Screening for Undiagnosed Heart Failure: A Viewpoint

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Abstract

The syndrome of heart failure (HF) is characterized by a triad of 1) signs and symptoms, 2) cardiac alterations and 3) natriuretic peptide elevation. Patients who exhibit alterations of cardiac structure or function without overt signs or symptoms of HF are staged as having “pre-HF”. However, many people with undiagnosed HF walk little and do not exercise, therefore they may be classified as having asymptomatic “pre-HF”, simply because they never exercise enough as to feel breathless. Moreover, many patients have comorbidities such as chronic obstructive pulmonary disease or obesity, and the physical limitations may be attributed to the comorbidities rather than to HF. Such comorbidities may also influence natriuretic peptide measurements. The potential implications of such HF misdiagnosis is that many patients may remain undertreated. This is illustrated with data from the HOMAGE (Heart Omics in AGEing) study which included asymptomatic people with mild natriuretic peptide elevation. When comparing patient characteristics, HOMAGE participants were similar to those of ALDO-DHF (Effect of Spironolactone on Diastolic Function and Exercise Capacity in Patients With Heart Failure With Preserved Ejection Fraction) who were classified as symptomatic HF patients. Given the confluence of HF with several cardiac-renal- and metabolic conditions, we propose a simplified, pragmatic and inclusive approach for an early HF diagnosis and treatment.

Key-words: heart failure screening; cardio-renal-metabolic conditions; prevention.

Background

The syndrome of heart failure (HF) is classically characterized by signs and symptoms of congestion (e.g., lung rales, peripheral edema), breathlessness and fatigue (often related to congestion and/or physical deconditioning), along with alterations of cardiac structure and function (e.g., enlargement of the atria, ventricular wall hypertrophy, left ventricle dilatation, increased filling pressures) which result in the elevation of natriuretic peptide levels. Thus, according to the current recommendations, for a patient to be diagnosed with HF the triad of 1) signs/symptoms, 2) cardiac alterations and 3) natriuretic peptide elevation must be met.[1,2] In some cases, natriuretic peptide elevation may not be required if other objective evidence of increased pulmonary or cardiac congestion is documented.[3]

In the early 2000s, the acknowledgment of HF as a progressive disease has led the American Heart Association (AHA) and the American College of Cardiology (ACC) to propose a model that classifies HF into four stages: “stage A” with cardiovascular risk factors, “stage B” with asymptomatic alterations of cardiac structure or function, “stage C” with HF signs or symptoms (past or present), and “stage D” with end-stage HF.[4] The reasoning behind this staging system was to complement the New York Heart Association (NYHA) functional classification system, which serves to classify the severity of symptoms over time of patients who are within “stages C or D”. Therefore, this staging system, along with the NYHA classification is believed to directly help staging and intensification of therapy. Once in “stage C” a patient could never return to “stage B”, even if symptoms regressed to NYHA class I. Discontinuation of therapy in such conditions, was shown to cause clinical deterioration.[5]

Many patients who exhibit alterations of cardiac structure and function do not have overt signs or symptoms suggestive of HF and, according to the AHA/ACC staging system, are staged as having “stage B” HF or “pre-HF” (as more recently named) and are at risk of progressing towards “stage C” HF (i.e., to become symptomatic).[3] However, many patients with alterations of cardiac structure and function walk little and do not exercise, therefore they may be classified as having asymptomatic (“stage B”) HF, simply because they never exercise enough as to feel breathless. Moreover, symptoms may be highly subjective as more stoic patients may attribute fatigue or breathlessness to ageing, stress, or deconditioning, for example. Also, a

significant proportion of patients has comorbidities such as chronic obstructive pulmonary disease (COPD) or obesity, and the physical limitations may be attributed to the comorbidities rather than to HF. Beyond the issues in correctly ascertaining HF signs and symptoms, many patients with HF may have normal- near normal natriuretic peptide levels as, for example, patients with obesity.[6] Therefore, applying the "universal definition of HF" with the above referenced triad of signs/symptoms, cardiac alterations, and natriuretic peptide elevation will leave many HF patients undiagnosed and undertreated. In this manuscript we will further explore why the HF definition may leave many HF patients undiagnosed and, consequently, undertreated and how we can be more inclusive in HF diagnosis and treatment to improve HF outcomes across the globe.

