ORIGINAL ARTICLE

Systematic Application of an Algorithm for Lipid Management in Cardiovascular High-Risk Patients. Impact on Lipid Goals

Aplicación sistemática de un algoritmo para el manejo lipídico en pacientes de muy alto riesgo cardiovascular. Impacto en los objetivos lipídicos

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ABSTRACT

Objective: The aim of this study was to analyze the indicated lipid-lowering therapy and verify the achievement of the recommended lipid goals during hospitalization and early follow-up, after the systematic application of a lipid management algorithm based on current recommendations.
Methods: Patients hospitalized for acute coronary syndrome or programmed revascularization surgery were prospectively included in the study. A lipid management algorithm, including; 1) early indication of high-intensity statins during hospitalization and 2) early follow-up (6 and 12-week controls), was systematically applied. The therapy indicated was based on position documents of the Argentine Society of Cardiology. Achievement of LDL-C goals (<70 mg/dl) at 6 and 12 weeks was analyzed.
Results: A total of 292 patients were prescribed statins (high-intensity in 95.9% of cases) at hospital discharge. At 6 weeks, 62.5% reached the LDL-C goal. The therapeutic plan was modified in 36.3% of patients (increased dose of statins in 19.7% and addition of ezetimibe in 67.7%). At 12 weeks, 69.1% of the subgroup which had not fulfilled the goal at 6 weeks, attained the lipid target. A PCSK9 inhibitor (PCSK9i) was indicated in 7 patients. Overall, 88.4% of patients achieved the LDL-C goal at 12 weeks.
Conclusion: Many cardiovascular high-risk patients reached LDL-C goals at 12 weeks with the systematic application of a guideline-based algorithm. The indication of a PCSK9i was reserved for a reduced group of patients.

Key words: Acute Coronary Syndrome – Angioplasty - Cardiac Surgical Procedures - Cholesterol, LDL - Algorithms

RESUMEN

Objetivo: Analizar el tratamiento hipolipemiante indicado y verificar el cumplimiento de las metas lipídicas recomendadas durante la internación y en el seguimiento precoz, luego de aplicar sistemáticamente un algoritmo para el manejo lipídico basado en las recomendaciones actuales.
Material y métodos: Se incluyeron en forma consecutiva pacientes internados con síndrome coronario agudo o revascularización programada. Se aplicó sistemáticamente un algoritmo para el manejo lipídico, que incluyó: 1) indicación precoz de estatinas de alta intensidad en la internación; 2) seguimiento precoz (controles a las 6 y 12 semanas). La terapia indicada se basó en los documentos de posición de la Sociedad Argentina de Cardiología. Se analizó el cumplimiento de las metas de C-LDL (<70 mg/dl) a las 6 y 12 semanas.
Resultados: Se incluyeron 292 pacientes. Se indicó estatinas (95,9% de alta intensidad) a todos los pacientes al alta hospitalaria. A las 6 semanas, el 62,5% alcanzó la meta de C-LDL. Se modificó el esquema terapéutico en el 36,3% de los sujetos (aumento de la dosis de estatinas: 19,7%; agregado de ezetimibe: 67,7%). A las 12 semanas, el 69,1% del subgrupo que no había alcanzado la meta a las 6 semanas logró el objetivo lipídico. Se indicó un inhibidor de la PCSK9 (iPCSK9) a 7 pacientes. Globalmente, el 88,4% alcanzó la meta de C-LDL a las 12 semanas.
Conclusión: La aplicación sistemática de un algoritmo basado en las guías determinó que muchos sujetos de alto riesgo cardiovascular alcanzaran las metas de C-LDL a las 12 semanas. La indicación de un iPCSK9 quedó reservada para un grupo reducido de pacientes.

Palabras clave: Síndrome coronario agudo – Angioplastia - Cirugía coronaria - LDL-Colesterol

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INTRODUCTION

Use of statins to reduce low-density lipoprotein cholesterol (LDL-C) and thus decrease cardiovascular events is one of the mainstays of cardiovascular prevention.

