ESC European Society of Cardiology

European Journal of Heart Failure (2023) **25**, 1891–1898
doi:10.1002/ejhf.3036

POSITION PAPER

Practical algorithms for early diagnosis of heart failure and heart stress using NT-proBNP: A clinical consensus statement from the Heart Failure Association of the ESC

Antoni Bayes-Genis[1]*, Kieran F. Docherty[2], Mark C. Petrie[2], James L. Januzzi[3], Christian Mueller[4], Lisa Anderson[5], Biykem Bozkurt[6], Javed Butler[7], Ovidiu Chioncel[8], John G.F. Cleland[9], Ruxandra Christodorescu[10], Stefano Del Prato[11], Finn Gustafsson[12], Carolyn S.P. Lam[13], Brenda Moura[14,15], Rodica Pop-Busui[16], Petar Seferovic[17,18], Maurizio Volterrani[19,20], Muthiah Vaduganathan[21], Marco Metra[22], and Giuseppe Rosano[23]

[1]Heart Institute, Hospital Unbiversitari Germasn Trias i Pujol, Universitat Autonoma de Barcelona, CIBERCV, Barcelona, Spain; [2]School of Cardiovascular and Metabolic Health, University of Glasgow, Glasgow, UK; [3]Cardiology Division, Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA; [4]Department of Cardiology and Cardiovascular Research Institute Basel (CRIB), University Hospital Basel, University of Basel, Basel, Switzerland; [5]Cardiovascular Clinical Academic Group, Molecular and Clinical Sciences Research Institute, St. George's, University of London and St George's University Hospitals NHS Foundation Trust, London, UK; [6]Baylor College of Medicine Medicine, DeBakey VA Medical Center, Houston, TX, USA; [7]Baylor Scott and White Research Institute, Dallas, Texas and University of Mississippi Medical Center, Jackson, MS, USA; [8]Emergency Institute for Cardiovascular Diseases 'Prof. C.C. Iliescu', and, University of Medicine Carol Davila, Bucharest, Romania; [9]British Heart Foundation Centre of Research Excellence, School of Cardiovascular and Metabolic Health, University of Glasgow, Glasgow, UK; [10]Department V Internal Medicine, University of Medicine and Pharmacy V. Babes Timisoara, Institute of Cardiology Research Center, TimiŞoara, Romania; [11]Department of Clinical and Experimental Medicine, University of Pisa and Sant'Anna School of Advanced Studies, Pisa, Italy; [12]Department of Cardiology, Rigshospitalet, Department of Clinical Medicine, University of Copenhagen, Copenhagen, Denmark; [13]National Heart Centre Singapore, Duke-National University of Singapore, Singapore, Singapore; [14]CINTESIS – Centro de Investigação em Tecnologias e Serviços de Saúde, Porto, Portugal; [15]Serviço de Cardiologia, Hospital das Forças Armadas, Pólo do Porto, Portugal; [16]Division of Metabolism, Endocrinology and Diabetes, Department of Internal Medicine, University of Michigan, Ann Arbor, MI, USA; [17]Faculty of Medicine, University of Belgrade, Belgrade, Serbia; [18]Serbian Academy of Sciences and Arts, Belgrade, Serbia; [19]Cardio Pulmonary Department, IRCCS San Raffaele, Rome, Italy; [20]Exercise Science and Medicine, San Raffaele Open University, Rome, Italy; [21]Cardiovascular Division, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA; [22]Cardiology and Cardiac Catheterization Laboratory, Cardio-Thoracic Department, Civil Hospitals; Department of Medical and Surgical Specialties, Radiological Sciences, and Public Health, University of Brescia, Brescia, Italy; and [23]IRCCS San Raffaele, Rome, Italy

Received 19 June 2023; revised 13 September 2023; accepted 13 September 2023; online publish-ahead-of-print 26 September 2023

Diagnosing heart failure is often difficult due to the non-specific nature of symptoms, which can be caused by a range of medical conditions. Natriuretic peptides (NPs) have been recognized as important biomarkers for diagnosing heart failure. This document from the Heart Failure Association examines the practical uses of N-terminal pro-B-type natriuretic peptide (NT-proBNP) in various clinical scenarios. The concentrations of NT-proBNP vary according to the patient profile and the clinical scenario, therefore values should be interpreted with caution to ensure appropriate diagnosis. Validated cut-points are provided to rule in or rule out acute heart failure in the emergency department and to diagnose *de novo* heart failure in the outpatient setting. We also coin the concept of 'heart stress' when NT-proBNP levels are elevated in an asymptomatic patient with risk factors for heart failure (i.e. diabetes, hypertension, coronary artery disease), underlying the development of cardiac dysfunction and further increased risk. We propose a simple acronym for healthcare professionals and patients, FIND-HF, which serves as a prompt to consider heart failure: Fatigue, Increased water accumulation, Natriuretic peptide testing,

*Corresponding author. Department of Medicine, UAB, Head, Heart Institute. Hospital Universitari Germans Trias i Pujol, Carretera del Canyet s/n, 08916 Badalona, Spain. Email: abayesgenis@gmail.com

[Correction added on 16 October 2023, after first online publication: Lisa Anderson's surname has been corrected in this version.]

and Dyspnoea. Use of this acronym would enable the early diagnosis of heart failure. Overall, understanding and utilizing NT-proBNP levels will lead to earlier and more accurate diagnoses of heart failure ultimately improving patient outcomes and reducing healthcare costs.

Keywords Heart failure • Natriuretic peptides • NT-proBNP

Introduction

Heart failure is common with major and adverse effects on quality of life, survival, and healthcare costs.[1] As heart failure treatments reduce hospitalizations and death, early diagnosis is essential. The most recent European Society of Cardiology (ESC) guidelines on heart failure recommend measuring concentrations of N-terminal pro-B-type natriuretic peptide (NT-proBNP), B-type natriuretic peptide (BNP), or mid-regional pro-atrial natriuretic peptide (MR-proANP) for the diagnostic evaluation of heart failure.[1] The very first ESC guideline on heart failure published in 1995 explicitly recommended the use of natriuretic peptides (NPs) to rule out a diagnosis of heart failure.[2] However, the most recent guidelines from the ESC, the American Heart Association/American College of Cardiology and the American Diabetes Association now suggest that NPs should also be considered to diagnosis (i.e. rule in) heart failure.[1,3–5] The universal definition of heart failure[6] also underscores the importance of measuring NPs for diagnosing heart failure. This paradigm shift recognizes NPs as a key component in the early detection of heart failure, benefiting both specialists and non-specialists alike.

