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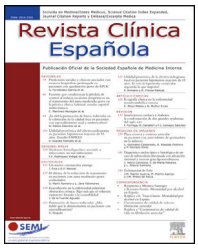

ORIGINAL ARTICLE

Failure of LDL-C goals achievement and underuse of lipid-lowering therapies in patients at high and very high cardiovascular risk: Spanish subset from the European SANTORINI study

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KEYWORDS
SANTORINI;
Spain;
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Risk;
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Low-density lipoprotein cholesterol

Abstract
Introduction: There are very few studies evaluating lipid-lowering treatments (LLTs) and low-density lipoprotein-cholesterol (LDL-C) goal attainment after the release of the 2019 guidelines of the European Societies of Cardiology (ESC) and Atherosclerosis (EAS). This manuscript shows baseline data of the Spanish subset from SANTORINI study (namely SANTORINI Spain) on LDL-C goal attainment and use of LLTs in patients at high and very high cardiovascular risk.
Methods: SANTORINI was a multinational, prospective, observational study involving patients at high and very high cardiovascular risk from 14 European countries in primary care and specialized healthcare settings. Sociodemographic data, blood lipid levels, and lipid treatments from the 1018 Spanish participants were separately analyzed and were put into perspective with the European cohort without Spanish participants.

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Results: According to physicians, 295 (29.0%) subjects were classified as high, and 723 (71.0%) as very high cardiovascular risk. Overall, 26.5% attained risk-based LDL-C targets recommended by 2019 European guidelines, with 23.1% of patients at high cardiovascular risk and 27.9% at very high cardiovascular risk. High-intensity statin therapy in monotherapy was used in 21.8%, LLT combination therapy in 41.2%, and 10.7% were not receiving any LLT.
Conclusions: Baseline data from SANTORINI Spain population show that only about one-fourth of patients attain LDL-C targets recommended by the 2019 ESC/EAS guidelines in patients at high and very high risk. Despite their cardiovascular risk, patients appear to be not adequately treated, and high-intensity and combination LLT seem to be underused for cardiovascular disease prevention in the real-world setting. ClinicalTrials.gov Identifier: NCT04271280.

PALABRAS CLAVE
SANTORINI;
España;
Cardiovascular;
Riesgo;
Terapia hipolipemiante;
Colesterol de lipoproteínas de baja densidad

Fracaso en la consecución de los objetivos de LDL-C e infrautilización de tratamientos hipolipemiantes en pacientes con riesgo cardiovascular alto y muy alto: subpoblación española del estudio europeo SANTORINI

Resumen
Introducción: Existen pocos estudios que hayan evaluado el tratamiento hipolipemiante (LLTs) y la consecución de objetivos de colesterol de lipoproteínas de baja densidad (C-LDL) después de la publicación de las guías de 2019 de la Sociedad Europea de Cardiología (ESC) y Aterosclerosis (EAS). Este manuscrito presenta los datos basales de la subpoblación española del estudio SANTORINI (denominado SANTORINI España) sobre la consecución de objetivos de LDL-C y el uso de LLTs en pacientes con riesgo cardiovascular alto y muy alto.
Métodos: SANTORINI fue un estudio multinacional, prospectivo y observacional que incluyó a pacientes con riesgo cardiovascular alto y muy alto de 14 países europeos en entornos de atención primaria y atención especializada. En el presente análisis se han analizado datos sociodemográficos, niveles de lípidos en sangre y tratamientos hipolipemiantes utilizados, en los 1018 participantes españoles, y se han puesto en perspectiva con la cohorte europea excluida la población española.
Resultados: Según el criterio de los médicos participantes, 295 (29,0%) pacientes fueron clasificados como de riesgo cardiovascular alto y 723 (71,0%) como de riesgo muy alto. Globalmente, el 26,5% alcanzó los objetivos de C-LDL recomendados por las guías europeas de 2019, un 23,1% de los pacientes con riesgo cardiovascular alto y un 27,9% de aquellos con riesgo cardiovascular muy alto. El tratamiento con estatinas de alta intensidad en monoterapia se utilizó en el 21,8%, la terapia combinada de hipolipemiantes en el 41,2%, y el 10,7% no recibió ningún LLT.
Conclusiones: Los datos basales de la población de SANTORINI España muestran que solo alrededor de una cuarta parte de los pacientes alcanza los objetivos de C-LDL recomendados por las guías ESC/EAS de 2019 en pacientes con riesgo cardiovascular alto y muy alto. A pesar de dicho riesgo, la utilización de tratamientos de alta intensidad y de tratamientos en combinación están infrautilizados. ClinicalTrials.gov: NCT04271280.

