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Núñez, Julio; Bayés-Genís, Antoni; Revuelta-López, Elena; Miñana, Gema; Santas, Enrique; ter Maaten, Jozine M.

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Optimal Carbohydrate Antigen 125 cutpoint for Identifying Low-Risk Patients after Acute Heart Failure Admission.

Authors: Julio Núñez MD, PhD¹,²*, Antoni Bayés-Genís MD, PhD²,³*, Elena Revuelta-López PhD²,⁴, Gema Miñana MD ¹,², Enrique Santas MD PhD¹, Jozine M. ter Maaten MD, PhD⁵, Rafael de la Espriella MD, Arturo Carratalá MD, PhD, Miguel Lorenzo MD¹, Patricia Palau MD, PhD¹,², Pau Llàcer MD, PhD⁵, Alfonso Valle MD, Vicent Bodi MD, PhD¹,², Eduardo Núñez MD, MPH¹, Josep Lupón MD, PhD²,³, Chim Lang MD, PhD⁷, Leong L. Ng MD, PhD⁸, Marco Metra MD, PhD⁹, Juan Sanchis MD, PhD¹,², and Adriaan A. Voors MD, PhD⁵
* Both authors contributed equally

Affiliations:

¹ Cardiology Department, Hospital Clínico Universitario de Valencia, Universitat de Valencia, INCLIVA, Valencia, Spain.
² CIBER Cardiovascular
³ Cardiology Department and Heart Failure Unit, Hospital Universitari Germans Trias i Pujol, Badalona. Department of Medicine, Autonomous University of Barcelona, Barcelona, Spain.
⁴ ICREC Research Program, Germans Trias i Pujol Health Science Research Institute, Can Ruti Campus, Badalona, Spain.
⁵ Cardiology Department, University of Groningen, University Medical Centre Groningen, Groningen, The Netherlands.
⁶ Biochemistry Department, Hospital Universitari Germans Trias I Pujol, Badalona, Spain
⁷ Division of Molecular & Clinical Medicine School of Medicine, University of Dundee, United Kingdom

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Address for correspondence:

Prof. Dr. Adriaan A. Voors

Department of Cardiology, University Medical Center Groningen

Hanzeplein 1, 9713 GZ, Groningen, The Netherlands

Tel: +31 (0)50 3616161

Fax: +31 (0)50 3618062

Email: a.a.voors@umcg.nl
ABSTRACT

Background. In patients admitted with acute heart failure (AHF), plasma levels of antigen carbohydrate 125 (CA125) have shown to be useful for risk stratification. We sought to determine a CA125 cutpoint for identifying patients at low risk of 1-month death or the composite of death/HF-readmission following admission for AHF.

Methods. The derivation cohort included consecutive patients admitted with AHF (n=3231). CA125 cut-off values measured during early admission that yielded a 90% negative predictive value (NPV) and sensitivity up to 85% were identified. Then, the adequacy of these cutpoints and the risk of 1-month death/HF-readmission was further tested in the multivariate survival analysis using the Royston-Parmar method. The cutpoint associated with the best-fitted model (using AIC and BIC criteria) was deemed as the optimal cutpoint. The chosen cutpoint was externally validated in a cohort of patients hospitalized from the BIOSTAT-CHF (n=1583).

Results. In the derivation cohort, median (IQR) CA125 was 57 U/mL (25.3-157); The optimal cut-off was < 23 U/ml (21.5% of patients), which yielded a NPVs of 99.3% and 94.1% for death and the composite endpoint, respectively. In multivariable survival analyses, a CA125<23 U/mL was independently associated with a lower risk of death (HR=0.20, CI 95%:0.08-0.50; p<0.001) and the combined endpoint (HR=0.63, CI95%:0.45-0.90; p=0.009). The ability of this cutpoint for discriminating patients at low 1-month risk was confirmed in the validation cohort (NPVs of 98.6% and 96.6% for deaths and the composite endpoint). This predicted ability of this cut-off remained significant at 6-month follow-up.

