National Medicines Information Centre

VOLUME 25
NUMBER 6
2019

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PHARMACOTHERAPY OF CHRONIC HEART FAILURE

- **The management of heart failure should be a shared responsibility between patients, their carers and healthcare professionals**
- **Pharmacological therapy has been shown to improve outcomes in patients with heart failure with reduced ejection fraction**
- **Patients with heart failure with reduced ejection fraction should be treated with an angiotensin-converting enzyme inhibitor/angiotensin II receptor blocker, beta blocker and mineralocorticoid receptor antagonist**
- **Patients with heart failure require close monitoring**

INTRODUCTION

Heart failure (HF) is one of the major chronic diseases in Ireland and one of the commonest reasons for hospitalisation in the elderly.[1] Chronic HF is associated with significant mortality, even though there have been improvements in therapies over the last 30 years.[2] **HF management programmes that incorporate primary care and hospital services have been shown to result in improved outcomes for patients with HF.[1]**

Renin-angiotensin-aldosterone system (RAAS) inhibitors (angiotensin-converting enzyme inhibitors [ACEIs] or angiotensin II receptor blockers [ARBs], and mineralocorticoid receptor antagonists [MRAs]) and beta blockers have become the optimal pharmacotherapy for patients with HF with reduced EF (HFrEF).[3-6] There is less evidence for benefits of specific pharmacotherapy for patients with HF with preserved EF (HFpEF) and HF with mid-range EF (HFmrEF).[6,7] This bulletin will review the pharmacological management of chronic HF.

MEDICAL TREATMENT OF PATIENTS WITH HFrEF

Guidelines recommend that patients with HFrEF should be treated with RAAS inhibitors and beta blockers (table 1);[3,6-9] this is based on evidence that long-term treatment with these therapies improves survival and reduces hospitalisations.[3,6,7] **Patients with symptomatic HFrEF should receive these medications titrated to the maximum tolerated dose (MTD) or target dose.[3]** In recent years, the angiotensin receptor-neprilysin inhibitor (ARNI), sacubitril/valsartan has been shown to further reduce mortality in symptomatic patients with HFrEF on optimal treatment; it is recommended as an option to replace the ACEI/ARB in symptomatic patients with HFrEF with an EF of ≤35%.[3,8] Ivabradine may also be considered for symptomatic patients with HFrEF, who are in sinus rhythm (SR) and have a heart rate of ≥70 or ≥75 bpm (varies in sources);[6-11] it is used in combination with optimal therapy, including ACEI, MRA and beta blocker, or when a beta blocker is contraindicated or not tolerated.[6-10] Cardiac resynchronisation therapy (CRT) may be an option for symptomatic patients on optimal therapy, who are in SR and who have a QRS duration of ≥130 msec.[7] Diuretics which relieve congestive symptoms, are also used in symptomatic patients with HFrEF.[7]

Table 1: Summary of the pharmacological management of HFrEF[7,11]

Patient with symptomatic HFrEF			
↓			
Treat with ACEI (or ARB if ACEI not tolerated) and beta blocker (up-titrate to maximum tolerated or target dose)			
↓			
Still symptomatic and LVEF ≤35%			
↓			↓
Yes			**No**
↓			↓
Add mineralocorticoid receptor antagonist (up-titrate to maximum tolerated or target dose)			
↓			
Still symptomatic and LVEF ≤35% →			**No**
↓			↓
Yes **Consider other specialist treatments**			
↓	↓	↓	↓
Able to tolerate ACEI (or ARB)	Sinus rhythm QRS duration ≥130 msec	Sinus rhythm HR ≥70 or ≥75 bpm*	↓
↓	↓	↓	↓
ARNI to replace ACEI (or ARB)	Evaluate need for CRT	Ivabradine	No further action required. Consider ↓ diuretic dose if applicable

HFrEF-heart failure reduced ejection fraction; ACEI-angiotensin-converting enzyme inhibitor; LVEF-left ventricular ejection fraction; CRT-cardiac resynchronisation therapy; ARNI-angiotensin receptor-neprilysin inhibitor; *-note some sources recommend ≥70bpm, while other sources including the summary of product characteristics (SmPC) recommend ≥75bpm

Other drugs which may also be used under specialist advice include digoxin and a combination of hydralazine (not licensed) and isosorbide dinitrate[7,8].

