

## Efficacy of Atorvastatin when not Administered Daily

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### Summary

**Background:** Statins are widely used because they reduce cardiac events. Although they are indicated for daily use, some doctors give prescriptions for every other day, mainly with the purpose of reducing costs.

**Objective:** To evaluate the efficacy of atorvastatin, when not administered everyday, on LDL-cholesterol (LDL-C) levels, and also to evaluate cost reduction.

**Methods:** A total of 100 patients with hypercholesterolemia in primary (PP) and secondary prevention (SP) were assessed. After a 12-week diet period, atorvastatin was initiated at a dose of 10 mg per day. After six weeks, LDL-C was determined, and if the levels were <80 or <104 mg/dL for SP and PP, respectively, two atorvastatin doses were subtracted per week. If LDL-C remained <80 or <104 mg/dL, a further reduction to three times a week was allowed, and the last determination was performed after six more weeks. The percentage variation in costs was the parameter to evaluate the saving.

**Results:** In 47 out of the 52 patients of this group, a reduction by 32% in LDL-C was observed, and daily atorvastatin was maintained. Forty one patients remained throughout the study and had their weekly dosage reduced. In 25 patients the medication was administered three times a week, and in 16, five times a week, with reductions of 42.4% and 46.1% in LDL-C, respectively. As regards costs, one of the groups had their monthly expense reduced from R\$ 106.65 to R\$ 74.65, and the other group from R\$ 106.65 to R\$ 53.33.

**Conclusion:** The results suggest that atorvastatin may be administered on a non-daily basis. A cost reduction between 30% and 50% was also observed. (Arq Bras Cardiol 2007;88(5):294-300)

**Key words:** Hypercholesterolemia; atorvastatin; statins; cholesterol.

### Introduction

Cardiovascular diseases are the leading cause of morbidity and mortality in Brazil<sup>1</sup> and worldwide<sup>2</sup> among men and women, and atherosclerosis is one of the major risk factors<sup>3-4</sup>. It has been well demonstrated that levels of total cholesterol and lipoproteins (low-density – LDL-C and high-density – HDL-C lipoproteins) have a close correlation with the incidence of cardiovascular events<sup>5-8</sup>.

The first 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitor – lovastatin, introduced in 1987, enabled the development of similar compounds, and thus statins became one of the more widely used therapeutic classes today<sup>9</sup>. It is effective in reducing cholesterol and cardiac events<sup>10</sup>, as been confirmed in several studies<sup>11-16</sup> and in meta-analysis<sup>17</sup>.

In the past ten years, only five studies attempted to evaluate the efficacy of statins used every other day<sup>18-22</sup>, and only one publication assessed atorvastatin<sup>23</sup>. Differences in the methodology and statin used in these studies hindered a

consensus on the subject, which was very well evaluated in a recent review<sup>24</sup>. On the other hand, the costs of this continuous, chronic treatment have been seldom considered.

The objective of this study was to evaluate the efficacy of atorvastatin not used everyday on the cholesterol levels of hypercholesterolemic individuals - using a more appropriate methodology -, as well as the impact that cost reduction may bring in the long term.

### Methods

**Study design** - This is a prospective study approved by the Institution's Research and Ethics Committee. Initially, 100 patients of both genders, age  $\geq 20$  years, and LDL-C levels  $\geq 160$  mg/dL for those in primary prevention (PP) or  $\geq 130$  mg/dL for those in secondary prevention (SP) were studied (Figure 1). Individuals receiving any antilipemic agent by the time of the tests, pregnant women, and individuals with triglyceride levels  $\geq 40$  mg/dL were not included in the study. Patients with abnormal levels of creatinine kinase and aminotransferases prior to or detected during the study, and those with chronic hepatitis were excluded. Previous intolerance to a statin, as well as patients with neoplasms and chronic obstructive pulmonary disease (COPD), uncontrolled diabetes mellitus or hypothyroidism based on values of fasting plasma glucose

