ESC European Society of Cardiology

European Journal of Heart Failure (2022) **24**, 1751–1766
doi:10.1002/ejhf.2664

REVIEW ARTICLE

Congestion in heart failure: a circulating biomarker-based perspective. A review from the Biomarkers Working Group of the Heart Failure Association, European Society of Cardiology

Julio Núñez[1,2], Rafael de la Espriella[1,2], Patrick Rossignol[3], Adriaan A. Voors[4], Wilfried Mullens[5], Marco Metra[6], Ovidiu Chioncel[7], James L. Januzzi[8], Christian Mueller[9], A. Mark Richards[10,11], Rudolf A. de Boer[4], Thomas Thum[12,13], Henrike Arfsten[14,15], Arantxa González[2,16], Magdy Abdelhamid[17], Stamatis Adamopoulos[18], Stefan D. Anker[19], Tuvia Ben Gal[20], Jan Biegus[21], Alain Cohen-Solal[22], Michael Böhm[23], Michele Emdin[24,25], Ewa A. Jankowska[21], Finn Gustafsson[26], Loreena Hill[27], Tiny Jaarsma[28], Pardeep S. Jhund[29], Yuri Lopatin[30], Lars H. Lund[31], Davor Milicic[32], Brenda Moura[33,34], Massimo F. Piepoli[35], Piotr Ponikowski[21], Amina Rakisheva[36], Arsen Ristic[37], Gianluigi Savarese[31], Carlo G. Tocchetti[38], Sophie Van Linthout[15,39], Maurizio Volterrani[40], Petar Seferovic[41,42], Giuseppe Rosano[43], Andrew J.S. Coats[44], and Antoni Bayes-Genis[2,45,46]*

[1]Hospital Clínico Universitario de Valencia, INCLIVA, Universidad de Valencia, Valencia, Spain; [2]CIBER Cardiovascular, Madrid, Spain; [3]Université de Lorraine, INSERM, Centre d'Investigations Cliniques-Plurithématique 14-33, INSERM U1116, CHRU Nancy, F-CRIN INI-CRCT (Cardiovascular and Renal Clinical Trialists), Nancy, France; [4]Department of Cardiology University Medical Center Groningen, University of Groningen, Groningen, The Netherlands; [5]Hospital Oost-Limburg, Genk, Belgium; [6]Department of Medical and Surgical Specialties, Radiological Sciences and Public Health, Cardiology. ASST Spedali Civili, University of Brescia, Brescia, Italy; [7]Emergency Institute for Cardiovascular Diseases 'Prof. C.C. Iliescu', University of Medicine Carol Davila, Bucharest, Romania; [8]Massachusetts General Hospital and Baim Institute for Clinical Research, Boston, MA, USA; [9]Department of Cardiology, University Hospital, Basel, Switzerland; [10]Cardiovascular Research Institute, National University of Singapore, Singapore, Singapore; [11]Christchurch Heart Institute, University of Otago, Dunedin, New Zealand; [12]Institute of Molecular and Translational Therapeutic Strategies (IMTTS) and Rebirth Center for Translational Regenerative Therapies, Hannover Medical School, Hannover, Germany; [13]Fraunhofer Institute of Toxicology and Experimental Medicine, Hannover, Germany; [14]Clinical Division of Cardiology, Department of Internal Medicine II, Medical University of Vienna, Vienna, Austria; [15]German Centre for Cardiovascular Research (DZHK), partner site Berlin, Berlin, Germany; [16]Program of Cardiovascular Diseases, CIMA Universidad de Navarra, Pamplona, Spain; IdiSNA, Navarra Institute for Health Research, Pamplona, Spain; [17]Faculty of Medicine, Cairo University, Giza, Egypt; [18]2nd Department of Cardiovascular Medicine, Onassis Cardiac Surgery Center, Athens, Greece; [19]Department of Cardiology (CVK); and Berlin Institute of Health Center for Regenerative Therapies (BCRT); German Centre for Cardiovascular Research (DZHK) partner site Berlin, Charité Universitätsmedizin Berlin, Berlin, Germany; [20]Cardiology Department, Rabin Medical Center, Petah Tikva, Israel; [21]Institute of Heart Diseases, Wroclaw Medical University, Wroclaw, Poland; [22]Inserm 942 MASCOT, Université de Paris, AP-HP, Hopital Lariboisière, Paris, France; [23]Universitätsklinikum des Saarlandes, Klinik für Innere Medizin III, Kardiologie, Angiologie und Internistische Intensivmedizin Homburg/Saar, Saarland University, Saarbrücken, Germany; [24]Institute of Life Sciences, Scuola Superiore Sant'Anna, Pisa, Italy; [25]Cardiology Division, Fondazione Toscana Gabriele Monasterio, Pisa, Italy; [26]Rigshospitalet-Copenhagen University Hospital, Heart Centre, Department of Cardiology, Copenhagen, Denmark; [27]Queen's University Belfast, Belfast, UK; [28]Linkoping University, Linkoping, Sweden; [29]BHF Glasgow Cardiovascular Research Centre, University of Glasgow, Glasgow, UK; [30]Volgograd State Medical University, Volgograd, Russia; [31]Department of Medicine, Karolinska Institutet, and Heart and Vascular Theme, Karolinska University Hospital, Stockholm, Sweden; [32]University of Zagreb, School of Medicine, Zagreb, Croatia; [33]Faculty of Medicine, University of Porto, Porto, Portugal; [34]Cardiology Department, Porto Armed Forces Hospital, Porto, Portugal; [35]Cardiology Division, Caste l San Giovanni Hospital, Castel San Giovanni, Italy; [36]Scientific Research Institute of Cardiology and Internal Medicine, Almaty, Kazakhstan; [37]School of Medicine, University of Belgrade, Belgrade, Serbia; [38]Cardio-Oncology Unit, Department of Translational Medical Sciences, Center for Basic and Clinical Immunology Research (CISI), Interdepartmental Center of Clinical and Translational Sciences (CIRCET), Interdepartmental Hypertension Research Center (CIRIAPA), Federico II University, Naples, Italy;

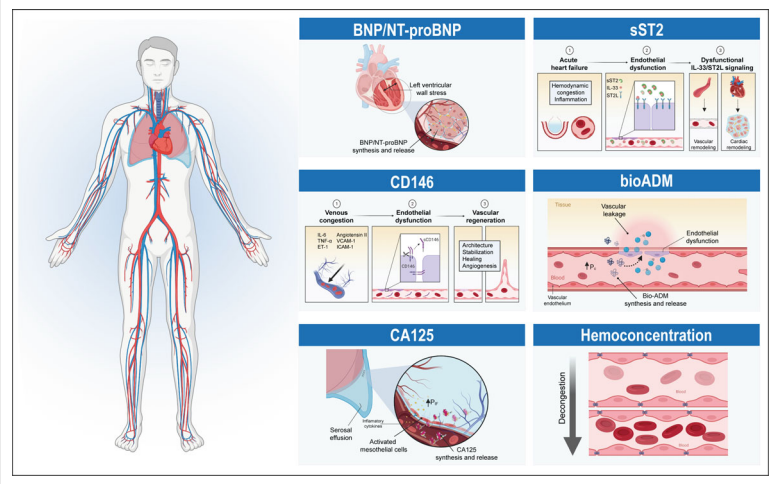
*Corresponding author. Cardiology Service, Hospital Universitari Germans Trias i Pujol, Carretera de Canyet s/n, 08916 Badalona, Spain. Tel: +34 934 978915, Email: abayesgenis@gmail.com

[39]Berlin Institute of Health (BIH) at Charité-Universitätmedizin Berlin, BIH Center for Regenerative Therapies (BCRT), Berlin, Germany; [40]IRCCS San Raffaele, Rome, Italy; [41]Faculty of Medicine, University of Belgrade, Belgrade, Serbia; [42]Serbian Academy of Sciences and Arts, Belgrade, Serbia; [43]St. George's Hospitals NHS Trust University of London, London, UK; [44]University of Warwick, Coventry, UK; [45]Institut del Cor, Hospital Universitari Germans Trias i Pujol, Barcelona, Spain; and [46]Department of Medicine, Universitat Autònoma de Barcelona, Barcelona, Spain

Received 4 May 2022; revised 22 August 2022; accepted 22 August 2022; online publish-ahead-of-print 7 September 2022

Congestion is a cardinal sign of heart failure (HF). In the past, it was seen as a homogeneous epiphenomenon that identified patients with advanced HF. However, current evidence shows that congestion in HF varies in quantity and distribution. This updated view advocates for a congestive-driven classification of HF according to onset (acute vs. chronic), regional distribution (systemic vs. pulmonary), compartment of distribution (intravascular vs. extravascular), and clinical vs. subclinical. Thus, this review will focus on the utility of circulating biomarkers for assessing and managing the different fluid overload phenotypes. This discussion focused on the clinical utility of the natriuretic peptides, carbohydrate antigen 125 (also called mucin 16), bio-adrenomedullin and mid-regional pro-adrenomedullin, ST2 (also known as interleukin-1 receptor-like 1), cluster of differentiation 146, troponin, C-terminal pro-endothelin-1, and parameters of haemoconcentration. The utility of circulation biomarkers on top of clinical evaluation, haemodynamics, and imaging needs to be better determined by dedicated studies. Some multiparametric frameworks in which these tools contribute to management are proposed.

Graphical Abstract



Schematic summary of circulating surrogate biomarkers of congestion. bioADM, biologically active adrenomedullin; BNP, B-type natriuretic peptide; CA125, carbohydrate antigen 125; CD146, cluster of differentiation 146; ET-1, endothelin-1; ICAM-1, intercellular adhesion molecule-1; IL, interleukin; NT-proBNP, N-terminal pro-B-type natriuretic peptide; TNF-α, tumour necrosis factor alpha; VCAM-1, vascular cell adhesion molecule-1.

Keywords Congestion • Acute heart failure • Biomarkers

Congestion in heart failure (HF) is defined as signs and symptoms of extracellular fluid accumulation that result from increased cardiac filling pressures.[1] It is induced and perpetuated by an imbalance between neurohormonal axes with opposite actions: sodium/water retention and vasoconstriction (mainly adrenergic, renin–angiotensin–aldosterone, and vasopressin systems) versus natriuretic and vasodilatation (mainly cardiac endocrine function).[1–4] Congestion is also a central component in the definition of HF,[5] and most HF hospitalizations are due to congestion either as predominantly fluid overload, compartmental fluid redistribution, or a mix of both mechanisms.[1,3,4] Beyond the traditional view as a surrogate for HF severity, the current perspective considers fluid accumulation/redistribution are causally involved in HF and organ damage progression. Thus, congestion contributes to the HF-associated impairment of functional and structural changes in multiple organs and systems (*Figure 1*).

Despite most patients with worsening HF (WHF) experience a substantial clinical improvement when treated with diuretics, there are several gaps in knowledge. First, the severity of congestion is not linearly associated with the severity of HF (left

