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Optimising outcomes in chronic heart failure

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SPECIAL REPORT

Optimising outcomes in chronic heart failure

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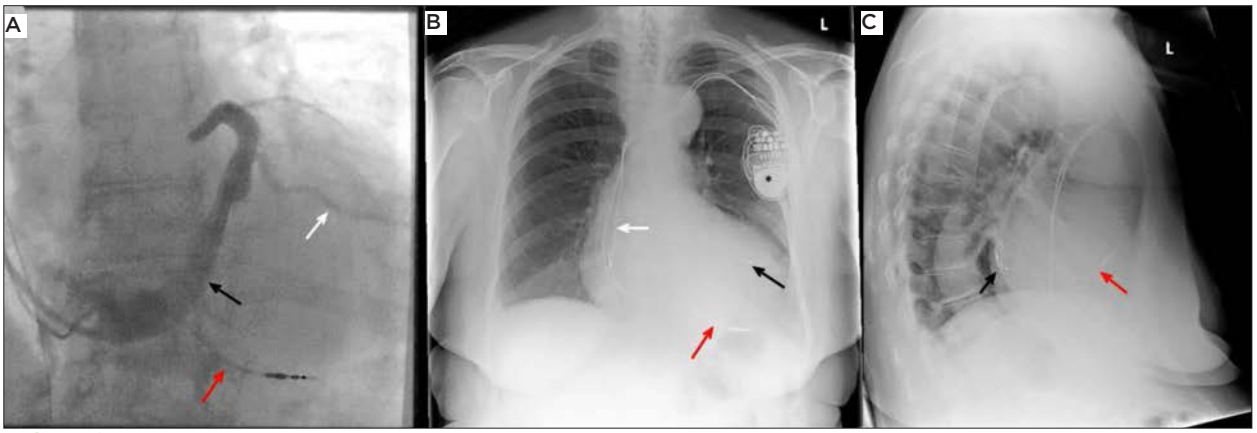

FIGURE 1
Images taken during and after cardiac resynchronisation therapy (CRT) device implantation
A Coronary sinus venogram taken during implantation. Contrast is injected into the coronary sinus (black arrow) to find an optimal branch for placing the left ventricular lead (white arrow). The right ventricular lead can also be seen (red arrow)
B Postero-anterior chest X-ray post-CRT implantation. The CRT generator can be seen over the left lung (*). Three pacing leads are also seen, right atrial (white arrow), right ventricular (red arrow) and coronary sinus (black arrow)
C Lateral film in the same patient post-CRT. The lateral film is particularly useful in showing adequate lead separation between the right ventricular (red arrow) and coronary sinus (black arrow) leads. The wider the separation the better the resynchronisation

How do patients present in primary care?

THE EUROPEAN SOCIETY OF CARDIOLOGY DEFINES HEART FAILURE (HF) AS 'A CLINICAL SYNDROME characterised by typical symptoms (e.g. breathlessness, ankle swelling and fatigue) that may be accompanied by signs (e.g. elevated jugular venous pressure, pulmonary crackles and peripheral oedema) caused by a structural and/or functional cardiac abnormality, resulting in a reduced cardiac output and/or elevated intracardiac pressures at rest or during stress'.[1]

A recent study using the Clinical Practice Research Datalink (CPRD) database reported that the prevalence of HF in the UK was 1.6% (standardised for age and sex), with an absolute number of 920,616 patients with an electronic health record diagnosis of HF in 2014, an increase from the previous decade despite a modest decrease in the incidence of new cases.[2] This probably reflects the increased life expectancy of HF patients due to advances in treatment. Although there is likely to be some inaccuracy with electronic health record case ascertainment, CPRD is well validated and any bias would be unlikely to mask overall trends.[3,4]

How should diagnosis be confirmed?

PRESENTATION

Although patients can present with non-specific symptoms and minimal clinical signs, generally, in the community, patients will present with symptoms of dyspnoea or fluid retention, raising the suspicion of HF as a potential cause. In order to confirm (or refute) the diagnosis, the 2018 NICE guideline[5] recommends conducting natriuretic peptide testing, ideally N-terminal pro B-type natriuretic peptide (NT-proBNP), in all patients with suspected HF.

