Nutrition, Metabolism & Cardiovascular Diseases (2024) **34**, 90–97

Available online at www.sciencedirect.com

Nutrition, Metabolism & Cardiovascular Diseases

journal homepage: www.elsevier.com/locate/nmcd

Patients who suffer a first atherosclerotic cardiovascular event while taking statins are often far off of lipid targets

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Received 31 March 2023; received in revised form 12 September 2023; accepted 21 September 2023
Handling Editor: D. Noto
Available online 11 October 2023

KEYWORDS
Low-density lipoprotein cholesterol;
Cardiovascular risk;
Lipid-lowering therapy;
Spain

Abstract *Background and aims:* Despite considerable evidence that lipid-lowering therapies (LLTs) afford clinical benefit, the control of low-density lipoprotein cholesterol (LDL-C) is suboptimal, and available LLTs are underused, especially in patients at high and very high cardiovascular (CV) risk. This study assesses the real-world LDL-C target attainment rate in patients on LLT before experiencing a first major acute cardiovascular event (MACE).
Methods and results: The HEARTBEAT was a retrospective, multicentre observational study. From March to June 2021 a total of 334 patients on LLT who had a first MACE while being on statins were included in the study. Of these patients, 83.2 % had a high (40.7 %) or very high CV risk (29.0 %) prior to MACE. Overall, 87.5 % and 89.7 % of the patients at high and very high CV risk, respectively, failed to reach the LDL-C target. Regarding LLTs, only 11.8 % and 19.6 % of the patients at high and very high risk had received high-intensity LLTs prior to MACE. It was estimated that if these patients had reached their recommended LDL-C targets, the risk of MACE may have been reduced by a median of 24.5 % and 23.2 % in patients at high and very high risk respectively.
Conclusions: Patients who suffer a first MACE while on statin therapy often were at high/very high CV risk. Despite their risk, LDL-levels and being on statins they are undertreated, and too far from lipid targets. A proper use of high-intensity LLTs led to an increase attainment of LDL targets and lower CV events.

1. Introduction

Cardiovascular disease (CVD) is the most frequent cause of death worldwide, accounting for 17.9 million deaths per year [1]. In Europe, CVD is responsible for more than four million deaths every year [2]. The development of CVD is influenced by multiple risk factors including age, gender, arterial hypertension, diabetes mellitus, dyslipidaemia, body mass index, and smoking [2]. Dyslipidaemia is a well-known major risk factor for CVD. Likewise, low-density lipoprotein cholesterol (LDL-C) is an independent predictor of atherosclerotic CVD (ASCVD) [2,3], and its aetiological role in ASCVD has been demonstrated. Lowering LDL-C values therefore has become the primary target in the management of dyslipidaemia. There is considerable

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https://doi.org/10.1016/j.numecd.2023.09.022

evidence demonstrating the clinical benefit of lowered LDL-C levels with a view to minimising ASCVD risk [3–8]. Each mmol/L decrease in LDL-C results in a 22 % decrease in the incidence of major cardiovascular events [9]. Accordingly, the 2019 European Society of Cardiology (ESC) and the European Atherosclerosis Society (EAS) guidelines recommend the reduction of LDL-C to specific targets, defined as <2.6 mmol/L (<100 mg/dL) for patients at moderate risk, and <1.8 mmol/L (<70 mg/dL) and <1.4 mmol/L (<55 mg/dL) for patients at high and very high risk, respectively, together with a 50 % reduction in LDL-C from baseline values [2,10]. Lowering LDL-C levels to guideline-recommended treatment targets is the cornerstone of CVD prevention. Despite recommendations on the use of high-intensity lipid-lowering therapy (LLT) for reducing LDL-C levels in patients at high and very high CV risk [2], the available intensive LLTs are generally underused in these patients in the real-world setting [11]. The primary prevention of CVD is of vital importance for avoiding a first major acute cardiovascular event (MACE) [12], though multiple studies in Europe [10,13–17] and Spain [18–21] have revealed poor LDL-C target attainment in primary prevention. However, most studies have not been conducted exclusively in the primary prevention scenario, and real-world data from different studies are heterogeneous due to divergences in baseline CV risk and comorbidities, patient types, the intensity of LLT, guideline-recommended LDL-C targets at the time when the studies were conducted, and clinical practice in different countries.

