ORIGINAL ARTICLE

Approach on the Use of Statins in a Sample of Doctors from Argentina. The COFEMA Study

Conductas frente a la utilización de estatinas en una muestra de médicos de la Argentina. Estudio COFEMA

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ABSTRACT

Background: Available information on the use of statins is very abundant and complex, and in recent years, different recommendations have been published in local and international guidelines. Since the evidence with statins has generated variations in their indication, it is interesting to know the degree of guideline acceptance and the approach of our medical community regarding their use.
Objective: The aim of this study was to identify physician approach on the use of statins in Argentina.
Methods: A 16-item survey was carried out to investigate the degree of agreement with different statin indications and usual dosage. A descriptive analysis was performed and comparisons by specialty and age group were carried out.
Results: The median age of the 598 respondents was 48 years. Most physicians agreed to indicate high doses of statins in secondary prevention and in diabetic patients. When LDL-C >190 mg/dL was the only risk criterion, 50% of respondents did not approve the indication. In primary prevention, one in three physicians agreed to discontinue treatment after normalizing cholesterol levels. In two controversial conditions, such as chronic coronary artery disease in patients on dialysis and advanced coronary heart failure, the indication of statins was high. Most respondents monitor adverse effects with hepatograms and CPK measurements in asymptomatic patients.
Conclusions: The survey reflects the opinion of participating physicians on the indication of statins in different scenarios, revealing a partial acceptance of guideline recommendations. Accurate indications, statin doses and the addition of other therapies such as ezetimibe continue to generate different proposals and must be re-elaborated and debated in order to optimize them.

Key words: Hydroxymethylglutaryl-CoA Reductase Inhibitors - Cardiovascular Disease - Behavior - Lipids - Ezetimibe

RESUMEN

Introducción: La información disponible sobre el uso de estatinas es muy abundante y compleja; en los últimos años se publicaron guías locales e internacionales con diversas recomendaciones. Dado que la evidencia con estatinas fue generando variaciones en sus indicaciones, resulta de interés conocer el grado de aceptación de las guías y las conductas de nuestra comunidad médica respecto de su utilización.
Objetivo: Identificar las conductas de los médicos en la Argentina frente a la utilización de estatinas.
Material y métodos: Se elaboró una encuesta de 16 puntos que indagó el grado de acuerdo con distintas indicaciones de estatinas y su posología habitual. Se realizó un análisis descriptivo y se efectuaron comparaciones por especialidad y grupo etario.
Resultados: La mediana de edad de los 598 encuestados fue de 48 años. La mayoría de los médicos estuvieron de acuerdo con indicar dosis altas de estatinas en prevención secundaria y en pacientes diabéticos. Cuando el C-LDL > 190 mg/dl era el único criterio de riesgo, el 50% no aprobó la indicación. En prevención primaria, uno de cada tres médicos estuvo de acuerdo con interrumpir el tratamiento una vez normalizado el nivel de colesterol. En dos condiciones controversiales como la coronariopatía crónica en pacientes en diálisis y la insuficiencia cardíaca avanzada de causa coronaria, la indicación de estatinas resultó elevada. La mayoría de los encuestados monitorizan efectos adversos con hepatogramas y mediciones de CPK en pacientes asintomáticos.

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Conclusiones: La encuesta refleja el pensamiento de los médicos participantes sobre las indicaciones de estatinas en diferentes escenarios, observándose una aceptación parcial de las recomendaciones de las guías. Las indicaciones precisas, las dosis de estatinas y la adición de otras terapias como el ezetimibe siguen generando planteos diversos y deben ser motivo de reelaboración y debate con el objeto de optimizarlas.