In the context of secondary prevention, evidence stemming from large randomized clinical trials with statins shows that reduced LDL-C decreases cardiovascular mortality, the incidence of acute myocardial infarction (AMI) and stroke and the need for revascularization therapy

In the last years, studies were designed to evaluate the hypothesis that a more intensive statin treatment would achieve greater benefit. Some clinical trials specifically included patients with acute coronary syndrome (ACS). (5, 6) A meta-analysis demonstrated that the application of intensive treatment with high-intensity statins compared with moderate treatment was associated with a significant reduction of major cardiovascular events. (7)

Taking into account the evidence generated during the last two decades, different practice guidelines established recommendations on lipid management, with constant updates and, occasionally, radical changes. Most current guidelines reinforce the recommendation to administer high-intensity statins during hospitalization in patients with ACS. (8-10) In addition, as use of statins during the in-hospital period improves long-term treatment adherence, this recommendation has been extended to patients hospitalized for programmed coronary or peripheral vascular revascularization. (11, 12)

Moreover, as the recommendation in high-risk patients, besides proposing a therapeutic goal suggests attaining >50% reduction in LDL-C levels, it is important to systematically assess baseline LDL-C. Hospital admission is the most adequate moment to evaluate the baseline lipid panel of a patient with ACS. (13, 14)

Another important point in lipid management after discharge is its monitoring and early treatment adjustments that should be done during the first weeks after the acute event. (9, 15) Some recently performed trials with non-statin lipid-lowering drugs [ezetimibe and proprotein convertase subtilisin/kexin type 9 inhibitors (PCSK9i)] in patients with established vascular disease showed a direct relationship between LDL-C values attained and clinical events. (16-18) Consequently, current guidelines consider that another lipid-lowering drug could be added in patients who despite full adherence to treatment under maximum tolerated statin dose do not achieve the therapeutic goals. (8, 9)

Thus, the aim of this study was to analyze the indicated lipid-lowering treatment and verify the achievement of the recommended lipid goals during hospitalization and early follow-up, after the systematic application of a lipid management algorithm based on current recommendations.

METHODS

An observational, prospective, single-center study, including consecutive patients admitted to the coronary care unit with ST-elevation or non-ST-segment elevation ACS diagnosis or with programmed coronary/peripheral revascularization (surgical or angioplasty), was performed between September 15, 2019 and January 15, 2020. Patients that could not be followed-up at our hospital were excluded from the study. Descriptive variables, cardiovascular risk factors on admission and pre- and post-hospital medication were identified.

Following training of coronary care physicians, a routine algorithm was applied for lipid management based on current recommendations. This algorithm included the following items:

1) Request an LDL-C measurement to all patients on admission or during the first 24 hours.
2) Together with reinforcement of hygienic-dietary measures, indicate, whenever possible, early high-intensity statins (atorvastatin 40-80 mg/day or rosuvastatin 20-40 mg/day) during hospitalization.
3) Request a lipid panel 6 weeks after discharge.
4) Telephone control or teleconsultation 6 weeks after discharge to evaluate the results.
5) If adherence and LDL-C >70 mg/dl were confirmed, add ezetimibe. If for any reason the patient were receiving a lower than indicated dose of statins, it is recommended to adjust the dose.
6) If treatment was modified in the first consultation, request a new lipid panel 6 weeks later (12 weeks after discharge).
7) Telephone control or teleconsultation 12 weeks after discharge to evaluate the results and consider the need to add a PCSK9i agent if LDL-C was >100 mg/dl.

The choice of a target LDL-C <70 mg/dl and a "threshold" value of LDL-C >100 mg/dl to consider PCSK9i administration was based on position documents on the adequate use of statins and PCSK9i published by the Argentine Society of Cardiology (SAC). (10, 19)

Statistical analysis

Continuous data between two groups were analyzed using Student's t test or the Mann-Whitney-Wilcoxon test, according to their distribution, and the chi-square test was used to analyze categorical data. A p value <0.05 was considered statistically significant (two-tailed tests).

A bivariate analysis was performed comparing variables among the population who achieved the LDL-C <70 mg/dl target and patients who did not fulfill this goal. A multivariate analysis was subsequently performed including variables that in the bivariate analysis evidenced a significant association. The strength of the association was expressed as odds ratio (OR) with its corresponding 95% confidence interval (95% CI).

Ethical considerations

The study protocol was approved by the institutional Ethics Committee.