Heart failure treatments in the early 2000s versus early 2020s

In the early 2000s, treatment with an angiotensin converting enzyme inhibitor (ACEi), angiotensin receptor blocker (ARB), and/or beta-blocker was recommended for selected patients with "stage B" HF. In patients with "stage C" HF, diuretics could be added for the management of congestion, and a steroidal mineralocorticoid receptor antagonist (MRA; spironolactone at the time), digitalis, hydralazine/nitrates and cardiac devices could be used in selected patients, as per guideline directed medical therapy (GDMT). Because of the concern about treatment-associated adverse effects (mainly hypotension, hyperkalemia, worsening kidney function); and despite a clear benefit-to-risk ratio, physicians would use these medications incrementally, according to patient's disease severity, and parsimoniously, with frequent under-dosing and discontinuation.[4]

However, scientific advances in the last twenty years have made more recent evidence-based HF treatments generally well tolerated and with a low risk of side-effects. For example, sodium glucose co-transporter 2 (SGLT2) inhibitors can reduce the incidence of hyperkalemia and slow the decline of renal function in chronic HF allowing the implementation or up-titration of other neurohormonal inhibitors.[7] In addition, novel drugs can be used to treat many associated cardiac, renal, and metabolic diseases (e.g., diabetes *mellitus* [DM], chronic kidney disease [CKD], obesity, fatty liver disease, and atherosclerotic cardiovascular disease). Thus, their use early enough in the process of the disease (i.e., when HF is still asymptomatic)

may be justified by cardiovascular, kidney, and metabolic (CKM) benefits, even in the absence of a HF diagnosis.[8] For example, SGLT2 inhibitors and MRA therapy with the non-steroidal drug finerenone may benefit patients with T2D and CKD by preventing cardiovascular events and kidney function deterioration, and glucagon-like peptide 1 receptor agonists (GLP1ra) may help patients with obesity, T2D and a high cardiovascular risk losing weight and reduce the risk of cardiovascular and renal events.[9]

Stage B and C HF: are they really different?

Remarkably, although clinical trials with SGLT2i, GLP1ra and finerenone in patients with T2D and/or obesity and atherosclerotic cardiovascular disease (ASCVD) and/or CKD enrolled a low proportion of patients with symptomatic HF, in most of such trials prevention of HF was a consistent benefit. Similarly, in almost all blood pressure lowering trials with RAAS inhibitors and MRAs, the largest benefit was prevention of new onset HF. It is therefore legitimate to suspect that a substantial proportion of patients in these trials had undiagnosed HF, because of undetected signs and/or symptoms (or symptoms not assigned as HF-related) and absence of natriuretic peptides measurements.[10]

Data from the HOMAGE (Heart Omics in AGEing; NCT02556450) study serve as an illustration of the poor discriminative capacity of HF symptoms. The rationale behind HOMAGE was to test whether spironolactone (compared to usual care) would decrease markers associated with cardiac fibrosis among people with a high cardiovascular risk but without HF. Through fibrosis reduction, spironolactone could potentially prevent HF. To be enrolled in HOMAGE patients had to be 60 years or older and have cardiovascular risk factors (e.g., hypertension, T2D, a prior myocardial infarction, or albuminuria) and slightly elevated natriuretic peptides, but could not report HF signs or symptoms or be treated with a loop diuretic i.e., they would be classified as “stage B” or “pre-HF”.[11]

