



**Additional material**

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

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**Annex 1**

## Baseline Characteristics Stratified by CA125.

	CA125 ≤35 U/ml (n=429)	CA125 >35 U/ml (n=793)	p
<i>Demographic and medical history</i>			
Age, years	73±11	73±11	.265
Female, n (%)	194 (45.2)	408 (51.4)	.038
Previous admission for AHF, n (%)	162 (37.8)	296 (37.3)	.881
Hypertension, n (%)	363 (84.6)	583 (73.5)	<.001
Dyslipidemia, n (%)	203 (47.3)	320 (40.3)	.019
Current smoker, n (%)	45 (10.5)	83 (10.5)	.990
Previous smoker, n (%)	72 (16.8)	160 (20.2)	.149
Ischemic heart disease, n (%)	167 (38.9)	299 (37.7)	.674
Valvular heart disease, n (%)	113 (26.3)	237 (29.9)	.191
ADHF, n (%)	246 (57.3)	590 (74.4)	<.001
Acute pulmonary edema, n (%)	123 (28.7)	142 (17.9)	<.001
Hypertensive AHF, n (%)	56 (13)	43 (5.4)	<.001
NYHA class III/IV, n (%)*	64 (14.9)	160 (20.2)	.023
Previous HF, n (%)	149 (34.7)	285 (35.9)	.674
COPD, n (%)	93 (21.7)	172 (21.7)	.996
PAD, n (%)	34 (7.9)	53 (6.7)	.420
Stroke, n (%)	39 (9.1)	87 (11)	.302
Renal failure, n (%)	66 (15.4)	139 (17.5)	.338
Radiological pleural effusion, n (%)	96 (22.4)	443 (55.9)	<.001
Peripheral edema, n (%)	178 (41.5)	502 (63.3)	<.001
Previous use of diuretics, n (%)	256 (59.7)	500 (63)	.246
Previous use of beta-blockers, n (%)	102 (23.8)	190 (24)	.943
Previous use of ACEI/ARB, n (%)	228 (53.1)	326 (41.1)	<.001
Previous use of statins, n (%)	134 (31.2)	196 (24.7)	.014
<i>Vital signs</i>			

Heart rate, bpm	100±29	101±29	.526
SBP, mmHg	157±39	146±34	<.001
DBP, mmHg	85±22	81±19	.003
<i>Electrocardiogram</i>			
Atrial fibrillation, n (%)	164 (38)	375 (47)	.002
QRS >120 ms, n (%)	131 (30.5)	227 (28.8)	.518
<i>Laboratory</i>			
Haemoglobin, g/dl	12.9±1.8	12.6±1.9	<.001
Serum creatinine, mg/dl	1.3±0.6	1.3±0.5	.386
Serum urea, mg/dl	63±31	64±37	.627
Uric acid, mg/dl	7.6±2.4	8±2.4	.004
Sodium, meq/l	139±4	139±5	.053
Troponin I, ng/ml	0 [0-0.33]	0 [0-0.21]	.002
Troponin I >0.2 ng/ml, n (%)	135 (31.5)	201 (25.3)	.022
BNP, pg/ml†	117 [65-214]	170 [94-328]	<.001
Relative lymphocyte count, %	19.1±10.6	17.2±9.5	.001
CA125, U/ml	18 [13-26]	101 [59-181]	<.001
Total cholesterol, mg/dl	180±42	165±44	<.001
Triglycerides, mg/dl	131±64	113±52	<.001
LDL cholesterol, mg/dl	110±34	101±35	<.001
HDL cholesterol, mg/dl	44±12	41±12	<.001
<i>Echocardiography</i>			
LVEF, %	53±15	50±15	<.001
LVEF ≤50%, n (%)	162 (37.8)	398 (50.2)	<.001
LAD, mm	42±7	45±8	<.001
LVDD, mm	55±9	56±9	.325
<i>Medical treatment</i>			
Beta-blockers, n (%)	224 (52.2)	411 (51.8)	.897
Diuretics, n (%)	418 (97.4)	780 (98.4)	.266
Spironolactone, n (%)	71 (16.5)	161 (20.3)	.110
ACEI, n (%)	181 (42.2)	324 (40.9)	.651
ARB, n (%)	138 (32.2)	223 (28.1)	.139
Statins, n (%)	171 (39.9)	284 (35.8)	.163
Oral anticoagulants, n (%)	160 (37.3)	333 (42)	.110

