EACVI Expert document on the role of multimodality imaging in the diagnosis, risk stratification and management of patients with dilated cardiomyopathies

Running title: Imaging in Dilated Cardiomyopathies

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Abstract

Dilated cardiomyopathy (DCM) is defined by the presence of left ventricular (LV) or biventricular dilatation and systolic dysfunction in the absence of abnormal loading conditions or coronary artery disease sufficient to explain this dysfunction. This is a heterogeneous disease frequently having a genetic background. Imaging is important for the diagnosis, the prognostic assessment and for guiding therapy. A multimodality imaging approach provides a comprehensive evaluation of all the issues related to this disease. The present document aims to provide recommendations for the use of multimodality imaging according to the clinical question. Selection of one or another imaging technique should be based on the clinical condition and context. Techniques are presented trying to underscore what is “clinically relevant” and what are the tools that “can be used”. There remain some gaps in evidence on the impact of multimodality imaging on the management and the treatment of DCM patients where ongoing research is important.

Key words: dilated cardiomyopathy, prognosis, treatment, echocardiography, cardiac magnetic resonance, nuclear imaging

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A- Unified introduction to DCM

Dilated cardiomyopathy (DCM) is defined by the presence of left ventricular (LV) or biventricular dilatation and systolic dysfunction in the absence of abnormal loading conditions (hypertension, valve disease) or coronary artery disease sufficient to cause global systolic impairment (Tables 1-2)[1-3].

DCM has an estimated prevalence of 1 case in 2500 individuals, is a major cause of heart failure with reduced ejection fraction and is the leading indication for heart transplantation worldwide[1-3, 2,3].

This heterogeneous disease encompasses a broad range of underlying causes, including genetic and acquired disorders (Table 3) that have been revisited within recent years with a growing proportion of familial/genetic causes (about one-third and up to half of cases) and increasing identification of

inflammatory cardiomyopathy that may be related to concealed myocarditis or unrecognized auto-immune diseases [1,2,4].

The appropriate recognition of DCM is of paramount importance. First, the correct identification of the cause through a dedicated diagnostic work-up will lead to an aetiology-oriented approach to therapy, which was illustrated and detailed in a recent Consensus document from the ESC Working Group on Myocardial & Pericardial diseases[2]. Second, over recent decades, research has shed new light on the natural history of DCM, and it is recognized that many patients have a long preclinical phase characterized by few (if any) symptoms and minor cardiac abnormalities that fall outside current disease definitions[2].The clinical spectrum of cardiac expression in DCM is described in Figure 1. Genes have been identified. But there are many forms of DCM that are isolated/sporadic cases and "idiopathic". In some relatives, there is a preclinical phase without cardiac expression that subsequently progresses towards mild cardiac abnormalities, such as isolated LV dilatation (present in ~25% of relatives of familial DCM) or arrhythmogenic features (ventricular or supra-ventricular arrhythmia or conduction defects) that can be observed in myocarditis or in the early phase of genetic diseases, such as Lamin A/C mutation DCM and neuromuscular disorders. The overt phase of systolic dysfunction is usually associated with LV dilatation though in some cases it may be absent, leading to diagnostic confusion. For this reason, a new category of *hypokinetic non-dilated cardiomyopathy* was recently proposed (Table 2) as well as a scoring system for characterization of clinical status in the early stage[2].

B- Imaging methods for diagnosing a DCM and for excluding ischemic aetiology

Symptoms of heart failure are the most common presenting clinical manifestations. Atrial or ventricular arrhythmias or even sudden death can occur at any stage of the disease but are more common in advanced disease. Imaging plays a key role in these patients. Imaging techniques should be used for the diagnosis and for excluding ischemic aetiology.

A comprehensive echocardiography is mandatory. A "Focused cardiac ultrasound (FoCUS) exam" (eventually using handheld ultrasound device) can only raise the suspicion of DCM and should always be complemented by a complete echocardiographic examination, integrating strain measurements and - increasingly - 3D imaging. Only comprehensive echocardiography provides all relevant information on haemodynamics, global ventricular anatomy and function, regional function,

dyssynchrony, valvular heart disease, right heart function, atrial characteristics, geometry (remodelling) that should be obtained[5,6,7].

Contrast agents could be considered to exclude a mural thrombus, or evoking a non-compaction DCM for instance. Transoesophageal echocardiography may be considered for assessing valvular function, presence of atrial thrombi and for guiding transcatheter therapy in patients with concomitant valvular heart disease (mostly secondary mitral and tricuspid regurgitation). CMR or CT could be indicated as well.

Excluding an ischemic aetiology is fundamental, but other conditions have to be listed:

- a tachycardiomyopathy should be also diagnosed by repeating the comprehensive echocardiography after correction of a rapid tachy-arrhythmia.
- In pregnant women, peripartum cardiomyopathy and screening for cardiomyopathy should be proposed when a heart dysfunction has been reported during a previous pregnancy.
- In patients treated for a cancer, treatments might induce a dilated cardiomyopathy but can also facilitate the expression of a DCM in patients at risk.
- Myocarditis or iron overload are potential reversible causes of DCM.

To exclude coronary artery disease, one of the three modalities listed below may be required:

Cardiovascular magnetic resonance imaging (CMRI) is clinically relevant. It provides useful myocardial tissue characterisation about the dysfunctional myocardium by detecting the presence and extent of myocardial oedema, scarring, fibrosis, and infiltration as well as iron overload. This additional unique non-invasive information can aid the identification of the final underlying diagnosis and provide prognostic value. CMR could be used for researching the ischemic component of LV-dysfunctions [8].

Radionuclide imaging techniques allow non-invasive assessment of myocardial perfusion and metabolism and even cardiac innervation through injection of radio-labelled targeted imaging compounds. Myocardial perfusion techniques are clinically relevant especially for distinguishing DCM from ischemic cardiomyopathy. In the presence of coronary artery disease, myocardial ischemia and viability play an important role for guiding therapy and have prognostic implications. We do not discuss ischemia in this document.

