

Original article

## Benefits of Statin Therapy Based on Plasma Carbohydrate Antigen 125 Values Following an Admission for Acute Heart Failure

Julio Núñez,<sup>a,\*</sup> Juan Sanchis,<sup>a</sup> Eduardo Núñez,<sup>a</sup> Gregg C. Fonarow,<sup>b</sup> Vicent Bodí,<sup>a</sup> Vicente Bertomeu-González,<sup>c</sup> Gema Miñana,<sup>a</sup> Patricia Palau,<sup>a</sup> Lorenzo Fácila,<sup>d</sup> Francisco J. Chorro,<sup>a</sup> Vicente Bertomeu-Martínez,<sup>c</sup> and Angel Llàcer<sup>a</sup>

<sup>a</sup>Servicio de Cardiología, Hospital Clínico Universitario, INCLIVA, Universitat de València, Valencia, Spain

<sup>b</sup>UCLA Division of Cardiology, Ahmanson-UCLA Cardiomyopathy Center, Los Angeles, California, United States

<sup>c</sup>Servicio de Cardiología, Hospital Universitario de San Juan de Alicante, Sant Joan d'Alacant, Alicante, Spain

<sup>d</sup>Servicio de Cardiología, Hospital Provincial de Castellón, Castellón de la Plana, Spain

Article history:

Received 15 March 2011

Accepted 29 May 2011

Available online 29 September 2011

Keywords:

Statin treatment

Carbohydrate antigen 125

Mortality

Heart failure

### ABSTRACT

**Introduction and objectives:** The prognostic benefit of statins in patients with heart failure is a topic of controversy. Under the hypothesis that statins may provide greater benefit in a subgroup of patients with heightened inflammatory activity, we sought to explore whether statins are associated with a decreased risk of long-term mortality in patients with acute heart failure based on elevated levels of carbohydrate antigen 125, a biomarker related to systemic congestion and proinflammatory status.

**Methods:** We analysed 1222 consecutive patients admitted with acute heart failure in a single teaching center during a median follow-up of 20 months. Carbohydrate antigen 125 was measured during index hospitalization and dichotomized according to the established reference cut-off (>35 U/mL).

**Results:** Increased levels of carbohydrate antigen 125 (>35 U/mL) were observed in 793 (64.9%) and prescription of statins registered in 455 (37.2%) patients. In patients with carbohydrate antigen 125 >35 U/mL, mortality was lower in statin-treated patients (1.89 vs 2.80 per 10 patient-years of follow-up,  $P < .001$ ). Conversely, in those with carbohydrate antigen 125 in normal range, mortality did not differ (1.76 vs 1.63 per 10 patient-years of follow-up,  $P = .862$ ). After covariate adjustment, this differential effect persisted ( $P$  for interaction = .024) and statin use was associated with a significant mortality reduction in patients with elevated values of carbohydrate antigen 125 (hazard ratio=0.65, 95% confidence interval: 0.51-0.82;  $P < .001$ ), but not in those with values equal to or below 35 U/mL (hazard ratio=1.02, 95% confidence interval: 0.74-1.41;  $P = .907$ ).

**Conclusions:** Elevation of carbohydrate antigen 125 (>35 U/mL) identified a subset of patients with acute heart failure who could benefit from statin treatment in regard to total mortality.

© 2011 Sociedad Española de Cardiología. Published by Elsevier España, S.L. All rights reserved.

### Beneficios del tratamiento con estatinas según los valores plasmáticos del antígeno carbohidrato 125 tras un ingreso por insuficiencia cardiaca aguda

### RESUMEN

**Introducción y objetivos:** La utilidad de las estatinas en pacientes con insuficiencia cardiaca es motivo de controversia. Bajo la hipótesis de que el tratamiento con estatinas sería útil en los pacientes con insuficiencia cardiaca y mayor actividad inmunoinflamatoria, pretendimos conocer si la elevación del antígeno carbohidrato 125, un biomarcador asociado a la congestión sistémica y actividad inflamatoria, identificaría a los que se beneficiarían, en cuanto a mortalidad, del tratamiento con estatinas tras un ingreso por insuficiencia cardiaca aguda.

**Métodos:** Analizamos a 1.222 pacientes consecutivos ingresados por insuficiencia cardiaca aguda. El antígeno carbohidrato 125 se determinó durante el ingreso hospitalario y se dicotomizó según los valores de referencia (> 35 U/ml).

**Resultados:** Se observaron valores elevados del antígeno carbohidrato 125 en 793 pacientes (64,9%) y a 455 (37,2%) se les prescribió estatinas. Entre los pacientes con antígeno carbohidrato 125 > 35 U/ml, la mortalidad de los tratados con estatinas fue inferior (1,89 frente a 2,80/10 pacientes-año de seguimiento;  $p < 0,001$ ). Por el contrario, la mortalidad de aquellos con valores de antígeno carbohidrato 125 ≤ 35 U/ml fue similar (1,76 frente a 1,63/10 pacientes-años de seguimiento;  $p = 0,862$ ). Tras un minucioso ajuste multivariable, este efecto diferencial atribuible al tratamiento con estatinas persistió (para la interacción,  $p = 0,024$ ). Así, el tratamiento con estatinas se asoció con una reducción significativa del riesgo de muerte de los sujetos con antígeno carbohidrato 125 > 35 U/ml (hazard ratio = 0,65; intervalo de confianza del 95%, 0,51-0,82;  $p < 0,001$ ); sin embargo, no fue así en aquellos con valores de

Palabras clave:

Estatinas

Antígeno carbohidrato 125

Mortalidad

Insuficiencia cardiaca

\* Corresponding author: Servicio de Cardiología, Hospital Clínico Universitario, Avda. Blasco Ibáñez 17, 46010 Valencia, Spain.

E-mail address: yulnunez@gmail.com (J. Núñez).

antígeno carbohidrato  $125 \leq 35$  U/ml (*hazard ratio* = 1,02; intervalo de confianza del 95%, 0,74-1,41;  $p = 0,907$ ).

**Conclusiones:** La elevación plasmática del antígeno carbohidrato 125 identificó un subgrupo de población que podría beneficiarse del tratamiento con estatinas en términos de mortalidad a largo plazo. © 2011 Sociedad Española de Cardiología. Publicado por Elsevier España, S.L. Todos los derechos reservados.

