

Treatment with atorvastatin is associated with a better prognosis in chronic heart failure with systolic dysfunction: results from The Daunia Heart Failure Registry

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Published online: 28 May 2013

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Abstract

Background Few works have evaluated the effect of statins on left ventricular dysfunction in patients with chronic heart failure (CHF), by using tissue Doppler imaging (TDI). We therefore aimed to investigate whether atorvastatin treatment may influence prognosis and myocardial performance evaluated by TDI in subjects with CHF.

Methods Five hundred thirty-two consecutive CHF outpatients enrolled in a local registry, the Daunia Heart Failure Registry, were prospectively analysed. 195 patients with CHF and left ventricular ejection fraction (LVEF) $\leq 40\%$, either in treatment with atorvastatin (N: 114) or without statins (N: 81), underwent TDI examination. Adverse events were evaluated during follow-up.

Results The atorvastatin group showed a lower incidence of adverse events (cardiac death: 0 % vs 7 %, $p < 0.01$), and better TDI performance (E/E' 15 ± 5.7 vs 18 ± 8.3 , $p < 0.001$) than controls. Ischaemic CHF patients in treatment with atorvastatin also showed a lower incidence of adverse events (death: 10 % vs 26 %, $p < 0.05$; sustained ventricular arrhythmias: 5 % vs 19 %, $p < 0.05$, cardiac death: 0 vs 8 %, $p < 0.05$) and better TDI performance (E/E' ratio: 15.00 ± 5.68 vs 19.72 ± 9.14 , $p < 0.01$; St: 353.70 ± 48.96 vs 303.33 ± 68.52 msec, $p < 0.01$) than controls. The association between atorvastatin and lower rates of cardiac death remained statistically significant even after correction in a multivariable analysis (RR 0.83, 95 % CI 0.71–0.96, $p < 0.05$ in CHF with LVEF $\leq 40\%$; RR 0.77, 95 % CI 0.62–0.95, $p < 0.05$ in ischaemic CHF with LVEF $\leq 40\%$).

Conclusions Treatment with atorvastatin in outpatients with systolic CHF is associated with fewer cardiac deaths, and a better left ventricular performance, as assessed by TDI.

Keywords Chronic heart failure · Atorvastatin · Echocardiography · Tissue Doppler imaging

Introduction

Chronic heart failure (CHF) is characterised by an impaired systolic and diastolic function and an inflammatory activation.

Left ventricular (LV) performance may be assessed with several methods: Tissue Doppler imaging (TDI) is an optimal echocardiographic tool for quantitative assessment of LV systolic and diastolic function. TDI can be used to measure systolic time (St) and ejection time (ET) intervals in a noninvasive, geometrically independent, easily applicable fashion [1, 2]. Few authors, however, have evaluated these intervals in CHF patients [3, 4].

Observational studies [5–7], prospective studies [8–12], and post-hoc analyses [13–16] of randomised clinical trials have suggested that statins could be beneficial in patients with CHF. The mechanisms of possible beneficial effects of statin administration in CHF patients are not completely known. Small prospective clinical studies with atorvastatin and simvastatin in systolic HF have documented an improved LV systolic function and decreased inflammatory biomarkers levels after statin therapy [17].

Few works, however, have evaluated the effect of statin therapy on LV dysfunction in patients with CHF, particularly using TDI [18]. We therefore aimed to investigate whether atorvastatin administration may influence prognosis and myocardial performance evaluated by TDI in subjects with

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CHF enrolled in a local registry of patients with CHF: the Daunia Heart Failure Registry.

Methods

Between 1 January 2009 and 1 January 2012, a total of 532 consecutive outpatients with CHF were enrolled in the

Daunia Heart Failure Registry [19]. We prospectively analysed 195 outpatients with CHF and left ventricular ejection fraction (LVEF) $\leq 40\%$ either on treatment with atorvastatin (N: 114) or without statins (N: 81); their clinical characteristics are given in Table 1. Medical history, heart rate, systolic blood pressure, body mass index, New York Heart Association class, and medications were recorded. All patients underwent conventional 2D and TDI

Table 1 Clinical characteristics of CHF with LVEF $\leq 40\%$ (atorvastatin group vs controls)

