Diagnosis and Management of Heart Failure with Reduced Ejection Fraction in Primary Care

Medscape UK X Guidelines
Primary Care Hacks

Authors: Dr Patricia Campbell, Consultant Cardiologist and Clinical Lead for Heart Failure, Northern Ireland; **Dr Eimear Darcy**, GP Partner, Grange Family Practice, Omagh; **Dr Kevin Fernando**, Portfolio GP, East Lothian, and Content Advisor, Medscape Global and UK (email: kfernando@webmd.net)

Classification of HF[3–7]

	HFrEF	HFmrEF	HFpEF
LVEF	<40%	40–49%	≥50%
Characteristics	• Signs/symptoms of HF	• Signs/symptoms of HF	• Signs/symptoms of HF • ↑ LV filling pressures • LV diastolic dysfunction • Usually ↑ natriuretic peptides
Proportion of people with HF	40%	10%	50%

HFimpEF is another suggested phenotype, defined as HF with a baseline LVEF <40% and a ≥10-point increase from baseline to a second LVEF measurement of >40%

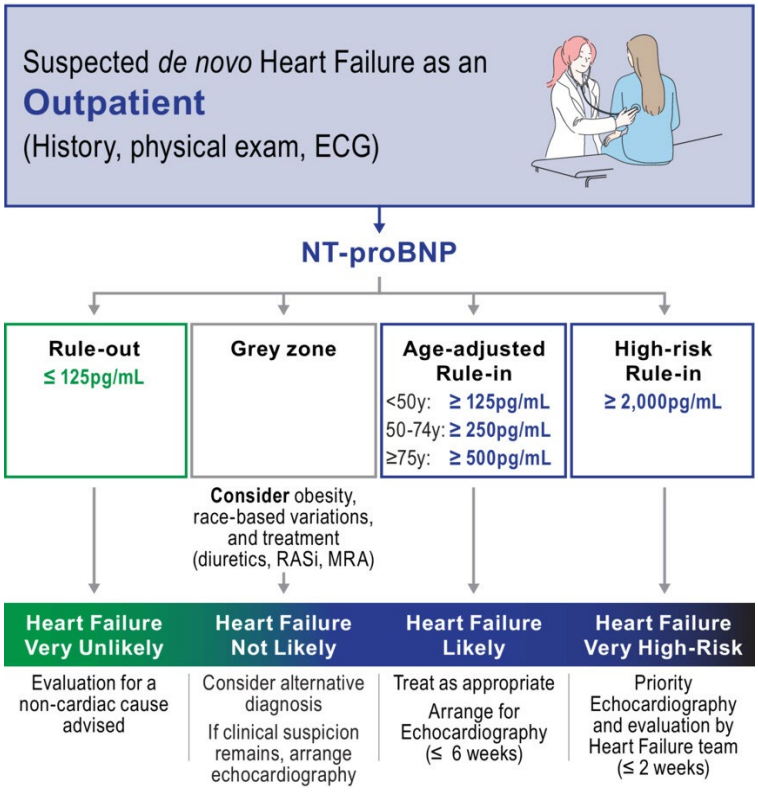
1. Individuals at Risk of HFrEF

Consider HF as a potential diagnosis in any individual who has been prescribed diuretics for ankle swelling with no known history of HF.[8]

Key risk factors:[4,9,10]

- older age
- male sex
- ASCVD (i.e. IHD/TIA/stroke/PVD)
- family history of HF
- hypertension
- diabetes
- dyslipidaemia
- obesity
- cardiovascular–kidney–metabolic syndrome
- heart valve disease
- atrial fibrillation
- LV dysfunction/hypertrophy
- exposure to cardiotoxic agents
- CKD and microalbuminuria
- OSAHS
- thyroid disorders
- anaemia.

Figure 1: NT-proBNP for Diagnosis of HF in the Outpatient Setting[15]



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2. Symptoms and Signs of HFrEF

Symptoms:[4,10–12]

- **typical:**
  - shortness of breath (SOBOE/SOBAR/orthopnoea/bendopnoea)
  - paroxysmal nocturnal dyspnoea
  - reduced exercise tolerance
  - ankle swelling
  - fatigue/tiredness ('tired all the time')
- **less typical:**
  - nausea
  - wheezing
  - nocturnal cough
  - loss of appetite/bloated feeling
  - dizziness
  - syncope
  - palpitations
  - confusion.

