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Abstract: Background: Familial hypercholesterolemia (FH) is a high cardiovascular risk condition. Less than 20% of patients achieve the LDL targets. Although PCSK9 inhibitors improve control and reduce cardiovascular events, official recommendations for their use are restrictive.
Aim: Assess the number of FH patients suitable for PCSK9 inhibition according to European guidelines.
Methods: A total of 2685 FH patients, with a minimum follow-up of 6 months, included in the Dyslipidemia Registry of the Spanish Arteriosclerosis Society were sorted according to the intensity of their lipid-lowering therapy (LLT) and LDL cholesterol levels achieved. The number of patients who met the recommendations for PCSK9 inhibition treatment according to European Atherosclerosis Society (ESC/EAS), Spanish Arteriosclerosis Society and the European Medicines Agency was calculated.
Results: In total, 1573 patients were on high-intensity LLT; 607 were on moderate-intensity statins; 82 were on low-intensity LLT, and 423 were neither on statins nor ezetimibe in the last visit registered. The mean LDL reduction among those on high-intensity LLT was 54%. Ninety-one percent of patients on high-intensity LLT had an LDL below 5.2 mmol/L, 53% below 3.4 mmol/L, and 23% below 2.6 mmol/L. Only 12% of FH patients with cardiovascular disease achieved 1.8 mmol/L. Despite this only 17% of patients qualified for PCSK9 inhibition according to ESC/EAS guidelines.
Conclusions: For patients with a condition that exposes them to high cardiovascular risk and who have extreme difficulties in achieving LDL targets, wider access to PCSK9 inhibitor therapy is warranted.

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Highlights

- Few FH patients achieve LDL targets despite high-intensity lipid-lowering therapy.
- Despite statin therapy, they are high cardiovascular risk patients.
- PCSK9 inhibitors increase significantly the number of patients achieving LDL targets.
- PCSK9 inhibitors by lowering LDL reduce cardiovascular risk.
- Only 17% FH are eligible for PCSK9 inhibitors according European guidelines.
- Wider access of FH patients to PCSK9 inhibitor therapy is warranted.

HOW MANY FAMILIAL HYPERCHOLESTEROLEMIA PATIENTS ARE ELIGIBLE FOR PCSK9 INHIBITION?

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ABSTRACT

Background: Familial hypercholesterolemia (FH) is a high cardiovascular risk condition. Less than 20% of patients achieve the LDL targets. Although PCSK9 inhibitors improve control and reduce cardiovascular events, official recommendations for their use are restrictive.

Aim: Assess the number of FH patients suitable for PCSK9 inhibition according to European guidelines.

Methods: A total of 2685 FH patients, with a minimum follow-up of 6 months, included in the Dyslipidemia Registry of the Spanish Arteriosclerosis Society were sorted according to the intensity of their lipid-lowering therapy (LLT) and LDL cholesterol levels achieved. The number of patients who met the recommendations for PCSK9 inhibition treatment according to European Atherosclerosis Society (ESC/EAS), Spanish Arteriosclerosis Society and the European Medicines Agency was calculated.

Results: In total, 1573 patients were on high-intensity LLT; 607 were on moderate-intensity statins; 82 were on low-intensity LLT, and 423 were neither on statins nor ezetimibe in the last visit registered. The mean LDL reduction among those on high-intensity LLT was 54%. Ninety-one percent of patients on high-intensity LLT had an LDL below 5.2 mmol/L, 53% below 3.4 mmol/L, and 23% below 2.6 mmol/L. Only 12% of FH patients with cardiovascular disease achieved 1.8 mmol/L. Despite this only 17% of patients qualified for PCSK9 inhibition according to ESC/EAS guidelines.

Conclusions: For patients with a condition that exposes them to high cardiovascular risk and who have extreme difficulties in achieving LDL targets, wider access to PCSK9 inhibitor therapy is warranted.

1. Introduction

Familial hypercholesterolemia (FH) is the primary genetic cause of premature coronary disease. Its prevalence is calculated to be approximately 1 in 250 individuals [1],[2], increasing up to 8% among patients suffering from premature myocardial infarction according to EUROASPIRE IV data [3]. FH is characterized by high LDL cholesterol levels from birth due to low or defective LDL receptor (LDLR) production as a result of LDLR-related gene mutations. Lifelong exposure to high cholesterol levels leads to higher arteriosclerosis risk and accelerated cardiovascular disease (CVD) [4],[5].

