Dilated Cardiomyopathy

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From Genetics to Clinical Management

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Abbreviations and Acronyms

ACEi	Angiotensin-converting enzyme inhibitor
AF	Atrial fibrillation
AHA/ACC	American Heart Association/American College of Cardiology
ARB	Angiotensin II type I receptor blockers
ARNI	Angiotensin receptor-neprilysin inhibitor
CRT-D	Cardiac resynchronization therapy-defibrillator
CRT-P	Cardiac resynchronization therapy-pacemaker
DCM	Dilated cardiomyopathy
ESC	European Society of Cardiology
FMR	Functional mitral regurgitation
HF	Heart failure
HT	Heart transplantation
ICD	Implantable cardioverter-defibrillator
LBBB	Left bundle branch block
LV	Left ventricular
LVAD	Implantable left ventricular assist device
LVEF	Left ventricular ejection fraction
MCS	Mechanical circulatory support
MRA	Mineralocorticoid receptor antagonists
MRI	Magnetic resonance imaging

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NIDCM	Nonischemic dilated cardiomyopathy
RV	Right ventricular
SCD	Sudden cardiac death
VT	Ventricular tachycardia

Dilated cardiomyopathy (DCM) is a frequent cause of heart failure (HF) and is characterized by dilation and impaired contraction of one or both ventricles. Patients affected by DCM have impaired systolic function and may or may not develop overt HF and atrial and/or ventricular arrhythmias. Sudden cardiac death (SCD) can occur at any stage of the disease. Important breakthroughs have redefined opportunities to change the natural history of the disease with familial and sport activity screening programs and a broad range of medical therapies, devices, and care strategies, including readmission reduction programs and ambulatory outpatient disease management for those with more advanced disease (Table 13.1, Fig. 13.1).

Table 13.1 Screening programs and pharmacological and non-pharmacological treatments of HF in DCM patients: levels of recommendations from ESC guidelines

	When?	Recommendation
Screening		
Familial screening program	– First-degree relatives, if a specific gene mutation is identified in the proband	Recommended (from age 10 to 12 years)
	– Family history of SCD in a first-degree relative	Can be useful
Sport activity screening	– For all young competitive athletes by history, physical examination, and ECG	Recommended by ESC
	– For all young competitive athletes with history and physical examination	Recommended by AHA/ACC
Pharmacological treatment		
ACEi	– Patients with asymptomatic LV systolic dysfunction, in order to prevent or delay the onset of HF	Recommended (**I B**)
	– Patients with symptomatic LV systolic dysfunction, in order to reduce HF, hospitalization, and death	Recommended (**I A**)
ARB	– Patients with symptomatic LV systolic dysfunction, in order to reduce HF hospitalization and death, unable to tolerate an ACE-I	Recommended (**I B**)
Beta-blocker	– Patients with symptomatic LV systolic dysfunction, in order to reduce HF, hospitalization, and death	Recommended (**I A**)
MRA	– Patients with LV systolic dysfunction still symptomatic with an optimized dosage of ACEi and beta-blocker, in order to reduce HF hospitalization and death	Recommended (**I A**)
Sacubitril/ Valsartan	– Patients with LV systolic dysfunction (EF $\leq$ 35%) still symptomatic (NYHA II–III) with an optimized dosage of ACEi (or ARB), beta-blocker, and MRA in order to reduce HF hospitalization and death	Recommended (**I B**)
Ivabradine	– Patients with LV systolic dysfunction (EF $\leq$ 35%) still symptomatic, in sinus rhythm and a resting heart rate $\geq$70 bpm, with an optimized dosage of ACEi(or ARB), beta-blocker, and MRA in order to reduce HF hospitalization and cardiovascular death	Recommended (**IIa B**)

Table 13.1 (continued)