This clinical consensus statement will focus on NT-proBNP, as it is the most utilized peptide for diagnosing and managing heart failure in Europe.[7] While there is a stoichiometric release of BNP and NT-proBNP, their half-lives differ. The estimated half-life for BNP is ~21 min, whereas for NT-proBNP, it is extended to around 70 min. Consequently, concentrations of NT-proBNP are higher than those of BNP.[8–10] Stability at room temperature facilitates the handling of specimens for NT-proBNP measurement in usually busy clinical laboratories; in this regard, NT-proBNP is a more convenient molecule to work with than BNP, whose stability is dependent on the specific assay and is largely unstable at room temperature.[11] Moreover, it is not affected by treatments that alter degradation of BNP (e.g. sacubitril/valsartan).[12,13] Others may wish to develop dedicated algorithms for BNP and MR-proANP.

To address the variability in healthcare professionals' diagnostic expertise, this clinical consensus statement utilizes cut-point recommendations for early diagnosis of heart failure and heart stress, rather than relying on NT-proBNP as a continuous variable. Furthermore, despite the prioritization of NP measurement in clinical guidelines, the implementation and interpretation of NT-proBNP levels in real-world clinical practice remains sub-optimal.[14] To bridge this gap, the Heart Failure Association (HFA) organized a workshop in London in February 2023. This document serves as a summary of the workshop's conclusions, offering practical advice on the utilization of NT-proBNP for the timely diagnosis of heart failure and heart stress. This document is an update to the 2019 HFA document of 'Cardiology practical guidance on the use of natriuretic peptide concentrations'.[15]

NT-proBNP for ruling out and ruling in heart failure in the emergency department

Approximately 60–80% of heart failure diagnoses are made for the first time in the emergency department (ED) as reported in a National Health Service audit.[16] It is important to note that these statistics may not necessarily mirror the situation in different global regions. When evaluating patients with possible heart failure, clinician uncertainty is associated with increased morbidity and mortality and prolongs hospital length of stay.[17] Studies have consistently demonstrated that the use of NP testing in the ED results in more accurate and timely diagnosis of heart failure, leading to faster initiation of life-saving therapies and earlier discharge, with resulting clinical and economic benefits.[18–24] The use of NT-proBNP-supported strategies results in reductions in initial hospitalizations (14.5%), admissions to cardiology (16.0%), admissions to intensive care units (12.5%), ED readmissions (3.2%), and hospital readmissions (21.6%).[25,26] As a result, the use of NP-based approaches leads to lower inpatient management costs and total treatment costs.

Despite compelling evidence supporting the use of NP testing for the early diagnosis of heart failure in ED, there is substantial variation in the availability of such testing across ESC member countries, as demonstrated by the HFA Atlas.[14] The highest use of NPs in ED was found in Germany (with 19.8 hospitals per million people), whereas Kyrgyzstan and North Macedonia reported the lowest use (none), followed by the Russian Federation (0.02 hospitals per million people). Certainly, differences in local healthcare system organization, delivery, local costs, and funding can contribute to discrepancies in the use of NT-proBNP in ED. Practical algorithms for the use of NT-proBNP in ED are needed to ensure consistency and standardization in the diagnosis of heart failure.

In the ED, higher NP cut-points are utilized compared to the outpatient setting, reflecting the presence of 'wet' NPs characterized by acutely elevated BNP/NT-proBNP levels due to severe congestion leading to greater myocardial stretching and increased NP secretion. A single cut-point of 300 pg/ml NT-proBNP is considered to rule out the diagnosis of heart failure (*Figure 1*), regardless of the patient's age.[27,28] When plasma NT-proBNP is below this value, clinicians should evaluate the patient for non-cardiac causes of dyspnoea.

For ruling in heart failure in the ED, age-adjusted cut-points have been established: ≥450 pg/ml for patients under 50 years,

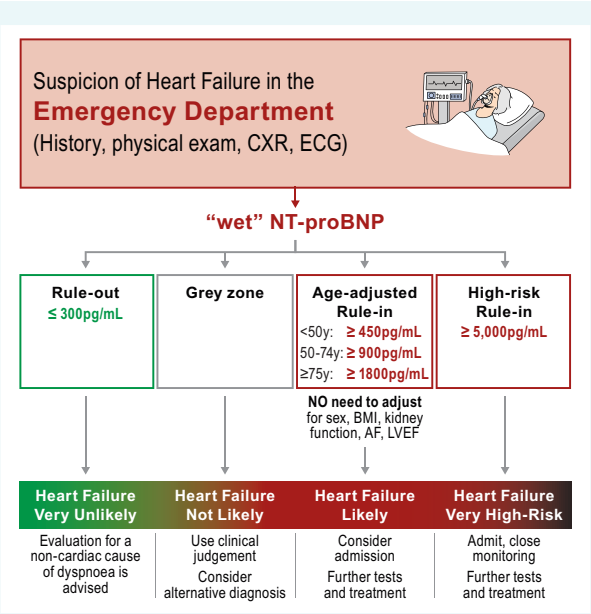

Figure 1 NT-proBNP for diagnosis of heart failure in the emergency department. AF, atrial fibrillation/flutter; BMI, body mass index; CXR, chest x-ray; ECG electrocardiogram; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro-B-type natriuretic peptide.

