

Prevalence, Treatment, and Control of Hypercholesterolemia in High Cardiovascular Risk Patients: Evidences from a Systematic Literature Review in Spain

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ABSTRACT

Introduction: Cardiovascular diseases (CVDs) represent a major Public Health burden. High serum cholesterol levels have been linked to major CV risk. The objectives of this study were to review the epidemiology of hypercholesterolemia in high risk CV patients from Spain, by assessing its prevalence, the proportion of diagnosed patients undergoing

pharmacological treatment and the degree of attained lipid control.

Methods: A systematic literature review was carried out using Medline and two Spanish databases. Manuscripts containing information on hypercholesterolemia in several high CV risk groups [diabetes mellitus (DM), Systematic COronary Risk Evaluation (SCORE) risk >5, or documented CVD], published between January 2010 and October 2014, were included.

Results: Of the 1947 published references initially retrieved, a full-text review was done on 264 manuscripts and 120 were finally

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included. Prevalence of hypercholesterolemia ranged from 50 to 84% in diabetics, 30–60% in patients with DM or elevated SCORE risk, 64–74% with coronary heart disease, 40–70% in stroke patients, and 60–80% in those with peripheral artery disease. Despite the finding that most of them were on pharmacological treatment, acceptable control of serum lipids was very variable, ranging from 15% to 65%. Among those with heterozygous familial hypercholesterolemia, 95–100% received treatment but less than 50% achieved their therapeutic goals.

Conclusions: An elevated prevalence of hypercholesterolemia can be found in targeted groups at high CV risk. Although most patients are receiving pharmacological treatment, rates of lipid control continue to be low, both in primary and secondary prevention.

Keywords: Cardiovascular disease; Control; Drug; Dyslipidemia; Hypercholesterolemia; Prevalence

INTRODUCTION

The overall prevalence of hypercholesterolemia in the Spanish adult population has been estimated between 34% and 50% in recent studies [1–3]. The importance of this high prevalence is due to the association of high levels of serum cholesterol with cardiovascular disease (CVD), which has been well established [4, 5]. For instance, the occurrence of CV events in patients with familial hypercholesterolemia has been highlighted, with a prevalence of premature CVD (before 55 years of age in men and before 65 years of age in women) of 10%, in contrast to less than 3% in relatives without familial hypercholesterolemia [6].

The therapeutic arsenal available for hypercholesterolemia includes the standard

treatment based on lifestyle and dietary modification strategies, and lipid-lowering medications, mainly statins [7]. Other existing treatments for controlling low-density lipoprotein cholesterol (LDLc) levels are ezetimibe (added to statins in primary hypercholesterolemia and homozygous familial hypercholesterolemia or as a monotherapy in cases of statin intolerance or if they are contraindicated), fibrates and bile-acid sequestrants. In addition, newly developed lipid-lowering drugs (monoclonal antibodies proprotein convertase subtilisin/kexin type 9 inhibitor) have been recently approved by the Food and Drug Administration and European Medicines Agency. Lipid-lowering treatments (LLT) are efficacious in reducing LDLc levels and reducing the burden of major CV events as well as CV mortality, even among populations without known CVD [8, 9]. Consequently, recent European Clinical Practice Guidelines have established LDLc targets accordingly to individual's CV risk [7]: LDLc levels <100 mg/dl for patients without CVD, but with diabetes mellitus (DM) or with high CV risk based on a Systematic COronary Risk Evaluation (SCORE) risk assessment >5 (Primary prevention hereinafter), and <70 mg/dl for patients with overt CVD, i.e., those who have suffered a previous CV event (Secondary prevention). However, according to the results published in a multinational study conducted between 2006 and 2007, despite the use of LLT, a significant proportion of patients did not attain target levels of LDLc [10], which means they still have a significant CV residual risk. Understanding the contemporary magnitude of this condition is of importance to plan additional interventions to reach LDLc targets and to reduce the burden of the related CV events and deaths. Thus, the objectives of the

present research were to review the published evidence addressing the prevalence of hypercholesterolemia, the usual clinical management of lipid profile, and the attained control of LDLc levels in patients with high CV risk from Spain.

METHODS

A systematic review of the literature was conducted in accordance with the accepted standards [11] and with a research question defined with reference to Patients, Interventions, Comparisons, Outcomes, and Study design (PICOS) (please see Table S1 in the supplementary material for details). The search was run on the second week of October 2014 (from 6th to 10th) in Medline and two Spanish electronic databases: *Biblioteca Virtual de la Salud (BVS)* and *Medes*. The search strategies included both controlled and free terms in both English and Spanish languages. The search strategies executed in each electronic public-access libraries are presented in Table S2 in the supplementary material.

