Heart, Lung and Circulation (2018) **27,** 1123–1208
1443-9506/04/$36.00
https://doi.org/10.1016/j.hlc.2018.06.1042

GUIDELINES

National Heart Foundation of Australia and Cardiac Society of Australia and New Zealand: Guidelines for the Prevention, Detection, and Management of Heart Failure in Australia 2018

Contents

1. Evidence-based Recommendations . . . 1128
2. Process for Developing the Guidelines . . . 1134
2.1. Conflicts of Interest Process . . . 1134
2.2. Development of Recommendations . . . 1135
3. Definition and Classification of Heart Failure . . . 1135
3.1. Epidemiology of Heart Failure . . . 1135
3.2. Definition . . . 1136
3.3. Classification . . . 1137
3.3.1. Heart Failure with Reduced Ejection Fraction . . . 1137
3.3.2. Heart Failure with Preserved Ejection Fraction . . . 1138
3.3.3. Ejection Fraction 40–50% . . . 1138
3.4. Terminology . . . 1139
3.5. Pathophysiology . . . 1139
3.5.1. Heart Failure with Reduced Ejection Fraction . . . 1139
3.5.2. Heart Failure with Preserved Ejection Fraction . . . 1139
4. Prevention of Heart Failure . . . 1142
4.1. Non-Pharmacological Prevention of Heart Failure . . . 1142
4.2. Pharmacological Prevention of Heart Failure . . . 1142
4.3. Screening for Preclinical Heart Failure . . . 1143
5. Diagnosis and Investigations . . . 1143
5.1. Dyspnoea . . . 1143
5.1.1. Causes of Dyspnoea . . . 1143
5.1.2. Dyspnoea Workup . . . 1143
5.1.3. Requirement for More Urgent Evaluation or Referral . . . 1143
5.2. Diagnostic Investigations for Heart Failure . . . 1143
5.2.1. Diagnosis of Heart Failure . . . 1143
5.2.1.1. 12-Lead electrocardiogram . . . 1143
5.2.1.2. Chest X-ray . . . 1145
5.2.1.3. B-type Natriuretic Peptide and N-terminal pro-B-type Natriuretic Peptide . . . 1145
5.2.1.4. Echocardiogram . . . 1145
5.2.1.5. Other imaging for diagnosis . . . 1146
5.2.2. Assessment of Aetiology . . . 1146
5.2.3. Risk Stratification and Prognosis . . . 1147
5.2.3.1. BNP and NT proBNP . . . 1147
5.2.3.2. Genetic Testing . . . 1147

5.2.3.3. CMR with LGE . . . 1148
5.2.4. Diagnostic Tests to Guide Therapy in Heart Failure . . . 1148
5.2.4.1. BNP and NT proBNP . . . 1148
6. Acute Heart Failure . . . 1149
6.1. Assessment . . . 1149
6.2. Oxygen Therapy in Acute Heart Failure . . . 1150
6.3. Opiate Therapy in Acute Heart Failure . . . 1151
6.4. Ventilatory Support in Acute Heart Failure . . . 1151
6.5. Diuretics in Acute Heart Failure . . . 1151
6.6. Vasodilator Therapy in Acute Heart Failure . . . 1152
6.7. Inotropic Therapy in Acute Heart Failure . . . 1153
6.8. Ultrafiltration and Haemodialysis in Acute Heart Failure . . . 1153
6.9. Mechanical Cardiac Support Devices in Acute Heart Failure . . . 1154
7. Pharmacological Management of Chronic Heart Failure . . . 1154
7.1. Heart Failure With Reduced Left Ventricular Ejection Fraction . . . 1154
7.1.1. Medications Recommended in All Patients with Heart Failure with Reduced Left Ventricular Ejection Fraction . . . 1155
7.1.1.1. Angiotensin Converting Enzyme Inhibitors . . . 1155
7.1.1.2. Beta Blockers . . . 1156
7.1.1.3. Mineralocorticoid Receptor Antagonists . . . 1157
7.1.2. Medications Recommended in Selected Patients with Heart Failure with Reduced Left Ventricular Ejection Fraction . . . 1158
7.1.2.1. Diuretics . . . 1158
7.1.2.2. Angiotensin Receptor Blockers . . . 1158
7.1.2.3. Angiotensin Receptor Neprilysin Inhibitor . . . 1159
7.1.2.4. Ivabradine . . . 1159
7.1.2.5. Hydralazine Plus Nitrates . . . 1160
7.1.2.6. Digoxin . . . 1160
7.1.2.7. Nutraceuticals . . . 1161
7.2. Heart Failure With Preserved Left Ventricular Ejection Fraction . . . 1161
8. Non-Pharmacological Management of Heart Failure . . . 1162
8.1. Systems of Care to Reduce Rehospitalisation . . . 1162
8.2. Models of Care to Improve Evidence-Based Practice . . . 1162
8.2.1. Multidisciplinary Heart Failure Disease Management Programs and Telemonitoring . . . 1162
8.2.2. Nurse-led Medication Titration Clinics . . . 1163
8.2.3. Non-pharmacological Heart Failure Management and Multimorbidity . . . 1164
8.2.3.1. Multimorbidity: Cognitive Impairment . . . 1164
8.3. Frequency of Follow-up . . . 1164
8.4. Self-management . . . 1165
8.5. Fluid Restriction and Daily Weighing . . . 1165
8.6. Sodium Intake . . . 1166
8.7. Exercise Training and Heart Failure . . . 1166
9. Devices, Surgery and Percutaneous Procedures . . . 1166
9.1. Cardiac Electronic Implantable Devices . . . 1166
9.1.1. Cardiac Resynchronisation Therapy . . . 1166
9.1.1.1. Cardiac Resynchronisation Therapy Efficacy and Qrs Morphology and Duration . . . 1167
9.1.1.2. Cardiac Resynchronisation Therapy Efficacy and Left Ventricular Ejection Fraction . . . 1167
9.1.1.3. Cardiac Resynchronisation Therapy Efficacy and Atrial Fibrillation . . . 1167
9.1.1.4. Other Predictors of Outcome . . . 1168
9.1.1.5. Cardiac Resynchronisation Therapy versus Right Ventricular Pacing . . . 1168
9.1.1.6. Cardiac Resynchronisation Therapy Defibrillator versus Cardiac Resynchronisation Therapy Pacemaker . . . 1168
9.1.2. Implantable Cardioverter Defibrillators . . . 1169
9.1.2.1. Programming and Type of Device . . . 1169
9.2. Pressure Monitoring Devices . . . 1169
9.3. Surgical Management of Heart Failure in Association With Ischaemic Heart Disease . . . 1170
9.4. Surgical or Percutaneous Management of Valvular Heart Disease in Association With Heart Failure . . . 1171

9.4.1. Mitral Regurgitation . . . 1171
9.4.1.1. Surgical Mitral Valve Repair or Replacement . . . 1171
9.4.1.2. Percutaneous Mitral Valve Procedures . . . 1171
9.4.2. Aortic Valve Disease . . . 1172
9.4.2.1. Surgical Aortic Valve Replacement . . . 1172
9.4.2.2. Transcutaneous Aortic Valve Implantation . . . 1172
9.5. Ventricular Assist Devices . . . 1172
9.6. Cardiac Transplantation . . . 1173
10. Comorbidities in Heart Failure . . . 1174
10.1. Hypertension . . . 1174
10.2. Coronary Artery Disease and Angina . . . 1175
10.3. Atrial Fibrillation . . . 1175
10.4. Diabetes . . . 1176
10.5. Chronic Kidney Disease, Hyperkalaemia, and Hypokalaemia . . . 1177
10.6. Hyponatraemia . . . 1177
10.7. Obesity . . . 1177
10.8. Chronic Obstructive Pulmonary Disease and Asthma . . . 1178
10.9. Sleep-disordered Breathing . . . 1178
10.10. Gout . . . 1179
10.11. Arthritis . . . 1179
10.12. Depression . . . 1179
10.13. Anaemia . . . 1180
10.14. Iron Deficiency . . . 1180
11. Chemotherapy-related Cardiotoxicity and Heart Failure . . . 1181
11.1. Medications That Cause Cardiotoxicity . . . 1181
11.1.1. Chemotherapy . . . 1181
11.1.1.1. Anthracyclines . . . 1181
11.1.1.2. Platinum-based Therapies . . . 1181
11.1.1.3. Antimetabolites (5-flurouracil) . . . 1181
11.1.1.4. Taxanes . . . 1181
11.1.1.5. Cyclophosphamide . . . 1181
11.1.2. Targeted Agents . . . 1181
11.1.2.1. HER2-targeted Agents . . . 1181
11.1.2.2. Tyrosine Kinase and Angiogenesis Inhibitors . . . 1181
11.2. Frequency of Cardiotoxicity . . . 1182
11.3. Risk Factors for Developing Cardiotoxicity . . . 1182
11.3.1. Cumulative Dose . . . 1182
11.3.2. Age . . . 1182
11.3.3. Other Risk Factors . . . 1182
11.4. Early Detection of Cardiotoxicity . . . 1182
11.4.1. Biomarkers . . . 1182
11.4.2. Imaging . . . 1182
11.5. Prevention and Treatment of Cardiotoxicity . . . 1183
12. Treatment of Heart Failure With Recovered Ejection Fraction . . . 1183
13. Special Situations . . . 1183
13.1. Driving . . . 1183
13.2. Travel . . . 1184
13.3. Vaccination . . . 1184
13.4. Sex . . . 1184
13.5. Pregnancy . . . 1184
13.6. Contraception . . . 1184
13.7. Weather . . . 1184
13.8. Caffeine Intake . . . 1184
14. Palliative Care in Heart Failure . . . 1185
15. Performance Measures . . . 1185
16. Areas for Future Research . . . 1186
17. Disclaimer . . . 1187

18. Acknowledgements 1187
19. Appendices 1187
19.1. Appendix 1: Abbreviations and Acronyms 1187
19.2. Appendix 2: Clinical Questions for External Literature Review 1189
19.3. Appendix 3: Summary of HFrEF and HFpEF Trials 1190
19.4. Appendix 4: Online Register of Conflicts of Interest 1193
19.5. Appendix 5: Endorsing Organisations 1193
20. References 1194

NHFA CSANZ Heart Failure Guidelines Working Group:[1]
John J. Atherton, MBBS, PhD, FRACP [a,b,c,d*],
Andrew Sindone, BMed, MD, FRACP [e,f],
Carmine G. De Pasquale, BMBS, FRACP, PhD, FCSANZ [g],
Andrea Driscoll, NP, PhD, FCSANZ [h,i],
Peter S. MacDonald, MD, PhD, FRACP [j],
Ingrid Hopper, MBBS, PhD, FRACP [k,l],
Peter M. Kistler, MBBS, FRACP, PhD [l,m], Tom Briffa, PhD [n],
James Wong, MBBS, PhD, FRACP [o],
Walter Abhayaratna, FRACP, FACC, PhD [p,q],
Liza Thomas, MBBS, FRACP, PhD [r,s,t],
Ralph Audehm, MBBS, DipRACOG [u], Phillip Newton, BN, PhD [v],
Joan O'Loughlin [w], Maree Branagan, MPH [x],
Cia Connell, BPharm, MClinPharm [x]

[a]Department of Cardiology, Royal Brisbane and Women's Hospital, Brisbane, Australia
[b]Faculty of Medicine, University of Queensland, Brisbane, Australia
[c]Faculty of Science, Health, Education and Engineering, University of Sunshine Coast, Australia
[d]Faculty of Health, Queensland University of Technology, Brisbane, Australia
[e]Heart Failure Unit and Department of Cardiac Rehabilitation, Concord Hospital, Sydney, Australia
[f]University of Sydney, Sydney, Australia
[g]Department of Cardiovascular Medicine, Flinders Medical Centre & Flinders University, Adelaide, Australia
[h]Department of Cardiology, Austin Health, Melbourne, Australia
[i]School of Nursing and Midwifery, Faculty of Health, Deakin University, Melbourne, Australia
[j]St Vincent's Hospital, Victor Chang Cardiac Research Institute, University of New South Wales, Sydney
[k]Department of Epidemiology and Preventive Medicine, Monash University, Melbourne, Australia
[l]Heart Centre, The Alfred Hospital, Melbourne, Australia
[m]Department of Medicine, University of Melbourne, Melbourne, Australia
[n]Centre for Health Services Research and Cardiovascular Research Group, School of Population Health, University of Western Australia, Perth, Australia
[o]Royal Melbourne Hospital, and University of Melbourne, Melbourne, Australia
[p]College of Medicine, Biology and Environment, Australian National University, Canberra, Australia
[q]Division of Medicine and Clinical Trials Unit, Canberra Hospital & Health Services, Canberra, Australia
[r]Department of Cardiology, Westmead Hospital
[s]Department of Medicine, University of Sydney
[t]Department of Medicine, University of New South Wales
[u]Department of General Practice and Primary Health Care, University of Melbourne, Melbourne, Australia
[v]Western Sydney Nursing & Midwifery Research Centre, Western Sydney University, Sydney, Australia
[w]Consumer representative
[x]National Heart Foundation of Australia

*Corresponding author. Email: John.Atherton@health.qld.gov.au

[1]The working group acknowledges Justin A Ezekowitz (Canada) for his feedback as a nominated document reviewer. The "National Heart Foundation of Australia and Cardiac Society of Australia and New Zealand Guidelines for the Prevention, Detection and Management of Heart Failure in Australia 2018" has been jointly developed by the Heart Foundation and the Cardiac Society of Australia and New Zealand. The Heart Foundation and the Cardiac Society of Australia and New Zealand are grateful for the contributions of all persons and entities involved in the development of the Guideline.

1. Evidence-based Recommendations

Recommendation	GRADE strength of recommendation	Quality of evidence
Prevention of heart failure—non-pharmacological		
Smoking cessation is recommended to decrease the risk of cardiovascular events and decrease the risk of developing heart failure.	Strong FOR	Low
Avoiding excess alcohol is recommended, to decrease the risk of developing heart failure.	Strong FOR	Very low
Weight reduction is recommended in patients who are overweight or obese, to decrease the risk of developing heart failure.	Strong FOR	Low
Regular physical activity is recommended to decrease the risk of cardiovascular events and decrease the risk of developing heart failure.	Strong FOR	Low
Prevention of heart failure—pharmacological		
Blood pressure (BP) lowering and lipid lowering according to published guidelines are recommended, to decrease the risk of cardiovascular events and decrease the risk of developing heart failure.	Strong FOR	High
Angiotensin converting enzyme (ACE) inhibitors should be considered in patients with cardiovascular disease to decrease the risk of cardiovascular events and decrease the risk of developing heart failure.	Strong FOR	Moderate
Sodium-glucose cotransporter 2 (SGLT2) inhibitors are recommended in patients with type 2 diabetes mellitus associated with cardiovascular disease and insufficient glycaemic control despite metformin, to decrease the risk of cardiovascular events and decrease the risk of hospitalisation for heart failure.	Strong FOR	High
ACE inhibitors are recommended in patients with left ventricular (LV) systolic dysfunction to decrease the risk of developing heart failure.	Strong FOR	High
Beta blockers should be considered in patients with LV systolic dysfunction to decrease the risk of developing heart failure.	Strong FOR	Low
Diagnosis		
A 12-lead electrocardiogram (ECG) is recommended in patients with either a suspected diagnosis or new diagnosis of heart failure, to assess cardiac rhythm, QRS duration, and the presence of underlying conditions such as myocardial ischaemia or LV hypertrophy.	Strong FOR	Low
A chest X-ray is recommended in patients with either a suspected diagnosis or new diagnosis of heart failure, to detect signs of pulmonary congestion and to identify alternative cardiac or non-cardiac causes for the patient's symptoms.	Strong FOR	Very low
Plasma B-type natriuretic peptide (BNP) or N-terminal proBNP (NT proBNP) levels are recommended for diagnosis in patients with suspected heart failure, when the diagnosis is uncertain.	Strong FOR	High
A transthoracic echocardiogram is recommended in patients with suspected heart failure, to improve diagnostic accuracy, and in patients with a new diagnosis of heart failure, to assess cardiac structure and function (including the measurement of LV ejection fraction [LVEF]), assist in classification and therefore guide management.	Strong FOR	Low
Invasive coronary angiography should be considered in patients with heart failure associated with refractory angina, resuscitated cardiac arrest, sustained ventricular arrhythmias, or with evidence of ischaemic heart disease on other investigations, or an intermediate-to-high pretest probability for coronary artery disease, to determine the need for coronary revascularisation.	Strong FOR	Low
Either computed tomography (CT) coronary angiography or cardiac magnetic resonance imaging (CMR) with late gadolinium enhancement (LGE) may be considered in patients with heart failure who have a low-to-intermediate pretest probability of coronary artery disease, to distinguish ischaemic and non-ischaemic causes of ventricular dysfunction.	Weak FOR	Low

(continued).

Recommendation	GRADE strength of recommendation	Quality of evidence
Non-invasive functional testing—stress echocardiography, single-photon emission CT scan (SPECT), positron emission tomography (PET) and CMR with LGE—may be considered in patients with heart failure and established coronary artery disease, for the assessment of myocardial ischaemia and viability to determine the need for coronary revascularisation.	Weak FOR	Very low
CMR with LGE should be considered in patients with heart failure associated with increased LV wall thickness that remains unexplained following clinical evaluation, including a 12-lead ECG and echocardiogram to identify inflammatory and infiltrative cardiomyopathies.	Strong FOR	Low
Either PET or bone scintigraphy may be considered in patients with heart failure associated with increased LV wall thickness that remains unexplained following clinical evaluation, including a 12-lead ECG and echocardiogram to identify infiltrative cardiomyopathies.	Weak FOR	Low
BNP and NT proBNP levels may be considered in patients with an established diagnosis of heart failure for prognostic stratification.	Weak FOR	High
Genetic testing may be considered in patients with dilated cardiomyopathy (DCM) associated with conduction disease, for prognostic stratification and to guide management regarding the use of implantable cardioverter defibrillators.	Weak FOR	Low
Transthoracic echocardiography should be considered in patients with heart failure with reduced ejection fraction (HFrEF) 3–6 months after the start of optimal medical therapy, or if there has been a change in clinical status, to assess the appropriateness for other treatments, including device therapy (implantable cardioverter defibrillator [ICD] or cardiac resynchronisation therapy [CRT], or both).	Weak FOR	Low
Acute heart failure		
Investigation and management of precipitating factors is recommended in all patients presenting with acute heart failure. Acute coronary syndrome (ACS), hypertensive crisis, arrhythmia, mechanical catastrophe (e.g., ruptured interventricular septum, mitral papillary muscle or LV free wall, or acute valvular regurgitation), and pulmonary embolism should be confirmed or excluded, and managed immediately.	Strong FOR	Low
Monitoring of peripheral arterial oxygen saturation is recommended in patients with acute heart failure.	Strong FOR	Very low
Oxygen therapy is recommended in patients with acute heart failure associated with oxygen saturation levels below 94%.	Strong FOR	Very low
Non-invasive ventilation should be considered in patients with acute heart failure associated with pulmonary congestion who remain hypoxaemic and tachypnoeic despite oxygen therapy, to improve symptoms and reduce the requirement for intubation.	Strong FOR	High
Intravenous loop diuretics are recommended in patients with acute heart failure associated with congestion, to improve symptoms of fluid overload.	Strong FOR	Low
Intravenous vasodilators may be considered in patients with acute heart failure if the systolic blood pressure is more than 90 mm Hg, to relieve symptoms of congestion.	Weak FOR	Low
Intravenous inotropic therapy may be considered in patients with acute heart failure associated with symptoms or signs of peripheral hypoperfusion (usually accompanied by a systolic BP <90 mm Hg) and congestion refractory to other treatment, to improve symptoms and end-organ function.	Weak FOR	Very low
Intravenous inotropic therapy should be avoided in patients without symptoms or signs of peripheral hypoperfusion and congestion refractory to other treatment.	Strong AGAINST	Low
Pharmacological management of chronic heart failure		
ACE inhibitors An ACE inhibitor is recommended in all patients with HFrEF associated with a moderate or severe reduction in LVEF (LVEF less than or equal to 40%) unless contraindicated or not tolerated to decrease mortality and decrease hospitalisation.	Strong FOR	High

(continued).

Recommendation	GRADE strength of recommendation	Quality of evidence
ACE inhibitors An ACE inhibitor may be considered in patients with HFrEF associated with a mild reduction in LVEF (LVEF 41–49%) unless contraindicated or not tolerated to decrease mortality and decrease hospitalisation.	Weak FOR	Low
Beta blockers A beta blocker[a] is recommended in all patients with HFrEF associated with a moderate or severe reduction in LVEF (LVEF less than or equal to 40%) unless contraindicated or not tolerated, and once stabilised with no or minimal clinical congestion on physical examination to decrease mortality and decrease hospitalisation. [a]Specifically, bisoprolol, carvedilol, metoprolol (controlled release or extended release) or nebivolol	Strong FOR	High
Beta blockers A beta blocker[a] may be considered in patients with HFrEF associated with a mild reduction in LVEF (LVEF 41–49%) unless contraindicated or not tolerated, and once stabilised with no or minimal clinical congestion on physical examination to decrease mortality and decrease hospitalisation. [a]Specifically, bisoprolol, carvedilol, metoprolol (controlled release or extended release) or nebivolol	Weak FOR	Low
Mineralocorticoid receptor antagonists (MRAs) An MRA is recommended in all patients with HFrEF associated with a moderate or severe reduction in LVEF (LVEF less than or equal to 40%) unless contraindicated or not tolerated, to decrease mortality and decrease hospitalisation for heart failure.	Strong FOR	High
Mineralocorticoid receptor antagonists (MRAs) An MRA may be considered in patients with HFrEF associated with a mild reduction in LVEF (LVEF 41–49%) unless contraindicated or not tolerated, to decrease mortality and decrease hospitalisation for heart failure.	Weak FOR	Low
Diuretics A diuretic should be considered in patients with heart failure and clinical symptoms, or signs of congestion, to improve symptoms and manage congestion.	Strong FOR	Very low
Angiotensin receptor blockers (ARBs) An ARB is recommended in patients with HFrEF associated with a moderate or severe reduction in LVEF (LVEF less than or equal to 40%) if an ACE inhibitor is contraindicated or not tolerated, to decrease the combined endpoint of cardiovascular mortality and hospitalisation for heart failure.	Strong FOR	Moderate
ARBs An ARB may be conisdered in patients with HFrEF associated with a mild reduction in LVEF (LVEF 41–49%) if an ACE inhibitor is contraindicated or not tolerated, to decrease the combined endpoint of cardiovascular mortality and hospitalisation for heart failure.	Weak FOR	Low
Angiotensin receptor neprilysin inhibitor (ARNI) An ARNI is recommended as a replacement for an ACE inhibitor (with at least a 36-hour washout window) or an ARB in patients with HFrEF associated with an LVEF of less than or equal to 40% despite receiving maximally tolerated or target doses of an ACE inhibitor (or ARB) and a beta blocker (unless contraindicated), with or without an MRA, to decrease mortality and decrease hospitalisation.	Strong FOR	High
Concomitant use of ACE inhibitors and ARNIs are contraindicated and these medications should not be administered within 36hours of each other, because of an increased risk of angioedema.	Strong AGAINST	Very low
Ivabradine Ivabradine should be considered in patients with HFrEF associated with an LVEF of less than or equal to 35% and a sinus rate of 70 beats per minute (bpm) and above, despite receiving maximally tolerated or target doses of an ACE inhibitor (or ARB) and a beta blocker (unless contraindicated), with or without an MRA, to decrease the combined endpoint of cardiovascular mortality and hospitalisation for heart failure.	Strong FOR	High

(continued).

Recommendation	GRADE strength of recommendation	Quality of evidence
Hydralazine plus nitrates Hydralazine plus nitrates may be considered in patients with HFrEF if an ACE inhibitor and ARB are contraindicated or not tolerated to decrease mortality.	Weak FOR	Low
Hydralazine plus nitrates may be considered in black patients of African descent with HFrEF despite receiving maximally tolerated or target doses of an ACE inhibitor (or ARB) and a beta blocker (unless contraindicated), with or without an MRA, to decrease mortality and hospitalisation for heart failure.	Weak FOR	Moderate
Digoxin Digoxin may be considered in patients with HFrEF associated with sinus rhythm and moderate to severe symptoms (New York Heart Association [NYHA] Class 3–4) despite receiving maximally tolerated or target doses of an ACE inhibitor (or ARB) to decrease hospitalisation for heart failure.	Weak FOR	Low
Nutraceuticals N-3 polyunsaturated fatty acids may be considered in patients with HFrEF despite receiving maximally tolerated or target doses of an ACE inhibitor (or ARB) and a beta blocker (unless contraindicated), with or without an MRA, to decrease mortality and cardiovascular hospitalisation.	Weak FOR	Low
Non-pharmacological management		
Models of care to improve evidence-based practice		
Referral to a multidisciplinary heart failure disease management program is recommended in patients with heart failure associated with high-risk features, to decrease mortality and rehospitalisation.	Strong FOR	High
In areas where access to a face-to-face multidisciplinary heart failure disease-management program after discharge is limited, patients should be followed up with a multidisciplinary telemonitoring or telephone support program.	Strong FOR	Moderate
Nurse-led medication titration is recommended in patients with HFrEF who have not achieved maximum tolerated doses of ACE inhibitors, ARBs, ARNIs, beta blockers or MRAs, to decrease hospitalisation.	Strong FOR	High
Self-management Educating patients and their carers about the self-management of heart failure is recommended in patients with heart failure, to decrease hospitalisation and mortality. It should commence soon after diagnosis, be patient-centred, appropriate to their level of health literacy, culturally appropriate, and revised throughout the person's life.	Strong FOR	High
Exercise Regular performance of up to moderate intensity (i.e. breathe faster but hold conversation) continuous exercise is recommended in patients with stable chronic heart failure, particularly in those with reduced LVEF, to improve physical functioning and quality of life, and to decrease hospitalisation.	Strong FOR	High
Devices, surgery and percutaneous procedures		
Cardiac resynchronisation therapy		
CRT is recommended in patients with HFrEF associated with sinus rhythm, an LVEF of less than or equal to 35% and a QRS duration of 150 ms or more despite optimal medical therapy, to decrease mortality and hospitalisation for heart failure and improve symptoms.	Strong FOR	High
CRT should be considered in patients with HFrEF associated with sinus rhythm, an LVEF of less than or equal to 35% and a QRS duration of 130–149 ms despite optimal medical therapy, to decrease mortality and hospitalisation for heart failure, and improve symptoms.	Strong FOR	Moderate
CRT may be considered in patients with HFrEF associated with AF, an LVEF of less than or equal to 35% and a QRS duration of 130 ms or more despite optimal medical therapy to decrease morbidity and mortality, and improve symptoms, provided this is accompanied by approaches to maximise biventricular capture (ideally at least 92% biventricular capture).	Weak FOR	Very low

(continued).

Recommendation	GRADE strength of recommendation	Quality of evidence
CRT should be considered in patients with HFrEF associated with an LV ejection fraction of less than or equal to 50% accompanied by high-grade atrioventricular (AV) block requiring pacing, to decrease hospitalisation for heart failure.	Weak FOR	Moderate
CRT should be considered in patients who have pre-existing right ventricular pacing who develop symptoms of heart failure with an LVEF of less than 35%, to decrease hospitalisation for heart failure.	Weak FOR	Low
CRT is contraindicated in patients with QRS duration of less than 130 ms, because of lack of efficacy and possible harm.	Strong AGAINST	Moderate
Implantable cardioverter defibrillators		
An ICD should be considered as a secondary prevention indication in patients following resuscitated cardiac arrest, sustained ventricular tachycardia in the presence of haemodynamic compromise and ventricular tachycardia associated with syncope and an LVEF of less than 40% to decrease mortality.	Strong FOR	High
An ICD should be considered as a primary prevention indication in patients at least 1 month following myocardial infarction associated with an LVEF of less than or equal to 30% to decrease mortality.	Strong FOR	High
An ICD should be considered as a primary prevention indication in patients with HFrEF associated with ischaemic heart disease and an LVEF of less than or equal to 35% to decrease mortality.	Strong FOR	Moderate
An ICD may be considered as a primary prevention indication in patients with HFrEF associated with dilated cardiomyopathy and an LVEF of less than or equal to 35%, to decrease mortality.	Weak FOR	Low
Pressure monitoring		
Implantable pulmonary arterial pressure monitoring may be considered in patients who have been previously hospitalised for heart failure associated with a reduced or preserved LV ejection fraction with persistent moderate (NYHA functional class III) heart failure symptoms, despite optimal care, to decrease hospitalisation for heart failure, provided systems are in place to ensure daily upload and at least weekly review of pressure monitoring data.	Weak FOR	Low
Surgical management and procedures		
Coronary artery bypass graft surgery (CABG) should be considered in patients with HFrEF associated with ischaemic heart disease and an LVEF of less than or equal to 35% if they have surgically correctable coronary artery disease, to improve symptoms (e.g., relief of angina and heart failure symptoms) and decrease morbidity and long-term mortality.	Strong FOR	Moderate
Mitral valve (MV) repair or replacement at the time of elective CABG should be considered in patients with moderate to severe mitral regurgitation in association with heart failure and ischaemic heart disease to improve symptoms.	Weak FOR	Low
Surgical MV repair or replacement may be considered in patients with severe mitral regurgitation complicating dilated cardiomyopathy with heart failure who remain symptomatic despite guideline-directed medical and cardiac device therapy to improve symptoms.	Weak FOR	Low
Percutaneous MV repair or replacement may be considered in patients with moderate to severe functional mitral regurgitation in association with heart failure who remain symptomatic despite guideline-directed medical and cardiac device therapy, particularly in those who are at high surgical risk to improve symptoms.	Weak FOR	Low
Surgical aortic valve replacement (SAVR) is recommended in patients with severe aortic stenosis or severe aortic regurgitation and heart failure in the absence of major comorbidities or frailty, to improve symptoms and decrease mortality.	Strong FOR	Low

(continued).

Recommendation	GRADE strength of recommendation	Quality of evidence
Transcatheter aortic valve implantation (TAVI) should be considered in patients with severe aortic stenosis and heart failure at intermediate to high operative mortality risk or considered inoperable for SAVR, and who are deemed suitable for TAVI following assessment by a heart team to improve symptoms and decrease mortality.	Strong FOR	Moderate
Referral to a specialist centre for consideration of ventricular assist device (VAD) implantation should be considered in patients with intractable, severe heart failure despite guideline-directed medical and pacemaker therapy, and who do not suffer from major comorbidities, to decrease mortality.	Strong FOR	Moderate
Implantation of a VAD as a bridge to transplant should be considered in patients actively listed for heart transplantation who become inotrope-dependent or who progress to needing acute mechanical circulatory support.	Strong FOR	Low
Referral for heart transplant assessment should be considered in patients with heart failure associated with intractable NYHA Class III–IV symptoms who have exhausted all alternative therapies and who do not have overt contraindications to decrease mortality.	Strong FOR	Low
Hypertension		
Diltiazem, verapamil, and moxonidine should be avoided in patients with HFrEF.	Strong AGAINST	Low
Atrial fibrillation		
Determination of the risk of stroke to guide the need for anticoagulation is recommended in patients with atrial fibrillation (AF).	Strong For	High
Pharmacological therapy aiming for a resting ventricular rate of 60–100 bpm should be considered in patients with heart failure associated with AF and a rapid ventricular response.	Strong For	Low
Catheter ablation for AF (either paroxysmal or persistent) should be considered in patients with HFrEF associated with an LVEF of less than or equal to 35%, who present with recurrent symptomatic AF, to decrease mortality and hospitalisation for heart failure.	Strong For	Moderate
Diabetes		
Thiazolidinediones (glitazones) are not recommended in patients with heart failure due to the risk that they will lead to worsening of heart failure.	Weak AGAINST	Moderate
Sleep disordered breathing		
Adaptive servoventilation is not recommended in patients with HFrEF and predominant central sleep apnoea because of an increased all-cause and cardiovascular mortality.	Strong AGAINST	Moderate
Anaemia		
Erythropoietin should not be used routinely for the treatment of anaemia in patients with heart failure because of an increased risk of thromboembolic adverse events.	Strong AGAINST	Moderate
Iron deficiency		
In patients with HFrEF associated with persistent symptoms despite optimised therapy, iron studies should be performed and, if the patient is iron deficient (i.e. ferritin <100 μg/L, or ferritin 100–300 μg/L with transferrin saturation <20%) intravenous iron should be considered, to improve symptoms and quality of life.	Strong FOR	Moderate
Treatment of heart failure with recovered ejection fraction		
Unless a reversible cause has been corrected, neurohormonal antagonists (ACE inhibitors or ARBs or ARNIs, beta blockers and MRAs) should be continued at target doses in patients with heart failure associated with a recovered or restored ejection fraction, to decrease the risk of recurrence.	Strong FOR	Low

(continued).

Recommendation	GRADE strength of recommendation	Quality of evidence
Palliative care		
Referral to palliative care should be considered in patients with advanced heart failure to alleviate end-stage symptoms, improve quality of life and decrease rehospitalisation. Involvement of palliative care should be considered early in the trajectory towards end stage heart failure.	Strong FOR	High

ACE, angiotensin converting enzyme; ACS, acute coronary syndrome; AF, atrial fibrillation; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor neprilysin inhibitor; AV, atrioventricular; BNP, B-type natriuretic peptide; BP, blood pressure; bpm, beats per minute; CABG, coronary artery bypass graft; CMR, cardiac magnetic resonance imaging; CRT, cardiac resynchronisation therapy; CT, computed tomography; ECG, electrocardiogram; DCM, dilated cardiomyopathy; GRADE, Grading of Recommendations Assessment, Development and Evaluation; HFrEF, heart failure with reduced ejection fraction; ICD, implantable cardioverter defibrillator; LGE, late gadolinium enhancement; LV, left ventriclular; LVEF, LV ejection fraction; MRA, mineralocorticoid receptor antagonist; MV, mitral valve; NT, N-terminal; NYHA, New York Heart Association; PET, positron emission tomography; SAVR, surgical aortic valve replacement; SGLT2, sodium-glucose cotransporter 2; SPECT, single-photon emission CT scan; TAVI, transcatheter aortic valve implantation; VAD, ventricular assist device.

2. Process for Developing the Guidelines

These clinical guidelines for the management of heart failure seek to provide guidance regarding the clinical care of adult patients with heart failure in Australia based on current evidence. They are intended to replace the 2011 update of the National Heart Foundation of Australia/Cardiac Society of Australia and New Zealand (NHFA/CSANZ) *Guidelines for the Prevention, Detection, and Management of Chronic Heart Failure in Australia* [1].

In late 2016, the NHFA began the process of developing the 2018 guidelines. A partnership between NHFA and CSANZ was formed to develop the guidelines, with the NHFA as the lead organisation. Clinical committees from both organisations were approached for advice regarding the content (scope) and development process for the guidelines.

Acting on advice from the previous expert panel involved in earlier editions of the guidelines, together with advice from the NHFA internal clinical advisory committees, members were approached to be in the working group, according to expertise.

Based on the determined scope, guideline writing groups were established to cover the following four topics: diagnosis, drugs, devices, and non-pharmacological management. For each writing group, a primary and secondary writer were appointed by group consensus, on the basis of expertise and previous experience in guideline development. The other members of the writing groups comprised members with recognised expertise, from stakeholder groups and the clinical community. The writing groups met on several occasions to discuss the content of the guidelines during the development process.

A reference group was established comprising appointed representatives of key stakeholder organisations with national relevance in the provision of heart failure care in Australia. The key roles of the group were to review and provide input into the scope of the guidelines, the questions being submitted for literature review, and the draft guidelines content and recommendations; and to facilitate implementation of the guidelines.

Informed by stakeholder consultation, the working group generated clinical questions to form the basis of external literature searches. Questions for external literature searches were prioritised according to uniqueness to Australia, and to areas not covered in recent European guidelines. These questions were reviewed and refined by the reference group, and the clinical expert committees from the NHFA and CSANZ. The questions proposed for literature review are provided in Appendix 2.

The literature reviewer was appointed through an open tender process in May 2017. The external literature review started in the second half of 2017 and was completed in December 2017. The evidence summaries generated were reviewed and signed off by the working group, and relevant content for the guidelines was based on the provided evidence summaries. At the same time, the writing group members reviewed evidence and drafted content for the topics (in the agreed scope) other than those sent for external literature searches.

In February 2018, the reference group was consulted on the first full draft of the guidelines. A public consultation period of 21 days was conducted in April 2018. Feedback received was reviewed by the expert working group prior to finalisation of the guidelines. Final approval by the clinical committees and the Boards of the NHFA and CSANZ and submission for journal publication was undertaken in June 2018.

2.1. Conflicts of Interest Process

Conflicts of interest were considered within a framework of both the relationship (direct or indirect) of the participating individual to any third party with interest in the topic under consideration within the guideline development process, and the nature (financial and non-financial) of the potential conflict. All members of the working groups and reference group were asked to declare all potential conflicts of interest and these declarations were updated every 6 months and at each

meeting. All conflicts of interest were managed by the working group chair or primary writer. A summary of the conflicts of interest and responses will be provided in an online Appendix and a full description of the governance process for the development of these guidelines will be available on the NHFA website.

2.2. Development of Recommendations

In addition to reviews of published trials and systematic reviews, guideline content was informed by other international clinical guidelines, and local clinical expertise. Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology [2] was used to formulate recommendations. GRADE highlights the strength of a recommendation for or against an intervention. This is determined by considering the quality of evidence, balance between benefits and harms, trade-offs between improving survival and quality of life, uncertainty or variability in patient values and preferences, and resource considerations. This methodology is increasingly being used by guideline developers in Australia and worldwide.

Each of the final recommendations was reviewed and refined by the writing groups and the reference group, with final review and endorsement by the whole working group. The definition of consensus was more than 80% agreement of all members of the working group.

The 'Rationale' section under each recommendation provides a brief summary of the key evidence underpinning the recommendations. Economic implications or other relevant system factors are discussed in the 'Resources and other considerations' section where appropriate.

For topics where there is a limited evidence base, or where the impact of interventions on clinical outcomes was considered to be modest, comments are included in the 'Practice advice' sections of the guideline. While medication dosing may be generally provided in this guideline, clinicians are advised to refer to additional resources such as the *Australian Medicines Handbook* [3] for relevant contraindications, precautions, drug interactions, and adverse effects.

Clinical decisions should carefully consider individual patient characteristics with known associations with poor prognosis due to vulnerability. These include cultural and linguistic diverse populations including recent migrants; Indigenous Australians; the cognitively impaired; those living in rural or remote areas; people of advanced age; and those who are incarcerated or institutionalised.

3. Definition and Classification of Heart Failure

3.1. Epidemiology of Heart Failure

Heart failure currently affects at least 38 million people worldwide [4]. The lifetime risk of developing heart failure for women and men at age 55 years is 29% and 33%, respectively [5], and more than one in 10 persons of age 75 years and over in developed countries are afflicted with heart failure. Population-based estimates of heart failure prevalence in Australia are limited [6,7], and the National burden of heart failure has been estimated using international prevalence rates. In 2014, it was estimated that there were 480,000 people aged 18 years or more with heart failure, representing 2.1% of the adult population [8]. Given the high rates of cardiovascular risk factors and the endemic rates of rheumatic heart disease (RHD) in Australia's Indigenous population, the age-standardised prevalence rates of heart failure in indigenous Australians is 1.7 times higher than in non-Indigenous Australians [9]. RHD may affect one or both left-sided heart valves and less commonly the right-sided heart valves. Prevalence estimates of RHD since 2000 have steadily increased to almost 2% of the Indigenous population in the Northern Territory and 3.2% of Indigenous people aged 35–44 years [3]. For Indigenous women of child-bearing age, the initial presentation may occur during pregnancy. Detailed guidelines for the evaluation and management of RHD are covered in the Australian guidelines for the prevention, diagnosis, and management of acute rheumatic fever and rheumatic heart disease [3]. Furthermore, Indigenous people with heart failure have more comorbidities and higher mortality than those who are not Indigenous, and Indigenous Australians are 1.4 times more likely to die from heart failure than non-Indigenous Australians [10].

The worldwide increase in heart failure prevalence is not associated with an increase in age-adjusted heart failure incidence, which has been observed to be either stable or decreasing, particularly in women [11]. The ageing demographic and improved survival of patients with heart failure due to the availability of diagnostic technology and more efficacious therapy could explain the increase in heart failure prevalence. In contrast, the reduction in age-adjusted incident heart failure, particularly associated with reduced left ventricular ejection fraction (HFrEF), may be related to better prevention programs for ischaemic heart disease and treatment strategies for acute coronary syndromes. Trends observed in international epidemiological studies would suggest that there is an increasing proportion of patients with heart failure associated with preserved ejection fraction (HFpEF) to the extent that this entity now represents more than half of heart failure cases [12].

In 2015–2016 there were about 173,000 hospitalisations where heart failure and cardiomyopathy were recorded as the main or additional diagnosis, representing 1.6% of all hospitalisations in Australia. Almost 40% of hospitalisations for heart failure and cardiomyopathy were recorded as the primary diagnosis. For these patients, hospitalisation rates overall were 1.5 times higher for males than females. Age-adjusted rates were higher among males than females in all age groups. Rates increased with age, with rates highest for males and females aged 85 years or more (at least 2.4 times higher than rates in the 75–84 years age group) [13]. In the NSW and ACT SNAPSHOT study of patients hospitalised with heart failure over 1 month in 2013, the median length of stay was 6 days and 58% were categorised as HFrEF [14].

Survival rates for heart failure vary across studies depending on whether the cohort has acute or chronic heart failure. For acute heart failure, survival rates at 1-month in contemporary studies are consistently around 80% and 57–80% at 1 year [15,16]. Survival rates for chronic heart failure range from 81 to 91% at 1 year and 52 to 63% at 5 years [17,18], reflecting a prognosis similar to non-haematological malignancies. While some studies have observed similar survival rates in patients with HFrEF and HFpEF [12,19], a literature-based meta-analysis of 17 studies with 24,501 patients showed a 4-year HFpEF mortality rate of 32.1% compared with a 40.6% mortality in HFrEF [20,21]. This finding was subsequently confirmed in a meta-analysis using data from 41,972 individual patients obtained from 31 studies. The 3-year adjusted mortality rate was 32% for HFrEF and 25% for HFpEF. Unlike HFrEF, as many as 30–40% of deaths in patients with HFpEF were non-cardiovascular. Interestingly, the difference in mortality rates diminished with increasing age, reflecting the increasing contribution of non-cardiovascular deaths in older patients with heart failure regardless of left ventricular ejection fraction (LVEF) [21].

3.2. Definition

Heart failure is a **complex clinical syndrome** with **typical symptoms and signs** that generally occur on **exertion**, but can also occur at **rest** (particularly when **recumbent**). It is secondary to an **abnormality of cardiac structure or function** that **impairs the ability of the heart to fill with blood at normal pressure** or **eject blood sufficient** to fulfil the needs of the metabolising organs.

The definition is complex, reflecting the disease state, and warrants expansion because it incorporates many key concepts related to heart failure, as discussed below.

Complex clinical syndrome: The diagnosis is a clinical one and the complexity of the syndrome reflects the impact of cardiac dysfunction on most organ systems.

Typical symptoms and signs: The clinical syndrome of heart failure has typical symptoms; however, they are often nonspecific. The cardinal symptom of heart failure is dyspnoea, which is particularly non-specific, but certain patterns of dyspnoea are typical of heart failure; e.g., orthopnoea and paroxysmal nocturnal dyspnoea, and (to a lesser degree) exertional dyspnoea and bendopnoea [22]. Other important symptoms of heart failure are fatigue and palpitations. Typical signs of heart failure can be divided into those related to cardiac dysfunction and strain (tachycardia, third heart sound, murmurs and displaced apex beat), reduced end-organ perfusion and, most strikingly, congestion (abnormal cardiac filling resulting in high venous pressure; e.g., elevated jugular venous pressure [JVP], hepatic enlargement and tenderness, peripheral oedema, pulmonary crackles, pleural effusions, and ascites) (Table 1).

On exertion, at rest, when recumbent: Symptoms of heart failure generally and initially manifest on physical (and occasionally emotional) exertion. As the heart failure syndrome progresses, symptoms occur on lower levels of physical activity and even at rest (Table 2). An exception is the fluid shift that occurs during recumbency, which accounts for orthopnoea and paroxysmal nocturnal dyspnoea.

Abnormality of cardiac structure or function: Despite the end-organ impact of the heart failure syndrome, the underlying problem is generally a cardiac one, most commonly involving ventricular myocardial systolic or diastolic dysfunction (or both). However, structural abnormalities of

Table 1 Symptoms and signs of heart failure.

Symptoms and signs of heart failure	
More typical symptoms	**More specific signs**
Dyspnoea (usually with exertion)	Elevated jugular venous pressure
Orthopnoea	Hepatojugular reflux
Paroxysmal nocturnal dyspnoea	Third heart sound
Fatigue	Laterally displaced apex beat
Less typical symptoms	**Less specific signs**
Nocturnal cough	Weight gain (>2 kg/wk)
Wheeze	Weight loss (in advanced heart failure)
Abdominal bloating	Peripheral oedema (ankle, sacrum)
Anorexia	Pulmonary crackles
Confusion (elderly)	Pleural effusions
Depression	Cardiac murmur
Palpitations	Tachycardia
Dizziness	Tachypnoea
Syncope	Cheyne–Stokes respiration
Bendopnoea (shortness of breath when leaning forward)	Ascites

Table 2 New York Heart Association functional classification of heart failure.

New York Heart Association functional classification of heart failure			
Class I	**Class II**	**Class III**	**Class IV**
No limitation of ordinary physical activity	Slight limitation of ordinary physical activity No symptoms at rest	Marked limitation of ordinary physical activity No symptoms at rest	Symptoms on any physical activity or at rest

virtually any cardiac component (ranging from the valves to the pericardium, endocardium, and conduction system) can lead to the syndrome of heart failure.

Impairs the ability of the heart to fill with blood at normal pressure: In diastole, the ventricle fills with blood. An inability to fill with blood without increased filling pressure (generally due to reduced ventricular compliance or active relaxation, or both) results in symptoms and signs of congestion of the vasculature and end organs.

Impairs the ability of the heart to eject sufficient blood: Intuitively, if the heart is regarded first and foremost as a pump, a reduction in blood ejection, and therefore in cardiac output, to the degree that it is insufficient for the metabolising needs of the tissues, will result in symptoms and signs.

3.3. Classification

As discussed in Section 3.2, heart failure is diagnosed clinically. Patients diagnosed with heart failure may then be classified according to their LVEF as follows.

The primary classification of heart failure is currently based on the LVEF, as discussed below. This should be measured using either two-dimensional echocardiography (usually with the biplane method of discs or modified Simpson's rule) or three-dimensional echocardiography. While global longitudinal strain may be a more sensitive marker of left ventricular (LV) contractility—given the variability between vendors and software [23], and that this measurement is not widely used in standard clinical practice—the writing group recommends the use of LVEF as the global measure of LV contractility to categorise heart failure following diagnosis. This well-established haemodynamic term reflects the percentage of ventricular volume that is ejected per heartbeat. The lower limit of normal for the LVEF is 50–55%.

$$EF = (EDV - ESV)/EDV \text{ (expressed as a percentage)}$$

where EF = ejection fraction; EDV = end diastolic volume; ESV = end systolic volume.

It follows that the EF is a measure of cardiac ejection and therefore of systolic function. This haemodynamic parameter is central to the modern classification of heart failure syndromes.

3.3.1. Heart Failure with Reduced Ejection Fraction

HFrEF (formerly systolic heart failure) is defined as the clinical symptoms with or without signs of heart failure ***and*** a measured LVEF of less than 50% (see Table 3). However, if the LVEF is only mildly reduced (LVEF 41–49%),

Table 3 Heart failure diagnostic criteria.

Heart failure diagnostic criteria	
HFrEF	**HFpEF**
• Symptoms ± signs of heart failure **and** • LVEF <50%[a]	• Symptoms ± signs of heart failure **and** • LVEF ≥50% **and** • Objective evidence of: ○ Relevant structural heart disease (LV hypertrophy, left atrial enlargement) **and/or** ○ Diastolic dysfunction, with high filling pressure demonstrated by any of the following: • invasive means (cardiac catheterisation) • echocardiography • biomarker (elevated BNP or NT proBNP) • exercise (invasive or echocardiography)

BNP: B-type natriuretic peptide, HFpEF: heart failure with preserved ejection fraction, HFrEF: heart failure with reduced ejection fraction, LV: left ventricular, LVEF: left ventriclular ejection fraction, NT: N-terminal.

[a]If LVEF mildly reduced (LVEF 41–49%), additional criteria required (e.g., signs of heart failure; diastolic dysfunction with high filling pressure demonstrated by invasive means or echocardiography or biomarker testing).

additional criteria are required (e.g., signs of heart failure or objective evidence of high filling pressure—see diastolic dysfunction below).

The LVEF cut-off chosen to identify patients with HFrEF in the large randomised controlled trials (RCTs) has varied from 25 to 40%, with most studies using a cut-off of 35%. We chose a 50% cut-off for reasons that are discussed further below. However, different cut-offs may be used to access specific therapies, largely guided by clinical trial evidence and local reimbursement or funding arrangements.

3.3.2. Heart Failure with Preserved Ejection Fraction

HFpEF (formerly diastolic heart failure) has proven much more difficult to define because the key objective marker of cardiac abnormality (the LVEF) is by definition preserved, leaving only clinical symptoms and signs, which are largely non-specific. Indeed, the definition of HFpEF remains an evolving and dynamic concept.

HFpEF is defined as all of the following (see Table 3):

- clinical symptoms with or without signs of heart failure;
- a measured EF of at least 50%;
- objective evidence of either relevant structural heart disease **or** diastolic dysfunction without an alternative cause (e.g., significant valvular heart disease).

The term 'relevant structural heart disease' refers to LV hypertrophy or left atrial enlargement. LV hypertrophy (increased LV wall thickness or LV mass index of more than 115 g/m^2 [men] or more than 95 g/m^2 [women]) reduces ventricular compliance. It is a common associated feature and potential cause of diastolic dysfunction, which results in high left-sided intracavity filling pressure. Left atrial enlargement (left atrial volume index of more than 34 mL/m^2) is a consequence of high left-sided intracavity filling pressure.

Diastolic function incorporates two components: LV compliance (the inverse of stiffness) and active ventricular relaxation. Reduced ventricular compliance and abnormal ventricular relaxation may both result in increased left-sided intracavity filling pressure.

Diastolic dysfunction refers to documentation of high left-sided intracavity filling pressure by any of the following:

- invasive means—e.g., pulmonary capillary wedge pressure (PCWP) of more than or equal to 15 mm Hg or LV end-diastolic pressure of more than 16 mm Hg;
- echocardiography—at least three of the following:
  - mitral annular velocity (septal) e′ of less than 7 cm/s/ (lateral) e′ of less than 10–cm/s;
  - average mitral valve early wave inflow velocity E/e′ ratio of more than 14;
  - left atrial volume index of more than 34 mL/m^2;
  - tricuspid valve regurgitation velocity of more than 2.8 m/s [24];
- biomarker analysis using rule-in cut-offs for natriuretic peptides (see Table 4).

Table 4 BNP and NT-proBNP diagnostic cut-off values[a]

BNP/NT −proBNP diagnostic cut-off values		
	BNP (ng/L)	**NT proBNP (ng/L)**
Heart failure rule-out	<100	<300
Heart failure rule-in	>400	Age <50 yr: >450 Age 50–75 yr: >900 Age >75 yr: >1800

BNP: B-type natriuretic peptide, NT: N-terminal.

[a]Defining cut-off values (particularly for rule-in) is complicated and somewhat limited in accuracy due to multiple factors influencing natriuretic peptide levels (see Section 5.2.1 - Diagnosis of Heart Failure).

Just as symptoms of heart failure can occur only *on exertion*, evidence of high intracavity filling pressure might only be present on exertion. Exercise testing may therefore be considered in patients where the clinical suspicion of HFpEF remains, despite not meeting the criteria above. Furthermore, exercise testing will provide an objective measure of exercise capacity, and exercise imaging will allow the evaluation for myocardial ischaemia as an alternative cause of symptoms. In these patients, the sensitivity of HFpEF diagnosis is improved with measurement of parameters of filling pressure either invasively (considered positive if PCWP >25 mm Hg), or with echocardiography (considered positive when all of the following occur: average E/e′ > 14 or septal E/e′ > 15 and peak tricuspid regurgitation velocity >2.8m/s during or immediately following exercise; and septal e′ velocity <7 cm/s at baseline) [24,25].

3.3.3. Ejection Fraction 40–50%

We chose a 50% cut-off to differentiate between HFrEF and HFpEF mainly for therapeutic reasons. The writing committee does not recommend a separate 'mid-range' EF (HFmrEF) category at this time. The main reasons for this are, first, that although HFrEF and HFpEF have different clinical spectrums and proposed pathophysiological mechanisms (see below), there is no clear defining syndrome recognised or postulated for HFmrEF. Second, although variability in LVEF measurement by echocardiography is improving, the EF range of only 10% is too narrow to confidently ascribe a new and separate group with current diagnostic test accuracy. Finally, it is unclear how introducing an additional category will inform clinical management. Indeed, post hoc analyses of the small number of patients with heart failure associated with a 'mid-range' EF evaluated in RCTs suggest they may receive similar benefits from blockade of the renin–angiotensin system [26], beta blockers [27], and mineralocorticoid receptor antagonists (MRAs) [28] to patients with heart failure associated with an LVEF of less than 40%.

We therefore recommend that, following a clinical diagnosis of heart failure, an LVEF of 50% or more be considered HFpEF and an LVEF of less than 50% be considered HFrEF to

inform management strategy. HFrEF where the EF has improved to more than 50% with treatment (so-called recovered HFrEF) should generally be considered and treated like HFrEF because the pathophysiology is not believed to have changed in most cases.

3.4. Terminology

Asymptomatic left ventricular dysfunction refers to reduced LVEF (<50%) with no current or prior clinical evidence of heart failure. Its importance lies in being a strong risk factor for the development of heart failure.

New onset or de novo heart failure refers to the first presentation and diagnosis of heart failure in a patient. The history of symptoms may be short (hours to days) or long (weeks to months). It follows that these patients have not previously received heart failure treatment.

Chronic heart failure refers to patients with diagnosed heart failure for a period of time (arbitrarily defined as a minimum of 3 months). It follows that these patients have received some heart failure treatment.

Acute heart failure can take many forms and represents a heterogeneous group. It refers to the acute onset or significant worsening of symptoms of heart failure sufficient to warrant treatment intervention. Specific subgroups of acute heart failure are described below:

Acute (cardiogenic) pulmonary oedema (APO)—A medical emergency characterised by the acute (often within minutes or hours) development of pulmonary oedema as the dominant clinical feature of left heart failure with redistribution of fluid into the pulmonary interstitium and then alveolar flooding. APO results in the rapid development of respiratory failure and potentially respiratory arrest and death without intervention.

Cardiogenic shock—A medical emergency with a particularly poor prognosis. Cardiogenic shock is typically characterised by the acute development of reduced cardiac output (cardiac index $<2.2\ L/min/m^2$) and hypotension (systolic blood pressure [BP] <90 mm Hg) in the setting of heart failure (PCWP > 18 mm Hg) to the point where end-organ perfusion is compromised. Without intervention, multiorgan failure and death ensues. Cardiogenic shock most commonly results from a large acute myocardial functional insult (e.g., acute myocardial infarction (MI) or acute fulminant myocarditis) or a catastrophic cardiac structural insult (e.g., acute torrential valvular regurgitation). Cardiogenic shock is increasingly seen in the older comorbid population as an end-stage phenomenon in the chronic heart failure (CHF) illness trajectory, where it typically has a more subacute onset.