The present study evaluates a new aspect, the incidence of failure to reach the guideline-recommended LDL-C targets before the occurrence of a first MACE in patients on LLT for primary prevention in Spain.

2. Methods

2.1. Study design and patients

The HEARTBEAT was a retrospective, multicentre observational study designed to characterise real-world attainment of LDL-C targets in patients in primary prevention in Spain before they suffer a first arteriosclerotic CV event. This study included adults (≥18 years of age) admitted to hospital between 1 January and December 31, 2019 due to a first MACE (including non-fatal myocardial infarction [MI], non-fatal stroke, cardiovascular death, coronary revascularisation, or unstable angina requiring hospitalisation) while on LLT for at least two years before MACE, and who had available data on LDL-C levels within the 12 months before MACE. Exclusion criteria included unavailable data on LLT in the last two years before MACE, hospitalisation for reasons other than MACE, and participation in another study involving LLTs.

Written informed consent was obtained from all patients before their inclusion in the study, which was conducted in accordance with the Declaration of Helsinki and was approved by an independent Ethics Committee.

2.2. Study endpoints

The primary endpoint was the proportion of patients administered LLT who did not reach the risk-based LDL-C targets recommended by the 2019 ESC/EAS guidelines (<1.4 mmol/L [55 mg/dL] for very high risk, <1.8 mmol/L [70 mg/dL] for high risk, and <2.6 mmol/L [100 mg/dL] for moderate risk patients) [2], according to LDL-C levels within the two years prior to MACE. The attainment of treatment targets according to the CV risk classification was only based on the achievement of LDL-C targets, i.e. without including the ≥50 % LDL-C reduction from baseline. Secondary endpoints included the description of the LLT used within 12 months before MACE, considering high-intensity (atorvastatin 80 mg, rosuvastatin 20 mg, and statins plus ezetimibe) and non-high-intensity LLT. Treatment adherence was indirectly defined as at least ≥10 % decrease in LDL-C maintained within the 12 months before the occurrence of MACE.

A retrospective medical chart review was conducted to collect data on demographic and clinical characteristics of the patients, including comorbidities, LLTs prior to MACE, patient characteristics at the time of MACE and MACE-related data, and LDL-C levels prior to MACE.

2.3. Statistical analysis

Continuous variables were reported as the mean and standard deviation (SD), or as the median and interquartile range (IQR), as appropriate. Categorical variables were reported as frequencies and percentages. Associations referred to LDL-C levels and CV risk were analysed using the Chi-square test. Differences in LDL-C target attainment according to cardiovascular risk factors (CVRFs) were analysed using the Fisher exact test. Post hoc analyses were performed to estimate the median distance of LDL-C levels in patients at high and very high risk before the MACE from the guideline recommended LDL-C targets (<70 and < 55 mg/dL, respectively) [2]. Based on this information, we estimated the percentage decrease in MACE that may be obtained if the patients had achieved the recommended LDL-C targets considering that each mmol/L of LDL-C decrease has proven a 22 % decrease in the incidence of MACE [9]. For this purpose, the median percentage decrease estimated, and the 95 % confidence intervals (95%CI) were calculated. Missing data were not considered in the analyses. Statistical significance was established with $P \geq 0.05$. All statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS) version 22.0 (SPSS Inc., Chicago, IL, USA).

