ORIGINAL ARTICLE

Use of Lipid-Lowering Agents and Therapeutic Goal Achievement in Cardiovascular High- Risk Patients in Argentina

Uso de agentes hipolipemiantes y cumplimiento de metas terapéuticas en pacientes de alto riesgo cardiovascular en la República Argentina

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ABSTRACT

Background: The correct management of lipid-lowering treatment is one of the key factors for the reduction of cardiovascular risk in secondary prevention patients. High-dose statins, ezetimibe, and more recently PCSK9 inhibitors (PCSK9i) are the main tools available to meet LDL cholesterol (LDL-C) therapeutic goals in these patients. Despite the overwhelming evidence in their favor, these therapies are greatly underutilized worldwide, with low levels of adherence and therapeutic inertia. In Argentina, there is scarce evidence on the quality of lipid-lowering treatment and the rate of patients in secondary prevention with a controlled lipid profile according to national and international guidelines.
Methods: A prospective, multicenter, cross-sectional study including consecutive patients in secondary prevention for cardiovascular events from hospitals of Argentina with a Medical Residency system affiliated to Argentine Council of Cardiology Residents (CONAREC), was carried out from March to August 2020. Data was collected on the lipid-lowering treatment received, the reasons behind the non-use of statins in adequate doses and the lipid profile levels in case of having a record from the last 6 months prior to inclusion.
Results: Among 1000 consecutive patients included from 24 centers corresponding to 11 provinces, 85.9% was treated with statins, 4.8% with ezetimibe, 2.4% with fibrates, and 13% was without treatment. In the case of patients treated with statin therapy, 67% was receiving high-dose statins (58% of the total number of patients). A total of 509 patients presented LDL-C assessment within the last 6 months. Mean LDL-C was 94 (90.6-97.8) mg/dL, HDL cholesterol 41 (40.7-42.6) mg/dL and triglycerides 151 (142.9-159.8) mg/ dL. In 30% of cases, LDL-C was below the cut-off value of 70 mg/ dL and in 16% below 55 mg/ dL. In 37% of patients, LDL-C was >100 mg/ dL .
Conclusions: In this multicenter secondary prevention study performed in Argentina, just over half of the patients presented high-dose statin treatment, with scarce use of ezetimibe. Undertreatment was reflected in LDL-C values, with more than two-thirds of patients outside the therapeutic range, and therefore far from clinical guideline recommendations.

Key words: Lipids – Prevention – Statins - Hydroxymethylglutaryl-CoA Reductase Inhibitors/ therapeutic use

RESUMEN

Introducción: Uno de los pilares fundamentales para la reducción del riesgo cardiovascular en pacientes en prevención secundaria es el correcto manejo del tratamiento hipolipemiante. Las estatinas en altas dosis, el ezetimibe, y más recientemente los inhibidores de PCSK9 (iPCSK9) son las principales herramientas farmacológicas con las que contamos para que estos pacientes cumplan metas terapéuticas de colesterol LDL. A pesar de la contundente evidencia a favor de estas terapéuticas, existe una gran subutilización de las mismas a nivel mundial, con bajos niveles de adherencia e inercia terapéutica. En Argentina existe escasa evidencia sobre la calidad del tratamiento hipolipemiante, y qué porcentaje de pacientes en prevención secundaria se encuentran con un perfil lipídico controlado acorde a guías nacionales e internacionales.
Materiales y métodos: Diseñamos un estudio de corte transversal en pacientes en prevención secundaria de eventos cardiovasculares incluídos de forma prospectiva, consecutiva y multicéntrica en hospitales de la República Argentina que poseen sistema de Residencia Médica afiliados a CONAREC. Se realizó la recolección de datos durante los meses de Marzo a Agosto del año 2020. Se relevó el tratamiento hipolipemiante que recibían, los motivos detrás de la no utilización de estatinas en dosis adecuadas, y los valores de perfil lipídico en caso de contar con un registro en los últimos 6 meses previos a la inclusión.
Resultados: Se incluyeron 1.000 pacientes consecutivos de 24 centros, correspondientes a 11 provincias. Un 85,9% se encontraba bajo tratamiento con estatinas, 4,8% con ezetimibe, 2,4% con fibratos, y 13% sin tratamiento. De aquellos pacientes en tratamiento con estatinas, un 67% recibía estatinas en altas dosis (58% del total de pacientes). Un total de 509 pacientes presentaban medición del LDL dentro de los últimos 6 meses. El valor promedio de LDL fue de 94 (90,6 – 97,8) mg/ dL , el de HDL 41 (40,7 – 42,6) mg/ dL, y el de triglicéridos 151 (142,9 – 159,8) mg/ dL . Un 30% se encontraba con valores por debajo del corte de 70 mg/ dL . Un 16% se encontraba con valores por debajo de 55 mg/ dL . Un 37% de los pacientes presentaba LDL >100 mg/ dL .
Conclusiones: En este estudio multicéntrico de pacientes en prevención secundaria desarrollado en la República Argentina, poco más de la mitad presentaba tratamiento con estatinas en altas dosis, con una escasa utilización de ezetimibe. El subtratamiento se reflejó en los valores de LDL, con más de dos tercios de los pacientes fuera de rango terapéutico, y por lo tanto lejos de las recomendaciones de las guías clínicas.

