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Management of heart failure with reduced ejection fraction in 2021:

an update for GPs

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INTRODUCTION

In February 2021, the National Institute for Health and Care Excellence (NICE) approved the use of dapagliflozin, a sodium-glucose co-transporter-2 inhibitor (SGLT2i) for patients with *or without* diabetes and with a left ventricular ejection fraction (LVEF) of <40%.[1] This article provides some practical guidance for GPs on implementing the recommendation.

WHAT DRUGS ARE CURRENTLY IN USE FOR HEART FAILURE WITH REDUCED EJECTION FRACTION TO IMPROVE PROGNOSIS?

Until recently, three groups of drugs were recommended by NICE as standard therapy to improve symptoms and prognosis in heart failure with reduced ejection fraction (HFrEF). The aspiration is for patients to receive them at the maximal tolerated doses (Table 1). The groups are: angiotensin-converting enzyme inhibitors (ACEI), angiotensin receptor blockers (ARB) or angiotensin-neprilysin inhibitors (ARNI); beta-blockers (BB); and — for patients remaining symptomatic — mineralocorticoid receptor antagonists (MRA).

In patients with persistent or worsening symptoms whose LVEF is <35%, any ACEI/ARB should be replaced with sacubitril–valsartan (Entresto®), the current sole licensed member of ARNI, as both symptoms and prognosis are improved.[2]

WHY IS DAPAGLIFLOZIN REQUIRED IN HEART FAILURE WITH REDUCED EJECTION FRACTION?

Chronic heart failure still carries a poor prognosis, worse than some cancers, with a mortality of 42% at 5 years after the diagnosis in the UK.[3] In part this reflects incomplete optimisation of existing therapies. GPs have a major role to play in spotting the need for medicines optimisation (Table 1), considering non-pharmacological interventions, and liaising with the community heart failure nurse and cardiac rehabilitation teams.

In the Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure (DAPA-HF) trial, addition of dapagliflozin reduced the composite cardiovascular endpoint (hospitalisation for heart failure, urgent outpatient diuretic, therapy, or cardiovascular death) by 26% with a Number Needed to Treat (NNT) of 21, effects being seen within days, and statistically significant within 4 weeks.[4] Benefits accrued irrespective of baseline drug or device therapies.

SGLT2is reduce renal tubular glucose and sodium reabsorption, resulting in a net decrease in blood glucose, without insulin stimulation.[5] To what extent the observed benefits of SGLT2is in HFrEF are due to a glycosuria-driven diuresis,[6] natriuresis, renoprotection, or an as yet unidentified mechanisms is unclear.[4]

As there is evidence of similar benefits in HFrEF from empagliflozin,[4] in the authors' view and pending national guidance, patients already prescribed this medication for their diabetes need not be changed to dapagliflozin.

HOW DOES STEPWISE PHARMACOTHERAPY WORK IN PRACTICE AND WHERE DOES DAPAGLIFLOZIN FIT IN?

All patients with newly diagnosed HFrEF should promptly receive adequate diuretics to achieve euvolemia. An ACEI/ARB is started as soon as baseline renal function is established. A low-dose beta-blocker is added once the patient is stabilised, or sooner if a tachycardic arrythmia such as fast atrial fibrillation demands. Drugs with prognostic benefit should be up-titrated to the maximum tolerated doses in 1–2 weekly intervals, taking careful account of heart rate (with beta-blockers), blood pressure, and renal function (Table 1). If symptoms persist, especially if LVEF is <35%, an MRA should be added, or substituted for a loop diuretic, to further reduce hospitalisations and improve prognosis.

Table 1. First- and second-line pharmacotherapy groups ('the four pillars') known to reduce mortality in HFrEF and approved by NICE[a]

Groups of pharmacotherapy for HFrEF	Starting dose (examples)	Number of titrations needed	Target dose (examples)
1. Beta-blocker	Bisoprolol 2.5 mg o.d.	3–4	Bisoprolol 10 mg o.d.
	Carvedilol 3.125 mg b.d.		Carvedilol 25–50 mg b.d.
2. ACEI or ARB or ARNI[b]	Ramipril 2.5 mg o.d.	3-4	Ramipril 10 mg o.d.
	Perindopril erbumine 2 mg o.d.		Perindopril erbumine 4–8 mg o.d.
	Lisinopril 2.5 mg o.d.		Lisinopril 35 mg o.d.
	Losartan 12.5 mg o.d.	4	Losartan 150 mg o.d.
	Valsartan 40 mg b.d.		Valsartan 160 mg b.d.
	Candesartan 4 mg o.d.		Candesartan 32 mg o.d.
	Sacubitril–valsartan 48/52 mg b.d., or 24/26 mg b.d. if BP low	1–2	97/103 mg b.d.
3. MRA	Spironolactone 25 mg o.d.	2–3	Spironolactone 50 mg o.d.
	Eplerenone 25 mg o.d.		Eplerenone 50 mg o.d.
4. SGLT2i	Dapagliflozin 10 mg o.d.	0	Dapagliflozin 10 mg o.d.