Palabras clave: Inhibidores de hidroximetilglutaril-CoA reductasas - Enfermedad cardiovascular - Conductas - Lípidos - Ezetimibe

Abbreviations

ACS	Acute coronary syndrome	**IMT**	Intima-media thickness
AHA/ACC	American Heart Association/American College of Cardiology	**HF**	Heart failure
ATP III	Adult Treatment Panel III	**CRF**	Chronic renal failure
CPK	Creatinine-phosphokinase	**LDL**	Low density lipoprotein
ESC	European Society of Cardiology	**SAC**	Argentine Society of Cardiology

INTRODUCTION

Statins play a central role in the primary and secondary prevention of cardiovascular diseases. They reduce overall mortality, cardiovascular mortality, brain and heart events, and their use is supported by large controlled studies and several meta-analyses. (1-5) This extensive information established its benefits in the treatment of coronary heart disease and its limitations in other clinical contexts, such as heart failure (HF) or severe chronic renal failure (CRF). (6-9) In the last decade direct comparative studies have shown advantages for high versus low statin doses (10-13) with an excellent safety margin. (5, 13) In addition, a large clinical trial recently reported on the effect of simvastatin in association with ezetemibe (14). Surprisingly, the Food and Drug Administration (FDA) rejected this indication on secondary prevention as it considered that the benefit was not relevant. (15)

Multiple aspects of indication, drug selection and dosage are controversial. The ATP III (Adult Treatment Panel III) consensus based its indications of treatment on achieving LDL cholesterol targets, (16) while that of the Argentine Society of Cardiology (SAC) establishes similar indications, focused on LDL targets and classified according to primary and secondary prevention scenarios. (17) The American Heart Association/American College of Cardiology (AHA/ACC) guideline presented at the end of 2013, focused on the desirable dose of statins according to the clinical context of the patient, regardless of specific LDL targets and with a clear orientation to high-dose administration (atorvastatin 40-80 mg and rosuvastatin 20-40 mg). (18) This proposal generated lengthy debates as it modifies drug and dose selection, reducing the relevance of controlling cholesterol levels. (19-21) Local guidelines have not yet been updated and we do not know to what extent these recommendations have changed doctors' approach on the subject. After the collection of our data, the ACC Expert Consensus Decision Pathway on the Role of Non-Statin Therapies for LDL-Cholesterol Lowering in the Management of Atherosclerotic Cardiovascular Disease Risk and the new guideline of the European Society of Cardiology (ESC) published in 2016, partially disagreed with the 2013 AHA/ACC guidelines and resumed the criteria guided by LDL levels. (22, 23)

Given that the evidence with statins generated variations in their indication during the last two decades, our work focused on the approach of physicians in Argentina regarding their use.

METHODS

The COFEMA (***CO****nductas* ***F****rente a la utilización de* ***E****statinas en una muestra de* ***M****édicos de la* ***A****rgentina) (Approach on the Use of Statins in a Sample of Argentine Physicians)* study was a project developed by the Clinical Cardiology Council and the Research Area of the SAC, in collaboration with the *Sociedad Argentina de Medicina* (Argentine Society of Medicine), which implemented a questionnaire for voluntary and anonymous registry aimed at cardiologists, clinicians and general practitioners. This survey consisted of 12 statements upon which the degree of agreement should be established using a five-option Likert scale (see Supplementary material).

The 12 statements proposed clinical scenarios on the main indications of statins, questions directed to its safety profile and others related to its use. Population variables (sex, age and specialty) were recorded and four multiple-choice questions were included to collect information on the most usual doses and the proportion of individuals receiving combinations with ezetimibe (both on secondary prevention scenarios).

Statistical analysis

The data corresponding to each item were graphically analyzed by percentages and comparisons were established by specialty and age group (dichotomizing the variable with a cut-off point at 40 years, considering the first decade after the end of the medical residency). For these comparisons the differences were analyzed using the chi square test or Fisher's exact test depending on the relative frequency of expected values. For the analysis of high dose on secondary prevention, a multivariate logistic regression model was constructed, adjusted by specialty and age group. Statistical significance was established with a two-tailed p value ≤ 0.05. The questionnaire was available in electronic format, through the website of the Argentine Society of Cardiology, from June to October 2015.

Ethical considerations

The COFEMA study was carried out by means of an anony-

mous and voluntary survey directed at physicians, so the management of the data did not allow in any way to know the identity of participants.

