

# PLACE 2022

## CMPD “non ischemica”: stato dell’arte

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# DISCLOSURE INFORMATION

Prof. Gianfranco Sinagra

Novartis, Bayer, Astrazeneca, Boston Scientific, Vifor Pharma, Menarini, Akcea Therapeutics

**Relatore a congressi**

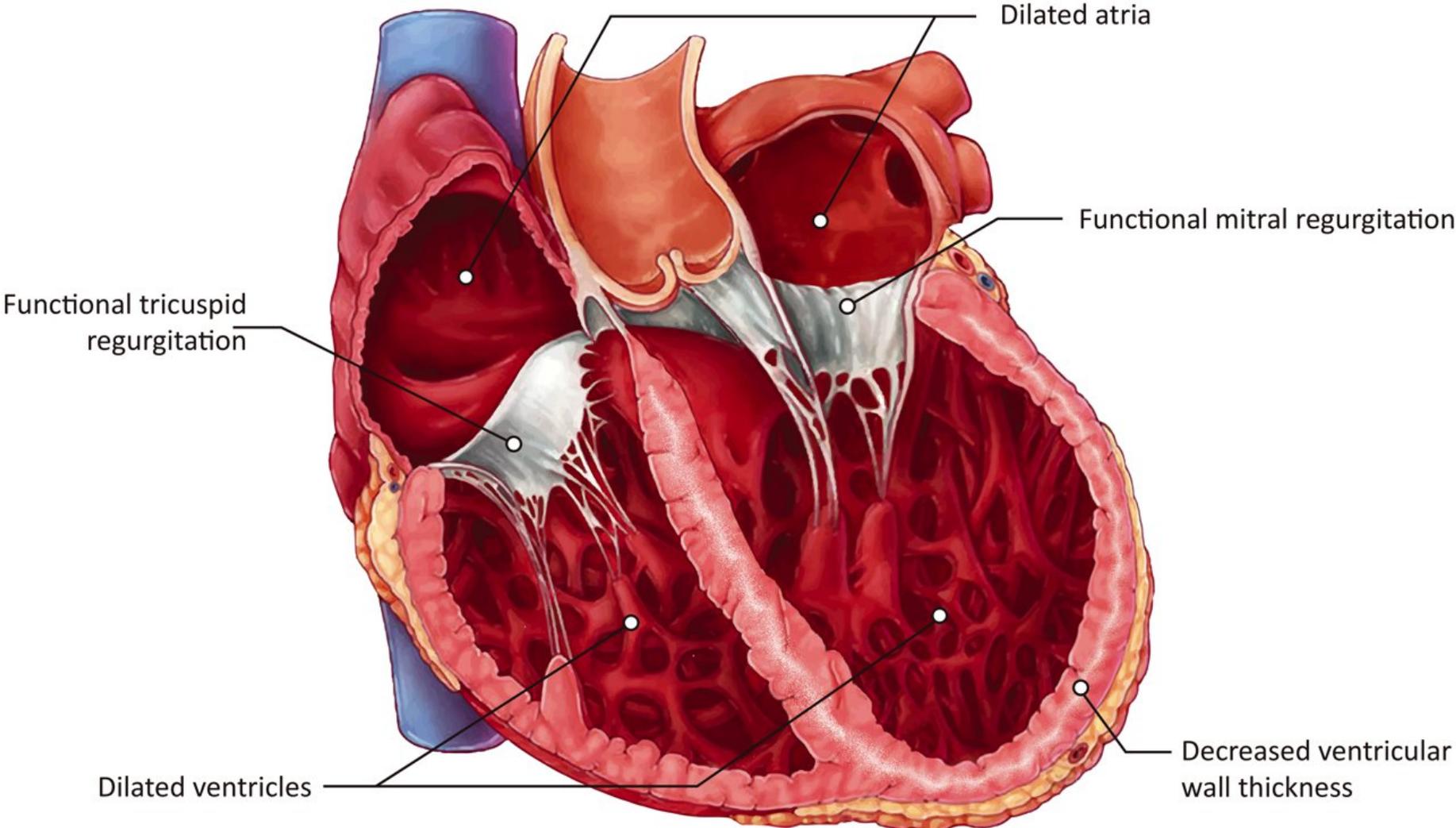
Novartis, Impulse Dynamics, Biotronik

**Consulenze e Collaborazione scientifica occasionale**

Ai sensi dell'Art. 10 L.675 del 31/12/1996 e dell'Art. 76, comma 4 dell'Accordo Stato-Regioni del 02/02/2017 e del paragrafo 4.5 del Manuale nazionale di accreditamento per l'erogazione di eventi ECM

# Heart failure in cardiomyopathies: a position paper from the Heart Failure Association of the European Society of Cardiology