[a]Typical starting and final doses of the most commonly used drugs are listed. Titrations are typically done every 1–2 weeks. [b]ARNIs' prognostic benefits are superior to ACEI or ARB but NICE reserves it for patients with LVEF <35% and symptoms. ACEI = angiotensin-converting enzyme inhibitor. ARB = angiotensin receptor blocker. ARNI = angiotensin-neprilysin inhibitor. b.d. = twice a day. BP = blood pressure. HFrEF = heart failure with reduced ejection fraction. LVEF = left ventricular ejection fraction. MRA = mineralocorticoid receptor antagonist. NICE = National Institute for Health and Care Excellence. o.d. = once a day.

If a patient remains symptomatic on combined ACEI/ARB, beta-blockers, and MRA, and has a qualifying ejection fraction (<40% for dapagliflozin and ≤35% for ARNI, as per NICE) then these two drug classes offer additive and complimentary benefits.[1] Although NICE recommends that dapagliflozin 10 mg (once a day) is added in symptomatic patients as an add-on to optimised standard care, the relative ease of prescribing dapagliflozin with its single dose and lesser monitoring requirements may promote its introduction before ARNI.

NICE advises that, where the indication is HFrEF, initiation of dapagliflozin should be on the advice of a heart failure specialist in primary, secondary, or community care.[1] Specialist input is to ensure contraindications are recognised, primarily type 1 diabetes mellitus, or previous history of diabetic ketoacidosis, and that due consideration is given to renal function, dose adjustment of co-prescribed oral hypoglycaemics, and risk factors for diabetic ketoacidosis.

Whether before or after dapagliflozin, specialist input such as from the community heart failure team is also required for replacement of the ACEI/ARB with ARNI and subsequent up-titration because ARNI are more inclined to cause hypotension, hyperkalaemia, and to potentiate diuretics. Notably, conversion from ACEI/ARB to ARNI requires a 48-hour wash-out period. Experience suggests avoidance in patients with a baseline systolic blood pressure of <95–100 mmHg.

In some patients, hypotension, bradycardia, or hyperkalaemia make it impossible to achieve the target doses for the 'four pillars' of drug therapy (Table 1). In such cases, most specialists advocate use of all indicated drugs at lower, tolerated doses. Reducing diuretic dose (MRAs) or frequency (loop diuretics) to the minimum possible when the patient is euvolaemic may help achieve target doses for the other drugs.

WHAT ARE THE POTENTIAL CHALLENGES WITH SODIUM-GLUCOSE CO-TRANSPORTER-2 INHIBITOR USAGE IN HEART FAILURE?

While most GPs have experience of initiating beta-blockers, ACEI, or ARB, they may be less familiar with SGLT2i, even in the context of diabetes mellitus. Ironically, prescribing of dapagliflozin for HFrEF is most straightforward in patients without diabetes. An SGLT2i does not lower blood glucose if a patient is normoglycaemic. However, if a patient with type 2 diabetes mellitus is on insulin or insulin secretagogues (sulfonylureas or meglitinides) their doses may need to be reduced by 20% and 25–50% respectively to reduce the risk of hypoglycaemia. Such dose reductions should be personalised and a diabetologist's input is advisable.

Many HFrEF patients have renal impairment. Although previous advice was to avoid initiating SGLT2is in patients with eGFR <60 ml/min/m^2 and to discontinue if it fell to <45 ml/min/m^2, this reflected the diminishing glucose-lowering impact as renal tubular function declines. When prescribing dapagliflozin for HfrEF the marketing authorisation and NICE simply cautioned that there is limited experience with dapagliflozin in HFrEF when eGFR is <30 ml/min/m^2. It is now widely accepted that SGLT2is are not only safe when eGFR is >20 ml/min/m^2 but SGLT2is also reduce the rate of decline in renal function in HFrEF. An imminent licence for renoprotection is anticipated.[4,7] No dose adjustment is required for dapagliflozin in renal impairment (unlike empagliflozin).

