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Safety and efficacy of statin treatment in very elderly patients

Segurança e eficácia do tratamento com estatinas em pacientes muito idosos

Renato Jorge Alves [1], **Cezar Emiliano Fernandes Goncalves** [2]

Abstract

Introduction and objectives: *The treatment of dyslipidemia over 75 years old is not well elucidated, due to the non-inclusion in large randomized clinical trials. The elderly people develop atherosclerosis more often and the worldwide population shows greater longevity. To evaluate the efficacy and safety of statin in very elderly people.* ***Methods***: *The patients were divided into two groups: over 75 years (very elderly) and up to 75 years (control group). We evaluated: coronary artery disease (CAD); stroke; clearance of creatinine; creatine phosphokinase (CPK) and transaminase (ALT, AST) levels; lipid profile; type, dosage, and time using statin.* ***Results***: *Sample of 120 patients, 53,2% male, age 74.1 (±11.1) years, 82.3 very elderly and 64.9 years the control group. The total cholesterol, low density lipoprotein cholesterol (LDL-C) and high-density lipoprotein (HDL-C) in very elderly and control were 162 and 166 (p=ns), 84 and 90 (p=ns), 52.5 and 47 mg/dL (p=0.07), respectively. CAD and stroke, respectively 52.5 and 78.8% (p=0.007), and 18.6 and 7.7% (p=0.09). The time using statin and number of drugs taken were the same in the groups. The CPK and ALT levels were 97 and 110 (p=ns) and 16.5 and 20 U/L (p=0.004), respectively. There was no statin dose reduction in the very elderly group despite the higher proportion of clinical comorbidities or renal dysfunction.* ***Conclusions***: *The statin treatment in very elderly patients is effective and safe. The increased risk of CAD and stroke in very elderly people corroborates the importance of statin use in this age group.*

Keywords: *Statin, Dyslipidemia, Patients, Elderly*

Resumo

Introdução e objetivos: *O tratamento da dislipidemia acima de 75 anos não está bem elucidado, devido à não inclusão em grandes ensaios clínicos randomizados. Os idosos desenvolvem aterosclerose com maior frequência e a população mundial apresenta maior longevidade. Nosso objetivo foi avaliar a eficácia e a segurança da estatina em pessoas muito idosas.* ***Métodos***: *Os pacientes foram divididos em dois grupos: acima de 75 anos (muito idosos) e até 75 anos (grupo controle). Avaliamos: doença arterial coronariana (DAC); Acidente Vascular Cerebral (AVC); depuração de creatinina; níveis de creatina fosfoquinase (CPK) e transaminase (ALT); perfil lipídico; tipo, dosagem e tempo de uso da estatina.* ***Resultados:*** *Amostra de 120 pacientes, 53,2% do sexo masculino, idade 74,1 ± 11,1 anos, 82,3 muito idosos e 64,9 anos o grupo controle. Colesterol total, colesterol de lipoproteína de baixa densidade (LDL-C) e de lipoproteína de alta densidade (HDL-C) em muito idosos e controle foram 162 e 166 (p=ns), 84 e 90 (p=ns), 52,5 e 47 mg/dL (p=0,07), respectivamente. DAC e AVC, respectivamente 52,5 e 78,8% (p=0,007), e 18,6 e 7,7% (p=0,09). O tempo de uso da estatina e o número de medicamentos tomados foram iguais nos dois grupos. Os níveis de CPK e ALT foram 97 e 110 (p=ns) e 16,5 e 20 U/L (p=0,004), respectivamente. Não houve redução da dose de estatina no grupo de muito idosos, apesar da maior proporção de comorbidades clínicas ou disfunção renal.* ***Conclusões:*** *O tratamento com estatina em pacientes muito idosos é eficaz e seguro. O risco aumentado de DAC e AVC em pessoas muito idosas corrobora a importância do uso de estatinas nessa faixa etária.*

Palavras-chave: *Estatina, Dislipidemias, Paciente, Idosos*

Introduction

It is known that cardiovascular disease (CVD) is the leading cause of death in the world. In addition, there is an aging world population with greater survival, and in Brazil, it is no different[1]. This fact could be explained by better pharmacological treatment and control of cardiovascular risk factors.