	When?	Recommendation
Diuretics	– To reduce symptoms and signs of congestion	Recommended (**I B**)
Hydralazine and isosorbide dinitrate	– Black patients with symptomatic LV systolic dysfunction in case of intolerance or contraindication to ACEi or ARB, in order to reduce mortality	Recommended (**IIb B**)
	– Patients with LV systolic dysfunction (EF ≤ 35%) and still symptomatic (NYHA III–IV) with an optimized dosage of ACEi and beta-blocker, in order to reduce HF hospitalization and death	Recommended (**IIa B**)
Non-pharmacological treatment		
ICD	– Patients with LV systolic dysfunction (EF ≤ 35%) and symptomatic (NYHA II–III) despite 3 months of OMT, in order to reduce SCD and all-cause mortality	Recommended (**I B**)
CRT	– Patients with LV systolic dysfunction (EF ≤ 35%), in sinus rhythm and symptomatic despite OMT, in order to reduce morbidity and mortality	
	• QRS duration ≥150 ms and LBBB QRS	Recommended (**I A**)
	• QRS duration 130–149 ms and LBBB QRS	Recommended (**I B**)
	• QRS duration ≥150 and non-LBBB QRS	Recommended (**IIa B**)
	• QRS duration 130–149 ms	Recommended (**IIb B**)
IABP or VA-ECMO	– Refractory acute HF or cardiogenic shock, with a short-term MCS, depending on patient age, comorbidities, and neurological function	Recommended (**IIb C**)
MitraClip	– HF patients with moderate to severe secondary FMR, inoperable or at high surgical risk, in order to improve symptoms and quality of life	Recommended (**IIb C**)
LVAD	– Patients with LV systolic dysfunction (LVEF ≤ 35%), end-stage HF despite OMT/device and eligible for HT, in order to improve symptoms and reduce the HF hospitalization and premature death (bridge to transplant)	Recommended (**IIa C**)
	– Patients with LV systolic dysfunction (LVEF ≤ 35%), end-stage HF despite OMT/device and not eligible for HT, in order to improve symptoms and reduce the HF hospitalization and premature death	Recommended (**IIa B**)
HT	– Patients with LV systolic dysfunction (LVEF ≤ 35%), end-stage HF despite OMT in the absence of contraindications, in order to increase survival, exercise capacity, and quality of life	Recommended

SCD sudden cardiac death, *ESC* European Society of Cardiology, *AHA* American Heart Association, *ACC* American College of Cardiology, *LV* left ventricle, *HF* heart failure, *ACEi* angiotensin-converting enzyme inhibitor, *ARB* angiotensin II type I receptor blockers, *MRA* mineralocorticoid/aldosterone receptor antagonists, *EF* ejection fraction, *ICD* implantable cardioverter-defibrillator, *CRT* cardiac resynchronization therapy, *FMR* functional mitral regurgitation, *IABP* intra-aortic balloon pump, *VA-ECMO* venoarterial extracorporeal membrane oxygenation, *LVAD* implantable left ventricular assist device, *HT* heart transplantation

