Cardiomyopathy phenotypes

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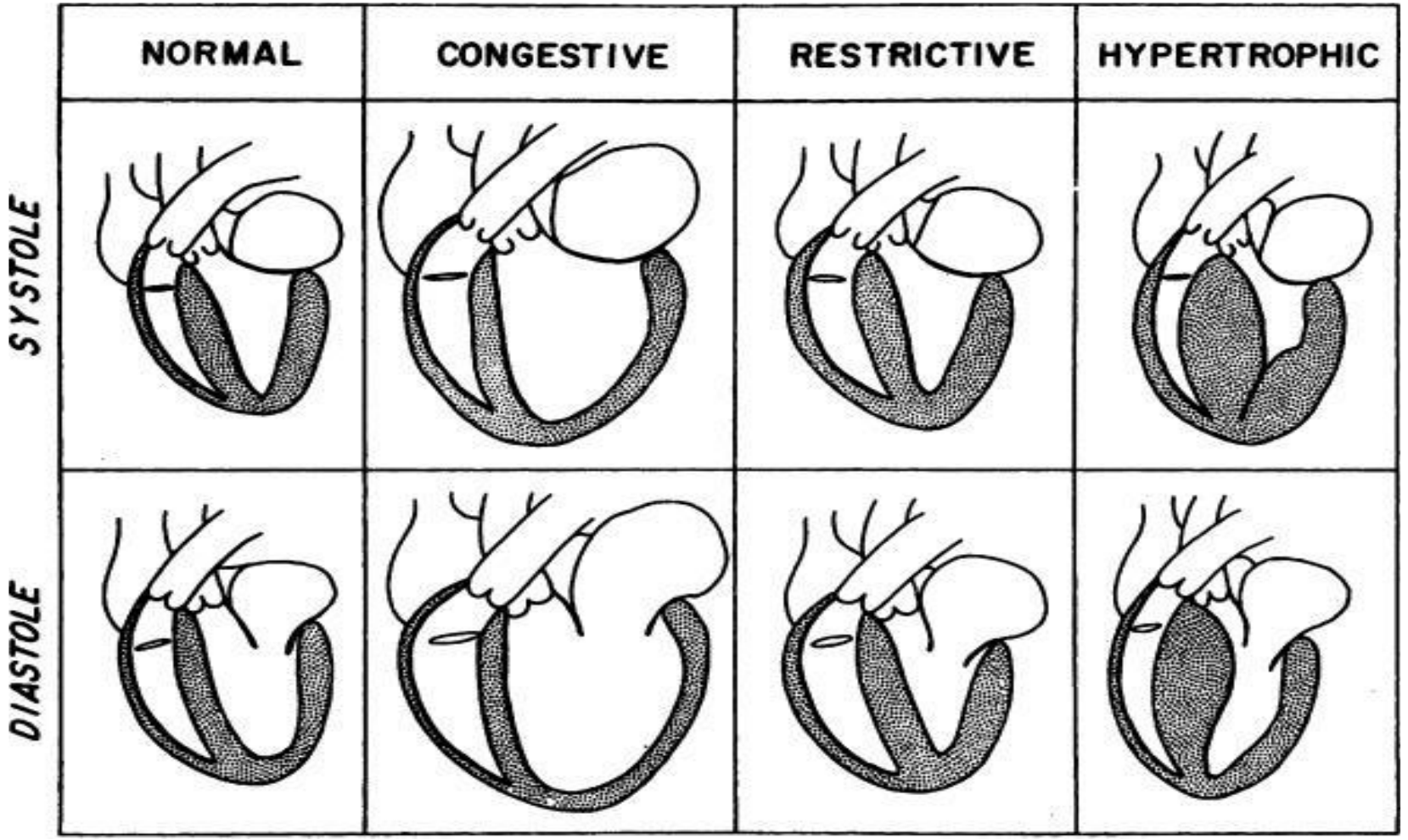
- *Primary myocardial disease, or cardiomyopathy:*
  - a disease of the heart muscle itself
  - not associated with congenital, valvular, or coronary heart disease or systemic disorders

- *Cardiomyopathy:*
  - three types
  - based on anatomic and functional features
  - hypertrophic, dilated (or congestive), and restrictive

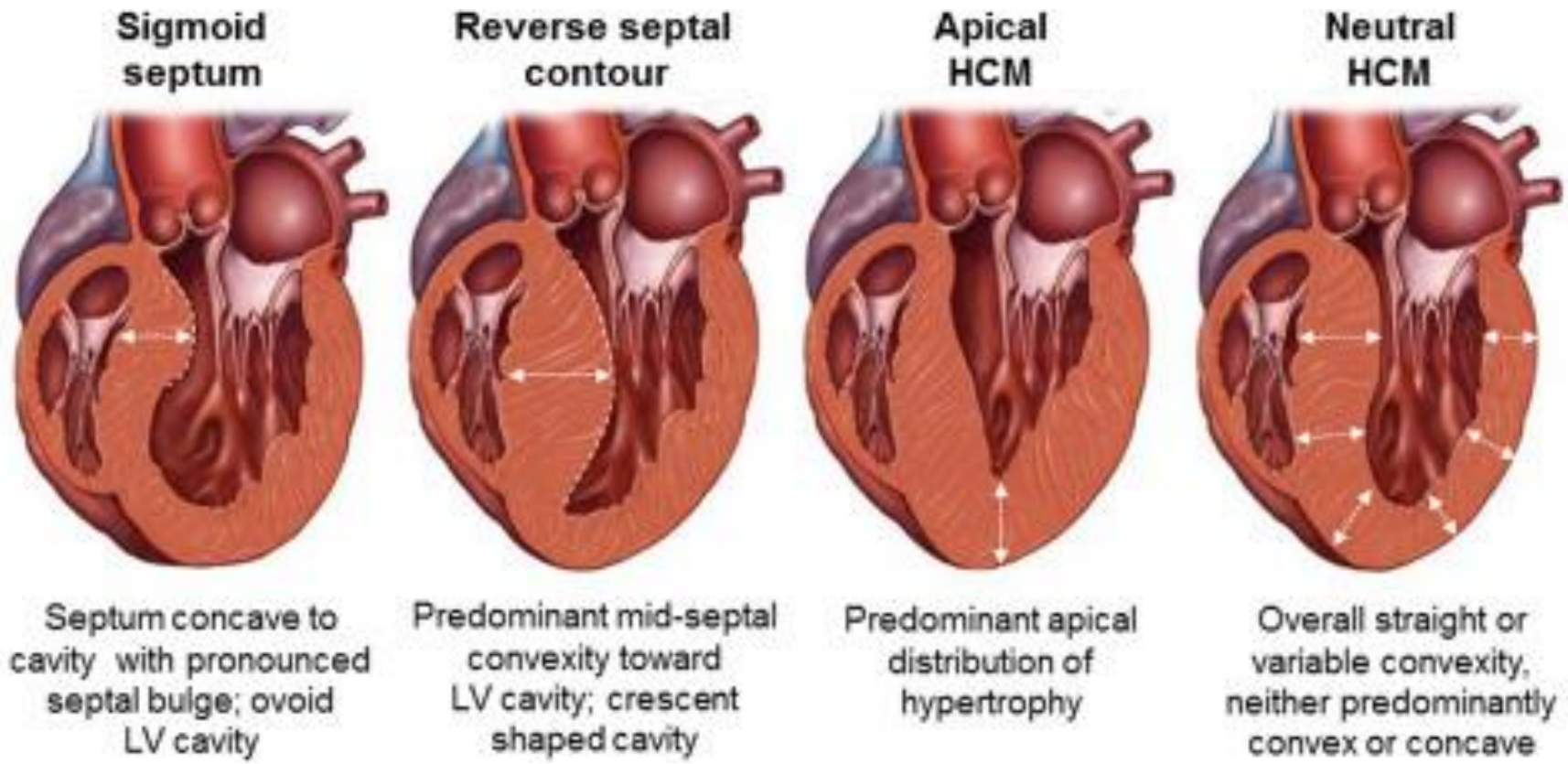
- *1.hypertrophic cardiomyopathy (HCM):*
  - massive ventricular hypertrophy with a smaller than normal ventricular cavity
  - Contractile function of the ventricle is enhanced, but ventricular filling is impaired by relaxation abnormalities

- ***2.*** *Dilated (or congestive) cardiomyopathy:*
  - decreased contractile function of the ventricle associated with ventricular dilatation
- Endocardial fibroelastosis and doxorubicin cardiomyopathy:
  - clinical features similar to those of dilated cardiomyopathy

- ***3.*** *Restrictive cardiomyopathy:*
  - a restriction of diastolic filling of the ventricles (usually infiltrative disease)
  - Contractile function of the ventricle may be normal, but there is marked dilatation of both atria


NORMAL
CONGESTIVE
RESTRICTIVE
HYPERTROPHIC
SYSTOLE
DIASTOLE

Hypertrophic Cardiomyopathy

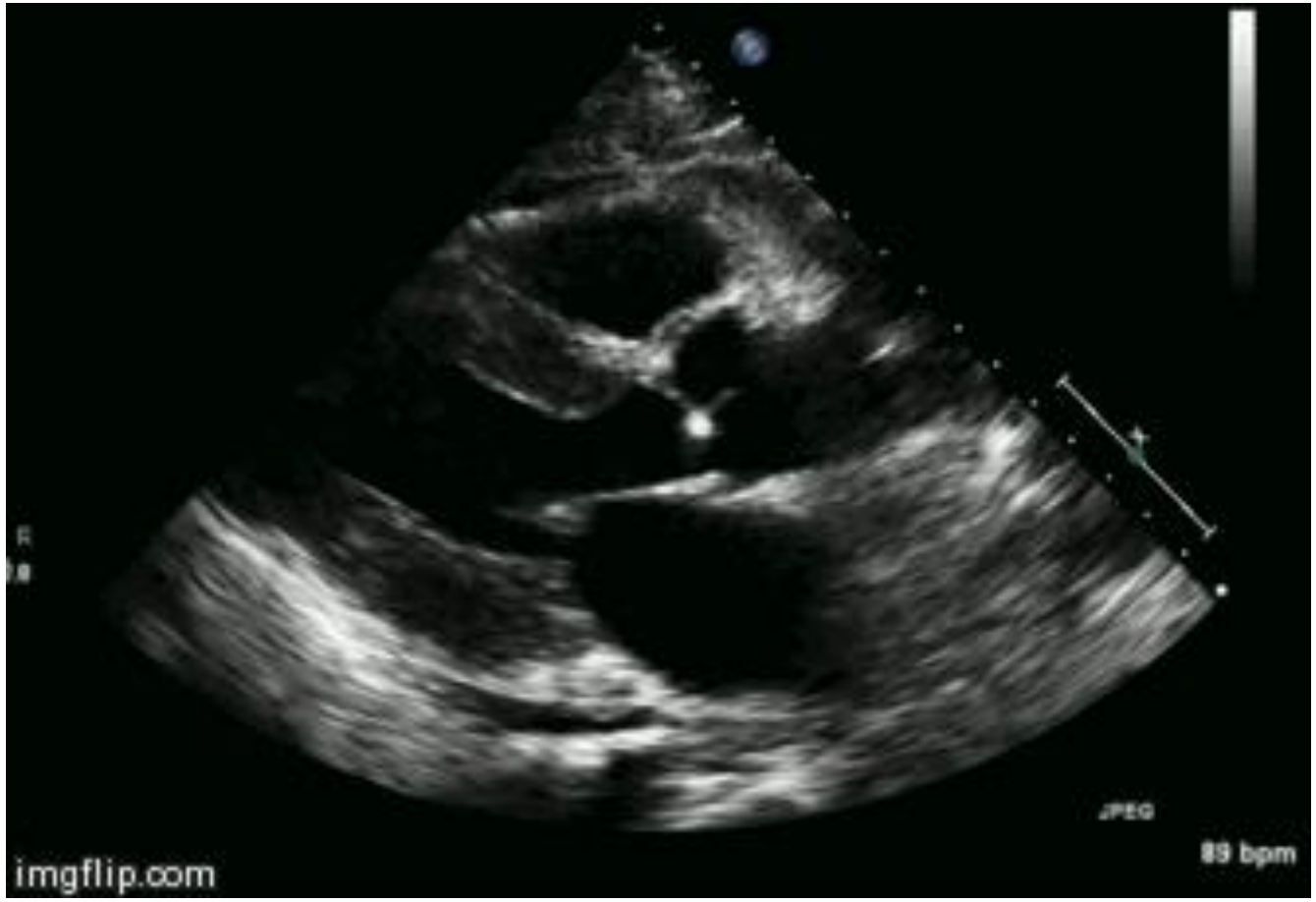

Sigmoid septum
Reverse septal contour
Apical HCM
Neutral HCM
Septum concave to cavity with pronounced septal bulge; ovoid LV cavity
Predominant mid-septal convexity toward LV cavity; crescent shaped cavity
Predominant apical distribution of hypertrophy
Overall straight or variable convexity, neither predominantly convex or concave

- heterogeneous
- usually familial disorder of heart muscle

- *In about 50% of cases:*
  - inherited as a mendelian autosomal dominant trait
  - mutations in one of 10 genes encoding protein components of the cardiac sarcomere

- *The remainder of the cases:*
  - occurs sporadically

- usually seen in adolescents and young adults
- equal gender distribution
- in children with LEOPARD syndrome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Dilated or Congestive Cardiomyopathy

CAUSE

- the most common form of cardiomyopathy
- *The most common cause of dilated cardiomyopathy:*
- idiopathic (>60%)
- followed by familial cardiomyopathy, active myocarditis, and other causes

Many cases of unexplained dilated cardiomyopathy may, in fact, result from subclinical myocarditis

- *familial type*:

- an autosomal dominant inheritance pattern is most frequent

Other causes of dilated cardiomyopathy:

1. *infectious causes* other than viral infection (bacterial, fungal, protozoal, rickettsial)
2. *endocrine-metabolic disorders* (hyper- and hypothyroidism, excessive catecholamines, diabetes, hypocalcemia)

3. nutritional disorders (kwashiorkor, beriberi, carnitine deficiency)

4. Cardiotoxic agents:

- such as doxorubicin

5. systemic diseases:

- such as connective tissue disease can also cause dilated cardiomyopathy

PATHOLOGY AND PATHOPHYSIOLOGY

- weakening of systolic contraction
- dilatation of all four cardiac chambers
- dilatation of the atria is in proportion to ventricular dilatation
- the ventricular walls are not thickened
- heart weight is increased

Restrictive Cardiomyopathy

- **PREVALENCE AND CAUSE**
  - extremely rare form of cardiomyopathy
  - 5% of cardiomyopathy cases in children

- may be idiopathic
- it may be associated with a systemic disease:

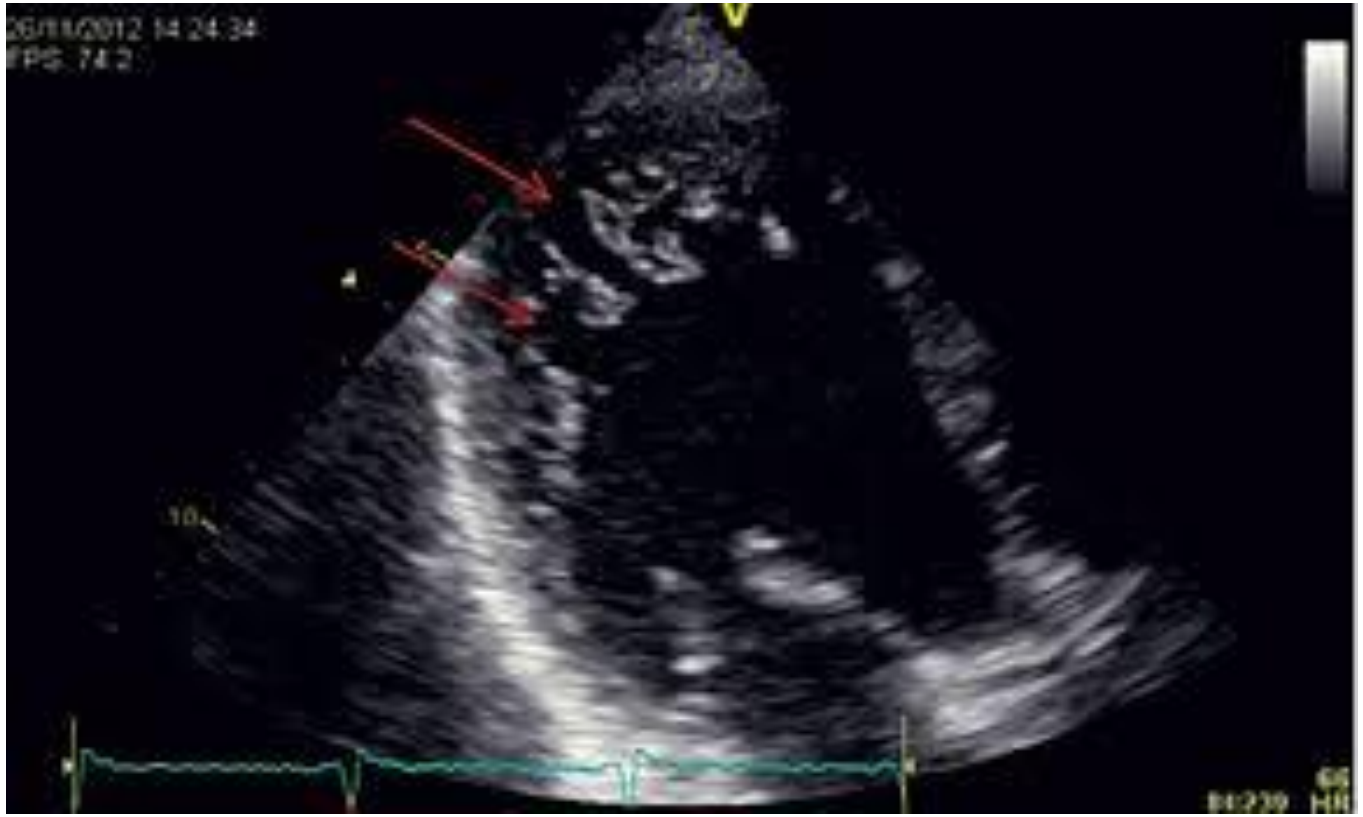
  Scleroderma, amyloidosis, Sarcoidosis, an inborn error of metabolism (mucopolysaccharidosis), Malignancies or radiation therapy

PATHOLOGY AND PATHOPHYSIOLOGY

- markedly dilated atria and generally normal ventricular dimensions
- *Ventricular diastolic filling is impaired:*
  - excessively stiff ventricular walls
- *Contractile function of the ventricle:*
  - normal

LV Hypertrabulation

- also known as left ventricular noncompaction
- an intrauterine arrest of normal compaction of the loose interwoven meshwork of the ventricular myocardium which normally occurs during the first month of fetal life



- affects LV with or without concomitant RV involvement
- systolic and diastolic ventricular dysfunction

- *Familial recurrence:*
  - up to 25%
  - with a less severe form of abnormalities

- The most common complication of the disease:

- heart failure

- Less commonly:

- thromboembolic events, ventricular arrhythmias, and Wolff-Parkinson White syndrome

Thanks for your attention

AHA scientific statement on CMP treatment in children

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Children Medical Center, TUMS

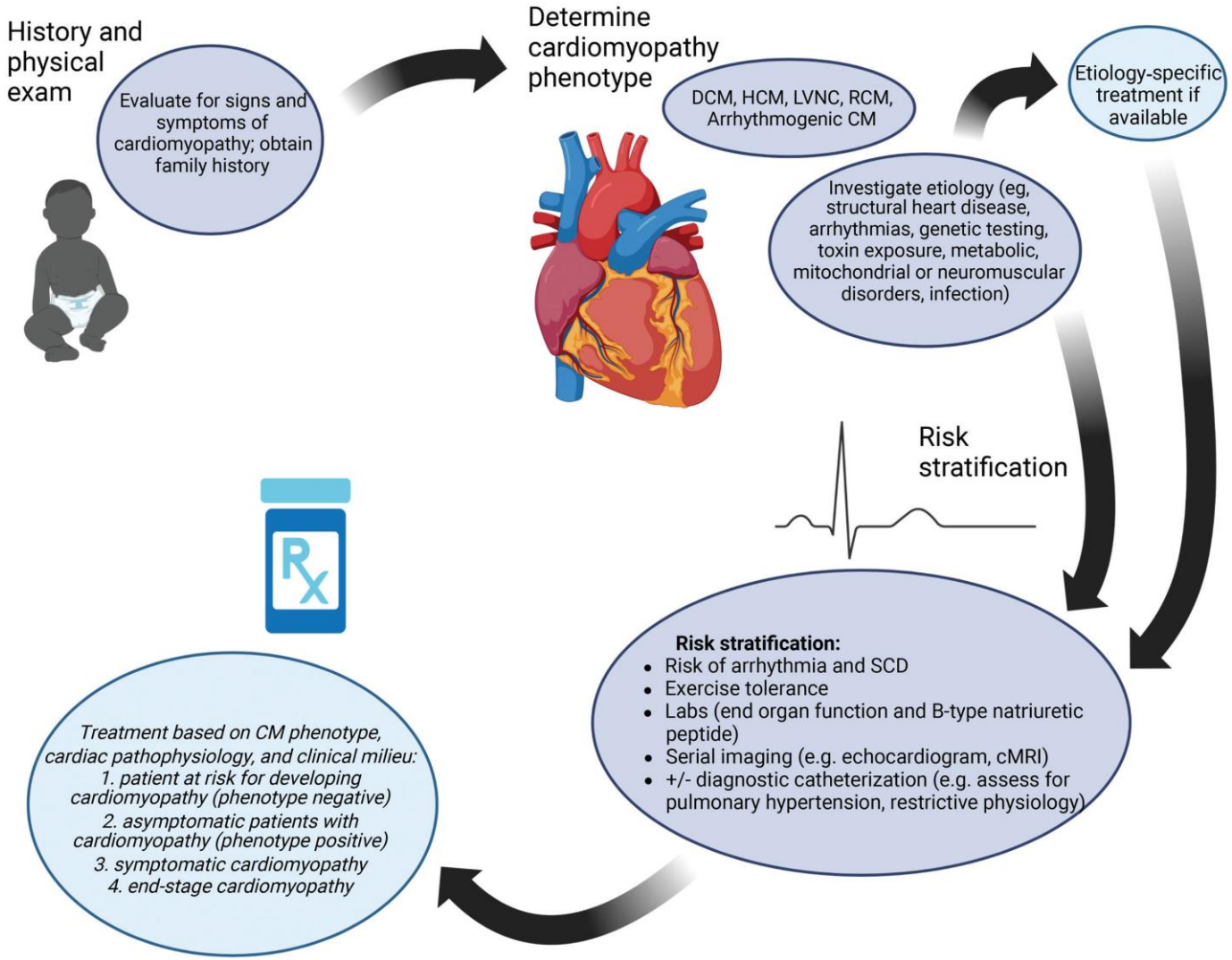
Circulation

AHA SCIENTIFIC STATEMENT

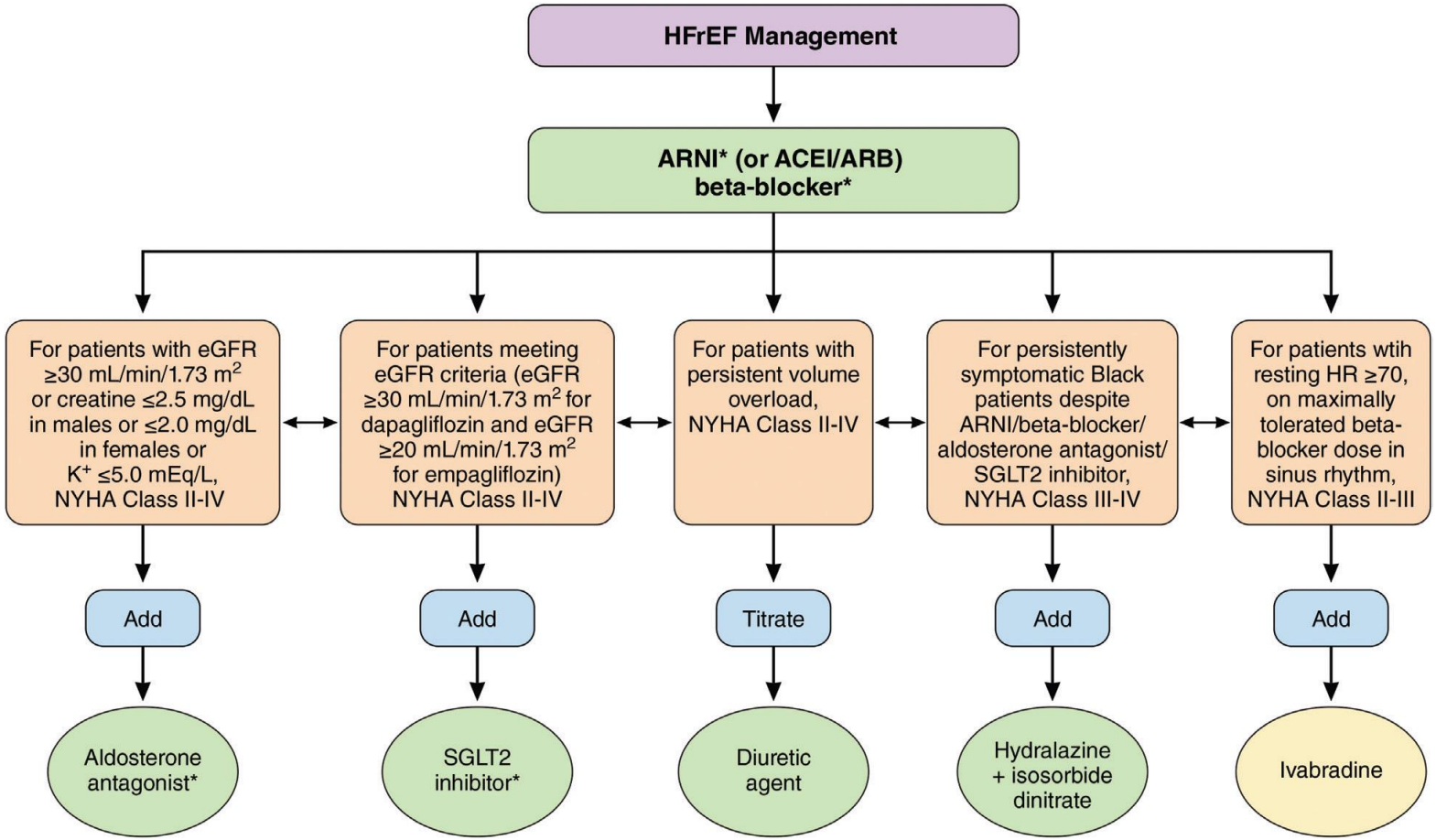
Treatment Strategies for Cardiomyopathy in Children: A Scientific Statement From the American Heart Association

Carmel Bogle, MD; Steven D. Colan, MD; Shelley D. Miyamoto, MD, FAHA; Swati Choudhry, MD; Nathanya Baez-Hernandez, MD; Molly M. Brickler, MSN, APNP; Brian Feingold, MD, MS, FAHA; Ashwin K. Lal, MD, FAHA; Teresa M. Lee, MD; Charles E. Canter, MD, FAHA, Vice Chair; Steven E. Lipshultz, MD, FAHA, Chair, on behalf of the American Heart Association Young Hearts Pediatric Heart Failure and Transplantation Committee of the Council on Lifelong Congenital Heart Disease and Heart Health in the Young (Young Hearts)

Central illustration



The most recent revision in adult patients



Different points of CMP charactristics in children

populations, there are additional barriers to executing clinical trials in children with heart conditions, including inadequate statistical power associated with small

Unique Characteristics of HF in Children

The pathophysiology of HF in children is similar to that in adults, although increasing evidence indicates

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some inherent differences in myocardial adaptations secondary to DCM. The natural history of pediatric DCM also differs from that of adult DCM in that death or transplantation usually occurs within 2 years after presentation with DCM, suggesting that many children and adolescents have advanced disease at presentation.[13,14] These differences may contribute

children with congenital heart disease but normal cardiac function.[23] In another study of explanted DCM hearts, genes associated with sarcomeric remodeling, inflammation, and fatty acid metabolism were upregulated in adults, whereas genes associated with cell adhesion and ion and transmembrane transport were upregulated in children.[20]

CLINICAL STATEMEN
AND GUIDELINES

Different points of CMP charactristics in children

als in children with HF treated with therapies developed for adults, as discussed previously. For example, total myocardial β-adrenergic receptor expression is decreased in both children and adults with idiopathic DCM, but children downregulate both the β-1 and the β-2 adrenergic receptors, whereas adults downregulate only the β-1 adrenergic receptors.[15] This differential receptor expression could influence the response of children to nonselective β-blocker drugs such as carvedilol because the effects of medical blockade of the already downregulated β-2 adrenergic receptors are unknown.

With respect to the phosphodiesterase system, both children and adults with idiopathic DCM have decreased myocardial cAMP concentrations, but these concentrations improve only in children treated with phosphodiesterase-3 inhibitors (eg, milrinone) and remain low in adults.[16] Although long-term treatment of adults with HF with phosphodiesterase-3 inhibitors is associated with increased morbidity and mortality, several clinical series

between adults and children are not limited to heart tissue. Among 1310 plasma proteins, a DNA aptamer array found 20 peptides and proteins that were significantly increased in pediatric patients with DCM compared with age-matched healthy control subjects and that circulating protein biomarkers differed greatly between children and adults with DCM.[24] Many studies have evaluated microRNAs as biomarkers of HF in adults, and although studies of children are fewer, the circulating microRNA profiles in children are unique compared with the profile seen in adults with DCM. An unbiased array revealed that 4 microRNAs (microRNA-155, -636, -646, and -639) were differentially regulated between children with DCM who required a heart transplantation and those who recovered ventricular function.[25,26] None of these 4 microRNAs are biomarkers of DCM in adults. Although the studies are limited by their cross-sectional nature, they provide a framework for understanding the novel molecular and biomarker signatures associated with

Stages of CMP

arrhythmogenic cardiomyopathy are discussed but in less detail. Figure 1 shows the central illustration of this article.