Characteristic alterations in cardiac morphology underlying heart failure in DCM

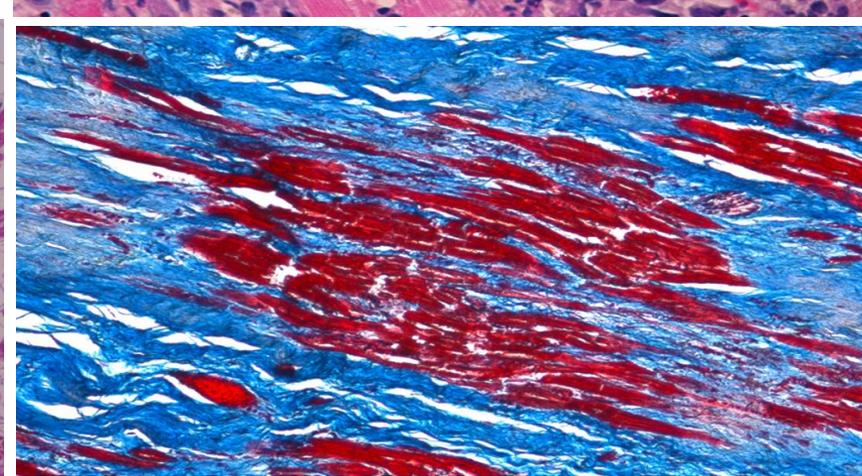
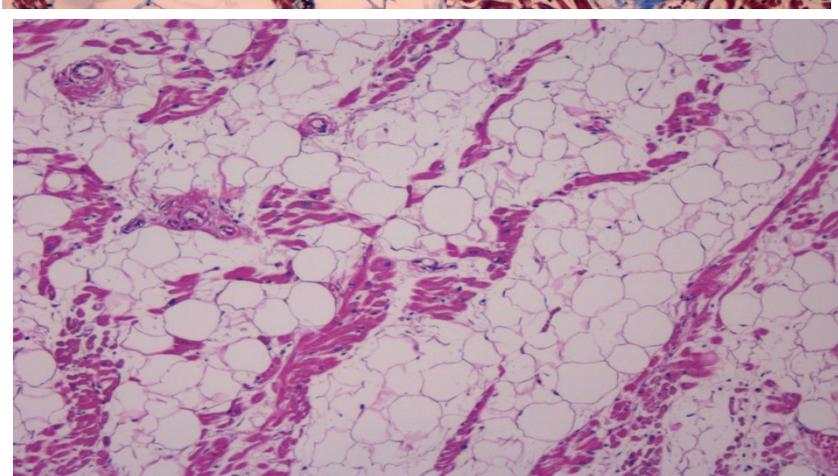
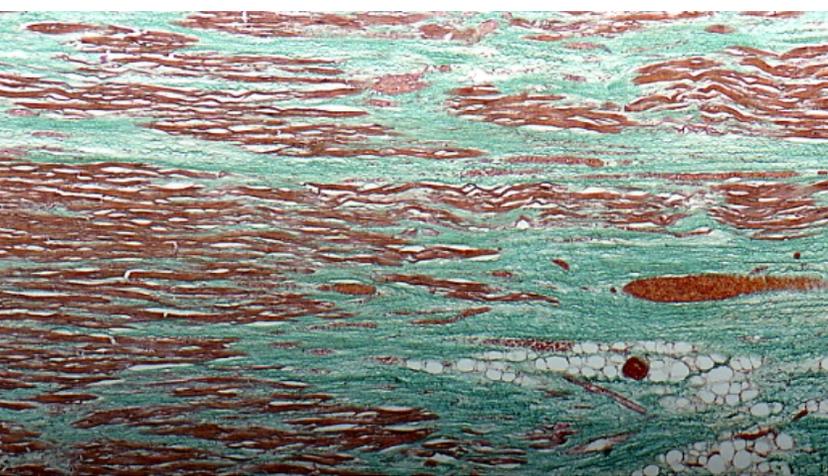
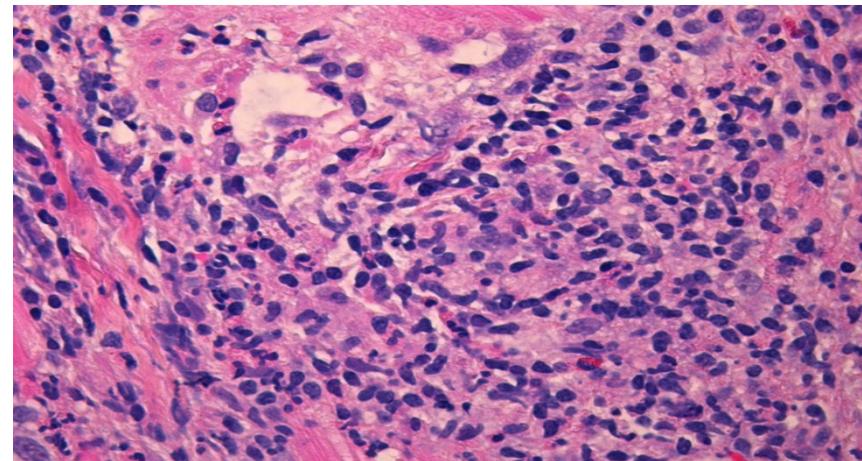
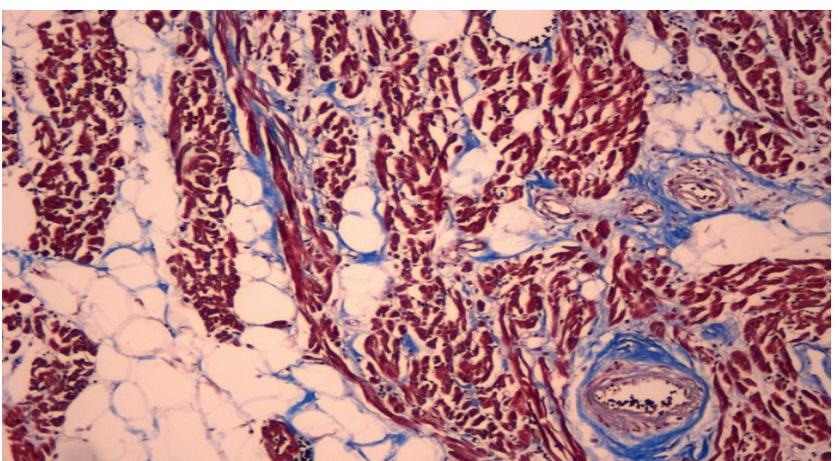
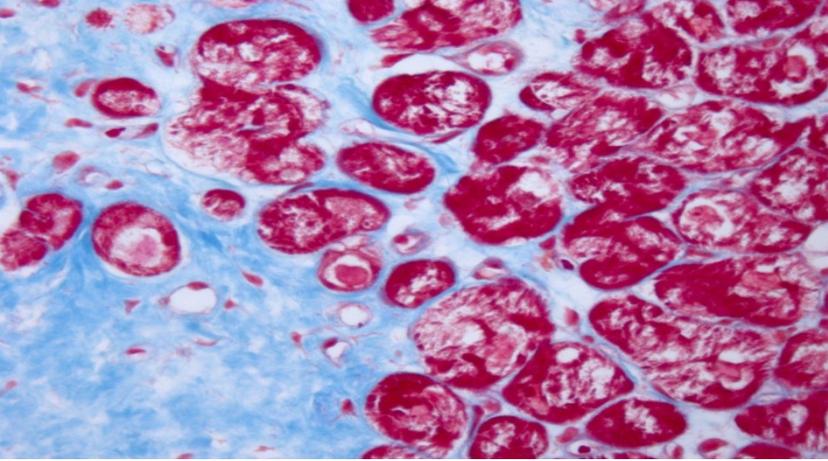
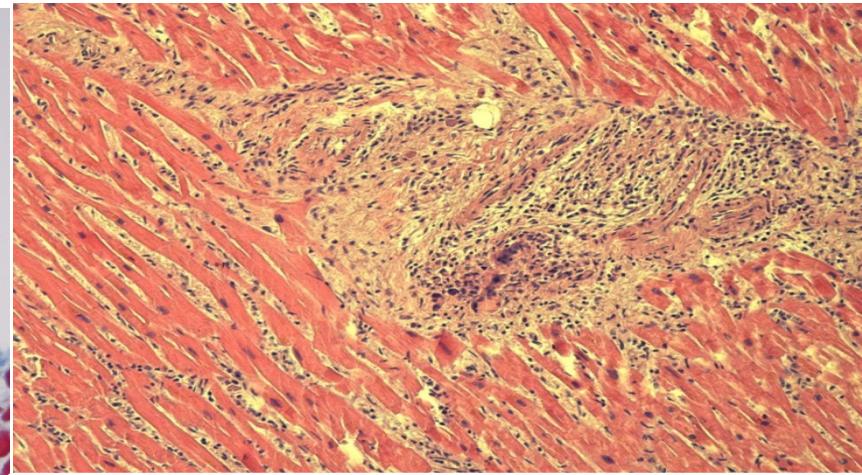
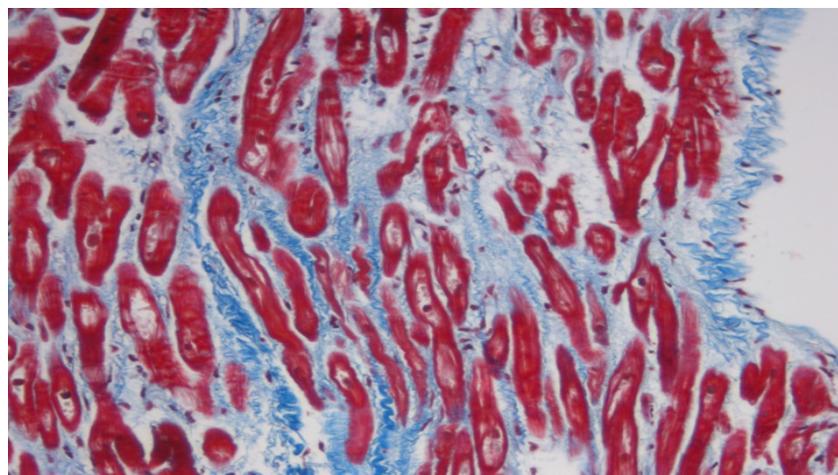
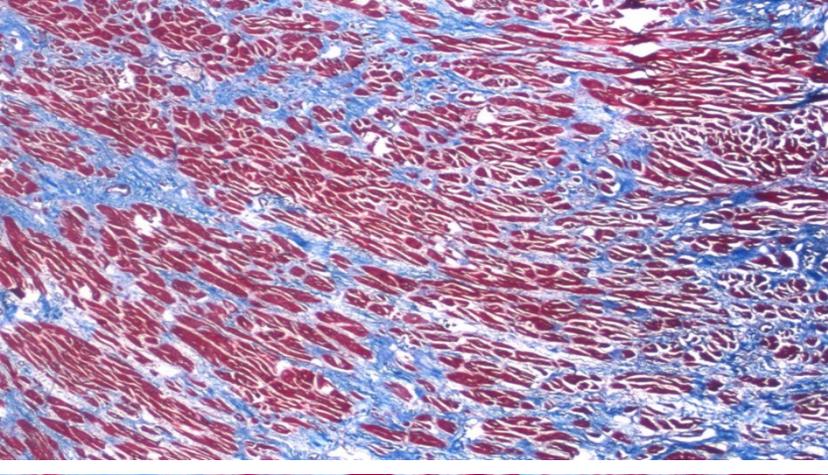