Acute decompensated heart failure (ADHF)—The most common form of acute heart failure in Australia is an acute deterioration (decompensation) in a previously stable patient with CHF. The precipitants for decompensation are multiple and varied, ranging from patient factors, disease state factors and comorbidities. The precipitants of decompensation often require attention in their own right, concurrent with management of the heart failure. While ADHF can present acutely, it more typically presents with a subacute history of several weeks of gradual deterioration with symptoms and signs of congestion [29].

Right heart failure refers to solitary or predominant failure of the right heart. Rare causes are right ventricular (RV) infarction or isolated tricuspid valve pathology; however, the most common cause of right heart failure is right heart pressure overload. The right heart is a low-pressure system, and consequently it is particularly sensitive to high afterload (pulmonary hypertension). Pulmonary hypertension is a consequence of many prevalent chronic diseases in Australian society; e.g., HFrEF, HFpEF, hypertension, left-sided valvular heart disease, atrial fibrillation (AF), obesity, chronic lung disease, sleep apnoea, chronic renal failure, pulmonary thromboemboli and, although not a disease entity, ageing itself. Unfortunately, right heart failure is an advanced illness phenomenon with a particularly poor prognosis. Indeed, it is the primary determinant of survival in many common cardiac and respiratory chronic diseases including HFrEF, HFpEF, valvular heart disease, chronic obstructive pulmonary disease (COPD), interstitial lung disease (ILD) and pulmonary arterial hypertension. The diagnosis and management of pulmonary arterial hypertension is beyond the scope of these guidelines.

3.5. Pathophysiology

3.5.1. Heart Failure with Reduced Ejection Fraction

Patients with HFrEF have reduced LV systolic function due to a number of underlying causes (see Table 5). Reduced systolic function will reduce cardiac output, which has multiple negative consequences (see Figure 1):

- reduced end-organ perfusion;
- activation of neurohormonal (e.g., renin-angiontensin-aldosterone system, sympathetic nervous system), and inflammatory systems;
- cardiac remodelling (LV dilatation, myocyte hypertrophy, and myocardial fibrosis);
- worsening cardiac function.

Together, these factors culminate in the malignant natural history of HFrEF of a generally gradual but relentless decline punctuated with acute decompensation episodes culminating in increased morbidity and eventual death. Importantly, these many and varied negative consequences of reduced cardiac output and heart failure also represent targets for intervention from which the greatest heart failure treatment successes have arisen.

3.5.2. Heart Failure with Preserved Ejection Fraction

The pathophysiology of HFpEF is less well defined. Its wide acceptance as a true syndromic entity remained under question until relatively recently [30]. It is accepted that this condition is a major source of heart failure morbidity, seen in typically comorbid and older patients. Specifically, the entity is more prevalent in older, female patients with a history of hypertension as well as obesity, diabetes, and AF.

Table 5 Causes of heart failure.

Causes of heart failure[a]	
Myocyte damage or loss	Ischaemia: • infarction • ischaemia • microvascular disease • stunning or hibernation
	Inflammation: • infection (e.g., viral or Chagas disease) • immune (autoimmune and hypersensitivity myocarditis, and connective tissue disease)
	Toxic damage: • alcohol, cobalt • drugs—cytotoxic drugs (e.g., anthracyclines), stimulant drugs (e.g., amphetamines, cocaine), immunomodulating drugs (e.g., trastuzumab), clozapine, anabolic steroids • radiation
	Infiltration: • malignancy • amyloid • sarcoid • haemochromatosis or iron overload • glycogen storage diseases • lysosomal storage diseases (e.g., Fabry disease)
	Endomyocardial pathology: • hypereosinophilic syndromes • endomyocardial fibrosis or fibroelastosis
	Metabolic abnormalities: • thyroid • growth hormone • cortisol • diabetes mellitus • phaeochromocytoma
	Nutritional abnormalities: • deficiencies (e.g., thiamine, selenium or iron) • malnutrition • obesity
	Genetic abnormalities: • dilated cardiomyopathy • hypertrophic cardiomyopathy • left ventricular noncompaction • arrhythmogenic right ventricular cardiomyopathy • muscular dystrophies • laminopathies
	Pregnancy and peripartum causes
Abnormal loading conditions	Hypertension
	Valve and myocardium: • valvular dysfunction (rheumatic and non-rheumatic) • congenital defects
	Pericardial pathology: • pericardial constriction or effusion
	High output states: • anaemia • sepsis • arteriovenous fistula • thyrotoxicosis • Paget disease
	Volume overload: • renal failure • iatrogenic fluid overload
Arrhythmias	Tachyarrhythmias: • atrial (e.g., atrial fibrillation) • ventricular arrhythmias
	Bradyarrhythmias: • sinus node or atrioventricular node dysfunction

[a]These are not mutually exclusive.

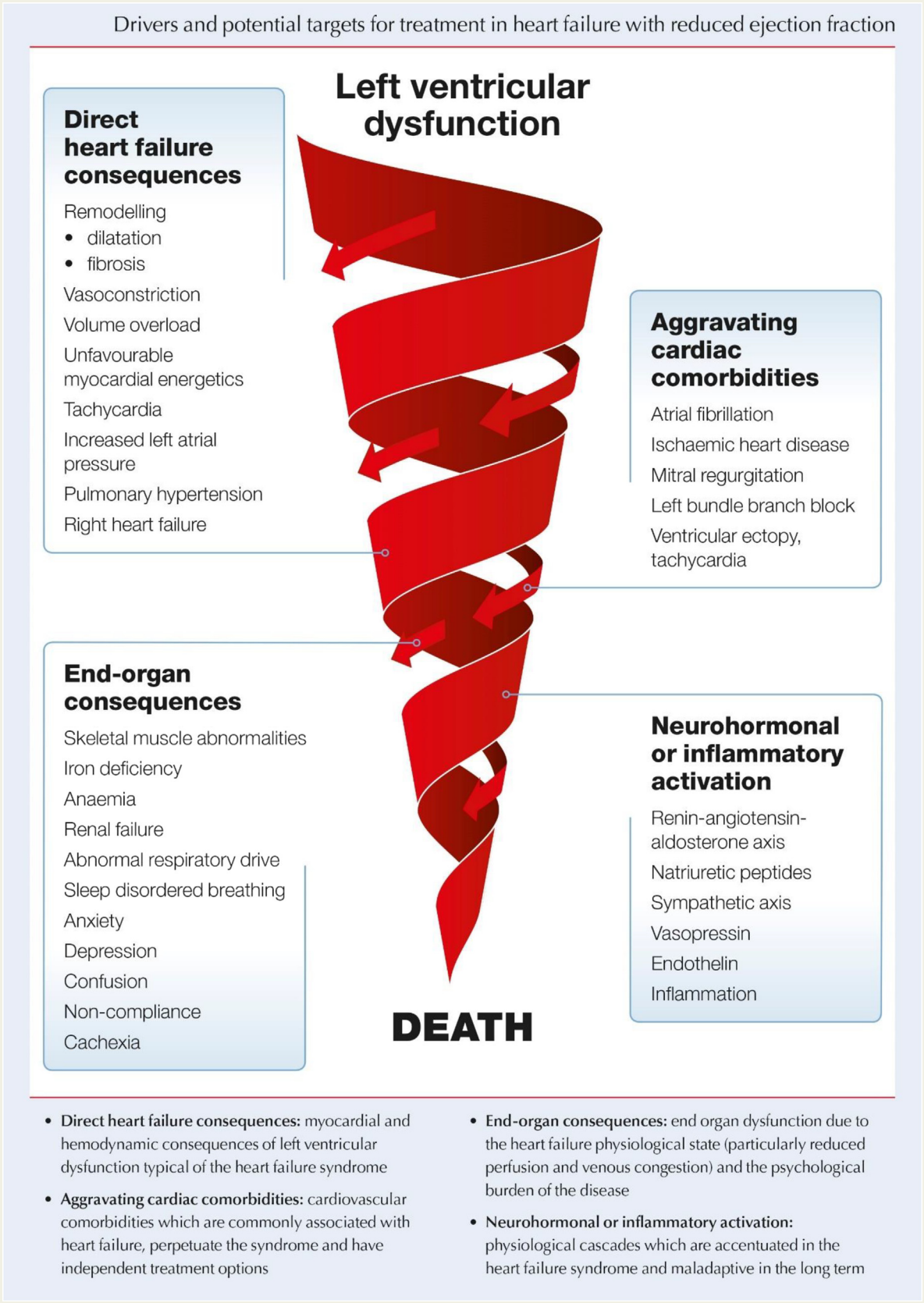

Figure 1 Drivers and potential targets for treatment in heart failure with reduced ejection fraction.

Prevailing current pathophysiological theories include:

- a causal role for comorbidities and consequent coronary microvascular inflammation leading to myocyte hypertrophy and reduced cyclic guanosine monophosphate, resulting in hypophosphorylation of titin (reducing myocardial relaxation) and myocardial fibrosis (reducing myocardial compliance) [31];
- central arterial stiffening, resulting in a rapidly reflected arterial pulse wave, thereby increasing LV afterload [32];
- skeletal muscle oxygen delivery and extraction abnormalities [33];
- subtle abnormalities in contractile and chronotropic reserve [34,35].

This ongoing pathophysiological uncertainty has undoubtedly contributed to the lack of treatment success for this common condition.

4. Prevention of Heart Failure

4.1. Non-Pharmacological Prevention of Heart Failure

Recommendation: Smoking cessation is recommended to decrease the risk of cardiovascular events and decrease the risk of developing heart failure.
(Strong recommendation FOR; low quality of evidence.)

Recommendation: Avoiding excess alcohol is recommended, to decrease the risk of developing heart failure.
(Strong recommendation FOR; very low quality of evidence.)

Recommendation: Weight reduction is recommended in patients who are overweight or obese, to decrease the risk of developing heart failure.
(Strong recommendation FOR; low quality of evidence.)

Recommendation: Regular physical activity is recommended to decrease the risk of cardiovascular events and decrease the risk of developing heart failure.
(Strong recommendation FOR; low quality of evidence.)

Rationale: Primary prevention of behavioural risk factors for heart failure will have a favourable effect on the incidence of the condition, and one should refer to published guidelines regarding recommended levels of physical activity, dietary recommendations, and alcohol intake.

The recommendation for smoking cessation is based on observational studies reporting an association between smoking and the risk of developing cardiovascular disease and heart failure [36]. Obesity and physical inactivity are associated with an increased risk of developing heart failure [37,38], and gastric bypass surgery was recently reported to be associated with a marked reduction in the incidence of heart failure [39]. Observational studies report a U-shaped relationship between alcohol consumption and risk of developing heart failure; however, alcohol intake over 14 standard drinks per week is not protective, and may be harmful [40–42].

4.2. Pharmacological Prevention of Heart Failure

Recommendation: BP lowering and lipid lowering according to published guidelines are recommended, to decrease the risk of cardiovascular events and decrease the risk of developing heart failure.
(Strong recommendation FOR; high quality of evidence.)

Recommendation: Angiotensin converting enzyme (ACE) inhibitors should be considered in patients with cardiovascular disease to decrease the risk of cardiovascular events and decrease the risk of developing heart failure.
(Strong recommendation FOR; moderate quality of evidence.)

Recommendation: Sodium-glucose cotransporter 2 (SGLT2) inhibitors are recommended in patients with type 2 diabetes mellitus associated with cardiovascular disease and insufficient glycaemic control despite metformin, to decrease the risk of cardiovascular events and decrease the risk of hospitalisation for heart failure.
(Strong recommendation FOR; high quality of evidence.)

Recommendation: ACE inhibitors are recommended in patients with LV systolic dysfunction to decrease the risk of developing heart failure.
(Strong recommendation FOR; high quality of evidence.)

Recommendation: Beta blockers should be considered in patients with LV systolic dysfunction to decrease the risk of developing heart failure.
(Strong recommendation FOR; low quality of evidence.)

Rationale: Interventions that decrease the risk of developing cardiovascular disease would be expected to decrease the risk of heart failure, with strong RCT evidence supporting the benefits of blood pressure lowering [43] and lipid lowering [44].

The effect of glucose lowering on the risk of cardiovascular events and heart failure in patients with diabetes mellitus has been less clear; however, longer term follow-up over 10 years suggests this will decrease the risk of cardiovascular events [45]. Two RCTs showed that SGLT2 inhibitors decreased the risk of cardiovascular events and decreased the risk of heart failure hospitalisation in patients with type 2 diabetes who were at high cardiovascular risk (most with cardiovascular disease) with a raised HbA1c despite background therapy, which included baseline prescription rates of 74–78% for metformin, 48–51% for insulin and 42–44% for sulfonylureas [46–48]. Clinicians need to be aware that euglycaemic ketoacidosis has been rarely reported with the use of SGLT2 inhibitors, so these agents should be withheld when the patient is acutely unwell or fasting for surgical procedures.

ACE inhibitors decrease the risk of cardiovascular events and decrease the risk of developing heart failure in patients with cardiovascular disease [49]. They have also been shown to decrease the risk of developing heart failure and improve survival [50–52] in patients with asymptomatic LV systolic dysfunction. It is less clear whether these benefits also apply to angiotensin receptor blockers (ARBs); however, if ACE inhibitors are either contraindicated or not tolerated, it is

reasonable to use ARBs. Beta blockers have been associated with a further reduction in the risk of developing heart failure on top of ACE inhibitors in patients with asymptomatic LV systolic dysfunction [53–55], and favourable trends were reported in an RCT evaluating carvedilol in patients with LV systolic dysfunction following MI [56].

4.3. Screening for Preclinical Heart Failure

Background: Screening with 12-lead electrocardiography (ECG), echocardiography, and plasma B-type natriuretic peptide (BNP) or N-terminal proBNP (NT proBNP) has been considered in ambulatory patients at high risk of developing heart failure to identify abnormalities in cardiac structure and function prior to the development of symptoms of heart failure and allow the use of therapies to prevent heart failure. This level of community screening in at-risk populations will have broader implications due to the sheer number of such patients and the impact of downstream investigations, such that the cost-effectiveness is uncertain.

Although a normal ECG implies that a reduced LVEF is unlikely, the low specificity of ECG abnormalities reduces the value of ECG as a screening tool [57,58]. Given the relatively low rates of asymptomatic LV systolic and advanced diastolic dysfunction [6,59,60], echocardiographic screening is not recommended. Two medium-sized prospective clinical trials have demonstrated screening BNP is associated with a reduction in incident heart failure events in ambulatory subjects with risk factors for developing heart failure (hypertension, diabetes mellitus, obesity, hypercholesterolaemia, vascular disease, valvular disease or arrhythmias). When the screening BNP was more than 50 ng/L or the NT proBNP more than 125 ng/L, subjects were investigated for heart failure and treated with renin–angiotensin system antagonists with or without beta blockers [61,62]. These studies both achieved their primary endpoint, but the number of clinical events were small, such that the clinical effectiveness of using BNP and NT proBNP for screening in high-risk populations is uncertain.

5. Diagnosis and Investigations

5.1. Dyspnoea

Dyspnoea is defined as the subjective sensation of abnormal breathing. Its subjective nature represents a major difficulty for the clinician; however, most commonly, the patient describes a sensation of 'inadequate breathing' or 'air hunger'. Moreover, although dyspnoea is the cardinal symptomatic manifestation of heart failure, its aetiology might represent a myriad of different pathological and physiological states besides heart failure. The patient's complaint of dyspnoea therefore represents a major and complex clinical challenge for the heart failure clinical care provider.

5.1.1. Causes of Dyspnoea

In considering the causes of dyspnoea, the entire physiological process of respiration must be considered because the problem might be at any point between oxygen uptake in the lungs and oxygen consumption by the tissues. This includes the brain (mind and respiratory control centre), lungs, musculoskeletal components of respiration, heart, vasculature, blood, and metabolising tissues. The list given in Table 6, is useful, but by no means exhaustive.

5.1.2. Dyspnoea Workup

Evaluation of a patient presenting with dyspnoea will vary dependent on clinical circumstances such as acuity, the patient's age, and their past medical history. The history should determine the duration and severity—based on the New York Heart Association (NYHA) functional classification—of dyspnoea and whether there are precipitating factors (e.g., exertion and emotion). If heart failure is suspected, one should enquire as to whether the patient has orthopnoea, paroxysmal nocturnal dyspnoea or associated symptoms such as chest pain, palpitations, dizziness, syncope, swollen ankles, and abdominal bloating. Physical examination should include assessment of vital signs (heart rate and rhythm, blood pressure, respiratory rate and temperature), peripheral perfusion, volume status (JVP, peripheral and sacral oedema, ascites and hepatic congestion), cardiac palpitation, and auscultation (apex beat, gallop rhythm, and murmurs) and auscultation of lung fields (air entry, crackles, and wheeze).

Basic investigations include non-invasive measurement of oxygen saturation, 12-lead ECG, chest X-ray, serum biochemistry (electrolytes, renal function, and liver function) and full blood count. Further investigations will depend on clinical circumstances and findings from the initial clinical workup, and may include serum cardiac troponin measurement, plasma natriuretic peptide levels, thyroid function tests, arterial blood gases, D-dimer, echocardiography, stress testing (assessment for ischaemia or filling pressures), coronary angiography (computed tomography [CT], invasive), right or left heart catheterisation, lung function tests, ventilation/perfusion lung scan, CT pulmonary angiography, high-resolution CT chest, cardiopulmonary exercise testing, and cardiac magnetic resonance (CMR) imaging.

5.1.3. Requirement for More Urgent Evaluation or Referral

A list of red flags that may require more urgent evaluation or specialist referral is included in Table 7.

5.2. Diagnostic Investigations for Heart Failure

5.2.1. Diagnosis of Heart Failure

5.2.1.1. 12-Lead electrocardiogram.

Recommendation: A 12-lead ECG is recommended in patients with either a suspected diagnosis or new diagnosis of heart failure, to assess cardiac rhythm, QRS duration, and the presence of underlying conditions such as myocardial ischaemia or LV hypertrophy.

(Strong recommendation FOR; low quality of evidence.)

Table 6 Causes of dyspnoea.

Causes of dyspnoea	
Cardiac	• Increased left-sided intracavity filling pressure – heart failure due to myocardial dysfunction (HFrEF, HFpEF) – left-sided valvular dysfunction (aortic or mitral stenosis or regurgitation) • Myocardial ischaemia • Arrhythmia (tachyarrhythmia, bradyarrhythmia, ectopy, AF, atrioventricular disassociation) • Low cardiac output (left-sided): – pulmonary hypertension – hypovolaemia – cardiac shunt – cardiac compression (pericardial constriction, cardiac tamponade, tension pneumothorax)
Respiratory	• Hypoxia – pulmonary parenchymal abnormality—infection (pneumonia), fibrosis, destruction (emphysema), oedema, alveolar haemorrhage and compression (pleural effusion and pneumothorax) – airway obstruction (asthma, bronchitis, upper airway) – ventilation–perfusion mismatch (pulmonary embolus and pulmonary shunt) • Central respiratory drive abnormality (pharmacological, metabolic) • Musculoskeletal respiration abnormality – skeletal myopathy – respiratory muscle fatigue – chest wall abnormality (kyphoscoliosis, thoracic skeletal pain and obesity)
Peripheral muscle oxygen extraction abnormality or inefficiency	• Poor physical fitness • Myopathy
Anxiety	• Panic attack, chronic anxiety state
Anaemia, iron deficiency	
Hyperventilation	• Acidosis (renal failure, ketoacidosis, shock) • Pharmacological cause • Thyrotoxicosis

AF: atrial fibrillation, HFpEF: heart failure with preserved ejection fraction, HFrEF: heart failure with reduced ejection fraction.

Table 7 When to consider early referral (red flags).

When to consider early referral in the community setting (red flags)	
Symptoms	• Orthopnoea • Paroxysmal nocturnal dyspnoea • Syncope • Ischaemic chest pain
Signs	• Tachycardia (heart rate >100 bpm) • Bradycardia (heart rate <40 bpm) • Hypotension (systolic BP <90 mm Hg) • Hypoxaemia • Gallop rhythm • Significant heart murmur
Investigations	• Evidence of ischaemia or infarction on 12-lead ECG • Pulmonary oedema on chest X-ray • Raised cardiac troponin level • Moderate or severe valvular heart disease on echocardiography • LVEF ≤40% • Ischaemia on stress testing

BP: blood pressure, ECG: electrocardiogram, LVEF: left ventricular ejection fraction.

5.2.1.2. Chest X-ray.

Recommendation: A chest X-ray is recommended in patients with either a suspected diagnosis or new diagnosis of heart failure, to detect signs of pulmonary congestion, and to identify alternative cardiac or non-cardiac causes for the patient's symptoms.

(Strong recommendation FOR; very low quality of evidence.)

5.2.1.3. B-type Natriuretic Peptide and N-terminal pro-B-type Natriuretic Peptide.

Recommendation: BNP or NT proBNP levels are recommended for diagnosis in patients with suspected heart failure, when the diagnosis is uncertain.

(Strong recommendation FOR; high quality of evidence.)

5.2.1.4. Echocardiogram.

Recommendation: A transthoracic echocardiogram is recommended in patients with suspected heart failure, to improve diagnostic accuracy, and in patients with a new diagnosis of heart failure, to assess cardiac structure and function (including measurement of LVEF), assist in classification and therefore guide management.

(Strong recommendation FOR; low quality of evidence.)

Rationale: The diagnostic workup of a patient with suspected heart failure is summarised in Figure 2. Highly recommended investigations include the 12-lead ECG, chest X-ray, transthoracic echocardiography and laboratory blood testing, to establish an initial working diagnosis and treatment plan. Although the ECG is usually abnormal in patients with heart failure, the abnormalities are often non-specific. A chest X-ray may rule in the diagnosis of heart failure or identify an alternative cause for the patient's symptoms; however, a normal chest X-ray does not rule out heart failure. An echocardiogram is an essential investigation in patients with a diagnosis of heart failure, to evaluate cardiac chamber volumes, LV wall thickness, LV systolic and diastolic function, RV systolic function, intracardiac filling pressures, valve structure and function, pulmonary artery pressure, and pericardial disease [23,24]. However, if the diagnosis is unclear following initial clinical assessment and an echocardiogram cannot be arranged in a timely fashion, measurement of plasma natriuretic peptide levels is recommended.

Natriuretic peptides can be viewed as the body's endogenous defence against hypervolaemia and hypertension. They are vasoactive peptides that result in natriuresis, diuresis, and vasodilation. The natriuretic peptides comprise atrial, B-type, and C-type natriuretic peptides. BNP is released from myocytes in response to elevated (predominately ventricular) wall tension as a pro-peptide. The pro-peptide (proBNP) is released into the circulation and then cleaved into biologically active BNP and its biologically inactive NT fragment (NT proBNP). Both peptides have been shown to correlate with intracavity cardiac filling pressures in patients with

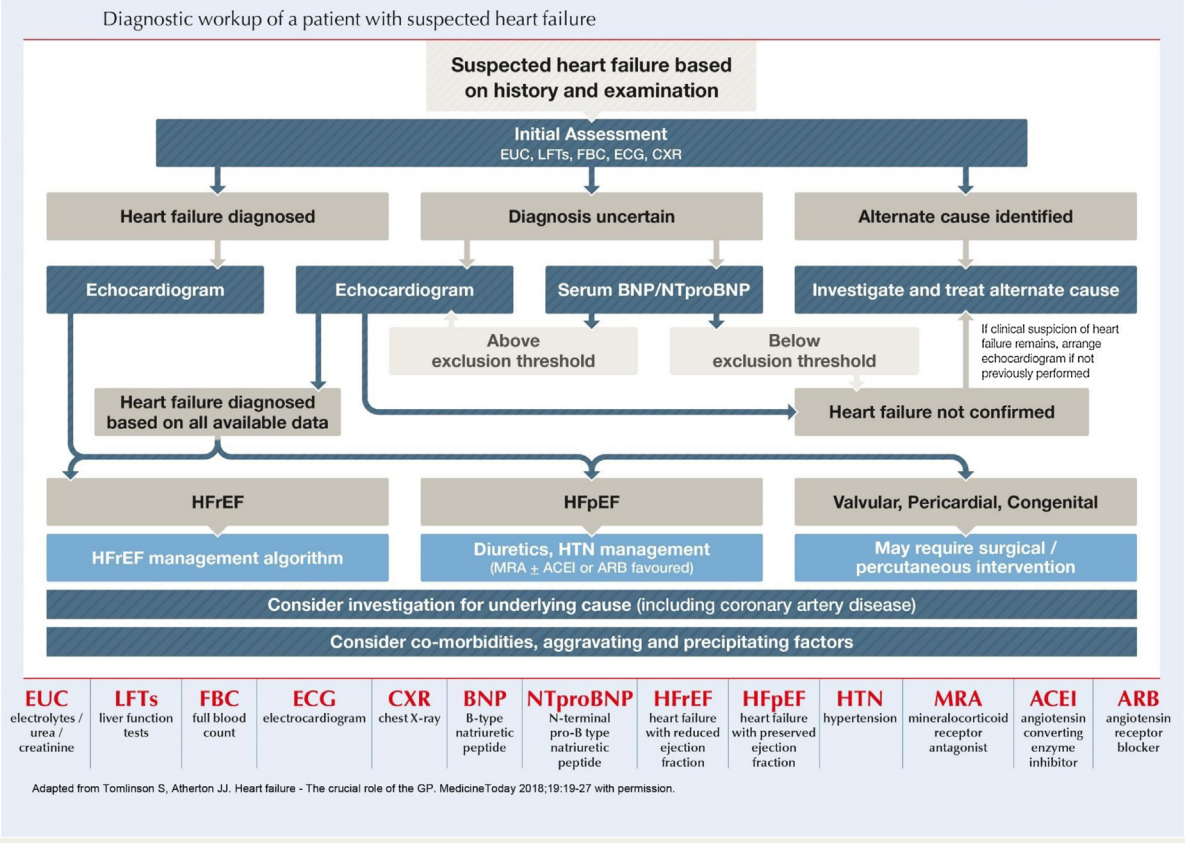

Figure 2 Diagnostic workup of a patient with suspected heart failure.

heart failure. Individual patient characteristics affect levels of these peptides, which increase with ageing, renal impairment, AF, and to a minor degree, female gender; levels are reduced in obesity [63].

Plasma BNP and NT proBNP levels are useful to rule out heart failure in patients with undifferentiated dyspnoea in the emergency [64–66] and primary care settings [67]. Patients with normal BNP or NT proBNP are unlikely to have heart failure, and alternative diagnoses should be considered. However, if the diagnosis of heart failure remains strongly suspected, further investigation with echocardiography may be helpful. Higher plasma BNP and NT proBNP cut-offs can be used to rule in the diagnosis of heart failure.

Practice advice

1. The initial workup of a patient with suspected heart failure includes taking a history, conducting a cardiorespiratory physical examination and arranging a chest X-ray. This may allow the diagnosis of heart failure to be ruled in (e.g., the presence of symptoms and signs specific for that diagnosis, see Table 1, or radiographic appearances consistent with pulmonary congestion); however, a normal physical examination and chest X-ray does not rule out the diagnosis.
2. A 12-lead ECG, blood biochemistry (electrolytes, urea, creatinine, glucose, liver function tests), full blood count, and thyroid function tests should be performed in patients with either a suspected diagnosis or new diagnosis of heart failure, to assess comorbid conditions and alternative causes for fluid overload.
3. The single most useful investigation in patients with suspected or confirmed heart failure is the echocardiogram. However, if the diagnosis is unclear and an echocardiogram cannot be arranged in a timely fashion, measurement of plasma BNP and NT proBNP has been shown to improve diagnostic accuracy.
4. The BNP and NT proBNP precise cut-offs are variable between trials and are affected by individual patient characteristics (e.g., age, weight, and renal function); however, we propose as a pragmatic guide to the clinician a BNP of less than 100 ng/L and an NT proBNP of less than 300 ng/L for rule-out.
5. Levels of BNP and NT proBNP are generally lower in HFpEF than in HFrEF; consequently, the 'rule-out' reliability of BNP and NT proBNP levels in suspected HFpEF is significantly weaker than in HFrEF. Other guidelines have used lower cut-offs in the ambulatory setting, however the trade-off is that this leads to more false positives and unnecessary downstream testing.
6. Levels of BNP and NT proBNP can be elevated in cardiovascular conditions other than heart failure (e.g., pulmonary thromboembolism, pulmonary arterial hypertension, AF, and acute coronary syndromes).

5.2.1.5. Other imaging for diagnosis.

Practice advice

1. Given the dose of ionising radiation required for nuclear imaging and the inability to assess diastolic function and valve function, radionuclide ventriculography is generally reserved for patients in whom echocardiography images are non-diagnostic, because of limited acoustic windows. CMR is a preferred alternative in this setting.
2. Bedside thoracic ultrasound may be considered in patients with suspected acute heart failure to detect interstitial oedema (ultrasonographic B lines) and pleural effusion [68,69]. However, there is insufficient evidence with which to recommend its routine use for the diagnosis of heart failure.

5.2.2. Assessment of Aetiology

Recommendation: Invasive coronary angiography should be considered in patients with heart failure associated with refractory angina, resuscitated cardiac arrest, sustained ventricular arrhythmias, or with evidence of ischaemic heart disease on other investigations, or an intermediate-to-high pretest probability of coronary artery disease, to determine the need for coronary revascularisation.
(Strong recommendation FOR; low quality of evidence.)

Recommendation: Either CT coronary angiography or CMR with late gadolinium enhancement (LGE) may be considered in patients with heart failure who have a low-to-intermediate pretest probability of coronary artery disease, to distinguish ischaemic and non-ischaemic causes of ventricular dysfunction.
(Weak recommendation FOR; low quality of evidence.)

Recommendation: Non-invasive functional testing—stress echocardiography, single-photon emission computerised tomography scan (SPECT), positron emission tomography (PET) and CMR with LGE—may be considered in patients with heart failure and established coronary artery disease for the assessment of myocardial ischaemia and viability, to determine the need for coronary revascularisation.
(Weak recommendation FOR; very low quality of evidence.)

Recommendation: CMR with LGE should be considered in patients with heart failure associated with increased LV wall thickness that remains unexplained following clinical evaluation including a 12-lead ECG and echocardiogram to identify inflammatory and infiltrative cardiomyopathies.
(Strong recommendation FOR; low quality of evidence.)

Recommendation: Either PET or bone scintigraphy may be considered in patients with heart failure associated with increased LV wall thickness that remains unexplained following clinical evaluation, including a 12-lead ECG and echocardiogram to identify infiltrative cardiomyopathies.
(Weak recommendation FOR; low quality of evidence.)

Rationale: In patients with recent-onset heart failure of uncertain aetiology with no obvious ischaemic basis, CMR with LGE and magnetic resonance coronary angiography (MRCA), and invasive coronary angiography (ICA) were compared against a gold standard consensus panel to determine the final diagnosis. LGE appeared to show diagnostic equivalence to ICA to detect ischaemic heart disease [70]. In another diagnostic accuracy study [71], patients were admitted for the management of heart failure of unknown

aetiology. Independent diagnoses were made using CMR, endomyocardial biopsies (EMB), echocardiograms and clinical data; these diagnoses were compared with a gold standard defined as the complete clinical data, CMR, and EMB. The findings of this study indicated that CMR, especially when combined with other diagnostic procedures, may have a capacity to diagnose the underlying aetiology in patients with heart failure, as well as or better than EMB.

Three prospective cohort studies [72–74] and one retrospective study [71] examined the value of CMR for further diagnostic clarification in patients with increased LV wall thickness on echocardiography. The various studies compared the diagnostic value of CMR against reference standards including echocardiographic examination [72,73], EMB [71]. and bone tracer scintigraphy [74]. Kwong et al. (2015) found the extent of left atrial LGE using CMR was highly predictive for the diagnosis of cardiac amyloidosis—showing, on average, a nearly twofold increase in the odds of cardiac amyloidosis diagnosis [73]. The study by Martinez-Naharro et al. (2017) suggests that, in patients with cardiac amyloidosis, LGE is always present, and appeared as diffuse subendocardial LGE in 29% of patients and transmural LGE in 71% [74]. Yoshida et al. (2013) found that the use of CMR demonstrated a diagnostic capability comparable with EMB. While both CMR and EMB misdiagnosed patients with hypertrophic cardiomyopathy (HCM), cardiac sarcoidosis (CS), and hypertensive heart disease (HHD), all of the patients who received accurate diagnoses with EMB alone were correctly diagnosed using the combined diagnosis with clinical data, echocardiogram, and CMR [71]. Bone scintigraphy has been shown to have a high sensitivity and specificity for the diagnosis of transthyretin-related cardiac amyloidosis [75].

Practice advice

1. The evaluation of heart failure aetiology should be initiated by a cardiologist or a treating physician on the advice of a cardiologist. Given the implications for therapy, patients with a reduced LVEF should have appropriate evaluation of coronary arteries, with the evaluation determined by the presence or absence of symptoms of coronary disease and the pretest probability of coronary artery disease.
2. In conjunction with ancillary laboratory testing for systemic conditions associated with infiltrative cardiomyopathies, non-invasive imaging with CMR or PET (or both) or bone scintigraphy should be carefully considered.

5.2.3. Risk Stratification and Prognosis

See Table 8 for a summary of investigations and considerations for risk stratification and prognosis.

5.2.3.1. BNP and NT proBNP.

Recommendation: BNP and NT proBNP levels may be considered in patients with an established diagnosis of heart failure for prognostic stratification.

(Weak recommendation FOR; high quality of evidence.)

Rationale: Consistent with their release and functional physiology, BNP and NT proBNP levels have demonstrated prognostic predictive value in heart failure [76–78]. Indeed, they are among the most powerful independent predictors of mortality and adverse cardiovascular events across the whole spectrum of heart failure. Moreover, they are similarly powerful predictors of major events in other cardiac diseases such as MI [79], pulmonary arterial hypertension [80], valvular heart disease [81], and pulmonary thromboembolism [82].

Table 8 Investigations and considerations for risk stratification and prognosis.

Investigations and considerations for risk stratification and prognosis
Age, sex
Ethnicity
NYHA functional class
Recent deterioration (e.g., hospitalisation for heart failure)
Frailty, weight loss
Comorbidities (e.g., IHD, AF, valvular heart disease, stroke, diabetes, COPD, depression, cognitive impairment and sleep apnoea)
Heart rate and rhythm, systolic blood pressure
Clinical congestion
QRS duration
Serum biochemistry: Na, K, eGFR, urate and liver function tests
Iron studies
Cardiac troponin levels
Haemoglobin
BNP and NT proBNP
Echocardiogram (LVEF, left atrial size, RV function, RVSP, diastolic function)
Cardiopulmonary exercise test, 6-min walk distance.

AF: atrial fibrillation, BNP: B-type natriuretic peptide, COPD: chronic obstructive pulmonary disease, eGFR: estimated glomerular filtration rate, IHD: ischaemic heart disease, LVEF: left ventricular ejection fraction, NT: N-terminal, NYHA: New York Heart Association, RV: right ventricular, RVSP: right ventricular systolic pressure.

Practice advice

The clinical impact and change in management resulting from the prognostic information gained from BNP and NT proBNP levels is less clear. There are also many other prognostic markers in heart failure. It is unclear whether and how changes in BNP and NT proBNP levels should alter management to improve patient care.

5.2.3.2. Genetic Testing.

Recommendation: Genetic testing may be considered in patients with dilated cardiomyopathy (DCM) associated with conduction disease, for prognostic stratification and to guide management regarding the use of implantable cardioverter defibrillators.

(Weak recommendation FOR; low quality of evidence.)

Rationale: The main value of genetic testing in patients with inherited heart diseases (including DCM) is to allow

predictive genetic testing in at-risk family members if a family mutation is identified and thereby facilitate clinical screening. Although some studies have reported earlier age of onset and decreased event-free survival with certain genetic causes, it is less clear what incremental risk prediction this provides in addition to clinical variables. A recent systematic meta-analysis reported a higher prevalence of sudden cardiac death, cardiac transplantation or ventricular arrhythmias in *LMNA* and phospholamban mutation carriers [83]. *LMNA* mutation carriers appear to be more likely to develop conduction disease, and to be at higher risk of ventricular arrhythmias even before the development of severe LV systolic dysfunction [83,84]. However, there is little evidence that the results of genetic testing resulted in a change in management practice.

5.2.3.3. CMR with LGE. *Rationale:* Two systematic reviews [85,86] and 22 cohort studies assessed the presence, extent, location, and patterns of LGE. The two reviews and most of the original studies were of patients with DCM; most of the patients with DCM had an LVEF of less than 45%. Overall, the reviews and individual studies found that the presence of LGE was a predictor of adverse cardiac outcomes. Both systematic reviews reported that LGE was a significant predictor of sudden cardiac death (SCD) or ventricular arrhythmia events. The extent, location, and patterns of LGE were not predictive of these outcomes in all the studies. None of the studies evaluated whether CMR led to improved outcomes.

In patients with HCM, LGE has been shown to be significantly associated with all-cause mortality [87,88], and SCD in two reviews [87,88], with a trend reported in another review [89]. Chan et al. (2014) [90] similarly reported that extent of LGE was a stronger predictor of SCD events than clinical risk factors in people with HCM; each 10% increase in LGE was accompanied by a 40% increase in risk of SCD (hazard ratio [HR], 1.46; 95% confidence interval [CI], 1.12–1.92). The number of events was small in all studies. None of the studies evaluated whether CMR led to improved outcomes.

Practice advice

CMR with LGE may be considered in patients with DCM and HCM to provide prognostic information and guide management decisions regarding the use of implantable cardioverter defibrillators. However, no studies to date have evaluated whether this will lead to improved outcomes.

5.2.4. Diagnostic Tests to Guide Therapy in Heart Failure

Recommendation: Transthoracic echocardiography should be considered in patients with HFrEF 3–6 months after the start of optimal medical therapy, or if there has been a change in clinical status, to assess the appropriateness for other treatments, including device therapy (implantable cardioverter defibrillator (ICD) or cardiac resynchronisation therapy (CRT), or both).

(Weak recommendation FOR; low quality of evidence.)

Practice advice

1. Regular assessment of symptoms, cardiorespiratory examination for vital signs and signs of congestion, serum biochemistry (electrolytes, urea, creatinine, and glucose), and full blood count should be performed in patients with heart failure at regular intervals (usually 6- to 12-monthly once stabilised), or if there is a change in clinical status, to adjust medications and review the need for further investigations to ascertain reasons for deterioration in clinical status.
2. A 12-lead ECG should be performed in patients with heart failure at regular intervals (usually 12-monthly once stabilised) or if there is a change in clinical status, to monitor the development of cardiac arrhythmias and to monitor QRS duration and morphology.
3. An echocardiogram is usually repeated 3–6 months after commencing medical therapy in patients with HFrEF or if there is a change in clinical status, to determine eligibility for other pharmacological treatments (e.g., switching an ACE inhibitor or angiotensin receptor blocker to an angiotensin receptor neprilysin inhibitor [ARNI], adding ivabradine) and device therapy (ICD and CRT).
4. Current evidence does not support routine right heart catheterisation to guide management in heart failure [91].

5.2.4.1. BNP and NT proBNP. *Rationale:* Many small-to-medium sized RCTs have addressed the question of the incremental benefit of HFrEF pharmacotherapy guidance using BNP and NT proBNP levels compared to usual clinical care [92–101]. Results have been mixed; however, meta-analyses [102,103] suggest a benefit. The most recent large RCT has failed to show a benefit of this management strategy [104].

Practice advice

1. Current evidence does not support routine measurement of plasma BNP and NT proBNP levels to guide titration of pharmacological therapy in ambulatory heart failure, in view of conflicting evidence that this will decrease mortality or hospitalisation.
2. BNP and NT proBNP levels change despite a stable physiological state because of biological variability. Present data suggests that a change in BNP of more than 40% or a change in NT proBNP of more than 25% is outside the accepted range of biological variability. Consequently, changes of this magnitude can be interpreted as a clinically significant worsening (if levels have increased) or improvement (if levels have decreased) of the heart failure status [105].
3. The use and uptitration of heart failure therapy (diuretics, ACE inhibitors, or ARBs and MRAs) reduces BNP and NT proBNP levels by their effect on intracardiac filling pressure and heart failure.
4. Beta blockers show a complex relationship with BNP and NT proBNP levels, with an initial increase in levels followed by a later fall [106]. This reflects the symptomatic changes seen with beta blockade in HFrEF, and is physiologically intuitive given the negative inotropic effects of these agents.
5. ARNIs have a complex effect on BNP and NT proBNP levels. NT proBNP is not a neprilysin substrate; hence, levels are reduced with ARNI use. BNP is a neprilysin

substrate (indeed this is probably at least in part a mechanism of action of the drug), and levels are therefore increased with ARNI use, while the beneficial effect of the drug on heart failure status will reduce BNP production. These opposed effects in totality may result in a small increase in overall BNP levels with ARNI use [107].

6. Acute Heart Failure

6.1. Assessment

Recommendation: Investigation and management of precipitating factors is recommended in all patients presenting with acute heart failure. Acute coronary syndrome (ACS), hypertensive crisis, arrhythmia, mechanical catastrophe (e.g., ruptured interventricular septum, mitral papillary muscle, or LV free wall, or acute valvular regurgitation) and pulmonary embolism should be confirmed or excluded, and managed immediately.

(Strong recommendation FOR; low quality of evidence.)

Rationale: Patients presenting with acute heart failure often present as medical emergencies, and early assessment and treatment is critical. Cardiogenic shock and acute respiratory failure must be identified and managed urgently. Most patients who present with an acute exacerbation of heart failure have a history of chronic heart failure [108,109]. As well as treating the symptomatic acute decompensation, treatment of the precipitating factors (Table 9) has also been shown to improve outcomes and response to therapy [109]. Treatment of underlying ischaemia, sepsis, anaemia, metabolic disorders and haemodynamic abnormalities (Table 9) can lead to further improvements in combination with treatment of the heart failure itself [110]. Acute coronary syndrome, hypertensive crisis, arrhythmia, mechanical catastrophe, and pulmonary embolism [108] should be excluded and managed appropriately.

The need for medications that can exacerbate heart failure symptoms or cause deterioration in cardiovascular haemodynamics should be re-evaluated (Table 10) [111], because their adverse effects may be reversible.

The presence or absence of congestion or hypoperfusion can guide management [108–110]. Clinical assessment for signs of congestion such as pulmonary crepitations, peripheral oedema, elevation of the JVP, pleural effusions, hepatic congestion and ascites may require diuretics [112,113] or vasodilator therapy [114–117]. Signs of reduced peripheral perfusion such as cold extremities, sweating, oliguria, confusion, and hypotension may require inotropic therapy [118,119] or vasopressor agents [120].

Benefits and harms: Patients with acute heart failure often constitute a medical emergency, and urgent treatment should not be delayed to try to find a precipitating factor [109,110]. Treating the underlying cause may improve outcomes more rapidly and, if the precipitating factor is identified, may reduce the likelihood of recurrence [109,110].

Resources and other considerations: Targeted investigations including 12-lead ECG [121], chest X-ray [122], biochemistry [108,123] and haematology [108] can assist in identification of aetiology and prognosis. Urgent echocardiography should not delay treatment and is only required if there are suspected mechanical issues (e.g., severe valvular stenosis or regurgitation, ruptured interventricular septum or LV-free wall, or pericardial tamponade) or if there is haemodynamic instability [108]. Invasive haemodynamic monitoring, including arterial lines, central venous lines and pulmonary arterial catheters, are usually not indicated for diagnosis, but may later become necessary in the intensive care or coronary care units [108]; however, pulmonary arterial catheterisation has not been shown to reduce mortality rehospitalisation [124]. Commencement of treatment that improves long-term prognosis, such as beta-adrenoreceptor antagonists, before hospital discharge increases the likelihood of long-term maintenance treatment with these agents [125].

Practice advice

1. A careful history should be taken to try to find a cause of ADHF (although this may be deferred while stabilising patients with emergent presentations).
2. Investigations should focus on the cause and severity of acute heart failure. This may include serial ECGs and

Table 9 Causes of acute decompensation of chronic heart failure.

Causes of acute decompensation of chronic heart failure	
Acute myocardial ischaemia or infarction	Hypoxia (e.g., pneumonia, pulmonary embolism)
Arrhythmia (e.g., atrial fibrillation, ventricular tachycardia/ectopy)	Noncompliance with medications, fluid or salt restriction
Infection (e.g., respiratory, endocarditis, urinary, skin)	Pericardial tamponade
Anaemia	Receiving drugs that may worsen chronic heart failure (see Table 10)
Hyperthyroidism or hypothyroidism	Adrenal insufficiency or corticosteroid excess
Increased sympathetic drive (e.g., phaeochromocytoma, Takotsubo cardiomyopathy, acute hypertension)	Mechanical catastrophe (e.g., ruptured interventricular septum, mitral papillary muscle or left ventricular free wall, or acute valvular regurgitation)
Acute renal failure	

Table 10 Medications that may cause or exacerbate chronic heart failure.

Medications that may cause or exacerbate heart failure	
Centrally acting calcium channel blockers	NSAIDs (nonselective and COX-2 selective)
Tricyclic antidepressants	Clozapine
Type I antiarrhythmic agents (e.g., flecainide, disopyramide and quinidine)	Drugs that prolong the QT interval
Corticosteroids	Moxonidine
Thiazolidinediones (glitizones)	TNF-α receptor antagonists (etanercept)
Tyrosine kinase inhibitors (e.g., sunitinib)	Trastuzumab (herceptin)
Saxagliptin	Minoxidil
Anthracycline chemotherapeutic agents	Recreational stimulants (e.g., amphetamines or cocaine)
Beta blockers, if used in unstable or unsuitable patients	

COX: cyclo-oxygenase, NSAID: nonsteroidal anti-inflammatory drug, TNF: tumour necrosis factor.

cardiac troponin (exclude acute coronary syndrome), chest X-ray (evaluate pulmonary congestion, cardiothoracic ratio, and exclude other pathology), blood biochemistry, full blood count, BNP measurement (confirm or exclude diagnosis), echocardiography (for diagnosis and evaluation for underlying aetiology and mechanical complications), and lung ultrasound.

3. More than one precipitating factor may exist.
4. The need for medications that may exacerbate heart failure should be re-evaluated.
5. Therapy should be guided according to the patient's vital signs, oxygen saturation, and the presence or absence of congestion and hypoperfusion.

6.2. Oxygen Therapy in Acute Heart Failure

Recommendation: Monitoring of peripheral arterial oxygen saturation is recommended in patients with acute heart failure.

(Strong recommendation FOR; very low quality of evidence.)

Recommendation: Oxygen therapy is recommended in patients with acute heart failure associated with oxygen saturation levels below 94%.

(Strong recommendation FOR; very low quality of evidence.)

Rationale: In the past, oxygen administration had been recommended in patients with acute heart failure to relieve symptoms of dyspnoea and possibly increase tissue oxygen delivery, particularly in patients with myocardial ischaemia. Recent studies, however, have demonstrated that oxygen therapy in nonhypoxic patients causes vasoconstriction (including coronary vasoconstriction), a reduction in cardiac output and possible oxygen free radical damage [126,127]. Oxygen therapy should be reserved for patients with acute heart failure and oxygen saturation levels below 94% to correct hypoxaemia [128].

In patients with ST elevation myocardial infarction, the Australian Air Versus Oxygen in Myocardial Infarction (AVOID) study [128] randomised 638 patients with oxygen saturation of 94% or more to oxygen vs no oxygen and found that oxygen therapy was associated with an increase in creatine kinase levels, recurrent MI and cardiac arrhythmia as well as an increase in myocardial infarct size on CMR imaging at 6 months. The DETO2X–SWEDEHEART study [129] randomised 6629 patients with suspected MI and oxygen saturation of 90% or more to oxygen vs ambient air. The study found that oxygen therapy was associated with no difference in mortality or recurrent MI at 1 year and no difference in peak troponin or cardiogenic shock, although there was a slight increase in hypoxaemia in the ambient air group.

Oxygen therapy in patients with COPD may increase ventilation–perfusion mismatch and suppress ventilation, causing hypercapnoea [108]; in these patients, and in all patients in whom oxygen is administered, oxygen saturation should be monitored by pulse oximetry [128]. Oxygen therapy should be prescribed in patients with initial oxygen saturation below 94% to a target oxygen saturation of 94–98%; however, a lower target (88–92%) may be applied in those at risk of hypercapnoea [127].

Benefits and harms: Oxygen may improve tissue oxygenation in patients who are hypoxaemic [108]. However, oxygen therapy increases costs with no proven benefit in patients who are not hypoxaemic [130]. In patients with COPD, oxygen therapy may increase ventilation–perfusion mismatch and suppress ventilation, causing hypercapnoea [108,130,131].

Resources and other considerations: Oxygen saturation should be monitored by pulse oximetry in patients in whom oxygen therapy is administered. Arterial blood gas analysis facilities should be available, particularly for patients at risk of hypercapnic type II respiratory failure.

Practice advice

1. Peripheral arterial oxygen saturation via pulse oximetry should be monitored in patients with acute heart failure.
2. Oxygen therapy is not recommended in acute patients with heart failure with oxygen saturation levels of 94% or above.

3. In hypoxic patients given oxygen therapy, a target oxygen saturation of 94–98% should be achieved.
4. In patients at risk of hypercapnoea (type II respiratory failure), an oxygen saturation of 88–92% should be targeted.
5. Arterial blood gases should be monitored in patients at risk of hypercapnic Type II respiratory failure.

6.3. Opiate Therapy in Acute Heart Failure

Rationale: Opiates relieve anxiety and symptoms of dyspnoea in pulmonary oedema. They have some beneficial effects on cardiac and respiratory status in acute heart failure where venodilatation and a reduction in respiratory drive and the work of breathing are desirable. However, opiates may lead to excessive respiratory depression, hypotension, nausea, bradycardia, and possibly increased need for intubation [131,132]. Opiates may be detrimental in acute MI and pulmonary oedema [133], and there are concerns about increased risk of adverse outcomes in patients with acute heart failure. If vasodilators are required, then other agents are preferred [131–133]. For similar reasons, anxiolytics and sedatives are not recommended unless agitation is not able to be controlled [108].

Benefits and harms: In patients who are distressed or agitated, opiates may relieve symptoms, induce venodilatation, mild arterial dilatation, and reduce heart rate [134]. These potential symptomatic effects should be weighed against the risk of hypotension, respiratory depression, and nausea (with the potential for aspiration), all of which may increase the need for invasive ventilation.

Resources and other considerations: If opiates are administered to patients with acute heart failure and respiratory distress, resources should be available in case of sudden deterioration in blood pressure or respiratory drive that may require vasopressor or ventilatory support.

Practice advice

1. Opiates should generally be avoided in patients with acute heart failure, particularly in those with hypotension or who are at risk of aspiration or hypoventilation.
2. Opiates may be used very cautiously in patients with uncontrollable agitation with the knowledge that the requirement for invasive ventilation is increased.

6.4. Ventilatory Support in Acute Heart Failure

Recommendation: Non-invasive ventilation should be considered in patients with acute heart failure associated with pulmonary congestion who remain hypoxaemic and tachypnoeic despite oxygen therapy, to improve symptoms and reduce the requirement for intubation.
(Strong recommendation FOR; high quality of evidence.)

Rationale: Patients with acute heart failure and pulmonary congestion or acute pulmonary oedema may experience respiratory distress. If the oxygen saturation falls below 94%, oxygen therapy may be administered (see Section 6.2). However, if the respiratory rate is more than 25 breaths/minute, non-invasive continuous positive airway pressure (CPAP) or bi-level positive airway pressure (BiPAP) ventilation is recommended to reduce pulmonary congestion and respiratory distress [135–139], and may reduce requirements for intubation and reduce mortality [129]. CPAP is generally the first-line modality, but BiPAP also involves inspiratory pressure support, which is useful in patients with coexistent type II respiratory failure with hypercapnoea and acidosis as well as acute pulmonary oedema.

If patients with acute heart failure and acute pulmonary congestion remain hypoxaemic (oxygen saturation <94%) or hypercapnic ($PaCO_2 > 50$ mm Hg) and develop respiratory fatigue despite non-invasive ventilation, then intubation is recommended [108,140]. Respiratory fatigue is usually associated with a reduced respiratory rate, reduced respiratory effort, hypercapnoea, and mental confusion [140]. Intubation and mechanical ventilation should be reserved for patients with acute respiratory failure who do not respond to oxygen, vasodilators, and non-invasive ventilation.

Resources and other considerations: Non-invasive ventilation may be commenced in the ambulance, emergency department, coronary care unit, or intensive care unit if resources are available. BiPAP often requires admission to an intensive care or coronary care unit with appropriate facilities. Oxygen saturation should be monitored by pulse oximetry and often via arterial lines with frequent arterial blood gas analysis.

Practice advice

1. Non-invasive ventilatory support is recommended in patients with acute pulmonary congestion who remain hypoxaemic ($SaO_2 < 94\%$) and tachypneic (respiratory rate > 25/min) despite oxygen therapy.
2. Patients with acute pulmonary congestion who have type II respiratory failure with hypercapnoea and acidosis who require non-invasive ventilatory support are suitable candidates for BiPAP.
3. Positive pressure ventilation may lead to marked reductions in cardiac output and blood pressure in patients with cardiogenic shock or severe RV failure, and should therefore be used cautiously in such patients.
4. Patients who develop respiratory fatigue, hypercapnoea, reduced respiratory rate, and mental confusion should be considered for intubation and mechanical ventilation.
5. Heart rhythm, blood pressure and oxygen saturation should be monitored.

6.5. Diuretics in Acute Heart Failure

Recommendation: Intravenous loop diuretics are recommended in patients with acute heart failure associated with congestion, to improve symptoms of fluid overload.
(Strong recommendation FOR; low quality of evidence.)

Rationale: Diuretics are recommended as first-line therapy in patients with acute heart failure and evidence of congestion for symptomatic relief. Signs of congestion include: pulmonary crepitations, peripheral oedema, elevation of

the JVP, pleural effusion, hepatic congestion and ascites [108,141]. Diuretics should not be given until adequate perfusion and blood pressure is established [108,113,142].

Intravenous diuretics are not limited by gastrointestinal hypoperfusion or bowel oedema, and they act more rapidly than oral diuretics [113,142]. Loop diuretics, such as furosemide (frusemide), are the usual first choice; they act by reducing sodium reabsorption in the ascending limb of the loop of Henle and result in increased sodium and water excretion [113,142].

Patients with acute heart failure and congestion often require higher doses of diuretics to lead to a greater improvement in dyspnoea and diuresis, but this may be associated with a transient deterioration in renal function [112]. The dose should be adjusted according to the renal function, but in patients who are already receiving diuretics, the intravenous dose should be at least equivalent to the regular oral dose [113]. Patients not taking regular diuretics and with normal renal function are usually initiated on furosemide (frusemide) 20–40 mg intravenous bolus. Those with renal impairment may require a higher dose [113,142].

In patients who have a suboptimal response to furosemide (frusemide) boluses, intravenous vasodilators may be added in the absence of hypotension. In the setting of furosemide (frusemide) resistance, sequential nephron blockade can be achieved by adding a thiazide or MRA (e.g., spironolactone), but renal function, potassium, magnesium, and fluid status must be monitored carefully [141,142]. A recent study demonstrated no additional efficacy using high-dose MRA in acute heart failure [143].

Benefits and harms: The benefits of diuretic therapy generally outweigh the harms (e.g., electrolyte abnormalities and acute renal impairment) in patients presenting with acute heart failure.

Resources and other considerations: There should be the ability to closely monitor clinical status (including heart rhythm, blood pressure, and oxygen saturation), electrolytes, renal function, and urine output.

Practice advice

1. Intravenous loop diuretics such as furosemide (frusemide) are first-line therapy in acute heart failure with congestion.
2. The intravenous dose should be at least equal to the oral dose taken at home.
3. In those who are not on diuretics previously, initial therapy is 20–40 mg intravenous furosemide (frusemide).
4. In patients with renal impairment, the dose may need to be increased.
5. In patients with no response to intravenous loop diuretic, intravenous vasodilators, oral thiazides or MRA such as spironolactone may be added, provided the patient is not hypotensive.
6. Heart rhythm, blood pressure, oxygen saturation, renal function, potassium, magnesium, and fluid status should be monitored.