The information gathered was manually cross-checked using the relevant references given in the publications included. To select the studies, titles and abstracts were first examined. After this, full text of selected manuscripts was reviewed. The selection criteria for publications were as follows:

Inclusion Criteria

Studies carried out in Spain and focused on lipid levels of patients belonging to one of the following groups: (a) heterozygous familial hypercholesterolemia (HeFH); (b) overt CVD including acute coronary syndrome (ACS), chronic coronary heart disease (CHD), ischemic stroke (IS) and peripheral arterial

disease (PAD); (c) DM; or (d) high CV risk. ACS was defined as acute myocardial infarction or unstable angina in the last 12 months. Chronic CHD refers to patients with ACS occurred longer than 12 months, or with stable angina or revascularization. Regarding CV risk, a SCORE risk assessment >5 (tables for countries with low CV risk) or equivalent was considered. Furthermore, according to the objectives described before, the studies had to include information on one of the following results: (a) prevalence of hypercholesterolemia; (b) rates of pharmacological treatment or (c) control of LDLc levels.

Exclusion Criteria

Manuscripts were discarded if any of the following conditions applied: (a) carried out outside Spain; (b) studies that did not include original patient data (i.e., reviews, editorials or letters); (c) studies that did not include human data; (d) studies with pediatric populations or (e) case reports.

Compliance with Ethics Guidelines

This article is based on previously conducted studies, and does not involve any new studies of human or animal subjects performed by any of the authors.

RESULTS

A total of 1362 publications were retrieved from PubMed, 537 from the BVS and 560 from Medes (512 were duplicates so an initial pool of 1947 original manuscripts were identified for title and abstract review). Following the selection process, the full text of 264 manuscripts was reviewed, of which a total of 120 original papers were finally considered (Fig. 1).

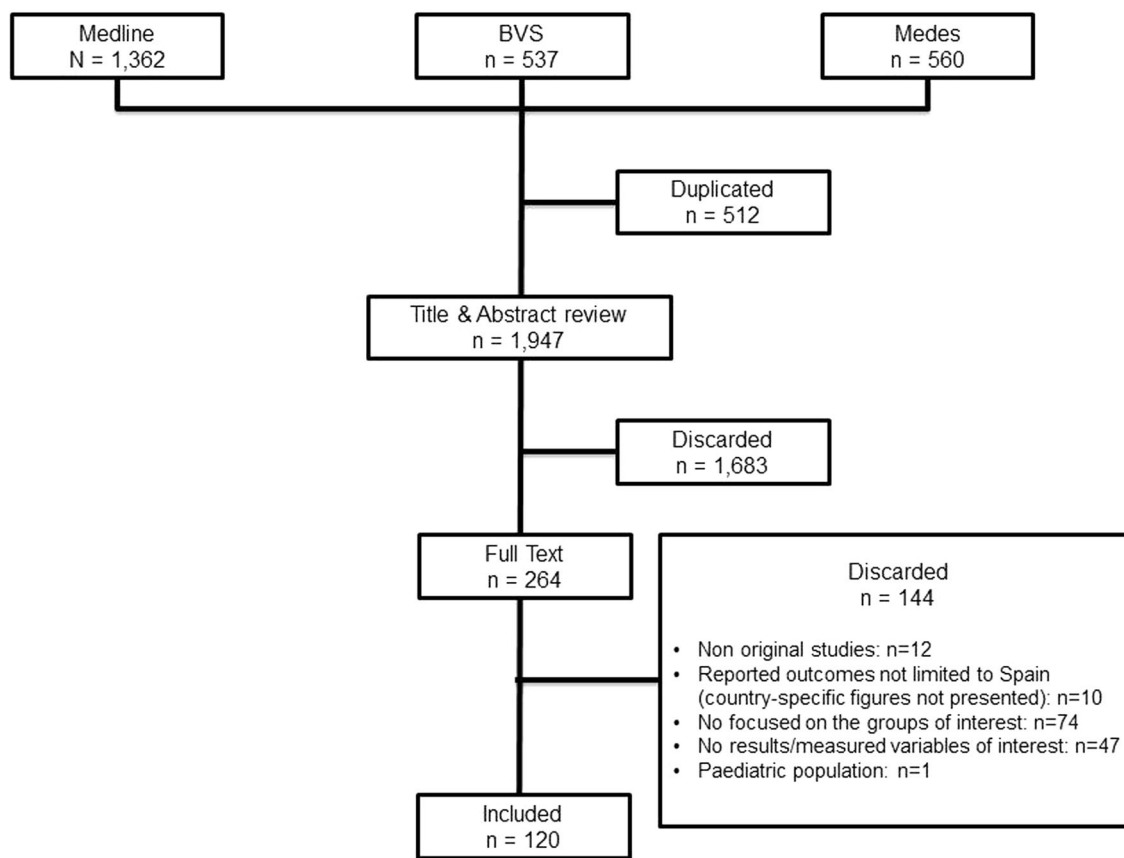


Fig. 1 Flow diagram showing the selection process of the included articles. *BVS* Biblioteca Virtual de la Salud

HeFH

In the study using data from the electronic database of the Spanish Familial Hypercholesterolemia Longitudinal Cohort Study (SAFEHEART) [12], 84% of the HeFH patients were receiving LLT at the time of inclusion (97% index cases and 78% HeFH relatives). 95% of treated patients received statins, 58% as monotherapy and 31% in combination, mostly with ezetimibe. Meanwhile, in another observational study [13] which included 241 patients with HeFH and 286 with combined familial hypercholesterolemia, 100% received LLT during a monitoring period of 1 year. Patients took an average of 1.5 lipid-lowering drugs (94% statins and 33% ezetimibe).

