Effect of Statin Treatment on Mortality in a Large Cohort of Heart Failure Patients

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We studied 3162 heart failure patients included in the Spanish BADAPIC registry in order to determine whether statin treatment influences prognosis. Patients were followed up for 35 (22) months (median, 32 months). Patients on statins were more often male and had higher prevalences of risk factors, ischemic heart disease, and systolic dysfunction (*P*<.001) than those not on statins. After adjustment for age, risk factors, ischemic heart disease, renal failure, ejection fraction, anemia, heart rate, and drug treatment, statin treatment was found to be a favorable independent predictor of survival: the hazard ratio for mortality was 0.73 (95% confidence interval, 0.45-0.88; *P*<.001). During follow-up, the 3-year survival rate was higher in patients treated with statins (75% vs 68%; *P*<.001). In patients with heart failure, statin treatment appears to be independently associated with better survival.

Key words: *Heart failure. Statins. Prognosis.*

Efecto del tratamiento con estatinas en la mortalidad de una gran cohorte de pacientes con insuficiencia cardiaca

Con el objetivo de determinar si el tratamiento con estatinas influye en el pronóstico de pacientes con insuficiencia cardiaca, se estudió a 3.162 pacientes con este diagnóstico incluidos en el registro BADAPIC, con seguimiento durante una media de 35 ± 22 (mediana, 32) meses. Los pacientes con estatinas eran con mayor frecuencia varones y tenían mayor prevalencia de factores de riesgo, cardiopatía isquémica y disfunción sistólica (p < 0,001). El tratamiento con estatinas tuvo un valor predictivo independiente favorable sobre la mortalidad (riesgo relativo = 0,73; intervalo de confianza del 95%, 0,45-0,88; p < 0,001) tras ajustar por edad, factores de riesgo, cardiopatía isquémica, insuficiencia renal, fracción de eyección, anemia, frecuencia cardiaca y tratamiento farmacológico. La supervivencia fue mejor en los pacientes tratados con estatinas (el 75 frente al 68%; p < 0,001) a los 3 años de seguimiento. El tratamiento con estatinas de pacientes con insuficiencia cardiaca parece mejorar la supervivencia de forma independiente.

Palabras clave: *Insuficiencia cardiaca. Estatinas. Pronóstico*

INTRODUCTION

Statins have shown they have a beneficial effect on the prognosis of patients with ischemic heart disease.

Heart failure has been related with inflammation, with cytokines[1] and C-reactive protein elevation.[2] Statins have been demonstrated to reduce cytokines and C-reactive protein in patients with heart failure.[3]

Our objective is to determine whether statin treatment influences prognosis of patients with heart failure included in the Spanish BADAPIC (database of patients with heart failure) registry.

METHOD

BADAPIC is an official registry of the Spanish Society of Cardiology Heart Failure, Heart Transplant and Alternative Treatment Section.[4] The data presented in this study correspond to 2000-2002 and refer to 3162 patients. We excluded 747 registry patients with characteristics similar to those enrolled due to lack of information on statin use. The treatment referred corresponds to the inclusion visit and was practically unchanged (patients with statins had increased by only 2% at the end of the follow-up). Participating centers and researchers are listed in the annexe.

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TABLE 1. **Clinical Characteristics in Relation to Statin Use**

