CHRONIC HEART FAILURE: THERAPY

Heart Failure with Reduced LVEF

General Measures

Certain measures may prevent or reduce the risk of heart failure (Tables 1 and 2).[1] Regular **aerobic exercise** is beneficial for patients with stable, non-decompensated heart failure, through various mechanisms.[2] Progressive **rehabilitation** intervention is also useful in patients who were hospitalized for acute decompensated heart failure.[3] **Salt restriction** is usually advisable, especially in patients with stage C and D, although a restriction to less than 100 mmol (<1500 mg/day) did not reduce clinical events.[4] **Potassium** levels in the intervals 2.8–4.1 mmol/L and 4.8–7.4 mmol/L are associated with an increased short-term mortality in chronic heart failure patients, compared with the reference interval of 4.2–4.4 mmol/L.[5] **Fluid restriction** to 1,5-2 L/day may be considered only in patients with severe symptoms and hyponatremia. **Weight loss** is advisable, especially in patients with coronary artery disease, and weight loss and decreases the risk of heart failure, but extreme wasting is an independent risk factor.[6, 7] **Alcohol** has a direct toxicity on myocardium and at high doses may cause hypertension and arrhythmias. It should be restricted to 2 units a day, and avoided in alcohol-related dilated cardiomyopathy. **Smoking cessation, avoidance of high altitude** (>1500 m), and **vaccination against influenza** and **pneumoniococcus** are recommended. **Pregnancy** carries a high risk in patients with heart failure, and any decision should be discussed on an individual basis. **Contraception** with combined hormonal contraceptives is contraindicated due to fluid retention and increased thrombotic risk. Progesteron-only forms are probably safer but still carry a risk of thrombotic risk and osteopenia.[8] Copper intrauterine devices or transcervical tubal occlusion are relatively safer.[8] **Sexual activity** is prohibited only in decompensated or advanced heart failure until stabilization.[9] Patients with **diabetes** should appropriately treated for blood pressure, lipid and glycaemic control, but avoiding hypoglycaemia potentially associated with drug therapy targeting a HbAc1<6.5.[10 6] *Metformin* can be used as long as LV dysfunction is not severe and renal function adequate (creatinine >1.5 mg/dl in men and >1.4 mg/dl in women).[11] *Sodium glucose transporter-2 inhibitors* reduce cardiovascular and total mortality in this setting as well as in patients without diabetes (see Drug Therapy). *Thiazolidinediones* may increase the risk of heart failure and should not be used in patients with symptomatic heart failure.[12] Saxagliptin and alogliptin, selective inhibitors of dipeptidyl peptidase 4 (*DPP-4*), have also been shown to increase the rate of hospitalization for heart failure in most trials.[13] **Non-steroidal anti-inflammatory drugs (**and especially **selective COX-2 inhibitors)** as well as **corticosteroids** and **herbal preparations** (licorice, ginseng, ma huang) cause salt and water retention and should be used with much

caution. In gout attacks **colchicine** is preferred to NSAIDs in symptomatic heart failure patients. **Aspirin** and other indicated antiplatelet agents, when indicated, should be continued in ischemic patients. Although there has been some evidence that aspirin may interfere with prostaglandin synthesis, leading to a reduced effectiveness of ACE inhibition, the clinical significance of this observation is negligible.[14-16] **Tricyclic antidepressants** are contraindicated due to proarrhythmic potential. The value of enhancement of **erythropoiesis** in anemia is controversial. Erythropoiesis stimulation with darbepoetin alfa corrects hemoglobin deficiency in systolic heart failure but fails to improve mortality or hospitalization rates and may increase thromboembolic risk.[17] A recent report by the American College of Physicians recommends against the use of erythropoiesis-stimulating agents in patients with mild to moderate anaemia and congestive heart failure or coronary heart disease.[18] **Iron deficiency** (ferritin <100 ng/mL or 100–300 ng/mL if transferrin saturation <20%) should be corrected with intravenous iron.[19, 20] However, IV ferric carboxymaltose reduces symptoms and possibly hospitalization but not mortality.[21-23] The optimal **serum potassium** concentration in both HFrEF and HFpEF appears to be in the range 4.2–5.0 mmol/L.[24] In patients with chronic HF, vitamin D deficiency is common, and high-dose **vitamin D3** supplementation is safe, and may be associated with a favorable effect on cardiac function.[25] **Omega-3 polyunsaturated fatty acid** supplementation may be useful.[26] Influenza vaccination is associated with a reduced risk of hospitalization.[27] **Chemotherapy-induced cardiomyopathy**, in general, can occur acutely soon after treatment, within a few months of treatment, or many years later, and may be prevented with an ARB or ACE inhibitor, and most probably beta blockers such as carvedilol (a beta blocker with antioxidant properties).[28-31] Most cardiotoxicity after anthracycline therapy occurs within the first year and is associated with anthracycline dose and LVEF status at the end of treatment. Early detection and prompt drug therapy are important for substantial recovery of cardiac function.[32] See Cardio-oncology for a detailed discussion. The Domain Management Framework provides a structured approach to optimizing HF care in in older adults with HF. Tools such as the Medication Appropriateness Index and the STOPP/ START criteria can be helpful for prioritizing medications in this patient group.[33]

Patients with heart failure should be enrolled in a multidisciplinary-care management program to reduce the risk of heart failure hospitalization.

Drug Therapy

Beta blockers and Renin Angiotensin System Inhibitors (RASi) ie angiotensin converting enzyme inhibitors (ACEI) or angiotensin receptor blockers (ARB) are the cornerstones of heart failure therapy (Figures 1-7, Tables 3-10). Adherence to maximum recommended doses is important.[34] Information on these drugs is also provided in the Chapter on Therapy of Hypertension.