≥900 pg/ml for patients aged 50–75 years, and ≥1800 pg/ml for patients over 75 years[27,28] (online supplementary *Table S1*). If NT-proBNP concentrations exceed these cut-points, acute heart failure is likely, and admission, further investigation, and treatment for heart failure should be advised. The age-adjusted rule-in values for NT-proBNP in the ED do not necessitate additional adjustments for factors that can influence NP levels, such as renal dysfunction (low estimated glomerular filtration rate [eGFR]), obesity, diabetes, or atrial fibrillation.[29–32]

The cut-points for the age-independent rule out and age-adjusted rule in of NT-proBNP levels were initially established by the International Collaborative of NT-proBNP (ICON) study in 2006.[27] These cut-points were further validated in the ICON-RELOADED study published in 2018, which included a more contemporary population of older and more comorbid patients.[28] The consistency in the use of these cut-points across different studies highlights their utility in clinical practice.[33]

The 'grey zone' in NT-proBNP refers to a range of plasma concentrations that lie between the rule-out and rule-in values. In patients with acute dyspnoea in the ED, the grey zone for NT-proBNP concentrations ranges between the age-independent rule-out value and the age-adjusted rule-in value. For example, among individuals under 50 years, the grey zone is between 300 and 450 pg/ml, for those aged 50 and 75 years, it is between 300 and 900 pg/ml, and for those over 75 years, it is between 300 and 1800 pg/ml. Patients falling within the grey zone require further diagnostic testing, such as echocardiography or cardiac imaging, and consideration of other clinical factors, to determine whether they have heart failure or another underlying condition.[34]

Patients presenting to the ED with very high NT-proBNP concentrations, particularly those above 5000 pg/ml, have a poor prognosis.[27,35] Patients with NT-proBNP concentrations above this threshold require hospital admission, often in critical care, urgent investigation and close monitoring. Treatment of congestion, usually administered intravenously, is necessary (*Figure 1*).

NT-proBNP is also a valuable diagnostic tool for identifying worsening heart failure in other care settings. To identify patients with known and treated heart failure, who are free from congestion, we utilize the term 'dry' NT-proBNP. Consequently, an NT-proBNP increase by more than 25% compared to the 'dry' NT-proBNP value suggests worsening heart failure. A comprehensive clinical evaluation is essential to diagnose and manage suspected worsening heart failure, as elevated NT-proBNP concentrations can be observed in other conditions.[15,36,37]

NT-proBNP for ruling out and ruling in *de novo* heart failure in the outpatient setting

The diagnosis of heart failure in the outpatient setting can be challenging due to the wide range of non-specific symptoms which patients can present to their general practitioner (GP). Many patients who present to hospital and are diagnosed with heart failure for the first time having previously presented to their GP with symptoms suggestive of heart failure yet did not receive investigations to diagnose heart failure (e.g. measurement of NP concentrations).[16] Although measurement of NPs as a diagnostic tool has been endorsed in guidelines for more than 20 years, their use has only increased slightly over time.[38] A significant deficit persists in the uptake of NP testing to diagnose or exclude heart failure in the community[39]; this document should serve as a call to action.

A single rule-out cut-point of 125 pg/ml for NT-proBNP has been consistently recommended by guidelines in the outpatient setting to exclude a diagnosis of heart failure, regardless of the patient's age (*Figure 2*).[1,3]

In contrast, the outpatient setting lacks well-defined rule-in values for NT-proBNP. The guidelines from the United Kingdom National Institute for Health and Care Excellence (NICE) propose a single rule-in threshold of 400 pg/ml for NT-proBNP.[40] However, population studies have revealed significant age- and sex-based variations in NT-proBNP concentrations, suggesting that a single rule-in threshold in the outpatient setting could result in unnecessary referrals for additional investigations such as echocardiography.[41–45] Additionally, comorbidities such as obesity and renal dysfunction may also affect NT-proBNP rule-in concentrations.[31] In order to ensure simplicity and ease of use, this consensus document adopts a compromise approach by utilizing age-specific rule-in cut-points exclusively. These cut-points are determined based on the 95th percentile of the Generation Scotland cohort,[41] following the same age strata as those employed in the ED. The age-adjusted rule-in cut-points in the outpatient setting have been established: ≥125 pg/ml for patients under 50 years, ≥250 pg/ml for patients aged 50-75 years, and ≥500 pg/ml for patients over 75 years. If NT-proBNP concentrations surpass

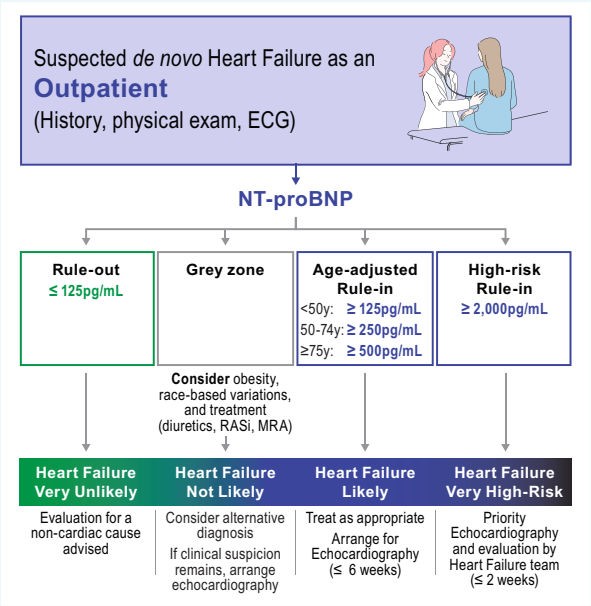

Figure 2 NT-proBNP for diagnosis of *de novo* heart failure in the outpatient setting. ECG electrocardiogram; MRA, mineralocorticoid receptor antagonist; NT-proBNP, N-terminal pro-B-type natriuretic peptide; RASi, renin–angiotensin system inhibitor.

these cut-points, it is indicative of likely heart failure, and arranging echocardiography within 6 weeks is advised (*Figure 2*).

Complex cut-point schemes that incorporate multiple comorbidities in addition to age can be taken into consideration, especially if they can be integrated into electronic health records that trigger an alarm when NT-proBNP concentrations exceed specified thresholds. These should include age- and sex-specific NT-proBNP cut-points for the diagnosis of HF with adjustments for renal dysfunction, atrial fibrillation or flutter including ventricular rate on the baseline resting electrocardiogram (ECG) and body mass index (BMI). *Table 1* shows suggested NT-proBNP cut-offs stratified by age and gender for non-obese patients without kidney failure and atrial fibrillation/flutter on baseline ECG.[46] The following suggested modifications for comorbid conditions are based more on expert opinion rather than on strong evidence and should be refined as more information becomes available. When eGFR is <30 ml/min/1.73 m^2, the cut-point for NT-proBNP should be increased by 35%; for eGFR between 30 and 45 ml/min/1.73 m^2 by 25% and for eGFR 45-60 ml/min/1.73 m^2 by 15%. When BMI is between 30 and 35 kg/m^2, the NT-proBNP cut-off should be reduced by 25%; for BMI between 35 and 40 kg/m^2 by 30% and over 40 kg/m^2 by 40%. For atrial fibrillation or flutter, the NT-proBNP cut-point should be increased by 50% when the ventricular rate is ≤90 bpm at the time of the blood draw or by 100% when the ventricular rate is >90 bpm.

