ESC European Society of Cardiology

European Journal of Heart Failure (2021)
doi:10.1002/ejhf.2295

REVIEW

Antigen carbohydrate 125 as a biomarker in heart failure: a narrative review

**Julio Núñez[1,2,3], Rafael de la Espriella[1,2], Gema Miñana[1,2,3], Enrique Santas[1,2], Pau Llácer[4], Eduardo Núñez[1], Patricia Palau[2], Vicent Bodí[1,2,3], Francisco J. Chorro[1,2,3], Juan Sanchis[1,2,3], Josep Lupón[3,5,6,7], and Antoni Bayés-Genís[3,5,6,7]*

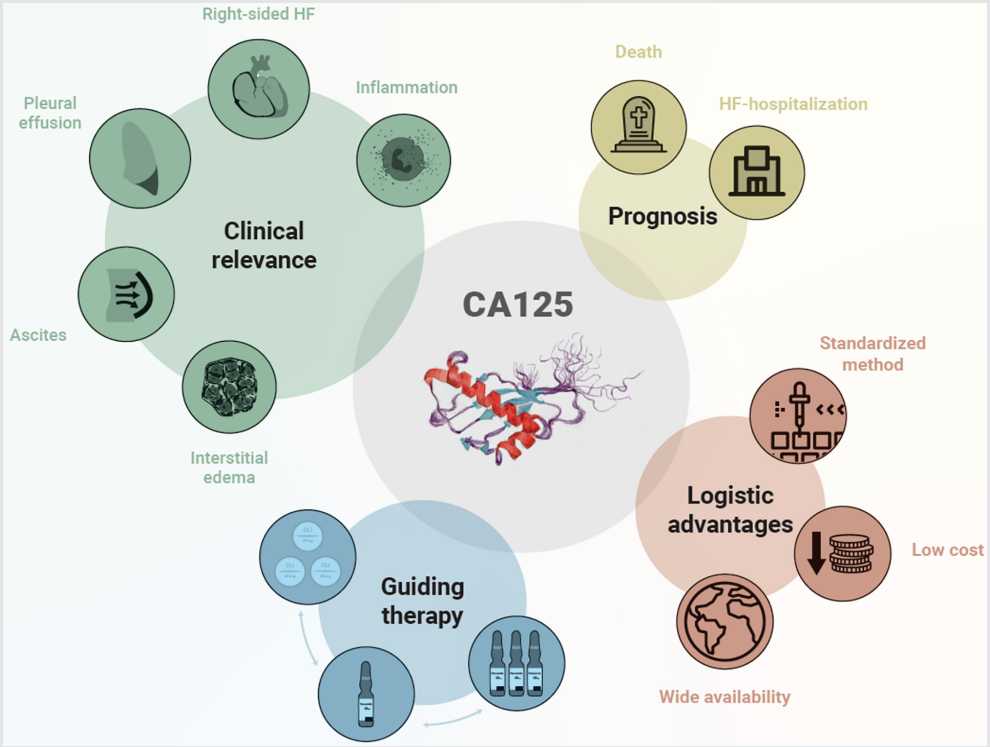
[1]Cardiology Department and Heart Failure Unit, Hospital Clínico Universitario de Valencia, INCLIVA, Valencia, Spain; [2]Universitat de Valencia, Valencia, Spain; [3]CIBER Cardiovascular, Madrid, Spain; [4]Internal Medicine Department, Hospital Universitario Ramón y Cajal, Madrid, Spain; [5]Cardiology Department and Heart Failure Unit, Hospital Universitari Germans Trias i Pujol, Badalona, Spain; [6]Department of Medicine, Autonomous University of Barcelona, Barcelona, Spain; and [7]ICREC Research Program, Germans Trias i Pujol Health Science Research Institute, Badalona, Spain

Received 22 January 2021; revised 5 July 2021; accepted 8 July 2021

Congestion explains many of the signs and symptoms of acute heart failure (AHF) and disease progression. However, accurate quantification of congestion is challenging in daily practice. Antigen carbohydrate 125 (CA125) or mucin 16 (MUC16), a large glycoprotein synthesized by mesothelial cells, has emerged as a reliable proxy of congestion and inflammation in patients with heart failure (HF). In AHF syndromes, CA125 is strongly associated with right-sided HF parameters and a higher risk of adverse clinical events beyond standard prognostic factors, including natriuretic peptides. Furthermore, CA125 has the potential for both monitoring and guide HF treatment following a decompensated HF event. The wide availability of CA125 in most clinical laboratories, together with its standardized measurement and reduced cost, makes this marker attractive for routine use in decompensated HF. Further research is required to understand better its biological role and its promising utility as a tool to guide decongestive therapy in HF.

*Corresponding author. Heart Institute and Heart Failure Unit, Hospital Universitari Germans Trias i Pujol, Badalona, Spain; Department of Medicine, Autonomous University of Barcelona, Barcelona, Spain. Email: abayesgenis@gmail.com

Graphical Abstract



Scheme of the pathophysiology, clinical utility, and logistic advantages of antigen carbohydrate 125 (CA125) in heart failure (HF). In acute HF syndromes, plasma CA125: (i) is associated with proxies of clinical congestion, right-sided HF, and inflammation; (ii) is positively associated with a higher risk of death and HF readmission; (iii) has emerged as a valuable tool for tailoring diuretic therapy; and (iv) is cheap, and widely available.

Keywords Heart failure • CA125 • MUC16

Introduction

The pathophysiology of acute heart failure (AHF) syndromes is complex, heterogeneous, and not completely understood.[1–3] In these clinical scenarios, congestion plays a key pathophysiological role and explains most of the symptoms and signs.[1–3] In contrast with its importance, the management of congestion in daily practice is highly empirical, highlighting the unmet need for novel biomarkers to improve diagnostic accuracy, risk stratification, monitoring, and therapy guidance. There is renewed interest in determining how these new markers can provide much additional information over the clinical condition, echocardiographic parameters, and natriuretic peptides (NPs) in the era of precision medicine.[4]

Carbohydrate antigen 125 [CA125, also called cancer antigen 125 or carcinoma antigen 125 and mucin 16 (MUC16)] is a complex glycoprotein encoded by the MUC16 gene in humans.[5–7] Initially recognized in 1981 by the 125th monoclonal antibody produced against an ovarian cancer cell line, this marker contains approximately 22 000 amino acids, making it the largest membrane-associated mucin.[5–7] It is composed of three different domains: a N-terminal domain, a tandem repeat domain, and a C-terminal domain. The N-terminal and tandem repeat domains are both entirely extracellular and highly glycosylated (*Figure 1*). All mucins contain a tandem repeat domain that repeats amino acid sequences high in serine, threonine, and proline.[5,6] The C-terminal domain has multiple extracellular sea urchin sperm protein, enterokinase, and agrin (SEA) modules,[5,6] a transmembrane domain, and a cytoplasmic tail. The extracellular region of MUC16 can be released from the cell surface via proteolytic cleavage, making it a valuable circulating biomarker[5,6] (*Figure 1*). CA125 is mainly synthesized by mesothelial cells in the pericardium, pleura, or peritoneum.[5,6] Although its biological role is not well understood, it appears to be involved in multiple pathways, including cell-mediated immune responses.[5–7]

CA125 has been studied extensively as a circulating biomarker for monitoring ovarian cancer.[5–7] However, elevated values can also

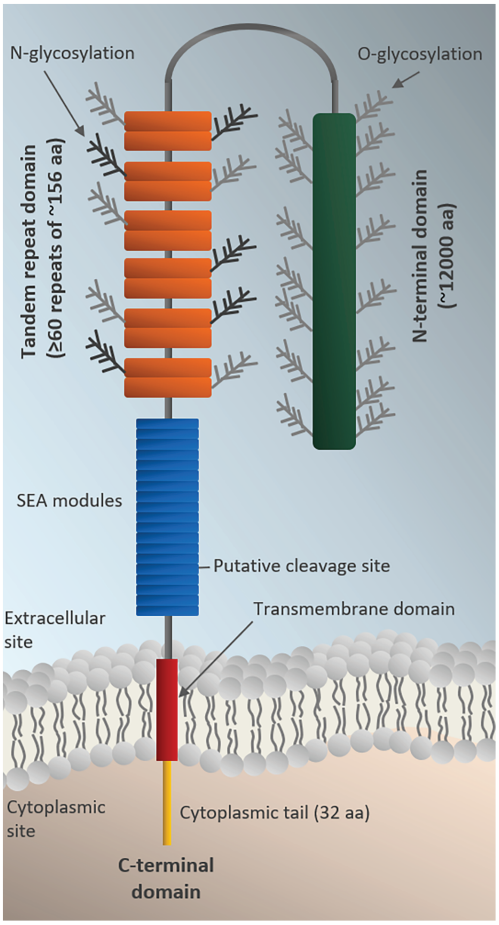


Figure 1 Schematic representation of carbohydrate antigen 125 (CA125) structure. CA125 contains three major domains [the N-terminal domain (>12 000 amino acids (aa), heavily glycosylated), the tandem repeat domain, which is interspersed with the sea urchin sperm protein, enterokinase, and agrin (SEA) domain, and the C-terminal domain]. The tandem repeat domain contains 18–60 repeats each with ~156 aa. The C-terminal domain is further divided into an extracellular portion, which contains the putative cleavage site, a transmembrane domain, and a cytoplasmic tail of 32 aa.

