

Table 1. ESC 2023 GL on Cardiomyopathies. Non-genetic causes of dilated cardiomyopathy

Infection (post-myocarditis)	
Viral (enteroviruses, adenoviruses, echoviruses, herpes viruses, parvovirus B19, HIV, SARS-CoV-2, etc.)	
Bacterial (Lyme disease)	
Mycobacterial	
Fungal	
Parasitic (Chagas disease)	
Toxic and overload	
Alcohol (ethanol)	
Cocaine, amphetamines, ecstasy	
Cobalt	
Anabolic/androgenic steroids	
Haemochromatosis and other causes of iron overload	
Endocrinology	
Hypo- and hyperthyroidism	
Cushing/Addison disease	
Pheochromocytoma	
Acromegaly	
Diabetes mellitus	
Nutritional deficiency	
Selenium deficiency	
Thiamine deficiency (Beri-Beri)	
Zinc and copper deficiency	
Carnitine deficiency	
Electrolyte disturbance	
Hypocalcaemia	
Hypophosphataemia	
Peripartum	
Autoimmune diseases	
Giant cell myocarditis	
Inflammatory (biopsy-proven, non-infectious myocarditis)	
Eosinophilic granulomatosis with polyangitis	
Systemic lupus erythematosus	
Sarcoidosis	
Rheumatoid arthritis	
Coeliac disease	
Primary biliary cirrhosis	
Myasthenia gravis	
Pemphigus pemphigoid	
Crohn disease	
Ulcerative colitis	
Polymyositis/dermatomyositis	
Reactive arthritis	
Drugs	
Antineoplastic drugs	Anthracyclines; antimetabolites; alkylating agents; Taxol; hypomethylating agent; monoclonal antibodies; tyrosine kinase inhibitors; immunomodulating agents
Psychiatric drugs	Clozapine, olanzapine; chlorpromazine, risperidone, lithium; methylphenidate; tricyclic antidepressants
Other drugs	All-trans retinoic acid; antiretroviral agents; phenothiazines

HIV, human immunodeficiency virus; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

Table 2. EHRA/HRS/APHRS/LAHS 2022 Consensus Statement on genetic testing. Genes implicated in dilated cardiomyopathy

Gene	Locus	Phenotype-syndrome	Protein (functional effect)	Frequency	ClinGen classification
<i>TTN</i>	2q31.2	DCM	Titin	~15–25%	Definitive
<i>LMNA</i>	1q22	DCM, ACM	Lamin A/C	~4–7%	Definitive
<i>MYH7</i>	14q11.2	HCM	Bêta Myosin heavy chain	~3–5%	Definitive
<i>TNNT2</i>	1q32.1	HCM, DCM	Troponin T	~2%	Definitive
<i>RBM20</i>	10q25.2	DCM	RNA-binding motif protein 20	~2%	Definitive
<i>PLN</i>	6q22.31	DCM, ACM	Phospholamban	~1% (<i>more in Netherlands</i>)	Definitive
<i>FLNC</i>	7q32.1	DCM»BiVACM	Filamin-C	~3%	Definitive
<i>BAG3</i>	10q26.11	DCM, myopathy	BAG family molecular chaperone regulator 3	~2%	Definitive
<i>DSP</i>	6p24.3	ARVC, DCM	Desmoplakin	1–3%	Strong
<i>TPM1</i>	15q22.1	HCM, DCM	alpha-tropomyosin	~1–2%	Moderate
<i>ACTC1</i>	15q11q14	HCM, DCM	Cardiac alpha-actin	<1%	Moderate
<i>ACTN2</i>	1q43	HCM, DCM, LVNC	Alpha-actinin-2	<1%	Moderate
<i>DES</i>	2q35	DCM, Myopathy, ACM	Desmin	<1%	Definitive
<i>JPH2</i>	20q13.12	DCM, HCM	Junctophilin 2	<1%	Moderate
<i>NEXN</i>	1p31.1	DCM, HCM	Nexilin	<1%	Moderate
<i>SCN5A</i>	3p22.2	LQTS, Brugada, DCM, ACM	Sodium channel protein type 5 subunit alpha	<1%	Definitive
<i>TNNC1</i>	3p21.1	DCM, HCM	Cardiac Troponin C	<1%	Definitive
<i>TNNI3</i>	19q13.4	HCM, DCM	Cardiac troponin I	<1%	Moderate
<i>VCL</i>	10q22.2	DCM	Metavinculin	<1%	Moderate

ACM, arrhythmogenic cardiomyopathy; DCM, dilated cardiomyopathy; HCM, hypertrophic cardiomyopathy.