6.6. Vasodilator Therapy in Acute Heart Failure

Recommendation: Intravenous vasodilators may be considered in patients with acute heart failure if the systolic blood pressure is more than 90 mm Hg to relieve symptoms of congestion.

(Weak recommendation FOR; low quality of evidence.)

Rationale: Intravenous vasodilators may be useful in patients with acute heart failure and pulmonary congestion who are not hypotensive (i.e. systolic blood pressure >90 mm Hg). They optimise preload by venodilatation, reduce afterload via a reduction in arterial tone and may also increase stroke volume. Blood pressure should be monitored frequently, and vasodilators are usually not recommended in patients with severe valvular stenosis [115].

Intravenous nitrates are predominantly venodilators with some epicardial coronary arterial dilatation, and higher doses cause systemic arterial dilatation [117]. They may be useful in acute heart failure secondary to myocardial ischaemia. Nitrates reduce pulmonary congestion, which may be useful in orthopnoea, and they do not increase myocardial oxygen consumption or impede tissue perfusion [115,117]. A small RCT showed high-dose intravenous nitrates (combined with low-dose furosemide [frusemide]) to be more effective than high-dose intravenous furosemide (frusemide) (combined with low-dose nitrates) in controlling severe pulmonary oedema [114]. Their ongoing administration may be limited by hypotension, headache and tolerance with use beyond 24–48 hours [115,117].

Sodium nitroprusside is usually reserved for patients with severe heart failure and hypertension because it may lower blood pressure dramatically and arterial monitoring is usually recommended [144]. Prolonged administration may lead to toxicity and is not recommended in patients with renal or hepatic failure. Patients should be weaned off sodium nitroprusside slowly to avoid rebound hypertension [144]. Recent studies with vasodilator agents (ularitide and serelaxin) failed to demonstrate a long-term benefit in ADHF [145,146].

Benefits and harms: Intravenous vasodilators improve symptoms and can assist in controlling blood pressure in hypertensive patients, and intravenous nitrates decrease myocardial ischaemia; however, these benefits are tempered by the potential harm of excessive falls in blood pressure.

Resources and other considerations: Frequent blood pressure monitoring is required for intravenous vasodilator therapy to guide titration.

Practice advice

1. Intravenous vasodilators may be used if the systolic blood pressure is more than 90 mm Hg.
2. Heart rhythm, blood pressure and oxygen saturation should be monitored frequently during intravenous vasodilator therapy.
3. Intravenous nitrate therapy is generally preferred; however, beyond 24–48 hours it may result in tolerance.

4. Intravenous nitrates are uptitrated according to symptom response, while monitoring blood pressure to avoid hypotension.
5. Sodium nitroprusside may lower blood pressure markedly, and arterial blood pressure monitoring is recommended. Prolonged sodium nitroprusside infusion may result in toxicity and should be avoided in renal or hepatic failure.

6.7. Inotropic Therapy in Acute Heart Failure

Recommendation: Intravenous inotropic therapy may be considered in patients with acute heart failure associated with symptoms or signs of peripheral hypoperfusion (usually accompanied by a systolic BP <90 mm Hg) and congestion refractory to other treatment, to improve symptoms and end-organ function.
(Weak recommendation FOR; very low quality of evidence.)

Recommendation: Intravenous inotropic therapy should be avoided in patients without symptoms or signs of peripheral hypoperfusion and congestion refractory to other treatment.
(Strong recommendation AGAINST; low quality of evidence.)

Rationale: Inotropic therapy is indicated in patients with acute heart failure associated with reduced cardiac output, poor organ perfusion and often hypotension [147] usually as short-term treatment [148]. The aim of inotropic therapy is to improve stroke volume, cardiac output, filling pressures, systemic and pulmonary vascular resistance, and ultimately symptoms. Inotropic therapy is reserved for patients not responding to first-line therapy for short-term support to assist in recovery from acute haemodynamic compromise [149].

Dobutamine is a beta agonist that has positive inotropic and vasodilatory activity, whereas dopamine has positive inotropic and vasopressor activity when administered at medium to high doses [149]. Three- to five-day intravenous infusions of dobutamine or dopamine have been found to be safe, aiming to achieve haemodynamic optimisation and clinical stability in patients with acute heart failure who meet these criteria [147–150]. Continuous home ambulatory infusions of inotropes may improve quality of life in patients who cannot be weaned from inotropic support and would otherwise be unable to be discharged from hospital, as a bridging strategy to transplantation or as palliation [151].

Two other inotropic agents with vasodilator activity are milrinone and levosimendan. Milrinone is a phosphodiesterase-3 inhibitor that is infrequently used in acute heart failure due to possible proarrhythmia [152,153]; however, it is unclear whether milrinone is any more proarrhythmic than other inotropic agents. Levosimendan is a calcium-sensitizing, vasodilatory inotropic agent [154], although there is debate regarding how much of its effect relates to phosphodiesterase-3 inhibition [155]. Levosimendan does not antagonise the effects of beta blockers [156], which may improve symptoms and haemodynamics in patients with acutely decompensated CHF [157]; however, levosimendan did not improve survival compared to dobutamine in acute heart failure at 180 days [158]. Although milrinone and levosimendan may be considered in patients on beta blockers who require inotropic therapy, given that the beta blockade is reversible, an alternative approach is to use higher doses of dobutamine.

Inotropic stimulation may cause sinus tachycardia, potentially increase myocardial oxygen consumption in patients with myocardial ischaemia and possibly promote arrhythmia [159,160]. Concerns remain about the safety of inotropic therapy, and the agents should be commenced at low doses and patients should be monitored in a coronary or intensive care unit.

Vasopressor inotropic agents such as noradrenaline (norepinephrine), high-dose dopamine or adrenaline (epinephrine) are indicated in patients with marked hypotension, to increase blood pressure and improve perfusion to vital organs when there is an inadequate response to inotropic therapy with or without intravenous fluids [120]. Adrenaline (epinephrine) is also included in resuscitation algorithms. Vasopressors should be used with caution and for short-term support only, because they increase afterload and may further decrease perfusion [120].

Benefits and harms: The short-term improvements in haemodynamics and symptoms need to be balanced by the potential harm caused by proarrhythmia and increased myocardial oxygen consumption.

Resources and other considerations: Patients receiving inotropic therapy should have continuous cardiac and haemodynamic monitoring facilities available.

Practice advice

1. Intravenous inotropes may be considered in patients with acute heart failure and peripheral hypoperfusion (usually accompanied by a systolic BP <90 mm Hg) not responsive to other treatments.
2. Heart rhythm, blood pressure and oxygen saturation should be monitored frequently during intravenous inotropic therapy.

6.8. Ultrafiltration and Haemodialysis in Acute Heart Failure

Rationale: Patients with acute heart failure and congestion may theoretically benefit from a non-pharmacological approach to remove excess fluid. This may be done via ultrafiltration, which involves removal of plasma water across a semipermeable membrane as a result of a transmembrane pressure gradient [161]. In one study, when there was a rise in serum creatinine to greater than 190 μmol/L, there was a reduced response to diuretics (diuretic resistance) and an increased risk of mortality in patients with heart failure [162]. Increasing the dose of diuretics or adding an additional diuretic may worsen renal function and potentially reduce plasma potassium, magnesium, and sodium levels.

Responses to ultrafiltration vary, but in some circumstances, it has been shown to increase renal blood flow and

therefore improve renal function leading to an improved response to diuretics. Ultrafiltration may also increase urine output, reduce symptoms of congestion, reduce LV and RV filling pressures, reduce sympathetic tone and reduce lung stiffness [163].

Ultrafiltration has been shown to reduce neurohormone levels and improve diuretic response [164–166]. Compared to diuretics in a study of 200 patients with acute heart failure, ultrafiltration reduced weight at 48 hours and had similar effects on dyspnoea score, with a reduction in rehospitalisation at 90 days [167]. In patients with acute heart failure, persistent congestion and cardiorenal syndrome, a randomised trial did not show a significant benefit of ultrafiltration compared to diuretics, with increased adverse events [168].

Renal function may deteriorate in patients with acute heart failure despite therapy. Indications for haemodialysis include acidosis, hyponatraemia, hyperkalaemia, uraemia, and overt uncontrolled fluid retention. These patients may be treated with haemodialysis or filtration or peritoneal dialysis. The modality depends on the individual patient characteristics and available facilities [169].

Benefits and harms: While ultrafiltration may reduce diuretic requirements, this should be balanced with the uncertain longer-term efficacy and adverse events including bleeding and catheter-related complications.

Resources and other considerations: Significant capital expenditure is required for the device, accompanied by the costs of consumables. Ultrafiltration requires veno-venous access, experienced staff, nursing support and renal physician input. Staff require training and experience in using the ultrafiltration equipment. Patients require close monitoring while undergoing ultrafiltration.

Practice advice

1. While ultrafiltration may be considered in patients with acute heart failure and congestion not responding to diuretics and other maximal therapy, it remains unclear how to best select these patients.
2. Ultrafiltration does not improve survival, length of hospital admission or rehospitalisation rates compared to diuretics.
3. Ultrafiltration is labour intensive and requires staff training and expert support.

6.9. Mechanical Cardiac Support Devices in Acute Heart Failure

Rationale: In patients with severely symptomatic (NYHA Class IV) heart failure requiring inotropic therapy [170], mechanical cardiac support (MCS) may be considered to reduce LV preload and afterload, and to maintain end-organ perfusion until improvement in cardiac and other organs occurs [108,171–174].

Short-term, extracorporeal MCS such as intra-aortic balloon counter-pulsation (IABP), extracorporeal life support (ECLS) or extracorporeal membrane oxygenation (ECMO) may be employed, and definitive devices (e.g., LV assist devices [LVAD]) may be implanted later, if clinically indicated [175,176] (see Section 9.5). The Survival After Veno-arterial ECMO (SAVE) score may help in assessment of prognosis in patients with cardiogenic shock [177].

The use of MCS in cardiogenic shock is controversial [108,171–174]. Cardiogenic shock is defined as hypotension with systolic BP of less than 90 mm Hg despite adequate filling status and with signs of hypoperfusion due to reduced cardiac output [108]. In patients who developed cardiogenic shock complicating MI, the use of IABP did not improve outcomes [171,172]. A meta-analysis comparing MCS and IABP in cardiogenic shock showed MCS to be safe and improve haemodynamics, but increased bleeding complications with no difference in 30-day mortality [178]. However, more recent Registry studies suggest that survival after cardiogenic shock complicating acute MI may be improved with early deployment of newer MCS devices. Pre-percutaneous coronary intervention (PCI) use of the percutaneous Impella 2.5 device was reported to improve survival in both men and women in post-acute MI cardiogenic shock compared with pre-PCI use of inotropes/IABP or post-PCI use of the Impella [179,180].

Benefits and harms: MCS can improve outcomes in patients who are critically ill and who may otherwise not survive acute heart failure. The devices are associated with increased risk of bleeding, infection, vascular complications, and embolisation.

Resources and other considerations: MCS devices are expensive and require expert centres for their implantation and monitoring. Many patients may require transfer to a specialist referral centre for consideration of device implantation. Short-term mechanical support should only be considered if a plan is made for bridge to recovery, transplantation or candidacy for transplantation (see Section 9.5).

Practice advice

1. Cardiogenic shock should be treated with pressor agents and/or mechanical support if clinically indicated.
2. IABP does not improve outcomes in patients with cardiogenic shock associated with acute MI.
3. Extracorporeal MCS may allow cardiac and end-organ recovery or assist the patient until definitive treatment.
4. Short-term mechanical support should only be considered if a plan is made for definitive treatment.

7. Pharmacological Management of Chronic Heart Failure

7.1. Heart Failure With Reduced Left Ventricular Ejection Fraction

Several treatments have been shown to improve outcomes in patients with HFrEF (refer to Appendix 3 for a summary of trials). Most of the drugs that have been shown to improve survival and reduce hospitalisation in HFrEF modulate neurohormonal systems that correlate with disease progression. These include agents that modulate the renin–angiotensin–aldosterone system, sympathetic nervous

system and natriuretic peptides [181–197]. According to the clinical trial evidence, the combination of an ACE inhibitor, beta blocker, and MRA would decrease mortality over 1–3 years by 50–60% [198]. An ARNI has been shown to further decrease mortality compared to an ACE inhibitor in patients with persistent HFrEF despite current best practice (including a beta blocker and ACE inhibitor or ARB with or without an MRA) [193].

Clinicians should aim for the target doses used in the RCT that showed the benefits of these drugs. However, this should not be to the exclusion of starting other drugs that have been shown to decrease mortality in patients with HFrEF.

An elevated sinus rate also appears to be a modifiable risk factor in HFrEF. The addition of ivabradine results in a decrease in heart rate, and a decrease in the combined endpoint of cardiovascular death and heart failure hospitalisation in patients with HFrEF associated with an elevated sinus rate despite current best practice (including a maximally tolerated dose of a beta blocker and ACE inhibitor or ARB) [199,200].

Most of the RCTs showing the benefits of these treatments were conducted in patients with heart failure associated with an LVEF of less than 35–40%; however, post hoc analyses of patients with heart failure associated with a mild reduction in LVEF enrolled in RCTs have reported similar benefits with ARBs, beta blockers and MRAs [26–28].

Clinicians should consider models of care that optimise medication prescription and titration, such as pharmacist- or nurse-led titration and the use of medication titration plans [201,202]. Most patients with HFrEF will also require either intermittent or long-term diuretic therapy for symptom relief and to manage congestion. Figure 3 briefly summaries the approach to management in patients with HFrEF. However, the reader should refer to the text for further detail.

7.1.1. Medications Recommended in All Patients with Heart Failure with Reduced Left Ventricular Ejection Fraction

7.1.1.1. Angiotensin Converting Enzyme Inhibitors.

Recommendation: An ACE inhibitor is recommended in all patients with HFrEF associated with a moderate or severe reduction in LVEF (LVEF less than or equal to 40%) unless contraindicated or not tolerated to decrease mortality and decrease hospitalisation.

(Strong recommendation FOR; high quality of evidence.)

Recommendation: An ACE inhibitor may be considered in patients with HFrEF associated with a mild reduction in LVEF (LVEF 41–49%) unless contraindicated or not tolerated to decrease mortality and decrease hospitalisation.

(Weak recommendation FOR; low quality of evidence.)

Recommendation: Concomitant use of ACE inhibitors and ARNIs are contraindicated and these medications

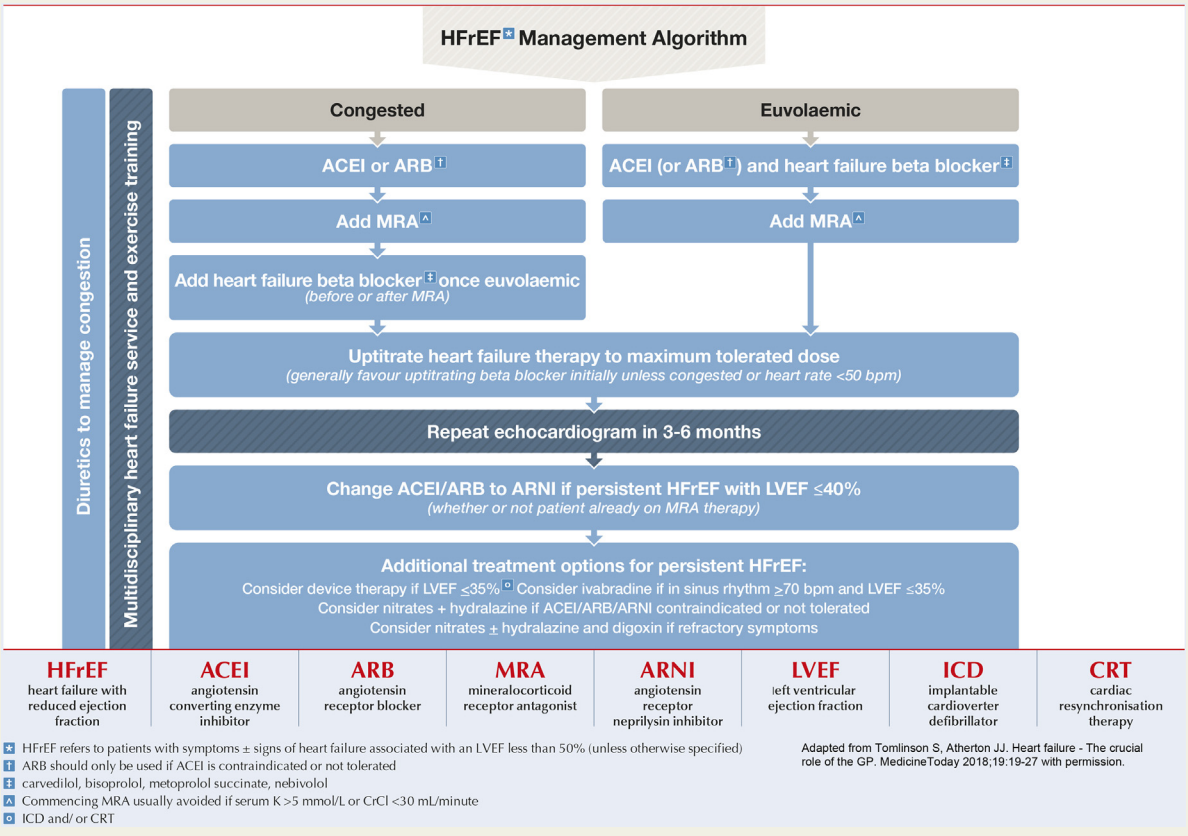

Figure 3 Management of patients with heart failure with reduced ejection fraction.

should not be administered within 36 hours of each other, because of an increased risk of angioedema.
(Strong recommendation AGAINST; very low quality of evidence.)

Rationale: Enalapril has been shown in RCTs to decrease mortality in patients with chronic heart failure associated with either severe symptoms (NYHA Class IV) and increased heart size determined radiologically, or mild or moderate symptoms (NYHA Class II, III) and an LVEF of less than or equal to 35% on top of background therapy, which included prescription rates of more than 80% for diuretics [181,184–186]. Enalapril has also been demonstrated to decrease hospitalisation [185]. Similar benefits have been demonstrated with other ACE inhibitors in patients with LV systolic dysfunction and/or heart failure following acute MI [51,184,203–205], so this is considered a class effect. This combined with a post hoc analysis from the Candesartan in Heart failure: Assessment of Reduction in Mortality and morbidity (CHARM) program reporting that angiotensin receptor blockers appear to be beneficial in patients with heart failure associated with an LVEF of 40–49% [26] suggests that ACE inhibitors are also likely to be beneficial in patients with symptoms and signs of heart failure associated with a mild reduction in LVEF.

An RCT comparing high-dose lisinopril with low-dose lisinopril in patients with HFrEF did not show a significant difference in mortality (the primary endpoint); however, the heart failure hospitalisation rate was lower in patients randomised to receive high-dose lisinopril [206].

Benefits and harms: The benefits far outweigh the potential harms of ACE inhibitors in most patients with HFrEF. ACE inhibitors can lower blood pressure, and increase serum creatinine and potassium, and are associated with an increased incidence of cough; however, they are generally well tolerated. They can rarely lead to angioedema, and the risk of this is increased in patients receiving neprilysin inhibitors [207]. Their benefits appear consistent across various subgroups including men, women, and patients with diabetes mellitus [208].

Practice advice

1. ACE inhibitors are usually started at low doses and uptitrated by doubling the dose every two weeks, aiming for target doses or maximum tolerated doses. Faster uptitration may occur with close monitoring (e.g., in an inpatient setting).
2. Patients should be reviewed following initiation and each dose escalation with monitoring of blood pressure and blood biochemistry (renal function, potassium) at 1–2 weeks and 6-monthly long term.
3. Uptitration of ACE inhibitors should not be to the detriment of starting other drugs that have been shown to decrease mortality in patients with HFrEF. A common example of this is in patients who are clinically euvolaemic, where beta blockers may be commenced before achieving target doses of ACE inhibitors.
4. Small rises in serum creatinine and asymptomatic falls in blood pressure are common following the commencement of ACE inhibitors. If the patient develops symptomatic hypotension, the estimated glomerular filtration rate (eGFR) decreases by more than 30%, or the serum potassium rises above 5.5 mmol/L, the volume status should be assessed and the need for other drugs not shown to improve outcomes in heart failure that lower blood pressure or impact on renal function and potassium (e.g., calcium channel blockers, nitrates, non-steroidal anti-inflammatory drugs [NSAIDs], diuretics and potassium supplements) should be reviewed. If these measures are not successful, the ACE inhibitor may need to be decreased (or ceased) and specialist advice sought.
5. If the patient develops angioedema, this should be managed, the ACE inhibitor ceased, and specialist advice sought.
6. If the patient develops a cough, one should consider whether this is due to pulmonary congestion or lung disease. If it is felt likely that the cough is related to the ACE inhibitor (usually this will be a dry, nonproductive cough) and is interfering with the patient's quality of life, the ACE inhibitor may be changed to an ARB.

7.1.1.2. Beta Blockers.

Recommendation: A beta blocker[a] is recommended in all patients with HFrEF associated with a moderate or severe reduction in LVEF (LVEF less than or equal to 40%) unless contraindicated or not tolerated, and once stabilised with no or minimal clinical congestion on physical examination, to decrease mortality and decrease hospitalisation.

[a]Specifically, bisoprolol, carvedilol, metoprolol (controlled release or extended release), or nebivolol

(Strong recommendation FOR; high quality of evidence.)

Recommendation: A beta blocker[a] may be considered in patients with HFrEF associated with a mild reduction in LVEF (LVEF 41–49%) unless contraindicated or not tolerated, and once stabilised with no or minimal clinical congestion on physical examination to decrease mortality and decrease hospitalisation.

[a]Specifically, bisoprolol, carvedilol, metoprolol (controlled release or extended release), or nebivolol

(Weak recommendation FOR; low quality of evidence.)

Rationale: Bisoprolol, carvedilol, and metoprolol (controlled release or extended release) have been shown in RCTs to decrease mortality and decrease hospitalisation in patients with chronic heart failure associated with mild, moderate, or severe symptoms (NYHA Class II, III, IV) and an LVEF of less than or equal to 35–40%, on top of background therapy, which included prescription rates of more than 80% for diuretics and ACE inhibitors (or ARBs) [182,183,187,189–191]. Nebivolol has been shown to decrease the combined endpoint of mortality and cardiovascular hospitalisation in an RCT enrolling patients aged 70 years or more with heart failure associated with a broad range of LVEFs (although most had reduced LVEF) [209]. Most patients enrolled in these studies were clinically stable with no overt clinical congestion. Given that the reported benefits have not been consistently observed with all beta blockers evaluated

[210,211], clinicians should use the beta blockers demonstrated to improve clinical outcomes in the large-scale RCTs. An individual patient data meta-analysis of 11 RCTs reported similar benefits in patients with heart failure associated with an LVEF of 41–49% to that observed in patients with an LVEF of less than or equal to 40% [27].

An RCT showed carvedilol dose-related improvements in survival in patients with HFrEF, but the number of events was small [212].

Benefits and harms: The benefits far outweigh the potential harms of beta blockers in most patients with HFrEF. Beta blockers may precipitate bronchospasm or heart failure, and decrease heart rate and blood pressure; however, they are generally well tolerated. Their benefits appear consistent across various subgroups including men, women, and patients with diabetes mellitus [208]. However, patients who were in AF at the time they were enrolled in the major RCTs were not shown to benefit [213,214]. Nonetheless, these patients generally require agents to control their ventricular rate, and beta blockers would be preferred provided the patient is haemodynamically stable and clinically euvolaemic.

Practice advice

1. Use the beta blockers shown to improve clinical outcomes in the large-scale RCTs—bisoprolol, carvedilol, metoprolol (controlled release or extended release), and nebivolol.
2. Ensure that the patient is clinically stable and euvolaemic before commencing beta blockers.
3. Beta blockers are usually commenced following the introduction of ACE inhibitors (or ARBs); however, if the patient is euvolaemic, they may be commenced before starting ACE inhibitors (or ARBs) [215].
4. Beta blockers are usually started at low doses and gradually uptitrated by doubling the dose every 2–4 weeks, aiming for target doses or maximum tolerated doses.
5. Patients should be reviewed following initiation and each dose escalation with monitoring of heart rate, blood pressure, and clinical evaluation of volume status at 1–2 weeks and 6-monthly long term.
6. Uptitration of beta blockers should not be to the detriment of starting other drugs that have been shown to decrease mortality in patients with HFrEF.
7. If the patient develops symptomatic bradycardia (<50 bpm), arrange an ECG to document the rhythm and review the need for other drugs not shown to improve outcomes in heart failure that lower heart rate (e.g., digoxin and amiodarone). If these measures are not successful, the beta blocker dose may need to be decreased and specialist advice sought.
8. If the patient develops symptomatic hypotension, assess volume status and review the need for other drugs not shown to improve outcomes in heart failure that lower blood pressure (e.g., calcium channel blockers, nitrates, and diuretics). If these measures are not successful, the beta blocker dose may need to be decreased and specialist advice sought.
9. If the patient develops increasing congestion, this can usually be managed by increasing the diuretic dose, but occasionally may require a reduction in the beta blocker dose. Temporary withdrawal may occasionally be required, especially if the beta blocker was recently commenced.

7.1.1.3. Mineralocorticoid Receptor Antagonists.

Recommendation: An MRA is recommended in all patients with HFrEF associated with a moderate or severe reduction in LVEF (LVEF less than or equal to 40%) unless contraindicated or not tolerated, to decrease mortality and decrease hospitalisation for heart failure.

(Strong recommendation FOR; high quality of evidence.)

Recommendation: An MRA may be considered in patients with HFrEF associated with a mild reduction in LVEF (LVEF 41–49%) unless contraindicated or not tolerated, to decrease mortality and decrease hospitalisation for heart failure.

(Weak recommendation FOR; low quality of evidence.)

Rationale: Low-dose spironolactone (up to 25–50 mg daily) has been shown in an RCT to decrease mortality and hospitalisations for heart failure in patients with chronic heart failure associated with moderate to severe symptoms (NYHA Class III, IV) and an LVEF of less than or equal to 35% on top of background therapy, which included prescription rates of more than 80% for diuretics and ACE inhibitors [188]. Low-dose eplerenone (up to 25–50 mg daily) has been shown in an RCT to decrease mortality and decrease hospitalisation in patients with chronic heart failure associated with mild symptoms (NYHA Class II) and an LVEF of less than or equal to 35% on top of background therapy, which included prescription rates of more than 80% for diuretics, ACE inhibitors (or ARBs) and beta blockers [192]. Similar incremental benefits were seen, whether or not patients were taking beta blockers. A post hoc analysis from the Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist (TOPCAT) study suggests that patients with heart failure associated with an LVEF of 45-49% also benefit from spironolactone [28].

Benefits and harms: The benefits outweigh the potential harms of MRAs in most patients with HFrEF, provided there is close monitoring of blood biochemistry (renal function and potassium), given that MRAs can lead to serious hyperkalaemia and renal impairment [216]. Their benefits appear consistent across various subgroups including men, women, and patients with diabetes mellitus [188,192].

Practice advice

1. MRAs should be avoided or used cautiously in patients with stage 4 or 5 chronic kidney disease (CKD) or serum potassium above 5 mmol/L.
2. Patients should be instructed to avoid foods high in potassium and potassium supplements (unless potassium levels are low).
3. Low doses are prescribed, starting with 25 mg daily for spironolactone or eplerenone and uptitrating in 4–8 weeks, aiming for target doses of 50 mg daily spironolactone or eplerenone.

4. Patients should be reviewed following initiation and each dose escalation with monitoring of blood pressure and blood biochemistry (renal function, potassium) at 1–2 weeks, then every 4 weeks for 12 weeks, at 6 months and then 6-monthly.
5. If the eGFR decreases by more than 30% or the serum potassium rises above 5.5 mmol/L, assess volume status and review the need for other drugs not shown to improve outcomes in heart failure that affect renal function and potassium (e.g., NSAIDs and potassium supplements). If these measures are not successful, the MRAs should be reduced. If the serum potassium rises above 6.0 mmol/L, the MRA should be ceased and specialist advice sought.
6. Patients who develop gynaecomastia on spironolactone may be switched to eplerenone.

7.1.2. Medications Recommended in Selected Patients with Heart Failure with Reduced Left Ventricular Ejection Fraction

7.1.2.1. Diuretics.

Recommendation: A diuretic should be considered in patients with heart failure and clinical symptoms, or signs of congestion, to improve symptoms and manage congestion.
(Strong recommendation FOR; very low quality of evidence.)

Rationale: A meta-analysis of small RCTs comparing diuretics with placebo reported decreases in mortality and decreases in worsening heart failure in patients with chronic heart failure. The studies were all small and involved mixed populations, different interventions, short follow-up and few events (15 deaths in total in the placebo-controlled trials) [217]. Although the comparative evidence for diuretics is limited, it should nonetheless be noted that diuretics were prescribed as background therapy in more than 80% of patients enrolled in all the large RCTs that have reported improved survival with other pharmacological treatments.

Benefits and harms: Diuretics may have an adverse effect on electrolyte balance and renal function. Diuretic dose requires regular review to ensure adequate management of congestion and avoidance of over-diuresis. It is important optimise initiation and titration of treatments that have been shown to decrease mortality and hospitalisation (including ACE inhibitors, ARBs, beta blockers, MRAs and ARNIs).

Practice advice

1. Diuretics should be started at low dose and treatment adjusted according to clinical response.
2. Loop diuretics are generally favoured initially because they increase free water clearance and have a rapid onset of action. Start with oral furosemide (frusemide) 20–40 mg daily or bumetanide (0.5–1.0 mg daily). If more than 80 mg daily furosemide (or >2 mg daily bumetanide) is required, consider splitting doses (usually given as morning and midday doses).
3. Clinicians should regularly assess volume status and biochemistry (renal function, sodium and potassium) to adjust diuretic dose at 1–2 weeks and 6-monthly long term. Once a euvolaemic state has been achieved, aim to decrease the dose unless this has previously resulted in exacerbation of heart failure.
4. Patients may also be educated to adjust the dose of diuretic (e.g., increase furosemide (frusemide) dose by 40 mg daily if weight increases over 2 kg).
5. Thiazide or thiazide-like diuretics may be added in patients with persistent congestion despite loop diuretics; however, these patients require closer monitoring of electrolytes and renal function.

7.1.2.2. Angiotensin Receptor Blockers.

Recommendation: An ARB is recommended in patients with HFrEF associated with a moderate or severe reduction in LVEF (LVEF less than or equal to 40%) if an ACE inhibitor is contraindicated or not tolerated, to decrease the combined endpoint of cardiovascular mortality and hospitalisation for heart failure.
(Strong recommendation FOR; moderate quality of evidence.)

Recommendation: An ARB may be considered in patients with HFrEF associated with a mild reduction in LVEF (LVEF 41–49%) if an ACE inhibitor is contraindicated or not tolerated, to decrease the combined endpoint of cardiovascular mortality and hospitalisation for heart failure.
(Weak recommendation FOR; low quality of evidence.)

Rationale: Candesartan and valsartan have been demonstrated in RCTs to improve combined mortality and morbidity endpoints in patients with chronic heart failure (mostly NYHA Class II and III) and an LVEF of less than or equal to 40% on top of background therapy, which included prescription rates of more than 80% for diuretics [194–196]. Benefits have been reported in patients who were intolerant of ACE inhibitors and when these medications were given on top of background ACE inhibitor therapy. There have been conflicting data from subgroup analyses regarding the benefit of adding an ARB on top of an ACE inhibitor and beta blocker [195,196]. A post hoc analysis from the Candesartan in Heart failure: Assessment of Reduction in Mortality and morbidity (CHARM) program reported that candesartan improved outcomes in patients with chronic heart failure to a similar degree if the LVEF was 40–49% to that seen if the LVEF was less than 40% [26].

An RCT comparing high-dose losartan with a lower dose of losartan in patients with HFrEF demonstrated a lower rate of the combined endpoint of death or heart failure hospitalisation (the primary endpoint); however, there was no significant difference in mortality [218].

Benefits and harms: The benefits outweigh the potential harms of ARBs in selected patients with HFrEF. The triple combination of an ACE inhibitor, ARB, and MRA is associated with a higher rate of hyperkalaemia and renal impairment [195]. Given that ACE inhibitors and MRAs have been shown to decrease mortality [181,185,188,192], ARBs are reserved for patients who do not tolerate either of these agents.

Practice advice

1. ARBs are usually reserved for patients with HFrEF who do not tolerate an ACE inhibitor. In occasional

circumstances, an ARB may be used in patients with HFrEF who do not tolerate an MRA, however usually the same side effects will apply. The triple combination of an ACE inhibitor, ARB and MRA should be avoided.
2. ARBs are usually started at low doses and uptitrated by doubling the dose every 2 weeks, aiming for target doses or maximum tolerated doses. Faster uptitration may occur with close monitoring (e.g., inpatient setting).
3. Patients should be reviewed following initiation and each dose escalation with monitoring of blood pressure and blood biochemistry (renal function, potassium) at 1–2 weeks and 6-monthly long term.
4. Uptitration of ARBs should not be to the detriment of starting other drugs that have been shown to decrease mortality in patients with HFrEF. A common example of this is in patients who are clinically euvolaemic, where beta blockers may be commenced before achieving target doses of ARBs.
5. Small rises in serum creatinine and asymptomatic falls in blood pressure are common following the commencement of ARBs. If the patient develops symptomatic hypotension, the eGFR decreases by more than 30% or the serum potassium rises above 5.5 mmol/L, assess volume status and review the need for other drugs not shown to improve outcomes in heart failure that lower blood pressure or impact on renal function and potassium (e.g., calcium channel blockers, nitrates, NSAIDs, diuretics and potassium supplements). If these measures are not successful, the ARB may need to be decreased (or ceased) and specialist advice sought.

7.1.2.3. Angiotensin Receptor Neprilysin Inhibitor.

Recommendation: An ARNI is recommended as a replacement for an ACE inhibitor (with at least a 36-hour washout window) or an ARB in patients with HFrEF associated with an LVEF of less than or equal to 40% despite receiving maximally tolerated or target doses of an ACE inhibitor (or ARB) and a beta blocker (unless contraindicated), with or without an MRA, to decrease mortality and decrease hospitalisation.

(Strong recommendation FOR; high quality of evidence.)

Recommendation: Concomitant use of ACE inhibitors and ARNIs are contraindicated and these medications should not be administered within 36 hours of each other, because of an increased risk of angioedema.

(Strong recommendation AGAINST; very low quality of evidence.)

Rationale: Sacubitril-valsartan has been demonstrated in an RCT to decrease the combined endpoint of cardiovascular death and heart failure hospitalisation associated with significant decreases in mortality and hospitalisation compared with the ACE inhibitor enalapril in patients with chronic heart failure (mostly NYHA Class II and III) and an LVEF of less than or equal to 40% (despite previously receiving a beta blocker and an ACE inhibitor or ARB) on top of background therapy, which included prescription rates over 80% for diuretics and beta blockers [193]. Similar benefits were reported, whether or not patients were receiving an MRA [193].

Benefits and harms: The benefits outweigh the potential harms of ARNIs in selected patients with HFrEF. Sacubitril-valsartan can lower blood pressure and increase serum creatinine and potassium; however, it is generally well tolerated. Sacubitril-valsartan can rarely cause angioedema, and has resulted in more hypotension than enalapril [193]. An increased risk of angioedema has been reported with the combination of ACE inhibition and neprilysin inhibition; therefore, sacubitril-valsartan should not be coprescribed with ACE inhibitors [207]. The benefits of sacubitril-valsartan appear consistent across various subgroups including men, women, and patients with diabetes mellitus [193].

Practice advice

1. Ensure that ACE inhibitors are stopped at least 36 hours before commencing an angiotensin receptor neprilysin inhibitor.
2. An angiotensin receptor neprilysin inhibitor is usually started at low or moderate doses and uptitrated by doubling the dose every 2–4 weeks, aiming for target doses or maximum tolerated doses.
3. Patients should be reviewed following initiation and each dose escalation with monitoring of blood pressure and blood biochemistry (renal function and potassium) at 1–2 weeks and 6-monthly long term.
4. Uptitration of ARNIs should not be to the detriment of starting other drugs (beta blockers and MRAs) that have been shown to decrease mortality in patients with HFrEF.
5. Small rises in serum creatinine and asymptomatic falls in blood pressure are common following the commencement of ARNIs. If the patient develops symptomatic hypotension, the eGFR decreases by more than 30% or the serum potassium rises above 5.5 mmol/L, assess volume status and review the need for other drugs not shown to improve outcomes in heart failure that lower blood pressure or affect renal function and potassium (e.g., calcium channel blockers, nitrates, NSAIDs, diuretics, and potassium supplements). If these measures are not successful, the ARNI may need to be decreased (or ceased) and specialist advice sought.
6. If the patient develops angioedema, this should be managed, the ARNI should be ceased, and specialist advice sought.

7.1.2.4. Ivabradine.

Recommendation: Ivabradine should be considered in patients with HFrEF associated with an LVEF of less than or equal to 35% and with a sinus rate of 70 bpm and above, despite receiving maximally tolerated or target doses of an ACE inhibitor (or ARB) and a beta blocker (unless contraindicated), with or without an MRA, to decrease the combined endpoint of cardiovascular mortality and hospitalisation for heart failure.

(Strong recommendation FOR; high quality of evidence.)

Rationale: Ivabradine has been shown in an RCT to decrease the combined endpoint of cardiovascular mortality and hospitalisation for heart failure in patients with chronic heart failure (mostly NYHA Class II and III), an LVEF of less

than or equal to 35%, and a sinus rate of 70 bpm or above on top of background therapy, which included prescription rates over 80% for diuretics, ACE inhibitors (or ARBs), and beta blockers [200]. Similar benefits were reported, whether or not patients were receiving an MRA [219].

Benefits and harms: The benefits outweigh the potential harms of ivabradine in selected patients with HFrEF. Ivabradine lowers heart rate and can result in visual changes (phosphenes); however, it is generally well tolerated. The benefits appear consistent across various subgroups including men, women, and patients with diabetes mellitus. Greater benefit was observed in patients with faster sinus rates [200].

Practice advice

1. Ensure patients are on maximally tolerated or target doses of beta blockers (unless contraindicated).
2. If sinus rate is 70 bpm or above despite maximally tolerated or target doses of beta blockers (unless contraindicated), ivabradine should be considered.
3. Ivabradine is usually started at 2.5–5.0 mg twice daily and uptitrated by doubling the dose every 2–4 weeks, aiming for a target dose of 7.5 mg twice daily or the maximum tolerated dose.
4. Patients should be reviewed following initiation and each dose escalation with monitoring of heart rate at 1–2 weeks and 6-monthly long term. Aim for a sinus rate between 50 and 60 bpm.
5. Prescribing and uptitration of ivabradine should not be to the detriment of starting other drugs that have been shown to decrease mortality in patients with HFrEF.
6. If the patient develops symptomatic bradycardia or asymptomatic bradycardia below 50 bpm, arrange an ECG to document the rhythm and review the need for other drugs not shown to improve outcomes in heart failure that lower heart rate (e.g., digoxin and amiodarone). If these measures are not successful, decrease the dose of ivabradine. If this persists despite the lowest dose of ivabradine (2.5 mg twice daily), then cease ivabradine and seek specialist advice.
7. If the patient develops persistent or permanent AF, cease ivabradine and review the need for ivabradine if and when the patient reverts to sinus rhythm

7.1.2.5. Hydralazine Plus Nitrates.

Recommendation: Hydralazine plus nitrates may be considered in patients with HFrEF if an ACE inhibitor and ARB are contraindicated or not tolerated, to decrease mortality.
(Weak recommendation FOR; low quality of evidence.)

Recommendation: Hydralazine plus nitrates may be considered in black patients of African descent with HFrEF despite receiving maximally tolerated or target doses of an ACE inhibitor (or ARB) and a beta blocker (unless contraindicated), with or without an MRA, to decrease mortality and hospitalisation for heart failure.
(Weak recommendation FOR; moderate quality of evidence.)

Rationale: Hydralazine plus isosorbide dinitrate has been shown in RCTs to be associated with a lower mortality compared with placebo (borderline statistical significance) and a higher mortality compared with the ACE inhibitor enalapril in men with chronic heart failure and either LV dilatation or an LVEF of less than 45% on top of background therapy that included diuretics and digoxin in all patients [220,221]. Hydralazine plus isosorbide dinitrate has been shown in an RCT to decrease a composite mortality, morbidity, and quality of life endpoint, and decrease mortality in patients self-identified as black (defined as of African descent) with chronic heart failure associated with moderate or severe symptoms (NYHA Class III, IV) and an LVEF of less than 35–45% on top of background therapy, which included prescription rates of more than 80% for diuretics and ACE inhibitors (or ARBs) [222].

The benefit of adding hydralazine plus nitrates on top of background optimal therapy (including ACE inhibitors or ARBs, beta blockers, and MRAs) in the Australian population is uncertain.

Benefits and harms: The benefits outweigh the potential harms of hydralazine plus nitrates in selected patients with HFrEF. Hydralazine plus nitrates lowers blood pressure and is associated with an increased incidence of headache. Isosorbide dinitrate was studied in the major clinical trials; the appropriate dosing and efficacy of isosorbide mononitrate is less clear.

Practice advice

1. Hydralazine plus nitrates may be considered in patients in whom ACE inhibitors and ARBs are contraindicated or not tolerated, and in patients with refractory moderate or severe symptoms despite best practice therapy.
2. Low doses of hydralazine (25 mg three times daily) plus nitrates (isosorbide dinitrate 20 mg three times daily or isosorbide mononitrate 60 mg once daily) are usually started and uptitrated over two to four weeks, aiming for target doses of hydralazine (50–75 mg three times daily) plus nitrates (isosorbide dinitrate 60 mg three times daily or isosorbide mononitrate 120 mg once daily) or maximum tolerated doses.
3. Patients should be reviewed following initiation and each dose escalation with monitoring of blood pressure at 1–2 weeks and 6-monthly long term.
4. Prescribing and uptitration of hydralazine plus nitrates should not be to the detriment of starting other drugs that have been shown to decrease mortality in patients with HFrEF.
5. If the patient develops symptomatic hypotension, assess volume status and review the need for other drugs not shown to improve outcomes in heart failure that lower blood pressure (e.g., calcium channel blockers, diuretics). If these measures are not successful, the hydralazine and nitrates may need to be decreased (or ceased) and specialist advice considered.

7.1.2.6. Digoxin.

Recommendation: Digoxin may be considered in patients with HFrEF associated with sinus rhythm and moderate to severe symptoms (NYHA Class 3–4) despite receiving maximally tolerated or target doses of an ACE inhibitor (or ARB), to decrease hospitalisation for heart failure.
(Weak recommendation FOR; low quality of evidence.)

Rationale: Digoxin has been shown in an RCT to have no effect on mortality (the primary endpoint), but decreased hospitalisation in patients with chronic heart failure (mostly NYHA Class II and III) associated with an LVEF of less than or equal to 45%, and sinus rhythm on top of background therapy, which included prescription rates of more than 80% for diuretics and ACE inhibitors [223]. The clinical effectiveness of digoxin prescribing on top of beta blockers in patients with HFrEF is uncertain.

Benefits and harms: The benefits outweigh the potential harms of digoxin in selected patients with HFrEF. Post hoc analyses from the Digitalis Investigation Group trial have demonstrated increased mortality associated with higher digoxin levels (≥1.2 ng/mL) [224,225]. Although some observational studies have reported increased mortality associated with digoxin prescribing, a recent systematic review suggests that this may reflect confounding by indication [226].

Practice advice

1. Clinicians should initially prescribe lower doses of digoxin (≤0.125 mg daily) for this indication, and consider checking digoxin levels after 4 weeks (aiming for 0.5–0.9 ng/mL), especially in patients who have a low body weight, impaired renal function or require higher doses.
2. Prescribing of digoxin should not be to the detriment of starting other drugs that have been shown to decrease mortality in patients with HFrEF.
3. The dose of digoxin should be reviewed if renal function deteriorates.

7.1.2.7. Nutraceuticals.

Recommendation: N-3 polyunsaturated fatty acids may be considered in patients with HFrEF despite receiving maximally tolerated or target doses of an ACE inhibitor (or ARB) and a beta blocker (unless contraindicated), with or without an MRA, to decrease mortality and cardiovascular hospitalisation.

(Weak recommendation FOR; low quality of evidence.)

Rationale: A number of RCTs have evaluated various nutraceuticals in patients with heart failure. N-3 polyunsaturated fatty acids (850–882 mg eicosapentaenoic acid and docosahexaenoic acid as ethyl esters in the average ratio of 1:1.2) have been shown in an RCT to modestly decrease mortality and decrease hospitalisations for cardiovascular disease in patients with chronic heart failure (mostly NYHA Class II and III) associated with a broad range of LVEFs (although most had a reduced LVEF) on top of background therapy, which included prescription rates of more than 80% for diuretics and ACE inhibitors (or ARBs) [227]. The modest treatment effect just achieved statistical significance in the prespecified adjusted analysis, with confidence intervals including a treatment effect that was not clinically relevant. It is uncertain whether a similar treatment effect would have been observed if a higher proportion of patients were on beta blockers and MRAs.

Studies conducted with nitrate-rich beetroot juice, micronutrient supplementation, co-enzyme Q10, hawthorn extract, magnesium, thiamine, vitamin C, vitamin E, and vitamin D have generally been small or underpowered to evaluate clinical outcomes [228–248]. While there is some evidence that co-enzyme Q10 may decrease mortality and hospitalisation, definite conclusions cannot be reached given either the size or quality of the studies [235,236]. One study reported that vitamin D supplementation was associated with a higher need for mechanical circulatory support and a non-significant trend for more hospitalisations; however, this should be interpreted with caution, because the study had inadequate power to detect significant treatment differences [248].

Practice advice

1. Clinicians should favour other treatments that have been clearly shown to decrease mortality. However, in patients with persistent HFrEF despite best-practice treatment, it is reasonable to add N-3 polyunsaturated fatty acids.

7.2. Heart Failure With Preserved Left Ventricular Ejection Fraction

Patients with heart failure associated with a preserved LVEF (HFpEF: LVEF ≥50%) are generally elderly with multiple comorbidities. The main aims of treatment are to improve symptoms and quality of life and decrease hospitalisation. None of the major RCTs conducted to date evaluating pharmacological therapies in patients with HFpEF have achieved their primary endpoint [249–252]—Perindopril in Elderly People with Chronic Heart Failure (PEP-CHF), Candesartan in Heart failure: Assessment of Reduction in Mortality and morbidity (CHARM)-Preserved (CHARM-Preserved), Irbesartan in Heart Failure with Preserved Ejection Fraction (I-PRESERVE), TOPCAT study, Japanese Diastolic Heart Failure Study (J-DHF) and Digitalis Investigation Group-Preserved Ejection Fraction (DIG-PEF)—although promising signals with reduced hospitalisations for heart failure have been reported for ARBs and MRAs (CHARM-Preserved and TOPCAT) (refer to Appendix 3 for a summary of trials). Patient selection for HFpEF trials remains problematic, with a post hoc analysis of the TOPCAT trial reporting that patients with lower natriuretic peptide levels were more likely to benefit from spironolactone [253].

Practice advice

1. Diuretics are usually required to manage congestion, with careful attention to avoid over-diuresis.
2. Loop diuretics are generally preferred, although thiazide diuretics are an alternative, especially if the patient is hypertensive.
3. Comorbidities including hypertension, ischaemic heart disease, diabetes and AF should be identified and actively managed.
4. While the evidence for neurohormonal antagonists is less robust, these agents are often used to manage comorbidities. Low-dose spironolactone may be considered to decrease hospitalisations for heart failure.

5. In patients with infiltrative cardiomyopathies such as cardiac amyloidosis, consider referral to specialised centres with expertise in this area.

8. Non-Pharmacological Management of Heart Failure

Effective long-term management of heart failure is key to reducing hospitalisation and improving survival. These guidelines highlight the complexities of managing a patient with heart failure, particularly in the setting of multiple comorbidities and polypharmacy. There are several non-pharmacological strategies that can improve evidence-based practice and patient outcomes to optimise a seamless transition of care across primary, hospital, and community sectors.

8.1. Systems of Care to Reduce Rehospitalisation

The rising burden of heart failure and increasing pressure on the health system has resulted in an urgent need to reduce rehospitalisations for heart failure. Potentially, this may be achieved through redesigning systems of care. A system of care is defined as a group of interventions implemented to improve service delivery.

Rationale: Evidence of systems of care involving disease-management programs, telemonitoring, role of nurse practitioners, and medication titration clinics are presented below. The evidence supporting systems of care excluding these areas is weak. Most studies were retrospective in design and comprised of comparing a collaborative care model between a GP/general physician and cardiologist to GP/general physician only. There was a reduction in mortality reported in patients in the collaborative care model compared to GP/general physician alone [254,255].

A retrospective study of a dedicated heart failure unit encompassing an inpatient and community service showed a significant reduction in mortality and rehospitalisation in patients seen in the dedicated heart failure unit compared with no heart failure unit [256,257].

A meta-analysis of heart failure care pathways has shown a reduction in rehospitalisation and in-hospital mortality compared with no-care pathway [258]. However, the meta-analysis was based on low-quality studies and should be interpreted with caution.

Several quality-improvement initiatives have involved interventions and tools to assist with improving the translation of evidence into clinical practice (Get With The Guidelines—Heart Failure [GWTG-HF], Better Outcomes for Older Adults through Safe Transitions project [BOOST], State Action on Avoidable Rehospitalizations Initiative [STAAR] and Hospital to Home program [H2H]). These observational studies reported a lower rehospitalisation rate favouring the intervention [259–263]. However, they warrant further investigation as RCTs.

Benefits and harms: The benefits of a collaborative care model between GPs or general physicians with involvement from cardiologists should be considered. Despite the strength of evidence being weak, there are numerous benefits of collaborative care in primary care, provided pathways for communication are well established such as continuity of care and shared management plans. The benefits of a dedicated heart failure unit should also be considered due to improved access to medical specialist input and services.

Practice advice

1. The development of collaborative care using 'shared care' models between the GP, heart failure nurse, and specialist physician should be encouraged. GPs have a vital role in the management of patients with heart failure in the community.
2. Systems of care for heart failure usually include a multidisciplinary heart failure specialist team and the patient's GP.

8.2. Models of Care to Improve Evidence-Based Practice

Two main models of care have been implemented into clinical services throughout Australia:

- multidisciplinary heart failure disease management programs and telemonitoring
- nurse-led titration clinics.

Both of these models of care involve advanced practice heart failure nurses or heart failure nurse practitioners.

Recommendation: Referral to a multidisciplinary heart failure disease-management program is recommended in patients with heart failure associated with high-risk features to decrease mortality and rehospitalisation.
(Strong recommendation FOR; high quality of evidence.)

Recommendation: In areas where access to a face-to-face multidisciplinary heart failure disease management program after discharge is limited, patients should be followed up with a multidisciplinary telemonitoring or telephone support program.
(Strong recommendation FOR; moderate quality of evidence.)

Recommendation: Nurse-led medication titration is recommended in patients with HFrEF who have not achieved maximum tolerated doses of ACE inhibitors, ARBs, ARNIs, beta blockers or MRAs, to decrease hospitalisation.
(Strong recommendation FOR: high quality of evidence.)

8.2.1. Multidisciplinary Heart Failure Disease Management Programs and Telemonitoring

Rationale: Numerous meta-analyses have shown that multidisciplinary heart failure disease management programs decrease rehospitalisation and mortality [264–266]. The effectiveness of these programs is due to a bundling of interventions [267,268] and a multidisciplinary workforce specialised in heart failure with meta-analyses comprising RCTs involving heart failure advanced practice nurses [264–266] and pharmacists [269].

The evidence supporting multidisciplinary heart failure disease management programs is well-established [264–266,268].

Table 11 Practical indicators of increased risk of premature morbidity and mortality.

Practical indicators of increased risk of premature morbidity and mortality
Practical indicators of increased risk of premature morbidity and mortality are the presence of two or more of the following: • age >65 years • NYHA Class III or IV symptoms • Charlson Index of Comorbidity Score of ≥2 • an LVEF of ≤30% • living alone or remote from specialist cardiac services • depression • language barrier (e.g., non-English speaking) • lower socioeconomic status • significant renal dysfunction (glomerular filtration rate <60 mL/min/1.73 m^2).

LVEF: left ventricular ejection fraction, NYHA: New York Heart Association.

These programs are now recommended as standard care for patients at high risk of rehospitalisation (Table 11). Multidisciplinary heart failure disease management programs comprise frequent home visits to support the patient during their transition from discharge from hospital back into the community with a range of heart failure multidisciplinary specialists involved in their management. Other models of disease management programs include telemonitoring and telephone support. Both telemonitoring and telephone-supported programs significantly decrease mortality and rehospitalisation [270,271]. A meta-analysis of 43 RCTs reported that telemonitoring decreased mortality (involving 3,740 participants from 17 RCTs) and rehospitalisation (involving 2,148 participants from eight RCTs). Telephone support programs also decreased mortality (9,222 participants from 22 RCTs) and rehospitalisation (7,030 participants from 16 RCTs) [270]. Telemonitoring has also shown greater reductions in rehospitalisation and mortality compared to telephone-supported programs [271].

8.2.2. Nurse-led Medication Titration Clinics

Rationale: A nurse-led medication titration clinic is also effective in reducing rehospitalisation and the time to achieve optimal dose of these medications and improving survival in patients with HFrEF. A meta-analysis of seven RCTs in 1,684 patients with HFrEF found that patients attending a nurse-led titration (NLT) clinic had a significant reduction in rehospitalisation and mortality [201]. These studies compared the titration of medications by a GP, cardiologist, or general internists with the titration of medications by an advanced practice heart failure nurse [201]. Patients seen in the NLT clinics reached optimal dose of beta-adrenergic blockers in half the time compared with titration of these medications by GPs. About 27 deaths could be avoided for every 1,000 people receiving NLT of beta blocking agents, ACE inhibitors, and ARBs [201].

Benefits and harms: The benefits of a multidisciplinary heart failure disease management program and telemonitoring or telephone support after discharge are supported by high-quality evidence; hence, enrolment of patients with heart failure into these programs post-hospital discharge should be standard care. There is evidence to support a face-to-face visit involving an advanced practice heart failure nurse being superior to telephone support in reducing hospitalisation and mortality.

A nurse-led medication titration clinic is recommended in patients diagnosed with HFrEF who are stable and euvolaemic. It is recommended that these clinics involve a nurse practitioner or advanced practice nurse experienced in heart failure supported by a cardiologist or physician with an interest in heart failure.

Resources and other considerations: Telemonitoring involves a specialised computerised program supported by an information technology department.

A nurse practitioner is defined as an advanced practice nurse that has been endorsed by the Nursing and Midwifery Board of Australia as a nurse practitioner and their scope of practice designates them to work within the specialisation of heart failure [272]. An advanced practice nurse is defined as a registered nurse with the expert knowledge base, complex decision-making skills and clinical competencies for expanded practice [273].

Practice advice

1. Multidisciplinary heart failure programs with or without telephone support/telemonitoring should comprise a specialist multidisciplinary heart failure team such as a cardiologist or physician specialising in heart failure, an advanced practice heart failure nurse, nurse practitioner, pharmacist, physiotherapist, occupational therapist, exercise physiologist, dietitian, psychologist, and palliative care physician, as appropriate.
2. Telemonitoring and telephone support systems require a comprehensive alert system to flag patients who are displaying signs of clinical deterioration and pathways for rapid medical review of the patient.
3. These programs should focus on high-risk patients, especially those recently discharged after hospitalisation for heart failure. A list of other high-risk features is provided in Table 11.
4. A nurse-led medication titration clinic is recommended in patients diagnosed with HFrEF who are stable, euvolaemic and have not achieved optimal doses of medications.
5. A heart failure nurse practitioner is required to run the medication titration clinic. If a nurse practitioner is not available then an advanced practice heart failure nurse can manage the clinic, using a preapproved medication titration protocol and individual cases discussed with medical staff.
6. Nurse-led medication titration clinics should be supported by a cardiologist or specialist physician with an interest in heart failure. In rural/remote settings, support is more likely to be provided by a general physician.