An NT-proBNP level >2,000 ng/L is highly suggestive of HF and NICE recommends echocardiography and specialist review within two weeks. Conversely, an NT-proBNP level < 400 ng/L suggests that a diagnosis of heart failure is unlikely, and other causes for the patient's symptoms should be considered. Patients with an NT-proBNP between 400 and 2,000 ng/L should have echocardiography and specialist assessment within six weeks. NT-proBNP should be interpreted accordingly; it is not a valid screening test if there is an abnormal electrocardiogram (ECG) or the patient is already on medication that could affect the result e.g. angiotensin-converting enzyme inhibitors (ACEI) or beta-blockers.

It is also important to note that obesity does lower natriuretic peptide levels (particularly if BNP is used rather than NT-proBNP), therefore HF may still need to be considered in patients with suspected HF and natriuretic peptide levels just below the diagnostic threshold, although there is no validated cut-off for a different threshold based on body mass index.

As well as echocardiography, an ECG should also be performed at baseline. Other basic tests such as chest X-ray, full blood count, renal, liver and thyroid function, lipids and glycosylated haemoglobin should also be carried out. Specialists may then also consider other investigations such as coronary angiography or cardiac magnetic resonance imaging in order to identify»

What are the management approaches?

specific aetiologies that may benefit from specific treatments, see table 1, below.

Less commonly, patients may present with left ventricular dysfunction identified when cardiac imaging is carried out for other reasons (e.g. evaluation of a murmur). These patients may even be asymptomatic. Importantly, the diagnosis of left ventricular systolic dysfunction can be made in symptomatic or asymptomatic patients. However, the diagnosis of HF is only given to symptomatic patients. The New York Heart Association (NYHA) classification of symptom status in HF patients is shown in table 2, below.

Patients with conditions such as diabetes, hypertension and chronic renal impairment are at higher risk than the general population of developing left ventricular dysfunction and therefore this diagnosis should be kept in mind. Those with asymptomatic left ventricular dysfunction are also at risk of developing symptomatic heart failure and typically should be treated in a similar manner to symptomatic patients. As well as these risk factors, an often overlooked but increasingly recognised component of the HF patient work-up is a family history of cardiomyopathy or sudden cardiac death, which may point to a genetic cause of HF.

HF with preserved ejection fraction (HFpEF) patients typically have risk factors such as hypertension, diabetes or obesity. The diagnosis of HFpEF is confirmed by clinical symptoms and signs of HF in conjunction with elevated natriuretic peptides and, importantly, the presence of echocardiographic structural abnormalities such as left ventricular hypertrophy or left atrial dilatation. The level of natriuretic peptide elevation does not distinguish between HF with reduced ejection fraction (HFrEF) and HFpEF.

Table 1

Common heart failure aetiologies

- Ischaemic heart disease
- Hypertension
- Valvular
- Tachyarrhythmia e.g. atrial fibrillation
- Myocarditis
- Genetic/familial e.g. hypertrophic cardiomyopathy, dilated cardiomyopathy, left ventricular non-compaction, arrhythmogenic right ventricular cardiomyopathy
- Infiltrative e.g. amyloidosis, sarcoid, haemochromatosis, Fabry disease
- Chemotherapy e.g. anthracyclines, trastuzumab
- Toxic e.g. alcohol
- Idiopathic

Table 2

New York Heart Association (NYHA) classification of heart failure symptoms

NYHA class	Definition
I	No limitation in normal physical activity
II	Mild symptoms in normal physical activity
III	Marked symptoms during daily activities, asymptomatic at rest
IV	Severe limitation, symptoms present at rest

MANAGEMENT

Pharmacological therapy

Commonly used drugs for HFrEF are listed in table 3, p23. The cornerstone of HFrEF pharmacological treatment involves initiation of renin-angiotensin aldosterone blockade with ACEI or angiotensin II receptor antagonists (ARB), and beta-blockers, with the addition of mineralocorticoid receptor antagonists (MRA) if patients remain symptomatic with a reduced ejection fraction (usually ≤ 35%). The majority of patients with HF will require a loop diuretic such as furosemide or bumetanide in order to relieve congestion and maintain fluid balance.

Generally, all treatments should be initiated at low doses and slowly uptitrated, usually at two-week intervals. These classes of drugs have been evaluated in several large outcome trials and have a substantial evidence base to support their use. Uptitration should be to the target doses suggested in table 3, p23, or maximal tolerated dose. Although elevated heart rate is associated with an adverse prognosis, in the beta-blocker clinical trials (and indeed all heart failure trials), uptitration was performed to a target dose rather than surrogate targets such as heart rate.