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## STUDY POPULATION

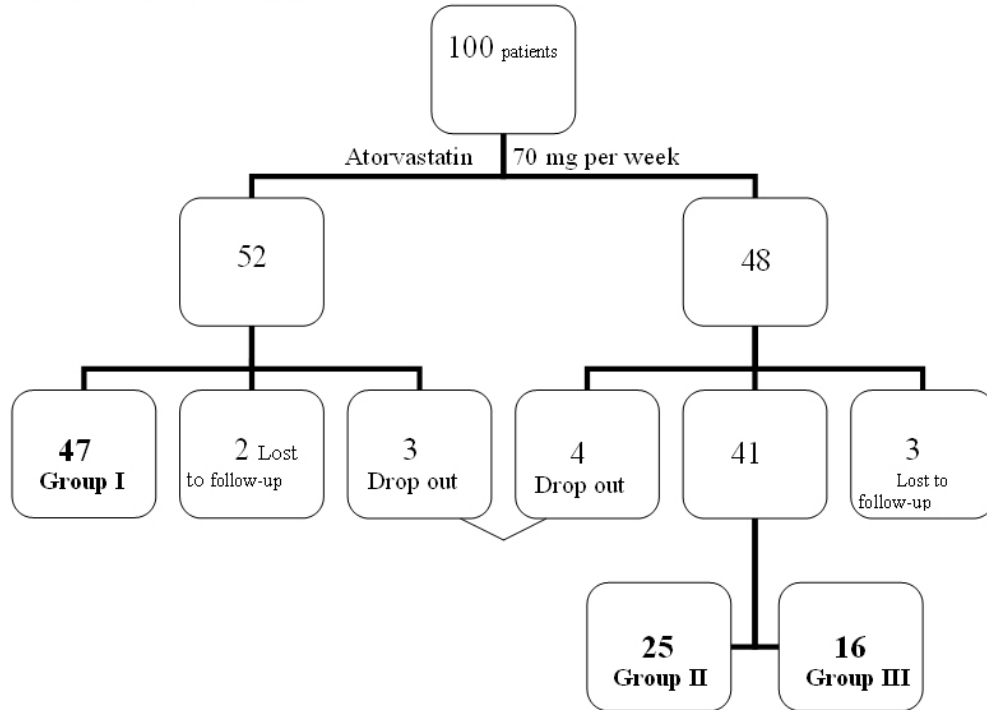


Fig. 1 - Flow chart of all patients who participated in the study (more details in text).

$\geq 140$  mg/dL or TSH  $\geq 4.2$  microIU/mL, and patients with unstable previous heart diseases such as heart failure or myocardial ischemia were also exclusion criteria. Before initiating atorvastatin, the patients followed the American Heart Association diet<sup>25</sup>. This diet was maintained during the whole study period and the response to a questionnaire at each visit confirmed the compliance to it. A menu was adapted to the diet prescribed, which corresponded to the following proportions: fat content  $< 30\%$ , polyunsaturated fats  $> 10\%$ , saturated fats  $< 7\%$ , monounsaturated fats  $> 10\%$  and cholesterol  $< 200$  mg/day.