8.2.3. Non-pharmacological Heart Failure Management and Multimorbidity

Adjusting management strategies in the setting of multimorbidity and heart failure is integral to better outcomes [274]. Together with a patient's values, preferences, and goals, a list of clinical priorities and an approach to match should be established. This may involve other specialists as appropriate. Discordant and contraindicated treatment options should be identified and managed as part of the overall healthcare plan. Employing a multidisciplinary, team-based approach to management, including a heart failure advanced practice nurse, provides the patient, their caregivers and family with the knowledge to facilitate better care and to provide advice on options relevant to their management. For example, more frequent monitoring will be required during periods of instability or optimisation of medication. Older adults may also benefit from more frequent monitoring, particularly home visitations [275]. Essentially, a more nuanced approach with clinical judgement and recognition of the contribution of personalised, patient-centred decisions is to be adopted.

8.2.3.1. Multimorbidity: Cognitive Impairment.

The ability of patients with heart failure who also have impaired cognition to adhere to medication regimens, keep appointments, recognise symptoms and signs of an exacerbation, and perform activities of daily living are likely to be compromised [276]. Education of patients with heart failure with impaired cognition should also include the caregiver particularly regarding self-management strategies and lifestyle changes. Educational resources aimed at low health literacy may be beneficial. Referral to a dietitian may also be beneficial to ensure patients are receiving a nutritional diet, particularly in patients with a reduced appetite or cardiac cachexia. Preventive treatments target patient support with disease management programs and efforts to slow progression of cognitive decline. Among the more promising areas of delaying progression include pharmacological therapy, exercise training, dietary changes, and CRT.

Screening for cognitive impairment in patients with heart failure is problematic. There is no universal agreement on its measurement, setting, frequency, referral pathway, and effective treatment. Assessment of a patient's cognitive impairment using a validated tool may guide further management. Multidisciplinary health teams should pay particular attention to the special needs of patients with heart failure and cognitive impairment who live alone and without social support.

8.2.3.2. Multimorbidity: Frailty.

Frailty is an important consideration in patients with heart failure with an estimated prevalence of 40–50% [277]. However, there is no consensus on which frailty instruments should be used or the best time to administer them [278]. A comprehensive assessment of frailty may provide additional prognostic benefits [279].

8.3. Frequency of Follow-up

Patients diagnosed with heart failure experience a high rate of hospitalisations. Discharge planning plays a key role in optimising their management after discharge to provide a seamless transition of care from the hospital into the community. Discharge planning should commence early during their hospitalisation and involves referrals to heart failure programs after discharge, community services as appropriate, heart failure exercise programs, early outpatient clinic appointments, and GP follow-up.

Rationale: Prospective comparative studies suggest that follow-up of patients within 7–10 days after discharge following hospitalisation for heart failure may be associated with lower rates of rehospitalisation. Results from the 'Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients With Heart Failure (OPTIMISE-HF)' and GWTG-HF quality-improvement programs found that patients with heart failure followed up in clinic within 7 days after discharge had a significant reduction in rehospitalisation within 30 days compared with those who were not followed up within 7 days [280]. Early follow-up with a cardiologist and their GP was also associated with better survival and a reduction in rehospitalisation compared with GP follow-up only [254].

In terms of type of follow-up visit, there is insufficient evidence to support that a home visit is superior to a clinic visit for follow-up after discharge. One RCT found no difference in freedom from unplanned rehospitalisation or death (the primary endpoint) between these two groups. However, there was a significant reduction in mortality in patients receiving home-based visits compared with clinic appointments [281].

Another RCT investigated the intensity of follow-up to determine the effect of low, moderate, or high intensity, after discharge follow-up with a heart failure nurse. Low-intensity follow-up comprised usual care of an outpatient appointment with a cardiologist within 2 months after discharge and then every 6 months. Moderate follow-up consisted of usual care and an additional nine outpatient appointments with a heart failure nurse. High-intensity follow-up also consisted of usual care and weekly telephone calls, and a home visit within the first month after discharge, followed by additional telephone calls with the heart failure nurse, two home visits, and two multidisciplinary appointments. There were no significant differences in heart failure mortality or hospitalisation between the intensity of follow-up appointments [282].

Benefits and harm: Although the evidence is limited, early post-hospital discharge appointments should be considered to identify potential issues or signs and symptoms that may indicate early exacerbation of heart failure.

Practice advice

Prospective studies and registry data have shown that the most vulnerable period for patients with heart failure is within the first few weeks post-hospital discharge. Ideally these patients should be reviewed within the first 7–14 days of discharge from hospital, regardless of the type of appointment. The frequency of their appointments should be guided by their clinical stability.

8.4. Self-management

Recommendation: Educating patients and their carers about the self-management of heart failure is recommended in patients with heart failure, to decrease hospitalisation and mortality. It should commence soon after diagnosis, be patient-centred, appropriate to their level of health literacy, culturally appropriate, and revised continually throughout the person's life.

(Strong recommendation FOR: high quality of evidence.)

Patients with heart failure are required to adhere to a complex regimen when managing their heart failure at home, to maintain stability, decrease hospitalisation and mortality, and improve quality of life. The regimen includes taking their medications at the right time and right dose, monitoring their heart failure specific signs and symptoms (to determine when these signs and symptoms indicate a deterioration in health), and collaboration with a health professional. Interventions have been implemented to support patients in self-managing their heart failure, and to empower them with the skills and knowledge to actively participate in symptom monitoring, problem-solving and decision-making in managing their heart failure. RCTs with self-care as a primary endpoint have shown mixed effects.

Interventions to improve self-management

An RCT of a 12-week training program in self-management of heart failure showed a significant improvement in daily weighs, and adherence to a low-sodium diet, medications, and exercising in patients attending the program [283]. However, there were no differences in rehospitalisation [283].

Other interventions have focused primarily on a heart failure education program. An RCT evaluated an education program for patients and their carers about heart failure and self-management at home, but found no significant differences in self-care maintenance, management, or knowledge of heart failure between those patients that received education and those that did not [284]. However, patients participating in the education program had significantly lower rates of rehospitalisation. [285]. A smaller, single-centre RCT of an education program delivered over the phone found an improvement in self-management [284]. However, a larger RCT will be required to determine whether these results translate into clinical benefits.

The effect of self-management on hospitalisations and mortality

Despite weak evidence supporting interventions that may improve self-management, there is strong evidence supporting the benefits of educating patients and their carers about the self-management of heart failure on reducing rehospitalisation and mortality. An individual patient-level data meta-analysis of 20 RCTs comprised data from 5624 patients with heart failure, with most of the interventions delivered by specialised heart failure nurses in an individualised face-to-face approach [286]. Self-management interventions significantly prolonged the time patients spent out of hospital and stayed alive accompanied with an improved quality of life [286].

Practice advice

Patient and carer education about heart failure and self-management is a key component of non-pharmacological management of heart failure and should be commenced soon after diagnosis, be patient centred and revised continually for life. Prior to commencing education, the patient's health literacy level should be determined and resources provided that are appropriate for their level of health literacy. The National Heart Foundation of Australia has low-health-literacy and higher-health-literacy heart failure resources available on the NHFA website.

8.5. Fluid Restriction and Daily Weighing

Most hospitalisations for heart failure are associated with congestion [29]. Volume management is essential in managing congestion. This is achieved through fluid and sodium restriction, prescribing of diuretics, and daily weighs.

Rationale: Previously there was little evidence, except for expert opinion, to support the restriction of fluid in heart failure and the specific level of fluid restriction [287]. A meta-analysis of six RCTs involving 751 patients with heart failure who were randomised to a control group of unlimited fluids and an intervention group of restricting fluid to 800 mL to 1.5 L/day reported no significant differences for hospitalisation, mortality, perceived thirst, serum sodium, and duration of intravenous diuretics [288]. However, this meta-analysis involved a small number of participants and further RCTs are warranted.

Several additional RCTs have also shown no significant difference in clinical stability or rehospitalisation and mortality in patients with or without a fluid restriction [289,290].

There is also no evidence beyond expert opinion to support the use of daily weighing as a surrogate marker of congestion and the amount of increase in weight indicating when to see their GP (e.g., an increase of 2 kg in 2 days). However, in clinical practice daily weighs are important to alert patients and their healthcare professionals that fluid is beginning to reaccumulate.

Benefits and harms: There are presumed benefits of fluid restriction in patients with overt congestion. However, in patients with no signs and symptoms of congestion, there is no evidence supporting the benefits of fluid restriction, and possible harm in situations associated with excess fluid loss (e.g., diarrhoeal illness and hot weather).

Practice advice

1. In patients with overt congestion, consider restricting fluid intake to 1.5 L/day.
2. If the patient's weight increases by 2 kg over 2 days, they should see their GP and consider a temporary increase in the dose of diuretics depending on haemodynamic status, renal function, and electrolytes.
3. In patients who are competent in self-managing their heart failure, consider a sliding scale of diuretics for the patient to manage.

8.6. Sodium Intake

Background: Heart failure guidelines provide varying advice regarding sodium intake in patients with heart failure [108,291]. There is no evidence to support the amount of dietary sodium restriction beyond expert opinion.

Practice advice

Our current advice is to apply the NHFA general population recommendation regarding sodium intake (<2 g/day). A referral to a dietitian should be considered as they can provide individualised strategies and support to patients regarding their low sodium diet.

8.7. Exercise Training and Heart Failure

Recommendation: Regular performance of up to moderate intensity (i.e. breathe faster but hold conversation) continuous exercise is recommended in patients with stable chronic heart failure, particularly in those with reduced LVEF, to improve physical functioning and quality of life, and to decrease hospitalisation.

(Strong recommendation FOR; high quality of evidence.)

Rationale: Exercise training embedded in cardiac rehabilitation is effective in reducing hospitalisation and improving physical functioning and muscle fitness. In 2014, a Cochrane review of people with heart failure (mostly HFrEF and NYHA classes II and III) found exercise-based rehabilitation compared with no exercise control decreased all-cause hospitalisation to 1 year (15 trials, 1328 participants: relative risk reduction [RRR] 0.75; 95% CI, 0.62–0.92, absolute risk reduction [ARR], 5.8%; number needed to treat [NNT], 17), decreased heart failure-related hospitalisation (12 trials, 1036 participants: RRR 0.61; 95% CI, 0.46–0.80, ARR, 7.2%; NNT, 14) and improved quality of life (13 trials, 1270 participants: mean difference, 5.8; 95% CI, 2.4–9.2) [292]. Exercise had no significant effect on mortality up to 1 year (25 trials, 1871 participants) or after 1 year [292]. The overall risk of bias across the heart failure trials was moderate. A separate meta-analysis of 2321 patients with HFrEF enrolled in 27 RCTs found resistance or combined continuous and resistance training was associated with improved peak VO_2, quality of life, and walking performance [293]. Another meta-analysis involving 276 patients with HFpEF enrolled in six RCTs found exercise training was associated with an improvement in physical functioning and quality of life [294].

Currently, moderate continuous endurance exercise is the best described and established form of training, because of its well-demonstrated efficacy and safety [295]. Moderate-intensity physical activity is associated with a moderate, noticeable increase in depth and rate of breathing, while still allowing the individual to whistle or talk comfortably. This advice is based mainly on a large multicentre exercise intervention trial (HF-ACTION [Heart Failure: A Controlled Trial Investigating Outcomes of Exercise Training]) with 2331 patients with chronic heart failure, which observed a moderate reduction of symptoms, improvement of exercise capacity, and a decrease in rehospitalisation for heart failure [296]. Another multicentre, exercise-intervention RCT involving 278 patients recently hospitalised with acute heart failure reported that it was safe and feasible to undertake exercise training. However, this study failed to decrease the combined endpoint of death and rehospitalisation on top of comprehensive heart failure disease management (EJECTION-HF [Exercise Joins Education: Combined Therapy to Improve Outcomes in Newly discharged Heart Failure]) [297]. Furthermore, high-intensity interval training was not superior to moderate continuous training in changing LV remodelling or aerobic capacity and its feasibility remains unresolved in this patient population [298]. Improvement in clinical outcomes is considered dose related, particularly with levels above three metabolic unit (MET)-hours per week of continuous endurance training [299].

Benefits and harms: Continuous endurance training increases physical functioning and exercise capacity, and improves systolic and diastolic function in patients with HFrEF. The combination of strength–endurance training induces more pronounced increases in muscle strength and muscle mass. Contemporary endurance training studies in patients with HFpEF have shown improved exercise capacity and diastolic function. Supervised exercise training programs are not associated with adverse outcomes in excess of standard care.

Resources and other considerations: Strength-endurance training typically involves a combination of facility and home-based routines. Both large muscle mass (walking and leg ergometry) and small muscle mass (arm ergometry and specific strength activities) exercises are performed. Flexibility and balance exercises are often incorporated. Exercise can be considered as soon as practical in clinically stable patients with heart failure. An initial period of supervision may be warranted to verify individual responses and tolerability, clinical stability and prompt recognition of a change in status warranting modification or termination of the routine.

Practice advice

1. Exercise studies in heart failure have been largely conducted in patients with HFrEF under the age of 70 years. However, evidence has emerged for the benefits of exercise training in HFpEF patients, which is more prevalent in older patients with heart failure and in women.
2. Continuous endurance training may be most effective, with the additional benefit from resistance training confounded by the combination of both modalities. The inclusion of resistance training may be of particular benefit for muscle strength and fitness in patients with advanced heart failure who are at risk of frailty and cachexia.

9. Devices, Surgery and Percutaneous Procedures

9.1. Cardiac Electronic Implantable Devices

9.1.1. Cardiac Resynchronisation Therapy

Recommendation: CRT is recommended in patients with HFrEF associated with sinus rhythm, an LVEF of less than or equal to 35% and a QRS duration of 150 ms or more

despite optimal medical therapy to decrease mortality and decrease hospitalisation for heart failure, and improve symptoms.
(Strong recommendation FOR; high quality of evidence.)

Recommendation: CRT should be considered in patients with HFrEF associated with sinus rhythm, an LVEF of less than or equal to 35% and a QRS duration of 130–149 ms despite optimal medical therapy to decrease mortality and decrease hospitalisation for heart failure, and improve symptoms.
(Strong recommendation FOR; moderate quality of evidence.)

Recommendation: CRT may be considered in patients with HFrEF associated with AF, an LVEF of less than or equal to 35% and a QRS duration of 130 ms or more despite optimal medical therapy to decrease morbidity and mortality, and improve symptoms, provided this is accompanied by approaches to maximise biventricular capture (ideally more than 92% biventricular capture).
(Weak recommendation FOR; very low quality of evidence.)

Recommendation: CRT should be considered in patients with HFrEF associated with an LVEF of less than or equal to 50% accompanied by high-grade atrioventricular (AV) block requiring pacing, to decrease hospitalisation for heart failure.
(Weak recommendation FOR; moderate quality of evidence.)

Recommendation: CRT should be considered in patients who have pre-existing RV pacing who develop symptoms of heart failure with an LVEF of less than or equal to 35%, to decrease hospitalisation for heart failure.
(Weak recommendation FOR; low quality of evidence.)

Recommendation: CRT is contraindicated in patients with QRS duration of less than 130 ms, because of lack of efficacy and possible harm.
(Strong recommendation AGAINST; moderate quality of evidence.)

Rationale: CRT has been shown to improve LV function, decrease mortality and decrease hospitalisations for heart failure in patients with HFrEF with intraventricular conduction delay (QRS ≥130 ms) (see Appendix 3) [300,301]. Dyssynergic contraction of the left ventricle, particularly in the setting of left bundle branch block, may contribute to a reduction in LV systolic function. Resynchronisation of ventricular contraction is achieved by pacing both the left and the right ventricles simultaneously. This may lead to improved LVEF and favourable reverse remodelling of the left ventricle.

In an attempt to isolate the benefits of CRT from that of an ICD, many studies have compared ICD therapy with or without CRT (i.e. CRT-defibrillator (CRT-D) vs ICD), whereas only two major studies have compared CRT with optimal medical therapy [301,302]. In the Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure (COMPANION) trial [301], patients were randomly assigned to CRT, CRT-D or optimal medical therapy. The rate of death or hospitalisation from any cause was decreased in the device groups compared with optimal medical therapy. In the Cardiac Resynchronization-Heart Failure (CARE-HF) study, CRT improved symptoms and decreased mortality compared with optimal medical therapy [302]. Subsequent studies have reported that CRT-D decreases mortality and decreases hospitalisations for heart failure compared with ICD [303–306].

Several studies have explored whether certain patient characteristics influence the clinical efficacy of CRT. However, LVEF and QRS width have been inclusion criteria in all the major randomised trials.

9.1.1.1. Cardiac Resynchronisation Therapy Efficacy and Qrs Morphology and Duration.
The initial premise was that the benefit of CRT was reliant on the delay between the posterolateral and anteroseptal wall depolarisation with the presence of a bundle branch block (BBB) pattern being a marker for dyssynchrony in many studies. However, for any given QRS duration, the mechanical activation delay between the right and left ventricles may vary significantly, as does the intraventricular activation. This may explain the reduced reliability of left BBB (LBBB) in predicting a favourable response observed in some studies [307]. For example, studies have shown that a QRS duration of 120–140 ms maybe due to other conditions rather than true LBBB, such as LV hypertrophy or extensive MI. The cause of the BBB morphology maybe more important in predicting a response to CRT than the morphology itself [308]. Despite this, the presence of LBBB is a stronger predictor of CRT response than either right BBB or non-specific intraventricular conduction delay [309,310].

Several studies reported a positive correlation between the initial QRS width and clinical efficacy. Recent meta-analyses have confirmed this [300,303,311,312], with two individual patient data meta-analyses reporting that QRS morphology did not provide additional predictive utility over and above QRS duration [300,303].

Echocardiographic assessment of dysynchrony was used in the Predictors of response to cardiac resynchronisation therapy (PROSPECT) trial, but was found not to be useful in predicting the response to CRT. The Echocardiography Guided Cardiac Resynchronization Therapy (EchoCRT) study reported that CRT did not decrease mortality or hospitalisations for heart failure in patients with HFrEF associated with a QRS duration of less than 130 ms, with a significant increase in mortality [313].

9.1.1.2. Cardiac Resynchronisation Therapy Efficacy and Left Ventricular Ejection Fraction. Most CRT studies have included patients with an LVEF of less than 35%. The response of CRT in patients with an LVEF of 35–40% has also been studied [314,315]. In the Multicentre Automatic Defibrillator Implantation Trial–Cardiac Resynchronization Therapy (MADIT-CRT) trial, a substudy assessing the effect of the baseline ejection fraction showed that the clinical benefit was evident regardless of baseline LVEF. The greatest reduction in LV end-diastolic volume was found in patients with a higher baseline LVEF [316].

9.1.1.3. Cardiac Resynchronisation Therapy Efficacy and Atrial Fibrillation. The use of CRT in the setting of AF

remains controversial. Information for CRT in this subset of patients who represent about 20% of the HFrEF population is scant, with only a small number of studies that have evaluated CRT in AF. The Multisite Stimulation In Cardiomyopathies (MUSTIC) study compared biventricular pacing with right ventricular pacing in patients with severe heart failure and atrial fibrillation requiring pacing. While the primary endpoint according to the intention-to-treat analysis was not achieved in this small study, an improvement in exercise capacity was observed in a post hoc analysis of patients who received effective pacing [317]. A subsequent pre-post biventricular pacing analysis demonstrated sustained benefits over 12 months [318]. In the Resynchronization–Defibrillation for Ambulatory Heart Failure (RAFT) study an AF subgroup was analysed and no benefit was found for CRT-D over ICD [319]. In this study, a low biventricular capture rate may have contributed to this. Evidence suggesting a benefit for CRT in patients with AF and heart failure comes from a small number of studies following AV node ablation. Brignole et al. (2011) showed that CRT after AV node ablation decreased hospitalisations for heart failure, compared to RV pacing alone [320], which was also reported in a subsequent meta-analysis [321]. In a subgroup considered traditionally CRT eligible (LVEF <35%, QRS >130 ms, and NYHA Class III–IV) a similar benefit was found [320]. CRT offered a greater improvement in the 6-minute walk test and ejection fraction, especially in patients with impaired systolic function or heart failure [322]. If CRT is undertaken in patients in AF, one should ensure at least 92% biventricular capture [312,323,324].

9.1.1.4. Other Predictors of Outcome. There are a number of other factors that may influence decision making, especially in patients with borderline indications for CRT. Reverse remodelling is an important predictor of a favourable response to CRT. As such, patients with a scarred ventricle, such as those with an ischaemic substrate, were less likely to demonstrate an improvement in systolic function [325]. Despite this, they may still receive a clinical benefit. A meta-analysis of data from individual patients reported that women were more likely to respond to CRT than were men [326]. In a subgroup analysis in the COMPANION trial, a prolonged PR interval was associated with a greater reduction in the endpoint [327]. However, in the REsynchronization reVErses Remodeling in Systolic left vEntricular dysfunction (REVERSE substudy), benefit was not affected by the duration of the PR interval [328]. Conversely, the MADIT-CRT trial reported that a PR interval of more than or equal to 230 ms identified patients with a non-LBBB pattern who were more likely to respond [329].

9.1.1.5. Cardiac Resynchronisation Therapy versus Right Ventricular Pacing. Pacing is often used in patients with advanced AV block, sinus node dysfunction, or to support AV node ablation in drug refractory AF. A minority of patients develop LV systolic dysfunction in response to dyssynchrony attributable to RV pacing. There was considerable interest in positioning leads within the right ventricular outflow tract or septum to provide more physiological ventricular activation, as opposed to the traditional site at the RV apex, in an attempt to reduce this complication. However, a randomised study comparing these two sites did not demonstrate a difference in LVEF [330].

There is an increased risk of developing heart failure in patients with a high proportion of RV pacing [331,332]. Pacemaker programming should be mindful of minimising ventricular pacing through various approaches to extend the atrioventricular delays to encourage intrinsic conduction. This may be particularly important in patients with reduced LVEF, where RV pacing may exacerbate heart failure [314,321]. The Biventricular versus Right Ventricular Pacing in Heart Failure Patients with Atrioventricular Block (BLOCK HF) trial [314] compared CRT and right ventricular pacing in patients with HFrEF associated with atrioventricular block. It showed that CRT decreased hospitalisations for heart failure compared with RV pacing.

9.1.1.6. Cardiac Resynchronisation Therapy Defibrillator versus Cardiac Resynchronisation Therapy Pacemaker. When CRT is indicated, a CRT-D is used, in most cases, rather than a CRT-pacemaker (CRT-P). The Danish Study to Assess the Efficacy of ICDs in Patients with Non-Ischemic Systolic Heart Failure on Mortality (DANISH) study [333] showed evidence that nonischaemic cardiomyopathy patients may not derive benefit from an implantable defibrillator. As such, there may be a greater call for CRT-P over CRT-D in these patients. In other circumstances—e.g., in patients who do not wish to have the potential for defibrillation, where the left ventricle is likely to improve, in the very elderly, or in those who retain a poorer prognosis but remain symptomatic—it would be reasonable to consider CRT-P over CRT-D, to improve their quality of life and longevity [301,302]. It remains controversial in patients who have an existing CRT-D that is up for renewal and whose ventricle has positively remodelled and experienced an improvement in ejection fraction as to whether a replacement with a CRT-P should be chosen over CRT-D.

Benefits and harms: In appropriately chosen patients, the prognostic and symptomatic benefits are greater for CRT-D compared with defibrillator alone and better for CRT-P compared with RV pacing alone. There is potential for harm when pacing without CRT in heart failure or with inappropriate use of CRT, e.g., a QRS of less than 130 ms.

Resources and other considerations: Expertise in implantation of LV wires is more likely with higher volume centres and operators. Other considerations include the cost of implantation and follow-up by both pacemaker and specialist heart failure services.

Practice advice

1. CRT (with or without an ICD) should be considered for patients with heart failure associated with an LVEF of less than or equal to 35% and a QRS duration of 130 ms or more despite optimal medical therapy.
2. The benefit of CRT is greater in patients with a broader QRS duration (especially QRS duration ≥150 ms).
3. Other factors that may influence decision-making, especially in patients with borderline indications, include the

underlying rhythm (stronger evidence in sinus rhythm), QRS morphology and PR interval, with greater benefit reported in some studies for LBBB morphology and prolonged PR interval.
4. If CRT is performed in patients in AF, measures are required to ensure at least 92% biventricular capture.
5. CRT is not beneficial (and may be harmful) in patients with a QRS duration of less than 130 ms.

9.1.2. Implantable Cardioverter Defibrillators

Recommendation: An ICD should be considered as a secondary prevention indication in patients following resuscitated cardiac arrest, sustained ventricular tachycardia in the presence of haemodynamic compromise and ventricular tachycardia associated with syncope and an LVEF of less than 40% to decrease mortality.
(Strong recommendation FOR; high quality of evidence.)

Recommendation: An ICD should be considered as a primary prevention indication in patients at least 1 month following MI associated with an LVEF of less than or equal to 30% to decrease mortality.
(Strong recommendation FOR; high quality of evidence.)

Recommendation: An ICD should be considered as a primary prevention indication in patients with HFrEF associated with ischaemic heart disease and an LVEF of less than or equal to 35% to decrease mortality.
(Strong recommendation FOR; moderate quality of evidence.)

Recommendation: An ICD may be considered as a primary prevention indication in patients with HFrEF associated with DCM and an LVEF of less than or equal to 35%, to decrease mortality.
(Weak recommendation FOR; low quality of evidence.)

Rationale: SCD is predominantly due to ventricular tachyarrhythmia and is the leading cause of mortality in patients with HFrEF, with the incidence increasing with declining LV systolic function. ICDs are the most effective tool in the prevention of SCD (see Appendix 3). Transvenous ICDs are effective in providing antitachycardia pacing or an internal shock to restore sinus rhythm. A randomised study comparing amiodarone with ICDs demonstrated a significant survival benefit for ICDs [334], with amiodarone equivalent to placebo.

The incidence of SCD is higher in patients with underlying ischaemic heart disease; thus, it is not surprising that the benefits of ICD therapy are more significant in these patients [335]. No individual randomised study has demonstrated a significant reduction in total mortality for ICDs compared with medical therapy in DCM. On the basis of the Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT), ICDs were recommended in patents with HFrEF associated with an LVEF of less than or equal to 35% and NYHA Class 2 or 3 symptoms, regardless of whether or not they had underlying coronary artery disease; however, subgroup analysis of the DCM group did not achieve statistical significance. The DANISH study randomised 556 patients with DCM and an LVEF of less than or equal to 35% to ICDs vs medical therapy, with no significant difference in total mortality between the groups [333]. A CRT was implanted in 58% of patients in both groups and there was a higher use of beta blockers (96%) compared with earlier randomised ICD studies. A Danish substudy with the prespecified endpoint of age identified a significant reduction in mortality in patients aged under 70 years [336]. Subsequent meta-analyses demonstrated a significant reduction in all-cause mortality with ICDs in patients with DCM, with the greatest benefit in younger patients who did not have a CRT [337].

Benefits and harms: The benefits of ICD therapy must be balanced against the impact of living with a device with complications related to implantation and psychological sequelae related to inappropriate shocks for atrial tachyarrhythmias or lead fracture.

9.1.2.1. Programming and Type of Device.

Practice advice

1. Generally single-chamber ICDs are recommended with an atrial lead included only if there is a separate bradycardia indication because dual chamber devices are associated with a higher rate of complications, device replacement and expense [338].
2. A CRT should also be considered in patients with HFrEF associated with a QRS duration of 130 ms or more and an LVEF of less than or equal to 35%.
3. The Multicenter Automatic Defibrillator Implantation Trial–Reduce Inappropriate Therapy (MADIT-RIT) study demonstrated the importance of programming with a reduction in inappropriate ICD therapy and total mortality with device therapies delivered at ventricular rates of more than 200 bpm or with a 60-second delay for rates of more than 170 bpm [339].
4. Device programming for bradycardia parameters should be at a lower rate of 40 bpm, to minimise ventricular pacing [331].
5. Subcutaneous ICDs may be considered in younger people for primary prevention, however, do not provide antitachycardia pacing or bradyarrhythmia pacing support.

9.2. Pressure Monitoring Devices

Recommendation: Implantable pulmonary arterial pressure monitoring may be considered in patients who have been previously hospitalised for heart failure associated with a reduced or preserved LVEF with persistent moderate (NYHA functional class III) heart failure symptoms despite optimal care to decrease hospitalisation for heart failure, provided systems are in place to ensure daily upload and at least weekly review of pressure monitoring data.
(Weak recommendation FOR; low quality of evidence.)

Rationale: Bedside clinical assessment of fluid balance is not only a valuable part of the physical examination of patients with heart failure, but more importantly can guide management. The concept of remote monitoring has theoretical benefits, but so far has been demonstrated to have only limited clinical benefit. This may in part be due to limitations in the technologies available, the type of data that can be measured

and its translation into clinical algorithms or changes in management. Change in pulmonary artery pressure is considered a marker of change in volume status and perhaps an early predictor of hospitalisation for heart failure. Traditional assessment of pulmonary artery pressure or left atrial pressure can be obtained by invasive catheter studies or estimated by echocardiography; however, these approaches only offer intermittent sampling of intracardiac pressure.

The Chronicle Offers Management to Patients with Advanced Signs and Symptoms of Heart Failure (COMPASS-HF) trial [340] used the Chronicle™ device (Medtronic) to continuously and remotely measure an estimate of pulmonary artery diastolic pressure, RV systolic and diastolic pressure, RV rate of rise of pressure (dP/dt), heart rate and activity. In a small study involving 275 patients over 6 months, there was a nonsignificant reduction in the composite clinical heart failure endpoint, although a retrospective analysis identified a nominally significant reduction in hospitalisation for heart failure. Nonetheless, this study did provide some evidence to suggest that pulmonary diastolic pressure rose gradually and often preceded overt clinical heart failure symptoms.

The CardioMEMS Heart Sensor Allows Monitoring of Pressure to Improve Outcomes in NYHA Class III Heart Failure Patients (CHAMPION) trial assessed the clinical efficacy of an implantable pulmonary artery pressure monitor for heart failure management using the CardioMEMS™ device compared with standard care. There were a larger number of changes made to heart failure drug therapy in the treatment group, which translated to significant reductions in hospitalisations for heart failure at 6 months (primary endpoint) and 15 months [341]. Similar benefits were reported in patients with reduced and preserved LVEF. In a subgroup of patients aged 65 years and over, all-cause 30-day rehospitalisation was reduced [342]. A subsequent analysis reported similar benefits using a pretest, post-test comparison in the patients who transitioned from the control group to having open-access to the haemodynamic data [341].

Several direct left atrial pressure monitoring devices are under development.

Benefits and harms: Remote monitoring of devices is possible, and is particularly helpful for patients living in remote areas. The adverse event rate for the CardioMEMS heart sensor submitted to Manufacturer and User Facility Device Experience after approval by the United States Food and Drug Administration in more than 5,500 patients was 2.8%. These were due predominantly to device failure or migration; less commonly to access site issues, arrhythmias, and pulmonary embolism or device thrombosis; and rarely to pulmonary artery injury [343].

Resources and other considerations: In addition to the facilities and staff required to insert the pressure-monitoring device, there needs to be daily upload and at least weekly review of the haemodynamic data by the treating clinician. It is also uncertain whether the benefits reported in the CHAMPION trial would apply in the Australian healthcare system, where there may be different models of care and different thresholds to hospitalisation.

9.3. Surgical Management of Heart Failure in Association With Ischaemic Heart Disease

Recommendation: Coronary artery bypass graft surgery (CABG) should be considered in patients with HFrEF associated with ischaemic heart disease and an LVEF of less than or equal to 35% if they have surgically correctable coronary artery disease to improve symptoms (e.g., relief of angina and heart failure symptoms) and decrease morbidity and long-term mortality.
(Strong recommendation FOR; moderate quality of evidence.)

Rationale: The Surgical Treatment for Ischemic Heart Failure (STICH) trial was the largest completed trial that was designed to define the role of cardiac surgery in the treatment of patients with heart failure and ischaemic heart disease. In this trial, 1212 patients with coronary artery disease and an LVEF of less than or equal to 35% were randomised to receive CABG on top of standard medical therapy compared with standard medical therapy alone [344]. There was no significant difference in the primary endpoint, all-cause mortality at 5 years; however, patients randomised to receive CABG had a lower cardiovascular mortality and a lower rate of mortality or cardiovascular hospitalisation. After 10 years, patients assigned to CABG experienced lower total mortality, lower cardiovascular mortality, and required fewer hospitalisations [345]. Percutaneous revascularisation may also be considered in selected patients with HFrEF associated with ischaemic heart disease, however a recent meta-analysis suggests that surgical revascularisation is associated with better outcomes [346].

The STICH study also randomised suitable patients to CABG combined with surgical ventricular reconstruction (SVR) or CABG alone. This study demonstrated no benefit for SVR [347]. Observational studies suggested that patients with more discrete areas of scar or aneurysm formation in association with coronary disease and heart failure may benefit from SVR [348,349]; however, a post hoc analysis from the STICH trial failed to identify any subgroup that benefited from SVR [350].

The value of myocardial viability testing (using either nuclear or echocardiographic techniques) in selecting patients for surgical revascularisation is uncertain. Although a meta-analysis of earlier studies suggested that patients with demonstrable myocardial viability had improved survival with surgical as compared with medical therapy [351], these studies were retrospective, non-randomised and conducted in an era prior to widespread use of beta blockers for the treatment of left ventricular dysfunction. A post hoc analysis of the STICH trial revealed that patients with evidence of myocardial viability and left ventricular dysfunction had improved survival compared with those without viability, however this difference was no longer significant after

adjustment for baseline characteristics [352]. Furthermore, the presence of myocardial viability did not identify patients with a differential survival benefit after CABG compared with medical therapy alone [352].

Benefits and harms: The benefits of CABG in patients with heart failure complicating ischaemic heart disease are relief of symptoms, fewer hospitalisations (after the surgical admission) and decreased cardiovascular mortality in the long term. These benefits must be balanced against the short-term morbidity and mortality risk related to the CABG. Factors unrelated to the severity of heart failure—including age, frailty and comorbidities—are important contributors to surgical risk and require careful evaluation before any decision to recommend CABG.

9.4. Surgical or Percutaneous Management of Valvular Heart Disease in Association With Heart Failure

9.4.1. Mitral Regurgitation

9.4.1.1. Surgical Mitral Valve Repair or Replacement.

Recommendation: Mitral valve (MV) repair or replacement at the time of elective CABG should be considered in patients with moderate to severe mitral regurgitation in association with heart failure and ischaemic heart disease to improve symptoms.
(Weak recommendation FOR; low quality of evidence.)

Recommendation: Surgical MV repair or replacement may be considered in patients with severe mitral regurgitation complicating dilated cardiomyopathy with heart failure who remain symptomatic despite guideline-directed medical and cardiac device therapy to improve symptoms.
(Weak recommendation FOR; low quality of evidence.)

Rationale: According to observational studies, the surgical management of mitral regurgitation complicating DCM with preservation of the subvalvular apparatus can produce significant improvement in both patient symptoms and preservation of LV function [353,354]. In a recent systematic review, the operative mortality of MV repair was half that of MV replacement [354]; however, in a prospective randomised trial comparing MV repair with MV replacement for ischaemic mitral regurgitation, overall clinical outcomes were similar between the two treatment groups [355]. MV repair was associated with a significantly higher rate of recurrent mitral regurgitation [355]. Regardless of the surgical technique, long-term mortality after surgical management of mitral regurgitation in association with heart failure is substantial, ranging from 22% to 53% at 5 years [354]. A post hoc analysis of the STICH trial reported that, in patients with moderate to severe mitral regurgitation in association with ischaemic LV dysfunction, MV repair at the time of CABG was associated with an improved long-term survival compared with CABG alone or medical therapy alone [356]. Nonetheless, five-year mortality was high for all three treatment groups [356], leading the authors to recommend that alternative approaches including heart transplantation and ventricular assist device (VAD) implantation should be considered for these patients. In another recent systematic review of MV surgery for moderate to severe mitral regurgitation at the time of elective CABG, the authors reported that MV surgery reduced the risk of late recurrence of mitral regurgitation, but did not affect perioperative or long-term mortality [357].

***Benefits and harms*:** The major reported benefit of surgical MV repair or replacement is symptomatic relief of dyspnoea. The potential harm is the exposure of the patient to the short-term morbidity and mortality risks associated with major cardiac surgery, with limited evidence that surgical correction of mitral regurgitation improves long-term survival.

9.4.1.2. Percutaneous Mitral Valve Procedures.

Recommendation: Percutaneous MV repair or replacement may be considered in patients with moderate to severe functional mitral regurgitation in association with heart failure who remain symptomatic despite guideline-directed medical and cardiac device therapy, particularly in those who are at high surgical risk to improve symptoms.
(Weak recommendation FOR; low quality of evidence.)

Rationale: A number of percutaneous catheter-based procedures for repairing or replacing the MV in patients with mitral regurgitation have been developed. These include the MitraClip System (Abbott Vascular; Santa Clara, CA, USA), which is based on the surgical technique of MV repair described by Alfieri [358]. In the Endovascular Valve Edge-to-Edge Repair Study (EVEREST) II trial, 279 patients with severe mitral regurgitation (86% of whom had a history of heart failure) were randomised to MitraClip versus surgical MV repair. At 12 months, more MitraClip patients required further surgery to correct residual mitral regurgitation; however, major adverse events were less frequent in the MitraClip group, and overall clinical outcomes including mortality were similar at 12 months and at 5 years [359,360]. A recent meta-analysis of MitraClip for the treatment of severe functional mitral regurgitation in association with CHF included 875 nonrandomised patients from nine studies. The authors reported a significant improvement in NYHA Class, 6-minute walk distance, and echocardiographic dimensions and function during a mean follow-up of 9 months [361]. A large randomised trial of MitraClip vs optimal medical therapy for treatment of moderate to severe functional mitral regurgitation in association with heart failure (Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients With Functional Mitral Regurgitation trial [COAPT]) will help to define the role of percutaneous MV repair in the management of functional mitral regurgitation in patients with heart failure.

Benefits and harms: The benefits of percutaneous MV repair or replacement are relief of symptoms and reduced procedural risks compared with surgical MV repair or replacement. Nonetheless, there are procedural risks and a higher rate of late mitral regurgitation recurrence compared with surgical correction. As with surgical MV repair, the impact of percutaneous MV repair on long-term survival remains uncertain.

9.4.2. Aortic Valve Disease

9.4.2.1. Surgical Aortic Valve Replacement.

Recommendation: Surgical aortic valve replacement (SAVR) is recommended in patients with severe aortic stenosis or severe aortic regurgitation and heart failure in the absence of major comorbidities or frailty, to improve symptoms and decrease mortality.
(Strong recommendation FOR; low quality of evidence.)

Rationale: Patients with haemodynamically severe aortic stenosis and symptoms of heart failure have an extremely poor prognosis. There is no effective medical treatment for these patients. Although there have not been any formal randomised trials of surgery vs medical therapy, there is expert consensus that SAVR improves symptoms and survival [362,363]. Patients with severe aortic stenosis and heart failure may have normal or reduced LV function. While it is important to consider and treat other causes of reduced LV function in these patients (particularly concomitant coronary artery disease), improvement in LV function can be expected following SAVR [362,363].

Similarly, patients with severe aortic regurgitation and heart failure have a poor prognosis with medical therapy. Severe aortic regurgitation may develop acutely (e.g., in association with aortic dissection or as a complication of endocarditis). This typically results in abrupt onset of severe LV failure (pulmonary oedema or even cardiogenic shock). Surgical risk will depend in part on the conventional risk factors such as age and pre-existing comorbidities, and also on the presence and extent of acute complications (e.g., dissection of major vessels or acute multiorgan failure) [362,363]. Patients with chronic severe aortic regurgitation often develop marked LV dilatation. Timing of surgery may be difficult to judge in asymptomatic patients and is extensively reviewed in other guidelines [362,363]. Patients with severe chronic AR who develop heart failure require aortic valve replacement regardless of the degree of LV dilatation or dysfunction, provided they are otherwise fit for surgery [362,364].

Benefits and harms: The benefits of SAVR for the patient with severe aortic stenosis or regurgitation (or a combination of the two) complicated by heart failure far outweigh the risks, provided that the patient has an acceptable surgical risk based on age, frailty, and comorbidities.

9.4.2.2. Transcutaneous Aortic Valve Implantation.

Recommendation: Transcatheter aortic valve implantation (TAVI) should be considered in patients with severe aortic stenosis and heart failure at intermediate to high operative mortality risk or considered inoperable for SAVR, and who are deemed suitable for TAVI following assessment by a heart team to improve symptoms and decrease mortality.
(Strong recommendation FOR; moderate quality of evidence.)

Rationale: TAVI was developed as a minimally invasive procedure to treat aortic stenosis in patients who were considered high risk for SAVR because of frailty or comorbidities. The Placement of AoRTic TraNscathetER Valve (PARTNER) 1 Study evaluated a balloon-expandable TAVI in elderly patients with severe aortic stenosis and heart failure (predominantly NYHA Class III–IV). The cohort that were considered unsuitable for SAVR (n = 358) were randomised to TAVI or medical therapy [365], and the cohort considered high risk for SAVR (n = 699) were randomised to TAVI or SAVR [366]. Compared with medical therapy, patients randomised to receive TAVI had a significantly decreased mortality, decreased repeat hospitalisation rate, and improved symptoms, but a higher rate of stroke and vascular complications at 1 year. Compared with SAVR, patients randomised to receive TAVI had similar mortality at 1 year [366]. The US CoreValve investigators evaluated a self-expanding TAVI in elderly patients with severe aortic stenosis and heart failure (predominantly NYHA Class III–IV) considered high risk for SAVR (n = 795). Compared with SAVR, patients randomised to receive TAVI had a significantly decreased mortality at 1 year [367]. The PARTNER 2 Study evaluated a balloon-expandable TAVI in 2032 elderly patients with severe aortic stenosis who were estimated to have intermediate operative mortality risk from SAVR [368]. Most patients had NYHA Class III–IV symptoms at baseline. Patients were randomised to TAVI or SAVR. About 76% of the TAVI cohort underwent the procedure via a transfemoral approach and 24% via a transapical approach. The primary endpoint of death or disabling stroke was similar in both groups over 2 years of follow-up; however, the primary outcome occurred less frequently in the subgroup who underwent TAVI via a transfemoral approach compared with the SAVR group [368]. Several studies have identified frailty as a predictor of increased morbidity and mortality after TAVI, suggesting that a formal frailty assessment should be included as part of the routine TAVI workup [369–371].

Benefits and harms: The major benefit of TAVI is relief of heart failure. This benefit needs to be balanced against the short-term morbidity and potential mortality and uncertainty regarding long-term benefit in patients who are usually elderly and often frail with multiple comorbidities.

Practice advice

1. Patients being considered for TAVI should be assessed by a multidisciplinary team ('heart team') that includes a cardiac imaging expert, interventional cardiologist, cardiac surgeon, cardiac anaesthetist, geriatrician, and allied health personnel, to consider the patient's risk and technical suitability for TAVI or SAVR, and the patient's frailty and cognitive function.
2. Multimodal imaging including transthoracic and transoesophageal echocardiography, multislice CT scanning, CMR imaging, aortoiliac and femoral arterial imaging is integral to assessing suitability for TAVI, sizing of the valve, and the vascular access route to be used.

9.5. Ventricular Assist Devices

Recommendation: Referral to a specialist centre for consideration of VAD implantation should be considered in patients with intractable, severe heart failure despite

guideline-directed medical and pacemaker therapy, and who do not suffer from major comorbidities to decrease mortality.
(Strong recommendation FOR; moderate quality of evidence.)

Recommendation: Implantation of a VAD as a bridge to transplant should be considered in patients actively listed for heart transplantation who become inotrope-dependent or who progress to needing acute mechanical circulatory support.
(Strong recommendation FOR; low quality of evidence.)

Rationale: Indications for VAD implantation fall into four broad categories:

- bridge to transplantation (BTT)—in patients with advanced heart failure who are awaiting heart transplantation;
- bridge to candidacy—in patients with advanced heart failure who are not eligible for transplantation at the time of VAD implantation, but who are expected to become suitable following a period of VAD support;
- bridge to recovery—typically in patients with acute severe heart failure complicating myocarditis or following cardiac surgery;
- destination therapy (DT)—in patients with advanced heart failure who are ineligible for heart transplantation and expected to remain ineligible after VAD implantation.

It is important to note that patients may move from BTT to DT (e.g., due to development of major VAD complications such as disabling stroke or due to development of high levels of immune sensitisation from repeated blood transfusion) while others may move from DT to BTT (e.g., due to marked improvement in functional class and reversal of frailty) [372]. In Australia (and New Zealand), approved indications for VAD implantation fall into the first three categories. Globally, however, 'destination' therapy has become the most common indication for VAD implantation [373,374]. The first RCT of LVAD therapy (REMATCH) was conducted in 'destination' patients, and demonstrated that implantation of a pulsatile LVAD was associated with improved survival and quality of life. There was, however, a greater than two-fold increased risk of serious adverse events, including infection, bleeding, thromboembolism, and device malfunction [173]. A second RCT (REMATCH II) compared a continuous-flow LVAD with a pulsatile-flow LVAD in patients with advanced CHF in whom current therapy had failed and who were ineligible for heart transplantation [174]. Almost 80% of the patients were receiving intravenous inotropes and 20% were on intra-aortic balloon pump support at the time of enrolment. The continuous-flow LVAD significantly improved the primary composite endpoint of survival free from disabling stroke and reoperation to repair or replace the device at 2 years (46% vs 11%, $p < 0.001$). Furthermore, actuarial survival at two years was improved (58% vs 24%, $p = 0.008$) and major adverse events and rehospitalisations were less frequent.

More recent registry publications have reported further improvements in postimplant survival following implantation of continuous-flow LVADs (about 80% at 1 year and 70% at 2 years). Further advances in continuous-flow pump design (from axial flow to magnetically levitated centrifugal flow) appear to have further reduced the life-threatening complications of pump malfunction and thrombosis [375,376]; however, other life-threatening complications including major bleeding (30–60%), infection (33%), and stroke (10–20%) are still common [373–376]. Gastrointestinal bleeding from angiodysplasia occurs in 15–20% of LVAD recipients and appears to be related to the continuous-flow haemodynamics. In the 2-year follow-up of the Momentum 3 trial, which randomised patients to the Heartmate 2 (axial flow) or the Heartmate 3 (centrifugal) LVAD, the overall event-free survival was superior in the Heartmate 3 cohort, due mainly to reduced pump thrombosis requiring pump exchange. The stroke rate was also significantly reduced with Heartmate 3 (10% vs 19%); however, disabling stroke was similar (7% vs 5%) [377].

Benefits and harms: LVAD support improves survival and allows rehabilitation of selected patients with refractory heart failure. Timing of implantation and patient selection are critical to achieving a successful outcome. In Australia, it provides a 'bridge to transplantation' in patients who would otherwise die waiting. Longer-term harms including disabling stroke, bleeding, and infection remain major limitations.

9.6. Cardiac Transplantation

Recommendation: Referral for heart transplant assessment should be considered in patients with heart failure associated with intractable NYHA Class III–IV symptoms who have exhausted all alternative therapies and who do not have overt contraindications, to decrease mortality.
(Strong recommendation FOR; low quality of evidence.)

Rationale: Heart transplantation is limited by donor organ availability and can only occur after the altruistic donation of the heart from a deceased donor. Recent developments in donor heart preservation have broadened the potential donor pool; however, the number of patients who might benefit from heart transplantation still far exceeds the number of potential donors [378,379]. Although there has never been a randomised trial of heart transplantation in the management of advanced heart failure, there is a general consensus that it is the most effective treatment for selected patients with refractory heart failure [380]. Patients with intractable NYHA Class III–IV symptoms who have exhausted all alternative therapies and who do not have overt contraindications should be referred for heart transplant assessment. Internationally accepted indications and contraindications for transplantation have recently been revised and are listed in Table 12 [381]. Timing of referral in patients with heart failure can be difficult to judge, but because these patients are at high risk of developing complications that may exclude them from heart transplant consideration (e.g., fixed pulmonary hypertension, multiorgan failure), early referral is recommended. Median survival for heart transplant recipients in Australia and New Zealand is about 15 years [382].

Table 12 Indications and contraindications for cardiac transplantation.

Indications	Relative contraindications
Definite • Persistent NYHA Class IV symptoms • Volume of oxygen consumed per minute at maximal exercise (VO_2 max) <14 mL/kg/min (VO_2 max <12 for patients on beta blockers) • Severe ischaemia not amenable to revascularisation • Recurrent uncontrollable ventricular arrhythmia *Probable* • Persistent NYHA Class III symptoms • Recurrent unstable angina with poor LV function not amenable to revascularisation *Inadequate* • LVEF <20% without significant symptoms • History of NYHA Class III or IV symptoms • VO_2 max >14 mL/kg/min. without other indication	• Age >65 years in association with frailty • Active infection • Previous malignancy: collaboration with oncology specialists should occur to stratify each patient by their risk of cancer recurrence. The wait time for transplantation after neoplasm remission will depend on the factors previously mentioned and no arbitrary time period for observation should be used • Fixed high pulmonary pressures (pulmonary vascular resistance >4 Wood units, or mean transpulmonary gradient >12 mm Hg, or pulmonary artery systolic pressure >60 mm Hg despite acute vasodilator challenge). Patients with fixed pulmonary hypertension may be considered for LVAD support as a bridge to candidacy with the expectation that pulmonary resistance will fall after prolonged (3–6 mo) LVAD support • Severe cerebrovascular or peripheral vascular disease not amenable to revascularisation • Current substance abuse (including tobacco and alcohol) • Coexisting systemic illness likely to limit survival • Severe and irreversible major organ dysfunction; patients may be considered for combined organ transplantation • Adverse psychosocial factors limiting compliance with medical therapy • Recent pulmonary embolism (<6 wk) • Diabetes mellitus with severe or progressive end-organ damage • Morbid obesity (BMI >35 kg/m^2) • Unhealed peptic ulceration

BMI: body mass index, LV: left ventricle, LVAD: left ventricular assist device, LVEF: left ventricular ejection fraction, NYHA: New York Heart Association.

Benefits and harms: For patients with end-stage heart disease, the benefits of heart transplantation both in terms of overall quality of life and life expectancy far outweigh the risks of the surgery itself or the harms related to lifelong immunosuppression.

Practice advice

1. Clinicians are advised to contact the specialist centres that provide these services regarding any patient with heart failure who is responding poorly to conventional medical or device therapy.
2. Transplant centres can also provide advice on management of myocarditis and rarer cardiomyopathies, including the roles of endomyocardial biopsy and immunosuppression.

10. Comorbidities in Heart Failure

Most patients with heart failure have comorbidities. The burden of comorbidity increases with age, and may exacerbate the disease process and clinical severity of heart failure, impact on outcomes, and interfere with optimal heart failure treatment. Patients with HFpEF have a higher burden of comorbidities than patients with HFrEF, although the pattern of disease is similar [383].

A structured framework has been proposed to acknowledge that comorbidity is usually associated with a worse prognosis, identify priorities and person-centred goals for management, and consider multidisciplinary case management to address multimorbidity [275]. Specialists from other fields will manage many comorbidities, and other guidelines will apply.

10.1. Hypertension

Recommendation: Diltiazem, verapamil, and moxonidine should be avoided in patients with HFrEF.
(Strong recommendation AGAINST; low quality of evidence.)

Rationale: Hypertension is the most prevalent modifiable risk factor for heart failure, and is a comorbidity in two-thirds of all patients with heart failure [384]. A higher blood pressure before treatment is a marker of better survival in patients with heart failure, which is likely due to more severe heart failure being associated with a lower blood pressure [385]. However, in a prospective cohort study in subjects with incident heart failure, higher baseline blood pressure was associated with worse outcomes [386], underscoring the importance of blood pressure control in heart failure.

ACE inhibitors, ARBs, ARNIs, beta blockers, and MRAs all have blood-pressure-lowering effects and decrease mortality and heart failure hospitalisation in HFrEF [387]. Diuretics

may also have a modest blood-pressure-lowering effect. The addition of amlodipine [388], felodipine [389], and hydralazine [222] is safe in patients with HFrEF for the management of hypertension, but they do not improve clinical outcomes from heart failure. Verapamil and diltiazem can worsen outcomes in patients with HFrEF [390], but can be used in patients with HFpEF. Moxonidine increased mortality in one trial in patients with HFrEF [391]. Alpha-adrenoceptor antagonists cause neurohormonal activation, fluid retention and worsening heart failure [392].

Practice advice

1. An ACE inhibitor, ARB or ARNI; and a beta blocker; and an MRA are recommended in patients with HFrEF. Carvedilol may be the preferred beta blocker due to its vasodilatory effects.
2. Optimally treated HFrEF is rarely associated with hypertension.
3. Optimal control of blood pressure is important in the treatment of HFpEF. An MRA, with or without an ACE inhibitor or ARB may be preferred. Use diuretics and venodilators cautiously as they may cause a fall in cardiac output and hypotension.
4. Blood pressure targets in heart failure are those recommended in hypertension guidelines [393].

10.2. Coronary Artery Disease and Angina

Rationale: Coronary artery disease is the most common cause of incident HFrEF and is present in up to half of all patients with heart failure [14]. It is an adverse prognostic indicator regardless of LVEF [394]. Angina is associated with greater functional limitation and higher risk of coronary events [395].

Beta blockers [191] and ivabradine [200] decrease morbidity and mortality in appropriate patients with HFrEF. Amlodipine [388] and nitrates [222] have been shown to be safe in HFrEF/LV dysfunction. Statin therapy has not been shown to improve outcomes in heart failure [396,397].

Practice advice

1. Ensure patients with HFrEF are on maximally tolerated or target doses of beta blockers (unless contraindicated).

2. If sinus rate is 70 bpm or above despite maximally tolerated or target doses of beta blockers (unless contraindicated), ivabradine should be considered in patients with HFrEF associated with an LVEF of less than or equal to 35%.

3. The combination of nicorandil and a nitrate should be avoided due to lack of additional efficacy.

4. Diltiazem and verapamil are unsafe in HFrEF [390] (although they can be used in HFpEF).

5. Statins should not be used to treat heart failure, but can be used in accordance with other guidelines.

10.3. Atrial Fibrillation

Recommendation: Determination of the risk of stroke to guide the need for anticoagulation is recommended in patients with AF.
(Strong recommendation FOR; high quality of evidence.)

Recommendation: Pharmacological therapy aiming for a resting ventricular rate of 60–100 bpm should be considered in patients with heart failure associated with AF and a rapid ventricular response (see Practice advice).
(Strong recommendation FOR; low quality of evidence.)

Recommendation: Catheter ablation for AF (either paroxysmal or persistent) should be considered in patients with HFrEF associated with an LVEF of less than or equal to 35%, who present with recurrent symptomatic AF, to decrease mortality and hospitalisation for heart failure.
(Strong recommendation FOR; moderate quality of evidence.)

Rationale: AF is common in patients with heart failure, and its prevalence and incidence increases with increasing severity of heart failure. Prevalence ranges from 5% in NYHA Class I up to 50% in NYHA Class IV, with annual incidence of 2–5% (higher in more severe heart failure) [398]. AF is also a common precipitant of heart failure, and conversely, heart failure is the strongest predictor for AF, and AF can result in myocardial dysfunction and heart failure [399]. AF in heart failure is associated with an increased risk of stroke, as well as higher mortality regardless of the type of heart failure [400]. The combination of loss of the atrial kick and irregular fast heart rhythm can reduce the cardiac output by up to 30% [401].

