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SPECIAL ARTICLE

The struggle towards a Universal Definition of Heart Failure—how to proceed?

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Definitions and classifications are crucial in medicine and provide the basis for proper and timely diagnosis to enable prompt, precise, and efficient therapies. The diagnosis of heart failure (HF) currently relies on signs (pulmonary crackles, peripheral oedema) and symptoms (dyspnoea on exertion, fatigue) that are not always objective, and neither sensitive nor specific.[1,2] Many patients are not diagnosed with HF before they get hospitalized for a decompensation. Although there are several evidence-based treatments for HF with reduced ejection fraction (HFrEF) and even for asymptomatic left ventricular (LV) dysfunction (ejection fraction <40%), the diagnosis is often made late, and valuable time has passed before effective treatments are initiated. Even in patients with symptoms, frequently it takes many months or even years until the diagnosis is made. Especially HF without significant reduction in LV ejection fraction may be mistaken even by cardiologists.

Against this background, the current debate articles, one of the first of this newly introduced format in the *European Heart Journal*, appraise the value of a universal definition of HF based on the determination of circulating natriuretic peptide (NP) levels.[3] The enormous theoretical advantage of NPs as central diagnostic markers for HF is that they would allow an objective diagnostic standard and that NPs are generally elevated before symptoms or signs of HF develop. Production of NPs—exclusively synthesized in myocardial tissue—depends on intra-cardiac volumes and filling pressures, which determine wall stress. Increased NP levels do not only reflect LV systolic function but may be secondary to other cardiac abnormalities such as diastolic dysfunction, valvular heart disease, right HF or atrial fibrillation.[3] Nevertheless, almost all of these culminate in elevations of plasma volume and dilatation of the left atrium, early events in HF development that precede clinical signs/symptoms. Thus, it is tempting to use NPs instead of non-specific signs/symptoms to set a new universal definition of HF. Despite concerns about sensitivity and specificity in some patients, NPs are already a crucial component for the diagnosis or exclusion of both acute HF and HF with preserved ejection fraction (HFpEF).[2,4] Given the difficulties in diagnosing and treating HFpEF, the endeavours of the Heart Failure Association (HFA) of the European Society of Cardiology (ESC) to better define this complex entity have led to the definition of a new subcategory of HFpEF in the 2016 ESC guidelines, i.e. HF with mid-range ejection fraction (HFmrEF), the diagnosis of which requires an ejection fraction of 40–49%, elevated NP levels and either relevant structural heart disease or diastolic dysfunction on echocardiography.[2] Albeit criticized by some, the introduction of this new subcategory has stimulated considerable research efforts, e.g. showing that neurohormonal modulators such as beta-blockers, candesartan, and spironolactone, are almost equally effective in reducing hard clinical outcomes in HFmrEF compared to HFrEF, which prompted respective HFA recommendations for the treatment of HFmrEF.[5,6] This example reiterates the importance of setting better definitions for complex diseases to stimulate research and pave the way to better diagnosis, treatment, and ultimately patient outcomes.

The concept for a universal definition of HF proposed by Cleland *et al.* provides an excellent basis for the current efforts of different HF societies and associations, including the HFA of the ESC, to develop a universal definition of HF that is accepted worldwide with the goal of improving diagnosis and treatment of (early stages of) HF globally. The authors compare their suggestion with the universal definition of myocardial infarction based on troponin levels. While troponins clearly have revolutionized diagnostic and treatment strategies for acute coronary syndromes (ACS), in most cases HF is undoubtedly a chronic disease with subtle onset lacking the acute symptom of chest pain that triggers troponin determination in suspected ACS. However, also in ACS, it took decades until the current 1-h rule-in/rule-out algorithm using high-sensitivity troponin was firmly established.[7] In their counterstatement, Pfeffer and Teerlink point out several important caveats precluding the simple introduction of NP elevation for HF diagnosis. More evidence is necessary before NPs can be used as the central diagnostic tool for HF in the broad, mostly asymptomatic population. These two excellent articles will clearly stimulate further discussion regarding a universal definition of HF that hopefully will lead to improved patient outcomes.

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Note added in proof: The debate is indeed timely at the light of the recent publication of an alternative "Universal Definition and Classification of Heart Failure" jointly developed by the HFA, the Heart Failure Society of America, and the Japanese Heart Failure Society.[8]

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The conceptual basis for a Universal Definition of Heart Failure: congestion due to cardiac dysfunction

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Introduction

Recently, the 4th Universal Definition of Myocardial Infarction was published.[1] Perhaps it is time to consider a First Universal Definition of Heart Failure. Objective, clinically verifiable, diagnostic criteria are desirable not only for the scientific classification of disease but also for describing its epidemiology, for informing patients on the nature and prognosis of their disease, for choosing and implementing treatment in a timely fashion, for strategic planning of clinical services, and for selection and risk stratification of those invited to participate in research.[2,3] Diagnostic uncertainty has far-reaching consequences but insisting on diagnostic certainty may also be detrimental if it delays intervention until the disease is severe, or inappropriately excludes patients from treatment, or underestimates the size of the problem. Diagnostic criteria that are sensitive might lack specificity, but this can be resolved by further investigation, creating the opportunity for an early, accurate diagnosis and timely intervention.

Currently, the diagnosis of heart failure is based mainly on subjective criteria and mostly made by clinicians who have little training in cardiology and even less in heart failure. Those who are trained have widely varying experience, opinions, motivations, and access to diagnostic investigations. Currently, for many patients, a diagnosis is made only when symptoms and signs are severe enough to require hospitalisation.[4–7] However, cardiac dysfunction often exists and progresses for years before a final insult causes the onset, often sudden and catastrophic, of symptoms and signs of heart failure. Many people have exertional breathlessness long before they receive a diagnosis of heart failure, which they attribute to being old or unfit, and manage by adopting a sedentary lifestyle. Waiting for diagnostic certainty, only once symptoms and signs are obvious, may miss the best opportunity to modify the natural history of heart failure.