With the aging world of the population, the indication of statins in primary prevention after the age of 75 years becomes a major challenge. However, the lipid-lowering treatment using statins in patients with hypercholesterolemia has a proven survival benefit for both primary prevention (patients without clinical evidence of coronary disease or stroke) and secondary

1. Santa Casa de São Paulo School of Medical. Sciences. Departament of Medical Clinic. São Paulo – SP - Brazil
2. Hospital do Servidor Público Estadual. São Paulo – SP – Brasil
Institution: *Santa Casa de Sao Paulo School of Medical Sciences. Departament of Medical Clinic. São Paulo - SP – Brazil*
Correspondence address: *Renato Jorge Alves. Rua Dr. Cesário Motta Júnior, 112 - Vila Buarque – 01221020 - São Paulo - SP – Brasil. E-mail: renatoalves178@gmail.com*

prevention (patients with established coronary disease or stroke), even when serum cholesterol concentrations are "normal" for the population or borderline high. Moreover, statins may also be beneficial in patients in secondary prevention and with heart failure[2,3].

Patients with CVD are at higher risk for future CVD events. Secondary prevention interventions are aimed at known modifiable risk factors for CVD events such as smoking, hypertension, diabetes, and elevated levels of low-density lipoprotein cholesterol (LDL-C). LDL-C lowering has been shown in large clinical trials to reduce the risk of CVD events and, in some populations, to reduce all-cause mortality[2]. However, most of the randomized trials excluded the very elderly population. According to the American Guideline of Dyslipidaemia and Atherosclerosis[4], in adults ≥ 75 years of age with an LDL-C level of 70 to 189 mg/dL (1.7 to 4.8 mmol/L), initiating a moderate-intensity statin may be reasonable, and it may be reasonable to stop statin therapy when functional status declines (physical or cognitive), or multimorbidity, frailty, and reduced life-expectancy limits the potential benefits of statin therapy, both approaches (class of recommendation IIb and level of evidence B-R).

The 2019 ESC/EAS Guidelines for the management of dyslipidaemias[5] consider that there is evidence that statins promote significant reductions in major vascular events regardless of age. Nonetheless, there is less evidence of this benefit in patients older than 75 years without occlusive vascular disease. Also, the safety and adverse effects of statins are major concerns in the elderly and very elderly people because they have other comorbidities, take multiple medications, and pharmacokinetic changes.

The Brazilian Guidelines of the Cardiogeriatric people and the Atherosclerosis Prevention Guideline corroborate that the approach of aggressive LDL-C lowering, starting with high-intensity statin, in patients with CVD or at high risk is since LDL-C plays a key role in the pathogenesis and perpetuation of atherosclerotic CVD[6]. However, the very elderly population shows important particularities, such as frailty, polypharmacy, and comorbidities[7].

The elevated levels of LDL-C are associated with an increased risk of CVD events and the decrease of LDL-C is associated with a reduction in events[8].

The first and more specific study in elderly people, the PROSPER study[9], included 5,804 patients randomly aged 70 to 82 years with vascular disease or cardiovascular risk factors to receive pravastatin 40 mg daily or placebo. It was the first randomized trial to prospectively evaluate the elderly. In just 3 years of follow-up, pravastatin reduced LDL-C by 34%, triglycerides by 13% and the risk of death from coronary artery disease (CAD), nonfatal MI and stroke by 15%. There was a significant risk reduction for the primary outcome (death from CAD, nonfatal myocardial infarction, and fatal or nonfatal stroke) with hazard ratio [HR] of 0.81 (95% CI 0.74-0.97). Moreover, there was no reduction in death from any cause (HR 0.97, 95% CI 0.83-1.14) or cognitive dysfunction. However, these results were found mainly in secondary prevention elderly people than primary prevention.

Therefore, safety and efficacy of the lowering lipid treatment in very elderly people (over 75 years of age) in primary prevention isn't fully elucidated.

Objectives

The primary objective of this study was to evaluate the efficacy and safety of hypolipidemic treatment with a statin in very elderly patients (over 75 years of age). A secondary objective was to assess the presence of comorbidities (CAD, hypertension, diabetes, and stroke) and the effect of the dose and type of statin (simvastatin or atorvastatin) in these patients. Both objectives are compared to those under 75 years old.

