

CONGRESSO

ROMA, 25 - 27 Giugno 2026

SEDE DEI LAVORI

A. Roma Lifestyle Hotel
Via Giorgio Zoega 59, Roma

Stratificazione del rischio di morte improvvisa nella Cardiomiopatia Non Ischemica (NICM): non solo FE del ventricolo sinistro

Gianfranco Sinagra, FESC, FHFA

Dipartimento Cardiotoracovascolare; ASUGI

Scuola di Specializzazione in Malattie dell'Apparato Cardiovascolare

Università degli Studi di Trieste

Disclosures

GIANFRANCO SINAGRA

in qualità di (moderatore, relatore, formatore, tutor, docente)

ai sensi dell'art. 76 sul Conflitto di Interessi, comma 4 dell'Accordo Stato-Regioni del 2 febbraio 2017 e del paragrafo 4.5. del Manuale nazionale di accreditamento per l'erogazione di eventi ECM

dichiara

Negli ultimi due anni ha avuto i seguenti rapporti con soggetti portatori di interessi in campo sanitario:

Astrazeneca, Pfizer, Alnylam, Novo Nordisk, Novartis, Bruno Farmaceutici, Boston Scientific, Menarini, Amgen, Sanofi, Boehringer Ingelheim (Relatore a congressi)

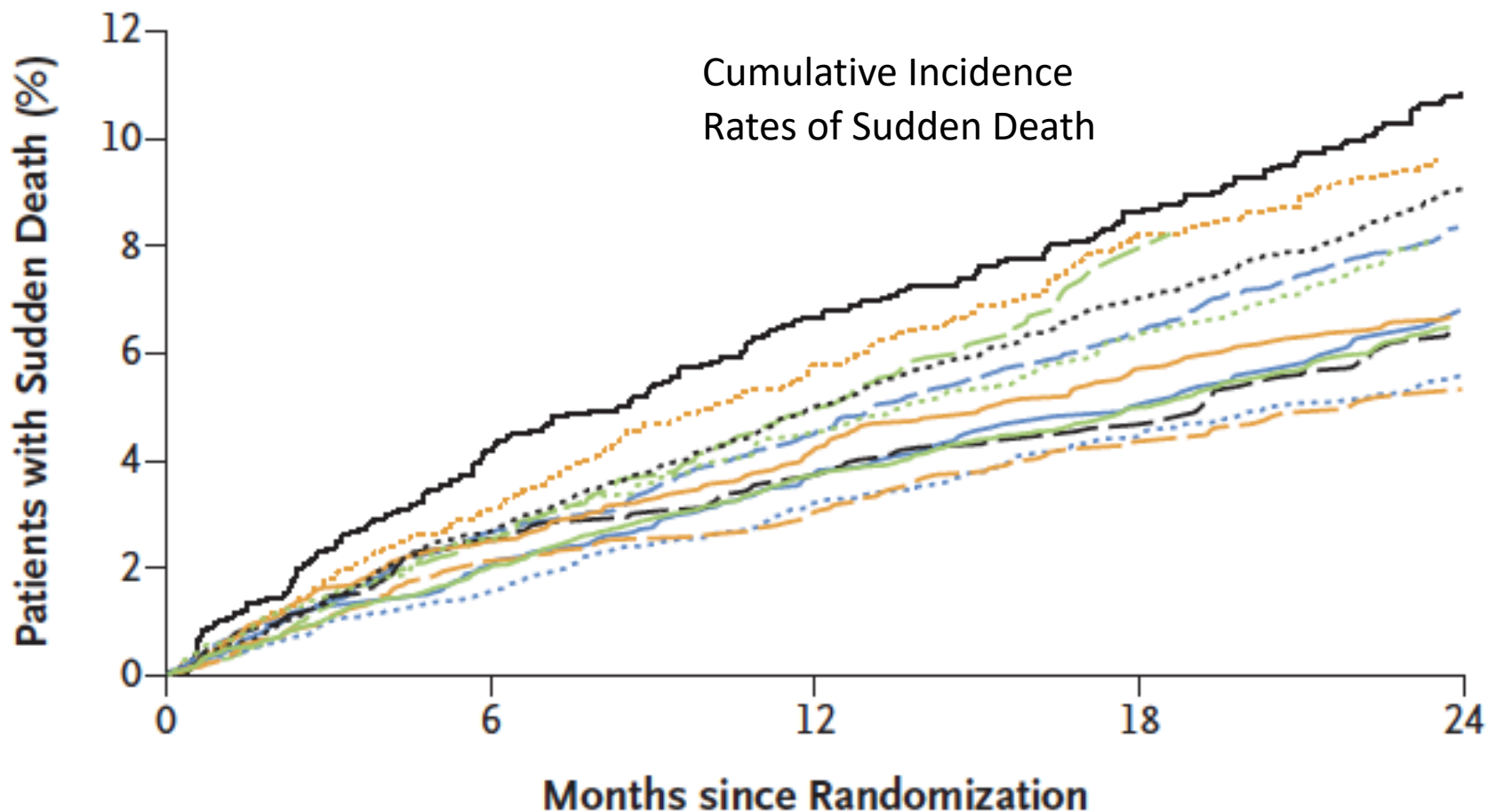
Bayer, BMS (Consulenze e Collaborazione scientifica occasionale)

Declining Risk of Sudden Death in Heart Failure



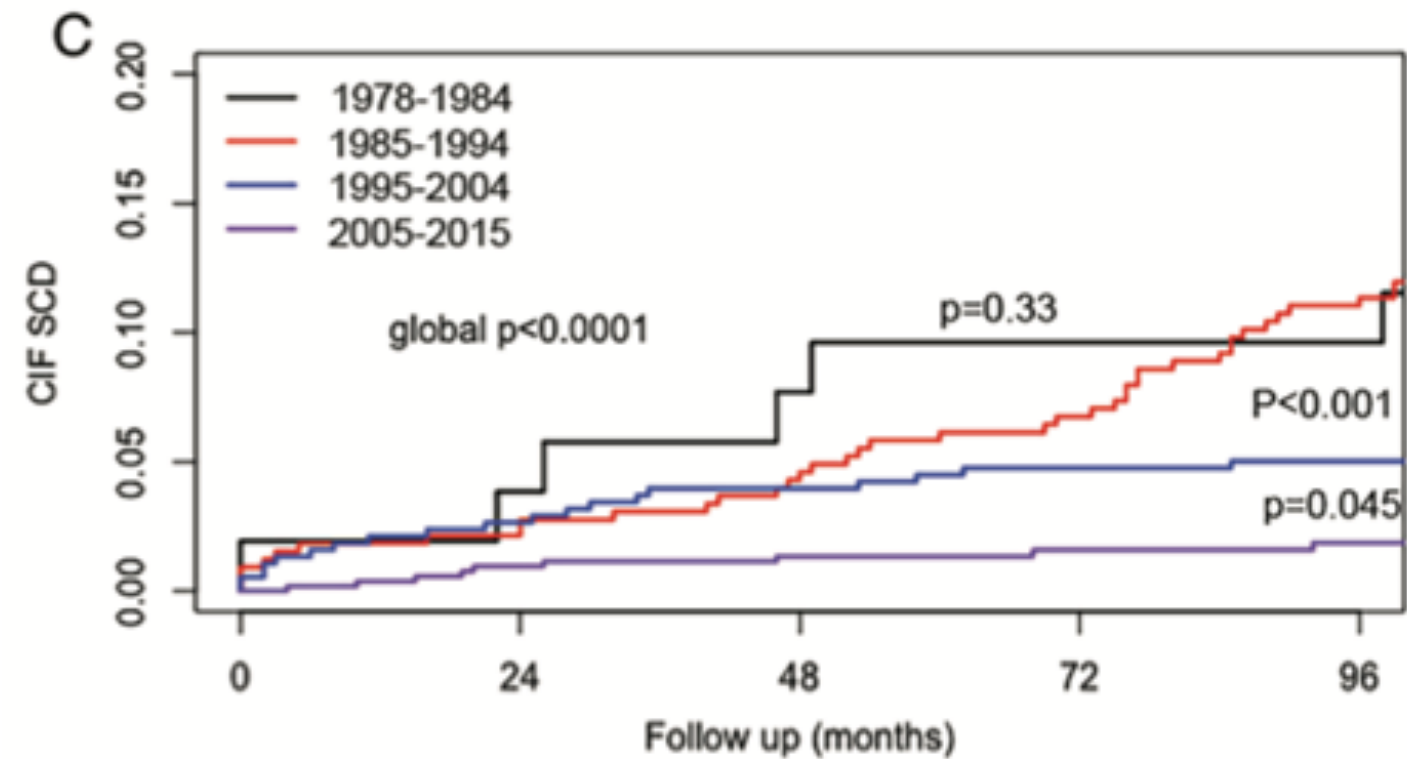
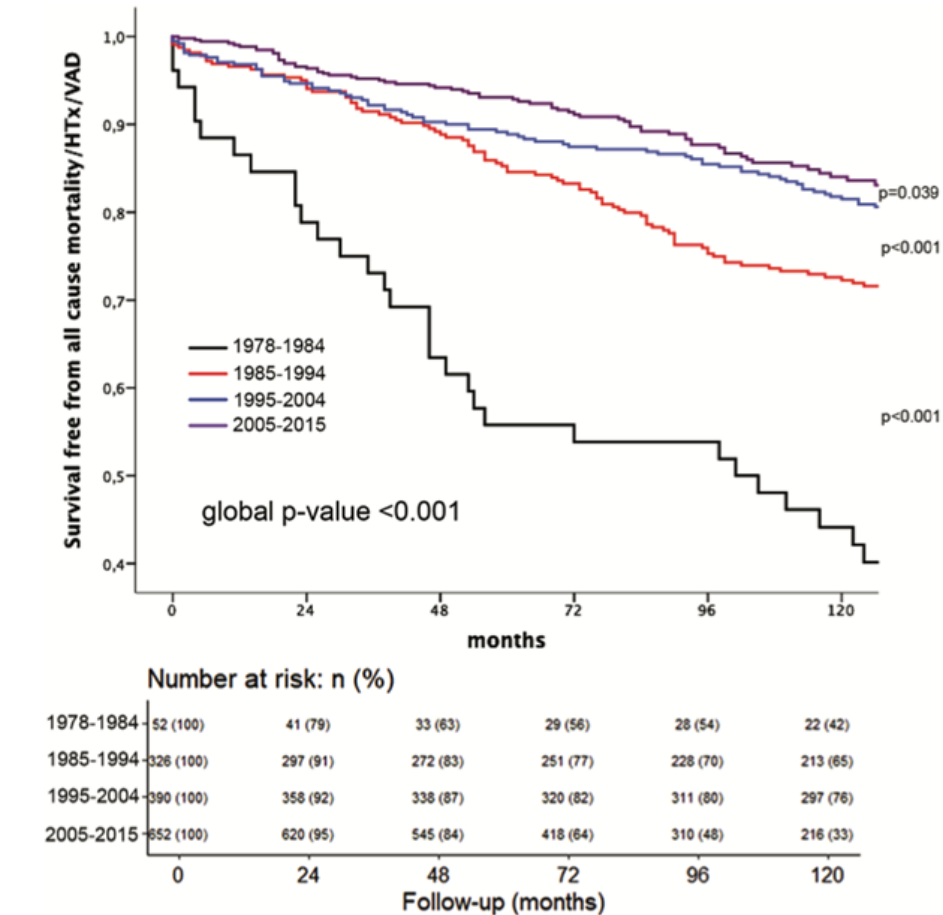
The NEW ENGLAND
JOURNAL of MEDICINE

RALES
MERIT-HF
CHARM-Alternative
GISSI-HF
BEST
Val-HeFT
CHARM-Added
EMPHASIS-HF
CIBIS-II
SCD-HeFT
CORONA
PARADIGM-HF



Contemporary survival trends and aetiological characterization in non-ischaeamic dilated cardiomyopathy

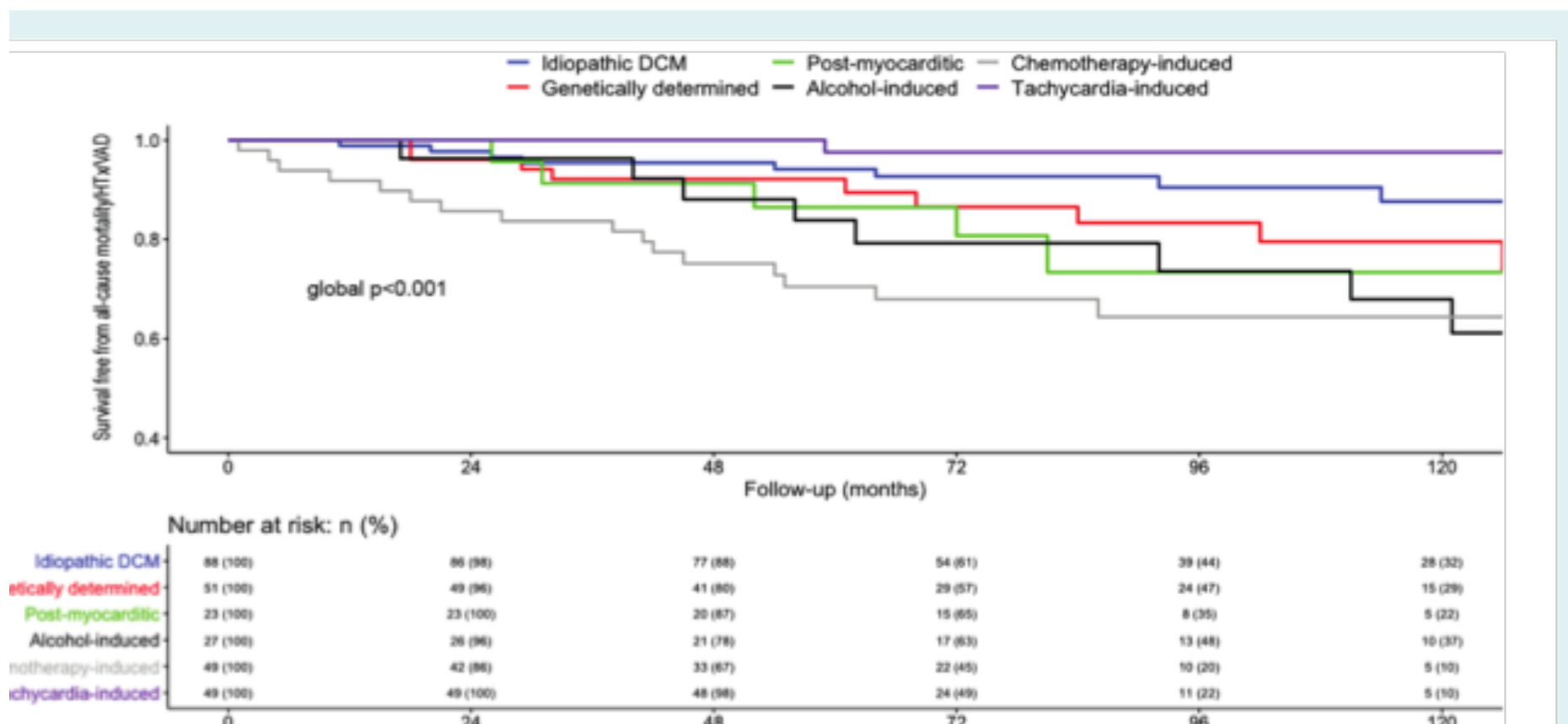
Marco Merlo^{1*†}, Antonio Cannatà^{1,2†}, Carola Pio Loco¹, Davide Stolfo¹, Giulia Barbati³, Jessica Artico¹, Piero Gentile¹, Valerio De Paris¹, Federica Ramani¹, Massimo Zecchin¹, Marta Gigli¹, Bruno Pinamonti¹, Renata Korcova¹, Andrea Di Lenarda⁴, Mauro Giacca², Luisa Mestroni⁵, Paolo G. Camici⁶, and Gianfranco Sinagra¹