RESULTS

A total of 292 patients (age 70.3±11.1 years; 81.4 % men) were included in the study. History of type 2 diabetes mellitus or prior cardiovascular disease was present in 23.9% and 52.5% of patients, respectively. Table 1 shows baseline population characteristics. Baseline

LDL-C was 103.0±37.6 mg/dl in the total population. This lipid value was significantly higher in the population untreated with lipid-lowering agents (120.4±31.8 mg/dl vs. 93.3±37.2 mg/dl, p <0.001).

In 63% of cases, patients were on statin therapy (30.1% with high-intensity statins) and 9.6% were receiving ezetimibe before hospitalization, but only 18.6% met the target LDL-C <70 mg/dl on admission.

At discharge, all patients received statin indication, which was high-intensity statins in 95.9% of cases. The most common schemes used were: rosuvastatin 40 mg (45.2%), atorvastatin 80 mg (28.4%), atorvastatin 40 mg (14.4%) and rosuvastatin 20 mg (7.9%); in 7.1% of cases, ezetimibe was added at discharge. Figure 1 shows a graphic representation of the lipid-lowering schemes used on admission and discharge.

The 6-week control showed that 62.5% of patients had reached the target LDL-C<70 mg/dl. However, only 63.5% of these patients achieved >50% decrease in their baseline LDL-C levels.

Patients who attained the LDL-C goal at 6 weeks were younger and with greater prevalence of male sex, diabetes mellitus and hypertension. In addition, baseline LDL-C level was significantly lower and prior use of high-intensity statins was significantly higher in the group of patients who achieved the LDL-C target (Table 2).

In the multivariate analysis, higher LDL-C (OR 0.97, 95% CI 0.96-0.98, p <0.001) and history of diabetes (OR 2.64, 95% CI 1.05-6.6, p=0.03) were significantly associated with lower and greater probability of achieving the lipid goal, respectively. In this control, the therapeutic plan was not modified in 63.7% of subjects. In the subgroup of patients with treatment modification, the dose of statins was decreased or increased in 12.7% and 19.6% of cases, respectively, while ezetimibe was added in 67.7% of patients.

Statin intolerance (myopathy) was very low (3.9%), and in all cases, they were myalgias without creatine-phosphokinase (CPK) elevation.

In the 12-week control, performed in the group of patients that had not reached the lipid target at 6 weeks, 69.1% of patients achieved the LDL-C goal (89.3% reduced this lipid marker by 50% or more). In this control, considering treatment compliance, the possibility or not of adjusting treatment based on statins and/or ezetimibe and the recommended threshold value, a PCSK9i was indicated in 7 patients (2.4% of the total sample).

Globally, at 12 weeks, 88.4% of all the population had met the LDL-C goal (85.9% achieved >50% reduction).

Figure 2 shows treatment variation and the lipid objectives attained at 6 and 12 weeks.

Table 1. Baseline population characteristics

Variable	N = 292
Age, years (mean ± SD)	70.3 ± 11.2
Male sex, %	81.4
Hypertension, %	68.2
Type 2 diabetes mellitus, %	23.9
Active smoker, %	20.2
Coronary heart disease, %	40.4
Peripheral vascular disease, %	16.8
Cerebrovascular disease, %	4.5
Chronic kidney failure, %	12.3
Admission diagnosis, %	
Non-ST-segment elevation ACS	34.3
ST-segment elevation ACS	13.4
Programmed percutaneous coronary intervention	21.2
Coronary artery bypass graft surgery	11.6
Peripheral vascular disease	19.5
Prior treatment %	
Aspirin	66.1
ACEI/ARBs	61.0
Betablockers	55.6
Calcium blockers	22.2
Diuretics	16.5
Statins	63.0
Ezetimibe	9.6