STAGES OF CARDIOMYOPATHY IN CHILDREN

Dilated Cardiomyopathy

Strategies for Treating Pediatric DCM

Recent AHA guidelines have proposed a 4-stage system for therapeutic interventions in adult heart failure (HF).[2] In stage A (at-risk patients), the patient is at risk for HF but has no structural heart disease or symptoms of HF. Stage B (asymptomatic patients) is characterized by structural heart disease but without signs or symptoms of HF. Stage C (symptomatic patients) is marked by cardiomyopathic heart disease with current or past symptoms of HF. Patients with stage D disease (refractory patients) have refractory HF requiring specialized interventions. This staging system can be harmonized with the various clinical milieus one can observe in pediatric DCM as a framework with which to consider specific therapeutic interventions.

Over the past 3 decades, a series of large, randomized, placebo-controlled clinical trials in adults with HF associated with reduced LV ejection fraction found that certain drugs reduced the incidence of hospitalization and mortality. These drugs are angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers, β-blockers, mineralocorticoid receptor antagonists, angiotensin receptor/neprilysin inhibitors, ivabradine, and most recently sodium-glucose cotransporter 2 inhibitors. Although there are evidence-based, goal-directed medical therapy treatment algorithms that are often updated by the AHA,[3] the American College of Cardiology,[4] and the European Society of Cardiology[5] (Figure 2),[4] a similar evidence basis does not yet exist for children.

Screening for phenotype positive asymptomatic DCM patients

adults and children without reducing the effectiveness of cancer therapies or increasing the incidence of secondary malignancies.[55–57] Dexrazoxane is the only drug approved by the US Food and Drug Administration for the primary prevention of cardiac toxicity in adults and has been granted pediatric orphan drug status.[58] Furthermore, in 2017, the European Medicines Agency issued a decision that treatment with dexrazoxane is no longer contraindicated in children expected to receive a cumulative dose of >300 mg/m^2 doxorubicin or the equivalent cumulative dose of another anthracycline.[59–61] The European Medicines Agency found no data indicating that dexrazoxane was associated with an increase in second primary malignancies, interfered with chemotherapy, or increased the risk for early death in children. This recent decision allows virtually all children to receive dexrazox-

guidelines recommend a 3-generation pedigree, cardiac screening, and cascade genetic testing for at-risk family members.[1] The Heart Failure Society of America recommends screening for children with a first-degree relative with DCM: annually for children 0 to 5 years of age, every 1 to 2 years for children 6 to 12 years of age, every 1 to 3 years for children 13 to 19 years of age, every 2 to 3 years for adults 20 to 50 years of age, and every 5 years for adults >50 years of age.[64] Treatment strategies at this stage focus on treating risk factors, intervening in structural heart disease when applicable, and initiating medical therapy with ACE inhibitors. ACE inhibitors are proposed as first-line therapy and β-blockers are also considered for patients with ejection fraction <40% in the recently proposed adult HF guidelines.[4]

Therapy in Symptomatic Pediatric Patients

CLINICAL STATEMENTS AND GUIDELINES

Therapy in asymptomatic stage B DCM

to screen, treat, follow, and conduct quality improvement (QI) and research in a systemic approach that will ideally improve outcomes.

Therapy in Pediatric Patients With DCM (Phenotype Positive) Who Are Asymptomatic

Identifying patients in this stage depends primarily on screening those with a family history of cardiomyopathy for an associated genetic variant or those such as dystrophinopathy or childhood cancer survivors who were at risk for developing DCM and undergo periodic surveillance for development of DCM. When cardiomyopathy is identified in a child without a known preexisting risk, panel genetic testing or whole-exome sequencing is recommended. A pathogenic or likely pathogenic variant in the proband should prompt cascade genetic testing of first-degree relatives who are at risk for cardiomyopathy.

tomatic HF found no difference between groups in the primary composite outcome.[10] However, several factors made interpretation of this trial challenging. First, symptom improvement in the placebo-treated study subjects was greater than expected and may have been related to the requirement for all subjects to be on ACE inhibitor therapy at the time of enrollment, with many being on additional HF treatments such as digoxin, diuretics, and spironolactone. Second, the trial enrolled subjects with HF from a wide range of diagnoses, including single ventricle and other forms of congenital heart disease. Although the study was not powered to evaluate the primary outcome in DCM specifically, subjects with a systemic LV treated with carvedilol did have an improvement in fractional shortening. In addition, a post hoc analysis[10,66] found that children with a systemic LV treated with

Therapy in asymptomatic stage B DCM

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CLINICAL STATEMENTS AND GUIDELINES

Therapy in stage C DCM patients

decision allows virtually all children to receive dexrazoxane starting with the first dose of anthracycline at the discretion of the treating health care professional.

Treating phenotype-negative pediatric patients at risk for developing DCM as described earlier for young children with dystrophinopathies and childhood cancer survivors has the potential to increase survival and to improve the quality of life for these high-risk patients. Identifying genetic, mechanistic-based, or lifestyle modification approaches to treating children with stage A disease and other cardiomyopathies could improve disease prevention and outcomes. Centers with dedicated HF teams have begun to form multidisciplinary teams that have begun to see patients with muscular dystrophy or cancer and survivors. Multidisciplinary programs are a platform to screen, treat, follow, and conduct quality improvement (QI) and research in a systemic approach that will ideally improve outcomes.

Therapy in Symptomatic Pediatric Patients With DCM

The current guidelines for adults with stage C HF (Figure 2) recommend combination therapy with angiotensin receptor/neprilysin inhibitors, β-blockers, mineralocorticoid receptor antagonists, and sodium-glucose cotransporter 2 inhibitors and the addition of ivabradine if the heart rate cannot be reduced enough with β-blockade. A combination of hydralazine and isosorbide dinitrate is recommended for persistently symptomatic Black patients.[4,65]

No large randomized controlled trials have identified effective therapies for stage C HF in children, although most clinical studies in pediatric cardiomyopathy have focused on these patients. A randomized, placebo-controlled trial of carvedilol for treating children with symptomatic HF found no difference between groups in the primary composite outcome.[10] However, several factors made interpretation of this trial challenging. First, symp-

Therapy in stage D DCM patients

that pediatric cardiologists increasingly treated these children with ACE inhibitors and β-blockade, as well as with mineralocorticoid receptor antagonists, between 2010 and 2020.[72] Newer therapies are being investigated in patients with stage C disease. In particular, this targeted approach may benefit children, who are more likely to have monogenetic forms of cardiomyopathy.

Newer therapies targeting the mechanisms producing cardiomyopathy in patients with stage C (symptomatic) disease are promising according to adult studies. The myosin activator omecamtiv mecarbil acts directly on the sarcomere to improve contractility in adults with HF with reduced ejection fraction.[73] Sodium-glucose cotransporter 2 inhibitors may also improve sarcomere function by improving passive stiffness of cardiomyocytes.[74]

targeted therapies.

Therapy in End-Stage Pediatric DCM

AHA stage D HF identifies patients with refractory HF who remain symptomatic despite maximal medical therapy. These patients may benefit from specialized interventional strategies such as mechanical circulatory support, continuous intravenous inotropic infusions, cardiac transplantation, and palliative or hospice care.[65] Acute decompensated HF in DCM is generally apparent; however, the gradual deterioration of chronic HF from stage C to D may be less noticeable. Identifying stage D HF is vital given the limited treatment options and substantial morbidity and mortality. The current treatment guidelines for children with advanced HF from DCM recommend

Future directions

FUTURE DIRECTIONS

Investigational Management Strategies

Pulmonary Artery Banding

The use of a pulmonary artery banding has emerged as a potential therapeutic alternative in infants with advanced HF due to DCM with preserved right ventricular function. Schranz et al[153] from Germany originally described the application of pulmonary artery banding as an additional strategy to delay or even avoid heart transplantation in infants and young children with end-stage HF due to DCM. This study was expanded to a multicenter retrospective analysis with participants from 11 different nations (World Network Reports) and found that pulmonary artery banding was associated with significant improvement in patients with DCM.[154] A recent multicenter retrospective analysis by Spigel and colleagues[155] from the United States and the World Network Reports by Schranz et al[154] found pulmonary artery banding to be associated with myocardial functional recovery in approximately one-third to one-half of the children with DCM.

ful collaborations that have produced spectacular results in collecting and using data to transform patient outcomes.[162]

This network approach has also been successful in pediatric cardiology, which now has collaborative networks that include the North American PCMR, the Pediatric Heart Transplant Society, and the Pediatric Heart Network. Specific to pediatric HF, ACTION (Advanced Cardiac Therapies Improving Outcomes Network) was developed in 2017.[164,165] ACTION involves the key stakeholders, including patients, families, clinicians, and researchers. This network provides invaluable support and education to families and patients.[165] One of the initial QI projects launched by ACTION was the "ABCs of stroke prevention." This project focused on preventing stroke in children with end-stage HF and VADs. Within 2 years, this project likely contributed significantly to stroke rates at participating sites dropping by 60%.[165,166] In particular, stroke rates among patients receiving pediatric durable VAD were significantly reduced from 30% to 11% in ACTION locations.[167] The Table displays the ongoing ACTION network HF-specific QI initiatives.

Linking large clinical registries is a popular strategy to broaden analytic options. Outcomes research using linked

Future directions

phenotype may occur in children and adolescents more frequently than has previously been appreciated.

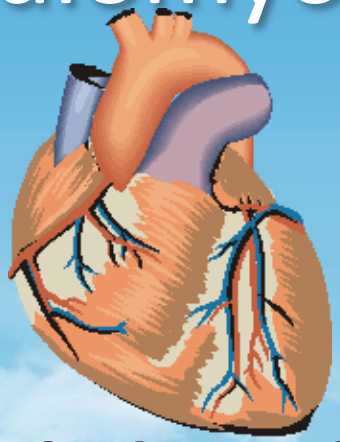
Therapeutic strategies for ventricular arrhythmias seen with desmosomopathies generally follow those used for similar complications in HCM. HF and LV dysfunction strategies in a similar fashion follow those used for DCMs. A unique therapeutic intervention for ARVC and other presentations of desmosomopathies is exercise limitation. Current consensus[149] states that exercise increases arrhythmic risk and structural dysfunction in patients with ARVC. Guidelines for the management of ARVC state

Cell-Based Therapies

Some stem cell studies have reported improved function and LV dimension in adults. Preliminary data in animal models of DCM have shown improved cardiac function and reduced myocardial fibrosis.[156,157] However, the results of stem cell therapy for children with DCM are mixed. Although some pediatric case reports have not described strong benefits,[158,159] other studies have reported that stem cell therapy improved ejection fraction and decreased LV end-diastolic volume.[160,161]

Thanks for your attention

Application of genetic testing in diagnosis and management of CHDs and cardiomyopathies



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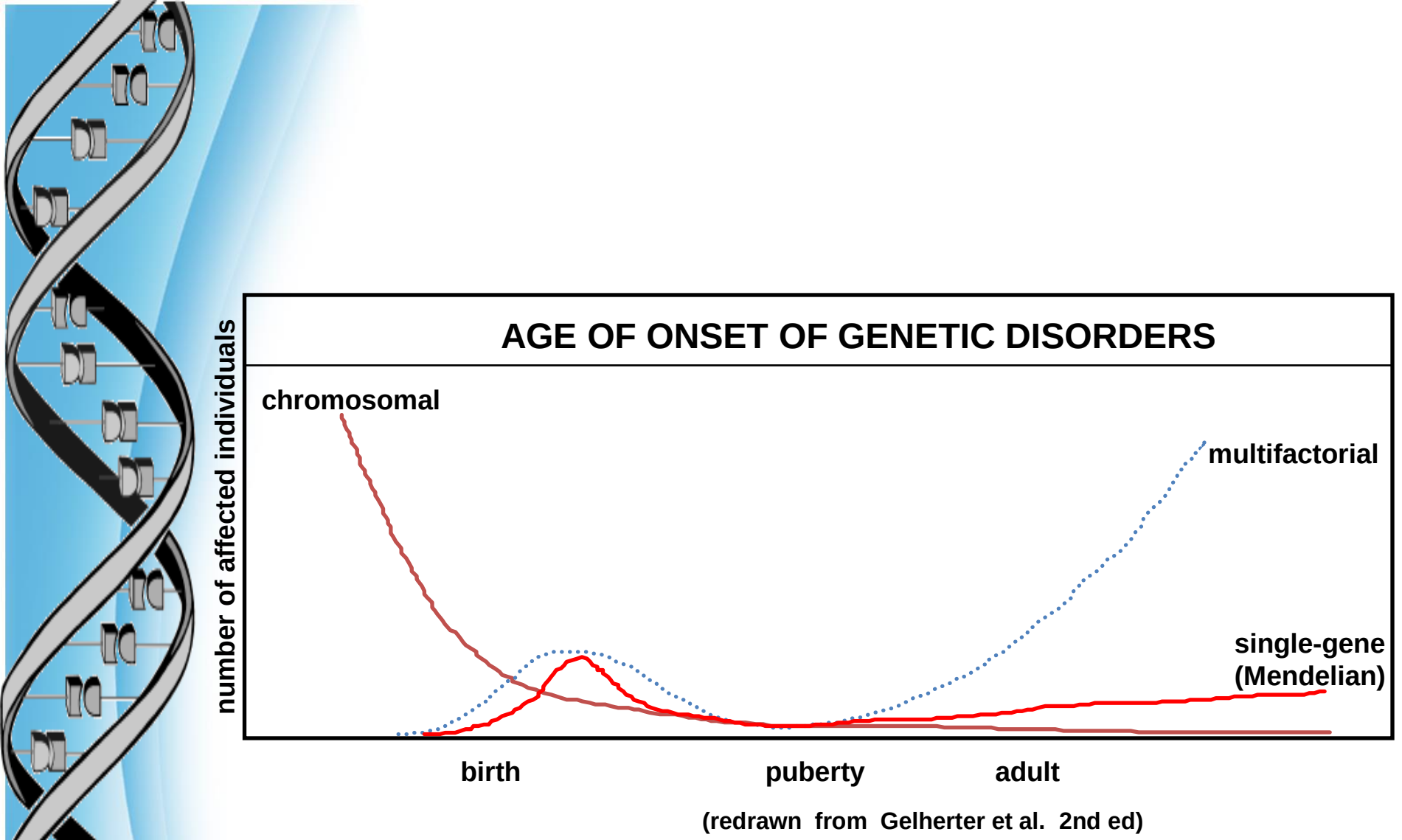
Jan 25, 2024



(redrawn from Gelherter et al. 2nd ed)

Congenital Heart Defects

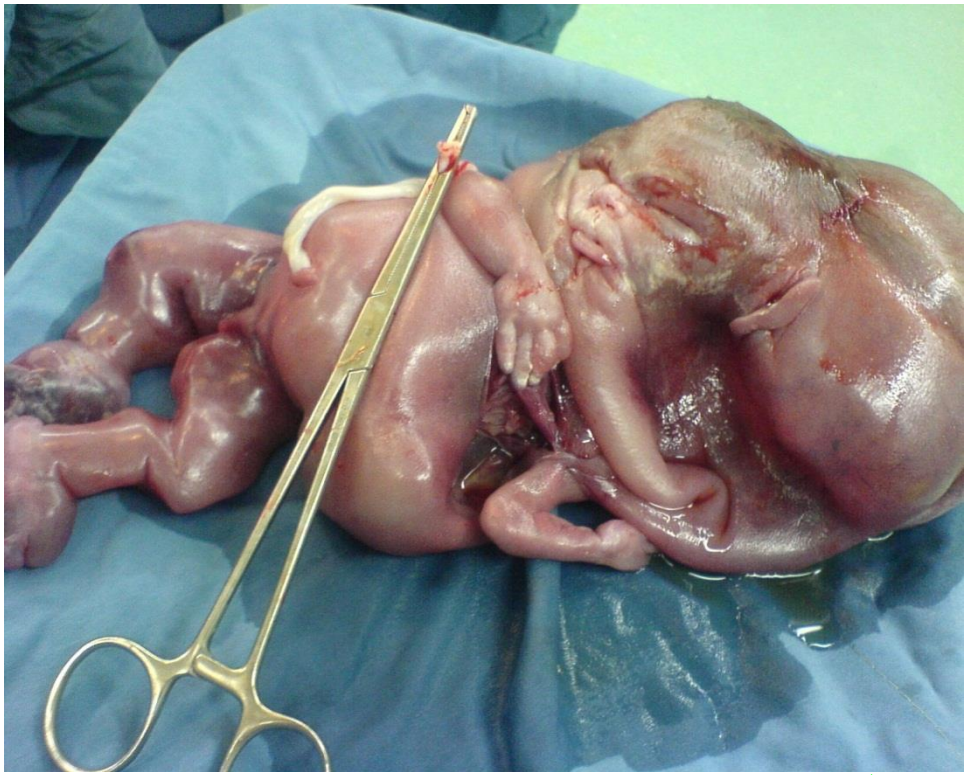
- The most common congenital anomaly
- Very heterogenic in ethiology:
  - Genetic:
    - Chromosomal, single gene, multifactorial
  - Non-Genetic:
    - Maternal factors, Teratogen exposure, …

Example of common CHDs

T21, T18, T13 Turner Syndrome	Numerical chr. Abn.
22q11.2DS Williams-Beuren Syndrome	Microdeletion syn.: Structural chr. Abn.
Marfan Syndrome	Single gene Disorders: Point mutations/ Indel
Noonan syndrome CardioMyopathy	Very heterogenic Single gene Disorders: Point mutations/ Indel

Anuploidy syndromes

Karyotype is the best choice for postnatal diagnosis



Microdeletion syndromes

22q11.2 deletion syndrome:

- ✓DiGeorge syndrome
- ✓Velocardiofacial syndrome
- ✓Conotruncal anomaly face syndrome
- ✓Autosomal dominant Opitz G/BBB syndrome
- ✓Sedlackova syndrome
- ✓Cayler cardiofacial syndrome

Williams-Beuren Syndrome

Del/Dup analysis for 22q11.2DS

Chromosomal microarray (CMA) (array CGH):

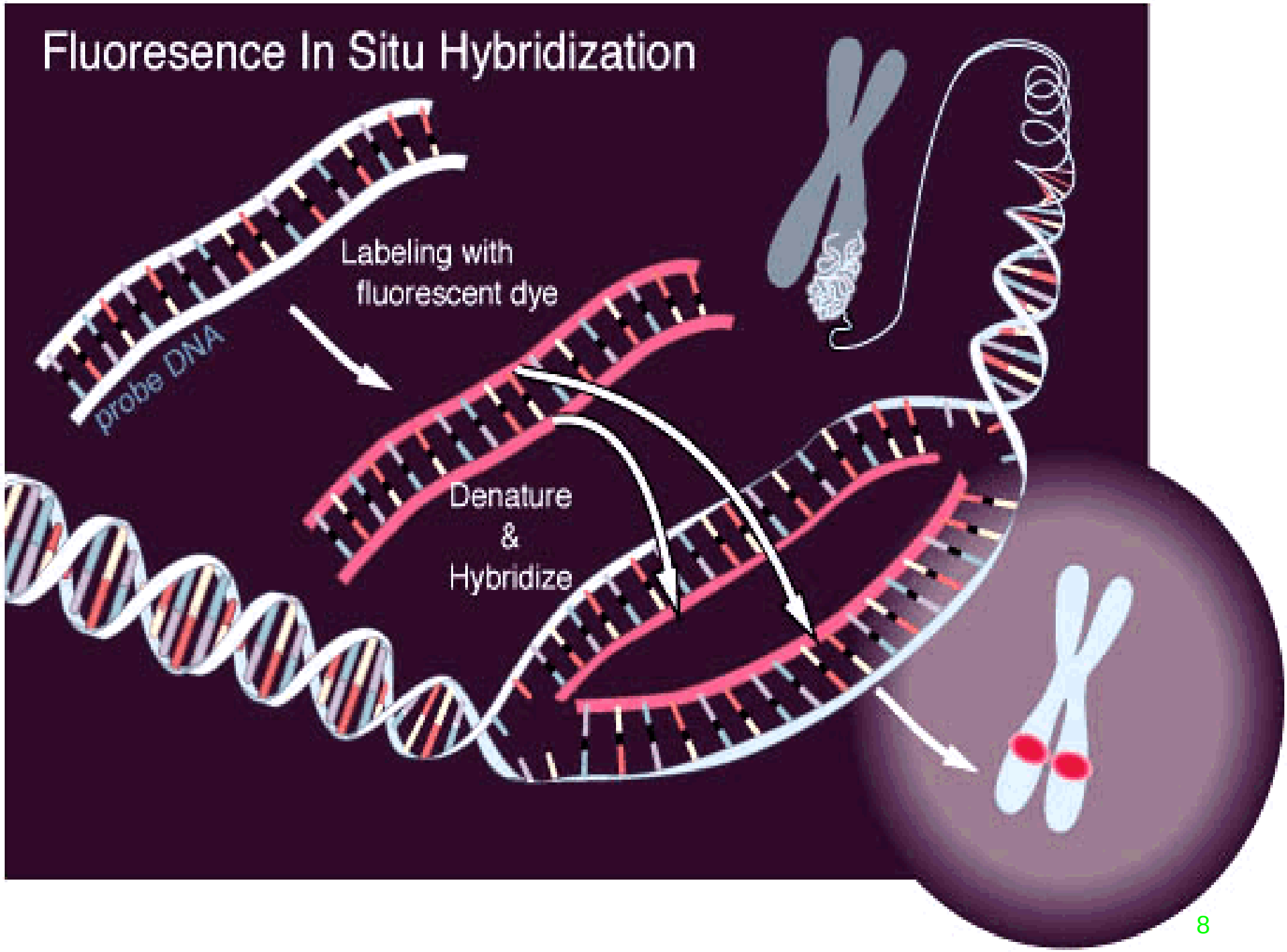
the most appropriate test to identify the 22q11.2 deletion in a proband because the phenotype is nonspecific and often performed as part of the evaluation of developmental delay or intellectual disability

FISH/MLPA:

rapid diagnosis if the syndrome is suspected clinically

confirmation of the deletion after CMA analysis

evaluating relatives of the proband for presence of the deletion


Fluoresence In Situ Hybridization
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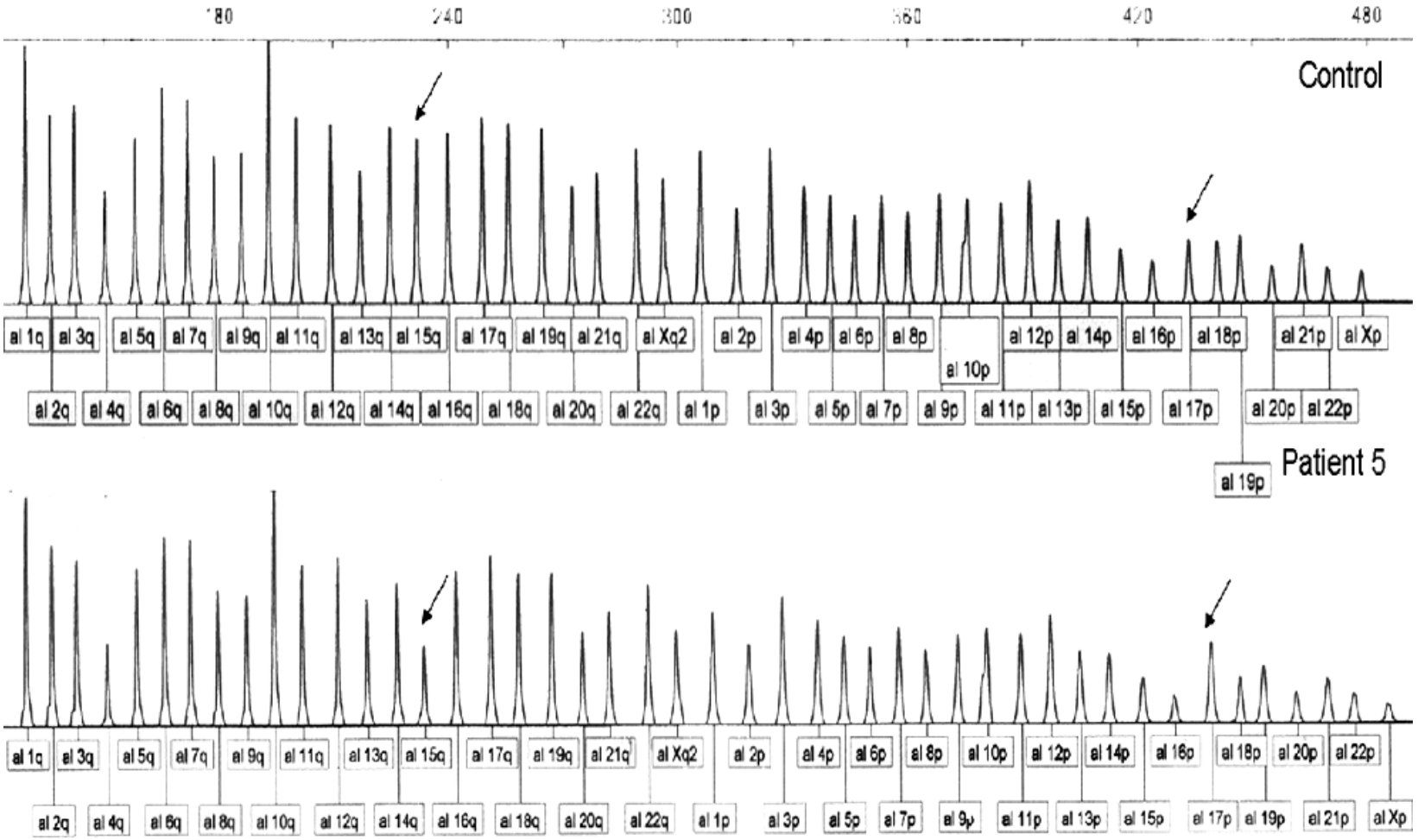
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Project: Untitled	**Compare Type:** MLPA Ratio
Technician:	**Normalization By:** Population Normalization
Report Time: 2/11/2012 - 23:40:7	**Quantification By:** Peak Height
Panel: P245_seri 1 10-02-2011	**Classification:** Loss < 0.73 <= Equivalent <= 1.35 < Gain
Control: Synthetic Control Sample	**Report Value Type:** Peak Ratio

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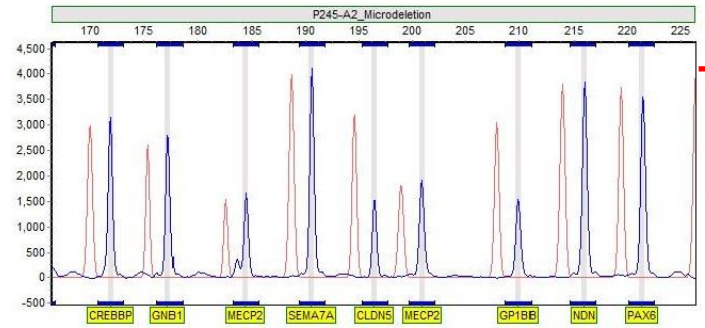

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Statistics	# Probes	Mean	StdDev
Control/Sample	0/52	0.00/0.98	0.00/0.13

Conclusion		
	Date	Initial

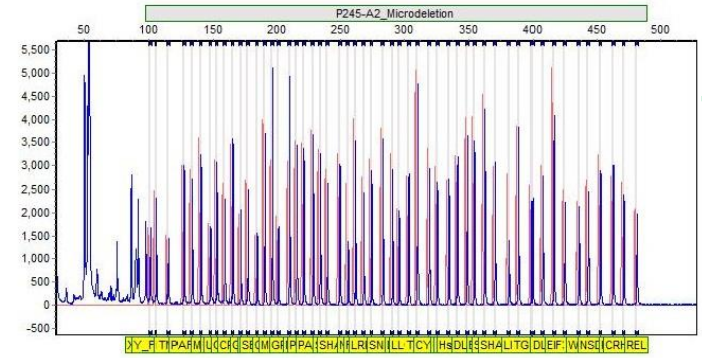
1	CLDN5	196.6	0.478
2	CREBBP	172.0	1.058
3	CRHR1	470.9	1.037
4	CRR9	283.6	1.090
5	CYP1A1	326.8	0.974
6	DBY	115.9	0.998
7	DLG1_a	355.1	0.996
8	DLG1_b	416.3	1.090
9	DMD	296.7	1.091
10	EIF3S3	424.3	0.925
11	ELN	311.2	1.017
12	ELN_b	363.0	0.954
13	FANCL	268.8	1.077
14	GABRD	165.6	0.985
15	GATA3	133.3	0.970
16	GNB1	177.4	1.078
17	GP1BB	209.9	0.509
18	Hs.538604	349.5	1.009
19	LETM1	234.0	0.983
20	LIMK1	389.4	0.965
21	LLGL1	303.9	0.981
22	LRRC48	274.9	1.013
23	MAPT	228.4	1.012
24	MAPT_b	342.1	0.963
25	MECP2	148.1	0.964
26	MECP2	184.5	1.071
27	MECP2	200.9	1.054
28	NDN	215.9	1.015
29	NF1_a	262.3	1.030
30	NF1_b	335.3	1.006
31	NSD1	152.9	1.040
32	NSD1_c	452.7	0.984
33	PAFAH1B1	240.6	0.960
34	PAFAH1B1	140.4	1.054
35	PAX6	221.4	0.947
36	RAI1	462.8	0.949
37	REL	481.4	1.000
38	SEMA7A	190.7	1.029
39	SHANK3_a	256.2	0.955
40	SHANK3_b	381.9	0.941
41	SNAP29	371.2	0.506
42	SNRPN-b	291.3	1.040
43	SNRPN_a	249.8	0.998
44	TERT	435.7	1.030
45	TGFBR1	320.4	1.074
46	TGFBR1_b	407.7	1.119
47	TNFRSF4	127.1	1.000

