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Improvement in risk stratification with the combination of the tumour marker antigen carbohydrate 125 and brain natriuretic peptide in patients with acute heart failure

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Aim Elevated brain natriuretic peptide (BNP) and tumour marker antigen carbohydrate 125 (CA125) levels have shown to be associated with higher risk for adverse outcomes in patients with acute heart failure (AHF). Nevertheless, no attempt has been made to explore the utility of combining these two biomarkers. We sought to assess whether CA125 adds prognostic value to BNP in predicting 6-month all-cause mortality in patients with AHF.

Methods and results We analysed 1111 consecutive patients admitted for AHF. Antigen carbohydrate 125 (U/mL) and BNP (pg/mL) were measured at a median of 72 ± 12 h after instauration of treatment. Antigen carbohydrate 125 and BNP were dichotomized based on proposed prognostic cutpoints, and a variable with four categories was formed (BNP–CA125): C1 = BNP < 350 and CA125 < 60 ($n = 394$); C2 = BNP ≥ 350 and CA125 < 60 ($n = 165$); C3 = BNP < 350 and CA125 ≥ 60 ($n = 331$); and C4 = BNP ≥ 350 and CA125 ≥ 60 ($n = 221$). The independent association between BNP–CA125 and mortality was assessed with the Cox regression analysis, and their added predictive ability tested by the integrated discrimination improvement (IDI) index. At 6 months, 181 deaths (16.3%) were identified. The cumulative rate of mortality was lower for patients in C1 (7.8%), intermediate for C2 and C3 (17.8% and 16.9%, respectively), and higher for C4 (37.2%), and *P*-value for trend <0.001. After adjusting for established risk factors, the highest risk was observed when both biomarkers were elevated (C4 vs. C1: HR = 4.05, 95% CI = 2.54–6.45; $P < 0.001$) and intermediate when only one of them was elevated: (C2 vs. C1: HR = 1.71, 95% CI = 1.00–2.93; $P = 0.050$) and (C3 vs. C1: HR = 2.10, 95% CI = 1.30–3.39; $P = 0.002$). Moreover, when CA125 was added to the clinical model + BNP, a 10.4% ($P < 0.0001$) improvement in the IDI (on the relative scale) was found.

Conclusion In patients admitted with AHF, CA125 added prognostic value beyond the information provided by BNP, and thus, their combination enables better 6-month risk stratification.

Keywords Tumour marker antigen carbohydrate 125 • Brain natriuretic peptide • Mortality • Acute heart failure

Introduction

The emergence of multiple biomarkers, and the recognition of their limitation when used individually as a predictive tool, has lead the research community to attempt pooling their prognostic value, particularly when they reflect different pathophysiological pathways.[1] In acute heart failure (AHF), several biomarkers,[2] including natriuretic peptides,[3–6] adenomedulin,[7] ST-2,[8] cardiac

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troponins,[9] and tumour marker antigen carbohydrate 125 (CA125)[10,11] have been shown to correlate with parameters of disease severity and independently associated with clinical outcomes.

B-type natriuretic peptide (BNP) is a neurohormone synthesized in ventricular myocardium and released into the circulation in response to ventricular dilatation and pressure overload,[12] whereas CA125 is a glycoprotein synthesized by epithelial serosal cells in response to fluid accumulation[13,14] and/or cytokine production.[15] Interestingly, fluctuations of both biomarkers have been observed in response to treatment,[4,6,11] although with different kinetics. For instances, BNP has shown a mean half-life of 20–30 min,[12] whereas CA125 has regularly shown a half-life higher than 1 week.[16]

Since these two biomarkers (CA125 and BNP) reflect different pathophysiological mechanisms for the progression of heart failure (HF), and their modification over time follows different response patterns, we speculate that their combination after initial treatment for AHF will enable a better risk stratification.

The aim of the present study was to assess whether in patients admitted to the hospital with a diagnosis of AHF, the combination of the prognostic utility of CA125 and BNP would improve mortality risk prediction at 6 months. As a secondary objective, we assessed their added predictive ability for cardiovascular (CV) and HF progression mortality.

Methods

Study group and protocol

We prospectively studied a cohort of 1111 patients consecutively admitted to the cardiology department of Hospital Clínico Universitario de Valencia from 1 January 2004 to 1 January 2009 with the diagnosis of AHF following current guidelines.[17–19] Diagnosis of AHF was defined as the rapid onset of symptoms and signs secondary to abnormal cardiac function and the presence of objective evidence of structural or functional abnormality of heart at rest (such as cardiomegaly, third heart sound, cardiac murmur, abnormality of the echocardiogram or raised natriuretic peptide). For the purpose of this study, AHF was the main diagnosis that prompted the hospitalization. By design, patients who died during the first 48 h were excluded from this analysis ($n = 19$). In addition, patients with a diagnosis of acute coronary syndrome, cancer, pneumonia, sepsis, severe hepatic disease, or end-stage renal disease undergoing dialysis treatment were excluded see (Supplementary material online, *Figure S1*). Demographic information, medical history, vital signs, 12-lead electrocardiogram, laboratory data and drug utilization were routinely determined in emergency department and throughout the hospital course following pre-established registry questionnaires. All patients received intravenous treatment with furosemide at least during the first 48 h of admission. Left ventricular ejection fraction (LVEF) was assessed through echocardiography (Agilent Sonos 5500-Phillips) during index hospitalization.

Treatment with angiotensin converting enzyme inhibitors (ACEI), angiotensin receptor blockers (ARB), beta-blockers, aldosterone antagonist, anticoagulants, and other therapeutic strategies were individualized following established guidelines operating at that time.[17–19] To our knowledge, treatment decision was not influenced nor guided based on CA125 and BNP values.

Follow-up was limited to 6 months. Patients' follow-up was censored if death or having undergone cardiac transplantation occurred within this period. All-cause mortality was selected as the main endpoint. Secondary endpoints were 6-month CV and HF progression death. The information about the cause of death was extracted from the patient's clinical chart and adjudicated by an investigator who was blinded to the values of BNP and CA125 markers. Once identified, the cause of death was categorized following the classification used by the American Heart Association.[20] Deaths were considered non-CV in origin if a specific non-CV cause was identified as the main trigger for the event. Otherwise, CV aetiology was considered and included sudden death, progressive HF death, deaths attributable to other CV causes (such as myocardial, infarction, stroke, etc.) and unknown cause of death. Sudden death was defined as the event that occurred unexpectedly in an otherwise stable patient and progressive HF death when it did occur in the setting of clinical progressive deterioration of HF symptoms with no other apparent cause. For the present study, those patients who died out-of-hospital (14.4%), in which the information about the circumstances around the death was provided by family members or by outpatient charts review, were assumed to be CV in origin. However, this category of unknown cause of death was treated independently from other CV causes in the competing risk analysis (it was not pooled with sudden death). This study was approved by an institutional review committee and patients gave informed consent.