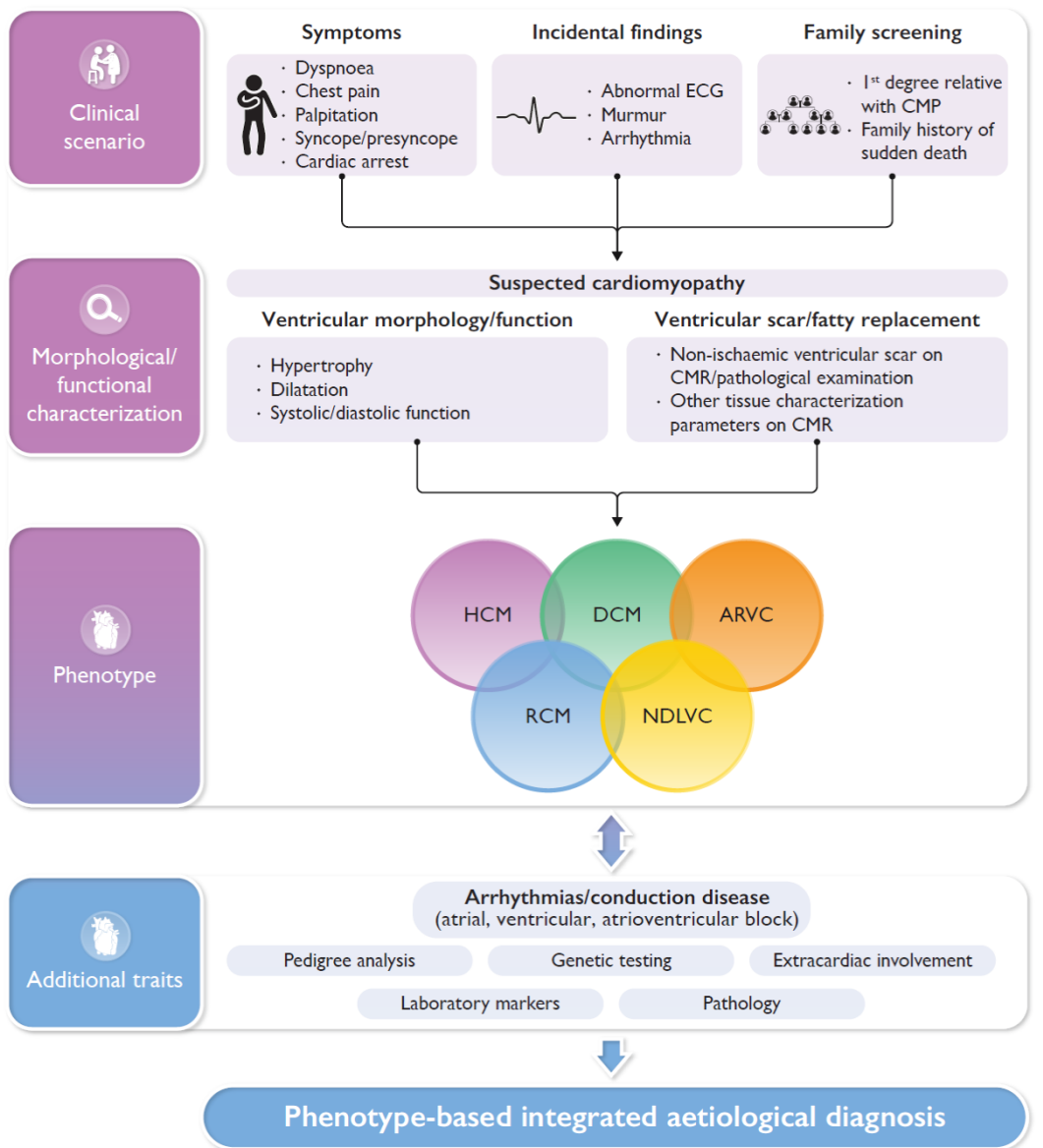




Contemporary survival trends and aetiological characterization in non-ischaemic dilated cardiomyopathy

Marco Merlo^{1*†}, Antonio Cannatà^{1,2†}, Carola Pio Loco¹, Davide Stolfo¹, Giulia Barbati³, Jessica Artico¹, Piero Gentile¹, Valerio De Paris¹, Federica Ramani¹, Massimo Zecchin¹, Marta Gigli¹, Bruno Pinamonti¹, Renata Korcova¹, Andrea Di Lenarda⁴, Mauro Giacca², Luisa Mestroni⁵, Paolo G. Camici⁶, and Gianfranco Sinagra¹





Novità 2023

NDLVC

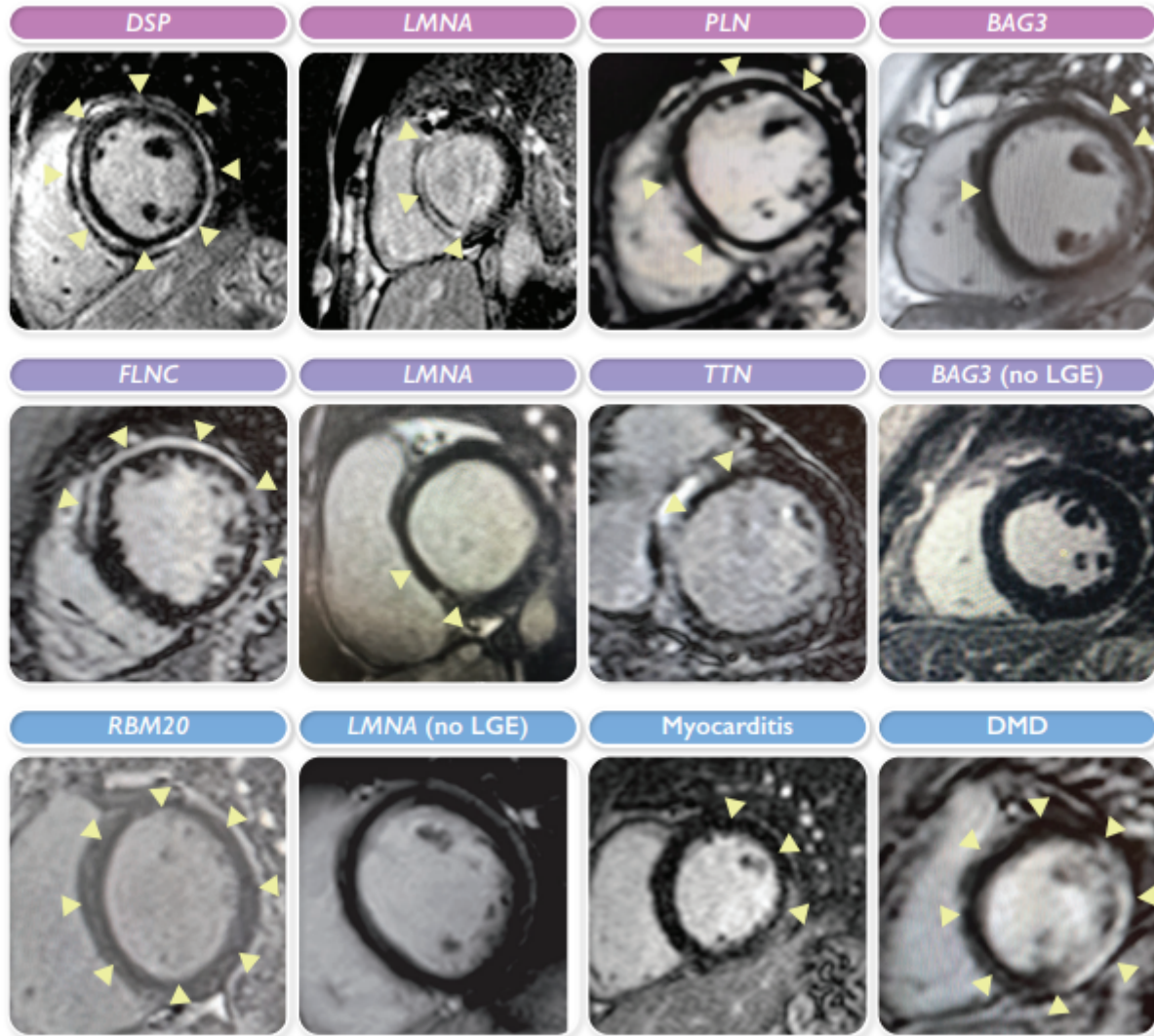
Takotsubo e LNVC escluse

Red-flags approach

Genetica integrata

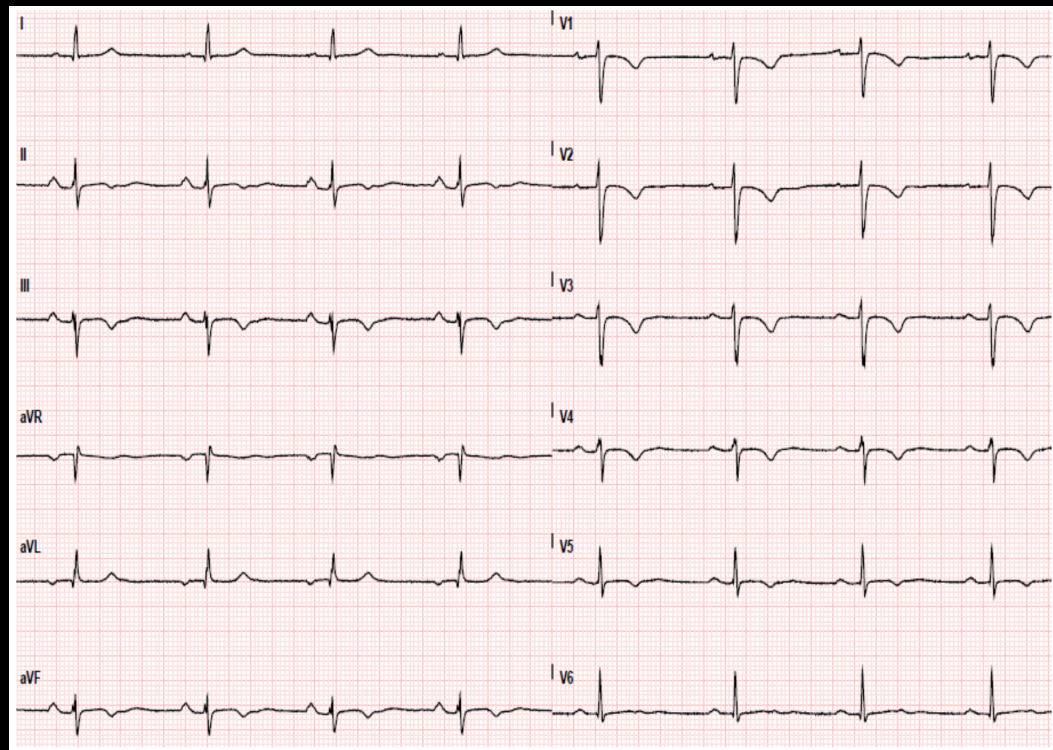
Focus su Management
(non solo terapia, es. Sport)

Cardiomiopatia NON DILATATA “del VSIN” (NDLVC)



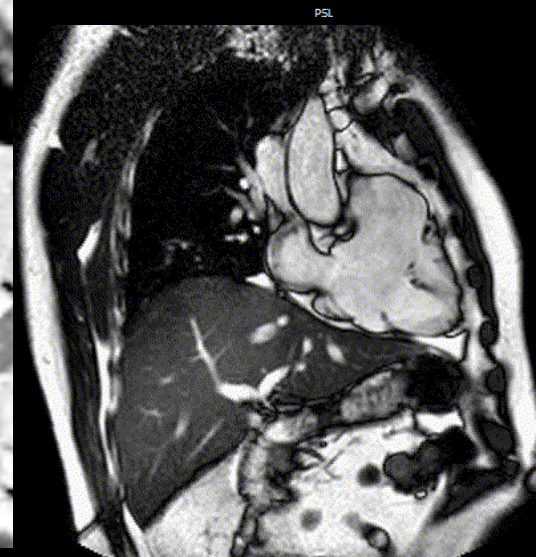
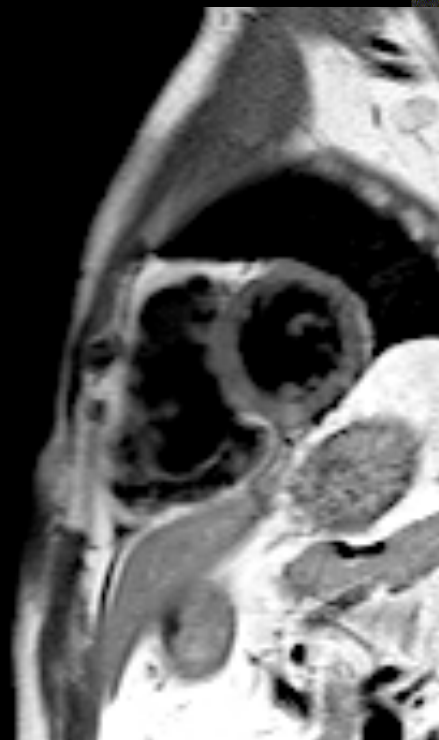
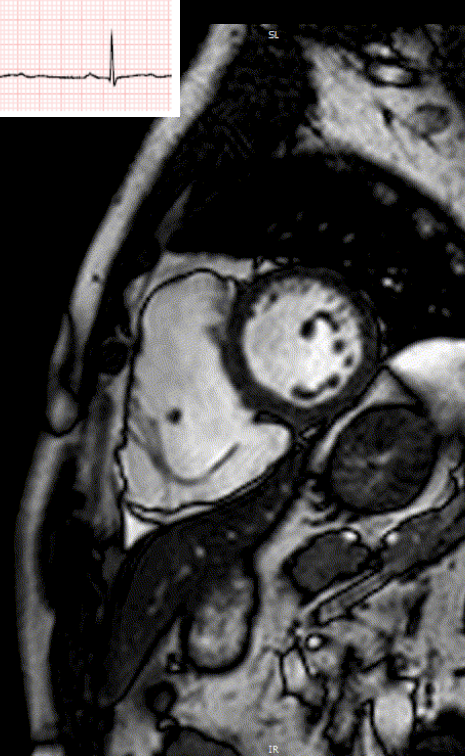
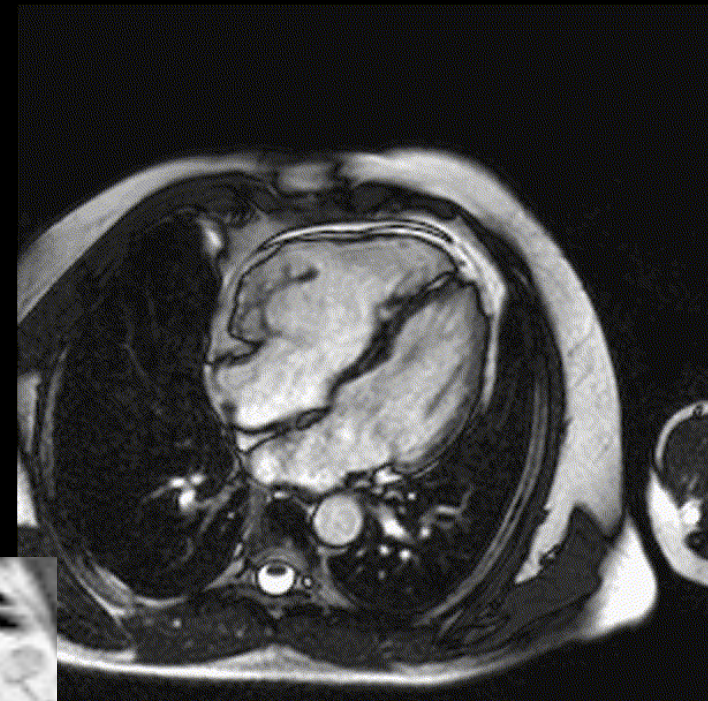
Definita da: **cicatrice miocardica alla RMN (LGE) OPPURE** disfunzione sistolica VS in assenza di dilatazione

- **incluse nella NDLVC:**
 - *Forme di ARVC con coinvolgimento sinistro*
 - *DCM "early": forme iniziali non ancora dilatate ma già disfunzionali*
 - *Post-miocardite: ≥ 2 segmenti LGE, senza dilatazione*



