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Diastolic function parameters are improved by the addition of simvastatin to enalapril-based treatment in hypertensive individuals☆

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ABSTRACT

Objective: Diastolic dysfunction (DD) is a frequent condition in hypertensive patients whose presence increases mortality and whose treatment remains unclear. The aim of this study was to investigate in a prospective, double-blinded, placebo-controlled randomized design the additive effect of simvastatin on DD in enalapril-treated hypertensive patients with average cholesterol levels.
Methods: Hypertensive patients with DD and LDL-cholesterol <160 mg/dL underwent a run-in phase to achieve a systolic blood pressure (SBP) <135 mmHg and diastolic blood pressure (DBP) <85 mmHg with enalapril. Hydrochlorothiazide was added when need to achieve blood pressure control. Four weeks after reaching the optimum anti-hypertensive regimen patients were randomized to receive 80 mg simvastatin ($n=27$) or placebo ($n=28$) for a period of 20 weeks. Echocardiograms were performed before and after treatment with measurement of maximum left atrial volume (LAV), conventional and tissue Doppler velocities in early diastole (E, e′) and late diastole (A, a′).
Results: After 20 weeks, the simvastatin group presented reduction in SBP (-4 ± 2 mmHg, $p=0.02$), increase in E/A ratio (1.0 ± 0.05 to 1.2 ± 0.06, $p=0.03$) and decrease of LAV indexed to body surface area (24.5 ± 0.9 to 21.1 ± 0.8 ml/m^2, $p=0.048$), as compared with placebo arm. No change in systolic function and no correlation between the E/A ratio, LAV and changes in blood pressure or lipid profile were observed.
Conclusions: The addition of simvastatin to enalapril in hypertensive patients with average cholesterol levels improves parameters of diastolic function independently of changes in blood pressure or cholesterol.

1. Introduction

Diastolic dysfunction (DD) is the most common and early form of hypertension target lesion seen in clinical practice [1]. Its presence is related to higher morbidity and mortality which may be independent of blood pressure (BP) levels or the degree of left ventricular hypertrophy (LVH) [1,2]. Despite the frequency and clinical relevance, the reversal of DD remains a challenge. Intensive BP-lowering [3] and the inhibition of the rennin–angiotensin system (RAS) [4,5] have both been demonstrated to attenuate DD through their beneficial effects on left ventricular hypertrophy and fibrosis. There is evidence, however, indicating that the DD can persist partially or completely in a substantial number of patients with BP under control and treated by RAS inhibitors, indicating the need for complementary treatments [5].

In animal models, treatment with statins has been reported to reduce hypertrophy and interstitial fibrosis in the left ventricle (LV) with consequent improvement of diastolic function [6,7]. To date, however, such effects have not been confirmed in randomized controlled clinical trials. Moreover, it is unknown whether the effect of statin in DD is additive or not to the effect of ACE inhibitors.

Thus, the aim of this study was to investigate in a prospective, double-blinded, placebo-controlled randomized design the additive effect of simvastatin on enalapril on DD, assessed by transthoracic echocardiography, in hypertensive patients with average cholesterol levels.

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2. Methods

2.1. Endpoints

The prespecified primary endpoints were changes in ratio of the early (E) to late (A) transmitral peak velocity (E/A ratio) and in early diastolic mitral annular velocity (e′). Secondary endpoints were changes in systolic blood pressure (SBP), diastolic blood pressure (DBP), maximum left atrial volume (LAV), LV mass, LV wall thickness, E-wave deceleration time (E-DT), E/e′ ratio and mitral annulus systolic velocity (s). This report satisfies the recommended reporting guidelines for randomized controlled trials [8].

2.2. Sample size calculation and patients' selection

The sample size calculation took into account a 90% power and an alpha error of 5%. By these criteria, it was predicted the need of randomizing 42 patients divided in two arms to detect a mean difference of 0.19 ± 0.25 cm/s in the E/A ratio [4] and a mean difference of 3 ± 2 cm/s in the e′ velocity [9].