Introduction

In Europe, cardiovascular disease (CVD) is responsible for more than 4 million deaths and a major burden for health care systems.[1,2] Low-density lipoprotein cholesterol (LDL-C) has been identified as a major predictor and causal factor of atherosclerotic CVD (ASCVD).[3,4] Consequently, reducing LDL- C concentration has become the primary goal in the prevention of cardiovascular (CV) events. Indeed, a relative risk reduction of up to 23% in major vascular and coronary events and 10% in total mortality over 5 years has been associated with each mmol/L LDL-C reduction.[4,5] The 2019 update of the European Society of Cardiology (ESC)/European Atherosclerosis Society (EAS) guidelines established stringent LDL-C targets and recommended lowering LDL-C levels to less than 1.8 mmol/L (<70 mg/dL) and 1.4 mmol/L (<55 mg/dL) and at least 50% reduction from baseline LDL-C levels in patients at high and very high CV risk, respectively.[4] Real-world studies conducted during the last decade, and based on higher LDL-C thresh-

olds, have consistently shown that many patients, including those at the highest CV risk, fail to achieve the recommended risk-based LDL-C targets in primary and secondary prevention.[6–14] In contrast to the extended literature on low LDL-C attainment rate using prior guideline targets,[6–12] data regarding the impact of the 2019 ESC/EAS guidelines on lipid-lowering treatments (LLTs) are lacking.[13,14] New studies are thus needed to provide an up-to-date picture of contemporary LDL-C treatment. In addition, as revealed in the EUROASPIRE V survey, the management of dyslipidemia notably varies among countries.[9] For this reason, studies characterizing the use of LLTs in Spain are also required.

The SANTORINI, i.e. Treatment of High and Very High riSk Dyslipidemic pAtients for the PreveNTion of CardiOvasculaR Events in Europe - a MultInatioNal ObservatIonal Study was aimed at describing the lipid management in the years following the 2019 update of the ESC/EAS guidelines, in patients at high and very high CV risk from 14 European countries in primary care and specialized healthcare settings.[14] The baseline data of 7210 patients with LDL-C complete information (2033 at high, 5173 at very high CV risk, and 4 having missing risk classification) have been recently published, showing that only 21.2% of them achieved the 2019 LDL-C goals.

In this article, we presented the baseline demographic and clinical characteristics, LDL-C goal attainment and use of LLTs of the Spanish subset of participants in SANTORINI study (namely SANTORINI Spain). Moreover, we focused on putting the data into perspective with the European cohort without Spanish participants (namely SANTORINI Europe without Spain).

Methods

Study design and patients

The design, objectives, and methodology of SANTORINI (NCT04271280) have been fully described elsewhere.[15] Briefly, the study enrolled adult (≥18 years) patients at high or very high CV risk according to their attending physician, and eligible for LLT, who had an anticipated life expectancy greater than 1 year at the time of study inclusion. No exclusion criteria were established.[15] After recruitment, each patient was followed-up for up to 12 months. Written informed consent was obtained from all participants. The study was carried out in accordance with the Declaration of Helsinki and was approved by an independent Ethics Committee.

Study endpoints

The primary objective of SANTORINI was to describe the lipid-lowering regimens being used in routine clinical practice for patients at high and very high CV risk, and the proportion of patients achieving the LDL-C goals recommended by the 2019 ESC/EAS dyslipidemia guidelines.[15] The CV risk for each patient was determined by the participating physicians at enrollment. In this manuscript, we present baseline data from SANTORINI Spain. Furthermore, data from SANTORINI Europe without Spain were also analyzed.