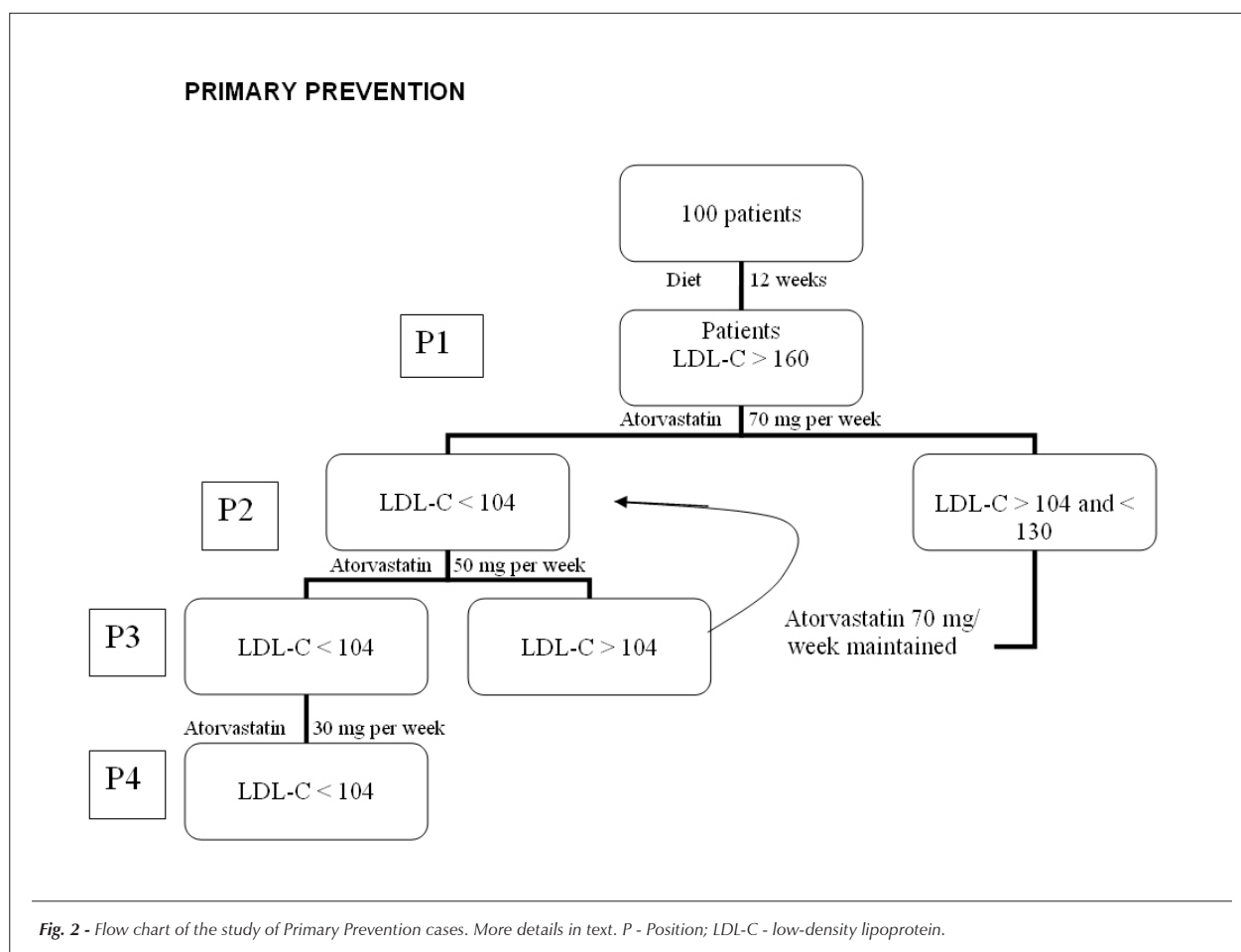
**Methods** - LDL-C goals were different for each individual, aiming at levels  $\leq 130$  mg/dl for those considered at low risk, which includes PP, and  $\leq 110$  mg/dL for those at high risk – SP or equivalent, such as individuals with diabetes<sup>26</sup>.

After a twelve-week period on diet alone, the first blood sample was collected (Figures 2 and 3 – P1), and therapy with atorvastatin was initiated for all patients at a daily dose of 10 mg after dinner (a total of 70 mg per week). Six weeks later, a second sample (P2) was collected, and if LDL-C levels were  $< 80$  or  $< 104$  mg/dL for SP and PP, respectively, 20mg of atorvastatin were subtracted from the weekly dosage, thus maintaining 50 mg/week. If in the following sample collected six weeks later (P3) LDL-C levels remained  $< 80$  or  $< 104$  mg/dL for PP and SP, respectively, another dosage adjustment was

made for 30 mg/week, that is, 10 mg every other day, fixed on Mondays, Wednesdays, and Fridays. The weekly dosage was not reduced if LDL-C values were not  $< 80$  or  $< 104$  mg/dL for PP and SP, respectively; in these cases the previous regimen of five-times a week was maintained (Figures 2 and 3). After six weeks, the last sample (P4) was collected to observe whether the LDL-C levels targeted had been achieved.