Further investigation is required to ascertain which of the two approaches, the simpler age-adjusted or the more sophisticated fully adjusted rule-in cut-points, offer a greater reduction in unnecessary referrals and echocardiograms.

Table 1 NT-proBNP cut-points for non-obese patients without kidney failure and atrial fibrillation/flutter on baseline electrocardiogram

	NT-proBNP (pg/ml)	
	Men	Women
<60 years	>75	>125
60–69 years	>125	>175
70–79 years	>175	>225
>80 years	>250	>250

NT-proBNP, N-terminal pro-B-type natriuretic peptide.

Implementing the proposed age-adjusted rule-in and age-independent rule-out criteria for patients with suspected heart failure in the outpatient setting introduces a grey zone. For individuals under 50 years, there is no grey zone. For patients aged 50–75 years, the grey zone ranges from 125 to 250 pg/ml, while for those over 75 years, it extends from 125 to 500 pg/ml. It is crucial to conduct a thorough evaluation of patients within the grey zone, considering factors such as obesity, race-based variations, and ongoing treatment (as many patients with a history of hypertension may already be on diuretics, renin–angiotensin system inhibitors, or mineralocorticoid receptor antagonists).

In the outpatient setting, the extent of elevation in NP concentrations at the time of heart failure diagnosis is closely linked to the risk of subsequent hospitalization and mortality.[16] As a result, there has been a suggestion to utilize NT-proBNP concentrations at the time of a community-based heart failure diagnosis as a triaging tool to prioritize access to expedited diagnostic echocardiography and to set up a follow-up plan for individuals with the highest short-term risk of adverse events. The authors of this consensus document align with the NICE guidelines on chronic heart failure, which recommend a cut-off value of NT-proBNP >2000 pg/ml.[40] In an analysis of primary care data from England, an NT-proBNP value of >2000 pg/ml was associated with a more than two-fold higher risk of heart failure hospitalization and 50% higher risk of mortality as compared with an NT-proBNP of 400–2000 pg/ml.[47] We suggest that, irrespective of age and sex, patients with an NT-proBNP >2000 pg/ml should be prioritized for echocardiography and clinical evaluation within 2 weeks of diagnosis (*Figure 2*).

NT-proBNP in asymptomatic patients with risk factors: heart stress

Various risk factors, such as hypertension, atherosclerotic cardiovascular disease, diabetes, obesity, and others, contribute to an increased susceptibility to the development of heart failure. In the absence of symptoms of heart failure, patients with risk factors may exhibit either heart health or heart stress. Heart health refers to individuals who have a structurally normal heart and normal plasma concentrations of NPs and troponins.

In this consensus document, a new condition termed 'heart stress' is introduced to identify asymptomatic individuals with risk factors and elevated plasma NPs, irrespective of the presence or absence of structural heart disease or cardiac dysfunction. NPs, produced by cardiomyocytes under strain caused by either cardiac volume or pressure overload, serve as indicators of the molecular stress experienced by the heart.[15] Patients with diabetes serve as an example of this concept, as they often appear to have a structurally and functionally normal heart on imaging but increased concentrations of NT-proBNP that predict an increased risk of developing heart failure and mortality.[48,49]

The proposed cut-points outlined in this consensus document primarily focus on patients with diabetes, as this is the population where most evidence exists. A recent consensus document by the American Diabetes Association advises the use of a single cut-point of 125 pg/ml to determine heart failure risk.[5]

Following a similar structure to the previous sections, and given the additional evidence emerged since that consensus was published,[50] here we propose rule-in and rule-out cut-points, including a grey zone in between. A rule-out cut-point of 50 pg/ml is suggested to provide reassurance to clinicians regarding the patient's heart health and may prompt routine check-ups on an annual basis.[48,51] Age-specific rule-in cut-points, consistent with the age strata used in the ED and outpatient setting, are proposed. For patients younger than 50 years, a rule-in level of 75 pg/ml is advised. For patients aged 50–74 years, a cut-point of 150 pg/ml, and for those over 75 years of age, a cut-point of 300 pg/ml is proposed (*Figure 3*). Increased concentrations indicate the likelihood of heart stress, prompting careful re-evaluation of the patient for problems such as atrial fibrillation and chronic kidney disease, lifestyle advice (e.g. dietary salt intake, exercise, smoking, etc.) and the treatment of risk factors such as hypertension. NT-proBNP concentrations may be re-evaluated within the following 6–12 months to determine the response to any intervention and the need for further investigation (*Figure 3*). This advice, based on a consensus decision, requires confirmation by prospective studies. It is important to validate the heart stress algorithm using clinical trial data; conducting post-hoc validation should be feasible from existing trial data or registries (such as the UK Biobank).

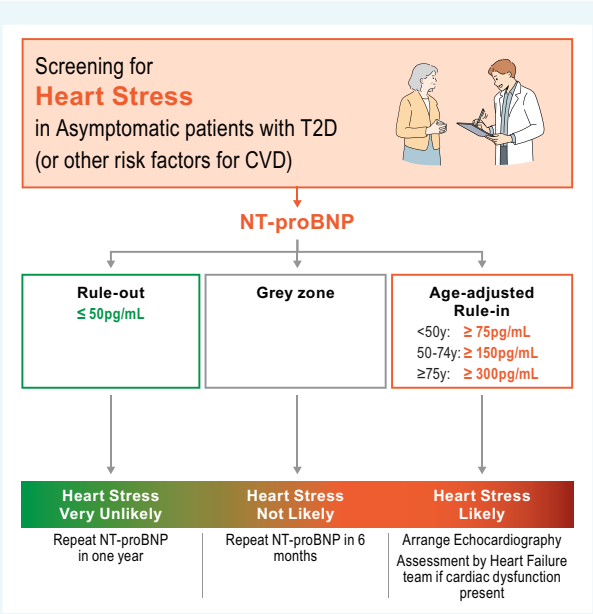

Figure 3 NT-proBNP for diagnosis of heart stress in asymptomatic patients with diabetes. CVD, cardiovascular disease; NT-proBNP, N-terminal pro-B-type natriuretic peptide; T2D, type 2 diabetes.