	Atorvastatin	Controls	<i>P</i>
Age (years)	66.39±10.026	60.36±14.949	0.000926
Male (%)	80	83	0.614004
BMI kg/m ²	29.23±4.534	28.82±4.868	0.574937
weight (Kg)	76.89±13.706	79.07±18.209	0.369687
Height (cm)	162.68±9.149	165.30±10.164	0.081052
HR (bpm)	75.48±15.194	81.05±18.568	0.024752
SBP(mmHg)	121.14±23.644	116.30±22.071	0.158772
Ischaemic heart disease (%)	61	33	0.000180
Hypertension (%)	71	39	0.000011
COPD(%)	56	46	0.147249
Diabetes(%)	25	23	0.675104
Chronic kidney failure(%)	38	28	0.136508
Creatinine	1.57±0.463	1.41±0.540	0.136997
III-IV NYHA (%)	70	77	0.249199
AICD/CRT-D(%)	41	38	0.862190
Ivabradine (%)	6	2	0.230706
ACE-/ARB (%)	82	72	0.316212
Beta-blockers (%)	93	85	0.077681
Digoxin (%)	10	17	0.128924
Diuretics (%)	95	85	0.023130
NT-pro-BNP (pg/ml)	1413.63±1478.539	2124.88±3122.134	0.018
CRP (mg/dl)	3.57±4.102	9.68±14.015	0.000000
LVEF(%)	29.61±6.59	28.11±6.43	0.116897
LVEDD (mm)	62.71±9.453	66.04±9.920	0.019201
LVESD (mm)	53.57±12.089	56.63±9.983	0.141467
E (cm/s)	82.23±32.838	97.66±34.572	0.003651
A (cm/s)	81.60±26.477	74.63±33.520	0.193353
E/A	1.76±0.870	2.20±0.888	0.001352
EDT (ms)	203.64±95.741	173.68±83.218	0.041187
E/E'	14.91±5.779	18.23±8.367	0.003135
S (cm/s)	8.09±2.7332	4.79±1.365	0.322023
E' (cm/s)	6.50±3.173	6.08±2.840	0.379821
Peak VO ₂ (ml/kg/m)	12.58±3.500	12.63±3.895	0.58
%AT	36.93	32.81	0.690214
VO ₂ /WR slope	10.74±1.526	10.93±2.386	0.044
O ₂ pulse %	76.42	58.00	0.003820
RER	1.05±0.127	1.08±0.081	0.378357
VE/VCO ₂ slope	30.76±6.304	32.92±6.183	0.281642
Watts	63.45±26.204	61.78±19.598	0.813435
6MWT (m)	301.60±106.051	314.80±90.320	0.837493

echocardiography in the ambulatory setting and under resting conditions. Clinical follow-up was performed every 6 months for a mean 318 ± 262 days follow-up. Clinical follow-up was anticipated in case of worsening decompensated HF. Patients were then analysed according to the presence of coronary heart disease (patients with a history of previous myocardial infarction, known coronary artery disease, prior percutaneous coronary interventions (PCI) and coronary artery bypass grafting (CABG)). Incidence of major adverse cardiac events (cardiac death, readmission for HF and ventricular arrhythmias) was evaluated by direct clinical examination or by direct interrogation of a next of a kin. Cardiac death was considered if death occurred suddenly or was associated with documented myocardial infarction, congestive HF and malignant ventricular arrhythmias.

All patients gave written informed consent. The study was approved by the local ethics committee and was conducted according the ethical standards for experiments in human subjects established by the Declaration of Helsinki.

Echocardiography

Conventional echocardiography was used to assess LV dimensions and ejection fraction (EF), peak velocities of trans-mitral early (E) and late diastolic (A) LV filling, the ratio of trans-mitral early to late (E/A ratio) LV filling velocity, and E-deceleration time (EDT). TDI measurements recorded at the mitral annulus in apical four-chamber view included systolic velocity (S'), early (E') and late (A') diastolic velocities, the ratio of early to late diastolic velocity (E'/A'). The trans-mitral to mitral annular early diastolic velocity ratio (E/E') was calculated.

ICT (ICT: end of A' wave to start of S), ET (start of S wave to end of S wave), St (end of A' wave to end of S wave), IRT (IRT: end of S wave to start of E'), FT (start of E' to end of A'), ICT/ET and MPI (Myocardial Performance Index: $[ICT + IRT]/ET$) were also calculated by TDI (Fig. 1).

