

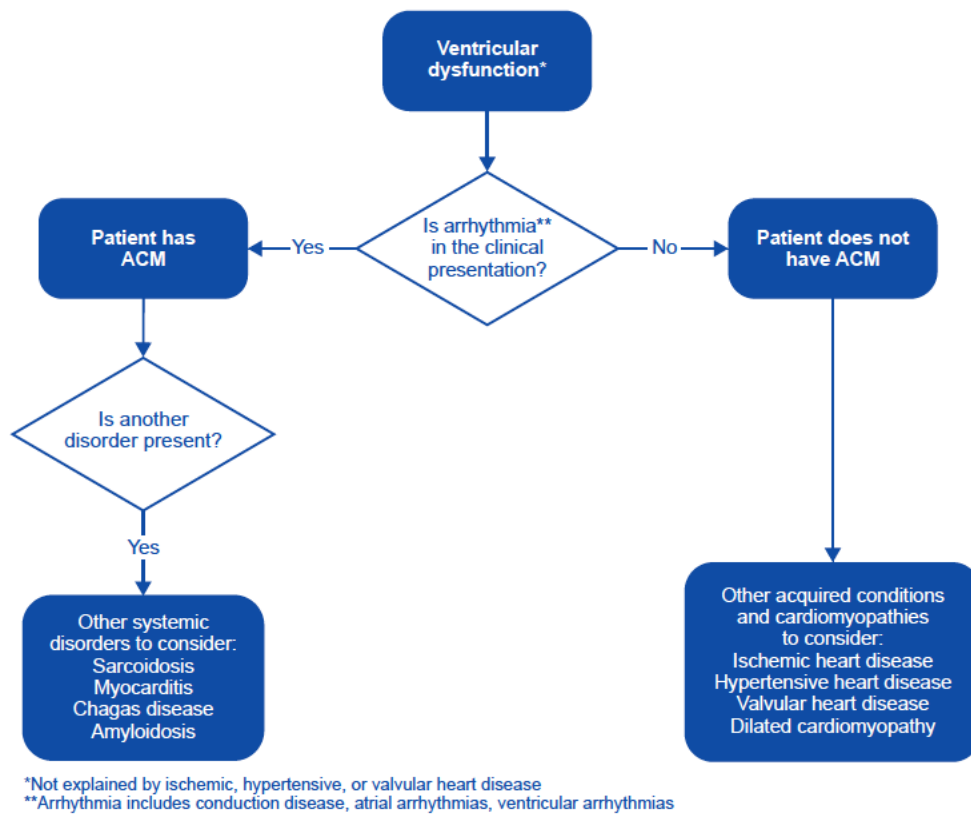


Figure 1. Algorithm to consider the presence of an arrhythmogenic cardiomyopathy (ACM).

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Genotype	Phenotype
Desmosomal	ARVC/ALVC, hair/skin abnormalities
Lamin A/C	Conduction disease, ventricular arrhythmia/sudden death, DCM, lipodystrophy, muscular dystrophy
SCN5A	Brugada syndrome, conduction disease, AF, VT/VF, DCM
PLN	Low-voltage ECG, VT/VF, DCM, HCM, ARVC
TMEM43	Sudden death M>F, DCM
FLNC	Sudden death, DCM
RBM20	DCM, AF; ventricular arrhythmia/sudden death uncommon as an early feature
Desmin	Skeletal myopathy, DCM; arrhythmia uncommon as an early feature

Figure 2. Phenotypes associated with the most common genetic causes of arrhythmogenic cardiomyopathy (ACM).

AF = atrial fibrillation; ALVC = arrhythmogenic left ventricular cardiomyopathy; ARVC = arrhythmogenic right ventricular cardiomyopathy; DCM = dilated cardiomyopathy; ECG = electrocardiogram; F = female; FLNC = filamin-C; M = male; HCM = hypertrophic cardiomyopathy; PLN = phospholamban; RBM20 = RNA binding motif protein 20; VF=ventricular fibrillation; VT=ventricular tachycardia; SCN5A=sodium voltage-gated channel alpha subunit 5; TMEM43=transmembrane protein 43.