Despite the high proportion of patients undergoing a LLT in both studies [12, 13], between 72% and 96%, approximately, did not reach a target LDLc below 100 mg/dl and only 45% reduced LDLc levels by >50% (Table 1).

Hypercholesterolemia in Secondary Prevention

ACS

In studies carried out among patients with ACS the prevalence of hypercholesterolemia was highly variable ranging from 45% to 80% [15–31]. The proportion of ACS patients undergoing LLT ranged between 33% and 90%, but control levels were poor with only 14% of patients with LDLc levels <70 mg/dl and

Table 1 Lipid-lowering treatments and LDL cholesterol targets in Heterozygous familial hypercholesterolemia

Study	Study size	Treatment	Control
[12] ^a	N = 1852 (1262 FH and 590 relatives non FH)	LLT: 83.7% (97% FH and 78% relatives FH) Statins monotherapy: 58.3% Statin + ezetimibe: 31.3%	LDLc <100 mg/dl: 33 (3.4%) of FH on LLT
[13] ^b	N = 527 (241 HeFH and 286 combined FH)	LLT: 100% 1 year after study entry Statins: 94.3% Ezetimibe: 33.4%	LDLc <100 mg/dl: 28.5%
[14]	37 HeFH and 37 controls	Statins: 100% HeFH and 100% no-HeFH Ezetimibe: 23 (62.2%) HeFH; 4 (10.8%) no-HeFH	LDLc <100 mg/dl: 11% of HeFH

LLT lipid-lowering treatment, FH familial hypercholesterolemia, LDLc low-density lipoprotein cholesterol, HeFH heterozygous familial hypercholesterolemia

^a Only 13% received maximum daily statin doses, defined as simvastatin 80 mg, pravastatin 40 mg, lovastatin 80 mg, fluvastatin 80 mg, atorvastatin 80 mg, rosuvastatin 20–40 mg or maximum statin dose plus ezetimibe 10 mg/day

^b The strength of the lipid-lowering treatment in HeFH patients was considered low (lovastatin 10–40 mg, fluvastatin 80 mg, pravastatin 20–40 mg, simvastatin 10–20 mg, atorvastatin 10 mg) in 6.9% of cases, moderate (lovastatin 80 mg, simvastatin 40 mg, atorvastatin 20–40 mg, rosuvastatin 5–10 mg, simvastatin + ezetimibe 20 + 10 mg) in 40% and high (atorvastatin 80 mg, rosuvastatin 20 mg, simvastatin + ezetimibe 40 + 10 mg) in 53%

56% meeting the target of LDLc <100 mg/dl [26] (Table 2; Fig. 2).

CHD

The prevalence of hypercholesterolemia in patients with chronic CHD was more uniform than that found in patients with ACS, according to the information collected, ranging from 64% to 74% [32–38, 44–46]. More than 80% of patients were receiving LLT, statins accounting for 95% of them [37]. Again, despite the high proportion of treatment, only between 26% and 55% of patients had LDLc levels <100 mg/dl (Table 2).

IS

The prevalence of hypercholesterolemia in patients with IS ranged from 40% to 70%

[39–41, 47–60]. The proportion of treated patients was lower than that found in ACS or CHD patients. Upon discharge from hospital following an IS episode, between 38% and 76% of patients were receiving LLT [39, 40, 49]. In addition, one observational study with 203 patients admitted for medium- to long-term stays in one hospital between 2009 and 2010 found that only 20% of the total number of post-event patients received the dosage recommended by current guidelines [54].

With regards to attained cholesterol levels, 3 studies were found [39–41], reporting figures on LDLc control of <100 mg/dl between 25% and 33%. In two additional studies [54, 61] in which targets were set at Total Cholesterol (TC) <175 mg/dl, control rates were between 43% and 77% (Table 2; Fig. 2).