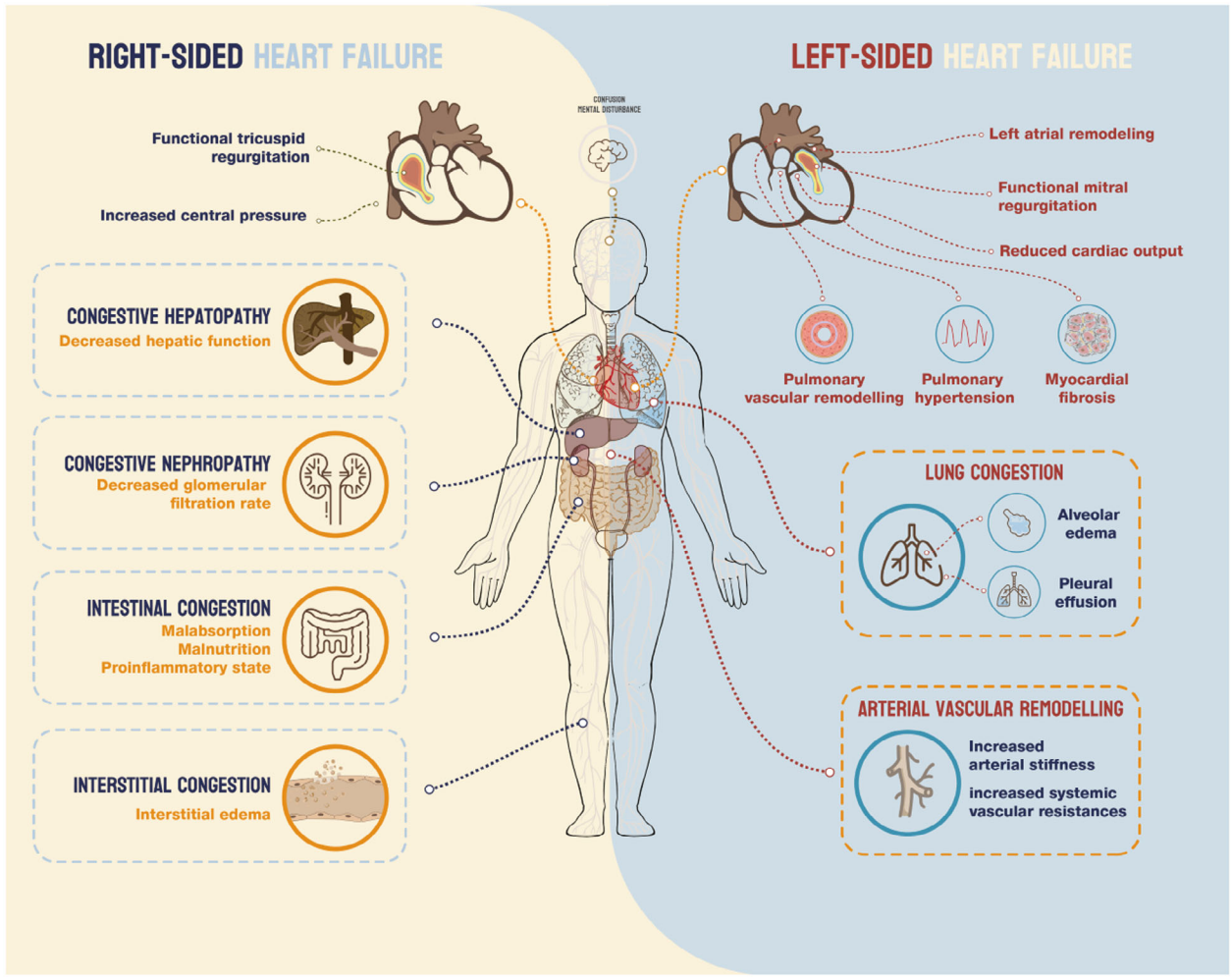


Figure 1 Clinical implications of organ congestion in heart failure. Congestion can lead to organ injury, dysfunction, and, ultimately, the failure of target organs (i.e. heart, lungs, kidneys, liver, intestine, vessels, and brain). Pulmonary congestion is the net result of increased left-sided filling pressures, which may lead to cardiopulmonary remodelling (i.e. endothelial dysfunction, fibrosis, and thickening of the extracellular matrix), pulmonary vasoconstriction, and, finally, pulmonary hypertension. Congestion of organs in the abdominal cavity is the net result of right-sided dysfunction and venous congestion. Passive congestive hepatopathy due to increased central venous pressure may initially lead to cholestasis. However, chronic hepatic congestion may result in hepatic fibrosis and cirrhosis. Congestive nephropathy due to increased central venous pressure and extrarenal compression (i.e. intra-abdominal hypertension) may lead to a pressure-induced reduction in renal blood flow, renal hypoxia, increased interstitial pressure, and finally, interstitial fibrosis. Intestinal congestion leads to increased gut permeability and translocation of endotoxins (pro-inflammatory state), gastrointestinal hypoperfusion, protein-losing enteropathy, and cardiac cachexia. Furthermore, gut involvement complicates chronic heart failure treatment by decreasing intestinal absorption. For instance, oedematous changes in the intestinal wall may alter the absorption rate of certain drugs such as furosemide. Additionally, the pro-inflammatory cytokine milieu resulting from bacterial and lipopolysaccharide translocation to the systemic circulation can also alter the expression of various drug-metabolizing enzymes and transporters.

or right ventricular dysfunction). In other words, some patients with severe left ventricular (LV) dysfunction remain euvolaemic and show no signs of congestion. In contrast, other patients have severe congestion with relatively mild objective structural or functional abnormalities.[1,6] For instance, high-output HF does not necessarily require significant structural cardiac abnormalities and should also be considered in differential diagnoses of patients with clinical congestion. Among them, high-output HF includes a wide variety of underlying conditions (i.e. obesity, severe anaemia, cirrhosis, arteriovenous shunts, chronic hypercapnia, among others) associated with reduced arterial vascular resistance and high output. The common factor in all these conditions seems to be a reflex increase in sympathetic activity through baroreceptors that leads to decreased renal blood flow, activation of the renin–angiotensin–aldosterone system, and sodium and water retention.[3,4] Second, the optimal decongestion strategy

remains elusive in most HF patients regardless of LV ejection fraction,[3,4] mostly reflecting the heterogeneous severity and organ distribution of fluid overload and the low accuracy of classic symptoms and signs in grading congestion.[1] Thus, searching for new clinical tools, especially those widely available in clinical practice, should be a research priority in the HF field.

Historically, fluid overload in HF was considered a homogeneous and uni-compartmental epiphenomenon that identified patients with more advanced disease. In contrast, current evidence shows that fluid and sodium accumulation in HF are heterogeneous in quantity and distribution. An updated view of congestion advocates for the classification of HF-related fluid overload according to onset (acute vs. chronic), regional distribution (systemic vs. pulmonary), compartment of distribution (intravascular vs. interstitial vs. third spaces), and clinical versus subclinical. A better understanding and identification of the different congestion 'phenotypes' could probably translate into improving HF management.

Therefore, this review will focus on the utility of circulating biomarkers in identifying and managing different congestion phenotypes.

Pressure–volume disconnection: fluid overload versus fluid redistribution

The pathophysiology of congestion in HF is highly complex and multifactorial. Although too simplistic, it can be viewed as a dynamic interplay between cardiac function, the roles of interstitial and intravascular fluid compartments, the integrity of the endothelium, and how the kidney manages the sodium/liquid homeostasis at the tubular level.[7] This multifactorial and complex pathogenesis may be conditioning the disconnection between congestion-driven pressures and congestion-driven volume expansion, resulting in patterns that varied widely between patients on severity and organ distribution.[6–9] For instance, some patients presenting with WHF and elevated cardiac filling pressures may have a predominant fluid redistribution (from splanchnic to pulmonary vascular territory) (*Figure 2*). In contrast, others may show a long-standing and gradual interstitial volume expansion (tissue congestion)[9] (*Figure 2*).

Congestion phenotypes

Congestion in HF can be characterized based on the compartment and regional distribution (*Figure 3*).

Regional distribution: pulmonary versus systemic

As stated before, regional/organ distribution of congestion is not a homogeneous process in HF.[6–9] In patients with predominant left-sided HF, pulmonary congestion dominates; however, with the involvement of right-sided chambers and/or pulmonary arterial hypertension, systemic congestion becomes a dominant presentation.[3,6–9] These differences in the distribution of fluid overload are also the basis of the re-classification of acute HF (AHF) recently proposed in the 2021 European Society of Cardiology (ESC) guidelines in (i) HF with predominant peripheral fluid accumulation, (ii) acute decompensated HF as patients with acutely decompensated HF where lung congestion – favoured by splanchnic district venoconstriction – led to acute pulmonary oedema.[3]

Compartment distribution: intravascular versus extravascular

Patients with decompensated HF showed marked elevation of cardiac filling pressures. In normal hearts and afterload held constant, LV torsion is a preload-dependent phenomenon in which volume loading results in a net increase in peak systolic LV twisting and subsequent early diastolic untwisting rate.[10] This interdependence between systolic twisting and diastolic untwisting (viscoelastic suction) explains why healthy hearts can accommodate a larger preload volume without significantly increasing pulmonary capillary wedge pressures. In HF, however, there are diverse LV twisting alterations and reduced and delayed untwisting. Consequently, the failing heart cannot adequately accommodate preload volume increase at rest or during exercise, leading to elevated pulmonary capillary wedge pressures.[11] Moreover, pulmonary pressures may also be high due to enhanced ventricular interdependence in the context of right ventricular–pulmonary arterial uncoupling at rest (i.e. isolated right-sided HF) or during exercise.[11] Although this elevation in filling pressures is commonly related to the inability of the heart to accommodate and distribute central blood volume, changes in systemic venous function also play a crucial (and under-appreciated) role in regulating central haemodynamics.[12]

Most blood volume resides within the venous circulation, and its distribution can be divided into stressed and unstressed volumes.[11,12] The unstressed volume (approximately 70% of venous blood volume) refers to the amount of blood necessary to fill the vascular space at a transmural pressure equal to zero. It represents a blood reservoir pooled in venous capacitance veins that can be mobilized into the central circulation when needed[11,12] (*Figure 4*). In contrast, the stressed volume (approximately 30% of venous blood volume) describes the additional volume of blood that increases wall tension, determining venous return and cardiac preload[11] (*Figure 2*). Importantly, the autonomic nervous system tightly regulates the distribution of stressed and unstressed blood volume.[13] Accordingly, increased sympathetic activation – common in patients with decompensated HF – may lead to a functional shift of blood from the unstressed volume (mainly from splanchnic veins) into the central circulation, resulting in a striking and acute increase in central venous pressures and the development of congestion-related symptoms.[13] Therefore, a substantial proportion of patients present with a predominantly vascular type of congestion.[3,13,14] In these patients, acute venous tone dysregulation rather than total blood volume expansion seems to be the principal underlying mechanism.

Another compartment phenotype is characterized by impaired sodium and water excretion due to increased neurohormonal activation and cardiorenal dysfunction.[1] As a result, there is a

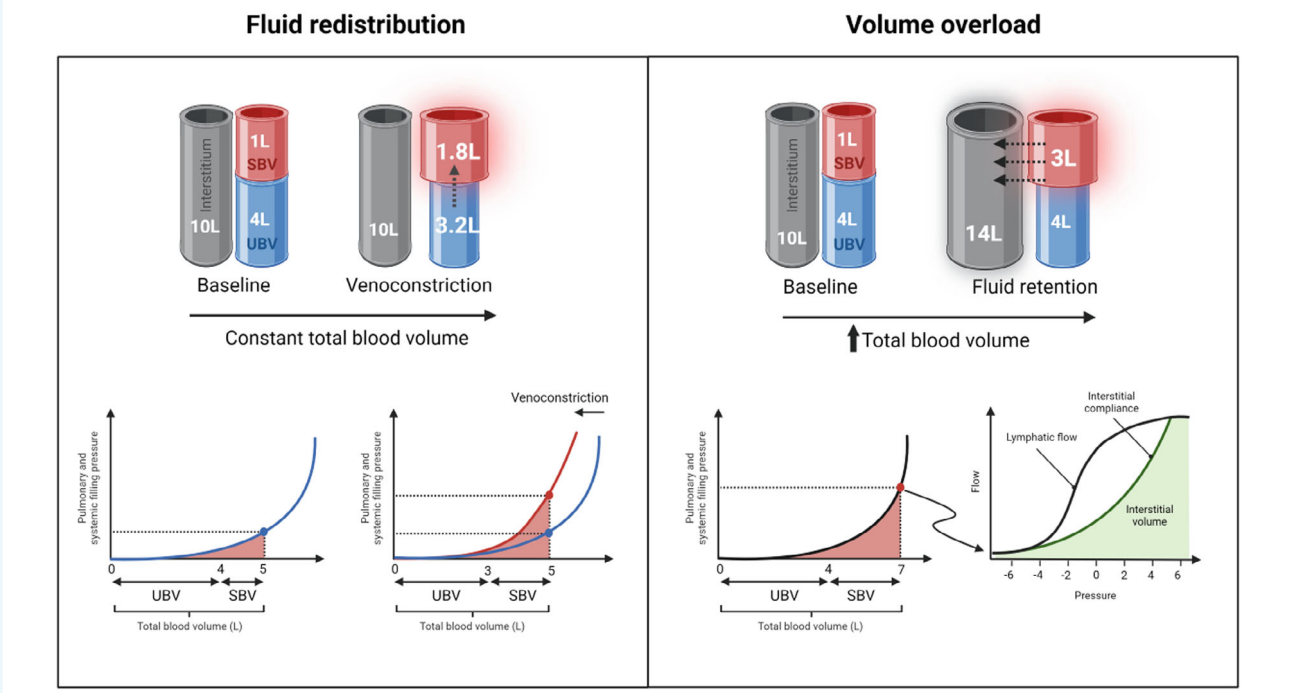


Figure 2 Fluid redistribution (*A*) versus volume overload (*B*). (*A*) The relationship between circulatory filling pressures (pulmonary and systemic) and total blood volume (unstressed blood volume [UBV] + stressed blood volume [SBV]) is non-linear, such that a significant amount of volume is required before any significant rise in circulatory filling pressures occurs. However, the venous tone is a crucial modifier of SBV in the setting of constant total blood volume. For instance, increased sympathetic activation – common in patients with decompensated heart failure – may lead to a functional shift of blood from the unstressed volume (systemic and pulmonary capacitance vessels), increasing circulatory filling pressures despite constant total blood volume. (*B*) Total blood volume progressively increases as fluid start to accumulate due to sodium and water retention since the early stages of an exacerbation. Because UBV is constant, there is a progressive rise in SBV and circulatory filling pressures. Together with other factors such as vascular permeability and Starling forces between the plasma and interstitium, part of the fluid overload is shifted towards the interstitial compartment because of net capillary filtration. Because of markedly increased lymphatic function, interstitial fluid is initially efficiently drained without fluid accumulation. Nevertheless, when lymph flow reaches a plateau, the rate of transudation from capillaries into the interstitium exceeds lymphatic capacity, and fluid starts to build up in the interstitial space.

relatively gradual development of vascular congestion reflecting an absolute increase in extracellular fluid and sodium content (tissue congestion), as is illustrated in *Figure 2*. The above will lead to a progressive and sustained increase in venous pressures that finally shift the Starling forces between the plasma and interstitium towards net capillary filtration. However, due to the limited compliance of the interstitial glycosaminoglycan (GAG) network and increased lymphatic function, interstitial fluid is initially efficiently drained, and there is no interstitial fluid accumulation.[15] However, once lymph flow is maximized, the rate of transudation from capillaries into the interstitium may then exceed lymphatic capacity, and fluid accumulates in the interstitial space.[15] Moreover, the long-term positive sodium balance may compromise the interstitial GAG network's integrity and buffering capacity, lowering its tensile force.[15] Consequently, the interstitial matrix becomes highly compliant, and slight increases in hydrostatic capillary pressure are sufficient to drive interstitial fluid expansion.[15,16] Other factors such as lower plasma osmolarity, inflammation and increased vascular permeability,[3,17] may also be playing a role in the pathogenesis of tissue congestion. Additionally, third-space fluid accumulation in serosal cavities is not uncommon.[2,3] However, the mechanisms behind the shift to a third-space fluid accumulation are not fully understood, requiring more evaluation.