be found in other malignancies as well as in benign conditions.[7–10] In recent years, increasing evidence supported the use of CA125 in cardiovascular diseases, particularly in decompensated heart failure (HF) and in the transition to clinical stability.[9,10] Indeed, high CA125 levels have been found elevated in almost two-thirds of patients with AHF and showed to be highly correlated to the severity of congestion.[9,10]

This review focus on the following points: (i) pathophysiology and biological role of CA125 up-regulation in HF; (ii) risk stratification; (iii) monitoring and therapy guidance; (iv) comparison with NPs; (v) CA125 and other HF biomarkers; (vi) clinical interpretation; (vii) logistic advantages; and (viii) gaps in evidence and future directions.

Pathophysiology and biological role of CA125 up-regulation in heart failure

CA125 is a large transmembrane glycoprotein generally expressed on the surface of cells derived from most mesothelial membranes.[5–7] In contrast to malignancies that overexpress mucins, the myocardium is not a source of CA125.[5–7] The mechanisms leading to CA125 up-regulation in decompensated HF are not well characterized; however, both haemodynamic and inflammatory stimuli seems to play a crucial role[8–10] (*Figure 2*). Activation of mesothelial cells in response to increased hydrostatic pressures, mechanical stress, and cytokine activation has been suggested to be the crucial mechanism promoting the synthesis of CA125.[11–13] Using a mesothelial cell monolayer as an *in vitro* model, Zeillemaker *et al.*[12] reported that CA125 secretion is enhanced by inflammatory cytokines, such as interleukin-1, tumour necrosis factor-α, and lipopolysaccharide. Recently, endoplasmic reticulum oxidoreductase 1 L (ERO1L), an enzyme that plays an important role in the development of lung cancer, has been described to regulate the expression of MUC16 through the secretion of cytokines in a positive feedback form.[14]

In HF, cumulative evidence supports the positive association of plasma levels of CA125 with congestion (*Table 1*)[15–19] and inflammation (*Table 2*).[12,18,20,21] These findings were recently confirmed in a large multinational, prospective, observational cohort that included patients with worsening HF.[18] In this study, CA125 clustered with a clinical congestion score, biomarkers of congestion [amino-terminal pro-brain natriuretic peptide (NT-proBNP) and bio-adrenomedullin], and inflammatory markers (interleukin-6 and growth differentiation factor 15). Considering that congestion and inflammation are largely inter-related,[11,22] long-term venous congestion may also stimulate the inflammatory system, resulting in cytokine-mediated CA125 synthesis and release by mesothelial cells, even in the absence of clinically evident serosal effusion.[20,23] Indeed, we reported a sustained reduction in plasma CA125 in parallel with improvement in the patient's clinical and congestion status after the onset of peritoneal dialysis in patients with refractory congestive HF, despite the serosal irritation induced by infusion of the osmotic solution into the peritoneum.[23] In addition, in a cohort of 2949 patients admitted with AHF, pleural effusion and the severity of tricuspid regurgitation (as a proxy of right-sided HF) were the two main independent predictors of CA125 variability.[17] In a more recent study in 191 patients admitted for AHF, CA125 was strongly and independently associated with intravascular parameters (inferior vena cava diameter) and clinical congestion (peripheral oedema and pleural effusion). In this study, NT-proBNP was marginally associated with the presence of pleural effusion and inferior vena cava diameter but not related to peripheral oedema.[19] More recently, CA125, but not NT-proBNP, predicted the existence of congestive intrarenal venous flow in patients with AHF.[24]

The biological role of CA125 is mostly unknown. It has been suggested that CA125 protects the epithelial surface from mechanical stress by acting as a lubricant.[5–7] Moreover, the interaction between transmembrane mucins and other mesothelial/interstitial

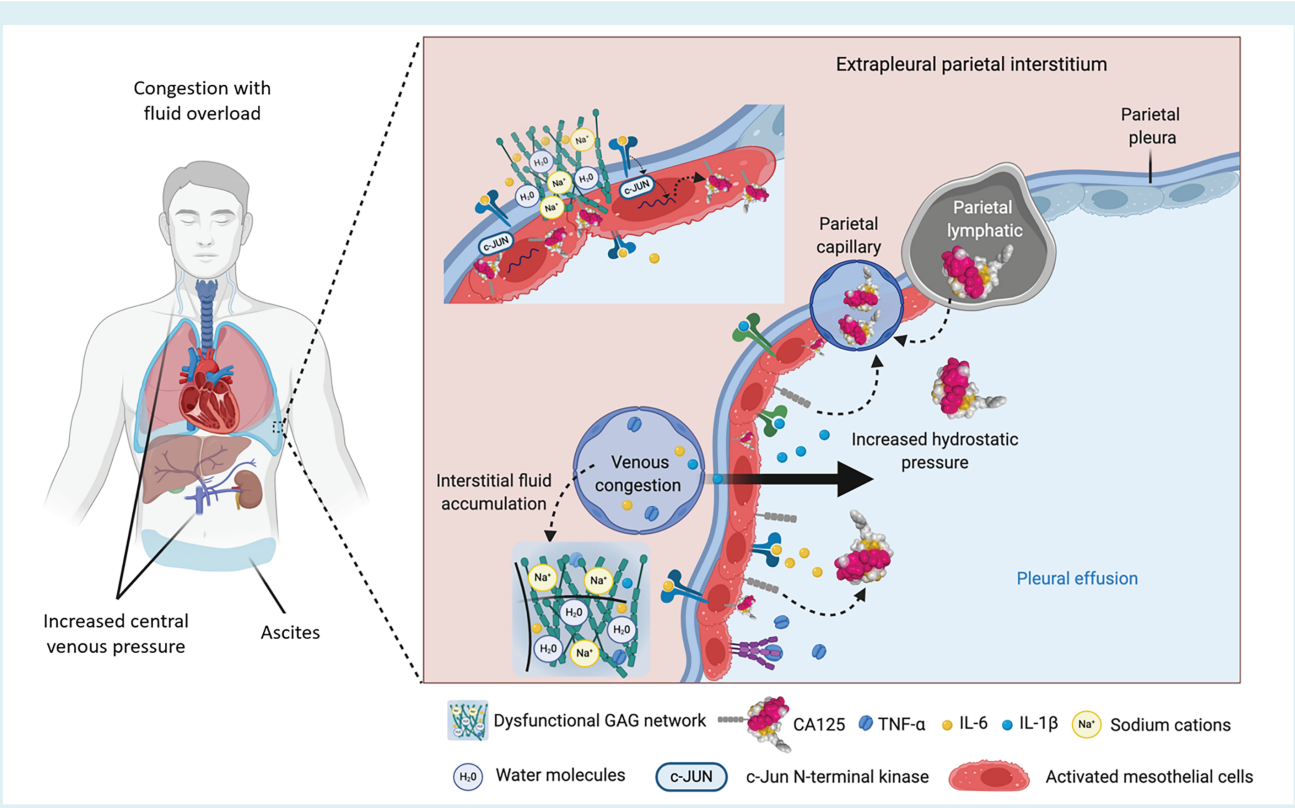


Figure 2 Pathophysiology of carbohydrate antigen 125 (CA125) in heart failure. Systemic and pulmonary venous congestion promote the transudation of plasma fluid into the interstitium. A dysfunctional interstitial glycosaminoglycan (GAG) network further facilitates this process because of longstanding congestion and sodium accumulation. Besides, lymphatic drainage becomes less efficient, promoting fluid accumulation. The injury resulting from mechanical stress and inflammatory stimuli activate mesothelial cells, leading to CA125 synthesis via c-Jun N-terminal kinase pathways. IL, interleukin; TNF, tumour necrosis factor.

proteins seems to support the role of CA125 in processes involving fluid and cell transport, inflammation, tissue repair, and tumour dissemination.[5–7] Also, CA125-associated N-glycans are involved in modulating the immune innate and adaptive response.[13] For example, CA125 has been shown to suppress natural killer activity by interacting with several carbohydrate-binding proteins, including the galectin family.[21,25] Indeed, CA125 has been demonstrated to serve as a lectin counter-receptor, exhibiting a higher affinity for galectin-1 and 3.[21,25] It is thought that CA125 may play a role in the cardiac remodelling process by regulating galectin activity or even modifying the mass and stiffness of the intercellular matrix. For instance, in patients admitted with decompensated HF, positive correlations were reported between galectin-3 and proxies of inflammation (interleukin-6 and tumour necrosis factor-α) only in those with CA125 values above the median but not in the rest.[21] Further studies are warranted to define its biological role in patients with HF. The proposed biological roles of CA125 in HF are illustrated in *Figure 3*.

