ORIGINAL MANUSCRIPT

Assessing the Impact of New Guidelines on the Use of Statins

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Abstract

Background: Coronary artery disease (CAD) is the leading cause of death in Brazil and has a direct connection with dyslipidemia.
Objective: To analyze the pattern of use of statins before and after the publication of the new guidelines on dyslipidemia in patients with a history of atherosclerotic cardiovascular disease.
Methods: Cross-sectional retrospective study. In this study, 515 consecutive patients with atherosclerotic were randomly evaluated at the outpatient facility of Instituto de Cardiologia de Santa Catarina, SC, Brazil, between 2011 and 2015.Of these, only 76.9% were using statins. Data relating to clinical history, risk factors for cardiovascular disease, laboratory data for cholesterol levels (HDL-c and LDL-c) and triglycerides (TG) were collected, as well as treatment concerning the choice of statins and their doses before and after October 2013, when the new guidelines were published.
Results: After the publication of the new guidelines, 477 patients used statins, representing 92.6% of the study sample (p=0.0001). As to the choice of statin, the use of simvastatin declined to 69.2% (p=0.02), atorvastatin increased to 25.2% (p=0.003) and rosuvastatin was 5.7% (p=ns). Before the release of the new guidelines, the average doses of simvastatin, atorvastatin and rosuvastatin were 33.6±9.4 mg, 32.1±18.9 mg, 13.1±7.9 mg, respectively. After publication, these average doses increased to: simvastatin 36.7±7.9 mg (p=0.0001) and atorvastatin 36.8±16.2 mg (p=0.0001).
Conclusions: The statin use rates in the study sample increased after the publication of the new ACC/AHA Guidelines and the V Brazilian Guidelines on Dyslipidemia. However, they reached a limited number of patients, associated with doses below the recommended and improper numerical targets of cholesterol, which can generate unfavorable prognostic implications.

Keywords: Hydroxymethylglutaryl-CoA reductase inhibitors; Dyslipidemias; Secondary prevention; Atherosclerosis

Introduction

Coronary artery disease (CAD) is the leading cause of death in Brazil and is directly related to dislipidemia.[1] According to the Brazilian Ministry of Health (DATASUS),[2] acute myocardial infarction (AMI) is the second cause of death in the country, with approximately 86,000 deaths from this cause in 2013.

An acute coronary event is the first manifestation of atherosclerotic disease in at least half of the individuals. Atherosclerosis is a multifactorial inflammatory process that affects the inner layer of the arteries of medium and large caliper, and suffers direct influence from serum levels of low density lipoprotein-cholesterol (LDL-c). Therefore, it is expected that cholesterol reductions through changes in lifestyle and/or use of drugs such as

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ABBREVIATIONS AND ACRONYMS

- *AMI – acute myocardial infarction*
- *ASCVD – atherosclerotic cardiovascular disease*
- *CAD – coronary artery disease*
- *DM – diabetes mellitus*
- *ICSC – Instituto de Cardiologia Santa Catarina*
- *PAOD – peripheral arterial occlusive disease*
- *SAH – systemic arterial hypertension*

statins have a great impact on reducing cardiovascular outcomes.[1] About the intensity of LDL-c reduction, there is huge variation depending on the choice of statin. This difference is primarily related to the initial dose of the drug.[1,3]

Evidence clearly shows that cardiovascular events are reduced to a greater extent when maximum intensity statins are used if well tolerated in those groups presenting any benefits.[1,3,4] The V Brazilian Guideline on dyslipidemia[1] recommends that the treatment should be based on LDL-c target levels, which may involve the use of statin of an inadequate intensity or in sub-doses for patients in secondary prevention of atherosclerotic cardiovascular disease (ASCVD). The guideline of the American College of Cardiology/American Heart Association[3] (ACC/AHA) 2013 advocates the use of high-intensity statins for all of these patients, except for some contraindications.[1,3]

In addition to reducing the process of atherosclerosis, statins also have anti-inflammatory properties that act on the stability of atherosclerotic plaques and in the reduction of free radicals.[1,3]

In order to identify the pattern of use of statins at the outpatient facility of Instituto de Cardiologia de Santa Catarina (ICSC), this study retrospectively analyzed, randomly, the medical records of patients who experienced cardiovascular events in order to improve knowledge of the therapeutic approach used in a reference hospital and compare it with strategies recommended in the guidelines.

Methods

This is a retrospective study with patients who had at least one previous cardiovascular event at the ICSC from 2011 to 2015. This study was by the Research Ethics Committee of the institution under no. 057613/2015. Because it is a retrospective study, Informed Consent Form was not required.

The study included 515 patients, older than 18, with known prior atherosclerosis and in secondary prevention of atherosclerotic cardiovascular disease (ASCVD). Exclusion criteria adopted: patients who were not in secondary prevention of ASCVD, despite the use of statins for the treatment of dyslipidemia.