3. Results

3.1. Patient characteristics and cardiovascular risk

From March to June 2021, a total of 355 patients were enrolled in the study at 29 hospitals distributed throughout Spain. Twenty-one patients were excluded due to non-compliance with the inclusion criteria (hospitalisation for

reasons other than first MACE: n = 20; non-availability of LDL-C levels within 12 months prior to MACE: n = 1). Thus, 334 patients were evaluable for the study analyses. Sociodemographic and clinical characteristics of the evaluable patients are reported in Table 1. The patients were predominantly male (66.5 %), Caucasian (93.4 %), and with a median age of 72 years. Regarding CVRF, 97 % of the patients presented hyperlipidaemia, 72.5 % arterial hypertension, and 43.4 % diabetes. The complete list of cardiovascular comorbidities is provided in Supplementary Table 1. Noteworthy, 69.7 % of the patients had high (40.7 %) or very high (29.0 %) cardiovascular risk according to the 2019 ESC/EAS guidelines, within the two years prior to MACE.

3.2. Lipid-lowering therapy

Most patients at high (88.2 %) and very high (80.4 %) cardiovascular risk had received non-high-intensity LLT prior to MACE. Only 11.8 % of the patients at high cardiovascular risk and 19.6 % of those at very high risk had received high-intensity LLT (Fig. 1). Overall, 15 % of the high or very high-risk patients were receiving high-intensity LLT at the time of the first MACE. Nine percent of the high or very high-risk patients were on statin plus ezetimibe combinations. The last LLT received by the patients before the first MACE is reported in Supplementary Table 2.

Table 1 Sociodemographic and clinical characteristics of the patients included in the study (N = 334).

Patient characteristics	Value
Age, median (IQR), years	72.0 (63.0–80.0)
Gender, male, n (%)	222 (66.5)
Race, Caucasian, n (%)[a,b]	310 (93.4)
CVRF, n (%)	
Hyperlipidaemia	324 (97.0)
Arterial hypertension	242 (72.5)
Diabetes	145 (43.4)
Smoking[c]	
Current smoker	83 (26.2)
Ex-smoker	99 (31.2)
Never smoker	135 (42.6)
Main comorbidities, n (%) [d]	
Respiratory	64 (19.2)
Cardiovascular[e,f]	55 (16.5)
Atrial fibrillation	19
Heart failure	4
Aortic stenosis	4
Peripheral arterial disease	4
Endocrine	47 (14.1)
Psychiatric	47 (14.1)
Cardiovascular risk within two years before first MACE, n (%)	
Low	24 (7.2)
Moderate	77 (23.1)
High	136 (40.7)
Very high	97 (29.0)

IQR: interquartile range; CVRF: cardiovascular risk factor; MACE: major acute cardiovascular event.
[a] Latin American: 13 (3.9 %), African: 3 (0.9 %), Asian: 1 (0.3 %), other (not specified): 5 (1.5 %). Missing data.
[b] n = 2.
[c] n = 17.
[d] n = 76.
[e] Most frequent (present in more than 3 patients) types of heart disease.
[f] Multiple response (patients can present more than one type of cardiovascular disease).

3.3. Attainment of LDL-C targets for CVD prevention

The estimated rate of failure to reach the recommended LDL-C target was 83.9 % (95%CI, 79.4–87.6 %). Overall, 87.5 % and 89.7 % of the patients at high and very high cardiovascular risk, respectively, did not achieve their LDL-C targets (Fig. 2A). Of note, 58.8 % of the high-risk patients and 40.2 % of the very high-risk subjects showed LDL-C >100 mg/dL after the optimisation of LLT. The distribution of LDL-C levels according to cardiovascular risk is shown in Fig. 2B. The median LDL-C value within the two years before MACE was 104.5 mg/dL (IQR, 82.0–129.0), with median LDL-C levels of 107.5 mg/dL (IQR, 85.7–136.0) and 89.0 mg/dL (IQR, 70.7–117.0) in patients at high and very high risk, respectively. Accordingly, the median distance to the recommended targets was 37.6 mg/dL (IQR, 15.9–66.1) and 34.1 mg/dL (IQR, 15.8–62.1) in patients at high and very high risk, respectively. It was estimated that if these patients had reached their recommended LDL-C targets, the risk of MACE may have been reduced by a median of 24.5 % (IQR, 14.2–40.6) in patients at high risk and by 23.2 % (IQR, 11.0–36.4) in those at very high risk. A LDL-C decrease ≥10 % that was maintained within the last 12 months before MACE was reached in 41.4 % of the patients (94 out of 227 individuals with available data).