Guidelines define heart failure as the presence of typical symptoms and signs due to cardiac dysfunction.[8] However, there are many causes of fatigue, breathlessness, and ankle swelling; symptoms and signs are neither sensitive nor specific for heart failure. Guidelines indicate that low plasma concentrations of B-type natriuretic peptide (BNP), or an N-terminal fragment of the pro-peptide (NT-proBNP), rule out a diagnosis of heart failure, but the perception that there are many reasons for a high BNP/NT-proBNP has led to recommendations that they should not be used to confirm ('rule-in') the diagnosis.[8] However, the problem may lie not with BNP/NT-proBNP but rather with the clinical and imaging 'gold standards' against which they are compared and a clinical convention focused on identifying symptomatic, late-stage disease rather than early detection and treatment to slow or prevent its evolution. Perhaps natriuretic peptides should be the gold standard against which other criteria are tested? Then there would be no such thing as a 'false-positive' test for BNP/NT-proBNP. There are many parallels between this situation and those that led to the adoption of high-sensitivity troponin in the Universal Definition of Myocardial Infarction.

For other medical conditions that have many different causes, such as diabetes and hypertension, diagnosis is based on a combination of pathophysiological concepts and objective measurements (such as blood pressure or glucose), with a threshold above which morbidity and mortality are predicted to increase and that might be modified by interventions. Should the strategy be any different for heart failure? Pathophysiologically, heart failure can be defined as cardiac dysfunction associated with the renal retention of water and salt, causing a rise in atrial and venous pressure and volume (i.e. venous engorgement or 'circulatory' congestion) followed by an increase in water and salt in tissues (oedema or 'tissue' congestion) (*Figure 1*) or, more simply, as cardiac dysfunction with congestion (*Table 1 and Figure 2*). All patients with heart failure ultimately have a cardio-renal syndrome. Congestion can also be due to renal disease with little evidence of cardiac dysfunction. Measurement of serum creatinine will determine where the patient lies on this cardio-renal spectrum of congestion and whether they should receive a diuretic or dialysis. Congestion causes symptoms when severe and is associated with a poor prognosis[9–13]; relief of congestion, whether by diuresis or dialysis, improves symptoms and outcomes.[14,15] Although evidence is

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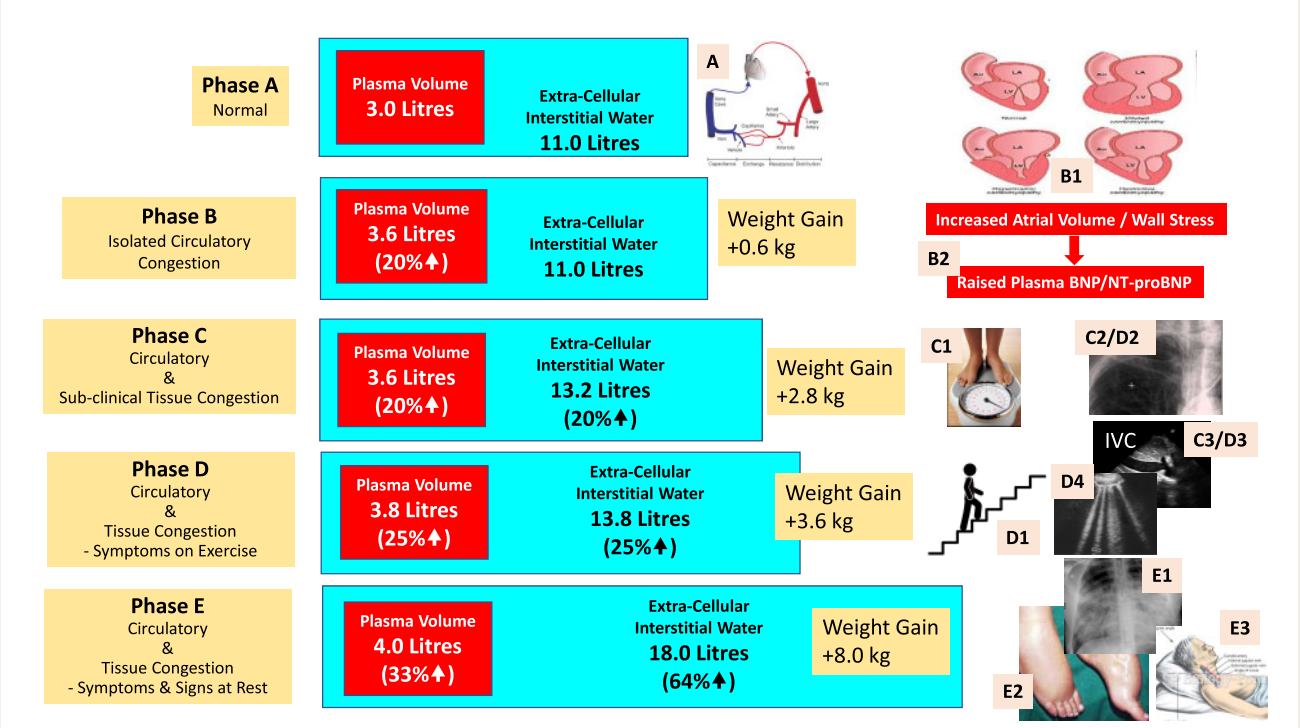