Biomarkers measurement

Measurement of biomarkers and a plan to study the prognostic value of the combination of these two biomarkers were prespecified. Antigen carbohydrate 125 and BNP serum levels were obtained simultaneously during patient's hospitalization (72 ± 12 h after admission) using commercially available immunoassay kits (Elecsys CA125 II assay-Roche Diagnostics and ADVIA Centaur, respectively). Following an overnight fast, venous blood samples were drawn between 8:30 and 10:30 h with patients in resting supine position for at least 15 min prior to sampling. Blood samples were immediately transported to the laboratory of our institution and the biomarker's assay performed by a blinded technician to patient's diagnosis and evolution.

The intra- and inter-assays coefficient of variations (CVs) for BNP were 1.8–4.3% at 29.4–1763 pg/mL and 2.3–4.7% at 29.4–1736 pg/mL, respectively. For CA125, the intra- and inter-assays coefficient of variations (CVs) were 1.1–0.7% at 34.5–104 U/mL and 2.86–3.52% at 34.5–104 U/mL.

Statistical analysis

Continuous variables were expressed as mean $\pm$ 1 standard deviation (SD) or median [interquartile range (IQR)] when appropriate. Discrete variables were presented as percentages. Baseline characteristics were compared between groups formed by dichotomizing both biomarkers using previously reported prognostic cutpoints:[3,4,6,10] CA125 ($\geq$60 U/mL) and BNP ($\geq$350 pg/mL). The adequacy of these cutpoints was supported by prognostic-driven methods, which define the point in which the value of the biomarker crossed the zero point in the log-hazard scale as indicative of the optimal cutpoint for our population.[21] Then, we combined these two binary markers and created a new variable with four categories (heretofore called CA125–BNP): C1 = BNP $<$ 350 pg/mL and CA125 $<$ 60 U/mL; C2 = BNP $\geq$ 350 pg/mL and CA125 $<$ 60 U/mL; C3= BNP $<$ 350 pg/mL and CA125 $\geq$ 60 U/mL; and C4 = BNP $\geq$ 350 pg/mL and CA125 $\geq$ 60 U/mL. The 6-month mortality rates among CA125–BNP categories were depicted using the Kaplan–Meier method and their differences tested by the Peto–Peto Prentice test. The independent association between CA125–BNP and 6-month mortality was

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assessed with the Cox regression analysis. For the secondary analysis, CV death and death attributable to HF progression were independently modelled with Cox adapted for competing risk events.[22] Candidate covariates for the initial multivariable model were chosen based on previous medical knowledge, and independent of their *P*-value. Then, a reduced and parsimonious model was derived by using backward stepdown selection. 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 by Harrell's *C*-statistics. The increment in the prognostic utility of BNP and CA125 when adding sequentially to the base model was evaluated by the integrated discrimination improvement (IDI) index. When two nested models are compared, IDI quantifies the increment in the predicted probabilities for the subset of patients experiencing the event and the decrement for those not experiencing the event. In simpler terms, it does reflect an improvement in the average of the true positive rate without sacrificing its average true negative rate.[23] In order to identify clinical variables associated with log-transformed CA125 and BNP, two multiple linear regression analyses were performed. Parsimonious although highly predictive models were obtained by the mean of backward stepdown selection. Variables retained in the final model were ranked based on the magnitude of change in the R^2.

We randomly sampled from the registry 89 patients for a test–retest reliability sub-study. From the repeated determinations of CA125 ($n = 89$; 72 with 2 and 17 with 3 repeated measures) and BNP ($n = 69$; 57 with 2 and 12 with 3 repeated measures), an intraclass correlation (IC) was estimated using a linear variance-components model including a random intercept on each patient. Intraclass correlation can be defined as the proportion of the total variance that is explained by between-subject correlation. It follows that values close to one are indicative of consistency in the repeated measures and, therefore, higher intra-cluster correlation.

A two-sided *P*-value of <0.05 was considered to be statistically significant for all analyses. All analyses were performed using STATA 11 (StataCorp. 2009. Stata Statistical Software: Release 11. College Station, TX, USA: StataCorp LP) and R *(R: A Language and Environment for Statistical Computing at http://www.R-project.org)*.

Results

Baseline characteristics stratified by antigen carbohydrate 125 and brain natriuretic peptide levels

The mean age in our sample was 73 ± 11 years; 51% were female, 54.6% of the patients exhibited LVEF > 50%. Medians (IQR) for BNP and CA125 were 237 pg/mL (97–434) and 59.1 U/mL (25.2–139.2), respectively (baseline characteristics of the entire group are presented in see Supplementary material online, *table S1*). *Tables 1* and *2* show the clinical characteristics of the study population according to CA125 and BNP categories. Elevation of CA125 (≥60 U/mL) and BNP (≥350 pg/mL) was more prevalent in patients with NYHA class III/IV (last measurement under clinically stable conditions and before the index admission), in males, in the presence of radiological pleural effusion and peripheral oedema and when LVEF ≤ 50%. On the contrary, hypertension, dyslipidemia, admission as hypertensive AHF, and previous treatment with statins were less prevalent among patients with both biomarkers elevated. Lower systolic and diastolic blood pressure, haemoglobin, and LVEF as well as higher serum uric acid were also observed when both biomarkers were elevated. No differences were detected in the sampling time among the two levels of BNP ($P = 0.968$) or CA125 ($P = 0.607$).

Clinical predictors of brain natriuretic peptide and antigen carbohydrate 125 in the setting of acute heart failure

Supplementary material online, *Table S2* listed those variables that were significantly associated with lnCA125 and lnBNP [presented with their respective β coefficients (standard errors) and *P*-values]. It is important to highlight differences in clinical predictors for both biomarkers (see Supplementary material online, *Table S2*). The most important predictors of lnCA125 (ranked in order of importance) were: (i) presence of pleural effusion and (ii) peripheral oedema (accounting for 57.8% and 12.9% of the total R^2, respectively). Similarly, patients with radiological pleural effusion and peripheral oedemas had a 3.5- and 1.8-fold increased likelihood of having CA125 ≥ 60 U/mL, respectively. For lnBNP the most important predictors were: (i) LVEF and (ii) serum creatinine (accounting for 41% and 20% of the total R^2, respectively). Likewise, displaying left ventricular (LV) systolic dysfunction (LVEF < 45%) and modelling serum creatinine as a continuous variable (per increase in 1 mg/dL) were associated with 2.6- and 1.6-fold increase in the likelihood of having BNP ≥ 350 pg/mL.

Moreover, these biomarkers showed to be differentially associated with the type of clinical presentation of AHF. Being admitted with the diagnosis of acute decompensate heart failure (ADHF) was independently and positively associated with CA125 values; in contrast, a presentation as acute pulmonary oedema was related to higher BNP values see (Supplementary material online, *Table S2*). These results were also reproduced in a context of a multivariable logistic regression, where admission with ADHF showed an increased risk of CA125 ≥ 60 (OR: 1.50, CI 95% = 1.12–2.02, $P = 0.007$), while acute pulmonary oedema was associated with BNP ≥ 350 pg/mL (OR: 1.66, CI 95% = 1.17–2.34, $P = 0.004$).