Signs:[4,10,12]

- **more specific:**
  - raised JVP
  - hepatojugular reflex
  - laterally displaced apical impulse
  - third heart sound
- **less specific:**
  - cardiac murmur
  - weight gain >2 kg per week
  - pulmonary crackles
  - peripheral pitting oedema, including sacral and ankle oedema
  - tachycardia
  - irregular pulse
  - tachypnoea
  - ascites
  - hepatomegaly
  - pleural effusion.

Consider documenting **NYHA functional classification** to aid description of HF severity:[4,10,12]

- **class I**—no limitation of physical activity (asymptomatic)
- **class II**—mild limitation of physical activity (symptoms with ordinary activity)
- **class III**—marked limitation of physical activity (symptoms with less-than-ordinary activity)
- **class IV**—severe limitation of physical activity (symptoms at rest).

ACEi=angiotensin-converting enzyme inhibitor; **AF**=atrial fibrillation; **ARB**=angiotensin receptor blocker; **ARNI**=angiotensin receptor/neprilysin inhibitor; **ASCVD**=atherosclerotic cardiovascular disease; **bid**=twice daily; **BMI**=body mass index; **BP**=blood pressure; **bpm**=beats per minute; **CKD**=chronic kidney disease; **COPD**=chronic obstructive pulmonary diseases; **COX-2**=cyclooxygenase-2; **CVD**=cardiovascular disease; **CVRM**=cardiovascular–renal–metabolic; **CXR**=chest X-ray; **CYP3A4**=cytochrome P450 3A4; **DNACPR**=Do Not Attempt Cardiopulmonary Resuscitation; **DPP4**=dipeptidyl peptidase 4; **ECG**=electrocardiogram; **ECHO**=echocardiogram; **eGFR**=estimated glomerular filtration rate; **ESC**=European Society of Cardiology; **FBC**=full blood count; **GRMT**=guideline-recommended medical therapy; **HbA_{1c}**=glycated haemoglobin; **HF**=heart failure; **HFimpEF**=heart failure with improved ejection fraction; **HFmrEF**=heart failure with mildly reduced ejection fraction; **HFpEF**=heart failure with preserved ejection fraction; **HFrEF**=heart failure with reduced ejection fraction; **HHF**=hospitalisation for heart failure; **HR**=heart rate; **IHD**=ischaemic heart disease; **IV**=intravenous; **JVP**=jugular venous pressure; **LBT**=liver blood test; **LTC**=long-term condition; **LV**=left-ventricular; **LVEF**=left-ventricular ejection fraction; **MRA**=mineralocorticoid receptor agonist; **NYHA**=New York Heart Association; **NSAID**=nonsteroidal anti-inflammatory drug; **NT-proBNP**=N-terminal pro–B-type natriuretic peptide; **od**=once daily; **OSAHS**=obstructive sleep apnoea/hypopnoea syndrome; **PAH**=pulmonary arterial hypertension; **PVD**=peripheral vascular disease; **QoL**=quality of life; **RAASi**=renin–angiotensin–aldosterone system inhibitor; **RASi**=renin–angiotensin system inhibitor; **SBP**=systolic blood pressure; **SGLT2i**=sodium–glucose co-transporter 2 inhibitor; **SOBAR**=shortness of breath at rest; **SOBOE**=shortness of breath on exertion; **SPC**=summary of product characteristics; **SU**=sulphonylurea; **T1D**=type 1 diabetes; **T2D**=type 2 diabetes; **TIA**=transient ischaemic attack; **TSH**=thyroid-stimulating hormone; **U&E**=urea and electrolytes; **uACR**=urinary albumin:creatinine ratio; **UKMEC**=UK Medical Eligibility Criteria; **WtHR**=waist-to-height ratio