Transthoracic echocardiography was performed with the use of iE33 (Philips Medical Systems, Andover, MA, USA). All echocardiographic studies were performed and interpreted by experienced physicians. LV dimensions and LVEF were calculated according to the recommendations in the combined American Society of Echocardiography/European Society of Cardiology guidelines. LVEF was calculated according to Simpson's rule. Pulsed Doppler mitral inflow velocities were obtained by placing a 1–2 mm sample volume between the tips of the mitral leaflets in the apical four-chamber view. The Doppler beam was aligned parallel to direction of flow.

TDI was performed using apical views for the long-axis motion of the ventricles as previously described [20]. Two-dimensional echocardiography with TDI colour imaging was

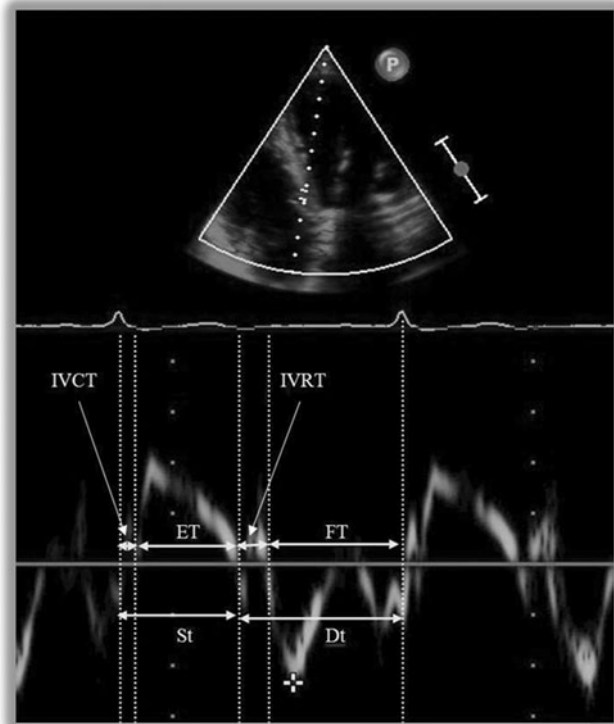


Fig. 1 TDI measurements recorded at the septal mitral annulus in the apical four-chamber view: ICT (ICT: end of A' wave to start of S), ET (start of S wave to end of S wave), St (end of A' wave to end of S wave), IRT (IRT: end of S wave to start of E'), FT (start of E' to end of A') and MPI (Myocardial Performance Index: $[ICT + IRT]/ET$) were calculated by TDI

performed with an S5-1 Sector Array Transducer with PureWave Crystal Technology (5 to 1 MHz). Two-dimensional echocardiography with TDI colour imaging views was optimised for pulse repetition frequency, colour saturation, sector size, and depth and was allowed the highest possible frame rate. At least three consecutive beats were stored, and the images were analysed offline with the aid of a customised software package (QLAB quantification software, Philips).

Statistical analysis

Continuous variables were expressed as mean \pm standard deviation, categorical variables were presented as percentages. Mean values were compared with Student's *t*-test for variables with a normal distribution or with the Mann–Whitney non-parametric *U* test for variables with a non-normal distribution. Percentages were compared with the χ^2 test. Event-free survival was shown with Kaplan-Maier curves and compared with the log-rank test. Univariate results were corrected in a multivariate analysis for age, gender and LVEF and other significant factors. A $p < 0.05$ was considered to be statistically significant.

Results

We prospectively analysed 195 outpatients with CHF and LVEF ≤40 %; in these patients, atorvastatin therapy was associated with a lower incidence of cardiac death (0 % vs 7 %, *p*<0.01) than in controls. The association remained statistically significant even after correction in a multivariable analysis for age, gender, LVEF, ACE-inhibitors and beta-blocker therapy (RR 0.83, 95 % CI 0.71–0.96, *p*<0.05 in CHF with LVEF ≤40 %) (Fig. 2).

Patients treated with atorvastatin were characterised by lower values of E (82.23±32.8 cm/sec vs 97.6±34.5 cm/sec, *p*: 0.01), E/A ratio (1.7±0.8 vs 2.2±0.8, *p*<0.001) and E/E' ratio (15±5.7 vs 18±8.3, *p*<0.01) and higher values of EDT (203.6±95.7 ms vs 173.6±83.2 ms, *p*<0.05) (Table 1).

