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

Kausik K. Ray,[1] Carlos Aguiar,[2] Marcello Arca,[3] Derek L. Connolly,[4] Mats Eriksson,[5] Jean Ferrières,[6] Ulrich Laufs,[7] Jose M. Mostaza,[8] David Nanchen,[9] Aurélie Bardet,[10] Mathias Lamparter,[10] Richa Chhabra,[10] Jarkko Soronen,[10] Ernst Rietzschel,[11] Timo Strandberg,[12] Hermann Toplak,[13] Frank L. J. Visseren,[14] Alberico L. Catapano[15,16] on behalf of the SANTORINI study investigators*

[1]Imperial Centre for Cardiovascular Disease Prevention, ICTU-Global, Imperial College London, London, UK; [2]Heart Institute, Carnaxide, Portugal; [3]Department of Translational and Precision Medicine, Sapienza Università di Roma, Rome, Italy; [4]Sandwell and West Birmingham NHS Trust, Birmingham City Hospital, Institute of Cardiovascular Sciences, University of Birmingham, and Aston Medical School, Birmingham, UK; [5]Karolinska University Hospital, Stockholm, Sweden; [6]Department of Cardiology and INSERM UMR 1295, Toulouse Rangueil University Hospital, Toulouse University School of Medicine, Toulouse, France; [7]University Hospital Leipzig, Leipzig, Germany; [8]La Paz-Carlos III Hospital, Madrid, Spain; [9]Center for primary care and public health (Unisanté), University of Lausanne, Lausanne, Switzerland; [10]Daiichi Sankyo Europe GmbH, Munich, Germany; [11]Ghent University and Ghent University Hospital, Ghent, Belgium; [12]University of Helsinki and Helsinki University Hospital, Helsinki, Finland, and University of Oulu, Center for Life Course Health Research, Oulu, Finland; [13]Department of Medicine, Division of Endocrinology and Diabetology, Medical University of Graz, Graz, Austria; [14]Department of Vascular Medicine, University Medical Center Utrecht, Utrecht, The Netherlands; [15]Department of Pharmacological and Biomolecular Sciences, University of Milan and [16]Multimedica IRCCS, Milan, Italy

A list of the SANTORINI study investigators is provided in the Supplementary Appendix, Tables 1 and 2.

Abstract

Aim: To assess whether implementation of the 2019 ESC/EAS dyslipidaemia guidelines observed between 2020–2021 improved between 2021–2022 in the SANTORINI study.

Methods: High- or very-high cardiovascular (CV) risk patients were recruited across 14 European countries from March 2020–February 2021, with 1-year prospective follow-up until May 2022. Lipid-lowering therapy (LLT) and 2019 ESC/EAS risk-based low-density lipoprotein 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. ~~CV events were assessed as a secondary objective~~.

Results: Of 9559 patients enrolled, 9136 (2626 high risk, 6504 very high risk) had any follow-up data, and 7210 (2033 high risk, 5173 very high risk) had baseline and follow-up LDL-C data. LLT 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 mmol/L 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%). ~~Event rates per 100 patient-years for CV death, and 4- and 3-component major adverse CV events were 0.96 (0.76–1.17), 5.60 (5.11–6.10) and 2.35 (2.03–2.67), respectively.~~

Conclusions: LLT 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 ~~and CV events remained high~~, hence strategies are needed to improve implementation of combination LLT.

Lay Summary

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

Key words: Real-World Clinical Trials; Lipid; Dyslipidemia; Europe; Cardiovascular Risk

Introduction

Despite decreases in age adjusted cardiovascular disease (CVD) mortality over the last 40 years, [1] there are more than 18 million deaths worldwide due to CVD each year, a large proportion of which are due to atherosclerotic cardiovascular disease (ASCVD). [2-4] The Global Burden of Disease Study in 2019 showed

that high levels of low-density lipoprotein cholesterol (LDL-C) was 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 (<1.8mmol/L) and very high (<1.4mmol/L) risk.[7] We conducted the Treatment of high and very high ri**S**k dyslipidemic p**A**tients for the preve**NT**ion of cardi**O**vascula**R** events in Europe - a mult**I**natio**N**al observat**I**onal (SANTORINI) study in the two 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 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, 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 (approximately 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. CV 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 >8 mmol/L [>310 mg/dL], familial hypercholesterolemia [FH], 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 with target organ damage or an additional major risk factor such as smoking, marked hypercholesterolemia, 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 >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, internal medicine specialist) and secondary (i.e., cardiologist, diabetologist, lipidologist, neurologist) care sites with no specific physician selection criteria.[8] Some sites were classified as both primary and secondary care. 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. CV events of interest included CV death, 3- component major adverse CV events (MACE; death from CV causes, nonfatal myocardial infarction (MI) or nonfatal stroke) and 4-component MACE (death from CV causes, nonfatal MI, nonfatal stroke, or coronary revascularisation 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 (CI) of 0.002 to 0.006 could be reached for 1–8% event rates. These rates correspond to the range of expected rates of CV death and 3-component MACE over 1 year. They are based on the ESC/EAS 2019 guidelines 10-year rate for CV death,[7] assuming exponential distribution of events and observed proportions of 3-component MACE events with regards to CV death observed in the FOURIER randomized clinical trials and REACH registry.[10,11] This would correspond to relative precisions of 0.07 to 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 dataset including patients with LDL-C data available at both baseline and follow-up. LDL-C values were considered as reported by the investigators. Only in case of absence of LDL-C value, and

presence of TC, HDL and 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 LTT; de-escalation=decrease in the number or intensity of LLT; **Supplementary Table 3**). 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 dataset; 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 (**Supplementary Figure 1**). 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 (**Supplementary Figure 1**).

Baseline demographic characteristics and LDL-C of patients in the LDL-C dataset 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 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 (**Supplementary Table 4**).

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 datasets (**Supplementary Table 5**). Mean LDL-C values in the LDL-C dataset across the countries ranged from 2.1–2.6 mmol/L (80.9–100.7 mg/dL) (**Supplementary Table 6**). 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 proportion of patients with diabetes was similar between risk categories (34.8% vs 35.0%; **Supplementary Table 7**). LDL-C was lower in patients at very high risk compared with high risk (2.3 mmol/L vs 2.7 mmol/L). Baseline demographics of patients with and without ASCVD are presented in **Supplementary Table 8**.

