug was used (combination therapy). The use of combination therapy was low at the start of the study (25.6%) but increased over 1 year to 37.9%, resulting in a better control of LDL-C at 1 year than observed at the start of the study. Nonetheless, only 31% of patients achieved their LDL-C target levels based on the European guidelines. A greater use of combination therapies is needed in order to improve the overall population-level control of LDL-C.

Graphical Abstract



Keywords Real-world clinical trials • Lipid • Dyslipidaemia • Europe • Cardiovascular risk

Introduction

Despite decreases in age-adjusted cardiovascular disease (CVD) mortality over the last 40 years,[1] more than 18 million deaths occur worldwide every year because of CVD, a large proportion of which are attributed to atherosclerotic CV disease (ASCVD).[2–4] The Global Burden of Disease Study in 2019 showed that high levels of low-density lipoprotein (LDL) cholesterol (LDL-C) were the second highest contributor to disability-adjusted life years lost globally, with an estimated 98.6 million life years lost.[5] In addition to diet and lifestyle, LDL-C-lowering pharmacotherapy is a proven strategy to prevent both incident and recurrent ASCVD events.[6] In 2019, the European Society of Cardiology (ESC) and the European Atherosclerosis Society (EAS) updated their joint guidelines to recommend more stringent LDL-C goals, particularly for those at high (<1.8 mmol/L) and very high (<1.4 mmol/L) risk.[7] We conducted the treatment of high- and very-high-riSk dyslipidaemic pAtients for the preveNTion of cardiOvasculaR events in Europe—a multInatioNal observatIonal (SANTORINI) study in the 2 years after these guidelines were published with the aim of evaluating their implementation gap.[8] In the previously published baseline analysis of SANTORINI (including more than 9000 patients across 14 European countries), only one-fifth of patients

achieved the 2019 risk-based LDL-C goals.[9] Overall, around 20% of patients had no documented evidence of lipid-lowering therapy (LLT) use, and most were receiving LLT monotherapy.[9]

In this prospective follow-up of the SANTORINI cohort, we assessed whether clinical practice improved with respect to LLT usage at 1 year compared with baseline. The impact of changes in LLT usage on LDL-C control and the attainment of risk-based LDL-C goals were also investigated. Moreover, the risk of CV events over 1 year of follow-up was assessed as a secondary endpoint.

Methods

Study design and objectives

SANTORINI (NCT04271280) was a prospective, observational, and descriptive study in high and very high CV risk patients across 14 European countries. Patients were recruited from 17 March 2020 to 11 February 2021, followed by 1 year of prospective follow-up (~12 ± 2 months after baseline) with a database lock on 31 May 2022. The rationale and methods used in SANTORINI have been described previously.[8] The primary objective of the 1-year follow-up was to assess changes in LLT and attainment of risk-based LDL-C goals (as per the 2019 ESC/EAS dyslipidaemia guidelines) at 1 year compared with baseline. Cardiovascular events during follow-up were assessed as a secondary objective, and all-cause death was assessed as an exploratory endpoint. Baseline and 1-year follow-up data were collected from the patient records of lipid-management-related visits during which a patient had been seen by the physician. No formal visits, examinations, laboratory tests, or procedures were mandated beyond the documentation of data on routine clinical practice.

Participants and variables

Patients requiring LLTs were eligible for enrolment if they were aged 18 years or older and considered by the investigator to be at high or very high CV risk. Briefly, based on the 2019 ESC/EAS guideline criteria, high-risk patients are those with a significantly elevated single risk factor [such as total cholesterol (TC) >8 mmol/L (>310 mg/dL), familial hypercholesterolaemia (FH), and elevated blood pressure], patients with diabetes mellitus with or without target organ damage or for more than 10 years, moderate chronic kidney disease [estimated glomerular filtration rate (eGFR) 30–59 mL/min], or calculated SCORE 10-year risk for fatal CVD ≥5 and <10%. Very high-risk patients are those with documented ASCVD, diabetes mellitus, type 1 diabetes mellitus with target organ damage or additional major risk factors such as smoking, marked hypercholesterolaemia, or marked hypertension, moderate or severe chronic kidney disease (eGFR <30 mL/min), or calculated SCORE 10-year risk for fatal CVD ≥10%. There were no specific exclusion criteria, but those enrolled had to have an anticipated life expectancy of >1 year.[7] The SANTORINI study was performed in accordance with the Declaration of Helsinki and Good Clinical Practice. All patients were asked to provide written informed consent before participating in the study. Patients were recruited from primary (i.e. general practitioner and internal medicine specialist) and secondary (i.e. cardiologist, diabetologist, lipidologist, and neurologist) care sites with no specific physician selection criteria.[8] Some sites were classified as both primary and secondary care. The CV risk category was assigned by the physician at enrolment, and the basis for risk classification was documented. Patients' characteristics, medical history, LLT, and other co-medications were documented at baseline. Data on routine management since baseline were documented at the 1-year follow-up visit. LDL-C goal attainment was based on thresholds from the 2019 ESC/EAS guidelines, defined as <1.4 mmol/L for patients at very high risk and <1.8 mmol/L for patients at high risk. Cardiovascular events of interest included CV death, three-component major adverse CV events [MACEs; death from CV causes, non-fatal myocardial infarction (MI), or non-fatal stroke], and four-component MACE (death from CV causes, non-fatal MI, non-fatal stroke, or coronary revascularization events). No adjudication was set up in this observational study, and events were analysed as reported by the investigators. In case the cause of death was unknown, in a worst-case approach, the event was considered in the analysis of CV death. A dedicated monitoring plan was implemented to ensure quality and exhaustively collect data. All-cause death was also assessed as an exploratory endpoint.

Statistical analysis

With a cohort of 9000 included patients, an absolute precision (mid-width) on the 95% confidence interval of 0.002–0.006 could be reached for 1–8% event rates. These rates correspond to the range of expected rates of CV death and three-component MACE over 1 year. They are based on the ESC/EAS 2019 guidelines' 10-year rate for CV death,[7] assuming an exponential distribution of events and observed proportions of three-component MACEs with regard to CV death observed in the FOURIER randomized clinical trials and REACH registry.[10,11] This would correspond to relative precisions of 0.07–0.21.

Analyses of baseline characteristics, LLTs, as well as CV events of interest were implemented on all included patients presenting with any available follow-up data [hereafter called full analysis set (FAS)]. Analyses of LDL-C values and goal achievement across follow-up were implemented on an LDL-C data set including patients with LDL-C data available at both baseline and follow-up. The LDL-C values were considered as reported by the investigators. Only in case of absence of the LDL-C value and presence of TC, high-density lipoprotein (HDL), and trigylceride (TG) values collected at the same date, missing LDL-C values were recalculated using the Friedewald formula.

Descriptive statistics are presented as standard summary measures [mean and standard deviation (SD), median and interquartile range (IQR), counts, and proportions]. No imputation was performed for missing data. No formal statistical tests were performed.