Although there was a widespread expectation that initiation of SGLT2is in patients on diuretics might lead to over-diuresis/dehydration,[6] in chronic heart failure (as opposed to acute decompensated patients) experience suggests the majority of patients do not routinely need diuretic dose reduction. After a transient dip of

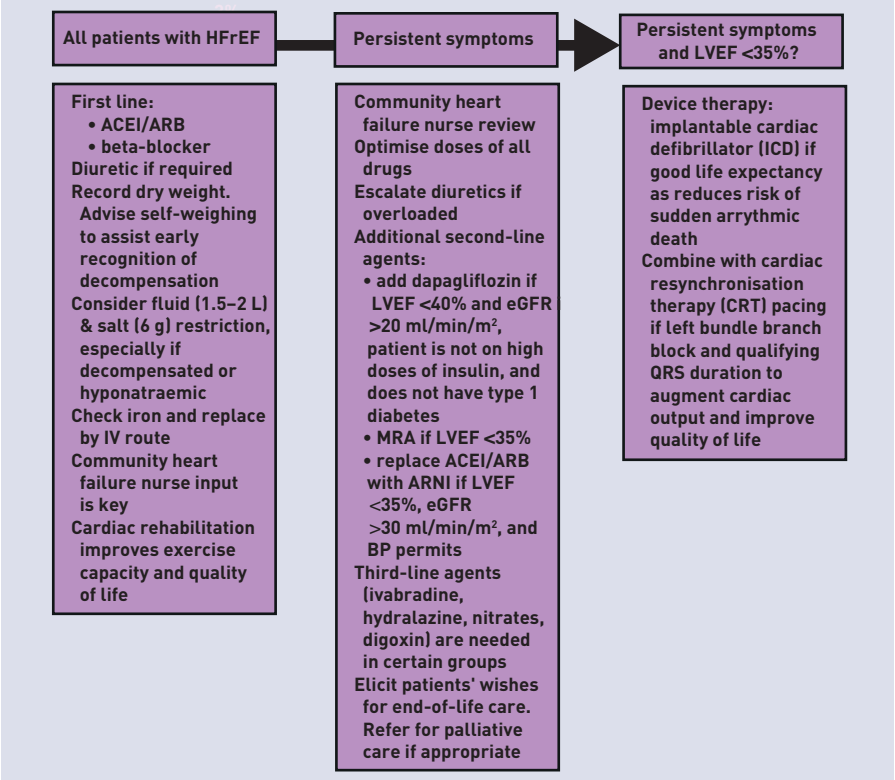

Figure 1. Comprehensive treatment for HFrEF.[a]
[a]At present NICE suggests step-wise delivery of pharmacotherapy guided by deterioration in symptoms and LVEF. ACEI = angiotensin-converting enzyme inhibitor. ARB = angiotensin receptor blocker. ARNI = angiotensin-neprilysin inhibitor. BP = blood pressure. eGFR = estimated glomerular filtration rate. HFrEF = heart failure with reduced ejection fraction. IV = intravenous. LVEF = left ventricular ejection fraction. MRA = mineralocorticoid receptor antagonist. NICE = National Institute for Health and Care Excellence.

up to 5 ml/min/m^2, dapagliflozin delays further decline in renal function. NICE recommends annual monitoring of renal function; or 2–4 times/year in patients with eGFR of 30–60 ml/min/m^2.[1]

Most concern surrounds the increased risk of ketoacidosis, potentially euglycaemic, but the risk is very low unless patients are on high-dose insulin or subject to fluid and calorie restriction during intercurrent infection or surgery. Dapagliflozin should be suspended in these contexts. Dapagliflozin's marketing authorisation warns against its initiation for treatment of heart failure in patients with type 1 diabetes mellitus. In the landmark DAPA-HF trial, the NNT of 21 compares with a Number Needed to Harm (NNH) relating to diabetic ketoacidosis of, the authors calculate, 790. Combining data from several SGLT2i heart failure trials gives an NNH that is higher still, around 4900, the authors estimate.

Genital mycotic infections (likely due to increased glucosuria) occur a little more frequently, mainly early after initiation, but respond to the usual topical and oral therapies.

Just one out of several trials has reported a low but increased risk of lower-limb amputation, in patients with diabetes mellitus and at higher prior risk (for example, peripheral vascular disease, prior amputation, recurrent infection).[8]

WHAT ARE OTHER ESSENTIAL COMPONENTS OF GOOD CARE FOR PATIENTS WITH HEART FAILURE WITH REDUCED EJECTION FRACTION?

Adding dapagliflozin to pharmacotherapy in HFrEF is only one element of a package of good care. GPs should be aware of the benefits of all four pillars of pharmacotherapy, implantable cardiac devices and cardiac rehabilitation, working closely with community heart failure nurses, and considering palliative care when appropriate.

Provenance

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Competing interests

The authors have declared no competing interests.

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