Methods

The study has a cross-sectional and non-randomized design, with data obtained from medical records or medical consultations at a cardiology outpatient clinic. For patients to be included in the study, it was set a criterion to be on statin treatment (simvastatin or atorvastatin) and to be regularly monitored at the cardiology outpatient clinic. Patients using fibrates were excluded. The sample was defined as all patients who were using statins during the data collection period (> 6 months in a row). For the measurement of total cholesterol and fractions, and triglycerides, the colorimetric method was used. For creatine kinase and transaminases, the enzymatic method was used.

A standardized questionnaire was used for all patients. The diagnosis of CAD was defined as a history of acute coronary syndrome (non-fatal acute myocardial infarction with or without ST elevation and unstable angina). The diagnosis of stroke was defined as patients with history of vascular events in the cerebral territory (ischemic or hemorrhagic). Finally, the diagnosis of hypertension and diabetes was made according to the medications in use by the patient. If using antihypertensive medications, included as having hypertension, and if using anti-diabetics, included as having diabetes. This work was registered in "Plataforma Brazil" and was approved by a Research Ethics Committee.

Statistical analysis: In this study, we compared

data obtained from the medical record of patients over 75 years old (very elderly group) with patients up to 75 years old (control group). To check the effectiveness of treatment with a statin, the lipid profile of both groups was verified. We compared total cholesterol levels and fractions (LDL-C and HDL-C), and triglycerides. To assess safety, we compare creatine phosphokinase (CPK) and transaminase levels.

The software used was SPSS version 22.0 software for Windows. We used the Shapiro-Wilk test to verify the normality of the continuous variables. As some are not normal in this sample, it was decided to use a non-parametric test (Mann-Whitney) for all variables to homogenize the analysis. To adjust the variables, we did a stratified analysis because some of the variables don't have a normal distribution. We considered the following groups: sex (male or female), presence or absence of comorbidities (CAD, stroke, hypertension, chronic kidney disease, and diabetes), and type and dosage of statin used. We also used a non-parametric test (Mann-Whitney) for continuous variables to verify if there was a difference between these stratified groups. To compare categorical variables, we used the Chi-square test, and to verify the correlation between two variables we used Spearman's rank correlation coefficient. The level of significance used was < 5%.

Results

The total sample consisted of 120 patients, who were divided into two groups. The very elderly group had 60 patients over 75 years old and the control group had 60 patients up to 75 years old. The mean age in the total sample was 74.1 (± 11.1) years, with 82.3 (± 4.9) years in the very elderly and 64.9 (± 8.7) years in the control group. The baseline characteristics are in the Table 1.

We highlight the high prevalence of hypertension and CAD in the total sample (80.2% and 65% respectively), and the higher prevalence of CAD in the control group, and stroke in the very elderly group (Table 2).

Tables 3 to 6 show history of coronary artery disease, stroke, hypertension, and diabetes, the levels of total cholesterol, LDL-C, HDL-c, and triglycerides, to check the effectiveness of statin treatment. The results of the total sample are displayed and stratified by groups.

To verify the safety of treatment, table 7 shows the levels of creatine phosphokinase and transaminases. Finally, the correlation of the safety profile and quantity of drugs taken in one day is shown in table 8.

The efficacy and safety of using statins in very elderly patients is shown in the central figure.

Discussion

The risk of atherosclerotic disease, mainly CAD increases greatly with age in both men and women, which corroborates the importance of hypolipidemic treatment in the elderly. Another fact to be considered is the increased longevity of the world population.

Table 1

Baseline characteristics – Data are mean (SD), n (%) or median (IQR).