Figure 1 Diagram to illustrate different phases of congestion. Red boxes indicate approximate plasma volume and blue boxes approximate extracellular, tissue water volume for a 75-kg person in various clinical states. Note that diuretics may have important and complex effects on the relationship between plasma volume and extra-cellular water that might produce further scenarios. We propose that the definition and diagnosis should not be delayed until Phase D but made at Phase B (a transient state) or Phase C, before the onset of symptoms. Phase A: health: blood volume is about 5.0 L of which 3.0 L is plasma. Approximately 70% of the blood volume is in the venous system, 10% in the lung, 10% in the systemic arterial system, 5% in systemic capillaries, and about 5% in the four chambers of the heart (A). Phase B: isolated circulatory congestion: defined as expanded plasma volume without an increase in interstitial water. Increased plasma volume leads to atrial distension (B1) and a rise in plasma B-type natriuretic peptides (BNP/NT-proBNP) due to increased wall stress (B2) that increase water and salt secretion to try to restore plasma volume. Circulatory congestion alone should be asymptomatic. This is a transient state because circulatory congestion leads to changes in capillary hydrostatic pressure and an increase in tissue water once any increase in lymphatic drainage is exceeded. Phase C: circulatory congestion with sub-clinical tissue congestion: expansion of plasma volume leads to an increase in interstitial water but no obvious symptoms or signs of congestion. The patient may be aware of weight gain (C1). Although the patient reports no symptoms, exercise capacity may be reduced. However, there are many reasons for a reduced exercise capacity and a large subjective component. As congestion progresses, there may be radiological (C2: upper lobe venous diversion) or ultrasound (C3: inferior vena cava distension) evidence of raised pulmonary or systemic venous pressures, but these may not be obvious until the patient has symptoms (D2/D3). Phase D: circulatory congestion with tissue congestion and symptoms on exercise: further expansion of plasma volume and increasing accumulation of interstitial water leads to the development of symptoms on exertion (D1). There may still be no signs of congestion at rest, although the patient may notice that their clothes and shoes are a tighter fit, indicating the development of peripheral oedema. There is increasing evidence of circulatory congestion (D2; D3) and interstitial (B lines) lung oedema (D4) may be observed. Phase E: circulatory congestion with tissue congestion and symptoms and signs at rest: even modest increases in lung water may cause alveolar pulmonary oedema (D1), which will provoke severe breathlessness even at rest. Some patients will swiftly move from Phase A to Phase D (for example rupture of mitral valve leaflets or extensive myocardial infarction), with re-distribution of fluid into the lung rather than renal retention of water. However, most patients are likely to have had long-standing cardiac dysfunction. Systemic congestion occurs more gradually, causing jugular venous distention (D2) and peripheral oedema (D3). Systemic congestion will affect all organs. Hepatic congestion will impair the degradation of aldosterone leading to further sodium and water retention. Renal congestion will also exacerbate water and salt retention. Weight gain may exceed 20 kg (20 L of water) in severe cases. Ao, aorta; IVC, inferior vena cava; LA, left atrium; LV, left ventricle.

lacking that conventional diuretic agents, such as furosemide, improve prognosis, they certainly often do. Within days of stopping diuretic treatment, congestion often worsens, symptoms often deteriorate, and many patients would die in pulmonary oedema if left untreated.[16]

What then might be an early and objective marker of congestion? Increased myocardial secretion of natriuretic peptides, which promote sodium and water excretion, is a key physiological defence against congestion; only when this defence is overwhelmed does congestion become clinically overt. Accordingly, increased plasma concentrations of BNP/NT-proBNP due to cardiac dysfunction could be considered diagnostic of heart failure, even in the absence of symptoms. Patients with cardiac dysfunction on imaging and a normal plasma BNP/NT-proBNP generally do not have congestion and have a good prognosis.[15] Those with raised plasma concentrations of

Table 1 Universal definition of myocardial infarction and heart failure

Universal definition	
Myocardial infarction	**Heart failure**
Predisposition[a]	**Predisposition**
Coronary artery disease[a]	Cardiac dysfunction without congestion
Myocardial Injury	**Congestion**
An increase in plasma troponin above the upper reference limit (99th centile)	An increase in plasma NPs[d] and/or atrial dilatation[e]
Acuity	**Acuity**
Acute: a non-sustained increase in troponin	Acute: a non-sustained increase in NPs[f]
Chronic: a sustained increase in troponin	Chronic: a sustained increase in NPs
Myocardial infarction	**Heart failure**
Acute myocardial injury (as defined above) with evidence of myocardial ischaemia	Congestion with cardiac dysfunction[b]
Type I: due to coronary occlusion (thrombus)	Type I: cardiac dysfunction is the primary cause of congestion
Type II: not due to coronary occlusion	Type II: cardiac dysfunction secondary to another cause of congestion (e.g. renal disease, fluid overload)
Severity of myocardial infarction[a]	**Severity of congestion**
Myocardial infarction size	Plasma concentration of NPs
Left ventricular ejection fraction	Symptomatic[c]: yes/no
Severity of congestion	Treatment with loop diuretics: yes/no

BNP, B-type natriuretic peptide; NPs, natriuretic peptides; NT-proBNP, amino-terminal fragment of the pro-B-type natriuretic peptide.
[a]Not part of the universal definition of myocardial infarction.
[b]Ventricular or valve disease or atrial dilatation.
[c]Orthopnoea, undue exertional breathlessness or dependant oedema.
[d]NT-proBNP, BNP or mid-regional pro-atrial natriuretic peptide above the upper reference limit for healthy people adjusted for age, sex and body mass index from a large healthy population, ideally also excluding patients who develop disease within a few years after testing. Until further information becomes available, an NT-proBNP of > 125 ng/L[8] or age and sex-related values based on Fulks *et al.*[41] and Hildebrandt *et al.*[42] (*Table 2*) may be used to define values above which congestion might be considered to exist and therefore, in the presence of cardiac dysfunction, heart failure.
[e]Left atrial diameter >2.6 cm/m^2 or left atrial volume >33 mL/m^2 (https://www.echopedia.org/wiki/Normal_Values_of_TTE).
[f]Does not return to normal if acute decompensation is on a background of, or heralds, chronic heart failure.