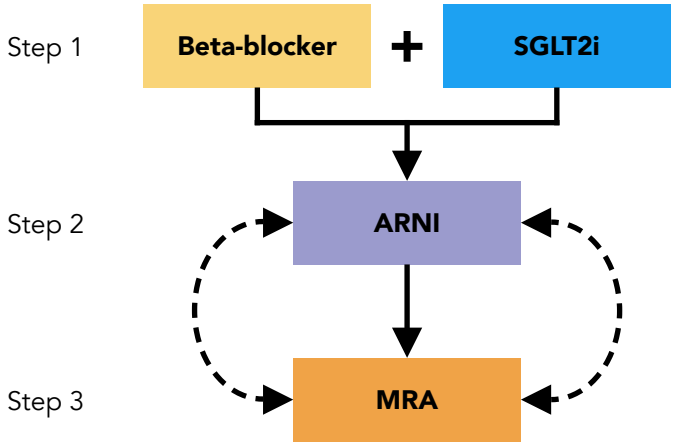
3. Testing and Referral of Possible HFrEF

- Auscultate for heart murmurs, check pulse to identify AF, and assess for frailty proactively at an early stage, using the Rockwood clinical frailty scale in those aged >65 years[10,13,14]
- Check **NT-proBNP** to identify likelihood of HFrEF (see Figure 1)[10,15,16]
- Consider further investigations to exclude alternative diagnoses, identify underlying modifiable risk factors, and/or detect any cardiac abnormalities:[10,12,16,17]
  - **FBC, U&E, TSH, lipids, LBTs, HbA_{1c}, iron studies** (see also the Primary Care Hacks on LBTs and iron studies)
  - **CXR, ECG**
    - on ECG, left-ventricular hypertrophy and left bundle-branch block are associated more with HFrEF than HFpEF[18]
  - **dipstick urine** for evidence of albuminuria and send sample for **uACR** (see also the Primary Care Hack on CKD)
  - **spirometry** (or peak flow if not available locally); be aware that HF may cause an obstructive pattern on spirometry due to pulmonary congestion[17]
  - **BMI** and **WtHR** (to assess for obesity)
- Consider OSAHS (using the Epworth sleepiness scale and the STOP-BANG questionnaire)[10,19]
- If HFrEF is suspected (see Figure 1), refer as appropriate via HF diagnostic pathways to a local HF service or Cardiology if unavailable.[16,20]

If HF is unlikely/uncertain, consider:

- **noncardiac mimics**[17,21–23]—e.g. COPD, asthma, obesity, deconditioning, frailty, ageing, nephrotic syndrome, liver failure/cirrhosis, anaemia, pleural disease, pulmonary embolism
- **cardiac mimics**[17,21–23]—e.g. hypertrophic cardiomyopathy, constrictive pericarditis, infiltrative disorders (amyloidosis, sarcoidosis, haemochromatosis), primary valvular disease, PAH, myocarditis.

Figure 2: Rapid Sequencing of GRMT Initiation for HFrEF[25]



All three steps achieved within 4 weeks

Uptitration to target doses thereafter

Packer M, McMurray J. Rapid evidence-based sequencing of foundational drugs for heart failure and a reduced ejection fraction. *Eur J Heart Fail* 2021; **23** (6): 882–894. doi: 10.1002/ejhf.2149
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4. Strong Clinical Suspicion of HF

While awaiting specialist assessment for suspected HF, consider management of congestion with diuresis (e.g. furosemide 40–80 mg or double pre-existing dose) **and initiation of an SGLT2i** (see *5. Guideline-Recommended Medical Therapy* and *Management of Congestion*).