DGS

Software: GeneMarker V1.60	**Analysis Type:** MLPA
Project: Untitled	**Compare Type:** MLPA Ratio
Technician:	**Normalization By:** Population Normalization
Report Time: 2/11/2012 - 23:51:41	**Quantification By:** Peak Height
Panel: P245_seri 5 -11.2.2012	**Classification:** Loss < 0.73 <= Equivalent <= 1.35 < Gain
Control: Synthetic Control Sample	**Report Value Type:** Peak Ratio

Synthetic Used: 89-10-15-S_P245-258.fsa /// 89-10-15-S_P245-285.fsa

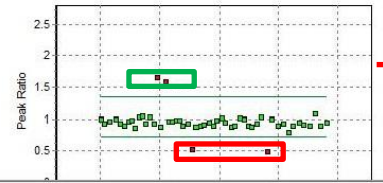
89-10-15-S_P245-216.fsa



Sample Name: P245-216
Machine: 3130geneticanalyzer-21264-017
Run Time: 1/5/2011 - 13:54:19 -> 1/5/2011 - 14:40:44

Statistics	# Probes	Mean	StdDev
Control/Sample	0/52	0.00/0.95	0.00/0.17

Conclusion		
	Date	Initial

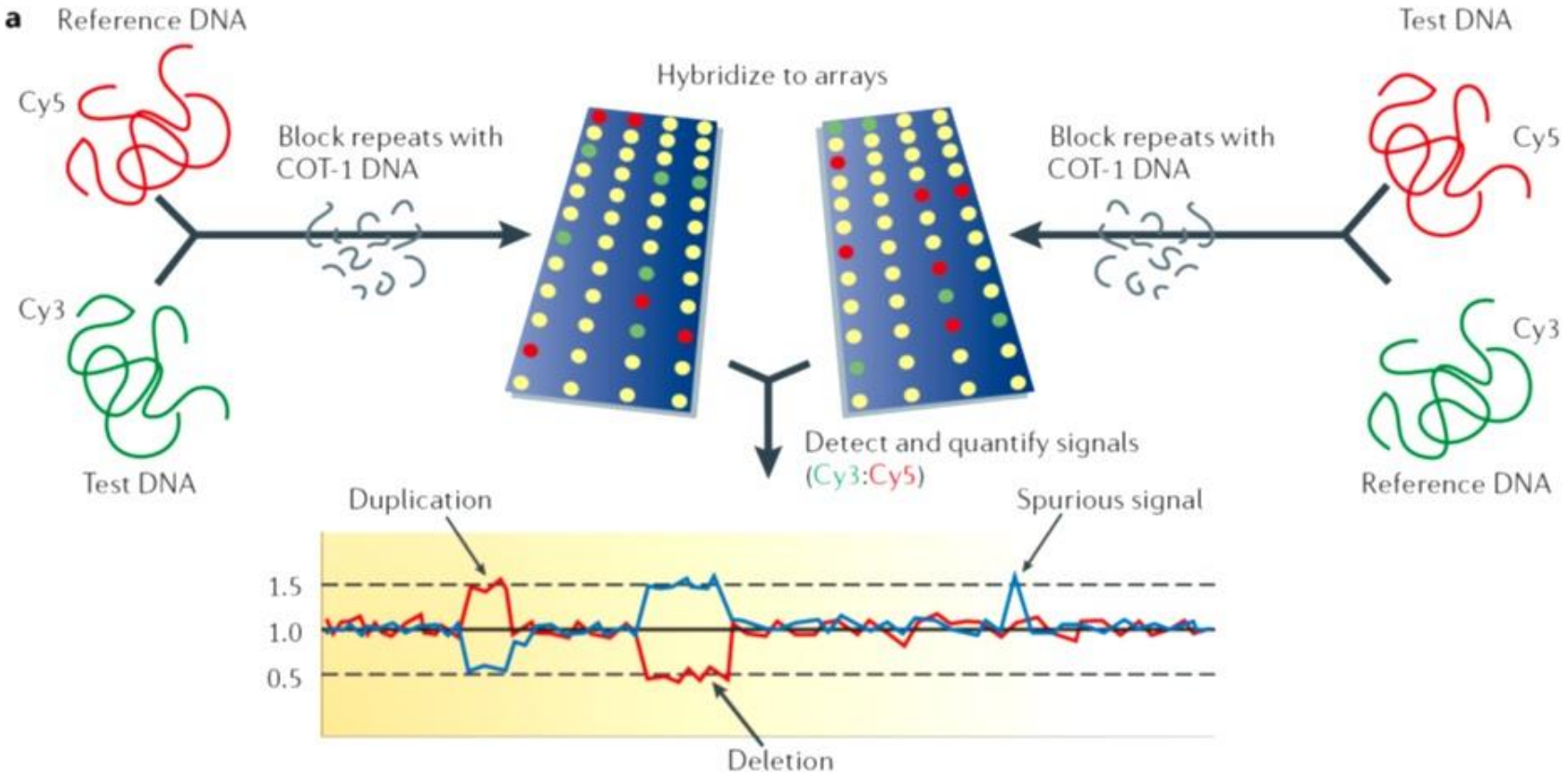


1	CLDN5	196.6	1.646
2	CREBBP	171.8	1.053
3	CRHR1	471.1	0.901
4	CRR9	283.2	0.941
5	CYP1A1	325.8	0.889
6	DBY	115.9	0.955
7	DLG1_a	354.9	0.873
8	DLG1_b	416.5	0.800
9	DMD	295.9	0.977
10	EIF3S3	425.1	0.891
11	ELN	310.5	0.939
12	ELN_b	363.0	0.929
13	FANCL	268.2	0.888
14	GABRD	165.5	1.035
15	GATA3	133.7	0.925
16	GNB1	177.4	0.933
17	GP1BB	210.0	1.586
18	Hs.538604	349.5	0.903
19	LETM1	234.1	0.975
20	LIMK1	389.5	0.992
21	LLGL1	303.4	1.016
22	LRRC48	274.3	0.916
23	MAPT	228.5	0.977
24	MAPT_b	341.7	0.989
25	MECP2	148.0	0.960
26	MECP2	184.6	1.030
27	MECP2	201.3	0.887
28	NDN	215.8	0.971
29	NF1_a	261.7	0.882
30	NF1_b	334.8	1.007
31	NSD1	153.0	0.987
32	NSD1_c	452.9	0.890
33	PAFAH1B1	239.8	0.902
34	PAFAH1B1	140.5	0.899
35	PAX6	221.2	0.967
36	RAI1	463.0	1.084
37	REL	481.5	0.941
38	SEMA7A	190.7	0.926
39	SHANK3_a	255.9	0.523
40	SHANK3_b	382.1	0.495
41	SNAP29	371.2	1.028
42	SNRPN-b	290.7	0.894
43	SNRPN_a	249.4	0.929
44	TERT	436.1	0.948
45	TGFBR1	319.7	0.872
46	TGFBR1_b	407.8	0.924
47	TNFRSF4	127.3	1.000

Cat eye syndrome

Phelan/McDermid syndrome

Chromosomal microarray analysis (CMA) (array CGH)



Feuk L etal. Structural variation in the human genome. *Nat Rev Genet* 2006; 7: 85-97

Marfan syndrome

Gene [1]	Test Method	Mutations Detected [2]	Mutation Detection Frequency by Test Method [3]
FBN1	Mutation scanning / sequence analysis	Sequence variants [4]	~70%-93%
	Complementary DNA sequence analysis		
	Deletion / duplication analysis [5]	Exonic and whole-gene deletions	Unknown

Even in the presence of a FBN1 mutation known to be associated with Marfan syndrome, establishing the diagnosis of Marfan syndrome relies on documentation of significant clinical findings

Testing strategy (out of date)

- Single gene testing (FNB1)

- Multi-gene testing:

  Clinical laboratories may offer a multi-gene Marfan syndrome/Loeys-Dietz syndrome/familial thoracic aortic aneurysms and dissections panel that includes FBN1 as well as a number of genes associated with disorders that include aortic aneurysms and dissections (Differential diagnosis)

Noonan Syndrome

Gene Symbol	Proportion of NS Attributed to Mutations in This Gene	Test Method	Mutations Detected
PTPN11	50%	Sequence analysis / mutation scanning [1, 2, 3]	Sequence variants [4]
		Deletion / duplication analysis [5]	Partial-and whole-gene deletion [6]
SOS1	10%-13% [7]	Sequence analysis / mutation scanning [1, 2, 8]	Sequence variants [4]
		Deletion / duplication analysis [5]	Partial-and whole-gene deletion [6]
RAF1	3%-17%	Sequence analysis [2, 9]	Sequence variants [4]
		Deletion / duplication analysis [5]	Partial- and whole-gene deletion [6]
KRAS	<5%	Sequence analysis	Sequence variants [4]
		Deletion / duplication analysis [5]	Partial- and whole-gene deletion [6]
NRAS	4 individuals to date	Sequence analysis	Sequence variants [4]
BRAF	<2% [10]	Sequence analysis / mutation scanning [1, 2]	Sequence variants [4]

Testing strategy (out of date)

- Sequential molecular genetic testing:
  1. Sequence analysis of PTPN11
  2. If no mutation is identified, sequence analysis of SOS1
  3. (etc.) RAF1
  4. KRAS
  5. NRAS
  6. BRAF
  7. MAP2K1

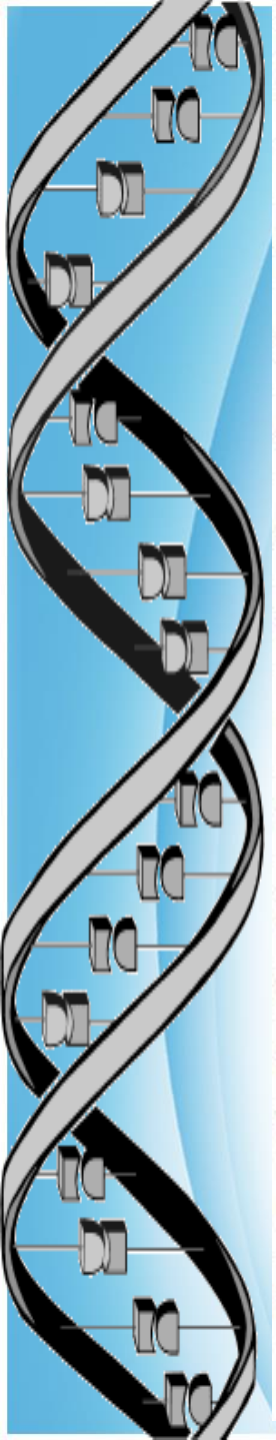
Testing strategy cont.

- Multigene panel:

  in which some or all of the genes in the RasMAPK pathway that cause Noonan syndrome, cardiofaciocutaneous syndrome, and Costello syndrome are sequenced simultaneously

Hypertrophic Cardiomyopathy

- Mutation of one of the genes that encodes a component of the sarcomere are found in approximately 50%-60% of probands (adult and children) with a family history of HCM, and approximately 20%-30% of probands without a family history of HCM
- Approximately 6% of affected individuals have more than one sarcomere gene DNA variant
- More than 1500 individual mutations have been identified



% of FHCM Caused by Mutations in This Gene	Gene [1]	Protein Name [1]	OMIM [1]
40%	*MYH7*	Myosin-7	160760 192600
40%	*MYBPC3*	Myosin-binding protein C, cardiac type	115197 600958
5%	*TNNT2*	Troponin T, cardiac muscle	115195 191045
5%	*TNNI3*	Troponin I, cardiac muscle	191044 613690
2%	*TPM1*	Tropomyosin alpha-1 chain	115196 191010
Unknown	*MYL2*	Myosin regulatory light chain 2, ventricular/cardiac muscle isoform	160781 608758
1%	*MYL3*	Myosin light chain 3	160790 608751
Unknown	*ACTC1*	Actin, alpha cardiac muscle 1	102540 612098
Unknown	*CSRP3*	Cysteine and glycine-rich protein 3	600824 612124
Unknown	*ACTN2*	Alpha-actinin-2	102573
Unknown	*MYH6*	Myosin-6	160710 613251
Unknown	*TCAP*	Telethonin	604488
Unknown	*TNNC1*	Troponin C, slow skeletal and cardiac muscles	191040 613243
Unknown	*PLN*	Cardiac phospholamban	172405 613874
Unknown	*MYOZ2*	Myozenin-2	605602

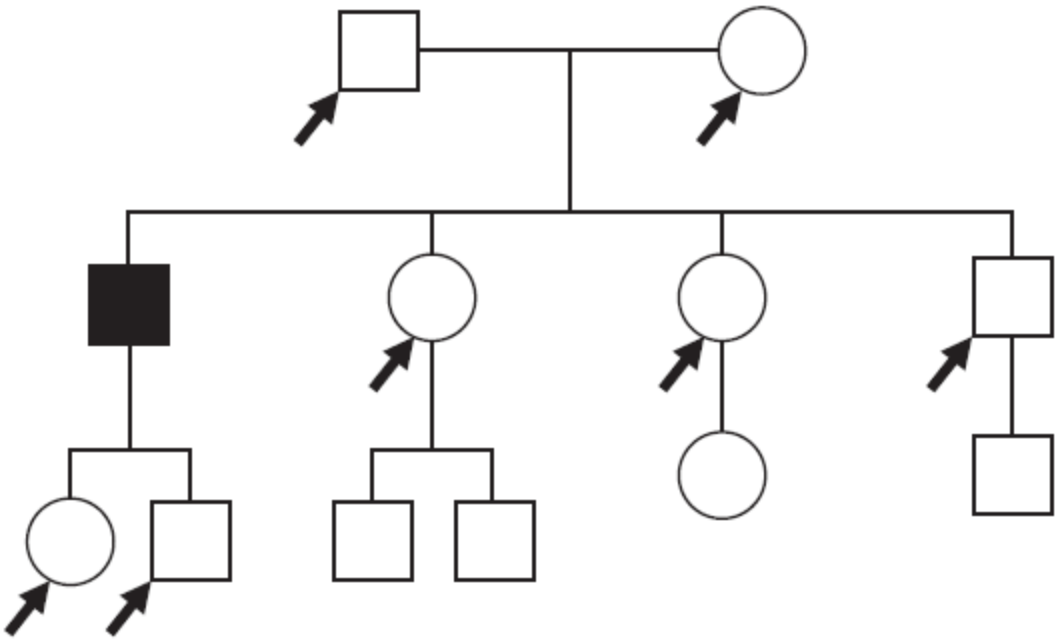
Implication of Genetic Testing in HCM

- (1) Genetic testing recommended in patients fulfilling diagnostic criteria for or with signs or symptoms suggestive of HCM (class I).
- (2) In patients with suspected HCM, comprehensive physical examination and complete medical and three-generation family history are recommended as part of the initial diagnostic assessment (class I).
- (3) Pathogenic variant-specific cascade screening is recommended (class I).

Implication of Genetic Testing in HCM

- (4) In first-degree relatives of patients with HCM, both clinical screening (ECG and echocardiography) and cascade genetic testing should be offered (class I).
- (5) Genetic testing should be considered in deceased patients with pathologically confirmed HCM to facilitate cascade screening (class I).
- (6) In families affected by HCM, preconception and prenatal reproductive and genetic counseling should be offered.

Clinical evaluation for 1st degree relatives



Proband: The solid square indicates a male with a diagnosis of HCM

AD inheritance (one parent is affected)

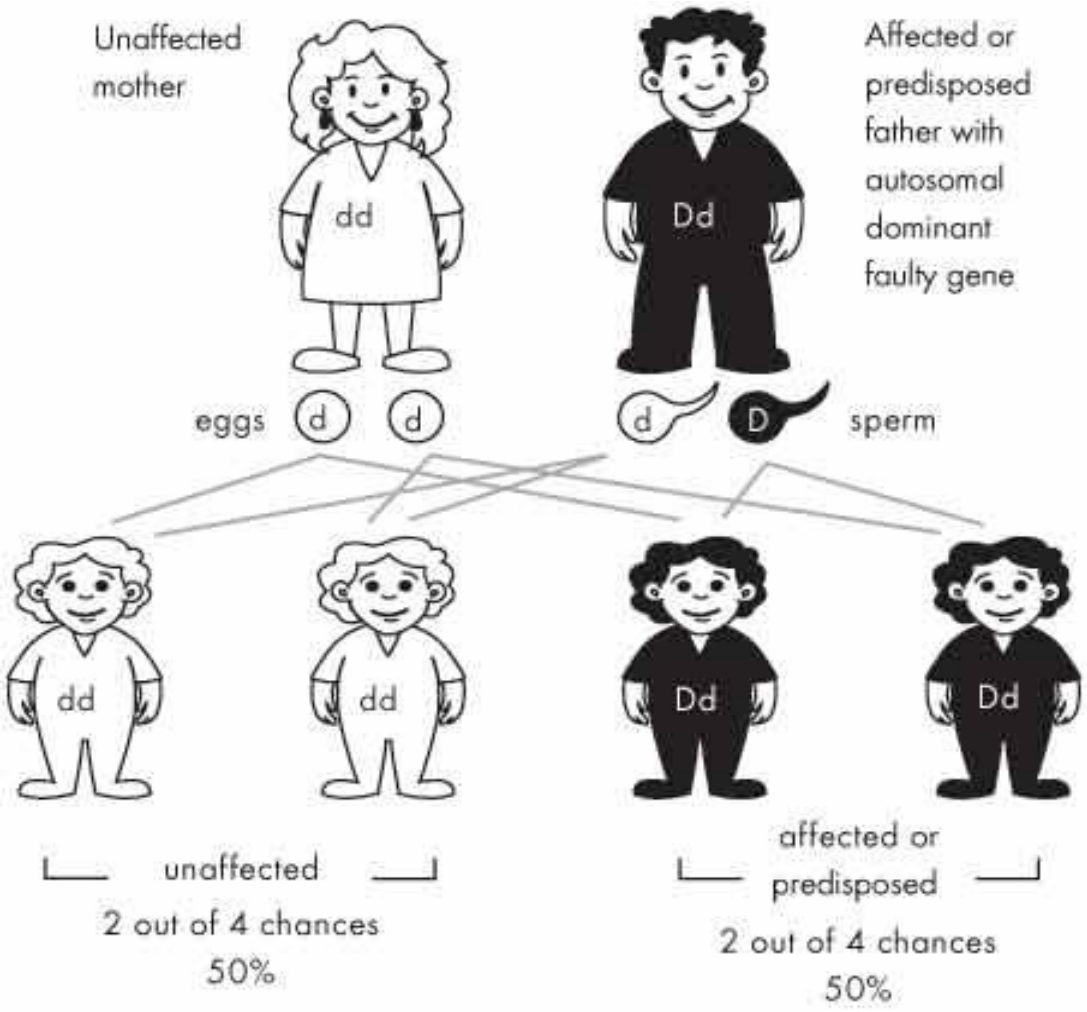
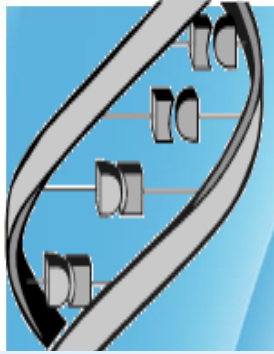


Table 2 Prevalence, inheritance pattern, genes and indications for genetic testing involved in specific cardiomyopathies

Inherited CMP	Prevalence	Pattern of inheritance	Key genes	Diagnostic yield of genetic testing	Recommendation for genetic testing
HCM	1 in 500	AD	MYH7, MYBPC3, TNNT2, TNNI3, TPM1, ACTC1, MYL2, MYL3, GLA, PRKAG2, LAMP2	30%-60%	For any patient with clinical diagnosis of HCM; Familial screening with a mutation after identified in the index case
DCM	1 in 2500	AD, X-linked	DES, DMD, DSP, FLNC, LMNA, MYH7, PLN, RBM20, TNNI3, TNNT2, TTN, TPM1	20%-30%	For patients with DCM and conduction disease and/or family history of SCD; Familial screening with a mutation after identified in the index case
ARVC	1 in 2000-5000	AD, AR	DSC2, DSG2, DSP, JUP, PLN, TMEM43	50%	Familial screening with a mutation after identified in the index case
RCM	Rare	AD, AR X-linked or mitochondrial	Troponin; MYBPC3, MYL3	Unknown	Familial screening with a mutation after identified in the index case

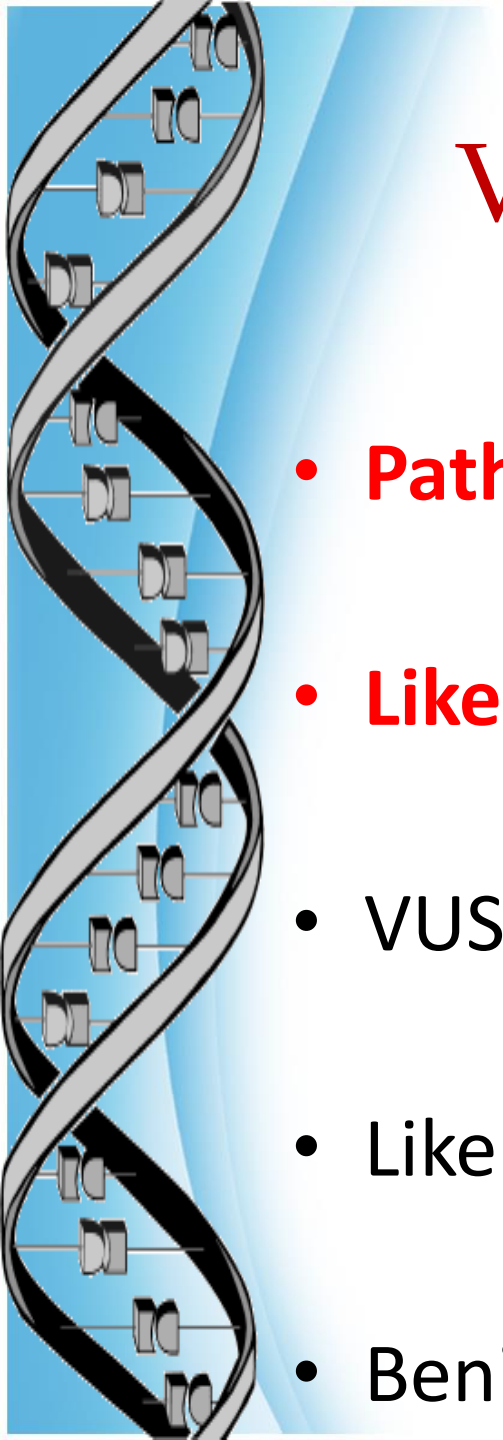
ARVC: Arrhythmogenic right ventricular cardiomyopathy; DCM: Dilative cardiomyopathy; HCM: Hypertrophic cardiomyopathy; RCM: Restrictive



Channelopathies That Lead to Sudden Cardiac Death

Table 1 Long QT genes.

Clinical name	Chromosomal locus	Gene name	Current Affected	Non cardiac effects
LQT1	11p15.5	*KCNQ1 (KVLQT1)*	K^+ (I_{Ks})	Deafness with recessive form (JLNS)
LQT2	7q35-36	*HERG (KCNH2)*	K^+ (I_{Kr})	
LQT3	3p21-24	*SCN5A*	Na^+ (I_{NA})	
LQT4	4q25-27	Ankyrin B	Na^+ (I_{NA})	
LQT5	21q22.1-22.2	*KCNE1* (minK)	K^+ (I_{Ks})	Deafness with recessive form (JLNS)
LQT6	21q22.1-22.2	*KCNE2* (MiRP1)	K^+ (I_{Kr})	
LQT7 (Anderson)	17q23	*KCNJ2*	K^+ ($K_{ir2.1}$)	Anderson-Tahwil syndrome with some mutation
LQT8 (Timothy)	*12p13.3*	*CACNA1C*	*Ca + +*($I_{Ca\text{-}L}$)	*Timothy syndrome with some mutations*
LQT9	*3p25*	*CAV3 (Caveolin)*	Na^+ (I_{NA})	
LQT10	*11q23.3*	*SCN4B*	Na^+ (I_{NA})	
LQT11	*7q21-q22*	*AKAP9 (A −anchor protein 9)*	K^+ (I_{Ks})	
LQT12	*20q11.2*	*SNTA1 (alpha-1 syntrophin)*	Na^+ (I_{NA})	
LQT13	*11q24.3*	*KCNJ5*	K^+ (K_{ir})	
LQT14	14q24-q31	*Calmodulin1*	Many[#]	Seizures, developmental delay
LQT15	2p21.1-p21.3	*Calmodulin2*	Many[#]	Seizures, developmental delay
LQT16	*19q13.2-q13.3*	*Calmodulin3*	Many[#]	Seizures, developmental delay
LQT17		*Triadin*		



Variant Classification

- **Pathogenic: cascade screening**
- **Likely Pathogenic: cascade screening**
- VUS
- Likely Benign
- Benign

Summary

- **Genetic testing** in heart failure clinics is useful for **family screening** and providing **individual prognostic insight**.
- Obtaining a **family history** of at least **three generations** is recommended for all patients with primary cardiomyopathy.
- Consultation with a **genetic counsellor** can aid in the success of a genetic evaluation.
- **Clinical screening** should be performed on all **first-degree relatives** of patients with genetic cardiomyopathy.

Any Questions?


Thanks for your attention

In His Sublime Name

Role of MRI in myocarditis diagnosis

Presented by:

Razieh Khazaei

Introduction

- Myocardial inflammation
  - often from the host immune response triggered by
    - Infection
    - autoimmune diseases
    - ischemic injury
    - Toxins
- Myocarditis
  - more specific term
    - a nonischemic inflammatory disease of the myocardium
  - diagnosis on histologic evaluation of the myocardium showing inflammation and myocyte damage
- Cardiac MRI
  - important role in assessment of suspected myocarditis
    - identification can affect patient management and prognosis
- The aim
  - an overview of the role of cardiac MRI
  - typical findings in patients with nonischemic myocardial inflammation
    - a focus on acute myocarditis after COVID-19 vaccination

Incidence and Pathophysiology

- Incidence
  - difficult to establish
    - clinical symptoms are nonspecific
      - chest pain
      - shortness of breath
    - endomyocardial biopsy is not frequently performed for definitive diagnosis
      - one-third of patients with acute coronary syndrome without substantial coronary artery disease are ultimately diagnosed with acute myocarditis

- Myocarditis
  - ultimately driven by an immune response
    - acute myocarditis
      - the initial trigger is either direct myocardial injury or immune dysregulation that induces inflammation by activating immune response
  - a spectrum of clinical severity
    - subclinical disease
    - myocarditis with preserved cardiac function
    - reduced systolic or diastolic function, arrhythmia, and rarely hemodynamic collapse and cardiogenic shock
  - In most patients
    - immune response is self-limited and downregulates with clearance of initial trigger. However, depending on the degree of myocardial injury, patients may have residual myocardial dysfunction and fibrosis
  - In a minority of patients
    - inflammatory response can persist or recur, leading to chronic myocarditis
  - **Most patients recover completely after acute myocarditis**
  - **less than 5% progress to dilated cardiomyopathy due to myocardial remodeling**

- The most common trigger in developed countries
  - viral infection
    - traditional serologic studies, viral cultures, and molecular techniques
      - lack both sensitivity and specificity
  - COVID-19
    - elevated troponin levels in more than 60% of hospitalized patients
      - Directly by binding to the angiotensin-converting enzyme 2
      - Indirectly by myocardial inflammation due to immune dysregulation

- Noninfectious causes
  - autoimmune and immune-mediated disorders
    - Vasculitis
    - connective tissue disorders (SLE …)
    - granulomatous diseases (giant cell myocarditis)
  - drugs
    - Amphetamines
    - immune check point inhibitors
  - after immunization
    - COVID-19 vaccination in a minority of patients

Diagnosis

- Establishing is important
  - timely recognition can impact patient management and outcomes
  - an important cause of sudden cardiac death in young adults
    - up to 12% of sudden cardiac death cases

- Endomyocardial biopsy
  - standard for definitive diagnosis
    - not frequently performed
      - invasive nature and associated risks
    - only indicated if the results will have a meaningful effect on therapeutic decisions

- Acute myocarditis is considered clinically suspected if
  - at least one clinical criterion and at least one diagnostic
    - Clinical criteria
      - acute chest pain
      - new onset dyspnea
      - Palpitations
      - unexplained arrhythmia symptoms
      - Syncope
      - sudden cardiac death
      - unexplained cardiogenic shock
    - Diagnostic criteria
      - EKG,Holter monitor or stress test abnormalities
      - elevated troponin levels
      - functional and structural abnormalities at cardiac imaging
      - typical tissue characterization features of edema and/ or late gadolinium enhancement (LGE) at cardiac MRI

- **Cardiac MRI**
  - important role for diagnosis
  - identifying or excluding other potential diagnoses
    - acute coronary syndrome or stress-induced cardiomyopathy
  - may suggest a specific potential cause

Imaging Myocardial Inflammation

- **Echocardiography**
  - often first imaging modality
    - widely available
    - rapid assessment of cardiac size and function
  - Typical findings
    - increased myocardial wall thickness and echogenicity
    - impaired global systolic function and strain
    - regional wall motion abnormalities
    - ventricular dilatation
      - relatively nonspecific
  - important prognostic information
    - increased LV size
    - impaired function
      - predictors of poor outcomes

- **Coronary CT angiography**
  - noninvasive modality
    - excluding obstructive coronary artery disease in patients with acute chest pain and elevated troponin levels
  - Late iodine enhancement
    - useful in evaluating myocardial damage
      - particularly in patients with a contraindication to MRI
    - limited data specifically in acute myocarditis

- PET
  - well established in evaluation of active myocardial inflammation
    - in the setting of cardiac **sarcoidosis**
  - Limited data demonstrate that PET can also identify inflammation in setting of acute myocarditis
  - typically performed in conjunction with CT for anatomic localization
  - more recently combined PET/MRI scanners

