Contemporary therapies for chronic heart failure with reduced ejection fraction

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Heart failure with reduced ejection fraction (HFrEF) is common, and without optimal guideline-mandated medical therapy, is disabling and fatal. As trials discover effective additional HFrEF therapies, it is essential that all healthcare practitioners develop competence in treating these patients optimally. This narrative review discusses the approach to the contemporary medical management of HFrEF.

Keywords: heart failure with reduced ejection fraction, optimal guideline-mandated therapy

Introduction

Heart failure (HF) is a clinical syndrome that reflects the heart’s inability to enable a person to tolerate activity without feeling short of breath, tired, or experience palpitations. There are numerous causes of heart failure. Cardiac causes include those involving the pericardium, epicardial coronary arteries, myocardium, the valves and endocardium. Extra-cardiac causes precipitate the clinical heart failure syndrome in an individual with existing structural and/or functional cardiac abnormalities. These causes may be related to thyrotoxicosis, severe anaemia and so on.1 This review article refers to HF caused by myocardial weakness, defined as HF with reduced ejection fraction (HFrEF), i.e. a left ventricular (LV) ejection fraction (LVEF) of less than 40%.

The principles of management of HFrEF include recognising the syndrome, establishing an aetiology and correcting it, as well as excluding a precipitating factor and treating it. An example of this can be HFrEF diagnosed by symptoms and the classic physical signs of a sinus tachycardia, a displaced LV apex beat with the patient lying in the left lateral position and an audible left-sided S3 gallop or as described: a Kentucky gallop (Ken [S1] Tuc [S2] Ky [S3]).2 This may be due to significant underlying coronary artery disease (aetiology) but precipitated by new-onset atrial fibrillation (AF). Once the aetiology and precipitating factor have received the required attention, the following principles apply to the general management of HFrEF, usually irrespective of cause.3

The first role for the treating physician and clinical nurse (known as the therapist) is to cause no harm. Offending agents such as the nonsteroidal anti-inflammatory drugs (NSAIDs) or COX-2 inhibitors, first-generation calcium antagonists – verapamil and diltiazem, thiazolidinediones (glitazones) – pioglitazone, pregabalin (Lyrica®) to name a few, need to be identified in a patient’s chronic medication list and stopped if possible.4,8

Following on this, the treating physician must then make the patient feel better. HFrEF has a significant impact on the patient’s quality of life (QOL).2 Try remembering the last time you ran upstairs and arrived at the top, panting, palpitating and dyspnoeic – this is how these patients feel while doing menial tasks. It is crucial to emphasise that initially these patients must be rested, so-called “house arrest” and taken out of the workplace to restore fluid intake control, improve renal perfusion and thereby diuresis and to allow gradual up-titration of optimal guideline-directed medical therapy (OGDMT). This also allows the patient and their family to come to terms with what is often a crushing blow diagnosis.

Achieving maximal doses of OGDMT is crucial for the patient’s long-term prognosis.1 The period of house arrest (no socialising, no shopping, no entertaining, no alcohol, but not to lie in bed) is also to be used to acquaint the patient with their “new friends” – the multiple packets of new medication, as HFrEF by its very nature is a polypharmacy condition. The therapist must identify each new medication, explain the syndrome of HF to the patient and discuss the LV remodelling and neurohormonal activation in simple terms and indicate how each medication described relieves the situation. This insight is crucial for the patient, as HFrEF is a chronic condition, whose success relies on a strong understanding by the patient, a good therapist-patient rapport, and hence this translates into the required adherence to fluid and activity restriction advice and compliance with the prescribed therapy. This aspect of HFrEF treatment cannot be over emphasised.10,11

Advances in cardiac imaging for heart failure diagnosis

Cardiac magnetic resonance (CMR) imaging is currently the gold standard for the structural assessment of the heart. Its superiority is evident in the assessment of the right ventricle and in patients with poor transthoracic echocardiographic windows.12 CMR imaging is also able to assess for the presence of myocardial fibrosis using late gadolinium enhancement (LGE) and T1 mapping to better define HF aetiologies such as sarcoidosis, amyloid infiltration, haemochromatosis, viral myocarditis and diffuse fibrosis.13 CMR imaging has also been demonstrated to detect myocardial ischaemia and viability in patients with HF and coronary artery disease.14 Cardiac computed tomography
angiography is another non-invasive useful ancillary aid to reliably exclude significant underlying coronary artery disease (CAD). This study is best indicated in patients with HFrEF with low intermediate pre-test probability for CAD.15,16