Current lipid-lowering therapies (LLT), mainly statins with or without ezetimibe, can reduce LDL cholesterol by 50 to 60%, attenuating the clinical impact of FH. Scientific societies recommend either achieving ambitious LDL cholesterol targets below 2.6 mmol/L or reducing LDL cholesterol levels by at least 50%[6–8]. Unfortunately, FH is underdiagnosed and undertreated; it is estimated that less than 10% of individuals with this condition are detected and, among those who are detected, less than 20% achieve LDL targets [9]; therefore, this represents a population at remarkably high risk for CVD. Recent data from Norwegian FH registries show that all FH patients have atherosclerotic disease at death [10]. Other studies have shown that, even in the statin era, the prevalence of CVD among FH patients is approximately 3 to 8 times higher than in the non-FH population [11],[12].

The low rate at which therapies result in patients achieving their objectives [13–15] can be explained, in part, by lack of adherence to current therapies, statin intolerance, improper diagnosis and under dosing[16],[17],[18], among others; however, a remarkable number of patients do not achieve recommended targets because their basal LDL cholesterol concentrations are too high. Therefore, there is a clinical need for more efficient therapies in this group of patients. PCSK9 inhibitors (PCSK9inh) induce an incremental LDL cholesterol reduction of approximately 60% on top of the

reduction from other LLTs [19]. Despite this evidence-based lipid-lowering effect[20] [21], the high price of these therapies makes their broad application difficult. Several official bodies and scientific societies have issued a variety of recommendations for PCSK9inh use in FH subjects. The European Medicines Agency (EMA)[22] has approved using PCSK9 inhibitors in FH patients with an LDL cholesterol above 2.6 mmol/L after optimising LLT. On the other hand, a task force from the European Society of Cardiology (ESC) and European Atherosclerosis Society (EAS)[23] has recommended their use in FH patients without cardiovascular disease only if LDL cholesterol concentrations under maximal LLT are higher than 4.5 or 5.2 mmol/L, depending on the presence of additional risk factors. The Spanish Arteriosclerosis Society (SEA)[24] defines the threshold for PCSK9inh use in FH primary prevention at 3.4 or 4.1 mmol/L, depending on additional risk factors.

Because the differences in these criteria can have important clinical implications and affect the vital prognosis of patients, we have analysed the number of FH patients eligible for PCSK9inh according to different guidelines in the Dyslipidemia Registry of the Spanish Arteriosclerosis Society (RDSEA).

2. Methods

2.1 Study design

All 2,685 patients with the clinical diagnosis of heterozygous (He) FH and a minimum follow-up of 6 months included in the RDSEA registry by December 10, 2016, were selected. They were sorted according to the intensity of their lipid-lowering therapy (LLT) and LDL cholesterol levels achieved in the last study visit after stable LLT. The number of patients who met the recommendations for PCSK9 inhibition treatment according to SEC/EAS, SEA and the European Medicines Agency was calculated.

Patients were classified as possible (3-5 points), probable (6-8 points) and definite (>8 points) HeFH according to the Dutch Lipid Clinic Network (DLCN) criteria at

diagnosis. The RDSEA is an active online registry, where 50 certified lipid units distributed throughout all regions of Spain report cases of various types of primary hyperlipidemias. The registry has been approved by a central ethical committee to include anonymous clinical data. The criteria for inclusion of data were previously standardised with 5 different training sessions that occurred before entering cases. The database includes personal and familial anamnesis, anthropometry, physical examination, biochemical data, clinical diagnosis and the presence of cardiovascular disease according to the international classification of diseases.

Genetic data regarding mutations in *LDLR, APOB* or *PCSK9* (positive, negative or unknown) are also recorded. Regarding pharmacological treatment, data on the age at which statin treatment began and lipid values in patients who have been on stable lipid-lowering treatment regimens for at least 6 months are also collected.

With respect to treatment, patients were classified into three categories: low intensity treatment (ezetimibe 5-10 mg, simvastatin 5-10 mg, lovastatin 20 mg, pravastatin 10-20 mg, fluvastatin 20-40 mg or pitavastatin 1 mg), moderate intensity statin treatment (atorvastatin 10-20 mg, rosuvastatin 5-10 mg, simvastatin 20-40 mg, fluvastatin 40 mg, lovastatin 40 mg, pravastatin 40 mg or pitavastatin 2-4 mg) and high intensity treatment (rosuvastatin 20-40 mg, atorvastatin 40-80 mg, or any daily statin doses plus ezetimibe).