Cardiac MRI

- ***the most important noninvasive cardiac imaging modality***
  - diagnosis
  - follow-up
  - risk stratification of patients with nonischemic myocardial inflammation
  - distinguishing myocarditis from other causes of acute chest pain in patients who have nonobstructive coronary arteries
  - if there is diagnostic uncertainty
  - determine the presence and extent of myo/pericardial inflammation and fibrosis

Updated Lake Louise Criteria

- The LLC
  - revised in 2018
    - incorporate parametric mapping
      - quantitative assessment of **regional and global myocardial T1 and T2 relaxation times and ECV**
    - In comparison to the original LLC
      - significantly higher sensitivity (88% vs 73%) while maintaining very high specificity (96%)

- According to the revised criteria
  - cardiac MRI
    - strong evidence of acute myocardial inflammation in patients with high clinical pretest probability
      - if at least one criterion in each of the following two categories is positive
        - » a T2-based marker of myocardial edema
        - » a T1-based marker of myocardial damage
          - The presence of only one marker
            - may support the diagnosis in the appropriate clinical context
              - lower specificity
          - these criteria were intended to be applied **in patients with clinically suspected** myocardial inflammation
          - not applied broadly as a screening test for myocardial injury in asymptomatic patients

T2-based Criteria for Myocardial Edema

- Tissue edema
  - hallmark of inflammation
    - often focal
      - although diffuse edema can also be identified
- T2-based criteria for myocardial edema
  - **regional high T2 signal intensity**
  - **global T2 signal intensity ratio (myocardium/skeletal muscle) ≥2**
  - **increase of myocardial T2 relaxation time**
  - Assessment of myocardial edema
    - previously on T2-weighted imaging
      - high diagnostic accuracy for focal edema
        - » although image quality can be degraded by artifact and signal inhomogeneity
    - T2 mapping allows for direct quantification of T2 relaxation times
        - » very high sensitivity (89%)
      - High T2 signal is specific for increased tissue water
        - » discriminate between active and healed myocarditis

T1-based Criteria for Myocardial Injury

- Severe inflammation
  - myocardial injury and necrosis
    - Fibrosis
  - T1 criteria for myocardial injury
    - **LGE in a nonischemic pattern (subepicardial or mid-myocardial)**
    - **increase of myocardial native T1 or ECV values**

- LGE imaging
  - one of the most important MRI techniques
    - Gadolinium-based contrast agents are retained within injured and necrotic tissue
      - hyperintensity at T1-weighted inversion-recovery imaging
  - The pattern is most commonly subepicardial or midwall and often **in a linear configuration**
    - the pattern of LGE in the setting of ischemic myocardial injury is **subendocardial to transmural** and corresponds to a coronary artery territory
  - The most common location for LGE in viral myocarditis
    - basal inferolateral wall
    - basal anterior septum
    - mid inferolateral wall
    - basal to mid inferior wall
    - Transmural enhancement and more diffuse LGE
      - particularly in severe cases of **fulminant and giant cell myocarditis**

Updated Lake Louise Criteria

- T2-based criteria for myocardial edema
  - **regional high T2 signal intensity**
  - **global T2 signal intensity ratio (myocardium/skeletal muscle) ≥2**
  - **increase of myocardial T2 relaxation time**
- T1 –based criteria for myocardial injury
  - **LGE in a nonischemic pattern (subepicardial or mid-myocardial)**
  - **increase of myocardial native T1 relaxation time or ECV values**
- supportive criteria
  - **wall motion abnormalities**
  - **signs of pericarditis**
    - **effusion or pericardial late enhancement**

- LGE both in the setting of
  - acute inflammation
    - myocyte necrosis and hyperemia
  - fibrosis
    - expansion of the extracellular space
      - **cannot reliably differentiate between acute and healed myocarditis**
- Over time, the extent of LGE usually decreases as inflammation resolves and scar contracts
  - T1 and ECV are elevated in setting of replacement myocardial fibrosis
    - Native T1
      - a composite measurement reflecting signal from both the intracellular (mainly myocytes) and extracellular (mainly interstitial) myocardial compartments
    - ECV
      - an estimate of proportion of the extracellular space only

- T1 and ECV
  - elevated in the setting of myocardial edema
    - although unlike elevated T2, these changes are not specific for acute inflammation
- in a patient with suspected myocarditis
  - corresponding elevated T2, T1, and ECV values
    - a high likelihood of myocardial edema
  - elevated T1 and ECV in the setting of normal T2
    - presence of fibrosis or infiltration without acute inflammation

LV Dysfunction

- In more severe cases of myocarditis
  - regional wall motion abnormalities
    - Myocardial strain quantification
      - has not been routinely implemented in clinical practice
  - systolic LV dysfunction
    - regional or global
      - a **supportive criterion** for myocarditis but is not required to make the diagnosis according to the revised LLC
      - After an acute episode of myocarditis
        - » global systolic function often improves rapidly and, in most cases, returns to normal
    - more severe in fulminant myocarditis
      - despite frequent improvement in the acute phase, LV function remains lower on average compared with nonfulminant cases at long-term follow-up

Pericardial Inflammation

- supportive for the diagnosis of myocarditis
  - pericardial enhancement
  - high T1 or T2 mapping values
  - pericardial effusion
    - most commonly involving the pericardium adjacent to areas of inflamed myocardium, although it can also be diffuse

Adverse Risk Markers at MRI

- LGE
  - a strong independent predictor of mortality
    - The risk of major adverse cardiovascular events increases by approximately 79% for every 10% increase in quantitative LGE extent
    - presence of LGE with concomitant T2 hyperintensity
      - better prognosis compared with isolated LGE without T2 hyperintensity
        - » LGE without associated edema typically
          - **fibrosis(irreversible)**
        - » LGE in the context of T2 hyperintensity
          - **at least partial recovery as edema improves over time**
- Global systolic dysfunction (LV ejection fraction < 40%)
- Higher T1 and ECV

- In patients with acute myocarditis with evidence of **myocardial edema and/or LV dysfunction**
  - follow-up cardiac MRI 3 to 6 months after the baseline study
    - » assess for functional recovery and the possibility of residual scarring

Cardiac MRI Protocol and Postprocessing

- MRI protocol
  - short- and long-axis cine sequences(cine SSFP)
    - assessment of **ventricular volumes and function**
      - biventricular size
      - EF
    - Presence or absence of regional wall motion abnormalities
      - common but nonspecific
      - **biventricular wall motion abnormality**
        - » **the main predictor of death or transplantation**

- MRI protocol
  - T2-based imaging (black blood T2-weighted imaging and/or T2 parametric maps)
    - Presence or absence and distribution of **focal myocardial edema**
    - Presence or absence and distribution of **pericardial edema**

- MRI protocol
  - T1-based imaging (LGE and/or pre– and post–contrast-enhancement T1 mapping)
    - Necrosis and fibrosis
    - Presence or absence, distribution and intensity of myocardial LGE
    - Optional quantification of myocardial **LGE extent**
      - **indication of irreversible myocardial necrosis and fibrosis**
    - Presence or absence and distribution of **pericardial enhancement**

- MRI protocol(optional)
  - EGE
    - EGE ratio greater than or equal to 4
      - regional vasodilatation and increased blood volume(Hyperemia)
  - First pass perfusion
    - Presence or absence and distribution of perfusion defect
      - capillary leak
  - ECV
    - Presence or absence of elevated ECV values
    - Extracellular edema and fibrosis

- values vary on the basis of technical and patient-specific factors
    - » field strength
        - T2 values are higher at 1.5 T compared with 3 T, while T1 values are substantially higher at 3 T compared with 1.5 T
            - mapping values should be compared with local reference ranges

- For highest diagnostic performance, MRI **should ideally be performed in the acute phase**
  - MRI markers of myocardial inflammation demonstrate rapid and continuous improvement during the first few weeks after the onset of symptoms
    - » sensitivity for detection of myocardial edema is much lower if patients are imaged weeks after the initial clinical presentation
    - » Establishing a diagnosis of nonacute myocarditis is challenging, as findings are often nonspecific.

Cardiac MRI in Specific Causes of Myocarditis

- Cardiac MRI findings
  - substantial overlap between different causes of myocarditis
    - clinical features are taken into consideration

COVID-19 miocarditis

- A recent study
  - T1 and T2 values were diffusely elevated in patients recovered from COVID-19 compared with patients with non–COVID-19 myocarditis
  - Other studies have reported more focal MRI abnormalities typical of non-COVID myocarditis
    - subepicardial LGE

Myocarditis after COVID-19 Vaccination

- Myocarditis
  - in a minority of people following administration of mRNA-based COVID-19 vaccines
    - Moderna
    - PfizerBioNTech)
      - symptom onset typically within a few days of vaccination (**median, 2–3 days**)
  - **3-5 times more frequent after the second dose** compared with the first
  - **patients with prior history of COVID-19** are at higher risk after the first dose
  - 1903 reports of myopericarditis among people who received at least one dose of a COVID-19 vaccine as of August 18, 2021,in the context of nearly 360 million total doses administrated
    - the risk of myocarditis following SARS-CoV-2 infection was much higher

- Typical cardiac MRI findings
  - similar to findings in nonvaccine myocarditis
  - **subepicardial LGE with a predilection for the basal inferolateral wall**
  - corresponding myocardial edema
  - pericardial enhancement
  - axillary lymphadenopathy ipsilateral to the vaccine administration site
  - **impaired LV ejection fraction**
    - **in 14%–25% of patients**

- Differentiating vaccine-associated myocarditis from other causes of myocardial injury at cardiac MRI
  - a challenge
    - the pattern of findings is similar
    - there are no longitudinal imaging studies to suggest how long abnormalities persist
  - accurate diagnosis is important
    - this could impact patient treatment
    - individuals who develop myocarditis or pericarditis after a dose of an mRNA vaccine **defer receiving a subsequent dose** until additional data are available
  - In patients with signs or symptoms suggestive of myocarditis following vaccination
    - cardiac MRI should ideally be performed as soon as possible after the onset of symptoms
      - maximize the likelihood of detecting **myocardial edema**, which would suggest an acute process

- If MRI is performed several weeks to months after symptom onset
  - No T2 abnormality
    - it is difficult to attribute myocardial tissue changes to a specific cause
      - a particular challenge in symptomatic patients who have received an mRNA vaccine and have a prior history of COVID-19
- No routine imaging of asymptomatic individuals after COVID-19 vaccination
- In most reported cases of myocarditis following COVID-19 vaccination
  - rapid resolution of symptoms and corresponding decreases in troponin levels over short-term follow-up
    - good long-term prognosis
      - the risk of myocardial injury and other severe outcomes after COVID-19 is higher
        - » current data are supportive of continued COVID-19 immunization on the basis of the balance of risks and benefits

Conclusion

- Cardiac MRI
  - an important imaging modality in patients with suspected myocarditis
    - noninvasive assessment of myocardial edema and injury
    - identification of potentially treatable underlying causes of inflammation
      - guide management and improve patient outcomes
  - particularly useful in patients presenting with signs and symptoms suggestive of myocarditis after COVID-19 vaccine administration, although further study is needed

Causes of Myocardial Inflammation and Typical MRI Findings

infection

- **Viral myocarditis**
  - Linear subepicardial or midwall LGE
  - commonly involving
    - basal inferolateral wall
    - basal anterior septum
    - mid inferolateral wall
    - basal to mid inferior wall
  - corresponding T2 hyperintensity

- **Chagas disease**
  - LGE in up to 70% of patients
    - usually midwall or subepicardial
    - less commonly subendocardial or transmural with apical aneurysms
    - most commonly at
      - left ventricular apex
      - apical inferior and lateral wall
      - basal to mid inferolateral wall

- **Bacterial and parasitic myocarditis**
  - no specific pattern

- **COVID-19**
  - similar to non-COVID viral myocarditis
    - higher prevalence of diffuse myocardial edema
    - global elevation of T1 and T2 mapping values

Causes of Myocardial Inflammation and Typical MRI Findings

Postvaccination

- limited MRI data, mostly from case series
- typical for viral myocarditis
  - severity and extent of MRI abnormalities relatively mild
  - axillary LAP ipsilateral to the vaccination site
    - a useful clue, particularly if a history of recent vaccine administration is not provided

Causes of Myocardial Inflammation and Typical MRI Findings :
systemic disease

- EGPA
  - patchy midwall and subepicardial LGE
  - corresponding T2 hyperintensity
  - **subendocardial apical LGE with or without apical thrombus**
  - **concomitant pulmonary opacities**

- **SLE**
  - Patchy or linear midwall and subepicardial LGE
  - elevated T1 and T2 value decrease following anti-inflammatory treatment
  - higher prevalence of pericardial and pleural effusion and thickening

- **Sarcoidosis**
  - Patchy and nodular LGE with associated high T2
  - most common at the basal septum and basal inferolateral segment
  - associated findings
    - mediastinal and hilar LAP
    - pulmonary opacities

Causes of Myocardial Inflammation and Typical MRI Findings :
Drug related

- **ICI-related**
  - Diffusely elevated T1 and T2 values
  - LGE present in 48% of patients
    - most commonly
      - subepicardial
      - midmyocardial
      - in the basal and mid inferior and inferolateral segments

Causes of Myocardial Inflammation and Typical MRI Findings : others

- Hypereosinophilic syndrome
  - Similar MRI findings to EGPA
    - **higher prevalence of subendocardial LGE**
- Giant cell myocarditis
  - similar to cardiac sarcoidosis
    - LGE tends to be more extensive
    - **right ventricular involvement** more common

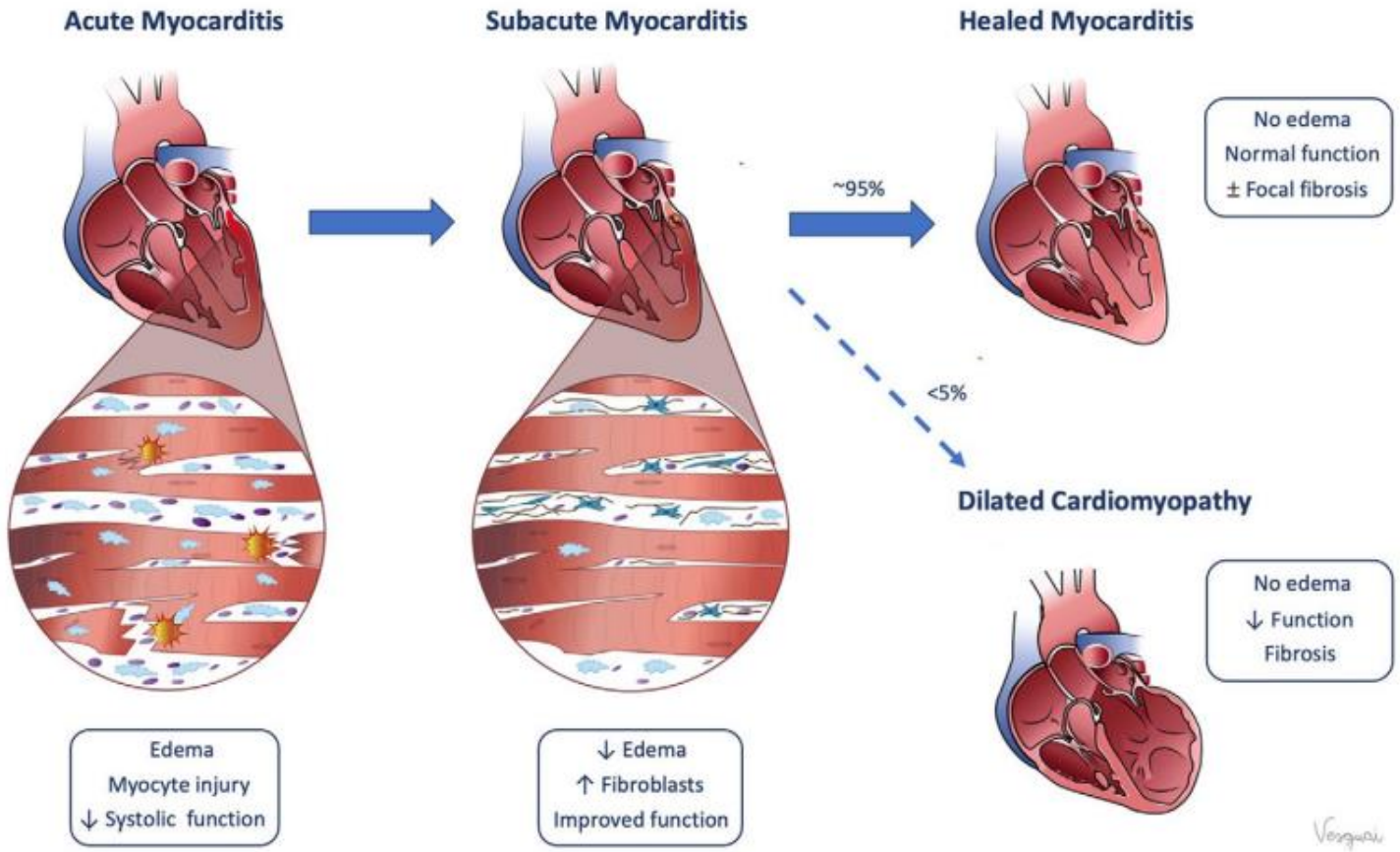


Figure 1: Pathophysiology of myocarditis. (Reprinted, with permission, from Valentina Sanchez Tijmes).

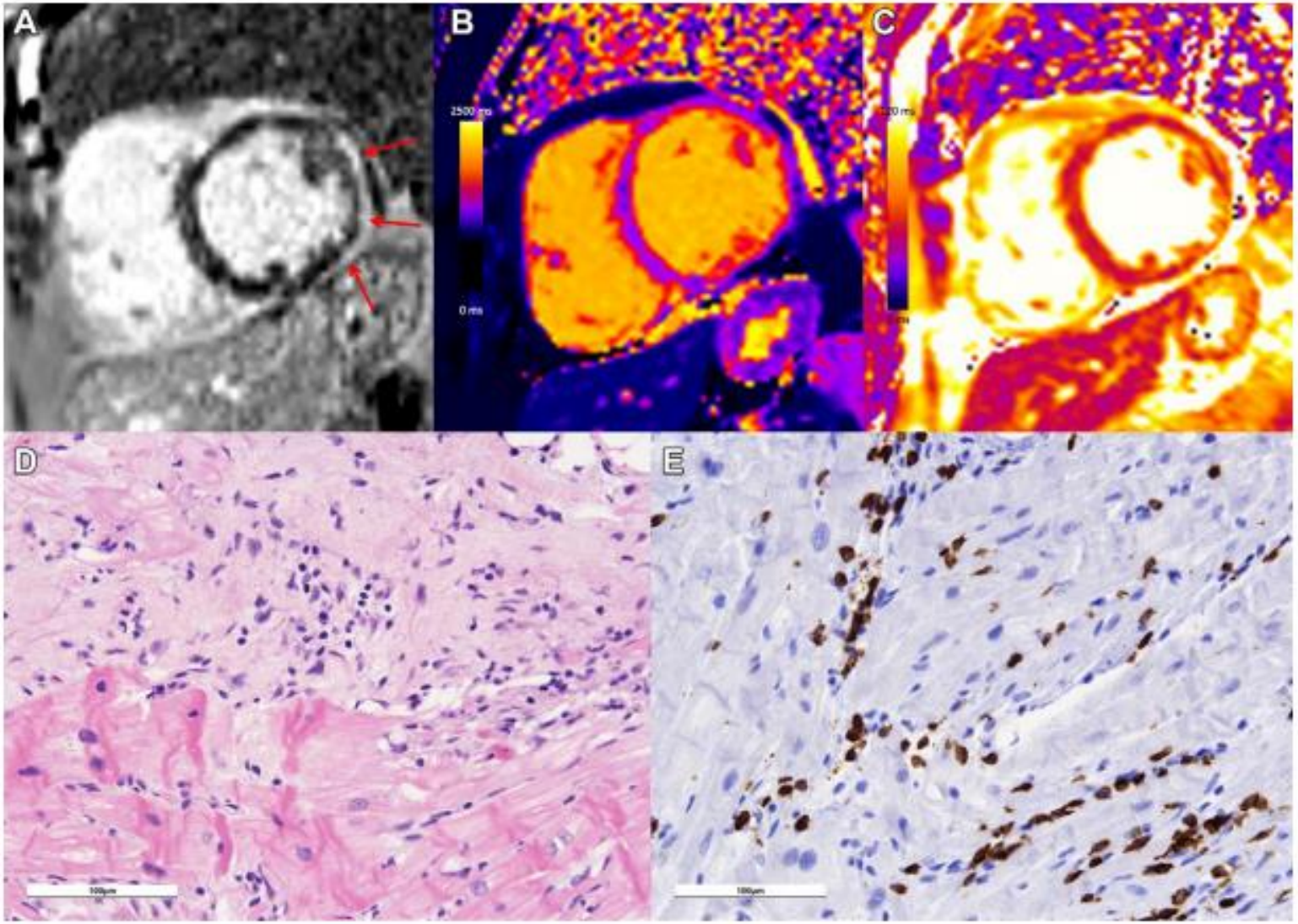


Figure 2: Case example in a 68-year-old woman with lymphocytic myocarditis related to immune checkpoint inhibitor therapy. Cardiac MRI performed at 1.5 T demonstrates extensive subepicardial late gadolinium enhancement at **(A)** the basal to mid anterior, anterior lateral, inferior lateral, and inferior wall (red arrows) with **(B)** corresponding high regional native T1 (1280 msec) and **(C)** high regional T2 (69 msec) on short-axis images, in keeping with myocardial edema and damage. **(D)** Histologic images from endomyocardial biopsy demonstrate inflammation, including an active (dense inflammation) and healing (looser mixed inflammation, expanded matrix) component, with myocyte damage evident as myocytolytic change, vacuolization, and atrophy on hematoxylin-eosin stain. **(E)** At CD3 immunohistochemistry, a substantial portion of the inflammatory population was CD3 positive, consistent with a T-cell-mediated (lymphocytic) active myocarditis. Both histologic images were acquired with a Leica DM2500 microscope with a 20× objective and an OMAX A35180U3 camera. Images were acquired with ToupView software; no further adjustments were made. Scale bars (100 μm) are as shown.

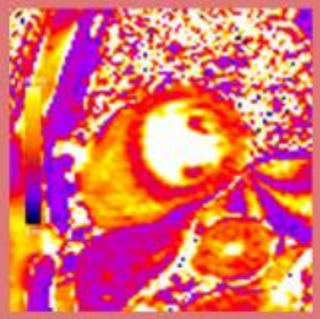
REVISED LAKE LOUISE CRITERIA FOR MYOCARDITIS

MAIN CRITERIA

T2 CRITERIA (EDEMA)

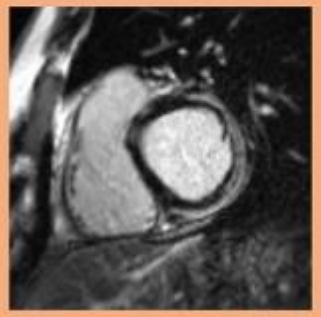
HIGH T2-SIGNAL INTENSITY

OR



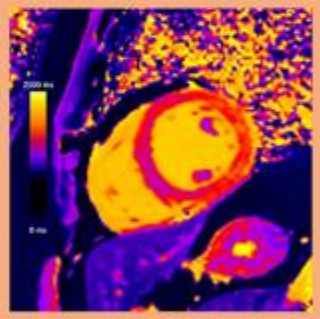
HIGH T2 VALUE

T1 CRITERIA (INJURY)



NON-ISCHEMIC LGE

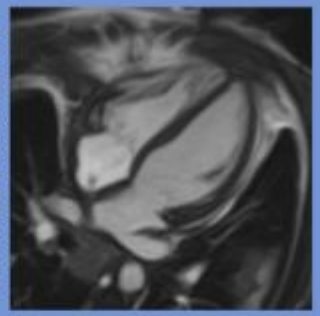
OR



HIGH T1 OR ECV

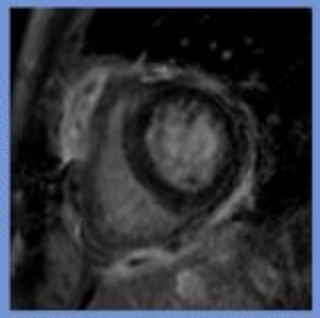
SUPPORTIVE CRITERIA

SYSTOLIC DYSFUNCTION



REGIONAL OR GLOBAL HYPOKINESIA

PERICARDITIS



PERICARDIAL ENHANCEMENT

In patients with high clinical pre-test probability of myocardial inflammation:

Fulfilment of any T2-criteria **AND** any T1-criteria → Strong evidence of myocardial inflammation

Fulfilment of any T2-criteria **OR** any T1-criteria → Possible evidence of myocardial inflammation

Left ventricular systolic dysfunction and pericarditis are supportive but are not required for diagnosis

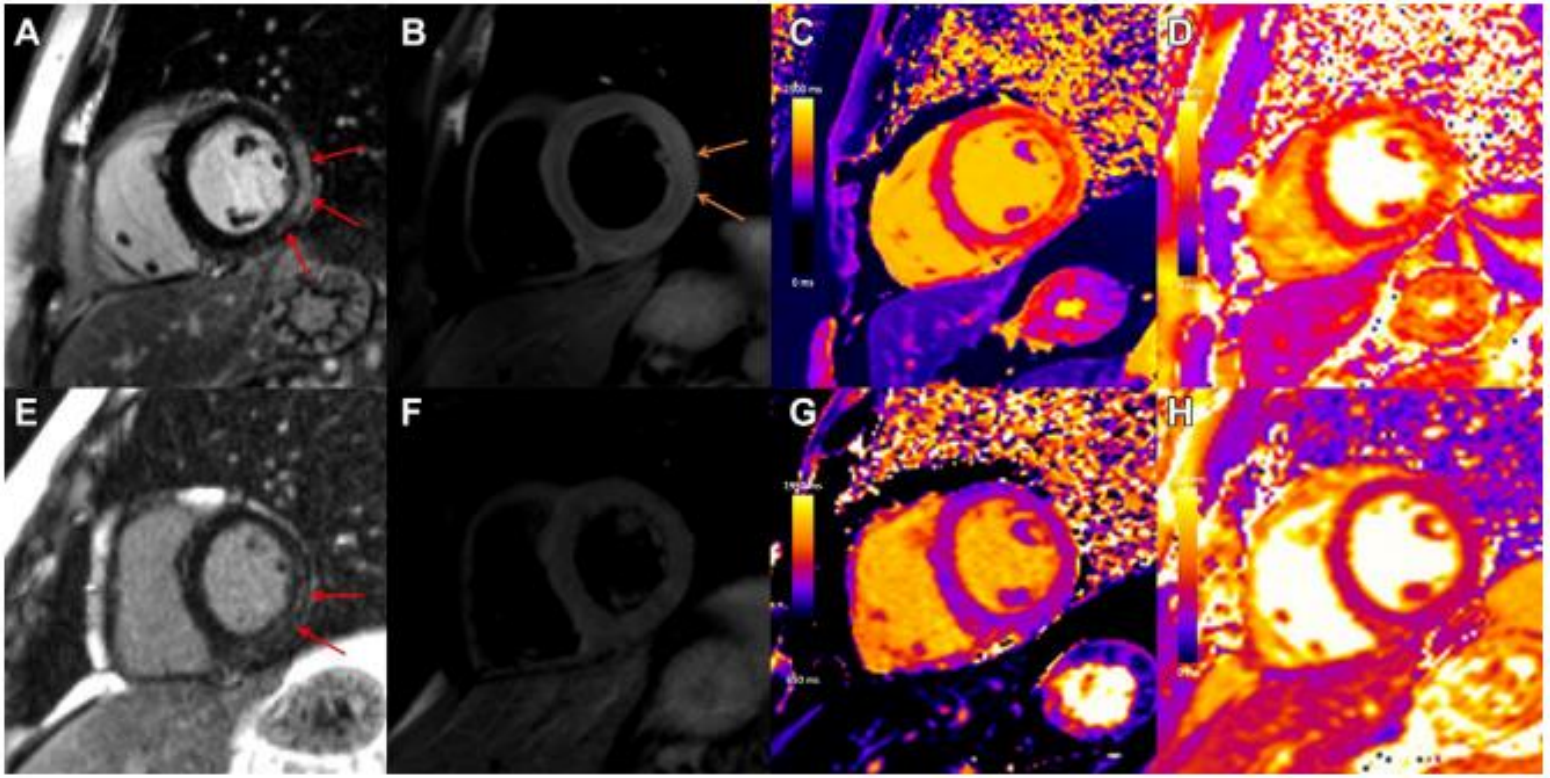


Figure 4: Case example in a 31-year-old man with viral myocarditis. Initial cardiac MRI performed at 3 T within 1 week of symptom onset demonstrates **(A)** subepicardial to nearly transmural late gadolinium enhancement (LGE) at the basal to mid anterior lateral, inferior lateral, and inferior wall (red arrows) with **(B)** corresponding high T2 signal, in keeping with edema (orange arrows), **(C)** high regional native T1 (1480 msec), and **(D)** high regional native T2 (56 msec) on short-axis images. Images from follow-up cardiac MRI performed at 1.5 T 5 months later demonstrate contraction of subepicardial LGE at the basal to mid inferior lateral and inferior wall (**E**, red arrows) with **(G)** corresponding high regional native T1 suggestive of fibrosis (1305 msec) and **(F)** resolution of edema with no corresponding high T2 signal and **(H)** normalization of T2 mapping values (46 msec).