Incidence of CV events of interest and all-cause death during follow-up were estimated based on first events and are presented as event rates per 100 patient-years (PY) at risk. Subgroup analyses were performed based on investigator-assessed risk classification at baseline, ASCVD status at baseline, baseline LDL-C levels, and treatment intensity (no-change = no-change in LLT; escalation = increase in the number or intensity of LLT; de-escalation = decrease in the number or intensity of LLT; Supplementary material online, *Table S3*). All statistical analyses were performed using Statistical Analysis System (SAS®) Version 9.4.

Results

Patient characteristics

A total of 9559 patients were enrolled, of whom 9136 had any available 1-year follow-up data and were included in the FAS. Of these 9136 patients, 7210 (78.9%) had LDL-C data available at both baseline and 1-year follow-up and were included in the LDL-C data set; 7069 (77.4%) had ASCVD; 3275 (35.8%) were enrolled at a primary care site and 7026 (76.9%) were enrolled at a secondary care site; 1165 (12.8%) patients were common to both type of sites (see Supplementary material online, *Figure S1*). Of the 9136 patients, 6504 (71.2%) were classified as very high risk and 2626 (28.7%) were classified as high risk by the investigator at baseline. Risk category classification was missing for six patients (see Supplementary material online, *Figure S1*).

Baseline demographic characteristics and LDL-C of patients in the LDL-C data set were generally similar to the patients in the FAS (*Table 1*). There were some differences in the demographic characteristics between patients enrolled at primary and secondary care sites, such as a higher proportion of males (66.4 vs. 74.5%) and very high CV risk patients (58.1 vs. 76.3%) and a lower proportion of heterozygous FH patients (14.8 vs. 9.1%) in the latter. However, age and risk factors such as LDL-C levels and systolic blood pressure were similar (see Supplementary material online, *Table S4*).

Among all 14 participating European countries, the highest proportion of patients were recruited from Germany (23.6%), Italy (21.8%), and Spain (11.1%). There were no major differences in the proportion of patients from different countries in the FAS or LDL-C data sets (see Supplementary material online, *Table S5*). Mean LDL-C values in the LDL-C data set across the countries ranged from 2.1 to 2.6 mmol/L (80.9 to 100.7 mg/dL; see Supplementary material online, *Table S6*). Compared with patients at high CV risk, those at very high risk had a larger proportion of patients with hypertension (66.5 vs. 73.2%); the

Table 1 Baseline characteristics for overall and LDL cholesterol patient population sets

Characteristic	Overall ($n = 9136$)	LDL-C data set ($n = 7210$)
Male, *n* (%)	6647 (72.8)	5197 (72.1)
Age, years, mean (SD)	65.5 (10.9)	65.0 (10.8)
Risk classification assigned by investigator, *n* (%)		
Missing risk	6 (0.1)	4 (0.1)
Very high risk	6504 (71.2)	5173 (71.8)
High risk	2626 (28.7)	2033 (28.2)
ASCVD, *n* (%)	7069 (77.4)	5521 (76.6)
BMI, kg/m^2, mean (SD)	28.3 (4.9)	28.2 (4.8)
Systolic blood pressure, mmHg, mean (SD)	134.0 (18.1)	133.7 (17.8)
Diastolic blood pressure, mmHg, mean (SD)	77.9 (10.5)	78.0 (10.3)
Hypertension, *n* (%)	6508 (71.2)	5090 (70.6)
Diabetes, *n* (%)	3192 (34.9)	2515 (34.9)
eGFR, mL/min/1.73 m^2, mean (SD)	77.9 (24.0)	78.8 (23.7)
Heterozygous familial hypercholesterolaemia, *n* (%)	934 (10.2)	800 (11.1)
Smoking history, *n* (%)		
Current	1504 (16.5)	1162 (16.1)
Former	3878 (42.5)	3032 (42.1)
Never	3664 (40.1)	2957 (41.0)
LDL-C, mean (SD)		
mmol/L	2.4 (1.2)	2.4 (1.2)
mg/dL	92.8 (46.5)	93.5 (47.1)

ASCVD, atherosclerotic cardiovascular disease; BMI, body mass index; eGFR, estimated glomerular filtration rate; LDL-C, LDL cholesterol; SD, standard deviation.

proportion of patients with diabetes was similar between risk categories (34.8 vs. 35.0%; Supplementary material online, *Table S7*). The LDL-C was lower in patients at very high risk compared with high risk (2.3 vs. 2.7 mmol/L). Baseline demographics of patients with and without ASCVD are presented in Supplementary material online, *Table S8*.

Lipid-lowering therapy use at baseline and end of follow-up

Table 2, *Figure 1*, and Supplementary material online, *Figure S2* report changes in LLT use from baseline to end of 1-year follow-up in the FAS. Over the course of 1-year follow-up, the proportion of individuals on no LLT fell from 20.9 to 3.3% in the overall FAS population. When stratified by high- and very-high-risk status, the proportion of patients receiving no LLT fell from 22.8 to 5.8% and 20.1 to 2.3%, respectively. In the overall FAS, the use of any LLT as monotherapy rose from 53.6 to 57.1% with a rise in statin monotherapy use from 49.4 to 52.7%. This increase in statin monotherapy use was higher in patients with high CV risk (54.0% at baseline to 61.5% at the end of 1-year follow-up) when compared with those with very high CV risk (47.6 to 49.1%). Overall, prescribing patterns of statin monotherapy at baseline and 1 year were: 1.5 vs. 1.3%, 25.5 vs. 24.7%, and 21.5 vs. 25.8% for low, moderate, and high-intensity statin use, respectively (see Supplementary material online, *Table S9* for statin intensity categorization). Changes in the use of any other oral LLT monotherapy regimen (ezetimibe or bempedoic acid) were modest, and the use of proprotein convertase subtilisin/kexin Type 9 inhibitors (PCSK9is) as monotherapy rose from 1.7 to 2.2% in the FAS.

The largest change was the increase in the use of any combination therapy from 25.6 to 37.9% in the overall group, with a greater increase in the number of patients at very high CV risk (28.2 to 42.4%) compared with those at high CV risk (19.1 to 26.9%). This mostly reflected an increased use of statin and ezetimibe combination in the overall group (17.1 to 26.4%), and high-risk (12.1 to 17.0%) and very-high-risk patients (19.1 to 30.3%). While the use of moderate intensity statins as part of oral combination therapy rose from 6.0 to 7.7% in the overall FAS, there was a greater use of high-intensity statins at the end of the study—an increase from 10.3 to 17.7% (*Table 2*). The use of PCSK9i as part of combination therapy with another oral LLT also increased from 4.7 to 6.6% in the FAS.

In general, similar patterns of higher intensity LLT regimen use (both monotherapy and combination therapy) were observed in primary and secondary care settings at the end of 1-year follow-up vs. baseline (see Supplementary material online, *Table S10*). Among patients with ASCVD, the use of high-intensity statin monotherapy increased from 24.0 to 28.7%. Combination therapy use increased from 27.3 to 41.2%. This reflected an increase in the use of statin and ezetimibe combination from 18.7 to 29.5%, with the greatest increase in the use of high-intensity statin combination, from 11.6 to 20.5% (see Supplementary material online, *Table S11*).