Conclusions. In patients admitted with AHF, patients with CA125<23 U/mL identified a subgroup of patients at low risk of short-term adverse events, a population that may not require intense post-discharge monitoring.
**Keywords**: CA125; antigen carbohydrate 125; Worsening Heart Failure; Congestion; Outcome.
CONDENSED ABSTRACT

In a cohort of 3321 consecutive patients with AHF, we aimed to determine the optimal CA125 cutpoint for identifying patients at a lower risk of death or death/HF-readmission at 1-month after discharge. Our results were replicated in the same cohort by testing both endpoints at 6-month, and in patients hospitalized in the BIOSTAT-CHF cohort (n=1583). We found that a cutpoint at <23 U/mL identified a subgroup of patients at low risk for either endpoint in both cohorts.

ABBREVIATIONS

AHF: Acute Heart Failure
BIOSTAT-CHF: A systems BIOlogy Study to TAilored Treatment in Chronic Heart Failure
CA125: Carbohydrate Antigen 125
eGFR: Estimated Glomerular Filtration Rate
FO: Fluid Overload
HF: Heart Failure
LVEF: Left Ventricle Ejection Fraction
NT-proBNP: N-terminal pro-brain Natriuretic Peptide
INTRODUCTION

The first months following a hospitalization for acute heart failure (AHF) are characterized by a high risk of death and heart failure hospital readmissions (1,2). Most of the risk stratification initiatives focus on identifying patients at higher risk after discharge and less emphasis on recognizing those at a lower risk. By accurately identifying this low-risk population, such stratification may translate into a better allocation of post-discharge resources (such as frequency of monitoring visits) to those patients at elevated risk.

In recent years, plasma levels of antigen carbohydrate 125 (CA125) have emerged as a useful prognostic marker in patients with AHF (3-12). Higher values of this glycoprotein have shown to be a valuable tool as a proxy of congestion, prediction of higher risk of adverse events, monitoring the course of the disease, and tailoring diuretic therapy during hospitalization and the first months after discharge (3-12).

Most of the commercial enzimo-immuno analyses recommend 35 U/mL as the cutpoint for defining normal values (Supplementary file 1). This cut-off was derived from cancer studies carried out in the 1980s (13,14). However, the evidence published on the use of CA125 as a prognostic marker in AHF (6,8) has shown an exponential increase in risk within the range of what is considered normal values. By looking at this stepped sigmoid-shaped risk curve, we hypothesize that the use of lower cutpoints may be useful in identifying patients at lower risk for early events.

In this study, we sought to evaluate the predictive value of CA125 at lower cut-off than the currently used 35 U/mL. Specifically, the goal was to determine the lowest useful CA125 cutpoints able to identify those patients with low risk of death and death/HF-readmission at 1-month following a hospitalization for AHF.
METHODS

Study samples

Derivation cohort

We retrospectively studied a cohort of 3302 consecutive patients who were admitted for AHF to the Cardiology Department of a third-level teaching center between January 2007 and June 2018. AHF was diagnosed by trained cardiologists according to the definition proposed by guidelines operating at the time of patients' inclusion. All patients presented on admission with symptoms (dyspnea at rest or minimal exertion) or signs attributable to congestion. Also, the diagnosis of heart failure (HF) was confirmed by the presence of echocardiographic evidence of a structural or functional abnormality of the heart assessed during hospitalization. Both patients with new-onset AHF and decompensated chronic HF were included. We excluded patients with a missing value of CA125 and who underwent surgical valve replacement, transcatheter valvular intervention during the index admission, or transfer to heart transplantation were excluded (n=71). The final study sample included 3231 patients.

All patients received intravenous treatment with furosemide, at least during the first 48 hours of admission. Left ventricle ejection fraction (LVEF) was assessed by two-dimensional echocardiography during the index hospitalization. Treatment with angiotensin-converting enzyme inhibitors (ACEI), angiotensin receptor blockers (ARB), beta-blockers, aldosterone antagonists, anticoagulants, and other therapeutic strategies was individualized following established guidelines.