LLT use at baseline and end of follow-up

Table 2, **Figure 1** and **Supplementary Figure 2** 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, 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 to 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 Table 9 for statin intensity categorisation**). 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 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%). Whilst 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 greater use of high intensity statins at the end of study —an increase from 10.3% to 17.7% (**Table 2**). 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 (**Supplementary Table 10**). Among patients with ASCVD, 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 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%. (**Supplementary Table 11**).

Among the FAS, there was an escalation in treatment for 29.3% (N=2674), no change in treatment for 66.6% (N=6080), and de-escalation in 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%, no change in treatment for 64.9% and de-escalation in treatment for 2.6% of patients. For patients with high CV risk, there was an escalation in treatment for 26.0%, no change in treatment for 70.6% and de-escalation in treatment for 2.2% of patients.

Use of LLT 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-C control over 1 year

Figure 3A shows LDL-C at baseline and 1-year follow-up in the overall LDL-C dataset and by physician classified CV risk at baseline. Mean (SD) LDL-C levels decreased from 2.4 (1.2) mmol/L to 2.0 (0.9) mmol/L in the overall population. This decrease reflects changes in both the high-risk group from 2.7 mmol/L to 2.3 mmol/L and the very-high risk group from 2.3 mmol/L 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] mmol/L vs 2.1 [1.0] mmol/L). At the end of 1-year follow-up, in the group not on LLT at baseline, 58.1% were on monotherapy and 28.2% on combination therapy, compared to 56.8% and 40.5%, respectively, for those who were on LLT at baseline (**Supplementary Table 12**). Among patients on LLT at baseline, mean (SD) LDL-C changed marginally over 1 year from 2.1 (1.0) mmol/L to 1.9 (0.9) mmol/L. Moreover, the patient population receiving LLT at baseline had a higher proportion of patients with hypertension (72.8% vs 65.4%) and diabetes (37.4% vs 25.5%) compared to those not on LLT (**Supplementary Table 13**). This pattern was consistent across countries (**Supplementary Table 14**). **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) mmol/L and 1.9 (0.9) mmol/L at the end of the follow-up period.

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

At baseline, among the 7210 patients in the LDL-C dataset, 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% ~~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.~~

Cardiovascular risk

In the FAS, 88 patients died due to CV causes; 497 had at least one 4-component MACE event, and 213 had at least one 3-component MACE event. These reflected 0.96 (0.76–1.17) CV deaths, 5.60 (5.11–6.10) first 4-component MACE events and 2.35 (2.03–2.67) first 3-component MACE events per 100 PY of follow-up. Among those categorized as very high risk by the investigator (N=6504), ~~66 died due to CV reasons, 410 had at least one 4-component MACE event, and~~ 164 had at least one 3-component MACE event~~. These correspond to 1.02 (0.77–1.26) CV deaths, 6.55 (5.92–7.19) first 4-component MACE events, and~~ corresponding to 2.55 (2.16–2.94) first 3-component MACE events per 100 PY of follow-up. Among those categorized as high risk by the investigator (N=2626), ~~22 died due to CV reasons, 86 had at least one 4-component MACE event, and~~ 49 had at least one 3-component MACE event ~~These corresponded to 0.83 (0.48–1.18) CV deaths, 3.30 (2.60–4.00) first 4-component MACE events, and~~ corresponding to 1.86 (1.34–2.39) first 3-component MACE events per 100 PY of follow-up.

Among patients with ASCVD (N=7069), 82 died due to CV causes; 476 had at least one 4-component MACE event, and 194 had at least one 3-component MACE event. These reflected rates of 1.16 (0.91–1.42) CV deaths, 7.01 (6.38–7.64) first 4-component MACE events and 2.78 (2.39–3.17) first 3-component MACE events per 100 PY of follow-up.

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 CV events

Of interest, among those with a non-fatal 3- and 4-component MACE events during the 1 year of follow-up, treatment escalation vs de-escalation was observed in 46 vs 3 (3-component MACE) and 193

vs 12 (4-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 revascularisation) very-high risk patients and in 9 vs 1 (MI or stroke) and 30 vs 2 (MI, stroke or revascularisation) 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 average 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 1 in 5 at baseline to approximately 1 in 3 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 average LDL-C levels for high- and very high-risk patients were approximately 0.4–0.5 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, one-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 that were on LLT and for those not receiving LLT at baseline. For instance, among patients receiving LLT at baseline, use of statin monotherapy fell by 10% and was accompanied by an increase in 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 + ezetimibe, and PCSK9i in combination with an oral agent. The low use of PCSK9i overall may reflect the stepwise approach advocated in the lipid 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 to 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 mmol/L vs 2.2 mmol/L), demographic characteristics and healthcare setting 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 event, perhaps highlighting the shortcomings in risk perception in otherwise asymptomatic patients, thereby to delays in LLT optimisation.

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 criteria. Examining changes in practice based on physician perception 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 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 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% 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%). However, a simulation study based on the Da Vinci dataset (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]

LDL-C levels in the population of high- and very high-risk patients improved by approximately 0.4–0.5 mmol/L, suggesting that at population level, CV event risk would have been reduced by about 10–11% in relative terms extrapolating from Cholesterol Treatment Trialists Collaboration.[20] Nevertheless, the high- and very-high risk groups were still 0.4–0.5 mmol/L above respective goals, meaning that a further lowering of risk by 10–11% 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 3- or 4-component MACE at 1 year were 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, three 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 acute coronary syndrome patients.[25]

Prior to this year, statins,[26] ezetimibe[26] and two different PCSK9i[10] had been shown to reduce LDL-C levels and MACE. In 2023, a fourth therapy, bempedoic acid, also demonstrated reductions in MACE.[27,28] Additionally, prespecified exploratory data from pooled phase 3 lipid lowering trials with inclisiran have shown indirect evidence of lowering CV risk.[29] With all of these therapies available to clinicians, it follows that the focus must now shift to evaluating strategies that better implement the 2019 lipid 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 use of wide inclusion criteria, an international design, 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 mmol/L 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 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 to those who were followed-up for a longer time. We examined these groups jointly, as well as separately and the general patterns of underutilisation of combination therapies was 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 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 earlier are warranted to better control LDL-C in high- and very high-risk patients.