Thus, three patient groups were formed, and 10 mg of atorvastatin were always used per dose: group I, with daily use in a total of 70mg of atorvastatin per week, for patients whose LDL-C was between 80 and 100 for SP or between 104 and 130 for PP; group II, of patients who received the medication five times a week (from Monday to Friday); and group III, of patients who received the medication three times a week (Mondays, Wednesdays and Fridays).

**Laboratory analysis** - Blood samples were collected in the morning after a 12-hour fasting period and 72 hours off alcohol. Total cholesterol (TC) and LDL-C levels were quantified by the CHOD-POD method and analyzed in the ADVIA 1650 Bayer equipment. For the analysis of triglyceride levels the GPO-POD enzymatic method was used. Samples were always collected in the day following a greater interval between one medication dose and the next one. Since the medication doses were kept on fixed days (Mondays, Wednesdays and Fridays or from Monday to Wednesday),



Monday corresponded, in theory, to the day with the lowest atorvastatin level. Aminotransferase and creatinine kinase levels were measured to verify the adverse effects of atorvastatin on liver function.

**Cost assessment** - Calculation was based on the month of continuous treatment comparing the groups that used the medication three or five times a week. The maximum consumer price of atorvastatin 10 mg 30-tablet pack, which has no generic equivalent on sale in the Brazilian market, is R\$ 106.65<sup>27</sup> (pharmacy discounts not included). For the saving achieved to be easily understood and not be outdated, percentage calculations were used in each group.

## Results

The three patient groups were: group I, considered standard response, with a mean LDL-C reduction of 32%, in which the mean age was 58 (39 to 90) years; 28 were females on daily use. In this group the goals were achieved without the possibility of a dose reduction, that is, LDL-C <130 and >104 mg/dL in PP and LDL-C <100 and >80 mg/dL in SP. Group I was initially comprised of 52 patients; two of them were lost to follow-up and three dropped; thus data on 47 patients were available for analysis (Figure 1). Despite the mean reduction of 32% in LDL-C levels, the goal was not

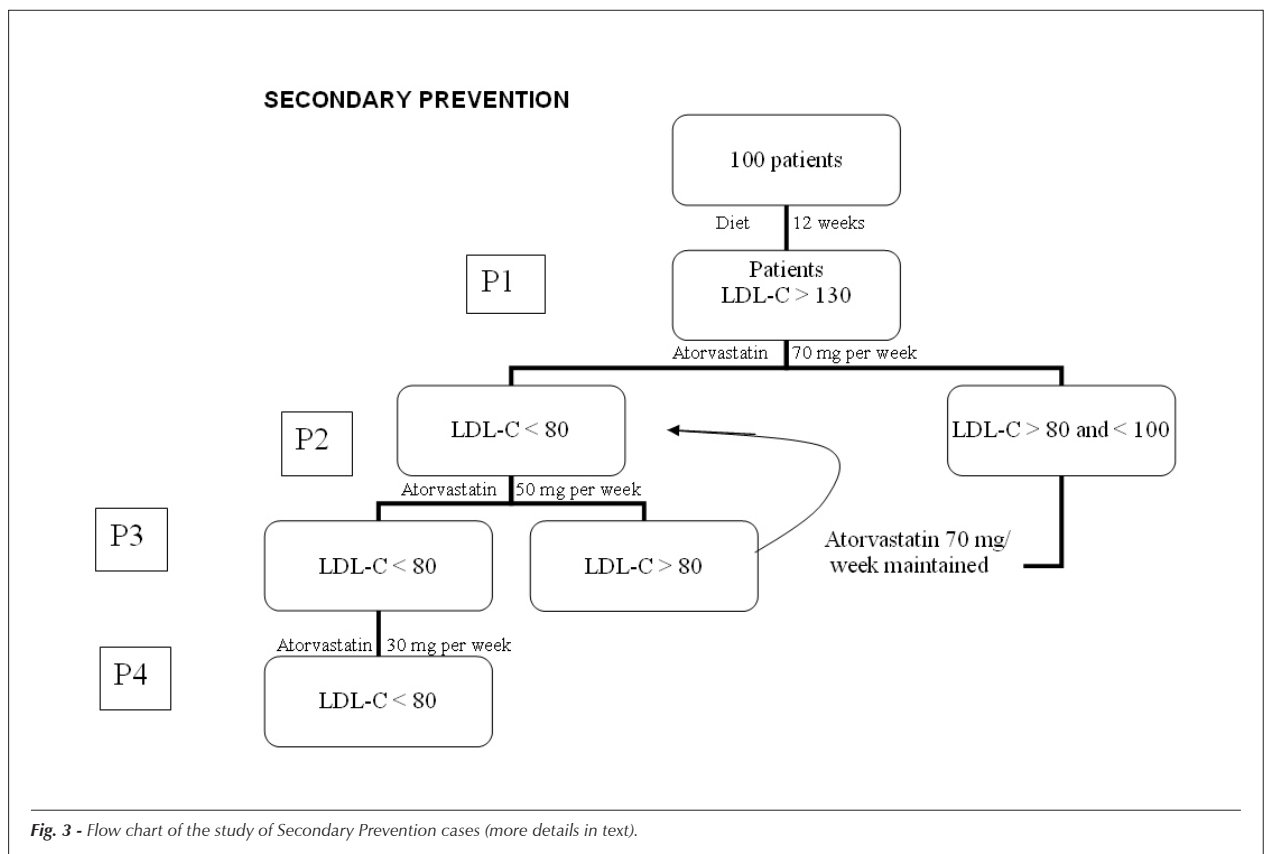
reached in four patients of this group due to high baseline levels of total cholesterol and LDL-C.