FIND-HF – The HFA acronym for early diagnosis of heart failure

To promote early diagnosis of heart failure and assist healthcare professionals and patients, we suggest the mnemonic acronym FIND-HF (Fatigue, Increased water accumulation, Natriuretic peptide testing, and Dyspnoea-Heart Failure), which serves as a reminder for healthcare providers to consider heart failure in patients with any of these features and the need to check NT-proBNP.

The presence of clinical congestion with ankle swelling, or pulmonary crackles should not be a prerequisite for suspecting heart failure. The diagnosis of heart failure should be made much earlier, long before symptoms and signs are so severe that the patient needs to be hospitalized.[41] Many individuals initially exhibit symptoms such as 'fatigue' and 'dyspnoea' before signs of congestion (peripheral oedema or increased jugular venous pressure). Recognizing this pattern is crucial, particularly for GPs, for the early detection of heart failure. By adopting the FIND-HF mnemonic, healthcare professionals should attain a higher level of suspicion for heart failure and have a lower threshold for making NP measurements.

Fatigue

Increased water accumulation

Natriuretic peptide testing

Dyspnoea

HF – heart failure

In summary, the implementation of NP testing is necessary to improve the diagnosis of heart failure. In the ED it can quickly rule a diagnosis of heart failure in or out. In the outpatient setting, NT-proBNP assists the early detection of heart failure, prompting further diagnostic tests, such as echocardiography, and the timely initiation of appropriate treatments that will improve well-being and reduce morbidity and mortality. We now introduce the concept of NT-proBNP as a measure of heart stress for asymptomatic patients with risk factors (i.e. diabetes) that which may be used to identify patients at increased risk of developing heart failure. Routine screening with NT-proBNP enables interventions to delay or prevent disease progression and the development of heart failure. The mnemonic FIND-HF is introduced as a reminder for early diagnosis of heart failure for both healthcare professionals and patients.

Supplementary Information

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

Conflict of interest: A.B.G. has participated in advisory boards and/or lectured for Abbott, AstraZeneca, Boehringer Ingelheim, Novartis, Roche Diagnostics, Vifor Pharma. M.C.P. has received research grants from SQ Innovations, AstraZeneca, Roche, Boehringer Ingelheim, Pharmacosmos, Eli Lilly, Napp Pharmaceuticals, Novartis, and Novo Nordisk, and has served on committees for AbbVie, Akero, Alnylam, AstraZeneca, Bayer, Boehringer Ingelheim, GlaxoSmithKline, Resverlogix, Teikoku, New Amsterdam and Novo Nordisk; he is a director of Global Clinical Trial Partners). J.L.J. is a Trustee of the American College of Cardiology; is a board member of Imbria Pharmaceuticals and Director at Jana Care; has received research support from Abbott, Applied Therapeutics, HeartFlow, Innolife, and Roche Diagnostics; has received consulting income from Abbott, Beckman, Bristol Myers Squibb, Boehringer Ingelheim, Janssen, Novartis, Pfizer, Merck, Roche Diagnostics, and Siemens; and participates in clinical endpoint committees/data safety monitoring boards for Abbott, AbbVie, Bayer, CVRx, Intercept, Janssen, 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, AstraZeneca, Beckman Coulter, Boehringer Ingelheim, Brahms, Idorsia, LSI Medience, Novartis, Ortho Clinical, Quidel, Roche, Siemens, Singulex, SpinChip, and Sphingotec, as well as speaker honoraria/consulting honoraria from AstraZeneca, Bayer, Boehringer Ingelheim, BMS, Idorsia, Osler, Novartis, Roche, Siemens, SpinChip, and Singulex, outside the submitted work, and all paid to the institution. B.B. has participated in consultation or advisory board roles for AstraZeneca, Amgen, Sanofi, Vifor, Roche, Boehringer Ingelheim, Abiomed, Zoll/ Respicardia, Johnson & Johnson, Hanger Institute, and serves on the Clinical Event Committees of Abbott Vascular, Data Safety Monitoring Committees of Liva Nova, Cardurion, and Renovacor. J.B. consultant, Abbott, American Regent, Amgen, Applied Therapeutic, AstraZeneca, Bayer, Boehringer Ingelheim, Bristol Myers Squibb, Cardiac Dimension, Cardior, CVRx, Cytokinetics, Edwards, Element Science, Innolife, Impulse Dynamics, Imbria, Inventiva, Lexicon, Lilly, LivaNova, Janssen, Medtronics, Merck, Occlutech, Novartis, Novo Nordisk, Pfizer, Pharmacosmos, Pharmain, Roche, Sequana, SQ Innovation, and Vifor. J.G.F.C. grants from British Heart Foundation and the National Institute of Health Research, personal fees from Abbott, Novartis, Idorsia, Servier, Boehringer Ingelheim, AstraZeneca, Biopeutics, Moderna, support for manuscript submission from Bristol Myers Squibb, personal fees and research support from Medtronic, grants and personal fees from Pharmacosmos, CSL-Vifor, Innolife, grants and stock options from Viscardia, personal fees and non-financial support from NI Medical, stock options from Heartfelt technologies. S.D.P. has served as president of EASD/EFSD (2020–2022); has received research grants to the institution from AstraZeneca and Boehringer Ingelheim; has served as advisor for Abbott, Applied Therapeutics, AstraZeneca, Boehringer Ingelheim, Eli Lilly & Co., EvaPharma, Jiangsu Hengrui Pharmaceuticals Co., Menarini International, Merck Sharpe & Dohme, Novartis Pharmaceutical Co., Novo Nordisk, Sanofi, Sun Pharmaceuticals; has received fees for speaking from AstraZeneca, Boehringer Ingelheim, Eli Lilly & Co., Laboratori Guidotti, Merck Sharpe & Dohme, Novo Nordisk. F.G. has received consulting honoraria from Abbott, FineHeart, Alnylam, Ionis, Bayer, AstraZeneca, and speaker's fee from Pfizer, Janssen, Novartis. C.S.P.L. has received research support from NovoNordisk and Roche Diagnostics; has received consulting fees from Alleviant Medical, Allysta Pharma, Amgen, AnaCardio AB, Applied Therapeutics, AstraZeneca, Bayer, Boehringer Ingelheim, Boston Scientific, Bristol Myers Squibb, CardioRenal, Cytokinetics, Darma Inc., EchoNous Inc, Eli Lilly, Impulse Dynamics, Intellia Therapeutics, Ionis Pharmaceutical, Janssen Research & Development LLC, Medscape/WebMD Global LLC, Merck, Novartis, Novo Nordisk, Prosciento Inc, Quidel Corporation, Radcliffe Group Ltd., Recardio Inc, ReCor Medical, Roche Diagnostics, Sanofi, Siemens Healthcare Diagnostics and Us2.ai; and is a co-founder and non-executive director of Us2.ai. R.P.B. has received research support to the University of Michigan from Novo Nordisk and Medtronic, and consulting fees from AstraZeneca, Bayer, Nevro, Roche, Procter & Gamble. M.M. has received honoraria from Cytokinetics and Vifor pharma for participation in committee for sponsored clinical trials and has received consulting honoraria from Abbott, AstraZeneca, Bayer, Boehringer Ingelheim, Roche Diagnostics in the last 3 years. All other authors have nothing to disclose.