RESULTS

Five hundred and ninety eight responses were obtained. The median age of the respondents was 48 years (interquartile range 38-59), with male (72% of total) and cardiology specialty predominance (Figure 1); cardiologists were 3 years younger than non-cardiologists (46 vs. 49 years, p=0.02). The questionnaire response rate was over 97% for all statements.

Following the registry format, the results are grouped according to the area of interest:

Primary prevention conducts

First question: In the case of a diabetic patient without previous cardiovascular event and with non-elevated LDL, the majority chose to indicate statins, although 21% disagreed, with significant differences according to specialty. (Figure 2)

Second question: In the case of a young woman with LDL>190 mg/dL and without other risk factors, the degree of agreement for statin indication was 52%, without significant differences by specialty or age group.

Third question: The strategy to discontinue treatment after achieving an adequate LDL reduction was consulted, and 34% of physicians supported this approach, with a predominance of young physicians (41% vs. 31%; p=0.022). (Figure 3)

Fourth question: It was aimed at evaluating the indication of statins in a low risk young man with LDL levels of 160 mg/dL and increased intima-media thickness (IMG) obtained by carotid Doppler ultrasound. The degree of agreement for statin indication was 69 %, with no difference between subgroups.

Fifth question: In the case of a dyslipidemic patient with hepatic steatosis, 90% of physicians agreed to use statins, with no differences between the subgroups analyzed.

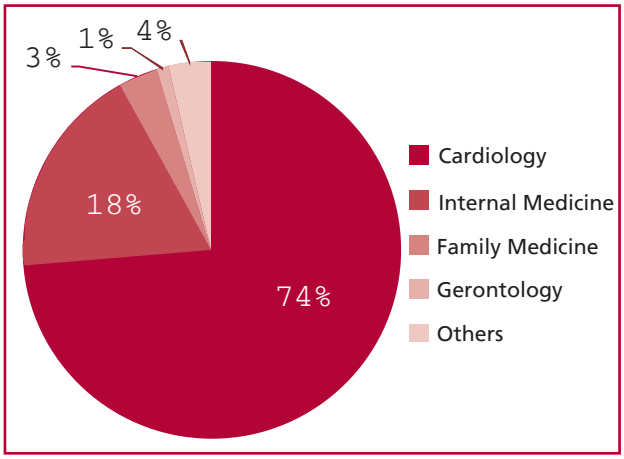

Fig. 1. Sample distribution according to specialty

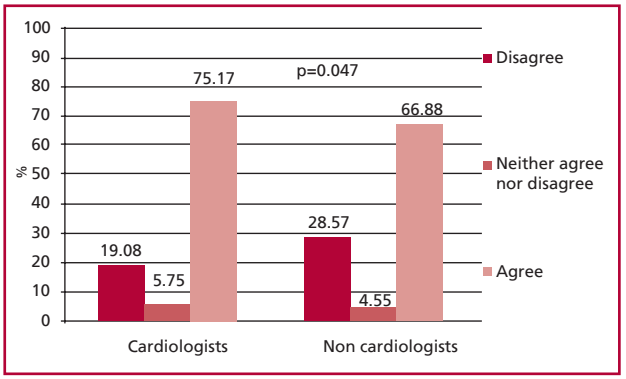

Fig. 2. Use of statins in type 2 diabetic patients with normal LDL cholesterol.

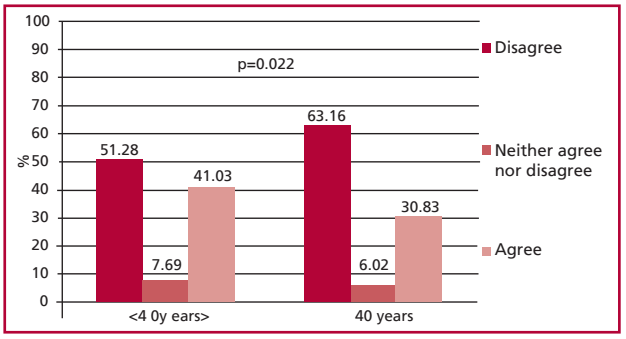

Fig. 3. Discontinuation of statin therapy in primary prevention patients after normalizing cholesterol levels.