Groups II and III (48 patients) were comprised of individuals for whom the weekly atorvastatin dosage could be reduced; they were analyzed together, but separately from group I. Seven patients were excluded from the study; three of them were lost to follow-up and four dropped (Figure 1).

In the remaining 41 patients, the mean age was 60 (34 to 80) years; 29 were females and eight were receiving estrogen replacement therapy, although four of them had initiated this therapy during the study. Thirty five patients were in PP and only six in SP. Systemic hypertension was also observed in 45% of the patients studied. Of these 41 patients who remained throughout the study, 25 (61%) had permission to receive the medication three times a week (Mondays, Wednesdays and Fridays), and 16 (39%) received the medication five times a week. In two cases the dosage was changed back to five times a week.

Group I values are shown in Table 1, where usual reductions of TC and LDL-C of 34.62 % and 31.95 %, respectively, can be observed.

Groups II and III values are shown in Table 2, where significant TC and LDL-C reductions of 31% up to 44.6%, respectively, can be observed.



**Table 1 - Summary of total cholesterol, LDL-C, HDL-C and triglyceride levels (expressed in mg/dL) of group I. Includes the statistical value (p)**

	Initial Mean	Final mean	Reduction	p
Total cholesterol	260	170	34.62 %	0.001
LDL-C	169	115	31.95 %	0.001
HDL-C	52	50	< 5 %	NS
Triglycerides	167	133	20 %	0.001

NS - not statistically significant.

**Table 2 - Summary of total cholesterol, LDL-C, HDL-C and triglyceride levels (expressed in mg/dL) of groups II and III. Includes the statistical value (p)**

	Initial Mean	Final mean	Reduction	p
Total cholesterol	263	181	31.0 %	0.001
LDL-C	182	101	44.6 %	0.0001
HDL-C	52	54	5 %	NS
Triglycerides	141	129	8.5 %	NS

NS - not statistically significant.

Initial and final mean values and percentage reduction of TC, LDL-C, HDL-C and TG of the 16 patients who received atorvastatin 50 mg/week (5 times a week) in group II are shown in Table 3.