Follow-up was limited to 6 months. Patients' follow-up was censored if they had died or had to undergo cardiac transplantation (n=2) within this period. An institutional review committee approved this study, and patients gave written informed consent.
BIOSTAT-CHF study (validation cohort)

The BIOlogy Study to TAilored Treatment in Chronic Heart Failure (BIOSTAT-CHF) was a multicentre, multinational, prospective, observational study that included 2516 patients with worsening signs or symptoms of HF from 69 centers in 11 European countries (15). The recruitment period was 24 months, from December 2010 to December 2012. Median follow-up was 21 months [interquartile range (IQR) 15–27 months]. Patients were included after presentation with either new onset or worsening HF, which was defined as LVEF \( \leq 40\% \) and/or brain natriuretic peptide (BNP) >400 pg/mL or N-terminal pro-brain natriuretic peptide (NT-proBNP)>2000 pg/mL. Patients were expected and encouraged to be up-titrated to recommended treatment doses. Patients included in BIOSTAT-CHF were either seen in the outpatient setting or in-hospital. The present study only included 1583 hospitalized patients. All patients enrolled in BIOSTAT-CHF provided written informed consent to participate in the study, and BIOSTAT-CHF was conducted in concordance with the declaration of Helsinki, national ethics, and legal requirements, as well as relevant European Union legislation. The study was also approved by national and local ethics committees. The characteristics of the BIOSTAT-CHF cohort have been described elsewhere (15).

Endpoints

All-cause mortality and the composite of death or HF-readmission at 1-month after admission were selected as co-primary endpoints. The secondary endpoints were the same but evaluated at 6-month follow-up. 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 the exposure.
**CA125 measurement**

In the derivation cohort, CA125 was measured during the patient's hospitalization (48±24 hours after admission) using a commercially available immunoassay kit (Elecsys CA125 II assay-Roche Diagnostics). In the validation cohort, CA125 was measured on admission using the ARCHITECT CA 125 II assay (lot.81007M800), a chemiluminescent microparticle immunoassay (CMIA), on the ARCHITECT/ System (Abbott Laboratories).

The half-life of the CA125 is 7 to 12 days, and prior studies have found no significant changes of CA125 during the first 72 following admission (6). The normal range of CA125 established for the assays is 35 U/mL (Supplementary file 1), and the reported total coefficient of variation is ≤ 10% for all the assays.

**Statistical analysis**

Baseline characteristics among CA125 categories were compared by either ANOVA, Kruskal–Wallis, or chi-squared tests, as appropriate.

**CA125 cut-off for low-risk prediction**

The receiving operating characteristic curve (ROC) was estimated for both endpoints at 1-month. To determine the optimal cut-off values of CA125 aimed at identifying low-risk patients, sensitivity, specificity, negative (NPV), and positive predictive (PPV) values were estimated along the continuum of the biomarker (diagt command). From a range of cut-offs considered to be predictive of low risk those with a negative predictive value of 90% or greater, sensitivity of 85% or greater, and those that classified at least 10% of patients to low risk were further analyzed in multivariable survival analysis. In this latter scenario, the best-cut-off was the one that showed the best performance using Akaike information criterion (AIC) and the Bayesian information criterion (BIC) criteria. Moreover, the prognostic adequacy of the cut-off deemed to be optimal was also tested at 6-month follow-up.
Sensitivity, NPV, AIC, and BIC for the preselected CA125 values are presented in the figure 1. The best cut-off was compared with prior reported cut-offs in the literature (traditional cut-off suggested by most of the assays: 35 U/ml, and prognostic cut-offs used in prior studies: 65 U/ml (6-11). For this comparison, patients were classified according to the following CA125 categories: C1:<23 U/mL; C2:23-34.9 U/mL; C3: 35-64.9 U/mL; and C4: ≥65 U/mL.