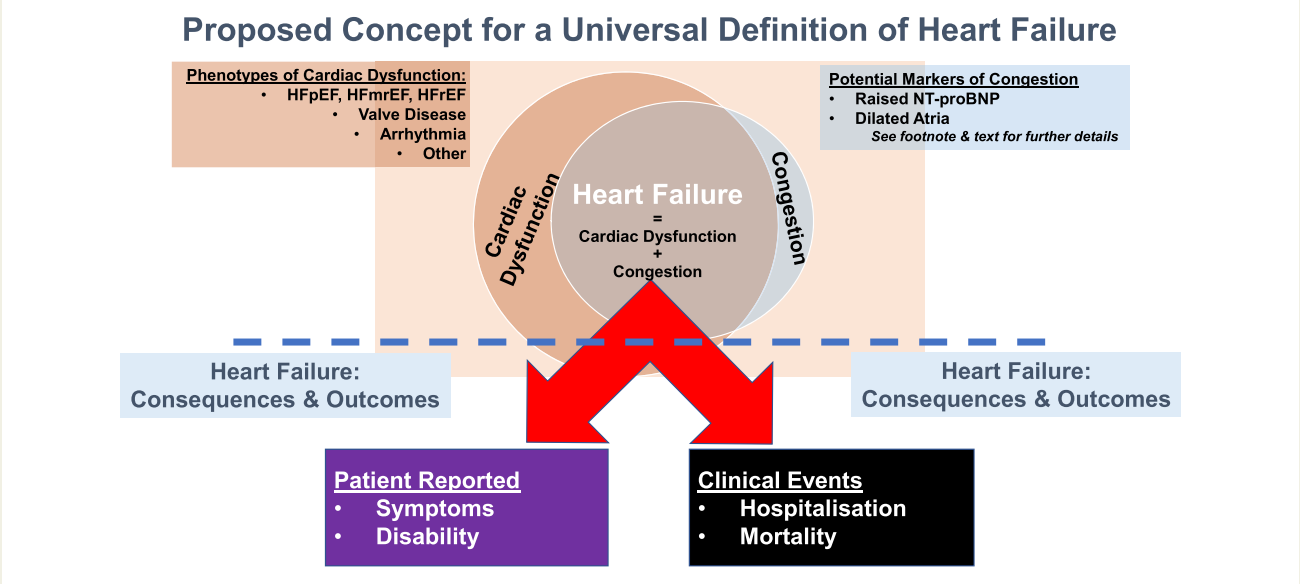

Figure 2 Proposed concept for a Universal Definition of Heart Failure comprising cardiac dysfunction (based on imaging) and congestion (based on natriuretic peptides). Plasma concentrations of B-type natriuretic peptide and the amino-terminal fragment of the pro-peptide (NT-proBNP) are usually elevated long before symptoms and signs of congestion are apparent. Note that cardiac dysfunction may be due to myocardial disease, valve disease, arrhythmia, or other rarer problems. Patients with end-stage renal disease, nephrotic syndrome, or severe nutritional disorders can develop congestion, but this will usually be complicated by cardiac dysfunction. These causes of congestion can be identified from the medical history and by measuring urine protein and serum creatinine. HFmrEF, heart failure with mid-range ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction.

BNP/NT-proBNP have an adverse prognosis regardless of the reason for cardiac dysfunction, unless it can be fixed.[17] Persistent reduction in plasma BNP/NT-proBNP among patients with heart failure is associated with myocardial remodelling and a favourable outcome.[14,15,18–20]

Natriuretic peptides are robust biomarkers of congestion but do not pinpoint its cause. Having established that congestion is present, a clinical history, blood tests, and imaging are required to determine the presence and nature of cardiac dysfunction or other causes of congestion such as renal disease and hypo-albuminaemia. There are some circumstances where plasma BNP/NT-proBNP might be misleadingly low, including obesity,[21,22] treatment with diuretics,[16] and more rarely, constrictive pericarditis. Imaging the atria and great veins, measurements of vascular or intra-cardiac pressures, assessment of lung congestion, and a variety of bio-impedance devices are other ways to assess congestion but may be less widely available, more expensive and have a less robust evidence base than do natriuretic peptides.[9,10,12,13,16,23] However, if necessary, these technologies can be used to confirm that congestion exists and to identify its cause, severity, and distribution.

An inverse relationship between body mass index (BMI) and plasma concentrations of natriuretic peptides exists both before and after heart failure has developed.[24–27] Obesity is common among patients with heart failure,[28] especially those with a normal left ventricular ejection fraction [heart failure with preserved ejection fraction (HFpEF)]. Rarely, when atrial pressures and volumes are increased, obese patients may not always have an elevated BNP/NT-proBNP by current criteria.[29] This might be explained by greater pericardial restraint due to an increase in epicardial adipose tissue causing a reduction in transmural atrial pressure, a major stimulus to myocardial secretion of natriuretic peptides.[29] Packer[22] has suggested further sub-types of HFpEF, including a group with severe obesity, increased plasma volume, and a low or normal plasma BNP/NT-proBNP, although in TOPCAT (Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist Trial), patients who had higher plasma volumes also had higher plasma NT-proBNP.[30] Most patients with heart failure will have an elevated BNP/NT-proBNP even if they have severe obesity. In a meta-analysis predominantly comprising heart failure with reduced ejection fraction (HFrEF), the median NT-proBNP was 357 (144–938) ng/L for those with a BMI of > 40 kg/m^2.[21] For patients with HFpEF and a BMI of > 35 kg/m^2 in the I-PRESERVE (Irbesartan in Heart Failure with Preserved Ejection Fraction) trial, the median NT-proBNP was 254 ng/L[31] and, for those >40 kg/m^2 enrolled in TOPCAT, the average was 1853 ng/L.[27] Overall, these observations suggest that BNP/NT-proBNP retains diagnostic value in severe obesity, although thresholds should be adjusted,[21] and highlight the need for further research into the relationship between obesity and heart failure.[32–35]

Although plasma concentrations of natriuretic peptides are, on average, lower in obese people, they still indicate a greater future risk of developing clinically overt heart failure.[24,36] Natriuretic peptides are also powerful prognostic markers for patients with HFrEF or HFpEF, even after adjusting for BMI.[26,27,37] There is a U-shaped relationship between BMI and prognosis with risk reaching a nadir for both HFrEF and HFpEF at a BMI of 33 kg/m^2, with risk being similar at values of 25 and 40 kg/m^2.[28] Therefore, obese patients may have lower plasma concentrations of natriuretic peptides, but they also have a better prognosis unless obesity is severe; in other words, natriuretic peptides track with prognosis rather than haemodynamics. Whether the 'obesity paradox' reflects reverse causality, or whether a higher BMI confers protection is uncertain.[38]