Statistical analysis

As an observational study, only descriptive analyses have been carried out. Baseline continuous variables are shown as mean and standard deviation (SD), or median and interquartile range (IQR), as appropriate. Categorical variables are reported as absolute and relative frequencies (percentages). Results are shown in the overall population and regarding CV risk, as assessed by physicians (high and very high risk). All analyses were performed in SAS version 9.4, SAS Institute Inc., Cary, NC, USA.

Results

Patient's CV risk and characteristics

Between March 2020 and February 2021, a total of 9559 patients were enrolled in SANTORINI. Out of these, 1043 patients were recruited from 82 Spanish healthcare centers, mainly hospitals (89.7%); however, 25 patients were excluded due to unavailability of complete data at baseline evaluation, leaving 1018 patients for analysis. Sociodemographic and clinical characteristics of evaluable patients in SANTORINI Spain are reported in Table 1. The patients were predominantly male (72.9%), with a mean age of 63.3 years (SD: 11.3), and a high proportion of subjects with hypertension (62.9%) and diabetes (41.4%). Overall, 67.4% had established atherosclerotic CVD. According to their physicians, 295 patients (29.0%) were classified as having high CV risk, whereas 723 (71.0%) as having very high CV risk.

Lipid-lowering therapy

Overall, 43.0% patients in SANTORINI Spain were treated with statin monotherapy, 42.4% of high and 43.3% of very high risk patients, respectively (Fig. 1). High-intensity statin monotherapy was prescribed in 12.9% and 25.5% of patients at high and very high CV risk, respectively. Other LLTs were used as monotherapy in the overall population in less than 2.0% of patients each: 1.9% ezetimibe, 1.6% proprotein convertase subtilisin/kexin type 9 inhibitors (PCSK9i), and 1.7% other oral LLTs. Of patients, 41.2% were treated with a combination of LLT, with 27.1% receiving statin plus ezetimibe combinations. Overall, 5.9% of patients were receiving a PCSK9i-based combination therapy. Finally, 10.7% of patients were not receiving any LLT.

LDL-C goal attainment

Overall, 26.5% of patients in SANTORINI Spain (LDL-C dataset N = 956) already achieved risk-based LDL-C targets recommended by the 2019 ESC/EAS guidelines at baseline, with 23.1% of patients at high CV risk and 27.9% at very high CV risk (Fig. 2). The mean LDL-C levels were 82.4 mg/dL (SD: 40.8) for all patients, 102.0 mg/dL (SD: 46.4) for high CV risk, and 74.4 mg/dL (SD: 35.2) for very high CV risk patients.

Table 1 Baseline sociodemographic and clinical characteristics in the overall population from SANTORINI Spain and by patient cardiovascular risk (as reported by physicians).

	Risk classification as reported by physicians		
Patient characteristics	Overall (n = 1018)	High risk (n = 295)	Very high risk (n = 723)
Male, n (%)	742 (72.9)	175 (59.3)	567 (78.4)
Age, mean (SD), years	63.3 (11.3)	59.6 (12.6)	64.8 (10.4)
BMI, mean kg/m^2 (SD)	28.4 (4.7)	28.1 (4.8)	28.5 (4.7)
Hypertension, n (%)	640 (62.9)	147 (49.8)	493 (68.2)
Diabetes, n (%)	421 (41.4)	105 (35.6)	316 (43.7)
Familial hypercholesterolemia, n (%)	151 (14.8)	96 (32.5)	55 (7.6)
eGFR, mL/min/1.73 m^2, mean (SD)	80.6 (23.9)	85.6 (22.8)	78.6 (24.1)
Smoking history, n (%)			
Current	164 (16.1)	57 (19.3)	107 (14.8)
Former	495 (48.6)	102 (34.6)	393 (54.4)
Never	359 (35.3)	136 (46.1)	223 (30.8)
Systolic blood pressure, mean (SD), mmHg	132.6 (18.5)	134.2 (18.1)	131.9 (18.6)
Diastolic blood pressure, mean (SD), mmHg	76.8 (11.4)	79.0 (11.3)	75.9 (11.3)
LDL-C, mean (SD)			
mmol/L	2.1 (1.1)	2.6 (1.2)	1.9 (0.9)
mg/dL	82.4 (40.8)	102.0 (46.4)	74.4 (35.2)