Inclusion criteria were hypertensive [10] men or postmenopausal women aged between 40 and 65 years old, fasting blood glucose <100 mg/dL and glucose tolerance test <140 mg/dL, waist circumference <102 cm (men) or < 88 cm (women), triglycerides <150 mg/dL, LDL-cholesterol ≤160 mg/dL, creatinine <1.2 mg/dL, sinus rhythm, the presence of grade 1 or 2 of DD with an LV ejection fraction (EF) > 55% and absence of myocardial ischemia during dobutamine stress echocardiography. The DD was considered in the presence of E-DT > 240 ms and E/A ratio < 0.9 and septal e′ < 10 cm/s (grade 1 or impaired relaxation) or E-DT = 160–240 ms, E/A ratio = 0.9–2.0, and septal e' < 8 cm/s in association with the LAV index ≥28 ml/m^2, septal E/e′ ≥ 15 or positive Valsalva maneuver (grade 2 or pseudonormal pattern) [11]. Exclusion criteria were thyroid dysfunction, acute or chronic liver disease, regular use of 3 or more antihypertensive drugs, secondary hypertension, symptoms or history of atherosclerotic disease, valvular dysfunction and use of statins in the last 6 months.

From 2006 to 2009, we evaluated 359 consecutive hypertensive men and women enrolled at the Brasilia's Health Department's Registry and who underwent detailed clinical examination and echocardiogram screening in order to select those who met all inclusion criteria. From this clinical screen, 62 patients were selected and accepted to participate in the study. The Institutional Ethics Committee approved the study and all participants signed the informed consent.

2.3. Study protocol

During the run-in phase, patients were treated by enalapril, which dose was adjusted weekly to achieve SBP ≤ 135 mmHg and DBP ≤ 85 mmHg. Hydrochlorothiazide 25 mg/day was added in 25 patients to achieve BP control. Seven patients were excluded because they require the addition of other antihypertensive drugs ($n = 3$) or had a persistent cough after enalapril ($n = 4$). Having reached the target SBP and DBP for four consecutive weeks in constant use of the same dose of antihypertensive drugs, patients underwent the drug treatment phase of the study and were allocated to simvastatin 80 mg/day (Zocor®, Merck, Sharp & Dohme, São Paulo, Brazil; $n = 27$) or placebo ($n = 28$) using block randomization stratified for gender during a treatment period of 20 weeks.

During experimental phase, patients were evaluated regularly every 4 weeks for assessment of BP, treatment adherence and presence of adverse effects. The study drugs were provided at each visit and treatment adherence was checked by counting pills remaining from the previous 4 weeks. The average of at least two measures of BP, after 10 min of rest, with properly calibrated sphygmomanometer was obtained [10]. Anti-hypertensive treatment was adjusted as necessary to maintain therapeutic goal.

2.4. Biochemical analyses

Every 8 weeks, the following measurements were performed: total cholesterol (CHOD-PAP, Roche Diagnostics, Mannheim, Germany), triglycerides (GPO-PAP, Roche Diagnostics, Mannheim, Germany), high-density lipoprotein (HDL) cholesterol (Roche Diagnostics, Mannheim, Germany), creatine phosphokinase (CPK), and alanine (ALT) and aspartate (AST) aminotransferases (Roche Diagnostics, Mannheim, Germany). LDL-cholesterol was calculated by the Friedewald formula. During the study, the results were made available exclusively for the Safety Monitoring Committee.

2.5. Echocardiography

All examinations were conducted by one experienced physician echocadiographer (A.L.S.B) who were blinded for the patient's experimental treatment. A comprehensive 2-dimensional and Doppler echocardiogram (HDI 5000, Philips ATL, Bothell, WA) using 2/4 MHz transducer and second harmonic imaging was carried out in the morning period in all patients at the beginning and end of experimental treatment. BP was measured at the time of echocardiographic exam initiation. LV M-mode measurements of wall thickness and end-diastolic and end-systolic diameters were used for calculation of fractional shortening, relative wall thickness (RWT) and LV mass, which was indexed to body surface area (BSA) [12]. LV remodeling was defined as RWT ≥ 0.42 and LVH was defined as LV mass index was >115 g/m^2 in men or >95 g/m^2 in women, respectively [12]. LV EF was determined by Teichholz method [12]. LAV was calculated by modified Simpson's method on the apical 4 and 2 chambers and indexed to BSA (LAVi) [12]. LAV was measured in the frame just before mitral valve opening excluding the LA appendage and pulmonary veins. The plane of mitral annulus defined the LA inferior border. Mitral inflow velocities were recorded in the apical 4-chamber view with the pulsed-wave Doppler sample volume placed at the level of the mitral valve tips. The peak velocity of early (E) and late (A) diastolic waves and the E-DT were measured. The E/A ratio was calculated at rest and during Valsalva maneuver. The peak myocardial systolic (s′), early diastolic (e′), and late diastolic (a′) velocities were measured in the apical 4- and 2-chamber views using Doppler tissue imaging (DTI) with a 2 mm sample volume placed at the at the septal, lateral, anterior and inferior mitral annulus. All DTI parameters were considered the average of these four sites. Mean E/e′ was calculated. All Doppler measurements were obtained during expiratory apnea. All data were stored on optical disk and an independent physician, blinded to clinical data and image process, performed the analyses off line. All values were the average of 3 beats.

