LDL cholesterol reduction variability with different types and doses of statins in monotherapy or combined with ezetimibe. Results from the Spanish Arteriosclerosis Society Dyslipidaemia Registry

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Abstract

Purpose: Low-density lipoprotein (LDL) cholesterol reduction by statin therapy is dose-dependent, varies among different statins and has wide inter-individual variability. The present study aimed to compare mean LDL cholesterol reduction achieved with different doses of the three statins most frequently used in monotherapy, or combined with ezetimibe, in a real clinical setting.

Methods: Of 5,620 cases with primary hypercholesterolaemia on the Spanish Arteriosclerosis Society Registry, 1,004 corresponded to non-monogenic hypercholesterolaemia and complete information on drug therapy and lipid profile were included.

Results: The lowest mean percentage LDL cholesterol reduction was observed with simvastatin 10 mg (32.5 ± 18.5%) while the highest mean percentage LDL reduction was obtained with rosuvastatin 40 mg (58.7 ± 18.8%). As to combined treatment, the lowest and highest mean percentage LDL cholesterol reductions were obtained with simvastatin 10 mg combined with ezetimibe (50.6 ± 24.6%) and rosuvastatin 40 mg combined with ezetimibe (71.6 ± 11.1%), respectively. Factors associated with a suboptimal response were male sex, age, body mass index and baseline LDL cholesterol levels. Combined treatment was associated with less variability in LDL cholesterol reduction (OR 0.603, $p < 0.001$).

Conclusion: In a real clinical setting, rosuvastatin was superior to the other statins in lowering LDL cholesterol, both as monotherapy or combined with ezetimibe. Factors associated with a suboptimal response in LDL cholesterol included sex, age, body mass index and baseline LDL cholesterol levels. Combined treatment was associated with less variability in LDL cholesterol improvement.

Keywords: cardiovascular risk; ezetimibe; LDL cholesterol; lipid-lowering treatment; statins.

Background

The 2019 *European Society of Cardiology* (ESC) / *European Atherosclerosis Society* (EAS) guidelines for the management of dyslipidaemias [1] continue to identify low-density lipoprotein (LDL) cholesterol as the primary therapeutic target and emphasise the need for aggressive treatment in patients at high/very high cardiovascular risk. The guidelines recommend using a statin with sufficient power to achieve the required reduction based on the LDL cholesterol goal, move on to the maximum tolerated dose if the aim is not achieved, add ezetimibe and, if the objective is still not reached, add a proprotein convertase subtilisin/kexin-type 9 (PCSK9) inhibitor. Although LDL cholesterol goals can be theoretically attained with a statin in monotherapy or combined with ezetimibe in many patients [2], the reality is that high cardiovascular risk patients are under-treated and the achievement rate of the therapeutic objective is unacceptably low [3,4]. According to the DYSIS study [5], even in patients with cardiovascular disease, the intensity regimen of statin therapy was mild and equivalent to 35 mg/day of simvastatin. In addition, patients who failed to reach the therapeutic goal maintained LDL cholesterol concentrations almost 1 mmol/L /38,6 mg/dl) from the recommended target level. Therefore, reduction is stopped in these patients by up to 20%.

Statins have become the most widely used lipid-lowering drugs and have been proven to be effective in different clinical settings and age groups [6-9]. The degree of LDL cholesterol reduction is dose-dependent and differs among statins. Furthermore, response to the same dose of statin presents considerable inter-individual variability [10-12], which has been attributed to demographic, phenotypic and genetic factors [13-

15]. LDL cholesterol reduction variability increases the risk of cardiovascular events in patients with cardiovascular disease [16] and even progression to dialysis in those with chronic kidney disease stage 3 [17]. Nevertheless, it has sometime been assumed that the relative reduction in LDL cholesterol is the same for each statin and dose and, therefore, variability in response to statins is often not considered when treating hypercholesterolaemic subjects for cardiovascular prevention.

