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Clinical utility of antigen carbohydrate 125 in heart failure

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Abstract In recent years, there has been a proliferation of new biomarkers with potential prognostic implication in heart failure (HF). Nevertheless, most of them do not fulfill the required criteria for being used in daily clinical practice. Tumor marker antigen carbohydrate 125 (CA125), a glycoprotein widely used for ovarian cancer monitoring, is synthesized by epithelial serous cells in response to fluid accumulation and/or cytokine stimuli. This glycoprotein has been emerged as a potential biomarker in HF. Plasma CA125 correlates with clinical, hemodynamic, and echocardiographic parameters related to the severity of the disease. High levels have shown to be present in the majority of acutely decompensated patients, and in this setting, it has shown to be independently related to mortality or subsequent admission for acute HF. In addition, certain characteristics such as wide availability and the close correlation between plasma changes with disease severity and clinical outcomes have increased the interest of researchers about the potential of this glycoprotein for monitoring and guiding therapy in HF. In this article, we have reviewed the available evidence supporting the potential role of CA125 as a biomarker in HF.

Keywords Antigen carbohydrate 125 · Prognosis · Heart failure · Biomarkers

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Introduction

In recent years, there has been a renewed interest in searching for new biomarkers with potential indications in heart failure (HF), with three main areas of coverage: diagnosis, risk assessment, and therapeutic monitoring. This has been translated into a proliferation of publications about the potential use of new molecules in HF [1–5].

Unfortunately, most of them do not currently fulfill the required conditions for being used in daily clinical practice [1–5]. Recent statements have defined the required conditions necessary to endorse the clinical usefulness of a new biomarker [1, 3, 4, 6]: (a) quality of the assay (easily measurable within a short period of time, widely available standardized methods, and reasonable cost); (b) the biomarker should reflect a pivotal pathophysiological process involved in the pathogenesis and progression of the disease; (c) it must provide clinically useful information and accurate estimation of prognosis; (d) the information provided by this biomarker must add to the clinical data and other biomarkers; and (e) it must supply a quantifiable value to support clinical decision-making.

Antigen carbohydrate 125 (CA125), also called MUC16, is a glycoprotein synthesized by epithelial serous cells [7], with extremely complex structure and high molecular weight [8]. Although CA125 is widely used for ovarian cancer therapy monitoring [9], high plasma levels have also been reported in other malignant and nonmalignant diseases (HF, nephrotic syndrome, liver cirrhosis, tuberculosis, or pelvic inflammatory disease, among others) [10]. Although the exact biological role of CA125 is unknown, the complexity of its structure points toward acting through several pathways. For instance, a role in cell-mediated immune response is an important pathway proposed. This explains the contributing effect of CA125 in the growth of

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ovarian tumors by suppressing the response of natural killer cells [11–13].

CA125 in HF: Pathophysiology

Currently, there is no clear understanding about the mechanisms leading to CA125 elevation in HF, although preliminary evidence points out toward a complex and multifactorial role [14–16]. This evidence suggests that CA125 is synthesized by serosal cells in response to the presence of serosal effusions and/or inflammatory stimulus [17–21], which explains the elevation of CA125 in patients with chronic HF with pericardial, pleural, and peritoneal effusions [17, 18, 20]. In a small case–control study, Turk et al. [17] showed higher mean values of CA125 in patients with chronic HF and pleural effusion (100.0 ± 129.4 U/ml), intermediate values in those with chronic HF and no pleural effusion (36.5 ± 35.2 U/ml), and lower values in the control group (8.9 ± 6.1 U/ml). Similarly, our group reported, in a cohort of 1,111 consecutive patients admitted for acute HF (AHF), that the most important predictors of CA125 were the presence of pleural effusion and peripheral edema (accounting for 57.8 and 12.9 % of the total model predictability, respectively) [22]. In fact, a recent review about this topic revealed that the presence of serosal effusions and/or signs of congestion were the most important factors that correlated with increased values of CA125 [23]. However, the fact that there is evidence showing elevation of this biomarker in absence of clinical evidence of serosal effusions and/or signs of congestion [17] calls for additional pathways. Furthermore, higher levels of this biomarker have shown to be associated with worse outcomes, independent of the presence of congestion [22]. This associated prognostic effect has led some authors to postulate that, perhaps, other and more complex pathophysiological processes might be involved in CA125 elevation [14–16, 24]. In this line, in vitro experiments have shown that inflammatory mediators [interleukin-1, tumor necrosis factor α (TNF-α), lipopolysaccharide] stimulate the secretion of CA125 from mesothelial cells [7, 19]. Indeed, Kosar et al. [21] reported in a case–control study that CA125 was highly correlated with TNF-α, interleukin-6, and interleukin-10 in 35 hospitalized HF patients and left ventricular systolic dysfunction. Similarly, in a prospective cohort of 132 nonselected AHF patients, Miñana et al. [25] found that CA125 levels above median (60 U/ml) were associated with higher levels of TNF-α, interleukin-6, and interleukin-1β, and lower relative lymphocyte count. Likewise, Hamdy et al. [26] reported a positive correlation between CA125 with TNF-α, interleukin-6, and T cell activation markers in a small group of obese HF patients.