Cardiac CT is highly valuable for excluding significant epicardial coronary artery disease. Additionally, its spatial resolution and ease of navigation make cardiac CT suitable when device implantation is

proposed (e.g. prosthesis, mechanical assist device or left ventricular pacing lead). In patients with atrial fibrillation, cardiac CT has high accuracy for excluding left atrial thrombus, and guiding ablation procedures using electroanatomical mapping of the left atrium. Fractional flow reserve via CT (FFR_{CT}) has demonstrated a substantial improvement in the identification of hemodynamically significant coronary artery disease; [9].

C – Specific issues -clinical scenarios

1) De novo diagnosis of unrecognized ventricular dysfunction/heart failure

The early detection of DCM can be done in still asymptomatic patients. It has to be based on risk factors (importance of the family tree and of the family history, uncontrolled cardiovascular risk factors like diabetes could be considered as well). The disease often has a long asymptomatic phase, with normal LVEF and or, sometimes dilated LV-cavity dimensions[2]. The subclinical phase of early myocardial dysfunction may, however, be identified with advanced imaging techniques[10]. The importance of the detection of subclinical disease (by careful analysis of LV size, diastolic function, global longitudinal strain) is important as it allows the institution of early preventive and therapeutic measures, such as lifestyle changes or medical treatments. It may alter the course of the disease[10,11,1,12]; and it may result in a substantial reduction of morbidity and mortality[5].

a- Early phenotypes

Decreased LVEF is a late and insensitive finding in the natural history of DCM, often reflecting irreversible myocardial dysfunction.

Considering echocardiography, tissue Doppler imaging (TDI) with the measurement of the positive peak mid-systolic velocity (averaging septal and lateral side of mitral annulus); normal value 8.9+1.6 cm[13]) can be considered as a clinically relevant early marker of LV longitudinal dysfunction[14]. Additionally, global longitudinal strain (GLS) by 2D speckle tracking echocardiography is the most commonly studied parameter for detecting preclinical disease and is highly reproducible when performed by trained operators [156, 16,17]. The current recommendation is to use the same vendor for serial surveillance. Inter-vendor variability is expected to improve after the work performed by the standardization Task Force initiated by EACVI and ASE [18].

Abnormal circumferential and radial deformation parameters as well as abnormal torsion have also been described in preclinical DCM patients[19]. Nevertheless, major limitations are the lack of reliable

cut-off values and the lack of large studies.

If these more advanced echocardiographic techniques are not available for preclinical screening[3,4], echocardiography is limited in only performing LVEF measurements (for detecting subtle abnormalities in LVEF). The quality of the acquisitions of the apical views should be optimized. The apex foreshortening should be carefully avoided. The relatively high variability of manually traced 2D LVEF (biplane Simpson's method), the concomitant use of LV cavity opacification or the use of automated 2D EF or 3D EF has to be considered for more reliable and reproducible assessments of small changes in left and right ventricular volumes and function[6].

- CMR may impact preclinical diagnosis. CMR should be considered in the case of suboptimal, borderline or doubtful echocardiographic data and in high-risk families when the diagnosis of DCM is still in doubt and would have direct implications on management[20]. Despite its relatively low availability and high cost, CMR may be used in the assessment of myocardial longitudinal strain and helps in early diagnosis of specific aetiologies (sarcoidosis, post-myocarditis DCM)[21]. The tissue characterization (early gadolinium enhancement, T2 and T1 weighted sequences or mapping, and late gadolinium enhancement (LGE)) are a key clinical feature of CMR[22]. The clinical value of CMR in the early detection of the disease must be further explored in larger trials.
- Cardiac CT: Despite its excellent spatial resolution, the role of cardiac CT for early diagnosis of DCM is limited due to its lower temporal resolution, radiation and the need for iodinated contrast. It can be useful, when echocardiographic images are suboptimal (and CMR contraindicated) and concomitant coronary artery or pericardial disease have to be excluded [11,23]. Cardiac-CT can make the diagnosis by demonstrating dilatation of left and right ventricles, pulmonary edema, dilatation of pulmonary arteries, and absence of CAD.
- Gated radionuclide imaging studies provide an accurate alternative to echocardiography or CMR to assess LV systolic function and regional contractility, . Radionuclide ventriculography can be used to assess LV systolic (and diastolic) function without any geometrical assumptions of the LV. Due to its low intraobserver variability, this technique has been used to detect small changes in EF in patients undergoing cardiotoxic chemotherapy[24]. Additionally, right ventricular systolic function can be assessed with radionuclide ventriculography (particularly using first-pass or equilibrium gated blood pool techniques).

b- Diagnostic criteria for relatives of familial DCM

DCM is idiopathic in 50% of cases, about one-third of which are hereditary. There are already more than 50 genes identified that are associated with DCM, many related to the cytoskeleton. The most frequent ones are titin, lamin and desmin. The ESC working group on myocardial and pericardial diseases recently proposed diagnostic criteria for relatives of familial DCM patients[2], integrating at least imaging methods and 12-lead ECG.

In this proposal, imaging criteria may be major (LVEF, LV dilatation) or minor (abnormal regional wall motion in the absence of conduction defects and non-ischaemic LGE CMR). The measurement of global longitudinal strain is encouraged, as mentioned in key point 4[25,26].

c- Timing of screening

A general time frame to perform echocardiography in first-degree relatives of patients with cardiomyopathy, when genetic results are not available, has been proposed[27]. More recently, specific recommendations were provided for familial DCM, in which echocardiography and ECG should be performed in all first-degree relatives starting in childhood (~10 year of age) and repeated every 2–3 years if cardiovascular tests are normal and every year if minor abnormalities are detected[2]. When to stop the screening remains an unresolved issue and it might differ according to the family history. The limit of 60-65 years of age has been proposed[27]. The screening intervals will also depend on the course of the specific types of DCM. For instance, in cardio-oncology patients, this screening will follow specific recommendations[28-30].