Finally, a summary of group III is shown in Table 4, where cholesterol and triglyceride levels of 25 patients whose initial mean LDL-C was 177 mg/dL, and final was 95 mg/dL, with a remarkable 46.1% reduction, although they had received

Table 3 - Summary of cholesterol and triglyceride levels for 16 patients who used atorvastatin 50mg/week (5 times a week) – Group II

	Initial Mean	Final mean	Reduction	p
Total cholesterol	271	187	31.1 %	0.001
LDL-C	192	110	42.4 %	0.001
HDL-C	49	52	6.0 %	NS
Triglycerides	144	121	16.3 %	NS

Table 4 - Summary of cholesterol and triglyceride levels for 25 patients who used atorvastatin 30 mg/week (3 times a week) – Group III

	Initial Mean	Final mean	Reduction	p
Total cholesterol	258	178	31.0 %	0.001
LDL-C	177	95	46.1 %	0.0001
HDL-C	53	56	4.5 %	NS
Triglycerides	140	135	3.2 %	NS

atorvastatin 30 mg per week (three times a week). No adverse effect, whether cardiologic or metabolic, that could interfere with the evaluation during the period studied was observed.

As regards the cost assessment, group II, with atorvastatin five times a week, had the monthly expense of R\$ 106.65 reduced to R\$ 74.65, thus providing a 30% saving per month. In group III, the expense of R\$ 106.65 was reduced to R\$ 53.33, which corresponded to a 50% saving.

## Discussion

When attempting to use statins in alternate days, the knowledge of their potency and half-lives is fundamental: lovastatin 2 hours, pravastatin 1-3h, fluvastatin and simvastatin 1-2h, and atorvastatin 14h<sup>28</sup>, the latter being chosen for having the longest half-life and greatest potency<sup>9</sup> up to the beginning of the study.

The third point is the knowledge of the pharmacokinetics of atorvastatin, which reduces LDL-C and TC within 24 to 72 hours<sup>29</sup>. After discontinuation, an increase in total cholesterol occurs on average 48 hours later and in LDL-C and apo-B within 72 hours. Thus, effective results were still obtained with non-daily use<sup>29</sup>. This information is really important and justifies the failure or discouraging results of other studies in which this statin was not used.

Metz and Lucas' study<sup>24</sup> concluded that more in-depth studies are necessary to give answers on the efficacy of alternate-day statins and they also summarized the main reports on this strategy<sup>18-22</sup>. Lovastatin, fluvastatin, short half-lives, low potency to reduce cholesterol, small groups studied, lack of a protocol, retrospective study and failure to observe cost saving were the major limitations of these protocols and perhaps discouraged other studies.

The differential of the present study was to evaluate the efficacy of non-daily atorvastatin administration in individuals whose response to the initial dose demonstrated

a reduction of LDL-C above the expected pattern. This fact is unpredictable and corresponds to an individual response because other methods for the assessment of the response to alternate-day statin were almost methods of discovery by chance; in other words, how many patients, regardless of any profile or protocol, would randomly benefit from this type of treatment.

The values used in this study as a guideline to enable 20-mg reductions of atorvastatin per week were based on the calculation that by reducing the medication by half, the result would correspond to half the atorvastatin efficacy. Thus, since the mean efficacy of 10-mg atorvastatin is of 37% of LDL-C reduction, a 15% margin was used for LDL-C levels, resulting in the < 80 or < 104 mg/dL values for SP and PP, respectively.

To date, there is no easy method to identify which individuals will have the best or worst response to this therapeutic class. Thus, studies which did not use a protocol to reduce statin doses are expected to show poor and discouraging results, unlike what was done in this research, and can be called dosage adjustment.

We observed that all participants in this study were alike at the first determination and became different after the results of the first sample. At this moment, the individuals are divided into a group with the best responses versus a group with standard responses, which also has a good response, although not enough to allow a reduction in the weekly dosage. This point can be put as the major differential for the positive responses obtained in this study.

The most recent study emphasizes the possibility of using atorvastatin or rosuvastatin every other day, thanks to their potency and half-lives<sup>30</sup>; the cost issue is mentioned, however the evaluation was performed at random and 20- mg doses of atorvastatin were used, which does not contribute to the cost issue. Another study using only atorvastatin considered the costs and tested the efficacy of its use every other day<sup>31</sup>. Details on the costs were missing, and the results were equivalent for

daily and alternate-day use, which is known not to be true for all patients. Other authors<sup>21,32</sup> that analyzed the responses to alternate-day atorvastatin refined their methodology; however they did not evaluate the saving provided by the different forms of treatment when doses of 10mg/day, 10mg every other day, and 20 mg every other day<sup>32</sup> were used, as we did in the present study.