Palabras clave: Lipidos - Prevención - Estatinas - Inhibidores de Hidroximetilglutaril-CoA Reductasas

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INTRODUCTION

Patients in secondary prevention of cardiovascular events present high risk of suffering a new event (above 10% at 10 years). (1) It is known that among high-risk markers, elevated LDL cholesterol (LDL-C) directly increases risk, and hence represents one of the main therapeutic goals. (2)

Lipid-lowering agents are key factors of cardiovascular risk reduction in secondary prevention, and hydroxymethylglutaryl-CoA reductase inhibitors, commonly known as statins, are their main prototype, having shown significant reduction of major cardiovascular events. (3) Moreover, high-intensity statin treatment is still more effective in decreasing event occurrence. (4)

Recently, PCSK9 inhibitors (PCSK9i) have generated a new paradigm shift in lipid-lowering treatment, decreasing even more cardiovascular risk by reducing mean LDL-C to up to 30 mg/ dL in patients with statin treatment. (5) This evidence has led national and international guidelines to recommend the use of high-intensity statins in secondary prevention patients, establishing the therapeutic goals, but insisting that the greater the LDL-C reduction the greater the cardiovascular risk reduction. (1, 6)

Despite abundant evidence in favor of lipid-lowering treatment, there is frequent scant or inadequate indication of these agents (therapeutic inertia), preventing the achievement of therapeutic LDL-C goals recommended by clinical practice guidelines.

The primary objective of the present nationwide review was to evaluate the state of lipid-lowering treatment in cardiovascular high-risk patients in Argentina, the attainment of therapeutic goals and the potential indication of PCSK9i therapy.

METHODS

Study design:

A multicenter, cross-sectional study of patients prospectively and consecutively included in hospitals of Argentina with a Medical Residency system affiliated to the Argentine Council of Cardiology Residents (CONAREC) was carried out from March to August 2020

Primary objectives:

1) To assess the number of cardiovascular high-risk patients on a secondary prevention strategy that receive statins or other lipid-lowering therapies, and at what doses.
2) To evaluate the reason why patients do not receive or adequately receive a lipid-lowering treatment.
3) To assess the number of patients meeting the LDL-C therapeutic goals established by the 2018 Argentine Society of Cardiology Guideline and the 2019 European Society of Cardiology (ESC) Dyslipidemia Guideline.
4) To assess the number of cardiovascular high-risk patients that would be candidates to receive PCSK9i therapy for not fulfilling the LDL-C therapeutic goals despite the best tolerated treatment.

Objectives 1) and 2) were evaluated in the total study population (n=1000), while objectives 3) and 4) were analyzed in the population who had an LDL-C profile (n=509).

Population

Inclusion criteria:

Patients >18 years, accepting voluntary participation, and in secondary prevention for at least one of the following cardiovascular events:

- Acute coronary syndrome: Unstable angina, non-ST-segment elevation acute myocardial infarction (NSTEMI) and ST-segment elevation acute myocardial infarction (STEMI)
- Chronic stable angina with functional test [single-photon emission computed tomography (SPECT), ergometry, or echo-stress] evidencing ischemia
- Prior surgical or percutaneous coronary revascularization procedure
- Presence of severe non-revascularized epicardial coronary lesions by invasive (coronary angiography) or non-invasive [computed tomography (TC) or nuclear magnetic resonance (NMR)] study
- Ischemic stroke or transient ischemic attack (TIA)
- Symptomatic lower limb peripheral vascular disease due to intermittent claudication or revascularization
- Carotid stenosis >70% or prior carotid surgical or percutaneous revascularization.

Implementation

- Patient source and data collection: Hospitalized or ambulatory patient inclusion was carried out through a personal interview or self- or hetero-administered questionnaire. Data was loaded on-line by means of a specially designed electronic questionnaire (SurveyMonkey) with exclusive access through an individual password, and immediately and automatically incorporated into the central database.
- LDL-C goals: Achievement of LDL-C therapeutic goals was performed on patients that had an LDL-C, HDL-C and triglyceride lab assessment in the last 6 months.

Endpoints

1. The prevalence of types and doses of pharmacological lipid-lowering treatments was evaluated for the first objective.
2. For the second objective, inadequate treatment was defined when the patient in secondary prevention did not receive high dose statins (atorvastatin 40 or 80 mg or rosuvastatin 20 or 40 mg). The reasons considered for not receiving lipid-lowering treatment were: patient decision, costs, adverse effects, aversion to take medication, treating physician decision, and other.
3. The following goals were used for the third objective:
   - LDL-C goal according to the 2019 ESC Dyslipidemia Guideline
     i. Secondary prevention: <55 mg/dl
     ii. Second vascular event in 2 years: <40 mg/dl
   - LDL-C goal according to the 2018 Argentine Society of Cardiology position document on the appropriate use of statins (7): <70 mg/dl
4. To define the potential indication of PCSK9i according to the 2017 Argentine Society of Cardiology position document, (8) the following criteria has to be met: LDL >100 mg/dl despite high-intensity statin therapy at maximum doses (atorvastatin 40 or 80 mg, rosuvastatin 20 or 40 mg) + ezetimibe, or failure to receive adequate statin doses due to intolerance for adverse effects.