Acknowledgements

The authors would like to thank Hannah Talbot and Martina Klinger-Sikora of inScience Communications, Springer Healthcare Ltd, UK, for providing editorial support, which was funded by Daiichi Sankyo Europe GmbH, Munich, Germany in accordance with Good Publication Practice (GPP 2022) guidelines (http://www.ismpp.org/gpp3). KKR acknowledges support from the NIHR Imperial Biomedical Centre. The work of ALC is supported in part by the grant Ricerca corrente from the Ministry of Health to IRCCS multimedica.

Funding

This study was funded by Daiichi Sankyo Europe GmbH, Munich, Germany.

Conflict of interest

KKR has received honoraria for consulting, lectures from Abbott Laboratories, Amgen, Astra Zeneca, 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 Ultragenix, plus stock options New Amsterdam Pharma, Scribe, Pemi 31. **ALC** 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, Viatris**. MA** 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. **AB**, **RC, ML** and **JS** are employees of Daiichi Sankyo. **HT** received grant support and lecturing fees from Daiichi Sankyo and participated in an advisory board run by Daiichi Sankyo. **TS** 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. **UL** received grant support from Daiichi Sankyo, Novartis and Amgen, lecturing fees from Daiichi Sankyo, Novartis, Amgen, Sanofi, Boehringer, MSD, Pfizer, Lilly and AstraZeneca. He has also participated in advisory boards for Daiichi Sankyo, Novartis, Amgen, Sanofi, Boehringer and MSD in addition to leadership/fiduciary roles with EAS, ESC, DGK and DACH.

Authors' Contributions

KKR, CA, MA, DLC, ME, JF, UL, JMM, DN, AB, JS, ML, RC, ER, TS, HT, FLJV and **ALC** contributed to investigation, writing, and reviewing and editing of this manuscript.

Data availability 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/.

References

1. Mensah GA, Wei GS, Sorlie PD, *et al.* Decline in Cardiovascular Mortality: Possible Causes and Implications. *Circ Res* 2017;**120**:366-380. doi: 10.1161/circresaha.116.309115
2. Roth GA, Mensah GA, Johnson CO, *et al.* Global Burden of Cardiovascular Diseases and Risk Factors, 1990-2019: Update From the GBD 2019 Study. *J Am Coll Cardiol* 2020;**76**:2982-3021. doi: 10.1016/j.jacc.2020.11.010
3. Song S, Guo C, Wu R, *et al.* Impact of the COVID-19 pandemic on cardiovascular mortality and contrast analysis within subgroups. *Front Cardiovasc Med* 2024;**11**:1279890. doi: 10.3389/fcvm.2024.1279890
4. Sidney S, Lee C, Liu J, *et al.* Age-Adjusted Mortality Rates and Age and Risk-Associated Contributions to Change in Heart Disease and Stroke Mortality, 2011-2019 and 2019-2020. *JAMA Netw Open* 2022;**5**:e223872. doi: 10.1001/jamanetworkopen.2022.3872
5. Zheng J, Wang J, Zhang Y, *et al.* The Global Burden of Diseases attributed to high low-density lipoprotein cholesterol from 1990 to 2019. *Front Public Health* 2022;**10**:891929. doi: 10.3389/fpubh.2022.891929

6. Ference BA, Ginsberg HN, Graham I, *et al.* Low-density lipoproteins cause atherosclerotic cardiovascular disease. 1. Evidence from genetic, epidemiologic, and clinical studies. A consensus statement from the European Atherosclerosis Society Consensus Panel. *Eur Heart J* 2017;**38**:2459-2472. doi: 10.1093/eurheartj/ehx144
7. Mach F, Baigent C, Catapano AL, *et al.* 2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk. *Eur Heart J* 2020;**41**:111-188. doi: 10.1093/eurheartj/ehz455
8. Ray KK, Haq I, Bilitou A, *et al.* Evaluation of contemporary treatment of high- and very high-risk patients for the prevention of cardiovascular events in Europe - Methodology and rationale for the multinational observational SANTORINI study. *Atheroscler Plus* 2021;**43**:24-30. doi: 10.1016/j.athplu.2021.08.003
9. Ray KK, Haq I, Bilitou A, *et al.* 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. *Lancet Reg Health Eur* 2023;**29**:100624. doi: 10.1016/j.lanepe.2023.100624
10. Sabatine MS, Giugliano RP, Keech AC, *et al.* Evolocumab and Clinical Outcomes in Patients with Cardiovascular Disease. *N Engl J Med* 2017;**376**:1713-1722. doi: 10.1056/NEJMoa1615664
11. Bhatt DL, Eagle KA, Ohman EM, *et al.* Comparative determinants of 4-year cardiovascular event rates in stable outpatients at risk of or with atherothrombosis. *JAMA* 2010;**304**:1350-1357. doi: 10.1001/jama.2010.1322
12. Ray KK, Molemans B, Schoonen WM, *et al.* EU-Wide Cross-Sectional Observational Study of Lipid-Modifying Therapy Use in Secondary and Primary Care: the DA VINCI study. *Eur J Prev Cardiol* 2020;**28**:1279-1289. doi: 10.1093/eurjpc/zwaa047
13. Brandts J, Bray S, Villa G, *et al.* Optimal implementation of the 2019 ESC/EAS dyslipidaemia guidelines in patients with and without atherosclerotic cardiovascular disease across Europe: a simulation based on the DA VINCI study. *Lancet Reg Health Eur* 2023;**31**:100665. doi: 10.1016/j.lanepe.2023.100665
14. Banach M, Penson PE, Farnier M, *et al.* Bempedoic acid in the management of lipid disorders and cardiovascular risk. 2023 position paper of the International Lipid Expert Panel (ILEP). *Prog Cardiovasc Dis* 2023;**79**:2-11. doi: 10.1016/j.pcad.2023.03.001
15. Ray KK, Dhalwani N, Sibartie M, *et al.* Low-density lipoprotein cholesterol levels exceed the recommended European threshold for PCSK9i initiation: lessons from the HEYMANS study. *Eur Heart J Qual Care Clin Outcomes* 2022;**8**:447-460. doi: 10.1093/ehjqcco/qcac009
16. Arca M, Celant S, Olimpieri PP, *et al.* Real-World Effectiveness of PCSK9 Inhibitors in Reducing LDL-C in Patients With Familial Hypercholesterolemia in Italy: A Retrospective Cohort Study Based on the AIFA Monitoring Registries. *J Am Heart Assoc* 2023;**12**:e026550. doi:
17. Cannon CP, Khan I, Klimchak AC, *et al.* Simulation of Lipid-Lowering Therapy Intensification in a Population With Atherosclerotic Cardiovascular Disease. *JAMA Cardiol* 2017;**2**:959-966. doi: 10.1001/jamacardio.2017.2289
18. Cannon CP, Sanchez RJ, Klimchak AC, *et al.* Simulation of the Impact of Statin Intolerance on the Need for Ezetimibe and/or Proprotein Convertase Subtilisin/Kexin Type 9 Inhibitor for Meeting Low-Density Lipoprotein Cholesterol Goals in a Population With Atherosclerotic Cardiovascular Disease. *Am J Cardiol* 2019;**123**:1202-1207. doi: 10.1016/j.amjcard.2019.01.028
19. Jun JE, Jeong I-K, Ahn KJ, Chung HY, Hwang Y-C. Combination of low- or moderate-intensity statin and ezetimibe vs. high-intensity statin monotherapy on primary prevention of cardiovascular disease and all-cause death: a propensity-matched nationwide cohort study. *European Journal of Preventive Cardiology* 2024. doi: 10.1093/eurjpc/zwae081
20. Trialists CT. Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170 000 participants in 26 randomised trials. *The Lancet* 2010;**376**:1670-1681. doi:
21. Catapano AL, Graham I, De Backer G, *et al.* 2016 ESC/EAS Guidelines for the Management of Dyslipidaemias. *Eur Heart J* 2016;**37**:2999-3058. doi: 10.1093/eurheartj/ehw272