Table 2 Lipid-lowering treatments and LDL cholesterol targets in secondary prevention

Study	Study size	Treatment	Control
Acute coronary syndrome (ACS)			
[26]	<i>N</i> = 4334	Statins: 90.8%	LDLc <70 mg/dl: 14.3%
		Statins + ezetimibe: 24.7%	LDLc <100 mg/dl: 55.7%
[28]	<i>N</i> = 1381		LDLc <70 mg/dl: 11% first ACS; 14.1% recurrent ACS
			LDLc 70–99 mg/dl: 24.1% first ACS; 23.2% recurrent ACS
Coronary heart disease (CHD)			
[32]	<i>N</i> = 7600	Statins: 80.6%	LDLc <100 mg/dl: 26.1%
[33]	<i>N</i> = 1452 (5256 visits)	Statins: 92.1%	LDLc <70 mg/dl: 292 (5.7%)
			LDLc 70–100 mg/dl (non DM): 916 (18%)
			LDLc 70–100 mg/dl (DM): 640 (12.6%)
			LDLc >100 mg/dl: 3244 (63.7%)
[34]	<i>N</i> = 1108	Statins: 967 (87.3%); non DM: 678 (85.8%); DM 289 (90.9%)	LDLc <100 mg/dl: 454 (41%); non DM: 301 (38.1%); DM: 153 (48.1%)
[35]	<i>N</i> = 7823	Statins: 80.4%	LDLc >100 mg/dl: 73.8%
[36]	<i>N</i> = 1038	Statins: 82.9%; 82.8% >65 years; 83.1% ≤65 years	LDLc <100: 42.4% >65years; 46.5% ≤65 years
		Ezetimibe 17.4%; 16.2% >65 years; 18.7% ≤65 years	
[37]	<i>N</i> = 2292	Statins: 94.1%	LDLc >100 mg/dl: 44.9%
		Statins monotherapy: 74%	
		Ezetimibe: 18.3%	
[38]	<i>N</i> = 2024		LDLc <100 mg/dl- BMI 20-24.9: 35.2%; BMI 25–29.9: 30.5%; BMI ≥30: 27.9%.
Ischemic stroke			
[39]	<i>N</i> = 473	LLT: 319 (67.4%)	LDLc <100 mg/dl: 33%
		Statins: 311 (65.8%)	
[40]	<i>N</i> = 955	LLT: 75.5%	LDLc <100 mg/dl: 28.9% of treated patients
		Statins: 695 (72.8%)	
		Ezetimibe: 76 (8%)	
[41]	<i>N</i> = 407	LLT: 193 (47.4%);	LDLc <100 mg/dl: 101 (24.8%); LDLc >100 mg/dl: 139 (34.2%); unknown: 167 (41.0%)
		Statins: 180 (44.2%)	

Table 2 continued

Study	Study size	Treatment	Control
Peripheral arterial disease (PAD)			
[42]	N = 4087	LLT: 79.1%	LDLc <100 mg/dl: 30.4%
		Statins: 76.2%	
[43]	N = 105	LLT: 45.7%	

LLT lipid-lowering treatment, FH familial hypercholesterolemia, DM diabetes mellitus, LDLc low-density lipoprotein cholesterol, ACS acute coronary syndrome, CHD coronary heart disease, BMI body mass index

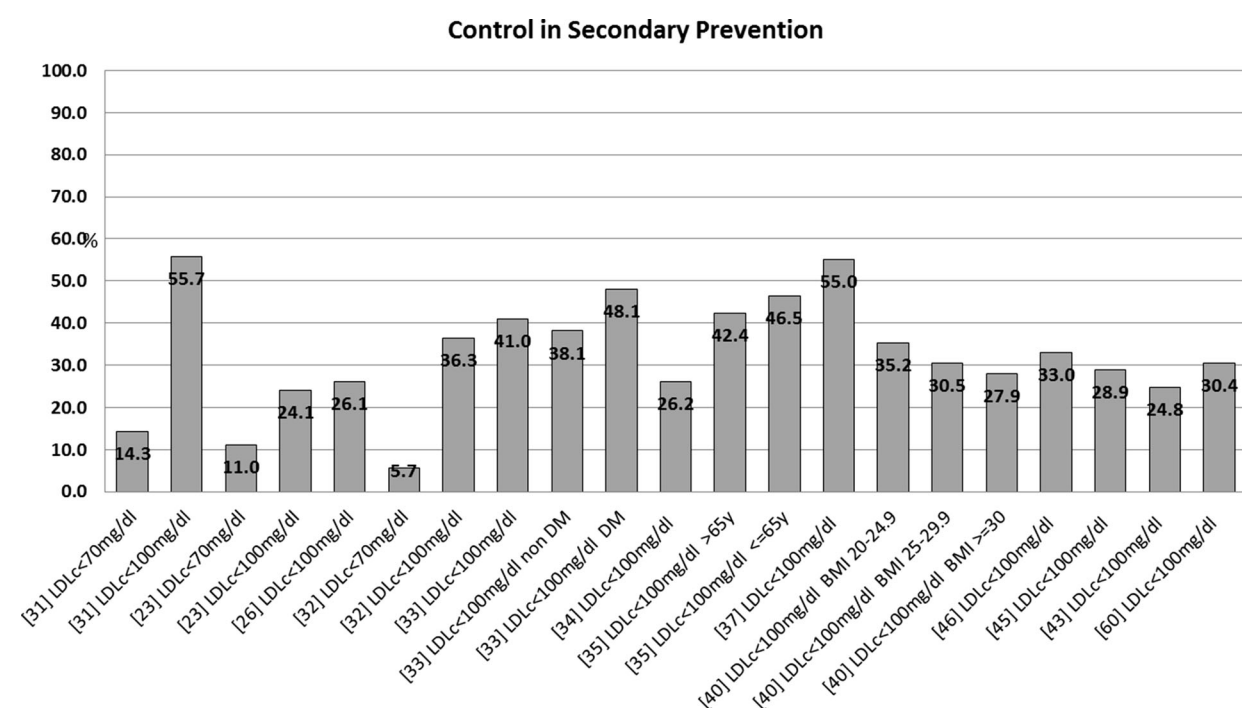


Fig. 2 Control in secondary prevention. LDLc low-density lipoprotein cholesterol, DM diabetes mellitus, BMI body mass index