CA125 and risk stratification

Nägele *et al.*[26] first described in 1999 higher levels of CA125 in 71 patients with HF on a transplant list. In this study, CA125 levels significantly correlated with neurohormones and filling pressures.[26] A plethora of studies over the last two decades have re-evaluated and confirmed the prognostic role of CA125 in HF (*Table 3*).[15,16,18,27–30] In summary, CA125 has shown a positive association with adverse clinical outcomes, particularly in the setting of AHF.[15,16,27–30] D'Aloia *et al.*[15] reported a significant association between CA125 levels >35 U/mL with death and readmission for worsening HF in a cohort of 286 congestive HF patients with reduced ejection fraction. Yilmaz *et al.*[16] reported a positive association between CA125 and the risk of mortality and readmission in a cohort of 150 stable patients with systolic dysfunction. Noteworthy, these findings in stable HF have been replicated in patients with AHF. In 529 patients admitted with AHF, CA125 emerged as an independent predictor of mortality at 6 months.[27] Notably, CA125 also provided additive prognostic value to standard risk prognostic factors, including NPs, in a cohort of 1111 patients admitted for AHF.[28] In this study, the combined use of CA125 and NPs improved 6-month mortality risk stratification compared to either of them alone.[28] A meta-analysis of 16 studies (15 cohort studies and one randomized trial) including 8401 AHF patients with either reduced or preserved ejection fraction reported that high CA125 levels were associated with an increased risk of all-cause mortality [hazard ratio

Table 1 Studies on carbohydrate antigen 125 and proxies of heart failure severity and congestion

Author	Year	Type of study	N	Patient population	CA125 values	Results
Seo *et al.*[a]	1993	Observational	57	Pericardial effusion of diverse aetiologies	Malignant disease: mean 163 ± 32 U/mL Benign condition: mean 154 ± 28 U/mL	CA125 serum levels were high in patients with large effusion and decreased as effusion decreased. No differences were found between CA125 levels and the nature of the underlying disease.
Nägele *et al.*[a]	1999	Observational	71	Advanced HF before and after HTx	401 ± 259 U/mL	CA125 correlated significantly with neurohormones and high-filling pressures.
Duman *et al.*[a]	2003	Observational	90	Mitral stenosis	Not reported	Elevated CA125 levels were detected in patients with severe symptomatic mitral stenosis and normal LVEF and LV dimensions.
D'Aloia *et al.*[15]	2003	Observational	286	Acute HFrEF	68 ± 83 U/mL (range 3–537)	Serum levels of CA125 correlated with clinical status (NYHA class), invasive and non-invasive haemodynamic abnormalities (particularly RAP and PAWP).
Turk *et al.*[a]	2003	Observational	36	Chronic HF vs. control group	100.0 ± 129.4 U/mL in patients with pleural effusion, 36.5 ± 35.2 U/mL in those without pleural effusion, and 8.9 ± 6.1 U/mL in the control group	Serum CA125 levels were higher in patients with HF and pleural effusion compared with both patients without pleural effusion and the control group.
Kouris *et al.*[a]	2005	Observational	77	AHF	22.4 U/mL (11.5–48.9)	Serum CA125 levels correlated with clinical status and the presence of fluid congestion (rales on auscultation, signs of congestion on chest X-ray and ankle oedema).
Varol *et al.*[a]	2005	Observational	44	Chronic HF vs. control group	81.9 ± 91 U/mL in the patient group and 7.5 ± 4.8 U/mL in the control group	CA125 seems to be specifically related to the presence and severity of HF and the presence of pleural effusion.
Duman *et al.*[a]	2008	Observational	49	Advanced HFrEF	44.0 U/mL (17.7–140)	BNP and left atrial volume were independent predictors of CA125. Most patients with elevated CA125 levels (75%) had no pleural or pericardial effusion.
Vizzardi *et al.*[a]	2008	Observational	200	Chronic HFrEF	24.79 ± 113.3 U/mL	CA125 levels correlated with Doppler mitral flow E/A ratio, isovolumetric relaxation time, and myocardial performance index.
Yilmaz *et al.*[16]	2011	Observational	150	Chronic HF	Not reported	CA125 was associated with LVEF, RV dilatation, and presence of pericardial effusion.
Yilmaz *et al.*[a]	2011	Observational	40	COPD patients hospitalized with exacerbation	33.94 U/mL (5.51–351) in the patient group and 9.76 U/mL (0–60.97) in the control group	CA125 levels were significantly higher in patients with RV failure, and CA125 levels were finely correlated with markers of RV dysfunction.
Karaca *et al.*[a]	2012	Observational	77	Non-ischaemic dilated cardiomyopathy	13.3 U/mL (3.8–465.5)	Increased CA125 levels were associated with LV volumes, LVEF, LV filling pressures, PASP, and the degree of functional mitral regurgitation.
Huang *et al.*[a]	2013	Observational	191	AHF	Not reported. Stratified according to CA125 levels: normal (CA125 ≤35 U/mL), and high (CA125 >35 U/mL)	CA125 levels were associated with the presence of SCE. In the absence of SCE, CA125 levels were also higher in HF patients than in non-HF patients and correlated with systemic inflammation and oxidative stress.
Zhuang *et al.*[a]	2014	Meta-analysis	4159 (23 studies)	Acute and chronic HF	Not reported	Positive correlation with natriuretic peptides, inflammatory cytokines, clinical systemic congestion surrogates, and NYHA functional class.
Miñana *et al.*[17]	2020	Observational	2949	AHF	58.1 U/mL (25–129)	Clinical surrogates of congestion and TR severity were the main factors associated with CA125.
Núñez *et al.*[18]	2020	Observational	2516	Worsening HF	38.6 U/mL (16–125)	Circulating levels of CA125 were associated with a congestion clinical score.
Llàcer *et al.*[19]	2021	Observational	191	AHF	58 U/mL (22,7–129)	CA125 was independently associated with congestion parameters such as inferior vena cava diameter, peripheral oedema, and pleural effusion.

AHF, acute heart failure; BNP, brain natriuretic peptide; CA125, carbohydrate antigen 125; COPD, chronic obstructive pulmonary disease; HF, heart failure; HFrEF, heart failure with reduced ejection fraction; HTx, heart transplantation; LV, left ventricular; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; PASP, pulmonary artery systolic pressure; PAWP, pulmonary artery wedge pressure; RAP, right atrial pressure; RV, right ventricular; SCE, serous cavity effusion; TR, tricuspid regurgitation.
[a]The complete list of references is detailed in online supplementary *File S1*.

Table 2 Carbohydrate antigen 125 and inflammation

Author	Year	Type of study	N	Patient population	Inflammatory markers	Results
Zeillemaker *et al.*[12]	1994	*In vitro*	–	Mesothelial cells from human omentum	IL-1β, TNF-α, lipopolysaccharide from *E. coli*	Human mesothelial monolayers secrete CA125 preferentially from their apical surfaces. The secretion of CA125 can be enhanced by the inflammatory cytokines IL-1β, TNF-α, and lipopolysaccharide from *E. coli*.
Zeimet *et al.*[a]	1997	*In vitro*	–	Ovarian cancer cell lines and human peritoneal mesothelial cells	TNF-α, IL-1β, IFN-γ	CA125 measurements in the culture medium clearly indicated differences in the pattern of CA125 expression and release between normal and malignant cells under the influence of inflammatory cytokines.
Kosar *et al.*[a]	2006	Observational	68	35 chronic HF patients and 33 normal controls	TNF-α, IL-1β, IL-6, and IL-10	CA125 levels were significantly increased in HF patients (with and without serosal effusion). Increased serum CA125 levels were positively correlated with serum TNF-α, IL-6, and IL-10 levels.
Miñana *et al.*[20]	2010	Observational	132	AHF	TNF-α, IL-1β, IL-6	CA125 levels above median (>60 U/mL) were associated with higher levels of TNF-α, IL-6 and IL-1β and lower relative lymphocyte count.
Hamdy *et al.*[a]	2011	Observational	90	60 HF patients, and 30 normal controls	TNF-α, IL-6, and IL-10, T-cell activation marker (sIL-2R/CD25)	CA125 was elevated in HF patients, and correlated with serum TNF-α, IL-6, and sIL-2R/CD25 levels.
De Gennaro *et al.*[a]	2012	Observational	106	48 patients with AF and 58 control patients in sinus rhythm	hs-CRP, IL-8, IL-6, sIL-2R, TNF-α	Increased circulating levels of IL-8, sIL-2R and TNF-α were found in the group of patients with AF. CA125 levels were related to TNF-α, IL-6 and IL-10 levels.
Núñez *et al.*[21]	2015	Observational	264	AHF	Gal-3	Gal-3 was strongly associated with greater inflammation burden in those with high CA125 (>67 U/mL).
Stanciu *et al.*[a]	2018	Observational	62	32 chronic HF patients and 30 healthy controls	IL-6, IL-1β, IL-8, TNF-α and IL-4	1) CA125 levels were closely related to IL-1β in serum sampled from coronary sinus; 2) peripheral CA125 was closely related to peripheral IL-6, peripheral TNF-α and LVEF; 3) CA125 was positively correlated with NT-proBNP both in coronary sinus and peripheral circulation.
Bulska-Będkowska *et al.* [a]	2019	Observational, cross-sectional	1565	Caucasian women aged 65–102 years	IL-6, and NT-proBNP	The concentration of CA125 was independent and positively related to age, history of hospitalization for HF, IL-6, and NT-proBNP.
Núñez *et al.*[18]	2020	Observational, prospective	2516	Worsening HF	GDF-15, IL-6	CA125 grouped with biomarkers of congestion (NT-proBNP and adrenomedullin) and inflammation (IL-6 and GDF-15).