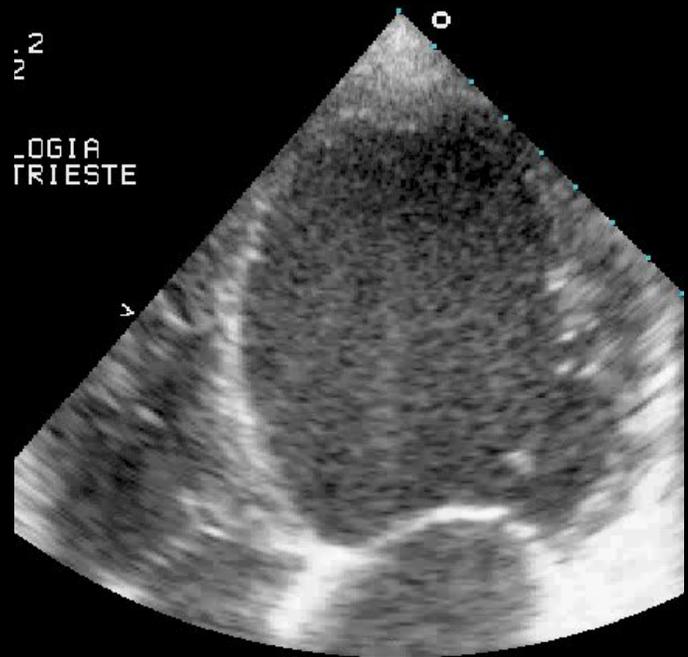
# «CMPD non ischemica» - DEFINIZIONE

**FEVsin <45%**

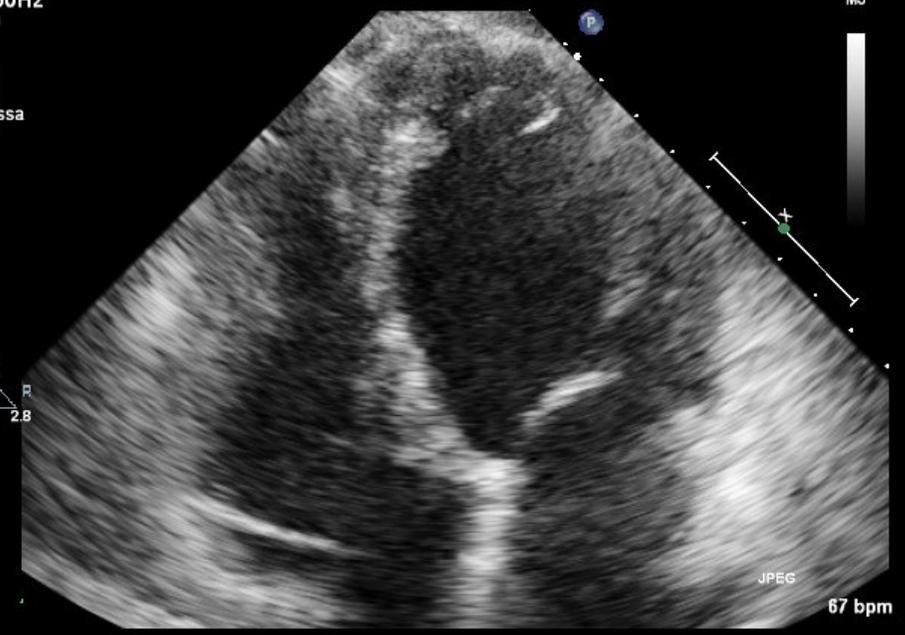
**DTDVsin > limiti superiori per età e BSA (112-117%);**

- **No CHD, stenosi > 50% in rami principali (sempre cgf o angio TC se >35 aa)**
- **No Miocardite mediante BEM**
- **No Ipertensione Arteriosa; PA <160/110**
- **No alcohol intake >100 g/die**
- **No tachiaritmie SVE con FC 130 min/ no AVNRT, PJRT**
- **No peripartum CMP**
- **No Cpt congenite**
- **No valvulopatie primitive emodinamicamente rilevanti**