If HFrEF patients remain symptomatic following uptitration of ACEI/ARBs, beta-blockers and MRAs to maximal tolerated doses, there are a number of options which specialists may recommend for use. Typically, at this stage, HF patients are jointly cared for by their GP, cardiologist and HF specialist nurse. This enables patients to be assessed for the full range of treatment options available.

The recent PARADIGM-HF randomised controlled trial provided overwhelming evidence for a substantial mortality benefit of the angiotensin-neprilysin inhibitor (ARNI) sacubitril/valsartan over the ACEI enalapril.[6] ARNIs, a novel class of drug, combine an ARB (valsartan) and a neprilysin inhibitor (sacubitril) that inhibits breakdown of endogenous natriuretic peptides. In the PARADIGM-HF trial, which included 8,442 patients with NYHA class II-IV HF and a left ventricular ejection fraction of ≤ 40%, sacubitril/valsartan produced a highly statistically significant 20% reduction in the primary outcome of cardiovascular death or HF hospitalisation and a 16% reduction in all cause mortality.

An important point to note is that all patients in this study were on ACEI/ARB at baseline, and therefore current recommendations are that patients should have tried an ACEI/ARB first and have this uptitrated to the maximal tolerated dose before being switched to an ARNI if they remain symptomatic. Most evidence for use of ARNIs is in the outpatient setting, however there are ongoing trials examining the safety of initiating ARNIs in recently hospitalised patients.[7]

Other medications which may be used include ivabradine (in patients in sinus rhythm with heart rate ≥ 75 bpm), digoxin (in patients in sinus rhythm) and the combination of hydralazine and isosorbide dinitrate. However, the evidence base for these therapies is less strong and these drugs should be initiated by specialists.

Device therapy

Another approach that may be considered by the specialist after initial treatment is device therapy. In appropriate patients with HFrEF who continue to have reduced ejection fraction after maximal uptitration of HF therapy, implantable cardioverter defibrillators (ICD) may be considered for primary prevention of sudden cardiac death. These devices have been shown to reduce mortality in HFrEF patients.

Additionally, in those patients with left bundle branch block (LBBB) and a broad QRS duration (typically above 120 ms), specialists may consider implantation of a cardiac resynchronisation therapy device (CRT), see figure 1, p21.

It is now established that the most reliable way to decide on whether a patient is suitable for CRT is based on QRS duration with classical LBBB. The CRT non-responder rate in the early clinical trials was around 30%, however with improved techniques, advanced device programming and better patient selection (for example, those with QRS

duration >130 ms), non-responder rates in modern clinical practice are probably less than this.[8] Although NICE recommends considering CRT therapy in patients with LBBB and a QRSd above 120 ms the authors would usually reserve CRT therapy for patients with a QRS duration above 130 ms.[9]

These devices are designed to reduce the dyssynchrony seen in LBBB when the septum and left ventricular free wall do not contract simultaneously by pacing both the right ventricle and left ventricle (via the coronary sinus) at the same time, and thus improve symptoms. They may be combined with a defibrillator (CRT-D) or simply provide bi-ventricular pacing alone (CRT-P). Patients with LBBB and very broad QRS durations (>150 ms) typically gain the most benefit, which can take up to six months to manifest. Patients with right bundle branch block or narrower QRS durations are less likely to benefit from CRT implantation.

Beyond device implantation, specialists may consider advanced therapies such as ventricular assist devices or heart transplantation, if appropriate, in carefully selected patients.

Heart failure with preserved ejection fraction

In contrast with HFrEF, there are very few evidence-based drug therapies for HFpEF. The main therapeutic approach for patients with HFpEF involves symptom control and relief of congestion with loop diuretics, and treatment of comorbidities such as hypertension and atrial fibrillation.

There is limited evidence for the use of spironolactone from the Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist (TOPCAT) trial of spironolactone vs placebo in HFpEF. This study did report a reduction in HF hospitalisation with spironolactone but no benefit on the composite primary outcome of mortality, aborted sudden cardiac death or HF hospitalisation.[10] Both treatment and prevention of HFpEF remain significant unmet needs and intense areas of research.

FUTURE TREATMENTS

There are several novel approaches to treatment of HF being studied in large clinical trials. One potentially promising class of therapy is the sodium-glucose co-transporter 2 (SGLT2) inhibitors, empagliflozin, dapagliflozin and canagliflozin. These medications are licensed for use in patients with type 2 diabetes, and all three large randomised controlled outcome trials of SGLT2 inhibitors demonstrated significant benefits on cardiovascular outcome compared with placebo.[11] The majority of this benefit was driven by a reduction in HF hospitalisation of around 30%.