AF, atrial fibrillation; AHF, acute heart failure; CA125, carbohydrate antigen 125; CD25, interleukin-2 receptor alpha chain; Gal-3, galectin-3; GDF-15, growth differentiation factor 15; HF, heart failure; hs-CRP, high-sensitivity C-reactive protein; IFN, interferon; IL, interleukin; LVEF, left ventricular ejection fraction; NT-proBNP, amino-terminal pro-brain natriuretic peptide; sIL-2R, soluble interleukin-2 receptor; TNF, tumour necrosis factor.
[a]The complete list of references is detailed in online supplementary *File S1*.

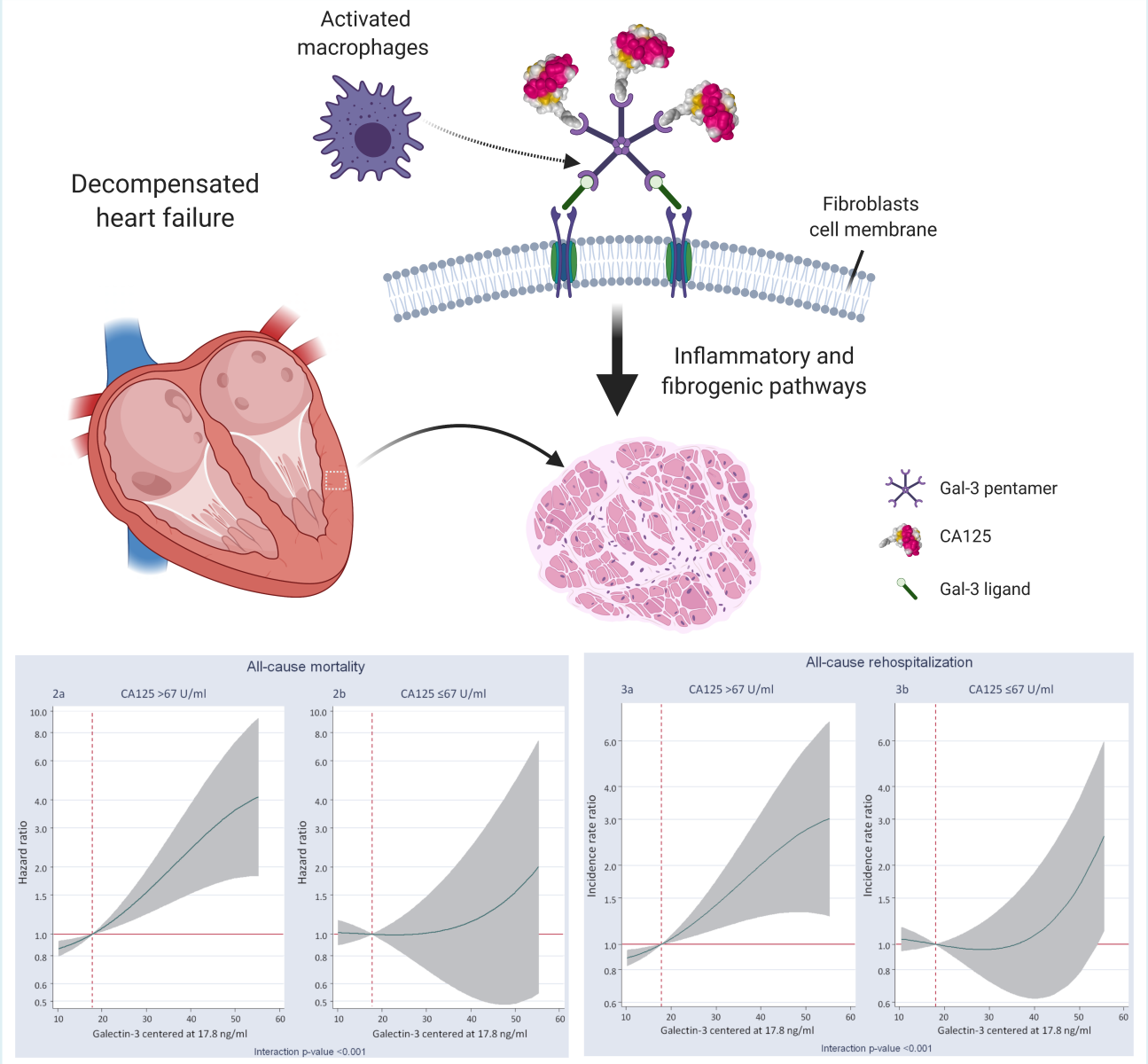


Figure 3 The proposed biological role of carbohydrate antigen 125 (CA125) in heart failure. Galectin-3 (Gal-3) is involved in adverse cardiac remodelling. CA125 has been recognized as a specific binding partner of galectin-1 and Gal-3 through its O-linked β-galactose-terminated oligosaccharide chains. The interaction between CA125 and Gal-3 may enhance the pro-fibrotic process and adverse cardiac remodelling. Adapted from Núñez *et al.*[24]

(HR) 1.44, 95% confidence interval (CI) 1.21–1.72; $P < 0.001$] and HF-related readmissions (HR 1.51, 95% CI 1.11–2.04; $P < 0.01$).[29]

More recently, the predictive value of CA125 has been replicated in a sub-analysis of the prospective multicentre BIOSTAT-CHF (Biology Study to Tailored Treatment in Chronic Heart Failure) study.[18] In this sub-study, including 2516 patients with worsening HF, CA125 was strongly associated with 1-year mortality risk and the composite of death/HF readmission. Interestingly, the risk associated with CA125 showed a non-linear pattern with an exponential increase in risk up to 200 U/mL and a plateau afterward.[18] This prognostic effect was independent of the severity of systemic congestion. Also, it did provide incremental discrimination over the BIOSTAT-CHF risk score, which includes robust and established prognostic factors with NPs among them.[18] In this same study, the association between CA125 and the 1-year risk of adverse outcomes was replicated in a validation cohort comprising 1630 patients with worsening HF.[18]

Table 3 Overview of the main studies of carbohydrate antigen 125 and prognosis in heart failure and other clinical scenarios