2) Prognosis and risk stratification: new parameters that can be used in clinical practice; a pragmatic approach

Despite advances in DCM-treatments, 10-year survival remains <60%, with deaths often preceded by numerous heart failure exacerbations, reflecting the difficulty in assessing the individual risk. Remarkably, the clinical course of DCM patients varies widely, ranging from rapidly progressive HF or SCD to LV reverse remodelling (RR), i.e., significant reduction of LV volumes along with sustained recovery of LVEF. Nearly 40% of newly diagnosed DCM patients experience LV-reverse remodeling under optimal medical therapy (OMT) at a median of 2 years follow-up, foreseeing a favourable long-term outcome[31,32]. This evidence questioned the appropriateness of at least 3 months of OMT in newly diagnosed DCM patients with HF before proceeding to device(s) implantation, as proposed by the current guidelines.[33] Additionally, the LV ejection-fraction cut-off of ≤35% in symptomatic (NYHA class II and III) DCM patients for primary prevention ICD placement (class I, Level of evidence B) [33] is

subject of controversies[34], considering its low sensitivity and specificity in identifying high-risk patients as well as the poor cost-effectiveness profile.

a- Prognostic markers

LV dilatation and impaired contractile function are major prognosticators (for cardiovascular death and hospitalization) in DCM (whatever the imaging technique used). While dilatation is associated with adverse outcome, reverse remodelling and normalization of the LV dimensions is associated with improved survival[31,35]. Reverse remodelling is a therapeutic objective that may take months/years to reach and is monitored by serial imaging. Other imaging parameters, associated with the risk of death or hospitalization for heat failure, include left atrial enlargement, right ventricular (RV) dilatation, and RV contractile dysfunction[36,37]. The latter may be caused by the intrinsic disease or develop secondary to left heart failure. LV-strain has also been repeatedly demonstrated as a key and independent prognostic marker in DCM[38-40].

Recently, RV strain imaging has been suggested as a tool of choice to consider to best define the risk of death and hospitalisation in patients with DCM[41]. The quantification of RV-function and size should be systematically reported in DCM patients[7,42].

LV filling pressure and diastolic function should be assessed and reported. The necessary parameters comprise at least LA-volume, E/A ratio and E velocity deceleration time, e', E/e', maximal velocity of tricuspid regurgitation have to be reported when a DCM-patient is scanned by echocardiography [43]. LA strain is a new promising approach tested but still underinvestigation[44,45].

Secondary (functional) mitral regurgitation (Carpentier I+ IIIb) is a potentially reversible consequence and aggravator of ventricular remodelling that is incrementally associated with adverse outcome[46]. In clinical practice, 2DTTE is used for quantification of secondary mitral regurgitation severity and potential response to therapy[47-49].

Stress echocardiography parameters, but also nuclear imaging measurements such as contractile reserve and coronary flow reserve, predict reverse remodelling and functional recovery in patients with DCM[50,51]. Coronary flow reserve assessment could be assessed by echocardiography in DCM patients with left bundle branch block[52,53]. Also, the presence of microvascular dysfunction (as assessed by position emission tomography) is associated with poorer outcomes and a higher risk of progression to overt heart failure and death[54] .

b- Specific Predictors for ventricular arrhythmias

Ventricular arrhythmias are the most feared complications in DCM. Compared to patients with ischaemic cardiomyopathy, the incidence of ventricular arrhythmias in patients with DCM is lower. Implantable cardioverter-defibrillator (ICD) implantation is the standard of care for prevention of sudden cardiac death (SCD) in high-risk patients[55]. The identification of high-risk individuals is difficult. Current guidelines recommend ICD for primary prevention, as a class IB indication in patients with non-ischaemic DCM and LVEF < 35%, on optimal medical therapy, and with more than 1-year life expectancy[55]. However, adherence to current guidelines has been questioned, and previous trials have not been convincing in the beneficial effect of primary prevention ICD in non-ischaemic patients[56-58]. Primary prevention ICD in patients with non-ischaemic DCM was less efficient at preventing total mortality compared to patients with ischaemic heart disease[59,60].A beneficial effect on all-cause mortality has only been shown in one randomized trial including patients with non-ischaemic heart disease (SCD-HeFT), even if a predefined SCD-HeFT subgroup analysis demonstrated that the benefit was significant only for the ischaemic subgroup [61]. The most recent study on this topic, the DANISH study, further showed the limited effect of primary prevention ICD on total mortality in patients with non-ischaemic DCM [58], indicating that recommendations for primary prevention ICD in these patients needed to be improved. Despite its known limitations, EF still remains the only imaging parameter to guide decisions on primary prevention ICD therapy in non-ischaemic DCM.

Other echocardiographic parameters have been proposed as risk markers of VT/VF, which are additive to EF; however, none of these echocardiographic markers have emerged to substantially influence patient care. The most important emerging parameters from echocardiography include global longitudinal strain (GLS)[62,63] and mechanical dispersion [64]. GLS has shown to be a better marker of ventricular arrhythmias in patients with DCM and remains a good predictor in patients with relatively preserved EF[62]. Reversed apical rotation and loss of LV torsion are also associated with significant LV remodelling and more impaired LV function, indicating a more advanced disease stage[65]. Mechanical dispersion has been suggested as a marker of unfavourable arrhythmic outcome[62,64](figures 2, 3). Mechanical dispersion is measured as the standard deviation of time from Q/R on ECG to peak strain by longitudinal strain in a 16 LV segment model. Mechanical dispersion reflects heterogeneous myocardial contraction and might be associated with increased myocardial interstitial fibrosis[66].