There is no clear evidence on how these two mechanisms (fluid overload/serosal effusions and/or inflammation) differentially participate in CA125 elevation in patients with HF. We, and others, have speculated that CA125 may increase, not only as a consequence of mesothelial cells irritation by serosal effusion but, perhaps, by mesothelial cell interaction with inflammatory mediators present in HF [14–16, 24]. In support of this postulate, we observed a sustained plasma reduction in CA125 after the onset of peritoneal dialysis in 25 patients with refractory congestive HF [from 70.9 U/ml (42.2–206.7) to 32.2 U/ml (22.1–49.6) at 6 weeks and 28.1 U/ml (18.2–75.6) at 24 weeks ($p < 0.005$ for both comparisons)] [27]. Notably, this reduction coincided with patients' clinical improvement and occurs despite the potential for serosal irritation that may be induced by the infusion of the osmotic solution into the peritoneum [14, 27]. Moreover, the interplay between fluid overload and inflammation in HF has been underlined in recent studies showing a pathogenic role of venous congestion by triggering an inflammatory cascade, which in turn activates the synthesis of CA125 by mesothelial cells [28].

In summary, we believe that increases in CA125 and serosal effusion are parallel processes that share a common pathophysiological mechanism and are not necessarily linked by cause effect; in their root, inflammation may play a pivotal role.

Regardless of the underlying pathophysiology, a biomarker that correlates with fluid overload and/or inflammatory activity appears a priori, an attractive and useful clinical tool. Systemic congestion/fluid redistribution is, in fact, the most frequent cause of HF decompensation. Moreover, none of the traditional symptoms/signs nor established biomarkers have consistently shown to be a reliable tools [29, 30]. In addition, the main drawbacks of using cytokines in clinical practice are as follows: high temporal variability, unstandardized measure techniques, pulsatile release, and short half-life [31].

CA125 and HF severity

Clinical

Varol et al. [18] reported higher serum values of CA125 in a small study of patients admitted for HF when compared with healthy volunteers (81.9 ± 91 vs. 7.5 ± 4.8 U/ml, $p < 0.001$). Similar findings were also found in a large and unselected cohort ($n = 565$) of patients admitted for AHF, where mean CA125 plasma levels were 7-fold higher as compared to a control group of asymptomatic HF patients matched on age, sex, and cardiovascular risk factors (105.2 ± 139 vs. 14.9 ± 22 U/ml; $p < 0.001$, respectively)

[32]. In this cohort of AHF patients, the prevalence of elevated levels of CA125 (>35 U/ml) was 66 %. Similar values have been reported in other large studies of patients hospitalized for AHF [22, 33].

In addition, numerous studies have reported that plasma CA125 highly correlates with NYHA functional class. In this regard, D'Aloia et al. [33] described, in a cohort of 286 patients with chronic HF [with mean left ventricular ejection fraction (LVEF) 30 ± 11 %], that higher levels of CA125 were parallel to an increase in NYHA functional class (15 ± 9 U/ml for NYHA class I/II, 57 ± 18 U/ml for class III, and 167 ± 94 U/ml for class IV patients; $p < 0.005$). Likewise, Faggiano et al. [34] reported, in 191 patients with mild-to-severe chronic HF and left ventricular systolic dysfunction, that mean CA125 levels were significantly higher in those with NYHA III (60 ± 22 UI/ml) and IV (192 ± 115 UI/ml) as compared to NYHA class I–II patients (16 ± 11) ($p < 0.05$). Similar positive correlation with functional class was observed in other studies [35, 36].