Author	Year	Type of study	N	Study population	Proposed CA125 cut-off	Results
D'Aloia *et al.*[15]	2003	Observational, prospective	286	Congestive HFrEF	35 U/mL	Compared to patients with CA125 <35 U/mL, those with higher CA125 levels were more likely to die or to be admitted with HF at 6-month follow-up.
Núñez *et al.*[27]	2007	Observational, prospective	529	AHF	35 U/mL	Compared to patients with CA125 <35 U/mL, those with higher CA125 levels were more likely to die at 6-month follow-up.
Núñez *et al.*[28]	2010	Observational, prospective	1111	AHF	60 U/mL	Compared to patients with CA125 <60 U/mL, those with higher CA125 levels were more likely to die at 6-month follow-up. The prognostic value was additive to BNP.
Yilmaz *et al.*[16]	2011	Observational, retrospective	150	Chronic HF	35 U/mL	Compared to patients with CA125 <35 U/mL, those with higher CA125 levels were more likely to die or to be admitted with HF.
Núñez *et al.*[28]	2010	Observational, prospective	1111	AHF	60 U/mL	Compared to patients with CA125 <60 U/mL, those with higher CA125 levels were more likely to die at 6-month follow-up. The prognostic value was additive to BNP.
Hung *et al.*[a]	2012	Observational, prospective	158	Women with chronic HFpEF, risk factors for HFpEF, and controls	Continuous and 17.29 U/mL	Patients with CA125 >17.29 U/mL had a greatest incidence of HF hospitalization at 2.3-year follow-up than those with lower CA125 values.
Husser *et al.*[a]	2013	Observational, prospective	228	Patients undergoing TAVI	Continuous and 15.7 U/mL	Serial CA125 measurements after TAVI were significant predictors of death and MACE. Patients with CA125 >15.7 U/mL showed an independent increase of risk for all-cause death or MACE after TAVI.
Zhuang *et al.*[a]	2014	Meta-analysis	4159 (23 studies)	Acute and chronic HF	Not specified	Patients with a higher risk of short- and long-term mortality showed higher CA125 levels.
Li *et al.*[29]	2018	Meta-analysis	8401 (16 studies)	AHF	Not specified	High CA125 levels were associated with an increase in the risk of death and HF readmission. High CA125 levels predicted an increased risk of hospital readmissions and mortality.
Falcao *et al.*[a]	2020	Observational, prospective	245	ST-elevation myocardial infarction	11.48 U/mL	Higher risk of 6-month all-cause mortality. Patients with CA125 ≥11.48 U/mL were more likely to die than those with CA125 <11.48 U/mL at 6-month follow-up.
Soler *et al.*[30]	2020	Observational, prospective	2961	AHF with TR	Continuous	Patients with higher CA125 values showed a higher risk of long-term all-cause mortality, with a greater effect in those with severe TR. NT-proBNP showed no prognostic value in those with severe TR.
Núñez *et al.*[18]	2020	Observational, prospective, multicentre	2516	Worsening HF	Quartiles, continuous	Patients with higher CA125 levels had a higher risk of 1-year all-cause mortality and the combined event of all-cause death and hospitalization for HF. CA125 levels were positively associated with clinical surrogates of congestion.

AHF, acute heart failure; BNP, brain natriuretic peptide; CA125, carbohydrate antigen 125; HF, heart failure; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; MACE, major adverse cardiac events; NT-proBNP, amino-terminal pro-brain natriuretic peptide; TAVI, transcatheter aortic valve implantation; TR, tricuspid regurgitation.
MACE was defined as a composite of all-cause death, AHF requiring admission, myocardial infarction, and stroke, whichever occurred first during follow-up.
[a]The complete list of references is detailed in online supplementary *File S1*.

Utility of CA125 for heart failure monitoring and therapy guidance

CA125 dynamics and heart failure monitoring

One of the most attractive properties of CA125 is the potential for monitoring the clinical course following HF decompensation. Small studies have reported that changes in CA125 parallel changes in clinical status (*Table 4*). More recent studies have also shown that changes within the first weeks following discharge are useful for risk stratification (*Table 4*).[15,23,26,31–33] In a cohort of 293 patients admitted for AHF (median CA125 during admission 72.6 U/mL), we found that CA125 decreased to ≤35 U/mL in 52.2% of the sample, decreased but remained >35 U/mL in 24.6%, and increased in 23.2% at the first outpatient visit after discharge (median 31 days). At a median follow-up of 18 months, patients who normalized CA125 values had the lowest risk of death.[31] In contrast, those with decreased but not normalized values and those with increased values had a higher adjusted risk of death (HR 2.41, 95% CI 1.40–4.17; $P = 0.002$; and HR 3.33; 95% CI 1.89–5.88; $P = 0.001$, respectively) compared to those with normal CA125 values.[31] In this same study, changes over time exhibited incremental reclassification indexes compared to the single measurement of CA125, or even changes in NT-proBNP.[32] The same categorical changes proved to be useful for the prediction of 6-month readmission. Patients who did not have CA125 ≤35 U/mL at the first outpatient visit had a threefold increased risk of 6-month HF readmission.[32]

More recently, the long-term evolving trajectory of CA125 measurements has been shown to be independently related to mortality.[33] In a study of 946 consecutive patients discharged for AHF, the long-term prognostic effect of repeated measures of CA125 (3402 observations during a mean follow-up of 2.64 years) markedly differed according to survival status (*Figure 4*). Most of the substantial decrease occurred within the first month after discharge, a behaviour that identified a lower risk subgroup. In contrast, CA125 remained elevated or increased in those who died at the end of the follow-up.[33] In this same study, longitudinal measurements of NT-proBNP were also associated with higher mortality risk, but, in contrast to changes in CA125, the magnitude of these changes was less notorious and attenuated over time (*Figure 4*). Interestingly, the transition from high to low or low to high CA125 during follow-up was strongly associated with a lower and higher risk of death, respectively.[33]

Some preliminary data suggest CA125 decreases in parallel to the intensification of depletive treatment. Indeed, the addition of acetazolamide to an intensive diuretic regimen or undergoing a continuous ambulatory peritoneal dialysis significantly decreased CA125 in patients with congestive refractory HF.[23,34] Likewise, a pilot study found a 1-month reduction of CA125 following empagliflozin administration in patients with stable HF and type 2 diabetes.[35]

In summary, this accumulated evidence endorses the role of CA125 in dynamic risk stratification. These reported risk estimates seem to be independent and additive to prognostic information gained by traditional proxies of HF severity and NPs.

CA125 for therapy guidance

In recent years, data from observational studies[36,37] and randomized clinical trials[38,39] highlighted the potential role of CA125 for tailoring diuretic therapy after AHF hospitalization. The CHANCE-HF trial enrolled 380 patients discharged for AHF and high CA125 levels (>35 U/mL); approximately half of them had HF with preserved ejection fraction.[38] In this study, the authors compared a CA125-guided therapy vs. standard of care. Briefly, the active arm consisted of intensifying diuretic treatment and monitoring frequency when CA125 increased or persisted at high levels during follow-up. When CA125 decreased below 35 U/mL, the protocol recommended down-titrating diuretics and spacing the frequency of outpatient visits. Patients allocated to the CA125-guided strategy had 50% more diuretic dose modification, and up to 21% of them received outpatient intravenous furosemide based on persistently high CA125 levels.[38] The guided strategy was superior to the standard of care in terms of reducing the risk of the composite 1-year death or AHF readmission. This reduction occurred at the expense of reducing both the risk of the first HF readmission and recurrent HF readmissions by 51% at 1-year follow-up.[38] More recently, the effect of the CA125-guided diuretic strategy on short-term renal parameters was evaluated in the IMPROVE-HF trial, an open-label multicentre randomized study of 160 patients with AHF and renal dysfunction at presentation (mean glomerular filtration rate 33.7 ± 11.3 mL/min/1.73 m^2).[39] In this challenging population, the CA125-guided group received higher furosemide equivalent dose than usual care when CA125 >35 U/mL (660 mg vs. 320 mg of intravenous furosemide over 72 h), with no difference in patients with low CA125 levels. Such approach translated into higher urine volume and early improvement in clinical and renal function parameters at 72 h, and a trend toward a lower risk of clinical adverse events at 30 days.[39]

CA125 and natriuretic peptides: different but complementary

Natriuretic peptides are secreted predominantly by the ventricular myocardium and used as a proxy of left ventricular myocardial stretch; thus, higher values are highly correlated with ventricular pressures and clinical severity.[40] Interestingly, and even though NPs and CA125 correlated positively, most of these associations are weak[9,10,18,28] or marginal.[17]

Several studies have also shown that CA125 provides additional prognostic information beyond NPs.[9,10,18,28,30] Interestingly, in some clinical scenarios characterized by overt systemic congestion and right ventricular dysfunction [e.g. patients with severe functional tricuspid regurgitation (TR)], CA125 may outperform NT-proBNP in predicting long-term mortality.[30] A recent study of 2961 patients discharged from AHF demonstrated a differential mortality risk association of CA125 and NT-proBNP across TR severity. Higher CA125 values were associated with elevated risk in the whole sample; however, the effect was greater in patients with severe TR.[30] Thus, we envision the complementary use of both markers for assessing the degree of each heart side participation, where CA125 and NPs mirrored the right and left-sided HF, respectively.