3.4. MACE episode

Myocardial infarction was the most common first MACE episode (62.0 %), followed by hospitalisation due to unstable angina (16.2 %). The MACE-related death rate was 2.5 % (8 patients). Overall, 84.1 % of the patients required coronary revascularisation after MACE, mainly with stent placement (94.4 %) (Table 2).

4. Discussion

The present study describes previous dyslipidaemia control in individuals who experience a first major cardiovascular event despite already being on LLT. The data are astonishing. The number of patients in cardiovascular primary prevention failing to reach the guideline-recommended LDL-C targets in this group of patients is unacceptably high (84 %). Less than one out of five of all hypercholesterolemic patients driven to a first cardiovascular event were properly treated. This finding is in line with the suboptimal LDL-C target achievements previously reported in primary prevention in European studies [10,13–17,22], and in studies conducted in Spain [18–21].

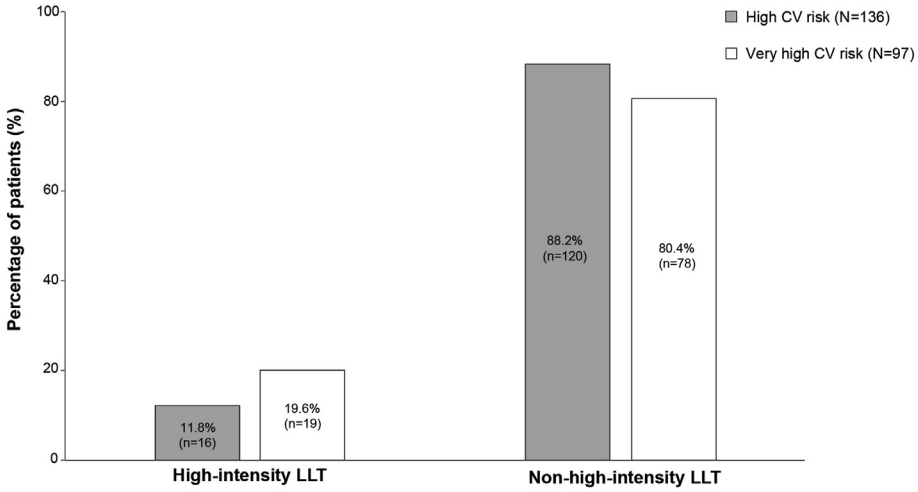

Figure 1 Intensity of the LLTs received within the 12 months before MACE in patients at high or very high cardiovascular risk.
* The target attainment classification was only based on LDL-C targets recommended by the 2019 ESC/EAS guidelines, i.e. without including the ≥50 % LDL-C reduction from baseline.

