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REVIEW ARTICLE

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A review of current key guidelines for managing high-risk patients with diabetes and heart failure and future prospects

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Abstract

We reviewed recent guidelines on the management of heart failure (HF) in patients with diabetes. Major recommendations in European and US society guidelines were scrutinized. First, sodium-glucose co-transporter 2 inhibitors are now recommended treatments for all patients with symptomatic HF (stage C and D; New York Heart Association class II-IV), irrespective of the presence of type 2 diabetes and left ventricular ejection fraction (LVEF). Second, patients with HF and reduced EF (LVEF ≤40%) should have foundational therapies from four drug classes (sodium-glucose co-transporter 2 inhibitor, angiotensin-receptor neprilysin inhibitor, beta-blocker and mineralocorticoid receptor antagonist). Third, patients with HF with mildly reduced (41%-49%) and preserved (≥50%) LVEF may also benefit from angiotensin-receptor neprilysin inhibitor, beta-blocker and mineralocorticoid receptor antagonist therapy, although evidence for these is less robust. Fourth, selected patients should be considered for other therapies such as diuretics (if congestion), anticoagulation (if atrial fibrillation) and cardiac device therapy. Fifth, glucose-lowering therapies such as thiazolidinediones and certain dipeptidyl peptidase-4 inhibitors (such as saxagliptin and alogliptin) should be avoided in patients with HF. Sixth, guidelines recommend enrolment of patients with HF into exercise rehabilitation and multidisciplinary HF management programmes. Particular attention should be paid to important comorbidities such as obesity, alongside pharmacological therapies. As diabetes and obesity are major risk factors for HF, earlier consideration of, and diagnosis of HF, followed by guideline-directed medical therapy can meaningfully improve patients' lives. Diabetes doctors would do well to understand the basics of such guidelines to help improve all aspects of HF diagnosis and care.

KEYWORDS
antidiabetic drug, diabetes complications, GLP-1 analogue, heart failure, SGLT2 inhibitor, type 2 diabetes

1 | BACKGROUND

Heart failure (HF) is now centre-stage in diabetes in part as HF rates have decreased far less in diabetes as compared with myocardial infarction or stroke rates.[1] Thus, diabetes specialists should be well-versed with fundamental principles in assessing their patients with suspected HF. HF should be suspected in anyone who has exertional breathlessness and/or signs of fluid retention, particularly in individuals with diabetes at higher risk of HF. Crucially, the early recognition of HF in patients with diabetes offers an opportunity to intervene and thus, substantially (and rapidly) reduce the risk of death and hospitalization.

The assessment of HF is covered earlier in this review series. In brief, B-type natriuretic peptide and N-terminal-pro-B-type natriuretic peptide are useful to support a diagnosis or exclusion of HF, and for risk stratification. Transthoracic echocardiography is the key investigation to evaluate cardiac structure and function. A 12-lead electrocardiograph helps optimize management, that is, determines eligibility for ivabradine (if sinus rhythm), digoxin and anticoagulation (if atrial fibrillation) and cardiac resynchronization therapy (if left bundle branch block for QRS duration). A chest X-ray is recommended to assess for cardiomegaly, pulmonary congestion and interstitial/alveolar oedema, and investigate for alternative causes of the patient's symptoms.

Diabetologists would also do well to be aware of the key recommended drugs to treat HF to reduce the risk of complications and improve quality of life (QoL), as such understanding may aid better collaboration between diabetes and HF specialists. Such therapies as well as additional treatments for selected patients are covered in this paper with complete alignment to recent major guidelines. We have carefully examined the following: European Society of Cardiology (ESC) (September 2021 HF guidelines), American Heart Association (AHA) (March 2022 type 2 diabetes scientific statement), AHA/American College of Cardiology (ACC)/Heart Failure Society of America (HFSA) (May 2022 HF guidelines), American Diabetes Association (ADA) (July 2022 HF consensus report) and ADA/European Association for the Study of Diabetes (EASD) (September 2022 type 2 diabetes consensus report).[2-6]

The article focuses on patients with symptomatic (stage C and D) HF, rather than asymptomatic (stage A and B) HF; the latter covered in other articles in this review series. First, we discuss sodium-glucose co-transporter 2 inhibitors (SGLT2is) as foundational therapy in HF. Second, we discuss the most important drugs to initiate in HF with reduced ejection fraction (HFrEF) (including the foundational four drug classes) (Figure 1). Third, we discuss treatments for patients with HF with mildly reduced EF (HFmrEF), HF with preserved EF (HFpEF) and HF with improved EF. Fourth, we discuss drugs or interventions for selected patients beyond the foundational drugs (Figure 2). Fifth, we discuss treatments for glycaemic control for patients with diabetes and HF, including which drugs to avoid. Sixth, we discuss other important principles in caring for these individuals.

The treatment of HF and use of guideline-directed medical therapy (GDMT) is broadly similar in individuals with and without diabetes, including the use of renin-angiotensin system inhibitors, beta-blockers, mineralocorticoid receptor antagonists (MRAs) and SGLT2is.[7,8] Guidelines recommend all patients with HF are enrolled in a multidisciplinary HF management programme. Patients with HF should be referred to a cardiologist particularly if they have refractory or unstable symptoms or signs of HF, coronary artery disease and arrhythmias, or are being considered for specialist therapies including valvular intervention, cardiac devices (i.e. implantable cardioverter defibrillator or cardiac resynchronization therapy) or advanced HF therapies (i.e. mechanical circulatory support or cardiac transplantation).