For patients with ***Chronic Kidney Disease and T2 Diabetes or albuminuria***, RASi and SGLT2i should be used as first-line therapy. If albuminuria persists, nonsteroidal mineralocorticoid receptor antagonist (MRA) or a GLP-1–based therapy should be added for further kidney and cardiovascular protection.[35]

Angiotensin converting enzyme inhibitors (ACEI)

ACEI have multiple pleiotropic actions including improved endothelial function, antiproliferative effects on smooth muscle cells, and antithrombotic effects. They decrease mortality in established heart failure (up to 23%) as well as in post-MI patients with reduced LVEF.[36] Enalapril, captopril, lisinopril have been mostly studied in CCF trials, and ramipril and trandolapril in post-MI trials, but their benefits appear to be a class effect without differences between tissue or non-tissue ACEI. Patients with heart failure may have increased plasma angiotensin II, and consequently, poor prognosis despite chronic ACE inhibitor therapy.[37]

Angiotensin receptor blockers (ARB)

ARB bind competitively to the AT1 receptor. ARB also reduce mortality in heart failure, are equally effective with ACEI in randomized trials,[38] and very suitable for patients unable to tolerate ACEI due to cough (occurs in 10% in whites, higher in Chinese). Mainly studied agents in CCF are valsartan and candesartan. Irbesartan has been mainly studied in hypertension and diabetic nephropathy trials. Losartan has produced controversial results on mortality at low doses. In patients with LVEF <=40% who remain symptomatic on ACEI and beta blockers, addition of eplerenone is preferred to an ARB. The addition of an ARB (or renin inhibitor) to the combination of an ACE inhibitor and a mineralocorticoid antagonist is not recommended because of the risk of renal dysfunction and hyperkalaemia. In hemodialysis patients with heart failure and LVEF ≤ 40% the addition of telmisartan to ACE significantly reduced all-cause and cardiac mortality, and hospital stays.[39] ARBs are not removed by dialysis and the benefits of the combination may be seen even in normotensive patients.[39]

Contraindications to the use of ACEI/ARB are bilateral renal stenosis, serum potassium> 5 mmol/l, and serum creatinine> 2.5mg/dl (relative contraindication). A history of angioedema or development of severe cough are contraindications for an ACEI. Angioedema is extremely rare with ARB. With GFR <30mL/min/1.73 m², an ARB can still be appropriate, particularly with albuminuric CKD. With eGFR <15mL/min/1.73 m², consider reducing/stopping if there are uremic symptoms or other problems.[40] An increase in serum creatinine of <50% above baseline, as long as eGFR remains >15 mL/ min/1.73 m2, is considered acceptable.[41] ACEI and ARB are not contraindicated in hospitalized patients with Covid-19.[42, 43] In adults withCKM syndrome stage 2 to 3 who have CKD and T2D, or CKD without T2D but with UACR ≥30 mg/g, and with eGFR ≥30

mL/min/1.73 m2, use of a RASi (eg, ACEi or ARB) at the maximum tolerated dose is recommended to reduce the loss of kidney function and to lower the risk of CVD.

Angiotensin-neprilysin inhibition (ARNI)

Neprilysin is a neutral endopeptidase responsible for the breakdown of several vasoactive peptides such as natriuretic peptides, bradykinin, and adrenomedullin that can attenuate vasoconstriction and sodium retention, and retard cardiac and vascular hypertrophy and remodelling.[44] The PARADIGM-HF trial has reported a 15% reduction in total and 20% reduction in cardiovascular mortality over 27 months with LCZ696, a combination of the neprilysin inhibitor **sacubitril** and **valsartan** (200 mg bd which is equivalent to 160 mg of valsartan).[45] Angiotensin-neprilysin inhibition (ARNI) also appears to prevent the clinical progression of surviving patients with heart failure more effectively than angiotensin-converting enzyme inhibition.[46] ARNI has also been found superior to enalapril in reducing both sudden cardiac deaths and deaths from worsening heart failure,[47] as well as causing less hyperkalemia when combined with an aldosterone antagonist.[48] The combination may also be useful in patients with mildly reduced LVEF.[49] Moderate eGFR decline that may be seen is not consistently associated with adverse outcomes, and should not deter continuation of sacubitril/valsartan or stall uptitration.[50]

Mineralocorticoid receptor antagonists (MRA)

The secondary hyperaldosteronism seen in patients with heart failure promote sodium retention, and endothelial dysfunction, and may contribute to myocardial fibrosis. Both the selective agent ***eplerenone*** (25-200 mg od) and the nonselective antagonist ***spironolactone*** (25-200 mg od) reduce mortality in post-MI patients with LVEF<40% and severe or mild symptoms, or patients with advanced heart failure.[51, 52] Spironolactone may cause painful gynecomastia in men (antagonist of aldosterone and androgen and progesterone receptors). ***Finerenone***, a novel non-steroidal MRA, with higher selectivity towards the mineralocorticoid receptor, improved heart failure outcomes in patients with chronic kidney disease and type 2 diabetes, irrespective of a history of HF.[53] Renal function and serum potassium levels must be closely monitored due to the risk of hyperkalemia especially when these agents are used together with an ACE or ARB. Correction of hyperkalemia with potassium binding agents such as the nonabsorbable plymer *patiromer*, or the inorganic *sodium zirconium cyclosilicate*, that might allow continuation of MRA and ACEI/ARBs is under study.[54, 55]

Contraindications to aldosterone antagonists are hyperkalemia (K >5 mmol/l), creatinine>2.5 mg/dl, and concomitant use of a combination of ACE and ARB (relative contraindication).

Aliskiren, a direct renin inhibitor, is not beneficial when added to standard therapy and cannot be used as an alternative to ACEI/ARBs.[56 57]

Beta blockers

Beta blockers up-regulate β-1 receptor density, blunt norepinephrine and renin production, and mitigate production of deleterious cytokines, including tumor necrosis factor alpha. In addition, β-adrenergic blockade induces effective anti-tumour T cell responses.[58] They reduce mortality (up to 35%) in heart failure in addition to that offered by ACEI in patients with sinus rhythm. Carvedilol, bisoprolol, and long-acting metoprolol unequivocally reduce mortality.[59-61] In patients with LVEF<=30%, QRS >=130 ms, and LBBB, carvedilol has been found more effective than metoprolol in reducing hospitalization and ventricular arrhythmias.[62] In addition, co-administration of carvedilol with enalapril has been reported to prevent the cardiotoxicity of anthracycline chemotherapy.[28] Nebivolol have also been found efficacious in the elderly.[63] Xamoterol, a beta blocker with intrinsic sympathomimetic activity and bucindolol, a non-selective beta blocker, have not been found beneficial. Paradoxically, the efficacy of beta blockers has been found reduced in the presence of concomitant AF.[64] Beta blockers are started on low doses (ie carvedilol 3.125 mg bd) and titrated upwards every 2 weeks. In patients with newly diagnosed heart failure it is safe to use either an ACEI or a beta blocker as first-line therapy.[61]

Contraindications to the use of beta blockers are severe asthma, second or third degree AV block and sick sinus syndrome (bradycardia<50 bpm) without permanent pacing, pheochromocytoma or cocaine use (unopposed a-receptors causing vasoconstriction). COPD is not a contraindication for their use.[65, 66] In patients with mild to moderate asthma (not in the acute phase) cardioselective beta blockers may be used in minimum doses.[67]