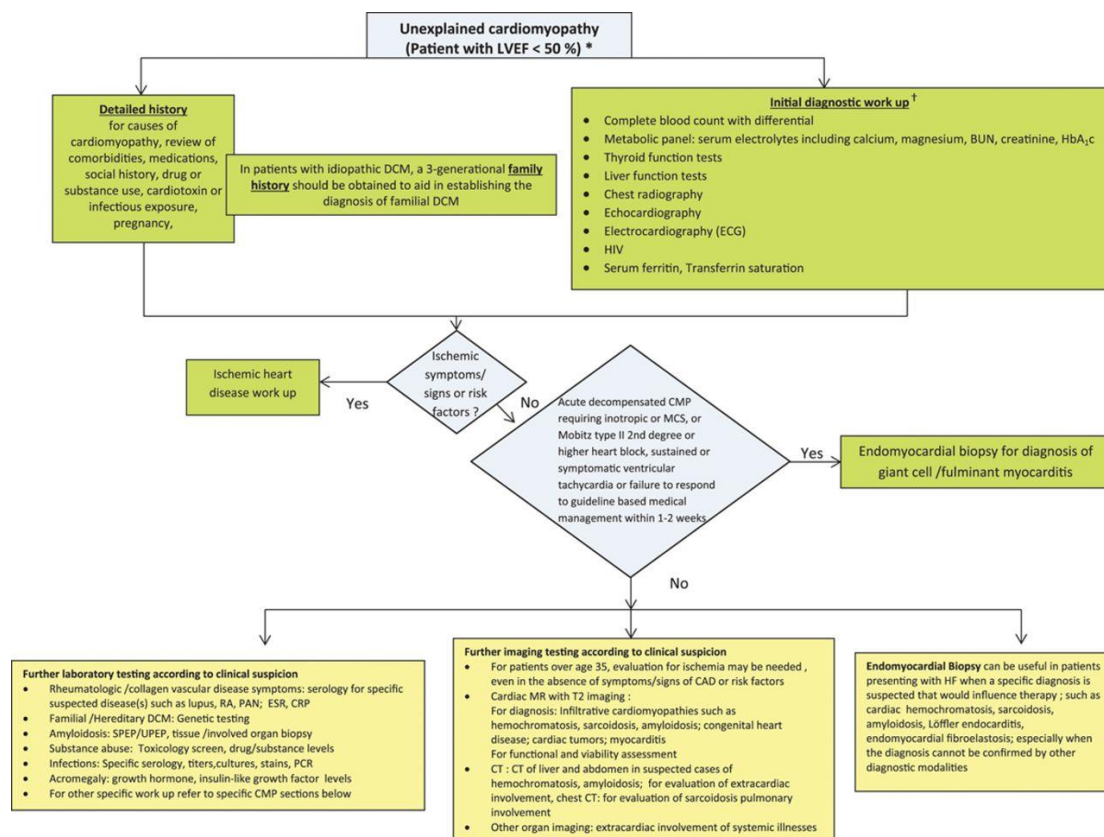


Figure 1. Diagnostic strategies in DCM.

BUN indicates blood urea nitrogen; CAD, coronary artery disease; CMP, cardiomyopathy; CRP, C-reactive protein; CT, computed tomography; DCM, dilated cardiomyopathy; ESR, erythrocyte sedimentation rate; HbA1c, hemoglobin A1c; HF, heart failure; LVEF, left ventricular ejection fraction; MCS, mechanical circulatory support; MR, magnetic resonance; PAN, polyarthritis nodosa; PCR, polymerase chain reaction; RA, rheumatoid arthritis; SPEP, serum protein electrophoresis; and UPEP, urine protein electrophoresis.

*Current definition per 2013 ACC/AHA guidelines on Heart failure. Heart failure with reduced ejection fraction (HFrEF; ejection fraction <40%) or heart failure with borderline preserved ejection fraction (HFpEF; borderline ejection fraction 41%-49%).

†These diagnostic tests are part of a routine workup of initial evaluation of a patient with heart failure.

Bozkurt B, et al. Current diagnostic and treatment strategies for specific dilated cardiomyopathies: A scientific statement from the American Heart Association. *Circulation*. 2016;134:e579-e646

TABLE 3. Genetic Testing**ESC 2021 GL on HF. Dilated cardiomyopathy or hypokinetic non-dilated cardiomyopathy: specific aspects of diagnosis and Treatment. Genetic counselling and testing**

Indication. All patients with a diagnosis of DCM or HNDC and all first-degree adult relatives of patients with DCM or HNDC and a definite disease-causing mutation, regardless of their phenotype, in order to identify genetically affected individuals at a preclinical phase.