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Table 1. Classification of likelihood of pathogenicity of a variant

Classification of variant	Description	Likelihood of being pathogenic
Class 5	Pathogenic	>95%
Class 4	Likely pathogenic	>90%
Class 3	Variant of uncertain significance	10—90%
Class 2	Likely benign	<10%
Class 1	Benign	<5%

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Table 2. Minimum set of genes to be prioritized in ACM

Gene	Protein type	Predominant type of mutation	OR/EF ¹⁰⁰	Signal: Background ⁹⁴	Remarks
<i>BAG3</i>	Chaperone	Truncating and missense	NA	NA	Also causes myofibrillar myopathy
<i>DES</i>	IF	Truncating and missense	NA	NA	Also causes myofibrillar myopathy
<i>DSC2</i>	Desm	Truncating and missense	NT 2.15 (EF 0.53); T 21.5* (EF 0.95)	ns	Rare
<i>DSG2</i>	Desm	Truncating and missense	NT 2.83* (EF 0.65) T 19.8* (EF 0.95)	2:1* (NT/T)	Rarely recessive
<i>DSP</i>	Desm	Truncating and missense	NT 2.1* (EF 0.52) T 89.9* (EF 0.99)	ns	Recessive: Carvajal syndrome
<i>FLNC</i>	Actin crosslink	Truncating and missense	NA	NA	Also causes myofibrillar myopathy
<i>JUP</i>	Desm	Missense	NT 7.8* (EF 0.87) T 28.1 (EF)	ns	Recessive: Naxos syndrome
<i>LDB3</i>	Z-band	Missense	NA	NA	Cypher/ZASP
<i>LMNA</i>	NE	Truncating and missense	NA	NA	AV block; CD
<i>NKX2-5</i>	Homeobox	Truncating and missense	NA	NA	AV block, CD, CHD
<i>PKP2</i>	Desm	Truncating	NT 1.3 (EF 0.23) T 484.7* (EF 1.0)	10:1* 42:1*	Large deletions 1-2%
<i>PLN</i>	Ca	Missense, nonsense, and deletion	NA	NA	Predominantly R14del
<i>RBM20</i>	Splice factor	Missense	NA	NA	Mostly in exon 9
<i>SCN5A</i>	Sodium channel	Mostly missense	NA	NA	Brugada, SND, CD
<i>TMEM43</i>	NE	Missense	NT 0.76 (EF—) T 13 (EF—)	ns	p.S358L disease-causing; also called LUMA

These genes have multiple lines of evidence indicating involvement in ACM and its subtypes (ALVC, ARVC). OR/EF and Signal: Background data are largely derived from cohorts with western European ancestry, and other ethnicities can be different.

ACM = arrhythmogenic cardiomyopathy; AV = atrioventricular; BV = biventricular; Ca = calcium handling; CD = conduction delay; CHD = congenital heart disease; CPVT = catecholaminergic polymorphic ventricular tachycardia; DES = desmin; Desm = desmosomal; DSC2 = desmocollin-2; DSG2 = desmoglein-2; EF=etioloical fraction; IF= intermediate filament; LD=left dominant; NA=data not available; NE=nuclear envelope; n=5not significant; NT=nontruncating variants; OR = odds ratio; RD = right dominant; SND = sinus node dysfunction; T = truncating variants.

*Genes with significant excess in cases over ExAc reference samples. Other genes that have been identified in ACM with insufficient or conflicting evidence are ABCC9, TGFB3, TTN, CTNNA3, sarcomeric genes (MYH7, MYBPC3), SCN3B, CDH2, TJP1.