5. Guideline-Recommended Medical Therapy

- The four pillars of therapy for HFrEF consist of **beta-blockers**, **SGLT2is**, **ARNIs** (or **ACEis/ARBs**), and **MRAs**[4,10,24]
  - **GRMT** involves the optimal use of **all four** classes of medication at either the target or highest tolerated dose[13,24]
  - target doses are associated with the best outcomes for mortality, HHF, symptoms, and QoL, but even low doses of GRMT show benefits[10,13,24]
  - lower doses of several medications are preferential to a high dose of one and none of the others[13,24]
- Initiation and titration of GRMT should happen **early** and **as rapidly as is safe and possible**, to give a greater cumulative benefit for long-term survival[4,13,24]
  - see Figure 2 for a recommended titration schedule[25]
  - some people may require slower titration schedules involving a switch to an ARNI from an ARB/ACEi:[13,24,26]
    - if a baseline ARB is used, no washout period is needed
    - if previously on an ACEi, ensure ≥36 hours' washout period before ARNI initiation
  - early initiation of beta-blocker in particular mitigates against sudden cardiac death[12]
- Be aware there is no prognostic or mortality benefit associated with use of **diuretics** in HFrEF, but they should be used to reduce signs/symptoms of congestion (see *Management of Congestion*)[10,16,24]
  - diuretics should not be delayed in people with oedema/fluid retention; loop diuretics are preferred[16,20,24]
- When initiating/titrating GRMT, consider the characteristics of the individual patient[13]
  - for example, people who still have significant congestion may tolerate ARNI initiation better[13] (avoid initiating beta-blocker in active pulmonary oedema/orthopnoea)
- SGLT2is, MRAs, ARNIs, ACEis, ARBs, loop diuretics, and certain beta-blockers **cannot** be taken during pregnancy or breastfeeding[13,26]
  - **discuss contraception and pregnancy in women of childbearing potential with HF**;[16] refer to the UKMEC.

6. Other Interventions

- Identify and treat associated LTCs, i.e. **CVRM management** (including management of T2D, hypertension, lipids/CVD prevention, CKD, and obesity)[10,13,16,17,20]
- Identify and manage **AF**[10]—aim for HR 80–90 bpm[17]
- Refer to a sleep clinic if **OSAHS** is suspected[10]
- **Physical activity**—recommend aerobic and resistance training[10,16]
  - consider referral to an exercise-based **cardiac rehabilitation** programme for all patients[10,16]
- Consider **anaemia**, which increases risk of HHF and mortality[10,27]
  - also consider **iron deficiency**;[10] see the Primary Care Hack on iron studies
  - the ESC recommends IV iron supplementation in individuals with symptomatic HFrEF/HFmrEF and iron deficiency[28]
- **Salt**—advise on limiting salt consumption as part of a healthy diet (ideally <2 g of sodium per day, equating to <5 g of sodium chloride)[10]
- Avoid overconsumption of **fluid**[10]
- **Smoking cessation**—assess smoking status and offer a brief intervention to stop smoking; signpost to smoking cessation services[10,16,29]
- **Alcohol**—current UK guidance advises limiting alcohol intake to ≤14 units/week[30]
- Assess for **depression** and **anxiety**[10,20]
- Offer **vaccinations** in line with national programmes (including annual flu and one-off pneumococcal vaccinations)[10,16]
- **Frailty** may be present in up to 45% of people with HF;[10] if significant frailty is identified:
  - consider medication adjustment
  - trial evidence has shown consistent benefits from SGLT2is across the range of frailty studied; QoL improved early and was more significantly affected in more severe frailty[20,31]
  - to enable **palliative care** considerations, assess people with HF at an early stage for severe frailty and last year of life[4,10,13]
  - as required, **develop individualised care plans** through needs-based holistic assessment and shared decision-making; these care plans may involve advance care planning, DNACPR considerations, and preference for virtual wards.[4,20]

HFmrEF

- **Diuretics** remain a class-1 recommendation for congestion in all subtypes of HF[10]
- For people with HFmrEF (LVEF 41–49%), **SGLT2is are now a class-I recommendation**.[28] The ESC has made weaker recommendations for the use of disease-modifying therapies that have class-I evidence for use in HFrEF[10,28]
  - **ACEis**, **ARBs**, **beta-blockers**, **MRAs**, and **ARNIs** can also be considered to reduce the risk of HHF and mortality.[10]

HFimpEF

People with an original HFrEF diagnosis and an improved LVEF (i.e. a more recent ECHO that shows LVEF ≥40%) should still be considered as having HFrEF and **must remain** on their prognostic medications.[20]

GRMT: Key Information[10,13,16,24,26,32,33]