Relationship of antigen carbohydrate 125 and brain natriuretic peptide with 6-month total mortality

At 6-month follow-up, a total of 181 (16.3%) deaths were identified: 63 occurred during the index hospitalization and 118 after discharge. One hundred and fifty-four of all deaths were CV (85%) and 99 were due to HF progression (54.7%). Brain natriuretic peptide and CA125 values were significantly higher in those patients who died when compared with those who remained alive [median (IQR): 401 (472) vs. 218 (308), $P < 0.001$ and 105 U/mL (144) vs. 52 U/mL (103), $P < 0.001$, respectively]. *Figure 1A* and *B* show that the intersection point between the value of BNP and CA125 with the log-hazard for mortality roughly agreed with the cutpoints selected for their dichotomization.

The cumulative mortality rates as estimated with the Kaplan–Meier method, were significantly higher for patients with CA125 ≥ 60 U/mL and BNP ≥ 350 pg/mL (25.2% vs. 10.8% and 28.8% vs. 11.9%, respectively, with $P < 0.001$ for both) as

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Table 1 Baseline characteristics stratified by CA125 categories

	CA125 < 60 U/mL (*n* = 554)	CA125 ≥ 60 U/mL (*n* = 557)	*P*-value
Demographic and medical history			
Age, years	74 ± 11	72 ± 12	0.047
Female, *n* (%)	307 (55.5)	259 (46.4)	0.003
Previous admission for AHF, *n* (%)	200 (36.1)	208 (37.3)	0.668
Hypertension, *n* (%)	465 (83.9)	401 (72.1)	<0.001
Dyslipidemia, *n* (%)	261 (47.2)	206 (37)	0.001
Current smoker, *n* (%)	60 (10.8)	59 (10.6)	0.914
Previous smoker, *n* (%)	87 (15.7)	109 (19.6)	0.091
Ischaemic heart disease, *n* (%)	215 (38.8)	206 (37)	0.546
Valvular heart disease, *n* (%)	136 (24.5)	163 (29.2)	0.076
ADHF, *n* (%)	330 (59.6)	425 (76.3)	<0.001
Acute pulmonary oedema, *n* (%)	152 (27.4)	91 (16.3)	<0.001
Hypertensive AHF, *n* (%)	66 (11.8)	27 (4.9)	<0.001
NYHA class III/IV, *n* (%)[a]	86 (15.5)	124 (22.3)	0.004
Chronic pulmonary obstructive disease, *n* (%)	125 (22.6)	110 (19.7)	0.251
Radiological pleural effusion, *n* (%)	151 (27.3)	335 (60.1)	<0.001
Peripheral oedema, *n* (%)	243 (44.1)	365 (65.5)	<0.001
Previous use of diuretics, *n* (%)	335 (60.5)	357 (64.1)	0.213
Previous use of beta-blockers, *n* (%)	127 (22.9)	131 (23.5)	0.814
Previous use of ACEI/ARB, *n* (%)	270 (48.7)	230 (41.3)	0.013
Previous use of statins, *n* (%)	163 (29.4)	118 (21.2)	0.002
Vital signs			
Heart rate, b.p.m.	102 ± 30	101 ± 29	0.653
Systolic blood pressure, mmHg	156 ± 37	144 ± 34	<0.001
Diastolic blood pressure, mmHg	85 ± 21	80 ± 19	<0.001
ECG			
Atrial fibrillation, *n* (%)	212 (38.3)	271 (48.6)	0.001
QRS > 120 ms, *n* (%)	156 (28.2)	168 (30.2)	0.463
Laboratory			
Haemoglobin (g/dL)	12.9 ± 1.9	12.6 ± 1.8	0.016
Serum creatinine (mg/dL)	1.28 ± 0.6	1.33 ± 0.5	0.134
Uric acid (mg/dL)	7.6 ± 2.3	8.1 ± 2.5	0.001
Sodium (mEq/L)	139 ± 4	139 ± 5	0.030
Troponin I (ng/mL)[b]	0 (0.24)	0 (0.07)	0.014
Troponin I > 0.2 ng/mL, *n* (%)	153 (27.6)	124 (22.3)	0.039
BNP (pg/mL)	280 ± 355	359 ± 387	<0.001
CA125 (U/mL)[b]	25 (23)	139 (127)	<0.001
Echocardiography			
LVEF (%)	53 ± 15	49 ± 15	<0.001
LVEF ≤ 50%, *n* (%)	212 (38.3)	292 (52.4)	<0.001
LAD (mm)	42 ± 7	45 ± 8	<0.001
LVDD (mm)	55 ± 9	56 ± 10	0.181
Medical treatment			
Beta-blockers, *n* (%)	288 (52)	274 (49.2)	0.352
Diuretics, *n* (%)	544 (98.2)	539 (96.8)	0.129
Spironolactone, *n* (%)	85 (15.3)	102 (18.3)	0.186
ACEI, *n* (%)	242 (43.7)	239 (42.9)	0.795
ARB, *n* (%)	161 (29.1)	148 (26.6)	0.354
Statins, *n* (%)	200 (36.1)	175 (31.4)	0.099

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Table 1 *Continued*

	CA125 < 60 U/mL (*n* = 554)	CA125 ≥ 60 U/mL (*n* = 557)	*P*-value
Oral anticoagulants, *n* (%)	193 (35.1)	232 (42.6)	0.010
Nitrates, *n* (%)	110 (19.9)	110 (19.7)	0.964
Digoxin, *n* (%)	128 (23.1)	153 (27.5)	0.094

CA125, antigen carbohydrate 125; AHF, acute heart failure; ADHF, acute decompensate heart failure; NYHA, New York Heart Association; ACEI, angiotensin converting enzyme inhibitors; ARB, angiotensin II receptor blockers; BNP, brain natriuretic peptide; LVEF, left ventricular ejection fraction; LAD, left atrial diameter; LVDD, left ventricular diastolic diameter. Values are expressed as mean (SD), unless otherwise specified; categorical variables are presented as percentages.
[a]Last NYHA functional class measured under clinically stable conditions.
[b]Value presented as the median (interquartile range).

illustrated in *Figure 2A* and *B*. By combining these two biomarkers (*Figure 2C*), those patients in C1 (BNP < 350 pg/mL and CA125 < 60 U/mL) exhibited the lowest cumulative rate of mortality (7.8%); intermediate for C2 (BNP ≥ 350 pg/mL and CA125 < 60 U/mL) and C3 (BNP < 350 pg/mL and CA125 ≥ 60 U/mL): 17.8% and 16.9%, respectively, and higher (37.2%) for C4 (BNP ≥ 350 pg/mL and CA125 ≥ 60 U/mL), *P*-value for trend <0.001.

In the univariate Cox analysis, the highest risk corresponded to patients with both biomarkers elevated (C4 vs. C1: HR = 5.89, 95% CI = 3.82–9.09; $P < 0.001$) and intermediate when only one biomarker was elevated: (C2 vs. C1: HR = 2.33, 95% CI = 1.38–3.96; $P = 0.002$) and (C3 vs. C1: HR = 2.31, 95% CI = 1.46–3.68; $P < 0.001$).