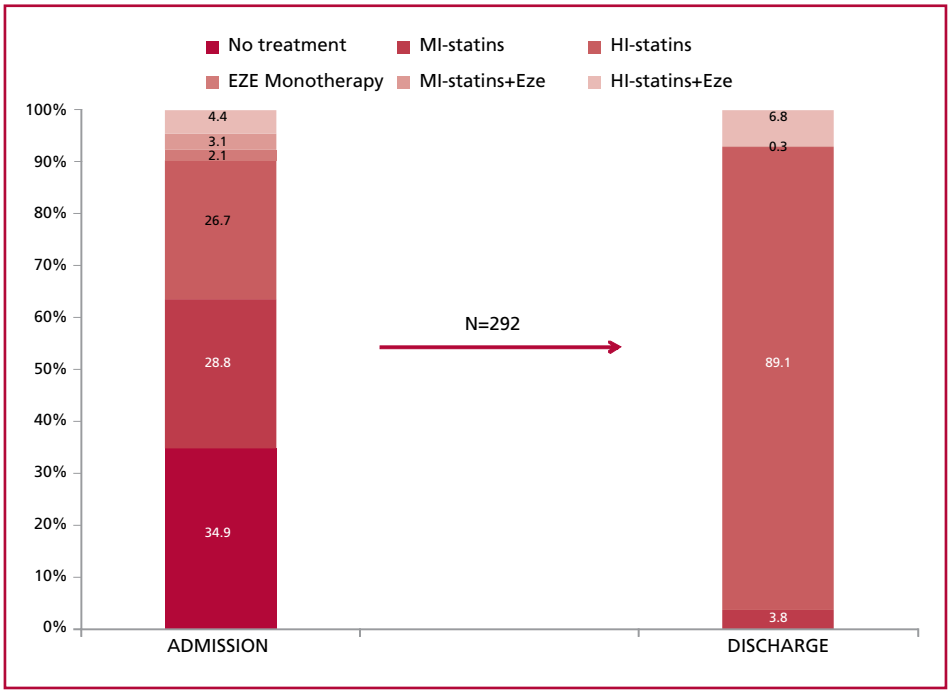
SD: Standard deviation. ACS: Acute coronary syndrome. ACEI: Angiotensin converting enzyme inhibitors. ARBs: Angiotensin II receptor blockers.

DISCUSSION

This study describes, for the first time in our country, lipid results in a population of cardiovascular high-risk patients, after systematic application of a lipid management guideline-based algorithm.

The first point contemplated by the algorithm was the administration of high-intensity statin doses during hospitalization. Current guidelines recommend this conduct based on results of several clinical trials. The MIRACL study demonstrated that use of high-intensity statins in patients hospitalized for ACS was associated with a significant reduction of adverse cardiovascular events at 16 weeks, compared with placebo. (20) In this study, statins were indicated within 24 and 96 hours of admission. The PROVE-IT and TNT studies, carried out in ACS and stable coronary artery disease patients, respectively, also showed an additional cardiovascular benefit with the administration of high-intensity statins. (5, 21) Our results revealed that 95.9% of patients were discharged with the indication of adequate statin doses. The choice of the lipid-lowering scheme was at the discretion of the treating physician.

The second point included in the algorithm was having a baseline LDL-C value, assessed within the first 24 h after admission. The relevance of this point lies in the recommendation of some guidelines to achieve 50% or more LDL-C reduction. In this sense, the REVERSAL trial showed that intense statin treatment reduced the progression of coronary artery dis-



Eze: Ezetimibe; MI: Moderate-intensity. HI: High-intensity.

Fig. 1. Lipid-lowering plan on admission and discharge.

Variable	LDL-C <70 mg/dl	LDL-C >70 mg/dl	*p*
Age, years [mean (SD)]	69.2 (11.2)	72.0 (10.7)	0.04
Baseline LDL-C, mg/dl [mean (SD)]	91.5 (32.4)	122.9 (37.8)	<0.0001
Male sex, %	84.8	74.8	0.04
Diabetes mellitus, %	28.7	16.8	0.02
Hypertension, %	75.3	57.9	0.002
Active smoker, %	16.3	26.2	0.13
Prior cardiovascular disease, %	55.1	52.3	0.65
Chronic kidney failure, %	11.8	12.2	0.93
Prior use of statins, %	64.5	62.9	0.79
Prior use of high-intensity statins, %	58.9	33.3	0.001
Prior use of ezetimibe, %	7.9	12.2	0.23

SD: Standard deviation.