		Starting Dose[10]	Target Dose[10]	Recommended Titration Schedule/Monitoring[13,16,26]	Key Contraindications (also consult individual SPCs)[24,26,32,33]
Beta-blockers	**Bisoprolol**	1.25 mg od	10 mg od	At intervals of no less than 2 weeks (to target/maximum tolerated dose) Monitor HR, BP, and clinical status	• Pregnancy • Second-/third-degree atrioventricular block (without a pacemaker) • Critical limb ischaemia • Asthma (a relative contraindication according to the choice of beta-blocker—be guided by the Cardiology team) • Known allergic/other adverse reaction
	Carvedilol	3.125 mg bid	25 mg bid[A]		
	Nebivolol	1.25 mg od	10 mg od		
SGLT2is	**Dapagliflozin**	10 mg od	10 mg od	—	• Pregnancy/breastfeeding • T1D • Symptoms of hypotension • SBP <95 mmHg • eGFR <20 ml/min/1.73 m^2 • Known allergic/other adverse reaction
	Empagliflozin	10 mg od	10 mg od		
ARNIs	**Sacubitril/ valsartan**	49/51 mg bid[B]	97/103 mg bid	At intervals of no less than 2 weeks (to target/maximum tolerated dose) Monitor BP and U&E	• Pregnancy/breastfeeding • Use of ACEis • Bilateral renal artery stenosis • Symptoms of hypotension • SBP <90 mmHg • eGFR <30 ml/min/1.73 m^2 • History of angioedema • Known allergic/other adverse reaction
MRAs	**Eplerenone**	25 mg od[C]	50 mg od	Dose can be increased after 4–8 weeks (to target/maximum tolerated dose) Monitor BP and U&E	• Known allergic/other adverse reaction
	Spironolactone	25 mg od[C]	50 mg od		
ARBs	**Candesartan**	4 mg od	32 mg od	At intervals of no less than 2 weeks (to target/maximum tolerated dose) Monitor U&E	• Pregnancy/breastfeeding • Bilateral renal artery stenosis • History of angioedema • Known allergic/other adverse reaction
	Losartan	50 mg od	150 mg od		
	Valsartan	40 mg bid	160 mg bid		

[A] A maximum dose of 50 mg bid is recommended if bodyweight >85 kg[10]

[B] For those with a history of symptomatic hypotension, or who are elderly or frail, a lower initial ARNI dose of 24/26 mg bid may be considered[10]

[C] For those who are elderly or frail, a lower initial MRA dose of 12.5 mg od may be considered. It is advised that MRAs are not initiated if eGFR <30 ml/min/1.73 m^2,[26] although it may be appropriate to continue MRAs if eGFR falls below this threshold.

Beta-blockers

- Initiate beta-blockers, at a low dose, in clinically stable, euvolaemic individuals[10]
- **Seek specialist advice before starting/titrating if:**[26]
  - severe HF (NYHA class IV)
  - HR <50 bpm
  - persistent congestion
  - <4 weeks from an exacerbation of HF
  - heart block
- **Temporary symptomatic deterioration** may occur during initiation or uptitration[26]
  - the diuretic effect of an SGLT2i can attenuate early beta-blocker side effects[24]
- To identify issues promptly, advise individuals to weight themselves daily (after waking and voiding, and before dressing and eating)[26]
  - if weight has increased by >1.5–2.0 kg/day for >2 days, advise individuals to increase their diuretic dose (see *Management of Congestion*)[26]
- If a person experiences certain signs/symptoms because of beta-blockers, make adjustments:
  - **increasing congestion**—increase diuretic dose initially and halve beta-blocker dose if no improvement;[26,32] discontinuation of beta-blocker is usually only indicated in cases of hypoperfusion (inadequate blood flow)[32]
  - **marked fatigue**—halve beta-blocker dose, review in 1–2 weeks, and seek specialist advice if no improvement[26]
  - **serious deterioration**—halve beta-blocker dose or stop the medication, and seek specialist advice[26]
  - **low HR/bradycardia:**[26,32]
    - if asymptomatic, continue therapy
    - if <50 bpm and worsening symptoms: halve beta-blocker dose
    - if severe deterioration: stop beta-blocker
    - review other drugs that may cause bradycardia (e.g. digoxin, ivabradine, amiodarone), arrange an ECG to exclude heart block, and seek specialist advice
  - **asymptomatic hypotension**—usually, no change in therapy required[26]
  - **symptomatic hypotension** (dizziness, light-headedness, or confusion):[13,26]
    - review other medications (e.g. vasodilators) and reduce dose or stop, if possible
    - symptoms may be due to overdiuresis; address this (e.g. by reducing diuretic dose) **before** deciding to lower doses of evidence-based therapies
    - if symptoms persist, seek specialist advice.