	>75 years (n=60)	*≤75 years (n=60)*
Age	82.3 (±4.9)	64.9(±8.7)
Sex		
Male	30 (50%)	33(55.7%)
Female	30 (50%)	27(44.3%)
History of coronary artery disease	31 (52.5%)	41(68.3%)
History of stroke	11 (18.6%)	4 (6.6%)
Treated hypertension	50 (84.7%)	39 (65%)
History of diabetes	23 (38.9%)	20(33.4%)
Total cholesterol (mg/dL)	161.4 (40.1)	167.4 (43)
LDL cholesterol (mg/dL)	84.7 (31.2)	88.9 (33)
HDL cholesterol (mg/dL)	52.5 (43.0-62.2)	47 (38-57)
Triglycerides (mg/dL)	108 (74.7-146.5)	133 (109-197)
Creatine phosphokinase U/L)	97 (75-141)	110 (77.7-161.2)
Alanine transaminase (U/L)	16.5 (13-19.7)	20 (15-24.7)
Aspartate transaminase (U/L)	21.4 (6.2)	20.5 (5.5)
Clearance of creatinine (mL/min)	49.2 (37.7-57.2)	72.8 (54.1-87)
Use of simvastatin	42 (70%)	33 (55%)
Use of atorvastatin	18 (30%)	27 (45%)
Time using statin (years)	6.0 (3.25-8.50)	5.0 (2.0-8.25)
Number of drugs taken in one day	5.0 (6.0-8.0)	7.0 (5.0-8.25)

Table 2

Prevalence of comorbidities in the sample. CAD= coronary artery disease

	Total sample (n=120)	*Very elderly (n=60)*	*Control group (n=60)*	*p (Chi-square)*
History of CAD	65%	52.5%	78.8%	0.007
History of stroke	13.5%	18.6%	6.6%	0.090
Treated hypertension	80.2%	84.7%	65%	0.190
History of diabetes	38.7%	38.9%	33.4%	0.950

Table 3

Level of total cholesterol (mg/dL) – Data are median (IQR).

	>75 years	*≤75 years*	*p (Mann-Whitney)*
Total cholesterol sample	162 (136-187)	166 (145-193)	0.543
Sex			
Male	143 (110.75-165)	160 (130-183.25)	0.081
Female	179 (161.5-208.5)	179 (152-209)	0.658
History of coronary artery disease			
Yes	156 (122-186)	160 (142.25-183.5)	0.427
No	174 (150.25-191.5)	191 (157-224)	0.221
History of stroke			
Yes	158 (108-174)	127.5 (98-238.75)	0.661
No	164.5 (143-188.5)	166 (150-193)	0.522
Treated hypertension			
Yes	166.5 (141.25-187.5)	166 (145-193)	0.820
No	154 (117-186)	166.5 (132.75-197.75)	0.345
History of diabetes			
Yes	152 (108-174)	167 (135.75-184.75)	0.151
No	170.5 (149.25-207)	164 (145-209)	0.880
Statin used			
Simvastatin	163.5 (130.25-189.75)	156.5 (143.5-170.5)	0.670
Atorvastatin	158 (145.5-177.5)	184 (153-209)	0.156
Dose of statin			
Simvastatin 20mg	149 (112-175)	156 (143-182)	0.220
Simvastatin 40mg	182 (164.5-212)	162 (145.5-169.5)	0.041
Atorvastatin 20mg	154 (136-214)	192 (140.5-215)	0.589
Atorvastatin 40mg	168 (145-196)	190 (154-209)	0.441
Atorvastatin 80mg	164 (143-181)	172 (113-181)	0.900

The current guidelines recommend statin use in the elderly after a risk-benefit assessment, as it would outweigh any cardiovascular risk, even in the face of a small increase in adverse effects (6. Guideline on the Management of Blood Cholesterol)[1,4]

A retrospective cohort study evaluated statin use in mortality and primary prevention for cardiovascular disease in patients over 75 years of age. Primary outcomes included deaths from any cause and cardiovascular causes. A total of 326,981 patients were evaluated and 17.5% of them started using a statin during the study period. The use of statins, when compared to non-use, demonstrated a relative reduction in cases of death from any cause by 25%, and cardiovascular death by 20%. In addition, these benefits were demonstrated early, in the first two years of medication use, and were maintained even in patients over 90 years of age[10].