References

1. 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. https://doi.org/10.1002/ejhf.2333
2. Guidelines for the diagnosis of heart failure. The Task Force on Heart Failure of the European Society of Cardiology. *Eur Heart J* 1995;**16**:741–751.
3. Heidenreich PA, Bozkurt B, Aguilar D, Allen LA, Byun JJ, Colvin MM, *et al.* AHA/ACC/HFSA Guideline for the management of heart failure: Executive summary: A report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *J Am Coll Cardiol* 2022;**79**:1757–1780. https://doi.org/10.1016/j.jacc.2021.12.011
4. Revuelta-López E, Barallat J, Cserkóová A, Gálvez-Montón C, Jaffe AS, Januzzi JL, *et al.* Pre-analytical considerations in biomarker research: Focus on cardiovascular disease. *Clin Chem Lab Med.* 2021;**59**:1747–1760.
5. Pop-Busui R, Januzzi JL, Bruemmer D, Butalia S, Green JB, Horton WB, *et al.* Heart failure: An underappreciated complication of diabetes. A consensus report of the American Diabetes Association. *Diabetes Care* 2022;**45**:1670–1690. https://doi.org/10.2337/dci22-0014
6. 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: Endorsed by the Canadian Heart Failure Society, Heart Failure Association of India, Cardiac Society of Australia and New Zealand, and Chinese Heart Failure Association. *Eur J Heart Fail* 2021;**23**:352–380. https://doi.org/10.1002/ejhf.2115
7. Chioncel O, Lainscak M, Seferovic PM, Anker SD, Crespo-Leiro MG, Harjola VP, *et al.* Epidemiology and one-year outcomes in patients with chronic heart failure and preserved, mid-range and reduced ejection fraction: An analysis of the ESC Heart Failure Long-Term Registry. *Eur J Heart Fail* 2017;**19**:1574–1585. https://doi.org/10.1002/ejhf.813
8. Mukoyama M, Nakao K, Hosoda K, Suga S, Saito Y, Ogawa Y, *et al.* Brain natriuretic peptide as a novel cardiac hormone in humans. Evidence for an exquisite dual natriuretic peptide system, atrial natriuretic peptide and brain natriuretic peptide. *J Clin Invest* 1991;**87**:1402–1412. https://doi.org/10.1172/JCI115146
9. Pemberton CJ, Johnson ML, Yandle TG, Espiner EA. Deconvolution analysis of cardiac natriuretic peptides during acute volume overload. *Hypertension* 2000;**36**:355–359. https://doi.org/10.1161/01.hyp.36.3.355
10. Meijers WC, Bayes-Genis A, Mebazaa A, Bauersachs J, Cleland JGF, Coats AJS, *et al.* Circulating heart failure biomarkers beyond natriuretic peptides: Review from the Biomarker Study Group of the Heart Failure Association (HFA), European Society of Cardiology (ESC). *Eur J Heart Fail* 2021;**23**:1610–1632. https://doi.org/10.1002/ejhf.2346
11. Azzazy HM, Christenson RH, Duh SH. Stability of B-type natriuretic peptide (BNP) in whole blood and plasma stored under different conditions when measured with the Biosite Triage or Beckman-Coulter Access systems. *Clin Chim Acta* 2007;**384**:176–178. https://doi.org/10.1016/j.cca.2007.05.025
12. Myhre PL, Prescott MF, Murphy SP, Fang JC, Mitchell GF, Ward JH, *et al.* Early B-type natriuretic peptide change in HFrEF patients treated with sacubitril/valsartan: A pooled analysis of EVALUATE-HF and PROVE-HF. *JACC Heart Fail* 2022;**10**:119–128. https://doi.org/10.1016/j.jchf.2021.09.007