PCSK9inh treatment suitability for HeFH patients was determined according to ESC/EAS, SEA and EMA recommendations. ESC/EAS's criteria include HeFH plus diabetes without target organ damage, lipoprotein(a) > 50 mg/dL (conversion to nmol/L x 2.4), marked hypertension, premature familial ASCVD and LDL cholesterol >4.5 mmol/L; HeFH plus CHD or diabetes with target organ damage, or a major risk factor such as smoking, or hypertension and LDL cholesterol >3.6 mmol/L; and HeFH without any of the previous conditions and LDL cholesterol >5.1 mmol/L, always after using the maximal tolerated statin therapy plus ezetimibe. SEA's criteria include HeFH with the absence of factors indicating high risk for CVD (i.e., neither the presence of CVD nor

risk factors including diabetes, lipoprotein(a) > 50 mmol/L, hypertension or current smoking) and LDL cholesterol >4.1 mmol/L, HeFH without active CVD, conditions that put the patient at risk for CVD, and LDL cholesterol > 3.4 mmol/L; HeFH with CVD and LDL cholesterol >2.6 mmol/L, always after maximal tolerated statin therapy plus ezetimibe. EMA's criteria include HeFH with LDL cholesterol > 2.6 mmol/L after maximal tolerated statin therapy.

2.2 Statistical analyses

All statistical analyses were performed using SPSS software v.20 (SPSS Inc. Chicago, IL). Data are presented as the mean ± standard deviation (SD) for continuous variables, the median and interquartile range for variables with a skewed distribution, and a frequency or percentage for categorical variables. Differences in the mean values of variables that followed a normal distribution were assessed using t-tests and ANOVA tests, and the Mann-Whitney U-test or Kruskal-Wallis H test was used for variables with a skewed distribution. Categorical variables were compared using the chi-square test.

3. Results

A total of 2685 HeFH patients were included. According to the DLCN, 671 had possible HeFH (3-5 points), 373 had probable HeFH (6-8 points) and 1641 had definite HeFH (> 8 points). Median (25^{th} percentile – 75^{th} percentile) basal LDL cholesterol levels according to diagnosis class were 5.4 (5.0-5.9), 6.6 (5.6-7.2) and 6.9(5.6-8.3) mmol/L respectively. A genetic study was performed in 85% of definite HeFH patients, and a functional mutation in LDLR-related genes was detected in 1310 patients (i.e., 93% of tested patients). Overall, 48.7% of the total sample had an identified mutation. In Table 1, we show anthropometric, clinical and biochemical parameters according to

treatment intensity. Fifty-eight percent of patients were on high-intensity LLT (i.e., high-dose, high-potency statins or statin/ezetimibe combination therapy). This group achieved the highest LDL cholesterol reduction, obtaining a mean LDL cholesterol value below 3.4 mmol/L. A mean of more than a 50% LDL cholesterol reduction was achieved in the high-intensity therapy group (Fig. 1). Despite this, the mean LDL cholesterol was 30% higher than recommended, and more than 75% of patients maintained LDL cholesterol levels above 2.6 mmol/L. Only 22% of those on high-intensity therapy achieved LDL cholesterol levels below the 2.6 mmol/L target (Fig. 2). In Table 2, we show the number of patients qualifying for PCSK9inh according to ESC/EAS and SEA recommendations and EMA approval criteria. According to ESC/EAS cut-off points, only 17% of our patients would be eligible for therapy. On the other hand, the greatest number of patients qualifying for therapy are those on secondary prevention or with major additional risk factors. Only 8.2% of FH patients without additional risk factors would be considered for PCSK9inh therapy despite 78% not reaching their LDL targets. According to SEA recommendations, the number of candidates increases to 34%, including a remarkable 29% of patients without cardiovascular event.