Heart failure with reduced ejection fraction medical management

Principles of diuretic therapy

Loop diuretics (furosemide, torasemide, bumetanide) are very effective when combined with fluid intake restriction (< 1.2–1.5 litres per 24 hours maximum) to restore fluid balance. A patient with warm peripheries, pedal oedema, an adequate blood pressure (> 110 mmHg systolic) without a narrow pulse pressure, may be safely managed as an outpatient on oral diuretic therapy. However, patients with cold peripheries, pedal oedema, hypotensive (< 100 mmHg) with a narrow pulse pressure (< 20 mmHg), often require admission and may require intravenous dobutamine together with an intravenous diuretic.17

The principles of diuretic therapy include:
1. Daily weight monitoring of the patient, and responded to appropriately.
2. Frequency of dose – the total diuretic dose is divided into 12 or 8 hourly intervals instead of front-loading a high once-a-day dose to avoid rebound sodium and water reabsorption by the kidney tubules.
3. Consideration to introduce a second class of diuretic agent, usually a thiazide, for a synergistic approach to diuresis, instead of maximising to a high dose of loop diuretic and ignoring the distal convoluting tubule’s compensatory hypertrophy and increased sodium reabsorption.
4. Eventual minimising of oral diuretic dose and maximising of OGDMT, recognising that hypotension, dizziness and renal dysfunction commonly relate to over diuresis.
5. There is controversy about salt restriction in HFrEF therapy. If the patient does not have hypertension, do not restrict salt, as hyponatraemia carries a poor prognosis and limits up-titration of OGDMT.
6. At present, there is no evidence that the type of loop diuretic chosen favours a different prognosis – potencies differ among the agents, but the diuretic effect is similar.

The building blocks of HFrEF therapy

The development of treatments that improve survival and reduce morbidity in patients with HFrEF is a wonderful therapeutic success story. The benefits of the majority of these treatments are achieved simply by using a pen, i.e. a correctly written

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**Figure 1:** Treatment algorithm for symptomatic patients with heart failure with a reduced ejection fraction. Blue indicates a class I recommendation (evidence and/or general agreement that the treatment is beneficial, useful or effective, i.e. treatment is indicated); yellow indicates a class IIa recommendation (weight of evidence or opinion is in favour of usefulness or efficacy, i.e. treatment should be considered)

ACE-I – angiotensin-converting enzyme inhibitor, ARB – angiotensin receptor blocker, ARNI – angiotensin receptor blocker neprilysin inhibitor, CRT – cardiac resynchronisation therapy, P – pacing, D – defibrillator, HFrEF – heart failure with a reduced ejection fraction, H-ISDN – hydralazine and isosorbide dinitrate, HR – heart rate, LVAD – left ventricular assist device, LVEF – left ventricular ejection fraction, MRA – mineralocorticoid receptor antagonist, SGLT2i – sodium-glucose co-transporter 2 inhibitor

* Although diuretics improve acute symptoms of heart failure, there are no randomised controlled trials that demonstrate a long-term mortality benefit

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**Appendix:**

- ACE-I/ARB: Angiotensin-converting enzyme inhibitors or angiotensin receptor blockers
- Beta blocker: Beta blockers
- MRA: Mineralocorticoid receptor antagonists
- ARNI: Angiotensin receptor blocker neprilysin inhibitor
- SGLT2i: Sodium-glucose co-transporter 2 inhibitors
- CRT-P/D: Cardiac resynchronisation therapy, pacing, and defibrillation
- IVABRADINE: Ivabradine
- H-ISDN: Hydralazine and isosorbide dinitrate
- LVAD or heart transplant: Left ventricular assist device or heart transplant
- Intravenous iron: Intravenous iron
- Digoxin: Digoxin
OGDMT for HFrEF prescription has a significant impact on the life of a HFrEF patient (Figure 1).