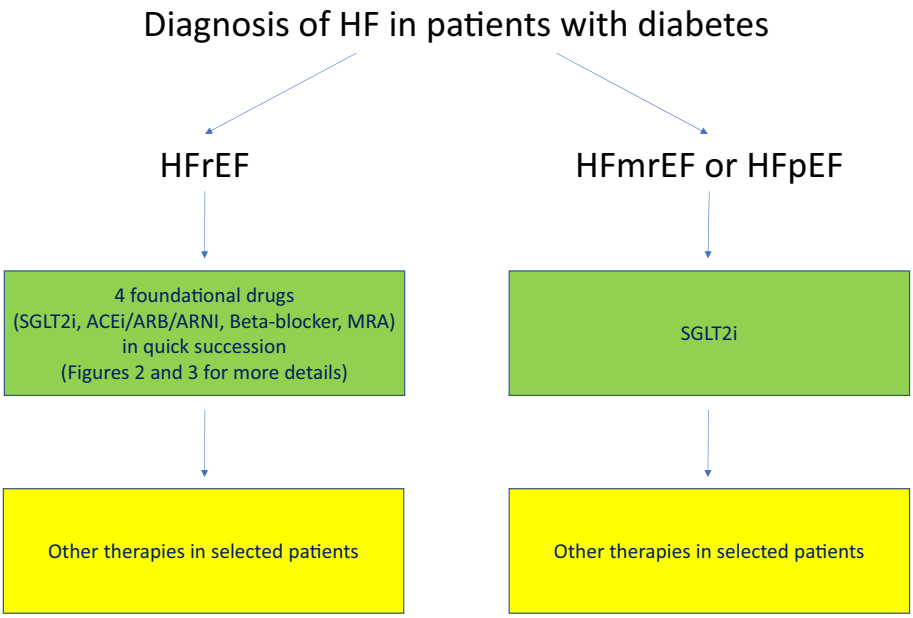

FIGURE 1 Management of patients with type 2 diabetes and heart failure. ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor neprilysin inhibitor; HF, heart failure; HFmrEF, heart failure with mildly reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; MRA, mineralocorticoid receptor antagonist; SGLT2i, sodium-glucose co-transporter 2 inhibitor.