	With Statins	Without Statins	*P*
Patients, n	1305	1857	
Age, mean (SD), y	66 (11)	67 (10)	.56
Men, n (%)	939 (72)	1151 (62)	<.001
SBP, mm Hg	110 (15)	111 (14)	.48
DBP, mm Hg	73 (8)	74 (9)	.53
BMI	23.2 (4.2)	22.6 (4.3)	.60
HBP, n (%)	809 (62)	1003 (54)	<.001
Dyslipidemia, n (%)	939 (72)	353 (19)	<.001
Diabetes mellitus, n (%)	522 (40)	520 (28)	<.001
Old myocardial infarction, n (%)	679 (52)	372 (20)	<.001
Revascularization surgery, n (%)	326 (25)	148 (8)	<.001
Hospitalization for heart failure, n (%)	809 (62)	1393 (75)	<.001
NYHA class III-IV, n (%)	326 (25)	446 (24)	.68
Heart rate, bpm	70 (8)	71 (9)	.47
Anemia (hemoglobin <12 g/dL), n (%)	391 (30)	557 (30)	.69
CKF (creatinine >2 mg/dL), n (%)	117 (9)	186 (10)	.51
Heart failure etiology, n (%)			<.001
Ischemic DCM	835 (64)	502 (27)	
Idiopathic DCM	157 (12)	743 (20)	
Valvular disease	52 (4)	241 (13)	
AF, n (%)	274 (21)	799 (43)	<.001
EF 0.38 (0.15)	0.31 (0.13)	<.001	
EF <0.45, n (%)	1096 (84)	1337 (72)	<.001
Treatment, n (%)			
Diuretics	1057 (81)	1615 (87)	<.001
Digoxin	365 (28)	817 (44)	<.001
ACE inhibitors	966 (74)	1430 (77)	.06
ARA-II	248 (19)	296 (16)	<.05
Spironolactone	496 (38)	687 (37)	.58
Beta-blockers	979 (75)	1263 (68)	<.001
Calcium antagonists	183 (14)	205 (11)	.12
Antiplatelet agents	811 (63)	631 (34)	<.001
Nitrates	548 (42)	434 (24)	<.001

ACE inhibitors indicates angiotensin converting enzyme inhibitors; AF, atrial fibrillation; ARA-II, angiotensin II receptor antagonists; DBP, diastolic blood pressure; BMI, body mass index; bpm, beats per minute; CKF, chronic kidney failure; DCM, dilated cardiomyopathy; EF, ejection fraction; HBP, high blood pressure; NYHA, New York Heart Association; SBP, systolic blood pressure.

To diagnose heart failure we used the Spanish Society of Cardiology Working Group on Heart Failure[5] and, from 2001, European Society of Cardiology criteria.[6] We defined preserved systolic function as ejection fraction (EF) ≥45% and systolic dysfunction as EF <45%. Follow-up was 35 (22) (median, 32) months. In the group with statins, 20 patients were lost during follow-up; in the group without statins, 29 were lost.

Statistical Analysis

Discrete variables are shown as percentages and continuous variables as mean (SD). Discrete variables were compared with χ^2 or Fisher exact test when frequencies expected were <5. Continuous variables with normal distribution are compared with Student *t* test. We constructed Kaplan-Meier survival curves for both groups and compared these using the log-rank test. We constructed a Cox multivariate logistic regression model of variables that were significant in univariate analysis and of others known to influence prognosis (gender, admission for heart failure). Incidence of events was expressed as incidence per 100 patients/year observation. Differences in rate were adjusted for age following Sahai et al.[7] We then compared incidence of events in both groups and obtained 95% confidence intervals (CI) using Ulm's method.[8] We considered $P<.05$ statistically significant. Statistical analysis was with SPSS.

RESULTS

Patients on statins (1305; 41%) were more frequently men and were clinically different to patients in the group without statins (Table 1).

TABLE 2. **Comparison of Rates of Events in Relation to Statin Use**

	Total	With Statins	Without Statins	Difference of Rates	*P*
Overall mortality	920 (9.69)	326 (8.65)	549 (10.66)	2.01 (1.34-7.67)	<.0001
Mortality due to heart failure	646 (6.81)	182 (4.82)	464 (8.35)	3.41 (2.06-6.34)	<.0001
Hospitalization for heart failure	8030 (7.41)	339 (8.96)	464 (8.36)	0.60 (–1.95 to 2.06)	.5687
Other cardiovascular hospitalizations	378 (3.97)	248 (6.56)	130 (2.34)	4.21 (1.64-5.20)	<.0001
Hospitalization for AMI	186 (1.96)	130 (3.44)	56 (0.98)	2.46 (1.16-9.30)	<.0001
Hospitalization for coronary revascularization	186 (1.96)	130 (3.44)	56 (0.98)	2.46 (1.16-9.30)	<.0001

AMI indicates acute myocardial infarction.
Events are expressed as absolute values (incidence per 100 patients/year observation). The difference of rates is expressed as difference of absolute rates (95% confidence interval).