Measurements of LAV and of conventional and tissue Doppler at rest were repeated in 10 patients by the same observer who performed the initial measures and by a second observer equally unaware of patient data to verify the intra- and inter-observer variability. The coefficients of intra-observer and inter-observer variability were 0.77% and 1.04% for the Doppler measurements, and 1.1% and 3.8% for LAV measurements, respectively.

2.6. Statistical methods

Patients, researchers and analysts of the results were blind to the echocardiographic findings and to the treatment used. Statistical analyses were performed using JMP and SAS 9.2 software applications (SAS Institute, Cary, NC, USA). All the analyses were performed on an intention to treat basis and were adjusted for gender and age. Continuous variables were presented as mean ± standard deviation

Table 1
Baseline characteristics of patients in the study groups.

Characteristics	Placebo (n = 28)	Statin (n= 26)	p
Age, years	54 ± 1.1	54.2± 1.1	0.93
Male, *n* (%)	15 (54)	13(50)	1.00
Smoking, *n* (%)	3 (11)	4 (15)	0.69
Body mass index (kg/m^2)	27 ± 1	26 ± 1	0.51
Family history of CAD, *n* (%)	5 (17.9)	0 (0)	0.05
Waist circumference (cm)	93 ± 1	91 ± 1	0.16
Sedentary, *n* (%)	11 (41)	16 (59)	0.17
Left ventricular hypertrophy, *n* (%)	2 (7.1)	0 (0)	0.49
Left ventricular remodeling, *n* (%)	1 (3.5)	3 (11.5)	0.35
Framingham risk score, % in 10 years	6.5 ± 0.9	6.5 ±1.3	0.86
Time from hypertension diagnosis (years)	11.3 ± 1.3	12.2 ± 1.6	0.67
Time of treatment for hypertension (years)	10.2 ± 1.0	11.5 ± 1.5	0.81
Medications prior to the study			
ACE Inhibitors, *n* (%)	27(96)	23 (88)	0.34
Beta blockers, *n* (%)	2 (7)	4 (15)	0.41
Diuretics, *n* (%)	9 (32)	13 (50)	0.18
Blood pressure prior to the study entry			
SBP (mmHg)	129 ± 14	137 ± 20	0.07
DBP (mmHg)	77 ± 11	81 ± 14	0.14
Medications at the randomization			
Enalapril dose (mg/day)	24 ± 2	24 ± 5	0.99
Use of hydrochlorothiazide, *n* (%)	15 (54)	10 (39)	0.29

and categorical variables as absolute number (n) and frequencies (%). Statistical significance was considered $p < 0.05$. Differences in baseline characteristics between groups were evaluated with the Student t test or the nonparametric Mann–Whitney test for continuous variables and the chi-square test for categorical variables. Comparisons between the groups regarding the effects of treatments on BP, lipid profile and echocardiographic variables were made by the Student t test for comparison variations between groups and within each group. To compare the dose of enalapril, a logarithmic scale was used to normalize the distribution. To evaluate the correlation between changes in diastolic parameters and variations in BP and lipid profile, we used the linear correlation coefficient of Pearson.

3. Results

3.1. Clinical baseline and follow-up data

Clinical data at the time of randomization are shown in Tables 1 and 2 (baseline). There was no significant difference between the groups. However, family history of coronary disease tended to be more frequent in the placebo group. Only two patients had LVH and four had LV remodeling. During the experimental phase, one patient of the simvastatin group was excluded after manifesting acute thyroiditis. Therefore, 54 patients completed the study. Adherence to therapy was 100% in both groups.

After run-in period, patients started the experimental phase of the study with an adequate control of BP (Table 2). The daily doses of enalapril were equivalent at randomization (Table 1) and at the end of the study in the placebo and simvastatin (27 ± 2 mg/day vs. 26 ± 2 mg/day; inter groups $p = 0.9$, respectively). The frequency of the use of hydrochlorothiazide were equivalent in both groups at randomization (Table 1) and during the experimental phase (54% vs. 39%, inter groups $p = 0.67$). There was no difference in the baseline measure and no change in BMI during the experimental period in both placebo and simvastatin arms (−0.1 ± 0.1 kg/m^2 vs. 0.03 ± 0.1 kg/m^2; inter groups $p = 0.65$, respectively).