Clinical implications

An integrative assessment of symptoms and signs, imaging, and circulating biomarkers seems necessary for identifying the predominant congestion phenotype (*Figure 3*). Additionally, some clinical characteristics may help to reveal the predominant phenotype. For instance, those with an acute presentation more frequently present intravascular pulmonary congestion due to fluid redistribution. On the other extreme, patients with predominant tissue congestion will also show long-term evolution, gradual onset, and greater severity of systemic congestion (*Figure 3*). Not infrequently, these distinct phenotypes overlapped, resulting in mixed clinical patterns. Moreover, these phenotypes may change over time – patients may transition from one predominantly to another along the course of the disease.

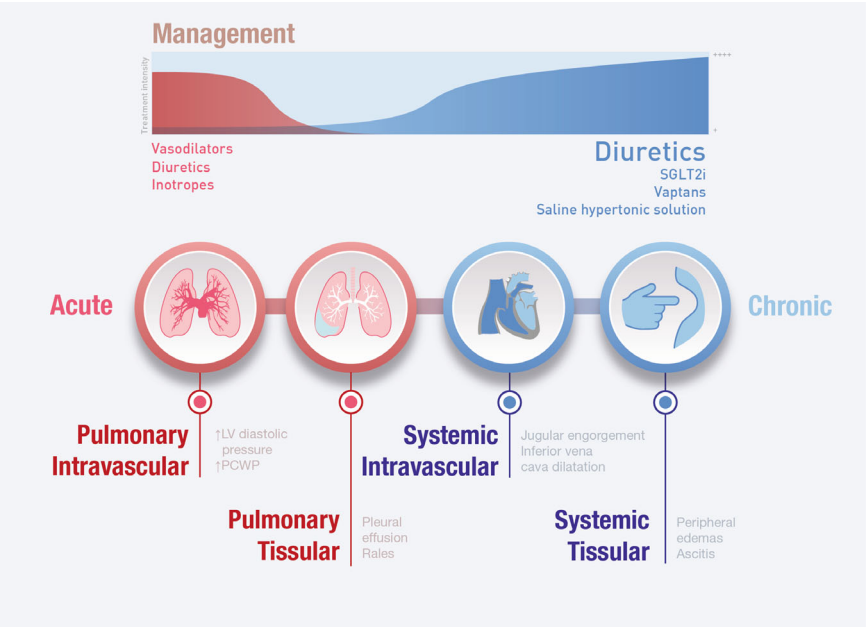


Figure 3 Congestion phenotypes. Time onset, utility of circulating biomarkers, and potential therapeutic implications. We propose four congestion phenotypes: pulmonary intravascular, pulmonary tissular, systemic intravascular, and systemic tissular. An integrative assessment using symptoms, signs, imaging, and circulating biomarkers may be useful for identifying the predominant congestion phenotype. Identification of the predominant congestion phenotype may imply crucial therapeutic implications as proposed. LV, left ventricle; PCWP, pulmonary capillary wedge pressures; SGLT2i, sodium–glucose cotransporter 2 inhibitor.

Beyond the pathophysiological considerations, this classification may also have important therapeutic implications. For instance, and contrary to those with dominant fluid overload – requiring more aggressive diuretic therapy – patients with predominant fluid redistribution may benefit from the use of vasodilators and not as much of an aggressive depletive strategy. In patients with predominant tissue congestion, strategies aiming to reduce vascular permeability and increase vascular refill, such as using hypertonic solutions with high doses of loop diuretics and sodium–glucose cotransporter 2 inhibitors (SGLT2i), or vaptans, may be more beneficial than other traditional diuretic approaches (*Figure 3*).[17] Also, congestion phenotyping may influence the pertinence and timing of other guideline-directed medical therapy. For instance, early initiation of SGLT2i and sacubitril/valsartan has been associated with a greater decongestive effect.[18,19] Conversely, early initiation of beta-blockers in patients with overt congestion status should be avoided.[3,4]

Role of circulating biomarkers for assessing the severity and distribution of congestion

A growing body of evidence supports an integrated and multiparametric evaluation of congestion by means of validated clinical scores, circulating biomarkers, and technical assessments (imaging, haemodynamics, and impedance-based tools).[1,20]

The current article provides an overview of the novel and established circulating biomarkers for identifying different modalities of congestion (*Graphical Abstract*). The biomarkers included in this review are those identified by the Biomarkers Working Group of the Heart Failure Association as the more relevant contemporary biomarkers in HF.

Ideal characteristics of a congestion biomarker

An ideal biomarker should be expressed and produced in different organs and systems affected by fluid accumulation. Indeed, several HF biomarkers predominantly reflect stress in other affected tissues and provide information beyond the heart.[21] An ideal biomarker in HF should include the following characteristics: (i) non-invasive, low-cost, easy, and standardized assessment, (ii) high sensitivity, allowing early detection and no overlap in values between wet and dry patients, (iii) provide specific information about the congestion phenotype, (iv) be unaffected, or minimally affected by comorbid conditions, and (v) their levels should be modified in response to treatment.

Natriuretic peptides

Several studies have correlated B-type natriuretic peptide (BNP) and its co-secreted amino-terminal propeptide congener (NT-proBNP) with increased left intracardiac filling pressures and

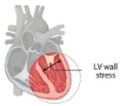
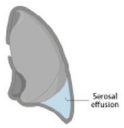
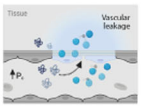
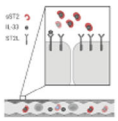
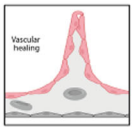
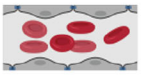
Circulating biomarker	Mechanisms of production	Regional distribution	Compartmental distribution	Pros	Cons	Reference values
BNP/NT-proBNP 	Released in response to myocardial wall tension due to increased transmural pressure	Pulmonary	Intravascular	- Widely available - Useful for diagnosis, triage, and prognostication	- Less accurate in obese individuals, elderly patients, and severe kidney dysfunction - Conflicting results for guiding HF therapy	- Diagnosis: >300 pg/mL in acute HF - Monitoring decongestion: >30% drop at the end of hospitalization
CA125 	Released by mesothelial cells in response to mechanical stress and inflammation	Pulmonary and systemic	Extravascular / tissue	- Useful for assessing congestion severity, guiding diuretic therapy, and risk stratification - Standarized commercially available assays, low cost	- Long half-life - Lagged effect - Non-HF-specific	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
bioADM 	Released to maintain vascular integrity and endothelial barrier function (reduce vascular leakage)	Systemic	Extravascular / tissue	May be useful for identifying patients at risk of residual congestion at discharge	- No information for guiding therapy - Is not widely available for routine use	The best cut-off value of bio-ADM to assess congestion (defined as a congestion score > 1) is 34 pg/mL
sST2 	Released in response to hemodynamic congestion and inflammation by vascular endothelium and lungs	Pulmonary and systemic	Intravascular	Useful for risk-stratification	Limited information about its utility for guiding therapy/monitoring decongestion	Available data have indicated an increase in risk when registering an sST2 concentration ≥35 ng/mL with the Presage ST2 assay
CD146 	Released in response to vascular stress. Mediates pleiotropic functions involved in vessel homeostasis and healing	Systemic	Intravascular	Preliminary data suggest that could be a specific biomarker of venous congestion	- No information about its utility for risk stratification, guiding therapy or monitoring decongestion - Is not widely available for routine use	Not available
Hemoconcentration 	Reflect a relative increase in haemoglobin levels as a result of a reduction in plasma volume	Systemic	Intravascular	- Widely available - Low cost - May help to interpret kidney function changes during decongestion	- May not be useful in patients with anemia or active bleeding - Long-term kinetics are not useful for monitoring decongestion	Not available

Figure 4 Biomarkers in a clinical context. bioADM, biologically active adrenomedullin; BNP, B-type natriuretic peptide; CA125, antigen carbohydrate 125; CD146, cluster of differentiation 146; HF, heart failure; NT-proBNP, aminoterminal pro-B-type natriuretic peptide; sST2, soluble ST2.

pulmonary capillary wedge pressures in patients with HF.[22–25] A summary of the evidence endorsing the association between natriuretic peptides (NPs) and haemodynamic parameters is presented in online supplementary *Appendix S1*. The reason why these peptides correlate with left cardiac pressures lies in their origin. The biomechanical wall stress induced by plasma volume expansion and/or pressure overload triggers the release of pre-synthesized proBNP and transcription of the NP precursor B (*NPPB*) gene, leading to the production of the 134-amino acid proBNP hormone precursor (pre-proBNP).[26,27] Following its production,

pre-proBNP is rapidly processed to yield $proBNP_{1-108}$, which is further cleaved into the bioactive BNP and its biologically inactive equivalent NT-proBNP by the action of proteases such as corin or furin.[28,29] After this initial processing, within minutes of their synthesis, both BNP and NT-proBNP are liberated into the plasma, providing a valuable reflection of the overall cardiac load.[2,3,22–25] The biologic actions of elevated BNP hormone (natriuretic and vasodilator effects) are counteracted by the peripheral resistance, which is established at receptorial and post-receptorial level,[30] making HF a condition characterized by second messenger cyclic guanosine monophosphate (cGMP) insufficiency, hence a target for several treatments.[31]

Despite the proven value of BNP and NT-proBNP for diagnosis and prognosis across the spectrum of HF syndromes,[3,4,32] several properties may limit their usefulness for assessing and grading congestion. First, NPs are mainly expressed by the heart, while fluid overload is systemically extended.[1,32,33] Thus, NPs are indirect congestion measures making them not the ideal markers for congestion. Second, a broad range of structural and functional cardiac and non-cardiac abnormalities are associated with increased ventricular wall tension leading to substantive elevation of levels of plasma NPs without being necessarily linked to fluid retention, such as ischaemia and atrial fibrillation.[32,33] Third, LV wall stress is the most potent trigger for NP synthesis and release.[27] Accordingly, NPs may fail to capture the contribution of right-sided HF and its consequences (systemic and extravascular congestion).[9,34] For instance, in-hospital single-measurements of NPs in AHF did not predict the severity of clinical congestion,[35] and it lacked prognostic effect in those with predominant right-sided HF, such as in patients with severe tricuspid regurgitation.[36] Fourth, in addition to primary generation via increased intracardiac pressures, plasma concentrations of both NT-proBNP and BNP levels are also influenced by common conditions in HF such as older age, atrial fibrillation, and renal dysfunction. Conversely, NPs are inversely related to body mass index.[33] Fifth, NPs are not perfect surrogates for filling pressures and are less accurate in ruling out HF with preserved ejection fraction (HFpEF), especially in the outpatient setting.[37] Furthermore, some specific conditions are associated with NP deficiency, such as polymorphisms in the *NPPB* gene, African ancestry, increased androgenicity in women, insulin resistance, hypercortisolism, and certain medications (e.g. spironolactone).[38] Thus, it is important to account for these factors when interpreting NP levels in the clinical setting.[33]

The role of repeated measurement for monitoring changes in fluid status is also a property that needs to be commented. In general, patients with a greater relative reduction in NPs after treatment exhibit a lower risk of adverse events.[33,39–41] For instance, in chronic HF with reduced ejection fraction (HFrEF), short-term changes in NP levels predicted the risk of hospitalization for WHF.[39] Likewise, recent observational data showed, in at least two consecutive outpatient visits in an ambulatory setting, that a decrease in NT-proBNP was associated with improved mortality and morbidity also in patients with HF and mildly reduced and preserved ejection fraction during routine care.[40] Following an episode of AHF, long-term repeated measurements of high NPs have also been shown to be independently associated with the risk of death.[41] A descending kinetic pattern identified those at lower risk of death, although the ability of serial measurements to predict survival was blunted at longer follow-up.[41] However, despite a clear relationship to cardiac filling pressures and prognosis, changes in NPs may show either absent or weak to moderate relationship with indicators of decongestion in AHF.[17]

The evidence endorsing the utility of NPs for guiding therapy is mixed. The largest trial and the more recent meta-analysis showed no prognostic benefit compared to usual care.[42,43] The GUIDE-IT included 894 patients with stable LV ejection fraction ≤40% and elevated NT-proBNP in the previous month.[43] The authors recommended therapy intensification in this study to achieve a target NT-proBNP of <1000 pg/ml.[43] The NT-proBNP guided therapy included, among others, up-titration of diuretic therapy if NT-proBNP >5000 pg/ml.[44] No differences were found in the mean loop diuretic dose over time between both treatment arms.[43] Thus, a single value of NPs may not provide relevant additional information about the overall congestion status.