Often, together with diuretic therapy, the angiotensin-converting enzyme inhibitor (ACEI) preferably, or the angiotensin receptor blocker (ARB), if the patient is intolerant of an ACEI, is started. The ACEI drugs that have the best data include enalapril and ramipril in BD doses, while lisinopril and trandolapril are prescribed in daily doses. Together with a beta blocker, they are recommended for symptomatic patients to reduce the risk of HF hospitalisation and death. These two classes of drug are often started simultaneously, but one can start with either first. The orally available beta blockers in South Africa (SA) include the non-selective twice daily carvedilol, and the β₁-selective once daily bisoprolol or nebivolol and the twice daily metoprolol succinate. It is imperative that the therapist knows and strives for the recommended maximum dosages that can be tolerated by the patient (Table I). Acceptable ARB drugs to be used in HFrEF include daily candesartan or losartan, or twice daily valsartan.

The patient’s renal function and electrolytes are initially followed every 5–7 days with up-titration of these drugs, especially with the introduction of the mineralocorticoid receptor antagonist (MRA), spironolactone or eplerenone – Inspra®. An ARB is usually never used in addition to ACEI and a MRA. This combination of therapy is not recommended as it increases the risk of renal dysfunction and hyperkalaemia. Gynaecomastia is an important and frequent side-effect of spironolactone, often starting with nipple tenderness and pain before the irreversible increase in breast tissue. Prompt recognition of this event is crucial. No breast biopsy is required, and eplerenone substituted in its place prevents this complication. When diagnosed late, the increased breast tissue often remains. If a patient cannot afford or the funder incorrectly refuses to cover eplerenone, then an ARB can be added to the ACEI in this one and only circumstance. The MRA is recommended for patients with HFrEF who remain symptomatic despite treatment with an ACEI + beta blocker. Oral potassium replacement often needs to be stopped on the introduction of an MRA and caution should be exercised when MRAs are used in patients with impaired renal function and in those with serum potassium levels > 5.0 mmol/l.

**Advances in HFrEF therapy**

**Angiotensin receptor blocker and neprilysin inhibitor (ARNI)**

The combination of an ARB (valsartan) and a neprilysin inhibitor (sacubitril) has shown to be superior to enalapril in a symptomatic HFrEF trial. Entresto in three different doses (50 mg BD equivalent to valsartan 40 mg BD, 100 mg BD equivalent to valsartan 80 mg BD, 200 mg BD equivalent to valsartan 160 mg BD plus increasing doses of sacubitril) is indicated in the current guidelines as an alternative to an ACEI to further reduce the risk of HF hospitalisation and death in patients with HFrEF who are still symptomatic despite treatment with an ACEI, beta blocker and MRA (known as triple therapy). Increasing evidence and contemporary use of the ARNI seems to support earlier use than is currently suggested, and as HFrEF carries a significant mortality (50% five-year mortality on average), using an agent that is superior to an ACEI is to be encouraged. The cost of the new therapy is what prevents its widespread and earlier use. When switching from an ACEI to an ARNI, withholding the ACEI for 36 hours prior to the introduction of the ARNI is important, to avoid the chance of angioneurotic oedema. Administering an ARNI to patients with a systolic blood pressure (SBP) < 95 mmHg must be done with extreme caution.

**Table I: Dosages of disease-modifying drugs for patients with heart failure with a reduced ejection fraction**

| Class            | Drug               | Initial dose (mg) | Target dose (mg) |
|------------------|--------------------|-------------------|------------------|
| Loop diuretics   | Furosemide         | 20–40             | 40–240 total daily dose |
|                  | Bumetanide         | 0.5–1.0           | 1–5 total daily dose |
|                  | Torasemide         | 5–10              | 10–20 total daily dose |
| ACE inhibitors   | Enalapril          | 2.5 BD            | 10 BD            |
|                  | Lisinopril         | 2.5–5.0 OD        | 20 OD            |
|                  | Ramipril           | 2.5 BD            | 5 BD             |
|                  | Trandolapril       | 0.5 OD            | 4 OD             |
| ARB              | Valsartan          | 40 BD             | 160 BD           |
|                  | Losartan           | 50 OD             | 150 OD           |
| Beta blockers    | Bisoprolol         | 1.25 OD           | 10 OD            |
|                  | Carvedilol         | 3.125 BD          | 50 BD            |
|                  | Metoprolol succinate | 12.5–25 OD     | 200 OD           |
|                  | Nebivolol          | 1.25 OD           | 10 OD            |
| MRA              | Eplerenone         | 25 OD             | 50 OD            |
|                  | Spironalactone     | 25 OD             | 50 OD            |
| ARNI             | Sacubitril/valsartan | 49/51 BD    | 97/103 BD        |
| If channel blocker | Ibrabradine       | 5 BD              | 7.5 BD           |
| SGL-2 inhibitors | Empagliflozin      | 10 OD             | 25 OD            |
|                  | Dapagliflozin      | 10 OD             | 10 OD            |