For instance, the primary prevention arm of the EURO-ASPIRE V survey, involving 2759 individuals at high cardiovascular risk from 16 European countries, in which 34.1 % received LLTs, revealed a low rate of LDL-C target (<2.6 mmol/L) attainment of 46.9 % [14]. In the DA VINCI observational study involving 2154 patients from Central and Eastern Europe in primary and secondary care, 37 % of the subjects in primary prevention (n = 664) reached the 2019 risk-based LDL-C target, with 19 % and 4 % of those at high and very high cardiovascular risk respectively reaching the LDL-C targets [17]. Interim results from the European SANTORINI observational study involving 9606 patients at high or very high cardiovascular risk has shown that only 20.1 % of them reached guideline-recommended LDL-C targets according to their cardiovascular risk [23]. Nevertheless, these European studies were centred on outpatients in primary or secondary prevention, and none of them included patients hospitalised due to a first cardiovascular event with LDL-C levels that had been characterised prior to occurrence of the event. In Spain, studies such as ENRICA [19], CODIMET [20], and REPAR [21], or the recent survey from the Cardio Right Care CV Risk Control project, have demonstrated suboptimal LDL-C control in primary prevention [24]. This situation is particularly worrying in the context of patients at high or very high risk. Importantly, in our study, nearly 70 % of the patients were at high or very high CV risk before a first major CV event according to the 2019 ESC/EAS guidelines applied by the responsible physician; with about 87 % and 82 % of them not reaching the recommended LDL-C targets, and being undertreated despite their elevated risk. In addition, despite their risk, only 15 % of these high and very high-risk patients were receiving high-intensity LLT at the time of MACE. The ESC/EAS guidelines recommend intensive LLT with statins in patients at high or very high cardiovascular risk [2]. Therapeutic planning tables have been made to determine the most appropriate LLT for each patient's therapeutic target [25]. In this regard, therapeutic strategies follow a stepwise approach, adding intensity and/or therapies in order to adequately achieve LDL-C targets. Nevertheless, the gap between guideline recommendations for LLT optimisation and the real-world use of intensive LLT for the primary prevention of CVD has been reported elsewhere [17,22]. In the DA VINCI study, only 33 % of the participants were on high-intensity statin monotherapy, and 4 % were being treated with ezetimibe combination therapy (plus moderate/high-intensity statin) at the time of enrolment [17]. In addition, adherence to LLTs remains poor [26]. Malo et al. [27], in a prospective study with 725 statin initiators for primary cardiovascular prevention, found that just one in three (29.5 %) of them were persistent with the treatment during the first year of follow-up. In fact, 15 % of the non-persistent users discontinued LLT after dispensation of the first prescription.

Diverse studies have pointed out to socioeconomic factors associated with the use of LLTs [28,29]. Indeed, older age, health insurance status, hypertension, diabetes mellitus, and history of early ASCVD have been correlated with a greater use of statins. Other studies have also pointed out the underuse of LLTs in women [30–32]. A large National retrospective cohort study evaluated the patient's factors that could influence the LLT prescription of patients at CV primary prevention in UK [33]. The study, involving data from 365,718 patients (aged 30–74 years, free from CVD, and not receiving LLTs), revealed that LLT prescription was strongly associated with increasing age (Odd ratio, OR 4.2 for ≥65 years); diabetes (OR 4.5); total cholesterol level ≥7 mmol/L (OR 2.2); and ≥4 blood pressure measurements in the last year (OR 4.2). Our study cannot provide evidence on the causes for such high-intensity LLT underuse; however it can highlight the consequences, i.e. experiencing the subsequent MACE, especially in patients at high and very high risk. An increased awareness for attaining the international guidelines by the healthcare specialists is ultimately required to improve the use of LLTs in clinical practice and aid more patients to achieve their LDL-C goals.