Among the FAS, there was an escalation in the treatment for 29.3% ($n = 2674$) of patients, no change in the treatment for 66.6% ($n = 6080$) of patients, and de-escalation in the treatment for 2.5% ($n = 227$) of patients. Treatment intensification could not be determined due to missing LLTs in 1.7% ($n = 155$) of patients. For patients at very high CV risk, there was an escalation in treatment for 30.6% of patients, no change in treatment for 64.9% of patients, and de-escalation in treatment for 2.6% of patients. For patients with high CV risk, there was an escalation in the treatment for 26.0% of patients, no change in the treatment for 70.6% of patients, and de-escalation in the treatment for 2.2% of patients.

Use of lipid-lowering therapy across countries

Results from the individual countries mirrored the trends observed in the overall population. At the end of 1-year follow-up, increased usage of more potent monotherapy regimens and combination therapies was observed across all countries with the highest increase in combination therapy use observed in Italy, Austria, and Belgium (33.8 vs. 55.5%, 28.2 vs. 45.6%, 26.1 vs. 38.5% for combination therapy at baseline and 1-year follow-up, respectively; *Figure 2*).

Changes in LDL cholesterol control over 1 year

Figure 3A shows LDL-C at baseline and 1-year follow-up in the overall LDL-C data set and by physician-classified CV risk at baseline. Mean (SD) LDL-C levels decreased from 2.4 (1.2) to 2.0 (0.9) mmol/L in the overall population. This decrease reflects changes in both the high-risk group from 2.7 to 2.3 mmol/L and the very-high-risk group from 2.3 to 1.9 mmol/L. As expected, patients not receiving LLT at baseline had a higher mean (SD) baseline LDL-C compared with those on LLT [3.5 (1.3) vs. 2.1 (1.0) mmol/L]. At the end of 1-year follow-up, in the patients not on LLT at baseline, 58.1% were on monotherapy and 28.2% on combination therapy, compared with 56.8 and 40.5%, respectively, for those who were on LLT at baseline (see Supplementary material online, *Table S12*). Among patients on LLT at baseline, mean (SD) LDL-C changed marginally over 1 year from 2.1 (1.0) to 1.9 (0.9) mmol/L. Moreover, the patient population receiving LLT at baseline had a higher proportion of patients with hypertension

Table 2 Lipid-lowering therapies at baseline and 1-year follow-up overall, and in patients with high cardiovascular risk and very high cardiovascular risk (full analysis set)

	Overall ($n = 9136$)		High CV risk ($n = 2626$)		Very high CV risk ($n = 6504$)	
LLT, *n* (%)	**Baseline**	**1-year follow-up**	**Baseline**	**1-year follow-up**	**Baseline**	**1-year follow-up**
Missing	0 (0.0)	155 (1.7)	0 (0.0)	32 (1.2)	0 (0.0)	123 (1.9)
No LLT	1909 (20.9)	303 (3.3)	598 (22.8)	152 (5.8)	1307 (20.1)	150 (2.3)
Total monotherapy	4892 (53.6)	5214 (57.1)	1527 (58.2)	1735 (66.1)	3363 (51.7)	3474 (53.4)
Statin alone	4516 (49.4)	4812 (52.7)	1417 (54.0)	1614 (61.5)	3097 (47.6)	3193 (49.1)
Missing intensity	89 (1.0)	80 (0.9)	34 (1.3)	26 (1.0)	55 (0.9)	54 (0.8)
Low intensity	135 (1.5)	116 (1.3)	48 (1.8)	47 (1.8)	87 (1.3)	69 (1.1)
Moderate intensity	2331 (25.5)	2258 (24.7)	896 (34.1)	984 (37.5)	1434 (22.1)	1270 (19.5)
High intensity	1961 (21.5)	2358 (25.8)	439 (16.7)	557 (21.2)	1521 (23.4)	1800 (27.7)
Ezetimibe alone	170 (1.9)	146 (1.6)	53 (2.0)	53 (2.0)	117 (1.8)	93 (1.4)
PCSK9i alone	151 (1.7)	202 (2.2)	32 (1.2)	45 (1.7)	119 (1.8)	157 (2.4)
Any other oral LLT alone[a]	55 (0.6)	54 (0.6)	25 (1.0)	23 (0.9)	30 (0.5)	31 (0.5)
Total combination therapy	2335 (25.6)	3464 (37.9)	501 (19.1)	707 (26.9)	1834 (28.2)	2757 (42.4)
Combination statin + ezetimibe	1561 (17.1)	2414 (26.4)	317 (12.1)	445 (17.0)	1244 (19.1)	1969 (30.3)
Missing intensity	43 (0.5)	56 (0.6)	8 (0.3)	12 (0.5)	35 (0.5)	44 (0.7)
Low intensity	37 (0.4)	39 (0.4)	8 (0.3)	9 (0.3)	29 (0.5)	30 (0.5)
Moderate intensity	544 (6.0)	706 (7.7)	127 (4.8)	174 (6.6)	417 (6.4)	532 (8.2)
High intensity	937 (10.3)	1613 (17.7)	174 (6.6)	250 (9.5)	763 (11.7)	1363 (21.0)
PCSK9i combination	430 (4.7)	600 (6.6)	99 (3.8)	142 (5.4)	331 (5.1)	458 (7.0)
Any other combination therapy[b]	344 (3.8)	450 (4.9)	85 (3.2)	120 (4.6)	259 (4.0)	330 (5.1)

BA, bempedoic acid; FDC, fixed dose combination; LLT, lipid-lowering therapy; PCSK9i, proprotein convertase subtilisin/kexin Type 9 inhibitor.
[a]This includes bempedoic acid alone.
[b]This category also includes BA FDC, BA combination therapy, and BA FDC + statin combination.

(72.8 vs. 65.4%) and diabetes (37.4 vs. 25.5%) compared with those not on LLT (see Supplementary material online, *Table S13*). This pattern was consistent across countries (see Supplementary material online, *Table S14*). *Figure 3B* shows the changes in LDL-C in those on LLT and those not on LLT at baseline, both overall and further stratified by risk category. Among patients with ASCVD, mean (SD) LDL-C levels at baseline were 2.3 (1.1) and 1.9 (0.9) mmol/L at the end of the 1-year follow-up period.

Risk-based LDL cholesterol goal attainment at baseline and follow-up

At baseline, among the 7210 patients in the LDL-C data set, 21.2% (overall), 24.4% (high risk), and 20.0% (very high risk) of patients were at goal. The proportion of patients at goal at the end of 1 year increased to 31.0% (high risk) and 30.9% (very high risk) reflecting overall goal attainment of 30.9% (*Figure 4*). This was largely driven by an overall improvement among those not on LLT at baseline, with goal attainment increasing from 4.9% at baseline to 29.0% at 1-year follow-up. In contrast, the improvement in goal attainment among those on LLT at baseline was modest, rising from 25.7% at baseline to 31.4% at 1-year follow-up (*Figure 5*).

When patients receiving no LLT at baseline were stratified by treatment type at 1-year follow-up [monotherapy ($n = 923$) or combination therapy ($n = 474$)], 39.9% of patients receiving combination therapy were at LDL-C goal at follow-up compared with 27.5% receiving monotherapy (*Figure 5A*).