From a practical point of view, changes in NPs should be interpreted together with cardiac structural and functional characteristics and clinical evaluation. Evaluating the relative modifications (%) based on each patient's plasma levels when stable ('dry levels') may be more informative about the severity of intracardiac pressure/volume overload than using a single measurement. In this context, a practical approach would consider changes >30% as clinically relevant.[32,45] For example, in stable ambulatory patients, a change of 50% seems to indicate a shift in filling pressures.[32,33] Despite the current evidence not supporting NPs as guiding therapy in HF, its short-term changes are useful for monitoring and guiding initial decongestive therapy in WHF with high levels at presentation (those with predominant pulmonary congestion).

Pitfalls in interpreting serial changes of natriuretic peptides in heart failure

First, NPs show a high intraindividual biological variation, hampering the clinical interpretation of serial measurements.[46] Second, the utility of kinetic of NPs in patients with intrinsically higher levels, such as the elderly, atrial fibrillation, and those with severe kidney dysfunction, needs to be more carefully evaluated.[33–36] Third, their utility in monitoring decongestion is even less clear in patients with overt systemic intravascular and tissue congestion, such as those with predominant right-sided HF.[33,36]

The clinical utility of mid-regional sequence of pro-A-type natriuretic peptide as a biomarker of congestion is less well documented despite its promising utility for long-term risk stratification.[33,47]

Carbohydrate antigen 125

Carbohydrate antigen 125 (CA125, also called mucin 16 [MUC16]) is a high molecular weight (220 kDa) glycoprotein encoded by the *MUC16* gene in humans.[48,49] It is expressed on the surface of cells derived from the coelomic epithelium (i.e. pleura, peritoneum, and pericardium) as a membrane-bound protein, or released in a soluble form via proteolytic cleavage, making it available as a circulating biomarker.[50,51] Although primarily used in monitoring

ovarian cancers,[48] CA125 has also been shown to be elevated in a wide range of other conditions related to volume expansion, including cirrhosis, renal failure, and AHF.[51] It has been postulated that elevated hydrostatic pressure, mechanical stress, and inflammatory stimuli in the setting of congestion may activate mesothelial cells in serosal surfaces, leading to CA125 overproduction and release.[50,51] Indeed, cumulative evidence supports the positive association between plasma levels of CA125 with tissue congestion/serosal effusions, increased cardiac filling pressures, and other proxies of right-sided HF.[34,51] CA125 levels have been shown to be substantially higher in patients with large serosal effusions and peripheral oedema than in those without these particular clinical surrogates of volume overload.[51] In a recent study including 2949 patients hospitalized for AHF, the severity of tricuspid regurgitation, presence of pleural effusion, and peripheral oedema were factors closely associated with the magnitude of circulating CA125.[34] Likewise, in a substudy of BIOSTAT-CHF, CA125 was positive and significantly associated with a clinical congestion score in patients with WHF.[52] More recently, CA125 has also been associated with intrarenal venous congestion and high intra-abdominal pressure in patients with AHF,[53,54] adding to the growing body of evidence supporting the role of this biomarker in identifying a phenotype of predominant systemic and extravascular congestion.[51] Evidence summarizing the association between CA125 and haemodynamic parameters is presented in online supplementary *Appendix S1*.

The close correlation between plasma changes in this biomarker with disease severity and clinical outcomes was described more than 20 years ago. Nägele *et al.*[55] found, in 71 candidate patients for heart transplantation, a significant decrease in this biomarker after heart transplantation (401 ± 259 U/ml vs. 33 ± 22 U/ml), and this trajectory was significantly associated with prognosis. Similarly, D'Aloia *et al.*[56] showed in 286 patients with predominant systolic dysfunction that mid-term fluctuations of plasma CA125 were correlated with clinical evolution and prognosis. More recent studies have confirmed the incremental predictive utility of CA125 changes, especially during the first months after a decompensated HF event, for predicting mortality and readmission.[41,51] For instance, a longitudinal study of 946 consecutive patients discharged for AHF showed that the long-term trajectory delineated by repeated measures of CA125 (3402 observations) predicted the risk of long-term mortality.[41] Most of the substantial decrease occurred within the first month after discharge, and this trajectory identified the subgroup of lower risk. In contrast, there was a higher risk in patients in whom CA125 levels remained high or increased along the course of follow-up.[41]

Regarding therapeutical implications, two small randomized clinical trials endorse the role of CA125 in guiding diuretic therapy.[57,58] In CHANCE-HF, 380 patients with a recent AHF decompensation and CA125 ≥35 U/ml were randomized to standard of care versus CA125-guided therapy. In the active arm, up/down-titration of diuretics was more frequent, and it translated to a significant reduction of the composite outcome of 1-year death/HF admissions, mainly by reducing HF hospitalizations.[57] The IMPROVE-HF trial tested the utility of CA125 for guiding diuretic therapy at presentation in patients with WHF and renal dysfunction.[58] In this last study, the CA125-guided diuretic therapy translated into a better short-term renal function performance.[58]

To correctly interpret CA125 as a surrogate marker of congestion and its evolution, it is important to highlight some fundamental aspects of its biology. First, there is a time gap between congestion onset and CA125 upregulation and release (lagged effect intrinsically related to long half-life that ranges from 5 to 12 days).[51,59] Accordingly, the subset of patients with progressive and long-standing fluid retention (days to weeks) are more likely to have elevated CA125 plasma levels than those presenting with a more acute-onset (minute to hours) presentation.[51] Therefore, besides being valuable for assessing and grading the severity of tissue/third space fluid accumulation, CA125 could also help estimate the chronicity of the congestion process.[51] Likewise, serial changes in CA125 following therapeutic intensification may not capture information about short-term decongestion (hours-days).[51,60] Conversely, weeks after depletive intensification, most patients reached CA125 <35 U/ml regardless of the wet peak value, and this trajectory was closely related to prognosis.[51] Along this same line, in a recent study in patients with AHF, variations in CA125 >10 days from admission, but not before, were associated with the risk of 1-year mortality.[60] Second, and in contrast to NPs, circulating CA125 levels are not meaningfully modified by age, LV status, and kidney function.[51] These properties may be advantageous for its assessment in the elderly, HFpEF, and those with cardiorenal syndrome. The clinical utility of this biomarking for tailoring decongestive therapy, despite initial encouraging results, requires larger confirmatory trials. Lastly, the low cost and wide availability of this biomarker make it easy to implant into daily clinical practice.[51]

Bio-adrenomedullin and mid-regional pro-adrenomedullin

Adrenomedullin (ADM) is a 52-amino acid peptide encoded by the *ADM* gene located on chromosome 11.[61] Upon its translation, the ADM precursor (a pre-prohormone composed of 185 amino acids) is cleaved to yield first proADM and then glycine-extended, inactive ADM.[62] The latter is subsequently converted to biologically active ADM (bio-ADM) by enzymatic amidation.[63,64] Although ADM is involved in a wide range of biological processes,[65] its dominant role is thought to be maintaining vascular integrity and permeability barrier function and regulating vascular tone.[66] ADM diffuses freely across the vascular barrier and exerts a differential effect on vascular endothelial cells (predominantly barrier stabilization) and vascular smooth muscle cells (vasodilatation).[67] Thus, in situations like HF and sepsis characterized by endothelial dysfunction, increased plasma bio-ADM levels may be interpreted as a compensatory attempt to limit vascular leakage by stabilizing the endothelial barrier function.[66,67] A growing body of literature suggests the utility of this peptide as a surrogate marker of congestion in HF.[66,68–72] In patients hospitalized for AHF, bio-ADM was associated with the severity of clinical congestion score at admission in a stepwise fashion, and its baseline values were significant predictors of the presence of residual congestion assessed by clinical congestion score by day 7.[70] In recent large cohorts, bio-ADM was associated with the presence of oedema, orthopnoea, hepatomegaly,

and elevated jugular venous pressure.[71,72] Interestingly, and even though CA125 and bio-ADM correlated positively in patients with WHF (either in-hospital or in the outpatient setting), the magnitude of the association was moderate ($r = 0.35$).[52] In a recent cohort of patients with stable advanced HFrEF undergoing right heart catheterization, bio-ADM correlates positively with both pulmonary capillary wedge pressure ($r = 0.37$, $p = 0.003$), mean right atrial pressure ($r = 0.46$, $p < 0.001$), and NT-proBNP ($r = 0.43$, $p < 0.001$).[73] Thus, bio-ADM may reflect the integrated assessment of both vascular and tissue types of congestion.

The activity of the ADM system may even help to personalize post-discharge diuretic treatment. Among 1886 patients with AHF, patients with above-median bio-ADM concentrations derived disproportional long-term benefits if treated with diuretics.[74] In the same study, mid-regional pro-ADM (MR-proADM), a stable precursor of ADM, had even higher accuracy for predicting 1-year all-cause mortality versus bio-ADM.[74] This last biomarker has shown to be strongly correlated with mean pulmonary artery pressure and pulmonary capillary wedge pressure and inversely correlated with pulmonary artery compliance in subjects with HFpEF.[75] A recent study suggests that the association between levels of bio-ADM and pulmonary capillary pressures decreased in patients with body mass index ≥ 35 kg/m^2. Interestingly, in this work, MR-proADM showed a robust correlation with pulmonary capillary pressures ($r = 0.62$, $p < 0.001$), with no differential relationship based on the presence of obesity.[76]

The information regarding the clinical value of changes over time of these biomarkers for monitoring is more limited. In patients with clinical signs of residual congestion 7 days after hospital admission, bio-ADM levels were high at baseline and remained high throughout the first week of hospitalization.[70] Serial short- and long-term increases in bio-ADM and MR-proADM concentrations have been reported in patients with HF following sacubitril/valsartan initiation due to inhibition of neprilysin.[77] However, no studies are available exploring the long-term kinetics of bio-ADM or MR-proADM across congestion status and clinical outcomes. Therefore, the role of bio-ADM and MR-proADM in monitoring congestion and guiding therapy remains to be defined. Additionally, further research is required to clarify whether its plasma levels are influenced by age, body mass index, LV systolic function, HF aetiology, and liver and renal function.

Online supplementary *Appendix S1* summarizes the evidence endorsing the association between both biomarkers and haemodynamic congestion.

Soluble ST2

ST2 (also known as interleukin-1 receptor-like 1 [IL1RL1]) is a member of the Toll-like/interleukin-1 receptor superfamily and is encoded by the gene *IL1RL1* located on chromosome 2.[78] Alternative splicing generates multiple ST2 isoforms, including a transmembrane form (ST2 ligand or ST2L) and a soluble circulating form (sST2),[79,80] which is a valuable prognostic biomarker in acute or chronic HF.[81,82] The biological action of the ST2 protein is mediated by the extracellular engagement of ST2L with its ligand, interleukin-33 (IL-33).[80] IL-33/ST2L signalling has anti-hypertrophic and anti-fibrotic effects via its activation of diverse intracellular pathways.[83] However, sST2 also avidly binds to IL-33 and is viewed as a decoy receptor, diminishing net transduction of the favourable effects of IL-33 through ST2L.[80]

Although sST2 levels are usually low in patients with stable HF, striking increases in plasma levels are common in AHF and provide valuable prognostic information.[84,85] The mechanisms behind sST2 upregulation in AHF seem to be related to the peripheral release of pro-inflammatory cytokines by activated vascular endothelial cells and lung tissue in response to haemodynamic congestion and inflammation.[86–88] Indeed, sST2 positively correlates with echocardiographic indicators of right-sided HF,[89] and invasively measured central venous pressure in AHF.[90] It has been recently identified as a surrogate marker of diuretic resistance in patients with AHF and renal dysfunction at presentation.[91] Accordingly, sST2 may be a surrogate marker of pulmonary and vascular congestion in HF.[92] Furthermore, the interaction between congestion/inflammation and sST2 upregulation results in dysfunctional IL-33/ST2L signalling that blocks its cardioprotective and vascular benefits.[83] Thus, this pathophysiological link could be one of the mechanisms by which congestion drives further progression of HF.