MEDICAL TREATMENT OF PATIENTS WITH HFpEF

The pharmacological management of a patient with HFpEF mainly involves 1) the control of symptoms and 2) the identification and treatment of co-morbid conditions that might exacerbate the HF.[3,7,11] Diuretics play an important role in improving symptoms.[3,7,11]Patients with co-morbidities (e.g. hypertension, diabetes), may require medications for those conditions e.g. beta blockers, ACEIs/ARBs and MRAs.[9]

Prospective studies of ACEIs, ARBs, beta blockers and MRAs failed to show that they convincingly reduce mortality in patients with HFpEF or HFmrEF.[3,6-8,12-17] Some evidence does suggest that ARBs and MRAs may reduce hospitalisations in specific patient populations.[15-17] A recent RCT that compared sacubitril/valsartan to valsartan did not find a significantly lower rate of hospitalisations for HF and death in patients with an EF of ≥45%.[18]

Prospective trials have not been conducted in patients with HFmrEF.[7] Post hoc analyses of studies found that candesartan, spironolactone and beta blockers reduced the risk of CV death and hospitalisations in patients with HFmrEF.[19-22] Recent ESC recommendations indicate that beta blockers, candesartan or spironolactone may be considered for patients with HFmrEF.[19]

MEDICATIONS USED IN HEART FAILURE

Angiotensin-converting enzyme inhibitors (ACEIs) inhibit RAAS and reduce hospitalisations and mortality in patients with HFrEF.[7,23-25] **ACEIs are recommended first-line for all patients with HFrEF**, unless they are contraindicated or not tolerated.[6,7,9] ACEIs are associated with angioedema in <1% of patients (more frequently in black people) and cough in 10 to 20% of patients.[6,9] They should be titrated to the MTD or target dose; **there is evidence that the majority of patients receive suboptimal doses of ACEIs.[7]**

Angiotensin II receptor blockers (ARBs) inhibit RAAS and reduce hospitalisations and mortality in patients with HFrEF.[26-30] ARBs do not inhibit the breakdown of bradykinin and are associated with a lower incidence of cough and angioedema than ACEIs.[9] **ARBs are recommended in patients with HFrEF who are intolerant of an ACEI.[7,11]** Patients on ARBs should be up-titrated to the MTD.[26] Table 2 summarises the special precautions and monitoring required for ACEIs and ARBs; the Summary of Product Characteristics (SmPC) provides full prescribing information including dose titration.

Table 2: Special precautions and monitoring of ACEIs and ARBs[8,31,32]

Drug Class	Special precautions include*	Monitoring includes:*
Angiotensin-converting enzyme inhibitors e.g. Ramipril**	C/I include history of angioedema, use with sacubitril/valsartan, significant bilateral renal artery stenosis, concomitant use of aliskiren in patients with DM or renal impairment Risk of hypotension, hyperkalaemia, cough, angioedema, renal impairment, hepatic failure, proteinuria, neutropenia/ agranulocytosis, hypoglycaemia, hyponatraemia Care in the elderly, renal impairment – consider reduced dose; care in renal artery stenosis Do not use in pregnancy	Measure serum sodium and potassium, and assess renal function, before and 1 to 2 weeks after starting drug and after each dose increment Measure BP before and after each dose increment
Angiotensin receptor blockers e.g. Candesartan**	C/I include severe hepatic impairment and cholestasis, concomitant use of aliskiren in patients with DM or renal impairment Risk of renal impairment, hypotension, hyperkalaemia, hypersensitivity Care in patients with renal artery stenosis Do not use in pregnancy	Once the target or MTD is reached, monitor patient monthly for 3 months and then every 6 months and any time a patient becomes acutely unwell

*refer to the full prescribing information in the Summary of Product Characteristics; ** - current preferred drug by the HSE Medicines Management Programme; C/I – contraindications; DM-diabetes mellitus; MTD-maximum tolerated dose