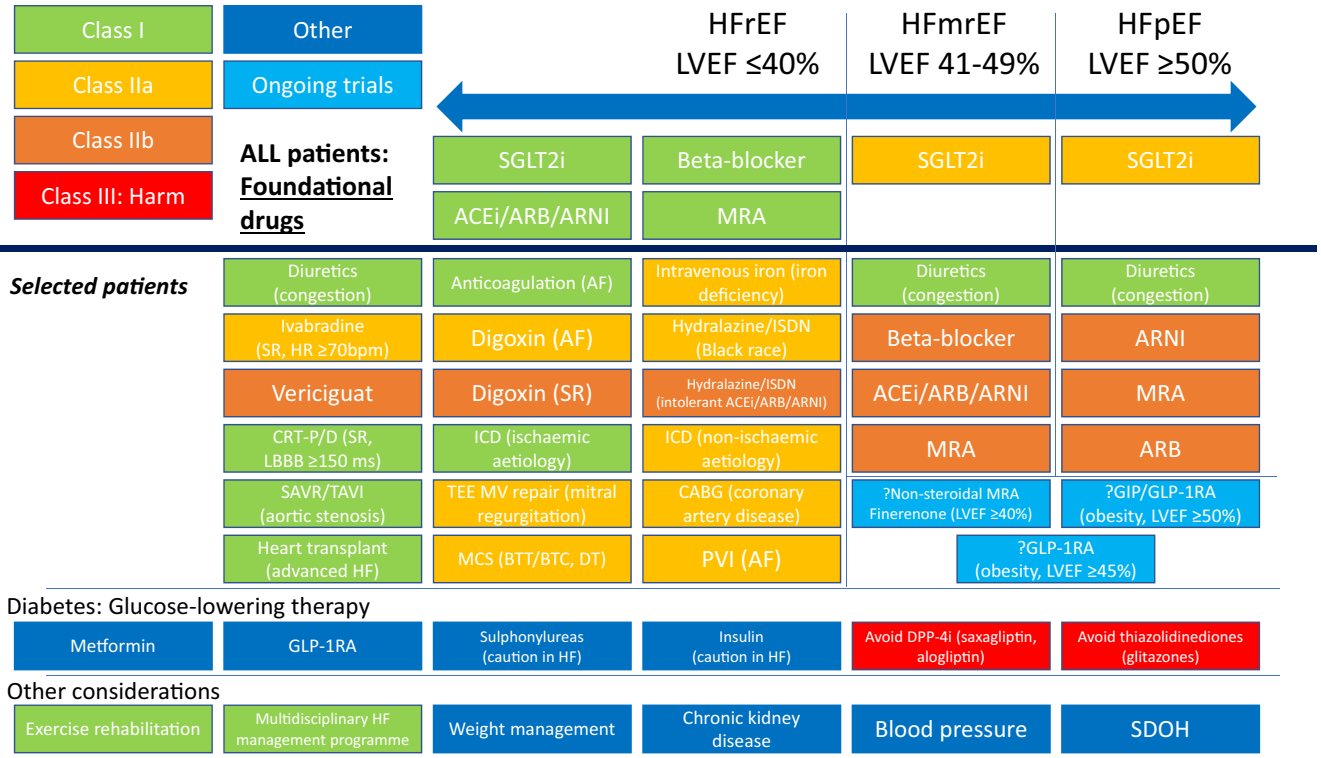

FIGURE 2 Management of patients with type 2 diabetes and heart failure. Level of recommendations from the 2021 ESC HF guidelines and 2022 ACC/AHA/HFSA HF guidelines. ACEi, angiotensin-converting enzyme inhibitor; AF, atrial fibrillation; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor neprilysin inhibitor; BTC, bridge to candidacy; BTT, bridge to transplantation; CABG, coronary artery bypass graft; CRT-P/D, cardiac resynchronization therapy-pacemaker/defibrillator; DPP-4i, dipeptidyl peptidase-4 inhibitors; DT, destination therapy; GIP, gastric inhibitory polypeptide; GLP-1RA, glucagon-like peptide-1 receptor agonist; HF, heart failure; HFmrEF, heart failure with mildly reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; HR, heart rate; ICD, implantable cardioverter-defibrillator; ISDN, isosorbide dinitrate; LBBB, left bundle branch block; LVEF, left ventricular ejection fraction; MCS, mechanical circulatory support; MRA, mineralocorticoid receptor antagonist; MV; mitral valve; PVI, pulmonary vein isolation; SAVR, surgical aortic valve replacement; SDOH, social determinants of health; SGLT2i, sodium-glucose co-transporter 2 inhibitor; SR, sinus rhythm; TAVI, transcatheter aortic valve implantation; TEE, transcatheter edge to edge.

2 | SODIUM-GLUCOSE CO-TRANSPORTER 2 INHIBITORS AS FOUNDATIONAL THERAPY IN HEART FAILURE WITH HIGHLY CONSISTENT ADVICE IN KEY GUIDELINES

SGLT2is should be used in people with HF [irrespective of left ventricular ejection fraction (LVEF)] (Figure 1), because they reduce cardiovascular (CV) death and HF hospitalization, as shown in CV outcome trials of dapagliflozin (DAPA-HF, DELIVER), empagliflozin (EMPEROR-Reduced, EMPEROR-Preserved) and sotagliflozin (SOLOIST-WHF).[9-13] SOLOIST-WHF found that sotagliflozin, a combined SGLT2/1 inhibitor, reduced CV and HF readmission in patients with type 2 diabetes and recent worsening HF, with consistent benefits seen in HFrEF and HFpEF.[13] However, sotagliflozin is not yet available for clinical use.

Several notable findings from these SGLT2i HF trials are worth highlighting. First, most of the benefits seen with SGLT2i on the composite endpoint of HF hospitalization and CV death, was because of reduction in the risk of HF hospitalization, rather than CV death. Second, the benefits seen occurred very early, that is, as soon as 28 days.[14-17] This underscores the importance of early initiation of SGLT2is and avoiding 'therapeutic inertia'. Third, the benefits were seen across all important subgroups, independent of type 2 diabetes status.[18-21] Fourth, improvements in kidney outcomes were seen, and benefits were seen across the spectrum of kidney function and irrespective of albuminuria levels at baseline.[11,12,22-25] These are particularly important findings in patients with diabetes at risk of, or with kidney disease. Fifth, improvements in health status and QoL were seen.[26-29] Finally, the rates of diabetic ketoacidosis (DKA) were extremely low, providing reassurance on the safety of SGLT2i use in patients with type 2 diabetes and HF.

The latest ADA/EASD consensus report (September 2022) recommends that all individuals with HF (HFrEF or HFpEF) should receive an agent from the SGLT2i class with proven benefit for HF.[6] The goal of organ protection with SGLT2i should be independent of background glucose-lowering therapies, current haemoglobin A1c (HbA1c) level or target HbA1c level.[6]

In patients with HFrEF, SGLT2is have a Class I recommendation in 2021 ESC HF guidelines and 2022 AHA/ACC/HFSA HF guidelines to reduce the risk of hospitalization for HF and CV death (Table 1).[2,4]

In patients with HFmrEF and HFpEF, SGLT2is have been granted a Class IIa recommendation in the 2022 AHA/ACC/HFSA HF

TABLE 1 Main SGLT2i guideline recommendations.

Guideline	Class	Recommendation
2021 ESC HF	I	SGLT2is (canagliflozin, dapagliflozin, empagliflozin, ertugliflozin, sotagliflozin) are recommended in patients with type 2 diabetes at risk of CV events to reduce hospitalizations for HF, major CV events, end-stage renal dysfunction, and CV death.
	I	SGLT2is (canagliflozin, dapagliflozin, empagliflozin, ertugliflozin, sotagliflozin) are recommended in patients with diabetes at high risk of CV disease or with CV disease in order to prevent HF hospitalizations.
	I	SGLT2is (dapagliflozin, empagliflozin, sotagliflozin) are recommended in patients with type 2 diabetes and HFrEF to reduce hospitalizations for HF and CV death.
	I	Dapagliflozin or empagliflozin are recommended for patients with HFrEF to reduce the risk of HF hospitalization and death.
2022 AHA/ ACC/HFSA HF	I	In patients with type 2 diabetes and either established CV disease or at high CV risk, SGLT2i should be used to prevent hospitalizations for HF.
	I	In patients with HF and type 2 diabetes, the use of SGLT2i is recommended for the management of hyperglycaemia and to reduce HF-related morbidity and mortality.
	I	In patients with symptomatic chronic HFrEF, SGLT2i are recommended to reduce hospitalization for HF and CV mortality, irrespective of the presence of type 2 diabetes.
	IIa	In patients with HFmrEF, SGLT2i can be beneficial in decreasing HF hospitalizations and CV mortality.
	IIa	In patients with HFpEF, SGLT2i can be beneficial in decreasing HF hospitalizations and CV mortality.

Abbreviations: CV, cardiovascular; HF, heart failure; HFmrEF, HF with mildly reduced ejection fraction; HFpEF, HF with preserved ejection fraction; HFrEF, HF with reduced ejection fraction; SGLT2i, sodium-glucose co-transporter 2 inhibitor.

guidelines.[4] Of note, these recommendations were published in May 2022 after the EMPEROR-Preserved trial results were published (October 2021), but before the DELIVER trial results were published (August 2022), so they will probably become Class I recommendations in the near future.