In the multivariate Cox analysis (*Figure 3A*), the risk gradient observed in the univariate analysis persisted; the highest risk was observed when both biomarkers were elevated (C4 vs. C1: HR = 4.05, 95% CI = 2.54–6.45; $P < 0.001$) and intermediate when only one of them was elevated: (C2 vs. C1: HR = 1.71, 95% CI = 1–2.93; $P = 0.050$) and (C3 vs. C1: HR = 2.10, 95% CI = 1.30–3.39; $P = 0.002$). No interactions were found between these two biomarkers when included in the model as continuous ($P = 0.733$). Moreover, no interactions were found between CA125–BNP and any of the covariates included in the final model for mortality, which confirm that the direction of the association with mortality applied to the most representative subgroups of patients with AHF such as older > 65 years, females, those with preserved systolic function, ischaemic heart disease, and even those patients in which radiological pleural effusion was not present (*Figure 3B*, *C*, *D*, *E*, and *F*, respectively).

Harrell's *C*-statistic was calculated from each regression model as a discriminative performance measure. The Cox model that included BNP–CA125 had a higher *C*-statistic (0.779) when compared with the model without it (0.755) or with the model that included only BNP (0.765). Because of the limitation of the *C*-statistic to detect a meaningful increase in discrimination when adding a new marker to a base model with already reasonable good discrimination,[24] and the lack of a standardized method to compare this index between nested models, we decided to estimate the IDI index as a more sensitive method to evaluate the added-value in discrimination performance of each biomarker. *Table 4* shows the IDI corresponding to the comparison for each pair of nested models. Absolute as well as relative IDI values were monotonically higher and statistically significant when BNP, CA125, and BNP–CA125 were consecutively added to the base model, indicating a significant improvement in risk prediction when CA125 was added to the base model + BNP.

Relationship of antigen carbohydrate 125 and brain natriuretic peptide with 6-month cardiovascular and heart failure progression death

Similar results were observed when BNP–CA125 was tested for CV and progressive HF mortality (*Table 3*). Patients with both biomarkers elevated (C4) displayed a 3.9 and 4.5 adjusted hazard ratios for CV and HF death. Patients with either of these biomarkers elevated (C2 or C3) showed an intermediate risk. Multivariable models for CV death that included BNP–CA125 showed a higher discriminative ability when compared with the model that included: (i) only BNP: 0.822 vs. 0.808; (ii) only CA125: 0.822 vs. 0.812; and (iii) none: 0.822 vs. 0.792. Similarly, multivariable models for progressive HF death that included BNP–CA125 showed a higher discriminative ability when compared with the model that included: (i) only BNP: 0.815 vs. 0.799; (ii) only CA125: 0.815 vs. 0.809; and (iii) none: 0.815 vs. 0.791. In summary, the inclusion of both biomarkers improves significantly the discriminative ability of the base models for both specific outcomes; however, the added utility for BNP was found only marginally significant when compared with CA125. Furthermore, the incremental prognostic effect of adding each of these two biomarkers (or both) to the base model or adding CA125 to the base model + BNP was also supported by the IDI index (*Table 4*).

Test–retest reliability sub-study

The between and within-patient SDs of the random intercept model for CA125 determinations were 155.8 and 27.2, respectively, resulting in an IC of 0.97, 95% CI = 0.96–0.98. For BNP, the corresponding values were 529.0 and 263.9, respectively, and the IC estimated at 0.8, 95% CI = 0.71–0.87 see (Supplementary material online, *Figure S2*). This difference allow us to conclude that CA125 was a more reliable biomarker than BNP, finding that indirectly support the notion of being a marker with a lagged response to acute haemodynamic changes.

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Table 2 Baseline characteristics stratified by BNP categories

	BNP < 350 pg/mL (*n* = 725)	BNP ≥ 350 pg/mL (*n* = 386)	*P*-value
Demographic and medical history			
Age, years	72 ± 11	74 ± 11	0.033
Female, *n* (%)	399 (55)	167 (43)	<0.001
Previous admission for AHF, *n* (%)	236 (32.5)	172 (44.6)	<0.001
Hypertension, *n* (%)	582 (80.3)	284 (73.8)	0.013
Dyslipidemia, *n* (%)	325 (44.9)	142 (36.8)	0.009
Current smoker, *n* (%)	77 (10.6)	42 (10.9)	0.888
Previous smoker, *n* (%)	121 (16.7)	75 (19.5)	0.250
Ischaemic heart disease, *n* (%)	251 (34.6)	170 (44.2)	0.002
Valvular heart disease, *n* (%)	196 (27)	103 (26.7)	0.900
ADHF, *n* (%)	496 (68.4)	259 (67.1)	0.655
Acute pulmonary oedema, *n* (%)	140 (19.3)	103 (26.7)	0.005
Hypertensive AHF, *n* (%)	76 (10.5)	17 (4.4)	<0.001
NYHA class III/IV, *n* (%)[a]	123 (17)	87 (22.5)	0.024
Chronic pulmonary obstructive disease, *n* (%)	159 (21.9)	76 (19.7)	0.384
Radiological pleural effusion, *n* (%)	298 (41.2)	188 (48.7)	0.017
Peripheral oedema, *n* (%)	373 (51.6)	235 (61)	0.003
Previous use of diuretics, *n* (%)	414 (57.1)	278 (72)	<0.001
Previous use of beta-blockers, *n* (%)	169 (23.3)	89 (23.1)	0.924
Previous use of ACEI/ARB, *n* (%)	319 (44)	181 (46.9)	0.356
Previous use of statins, *n* (%)	203 (28)	78 (20.2)	0.004
Vital signs			
Heart rate, b.p.m.	104 ± 30	98 ± 27	0.005
Systolic blood pressure, mmHg	154 ± 36	143 ± 35	<0.001
Diastolic blood pressure, mmHg	84 ± 21	79 ± 18	<0.001
ECG			
Atrial fibrillation, *n* (%)	336 (46.3)	147 (38.1)	0.008
QRS > 120 ms, *n* (%)	175 (24.1)	149 (38.6)	<0.001
Laboratory			
Haemoglobin (g/dL)	12.8 ± 1.9	12.6 ± 1.9	0.037
Serum creatinine (mg/dL)	1.21 ± 0.5	1.47 ± 0.6	<0.001
Uric acid (mg/dL)	7.6 ± 2.3	8.3 ± 2.5	<0.001
Sodium (mEq/L)	139 ± 4	138 ± 5	<0.001
Troponin I (ng/mL)	0 ± 0.09	0 ± 0.27	0.078
Troponin I > 0.2 ng/mL, *n* (%)	163 (22.5)	114 (29.5)	0.010
BNP (pg/mL)	149 ± 96	640 ± 477	<0.001
CA125 (U/mL)[b]	52 (105)	75 (124)	<0.001
Echocardiography			
LVEF (%)	54 ± 14	45 ± 15	<0.001
LVEF ≤ 50%, *n* (%)	264 (36.4)	240 (62.2)	<0.001
LAD (mm)	43 ± 8	44 ± 7	0.326
LVDD (mm)	55 ± 9	58 ± 10	<0.001
Medical treatment			
Beta-blockers, *n* (%)	394 (54.3)	168 (43.5)	0.001
Diuretics, *n* (%)	710 (97.9)	373 (96.6)	0.188
Spironolactone, *n* (%)	134 (18.5)	53 (13.7)	0.044
ACEI, *n* (%)	311 (42.9)	170 (44)	0.714
ARB, *n* (%)	205 (28.3)	104 (26.9)	0.637
Statins, *n* (%)	267 (36.8)	108 (28)	0.003