Loop diuretics

These are natriuretic agents by blocking sodium-potassium-chloride cotransporters in the loop of Henle, dilate blood vessels directly, and activate the renin-angiotensin-aldosterone system. Loop diuretics such as frusemide (160 to 320 mg daily) are the only therapy that can acutely produce symptomatic improvement. However, no clinical trial has assessed their effect on mortality in heart failure. They should not be used alone in heart failure since they do not prevent the progression of disease or maintain clinical stability over time. Torsemide (10-20 mg od) and bumetanide (0.5-5 mg od) have higher and more consistent bioavailability without absorption-limited kinetics in comparison with frusemide.[68] However, in the TRANSFORM-HF RCT, t he effects of torsemide and furosemide on patient-reported outcomes were similar regardless of ejection fraction, previous loop diuretic use, and baseline health status.[69] Subcutaneous frusemide is also now available and may offer better bioavailability.[70] Renal function and electrolytes should be regularly measured with the use of diuretics due to the risk of hyperkalemia, elevation of BUN, and dilutional hyponatremia. In patients resistant to loop diuretics a thiazide may be added in combination. Chronic use of loop diuretics can lead to hypertrophy of the more distal nephrons, such that even a low dose

of a thiazide-like diuretic had a large diuretic effect and consequently, a downstream effect on electrolytes and kidney function.

Several effects such as the braking phenomenon (acute reduction in diuretic efficacy with repeated loop diuretic dosing), post-diuretic effect (increased sodium retention after the loop diuretic has worn off), rebound sodium retention (increased distal nephron sodium reabsorption due to factors such as distal tubule hypertrophy), increased angiotensin II levels due to persistent volume reduction, and renal adaptation (hypertrophy and hyperfunction of distal tubule cells causing increased local sodium uptake and aldosterone secretion), lead to ***diuretic resistance***.[71] In diuretic resistance, bolus doses of 80 mg of frusemide or infusions at a rate of 10-30 mg/h can be used with a goal of treatment 3-5 L urinary volume per day. Worsening renal function, defined as a rise of serum creatinine >0.4 mg/dL, may not portend a poor prognosis when it occurs in patients with effective decongestion.[68] By blocking distal tubule sodium reabsorption, thiazides or thiazide-like drugs such as metolazone (up to 10 mg daily for 3-5 days) can also antagonize the renal adaptation to chronic loop diuretic therapy and potentially improve diuretic resistance due to rebound sodium retention, even in patients with renal failure.[71] However, there is increased risk of hypokalemia, worsening of renal function, fluid depletion that may require fluid resuscitation, and hyponatremia. Addition of an aldosterone antagonist may reduce hypokalemia and improve natriuresis. In stable patients on optimal therapy, furosemide discontinuation should be considered.[72]

Acetazolamide (500 mg od) added to loop diuretics may be beneficial, especially In acute decompensated heart failure.[73]

Sodium–glucose cotransporter-2 inhibitors (SGLT2i) and glucagon-like peptide-1 (GLP-1)

SGLT2i 1 have been found beneficial in patients with,[74-76] or without diabetes. [76-78] The agents also improve renal function, with few adverse effects.[79] SGLT2i are now recommended in patients with CCD and heart failure irrespective of diabetes status (Figure 8). Among patients with Type 2 Diabetes (T2D) with CVD or at increased risk for CVD, in addition to lifestyle modification, weight management, and risk factor control, utilization of cardioprotective antihyperglycemic is recommended, including SGLT2, or glucagon-like peptide-1 (GLP-1)–based therapy, or both, to improve cardiovascular and kidney outcomes.[35]

Digoxin

Digoxin may still have a role in patients with systolic heart failure and concomitant atrial fibrillation. In patients with sinus rhythm digoxin (concentrations of 0.5-0.8 mcg/L) has been shown to offer a reduction of hospital admissions, without any impact on mortality (DIG trial).[80 81] Digoxin blocks the sodium-potassium (Na-K) ATPase, raising intracellular sodium, and reducing Ca efflux by sodium-calcium exchange. Ca overload of the sarcoplasmic reticulum may trigger arrhythmias. In a recent analysis of the AFFIRM study, digoxin was

associated with a significant increase in all-cause mortality in patients with AF, even in the presence of HF,[82] but this finding was not verified in another analysis of the same study.[83] If used in patients with HF and AF, serum levels should be <1.0 ng/ml. In the DIG RCT, low serum digoxin concentrations (0.5 to 0.8 ng per milliliter) were associated with better clinical outcomes than placebo, whereas concentrations above 1.0 ng per milliliter were associated with worse outcomes.[84] Treatment with low-dose digitoxin has also led to a lower combined risk of death from any cause or hospital admission for worsening heart failure than placebo among patients with heart failure and reduced ejection fraction who received guideline-directed medical therapy (DIGIT-HF RCT).[85] The results of the DECISION RCT indicated that in patients with heart failure and reduced or mildly reduced ejection fraction, low-dose digoxin did not significantly reduce the composite endpoint of total worsening heart failure events or cardiovascular mortality,[86] but the trend to reduce HF events aligned with previous trials in the 9013 patient meta-analysis.[87] In these two RCTs, benefit was similar with and without atrial fibrillation, which was excluded from the original DIG trial due to assumed benefit.[87] Discontinuation of digoxin after long-term treatment is associated with clinical deterioration in patients with HF and a reduced or mildly reduced ejection fraction.[88]

Other therapies

Hydralazine and nitrates are inferior to ACE inhibitors. However, in African-American heart failure patients (who generally have low plasma renin concentrations and, thus, are theoretically less responsive to RAAS blockade), hydralazine and nitrates are helpful.[89] Complications are arthralgia and increased antinuclear antibodies (lupus-like syndrome is rare).

The selective cardiac myosin activator ***omecamtiv mecarbil*** is a myotrope that improves left ventricular function without meaningful changes in blood pressure making it potentially attractive for patients with low systolic BP.[90] It has been shown to lower incidence of a composite of a heart-failure event or death from cardiovascular causes (GALACTIC-HF RCT).[91] The benefit was modest but statistically significant. Patients who received the drug had a small increase in the cardiac troponin I level, but not an increased incidence of cardiac ischemia or ventricular arrhythmias.