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

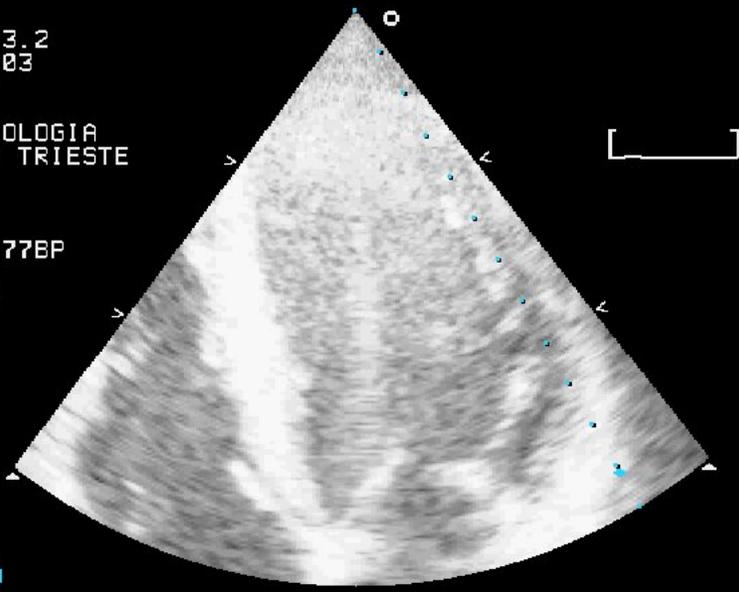


MI: 1.6  
S3 1.6/3.2  
11 NOV 03  
15:41:26  
1/0/D/H5  
UD CARDIOLOGIA  
OSPEDALE TRIESTE  
Echolab

CRT2624/77BP

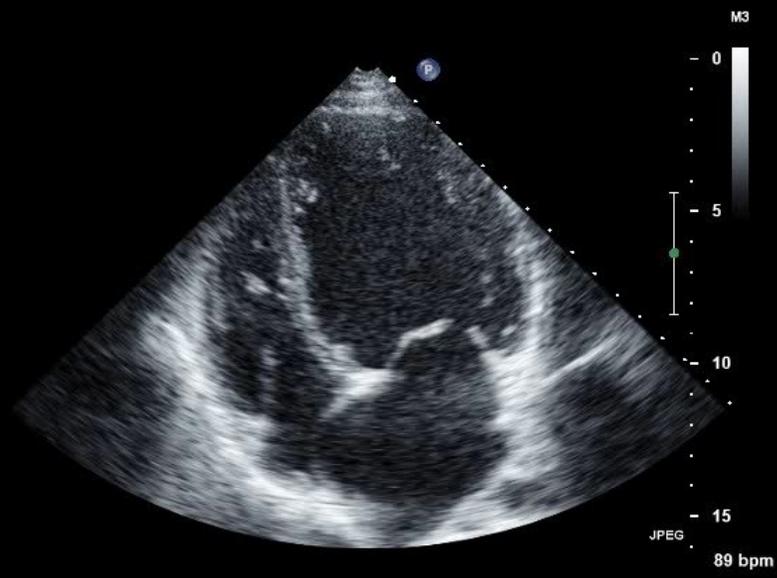
06383  
GUAD 91  
COMP 49  
90BPM

12CM  
40HZ



FR 49Hz  
16cm  
2D  
58%  
C 58  
P Bassa  
AGen

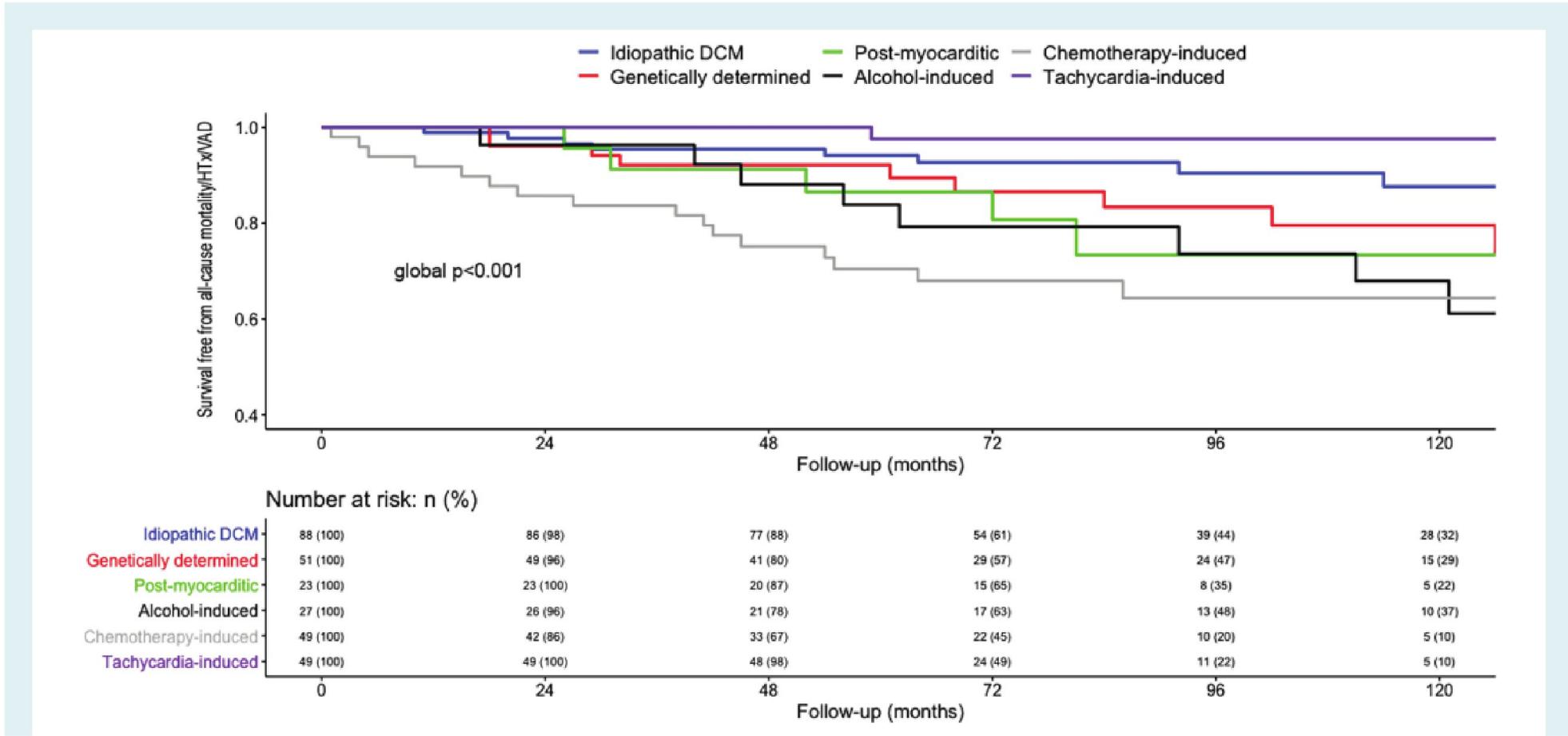
G  
P R  
1.7 3.4



| DCM - 7 CAUSES                                |              |              |             |             |             |                    |                     |         |
|---|--------------|--------------|-------------|-------------|-------------|--------------------|---------------------|---------|
| BASELINE – All enrollment cohorts (1978-2015) |              |              |             |             |             |                    |                     |         |
| DCM causes                                    | iDCM         | Hypert-DCM   | PostMyocDCM | Alcol-DCM   | Chemoth-DCM | Tachi-DCM          | Gen-DCM             | p value |
| <b>n</b>                                      | 977          | 137          | 46          | 31          | 51          | <b>54</b>          | <b>124</b>          |         |
| <b>Age, (mean ± SD)</b>                       | 46,8±15      | 62,2±12      | 43,8±15     | 57,5±10     | 56,8±13     | <b>50,9±15</b>     | <b>40,1±13</b>      | <0,001  |
| <b>Familial History of DCM (%)</b>            | 193 (20,10%) | 2 (2,30%)    | 1 (2,20%)   | 1 (3,20%)   | 2 (4%)      | <b>0 (0%)</b>      | <b>67 (54%)</b>     | <0,001  |
| <b>Hist f Syncope, n (%)</b>                  | 71 (7,80%)   | 4 (4,60%)    | 4 (8,90%)   | 1 (3,20%)   | 0 (0%)      | <b>2 (3,70%)</b>   | <b>14 (11,30)%</b>  | 0,125   |
| <b>Synus Rhythm, n (%)</b>                    | 853 (88,50%) | 101 (79,50%) | 43 (93,50%) | 28 (90,30%) | 32 (87,50%) | <b>4 (8,50%)</b>   | <b>114 (93,40%)</b> | <0,001  |