Ischaemic CHF patients with LVEF ≤40 % on treatment with atorvastatin also showed a lower incidence of adverse events (death: 10 % vs 26 %, *p*<0.05; sustained ventricular arrhythmias: 5 % vs 19 %, *p*<0.05, cardiac death: 0 vs 8 %, *p*<0.05) and better Doppler findings, as lower values of E/E' ratio (15.00±5.68 vs 19.72±9.14, *p*<0.01), E/A ratio (1.85±0.90 vs 2.48±0.82, *p*<0.01), higher values of St: 353.70±48.96 vs 303.33±68.52 msec, *p*<0.01) than controls. The association between atorvastatin and lower rates of cardiac death in this group remained statistically significant even after correction in a multivariable analysis for age, gender, LVEF, ACE-inhibitor and beta-blocker therapy (RR 0.77, 95 %-CI 0.62–0.95, *p*<0.05 in ischaemic CHF with LVEF ≤40 %) (Fig. 3). Kaplan-Maier survival analysis

showed higher rates of cardiac death in subjects not receiving therapy with atorvastatin (log rank *p*<0.01) (Fig. 4).

Ischaemic CHF outpatients in treatment with atorvastatin (N: 137), showed longer systolic and diastolic time intervals: (IRT: 124.06±49.23 vs 86.35±32.87 ms, *p*<0.01; St: 354.00±44.82 vs 322.18±62.54 ms, *p*<0.05; FT: 379.37±121.08 vs 317.94±87.61, *p*<0.05; Dt: 503.43±131.94 vs 404.29±89.82, *p*<0.01) than controls (N: 44). (Table 2).

Discussion

Chronic heart failure is a major healthcare problem associated with high morbidity and mortality. Despite significant progress in treatment strategies, the prognosis of heart failure patients remains poor [21]. Several observational studies on HF cohorts have linked statin therapy with an improved survival [10–15]. The current available evidence suggests that statins work just as well in women as in men, for preventing both heart attacks and strokes [22].

Previous evidence shows that, in patients with prior myocardial infarction, statin therapy initiated before hospital discharge significantly reduces subsequent hospitalisations for HF [23, 24]; initiation and maintenance of treatment with statins is associated with better survival in patients with LV systolic dysfunction [25] and a significant reduction in cardiac morbidity [26]. However, the mechanisms of possible beneficial effects are not completely understood.

Fig. 2 Multivariable analysis for age, gender, LVEF, ACE-inhibitors and beta-blockers therapy in CHF patients with LVEF ≤40 % (ischaemic and non aetiology)