ACE – angiotensin-converting enzyme, ARB – angiotensin receptor blocker, ARNI – angiotensin receptor neprilysin inhibitor, BD – twice daily, MRA – mineralocorticoid receptor antagonist, OD – once daily, SGL – sodium-glucose co-transporter, TID – three times a day
caution and close assessment of the blood pressure. During the up-titration, renal function and electrolytes must also be monitored.\textsuperscript{28,29}

**Sodium-glucose co-transporter 2 (SGLT2) inhibitors**

SGLT2 inhibitors (empagliflozin – Jardiance\textsuperscript{a}, dapagliflozin – Farxiga\textsuperscript{a}) which act as glycosuric agents that reduce HBA1c, protect against renal function decline, induce weight loss and also prevent the development of HF in patients with type 2 diabetes (T2D), with either underlying established vascular disease or in the presence of other cardiovascular risk factors. Dapagliflozin (10 mg) can also be used to treat symptomatic patients with HFrEF (and an eGFR > 30 ml/min/1.73 m\textsuperscript{2}; SBP > 95 mmHg), in addition to an ACEi or ARB or ARNI + beta blocker + MRA, with or without diabetes.\textsuperscript{30,31} Total mortality, cardiovascular death, HF hospitalisation or urgent HF visits are significantly re-dced by dapagliflozin, and patients experience a significantly improved QOL by the end of the first month of therapy. Updated HF guidelines are eagerly awaited to position this well-tolerated, non-renin related, non-hypoglycaemia inducing HFrEF therapy in non-diabetics.\textsuperscript{30}

**If channel inhibitor**

Ivabradine (Coralan\textsuperscript{a}) should be considered in symptomatic HFrEF patients in sinus rhythm, who despite maximally tolerated beta blocker doses (carvedilol 50 mg BD, bisoprolol 10 mg daily) and on background ACEi or ARB/MRA have a resting heart rate of more than > 70 beats/minute.\textsuperscript{32} If a similar patient cannot tolerate a beta blocker, then ivabradine (5 mg BD up to 7.5 mg BD) can be used alone. This drug predominately reduces HF hospitalisations.

**Additional useful pharmacological treatments**

**Hydralazine and isosorbide dinitrate (mononitrate)**

This oral combination (hydralazine up to 75 mg TDS, isosorbide dinitrate up to 40 mg TDS or the more available isosorbide mononitrate 40 mg BD), although not widely used, should be considered in addition, in all patients with symptomatic HFrEF despite the usual triple background therapy. It has been found to be particularly effective in self-identified black patients. The combination reduces HF hospitalisation and death. It is also particularly useful in patients where the usual triple therapy is not tolerated or is contraindicated. This is particularly seen in the HFrEF patient with hypotension, significant renal dysfunction, and poor perfusion.\textsuperscript{33} This combination then acts as a bridge to place the patient on oral therapies after a period of intravenous support, and once there is sustained improvement, the usual staged approach of introducing the triple therapy can be followed, with possible weaning of the hydralazine and nitrate combination.

**Digoxin**

The main role for digoxin (to reduce both all-cause and HF hospitalisation) in HFrEF therapy is in the symptomatic patient with AF, who has a rapid ventricular resting rate of more than 100 beats/minute. It may also be used in patients in sinus rhythm who remain symptomatic despite triple therapy.\textsuperscript{34} Physicians should beware of toxicity in the patient with renal dysfunction, low body weight, the elderly and females. Therapeutic levels should be approximately 0.9 ng/ml. Hypokalaemia has also been reported to increase digoxin’s arrhythmic potential. Therefore, patients treated with digoxin should regularly have their electrolytes monitored and appropriately corrected.