Heart rate that has been identified as a risk factor in chronic heart failure, and ***ivabradine***, a selective inhibitor of hyperpolarisation-activated cyclic-nucleotide-gated *funny* current (I*f*) involved in pacemaking-generation and responsiveness of the sinoatrial node, has been found to improve outcome (composite of cardiac death or hospital admission) in patients with heart failure.[92, 93] However, an increased incidence of AF has been associated with ivabradine,[94] and the addition of ivabradine in patients with heart failure and CAD did not improve outcomes, despite a reduction in admissions for myocardial infarctions and

revascularization.[95] The eligible patients population, mainly inability to take adequate beta blockade, is a small fraction of those with heart failure overall.[93]

In heart failure, endothelial dysfunction and reactive oxygen species reduce nitric oxide bioavailability, resulting in relative deficiency of soluble guanylate cyclase and reduced cyclic GMP generation. ***Vericiguat*** enhances the cyclic GMP pathway by sensitizing soluble guanylate cyclase to endogenous nitric oxide and has reduced the incidence of death from cardiovascular causes or hospitalization over a 10-month period (VICTORIA trial).[96] In the VICTOR RCT, vericiguat led to a significant 17% relative risk reduction for cardiovascular death and a 16% relative risk reduction for all-cause death. Similarly, 25% and 29% relative risk reductions were seen for sudden cardiac death and death due to HF, respectively (both significant).[97]

Direct sodium removal with a sodium-free osmotic peritoneal solution represents a new potential therapy for nonrenal sodium and fluid removal in edematous disorders such as heart failure.[98]

Initiation of ***lipid-lowering therapy*** is not recommended in patients with HF in the absence of other indications for their use.[99] However, the effect of statins in this setting is controversial.[100]

Allopurinol increases ATP conservation and might be beneficial.[101] However, and in large population-based cohort study allopurinol use was associated with an increased risk of non-fatal CV events and all-cause mortality compared to benzbromarone.[102]

Aspirin use is associated with an increased risk of HF in patients with or without a previous history of CVDs (HOMAGE database),[103] and it should be avoided especially by nonischaemic patients without any other indication.[104] Its role in ischemic patients is controversial.

Verapamil and ***diltiazem*** are negative inotropes and are contraindicated in patients with heart failure. Dihydropyridine calcium channel blockers such as ***amlodipine*** and ***felodipine*** are safer but should be still avoided.[105]

The use of ***inotropes*** and ***phosphodiesterase inhibitors*** in chronic heart failure is not indicated since it is associated with increased mortality.[106] The PROMISE study found that oral milrinone increases mortality,[107] whereas oral enoximone does not offer any improvement.[108] Oral levosimendan may improve symptoms but without any effect on hospitalizations or mortality (PERSIST).[109]

Oral ***magnesium*** may be beneficial in patients with hypomagnesemia (<1.7mg/dL).[110]

Influenza vaccination may improve outcome in patients with heart failure.[111]

Anticoagulation Heart failure is accompanied by a hypercoagulable state, and patients have a 1-3.5% annual risk of stroke that is independent of atrial fibrillation.[112] [113] However, there are no sufficient data to support the use of ***warfarin*** in patients in normal sinus rhythm without a

history of thromboembolic events or echocardiographic evidence of LV thrombus. A reduced risk of ischemic stroke with warfarin used instead of aspirin or aspirin (WARCEF trial) and clopidogrel (WATCH trial) is offset by an increased risk of major hemorrhage.[14, 15] No differences in mortality were seen although a subanalysis of the WARCEF demonstrated lower event rate (ischemic stroke, intracerebral hemorrhage, or death combined) in patients <60 years old.[114] ***Rivaroxaban*** at a dose of 2.5 mg twice daily was also not associated with a significantly lower rate of death, myocardial infarction, or stroke than placebo among patients with worsening chronic heart failure, LVEF<40%, coronary artery disease, and no atrial fibrillation (COMMANDER HF trial).[115] However, rivaroxaban 2.5 mg bd reduced the risk of stroke (a component of the primary end-point) and should be considered following an episode of worsening HF.[116] In the COMPASS trial on patients with a history of mild to moderate heart failure (30%<LVEF<40%) combination rivaroxaban 2.5 mg BID and aspirin compared with aspirin alone demonstrated similar relative risk reduction but higher absolute risk reduction for major adverse cardiovascular events and mortality compared with those without heart failure.[117]

Device Therapy

Several device-based therapies have been approved or are under trial for the therapy of HF.[118]

Implantable Cardioverter Defibrillator (ICD)

In certain patients with heart failure an ICD is indicated for either secondary (after VT/VF) or primary prevention (Table 11-see also Chapter on VT). In trials of ***primary prevention*** in patients with heart failure, ICD reduced mortality in post-MI patients with LVEF<30% (MADIT II) [119] and ischemic or non-ischemic cardiomyopathy with LVEF<35% (SCD-HeFT).[120] In ischemic patients, ICD should be considered if indications exist at least 40 days after MI (see Chaptes on ACS). In patients with non-ischemic heart failure and LVEF<35% results have been controversial, but there is now evidence that an ICD may be favourable (see Chapter 60 for a detailed discussion). In patients with end-stage heart failure (NYHA IV), the risks of multiple shocks and quality of life deterioration must be carefully weighed against the survival benefits. ICD may aggravate heart failure either by right ventricular apical pacing that produces dyssynchrony, or multiple shocks.

Cardiac Resynchronization Therapy (CRT)

Mechanical dyssynchrony refers to nonsynchronous contraction of the wall segments of the left ventricle (intraventricular) or between the left and right ventricles (interventricular). Dyssynchrony impairs systolic function and ventricular filling, increases wall stress, and worsens mitral regurgitation. It is most readily defined by the presence of QRS widening and LBBB configuration on the electrocardiogram and may be visualized on 2-dimensional echocardiography.

Biventricular pacing

Biventricular pacing by atrial-synchronized pacing of the RV and the LV via the coronary sinus to the basal or midventricular LV region, accomplishes reverse remodeling of the LV. This remodeling effect, as well as survival benefit is greater in non-ischemic patients, although clinical improvement with CRT has been shown in both ischemic and non-ischemic heart failure. In patients with NYHA III or IV heart failure, LVEF<35%, and QRS duration >120 ms in the presence of LBBB, CRT reduces morbidity and mortality (up to 36%) even without a defibrillator (CARE-HF trial, and others) (Table 11, and Figures 8-11).[121]