Aim. First-degree adult relatives should have their evaluation repeated every 5 years or less when aged <50 years or non-diagnostic abnormalities are found.

Clinical evaluation, ECG, echocardiography and possibly CMR, must be performed in first-degree relatives of patients.

Aims. Can identify patients with DCM or HNDC at highest risk of arrhythmia and/or deserving other specific treatments.

Early identification of asymptomatic relatives may lead to early treatment and prevention of progression to HF and proper genetic counseling.

Minimal set of genes^a: TTN, LMNA, MHC, TNNT, troponin-C, MYPC, RBM20, PLN, sodium channel alpha unit, BAG3, actin alpha cardiac muscle, nexilin, tropomyosin-1, vinculin.

The use of additional sequencing for the analysis of very large panel of genes may be considered when there is a clear familial history or structural phenotype, by preference combined with family segregation.

TNNT = troponin-T; LMNA = lamin A/C; RBM20 = ribonucleic acid binding motif 20; PLN = phospholamban; FLN = filamin; TTN = titin; BAG3 = Bcl2-associated athanogene 3; CMR = cardiac magnetic resonance; ECG = electrocardiogram; HF = heart failure; HFrEF = heart failure with reduced ejection fraction; ICD = implantable cardioverter-defibrillator; LV = left ventricular; LVEF = left ventricular ejection fraction; MHC = myosin heavy chain; MYPC = myosin-binding protein C; NSVT = non-sustained ventricular tachycardia; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2;

^aThis list of genes is not exhaustive, and will change over time, with increasing knowledge of the pathogenicity. Contact the genetic department to ask which core panel of genes they are using.

^bRisk factors in patients with a confirmed LMNA mutation: NSVT during ambulatory ECG monitoring, LVEF <45% at first evaluation, male sex and non-missense mutations (insertion, deletion, truncations, or mutations affecting splicing).

EHRA/HRS/APHRS/LAHS 2022 Consensus Statement on genetic testing.

Impact of genetic testing for the index case

Disease	Diagnostic	Prognostic	Therapeutic
DCM	++	+++	++

Recommendations

Should do

Genetic testing for probands with DCM and family history of DCM, and the initial tier of genes tested should include genes with definitive or strong evidence of pathogenicity (currently BAG3, DES, FLNC, LMNA, MYH7, PLN, RBM20, SCN5A, TNNC1, TNNT2, TTN, DSP).

Genetic testing for patients with DCM and family history of premature unexpected sudden death or in a DCM patient with clinical features suggestive of a particular/rare genetic disease (such as atrioventricular block or sinus dysfunction or creatine phosphokinase elevation).

Variant-specific genetic testing is recommended for family members and appropriate relatives following the identification of the disease-causative variant.

Predictive genetic testing in related children in those aged >10–12 years.

May do

For genetic testing in a proband with DCM, the initial tier of genes tested may include genes with moderate evidence of pathogenicity (ACTC1, ACTN2, JPH2, NEXN, TNNI3, TPM1, VCL).

Genetic testing for patients with apparently sporadic DCM, particularly in the presence of either severe systolic dysfunction (left ventricular ejection fraction < 35%), or a malignant arrhythmia phenotype (e.g. sustained ventricular tachycardia/fibrillation), or particularly at a younger age.

Genetic testing for patients with DCM related to an acquired or environmental cause that may overlap with a genetic cause (such as peripartum or alcoholic cardiomyopathy).

Genetic testing for patients with DCM to improve risk stratification and guide therapy.

Predictive genetic testing in related children aged below 10–12 years, especially where there is a family history of early-onset disease.

ESC 2022 GL on VA and SCD. Recommendations for risk stratification, sudden cardiac death prevention, and treatment of ventricular arrhythmias in dilated cardiomyopathy/hypokinetic non-dilated cardiomyopathy

Diagnostic evaluation and general recommendations

Genetic testing (including at least LMNA, PLN, RBM20, and FLNC genes) in patients with DCM/HNDCM and AV conduction delay at 50 years, or who have family history of DCM/HNDCM or SCD in a first-degree relative (at age 50 years). I B

CMR with LGE in DCM/HNDCM patients for assessing the aetiology and the risk of VA/SCD. IIa B

Genetic testing (including at least LMNA, PLN, RBM20, and FLNC genes) for risk stratification in patients with apparently sporadic DCM/HNDCM, who present at young age, or with signs suspicious for an inherited aetiology. IIa C