ACEI/ARBs should be used with caution in patients with low BP, renal insufficiency or elevated serum potassium.[9] Consultation with a renal physician should be considered for patients with severe renal impairment. [8] An increase in serum creatinine or decrease in eGFR of up to 20-30% may occur when an ACEI/ARB is introduced; if the increase stabilises at ≤20-30% there is no immediate need to decrease the drug dose, however close monitoring is required.[6,33] It is estimated that <5% of patients, usually those with severe pre-existing renal disease, require discontinuation of treatment.[33] **Initiation of an ACEI/ARB may result in hypotension, especially when introduced at a high dose, in combination with a diuretic and in patients with renal impairment.[6]** Supine and erect BPs should be checked to assess for orthostatic hypotension.[6]

The combination of an ACEI and an ARB in patients with HF (especially in patients with diabetic nephropathy) is not recommended due to an increased risk of hyperkalaemia, hypotension and decreased renal function (including acute renal failure).[6,31,34] If this combination is considered absolutely necessary, it must be under specialist supervision with close monitoring.[34]

Beta blockers reduce hospitalisations and mortality in patients with HFrEF.[7,25,35-38] They are recommended for use in combination with ACEIs in patients with stable HFrEF.[6,7] **Beta blockers should be started in clinically stable patients at a low dose with gradual up-titration to the MTD**; close monitoring is required.[6,7,11,39-41] Patients may experience transient worsening of HF, hypotension or bradycardia during the titration period.[6,39-41] In these situations, reconsideration of the dose of concomitant medication is required; it may be necessary to temporarily reduce the

dose or gradually discontinue the beta blocker.[6,39,40] **Once the patient is stable again, the reintroduction and/or up-titration of the beta blocker should be considered.[39,40]** Table 3 summarises the special precautions and monitoring required; the SmPC provides full prescribing information.

Table 3: Special precautions and monitoring of beta blockers[8,39]

Drug Class	Special precautions include*	Monitoring includes:*
Beta blockers e.g. Bisoprolol**	C/I include AHF, heart block, severe asthma Caution in patients with bronchospasm, diabetes, heart block, peripheral vascular disease, hypersensitivity Patient may experience worsening HF	Introduce at a low dose and slowly increase to target of MTD Assess BP, HR and clinical status before and after each dose increase If MTD not well tolerated, consider gradual dose reduction (do not stop abruptly)

*refer to the full prescribing information in the Summary of Product Characteristics; **- current preferred drug by the HSE Medicines Management Programme; C/I – contraindications; HF-heart failure; MTD-maximum tolerated dose

Mineralocorticoid/aldosterone receptor antagonists (MRAs) inhibit RAAS;[3,7,25] spironolactone and eplerenone reduce hospitalisations and mortality in patients with HFrEF, when used with standard therapy (e.g. an ACEI and beta blocker).[4,42,43] **MRAs are recommended in symptomatic patients with HFrEF on optimal therapy.[7]** MRAs should be used with caution in patients with impaired renal function and those with serum potassium >5.0 mmol/L.[7] Table 4 summarises the special precautions and monitoring required; the SmPC provides full prescribing information.

Table 4: Special precautions and monitoring of MRAs[8,44,45]

Drug Class	Special precautions include*	Monitoring includes:*
Mineralocorticoid/aldosterone receptor antagonists e.g. spironolactone, eplerenone	C/I include severe renal insufficiency Risks of hyperkalaemia, renal impairment, gynaecomastia (spironolactone) Risk of drug interactions	Measure serum sodium and potassium, and assess renal function, before and after starting drug and after each dose increment Measure BP before and after each dose increment Once the target or MTD is reached, monitor patient monthly for 3 months and then every 6 months and any time a patient becomes acutely unwell

*refer to the full prescribing information in the Summary of Product Characteristics; C/I – contraindications; MTD-maximum tolerated dose