CA125 and outcomes: multivariate analyses.

Employing a flexible parametric regression modeling –Royston-Parmar model– we determined the independent prognostic effect of CA125 categories with both clinical outcomes. To hold a linearity assumption with the outcome when modelled as continuous exposure, the best fractional polynomials transformation was chosen based on AIC/BIC criteria. In the derivation cohort, regression estimates from the mortality model were adjusted for age, gender, prior admission for AHF, prior New York Heart Association (NYHA) before admission, etiology, atrial fibrillation, heart rate, systolic blood pressure, hemoglobin, blood urea nitrogen, NT-proBNP, LVEF, use of beta-blockers during admission, and furosemide equivalent dose on admission. For the composite endpoint, Charlson comorbidity index and severe tricuspid regurgitation were added to the mortality set of covariates. Under the same multivariate scenario, the prognostic adequacy of the different CA125 cut-offs were also tested.

A similar modeling strategy was applied to the validation cohort, except that these regression estimates were only adjusted with an outcome-specific risk score (BIOSTAT-risk score) (16). The BISTAT risk score for mortality included age, blood urea nitrogen, NT-proBNP, serum hemoglobin, and the use of beta-blockers. The BISTAT risk score for the composite endpoint included age, previous HF-hospitalization, peripheral edema, systolic blood pressure, NT-proBNP, hemoglobin, high-density lipoprotein, sodium, and use of beta-blockers. In a sensitivity analysis on the derivation cohort, risk estimates were also adjusted
for the appropriate BIOSTAT risk scores for both endpoints (16). Estimates of risk across
sex, LVEF (≥50% and <50%), glomerular filtration rate (>60mL/min/1.73m² vs. ≤60
mL/min/1.73m²), and NT-proBNP (above or equal median vs. below median) were also
calculated. All estimates were presented as hazard ratios (HR) with 95% CIs. Harrell C-
statistics was used as the metric for model's discrimination performance and presented in
figure legends.

We set a two-sided p-value of <0.05 as the threshold for statistical significance. Stata
15.1 (Stata Statistical Software, Release 15 [2017]; StataCorp LP, College Station, TX, USA)
was used for the main analysis.
RESULTS

The mean age of the sample of the derivation cohort was 73.6±11.3 years; 1553 (48.1%) were female, 861 (26.7%) had a prior hospitalization for AHF, 1142 (35.4%) history of ischemic heart disease and 1697 (52.5%) showed a LVEF ≥50%. Median (IQR) of CA125, NT-proBNP, and estimated glomerular filtration rate (eGFR) were 57 U/mL (25.3-127), 3418 pg/mL (1831-6918), and 60 mL/min/1.73m² (43.9-76.3), respectively. Baseline characteristics across categories of CA125 are shown in table 1. Patients in the lower category were more frequently females and showed a higher proportion of HF with preserved ejection fraction. Overall, they showed a better clinical risk profile (Table 1). For instance, they showed higher blood pressure, fewer signs of congestion, better renal function, and lower NT-proBNP. Likewise, they received lower intravenous loop diuretic doses and were less frequently treated with aldosterone receptor antagonists.

The mean age of the validation cohort was 69±12.3 years; 1141 (72.1%) were male, and 425 (26.8%) had a prior hospitalization for AHF. The median of CA125 (IQR) was 64 U/mL (21-69), and the distribution and characteristics of patients according to CA125 categories are shown in Table 2. Overall, the profile of patients with lower CA125 was similar than found in the derivation cohort (Table 2).