Statistical analysis

Continuous variables are expressed as mean and standard

deviation or median and interquartile range, according to their distribution, and their normality was assessed using graphical tools (histograms, normal distribution charts, etc.) and the Shapiro-Wilk test or the Kolmogorov-Smirnov test, as appropriate. Categorical variables are expressed as number and percentages and were compared using the chi-square test.

During the phase of study design, it was decided to recruit 1000 patients to obtain acceptably narrow 95% confidence intervals (95% CI).

Ethical considerations

The study was evaluated by the Ethics Committee of each center that included patients in the registry and was performed in accordance to national and international regulations on the protection of research in human subjects, such as the Declaration of Helsinki, Resolution 1480/2011 of the National Ministry of Health, CABA law 3301 (if applicable) and ANMAT 6677/10 resolution and its 4008 and 4009 modifications.

In accordance with the personal data protection law N° 25 326, the data obtained was treated confidentially and suitably examined by the Research Ethics Committee of each participating center entering patients in the registry. These registries will always be kept confidentially.

RESULTS

The study included 1000 patients from 24 centers in CABA and 11 provinces: 35.5% were from the province of Buenos Aires, 29.5% from CABA, 8.8% from Santa Fe, 6.8% from Corrientes, 6.4% from Mendoza, 5% from Chaco, 2.7% from Río Negro, 1.3% from Santiago del Estero, 1.2% from Córdoba and Jujuy, 1% from Formosa and 0.6% from Neuquén (Supplementary Figure 1). The supplementary material shows the participating centers (Supplementary material Table 2) and the sub-investigators of each center.

Among the total population, 756 (75.6%) were men, and mean age was 68±12.6 years. Table 1 shows the characteristics of the study population, with hypertension as the most prevalent comorbidity (80%), followed by dyslipidemia (55.6%) and diabetes (33.7%). Definitions of risk factors can be found in the supplementary material. The same table shows the frequency of the criteria that allowed inclusion in this registry. Most participants were revascularized (42%), either by coronary artery bypass grafting (CABG) or percutaneous coronary intervention (PCI). Similar percentages of patients with unstable angina, NSTEMI and STEMI (21.7%, 21.5% and 21.7%, respectively) were included in the study. In 81% of cases, patients were admitted for at least one event corresponding to ischemic heart disease.

Regarding lipid-lowering treatments, 85.9% were receiving statins, 4.8% were treated with ezetimibe, 2.4% with fibrates, and 13% were not receiving treatment at the time of inclusion. Among patients who were under statin treatment, 67% were receiving high doses (58% of all patients), with atorvastatin 40-80 mg/day as the most used agent (Table 2), which was also the most widely used statin in these patients, followed by rosuvastatin and simvastatin.

LDL-C Goals:

Information on the lipid profile was obtained in 50.9% of participants (n=509). Mean lipid levels can be seen in Figure 1. Mean LDL-C in this group of patients was 94.2 mg/dL (95% CI 90.6-97.8).

Regarding general achievement of LDL-C goals, 30% of patients attained them following SAC guideline and 16% ESC guideline recommendations (Figure 2). According to the indication of high vs. non-high dose statins, SAC goals were met by 40.6% vs. 24.6% of patients (p <0.001) and ESC goals by 20.5% vs. 13% (p=0.03). No differences were found in the fulfillment of SAC or ESC guideline therapeutic goals according to the inclusion diagnosis in the registry, either in the type of ACS (unstable angina, STEMI, NSTEMI) or

Table 1. Baseline characteristics

	%
Age, years (mean±SD)	68.09±12.6)
Male gender	75.6%
HTN	80%
Dyslipidemia	55.6%
Non-IR type II diabetes	24.3%
IR type II diabetes	9.4%
Sedentary lifestyle	56.1%
Overweight	52.4%
Smoking	20.5%
Former smoking	39.9%
Unstable angina	21.7%
NSTEMI	21.5%
STEMI	21.7%
CSA	7%
Revascularization	42.1%
Stroke/TIA	10.8%
PVD	16.1%
Carotid stenosis	5%

SD: Standard deviation. HTN: Hypertension. IR: Insulin resistance. NSTEMI: Non-ST-segment elevation acute myocardial infarction. STEMI: ST-segment-elevation acute myocardial infarction. CSA: Chronic stable angina. TIA: Transient ischemic attack. PVD: Peripheral vascular disease.

Table 2. Statin doses used

	5 mg	10 mg	20 mg	40 mg	80 mg
Atorvastatin (n=469)	0.4%	8.5%	25.1%	52%	14%
Rosuvastatin (n=368)	1.6%	24.7%	40.5%	33.2%	-
Simvastatin (n=23)	4.3%	47.8%	39.1%	8.8%	-

other diagnoses of vascular disease (chronic stable angina, stroke/TIA, peripheral vascular disease, or carotid artery disease). Only 5% of patients who suffered 2 or more events in the last 2 years (n=83), met the ESC goal of LDL-C <40mg/dL.