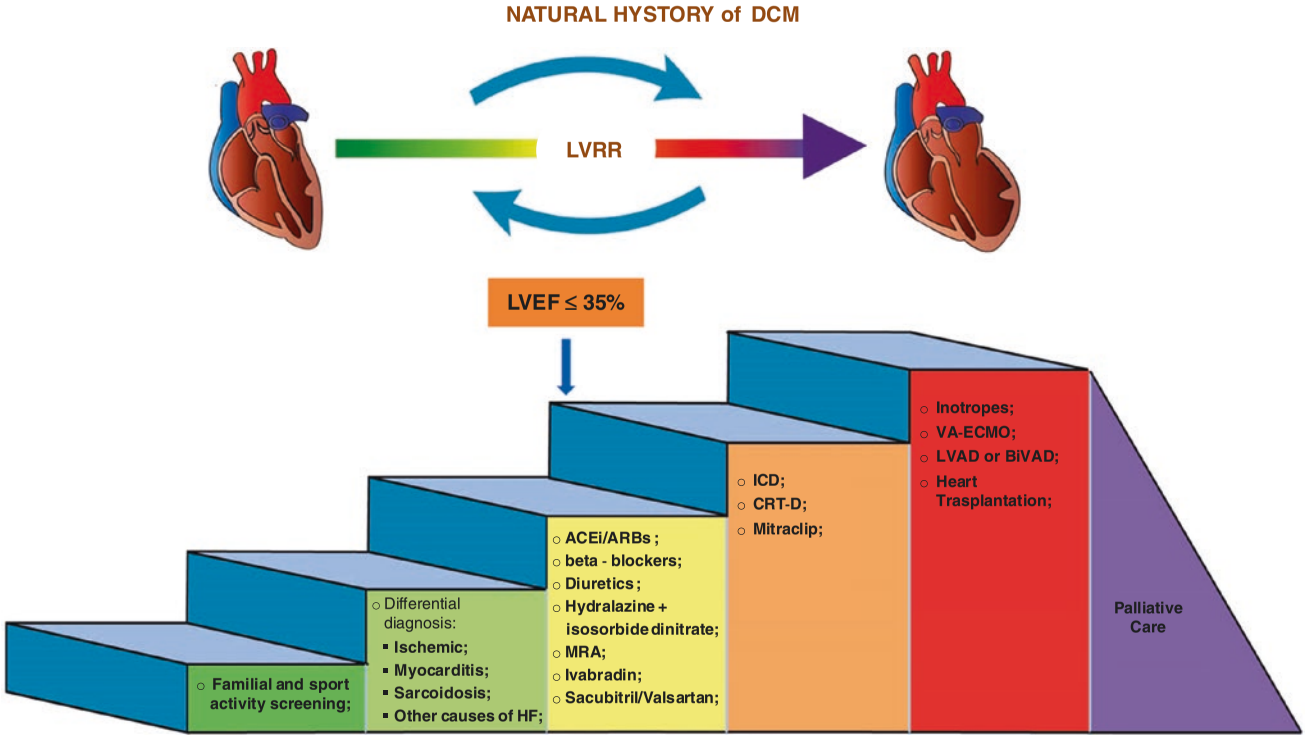

Fig. 13.1 Management and escalation therapy for HF in DCM. *ACEi* angiotensin-converting enzyme inhibitor, *ARB* angiotensin II type I receptor blockers, *MRA* mineralocorticoid/aldosterone receptor antagonists, *ICD* implantable cardioverter defibrillator, *CRT* cardiac resynchronization therapy, *VA-ECMO* veno-arterial extracorporeal membrane oxygenation, *LVAD* implantable left ventricular assist device, *BiVAD* biventricular assist device

13.1 Familial Screening Program

Contrary to what was believed in the past, in the broad spectrum of DCM, 20–50% forms are now known to be familial [1]. Autosomal dominant inheritance is the most frequent pattern of transmission, with less than 50% chance of inheriting the disease for each pregnancy because of incomplete penetrance [2].

These elements represent the rationale to perform a complete family screening in order to identify preclinic manifestations of DCM among relatives, taking into account that DCM has a progressive course [3] and family members can remain asymptomatic for a long period [4–7]. Familial screening program, recommended to proband's first-degree relatives, allows an early identification and treatment of the disease, reducing morbidity and mortality and preventing the high costs of advanced HF management [8].

Family history of at least three generations is recommended in order to recognize the potential heritability of the disease [9]. The pedigree analysis should investigate family occurrence of HF of unknown etiology before the age of 60, SCD, and pacemaker implantation early in life [4]. Furthermore, family history of skeletal myopathies (as Duchenne or Becker disease) or presence of sensorineural hearing loss (congenital or occurred after the second decade of life) can suggest the diagnosis of a syndromic disease involving also the heart.

When the disease is recognized in at least two close relatives, a final diagnosis of familial DCM can be made [3, 4, 10].

In addition to family history, periodic screening, consisting of physical examination and instrumental evaluation (ECG and echocardiogram), can mark the transition to the phenotypic expression of the disease, even when the relative is yet asymptomatic [4, 6]. An early detection of this transition represents the rationale for familial screening proposed by European and American guidelines [11, 12].

According to guidelines, genetic testing is recommended for first-degree relatives when a specific mutation is identified in the proband [4, 11, 13], starting from the age of 10–12, although earlier testing can be considered in laminopathies [11].

In genotype-positive relatives, annual clinical follow-up is recommended in order to recognized an early expression of the disease [11]. Conversely, clinical follow-up is not required in the case of negative genetic testing, which excludes future development of the disease and the risk of its transmission to the offspring [11].

In case of proband's death, postmortem molecular analyses can be useful to detect the disease-causing mutation in addition to an accurate histological and morphological evaluation of the heart in order to clarify the disease phenotype [14].

Genetic testing, however, is not always conclusive: identification of uncertain significant genetic variants or the absence of any identified mutation in the proband on extensive gene screening represents an example of diagnostic ineffectiveness. In these settings, genetic testing is not recommended for close relatives [15].

Repeated cardiac evaluation should be performed at regular intervals: every 1–3 years until the age of 10, 1–2 years between 10 and 20 years, and then every 2–5 years until the age of 50–60, when the penetrance of DCM is usually complete [11].