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

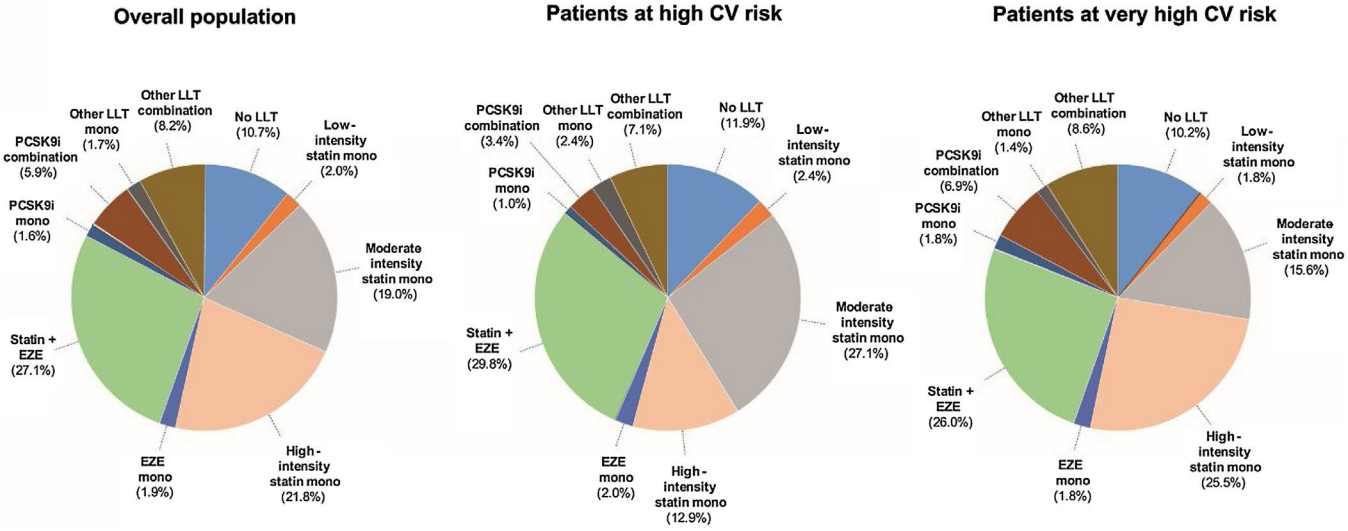

Figure 1 Use of lipid-lowering therapy in SANTORINI Spain, in the overall population and in high and very high risk subjects (physician-assessed risk classification).
CV, cardiovascular; EZE, ezetimibe; LLT, lipid-lowering therapy; PCSK9i, proprotein convertase subtilisin/kexin type 9 inhibitor.

Perspective of SANTORINI Spain in relation to SANTORINI Europe without Spain

When relating the data with SANTORINI Europe without Spain, the proportion of patients who were not receiving LLTs in SANTORINI Spain was lower (10.7% and 22.2%, respectively) (Fig. 3). The use of statin plus ezetimibe (27.1% and 15.8%) and PCSK9i-based (5.9% and 4.6%) therapy combinations were higher in SANTORINI Spain, leaving a little smaller proportion of patients receiving high-intensity statin monotherapy (21.8% and 21.4%, respectively). LDL-C goal attainment in SANTORINI Spain (LDL-C dataset) was higher (26.5% and 20.4%), especially in patients at very high risk (27.9% and 18.8%) (Fig. 2).

Discussion

The results of the present analysis, involving the Spanish patients from SANTORINI (SANTORINI Spain), confirmed the suboptimal LDL-C goal achievement in patients at high and very high CV risk, with only 26.5% of the patients achieving the 2019 risk-based LDL-C targets. Of note, despite guidelines recommendations for treating subjects at highest risk, high-intensity statins, and combination LLT were underused in these patients. In addition, it is necessary to remark that the CV risk of our patients was established by the participating physicians based on their perception.