A single determination of ST2 is associated with additive prognostic information to those provided by clinical variables and cardiac biomarkers in chronic and acute HF.[85,93,94]

Interestingly, the prognostic value of sST2 appears not to be influenced by renal function.[95] However, longitudinal studies are scarce. In a population of 150 patients with decompensated HF undergoing daily blood sampling for sST2, percent change in ST2 was strongly predictive of 90-day mortality: patients whose ST2 values decreased by 15.5% or more during the study period had a 7% chance of death, whereas patients whose ST2 levels failed to decrease by 15.5% in this time interval had a 33% chance of death.[96] In this study, the prognostic value of sST2 changes was independent of variations in NT-proBNP.[96] In a recent subanalysis of the PIONEER-HF trial (comparison of the effect of sacubitril/valsartan vs. enalapril on NT-proBNP in patients stabilized from an AHF episode), baseline sST2 concentrations yielded prognostic significance for the composite outcome of cardiovascular death or HF rehospitalization.[97] Notably, patients in the sacubitril/valsartan arm displayed a greater reduction in circulating sST2 than those receiving enalapril by as early as 1 week, as well as a potentially better outcome.[97]

The exact mechanisms explaining the kinetic of sST2 and the relationship between changes in this biomarker with clinical outcomes warrants a more profound evaluation. Additionally, further studies evaluating potential interactions with common confounders in HF and the ability of this biomarker for monitoring congestion status or guiding depletive therapy are warranted. A summary of the data linking the association between sST2 and vascular congestion is presented in online supplementary *Appendix S1*.

CD146

Cluster of differentiation 146 (CD146) is a 113 kDa glycoprotein encoded by the *CD146* gene located on chromosome 11.[98] It

contains a signal sequence of 28 amino acids, an extracellular portion composed of five immunoglobulin-like domains, a hydrophobic transmembrane region of 24 amino acids, and a short intracytoplasmic domain.[99] Three isoforms of CD146 have been described: two membrane-bound isoforms (lgCD146 and shCD146), and a soluble form (sCD146), which results from the shedding of the extracellular portion of CD146 through cleavage by matrix metalloproteinases.[99] CD146 is expressed on endothelial cells (mainly at the endothelial junction), smooth muscle cells, and pericytes within the whole vascular tree regardless of vessel size and location.[100,101] This glycoprotein interacts with various ligands and mediates pleiotropic functions in vessel homeostases, such as permeability, angiogenesis, vessel architecture, stabilization, and healing.[99] Not surprisingly, sCD146 is overexpressed in conditions associated with inflammation, vascular injury, and endothelial dysfunction (all usually present in AHF syndromes).[102–105]

Current data points to sCD146 as an emerging surrogate of congestion in HF.[106,107] Higher sCD146 levels have been reported in patients with peripheral oedema and/or dilated vena cava than in those without signs of congestion.[107] Moreover, sCD146 accurately identified overhydrated haemodialysis patients irrespective of their BNP values.[108] Similarly, a peripheral venous stress study performed by inflating a pressure cuff over forearm veins induced a rapid and pronounced increase in circulating sCD146 but not of NT-proBNP in the congested arm.[109] Taken together, these preliminary data further indicate that sCD146 is a specific biomarker of venous congestion and, accordingly, could be of value in differentiating between central and peripheral congestion. However, to date, the evidence endorsing the association of this biomarker with haemodynamics and its clinical utility over symptoms/signs and other proxies of congestion is weak or even missing. Additionally, how this biomarker is influenced by common comorbidities and different clinical scenarios in HF requires further clarification.

Troponin

There is a paucity of data linking high levels of troponin with clinical congestion. In patients with advanced HF, after optimization of medical therapy, patients with detectable cardiac troponin I showed higher pulmonary artery and pulmonary capillary wedge pressures.[110] In another study including 133 subjects hospitalized for decompensated HF, the authors showed that peripheral oedema and pulmonary rales on admission were associated with troponin levels on discharge.[111] More recently, an elevated troponin was associated with clinical congestion score in multivariable models after controlling for ventricular filling pressures and NP levels, suggesting that subclinical myocardial injury may be an important contributor to the pathophysiology of congestion.[112] However, the greatest elevation of this biomarker occurs in situations outside acute and chronic HF.[4] This fact and the lack of studies correlating the changes over time of this biomarker and clinical congestion limits the clinical applicability of using troponin as a surrogate of congestion. Online supplementary *Appendix S1* summarizes the evidence endorsing troponin and haemodynamic congestion.

C-terminal pro-endothelin-1

Endothelin-1 (ET-1) is a strong vasoconstrictor, which is involved in inflammation and neurohormonal activation.[113] C-terminal pro-endothelin-1 (CT-proET-1) is the stable circulating precursor protein of ET-1.[113] Circulating levels of CT-proET-1 are higher in patients with HFpEF compared to controls at rest and during exercise.[75] In this same study, CT-proET-1 was strongly correlated with mean pulmonary artery pressure ($r = 0.73$) and pulmonary capillary wedge pressure ($r = 0.67$).[75] In a more recent study of subjects with unexplained dyspnoea, CT-proET-1 was highly correlated with pulmonary capillary wedge pressures and mean pulmonary artery pressures and did not display any differential relationship with body mass index.[76] Future studies are warranted to confirm prior findings and expand the evidence about the utility of this parameter as a surrogate of congestion.

Haemoconcentration

Haemoconcentration, as indicated by increases in haemoglobin or haematocrit following intensive depletive treatment, has also been proposed as a parameter of decongestion.[17] Large studies have shown that haemoconcentration is associated with greater weight and fluid loss, greater reductions in filling pressures, and greater decongestion.[114–116] Interestingly, decongestion with stable haematocrit during treatment has been suggested as a marker of adequate intravascular plasma refill rate.[117]

Likewise, widely accessible indices for estimating changes in plasma volume, which incorporates haemoglobin and/or haematocrit and/or weight, have been shown to correlate with plasma volume assessed by isotopic techniques in healthy volunteers patients with HF.[118,119] Although other studies have questioned their reliability for volume estimation,[120] estimated plasma volume status (ePVS) has been related to adverse outcomes in different HF studies.[118,119,121]

Based on the latest published data with the Duarte's Strauss-derived instantaneous assessment of ePVS (Strauss–Duarte) in acutely decompensated or chronic HF, an actionable threshold of >5.5 ml/g was proposed to define an excessive congestive status associated with poor outcomes, which may allow a prospective evaluation to be used as a trigger for therapeutic action.[122]

Changes in kidney function parameters (serum creatinine and estimated glomerular filtration rate) have also been proposed to play a role as markers of haemoconcentration in HF. In patients with successful decongestion, an increase in creatinine may reflect haemoconcentration rather than worsening renal function.[123–127] In contrast, a decrease in renal function together with clinical data showing persistent congestion is more likely to indicate true 'worsening renal function'.[122–127] Along this line, a recent analysis of two large cohorts of patients with AHF (PROTECT, $n = 1698$ and RELAX-AHF-2, $n = 5586$) showed that worsening renal function, defined as a creatinine increase ≥0.3 mg/dl, in the first 4 days was not associated with worse outcomes when patients had an adequate diuretic response.[128] However, it is fair to recognize that haemoconcentration parameters lacked specificity, and their utility in a single patient required a careful and comprehensive evaluation.

Putting the circulatory biomarkers in the clinical context and future roadmap

A summary of the congestion-related clinical information provided by circulating biomarkers is presented in *Figure 4*, together with tips and caveats for their use and interpretation.

Evaluating congestion in HF is a difficult task as it is crucial to tailor diuretic treatment to the patient's needs,[129] and strongly recommended as class I by the ESC guidelines.[4] The various available tools need to be applied coherently and effectively within each stage of the patient management cycle (i.e. pre-hospital, at the emergency room, during hospitalization, and post-discharge). Whether all patients or a subset could benefit from a multiparametric approach – including clinical evaluation, biological biomarkers, haemodynamics, and imaging (either sequentially or combined) – to detect signs of congestion, help optimize treatment, and improve outcomes has yet to be determined in dedicated studies. Some frameworks in which these tools could (co)-operate have already been proposed in the current document.[1,20] The optimal set of tools required to identify the predominant congestion phenotype in each patient is still to be determined. Therefore, we postulate that further evaluation of different multiparametric approaches requires the inclusion of NPs and additional circulating biomarkers, especially those related to tissue congestion. A proposal for an integrative assessment is provided in *Figure 3*.

Other less specific circulating biomarkers related to congestion status, such as blood urea nitrogen to creatinine ratio, cholestatic parameters, and serum sodium, may also have a useful clinical role in a proper clinical context.[4,20,130]

Another issue that deserves to be evaluated is the interactions between circulating biomarkers and common associated conditions in patients with HF, such as renal dysfunction.[131] As already emphasized, the interplay between the heart and the kidney is crucial in HF while also contributing to cardiorenal syndromes.[123–128,131] Importantly, such mutual engagement may jeopardize the interpretation of variations in the estimated glomerular filtration rate. Indeed, 'true' worsening renal function may be associated with worse clinical outcomes, while 'pseudo' worsening renal function – when initiating depletive therapies – would not.[127] The magnitude of changes in traditional renal function markers for defining true worsening renal function remains to be better defined. Prior studies suggest traditional cutpoints for determining worsening renal function (a drop ≥20%) in patients with AHF treated with intensive intravenous diuretics are not associated with increased markers of kidney tubular injury.[123] The value of acute kidney injury biomarkers in helping to discriminate between true versus pseudo worsening renal function is yet uncertain.[123,127,132,133] For instance, serum neutrophil gelatinase-associated lipocalin (sNGAL), a biomarker that predicts acute kidney injury in multiple conditions, has shown inconsistent findings in AHF.[133] The AKINESIS study showed that sNGAL proved not to be superior to creatinine for predicting worsening renal function or in-hospital adverse events in a large cohort of patients with AHF.[133] However, more recent substudies suggest an interaction with parameters of decongestion.[134] The value of serum and urinary novel tubular markers in HF requires more evaluation.

Moreover, the interpretation of congestion biomarkers might also be challenging in the setting of acute or chronic variations in kidney function. Indeed, there is no consensus on cut-off values used to define HF in patients with acute kidney injury. In patients with chronic kidney disease, independent of HF status, elevated plasma levels of NPs are often found as a result of reduced renal clearance.[32,33]

Similar uncertainties about the clinical interpretation of circulating biomarkers in the setting of elderly patients with HF and those with concomitant atrial fibrillation, liver dysfunction, and obesity deserve to be clarified.

Additionally, we must be extremely rigorous in analysing and implementing novel biomarkers to adopt only those that provide an extra added value to the physician in terms of understanding and handling the disease. Antoniou *et al.*[135] have recently undertaken a comprehensive review of biomarker-guided adaptive trial designs. Their in-depth overview provided clarity in definition, methodology, and terminology for biomarker-guided adaptive trial designs.[135] Eventually, this should help in designing future trials in a more homogeneous and reproducible way. Finally, a cost-effectiveness evaluation of implementing these biomarkers into clinical practice requires profound consideration.

Conclusions

Together with NPs, some circulating biomarkers may help clinicians identify the predominant congestion phenotype of each patient with HF. Ideally, some circulating biomarkers may also be useful for monitoring and guiding decongestive therapies. However, further studies are required to determine which subset of circulating biomarkers should be included in a multiparametric approach for assessing congestion.

Supplementary Information

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

Funding

This work was supported by grants from the Ministry of Economy and Competitiveness, Instituto Carlos III (PI20/00392), CIBER Cardiovascular (16/11/00420 and 16/11/00403).