Furthermore, similar stratification by treatment type at 1-year follow-up in patients receiving LLT at baseline [monotherapy ($n = 3065$) or combination therapy ($n = 2531$)] showed that 39.4% of patients receiving combination therapy were at LDL-C goal at follow-up compared with 25.5% receiving monotherapy (*Figure 5B*). Among patients with ASCVD, the proportion of patients achieving risk-based LDL-C goals increased from 22.0% at baseline to 33.0% at 1-year follow-up.

The proportions of patients achieving LDL-C goals for all countries are presented in *Figure 6*. When data were assessed by country, the greatest improvement in the proportion of patients achieving risk-based LDL-C goals at the end of 1-year follow-up vs. baseline was observed in Switzerland (36.3 vs. 15.7%) followed by Italy (35.0 vs. 20.8%; *Figure 6*). Of note, in Portugal, the proportion of patients at goal fell from 30.4 to 22.5%.

Cardiovascular risk

In the FAS, 88 patients died due to CV causes; 497 had at least one four-component MACE, and 213 had at least one three-component MACE. These reflected 0.96 (0.76–1.17) CV deaths, 5.60 (5.11–6.10) first four-component MACEs, and 2.35 (2.03–2.67) first three-component MACEs per 100 PY of follow-up. Among those categorized as very high risk by the investigator ($n = 6504$), 164 had at least one three-component MACE corresponding to 2.55 (2.16–2.94) first three-component MACEs per 100 PY of follow-up. Among those categorized as high risk by the investigator ($n = 2626$), 49 had at least one three-component MACE corresponding to 1.86 (1.34–2.39) first three-component MACEs per 100 PY of follow-up.

Among patients with ASCVD ($n = 7069$), 82 died due to CV causes; 476 had at least one four-component MACE, and 194 had at least one three-component MACE. These reflected rates of 1.16 (0.91–1.42) CV deaths, 7.01 (6.38–7.64) first four-component MACEs, and 2.78 (2.39–3.17) first three-component MACEs per 100 PY of follow-up.

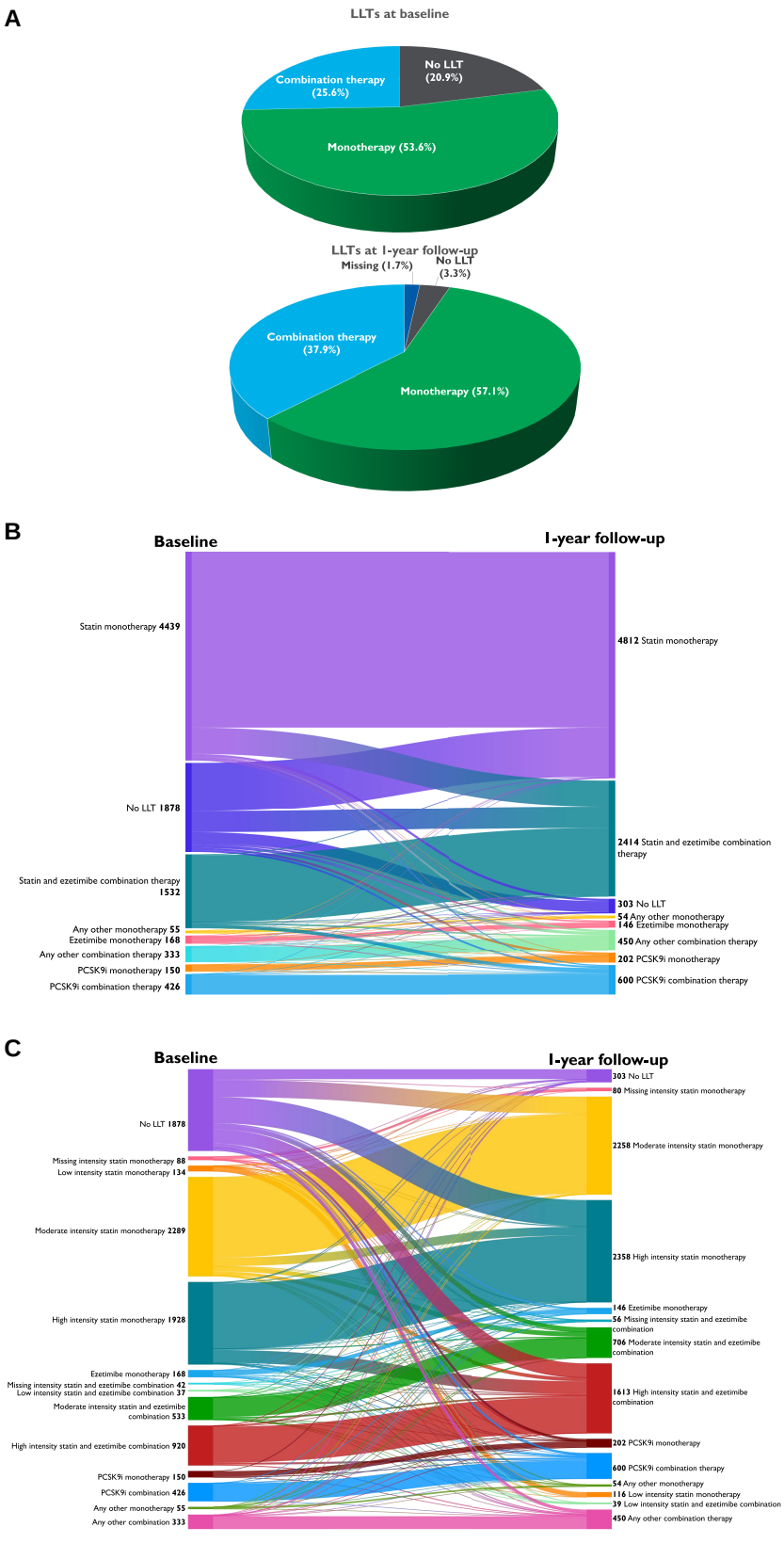


Figure 1 (*A*) Monotherapy and combination therapy at baseline and 1-year follow-up; (*B*) flow of patients between different lipid-lowering therapies at baseline and 1-year follow-up; (*C*) flow of patients between different intensities of statin at baseline and 1-year follow-up. LLT, lipid-lowering therapy; PCSK9i, proprotein convertase subtilisin/kexin Type 9 inhibitor. Sankey diagrams created using Flourish [flourish.studio].