Clinicians should be aware of the risk of euglycaemic DKA in patients on SGLT2i treatment. The risk of DKA can be mitigated with guidance and education on DKA symptoms that should prompt medical attention and temporary discontinuation of SGLT2is in clinical situations that predispose to ketoacidosis such as acute illness, perioperatively and during prolonged fasting.[30-34] Ketosis and ketoacidosis are major risks in patients with type 1 diabetes.

In theory, SGLT2is generate excess ketones, which might augment delivery of efficient fuels for the heart and kidneys.[35] However, this mechanism is speculated as a reason for the effectiveness of SGLT2is in individuals with HF.

3 | FOUNDATIONAL THERAPY WITH FOUR DRUG CLASSES IN HEART FAILURE WITH REDUCED EJECTION FRACTION

The main therapeutic goals in HF are to reduce mortality, prevent HF hospitalization and improve QoL. Pharmacotherapy should be implemented alongside lifestyle measures, and before considering device therapy.

Patients with HFrEF benefit from GDMT that includes foundational therapy with four drug classes: (1) SGLT2is, (2) sacubitril/valsartan, (3) beta-blockers, and (4) MRAs (Figures 1-3). These agents exhibit their effects in part via modulation of the renin-angiotensin-aldosterone and sympathetic nervous systems though mechanisms of benefit for SGLT2i appear to be via haemodynamic or other cellular effects. Large-scale trials showed the efficacy of these agents, including and particularly when combined, to improve survival, reduce the risk of HF hospitalizations, reduce symptoms and promote beneficial reverse cardiac remodelling.

3.1 | Sequencing and titration

The sequencing of the four foundational treatments in HFrEF has been discussed in recent seminal articles.[36] Conventionally, these drugs are prescribed in the order in which they were tested in clinical trials [i.e. (1) angiotensin-converting enzyme inhibitor (ACEi)/angiotensin receptor blocker (ARB); (2) beta-blocker; (3) MRA; (4) neprilysin inhibitor; and then (5) SGLT2i], with each drug titrated to target doses before initiating the next drug class. However, this approach may take ≥6 months to prescribe optimal doses of all four foundational treatments, which represents an unacceptable delay, resulting in unnecessary hospitalizations and deaths.

A proposed new sequencing (Figure 3) suggests step 1 as the simultaneous initiation of a beta-blocker and an SGLT2i. Step 2 is the addition of sacubitril/valsartan, within 1-2 weeks of step 1. Finally, step 3 is the addition of an MRA, within 1-2 weeks of step 2, thus achieving all three steps within 4 weeks, with uptitration to target doses thereafter. Of note, the SGLT2i starting dose is identical to the target dose (dapagliflozin 10 mg daily and empagliflozin 10 mg daily were the doses used in the HF outcome trials). This sequencing is not guideline recommended per se, but it is one that many cardiologists are following given the evidence base discussed herein. For the many patients who will already be on two or three foundational therapies, their treatment regimen should be continually optimized according to latest guidelines.

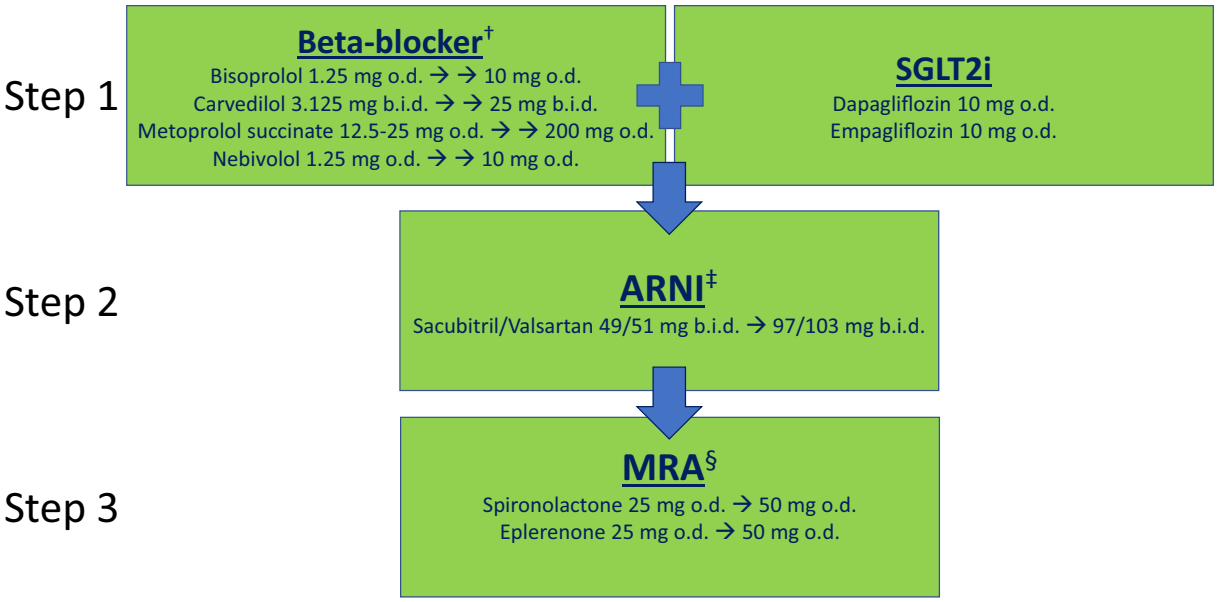

FIGURE 3 Suggested sequencing and uptitration strategies for foundational therapy in ambulatory patients with heart failure with reduced ejection fraction. Adapted from McMurray JJV, Packer M. *Circulation*. 2021;143:875-877. This sequencing is not guideline recommended per se, but it is one that many cardiologists are following given the evidence base discussed herein. ARNI, angiotensin receptor neprilysin inhibitor; b.i.d., bis in die (twice daily); MRA, mineralocorticoid receptor antagonist; o.d., omne in die (once daily); SGLT2i, sodium-glucose co-transporter 2 inhibitor. → indicates one uptitration step; → → indicates more than one uptitration step. †Carvedilol maximum dose of 50 mg b.i.d. in patients weighing >85 kg; metoprolol succinate extended release (CR/XL); nebivolol not shown to reduce cardiovascular or all-cause mortality in patients with heart failure (or shown to be non-inferior to a treatment that does). ‡Sacubitril/valsartan may have an optional lower starting dose of 24/26 mg b.i.d. for those with a history of symptomatic hypotension. §Spironolactone has an optional starting dose of 12.5 mg in patients where renal status or hyperkalaemia warrant caution.