The efficacy of lipid-lowering therapy is interpreted based on mean reductions in LDL cholesterol within randomised trials and head-to-head comparisons among statins [18], with limited information regarding variability in cholesterol improvement [19-20]. In Spain, most cases of difficult-to-treat dyslipidaemia, either because they have high lipid levels or are at high/very high cardiovascular risk, are controlled at specialised lipid units distributed throughout the country, organised in a network within the Spanish Arteriosclerosis Society (SEA). This provides an excellent framework for evaluating the impact of lipid-lowering therapies in a real clinical scenario.

The main aim of the present study was to compare mean LDL cholesterol reduction and its variability achieved with different doses of the 3 most frequently used statins (atorvastatin, rosuvastatin and simvastatin) in monotherapy or combined with ezetimibe, using individual data of patients with primary non-monogenic hypercholesterolaemia from the SEA Dyslipidaemia Registry. Factors associated with a suboptimal response of LDL cholesterol, as well as with greater variability of this parameter, were also evaluated.

Methods

Study characteristics

This observational, retrospective, multicentre, national study was designed to determine the impact of statin therapy. The information was obtained from the SEA Dyslipidaemia

Registry, an active on-line registry in which 50 certified lipid units distributed throughout Spain enter cases with different primary hyperlipidaemias using homogeneous clinical diagnostic criteria [21]. Anonymous clinical data collection in this registry was approved by a Central Ethics Committee (Comité Ético de Investigación Clínica de Aragón, Zaragoza, Spain) and participants gave their written informed consent. Minimum data for the inclusion of cases in the registry are: age, sex, smoking status, personal history of diabetes, hypertension and cardiovascular disease and age at diagnosis, body mass index, waist circumference, complete lipid profile including total cholesterol, LDL cholesterol, triglycerides and high-density lipoprotein (HDL) cholesterol levels without lipid-lowering treatment at diagnosis, and lipid and biochemical parameters at the time of inclusion in the registry. The registry is designed so that, at least once a year, clinical evolution of patients is updated with new anthropometric data, changes in risk factors or medication, and new cardiovascular events.

In the present study, all hypercholesterolaemic patients ≥ 18 years old from the registry with non-monogenic hypercholesterolaemia and completed information were included. Exclusion criteria were patients with probable (6–8 points) or definite (> 8 points) familial hypercholesterolaemia according to the Dutch Lipid Clinic Network criteria [22] or, as mentioned, lack of data on lipid-lowering therapy or lipid subfraction levels. Patients who had received lipid-lowering other than atorvastatin, rosuvastatin or simvastatin, in monotherapy or combined with ezetimibe, were also excluded from the analysis.

The last lipid-lowering drug treatment followed by the patient for at least 3 months without changes was reported. Values of the analytical and biological variability of LDL cholesterol are 2-10% and 14%, respectively [23]. For this reason, we

considered excessive variability as a consequence of the therapeutic intervention level ≥ 15%.

Finally, suboptimal LDL cholesterol improvement is defined as a < 15% reduction in LDL cholesterol levels compared to baseline for patients on low- to moderate-intensity statin treatment (simvastatin 10-40 mg, atorvastatin 10-20 mg and rosuvastatin 5-10 mg). This definition is based on clinical experience and previous studies since no standard criteria have been established. Moreover, based on the results of the VOYAGER meta-analysis [20], this cut-of level was upgraded to a < 30% reduction for subjects receiving high-intensity statins (atorvastatin 40-80 mg or rosuvastatin 20-40 mg).

Statistical analysis

Data were expressed as mean ± standard deviation for continuous variables. Categorical variables were expressed as percentages and frequencies. The percentage change from baseline in LDL cholesterol was calculated for each patient according to the different types of statin and dose. A multiple logistic regression model was applied and odds ratios (OR) with 95% confidence intervals (CI) were calculated to assess factors related to suboptimal LDL cholesterol improvement and to greater variability in LDL cholesterol reduction. A two-sided p value < 0.05 was considered statistically significant. Analyses were performed with SPSS (version 19.0 for Windows; SPSS, Chicago, IL).