Currently, European Society of Cardiology (ESC) guidelines suggest that an NT-proBNP of < 125 ng/L (<35 ng/L for BNP) excludes chronic heart failure but provide no specific advice on adjustments for age, sex, BMI, renal function, or heart rhythm.[8] An NT-proBNP of 125 ng/L is already several times higher than the average for a healthy person aged <60 years.[39,40] Insurance data from the USA on almost a quarter of a million people, who may not always have reported if they had heart disease, found that 91% of men and 74% of women aged <60 years had an NT-proBNP of ≤ 75 ng/L and values rarely exceeded 300 ng/L in people of either sex aged <80 years.[41] However, the relative risk of all-cause mortality increased substantially when NT-proBNP exceeded 75 ng/L for all groups other than younger women, possibly an artefact due to small numbers in this group. In an individual participant data meta-analysis including almost 100 000 people without prevalent cardiovascular disease, plasma NT-proBNP rarely exceeded 125 ng/L in people <80 years.[36] In men aged <60 years, the geometric mean plasma NT-proBNP was about 30 ng/L, but about 60 ng/L for women. Plasma concentrations of NT-proBNP climbed steadily with age thereafter, with the gap between men and women closing (*Figure 3*). During a median follow-up of 7.8 years almost 10,000 cardiovascular events had occurred; those with an NT-proBNP >100 ng/L had a substantially greater risk of events. A meta-analysis of studies conducted in primary care suggested a diagnostic threshold for HFrEF of < 50 ng/L for people aged <50 years, 75 ng/L for those aged 50–75 years, and 250 ng/L for those aged >75 years.[42] However, other causes of heart failure and the effects of heart rhythm and renal function on NT-proBNP were not considered that might have improved diagnostic performance still further. Large trials of patients with stable ischaemic heart disease or diabetes suggest that 50% or more will have a plasma NT-proBNP >125 ng/L, which is associated with an adverse prognosis, a key aspect of the heart failure syndrome.[43,44] Patients with diabetes, hypertension, or coronary artery disease who have an elevated BNP/NT-proBNP, indicating congestion, have higher rates of morbid events and mortality. Surely this fulfils the criteria for a definition of heart failure for those who are not willing to wait until symptoms and signs are also present. Many of these patients would have breathlessness and a reduced exercise capacity if they were asked to do an exercise test. However, there are many causes of breathlessness and exercise intolerance that are not due to cardiac dysfunction, there is a large subjective component to exercise, and there are problems with standardising exercise tests, their reproducibility and recording of results that do not provide a robust foundation for a diagnosis of heart failure.

ESC guidelines recommend that raised plasma concentrations of BNP/NT-proBNP should not be used to establish a diagnosis of heart failure, stating that 'there are numerous cardiovascular and non-cardiovascular causes of elevated natriuretic peptides that may weaken their diagnostic utility in heart failure'.[8] However, most problems associated with increases in BNP/NT-proBNP cause cardiovascular dysfunction and congestion and are associated with a poor prognosis. Plasma concentrations of BNP/NT-proBNP rise with age, which may reflect declining diastolic ventricular performance and renal function

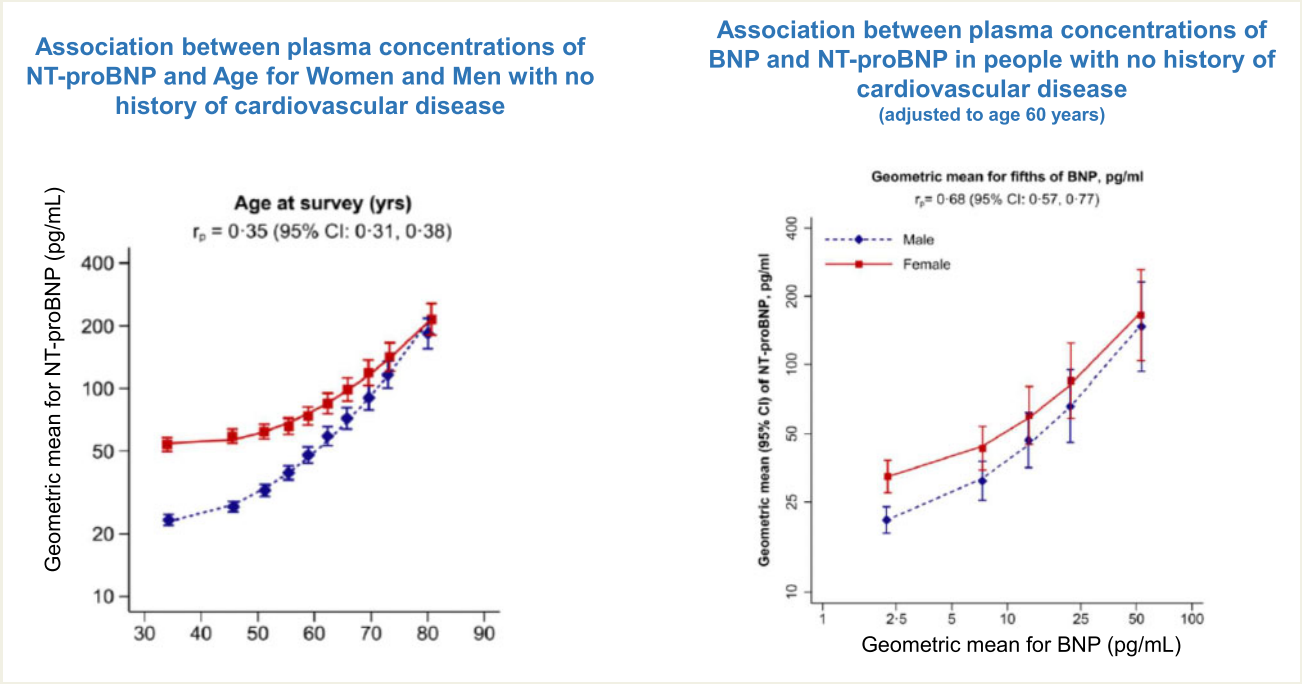

Figure 3 Relationship between age and the amino-terminal fragment of the pro-B-type natriuretic peptide (NT-proBNP) stratified by sex (left panel) and between B-type natriuretic peptide and NT-proBNP stratified by sex (right panel) for a meta-analysis including 95,617 participants. CI, confidence interval. Adapted from Reference [36].