When a relative is diagnosed as a new case of DCM, even if asymptomatic, the clinical work-up described for the proband starts, including additional tests, such as cardiopulmonary exercise and/or cardiac magnetic resonance imaging (MRI) [11].

13.2 Sport Activity Screening Program

SCD has been associated to competitive sport activity in the adolescents and young adult athletes [16, 17], with an increased risk compared with nonathletic counterparts [18]. Specific cardiomyopathies have been recognized as leading causes of sport-related cardiac arrest such as hypertrophic cardiomyopathy in the USA and arrhythmogenic right ventricular cardiomyopathy in Italy [18, 19].

DCM has been also taken into account as a possible cause of SCD: in international records 1–8% of fatalities of cardiovascular origin have been related to DCM [18–20]. In this context, clinical evaluation of athletes has the important goal of identifying the disease when asymptomatic and protecting them from SCD by sport competition restriction and specific treatment.

American Heart Association/American College of Cardiology (AHA/ACC) and European Society of Cardiology (ESC) recommendations agree that cardiovascular screening for young athletes is justifiable and compelling on ethical, legal, and medical grounds [21, 22], but the two societies propose different screening programs.

The AHA/ACC focuses screening only on physical examination and medical history with consequent cost restriction and reduction of false-positive ECG [22]. On the other hand, ESC and International Olympic Committee recommend also to perform a resting 12-lead ECG [21, 23], in order to detect abnormalities connected to preclinical pathological cardiovascular conditions that cannot be identified by the only clinical approach [21, 23, 24].

The most frequent ECG abnormal findings always requiring further assessment to exclude the presence of a cardiomyopathy are the following:

- T-wave inversion in lateral, infero-lateral, or extended to anterior leads
- ST-segment depression
- Pathologic Q waves
- Complete left bundle branch block (LBBB)
- Multiple premature ventricular beats

When pathological findings emerge, the initial evaluation requires additional tests [18, 21], as recommended by the ESC section of *Sports Cardiology*, based itself on the Italian protocol [21]: echocardiography, stress testing, Holter ECG monitoring, and eventually cardiac MRI in selected cases [24, 25].

In some cases, differential diagnosis between DCM and athlete's heart may be challenging. Indeed, athlete's heart is a clinical phenotype derived from cardiac remodeling induced by sport activity, mostly in endurance sports, and is characterized by enlarging left ventricle with borderline or mildly reduced left ventricular

ejection fraction (LVEF) (i.e., between 45 and 55%) [26]. There are many hints helping to distinguish DCM from athlete's heart [25]:

- Positive family history of SCD, cardiac arrest, or cardiac disease
- ECG abnormalities
- Ventricular arrhythmias at 24-h Holter ECG monitoring or stress testing
- LVEF below 45% and regional wall motion abnormalities
- Right ventricular dysfunction associated with LV dysfunction
- Late gadolinium enhancement (LGE) at cardiac MRI

In doubt or borderline cases, demonstrating a significant increase in LVEF during exercise echocardiography or LVEF and diameter normalization at cardiac MRI after an adequate period of detraining may support the diagnosis of athlete's heart [27]. Sport screening benefits go beyond the detection of DCM in the single athlete: when the disease is recognized, a cardiological evaluation can be extended to the first-degree relatives in order to identify other potential affected family members [18].

Athletes recognized to be affected by DCM should not participate in competitive sports because of an increased risk of SCD during exercise [21]. Finally, there are no sufficient evidences supporting that sport activity increases the risk of DCM development or SCD in genotype-positive/phenotype-negative athletes [25].

13.3 Medical Treatment

DCM is a common cause of HF and treatment reflects the management of chronic HF. DCM patients, indeed, can be divided into two different classes on the base of the presence of clinical symptoms:

- Asymptomatic left ventricular systolic dysfunction: in patients with depressed LV systolic function in the absence of symptoms, onset of HF should be delayed or prevented primarily by controlling hypertension [28] and, when the LVEF is ≤40%, by initiating angiotensin-converting enzyme inhibitor (ACEi) therapy [29] prior to beta-blocker therapy, since the evidences supporting ACEi therapy are stronger [30].
- Symptomatic HF with reduced ejection fraction: patients of this category should all be treated. The goals of therapy are to reduce mortality and morbidity; improve symptoms, quality of life, and functional status and decrease hospitalization rate [31].