SGLT2 inhibitors are now recommended as add-on therapy to metformin in patients with type 2 diabetes and high risk of HF. However, importantly, the majority of patients in these trials did not have HF at baseline, and the type of HF was not reported, so their use as treatment in patients with established HF is still not fully defined.

In order to fill this evidence gap, SGLT2 inhibitors are also now being studied in several large outcome trials involving patients with HFrEF and HFpEF, with or without diabetes (HFrEF: DAPA-HF, NCT03036124, EMPEROR-Reduced, NCT03057977; HFpEF: DELIVER, NCT03619213, EMPEROR-Preserved NCT03057951). These trials are due to report in the next few years.

Another approach that is being tested »

Table 3

Typical medications used in heart failure, target doses and common side effects

	Starting dose	Target dose	Common side effects of drug class
ACE inhibitors			
Ramipril	2.5 mg od	5 mg bd (or 10 mg od)	Renal impairment, hyperkalaemia, hypotension
Enalapril	2.5 mg bd	10-20 mg bd	
Captopril	6.25 mg tds	50 mg tds	
Perindopril	2 mg od	4 mg od	
Lisinopril	2.5 mg od	20 mg od	
Angiotensin receptor blockers			
Valsartan	40 mg bd	160 mg bd	Renal impairment, hyperkalaemia, hypotension
Losartan	50 mg bd	150 mg bd	
Candesartan	4 mg od	32 mg od	
Beta-blockers			
Bisoprolol	1.25 mg od	10 mg od	Hypotension, fatigue, bradycardia
Metoprolol	12.5 mg od	200 mg od	
Carvedilol	3.125 mg bd	25 mg bd	
Mineralocorticoid receptor antagonists			
Spironolactone	25 mg od	50 mg od	Renal impairment, hyperkalaemia, hypotension, gynaecomastia (spironolactone only)
Eplerenone	25 mg od	50 mg od	
Angiotensin receptor neprilysin inhibitors			
Sacubitril/valsartan	24 mg/26 mg bd	97 mg/103 mg bd	Renal impairment, hyperkalaemia, hypotension
If channel inhibitors			
Ivabradine	5 mg bd	7.5 mg bd	Bradycardia, atrial fibrillation

key points

SELECTED BY

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Although patients can present with non-specific symptoms and minimal clinical signs, generally, in the community, patients with heart failure (HF) present with symptoms of dyspnoea or fluid retention. In order to confirm (or refute) the diagnosis, NICE recommends natriuretic peptide testing (ideally N-terminal pro B-type natriuretic peptide; NT-proBNP) in all patients with suspected HF. An NT-proBNP level > 2,000 ng/L is highly suggestive of HF and NICE recommends echocardiography and specialist review within 2 weeks. Conversely, an NT-proBNP level < 400 ng/L suggests that a diagnosis of HF is unlikely. Patients with an NT-proBNP of 400-2,000 ng/L should have echocardiography and specialist assessment within 6 weeks.

As well as echocardiography, an ECG should also be performed at baseline. Other basic tests such as chest X-ray, full blood count, renal, liver and thyroid function, lipids and glycosylated haemoglobin should also be carried out. Those with asymptomatic left ventricular dysfunction are also at risk of developing symptomatic HF and should be treated in a similar manner to symptomatic patients.

Heart failure with preserved ejection fraction (HFpEF) patients typically have risk factors such as hypertension, diabetes or obesity. The diagnosis of HFpEF is confirmed by clinical symptoms and signs of HF in conjunction with elevated natriuretic peptides and, importantly, the presence of echocardiographic structural abnormalities such as left ventricular hypertrophy or left atrial dilatation.

The cornerstone of pharmacological treatment for heart failure with reduced ejection fraction (HFrEF) involves initiation of renin-angiotensin aldosterone blockade with ACEI or ARB, and beta-blockers, with the addition of mineralocorticoid receptor antagonists if patients remain symptomatic with a reduced ejection fraction. The PARADIGM-HF randomised controlled trial provided overwhelming evidence of a substantial mortality benefit of the angiotensin-neprilysin inhibitor (ARNI) sacubitril/valsartan over the ACEI enalapril. In contrast with HFrEF there are very few evidence-based drug therapies for HFpEF. The main therapeutic approach for patients with HFpEF involves symptom control and relief of congestion with loop diuretics, and treatment of comorbidities such as hypertension and atrial fibrillation.