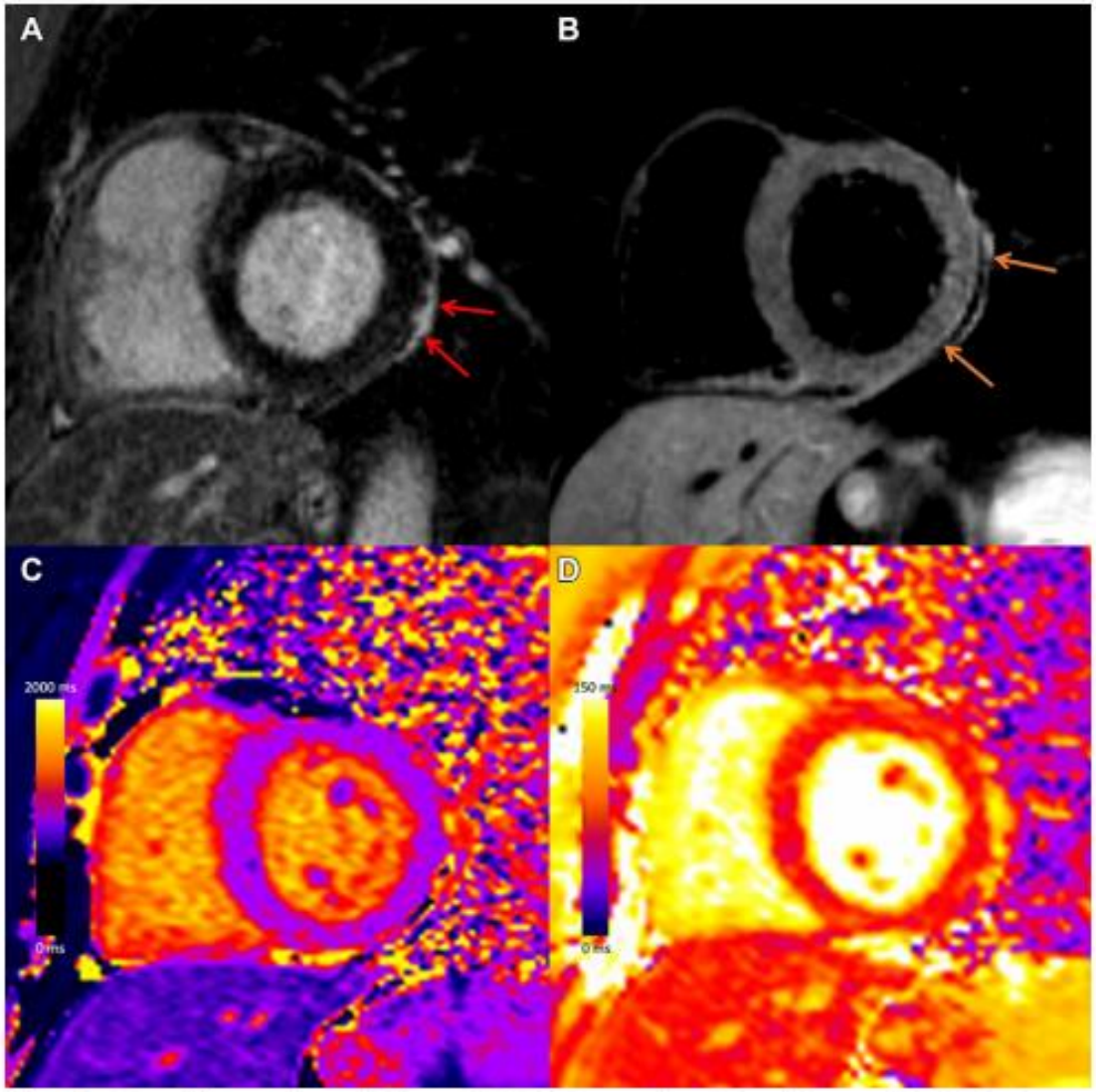


Figure 5: Myocardial injury and pericarditis following COVID-19. Case example in a 57-year-old woman with COVID-19 who presented with chest pain after having elevated troponin levels. Cardiac MRI performed at 1.5 T 4 weeks after polymerase chain reaction–confirmed diagnosis of SARS-CoV-2 infection demonstrates subepicardial late gadolinium enhancement at the **(A)** basal inferior lateral wall with adjacent pericardial enhancement (red arrows), with **(B)** corresponding high T2 signal (orange arrows), and **(C)** high regional native T1 (1236 msec) and **(D)** high regional native T2 (67 msec) on short-axis images, in keeping with myopericarditis.

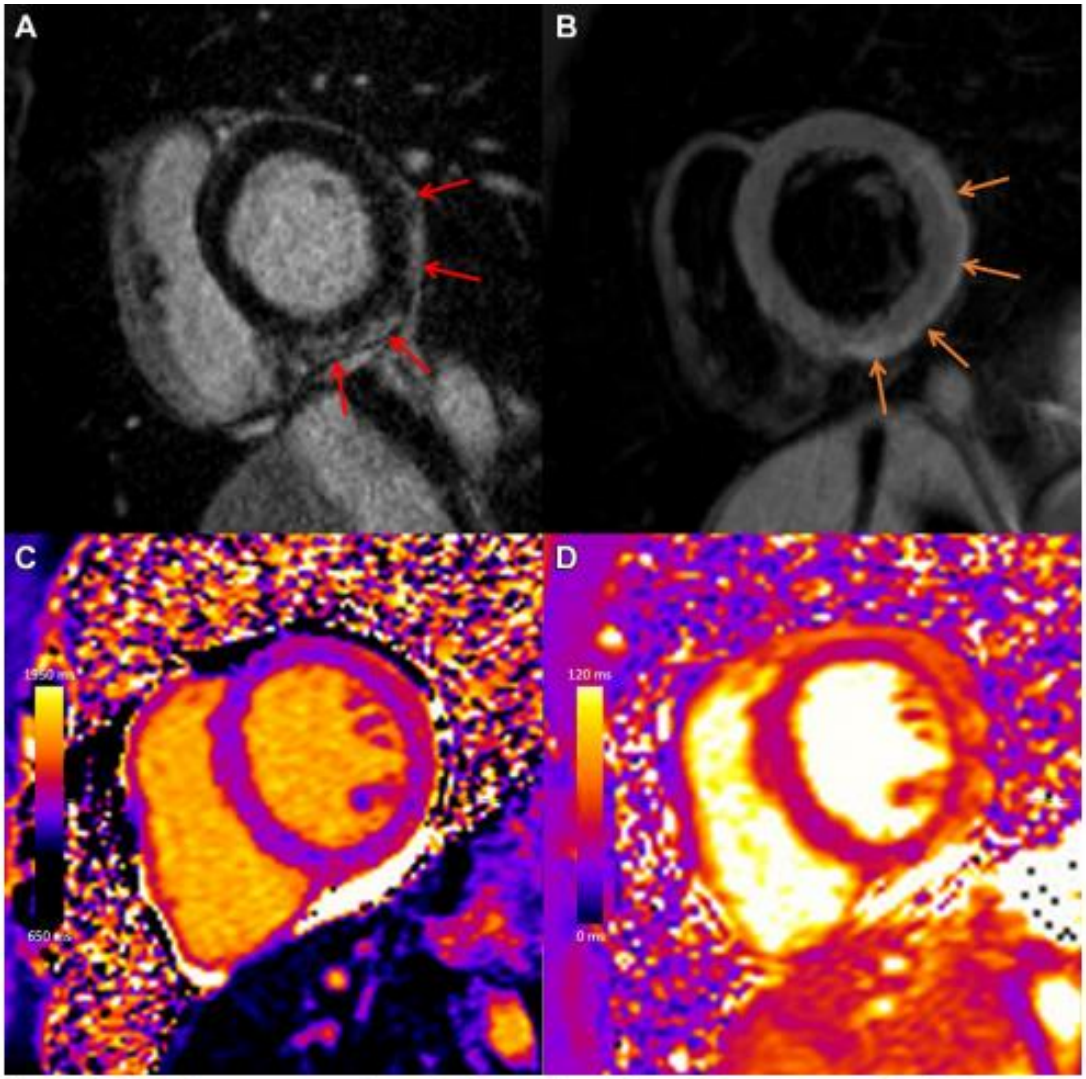
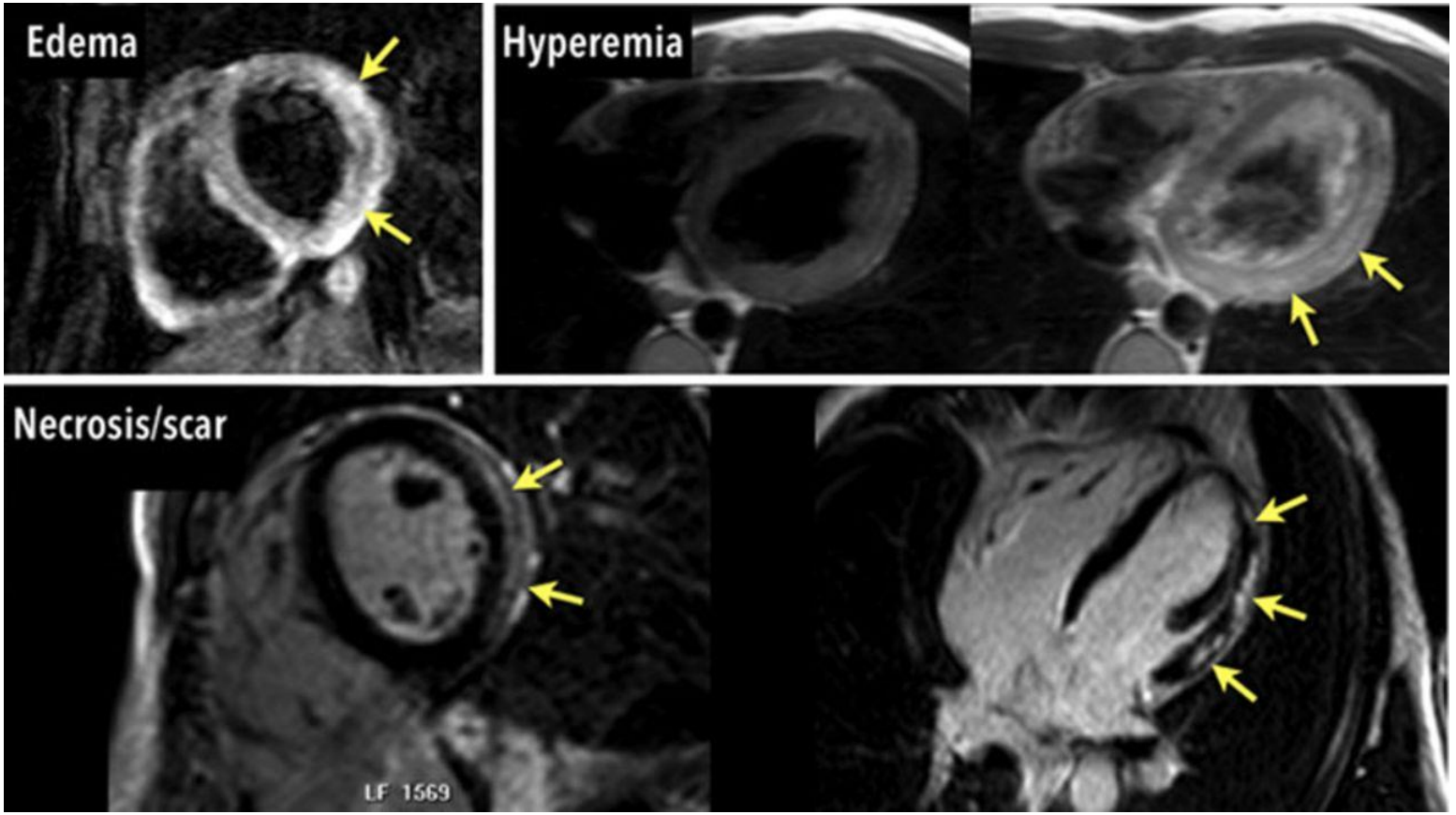
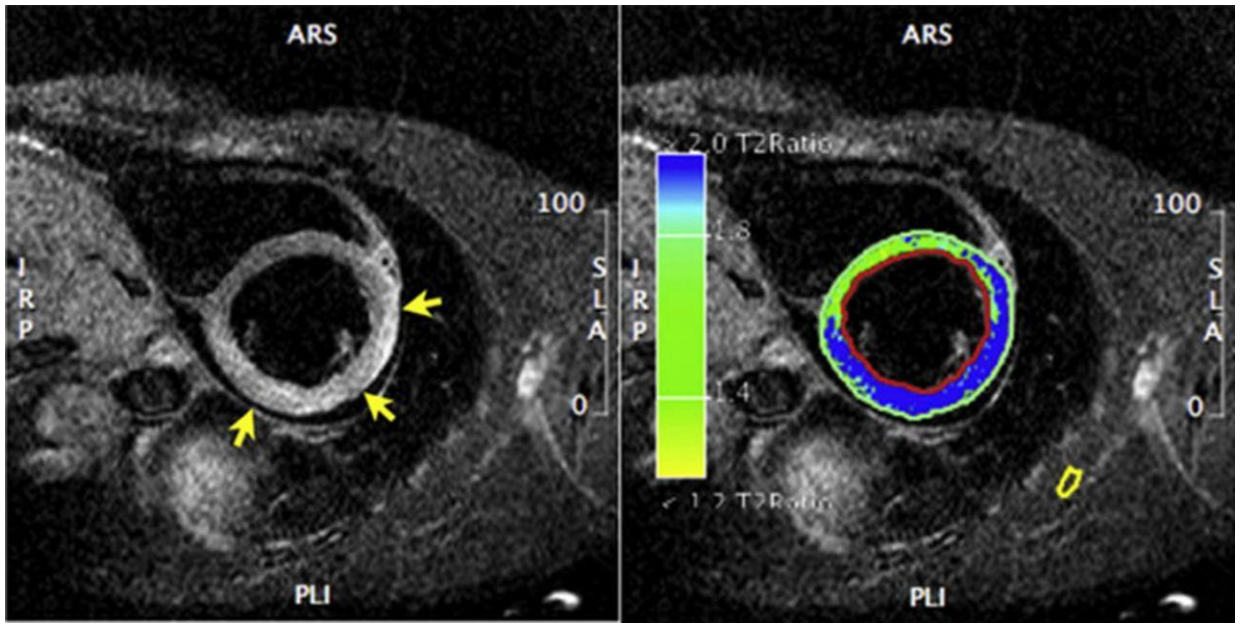


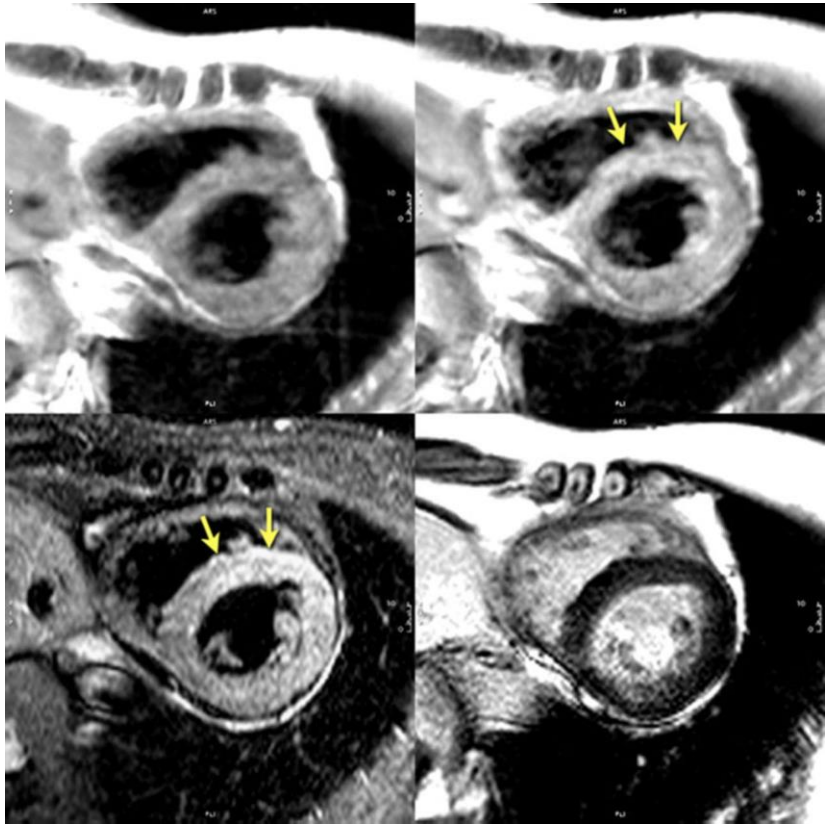
Figure 6: COVID-19 vaccine–associated myocarditis. Case example in a 27-year-old man with myocarditis 3 days following COVID-19 vaccine administration. Images from cardiac MRI performed at 1.5 T demonstrate subepicardial late gadolinium enhancement at the **(A)** basal to mid anterior lateral, inferior lateral, and inferior wall (red arrows), with **(B)** corresponding high T2 signal (orange arrows). **(C)** high regional native T1 (1173 msec), and **(D)** high regional native T2 (59 msec) on short-axis images.



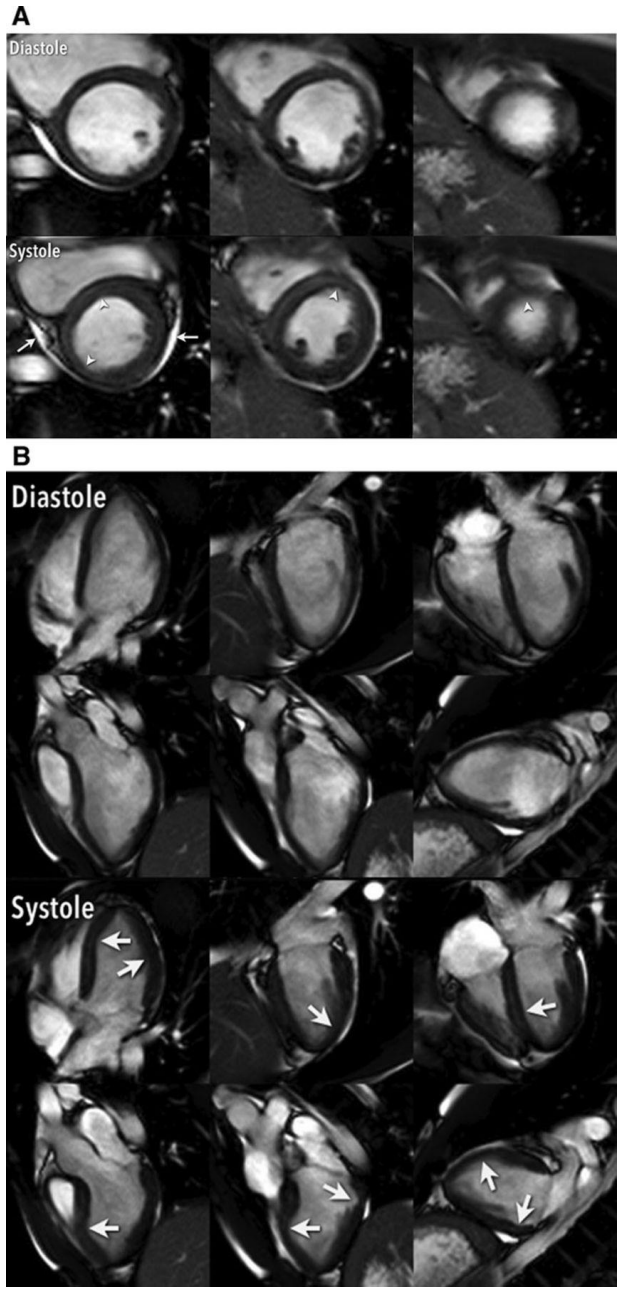
Cardiovascular magnetic resonance criteria for myocarditis (Lake Louise Criteria) : regional myocardial edema (**top left**), hyperemia in images acquired early after contrast injection (**top right**), and inflammatory necrosis in images acquired late (>10 minutes) after contrast injection (**bottom**). All 3 criteria are positive



Myocardial edema in a patient with clinically acute myocarditis. **Left**, Water-sensitive cardiovascular magnetic resonance image in a midventricular short-axis view as acquired with the body coil (note the homogeneous signal distribution in the field of view). There is increased signal intensity in the anterior anterolateral, lateral, inferolateral, and inferior segments, which seems more pronounced in the subepicardial layer. **Right**, signal intensity ratio map showing pixels with a ratio of ≥2.0 (compared with the region of interest in the skeletal muscle marked by the yellow contour) as blue. The normal signal intensity in the septal segments (≈1.6) indicates absence of a low–signal intensity artifact. Note that there is mild pericardial effusion that seems black because of the flow suppression pulse of this sequence



Reversible myocardial injury in a patient with clinically acute myocarditis. **Upper**, short-axis view before (**left**) and early after (**right**) injection of gadolinium showing myocardial hyperemia with regionally more pronounced uptake in the anteroseptal segment (arrows). **Lower**, myocardial edema (arrows; **left**); late gadolinium enhancement image without apparent high–signal intensity areas indicating the absence of necrosis in the edematous regions (**right**). The quantitative evaluation (early gadolinium enhancement ratio) indicated a globally increased early gadolinium uptake. Thus, 2 of 3 Lake Louise Criteria are positive in this patient (regional edema and increased global early gadolinium enhancement ratio)



Cine cardiovascular magnetic resonance (CMR) images in 3 short-axis views in diastole (**top**) and systole (**bottom**) in a patient with suspected active myocarditis. Note multiregional hypokinesis/lack of systolic wall thickening (arrowheads) and mild pericardial effusion (arrows). A movie is available in the online-only Data Supplement. **B**, Rotational long-axis cine CMR images of the same patient in diastole (**top**) and systole (**bottom**). Arrows indicate areas with regional hypokinesis of various degrees of severity

MRI vs. Echo

- In recent years
  - cardiac MRI
    - gold standard for EF
    - the best modality for calculating EF
      - range of hemodynamic measurements
      - 3D representation of images
      - high contrast resolution
        - » a well-defined endocardial border that is important for measuring EF

- Limitations of MRI
  - patients with ectopic beats or cardiac arrhythmias
    - degraded image quality
  - patients with implantable devices causing metallic susceptibility artifacts
    - cardioverter defibrillators and pacemakers

- Echocardiography
  - low cost, portability, and lack of ionizing radiation
  - more geometric assumptions than MRI
  - insufficient acoustic windows that lead to poor image quality
  - **Underestimate LVEF**

- 2D echocardiography
  - need for significant geometrical assumptions
    - Limitation in
      - asymmetry of contraction, such as wall motion abnormalities
- 3D echocardiography
  - image data is typically obtained over several heartbeats
    - breathing or an ectopic beat lead to artifacts that may change the endocardial border, with segments of the left ventricle appearing to contract at different times

- cardiac MRI
  - low variability
    - superior to echo volumetric imaging techniques

- ***Thanks***

Dilated cardiomyopathy

- left heart
  - markedly dilated and thinned
  - mid-wall enhancement especially in the septum
    - in more than 50% of patients
- LGE
  - characteristically in mid- or subepicardial myocardium
    - differentiation from ischemic cardiomyopathy

Hypertrophic cardiomyopathy

- superior to echocardiography
  - identifying areas of segmental hypertrophy not reliably visualized or underestimated by echocardiography
    - anterolateral and apical segments
- left ventricular systolic dysfunction
- left ventricular hypertrophy
  - with or without right ventricular hypertrophy
  - predilection for the basal interventricular septum
- Systolic anterior motion (SAM) of mitral valve
  - mitral regurgitation
- left ventricular apical aneurysms
- morphologic variations involving mitral valve (e.g. papillary muscles)
- in asymptomatic HCM mutation carriers
  - myocardial crypts
  - elongated mitral valve leaflets

Hypertrophic cardiomyopathy

- LGE
  - patchy/streaky intramyocardial patterns at right ventricular insertion sites within the hypertrophied myocardium
- differentiating the mass-like HCM variant from a discrete cardiac mass
  - presence of contractility
  - iso-intense to myocardium on T1- and T2-weighted images
  - first-pass enhancement
  - patchy and midventricular type of delayed enhancement

Restrictive cardiomyopathy

- Biatrial enlargement
- minimal or no ventricular enlargement
- Cine MRI
  - altered diastolic filling

Arrhythmogenic right ventricular cardiomyopathy

- Major diagnostic criteria
  - regional RV akinesia or dyskinesia or dyssynchronous RV contraction and 1 of the following:
    - ratio of RV end-diastolic volume to BSA ≥110 mL/m^2 (male) or ≥100 mL/m^2 (female)
    - RV EF ≤40%
- Minor diagnostic criteria:
  - regional RV akinesia or dyskinesia or dyssynchronous RV contraction and 1 of the following:
  - ratio of RV end-diastolic volume to BSA ≥100 to <110 mL/m^2 (male) or ≥90 to <100 mL/m^2 (female)
  - RV EF>40% to ≤45%
- fatty infiltration in the right ventricle (and occasionally in the left ventricle)
- A corrugated pattern to the right ventricular wall
  - “accordion sign”
- Focal left ventricular dyskinesia with fatty infiltration within the left ventricle
- evaluation of myocardial fibrosis and scarring

Endocardial fibroelastosis

- endocardial thickening
- apical filling defect
- atrial or ventricular thrombus formation
- diffuse endocardial LGE

Takotsubo cardiomyopathy

- four distinct patterns of dyskinesia and ballooning
  - apical (most common)
  - biventricular
  - mid-ventricular
  - basal
- absence of late enhancement on delayed contrast sequences, which differentiates takotsubo cardiomyopathy from anterior STEMI

- high T2 intensity signal (directly relating to water content in the myocardial wall)
- apical mid-ventricular planes and spares the basal plane, and matches the wall-motion abnormalities seen on cine MRI.
- **MR perfusion**
  - usually normal

What is new about Heart Failure In early 2024

Marjan Hajahmadi, MD.
Advanced Heart failure and transplant cardiologists
Assistant professor of medicine
IUMS

HF Is A Public Health Emergency

- 64.3 million people are living with heart failure worldwide
- 1 million new HF occur annually in people more than 55 of age

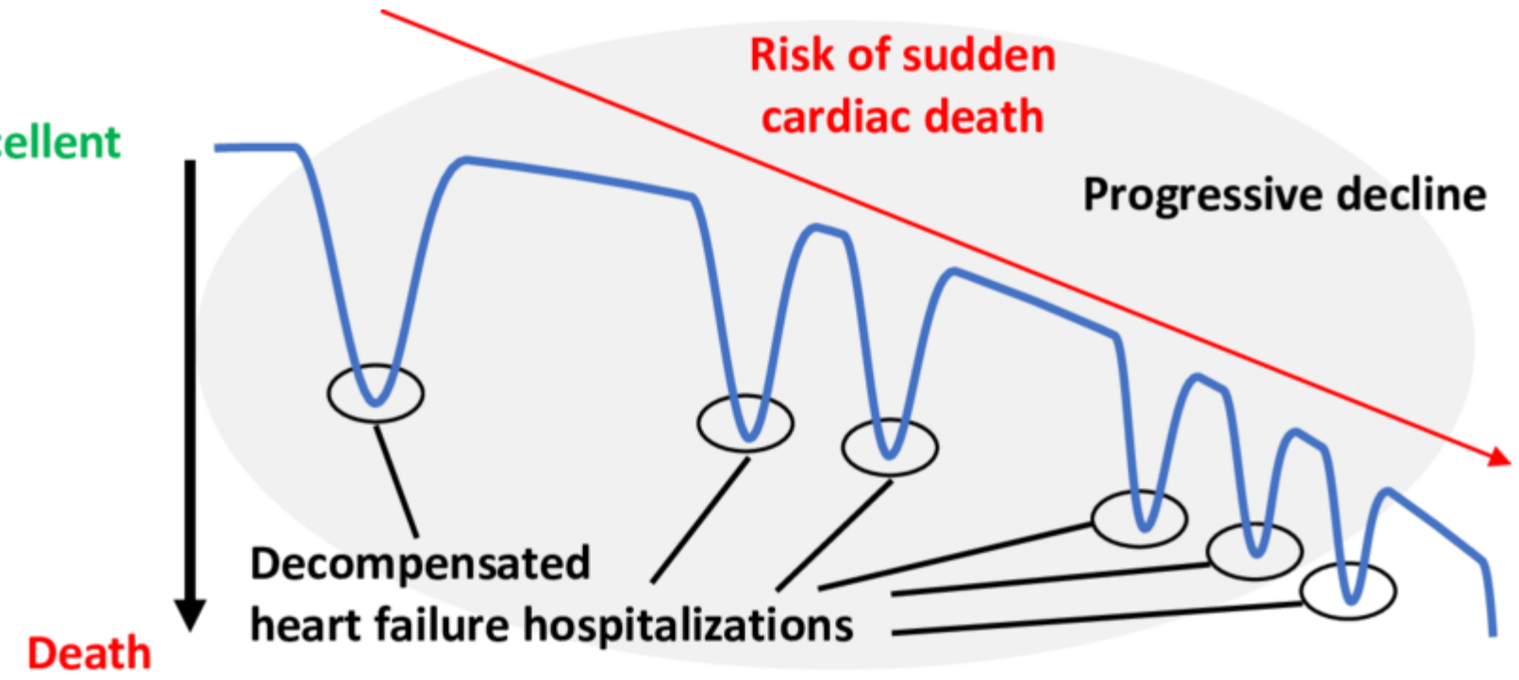
From 2020 to 2030

46% increase in HF population

50% mortality in 5 years

60% increase in cost

HF Is Progressive



ESC
European Society
of Cardiology

European Heart Journal (2021) **42**, 3599–3726
doi:10.1093/eurheartj/ehab368

ESC GUIDELINES

2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure

Developed by the Task Force for the diagnos and chronic heart failure of the European So

With the special contribution of the Heart (HFA) of the ESC

Authors/Task Force Members: Theresa A. McDonagh

JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY
VOL. ■, NO. ■, 2022

PUBLISHED BY ELSEVIER

CLINICAL PRACTICE GUIDELINE: FULL TEXT

2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure

A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines

, FHFSA,
-IFSA,

Adrian F. Hernandez, MD, MHS‡
Prateeti Khazanie, MD, MPH, FHFSA†
Michelle M. Kittleson, MD, PhD†
Christopher S. Lee, PhD, RN, FAHA, FHFSA†

ESC
European Society
of Cardiology

European Heart Journal (2023) **00**, 1–13
https://doi.org/10.1093/eurheartj/ehad195