SR

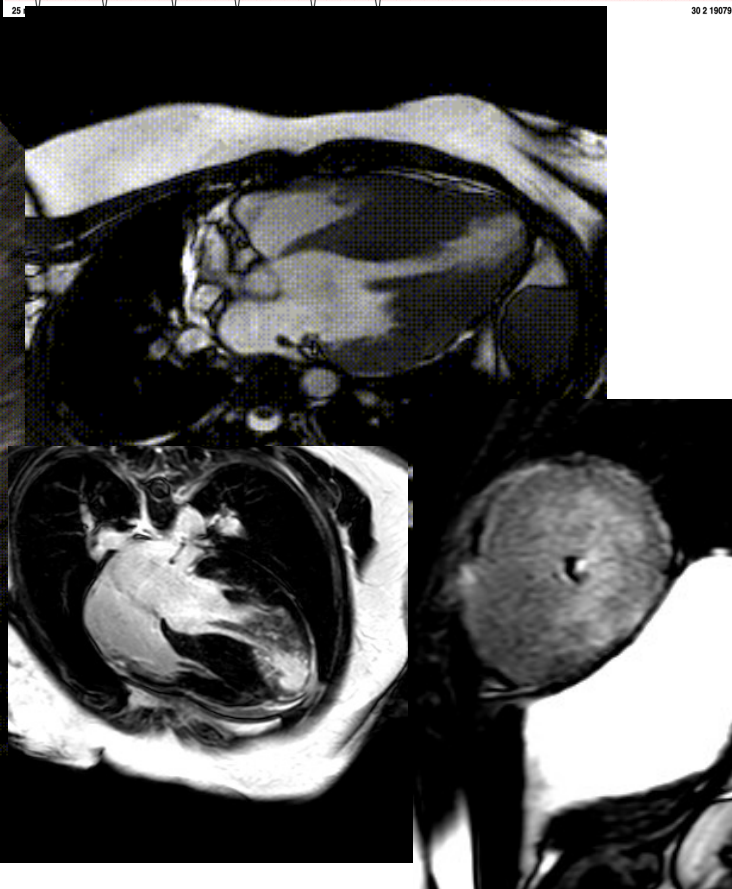
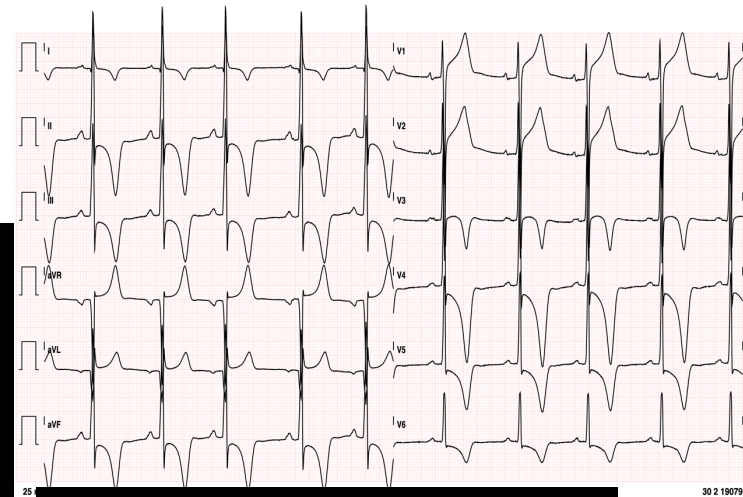
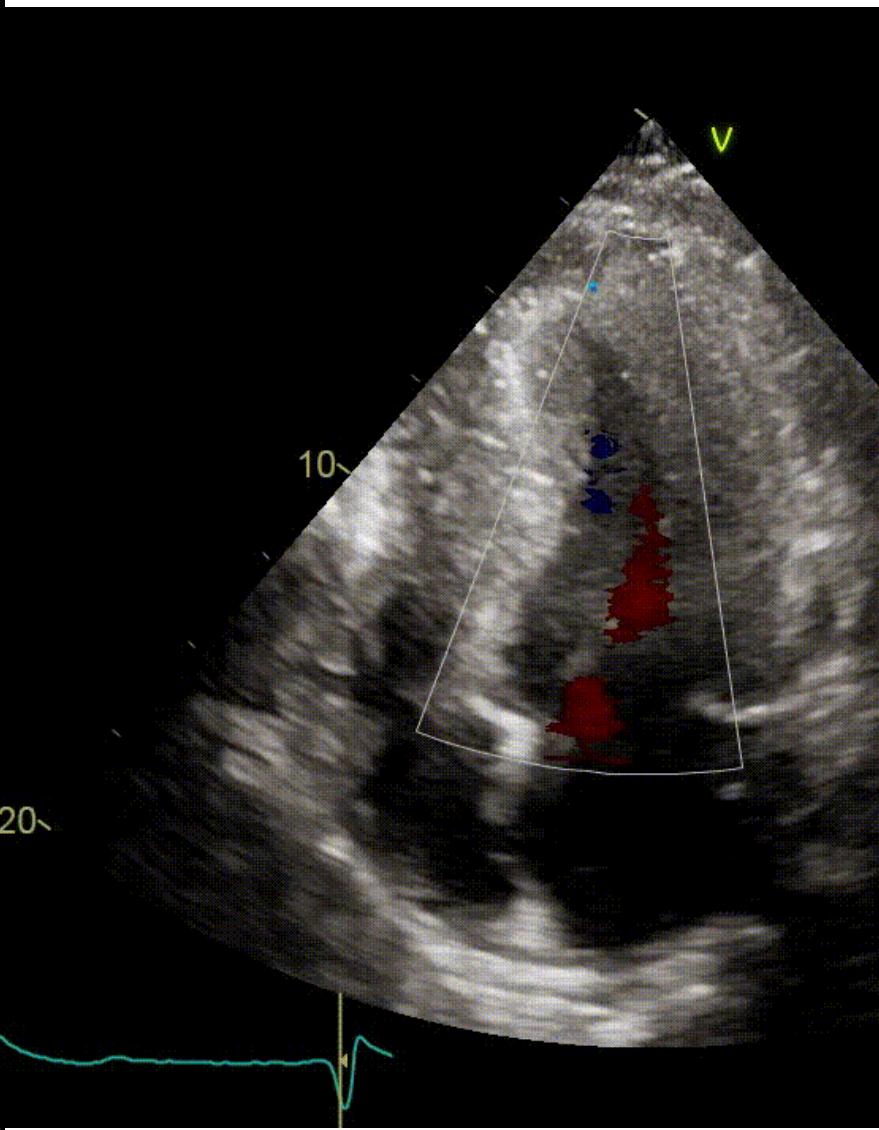
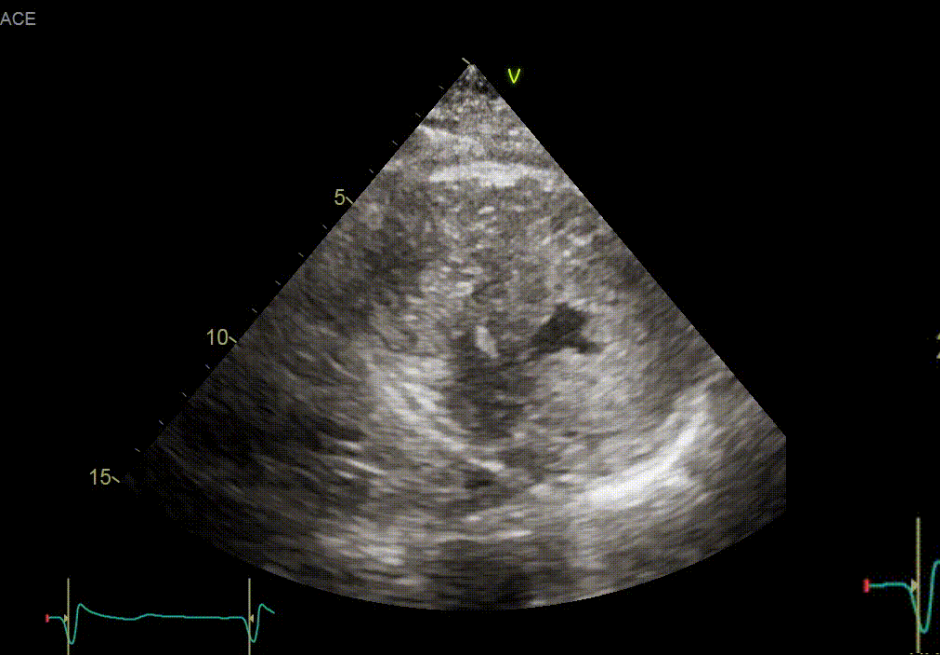
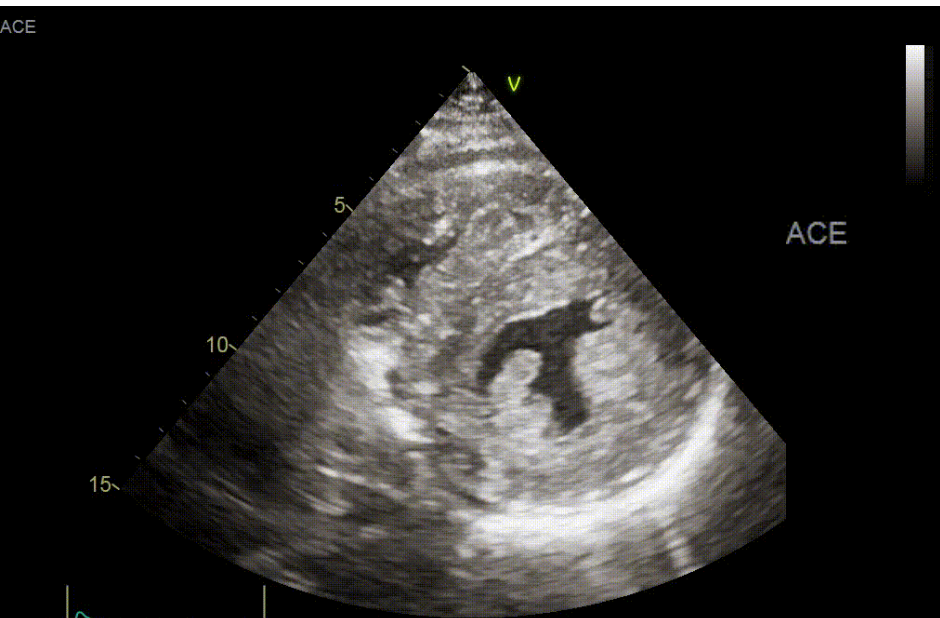
AIR



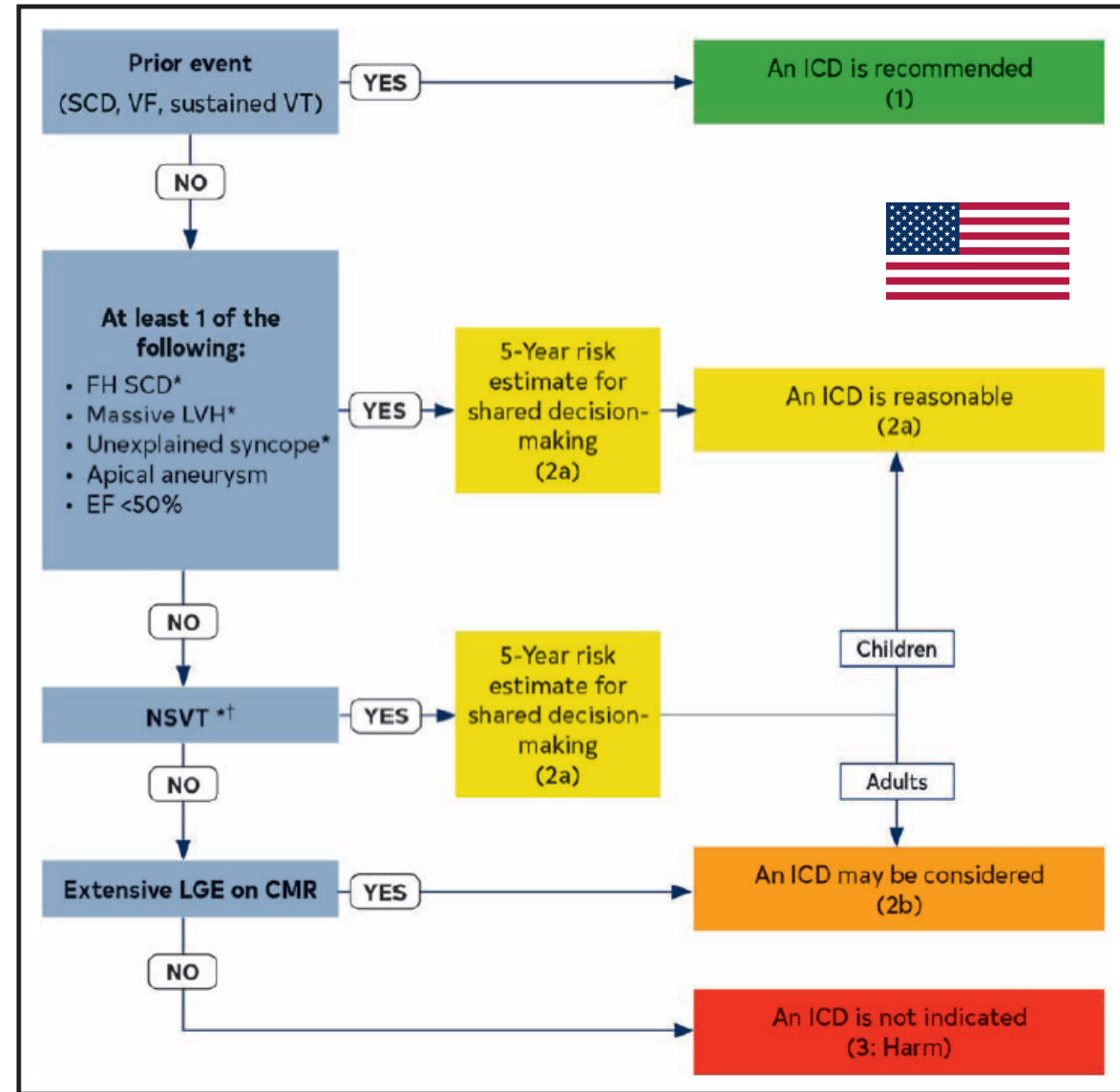
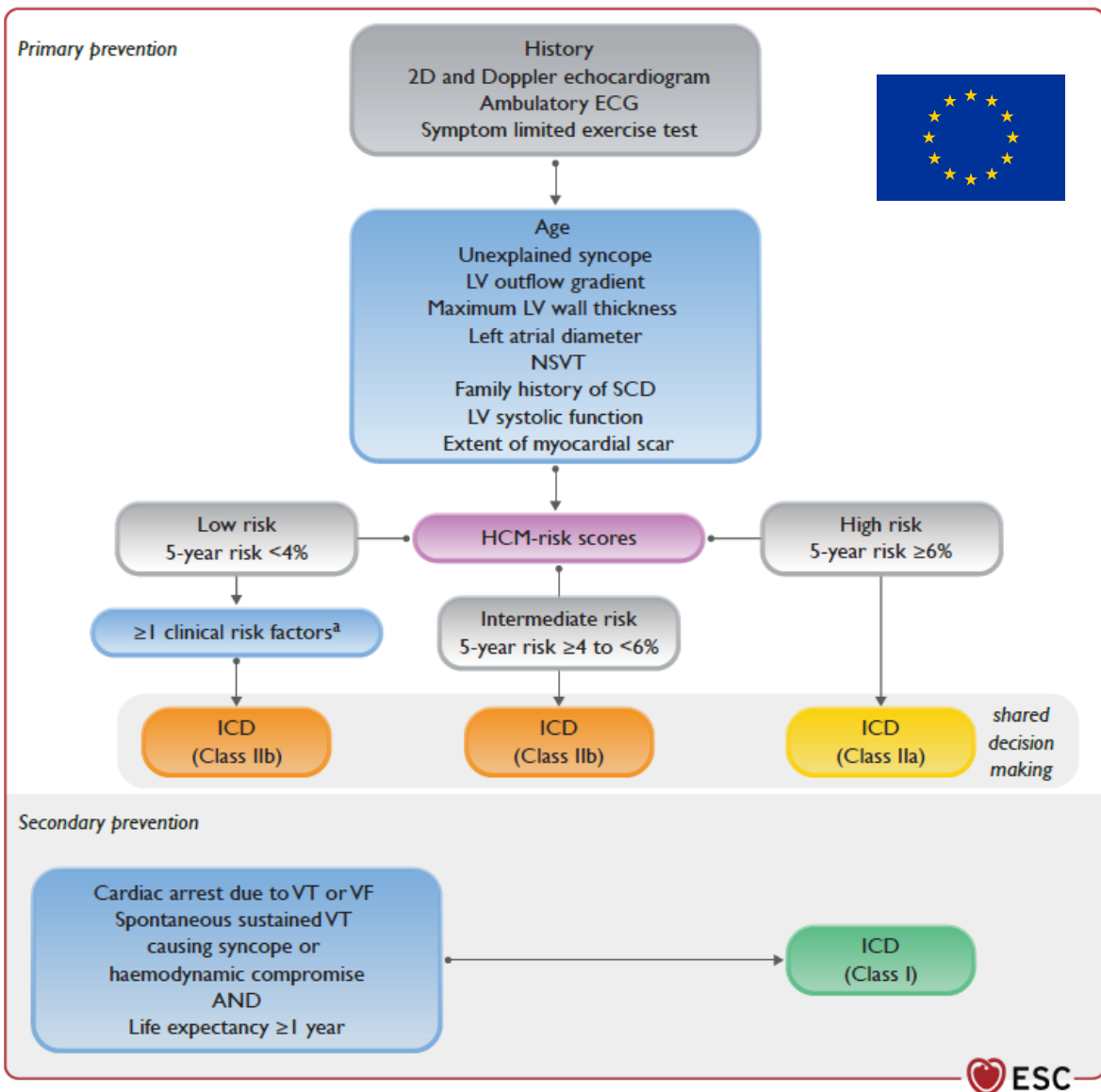
PSL

51.23

UOMO, 52 ANNI.
FAMILIARITÀ PER CMP-SD.; **Sincope da TVS**
ANALISI GENETICA: MUTAZIONE **PKP-2**.