However, even with such selection criteria, HOMAGE participants were found to have more advanced HF than patients classified as having “stage C” symptomatic HF who were enrolled in the ALDO-DHF (Effect of Spironolactone on Diastolic Function and Exercise Capacity in Patients With Heart Failure With Preserved Ejection Fraction; ISRCTN94726526) trial. Specifically, HOMAGE participants had,

on average, higher natriuretic peptide levels, greater left atrial enlargement, and worse kidney function than ALDO-DHF participants, and had, to a great extent, similar characteristics to patients with symptomatic heart failure with preserved ejection fraction (HFpEF) enrolled in TOPCAT-Americas (Aldosterone Antagonist Therapy for Adults With Heart Failure and Preserved Systolic Function; NCT00094302) and FINEARTS-HF (Finerenone Trial to Investigate Efficacy and Safety Superior to Placebo in Patients with Heart Failure; NCT04435626) trials. *Table 1*. Furthermore, most HOMAGE participants, although not reporting HF symptoms on anamneses, were found to complain from symptoms at exertion when performing the shuttle walk test.[12] Therefore, HOMAGE participants actually had "stage C" HF but had been classified as not having HF by their assistant clinicians.

Symptom-based heart failure diagnosis may be misleading

Large trials, enrolling mostly symptomatic HF patients, have established the clinical benefit of drug and device therapies. However, HF survival rates have not improved substantially in the last two decades. Worrisomely, real world observations reported a recent reversal of the initial decline in HF mortality in the United State of America.[13] Lack of awareness, delays in diagnosis pathway and suboptimal use of treatments are likely the main contributors to lack of progress over time.

It should be noted that patients with advanced disease (e.g., with terminal diseases such as advanced cancer, a high systemic multi-morbidity burden, or end-stage kidney disease) may benefit less from treatments in terms of morbidity and mortality reduction, because it may be "too late" to substantially modify the course of the disease.[14] As above exemplified, the symptom-based HF staging system may delay diagnosis and treatment of HF, depriving patients from long-term prognosis modification,[15] even though, patients with minimal symptoms and less advanced disease may experience greater long-term event-free survival.[16]

Given the subjectivity of HF symptoms and the impracticality of performing walking tests in all patients, easier, more inclusive, and generalisable strategies are needed to identify patients who may benefit from early initiation of disease-modifying treatments.[17]

Challenges and limitations of proactive screening for HF

Given the confluence of HF with several CKM conditions, and given that many treatments may benefit each and all of these confluent conditions, it is suggested to pro-actively screen patients at risk of HF, even if seemingly asymptomatic, and certainly if they present with breathlessness. Such a strategy is being tested in United Kingdom under the acronym of BEATHF (Breathlessness, Exhaustion, Ankle swelling, Time; https://beathf.org.uk/). Furthermore, a screening programs using brain natriuretic peptide levels and collaborative care have shown that is possible to reduce the incidence of cardiac dysfunction and HF.[18]

While natriuretic peptides (NP) are central for HF diagnosis and prognosis and should be requested whenever possible, they are not widely available, particularly in primary care settings. Moreover, NP concentrations are influenced by various conditions, medications, and comorbidities, such as the use of diuretics, CKD, atrial fibrillation, obesity, and simply, age. For example, it is well-documented that patients with impaired kidney function and those with older age tend to have elevated NP levels even in the absence of HF. Conversely, patients with obesity tend to have up to 20-30% lower levels of NPs compared to non-obese patients.[19] For example, in the SUMMIT trial (A Randomized, Double-Blind, Placebo-Controlled, Phase 3 Study Comparing the Efficacy and Safety of Tirzepatide Versus Placebo in Patients With Heart Failure With Preserved Ejection Fraction and Obesity; NCT04847557) the median NT-proBNP level was below 200 pg/mL and approximately 25% of patients had normal- near normal NT-proBNP levels; still, patients with NT-proBNP levels <200 pg/mL experienced a marked benefit from tirzepatide therapy.[6]

An electrocardiogram (ECG) is inexpensive and should be ordered in all patients with cardiovascular risk factors, beyond its utility to screen rhythm and conductance disturbances, a completely normal ECG is uncommon in HF patients. In this regard, artificial intelligence (AI)-enabled ECG reading may help in the diagnosis of HF, including in the identification of patients with reduced ejection fraction.[20]

Although in patients with low NP levels, a normal ECG, and a normal cardiovascular physical exam an echocardiogram may be exempted, most patients with suspected HF should be ordered an echocardiogram (even if the exam is not readily available), not only to assess left ventricular ejection fraction, but also to study valvular structure, specific disease patterns (e.g., amyloidosis or hypertrophic

cardiomyopathy), and right ventricle function including indirect signs of pulmonary hypertension.