In appropriate patients with HFrEF who continue to have reduced ejection fraction after maximal uptitration of HF therapy, implantable cardioverter-defibrillators may be considered for primary prevention of sudden cardiac death. Additionally, in those patients with left bundle branch block and a broad QRS duration (typically above 120 ms), specialists may consider implantation of a cardiac resynchronisation therapy device.

HF patients should be offered a personalised, exercise- based cardiac rehabilitation programme, assuming their condition is stable. This programme should also include a psychological and education component.

for patients with HF is intravenous iron supplementation. Iron deficiency, with or without anaemia, is present in up to 50% of HF patients. Oral iron therapy tends to be poorly tolerated. However, several small studies have suggested improvements in symptoms, exercise capacity and quality of life with intravenous iron given to HF patients (irrespective of renal function), which tends to be better tolerated.[12] Several large outcome trials are taking place worldwide, including the IRONMAN study in the UK (NCT02642562), which will provide evidence as to whether intravenous iron replacement is beneficial.

MONITORING AND FOLLOW-UP

Beyond pharmacological and device treatments, the mainstay of care of chronic HF patients is long-term follow-up in order to identify potential decompensations at an early stage. Many units now have HF specialist nurses who work in conjunction with cardiologists and GPs to adjust and uptitrate treatments, provide advice and support to patients and a link to help coordinate care. The benefits of HF specialist nurses have been shown in clinical trials.

There is also increasing evidence that cardiac rehabilitation, more commonly offered to patients following myocardial infarction, may also be of benefit in HF.[13] Current recommendations from NICE are that HF patients should be offered a 'personalised, exercise-based cardiac rehabilitation programme,' assuming their condition is stable. This programme should also include a psychological and education component, and may be provided at the hospital, in the community or at home. Depression is common in HF patients (up to 40%) and is associated with poor prognosis.[14] Standard depression screening tools can be used in HF patients. Selective serotonin reuptake inhibitors are generally safe in HF patients, though randomised placebo-controlled trials of sertraline and escitalopram did not show any significant reduction in symptoms of depression. Tricyclic antidepressants should be avoided due to the risks of worsening HF and arrhythmia.

HF patients require regular monitoring dependent on symptoms and disease course. In the early phase after diagnosis, or after a decompensation, patients may require review every 1-2 weeks in order to uptitrate medications, assess clinical response and monitor for side effects such as hypotension, hyperkalaemia and renal impairment. In the more stable, chronic phase, NICE recommends that patients will still require monitoring every six months, which may be in the primary or secondary care setting, to ensure that they are still on appropriate therapy and do not require any adjustments. Lifestyle advice is also important, with support for smoking cessation and addressing alcohol misuse, as well as dietary advice. Vaccination for influenza and pneumococcus should also be offered.

As a minimum during review, monitoring of blood pressure and renal function as well as assessment of symptoms should be carried out. Changes to HF therapies may be made due to intercurrent illness, for example acute kidney injury or gastrointestinal illness leading to reduction or cessation of ACEI/ARBs; it is important that following this, if appropriate, HF therapies are reinstated. Although there is increasing recognition of acute kidney injury, the prognostic importance of HF medications cannot be understated, and we would recommend that these drugs are not stopped, even for a short time, unless absolutely necessary, and potentially after discussion with a specialist. The British Society for Heart Failure recently published useful guidance on sick day rules (www.bsh.org.uk/files/download.php?m=documents&f=160323110309-Acutekidneyinjuryandsickdayrules.docx).

CONCLUSION

HF is increasingly prevalent, and despite the multitude of new treatments available, HF patients remain at substantial risk of mortality and morbidity if not optimally treated. Key to this is multidisciplinary teamwork including the GP and the HF specialist in order to optimise patient outcomes.

Competing interests: None

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Useful information

Heart failure guidelines
NICE NG106
www.nice.org.uk/guidance/ng106

SIGN 147
www.sign.ac.uk/sign-147-management-of-chronic-heart-failure.html

European Society of Cardiology
https://academic.oup.com/eurheartj/article/37/27/2129/1748921#109987048

Professional bodies
British Society for Heart Failure
www.bsh.org.uk/

Heart Failure Association of the European Society of Cardiology
https://www.escardio.org/Sub-specialty-communities/Heart-Failure-Association-of-the-ESC-(HFA)

Patient groups
The Pumping Marvellous Foundation
https://pumpingmarvellous.org/

Cardiomyopathy UK
https://www.cardiomyopathy.org/

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