Approximately 30-35% of patients are 'nonresponders', in whom CRT fails to result in benefit despite appropriate indications for therapy.[122, 123] The presence of RBBB, initial r wave in lead V1, advanced heart failure (NYHA 4), advanced age, and ischemic cardiomyopathy are predictors of poor outcome with CRT, whereas LBBB and QRS>150 sec, female gender and non-ischemic aetiology are predictors of response.[121, 124, 125] However, patients with intraventricular conduction delay and QRS duration ≥150 ms might benefit from CRT even in the absence of LBBB.[126] In patients with LVEF ≤35%, symptoms of heart failure, but a QRS duration <120 ms (LESSER-EARTH trial),[127] or even <130 ms (Echo CRT),[128] may be detrimental. Women are probably more likely than men to achieve a benefit with QRS 130-149 ms.[129] CRT-D may also be beneficial in non-LBBB patients with PR interval prolongation and LVEF <30%, QRS duration ≥130 ms, and mild heart failure.[130] Patients with QRS>130 ms might also respond to CRT even if LVEF>30%,[131] while CRT may be beneficial even in mildly symptomatic patients (NYHA I or II) and a QRS>120 msec, especially in presence of LBBB morphology.[132, 133] CRT is also preferable to RV pacing in the presence of LVEF<50% and AV block, but the potential of increased LV lead-related complications should be considered (BLOCK-HF trial).[134] The possibility of increased QT interval should be also considered.[135]

For device programming an AV delay of 120 ms without VV interval are initially chosen.[136] A PR>=230 ms is associated with increased rates oh hospitalization and AV optimization is warranted.[137] A short-paced QRS and tall R in V1 are usually seen in effective CRT.[136] In patients in sinus rhythm, a DDD pacing mode is preferred but the base rate should allow sensing of intrinsic sinus rhythm as much as possible to avoid unnecessary atrial pacing.[138] Rate-adaptive pacing should be programmed off until the presence of significant iatrogenic or intrinsic chronotropic incompetence affecting exercise intolerance is proven, bearing in mind that simple age-related rate-adaptive pacing does not improve exercise capacity and may be disadvantageous in some.[138] The adaptive CRT algorithm withholds right ventricular pacing during periods of intrinsic conduction with an atrioventricular interval of 200 ms or less and delivers left ventricular-only stimulation synchronised with right ventricular activation (synchronized left ventricular stimulation). Although theoretically

useful, its clinical value is not established.[139]

Echocardiography techniques for measurements of intra- and inter-ventricular delay do not reliably identify responders to CRT, and the mortality benefit of CRT may occur in the absence of prospective echocardiographic predictors (PROSPECT and SMART-AV).[140, 141] In addition to the ability to accurately detect mechanical delay, successful CRT is also affected by myocardial scar burden and lead position relative to dyssynchronous segments. Thus, decisions to use CRT should not be based on currently available echocardiographic/Doppler variables. Echocardiography may be used to identify the AV delay yielding optimal LV filling, and new indices such as the LV global longitudinal strain may be useful.[142] Device-based AV and VV optimization algorithms have also been proposed.[143]

The degree of LV electric delay, assessed by the QLV interval as measured from the onset of the surface (lead II) QRS to the first major peak (positive or negative) of the LV the LV electrogram may predict MR.[144] Super-response, defined as an absolute increase in LVEF>=10%, or a decrease in ESVI>=30%, or a decrease in EDVI>-20% is an indication of favourable outcome after RCT.[145]

In summary, biventricular pacing is clearly indicated in:

SR, QRS>150 msec, LBBB, LVEF<=35% and NYHA II - IV

It is also reasonable in LVEF<=35%, and QRS>130 ms with LBBB, or non-LBBB but QRS>=150 ms.

Randomized studies on CRT have been almost exclusively restricted to patients with SR. **Permanent AF** is present in 25-30% of CRT candidates, but there is little evidence that CRT is effective in AF (RAFT trial).[146] In patients with AF who are treated with CRT, AV nodal ablation (modification) has been suggested as a superior strategy compared to rate-slowing drugs. [147] [148] However, in the CAAN-AF RCT, AVN ablation did not reduce all-cause mortality or nonfatal heart failure events compared with medical rate-control therapy in patients with permanent AF and CRT-D. Pre-ablation average heart rate of these patients, however, was low (72 bpm).[149]

Technical issues for lead placement are discussed in the relevant Chapter.

CRT with ICD

When CRT is also indicated in HF patients, a combined device with ICD capabilities (CRT-D) should be implanted.

The incremental benefits of combined CRT plus implantable cardioverter-defibrillator (ICD) devices vs CRT-alone devices in patients with LV systolic dysfunction remain uncertain, especially in patients with non-ischaemic cardiomyopathy.[150-153] In patients with LVEF<35%, advanced heart failure (NYHA class III or IV) due to ischemic or nonischemic cardiomyopathies and a QRS interval > 120 msec, the presence of ICD capabilities also reduced mortality (COMPANION).[154] This effect was seen in non-ischaemic

patients,[155] in contrast with the results of another observational study,[156] and a meta-analysis.[153]

Addition of CRT to patients who already need an ICD also reduces mortality. In the RAFT trial in patients with NYHA II or III heart failure, LEVF<=30%, and a QRS>=120 msec or paced QRS >=200 msec, the addition of CRT to ICD improved survival, albeit at a cost of increased implantation-related complications.[157] The survival benefit was sustained over a 14-year follow-up.[158] In the MADIT-CRT, in patients with ischemic (NYHA I or II) or nonischemic (NYHA II) cardiomyopathy, LVEF<=30%, and QRS>=130 msec with LBBB morphology, CRT offered a 11% reduction in mortality compared to ICD alone.[132] The composite end-point of heart failure or death was lower among patients with a CRT-D system as compared with those with an ICD alone, only when restricted to those with at least 90% biventricular pacing.[159] In a real world retrospective cohort study using National Cardiovascular Registry data linked with Medicare claims, patients who were eligible for CRT-D according to established criteria and who received CRT-D had significantly lower risks for death and readmission than those who received ICD therapy alone.[160] Improvements in both survival and heart failure hospitalizations with CRT-D compared to ICD alone are greatest in patients with a QRS ≥180 ms with or without LBBB, whereas patients with a QRS 150-179 ms without LBBB may have no improvement in survival with CRT-D.[161] In pacemaker or ICD patients with significant RV pacing burden and LVEF <=35%, upgrade to CRT-D compared with ICD therapy also reduced the combined risk of all-cause mortality.[162] No benefit of CRT-D compared with CRT was seen in an analysis of a German health insurance database on patients without an indication for implantation of an implantable cardioverter defibrillator for secondary prevention.[163]

Patients with CRT-D who achieve LVEF normalization (>50%) have very low absolute and relative risk of ventricular arrhythmias and a favorable clinical course within 2.2 years of follow-up. Risk of inappropriate ICD therapy is still present and these patients could be considered for downgrade from CRT-D to CRT-P at time of battery-depletion if no ventricular arrhythmias have occurred.[164] In a subsequent meta-analysis, patients with improvement of LVEF ≥45% and those with primary prevention indication for ICD appear to be at lowest risk.[165]

Conduction system pacing

Specific ***His bundle pacing*** may offer better results to biventricular pacing by means of cardiac resynchronization.[166] ***Left bundle branch pacing*** -CRT, in particular, has demonstrated greater LVEF improvement than biventricular pacing-CRT,[167-171] and may be associated with associated with a lower incidence of sustained VT/VF and new-onset AF compared with biventricular pacing in heart failure patients.[172] However, three recent RCTs comparing biventricular to conduction system pacing provided conflicting results.[173-175] The

presence of an anteroseptal scar influences the efficiency of conduction system pacing.[176] Thus, the strength of evidence for CRT in heart failure is still greater than what is available to support Conduction system pacing.[133] The HRS recommendations are presented in Figures 14 and 15.