Patient data were collected from Micromed® electronic medical records. Data concerning clinical history, risk factors for cardiovascular disease, laboratory data relating to cholesterol levels (HDL-c and LDL-c) and triglycerides (TG) were collected. Treatment was established according to the choice of statins and their doses before and after October 2013, when the ACC/AHA Guidelines were published.[3]

Statistical analysis

The categorical variables were expressed as frequency and percentage and were analyzed using the Fisher's exact test or the chi-square test. The continuous variables were expressed as medians and standard deviation. Intra- and intergroup comparison of continuous variables was performed using paired and/or unpaired Student's t-test; the values were considered significant when $p<0.05$. Data were analyzed using Microsoft Excel® 2007 and the statistical analysis program GraphPad InStat®.

Results

From a random selection, 515 patients were evaluated. The average age was 63.6±11.0, of which 62.9% were men. As for ethnicity, there was prevalence of whites (96.5%), followed by 2.1% black and 1.4% of a mixed ethnicity.

The mean total cholesterol was 168.1±42.3 mg/dL. Mean HDL-c and LDL-c was 44.2±11.3 mg/dL and 91.7±32.2 mg/dL, respectively. The average triglyceride value was 162.7±114.4 mg/dL. Mean systolic and diastolic blood pressure were 131.5±24.3 mmHg and 76.8±13.3 mmHg, respectively (Table 1).

Analyzing the LDL-c values to correlate the numerical targets recommended in the Brazilian guidelines and the values actually achieved in practice, the following was observed in the group of 298 patients who had LDL-c levels available: 79 (26.5%) patients with <70 mg/dL; 122 (40.9%) of 71-99 mg/dL; and 97 (32.6%) patients with levels >100 mg/dL (Table 2).

Table 1
Clinical variables of the sample studied

Clinical variables	Mean±SD	n
Total cholesterol	168.1 ± 42.3	316
HDL-c	44.2 ± 11.3	310
Triglycerides	162.7 ± 114.4	317
LDL-c	91.7 ± 32.2	298
LDL-c (median)	127	298
Systolic blood pressure	131.5 ± 24.3	515
Diastolic blood pressure	76.8 ± 13.3	515

SD – standard deviation; HDL-c – high density lipoprotein cholesterol; LDL-c – low density lipoprotein cholesterol

Table 2
Average lipid levels (LDL-c) of the sample studied

Variables	n	%
<70 mg/dL	79	26.5
Between 71–99 mg/dL	122	40.9
>100 mg/dL	97	32.6

As for the risk factors for cardiovascular disease, 75.7% were hypertensive, 31.1% had diabetes mellitus and 28.5% were smokers.

Regarding previous coronary events, 30.7% had unstable angina and 73.0% had acute myocardial infarction.

Of the patients evaluated, 76.9% were using statins. Before the new guidelines of 2013, 363 (70.5%) were using statins. After the publication, 477 (92.6%) patients started using statins (p=0.0001).

Before the publication of the new guidelines in 2013, 70.5% of the patients analyzed were using statins for secondary prevention of cardiovascular diseases:78.8% used simvastatin, 16.8% used atorvastatin and 4.4% used rosuvastatin.

Since the publication, the use of simvastatin dropped to 69.2% (p=0.02); the use of atorvastatin significantly increased to 25.2% (p=0.003) and the increase in the use of rosuvastatin to 5.7% was not significant (Figure 1).

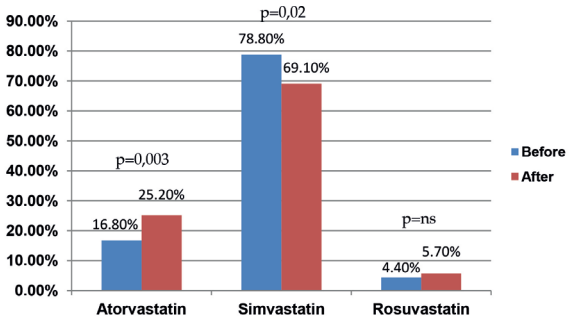

Figure 1
Classes of statins used before and after the publication of the new guidelines

The doses used by the patients were also evaluated. Before the new guidelines, the average doses of simvastatin, atorvastatin and rosuvastatin were 33.6±9.4 mg, 32.1±18.9 mg, 13.1±7.9 mg, respectively. There was an increase in the average doses after the publication of the guidelines, with statistical significance for simvastatin doses (36.7±7.9 mg) and atorvastatin doses (36.8±16.28 mg) with p=0, 0001. Concerning rosuvastatin (13.0±4.7 mg) there was no change with statistical significance, p=ns (Figure 2).