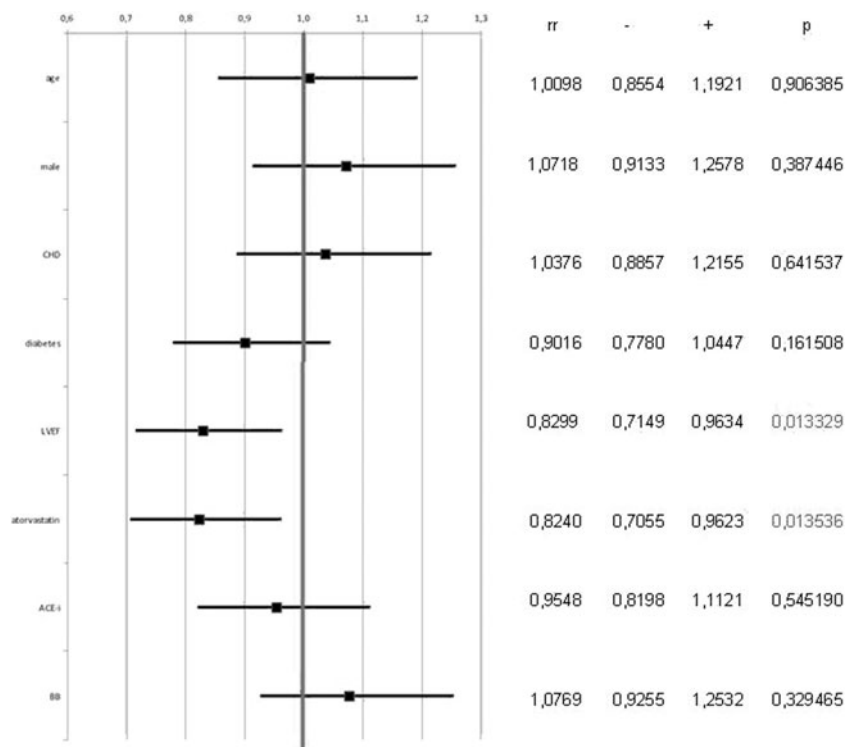
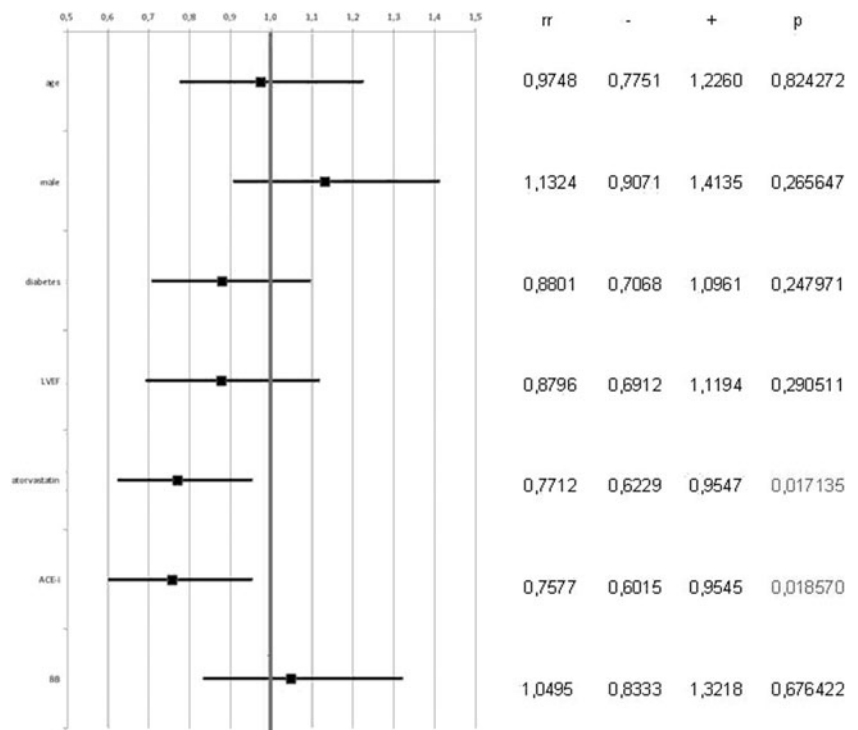


Fig. 3 Multivariable analysis for age, gender, LVEF, ACE-inhibitors and beta-blockers therapy in ischemic CHF patients with LVEF ≤40 %



Krum et al. [13] retrospectively analysed the Valsartan Heart Failure Trial (Val-HeFT) database to determine outcomes in CHF patients with mild to moderate systolic chronic heart failure according to statin use at baseline, and they showed that mortality over a mean 2-year follow-up was 17.9 % on statins versus 20.3 % without statins ($p=0.029$). Even if these findings suggest a prognostic benefit for statins in established CHF, prospective data were required to definitively address this issue.

Small prospective clinical studies on atorvastatin and simvastatin in systolic HF documented an improved

ventricular systolic function and decreased levels of inflammatory biomarkers after statin therapy [27].

In a previous paper, Sankaranarayanan et al. [28] showed that mortality in patients with ischaemic CHF treated with statins was significantly lower than in controls. Univariate analysis also showed fewer HF readmissions (7 % vs 32 %) and HF deaths (4 % vs 13 %), with effects independent of cholesterol levels, age, sex, drugs, revascularisation, and implantable cardioverter-defibrillator or cardiac resynchronisation therapy at multivariable analysis. Our study results seem to confirm this prior evidence; therapy with atorvastatin was

Fig. 4 Kaplan-Maier survival analysis showed higher rates of cardiac death in subjects not receiving therapy with atorvastatin (log rank $p<0.01$)