Cardiovascular magnetic resonance (CMR) holds promises in this context by showing that newly diagnosed DCM patients without mid-wall LGE are more likely to experience LV-reverse remodelling than those with LGE, irrespective of the severity of clinical status and of LV dilatation and dysfunction at initial evaluation[32]. Moreover, CMR renders available important risk markers at multiple levels in addition to LV functional parameters. As an example, right ventricular systolic dysfunction (ejection-fraction≤45%), as quantified by CMR, is a powerful and independent adverse predictor of transplant-free survival and other heart failure outcomes[67]. About one-third of DCM patients show mid-wall LGE, reflecting replacement fibrosis, and this has been shown to be a strong and independent predictor of all-cause mortality, cardiovascular death/transplantation and sudden cardiac death [35,68-71] with incremental prognostic value to LV ejection-fraction[35,68,69]. DCM patients with mid-wall LGE had been reported with a 4-fold increased risk of SCD or aborted SCD after correction for other confounders, refining the arrhythmic risk estimation with potential important implications for public health and resource utilization (figure 4). [35,69-71]. Mid-wall fibrosis has been shown to be an effective prognosticator amongst a wide range of disease severity, including in DCM patients without history of heart failure (class B of HF) and in candidates for device(s) treatment. [68,69,71-73] Patients with DCM and mid-wall fibrosis receiving CRT were less likely to exhibit LV reverse remodelling and had worse clinical outcomes compared to non-LGE patients, and these outcomes were similar to those of ischaemic cardiomyopathy patients. [72] These data are in line with a meta-analysis on nine studies, including nearly 1500 patients with DCM, which reported that LGE has an excellent prognostic value for all-cause mortality, HF hospitalization and SCD. [74] Several studies have proposed diverse cut-off values for fibrosis extent for predicting clinical outcomes, but currently there is no consensus about which cut-off can effectively stratify DCM patients. [69,70] Nonetheless, mid-wall fibrosis retained its prognostic value when considered as a continuous variable, supporting the concept that the extent and not only the presence of fibrosis may be a prognostic marker[35,75].

Parametric mapping sequences have been applied in DCM cohorts to quantify myocardial native T1 and T2 relaxation times as well as extracellular volume fraction (ECV). The results from different studies using different T1 mapping sequences at diverse magnetic fields were concordant in their reporting of higher native T1 and ECV values in DCM patients compared to controls. [76,77] In DCM patients, myocardial ECV reflects histology-verified collagen content and may serve as a potential non-invasive marker of diffuse interstitial fibrosis and for monitoring the response to anti-remodelling treatments. [78] Recently, a higher native T1 value of myocardium was demonstrated as an

independent predictor of all-cause mortality and heart failure events in a cohort of 637 patients with DCM. [77]

Despite the adoption of parametric imaging as a promising tool in DCM patients and potentially providing diagnostic as well prognostic information in addition to LGE, multicentre, multivendor, multi-sequence studies in large cohorts of normal subjects and DCM patients are still warranted.

Cardiac radionuclide imaging techniques:

-Single photon emission computed tomography (SPECT)):- DCM are among the major predisposing factor for ventricular arrhythmias, whose genesis relies on the combined presence of a triggering mechanism that initiates the arrhythmia and of an anatomic substrate that maintains the arrhythmia once it is initiated (i.e islands of scar tissue after myocarditis) . One of the most relevant factors that may trigger ventricular arrhythmias is represented by an abnormality of cardiac sympathetic tone. Preliminary data indicated that impairment of cardiac adrenergic innervation may represent a relevant marker of adverse prognosis, particularly predisposing to the development of malignant ventricular arrhythmias[79]. Nuclear imaging might offer the chance to shed light on cardiac sympathetic tone through the use of a dedicated nervous radiotracer [123I-metaiodobenzyl-guanidine (123I-MIBG)] (figure 5). From planar images, 123I-MIBG uptake is semi-quantitatively assessed by calculating the heart-to-mediastinum (H/M) ratio and the washout rate, which estimates cardiac global adrenergic receptor density and has been associated with adverse prognosis[80]. However, despite their excellent reproducibility, those planar scintigraphic measures are unable to unmask regional alterations of cardiac adrenergic tone, whose presence has been shown to be associated with different cardiac pathologies, independently predicting patient outcomes. Some studies have suggested that a regional 123I-MIBG defect score, derived from SPECT images, may be superior to the H/M ratio in predicting patients' adverse prognosis, highlighting the independent detrimental effect of regional adrenergic innervation heterogeneity[81].

The use of new solid-state cardiac cameras with cadmium–zinc–telluride (CZT) detectors, characterized by higher photon sensitivity and spatial resolution than standard cameras allow a comprehensive assessment of myocardial innervation and perfusion in a single imaging session and with a limited radiation burden[82,83]. However, more data are needed in order to use 123I-MIBG in clinical routine..

- Positron emission tomography (PET) remains the reference standard for the non-invasive evaluation of myocardial adrenergic tone, allowing the absolute quantification of sympathetic nerve terminal activity [84].

The versatility of PET radiotracers allows performance of a combined investigation of both pre-synaptic and post-synaptic receptor density. Accordingly, the positron tracers [11C] hydroxyephedrine and [11C]epinephrine permit quantification of the density of sympathetic nerve terminals[84], while postsynaptic receptor density can be assessed with [11C]CGP12177, which has been shown to independently predict patients' adverse prognosis, particularly related to the incidence of symptomatic HF.

Risk stratification of ventricular arrhythmias in patients with familial DCM

A particular subset of patients with familial non-ischaemic DCM have a genetic aetiology, especially patients with Lamin A/C (LMNA) mutations. These patients with LMNA mutations typically have early onset of atrioventricular (AV)-block, supraventricular and ventricular arrhythmias and progressive DCM. Sudden cardiac death due to ventricular arrhythmias is frequent and often occurs before the development of DCM[85-87]. Compared to patients with DCM of another aetiology, risk stratification of ventricular arrhythmias in these patients requires a different approach since these patients have a significantly higher risk of SCD. Reduced EF is a late symptom and cannot be used as the decision tool for ICD. Conduction block, male gender, septal LGE, non-sustained ventricular tachycardia, reduced functional capacity, genotype and previous competitive sports are suggested as risk markers, and ICD implantation for primary prevention in LMNA patients [2] should be considered quite early.[85,87,88] Additional imaging markers from echocardiography in these patients include septal strain and mechanical dispersion[89].