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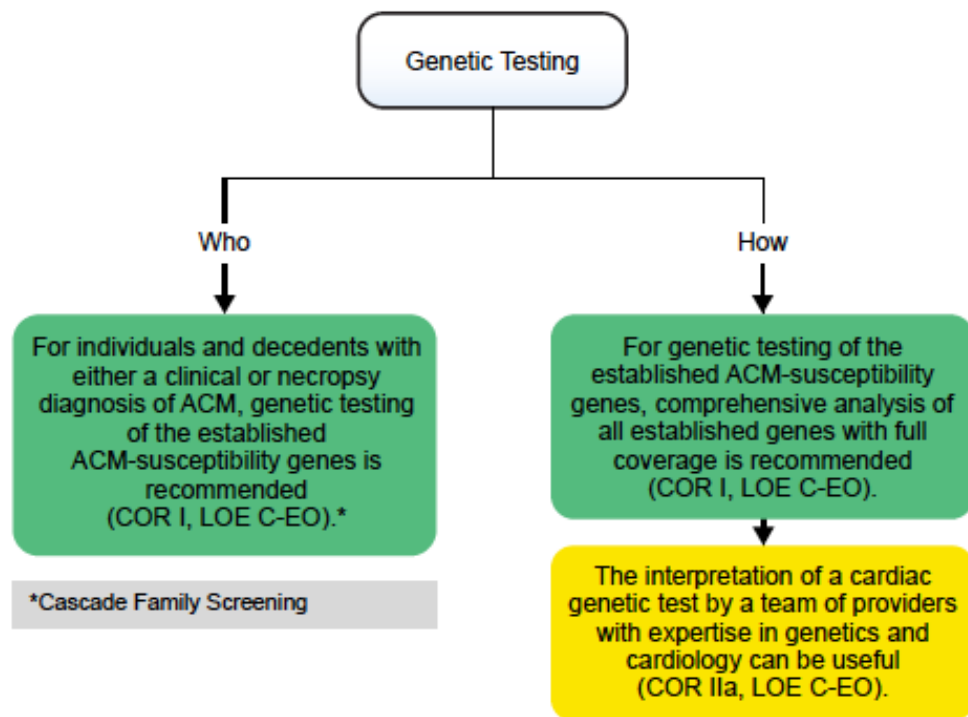


Figure 3. Genetic testing recommendations.

ACM = arrhythmogenic cardiomyopathy; COR = Class of Recommendation; LOE=5 Level of Evidence.

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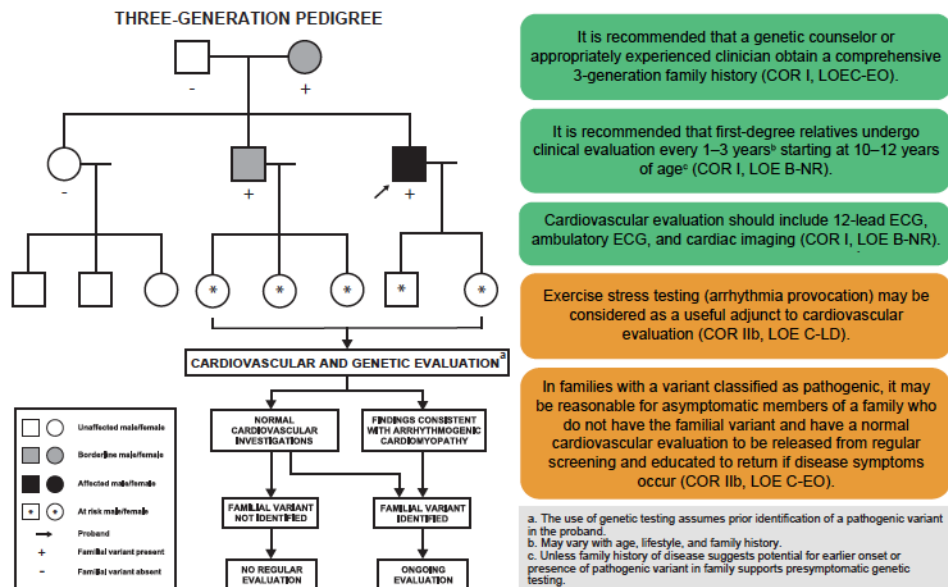


Figure 4. Summary of family screening recommendations.