4. Discussion

In this work, we show the number of HeFH patients achieving different LDL thresholds while on high-intensity lipid-lowering therapy using real data obtained from RDSEA. An unacceptable 12.5% of FH patients with a cardiovascular event achieve an LDL cholesterol below 1.8 mmol/L and 22.7 % without event reach the 2.6 target (Figure 2). While the number of patients achieving LDL objectives remains very low, approximately 90% of treated HeFH patients have LDL cholesterol levels below 5.2 mmol/L, which is the recommended threshold for PCSK9inh therapy according to EAS/ESC for patients with HeFH and without comorbidities. Therefore, the great

majority of patients, despite being far from objectives, would not be suitable for PCSK9 inhibition treatment

Even in the statin era, FH can be considered a high CVD risk condition[7]. Currently, the prevalence of cardiovascular diseases is several folds higher in FH patients than non-FH subjects[5,11,12]. One possible explanation for the higher risk in these patients could be that they have higher cholesterol levels from birth and, therefore, an increased body cholesterol burden leading to accelerated atherosclerosis. It is accepted that major cardiovascular events occur approximately 10 years earlier in FH males and 20 in FH females. All these considerations define a clear unmet clinical need. Statin therapy was a great achievement in FH management; however, current lipid lowering therapies neither control LDL levels according to recommendations nor normalise cardiovascular risk in FH patients. The introduction of PCSK9inh in this field has been received with hope by both physicians and patients. PCSK9inh induces an incremental LDL cholesterol decrease of approximately 60% in HeFH patients when added on to optimised conventional LLT without significant side effects, leading to an unprecedented 80% of patients achieving recommended LDL targets [25,26]. Moreover, its impact on atherosclerosis has been recently documented. The Glagov data showed that achieving even lower LDL concentrations leads to atheroma regression[20]. The achievement of primary and secondary objectives in the Fourier study confirms the impact of LDL cholesterol-lowering therapies in general and PCSK9inh in particular on CVD events[27]. Although no specific data on FH patients are currently available, the scientific evidence linking LDL reduction and cardiovascular event reduction is sufficiently robust.

Current PCSK9inh recommendations for FH patients is rather limited, resulting from a compromise between benefits and cost. Several studies have addressed this question; while some of them suggest an acceptable cost-benefit ratio [28], others consider it unacceptable[29]. In the cost-benefit equation, there are three main

elements: treatment price, cardiovascular risk reduction based on a decrease in LDL, and absolute population risk. Considering PCSK9inh's LDL-lowering capacity, the number of patients necessary to treat (NNT) to prevent one event is lower than 50 in five years in groups with a global risk above 30% and LDL above 3.4 mmol/L, which includes FH patients[30]. Global European recommendations should be made with caution due to different cardiovascular risks among countries and drug price variation ranging from less than 5000 to more than 8000 euros per year (still far from 14000 dollars in the USA); therefore, treatment criteria guidelines should be customised by country.

Our results have several limitations. Our registry includes data from multiple centres with clinical and analytical methodologies that can vary among sites; however, clinical data were extensively homogenised before inclusion in the registry. Genetic analysis is not available at some centres; however, the recommendations for PCSK9inh use is not based on genetic data. In their recommendations, ESC/EAS and SEA use acute or recurrent CVD to classify individuals, but this information was not available in our data. Lastly, the reason why some subjects with very high risk are not on high-intensity lipid-lowering treatment is not explored in our registry; these subjects are most likely statin intolerant patients who would fulfil criteria for PCSK9 inhibitors anyway.

Evidence suggests PCSK9 inhibitors are an excellent treatment option for FH patients and, prescribed in a personalised way, will increase clinical benefits. Our data, collected in real-life clinical situations, will help in making clinical decisions and refining official guidelines for PCSK9 inhibitor use.

Conflict of interest

Luis Masana: Advisory and lecture fees from Amgen, Sanofi, MSD; Nuria Plana: Lecture fees from Amgen, Sanofi, MSD; Sofia Pérez-Calahorra: None; Daiana Ibarretxe : Lecture fees from Sanofi, Esteve y MSD; Itziar Lamiqui-Moneo: None; Juan-Carlos Pedro-Botet : Advisory and/or Lecture fees from Astra-Zeneca, Esteve, Ferre, Mylan, Sanofi, MSD; Manuel Suarez Tembra: None; Pedro Valdivielso; Advisory and lecture fees from: Amgen, Sanofi, MSD. Grants from: Ferrer; Emilio Ortega : Advisory fees from: Sanofi, MSD. Lecture fees from Amgen; Fernando Civeira : Advisory and lecture fees from Amgen, Sanofi Aventis, Pfizer, MSD, and Ferrer.