Continued

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Table 2 *Continued*

	BNP < 350 pg/mL (*n* = 725)	BNP ≥ 350 pg/mL (*n* = 386)	*P*-value
Oral anticoagulants, *n* (%)	315 (43.7)	110 (29.4)	<0.001
Nitrates, *n* (%)	123 (17)	97 (25.1)	0.001
Digoxin, *n* (%)	188 (25.9)	93 (24.1)	0.502

BNP, brain natriuretic peptide; AHF, acute heart failure; ADHF, acute decompensate heart failure; NYHA, New York Heart Association; COPD, chronic pulmonary obstructive disease; PAD, peripheral arterial disease; ACEI, angiotensin converting enzyme inhibitors; ARB, angiotensin II receptor blockers; pO2, arterial oxygen partial pressure; pCO2, arterial carbon dioxide partial pressure; CA125, antigen carbohydrate 125; LVEF, left ventricular ejection fraction; LAD, left atrial diameter; LVDD, left ventricular diastolic diameter; and LV mass, left ventricular mass. Values are expressed as mean (SD), unless otherwise specified; categorical variables are presented as percentages.
[a]Last NYHA functional class measured under clinically stable conditions.
[b]Value presented as the median (interquartile range).

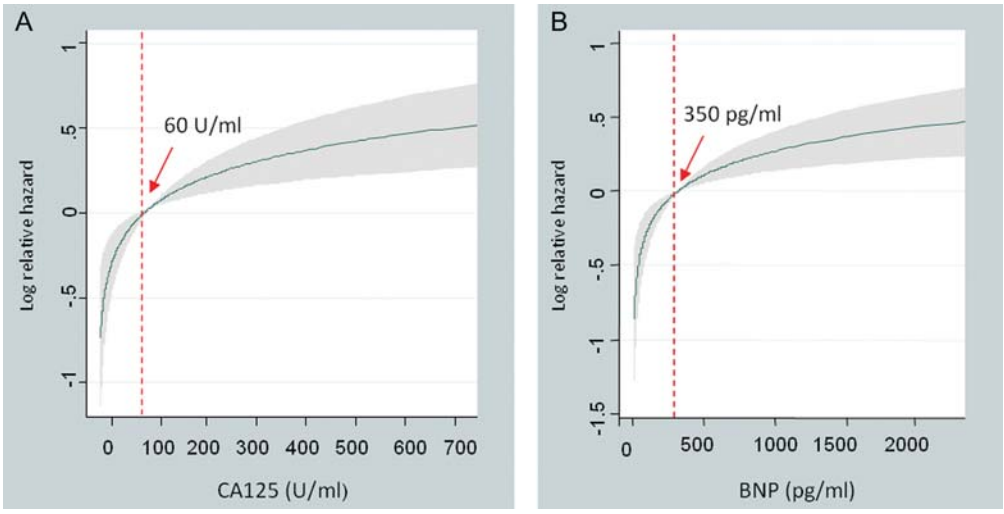

Figure 1 Functional forms of CA125 and BNP derived from a multivariable Cox regression model. Using fractional polynomials with four degrees of freedom, their continuum values were plotted against the log-hazard for mortality. Dotted lines indicate the intersection with the point of zero risk, which is assumed to be the optimal threshold for characterizing the study population above and below the risk for mortality. [†]Sensibility and specificity (receiver operating characteristic curve analysis) of cutpoints were 69% and 56% for CA ≥ 60 U/mL and 57% and 70% for BNP ≥ 350 pg/mL. CA125, serum antigen carbohydrate 125; BNP, brain natriuretic peptide.

Discussion

In this study, we have shown in a non-selected hospitalized population of patients with AHF that combining the prognostic information of BNP and CA125 allows us to characterize various subgroups in regard to 6-month mortality risk: low (when both biomarkers are below the chosen cutpoints), intermediate (when only one biomarker was elevated), and high risk (when both biomarkers are elevated). We also found a dose-response association between BNP and CA125 with CV and HF progression mortality, this last outcome being the most prevalent cause of death in our registry. Furthermore, we found that the prognostic utility provided by these two biomarkers was consistently applied to the most representative subgroups of patients with AHF. We believe that, by knowing that CA125 is a widely available biomarker, cheap, and a surrogate of fluid overload,[10,11,13,14] our results open the possibility of its addition to a routine use of BNP for a better risk stratification in AHF.

Fluid overload and antigen carbohydrate 125

Most patients with AHF exhibit signs of fluid accumulation or central fluid redistribution.[25,26] The severity of congestion has become one of the most important therapeutic targets in AHF[18,19] and associated with poor prognosis.[27] Traditionally, signs of congestion (pleural, pericardial and peritoneal effusions, and peripheral oedema) are not routinely used for risk stratification since their presence and quantification are not traditionally evaluated and recorded in HF registries. Antigen carbohydrate 125 has been shown to be associated with clinical (higher NYHA class, and signs of fluid congestion),[10,11,13,14,28–30]