22. Ray KK, Reeskamp LF, Laufs U, *et al.* Combination lipid-lowering therapy as first-line strategy in very high-risk patients. *Eur Heart J* 2021;**43**:830-833. doi: 10.1093/eurheartj/ehab718
23. Hong SJ, Lee YJ, Lee SJ, *et al.* Treat-to-Target or High-Intensity Statin in Patients With Coronary Artery Disease: A Randomized Clinical Trial. *JAMA* 2023;**329**:1078-1087. doi: 10.1001/jama.2023.2487
24. Kim BK, Hong SJ, Lee YJ, *et al.* Long-term efficacy and safety of moderate-intensity statin with ezetimibe combination therapy versus high-intensity statin monotherapy in patients with atherosclerotic cardiovascular disease (RACING): a randomised, open-label, non-inferiority trial. *Lancet* 2022;**400**:380-390. doi: 10.1016/s0140-6736(22)00916-3
25. Lewek J, Niedziela J, Desperak P, *et al.* Intensive Statin Therapy Versus Upfront Combination Therapy of Statin and Ezetimibe in Patients With Acute Coronary Syndrome: A Propensity Score Matching Analysis Based on the PL-ACS Data. *J Am Heart Assoc* 2023;**12**:e030414. doi: 10.1161/jaha.123.030414
26. Cannon CP, Blazing MA, Giugliano RP, *et al.* Ezetimibe Added to Statin Therapy after Acute Coronary Syndromes. *N Engl J Med* 2015;**372**:2387-2397. doi: 10.1056/NEJMoa1410489
27. Nissen SE, Lincoff AM, Brennan D, *et al.* Bempedoic Acid and Cardiovascular Outcomes in Statin-Intolerant Patients. *N Engl J Med* 2023;**388**:1353-1364. doi: 10.1056/NEJMoa2215024
28. Nissen SE, Menon V, Nicholls SJ, *et al.* Bempedoic Acid for Primary Prevention of Cardiovascular Events in Statin-Intolerant Patients. *JAMA* 2023;**330**:131-140. doi: 10.1001/jama.2023.9696
29. Ray KK, Raal FJ, Kallend DG, *et al.* Inclisiran and cardiovascular events: a patient-level analysis of phase III trials. *Eur Heart J* 2022;**44**:129-138. doi: 10.1093/eurheartj/ehac594

Figure legends

Graphical abstract. Legend: CV, cardiovascular, LDL-C, low-density lipoprotein cholesterol; LLT, lipid-lowering therapy; MACE, major cardiovascular adverse event; PY, patient-year.

Figure 1. A) Monotherapy and combination therapy at baseline and 1-year follow-up; B) flow of patients between different LLTs 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

Figure 2. Use of LLT by country

LLT, lipid-lowering therapy

Figure 3. A) LDL-C at baseline and 1-year follow-up in very high CV risk, high CV risk and overall populations (LDL-C dataset) **B)** LDL-C at baseline and one-year follow-up in patients with LLT and no LLT at baseline (LDL-C dataset)

CV, cardiovascular; LDL-C, low-density lipoprotein cholesterol; LLT, lipid-lowering therapy

Figure 4. Risk-based LDL-C goal attainment at baseline and 1-year follow-up (LDL-C dataset)

FU, follow-up; LDL-C, low-density lipoprotein cholesterol

Figure 5. LDL-C and ESC/EAS guideline recommended risk-based LDL-C goal achievement at baseline and 1-year follow-up in A) Patients with no LLT at baseline receiving monotherapy or combination therapy at 1-year follow-up and B) Patients with LLT 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).