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Author contribution:

Study conception and design: LM, FC,

Acquisition of data: NP, S P-C; DI; I L-M; J P-B; M S-T; P V; EO.

Analysis and interpretation of data: LM; FC; S P-C.

Drafting of manuscript: LM; FC

Critical revision: NP, S P-C; DI; I L-M; J P-B; M S-T; P V; EO

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The investigators contributing to RDSEA are listed in the appendix.

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Figure caption:

Figure 1. Percent LDL cholesterol reduction in subjects with and without CVD according to LLT groups.

LLT denotes lipid lowering treatment; CVD, cardiovascular disease.

Figure 2. Percent of HeFH patients achieving different LDL cholesterol thresholds.

LLT denotes lipid lowering therapy; CVD, cardiovascular disease; HeFH, heterozygous familial hypercholesterolemia.

STATEMENT OF ORIGINALITY

I declare that this article contains original data and has not been submitted for publication in any other journal.

Sincerely

Luis Masana

To Atherosclerosis Chief Editor

Dear Sir,

Please find enclose our article entitled: "HOW MANY FAMILIAL HYPERCHOLESTEROLEMIA PATIENTS ARE ELIGIBLE FOR PCSK9 INHIBITION?" that we would like to be considered for publication in Atherosclerosis.

The PCSK9 inhibitors have changed the paradigm of lipid derangements treatment. Among these alterations, Familial Hypercholesterolemia is one of the more important. Despite high-intensity lipid-lowering therapy only a minor part of patients, achieve recommended targets. The EAS has issued a guideline for use of PCSK9 inhibitors in FH patients. We report the magnitude of patients eligible for therapy according to EAS rules.

We believe the information we provide, based on data from 2685 FH patients, can be a useful tool to evaluate the impact of these therapies according to current and future guidelines.

This work has not been submitted for publication in any other journal.

All authors have seen and approved the final version of the manuscript.

Conflict of interest disclosures is enclosed in the main manuscript.

Proposed reviewers:

Editor: R Santos: Reviewers: Michel Farnier; Maciej Banach; Kees Hovingh; Alberico Catapano.

(Contact details are enclosed in the submission system).

We are looking forward to hearing from you

Sincerely

Luis Masana

***Conflict of interest form**

Conflict of interest

Luis Masana: Advisory and lecture fees from Amgen, Sanofi, MSD; Nuria Plana: Lecture fees from Amgen, Sanofi, MSD; Sofia Pérez-Calahorra: None; Daiana Ibarretxe : Lecture fees from Sanofi, Esteve y MSD; Itziar Lamiqui-Moneo: None; Juan-Carlos Pedro-Botet : Advisory and/or Lecture fees from Astra-Zeneca, Esteve, Ferre, Mylan, Sanofi, MSD; Manuel Suarez Tembra: None; Pedro Valdivielso; Advisory and lecture fees from: Amgen, Sanofi, MSD. Grants from: Ferrer; Emilio Ortega : Advisory fees from: Sanofi, MSD. Lecture fees from Amgen; Fernando Civeira : Advisory and lecture fees from Amgen, Sanofi Aventis, Pfizer, MSD, and Ferrer.