As expected, the statin group presented a reduction of LDL-cholesterol and triglyceride levels, reaching significance from the 8th and 20th weeks, respectively (Table 2). The levels of

Table 2
Changes in SBP, DBP, heart rate and lipid profile during the experimental treatment.

	Baseline	4 weeks	8 weeks	12 weeks	16 weeks	20 weeks	Variation
SBP (mmHg)							
Placebo	125 ± 2	129 ± 3	124 ± 3	124 ± 2	122 ± 3	129 ± 3	5 ± 3
Statin	130 ± 3	127 ± 3	128 ± 3	127 ± 3	124 ± 2	126 ± 3*	−4 ± 2*
DBP (mmHg)							
Placebo	73 ± 2	76 ± 2	73 ± 1	72 ± 1	74 ± 2	75 ± 2	2 ± 2
Statin	73 ± 2	76 ± 2	75 ± 2	76 ± 2	74 ± 2	74 ± 2	2 ± 2
Heart rate (bpm)							
Placebo	71 ± 2	71 ± 2	67 ± 2	67 ± 2	68 ± 2	71 ± 2	−0.4 ± 2.4
Statin	68 ± 2	67 ± 1	70 ± 1	67 ± 1	67 ± 2	68 ± 2	−0.2 ± 2.7
LDL-cholesterol (mg/dL)							
Placebo	122 ± 5	–	124 ± 6	–	129 ± 6	130 ± 6	10 ± 5
Statin	119 ± 6	–	74 ± 5‡	–	75 ± 4‡	78 ± 5‡	−41 ± 6‡
HDL-cholesterol (mg/dL)							
Placebo	51 ± 3	–	51 ± 2	–	50 ± 2	47 ± 2	−3 ± 1
Statin	47 ± 3	–	48 ± 2	–	47 ± 2	46 ± 2	−2 ± 2
Triglycerides (mg/dL)							
Placebo	114 ± 11	–	117 ± 12	–	113 ± 13	129 ± 13	15 ± 8
Statin	117 ± 11	–	102 ± 9	–	91 ± 6	94 ± 7**	−23 ± 11**

* $p < 0.05$.
** $p < 0.001$.
‡ $p < 0.0001$ for the difference between treatment groups.

Table 3
Echocardiographic changes during treatment with simvastatin or placebo.

	Placebo ($n=28$)		Statin ($n=26$)		Variation		
Variables	Baseline	20th week	Baseline	20th week	Placebo	Statin	Inter groups p
Indexed LAV (ml/m^2)	23.5 ± 1.0	23.2 ± 1.1	24.5 ± 0.9	21.1 ± 0.8	−0.3 ± 1.2	−3.3 ± 0.9**	0.048
Septal thickness (mm)	8.54 ± 0.84	8.19 ± 0.84	8.48 ± 0.81	8.10 ± 0.89	−0.34 ± 0.91*	−0.38 ± 0.85*	0.88
Posterior wall thickness (mm)	8.66 ± 0.84	8.19 ± 0.84	8.55 ± 0.81	8.15 ± 0.89	−0.47 ± 0.89*	−0.39 ± 0.82*	0.76
LV diastolic diameter (mm)	48.4 ± 0.7	49.1 ± 0.7	46.7 ± 0.7	48.4 ± 0.7	0.69 ± 0.4	1.69 ± 0.4**	0.12
LV systolic diameter (mm)	29.3 ± 0.6	29.0 ± 0.6	28.6 ± 0.6	29.0 ± 0.6	−0.28 ± 0.3	0.42 ± 0.45	0.15
LV ejection fraction (%)	69.3 ± 0.9	71.3 ± 0.9	68.7 ± 0.9	70.0 ± 1.0	2.1 ± 0.8	1.3 ± 0.9	0.53
Relative wall thickness	0.35 ± 0.0	0.33 ± 0.0	0.36 ± 0.0	0.34 ± 0.0	−0.02 ± 0.0*	−0.03 ± 0.0**	0.71
Indexed LV mass (g/m^2)	81 ± 3	79 ± 3	78 ± 3	76 ± 3	−2 ± 3	−1.8 ± 3.1	0.94
Conventional Doppler							
Transmitral E velocity (cm/s)	64 ± 3	66 ± 3	63 ± 4	69 ± 4	2.3 ± 2.7	5.4 ± 2.4*	0.37
Transmitral A velocity (cm/s)	63 ± 3	64 ± 3	65 ± 3	63 ± 4	0.9 ± 2.6	−2.7 ± 2.9	0.37
E/A ratio	1.1 ± 0.1	1.1 ± 0.1	1.0 ± 0.1	1.2 ± 0.1	0.0 ± 0.05	0.2 ± 0.1**	0.03
E deceleration time (ms)	242 ± 12	222 ± 10	229 ± 10	216 ± 10	−12 ± 3	−14 ± 3	0.93
Tissue Doppler							
Peak velocity of e′ (cm/s)	9.7 ± 0.6	10.1 ± 0.6	9.6 ± 0.6	10.2 ± 0.5	0.3 ± 0.3	0.6 ± 0.3	0.51
Peak velocity of a′ (cm/s)	10.5 ± 0.3	10.5 ± 0.3	10.0 ± 0.3	10.1 ± 0.3	−0.02 ± 0.3	0.08 ± 0.3	0.76
Peak velocity of s (cm/s)	8.8 ± 0.4	9.0 ± 0.5	8.6 ± 0.5	8.9 ± 0.5	0.2 ± 0.2	0.2 ± 0.2	0.84
e′/a′ ratio	1.1 ± 0.1	1.0 ± 0.04	1.0 ± 0.1	1.0 ± 0.1	−0.1 ± 0.1	0.1 ± 0.1	0.40
E/e′ ratio	6.9 ± 0.4	6.9 ± 0.4	7.1 ± 0.4	7.1 ± 0.4	−0.0 ± 0.2	−0.1 ± 0.3	0.99