Table 2. Characteristics of the population who achieved the LDL-C target at 6 weeks compared with the one who did not attain this lipid goal.

ease when LDL-C reduction reached 50%. (22) In addition, knowing the admission LDL-C value helps the diagnosis of familial hypercholesterolemia. (23)

A third point incorporated in this algorithm is early follow-up. Several authors have recommended the performance of early controls after discharge. (15, 24) This strategy allows to verify the fulfillment of lipid goals, but even more important, it allows to adjust treatment, if necessary. In our population, the application of the algorithm allowed 62.5% of patients to attain the LDL-C target at 6 weeks. Treatment intolerance due to myopathy was very low, and in all cases without CPK elevation. However, achieving an LDL-C level <70 mg/dl does not necessarily imply 50% or more decrease in this marker. The guidelines followed in this study contemplated, as criterion to modify treatment, a target LDL-C <70 mg/dl, because SAC recommendations suggest that percent LDL-C reduction is complementary to the classic lipid goal. The latest European guidelines for cholesterol management consider that both conditions should be concomitantly met. (9) Consequently, future algorithms should contemplate both data when taking decisions regarding treatment adjustment.

Our results demonstrated that patients with more elevated baseline LDL-C reached less frequently the lipid goal in the first control. This is reasonable since, for a normal response according to the dose, the higher the initial value, the higher the final value will be. On the other hand, the lipid target was more often reached by the population with diabetes. This finding is opposed to previous reports, where patients

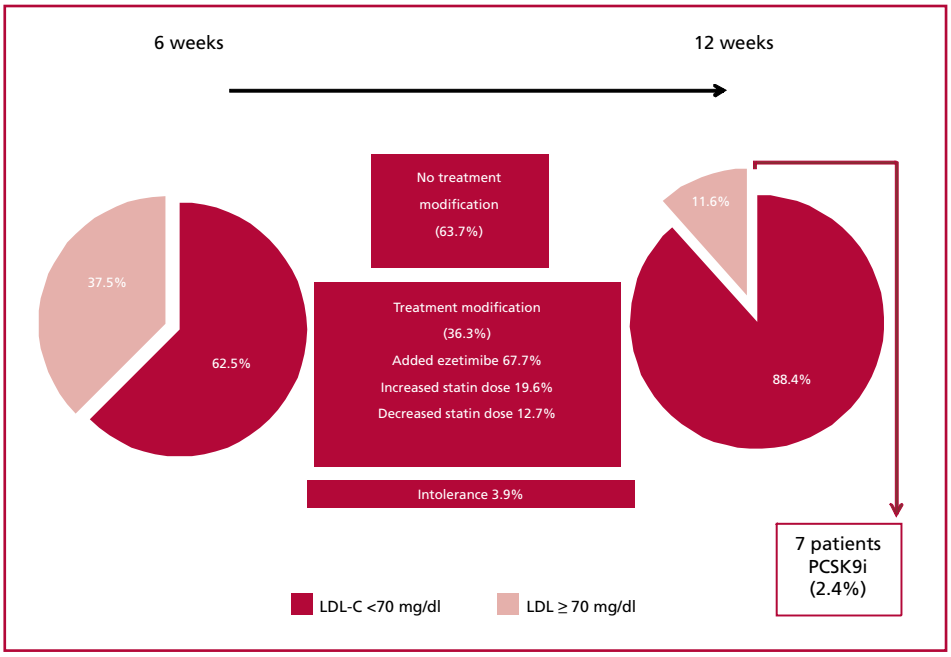


Fig. 2. Lipid control during follow-up.

with diabetes showed a lower than expected response to statins (hypo-responders). (25) Diabetic patients could present lower cholesterol liver synthesis (with a reduced response to statins) and, conversely, have greater intestinal absorption. However, some authors have reported that the inverse correlation between cholesterol synthesis and absorption observed in subjects with metabolic disorders could be altered with the development of diabetes, leading to a not always homogeneous pharmacological response. (26) In this sense, another international registry evaluating LDL-C goals (at 6 and 12 months) after systematic simvastatin 40 mg indication demonstrated that the population with coronary artery disease and diabetes achieved more frequently the lipid target compared with subjects with only diabetes or coronary artery disease. (27)

Several registries performed in the last years showed that lipid-lowering treatment and, consequently, the achievement of recommended lipid goals, is deficient. The EUROASPIRE V survey, which analyzed patients with history of vascular disease 6 months after the event, reported that even though 80% of patients was medicated with statins, only 50% was receiving high-intensity agents. As a result, 71% of subjects had an out-of-target LDL-C. (28) Recently, the PURE study demonstrated that the control of dyslipidemia is worse in poor or low-income countries. (29)