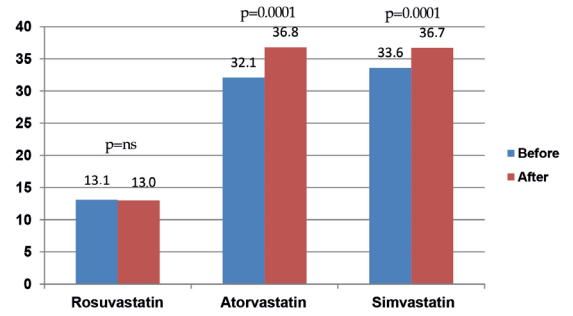

Figure 2
Average doses (in mg) of statins before and after the publication of the new guidelines

Discussion

Both primary prevention and secondary prevention of coronary artery disease have an undeniable importance in public health. Preventive measures for CAD can also reduce other manifestations of atherosclerosis such as stroke and peripheral arterial occlusive disease (PAOD), and have an impact on systemic arterial hypertension (SAH), diabetes mellitus (DM) and other chronic conditions.[5]

In this study, there has been a predominance of males, which is consistent with the literature, showing that cardiovascular disease still affects more men than women, in which case gender is a non-modifiable risk factor. With the onset of menopause, cardiovascular risk tends to be equal to men. The impact of risk factors seems to be similar between men and women, although the harmful effects of DM and the protective effect of moderate physical exercise and alcohol consumption are more important among females.[6]

There was a predominance of whites in the sample, but it is known that the risk is similar for different ethnic groups. There is heterogeneity in the response to therapy among whites and blacks.[6-8]

The LDL-c values found in the patients of this study are not the ones expected for the approach in secondary prevention, if the V Brazilian guidelines on dyslipidemia are used as a parameter, whose goal is LDL-c <70 mg/dL, as patients at high cardiovascular risk are involved. Most patients presented, however, LDL-c values between 71-99 mg/dL (40.9%). As for total cholesterol, this should remain at <200 mg/dL, HDL-c >60 mg/dL and non-HDL cholesterol between 130-159 mg/dL. These are the desirable values for any adult older than 20 years old.[1]

Most randomized multicenter studies brought together in the ACC/AHA 2013[3] guidelines indicates that treatment with statins should not be based on target lipids, but on moderate or high intensity due to other potential benefits presented by statins.[3,9]

In randomized clinical trials analyzed in the guidelines, the onset of moderate-intensity therapy (with reduction of LDL-c values of approximately 30-50%) or high intensity (with reduction of LDL-c values ≥50%) is a critical factor in reducing cardiovascular events. In addition, therapy with statins reduces cardiovascular events in the whole spectrum of baseline levels of LDL-c ≥70 mg/dL, being proportional to cardiovascular risk reduction.[3,7,8]

For each 38.7 mg/dL reduction in LDL-c, there is a reduced relative risk for cardiovascular events by 28%.[10-12]

Several studies have compared statin intensity and doses in secondary prevention and reduction of events. The studies REVERSAL[13] and IDEAL[10] compared moderate and high intensity statins in the reduction of major events, nonfatal AMI, nonfatal stroke and showed a reduction of events and deaths from cardiovascular causes in patients using atorvastatin 80 mg. There was no significant difference between the groups compared; only in patients who had a history of AMI.[10,13]

Before the publication of the new guidelines, only 70.5% of secondary prevention patients received statins; after publication, 92.6% were prescribed statins (p=0.0001).

As recommended by the ACC/AHA 2013[3] guidelines, only 30.9% of patients in secondary prevention would be using high-potency statins (atorvastatin or rosuvastatin).[3] The study of Maddox et al.,[14] conducted in the United States, found that only 32.4% of patients eligible for statin use were receiving continuous treatment before the publication of the new guidelines, and that there should be a significant increase in the use of statins to suit the current recommendations.[14]

According to Zupec et al.,[15] after the publication of the ACC/AHA 2013[3] guidelines, there was an increase of 25.5% to 41.8% in the number of high-risk patients who initiated or modified statin therapy to high-intensity, suggesting an alignment with the recommendations.

Even though there was reduced use of simvastatin (p=0.02) and increased use of atorvastatin (p=0.003), as well as a significant increase in the average doses of both statins after the publication of the new guidelines (simvastatin p=0.0001 and atorvastatin p=0.0001), the mean doses of atorvastatin (36.8±16.2 mg) or rosuvastatin (13.0±4.7 mg) were below the recommendations in the current American guidelines, which recommends the use of atorvastatin at a dose of 40-80 mg/day and rosuvastatin

at a dose of 5-20 mg/day or 40 mg/day at the most, if tolerated.

The possible reasons for the incorrect application of the guidelines are: unavailability of medications in public hospitals, little medical knowledge about the current guidelines, bureaucratic and financial issues involving the use of atorvastatin/rosuvastatin and well-established clinical practice as to the use of simvastatin. This study points to the need for improving behaviors and routines to be followed in the institution.

Limitations

As this is a retrospective study, it was difficult to conduct a standardized collection of data recorded in the medical records. As the medical attention at the outpatient clinic was given by different professionals, this might have influenced the final results of the study, since specific standards of professional management were not analyzed.

Conclusions

The statin use rates in the group studied increased after the publication of the new ACC/AHA guidelines and the V Brazilian Guidelines on dyslipidemia. However, it reached a limited number of patients, associated with doses below the recommended and inadequate numerical target cholesterol, which may lead to unfavorable prognostic implications.

Potential Conflicts of Interest
This study has no relevant conflicts of interest.

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Academic Association
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