Table 4 Carbohydrate antigen 125 changes and clinical status

Author	Year	N	Follow-up	LVEF	Changes in CA125	Results
Nägele *et al.*[26]	1999	71	1.9 ± 0.8 years prior to HTx and 2.29 ± 1.85 years after HTx	HFrEF	Absolute changes	Decreased levels after HTx or stabilization and an increase during HF worsening
D'Aloia *et al.*[15]	2003	286	6 ± 3 months	HFrEF	Absolute changes	Significant decrease after clinical stabilization in those who NYHA class decreased by more than one grade
Faggiano *et al.*[a]	2005	30	5–20 days	HFrEF	Absolute changes	Significant decrease when a clinical improvement (reduction of at least one NYHA class) was reached.
Núñez *et al.*[31]	2012	293	18 (10–32) months	52.9% HFrEF	Categorical changes between discharge and first ambulatory visit (median 31 days after)	Normalization of CA125 (<35 U/mL) was associated with lower risk. Persistence of CA125 ≥35 U/mL was associated with higher risk.
Miñana Escrivá *et al.*[32]	2012	293	6 months	52.9% HFrEF	Categorical changes between discharge and first ambulatory visit (median 31 days after)	Elevation of CA125 levels (>35 U/mL) after the first weeks of admission for AHF (absolute, relative or categorical changes) was associated with an increased risk of readmission for AHF. Categorical changes showed the best discriminative accuracy.
Núñez *et al.*[23]	2012	25	6 and 24 weeks	40 ± 12%	Absolute changes	After peritoneal dialysis CA125 significantly decreased at 6 and 24 weeks, in parallel to a significant improvement in quality of life, 6MWT, and NYHA class.
Núñez *et al.*[33]	2017	946	2.64 (1.20–5.36) years	51% HFrEF	Absolute changes and dichotomic variable (35 U/mL)	Longitudinal trajectory of CA125 and NT-proBNP were associated with higher risk of mortality. Incremental prognostic value over single measurements.

6MWT, six-minute walk test; AHF, acute heart failure; CA125, carbohydrate antigen 125; HF, heart failure; HFrEF, heart failure with reduced ejection fraction; HTx, heart transplantation; LVEF, left ventricular ejection fraction; NT-proBNP, amino-terminal pro-brain natriuretic peptide; NYHA, New York Heart Association.
[a]The complete list of references is detailed in online supplementary *File S1*.

Other differences are worth noticing. First, the half-life of CA125 (range 5.1–12 days) is significantly higher than that of NPs (measured in minutes).[9,10] Indeed, the differences in the clinical information provided by NPs and CA125 could be viewed as the role played by serum glucose and glycosylated haemoglobin, respectively, in diabetes. Secondly, in contrast to NPs,[40] CA125 levels do not appear to be substantially modified by age and renal dysfunction.[17] Thirdly, the levels of this biomarker seem not to differ broadly across the spectrum of left ventricular ejection fraction.[17] However, its possible correlation with other parameters such as body mass index or other common comorbidities in HF has not been deeply evaluated. With these differences in mind, we expect advantages of CA125 over NPs in the following circumstances: patients with predominant right-sided involvement, particularly in those with HF with preserved ejection fraction, patients with more severe renal dysfunction, and in the elderly. Conversely, NPs may provide incremental clinical utility over CA125 in euvolaemic or mild congestive patients with predominant left-sided HF. Although a formal comparison between both biomarkers is warranted in the latter situations, we envision both biomarkers may play a complementary role in HF.

CA125 and other heart failure biomarkers

Beyond the reported positive association between NPs and some inflammatory markers with CA125, this glycoprotein has also correlated with other biomarkers in HF. For instance, in a large cohort of patients with AHF, CA125 was positively related to

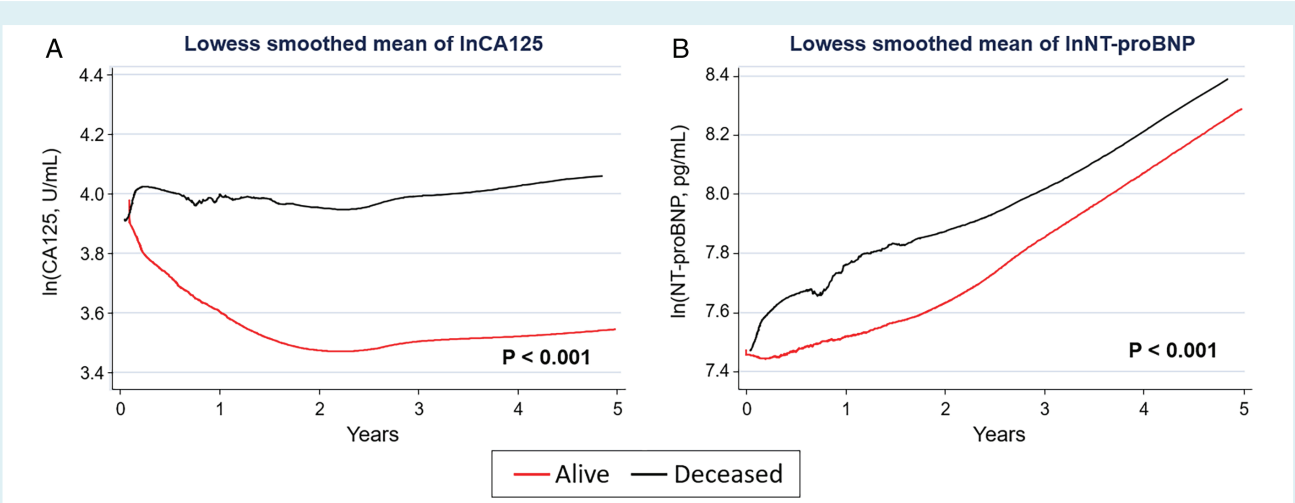


Figure 4 Longitudinal changes of carbohydrate antigen 125 (CA125) and amino-terminal pro-brain natriuretic peptide (NT-proBNP) after an acute heart failure event across patients' survival. Adapted from Núñez *et al.*[33]

bio-adrenomedullin, a surrogate of congestion. Interestingly, in a cluster analysis, both biomarkers grouped together.[18] A significant prognostic interaction showed a differential effect of galectin-3 across different levels of CA125 in patients with AHF.[21] In patients with CA125 levels above the median, galectin-3 was associated with a greater inflammatory burden and a higher risk of adverse events. Conversely, galectin-3 was not related to inflammatory activity or clinical outcomes in those with lower CA125 levels.[21] However, no studies have currently compared the clinical utility of CA125 vs. other emerging biomarkers of congestion or inflammation in decompensated HF.

Clinical interpretation

The clinical value of circulating levels of CA125 in HF is summarized in the *Graphical Abstract*. However, some issues are worth to know when interpreting plasma CA125 levels in patients with HF.

A valuable biomarker in the proper clinical context

As previously mentioned, CA125 is not cardiac-specific, and its up-regulation may also occur in several benign and neoplastic diseases. Thus, in the absence of HF diagnosis, elevated CA125 values may indicate widely and heterogeneous conditions which require a comprehensive clinical evaluation. CA125 levels in ovarian and metastatic malignancies usually exhibit much higher levels than those reported in acute and stable HF.[5,7,9,10] In patients with AHF, up to two-thirds of patients have CA125 levels >35 U/mL, and their values strongly correlated with signs of congestion (*Table 1*). In contrast, most patients with stable HF have CA125 levels ≤35 U/mL. Therefore, the information provided by CA125 should take into account symptoms/signs, echocardiographic parameters, and the status of other biomarkers, such as NPs.

In contrast to the information provided by elevated levels of CA125, levels in the low to normal range (CA125 <23 U/mL) can be used to identify a subgroup at low risk of short-term adverse events following an AHF admission, as our team recently showed in a large derivation ($n = 3231$) and validation ($n = 1583$) cohort.[41]

The utility of CA125 measurement during and following heart failure decompensation

Patients with decompensated HF and elevated CA125 levels require a thorough evaluation of congestion and right-sided HF performance parameters. These patients may also benefit from an intensive depletive strategy with closer monitoring. During the first weeks or months after discharge, CA125 kinetics closely correlated with the patient's clinical course. Regardless of the initial values after discharge, normalization of CA125 (≤35 U/mL) is the pattern that occurred most frequently and associated with clinical improvement and lower risk of events (*Table 4*). Increased values or lack of normalization during the first weeks after discharge may indicate persistent congestion and posed a higher risk of adverse clinical events (*Table 4*). In this subset of patients, we recommend close monitoring and considering intensive depletive treatment. In summary, a continuously ascending trajectory of CA125 over time in an apparently stable patient might be an alarming sign and will require further evaluation.

The importance of the CA125 half-life

CA125 is a circulating biomarker with a long half-life.[9,10] CA125 provides information about the fluid status during the last weeks and does not necessarily reflect acute haemodynamic changes (lagged effects). Thus, in patients with abrupt HF onset, CA125 may have had the time to be up-regulated.[28] Additionally, during the following days after a decompensation, CA125 may persist stable

Table 5 Potential areas of utility of carbohydrate antigen 125 to be confirmed in further studies

Clinical utility	Description
CA125 for assessing congestion	High values of CA125 as an indicator of: - Subclinical congestion - Predominant extravascular congestion - Predominant right-sided HF
Additional clinical utility using a multimarker panel	Value of multimarker approach for phenotyping and risk stratification. Multimarker panel including: - Natriuretic peptides - Urinary sodium - Bio-ADM - ST2 - Galectin-3
Guiding decongestive therapy	Although two small RCTs suggested that CA125 could be useful for tailoring depletive therapy, further larger and controlled RCTs are needed to confirm these preliminary findings
CA125 as a therapeutic target	Further studies should unravel the biological role of CA125 in HF and whether targeting CA125 may open a new line of treatment

ADM, adrenomedullin; CA125, carbohydrate antigen 125; HF, heart failure; RCT, randomized controlled trial.

or even increase, making serial measurements during the first days after a hospitalization futile for capturing information about acute response to therapy.[28] On the contrary, CA125 kinetics weeks-months following a decompensation have emerged as a promising monitoring tool.