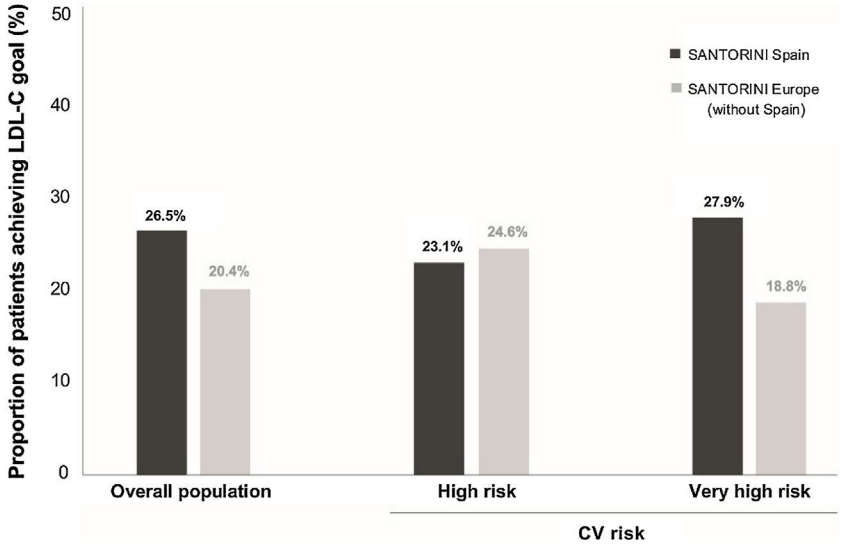

Figure 2 Perspective of LDL-C goal attainment by physician risk-assessment in SANTORINI Spain in relation with SANTORINI Europe without Spain.
CV, cardiovascular.

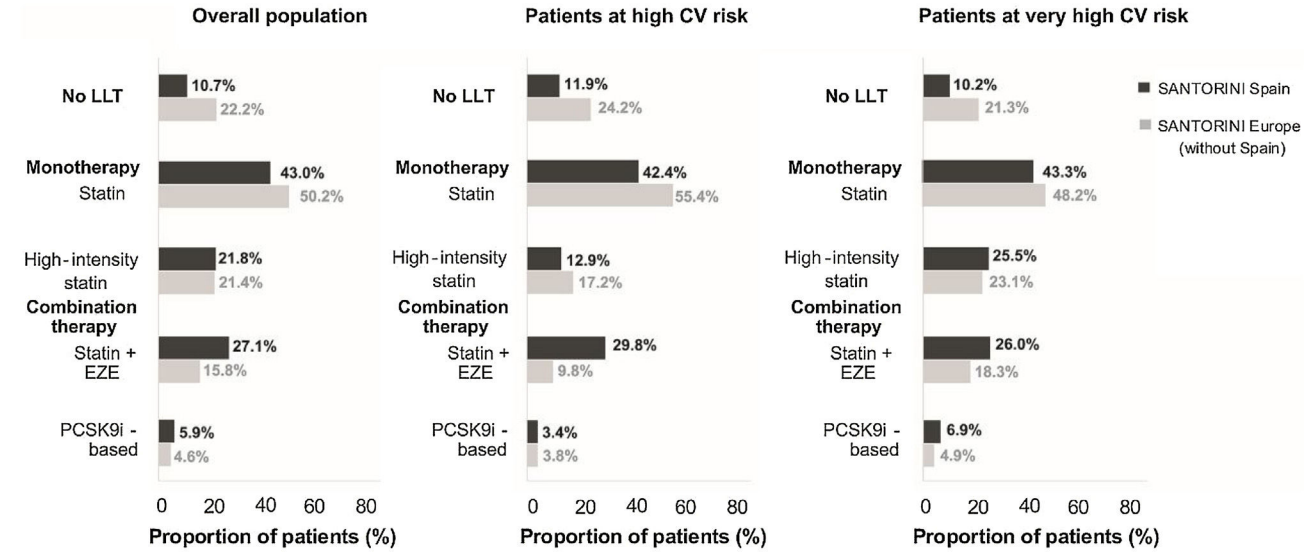

Figure 3 Perspective of use of lipid-lowering therapy in SANTORINI Spain in relation with SANTORINI Europe without Spain.
CV, cardiovascular; EZE, ezetimibe; LLT, lipid-lowering therapy; PCSK9i, proprotein convertase subtilisin/kexin type 9 inhibitor.