CA125 cut-off for selecting low-risk patients

The area under the ROC curve of CA125 for 1-month death and the composite of death/HF readmission were 0.639 and 0.570, respectively. For 1-month mortality, a range of values from 15 to 34 U/ml were preselected. For 1-month composite endpoint, a range of values from 15 to 24 U/ml were preselected. Sensitivity, NPV, AIC, and BIC for the preselected CA125 values are presented in figure 1.
A cut-off of 23 U/ml identified 21.5% of the patients with a NPV and sensitivity of 99.3% and 96.4% for 1-month death. The respective diagnostic accuracy measures for the composite endpoint were and 94.1% and 87.9%, respectively. After a comprehensive multivariate evaluation, CA125 of 23 U/ml showed the lowest AIC/BIC for both outcomes (Figure 1).

**Low CA125 and adverse outcomes**

**Derivation cohort**
At 1-month follow-up, 137 (4.2%) deaths and 328 (10.2%) composite endpoint were registered.

Crude rates of both endpoints increased when moving from lower to higher CA125 categories (Table 1). Kaplan-Meier curves showed a progressive separation of curves along the entire follow up with a tangible separation of curves within the first month for both endpoints and especially for those with CA125<23 U/ml (Figure 2a and 2b). After a multivariate adjustment, and compared to CA125≥23, those with CA125<23 U/mL showed an 80% reduction of risk of death (HR=0.20, CI 95%:0.08-0.50; p<0.001) and 37% reduction of the combined endpoint (HR=0.63, CI 95%:0.45-0.89; p=0.009). A similar reduction of risk were also found when compared to patients with CA125 between 23-35 U/ml (HR=0.20; CI 95%:0.07-0.53; p=0.001 and HR=0.52; CI 95%:0.34-0.79; p=0.002 for death and death/HF-readmission, respectively). Survival curves among the prespecified subgroups are presented in Supplementary files 2 and 3. Multivariate analyses revealed a non-differential association across sex (male vs. female), LVEF (≥50% and <50%), NT-proBNP categories [above or equal median (≥3480 pg/ml) vs. below median (<3480 pg/ml)], and renal function (eGFR >60mL/min/1.73m² vs. ≤60 mL/min/1.73m²) (Figure 3).
A sensitivity analysis, adjusting for the BIOSTAT risk scores, also revealed the same pattern of risk for 1-month endpoints. Patients with CA125<23 U/mL remained associated with a similar lower risk (HR\textsubscript{1-month death}=0.17, CI 95\%:0.07-0.41; p<0.001; and HR\textsubscript{1-month death/HF-readmission}=0.43; CI 95\%:0.31-0.59; p<0.001).

At a 6-month follow-up, we registered 424 (13.1\%) deaths and 863 (26.7\%) combined endpoints. At this time point, the differences indicating lower risk for patients with CA125<23 U/ml were of lower magnitude but remained significant for both endpoints (Figure 2a and 2b). Regarding these secondary endpoints, adjusted risk estimates confirmed that CA125<23 U/ml identified a subgroup of patients with a 51\% lower risk of death (HR=0.49, CI 95\%:0.35-0.69; p<0.001) and 22\% of death/HF-readmission (HR=0.78, CI 95\%:0.64-0.94; p=0.010).

Validation cohort

At 1-month follow-up, 42 (2.6\%) and 120 (7.6\%) patients died and experienced the combined endpoint, respectively. At 6-month follow-up, 184 (11.6\%) died, and 371 (23.4\%) died or were readmitted for HF. The NPVs and sensitivity of CA125<23 U/ml for 1-month mortality were 98.6\% and 85.7\%, respectively. The same parameters for 1-month death/HF-readmission were 96.6\% and 88.3\%, respectively. Table 2 shows the crude rates for 1 and 6-month endpoints across CA125 categories.