## Abbreviations

AHF: acute heart failure  
CA125: carbohydrate antigen 125  
HF: heart failure

## INTRODUCTION

Inflammation is a key pathogenic process associated with the progression of heart failure (HF).<sup>1</sup> The pleiotropic anti-inflammatory properties of statins appear to be an attractive feature for targeting the inflammatory component in patients with advanced HF.<sup>2</sup> In contrast to large-scale observational studies that have shown a reduction in clinical outcomes in patients with HF and treated with statins,<sup>3–5</sup> two recent randomized controlled trials of statins in HF failed to demonstrate any survival benefit.<sup>6,7</sup> Nevertheless, a post hoc analysis of the CORONA trial showed decreased mortality with rosuvastatin in patients exhibiting high inflammatory activity as measured by serum C-reactive protein (CRP) ( $>2$  mg/dL).<sup>8</sup>

Accumulated evidence has pointed to carbohydrate antigen 125 (CA125) as a reliable marker for congestion and inflammation in patients with acute heart failure (AHF)<sup>9–12</sup> and as being independently associated to all-cause and cardiovascular mortality.<sup>11,12</sup> The fact that serum levels of CA125 have shown to be very reliable over time<sup>12,13</sup> has led to postulating this biomarker as an ideal candidate for measuring the degree of inflammation in AHF. Thus, and assuming that patients with AHF and high CA125 levels ( $>35$  U/mL) represent a subset of patients with elevated inflammatory activity, we sought to evaluate whether statin treatment following an episode of AHF has differential prognostic effect in terms of total and cardiovascular mortality according to CA125 categories.

## METHODS

### Study Group and Protocol

We prospectively studied a cohort of 1222 patients consecutively admitted to the cardiology department of a third level center from January 1, 2004 to November 1, 2009 with the diagnosis of AHF as defined by current guidelines.<sup>14–16</sup> By design, patients who died before CA125 measurement were excluded from this analysis ( $n = 21$ ). In addition, patients with a primary diagnosis of acute coronary syndrome ( $n = 20$ ), cancer ( $n = 18$ ), pneumonia ( $n = 16$ ), sepsis ( $n = 8$ ), severe hepatic disease ( $n = 1$ ), or end-stage renal disease undergoing dialysis treatment were also excluded ( $n = 3$ ).

Demographic information, medical history, vital signs, 12-lead electrocardiogram, laboratory data, and drug utilization were routinely determined on admission and throughout the hospital course, using pre-established registry questionnaires. All patients received intravenous treatment with furosemide for at least the first 48 h after admission. Left ventricular ejection fraction (LVEF) was assessed through echocardiography (Agilent Sonos

5500-Phillips) during index hospitalization. Treatment with angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, beta-blockers, aldosterone antagonist, anticoagulants, diuretics, and other therapeutic strategies was individualized following established guidelines in force at the time of recruitment.<sup>14–16</sup> The statin treatment decision was made at the discretion of the cardiologist in charge of the patient and was not influenced nor guided by CA125 values.

Patients were followed until death, and censored if lost to follow-up or by having undergone valve replacement or cardiac transplantation. All-cause mortality was selected as the main endpoint and cardiovascular mortality as a secondary one. The information regarding cause of death was extracted from the patient's clinical chart and adjudicated by an investigator blinded to patients' treatment and CA125 values. Once identified, the cause of death was categorized following the classification used by the American Heart Association.<sup>17</sup> Deaths were considered non-cardiovascular in origin if a specific non-cardiovascular cause was identified as the main trigger for the event. Otherwise, cardiovascular etiology was considered and included sudden death, progressive HF death, other cardiovascular causes, and unknown cause of death. Sudden death was defined as an event that occurred unexpectedly in an otherwise stable patient and progressive HF death as occurring in the setting of clinical progressive deterioration of HF symptoms. For the present study, deaths occurring outside the hospital were assumed to be cardiovascular in origin, whether information about the circumstances surrounding the death was provided by family members or by reviewing outpatient charts. This study conforms with the principles outlined in the Declaration of Helsinki, was approved by an institutional review committee, and patients gave informed consent.

### Carbohydrate Antigen 125 Measurements

CA125 was measured during the patient's hospitalization ( $72 \pm 12$  h after admission) using commercially available immunoassay kits (Elecsys CA125 II assay-Roche Diagnostics).

### Statin Treatment

Patients were considered taking statins if they were prescribed at hospital discharge or, in cases of early death, only when treatment was initiated at least 24 h before death. No specific guidelines were followed for initiation of statin treatment or selection of specific class or dosage. Based on low-density lipoprotein (LDL)<sup>18</sup> and CRP reduction efficacy,<sup>19</sup> the therapeutic equivalence between statins was characterized as low and medium-high doses. Low dose included atorvastatin  $\leq 10$  mg, simvastatin  $\leq 20$  mg, pravastatin  $\leq 40$  mg, lovastatin  $\leq 40$  mg or fluvastatin  $\leq 80$  mg, and medium-high dose included atorvastatin  $\geq 20$  mg or simvastatin  $\geq 40$  mg.

### Statistical Analysis

Continuous variables were expressed as mean  $\pm 1$  standard deviation or median (interquartile range [IQR]) when appropriate.