3) The role of cardiac imaging in the decision of heart failure therapies

a. Cardiac Resynchronization Therapy (CRT) /Left Ventricular Assistance Devices (LVAD)

Resynchronization Therapy

<u>Global LV function assessment</u>

LVEF below 35% is a prerequisite for CRT according to current guidelines[21].

Although global longitudinal strain (GLS) has emerged as a sensitive and robust measure of global LV function, there is currently no sufficient evidence for recommending a certain cut-off value for this parameter for patient selection. No randomized study with a control group has demonstrated that GLS based implantation of a CRT-device change the outcomes.

Regional LV functional assessment

CRT resynchronizes the contraction of the cardiac walls, which improves cardiac performance and induces reverse remodelling[90]. Consequently, the assessment of mechanical dyssynchrony has been proposed as a selection-criteria in CRT candidates. Unlike nonspecific parameters, which showed no added predictive value over ECG criteria[91,92], parameters reflecting the typical deformation patterns amendable to CRT can accurately identify responders to CRT[93-95]. In particular, early systolic septal shortening with inward motion (septal bounce, septal flash)[96,97] followed by late systolic stretch of the septum and an apex motion towards the late contracting lateral wall (apical rocking)[93,98-100] are strong predictors of CRT success[93,95]. These patterns are visually recognizable[93,97-99], but less experienced readers may benefit from their quantitative assessment[101]. A low-dose dobutamine challenge can unmask apical rocking and septal flash in a minority of patients where typical dyssynchrony patterns are difficult to recognize[99,102]. The modality of choice for the assessment of mechanical dyssynchrony is echocardiography, as it combines the best temporal resolution with the option of quantification by tissue Doppler or speckle tracking techniques[6]. CMR and radionuclide imaging techniques may also serve this purpose[103].

Unlike echocardiography, SPECT myocardial perfusion imaging provides a single parameter to define mechanical dyssynchrony (phase analysis derived standard deviation SD) which is reproducible, repeatable on serial imaging testing, and easy to derive. (AlJaroudi W, Chen J, Jaber WA, Lloyd SG, Cerqueira MD, Marwick T. Nonechocardiographic imaging in evaluation for cardiac resynchronization therapy. Circulation Cardiovasc Img 2011;4:334–43).

Regional myocardial work can be estimated from echocardiographic pressure strain loops[104,105]and has been shown to be related to reverse remodelling after CRT[106,107]. To what extent these methods predict CRT success beyond dyssynchrony assessment remains to be determined with a control group and not on patients that are all implanted according to current guidelines [107,108](figures 3 and 6).

Ischaemia & Viability

Scar burden reduces the effect of CRT and must be assessed before device implantation. This is much less important in DCM (and much more complicated to quantify) than in ischemic heart disease. Nevertheless, CMR is the method of choice as it shows interstitial fibrosis (T1 mapping) but also authentic scar tissue in post myocarditis cardiomyopathies for instance[109,110]. The level of evidence and the inter-machine variability justify to abstain from a recommendation to use T1-mapping approaches in daily routine practice at the present time. Upon availability, SPECT or a combined FDG/ammonia-PET study may also serve to assess myocardial viability prior to CRT implantation.

Procedure Planning

Cardiac CT can visualize the coronary veins non-invasively if pre-procedural planning of LV lead placement is needed[111]. Hybrid imaging methods may be used to overlay coronary vein anatomy with myocardial viability from PET and cardiac phase analysis from gated SPECT studies and thereby guide noninvasively the implantation of left ventricular pacing leads.

Therapy Response and Reverse Remodelling

AV and VV optimization could be performed to increase the response rate to CRT. AV optimization can be guided during imaging by aiming at a maximal trans-mitral filling time or stroke volume[112,113]. VV optimization may be attempted by means of regional deformation analysis. However, there is limited evidence on the effect on patient outcome[113]. Cessation of apical rocking and of septal flash is an immediate marker of successful CRT implantation and predicts reverse remodelling and survival benefit[93]. Echocardiography is the method of choice for all functional assessments following CRT implantation.

In addition to clinical improvement and survival benefit, increases in LV-function and decreases in LV-volume are long-term signs of favourable CRT-response. The latter is frequently accompanied by a normalization of wall thickness, i.e., an increase in septal and decrease in lateral wall thickness. Echocardiography is the “first line method” to document this so-called “reverse remodelling”. Although CMR might have higher accuracy, it is usually not a convenient approach to perform a routine CMR scan in a patient with an implanted electronic device (Image quality could be impaired due to the metal artefact of the device) [114]. However, CMR in patients with pacemakers and ICD both MR-conditional, and more recently also in non-conditional devices, can be performed safely in expert CMR centres[115]. An LV end-systolic volume decrease of more than 15% within the first year is

a commonly accepted cut-off for successful CRT. It must be assumed, however, that in certain patients, less reverse remodelling might also be related to survival benefit, while in some patients, the pure stabilization of LV size, i.e., the prevention of further remodelling, might be a therapeutic success[116].

Left Ventricular Assist Devices

Patient Assessment

The absence of severe right ventricular and tricuspid valve dysfunction are relevant criteria to determine the eligibility of patients for the implantation of a left ventricular assist device (LVAD)[21,117]. RV longitudinal strain has demonstrated useful and independently predicts RV failure after LVAD implant[118,119].

Echocardiography is the first line method of choice for the initial assessment of cardiac morphology and function of an LVAD candidate (table 4) [117,120]. RV size should be routinely assessed by conventional two-dimensional echocardiography using multiple acoustic windows, and the report should include both qualitative and quantitative parameters[121]. Three-dimensional echocardiography may be used in laboratories with experience and the necessary equipment[6,21].

Extra-cardiac anatomic structures, such as the great vessels, may be imaged with MRI or, in case of implanted devices, CT[111].

Patient follow up(Table 5)

In addition to the assessment of left and right ventricular morphology and function, the 2D and Doppler examination of the LVAD cannula within the LV is relevant for the functional assessment of the device[122-124].

b. **Secondary (Functional) mitral regurgitation (MR)**

Secondary MR is an important issue in DCM patients. A clear prognostic value of this type of MR has been reported.