Many real-world studies conducted prior to publication of the 2019 ESC/EAS guidelines in Europe[9–12] and specifically in Spain[6–8] showed that LDL-C goal attainment was already challenging, even with their less strict targets. For instance, in the DA VINCI study, a cross-sectional observational study aimed at providing information on LDL-C goal attainment across 18 European countries and 5888 patients (3000 and 2888 from primary and secondary prevention, respectively), 54% of them achieved their risk-based 2016 goals (63%, 75%, 63%, and 39% for low, moderate, high, and very high risk).[11] Similarly, in the EUROASPIRE V survey performed in patients with coronary heart disease from 27 European countries[9] and in the PATIENT CARE registry[10] performed in 7824 and 1408 patients, respectively, only 29% and 41.9% of patients reached the <1.8 mmol/L (<70 mg/dL) LDL-C target recommended by the 2016 ESC/EAS guidelines.

By contrast, real-world data on LDL-C goal achievement after the 2019 update of the ESC/EAS guidelines are limited to only two studies, i.e. SANTORINI[14] and the Dyslipidemia Observatory.[13] The latter one refers to a cross-sectional, observational, multicenter study in Spain with data from 4010 patients at high and very high CV risk in which only 22% and 25% of them, respectively, attained the 2019 risk-based LDL-goals.[13] These results are very comparable to the ones presented here. They were collected in a similar time-frame, and also by physicians from primary care (28% of them), and internal medicine (24%), endocrinology (13%) and cardiology departments (34%), although in a different proportion.

SANTORINI reported an LDL-C goal attainment rate of 20.1% in patients having high and very high CV risk.[14] When the data are in perspective with SANTORINI, our results show

a higher proportion of patients attaining their LDL-C goal in SANTORINI Spain. Differences between SANTORINI Spain and SANTORINI are found depending on patient's risk. Indeed, whereas in SANTORINI Spain (LDL-C dataset) a greater number of patients at very high CV risk met the LDL-C risk based goals than those at high risk (27.9% versus 23.1%), in SANTORINI, it was the opposite, the higher number came from patients at high CV than those at very high CV risk (17.3% versus 24.2%).[14]

Findings from prior studies along with the results from SANTORINI Spain show the substantial gap existing between guideline recommendations for CVD prevention and routine clinical practice, highlighting the need for more intensive LDL-C lowering therapy for patients at high and very high CV risk.

The low LDL-C target achievement rate in our cohort may derive to some extent, from the low rate of prescription of high-intensity statins and combination therapy with ezetimibe or other LLTs. In our analysis, we found that, despite the low proportion of subjects attaining lipid targets, only 27.1% were receiving statin plus ezetimibe combination therapy. Additionally, PCSK9i-based combinations were used in 5.9% of patients. A retrospective real-world study conducted in Spain reported the use of optimized treatment (namely high-intensity statins or statins in combination with ezetimibe) in 46.2% of patients with CAD.[16] Prior European studies evaluating the impact of the 2019 ESC/EAS guidelines on LLT prescription patterns also evidenced the underuse of guideline recommended optimized LLT. For example, a retrospective analysis of the Swiss Secondary Prevention Registry (SwissPR) in 875 patients with CAD reported the use of combination therapy with ezetimibe in only 18% of patients at cardiac rehabilitation entry (and 51% at discharge) after publication of 2019 guidelines, with only 2% of patients being prescribed PCSK9i.[17] Compared with prior studies evaluating clinical management after release of the 2019 European guidelines, the baseline data from SANTORINI showed that the use of combination therapies for lowering LDL-C has increased but remains unacceptably low.[14] By putting on perspective the data from SANTORINI Spain with SANTORINI,[14] we found that the number of patients using statin plus ezetimibe combination therapy and PCSK9i-based therapies were markedly higher in SANTORINI Spain than SANTORINI (27.1% versus 14.7% and 7.5% versus 7.0%, respectively). In addition, the percentage of patients who were not receiving any LLT in SANTORINI Spain (10.7%) was lower than in SANTORINI (23.1%).[14] Both results may explain the higher LDL-C attainment rate in SANTORINI Spain (26.5%) than SANTORINI (19.3%).[14] The differences in the use of LLT with other European countries may be explained due to divergences in the routine clinical practice according to local guideline recommendations, healthcare systems, prescription patterns and requirements (i.e. reimbursement limitations) for prescription of LLT, and availability of statins at specific doses. Furthermore, differences in LDL cholesterol attainment and LLT use among Spanish regions have also been evidenced.[18]