**Table 1**  
Baseline Characteristics of the Population Stratified by Statin Therapy

	All (n = 1222)	Statins (n = 455)	No statins (n = 767)	P
<i>Demographic and medical history</i>				
Age, years	73 ± 11	73 ± 10	73 ± 12	.559
Female, n (%)	620 (50.7)	211 (46.4)	409 (53.3)	.019
Previous admission for AHF, n (%)	458 (37.5)	170 (37.4)	288 (37.5)	.948
Hypertension, n (%)	946 (77.4)	393 (86.4)	553 (72.1)	<.001
Dyslipidemia, n (%)	523 (42.8)	342 (75.2)	181 (23.6)	<.001
Current smoker, n (%)	128 (10.5)	53 (11.6)	75 (9.8)	.302
Previous smoker, n (%)	232 (19)	109 (24)	123 (16)	.001
Ischemic heart disease, n (%)	466 (38.1)	261 (57.4)	205 (26.7)	<.001
Valvular heart disease, n (%)	350 (28.6)	97 (21.3)	253 (33)	<.001
ADHF, n (%)	836 (68.4)	293 (64.4)	543 (70.8)	.020
Acute pulmonary edema, n (%)	265 (21.7)	119 (26.1)	146 (19)	.004
Hypertensive AHF, n (%)	99 (8.1)	41 (9)	58 (7.6)	.369
NYHA class III/IV, n (%) <sup>a</sup>	224 (18.3)	79 (17.4)	145 (18.9)	.501
Previous HF, n (%)	434 (35.5)	165 (36.3)	269 (35.1)	.674
COPD, n (%)	265 (21.7)	108 (23.7)	157 (20.5)	.180
PAD, n (%)	87 (7.1)	43 (9.4)	44 (5.7)	.015
Stroke, n (%)	126 (10.3)	58 (12.7)	68 (8.9)	.031
Renal failure, n (%)	205 (16.8)	93 (20.4)	112 (14.6)	.008
Radiological pleural effusion, n (%)	539 (44.1)	185 (40.7)	354 (46.1)	.061
Peripheral edema, n (%)	680 (55.6)	238 (52.3)	442 (57.6)	.070
Previous use of diuretics, n (%)	756 (61.9)	288 (63.3)	468 (61)	.428
Previous use of beta-blockers, n (%)	292 (23.9)	144 (31.6)	148 (19.3)	<.001
Previous use of ACEI/ARB, n (%)	554 (45.3)	250 (54.9)	304 (39.6)	<.001
Previous use of statins, n (%)	330 (27)	260 (57.1)	70 (9.1)	<.001
<i>Vital signs</i>				
Heart rate, bpm	101 ± 29	99 ± 28	102 ± 30	.018
SBP, mmHg	150 ± 36	152 ± 36	149 ± 36	.152
DBP, mmHg	83 ± 20	83 ± 21	82 ± 20	.291
<i>Electrocardiogram</i>				
Atrial fibrillation, n (%)	539 (44.1)	153 (33.6)	386 (50.3)	<.001
QRS >120 ms, n (%)	358 (29.4)	139 (30.5)	219 (28.7)	.494
<i>Laboratory</i>				
Haemoglobin, g/dL	12.7 ± 1.9	12.8 ± 1.9	12.6 ± 1.9	.090
Serum creatinine, mg/dL	1.3 ± 0.6	1.3 ± 0.6	1.3 ± 0.6	.146
Serum urea, mg/dL	63 ± 35	63 ± 29	63 ± 38	.975
Uric acid, mg/dL	7.9 ± 2.4	7.7 ± 2.2	8 ± 2.5	.081
Sodium, mEq/L	139 ± 5	139 ± 4	139 ± 5	.459
Troponin I, ng/mL	0 [0-0.23]	0.2 [0-0.33]	0 [0-0.17]	<.001
Troponin I >0.2 ng/mL, n (%)	336 (27.5)	150 (33)	186 (24.2)	.001
BNP, pg/mL	145 [85-292]	136 [72-284]	151 [89-302]	.014
Relative lymphocyte count, %	17.9 ± 9.9	18.9 ± 9.9	17.3 ± 9.9	.008
CA125, U/mL	57 [25-129]	53 [24-113]	59 [26-141]	.021
Total cholesterol, mg/dL	170 ± 44	177 ± 47	166 ± 41	<.001
Triglycerides, mg/dL	120 ± 57	135 ± 65	110 ± 49	<.001
LDL cholesterol, mg/dL	104 ± 35	107 ± 40	102 ± 32	.019
HDL cholesterol, mg/dL	42 ± 12	44 ± 12	42 ± 13	.016
<i>Echocardiography</i>				
LVEF, %	51 ± 15	49 ± 15	52 ± 15	<.001
LVEF ≤50%, n (%)	560 (45.8)	243 (53.4)	317 (41.3)	<.001
LAD, mm	44 ± 8	43 ± 7	44 ± 8	.001
LVDD, mm	56 ± 9	57 ± 9	55 ± 9	<.001
<i>Medical treatment</i>				
Beta-blockers, n (%)	635 (52)	258 (56.7)	377 (49.1)	.011
Diuretics, n (%)	1198 (98)	444 (97.6)	754 (98.3)	.379

**Table 1**  
Baseline Characteristics of the Population Stratified by Statin Therapy (continued)

	All (n = 1222)	Statins (n = 455)	No statins (n = 767)	P
Spironolactone, n (%)	232 (19)	97 (21.3)	135 (17.6)	.109
ACEI, n (%)	505 (41.3)	170 (37.4)	335 (43.7)	.030
ARB, n (%)	361 (29.5)	159 (34.9)	202 (26.3)	.001
Oral anticoagulants, n (%)	493 (40.3)	150 (33)	343 (44.7)	<.001
Nitrates, n (%)	246 (20.1)	134 (29.4)	112 (14.6)	<.001
Digoxin, n (%)	313 (25.6)	94 (20.7)	219 (28.5)	.002

ACEI, angiotensin converting enzyme inhibitors; ADHF, acute decompensate heart failure; AHF, acute heart failure; ARB, angiotensin receptor blockers; BNP, brain natriuretic peptide; CA125, antigen carbohydrate 125; COPD, chronic pulmonary obstructive disease; DBP, diastolic blood pressure; HDL, high-density lipoprotein; HF, heart failure; LAD, left atrial diameter; LDL, low-density lipoprotein; LVDD, left ventricular diastolic diameter; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; PAD, peripheral artery disease; SBP, systolic blood pressure.

Data are expressed as mean  $\pm$  standard deviation, n (%) or median [interquartile range].

<sup>a</sup> Last NYHA functional class measured under clinically stable conditions.

Discrete variables were presented as percentages. Mortality rates across statin therapy and CA125 categories ( $\leq$  or  $>35$  U/mL) were depicted using the Kaplan-Meier method and their differences tested by the Peto-Peto Prentice test. The independent association between statin treatment and long-term mortality was assessed with Cox regression analysis. For the secondary analysis, cardiovascular death was independently modeled with Cox adapted for competing risk events.<sup>20</sup> Candidate covariates for the initial multivariable model were chosen based on previous medical knowledge (see variables in Table 1), and independent of their *P*-value. A reduced, parsimonious, although highly predictive model was then derived by a backward elimination procedure using the “multivariable fractional polynomial” algorithm. The proportionality assumption for the hazard function over time was tested by means of the Schoenfeld residuals. The discriminative ability of the models was assessed using Harrell’s C-statistics and their calibration by the Gronnesby and Borgan test. Covariates that were included in the final models are specified in the respective figure and table legends. To provide clinical meaning to the Cox regression results, absolute measures for the association between statins and mortality were calculated. Adjusted absolute risk differences were estimated across CA125-binary status and at specific time points during the follow-up (3 and 6 months, 1, 3 and 5 years).<sup>21</sup> Number needed to treat (NNT) and their 95% confidence interval (95%CI) were obtained by taking the reciprocal of the risk difference.

A 2-sided *P*-value of  $<.05$  was considered to be statistically significant for all analyses. All analyses were performed using STATA 11.1 (StataCorp. 2009. Stata Statistical Software: Release 11. College Station, Texas: StataCorp LP, United States).

## RESULTS

The mean age in our sample was  $73 \pm 11$  years; 50.8% were female, 54% exhibited LVEF  $>50\%$ , 64.9% had higher levels of CA125 ( $>35$  U/mL) and 37.2% received statin therapy. Among patients that received statins, atorvastatin (61.5%), pravastatin (20.7%), and simvastatin (15.4%) were, in that order, the most frequent prescriptions. Among patients receiving statins, the median [IQR] dose for atorvastatin, pravastatin, and simvastatin were 20 mg (20–40), 40 mg (20–40) and 20 mg (10–20), respectively. According to statin dose categorization, 210 (46.2%) and 245 (53.8%) patients were treated with low and medium-high dose, respectively. Clinical characteristics of the study population are shown in Table 1.