Intra-group differences: *$p<0.05$, **$p<0.001$; LAV: left atrial volume; LV: left ventricle.

HDL-cholesterol did not change significantly in either group (Table 2). There was a significantly difference in the changing of SBP in the statin group as compared to the placebo group reaching significance at the 20th week (Table 2). There was a significantly greater reduction in SBP in the statin group compared to the placebo group reaching significance at the 20th week (Table 2). The changes in DBP and in heart rate during the experimental phase were not significantly different between groups. There was a moderate and significant positive correlation between changes in SBP and in LDL-cholesterol in the statin group ($r=0.54$, $p=0.004$).

In the statin group, one patient complained of nausea and three patients manifested hypotension requiring the reduction of the antihypertensive dose. In the placebo group one patient had nausea and diarrhea that remitted spontaneously. Elevation of ALT was significantly higher in the statin group than the placebo group (statin: 38 ± 3 to 54 ± 4 U/L vs. placebo: 38 ± 3 to 42 ± 3 U/L; $p<0.05$). There was no significant difference in the elevation of AST (statin: 19 ± 1 to 31 ± 2 U/L vs. placebo: 19 ± 1 to 24 ± 2 U/L; p = NS) and CPK (statin: 89 ± 7 to 117 ± 14 U/L vs. placebo: 102 ± 10 to 162 ± 27 U/L; p = NS) between the groups.

3.2. Echocardiography

At randomization, there was no significant difference in echocardiographic parameters between the groups (Table 3). After 20 weeks, there was a slight but significant reduction in posterior wall thickness, interventricular septum thickness and relative thickness of the LV in both groups ($p<0.05$) but there were no differences between groups.

The statin group presented increase in E/A ratio (1.0 ± 0.05 to 1.2 ± 0.06, intra group $p=0.005$ and inter groups $p=0.03$) and decrease of LAVi (24.5 ± 0.9 to 21.1 ± 0.8 ml/m^2, intra group $p<0.001$, inter group $p=0.048$), as compared with placebo arm. The difference between groups in E/A ratio and LAVi were significant even after adjustment for gender, age and baseline values ($p<0.05$). Also, it was observed slight but significant increases in E velocity ($p=0.04$) and trend to increase e′ velocity ($p=0.05$), however, these changes did not reach statistical significance in the comparison between groups. There were no significant differences in the changes of other Doppler diastolic (A, a', e/a ratio, E/e' ratio) or systolic(s) variables between the groups (Table 3). No significant correlations between the E/A ratio, LAVi and changes in BP or lipid profile were observed.