The EUROASPIRE V survey also evidenced the differences in the management of dyslipidemia among countries.[9] The country with the highest proportion of patients receiving high-intensity LLTs (defined as daily dosages that are on average associated with a $\geq$50% LDL-C reduction) was Latvia (88.5%, n = 115/130), followed by Spain (81.7%, n = 276/338), Sweden (76.2%, n = 186/244), and UK (72.0%, n = 288/400). By contrast, the countries with lowest percentage were Kyrgyzstan (9.0%, n = 30/335), Kazakhstan (15.8%, n = 64/405), and Ukraine (21.3%, n = 76/357).

In addition to the underuse of high-intensity LLT and combination therapy for CVD prevention, the low guideline-recommended LDL-C goals achievement may be also explained by a usual delay in the implementation of the guidelines into clinical practice, considering the release of the update of 2019 and the study enrollment period initiated from March 2020 in SANTORINI. Barriers that may justify the reduced control of LDL-C could be related to the physician (clinical inertia or the consideration that the LDL target has been already reached), to the patient (non-compliance with the prescribed medications), to the medication (maximum tolerated dose, development of adverse events), or to the healthcare system (limited access to combination therapy and/or add-on therapies).[19,20]

The main limitation of this study derives from the fact that sites participating in research are often more experienced; therefore, the present findings may reflect best-case scenario. Regarding LLT use, the treatment of patients might not have been optimized at the time of the study inclusion. The study was conducted during the COVID pandemic what could have influenced in the final results. For this reason, data on one year of follow-up are needed to corroborate the present results. Moreover, no associations between LDL-C and LLT can be inferred from the study as not specifically designed to address it. Besides all these limitations, to our knowledge, this is first prospective study and the largest series providing up-to-date real-world data on lipid management and LDL-C goals attainment in patients at highest CV risk after the 2019 ESC/EAS guidelines publication in Spain.

Conclusion

The baseline data from SANTORINI Spain show a suboptimal LDL-C goal attainment in patents at high and very high risk, with only around one-fourth of patients achieving their risk-based LDL-C targets recommended by the 2019 ESC/EAS guidelines. Despite their CV risk, patients appear to be not adequately treated, and combination LLT seem to be underused for management of CVD prevention in the real-world setting.

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Declaration of competing interest

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Rovi. Luis Manzano-Espinosa declares that he has received grants/contracts from Amgen and Novartis; and consulting fees, payments/honoraria, and support for attending meetings from Novartis. Alberico L. Catapano declares that he has received grants/contracts from Amryt Pharma, Menarini, and Ultragenyx; and fees/honoraria from Amarin Amgen Amryt Pharma, Astrazeneca, Daiichi Sankyo, Esperion Ionis Pharmaceutical Medscaper, Menarini, Merck, Novartis, NovoNordisk, Peervoice Pfizer Recordati Regeneron, Sandoz, Sanofi The Corpus, Ultragenyx, and Viatris. Kausik K. Ray discloses that it has received editorial support from Springer funded by Daiichi Sankyo Europe; consultancy from Daiichi for the development of the statistical analysis plan, protocol, supervision as PI; grants/contracts from Amgen, Daiichi Sankyo, Sanofi, Regeneron, and Ultragenyx; consulting fees 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; payments/honoraria from Novartis, Daiichi Sankyo, Novo Nordisk, Amgen, Sanofi, and Boehringer Ingelheim; and stock options from New Amsterdam Pharma, Scribe, Pemi31. He is also the President of EAS. G.D.M. is an employee of Daiichi Sankyo. Juan Pedro-Botet Montoya reports that he has received consulting fees from Sanofi, Amgen, Amarin, Daiichi Sankyo; payments/honoraria from Almirall, Amarin, Amgen, Daiichi Sankyo, Esteve, Organon, Sanofi; and support for attending Daiichi Sankyo meetings. Luis García-Ortiz, Pedro Talavera Calle, Javier Chimeno García, Vanessa Escolar Pérez and Jose Luis Díaz-Díaz declare that they have no conflicts of interest.

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