| <b>Heart Rate, (mean ± SD)</b>                | 75±17        | 72±17        | 83±23       | 74±22       | 79±15       | <b>127±34</b>      | <b>73±17</b>        | <0,001  |
| <b>LBBB, n (%)</b>                            | 302 (31,40%) | 52 (40,90%)  | 13 (29,50%) | 7 (22,60%)  | 16 (32,70%) | <b>1 (1,90%)</b>   | <b>23 (18,90%)</b>  | <0,001  |
| <b>QRS (mean ± SD)</b>                        | 112,8±33     | 126,8±37     | 107,3±27    | 125,4±28    | 115,5±30    | <b>108±25</b>      | <b>107,5±36</b>     | 0,23    |
| <b>LVEF %, (mean ± SD)</b>                    | 32,6±11      | 34,2±9       | 30,6±10     | 30,4±9      | 38,1±13     | <b>33,7±9</b>      | <b>33,9±11</b>      | 0,005   |
| <b>LVEF &lt;35%, n (%)</b>                    | 526 (60,20%) | 70 (52,60%)  | 29 (69%)    | 22 (73,30%) | 21 (42%)    | <b>27 (50%)</b>    | <b>68 (55,30%)</b>  | 0,018   |
| <b>LVEDVI, (mean ± SD)</b>                    | 97,4±40      | 79,7±28      | 87,8±28     | 89,8±30     | 68,5±26     | <b>64,8±20</b>     | <b>93,3±37</b>      | <0,001  |
| <b>LAAI (mean ± SD)</b>                       | 13,6±4       | 14,8±4       | 13,5±4      | 14,6±5      | 11,9±4      | <b>13,5±3</b>      | <b>13,2±4</b>       | 0,039   |
| <b>RFP, n (%)</b>                             | 324 (36,20%) | 13 (21,30%)  | 19 (47,50%) | 4 (19,00%)  | 1 (100%)    | <b>15 (44,10%)</b> | <b>36 (33%)</b>     | 0,033   |
| <b>RV Dysfunction , n (%)</b>                 | 154 (21,30%) | 12 (20%)     | 8 (34,80%)  | 6 (19,40%)  | 11 (23,90%) | <b>22 (47,80%)</b> | <b>26 (25,00%)</b>  | 0,003   |
| <b>Moderate-Severe MR, n (%)</b>              | 84 (9,10%)   | 17 (14,70%)  | 5 (13,50%)  | 3 (9,70%)   | 4 (8,50%)   | <b>3 (5,90%)</b>   | <b>13 (11,50%)</b>  | 0,477   |
| <b>ICD during follow-up, n (%)</b>            | 182 (18,60%) | 20 (14,60%)  | 10 (21,70%) | 6 (19,40%)  | 4 (7,80%)   | <b>3 (5,60%)</b>   | <b>61 (49,20%)</b>  | <0,001  |
| <b>CRT during follow-up, n (%)</b>            | 89 (9,10%)   | 14 (10,20%)  | 3 (6,50%)   | 0 (0%)      | 7 (13,70%)  | <b>2 (3,70%)</b>   | <b>18 (14,50%)</b>  | 0,092   |