ESC GUIDELINES

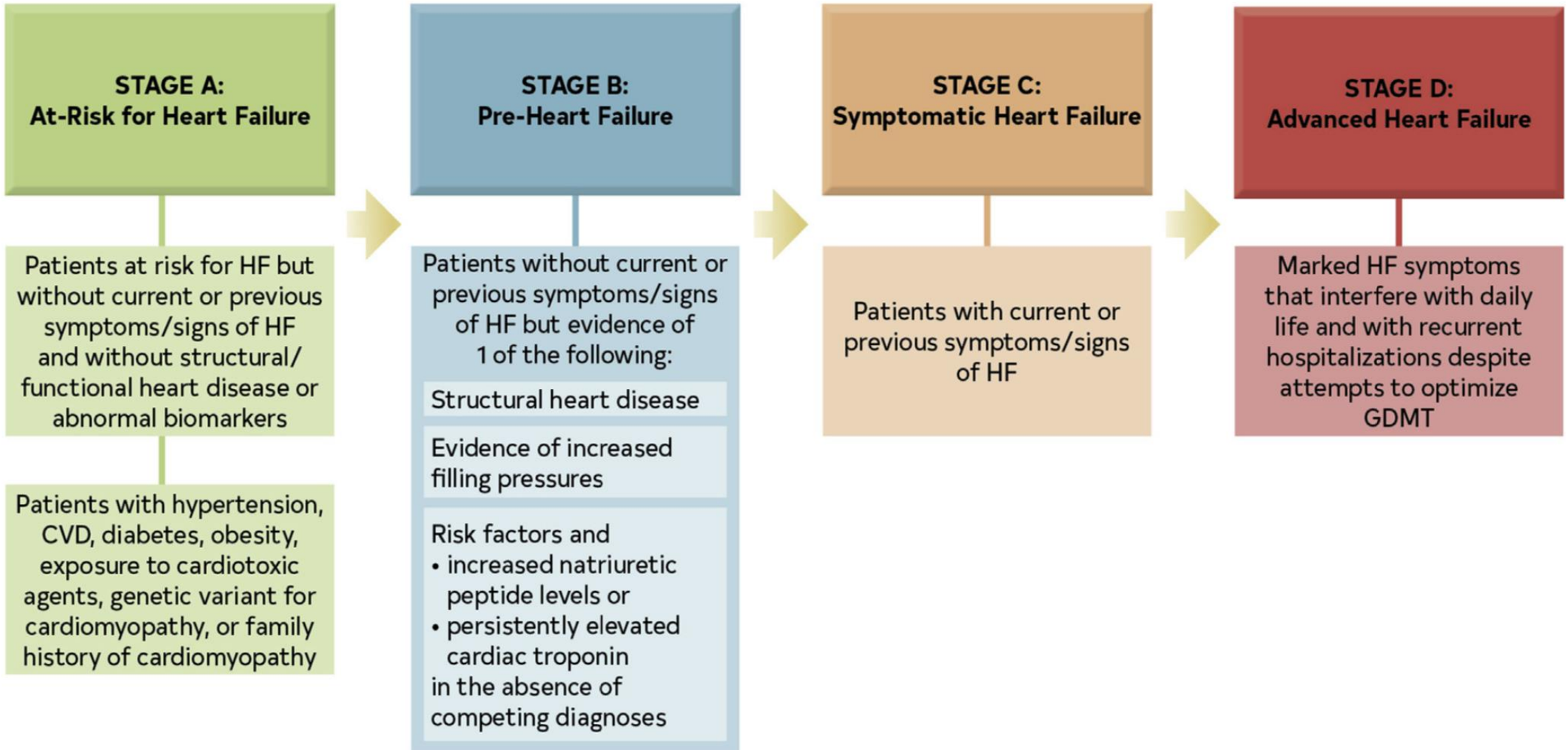
2023 Focused Update of the 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure

Developed by the task force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC)

With the special contribution of the Heart Failure Association (HFA) of the ESC

Authors/Task Force Members: Theresa A. McDonagh *†, (Chairperson) (United

ACC/AHA Stages of HF



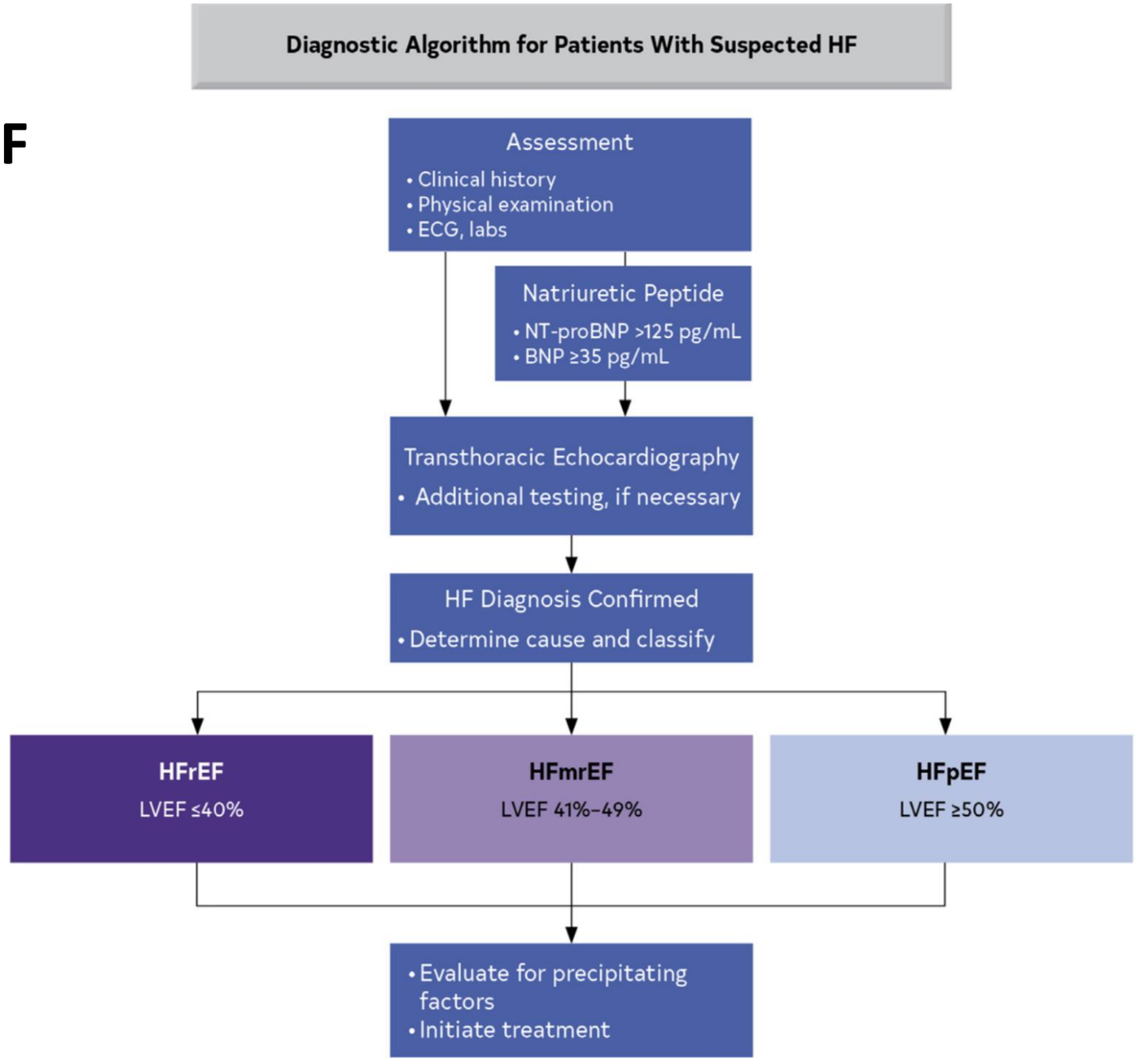
Trajectory of Class C HF

The trajectory of stage C HF is displayed. Patients whose symptoms and signs of HF are resolved are still stage C and should be treated accordingly. If all HF symptoms, signs, and structural abnormalities resolve, the patient is considered to have HF in remission.

***Full resolution of structural and functional cardiac abnormalities is uncommon.**

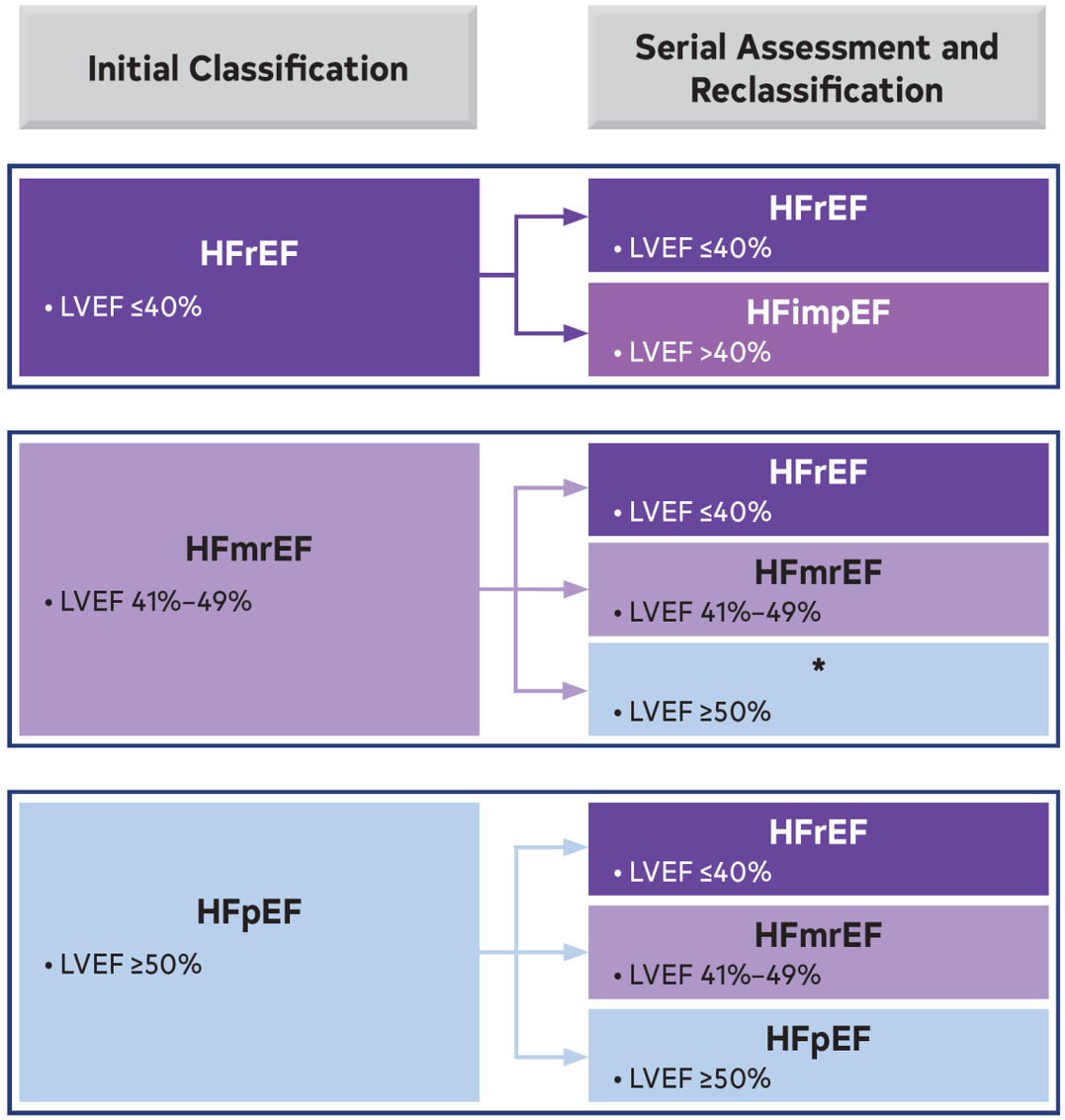
New Onset/De Novo HF:	Resolution of Symptoms:	Persistent HF:	Worsening HF:
• Newly diagnosed HF • No previous history of HF	• Resolution of symptoms/ signs of HF Stage C with previous symptoms of HF with persistent LV dysfunction → HF in remission with resolution of previous structural and/or functional heart disease*	• Persistent HF with ongoing symptoms/signs and/or limited functional capacity	• Worsening symptoms/ signs/functional capacity

Diagnostic Algorithm for HF and EF-Based Classification



The algorithm for a diagnosis of HF and EF-based classification is shown.
BNP indicates B-type natriuretic peptide; ECG, electrocardiogram; EF, ejection fraction; HF, heart failure; HFmrEF, heart failure with mildly reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; LVEF, left ventricular ejection fraction; LV, left ventricular; NP, natriuretic peptides; and NT-proBNP, N-terminal pro-B type natriuretic peptide.

Figure 3. Classification and Trajectories of HF Based on LVEF



American Heart Association.

CLASS (STRENGTH) OF RECOMMENDATION

CLASS 1 (STRONG) **Benefit >>> Risk**

Suggested phrases for writing recommendations:
- Is recommended
- Is indicated/useful/effective/beneficial
- Should be performed/administered/other
- Comparative-Effectiveness Phrases†:
  - Treatment/strategy A is recommended/indicated in preference to treatment B
  - Treatment A should be chosen over treatment B

CLASS 2a (MODERATE) **Benefit >> Risk**

Suggested phrases for writing recommendations:
- Is reasonable
- Can be useful/effective/beneficial
- Comparative-Effectiveness Phrases†:
  - Treatment/strategy A is probably recommended/indicated in preference to treatment B
  - It is reasonable to choose treatment A over treatment B

CLASS 2b (WEAK) **Benefit ≥ Risk**

Suggested phrases for writing recommendations:
- May/might be reasonable
- May/might be considered
- Usefulness/effectiveness is unknown/unclear/uncertain or not well-established

CLASS 3: No Benefit (MODERATE) **Benefit = Risk**
(Generally, LOE A or B use only)

Suggested phrases for writing recommendations:
- Is not recommended
- Is not indicated/useful/effective/beneficial
- Should not be performed/administered/other

Class 3: Harm (STRONG) **Risk > Benefit**

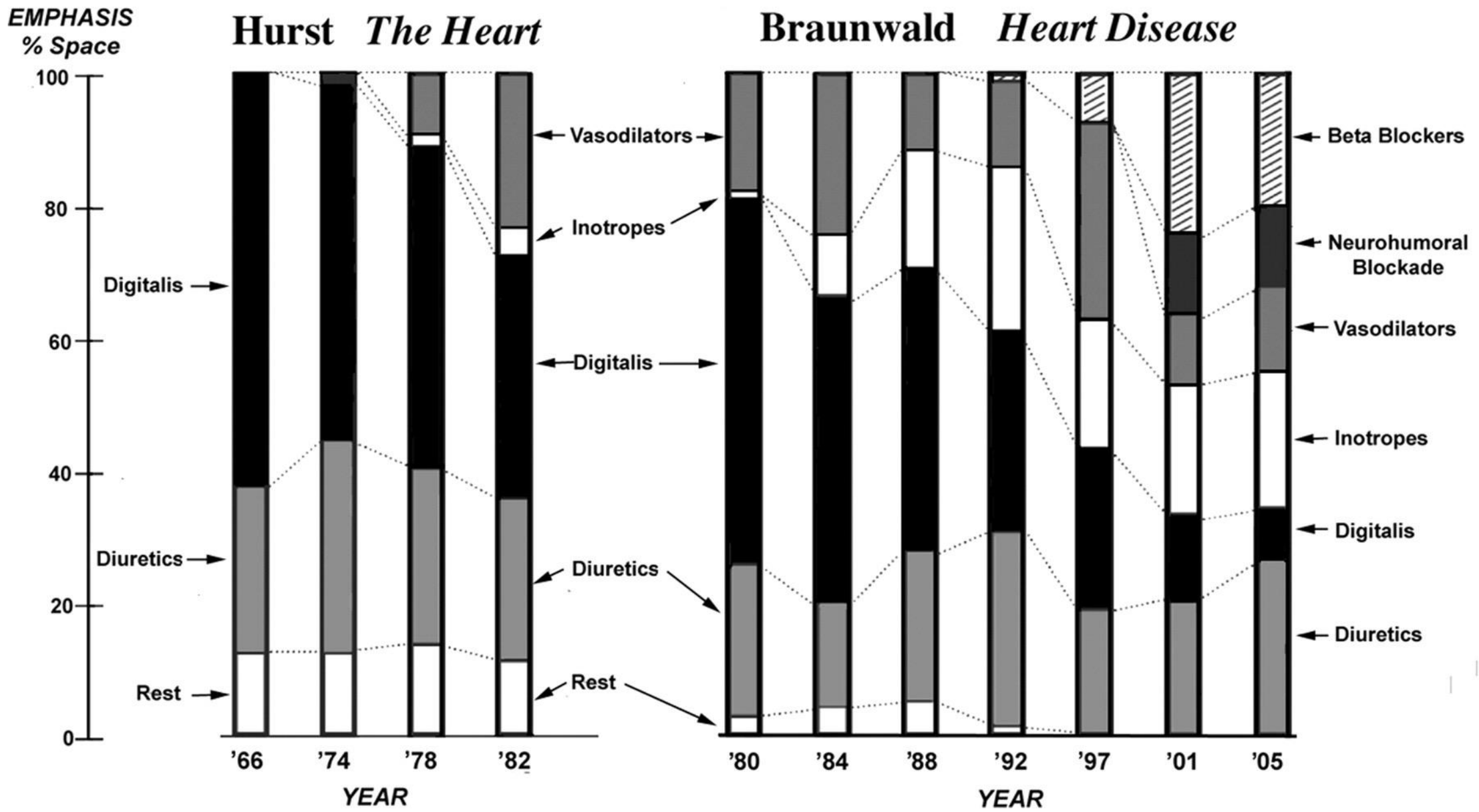
Suggested phrases for writing recommendations:
- Potentially harmful
- Causes harm
- Associated with excess morbidity/mortality
- Should not be performed/administered/other

LEVEL (QUALITY) OF EVIDENCE‡
LEVEL A
• High-quality evidence‡ from more than 1 RCT • Meta-analyses of high-quality RCTs • One or more RCTs corroborated by high-quality registry studies
LEVEL B-R (Randomized)
• Moderate-quality evidence‡ from 1 or more RCTs • Meta-analyses of moderate-quality RCTs
LEVEL B-NR (Nonrandomized)
• Moderate-quality evidence‡ from 1 or more well-designed, well-executed nonrandomized studies, observational studies, or registry studies • Meta-analyses of such studies
LEVEL C-LD (Limited Data)
• Randomized or nonrandomized observational or registry studies with limitations of design or execution • Meta-analyses of such studies • Physiological or mechanistic studies in human subjects
LEVEL C-EO (Expert Opinion)
• Consensus of expert opinion based on clinical experience

Value statements were created for select recommendations where high-quality, cost-effectiveness studies of the intervention have been published.

Therapeutic Objectives: Clinical

Changing management of heart failure over the past 50 years.



Arnold M. Katz Circ Heart Fail. 2008;1:63-71

In 2021, we had 34 years of heart failure therapy to consider

ESC

CONSENSUS
Enalapril vs placebo

V-HeFT II
Enalapril vs hydralazine and isosorbide dinitrate

Packer et al
Carvedilol vs placebo

RALES
Spironolactone vs placebo

Val-HeFT
Valsartan vs placebo

COMPANION
CRT-D vs CRT-P

CARE-HF
CRT vs medical therapy alone

SHIFT²
Ivabradine vs placebo

RAFT
CRT-D vs ICD

EchoCRT
CRT turned on vs off

VICTORIA

DAPA-HF

GALACTIC-HF

1985 1990 1995 2000 2005 2010 2015 2020

V-HeFT I
Hydralazine and isosorbide dinitrate vs placebo or prazosin

SOLVD-T
Enalapril vs placebo

SOLVD-P
Enalapril vs placebo

DIG
Digoxin vs placebo

COPERNICUS
Carvedilol vs placebo

REMATCH
LVAD vs medical therapy alone

A-HeFT
Hydralazine and isosorbide dinitrate vs placebo

SCD-HeFT
ICD vs amiodarone or placebo

MADIT-CRT
CRT-D vs ICD

EMPHASIS-HF
Eplerenone vs placebo

PARADIGM-HF
Sacubitril / valsartan vs enalapril

PARAGON-HF

EMPEROR-REDUCED

ACEi or ARB
BB
MRA
Sacubitril valsartan
Hydralazine or nitrate
Devices
SGLT2i
Others

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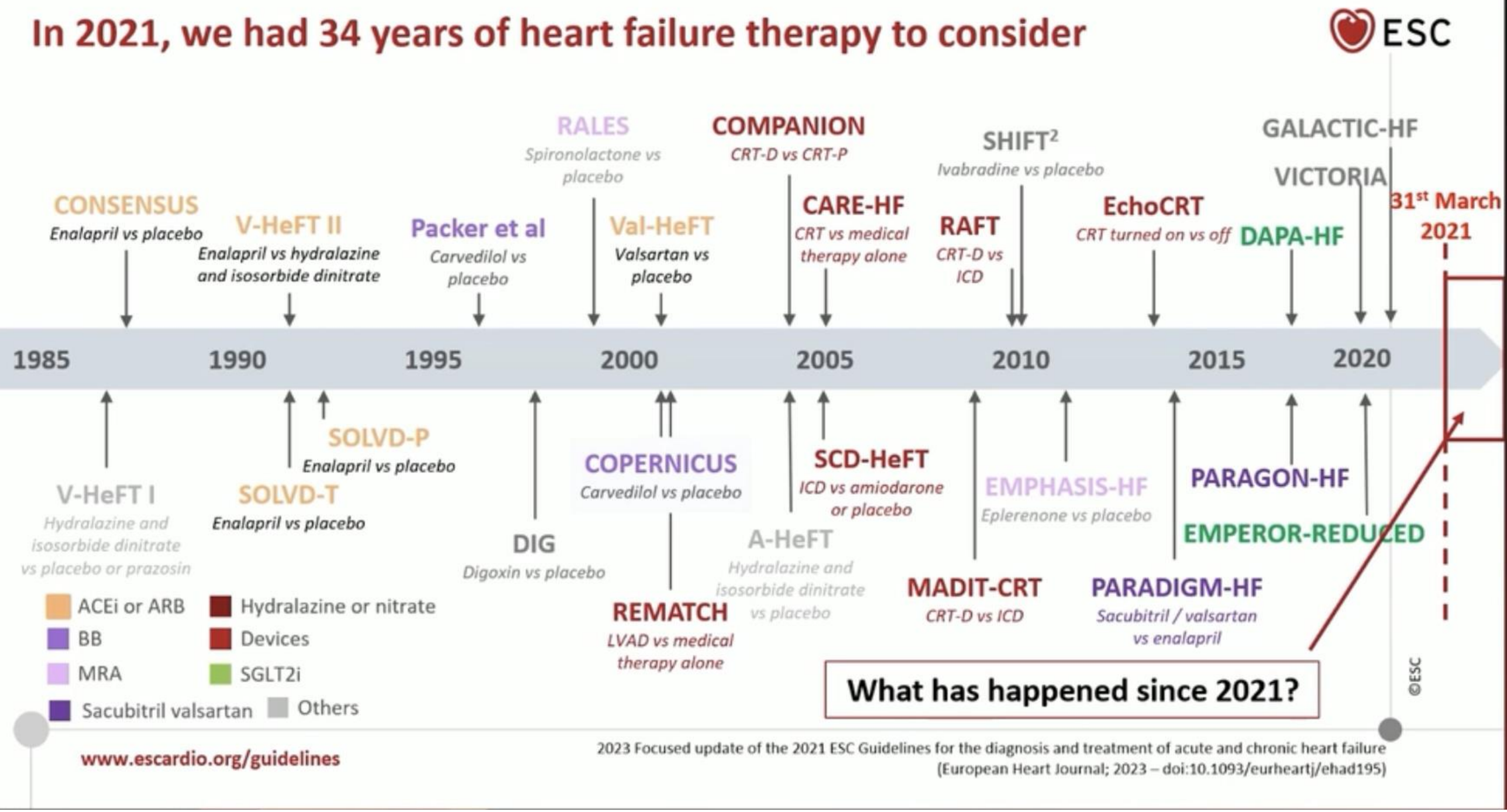
2023 Focused update of the 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure
(European Heart Journal; 2023 – doi:10.1093/eurheartj/ehad195)

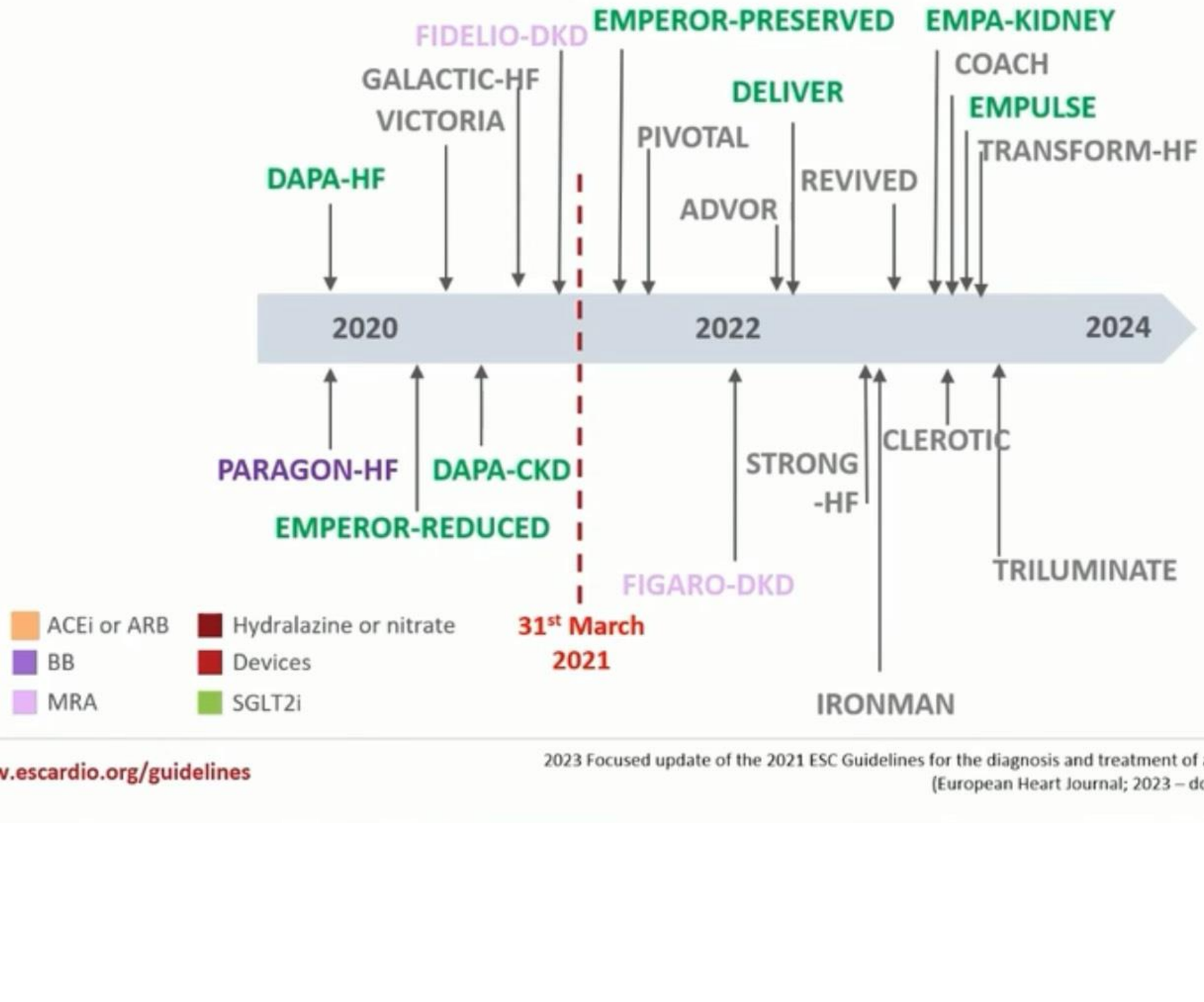
In 2021, we had 34 years of heart failure therapy to consider



www.escardio.org/guidelines

2023 Focused update of the 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure (European Heart Journal; 2023 – doi:10.1093/eurheartj/ehad195)

Amazing progress in heart failure



www.escardio.org/guidelines

2023 Focused update of the 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure
(European Heart Journal; 2023 – doi:10.1093/eurheartj/ehad195)

Management of patients with HFrEF

- ACE-I/ARNI[a]
- Beta-blocker
- MRA
- Dapagliflozin/Empagliflozin
- Loop diuretic for fluid retention (Class I)

LVEF ≤35% and QRS <130 ms and where appropriate	LVEF >35% or device therapy not indicated or inappropriate	SR and LVEF ≤35% and QRS ≥130 ms
ICD		**CRT-D[b]/-P**
Non-ischaemic (Class IIa); Ischaemic (Class I)		QRS 130–149 ms (Class IIa); QRS ≥150 ms (Class I)

If symptoms persist, consider therapies with Class II recommendations

ESC

Pharmacological treatments indicated in patients with (NYHA class II–IV) heart failure with reduced ejection fraction (LVEF ≤40%)

Recommendations	Class[a]	Level[b]
An ACE-I is recommended for patients with HFrEF to reduce the risk of HF hospitalization and death.[110–113]	I	A
A beta-blocker is recommended for patients with stable HFrEF to reduce the risk of HF hospitalization and death.[114–120]	I	A
An MRA is recommended for patients with HFrEF to reduce the risk of HF hospitalization and death.[121,122]	I	A
Dapagliflozin or empagliflozin are recommended for patients with HFrEF to reduce the risk of HF hospitalization and death.[108,109]	I	A
Sacubitril/valsartan is recommended as a replacement for an ACE-I in patients with HFrEF to reduce the risk of HF hospitalization and death.[105]	I	B

PARADIGM-HF: Summary of Findings

LCZ696 was *more effective* than enalapril in . . .