Secondary prevention conduct

Sixth question: Eighty-six percent of respondents agreed to indicate high doses of statins on secondary prevention, an approach that was more frequent among cardiologists (88.7 vs. 76.8; p=0.001).

Seventh question: The question was whether a patient with history of acute coronary syndrome (ACS) who spontaneously has an LDL level of 90 mg/dL should receive statins. Eighty-nine percent answered positively, with a predominance of cardiologists (91% vs. 83%; p=0.017).

Eighth question: In the case of a patient treated with atorvastatin/ezetimibe 20/10 mg and ideal levels of LDL after an ACS, they were asked whether they would change the treatment for atorvastatin 80 mg. Thirty-four per cent agreed, while 52% opposed this approach. (Figure 4) Significant differences were found in favor of the change between doctors <40 years (40% vs. 31%; p = 0.033).

Ninth question: The indication of statins to a stable, elderly patient with CRF on dialysis was presented and 90% answered positively, with a significant difference in favor of cardiologists (91% vs. 86%; p<0.05).

Tenth question: In the case of a patient with HF with severe ventricular dysfunction of coronary origin, 81% would indicate statins, with no significant differences between the subgroups analyzed.

Conducts related to adverse effect monitoring

Questions 11 and 12 were about monitoring adverse effects with liver enzymes and creatine phosphokinase (CPK) levels in asymptomatic patients treated with statins. The agreement to request liver enzymes periodically was 73%, with no significant differences between the subgroups; 58% confirmed the periodic assessment of plasma CPK, with a greater tendency in physicians >40 years (62.7% vs. 47.9; p=0.003).

Usual dosage

When inquiring about the usual dose of the three most prescribed statins on secondary prevention, high use of simvastatin was observed, especially by physicians >40 years (almost 67% use it). Overall, the use of high doses of statins on secondary prevention was 65%; cardiologists and physicians <40 years of age significantly reported using them more frequently. (Figure 5)

Overall ezetimibe use on secondary prevention was low: 74% of respondents did not use it or it was used in less than 20% of patients treated with statins. Young physicians reported lower use of this drug (p <0.01) and no significant differences were found by specialty.

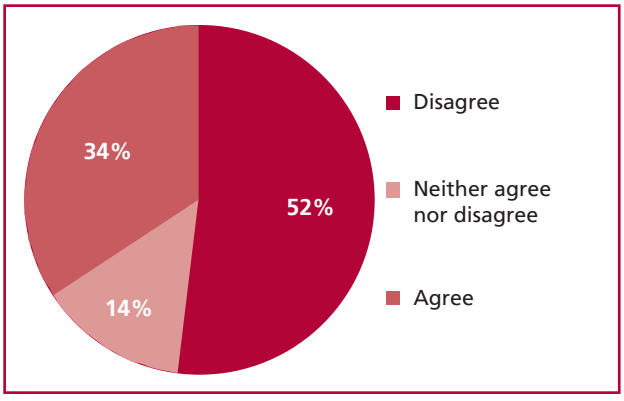

Fig. 4. Replacement of moderate dose statins associated with ezetimibe by high dose statin in a patient with recent acute coronary syndrome and low LDL cholesterol levels

DISCUSSION

Our survey provides interesting information regarding the approach on the use of statins in a sample of physicians from Argentina.

In adult diabetics, guidelines recommend statins universally regardless LDL levels (17, 18, 23, 24) and based upon evidence. (25) Although we observe a high agreement on this point, 21% of respondents do not indicate them. Perhaps the omission of statins in national diabetes guidelines developed years ago may have conditioned this particular conduct. (26) Local and international guidelines recommend statin therapy for all patients with LDL>190 mg/dL, (17, 18, 23) although as this criterion is based on consensus of experts and population series (27, 28) and is not supported by clinical trials, the disparity of opinion registered was predictable. It was also observed that one out of every three physicians agreed to discontinue statins when the LDL target level was achieved; however, guidelines do not recommend this behavior, so their justification is not clear.