Registry survivors were significantly younger, had fewer risk factors, presented lower incidence of ischemic heart disease, atrial fibrillation, systolic dysfunction, anemia (hemoglobin, <12 g/dL), kidney failure (creatinine, >2 mg/dL), and lower heart rate. They took more statins (44% vs 35%; *P*<.001), beta-blockers and angiotensin converting enzyme inhibitors, and less spironolactone, antiplatelet agents and nitrates, than non-survivors. We found no differences in body mass index or blood pressure. In the Cox proportional hazards analysis–-which included the significant variables identified in the univariate study including NYHA class III-IV (*P*=.05), gender, and hospitalizations for heart failure–-taking statins was a favorable independent predictor of survival (relative risk [RR] =0.73; 95% CI, 0.45-0.88; *P*<.001). In the final model, as well as statins, independent predictors of mortality were age (RR=1.66; 95% CI, 1.17-2.06), ischemic heart disease (RR=1.61; 95% CI, 1.04-1.95), anemia (RR=1.59; 95% CI, 1.20-2.03), kidney failure (RR=1.41; 95% CI, 1.11-2.59), and beta-blocker treatment (RR=0.82; 95% CI, 0.47-0.95). The Kaplan-Meier curves showed better survival for patients on statins (Figure).

The normalized rate of events appears in Table 2. Mortality was lower in patients on statins but hospitalizations for ischemic heart disease and other cardiovascular hospitalizations were more frequent.

The reduced mortality rate was maintained in the subgroups analyzed. In patients with EF <0.45, rates were 9.19 versus 11.2 deaths/100 patients/year, and with EF >0.45, 7.92 versus 9.9. In patients with ischemic heart disease, rates were 9.94 versus 12.26 and in nonischemic patients, 7.30 versus 9.41. In NYHA class III-IV patients rates were 11.06 versus 14.03 and in class I-II patients they were 6.51 versus 8.49 (all comparisons, *P*<.0001).

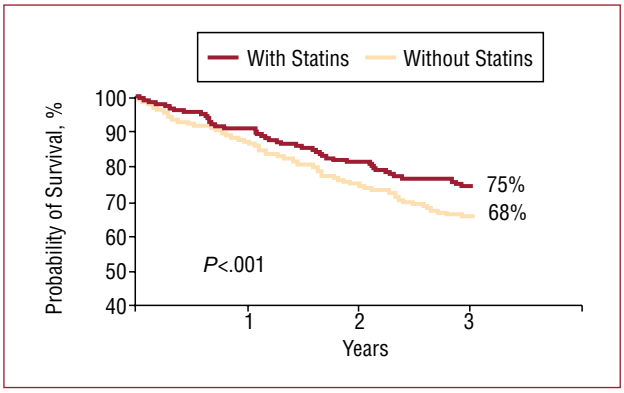

Figure 1. Probability of survival in relation to treatment with or without statins.

DISCUSSION

In this registry, statins were prescribed on the indication of the physician. Therefore, differences existed between patients treated on statins and patients not on statins, as described elsewhere.[9] Despite a greater prevalence of bad prognostic factors, patients on statins had significantly better 3-year survival (Figure) and treatment maintained the independent predictive survival value (RR=0.73). Several observational studies concur with ours–-the first large cohort study conducted in Spain–-finding favorable results for statins on the prognosis of patients with heart failure.[10-12] However, at the time of writing, results of the Controlled Rosuvastatin Multinational Trial in Heart Failure (CORONA) study[13] have recently been published. This clinical trial randomized patients aged >60 years and diagnosed with systolic ischemic heart failure to 10 mg of rosuvastatin or placebo. There were no significant differences with respect to the placebo in the principal outcome (cardiovascular death, nonfatal myocardial infarction or nonfatal stroke).