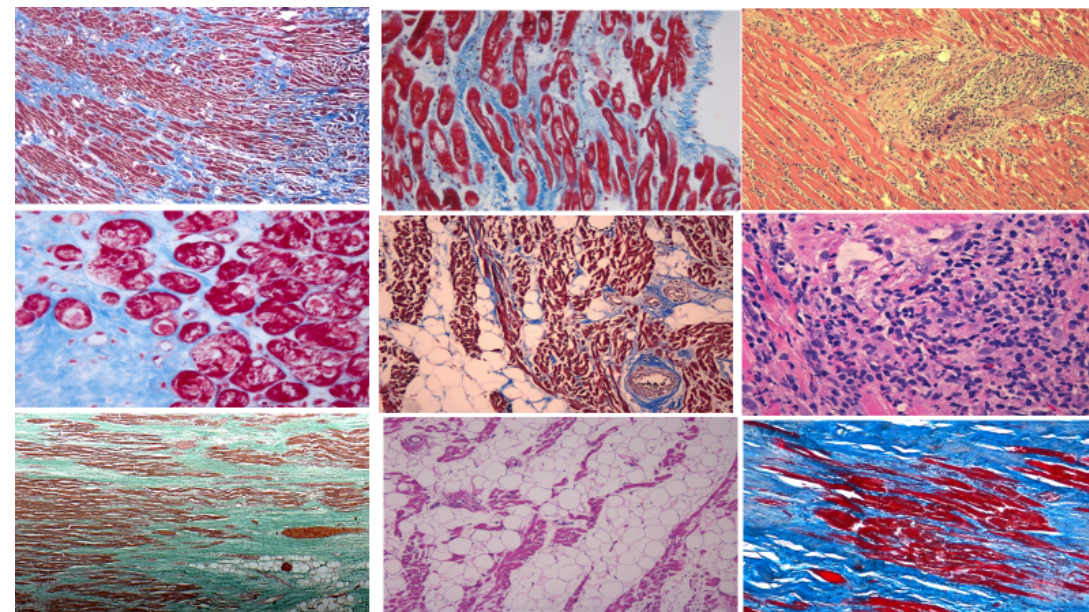
Current SCD risk stratification: ESC 2023/AHA 2024



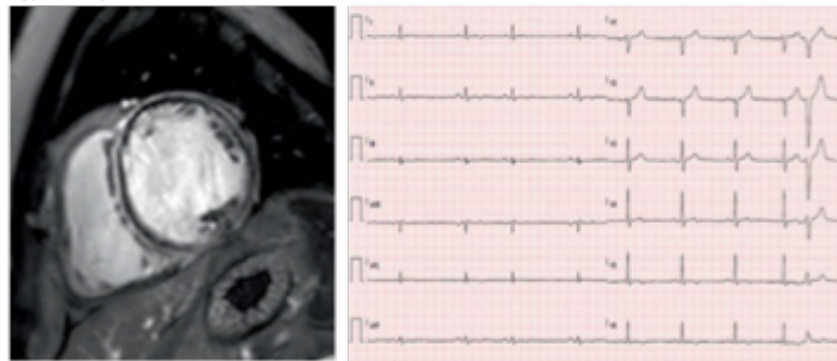
Eur Heart J. 2023 Oct 1;44(37):3503-3626

Pathophysiology of dilated cardiomyopathy: from mechanisms to precision medicine

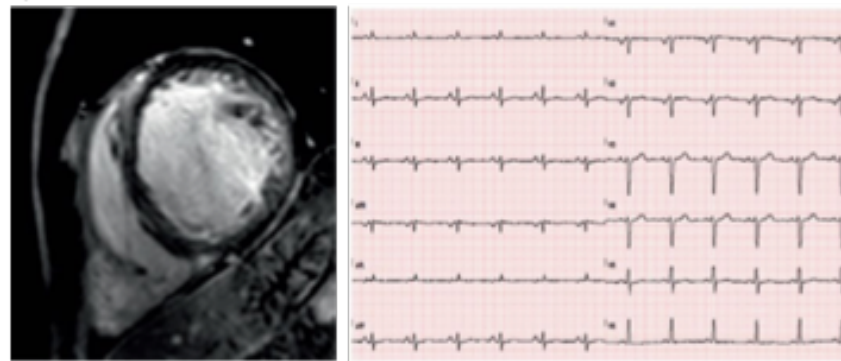
Marta Gigli¹, Davide Stolfo^{1,2}, Marco Merlo¹, Gianfranco Sinagra¹, Matthew R. G. Taylor³ & Luisa Mestroni⁴✉



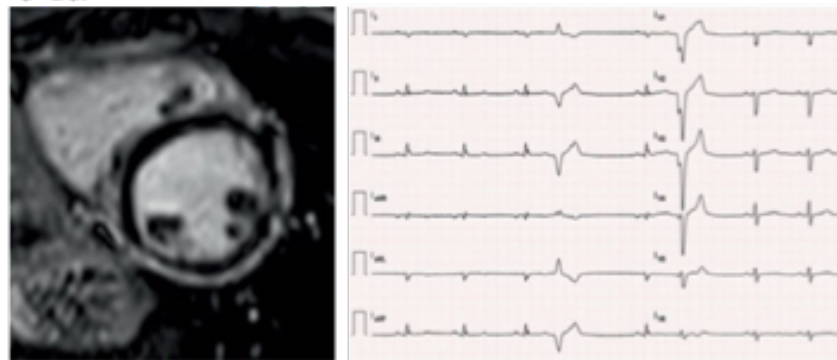
a *FLNC*



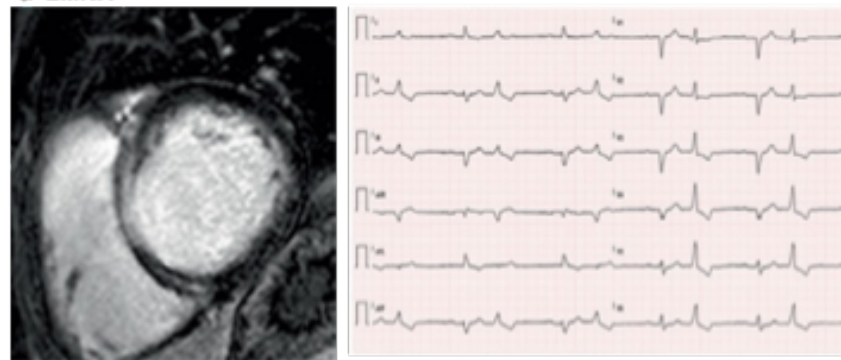
b *TTN*



c *DSP*



d *LMNA*



Arrhythmogenic Phenotype in Dilated Cardiomyopathy: Natural History and Predictors of Life-Threatening Arrhythmias

Anita Spezzacatene, MD; Gianfranco Sinagra, MD; Marco Merlo, MD; Giulia Barbati, PhD; Sharon L. Graw, PhD; Francesca Brun, MD; Dobromir Slavov, PhD; Andrea Di Lenarda, MD; Ernesto E. Salcedo, MD; Jeffrey A. Towbin, MD; Jeffrey E. Saffitz, MD, PhD; Frank I. Marcus, MD; Wojciech Zareba, MD; Matthew R. G. Taylor, MD, PhD; Luisa Mestroni, MD, FACC, FAHA, FESC; on behalf of the Familial Cardiomyopathy Registry

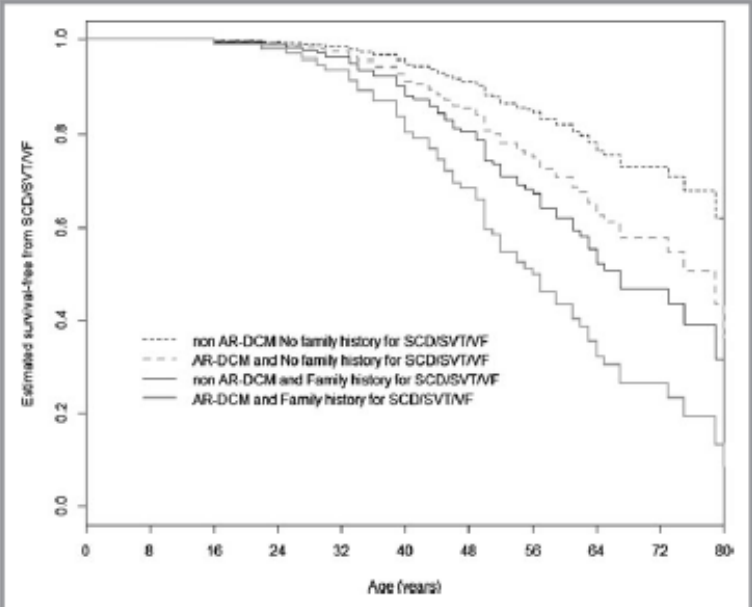
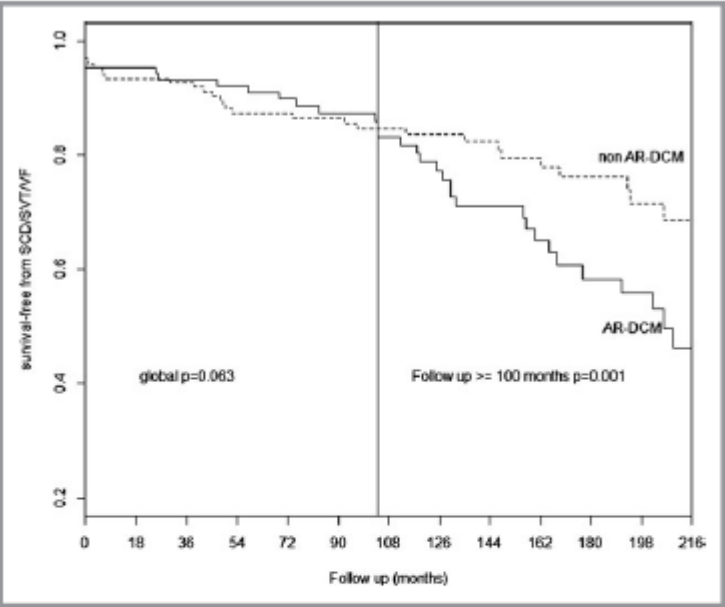
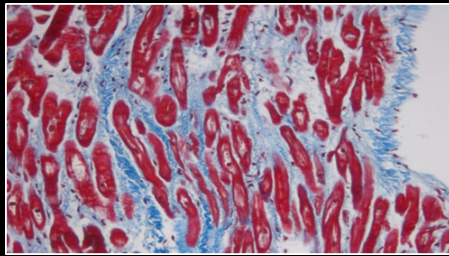


Table 1. Arrhythmic Profile of 109 AR-DCM Patients

Criteria	AR-DCM Patients, n (%)
NSVT (≥5 beats, ≥150 bpm)	43 (39.4)
≥1000 PVCs/24 h	90 (82.6)
≥50 Couplets/24 h	40 (36.7)
Syncope	8 (7.3)



UO CARDIOLOGIA
OSPEDALE TRIESTE
Echolab

CRT3/93
ED
06159
GUAD 71
COMP 70
91BPM

13CM
71HZ

E
P 1.6 3.2

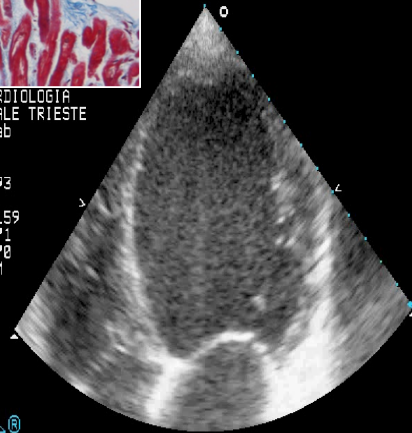
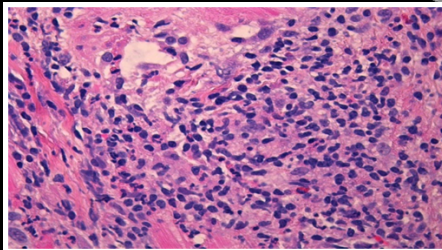


MI:1.6
S3 1.6/3.2
11 NOV 03
15:41:26
1/0/D/HS
UO CARDIOLOGIA
OSPEDALE TRIESTE
Echolab

CRT2624/77BP

06383
GUAD 91
COMP 49
98BPM

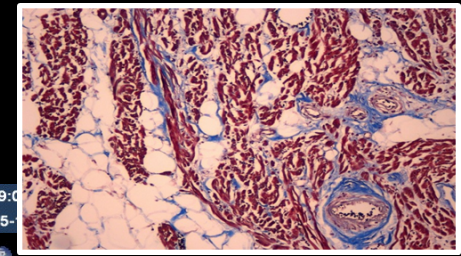
12CM
40HZ



PHILIPS 24/09/2009 09:00
INDEFINITO-1853 S5-

FR 50Hz
15cm
2D
55%
C 60
P Bassa
APen

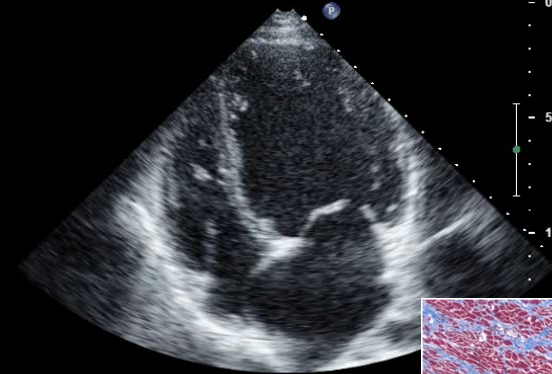
G
P 1.4 R 2.8



FR 49Hz
16cm

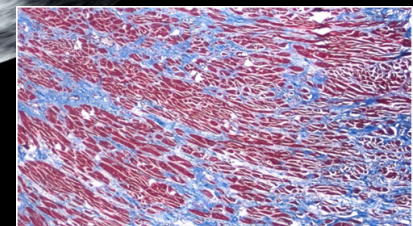
2D
58%
C 58
P Bassa
AGen

G
P 1.7 R 3.4



M3

0
5
10



JPEG
67 bpm

ARRHYTHMIC PREDICTORS IN DCM	
CLINICAL	- Etiological characterization - Personal and family history (syncope, familial history of SCD)
ECG and Holter ECG	- Fragmented QRS - Long QRS - Low QRS amplitude - Anterolateral T wave inversion - NSVT (≥ 5 beats, ≥ 150 bpm) - Frequent PVCs (1000/24h) and couplets ($\geq 50/24h$)
ECHOCARDIOGRAPHY	- LVEF $\leq 35\%$ - Reduced GLS
CMR	- LGE presence - LGE extent and location (i.e. septal and free-wall) - T1-mapping (increased T1 relaxation time)
GENETIC TESTING	- LMNA - FLNC, PLN, RBM20 - SCN5A - TTN *
ELECTROPHYSIOLOGICAL PARAMETERS	Abnormal mTWA test