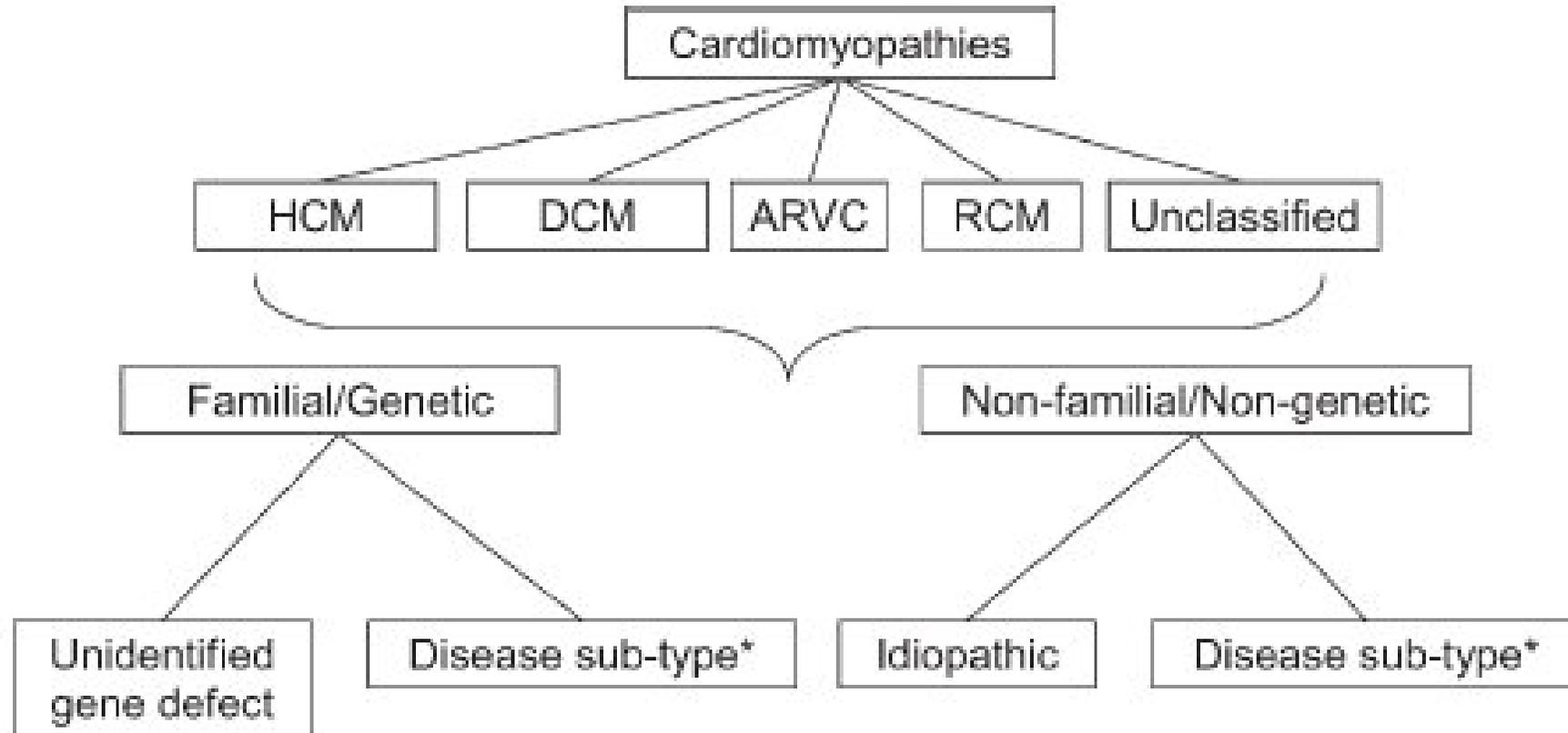
# Contemporary survival trends and aetiological characterization in non-ischaemic dilated cardiomyopathy

Marco Merlo<sup>1</sup>ef, Antonio Cannata<sup>1,2†</sup>, Carola Pio Loco<sup>1</sup>, Davide Stolfo<sup>1</sup>, Giulia Barbati<sup>3</sup>, Jessica Artico<sup>1</sup>, Piero Gentile<sup>1</sup>, Valerio De Paris<sup>1</sup>, Federica Ramani<sup>1</sup>, Massimo Zecchin<sup>1</sup>, Marta Gigli<sup>1</sup>, Bruno Pinamonti<sup>1</sup>, Renata Korcova<sup>1</sup>, Andrea Di Lenarda<sup>4</sup>, Mauro Giacca<sup>2</sup>, Luisa Mestroni<sup>5</sup>, Paolo G. Camici<sup>6</sup>, and Gianfranco Sinagra<sup>1</sup>



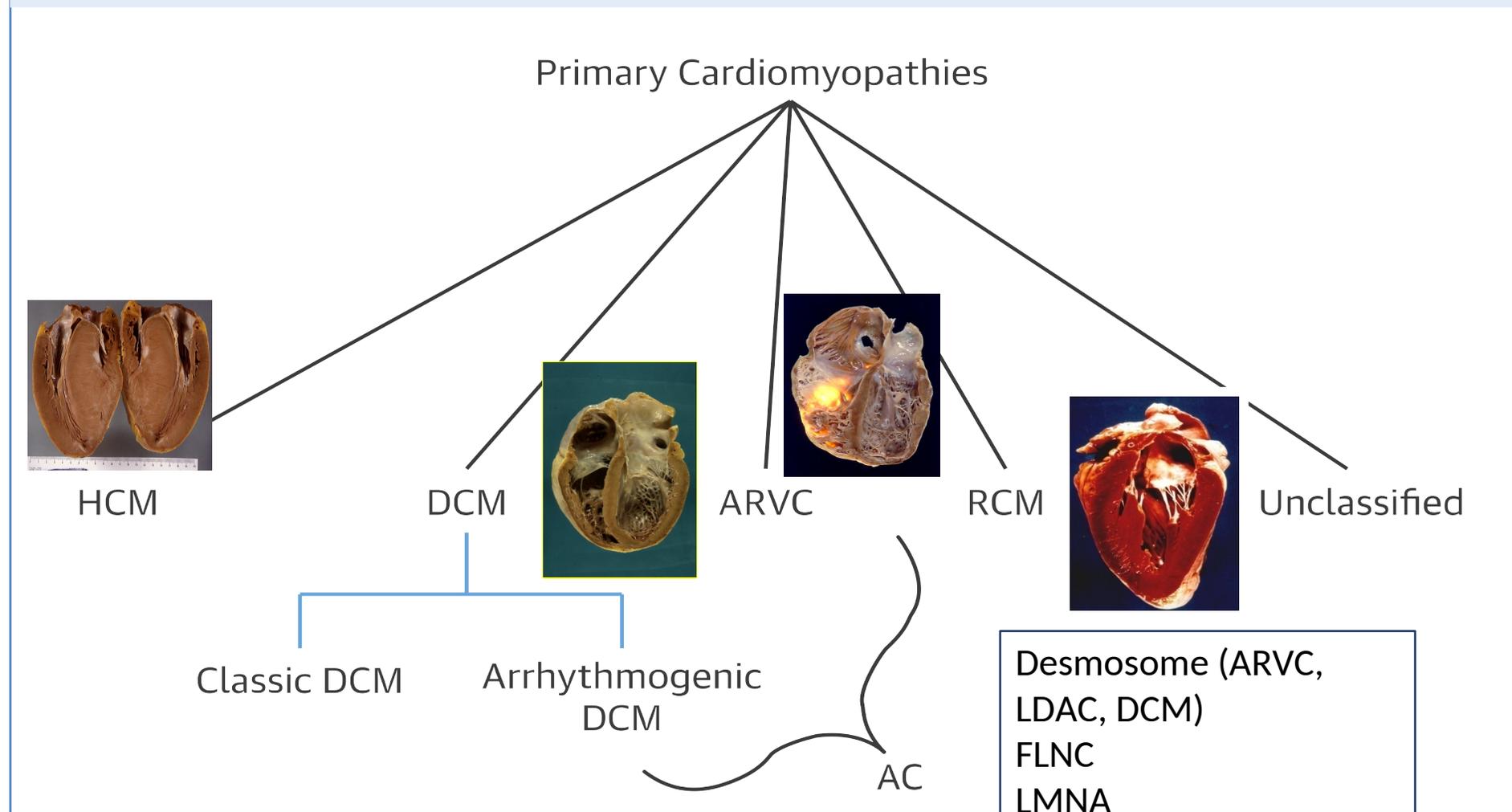
**Figure 4** Kaplan–Meier curves for all-cause mortality/heart transplantation (HTx)/ventricular assist device (VAD) implantation, according to the specific aetiologies of dilated cardiomyopathy (DCM).