In our study, the algorithm recommended modification in patients who did not achieve the LDL-C target at 6 weeks was the addition of ezetimibe (which was accomplished in 67.7% of patients that did not attain the target value in the first control). This recommendation is based on the IMPROVE-IT study, which demonstrated that the association of ezetimibe and simvastatin compared with simvastatin monotherapy in patients with recent ACS was associated with a modest benefit in patients who received the association, after almost 7 years of treatment. (16)

Following our algorithm, around 70% of patients who had not attained de LDL-C target in the first control, did so at 12 weeks. Moreover, following SAC recommendations, in this context, only 2.4% would be candidates to receive PCSK9i. The FOURIER and ODYSSEY OUTCOMES studies demonstrated the efficacy and clinical benefit of PCSK9i treatment (evolocumab and alirocumab, respectively) in patients with previous vascular disease and LDL-C >70 mg/dl. (17, 18) However, the SAC consensus establishes a threshold value for treatment, mainly based on cost-effectiveness issues.

A large simulation study showed that only 25.5% of secondary prevention patients reached the target LDL-C <70 mg/dl. (30) After intensifying the simulated treatment (considering 100% adherence), 99.3% attained the lipid goal using statin monotherapy, dual therapy (statins and ezetimibe) or triple scheme (adding PCSK9i) in the following proportions: 67.3%, 18.7% and 14%, respectively. Another study performed the same simulation, but considering statin intolerance. (31) Assuming in the population 10% of partial intolerance (intolerance to maximum doses), use of combined therapy with ezetimibe or with the inclusion of a PCSK9i agent increased the rate of expected therapeutic goal to 34.9% and 15.5%, respectively. When intolerance of this fraction was assumed as complete (intolerance to any statin dose), use of ezetimibe and PCSK9i increased the rate of expected achievement to 38.5% and 19,7%, respectively.

Similar to this simulation study, our findings showed that a considerable proportion of patients reached the LDL-C target. However, the indication of PCSK9i was much lower in our study. The explanation probably lies in that our work considered a threshold value to indicate monoclonal antibodies. Also, our work incorporated teleconsultation in the follow-up phase of the applied algorithm. This tool was developed in the last years and has been constantly growing, with application in different clinical scenarios. Gabriel et al reported marked improvements in the usual care of patients with stroke after applying a teleconsultation program (32). In addition, a recent work demonstrated that teleconsultation-based follow-up in patients with stable coronary heart disease was safe and that control of risk factors in these patients was not inferior to that achieved in patients with in-person follow-up. (33) Remote monitoring of the prescribed medication in patients with heart failure has also been safe and efficient. (34)

It should be mentioned that our algorithm did not contemplate the use of non-statin drugs in the coronary care unit. Other groups have recommended adding ezetimibe at discharge, considering baseline LDL-C and prior use of statins. (35) Also, a recently published study demonstrated that the addition of PCSK9i (evolocumab) in the coronary care unit was associated with an elevated proportion of patients that attained the LDL-C target during early follow-up (>95%). (36)

Our study has certain limitations. First, it evaluated the target LDL-C <70 mg/dl and the therapeutic threshold to indicate a PCSK9i was LDL-C >100 mg/dl. The application of an algorithm that postulates more demanding lipid goals or strategies not based on a threshold value to indicate PCSK9i could modify the results. Second, LDL-C was the only lipid target assessed in our work. The analysis of other lipid goals, as non-HDL cholesterol or apolipoprotein B were not considered in this analysis. Finally, as stated above, the decision for treatment change was based on fulfillment or not of the LDL-C goal, without considering the percent reduction of this lipid marker.

CONCLUSIONS

The systematic application of an algorithm based on current guidelines focusing on LDL-C testing on admission, the indication of high-intensity statins during hospitalization and an early control to adjust the medication, succeeded in achieving a large proportion of high cardiovascular risk patients to attain LDL-C targets at 12 weeks of follow-up. The indication of PCSK9i would be reserved for a very selected group of patients.

Conflicts of interest

None declared.

(See authors' conflicts of interest forms on the website/Supplementary material)

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