Figure 1

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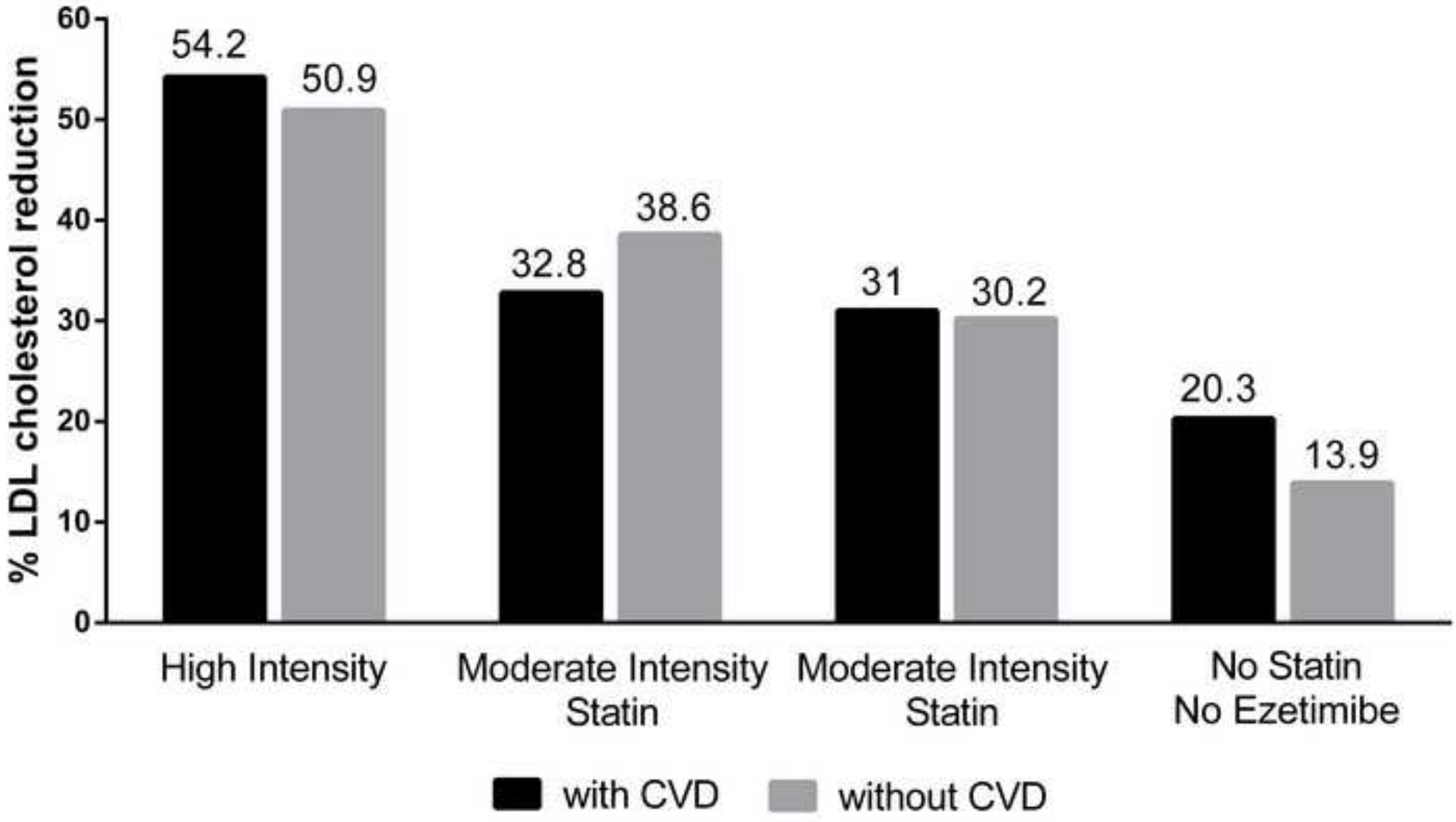