### Clinical Predictors of Carbohydrate Antigen 125 Elevation

Patients with CA125 values  $>35$  U/mL displayed the worst baseline risk profile as evidenced by higher proportion of

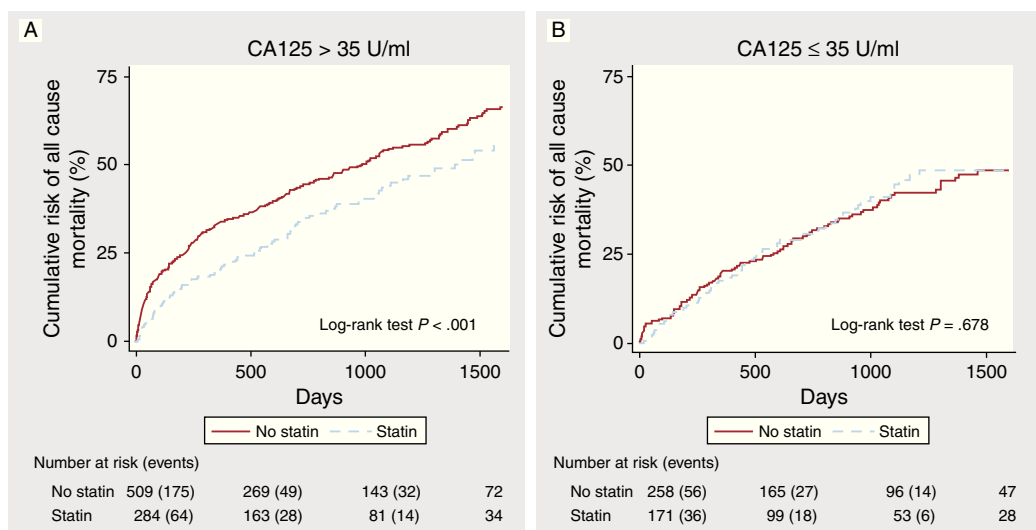
admission as acute decompensated heart failure, NYHA III/IV at stable phase of the disease, pleural effusion, peripheral edema, atrial fibrillation, and left ventricular systolic dysfunction. Likewise, higher means of uric acid, brain natriuretic peptide (BNP), and left atrial and ventricular dimensions, and lower means of systolic and diastolic blood pressure, serum hemoglobin, relative lymphocyte count, cholesterol (total, LDL and high-density lipoprotein [HDL]), and triglycerides were observed in this group of patients (supplementary material, annex 1). The most important variables that were independently associated with CA125  $>35$  U/mL were: a) presence of radiologic pleural effusion; b) BNP serum values, and c) peripheral edema, explaining 50.9%, 13.9% and 8% of the total  $R^2$ , respectively.

### Clinical Predictors of Statin Prescription

Table 1 lists those variables significantly associated with statin prescription. The most important independent predictors (ranked in order of importance) were: a) previous treatment with statins (60% of total  $R^2$ ); b) history of dyslipidemia (12.8% of total  $R^2$ ), and c) history of myocardial infarction (7.5% of total  $R^2$ ). In this population, serum lipid levels contributed marginally to the odds of statin prescription (5.7%, 5.2%, and 2.6% of total  $R^2$  for HDL, LDL and triglycerides, respectively). It is notable that CA125, whether evaluated as a continuous or binary (CA125  $>35$  U/mL) variable, was not independently associated with statin prescription (odds ratio [OR] = 0.99; 95%CI: 0.99–1.00, *P* = .524 and OR = 1.29; 95%CI: 0.90–1.87, *P* = .168, respectively).

### Statin Therapy and All-Cause Mortality Across Carbohydrate Antigen 125 Status

At a median follow-up of 20 months (IQR = 8–38), 542 (44.4%) deaths were ascertained. Of these, 418 were attributed as cardiovascular (77.1%) and 194 (35.8%) were due to HF progression. In univariate analysis, a differential prognostic effect between statin treatment and CA125 categories was observed (*P* for interaction = .019). In patients with CA125  $>35$  U/mL, mortality was lower in statin-treated patients (1.89 vs 2.80 per 10 patient-years of follow-up, respectively, *P*  $<.001$ ), with differences observed since the first months of follow-up and reaching a maximum between the first and second year (Fig. 1A). Conversely, in those with CA125  $\leq 35$  U/mL, mortality rates did not differ by statin treatment (1.76 vs 1.63 per 10 patient-years of follow-up, *P* = .862) (Fig. 1B). After a thorough multivariable adjustment, this interaction persisted (*P* for interaction = .024); treatment with statins was associated with a significant adjusted risk reduction in patients with elevated values of CA125 (HR = 0.65, 95%CI: 0.51–0.82; *P*  $<.001$ ), but not in those with values equal or below 35 U/mL (HR = 1.02, 95%CI: 0.74–1.41; *P* = .907). This



**Figure 1.** Cumulative risk of mortality across statin therapy. A: In patients with carbohydrate antigen 125 >35 U/mL. B: In patients with carbohydrate antigen 125 ≤35 U/mL. CA125, carbohydrate antigen 125.

interaction was also present when CA125 was evaluated as continuous or dichotomized by its median value (supplementary material, annex 2). Moreover, several sensitivity analyses were performed with the aim to further support our findings. All of them confirmed the prognostic benefit of statins in patients with CA125 >35 U/mL: a) by forcing in the model the most important variables associated to statin prescription (previous treatment with statins, history of dyslipidemia, previous myocardial infarction, and raw lipid values); b) by testing statins dosages (low vs medium-high), and c) by testing, independently, the predictive value of the two most frequent statin classes prescribed (atorvastatin and pravastatin) (Fig. 2).

Furthermore, subgroup analyses revealed that this prognostic benefit of statins (in patients with high CA125 values) was uniform in the most representative subset of patients with AHF, such as those >75 years old, females, LVEF < 50%, ischemic etiology, diabetes mellitus, and previous admission for AHF, even in patients with no previous dyslipidemia and total cholesterol and LDL cholesterol below the median (Fig. 3).

The absolute association of statins with total mortality across CA125-binary status was evaluated by estimating an adjusted absolute risk difference (and NNT) at 3 and 6 months and 1, 3 and 5 years after admission (Table 2). In the group with CA125 >35 U/mL there was a consistent association of statins with mortality along the entire follow-up, and independently of the baseline hazard function for mortality; no association was shown in those patients belonging to the group of CA125 ≤35 U/mL. The equivalent translation to NNT is depicted in Table 2. Overall, treatment with statins in this population of patients with AHF was associated with 1 less death for every 7 to 14 patients treated, depending on the time at which it was evaluated.

### Statin Therapy and Cardiovascular Mortality Across Carbohydrate Antigen 125 Categories

During follow-up, 418 cardiovascular deaths were registered (77.1%). Similar to all-cause mortality, those patients treated with statins and high levels of CA125 showed a marked decrease in the cumulative incidence function for cardiovascular mortality as compared to: a) non-statin-treated patients with CA125 >35 U/mL, and b) patients with normal CA125 values