Hemodynamics

Antigen carbohydrate 125 (CA125) levels have been correlated with echocardiographic and hemodynamic parameters of HF severity. Nägele et al. [37] in advanced HF patients candidates for heart transplantation found a positive correlation between CA125 with right atrial pressure ($r = 0.41$, $p < 0.001$), and pulmonary capillary wedge pressure ($r = 0.27$, $p < 0.001$). D'Aloia et al. [33] showed that CA125 levels were not only related to right atrial pressure ($r = 0.69$, $p < 0.05$), and pulmonary artery capillary wedge pressure ($r = 0.66$, $p < 0.05$), but also to left ventricular diastolic function parameters [E wave deceleration time on Doppler echocardiography ($r = -0.63$, $p < 0.05$)]. CA125 has also shown a correlation with left atrial volumes in women with HF and preserved ejection fraction [38] as well as in patients with left ventricular systolic dysfunction [36]. In addition, CA125 levels correlated as well with right ventricular dilatation and dysfunction [39]. Unfortunately, these observations have been extracted either from small studies or highly selected patients and, therefore, should be interpreted with caution.

Other biomarkers

A positive correlation between CA125 and surrogates for neurohormonal activation has been reported. Nagele et al. [40] described a positive correlation with norepinephrine and atrial natriuretic peptide in 71 patients with advanced chronic HF undergoing heart transplantation. More recent studies, including patients with left ventricular systolic dysfunction, have found strong and significant correlations with natriuretic peptides [33, 36, 41, 42]. For instance, Duman et al. [36] reported in 49 NYHA III–IV patients that CA25 serum levels were significantly associated (standardized beta coefficient = 0.58, $p < 0.001$) with brain natriuretic peptide (BNP). Larger studies, including nonselected populations, have reported a significant although a weaker correlation with BNP [22]. These discrepancies have been explained by differences in patients' characteristics, time of measurement, and the different kinetics of both biomarkers.

Risk stratification

Single measurement

A positive and independent association between CA125 and clinical endpoints has been shown by different authors. D'Aloia et al. [33] described, in a cohort of 286 congestive HF patients, a positive (although unadjusted) association between CA125 and the combined endpoint of death and readmission for worsening HF at a median follow-up of 6 months. The combined endpoint was achieved in 12.6 % patients with CA125 <35 U/ml, compared with 61.9 % patients with CA125 >35 U/ml ($p < 0.01$). In a subsequent study, including patients with both preserved and systolic dysfunction, CA125 was independently associated with increased risk of mortality at 6 months [32]. In this study, risk estimates were adjusted by age, gender, diabetes, NYHA class, etiology, systolic blood pressure, serum creatinine, and hemoglobin. More recently, CA125 levels were related to 6-month mortality in 1,111 patients admitted for AHF [22]. Interestingly, CA125 added significant prognostic value in terms of 6-month total, cardiovascular, and progressive HF mortality, beyond the information provided by BNP (Fig. 1). In the multivariate analysis, after adjusting for well-established risk factors, the simultaneous use of these two biomarkers provided a substantial improvement in 6-month risk stratification, when compared with either of them alone [23].

The association between CA125 and worse clinical outcomes has also been found in special populations of patients with HF, such as women with preserved ejection fraction [38], mild-to-moderate HF severity [43], highly advanced HF patients referred for heart transplantation [44], aortic stenosis [45, 46], hypertrophic cardiomyopathy [47], non-ischemic dilated cardiomyopathy [48], and African-American patients with AHF [42].

Serial measurements: a useful biomarker for monitoring?

