Lipophylic Statins in Heart Failure

Estatinas lipófilas en la insuficiencia cardiaca

To the Editor,

Current clinical practice guidelines do not recommend the use of statins in heart failure (HF).[1] This recommendation is supported by 2 trials that studied hydrophilic statins.[2,3] We conducted a retrospective study of patients admitted with HF between December 2007 and June 2011 to Hospital de Santa Tecla, Spain. The primary objective was to analyze the usefulness of lipophilic statins in these patients and the secondary objective was to compare real use with the theoretical indication for statins. Exclusion criteria were patients younger than 18 years or older than 85 years, those with neoplastic, infectious, or end-stage disease, and those receiving hydrophilic statins. We reviewed 680 patients, and considered only the first admission in patients who were re-admitted during the study. We compared patients receiving lipophilic statins with those not receiving any statins, and we calculated the percentage of patients who fulfilled the theoretical indications for receiving statins in accordance with the European Society of Cardiology Guidelines for the management of dyslipidemias.[4] Quantitative variables are expressed as mean ± standard deviation, and data were compared with the Student *t* test or ANOVA. We used the chi-square test to compare qualitative variables, the Mann-Whitney test for nonparametric data, and logistic regression for the multivariable analysis. The SPSS package version 20.0 was used for the statistical analysis. Statistical significance was defined as $P < .05$.

A total of 270 patients were enrolled (Table 1). Compared with the nonstatin group, the statin group had lower levels of low-density lipoprotein cholesterol (LDL-C) (80 ± 25 mg/dL vs 98 ± 35 mg/dL; $P = .01$), hemoglobin (11.6 ± 1.9 g/L vs 12.2 ± 2.2 g/L; $P = .04$), and glomerular filtration rate (55.2 ± 23 mL/min/m^2 vs 61.5 ± 26 mL/min/m^2; $P = .04$). There was a higher prevalence of treatment with aspirin, clopidogrel, and angiotensin-converting enzyme inhibitors or angiotensin receptor blockers in the statin group than in the nonstatin group (45.4% vs 26.5%; $P = .01$; 33.6% vs 13.5%; $P < .001$; and 76.1% vs 53%; $P = .01$, respectively). The statin group also had a higher prevalence of hypertension, diabetes mellitus and dyslipidemia, and HF of ischemic etiology. There were no differences in cardiovascular or all-cause mortality or re-admission (Table 2). A multivariable regression was performed, adjusting for age, sex, hypertension, diabetes mellitus, dyslipidemia, HF of ischemic etiology, glomerular filtration rate (< 60 mL/min/m^2), anemia (hemoglobin < 12 g/L) and LDL-C (< 80 mg/dL). We found that lipophilic statins were not associated with cardiovascular mortality (odds ratio [OR] = 1.12; 95% confidence interval [95%CI], 0.22-5.64; $P = .88$) or all-cause mortality (OR = 4.94; 95%CI, 0.90-27.11; $P = .06$), or with cardiovascular re-admission (OR = 0.91; 95%CI, 0.63-1.34; $P = .66$) or all-cause re-admission (OR = 1.06; 95%CI, 0.82-1.38; $P = .61$). In theory, at least 84.9% of the study patients should have been receiving statin therapy, but in practice, this figure was 40.9%.

This study has similar characteristics to those reported in recent studies in our setting.[5] The higher prevalence of hypertension,

Table 1
Characteristics of the Study Patients

Patients, n	270
Age, years	74 ± 8
Men	55.3
DLP	40.9
DM	47.6
HT	73.3
Smoker	17.0
Atherosclerotic history	
Cerebrovascular disease (ischemic)	15.7
Ischemic heart disease	46.7
Peripheral arterial disease	15.0
Any cardiovascular disease	58.8
Etiology	
Ischemic	46.0
Arrhythmogenic	49.6
Valvular	27.7
Hypertensive	40.1
Treatment	
Statins	40.9
Clopidogrel or ASA	44.3
ARB or ACE inhibitors	61.5
Aldosterone antagonists	13.5
Beta-blockers	31.8
Diuretics	63.5
EF, %	49.6 ± 14.3

ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blockers; ASA, acetylsalicylic acid; DLP, dyslipidemia; DM, diabetes mellitus; EF, ejection fraction; HT, hypertension; NYHA, New York Heart Association functional class.
Data are expressed as a percentage or mean ± standard deviation, unless otherwise indicated.