In our study, the statin treatment is effective because the levels of lipids observed in patients aged 75 years or older were equal to or even lower than in younger patients. The levels of total cholesterol and LDL-C were the same when stratifying the group by sex, comorbidities, and type of statin used. HDL-C levels are more appropriate in very elderly patients, especially in male patients. And the group of very elderly patients also has a more adequate level of triglycerides than younger patients, with statistical significance. Both groups used statins for a similar and sufficient time for the medication to have an adequate effect. And statin treatment in very elderly people is safe because the levels of creatine phosphokinase and transaminases were similar between groups, despite the greater number of comorbidities among the elderly, especially chronic kidney disease. The safety profile did not correlate with the number of

Table 4

Level of LDL-C (mg/dL) – Data are median (IQR).

	>75 years	*≤75 years*	*p (Mann-Whitney)*
LDL-c Total sample	84 (62-106)	90 (65-103)	0.543
Sex			
Male	74.5 (50.25-89)	87 (65-98)	0.162
Female	92 (74.5-113)	96 (64.75-110.5)	0.761
History of coronary artery disease			
Yes	82 (60-100)	88.5 (64.75-98.25)	0.462
No	89 (65.5-107.75)	101 (69-135)	0.379
History of stroke			
Yes	87 (54-93)	69.5 (41.75-138.5)	0.753
No	83.5 (64-106.75)	90 (65.5-103)	0.564
Treated hypertension			
Yes	83.5 (63.5-106.25)	88.5 (63.75-104.5)	0.677
No	85 (51.5-102.5)	93 (65-97)	0.603
History of diabetes			
Yes	82 (51-92)	89.5 (60.25-102)	0.263
No	88.5 (70-110.25)	90 (65.5-114)	0.905
Statin used			
simvastatin	84.5 (61.5-106.25)	88.5 (65.75-98.75)	0.679
atorvastatin	83 (73.5-107)	97 (63-117.5)	0.794
Dose of statin			
Simvastatin 20mg	70 (51-92)	88 (65-95)	0.124
Simvastatin 40mg	103 (75-114.25)	89 (63.5-100)	0.277
Atorvastatin 20mg	88 (69.25-127.5)	117.5 (54-129.75)	0.818
Atorvastatin 40mg	88 (72.5-112)	96 (60-114.25)	0.900
Atorvastatin 80mg	82 (70-108)	98 (65-103)	0.900

Table 5

Level of HDL-C (mg/dL) – Data are median (IQR).

	>75 years	*≤75 years*	*p (Mann-Whitney)*
HDL-c Total sample	52.5 (43-62.25)	47 (38-57)	0.072
Sex			
Male	49 (36.5-60)	44.5 (33.25-49)	0.049
Female	53 (46-67.5)	55 (45-64)	0.740
History of coronary artery disease			
Yes	50 (39-60)	46 (36-53)	0.139
No	54 (46.75-66.75)	61 (45-64)	0.792
History of stroke			
Yes	53 (47-61)	41.5 (30-47)	0.078
No	51 (43-63)	49 (40-58)	0.166
Treated hypertension			
Yes	53 (43-61.5)	47 (38-55)	0.063
No	49 (40.5-68.5)	52 (32.25-63.75)	0.554
History of diabetes			
Yes	48 (38-60)	47.5 (38.5-53.75)	0.643
No	55 (46-66)	47 (36-61)	0.062
Statin used			
simvastatin	53 (42.5-66.5)	48 (38.5-54.75)	0.120
atorvastatin	51 (45.5-55.5)	45 (35-61)	0.430
Dose of statin			
Simvastatin 20mg	49 (41.25-67)	53 (38-59)	0.722
Simvastatin 40mg	55.5 (40-60.75)	46 (39.5-47)	0.111
Atorvastatin 20mg	46.5 (29-55.25)	45 (30.5-58.75)	0.900
Atorvastatin 40mg	52 (47.5-61)	57 (42-70)	0.900
Atorvastatin 80mg	61 (38-73)	41 (28-49)	0.400

Table 6

Level of triglycerides (mg/dL) – Data are median (IQR).