Additional Device Therapies

Cardiac contractility modulation (CCM) is a device-based therapy for heart failure that involves applying relatively high-voltage (≈7.5 V), long-duration (≈20 milliseconds), biphasic electric signals to the right ventricular septal wall during the absolute myocardial refractory period. CCM signals do not elicit a new contraction, but they induce reverse LV remodeling and improve LVEF over time. There has been some evidence that CCM provides benefit, particularly those with LVEF between 25% and 45%.[177]

Placement of an **inter-atrial shunt device** reduces PCWP during exercise in patients with class III or ambulatory class IV HF, EF ≥40%, exercise PCWP ≥25 mm Hg, and PCWP-right atrial pressure gradient ≥5 mm Hg, reduced PCWP during exercise,[178] but did not reduce the total rate of heart failure events or improve health status.[179]

Cardiac remuscularization with biologic ventricular assist tissue **(BioVAT)** derived from allogeneic induced pluripotent stem cells is a new promising modality.[180]

In selected patients with MR, trans-catheter edge to edge repair may be indicated (Figure 12).

Heart Failure with Preserved LVEF

Effective therapies of heart failure with preserved systolic function are not established (Table 12 and Figure 13). Therapies addressing specific patient phenotypes may prove to be a more effective approach than the traditional model of applying a uniform treatment.[181, 182] Blood pressure control, rate/rhythm control in underlying AF, control of pulmonary congestion with diuretic agents, and revascularization when indicated are recommended. Blood pressure control improves diastolic function irrespective of the type of antihypertensive agent used.[183] ***ARBs, beta blockers*** to control tachycardia and increase the duration of diastole, diuretics in smaller doses than in systolic heart failure, and calcium channel blockers (***diltiazem or verapamil***) are used for symptomatic relief. Despite a lower rate of hospitalizations, no reduction in mortality has been shown with ACEI or ARBs, or beta blockers.[184, 185] In addition, an unexpected worsening of renal function with ARB therapy has been reported,[186, 187] and β-blocker withdrawal improved maximal functional capacity in patients with HFpEF and chronotropic incompetence.[188] ***Angiotensin/neprilysin inhibition*** may be beneficial,[49, 189] especially in patients with high blood pressure despite optimum therapy.[190] ***SGLT2 inhibitors*** should be initiated in all HFpEF patients without contraindications.[191] Empagliflozin reduced

the combined risk of cardiovascular death or hospitalization for heart failure in patients with heart failure and preserved ejection fraction, regardless of the presence or absence of diabetes (EMPEROR-Preserved RCT).[192] and similar benefits were reported for dapagliflozin (DELIVER RCT).[193] ***Tirzepatide***, a long-acting agonist of glucose-dependent insulinotropic polypeptide and glucagon-like peptide-1 receptors,has been shown to produce ≈12% to 21% weight loss in patients with obesity. In the SUMMIT RCT, tirzepatide led to a lower risk of a composite of death from cardiovascular causes or worsening heart failure than placebo and improved health status in patients with heart failure with preserved ejection fraction and obesity.[194, 195] Spironolactone has not been beneficial in patients already taking ACEI/ARBs and diuretics (TOPCAT RCT).[196] However, ***finerinone***, another nonsteroidal mineralocorticoid receptor antagonist, resulted in a significantly lower rate of a composite of total worsening heart failure events and death from cardiovascular causes than placebo in patients with heart failure and mildly reduced or preserved ejection fraction.[197] Ivabradine has not been found beneficial for improving exercise capacity.[198] Nitrates are not indicated.[199] Phosphodiesterase 9A (PDE9A) inhibition that is not dependent on nitric oxide levels, as occurs with conventional PDE5A inhibitors used in pulmonary hypertension, has been found promising in animals with induced cardiac hypertrophy and heart failure.[200]

Comorbidities in Heart Failure

Coronary Artery Disease

Revascularization is thought to improve survival in patients with ischemic cardiomyopathy and proven myocardial viability by perfusion tests, stress echocardiography, or MRI.[201, 202] Although this was not verified in both the STICH and the smaller Heart trial, [203, 204] the value of CABG over medical therapy is now generally accepted. In patients with extensive disease and at least 2 of prognostic factors such as presence of 3-vessel CAD, LVEF below the median (27%), and end-systolic volume index (ESVI) above the median (79 ml/m^2), CABG did reduce mortality compared to medical therapy alone.[205] In addition, over a 10-year follow-up of the STICH, total as well as cardiac mortality was significantly lower in the CABG group (STICHES trial).[206] In patients with LVEF>=35% indications for CABG are as in IHD. In patients with ischemic cardiomyopathy subjected to CABG, surgical LV reconstruction reduces LV volumes and LV wall stress but offers no benefit in mortality or hospitalizations (STICH Hypothesis 2 trial).[207] Thus, routine LV reconstruction is not recommended. Ventricular reshaping techniques with new devices are under study.[208] Recommendations are provided in Table 13 and Figure 14.

Valve Disease

In heart failure due to valve disease such as AS or MS, surgical or interventional correction

may restore almost normal heart function. Functional MR is characterized by annular dilatation and leaflet noncoaptation in the setting of anatomically normal papillary muscles, and valve leaflets. Ischemic or infarct-related, functional MR is typically associated with leaflet tethering and displacement, related to abnormal LV wall motion and geometry or papillary muscle dysfunction. The role of MV surgery (replacement or repair) in this setting remains controversial. Detailed discussions are provided in the Chapters on Valve Disease.