Nitrates, n (%)	80 (18.6)	166 (20.9)	.342
Digoxin, n (%)	97 (22.6)	216 (27.2)	.077

ACEI, angiotensin converting enzyme inhibitors; ADHF, acute decompensate heart failure; AHF, acute heart failure; ARB, angiotensin II 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 and; LDL, low-density lipoprotein; LVEF, left ventricular ejection fraction; LVDD, left ventricular diastolic diameter. NYHA, New York Heart Association; PAD, peripheral artery disease; SBP, systolic blood pressure.

\* Last NYHA functional class measured under clinically stable conditions.

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

**Annex 2**

Adjusted HRs for the Effect of Statins on Mortality, Using Different Ways of Modeling CA125 Values.

<i>CA125 variables</i>	<i>Statin therapy</i>	<b>p-value for the interaction</b>
	<i>HR (95% CI)</i>	
<i>All-cause mortality<sup>a</sup></i>		
<i>CA125&gt;35 U/ml</i>	0.65 (0.51-0.82)	.024
<i>CA125≤35 U/ml</i>	1.02 (0.74-1.41)	
<i>CA125&gt;57 U/ml</i>	0.61 (0.47-0.49)	.022
<i>CA125≤57 U/ml</i>	0.94 (0.71-1.24)	
<i>lnCA125</i>		.017
<i>25 percentile</i>	0.64 (0.40-1.03)	
<i>50 percentile</i>	0.54 (0.29-0.99)	
<i>75 percentile</i>	0.45 (0.21-0.96)	
<i>Cardiovascular mortality<sup>b</sup></i>		
<i>CA125&gt;35 U/ml</i>	0.62 (0.47-0.81)	.051
<i>CA125≤35 U/ml</i>	0.97 (0.66-1.41)	
<i>CA125&gt;57 U/ml</i>	0.56 (0.42-0.76)	.022
<i>CA125≤57 U/ml</i>	0.93 (0.68-1.27)	
<i>lnCA125</i>		.018
<i>25 percentile</i>	0.61 (0.35-1.05)	
<i>50 percentile</i>	0.50 (0.25-1.01)	
<i>75 percentile</i>	0.41 (0.18-0.98)	

CA125, antigen carbohydrate 125; HR, hazard ratio; Q, quartiles.

<sup>a</sup> Multivariable Cox model adjusted by: age (years), gender, previous admission for AHF (yes/no), admission as ADHF (yes/no), last NYHA class at stable phase of the disease, length of stay (days), ischemic etiology, heart rate (bpm) interacting with atrial fibrillation (yes/no), systolic blood pressure (mmHg) interacting with left ventricular ejection fraction <50% (yes/no), radiologic evidence of pleural effusion (yes/no), peripheral artery disease (yes/no), serum sodium (mEq/L), serum brain natriuretic peptide (pg/mL), serum hemoglobin (g/mL), serum urea (g/mL), relative lymphocyte count (%), treatment with beta-blockers (yes/no) and oral

anticoagulants (yes/no). <sup>b</sup> Cox adapted for competing risk events adjusted by: age (years), gender, previous admission for acute heart failure (yes/no), admission as acute decompensate heart failure (yes/no), etiology, heart rate (bpm), systolic blood pressure (mmHg), radiologic evidence of pleural effusion (yes/no), previous stroke, serum sodium (mEq/L), serum brain natriuretic peptide (pg/mL), serum hemoglobin (g/mL), serum urea (g/mL) and controlling by non-cardiovascular deaths as competing event.

### Annex 3