Table 2 Potential diagnostic thresholds stratified by age and sex[a]

	Men (ng/L)	Women (ng/L)
<60 years	>75	>125[c]
60–69 years	>125[b]	>175[c]
70–79 years	>175[b]	>225[c]
>80 years	>250	>250

[a]Proposed thresholds extrapolated from Fulks *et al.*[41] and Hildebrandt *et al.*[42] and require further validation in clinical trials and practice. Further adjustment for body mass index should be considered. Plasma concentrations will be higher in patients with atrial fibrillation and those with important renal dysfunction. An increased plasma concentration should be interpreted in the context of heart rhythm (an electrocardiogram) and renal function (serum creatinine). Diagnostic thresholds may be personalized using a combination of age, sex, body mass index, heart rhythm, and serum creatinine in a calculator similar to that for glomerular filtration rate.
[b]50 ng/L higher than for previous decade.
[c]50 ng/L higher than for men in the same age group.

and the development of occult or overt cardiovascular disease.[40] The risk of dying also increases steeply with age. Using higher threshold values to define disease in older people might not be appropriate, other than as a way of rationing health care.[45] Women have slightly higher plasma BNP/NT-proBNP but, in general, a better prognosis and therefore some adjustment of diagnostic thresholds for sex seems appropriate, especially for younger women.[40] Patients with a higher BMI have lower plasma concentrations of natriuretic peptides but have a better prognosis unless obesity is severe (BMI >40 kg/m^2).[28] Renal dysfunction is also associated with higher plasma BNP/NT-proBNP, due both to reduced clearance of these peptides and to more severe congestion because of water retention, anaemia, co-existing cardiovascular disease, and uraemic cardiomyopathy.[39] A raised plasma concentration of BNP/NT-proBNP indicates a poor prognosis precisely because it reflects the adverse impact of both renal and cardiac dysfunction. BNP and NT-proBNP retain their prognostic value even when renal dysfunction is severe.[46] Atrial fibrillation also adversely affects prognosis and causes plasma concentrations of natriuretic peptides to rise, either due to the arrhythmia itself or to atrial dilatation and myopathy.[47,48] BNP/NT-proBNP is often elevated in patients who are acutely unwell with sepsis or trauma. Just as an elevation in troponin may indicate myocardial injury (Type II myocardial infarction), an elevation in BNP/NT-proBNP associated with an acute illness may indicate congestion due to cardiac and renal dysfunction.[49] Whether these patients have a form of heart failure (*Table 1*: Type II heart failure) and would benefit from treatment directed at congestion is untested and should be explored. In summary, elevated plasma concentrations of natriuretic peptides are 'bad news'; the cause should be identified, which will usually be congestion associated with cardiac and renal dysfunction.

Plasma concentrations of BNP/NT-proBNP above the diagnostic threshold indicate the need for imaging to confirm the presence of congestion (i.e. atrial dilatation) and identify its cause. If the diagnostic threshold for BNP/NT-proBNP is set high, this will identify a small

number of people who have severe disease and a high risk of events. If the threshold is set low, this will identify a large number of people with milder disease and a modest increase in risk. Having different thresholds might be useful depending on whether sensitivity or specificity is the priority. If resources allow, a relatively low actionable threshold would be desirable. Thresholds of 75 ng/L or lower may be appropriate for men aged <60 years but higher thresholds for women and older people may be appropriate, perhaps up to 250 ng/L for patients of either sex aged >80 years (*Figure 3* and *Table 2*). Higher thresholds for BNP/NT-proBNP will have greater specificity but may miss important, treatable disease. Plasma concentrations of BNP/NT-proBNP should be interpreted not only with knowledge of age and sex, but also BMI, renal function, and heart rhythm. Ultimately, just as glomerular filtration rate can be derived by entering four to six variables into a computer program, so could the expected normal BNP/NT-proBNP for an individual be calculated, substantial deviation from which might be the best method to determine the presence of congestion and the need for further investigation.

The incidence of myocardial infarction and prevalence of diabetes were profoundly affected by changes to their definitions.[1,50] A new definition of heart failure (*Table 1* and *Figure 2*) might have a similarly large effect on the incidence and prevalence of heart failure, which might swamp diagnostic services. Moreover, there is still a paucity of evidence that treating patients for heart failure before the onset of symptoms improves outcomes.[51,52] Such considerations did not prevent changes to the definition of either myocardial infarction or diabetes. If raised troponin concentrations (indicative of myocardial injury) were held to the same standard as natriuretic peptides, we might still be measuring the MB band of creatine phosphokinase to diagnose acute myocardial infarction. A robust and objective definition of heart failure will be a catalyst to improve understanding of its epidemiology and treatment.

We should now test the utility of this proposal by conducting clinical trials to demonstrate that interventions can improve the outcome of patients who have few or no symptoms but meet the criteria we propose. Indeed, we have already begun[51–53]; more trials are underway [https://clinicaltrials.gov/ct2/show/NCT02556450]. Ultimately, diagnostic criteria are most robust when they benefit patient care, either by helping choose treatments that improve symptoms or prognosis or by predicting what is likely to happen to the patient and when. Our proposal should stimulate a discussion to agree an objective, verifiable Universal Definition of Heart Failure. Doubtless, as for other diseases, diagnostic criteria will evolve.

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Counter point: no evidence for the proposed Universal Definition of Heart Failure

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The diagnosis of heart failure is currently based on a historic constellation of clinically assessed signs and symptoms leading to our well-recognized syndrome designated 'heart failure' (Supplementary material online, *Table S1* and Supplementary material online, Text).[1,2] The time-honoured diagnostic criteria using both signs and symptoms augmented by clinical judgement, biomarkers, pulmonary, and cardiac imaging have served us well in establishing frameworks for both understanding this major disease and quantifying the benefits and risks of each of our current therapeutic modalities.[3,4] Admittedly, the current diagnosis of heart failure might be considered demanding, requiring clinical attention and acumen. Moreover, in the not uncommon grey zone with other often concomitant co-morbidities, the diagnosis is at times confounded, not readily verifiable, and misclassifications can be anticipated. It is in this context that several leading heart failure experts, indeed authorities, make their case for 'a new Universal Definition of Heart Failure'. Their central theme is that natriuretic peptides (either B-type natriuretic peptide or N-terminal pro-B-type natriuretic peptide) can be used to identify those with congestive physiology. Since the 'normal' distributions of natriuretic peptide levels are altered by age, sex, body mass, renal function, and atrial fibrillation, they propose to adjust the threshold diagnostic values based on these factors. In their view, if one identifies a person with a natriuretic peptide value above the expected range, especially if coupled with an imaging measure of left atrial enlargement, *presto voila*, you have a verifiable laboratory-based diagnosis of heart failure; no need for a time-consuming history and troublesome physical examination!