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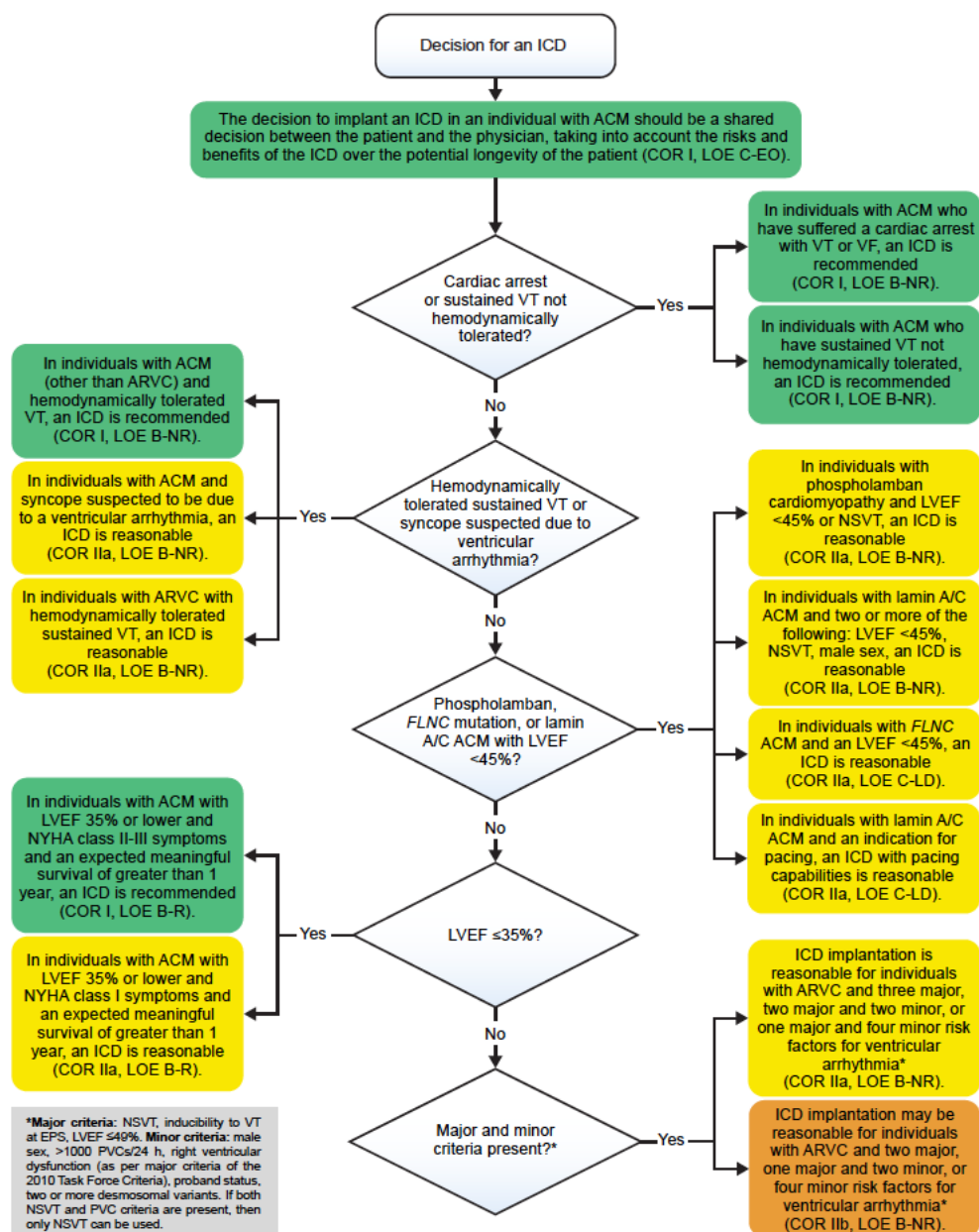


Figure 5. Implantable cardioverter defibrillator (ICD) recommendations.

See Chapter 39 for recommendations regarding amyloidosis, and Chapter 42 for recommendations regarding left ventricular noncompaction.

ACM = arrhythmogenic cardiomyopathy; ARVC = arrhythmogenic right ventricular cardiomyopathy; COR = Class of Recommendation; FLNC = filamin-C; LOE = Level of Evidence; LVEF = left ventricular ejection fraction; NSVT = nonsustained ventricular tachycardia; NYHA = New York Heart Association; PVC = premature ventricular contraction; VF = ventricular fibrillation; VT = ventricular tachycardia