Figure 2

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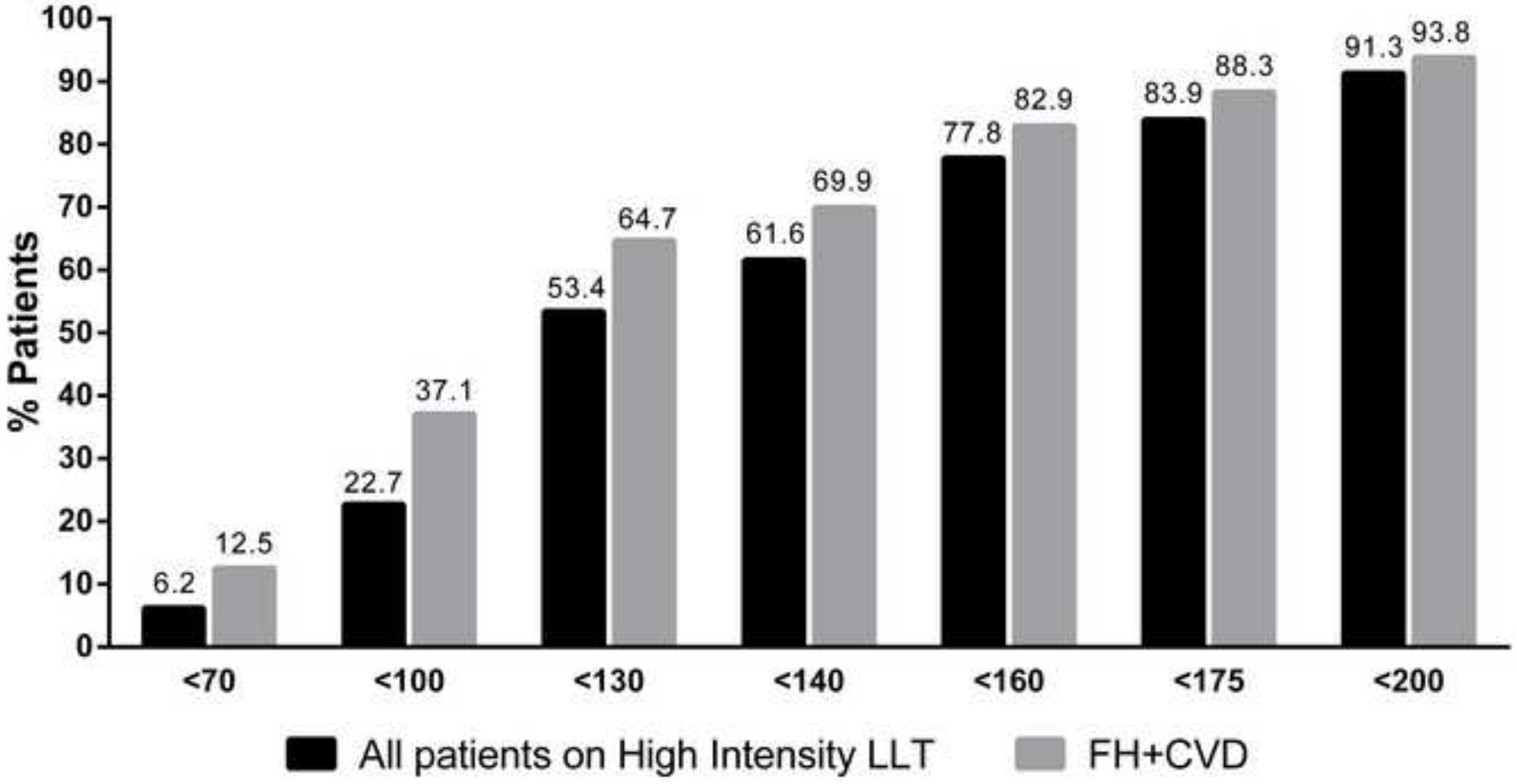

RDSEA collaborators

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Table 1

Anthropometric, clinical and biochemical characteristics at the time of inclusion in the registry according to lipid-lowering treatment.

Variables	**High Intensity N=1573**	**Moderate Intensity Statin n=607**	**Low Intensity Statin or Ezetimibe n= 82**	**No statin and no ezetimibe n= 423**	***p***
Gender (male), n (%) [a]	794 (50.4)	278 (45.8)	27 (32.9)	212 (49.3)	.05
Age, years	55 (45-63)	51 (38-61)	56.5 (41.7-66.0)	51 (36-60)	<.001
DLCN, points [b]	13 (8-18)	7 (4-12)	6 (4-12)	9 (4-15)	<.001
FH genetic test, n (% positive)	888 (56.7)	216 (35.6)	25 (30.5)	181 (42.1)	<.001
Cardiovascular Disease, n (%)	305 (19.6)	22 (3.6)	9 (11.0)	49 (11.4)	<.001
Current Smokers, n (%)	378 (24.2)	120 (19.8)	8 (9.8)	91 (21.5)	.034
Hypertension, n (%)	390 (24.9)	100 (16.5)	18 (22.0)	78 (18.1)	<.001
Diabetes, n (%)	139 (8.9 %)	29 (4.8 %)	5 (6.1 %)	33 (7.8 %)	.013
Total Cholesterol, mmol/L	5.3 (4.6-6.1)	5.6 (4.9-6.2)	6.0 (5.2-7.0)	6.6 (5.1-7.8)	<.001
HDL Cholesterol, mmol/L	1.4 (1.2-1.6)	1.5 (1.2-1.7)	1.6 (1.4-1.8)	1.4 (1.2-1.7)	<.001
LDL Cholesterol, mmol/L [c]	3.2 (2.6-4.0)	3.4 (2.8-4.1)	3.8 (3.2-4.8)	5.1 (4.4-6.0)	<.001
Triglycerides, mmol/L	1.1 (0.8-1.5)	1.1 (0.8-1.6)	1.0 (0.7-1.5)	1.2 (0.8-1.7)	.022