Pharmacologic and device therapy should be primarily accompanied by the management of contributing factors of HF and by lifestyle modification. For instance, hypertension and ischemic heart disease can impair cardiac function and exacerbate HF clinical symptoms; therefore, they should be considered and treated in DCM patients [12]. The main lifestyle recommendations are sodium and fluid restriction, abstinence from alcohol intake, and adequate body weight loss [31].

For patients with symptomatic HF, a new therapeutic algorithm has been proposed by the current European guidelines [31]. Neurohormonal antagonists, ACEi or angiotensin II type I receptor blockers (ARB) in case of ACEi intolerance, are recommended from the beginning in association with beta-blocker. The addition of mineralocorticoid receptor antagonists (MRA) should be considered in patients still symptomatic with an optimized dosage of ACEi and beta-blocker. ACEi [29, 32, 33], ARB [34, 35], beta-blocker [36–38], and MRA [39, 40] have demonstrated, in several clinical trials, to reduce risk of HF hospitalization and death in patient with HF and reduced EF.

More recently, two new molecules have been included to the recommended pharmacological therapy: an angiotensin receptor-neprilysin inhibitor (ARNI) and the hyperpolarization channel blocker ivabradine [31]. In particular, Sacubitril/Valsartan, tested in PARADIGM trial, is recommended for patients on optimal medical therapy, tolerating ACEi or ARB, but still in II–III NYHA class [31, 41]. Ivabradine is indicated for patients in sinus rhythm that continue to have a resting heart rate over 70 bpm even on beta-blocker therapy based on SHIFT trial [31, 42]. Both these two drugs have shown to improve survival and reduce hospitalization in patients with HF [41, 42].

Diuretic therapy is intended to reduce symptoms and signs of congestion, but no clinical trial could demonstrate any effect on morbidity and mortality [31].

Finally, in case of intolerance or contraindication to ACEi or ARB, combination of hydralazine and isosorbide dinitrate (not approved in Italy) in symptomatic patients with HF and reduced LVEF has demonstrated to reduce mortality [43]. The same association, combined with conventional HF therapy, in NYHA class III–IV black patients, can reduce mortality and HF hospitalizations [44].

Cardioactive pharmacological drugs should be adjusted and up-titrated every 2 weeks to the maximally tolerated doses that should be achieved within 3–6 months from initial diagnosis of HF [45]. During follow-up, frequent reassessment of the clinical status, biohumoral parameters, and ventricular function should be performed in order to achieve therapeutic decision about possible defibrillator or biventricular pacing implantation [31].

13.4 Ventricular and Supraventricular Arrhythmias

Ventricular and supraventricular arrhythmias often coexist with DCM and HF. The treatment of atrial fibrillation (AF) can substantially alter long-term outcomes in patients with heart failure, but the subject of what is the most effective management strategy is debated. Rhythm control with antiarrhythmic drugs is not superior to rate control in patients with coexisting HF and AF [46]. Catheter ablation is a well-established option for symptomatic atrial fibrillation that is resistant to drug therapy in patients with otherwise normal cardiac function, and various studies have shown that ablation is associated with positive outcomes in patients with heart failure [47]. A recent study showed that catheter ablation for AF in patients with HF was associated with a significantly lower rate of a composite end point of death from any cause or hospitalization for worsening heart failure than was medical therapy [48].

Finally, a common feature of DCM regardless of the underlying cause is a propensity to ventricular arrhythmias, being expression of disease's end stage or an intrinsic characteristic of the disease, often connected to particular genotype (i.e., laminopathies). Therapy for ventricular arrhythmias is also needed for recurrent arrhythmias that cause symptoms, most commonly recurrent ICD shocks. Amiodarone is the preferred major antiarrhythmic agent, particularly when ventricular function is severely depressed. In patients with compensated heart failure, sotalol is an option. For patients with recurrent sustained monomorphic ventricular tachycardia (VT), catheter ablation is a therapeutic option to consider, but experience is limited in comparison with that for VTs that occur in patients with coronary artery disease. Success rates depend on VT substrate location, which can be endocardial, intramural, or epicardial. Endocardial VTs can be generally ablated, whereas an epicardial approach is necessary in one-third of cases, but it is associated with higher complication rates. However, sustained monomorphic VT that triggers frequent ICD shocks or electrical storms can be controlled with ablation and adjunctive antiarrhythmic medications in the majority of cases. Experienced centers performing catheter ablation in patients with nonischemic cardiomyopathy have reported that complete absence of inducible VT can be achieved in 38–67% of patients [49].

