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Original article

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

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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. **C**arbohydrate 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.

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

Palabras clave:
Estatinas
Antígeno carbohidrato 125
Mortalidad
Insuficiencia cardiaca

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

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antígeno carbohidrato 125 ≤ 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.

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).[1] The pleiotropic anti-inflammatory properties of statins appear to be an attractive feature for targeting the inflammatory component in patients with advanced HF.[2] In contrast to large-scale observational studies that have shown a reduction in clinical outcomes in patients with HF and treated with statins,[3–5] two recent randomized controlled trials of statins in HF failed to demonstrate any survival benefit.[6,7] 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).[8]

Accumulated evidence has pointed to carbohydrate antigen 125 (CA125) as a reliable marker for congestion and inflammation in patients with acute heart failure (AHF)[9–12] and as being independently associated to all-cause and cardiovascular mortality.[11,12] The fact that serum levels of CA125 have shown to be very reliable over time[12,13] 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.[14–16] 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.[14–16] 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.[17] 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 ± 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)[18] and CRP reduction efficacy,[19] the therapeutic equivalence between statins was characterized as low and medium-high doses. Low dose included atorvastatin ≤10 mg, simvastatin ≤20 mg, pravastatin ≤40 mg, lovastatin ≤40 mg or fluvastatin ≤80 mg, and medium-high dose included atorvastin ≥20 mg or simvastatin ≥40 mg.

Statistical Analysis

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