Thirty-seven percent of patients had LDL-C >100 mg/dL, making them potential candidates for PCSK9i, indication. In this group, 38% of cases were under treatment with high-dose statins, and 3% were also receiving a combination with ezetimibe. This means that 3% of the patients evaluated would meet the criteria to receive PCSK9i according to the SAC position document on the use of PCSK9i. Regarding the remaining 62% of patients, 14% were undermedicated (that is, without high-dose statins) due to adverse effects, mainly myopathies, and the remaining 48% was divided between lack of indication from their treating physician, refusal to take the medication, fear of statin adverse effects, and having run out of prescription and not requesting its renewal.

DISCUSSION

In our national multicenter registry, just over half of 1000 patients in secondary prevention of cardiovascular events were on high-dose statins, and these were associated with ezetimibe in a very low percentage of cases. Mean LDL-C in the subgroup of patients in whom this data was available was above any therapeutic goal recommended by clinical practice guidelines. In line with these findings, only 30% of patients were meeting therapeutic goals according to the Argentine Society of Cardiology clinical practice guideline (LDL-C <70 mg/dl), and only 16% according to the European Society of Cardiology guideline (LDL-C <55 mg/

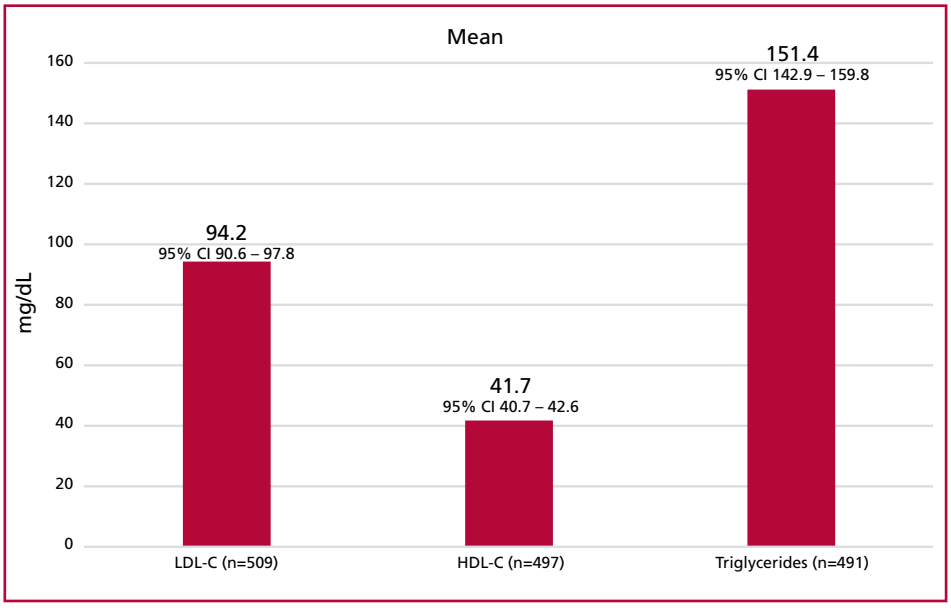

Fig. 1. Lipid values (n=509)

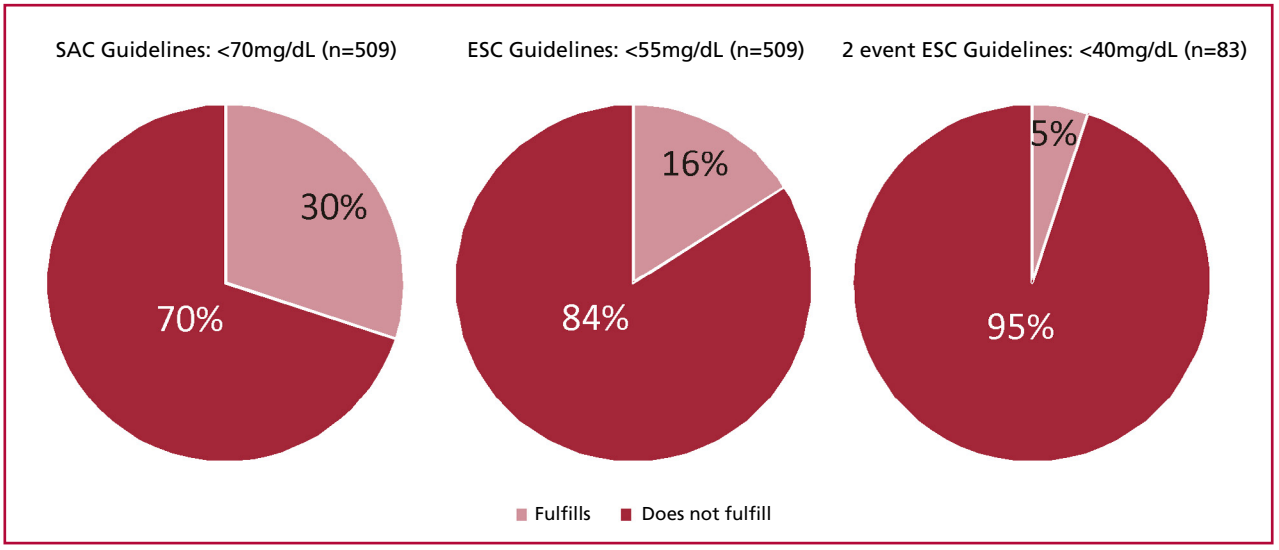

Fig. 2. Achievement of therapeutic goals according to guidelines

dl). Achievement of therapeutic goals was higher in patients medicated with high-dose statins.