13.5 Implantable Cardioverter-Defibrillator

Prophylactic implantation of an ICD is a class I recommendation for patients with nonischemic dilated cardiomyopathy (NIDCM), symptomatic HF with NYHA class II–III, and an LVEF $\leq$ 35% [31]. However, the evidence for a benefit is stronger for patients with ischemic heart disease than it is for patients with other HF etiologies. Among patients with NIDCM, these indications are based on two randomized trials, the DEFINITE and SCD-HeFT trial, performed in the 2000s, which showed a trend toward a reduction of mortality in the ICD arm [50–52]. Accordingly, the current recommendation is based on analysis of subgroup of NIDCM patients of minor trials or on meta-analysis of smaller studies with NIDCM patients [51].

The recent DANISH trial [53] casts a shadow on this strong recommendation: 1156 patients with severe nonischemic LV systolic impairment were randomly assigned to receive an ICD on top of medical therapy or medical therapy alone and followed for a median of 5.6 years. In both ICD and control arms, 58% of the patients received cardiac resynchronization therapy (CRT). Although ICD was associated with a risk of SCD that was half that associated with conventional therapy, mortality from any cause was similar in the ICD and control groups (HR 0.87; 95% CI 0.68–1.12), as well as in patients with CRT-defibrillator (CRT-D) and CRT-pacemaker (CRT-P) (p = 0.59), leaving unclear whether patients eligible for CRT should routinely receive an ICD. These results, probably due to lower rates of events in NIDCM than ischemic patients and the comprehensive medical therapy plus CRT of study population, urge the search for other predictors of sudden death over LVEF, in order to identify the patient who can best benefit from ICD, potentially reducing

device-related adverse events in those who will not experience appropriate ICD interventions. Other noninvasive markers of arrhythmic risk may help to improve the appropriateness of ICD implantation: fibrosis identification by late gadolinium enhancement in cardiac MRI seems the most promising risk predictor [54].

13.6 Cardiac Resynchronization Therapy

Approximately 30% of patients with HF and LV systolic function impairment have a wide QRS complex on the surface electrocardiogram [55], and cumulative mortality increases proportionally with QRS duration [56]. Left bundle branch block (LBBB), associated itself with increased mortality, determines ventricular dyssynchrony as the final result of transmural functional line of block located between the LV septum and the lateral wall with a prolonged activation time [57]. Use of biventricular pacing had been proposed in pharmacological refractory HF patients with intraventricular conduction delay to optimize cardiac performance, through epicardial and then transvenous electrodes. Since then, many trials have demonstrated that CRT, in appropriately selected patients, reduces mortality and morbidity [58] and improves systolic function, symptoms, and quality of life [59, 60].

The effect of CRT, compared to optimized medical therapy, was evaluated by two trials. The COMPANION study demonstrated for the first time a better outcome in patients implanted with CRT plus a defibrillator with advanced HF and a QRS interval > 120 ms than those under pharmacological therapy alone [61]: in the subgroup analyses, hazard ratios for death from any cause of CRT-D as compared with pharmacologic therapy were 0.50 (95% CI, 0.29–0.88) in NIDCM. In the CARE-HF study, CRT reduced all-cause mortality, and the survival benefit with CRT-D over an implantable ICD was consistent in a subgroup analysis of patients with ischemic and nonischemic DCM [62].

Patients enrolled in CRT trials had severe LV systolic dysfunction: most patients had a LVEF < 35%, but other, as MADIT-CRT [59] or RAFT [63], considered LVEF < 30%. Only few patients with an LVEF of 35–40% have been randomized.

As a result, CRT is indicated, according to ESC guidelines [31], as class I recommendation for patients in sinus rhythm, with LBBB, a QRS longer than 130 ms, and LVEF of 35% or less. Evidences are weaker for non-LBBB intraventricular conduction delay and QRS < 150 ms. CRT is contraindicated when QRS is not prolonged: a recent study demonstrated that in patients with systolic HF and a QRS duration < 130 ms, CRT may increase mortality and has no effect on the rate of death or hospitalization for HF [64].