# Classification of the cardiomyopathies: a position statement from the european society of cardiology working group on myocardial and pericardial diseases

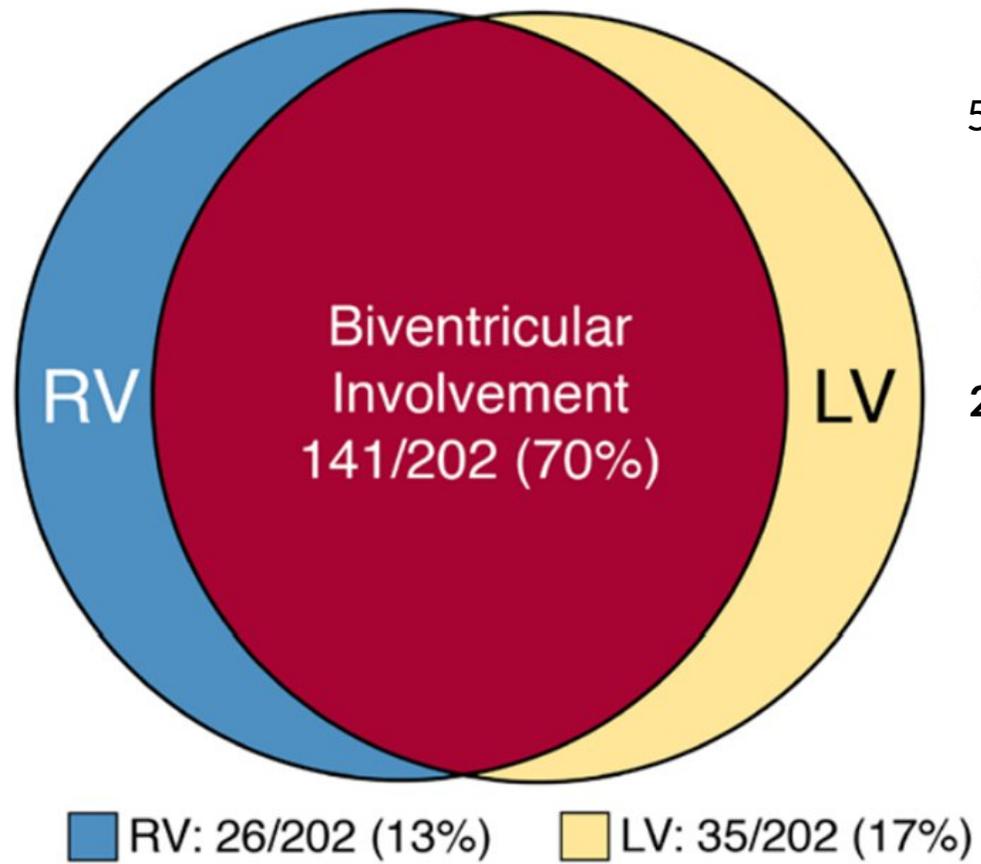


# Common Hereditary Cardiomyopathies as Prototypes of Single-Gene Disorders

**FIGURE 2** Common Forms of Primary Cardiomyopathies J Am Coll Cardiol 2016;68:2831-49



# Sudden Death and Left Ventricular Involvement in Arrhythmogenic Cardiomyopathy



5205 consecutive SCD cases referred to the national cardiac pathology Center (St. George's, University of London) 1994-2018

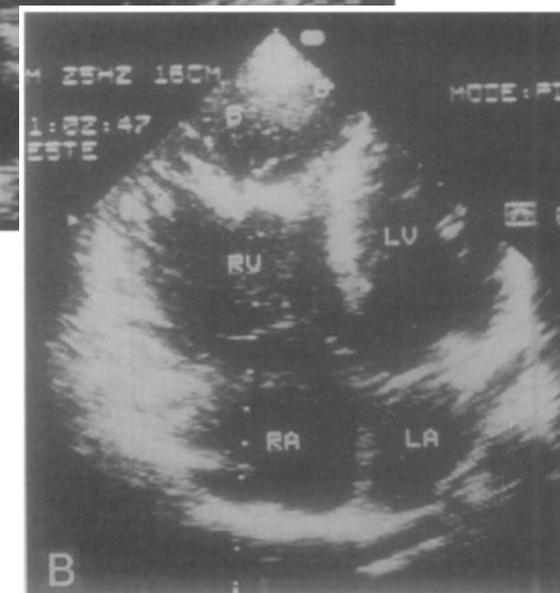
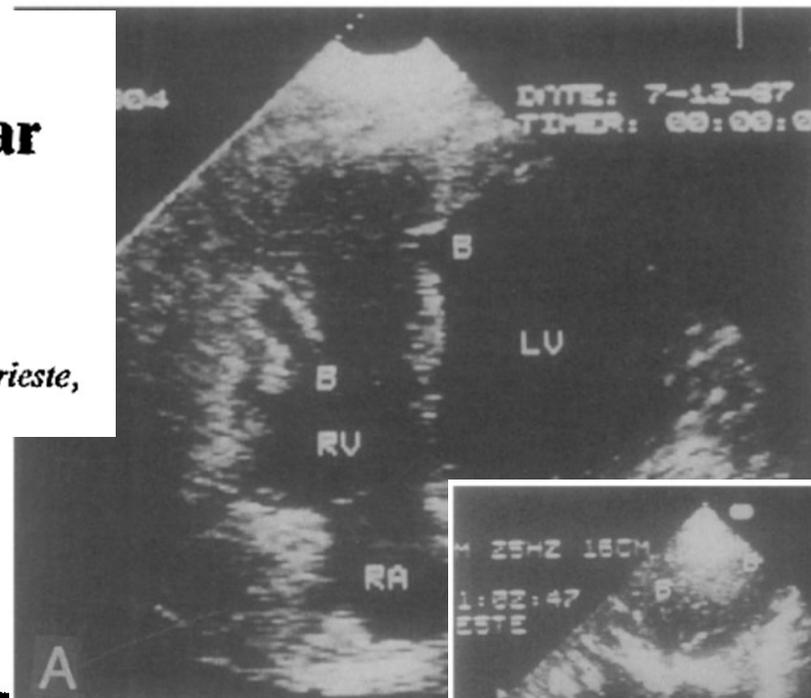
202 cases : pathological diagnosis of ACM.