Participation in high-intensity exercise including competitive sports is not recommended for individuals with DCM/HNDCM and a LMNA mutation. III C

Table 4. ESC 2023 GL on Cardiomyopathies. High-risk genotypes and associated predictors of sudden cardiac death

Gene	Annual SCD rate	Predictors of SCD
LMNA ^{185,186,438,541,865,878,879}	5–10%	Estimated 5-year risk of life-threatening arrhythmia using LMNA risk score (https://lmna-risk-vta.fr)
FLNC-truncating variants ^{864,867,880}	5–10%	LGE on CMR LVEF < 45%
TMEM43 ^{868,881}	5–10%	Male Female and any of the following: LVEF < 45%, NSVT, LGE on CMR, > 200 VE on 24h Holter ECG
PLN ^{542,882,883}	3–5%	Estimated 5-year risk of life-threatening arrhythmia using PLN risk score (https://plnriskcalculator.shinyapps.io/final_shiny/) LVEF < 45% LGE on CMR NSVT
DSP ^{185,186}	3–5%	LGE on CMR LVEF < 45%
RBM20 ⁸⁶⁹	3–5%	LGE on CMR LVEF < 45%

CMR, cardiac magnetic resonance; DSP, desmoplakin; ECG, electrocardiogram; FLNC, filamin C; LGE, late gadolinium enhancement; LMNA, lamin A/C; LVEF, left ventricular ejection fraction; NSVT, non-sustained ventricular tachycardia; PLN, phospholamban; RBM20, RNA binding motif protein; SCD, sudden cardiac death; VE, ventricular ectopic beats.

Table 5. General Recommendations and Therapy**ACC/AHA/HRS 2017 GL on VA/SCD. Nonischemic Cardiomyopathy (NICM)**

Cardiac MRI with late gadolinium enhancement in suspected myocardial infiltrative processes	I-B-NR
Cardiac MRI with late gadolinium enhancement for assessing risk of SCA/SCD.	IIa-B-NR
Genetic counseling and genetic testing in patients who develop conduction disease or LV dysfunction at < 40 years of age, or who have a family history of NICM or SCD in a first-degree relative (<50 years of age).	IIa-C-EO

Table 8. Prevention of sudden cardiac death**ACC/AHA/HRS 2017 GL on VA/SCD.****Secondary Prevention of SCD in Patients With NICM**

ICD if meaningful survival of greater than 1 year is expected in:

Survival of SCA due to VT/VF or experience of hemodynamically unstable VT not due to reversible causes	I-B-R
Stable VT not due to reversible causes	I-B-NR
ICD or electrophysiological study in syncope presumed to be due to VA but not indications for a primary prevention ICD	IIa-B-NR
Amiodarone in patients ineligible for an ICD (due to a limited life expectancy and/or functional status or lack of access to an ICD) for prevention of SCD	IIb-B-R

Primary Prevention of SCD in Patients With NICM

ICD if meaningful survival of greater than 1 year is expected in:

LVEF ≤ 35% with NYHA class II-III HF despite GDMT.	I-A
NICM due to a <i>Lamin A/C</i> mutation who have 2 or more risk factors (NSVT, LVEF <45%, nonmissense mutation, and male sex)	IIa-B-NR
LVEF ≤ 35% with NYHA class I HF despite GDMT.	IIb-B-R
In patients with medication-refractory NYHA class IV HF who are not also candidates for cardiac transplantation, an LVAD, or a CRT-D an ICD should not be implanted	I-C-EO No benefit

Recurrent VA in Patients With NICM

A beta blocker, amiodarone or sotalol in patients with ICD and spontaneous VA or recurrent appropriate shocks despite optimal device programming	Ila-B-R
Catheter ablation in patients with NICM and recurrent sustained monomorphic VT who fail or are intolerant of antiarrhythmic medications.	Ila-B-NR

ESC 2022 GL on VA and SCD. Recommendations for risk stratification, sudden cardiac death prevention, and treatment of ventricular arrhythmias in dilated cardiomyopathy/hypokinetic non-dilated cardiomyopathy