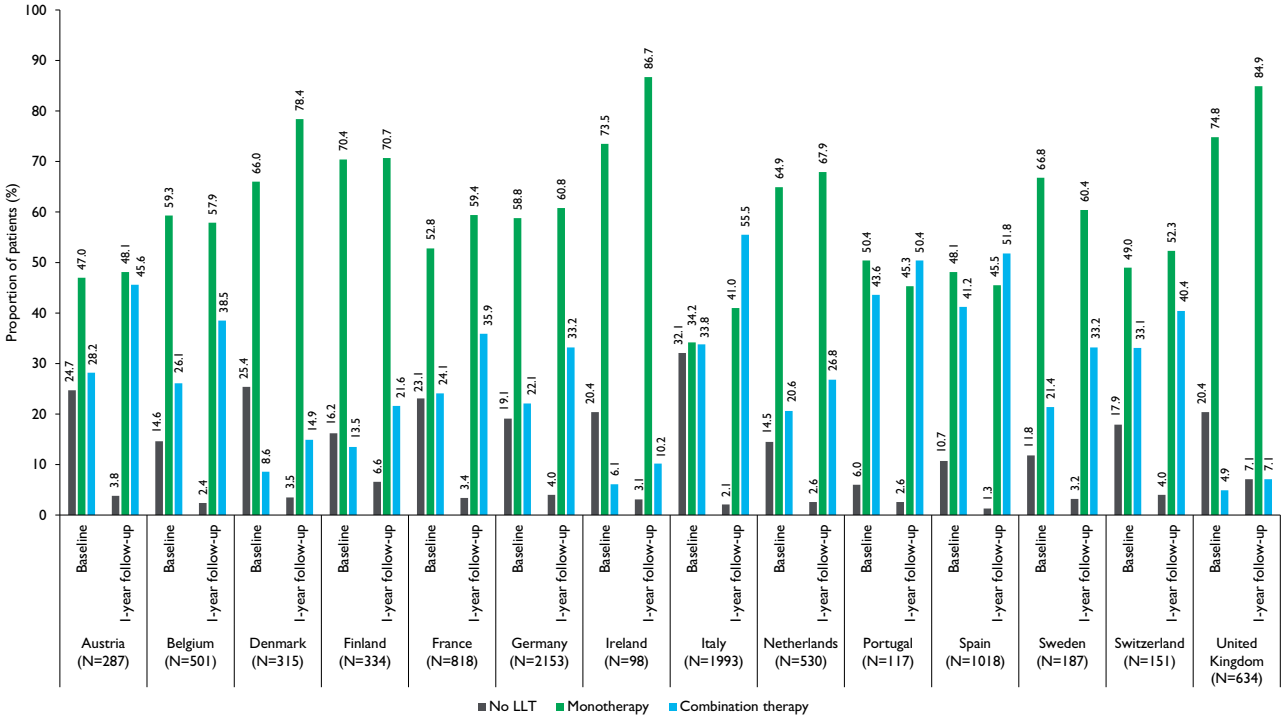


Figure 2 The use of lipid-lowering therapy by country. LLT, lipid-lowering therapy.

All-cause death

In the FAS, 152 patients died due to any cause, reflecting 1.66 (1.40–1.93) deaths per 100 PY of follow-up. Among those categorized as very high risk by the investigator, 122 died due to any cause reflecting 1.88 (1.55–2.22) deaths per 100 PY of follow-up. Among those categorized as high risk by the investigator, 30 died due to any cause reflecting 1.14 (0.73–1.54) deaths per 100 PY of follow-up.

Reflexive treatment intensification after cardiovascular events

Of interest, among those with non-fatal three- and four-component MACEs during the 1-year follow-up, treatment escalation vs. de-escalation was observed in 46 vs. 3 (three-component MACE) and 193 vs. 12 (four-component MACE) patients overall. Treatment escalation occurred more often in patients classified as very high risk at baseline and who had CV events compared with high-risk patients. Escalation vs. de-escalation was observed in 37 vs. 2 (MI or stroke) and 162 vs. 10 (MI, stroke, or revascularization) very-high-risk patients and in 9 vs. 1 (MI or stroke) and 30 vs. 2 (MI, stroke, or revascularization) high-risk patients.

Discussion

In the largest European study to date conducted after the 2019 ESC/EAS guidelines for the management of dyslipidaemia were published,[7] we observed improvements in mean LDL-C levels of ~0.4 mmol/L in both high- and very-high-risk patients over 1 year of longitudinal follow-up. This was largely driven by the initiation of LLT among those not on LLT at baseline, as well as a greater use of combination therapies over the follow-up period. Lower LDL-C levels translated into greater LDL-C goal attainment, increasing from one in five at baseline to ~one in three at 1-year follow-up. The findings of the present study are consistent with previous data suggesting that combination therapies improve LDL-C goal attainment.[12–14]

Despite improvements in LLT implementation, the mean LDL-C levels for high- and very-high-risk patients were ~0.4 to 0.5 mmol/L above respective risk-based LDL-C goals. Treatment intensification over the follow-up period was mostly in the form of oral combination therapies with the addition of ezetimibe to statins. In patients not using LLT at baseline, 1-year LDL-C goal attainment was higher among those receiving combination therapy than any monotherapy. Notably, LLT regimens were not intensified for two-thirds of patients over the follow-up period.

The approaches to lipid-lowering management changed during follow-up both for patients who were on LLT and for those not receiving LLT at baseline. For instance, among patients receiving LLT at baseline, the use of statin monotherapy fell by 10% and was accompanied by an increase in the use of combination therapy, including ezetimibe and PCSK9i as combining agents. Among patients not receiving LLT at baseline, at 1 year, the approaches to lipid management mirrored the treatment choice of those on LLT at baseline, namely statin monotherapy, statin plus ezetimibe, and PCSK9i in combination with an oral agent. The low use of PCSK9i overall may reflect the stepwise approach advocated in the 2019 ESC/EAS guidelines and the relatively higher cost of injectables, as well as restrictions to their access/reimbursement in different countries.[15,16] Use of bempedoic acid was low, reflecting the relatively recent entry of this therapy into the healthcare system from 2020 onwards. Notably, in Germany, the lipid pathways based on reimbursement criteria now mandate the use of statins plus ezetimibe plus bempedoic acid prior to either PCSK9i (i.e. evolocumab or alirocumab) or small interfering ribonucleic acid-based therapy (i.e. inclisiran).

There was no obvious explanation for the proportionally greater use of oral combination therapies over 1 year in those not receiving any LLT at baseline. With the exception of higher LDL-C levels (3.5 vs. 2.2 mmol/L),