PAD

A very limited number of studies were identified for this particular subgroup [42, 62–64]. In these studies, the clinical diagnosis of PAD was based on an ankle-brachial index <0.9. A prevalence of hypercholesterolemia between 60% and 80% was reported. With regard to treatment applied and results achieved, between 46% and 79% of patients received LLT. However, only 30% of

them achieved a target LDLc <100 mg/dl (Table 2; Fig. 2).

Hypercholesterolemia in Primary Prevention

DM

In accordance with a previous diagnosis or the use of LLT, data indicated that between 50%

Table 3 Lipid-lowering treatments and LDL cholesterol targets in primary prevention: diabetes mellitus

Study	Study size	Treatment	Control
[33]	<i>N</i> = 1452 (612 DM) patients; 5256 visits	Statins: 92.1%	LDLc <70 mg/dl: 292 (5.7%) LDLc 70–100 mg/dl non DM: 916 (18%) LDLc 70–100 mg/dl DM: 640 (12.6%) LDLc >100 mg/dl: 3244 (63.7%)
[71]	<i>N</i> = 3703 (1445 DM)	Statins: 100% (during at least 3 months)	LDLc >100 mg/dl: 59.2% of DM patients LDLc >100 mg/dl: 44.5% of non DM patients
[72]	<i>N</i> = 1828 (320 DM). 2 visits	At baseline, 55.4% received ≥ 1 drug: Statins: 830 (45.4%) Ezetimibe: 126 (6.9%) Statin + ezetimibe: 8 (0.4%) At follow up: Statins: 1232 (67.4%) Ezetimibe: 332 (18.2%) Statin + ezetimibe: 61 (3.3%)	LDLc <100 mg/dl in DM or CVD and LDLc <115 in high risk patients: Baseline: All 30.5%; CVD 40.4%; DM 35.8% Follow up: All 44.7%; CVD 65.3%; DM 50.4% LDLc <70: CVD 17.9%; DM 16.5%
[26]	<i>N</i> = 4402 (1748 DM)	Statins: 76.7%: Statins + ezetimibe: 18.8%	LDLc >100 mg/dl: 56.9% LDLc >70 mg/dl: 84.7%
[73]	<i>N</i> = 3710 (39% DM)	Statins: 100% Ezetimibe: 17.4%	LDLc >100 mg/dl in high risk or >120 mg/dl in low risk: 63.1% CVD (<i>n</i> = 846); LDLc >100 mg/dl: 64.7%
[3]	<i>N</i> = 11,544 Rate of awareness: 53.6% (53.5% males; 53.7% women)	LLT treatment: 44.1% of patients aware of elevated LDLc 23.7% of all patients with elevated LDLc	LDLc <115 mg/dl (<100 mg/dl DM and CVD): 40.2% of treated patients (9.5% of total sample with elevated LDLc) LDLc <115 mg/dl (<70 DM and CVD): 31.3% (7.3%) % of DM or CVD patients with LDLc <100 mg/dl: 40.5% or 43.6%, respect % of DM or CVD patients with LDLc <70 mg/dl: 7.0% or 5.2% respectively

Table 3 continued

Study	Study size	Treatment	Control
[67]	<i>N</i> = 2412	Before clinical session: Statins: 59.5% Ezetimibe: 0.9% At clinical session: Statins: 65.5% Ezetimibe: 4.2%	Before clinical session: LDLc <100 mg/dl: 22.7% At clinical session: LDLc <100 mg/dl: 28.6%
[68]	<i>N</i> = 1177	Statins 48%	LDLc <100 mg/dl: 25.6%
[74]	<i>N</i> = 4776 (12.5% DM patients)		In <i>n</i> = 409 DM patients LDL ≤100 mg/dl: 45.3% LDL ≤70 mg/dl: 11.8%
[66]	<i>N</i> = 771 DM	Statin: 722 (93.6%) Ezetimibe: 151 (19.6%)	LDLc >70 mg/dl: 501 (73.4%) LDLc >100 mg/dl: 243 (31.5%)
[75]	<i>N</i> = 2704 (1067 DM)	LLT: 1634 (60.4%)	LDLc <100 mg/dl in DM or CVD; <130 mg/dl others: 930 (34.4%) LDLc <100 mg/dl: 34.7% DM; 34.2% CVD
[76]	<i>N</i> = 1748 DM and CHD <i>N</i> = 2654 DM without CHD	LLT: 76.7% Statin and ezetimibe: 18.8%	LDLc >100 mg/dl: 56.9% LDLc >70 mg/dl: 84.7%
[69]	<i>N</i> = 320 DM	Statins: 60%	LDLc ≤100 mg/dl: males 41.7%; females 39.1%

LLT lipid-lowering treatment, FH familial hypercholesterolemia, DM diabetes mellitus, CVD cardiovascular disease, LDLc low-density lipoprotein cholesterol, CHD coronary heart disease

and 84% of DM patients would present with hypercholesterolemia [44, 57, 65–68].