Atrial Fibrillation

AF constitutes a strong and independent risk factor for the development of heart failure, and both conditions frequently co-exist, partly because of common risk factors. [209] The prevalence of atrial fibrillation in heart failure is 5% (NYHA I) to 25-50% (NYHA III/IV) and new-onset AF is most probably associated with increased subsequent risk of mortality and morbidity.[210] It is very important to detect those patients with fast AF who have developed heart failure due to tachycardia-induced cardiomyopathy. Atrial kick contributes up to 30% of stroke volume, and an analysis of the CHF-STAT trial indicated that patients with heart failure who maintained sinus rhythm on amiodarone had improved survival,[211] but in a randomized comparison patients with AF and congestive heart failure, the rhythm control strategy using cardioversions and drugs has not been shown to be superior to rate control.[212]

Several RCTS have evaluated catheter ablation for HFrEF. Restoration of sinus rhythm with catheter ablation has been shown to result in significant improvements in ventricular function (CAMFAT trial),[213] particularly in the absence of ventricular fibrosis on CMR (CAMERA-MRI trial). [214] Catheter ablation is also superior to amiodarone in achieving freedom from AF at long-term follow-up and reducing unplanned hospitalization and mortality in patients with heart failure and persistent AF (AATAC trial).[215] In the CASTLE-AF trial, catheter ablation was associated with a significantly lower rate of a composite end point of death from any cause or hospitalization for worsening heart failure compared to medical therapy,[216] although caveats should be considered.[217] In the CASTLE HTx trial, among patients with end-stage heart failure, the combination of catheter ablation and medical therapy was associated with a lower likelihood of a composite of death from any cause, implantation of a left ventricular assist device, or urgent heart transplantation than medical therapy alone.[218] In two meta-analyses, catheter ablation has been associated with all-cause mortality benefit in patients with AF and heart failure with reduced ejection fraction.[219, 220]

However, in patients with AF and significantly reduced LVEF (<=35%) no benefit of catheter ablation has been demonstrated in the AMICA trial.[221] This was mainly due to the fact that at 1 year, LVEF had increased in ablation patients to a similar extent as in medical therapy patients, despite the fact that at any time during follow-up, ablation-group patients had more often SR and a lower AF burden than medical therapy patients. In the RAFT AF trial on patients with high-burden AF and HF, there was no statistical difference in all-cause

mortality or HF events with ablation-based rhythm control versus rate control at an average 3 year follow-up.[222] There was a nonsignificant trend for improved outcomes such as LVEF and quality of life with ablation-based rhythm control over rate control. The trial was stopped early because of apparent futility at the time of the interim analysis. Among all relevant RCTs, only CASTLE-AF and AATAC showed a reduction in mortality with catheter ablation.[217]

In patients with AF and heart failure with a predominantly preserved LVEF, the stringency of rate control may have no effect on cardiovascular morbidity and mortality,[223] but in patients with heart failure and reduced LVEF, there is greater mortality when resting heart rate was >100 bpm, and the use of β-blockers is associated with improved survival.[224] [212] b-blockers are the cornerstone of therapy in patients with systolic heart failure, and confer a 27% reduction in the incidence of new-onset AF.[225] b-blockers with or without digoxin are used for rate control aiming at a heart rate <100 bpm. A non-dihydropyridine calcium channel blocker with digoxin may be considered in patients with heart failure and preserved LVEF. Catheter ablation is also preferable to a rate-control strategy with beta blockers and/or digoxin by means of symptoms and neurohormonal status,[226] and to amiodarone by means of reduced AF burden and mortality (AATAC trial).[215] AV nodal ablation and biventricular pacing reduces hospitalizations and mortality compared to pharmacological rate control (APAF-CRT trial),[227] but catheter ablation for pulmonary vein isolation has been found superior to AV nodal ablation and biventricular pacing (PABA-CHF trial).[228] His pacing may be preferable to biventricular pacing.[229]

In patients with AF and heart failure dronedarone increased mortality,[230] whereas dofetilide prevented AF recurrences without any effect on mortality.[231] Amiodarone is the only agent that is recommended for prevention of atrial arrhythmias recurrence in patients with heart failure and/or reduced LVEF, but its potential toxicity, as well as concerns about the possibility of increased mortality,[232] should be considered.

Anticoagulation is recommended in all patients with heart failure and AF (by definition CHA2DS2-VASC >=1). Ischemic patients are treated with antiplatelet agents when indicated. However, there have been no randomized trials examining the impact of aspirin alone versus placebo in stroke reduction in HF,[112] and routine addition of single-antiplatelet therapy to warfarin in patients with heart failure, AF and vascular disease is not indicated.[233] DOAC, as a class, reduce the risk of systemic embolism, as well as major and intracranial bleeding compared to warfarin in patients with AF and heart failure.[234] The value of CRT in heart failure with AF is not proven (see CRT).

Recommendations are provided In Table 14 and Figure 15.

Conduction disturbances

In patients with HFrEF (<40%) regardless of NYHA class who have an indication for ventricular pacing and high-degree AVB, CRT rather than RV pacing is recommended, regardless of NYHA class, in order to reduce morbidity (ESC 2021 GL on pacing and CRT, I-A). This includes patients with AF.[235]

Ventricular Arrhythmias

In patients not eligible or who have no access to ICD, amiodarone may reduce the risk of sudden cardiac death but not overall mortality,[236] and it may increase noncardiac mortality in patients with NYHA class III heart failure.[237] Amiodarone decreased mortality in the GESICA trial (60% non-ischemic patients) [238] but had no significant effect in the SCD-HeFT (70% ischemic patients).[120] It is still recommended in patients with an ICD to reduce shocks, or in patients with VT in whom ICD is not an option. Dronedarone is detrimental in heart failure patients.[230] Other antiarrhythmic drugs are contraindicated in heart failure due to proarrhythmic potential, and negative inotropic effects.

Chronic Kidney Disease (CKD)

The presence of CKD is associated with more severe heart failure, and CKD itself is a strong independent risk factor of poor cardiovascular outcome.[35] Although an initial decline in eGFR is observed on initiation of several HFrEF drug classes (angiotensin-converting enzyme inhibitors/angiotensin II receptor blockers/mineralocorticoid receptor antagonists/angiotensin receptor blocker neprilysin inhibitors/sodium glucose cotransporter 2 inhibitors), renal function often stabilizes over time, and the drugs maintain their clinical efficacy. A decline in eGFR in the context of a stable or improving clinical condition should not lead to discontinuation of therapy. Recommendations are provided in Figures 16-18 and Table 15.