MR in DCM is not mainly due to a disease of the leaflets but to the symmetrical or asymmetrical dilation of the left ventricle. The detection of the MR should not wait that the LV-dysfunction become too severe. When the LV is too enlarged and the function too decrease, MR looses its prognostic value[125].

Secondary MR needs to be carefully assessed[48](figures 7 and 8). Medical treatment including CRT will impact on the severity of the MR.

If MR remains severe and symptomatic, surgery and percutaneous correction of the regurgitation could be considered. The ESC guidelines in valvular heart disease provide a class IIbC indication for the percutaneous edge-to-edge procedure or valve surgery after careful evaluation for ventricular assist device or heart transplant, according to individual patient characteristics in patients with severe secondary mitral regurgitation and LVEF < 30% who remain symptomatic despite optimal medical management (heart team decision).

However, how should the secondary MR be defined as severe? This should be based on an integrative approach including an anatomic assessment of the heart. Degree of LV dilatation and the degree of leaflet tethering should be carefully evaluated. Then, the regurgitation has to be quantified according to the specific recommendations and guidelines proposed by the ESC and the EACVI.

Discrepancy between European and American approaches for defining a severe secondary MR exist[49,126]. This issue is related to a gap in evidence. The recent Mitra-FR and COAPT trials are encouraging the use of regurgitant volume > 45 ml and/or regurgitant orifice area > 30mm² for deciding for the implantation of clips in patients symptomatic and having a LVEF >20% [127-130].

D- Appropriateness of each imaging technique to assess patients with DCM

European appropriateness criteria for the use of cardiovascular imaging in heart failure (HF) have been developed using a rigorous process described elsewhere[131]. This document provides a framework for decisions regarding judicious utilization of imaging in the management of patients with HF seen in clinical practice. However, the appropriate use of each non-invasive cardiovascular imaging (CVI) technique in DCM has not been studied extensively. As in HF patients, cardiovascular imaging can be used for DCM patients in various clinical scenarios and settings: 1/ for the diagnosis of the DCM, 2/ for the planning of the treatment (CRT/LVAD) and 3/ for the follow-up of the DCM patients. The appropriateness of use for each technique may be dependent on the mode of presentation (urgent or not), the stage of the DCM (early vs. clinical), the symptomatic status, and the need to perform a screening. It should also reflect practice heterogeneity across Europe, with broad variations in access to modern technology and imaging facilities, educational platforms, training requirements, certification guidelines, and reimbursement systems.

E- Challenges and gaps in evidence

Large studies testing imaging-based approach to disease treatment vs non-imaging-based approach are lacking. The literature suggests that imaging, especially echocardiography which was tested, was unsuccessful to improve patients' selection for CRT. Nevertheless, imaging techniques are becoming more mature in the precision and the potential clinical value of parameters offered Scientific Associations, like the EACVI, are committed to define the most appropriate imaging approach and patients' pathways[132]. Individual modalities and multimodality imaging appropriateness criteria are warranted, as well as randomized prospective large studies involving imaging strategy scenarios. In an era of precision medicine, imaging phenotyping might play a key role in therapeutic decisions and management.

F- Perspectives

Despite several imaging and genetic improvements, several challenges persist concerning the diagnosis, genetics and other aetiologies, prognosis, and even definition of DCM. Although a revised definition of DCM has recently been proposed (2), including the creation of a new category of hypokinetic non-dilated cardiomyopathies, several uncertainties persist. Multimodality imaging combined with genetic studies could have a central role in the evaluation of DCM.

In the present document the differential diagnoses of DCM (excepting the ischemic aetiology) is not specifically addressed. One of the major challenges is being able to both make an early diagnosis of DCM, leading to earlier and more effective preventive and therapeutic strategies, but to avoid erroneous diagnosis and misinterpretation of physiological variants. Two such examples are the "grey-zone" LV modifications observed in athletes [133]and the frequently difficult diagnosis of LV non-compaction, with the known risk of both over- and under-diagnosis. A unified definition of the diagnostic criteria for LV-non compaction is waiting for results from ongoing studies[134,135].

In all these difficult situations, the combined use of 2 different imaging modalities is recommended, including preferably echocardiography or CMR. These techniques give additional information and should frequently be used in combination in the same patient to maximize diagnostic performance.

Additional studies are warranted to select the most appropriate utilization of each imaging technique when facing a patient with suspected or definite DCM[2,136]. Finally, additional investigations such as familial screening, and genetic studies are frequently necessary.

Patients with suspected DCM should be referred to specialized centres that can provide a multidisciplinary team approach for early diagnosis, avoiding over-diagnosis, providing adequate familial counselling, prognostic stratification, and finally optimal patients' management.

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Figures and Tables

Figure 1: (from Pinto [2]): clinical spectrum of the DCM with the important pre-clinical period.

Figure 2: example of a DCM with a typical pattern of mechanical dyssynchrony: too early contraction of the septum before the aortic valve opening and lengthening of the anterolateral wall leading to a delayed shortening of this wall. (longitudinal strain imaging – take care at the timing and at the color according to each left ventricular wall).

Figure 3: About one-third of DCM patients show mid-wall late gadolinium enhancement (arrow - LGE), reflecting replacement fibrosis, and this has been shown to be a strong and independent predictor of all-cause mortality, cv-death/transplantation and sudden cardiac death (see the text).

Figure 4: mechanical dispersion: the longitudinal peaks of longitudinal deformation are not reaching their peak at the same period of time in patients with DCM at increased risked of ventricular arrhythmias.

Figure 5: A 62 years old female with idiopathic cardiomyopathy and a history of ventricular arrhythmias presenting recurrent episodes of ventricular tachycardia. A) The scintigraphic perfusion images show homogeneous perfusion in the whole left ventricle, with the exception of a minimum reduction of perfusion in the proximal portion of the inferior wall (SRS 1, not significant). The innervation images (lower rows) reveal an extensive area of denervation involving the lateral and inferior walls (SS-MIBG 17) with a big innervation/perfusion mismatch. B) At EP study located the sites of origin of the arrhythmia at the level of the inferior and infero-lateral LV walls.