Conflict of interest: J.N. reports personal fees from AstraZeneca, Novartis, Boehringer Ingelheim, Eli Lilly, Rovi, NovoNordisk, and Vifor Pharma (outside the submitted work). R.d.l.E. reports personal fees from AstraZeneca, Novartis, Boehringer Ingelheim, and NovoNordisk (outside the submitted work). P.R. reports consulting for Bayer, CinCor, G3P, Idorsia, and KBP; honoraria from Ablative Solutions, AstraZeneca, Bayer, Boehringer Ingelheim, Corvidia, CVRx, Fresenius, Novartis, Novo Nordisk, Relypsa Inc., a Vifor Pharma Group Company, Roche, Sanofi, Sequana Medical, Servier, and Vifor Fresenius Medical Care

Renal Pharma; Cofounder: CardioRenal, a company developing potassium and creatinine sensors for home monitoring. A.A.V. has received consultancy fees and/or research grants from Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, Cytokinetics, Merck, Myokardia, Novartis, Novo Nordisk, and Roche Diagnostics. W.M. has received research grants from Novartis, Vifor, Medtronic, Biotronik, Abbott, and Boston Scientific. M.M. and O.C. report grants from Servier, Vifor and Novartis and other from Boehringer Ingelheim. J.L.J. is a Trustee of the American College of Cardiology, a board member of Imbria Pharmaceuticals, has received grant support from Applied Therapeutics, Innolife, Novartis Pharmaceuticals and Abbott Diagnostics, consulting income from Abbott, Janssen, Novartis, and Roche Diagnostics, and participates in clinical endpoint committees/data safety monitoring boards for Abbott, AbbVie, Amgen, Bayer, CVRx, Janssen, MyoKardia and Takeda. C.M. has received research support from the Swiss National Science Foundation, the Swiss Heart Foundation, the KTI, the University Hospital Basel, the University of Basel, Abbott, Astra Zeneca, Beckman Coulter, Brahms, Idorsia, Novartis, LSI Medience Corporation, Ortho Clinical Diagnostics, Quidel, Roche, Siemens, Singulex, Sphingotec, all outside the current work, as well as speaker honoraria/consulting honoraria from Abbott, Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, BMS, Idorsia, Novartis, Osler, Roche, Sanofi, and Singulex, all outside the current work and paid to the institution. A.M.R. reports research grants, advisory board fees and/or speakers honoraria/travel costs from AstraZeneca, NovoNordisk, Roche Diagnostics, Abbott Laboratories, Thermo Fisher, Critical Diagnostics, Novartis, Pfizer, Bayer, Medtronic, Boston Scientific, Sphingotec, and MiRXES. R.A.d.B. received speaker fees from Abbott, AstraZeneca, Bayer, Novartis, and Roche (outside the submitted the work). The UMCG, which employs Dr. de Boer has received research grants and/or fees from AstraZeneca, Abbott, Boehringer Ingelheim, Cardior Pharmaceuticals Gmbh, Ionis Pharmaceuticals, Inc., NovoNordisk, and Roche (outside the submitted work). S.D.A. reports receiving fees from Abbott, Actimed, Bayer, Boehringer Ingelheim, Cardiac Dimension, Cordio, Impulse Dynamics, Novartis, Occlutech, Servier, and Vifor Pharma, and grant support from Abbott and Vifor Pharma. A.C.S. received fees or grants from Bayer, Merck, AstraZeneca, Boehringer Ingelheim, Abbott, Novartis, We-Health, Sanofi, and Vifor Pharma. M.B. is supported by the Deutsche Forschungsgemeinschaft (German Research Foundation; TTR 219, project number 322900939) and reports personal fees from Abbott, Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, Cytokinetics, Medtronic, Novartis, Servier and Vifor. E.A.J. reports grants and personal fees from Vifor Pharma, personal fees from Bayer, Novartis, Abbott, Boehringer Ingelheim, Pfizer, Servier, AstraZeneca, Berlin Chemie, Cardiac Dimensions, Respicardia, Takeda, Swixx Biopharma, Gedeon Richter, Radcliffe Group, Translational Medicine Academy, outside the submitted work. F.G. is an advisor to Pfizer, Ionis, Alnylam, Bayer, Pharmacosmos and Abbott; received speaker honoraria from Novartis, Orion Pharma, AstraZeneca, Vifor Pharma and Boehringer Ingelheim. P.S.J. employer the University of Glasgow has received payment from Novartis, AstraZeneca, NovoNordisk and Bayer for work on clinical trials, research support from Boehringer Ingelheim and Analog Devices Inc and speakers and advisory board fees from AstraZeneca, Novartis and Boehringer Ingelheim. L.H.L. reports grants, consulting fees and/or speaker's honoraria from Myocardia, AstraZeneca, Roche, Boehringer Ingelheim, Novartis, Bayer, Vifor, Sanofi, Servier, Abbott, Pharmacosmos, Medscape, Radcliffe, TMA, Orion Pharma, and stock ownership in AnaCardio, all outside the submitted work. B.M. reports personal fees and/or advisory board from AstraZeneca, Novartis, Boehringer Ingelheim, Eli-Lilly, Servier, and Vifor Pharma. P.P. reports fees from Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, Corida, Cytokinetics, Impulse Dynamics, Novartis, Radcliffe, Servier, Vifor, all outside the current work. G.S. reports grants and personal fees from Vifor, AstraZeneca, grants from Boehringer Ingelheim, Novartis, Boston Scientific, Pharmacosmos, Merck, Bayer, personal fees from Società Prodotti Antibiotici, Roche, Servier, GENESIS, Cytokinetics, Medtronic, Teva, TMA, outside the submitted work. C.G.T. received funding from Amgen and personal fees from VivaLyfe, and is listed as an inventor on two heart failure patents. A.B.G. reports personal fees and/or advisory board from AstraZeneca, Novartis, Boehringer Ingelheim, Abbott, Roche Diagnostics, and Vifor Pharma. All other authors have nothing to disclose.

References

1. Mullens W, Damman K, Harjola VP, Mebazaa A, Brunner-La Rocca HP, Martens P, et al. The use of diuretics in heart failure with congestion – a position statement from the Heart Failure Association of the European Society of Cardiology. *Eur J Heart Fail*. 2019;**21**:137–55.
2. Packer M. Evolution of the neurohormonal hypothesis to explain the progression of chronic heart failure. *Eur Heart J*. 1995;**16**:4–6.
3. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JGF, Coats AJS, et al. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur J Heart Fail*. 2016;**18**:891–975.
4. McDonagh TA, Metra M, Adamo M, Gardner RS, Baumbach A, Böhm M, et al.; ESC Scientific Document Group. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: developed by the Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). With the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur J Heart Fail*. 2022;**24**:4–131.
5. Bozkurt B, Coats AJS, Tsutsui H, Abdelhamid CM, Adamopoulos S, Albert N, et al. Universal definition and classification of heart failure: a report of the Heart Failure Society of America, Heart Failure Association of the European Society of Cardiology, Japanese Heart Failure Society and Writing Committee of the Universal Definition of Heart Failure. *Eur J Heart Fail*. 2021;**23**:352–80.
6. Miller WL. Fluid volume overload and congestion in heart failure: time to reconsider pathophysiology and how volume is assessed. *Circ Heart Fail*. 2016;**9**:e002922.
7. Soloveva A, Fudim M. A contemporary picture of congestion in heart failure: from dropsy impression to multifaceted reality. *J Cardiovasc Transl Res*. 2020;**13**:507–8.
8. Yaranov DM, Jefferies JL, Silver MA, Burkhoff D, Rao VN, Fudim M. Discordance of pressure and volume: potential implications for pressure-guided remote monitoring in heart failure. *J Card Fail*. 2022;**28**:870–2.
9. Miller WL, Sorimachi H, Grill DE, Fischer K, Borlaug BA. Contributions of cardiac dysfunction and volume status to central haemodynamics in chronic heart failure. *Eur J Heart Fail*. 2021;**23**:1097–105.
10. Weiner RB, Weyman AE, Khan AM, Reingold JS, Chen-Tournoux AA, Scherrer-Crosbie M, et al. Preload dependency of left ventricular torsion: the impact of normal saline infusion. *Circ Cardiovasc Imaging*. 2010;**3**:672–8.
11. Verbrugge FH, Guazzi M, Testani JM, Borlaug BA. Altered hemodynamics and end-organ damage in heart failure: impact on the lung and kidney. *Circulation*. 2020;**142**:998–1012.