AF is an under-recognised reversible cause of HFrEF, particularly in patients who present with both conditions in the absence of other identifiable causes such as valvular or ischaemic heart disease. Although a randomised comparison of rate compared with rhythm control using pharmacological strategies in AF in HFrEF did not demonstrate superiority [402], this has been challenged by catheter ablation studies. Several randomised studies comparing catheter ablation for AF and medical rate control have demonstrated significant improvements in LVEF, NYHA functional class symptoms and reductions in BNP with catheter ablation [403,404]. The greatest improvements in LVEF with catheter ablation are seen in patients without delayed enhancement on CMR [403].

Most recently, the Catheter Ablation vs Standard conventional Treatment in patients with Left ventricular dysfunction and Atrial Fibrillation (CASTLE-AF) trial showed a reduction in all-cause mortality and reductions in hospitalisations for heart failure with catheter ablation in patients with symptomatic paroxysmal and persistent AF and HFrEF (LVEF $\leq$35%) (see Appendix 3) [405].

Some heart failure treatments prevent AF, including ACE inhibitor, ARB, and beta blockers [406]. A meta-analysis demonstrated that beta blockers in patients with HFrEF associated with AF do not confer the mortality benefits seen in sinus rhythm [407]. Class I antiarrhythmics and dronedarone have been associated with increased mortality in patients with heart failure or coronary artery disease [408,409].

Benefits and harms: Catheter ablation has the benefits of superiority in restoring sinus rhythm ***and*** survival advantage without the long-term morbidity of pharmacologic rhythm control agents such as amiodarone. However, catheter

ablation may need to be repeated in 30–40% and may be associated with complications in up to 5%.

Resources and other considerations: Catheter ablation is not available at all Australian hospitals and should be performed by experienced electrophysiologists with expertise in complex mapping.

Practice advice

1. Treat reversible causes of AF (electrolyte imbalances, hypothyroidism or hyperthyroidism, uncontrolled hypertension, mitral valve disease).
2. Determine the risk of stroke and treat the patient with anticoagulants, as required.
3. Aim for a ventricular rate of 60–100 bpm in patients with heart failure associated with AF and a rapid ventricular response.[410] Beta blockers and/or digoxin are generally favoured for ventricular rate control. Amiodarone or nondihydropyridine calcium entry blockers may be considered in specific circumstances (see below).
4. Give oral beta blockers to control the ventricular rate of AF if euvolaemic and not haemodynamically compromised.
5. Give intravenous or oral digoxin to control the ventricular rate of AF if congested or haemodynamically compromised or if the ventricular rate is not sufficiently controlled with beta blockers.
6. Consider intravenous amiodarone (to control the ventricular rate or facilitate cardioversion) or electrical cardioversion if haemodynamically unstable or if there is insufficient ventricular rate control with the above measures.
7. Consider nondihydropyridine calcium entry blockers in patients with HFpEF to control the ventricular rate of AF; however, these drugs should be avoided in patients with HFrEF.
8. Consider oral amiodarone in patients with heart failure associated with AF to facilitate attainment and maintenance of sinus rhythm (with or without electrical cardioversion) to improve symptoms or guide decisions regarding the need for more invasive approaches (e.g., AF catheter ablation or AV node ablation).
9. Consider catheter ablation in patients with recurrent symptomatic AF particularly with newly diagnosed or worsening HFrEF.
10. Consider AV node ablation with ventricular pacing if ventricular rate insufficiently controlled on medical therapy.

10.4. Diabetes

Recommendation: Thiazolidinediones (glitazones) are not recommended in patients with heart failure due to the risk that they will lead to worsening of heart failure.
(Weak recommendation AGAINST; moderate quality of evidence.)

Rationale: Diabetes mellitus is an independent risk factor for the development of heart failure [411] and affects 30–40% of patients with heart failure [412]. Furthermore, diabetes is associated with a poorer prognosis in patients with heart failure that is independent of associated comorbidities [413].

In HFrEF, interventions that decrease morbidity and mortality have similar benefit in the presence or absence of diabetes [414]. A U-shaped curve between HbA1c and mortality has been shown in patients with heart failure with diabetes mellitus, with the lowest risk in patients with moderate glycaemic control (HbA1c 7.1–8.0%) [415].

Metformin has been shown to be safe in heart failure contrary to previous concerns [416]. It is contraindicated in severe renal or hepatic impairment, due to a possible risk of lactic acidosis. Thiazolidinediones (glitazones) cause sodium and water retention, increasing the risk of worsening heart failure and hospitalisation, although this may not be associated with an increased risk of cardiovascular death [417].

SGLT2 inhibitors have been shown in two RCTs to have beneficial effects in patients with type 2 diabetes at elevated cardiovascular risk. Empagliflozin and canagliflozin both decreased major cardiovascular events and heart failure hospitalisation [47,48,418]. Similar benefits were observed in patients with a pre-existing diagnosis of heart failure; however, the studies were not powered to assess this patient subgroup. Trials examining the clinical efficacy of SGLT2 inhibitors in patients with heart failure (with or without diabetes) are ongoing.

Insulin use causes sodium retention and can worsen heart failure. Sulphonylureas have been associated with an increased risk of developing heart failure; however, the possibility of indication bias cannot be excluded [419]. Dipeptidylpeptidase-4 (DPP-4) inhibitors have a neutral effect on cardiovascular outcomes [420]. Saxagliptin was associated with an increased risk of heart failure hospitalisation in a large RCT [421]; however, this may not be a class effect. Long-acting glucagon-like peptide 1 (GLP-1) agonists have been shown to either have a neutral effect or decrease cardiovascular events (but, not heart failure hospitalisation) in large RCTs; however, their safety and efficacy in patients with heart failure is uncertain [422].

Benefits and harms: The benefit of metformin outweighs the risk, but it should be not be used in severe renal or hepatic impairment. The risk of thiazolidinediones may outweigh the benefits.

Practice advice

1. The aims with glycaemic control will depend on factors including the patient's age and comorbidities. Gradual glucose lowering with moderate glycaemic targets is appropriate, around HbA1c 7.1–8.0%.
2. Metformin is generally the first-line oral hypoglycaemic agent if diet and lifestyle measures do not result in adequate glycaemic control.
3. SGLT2 inhibitors are preferred as second-line oral hypoglycaemic agent in patients with cardiovascular disease. SGLT2 inhibitors have a diuretic effect (osmotic) and may increase the effect of loop diuretics. Consider reducing the dose of the diuretic in euvolaemic patients to avoid further volume depletion.

4. Insulin may cause sodium and fluid retention, which may aggravate heart failure.
5. Sulphonylureas may be used with caution.
6. Increased heart failure hospitalisation has been observed with saxagliptin.

10.5. Chronic Kidney Disease, Hyperkalaemia, and Hypokalaemia

CKD is a powerful predictor of incident heart failure [423]. Moderate and severe renal impairment (usually defined as eGFR <60 mL/min/1.73 m^2 and <30 mL/min/1.73 m^2, respectively) and worsening renal function (defined as an increase in creatinine of 0.3 mg/dL or 27 μmol/L) are associated with poor outcomes [424]. A large meta-analysis found that CKD is present in over 60% of patients with heart failure, and moderate to severe CKD is present in around 30% of patients with heart failure [425]. Patients with severe renal dysfunction have been excluded from most RCTs, so the dosing, safety. and efficacy of most evidence-based therapies is uncertain in this group. No medical therapies have been shown to improve renal function; however, improvement in cardiac function can improve renal function.

There is a U-shaped relationship between the serum potassium level and mortality; however, what the ideal potassium level should be is controversial. A large, nationwide registry reported that a serum potassium level of 4.2 mmol/L to 4.7 mmol/L was associated with the lowest mortality in patients with chronic heart failure [426]. However, it is unclear what clinicians should do when levels fall outside this range, especially if mildly elevated given the recognised survival benefits of renin–angiotensin–aldosterone system inhibition.

Practice advice

1. A rise in serum creatinine of up to 30% can be expected on commencement of renin–angiotensin–aldosterone system inhibitors and in isolation should not be a reason to cease therapy.
2. Potentially reversible causes should be excluded in patients with a deterioration in renal function, which includes an evaluation of volume status, considering the need for nephrotoxic drugs, and excluding renovascular disease and urinary outflow tract obstruction.
3. Renin–angiotensin–aldosterone inhibitors should be temporarily ceased when acute hyperkalaemia occurs (K >6.0 mmol/L) and should be carefully reintroduced when potassium levels normalise.
4. Patients should be instructed on dietary measures to increase (if hypokalaemic) or decrease (if hyperkalaemic) their potassium intake.
5. Potassium binders can decrease the risk of recurrent hyperkalaemia in heart failure, and may be considered.

10.6. Hyponatraemia

Hyponatraemia is present in about 20% of hospitalised HF patients, and independently predicts prolonged hospital stay and post-discharge mortality [427]. Hyponatraemia in heart failure is predominantly dilutional, secondary to neurohormonal activation, particularly activation of arginine vasopressin which results in water retention and volume overload [428]. Less commonly, diuretics including thiazides, spironolactone and loop diuretics are the cause. The severity of hyponatraemia reflects the degree of neurohormonal activation, and development is usually gradual with subtle clinical manifestations compared with abrupt onset hyponatraemia.

Arginine vasopressin type 2 receptor antagonists, including tolvaptan, rapidly correct symptomatic hyponatraemia with hypervolaemia and congestion by promoting electrolyte-free diuresis through the kidneys via blockade of vasopressin receptors. No reduction in rehospitalisation or mortality has been shown [429].

Practice advice

1. Hyponatraemia is considered to be serum sodium below normal (<135 mmol/L). Correction of hyponatraemia in heart failure is rarely urgent due to its chronicity. Potentially reversible causes should be excluded, and volume status assessed. Fluid restriction should be considered unless hypovolaemic. Reconsider the need for diuretics (unless overloaded).
2. In patients with heart failure and resistant hyponatraemia (serum sodium <130 mmol/l), the use of arginine vasopressin type 2 receptor antagonists may be considered to reverse hyponatraemia and assist in aquaresis. They can be used in hypervolaemic or euvolaemic hyponatraemia, but are contraindicated in hypovolaemic hyponatraemia.

10.7. Obesity

Obesity is present in one-third to one-half of patients with heart failure [384]. Obesity is a risk factor for the development of heart failure [430]. There is a U-shaped curve for mortality in heart failure, with the lowest risk for overweight patients with heart failure with body mass index (BMI) 30.0–34.9 kg/m^2 [431]. It is not clear why survival is better, but proposed reasons include the additional adipose tissue providing greater reserves against catabolic changes associated with the progression of heart failure, or that obese patients have more functional impairment and present earlier with their heart failure [432]. Furthermore, this may vary according to the type of heart failure, with a recent analysis from the TOPCAT trial reporting a higher mortality in patients with HFpEF associated with abdominal obesity compared to those without abdominal obesity [433].

Prospective large-scale studies that examine the outcome of weight loss by diet, exercise, or bariatric surgery in obese patients with heart failure have not been performed [432]. One small retrospective study found bariatric surgery to be safe in heart failure with morbid obesity [434].

Practice advice

1. Obesity can complicate the diagnosis of heart failure, as an alternative cause of exercise intolerance, and is associated with lower natriuretic peptide levels.

2. For moderate obesity (BMI <35 kg/m^2), weight loss is not recommended in patients with HFrEF.
3. For severe obesity (BMI ≥35 kg/m^2), weight loss may be considered for symptomatic benefit and to improve exercise capacity. Consider referral to an appropriate multidisciplinary team.

10.8. Chronic Obstructive Pulmonary Disease and Asthma

Around 20% of patients with heart failure have coexisting COPD [384,435]. COPD is under-recognised in patients with heart failure [436] and negatively impacts on prognosis [437].

Beta-2-agonists or antimuscarinic agents are the mainstay of COPD treatment; however, beta-2-agonists exert the opposite effect of beta blockers and may decrease their beneficial effects in heart failure [438]. Beta-2-agonists do not improve mortality in COPD; they are cardio-active and may be harmful in heart failure [438]. Inhaled salmeterol improved forced expiratory volume (FEV) 1 in a small study in eight patients with NYHA II or III heart failure [439]. Inhaled corticosteroids have a better side effect profile than oral steroids [440]. Use of oral corticosteroids can increase fluid retention, and doses over 20 mg/day have been associated with acute decompensated heart failure [440].

Observational studies have shown that beta blockers decrease mortality in patients with heart failure associated with COPD [441], but RCTs have not been performed. Bronchoconstriction is mediated by beta$_2$-adrenoceptor blockade, and cardio-selective beta$_1$ blockers do not worsen symptoms in COPD, do not alter forced expiratory volume in 1 second (FEV1) and do not alter the FEV1 treatment response to long-acting beta$_2$-agonists (LABA) [442]. Beta blockers are underused in heart failure when concomitant COPD is present [443]. The concern with beta blockers in asthma stems from reports of acute bronchospasm in asthmatics given nonselective beta blockers [438].

Practice advice

1. Carefully assess the cause of dyspnoea and objectively document airflow obstruction. Spirometry is a key investigation used to diagnose COPD, but may be difficult to interpret, especially in patients who have suffered a recent decompensation.
2. Beta blockers can be safely used in most patients with COPD.
3. Antimuscarinic agents are preferred over beta-2-agonists. Use inhaled beta-2-agonists for symptom relief only. Minimise the dose and frequency. Avoid oral beta-2 agonists.
4. Inhaled corticosteroid and/or a long-acting antimuscarinic drug such as tiotropium, glycopyrronium, aclidinium, or umeclidinium can be substituted in patients requiring regular inhaled beta-2-agonists.
5. Oral corticosteroids cause sodium and water retention; however, inhaled corticosteroids do not.
6. Theophylline is not recommended for patients with heart failure.
7. Asthma is a relative contraindication to beta blockers. Start with a low dose of a more cardio-selective B1 adrenoceptor antagonist (bisoprolol, metoprolol, or nebivolol), with close follow-up for airway obstruction (e.g., increasing dyspnoea or cough, wheeze, monitoring of peak flows, repeat spirometry). Specialist supervision is recommended.
8. Ivabradine can be considered if beta blockers cannot be used and sinus rate is at least 70 bpm.

10.9. Sleep-disordered Breathing

Recommendation: Adaptive servoventilation is not recommended in patients with HFrEF and predominant central sleep apnoea because of an increased all-cause and cardiovascular mortality.

(Strong recommendation AGAINST; moderate quality of evidence.)

Rationale: Sleep-disordered breathing affects 50–75% of patients with heart failure [444,445] and is an adverse prognostic marker [446]. The primary indication to treat sleep apnoea in the general population is to improve quality of life and decrease sleepiness [447]. However, excess daytime sleepiness is relatively uncommon in patients with heart failure associated with sleep apnoea.

In one RCT, despite attenuation of central sleep apnoea (CSA) and improved nocturnal oxygenation with CPAP in patients with HFrEF associated with predominant CSA, CPAP did not improve transplant-free survival. There were improvements in exercise capacity, but no improvement in quality of life or hospitalisation rates [448]. In another RCT, adaptive servoventilation in patients with HFrEF associated with predominant CSA was neutral on the composite primary endpoint (all-cause death and lifesaving cardiovascular intervention—that is, cardiac transplantation, VAD, resuscitation after cardiac arrest, appropriate lifesaving shock, unplanned hospitalisation for worsening heart failure), but led to an increased all-cause and cardiovascular mortality [449].

A meta-analysis of RCTs evaluating positive pressure ventilation in patients with HFrEF associated with predominant obstructive sleep apnoea reported an increase in LVEF [450]; however, there have been no completed major outcome studies. In a large RCT, CPAP in patients with cardiovascular disease and predominant obstructive sleep apnoea failed to improve major cardiovascular outcomes (cardiovascular death, MI, stroke, or hospitalisation for unstable angina, heart failure, or transient ischaemic attack); however, there were improvements in quality of life and mood [451].

Therefore, while clinicians may consider positive pressure ventilation to improve quality of life and decrease sleepiness in patients with predominant obstructive sleep apnoea, the primary aim in patients with predominant CSA should be to treat the heart failure [452,453]. Other approaches including phrenic nerve stimulation, lateral or semirecumbent positional therapy, and respiratory stimulants such as acetazolamide have either shown promise or are undergoing further evaluation [454–458].

Benefits and harms: The harms of adaptive servo-ventilation outweigh the benefits in HFrEF.

Practice advice

1. If sleep apnoea is suspected, referral to a sleep physician is indicated.
2. Predominant obstructive sleep apnoea with nocturnal hypoxaemia and apnoea/hypopnoea index over 30 per hour in patients with heart failure may be treated with nocturnal oxygen supplementation, CPAP, BiPAP or adaptive servo-ventilation to improve quality of life and decrease sleepiness.
3. The primary aim in patients with predominant CSA should be to treat the heart failure.

10.10. Gout

Gout is common in heart failure, and is a risk factor for incident heart failure [459]. Hyperuricaemia is present in 37–54% of patients with heart failure [460] and elevated plasma urate levels are an adverse prognostic marker in moderate to severe heart failure [461].

NSAIDs and cyclo-oxygenase (COX)-2 inhibitors cause sodium and water retention, increase hospitalisations for heart failure and worsen renal function [462]. Many heart failure drugs affect uric acid levels [463]. Diuretics (loops and thiazide) can cause or exacerbate gout, although spironolactone does not alter uric acid levels. Losartan has a modest uricosuric effect. Two RCTs in which xanthine oxidase inhibition was evaluated in patients with HFrEF failed to demonstrate improved outcomes including mortality and quality of life [464,465].

Practice advice

1. Acute gout—treat with colchicine or a short course of oral prednisolone. Avoid or minimise use of NSAIDs and COX-2 inhibitors in heart failure. For monoarticular gout, intra-articular steroids can be considered, but is contraindicated in the presence of anticoagulation.
2. Prevention—use allopurinol to lower uric acid after an acute gout episode has completely resolved, and aim for serum urate level of less than 0.36 μmol/L (6 mg/dL), or 0.30 μmol/L (5 mg/dL) if tophi are present. Commence allopurinol at low dose and titrate upwards. Low dose colchicine may be required for the first 2–3 months to avoid precipitating gout when starting allopurinol. Lower doses of allopurinol are required to obtain this urate level in renal impairment. Address lifestyle including diet.
3. Febuxostat can be used if allergic or intolerant to allopurinol. Starting dose is 40 mg; increase to 80 mg if serum urate is greater than 0.36 μmol/L after 2–4 weeks.
4. Asymptomatic hyperuricaemia does not require treatment.

10.11. Arthritis

Rationale: Osteoarthritis and rheumatoid arthritis are common comorbidities in elderly patients with heart failure [383]. Rheumatoid arthritis affects 1% of the population and is associated with increased cardiovascular risk and risk of heart failure. Pain and joint deformities contribute to physical inactivity which can worsen heart failure clinical status.

NSAIDs are associated with an increased risk of heart failure in the elderly [466], and two major clinical trials of celecoxib were stopped early due to cardiovascular concerns [467,468]. Tumour necrosis factor (TNF) inhibitors were shown in one study to decrease the risk of heart failure in patients with rheumatoid arthritis [469]. However, they do not improve outcomes in patients with heart failure and should be used with caution [470].

Practice advice

1. Patients with severe systolic dysfunction or hyponatraemia should not be treated with large doses of COX inhibitors (both nonselective and COX-2 selective) for arthritis, as they may increase the risk of worsening CHF.
2. TNF inhibitors should be used cautiously for rheumatoid arthritis only if symptoms of heart failure are well controlled, with close follow-up.

10.12. Depression

Depression is common in heart failure, is clinically significant in around 20%, and is more common in inpatients than outpatients [471]. Depression is a risk factor for incident heart failure [472], and is an adverse prognostic marker in heart failure [473]. Diagnosis can be complicated by overlap of symptoms with heart failure. Screening for depression should be undertaken using a validated questionnaire, such as the Patient Health Questionnaire-9. Alternatively, the PHQ-2 can be used as an initial screen, and if either question is positive, one may proceed to the PHQ-9 [474].

An RCT evaluating cognitive behaviour therapy (CBT) in patients with heart failure associated with comorbid major depression reported a reduction in symptoms of depression and improved health-related quality of life [475]. A meta-analysis of CBT trials found greater improvement in depression scores immediately after CBT and at 3 months, compared with usual care, but there was no difference in hospitalisation and mortality [476]. An RCT evaluating a selective serotonin reuptake inhibitor (SSRI) (sertraline) in patients with HFrEF associated with clinical depression demonstrated the safety of sertraline, but the reduction in symptoms of depression was similar to placebo, and there was no significant effect on cardiovascular status [477].

Another RCT with SSRI (escitalopram) did not improve symptoms of depression compared with placebo, and did not improve cardiovascular outcomes [478]. A meta-analysis of RCTs evaluating exercise training in patients with heart failure associated with symptoms of depression reported a reduction in symptoms of depression [479].

Practice advice

1. Regularly screen for depression using a validated questionnaire.
2. CBT, pharmacological treatment and exercise training may be considered in patients with heart failure associated with depression.

3. SSRIs are the safest choice if pharmacological treatment is used.
4. Avoid tricyclic antidepressants, which can cause tachyarrhythmias, hypotension, and worsening heart failure. Citalopram and mirtazapine can prolong corrected QT (QTc) and cause torsades de pointes.

10.13. Anaemia

Recommendation: Erythropoietin should not be used routinely for the treatment of anaemia in patients with heart failure because of an increased risk of thromboembolic adverse events.
(Strong recommendation AGAINST; moderate quality of evidence.)

Rationale: Anaemia is defined by the World Health Organization as: Hb <120 g/L in females and Hb <130 g/L in males [480]. Anaemia is present in about one-third of patients with chronic heart failure [481]. It is an independent predictor of increased hospitalisations and mortality regardless of the type of heart failure [482], and associated with reduced exercise tolerance [483] and quality of life [484].

Anaemia and iron deficiency (defined as ferritin <100 μg/L, or ferritin 100–300 μg/L with transferrin saturation <20%) are both highly prevalent in patients with heart failure, and often overlap, but can be present independently. Iron deficiency is the most common cause of anaemia, but vitamin B12 and folate deficiency and CKD can contribute. Anaemia can be complicated by haemodilution, inflammation, and the use of cardiovascular medications [485].

A meta-analysis of small trials comparing erythropoiesis stimulating agents with placebo did not show improvements in mortality, cardiovascular events, or hospitalisations [486]. A randomised double-blind trial of darbepoetin alpha compared with placebo in patients with an LVEF of less than or equal to 40% with a target Hb of 13.0 g/dL reported no effect on the primary outcome of death or first hospitalisation for heart failure, but was associated with a significant increase in thromboembolic adverse events [487].

Benefits and harms: The potential harms of erythropoiesis stimulating agents in heart failure outweigh the benefits for routine use.

Practice advice

1. Treat reversible causes of anaemia; e.g., blood loss, iron or vitamin B12 or folic acid deficiency (refer to the next section for the management of iron deficiency).
2. Referral to a haematologist or renal physician for consideration of erythropoiesis stimulating agents may be considered in patients with CKD.

10.14. Iron Deficiency

Recommendation: In patients with HFrEF associated with persistent symptoms despite optimised therapy, iron studies should be performed and, if the patient is iron deficient (i.e. ferritin <100 μg/L, or ferritin 100–300 μg/L with transferrin saturation <20%), intravenous iron should be considered, to improve symptoms and quality of life.
(Strong recommendation FOR; moderate quality of evidence.)

Rationale: Iron deficiency (serum ferritin <100 mg/L or ferritin between 100 and 300 mg/L with transferrin saturation <20%) is at least twice as common in heart failure as anaemia, and is present in about 50% of patients with heart failure [488]. While the prevalence is higher in patients with heart failure who are anaemic (about 60%), it is still common in patients who are not anaemic (about 45%) [488]. Iron deficiency is itself an independent prognostic indicator, whether or not anaemia is also present, and is associated with reduced exercise tolerance, reduced quality of life, increased risk of hospitalisation and mortality [488,489].

Treatment of iron deficiency in patients with HFrEF with intravenous iron was shown in a meta-analysis of RCTs to be associated with improved heart failure symptoms, exercise capacity, quality of life, renal function, NYHA functional class, LVEF, and decreased heart failure hospitalisation and NT-pro BNP [490]. The effects on mortality are uncertain. An RCT comparing intravenous iron given for 24 weeks with placebo reported improved exercise capacity measured by peak VO_2 in symptomatic patients with stable heart failure [491]. Total doses of ferric carboxymaltose of 1000–1500 mg have been used in studies in HFrEF [492]. Oral iron alters iron stores minimally and, when compared with placebo, did not improve exercise capacity in patients with HFrEF associated with iron deficiency, probably due to reduced absorption and reduced uptake secondary to the effects of hepcidin [493].

Benefits and harms: The benefit of intravenous iron replacement outweigh the potential harms; however, in patients who are congested, clinicians should monitor fluid status, and favour lower volume infusion. Long-term effects are uncertain.

Resources and other considerations: Appropriate facilities are required to administer intravenous infusions with monitoring.

Practice advice

1. Clinicians should consider measuring iron studies and a full blood count in patients with persistent HFrEF.
2. If iron deficiency is diagnosed, one should consider investigation for gastrointestinal pathology, including peptic ulcer and malignancy (especially if also anaemic).
3. In the studies demonstrating the benefits of intravenous iron in HFrEF, iron deficiency was usually defined as serum ferritin of less than 100 mg/L or ferritin 100–300 mg/L with transferrin saturation (TSAT) of less than 20%. Two different ranges are provided because ferritin is an acute phase reactant, and may become elevated in the presence of inflammation. A TSAT of less than 20% indicates functional iron deficiency, with insufficient circulating iron to supply metabolising cells.
4. Intravenous iron should be considered in patients with HFrEF associated with iron deficiency with or without anaemia. Recheck iron studies after 4 months.
5. Intravenous ferric carboxymaltose was evaluated in most of the randomised controlled studies, usually involving one to two doses between 500 and 1000 mg [494].

6. Oral iron supplementation is ineffective at normalising iron status or improving quality of life in patients with HFrEF.

11. Chemotherapy-related Cardiotoxicity and Heart Failure

Cancer therapies have been more effective in recent years, and with cancer screening programs, early diagnosis, and novel therapies, cancer survival rates are increasing [495,496]. There are several cardiovascular complications that may occur secondary to cancer therapy, including myocardial dysfunction and consequent heart failure, hypertension, arrhythmias, coronary artery disease, valvular and pericardial disease, thromboembolism, and pulmonary hypertension. Cardiotoxicity as currently defined in guidelines is limited to alterations in LVEF in the resting state [497]; a drop in LVEF by 10% compared to baseline to less than 53% in asymptomatic patients, or a drop of 5% compared to baseline to less than 53% in symptomatic patients, is regarded as cardiotoxicity. This section will mainly focus on LV dysfunction and consequent heart failure secondary to chemotherapy.

11.1. Medications That Cause Cardiotoxicity

There are several changes observed inthe cardiovascular system consequent to cancer therapies, including alteration in LV function and in haemodynamics [498]. LV dysfunction has broadly been classified into irreversible LV dysfunction (type 1 cancer therapeutics-related cardiac dysfunction [CTRCD]) or to a more transient LV dysfunction that is reversible (type 2 CTRCD) [499]. The former is thought to be consequent to myocyte apoptosis and usually due to chemotherapy, while the latter is thought to be consequent to myofibrillar dysfunction and is more commonly seen with targeted therapies [499].

11.1.1. Chemotherapy

11.1.1.1. Anthracyclines. Anthracyclines remain the cornerstone of treatment of breast cancer, lymphoma, leukaemia, and sarcoma; they are an antibiotic group derived from *Streptomyces* bacteria [500]. Commonly used anthracyclines include doxorubicin, epirubicin, daunorubicin, mitoxantrone, and idarubicin [498]. There are several mechanisms by which anthracyclines induce cardiotoxicity, including oxidative stress through the production of excess free radicals [501], modulation of topoisomerase-2 beta activity [502], alteration in multidrug-resistant efflux proteins [503] and a decrease in cardiac mesenchymal and circulating progenitor cells [504]. The cardiotoxic effects of anthracycline are largely related to their cumulative administered dose.

11.1.1.2. Platinum-based Therapies. Cisplatin is commonly used to treat solid tumours (genitourinary, testicular, lung, head and neck, and gastrointestinal). Vascular toxicity is one of the most concerning side effects [505], and includes hypertension, dyslipidaemia, early atherosclerosis, coronary artery disease, and thromboembolic events [506]. However, in the absence of concurrent therapy with anthracyclines, development of LV systolic dysfunction has only been reported in rodents [507].

11.1.1.3. Antimetabolites (5-flurouracil). 5-Fluorouracil is an antimetabolite, with myocardial ischaemia being the most common cardiovascular complication [508]. Symptoms are more common in patients with underlying coronary artery disease. Cardiomyopathy or heart failure has not been specifically reported.

11.1.1.4. Taxanes. Taxanes (paclitaxel and docetaxel) are multitubule inhibitors, used in the treatment of solid tumours (breast and ovarian). Arrhythmias (bradycardia, AF, atrial flutter, and atrial tachycardia) are the most commonly observed cardiovascular complications [509]. There are some reports of taxane treatment and LV dysfunction [510]; however, it is more likely that taxanes contribute to a higher incidence of LV dysfunction when used in conjunction with anthracyclines or trastuzumab.

11.1.1.5. Cyclophosphamide. Cyclophosphamide is an alkylating agent that has cardiotoxic effects, including development of LV dysfunction and heart failure [511]. The specific cardiotoxic effects appear to be associated with administration of a single higher dose of the drug rather than its cumulative dose.

11.1.2. Targeted Agents

11.1.2.1. HER2-targeted Agents. This group of drugs specifically targets HER 2/neu receptors, including trastuzumab, lapatinib, pertuzamab, and ado-trastuzumab emtansine. Their most serious side effect is myocardial dysfunction and heart failure. The primary mechanism for cardiotoxicity is mediated by disruption of the neuregulin-ERBB2 signalling pathway on cardiomyocytes, which is critical for normal myocyte growth and survival [512]. Additionally, they increase noradrenaline (norepinephrine) levels, with an increase in heart rate and blood pressure [513]. Trastuzumab, when administered concomitantly with anthracyclines, was associated with a 27% incidence in heart failure [514]. The incidence of heart failure was significantly reduced when trastuzumab was not concurrently administered with anthracyclines, although cardiotoxic effects are enhanced with previous administration of anthracyclines [515].

11.1.2.2. Tyrosine Kinase and Angiogenesis Inhibitors. These include inhibitors of vascular endothelial growth factor (VEGF) such as bevacizumab, as well as small molecule VEGF receptor tyrosine kinase inhibitors (TKI) (e.g., lapatinib, imatinib, sunitinib, sorafenib, and desatinib). These agents all cause an increase in blood pressure, and the hypertensive effects appear dose related [516]. Arterial thromboembolism is increased [517] and cardiac contractile dysfunction has been reported with treatment with bevacizumab [518]. Other TKIs, such as sunitinib, have been associated with myocardial dysfunction [519,520].

11.2. Frequency of Cardiotoxicity

As cancer survivorship increases, there will be an increase in chemotherapy-related cardiotoxicity. Importantly, with both adjuvant radiation and administration of newer agents, a combined and enhanced cardiotoxic effect is likely observed compared with that of standard chemotherapy regimens. Moreover, with a worldwide ageing population, cancer patients in the older age groups are likely to have a higher incidence of cardiovascular disease and cardiac risk factors.

Long-term childhood cancer survivors had about 15-fold increased rates of CHF compared with controls [521]. It is likely that older adults, with an increased number of cardiovascular risk factors have a greater potential for development of heart failure when exposed to chemotherapy.

Clinical trials have reported relatively low incident rates (<5% for heart failure and <10% for LV dysfunction) [522]. However, epidemiologic data report a higher incidence, likely due to associated comorbidities, duration of follow-up and adjuvant therapies. Data from the Surveillance, Epidemiology, and End Results (SEER) database review of elderly breast cancer patients reported that the cumulative incidence of heart failure at 10 years was 38% after anthracyclines, 32.5% with nonanthracycline chemotherapy regimens and 29% with no adjuvant chemotherapy [523]. Heart failure also occurs with several other traditional chemotherapeutic agents, including cyclophosphamide and docetaxel. LV dysfunction consequent to targeted therapies has been well documented in up to 4% of patients in clinical trials in which trastuzumab was added to traditional chemotherapy [524]. Cardiac dysfunction has less commonly been reported with angiogenesis inhibitors, including bevacizumab and sunitinib.

11.3. Risk Factors for Developing Cardiotoxicity

11.3.1. Cumulative Dose

There is a clear correlation between cumulative dose received and the development of cardiotoxicity for anthracyclines, with incidence of cardiotoxicity noted to be 5%, 26%, and 48% at cumulative doses of 400 mg/m^2, 550 mg/m^2, and 700 mg/m^2, respectively, in a meta-analysis of three trials [525]. Nonetheless, LV dysfunction has been documented even at doses below the current threshold of 450 mg/m^2 [499].

11.3.2. Age

Patients at extremes of age (<18 years or >65 years) are also considered at increased risk; a recent report demonstrated that children with heart failure following chemotherapy had earlier morbidity and increased mortality compared with adults who had received similar therapy [526]. The SEER database showed that the likelihood of anthracycline induced heart failure almost doubles with each 10-year increase in age [523,527].

11.3.3. Other Risk Factors

Patients with pre-existing cardiovascular disease, risk factors for cardiac disease and those who had received previous or concurrent radiotherapy are at increased risk [525]. As previously mentioned, combination chemotherapy (i.e. anthracyclines with trastuzumab or taxanes) may increase the risk of cardiotoxicity [527].

11.4. Early Detection of Cardiotoxicity

11.4.1. Biomarkers

Several cardiac biomarkers have been considered, including cardiac troponin, C-reactive protein, and natriuretic peptide. Of these, cardiac troponin has been shown to be the most useful marker of cardiotoxicity. Troponins are early markers of myocardial damage, with levels increasing in 2–3 hours [528–530]. Although there is little variability with measurement of troponin, the exact timing related to administration of chemotherapy and extent of variation in biomarker level has not been defined. Serial troponin I was measured before, within three days of chemotherapy (early) and at 1 month after chemotherapy (late) in 703 patients who were followed up for over 3 years. Patients with late elevation in troponin had the highest incidence of LV dysfunction and adverse events (84%) vs those with an early increase in troponin with subsequent normalisation (37%) vs those with no change in serial troponin (1%) [528]. More recently, high sensitivity (*hs*) assays have been used to measure troponin levels, and an increase in the absolute value of troponin after completion of anthracycline therapy was found to be associated with the highest risk of cardiotoxicity [510].

11.4.2. Imaging

Echocardiography is the most widely available and commonly used imaging modality to evaluate cardiac function. LVEF is the most common measure of cardiac function. However, this measurement has technical limitations, including reliance on image quality, geometric assumptions, load dependency, and test–retest variability, making it less suitable for early detection of cardiotoxicity [531]. More recently, the development of strain analysis that evaluates myocardial deformation has been shown to be a more sensitive measure of LV dysfunction [531]. Several studies have shown an alteration in LV strain following cancer therapy in the absence of significant alterations in LVEF [532–534]. A 10–15% relative reduction in two-dimensional speckle tracking strain had the highest correlation with a subsequent reduction in LVEF [531]. Current guidelines indicate that a relative reduction in global longitudinal strain of less than 8% of baseline value suggests no LV dysfunction, whereas a reduction of more than 15% of baseline value would suggest subclinical LV dysfunction [497].

Multiple gated acquisition scans (MUGA) have also been used, and although there is less observer variability, this approach is not sensitive to early chemotherapy-related changes in myocardial function, with the additional disadvantage that patients are subjected to radiation [525].

CMR is the gold standard for measurement of LV volumes and LVEF, with image quality not limited by acoustic windows [535] and its unique capability for tissue characterisation [536]. Early gadolinium enhancement [537], as well as T1

and T2 mapping techniques, have demonstrated early alterations in humans [538] and animal models [539]. At present, however, what is lacking are large prospective data with specific cut-offs to define significant cardiac dysfunction, as well as correlation of early changes with subsequent development of LV dysfunction and heart failure [535].

11.5. Prevention and Treatment of Cardiotoxicity

Prevention of cardiotoxicity is largely based on close monitoring, limiting the cumulative dose of chemotherapeutic agent, and avoiding concomitant therapy (i.e. trastuzumab and anthracyclines). Administration of anthracyclines as an infusion rather than as a bolus has also been demonstrated to reduce toxic effects. Dexrazoxane has been used as a specific therapy to reduce cardiotoxicity, especially in patients with metastatic breast cancer who may require more than standard therapy (>300 mg/m^2 of doxorubicin) with anthracyclines [540].

The treatment of cardiotoxicity is similar to the treatment of HFrEF and asymptomatic LV systolic dysfunction including ACE inhibitors, ARBs, beta blockers and MRAs [541,542].

Several RCTs have evaluated whether various agents including ACE inhibitors or ARBs, beta blockers, MRAs and statins can prevent a subsequent reduction in LVEF in patients who have received chemotherapy [543–555]. These studies reported conflicting results, were generally small, and were insufficiently powered to evaluate the effect on clinical outcomes.

Benefits and harms: Given the uncertainty of benefit, and that these agents may increase the risk of hypotension, renal impairment and electrolyte abnormalities, their routine prescription cannot be recommended at this point in time in the absence of another indication.

Practice advice

1. Patients receiving chemotherapy that may be associated with cardiotoxicity should have regular monitoring of LV function to allow early detection and management of cardiotoxicity.
2. The frequency of monitoring depends on the agent and dose administered and the results of previous investigations. As a minimum, this would often involve monitoring at 3-monthly intervals while receiving chemotherapy, 6 months following completion of chemotherapy, and prior to additional chemotherapy.
3. Patients who develop cardiotoxicity should be managed in the same way as other patients with HFrEF or asymptomatic LV systolic dysfunction.
4. If a decision is made to reduce the dose of or cease the chemotherapeutic agent, this should be reevaluated if left ventricular function improves in response to HFrEF therapy.

12. Treatment of Heart Failure With Recovered Ejection Fraction

Recommendation: Unless a reversible cause has been corrected, neurohormonal antagonists (ACE inhibitors or ARBs or ARNIs, beta blockers, and MRAs) should be continued at target doses in patients with heart failure associated with a recovered or restored ejection fraction, to decrease the risk of recurrence.

(Strong recommendation FOR; low quality of evidence.)

Rationale: There is no consensus definition for heart failure with recovered ejection fraction, with a variable cut-point in the literature for LVEF (≥40% to ≥50%). Patients who respond well to heart failure therapies have a better prognosis. However, cardiac function may not be normal despite a normal LVEF, with studies showing persistent abnormalities in biomarkers, abnormal functional capacity, and poor contractile reserve in patients with a normal LVEF. Unless a reversible cause has been corrected, recovery is likely to represent remission rather than cure in most cases, and cessation of neurohormonal antagonists may lead to clinical deterioration.

Three small clinical trials of beta blocker withdrawal in heart failure with recovered ejection fraction were associated with decreases in ejection fraction, and recurrence of heart failure and deaths; a retrospective study identified cessation of heart failure medications as the only predictor of recurrence in heart failure with recovered ejection fraction [556]. There have been no studies of ACE inhibitor or aldosterone antagonist withdrawal in heart failure with recovered ejection fraction.

Benefits and harms: The benefits of continuing beta blockers and renin–angiotensin–aldosterone inhibitors outweigh the potential harms of withdrawing either or both classes of drug.

Practice advice

1. Loop diuretics and thiazides may be weaned and ceased as tolerated, unless there is another indication (e.g., hypertension).
2. Cessation of neurohormonal antagonists can be considered in certain circumstances with specialist advice and close monitoring, such as heart failure with recovered ejection fraction due to peripartum cardiomyopathy, alcohol, and treated thyroid disease, where there are no other indications for these treatments (e.g., hypertension or vascular disease).
3. If neurohormonal antagonist dose is reduced or ceased, close follow-up (e.g., natriuretic peptides, serial imaging of LV size and function) should be undertaken or considered.

13. Special Situations

13.1. Driving

The AusRoads Assessing Fitness to Drive Guidelines [557] address medical standards for private and commercial licenses. In general, people with heart failure cannot hold an unconditional license, and periodic medical review is required at least annually. Implantable cardiac defibrillators pose a risk of sudden incapacity related to cardiac arrest and

risk of inappropriate discharge. This risk is considered unacceptable for a commercial license, whether the ICD is for primary or secondary prevention. The driver license authority may consider the advice of an independent specialist in electrophysiology in exceptional circumstances.

13.2. Travel

Air travel is not recommended if symptoms of heart failure are poorly controlled. Patients with stable chronic heart failure and no recent changes to medication are likely to tolerate the hypoxia associated with air travel [558,559]. Careful consideration should be taken before patients with NYHA Class IV symptoms consider flying. Patients with NYHA III and IV symptoms should request airport assistance and request in-flight oxygen be available.

Short-distance air travel appears to be of low risk. Long flights may predispose patients to accidental omission of medicines, lower limb oedema, dehydration, and deep venous thrombosis (DVT), but are not necessarily contraindicated. If long flights are planned and risk of DVT is significant, consider DVT prophylaxis with a single dose of non-vitamin K oral anticoagulant, or a single injection of low-molecular-weight heparin. Graduated compression stockings plus calf stretching during the flight should be considered.

High-altitude destinations should be avoided because of relative hypoxia. Travellers to very humid or hot climates should be counselled on dehydration and modification of diuretic doses.

13.3. Vaccination

Heart failure patients are at increased risk of respiratory infection and such infections are a major cause of decompensation. Patients should be vaccinated against influenza and pneumococcal disease. There is some evidence suggesting that influenza and pneumococcal vaccination may have a protective effect in heart failure [560].

13.4. Sex

Problems with sexual function are common in patients with heart failure, and affect quality of life. Men are more likely to report a problem with sexual function or interest, but overall, men and women report being equally affected [561]. Sexual activity requires mild to moderate exertion, equivalent to three to five METs, which is similar to climbing three flights of stairs, general housework or gardening. It is reasonable to undertake sexual activity for patients with mild or no symptoms (NYHA Class I/II), but such activity should be deferred in patients with decompensated or advanced heart failure until symptomatically controlled [562]. Erectile dysfunction may be worsened by thiazide diuretics, spironolactone, and beta blockers. Treatment with phosphodiesterase type-5 inhibitors is generally safe in compensated heart failure, but should be avoided in patients with high cardiac risk or patients receiving nitrates [563]. Intracavernosal injections and intrameatal gel treatment are not recommended, because there is little evidence about their use.

13.5. Pregnancy

Women considering pregnancy should be made aware that heart failure greatly increases the risk of maternal and neonatal morbidity and mortality, and pregnancy and delivery may cause deterioration in women with moderate to severe symptomatic CHF, severe LV systolic dysfunction, pulmonary arterial hypertension and severe mitral or aortic stenosis [564,565]. In mildly symptomatic CHF, pregnancy may be considered for a fully informed patient and her partner. Patients with peripartum cardiomyopathy following a previous pregnancy have increased risks of recurrence, especially if there is persisting LV systolic dysfunction [566]. Risk of genetic transmission to the fetus should be considered in familial cardiomyopathies. Many of the medicines used in treatment are contraindicated in pregnancy.

13.6. Contraception

Various contraceptive options are available for patients with heart failure [567]. Low-dose oral contraceptive usage appears to be associated with a small risk of hypertension or thrombogenicity, but these risks must be weighed against those of pregnancy. Other methods include barrier methods (which have a higher failure rate), intrauterine devices (IUDs), tubal ligation, or partner vasectomy.

13.7. Weather

Heart failure patients have reduced thermoregulatory control due to the effects of altered cardiovascular and autonomic function, and pharmacologic therapy, and this is particularly so during exercise [568]. Heatwaves in Australia are associated with increased cardiac events but no excess mortality, possibly due to adaptive behaviour to regular hot weather [569]. Patients should be educated to wear appropriate clothing, avoid exercise on hot days, and remain in an air-conditioned environment if possible. Fluid intake may need to be increased, or diuretics decreased temporarily.

Seasonal variation in heart failure hospitalisation is seen in Australia, with a peak in the coldest months and older people being at highest risk [570]. This is thought to be related to increased haemodynamic stress and neurohormonal activation, leading to myocardial ischaemia, cardiac arrhythmias and acute heart failure, as well as an increase in respiratory infections. Immunisation, appropriate heating and increased vigilance in the cold months is required.

13.8. Caffeine Intake

Habitual coffee consumption is likely to be safe in patients with heart failure. A meta-analysis of prospective cohort studies showing a J-shaped curve for incident heart failure, with the risk being lowest at four cups a day compared with none [571]. Epidemiological studies show beneficial effects on mortality, including cardiovascular mortality [572]. As caffeine beverages also contribute to fluid intake and may alter plasma electrolyte levels in the presence of diuretics, patients should be limited to one or two cups of caffeinated beverages a day.

14. Palliative Care in Heart Failure

Recommendation: Referral to palliative care should be considered in patients with advanced heart failure to alleviate end-stage symptoms, improve quality of life, and decrease rehospitalisation. Involvement of palliative care should be considered early in the trajectory towards end-stage heart failure.
(Strong recommendation FOR; high quality of evidence.)

Rationale: Nearly 40% of patients diagnosed with heart failure will die within 12 months of their first hospitalisation for heart failure [573]. As their heart failure progresses towards end-stage, patients begin to experience diverse debilitating symptoms, increasing the distress of both the patient and their carers, particularly during their last 6 months of life [574–576]. As their disease progresses, a decision to shift treatment from prevention of disease progression to improving quality of life, with a palliative care focus, should be discussed with the patient, family, cardiologist or physician with a special interest in heart failure, multidisciplinary heart failure team, and GP. It is important to have palliative care involvement early in the heart failure trajectory to reduce the suffering and distress associated with these symptoms and a terminal condition. The palliative care approach focuses on alleviation of symptoms and the patient's physical, psychosocial and spiritual needs. Despite its benefits, palliative care strategies continue to be underused for patients with advanced heart failure and their families [577–579].

The integration of palliative care into the multidisciplinary heart failure team is effective in reducing the symptom burden and distress experienced by caregivers and patients with end-stage heart failure. A meta-analysis of 43 RCTs involving 12,731 patients with a terminal illness found that palliative care was associated with significant improvements in quality of life and reduction in symptom burden [580]. A narrative synthesis found an improvement in advance care planning, patient and caregiver satisfaction with care, and lower use of healthcare services [580]. Several RCTs reported an improvement in symptoms, particularly quality of life, symptom burden [581–584], and depression [582–584]. Palliative care services in the home were also effective in reducing rehospitalisation [585,586].

Benefits and harm: The benefits of a palliative care service should be considered in patients diagnosed with advanced heart failure.

Practice advice

1. Ideally, referrals to a palliative care service should be implemented early in patients with advanced heart failure.
2. The palliative care service should work collaboratively with the patient's heart failure team and GP. This could also be extended to joint home visits by a heart failure nurse and palliative care nurse until the patient develops a strong collaborative relationship with the palliative care team, after which time the heart failure nurse may reduce their visits.
3. It is important that the collaborative care plan is patient and family centred.
4. In patients with an ICD, discussions concerning deactivation should occur between the patient and family and their cardiologist.
5. Patients with heart failure should be encouraged to have an advanced care plan, regardless of clinical status and soon after diagnosis.

15. Performance Measures

Treatment gaps and variations in the quality of care provided have been documented in a number of registries enrolling patients with heart failure [14,412]. While the need for new treatments remains, substantial gains will be realised by implementing what we already know is effective, with prior studies reporting that better adherence to guidelines is associated with better outcomes [587–589]. There is a need for ongoing audit and feedback systems, which are integrated into work practices, in order to improve and maintain the quality of care of patients with heart failure, and provide valuable data on patient outcomes and effectiveness of care initiatives. Table 13 provides a summary of the evidence for the management of HFrEF, with selected strongly recommended treatments highlighted in bold that could inform process measures of healthcare.

A broader list of potentially useful quality and outcome indicators for patients with heart failure include:

Performance measures:

Process measures:

1. What proportion of patients newly diagnosed with heart failure have had an ECG?
2. What proportion of patients newly diagnosed with heart failure have had an echocardiogram?
3. What proportion of patients hospitalised with heart failure and surviving to hospital discharge have been reviewed within 2 weeks?
4. What proportion of patients hospitalised with heart failure and surviving to hospital discharge have been referred to a multidisciplinary heart failure disease-management program or a multidisciplinary telemonitoring or telephone support program?
5. What proportion of patients hospitalised with heart failure and surviving to hospital discharge have been referred to an exercise training program?
6. What proportion of patients with heart failure have an advanced healthcare directive?
7. What proportion of patients with heart failure have been screened for depression?
8. What proportion of patients hospitalised with heart failure and surviving to hospital discharge have a written discharge summary and heart failure action plan?
9. What proportion of eligible* patients with HFrEF receive a prescription for an ACE inhibitor, ARB, or ARNI?

Table 13 Evidence summary for HFrEF management.

Evidence summary for HFrEF management			
Treatment effect	**All patients**	**Selected patients**	
		Strong recommendation	**Weak recommendation**
Decrease morbidity/ mortality	**ACEi (or ARB[a])** **Beta blocker[b]** **MRA**	**Switch ACEi or ARB to ARNI (LVEF ≤40%)** Ivabradine (SR ≥70 bpm, LVEF ≤35%) **Multidisciplinary HF disease management** Nurse-led medication titration **ICD (LVEF ≤35%, IHD)** **CRT (SR, QRS ≥130 ms, LVEF ≤35%)** AF ablation (paroxysmal/persistent AF, LVEF ≤35%) CABG (IHD, LVEF ≤35%)) VAD (intractable severe HF) Heart transplantation (intractable severe HF)	ICD (LVEF ≤35%, DCM) CRT (AF, QRS ≥130 ms, LVEF ≤35%) Hydralazine + nitrates n-3 polyunsaturated fatty acids
Improve symptoms		Diuretics (congested) **Exercise training (also decreases hospitalisation)** Intravenous iron (iron deficient)	Digoxin (refractory symptoms)

HFrEF: heart failure with reduced ejection fraction, ACEi: angiotensin converting enzyme inhibitor, ARB: angiotensin receptor blocker, MRA: mineralocorticoid receptor antagonist, ARNI: angiotensin receptor neprilysin inhibitor, LVEF: left ventricular ejection fraction, SR: sinus rhythm, ICD: implantable cardioverter defibrillator, IHD: ischaemic heart disease, CRT: cardiac resynchronization therapy, AF: atrial fibrillation, CABG: coronary artery bypass graft surgery, VAD: ventricular assist device, DCM: dilated cardiomyopathy.

[a]ARB should only be used if ACEi is contraindicated or not tolerated.

[b]Carvedilol, bisoprolol, metoprolol succinate, nebivolol.

10. What proportion of eligible* patients with HFrEF receive a prescription for a guideline recommended beta blocker?
11. What proportion of eligible* patients with HFrEF receive a prescription for an MRA?
12. What proportion of eligible* patients with HFrEF have achieved the target dose of an ACE inhibitor, ARB, or ARNI by 6 months following commencement?
13. What proportion of eligible* patients with HFrEF have achieved the target dose of a guideline recommended beta blocker by 6 months following commencement?
14. What proportion of eligible* patients with HFrEF have achieved the target or maximum tolerated dose of an ACE inhibitor, ARB, or ARNI by 6 months following commencement?
15. What proportion of eligible* patients with HFrEF have achieved the target or maximum tolerated dose of a guideline recommended beta blocker by 6 months following commencement?
16. What proportion of eligible* patients with HFrEF associated with an LVEF of less than or equal to 35% despite medical therapy have been referred for consideration of device therapy**?
17. What proportion of eligible* patients with heart failure associated with atrial fibrillation are on anticoagulant therapy?

Outcome measures:

1. What is the 30-day and 6-month mortality rate for patients hospitalised with heart failure?
2. What is the 30-day and 6-month rehospitalisation rate for patients hospitalised with heart failure?

*Eligible refers to meeting inclusion criteria for that measure (e.g., for CRT therapy: heart failure with an LVEF of less than or equal to 35% despite medical therapy and QRS duration of 130ms or more) with no exclusion criteria (e.g., for the process measures this may include documented contraindication to therapy; patient deceased; documented that patient declined therapy).

**Device therapy refers to CRT and/or ICD.

16. Areas for Future Research

The following are areas for future research:

- Screening for structural heart disease and prevention of heart failure.
- Epidemiology of heart failure in Australia.
- Diagnosis of heart failure in the community, including the role of biomarkers and diastolic stress echo for suspected HFpEF.
- Better phenotype characterisation of HFpEF.
- Risk stratification in patients with heart failure.
- Management of acute heart failure.
- Outcome studies in the very elderly and in HFpEF (including evaluation of the efficacy of new drugs and exercise training).
- Management of comorbidities (including atrial fibrillation, diabetes, hyperkalaemia, obesity, iron deficiency).

- Management of cachexia in patients with end-stage heart failure.
- Transitional care and systems of care in primary care to improve evidence-based practice and reduce rehospitalisation.
- Effect of fluid and salt restriction on clinical outcomes.
- Health economic evaluation of various diagnostic and therapeutic strategies in both the hospital and primary care settings.

17. Disclaimer

This document has been produced by the National Heart Foundation of Australia (Heart Foundation) for the information of health professionals. The statements and recommendations it contains are, unless labelled as 'expert opinion', based on independent review of the available evidence at the time of writing. Interpretation of this document by those without appropriate medical and/or clinical training is not recommended other than under the guidance of, or in consultation with, a suitably-qualified health professional.

While care has been taken in preparing the content of this material, the Heart Foundation and its employees do not accept any liability, including for any loss or damage, resulting from the reliance on the content, or for its accuracy, currency and completeness. The information is obtained and developed from a variety of sources including, but not limited to, collaborations with third parties and information provided by third parties under licence. It is not an endorsement of any organisation, product or service.

This material may be found in third parties' programs or materials (including but not limited to show bags or advertising kits). This does not imply an endorsement or recommendation by the Heart Foundation for such third parties' organisations, products or services, including their materials or information. Any use of Heart Foundation materials or information by another person or organisation is at the user's own risk.

18. Acknowledgements

The "National Heart Foundation of Australia and Cardiac Society of Australia and New Zealand Guidelines for the Prevention, Detection and Management of Heart Failure in Australia 2018" has been jointly developed by the Heart Foundation and the Cardiac Society of Australia and New Zealand. The Heart Foundation and the Cardiac Society of Australia and New Zealand are grateful for the contributions of all persons and entities involved in the development of the Guideline.