**Intravenous iron**

Iron deficiency, with or without anaemia, is common in HF and is associated with a poor prognosis.\textsuperscript{35} Intravenous iron therapy has been found to reduce HF hospitalisation rates, improve HF symptoms, exercise capacity and QOL.\textsuperscript{36} HF patients diagnosed with iron deficiency (serum ferritin < 100 ug/L or ferritin between 100 and 299 ug/L with a transferrin saturation of < 20%) should be offered intravenous iron replacement to improve their functional capacity, HF symptoms and QOL.

**Heart failure device therapies**

**Cardiac resynchronisation therapy (CRT)**

CRT in symptomatic HFrEF patients on OGDMT who are in sinus rhythm, usually involves the implanting of three pacing leads via an axillary or subclavian vein. These leads are positioned in the right atrium, right ventricle and via the coronary sinus, which drains into the right atrium and into a lateral cardiac vein overlying the lateral wall of the left ventricle (CRT-P). The best responders to CRT-P appear to be those with a LVEF < 35\%, a left bundle branch block (LBBB), QRS morphology with a QRS duration as measured on the electrocardiogram of > 150 ms.\textsuperscript{37} Other QRS morphologies can be acceptable if the QRS duration is prolonged and not < 130 ms. This device improves symptoms, survival and reduces hospitalisations.

**Implantable cardioverter-defibrillator (ICD)**

Sudden cardiac death (SCD) is a common feature in chronic HF. The ICD treats significant bradyarrhythmia via demand pacing and manages tachyarrhythmia by converting the sporadic episode of ventricular tachycardia through overdrive pacing, or, as with ventricular fibrillation, by an internally delivered shock of 20–30 joules of energy. All HFrEF patients, who would survive > 1 year and had survived a SCD event should receive an ICD (known as secondary prevention).\textsuperscript{38} An ICD may involve one right ventricular lead (single-chamber ICD) or a right atrial and right ventricular lead (dual-chamber ICD).

In a patient who has never experienced a SCD event (primary prevention), an ICD is indicated to reduce all-cause mortality in symptomatic HFrEF, irrespective of aetiology, despite > 3 months of OGDMT, and who is > 40 days post myocardial infarction.\textsuperscript{39} An ICD is also often combined with a CRT (CRT-D). There is nuanced decision making with regards to deciding on a CRT-P, or a CRT-D or ICD alone, and each patient needs to be individually assessed. Pacemaker sepsis, infective endocarditis, inappropriate “shocks”, and CRT-P non-responders are just some of the challenges one needs to navigate when treating these patients.
Atrial fibrillation (AF)

AF is the most common arrhythmia encountered in HF clinical practice. More than a third of patients randomised into the PARADIGM-HF trial, had AF. AF, especially with ventricular rates > 150 beats/min may cause HFrEF (tachy-cardiomyopathy). Patients with AF and HF are at an increased risk of cardioembolic events (particularly stroke) and more HF-related morbidity and mortality. Briefly, AF treatment strategies include anticoagulation, electrical cardioversion, amiodarone therapy and beta blockers in a rhythm control strategy. Anticoagulation, digoxin/ beta blockers or AV node ablation and CRT-P implantation are considered in those where a rate control strategy is chosen. An invasive procedure, involving crossing the interatrial septum from the right atrium and isolating the four pulmonary veins that drain into the left atrium (pulmonary vein isolation – PVI) with a catheter (cryoablation or radiofrequency ablation) has been shown to be superior to OGDMT in symptomatic HFrEF + AF patients, all of whom had an ICD. This procedure reduced mortality and HF hospitalisation and more patients remained in sinus rhythm at five years.40,41 This provides an additional way to manage HFrEF complicated by AF.

Conclusion

Physicians treating patients with HFrEF need to recognise the clinical syndrome of HF while simultaneously investigating the most likely cause for HF and excluding common precipitating factors. They also need to educate, rehabilitate and treat the HFrEF patient according to well-established guidelines, in order to maximise the survival benefit conferred by these therapies. Furthermore, HF patients need close follow-up and supervision to up-titrate current therapies to target dosages as well as adopting new drug/device developments.

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References

1. Ponikowski P, Voors AA, Anker SD, et al. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) developed with the special contribution of the Heart Failure Association (HFA) of the ESC. Eur Heart J. 2016;37(27):2129-200. https://doi.org/10.1093/eurheartj/ehw128. PMID: 27206619.