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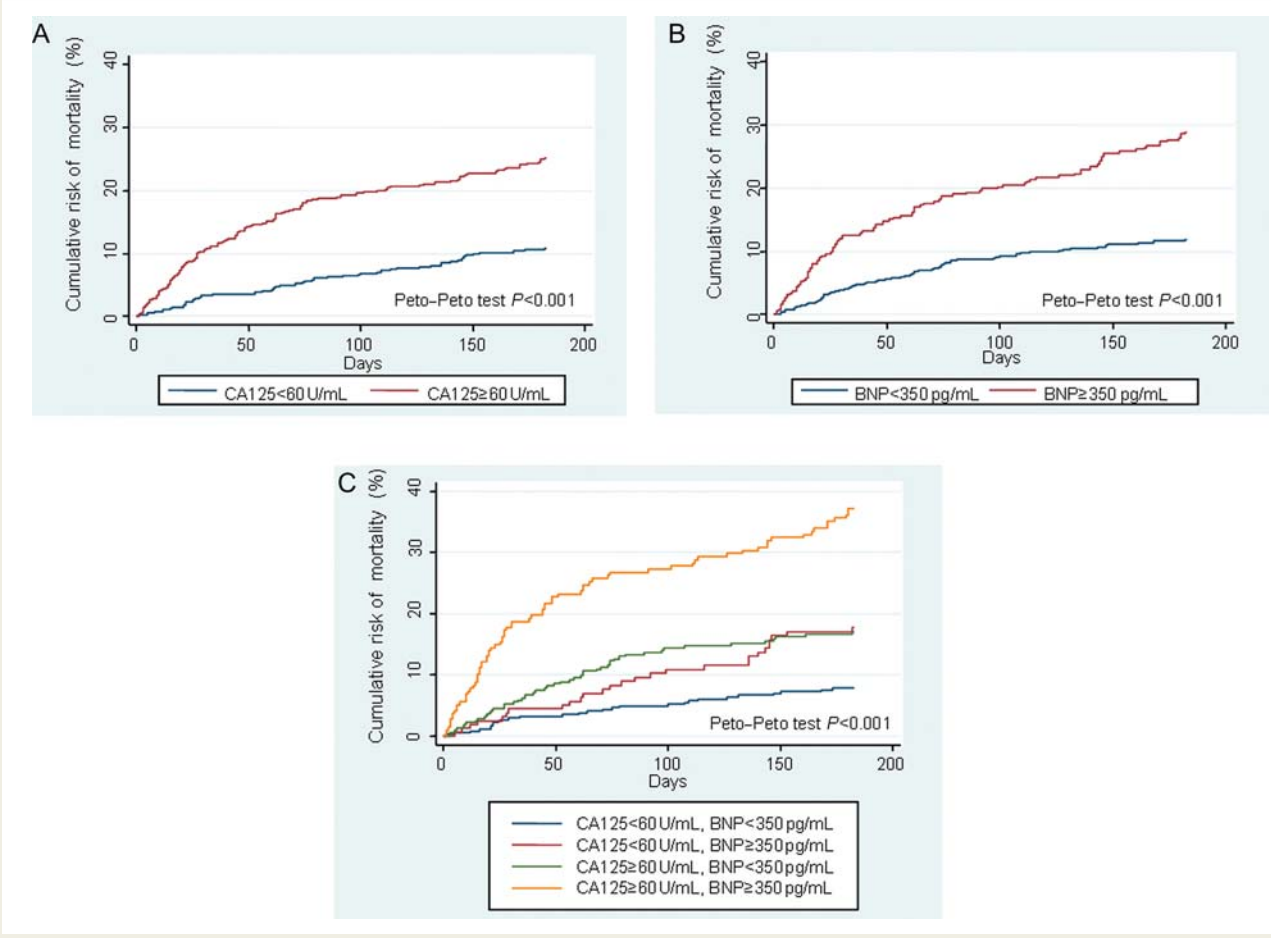

Figure 2 Kaplan–Meier curves for total mortality. (*A*) Stratified by CA125. (*B*) Stratified by BNP. (*C*) Stratified by BNP–CA125. CA125, serum antigen carbohydrate 125; BNP, brain natriuretic peptide.

haemodynamic (correlated with pulmonary artery wedge pressure and right atrial pressure)[11,29] and echocardiographic parameters (inverse correlation with the deceleration time of early filling on transmitral Doppler), and consequently indicative as a surrogate for HF severity.[11] In addition, high correlations have been reported between CA125 and proinflammatory cytokines (TNF-α and IL-6) and neurohormones (BNP).[15,29,31] Although the exact pathophysiological mechanism leading to CA125 elevation in HF have not been totally elucidated, preliminary findings have suggested that CA125 is synthesized by serosal cells in response to presence of serosal effusions,[13,14,32–34] or in response to proinflammatory stimulus.[15,35] Moreover, CA125 has been shown to be related with adverse outcomes in patients with HF.[10,11,29,30] In the present study, the presence of pleural effusion and peripheral oedema were the most important clinical predictors of CA125 serum levels. Surprisingly however, we found that CA125 was associated with 6-month mortality independently of radiological evidence of pleural effusion, which suggests that in addition to being a surrogate for systemic fluid congestion, its elevation may also be influenced by other pathophysiological pathways in AHF.

More recently, it has been reported that CA125 serum levels fluctuated according to clinical improvement led by medical treatment,[11,13–15,29,30] observation that may open a new research avenue about its potential role for monitoring the response to therapy.

Biological plausibility of our findings and clinical implications

Previous studies have suggested a high correlation between BNP and CA125[31], finding that we could not corroborated. Maybe differences in kinetics, and/or the fact that our HF population seems to be more heterogeneous when compared with other studies (majority of patients with LV systolic dysfunction) are potential explanations for the weak correlation found ($r = 15\%$; $R^2 = 2.2\%$; $P < 0.001$). By taking into consideration the fact that CA125 has a half-life varying from 5.1 to 12 days (as shown in different cancer studies)[16] and that BNP has a shorter mean half-life of 20 min (with significant variation in response to initial treatment),[4,6] we envision the potential of integrating acute haemodynamic information in response to initial therapy (provided by BNP) with information regarding HF chronicity (provided by CA125 and assuming it will prove to be a reliable surrogate for the presence of fluid congestion during prior weeks). This

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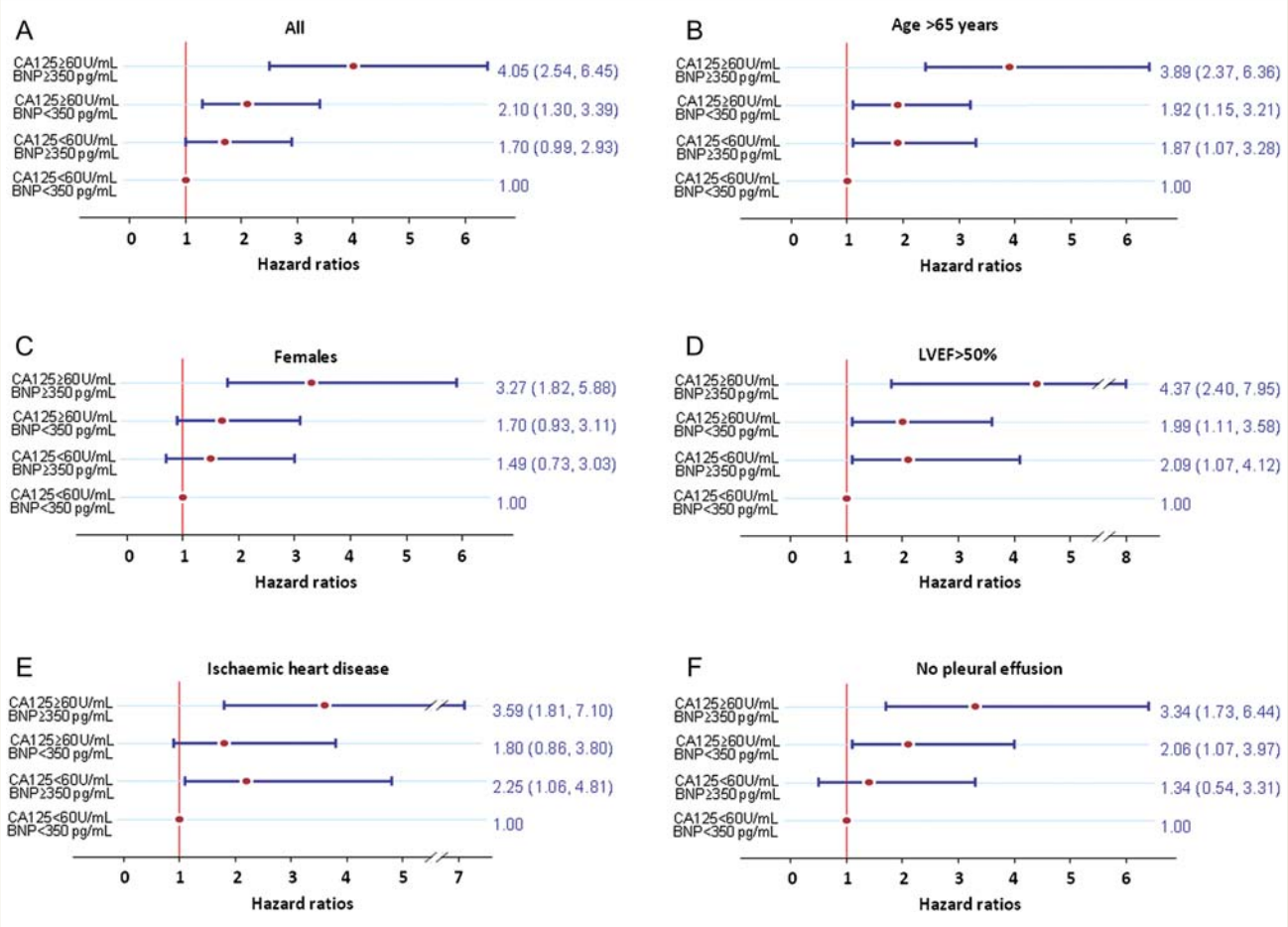