The SAC consensus establishes the use of carotid Doppler ultrasound as class IIb in the low risk population. (17) The scenario presented by a patient with these characteristics and an increase in IMT as the only pathological finding in a routine study led to the indication of statins in most respondents. Consistent with the SAC consensus, recent publications discourage the use of carotid Doppler ultrasound for IMT assessment due to the small increase it generates in the area under the ROC (Receiver Operating Characteristic) curve constructed with the classical risk prediction models. (29) Thus, in the absence of atheromatous plaques, increased IMT does not substantially expand the discriminative capacity or change the risk category of patients classified with the traditional models. (17, 30)

The general agreement of statin indication on sec-

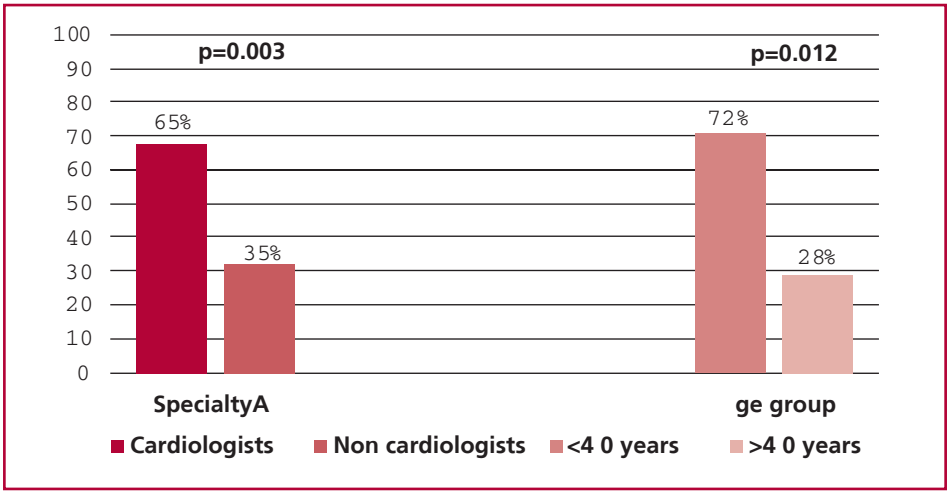

Fig. 5. Use of high dose statins in secondary prevention

ondary prevention and its use in coronary heart disease was high. Even in a hemodialysis scenario in a patient with stable coronary disease, 90% agreed to indicate them. However, two controlled studies have been performed with non-favorable results (6, 7) and neither could the benefit hypothesis be demonstrated by subgroup analysis in which the coronary patients did not perform differently from the rest. The SAC consensus cites this evidence but reduces the importance of the result considering other studies that included less severe patients and establishing that "treatment with statins is recommended in all subjects with CRF." (17) That is to say, it does not discriminate between those who are under dialysis and those who are not, a fact that could support the approach reported by the respondents.

In the presence of chronic coronary artery disease in patients with HF and severe systolic dysfunction, 81% of respondents chose to indicate statins. Two clinical trials with 10 mg rosuvastatin with negative results have been published. In the GISSI-HF study, 40% of participants had coronary heart disease and the subgroup analysis found no benefit, consistent with the overall outcome; (9) the CORONA study only included patients with coronary heart disease and could neither demonstrate benefit in terms of hard event reduction. (8) These results disagree with observational series and, as observed in our survey, were not considered as criteria of truth by the medical community. One of the criticisms is that both studies were performed with moderate doses of the same statin and perhaps the results could have been different with other doses or therapeutic agents.

We observed a strong support for the indication of high doses of statins on secondary prevention. However, when specifically asked about standard dosing, only 65% of physicians reported using them, with a significant difference in favor of cardiologists and physicians <4 0 years. It is interesting to analyze the high use of simvastatin on secondary prevention reported in our survey (62%). The latest ACC/AHA guideline presented at the end of 2013 (18) excludes it from the secondary prevention scenario preferring high doses of rosuvastatin or atorvastatin. It should be noted that simvastatin 40 mg, was the first statin that demonstrated a reduction in mortality in post-myocardial infarction patients. (3) Studies with simvastatin 80 mg showed little incremental benefit and greater adverse effects, so this dose is not currently recommended (31, 32) and the trend has been towards its replacement due to the limitations in decreasing LDL beyond 45 % vs. 55% achieved with rosuvastatin 40 mg or 49% achieved with atorvastatin 80 mg. (33) In a recent analysis of the Epi-Cardio Registry on discharge indications following an ACS in 22,905 patients, Travetto et al. observed a progressive reduction in simvastatin indication from 44.5% in 2005-2006 to 10.8% in 2014, at the expense of increased use of atorvastatin and rosuvastatin. (34)