2. Davie AP, Francis CM, Caruana L, Sutherland GR, McMurray JJ. Assessing diagnosis in heart failure: which features are any use? QJM. 1997;90(5):335-9. https://doi.org/10.1093/qjmed/90.5.335. PMID: 920566.

3. Fonseca C. Diagnosis of heart failure in primary care. Heart Fail Rev. 2006;11(2):95-107. https://doi.org/10.1007/s10741-006-9481-0. PMID: 16937029.

4. Eschenhagen T, Force T, Ewer MS, et al. Cardiovascular side effects of cancer therapies: a position statement from the Heart Failure Association of the European Society of Cardiology. Eur J Heart Fail. 2011;13(1):1-10. https://doi.org/10.1093/europx/hfr213. PMID: 21169385.

5. Hernandez AV, Usmani A, Rajamaniakam A, Hoheet A, Thiazolidinediones and risk of heart failure in patients with or at high risk of type 2 diabetes mellitus: a meta-analysis and meta-regression analysis of placebo-controlled randomized clinical trials. American Journal of Cardiovascular Drugs: drugs, devices, and other interventions. 2011;11(12):15-28. https://doi.org/10.2156/11587580-000000000-00000. PMID: 21294599.

6. Komajda M, McMurray JJ, Beck-Nielsen H, et al. Heart failure events with rosiglitazone in type 2 diabetes: data from the RECORD clinical trial. Eur Heart J. 2010;31(7):824-31. https://doi.org/10.1093/eurheartj/ehp604. PMID: 20118714.

7. Huerta C, Varas-Lorenzo C, Castellague J, Garcia Rodriguez LA. Non-steroidal anti-inflammatory drugs and risk of first hospital admission for heart failure in the general population. Heart. 2006;92(11):1610-5. https://doi.org/10.1136/hrt.2005.082388. PMID: 16717069. PMCID: PMC1861219.

8. Packer M, O’Connor CM, Galioli J, et al. Effect of amiodipine on morbidity and mortality in severe chronic heart failure. Prospective Randomized Amiodipine Survival Evaluation Study Group. N Engl J Med. 1996;335(15):1107-14. https://doi.org/10.1056/nejm199610103351504. PMID: 8813041.

9. Ambrosy AP, Fonarow GC, Butler J, et al. The global health and economic burden of hospitalizations for heart failure: lessons learned from hospitalized heart failure registries. J Am Coll Cardiol.2014;63(12):1123-33. https://doi.org/10.1016/j.jacc.2014.02.015. PMID: 24491689.

10. Stewart S, Vandenbroek AJ, Pearson S, Horowitz JD. Prolonged beneficial effects of a home-based intervention on unplanned readmissions and mortality among patients with congestive heart failure. Arch Intern Med. 1999;159(3):257-61. https://doi.org/10.1001/archinte.159.3.257. PMID: 9985937.

11. Feltner C, Jones CD, Cene CW, et al. Transitional care interventions to prevent readmissions for persons with heart failure: a systematic review and meta-analysis. Ann Intern Med. 2014;160(11):774-84. https://doi.org/10.7326/m14-0083. PMID: 24862840.

12. Gonzalez JA, Kramer CM. Role of imaging techniques for diagnosis, prognosis and management of heart failure patients: cardiac magnetic resonance. Curr Heart Fail Rep. 2015;12(4):276-83. https://doi.org/10.1007/s11897-015-0261-9. PMID: 26041670. PMCID: PMC4496303.

13. Yoshida A, Ishibashi-Ueda H, Yamada N, et al. Direct comparison of the diagnostic capability of cardiac magnetic resonance and endomyocardial biopsy in patients with heart failure. Eur J Heart Fail. 2015;17(2):166-75. https://doi.org/10.1093/europmef/mfs206. PMID: 23329703.

14. Bonow RO, Carstelvecchio S, Panza JA, et al. Severity of remodeling, myocardial viability, and survival in ischemic LV dysfunction after surgical revascularization. JACC Cardiovasc Imaging. 2015;8(10):1121-9. https://doi.org/10.1016/j.jcmg.2015.03.013. PMID: 26363840.