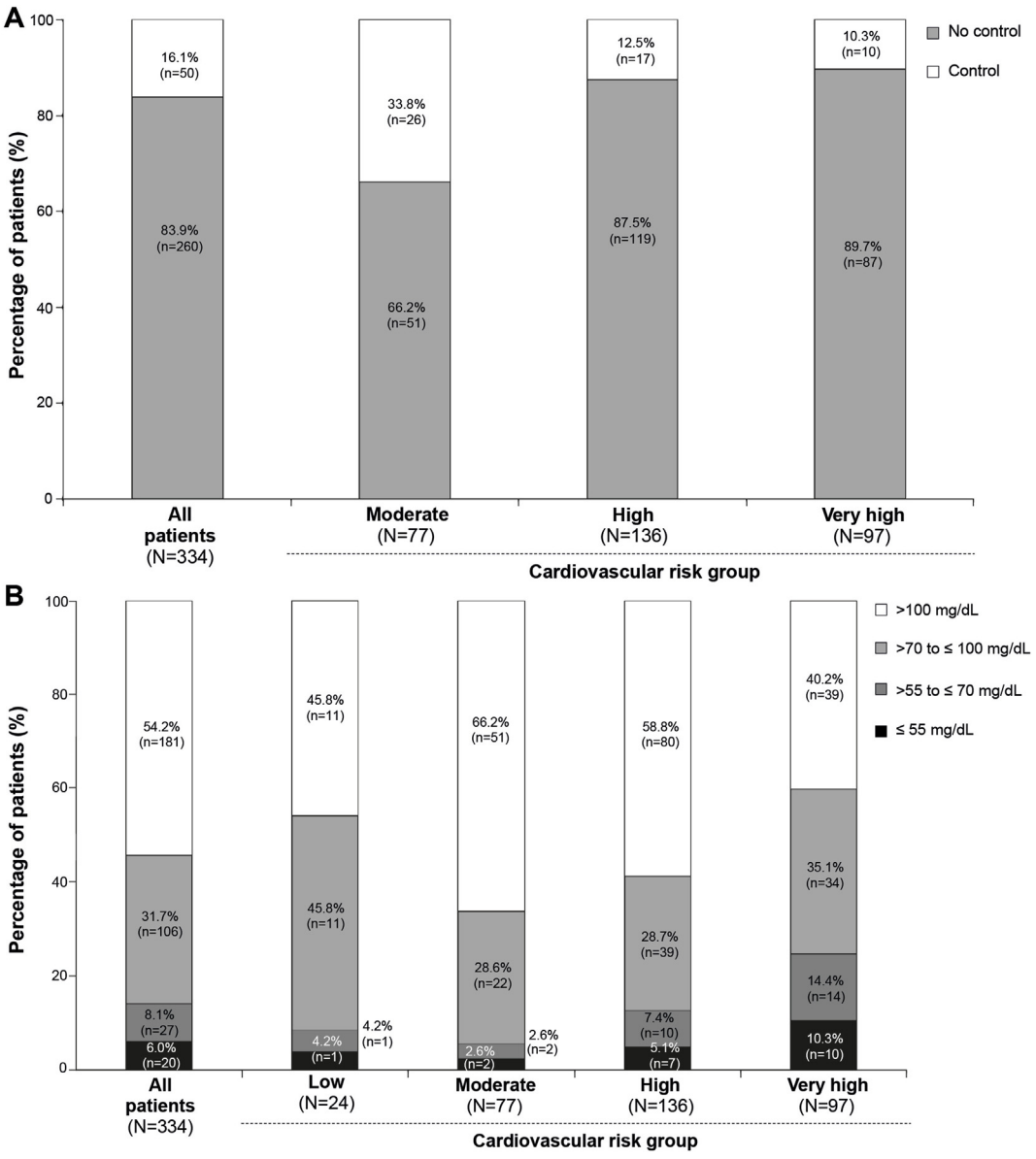

Figure 2 Attainment of LDL-C target in all patients and according to cardiovascular risk **(A)** and the distribution of LDL-C levels according to patient cardiovascular risk **(B)**.

* The target attainment classification was only based on LDL-C targets recommended by the 2019 ESC/EAS guidelines, i.e. without including the ≥50 % LDL-C reduction from baseline.

If the treatment had been adequately prescribed and maintained, high-intensity LLTs might have reduced the LDL-C levels more than 50 % in these patients [2,25]. In our study, post hoc analyses showed an estimated median distance to the recommended targets of 37.6 mg/dL and 34.1 mg/dL in patients at high and very high CV risk, respectively. Additionally, applying the data from the Cholesterol Treatment Trialist Collaboration [9] metanalyses showing that each mmol/L of LDL-C decrease leads to 22 % relative risk reduction we estimated that if these patients had reached the recommended LDL-C targets, the risk of MACE might have been lowered by a median of 24.1 % and 23.2 % in patients at high and very high risk, respectively. This finding is in agreement with data found in the literature [34], though comparison requires careful interpretation. A recent systematic review and meta-analysis including 21 randomised clinical trials that evaluated the effectiveness of statins in primary and secondary prevention evidenced a relative risk reduction of 9 % (95% CI, 5–14 %) for all-cause mortality, 29 % (95%CI, 22–34 %) for myocardial infarction, and 14 % (95%CI, 5–22 %) for stroke associated with their use [35].