Angiotensin receptor-neprilysin inhibitors (ARNI): Sacubitril/valsartan acts on RAAS and the neutral endopeptidase system.[9,11,25,46,47] A RCT found that sacubitril/valsartan was superior to enalapril in reducing hospitalisations and overall mortality in patients with stable HFrEF (with EF ≤35%).[46] **Sacubitril/valsartan is recommended in symptomatic patients with HFrEF (EF ≤35%) with elevated natriuretic peptides and those on optimal treatment (an ACEI/ARB, beta blocker and MRA) in place of the ACEI/ARB.[7,19]** ARNIs have similar tolerability and adverse effects as ACEIs and require similar monitoring (table 5).[6] Treatment should not be initiated in patients with serum potassium ≥5.4 mmol/L or those with systolic BP <100 mmHg.[47] ARNIs should not be used in those with a history of angioedema.[6,7,47] **Patients started on sacubitril/valsartan should have their ACEI stopped for at least 36 hours before commencing treatment,** to reduce the risk of angioedema caused by overlapping ACE and neprilysin inhibition.[7,9] ARNIs cause increased BNP levels, therefore NT-proBNP levels are preferred to BNP.[6] Studies suggest that sacubitril/valsartan may be beneficial in patients with HFrEF when initiated after an episode of acute decompensated HF, even in patients not previously on ACEIs or ARBs.[48-51]

Table 5: Special precautions and monitoring of ARNIs[47]

Drug Class	Special precautions include*	Monitoring includes:*
Angiotensin receptor-neprilysin inhibitor Sacubitril/valsartan#▼	Risk of hypotension, renal impairment, hyperkalaemia, angioedema Care in renal artery stenosis. Do not use in pregnancy Risk of drug interactions	Start at recommended starting dose and increase to target dose within 2 to 4 weeks** Patients need a washout period of 36 hours between an ARNI and ACEI to decrease the risk of angioedema Measure BP, renal function and potassium before and after each dose increase Once the target or MTD is reached, monitor monthly for 3 months and then every 6 months and any time a patient becomes acutely unwell

*refer to the full prescribing information in the Summary of Product Characteristics; **-lower starting dose in patients with hypotension; #- approval for individual patient reimbursement must be obtained from the HSE through the primary care reimbursement service (PCRS); ▼ – subject to additional monitoring; MTD-maximum tolerated dose

Ivabradine reduces the increased heart rate often seen in patients with HFrEF;[7,25] it has been shown to reduce hospitalisations and mortality in patients with HFrEF who are in SR and who have a heart rate of ≥70 or ≥75 bpm (varies in sources).[6-11,52] **Ivabradine should only be used in patients in SR;[6,6,7,8] some guidelines recommend use of ivabradine only on specialist advice.[8,11]** It should only be initiated after a stabilisation period of 4 weeks on standard therapy with an ACEI, beta blocker and MRA.[8] Monitoring of the patient's heart rate and BP is recommended. Potential drug interactions should be considered. Common adverse effects include headache, luminous phenomena, blurred vision, bradycardia, first degree block, AF and uncontrolled BP.[10] The SmPC provides full prescribing information.

OTHER DRUGS

Other drugs used for the treatment of patients with HF include diuretics, a combination of hydralazine and isosorbide dinitrate, and digoxin[7,8].

Diuretics are used for symptomatic relief of patients with HF.[3,7,11] The effects of diuretics on mortality have not been

assessed in RCTs,[7,25] however diuretics improve symptoms and exercise capacity and reduce hospitalisations.[11] Loop diuretics produce a more intense and shorter diuresis than thiazides.[7,11] Loop and thiazide diuretics act synergistically; the combination may be used to treat resistant oedema.[7,11] **However, combinations of diuretics should only be used with care, as adverse effects are more likely to occur.**[7] The dose of the diuretic needs to be individualised to the patient to reduce fluid retention and relieve symptoms, without over-treating, potentially resulting in dehydration, renal dysfunction or worsening HF.[3,7,8,11] Once optimal decongestion has been achieved for a patient, the lowest dose of diuretic that maintains euvolaemia should be prescribed.[3] **Patients can be educated on how to self-adjust their diuretic dose based on their signs and symptoms and daily weight measurements.**[7,11]

Combination of hydralazine and isosorbide dinitrate has been shown to reduce mortality in black patients,[6,7] however there is no evidence to suggest benefit in all patients with HFrEF.[7] This combination may be considered in patients with HFrEF of black African or Caribbean family origin or those unable to tolerate an ACEI, ARB or ARNI because of hyperkalaemia or renal dysfunction.[6-8] **Specialist advice is recommended**.