13. Myhre PL, Prescott MF, Claggett B, Felker GM, Butler J, Piña IL, *et al.* Comparative effect of angiotensin receptor neprilysin inhibition on B-type natriuretic peptide levels measured by three different assays: The PROVE-HF study. *Clin Chem* 2022;**68**:1391–1398. https://doi.org/10.1093/clinchem/hvac148
14. Seferović PM, Vardas P, Jankowska EA, Maggioni AP, Timmis A, Milinković I, *et al.* The Heart Failure Association Atlas: Heart failure epidemiology and management statistics 2019. *Eur J Heart Fail* 2021;**23**:906–914. https://doi.org/10.1002/ejhf.2143
15. 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**:715–731. https://doi.org/10.1002/ejhf.1494
16. Bottle A, Kim D, Aylin P, Cowie MR, Majeed A, Hayhoe B. Routes to diagnosis of heart failure: Observational study using linked data in England. *Heart* 2018;**104**:600–605. https://doi.org/10.1136/heartjnl-2017-312183
17. Green SM, Martinez-Rumayor A, Gregory SA, Baggish AL, O'Donoghue ML, Green JA, *et al.* Clinical uncertainty, diagnostic accuracy, and outcomes in emergency department patients presenting with dyspnea. *Arch Intern Med* 2008;**168**:741–748. https://doi.org/10.1001/archinte.168.7.741
18. Dao Q, Krishnaswamy P, Kazanegra R, Harrison A, Amirnovin R, Lenert L, *et al.* Utility of B-type natriuretic peptide in the diagnosis of congestive heart failure in an urgent-care setting. *J Am Coll Cardiol* 2001;**37**:379–385. https://doi.org/10.1016/s0735-1097(00)01156-6
19. Collins SP, Lindsell CJ, Storrow AB, Abraham WT; ADHERE Scientific Advisory Committee, Investigators and Study Group. Prevalence of negative chest radiography results in the emergency department patient with decompensated heart failure. *Ann Emerg Med* 2006;**47**:13–18. https://doi.org/10.1016/j.annemergmed.2005.04.003
20. Bayés-Genís A, Santaló-Bel M, Zapico-Muñiz E, López L, Cotes C, Bellido J, *et al.* N-terminal probrain natriuretic peptide (NT-proBNP) in the emergency diagnosis and in-hospital monitoring of patients with dyspnoea and ventricular dysfunction. *Eur J Heart Fail* 2004;**6**:301–308. https://doi.org/10.1016/j.ejheart.2003.12.013
21. Lam LL, Cameron PA, Schneider HG, Abramson MJ, Müller C, Krum H. Meta-analysis: Effect of B-type natriuretic peptide testing on clinical outcomes in patients with acute dyspnea in the emergency setting. *Ann Intern Med* 2010;**153**:728–735. https://doi.org/10.7326/0003-4819-153-11-201012070-00006
22. Moe GW, Howlett J, Januzzi JL, Zowall H; Canadian Multicenter Improved Management of Patients with Congestive Heart Failure (IMPROVE-CHF) Study Investigators. N-terminal pro-B-type natriuretic peptide testing improves the management of patients with suspected acute heart failure: Primary results of the Canadian prospective randomized multicenter IMPROVE-CHF study. *Circulation* 2007;**115**:3103–3110. https://doi.org/10.1161/CIRCULATIONAHA.106.666255
23. Kozhuharov N, Sabti Z, Wussler D, Nowak A, Badertscher P, Twerenbold R, *et al.*; BASEL V Investigators. Prospective validation of N-terminal pro B-type natriuretic peptide cut-off concentrations for the diagnosis of acute heart failure. *Eur J Heart Fail* 2019;**21**:813–815. https://doi.org/10.1002/ejhf.1471
24. Mueller C, Scholer A, Laule-Kilian K, Martina B, Schindler C, Buser P, *et al.* Use of B-type natriuretic peptide in the evaluation and management of acute dyspnea. *N Engl J Med* 2004;**350**:647–654. https://doi.org/10.1056/NEJMoa031681
25. Siebert U, Milev S, Zou D, Litkiewicz M, Gaggin HK, Tirapelle L, *et al.* Economic evaluation of an N-terminal pro B-type natriuretic peptide-supported diagnostic strategy among dyspneic patients suspected of acute heart failure in the emergency department. *Am J Cardiol* 2021;**147**:61–69. https://doi.org/10.1016/j.amjcard.2021.01.036
26. Mueller C, Laule-Kilian K, Schindler C, Klima T, Frana B, Rodriguez D, *et al.* Cost-effectiveness of B-type natriuretic peptide testing in patients with acute dyspnea. *Arch Intern Med* 2006;**166**:1081–1087. https://doi.org/10.1001/archinte.166.10.1081
27. Januzzi JL, van Kimmenade R, Lainchbury J, Bayes-Genis A, Ordonez-Llanos J, Santalo-Bel M, *et al.* NT-proBNP testing for diagnosis and short-term prognosis in acute destabilized heart failure: An international pooled analysis of 1256 patients: The International Collaborative of NT-proBNP study. *Eur Heart J* 2006;**27**:330–337. https://doi.org/10.1093/eurheartj/ehi631
28. Januzzi JL Jr, Chen-Tournoux AA, Christenson RH, Doros G, Hollander JE, Levy PD, *et al.*; ICON-RELOADED Investigators. N-terminal pro-B-type natriuretic peptide in the emergency department: The ICON-RELOADED study. *J Am Coll Cardiol* 2018;**71**:1191–1200. https://doi.org/10.1016/j.jacc.2018.01.021
29. Bayes-Genis A, Lloyd-Jones DM, van Kimmenade RR, Lainchbury JG, Richards AM, Ordoñez-Llanos J, *et al.* Effect of body mass index on diagnostic and prognostic usefulness of amino-terminal pro-brain natriuretic peptide in patients with acute dyspnea. *Arch Intern Med* 2007;**167**:400–407. https://doi.org/10.1001/archinte.167.4.400
30. van Kimmenade RR, Januzzi JL Jr, Baggish AL, Lainchbury JG, Bayes-Genis A, Richards AM, *et al.* Amino-terminal pro-brain natriuretic peptide, renal function, and outcomes in acute heart failure: Redefining the cardiorenal interaction? *J Am Coll Cardiol* 2006;**48**:1621–1627. https://doi.org/10.1016/j.jacc.2006.06.056
31. de Filippi CR, Seliger SL, Maynard S, Christenson RH. Impact of renal disease on natriuretic peptide testing for diagnosing decompensated heart failure and predicting mortality. *Clin Chem* 2007;**53**:1511–1519. https://doi.org/10.1373/clinchem.2006.084533