Cancer

Several ***chemotherapeutic agents*** increase the risk of heart failure, and during cancer treatment with potential cardiotoxic therapies, LV systolic function can be monitored through echocardiography. [239-243] Variants in cardiomyopathy genes contribute to cancer therapy–induced cardiomyopathy susceptibility among adult and paediatric patients with cancer.[244] The relative risk of heart failure with preserved or midrange LVEF (>40%) increases with cardiac radiation exposure during contemporary conformal breast cancer radiotherapy.[245] In the PRADA RCT, anthracycline-containing adjuvant therapy for early breast cancer was associated with a decline in LVEF during extended follow-up. Candesartan during adjuvant therapy did not prevent reduction in LVEF at 2 years, but was associated with modest reduction in left ventricular end-diastolic volume and preserved global longitudinal strain.[246] In a subsequent meta-analysis, beta-blockers or ACEI/ARBs were significantly associated with higher LVEFs in patients treated with trastuzumab. For anthracyclines, a similar trend was found, although nonsignificant.[247] Thus, treatment with an ACE-I and a beta-blocker

(preferably carvedilol) should be started in patients on chemotherapy who develop LV systolic dysfunction, defined as 10% or more absolute reduction in LVEF to a value below 50% (Table 15).[239]

Other comorbidities

Recommendations for other comorbidities are provided in Table 17, and Figure 19. Influenza vaccination is associated with a reduced risk of all-cause death in patients with HF and influenza and pneumococcal vaccination, as well as COVID-19 vaccination, when available, should be considered in patients with HF.[239]

Advanced Heart Failure

Definition and identification of patients with advanced HF are presented in Table 18, and Figures 20 and 21. The INTERMACS classification is presented in Figure 22. Principles of therapy are indicated in Tables 19-21, and Figure 23. It should be noted that inotropic agents have not shown improved survival in patients with HF. However, regardless of their mechanism of action (eg, inhibition of phosphodiesterase, stimulation of adrenergic or dopaminergic receptors, calcium sensitization), parenteral inotropes remain an option to help the subset of patients with HF who are refractory to other therapies and are suffering consequences from end-organ hypoperfusion.[105] Inotrope dependent patients (ie levels 1 to 3 according to the Interagency Registry for Mechanical Assist Devices-INTERMACS classification) who can be maintained on a single inotropic agent can be discharged home either on long-term IV inotropic support or on oral levosimendan but with detrimental or no effect on mortality.

Acute heart failure and cardiogenic shock are discussed in the relevant Chapter.

Mechanical Circulatory Support

Mechanical circulatory support is now a therapeutic option for patients with advanced HF. Left-ventricular assist devices (**LVAD**) are portable blood pumps that can be used in patients with end-stage heart failure (Tables 22-24). As bridge to recovery in people with potentially reversible forms of heart failure, such as myocarditis or post-partum cardiomyopathy.

- As bridge to transplantation within the next weeks
- As destination therapy for patients unsuitable for transplantation.

The randomized REMATCH trial in patients with end-stage heart failure unsuitable for transplantation detected a significantly better survival at one year in the device group (52%) than in the medical therapy group (52 vs 25% at one year and 23 vs 8% at two years, respectively.[248] The FDA has approved three devices, HVAD, HeartMate II, and HeartMate III as destination therapy for patients with end-stage heart failure, but Medtronic discontinued the production of HVAD in 2021.[249] Sufficient recovery to allow device explantation that is

used either as bridge or destination therapy has been observed in 5% to 24% of patients.[250] Continuous flow devices comprise the overwhelming majority of LVAD implantations in the USA.[251] Continuous-flow centrifugal pumps with a magnetically levitated rotor (such as HeartMate 3) are designed to allow an artificial pulse and thus enhance hemocompatibility (i.e. bleeding and thrombosis events) and avert pump thrombosis and strokes. [252-255]

Bleeding complications, especially gastrointestinal bleeding, due to aggressive anticoagulation, and, later acquired von Willebrand disease, platelet damage, stroke, device infection, and thrombosis of the inflow cannula, pump chamber, or outflow graft and aortic anastomosis are the most common post-operative adverse events (up to 30%).[256, 257] In patients undergoing isolated LVAD implantation, ≥20% of them experience acute RV failure, which is a leading cause of premature morbidity and mortality.[258] Although the long-term efficacy and safety of LVADs as an alternative to heart transplantation or medical therapy remains uncertain, the limited availability of organs and their use as bridge to recovery, especially before terminal stages of the disease, suggest expansion of their use although concerns about cost-effectives have been raised.[259-262]

Recommendations on cardiopulmonary resuscitation in patients with mechanical circulatory support have been published by AHA and are presented in the Chapter on VT.[263] Recommendations on arrhythmia management in this setting have also been published by AHA.[264] The benefits of pulmonary artery catheters are not proven, but they may be useful in patients with persistent normotensive-hypoperfusion preshock (ie, systolic blood pressure >90 mmHg without inotropes or pressors but with clear evidence of worsened end-organ function).[265]

Heart Transplantation

Approximately 5% and 10% of all patients with heart failure have advanced disease, which is associated with a very high mortality and very poor quality of life (Table 25). Heart transplantation is the treatment of choice for patients with advanced heart failure in the absence of contraindications, with an overall median survival of 12.5 years and conditional survival of 14.8 years for those who survive the first year.[266] Approximately 10% of adult heart transplant recipients develop a de novo malignancy between years 1 and 5 after transplantation.[267] Listing criteria and evaluation and management of patients undergoing cardiac transplantation have been described in detail by the International Society for Heart and Lung Transplantation.[268] Heart transplantation is indicated in hospitalised patients with status I classification (United Network of Organ Sharing), who need intravenous inotropes or a circulatory support device.[260] In ambulatory (status II) patients, transplantation does not improve survival; these patients might benefit from long-term LVAD unloading that may

allow recovery of myocardial contractility in patients with dilated cardiomyopathy. According to the 2016 International Society for Heart Lung Transplantation listing criteria for heart transplantation, amyloid heart disease, HIV, and hepatitis B and C infections are no longer contraindications for transplantation.[269] Indication for permanent pacing are presented in the relevant Chapter.

Non-cardiac Surgery

Recommendations by the ESC are provided in Table 26.

New therapeutic approaches

A number of new pharmacological pathways, device therapies and biologicals are undergoing advanced stages of investigation with potential for clinical utility in the near future.[270] Autologous stem cell intracoronary transplantation may also improve LVEF and clinical outcomes in ischaemic heart failure.[271-273]

Rehabilitation and Sports

Recommendations for exercise and sports in patients with heart failure or heart transplantation are provided in Tables 27-30.

Hospital Discharge and Integration of Care and End of Life Considerations

Recommendations for discharge and follow-up are provided In Tables 31-35 and Figure 24, and end-of-life considerations in Table 36.

Special Populations

Issues of special populations are presented in Tables 37 and 38.

Pregnancy

Recommendations for pregnant women with heart failure are presented in Tables 39-43.

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