	>75 years	*≤75 years*	*p (Mann-Whitney)*
Triglycerides Total sample	108 (74.75-146.5)	133 (109-196.75)	0.003
Sex			
Male	89 (66-133.5)	136 (99-195)	0.005
Female	111 (94-160.5)	129 (115-202)	0.088
History of coronary artery disease			
Yes	108 (68-148.75)	124 (105-194)	0.052
No	108 (76.25-145.75)	167 (126-219)	0.005
History of stroke			
Yes	105 (77-145)	105 (99-140)	0.456
No	110 (74-151)	134 (111-195)	0.007
Treated hypertension			
Yes	106 (75.75-152)	135 (110.5-204.25)	0.006
No	113 (55.5-120)	123.5 (92.25-188)	0.208
History of diabetes			
Yes	109 (68-176)	137.5 (115.25-199)	0.077
No	107 (76-144)	125 (103.5-199)	0.019
Statin used			
simvastatin	105 (71.5-145.5)	120 (92-189)	0.097
atorvastatin	120 (78.5-170.5)	150 (115-219)	0.027
Dose of statin			
Simvastatin 20mg	89 (66-131)	119 (85-176)	0.088
Simvastatin 40mg	131 (105-155)	128 (107.75-279)	0.904
Atorvastatin 20mg	119 (103.25-214.75)	176 (129.25-246)	0.240
Atorvastatin 40mg	120 (78.5-172)	139 (111-211)	0.377
Atorvastatin 80mg	61 (46-176)	145 (99-163)	0.700

Table 7

Safety profile. Data are median (IQR).

	>75 years	*≤75 years*	*p (Mann-Whitney)*
Creatine phosphokinase (U/L)	97	110	0.202
Alanine transaminase (U/L)	16.5	20	0.004
Aspartate transaminase (U/L)	21	20	0.323

Table 8

Correlation between quantity of drugs and safety profile. Data are Spearman's rank correlation coefficient (p).

	Total sample	*>75 years*	*≤75 years*
Creatine phosphokinase (U/L)	-0.053 (0.598)	-0.480 (0.733)	-0.121 (0.414)
Alanine transaminase (U/L)	-0.126 (0.207)	-0.036 (0.794)	-0.304 (0.038)
Aspartate transaminase (U/L)	-0.215 (0.030)	-0.245 (0.071)	-0.168 (0.258)

drugs taken in one day in the patients in this sample (Figure 1).

Of course, elderly people have their own peculiarities, such as the presence of one or more clinical comorbidities and the concomitant use of various medications. Consequently, the safety of hypolipidemic drugs and drug interactions should be carefully evaluated in this age group. Age-related reduction in the efficacy of some metabolic pathways (particularly in the liver) may be a possible mechanism. Moreover, older individuals receive a greater number of medications, some of which may compete for hepatic detoxification.

As the data in this study were obtained from patients seen at a cardiology outpatient clinic, most of them were using statins for secondary prevention, and the main comorbidity observed was hypertension (80.2% of the total sample). In patients up to 75 years old, the prevalence of CAD is very important, and in the elderly over 75 years old, the prevalence of stroke (Table 2). This is due to the design of the study and because the antecedent of CAD is a very important indication for the treatment with statin in patients up to 75 years old. In the general population, the prevalence of CAD increases with age.