With expanded availability of point of care ultrasound (POCUS) and AI algorithms capable of analysing echocardiographic images, it is expected that echocardiography becomes widely available in primary care leading to a better screening of clinically important cardiac alterations requiring a standard echocardiographic exam and specialist referral.[21]

After HF work-up it is expected that most patients with suspected HF present with preserved ejection fraction, relatively modest elevation of NPs, and mild cardiac alterations (e.g., left atrial enlargement or left ventricular hypertrophy). Therefore, most of these patients do not require hospital interventions and may be managed in the outpatient setting, with particular emphasis on primary care. For this vast majority of patients, it is our opinion that SGLT2 inhibitors should be a first-line therapy. SGLT2 inhibitors improve the prognosis across several CKM conditions, including HF, CKD, and T2D and should be provided to patients who have one or more of these conditions, even in the absence of a HF diagnosis or while waiting for diagnostic confirmation.[8]

Probabilistic HF scores are available and may help identifying patients more likely to have HF using routinely available clinical information.[22,23] These scores may be used to rule-out HF; however, among patients with intermediate- to high-risk of HF a diagnostic work-up including, at least, an ECG, blood samples with NPs, urine samples with albuminuria, and an echocardiogram should be performed and treatment with a SGLT2 inhibitor promptly initiated, even whilst waiting for the results of the requested exams.

Why should SGLT2 inhibitors be a first line therapy across the CKM spectrum?

SGLT2 inhibitors improved cardiovascular and kidney outcomes in HF, irrespective of ejection fraction, but also in high-risk populations without overt HF, including patients with CKD with and without T2D, and T2D with atherosclerotic disease.[24-26] Furthermore, SGLT2 inhibitors are safe, well-tolerated, and cost-effective.[27,28] In some parts of the world SGLT2 inhibitors are now generic drugs, and more generics

will become available in a near future, which will further reduce the cost of therapy improving its inclusiveness.

Given the robust evidence on efficacy and safety with favorable cost-effectiveness, and beyond established HF, we suggest that SGLT2 inhibitors are initiated in patients CKD or T2D even if a HF diagnosis is not confirmed or while the HF diagnosis workup in underway. After the initiation of a SGLT2 inhibitor, the patient should be reassessed, at least once, within 3 to 6 months. This reassessment will allow to better establish the effects of SGLT2 inhibitors on clinical and laboratorial parameters, while refining the diagnostic workup and considering other therapies and/or interventions, whenever indicated. For example, patients with symptomatic HF or persistent albuminuria and T2D may be suitable for therapy with an MRA, particularly finerenone, and patients with a high cardiovascular risk and obesity, T2D or symptomatic HFpEF may be candidates for GLP1ra therapy. Other concomitant conditions such as high blood pressure, dyslipidemia, atherosclerotic cardiovascular disease, tobacco use or alcohol abuse should be concomitantly addressed.

Notwithstanding, it should be highlighted that with SGLT2 inhibitor treatment, many patients may experience important reductions in albuminuria, body weight, blood pressure, NPs, and even blood lipids; thus, it may occur that SGLT2 inhibitors alone may be sufficient to control HF and associated CKM conditions in some patients.[8,29]

Given the aforementioned, we propose a pragmatic and simplified approach with early SGLT2 inhibitor treatment initiation for an early treatment of HF and associated co-morbid conditions. *Figure 1*.

After this workup, it is expected that only a minority of patients require further testing and referral to specialist care. For example, when structural heart disease is present (e.g., left ventricular systolic dysfunction, valvular disease, suspected pulmonary hypertension, hypertrophic cardiomyopathy, or amyloidosis suspicion), or when overly symptomatic for further invasive testing (e.g., coronary angiography), or regarding decisions on certain therapies (e.g., devices).

This strategy would empower general practitioners to manage early stages of HF, saving the scarce resources of HF specialists for more severe patients.