EAS, European Atherosclerosis Society; ESC, European Society of Cardiology; LDL-C, low-density lipoprotein cholesterol; LLT, lipid-lowering therapy; SD, standard deviation

Figure 6. Proportion of patients achieving ESC/EAS guideline recommended risk-based LDL-C goals at baseline and 1-year follow-up by country (LDL-C dataset)

EAS, European Atherosclerosis Society; ESC, European Society of Cardiology; LDL-C, low-density lipoprotein cholesterol

Table legends

Table 1. Baseline characteristics for overall and LDL-C patient population sets

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

Table 2. LLTs at baseline and 1-year follow-up in overall, patients with high CV risk and very high CV risk (FAS)

*This includes bempedoic acid alone; †This category also includes BA FDC, BA combination therapy, and BA FDC + statin combination

BA, bempedoic acid; FDC, fixed dose combination; LLT, lipid-lowering therapy; PCSK9i, proprotein convertase subtilisin/kexin type 9 inhibitor

Table 1. Baseline characteristics for overall and LDL-C patient population sets

Characteristic	Overall (N=9136)	LDL-C dataset (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, 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/1.73m^2, mean (SD)	77.9 (24.0)	78.8 (23.7)
Heterozygous familial hypercholesterolemia, 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, low-density lipoprotein cholesterol; SD, standard deviation

Table 2. LLTs at baseline and 1-year follow-up overall, and in patients with high CV risk and very high CV risk (FAS)

	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	32 (1.2)	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*	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†	344 (3.8)	450 (4.9)	85 (3.2)	120 (4.6)	259 (4.0)	330 (5.1)

*This includes bempedoic acid alone; †This category also includes BA FDC, BA combination therapy, and BA FDC + statin combination

BA, bempedoic acid; FAS, full analysis set; FDC, fixed dose combination; LLT, lipid-lowering therapy; PCSK9i, proprotein convertase subtilisin/kexin type 9 inhibitor

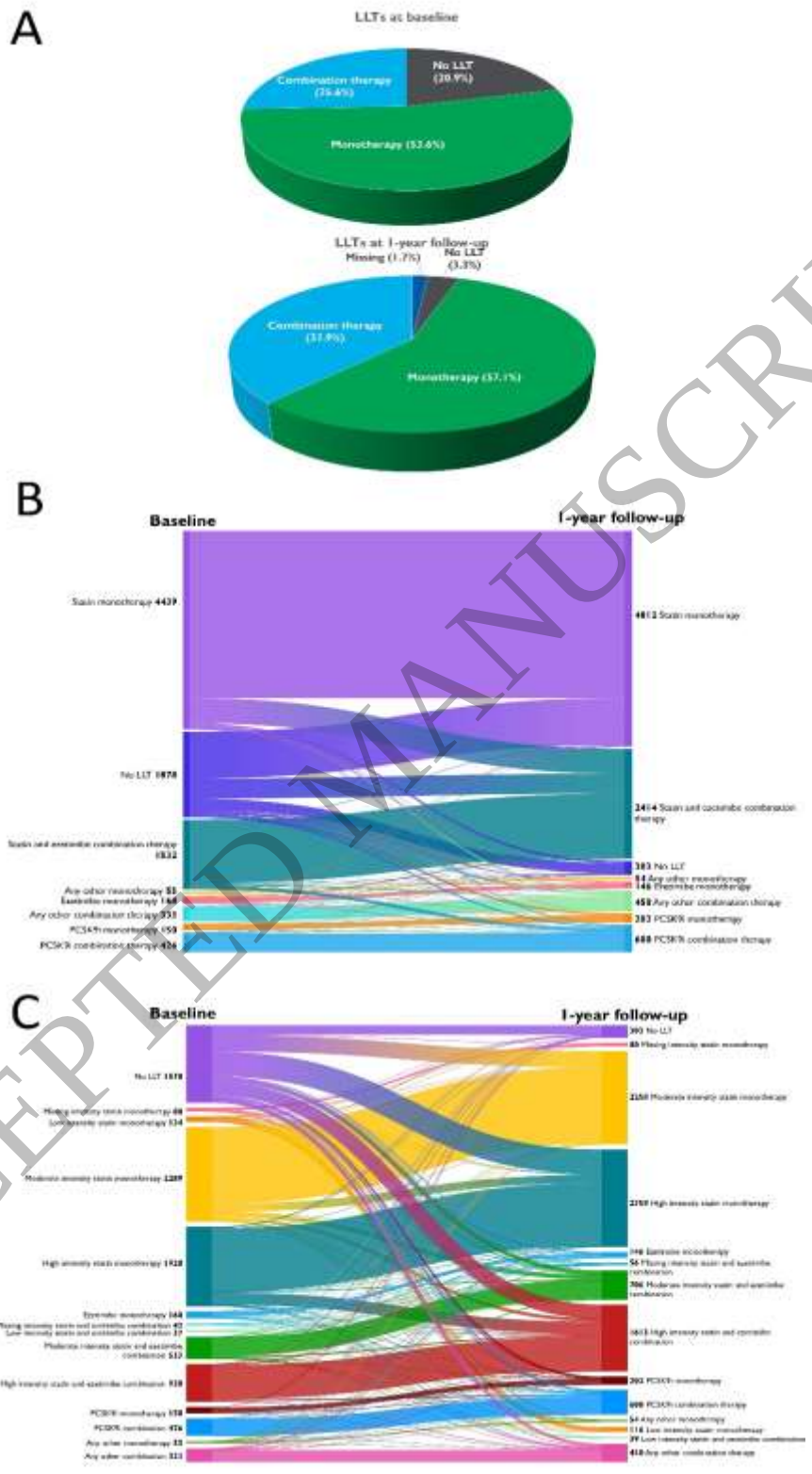


Figure 1
279x559 mm (x DPI)