Some studies have revealed that serum levels of CA125 fluctuate parallel to changes in clinical status [14, 27, 33,

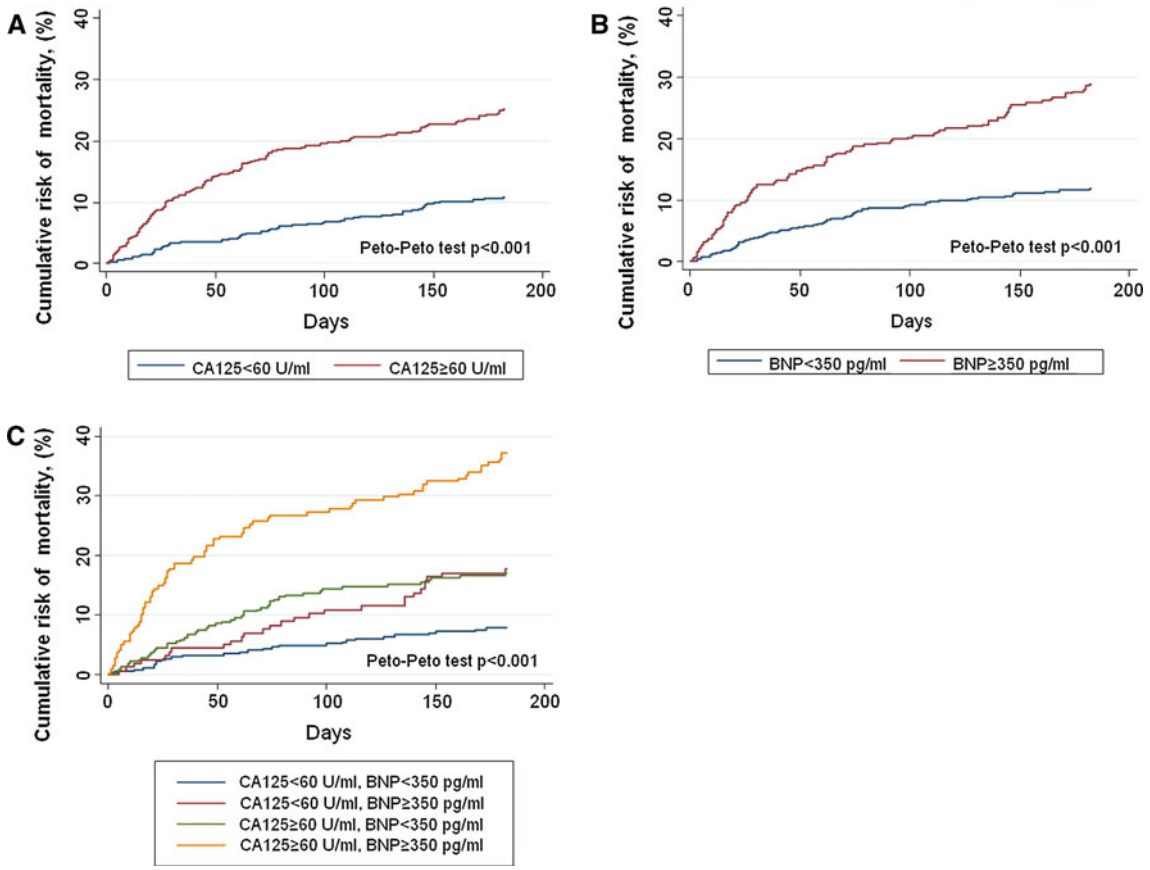

Fig. 1 Reproduced with permission from Eur Heart J 2010; 14:1752–1763). Kaplan–Meier curves for total mortality. **a** Stratified by CA125. **b** Stratified by BNP. **c** Stratified by BNP-CA125–CA125: serum antigen carbohydrate 125, *BNP* brain natriuretic peptide