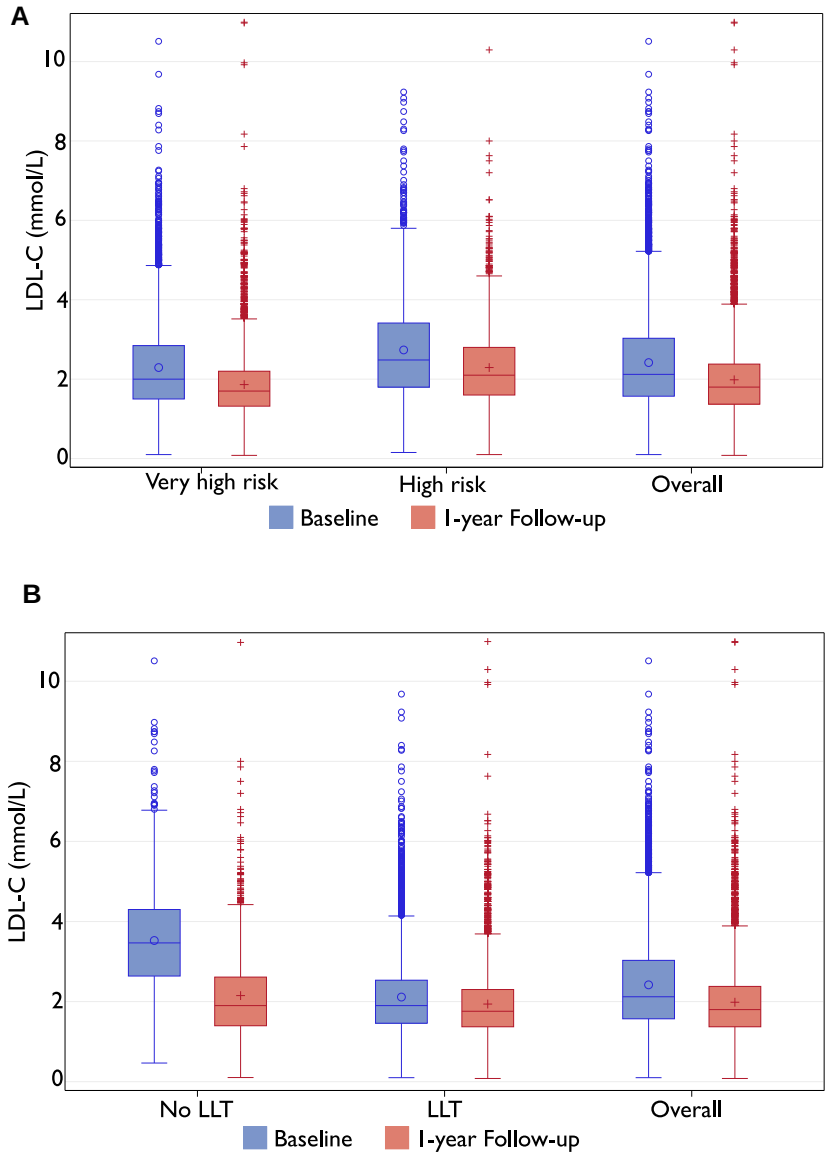


Figure 3 (*A*) The LDL cholesterol at baseline and 1-year follow-up in very high cardiovascular risk, high cardiovascular risk, and overall populations (LDL cholesterol data set). (*B*) The LDL cholesterol at baseline and 1-year follow-up in patients with lipid-lowering therapy and no lipid-lowering therapy at baseline (LDL cholesterol data set). LDL-C, LDL cholesterol; LLT, lipid-lowering therapy.

demographic characteristics and healthcare settings were generally similar. It was not known, for instance, how long those on LLT at baseline were maintained on the initial regimens prior to entry into the study. The modest treatment intensification during the 1 year of follow-up may reflect a lack of urgency to optimize LLT in asymptomatic patients. Moreover, escalation of LLT occurred in some patients after a non-fatal MACE, perhaps highlighting the shortcomings in risk perception in otherwise asymptomatic patients, thereby to delays in LLT optimization.

Approaches to the management of patients with and without ASCVD over the course of the follow-up period varied. For instance, among patients with ASCVD, use of statin monotherapy, statin plus ezetimibe combination therapy, and PCSK9i combination, increased by 1.8, 10.8, and 1.9%, respectively, whereas for those without ASCVD, the corresponding figures were 8.0, 4.2, and 1.7%, respectively. As noted in our previous publication,[9] at baseline, many physicians misclassified patients with ASCVD as high risk, when they should have been considered as very high risk, based on the ESC/EAS guideline criteria. Examining changes in practice based on physician perceptions of risk merits comparison with the objective assessment of ASCVD (present or absent). Intensification of LLT during follow-up also differed between care settings. For instance, among patients in primary care, use of statin monotherapy, statin plus ezetimibe combination therapy, and PCSK9i combination, increased by 1.8, 4.9, and 1.9%, respectively, whereas for those in secondary care, the corresponding figures were 3.1, 10.9, and 2.0%, respectively. Although most demographic characteristics were similar, there were fewer patients with ASCVD managed by primary care in SANTORINI. Taken together, these data suggest that intensification of LLT occurred for patients with ASCVD, more often in secondary care, and through the addition of ezetimibe to statin therapy.

The pattern of care across individual countries in Europe generally reflected the overall findings, with the vast majority of those not receiving LLT at the start of the study initiating LLT and a greater use of

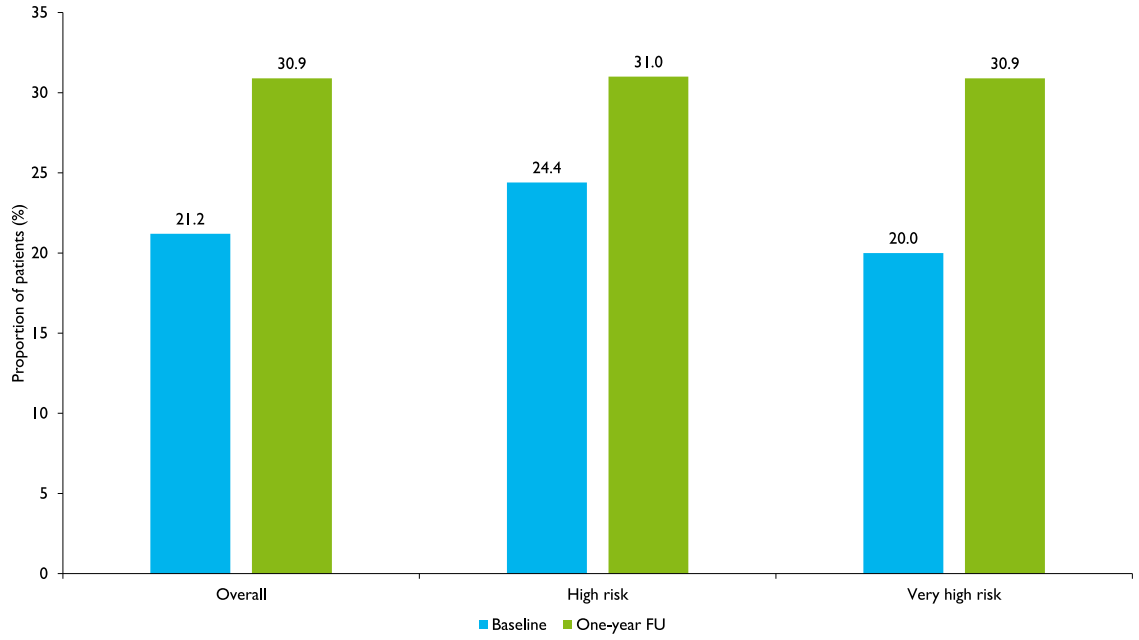


Figure 4 Risk-based LDL cholesterol goal attainment at baseline and 1-year follow-up (LDL cholesterol data set). FU, follow-up; LDL-C, LDL cholesterol.

combination therapies in general used over the year. That said, the use of combination therapies varied widely at the end of follow-up, ranging from 7.1% in the UK to 55.0% in Italy. With respect to risk-based goal attainment, this was lowest in France and Germany with only ~23% of patients at LDL-C goal, the highest was Austria at 43.9% and no country achieved more than 50% of patients at goal. It is not clear whether a greater proportion of patients would have reached their risk-based goals with longer follow-up. Ezetimibe is an effective, well tolerated, and accessible add-on therapy to statins. A greater proportion of patients may have reached their risk-based goals with greater use of ezetimibe and statin combination therapy, which was underutilized in this population at 1-year follow-up (26.4% of patients). However, a simulation study based on the Da Vinci data set (thus prior to publication of the ESC/EAS 2019 guidelines) suggested that even if statins and ezetimibe were optimized, only about half of patients at very high risk would achieve goal with two therapies, with either the need for a third oral agent, such as bempedoic acid, or an injectable therapy directed against PCSK9.[13] A similar simulation using a large administrative database of US medical and pharmacy claims found that 67.3% of patients could achieve an LDL-C level of 70 mg/dL with statin monotherapy, a further 18.7% with statins plus ezetimibe, and a further 14% with an injectable therapy directed against PCSK9.[17] Introducing partial and full statin intolerance to 10% of the overall population in this simulation increased the need for ezetimibe to 34.9 and 38.5%, respectively, and the need for PCSK9i to 15.5 and 20%, respectively.[18,19]