Figure 6: new approach of longitudinal strain (globally and regionally). The strain curves are computed according to the blood pressure and the calculation of the intra-left ventricular pressures (pressure - strain loops). Promising approach for calculating the myocardial work and the potential clinical value for predicting better the response to cardiac resynchronization therapy.

Figure 7: Native T1 mapping (MOLLI) of basal LV short axis showing increased values in the septum (a). Post contrast T1 mapping of basal LV short axis (b). Post contrast basal LV short axis, showing mid-wall myocardial late enhancement (yellow arrows) (c). Basal LV short axis cine (d).

Figure 8: Four chamber cine of patient affected by DCM and severe LV systolic dysfunction and LBBB in diastole (a) and systole (b); Mid ventricle LV short axis view used for tissue tracking analysis (c); schematic representation of radial strain (%) curves: the two arrows represent the dyssynchrony between the septum and the lateral walls.

Figure 9: A woman 75 yo, idiopathic DCM, who justified a cardiac resynchronization therapy and an ICD. After few years, despite an optimal medical therapy she is still NYHA II+ and recently hospitalized for acute HF. The trans thoracic echocardiography completed by a trans-esophageal exam allows to describe the spherization of the left ventricle (LVEF 35% and LV end-diastolic diameter 64mm). The tethering effect related to this LV remodeling on both mitral leaflets. The leaflets are thin without any large indentation, without any calcification and the regurgitant jet is greater than 45ml/beat (regurgitant orifice area > 20 mm^2) and maximal in regard to A2P2.

Table 1 (central table). Key points of the recommendation paper based on scientific background and experts 'consensus.

Key point 1:	Dilated cardiomyopathy (DCM) is defined by the presence of left ventricular (LV) or biventricular dilatation and systolic dysfunction in the absence of abnormal loading conditions (hypertension, valve disease) or coronary artery disease sufficient to cause global systolic impairment.
Key Point 2:	All the imaging techniques should not be performed and repeated in every single DCM-patient. They should be used to answer a specific clinical question.
Key point 3:	Echocardiography is the "first step" imaging technique. It provides information about anatomy, function and haemodynamic, as well as prognostic information, for the best treatment selection.
Key point 4:	Imaging techniques should be used for screening individuals with risk factors for non-familial DCM and for early diagnosis of first-degree relatives in familial DCM.
Key point 5:	Cardiac magnetic resonance (CMR) is an important tool to consider (at least once) in every patient with DCM. It is the gold standard for measuring LV-, RV-volumes and ejection fraction. It also provides tissue characterization and may suggest the cause of ventricular dysfunction.

Key point 6:	Nuclear imaging is not used in the routine assessment of every DCM. It is the reference standard for the non-invasive evaluation of myocardial adrenergic tone.
Key point 7:	Cardiac-CT is highly valuable to exclude significant epicardial coronary artery disease. Additionally, the good spatial resolution and ease of navigation make cardiac-CT suitable when device implantation is proposed (e.g. transcatheter prosthesis, ventricular assist device or left ventricular pacing lead).
Key point 8:	LV longitudinal dysfunction is a sensitive marker of subclinical, early myocardial dysfunction, usually assessed with the measurement of long axis myocardial velocities and by longitudinal deformation. The measurement of s' and the use of global longitudinal strain is recommended.
Key point 9:	Though the level of evidence remains insufficient, there are strong elements encouraging the use of speckle tracking echocardiography, CMR or MIBG-SPECT-imaging for best assessing DCM patients at risk for ventricular arrhythmias.
Key point 10:	Early systolic septal shortening with inward motion (septal bounce, septal flash) followed by late systolic stretch of the septum and an apex motion towards the late contracting lateral wall (apical rocking) are strong predictors of CRT-response. New semi-automatic approaches based on the use of regional longitudinal strain curves are highly promising.
Key point 11:	The quantification of RV function is mandatory in addition to the assessment of diastolic function and valvular function during the follow-up of a DCM-patient. Imaging of DCM should not be limited to the LV size and function.

Key point 12:	Echocardiographic (and sometimes hemodynamic) testing provides an objective means of optimizing revolutions per minute and of guiding medical management. It must still be assessed for improving the quality of life and clinical outcomes of LVADs carriers.
Key point 13:	Secondary MR is a key prognostic marker in DCM. It should be assessed carefully. Tenting, mitral valve area in diastole, anatomy of the leaflets, localization of the regurgitant jet, size of the heart's four cavities, and degree of tricuspid regurgitation and left and right ventricular dysfunctions should be precisely analysed before discussing a potential correction of the MR. The absence of inter-atrial severe aneurysm of paten foramen oval should be looked for.

Table 2. Diagnostic criteria (from Pinto et al[2]).

Dilated Cardiomyopathy (DCM):	Left ventricular or biventricular systolic dysfunction (defined as LVEF<50%) and dilatation* that are not explained by abnormal loading conditions or coronary artery disease. **(LV dilatation is defined by LV end diastolic (ED) volumes or diameters >2SD from normal according to normograms (Z scores >2 standard deviations) corrected for body surface area (BSA) and age or BSA and gender)*
Hypokinetic non-dilated cardiomyopathy (HNDC):	*Left ventricular or biventricular global systolic dysfunction without dilatation (defined as LVEF<45%), not explained by abnormal loading conditions or coronary artery disease.*

Table 3: Main causes of a dilated cardiomyopathy (DCM)

Causes	Sub-type of causes
Genetic causes	- Main genes, such as titin, are related to predominant cardiac expression - Neuromuscular disorders - Syndromic diseases[2]
Infectious causes (chronic myocarditis)	Viral, bacterial, fungal, parasitic causes
Toxic and overload	Such as ethanol, cocaine, iron overload
Electrolyte disturbance	Such as hypocalcaemia
Endocrinology causes	Such as dysthyroidism, acromegaly
Nutritional deficiency	Such as selenium, thiamine, carnitine deficiencies
Auto-immune diseases	Organ-specific (such as inflammatory cardiomyopathy) or not (such as polymyositis)
Drugs-induced	Such as antineoplastic and psychiatric drugs
Tachycardia-induced cardiomyopathy[137]	
Peripartum cardiomyopathy[138]	

Table 4: LVAD preimplantation echocardiographic abnormal findings to look for.