34, 37, 40, 49]. For instance, Nägele et al. [40] found, in 71 candidate patients for heart transplantation, a significant decrease in this biomarker after heart transplantation (401 ± 259 vs. 33 ± 22 U/l, $p < 0.001$) or clinical stabilization (429 ± 188 vs. 78 ± 35 U/l, $p < 0.001$), and an increase during worsening of HF (42 ± 25 vs. 89 ± 32 U/l, $p < 0.01$). D'Aloia et al. [33] reported that after medical treatment optimization, CA125 levels decreased from 125 ± 98 to 53 ± 61 U/ml ($p < 0.001$) only in those patients in whom the NYHA class functional status improved, with no significant differences among those in whom the NYHA class was unchanged. Faggiano et al. [34] reported, in 30 patients with NYHA class IV, a decrease in CA125 serum levels from 107 ± 85 to 19 ± 8 U/ml ($p < 0.05$) when a clinical improvement was achieved after aggressive medical treatment. A similar correlation with fluctuation in clinical status has been documented by our group. Indeed, we found, using an unselected cohort of 293 consecutive patients admitted for AHF, a decrease in CA125 (76.8 %) between discharge and the first outpatient visit (at a median of 31 days). Noticeably, 52.2 % of them returned to normal values. CA125 elevation was documented in 23.2 % independently of CA125 starting values [49]. During a median follow-up of 18 months, patients who normalized CA125 levels exhibited the lowest adjusted risk of death, intermediate for those who decreased but not normalized (HR = 2.41; 95 % CI 1.40–4.17; $p = 0.002$), and higher for those which CA125 increased but remained >35 U/ml at the first outpatient visit (HR = 3.33; 95 % CI 1.89–5.88; $p < 0.001$). Moreover, these changes over time showed an incremental discriminative ability (in terms of integrated discrimination improvement index) to predict worse outcomes compared to a one-time measurement or even BNP changes [49]. These findings were also reproduced in the same cohort of patients when the endpoint was a 6-month risk of readmission for AHF [50]. More recently, Husser et al. [51] found, in 228 patients with aortic stenosis undergoing transcatheter aortic valve implantation (TAVI), that longitudinal evolution of CA125 levels predicted adverse clinical outcomes after TAVI.

Why a similar prognostic behavior has not been reproduced with natriuretic peptides is not clear [52, 53], although we postulate that having CA125 a half-life longer than 1 week [54] may, at least in part, explain this correlation between changes in clinical status with its levels.

Potential therapeutic implications

The use of biomarkers to guide the optimal management of HF patients has become a topic of interest in recent years. The intended aim is to identify subgroups of patients who may require more aggressive treatment, while minimizing at the same time, a potential for adverse effects. Unfortunately, most of the clinical available evidence has produced conflicting results in regard to the use of natriuretic peptides (BNP or NT-proBNP) for this indication [55]. In this context, some studies have suggested this biomarker may play a role for guiding therapy in HF.

CA125 and statins in HF

Despite the fact that prior randomized clinical trials have failed to demonstrate a prognostic benefit of statins in chronic HF [56, 57], evidence coming from observational studies has supported its clinical benefit in pre-specified subgroups of patients [58, 59]. A post hoc analysis of CORONA trial showed lower risk for the composite primary endpoint of cardiovascular death, nonfatal myocardial infarction, or stroke associated with the use of statins in the subgroup of patients with lower serum values of NT-proBNP (<102.7 pmol/l) and high serum values of high-sensitivity C-reactive protein (>2 mg/l) [58]. Moreover, a post hoc analysis of the PEARL study [59] showed that the prognostic effect of statins varied according to LVEF status, with lower risk of cardiovascular mortality and rehospitalization for HF in patients with LVEF ≥30 % but not in those with LVEF <30 % (p for interaction = 0.018). Likewise, we evaluated the long-term mortality associated with statin therapy in 1,222 consecutive patients admitted with AHF and explored if this risk varied according to