19. Appendices

19.1. Appendix 1: Abbreviations and Acronyms

ACE	Angiotensin converting enzyme
ACS	Acute coronary syndrome
ADHF	Acute decompensated heart failure
AF	Atrial fibrillation
AIHW	Australian Institute of Health and Welfare
APO	Acute pulmonary oedema
ARB	Angiotensin receptor blocker
ARNI	Angiotensin receptor neprilysin inhibitor
ARR	Absolute risk reduction
AV	Atrioventricular
AVOID trial	Australian Air Versus Oxygen in Myocardial Infarction trial
BBB	Bundle branch block
BiPAP	Bi-level positive airway pressure
BLOCK HF	Biventricular versus Right Ventricular Pacing in Heart Failure Patients with Atrioventricular Block
BMI	Body mass index
BNP	B-type natriuretic peptide
BOOST project	Better Outcomes for Older Adults through Safe Transitions project
BP	Blood pressure
bpm	Beats per minute
BTT	Bridge to transplantation
CABG	Coronary artery bypass graft surgery
CARE-HF study	Cardiac Resynchronization-Heart Failure study
CASTLE-AF study	Catheter Ablation versus Standard conventional Treatment in patients with leftventricular dysfunction and Atrial Fibrillation study
CBT	Cognitive behaviour therapy
CHAMPION trial	Cardiomems Heart Sensor Allows Monitoring of Pressure to Improve Outcomes in NYHA Class III Heart Failure Patients trial
CHARM-Preserved study	Candesartan in Heart failure: Assessment of Reduction in Mortality and morbidity (CHARM)-Preserved study
CHF	Chronic heart failure
CI	Confidence interval
CKD	Chronic kidney disease
CMR	Cardiac magnetic resonance imaging

COAPT trial	Cardiovascular Outcomes Assessment of the mitraclip Percutaneous Therapy for Heart Failure Patients With Functional Mitral Regurgitation trial
COMPANION trial	The Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure
COMPASS-HF trial	Chronicle Offers Management to Patients with Advanced Signs and Symptoms of Heart Failure trial
COPD	Chronic obstructive pulmonary disease
COX	Cyclo-oxygenase
CPAP	Continuous positive airway pressure
CRT	Cardiac resynchronisation therapy
CRT-D	CRT-defibrillator
CRT-P	CRT-pacemaker
CS	Cardiac sarcoidosis
CSA	Central sleep apnoea
CSANZ	Cardiac Society of Australia and New Zealand
CT	Computed tomography
CTRCD	Cancer therapeutics-related cardiac dysfunction
DANISH study	Danish Study to Assess the Efficacy of ICDs in Patients with Non-Ischemic Systolic Heart Failure on Mortality
DCM	Dilated cardiomyopathy
DETO2X–SWEDEHEART study	Determination of the Role of Oxygen in Suspected Acute Myocardial Infarction (DETO2X-AMI) – Using Swedish Web System for Enhancement and Development of Evidence-Based Care in Heart Disease Evaluated According to Recommended Therapies (SWEDEHEART)
DIG-PEF study	Digitalis Investigation Group-Preserved Ejection Fraction study
DPP-4	Dipeptidylpeptidase-4
DT	Destination therapy
DVT	Deep vein thrombosis
ECG	Electrocardiography
EchoCRT study	Echocardiography Guided Cardiac Resynchronization Therapy study
ECLS	Extracorporeal life support
ECMO	Extracorporeal membrane oxygenation
EDV	End diastolic volume
EF	Ejection fraction
eGFR	Estimated glomerular filtration rate
EJECTION-HF	Exercise Joins Education: Combined Therapy to Improve Outcomes in Newly-discharged Heart Failure
EMB	Endomyocardial biopsy
ESV	End systolic volume
EVEREST II	Endovascular Valve Edge-to-Edge Repair Study
FEV	Forced expiratory volume
GLP-1	Glucagon-like peptide 1
GRADE	Grading of Recommendations Assessment, Development and Evaluation
GWTG-HF	Get with the guidelines—heart failure
H2H program	Hospital to Home program
HCM	Hypertrophic cardiomyopathy
HF	Heart failure
HF-ACTION trial	Heart Failure: A Controlled Trial Investigating Outcomes of Exercise Training
HFmrEF	Heart failure with mid-range ejection fraction
HFpEF	Heart failure with preserved ejection fraction
HFrEF	Heart failure with reduced ejection fraction
HHD	Hypertensive heart disease
HR	Hazard ratio
IABP	Intra-aortic balloon counter-pulsation
ICA	Invasive coronary angiography
ICD	Implantable cardioverter defibrillator
ILD	Interstitial lung disease
I-PRESERVE study	Irbesartan in Heart Failure with Preserved Ejection Fraction study
J-DHF	Japanese diastolic heart failure study
JVP	Jugular venous pressure
LABA	Long-acting beta$_2$-agonists
LBBB	Left bundle branch block
LGE	Late gadolinium enhancement
LV	Left ventricular
LVAD	Left ventricular assist device
LVEF	Left ventriclular ejection fraction
MADIT-CRT trial	Multicenter Automatic Defibrillator Implantation Trial–Cardiac Resynchronization Therapy trial
MADIT-RIT	Multicenter Automatic Defibrillator Implantation Trial–Reduce Inappropriate Therapy
MCS	Mechanical cardiac support
MET	Metabolic unit
MI	Myocardial infarction

MRA	Mineralocorticoid receptor antagonist
MRCA	Magnetic resonance coronary angiography
MUGA	Multiple gated acquisition scans
MUSTIC	Multisite Stimulation In Cardiomyopathies
MV	Mitral valve
NHFA	National Heart Foundation of Australia
NLT	Nurse-led titration
NNT	Number needed to treat
NSAID	Nonsteroidal anti-inflammatory drug
NT proBNP	N-terminal pro B-type natriuretic peptide
NYHA classification	New York Heart Association Functional classification
OPTIMISE-HF program	Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients With Heart Failure
PARTNER trial	Placement of AoRTic TraNscathetER Valve trial
PCI	Percutaneous coronary intervention
PCWP	Pulmonary capillary wedge pressure
PEP-CHF study	Perindopril in Elderly People with Chronic Heart Failure study
PET	Positron emission tomography
PHQ	Patient Health Questionnaire
PROSPECT study	Predictors of response to cardiac resynchronization therapy study
RAFT trial	Resynchronization–Defibrillation for Ambulatory Heart Failure trial
RCT	Randomised controlled trial
REMATCH trial	Randomized Evaluation of Mechanical Assistance for the Treatment of Congestive Heart Failure trial
REVERSE trial	REsynchronization reVErses Remodeling in Systolic left vEntricular dysfunction trial
RHD	Rheumatic heart disease
RRR	Relative risk reduction
RV	Right ventricular
RVSP	Right ventricular systolic pressure
SAVE	Survival After Veno-arterial ECMO
SAVR	Surgical aortic valve replacement
SCD	Sudden cardiac death
SCD-HeFT study	Sudden Cardiac Death in Heart Failure Trial
SEER	Surveillance, Epidemiology, and End Results database
SGLT2	Sodium-glucose cotransporter 2
SPECT	Single-photon emission computerised tomography scan
SSRI	Selective serotonin reuptake inhibitor
STAAR	State Action on Avoidable Rehospitalizations Initiative
STICH trial	Surgical Treatment for Ischemic Heart Failure trial
SVR	Surgical ventricular reconstruction
TAVI	Transcatheter aortic valve implantation
TKI	Tyrosine kinase inhibitors
TNF	Tumour necrosis factor
TOPCAT trial	Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist trial
TSAT	Transferrin saturation
VAD	Ventricular assist device
VEGF	Vascular endothelial growth factor

19.2. Appendix 2: Clinical Questions for External Literature Review

Heart failure guideline 2017–2018: prioritised clinical questions for external literature review

1. *What is the clinical value of CMR in addition to prior tests in:*
a) *patients or family members in whom echocardiography suggests increased LV wall thickness, an HCM or RCM is suspected, and further diagnostic clarification is required?*
b) *patients in whom echocardiography suggests DCM, and further diagnostic clarification is required?*
2. *What is the clinical value of genetic testing in addition to prior tests in patients in whom echocardiography suggests DCM, and further patient characterisation is required?*
3. *What evidence is there that treating patients with chemotherapy that is associated with cardiotoxicity with ACE inhibitors, angiotensin receptor blockers, mineralocorticoid receptor antagonists (or aldosterone antagonists), beta blockers, statins, and/or antihypertensive therapy (or blood pressure lowering) improves clinical outcomes?*
4. *What evidence is there that treating patients with heart failure with nutraceuticals (including Vitamin D, A, C, E, B6, B12, Folate, Thiamine, selenium, St John's Wort, hawthorn, celery extract, magnesium supplements, co-enzyme Q10, polyunsaturated fatty acids, fish oil, olive oil, beetroot juice, probiotics, antioxidants) improves or worsens clinical outcomes?*

19.3. Appendix 3: Summary of HFrEF and HFpEF Trials

Major randomised controlled trials performed in patients with heart failure associated with a reduced left ventricular ejection fraction (HFrEF) that achieved their morbidity/mortality primary endpoint

	Inclusion criteria	Treatment groups	Background treatment [a]	Outcomes (primary endpoint bolded for active treatment vs. control)
CONSENSUS	NYHA 4 Increased CTR	Enalapril (n = 127) Placebo (n = 126)	Furosemide 98% Digoxin 92–94% MRA 50–55%	**Mort. (88 events) 26% vs. 44%, 40% RRR, NNT 6 over 6 mo.**
SOLVD-T	NYHA 1–4 LVEF ≤35%	Enalapril (n = 1285) Placebo (n = 1284)	Diuretic 85–86% Digoxin 66–68%	**Mort. (962 events) 35.2% vs. 39.7%, RRR 16%, NNT 22 over 41.4 mo.** Hosp. RRR 6%. HF hosp. RRR 30%. Mort./HF hosp. RRR 26%, NNT 9 over 41.4 mo.
CIBIS-II	NYHA 3,4 LVEF ≤35%	Bisoprolol (n = 1327) Placebo (n = 1320)	Diuretic 99% ACEI 96% Nitrates 58% Digoxin 52%.	**Mort. (384 events) 11.8% vs. 17.3%, RRR 34%, NNT 18 over 1.3 yr.** Hosp. RRR 20%. HF hosp. RRR 32%. CV mort./hosp. RRR 21%, NNT 17 over 41.4 mo.
MERIT-HF	NYHA 2–4 LVEF ≤40%	Metroprolol CR/XL (n = 1990) Placebo (n = 2001)	ACEI/ARB 96% Diuretic 90% Digoxin 64%.	**Mort. (362 events) 7.2% vs. 11.0%, RRR 34%, NNT 26 over 1 yr.** Hosp. RRR 18%. HF hosp. RRR 35%. Mort./HF hosp. RRR 31%, NNT 16 over 1 yr.
COPERNICUS	NYHA 3,4 LVEF <25%	Carvedilol (n = 1156) Placebo (n = 1133)	Diuretic 99% ACEI/ARB 97% Digoxin 65-67%.	**Mort. (320 events) 11.4% vs. 18.5%, RRR 35%, NNT 14 over 10.4 mo.** Hosp. RRR 15%. HF hosp. RRR 28%. Mort./HF hosp. RRR 31%, NNT 8 over 10.4 mo.
SENIORS	NYHA 1–4 Age ≥70 y + (LVEF ≤ 35% or HF hosp. last 12 mo)	Nebivolol (n = 1067) Placebo (n = 1061)	ACEI 82%, ARB 7% Diuretic 86%	**Mort./CV hosp. (707 events) 31.1% vs. 35.3%, RRR 14%, NNT 24 over 21 mo.**
RALES	NYHA 3,4 LVEF ≤35%	Spironolactone (n = 822) Placebo (n = 841)	Loop diuretic 100% ACEI 94-95% Digoxin 72-75%	**Mort. (670 events) 35% vs. 46%, RRR 30%, NNT 7 over 24 mo.** HF hosp. RRR 35%. Mort./cardiac hosp. RRR 32%.
EMPHASIS-HF	NYHA 2 LVEF ≤35%	Eplerenone (n = 1364) Placebo (n = 1373)	ACEI/ARB 93% Beta blocker 87% Diuretic 85%	**CV mort./HF hosp. (605 events) 18.3% vs. 25.9%, RRR 37%, NNT 13 over 21 mo.** Mort. RRR 24%, NNT 33 over 21 mo. Hosp. RRR 22%. HF hosp. RRR 39%.

(continued).

	Inclusion criteria	Treatment groups	Background treatment [a]	Outcomes (primary endpoint bolded for active treatment vs. control)
PARADIGM-HF	NYHA 2–4 LVEF ≤35–40% Increased BNP/NT-proBNP	Sacubitril/Valsartan (n = 4187) Enalapril (n = 4212)	Beta blocker 93% Diuretic 80% MRA 56%.	**CV mort./HF hosp. (2013 events) 21.8% vs. 26.5%, RRR 20%, NNT 21 over 27 mo.** CV death RRR 20%, NNT 32 over 27 mo. HF hosp. RRR 21%. Mort. RRR 16%, NNT 36 over 27 mo.
SHIFT	NYHA 2–4 LVEF <35% Sinus rhythm ≥70bpm	Ivabradine (n = 3268) Placebo (n = 3290)	ACEI 79%, ARB 14% Beta blocker 89% Diuretic 83% MRA 60%	**CV mort./HF hosp. (1730 events) 24% vs. 29%, RRR 18%, NNT 20 over 23 mo.** Hosp. RRR 11%. HF hosp. RRR 26%.
CHARM-Alt	NYHA 2–4 LVEF ≤40%	Candesartan (n = 1013) Placebo (n = 1015)	Diuretic 85% Beta blocker 55%	**CV mort./HF hosp. (740 events) 33% vs. 40%, RRR 23%, NNT 14 over 34 mo.** HF hosp. RRR 32%.
CHARM-Add	NYHA 2–4 LVEF ≤40%	Candesartan (n = 1276) Placebo (n = 1272)	ACEI 100% Diuretic 90% Digoxin 58% Beta blocker 55%	**CV mort./HF hosp. (1021 events) 38% vs. 42%, RRR 15%, NNT 23 over 41 mo.** CV mort. RRR 16%, NNT 28 over 41 mo. HF hosp. RRR 17%.
ValHeFT	NYHA 2–4 LVEF <40%	Valsartan (n = 2511) Placebo (n = 2499)	ACEI 93% Diuretic 85–86% Digoxin 67–68%	**Mort./ACA/HF hosp./IV inotropes or vasodilators over 4 hr (1524 events) 28.8% vs. 32.1%, RRR 13%, NNT 30 over 23 mo.** **No significant difference mort.** HF hosp. RRR 28%.
VHeFT	NYHA 1–4 (Inc. CTR or Inc. LVEDD or LVEF < 45%) + Dec. VO_2.	Hydralazine/nitrate (n = 186) Placebo (n = 273)	Diuretic 100% Digoxin 100%	**Mort. (192 events) 25.6% vs. 34.3%, RRR 34%, NNT 11 over 2 yr. (borderline significance)**
A-HeFT	Self-identified black NYHA 3,4 LVEF ≤35–45%	Hydralazine/nitrate (n = 518) Placebo (n = 532)	Diuretic 88–92% ACEI 69–70%, ARB 17% Beta blocker 74% Digoxin 59–61%	**Mort/HF hosp./quality of life improved over 10 mo.** Mort. (86 events) RRR 43%. HF hosp. RRR 33%.
GISSI-HF	NYHA 2–4 LVEF ≤40% or HF hosp. last 12 mo.	n-3 PUFA (n = 3494) Placebo (n = 3481)	ACEI/ARB 93% Diuretic 90% Beta blocker 65%	**Mort. (1969 events) 27% vs. 29%, RRR 9%, NNT 56 over 3.9 yr.** **Mort/CV hosp. (4034 events) 57% vs. 59%, RRR 8%, NNT 44 over 3.9 yr.**
MADIT-2	Prior MI ≥1 mo ago LVEF ≤30%	ICD (n = 742) Standard care (n = 490)	Diuretic 72–81% ACEI 68–72% Beta blocker 70% Digoxin 57%	**Mort. (202 events) 14.2% vs. 19.8%, RRR 31%, NNT 18 over 20 mo.**

(continued).

	Inclusion criteria	Treatment groups	Background treatment [a]	Outcomes (primary endpoint bolded for active treatment vs. control)
SCD-HeFT	NYHA 2–4 LVEF ≤35%	ICD (n = 829) Standard care (n = 847)	ACEI 84%, ARB 15% Loop diuretic 82% Beta blocker 69% Digoxin 68%	**Mort. (426 events) 22% vs. 29%, RRR 23%, NNT 14 over 5 yr.**
COMPANION	NYHA 3,4 LVEF ≤35% Sinus rhythm QRS ≥120ms, PR >150ms HF hosp. last 12 mo	CRT (n = 617) CRT-D (n = 595) Standard care (n = 308)	Loop diuretic 94–97% ACEI or ARB 89–90% Beta blocker 66–68% MRA 53–55%	**CRT: Mort./hosp. (630 events) 56% vs. 68%, RRR 19%, NNT 8 over 12 mo.** **CRT-D: Mort./hosp. (606 events) 56% vs. 68%, RRR 20%, NNT 8 over 16 mo.** CRT-D: Mort. (182 events) RRR 36% over 16 mo.
CARE-HF	NYHA 3,4 LVEF ≤35% Sinus rhythm QRS ≥120ms	CRT Standard care	ACEI or ARB 95% Beta blocker 72% MRA 56%	**Mort./CV hosp. (383 events) 39% vs. 55%, RRR 37%, NNT 6 over 29 mo.** Mort. (202 events) RRR 36%, NNT 10 over 29 mo. Unplanned HF hosp. RRR 52%.
MADIT-CRT	NYHA 1,2 LVEF ≤30% Sinus rhythm QRS ≥130ms	CRT-D (n = 1089) ICD (n = 731)	ACEI 77%, ARB 21% Beta blocker 93% Diuretic 75%	**Mort./HF events. (372 events) 17% vs. 25%, RRR 34%, NNT 12 over 29 mo.**
RAFT	NYHA 2,3 LVEF ≤30% Intrinsic QRS ≥120ms or paced QRS ≥200ms	CRT-D (n = 894) ICD (n = 904)	ACEI or ARB 97% Beta blocker 90% Diuretic 84%	**Mort./HF hosp. (661 events) 33.2% vs. 40.3%, RRR 25%, NNT 14 over 40 mo.** Mort. (422 events) RRR 25%, NNT 19 over 40 mo. HF hosp. RRR 32%. Significant benefit NYHA 2: Primary EP NNT 14, mort. NNT 18.
CASTLE-AF	Paroxysmal or persistent AF NYHA 2–4 LVEF ≤35% ICD or CRT-D	AF ablation (n = 179) Medical therapy (n = 184)	ACEI or ARB 91–94% Beta blocker 93–95% Diuretic 93%	**Mort./HF hosp. (133 events) 28.5% vs. 44.6%, RRR 38%, NNT 6 over 38 mo.** Mort. (70 events) RRR 47%, NNT 9 over 38 mo. HF hosp. RRR 46%.

[a]Reported baseline prescription rates for heart failure drugs that were over 50%.

NYHA: New York Heart Association functional classification, CTR: cardiothoracic ratio, MRA: mineralocorticoid receptor antagonist, mort.: mortality, RRR: relative risk reduction, NNT: number needed to treat to prevent event, LVEF: left ventricular ejection fraction, HF: heart failure, hosp.: hospitalisation, ACEI: angiotensin converting enzyme inhibitor, CV: cardiovascular, ARB: angiotensin receptor blocker, ACA: aborted cardiac arrest, IV: intravenous, LVEDD: left ventricular internal diameter in diastole, VO_2: exercise oxygen consumption, PUFA: polyunsaturated fatty acids, MI: myocardial infarction, ICD: implantable cardioverter defibrillator, CRT: cardiac resynchronisation therapy, CRT-D: cardiac resynchronisation therapy plus implantable cardioverter defibrillator, AF: atrial fibrillation.

Major randomised controlled trials performed in patients with heart failure associated with a preserved left ventricular ejection fraction (HFpEF) that were powered to evaluate morbidity/mortality endpoints.

	Inclusion criteria	Treatment groups	Outcomes (primary endpoint bolded for active treatment vs. control)
PEP-CHF	Clinical HF due to LV diastolic dysfunction Age ≥70 yr CV hosp. last 6 mo Approx. LVEF >40%	Perindopril (n = 424) Placebo (n = 426)	**Mort./HF hosp. (207 events) 24% vs. 25% (p = 0.55) over 2.1 yr.** Insufficient power for primary endpoint, partly due to high withdrawal rates (26–28%). Lower HF hosp. with perindopril in the first year.
CHARM-Pres	NYHA 2–4 LVEF ≥40% Prior CV hosp.	Candesartan (n = 1514) Placebo (n = 1509)	**CV death/HF hosp. (699 events) 22% vs. 24% (p = 0.12) over 37 mo.** Lower HF hosp. with candesartan.
I-PRESERVE	NYHA 2–4 Age ≥60 yr LVEF ≥45%	Irbesartan (n = 2067) Placebo (n = 2061)	**Mort./CV hosp. (1505 events) 36% vs. 37% (p = 0.35) over 50 mo.**
J-DHF	Clinical HF LVEF >40%	Carvedilol (n = 120) No carvedilol (n = 125)	**CV mort./Hosp. (63 events) 24% vs. 27% (p = 0.69) over 3.2 yr.**
TOPCAT	Clinical HF LVEF ≥45% HF hosp. last 12 mo or increased BNP/NT-proBNP	Spironolactone (n = 1722) Placebo (n = 1723)	**CV mort./ACA/HF hosp (671 events) 18.6% vs. 20.4% (p = 0.14) over 3.3 yr.** Lower HF hosp. with spironolactone.
DIG-PEF	Clinical HF LVEF >45% Sinus rhythm	Digoxin (n = 492) Placebo (n = 496)	**HF mort./HF hosp. (221 events) 21% vs. 24% (p = 0.14) over 37 mo.**

HF: heart failure, LV: left ventricular, CV: cardiovascular, LVEF: left ventricular ejection fraction, mort.: mortality, hosp.: hospitalisation, NYHA: New York Heart Association functional classification, ACA: aborted cardiac arrest.

19.4. Appendix 4: Online Register of Conflicts of Interest

Available at: https://www.heartfoundation.org.au/for-professionals/clinical-information/heart-failure

19.5. Appendix 5: Endorsing Organisations

The following organisations have endorsed these guidelines:

Australian College of Nursing

Australian College of Rural & Remote Medicine
WORLD LEADERS IN RURAL PRACTICE

AUSTRALIAN COMMISSION ON SAFETY AND QUALITY IN HEALTH CARE

CRANAplus improving remote health

AUSTRALIAN & NEW ZEALAND SOCIETY OF CARDIAC & THORACIC SURGEONS

20. References

[1] National Heart Foundation of Australia and the Cardiac Society of Australia and New Zealand (Chronic Heart Failure Guidelines Expert Writing Panel). Guidelines for the prevention, detection and management of chronic heart failure in Australia, 2011.

[2] Grading of Recommendations A, Development and Evaluation (GRADE) Working Group. GRADE Handbook. Updated October 2013. Available at: http://gdt.guidelinedevelopment.org/app/handbook/handbook.html. Accessed 21/02/18.

[3] Australian Medicines Handbook. Australian Medicines Handbook Pty Ltd; 2018.

[4] Vos T, Flaxman AD, Naghavi M, Lozano R, Michaud C, Ezzati M, et al. Years lived with disability (YLDs)for 1160 sequelae of 289 diseases and injuries 1990–2010: a systematic analysis for the Global Burden of Disease Study 2010. Lancet 2012;380(9859):2163–96.

[5] Bleumink GS, Knetsch AM, Sturkenboom MC, Straus SM, Hofman A, Deckers JW, et al. Quantifying the heart failure epidemic: prevalence, incidence rate, lifetime risk and prognosis of heart failure –The Rotterdam Study. Eur Heart J 2004;25(18):1614–9.

[6] Abhayaratna WP, Smith WT, Becker NG, Marwick TH, Jeffery IM, McGill DA. Prevalence of heart failure and systolic ventricular dysfunction in older Australians: the Canberra Heart Study. Med J Aust 2006;184(4):151–4.

[7] Sahle BW, Owen AJ, Mutowo MP, Krum H, Reid CM. Prevalence of heart failure in Australia: a systematic review. BMC Cardiovasc Disord 2016;16:32.

[8] Chan YK, Tuttle C, Ball J, Teng TK, Ahamed Y, Carrington MJ, et al. Current and projected burden of heart failure in the Australian adult population: a substantive but still ill-defined major health issue. BMC Health Serv Res 2016;16(1):501.

[9] Woods JA, Katzenellenbogen JM, Davidson PM, Thompson SC. Heart failure among Indigenous Australians: a systematic review. BMC Cardiovasc Disord 2012;12:99.

[10] Australian Bureau of Statistics. Causes of Death 2016. ABS cat. no. 3303.0, September, 2017.

[11] Najafi F, Jamrozik K, Dobson AJ. Understanding the 'epidemic of heart failure': a systematic review of trends in determinants of heart failure. Eur J Heart Fail 2009;11(5):472–9.

[12] Owan TE, Hodge DO, Herges RM, Jacobsen SJ, Roger VL, Redfield MM. Trends in prevalence and outcome of heart failure with preserved ejection fraction. N Engl J Med 2006;355(3):251–9.

[13] Australian Institute of Health and Welfare (AIHW). Cardiovascular health compendium. Web report. Updated 22 Dec 2017. Accessed 20/2/18.

[14] Newton PJ, Davidson PM, Reid CM, Krum H, Hayward C, Sibbritt DW, et al. Acute heart failure admissions in New South Wales and the Australian Capital Territory: the NSW HF Snapshot Study. Med J Aust 2016;204(3):113. e1–8.

[15] Blackledge HM, Tomlinson J, Squire IB. Prognosis for patients newly admitted to hospital with heart failure: survival trends in 12 220 index admissions in Leicestershire 1993–2001. Heart 2003;89(6):615–20.

[16] Parenica J, Spinar J, Vitovec J, Widimsky P, Linhart A, Fedorco M, et al. Long-term survival following acute heart failure: the Acute Heart Failure Database Main registry (AHEAD Main). Eur J Intern Med 2013;24(2):151–60.

[17] Tsutsui H, Tsuchihashi-Makaya M, Kinugawa S, Goto D, Takeshita A, Investigators J-G. Characteristics and outcomes of patients with heart failure in general practices and hospitals. Circ J 2007;71(4):449–54.

[18] Taylor CJ, Ryan R, Nichols L, Gale N, Hobbs FR, Marshall T. Survival following a diagnosis of heart failure in primary care. Fam Pract 2017;34(2):161–8.

[19] Bhatia RS, Tu JV, Lee DS, Austin PC, Fang J, Haouzi A, et al. Outcome of heart failure with preserved ejection fraction in a population-based study. N Engl J Med 2006;355(3):260–9.

[20] Somaratne JB, Berry C, McMurray JJ, Poppe KK, Doughty RN, Whalley GA. The prognostic significance of heart failure with preserved left ventricular ejection fraction: a literature-based meta-analysis. Eur J Heart Fail 2009;11(9):855–62.

[21] Meta-analysis Global Group in Chronic Heart Failure (MAGGIC). The survival of patients with heart failure with preserved or reduced left ventricular ejection fraction: an individual patient data meta-analysis. Eur Heart J 2012;33(14):1750–7.

[22] Thibodeau JT, Turer AT, Gualano SK, Ayers CR, Velez-Martinez M, Mishkin JD, et al. Characterization of a novel symptom of advanced heart failure: bendopnea. JACC Heart Fail 2014;2(1):24–31.

[23] Lang RM, Badano LP, Mor-Avi V, Afilalo J, Armstrong A, Ernande L, et al. Recommendations for cardiac chamber quantification by echocardiography in adults: An update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. Eur Heart J Cardiovasc Imaging 2015;16(3):233–71.

[24] Nagueh SF, Smiseth OA, Appleton CP, Byrd 3rd BF, Dokainish H, Edvardsen T, et al. Recommendations for the evaluation of left ventricular diastolic function by echocardiography: an update From the American Society of Echocardiography and the European Association of Cardiovascular Imaging. J Am Soc Echocardiogr 2016;29(4):277–314.

[25] Obokata M, Kane GC, Reddy YN, Olson TP, Melenovsky V, Borlaug BA. Role of diastolic stress testing in the evaluation for heart failure with preserved ejection fraction: a simultaneous invasive-echocardiographic study. Circulation 2017;135(9):825–38.

[26] Lund LH, Claggett B, Liu J, Lam CS, Jhund PS, Rosano GM, et al. Heart failure with mid-range ejection fraction in CHARM: characteristics, outcomes and effect of candesartan across the entire ejection fraction spectrum. Eur J Heart Fail 2018. http://dx.doi.org/10.1002/ejhf.1149 [Epubaheadofprint].

[27] Cleland JGF, Bunting KV, Flather MD, Altman DG, Holmes J, Coats AJS, et al. Beta-blockers for heart failure with reduced, mid-range, and preserved ejection fraction: an individual patient-level analysis of double-blind randomized trials. Eur Heart J 2018;39(1):26–35.

[28] Solomon SD, Claggett B, Lewis EF, Desai A, Anand I, Sweitzer NK, et al. Influence of ejection fraction on outcomes and efficacy of spironolactone in patients with heart failure with preserved ejection fraction. Eur Heart J 2016;37(5):455–62.

[29] Zile MR, Bennett TD, St John Sutton M, Cho YK, Adamson PB, Aaron MF, et al. Transition from chronic compensated to acute decompensated heart failure: Pathophysiological insights obtained from continuous monitoring of intracardiac pressures. Circulation 2008;118(14):1433–41.

[30] Zile MR, Baicu CF, Gaasch WH. Diastolic heart failure—abnormalities in active relaxation and passive stiffness of the left ventricle. N Engl J Med 2004;350(19):1953–9.

[31] Paulus WJ, Tschope C. A novel paradigm for heart failure with preserved ejection fraction: Comorbidities drive myocardial dysfunction and remodeling through coronary microvascular endothelial inflammation. J Am Coll Cardiol 2013;62(4):263–71.

[32] Weber T, Auer J, O'Rourke MF, Punzengruber C, Kvas E, Eber B. Prolonged mechanical systole and increased arterial wave reflections in diastolic dysfunction. Heart 2006;92(11):1616–22.

[33] Kitzman DW, Nicklas B, Kraus WE, Lyles MF, Eggebeen J, Morgan TM, et al. Skeletal muscle abnormalities and exercise intolerance in older patients with heart failure and preserved ejection fraction. Am J Physiol Heart Circ Physiol 2014;306(9):H1364–70.

[34] Phan TT, Shivu GN, Abozguia K, Davies C, Nassimizadeh M, Jimenez D, et al. Impaired heart rate recovery and chronotropic incompetence in patients with heart failure with preserved ejection fraction. Circ Heart Fail 2010;3(1):29–34.

[35] Borlaug BA, Melenovsky V, Russell SD, Kessler K, Pacak K, Becker LC, et al. Impaired chronotropic and vasodilator reserves limit exercise capacity in patients with heart failure and a preserved ejection fraction. Circulation 2006;114(20):2138–47.

[36] He J, Ogden LG, Bazzano LA, Vupputuri S, Loria C, Whelton PK. Risk factors for congestive heart failure in US men and women: NHANES I epidemiologic follow-up study. Arch Intern Med 2001;161(7):996–1002.

[37] Pandey A, Garg S, Khunger M, Darden D, Ayers C, Kumbhani DJ, et al. Dose–response relationship between physical activity and risk of heart failure: a meta-analysis. Circulation 2015;132(19):1786–94.

[38] Aune D, Sen A, Norat T, Janszky I, Romundstad P, Tonstad S, et al. Body mass index, abdominal fatness, and heart failure incidence and mortality: a systematic review and dose–response meta-analysis of prospective studies. Circulation 2016;133(7):639–49.

[39] Sundstrom J, Bruze G, Ottosson J, Marcus C, Naslund I, Neovius M. Weight loss and heart failure: a nationwide study of gastric bypass surgery versus intensive lifestyle treatment. Circulation 2017;135(17):1577–85.

[40] Goncalves A, Claggett B, Jhund PS, Rosamond W, Deswal A, Aguilar D, et al. Alcohol consumption and risk of heart failure: the Atherosclerosis Risk in Communities Study. Eur Heart J 2015;36(15):939–45.

[41] Dorans KS, Mostofsky E, Levitan EB, Hakansson N, Wolk A, Mittleman MA. Alcohol and incident heart failure among middle-aged and elderly men: cohort of Swedish men. Circ Heart Fail 2015;8(3):422–7.
[42] Larsson SC, Orsini N, Wolk A. Alcohol consumption and risk of heart failure: a dose–response meta-analysis of prospective studies. Eur J Heart Fail 2015;17(4):367–73.
[43] Ettehad D, Emdin CA, Kiran A, Anderson SG, Callender T, Emberson J, et al. Blood pressure lowering for prevention of cardiovascular disease and death: a systematic review and meta-analysis. Lancet 2016;387(10022):957–67.
[44] Preiss D, Campbell RT, Murray HM, Ford I, Packard CJ, Sattar N, et al. The effect of statin therapy on heart failure events: a collaborative meta-analysis of unpublished data from major randomized trials. Eur Heart J 2015;36(24):1536–46.
[45] Holman RR, Paul SK, Bethel MA, Matthews DR, Neil HA. 10-Year follow-up of intensive glucose control in type 2 diabetes. N Engl J Med 2008;359(15):1577–89.
[46] Fitchett D, Zinman B, Wanner C, Lachin JM, Hantel S, Salsali A, et al. Heart failure outcomes with empagliflozin in patients with type 2 diabetes at high cardiovascular risk: results of the EMPA-REG OUTCOME(R) trial. Eur Heart J 2016;37(19):1526–34.
[47] Zinman B, Wanner C, Lachin JM, Fitchett D, Bluhmki E, Hantel S, et al. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. N Engl J Med 2015;373:2117–28.
[48] Neal B, Perkovic V, Mahaffey KW, de Zeeuw D, Fulcher G, Erondu N, et al. Canagliflozin and cardiovascular and renal events in type 2 diabetes. N Engl J Med 2017;377(7):644–57.
[49] Dagenais GR, Pogue J, Fox K, Simoons ML, Yusuf S. Angiotensin-converting-enzyme inhibitors in stable vascular disease without left ventricular systolic dysfunction or heart failure: a combined analysis of three trials. Lancet 2006;368(9535):581–8.
[50] The SOLVD Investigators. Effect of enalapril on mortality and the development of heart failure in asymptomatic patients with reduced left ventricular ejection fractions. N Engl J Med 1992;327:685–91.
[51] Pfeffer MA, Braunwald E, Moye LA, Basta L, Brown Jr EJ, Cuddy TE, et al. Effect of captopril on mortality and morbidity in patients with left ventricular dysfunction after myocardial infarction. Results of the survival and ventricular enlargement trial. The SAVE Investigators. N Engl J Med 1992;327(10):669–77.
[52] Jong P, Yusuf S, Rousseau MF, Ahn SA, Bangdiwala SI. Effect of enalapril on 12-year survival and life expectancy in patients with left ventricular systolic dysfunction: a follow-up study. Lancet 2003;361:1843–8.
[53] Vantrimpont P, Rouleau JL, Wun CC, Ciampi A, Klein M, Sussex B, et al. Additive beneficial effects of beta-blockers to angiotensin-converting enzyme inhibitors in the Survival and Ventricular Enlargement (SAVE) Study. J Am Coll Cardiol 1997;29(2):229–36.
[54] Exner DV, Dries DL, Waclawiw MA, Shelton B, Domanski MJ. Beta-adrenergic blocking agent use and mortality in patients with asymptomatic and symptomatic left ventricular systolic dysfunction: a post hoc analysis of the studies of left ventricular dysfunction. J Am Coll Cardiol 1999;33:916–23.
[55] Aronow WS, Ahn C, Kronzon I. Effect of beta blockers alone, of angiotensin-converting enzyme inhibitors alone, and of beta blockers plus angiotensin-converting enzyme inhibitors on new coronary events and on congestive heart failure in older persons with healed myocardial infarcts and asymptomatic left ventricular systolic dysfunction. Am J Cardiol 2001;88(11):1298–300.
[56] Dargie HJ. Effect of carvedilol on outcome after myocardial infarction in patients with left-ventricular dysfunction: The CAPRICORN randomised trial. Lancet 2001;357:1385–90.
[57] Davie AP, Francis CM, Love MP, Caruana L, Starkey IR, Shaw TR, et al. Value of the electrocardiogram in identifying heart failure due to left ventricular systolic dysfunction. BMJ 1996;312(7025):222.
[58] Galasko GI, Barnes SC, Collinson P, Lahiri A, Senior R. What is the most cost-effective strategy to screen for left ventricular systolic dysfunction: natriuretic peptides, the electrocardiogram, hand-held echocardiography, traditional echocardiography, or their combination? Eur Heart J 2006;27(2):193–200.
[59] Redfield MM, Jacobsen SJ, Burnett Jr JC, Mahoney DW, Bailey KR, Rodeheffer RJ. Burden of systolic and diastolic ventricular dysfunction in the community: appreciating the scope of the heart failure epidemic. JAMA 2003;289(2):194–202.
[60] Abhayaratna WP, Marwick TH, Smith WT, Becker NG. Characteristics of left ventricular diastolic dysfunction in the community: an echocardiographic survey. Heart 2006;92(9):1259–64.
[61] Ledwidge M, Gallagher J, Conlon C, Tallon E, O'Connell E, Dawkins I, et al. Natriuretic peptide-based screening and collaborative care for heart failure: the STOP-HF randomized trial. JAMA 2013;310(1):66–74.
[62] Huelsmann M, Neuhold S, Resl M, Strunk G, Brath H, Francesconi C, et al. PONTIAC (NT-proBNP selected prevention of cardiac events in a population of diabetic patients without a history of cardiac disease): a prospective randomized controlled trial. J Am Coll Cardiol 2013;62(15):1365–72.
[63] Troughton R, Michael Felker G, Januzzi Jr JL. Natriuretic peptide-guided heart failure management. Eur Heart J 2014;35(1):16–24.
[64] Maisel AS, Krishnaswamy P, Nowak RM, McCord J, Hollander JE, Duc P, et al. Rapid measurement of B-type natriuretic peptide in the emergency diagnosis of heart failure. N Engl J Med 2002;347(3):161–7.
[65] Januzzi Jr JL, Camargo CA, Anwaruddin S, Baggish AL, Chen AA, Krauser DG, et al. The N-terminal Pro-BNP investigation of dyspnea in the emergency department (PRIDE) study. Am J Cardiol 2005;95(8):948–54.
[66] Doust JA, Glasziou PP, Pietrzak E, Dobson AJ. A systematic review of the diagnostic accuracy of natriuretic peptides for heart failure. Arch Intern Med 2004;164(18):1978–84.
[67] Wright SP, Doughty RN, Pearl A, Gamble GD, Whalley GA, Walsh HJ, et al. Plasma amino-terminal pro-brain natriuretic peptide and accuracy of heart-failure diagnosis in primary care: a randomized, controlled trial. J Am Coll Cardiol 2003;42(10):1793–800.
[68] Jambrik Z, Monti S, Coppola V, Agricola E, Mottola G, Miniati M, et al. Usefulness of ultrasound lung comets as a nonradiologic sign of extravascular lung water. Am J Cardiol 2004;93(10):1265–70.
[69] Volpicelli G, Elbarbary M, Blaivas M, Lichtenstein DA, Mathis G, Kirkpatrick AW, et al. International evidence-based recommendations for point-of-care lung ultrasound. Intensive Care Med 2012;38(4):577–91.
[70] Assomull RG, Shakespeare C, Kalra PR, Lloyd G, Gulati A, Strange J, et al. Role of cardiovascular magnetic resonance as a gatekeeper to invasive coronary angiography in patients presenting with heart failure of unknown etiology. Circulation 2011;124(12):1351–60.
[71] Yoshida A, Ishibashi-Ueda H, Yamada N, Kanzaki H, Hasegawa T, Takahama H, et al. Direct comparison of the diagnostic capability of cardiac magnetic resonance and endomyocardial biopsy in patients with heart failure. Eur J Heart Fail 2013;15(2):166–75.
[72] Kim KH, Kim HK, Hwang IC, Lee SP, Park EA, Lee W, et al. Myocardial scarring on cardiovascular magnetic resonance in asymptomatic or minimally symptomatic patients with pure apical hypertrophic cardiomyopathy. J Cardiovasc Magn Reson 2012;14(52):1–9.
[73] Kwong RY, Heydari B, Abbasi S, Steel K, Al-Mallah M, Wu H, et al. Characterization of cardiac amyloidosis by atrial late gadolinium enhancement using contrast-enhanced cardiac magnetic resonance imaging and correlation with left atrial conduit and contractile function. Am J Cardiol 2015;116(4):622–9.
[74] Martinez-Naharro A, Treibel TA, Abdel-Gadir A, Bulluck H, Zumbo G, Knight DS, et al. Magnetic resonance in transthyretin cardiac amyloidosis. J Am Coll Cardiol 2017;70(4):466–77.
[75] Gillmore JD, Maurer MS, Falk RH, Merlini G, Damy T, Dispenzieri A, et al. Nonbiopsy diagnosis of cardiac transthyretin amyloidosis. Circulation 2016;133(24):2404–12.
[76] Bettencourt P, Azevedo A, Pimenta J, Frioes F, Ferreira S, Ferreira A. N-terminal-pro-brain natriuretic peptide predicts outcome after hospital discharge in heart failure patients. Circulation 2004;110(15):2168–74.
[77] Januzzi Jr JL, Sakhuja R, O'Donoghue M, Baggish AL, Anwaruddin S, Chae CU, et al. Utility of amino-terminal pro-brain natriuretic peptide testing for prediction of 1-year mortality in patients with dyspnea treated in the emergency department. Arch Intern Med 2006;166(3):315–20.
[78] Lam LL, Cameron PA, Schneider HG, Abramson MJ, Muller C, Krum H. Meta-analysis. Effect of B-type natriuretic peptide testing on clinical outcomes in patients with acute dyspnea in the emergency setting. Ann Intern Med 2010;153(11):728–35.
[79] Richards AM, Nicholls MG, Espiner EA, Lainchbury JG, Troughton RW, Elliott J, et al. B-type natriuretic peptides and ejection fraction for prognosis after myocardial infarction. Circulation 2003;107(22):2786–92.
[80] Nagaya N, Nishikimi T, Uematsu M, Satoh T, Kyotani S, Sakamaki F, et al. Plasma brain natriuretic peptide as a prognostic indicator in patients with primary pulmonary hypertension. Circulation 2000;102(8):865–70.

[81] Bergler-Klein J, Klaar U, Heger M, Rosenhek R, Mundigler G, Gabriel H, et al. Natriuretic peptides predict symptom-free survival and postoperative outcome in severe aortic stenosis. Circulation 2004;109 (19):2302–8.
[82] Kucher N, Printzen G, Goldhaber SZ. Prognostic role of brain natriuretic peptide in acute pulmonary embolism. Circulation 2003;107 (20):2545–7.
[83] Kayvanpour E, Sedaghat-Hamedani F, Amr A, Lai A, Haas J, Holzer DB, et al. Genotype–phenotype associations in dilated cardiomyopathy: meta-analysis on more than 8000 individuals. Clin Res Cardiol 2017;106(2):127–39.
[84] van Berlo JH, de Voogt WG, van der Kooi AJ, van Tintelen JP, Bonne G, Yaou RB, et al. Meta-analysis of clinical characteristics of 299 carriers of LMNA gene mutations: do lamin A/C mutations portend a high risk of sudden death? J Mol Med (Berl) 2005;83(1):79–83.
[85] Di Marco A, Anguera I, Schmitt M, Klem I, Neilan TG, White JA, et al. late gadolinium enhancement and the risk for ventricular arrhythmias or sudden death in dilated cardiomyopathy: systematic review and meta-analysis. JACC Heart Fail 2017;5(1):28–38.
[86] Duan X, Li J, Zhang Q, Zeng Z, Luo Y, Jiang J, et al. Prognostic value of late gadolinium enhancement in dilated cardiomyopathy patients: a meta-analysis. Clin Radiol 2015;70(9):999–1008.
[87] Briasoulis A, Mallikethi-Reddy S, Palla M, Alesh I, Afonso L. Myocardial fibrosis on cardiac magnetic resonance and cardiac outcomes in hypertrophic cardiomyopathy: a meta-analysis. Heart 2015;101 (17):1406–11.
[88] Weng Z, Yao J, Chan RH, He J, Yang X, Zhou Y, et al. Prognostic value of LGE-CMR in HCM: a meta-analysis. JACC Cardiovasc Imaging 2016;9(12):1392–402.
[89] Green JJ, Berger JS, Kramer CM, Salerno M. Prognostic value of late gadolinium enhancement in clinical outcomes for hypertrophic cardiomyopathy. JACC Cardiovasc Imaging 2012;5(4):370–7.
[90] Chan RH, Maron BJ, Olivotto I, Pencina MJ, Assenza GE, Haas T, et al. Prognostic value of quantitative contrast-enhanced cardiovascular magnetic resonance for the evaluation of sudden death risk in patients with hypertrophic cardiomyopathy. Circulation 2014;130(6):484–95.
[91] Binanay C, Califf RM, Hasselblad V, O'Connor CM, Shah MR, Sopko G, et al. Evaluation study of congestive heart failure and pulmonary artery catheterization effectiveness: the ESCAPE trial. JAMA 2005;294 (13):1625–33.
[92] Januzzi Jr JL, Rehman SU, Mohammed AA, Bhardwaj A, Barajas L, Barajas J, et al. Use of amino-terminal pro-B-type natriuretic peptide to guide outpatient therapy of patients with chronic left ventricular systolic dysfunction. J Am Coll Cardiol 2011;58(18):1881–9.
[93] Troughton RW, Frampton CM, Yandle TG, Espiner EA, Nicholls MG, Richards AM. Treatment of heart failure guided by plasma amino-terminal brain natriuretic peptide (N-BNP) concentrations. Lancet 2000;355(9210):1126–30.
[94] Berger R, Moertl D, Peter S, Ahmadi R, Huelsmann M, Yamuti S, et al. N-terminal pro-B-type natriuretic peptide-guided, intensive patient management in addition to multidisciplinary care in chronic heart failure a 3-arm, prospective, randomized pilot study. J Am Coll Cardiol 2010;55(7):645–53.
[95] Jourdain P, Jondeau G, Funck F, Gueffet P, Le Helloco A, Donal E, et al. Plasma brain natriuretic peptide-guided therapy to improve outcome in heart failure: the STARS-BNP Multicenter Study. J Am Coll Cardiol 2007;49(16):1733–9.
[96] Lainchbury JG, Troughton RW, Strangman KM, Frampton CM, Pilbrow A, Yandle TG, et al. N-terminal pro-B-type natriuretic peptide-guided treatment for chronic heart failure: results from the BATTLESCARRED (NT-proBNP-Assisted Treatment To Lessen Serial Cardiac Readmissions and Death) trial. J Am Coll Cardiol 2009;55(1):53–60.
[97] Pfisterer M, Buser P, Rickli H, Gutmann M, Erne P, Rickenbacher P, et al. BNP-guided vs symptom-guided heart failure therapy: the Trial of Intensified vs Standard Medical Therapy in Elderly Patients With Congestive Heart Failure (TIME-CHF) randomized trial. JAMA 2009;301(4):383–92.
[98] Eurlings LW, van Pol PE, Kok WE, van Wijk S, Lodewijks-van der Bolt C, Balk AH, et al. Management of chronic heart failure guided by individual N-terminal pro-B-type natriuretic peptide targets: results of the PRIMA (Can PRo-brain-natriuretic peptide guided therapy of chronic heart failure IMprove heart fAilure morbidity and mortality?) study. J Am Coll Cardiol 2010;56(25):2090–100.
[99] Persson H, Erntell H, Eriksson B, Johansson G, Swedberg K, Dahlstrom U. Improved pharmacological therapy of chronic heart failure in primary care: A randomized Study of NT-proBNP Guided Management of Heart Failure—SIGNAL-HF (Swedish Intervention study—Guidelines and NT-proBNP AnaLysis in Heart Failure). Eur J Heart Fail 2010;12(12):1300–8.
[100] Shah MR, Califf RM, Nohria A, Bhapkar M, Bowers M, Mancini DM, et al. The STARBRITE trial: a randomized, pilot study of B-type natriuretic peptide-guided therapy in patients with advanced heart failure. J Card Fail 2011;17(8):613–21.
[101] Karlstrom P, Alehagen U, Boman K, Dahlstrom U, group UP-s. Brain natriuretic peptide-guided treatment does not improve morbidity and mortality in extensively treated patients with chronic heart failurer: responders to treatment have a significantly better outcome. Eur J Heart Fail 2011;13(10):1096–103.
[102] Porapakkham P, Porapakkham P, Zimmet H, Billah B, Krum H. B-type natriuretic peptide-guided heart failure therapy: a meta-analysis. Arch Intern Med 2010;170(6):507–14.
[103] Troughton RW, Frampton CM, Brunner-La Rocca HP, Pfisterer M, Eurlings LW, Erntell H, et al. Effect of B-type natriuretic peptide-guided treatment of chronic heart failure on total mortality and hospitalization: an individual patient meta-analysis. Eur Heart J 2014;35 (23):1559–67.
[104] Felker GM, Anstrom KJ, Adams KF, Ezekowitz JA, Fiuzat M, Houston-Miller N, et al. Effect of natriuretic peptide-guided therapy on hospitalization or cardiovascular mortality in high-risk patients with heart failure and reduced ejection fraction: a randomized clinical trial. JAMA 2017;318(8):713–20.
[105] Araujo JP, Azevedo A, Lourenco P, Rocha-Goncalves F, Ferreira A, Bettencourt P. Intraindividual variation of amino-terminal pro-B-type natriuretic peptide levels in patients with stable heart failure. Am J Cardiol 2006;98(9):1248–50.
[106] Davis ME, Richards AM, Nicholls MG, Yandle TG, Frampton CM, Troughton RW. Introduction of metoprolol increases plasma B-type cardiac natriuretic peptides in mild, stable heart failure. Circulation 2006;113(7):977–85.
[107] Zile MR, Claggett BL, Prescott MF, McMurray JJ, Packer M, Rouleau JL, et al. Prognostic implications of changes in N-terminal pro-B-type natriuretic peptide in patients with heart failure. J Am Coll Cardiol 2016;68(22):2425–36.
[108] The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. Eur Heart J 2016;37:2129–200.
[109] Ponikowski P, Jankowska EA. Pathogenesis and clinical presentation of acute heart failure. Revista espanola de cardiologia 2015;68(4):331–7.
[110] Nohria A, Tsang SW, Fang JC, Lewis EF, Jarcho JA, Mudge GH, et al. Clinical assessment identifies hemodynamic profiles that predict outcomes in patients admitted with heart failure. J Am Coll Cardiol 2003;41(10):1797–804.
[111] Page RL, O'Bryant CL, Cheng D, Dow TJ, Ky B, Stein CM, et al. Drugs that may cause or exacerbate heart failure: a scientific statement from the American Heart Association. Circulation 2016;134(6): e32–69.
[112] Mebazaa A, Yilmaz MB, Levy P, Ponikowski P, Peacock WF, Laribi S, et al. Recommendations on pre-hospital & early hospital management of acute heart failure: a consensus paper from the Heart Failure Association of the European Society of Cardiology, the European Society of Emergency Medicine and the Society of Academic Emergency Medicine. Eur J Heart Fail 2015;17(6):544–58.
[113] Felker GM, Lee KL, Bull DA, Redfield MM, Stevenson LW, Goldsmith SR, et al. Diuretic strategies in patients with acute decompensated heart failure. N Engl J Med 2011;364(9):797–805.
[114] Cotter G, Metzkor E, Kaluski E, Faigenberg Z, Miller R, Simovitz A, et al. Randomised trial of high-dose isosorbide dinitrate plus low-dose furosemide versus high-dose furosemide plus low-dose isosorbide dinitrate in severe pulmonary oedema. Lancet 1998;351(9100): 389–93.
[115] Wakai A, McCabe A, Kidney R, Brooks SC, Seupaul RA, Diercks DB, et al. Nitrates for acute heart failure syndromes. Cochrane Database Syst Rev):2013;(8)CD005151.
[116] Mebazaa A, Parissis J, Porcher R, Gayat E, Nikolaou M, Boas FV, et al. Short-term survival by treatment among patients hospitalized with acute heart failure: the global ALARM-HF registry using propensity scoring methods. Intensive Care Med 2011;37(2):290–301.
[117] Sharon A, Shpirer I, Kaluski E, Moshkovitz Y, Milovanov O, Polak R, et al. High-dose intravenous isosorbide-dinitrate is safer and better than Bi-PAP ventilation combined with conventional treatment for severe pulmonary edema. J Am Coll Cardiol 2000;36(3):832–7.