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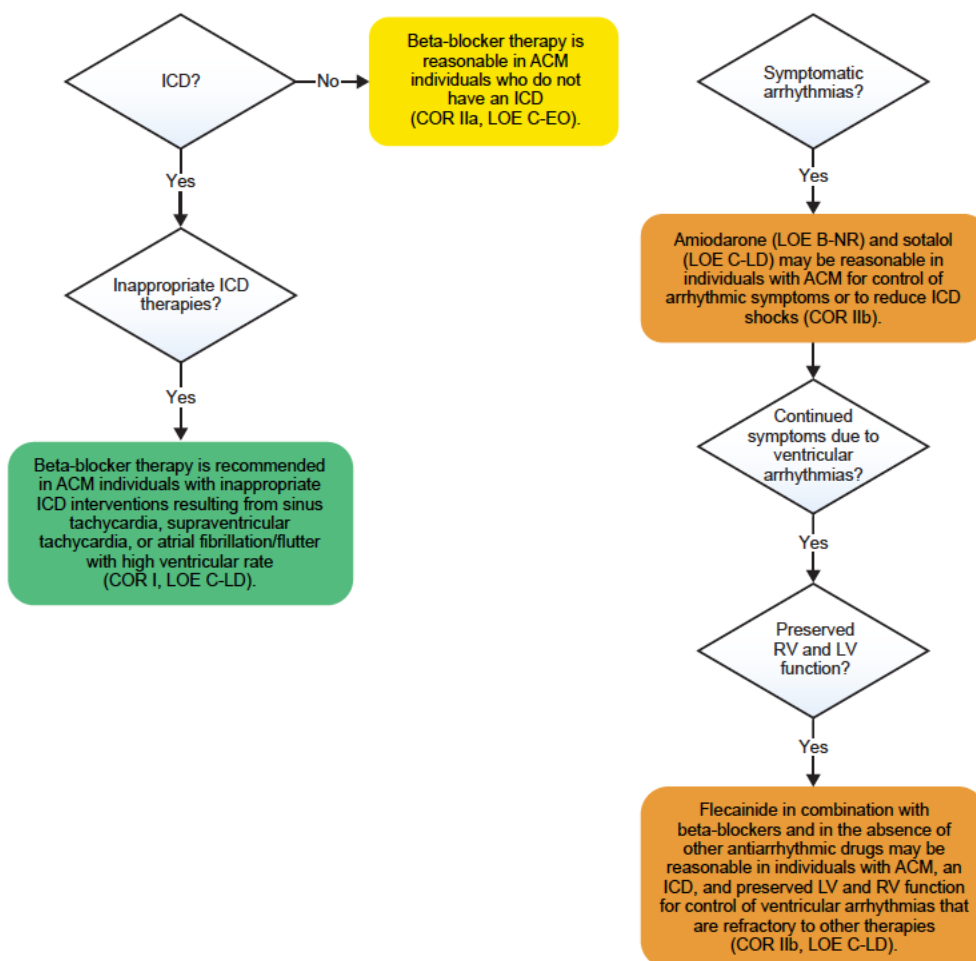


Figure 6. Medical therapy recommendations for arrhythmias.

ACM=arrhythmogenic cardiomyopathy; COR=Class of Recommendation; ICD=implantable cardioverter defibrillator; LOE = Level of Evidence; LV = left ventricular; RV = right ventricular

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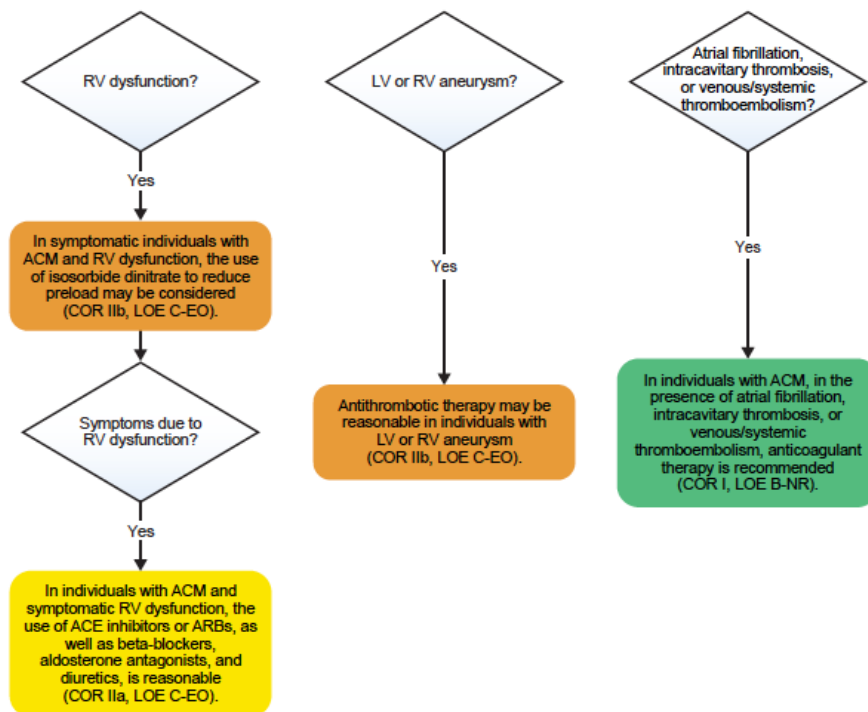


Figure 7. Recommendations for ventricular dysfunction and antithrombotic medical therapy in individuals with arrhythmogenic cardiomyopathy (ACM).