In accepting the Editors' invitation to provide a counterpoint to this Current Opinion—Universal Definition of Heart Failure, we acknowledge sharing their lofty objectives. There is no argument that a reproducible laboratory value-based biomarker measurement with categorical cut point criteria, if accurate and specific for heart failure, would, as they contend, 'improve scientific classifications, epidemiological descriptions, better inform patients and caregivers on treatment choices and participation in research and more broadly allow better strategic planning for clinical services'. In their Current Opinion, these experts also make the point that adoption of such an objective measure as proposed would facilitate the earlier diagnosis and implementation of disease-modifying therapy without 'waiting until florid symptoms and signs are present at rest'. Such a list of laudatory objectives is reminiscent of the lyrics from a song in My Fair Lady 'Wouldn't it be loverly?'[5] There would be no debate if, and capitalize IF, there were robust data that adding our evidence-based heart failure medications and devices to the prudent recommendations for lifestyle measures and risk factor modifications in those patients so identified by the proposed Universal Definition would safely improve clinical outcomes.

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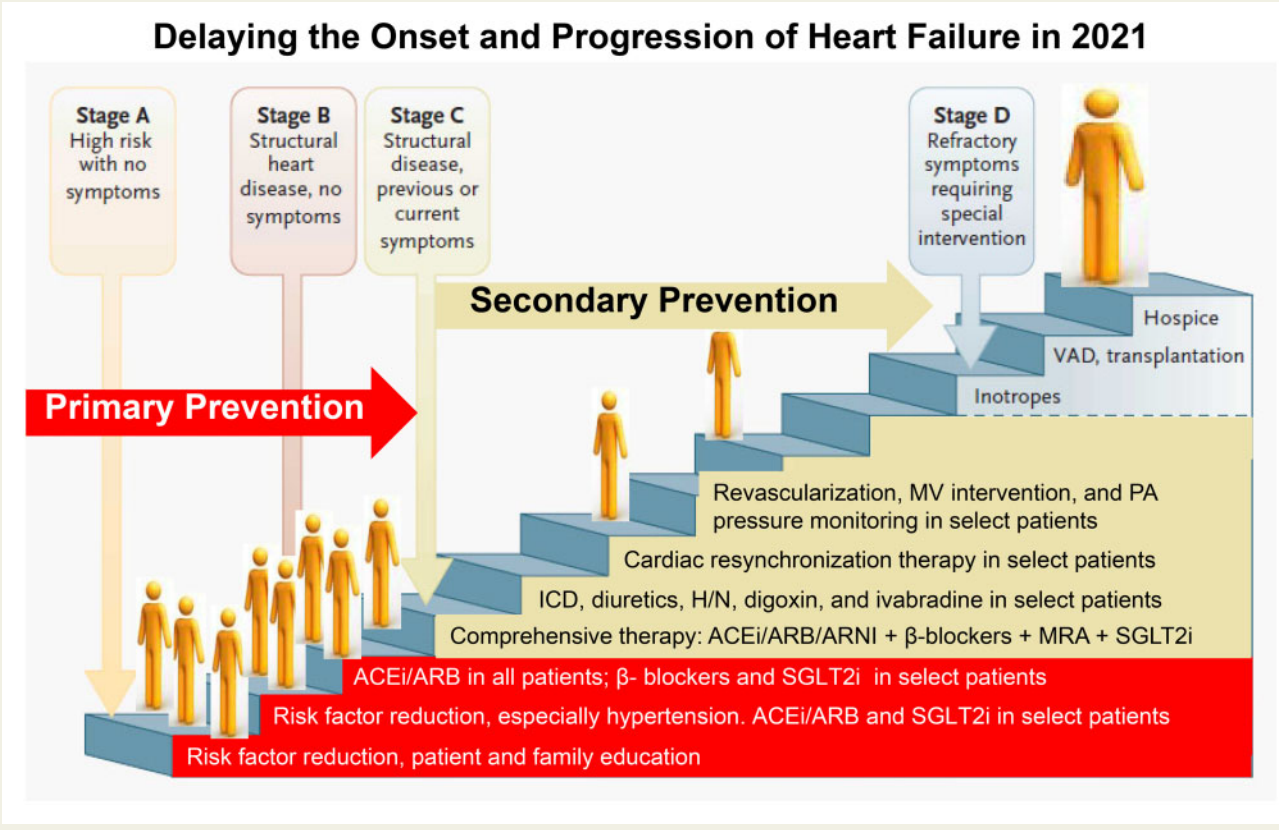

Figure 1 Stages of heart failure and treatment options for systolic heart failure. Stages A+B suggest treatment regimens before the actual appearance of symptomatic heart failure. Adapted from Reference.[23] ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor-neprilysin inhibitor; H/N, Hydralazine/ Isosorbide dinitrate; ICD, implantable cardioverter-defibrillator; SGLT-2, sodium-glucose co-transporter 2; VAD, ventricular assist device. Referral to multidisciplinary group should be considered for stages C+D. Vericiguat and omecamtiv mecarbil may be considered for selected advanced patients.

However, the current absence of such critical data linking treatments (benefits and risks) of the proposed natriuretic peptide identified individual (who would not have already been diagnosed as having heart failure by our existing tried and true 'cumbersome', as per Cleland *et al.*, clinical criteria) to improved outcomes, renders null and void their proposed 'New Universal Definition of Heart Failure'.

The authors initiate their discussion by invoking the seductive analogy of the Fourth Universal Definition of Myocardial Infarction.[6] As tempting as it may be, it is essential that we do not succumb to this siren song of simplicity, where the utility of a biomarker in defining a temporally distinct and time-limited event such as a myocardial infarction is conflated with the potential role of a biomarker to define a complex, multi-system clinical syndrome and disease process that may evolve over months to years. While the measurement of troponin has assumed a central role in the diagnosis of myocardial infarction, the actual diagnosis according to this universal definition also requires 'clinical evidence of acute myocardial ischemia', of which the primary manifestation and impetus for additional diagnostic investigations are symptoms.[6] The application of a threshold value for a biomarker such as troponin is commensurate with the abrupt nature of the pathophysiology of a myocardial infarction—death of myocytes. However, heart failure is not an entity that lends itself to such a definition of a discrete event and requires a more comprehensive definition to account for its complexity.

Hypertension is offered as another example where a numerical verifiable diagnostic definition is effectively used to establish the diagnosis. However, this is based on the decades of randomized clinical outcome trials generating the necessary data linking the threshold blood pressure selected to use of a therapy to improve prognosis, not just the pressure.[7,8] These key data provide caregivers and patients a framework to attempt to address the fundamental operational decision—at what point (threshold blood pressure) does the benefit of initiating chronic therapy outweigh the risks, inconvenience, and cost. Even in this seemingly straightforward example above, with a threshold blood pressure to diagnose hypertension, most physicians place the blood pressure number in clinical context (good old history including co-morbidities and physical exam) before establishing a diagnosis and initiating chronic therapy.