The LDL-C levels in the population of high- and very-high-risk patients improved by ~0.4 to 0.5 mmol/L, suggesting that at the population level, CV event risk would have been reduced by ~10 to 11% in relative terms extrapolating from Cholesterol Treatment Trialists' Collaboration.[20] Nevertheless, the high- and very-high-risk groups were still 0.4 to 0.5 mmol/L above respective goals, meaning that a further lowering of risk by 10 to 11% would be feasible if LLT goals were achieved. Although we were unable to assess the relationship between improvement in LDL-C control and subsequent outcomes due to the very short follow-up, the risk of three- or four-component MACE at 1 year was high. Indeed, considering that all but one-fifth were on LLT at baseline, the 1-year risk of CV death approached the 1% per year used to define high-risk primary prevention prior to LLT (based on the old SCORE risk assessment tool).[21] Event rates tend to be higher with higher LDL-C levels.

The 2019 ESC/EAS guidelines only recommend initiating upfront combination therapy if a patient is >50% away from their LDL-C goal; all other patients are managed using a stepwise approach. The stepwise approach advocated by the ESC/EAS 2019 Dyslipidaemia and the 2021 ESC Prevention Guidelines inevitably delays goal achievement owing to the number of steps involved. This could easily be circumvented by reducing the number of steps involved by starting upfront combination therapy with high-intensity statin and ezetimibe for high- and very-high-risk patients. If care pathways provided a time window of, for instance, 3 months, to evaluate the patient response before adding a third oral agent or an injectable, this would reduce the number of steps and potentially result in more patients at goal.[13,14,22] Trial data suggest that the association between LDL-C levels and outcomes depends upon the magnitude and duration of LDL-C lowering rather than how it is achieved.[23,24] Observational data suggest there are mortality benefits to be gained from upfront combination therapy, for instance, in patients with acute coronary syndrome.[25]

Prior to 2023, statins,[26] ezetimibe,[26] and two different PCSK9is[10,27] had been shown to reduce LDL-C levels and MACEs. In 2023, a fourth therapy, bempedoic acid, also demonstrated reductions in MACEs.[28,29] Additionally, pre-specified exploratory data from pooled Phase 3 lipid-lowering trials with inclisiran have shown indirect evidence of lowering CV risk.[30] With all of these therapies available to clinicians, it follows that the focus must now shift to evaluating strategies that better implement the 2019 ESC/EAS guidelines, with a particular focus on implementing early and greater use of combination LLTs.

As with any observational study, this study was prone to several inherent biases, which were mitigated as far as possible. Selection bias was limited via the use of wide inclusion criteria, an international design,

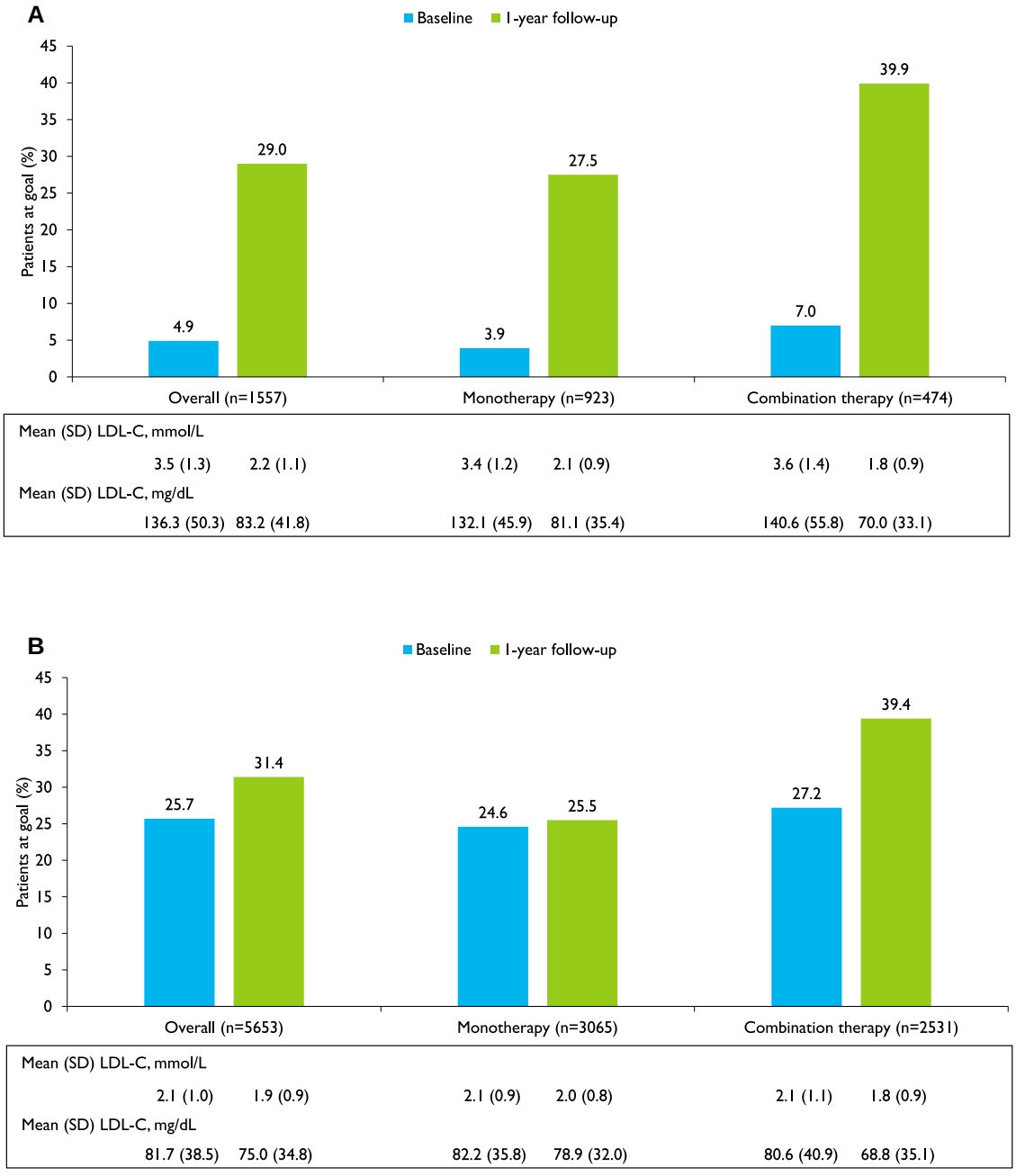


Figure 5 The LDL cholesterol and European Society of Cardiology/European Atherosclerosis Society guideline recommended risk-based LDL cholesterol goal achievement at baseline and 1-year follow-up in (*A*) patients with no lipid-lowering therapy at baseline receiving monotherapy or combination therapy at 1-year follow-up and (*B*) patients with lipid-lowering therapy at baseline receiving monotherapy or combination therapy at 1-year follow-up. Baseline/follow-up LDL <1.4 mmol/L (very high-risk patient at baseline/follow-up) or <1.8 mmol/L (high-risk patient at baseline/follow-up). (Goal attainment definition used by SANTORINI.) LDL-C, LDL cholesterol; SD, standard deviation.