Risk Stratification in Nonischemic Dilated Cardiomyopathy Using CMR Imaging

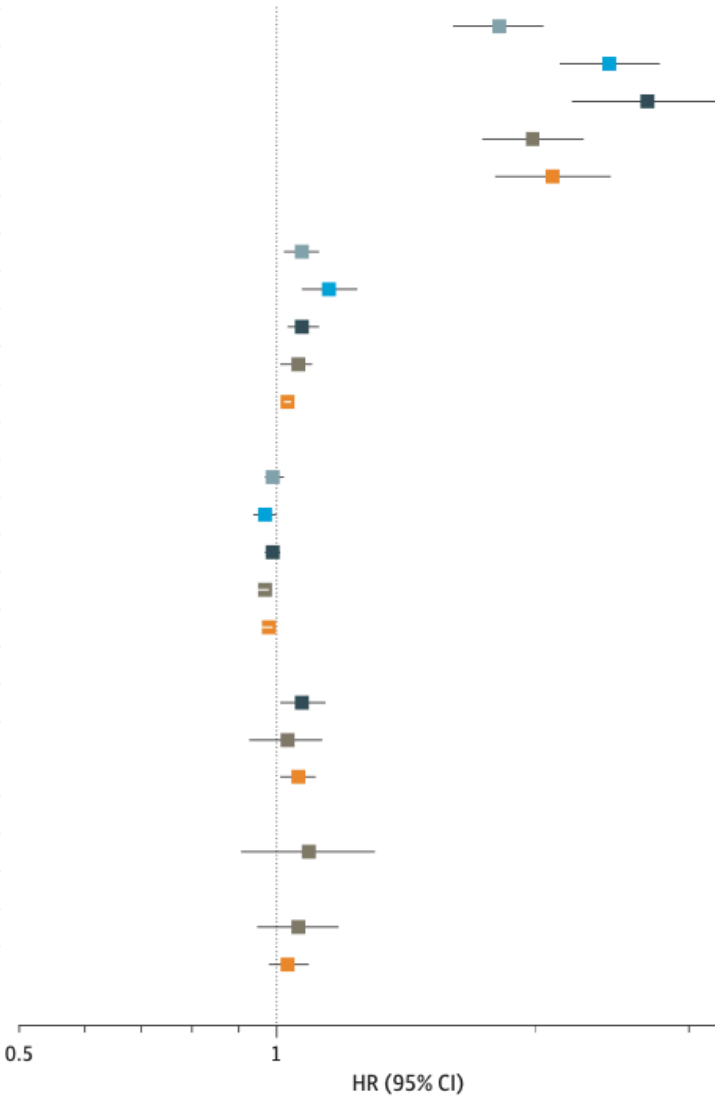
A Systematic Review and Meta-Analysis

Table. Study and Participant Characteristics

Study characteristic	Total population	Late gadolinium enhancement presence	Late gadolinium enhancement extent	LVEF	Native T1 mapping relaxation times	Extracellular volume fraction	Global longitudinal strain
No. of studies	103	96	28	47	7	3	9
No. of patients	29 687	27 590	7344	14 180	2461	1372	2226
Cardiac function, median (IQR)							
LVEF, %	29.5 (25.0-36.4)	29.5 (25.0-36.3)	28.4 (24.1-35.7)	28.0 (25.0-36.4)	30.7 (23.4-41.4)	40.7 (24.9-42.0)	23.7 (21.0-36.7)
LVEDVi, mL/m ²	130.6 (119.7-146.3)	129.3 (119.7-145.1)	138.4 (122.0-159.1)	136.8 (120.6-158.9)	142.1 (111.0-188.8)	112.0 (110.0-159.1)	136.8 (123.0-167.9)
LVEDV, mL	243.3 (211.5-272.6)	241.1 (210.0-270.0)	277.0 (259.1-284.3)	270.0 (244.6-286.8)	NA	NA	NA

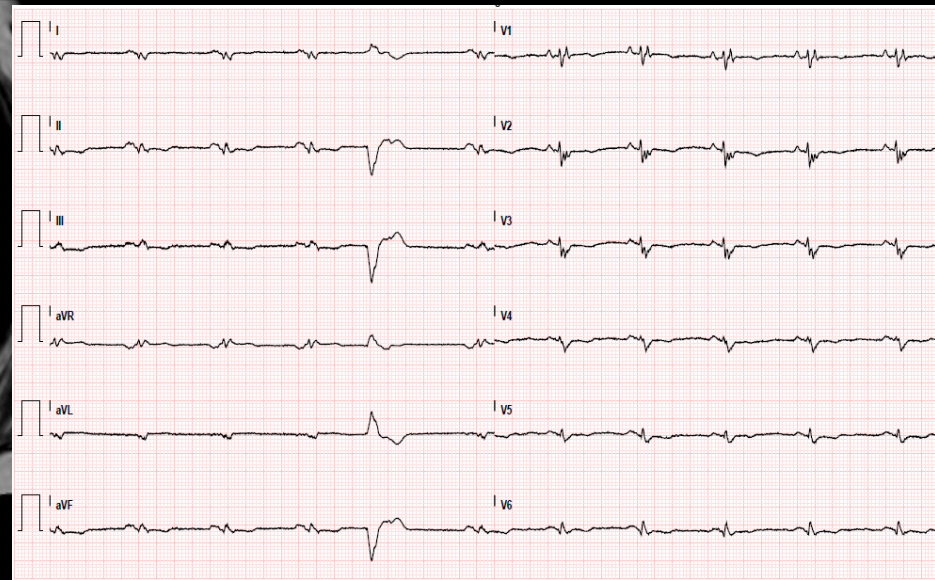
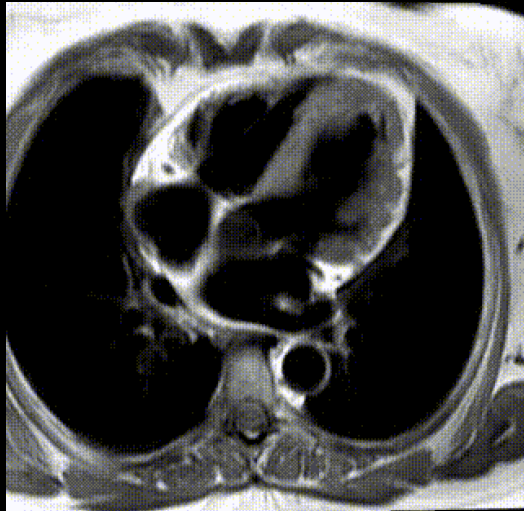
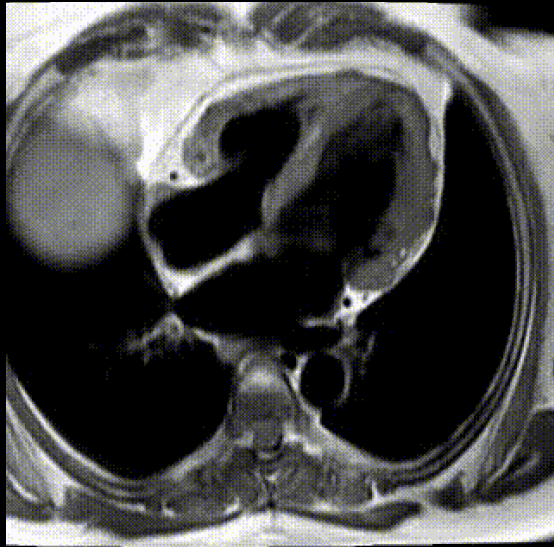
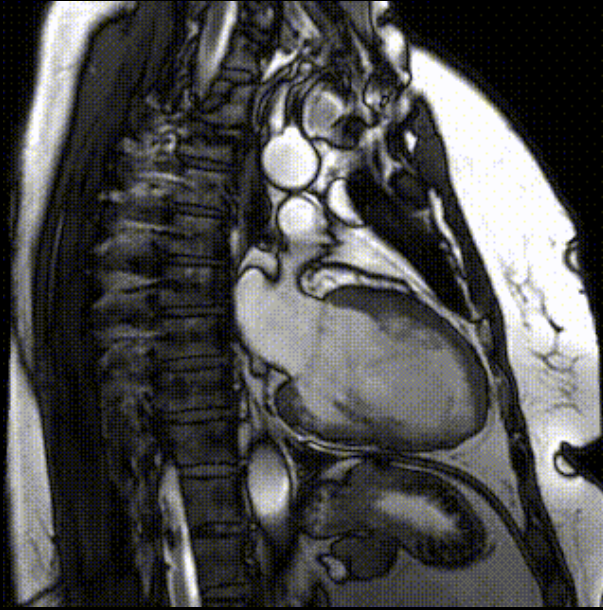
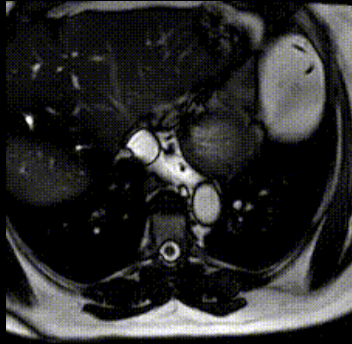
Figure 1. Cardiac Magnetic Resonance (CMR) Imaging Parameters and Clinical Outcomes

Parameter	Studies/ patients, No.	HR (95% CI)
Late gadolinium enhancement presence (yes/no)		
All-cause mortality	23/9738	1.81 (1.60-2.04)
Cardiovascular mortality	19/5228	2.43 (2.13-2.78)
Arrhythmia	40/13 791	2.69 (2.20-3.30)
Heart failure	32/9464	1.98 (1.73-2.27)
MACE	54/12 040	2.09 (1.79-2.44)
Late gadolinium enhancement extent (per 1%)		
All-cause mortality	4/1852	1.07 (1.02-1.12)
Cardiovascular mortality	3/1323	1.15 (1.07-1.24)
Arrhythmia	9/2086	1.07 (1.03-1.12)
Heart failure	6/1686	1.06 (1.01-1.10)
MACE	13/3004	1.03 (1.02-1.04)
Left ventricular ejection fraction (per 1%)		
All-cause mortality	5/3220	0.99 (0.97-1.02)
Cardiovascular mortality	7/3522	0.97 (0.94-1.00)
Arrhythmia	12/5055	0.99 (0.97-1.01)
Heart failure	10/4576	0.97 (0.95-0.98)
MACE	24/5446	0.98 (0.96-0.99)
T1 relaxation time (per 10 ms)		
Arrhythmia	5/1778	1.07 (1.01-1.14)
Heart failure	3/2198	1.03 (0.93-1.13)
MACE	3/962	1.06 (1.01-1.11)
Extracellular volume (per 1%)		
Heart failure	3/1372	1.09 (0.91-1.30)
Global longitudinal strain (per 1%)		
Heart failure	3/1001	1.06 (0.95-1.18)
MACE	7/1397	1.03 (0.94-1.14)



Pooled hazard ratios (HRs) for the association between CMR imaging–derived measurements of late gadolinium enhancement (LGE) presence, LGE extent, left ventricular ejection fraction, native T1 relaxation times, extracellular volume

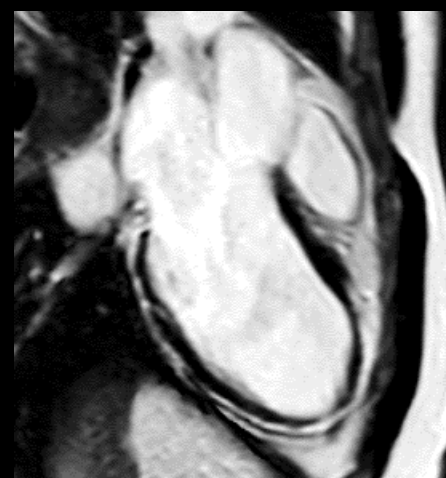
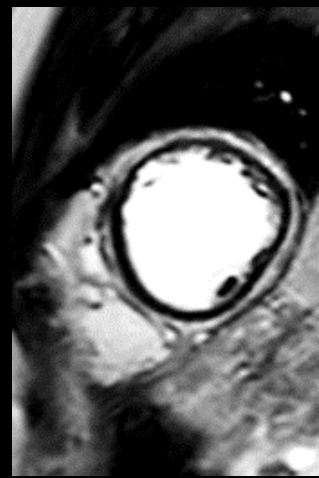
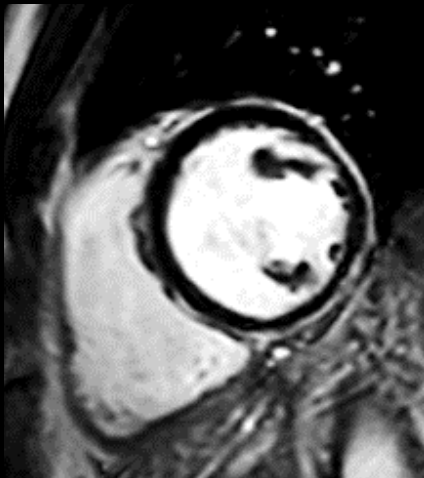
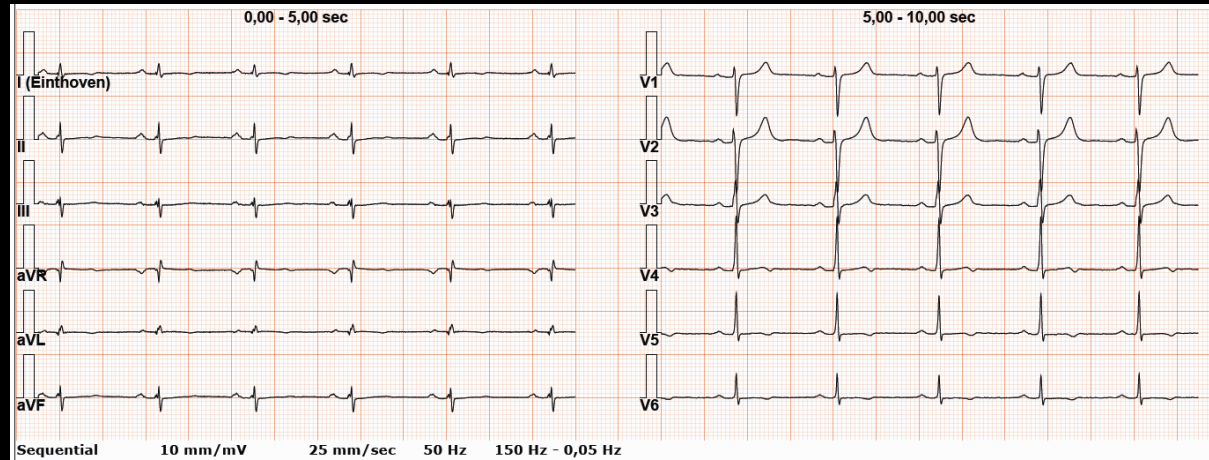
fraction, and global longitudinal strain and clinical outcomes when 3 or more studies were available for meta-analysis. MACE indicates major adverse cardiovascular events.