Additionally, 37% of patients had LDL-C values above 100 mg/dl, although a small percentage was under maximum treatment with statins associated with ezetimibe. This subgroup of patients would therefore be candidates to receive PCSK9i to improve LDL-C levels.

Cardiovascular disease (CVD) has been recognized as the leading cause of death in the United States and in the rest of the world for decades. Although CVD deaths decreased by 31% between 2001 and 2011 in the United States, CVD still accounts for one in three deaths (7).

Lipid-lowering treatment plays a critical role in the prognosis of patients in secondary prevention. However, proper management of LDL-C levels constitutes the great challenge of prevention in high-risk patients.

For a long time, there has been evidence that high cholesterol levels and cardiovascular mortality have a direct relationship with the development of coronary heart disease, and that, conversely, lowering LDL-C levels directly reduces risk (2). In the 4S study (1994), a decrease of 30% mortality was observed at a 5.4-year follow-up when the administration of simvastatin in patients with AMI or coronary heart disease was compared with placebo (9). Two years later, the CARE study (1996) was published, showing a significant 24% reduction in the primary endpoint of coronary death or reinfarction in AMI patients (10), using pravastatin 40 mg. The IMPROVE-IT study demonstrated that in post-AMI patients, the addition of ezetimibe 40 mg to simvastatin produced an even greater reduction in LDL-C, and was consequently accompanied by a decrease in the risk of cardiovascular events (11). After the publication of numerous large-scale randomized clinical trials, the meta-analysis carried out by the CTT group (4) showed that for every 38.6 mg/dL decrease in LDL-C levels, there is 22% reduction in the rate of major cardiovascular events, 23% in that of coronary events, 20% in death of coronary origin, and 10% in total mortality. The use of high-dose statins was also shown to be superior, as observed in the PROVE-IT study, which demonstrated that 80 mg compared with 40 mg atorvastatin reduced the risk of major cardiovascular events by 16% (12), or the TNT study, that showed 22% reduction in the risk of events when comparing atorvastatin 80 mg vs. 10 mg (13). This was confirmed again with the CTT meta-analysis (4), showing that the use of high-dose statins produces 15% reduction in the risk of major cardiovascular events compared with lower-intensity statins.

The emergence of PCSK9i has deepened the concept that the greater the LDL-C reduction, the greater the risk reduction. These drugs significantly decrease LDL-C levels, and even have greater effect in patients under treatment with statins, since the latter increase the expression of circulating PCSK9. In patients with maximum tolerated statin dose, PCSK9i reduce LDL-C between 40% and 70% more compared with placebo, and 30% more compared with ezetimibe (14). Moreover, there is high methodological quality evidence that PCSK9i reduce the incidence of cardiovascular events. In the FOURIER study, more than 27 000 patients with cardiovascular disease, LDL-C >70 mg/dl, and statin treatment, were randomized to receive evolocumab or placebo. Mean LDL-C level decreased from a baseline value of 92 mg/dl to 30 mg/dl, and the risk of a composite cardiovascular event including cardiovascular death, AMI, stroke, unstable angina, and revascularizations was reduced by 15% (15). The ODDYSEY Outcomes study demonstrated a similar risk reduction with the use of alirocumab on a composite of cardiovascular death, non-fatal infarction, stroke, or unstable angina in patients with AMI or recent unstable angina, (16).

Since there is so much evidence that lowering LDL-C is extremely beneficial for reducing cardiovascular risk in secondary prevention patients, both national and international clinical practice guidelines propose different therapeutic goals, which tend to be increasingly ambitious, aiming at the use of high-intensity statins on a sustained basis. Thus, the Argentine Society of Cardiology proposed in 2018 a target value for patients in secondary prevention of 70 mg/dl (7). In contrast, a year later, the ESC proposed a goal of 55 mg/dl, and even a lower target of 40 mg/dl in patients with two or more events in two years (1). Regarding the use of PCSK9i, given its high cost, we sought to identify a group of patients at higher risk, who would benefit the most from these drugs, and thus improve the cost/benefit balance. Therefore, its indication is recommended in patients in secondary prevention who have an LDL-C level >100 mg/dl with a maximum tolerated statin dose in combination with ezetimibe, or with clearly documented intolerance (8).