[118] Elkayam U, Tasissa G, Binanay C, Stevenson LW, Gheorghiade M, Warnica JW, et al. Use and impact of inotropes and vasodilator therapy in hospitalized patients with severe heart failure. Am Heart J 2007;153 (1):98–104.
[119] Belletti A, Castro ML, Silvetti S, Greco T, Biondi-Zoccai G, Pasin L, et al. The effect of inotropes and vasopressors on mortality: a meta-analysis of randomized clinical trials. Br J Anaesth 2015;115(5):656–75.
[120] De Backer D, Biston P, Devriendt J, Madl C, Chochrad D, Aldecoa C, et al. Comparison of dopamine and norepinephrine in the treatment of shock. N Engl J Med 2010;362(9):779–89.
[121] Wang CS, FitzGerald JM, Schulzer M, Mak E, Ayas NT. Does this dyspneic patient in the emergency department have congestive heart failure? JAMA 2005;294(15):1944–56.
[122] Chakko S, Woska D, Martinez H, de Marchena E, Futterman L, Kessler KM, et al. Clinical, radiographic, and hemodynamic correlations in chronic congestive heart failure: Conflicting results may lead to inappropriate care. Am J Med 1991;90(3):353–9.
[123] van Deursen VM, Damman K, Hillege HL, van Beek AP, van Veldhuisen DJ, Voors AA. Abnormal liver function in relation to hemodynamic profile in heart failure patients. J Card Fail 2010;16(1):84–90.
[124] The ESCAPE Investigators and ESCAPE Study Coordinators. Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness: the ESCAPE Trial. JAMA 2005;294(13):1625–33.
[125] Gattis WA, O'Connor CM, Gallup DS, Hasselblad V, Gheorghiade M, Investigators I-H, et al. Predischarge initiation of carvedilol in patients hospitalized for decompensated heart failure: results of the Initiation Management Predischarge: Process for Assessment of Carvedilol Therapy in Heart Failure (IMPACT-HF) trial. J Am Coll Cardio 2004;43 (9):1534–41.
[126] Park JH, Balmain S, Berry C, Morton JJ, McMurray JJ. Potentially detrimental cardiovascular effects of oxygen in patients with chronic left ventricular systolic dysfunction. Heart 2010;96(7):533–8.
[127] O'Driscoll BR, Howard LS, Earis J, Mak V. British Thoracic Society Guideline for oxygen use in adults in healthcare and emergency settings. BMJ Open Respir Res 2017;4(1):e000170.
[128] Stub D, Smith K, Bernard S, Nehme Z, Stephenson M, Bray JE, et al. Air versus oxygen in ST-segment-elevation myocardial infarction. Circulation 2015;131(24):2143–50.
[129] Hofmann R, James SK, Jernberg T, Lindahl B, Erlinge D, Witt N, et al. Oxygen therapy in suspected acute myocardial infarction. N Engl J Med 2017;377(13):1240–9.
[130] Sepehrvand N, Ezekowitz JA. Oxygen therapy in patients with acute heart failure: friend or foe? JACC Heart Fail 2016;4(10):783–90.
[131] Iakobishvili Z, Cohen E, Garty M, Behar S, Shotan A, Sandach A, et al. Use of intravenous morphine for acute decompensated heart failure in patients with and without acute coronary syndromes. Acute Card Care 2011;13(2):76–80.
[132] Peacock WF, Hollander JE, Diercks DB, Lopatin M, Fonarow G, Emerman CL. Morphine and outcomes in acute decompensated heart failure: an ADHERE analysis. Emerg Med J 2008;25(4):205–9.
[133] Meine TJ, Roe MT, Chen AY, Patel MR, Washam JB, Ohman EM, et al. Association of intravenous morphine use and outcomes in acute coronary syndromes: results from the CRUSADE Quality Improvement Initiative. Am Heart J 2005;149(6):1043–9.
[134] Lee G, DeMaria AN, Amsterdam EA, Realyvasquez F, Angel J, Morrison S, et al. Comparative effects of morphine, meperidine and pentazocine on cardiocirculatory dynamics in patients with acute myocardial infarction. Am J Med 1976;60(7):949–55.
[135] Weng CL, Zhao YT, Liu QH, Fu CJ, Sun F, Ma YL, et al. Meta-analysis: noninvasive ventilation in acute cardiogenic pulmonary edema. Ann Intern Med 2010;152(9):590–600.
[136] Gray AJ, Goodacre S, Newby DE, Masson MA, Sampson F, Dixon S, et al. A multicentre randomised controlled trial of the use of continuous positive airway pressure and non-invasive positive pressure ventilation in the early treatment of patients presenting to the emergency department with severe acute cardiogenic pulmonary oedema: the 3CPO trial. Health Technol Assess 2009;13(33):1–106.
[137] Vital FM, Ladeira MT, Atallah AN. Non-invasive positive pressure ventilation (CPAP or bilevel NPPV) for cardiogenic pulmonary oedema. Cochrane Database Syst Rev):2013;(5)CD005351.
[138] Park M, Sangean MC, Volpe Mde S, Feltrim MI, Nozawa E, Leite PF, et al. Randomized, prospective trial of oxygen, continuous positive airway pressure, and bilevel positive airway pressure by face mask in acute cardiogenic pulmonary edema. Crit Care Med 2004;32(12):2407–15.
[139] Gray A, Goodacre S, Newby DE, Masson M, Sampson F, Nicholl J, 3CPO Trialists. Noninvasive ventilation in acute cardiogenic pulmonary edema. N Engl J Med 2008;359:142–51.
[140] Nieminen MS, Bohm M, Cowie MR, Drexler H, Filippatos GS, Jondeau G, et al. Executive summary of the guidelines on the diagnosis and treatment of acute heart failure: the Task Force on Acute Heart Failure of the European Society of Cardiology. Eur Heart J 2005;26(4):384–416.
[141] Vasko MR, Cartwright DB, Knochel JP, Nixon JV, Brater DC. Furosemide absorption altered in decompensated congestive heart failure. Ann Intern Med 1985;102(3):314–8.
[142] Brater DC. Clinical pharmacology of loop diuretics. Drugs 1991;41 (Suppl 3):14–22.
[143] Butler J, Anstrom KJ, Felker GM, Givertz MM, Kalogeropoulos AP, Konstam MA, et al. Efficacy and safety of spironolactone in acute heart failure: the ATHENA-HF Randomized Clinical Trial. JAMA Cardiol 2017;2(9):950–8.
[144] Cohn JN, Franciosa JA, Francis GS, Archibald D, Tristani F, Fletcher R, et al. Effect of short-term infusion of sodium nitroprusside on mortality rate in acute myocardial infarction complicated by left ventricular failure: results of a Veterans Administration cooperative study. N Engl J Med 1982;306(19):1129–35.
[145] Packer M, O'Connor C, McMurray JJV, Wittes J, Abraham WT, Anker SD, et al. TRUE-AHF Investigators. Effect of ularitide on cardiovascular mortality in acute heart failure. N Engl J Med 2017;376:1956–64.
[146] Teerlink JR, Voors AA, Ponikowski P, Pang PS, Greenberg BH, Filippatos G, et al. Serelaxin in addition to standard therapy in acute heart failure: Rationale and design of the RELAX-AHF-2 study. Eur J Heart Fail 2017;19(6):800–9.
[147] Colucci WS. Positive inotropic/vasodilator agents. Cardiol Clin 1989;7 (1):131–44.
[148] Om A, Hess ML. Inotropic therapy of the failing myocardium. Clin Cardiol 1993;16(1):5–14.
[149] Packer M. Vasodilator and inotropic drugs for the treatment of chronic heart failure: distinguishing hype from hope. J Am Coll Cardiol 1988;12(5):1299–317.
[150] Leier CV. Current status of non-digitalis positive inotropic drugs. Am J Cardiol 1992;69(18):120G–8G. disc 8G–9G.
[151] Sindone AP, Keogh AM, Macdonald PS, McCosker CJ, Kaan AF. Continuous home ambulatory intravenous inotropic drug therapy in severe heart failure: Safety and cost efficacy. Am Heart J 1997;134 (5 Pt 1):889–900.
[152] Tang X, Liu P, Li R, Jing Q, Lv J, Liu L, et al. Milrinone for the treatment of acute heart failure after acute myocardial infarction: a systematic review and meta-analysis. Basic Clin Pharmacol Toxicol 2015;117 (3):186–94.
[153] Cuffe MS, Califf RM, Adams Jr KF, Benza R, Bourge R, Colucci WS, et al. Short-term intravenous milrinone for acute exacerbation of chronic heart failure: a randomized controlled trial. JAMA 2002;287 (12):1541–7.
[154] Gong B, Li Z, Yat Wong PC. Levosimendan treatment for heart failure: a systematic review and meta-analysis. J Cardiothorac Vasc Anesth 2015;29(6):1415–25.
[155] Orstavik O, Ata SH, Riise J, Dahl CP, Andersen GØ, Levy FO, et al. Inhibition of phosphodiesterase-3 by levosimendan is sufficient to account for its inotropic effect in failing human heart. Br J Pharmacol 2014;23:5169–81.
[156] Follath F, Cleland JG, Just H, Papp JG, Scholz H, Peuhkurinen K, et al. Efficacy and safety of intravenous levosimendan compared with dobutamine in severe low-output heart failure (the LIDO study): a randomised double-blind trial. Lancet 2002;360(9328):196–202.
[157] Teerlink JR, Massie BM, Colucci WS, Young JB, Packer M, Fisher LD, et al. Levosimendan reduces length of initial hospital stay: the REVIVE II study. J Card Fail 2006;12(6 Suppl 1):S84.
[158] Mebazaa A, Nieminen MS, Packer M, Cohen-Solal A, Kleber FX, Pocock SJ, et al. Levosimendan vs dobutamine for patients with acute decompensated heart failure: the SURVIVE Randomized Trial. JAMA 2007;297(17):1883–91.
[159] Chatterjee K, Wolfe CL, DeMarco T. Nonglycoside inotropes in congestive heart failure. Are they beneficial or harmful? Cardiol Clin 1994;12 (1):63–72.
[160] Wang XC, Zhu DM, Shan YX. Dobutamine therapy is associated with worse clinical outcomes compared with nesiritide therapy for acute decompensated heart failure: a systematic review and meta-analysis. Am J Cardiovasc Drugs 2015;15(6):429–37.
[161] Mentz RJ, Kjeldsen K, Rossi GP, Voors AA, Cleland JG, Anker SD, et al. Decongestion in acute heart failure. Eur J Heart Fail 2014;16(5):471–82.

[162] Neuberg GW, Miller AB, O'Connor CM, Belkin RN, Carson PE, Cropp AB, et al. Diuretic resistance predicts mortality in patients with advanced heart failure. Am Heart J 2002;144(1):31–8.
[163] Bourge RC, Ultrafiltration Tallaj JA. A new approach toward mechanical diuresis in heart failure. J Am Coll Cardiol 2005;46(11): 2052–3.
[164] Jaski BE, Ha J, Denys BG, Lamba S, Trupp RJ, Abraham WT. Peripherally inserted veno-venous ultrafiltration for rapid treatment of volume overloaded patients. J Card Fail 2003;9(3):227–31.
[165] Costanzo M, Saltzburg M, O'Sullivan J, et al. EUPHORIA trial: early ultrafiltration therapy in patients with decompensated heart failure and observed resistance to intervention with diuretic agents. J Card Fail)2004;(Suppl). S78.
[166] Bart BA, Boyle A, Bank AJ, Anand I, Olivari MT, Kraemer M, et al. Ultrafiltration versus usual care for hospitalized patients with heart failure: the Relief for Acutely Fluid-Overloaded Patients With Decompensated Congestive Heart Failure (RAPID-CHF) trial. J Am Coll Cardiol 2005;46(11):2043–6.
[167] Costanzo MR, Guglin ME, Saltzberg MT, Jessup ML, Bart BA, Teerlink JR, et al. Ultrafiltration versus intravenous diuretics for patients hospitalized for acute decompensated heart failure. J Am Coll Cardiol 2007;49(6):675–83.
[168] Bart BA, Goldsmith SR, Lee KL, Givertz MM, O'Connor CM, Bull DA, et al. Ultrafiltration in decompensated heart failure with cardiorenal syndrome. N Engl J Med 2012;367(24):2296–304.
[169] Sharma A, Hermann DD, Mehta RL. Clinical benefit and approach of ultrafiltration in acute heart failure. Cardiology 2001;96(3–4):144–54.
[170] AbouEzzeddine OF, Redfield MM. Who has advanced heart failure? Definition and epidemiology. Conges Heart Fail 2017;17(4):160–8.
[171] Thiele H, Zeymer U, Neumann F-J, et al. Intraaortic balloon support for myocardial infarction with cardiogenic shock. N Engl J Med 2012;367:1287–96.
[172] Thiele H, Zeymer U, Neumann F-J, et al. Intra-aortic balloon counterpulsation in acute myocardial infarction complicated by cardiogenic shock (IABP-SHOCK II): final 12 month results of a randomised, open-label trial. Lancet 2013;382:1638–45.
[173] Rose EA, Gelijns AC, Moskowitz AJ, Heitjan DF, Stevenson LW, Dembitsky W, et al. Long-term use of a left ventricular assist device for end-stage heart failure. N Engl J Med 2001;345(20):1435–43.
[174] Slaughter MS, Rogers JG, Milano CA, Russell SD, Conte JV, Feldman D, et al. Advanced heart failure treated with continuous-flow left ventricular assist device. N Engl J Med 2009;361(23):2241–51.
[175] Stewart GC, Givertz MM. Mechanical circulatory support for advanced heart failure: Patients and technology in evolution. Circulation 2012;125:1304–15.
[176] Riebandt J, Haberl T, Mahr S, Laufer G, Rajek A, Steinlechner B, et al. Preoperative patient optimization using extracorporeal life support improves outcomes of INTERMACS level I patients receiving a permanent ventricular assist device. Eur J Cardiothorac Surg 2014;46:486–92.
[177] Schmidt M, Burrell A, Roberts L, Bailey M, Sheldrake J, Rycus PT, et al. Predicting survival after ECMO for refractory cardiogenic shock: the survival after veno-arterial-ECMO (SAVE)-score. Eur Heart J 2015;36:1–11.
[178] Cheng JM, den Uil CA, Hoeks SE, van der Ent M, Jewbali LS, van Domburg RT, et al. Percutaneous left ventricular assist devices vs. intra-aortic balloon pump counterpulsation for treatment of cardiogenic shock: a meta-analysis of controlled trials. Eur Heart J 2009;30:2102–18.
[179] O'Neill WW, Schreiber T, Wohns DH, Rihal C, Naidu SS, Civitello AB, et al. The current use of Impella 2.5 in acute myocardial infarction complicated by cardiogenic shock: results from the USpella Registry. J Interv Cardiol 2014;27(1):1–11.
[180] Joseph SM, Brisco MA, Colvin M, Grady KL, Walsh MN, Cook JL, genVAD Working Group. Women With cardiogenic shock derive greater benefit from early mechanical circulatory support: an update from the cVAD Registry. J Interv Cardiol 2016;29(3):248–56.
[181] The CONSENSUS Trial Study Group. Effects of enalapril on mortality in severe congestive heart failure. Results of the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS). N Engl J Med 1987;316(23):1429–35.
[182] The Cardiac Insufficiency Bisoprolol Study II (CIBIS-II): a randomised trial. Lancet 1999;353(9146):9–13.
[183] MERIT-HF Study Group. Effect of metoprolol CR/XL in chronic heart failure: metoprolol CR/XL randomised intervention trial in congestive heart failure (MERIT-HF). Lancet 1999;353(9169):2001–7.
[184] Flather MD, Yusuf S, Kober L, Pfeffer M, Hall A, Murray G, et al. ACE-Inhibitor Myocardial Infarction Collaborative Group. Long-term ACE-inhibitor therapy in patients with heart failure or left-ventricular dysfunction: a systematic overview of data from individual patients. Lancet 2000;355(9215):1575–81.
[185] The SOLVD Investigators. Effect of enalapril on survival in patients with reduced left ventricular ejection fractions and congestive heart failure. N Engl J Med 1991;325(5):293–302.
[186] Garg R, Yusuf S, Collaborative Group on ACE Inhibitor Trials. Overview of randomized trials of angiotensin-converting enzyme inhibitors on mortality and morbidity in patients with heart failure. JAMA 1995;273(18):1450–6.
[187] Packer M, Bristow MR, Cohn JN, Colucci WS, Fowler MB, Gilbert EM, et al. U. S. Carvedilol Heart Failure Study Group. The effect of carvedilol on morbidity and mortality in patients with chronic heart failure. N Engl J Med 1996;334(21):1349–55.
[188] Pitt B, Zannad F, Remme WJ, Cody R, Castaigne A, Perez A, et al. The effect of spironolactone on morbidity and mortality in patients with severe heart failure. N Engl J Med 1999;341(10):709–17.
[189] Hjalmarson A, Goldstein S, Fagerberg B, Wedel H, Waagstein F, Kjekshus J, et al. MERIT-HF Study Group. Effects of controlled-release metoprolol on total mortality, hospitalizations, and well-being in patients with heart failure: the Metoprolol CR/XL Randomized Intervention Trial in congestive heart failure (MERIT-HF). JAMA 2000;283 (10):1295–302.
[190] Packer M, Coats AJ, Fowler MB, Katus HA, Krum H, Mohacsi P, et al. Effect of carvedilol on survival in severe chronic heart failure. N Engl J Med 2001;344(22):1651–8.
[191] Packer M, Fowler MB, Roecker EB, Coats AJ, Katus HA, Krum H, 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.
[192] Zannad F, McMurray JJ, Krum H, van Veldhuisen DJ, Swedberg K, Shi H, et al. Eplerenone in patients with systolic heart failure and mild symptoms. N Engl J Med 2011;364(1):11–21.
[193] McMurray JJ, Packer M, Desai AS, Gong J, Lefkowitz MP, Rizkala AR, et al. Angiotensin-neprilysin inhibition versus enalapril in heart failure. N Engl J Med 2014;371(11):993–1004.
[194] Granger CB, McMurray JJ, Yusuf S, Held P, Michelson EL, Olofsson B, 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 2003;362(9386):772–6.
[195] McMurray JJ, Ostergren J, Swedberg K, Granger CB, Held P, Michelson EL, et al. Effects of candesartan in patients with chronic heart failure and reduced left-ventricular systolic function taking angiotensin-converting-enzyme inhibitors: the CHARM-Added trial. Lancet 2003;362 (9386):767–71.
[196] Cohn JN, Tognoni G. Valsartan Heart Failure Trial I. A randomized trial of the angiotensin-receptor blocker valsartan in chronic heart failure. N Engl J Med 2001;345(23):1667–75.
[197] Young JB, Dunlap ME, Pfeffer MA, Probstfield JL, Cohen-Solal A, Dietz R, et al. Mortality and morbidity reduction with Candesartan in patients with chronic heart failure and left ventricular systolic dysfunction: results of the CHARM low-left ventricular ejection fraction trials. Circulation 2004;110(17):2618–26.
[198] Burnett H, Earley A, Voors AA, Senni M, McMurray JJ, Deschaseaux C, et al. Thirty years of evidence on the efficacy of drug treatments for chronic heart failure with reduced ejection fraction: a network meta-analysis. Circ Heart Fail 2017;10(1). http://dx.doi.org/10.1161/CIRCHEARTFAILURE.116.003529.
[199] Bohm M, Swedberg K, Komajda M, Borer JS, Ford I, Dubost-Brama A, et al. Heart rate as a risk factor in chronic heart failure (SHIFT): the association between heart rate and outcomes in a randomised placebo-controlled trial. Lancet 2010;376(9744):886–94.
[200] Swedberg K, Komajda M, Bohm M, Borer JS, Ford I, Dubost-Brama A, et al. Ivabradine and outcomes in chronic heart failure (SHIFT): a randomised placebo-controlled study. Lancet 2010;376(9744):875–85.
[201] Driscoll A, Currey J, Tonkin A, Krum H. Nurse-led titration of angiotensin converting enzyme inhibitors, beta-adrenergic blocking agents, and angiotensin receptor blockers for people with heart failure with reduced ejection fraction. Cochrane Database Syst Rev):2015;(12) CD009889.
[202] Hickey A, Suna J, Marquart L, Denaro C, Javorsky G, Munns A, et al. Improving medication titration in heart failure by embedding a structured medication titration plan. Int J Cardiol 2016;224:99–106.

[203] The Acute Infarction Ramipril Efficacy (AIRE) Study Investigators. Effect of ramipril on mortality and morbidity of survivors of acute myocardial infarction with clinical evidence of heart failure. Lancet 1993;342(8875):821–8.
[204] Kober L, Torp-Pedersen C, Carlsen JE, Bagger H, Eliasen P, Lyngborg K, et al. Trandolapril Cardiac Evaluation (TRACE) Study Group. A clinical trial of the angiotensin-converting-enzyme inhibitor trandolapril in patients with left ventricular dysfunction after myocardial infarction. N Engl J Med 1995;333(25):1670–6.
[205] Ambrosioni E, Borghi C, Magnani B. The Survival of Myocardial Infarction Long-Term Evaluation (SMILE) Study Investigators. The effect of the angiotensin-converting-enzyme inhibitor zofenopril on mortality and morbidity after anterior myocardial infarction. N Engl J Med 1995;332(2):80–5.
[206] Packer M, Poole-Wilson PA, Armstrong PW, Cleland JG, Horowitz JD, Massie BM, et al. ATLAS Study Group Comparative effects of low and high doses of the angiotensin-converting enzyme inhibitor, lisinopril, on morbidity and mortality in chronic heart failure. Circulation 1999;100(23):2312–8.
[207] Kostis JB, Packer M, Black HR, Schmieder R, Henry D, Levy E. Omapatrilat and enalapril in patients with hypertension: the Omapatrilat Cardiovascular Treatment vs. Enalapril (OCTAVE) trial. Am J Hypertens 2004;17(2):103–11.
[208] Shekelle PG, Rich MW, Morton SC, Atkinson CS, Tu W, Maglione M, et al. Efficacy of angiotensin-converting enzyme inhibitors and beta-blockers in the management of left ventricular systolic dysfunction according to race, gender, and diabetic status: a meta-analysis of major clinical trials. J Am Coll Cardiol 2003;41(9):1529–38.
[209] Flather MD, Shibata MC, Coats AJ, Van Veldhuisen DJ, Parkhomenko A, Borbola J, 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.
[210] Eichhorn EJ, Domanski MJ, Krause-Steinrauf H, Bristow MR, Lavori PW. Beta-Blocker Evaluation of Survival Trial I. A trial of the beta-blocker bucindolol in patients with advanced chronic heart failure. N Engl J Med 2001;344(22):1659–67.
[211] Poole-Wilson PA, Swedberg K, Cleland JG, Di Lenarda A, Hanrath P, Komajda M, et al. Comparison of carvedilol and metoprolol on clinical outcomes in patients with chronic heart failure in the Carvedilol Or Metoprolol European Trial (COMET): randomised controlled trial. Lancet 2003;362(9377):7–13.
[212] Bristow MR, Gilbert EM, Abraham WT, Adams KF, Fowler MB, Hershberger RE, et al. MOCHA Investigators: carvedilol produces dose-related improvements in left ventricular function and survival in subjects with chronic heart failure. Circulation 1996;94(11):2807–16.
[213] Rienstra M, Damman K, Mulder BA, Van Gelder IC, McMurray JJ, Van Veldhuisen DJ. Beta-blockers and outcome in heart failure and atrial fibrillation: a meta-analysis. JACC Heart Fail 2013;1(1):21–8.
[214] Kotecha D, Holmes J, Krum H, Altman DG, Manzano L, Cleland JG, et al. Efficacy of beta blockers in patients with heart failure plus atrial fibrillation: an individual-patient data meta-analysis. Lancet 2014;384 (9961):2235–43.
[215] Willenheimer R, van Veldhuisen DJ, Silke B, Erdmann E, Follath F, Krum H, et al. Effect on survival and hospitalization of initiating treatment for chronic heart failure with bisoprolol followed by enalapril, as compared with the opposite sequence: results of the randomized Cardiac Insufficiency Bisoprolol Study (CIBIS) III. Circulation 2005;112(16):2426–35.
[216] Zannad F, Gattis Stough W, Rossignol P, Bauersachs J, McMurray JJ, Swedberg K, et al. Mineralocorticoid receptor antagonists for heart failure with reduced ejection fraction: integrating evidence into clinical practice. Eur Heart J 2012;33(22):2782–95.
[217] Faris RF, Flather M, Purcell H, Poole-Wilson PA, Coats AJ. Diuretics for heart failure. Cochrane Database Syst Rev):2012;(2)CD003838.
[218] Konstam MA, Neaton JD, Dickstein K, Drexler H, Komajda M, Martinez FA, et al. Effects of high-dose versus low-dose losartan on clinical outcomes in patients with heart failure (HEAAL study): a randomised, double-blind trial. Lancet 2009;374(9704):1840–8.
[219] Komajda M, Bohm M, Borer J, Ford I, Krum H, Tase A, et al. Influence of background treatment with mineralocorticoid receptor antagonists on ivabradine's effects in patients with chronic heart failure. Eur J Heart Fail 2013;15(1):79–84.
[220] Cohn JN, Archibald DG, Ziesche S, Franciosa JA, Harston WE, Tristani FE, et al. Effect of vasodilator therapy on mortality in chronic congestive heart failure: results of a Veterans Administration Cooperative Study. N Engl J Med 1986;314(24):1547–52.
[221] Cohn JN, Johnson G, Ziesche S, Cobb F, Francis G, Tristani F, et al. A comparison of enalapril with hydralazine-isosorbide dinitrate in the treatment of chronic congestive heart failure. N Engl J Med 1991;325 (5):303–10.
[222] Taylor AL, Ziesche S, Yancy C, Carson P, D'Agostino Jr R, Ferdinand K, et al. Combination of isosorbide dinitrate and hydralazine in blacks with heart failure. N Engl J Med 2004;351(20):2049–57.
[223] Digitalis Investigation G. The effect of digoxin on mortality and morbidity in patients with heart failure. N Engl J Med 1997;336(8):525–33.
[224] Rathore SS, Curtis JP, Wang Y, Bristow MR, Krumholz HM. Association of serum digoxin concentration and outcomes in patients with heart failure. JAMA 2003;289(7):871–8.
[225] Adams Jr KF, Patterson JH, Gattis WA, O'Connor CM, Lee CR, Schwartz TA, et al. Relationship of serum digoxin concentration to mortality and morbidity in women in the digitalis investigation group trial: a retrospective analysis. J Am Coll Cardiol 2005;46(3): 497–504.
[226] Ziff OJ, Lane DA, Samra M, Griffith M, Kirchhof P, Lip GY, et al. Safety and efficacy of digoxin: systematic review and meta-analysis of observational and controlled trial data. BMJ 2015;351. h4451.
[227] Tavazzi L, Maggioni AP, Marchioli R, Barlera S, Franzosi MG, Latini R, et al. Effect of n-3 polyunsaturated fatty acids in patients with chronic heart failure (the GISSI-HF trial): a randomised, double-blind, placebo-controlled trial. Lancet 2008;372(9645):1223–30.
[228] Coggan AR, Leibowitz JL, Spearie CA, Kadkhodayan A, Thomas DP, Ramamurthy S, et al. Acute dietary nitrate intake improves muscle contractile function in patients with heart failure: a double-blind, placebo-controlled, randomized trial. Circ Heart Fail 2015;8(5):914–20.
[229] Hirai DM, Zelt JT, Jones JH, Castanhas LG, Bentley RF, Earle W, et al. Dietary nitrate supplementation and exercise tolerance in patients with heart failure with reduced ejection fraction. Am J Physiol Regul Integr Comp Physiol 2017;312(1):R13–22.
[230] Zamani P, Rawat D, Shiva-Kumar P, Geraci S, Bhuva R, Konda P, et al. Effect of inorganic nitrate on exercise capacity in heart failure with preserved ejection fraction. Circulation 2015;131(4):371–80.
[231] Bonilla-Palomas JL, Gámez-López AL, Castillo-Domínguez JC, Moreno-Conde M, López Ibáñez MC, Alhambra Expósito R, et al. Nutritional intervention in malnourished hospitalized patients with heart failure. Arch Med Res 2016;47(7):535–40.
[232] McKeag NA, McKinley MC, Harbinson MT, Noad RL, Dixon LH, McGinty A, et al. The effect of multiple micronutrient supplementation on left ventricular ejection fraction in patients with chronic stable heart failure: a randomized, placebo-controlled trial. JACC 2014;2(3):308–17.
[233] Hofman-Bang C, Rehnqvist N, Swedberg K, Wiklund I, Astrom H. The Q10 Study Group. Coenzyme Q10 as an adjunctive in the treatment of chronic congestive heart failure. J Card Fail 1995;1(2):101–7.
[234] Khatta M, Alexander BS, Krichten CM, Fisher ML, Freudenberger R, Robinson SW, et al. The effect of coenzyme Q10 in patients with congestive heart failure. Ann Intern Med 2000;132(8):636–40.
[235] Morisco C, Trimarco B, Condorelli M. Effect of coenzyme Q10 therapy in patients with congestive heart failure: a long-term multicenter randomized study. Clin Investig 1993;71(8 Suppl):S134–6.
[236] Mortensen SA, Rosenfeldt F, Kumar A, Dolliner P, Filipiak KJ, Pella D, et al. The effect of coenzyme Q10 on morbidity and mortality in chronic heart failure: Results from Q-SYMBIO: a randomized double-blind trial. JACC Heart Fail 2014;2(6):641–9.
[237] Zhao Q, Kebbati AH, et al. Effect of coenzyme Q10 on the incidence of atrial fibrillation in patients with heart failure. J Investig Med 2015;63 (5):735–9.
[238] Holubarsch CJ, Colucci WS, Meinertz T, Gaus W, Tendera M. The efficacy and safety of Crataegus extract WS 1442 in patients with heart failure: the SPICE trial. Eur J Heart Fail 2008;10(12):1255–63.
[239] Zick SM, Vautaw BM, Gillespie B, Aaronson KD. Hawthorn Extract Randomized Blinded Chronic Heart Failure (HERB CHF) trial. Eur J Heart Fail 2009;11(10):990–9.
[240] Stepura OB, Martynow AI. Magnesium orotate in severe congestive heart failure (MACH). Int J Cardiol 2009;134(1):145–7.
[241] Shimon I, Almog S, Vered Z, Seligmann H, Shefi M, Peleg E, et al. Improved left ventricular function after thiamine supplementation in patients with congestive heart failure receiving long-term furosemide therapy. Am J Med 1995;98(5):485–90.
[242] Ho C. Effects of antioxidant on cardiovascular performance, exercise capacity, and functional status in patients with chronic heart failure. In: DPhil Dissertation. Case Western Reserve University; 2007.
[243] Keith ME, Jeejeebhoy KN, Langer A, Kurian R, Barr A, O'Kelly B, et al. A controlled clinical trial of vitamin E supplementation in patients with congestive heart failure. Am J Clin Nutr 2001;73(2):219–24.

[244] Boxer RS, Kenny AM, Schmotzer BJ, Vest M, Fiutem JJ, Pina IL. A randomized controlled trial of high dose vitamin D3 in patients with heart failure. JACC Heart Fail 2013;1(1):84–90.
[245] Boxer RS, Hoit BD, Schmotzer BJ, Stefano GT, Gomes A, Negrea L. The effect of vitamin D on aldosterone and health status in patients with heart failure. J Card Fail 2014;20(5):334–42.
[246] Schleithoff SS, Zittermann A, Tenderich G, Berthold HK, Stehle P, Koerfer R. Vitamin D supplementation improves cytokine profiles in patients with congestive heart failure: a double-blind, randomized, placebo-controlled trial. Am J Clin Nutr 2006;83(4):754–9.
[247] Witte KK, Byrom R, Gierula J, Paton MF, Jamil HA, Lowry JE, et al. Effects of vitamin D on cardiac function in patients with chronic HF: the VINDICATE Study. J Am Coll Cardiol 2016;67(22):2593–603.
[248] Zittermann A, Ernst JB, Prokop S, Fuchs U, Dreier J, Kuhn J, et al. Effect of vitamin D on all-cause mortality in heart failure (EVITA): a 3-year randomized clinical trial with 4000 IU vitamin D daily. Eur Heart J 2017;38:2279–86.
[249] Yusuf S, Pfeffer MA, Swedberg K, Granger CB, Held P, McMurray JJ, et al. Effects of candesartan in patients with chronic heart failure and preserved left-ventricular ejection fraction: the CHARM-Preserved Trial. Lancet 2003;362(9386):777–81.
[250] Massie BM, Carson PE, McMurray JJ, Komajda M, McKelvie R, Zile MR, et al. Irbesartan in patients with heart failure and preserved ejection fraction. N Engl J Med 2008;359(23):2456–67.
[251] Cleland JG, Tendera M, Adamus J, Freemantle N, Polonski L, Taylor J, et al. The perindopril in elderly people with chronic heart failure (PEP-CHF) study. Eur Heart J 2006;27(19):2338–45.
[252] Pitt B, Pfeffer MA, Assmann SF, Boineau R, Anand IS, Claggett B, et al. Spironolactone for heart failure with preserved ejection fraction. N Engl J Med 2014;370(15):1383–92.
[253] Anand IS, Claggett B, Liu J, Shah AM, Rector TS, Shah SJ, et al. Interaction between spironolactone and natriuretic peptides in patients with heart failure and preserved ejection fraction: from the TOPCAT trial. JACC Heart Fail 2017;5(4):241–52.
[254] Lee DS, Stukel TA, Austin PC, Alter DA, Schull MJ, You JJ, et al. Improved outcomes with early collaborative care of ambulatory heart failure patients discharged from the emergency department. Circulation 2010;122(18):1806–14.
[255] Boom NK, Lee DS, Tu JV. Comparison of processes of care and clinical outcomes for patients newly hospitalized for heart failure attended by different physician specialists. Am Heart J 2012;163(2):252–9.
[256] Fonseca C, Ceia F, Sarmento PM, Marques F, Covas R, Aleixo A. Translating guidelines into clinical practice: Benefits of an acute heart failure unit. Rev Port Cardiol 2007;26(11):1111–28.
[257] Zuily S, Jourdain P, Decup D, Agrinier N, Loiret J, Groshens S, et al. Impact of heart failure management unit on heart failure-related readmission rate and mortality. Arch Cardiovasc Dis 2010;103(2):90–6.
[258] Kul S, Barbieri A, Milan E, Montag I, Vanhaecht K, Panella M. Effects of care pathways on the in-hospital treatment of heart failure: a systematic review. BMC Cardiovasc Disord 2012;12:81.
[259] Hansen LO, Greenwald JL, Budnitz T, Howell E, Halasyamani L, Maynard G, et al. Project BOOST: effectiveness of a multihospital effort to reduce rehospitalization. J Hosp Med 2013;8(8):421–7.
[260] Boutwell AE, Johnson MB, Rutherford P, Watson SR, Vecchioni N, Auerbach BS, et al. An early look at a four-state initiative to reduce avoidable hospital readmissions. Health Affairs 2011;30(7):1272–80.
[261] Bradley EH, Curry L, Horwitz LI, Sipsma H, Thompson JW, Elma M, et al. Contemporary evidence about hospital strategies for reducing 30-day readmissions: a national study. J Am Coll Cardiol 2012;60(7):607–14.
[262] American College of cardiology (ACC). H2H National Quality Improvement Initiative. Available at: https://cvquality.acc.org/initiatives/hospital-to-homeH2H. Accessed January 2018.
[263] American Heart Association. Get With The Guidelines. Available at: http://www.heart.org/HEARTORG/Professional/GetWithTheGuidelines/Get-With-The-Guidelines—HFStroke_UCM_001099_SubHomePage.jsp. Accessed 21/02/18.
[264] McAlister FA, Stewart S, Ferrua S, McMurray JJ. Multidisciplinary strategies for the management of heart failure patients at high risk for admission: a systematic review of randomized trials. J Am Coll Cardiol 2004;44(4):810–9.
[265] Phillips CO, Singa RM, Rubin HR, Jaarsma T. Complexity of program and clinical outcomes of heart failure disease management incorporating specialist nurse-led heart failure clinics: a meta-regression analysis. Eur J Heart Fail 2005;7(3):333–41.
[266] Whellan DJ, Hasselblad V, Peterson E, O'Connor CM, Schulman KA. Metaanalysis and review of heart failure disease management randomized controlled clinical trials. Am Heart J 2005;149(4):722–9.
[267] Tuso P, Watson HL, Garofalo-Wright L, Lindsay G, Jackson A, Taitano M, et al. Complex case conferences associated with reduced hospital admissions for high-risk patients with multiple comorbidities. Perm J 2014;18(1):38–42.
[268] Leppin AL, Gionfriddo MR, Kessler M, Brito JP, Mair FS, Gallacher K, et al. Preventing 30-day hospital readmissions: a systematic review and meta-analysis of randomized trials. JAMA Intern Med 2014;174(7):1095–107.
[269] Koshman SL, Charrois TL, Simpson SH, McAlister FA, Tsuyuki RT. Pharmacist care of patients with heart failure: a systematic review of randomized trials. Arch Intern Med 2008;168(7):687–94.
[270] Inglis SC, Clark RA, Dierckx R, Prieto-Merino D, Cleland JG. Structured telephone support or non-invasive telemonitoring for patients with heart failure. Cochrane Database Syst Rev):2015;(10)CD007228.
[271] Kotb A, Cameron C, Hsieh S, Wells G. Comparative effectiveness of different forms of telemedicine for individuals with heart failure (HF): a systematic review and network meta-analysis. PloS One 2015;10(2):e0118681.
[272] Nursing and Midwifery Board of Australia. Nurse Practitioner Standards of Practice, 2013.
[273] International Council of Nurses. Nurse practitioner/advanced practice nurse: definitions and characteristics. Nursing Matters Fact Sheet 2009:3.
[274] Arnett DK, Goodman RA, Halperin JL, Anderson JL, Parekh AK, Zoghbi WA. AHA/ACC/HHS strategies to enhance application of clinical practice guidelines in patients with cardiovascular disease and comorbid conditions: from the American Heart Association, American College of Cardiology, and US Department of Health and Human Services. Circulation 2014;130(18):1662–7.
[275] Stewart S, Riegel B, Boyd C, Ahamed Y, Thompson DR, Burrell LM, et al. Establishing a pragmatic framework to optimise health outcomes in heart failure and multimorbidity (ARISE-HF): a multidisciplinary position statement. Int J Cardiol 2016;212:1–10.
[276] Ampadu J, Morley JE. Heart failure and cognitive dysfunction. Int J Cardiol 2015;178:12–23.
[277] Denfeld QE, Winters-Stone K, Mudd JO, Gelow JM, Kurdi S, Lee CS. The prevalence of frailty in heart failure: a systematic review and meta-analysis. Int J Cardiol 2017;236:283–9.
[278] McDonagh J, Martin L, Ferguson C, Jha SR, Macdonald PS, Davidson PM, et al. Frailty assessment instruments in heart failure: a systematic review. Eur J Cardiovasc Nurs 2017.
[279] Jha SR, Hannu MK, Gore K, Chang S, Newton P, Wilhelm K, et al. Cognitive impairment improves the predictive validity of physical frailty for mortality in patients with advanced heart failure referred for heart transplantation. J Heart Lung Transplant 2016;35(9):1092–100.
[280] Hernandez AF, Greiner MA, Fonarow GC, Hammill BG, Heidenreich PA, Yancy CW, et al. Relationship between early physician follow-up and 30-day readmission among Medicare beneficiaries hospitalized for heart failure. JAMA 2010;303(17):1716–22.
[281] Stewart S, Carrington MJ, Horowitz JD, Marwick TH, Newton PJ, Davidson PM, et al. Prolonged impact of home versus clinic-based management of chronic heart failure: Extended follow-up of a pragmatic, multicentre randomized trial cohort. Int J Cardiol 2014;174(3):600–10.
[282] Jaarsma T, van der Wal MH, Lesman-Leegte I, Luttik ML, Hogenhuis J, Veeger NJ, et al. Effect of moderate or intensive disease management program on outcome in patients with heart failure: coordinating study evaluating outcomes of advising and counseling in heart failure (COACH). Arch Intern Med 2008;168(3):316–24.
[283] Young L, Hertzog M, Barnason S. Effects of a home-based activation intervention on self-management adherence and readmission in rural heart failure patients: the PATCH randomized controlled trial. BMC Cardiovasc Disord 2016;16(1):176.
[284] Boyde M, Peters R, New N, Hwang R, Ha T, Korczyk D. Self-care educational intervention to reduce hospitalisations in heart failure: a randomised controlled trial. Eur J Cardiovasc Nurs 2018;17(2):178–85.
[285] Hancock HC, Close H, Mason JM, Murphy JJ, Fuat A, de Belder M, et al. Feasibility of evidence-based diagnosis and management of heart failure in older people in care: a pilot randomised controlled trial. BMC Geriatr 2012;12:70.

[286] Jonkman NH, Westland H, Groenwold RH, Agren S, Atienza F, Blue L, et al. Do self-management interventions work in patients with heart failure? an individual patient data meta-analysis. Circulation 2016;133 (12):1189–98.
[287] Reilly CM, Higgins M, Smith A, Culler SD, Dunbar SB. Isolating the benefits of fluid restriction in patients with heart failure: a pilot study. Eur J Cardiovasc Nurs 2015;14(6):495–505.
[288] Li Y, Fu B, Qian X. Liberal versus restricted fluid administration in heart failure patients. a systematic review and meta-analysis of randomized trials. Int Heart J 2015;56(2):192–5.
[289] Aliti GB, Rabelo ER, Clausell N, Rohde LE, Biolo A, Beck-da-Silva L. Aggressive fluid and sodium restriction in acute decompensated heart failure: a randomized clinical trial. JAMA Intern Med 2013;173(12): 1058–64.
[290] Albert NM, Nutter B, Forney J, Slifcak E, Tang WH. A randomized controlled pilot study of outcomes of strict allowance of fluid therapy in hyponatremic heart failure (SALT-HF). J Card Fail 2013;19(1):1–9.
[291] Writing Committee M, Yancy CW, Jessup M, Bozkurt B, Butler J, Casey Jr DE, et al. 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/ American Heart Association Task Force on practice guidelines. Circulation 2013;128(16):e240–327.
[292] Sagar VA, Davies EJ, Briscoe S, Coats AJS, Dalal H, Lough F, et al. Exercise-based rehabilitation for heart failure: systematic review and meta-analysis. Open Heart 2015.
[293] Jewiss D, Ostman C, Smart NA. The effect of resistance training on clinical outcomes in heart failure: a systematic review and meta-analysis. Int J Cardiol 2016;221:674–81.
[294] Pandey A, Parashar A, Kumbhani DJ, Agarwal S, Garg J, Kitzman D, et al. Exercise training in patients with heart failure and preserved ejection fraction: meta-analysis of randomized control trials. Circ Heart Fail 2015;8:33–40.
[295] Lavie CJ, Arena R, Swift DL, Johannsen NM, Sui X, Lee D-C, et al. Exercise and the cardiovascular system clinical science and cardiovascular outcomes. Circ Res 2015;117:207–19.
[296] O'Connor CM, Whellan DJ, Lee KL, Keteyian SJ, Cooper LS, Ellis SJ, et al. Efficacy and safety of exercise training in patients with chronic heart failure: HF-ACTION randomized controlled trial. JAMA 2009;301(14):1439–50.
[297] Mudge AM, Denaro CP, Scott AC, Meyers D, Adsett JA, Mullins RW, et al. Addition of supervised exercise training to a post-hospital disease management program for patients recently hospitalized with acute heart failure: the EJECTION-HF randomized phase 4 trial. JACC Heart Failure 2018;6(2):143–52.
[298] Ellingsen Ø, Halle M, Conraads V, Støylen A, Dalen H, Delagardelle C, et al. High-intensity interval training in patients with heart failure with reduced ejection fraction. Circulation 2017;135:839–49.
[299] Gielen S, Laughlin MH, O'Conner C, Duncker DJ. Exercise training in patients with heart disease: review of beneficial effects and clinical recommendations. Prog Cardiovasc Dis 2015;57:347–55.
[300] Cleland JG, Abraham WT, Linde C, Gold MR, Young JB, Claude Daubert J, 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.
[301] Bristow MR, Saxon LA, Boehmer J, Krueger S, Kass DA, De Marco T, et al. Cardiac-resynchronization therapy with or without an implantable defibrillator in advanced chronic heart failure. N Engl J Med 2004;350(21):2140–50.
[302] Cleland JG, Daubert JC, Erdmann E, Freemantle N, Gras D, Kappenberger L, et al. The effect of cardiac resynchronization on morbidity and mortality in heart failure. N Engl J Med 2005;352(15):1539–49.
[303] Woods B, Hawkins N, Mealing S, Sutton A, Abraham WT, Beshai JF, et al. Individual patient data network meta-analysis of mortality effects of implantable cardiac devices. Heart 2015;101(22):1800–6.
[304] Goldenberg I, Kutyifa V, Klein HU, Cannom DS, Brown MW, Dan A, et al. Survival with cardiac-resynchronization therapy in mild heart failure. N Engl J Med 2014;370(18):1694–701.
[305] Tang AS, Wells GA, Talajic M, Arnold MO, Sheldon R, Connolly S, et al. Cardiac-resynchronization therapy for mild-to-moderate heart failure. N Engl J Med 2010;363(25):2385–95.
[306] Moss AJ, Hall WJ, Cannom DS, Klein H, Brown MW, Daubert JP, et al. Cardiac-resynchronization therapy for the prevention of heart-failure events. N Engl J Med 2009;361(14):1329–38.
[307] Molema SA, Bleeker GB, Vander Wall EE. Usefulness of QRS duration to predict response to cardiac resynchronisation therapy in patients with end stage heart failure. Am J Cardiol 2007;100:1665–70.
[308] Auricchio A, Fantoni C, Regoli F, Carbucicchio C, Goette A, Geller C, et al. Characterization of left ventricular activation in patients with heart failure and left bundle-branch block. Circulation 2004;109 (9):1133–9.
[309] Zareba W, Klein H, Cygankiewicz I, Hall WJ, McNitt S, Brown M, et al. Effectiveness of cardiac resynchronization therapy by QRS morphology in the multicenter automatic defibrillator implantation trial-cardiac resynchronization therapy (MADIT-CRT). Circulation 2011;123 (10):1061–72.
[310] Sipahi I, Chou JC, Hyden M, Rowland DY, Simon DI, Fang JC. Effect of QRS morphology on clinical event reduction with cardiac resynchronization therapy: meta-analysis of randomized controlled trials. Am Heart J 2012;163(2):260–7. e3.
[311] Sipahi I, Carrigan TP, Rowland DY, Stambler BS, Fang JC. Impact of QRS duration on clinical event reduction with cardiac resynchronization therapy: meta-analysis of randomized controlled trials. Arch Intern Med 2011;171(16):1454–62.
[312] Chung ES, Leon AR, Tavazzi L, Sun JP, Nihoyannopoulos P, Merlino J, et al. Results of the predictors of response to CRT (PROSPECT) trial. Circulation 2008;117(20):2608–16.
[313] Ruschitzka F, Abraham WT, Singh JP, Bax JJ, Borer JS, Brugada J, et al. Cardiac-resynchronization therapy in heart failure with a narrow QRS complex. N Engl J Med 2013;369(15):1395–405.
[314] Curtis AB, Worley SJ, Adamson PB, Chung ES, Niazi I, Sherfesee L, et al. Biventricular pacing for atrioventricular block and systolic dysfunction. N Engl J Med 2013;368:1585–93.
[315] Linde C, Gold MR, Abraham WT, St John Sutton M, Ghio S, Cerkvenik J, et al. Long-term impact of cardiac resynchronization therapy in mild heart failure: 5-Year results from the REsynchronization reVErses Remodeling in Systolic left vEntricular dysfunction (REVERSE) study. Eur Heart J 2013;34(33):2592–9.
[316] Kutyifa V, Kloppe A, Zareba W, Solomon SD, McNitt S, Polonsky S, et al. The influence of left ventricular ejection fraction on the effectiveness of cardiac resynchronization therapy: MADIT-CRT (Multicenter automatic defibrillator implantation trial with cardiac resynchronization therapy). J Am Coll Cardiol 2013;61(9):936–44.
[317] Leclercq C, Walker S, Linde C, Clementy J, Marshall AJ, Ritter P, et al. Comparative effects of permanent biventricular and right-univentricular pacing in heart failure patients with chronic atrial fibrillation. Eur Heart J 2002;23(22):1780–7.
[318] Linde C, Leclercq C, Rex S, Garrigue S, Lavergne T, Cazeau S, et al. Long-term benefits of biventricular pacing in congestive heart failure: results from the MUltisite STimulation in cardiomyopathy (MUSTIC) study. J Am Coll Cardiol 2002;40(1):111–8.
[319] Healey JS, Hohnloser SH, Exner DV, Birnie DH, Parkash R, Connolly SJ, et al. Cardiac resynchronization therapy in patients with permanent atrial fibrillation: results from the resynchronization for ambulatory heart failure trial (RAFT). Circ Heart Fail 2012;5(5):566–70.
[320] Brignole M, Botto G, Mont L, Iacopino S, De Marchi G, Oddone D, et al. Cardiac resynchronization therapy in patients undergoing atrioventricular junction ablation for permanent atrial fibrillation: a randomized trial. Eur Heart J 2011;32(19):2420–9.
[321] Stavrakis S, Garabelli P, Reynolds DW. Cardiac resynchronization therapy after atrioventricular junction ablation for symptomatic atrial fibrillation: a meta-analysis. Europace 2012;14(10):1490–7.
[322] Doshi RN, Daoud EG, Fellows C, Turk K, Duran A, Hamdan MH, et al. Left ventricular-based cardiac stimulation post AV nodal ablation evaluation (the PAVE study). J Cardiovasc Electrophysiol 2005;16 (11):1160–5.
[323] Koplan BA, Kaplan AJ, Weiner S, Jones PW, Seth M, Christman SA. Heart failure decompensation and all cause mortality in relation to percent biventricular pacing in patients with heart failure: is a goal of 100% biventricular pacing necessary? J Am Coll Cardiol 2009;53:355–60.
[324] Hayes DL, Boehmer JP, Day JD, Gilliam 3rd FR, Heidenreich PA, Seth M, et al. Cardiac resynchronisation therapy and the relationship of percent biventricular pacing to symptoms and survival. Heart Rhythm 2011;8:1469–75.
[325] Cleland JG, Mareev Y, Linde C. Reflections on EchoCRT: sound guidance on QRS duration and morphology for CRT? Eur Heart J 2015;36 (30):1948–51.
[326] Zusterzeel R, Selzman KA, Sanders WE, Canos DA, O'Callaghan KM, Carpenter JL, et al. Cardiac resynchronization therapy in women: US

Food and drug administration meta-analysis of patient-level data. JAMA Intern Med 2014;174(8):1340–8.
[327] Olshansky B, Day JD, Sullivan RM, Yong P, Galle E, Steinberg JS. Does cardiac resynchronization therapy provide unrecognized benefit in patients with prolonged PR intervals? The impact of restoring atrioventricular synchrony: an analysis from the COMPANION trial. Heart Rhythm 2012;9(1):34–9.
[328] Senfield J, Daubert C, Abraham WT, Ghio S, St John Sutton M, Cerkvenik J, et al. The impact of the PR interval in patients receiving cardiac resynchronization therapy: results from the REVERSE Study. Focus on new insights in cardiac resynchronization. JACC: Clin Electrophysiol 2017;3(8):818–26.
[329] Kutyifa V, Stockburger M, Daubert JP, Holmqvist F, Olshansky B, Schuger C, et al. PR interval identifies clinical response in patients with non-left bundle branch block: a Multicenter automatic defibrillator implantation trial-cardiac resynchronization therapy substudy. Circ Arrhythm Electrophysiol 2014;7(4):645–51.
[330] Kaye GC, Linker NJ, Marwick TH, Pollock L, Graham L, Pouliot E, et al. Effect of right ventricular pacing lead site on left ventricular function in patients with high-grade atrioventricular block: results of the Protect-Pace study. Eur Heart J 2015;36(14):856–62.
[331] Wilkoff BL, Cook JR, Epstein AE, Greene HL, Hallstrom AP, Hsia H, et al. Dual-chamber pacing or ventricular backup pacing in patients with an implantable defibrillator: the dual chamber and VVI implantable defibrillator (DAVID) trial. JAMA 2002;288(24):3115–23.
[332] Sweeney MO, Hellkamp AS, Ellenbogen KA, Greenspon AJ, Freedman RA, Lee KL, et al. Adverse effect of ventricular pacing on heart failure and atrial fibrillation among patients with normal baseline QRS duration in a clinical trial of pacemaker therapy for sinus node dysfunction. Circulation 2003;107(23):2932–7.
[333] Kober L, Thune JJ, Nielsen JC, Haarbo J, Videbaek L, Korup E, et al. Defibrillator Implantation in Patients with nonischemic systolic heart failure. N Engl J Med 2016;375(13):1221–30.
[334] Bardy GH, Lee KL, Mark DB, Poole JE, Packer DL, Boineau R, et al. Amiodarone or an implantable cardioverter-defibrillator for congestive heart failure. N Engl J Med 2005;352(3):225–37.
[335] Moss AJ, Zareba W, Hall W, Klein H, Wilber DJ, Cannom DS, et al. Prophylactic implantation of a defibrillator in patients with myocardial infarction and reduced ejection fraction. N Engl J Med 2002;346:877–83.
[336] Elming MB, Nielsen JC, Haarbo J, Videbaek L, Korup E, Signorovitch J, et al. Age and outcomes of primary prevention implantable cardioverter-defibrillators in patients with nonischemic systolic heart failure. Circulation 2017;136(19):1772–80.
[337] Stavrakis S, Asad Z, Reynolds D. Implantable cardioverter defibrillators for primary prevention of mortality in patients with nonischemic cardiomyopathy: a meta-analysis of randomized controlled trials. J Cardiovasc Electrophysiol 2017;28(6):659–65.
[338] Defaye P, Boveda S, Klug D, Beganton F, Piot O, Narayanan K, et al. Dual- vs: single-chamber defibrillators for primary prevention of sudden cardiac death: long-term follow-up of the defibrillateur automatique implantable-prevention primaire registry. Europace 2017;19(9):1478–84.
[339] Moss AJ, Schuger C, Beck CA, Brown MW, Cannom DS, Daubert JP, et al. Reduction in inappropriate therapy and mortality through ICD programming. N Engl J Med 2012;367(24):2275–83.
[340] Bourge RC, Abraham WT, Adamson PB, Aaron MF, Aranda Jr JM, Magalski A, et al. Randomized controlled trial of an implantable continuous hemodynamic monitor in patients with advanced heart failure: the COMPASS-HF study. J Am Coll Cardiol 2008;51(11):1073–9.
[341] Abraham WT, Stevenson LW, Bourge RC, Lindenfeld JA, Bauman JG, Adamson PB, et al. Sustained efficacy of pulmonary artery pressure to guide adjustment of chronic heart failure therapy: complete follow-up results from the CHAMPION randomised trial. Lancet 2016;387(10017):453–61.
[342] Adamson PB, Abraham WT, Stevenson LW, Desai AS, Lindenfeld J, Bourge RC, et al. Pulmonary artery pressure-guided heart failure management reduces 30-day readmissions. Circ Heart Fail 2016;9(6).
[343] Vaduganathan M, DeFilippis EM, Fonarow GC, Butler J, Mehra MR. Postmarketing adverse events related to the CardioMEMS HF System. JAMA Cardiol 2017;2(11):1277–9.
[344] Velazquez EJ, Lee KL, Deja MA, Jain A, Sopko G, Marchenko A, et al. Coronary-artery bypass surgery in patients with left ventricular dysfunction. N Engl J Med 2011;364(17):1607–16.
[345] Velazquez EJ, Lee KL, Jones RH, Al-Khalidi HR, Hill JA, Panza JA, et al. Coronary-artery bypass surgery in patients with ischemic cardiomyopathy. N Engl J Med 2016;374(16):1511–20.
[346] Wolff G, Dimitroulis D, Andreotti F, Kolodziejczak M, Jung C, Scicchitano P, et al. Survival benefits of invasive versus conservative strategies in heart failure in patients with reduced ejection fraction and coronary artery disease: a meta-analysis. Circ Heart Fail 2017;10(1).
[347] Jones RH, Velazquez EJ, Michler RE, Sopko G, Oh JK, O'Connor CM, et al. Coronary bypass surgery with or without surgical ventricular reconstruction. N Engl J Med 2009;360(17):1705–17.
[348] Athanasuleas CL, Buckberg GD, Stanley AW, Siler W, Dor V, Di Donato M, et al. Surgical ventricular restoration in the treatment of congestive heart failure due to post-infarction ventricular dilation. J Am Coll Cardiol 2004;44(7):1439–45.
[349] Klein P, Holman ER, Versteegh MI, Boersma E, Verwey HF, Bax JJ, et al. Wall motion score index predicts mortality and functional result after surgical ventricular restoration for advanced ischemic heart failure. Eur J Cardiothorac Surg 2009;35(5):847–52.
[350] Prior DL, Stevens SR, Holly TA, Krejca M, Paraforos A, Pohost GM, et al. Regional left ventricular function does not predict survival in ischaemic cardiomyopathy after cardiac surgery. Heart 2017;103(17):1359–67.
[351] Allman KC, Shaw LJ, Hachamovitch R, Udelson JE. Myocardial viability testing and impact of revascularization on prognosis in patients with coronary artery disease and left ventricular dysfunction: a meta-analysis. J Am Coll Cardiol 2002;39(7):1151–8.
[352] Bonow RO, Maurer G, Lee KL, Holly TA, Binkley PF, Desvigne-Nickens P, et al. Myocardial viability and survival in ischemic left ventricular dysfunction. N Engl J Med 2011;364(17):1617–25.
[353] Romano MA, Bolling SF. Update on mitral repair in dilated cardiomyopathy. J Card Surg 2004;19(5):396–400.
[354] Andalib A, Chetrit M, Eberg M, Filion KB, Theriault-Lauzier P, Lange R, et al. A systematic review and meta-analysis of outcomes following mitral valve surgery in patients with significant functional mitral regurgitation and left ventricular dysfunction. J Heart Valve Dis 2016;25(6):696–707.
[355] Acker MA, Parides MK, Perrault LP, Moskowitz AJ, Gelijns AC, Voisine P, et al. Mitral-valve repair versus replacement for severe ischemic mitral regurgitation. N Engl J Med 2014;370(1):23–32.
[356] Deja MA, Grayburn PA, Sun B, Rao V, She L, Krejca M, et al. Influence of mitral regurgitation repair on survival in the surgical treatment for ischemic heart failure trial. Circulation 2012;125(21):2639–48.
[357] Virk SA, Tian DH, Sriravindrarajah A, Dunn D, Wolfenden HD, Suri RM, et al. Mitral valve surgery and coronary artery bypass grafting for moderate-to-severe ischemic mitral regurgitation: meta-analysis of clinical and echocardiographic outcomes. J Thorac Cardiovasc Surg 2017;154(1):127–36.
[358] Alfieri O, Maisano F, De Bonis M, Stefano PL, Torracca L, Oppizzi M, et al. The double-orifice technique in mitral valve repair: a simple solution for complex problems. J Thorac Cardiovasc Surg 2001;122(4):674–81.
[359] Feldman T, Kar S, Elmariah S, Smart SC, Trento A, Siegel RJ, et al. randomized comparison of percutaneous repair and surgery for mitral regurgitation: 5-Year results of EVEREST II. J Am Coll Cardiol 2015;66(25):2844–54.
[360] Feldman T, Foster E, Glower DD, Kar S, Rinaldi MJ, Fail PS, et al. Percutaneous repair or surgery for mitral regurgitation. N Engl J Med 2011;364(15):1395–406.
[361] D'Ascenzo F, Moretti C, Marra WG, Montefusco A, Omede P, Taha S, et al. Meta-analysis of the usefulness of Mitraclip in patients with functional mitral regurgitation. Am J Cardiol 2015;116(2):325–31.
[362] Bonow RO, Carabello BA, Chatterjee K, de Leon Jr AC, Faxon DP, Freed MD, et al. 2008 Focused update incorporated into the ACC/AHA 2006 guidelines for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association TAsk force on practice guidelines (Writing Committee to Revise the 1998 Guidelines for the Management of Patients With Valvular Heart Disease): endorsed by the Society of Cardiovascular Anesthesiologists, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. Circulation 2008;118(15):e523–661.
[363] Baumgartner H, Falk V, Bax JJ, De Bonis M, Hamm C, Holm PJ, et al. 2017 ESC/EACTS Guidelines for the management of valvular heart disease. Eur Heart J 2017;38(36):2739–91.