Results

Of the 5,620 cases with primary hypercholesterolaemia recruited in the SEA registry, 1,004 with non-monogenic hypercholesterolaemia were finally included, after excluding those receiving other lipid-lowering treatment other than the statins previously

mentioned with or without ezetimibe. Patients with familial hypercholesterolaemia were also excluded from the analysis (**Figure 1**).

Baseline characteristics

Mean age of the 1,004 included patients was 60.5 ± 13.2 years and mean body mass index of 26.8 ± 4.0 kg/m^2. Four hundred and fifty-six (45.4%) were males. One hundred and sixty-four (16.3%) were current smokers, 97 (9.7%) had cardiovascular disease, 108 (10.7%) type 2 diabetes mellitus and 280 (27.9%) hypertension. The rest of the baseline characteristics of patients, including baseline lipid profile, are described in **Table 1**.

Four hundred and twenty-one (42%) patients were treated with a statin alone and the remaining 583 (58%) with a statin plus ezetimibe.

LDL cholesterol change

Statin monotherapy

Regarding statin monotherapy, the lowest mean percentage LDL cholesterol reduction was observed with simvastatin 10 mg, while the highest mean percentage LDL reduction was achieved with rosuvastatin 40 mg. Focusing on the most used statins, atorvastatin 10-80 mg lowered LDL cholesterol by a mean of 45.8 ± 18.8% to 51.8 ± 21.7%. As to rosuvastatin, doses 5-40 mg reduced LDL cholesterol levels from 43.0 ± 25.7% to 58.7 ± 18.8%. Finally, simvastatin 10-40 mg reduced LDL cholesterol levels from 32.5 ± 18.5% to 49.9 ± 17.7% **(Figure 2).**

Statins combined with ezetimibe

Regarding combined treatment with statins and ezetimibe, the lowest and highest mean percentage LDL cholesterol reductions were obtained with simvastatin 10 mg and rosuvastatin 40 mg, respectively. Atorvastatin 10-80 mg with ezetimibe reduced LDL cholesterol from 54.8 ± 18.9% to 68.4 ± 14.3%. As to rosuvastatin, doses 5-40 mg combined with ezetimibe lowered LDL cholesterol levels from 55.6 ± 26.5% to 71.6 ±

11.1%, whereas simvastatin 10-40 mg with ezetimibe achieved a reduction in LDL cholesterol levels from 50.6 ± 24.6% to 65.3 ± 9.0% **(Figure 2).** When any daily statin dose plus ezetimibe was considered, LDL cholesterol variability ranged from 9 to 26.5%. It should be noted that the highest dose of any of the three statins combined with ezetimibe induced the lower variability in LDL cholesterol reduction.

Factors associated with suboptimal LDL cholesterol level improvement and greater variability in LDL cholesterol reduction

A multiple logistic regression model was used to assess factors related to suboptimal response in LDL cholesterol with statin therapy. In this respect, when suboptimal response was considered < 15% reduction in LDL cholesterol levels, male sex was independently associated with a greater probability of being a hypo-responder. Moreover, increased age, body mass index or baseline LDL cholesterol were associated with a higher decreased odds of poor response to statins. When suboptimal response was defined as a < 30% reduction in LDL cholesterol levels (patients being treated with atorvastatin 40-80 mg, rosuvastatin 20-40 mg), the same factors were observed as those with low- and moderate- statin dosage **(Table 2).**

Factors associated with greater variability (≥ 15%) in LDL cholesterol reduction were evaluated regardless of the statin type received. To this respect, the presence of cardiovascular disease was associated with greater variability (OR 3.260, 95% CI 1.053 to 10.088; p = 0.040). By contrast, receiving combined treatment with statins and ezetimibe was associated with less variability in LDL cholesterol reduction (OR 0.603, 95% CI 0.509 to 0.715; p < 0.001).