In the absence of clinically assessed signs and symptoms of heart failure, we contend that a natriuretic peptide laboratory-based threshold definition would only serve as a verifiable identification of a person with a natriuretic peptide out of a range of normal on that particular day. We agree that a person so identified would be at increased risk for death and several types of major cardiovascular disorders (not just heart failure). This laboratory finding is not a specific diagnosis of heart failure that justifies the initiation of medications proven in randomized trials of participants selected by the clinical diagnostic criteria. Since the population selected by isolated

natriuretic peptide measurements without assessment of signs or symptoms has not been the focus of randomized clinical outcome trials, neither the benefits nor the risks of our evidence-based heart failure therapies are applicable for this proposed laboratory-based diagnosis.

We have no disagreement with the major prognostic information encapsulated in a measurement of a natriuretic peptide. Indeed, the evidence that a natriuretic peptide value higher than expected is associated with greater risk across a broad range of populations is beyond refuting. In fact, let us agree that in almost every large observational cohort, there is a graded (without a clear, discrete threshold value) increased risk for death with higher natriuretic peptide concentrations. This relationship of risk is established in community-based epidemiological studies,[9–11] as well as clinical trials of subjects whether or not selected for classically diagnosed heart failure.[12,13] However, it must also be acknowledged that similar graded, non-obvious threshold relationships between natriuretic peptides and risk are also seen across diverse cohorts selected for hypertension,[14] diabetes,[15] chronic kidney disease,[16] coronary artery disease,[17] acute myocardial infarction,[18] and other non-cardiovascular disorders such as chronic obstructive pulmonary disease.[19] The prognostic information offered by an ascertainment of a natriuretic peptide is so encompassing that in two independent populations of patients with type 2 diabetes mellitus, the *c*-statistic for death when used as a single variable (by itself) was comparable to that obtained using an extensive multivariable clinical risk factor profile.[15,18] Indeed, as the proposers of the natriuretic peptide-based Universal Definition of Heart Failure astutely indicate, life insurance companies use natriuretic peptides in determining risks for the pricing of their policies.[20] No question, almost across the board, higher natriuretic peptides are indicative of greater risk of death. What is critically missing is that this risk of having a natriuretic peptide level above an arbitrary threshold is solely attributable to heart failure and that therapies proven to improve outcomes in those with the classically diagnosed heart failure syndrome would also be effective in these multiple other conditions.

The proposers of a New Universal Definition of Heart Failure raise another major point that we feel obliged to counter. They assert that their proposed natriuretic peptide-based recognition of congestion would allow for the earlier diagnosis and implementation of therapy. Their statement that the current diagnosis of heart failure 'is based mainly on subjective criteria and mostly made by clinicians who have little training in cardiology and even less in heart failure' appears (even though surely unintended) to be condescending to the unsung primary caregivers that have been conscientiously treating early, even asymptomatic individuals. There are robust unselected countrywide data demonstrating that these non-subspecialists have been effective in reducing age-adjusted rates of heart failure, as proven by forestalling first hospitalization by years in the general unselected population.[21,22]

We also find this position that clinicians need a natriuretic peptide diagnosis of heart failure to initiate therapy ignores current evidence and already existing American Heart Association/American College of Cardiology/Heart Failure Society of America and European Society of Cardiology recommendations. All our major Societies clearly recommend lifestyle measures and use of medications proven effective in at-risk asymptomatic individuals to prevent heart failure (Stages A and B) (*Figure 1*).[23]

A core primary care practice to identify those with elevated arterial pressure to initiate sustained antihypertensive therapy is based on the most enduring and robust legacy of randomized trial data in cardiovascular medicine.[24] There is no debate: pharmacological therapy to lower elevated blood pressure reduces cardiovascular mortality and morbidity. The risk reductions for heart failure are generally even greater than for stroke, myocardial infarction, and progression of kidney disease.[25,26] Over the decades, the threshold value for the initiation of therapy has changed based on randomized trials redefining operational thresholds where the benefits of pharmacological therapy outweigh the adverse risks, inconvenience and costs. Unlike hypertension, unfortunately, a natriuretic peptide-based diagnosis of heart failure would currently be associated with an evidence-free zone for this major treatment decision.

Important recent data identifying a non-trivial cohort of patients with heart failure, cardiac dysfunction, and yet normal B-type natriuretic peptide measurements expose another major limitation against using the proposed natriuretic peptide-based diagnosis of heart failure. Indeed, these findings are so striking that the investigators propose natriuretic peptide deficiency as a contributing factor to the clinical heart failure in these patients.[27]

Their straw man argument that physicians wait for florid symptoms before initiating heart failure treatment also seems to ignore the deliberate efforts of caregivers to screen and identify asymptomatic individuals with left ventricular dysfunction (Stage B). As with the treatment of high blood pressure, a recommendation of pharmacological therapy for an asymptomatic person at risk is based on randomized, placebo-controlled trial data informing the benefits as well as potential adverse experiences.[4] The discoveries nearly 30 years ago from the Studies of Left Ventricular Dysfunction (SOLVD Prevention) and the Survival and Ventricular Enlargement trial generated the critical data that treatment of asymptomatic left ventricular dysfunction reduces cardiovascular deaths and hospitalizations for heart failure, providing the impetus to screen and identify appropriate individuals based on a measurement of left ventricular ejection fraction for proven preventive therapy.[28,29]

The Current Opinion on the Universal Definition of Heart Failure, as intended, delineates issues concerning the clinical diagnosis of heart failure and offers an on-the-surface appealing, provoking natriuretic peptide-based alternative. Continuing the dialogue on a natriuretic peptide-based Universal Definition of Heart Failure will surely be enlightening and shaping future considerations. However, if accepted more concretely than intended, adoption of a natriuretic peptide-based definition to initiate therapies that were proven to be of benefit in a distinctly different patient population would be a setback. We are in agreement with our colleagues and would consider this point/counter point exchange productive if it contributed to expanding the dialogues and critical research concerning the definition of heart failure and/or the better use of the incredible prognostic tool of natriuretic peptides.

Supplementary material

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

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