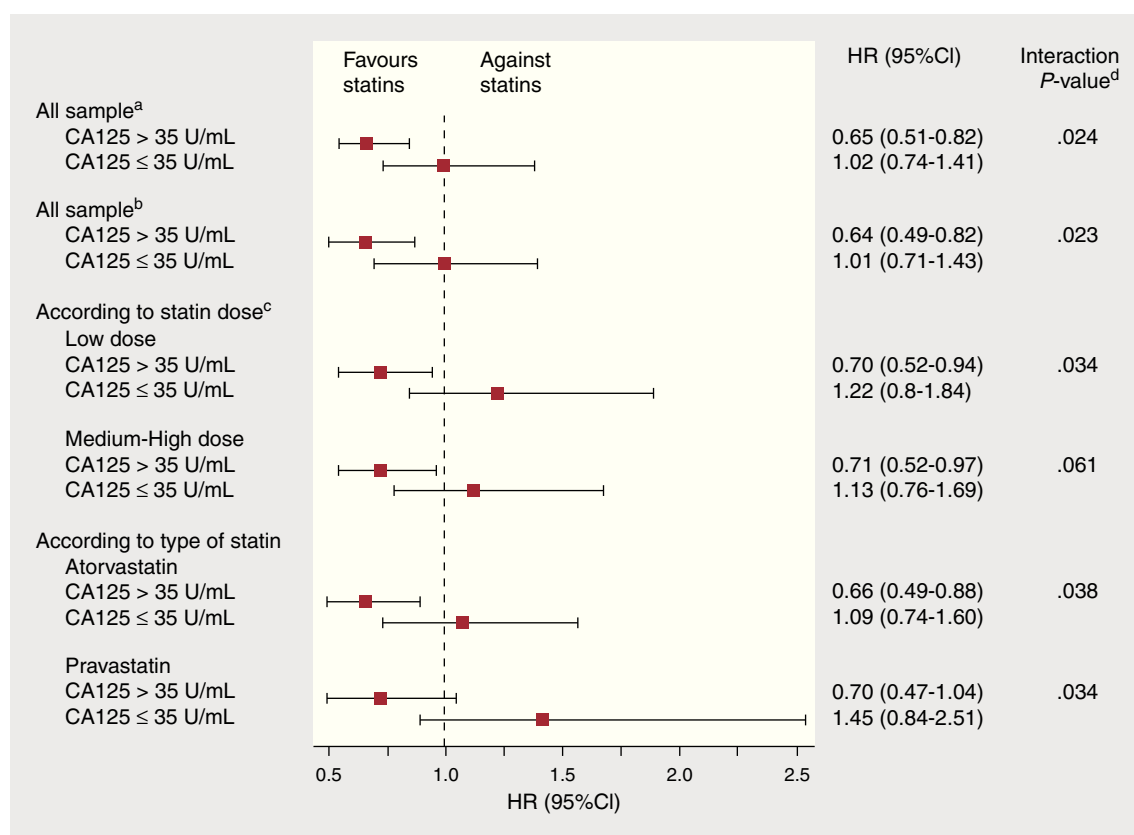
treated or not with statins (no significant difference in the cumulative incidence of cardiovascular death across statin therapy), as illustrated in supplementary material annex 3. Failure probabilities according to cause of death showed homogeneous mortality reduction for statin-treated patients with CA125 >35 U/mL for the most important causes of cardiovascular death (progressive HF and sudden death) and also for non-cardiovascular death (Table 3).

In multivariable analysis, while accounting for non-cardiovascular death as a competing event, the interaction between CA125 and statins was borderline significant (*P*-value for interaction = .051). Constrained by this interaction, those patients displaying CA125 >35 U/mL and treated with statins showed a significant 38% risk reduction (HR = 0.62, 95%CI: 0.47-0.81; *P* < .001), whereas statin therapy failed to show any benefit in those with normal CA125 values (HR = 0.97, 95%CI: 0.66-1.41; *P* = .703), as shown in supplementary material annex 2.

### DISCUSSION

In the present study, we found that in patients with AHF the association of statins with long-term mortality was differentially determined by CA125 serum levels. In contrast to patients with normal CA125 values (≤35 U/mL), where no association was observed, in patients exhibiting high CA125 values (>35 U/mL) statin treatment was associated with a significant 35% reduction in total mortality. The consistency of this differential prognostic effect was confirmed despite a thorough covariate adjustment (including lipid levels), and also observed among the most important clinical subgroups, including patients with non-ischemic HF etiology and those with preserved systolic function. Moreover, the beneficial association of statins observed in the subgroup of patients with CA125 >35 U/mL was also endorsed by a significant difference in absolute risk shown along the entire follow-up.

Although the findings of subgroup analyses should be cautiously interpreted, we believe that our main finding provides additional support to the results of a recent analysis of the CORONA trial,<sup>6</sup> where the main prognostic benefit of statins in HF was observed only in patients with elevated proinflammatory activity.<sup>8</sup>



**Figure 2.** Total mortality adjusted hazard ratio (95% confidence interval) for the effect of statins among patients with carbohydrate antigen 125 > 35 U/mL. CA125, carbohydrate antigen 125; 95%CI, 95% confidence interval; HR, hazard ratio. <sup>a</sup>Model 1: final multivariate Cox model adjusted by: age, gender, previous admission for acute heart failure (yes/no), admission as acute decompensate heart failure (yes/no), last New York Heart Association functional class at stable phase of the disease, length of stay, ischemic etiology, heart rate interacting with atrial fibrillation (yes/no), systolic blood pressure interacting with left ventricular ejection fraction < 50% (yes/no), radiologic evidence of pleural effusion (yes/no), peripheral artery disease (yes/no), serum sodium, serum brain natriuretic peptide, serum hemoglobin, serum urea, relative lymphocyte count, treatment with beta-blockers (yes/no) and oral anticoagulants (yes/no). Harrell's C-statistics of the model was 0.752. The Gronnesby and Borgan test of goodness-of-fit showed a good model's calibration ( $P = .579$ ). <sup>b</sup>Model 2: Multivariate Cox model adjusted by the same set of the covariates of model 1 plus main variables associated to statin prescription: previous treatment with statins (yes/no), history of dyslipidemia (yes/no), previous myocardial infarction (yes/no) and serum lipid levels. Harrell's C-statistics of the model was 0.752. The Gronnesby and Borgan test of goodness-of-fit showed a good model's calibration ( $P = .555$ ). <sup>c</sup>Dose categories included: low dose (atorvastatin ≤ 10 mg, simvastatin ≤ 20 mg, pravastatin ≤ 40 mg, lovastatin ≤ 40 mg and fluvastatin ≤ 80 mg) and medium-high dose (atorvastatin ≥ 20 mg and simvastatin ≥ 40 mg). <sup>d</sup>Interaction P-value refers to the interaction between treatment with statins and CA125-binary status.