Logistic advantages

CA125 has several logistical advantages over other biomarkers that facilitate its transition from clinical investigation to daily clinical practice. First, CA125 has been used routinely in clinical practice for more than 30 years, primarily for diagnosing and monitoring patients with ovarian cancer[5–7,24]; unlike other novel biomarkers currently limited to the research field, CA125 is widely available at any hospital laboratory. Second, CA125 is measured following standardized and highly reproducible methods. Different antibodies recognize CA125, the most commonly used being OC125-like and M11-like antibodies. These antibodies provide the basis for CA125 detection by enzyme-linked immunosorbent assays.[5–7,24] A list of commercially available assays is presented in online supplementary *File S2*. Third, CA125 measurement is not dependent on processing time, EDTA plasma, or serum. Finally, the cost of CA125 assessment is significantly lower than the cost of assessing NPs.[42]

Gaps in evidence and future directions

Several gaps in current knowledge are worth mentioning. First, the pathophysiology of CA125 up-regulation in HF is not well known. Second, whether CA125 plays a role in disease progression remains mostly speculative. Third, the clinical utility of this glycoprotein for risk stratification, monitoring, and tailoring diuretic therapy should be confirmed in larger multicentre studies. Specifically, the utility of CA125 for guiding treatment in patients with a recent episode of decompensated HF is an exciting field to be developed in the following years. Lastly, the optimal cut-off for defining normal vs. abnormal values in different HF scenarios should be established, as the cut-off of 35 U/mL was derived primarily from cancer studies. Future priority lines of research are summarized in *Table 5*.

Conclusions

CA125 has emerged as a promising surrogate of congestion and inflammation in different AHF scenarios. Current evidence supports its potential role in risk stratification, monitoring, and guidance of depletive therapy during the first weeks and months after an AHF event. The wide availability of this biomarker would make easy its widespread implementation in clinical practice.

Supplementary Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Funding

PIE15/00013 and CIBER Cardiovascular (16/11/00420 and 16/11/00403).

Conflict of interest: none declared.

References

1. Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE Jr, Colvin MM, Drazner MH, Filippatos GS, Fonarow GC, Givertz MM, Hollenberg SM, Lindenfeld J, Masoudi FA, McBride PE, Peterson PN, Stevenson LW, Westlake C. 2017 ACC/AHA/HFSA focused update of the 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Failure Society of America. *J Am Coll Cardiol* 2017;**70**:776–803.
2. Hollenberg SM, Warner Stevenson L, Ahmad T, Amin VJ, Bozkurt B, Butler J, Davis LL, Drazner MH, Kirkpatrick JN, Peterson PN, Reed BN, Roy CL, Storrow AB. 2019 ACC expert consensus decision pathway on risk assessment, management, and clinical trajectory of patients hospitalized with heart failure: a report of the American College of Cardiology Solution set Oversight Committee. *J Am Coll Cardiol* 2019;**74**:1966–2011.
3. Gheorghiade M, Follath F, Ponikowski P, Barsuk JH, Blair JE, Cleland JG, Dickstein K, Drazner MH, Fonarow GC, Jaarsma T, Jondeau G, Sendon JL, Mebazaa A, Metra M, Nieminen M, Pang PS, Seferovic P, Stevenson LW, van Veldhuisen DJ, Zannad F, Anker SD, Rhodes A, McMurray JJ, Filippatos G; European Society of Cardiology; European Society of Intensive Care Medicine. Assessing and grading congestion in acute heart failure: a scientific statement from the Acute Heart Failure Committee of the Heart Failure Association of the European Society of Cardiology and endorsed by the European Society of Intensive Care Medicine. *Eur J Heart Fail* 2010;**12**:423–433.