The 2022 AHA/ACC/HFSA HF guidelines recommend the titration of GDMT dosing to achieve target doses to reduce CV mortality and HF hospitalizations (Table 2).[4] Detailed guidelines and expert consensus statements detail the rationale, selection of agents, initiation, titration and monitoring.[37,38]

Hospitalization is a pivotal moment in a patient's disease journey.[39] A HF hospitalization presents an opportunity to adopt a comprehensive approach to identify and treat causes, and importantly to optimize therapies.[40] In the STRONG-HF trial, an intensive strategy of rapid uptitration of GDMT and close follow-up after an acute HF admission reduced symptoms, improved QoL and reduced the risk of 180-day all-cause death or HF readmission compared with usual care.[41] The EMPULSE trial lends support to the safety of in-hospital initiation of the SGLT2i empagliflozin in patients hospitalized for acute HF who have been stabilized.[42]

TABLE 2 HFrEF guideline recommendations on GDMT.

Guideline	Class	Recommendation
2022 AHA/ACC/HFSA HF	I	In patients with HFrEF, titration of guideline-directed medication dosing to achieve target doses showed to be efficacious in randomized controlled trials is recommended, to reduce CV mortality and HF hospitalizations, unless not well tolerated.
	IIa	In patients with HFrEF, titration and optimization of guideline-directed medications as frequently as every 1–2 weeks depending on the patient's symptoms, vital signs, and laboratory findings can be useful to optimize management.

Abbreviations: CV, cardiovascular; GDMT, guideline-directed medical therapy; HF, heart failure; HFrEF, HF with reduced ejection fraction.

3.2 | Sodium-glucose co-transporter 2 inhibitors

The use of SGLT2is in individuals with HFrEF has been discussed in Section 2.

3.3 | Renin-angiotensin system inhibitors

Angiotensin receptor neprilysin inhibitors (ARNIs) (e.g. sacubitril/valsartan) are recommended as first-line therapy in patients with HFrEF (Class I recommendation by 2021 ESC HF guidelines and 2022 AHA/ACC/HFSA HF guidelines), and as replacement for ACEis.[38] ARBs are generally considered when patients are intolerant of either an ACEi or ARNI. Please refer to Table S1 in Data S1 for more details.

Although ACEis were the first class of drugs shown to reduce mortality and morbidity as well as improve symptoms in patients with HFrEF,[43-46] subsequently the PARADIGM-HF trial showed that the ARNI sacubitril/valsartan was superior to the ACEi enalapril in reducing hospitalization for worsening HF, CV mortality and all-cause mortality in individuals with ambulatory HFrEF (LVEF ≤40%, changed to

≤35% during the study), with the benefit of sacubitril/valsartan compared with enalapril consistent across the range of HbA1c.[47,48] Furthermore, ARNI therapy was associated with a lower incidence of diabetes requiring insulin treatment.[49]

Both ACEis and ARNIs should be avoided in individuals with a history of angioedema. Concomitant use of ACEi and neprilysin inhibition can lead to higher rates of angioedema. Therefore, when switching from an ACEi to ARNI, patients should be allowed a 36-h washout period (i.e. wait at least 36 h when switching to or from ACEi). When switching from an ARB to ARNI, no washout period is required. ARBs are alternatives in those who are intolerant of ACEi (i.e. because of cough or angioedema) or ARNI.

3.4 | Beta-blockers

Beta-blockers are recommended for patients with HFrEF (Class I recommendation by 2021 ESC HF guidelines and 2022 AHA/ACC/HFSA HF guidelines) (Data S1, Table S2). Beta-blockers reduce mortality and morbidity in patients with HFrEF,[50-56] improve symptoms,[57] and improve LVEF.[58] Metoprolol succinate, carvedilol and bisoprolol have proven benefit in patients with HFrEF and type 2 diabetes.[59]

Beta-blockers should be initiated in clinically stable, euvolaemic, patients at a low dose, which is then gradually uptitrated to the maximally tolerated dose. In patients with acute HF, beta-blockers should be cautiously started once the patient is haemodynamically stable, after intravenous therapy has been discontinued for several days and the patient is clinically euvolaemic, defined as the absence of rales and ascites and the presence of no more than minimal peripheral oedema.[36]

3.5 | Mineralocorticoid receptor antagonist

MRAs are recommended for patients with HFrEF (Class I recommendation by 2021 ESC HF guidelines and 2022 AHA/ACC/HFSA HF guidelines) (Data S1, Table S3). MRAs (spironolactone and eplerenone) reduce mortality, the risk of HF hospitalization, and improve symptoms in patients with HFrEF.[60,61]

MRAs should be used with caution in patients with serum potassium >5.0 mmol/L and renal impairment.[62,63] Eplerenone is more specific for aldosterone blockade and is less likely to cause gynaecomastia compared with spironolactone.