### Carbohydrate Antigen 125 as a Marker of Inflammation and Its Theoretical Advantages Over Other Inflammatory Biomarkers

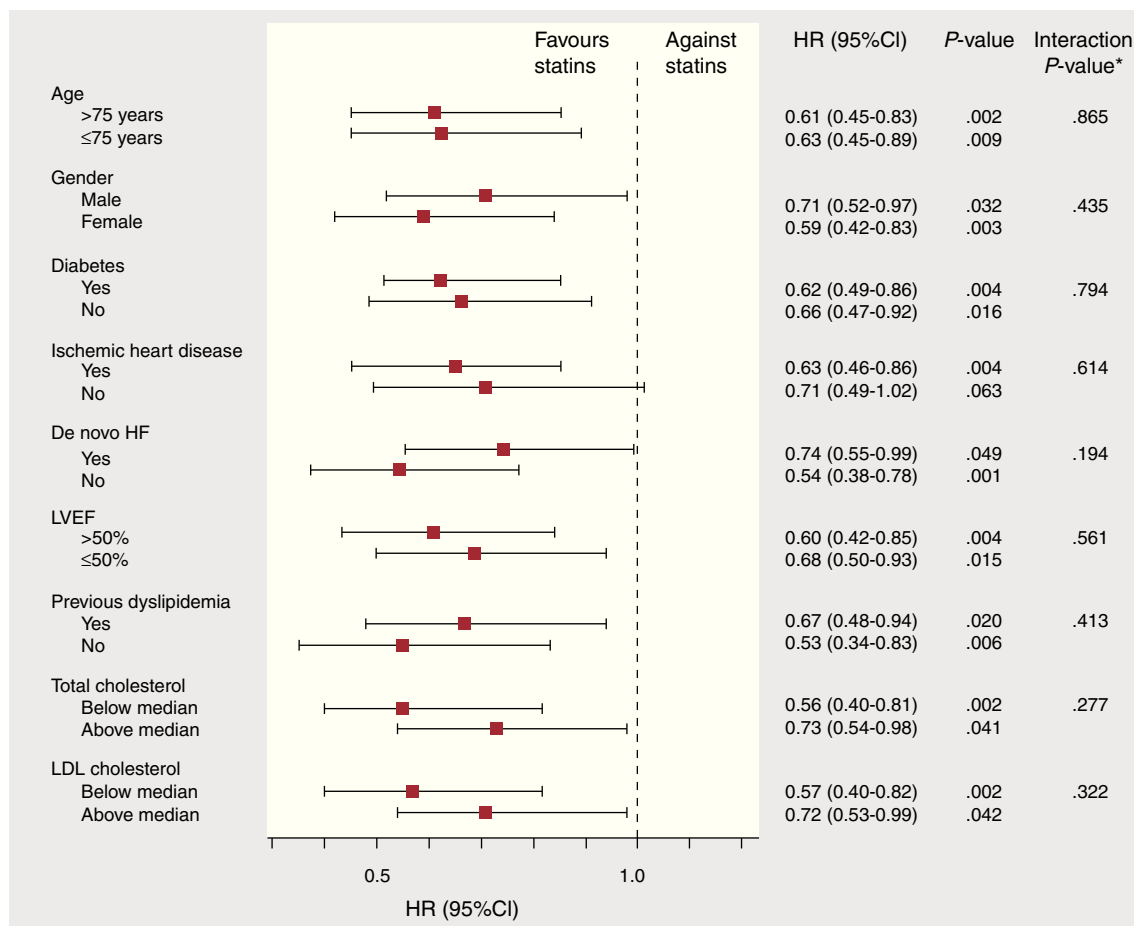
There is increased evidence underlying the prognostic role of CA125 in advanced HF.<sup>11,12</sup> Although the exact mechanism for this association has not yet been determined, it is believed to be related to complex pathophysiological processes linking inflammation and systemic congestion.<sup>22</sup> For instance, in AHF setting, CA125 levels did show to correlate with proinflammatory cytokines and low relative lymphocytes count.<sup>9,10</sup> Furthermore, *in vitro* studies have shown that proinflammatory cytokines such as interleukin-1, tumor necrosis factor- $\alpha$  and lipopolysaccharide can stimulate human mesothelial cells to increase secretion of CA125.<sup>23</sup>

Compared to other inflammatory biomarkers not yet ready for routine clinical use, CA125 offers some meaningful potential advantages such as wide availability in routine clinical practice, standardized measurement, low cost and pharmacokinetics reliability. It is well known that most proinflammatory cytokines exhibited high temporal variability for reasons that are out of the scope of this work (unstandardized measure techniques, pulsatile release, short half-lives, etc.).<sup>24</sup> In contrast, CA125 kinetic displays a mean span-life higher than 1 week,<sup>13</sup> even much longer than 18-20 h of CRP plasma half-life,<sup>25</sup> which allows us to postulate

CA125 as a reliable biomarker for baseline identification of heightened inflammatory activity. On the other hand, clinical observations have shown that serial changes of CA125 over time are kept within values that reflect the patient's clinical status and prognosis.<sup>26,27</sup> Based on all of these attractive properties, we believe that this glycoprotein may have a potential role for monitoring and guiding therapy in HF, either as stand-alone or combined with natriuretic peptides. Not surprisingly, the main clinical use of this biomarker, outside HF setting, is for monitoring therapy in ovarian cancer.<sup>28</sup>

### Pleiotropic Effects of Statins. A Matter of Debate

Several mechanisms have been proposed to explain the unexpected (and disappointing) results of the CORONA<sup>6</sup> and GISSI<sup>7</sup> trials. On one hand, lipoproteins have been shown to neutralize the endotoxin inflammatory response, and thus, by lowering them with statins, the bioactivity of bacterial endotoxins may potentially increase.<sup>2,29</sup> Statins also reduce plasma levels of ubiquinone, a coenzyme in mitochondrial respiration, which at least on theoretical ground, may affect myocardial function.<sup>2</sup> On the positive side, however, a large number of studies have



**Figure 3.** Adjusted hazard ratio for the effect of statins on total mortality across main subgroups of patients with carbohydrate antigen 125 >35 U/mL. 95%CI, 95% confidence interval; HF, heart failure; HR, hazard ratio; LDL, low-density lipoprotein; LVEF, left ventricular ejection fraction. \*Interaction P-value refers to the interaction between treatment with statins and each variable identifying the clinical subgroups.

shown the effects of statins in reducing inflammatory markers (CRP, tumor necrosis factor- $\alpha$ , interleukin-1 and interleukin-6) including patients with HF.<sup>30</sup> The longstanding success of statins in HF speaks in favor of the hypothesis that the net effect of these opposite forces goes in favor of the anti-inflammatory effect. The clinical benefit of statin therapy based on inflammatory status is also reinforced in general population by the results of JUPITER trial, where in healthy persons without dyslipidemia but with elevated CRP levels, rosuvastatin significantly reduced the incidence of

major cardiovascular events.<sup>31</sup> Nevertheless, generating more debate, a recent substudy of the Heart Protection Study showed that reducing LDL cholesterol with simvastatin reduces the risk of major vascular events to a similar extent irrespective of CRP concentration.<sup>32</sup>

In AHF, elevated inflammatory activity interacts through complex pathophysiological pathways with systemic congestion,<sup>22</sup> and is thought to contribute to the high morbidity and mortality observed after the first months following the acute

**Table 2**

Adjusted Absolute Risk Difference and Number Needed to Treat for the Effect of Statins on Mortality, Among Carbohydrate Antigen 125-binary Status at the Specified Time Points

Time points	CA125 > 35 U/mL		CA125 ≤ 35 U/mL	
	Adjusted ARD (95%CI)	NNT (95%CI)	Adjusted ARD (95%CI)	NNT (95%CI)
3 months	0.08 (0.03 to 0.12)	13.1 (8.3 to 30.9)	-0.01 (-0.06 to 0.04)	-88.6 (27.5 to -17.0)
		(P=.001)		(P=.642)
6 months	0.07 (0.02 to 0.12)	13.8 (8.1 to 46.8)	-0.004 (-0.06 to 0.06)	-270.9 (18.2 to -16.0)
		(P=.005)		(P=.902)
1st year	0.11 (0.05 to 0.17)	9.3 (6.0 to 20.6)	0.01 (-0.07 to 0.08)	113.7 (11.9 to -15.1)
		(P<.001)		(P=.819)
3rd year	0.11 (0.03 to 0.19)	9.2 (5.3 to 35.9)	-0.01 (-0.12 to 0.09)	-73.9 (10.6 to -8.2)
		(P=.008)		(P=.806)
5th year	0.14 (0.05 to 0.23)	7.1 (4.3 to 19.7)	-0.004 (-0.13 to 0.12)	-232.5 (8.2 to -7.6)
		(P=.002)		(P=.947)

ARD, absolute risk difference; CA125, carbohydrate antigen 125; NNT, number needed to treat.