4. Stienen S, Bhatt A, Ferreira JP, Vaduganathan M, Januzzi J, Adams K, Tardif JC, Rossignol P, Zannad F. Bias in natriuretic peptide-guided heart failure trials: time to improve guideline adherence using alternative approaches. *Heart Fail Rev* 2021;**26**:11–21.
5. Scholler N, Urban N. CA125 in ovarian cancer. *Biomark Med* 2007;**1**:513–523.
6. Lloyd KO, Yin BW. Synthesis and secretion of the ovarian cancer antigen CA 125 by the human cancer cell line NIH:OVCAR-3. *Tumour Biol* 2001;**22**:77–82.
7. Zhang M, Zhang Y, Fu J, Zhang L. Serum CA125 levels are decreased in rectal cancer but increased in fibrosis-associated diseases and in most types of cancers. *Prog Mol Biol Transl Sci* 2019;**162**:241–252.
8. Sikaris KA. CA125: a test with a change of heart. *Heart Lung Circ* 2011;**20**:634–640.
9. Núñez J, Miñana G, Núñez E, Chorro FJ, Bodí V, Sanchis J. Clinical utility of antigen carbohydrate 125 in heart failure. *Heart Fail Rev* 2014;**19**:575–584.
10. Llàcer P, Bayés-Genís A, Núñez J. Carbohydrate antigen 125 in heart failure. New era in the monitoring and control of treatment. *Med Clin (Barc)* 2019;**152**:266–273.
11. Murphy SP, Kakkar R, McCarthy CP, Januzzi JL Jr. Inflammation in heart failure: JACC state-of-the-art review. *J Am Coll Cardiol* 2020;**75**:1324–1340.
12. Zeillemaker AM, Verbrugh HA, Hoynck van Papendrecht AA, Leguit P. CA 125 secretion by peritoneal mesothelial cells. *J Clin Pathol* 1994;**47**:263–265.
13. Huang F, Chen J, Liu Y, Zhang K, Wang J, Huang H. New mechanism of elevated CA125 in heart failure: the mechanical stress and inflammatory stimuli initiate CA125 synthesis. *Med Hypotheses* 2012;**79**:381–383.
14. Lei Y, Zang R, Lu Z, Zhang G, Huang J, Liu C, Wang Z, Mao S, Che Y, Wang X, Zheng S, Fang L, Sun N, He J. ERO1L promotes IL6/sIL6R signaling and regulates MUC16 expression to promote CA125 secretion and the metastasis of lung cancer cells. *Cell Death Dis* 2020;**11**:853.
15. D'Aloia A, Faggiano P, Aurigemma G, Bontempi L, Ruggeri G, Metra M, Nodari S, Dei Cas L. Serum levels of carbohydrate antigen 125 in patients with chronic heart failure: relation to clinical severity, hemodynamic and Doppler echocardiographic abnormalities, and short-term prognosis. *J Am Coll Cardiol* 2003;**41**: 1805–1811.
16. Yilmaz MB, Zorlu A, Tandogan I. Plasma CA-125 level is related to both sides of the heart: a retrospective analysis. *Int J Cardiol* 2011;**149**:80–82.
17. Miñana G, de la Espriella R, Mollar A, Santas E, Núñez E, Valero E, Bodí V, Chorro FJ, Fernández-Cisnal A, Martí-Cervera J, Sanchis J, Bayés-Genís A, Núñez J. Factors associated with plasma antigen carbohydrate 125 and amino-terminal pro-B-type natriuretic peptide concentrations in acute heart failure. *Eur Heart J Acute Cardiovasc Care* 2020;**9**:437–447.
18. Núñez J, Bayés-Genís A, Revuelta-López E, Ter Maaten JM, Miñana G, Barallat J, Cserkóová A, Bodi V, Fernández-Cisnal A, Núñez E, Sanchis J, Lang C, Ng LL, Metra M, Voors AA. Clinical role of CA125 in worsening heart failure: a BIOSTAT-CHF study subanalysis. *JACC Heart Fail* 2020;**8**:386–397.
19. Llàcer P, Gallardo MÁ, Palau P, Moreno MC, Castillo C, Fernández C, de la Espriella R, Mollar A, Santas E, Miñana G, Manzano L, Bayés-Genís A, Núñez J. Comparison between CA125 and NT-proBNP for evaluating congestion in acute heart failure. *Med Clin (Barc)* 2021;**156**:589–594.
20. Miñana G, Núñez J, Sanchis J, Bodí V, Núñez E, Llàcer A. CA125 and immunoinflammatory activity in acute heart failure. *Int J Cardiol* 2010;**145**:547–548.
21. Núñez J, Rabinovich GA, Sandino J, Mainar L, Palau P, Santas E, Villanueva MP, Núñez E, Bodí V, Chorro FJ, Miñana G, Sanchis J. Prognostic value of the interaction between galectin-3 and antigen carbohydrate 125 in acute heart failure. *PLoS One* 2015;**10**:e0122360.
22. Colombo PC, Onat D, Harxhi A, Demmer RT, Hayashi Y, Jelic S, LeJemtel TH, Bucciarelli L, Kebschull M, Papapanou P, Uriel N, Schmidt AM, Sabbah HN, Jorde UP. Peripheral venous congestion causes inflammation, neurohormonal, and endothelial cell activation. *Eur Heart J* 2014;**35**:448–454.
23. Núñez J, Miñana G, González M, Garcia-Ramón R, Sanchis J, Bodí V, Núñez E, Chorro FJ, Llàcer A, Miguel A. Antigen carbohydrate 125 in heart failure: not just a surrogate for serosal effusions? *Int J Cardiol* 2011;**146**:473–474.
24. Núñez G, de la Espriella R, Santas E, Lorenzo M, Miñana G, Núñez E, Bodí V, González M, Górriz JL, Sanchis J, Bayés-Genís A, Núñez J. CA125 but not NT-proBNP predicts the presence of a congestive intrarenal venous flow in patients with acute heart failure. *Eur Heart J Acute Cardiovasc Care* 2021;**10**:475–483.
25. Bottoni P, Scatena R. The role of CA 125 as tumor marker: biochemical and clinical aspects. *Adv Exp Med Biol* 2015;**867**:229–244.
26. Nägele H, Bahlo M, Klapdor R, Schaeperkoetter D, Rödiger W. CA 125 and its relation to cardiac function. *Am Heart J* 1999;**137**:1044–1049.
27. Núñez J, Núñez E, Consuegra L, Sanchis J, Bodí V, Martínez-Brotons A, Bertomeu-González V, Robles R, Bosch MJ, Fácila L, Darmofal H, Llàcer A. Carbohydrate antigen 125: an emerging prognostic risk factor in acute heart failure? *Heart* 2007;**93**:716–721.
28. Núñez J, Sanchis J, Bodí V, Fonarow GC, Núñez E, Bertomeu-González V, Miñana G, Consuegra L, Bosch MJ, Carratalá A, Chorro FJ, Llàcer A. Improvement in risk stratification with the combination of the tumour marker antigen carbohydrate 125 and brain natriuretic peptide in patients with acute heart failure. *Eur Heart J* 2010;**31**:1752–1763.
29. Li KHC, Gong M, Li G, Baranchuk A, Liu T, Wong MCS, Jesuthasan A, Lai RWC, Lai JCL, Lee APW, Bayés-Genis A, de la Espriella R, Sanchis J, Wu WKK, Tse G, Nuñez J; International Health Informatics Study (IHIS) Network. Cancer antigen-125 and outcomes in acute heart failure: a systematic review and meta-analysis. *Heart Asia* 2018;**10**:e011044.
30. Soler M, Miñana G, Santas E, Núñez E, de la Espriella R, Valero E, Bodí V, Chorro FJ, Fernández-Cisnal A, D'Ascoli G, Marti-Cervera J, Sanchis J, Bayes-Genís A, Núñez J. CA125 outperforms NT-proBNP in acute heart failure with severe tricuspid regurgitation. *Int J Cardiol* 2020;**308**:54–59.
31. Núñez J, Núñez E, Sanchis J, Bodí V, Fonarow GC, Miñana G, Palau P, Bertomeu-González V, Carratalá A, Mainar L, Chorro FJ, Llàcer A. Antigen carbohydrate 125 and brain natriuretic peptide serial measurements for risk stratification following an episode of acute heart failure. *Int J Cardiol* 2012;**159**:21–28.
32. Miñana Escrivá G, Núñez J, Sanchis J, Bodi V, Núñez E, Chorro FJ, Llàcer A. Carbohydrate antigen 125 serial measurements after an admission for acute heart failure and risk of early readmission. *Med Clin (Barc)* 2012;**139**:479–486.
33. Núñez J, Núñez E, Bayés-Genís A, Fonarow GC, Miñana G, Bodí V, Pascual-Figal D, Santas E, Garcia-Blas S, Chorro FJ, Rizopoulos D, Sanchis J. Long-term serial kinetics of N-terminal pro B-type natriuretic peptide and carbohydrate antigen 125 for mortality risk prediction following acute heart failure. *Eur Heart J Acute Cardiovasc Care* 2017;**6**:685–696.
34. Núñez J, Heredia R, Payá A, Sanchis I, Del Prado S, Miñana G, Santas E, de la Espriella R, Núñez E, Sanchis J, Bayés-Genís A. Use of acetazolamide in the treatment of patients with refractory congestive heart failure. *Cardiovasc Ther* 2018;**36**:e12465.
35. Núñez J, Palau P, Domínguez E, Mollar A, Núñez E, Ramón JM, Miñana G, Santas E, Fácila L, Górriz JL, Sanchis J, Bayés-Genís A. Early effects of empagliflozin on exercise tolerance in patients with heart failure: a pilot study. *Clin Cardiol* 2018;**41**:476–480.
36. Núñez J, Llàcer P, Núñez E, Ventura S, Bonanad C, Bodí V, Miñana G, Santas E, Mascarell B, Fonarow GC, Chorro FJ, Sanchis J. Antigen carbohydrate 125 and creatinine on admission for prediction of renal function response following loop diuretic administration in acute heart failure. *Int J Cardiol* 2014;**174**:516–523.
37. Núñez J, Núñez E, Miñana G, Bodí V, Fonarow GC, Bertomeu-González V, Palau P, Merlos P, Ventura S, Chorro FJ, Llàcer P, Sanchis J. Differential mortality association of loop diuretic dosage according to blood urea nitrogen and carbohydrate antigen 125 following a hospitalization for acute heart failure. *Eur J Heart Fail* 2012;**14**:974–984.
38. Núñez J, Llàcer P, Bertomeu-González V, Bosch MJ, Merlos P, García-Blas S, Montagud V, Bodí V, Bertomeu-Martínez V, Pedrosa V, Mendizábal A, Cordero A, Gallego J, Palau P, Miñana G, Santas E, Morell S, Llàcer A, Chorro FJ, Sanchis J, Fácila L; CHANCE-HF Investigators. Carbohydrate antigen-125-guided therapy in acute heart failure: CHANCE-HF: a randomized study. *JACC Heart Fail* 2016;**4**:833–843.
39. Núñez J, Llàcer P, García-Blas S, Bonanad C, Ventura S, Núñez JM, Sánchez R, Fácila L, de la Espriella R, Vaquer JM, Cordero A, Roqué M, Chamorro C, Bodi V, Valero E, Santas E, Moreno MDC, Miñana G, Carratalá A, Rodríguez E, Mollar A, Palau P, Bosch MJ, Bertomeu-González V, Lupón J, Navarro J, Chorro FJ, Górriz JL, Sanchis J, Voors AA, Bayés-Genís A. CA125-guided diuretic treatment versus usual care in patients with acute heart failure and renal dysfunction. *Am J Med* 2020;**133**:370–380.e4.
40. Mueller C, McDonald K, de Boer RA, Maisel A, Cleland JGF, Kozhuharov N, Coats AJS, Metra M, Mebazaa A, Ruschitzka F, Lainscak M, Filippatos G, Seferovic PM, Meijers WC, Bayes-Genis A, Mueller T, Richards M, Januzzi JL Jr; Heart Failure Association of the European Society of Cardiology. Heart Failure Association of the European Society of Cardiology practical guidance on the use of natriuretic peptide concentrations. *Eur J Heart Fail* 2019;**21**:715–731.
41. Nuñez J, Bayés-Genís A, Revuelta-López E, Miñana G, Santas E, ter Maaten JM, de la Espriella R, Carratalá A, Lorenzo M, Palau P, Llàcer P, Valle A, Bodi V, Núñez E, Lupon J, Lang C, Ng LL, Metra M, Sanchis J, Voors AA. Optimal carbohydrate antigen 125 cutpoint for identifying low-risk patients after acute heart failure admission. *Rev Esp Cardiol (Engl Ed)* 2021 Mar 18. https://doi.org/10.1016/j.rec.2021.02.002 [Epub ahead of print].
42. Ordu S, Ozhan H, Alemdar R, Aydin M, Caglar O, Yuksel H, Kandis H. Carbohydrate antigen-125 and N-terminal pro-brain natriuretic peptide levels: compared in heart-failure prognostication. *Tex Heart Inst J* 2012;**39**:30–35.