4 | HEART FAILURE WITH LEFT VENTRICULAR EJECTION FRACTION >40%: HEART FAILURE WITH MILDLY REDUCED EJECTION FRACTION, WITH PRESERVED EJECTION FRACTION AND WITH IMPROVED EJECTION FRACTION

The guideline summaries for this group are given in Table S4 in Data S1. For patients with HFmrEF (LVEF 41%-49%), the 2022 AHA/ACC/HFSA HF guidelines have granted Class IIb recommendations for ACEi/ARB/ARNI, beta-blockers and MRAs (Figure 2). For patients with HFpEF (LVEF ≥50%), the 2022 AHA/ACC/HFSA 2022 guidelines have given Class IIb recommendations for ARNI and ARB (Figure 2). In patients with LVEF >40%, these drugs are commonly used to treat indications other than HF. For example, ACEis/ARBs/MRAs to treat hypertension, beta-blockers to treat angina, coronary artery disease or AF, all of which are common comorbidities in patients with HFmrEF and HFpEF.

In PARAGON-HF, sacubitril/valsartan was associated with a 13% non-significant reduction in the composite of total hospitalization for HF and CV death in HF with an LVEF ≥45%; among subgroups, the benefit was greater in women and those with LVEF ≤57%.[64] The US Food and Drug Administration (FDA) have granted sacubitril/valsartan an expanded indication for HF across most of the range of LVEF, with benefits most clearly evident in patients with LVEF below normal.[65]

In TOPCAT, spironolactone was beneficial in those with an LVEF <50% and particularly those with diabetes.[66,67] FINEARTS-HF (NCT04435626) is investigating the efficacy of the non-steroidal MRA, finerenone, in patients with HFpEF (LVEF ≥40%) (Figure 2).[68]

5 | DRUGS OR INTERVENTIONS FOR SELECTED PATIENTS: THAT IS, BEYOND FOUNDATIONAL DRUGS

5.1 | Diuretics

Loop diuretics are useful to treat fluid retention (Figure 2, Table S5 in Data S1). To avoid over- and underhydration, their use should be at the minimally effective dose with careful clinical evaluation of congestion signs. Greater use of ARNI and SGLT2i may help reduce the requirement for loop diuretic therapy.[69,70] If patients are resistant to loop diuretics, thiazide diuretics (e.g. metolazone) may provide a 'boost' effect.[5]

5.2 | Atrial fibrillation

Long-term anticoagulation has a Class I recommendation for patients with atrial fibrillation, HF and CHA2DS2-VASc score ≥2 in men or ≥3 in women.[71-76] In selected patients, digoxin may be helpful for rate control, and catheter ablation might be a helpful for rhythm control (Data S1, Table S6).

5.3 | Other therapies in heart failure with reduced ejection fraction

Ivabradine is recommended for patients with HFrEF in sinus rhythm with a resting heart rate ≥70 bpm and receiving maximally tolerated beta-blocker, to reduce the risk of hospitalization for HF (Class IIa

recommendation) (Data S1, Table S7).[77] Ivabradine is effective and safe in these patients, irrespective of diabetes status.[78]

The combination of hydralazine and isosorbide dinitrate is an alternative to ARNI/ACEi/ARB particularly in Black patients with HFrEF (Class IIa),[79] and hyperkalaemia and/or worsening kidney function with renin-angiotensin system inhibitors or symptoms despite first-line GDMT (Class IIb recommendation) (Data S1, Table S7). There are no randomized data on hydralazine and isosorbide dinitrate by diabetes status.

Vericiguat, a soluble guanylate cyclase stimulator, has a Class IIb recommendation for HF with an LVEF <45% and recent hospitalization for HF,[80] but should be added only after other GDMT has been optimized (Data S1, Table S7).

For patients with HFrEF and iron deficiency with or without anaemia, intravenous iron replacement has a Class IIa recommendation (Data S1, Table S7).[81,82]

Coronary revascularization outcomes are less robust among those with diabetes.[83] The main indications for coronary revascularization are for limiting angina and/or to reduce mortality.[84,85] The 2021 ESC HF guidelines have recommended that coronary artery bypass graft surgery should be considered as the first-choice revascularization strategy, in patients suitable for surgery, particularly if they have diabetes and for those with multivessel disease (Class IIa recommendation) (Data S1, Table S7).[86-89] The indications for coronary artery bypass graft surgery are for mortality benefit including left main trunk coronary artery disease and multi-vessel coronary artery disease with reduced left ventricular function.[83,90]

The benefits of cardiac resynchronization therapy and implantable cardioverter defibrillators in patients with HF are seen in those with and without diabetes (Data S1, Table S7).[91-93]

6 | GLYCAEMIC CONTROL AND DRUGS TO AVOID: THIAZOLIDINEDIONES AND SAXAGLIPTIN

Before CV outcome trials, glucose-lowering was the main therapeutic goal in diabetes trials because near-normal glycaemia reduced microvascular complications (nephropathy, retinopathy, neuropathy).[94,95] The risk of HF was most apparent when HbA1c >8.0% (>64 mmol/mol).[96] However, there are no data to support intensive glycaemic control to reduce the risk of HF in individuals with type 2 diabetes. Large prospective type 2 diabetes trials which reported HF as a secondary outcome showed no differences between intensive (mean HbA1c 6.4%-7.0%) and standard (mean HbA1c 7.3%-8.4%) treatment arms.[95,97,98]

Glycaemic targets should be tailored to reflect comorbidity burden and potential benefits with lowering HbA1c, life expectancy, and consider risk of harms of intensive treatment (hypoglycaemia, polypharmacy, treatment burden, costs of care).[99,100]

Glucose-lowering drugs differ in their effects in patients with HF and therefore, drugs that are safe and reduce HF-related events should be prioritized.[7,8,101]