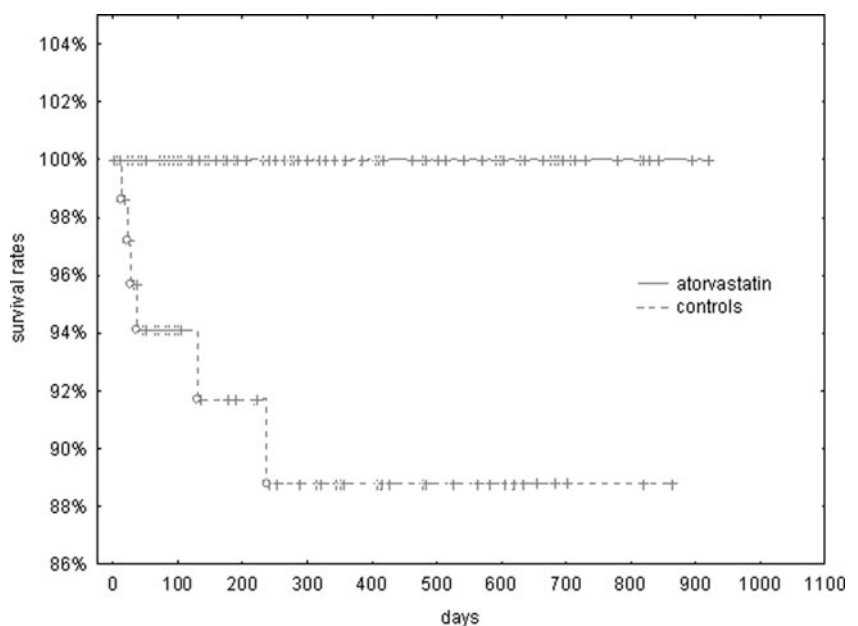


Table 2 Clinical characteristics of ischaemic CHF (atorvastatin group vs controls)

	Atorvastatin	Controls	<i>p</i>
Age (years)	66.95±9.82	70.18±11.35	0.06926
Male (%)	87	77	0.127365
BMI kg/m ²	28.87±4.56	28.42±4.27	0.574937
Weight (Kg)	77.84±12.14	77.00±18.54	0.369687
Height (cm)	164.35±6.97	158.97±18.40	0.008105
HR (bpm)	73.9±12.28	80.72±13.31	0.002259
SBP(mmHg)	122.37±24.56	124.14±22.55	0.158772
Ischaemic heart disease(%)	100	100	
Hypertension(%)	15	23	0.209274
COPD(%)	48	57	0.299849
Diabetes(%)	32	39	0.427626
Chronic kidney failure	37	39	0.699283
Creatinine	1.53±0.56	1.53±0.54	0.976749
III-IV NYHA (%)	58	89	0.001469
AICD/CRT-D(%)	28	34	0.638949
Ivabradine (%)	12	2	0.051003
ACE (%)	59	55	0.645563
ARB (%)	21	7	0.032010
Beta-blockers (%)	79	72	0.3681
Digoxin (%)	8	23	0.0088
Diuretics (%)	81	90	0.155369
NT-pro-BNP	1159.00±1447.28	1181.75±1507.064	0.977292
CRP	6.56±11.32	32.36±12.79	0.000867
LVEF(%)	38.61±11.59	35.11±12.67	0.19749
LVEDD (mm)	58.51±10.61	57.81±10.81	0.727871
LVESD (mm)	50.21±13.86	53.73±9.32	0.354087
E (cm/s)	76.79±28.95	107.20±35.62	0.000005
A (cm/s)	84.39±23.69	78.25±34.65	0.344733
E/A	1.59±0.82	2.25±0.88	0.000163
EDT (ms)	221.12±89.02	191.07±90.46	0.132104
E/E'	13.71±5.32	18.47±8.19	0.000259
S (cm/s)	8.59±2.692	5.38±1.84	0.532207
E' (cm/s)	6.35±2.64	6.14±2.20	0.687242
IVCT (ms)	94.12±40.010	81.18±27.605	0.214355
ET (ms)	259.88±45.462	241.00±44.798	0.132284
IVRT (ms)	124.06±49.231	86.35±32.873	0.003923
St (ms)	354.00±44.824	322.18±62.542	0.020265
FT (ms)	379.37±121.081	317.94±87.617	0.054558
Dt (ms)	503.43±131.943	404.29±89.829	0.004705

associated with a lower incidence of cardiac death, and association remained statistically significant even after correction in a multivariable analysis. Furthermore, ischaemic HF patients receiving therapy with atorvastatin showed a lower incidence of death, cardiac death and sustained ventricular arrhythmias.