Patients with CA125 <23 U/mL displayed the lowest rates of adverse events with differences already present since the first month. (Figure 4a and 4b). After multivariate adjustment for the BIOSTAT risk score, patients with CA125 <23 U/mL remained showing lower risk when compared to those with CA125 >23 U/mL for 1-month death/HF readmission (HR=0.54; CI 95\%:0.32-0.91; p=0.021). The adjusted risk estimates for 1-month mortality did not reach statistical significance (HR=0.61; CI 95\%:0.26-1.47; p=0.267). At 6-
month, CA125<23 U/ml was associated with lower risk of both endpoints (HR_{6-month death}=0.59, CI 95%:0.39-0.90; p=0.014; and HR_{6-month death/HF-readmission}=0.65; CI 95%:0.49-0.86; p=0.002).
DISCUSSION

The present study confirms the role of CA125 for short and mid-term risk stratification following a hospitalization for AHF. Moreover, a new cutpoint able to identify those patients at low risk for clinical events at 30-day post-discharge is proposed. Indeed, we found that a cutpoint at CA125 <23 U/mL (instead of the conventional >35 U/ml) emerged useful for identifying patients at a lower risk of short-term adverse events. The fact that this novel cutpoint (covering 21% of the population) performed equally well for the composite of 1-month death/HF-readmission adds robustness to our findings.

This cut-off also showed excellent performance for both endpoints measured at a 6-month follow-up. The magnitude of risk estimates, however, were smaller as compared with all-cause mortality at 1-month. These findings were successfully replicated in hospitalized patients from the BIOSTAT international cohort of patients with worsening heart failure.

CA125 in AHF syndromes

CA125, also called MUC16, is an extremely complex high molecular glycoprotein, synthesized by coelomic epithelial cells at sites such as the pericardium, pleura, or peritoneum (4,5,17). Although widely used for ovarian cancer monitoring, high plasma levels are present in up 2/3 of patients with AHF syndromes (4-6). Although the exact mechanisms leading to CA125 upregulation remain unknown, most of the evidence points out toward increased venous pressures and inflammation as crucial mechanisms (4,5,17). In patients with AHF, the most important factors positively related to CA125 values are well-known proxies of congestion and right-sided HF (4-8,17,18). Hence, this glycoprotein has gained the attention of clinicians as a surrogate marker of congestion (17), especially given its wide availability, low cost, and limited value of symptoms/signs and natriuretic peptides for accurately quantify the severity of congestion (4,5,19,20).
For risk stratification, higher CA125 has consistently shown to be associated with a higher risk of death and HF-readmission in different AHF scenarios (3-8). Indeed, a recent substudy of the BIOSTAT registry confirmed the association of this biomarker with a higher risk of 1-year death and HF-readmission independently of traditional prognosticators, including symptoms and signs of congestion (8).

Interestingly, this biomarker showed attractive properties for monitoring the first months after decompensation and guiding depletive treatments (9-11). A recent study in 946 patients discharged with AHF, a longitudinal assessment of CA125, showed that the trajectory of this biomarker was independently associated with the risk of mortality (9). Persistently increased values were found in those at higher risk of mortality, whereas CA125 normalization was found those with higher survival (9). Furthermore, the CHANCE-HF randomized clinical trial found that a strategy of titrating diuretics based and tailoring the intensity of monitoring on CA125 levels was superior to standard of care in terms of reducing the risk of 1-year death or HF-readmission (10). More recently, CA125-guided diuretic therapy was also associated with renal function improvement over usual care in 160 patients with acute HF and concomitant renal dysfunction (11).