6.1 | Metformin

Metformin was historically contraindicated in HF, but a meta-analysis of nine cohort studies of 34 000 individuals with diabetes and HF showed that metformin was associated with a 20% lower mortality risk and lower all-cause hospitalization.[97,102] A large propensity-matched observational study showed that metformin initiation was associated with a lower risk of HF hospitalization than sulphonylureas.[103] However, to date, there has been no dedicated randomized controlled outcome trials of metformin in patients with HF. Metformin should be discontinued in lactic acidosis, cardiogenic or distributive shock.[5] Metformin is felt to be safe in patients with HF, compared with insulin and sulphonylureas, based on observational studies.[102,104]

6.2 | Sulphonylureas

Sulphonylureas promote weight gain and fluid retention.[105] Observational studies show that sulphonylureas are associated with higher risk of HF events compared with metformin or other agents.[97] In a large retrospective cohort study of 24 685 metformin and 24 805 sulphonylurea users with reduced kidney function, there were fewer HF hospitalizations per 1000 person-years for metformin compared with sulphonylureas.[106] Sulphonylureas are associated with a higher risk of HF events in some analyses.[103,107] Therefore, sulphonylureas are not preferred in patients with HF but if required, clinicians should monitor for worsening HF (Figure 2).[7,101]

6.3 | Dipeptidyl peptidase-4 inhibitors

The dipeptidyl peptidase-4 (DPP-4) inhibitor saxagliptin increased HF hospitalization in patients with diabetes in SAVOR-TIMI 53.[108,109] The DPP-4 inhibitor alogliptin did not increase HF hospitalization in EXAMINE, but in a post hoc analysis, there was a relative increase in hospitalization for HF.[110,111] However, neither omarigliptin, sitagliptin nor linagliptin increased the risk of hospitalization for HF in clinical trials.[112-116] Vildagliptin increased left ventricular volumes with a numerically greater number of deaths and CV events in VIVIDD, a small trial of patients with diabetes and HF.[117] In meta-analyses, DPP-4 inhibitors have neutral effects on mortality or CV events.[118,119] Therefore, DPP-4 inhibitors are not recommended to reduce CV events in patients with diabetes and HF.[2,4] Specifically, saxagliptin and alogliptin should be avoided in patients with HF (Class III recommendation) (Table 3 and Figure 2).[109,111,120]

6.4 | Thiazolidinediones

Thiazolidinediones are contraindicated in patients with HF (Class III recommendation) (Table 4 and Figure 2). Thiazolidinediones cause

TABLE 3 Guideline recommendations on DPP-4i in patients with HF.

Guideline	Class	Recommendation
2021 ESC HF	III	The DPP-4i saxagliptin is NOT recommended in patients with HF.
2022 AHA/ACC/HFSA HF	III	In patients with type 2 diabetes and high CV risk, the DPP-4 inhibitors saxagliptin and alogliptin increase the risk of HF hospitalization and should be AVOIDED in patients with HF.

Abbreviations: CV, cardiovascular; DPP-4i, dipeptidyl peptidase-4 inhibitor; HF, heart failure.

TABLE 4 Guideline recommendations on thiazolidinediones in patients with HF.

Guideline	Class	Recommendation
2021 ESC HF	III	Thiazolidinediones (glitazones) are NOT recommended in patients with HF, as they increase the risk of HF worsening and HF hospitalization.
2022 AHA/ACC/HFSA HF	III	In patients with LVEF <50%, thiazolidinediones should NOT be used because they increase the risk of HF, including hospitalizations.
	III	In patients with HFrEF, thiazolidinediones increase the risk of worsening HF symptoms and hospitalizations.

Abbreviations: HF, heart failure; HFrEF, heart failure with reduced ejection fraction; LVEF, left ventricular ejection fraction.

sodium and water retention and increase the risk of hospitalization for HF or death, promote weight gain, lower extremity oedema and increase CV risk, particularly when combined with insulin, as shown in meta-analyses and randomized controlled trials (RCTs).[121-125] Side effects are mitigated by using lower doses and combining thiazolidinediones with other medications [e.g. SGLT2is and glucagon-like peptide-1 receptor agonists (GLP-1RAs)] that promote weight loss and sodium excretion.[126,127]

6.5 | Insulin

Insulin is needed in patients with type 1 diabetes, and in some patients with type 2 diabetes. There is concern that insulin may exacerbate fluid retention, as it is a sodium-retaining hormone, as well as cause weight gain and hypoglycaemia. In an RCT of patients with type 2 diabetes, impaired glucose tolerance and impaired fasting glucose, insulin did not increase the risk of incident HF.[128] In the DEVOTE trial, there was no difference in HF events with insulin glargine versus degludec.[129] Insulin use has been associated with poorer outcomes in patients with diabetes and HF, based on retrospective analyses of randomized trials and administrative databases, although this could simply reflect patients being sicker in general.[130,131] Nevertheless, the 2021 ESC HF guidelines recommend that if insulin is required in patients with HF, clinicians should monitor for evidence of worsening HF (Figure 2).

6.6 | Glucagon-like peptide-1 receptor agonist

While albiglutide and efpeglenatide reduced incident HF hospitalization in the HARMONY Outcomes and AMPLITUDE-O trials, respectively,[132,133] no dedicated large outcome trials have been done in patients with HF. Rather, there have only been small trials of GLP-1RA in patients with HF. In LIVE, liraglutide had no effect on LVEF, but increased heart rate and increased serious cardiac events in an RCT of 241 patients with HFrEF with and without diabetes.[134] In FIGHT, liraglutide had neutral results on the primary endpoint in 300 patients with HFrEF, with a trend towards increased risk of all-cause death or total HF hospitalizations and total arrhythmias.[135,136]

STEP-HFpEF DM (NCT04916470) and STEP-HFpEF (NCT04788511) are investigating the efficacy of the GLP-1RA, semaglutide, in patients with HFpEF (LVEF ≥45%) and obesity, with and without diabetes mellitus, respectively.[137,138] SUMMIT (NCT04847557) will inform us on the efficacy of tirzepatide, a dual gastric inhibitory polypeptide/GLP-1RA in patients with HFpEF (LVEF ≥50%) and obesity.[139] The results of these trials may further change clinical guidance in those with diabetes and HFpEF (Figure 2).