Notwithstanding, future research should focus on how whether such pragmatic and inclusive approach of early SGLT2 inhibitor initiations improves patient outcomes. In this regard, ongoing trials with SGLT2 inhibitors in patients with arterial hypertension (e.g., SGLT2 HYPE: SGLT2 inhibition for cardiovascular endpoint reduction in hypertension; NCT0680416) will further elucidate whether our proposed strategy should be applied to a broad population with cardiovascular risk, even in the absence of a HF diagnosis, CKD, or T2D.

Conclusions

Heart failure is often characterized by a triad of signs and symptoms, elevated natriuretic peptides, and alterations of cardiac structure and function. However, HF signs and symptoms are often difficult to identify and are prone to confounding by other conditions and comorbidities, and natriuretic peptides may be influenced by many factors, including a substantial reduction of its levels in the presence of obesity. Thus, a large proportion of ambulatory HF patients may remain undiagnosed and, consequently, undertreated. We propose an early pragmatic and inclusive HF diagnostic and treatment approach based on related CKM comorbidities and early SGLT2 inhibitor initiation. Future research should focus on how whether such pragmatic and inclusive approach improves patient outcomes.

References

1. McDonagh TA, Metra M, Adamo M, Gardner RS, Baumbach A, Böhm M, Burri H, Butler J, Čelutkienė J, Chioncel O, et al. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. *Eur Heart J*. 2021;42:3599-3726. doi: 10.1093/eurheartj/ehab368
2. Heidenreich PA, Bozkurt B, Aguilar D, Allen LA, Byun JJ, Colvin MM, Deswal A, Drazner MH, Dunlay SM, Evers LR, et al. 2022 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. doi: 10.1016/j.jacc.2021.12.011
3. Bozkurt B, Coats AJ, Tsutsui H, Abdelhamid M, Adamopoulos S, Albert N, Anker SD, Atherton J, Böhm M, Butler J, 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. *J Card Fail*. 2021. doi: 10.1016/j.cardfail.2021.01.022
4. Hunt SA, Abraham WT, Chin MH, Feldman AM, Francis GS, Ganiats TG, Jessup M, Konstam MA, Mancini DM, Michl K, et al. ACC/AHA 2005 Guideline Update for the Diagnosis and Management of Chronic Heart Failure in the Adult: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Update the 2001 Guidelines for the Evaluation and Management of Heart Failure): developed in collaboration with the American College of Chest Physicians and the International Society for Heart and Lung Transplantation: endorsed by the Heart Rhythm Society. *Circulation*. 2005;112:e154-235. doi: 10.1161/circulationaha.105.167586
5. Halliday BP, Wassall R, Lota AS, Khalique Z, Gregson J, Newsome S, Jackson R, Rahneva T, Wage R, Smith G, et al. Withdrawal of pharmacological treatment for heart failure in patients with recovered dilated cardiomyopathy (TRED-HF): an open-label, pilot, randomised trial. *Lancet*. 2019;393:61-73. doi: 10.1016/s0140-6736(18)32484-x
6. Packer M, Zile MR, Kramer CM, Baum SJ, Litwin SE, Menon V, Ge J, Weerakkody GJ, Ou Y, Bunck MC, et al. Tirzepatide for Heart Failure with Preserved Ejection Fraction and Obesity. *N Engl J Med*. 2024. doi: 10.1056/NEJMoa2410027
7. Ferreira JP, Zannad F, Butler J, Filippatos G, Ritter I, Schüler E, Kraus BJ, Pocock SJ, Anker SD, Packer M. Empagliflozin and serum potassium in heart failure: an analysis from EMPEROR-Pooled. *Eur Heart J*. 2022. doi: 10.1093/eurheartj/ehac306
8. Ferreira JP, Zannad F. We Need Simpler and More Integrated Guidelines in Cardio-Kidney-Metabolic Diseases. *JACC Heart Fail*. 2025;13:371-374. doi: 10.1016/j.jchf.2024.10.025
9. Ferreira JP, Packer M, Butler J, Zannad F. Reconsidering the ejection fraction centric view of pharmacologic treatment for heart failure. *Eur J Heart Fail*. 2022. doi: 10.1002/ejhf.2457
10. Yusuf S, Pitt B, Davis CE, Hood WB, Jr., Cohn JN. Effect of enalapril on mortality and the development of heart failure in asymptomatic patients with