However, randomised controlled trials (Controlled Rosuvastatin Multinational Trial in Heart Failure [CORONA] [29] and The Gruppo Italiano per lo Studio della Sopravvivenza nell'Insufficienza cardiaca Heart Failure [GISSI-HF]) [30] led

to different findings. In both studies, 10 mg rosuvastatin reduced blood cholesterol and inflammatory parameters without any effect on mortality. According to a recent meta-analysis by Zhang et al. [31] on 13 trials involving 10,447 chronic HF patients, a potential explanation for this discrepancy could be hypothesised in the different lipophilicity and hydrophilicity among statins. The lipophilic simvastatin and atorvastatin had a higher uptake in cardiac tissue than the hydrophilic rosuvastatin. The greater uptake of lipophilic statins by the

heart might contribute to the improvement in cardiac function and subsequently improve the clinical outcomes of chronic HF patients in treatment with atorvastatin or simvastatin. Zhang et al. [31] demonstrated that atorvastatin treatment was associated with reduced all-cause mortality and readmission rate for HF, and the superiority of statin therapy was significant in chronic HF patients younger than 65 years.

In previous works, statins appear to benefit patients with non-ischaemic and ischaemic cardiomyopathy similarly [32]; our results, however, seem to suggest a wider benefit of atorvastatin therapy in patients with coronary heart disease. In fact, besides a lower incidence of cardiac death, those receiving therapy with atorvastatin also showed a lower incidence of ventricular arrhythmias. Previous authors have already shown that non anti-arrhythmic drugs, such as renin-angiotensin-aldosterone system inhibitors, fish oil, and statins, can reduce the likelihood of future ventricular tachycardia/ventricular fibrillation in patients with coronary artery disease or congestive HF [33]. Desai et al. [34] similarly found that statins may reduce appropriate cardioverter-defibrillator shocks and mortality in 209 patients with HF treated with combined cardiac resynchronisation therapy and implantable cardioverter-defibrillator therapy.

Possible mechanisms by which statins exert their positive effect are not completely known. In our study, statin administration was related to a better LV performance at TDI. There is evidence that abnormal parameters by TDI may identify subjects at risk for adverse events in major cardiac diseases, such as HF [35]. In particular, patients with reduced S' or E' values of <3 cm/s have a very poor prognosis. In HF and after myocardial infarction, non-invasive assessment of LV diastolic pressure by trans-mitral to mitral annular early diastolic velocity ratio (E/E') is a strong prognosticator, especially when E/E' is ≥ 15 .

A few authors have assessed the effect of statin therapy on LV function by TDI; previous authors showed that in coronary artery disease patients, when compared with the baseline, S' and E' increased significantly after the therapy in the atorvastatin group [36]. In our study, HF patients receiving statins were characterised by lower values of E/A and E/E' and higher values of EDT; furthermore lower values of E/E' ratio and higher EDT, suggesting minor grade of diastolic dysfunction, were shown in ischaemic CHF patients receiving therapy with statins. Few authors have evaluated these intervals in CHF patients; Reant et al. [3], showed that St intervals can be used for detecting alterations in LV systolic function. Cheng et al. determined the cutoff values for ET in predicting high N-terminal pro-brain natriuretic peptide levels [4]. Time intervals assessed by TDI, ET and St may be helpful in predicting the risk of rehospitalisation in subjects with chronic HF [37].

Recently we showed higher values of ET and St in ischaemic CHF patients receiving therapy with statins than controls [19]. So, lower values of St intervals, as ET, in patients not treated with statins, might also suggest a higher

grade of LV diastolic dysfunction characterising these patients [38]. These previous data [19] seem to be confirmed in CHF patients with systolic dysfunction in atorvastatin therapy. We were also able to show, in atorvastatin therapy patients, a lower grade of diastolic dysfunction than in controls by conventional Doppler (E/A and EDT) and TDI (E/E') and longer systolic intervals (St).

Other possible mechanisms by which statins exert their positive effect may be hypothesised in non-lipid related or pleiotropic effects. Statins may inhibit or reverse myocardial remodelling [39–41], inhibit inflammation in HF, improve endothelial function [11, 42, 43] and restore autonomic nervous system balance [17]. In fact, Tousoulis et al. [44] recently demonstrated that 4 weeks of administration of atorvastatin 40 mg/d in patients with ischaemic HF improved endothelial function and arterial stiffness, indices of left ventricular remodelling and adhesion molecules. The effects of atorvastatin on indices of arterial function were dose dependent because no significant changes were found after treatment with atorvastatin 10 mg/d.

Limitations

These are preliminary data coming from a non-randomised observational registry with a limited number of patients enrolled. Statin administration only depended on clinician judgement. Further randomised trials are needed to confirm these results.

Conclusions

CHF outpatients with LVEF ≤ 40 %, receiving atorvastatin treatment, showed fewer cardiac deaths and a better LV performance assessed by TDI.

Conflict of interest None declared.

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