SGLT2is

- See also the Primary Care Hack on extra-glycaemic indications of SGLT2is
- The diuretic effect of an SGLT2i can attenuate early beta-blocker side effects[24]
- **Caution**—people living with T2D who are taking SUs/insulin may need dose adjustment on addition of an SGLT2i, to minimise risk of hypoglycaemia (if eGFR >45 ml/min/1.73 m²)[33]
- SGLT2is may reduce hyperkalaemia risk.[34]

ARNIs

- Consider directly initiating ARNI rather than ACEi/ARB whenever possible, to avoid delays in optimising GRMT[10,13,26]
- When initiating sacubitril/valsartan, a patient should have SBP >90 mmHg, eGFR >30 ml/min/1.73 m², and no signs of volume depletion[10,26]
- For management of **ARNI-related hyperkalaemia**, refer to the table on managing acute changes in kidney function in the Primary Care Hack on CKD
- **Cough** may occur as a side effect of ARNIs; if troublesome, substitution with an ARB is recommended[26]
- **Cautions:**
  - **a washout period of ≥36 hours after ACEi therapy is required to minimise the risk of angioedema[13,24]**
  - drug interactions to look out for: K^+ supplements, K^+-sparing diuretics, NSAIDs, trimethoprim, low-salt substitutes with high K^+ content, MRAs, renin inhibitors (e.g. aliskiren)[26]
- If **hypotension** is encountered:
  - if asymptomatic—usually, no change required[26]
  - dizziness/light-headedness is common with ARNI initiation and tends to **improve with time**—if tolerated, simply reassure individuals[26]
  - if symptoms do not improve or are poorly tolerated:
    - review other medications (e.g. vasodilators) and reduce dose/stop, if possible[26,35]
    - symptoms may be due to overdiuresis; address this (e.g. by reducing diuretic dose) **before** deciding to lower doses of evidence-based therapies[13,26,35]
    - consider halving the ARNI dose
    - if symptoms persist, seek specialist advice.[26]