reduced left ventricular ejection fractions. *N Engl J Med*. 1992;327:685-691. doi: 10.1056/nejm199209033271003
11. Cleland JGF, Ferreira JP, Mariottoni B, Pellicori P, Cuthbert J, Verdonschot JAJ, Petutschnigg J, Ahmed FZ, Cosmi F, Brunner La Rocca HP, et al. The effect of spironolactone on cardiovascular function and markers of fibrosis in people at increased risk of developing heart failure: the heart 'OMics' in AGEing (HOMAGE) randomized clinical trial. *Eur Heart J*. 2020. doi: 10.1093/eurheartj/ehaa758
12. Wei FF, Mariottoni B, An DW, Pellicori P, Yu YL, Verdonschot JAJ, Liu C, Ahmed FZ, Petutschnigg J, Rossignol P, et al. Heart rate reactivity, recovery, and endurance of the incremental shuttle walk test in patients prone to heart failure. *ESC Heart Fail*. 2024;11:4116-4126. doi: 10.1002/ehf2.15000
13. Sayed A, Abramov D, Fonarow GC, Mamas MA, Kobo O, Butler J, Fudim M. Reversals in the Decline of Heart Failure Mortality in the US, 1999 to 2021. *JAMA Cardiol*. 2024;9:585-589. doi: 10.1001/jamacardio.2024.0615
14. Ferreira JP, Pitt B, McMurray JJV, Pocock SJ, Solomon SD, Pfeffer MA, Zannad F, Rossignol P. Steroidal MRA Across the Spectrum of Renal Function: A Pooled Analysis of RCTs. *JACC Heart Fail*. 2022;10:842-850. doi: 10.1016/j.jchf.2022.06.010
15. Ferreira JP, Taveira-Gomes T, Canelas-Pais M, Phan P, Bernardo F, Andersson Sundell K, Almeida M, Martinho H, Gavina C. Missed opportunities in the diagnosis of heart failure: a real-world assessment. *ESC Heart Fail*. 2023;10:3438-3445. doi: 10.1002/ehf2.14531
16. Ferreira JP, Docherty KF, Stienen S, Jhund PS, Claggett BL, Solomon SD, Petrie MC, Gregson J, Pocock SJ, Zannad F, et al. Estimating the Lifetime Benefits of Treatments for Heart Failure. *JACC Heart Fail*. 2020. doi: 10.1016/j.jchf.2020.08.004
17. Taylor CJ, Hartshorne-Evans N, Satchithananda D, Hobbs FR. FASTer diagnosis: Time to BEAT heart failure. *BJGP Open*. 2021;5. doi: 10.3399/bjgpo.2021.0006
18. Ledwidge M, Gallagher J, Conlon C, Tallon E, O'Connell E, Dawkins I, Watson C, O'Hanlon R, Bermingham M, Patle A, et al. Natriuretic peptide-based screening and collaborative care for heart failure: the STOP-HF randomized trial. *Jama*. 2013;310:66-74. doi: 10.1001/jama.2013.7588
19. Singh S, Pandey A, Neeland IJ. Diagnostic and prognostic considerations for use of natriuretic peptides in obese patients with heart failure. *Prog Cardiovasc Dis*. 2020;63:649-655. doi: 10.1016/j.pcad.2020.09.006
20. Attia ZI, Kapa S, Lopez-Jimenez F, McKie PM, Ladewig DJ, Satam G, Pellikka PA, Enriquez-Sarano M, Noseworthy PA, Munger TM, et al. Screening for cardiac contractile dysfunction using an artificial intelligence-enabled electrocardiogram. *Nat Med*. 2019;25:70-74. doi: 10.1038/s41591-018-0240-2
21. Dos Santos J, Nobre JP, Ferreira JP, MI MM, Henriques M, Cardim N, Villanueva T, Gonçalves A. PRIMARY-HF: Heart Failure Screening in Primary Care using Point-of-Care. *Acta Med Port*. 2025. doi: 10.20344/amp.22463
22. Reddy YNV, Carter RE, Sundaram V, Kaye DM, Handoko ML, Tedford RJ, Andersen MJ, Sharma K, Obokata M, Verbrugge FH, et al. An evidence-based screening tool for heart failure with preserved ejection fraction: the HFpEF-ABA score. *Nat Med*. 2024;30:2258-2264. doi: 10.1038/s41591-024-03140-1