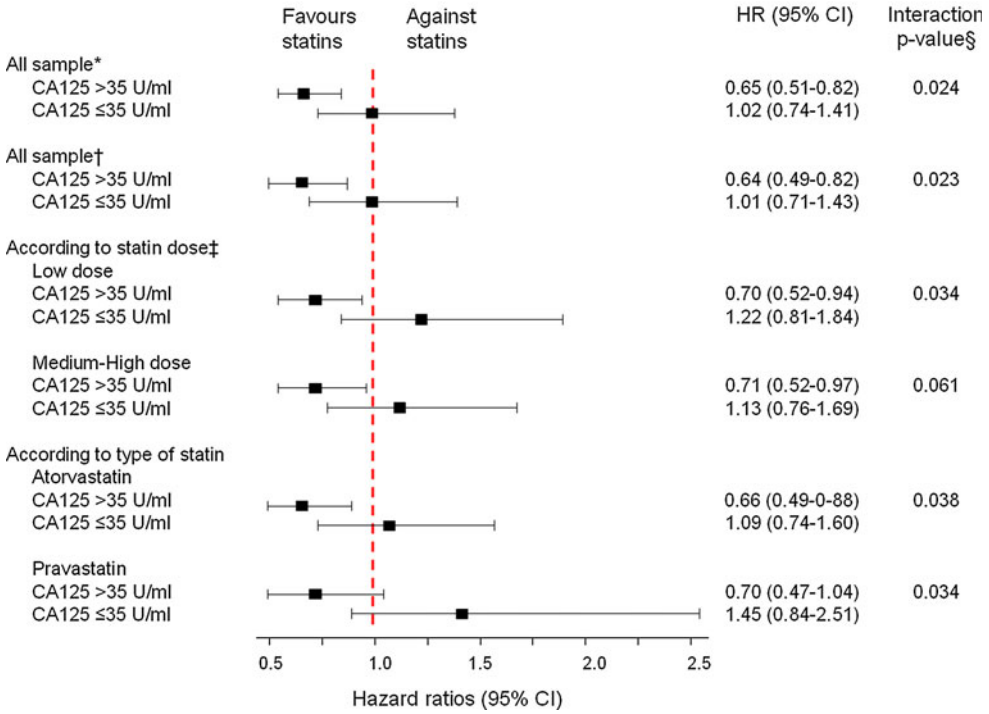

Fig. 2 Reproduced with permission from Rev Esp Cardiol 2011; 64:1100–1108. Total mortality adjusted HR (95 % CI) for the effect of statins among patients with CA125 >35 U/ml. *Model 1: Final multivariate Cox model adjusted by age, gender, previous admission for AHF (yes/no), admission as acute decompensate heart failure (yes/no), last NYHA 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 LVEF <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 ($p = 0.579$). †Model 2: Multivariate Cox model adjusted by the same set of the covariates of model 1 plus main variables associated with 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 ($p = 0.555$). ‡Dose categories included the following: low dose (atorvastatin ≤10 mg, simvastatin ≤20 mg, pravastatin ≤40 mg, lovastatin ≤40 mg, and fluvastatin ≤80 mg) and medium–high dose (atorvastin ≥20 mg and simvastatin ≥40 mg). §Interaction p value refers to the interaction between treatment with statins and CA125-binary status. *HR* hazard ratio, *CI* confidence interval, *CA125* antigen carbohydrate 125, *AHF* acute heart failure, *ADHF* acute decompensate heart failure, *NYHA* New York Heart Association Functional Class, and *LVEF* left ventricular ejection fraction

CA125. Indeed, we found that the risk of mortality was determined by the interaction between the use of statins and the category of CA125 (above/below 35 U/ml), with an adjusted p value = 0.024. Statin use was associated with a significant mortality reduction in patients with elevated CA125 values (HR = 0.65; 95 % CI 0.51–0.82; $p < 0.001$), but not in those with normal values (HR = 1.02; 95 % CI 0.74–1.41; $p = 0.907$) [60] (Fig. 2). Despite the fact that current evidence does not support the use of statin treatment in patients with HF [61], the above results are very encouraging and indirectly support a complex interplay between CA125, inflammation milieu, statins, and prognosis in HF [62–64].

CA125 and BUN

Even though still controversial, numerous studies have shown that a higher dose of loop diuretic is associated with a higher risk of adverse outcomes in patients with HF [65–67]. As a theoretical surrogate of fluid overload, our group reported that the high mortality risk associated with the use of high-dose loop diuretics was strongly dependent on serum levels of blood urea nitrogen (BUN) and CA125 (p for interaction <0.001). We showed that high-dose loop diuretics was associated with higher risk of mortality in most patients; however, we identified, within this population, an important subgroup (32 %) in which the use of high-dose loop diuretics was associated with a 27 % adjusted risk reduction [68]. This subgroup was characterized by having elevated BUN and CA125 (BUN ≥24.8 mg/dl and CA125 >35 U/ml) (Fig. 3). These results are in agreement with recent studies that suggest that the degree of renal dysfunction and/or neurohormonal activation depends not only on arterial hypoperfusion but also on venous congestion [69, 70].