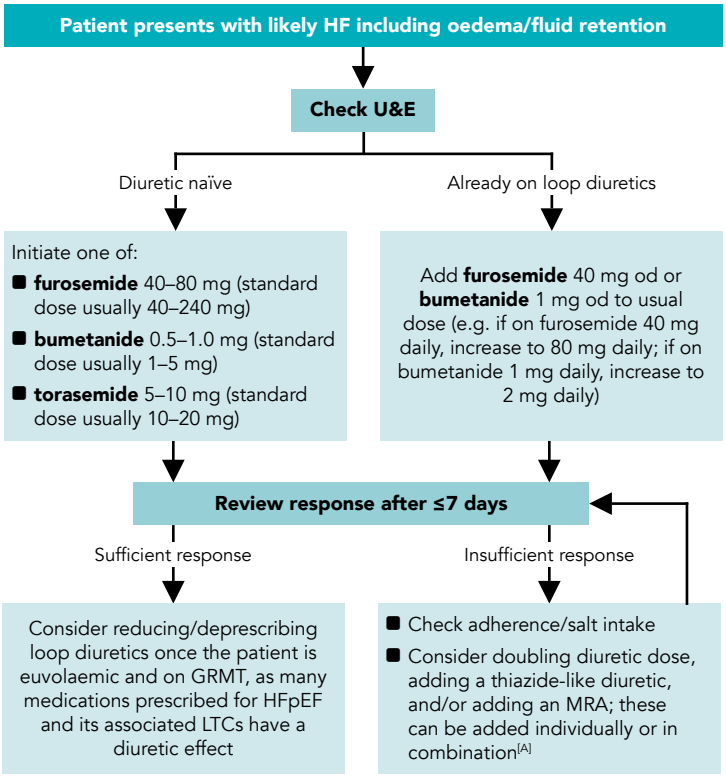
MRAs

- Exercise caution when prescribing MRAs for people with eGFR <30 ml/min/1.73 m² or serum K^+ >5.0 mmol/l[10,12]
- Drug interactions to look out for: K^+ supplements, K^+-sparing diuretics, NSAIDs, trimethoprim, low-salt substitutes with high K^+ content, CYP3A4 inhibitors, ACEis, ARBs, renin inhibitors (e.g. aliskiren)[26]
- For management of **MRA-related hyperkalaemia**, refer to the table on managing acute changes in kidney function in the Primary Care Hack on CKD
- In rare cases, men treated with spironolactone may develop gynaecomastia or breast discomfort; consider eplerenone.[26]

ARBs and ACEis (If Already Prescribed)

- The ESC recommends replacing an ACEi or ARB with an ARNI in people with HFrEF who have symptoms despite optimal treatment[10]
- For management of **RAASi-related hyperkalaemia**, refer to the table on managing acute changes in kidney function in the Primary Care Hack on CKD
- **Cough** is a common side effect of ACEis (~20% of patients[12]); if troublesome, substitution with an ARB is recommended[26]
- If **hypotension** is identified, see the relevant advice in the *ARNIs* section[26]
- Caution is advised when prescribing in individuals with low BP (SBP <80 mmHg), CKD, or hyperkalaemia[12]
- Drug interactions to look out for: K^+ supplements, K^+-sparing diuretics, NSAIDs, trimethoprim, low-salt substitutes with high K^+ content, MRAs, renin inhibitors (e.g. aliskiren).[26]

Management of Congestion[10,17,20,26]



Notes

- U&E should be checked before and after dose adjustments (within 2 weeks)
- Ongoing diuretic management is required for both dose increases (in periods of congestion) and dose decreases (if the patient becomes euvolaemic or dehydrated)
- People with HF should be taught how to adjust their own diuretic dose according to daily weight measurements and signs/symptoms of congestion
- Measure weight daily in the morning to check trend (bodyweight reduction of 0.75–1.0 kg/day is generally considered an effective rate during active diuresis).

[A] Think about contacting the patient's HF team, as they may consider addition.

Prescribing Pearls

- For management of **GRMT-related hyperkalaemia**, refer to the table on managing acute changes in kidney function in the Primary Care Hack on CKD
  - in the DIAMOND trial, K^+ binders aided continuation of GRMT for HFrEF[36]
- Give sick day guidance for relevant medicines
- **If low K^+ noted from e.g. diuretics, consider starting or uptitrating an MRA** instead of giving K^+ supplements (if there is no contraindication to MRAs[13,26]
- **T2D:**
  - avoid DPP4 inhibitors (saxagliptin) and pioglitazone in people living with T2D and HF[10,17]
  - those on SUs/insulin may need dose adjustment with addition of an SGLT2i, to minimise risk of hypoglycaemia (if eGFR >45 ml/min/1.73 m²)[33]
- **Avoid verapamil, diltiazem, and short-acting dihydropyridine agents** in HF[16]
- **Avoid NSAIDs and COX-2 inhibitors**, as they increase the risk of acute HF decompensation and HHF[10]
- **Discuss contraception and pregnancy in women of childbearing potential with HF**;[16] refer to the UKMEC.

Patient Resources

- The Pumping Marvellous website
- The British Heart Foundation
- Cardiomyopathy UK.

This Primary Care Hack was developed by Dr Patricia Campbell, Consultant Cardiologist and Clinical Lead for Heart Failure, Northern Ireland; Dr Eimear Darcy, GP Partner, Grange Family Practice, Omagh; and Dr Kevin Fernando, Portfolio GP, East Lothian, and Content Advisor, Medscape Global and UK. Primary Care Hacks are for information for primary healthcare professionals in the UK only. They bring together currently available recommendations and/or prescribing information and indications for therapeutics licensed within Great Britain. Licensed indications and/or prescribing information for Northern Ireland may differ. You are advised to review local licensed indications before prescribing any therapeutic. Primary Care Hacks are reviewed intermittently to ensure the information is up to date at the time of publication. Primary Care Hacks are independently produced by WebMD, LLC and have not been created in conjunction with any guideline or prescribing body.