Risk stratification and primary prevention of SCD

ICD implantation in patients with DCM/HNDCM, symptomatic heart failure (NYHA class II–III), and LVEF $\leq 35\%$ after ≥ 3 months of OMT.	Ila A
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ICD implantation should be considered in DCM/HNDCM patients with a pathogenic mutation in LMNA gene, if the estimated 5-year risk of life-threatening VA is $\geq 10\%$ ^a and in the presence of NSVT or LVEF $< 50\%$ or AV conduction delay.	Ila B
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ICD implantation in DCM/ HNDCM patients with a LVEF $< 50\%$ and ≥ 2 risk factors (syncope, LGE on CMR, inducible SMVT at PES, pathogenic mutations in LMNA, ^b PLN, FLNC, and RBM20 genes).	Ila C
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In DCM/HNDCM patients, electrophysiological evaluation should be considered when syncope remains unexplained after non-invasive evaluation.	Ila C
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Secondary prevention of SCD and treatment of VAs

ICD implantation in patients with DCM/HNDCM, who survive SCA due to VT/VF or experience haemodynamically not-tolerated SMVT.	I B
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Catheter ablation in specialized centres in patients with DCM/HNDCM and recurrent, symptomatic SMVT or ICD shocks for SMVT, in whom AADs are ineffective, contraindicated, or not tolerated.	Ila C
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Addition of oral amiodarone or replacement of beta-blockers by sotalol in patients with DCM/HNDCM and an ICD who experience recurrent, symptomatic VA despite optimal device programming and beta-blocker treatment.	Ila B
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ICD implantation in patients with DCM/HNDCM and haemodynamically tolerated SMVT.	Ila C
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Management of relatives of a patient or SCD victim with DCM/HNDCM

In a first-degree relative of a DCM/HNDCM patient, an ECG and an echocardiogram, if: I C	
• the index patient was diagnosed < 50 years of age or has clinical features suggestive of an inherited cause, or	
• there is family history of DCM/HNDCM, or premature unexpected SD.	

ECG and echocardiogram in a first-degree relative of a patient with apparently sporadic DCM/HNDCM.	Ilb C
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AAD, anti-arrhythmic drug; AV, atrioventricular; CMR, cardiac magnetic resonance; DCM, dilated cardiomyopathy; ECG, electrocardiogram; HNDCM, hypokinetic non-dilated cardiomyopathy; ICD, implantable cardioverter defibrillator; LGE, late gadolinium enhancement; LVEF, left ventricular ejection fraction; NSVT, non-sustained ventricular tachycardia; NYHA, New York Heart Association; OMT, optimal medical therapy; PES, programmed electrical stimulation; SCA, sudden cardiac arrest; SCD, sudden cardiac death; SD, sudden death; SMVT, sustained monomorphic ventricular tachycardia; VA, ventricular arrhythmia; VF, ventricular fibrillation; VT, ventricular tachycardia.

^a Based on the risk calculator <https://lmna-risk-vta.fr/>

^b See specific recommendations for LMNA.

ESC 2023 GL on Cardiomyopathies. Recommendations for an implantable cardioverter defibrillator in patients with dilated cardiomyopathy

Secondary prevention		
An ICD is recommended to reduce the risk of sudden death and all-cause mortality in patients with DCM who have survived a cardiac arrest or have recovered from a ventricular arrhythmia causing haemodynamic instability. ^{530,531,884}	I	B
Primary prevention		
An ICD should be considered to reduce the risk of sudden death and all-cause mortality in patients with DCM, symptomatic heart failure, and LVEF ≤35% despite >3 months of OMT. ^{861,885}	IIa	A
The patient's genotype should be considered in the estimation of SCD risk in DCM. ^{185,186,869,886}	IIa	B
An ICD should be considered in patients with DCM with a genotype associated with high SCD risk and LVEF >35% in the presence of additional risk factors (see Table 21). ^{541,542,867,869,873,878,881,886}	IIa	C
An ICD may be considered in selected patients with DCM with a genotype associated with high SCD risk and LVEF >35% without additional risk factors (see Table 21). ^{869,873,881,886}	IIb	C
An ICD may be considered in patients with DCM without a genotype associated with high SCD risk and LVEF >35% in the presence of additional risk factors. ^{138,873,874}	IIb	C

CMR, cardiac magnetic resonance; DCM, dilated cardiomyopathy; ICD, implantable cardioverter defibrillator; LGE, late gadolinium enhancement; LVEF, left ventricular ejection fraction; OMT, optimal medical therapy; SCD, sudden cardiac death.

^c Additional risk factors should include syncope, LGE presence on CMR.

Table 7. ESC 2021 GL on pacing and CRT.

Recommendation for patients with LMNA gene mutations

In patients with LMNA gene mutations, including Emery-Dreifuss and limb-girdle muscular dystrophies who fulfil conventional criteria for pacemaker implantation or who have prolonged PR interval with LBBB, ICD implantation with pacing capabilities if at least 1- year survival is expected.