The differences in results between the CORONA trial and earlier observational studies like BADAPIC, have several possible causes. Firstly, our study design is based on the observation of a heart failure registry. Although the beneficial results of statins are corrected for several variables, patients with and without statins are not randomized so groups may have differed in ways we were unable to take into account in the Cox analysis. Secondly, BADAPIC

registry patients differ from CORONA trial patients in that 32% had EF >0.45, 59% had nonischemic etiology, and 10% had serum creatinine >2 mg/dL; all such patients were excluded from CORONA. Another clinical trial with rosuvastatin is currently under way, the GISSI-heart failure study.[14] This trial includes patients with nonischemic dilated cardiomyopathy and patients with heart failure and preserved EF. It will probably give us a definitive answer to the role of statins in treating heart failure.

The results of a trial like CORONA should prevail over those of an observational study, although some issues need highlighting. The prognostic benefits of the statin used, rosuvastatin, have yet to be demonstrated in coronary heart disease, and the 10 mg dose used in CORONA may not be enough to benefit patients. Furthermore, in CORONA, rosuvastatin reduced neither incidence of coronary events (9.3 vs 10/patient/year; *P*=.18) nor of stroke with respect to a placebo. Other statins may well have produced different effects.

In conclusion, in our registry, patients with heart failure treated with statins had better long-term survival. These results contrast with the absence of favorable effects observed in the CORONA clinical trial. Despite the evidence of observational studies and the BADAPIC registry, the current use of statins in standard treatment of heart failure cannot be justified. Results from the GISSI-heart failure trial may offer more definite information.

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ANNEXE. **Centers and Researchers Participating in the BADAPIC Registry (Database of Patients With Heart Failure)**