Transcatheter aortic valve implantation

Recently, the role of CA125 as a predictive biomarker was evaluated in 228 patients with aortic valve disease who have undergone a TAVI procedure. In a multivariable analysis

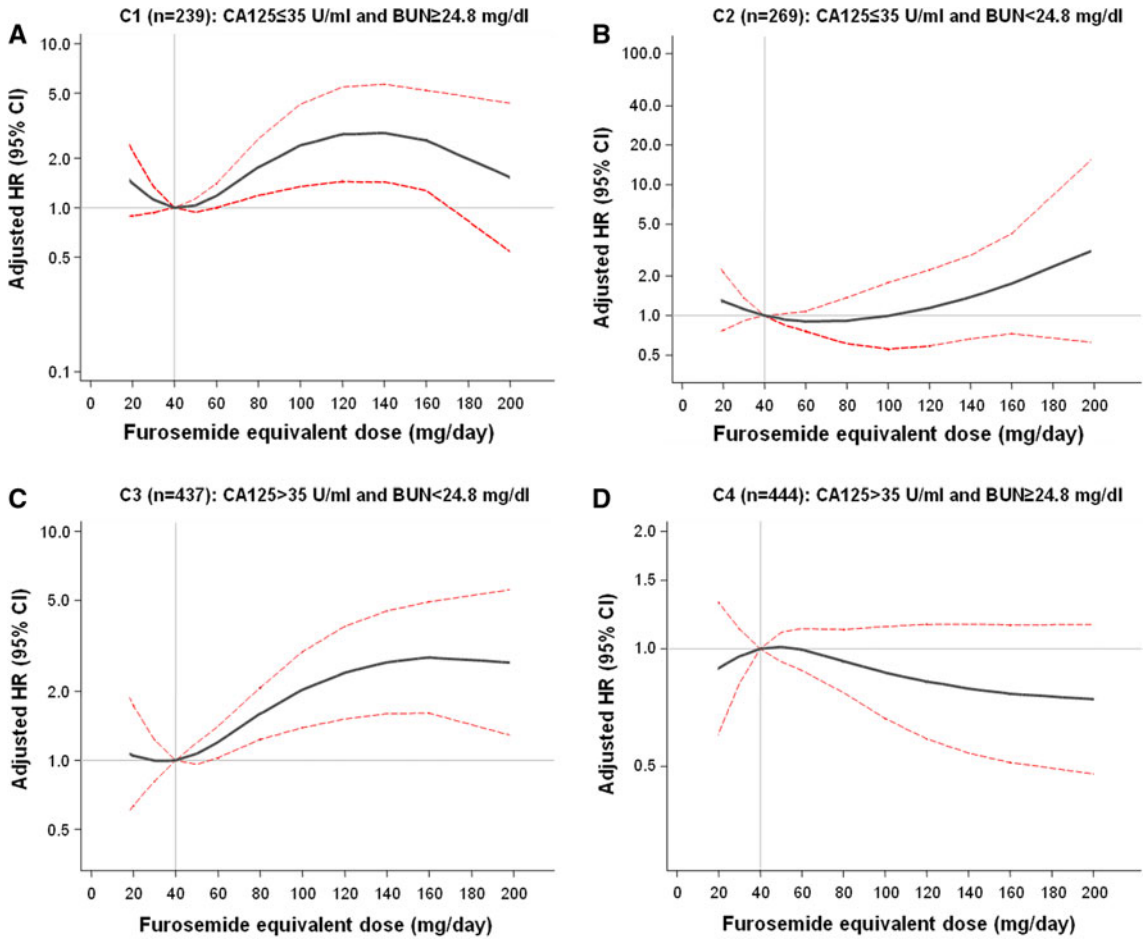

Fig. 3 Reproduced with permission from Eur J Heart Fail 2012; 14: 974–984. Adjusted HR (95 % CI) for the effect of furosemide equivalent dose on mortality at each BUN-CA125 category. Furosemide equivalent dose is modeled with 4 degrees of freedom RCS. Hazard ratios are calculated against the value of 40 mg/days as reference point. *BUN* blood urea nitrogen *CA125* antigen carbohydrate 125; *HR* hazard ratio, *CI* confidence interval, and *RCS* restricted cubic splines

adjusted for logistic Euro Score, NYHA class III/IV, and device success, baseline values of CA125 (dichotomized by the median, 15.7 U/ml) independently predicted death (HR 2.18; 95 % CI 1.11–4.26; $p = 0.023$) and major cardiac events (HR 1.77; 95 % CI 1.05–2.98; $p = 0.031$). Interestingly, in a longitudinal analysis, CA125 (as a time-varying exposure) was also associated with both endpoints [50].