**Table 3**  
Failure Probabilities According to Cause of Death

Time (year)	CA125 ≤35 U/mL No statins (n=258)		CA125 ≤35 U/mL Statins (n=171)		CA125 >35 U/mL No statins (n=509)		CA125 >35 U/mL Statins (n=284)		Total (n=1222)
	Died, (No.)	1-KM	Died, (No.)	1-KM	Died, (No.)	1-KM	Died, (No.)	1-KM	Died, (No.)
<i>Cardiovascular-death (n=418)</i>									
1	38	0.1575	22	0.1479	134	0.2825	49	0.1826	243
2	52	0.2312	33	0.2348	168	0.3761	64	0.264	317
3	65	0.3238	44	0.3616	189	0.4549	77	0.3664	375
4	72	0.3963	46	0.3928	203	0.5331	82	0.4257	403
5	73	0.4107	47	0.4217	209	0.5778	83	0.4417	412
6	73	0.4107	48	0.4743	210	0.5947	84	0.4789	415
<i>Progressive heart failure death (n=194)</i>									
1	18	0.0754	11	0.0741	83	0.1799	27	0.1029	139
2	22	0.099	13	0.0924	93	0.2136	33	0.1382	161
3	26	0.1332	15	0.119	98	0.2371	39	0.1954	178
4	29	0.1729	16	0.1416	103	0.278	39	0.1954	187
5	29	0.1729	16	0.1416	105	0.2998	40	0.2178	190
6	29	0.1729	16	0.1416	106	0.3278	41	0.2699	192
<i>Sudden death (n=55)</i>									
1	6	0.0268	3	0.0223	20	0.0499	8	0.0325	37
2	6	0.0268	4	0.0313	24	0.0649	9	0.0407	43
3	8	0.0489	9	0.107	25	0.0701	10	0.0524	52
4	9	0.0631	10	0.1283	26	0.082	10	0.0524	55
5	9	0.0631	10	0.1283	26	0.082	10	0.0524	55
6	9	0.0631	10	0.1283	26	0.082	10	0.0524	55
<i>Non-cardiovascular death (n=124)</i>									
1	12	0.0547	5	0.0330	28	0.0730	6	0.0253	51
2	19	0.0958	11	0.0952	38	0.1106	19	0.1073	87
3	24	0.1356	12	0.1129	46	0.1582	20	0.1167	102
4	25	0.1461	14	0.1524	52	0.2105	22	0.1497	113
5	25	0.1461	15	0.1877	55	0.2529	24	0.1998	119
6	26	0.1802	15	0.1877	55	0.2529	24	0.1998	120

CA125: carbohydrate antigen 125; KM: Kaplan Meier.

episode. Several observational studies have reported better survival among statin treated patients in the setting of AHF<sup>3,5</sup> and in patients with severe bacterial infections,<sup>33</sup> where inflammation plays a crucial pathogenic role. We believe, however, that AHF represents an inhomogeneous clinical entity, not only in aetiology and LVEF, but also in levels of systemic inflammation. AHF patients, especially those with over-activity of the immune system constitute a plausible target to further investigate the statin therapeutic effects.

### Limitations

There are a number of potential limitations in this study: a) this is a single-center observational study where, by design, different types of bias and residual confounding may be operating; b) the adjudication of specific cause of death was mainly done through patients' chart review which, to some extent, may introduce some degree of endpoint misclassification; c) with the present data, we cannot address the complex pathogenic mechanisms that may be operating between statins, HF and mortality; d) knowing that the indication for statins in our cohort was for the treatment of dyslipidemia, we are unable to discard that our results may be confounded by this indication; e) due to the small size of our cohort and the many different types and doses of statins, it was not possible to determine whether a dose-response or a class effect

was present; f) we did not evaluate either the adherence to statin therapy or the impact that serial changes in CA125 would have had on our results, and g) the lack of measurement of CRP in all patients precludes to include this biomarker in this analysis.

### CONCLUSIONS

In conclusion, in this hypothesis generating study, statin therapy in AHF was associated with a decreased risk of mortality, but only for those patients with CA125 levels >35 U/mL. These results provide a rationale to further investigate the therapeutic role of statins among HF patients with evidence of systemic inflammation as evidenced by elevated CA125 levels in a more controlled scenario.

### FUNDING

This study was supported by a grant from *Conselleria de Sanitat (Direcció General de Ordenació, Evaluació e Investigació Sanitària para el fomento de la investigació en la Comunitat Valenciana: AP-132/08)* and by the *Ministerio de Sanidad y Consumo, Instituto de Salud Carlos III, RED HERACLES RD06/0009/1001 (Madrid, Spain)*.



## CONFLICT OF INTERESTS

Dr. Gregg Fonarow has research from the National Institutes of Health, received honorarium from GlaxoSmithKline, Medtronic, Novartis, and Pfizer, and consulted for GlaxoSmithKline, Merck, Novartis, and Pfizer.

## SUPPLEMENTARY MATERIAL



Supplementary material associated with this article can be found in the online version available at [doi:10.1016/j.rec.2011.05.033](https://doi.org/10.1016/j.rec.2011.05.033).