IIa C

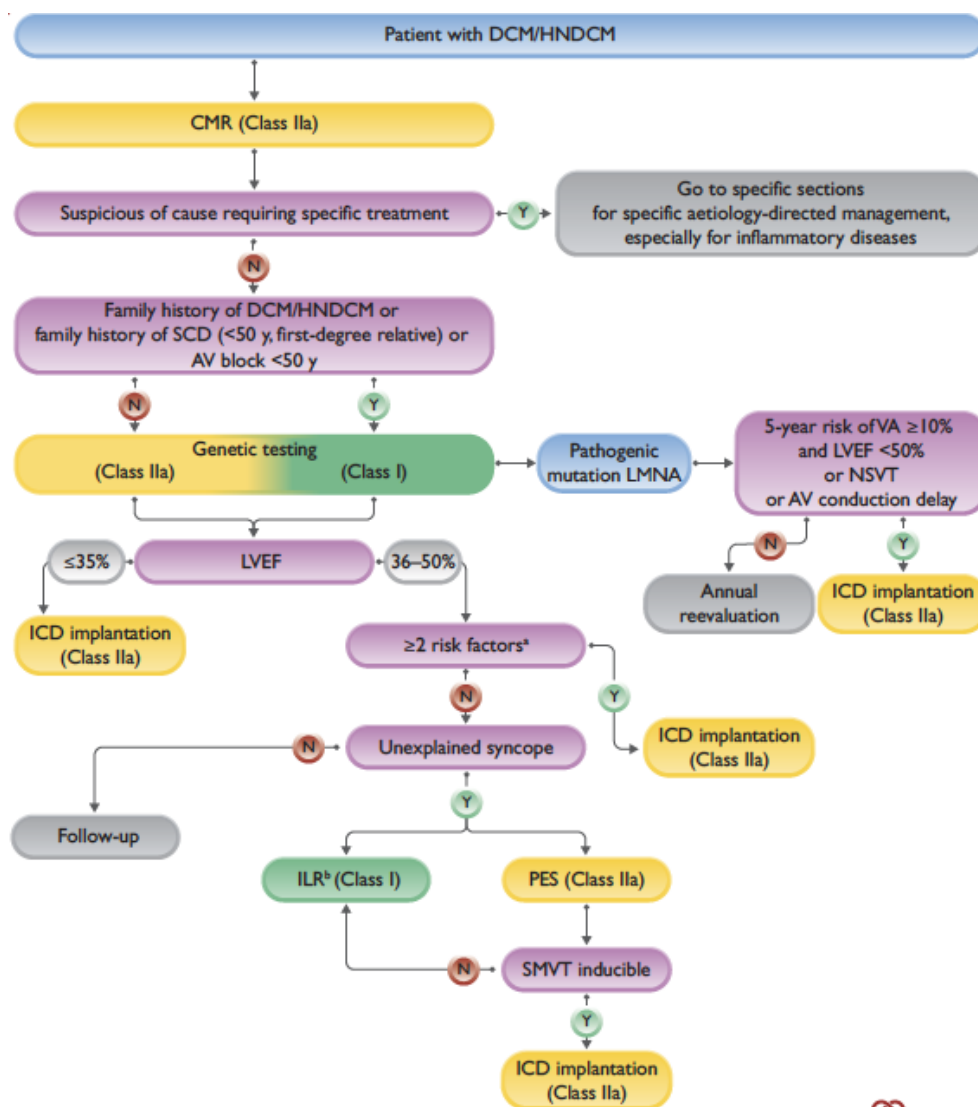


Figure 2. ESC 2022 GL on VA and SCD. Algorithm for risk stratification and primary prevention of sudden cardiac death in patients with dilated cardiomyopathy/hypokinetic nondilated cardiomyopathy.

AV, atrioventricular; CMR, cardiac magnetic resonance; DCM, dilated cardiomyopathy; HNDCM, hypokinetic non-dilated cardiomyopathy; ICD, implantable cardioverter defibrillator; ILR, implantable loop recorder; LMNA: lamin A/C gene; LVEF, left ventricular ejection fraction; N, No; NSVT, non-sustained ventricular tachycardia; PES, programmed electrical stimulation; SCD, sudden cardiac death; SMVT, sustained monomorphic ventricular tachycardia; VA, ventricular arrhythmias; Y, Yes.

^aRisk factors: unexplained syncope, pathogenic variants in PLN, FLNC, or RBM20, LGE on CMR, inducible SMVT at PES.

^bThe 2018 ESC Guidelines for the diagnosis and management of syncope.