6.7 | Other considerations in diabetes management

Other considerations for diabetes management are diabetes technologies such as continuous glucose monitoring that have proven benefits in minimizing hypoglycaemia risk and optimizing glucose control in type 1 diabetes and type 2 diabetes.[5] In addition, consider diabetes self-management education and support referral to promote self-efficacy in the achievement of goals.[6]

7 | OTHER PRINCIPLES IN CARING FOR PATIENTS WITH DIABETES AND HEART FAILURE

7.1 | Multidisciplinary care, individualized personalized approach and education

All individuals should have the requisite thoughtful clinical evaluation and involvement of multidisciplinary care (Table 5).[5] Patients with stage C and D HF should be referred to a CV specialist.[5] Individual preferences, motivations and circumstances should inform choice, with shared decision-making to contextualize evidence on benefits, safety and risks.[6]

Lifestyle advice such as minimizing alcohol intake and avoiding smoking are important.[97,140] Strict fluid salt intake is imposed only when clear fluid overload or sensitivity to fluid intake is not readily

TABLE 5 Guideline recommendations on management programmes, vaccinations, and self-care support.

Guideline	Class	Recommendation
2021 ESC HF	I	It is recommended that HF patients are enrolled in a multidisciplinary HF management programme to reduce the risk of HF hospitalization and mortality.
	I	Self-management strategies are recommended to reduce the risk of HF hospitalization and mortality.
	I	Either home-based and/or clinic-based programmes improve outcomes and are recommended to reduce the risk of HF hospitalization and mortality.
	IIa	Influenza and pneumococcal vaccinations should be considered in order to prevent HF hospitalizations.
2022 AHA/ACC/HFSA HF	I	Patients with HF should receive care from multidisciplinary teams to facilitate the implementation of GDMT, address potential barriers to self-care, reduce the risk of subsequent rehospitalization for HF, and improve survival.
	I	Patients with HF should receive specific education and support to facilitate HF self-care in a multidisciplinary manner.
	IIa	In patients with HF, vaccinating against respiratory illnesses is reasonable to reduce mortality.
	IIa	In adults with HF, screening for depression, social isolation, frailty, and low health literacy as risk factors for poor self-care is reasonable to improve management.

Abbreviations: HF, heart failure; GDMT, guideline-directed medical therapy.

TABLE 6 Guideline recommendations on exercise and cardiac rehabilitation.

Guideline	Class	Recommendation
2021 ESC HF	I	Exercise is recommended for all patients who are able in order to improve exercise capacity, QoL, and reduce HF hospitalization (in those who are able to adhere to the exercise programme).
	IIa	A supervised, exercise-based, cardiac rehabilitation programme should be considered in patients with more severe disease, frailty, or with comorbidities.
2022 AHA/ACC/HFSA HF	I	For patients with HF who are able to participate, exercise training (or regular physical activity) is recommended to improve functional status, exercise performance, and QoL.
	IIa	In patients with HF, a cardiac rehabilitation program can be useful to improve functional capacity, exercise tolerance, and health-related QoL.

Abbreviations: HF, heart failure; QoL, quality of life.

controlled by diuretic therapy.[37,140] Patients should be provided trajectory education, and management strategies to limit disease progression and HF hospitalization.[5] Care should consider broader social community engagement with families, caregivers and communities across multiple settings.[141] Newer approaches include messaging tools and virtual/E-consults.[142]

A comprehensive multidisciplinary team approach should be implemented to mitigate the impact of adverse social determinants of health on achievement of goals.[5,6] These approaches include actively screening for job and food insecurity, health literacy, access to housing, access to health care and medication.[143-147] There should be equity of access to the same management framework for various groups, including women, type 1 diabetes and those with high-burdened social determinants of health.[5]

7.2 | Exercise rehabilitation

There is an association between HF and physical inactivity, including in patients with diabetes.[148] Cardiac stiffness accelerates in midlife but could be reversed by aerobic exercise.[148] The HF-ACTION trial of 2331 patients with HFrEF (32% with diabetes) over a median follow-up of 2.5 years, showed that compared with usual care, aerobic exercise. Improved peak oxygen uptake and 6-minute walk distance.[149] Exercise is recommended in patients with diabetes and HF to improve functional capacity.[149] Patients should have tailored plans and risk stratification, before initiating exercise training.[148]

In individuals with diabetes, cardiac rehabilitation improves exercise capacity.[150] In individuals with diabetes who underwent percutaneous coronary intervention, cardiac rehabilitation reduced all-cause mortality by 44% and reduced the composite outcome of mortality, myocardial infarction or revascularization by 23% over a median follow-up of 8.1 years.[151] Guidelines have given a Class I recommendation for cardiac rehabilitation for patients with HF (Table 6 and Figure 2).[152,153] Worryingly, the presence of diabetes is associated with a lower likelihood of cardiac rehabilitation utilization.[151] Home-based cardiac rehabilitation is an alternative strategy.[154]

8 | CONCLUSION

The management of HF has come a long way in the last two decades, with major advances in the last 3-4 years, nicely captured by recent guidelines as reviewed. As a result, the diagnosis of HF is no longer feared as it once was. Rather, as diabetes and obesity are major risk factors for HF, earlier consideration of, and diagnosis of HF followed by GDMT can meaningfully improve patients' lives. Diabetes doctors would do well to understand the basics of such guidelines to help improve all aspects of HF diagnosis and care.

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All supporting data are available within the article, its online supplementary files, and cited references.

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