The use of ezetimibe reported in our survey was low, as in the work of Travetto et al. where it was used in less than 1% of patients. (34) However, the response to the clinical case reflected other complex aspects of medical performance, since the scenario of a patient who achieved acceptable levels of LDL cholesterol with atorvastatin/ezetimibe 20/10 mg at 6 months of an ACS motivated the change of treatment to 80 mg atorvastatin in only one third of respondents. The conduct on this clinical scenario is not contemplated by the latest guidelines, so the response should be contextualized within medical practice where optimizing adherence to medication is complex and changing drugs having achieved desired therapeutic targets requires posing this conduct change to the patient.

Regarding monitoring of adverse effects, the SAC consensus does not establish its periodicity except in children and adolescents, noting that overestimating the risk of treatment with statins is one of the limitations for its use. (17) In the same sense, international guidelines do not recommend routine monitoring with liver enzymes and CPK levels in the absence of justifiable symptoms. (18, 23) In spite of the recommendations and the low frequency of serious adverse effects with the use of statins (35), routine monitoring among respondents was a common practice, perhaps reflecting the penetration of the subject in the society and the media. There is recent evidence that fear of statin adverse effects decreases the adherence of physicians and patients, increasing cases of myocardial infarction and cardiovascular mortality. (36)

Despite the extensive information collected by the survey, our study has the following limitations:

- It was not a randomized sample study, limiting the external validity of the results by provoking a selection bias, with overrepresentation of cardiologists and male gender.
- Part of the questionnaire was developed with clinical cases which, according to the authors, reflect controversial scenarios of the usual practice. It was not intended to assess the knowledge on the subject but to investigate the attitudes adopted by physicians in hypothetical cases. Although we do not perceive induction biases in the responses, they cannot be excluded.
- The barriers in the use of high doses were not inquired, which would explain the gap observed between the general agreement on their efficacy and the reported dose, One could be their high cost compared to other treatments as for example antihypertensive drugs. Thirty-six per cent of the Argentine population has only coverage by the public health system (37) that distributes drugs through the RemediAR program. This program only includes simvastatin 20 mg in its vademecum, (38) a factor that could motivate its high prescription on secondary prevention and, consequently, the low use of high doses. In the study by Travetto et al. the use of simvastatin was significantly higher

in public hospitals. (34)
- The percentage of physicians pursuing LDL targets was not inquired, as recommended by the ATP III and SAC consensuses. (16, 17)
- Finally, we omitted to ask the frequency in which physicians determine C-reactive protein levels as a tool to guide treatment, as proposed in the JUPITER study. (39) However, this conduct is not recommended by the guidelines due to recent evidence disregarding its role as a cardiovascular risk factor and its usefulness to stratify patients. (40, 41)
- Data from our study were collected prior to publication from the ACC Expert Decision Consensus on the Role of Non-statin Therapies for LDL-Cholesterol Lowering in the Management of Atherosclerotic Cardiovascular Disease Risk and the new ESC guideline. (22, 23) It is therefore likely that these new recommendations could generate a current change in the answers to questions 8 and 16.

CONCLUSIONS

We can conclude that there are numerous controversial areas in the practical application of the information provided by controlled trials and guideline recommendations. Our survey provides relevant data on specific clinical scenarios and conducts regarding the use of statins in a sample of physicians from Argentina. It is the responsibility of the scientific societies and the State to discuss this information to develop strategies to optimize their use in order to improve the health of our population.

Conflicts of interest

None declared. (See authors' conflicts of interest forms in the website/Supplementary material).

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