Discussion

The present study reinforced the notion of the wide variability in LDL cholesterol reduction obtained with different types and doses of statins, in monotherapy

or combined with ezetimibe, in a real clinical setting in patients with non-monogenic hypercholesterolaemia. In this respect, statin plus ezetimibe administration showed less variability in lowering LDL cholesterol.

As mentioned previously, the ESC/EAS 2019 guidelines [1] focus on LDL cholesterol levels as a specific therapeutic target for patients with high/very high cardiovascular risk. However, it is important to emphasise that these recommendations do not always consider the wide variability among individuals in lipid profile normalisation in response to different statin types and doses. In this respect, the "Comparative Dose Efficacy Study of Atorvastatin Versus Simvastatin, Pravastatin, Lovastatin, and Fluvastatin in Patients with Hypercholesterolaemia (CURVES study) in 1998 [24] was the first trial to compare the lipid-lowering efficacy of diverse HMG-CoA reductase inhibitors doses. In that trial, atorvastatin 10, 20 and 40 mg produced greater reductions in LDL cholesterol than the milligram-equivalent doses of simvastatin, pravastatin, lovastatin and fluvastatin. Atorvastatin 10-80 mg presented a mean percentage reduction in LDL cholesterol from 38 ± 10% to 54 ± 9% compared to the 45.8 ± 18.8% to 51.8 ± 21.7% obtained in the present study, with the latter obtaining greater variability in LDL cholesterol reduction. On the same lines, the VOYAGER meta-analysis [20], which included 32,258 subjects, observed a mean LDL cholesterol reduction ranging from 28.4 to 55.5% after lipid-lowering treatment with atorvastatin 10-80 mg, rosuvastatin 5-40 mg or simvastatin 10-40 mg. Moreover, the standard deviation of LDL cholesterol reduction for all statins and doses ranged from 12.8 to 17.9%. In the present study, once again, greater variability was observed, with a standard deviation ranging from 17.7 to 34.4%.

Hence, this variability could translate into a significant number of patients never achieving LDL cholesterol therapeutic targets. In this respect, Karlson et al [20]

reported that a significant number of patients (2.7 to 12.7%) had a suboptimal response (< 15% reduction in LDL cholesterol levels). In general, although lower-dose statins such as simvastatin (10-20 mg) or atorvastatin (10 mg) were associated with higher rates of suboptimal responses, high-dose statins such as rosuvastatin (40 mg) and atorvastatin (80 mg) also obtained suboptimal responses in some cases (2.7 and 4.7% of patients, respectively). In the present study, 15.6% (atorvastatin 10-20 mg), 14.5% (rosuvastatin 5-10 mg) and 24.4% (simvastatin 10-40 mg) of subjects presented a suboptimal response, defined as a < 15% reduction in LDL cholesterol levels. When high-intensity statins (atorvastatin 40-80 mg and rosuvastatin 20-40 mg) were considered, nearly 20% of subjects presented a < 30% reduction in LDL cholesterol levels. Thus, the variability observed in lipid-lowering response without achieving therapeutic goals in some cases may indicate the need to initiate combined treatment.

The effect of combined treatment with different types and doses of statins plus ezetimibe in lowering LDL cholesterol levels was also evaluated. The decrease in LDL cholesterol levels was almost 22% higher when ezetimibe was combined with rosuvastatin 40 mg than when the statin alone was given, with 32 and 31% increases also being observed after ezetimibe was added to atorvastatin 80 mg or simvastatin 40 mg, respectively. A recent meta-analysis including 12 studies [25] found that the ezetimibe plus statin combination achieved a greater absolute LDL cholesterol reduction than statin monotherapy, with a mean difference of 21.86 mg/dL (95% CI 26.56 to 17.17; $p < 0.0001$) after 6 months of treatment. These results being consistent with the 19–23% LDL cholesterol reduction previously described for ezetimibe when added to statin therapy [26,27]. When any daily statin dose plus ezetimibe was taken into account, variability in LDL cholesterol reduction dropped from 17.7-34.4% to 9-26.5%, with combined therapy being associated to reduced variability in LDL cholesterol

reduction (OR 0.603, 95% CI 0.509 to 0.715; $p < 0.001$). Thus, combination therapy may represent a valid therapeutic option for LDL cholesterol reduction, both from a clinical efficacy standpoint as for reduced LDL cholesterol variability. Less variability also offers the advantage of better precision and accuracy in predicting treatment response.