Hospital General de Albacete: Pablo Domínguez Barrio
Fundación Hospital Alcorcón: Elena España Barrio and Elena Batlle López
Hospital General de Alicante: Francisco Sogorb Garri and Vicente Climent Payá
Hospital de Antequera: Jesús Álvarez Rubiera and Álvaro Rubio Alcaide
Hospital San Agustín de Avilés: Gerardo Casares García
Hospital Infanta Cristina de Badajoz: León Martínez de la Concha
Hospital Can Ruti de Badalona: José Lupón Roses and Teresa Pajarón Rodríguez
Hospital San Eloy de Baracaldo: Javier Andrés Novales
Hospital Vall d'Hebron de Barcelona: Stella Méndez and Enrique Galve
Hospital de Terrassa: MA de Miguel and David López Gómez
Hospital Mútua de Terrassa: Leandro Sáenz and Amparo Álvarez
Hospital Sant Pau de Barcelona: Domingo Ruiz Hidalgo and Josep Antón Montiel Dacosta
Hospital Clínic i Provincial de Barcelona: Eulalia Roig Monguell and Alfredo Cupoletti Beange
Hospital Sagrat Cor de Barcelona: Francesc Rossell Abaurrea and César Morcillo Serra
Hospital de Basurto de Bilbao: Nekane Murga Eizagaechaverria and Inmaculada Lluís Serret
Hospital San Pedro de Alcántara de Cáceres: Concepción de la Concepción Palomino and Yolanda Porras Ramos
Hospital General de Castellón: José Luis Diago Torrent and Álex Navarro Bellver
Hospital Reina Sofía de Córdoba: Manuel Anguita Sánchez and Soledad Ojeda Pineda
Hospital de Elche, Alicante: Fernando García de Burgos y de Rico, and Alejandro Jordá Torrent
Hospital de Galdakao, Vizcaya: Javier Zumalde Otegui and Alberto Salcedo Arruti
Hospital de Gandía, Valencia: Plácido Orosa Fernández and Catherine Lauwers Nelisen
Hospital Virgen de las Nieves, Granada: Óscar Baun and José Luis Ventin Pereira
Hospital General de Granollers, Barcelona: Santiago Montull Morer and Rosa Guitard
Hospital del SAS de Jerez, Cádiz: José Carlos Vargas Machuca and Fernando García-Arboleya Puerto
Hospital de Bellvitge, L'Hospitalet, Barcelona: Nicolás Manito Lorite and Edgardo Kaplinsky
Complejo Hospitalario de León: Julián Bayon Fernández and Manuela Montes Montes
Hospital La Paz, Madrid: Isidoro González Maqueda, Gabriela Guzmán Martín, Llanos Soler Rangel, and Francisco Arnalich Fernández
Hospital Severo Ochoa, Leganés, Madrid: Ana Isabel Huelmos Rodrigo and Ángel Grande Ruiz
Hospital de la Princesa, Madrid: Mercedes Fernández Escribano
Hospital Costa del Sol, Marbella, Málaga: Emilio González Cocina and Francisco Torres Calvo
Hospital Carlos Haya, Málaga: Manuel de Mora Martín and José María Pérez Ruiz
Hospital Virgen de la Victoria, Málaga: Eduardo de Teresa Galván, Encarnación Molero Campos, and Manuel Jiménez Navarro
Hospital Comarcal de Mendaro, Guipúzcoa: Esther Recalde del Vigo and Nicolás Gurrutxaga Arrillaga
Hospital Provincial Santa María Madre, Orense: Miguel A. Pérez de Juan and Manuel de Toro Santos
Hospital Central de Asturias: Beatriz Díaz Molina and José Luis Rodríguez Lambert
Hospital Río Carrión, Palencia: Fausto Librada Escribano
Hospital General de Mallorca: Josefina Gutiérrez Alemany
Hospital de Santa Bárbara, Puertollano, Ciudad Real: José Portillo Sánchez
Hospital Sant Joan de Reus, Tarragona: Francesc Marimón Cortés and Oscar Palazón Molina
Hospital Clínico Universitario de Salamanca: Pedro Luis Sánchez Fernández and Francisco Martín Herrero
Hospital Donostia de San Sebastián: Ramón Querejeta Iraola and Eloy Sánchez Haya
Hospital Marqués de Valdecilla, Santander: José Ramón Berrazueta Fernández
Hospital Clínico Universitario de Santiago de Compostela: José R. González Juanatey and Inés Gómez Otero
Hospital Universitario de Valme, Sevilla: Juan C. Beltrán Rodríguez and Luis Pastor Torres
Hospital Virgen del Rocío, Sevilla: Ángel Martínez Martínez
Hospital Joan XXIII de Tarragona: Alfredo Bardají Ruiz and Ramón de Castro Aritmediz
Hospital Sant Pau i Santa Tecla, Tarragona: Lluis Carles Olivan Sayrol and Juan Carlos Soriano Giménez
Hospital Universitario de Canarias, Tenerife: Antonio Lara Padrón and Francisco Marrero Rodríguez
Hospital General de Valencia: José Antonio Velasco Rami and Francisco Ridocci Soriano
Hospital La Fe, Valencia: Luis Almenar and Joaquín Rueda Soriano
Hospital Doctor Peset, Valencia: Begoña Sevilla Toral and Antonio Salvador Sanz
Hospital Clínico de Valencia: Ángel Llácer and Jaime Muñoz
Hospital Clínico Universitario de Valladolid: Luis de la Fuente Galán
Hospital do Meixoeiro de Vigo, Pontevedra: Francisco Calvo Iglesias and José Luis Escribano Arias
Hospital de Txagorritxu, Vitoria: Fernando Arós Borau
Hospital Clínico Universitario Lozano Blesa, Zaragoza: Alfonso del Río Lligorit and Antonio San Pedro Feliú
Hospital Miguel Servet, Zaragoza: Marisa Sanz Julve and Teresa Blasco Peiró
Roche Pharma, Barcelona: Isidro Lázaro and María José Ramírez