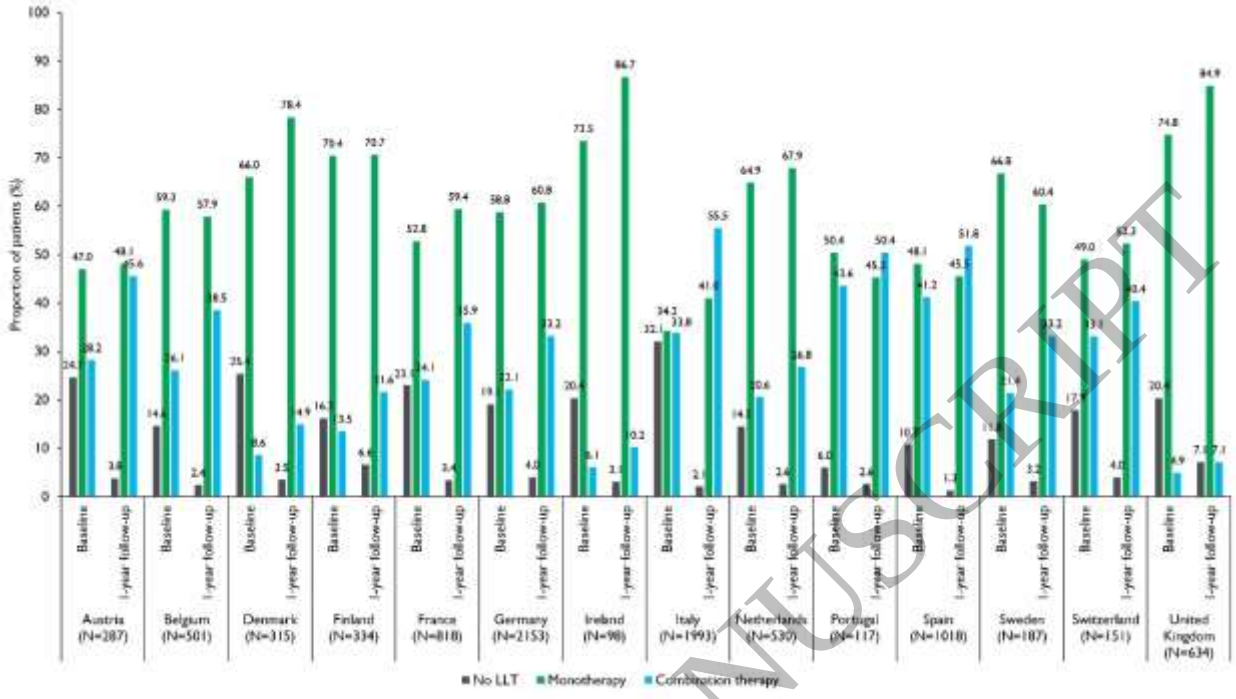


Figure 2
339x190 mm (x DPI)

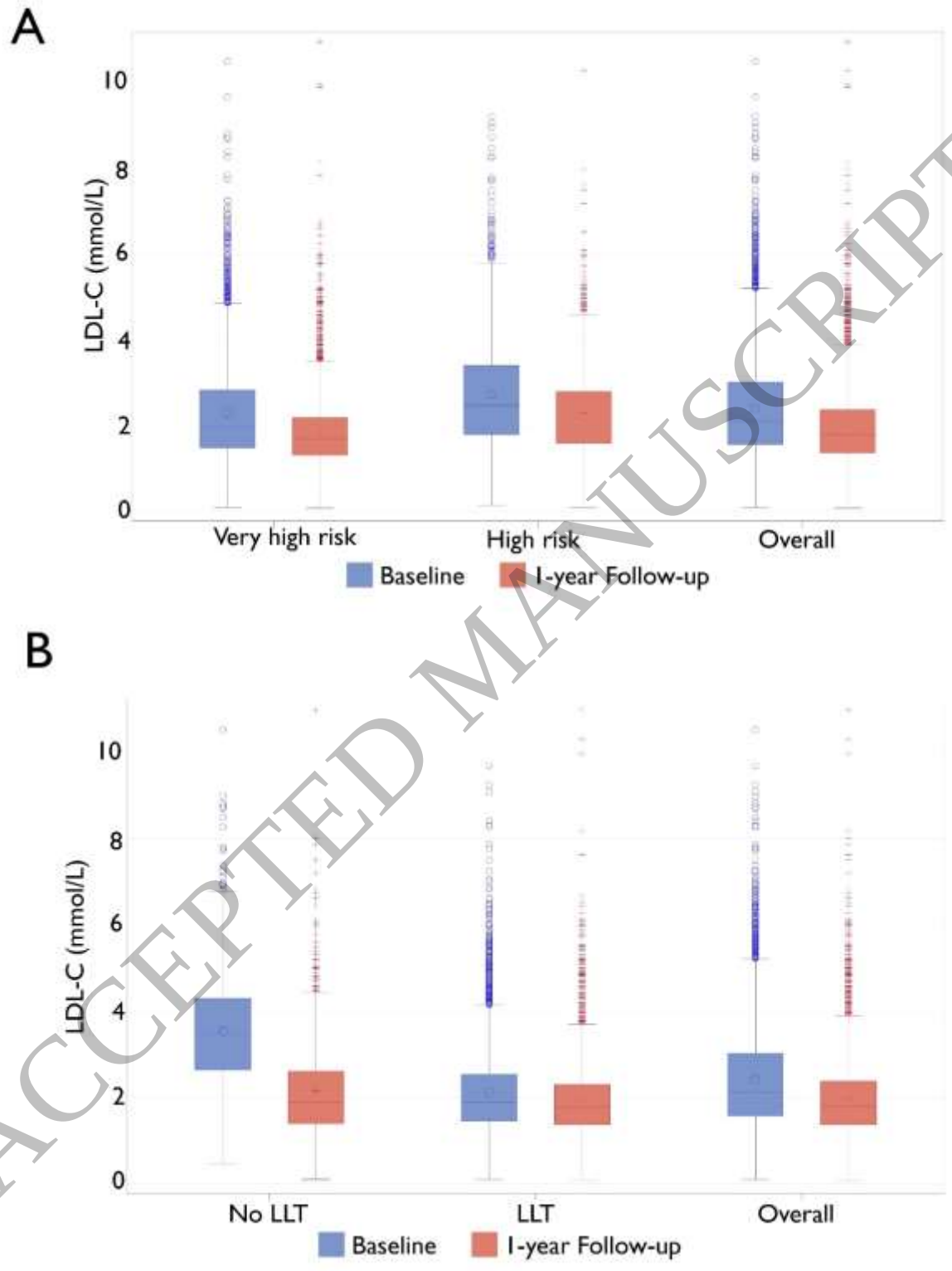


Figure 3
339x430 mm (x DPI)