## REFERENCES

- Yndestad A, Damas JK, Oie E, Ueland T, Gullestad L, Aukrust P. Systemic inflammation in heart failure—the whys and wherefores. *Heart Fail Rev*. 2006;11:83–92.
- Tsouli SG, Liberopoulos EN, Goudevenos JA, Mikhailidis DP, Elisaf MS. Should a statin be prescribed to every patient with heart failure? *Heart Fail Rev*. 2008;13:211–25.
- Anker SD, Clark AL, Winkler R, Zugck C, Ciccoira M, Ponikowski P, et al. Statin use and survival in patients with chronic heart failure —results from two observational studies with 5200 patients. *Int J Cardiol*. 2006;112:234–42.
- Footy JM, Shah R, Galusha D, Masoudi FA, Havranek EP, Krumholz HM. Statins and mortality among elderly patients hospitalized with heart failure. *Circulation*. 2006;113:1086–92.
- Go AS, Lee WY, Yang J, Lo JC, Gurwitz JH. Statin therapy and risks for death and hospitalization in chronic heart failure. *JAMA*. 2006;296:2105–11.
- Kjekshus J, Apetrei E, Barrios V, Bohm M, Cleland JG, Cornel JH, et al. Rosuvastatin in older patients with systolic heart failure. *N Engl J Med*. 2007;357:2248–61.
- Gissi-HF Investigators, Tavazzi L, Maggioni AP, Marchioli R, Barlera S, Franzosi MG, Latini R, et al. Effect of rosuvastatin in patients with chronic heart failure (the GISSI-HF trial): a randomised, double-blind, placebo-controlled trial. *Lancet*. 2008;372:1231–9.
- McMurray JJ, Kjekshus J, Gullestad L, Dunselman P, Hjalmarsen A, Wedel H, et al.; CORONA Study Group. Effects of statin therapy according to plasma high-sensitivity C-reactive protein concentration in the controlled rosuvastatin multinational trial in heart failure (CORONA): a retrospective analysis. *Circulation*. 2009;120:2188–96.
- Kosar F, Aksoy Y, Ozguntekin G, Ozerol I, Varol E. Relationship between cytokines and tumour markers in patients with chronic heart failure. *Eur J Heart Fail*. 2006;8:270–4.
- Miñana G, Núñez J, Sanchis J, Bodí V, Núñez E, Llàcer A. CA125 and immunoinflammatory activity in acute heart failure. *Int J Cardiol*. 2010;145:547–8.
- Núñez J, Núñez E, Consuegra L, Sanchis J, Bodí V, Martínez-Brotos A, et al. Carbohydrate antigen 125: An emerging prognostic risk factor in acute heart failure? *Heart*. 2007;93:716–21.
- Núñez J, Sanchis J, Bodí V, Fonarow GC, Núñez E, Bertomeu-González V, et al. Improvement in risk stratification with the combination of the tumour marker antigen carbohydrate 125 and brain natriuretic peptide in patients with acute heart failure. *Eur Heart J*. 2010;31:1752–63.
- Bidart JM, Thuillier F, Augereau C, Chalas J, Daver A, Jacob N, et al. Kinetics of serum tumor marker concentrations and usefulness in clinical monitoring. *Clin Chem*. 1999;45:1695–707.
- Remme WJ, Swedberg K. Guidelines for the diagnosis and treatment of chronic heart failure. *Eur Heart J*. 2001;22:1527–60.
- Nieminen MS, Bohm M, Cowie MR, Drexler H, Filippatos GS, Jondeau G, et al.; ESC Committee for Practice Guideline (CPG). Executive summary of the guidelines on the diagnosis and treatment of acute heart failure: the Task Force on Acute Heart Failure of the European Society of Cardiology. *Eur Heart J*. 2005;26:384–416.
- Task Force for Diagnosis and Treatment of Acute and Chronic Heart Failure 2008 of European Society of Cardiology., Dickstein K, Cohen-Solal A, Filippatos G, McMurray JJ, Ponikowski P, Poole-Wilson PA, et al. ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2008: the Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2008 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association of the ESC (HFA) and endorsed by the European Society of Intensive Care Medicine (ESICM). *Eur Heart J*. 2008;29:2388–442.
- Roger VL, Go AS, Lloyd-Jones DM, Adams RJ, Berry JD, Brown TM, et al.; American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Heart disease and stroke statistics—2011 update: a report from the American Heart Association. *Circulation*. 2011;123:e18–209.
- Jones P, Kafonek S, Laurora I, Hunninghake D. Comparative dose efficacy study of atorvastatin versus simvastatin, pravastatin, lovastatin, and fluvastatin in patients with hypercholesterolemia (the curves study). *Am J Cardiol*. 1998;81:582–7.
- Jialal I, Stein D, Balis D, Grundy SM, Adams-Huet B, Devaraj S. Effect of hydroxymethyl glutaryl coenzyme a reductase inhibitor therapy on high sensitive C-reactive protein levels. *Circulation*. 2001;103:1933–5.
- Fine J, Gray R. A proportional hazard model for the subdistribution of a competing risk. *J Am Stat Assoc*. 1999;94:496–509.
- Laubender RP, Bender R. Estimating adjusted risk difference (RD) and number needed to treat (NNT) measures in the Cox regression model. *Stat Med*. 2010;29:851–9.
- Colombo PC, Jorde UP. Papel activo de la congestión venosa en la fisiopatología de la insuficiencia cardiaca aguda descompensada. *Rev Esp Cardiol*. 2010;63:5–8.
- Zeillemaker AM, Verbrugh HA, Hoyneck Van Papendrecht AA, Leguit P. CA 125 secretion by peritoneal mesothelial cells. *J Clin Pathol*. 1994;47:263–5.
- Dibbs Z, Thornby J, White BG, Mann DL. Natural variability of circulating levels of cytokines and cytokine receptors in patients with heart failure: implications for clinical trials. *J Am Coll Cardiol*. 1999;33:1935–2012.
- Ridker PM. Clinical application of C-reactive protein for cardiovascular disease detection and prevention. *Circulation*. 2003;107:363–9.
- D'Aloia A, Faggiano P, Aurigemma G, Bontempi L, Ruggeri G, Metra M, et al. Serum levels of carbohydrate antigen 125 in patients with chronic heart failure: relation to clinical severity, hemodynamic and Doppler echocardiographic abnormalities, and short-term prognosis. *J Am Coll Cardiol*. 2003;41:1805–11.
- Núñez J, Núñez E, Sanchis J, Bodí V, Fonarow GC, Miñana G, et al. Antigen carbohydrate 125 and brain natriuretic peptide serial measurements for risk stratification following an episode of acute heart failure. *Int J Cardiol*. 2011. [doi:10.1016/j.ijcard.2011.02.001](https://doi.org/10.1016/j.ijcard.2011.02.001).
- Scholler N, Urban N. Ca125 in ovarian cancer. *Biomark Med*. 2007;1:1513–23.
- Rauchhaus M, Coats AJ, Anker SD. The endotoxin-lipoprotein hypothesis. *Lancet*. 2000;356:930–3.
- Zhang L, Zhang S, Jiang H, Sun A, Wang Y, Zou Y, et al. Effects of statin therapy on inflammatory markers in chronic heart failure: a meta-analysis of randomized controlled trials. *Arch Med Res*. 2010;41:464–71.
- Ridker PM, Danielson E, Fonseca FA, Genest J, Gotto Jr AM, Kastelein JJ, et al. Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein. *N Engl J Med*. 2008;359:2195–207.
- Emberson J, Bennett D, Link E, Parish S, Danesh J, Armitage J, et al.; Heart Protection Study Collaborative Group. C-reactive protein concentration and the vascular benefits of statin therapy: an analysis of 20,536 patients in the Heart Protection Study. *Lancet*. 2011;377:469–76.
- Bjorkhem-Bergman L, Bergman P, Andersson J, Lindh JD. Statin treatment and mortality in bacterial infections—a systematic review and meta-analysis. *PLoS One*. 2010;5:e110702.