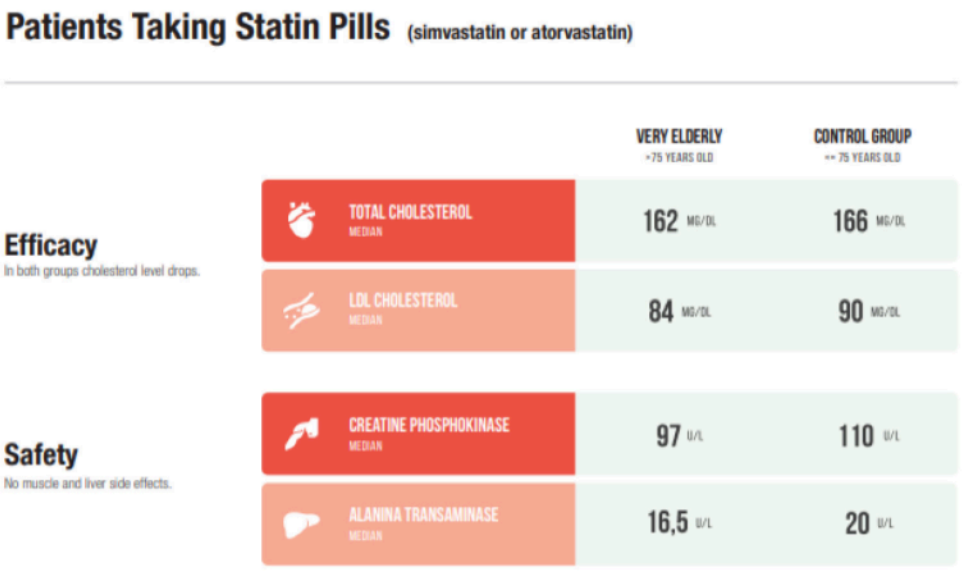

Figure 1 - The efficacy and safety of using statins in very elderly patients

In this work, statin treatment was effective in very elderly patients because the lipid level achieved was equal to or lower than the control group, as shown in tables 3 to 6. The level of total cholesterol (Table 3) is the same between groups. In the stratified analysis between the groups, this pattern is maintained, except for those using simvastatin 40mg. As this dose did not interfere with the levels of cholesterol fractions, and this result was not observed with other doses, this difference was probably due to chance. The LDL-C level (Table 4) is also the same between very elderly patients and the control group, and there was also no difference in the analysis stratified by groups, which corroborates the homogeneity between groups. HDL-C is also the same between groups (Table 5), with a tendency to be higher in the very elderly (and, therefore, these have a better lipid profile). In the analysis stratified by groups, it is observed that in male patients the HDL-C level is better in very elderly patients with statistical significance ($p = 0.049$). However, this difference was not observed in female patients. Triglyceride levels were significantly lower in the very elderly in this sample ($p = 0.003$). In the stratified analysis between groups (Table 6), this difference was observed in male patients and in those without a history of CAD, stroke, or diabetes. The type of statin also had an impact on triglyceride levels, being more significant with the use of atorvastatin. Therefore, very elderly patients have a better lipid profile compared to the control group in this sample. Both groups received similar treatment. This finding could be explained because very elderly patients over 75 years old are already naturally survivors, with better levels of lipids compared to the control group.

In patients over 65 years of age, the risk of ST-segment elevation infarction was much lower in chronic statin users compared to non-users. The estimates, according to one study, were similar in patients with and without a previous history of hypercholesterolemia, with benefit even after the age of 76 years[11].

In another study, those that stopped statins and continued with their other medication were at increased risk to be admitted to a hospital for heart failure complications, HR: 1.24 (1.07 - 1.43); have any cardiovascular outcome, HR: 1.14 (1.03 - 1.26); mortality, HR: 1.15 ((1.02 - 1.30) and have an emergency admission for any cause HR: 1.12 (1.05 – 1.19)[12].

To evaluate the effectiveness of the treatment, it is also important to check the time that the patients have been using the medication. According to Table 1, the median for the very elderly is 6 years, and 5 years for the control group. The distribution of this time between the groups is the same, with $p = 0.380$ (Mann-Whitney). Therefore, both groups have been using statins for a similar time, and this is sufficient for the full effect of the medication.

In this study, very elderly patients had important comorbidities such as chronic kidney disease (Table 1). The median creatinine clearance was 49.2 and 72.8 mL/min in very elderly patients and the control group, respectively, with $p < 0.001$ (Mann-Whitney). However, statin treatment in very elderly patients was safe in this sample.

Thus, the statins treatment is generally well tolerated, and their adverse effects are mild and transient, even in the elderly. There was no increase in muscle or liver enzymes in the included patients. According to Table 7, the ALT level was even lower

in very elderly patients than in the control group (p=0.004). A meta-analysis[13] in patients with 60 years of age and older showed that the main adverse effects of statin treatment are musculoskeletal symptoms with elevated CPK and liver enzymes. However, elevations of transaminases and CPK were similar in the statin and placebo group as well as the withdrawal of side effects. It is possible to start treatment with lower doses and progressively make the necessary adjustments according to drug tolerance, to minimize possible side effects.