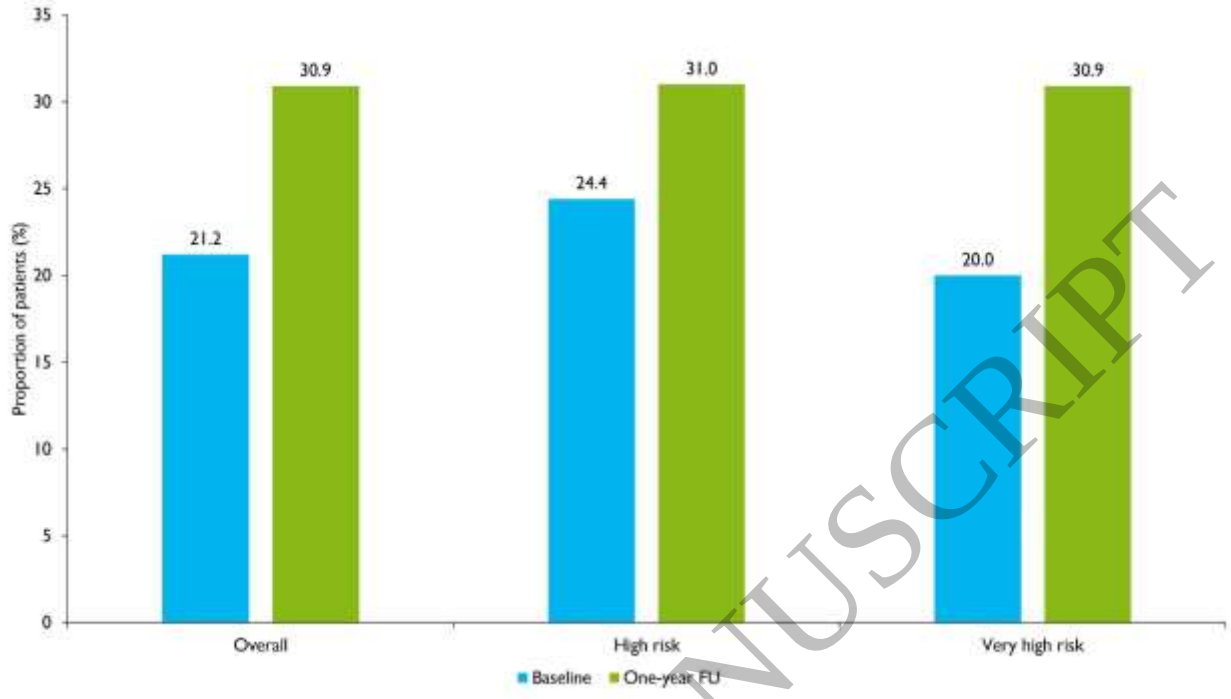


Figure 4
339x190 mm (x DPI)

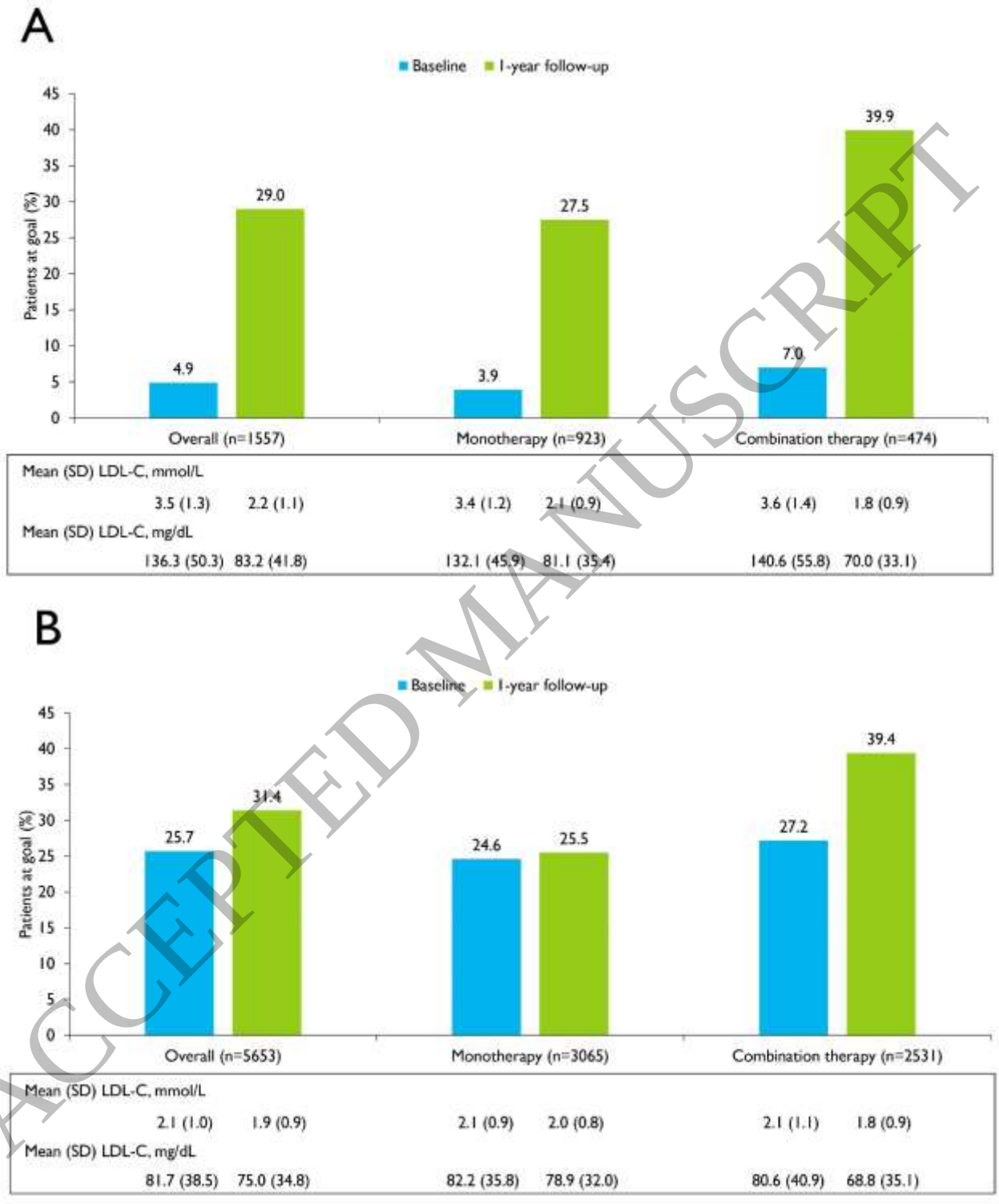


Figure 5
339x430 mm (x DPI)