However, despite the abundant evidence and international demanding guidelines, lipid-lowering therapy generally does not meet these high standards. A 2008 study of 15 000 patients performed in the United States showed that non-adherence to statins was 26%, and that non-adherent patients had a higher risk of total and cardiovascular mortality (17). Another 2013 study from the United States sought to assess the causes behind statin non-adherence. After a multivariate analysis, the most related variables were myalgia, not having health insurance, and interestingly, the internet search of patients and poor communication with the treating physician (18). The well-known "nocebo" effect has an extremely high impact on statin adherence. The popularization of the information that statins cause myalgia caused a sharp increase in the report of this adverse effect, being up to 15% in different series, whereas in randomized, double-blind trials, such as the HOPE-3 study, the incidence barely exceeded 5%, only 1% higher than in the placebo group (19). Another initially reported adverse effect is

cognitive impairment due to an excessive decrease in LDL-C (20). However, the EBBINGHAUS study (21) did not demonstrate a higher incidence of neurocognitive events, using the CANTAB survey in patients receiving PCSK9i treatment, and a Cochrane meta-analysis reached the same conclusion in patients with statins (22).

Regarding the limitations of our study, we can mention that only patients from centers with a cardiology residency system affiliated to CONAREC were incorporated, which may generate a bias when analyzing the data. Most of the patients included in the study were admitted to a coronary care unit, and although patients in the outpatient setting were also included, this may affect the external validity of the results. Another possible limitation is that the recruitment of patients was carried out during months in which there was a pandemic in Argentina and worldwide, which may have changed the characteristics of access to medical treatment of patients, and thus influenced the results obtained.

In conclusion, we have observed that in our country, just over half of the patients in secondary prevention were under treatment with high-dose statins. Consequently, achievement of therapeutic goals is very low, which certainly has a direct impact on the cardiovascular risk of patients.

Correct lipid-lowering treatment with high-dose statins has shown efficacy in this scenario; however, some myths about adverse effects and other associated barriers threaten the appropriate use of these agents and the attainment of recommended therapeutic goals. Therefore, we believe that it is essential to encourage the correct and sustained use of high-intensity statins and the strict control of LDL-C.

Conflicts of interest

None declared.

(See authors' conflict of interests forms on the web/Additional material.)

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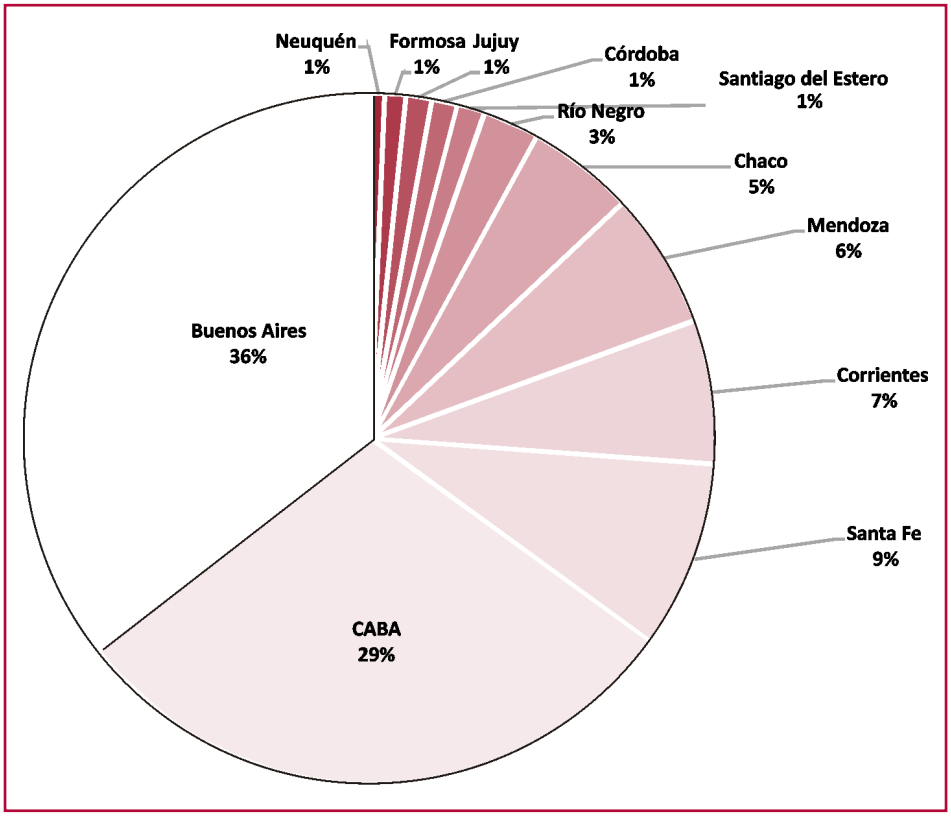
SUPPLEMENTARY MATERIAL

Variables requested in the upload form:

- Province
- City
- Center
- Name of the resident loading the data
- Date of birth
- Gender
- Medical coverage
- Cardiovascular risk factors
- Hypertension
- Diabetes
- Dyslipidemia
- Active or former smoker
- Sedentary lifestyle
- Obesity
- Family history of early cardiovascular disease (Men under 55, women under 65)
- Inclusion criteria
- Select which of the following criteria are met
- When did you have the event:
- In the last year
- In the last 2 years
- More than 2 years ago
- Have you had more than one vascular event in the last 2 years?
- Treatment:
- Statins, fibrates, ezetimibe, PCSK9i, OMEGA 3 fatty acids, niacin, other.
- Dose and weekly frequency
- Last LDL-C value with the current treatment and assessment date
- If you are not on high-dose statins and/or ezetimibe:
- Reason: suspension by own decision (costs, adverse effects, aversion to medication), prescription by general practitioner, suspension by general practitioner, never indicated, other

Supplementary Figure 1. Participating Provinces



Definitions:

Cardiovascular risk factors:

- Hypertension (HTN): Self-referential: Baseline office blood pressure values >140/90 mmHg (130/80 mmHg in diabetic and chronic kidney failure patients), or patients under antihypertensive treatment. Values >135/85 mmHg obtained by Ambulatory Blood Pressure Monitoring (ABPM) or Home Blood Pressure Monitoring (HBPM). Patients receiving antihypertensive medication.
- Diabetes (DBT): According to the diagnostic criteria of the American Diabetes Society. Fasting blood glucose >126 mg%, oral glucose tolerance test (OGTT) >200 mg% at 2 h, or random blood glucose test >200 mg% prior to the event. Patients receiving treatment with hypoglycemic drugs or insulin. Self-referential.
- Type I: Autoimmune destruction of islets of Langerhans beta cells. Absolute insulin deficiency.
- Type II: Insulin resistance, in treatment with oral or injectable non-insulin hypoglycemic agents.

Supplementary Table 1. Number of patients according to coverage

	n	%
IOMA	260	26.0
PAMI	137	13.7
OSDE	112	11.2
GALENO	96	9.6
Other	54	5.4
IAPOS	40	4.0
No coverage	26	2.6
IOSFA	25	2.5
SMG	24	2.4
Public Health System	24	2.4
IOSCOR	23	2.3
INSSSEP	21	2.1
OSECAC	20	2.0
MEDICUS	19	1.9
OSEP (Mendoza)	16	1.6
OMINT	15	1.5
PROFE	14	1.4
UP	10	1.0
OSPE	9	.9
OSSEG	8	.8
MEDIFE	6	.6
APROSS (Córdoba)	6	.6
IPROSS	6	.6
OSDEPYM	5	.5
AMEBPBA	5	.5
FEMEBA	4	.4
H. Británico	3	.3
SANCOR	3	.3
FEMECHACO	3	.3
ISNN (Neuquén)	2	.2
Luis Pasteur	2	.2
CEMIC	1	.1
W. Hope	1	.1
Total	1000	100.0

Supplementary Table 2. Participating centers

Center	n	%
Hospital Italiano de La Plata (PBA)	313	31.3
ICBA (CABA)	197	19.7
Sanatorio Mitre (CABA)	77	7.7
Instituto de Cardiología Juana Francisca Cabral (Corrientes)	68	6.8
Sanatorio Güemes (Chaco)	50	5.0
Hospital Italiano de Mendoza	40	4.0
San Gerónimo (Santa Fe)	34	3.4
Sanatorio Británico (Rosario)	32	3.2
Fundación Médica de Río Negro y Neuquén	28	2.8
Hospital José María Cullen (Santa Fe)	21	2.1
Clínica IMA (PBA)	18	1.8
Hospital Español de Mendoza	16	1.6
Presidente Perón de Avellaneda (PBA)	15	1.5
Clínica Yunes (Santiago del Estero)	13	1.3
Clínica Vélez Sarsfield (Córdoba)	12	1.2
Sanatorio Nuestra Señora del Rosario (Jujuy)	12	1.2
Sanatorio Finochietto (CABA)	12	1.2
Hospital Naval (CABA)	11	1.1
Hospital de Alta Complejidad Juan Domingo Perón (Formosa)	10	1.0
Hospital Lagomaggiore (Mendoza)	7	.7
Higa Penna de Bahía Blanca (PBA)	7	.7
Hospital Castro Rendón (Neuquén)	5	.5
Hospital El Carmen	1	.1
Sanatorio Mayo (Córdoba)	1	.1
Total	1000	100.0

- Type II Insulin dependence: Same as type II, but requires insulin treatment.
- Tobacco smoking (TS): Regular or occasional tobacco use within the last year.
- Ex-tobacco smoking (ExTS): Absence of tobacco consumption for a period equal to or greater than one year, having previously been a smoker.
- Dyslipidemia (DLP): Total cholesterol >200 mg/dL, LDL-C >160 mg/dL, or HDL-C <40mg/dL in men and <48 mg/dL in women.
- Obesity (OBS): body mass index ≥30.
- Family history of early cardiovascular disease (FH): History of cardiovascular event in direct relatives under 55 years of age in men, and 65 years of age in women.
- Sedentary lifestyle: Performance of less than 150 minutes of physical activity per week.