12. Maurer MS, Packer M. Impaired systemic venous capacitance: the neglected mechanism in patients with heart failure and a preserved ejection fraction? *Eur J Heart Fail*. 2020;**22**:173–6.
13. Fudim M, Hernandez AF, Felker GM. Role of volume redistribution in the congestion of heart failure. *J Am Heart Assoc*. 2017;**6**:e006817.
14. Sorimachi H, Burkhoff D, Verbrugge FH, Omote K, Obokata M, Reddy YNV, et al. Obesity, venous capacitance, and venous compliance in heart failure with preserved ejection fraction. *Eur J Heart Fail*. 2021;**23**:1648–58.
15. Nijst P, Verbrugge FH, Grieten L, Dupont M, Steels P, Tang WHW, et al. The pathophysiological role of interstitial sodium in heart failure. *J Am Coll Cardiol*. 2015;**65**:378–88.
16. Wiig H, Luft FC, Titze JM. The interstitium conducts extrarenal storage of sodium and represents a third compartment essential for extracellular volume and blood pressure homeostasis. *Acta Physiol (Oxf)*. 2018;**222**:e13006.
17. Boorsma EM, Ter Maaten JM, Damman K, Dinh W, Gustafsson F, Goldsmith S, et al. Congestion in heart failure: a contemporary look at physiology, diagnosis and treatment. *Nat Rev Cardiol*. 2020;**17**:641–55.
18. Damman K, Beusekamp JC, Boorsma EM, Swart HP, Smilde TDJ, Elvan A, et al. Randomized, double-blind, placebo-controlled, multicentre pilot study on the effects of empagliflozin on clinical outcomes in patients with acute decompensated heart failure (EMPA-RESPONSE-AHF). *Eur J Heart Fail*. 2020;**22**:713–22.
19. Selvaraj S, Claggett B, Pozzi A, McMurray JJV, Jhund PS, Packer M, et al. Prognostic implications of congestion on physical examination among contemporary patients with heart failure and reduced ejection fraction: PARADIGM-HF. *Circulation*. 2019;**140**:1369–79.
20. Girerd N, Seronde MF, Coiro S, Chouihed T, Bilbault P, Braun F, et al. Integrative assessment of congestion in heart failure throughout the patient journey. *JACC Heart Fail*. 2018;**6**:273–85.
21. Du W, Piek A, Schouten EM, van de Kolk CWA, Mueller C, Mebazaa A, et al. Plasma levels of heart failure biomarkers are primarily a reflection of extracardiac production. *Theranostics*. 2018;**8**:4155–69.
22. Haug C, Metzele A, Kochs M, Hombach V, Grünert A. Plasma brain natriuretic peptide and atrial natriuretic peptide concentrations correlate with left ventricular end-diastolic pressure. *Clin Cardiol*. 1993;**16**:553–7.
23. Kazanegra R, Cheng V, Garcia A, Krishnaswamy P, Gardetto N, Clopton P, et al. A rapid test for B-type natriuretic peptide correlates with falling wedge pressures in patients treated for decompensated heart failure: a pilot study. *J Card Fail*. 2001;**7**:21–9.
24. Taub PR, Daniels LB, Maisel AS. Usefulness of B-type natriuretic peptide levels in predicting hemodynamic and clinical decompensation. *Heart Fail Clin*. 2009;**5**:169–75.
25. Yoshimura M, Yasue H, Okumura K, Ogawa H, Jougasaki M, Mukoyama M, et al. Different secretion patterns of atrial natriuretic peptide and brain natriuretic peptide in patients with congestive heart failure. *Circulation*. 1993;**87**:464–9.
26. Ichiki T, Burnett JC. Post-transcriptional modification of pro-BNP in heart failure: is glycosylation and circulating furin key for cardiovascular homeostasis? *Eur Heart J*. 2014;**35**:3001–3.
27. Ibrahim NE, Januzzi JL. Established and emerging roles of biomarkers in heart failure. *Circ Res*. 2018;**123**:614–29.
28. Sawada Y, Suda M, Yokoyama H, Kanda T, Sakamaki T, Tanaka S, et al. Stretch-induced hypertrophic growth of cardiocytes and processing of brain-type natriuretic peptide are controlled by proprotein-processing endoprotease furin. *J Biol Chem*. 1997;**272**:20545–54.
29. Yan W, Wu F, Morser J, Wu Q. Corin, a transmembrane cardiac serine protease, acts as a pro-atrial natriuretic peptide-converting enzyme. *Proc Natl Acad Sci U S A*. 2000;**97**:8525–9.
30. Clerico A, Recchia FA, Passino C, Emdin M. Cardiac endocrine function is an essential component of the homeostatic regulation network: physiological and clinical implications. *Am J Physiol Heart Circ Physiol*. 2006;**290**:H17–29.
31. Emdin M, Aimo A, Castiglione V, Vergaro G, Georgiopoulos G, Saccaro LF, et al. Targeting cyclic guanosine monophosphate to treat heart failure: JACC review topic of the week. *J Am Coll Cardiol*. 2020;**76**:1795–807.
32. Thygesen K, Mair J, Mueller C, Huber K, Weber M, Plebani M, et al.; Study Group on Biomarkers in Cardiology of the ESC Working Group on Acute Cardiac Care. Recommendations for the use of natriuretic peptides in acute cardiac care: a position statement from the study group on biomarkers in cardiology of the ESC. Working group on acute cardiac care. *Eur Heart J*. 2012;**33**:2001–6.
33. Mueller C, McDonald K, de Boer RA, Maisel A, Cleland JGF, Kozhuharov N, et al. Heart Failure Association of the European Society of Cardiology practical guidance on the use of natriuretic peptide concentrations. *Eur J Heart Fail*. 2019;**21**:715–31.
34. Miñana G, de la Espriella R, Mollar A, Santas E, Núñez E, Valero E, et al. 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**:437–47.
35. Llàcer P, Gallardo MÁ, Palau P, Moreno MC, Castillo C, Fernández C, et al. Comparison between CA125 and NT-proBNP for evaluating congestion in acute heart failure. *Med Clin (Barc)*. 2021;**156**:589–94.
36. Soler M, Miñana G, Santas E, Núñez E, de la Espriella R, Valero E, et al. CA125 outperforms NT-proBNP in acute heart failure with severe tricuspid regurgitation. *Int J Cardiol*. 2020;**308**:54–9.
37. Verbrugge FH, Omote K, Reddy YNV, Sorimachi H, Obokata M, Borlaug BA. Heart failure with preserved ejection fraction in patients with normal natriuretic peptide levels is associated with increased morbidity and mortality. *Eur Heart J*. 2022;**43**:1941–51.
38. Shah SJ. BNP: biomarker not perfect in heart failure with preserved ejection fraction. *Eur Heart J*. 2022;**43**:1952–4.
39. Savarese G, Musella F, D'Amore C, Vassallo E, Losco T, Gambardella F, et al. Changes of natriuretic peptides predict hospital admissions in patients with chronic heart failure: a meta-analysis. *JACC Heart Fail*. 2014;**2**:148–58.
40. Savarese G, Hage C, Orsini N, Dahlström U, Perrone-Filardi P, Rosano GM, et al. Reductions in N-terminal pro-brain natriuretic peptide levels are associated with lower mortality and heart failure hospitalization rates in patients with heart failure with mid-range and preserved ejection fraction. *Circ Heart Fail*. 2016;**9**:e003105.
41. Núñez J, Núñez E, Bayés-Genís A, Fonarow GC, Miñana G, Bodí V, et al. 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**:685–96.
42. McLellan J, Bankhead CR, Oke JL, Hobbs FDR, Taylor CJ, Perera R. Natriuretic peptide-guided treatment for heart failure: a systematic review and meta-analysis. *BMJ Evid Based Med*. 2020;**25**:33–7.
43. Felker GM, Anstrom KJ, Adams KF, Ezekowitz JA, Fiuzat M, Houston-Miller N, et al. Effect of natriuretic peptide-guided therapy on hospitalization or cardiovascular mortality in high-risk patients with heart failure and reduced ejection fraction: a randomized clinical trial. *JAMA*. 2017;**318**:713–20.
44. Felker GM, Ahmad T, Anstrom KJ, Adams KF, Cooper LS, Ezekowitz JA, et al. Rationale and design of the GUIDE-IT study: Guiding Evidence Based Therapy Using Biomarker Intensified Treatment in Heart Failure. *JACC Heart Fail*. 2014;**2**:457–65.
45. Schou M, Gustafsson F, Kjaer A, Hildebrandt PR. Long-term clinical variation of NT-proBNP in stable chronic heart failure patients. *Eur Heart J*. 2007;**28**:177–82.
46. Bruins S, Fokkema MR, Römer JW, Dejongste MJ, van der Dijs FP, van den Ouweland JM, et al. High intraindividual variation of B-type natriuretic peptide (BNP) and amino-terminal proBNP in patients with stable chronic heart failure. *Clin Chem*. 2004;**50**:2052–8.
47. Odermatt J, Hersberger L, Bolliger R, Graedel L, Christ-Crain M, Briel M, et al. The natriuretic peptide MR-proANP predicts all-cause mortality and adverse outcome in community patients: a 10-year follow-up study. *Clin Chem Lab Med*. 2017;**55**:1407–16.
48. Scholler N, Urban N. CA125 in ovarian cancer. *Biomark Med*. 2007;**1**:513–23.
49. 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.
50. Zeillemaker AM, Verbrugh HA, Hoynck van Papendrecht AA, Leguit P. CA 125 secretion by peritoneal mesothelial cells. *J Clin Pathol*. 1994;**47**:263–5.
51. Núñez J, de la Espriella R, Miñana G, Santas E, Llácer P, Núñez E, et al. Antigen carbohydrate 125 as a biomarker in heart failure: a narrative review. *Eur J Heart Fail*. 2021;**23**:1445–57.
52. Núñez J, Bayés-Genís A, Revuelta-López E, Ter Maaten JM, Miñana G, Barallat J, et al. Clinical role of CA125 in worsening heart failure: a BIOSTAT-CHF study subanalysis. *JACC Heart Fail*. 2020;**8**:386–97.
53. Núñez-Marín G, de la Espriella R, Santas E, Lorenzo M, Miñana G, Núñez E, et al. 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**:475–83.
54. Rubio-Gracia J, Crespo-Aznarez S, de la Espriella R, Nuñez G, Sánchez-Marteles M, Garcés-Horna V, et al. Utility of plasma CA125 as a proxy of intra-abdominal pressure in patients with acute heart failure. *Eur Heart J Acute Cardiovasc Care*. 2022;**11**:453–60.
55. Nägele H, Bahlo M, Klapdor R, Schaeperkoetter D, Rödiger W. CA 125 and its relation to cardiac function. *Am Heart J*. 1999;**137**:1044–9.
56. D'Aloia A, Faggiano P, Aurigemma G, Bontempi L, Ruggeri G, Metra M, et al. 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**:1805–11.
57. Núñez J, Llàcer P, Bertomeu-González V, Bosch MJ, Merlos P, García-Blas S, et al.; CHANCE-HF Investigators. Carbohydrate antigen-125-guided therapy in acute heart failure: CHANCE-HF: a randomized study. *JACC Heart Fail*. 2016;**4**:833–43.

58. Núñez J, Llàcer P, García-Blas S, Bonanad C, Ventura S, Núñez JM, et al. CA125-guided diuretic treatment versus usual care in patients with acute heart failure and renal dysfunction. *Am J Med*. 2020;**133**:370–80.e4.
59. Yoshikawa T, Takano M, Kita T, Kudoh K, Sasaki N, Kato M, et al. Normal serum CA125 half-life and normal serum nadir CA125 level in patients with ovarian cancers. *Eur J Gynaecol Oncol*. 2012;**33**:269–73.
60. Lourenço P, Cunha FM, Elias C, Fernandes C, Barroso I, Guimarães JT, et al. CA-125 variation in acute heart failure: a single-centre analysis. *ESC Heart Fail*. 2022;**9**:1018–26.
61. Ishimitsu T, Kojima M, Kangawa K, Hino J, Matsuoka H, Kitamura K, et al. Genomic structure of human adrenomedullin gene. *Biochem Biophys Res Commun*. 1994;**203**:631–9.
62. Kitamura K, Kato J, Kawamoto M, Tanaka M, Chino N, Kangawa K, et al. The intermediate form of glycine-extended adrenomedullin is the major circulating molecular form in human plasma. *Biochem Biophys Res Commun*. 1998;**244**:551–5.
63. Hinson JP, Kapas S, Smith DM. Adrenomedullin, a multifunctional regulatory peptide. *Endocr Rev*. 2000;**21**:138–67.
64. Smith DM, Coppock HA, Withers DJ, Owji AA, Hay DL, Choksi TP, et al. Adrenomedullin: receptor and signal transduction. *Biochem Soc Trans*. 2002;**30**:432–7.
65. Schönauer R, Els-Heindl S, Beck-Sickinger AG. Adrenomedullin – new perspectives of a potent peptide hormone. *J Pept Sci*. 2017;**23**:472–85.
66. Voors AA, Kremer D, Geven C, Ter Maaten JM, Struck J, Bergmann A, et al. Adrenomedullin in heart failure: pathophysiology and therapeutic application. *Eur J Heart Fail*. 2019;**21**:163–71.
67. Geven C, Bergmann A, Kox M, Pickkers P. Vascular effects of adrenomedullin and the anti-adrenomedullin antibody adrecizumab in sepsis. *Shock*. 2018;**50**:132–40.
68. Nishikimi T, Nakagawa Y. Adrenomedullin as a biomarker of heart failure. *Heart Fail Clin*. 2018;**14**:49–55.
69. Tsuruda T, Kato J, Kuwasako K, Kitamura K. Adrenomedullin: continuing to explore cardioprotection. *Peptides*. 2019;**111**:47–54.
70. Kremer D, Ter Maaten JM, Voors AA. Bio-adrenomedullin as a potential quick, reliable, and objective marker of congestion in heart failure. *Eur J Heart Fail*. 2018;**20**:1363–5.
71. ter Maaten JM, Kremer D, Demissei BG, Struck J, Bergmann A, Anker SD, et al. Bio-adrenomedullin as a marker of congestion in patients with new-onset and worsening heart failure. *Eur J Heart Fail*. 2019;**21**:732–43.
72. Pandhi P, Ter Maaten JM, Emmens JE, Struck J, Bergmann A, Cleland JG, et al. Clinical value of pre-discharge bio-adrenomedullin as a marker of residual congestion and high risk of heart failure hospital readmission. *Eur J Heart Fail*. 2020;**22**:683–91.
73. Goetze JP, Balling L, Deis T, Struck J, Bergmann A, Gustafsson F. Bioactive adrenomedullin in plasma is associated with biventricular filling pressures in patients with advanced heart failure. *Eur J Heart Fail*. 2021;**23**:489–91.
74. Kozhuharov N, Ng L, Wussler D, Strebel I, Sabti Z, Hartmann O, et al. Activity of the adrenomedullin system to personalise post-discharge diuretic treatment in acute heart failure. *Clin Res Cardiol*. 2021;**111**:627–37.
75. Obokata M, Kane GC, Reddy YNV, Melenovsky V, Olson TP, Jarolim P, et al. The neurohormonal basis of pulmonary hypertension in heart failure with preserved ejection fraction. *Eur Heart J*. 2019;**40**:3707–17.
76. Obokata M, Reddy YNV, Melenovsky V, Sorimachi H, Jarolim P, Borlaug BA. Uncoupling between intravascular and distending pressures leads to underestimation of circulatory congestion in obesity. *Eur J Heart Fail*. 2022;**24**:353–61.
77. Arfsten H, Goliasch G, Bartko PE, Prausmüller S, Spinka G, Cho A, et al. Increased concentrations of bioactive adrenomedullin subsequently to angiotensin-receptor/neprilysin-inhibitor treatment in chronic systolic heart failure. *Br J Clin Pharmacol*. 2021;**87**:916–24.
78. Dale M, Nicklin MJ. Interleukin-1 receptor cluster: gene organization of IL1R2, IL1R1, IL1RL2 (IL-1Rrp2), IL1RL1 (T1/ST2), and IL18R1 (IL-1Rrp) on human chromosome 2q. *Genomics*. 1999;**57**:177–9.
79. Bergers G, Reikerstorfer A, Braselmann S, Graninger P, Busslinger M. Alternative promoter usage of the Fos-responsive gene Fit-1 generates mRNA isoforms coding for either secreted or membrane-bound proteins related to the IL-1 receptor. *EMBO J*. 1994;**13**:1176–88.
80. Kakkar R, Lee RT. The IL-33/ST2 pathway: therapeutic target and novel biomarker. *Nat Rev Drug Discov*. 2008;**7**:827–40.
81. Bayés-Genís A, Núñez J, Lupón J. Soluble ST2 for prognosis and monitoring in heart failure: the new gold standard? *J Am Coll Cardiol*. 2017;**70**:2389–92.
82. Aimo A, Januzzi JL, Bayes-Genis A, Vergaro G, Sciarrone P, Passino C, et al. Clinical and prognostic significance of sST2 in heart failure: JACC review topic of the week. *J Am Coll Cardiol*. 2019;**74**:2193–203.
83. Sanada S, Hakuno D, Higgins LJ, Schreiter ER, McKenzie ANJ, Lee RT. IL-33 and ST2 comprise a critical biomechanically induced and cardioprotective signaling system. *J Clin Invest*. 2007;**117**:1538–49.
84. Shah RV, Januzzi JL. ST2: a novel remodeling biomarker in acute and chronic heart failure. *Curr Heart Fail Rep*. 2010;**7**:9–14.
85. Aimo A, Vergaro G, Ripoli A, Bayes-Genis A, Pascual Figal DA, de Boer RA, et al. Meta-analysis of soluble suppression of tumorigenicity-2 and prognosis in acute heart failure. *JACC Heart Fail*. 2017;**5**:287–96.
86. Bartunek J, Delrue L, Van Durme F, Muller O, Casselman F, De Wiest B, et al. Non myocardial production of ST2 protein in human hypertrophy and failure is related to diastolic load. *J Am Coll Cardiol*. 2008;**52**:2166–74.
87. Demyanets S, Kaun C, Pentz R, Krychtiuk KA, Rauscher S, Pfaffenberger S, et al. Components of the interleukin-33/ST2 system are differentially expressed and regulated in human cardiac cells and in cells of the cardiac vasculature. *J Mol Cell Cardiol*. 2013;**60**:16–26.
88. Pascual-Figal DA, Pérez-Martínez MT, Asensio-Lopez MC, Sanchez-Más J, García-García ME, Martinez CM, et al. Pulmonary production of soluble ST2 in heart failure. *Circ Heart Fail*. 2018;**11**:e005488.
89. de Filippi C, Daniels LB, Bayes-Genis A. Structural heart disease and ST2: cross-sectional and longitudinal associations with echocardiography. *Am J Cardiol*. 2015;**115**:59B–63B.
90. Zilinski JL, Shah RV, Gaggin HK, Gantzer ML, Wang TJ, Januzzi JL. Measurement of multiple biomarkers in advanced stage heart failure patients treated with pulmonary artery catheter guided therapy. *Crit Care*. 2012;**16**:R135.
91. de la Espriella R, Bayés-Genis A, Revuelta-López E, Miñana G, Santas E, Llàcer P, et al.; IMPROVE-HF Investigators. Soluble ST2 and diuretic efficiency in acute heart failure and concomitant renal dysfunction. *J Card Fail*. 2021;**27**:427–34.
92. Bayés-Genis A, González A, Lupón J. ST2 in heart failure. *Circ Heart Fail*. 2018;**11**:e005582.
93. Emdin M, Aimo A, Vergaro G, Bayes-Genis A, Lupón J, Latini R, et al. sST2 predicts outcome in chronic heart failure beyond NT-proBNP and high-sensitivity troponin T. *J Am Coll Cardiol*. 2018;**72**:2309–20.
94. Lassus J, Gayat E, Mueller C, Peacock WF, Spinar J, Harjola VP, et al.; GREAT Network. Incremental value of biomarkers to clinical variables for mortality prediction in acutely decompensated heart failure: the Multinational Observational Cohort on Acute Heart Failure (MOCA) study. *Int J Cardiol*. 2013;**168**:2186–94.
95. Bayes-Genis A, Zamora E, de Antonio M, Galán A, Vila J, Urrutia A, et al. Soluble ST2 serum concentration and renal function in heart failure. *J Card Fail*. 2013;**19**:768–75.
96. Boisot S, Beede J, Isakson S, Chiu A, Clopton P, Januzzi J, et al. Serial sampling of ST2 predicts 90-day mortality following destabilized heart failure. *J Card Fail*. 2008;**14**:732–8.
97. Morrow DA, Velazquez EJ, DeVore AD, Prescott MF, Duffy CI, Gurmu Y, et al. Cardiovascular biomarkers in patients with acute decompensated heart failure randomized to sacubitril-valsartan or enalapril in the PIONEER-HF trial. *Eur Heart J*. 2019;**40**:3345–52.
98. Kuske MD, Johnson JP. Assignment of the human melanoma cell adhesion molecule gene (MCAM) to chromosome 11 band q23.3 by radiation hybrid mapping. *Cytogenet Cell Genet*. 1999;**87**:258.
99. Leroyer AS, Blin MG, Bachelier R, Bardin N, Blot-Chabaud M, Dignat-George F. CD146 (cluster of differentiation 146). *Arterioscler Thromb Vasc Biol*. 2019;**39**:1026–33.
100. Cooper AD, Niejadlik D, Huston K. Liver disease in nonparenteral drug abusers. *JAMA*. 1975;**233**:964–6.
101. Crisan M, Yap S, Casteilla L, Chen CW, Corselli M, Park TS, et al. A perivascular origin for mesenchymal stem cells in multiple human organs. *Cell Stem Cell*. 2008;**3**:301–13.
102. Bardin N, Moal V, Anfosso F, Daniel L, Brunet P, Sampol J, et al. Soluble CD146, a novel endothelial marker, is increased in physiopathological settings linked to endothelial junctional alteration. *Thromb Haemost*. 2003;**90**:915–20.
103. Bardin N, Reumaux D, Geboes K, Colombel JF, Blot-Chabaud M, Sampol J, et al. Increased expression of CD146, a new marker of the endothelial junction in active inflammatory bowel disease. *Inflamm Bowel Dis*. 2006;**12**:16–21.
104. Fan Y, Fei Y, Zheng L, Wang J, Xiao W, Wen J, et al. Expression of endothelial cell injury marker CD146 correlates with disease severity and predicts the renal outcomes in patients with diabetic nephropathy. *Cell Physiol Biochem*. 2018;**48**:63–74.
105. Pasquier E, Bardin N, De Saint Martin L, Le Martelot MT, Bohec C, Roche S, et al. The first assessment of soluble CD146 in women with unexplained pregnancy loss. A new insight? *Thromb Haemost*. 2005;**94**:1280–4.