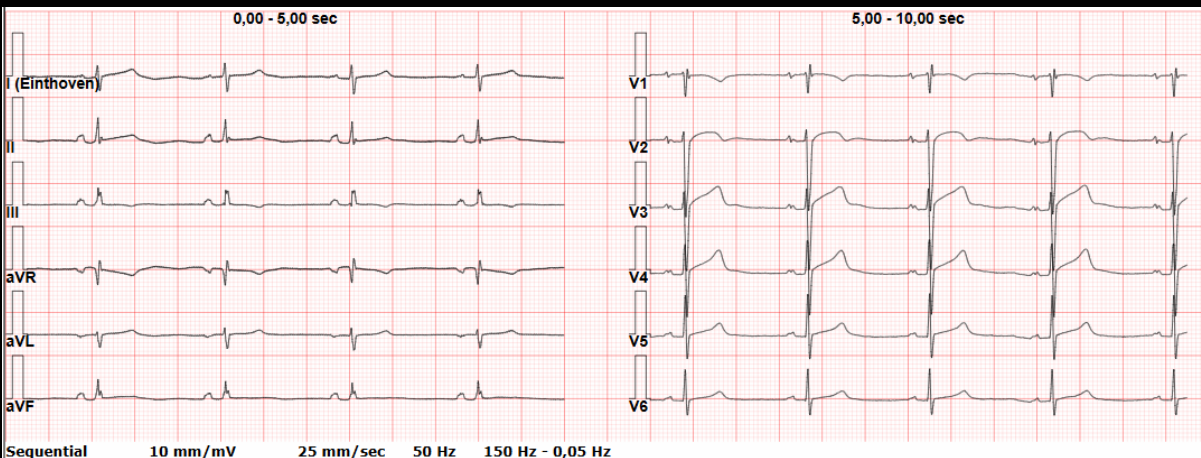
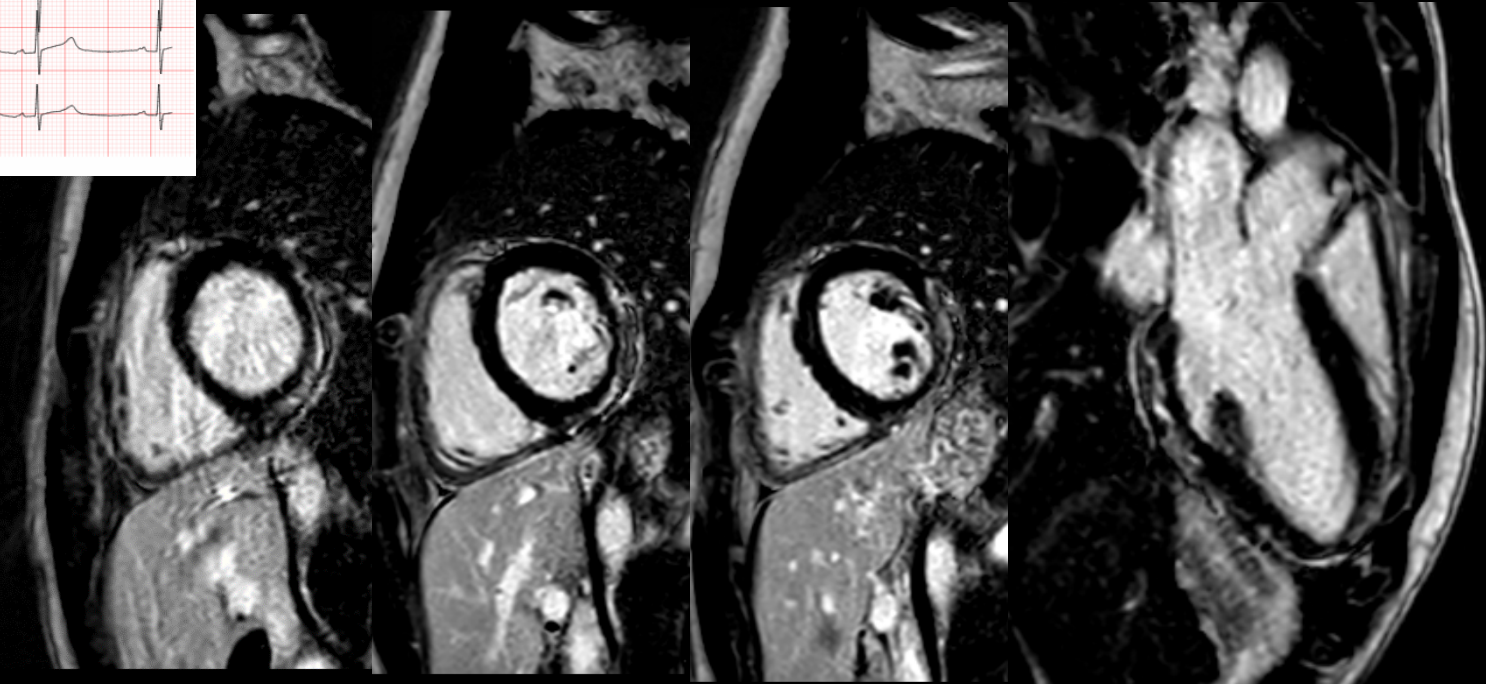
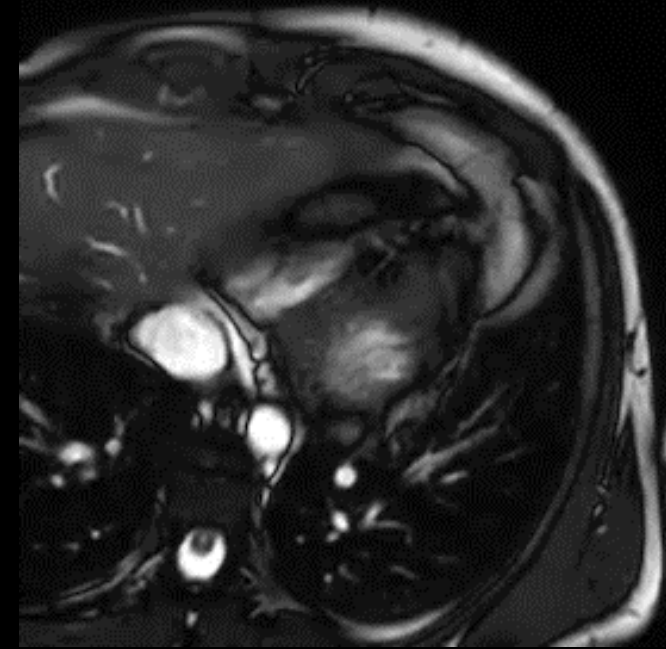


UOMO, 51 ANNI; NYHA III; FEVsin 28%

FAMILIARITÀ PER CMPD-SC refrattario E SCD

ANALISI GENETICA: MUTAZIONE FLNC



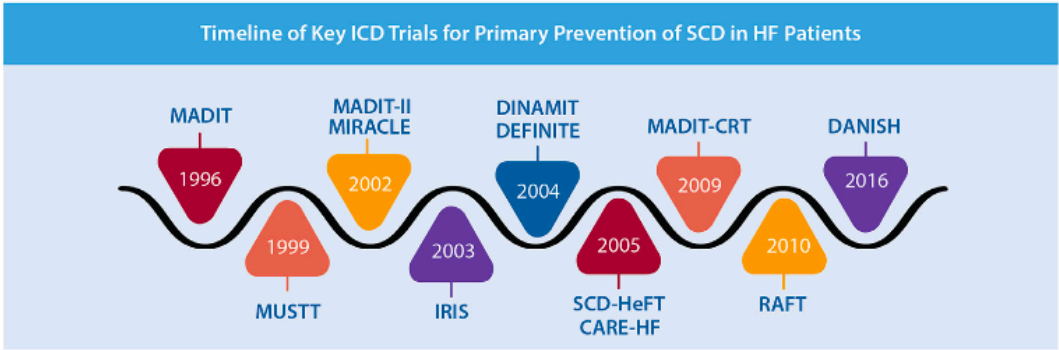


UOMO, 27 ANNI.

ACR DA FV DURANTE PARTITA DI CALCIO.

ANALISI GENETICA: NON VARIANTI PATOGENETICHE, MA PADRE e FRATELLO MOSTRERANNO IL FENOTIPO DI MALATTIA (ECG, RM e ARITMIE)

Sudden Cardiac Death Trials



Yehya A, et al. JACC Heart Fail. 2025;13(1):1–13.

DANISH-Trial-Age analysis (2017); All Cause Mortality

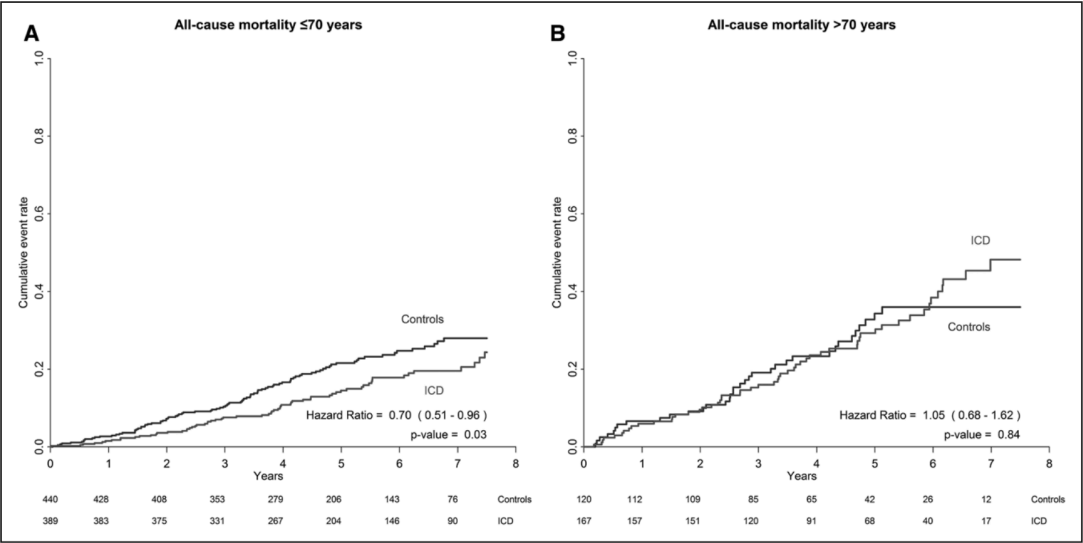


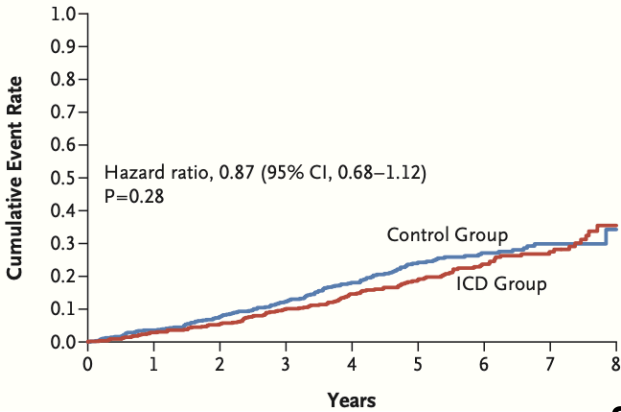
Figure 4. All-cause mortality for the entire population in (A) patients ≤70 years old and (B) patients >70 years old. Black lines represent patients in the control group; gray lines, patients randomized to implantable cardioverter-defibrillator (ICD) treatment.

Circulation. 2017;136:1772–1780.

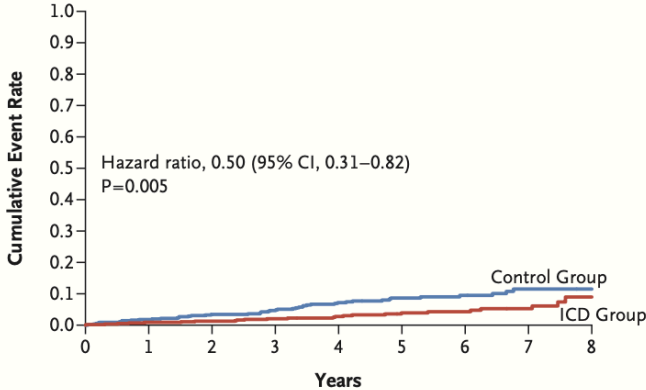
DANISH-Trial (2016)

-Inclusion criteria: EF<35% **non-ischemic**.
-Follow up: 67 months.

A Death from Any Cause

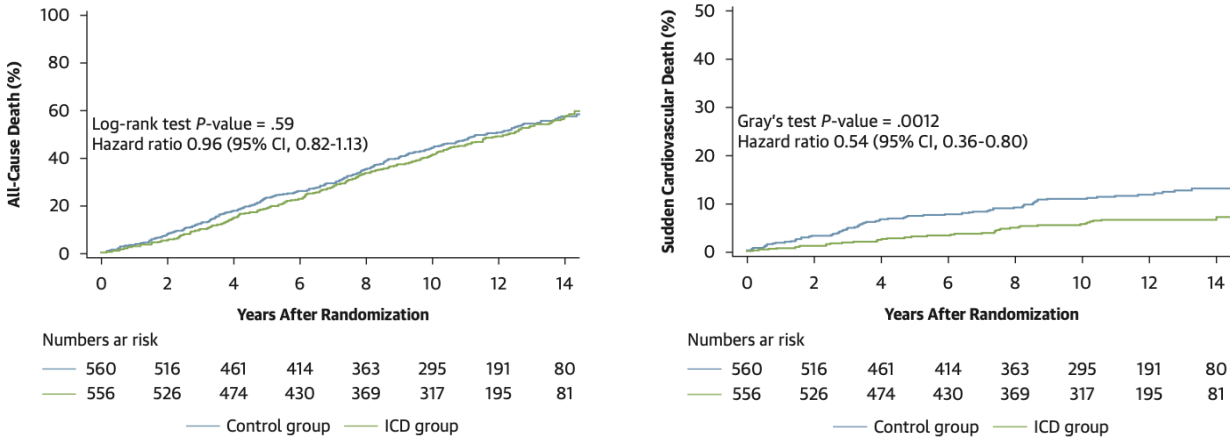


C Sudden Cardiac Death



2016 N Engl J Med 2016;375:1221-1230

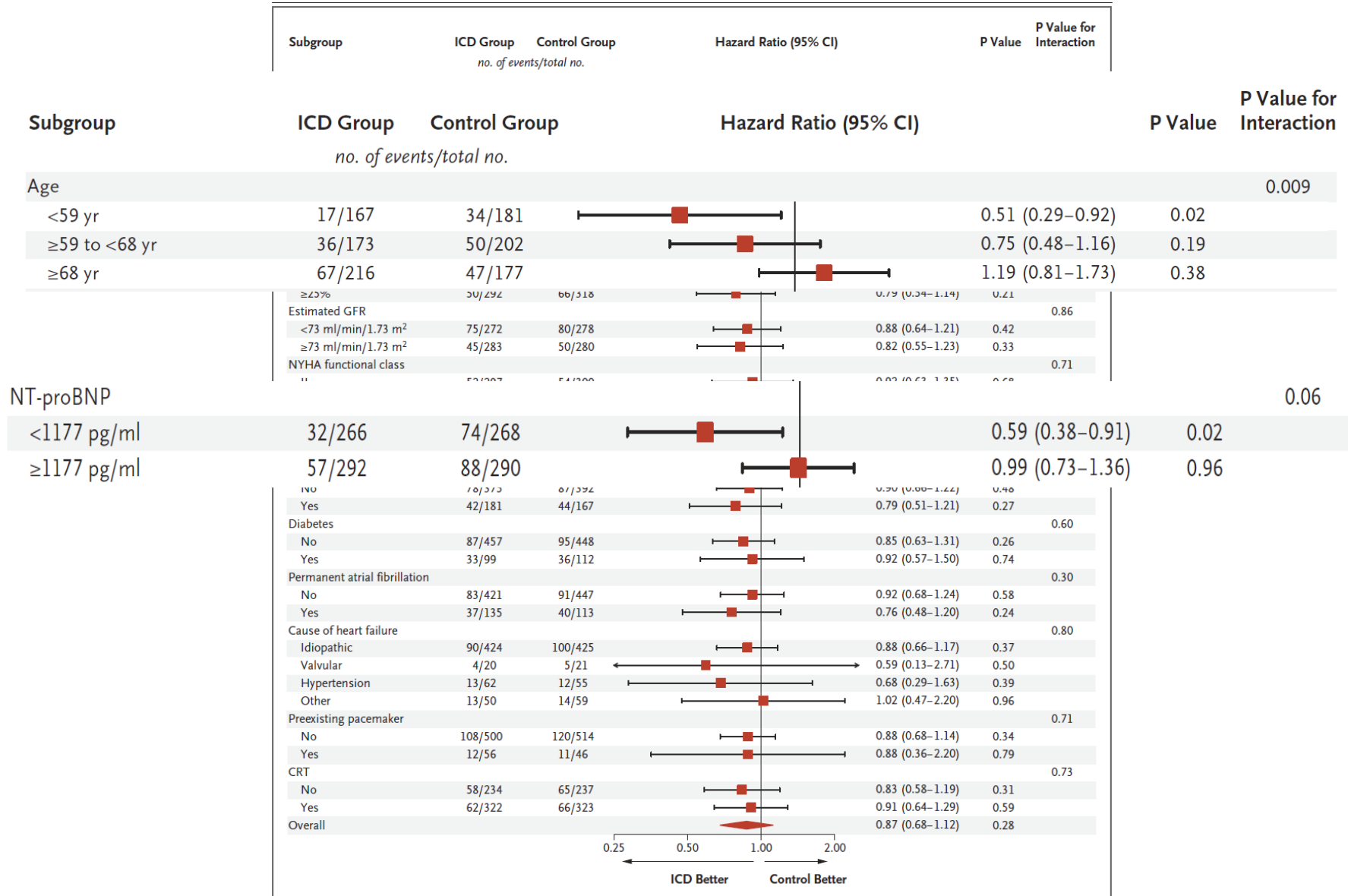
Extended Follow-Up Analysis of DANISH (2025)



Overall Age, years	Events (%)		Hazard ratio (95% CI)
	ICD	Controls	
	294 (52.9%)	299 (53.4%)	0.96 (0.82-1.13)
>70	123 (73.7%)	95 (79.2%)	0.92 (0.70-1.22)
≤70	171 (44.0%)	204 (46.4%)	0.89 (0.73-1.10)

Extended Follow-Up Analysis of DANISH-JACC 2025 JACC; 2025

Defibrillator Implantation in Patients with Nonischemic
Systolic Heart Failure



HFrEF – implantable devices: ICD

ESC GUIDELINES

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)

Primary prevention		
An ICD is recommended to reduce the risk of sudden death and all-cause mortality in patients with symptomatic HF (NYHA class II–III) of an ischaemic aetiology (unless they have had a MI in the prior 40 days—see below), and an LVEF $\leq 35\%$ despite ≥ 3 months of OMT, provided they are expected to survive substantially longer than 1 year with good functional status. ^{161,165}	I	A
An ICD should be considered to reduce the risk of sudden death and all-cause mortality in patients with symptomatic HF (NYHA class II–III) of a non-ischaemic aetiology, and an LVEF $\leq 35\%$ despite ≥ 3 months of OMT, provided they are expected to survive substantially longer than 1 year with good functional status. ^{161,166,167}	IIa	A

«...it should be remembered that NICM is a heterogeneous condition, and certain subgroups (e.g. laminopathies, sarcoidosis) are at higher risk of sudden death and therefore merit careful consideration of ICD implantation.»