Inclusion criteria

- Stable angina: Anginal pain that did not modify its characteristics in terms of pain intensity and triggering stimuli in the last 3 months.
- Unstable angina: Myocardial ischemia at rest or on exertion, manifested as angina or anginal equivalents, without identifiable biomarkers of myocardial damage in blood tests.
- Non-ST-segment elevation acute myocardial infarction: Myocardial ischemia at rest or on exertion, manifested as angina or anginal equivalents, with identifiable biomarkers of myocardial damage in blood tests. No persistent ST-segment elevation.
- ST-segment elevation acute myocardial infarction: Myocardial ischemia at rest or on exertion, manifested as angina or anginal equivalents, with persistent ST-segment elevation.
- Previous coronary artery revascularization: Programmed or urgent balloon or stent PCI. Surgical revascularization by venous or arterial coronary artery bypass grafting.
- Presence of non-revascularized severe epicardial coronary lesions, identified by invasive study (coronary angiography) or non-invasive study (CT or NMR); ≥70% obstruction, except in left main coronary artery where the obstruction must be >50%.
- Ischemic stroke: Focal cerebral ischemia associated with permanent brain infarction, with or without motor or sensory neurological sequelae.

Supplementary Table 3. Average LDL-C levels according to medical coverage

Medical Coverage	Average LDL-C (mg/dl)	Average HDL-C (mg/dl)	Average Triglycerides (mg/dl)
OSDE (n=62)	82.36	38.36	126.77
PAMI (n=65)	89.03	39.29	142.17
IOMA (n=178)	91.79	42.63	160.83
IOSFA (n=4)	120.25	47.00	189.50
GALENO (n=83)	100.24	44.05	123.51
SMG (n=16)	94.44	43.21	137.25
CEMIC (n=1)	70.00	40.00	200.00
IAPOS (n=5)	106.40	41.20	190.00
APROSS (Córdoba) (n=3)	115.33	38.00	226.00
IOSCOR (n=5)	75.00	42.50	139.50
MEDICUS (n=8)	80.25	45.13	150.38
W. Hope (n=1)	71.00	41.00	192.00
OMINT (n=8)	87.25	43.63	112.14
OSECAC (n=13)	96.70	39.38	183.54
OSEP (Mendoza) (n=11)	94.96	42.94	179.40
OSPE (n=8)	94.20	47.88	151.13
PROFE (n=4)	109.00	31.75	210.75
SANCOR (n=1)	140.00	60.00	127.00
Public Health System (n=13)	120.85	36.54	212.62
Unión Personal (n=5)	93.66	46.40	132.20
OSSEG (n=5)	75.68	35.75	188.25
AMEBPBA (n=4)	85.55	35.75	246.25
FEMEBA (n=4)	65.85	41.20	103.00
No coverage (n=20)	97.71	37.33	160.88

Supplementary Table 4. Achievement of LDL-C therapeutic goals according to medical coverage (Medical coverage represented by at least 50 participants are included)

Medical Coverage	SAC Meta guideline (LDL-C <70mg/dL)	ESC Meta guideline (LDL-C <55 mg/dL)
OSDE	45%	29%
PAMI	39%	15%
IOMA	31%	19%
GALENO	26%	13%

- TIA: Transient ischemic attack. Abrupt focal neurological deficit lasting less than 24 hours, without physical sequelae or imaging studies.
- Symptomatic peripheral vascular disease: Partial (greater than 70%) or total obstruction of any lower limb artery, including primitive iliac arteries, by cholesterol plaques which generate symptoms of intermittent claudication.
- Intermittent claudication: Muscle pain or cramps in lower limb muscles produced when walking, and decreasing with rest.
- Carotid stenosis: Right or left internal carotid lumen obstruction >70% by cholesterol plaque.

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- ICBA: Federico Weckesser
- Sanatorio Mitre: Sebastián Mrad
- Juana Cabral: Marilín Traviesa, Diego Picchio
- Sanatorio Guemes (Chaco): Juan Roa
- Hospital Italiano Mendoza: Ludmila Morcos, Andres Nadal
- San Gerónimo: Fiama Caimi
- Sanatorio Británico Rosario: Julieta Cocco
- Fundación Médica de Río Negro y Neuquén: María Lara Vitulich, Celeste Zanoni
- Clínica IMA: Diego Novielli
- Hospital Español de Mendoza: Marcia Zuloaga
- Presidente Perón (Avellaneda): Rodrigo Ocampos
- Hospital José María Cullen: Mariana Salcerini
- Clínica Yunes: Fernando Orellana
- Clínica Vélez Sarsfield: Macarena Grassi
- Sanatorio Nuestra señora del Rosario: Rosana Carolina Benitez
- Sanatorio Finochietto: Melissa Antonioli
- Hospital Naval: Lucas Campana
- Hospital de alta complejidad juan domingo perón de Formosa: Cesar Villalba
- Hospital Lagomaggiore: Belen Barrionuevo
- HIGA Penna de Bahía Blanca: Daiana Alzogaray
- Hospital Castro Rendón: Ruben Catacata
- Hospital El Carmen: Celeste Vera
- Sanatorio Mayo: Camila Ferreira Campos