For the analysis of the safety profile, we also checked the effect of other medications in use by patients in the safety profile. According to Table 1, the median number of drugs taken in one day by very elderly patients and the control group were 5 and 7 respectively, with no statistical difference, with p = 0.211 (Mann-Whitney). In this sample, the levels of CPK and transaminases did not increase with the number of drugs taken. On the contrary, they have decreased (Table 8), which suggests that the use of statins is safe in patients receiving other drugs such as antihypertensives and anti-diabetics. This finding should be interpreted with caution because it is a cross-sectional, non-randomized study. Further studies with appropriate design would be needed to better infer about drug safety.

In the PROSPER[9] study, for example, there was an increase in new cancer cases in patients treated with pravastatin (HR 1.25, CI 1.04-1.51). Subsequent meta-analyses were performed, including the PROSPER study itself, which did not confirm evidence of increased cancer risk and statin treatment[14].

A post-hoc analysis of the IMPROVE-IT study[15] showed that patients older than 75 years benefited from intensive hypolipidemic treatment compared to patients aged 65 to 74 years after hospitalization for acute coronary syndrome. Very elderly patients had an absolute cardiovascular risk reduction of 8.7% with intensive care (combination of ezetimibe and simvastatin). However, the absolute risk reduction was only 0.8% in patients aged 65 to 74 years and 0.9% aged 50 to 64 years. The IMPROVE-IT study showed a 6.4% reduction in the relative risk of primary outcome at 7 years. There was a tendency for greater relative risk reduction in very elderly patients. Therefore, it corroborates the benefit of intensive hypolipidemic therapy to reduce LDL-C level in elderly individuals with atherosclerotic cardiovascular disease. In a nationwide population-based cohort study in France[16], statin discontinuation was associated with 33% increased risk of admission for cardiovascular event in 75-year-old primary prevention patients. Also, this association was stronger for admissions for coronary events than for admissions for cerebrovascular events (46% and 26% increased risk, respectively).

The Cholesterol Treatment Trialists' (CTT) Collaboration did a very important meta-analysis[17] to verify the efficacy and safety of statin therapy in older people. They analyzed individual participant data from 27 randomized controlled trials. During 4.9 years of follow-up, major vascular events were significantly reduced by statin therapy among all age groups, including among the participants who were older than 75 years at randomization. But the trend towards smaller relative reductions with increasing age persisted, even after excluding heart failure and dialysis trials. However, as the absolute risk of these events was higher in older people, the absolute benefits were like those at young ages. They observed significant efficacy regardless of age among participants with previous vascular disease. And, despite previous concerns, they found no adverse effects on cancer or non-vascular mortality in any age group. They concluded that statins reduced vascular events irrespective of age, including in people older than 75 years. However, in the primary prevention setting among people older than 75 years, there is less evidence of the effects of statin therapy. But evidence supports the use of statin therapy in older people considered to have a sufficiently high risk of occlusive vascular events.

Although fewer patients older than 75 years were enrolled in clinical trials, a benefit has been seen in virtually every subgroup analysis[18]. The absolute CVD risk is much higher in older individuals, so the number of events potentially prevented with statin therapy is greater.

Addressed the evidence about deprescribing statins, with a focus on those with a life expectancy of less than a year. Researchers have found an increase in quality of life and no increases in cardiovascular events or death when statins were deprescribed.

Clinicians have debated whether prescribing statins to patients older than 75 for the prevention of cardiovascular events is appropriate.

Study limitations

Despite the interesting findings, our study has some limitations. It is a cross-sectional study, therefore without information on patient follow-up. Patients who presented significant intolerance or severe side effects due to treatment with statin requiring its interruption did not enter the sample according to the inclusion criteria adopted (being in use of statin at the moment of collection of data). This bias would be minimized if the study design was not transversal. Another limitation is the fact that it is a study made

of medical notes records. Therefore, it is assumed that patients were taking their medications correctly.

Conclusions

With the data obtained in this work, it is concluded that statin treatment in very elderly people is effective and safe. However, the decision whether to treat hypercholesterolemia in primary prevention in an older individual should be individualized, based on both chronological and biologic age. A patient with a limited life span from a concomitant illness (e.g., advanced cancer) is probably not a candidate for drug therapy. On the other hand, an otherwise healthy older individual should not be denied drug therapy simply based on age alone. These data encourage the use of these drugs in very elderly patients.

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