Some study limitations must be acknowledged. The main limitation of our study is its retrospective nature, using information recorded for non-research purposes in the medical charts. Additionally, the intensity of the last LLT received before MACE was classified as high or non-high as a post hoc analysis. Yet, the study provides an up-to-date picture of the suboptimal performance in reaching LDL-C targets and of undertreatment in patients on LLT at the time

Table 2 Patient characteristics at MACE and MACE characterisation.

Patient characteristics	Value
Demographics and clinical characteristics at first MACE	
Age, median (range), years	69.0 (61.0 −78.0)
BMI, median (range), kg/m^2	28.4 (25.7 −31.9)
CRP, median (range), mg/dL	1.3 (0.4−5.0)
Concomitant therapy, n (%)[a]	
Antidiabetic therapy	123 (36.8)
Antihypertensive	390
Antiplatelet	106 (31.7)
Anxiolytic	46 (13.77)
Antidepressant	44 (13.2)
MACE event	
MACE, (n %)	
Myocardial infarction	207 (62.0)
Unstable angina requiring hospitalisation	54 (16.2)
Ischaemic stroke	45 (13.5)
Coronary revascularisation	16 (4.8)
Transient ischaemic stroke	8 (2.4)
Ischaemic peripheral arterial disease	4 (1.2)
Coronary revascularisation after the acute event, n (%)	233 (84.1)
Stent placement	218 (94.4)
Conventional surgery	13 (5.6)
MACE-related death, n (%)[b]	8 (2.5)

BMI: body mass index; CRP: C-reactive protein; MACE: major acute cardiovascular event.
[a] Missing data: n = 14.
[b] CRP assessment available in 150 patients.

of occurrence of a first MACE. Furthermore, to our knowledge, this is the first study to characterise LDL-C target attainment exclusively in patients in primary prevention before the occurrence of a first MACE in Europe and Spain.

In conclusion, patients on LLT for primary prevention, especially those at high and very high cardiovascular risk, are generally too far from reaching the lipid control target at the time of occurrence of a first MACE according to their risk in Spain. Despite their high cardiovascular risk and remarkably high LDL-C levels, patients are not adequately treated, and high-intensity LLTs are underused in the primary prevention setting. This study therefore calls for action to optimise primary prevention strategies using more effective/intensive LLTs tailored to cardiovascular risk, to avoid first occurrence of MACE.

Funding

This work was funded by Daiichi-Sankyo Spain. Medical writing support was provided by Evidenze Health España S.L. and funded by Daiichi-Sankyo Spain.

Declaration of competing interest

L.M. declares that he has received fees for lectures or advisory work from Amarin, Amgen, Amryt, Daiichi-Sankyo, Ferrer, Novartis, Sanofi, Ultragenix, and Viatris. G.D.M is an employee from Daiichi Sankyo España. L.P.d.I declares that he has received fees for presentations, research, and consultory from Daichii-Sankyo, Menarini, Sanofi, Amgen, MSD, Novartis, and Ferrer.

Acknowledgements

The authors would like to thank Daiichi-Sankyo Spain for supporting the study.