15. Williams MC, Hunter A, Shah ASV, et al. Use of coronary computed tomographic angiography to guide management of patients with coronary disease. J Am Coll Cardiol. 2016;67(15):1759-68. https://doi.org/10.1016/j.jacc.2016.02.026. PMID: 27081014.

16. Cheng YY, Berman DS, Rozanski A, Dunning AM, et al. Performance of the 150/100 beats/min cut-off for defining different forms of heart failure: a meta-analysis and meta-regression analysis of placebo-controlled randomized clinical trials. American Journal of Cardiovascular Drugs: drugs, devices, and other interventions. 2011;11(12):15-28. https://doi.org/10.2156/11587580-000000000-00000. PMID: 21294599.

17. Cheng VY, Berman DS, Rozanski A, Dunning AM, et al. Performance of the 150/100 beats/min cut-off for defining different forms of heart failure: a meta-analysis and meta-regression analysis of placebo-controlled randomized clinical trials. American Journal of Cardiovascular Drugs: drugs, devices, and other interventions. 2011;11(12):15-28. https://doi.org/10.2156/11587580-000000000-00000. PMID: 21294599.
Contemporary therapies for chronic heart failure with reduced ejection fraction

17. Faris RF, Flather M, Purcell H, Poole-Wilson PA, Coats AJ. Diuretics for heart failure. Cochrane Database Syst Rev. 2012(2):CD003838. https://doi.org/10.1002/14651858.cd003838.pub3. PMID: 22336795.

18. Garg R, Yusuf S. Overview of randomized trials of angiotensin-converting enzyme inhibitors on mortality and morbidity in patients with heart failure. Collaborative Group on ACE Inhibitor Trials. JAMA. 1995;273(10):1450-6. PMID: 7654275.

19. Packer M, Coats AJ, Fowler MB, et al. Effect of carvedilol on survival in severe chronic heart failure. N Engl J Med. 2001;344(22):1651-8. https://doi.org/10.1056/nejmoa013474. PMID: 11907286.

20. Packer M, Fowler MB, Roecker EB, et al. Effect of carvedilol on the morbidity of patients with severe chronic heart failure: results of the carvedilol prospective randomized cumulative survival (COPERNICUS) study. Circulation. 2002;106(17):2194-9. https://doi.org/10.1161/01.CIR.0000035653.72855.LF. PMID: 12390947.

21. Flather MD, Shibata MC, Coats AJ, et al. Randomized trial to determine the effect of nebivolol on mortality and cardiovascular hospital admission in elderly patients with heart failure (SENIORS). Eur Heart J. 2005;26(3):215-25. https://doi.org/10.1093/eurheartj/ehi115. PMID: 15642700.

22. Granger CB, McMurray JJ, Yusuf S, et al. Effects of candesartan in patients with chronic heart failure and reduced left-ventricular systolic function intolerant to angiotensin-converting-enzyme inhibitors: the CHARM-Alternative trial. Lancet (London, England). 2003;362(9360):772-6. https://doi.org/10.1016/s0140-6736(03)14284-5. PMID: 13678870.

23. Zannad F, McMurray JJ, Krum H, et al. Eplerenone in patients with systolic heart failure and mild symptoms. N Engl J Med. 2011;364(1):11-21. https://doi.org/10.1056/nejmoa1009492. PMID: 21073363.

24. Pitt B, Zannad F, Remme WJ, et al. The effect of spironolactone on morbidity and mortality in patients with severe heart failure. Randomized Aldactone Evaluation Study Investigators. N Engl J Med. 1999;341(10):709-17. https://doi.org/10.1056/nejm199909023411001. PMID: 10471456.

25. McMurray JJ, Packer M, Desai AS, et al. Angiotensin-NEPrilisyn inhibition versus enalapril in heart failure. N Engl J Med. 2014;371(11):993-1004. https://doi.org/10.1056/nejmoa1409294. PMID: 25176015.

26. Volpe M, Rubattu S, Battistoni A. ARNi: A novel approach to counteract cardiovascular diseases. Int J Mol Sci. 2019;20(9). https://doi.org/10.3390/ijms20092092. PMID: 31035359.