Time on Statin, years	9 (4-14)	4 (2-9)	4 (1-7)	2 (0-10)	<.001
Age Statin Onset, years	41 (31-50)	42 (28-51)	50 (40.5-56.0)	43 (32-50)	.05
Ezetimibe Treatment, n (%)	1028 (65.6)	0	23 (28.0)	0	<.001

"a" Values are numbers (%), mean ± standard deviation (SD) or median (25^{th} percentile – 75^{th} percentile), as applicable. P-values refer to the results of chi-square, Mann-Whitney, Wilcoxon or ANOVA tests as appropriate. CVD denotes cardiovascular disease; HDL, high-density lipoprotein; LDL and LDL-c, low-density lipoprotein; DLCN, Dutch Lipid Clinic Network.

"b" DLCN: Duch Lipid Clinics Network

"c" Basal LDL: Median (25th percentile – 75th percentile) basal LDL-c levels according to treatment intensity group were 6.8 (5.7-8.1) mmol/L for high intensity; 5.5 (5.1-6.3) mmol/L for moderate intensity; 5.5 (5-6.1) mmol/L for low intensity and 6 (5.2-7.2) mmol/L for those on neither statin nor ezetimibe at enrolment.

Table 2

Number of subjects who are candidates for PCSK9 inhibition therapy according to the recommendations of the European Society of Cardiology (ESC)/European Atherosclerosis Society (EAS), the Spanish Atherosclerosis Society (Sociedad Española de Arteriosclerosis, SEA) and European Medicines Agency (EMA), for heterozygous subjects with familial hypercholesterolemia after maximal tolerated statin therapy plus ezetimibe.

HeFH Group	**LDL Cholesterol for PCSK9 inhibitors**	**High Intensity Therapy N=1573**	**Presence of Cardiovascular Disease N=385**	**Positive Genetic Diagnosis N=1310**	**All N= 2685**
ESC/EAS recommendations					
Without Very High Risk [a], n (%)	>5.2 mmol/L	34 (2.2)	-	70 (5.3)	119 (4.4)
Very High Risk without CVD, nor Diabetes with Target Organ Damage or a Major Risk Factor [b] , n (%)	>4.5 mmol/L	84 (5.3)	-	70 (5.3)	189 (7.0)
With CVD or Diabetes with Target Organ Damage or a Major Risk Factor,	>3.6 mmol/L	110 (7.0)	116 (30.1)	79 (6.0)	148 (5.5)

n (%)					
TOTAL		**228 (14.5)**	**116 (30.1)**	**219 (16.7)**	**456 (17.0)**
SEA recommendations					
Low Risk [c], n (%)	>4.1 mmol/L	40 (2.5)	-	100 (7.6)	148 (5.5)
Without Low Risk, n (%)	>3.4 mmol/L	337 (21.4)	-	288 (22.0)	650 (24.2)
With CVD, n (%)	>2.6 mmol/L	198 (12.6)	242 (62.9)	136 (10.4)	242 (9.0)
TOTAL		**575 (36.6)**	**242 (62.9)**	**524 (40.0)**	**1040 (38.7)**
EMA approval					
All FH	**>2.6** mmol/L	**1218 (77.4)**	**242 (62.9)**	**1096 (83.7)**	**2154 (80.2)**

CVD denotes cardiovascular disease; LDL, low-density lipoprotein; Lp(a), lipoprotein(a); PCSK9, proprotein convertase subtilisin kexin 9.

"a" Risk factors indicating a very high cardiovascular risk include diabetes mellitus, lipoprotein(a) > 50 mg/dL (conversion to nmol/L x 2.4), marked hypertension, and premature familial ASCVD (<55 years in males and <60 years in females).

"b" Diabetes mellitus with target organ damage such as proteinuria or with a major risk factor such as smoking or hypertension.

[c] Risk factors excluding low cardiovascular risk included diabetes mellitus, lipoprotein(a) > 50 mg/dL (conversion to nmol/L x 2.4), hypertension, current smoking.