Regarding the rates of LLT usage (Table 3; Fig. 3), between 45% and 90% of DM patients were using a LLT [26, 69, 70]. With respect to the lipid control achieved in this population, rates ranged from 40% to 50% in DM patients with no CVD history (LDLc goal <100 mg/dl), to only 15% in DM patients with a history of CVD (LDLc goal <70 mg/dl).

Patients with High CV Risk

Within this group of special interest in the prevention of CVD, between 30% and 60% had a specific diagnosis of hypercholesterolemia, based on a TC >200 mg/dl or previous treatment [1, 3, 76–78].

LLT was used in 50% to 60% of these patients [1], while control rates ranged from 35% to 65%, considering a LDLc target of <100 mg/dl [1, 72, 73]. Table 4 and Fig. 4 summarize these data.

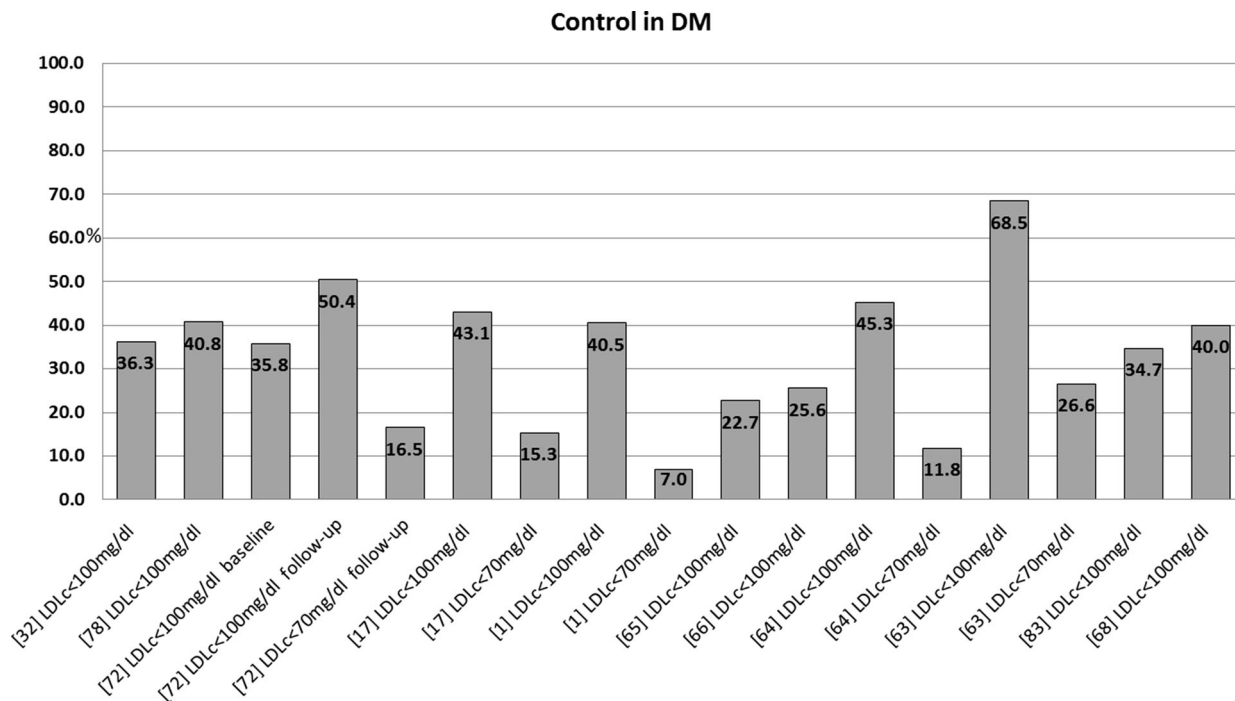


Fig. 3 Control in primary prevention: diabetes mellitus. *LDLc* low-density lipoprotein cholesterol, *DM* diabetes mellitus

DISCUSSION

It has been shown that hypercholesterolemia is significantly present among patients with an increased vascular risk and those who have already suffered a CV event: 50–84% of patients with DM [44, 57, 67, 68, 74], 30–50% of high risk patient [1, 3, 76–78], and between 35% and above 80% in those with overt CVD, depending on the type of event [15–41, 44–60]. The association of this condition with the risk of CV events [9, 83] makes it all the more necessary to endorse the interventions aimed at managing the modifiable risk factors (diet and exercise), to prescribe a LLT accordingly to individual’s CV risk [7], and also to plan an adequate monitoring of the pharmacological therapies implemented to maximize their benefit. There are many examples of this relationship in our country: hypercholesterolemia doubled the risk of an ischemic disease [84, 85], and would be the

cause of 22% of all coronary events. The risk increased significantly among patients who did not have their lipid values controlled, while among those diagnosed with controlled hypercholesterolemia and, who are undergoing a lipid-lowering treatment, the increased risk of ischemic heart disease was not statistically significant [84].