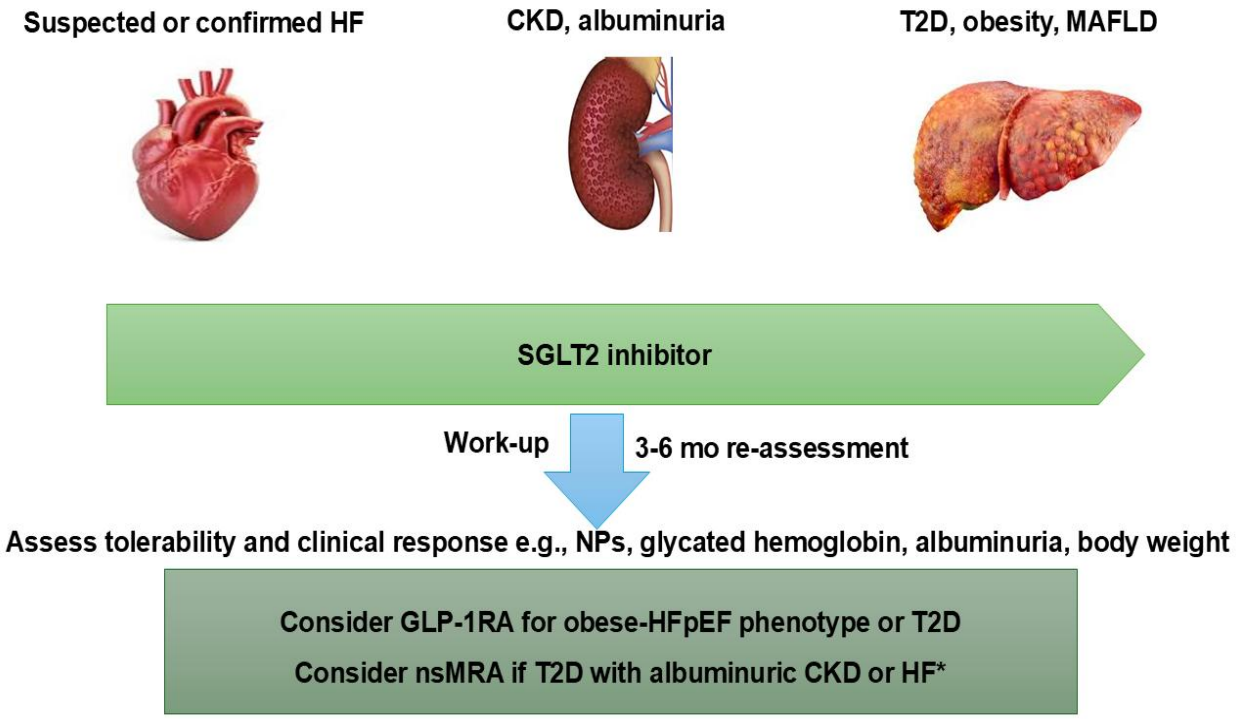
23. Khan SS, Coresh J, Pencina MJ, Ndumele CE, Rangaswami J, Chow SL, Palaniappan LP, Sperling LS, Virani SS, Ho JE, et al. Novel Prediction Equations for Absolute Risk Assessment of Total Cardiovascular Disease Incorporating Cardiovascular-Kidney-Metabolic Health: A Scientific Statement From the American Heart Association. *Circulation*. 2023;148:1982-2004. doi: 10.1161/cir.0000000000001191
24. McGuire DK, Shih WJ, Cosentino F, Charbonnel B, Cherney DZI, Dagogo-Jack S, Pratley R, Greenberg M, Wang S, Huyck S, et al. Association of SGLT2 Inhibitors With Cardiovascular and Kidney Outcomes in Patients With Type 2 Diabetes: A Meta-analysis. *JAMA Cardiol*. 2021;6:148-158. doi: 10.1001/jamacardio.2020.4511
25. Zannad F, Ferreira JP, Pocock SJ, Anker SD, Butler J, Filippatos G, Brueckmann M, Ofstad AP, Pfarr E, Jamal W, et al. SGLT2 inhibitors in patients with heart failure with reduced ejection fraction: a meta-analysis of the EMPEROR-Reduced and DAPA-HF trials. *Lancet*. 2020. doi: 10.1016/s0140-6736(20)31824-9
26. Vaduganathan M, Docherty KF, Claggett BL, Jhund PS, de Boer RA, Hernandez AF, Inzucchi SE, Kosiborod MN, Lam CSP, Martinez F, et al. SGLT-2 inhibitors in patients with heart failure: a comprehensive meta-analysis of five randomised controlled trials. *Lancet*. 2022;400:757-767. doi: 10.1016/s0140-6736(22)01429-5
27. Scheen AJ. An update on the safety of SGLT2 inhibitors. *Expert Opin Drug Saf*. 2019;18:295-311. doi: 10.1080/14740338.2019.1602116
28. McEwan P, Darlington O, Miller R, McMurray JJV, Wheeler DC, Heerspink HJL, Briggs A, Bergenheim K, Garcia Sanchez JJ. Cost-Effectiveness of Dapagliflozin as a Treatment for Chronic Kidney Disease: A Health-Economic Analysis of DAPA-CKD. *Clin J Am Soc Nephrol*. 2022;17:1730-1741. doi: 10.2215/cjn.03790322
29. Ferreira JP, Sharma A, Butler J, Packer M, Zannad F, Vasques-Nóvoa F, Leite-Moreira A, Neves JS. Glucagon-like peptide-1 receptor agonists across the spectrum of heart failure. *J Clin Endocrinol Metab*. 2023. doi: 10.1210/clinem/dgad398