Table 2
Clinical Data and Lipid Profile of Patients Receiving Lipophilic Statins and Those not Receiving Statins

	Lipophilic statins	No statins	*P*
Patients, n	106	164	
Age, years	75.2 ± 7.3	74.1 ± 9.1	.30
Men	58	52.8	.23
DLP	66	23	< .001
DM	57	40	.05
HT	88	64	< .001
Smoker	17	17	.37
EF, %	48.4 ± 15.5	50.4 ± 13.3	.30
NYHA			
II	34	31	.79
III	31	31	.66
IV	28	29	.67
Etiology			
Ischemic	58	34	< .00
Arrhythmogenic	43	53	.06
Valvular	32	24	.11
Hypertensive	45	35	.08
Lipid profile, mg/dL			
Total cholesterol	149 ± 35.5	158 ± 42.0	.07
LDL-C	80 ± 25	98 ± 35	.01
HDL-C	42 ± 8	41 ± 12	.68
Triglycerides	130 ± 53	118 ± 66	.13

HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; DLP, dyslipidemia; DM, diabetes mellitus; EF, ejection fraction; HT, hypertension; NYHA, New York Heart Association functional class;.
Data are expressed as a percentage or mean ± standard deviation, unless otherwise indicated.

diabetes mellitus, dyslipidemia, and HF of ischemic etiology in patients receiving lipophilic statins is probably explained by worse underlying atherosclerosis. In fact, 58.8% of all patients had already experienced an ischemic event before admission. Both the lower glomerular filtration rate and the higher prevalence of antiplatelet agents and angiotensin-converting enzyme inhibitors or angiotensin receptor blockers can be similarly explained. Patients receiving lipophilic statins had lower LDL-C levels, but these levels did not result in improved clinical outcome. While statins do indeed prevent the onset of ischemic events, there is also a known association between very low cholesterol levels and lower survival in HF.[1] Furthermore, anemia is associated with more re-admissions and lower survival in elderly, hospitalized patients with HF,[1] an association corroborated by our study. The multivariable regression analysis showed no association between lipophilic statins and lower cardiovascular or all-cause re-admissions or mortality. The equivalent mean atorvastatin dose in our study (54.6 mg) may not have been high enough to produce evidence of these benefits, because a *post hoc* analysis of high-dose lipophilic statins found that they do appear to be useful in HF.[6] Evidence of lower re-admission rates for HF reported with hydrophilic statins[2] means that we should reconsider whether statin solubility plays a role in this context. Finally, only 40.9% of patients in our study were receiving statin therapy, which is much lower than the 85.9% calculated according to current guidelines for the management of dyslipidemias.[4]

In light of these results, it appears reasonable to maintain statin therapy at least in patients with HF of atherosclerotic origin.

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Fetal Arrhythmias: Diagnosis, Treatment and Perinatal Outcome

Arritmias fetales: diagnóstico, tratamiento y resultado perinatal

To the Editor,

Normal fetal heart rate ranges between 100 and 180 beats per minute. Fetal arrhythmias occur in 1% to 2% of pregnancies. The most common fetal arrhythmias are atrial extrasystoles, followed by supraventricular tachycardias (SVT), which are classified as sustained (present for more than 50% of the echocardiographic examination) or intermittent nonsustained (less than 50% of the examination). Sustained SVT is a major cause of nonimmune fetal hydrops, prematurity, and perinatal morbimortality. Treatment depends on gestational age, duration of the SVT, the degree of fetal involvement, maternal health status, and the possible risks of treatment for the mother and fetus. The goal of treatment is to restore sinus rhythm (SR) or to reduce the heart rate for long enough to resolve or prevent ventricular dysfunction.

Between July 2003 and November 2014, 6100 pregnant women at our center were referred for fetal echocardiography. Examinations were performed using the combined M-mode and pulsed Doppler approach.[1] Arrhythmias were detected in 2.7% of pregnancies (165 fetuses). The women gave informed consent, and electrocardiograms and blood drug concentrations were obtained from all study participants. Electrocardiograms and echocardiograms were obtained from all newborns.

The following arrhythmias were detected:

- Atrial extrasystoles in 137 (83%) of fetuses, with no development of other arrhythmias.
- Supraventricular tachycardia in 28 (17%) of fetuses (Figure 1):
  - Tachycardia with a short ventriculoatrial (VA) interval was detected in 17 fetuses: *a)* 4 had nonsustained tachycardia without hydrops and received no treatment; *b)* sustained tachycardia without hydrops was detected in 8 fetuses, and maternal oral digoxin therapy restored SR in all cases, and *c)* the remaining 5 fetuses had tachycardia with hydrops. Tachycardia was successfully reverted in 3 of these fetuses by combined maternal therapy with digoxin and sotalol. In the 2 fetuses that failed to respond, sotalol was replaced with flecainide. After continued failure to respond, a decision was made to induce delivery at 36 weeks gestation. Postnatal diagnosis confirmed Wolff–Parkinson–White syndrome, which was treated with adenosine (Figure 1).
  - Atrial flutter was detected in 9 fetuses (Figure 2): *a)* 7 did not have hydrops, and maternal digoxin therapy reduced heart rate sufficiently to allow delivery at term in 5 of them; *b)* the other 2 fetuses failed to respond to digoxin alone, and sotalol therapy was added, restoring SR in both fetuses. The 2 fetuses with hydrops did not respond to combined maternal therapy with digoxin and sotalol, and delivery was induced at 36 weeks gestation. The 7 newborns with atrial flutter underwent electric cardioversion.
  - One fetus had long VA interval tachycardia (190 beats per minute) with no hydrops. Maternal flecainide therapy was given and the neonate was born with sinus tachycardia and congenital listeriosis.