27. Mozaffarian D, Benjamin EJ, Go AS, et al. Heart disease and stroke statistics--2015 update: a report from the American Heart Association. Circulation. 2015;131(4):e29-322. https://doi.org/10.1161/ciri.0000000000000152. PMID: 25520374.

28. Gori M, Volterrani M, Piepoli M, Senni M. Angiotensin receptor-neprilysin inhibitor (ARNI): Clinical studies on a new class of drugs. Int J Cardiol. 2016. https://doi.org/10.1016/j.ijcard.2016.06.083. PMID: 27378659.

29. Okumura N, Jhund PS, Gong J, et al. Importance of clinical worsening of heart failure treated in the outpatient setting: evidence from the prospective comparison of ARNI with ACEI to determine impact on global mortality and morbidity in heart failure trial (PARADIGM-HF). Circulation. 2016;133(23):2254-62. https://doi.org/10.1161/circulationaha.115.020729. PMID: 27143684.

30. McMurray JJV, Solomon SD, Inzucchi SE, et al. Dapagliflozin in patients with heart failure and reduced ejection fraction. N Engl J Med. 2019;381(21):1995-2008. https://doi.org/10.1056/nejmoa1911303. PMID: 31535829.

31. Zinman B, Wanner C, Lachin JM, et al. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. N Engl J Med. 2015;373(22):2117-28. https://doi.org/10.1056/nejmoa1504720. PMID: 26378978.

32. Swedberg K, Komajda M, Bohn M, et al. Ixabradine and outcomes in chronic heart failure (SHIFT): a randomized placebocontrolled study. Lancet (London, England). 2010;376(9744):875-85. https://doi.org/10.1016/j.1044-4469(10)61198-1. PMID: 20801500.

33. Taylor AL, Ziesche S, Yancy C, et al. Combination of isosorbide dinitrate and hydralazine in blacks with heart failure. N Engl J Med. 2004;351(20):2049-57. https://doi.org/10.1056/nejmoa042934. PMID: 15533851.

34. Digitalis Investigation Group. The effect of digoxin on mortality and morbidity in patients with heart failure. N Engl J Med. 1997;336(8):525-33. https://doi.org/10.1056/nejmoa199707203360801. PMID: 9360306.

35. Jankowska EA, Von Haehling S, Anker SD, Macdougall IC, Ponikowski P. Iron deficiency and heart failure: diagnostic dilemmas and therapeutic perspectives. Eur Heart J. 2013;34(11):816-29. https://doi.org/10.1093/eurheartj/ehs224. PMID: 23100285.

36. Jankowska EA, Tkaczyszyn M, Suchocki T, et al. Effects of intravenous iron therapy in iron-deficient patients with systolic heart failure: a meta-analysis of randomized controlled trials. Eur J Heart Fail. 2016;18(7):786-95. https://doi.org/10.1002/ejhf.2462. PMID: 26821594.

37. Clanden JG, Abraham WT, Linde C, et al. An individual patient meta-analysis of five randomized trials assessing the effects of cardiac resynchronization therapy on morbidity and mortality in patients with symptomatic heart failure. Eur Heart J. 2013;34(46):3547-56. https://doi.org/10.1093/eurheartj/eht290. PMID: 23900969.

38. Connelly SJ, Hallstrom AP, Cappato R, et al. Meta-analysis of the implantable cardioverter-defibrillator secondary prevention trials. AVID, CASH and CIDS studies. Antiarrhythmics vs implantable defibrillator study. Cardiac Arrest Study Hamburg. Canadian Implantable Defibrillator Study. Eur Heart J. 2000;21(24):2071-8. https://doi.org/10.1053/euhj.2000.2476. PMID: 11102258.

39. Moss AJ, Zareba W, Hall WJ, et al. Prophylactic implantation of a defibrillator in patients with myocardial infarction and reduced ejection fraction. N Engl J Med. 2002;346(12):877-83. https://doi.org/10.1056/nejmoa1911303. PMID: 31535829.

40. Vrachatis D, Deftereos S, Kekeris V, Tsoukala S, Giannopoulos G. Catheter ablation for atrial fibrillation in systolic heart failure patients: Stone by Stone, a CASTLE-AF Study Hamburg. Canadian Implantable Defibrillator Study. Eur Heart J. 2010;31(18):2042-51. https://doi.org/10.1093/eurheartj/ehq238. PMID: 19307047.