It would be useful in clinical practice to better understand the factors involved in a higher likelihood of failing to achieving therapeutic goals.

In the present study, when low-moderate-intensity statin treatment was considered, male sex was independently associated with a greater probability of being a hypo-responder. Furthermore, as age, body mass index or baseline LDL cholesterol levels were higher, the possibility of presenting a poor response to statins was lower. Similarly, the VOYAGER database [20] showed low baseline LDL cholesterol and younger age to be factors associated with suboptimal response. A further study evaluating hypo-responders also reported male sex, younger age, presence of diabetes and low baseline LDL cholesterol levels to be associated with a lower statin response in lowering LDL cholesterol levels [28]. However, no previous study found body mass index to be a factor related to suboptimal response. In this respect, the association of higher body mass index with lower suboptimal response could be linked to either awareness of the higher risk in patients with obesity or the relatively desirable low baseline LDL cholesterol levels in obese patients [29].

The present study has some limitations. Firstly, it is an observational study and lipid-lowering treatment was assigned to each patient following clinical criteria instead of a standardised protocol. Secondly, all subjects included in this study were extracted from the Dyslipidaemia Registry of the Spanish Arteriosclerosis Society. These patients are therefore treated and followed at specialised lipid clinics and, consequently, the

present results cannot be extrapolated. Patients with different types of primary non-monogenic hypercholesterolaemia were included in the analysis. Moreover, as the study was conducted in real world clinical practice conditions, lipid profile determinations were not measured at a centralised laboratory. This study focused on the most frequently used statins and, owing to the limited number of patients, did not include results on less frequently-used ones. Other potential contributors to LDL cholesterol reduction variability, such as diet, lifestyle modifications or concomitant medications that could influence lipid metabolism, were not registered.

Conclusions

The present study aimed to provide new insights into LDL cholesterol variability in response to statin therapy with potential relevance for future clinical guidelines and, consequently, aid clinicians in making therapeutic decisions.

In a real clinical setting, our data supported a great variability in LDL cholesterol reduction with different doses of the three most frequently used statins. The highest tdosis of any of the three statins combined with ezetimibe were associated to lower variability in LDL cholesterol reduction. Factors associated with suboptimal response in LDL cholesterol reduction were male sex, age, body mass index and baseline LDL cholesterol levels.

Declarations

- **Funding:** The authors did not receive support from any organisation for the submitted work.

- **Conflicts of interest**: The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.
- **Ethics approval and consent to participate:** Anonymous clinical data collection in this registry was approved by a central ethics committee (Comité Ético de Investigación Clínica de Aragón, Zaragoza, Spain) and participants gave their written informed consent.
- **Consent for publication:** Not applicable.
- **Availability of data and material:** Not applicable.
- **Code availability:** Not applicable.
- **Authors' contributions:** All authors contributed to the study conception and design. Material preparation and data collection were performed by all authors. Data analysis was performed, and the first draft of the manuscript was written by EC, DB and J.P-B, and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Figure Legends

Fig. 1 Study flow diagram of the patients included in the database.

HeFH: heterozygous familial hypercholesterolaemia; HoFH: homozygous familial hypercholesterolaemia; PCSK9: proprotein convertase subtilisin/kexin type 9.

Fig. 2 Mean percentage change in LDL cholesterol with statin treatment alone and combined with ezetimibe.

ATV: atorvastatin; LDL: low-density lipoprotein; RSV: rosuvastatin; SIM: simvastatin.

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