Left Ventricle and Interventricular Septum

LV size and morphology: should not be too small and with increased LV trabeculation or thrombi

Make sure that there is no LV apical aneurysm and no Ventricular septal defect

Right Ventricle

RV dilatation

RV systolic dysfunction: that is challenging and that should consider the pulmonary pressures (afterload) and all the qualitative and quantitative parameters available (including the subcostal window)

Atrial, Interatrial septum and Inferior vena cava

Left atrial appendage thrombus, PFO or atrial septal defect should be looked for

Valvular Abnormalities

Any prosthetic valve (mechanical should be avoided)

The degree of aortic regurgitation should be assessed extremely carefully. TOE could be necessary.

All the other valve should not be significantly abnormal or be planed for correction at the time of the LVAD implantation (tricuspid regurgitation especially)

Aorta and make sure there is no congenital heart disease

Aortic aneurysm, dissection, atheroma, coarctation but also mobile mass lesion should be looked for (consider TOE)

LV, left ventricular; RV: right ventricular; *PFO,* patent foramen ovale; TOE: transesophageal echocardiography; LVAD, left ventricular assistance device

Table 5: Post-LVAD implantation complications. Value of echocardiography.

One has to be systematic and specialized in the assessment of patients with LVAD (being aware of

the device implanted, the patient and its history):

1- pericardial effusion or hematoma.

cardiac tamponade will lead to RV compression and decrease in RV outflow track velocity time integral. Check for the pericardium using all the echocardiographic windows (TOE if needed) and assess right heart output

2- LV failure related to LV over-loading

Important of serial exam comparison

a. 2D/3D: increasing LV size; increased AV opening duration, increased left atrial volume.
b. Doppler: increased mitral inflow peak E-wave diastolic velocity, increased E/A and E/e' ratio, decreased deceleration time of mitral E velocity, worsening functional MR, and elevated pulmonary artery systolic pressure.

3- RV failure

a. 2D: increased RV size, decreased RV systolic function, high RAP (dilated IVC/**leftward atrial septal shift), leftward deviation of ventricular septum**.
b. Doppler: increased TR severity, reduced RVOT SV, reduced LVAD inflow cannula and/or outflow-graft velocities (<0.5 m/sec with severe failure); inflow-cannula high velocities if associated with a suction event.

Of Note: a ''too-high'' **LVAD pump speed may contribute to RV failure by increasing TR** (septal shift) **and/or by increasing RV preload**.

4- Inadequate LV-filling or excessive LV-unloading

Small LV dimensions (typically <3 cm and/or marked deviation of interventricular septum towards LV). **Danger to not misinterpret a RV failure and/or pump speed too high for loading conditions**.

5- LVAD-suction with induced ventricular ectopy

Underfilled LV and mechanical impact of inflow cannula with LV endocardium, typically septum, resolves with speed turndown.

6- LVAD-related continuous aortic insufficiency

Clinically significant—at least moderate and possibly severe—characterized by an AR vena contracta >3 mm; increased LV size and relatively decreased RVOT SV despite normal/increased inflow cannula and/or outflow graft flows.

7- LVAD-related mitral regurgitation

a. Primary: inflow cannula interference with mitral apparatus.
b. Secondary: MR-functional, related to partial LV unloading/persistent heart failure.

8- Intracardiac Thrombus

Including right and left atrial, LV apical, and aortic root thrombus

9- Inflow-cannula abnormality

a. *2D/3D*: small or crowded inflow zone with or without evidence of localized obstructive muscle trabeculation, adjacent MV apparatus or thrombus; mispositioned inflow cannula.
b. *High-velocity* color or spectral Doppler at inflow orifice. Results from malposition, suction event/other inflow obstruction: aliased color-flow Doppler, CW Doppler velocity >1.5 m/s.
c. *Low-velocity* inflow (markedly reduced peak systolic and nadir diastolic velocities) may indicate internal inflow-cannula thrombosis or more distal obstruction within the system. Doppler flow velocity profile may appear relatively ‘‘continuous’’ (decreased phasic /pulsatile pattern).

10- Outflow-graft abnormality

Typically, due to obstruction/pump cessation.

a. 2D imaging (TOE): visible kink or thrombus.
b. Doppler: peak outflow-graft velocity >2 m/s at the obstruction site; but diminished or no

spectral Doppler signal if sample volume is remote from obstruction location, combined with lack of RVOT SV change and/or expected LV-dimension change with pump-speed changes.

11- Pump malfunction/pump arrest

a. Reduced inflow-cannula or outflow-graft flow velocities on color and spectral Doppler or, with pump arrest, shows diastolic flow reversal.
b. Signs of worsening HF: including dilated LV, worsening MR, worsened TR, and/or increased TR velocity; attenuated speed-change responses: decrease or absence of expected changes in LV linear dimension,

Abbreviations:

2D, Two-dimensional; *3D,* three-dimensional; *AR,* aortic regurgitation; *AV,* aortic valve; *BP,* blood pres- sure; *CW,* continuous-wave; *E,* mitral valve early peak diastolic velocity; e', mitral annular velocity; *IVC,* inferior vena cava; *LV,* left ventricular; *LVAD,* left ventricular assist device; *LVOT,* left ventricular outflow tract; *MR,* mitral regurgitation; *MV,* mitral valve; *RAP,* right atrial pressure; *RV,* right ventricular; *RVOT,* right ventricular outflow tract; *SV,* stroke volume; *TR,* tricuspid regurgitation.

Adapted from Estep et al and Stainback et al.[139,140]