The authors would like to acknowledge the HEARTBEAT study investigators for their valuable contribution to the study: Dra Núria Plana, Hospital Universitario Sant Joan, Reus, Spain; Dra. Natalia Andreychuk, Hospital Universitario Sant Joan, Reus, Spain; Dr. Martín Ruiz Ortiz, Hospital Reina Sofía, Córdoba, Spain; Dr. Norberto Herrera, Hospital Universitario San Cecilio, Granada, Spain; Dr. Juan José Gómez Doblas, Hospital Universitario Virgen de la Victoria, Málaga, Spain; Dr. Jorge Rodríguez Capitán, Hospital Universitario Virgen de la Victoria, Málaga, Spain; Dr. Rafael Vazquez Garcia, Hospital Universitario Puerta del Mar, Cádiz, Spain; Dr. Daniel Bartolomé, Hospital Universitario Puerta del Mar, Cádiz, Spain; Dr. William Delgado, Hospital Universitario Puerta del Mar, Cádiz, Spain; Dr. Onofre Caldés, Hospital Universitario Son Espases, Palma, Spain; Dr. Aritz Gil, Hospital Universitario Marqués de Valdecilla, Santander, Spain; Dra. Verònica Perea, Mutua Terrassa, Barcelona, Spain; Dr. Alessandro Sionis, Hospital de la Santa Creu i Sant Pau, Barcelona, Spain; Dra. Silvia Herráez, Hospital de la Santa Creu i Sant Pau, Barcelona, Spain; Dr. Carles Jericó, Hospital Moisés Broggi, Barcelona, Spain; Dr. Xavier Pintó, Hospital Universitario de Bellvitge, Barcelona, Spain; Dra. María de los Ángeles Rodríguez, Hospital Universitario de Bellvitge, Barcelona, Spain; Dra. Mònica Domènech, Hospital Clinic i Provincial de Barcelona, Barcelona, Spain; Dr. José Luis Santos, Complejo Publico Asistencial de Zamora (Hospital Virgen de la Concha), Zamora, Spain; Dr. Eduardo Enriquez, Hospital Santa Bárbara (Complejo Hospitalario de Soria), Soria, Spain; Dr. Patricio Arribas, Hospital Santa Bárbara (Complejo Hospitalario de Soria), Soria, Spain; Dra. Carmen García Corrales, Complejo Hospitalario Universitario de Badajoz, Badajoz, Spain; Dra. Marisol Bravo Amaro, Hospital Universitario Álvaro Cunqueiro, Vigo, Spain; Dra. Inmaculada González, Hospital Universitario Álvaro Cunqueiro, Vigo, Spain; Dra. Berenice Caneiro, Hospital Universitario Álvaro Cunqueiro, Vigo, Spain; Dr. Carlos Gonzalez Juanatey, Hospital Universitario Lucus Augusti, Lugo, Spain; Dra. Elizabet Méndez Eirin, Hospital Universitario de A Coruña, A Coruña, Spain; Dr. Alejandro Curcio Ruigómez, Hospital Fuenlabrada, Madrid, Spain; Dra. Rosa María Jiménez, Hospital Fuenlabrada, Madrid, Spain; Dra. Carmen Cristobal, Hospital Fuenlabrada, Madrid, Spain; Dr. Eduardo Armada Romero, Hospital La Paz − Carlos III, Madrid, Spain; Dr. Sem Briongos, Hospital Universitario Infanta Leonor, Madrid, Spain; Dra. Varinia Gabriela Vallarino Terán, Hospital Universitario General de Villalba, Madrid, Spain; Dr. Domingo Pascual, Hospital Virgen de la Arrixaca, Murcia, Spain; Dr. Francisco Marín Ortuño, Hospital Virgen de la Arrixaca, Murcia, Spain; Dr.

Antonio Tello Montoliu, Hospital Virgen de la Arrixaca, Murcia, Spain; Dr. Ignacio Roy, Complejo Hospitalario Navarra, Pamplona, Spain; Dr. Lorenzo Facila Rubio, Hospital General Universitario de Valencia, Valencia, Spain; Dr. Vicente Montagud, Hospital General Universitario de Valencia, Valencia, Spain; Dra. Clara Bonanat, Hospital Clínico Universitario de Valencia, Valencia, Spain; Dr. Vicente Arrarte Esteban, Hospital General Universitario de Alicante, Alicante, Spain; Dra. Laura Fuertes, Hospital General Universitario de Alicante, Alicante, Spain; Dra. Ana María García, Hospital General Universitario de Alicante, Alicante, Spain; Dr. Alberto Cordero, Hospital Universitario San Joan de Alicante, Alicante, Spain; Dr. Miguel Ángel Arnau, Hospital Universitario y Politécnico La Fe, Valencia, Spain; and Dra. Diana Domingo Valero, Hospital Universitario y Politécnico La Fe, Valencia, Spain.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.numecd.2023.09.022.

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