32. O'Donoghue M, Kenney P, Oestreicher E, Anwaruddin S, Baggish AL, Krauser DG, *et al.* Usefulness of aminoterminal pro-brain natriuretic peptide testing for the diagnostic and prognostic evaluation of dyspneic patients with diabetes mellitus seen in the emergency department (from the PRIDE study). *Am J Cardiol* 2007;**100**:1336–1340. https://doi.org/10.1016/j.amjcard.2007.06.020
33. Lee KK, Doudesis D, Anwar M, Astengo F, Chenevier-Gobeaux C, Claessens YE, *et al.* CoDE-HF investigators. Development and validation of a decision support tool for the diagnosis of acute heart failure: Systematic review, meta-analysis, and modelling study. *BMJ* 2022;**377**:e068424. https://doi.org/10.1136/bmj-2021-068424
34. van Kimmenade RR, Pinto YM, Januzzi JL Jr. Importance and interpretation of intermediate (gray zone) amino-terminal pro-B-type natriuretic peptide concentrations. *Am J Cardiol* 2008;**101**:39–42. https://doi.org/10.1016/j.amjcard.2007.11.018
35. Salah K, Kok WE, Eurlings LW, Bettencourt P, Pimenta JM, Metra M, *et al.* A novel discharge risk model for patients hospitalised for acute decompensated heart failure incorporating N-terminal pro-B-type natriuretic peptide levels: A European coLlaboration on Acute decompeNsated Heart Failure: ELAN-HF score. *Heart* 2014;**100**:115–125. https://doi.org/10.1136/heartjnl-2013-303632
36. 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**:177–182. https://doi.org/10.1093/eurheartj/ehl449
37. Januzzi JL, Troughton R. Are serial BNP measurements useful in heart failure management? Serial natriuretic peptide measurements are useful in heart failure management. *Circulation* 2013;**127**:500–508. https://doi.org/10.1161/CIRCULATIONAHA.112.120485
38. Roalfe AK, Lay-Flurrie SL, Ordóñez-Mena JM, Goyder CR, Jones NR, Hobbs FDR, *et al.* Long term trends in natriuretic peptide testing for heart failure in UK primary care: A cohort study. *Eur Heart J* 2021;**43**:881–891. https://doi.org/10.1093/eurheartj/ehab781
39. Bayes-Genis A, Coats AJS. 'Peptide for Life' in primary care: Work in progress. *Eur Heart J* 2022;**43**:892–894. https://doi.org/10.1093/eurheartj/ehab829
40. National Institute for Health and Care Excellence. Heart failure guidance. www.nice.org.uk/Guidance/Conditions-and-diseases/Cardiovascular-conditions/Heart-failure. Accessed 17 September 2023.
41. Welsh P, Campbell RT, Mooney L, Kimenai DM, Hayward C, Campbell A, *et al.* Reference ranges for NT-proBNP (N-terminal pro-B-type natriuretic peptide) and risk factors for higher NT-proBNP concentrations in a large general population cohort. *Circ Heart Fail* 2022;**15**:e009427. https://doi.org/10.1161/CIRCHEARTFAILURE.121.009427
42. Mu S, Echouffo-Tcheugui JB, Ndumele CE, Coresh J, Juraschek S, Brady T, *et al.* NT-proBNP reference intervals in healthy U.S. children, adolescents, and adults. *J Appl Lab Med* 2023;**8**:700–712. https://doi.org/10.1093/jalm/jfad024
43. Myhre PL, Claggett B, Yu B, Skali H, Solomon SD, Røsjø H, *et al.* Sex and race differences in N-terminal pro-B-type natriuretic peptide concentration and absolute risk of heart failure in the community. *JAMA Cardiol* 2022;**7**:623–631. https://doi.org/10.1001/jamacardio.2022.0680
44. Keyzer JM, Hoffmann JJ, Ringoir L, Nabbe KC, Widdershoven JW, Pop VJ. Age- and gender-specific brain natriuretic peptide (BNP) reference ranges in primary care. *Clin Chem Lab Med* 2014;**52**:1341–1346. https://doi.org/10.1515/cclm-2013-0791
45. Hildebrandt P, Collinson PO, Doughty RN, Fuat A, Gaze DC, Gustafsson F, *et al.* Age-dependent values of N-terminal pro-B-type natriuretic peptide are superior to a single cut-point for ruling out suspected systolic dysfunction in primary care. *Eur Heart J* 2010;**31**:1881–1889. https://doi.org/10.1093/eurheartj/ehq163
46. Cleland JGF, Pfeffer MA, Clark AL, Januzzi JL, McMurray JJV, Mueller C, *et al.* The struggle towards a universal definition of heart failure – how to proceed? *Eur Heart J* 2021;**42**:2331–2343. https://doi.org/10.1093/eurheartj/ehab082
47. Taylor CJ, Lay-Flurrie SL, Ordóñez-Mena JM, Goyder CR, Jones NR, Roalfe AK, *et al.* Natriuretic peptide level at heart failure diagnosis and risk of hospitalisation and death in England 2004-2018. *Heart* 2022;**108**:543–549. https://doi.org/10.1136/heartjnl-2021-319196
48. Natriuretic Peptides Studies Collaboration;Willeit P, Kaptoge S, Welsh P, Butterworth AS, Chowdhury R, Spackman SA, *et al.*, Natriuretic peptides and integrated risk assessment for cardiovascular disease: An individual-participant-data

meta-analysis. *Lancet Diabetes Endocrinol* 2016 **4**(10):840–849. https://doi.org/10.1016/S2213-8587(16)30196-6

49. Scirica BM, Braunwald E, Raz I, Cavender MA, Morrow DA, Jarolim P, *et al.* SAVOR-TIMI 53 Steering Committee and Investigators*. Heart failure, saxagliptin, and diabetes mellitus: Observations from the SAVOR-TIMI 53 randomized trial. *Circulation* 2014;**130**:1579–1588. https://doi.org/10.1161/CIRCULATIONAHA.114.010389
50. Magnusson M, Melander O, Israelsson B, Grubb A, Groop L, Jovinge S. Elevated plasma levels of Nt-proBNP in patients with type 2 diabetes without overt cardiovascular disease. *Diabetes Care* 2004;**27**:1929–1935. https://doi.org/10.2337/diacare.27.8.1929
51. Verma S, Sharma A, Kanumilli N, Butler J. Predictors of heart failure development in type 2 diabetes: A practical approach. *Curr Opin Cardiol* 2019;**34**:578–583. https://doi.org/10.1097/HCO.0000000000000647