ACE = angiotensin-converting enzyme; ARBs = angiotensin receptor blockers; COR = Class of Recommendation; LOE = Level of Evidence; LV = left ventricular; RV = right ventricular

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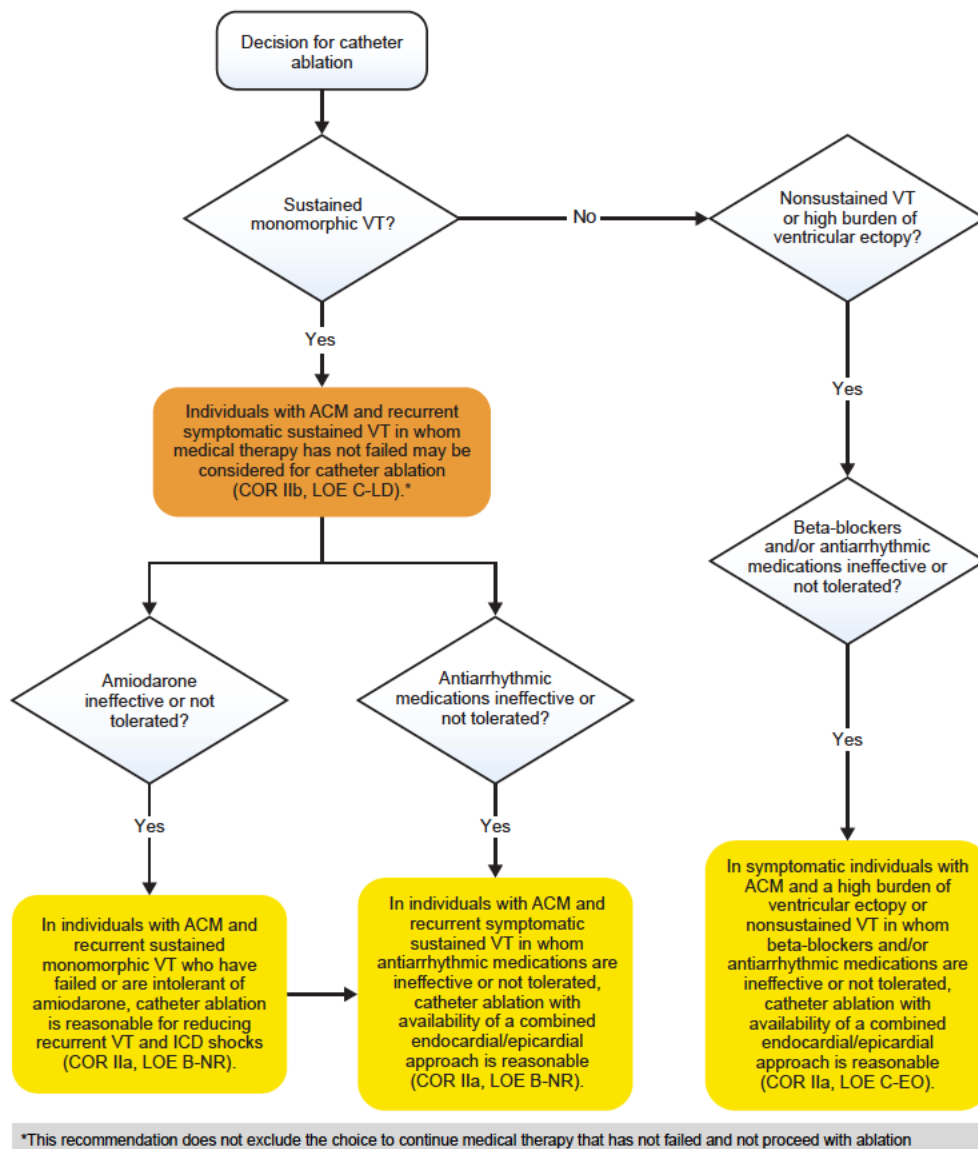


Figure 8. Catheter ablation recommendations for individuals with arrhythmogenic cardiomyopathy (ACM).

ICD = implantable cardioverter defibrillator; LOE = Level of Evidence; VT = ventricular tachycardia.

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