106. Simonavičius J, Mikalauskas A, Brunner-La Rocca HP. Soluble CD146 – an underreported novel biomarker of congestion: a comment on a review concerning congestion assessment and evaluation in acute heart failure. *Heart Fail Rev*. 2021;**26**:731–2.
107. Gayat E, Caillard A, Laribi S, Mueller C, Sadoune M, Seronde MF, et al. Soluble CD146, a new endothelial biomarker of acutely decompensated heart failure. *Int J Cardiol*. 2015;**199**:241–7.
108. Arrigo M, Von Moos S, Gerritsen K, Sadoune M, Tangvoraphonkchai K, Davenport A, et al. Soluble CD146 and B-type natriuretic peptide dissect overhydration into functional components of prognostic relevance in haemodialysis patients. *Nephrol Dial Transplant*. 2018;**33**:2035–42.
109. Arrigo M, Truong QA, Onat D, Szymonifka J, Gayat E, Tolppanen H, et al. Soluble CD146 is a novel marker of systemic congestion in heart failure patients: an experimental mechanistic and transcardiac clinical study. *Clin Chem*. 2017;**63**:386–93.
110. Horwich TB, Patel J, MacLellan WR, Fonarow GC. Cardiac troponin I is associated with impaired hemodynamics, progressive left ventricular dysfunction, and increased mortality rates in advanced heart failure. *Circulation*. 2003;**108**:833–8.
111. Negi S, Sawano M, Kohsaka S, Inohara T, Shiraishi Y, Kohno T, et al. Prognostic implication of physical signs of congestion in acute heart failure patients and its association with steady-state biomarker levels. *PLoS One*. 2014;**9**:e96325.
112. Thibodeau JT, Pham DD, Kelly SA, Ayers CR, Garg S, Grodin JL, et al. Subclinical myocardial injury and the phenotype of clinical congestion in patients with heart failure and reduced left ventricular ejection fraction. *J Card Fail*. 2022;**28**:422–30.
113. Buendgens L, Yagmur E, Bruensing J, Herbers U, Baeck C, Trautwein C, et al. C-terminal proendothelin-1 (CT-proET-1) is associated with organ failure and predicts mortality in critically ill patients. *J Intensive Care*. 2017;**5**:25.
114. Testani JM, Chen J, McCauley BD, Kimmel SE, Shannon RP. Potential effects of aggressive decongestion during the treatment of decompensated heart failure on renal function and survival. *Circulation*. 2010;**122**:265–72.
115. Greene SJ, Gheorghiade M, Vaduganathan M, Ambrosy AP, Mentz RJ, Subacius H, et al.; EVEREST Trial investigators. Haemoconcentration, renal function, and post-discharge outcomes among patients hospitalized for heart failure with reduced ejection fraction: insights from the EVEREST trial. *Eur J Heart Fail*. 2013;**15**:1401–11.
116. van der Meer P, Postmus D, Ponikowski P, Cleland JG, O'Connor CM, Cotter G, et al. The predictive value of short-term changes in hemoglobin concentration in patients presenting with acute decompensated heart failure. *J Am Coll Cardiol*. 2013;**61**:1973–81.
117. Boyle A, Sobotka PA. Redefining the therapeutic objective in decompensated heart failure: hemoconcentration as a surrogate for plasma refill rate. *J Card Fail*. 2006;**12**:247–9.
118. Martens P, Nijst P, Dupont M, Mullens W. The optimal plasma volume status in heart failure in relation to clinical outcome. *J Card Fail*. 2019;**25**:240–8.
119. Ling HZ, Flint J, Damgaard M, Bonfils PK, Cheng AS, Aggarwal S, et al. Calculated plasma volume status and prognosis in chronic heart failure. *Eur J Heart Fail*. 2015;**17**:35–43.
120. Fudim M, Miller WL. Calculated estimates of plasma volume in patients with chronic heart failure – comparison with measured volumes. *J Card Fail*. 2018;**24**:553–60.
121. Duarte K, Monnez JM, Albuisson E, Pitt B, Zannad F, Rossignol P. Prognostic value of estimated plasma volume in heart failure. *JACC Heart Fail*. 2015;**3**:886–93.
122. Kobayashi M, Girerd N, Duarte K, Chouihed T, Chikamori T, Pitt B, et al. Estimated plasma volume status in heart failure: clinical implications and future directions. *Clin Res Cardiol*. 2021;**110**:1159–72.
123. Ahmad T, Jackson K, Rao VS, Tang WHW, Brisco-Bacik MA, Chen HH, et al. Worsening renal function in patients with acute heart failure undergoing aggressive diuresis is not associated with tubular injury. *Circulation*. 2018;**137**:2016–28.
124. Metra M, Davison B, Bettari L, Sun H, Edwards C, Lazzarini V, et al. Is worsening renal function an ominous prognostic sign in patients with acute heart failure? The role of congestion and its interaction with renal function. *Circ Heart Fail*. 2012;**5**:54–62.
125. McCallum W, Tighiouart H, Testani JM, Griffin M, Konstam MA, Udelson JE, et al. Acute kidney function declines in the context of decongestion in acute decompensated heart failure. *JACC Heart Fail*. 2020;**8**:537–47.
126. Núñez J, Miñana G, Santas E, Bertomeu-González V. Cardiorenal syndrome in acute heart failure: revisiting paradigms. *Rev Esp Cardiol (Engl Ed)*. 2015;**68**:426–35.
127. Mullens W, Damman K, Testani JM, Martens P, Mueller C, Lassus J, et al. Evaluation of kidney function throughout the heart failure trajectory – a position statement from the Heart Failure Association of the European Society of Cardiology. *Eur J Heart Fail*. 2020;**22**:584–603.
128. Emmens JE, Ter Maaten JM, Matsue Y, Figarska SM, Sama IE, Cotter G, et al. Worsening renal function in acute heart failure in the context of diuretic response. *Eur J Heart Fail*. 2022;**24**:365–74.
129. Rossignol P, Hernandez AF, Solomon SD, Zannad F. Heart failure drug treatment. *Lancet*. 2019;**393**:1034–44.
130. Parrinello G, Torres D, Testani JM, Almasio PL, Bellanca M, Pizzo G, et al. Blood urea nitrogen to creatinine ratio is associated with congestion and mortality in heart failure patients with renal dysfunction. *Intern Emerg Med*. 2015;**10**:965–72.
131. Zannad F, Rossignol P. Cardiorenal syndrome revisited. *Circulation*. 2018;**138**:929–44.
132. Aimo A, Lupón J, Bayes-Genis A, Emdin M. Urinary NGAL in acute heart failure revisited: the game is not over yet. *Int J Cardiol*. 2022;**357**:113–4.
133. Maisel AS, Wettersten N, van Veldhuisen DJ, Mueller C, Filippatos G, Nowak R, et al. Neutrophil gelatinase-associated lipocalin for acute kidney injury during acute heart failure hospitalizations: the AKINESIS study. *J Am Coll Cardiol*. 2016;**68**:1420–31.
134. Horiuchi Y, Wettersten N, van Veldhuisen DJ, Mueller C, Filippatos G, Nowak R, et al. Decongestion, kidney injury, and prognosis in patients with acute heart failure. *Int J Cardiol*. 2022;**354**:29–37.
135. Antoniou M, Jorgensen AL, Kolamunnage-Dona R. Biomarker-guided adaptive trial designs in phase II and phase III: a methodological review. *PLoS One*. 2016;**11**:e0149803.