Due, in large part, to the information above, the use of lipid-lowering drugs in Spain has increased from 18.9 defined daily doses (DDD) per 1000 inhabitants per day (DDD/1000 inhabitants/day) in the year 2000 to 102.6 DDD/1000 inhabitants/day in the year 2012, an increase of 442% [86]. Statins are the most commonly used drugs (91.7 DDD/1000 inhabitants/day in 2012) representing 89.3% of all LLT, but also fibrates, bile-acid sequestrants, ezetimibe, and omega 3 fatty acids contributed during 2012 to LLT use [86]. The increase in the use of LLT can be justified by

Table 4 Lipid-lowering treatments and LDL cholesterol targets in primary prevention: high cardiovascular risk patients

High or very high cardiovascular risk			
Study	Study size	Treatment	Control
[73]	<i>N</i> = 3710 (39% DM)	Statins: 100% Ezetimibe: 17.4%	High risk patients (CVD, DM or SCORE >5%; <i>n</i> = 2574), LDLc >100 mg/dl: 60.7% SCORE >5% without CVD nor DM (<i>n</i> = 407), LDLc >100 mg/dl: 83.2%
[72]	<i>N</i> = 1828 2 visits	At baseline, 1013 (55.4%) received at least 1 drug: Statins: 830 (45.4%) Ezetimibe: 126 (6.9%) Statin + ezetimibe: 8 (0.4%) At follow up: Statins: 1232 (67.4%) Ezetimibe: 332 (18.2%) Statin + ezetimibe: 61 (3.3%)	LDLc levels <100 mg/dl in DM or CVD and LDLc <115 in high risk patients: Baseline: All 30.5%; CVD 40.4%; DM 35.8% Follow up: All 44.7%; CVD 65.3%; DM 50.4% LDLc <70 mg/dl: CVD 17.9%; DM 16.5%
[79]	RCT. 2 arms: Experimental-EG (<i>n</i> = 33) Supportive system to decision making Control-CG (<i>n</i> = 44)	Use of High intensity statins: EG: 74.6%/CG: 25.4% Statins + ezetimibe or niacin/laropiprant: GI: 32.4%/GC: 2.3%	After 12 weeks: LDLc <70: 55% GI; 12.5% GC LDLc <100: 75% GI; 45.8% GC
[80]	<i>N</i> = 37	Statins: 100% Ezetimibe: 10.8%	LDLc <130 md/dl: 43%
[81]	<i>N</i> = 222.	LLT: 85%	LDLc <100 mg/dl: 51.3% of high risk patients LDLc <70 mg/dl: 7.5% of high risk patients
[77]	<i>N</i> = 3716 (15.5% calibrated-SCORE >5)	Statins: 25.3%	Patients with SCORE between 5 and 10: LDLc <100 mg/dl: 10.61% SCORE >10 LDLc <70 mg/dl: 1.79%
[1]	<i>N</i> = 27,903 (<i>n</i> = 9335 with dyslipidemia) High-very high risk: 11.3% males and 2.3% female	LLT REGICOR >10: 50% males, 59% females	LDLc <100 mg/dl in DM or high-very high risk: <3% LDLc <100 mg/dl in DM or <130 mg/dl in moderate to very high risk or <160 mg/dl in low risk): 46% males, 52% females

Table 4 continued

High or very high cardiovascular risk			
Study	Study size	Treatment	Control
[75]	<i>N</i> = 2704	LLT: 1634 (60.4%)	LDLc <100 mg/dl in DM or CVD; <130 mg/dl others: 930 (34.4%) LDLc <100 mg/dl: 34.7% DM; 34.2% CVD
[82]	<i>N</i> = 217	Ezetimibe (monotherapy): 42.4% Ezetimibe + statins: 43.3%	LDLc <100 mg/dl or 70 mg/dl: 43.8% of high or very high risk patients
[3]	<i>N</i> = 11,544 Rate of awareness: 53.6% (53.5% males; 53.7% women)	LLT treatment: 44.1% of patients aware of elevated LDLc 23.7% of all patients with elevated LDLc	LDLc <115 mg/dl (<100 DM and CVD): 40.2% of treated patients (9.5% of total sample with elevated LDLc) LDLc <115 mg/dl (<70 DM and CVD): 31.3% (7.3%) % of DM or CVD patients with LDLc < 100 mg/dl: 40.5% or 43.6%, respect. % of DM or CVD patients with LDLc <70 mg/dl: 7.0% or 5.2% respectively

LLT lipid-lowering treatment, *FH* familial hypercholesterolemia, *DM* diabetes mellitus, *CVD* cardiovascular disease, *LDLc* low-density lipoprotein cholesterol, *EG* experimental group, *CG* control group

their ability to reduce the risk of CV events, and the associated burden of disease.