Digoxin: There are inconsistent results on the benefits of digoxin in patients with HF;[6,7] it improves clinical symptoms however it does not improve survival.[25] It may be considered in symptomatic patients on optimal treatment for HFrEF in SR.[3,6,7] Digoxin may be useful in the treatment of patients with HFrEF and AF who have a rapid ventricular rate, when other therapeutic options have failed.[7] **Digoxin should always be prescribed under specialist supervision.**[7,8] Digoxin can cause arrhythmias especially in patients with co-existing hypokalaemia and/or renal dysfunction. **Potassium and renal function should be monitored, especially on starting or changing dose, when used with an interacting drug or dehydrating illness.**[6] Routine digoxin levels are not required, apart from assessing digoxin toxicity.[6,8]

PRACTICAL ASPECTS OF PHARMACOTHERAPY

The monitoring of a patient with HF should consider 1) clinical assessment of the patient, 2) review of the patient's medication and 3) avoidance of adverse events associated with the medication (e.g. hypotension, hyperkalaemia);[8] the frequency of monitoring depends on the individual patient.[8] Factors that may reduce the risk of adverse events include 1) gradual up-titration of the individual drug, 2) monitoring of the patients, 3) the discontinuation of drugs that may cause hypotension (e.g. calcium-channel blockers, alpha blockers and nitrates) and 4) avoiding the co-administration of interacting drugs (e.g. NSAIDs and potassium supplements).[3] **In patients who experience persistent or severe hyperkalaemia, hypotension or severe renal impairment, down-titration of doses or discontinuation of RAAS inhibitors may be required, however attempts at re-initiation or up-titration of therapy should be implemented as soon as possible.**[3]

Adherence to evidence based guidelines has been shown to be associated with improved outcomes for patients with HF,[3,53,54] however there are a significant number of patients not on the recommended or on suboptimal doses of medications.[3,5,7,54-56] **Patients who are non-adherent or on submaximal doses of medications for HFrEF, are at an increased risk of HF hospitalisations and mortality.**[3,53,54,57] A UK study (2015) found that following hospital discharge with specialist input, 84% of patients with HFrEF were on an ACEI/ARB, 86% on a beta blocker and 52% on a MRA; only 42% of patients were on all three medications.[58] Barriers to medication titration include health-provider knowledge; patient related factors (e.g. age, BMI, co-morbidities and polypharmacy), concern regarding adverse events (e.g. hypotension and hyperkalaemia) and limited time and support structures to facilitate regular monitoring.[3,56]

OTHER TREATMENTS

Other therapies that may be considered in patients with HFrEF include devices such as cardiac resynchronisation therapy (CRT) and implantable cardiovertor defibrillators (ICD).[3,7,11,59] Patients with HF may have asynchronous contraction of their ventricles, which is noted as prolonged QRS. Ventricular function is improved by pacing the left and right ventricle simultaneously (also known as CRT).[11] CRT reduces morbidity and mortality in selected patients with a prolonged QRS.[7,59] ICDs improve mortality by resuscitating patients who sustain a tachyarrhythmia.[11] ICDs are recommended in selected patients with HF to reduce the risk of sudden death.[7,11]

TREATMENTS OF UNPROVEN BENEFIT

Statins: Evidence does not support the initiation of statins in most patients with HF, however statins should be continued in patients who are already on a statin because of underlying coronary artery disease and/or hyperlipidaemia.[6,7]

Antiplatelets or anticoagulants: There is no evidence of benefit for anticoagulants/antiplatelets in patients with HF, unless there is a specific indication for anticoagulation (e.g. AF) or for antiplatelets (e.g. secondary CV protection).[6,7]

Aliskiren (direct renin inhibitor) does not improve outcomes for patients with HF.[7,25] It is not recommended as an alternative to an ACEI or ARB.[7]

Non-dihydropyridine calcium-channel blockers (CCBs), such as diltiazem and verapamil, have shown worsening HF outcomes; they are not indicated for patients with HF.[6,7,25] There is only evidence on safety for one dihydropyridine CCB, amlodipine, which should only be used for other indications in patients with HFrEF (e.g. persistent hypertension or angina symptoms).[6,7,25]

Non-steroidal anti-inflammatory drugs (NSAIDs) are not recommended in patients with HF. They cause sodium and water retention, worsen renal function and interact with HF medications (e.g. ACEI/ARB).[6]

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