AHA/ACC/HFSA CLINICAL PRACTICE GUIDELINE

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

COR	LOE	Recommendations
1	A	1. In patients with nonischemic DCM or ischemic heart disease at least 40 days post-MI with LVEF $\leq 35\%$ and NYHA class II or III symptoms on chronic GDMT, who have reasonable expectation of meaningful survival for >1 year, ICD therapy is recommended for primary prevention of SCD to reduce total mortality. ^{1–9}

«...specific arrhythmogenic genetic variants such as **LMNA/C**, **desmosomal proteins**, **phospholamban**, and **Filamin-C** carry implications for implantation of ICDs for primary prevention of sudden death even in patients who have LVEF $>35\%$, or <3 months of GDMT.»

Value Statement: High Value (A)	2. A transvenous ICD provides high economic value in the primary prevention of SCD particularly when the patient's risk of death caused by ventricular arrhythmia is deemed high and the risk of nonarrhythmic death (either cardiac or noncardiac) is deemed low based on the patient's burden of comorbidities and functional status. ^{10–15}
--	--

High-risk Genotype in DCM/NDLVC

Table 21 High-risk genotypes and associated predictors of sudden cardiac death

Gene	Annual SCD rate	Predictors of SCD
<i>LMNA</i> ^{185,186,438,541,865,878,879}	5–10%	Estimated 5-year risk of life-threatening arrhythmia using <i>LMNA</i> risk score (https://lmna-risk-vta.fr)
<i>FLNC</i> -truncating variants ^{866,867,880}	5–10%	LGE on CMR LVEF < 45%
<i>TMEM43</i> ^{868,881}	5–10%	Male Female and any of the following: LVEF <45%, NSVT, LGE on CMR, >200 VE on 24h Holter ECG
<i>PLN</i> ^{542,882,883}	3–5%	Estimated 5-year risk of life-threatening arrhythmia using <i>PLN</i> risk score (https://plnriskcalculator.shinyapps.io/final_shiny) LVEF < 45% LGE on CMR NSVT
<i>DSP</i> ^{185,186}	3–5%	LGE on CMR LVEF < 45%
<i>RBM20</i> ⁸⁶⁹	3–5%	LGE on CMR LVEF < 45%

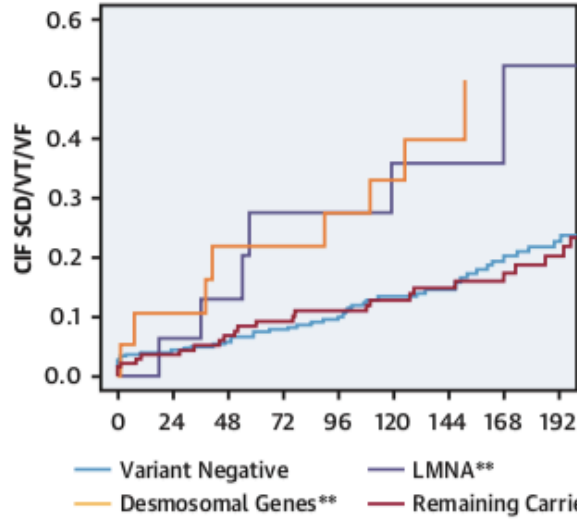
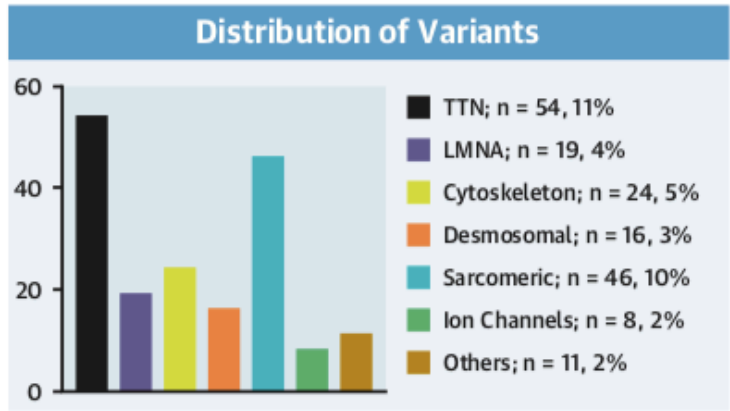
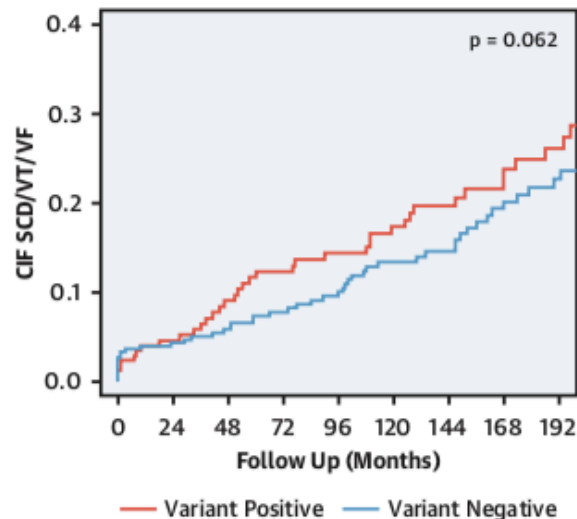
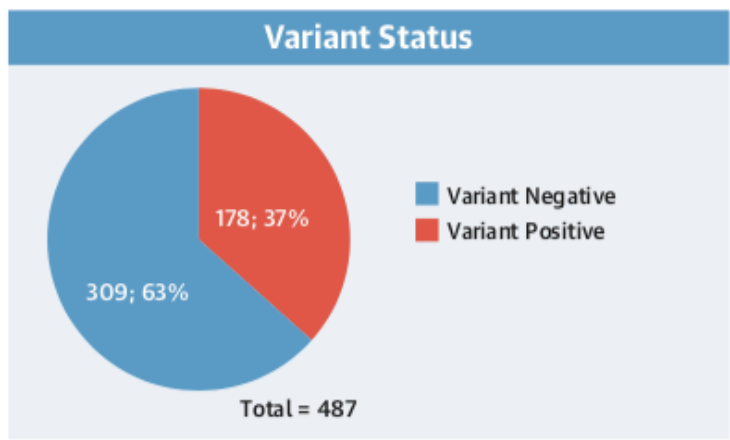
© ESC 2023

Genetic Risk of Arrhythmic Phenotypes in Patients With Dilated Cardiomyopathy

Marta Gigli, MD,^{a,b,*} Marco Merlo, MD,^{a,*} Sharon L. Graw, PhD,^b Giulia Barbati, PhD,^c Teisha J. Rowland, PhD,^b Dobromir B. Slavov, PhD,^b Davide Stolfo, MD,^a Mary E. Haywood, PhD,^b Matteo Dal Ferro, MD,^a Alessandro Altinier, MD,^a Federica Ramani, PhD,^a Francesca Brun, MD,^a Andrea Cocciolo, MD,^{a,b} Ilaria Puggia, MD,^{a,b} Gaetano Morea, MD,^{a,b} William J. McKenna, MD, DSc,^{d,e} Francisco G. La Rosa, MD,^f Matthew R.G. Taylor, MD, PhD,^b Gianfranco Sinagra, MD,^a Luisa Mestroni, MD^b



CENTRAL ILLUSTRATION Effect of Genotype on Outcome in Dilated Cardiomyopathy



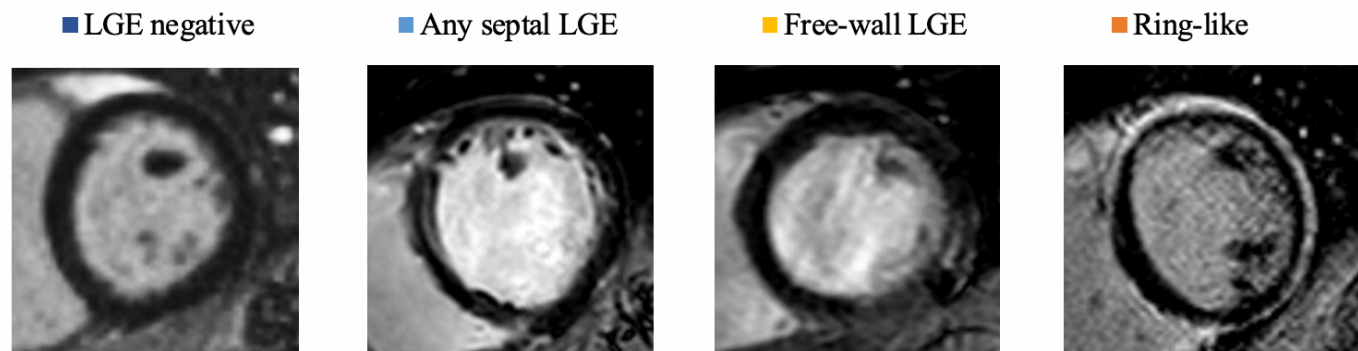
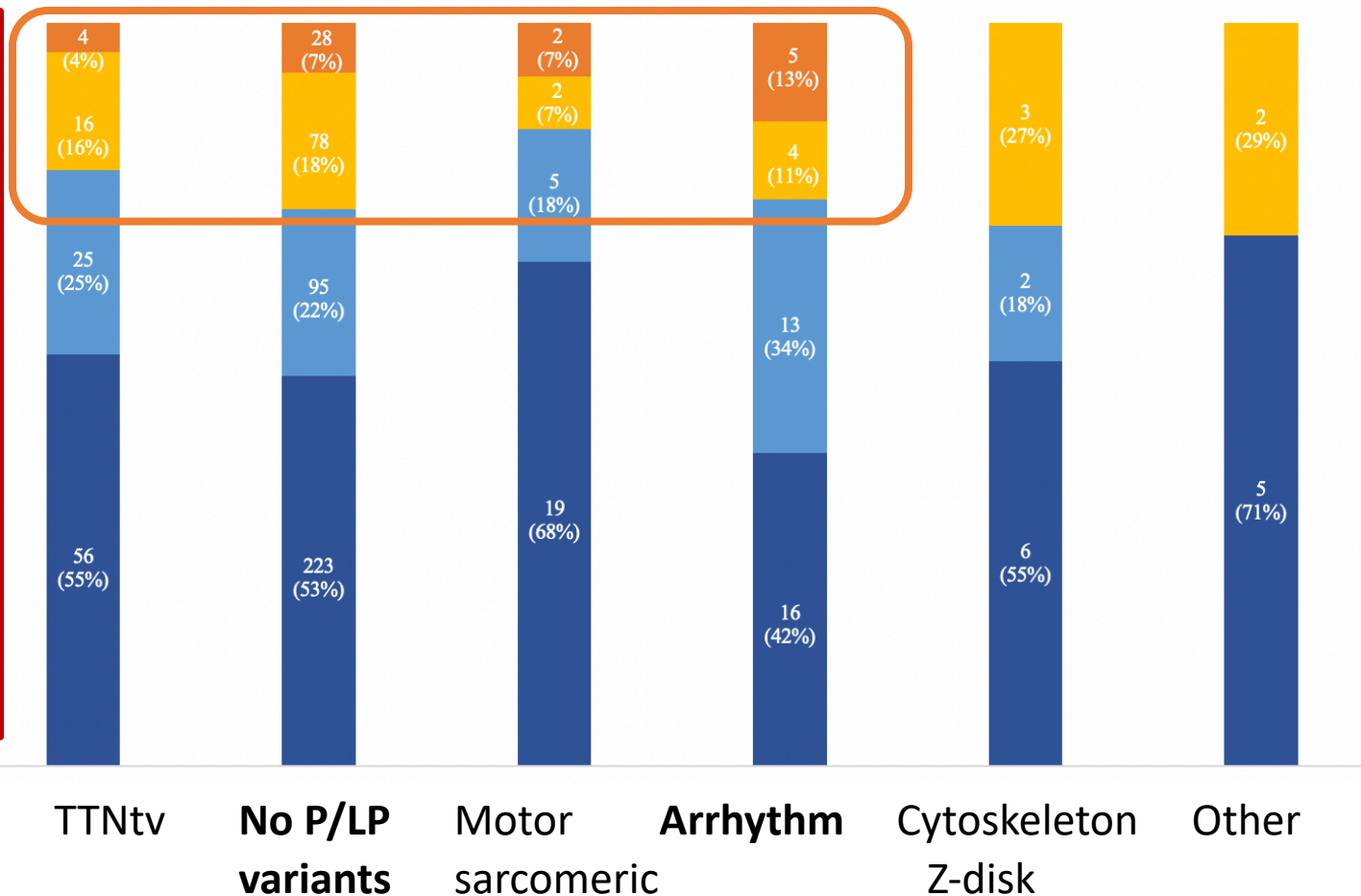
Gigli M., Sinagra G et al. J Am Coll Cardiol 2019; 74:1480

616 patients
(289 Trieste cohort, 303
Maastricht cohort, 24
Denver cohort)

CMR + genetic analysis

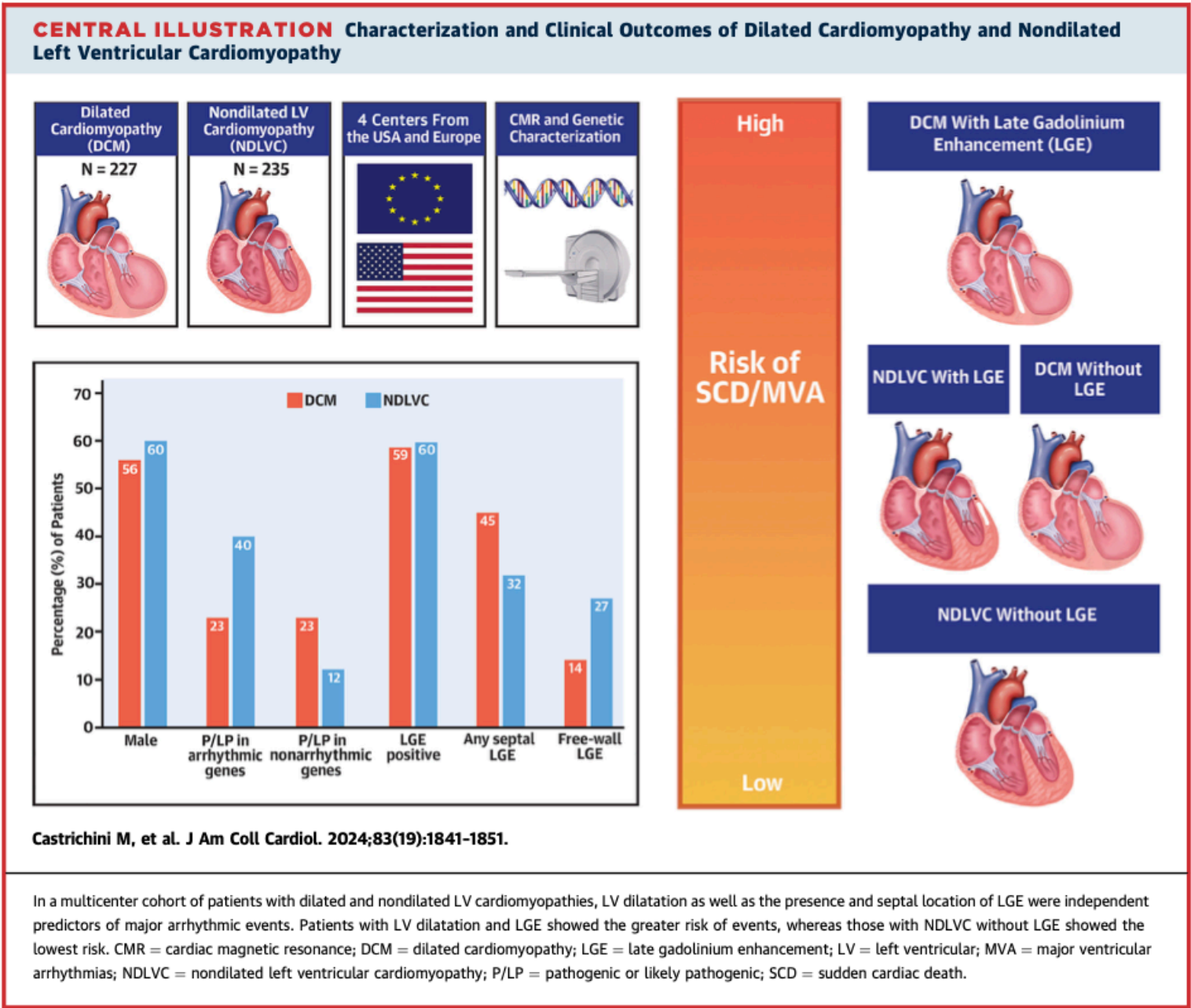
462 DCM, 154 NDLVC

Mean age 51 ± 14 years
209 (34%) females



Setti, Iseppi, Sinagra et al,
EurJHF 2025, accepted

Magnetic Resonance Imaging
Characterization and Clinical Outcomes
of Dilated and Arrhythmogenic
Left Ventricular Cardiomyopathies