- Reducing the risk of CV death and HF hospitalization
- Reducing the risk of CV death by 20%
- Reducing the risk of HF hospitalization by 21%
- Reducing all-cause mortality by 16%

In ambulatory patients with .. .

- Chronic heart failure
- Elevated NP levels
- Able to tolerate Enalapril 10 mg x 2
- With no history of angioedema or RAASi induced cough

Burning Issues - Should I always start with an ACE inhibitor?

- Always except for
  - Symptomatic HFrEF patients despite guideline recommended therapies and able to tolerate ACEi equivalent to Enalapril 20 mg
  - Hospitalised patients with HFrEF who were already receiving an ACEi equivalent to 20 mg

Renin-Angiotensin System Inhibition With ACEi or ARB or ARNi

In patients with chronic symptomatic HFrEF, treatment with an ARNi instead of an ACEi provides high economic value.

COR	LOE	Recommendations
1	A	• In patients with HFrEF and NYHA class II to III symptoms, the use of ARNi is recommended to reduce morbidity and mortality.
1	A	• In patients with previous or current symptoms of chronic HFrEF, the use of ACEi is beneficial to reduce morbidity and mortality when the use of ARNi is not feasible.
1	A	• In patients with previous or current symptoms of chronic HFrEF who are intolerant to ACEi because of cough or angioedema and when the use of ARNi is not feasible, the use of ARB is recommended to reduce morbidity and mortality.
Value Statement: High Value (A)		• In patients with previous or current symptoms of chronic HFrEF, in whom ARNi is not feasible, treatment with an ACEi or ARB provides high economic value.
1	B-R	• In patients with chronic symptomatic HFrEF NYHA class II or III who tolerate an ACEi or ARB, replacement by an ARNi is recommended to further reduce morbidity and mortality.

Multiple model-based analyses evaluated the economic value of ARNi therapy compared with ACEi therapy using the results of PARADIGM-HF. Three high-quality analyses consistently found costs per QALY <$60,000, which provides high value according to the benchmarks adopted for the current clinical practice guideline

Standard Therapies

ARNI, ACEI, ARB

Beta-Blocker

SGLT2i

MRA

Individualized Therapies

Loop Diuretic
Dosed according to symptoms

IV Iron
Iron deficiency

Digoxin
Symptoms despite standard therapy

Ivabradine
Symptoms despite standard therapy with sinus rhythm and HR ≥70 bpm

Hydralazine plus Nitrate
Cannot tolerate ARNI/ACEI/ARB or black race with symptoms despite standard therapy

Vericiguat
Recent worsening of symptoms despite standard therapy

HFmrEF 2021

Recommendations	Class[a]	Level[b]
Diuretics are recommended in patients with congestion and HFmrEF in order to alleviate symptoms and signs.[137]	I	C
An ACE-I may be considered for patients with HFmrEF to reduce the risk of HF hospitalization and death.[11]	IIb	C
An ARB may be considered for patients with HFmrEF to reduce the risk of HF hospitalization and death.[245]	IIb	C
A beta-blocker may be considered for patients with HFmrEF to reduce the risk of HF hospitalization and death.[12,119]	IIb	C
An MRA may be considered for patients with HFmrEF to reduce the risk of HF hospitalization and death.[246]	IIb	C
Sacubitril/valsartan may be considered for patients with HFmrEF to reduce the risk of HF hospitalization and death.[13,247]	IIb	C

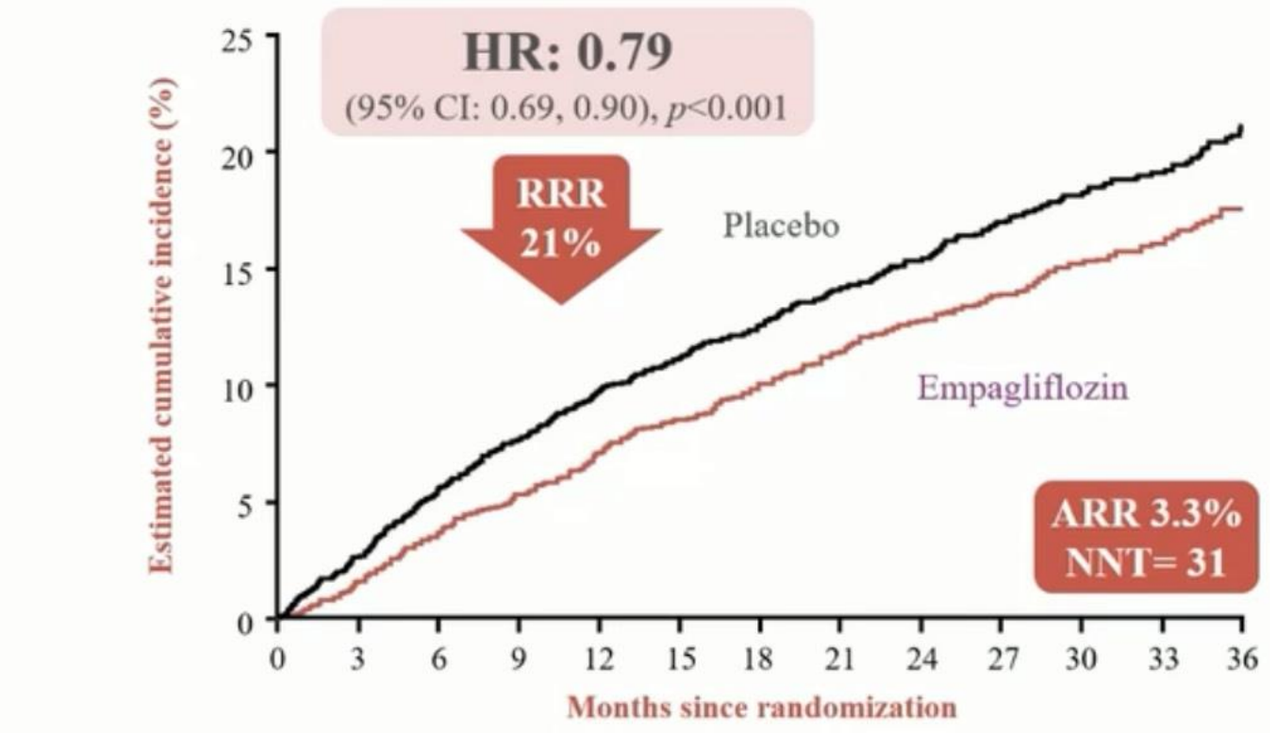
HFpEF 2021

Recommendations for the treatment of patients with heart failure with preserved ejection fraction

Recommendations	Class[a]	Level[b]
Screening for, and treatment of, aetiologies, and cardiovascular and non-cardiovascular comorbidities is recommended in patients with HFpEF (see relevant sections of this document).	I	C
Diuretics are recommended in congested patients with HFpEF in order to alleviate symptoms and signs.[137]	I	C

EMPEROR-PRESERVED

- Empagliflozin vs placebo
- HFmrEF/HFpEF
- T2DM/non-T2DM
- 5988 patients; 72yrs; 45% ♀
- 51% AF; 49% DM
- F/U: 26 months
- Primary endpoint:
  - Time to first event of adj CV death or HF hospitalisation



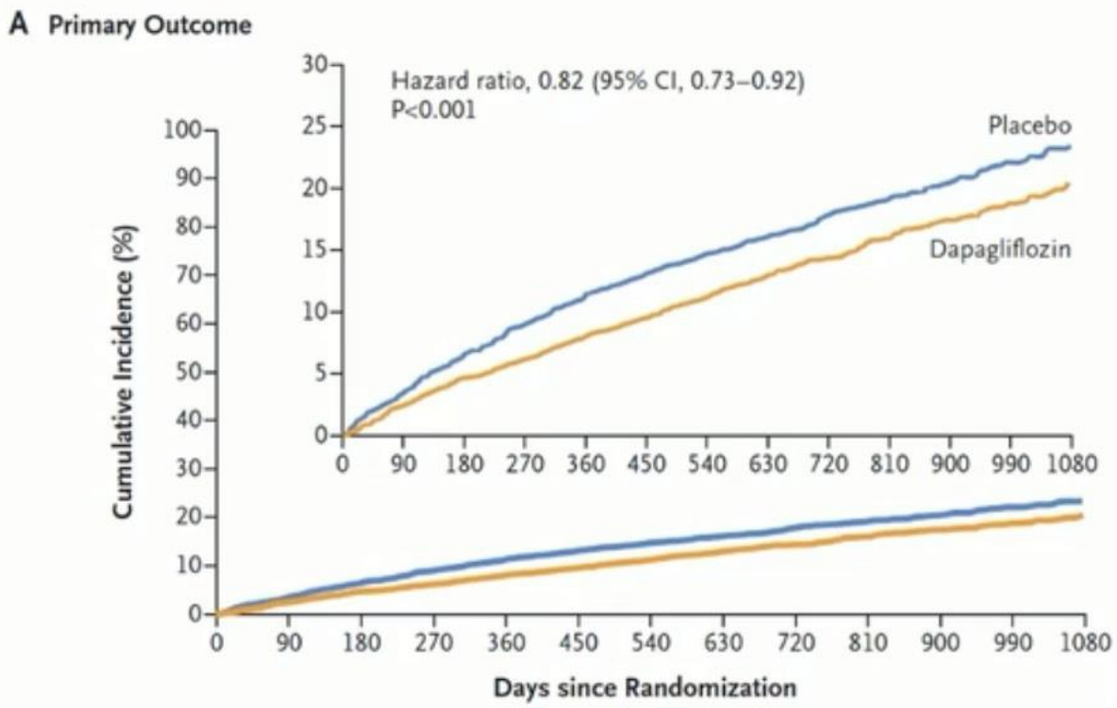
Patients at risk

Placebo	2991	2888	2786	2706	2627	2424	2066	1821	1534	1278	961	681	400
Empagliflozin	2997	2928	2843	2780	2708	2491	2134	1858	1578	1332	1005	709	402

Anker S *et al. N Engl J Med.* 2021; DOI: 10.1056/NEJMoa2107038

DELIVER

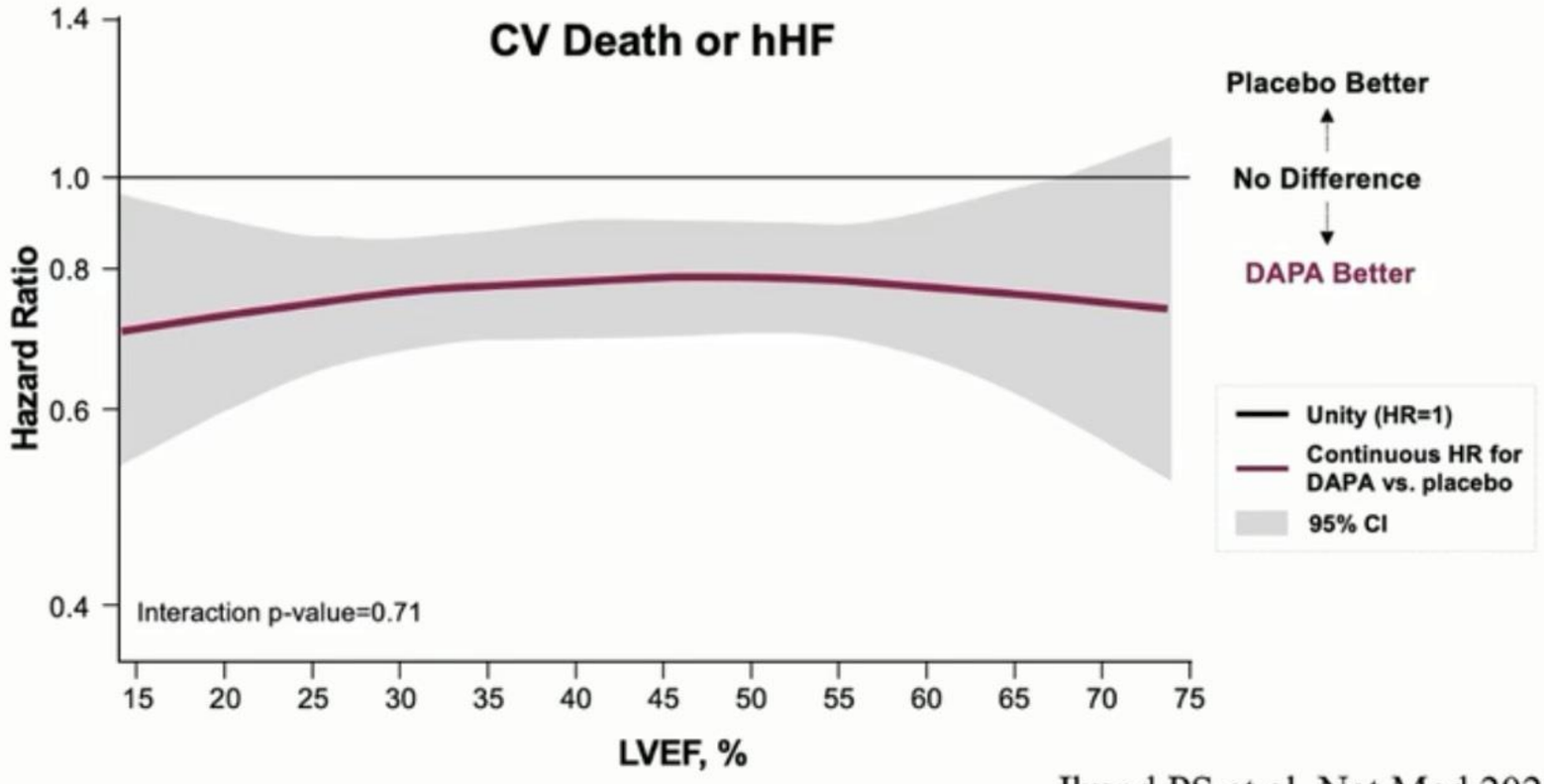
- Dapagliflozin 10mg od vs placebo
- LVEF >40%
- 6263 patients
- F/U 2.3 years
- Primary outcome: 18% RRR composite of worsening HF or CV death
  - 21% RRR in worsening heart failure
  - No effect on CV mortality alone
  - Improved symptom burden
- Results were similar:
  - LVEF ≥60% vs <60%
  - Patients with or without diabetes



Solomon et al. NEJM Aug 2022

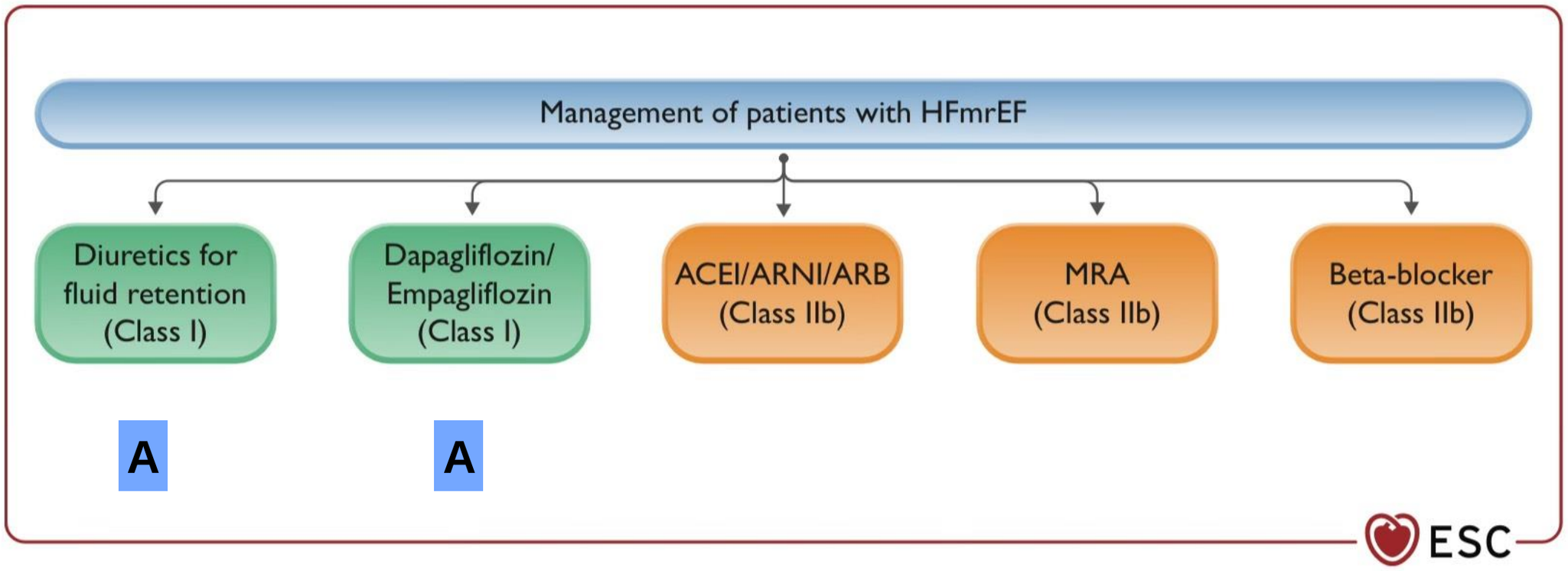
Effect of dapagliflozin across the range of ejection fraction

DAPA-HF ← Pre-specified patient-level pooled analysis → DELIVER

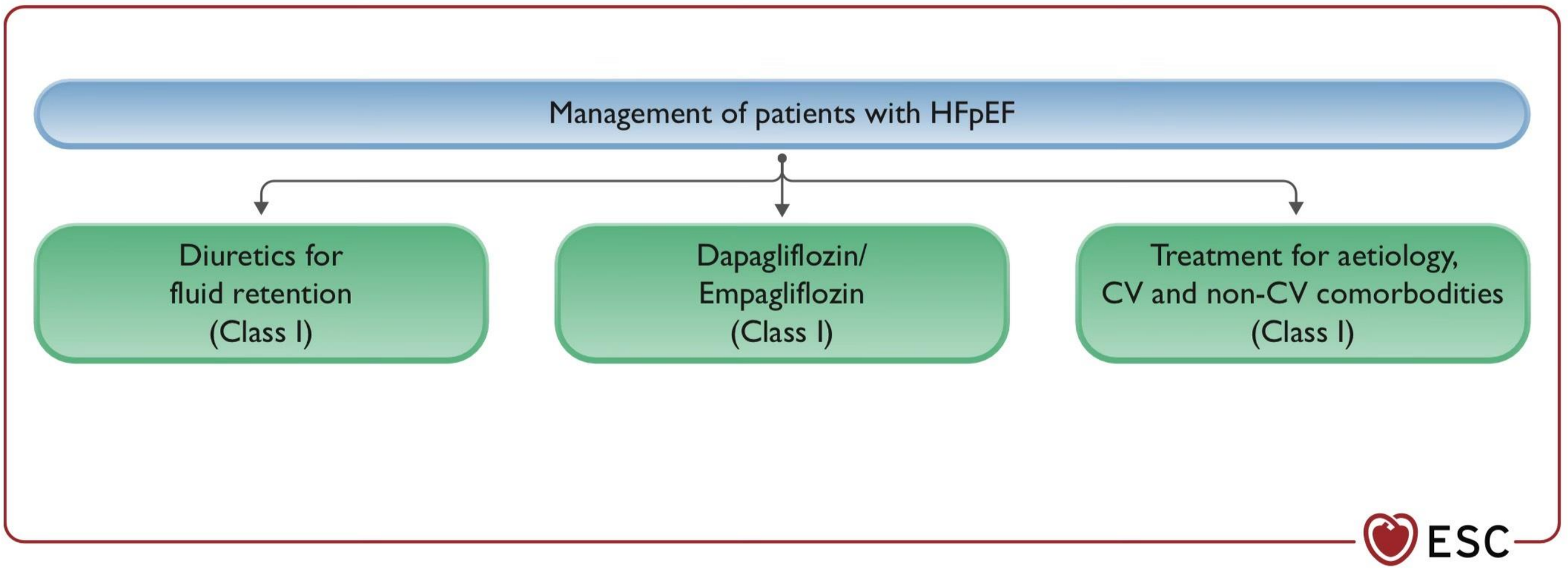


Jhund PS et al. Nat Med 2022;28:1956–1964

HFmrEF 2023


Management of patients with HFmrEF
Diuretics for fluid retention (Class I)
Dapagliflozin/ Empagliflozin (Class I)
ACEI/ARNI/ARB (Class IIb)
MRA (Class IIb)
Beta-blocker (Class IIb)
A
A
ESC

HFpEF 2023


Management of patients with HFpEF
Diuretics for fluid retention (Class I)
Dapagliflozin/ Empagliflozin (Class I)
Treatment for aetiology, CV and non-CV comorbodities (Class I)
ESC

HF Prevention 2021
Asymptomatic

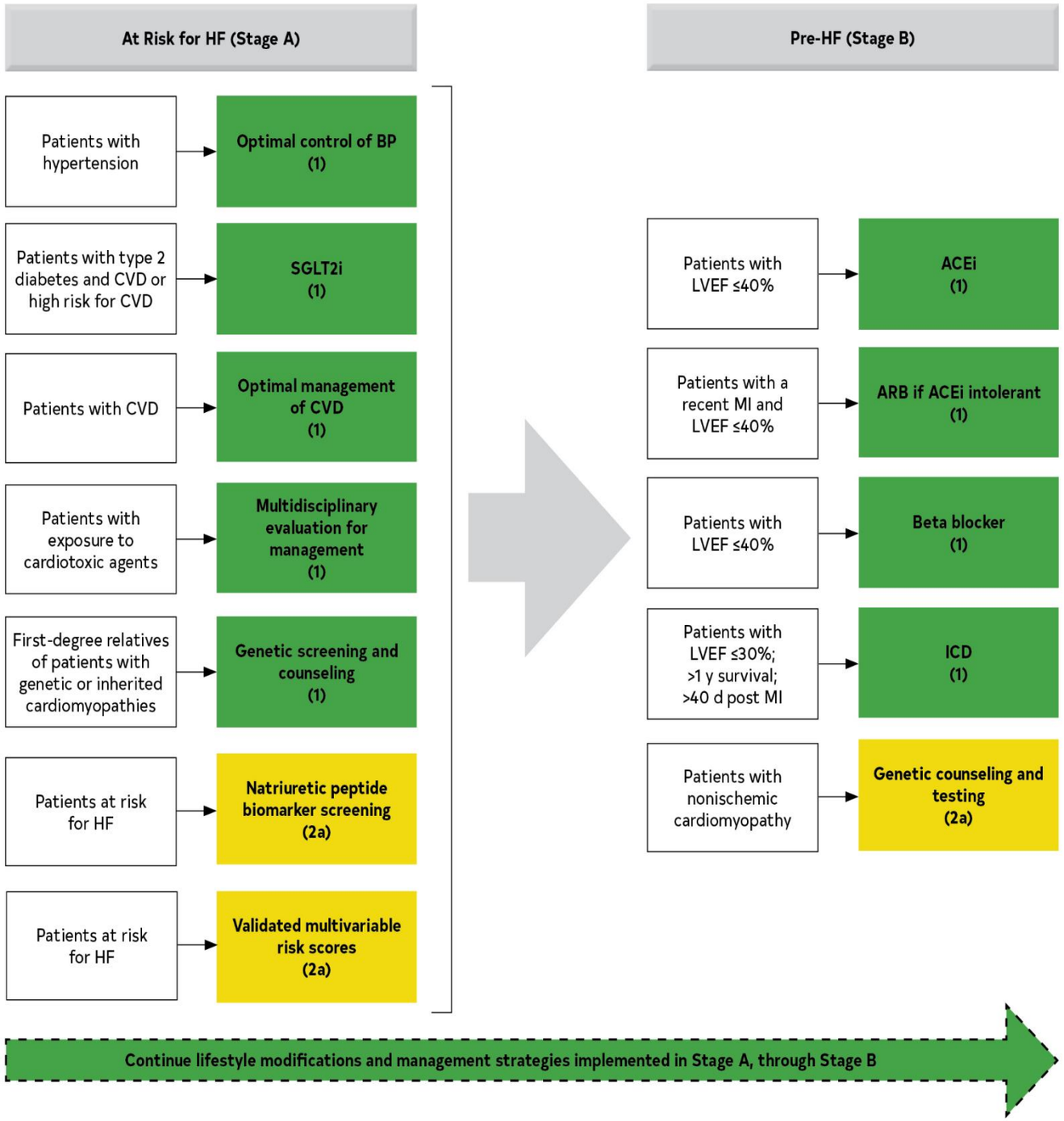
Recommendations for the primary prevention of heart failure in patients with risk factors for its development

Recommendations	Class[a]	Level[b]
Treatment of hypertension is recommended to prevent or delay the onset of HF, and to prevent HF hospitalizations.[287–290]	I	A
Treatment with statins is recommended in patients at high risk of CV disease or with CV disease in order to prevent or delay the onset of HF, and to prevent HF hospitalizations.[291,292]	I	A
SGLT2 inhibitors (canagliflozin, dapagliflozin, empagliflozin, ertugliflozin, sotagliflozin) are recommended in patients with diabetes at high risk of CV disease or with CV disease in order to prevent HF hospitalizations.[293–297]	I	A
Counselling against sedentary habit, obesity, cigarette smoking, and alcohol abuse is recommended to prevent or delay the onset of HF.[298–302]	I	C

Recommendations (Class 1 and 2a) for Patients at Risk of HF (Stage A) and Those With Pre-HF (Stage B)

Colors correspond to COR

Class 1 and Class 2a recommendations for patients at risk for HF (stage A) and those with pre-HF (stage B) are shown. Management strategies implemented in patients at risk for HF (stage A) should be continued though stage B. ACEi indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BP, blood pressure; CVD, cardiovascular disease; HF, heart failure; ICD, implantable cardioverter-defibrillator; LVEF, left ventricular ejection fraction; MI, myocardial infarction; and SGLT2i, sodium glucose cotransporter 2 inhibitor.