Figure 3 HRs for the association between BNP–CA125 and total mortality. (*A*) All patients; (*B*) older than 65 years; (*C*) women; (*D*) preserved systolic function (LVEF > 50%); (*E*) ischaemic heart disease; and (*F*) no pleural effusion. Category C1 (CA125 < 60 U/mL and BNP < 350 pg/mL) served as a reference group. HR, hazard ratio; CA125, serum antigen carbohydrate 125; BNP, brain natriuretic peptide.

prognostic integration resembles what happens with serum glucose (BNP in our proposal) and glycosilated haemoglobin (represented by CA125) in diabetes. With this in mind, we hypothesized that the four categories of BNP–CA125 represent distinct pathophysiological states related to HF severity: (i) C1: mild/no fluid overload during last weeks and not excessively high filling pressures following initial treatment; (ii) C2: mild/no fluid congestion and presence of high filling pressures despite initial treatment; (iii) C3: fluid congestion and not high filling pressures following initial treatment; and (iv) C4: fluid congestion and high filling pressures despite initial treatment. We believe that CA125 should be incorporated into clinical practice as a tool to reliably quantify the burden of fluid accumulation/redistribution in patients with acute HF. If further research along this line supports our findings, we feel that this multi-marker approach may become a promising tool for therapy guiding.

Limitations

Some limitations need to be acknowledged: (i) the population included in this study comes from a single centre, which may limit the extrapolation of our results; this is particularly true when considering how homogeneous is this population regarding race; (ii) by design, this study is observational in nature and, consequently, not immune to different types of bias and residual confounding; (iii) the calculation of IDI as a measure of discrimination accuracy does not take into account the censored nature of the data; (iv) the diagnostic and prognostic roles of CA125 needs to be further validated in different populations, in order to recommend its implementation as a routine-valued biomarker; (v) the adjudication of specific cause of death was mainly done using patient's chart review which it may introduce some error on the competing risk estimates; (vi) despite the observed correlation of CA125 with systemic congestion parameters such as pleural effusion, ascites, and pericardial effusion, the use of these variables in our multivariable modelling was precluded by the fact that they were not consistently quantified; and (vii) for patient's recruited before 2005, the adjudication of the type of AHF proposed by European Society of Cardiology was performed in a retrospective way by a chart review.

Conclusions

Antigen carbohydrate 125 added significant prognostic value in patients with AHF in terms of 6-month total CV and progressive

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Table 3 BNP–CA125 hazard ratios for 6-month total CV and progressive HF mortality

Cox models	Unadjusted hazard ratios		Adjusted hazard ratios	
	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
All-cause mortality[a]				
log BNP	1.80 (1.45–2.22)	<0.001	1.40 (1.08–1.79)	0.011
log CA125	1.67 (1.38–2.03)	<0.001	1.54 (1.24–1.91)	<0.001
C1	1	<0.001[b]	1	<0.001[b]
C2	2.33 (1.38–3.96)	0.002	1.71 (1–2.93)	0.050
C3	2.31 (1.46–3.68)	<0.001	2.10 (1.30–3.39)	0.001
C4	5.89 (3.82–9.09)	<0.001	4.05 (2.54–6.45)	<0.001
CV mortality[c]				
log BNP	1.82 (1.52–2.17)	<0.001	1.48 (1.24–1.77)	<0.001
log CA125	1.64 (1.41–1.91)	<0.001	1.50 (1.30–1.74)	<0.001
C1	1	<0.001[b]	1	<0.001[b]
C2	1.97 (1.06–3.66)	0.031	1.43 (0.77–2.77)	0.259
C3	2.32 (1.38–3.90)	0.001	1.96 (1.16–3.31)	0.012
C4	6.76 (4.19–10.91)	<0.001	3.92 (2.40–6.40)	<0.001
HF mortality[d]				
log BNP	1.77 (1.43–2.19)	<0.001	1.47 (1.19–1.81)	<0.001
log CA125	1.65 (1.38–1.99)	<0.001	1.49 (1.24–1.78)	<0.001
C1	1	<0.001[b]	1	<0.001[b]
C2	3.07 (1.40–6.72)	0.005	2.42 (1.10–5.32)	0.028
C3	3.57 (1.79–7.09)	<0.001	3.04 (1.50–6.18)	0.002
C4	7.89 (4.06–15.32)	<0.001	4.54 (2.28–9.05)	<0.001

HF, heart failure; BNP, brain natriuretic peptide; CA125, antigen carbohydrate 125; HR, hazard ratio; CI, confidence intervals; BNP–CA125 categories: C1 (BNP < 350 pg/mL and CA125 < 60 U/mL); C2 (BNP ≥ 350 pg/mL and CA125 < 60 U/mL); C3 (BNP < 350 pg/mL and CA125 ≥ 60 U/mL); and C4 (BNP ≥ 350 pg/mL and CA125 ≥ 60 U/mL).
[a]Covariates for the adjusted model: age (year), gender, prior admission for AHF, AHF category (acute decompensate heart failure vs. others), admission systolic blood pressure (mmHg), admission heart rate (b.p.m.), atrial fibrillation, evidence of pleural effusion, left ventricular ejection fraction < 50%, serum creatinine (mg/dL), serum sodium ≤ 130 mEq/L, and treatment with angiotensin receptor blockers and beta-blockers.
[b]Omnibus *P*-value for BNP–CA125.
[c]Covariates for the adjusted competing risk model: age (years), gender, prior admission for AHF, AHF category (acute decompensate heart failure vs. others), valvular heart disease aetiology, admission systolic blood pressure (mmHg), admission heart rate (b.p.m.), evidence of pleural effusion, serum creatinine (mg/dL), serum sodium (mEq/L), and treatment with angiotensin receptor blockers. This model used non-CV mortality as competing event.
[d]Covariates for the adjusted competing risk model: age (years), gender, prior admission for AHF, valvular heart disease aetiology, admission systolic blood pressure (mmHg), admission heart rate (b.p.m.), evidence of pleural effusion, serum creatinine (mg/dL), and serum sodium (mEq/L). This model used sudden death, other cardiovascular mortality, non-cardiovascular mortality, and unknown death as competing events.