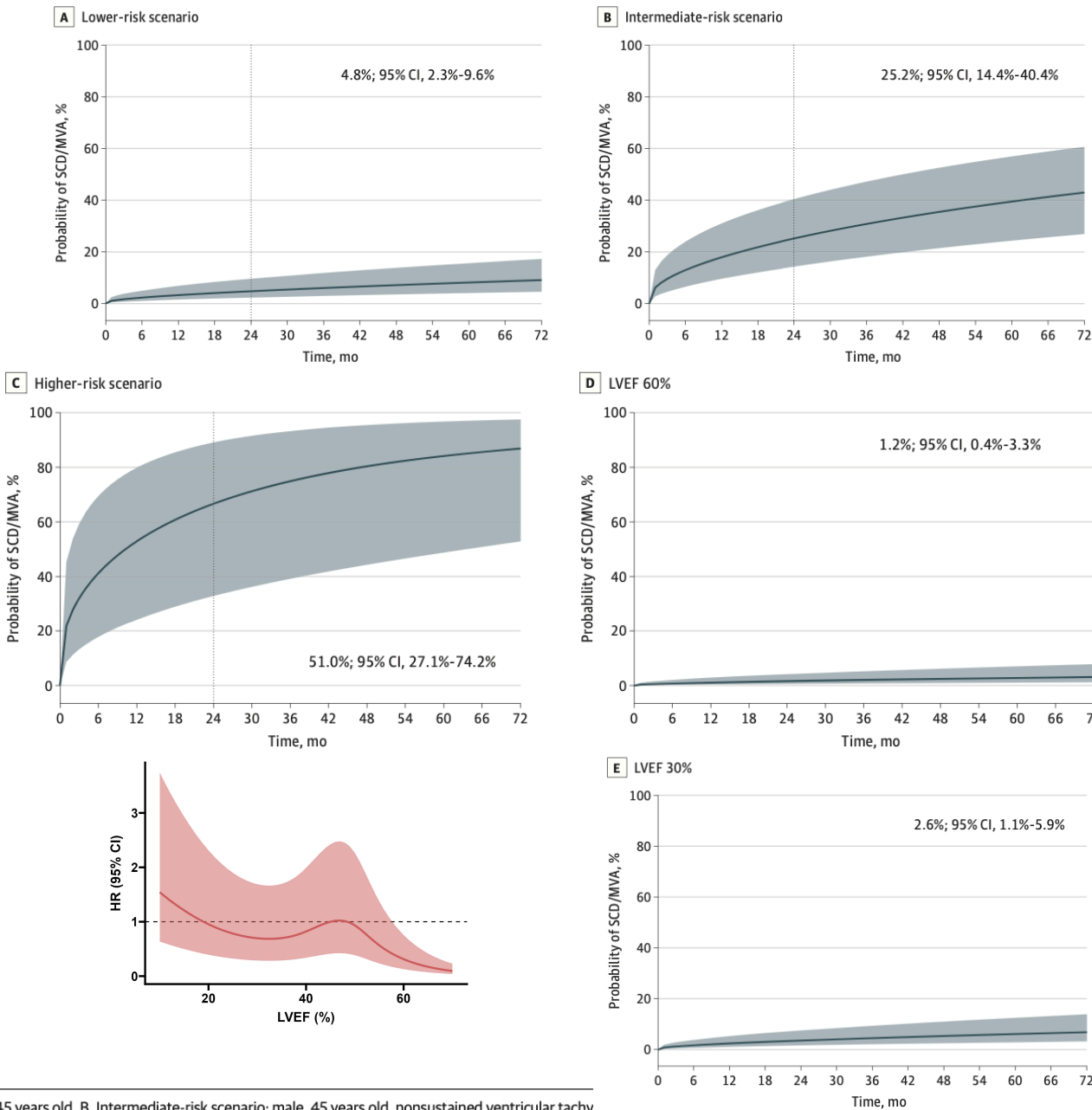
Arrhythmic Risk Stratification of Carriers of Filamin C Truncating Variants

Table 2. Results of Univariable and Multivariable Cause-Specific Royston-Parmar Analysis in the Overall Imputed Cohort Generating The Predictive Model for the Sudden Cardiac Death (SCD)/Major Ventricular Arrhythmia (MVA) Risk Estimation

Characteristic	Univariable		Multivariable	
	HR (95% CI) ^a	P value	HR (95% CI)	P value
Proband status	3.17 (1.97-5.09)	<.001	NA	NA
Age (for 1-y increase)	1.02 (1.01-1.04)	.01	1.02 (1.1-1.14)	.03
Male sex	2.60 (1.52-4.45)	.001	2.95 (1.64-5.32)	<.001
Variant mapping				
ABD	1.74 (0.60-5.06)	.31	NA	NA
ROD1	1 [Reference]	NA	NA	NA
ROD2	1.73 (0.85-3.50)	.13	NA	NA
Dimerization	0.89 (0.44-1.81)	.75	NA	NA
Variant mapping				
Z-line	0.83 (0.43-1.61)	.58	NA	NA
Family history cardiomyopathy	0.99 (0.56-1.77)	.92	NA	NA
Family history SCD	0.93 (0.55-1.58)	.91	NA	NA
Phenotype negative	0.15 (0.04-0.55)	.01	NA	NA
Syncope	3.74 (2.22-6.29)	<.001	2.62 (1.42-4.82)	.002
AF	1.29 (0.70-2.40)	.61	NA	NA
AVB	2.69 (1.31-5.53)	.007	NA	NA
LBBB	1.93 (0.97-3.87)	.08	NA	NA
RBBB	2.18 (0.89-5.37)	.07	NA	NA
NYHA	1.05 (0.76-1.46)	.97	NA	NA
Negative anterior T waves	1.50 (0.79-2.84)	.21	NA	NA
NSVT	3.21 (1.98-5.21)	<.001	2.02 (1.09-3.75)	.03
LVEF (cubic spline), ^b %		<.001		.04
30 vs 45	0.73 (0.32-1.68)	NA	0.70 (0.29-1.69)	NA
60 vs 45	0.20 (0.09-0.46)	NA	0.30 (0.13-0.79)	NA
LVEDD	1.04 (1.01-1.07)	.01	NA	NA
RVD	1.29 (0.71-2.36)	.54	NA	NA
CMR LGE % (No.) ^c	2.78 (1.04-7.40)	.04	1.48 (0.50-4.34)	.48

Gigli M. Sinagra G et al JAMA Cardiol. 2025:e245543

Figure 3. Examples of Low, Intermediate, and High Estimated Risk of Sudden Cardiac Death (SCD)/Major Ventricular Arrhythmias (MVA) Based on the Obtained Predictive Model and Comparison Between Low vs Normal Left Ventricular Ejection Fraction (LVEF) in Absence of Other Risk Factors



A, Lower-risk scenario: female, 45 years old. B, Intermediate-risk scenario: male, 45 years old, nonsustained ventricular tachy male, 55 years old, history of syncope, NSVT, and LVEF 53%. D, LVEF 60%. E, LVEF 30%. The risk calculator is available online.²³



ESC

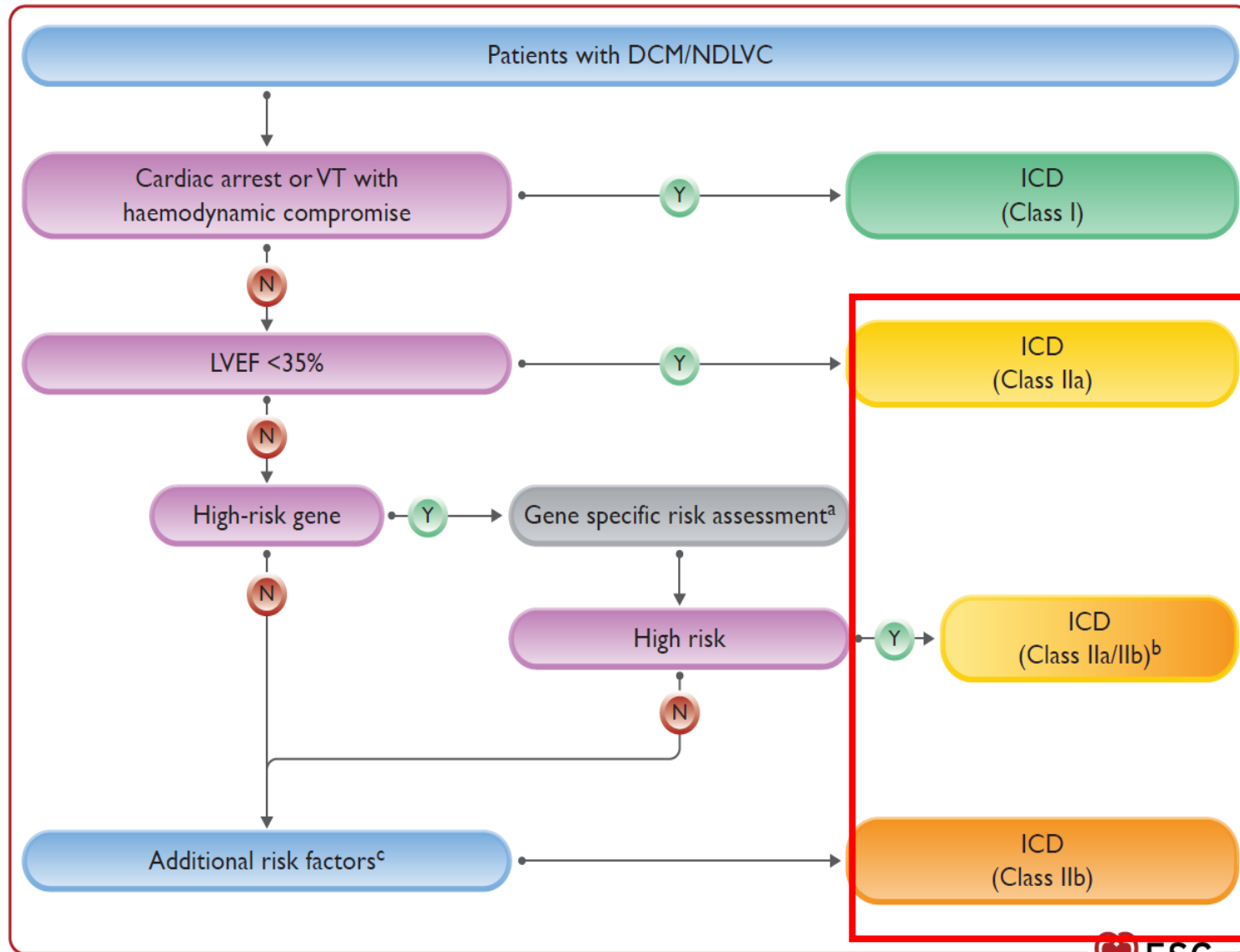
European Society
of Cardiology

European Heart Journal (2023) 00, 1–124

<https://doi.org/10.1093/eurheartj/ehad194>

2023 ESC Guidelines for the management of cardiomyopathies

Developed by the task force on the management of cardiomyopathies of the European Society of Cardiology (ESC)

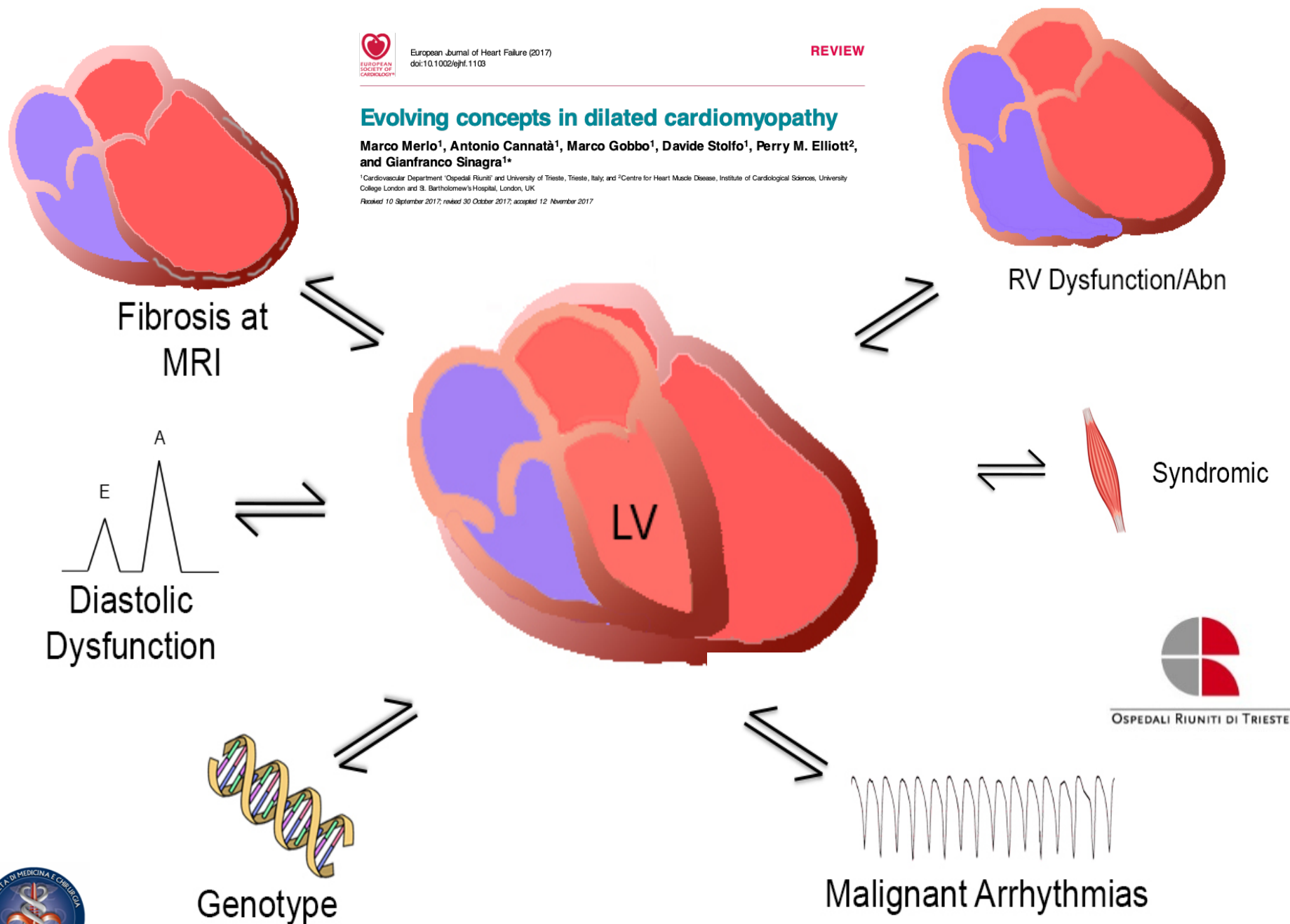


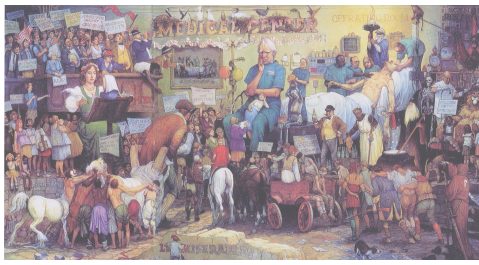
Evolving concepts in dilated cardiomyopathy

Marco Merlo¹, Antonio Cannatà¹, Marco Gobbo¹, Davide Stolfo¹, Perry M. Elliott²,
and Gianfranco Sinagra^{1*}

¹Cardiovascular Department 'Ospedal Riuniti' and University of Trieste, Trieste, Italy; and ²Centre for Heart Muscle Disease, Institute of Cardiological Sciences, University College London and St. Bartholomew's Hospital, London, UK

Received 10 September 2017; revised 30 October 2017; accepted 12 November 2017





".... specializzazione che spesso frammenta i contesti, la globalità, la complessità. La specializzazione "as-trae" ossia estrae un oggetto dal suo insieme, ne rifiuta i legami e le interconnessioni con l'ambiente, lo inserisce in un settore concettuale astratto che è quello della disciplina compartimentata, in cui le frontiere spezzano arbitrariamente la sistemicità e la multidimensionalità dei fenomeni..."
(Edgar Morin 2003)