Low CA125, prognosis and potential clinical implications

Traditional cutpoints for defining low vs. high CA125 values were derived from studies focused on the diagnostic utility of this biomarker for ruling in/out ovarian and other malignancies (13,14,21). For instance, Klug et al., found that CA125 <35 U/mL was able to distinguish between healthy individuals and patients with ovarian cancer clearly; while the 65 U/ml, maximized the difference between patients with benign disease and ovarian carcinoma (13). In other malignancies, CA125>35 U/ml has also chosen as the most accepted cutpoint for defining low vs. high values (21). Up to now, however, these cancer-driven cutpoints has
been used in AHF, with no data on specific cutpoints optimally evaluated for AHF population. Our findings suggest that a cutpoint at CA125<23 U/ml indeed identified a low-risk subgroup of patients with a stepwise increase of risk for the immediate upper categories (such as CA12523-35 U/ml or above). This prognostic effect was seen in both endpoints tested, although stronger for the mortality. In fact, the crude rates of 1 and 6-month mortality were about 1% and 5% for patients with CA125<23 U/ml. These findings were consistent in both sexes, in patients with preserved and reduced ejection fraction, renal dysfunction, and independently of NT-proBNP status. Moreover, the prognostic ability of CA125<23 U/ml were also found at 6-month follow-up and positively validated in the BIOSTAT international cohort. Also, these findings are in agreement with prior studies reporting values <20 U/ml in healthy people. For instance, Bast et al. reported a mean ±SD of CA125 in 888 healthy blood donors males and females of 8±9.4 U/ml and 9.9±8 U/ml (14).

We envision that our findings may provide a widely available tool for phenotyping the underlying pathophysiology of AHF syndromes. For instance, low CA125 may indicate predominant intravascular congestion or vascular redistribution rather than extravascular or tissue congestion (22). From a clinical point of view, these patients may benefit more from a less intensive diuretic strategy, a more rapid up-titration of recommended standard HF-treatments, and probably a more flexible post-discharge monitoring.

Limitations

Some limitations need to be acknowledged. First, these results do not apply to patients with stable chronic HF. CA125 were not measured at the same time point in both cohorts. In the derivation cohort, CA125 was measured during the course of hospitalization and on admission in the validation cohort. This issue may not have a substantial role for CA125
given the long half-life of this biomarker (4,6,17). Second, we did not evaluate the effect of the intensity of monitoring or the changes in treatments after discharge on the 'outcomes' incidence. Third, since this is a predominant cohort of caucasian patients, these findings cannot be extrapolated to other races.

CONCLUSION

In patients hospitalized with AHF admission, a cutpoint at CA125 <23 U/mL identified a subgroup of patients at low risk of short-term mortality and the composite of death/HF-hospitalization. This same cutpoint holds its predictive ability for both endpoints measured at a 6-month follow-up. Further studies should confirm these findings and evaluate whether this subgroup of patients may receive a more relaxed monitoring schedule during the transitional phase.
REFERENCES


FIGURE LEGENDS

Figure 1. Performance of different CA125 cut-offs for predicting 1-month adverse events.
1a. All-cause mortality
1b. All-cause mortality/HF-readmission
AIC: Akaike information criterion; BIC: Bayesian information criterion; CA125: carbohydrate antigen 125; HF: heart failure; NPV: negative predictive value.

Figure 2. Kaplan Meier survival curves across CA125 categories.
2a. All-cause mortality
2b. All-cause mortality/HF-readmission
CA125: carbohydrate antigen 125; HF: heart failure.

Figure 3. Multivariate risk estimates. Subgroup analyses
3a. All-cause mortality
3b. All-cause mortality/HF-readmission
* For all patients, estimates of risks for mortality were adjusted for age, gender, prior admission for AHF, previous New York Heart Association class before admission, etiology, atrial fibrillation, heart rate, systolic blood pressure, hemoglobin, blood urea nitrogen, NT-proBNP, LVEF, use of beta-blockers during hospitalization, and furosemide equivalent dose on admission. For the composite endpoint, Charlson comorbidity index and severe tricuspid regurgitation were added to the mortality set of covariates.
Harrell’s C-statistics for multivariate models for mortality and the composite endpoints were 0.81 and 0.71, respectively.
AHF: acute heart failure; CA125: carbohydrate antigen 125; eGFR: estimated glomerular filtration rate; HF: heart failure; LVEF: left ventricle ejection fraction; NT-proBNP: N-terminal pro-brain natriuretic peptide.

**Figure 4:** Kaplan Meier survival curves. BIOSTAT international cohort.

4a. All-cause mortality

4b. All-cause mortality/HF-readmission

CA125: carbohydrate antigen 125; HF: Heart failure.