Table 4 Added incremental prognostic value of BNP and CA125 measured by IDI index

Performance measures	Total mortality at 6 months		CV mortality at 6 months		HF progression mortality at 6 months	
	IDI (%) (*P*-value)		IDI (%) (*P*-value)		IDI (%) (*P*-value)	
	Absolute	Relative	Absolute	Relative	Absolute	Relative
Model 2 vs. 1	1.51 (0.0041)	8.74 (0.0041)	1.23 (0.0298)	6.6 (0.0298)	0.95 (0.0531)	7.28 (0.0531)
Model 3 vs. 1	2.08 (0.0001)	12.08 (0.0001)	2.31 (0.0001)	12.41 (0.0001)	1.66 (0.0013)	12.74 (0.0013)
Model 4 vs. 1	3.45 (<0.0001)	20.03 (<0.0001)	3.65 (0.001)	19.56 (0.001)	2.47 (0.0001)	18.91 (0.0001)
Model 4 vs. 2	1.95 (0.0002)	10.39 (0.0002)	2.41 (0.0001)	12.16 (0.0001)	1.52 (0.0017)	10.85 (0.0017)

BNP, brain natriuretic peptide; CA125, antigen carbohydrate 125; NRI, net reclassification improvement; IDI, integrated discrimination improvement.
Model 1 = base model.
Model 2 = base model + BNP dichotomized at 350 pg/mL.
Model 3 = base model + CA125 dichotomized at 60 U/mL.
Model 4 = base model + BNP–CA125 categories.

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HF mortality, beyond the information provided by BNP and independently of other markers and clinical risk factors. The simultaneous use of these biomarkers provided a substantial improvement in 6-month risk stratification, when compared with either of them alone. Because of its low cost and consequently widely available, further studies are warranted to: (i) confirm our results, (ii) address the mechanisms underlying the association with mortality, and (iii) seek for its potential as a therapeutic-guided biomarker.

Supplementary material

Supplementary material is available at *European Heart Journal* online.

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Conflict of interest: G.C.F. has research from the NIH, received honorarium from AstraZenca, GlaxoSmithKline, Novartis, and Pfizer, and consulted for ARCA, GlaxoSmithKline, Merck, Novartis, and Pfizer.

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CARDIOVASCULAR FLASHLIGHT

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It hurts so bad like a needle through the heart

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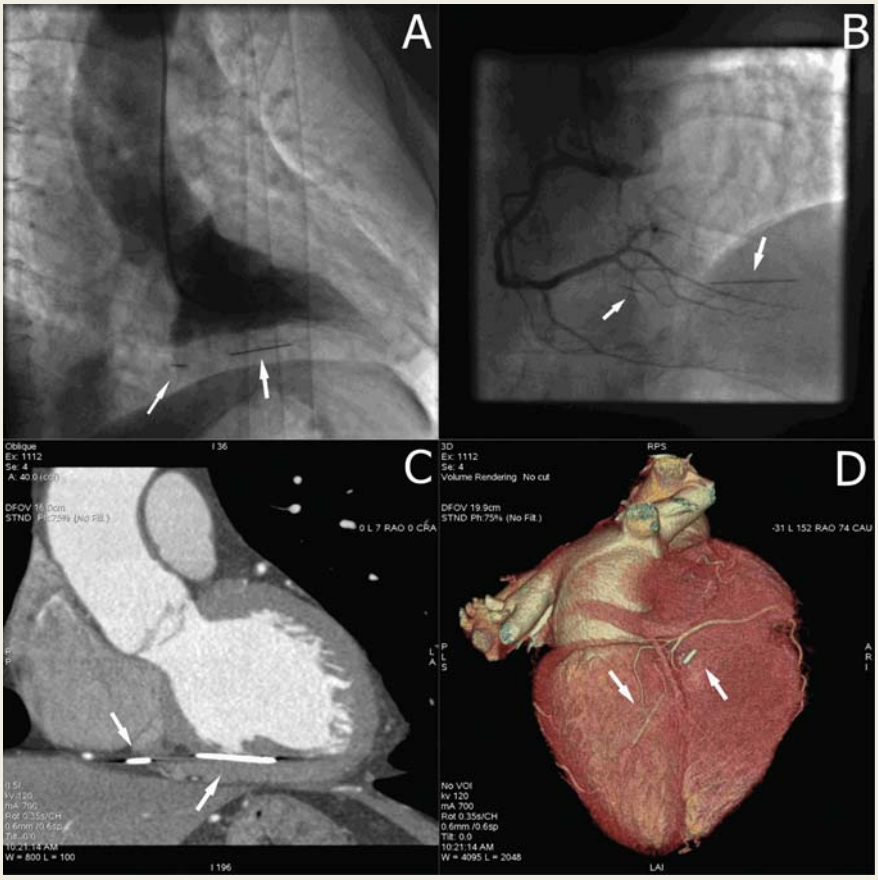
A 62-year-old male patient with no cardiovascular risk factors was followed in our Cardiology outpatient clinic for 2 years because of some episodes of chest pain that resembled angor pectoris. He underwent several treadmill tests with mild positive exercise electrocardiograms in lateral leads in the latter stages (ischaemic threshold at 9 min and maximum exercise workload of 10 METs). There was no adequate response to antianginal drugs and cardiac catheterization was indicated. Two linear radiopaque structures that moved with the beat of the heart were visualized. On contrast ventriculography, both structures appeared to be outside the ventricular cavity (*Panel A*). Coronary angiogram did not show any significant lesion and the radiopaque structures seemed to be located inside the myocardium (*Panel B*).



The patient was reinterrogated, and he remembered falling over a sewing basket in his childhood. A knitting needle, that had entered 2 cm through his chest at subxifoid level, then was removed. The wound healed without complications. A multidetector computed tomographic angiography was performed and confirmed the presence of the two needles located in the inferior area of the left ventricle. One of the needles, 11 mm long, lies in the posterior interventricular groove. The other one, 29 mm long, is intramyocardial and goes through the posterior interventricular septum and the inferior segment of the left ventricle (*Panels C* and *D*).

Panel A Ventriculography shows two radiopaque structures outside the ventricular cavity.

Panel B Radiopaque structures inside the myocardium.

Panels C and *D* Computed tomographic images show two needles, one in the posterior interventricular groove and other going through the posterior interventricular septum and the inferior area of the left ventricle.

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