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Empagliflozin in Patients with Chronic Kidney Disease

The EMPA-KIDNEY Collaborative Group*

EMPA-KIDNEY Results

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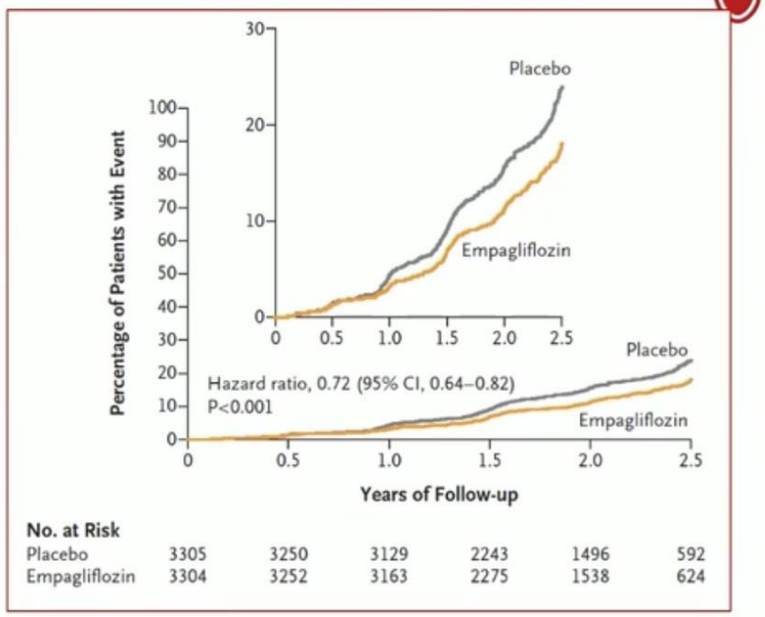

Population= 6609 patients

96% T2DM

10% History HF

Median FU= 2 years

PRIMARY ENDPOINT:

Sustained decline in the estimated GFR of at least 40%, end-stage kidney disease, or death from renal or CV causes

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The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Dapagliflozin in Patients with Chronic Kidney Disease

Hiddo J.L. Heerspink, Ph.D., Bergur V. Stefánsson, M.D., Ricardo Correa-Rotter, M.D., Glenn M. Chertow, M.D., Tom Greene, Ph.D., Fan-Fan Hou, M.D., Johannes F.E. Mann, M.D., John J.V. McMurray, M.D., Magnus Lindberg, M.Sc., Peter Rossing, M.D., C. David Sjöström, M.D., Roberto D. Toto, M.D., Anna-Maria Langkilde, M.D., and David C. Wheeler, M.D., for the DAPA-CKD Trial Committees and Investigators*

DAPA-CKD Results

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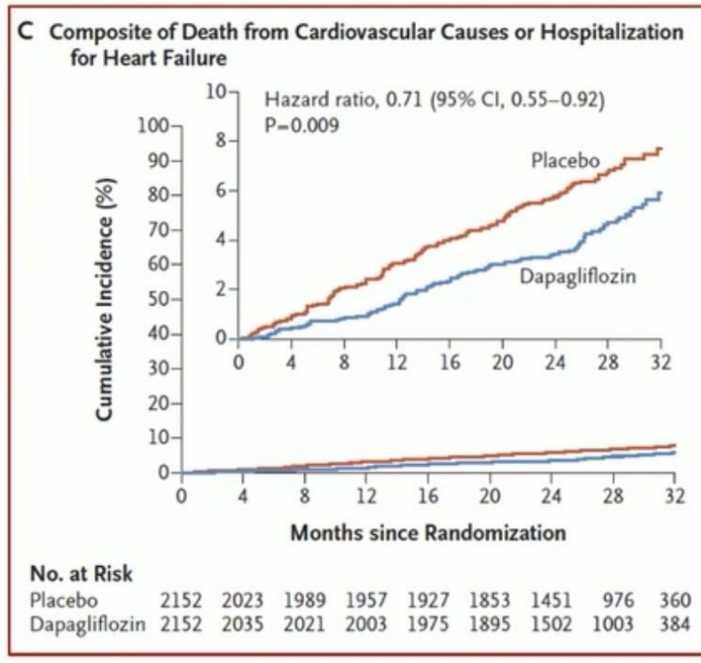

Population= 4304 patients

68% T2DM

11% History HF

Median FU= 2.4 years

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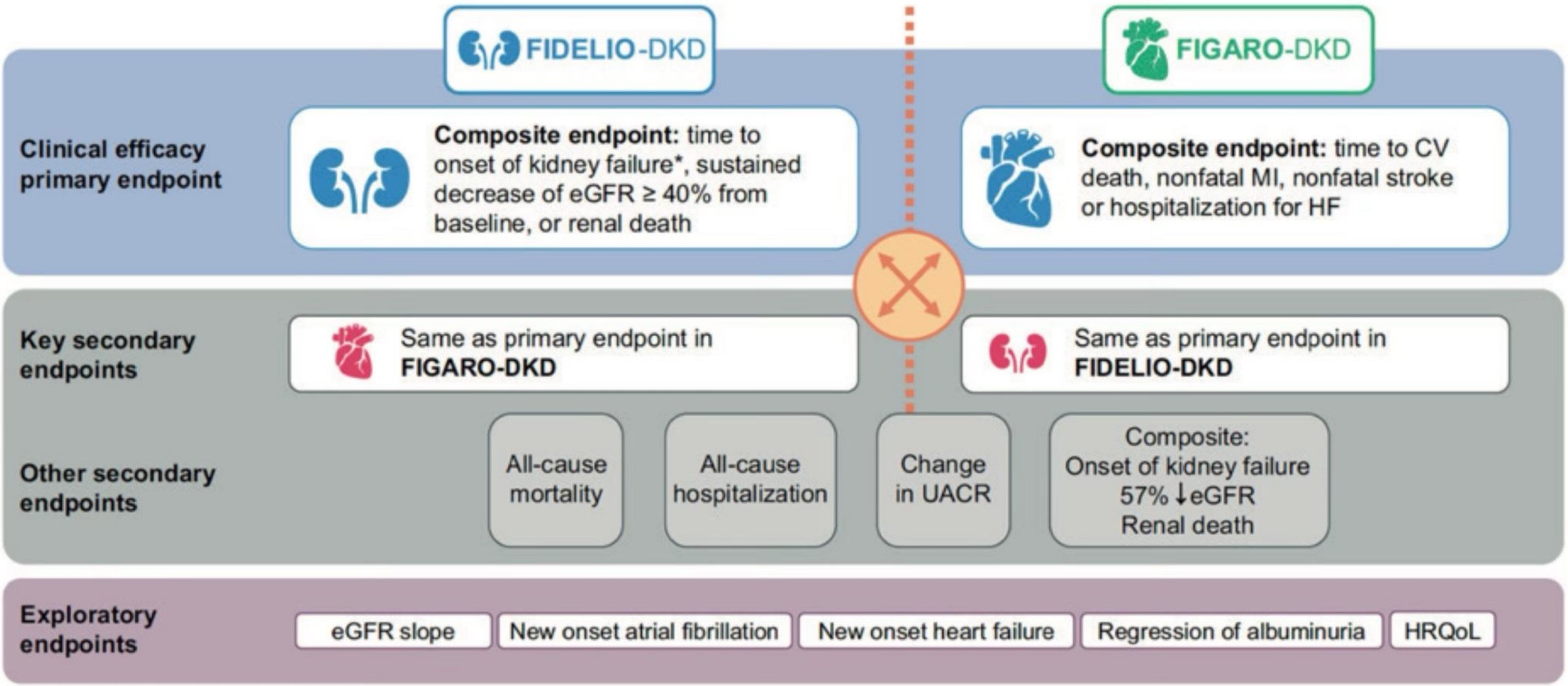
2023 Focused update of the 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure
(European Heart Journal; 2023 – doi:10.1093/eurheartj/ehad195)

Fidelity


FIDELIO-DKD
FIGARO-DKD
Clinical efficacy primary endpoint
Composite endpoint: time to onset of kidney failure*, sustained decrease of eGFR ≥ 40% from baseline, or renal death
Composite endpoint: time to CV death, nonfatal MI, nonfatal stroke or hospitalization for HF
Key secondary endpoints
Same as primary endpoint in FIGARO-DKD
Same as primary endpoint in FIDELIO-DKD
Other secondary endpoints
All-cause mortality
All-cause hospitalization
Change in UACR
Composite: Onset of kidney failure 57% ↓eGFR Renal death
Exploratory endpoints
eGFR slope
New onset atrial fibrillation
New onset heart failure
Regression of albuminuria
HRQoL

HF Prevention 2023
Asymptomatic

Recommendations	Class[a]	Level[b]
In patients with T2DM and CKD,[c] SGLT2 inhibitors (dapagliflozin or empagliflozin) are recommended to reduce the risk of HF hospitalization or CV death.[5,7,35]	I	A
In patients with T2DM and CKD,[c] finerenone is recommended to reduce the risk of HF hospitalization.[10,11,34,40]	I	A

Pre discharge 2021

Recommendations for management of patients after HF hospitalization	
It is recommended that patients hospitalized for HF be carefully evaluated to exclude persistent signs of congestion before discharge and to optimize oral treatment.	I
It is recommended that evidence-based oral medical treatment be administered before discharge.	I
An early follow-up visit is recommended at 1–2 weeks after discharge to assess signs of congestion, drug tolerance, and start and/or uptitrate evidence-based therapy.	I

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McDonagh TA, Metra M et al, Eur Heart J and Eur J Heart Failure 2021

Optimal GDMT implementation remains low despite the striking benefits

Up to **8.3** **additional years** free from CV death or hospital admission for heart failure[1]

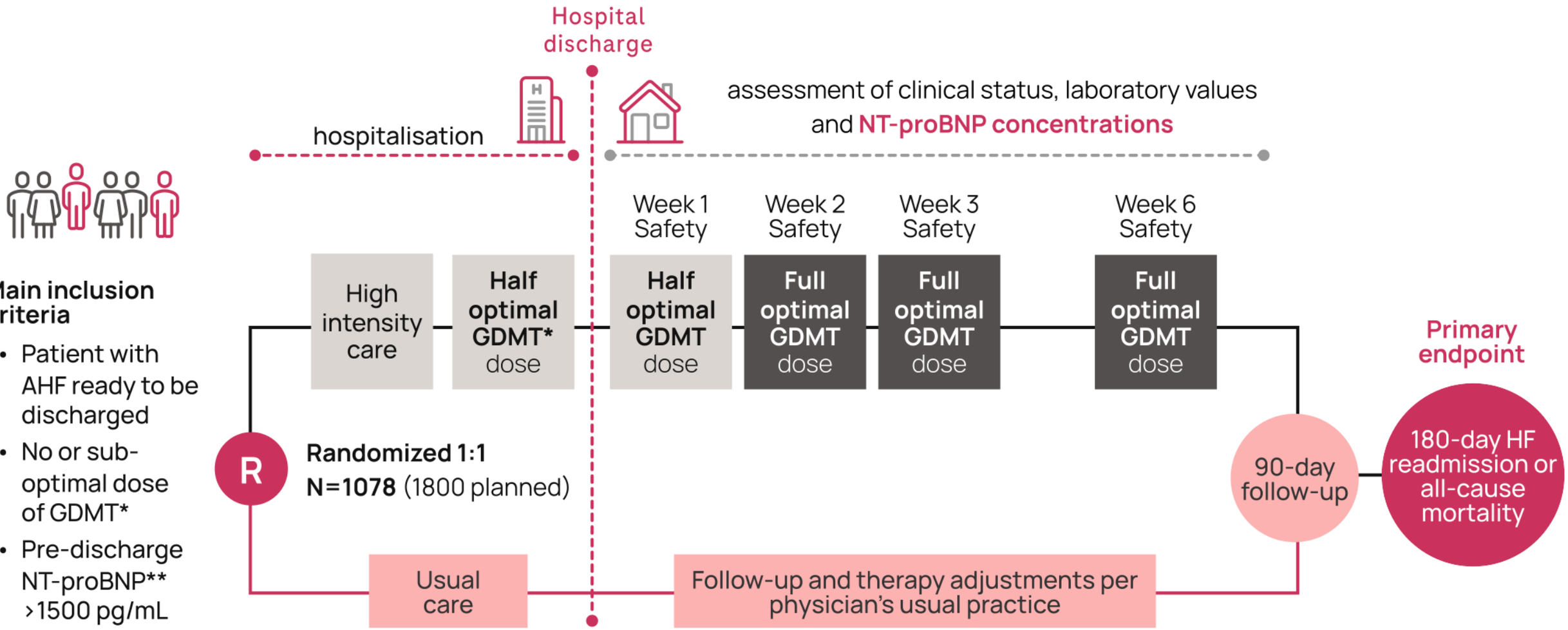
Up to **61%** **reduction in all-cause mortality** vs. conventional therapy[1,2]

CHAMP-HF: Only 1% of eligible patients were simultaneously treated with **target doses** of all ACEi/ARB/ARNI, BBs and MRA therapy[3]

ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor neprilysin inhibitor; BB, beta blocker; CV, cardiovascular; MRA, mineralocorticoid receptor antagonist; SGLT2i, sodium-glucose co-transporter-2 inhibitor.

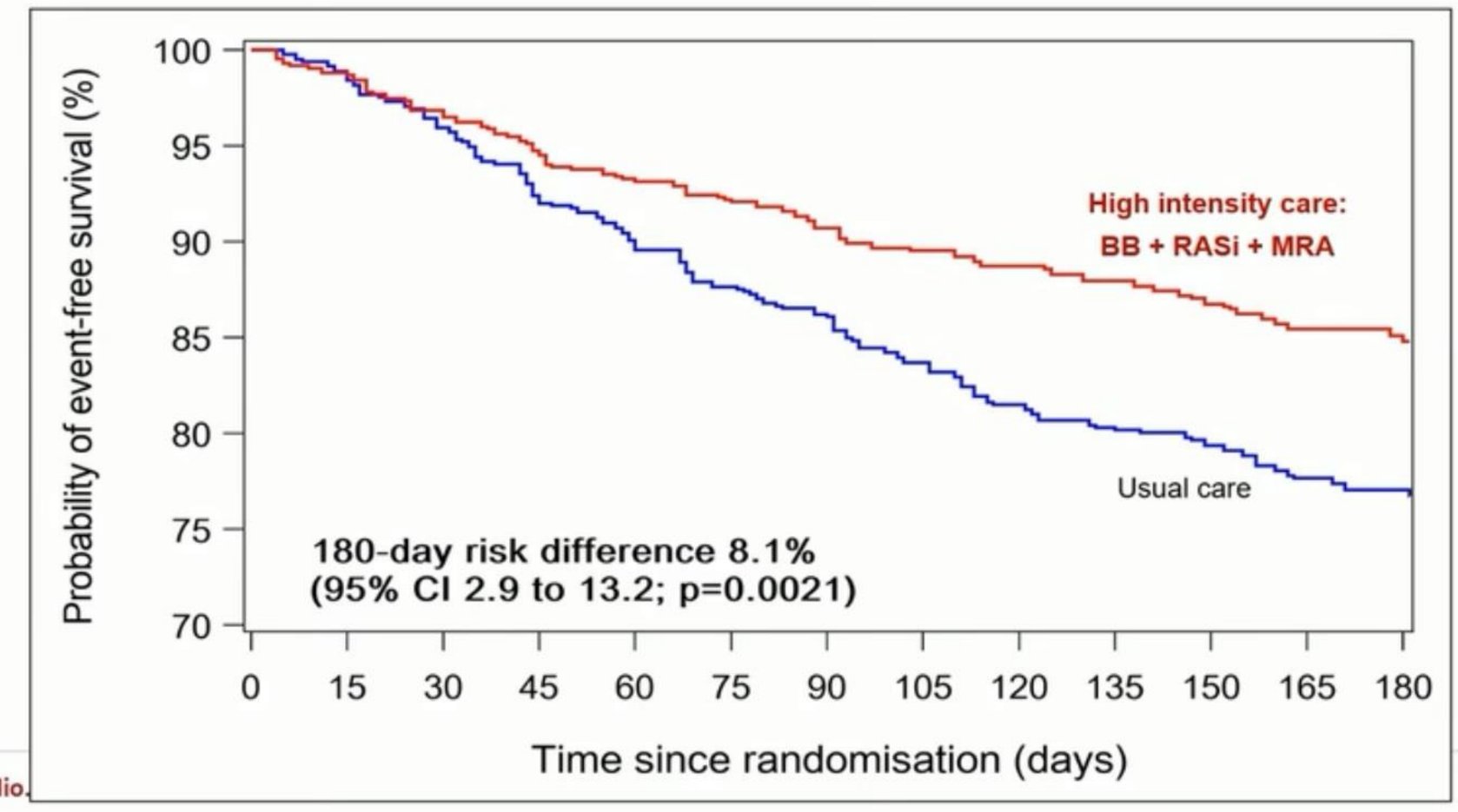
1. Vaduganathan M, *et al. Lancet* 2020; 396:121–128; 2. Tromp J, *et al. JACC Heart Fail* 2022; 10:73–84; 3. Greene SJ, *et al. J Am Coll Cardiol* 2018; 72:351–366

Strong HF


Hospital discharge
hospitalisation
assessment of clinical status, laboratory values and NT-proBNP concentrations
Week 1 Safety
Week 2 Safety
Week 3 Safety
Week 6 Safety
High intensity care
Half optimal GDMT* dose
Half optimal GDMT dose
Full optimal GDMT dose
Full optimal GDMT dose
Full optimal GDMT dose
Main inclusion criteria
• Patient with AHF ready to be discharged
• No or sub-optimal dose of GDMT*
• Pre-discharge NT-proBNP** >1500 pg/mL
R
Randomized 1:1
N=1078 (1800 planned)
Usual care
Follow-up and therapy adjustments per physician's usual practice
90-day follow-up
Primary endpoint
180-day HF readmission or all-cause mortality

STRONG-HF: Primary endpoint:

180-Day Readmission for HF or All-Cause Death



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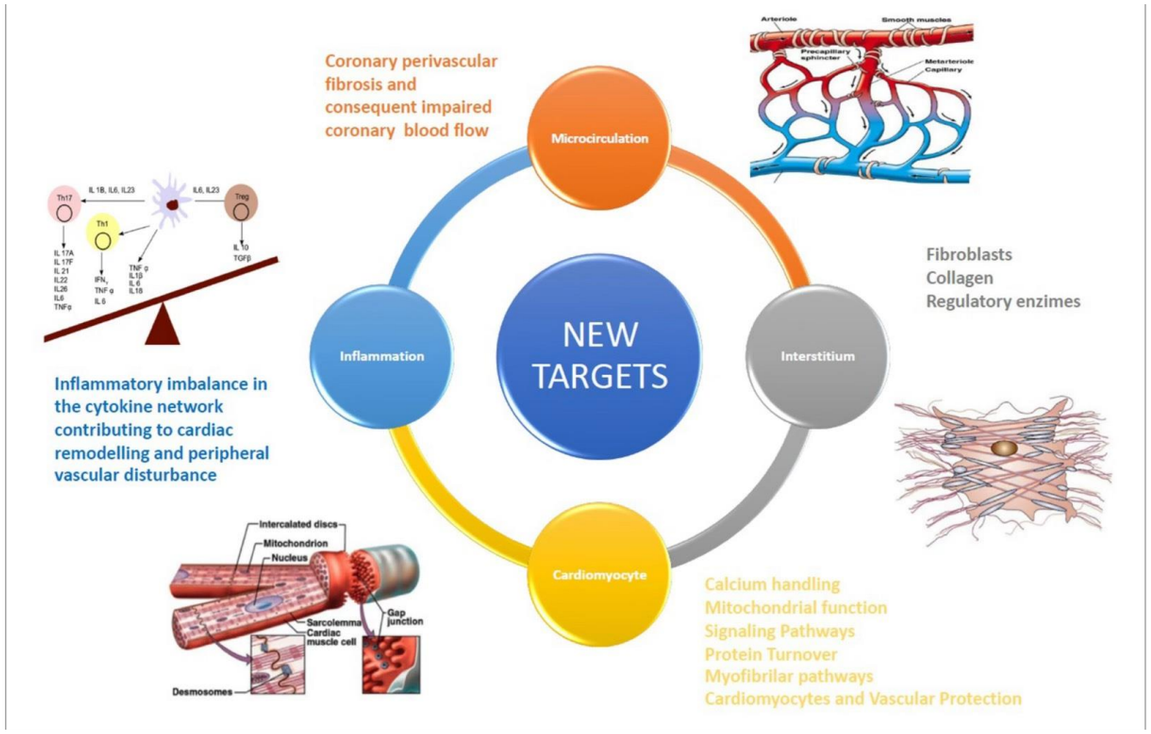
Mebazaa A et al, Lancet 2022

Pre discharge 2023

Recommendation	Class[a]	Level[b]
An intensive strategy of initiation and rapid up-titration of evidence-based treatment before discharge and during frequent and careful follow-up visits in the first 6 weeks following a HF hospitalization is recommended to reduce the risk of HF rehospitalization or death.[c,d,e] [16]	I	B

During the follow-up visits, particular attention needs to be paid to **symptoms and signs of congestion, blood pressure, heart rate, NT-proBNP values, potassium concentrations, and estimated glomerular filtration rate (eGFR).**

What tomorrow brings us



Cytokinetics

Area target	Targets	New promising drugs	HF form
Microcirculation	Targeting EC metabolism Targeting EC nutrient transport	Only translation drugs	HFpEF
Interstitium	Myocardial interstitial fibrosis Chymase	Sacubitril/ valsartan; Empagliflozin Fulacimstat	HFrEF HFpEF
Cardiomyocyte (calcium handling)	SERCA2a	Istaroxime	
Cardiomyocyte (nitroxyl donors)	SERCA2a	BMS-986231	AHF-HFrEF
Mitochondria	Partial adenosine A1 receptor	Neladenoson	HFrEF; HFpEF
	Cytochrome C	Elamipretide	HFrEF
Signaling pathways	Soluble guanylate cyclase (sGC)	Vericiguat	HFrEF; HFpEF
	Arginine vasopressin signaling	Pecavaptan	HFrEF; HFpEF
Myofibrillar pathway	Myosin	Omecamtiv mecarbil	HFrEF
Inflammation	Interleukin-1 receptor	Canakinumab	HFrEF
	Interleukin-1 receptor	Anakinra	HFrEF


بسم الله الرحمن الرحیم

Myocarditis and Heart failure
Clinic & lab

Ali Akbar Zeinaloo , Professor of Pediatric cardiology

TUMS

- **مکانیسم های بیماری زا در التهاب میوکارد شامل**

- **فعال سازی اینفلامازوم و به دنبال آن تخریب میوسیت، میوکاردیت و پریکاردیت می باشد.**
- **اینفلامازوم ها، گروهی از پروتئین های الیگومر سیتوزولی سیستم ایمنی ذاتی هستند که میکروارگانیسم های بیماری زا و عوامل استرس زای استریل را شناسایی می کنند.**
- **اینفلامازوم ها متشکل از پروتئین های وابسته به آپوپتو و حسگرهای پروتینی خانواده NLR (NOD-like receptor) می باشند که باعث فعال شدن اینترلوکین ۱۸ (IL-18) و سیتوکاین پیش التهابی IL-1β می شوند**

در التهاب میوکارد

- ، تخریب میوسیت ها می تواند نتیجه عفونت ویروسی، باکتریایی، تروما، تحریک در مرحله اولیه فاز ایمنی ذاتی و یا دیرهنگام ایمنی اکتسابی باشد.

- نکروز میوسیت در میوکاردیت با اندازه گیری سطح سرمی تروپونین T,I (TnI) که با علائم نارسایی قلبی ارتباط دارد و معمولاً زودتر از CK-MB در میوکاردیت حاد کودکان و بزرگسالان قابل ارزیابی است، مشخص می گردد.
- اندازه گیری hs-CRP و CRP و میزان رسوب گلبول های قرمز (ESR) که نشانگرهای سرمی غیر اختصاصی التهاب سیستمیک هستند، برای ارزیابی نارسایی قلبی مفید باشند.
- اندازه گیری پپتید ناتریورتیک مغزی N- ترمینال (NT-pro BNP) یک مارکر سرمی مناسب برای تشخیص نارسایی قلبی محسوب می گردد.

- بیوپسی میوکارد درتشخیص این بیماری و علل ایجاد آن از نظر نوع سلولی های التهابی و تغییرات بافتی PCRو ایمونولوژیکی بسیار ضروری،حیاتی و تعیین کننده است و بر اساس آن درمان طراحی می گردد.

- MRIاستاندارد طلایی غیر تهاجمی تشخیصی است

- شایعترین علت میوکاردیت التهابی در سطح جهان عفونتهای ویروسی است .
- در سال های اخیر عوامل ویروس ایجاد کننده تغییر یافته است بطوریکه Parvovirus B19 و Human Herpes virus 6 جای آدنوویروس و انتروویروس را گرفته است.

- مطالعات جدید نشان می دهد که تقریبا ۵۰% بیماران باعلائم بالینی Dilated cardiomyopathy (DCM) نشانه ایمونوهیستوکمیکال میوکاردیت یا inflammatory cardiomyopathy(ICM) دارند و شایعترین علت DCM همان میوکاردیت ICM می باشد

از نظر بالینی

- این بیماری ممکن است بدون علامت باشد یا بصورت برق آسا ظاهر شود و یا فاز های مختلف التهابی و اختلال عملکرد قلب و سیستم هدایتی وآریتمی را طی نموده وتبدیل به کاردیو مایوپاتی اتساعی در سنین مختلف شود.
- بیوپسی میوکاردیت میتواند سیر و ایمونولوژی بیماری را تعیین نماید. بهر حال شایعترین تظاهر این بیماری نارسایی قلبی است، که عمدتا بصورت نارسایی احتقانی نشانه های بالینی دارد. اما ممکن است بیمار با درد سینه یا تابلوی آریتمی به کلینیک مراجعه نماید.
- از نظر تشخیص به معیارهای تشخیصی و نشانه های بالینی بستگی دارد.
- نشانه های بالینی شامل دردسینه-نارسایی حاد یا مزمن قلبی- نشانه های آریتمی(سنکوپ،تاکیکاردی ومرگ ناگهان قلبی

معیارهای تشخیص:

- تغییرات ولتاژ-تعداد ضربان-در فواصل و ریتم و امواج RST Qدر نوار قلب
- مارکرهای نکروزمیوکارد مثل افزایش تروپونینT,I و CPK-MB
- افزایش مارکرهای التهاب قلبی وتغییر شکل قلب و فشار قلب: hs-CRP,CRP به عنوان مارکر التهاب و NT-proB NP که وجودشان بدتربودن بیماری را تأیید می کند
- تغییرات ساختاری و عملکردی در اکوکاردیوگرافی و CMRI
- تغییرات اختصاصی سلولی در MRI (Lake Louise Criteria) در این مطالعه با گادولینیوم هرچه LEG بالاتر و بیشتر باشد پیشگوی مرگ و میر بیشتر قلبی میباشد.
- وجود بعضی آنتی بادی های ضدمیوسیت که در صورت مثبت بودن شانس پاسخ بیمار به ایمونوسوپرسیو رابالا میبرد.

متدهای جدید و رضایت بخش و کم تهاجمی و یا غیرتهاجمی

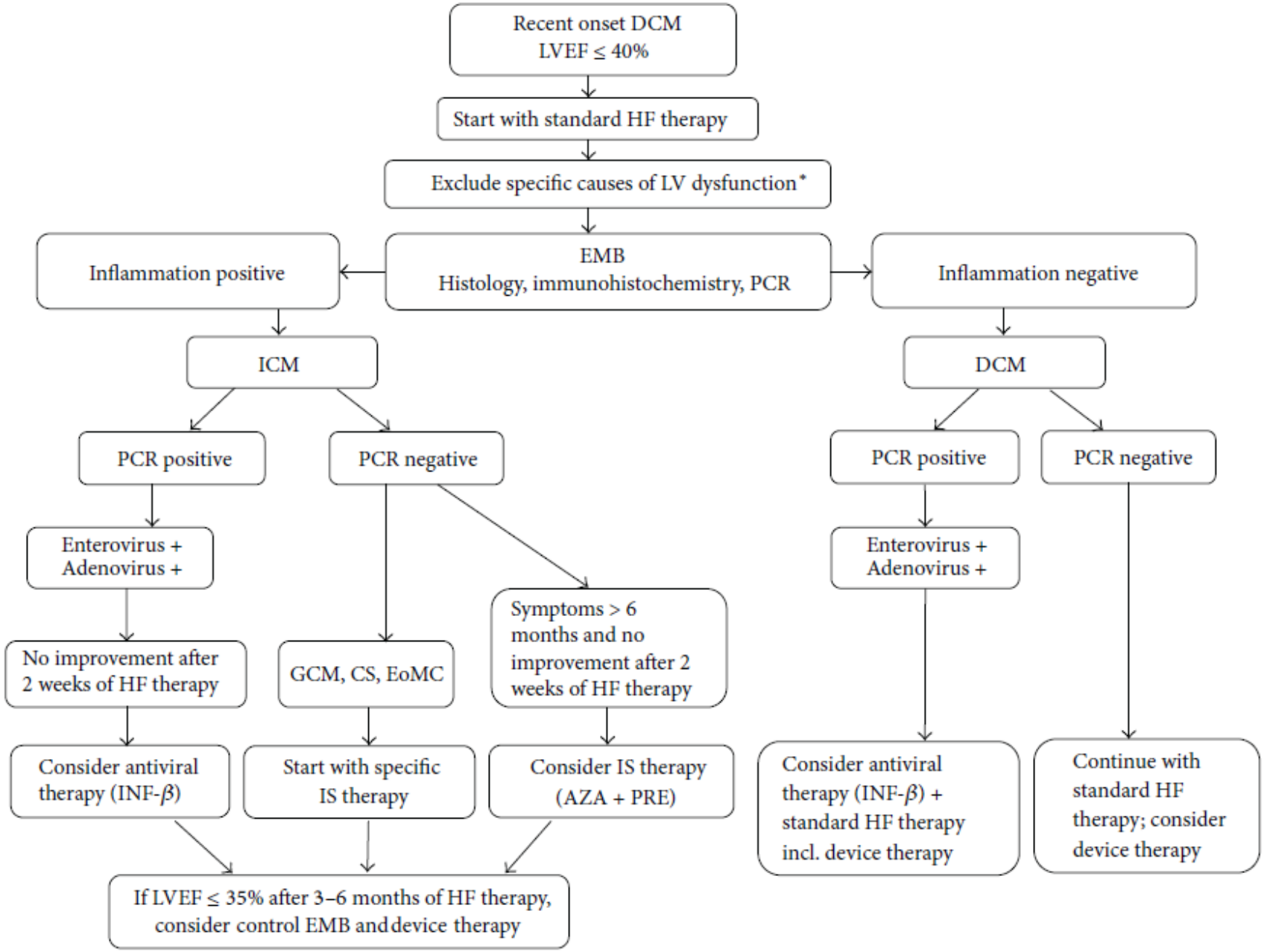
- در تشخیص میوکاردیت نقش برجسته ای پیدا کرده
- متد کشف different gene Transcription است که بعلت حساسیت و دقت بالا در تشخیص این بیماری جایگاه مناسبی پیدا کرده ست.
- متد دیگر ارزیابی سطح miRNA است که در تشخیص میوکاردیت با زمینه ی PV B19 ارزشمند است و سطح این ذره ی ژنتیکی افزایش می یابد ،
- این متد می تواند در Prognostic stratification و تصمیم گیری درمانی مورد استفاده قرارگیرد.

درمان بیماری

- در مرحله حاد میوکاردیت با زمینه التهابی و ویروسی و اتوایمیون مصرف IVIG توصیه می شود
- هرچند که هنوز مکانیسم های عملکردی IVIG به طور کامل مشخص نشده است اما در طی یک دهه گذشته، تحولات بزرگی در درک مکانیسم عملکرد آن رخ داده است.
- احتمالا IVIG عملکرد خود را بر چندین مؤلفه انتی بادی ها از جمله مناطق متغیر $F(ab)_2$، گیرنده Fc و کمپلکس کمپلمان-Fc اعمال می نماید

- **این ماده حاوی ترکیبی از آنتی بادی های طبیعی IgG، آنتی آیدیوتایپ ها، آنتی بادی علیه پاتوژن ها و مولکول های تعدیل کننده سیستم ایمنی است و سبب کاهش سطح سایتوکاین ها می گردد.**
- **مطالعات نشان می دهد که شروع زود هنگام درمان با IVIG، اثرات درمانی آنرا در میوکاردیت افزایش می دهد ولی در بزرگسالان اثر آن کمتر است**

- مصرف اینترفرون IFN(IFN-ß1) به عنوان داروی ضدویروس در درمان میوکاردیت آدنوویروس-انتروویروس و کوکساکی با دوز $4*10^6$-$8*10^6$IU در حذف ژنوم ویروس –کاهش التهاب میوکارد و پریکارد و بهبود همودینامیک قلب تأیید شده است ولی اثر آن در ویروس های PVB19 وHHV6 تأیید نشده است.


Recent onset DCM
LVEF ≤ 40%
Start with standard HF therapy
Exclude specific causes of LV dysfunction*
EMB
Histology, immunohistochemistry, PCR
Inflammation positive
Inflammation negative
ICM
DCM
PCR positive
PCR negative
PCR positive
PCR negative
Enterovirus +
Adenovirus +
Enterovirus +
Adenovirus +
No improvement after
2 weeks of HF therapy
GCM, CS, EoMC
Symptoms > 6
months and no
improvement after 2
weeks of HF therapy
Consider antiviral
therapy (INF-β)
Start with specific
IS therapy
Consider IS therapy
(AZA + PRE)
Consider antiviral
therapy (INF-β) +
standard HF therapy
incl. device therapy
Continue with
standard HF
therapy; consider
device therapy
If LVEF ≤ 35% after 3–6 months of HF therapy,
consider control EMB and device therapy