[364] Chaliki HP, Mohty D, Avierinos JF, Scott CG, Schaff HV, Tajik AJ, et al. Outcomes after aortic valve replacement in patients with severe aortic regurgitation and markedly reduced left ventricular function. Circulation 2002;106(21):2687–93.
[365] Leon MB, Smith CR, Mack M, Miller DC, Moses JW, Svensson LG, et al. Transcatheter aortic-valve implantation for aortic stenosis in patients who cannot undergo surgery. N Engl J Med 2010;363(17):1597–607.
[366] Smith CR, Leon MB, Mack MJ, Miller DC, Moses JW, Svensson LG, et al. Transcatheter versus surgical aortic-valve replacement in high-risk patients. N Engl J Med 2011;364(23):2187–98.
[367] Adams DH, Popma JJ, Reardon MJ, Yakubov SJ, Coselli JS, Deeb GM, et al. Transcatheter aortic-valve replacement with a self-expanding prosthesis. N Engl J Med 2014;370(19):1790–8.
[368] Leon MB, Smith CR, Mack MJ, Makkar RR, Svensson LG, Kodali SK, et al. Transcatheter or surgical aortic-valve replacement in intermediate-risk patients. N Engl J Med 2016;374(17):1609–20.
[369] Kleczynski P, Dziewierz A, Bagienski M, Rzeszutko L, Sorysz D, Trebacz J, et al. Impact of frailty on mortality after transcatheter aortic valve implantation. Am Heart J 2017;185:52–8.
[370] Shimura T, Yamamoto M, Kano S, Kagase A, Kodama A, Koyama Y, et al. Impact of the clinical frailty scale on outcomes after transcatheter aortic valve replacement. Circulation 2017;135(21):2013–24.
[371] Puls M, Sobisiak B, Bleckmann A, Jacobshagen C, Danner BC, Hunlich M, et al. Impact of frailty on short- and long-term morbidity and mortality after transcatheter aortic valve implantation: risk assessment by Katz Index of activities of daily living. EuroIntervention 2014;10(5):609–19.
[372] Jha SR, Hannu MK, Newton PJ, Wilhelm K, Hayward CS, Jabbour A, et al. Reversibility of frailty after bridge-to-transplant ventricular assist device implantation or heart transplantation. Transplant Direct 2017;3(7):e167.
[373] Kirklin JK, Cantor R, Mohacsi P, Gummert J, De By T, Hannan MM, et al. First annual imacs report: a global international society for heart and lung transplantation registry for mechanical circulatory support. J Heart Lung Transplant 2016;35(4):407–12.
[374] Kirklin JK, Pagani FD, Kormos RL, Stevenson LW, Blume ED, Myers SL, et al. Eighth annual INTERMACS report: special focus on framing the impact of adverse events. J Heart Lung Transplant 2017;36(10):1080–6.
[375] Mehra MR, Naka Y, Uriel N, Goldstein DJ, Cleveland Jr JC, Colombo PC, et al. A fully magnetically levitated circulatory pump for advanced heart failure. N Engl J Med 2017;376(5):440–50.
[376] Rogers JG, Pagani FD, Tatooles AJ, Bhat G, Slaughter MS, Birks EJ, et al. Intrapericardial left ventricular assist device for advanced heart failure. N Engl J Med 2017;376(5):451–60.
[377] Mehra MR, Goldstein DJ, Uriel N, Cleveland Jr JC, Yuzefpolskaya M, Salerno C, et al. Two-year outcomes with a magnetically levitated cardiac pump in heart failure. N Engl J Med 2018;378:1386–95.
[378] Dhital KK, Iyer A, Connellan M, Chew HC, Gao L, Doyle A, et al. Adult heart transplantation with distant procurement and ex-vivo preservation of donor hearts after circulatory death: a case series. Lancet 2015;385(9987):2585–91.
[379] Zych D, Sabashnikov B, Bowles A, De Robertis CT, Mohite F, et al. Evaluation of the organ care system in heart transplantation with an adverse donor/recipient profile. Ann Thorac Surg 2014;98(6):2099–105.
[380] Lund LH, Edwards LB, Dipchand AI, Goldfarb S, Kucheryavaya AY, Levvey BJ, et al. The registry of the international society for heart and lung transplantation: thirty-third adult heart transplantation report-2016; Focus theme: primary diagnostic indications for transplant. J Heart Lung Transplant 2016;35(10):1158–69.
[381] Mehra MR, Canter CE, Hannan MM, Semigran MJ, Uber PA, Baran DA, et al. The 2016 International Society for Heart Lung Transplantation listing criteria for heart transplantation: a 10-year update. J Heart Lung Transplant 2016;35(1):1–23.
[382] Keogh A, Williams T, Pettersson R. Australia and New Zealand Cardiothoracic Organ Transplant Registry Report. Darlinghurst, NSW, Australia: St Vincent's Hospital; 2016.
[383] Chamberlain AM, St Sauver JL, Gerber Y, Manemann SM, Boyd CM, Dunlay SM, et al. Multimorbidity in heart failure: a community perspective. Am J Med 2015;128(1):38–45.
[384] Conrad N, Judge A, Tran J, Mohseni H, Hedgecott D, Crespillo AP, et al. Temporal trends and patterns in heart failure incidence: a population-based study of 4 million individuals. Lancet 2017;391(10120):572–80.
[385] Kalantar-Zadeh K, Block G, Horwich T, Fonarow GC. Reverse epidemiology of conventional cardiovascular risk factors in patients with chronic heart failure. J Am Coll Cardiol 2004;43(8):1439–44.
[386] Lip GYH, Skjøth F, Overvad K, Rasmussen LH, Larsen TB. Blood pressure and prognosis in patients with incident heart failure: the Diet, Cancer and Health (DCH) cohort study. Clin Res Cardiol 2015;104:1088–96.
[387] Manickavasagam S, Merla R, Koerner MM, Fujise K, Kunapuli S, Rosanio S, et al. Management of hypertension in chronic heart failure. Expert Rev Cardiovasc Ther 2009;7(4):423–33.
[388] Packer M, O'Connor CM, Ghali JK, Pressler ML, Carson PE, Belkin RN, et al. Prospective Randomized Amlodipine Survival Evaluation Study Group: effect of amlodipine on morbidity and mortality in severe chronic heart failure. N Engl J Med 1996;335(15):1107–14.
[389] Cohn JN, Ziesche S, Smith R, Anand I, Dunkman WB, Loeb H, et al. Vasodilator-Heart Failure Trial (V-HeFT) Study Group. Effect of the calcium antagonist felodipine as supplementary vasodilator therapy in patients with chronic heart failure treated with enalapril: V-HeFT III. Circulation 1997;96(3):856–63.
[390] Goldstein RE, Boccuzzi SJ, Cruess D, Nattel S. The Adverse Experience Committee and the Multicenter Diltiazem Postinfarction Research Group. Diltiazem increases late-onset congestive heart failure in post-infarction patients with early reduction in ejection fraction. Circulation 1991;83:52–60.
[391] Cohn JN, Pfeffer MA, Rouleau J, Sharpe N, Swedberg K, Straub M, et al. Adverse mortality effect of central sympathetic inhibition with sustained-release moxonidine in patients with heart failure (MOXCON). Eur J Heart Fail 2003;5(5):659–67.
[392] Bayliss J, Norell MS, Canepa-Anson R, Reid C, Poole-Wilson P, Sutton G. Clinical importance of the renin-angiotensin system in chronic heart failure: double blind comparison of captopril and prazosin. Br Med J (Clin Res Ed) 1985;290(6485):1861–5.
[393] National Heart Foundation of Australia. Guideline for the diagnosis and management of hypertension in adults – 2016. Melbourne, Australia: National Heart Foundation of Australia; 2016.
[394] Mentz RJ, Allen BD, Kwasny MJ, Konstam MA, Udelson JE, Ambrosy AP, et al. Influence of documented history of coronary artery disease on outcomes in patients admitted for worsening heart failure with reduced ejection fraction in the EVEREST trial. Eur J Heart Fail 2013;15(1):61–8.
[395] Badar AA, Perez-Moreno AC, Hawkins NM, Brunton AP, Jhund PS, Wong CM, et al. Clinical characteristics and outcomes of patients with angina and heart failure in the CHARM (Candesartan in heart failure assessment of reduction in mortality and morbidity) programme. Eur J Heart Fail 2015;17(2):196–204.
[396] Kjekshus J, Apetrei E, Barrios V, Bohm M, Cleland JG, Cornel JH, et al. Rosuvastatin in older patients with systolic heart failure. N Engl J Med 2007;357(22):2248–61.
[397] Tavazzi L, Maggioni AP, Marchioli R, Barlera S, Franzosi MG, Latini R, et al. Effect of rosuvastatin in patients with chronic heart failure (the GISSI-HF trial): a randomised, double-blind, placebo-controlled trial. Lancet 2008;372(9645):1231–9.
[398] Maisel WH, Stevenson LW. Atrial fibrillation in heart failure: epidemiology, pathophysiology, and rationale for therapy. Am J Cardiol 2003;91(6a):2d–8d.
[399] Benjamin EJ, Levy D, Vaziri SM, D'Agostino RB, Belanger AJ, Wolf PA. Independent risk factors for atrial fibrillation in a population-based cohort. the Framingham Heart Study. JAMA 1994;271(11):840–4.
[400] Mamas MA, Caldwell JC, Chacko S, Garratt CJ, Fath-Ordoubadi F, Neyses L. A meta-analysis of the prognostic significance of atrial fibrillation in chronic heart failure. Eur J Heart Fail 2009;11(7):676–83.
[401] Wyse DG. Therapeutic considerations in applying rate control therapy for atrial fibrillation. J Cardiovasc Pharmacol 2008;52(1):11–7.
[402] Roy D, Talajic M, Nattel S, Wyse DG, Dorian P, Lee KL, et al. Rhythm control versus rate control for atrial fibrillation and heart failure. N Engl J Med 2008;358(25):2667–77.
[403] Prabhu S, Taylor AJ, Costello BT, Kaye DM, McLellan AJA, Voskoboinik A, et al. Catheter ablation versus medical rate control in atrial fibrillation and systolic dysfunction: the CAMERA-MRI study. J Am Coll Cardiol 2017;70(16):1949–61.
[404] Jones DG, Haldar SK, Hussain W, Sharma R, Francis DP, Rahman-Haley SL, et al. A randomized trial to assess catheter ablation versus rate control in the management of persistent atrial fibrillation in heart failure. J Am Coll Cardiol 2013;61(18):1894–903.

[405] Marrouche NF, Brachmann J, Andresen D, Siebels J, Boersma L, Jordaens L, et al. Catheter ablation for atrial fibrillation with heart failure. N Engl J Med 2018;378(5):417–27.
[406] Kotecha D, Piccini JP. Atrial fibrillation in heart failure: what should we do? Eur Heart J 2015;36(46):3250–7.
[407] Kotecha D, Holmes J, Krum H, Altman DG, Manzano L, Cleland JG, et al. Efficacy of beta blockers in patients with heart failure plus atrial fibrillation: an individual-patient data meta-analysis. Lancet 2014;384 (9961):2235–43.
[408] Chatterjee S, Ghosh J, Lichstein E, Aikat S, Mukherjee D. Meta-analysis of cardiovascular outcomes with dronedarone in patients with atrial fibrillation or heart failure. Am J Cardiol 2012;110(4):607–13.
[409] Echt DS, Liebson PR, Mitchell LB, Peters RW, Obias-Manno D, Barker AH, et al. Mortality and morbidity in patients receiving encainide, flecainide, or placebo. The Cardiac Arrhythmia Suppression trial. N Engl J Med 1991;324(12):781–8.
[410] Li SJ, Sartipy U, Lund LH, Dahlstrom U, Adiels M, Petzold M, et al. Prognostic significance of resting heart rate and use of beta-blockers in atrial fibrillation and sinus rhythm in patients with heart failure and reduced ejection fraction: findings from the Swedish Heart Failure Registry. Circ Heart Fail 2015;8(5):871–9.
[411] de Simone G, Devereux RB, Chinali M, Lee ET, Galloway JM, Barac A, et al. Diabetes and incident heart failure in hypertensive and normotensive participants of the strong heart study. J Hypertens 2010;28 (2):353–60.
[412] Atherton JJ, Hayward CS, Wan Ahmad WA, Kwok B, Jorge J, Hernandez AF, et al. Patient characteristics from a regional multicenter database of acute decompensated heart failure in Asia Pacific (ADHERE International-Asia Pacific). J Card Fail 2012;18(1):82–8.
[413] Johansson I, Dahlstrom U, Edner M, Nasman P, Ryden L, Norhammar A. Prognostic implications of Type 2 diabetes mellitus in ischemic and nonischemic heart failure. J Am Coll Cardiol 2016;68(13): 1404–16.
[414] Gilbert RE, Krum H. Heart failure in diabetes: effects of anti-hyperglycaemic drug therapy. Lancet 2015;385(9982):2107–17.
[415] Elder DH, Singh JS, Levin D, Donnelly LA, Choy AM, George J, et al. Mean HbA1c and mortality in diabetic individuals with heart failure: a population cohort study. Eur J Heart Fail 2016;18(1):94–102.
[416] Crowley MJ, Diamantidis CJ, McDuffie JR, Cameron CB, Stanifer JW, Mock CK, et al. Clinical outcomes of metformin use in populations with chronic kidney disease, congestive heart failure, or chronic liver disease: a systematic review. Ann Intern Med 2017;166(3):191–200.
[417] Hernandez AV, Usmani A, Rajamanickam A, Moheet 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. Am J Cardiovasc Drugs 2011;11:115–28.
[418] Zhang XL, Zhu QQ, Chen YH, Li XL, Chen F, Huang JA, et al. Cardiovascular safety, long-term noncardiovascular safety, and efficacy of sodium-glucose cotransporter 2 inhibitors in patients with type 2 diabetes mellitus: a systemic review and meta-analysis with trial sequential analysis. J Am Heart Assoc 2018;7(2).
[419] Varas-Lorenzo C, Margulis AV, Pladevall M, Riera-Guardia N, Calingaert B, Hazell L, et al. The risk of heart failure associated with the use of noninsulin blood glucose-lowering drugs: systematic review and meta-analysis of published observational studies. BMC Cardiovasc Disord 2014;14:129.
[420] Liu J, Li L, Deng K, Xu C, Busse JW, Vandvik PO, et al. Incretin based treatments and mortality in patients with type 2 diabetes: systematic review and meta-analysis. BMJ 2017;357:j2499.
[421] Scirica BM, Bhatt DL, Braunwald E, Steg PG, Davidson J, Hirshberg B, et al. Saxagliptin and cardiovascular outcomes in patients with type 2 diabetes mellitus. N Engl J Med 2013;369(14):1317–26.
[422] Bethel MA, Patel RA, Merrill P, Lokhnygina Y, Buse JB, Mentz RJ, et al. Cardiovascular outcomes with glucagon-like peptide-1 receptor agonists in patients with type 2 diabetes: a meta-analysis. Lancet Diabetes Endocrinol 2018;6(2):105–13.
[423] Kottgen A, Russell SD, Loehr LR, Crainiceanu CM, Rosamond WD, Chang PP, et al. Reduced kidney function as a risk factor for incident heart failure: the atherosclerosis risk in communities (ARIC) study. J Am Soc Nephrol 2007;18(4):1307–15.
[424] Damman K, Valente MA, Voors AA, O'Connor CM, van Veldhuisen DJ, Hillege HL. Renal impairment, worsening renal function, and outcome in patients with heart failure: an updated meta-analysis. Eur Heart J 2014;35(7):455–69.
[425] Smith GL, Lichtman JH, Bracken MB, Shlipak MG, Phillips CO, DiCapua P, et al. Renal impairment and outcomes in heart failure: systematic review and meta-analysis. J Am Coll Cardiol 2006;47(10):1987–96.
[426] Aldahl M, Jensen AC, Davidsen L, Eriksen MA, Moller Hansen S, Nielsen BJ, et al. Associations of serum potassium levels with mortality in chronic heart failure patients. Eur Heart J 2017;38(38):2890–6.
[427] Gheorghiade M, Abraham WT, Albert NM, Gattis Stough W, Greenberg BH, O'Connor CM, et al. Relationship between admission serum sodium concentration and clinical outcomes in patients hospitalized for heart failure: an analysis from the OPTIMIZE-HF registry. Eur Heart J 2007;28(8):980–8.
[428] Gheorghiade M, Rossi JS, Cotts W, Shin DD, Hellkamp AS, Pina IL, et al. Characterization and prognostic value of persistent hyponatremia in patients with severe heart failure in the ESCAPE trial. Arch Intern Med 2007;167(18):1998–2005.
[429] Konstam MA, Gheorghiade M, Burnett Jr JC, Grinfeld L, Maggioni AP, Swedberg K, et al. Effects of oral tolvaptan in patients hospitalized for worsening heart failure: the EVEREST outcome trial. JAMA 2007;297 (12):1319–31.
[430] Kenchaiah S, Evans JC, Levy D, Wilson PW, Benjamin EJ, Larson MG, et al. Obesity and the risk of heart failure. N Engl J Med 2002;347 (5):305–13.
[431] Padwal R, McAlister FA, McMurray JJ, Cowie MR, Rich M, Pocock S, et al. The obesity paradox in heart failure patients with preserved versus reduced ejection fraction: a meta-analysis of individual patient data. Int J Obes (Lond) 2014;38(8):1110–4.
[432] Gupta PP, Fonarow GC, Horwich TB. Obesity and the obesity paradox in heart failure. Can J Cardiol 2015;31(2):195–202.
[433] Tsujimoto T, Kajio H. Abdominal obesity is associated with an increased risk of all-cause mortality in patients with HFpEF. J Am Coll Cardiol 2017;70(22):2739–49.
[434] Ramani GV, McCloskey C, Ramanathan RC, Mathier MA. Safety and efficacy of bariatric surgery in morbidly obese patients with severe systolic heart failure. Clin Cardiol 2008;31(11):516–20.
[435] Editorial: Heart failure in an ageing population. Lancet 2017;390 (10110):2326.
[436] Apostolovic S, Jankovic-Tomasevic R, Salinger-Martinovic S, Djordjevic-Radojkovic D, Stanojevic D, Pavlovic M, et al. Frequency and significance of unrecognized chronic obstructive pulmonary disease in elderly patients with stable heart failure. Aging Clin Exp Res 2011;23(5-6):337–42.
[437] Rusinaru D, Saaidi I, Godard S, Mahjoub H, Battle C, Tribouilloy C. Impact of chronic obstructive pulmonary disease on long-term outcome of patients hospitalized for heart failure. Am J Cardiol 2008;101 (3):353–8.
[438] Hawkins NM, Petrie MC, Macdonald MR, Jhund PS, Fabbri LM, Wikstrand J, et al. Heart failure and chronic obstructive pulmonary disease the quandary of beta-blockers and beta-agonists. J Am Coll Cardiol 2011;57(21):2127–38.
[439] Ng TM, Munger MA, Lombardi WL, Doing TH, Ryujin DT, Young DC, et al. Chronically inhaled salmeterol improves pulmonary function in heart failure. J Cardiovasc Pharmacol 2002;40(1):140–5.
[440] Jaiswal A, Chichra A, Nguyen VQ, Gadiraju TV, Le Jemtel TH. Challenges in the management of patients with chronic obstructive pulmonary disease and heart failure with reduced ejection fraction. Curr Heart Fail Rep 2016;13(1):30–6.
[441] Etminan M, Jafari S, Carleton B, FitzGerald JM. Beta-blocker use and COPD mortality: a systematic review and meta-analysis. BMC Pulm Med 2012;12:48.
[442] Ni Y, Shi G, Wan H. Use of cardioselective beta-blockers in patients with chronic obstructive pulmonary disease: a meta-analysis of randomized, placebo-controlled, blinded trials. J Int Med Res 2012;40 (6):2051–65.
[443] Lipworth B, Skinner D, Devereux G, Thomas V, Ling Zhi Jie J, Martin J, et al. Underuse of beta-blockers in heart failure and chronic obstructive pulmonary disease. Heart 2016;102(23):1909–14.
[444] Oldenburg O, Lamp B, Faber L, Teschler H, Horstkotte D, Topfer V. Sleep-disordered breathing in patients with symptomatic heart failure: a contemporary study of prevalence in and characteristics of 700 patients. Eur J Heart Fail 2007;9(3):251–7.
[445] Oldenburg O, Wellmann B, Buchholz A, Bitter T, Fox H, Thiem U, et al. Nocturnal hypoxaemia is associated with increased mortality in stable heart failure patients. Eur Heart J 2016;37(21):1695–703.
[446] Khayat R, Jarjoura D, Porter K, Sow A, Wannemacher J, Dohar R, et al. Sleep disordered breathing and post-discharge mortality in patients with acute heart failure. Eur Heart J 2015;36(23):1463–9.

[447] Giles TL, Lasserson TJ, Smith BH, White J, Wright J, Cates CJ. Continuous positive airways pressure for obstructive sleep apnoea in adults. Cochrane Database Syst Rev):2006;(3)CD001106.
[448] Bradley TD, Logan AG, Kimoff RJ, Series F, Morrison D, Ferguson K, et al. Continuous positive airway pressure for central sleep apnea and heart failure. N Engl J Med 2005;353(19):2025–33.
[449] Cowie MR, Woehrle H, Wegscheider K, Angermann C, d'Ortho M-P, Erdmann E, et al. Adaptive servo-ventilation for central sleep apnea in systolic heart failure. N Engl J Med 2015;373(12):1095–105.
[450] Sun H, Shi J, Li M, Chen X. Impact of continuous positive airway pressure treatment on left ventricular ejection fraction in patients with obstructive sleep apnea: a meta-analysis of randomized controlled trials. PloS One 2013;8(5):e62298.
[451] McEvoy RD, Antic NA, Heeley E, Luo Y, Ou Q, Zhang X, et al. CPAP for prevention of cardiovascular events in obstructive sleep apnea. N Engl J Med 2016;375(10):919–31.
[452] Walsh JT, Andrews R, Starling R, Cowley AJ, Johnston ID, Kinnear WJ. Effects of captopril and oxygen on sleep apnoea in patients with mild to moderate congestive cardiac failure. Br Heart J 1995;73(3):237–41.
[453] Tamura A, Kawano Y, Naono S, Kotoku M, Kadota J. Relationship between beta-blocker treatment and the severity of central sleep apnea in chronic heart failure. Chest 2007;131(1):130–5.
[454] Costanzo MR, Ponikowski P, Javaheri S, Augostini R, Goldberg L, Holcomb R, et al. Transvenous neurostimulation for central sleep apnoea: a randomised controlled trial. Lancet 2016;388(10048):974–82.
[455] Oksenberg A, Gadoth N. Are we missing a simple treatment for most adult sleep apnea patients? The avoidance of the supine sleep position. J Sleep Res 2014;23(2):204–10.
[456] Basoglu OK, Keskin B, Tasbakan MS, Gurgun C. Effect of semirecumbent sleep position on severity of obstructive sleep apnea in patients with heart failure. J Card Fail 2015;21(10):842–7.
[457] Pinna GD, Robbi E, La Rovere MT, Taurino AE, Bruschi C, Guazzotti G, et al. Differential impact of body position on the severity of disordered breathing in heart failure patients with obstructive vs. central sleep apnoea. Eur J Heart Fail 2015;17(12):1302–9.
[458] Javaheri S. Acetazolamide improves central sleep apnea in heart failure: a double-blind, prospective study. Am J Respir Crit Care Med 2006;173(2):234–7.
[459] Krishnan E. Gout and the risk for incident heart failure and systolic dysfunction. BMJ Open 2012;2(1):e000282.
[460] Okafor ON, Farrington K, Gorog DA. Allopurinol as a therapeutic option in cardiovascular disease. Pharmacol Ther 2017;172:139–50.
[461] Anker SD, Doehner W, Rauchhaus M, Sharma R, Francis D, Knosalla C, et al. Uric acid and survival in chronic heart failure: validation and application in metabolic, functional, and hemodynamic staging. Circulation 2003;107(15):1991–7.
[462] Scott PA, Kingsley GH. D.L.S. Non-steroidal anti-inflammatory drugs and cardiac failure: meta-analyses of observational studies and randomised controlled trials. Eur J Heart Fail 2008;10:1102–7.
[463] Bardin T, Richette P. Impact of comorbidities on gout and hyperuricaemia: an update on prevalence and treatment options. BMC Med 2017;15(1):123.
[464] Hare JM, Mangal B, Brown J, Fisher Jr C, Freudenberger R, Colucci WS, et al. Impact of oxypurinol in patients with symptomatic heart failure. Results of the OPT-CHF study. J Am Coll Cardiol 2008;51 (24):2301–9.
[465] Givertz MM, Anstrom KJ, Redfield MM, Deswal A, Haddad H, Butler J, et al. Effects of xanthine oxidase inhibition in hyperuricemic heart failure patients: the Xanthine Oxidase Inhibition for Hyperuricemic Heart Failure Patients (EXACT-HF) study. Circulation 2015;131 (20):1763–71.
[466] Page J, Henry D. Consumption of NSAIDs and the development of congestive heart failure in elderly patients: an underrecognized public health problem. Arch Intern Med 2000;160(6):777–84.
[467] Meinert CL, McCaffrey LD, Breitner JC. Alzheimer's Disease Anti-inflammatory Prevention Trial: design, methods, and baseline results. Alzheimers Dement 2009;5(2):93–104.
[468] Bertagnolli MM, Eagle CJ, Zauber AG, Redston M, Breazna A, Kim K, et al. Five-year efficacy and safety analysis of the adenoma prevention with celecoxib trial. Cancer Prev Res Phila 2009;2(4):310–21.
[469] Wolfe F, Michaud K. Heart failure in rheumatoid arthritis: rates, predictors, and the effect of anti–tumor necrosis factor therapy. Am J Med 2004;116:305–11.
[470] Gullestad L. Review of trials in chronic heart failure showing broad-spectrum anti-inflammatory approaches. Am J Cardiol 2005;95:17C–23C. discussion 38C–40C.
[471] Rutledge T, Reis VA, Linke SE, Greenberg BH, Mills PJ. Depression in heart failure a meta-analytic review of prevalence, intervention effects, and associations with clinical outcomes. J Am Coll Cardiol 2006;48 (8):1527–37.
[472] Gustad LT, Laugsand LE, Janszky I, Dalen H, Bjerkeset O. Symptoms of anxiety and depression and risk of heart failure: the HUNT study. Eur J Heart Fail 2014;16(8):861–70.
[473] Faris R, Purcell H, Henein MY, Coats AJ. Clinical depression is common and significantly associated with reduced survival in patients with non-ischaemic heart failure. Eur J Heart Fail 2002;4(4):541–51.
[474] Lichtman JH, Bigger Jr JT, Blumenthal JA, Frasure-Smith N, Kaufmann PG, Lesperance F, et al. Depression and coronary heart disease: Recommendations for screening, referral, and treatment: a science advisory from the American Heart Association Prevention Committee of the Council on Cardiovascular Nursing, Council on Clinical Cardiology, Council on Epidemiology and Prevention, and Interdisciplinary Council on Quality of Care and Outcomes Research: endorsed by the American Psychiatric Association. Circulation 2008;118(17):1768–75.
[475] Freedland KE, Carney RM, Rich MW, Steinmeyer BC, Rubin EH. Cognitive behavior therapy for depression and self-care in heart failure patients: a randomized clinical trial. JAMA Intern Med 2015;175 (11):1773–82.
[476] Jeyanantham K, Kotecha D, Thanki D, Dekker R, Lane DA. Effects of cognitive behavioural therapy for depression in heart failure patients: a systematic review and meta-analysis. Heart Fail Rev 2017.
[477] O'Connor CM, Jiang W, Kuchibhatla M, Silva SG, Cuffe MS, Callwood DD, et al. Safety and efficacy of sertraline for depression in patients with heart failure: results of the SADHART-CHF (Sertraline Against Depression and Heart Disease in Chronic Heart Failure) trial. J Am Coll Cardiol 2010;56(9):692–9.
[478] Angermann CE, Gelbrich G, Stork S, Gunold H, Edelmann F, Wachter R, et al. Effect of escitalopram on all-cause mortality and hospitalization in patients with heart failure and depression: the MOOD-HF randomized clinical trial. JAMA 2016;315(24):2683–93.
[479] Tu RH, Zeng ZY, Zhong GQ, Wu WF, Lu YJ, Bo ZD, et al. Effects of exercise training on depression in patients with heart failure: a systematic review and meta-analysis of randomized controlled trials. Eur J Heart Fail 2014;16(7):749–57.
[480] World Health Organization. Haemoglobin concentrations for the diagnosis of anaemia and assessment of severity. In: Vitamin and Mineral Nutrition Information System (VMNIS). Geneva: World Health Organization; 2011.
[481] Ather S, Chan W, Bozkurt B, Aguilar D, Ramasubbu K, Zachariah AA, et al. Impact of noncardiac comorbidities on morbidity and mortality in a predominantly male population with heart failure and preserved versus reduced ejection fraction. J Am Coll Cardiol 2012;59(11):998–1005.
[482] Groenveld HF, Januzzi JL, Damman K, van Wijngaarden J, Hillege HL, van Veldhuisen DJ, et al. Anemia and mortality in heart failure patients a systematic review and meta-analysis. J Am Coll Cardiol 2008;52 (10):818–27.
[483] Ebner N, Jankowska EA, Ponikowski P, Lainscak M, Elsner S, Sliziuk V, et al. The impact of iron deficiency and anaemia on exercise capacity and outcomes in patients with chronic heart failure. Results from the Studies Investigating Co-morbidities Aggravating Heart Failure. Int J Cardiol 2016;205:6–12.
[484] Adams Jr KF, Pina IL, Ghali JK, Wagoner LE, Dunlap SH, Schwartz TA, et al. Prospective evaluation of the association between hemoglobin concentration and quality of life in patients with heart failure. Am Heart J 2009;158(6):965–71.
[485] Abramov D, Cohen RS, Katz SD, Mancini D, Maurer MS. Comparison of blood volume characteristics in anemic patients with low versus preserved left ventricular ejection fractions. Am J Cardiol 2008;102 (8):1069–72.
[486] Kotecha D, Ngo K, Walters JA, Manzano L, Palazzuoli A, Flather MD. Erythropoietin as a treatment of anemia in heart failure: systematic review of randomized trials. Am Heart J 2011;161(5):822–31.
[487] Swedberg K, Young JB, Anand IS, Cheng S, Desai AS, Diaz R, et al. Treatment of anemia with darbepoetin alfa in systolic heart failure. N Engl J Med 2013;368(13):1210–9.
[488] Klip IT, Comin-Colet J, Voors AA, Ponikowski P, Enjuanes C, Banasiak W, et al. Iron deficiency in chronic heart failure: an international pooled analysis. Am Heart J 2013;165(4):575–82.
[489] Jankowska EA, Rozentryt P, Witkowska A, Nowak J, Hartmann O, Ponikowska B, et al. Iron deficiency: an ominous sign in patients with systolic chronic heart failure. Eur Heart J 2010;31(15):1872–80.

[490] Jankowska EA, Tkaczyszyn M, Suchocki T, Drozd M, von Haehling S, Doehner W, 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.
[491] van Veldhuisen DJ, Ponikowski P, van der Meer P, Metra M, Bohm M, Doletsky A, et al. Effect of ferric carboxymaltose on exercise capacity in patients with chronic heart failure and iron deficiency. Circulation 2017;136(15):1374–83.
[492] Saraon T, Katz SD. Targeting iron deficiency anemia in heart failure. Prog Cardiovasc Dis 2016;58(4):407–15.
[493] Lewis GD, Malhotra R, Hernandez AF, McNulty SE, Smith A, Felker GM, et al. Effect of oral iron repletion on exercise capacity in patients with heart failure with reduced ejection fraction and iron deficiency: the IRONOUT HF randomized clinical trial. JAMA 2017;317(19):1958–66.
[494] Ponikowski P, van Veldhuisen DJ, Comin-Colet J, Ertl G, Komajda M, Mareev V, et al. Rationale and design of the CONFIRM-HF study: a double-blind, randomized, placebo-controlled study to assess the effects of intravenous ferric carboxymaltose on functional capacity in patients with chronic heart failure and iron deficiency. ESC Heart Fail 2014;1(1):52–8.
[495] Howlader N, Ries LA, Mariotto AB, Reichman ME, Ruhl J, Cronin KA. Improved estimates of cancer-specific survival rates from population-based data. J Natl Cancer Inst 2010;102(20):1584–98.
[496] Jemal A, Ward E, Thun M. Declining death rates reflect progress against cancer. PloS One 2010;5(3):e9584.
[497] Plana JC, Galderisi M, Barac A, Ewer MS, Ky B, Scherrer-Crosbie M, et al. Expert consensus for multimodality imaging evaluation of adult patients during and after cancer therapy: a report from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. J Am Soc Echocardiogr 2014;27(9):911–39.
[498] Lenneman CG, Sawyer DB. Cardio-Oncology. An update on cardiotoxicity of cancer-related treatment. Circ Res 2016;118(6):1008–20.
[499] Ewer MS, Ewer SM. Cardiotoxicity of anticancer treatments. Nat Rev Cardiol 2015;12(9):547–58.
[500] Vasanthakumar A, Kattusamy K, Prasad R. Regulation of daunorubicin biosynthesis in Streptomyces peucetius –feed forward and feedback transcriptional control. J Basic Microbiol 2013;53(8):636–44.
[501] Horenstein MS, Vander Heide RS, L'Ecuyer TJ. Molecular basis of anthracycline-induced cardiotoxicity and its prevention. Mol Genet Metab 2000;71(1–2):436–44.
[502] Zhang S, Liu X, Bawa-Khalfe T, Lu LS, Lyu YL, Liu LF, et al. Identification of the molecular basis of doxorubicin-induced cardiotoxicity. Nat Med 2012;18(11):1639–42.
[503] McCaffrey TA, Tziros C, Lewis J, Katz R, Siegel R, Weglicki W, et al. Genomic profiling reveals the potential role of TCL1A and MDR1 deficiency in chemotherapy-induced cardiotoxicity. Int J Biol Sci 2013;9(4):350–60.
[504] De Angelis A, Piegari E, Cappetta D, Marino L, Filippelli A, Berrino L, et al. Anthracycline cardiomyopathy is mediated by depletion of the cardiac stem cell pool and is rescued by restoration of progenitor cell function. Circulation 2010;121(2):276–92.
[505] Nuver J, Smit AJ, van der Meer J, van den Berg MP, van der Graaf WT, Meinardi MT, et al. Acute chemotherapy-induced cardiovascular changes in patients with testicular cancer. J Clin Oncol 2005;23(36):9130–7.
[506] Haugnes HS, Wethal T, Aass N, Dahl O, Klepp O, Langberg CW, et al. Cardiovascular risk factors and morbidity in long-term survivors of testicular cancer: a 20-year follow-up study. J Clin Oncol 2010;28(30):4649–57.
[507] Ma H, Jones KR, Guo R, Xu P, Shen Y, Ren J. Cisplatin compromises myocardial contractile function and mitochondrial ultrastructure: role of endoplasmic reticulum stress. Clin Exp Pharmacol Physiol 2010;37(4):460–5.
[508] Alter P, Herzum M, Soufi M, Schaefer JR, Maisch B. Cardiotoxicity of 5-fluorouracil. Cardiovasc Hematol Agents Med Chem 2006;4(1):1–5.
[509] Rowinsky EK, Eisenhauer EA, Chaudhry V, Arbuck SG, Donehower RC. Clinical toxicities encountered with paclitaxel (Taxol). Semin Oncol 1993;20(4 Suppl 3):1–15.
[510] Ky B, Putt M, Sawaya H, French B, Januzzi Jr JL, Sebag IA, et al. Early increases in multiple biomarkers predict subsequent cardiotoxicity in patients with breast cancer treated with doxorubicin, taxanes, and trastuzumab. J Am Coll Cardiol 2014;63(8):809–16.
[511] Dow E, Schulman H, Agura E. Cyclophosphamide cardiac injury mimicking acute myocardial infarction. Bone marrow transplant 1993;12(2):169–72.
[512] Crone SA, Zhao YY, Fan L, Gu Y, Minamisawa S, Liu Y, et al. ErbB2 is essential in the prevention of dilated cardiomyopathy. Nat Med 2002;8(5):459–65.
[513] Lenneman CG, Abdallah WM, Smith HM, Abramson V, Mayer IA, Silverstein C, et al. Sympathetic nervous system alterations with HER2 + antagonism: an early marker of cardiac dysfunction with breast cancer treatment? Ecancermedicalscience 2014;8:446.
[514] Slamon DJ, Leyland-Jones B, Shak S, Fuchs H, Paton V, Bajamonde A, et al. Use of chemotherapy plus a monoclonal antibody against HER2 for metastatic breast cancer that overexpresses HER2. N Engl J Med 2001;344(11):783–92.
[515] Moudgil R, Yeh ET. Mechanisms of cardiotoxicity of cancer chemotherapeutic agents: cardiomyopathy and beyond. Can J Cardiol 2016;32(7):863–70.
[516] Demetri GD, van Oosterom AT, Garrett CR, Blackstein ME, Shah MH, Verweij J, et al. Efficacy and safety of sunitinib in patients with advanced gastrointestinal stromal tumour after failure of imatinib: a randomised controlled trial. Lancet 2006;368(9544):1329–38.
[517] Scappaticci FA, Skillings JR, Holden SN, Gerber HP, Miller K, Kabbinavar F, et al. Arterial thromboembolic events in patients with metastatic carcinoma treated with chemotherapy and bevacizumab. J Natl Cancer Inst 2007;99(16):1232–9.
[518] Izumiya Y, Shiojima I, Sato K, Sawyer DB, Colucci WS, Walsh K. Vascular endothelial growth factor blockade promotes the transition from compensatory cardiac hypertrophy to failure in response to pressure overload. Hypertension 2006;47(5):887–93.
[519] Chu TF, Rupnick MA, Kerkela R, Dallabrida SM, Zurakowski D, Nguyen L, et al. Cardiotoxicity associated with tyrosine kinase inhibitor sunitinib. Lancet 2007;370(9604):2011–9.
[520] Ghatalia P, Morgan CJ, Je Y, Nguyen PL, Trinh QD, Choueiri TK, et al. Congestive heart failure with vascular endothelial growth factor receptor tyrosine kinase inhibitors. Crit Rev Oncol Hematol 2015;94(2):228–37.
[521] Armstrong GT, Kawashima T, Leisenring W, Stratton K, Stovall M, Hudson MM, et al. Aging and risk of severe, disabling, life-threatening, and fatal events in the childhood cancer survivor study. J Clin Oncol 2014;32(12):1218–27.
[522] Slamon D, Eiermann W, Robert N, Pienkowski T, Martin M, Press M, et al. Adjuvant trastuzumab in HER2-positive breast cancer. N Engl J Med 2011;365(14):1273–83.
[523] Pinder MC, Duan Z, Goodwin JS, Hortobagyi GN, Giordano SH. Congestive heart failure in older women treated with adjuvant anthracycline chemotherapy for breast cancer. J Clin Oncol 2007;25(25):3808–15.
[524] Curigliano G, Cardinale D, Dent S, Criscitiello C, Aseyev O, Lenihan D, et al. Cardiotoxicity of anticancer treatments: epidemiology, detection, and management. CA Cancer J Clin 2016;66(4):309–25.
[525] Swain SM, Whaley FS, Ewer MS. Congestive heart failure in patients treated with doxorubicin: a retrospective analysis of three trials. Cancer 2003;97(11):2869–79.
[526] Franzon J, Berry NM, Ullah S, Versace VL, McCarthy AL, Atherton J, et al. Heart failure following blood cancer therapy in pediatric and adult populations. Asia Pac J Clin Oncol 2017.
[527] Crozier JA, Swaika A, Moreno-Aspitia A. Adjuvant chemotherapy in breast cancer: to use or not to use, the anthracyclines. World J Clin Oncol 2014;5(3):529–38.
[528] Cardinale D, Sandri MT, Colombo A, Colombo N, Boeri M, Lamantia G, et al. Prognostic value of troponin I in cardiac risk stratification of cancer patients undergoing high-dose chemotherapy. Circulation 2004;109(22):2749–54.
[529] Colombo A, Sandri MT, Salvatici M, Cipolla CM, Cardinale D. Cardiac complications of chemotherapy: Role of biomarkers. Curr Treat Options Cardiovasc Med 2014;16(6):313.
[530] Hequet O, Le QH, Moullet I, Pauli E, Salles G, Espinouse D, et al. Subclinical late cardiomyopathy after doxorubicin therapy for lymphoma in adults. J Clin Oncol 2004;22(10):1864–71.
[531] Thavendiranathan P, Poulin F, Lim KD, Plana JC, Woo A, Marwick TH. Use of myocardial strain imaging by echocardiography for the early detection of cardiotoxicity in patients during and after cancer chemotherapy: a systematic review. AJ Am Coll Cardiol 2014;63(25 Pt A):2751–68.
[532] Fallah-Rad N, Walker JR, Wassef A, Lytwyn M, Bohonis S, Fang T, et al. The utility of cardiac biomarkers, tissue velocity and strain imaging, and cardiac magnetic resonance imaging in predicting early left ventricular dysfunction in patients with human epidermal growth factor receptor II-positive breast cancer treated with adjuvant trastuzumab therapy. J Am Coll Cardiol 2011;57(22):2263–70.

[533] Boyd A, Stoodley P, Richards D, Hui R, Harnett P, Vo K, et al. Anthracyclines induce early changes in left ventricular systolic and diastolic function: a single centre study. PloS One 2017;12(4): e0175544.
[534] Negishi K, Negishi T, Hare JL, Haluska BA, Plana JC, Marwick TH. Independent and incremental value of deformation indices for prediction of trastuzumab-induced cardiotoxicity. J Am Soc Echocardiogr 2013;26(5):493–8.
[535] Thavendiranathan P, Wintersperger BJ, Flamm SD, Marwick TH. Cardiac MRI in the assessment of cardiac injury and toxicity from cancer chemotherapy: a systematic review. Circ Cardiovasc Imaging 2013;6 (6):1080–91.
[536] Lightfoot JC, D'Agostino Jr RB, Hamilton CA, Jordan J, Torti FM, Kock ND, et al. Novel approach to early detection of doxorubicin cardiotoxicity by gadolinium-enhanced cardiovascular magnetic resonance imaging in an experimental model. Circ Cardiovasc Imaging 2010;3 (5):550–8.
[537] Wassmuth R, Lentzsch S, Erdbruegger U, Schulz-Menger J, Doerken B, Dietz R, et al. Subclinical cardiotoxic effects of anthracyclines as assessed by magnetic resonance imaging—a pilot study. Am Heart J 2001;141(6):1007–13.
[538] Jordan JH, D'Agostino Jr RB, Hamilton CA, Vasu S, Hall ME, Kitzman DW, et al. Longitudinal assessment of concurrent changes in left ventricular ejection fraction and left ventricular myocardial tissue characteristics after administration of cardiotoxic chemotherapies using T1-weighted and T2-weighted cardiovascular magnetic resonance. Circ Cardiovasc Imaging 2014;7(6):872–9.
[539] Cottin Y, Ribuot C, Maupoil V, Godin D, Arnould L, Brunotte F, et al. Early incidence of adriamycin treatment on cardiac parameters in the rat. Can J Physiol Pharmacol 1994;72(2):140–5.
[540] Hensley ML, Hagerty KL, Kewalramani T, Green DM, Meropol NJ, Wasserman TH, et al. American Society of Clinical Oncology 2008 clinical practice guideline update: use of chemotherapy and radiation therapy protectants. J Clin Oncol 2009;27(1):127–45.
[541] Ammon M, Arenja N, Leibundgut G, Buechel RR, Kuster GM, Kaufmann BA, et al. Cardiovascular management of cancer patients with chemotherapy-associated left ventricular systolic dysfunction in real-world clinical practice. J Card Fail 2013;19(9):629–34.
[542] Cardinale D, Colombo A, Lamantia G, Colombo N, Civelli M, De Giacomi G, et al. Anthracycline-induced cardiomyopathy: clinical relevance and response to pharmacologic therapy. J Am Coll Cardiol 2010;55(3):213–20.
[543] Kalay N, Basar E, Ozdogru I, Er O, Cetinkaya Y, Dogan A, et al. Protective effects of carvedilol against anthracycline-induced cardiomyopathy. J Am Coll Cardiol 2006;48(11):2258–62.
[544] Kaya MG, Ozkan M, Gunebakmaz O, Akkaya H, Kaya EG, Akpek M, et al. Protective effects of nebivolol against anthracycline-induced cardiomyopathy: a randomized control study. Int J Cardiol 2013;167 (5):2306–10.
[545] Mostafavi Toroghi A, Hosseini H, Zarifian G, Homaei Shandiz A, Fazlinezhad F. Carvedilol administration can prevent doxorubicin-induced cardiotoxicity: a double-blind randomized trial. Cardiology 2016;134(1):47–53.
[546] Akpek M, Ozdogru I, Sahin O, Inanc M, Dogan A, Yazici C, et al. Protective effects of spironolactone against anthracycline-induced cardiomyopathy. Eur J Heart Fail 2015;17(1):81–9.
[547] Acar Z, Kale A, Turgut M, Demircan S, Durna K, Demir S, et al. Efficiency of atorvastatin in the protection of anthracycline-induced cardiomyopathy. J Am Coll Cardiol 2011;58(9):988–9.
[548] Boekhout AH, Gietema JA, Milojkovic Kerklaan B, van Werkhoven ED, Altena R, Honkoop A, et al. Angiotensin II-receptor inhibition with candesartan to prevent trastuzumab-related cardiotoxic effects in patients with early breast cancer: a randomized clinical trial. JAMA Oncol 2016;2(8):1030–7.
[549] Cadeddu C, Piras A, Mantovani G, Deidda M, Dessi M, Madeddu C, et al. Protective effects of the angiotensin II receptor blocker telmisartan on epirubicin-induced inflammation, oxidative stress, and early ventricular impairment. Am Heart J 2010;160(3):487. e1–7.
[550] Dessi M, Madeddu C, Piras A, Cadeddu C, Antoni G, Mercuro G, et al. Long-term, up to 18 months, protective effects of the angiotensin II receptor blocker telmisartan on Epirubin-induced inflammation and oxidative stress assessed by serial strain rate. Springerplus 2013;2 (1):198.
[551] Georgakopoulos P, Roussou P, Matsakas E, Karavidas A, Anagnostopoulos N, Marinakis T, et al. Cardioprotective effect of metoprolol and enalapril in doxorubicin-treated lymphoma patients: a prospective, parallel-group, randomized, controlled study with 36-month follow-up. Am J Hematol 2010;85(11):894–6.
[552] Pituskin E, Mackey JR, Koshman S, Jassal D, Pitz M, Haykowsky MJ, et al. Multidisciplinary Approach to Novel Therapies in Cardio-Oncology Research (MANTICORE 101-Breast): a randomized trial for the prevention of trastuzumab-associated cardiotoxicity. J Clin Oncol 2017;35(8):870–7.
[553] Cardinale D, Colombo A, Sandri MT, Lamantia G, Colombo N, Civelli M, et al. Prevention of high-dose chemotherapy-induced cardiotoxicity in high-risk patients by angiotensin-converting enzyme inhibition. Circulation 2006;114(23):2474–81.
[554] Gulati G, Heck SL, Ree AH, Hoffmann P, Schulz-Menger J, Fagerland MW, et al. Prevention of cardiac dysfunction during adjuvant breast cancer therapy (PRADA): A 2 × 2 factorial, randomized, placebo-controlled, double-blind clinical trial of candesartan and metoprolol. Eur Heart J 2016;37(21):1671–80.
[555] Elitok A, Oz F, Cizgici AY, Kilic L, Ciftci R, Sen F, et al. Effect of carvedilol on silent anthracycline-induced cardiotoxicity assessed by strain imaging: a prospective randomized controlled study with six-month follow-up. Cardiol J 2014;21(5):509–15.
[556] Hopper I, Samuel R, Hayward C, Tonkin A, Krum H. Can medications be safely withdrawn in patients with stable chronic heart failure? Systematic review and meta-analysis. J Card Fail 2014;20(7):522–32.
[557] Austroads Assessing Fitness to Drive for commercial and private vehicledrivers (2016). Medical standards for licensing and clinical management guidelines –A resource for health professionals in Australia. As amended up to August 2017. Available at: https://www.onlinepublications.austroads.com.au/items/AP-G56-17. Accessed 22/2/18.
[558] Hobkirk JP, Damy T, Walters M, Bennett A, Smith SJ, Ingle L, et al. Effects of reducing inspired oxygen concentration for one hour in patients with chronic heart failure: implications for air travel. Eur J Heart Fail 2013;15(5):505–10.
[559] Smith D, Toff W, Joy M, Dowdall N, Johnston R, Clark L, et al. Fitness to fly for passengers with cardiovascular disease. Heart 2010;96(Suppl 2):ii1–16.
[560] Kadoglou NPE, Bracke F, Simmers T, Tsiodras S, Parissis J. Influenza infection and heart failure-vaccination may change heart failure prognosis? Heart Fail Rev 2017;22(3):329–36.
[561] Fischer S, Bekelman D. Gender differences in sexual interest or activity among adults with symptomatic heart failure. J Palliat Med 2017;20 (8):890–4.
[562] Levine GN, Steinke EE, Bakaeen FG, Bozkurt B, Cheitlin MD, Conti JB, et al. Sexual activity and cardiovascular disease: A scientific statement from the American Heart Association. Circulation 2012;125(8):1058–72.
[563] Jaarsma T. Sexual function of patients with heart failure: Facts and numbers. ESC Heart Fail 2017;4(1):3–7.
[564] Grewal J, Siu SC, Ross HJ, Mason J, Balint OH, Sermer M, et al. Pregnancy outcomes in women with dilated cardiomyopathy. J Am Coll Cardiol 2009;55(1):45–52.
[565] (ESC) ESoC. ESC guidelines on the management of cardiovascular diseases during pregnancy. Eur Heart J 2011;32:3147–97.
[566] Elkayam U, Tummala PP, Rao K, Akhter MW, Karaalp IS, Wani OR, et al. Maternal and fetal outcomes of subsequent pregnancies in women with peripartum cardiomyopathy. N Engl J Med 2001;344 (21):1567–71.
[567] Sedlak T, Bairey Merz CN, Shufelt C, Gregory KD, Hamilton MA. Contraception in patients with heart failure. Circulation 2012;126 (11):1396–400.
[568] Balmain BN, Sabapathy S, Jay O, Adsett J, Stewart GM, Jayasinghe R, et al. Heart failure and thermoregulatory control: can patients with heart failure handle the heat? J Card Fail 2017;23(8):621–7.
[569] Nitschke M, Tucker GR, Bi P. Morbidity and mortality during heatwaves in metropolitan Adelaide. Med J Aust 2007;187(11–12): 662–5.
[570] Inglis SC, Clark RA, Shakib S, Wong DT, Molaee P, Wilkinson D, et al. Hot summers and heart failure: seasonal variations in morbidity and mortality in Australian heart failure patients (1994–2005). Eur J Heart Fail 2008;10(6):540–9.
[571] Mostofsky E, Rice MS, Levitan EB, Mittleman MA. Habitual coffee consumption and risk of heart failure: a dose–response meta-analysis. Circulation Heart Fail 2012;5(4):401–5.
[572] O'Keefe JH, Bhatti SK, Patil HR, DiNicolantonio JJ, Lucan SC, Lavie CJ. Effects of habitual coffee consumption on cardiometabolic disease, cardiovascular health, and all-cause mortality. J Am Coll Cardiol 2013;62(12):1043–51.

[573] Liu L, Eisen HJ. Epidemiology of heart failure and scope of the problem. Cardiol Clin 2014;32(1):1–8. vii.
[574] Evangelista LS, Lombardo D, Malik S, Ballard-Hernandez J, Motie M, Liao S. Examining the effects of an outpatient palliative care consultation on symptom burden, depression, and quality of life in patients with symptomatic heart failure. J Card Fail 2012;18(12): 894–9.
[575] Buck HG, Zambroski CH. Upstreaming palliative care for patients with heart failure. J Cardiovasc Nurs 2012;27(2):147–53.
[576] Adler ED, Goldfinger JZ, Kalman J, Park ME, Meier DE. Palliative care in the treatment of advanced heart failure. Circulation 2009;120 (25):2597–606.
[577] Bakitas M, Macmartin M, Trzepkowski K, Robert A, Jackson L, Brown JR, et al. Palliative care consultations for heart failure patients: how many, when, and why? J Card Fail 2013;19(3):193–201.
[578] Fernandes S, Guthrie DM. A comparison between end-of-life home care clients with cancer and heart failure in Ontario. Home Health Care Serv Q 2015;34(1):14–29.
[579] Greener DT, Quill T, Amir O, Szydlowski J, Gramling RE. Palliative care referral among patients hospitalized with advanced heart failure. J Palliat Med 2014;17(10):1115–20.
[580] Kavalieratos D, Corbelli J, Zhang D, Dionne-Odom JN, Ernecoff NC, Hanmer J, et al. Association between palliative care and patient and caregiver outcomes: a systematic review and meta-analysis. JAMA 2016;316(20):2104–14.
[581] Brannstrom M, Boman K. Effects of person-centred and integrated chronic heart failure and palliative home care: PREFER: a randomized controlled study. Eur J Heart Fail 2014;16(10):1142–51.
[582] Rogers JG, Patel CB, Mentz RJ, Granger BB, Steinhauser KE, Fiuzat M, et al. Palliative care in heart failure: the PAL-HF Randomized, Controlled Clinical Trial. J Am Coll Cardiol 2017;70(3):331–41.
[583] Sidebottom AC, Jorgenson A, Richards H, Kirven J, Sillah A. Inpatient palliative care for patients with acute heart failure: outcomes from a randomized trial. J Palliat Med 2015;18(2):134–42.
[584] Wong FK, Ng AY, Lee PH, Lam PT, Ng JS, Ng NH, et al. Effects of a transitional palliative care model on patients with end-stage heart failure: a randomised controlled trial. Heart 2016;102(14): 1100–8.
[585] Brumley R, Enguidanos S, Jamison P, Seitz R, Morgenstern N, Saito S, et al. Increased satisfaction with care and lower costs: results of a randomized trial of in-home palliative care. J Am Geriatr Soc 2007;55(7):993–1000.
[586] Diop MS, Rudolph JL, Zimmerman KM, Richter MA, Skarf LM. Palliative Care Interventions for Patients with Heart Failure: a Systematic Review and Meta-Analysis. J Palliat Med 2017;20(1):84–92.
[587] Fonarow GC, Albert NM, Curtis AB, Gheorghiade M, Heywood JT, Liu Y, et al. Associations between outpatient heart failure process-of-care measures and mortality. Circulation 2011;123(15):1601–10.
[588] Ouwerkerk W, Voors AA, Anker SD, Cleland JG, Dickstein K, Filippatos G, et al. Determinants and clinical outcome of uptitration of ACE-inhibitor and beta-blocker in patients with heart failure: a prospective European study. Eur Heart J 2017;38(243):1883–90.
[589] Komajda M, Cowie MR, Tavazzi L, Ponikowski P, Anker SD, Filippatos GS, et al. Physicians' guideline adherence is associated with better prognosis in outpatients with heart failure with reduced ejection fraction: the QUALIFY international registry. Eur J Heart Fail 2017;19 (11):1414–23.