Table 1. Comparison of patient's characteristics between stage B pre-HF and stage C HF

Characteristics	**HOMAGE**	**ALDO-DHF**	**TOPCAT**	**FINEARTS-HF**
Population	Stage B, pre-HF	Stage C HFpEF	Stage C HFpEF	Stage C HFpEF
Patients	527	422	1767	6001
Age, years	73 (69-79)	67 (±8)	72 (64-79)	72 (±10)
Men (%)	74	48	50	46
CAD/MI (%)	72	40	20*	26
Hypertension (%)	78	92	91	89
Diabetes *mellitus* (%)	40	17	45	41
Atrial fibrillation (%)	Excluded	5	42	38
SBP, mmHg	140 (128-154)	135 (±18)	129 (118-138)	129 (±15)
BMI, Kg/m^2	28 (25-31)	29 (±4)	33 (28-38)	30 (±6)
Diuretic (%)	LD Excluded	54	89	87
eGFR, $ml/min/1.73m^2$	72 (62-85)	79 (±19)	61 (49-77)	62 (±20)
NT-proBNP, pg/mL	214 (137-356)	158 (83-299)	900 (557-1920)**	1041 (450-1950)
LVEF, %	63 (58-67)	67 (8)	58 (53-64)	53 (±8)

Legend: CAD/MI, coronary artery disease or myocardial infarction if *; SBP, systolic blood pressure; eGFR, estimated glomerular filtration rate; LVEF, left ventricular ejection fraction. Only patients from "the Americas" are described for TOPCAT. **Present for 257 patients who required a NT-proBNP level >360 pg/mL to enter the trial.

Figure 1. Simplified work-up and treatment approach for heart failure and associated cardio-kidney-metabolic conditions



Legend: HF, heart failure; MAFLD, metabolically associated fatty liver disease; CKD, chronic kidney disease; NP, natriuretic peptides. *Spironolactone or eplerenone can be used for the treatment of heart failure.