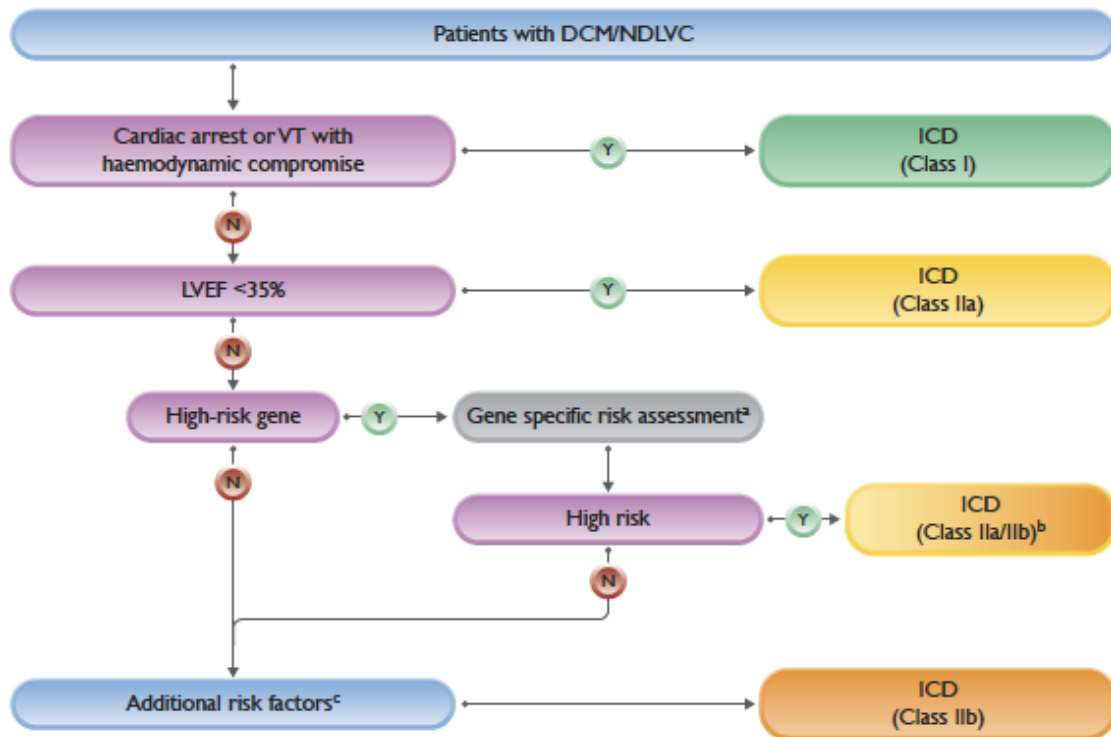


Figure 3. ESC 2023 GL on Cardiomyopathies. Implantation of implantable cardioverter defibrillators in patients with dilated cardiomyopathy or non-dilated left ventricular cardiomyopathy flowchart.

CMR, cardiac magnetic resonance; DCM, dilated cardiomyopathy; ICD, implantable cardioverter defibrillator; LGE, late gadolinium enhancement; LVEF, left ventricular ejection fraction; NDLVC, non-dilated left ventricular cardiomyopathy; VE, ventricular ectopic beats; VT, ventricular fibrillation.
a See relevant Table.

b Strength of recommendation depends on gene and context.

c Additional risk factors include syncope, LGE presence on CMR.