Future directions

In view of the encouraging evidence presented, our group has designed a multicenter, randomized, open, and parallel clinical trial [CHANCE-HF (Eudract 2011-000414-20)], where 380 patients recently hospitalized for AHF and having high plasma levels of CA125 (>35 U/ml) were randomized either to the CA125-guided-therapy arm or to conventional treatment strategy. Physician in charge of patients allocated to the CA125 guided-therapy are encouraged to tailor the type and dose of diuretics and statins according to levels of CA125. The goal is to intensify the treatment in order to keep the CA125 values below 35 U/ml. After 1 year follow-up, these two groups will be compared on hard clinical endpoints (all-cause mortality and/or readmission for AHF). This project was launched in December 2011, and the follow-up of patients is currently ongoing.

Comparison with other biomarkers

Table 1 summarizes the most important current clinical applications of different biomarkers related to congestion and inflammation in HF. Except for HF diagnosis, CA125 has shown potential utility for risk stratification, monitoring, and tailoring therapy, properties that do not meet other biomarkers together (Table 1). We envision these potential clinical advantages over natriuretic peptides, and other biomarkers may be explained, at least in part, by (a) a prolonged half-life (longer than 1 week), providing higher reliability over time (lesser noise variability) [54] and (b) CA125 levels appear not to be substantially modified by conditions known to be common confounders in HF patients, such as age and renal dysfunction [22, 32, 49]. In addition, some other logistical advantages deserve to be highlighted, such as low cost, wide availability, and standardized and highly reproducible method of measurement.

Strengths and limitations of CA125 as a biomarker in HF

There are, however, some areas of uncertainty and pitfalls that should to be stated: (a) the pathophysiology of CA125

Table 1 Clinical considerations between CA125 and other biomarkers in heart failure

	Mechanism of production	Half-life	Useful for diagnosis	Useful for risk stratification	Useful for monitoring	Therapeutic implications	Cost
CA125 [7, 10, 22, 32, 49]	Activation of mesothelial cells	Weeks	−	+	+	+	<5 USD
Natriuretic peptides [4, 55, 71–73]	Myocyte stretch	20–30 min	++	++	±	±	>20 USD
Interleukins (IL-1, IL-6, TNF-α) [74]	Inflammatory mediators	Minutes–hours	−	+	−	±	10–20 USD
CRP [58, 75, 76]	Liver production in response to IL-6 ↑	Hours–few days	−	+	?	+	>20 USD
Galectin-3 [71–73, 76]	Macrophage activation	?	+	+	+	+	>20 USD
ST-2 [71–73, 77]	Myocyte/fibroblast mechanical stretch	?	+	+	+	?	>20 USD

CA125, antigen carbohydrate 125; IL-1, interleukin 1; IL-6, interleukin 6; TNF-α, tumor necrosis factor-α; CRP, C-reactive protein; ST-2, suppression of tumorigenicity 2; ?, Unknown; −, Negative results; ±, Conflictive results; +, Potential; ++, Accepted

elevation in HF is not fully characterized and (b) CA125 cannot be used with diagnostic purposes because it is elevated in a wide-range number of conditions not related to HF such as malignancies, pregnancy, benign pelvic tumors, pelvic inflammatory diseases, peritonitis, and many diseases leading to pleural effusion or ascites [10].

Conclusions

We believe that the present evidence endorses a potential role of CA125 as a biomarker for clinical use in HF. This biomarker fulfills most of the required criteria for being used in daily clinical practice: (a) it is widely available, cheap, and measured with standardized methods; (b) it is related to common pathophysiological processes in HF, such as fluid overload and heightened inflammatory activity; (c) it is associated with severity of HF and worse adverse outcomes, providing additional information over standard risk factors; (d) serial changes are related to clinical status and prognosis; and (e) it may be a useful tool for guiding therapy.

Further studies, especially in more controlled scenarios, are warranted to elucidate the pathophysiology, biological role, and the utility of this biomarker for risk stratification, monitoring, and guiding therapy in subjects with HF.

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Conflict of interest Drs. Julio Núñez, Gema Miñana, Eduardo Núñez, Francisco J. Chorro, Vicent Bodí, and Juan Sanchis have no conflicts of interest or financial ties to disclose.

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