Although treatments available have led to an improvement in the clinical situation and prognosis of these cases, it is clear that there is a lot of effort still to be made until LDLc targets defined by current European guidelines [7] can be reached by most of patients. In all of the groups analyzed, an important number could still be found with total cholesterol and LDLc levels above the acceptable threshold. For example, among diabetics, only between 15% (in case of those with previous CVD) and 40–50% (in those without CVD) attained recommended levels of lipids in the blood [26, 69–71], and the situation is not better in secondary prevention or among patients with HeFH. This picture, which is similar to other western countries [87–89], highlights the need

to continue maximizing the control of lipids in the blood and to minimize therapeutic inertia. Regarding this, in one recent study with CHD patients, therapeutic inertia was estimated to be as high as 73% [33].

It should be noted, as the main limitation of the present work, how difficult it is to make a more exact approximation of the estimations presented in this manuscript. This is due in great part to the sheer heterogeneity of the criteria used in the various studies in defining hypercholesterolemia, CV risk, ACS or CHD. In addition, one other relevant aspect to consider is the nature of the studies included. They are mainly cross-sectional investigations and with a wide range of different sampling procedures and sample sizes. Even more, many studies are based on the analysis of individuals coming from the same national databases or registries.

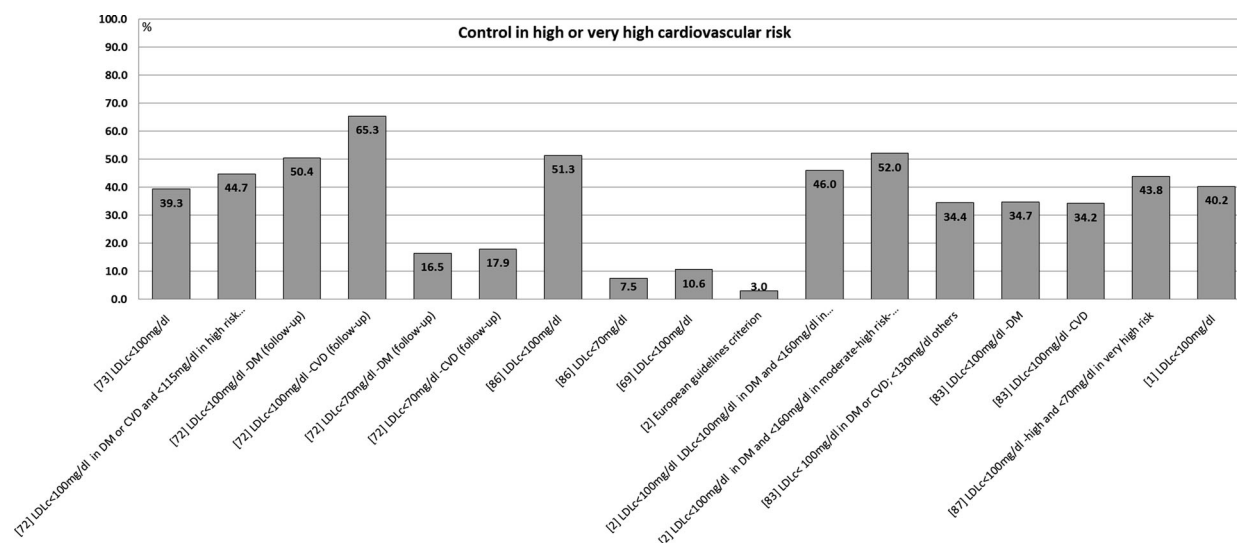


Fig. 4 Control in primary prevention: high or very high risk patients. *LDLc* low-density lipoprotein cholesterol, *DM* diabetes mellitus, *CVD* cardiovascular disease

Considering these important constraints, a more analytic approach as meta-analysis might be applied at least with those studies following comparable clinical criteria to have a more accurate estimation of disease prevalence and control in each of the groups of interest, and to highlight the significance of the heterogeneity found between studies. Despite this, an important strength of the present manuscript is that all the relevant studies carried out in Spain and published in peer review journals have been systematically identify and reviewed to facilitate a global but comprehensive report of this condition in our country.

CONCLUSIONS

There is an elevated prevalence of hypercholesterolemia in Spain among those selected groups with a high CV risk. Although LLT is present in an elevated proportion, controls rates of lipid levels need to be improved both in primary and secondary prevention.

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Compliance with ethics guidelines. This article is based on previously conducted studies, and does not involve any new studies of human or animal subjects performed by any of the authors.

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