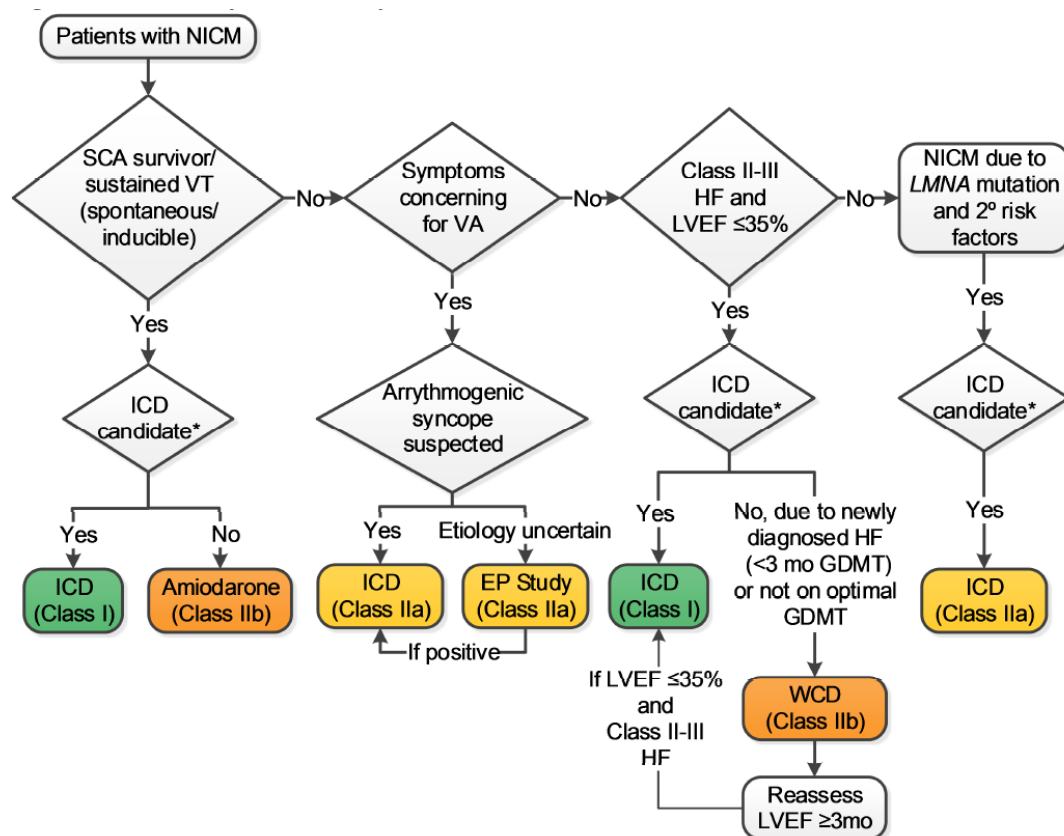


Figure 4. ACC/AHA/HRS 2017 GL on VA/SCD. Secondary and Primary Prevention of SCD in Patients With NICM

*ICD candidacy as determined by functional status, life expectancy or patient preference.

2° indicates secondary; EP, electrophysiological; GDMT, guideline-directed management and therapy; HF, heart failure; ICD, implantable cardioverter-defibrillator; LVEF, left ventricular ejection fraction; NICM, nonischemic cardiomyopathy; SCA, sudden cardiac arrest; SCD, sudden cardiac death; VA, ventricular arrhythmia; and WCD, wearable cardiac defibrillator.

Table 8. ESC 2022 GL on VA and SCD. Recommendations for the treatment of ventricular arrhythmias in Chagas' cardiomyopathy

Amiodarone to reduce arrhythmia burden in patients with Chagas' Cardiomyopathy who present with symptomatic PVCs or VT.	Ila C
In patients with Chagas' cardiomyopathy and recurrent, symptomatic SMVT or ICD shocks for SMVT in whom AADs are ineffective, contraindicated, or not tolerated, catheter ablation in specialized centres.	Ila C
ICD in patients with Chagas' cardiomyopathy and symptomatic VT in whom AADs (amiodarone and beta-blockers) are ineffective or not tolerated.	Ilb C
AAD, anti-arrhythmic drug; ICD, implantable cardioverter defibrillator; PVCs, premature ventricular complexes; SMVT, sustained monomorphic ventricular tachycardia; VT, ventricular tachycardia.	

Table 9. ESC 2023 GL on Cardiomyopathies. Exercise recommendations for patients with cardiomyopathy

Moderate- and high-intensity exercise should be considered in individuals who are gene positive and phenotype negative (with the exception of pathogenic variants in LMNA and TMEM43) who seek to do so	Ila C
High-intensity exercise and competitive sport may be considered in a select group of asymptomatic and optimally treated individuals with a left ventricular ejection fraction $\geq 50\%$ in the absence of exercise-induced complex arrhythmias	Ilb C
Moderate-intensity exercise may be considered in asymptomatic and optimally treated individuals with a left ventricular ejection fraction of 40–49% in the absence of exercise-induced complex arrhythmias.	Ilb C
High-intensity exercise, including competitive sport is not recommended in symptomatic individuals, those with a left ventricular ejection fraction $\leq 40\%$, exercise-induced arrhythmias or pathogenic variants in LMNA or TMEM43.	III C

LMNA, lamin A/C; NDLVC, non-dilated left ventricular cardiomyopathy; TMEM43, transmembrane protein 43.

Table 10. ESC 2025 GL on Pregnancy. Dilated cardiomyopathy

In women with DCM and worsening of EF during pregnancy, counselling on the risk of recurrence during a subsequent pregnancy is recommended in all cases, even after recovery of LV function	I C
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