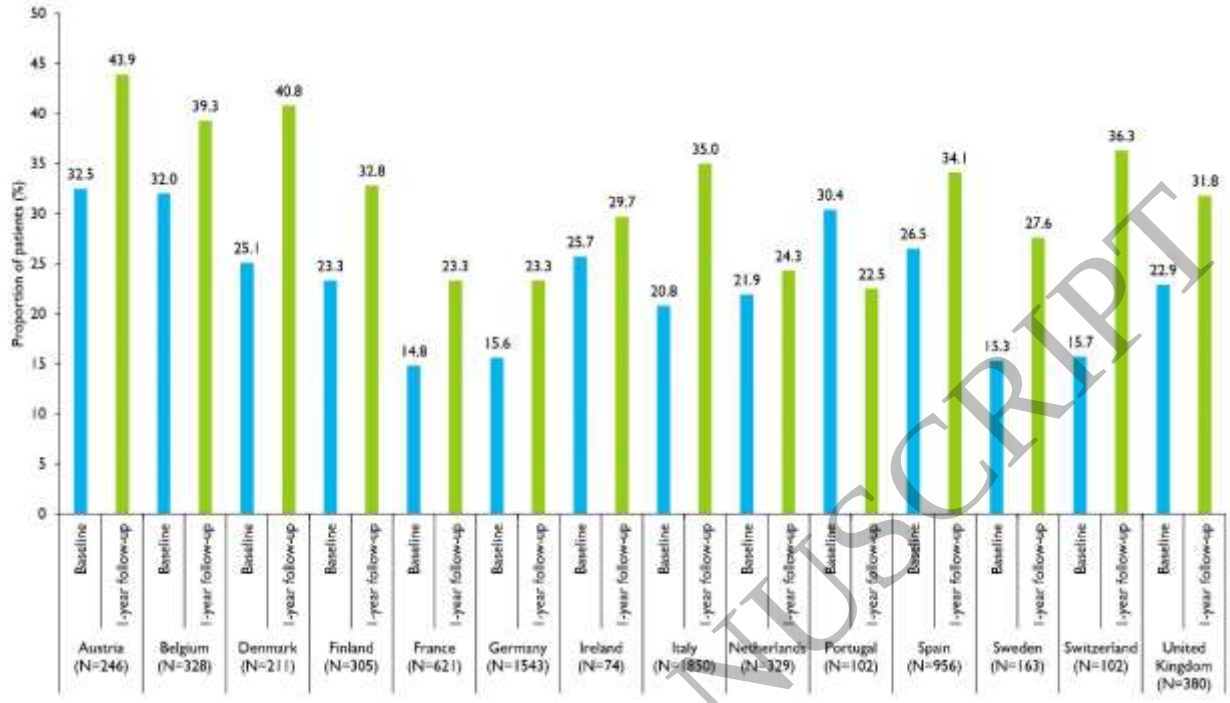
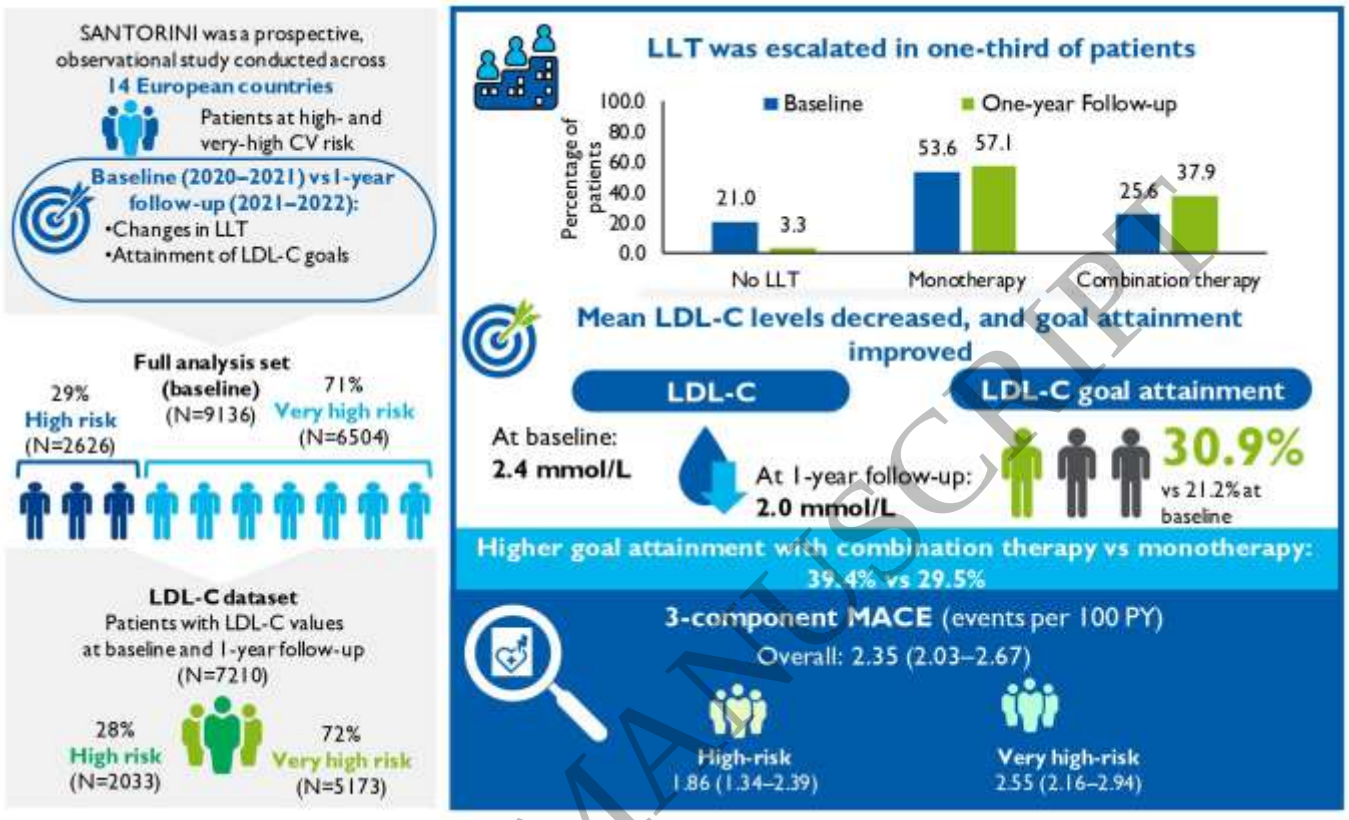


Figure 6
339x190 mm (x DPI)



Graphical Abstract
180x110 mm (x DPI)