large sample size, and a high level of external validity, with data monitoring processes to ensure the quality of the collected data. That said, sites that participate in research are often different from sites that do not participate; hence, the present data may be a 'best case scenario'. Analyses may have been limited by missing data, which we attempted to mitigate. While analysing patients at LDL-C goal, only risk-based absolute goals of 1.4 and 1.8 mmol/L were considered, and the additional criterion of 50% reduction in LDL-C from baseline was not considered. However, we have presented the goal attainment in patients with no LLT at baseline using the additional criterion of 50% reduction from baseline to provide a picture of the impact on such a population. Lack of LDL-C data at 1-year follow-up reduced the overall sample size available for some analyses by about 15%. Nevertheless, clinical characteristics and management at baseline were very similar in patients included to those excluded from analyses. No formal hypotheses were tested, and these data were observational in nature; therefore, caution

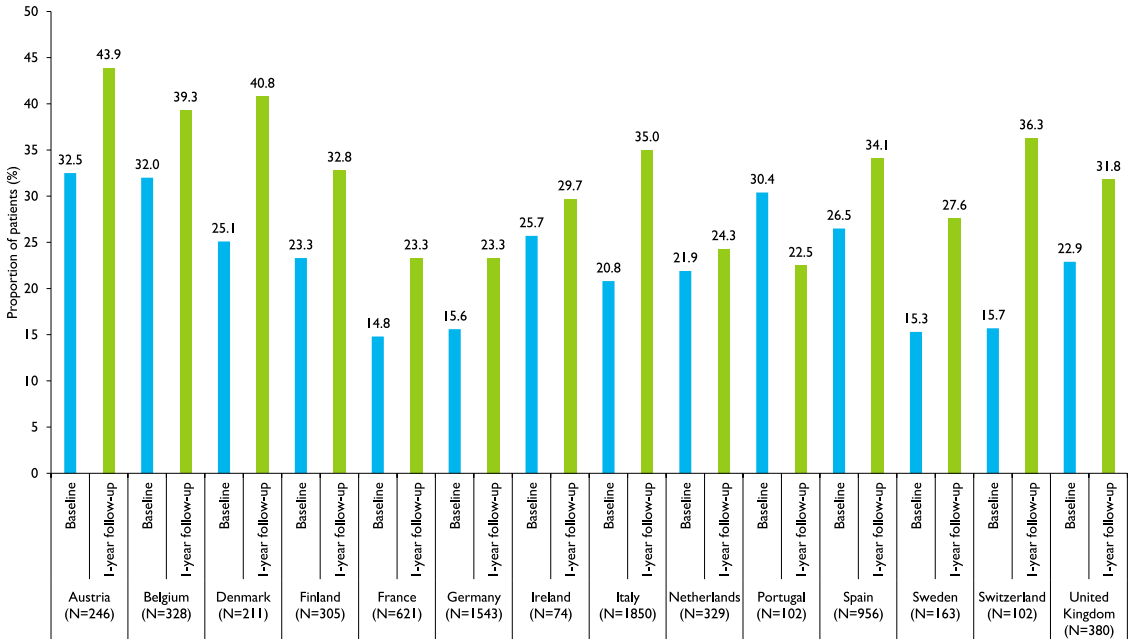


Figure 6 Proportion of patients achieving European Society of Cardiology/European Atherosclerosis Society guideline recommended risk-based LDL cholesterol goals at baseline and 1-year follow-up by country (LDL cholesterol data set).

is needed when interpreting any presented associations. Approximately 20% of patients not treated at baseline may have been enrolled at their first contact with physicians and may have been managed differently compared with those who were followed up for a longer time. We examined these groups jointly, as well as separately, and the general patterns of underutilization of combination therapies were equally applicable to both groups. Lastly, the duration of follow-up was too short to assess statistically whether treatment intensification or LDL-C control was associated with improvements in CV outcomes.

In the largest observational study performed to date in Europe since the 2019 lipid guidelines were published, we observed an increase in the intensity of LLT regimens over 1 year, mostly with the addition of ezetimibe to statins, along with modest improvements in the proportion of patients achieving their risk-based LDL-C goal. Nevertheless, across Europe, two-thirds remained above risk-based goals, and CV events in high- and very-high-risk patients remained high. Where combination therapies were utilized, more patients achieved their LDL-C goals. Approaches to better implement combination therapies for the majority of patients at an early stage are warranted to better control LDL-C in high- and very-high-risk patients.

Supplementary material

Supplementary material is available at *European Journal of Preventive Cardiology*.

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Author contribution

K.K.R., C.A., M.A., D.L.C., M.E., J.F., U.L., J.M.M., D.N., A.B., J.S., M.L., R.C., E.R., T.S., H.T., F.L.J.V., and A.L.C. contributed to the investigation, writing, and reviewing and editing of this manuscript.

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Conflict of interest: K.K.R. has received honoraria for consulting, lectures from Abbott Laboratories, Amgen, AstraZeneca, Bayer Healthcare Pharmaceuticals, Boehringer Ingelheim, Cargene, CRISPR, Daiichi Sankyo, Eli Lilly Company, Emendobio, Esperion, Kowa, New Amsterdam Pharma, Novartis Corporation, Nodthera, GSK, 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, Regeneron, and Ultragenyx, plus stock options from New Amsterdam Pharma, Scribe, and Pemi 31. A.L.C. received research grant support from Amryt Pharma, Menarini, Ultragenyx, and Viatris, and lecturing fees from Amarin, Amgen, Amryt Pharma, AstraZeneca, Daiichi Sankyo, Esperion, Ionis Pharmaceutical, Medscaper, Menarini, Merck, Novartis, Peervoice, Pfizer, Recordati, Regeneron, Sandoz, Sanofi, The Corpus, Ultragenyx, and Viatris. M.A. received research grant support and lecturing fees from Alfasigma, Amgen, Amryt, Daiichi Sankyo, Ionis Pharmaceuticals/Akcea Therapeutics, Novartis, Pfizer, Regeneron Pharmaceuticals, Sanofi, Sobi, Viatris, and Ultragenyx. A.B., R.C., M.L., and J.S. are employees of Daiichi Sankyo. H.T. received grant support and lecturing fees from Daiichi Sankyo and participated in an advisory board run by Daiichi Sankyo. T.S. received consulting fees from Amgen, Novartis, Orion Pharma, and Valio, and lecturing fees from Amarin, Pfizer, and GSK. He is a patient on statin and ezetimibe therapy. U.L. received grant

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Data availability

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/.

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