4. Discussion

This is the first randomized, double-blind, placebo-controlled study designed to evaluate the effect of statins on DD parameters of hypertensive patients with average cholesterol levels and with blood-pressure controlled by RAS inhibitor. The major new finding of this research is that statins improves parameters of LV diastolic function in such patients. Although the effect on diastolic function parameters was small in magnitude, the potential relevance of this effect was reflected by the significant reduction of the LAV.

As expected, enalapril treatment reduced the relative thickness of the LV. Importantly, such reversal LV remodeling was mostly observed in patients in early stage of hypertension. In parallel to this RAS inhibitor effect, patients who also received simvastatin had significant increase of E/A ratio and decrease of the LAVi. Consistently, the e′ wave presented a trend to increase in the group treated by simvastatin, but not in the placebo group. For the latter, however, the study was not powered enough to detect inter groups difference.

In normotensive, hypercholesteromic individuals, previous investigations of the statin effect on DD have shown conflicting results [13–15]. The limited sample size, the nonrandomized uncontrolled design and the difference in the clinical background between these investigations and the present study hampers any comparison of results.

Isolated increase of the E/A ratio does not necessarily indicate attenuation of DD. It may indicate a pseudonormalization of E/A ratio by increasing the filling pressures of the LV [11]. In the pseudonormalization, however, as the LV filling pressure increases, the volume of LA increases [16]. Hence, in the presence of LAV reduction, the concomitant increase in the E/A ratio suggests decrease in the LV filling pressure and therefore the improvement of the diastolic function.

The change in E/A ratio and LAV did not correlate with the change in BP or in the relative thickness of the LV, suggesting that the action of statin on the DD, in this well-treated hypertensive population, is at least partly independent of its anti-hypertensive effect and its effect on the regression of the LV mass. Although a reduction in BP and LV mass are undoubtedly important determinants of improvement in diastolic function [3,5], evidences indicate that regression of myocardial fibrosis also play a significant and independent role [4]. In fact, myocardial fibrosis is associated with decrease of E/A ratio [17] and increase of LAV [18].

In the mechanistic standpoint, studies in animal models have demonstrated that statins reduce myocardial fibrosis by increasing the bioavailability of nitric oxide, reducing inflammation, RAS activity, oxidative stress and content of collagen type I in the LV wall [6,7]. This effect seems to be at least partially independent of plasma cholesterol lowering. In parallel, LAV has a positive correlation with the time constant of relaxation [19]. Thus, as not mutually exclusive mechanisms, it is possible that the effect of statins on the DD occurs by a combined effect on LV stiffness and relaxation. Nevertheless, further studies are required to confirm this assumption.

Consistent with a recent meta-analysis [20], we observed a significant reduction in rest peripheral SBP after treatment with statins. In the present study, however, in contrast with a prior study in our group [21], the reduction only reached statistical significance for SBP. Possibly the lower levels of plasma cholesterol and DBP in the present study participants and the adjustment of antihypertensive medications to keep SBP and DBP under control may have caused the difference in results. It is plausible to infer that part of the effect of the statin treatment in attenuating DD has elapsed from SBP reduction. Even in the absence of correlation between the change in SBP and changes in parameters of diastolic function, the role of SBP cannot be ruled out.

In interpreting our results, certain limitations must be considered. Firstly, despite the reversal of DD have been demonstrated in animal models after 8 weeks of treatment with statins [6], the time required to verify the maximal effect of statins on the DD of hypertensive individuals remains unknown. Secondly, the marginal statistical significance we found in some results suggests that the sample size may have been underestimated and hidden subtle differences between the groups. Thirdly, as the study was conducted in a specific population, our findings cannot be extrapolated to patients with other diseases that directly or indirectly influence the diastolic function such as diabetes mellitus or obesity. To compensate these limitations, the study was assessed in a rigorous randomized, double-blind, placebo-controlled.

In hypertensive patients, observational studies have indicated that for each decrease of 0.3 in the E/A ratio there is a 21% increase in the risk of cardiovascular events [2]. In parallel, the increase of the LAV independently predicts the incidence of atrial fibrillation, heart failure, stroke and cardiovascular death even in patients without known cardiovascular disease [22]. Hence, even such small increase in E/A ratio and reduction of LAV, as observed in this study, deserves consideration for its potential clinical impact. Still, studies with clinical endpoints in hypertensive patients with DD are required to confirm such a new target for statin treatment.

In conclusion, in this randomized, double-blind, placebo-controlled clinical trial, a 20-week period of treatment with simvastatin at high dose (80 mg/day) increases the E/A ratio and decreases the LAV in hypertensive individuals presenting DD and average cholesterol levels.

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