Reverse remodeling is one of the most important mechanisms of action of CRT, but not all patients respond successfully: patients with nonischemic etiology have greater improvement in LV function and decrease in NYHA class after CRT [65]. Data from MADIT-CRT were used to identify factors associated with positive response: female sex, nonischemic etiology, QRS ≥ 150 ms, LBBB, prior HF hospitalization, baseline LVEDV < 125 mL/m^2, and LAVI (left atrial volume index) < 40 mL/m^2 were associated with favorable reverse modeling after CRT implantation [66].

Choice between CRT-P and CRT-D may be hard in selected patients, since most of them with LVEF ≤ 35% have an indication for a concomitant ICD. There are no prospective data proving a benefit of CRT-D over CRT-P, and the only randomized trial to compare CRT-P and CRT-D failed to demonstrate a difference in morbidity or mortality between these strategies [61]. Observational and retrospective studies show that older patients (age ≥ 75 years), particularly if without dilated LV and with nonischemic etiology, and pacemaker-dependent patients are less likely to benefit from CRT-D compared with CRT-P [67, 68].

13.7 Advanced Heart Failure, Mechanical Circulatory Support, Functional Mitral Regurgitation Correction, Heart Transplantation, and Palliative Care

Use of optimal medical therapy, cardiac resynchronization, and implantable defibrillators has changed HF prognosis dramatically. However, 0.5–5% of patients respond poorly to recommended therapy and can develop severe chronic advanced HF with a wide scenario going from refractory deterioration up to cardiogenic shock [69].

Mechanical circulatory support (MCS) devices can be used in critically ill HF patients who can't be stabilized by medical therapy alone. Their goals are to unload the failing ventricle and maintain an adequate end-organ perfusion. Acute and chronic settings require different types of MCS, with short- or mid-/long-term action.

Short-term MCS (few days to weeks) are the systems of choice in patients with acute HF or cardiogenic shock: they include intra-aortic balloon pump and venoarterial extracorporeal membrane oxygenation. They permit to stabilize hemodynamics and gain time for recovery or reevaluation for the possibility of either a more durable MCS or heart transplant.

In a more chronic setting, functional mitral regurgitation (FMR) is a common finding in patients with DCM and left ventricular impairment and is associated with a poor prognosis [70]. In recent years percutaneous correction of mitral regurgitation with the MitraClip system has been established as an alternative treatment option for surgically high-risk patients with degenerative and FMR [71]. Worldwide experience reports high procedural success rates and favorable clinical outcomes in patients with systolic HF and FMR [71, 72]. Patient selection is a crucial issue to obtain the best benefit for patients. A recent report showed that anteroposterior diameter of the mitral annulus and LV end-diastolic volume were significantly associated with device failure during follow-up, and the assessment of these two parameters might be particularly useful for the selection of the optimal candidates to percutaneous treatment of FMR [73].

Heart transplantation (HT) is a well-recognized treatment that significantly increases quality of life and survival for eligible patients with advanced HF, severe symptoms, poor prognosis, and no remaining alternative choices [74]. Unfortunately suitable donor availability is extremely limited. In these cases, implantable left ventricular assist device (LVAD) technology has improved considerably in the last

years. This MCS, historically used only for short periods as bridge-to-transplantation, nowadays is being used increasingly also as a permanent treatment or "destination therapy" [75]. In this scenario, right ventricular (RV) assessment is crucial considering RV failure to occur in up to 50% of cases following LVAD implantation and resulting in high perioperative mortality and morbidity rates [76–78]. An important contribution to evaluation for candidacy to LVAD was the introduction of the INTERMACS classification, which categorizes patients for the purpose of risk assessment prior to LVAD implant or HT [79], ranging from 1 (cardiogenic shock) to 7 (advanced NYHA III), and describes patient's clinical status in terms of hemodynamic stability, inotrope dependence, and functional capacity. Since outcomes in INTERMACS 3 (stable on inotropes) are better than in class I–II, this class has been advocated as the optimal group for implantation. However, the choice remains tough for clinicians, since patients can experience adverse events and complications in up to 60% of cases by 6 months postimplantation, including bleeding, thromboembolic events, infections, and right ventricle failure [80].

Advanced ages, multiple comorbidities, and poorly controlled symptoms characterize the HF terminal stage. In this setting, symptoms management and emotional support of the patients and their family are the principal components of palliative care in advanced HF, in order to improve quality of life [31]. Currently, no consensus has been reached in international guidelines about the right time to start palliative care because of the absence of end-of-life objective criteria. However, the decisions should be always taken by physicians according to the patient and the family.

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