An attempt, more recent than those with lovastatin and fluvastatin, using another statin with a short half life like pravastatin<sup>33</sup> found that the weekly dosage could not be reduced, basically because of the half life, although doses of pravastatin of up to 80mg per day had been used. As can be seen, there is an intention of changing the statin dosage; however, there is a wide variation of methodologies used in each study.

In the evaluation of simvastatin<sup>34</sup>, a small group was studied and LDL-C target levels were not well established; also, simvastatin doses were doubled when the drug was used every other day. This did not enable a cost reduction and increased the adverse effects. Similarly, in the study that evaluated a group of 35 patients receiving atorvastatin 10mg per day or every other day in the second phase of the study, the dose was doubled and efficacy was evaluated, however without providing cost reduction or efficacy with lower weekly doses<sup>23</sup>.

The results of the present study, in which the largest population ever was evaluated, identified standard responders (group I) and individuals considered *optimal responders* groups II and III. Despite presenting hypercholesterolemia, some patients show different responses to the lipid-lowering therapy, and these responses were considered in our study.

This study was the only one to show a more rational attitude in the evaluation of the non-daily dose, unlike all the others that left to chance the finding out of the patients who could be treated in a non-daily basis. In this assessment, all individuals receive the initial standard dose, and after the first lipid profile determination a dose adjustment is considered. It does not seem rational to increase or double the dose, as occurred in other studies.

Statins are recognized by our health system and are part of a list of expensive medications. Effective statin doses cost approximately R\$ 25.00, the total treatment sometimes reaching approximately R\$ 150.00 per month; it should also be considered that these treatments are not temporary but are maintained indefinitely.

The monthly cost of atorvastatin is R\$ 106.65 at the dose of 10mg. The annual treatment cost would be of R\$ 1,279.80 (based on the maximum consumer price and not including pharmacy discounts).

The lowest available dose of atorvastatin is 10mg. The use of a daily 5-mg dose, that is, half a tablet, may be very difficult because the tablets are not scored and it does not seem practical for patients, mainly for the elderly ones. Thus, the use of a whole tablet every other day seems more practical than trying to split a tablet in two halves, unlike some studies that did the opposite, that is, used double the dose every other day, which eliminates the possibility of a less expensive treatment.

Thus, the possibility of reducing the medication dose

undoubtedly provided patients with a cost reduction, not to mention that most of the times there are other medications being used for the control of other diseases, such as diabetes and hypertension.

In this study, group II costs were reduced by 30%, which is equivalent to R\$ 32.00 per month, and in group three costs were reduced by 50%, that is, R\$ 53.32 per month, in a total of a R\$ 384.00 and R\$639.90 yearly saving, respectively; these amounts cannot be disregarded.

When a cost-effectiveness analysis is made, the investment per life saved is considered to be worthier the higher the cardiac risk of that individual is. Thus, when this type of treatment is adopted there is undoubtedly a cost reduction, as well as a justification for the use of the medication<sup>24</sup>.

It is important to observe that the use of atorvastatin was safe and that the incidence of major or minor side effects was quite low.

Thus, the efficacy of atorvastatin used every other day on cholesterol levels of hypercholesterolemic individuals could be confirmed, based on a customized adjustment every six weeks in the initial period of treatment.

With this frequency of atorvastatin administration per week, costs were reduced by 30% to 50% according to the number of doses per week, thus providing those who need this treatment with a significant saving, and generating an economic impact for the population and public agencies that supply medications.

*Study limitations* - A moderate treatment drop-out rate could be observed. In none of the cases the reason was a side effect. Asymptomatic hypercholesterolemia before the occurrence of a cardiovascular event, medication cost, and the idea of a treatment for an indefinite time were study limitations. Patients believe that if the medication is discontinued after reduction of cholesterol levels the results will not be affected. A reduction in the weekly dosage, for those whose response to treatment thus permits, could be perceived as a treatment bonus by the patients and a means to increase compliance to long-term treatment.

### Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

### Sources of Funding

There were no external funding sources for this study.

### Study Association

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