*European Heart Journal* (1989)

## **Left ventricular involvement in right ventricular cardiomyopathy**

B. PINAMONTI, A. SALVI, F. SILVESTRI\*, G. SINAGRA AND F. CAMERINI

*Departments of Cardiology and \*Pathology, Ospedale Maggiore and University of Trieste, Trieste, Italy*



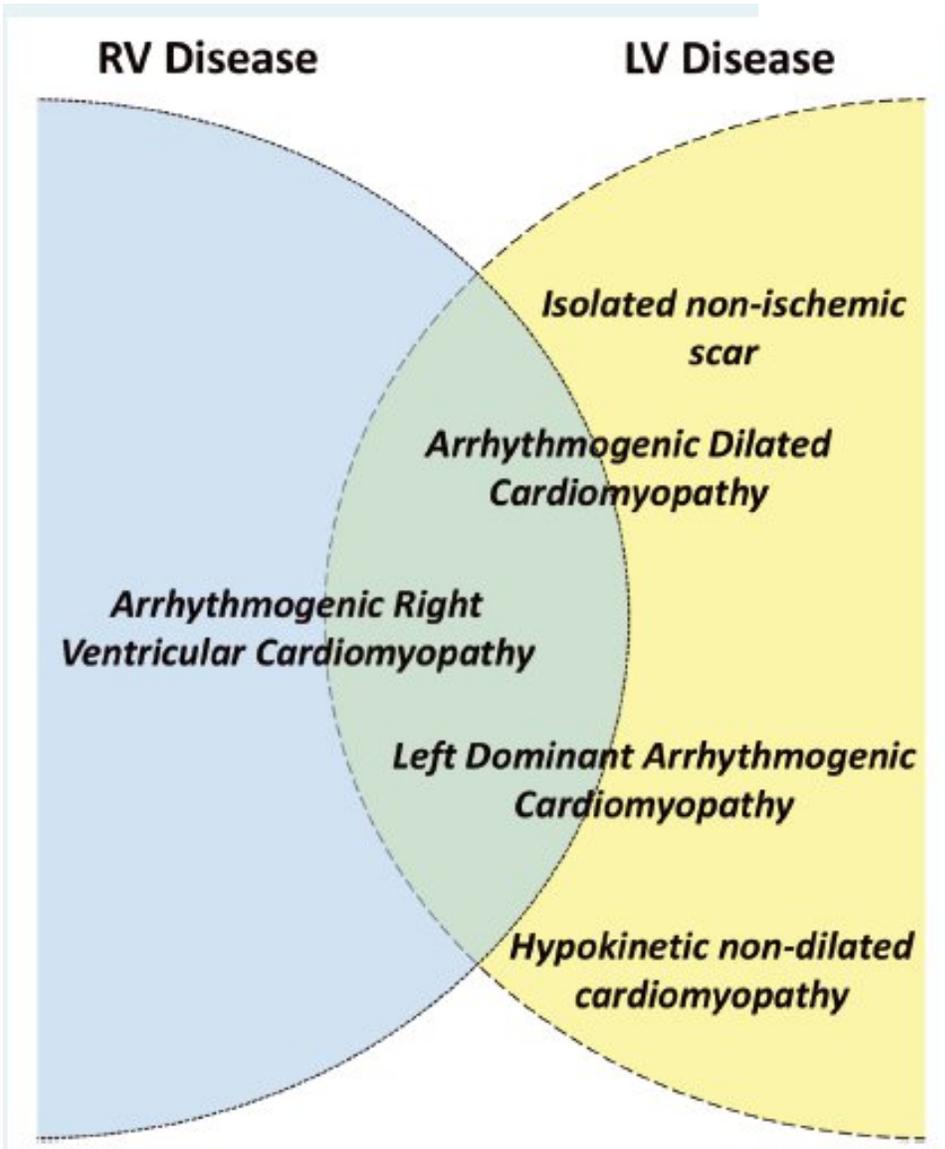
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## **Left ventricular involvement in right ventricular dysplasia**

Bruno Pinamonti, MD, Gianfranco Sinagra, MD, Alessandro Salvi, MD, Andrea Di Lenarda, MD, Tullio Morgera, MD, Furio Silvestri, MD, Rossana Bussani, MD, and Fulvio Camerini, MD. *Trieste, Italy*

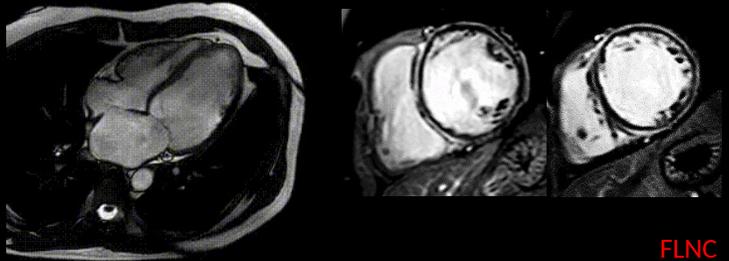
**March 1992**  
**American Heart Journal**

# What is arrhythmogenic cardiomyopathy?

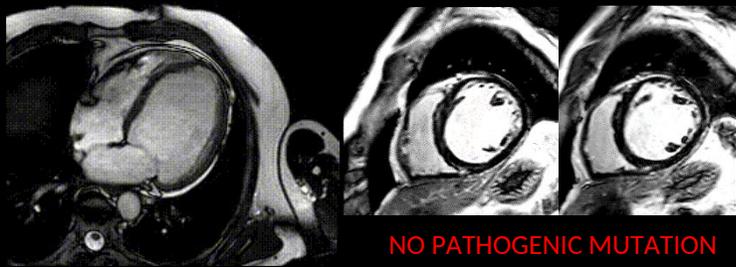


**Table 2** Observed phenotypes associated with mutations in arrhythmogenic cardiomyopathy-related genes

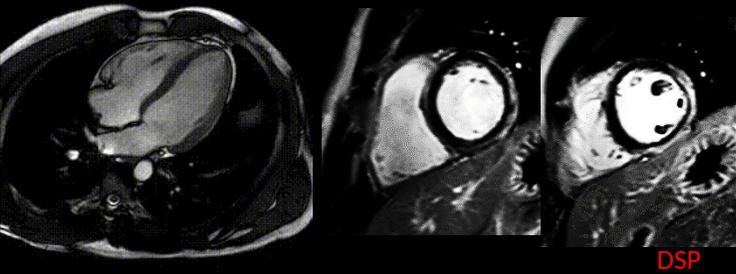
| Gene      | Predominant RV disease | Biventricular disease | Predominant LV disease | Other characteristics           | Ref.  |
|-----------|------------------------|-----------------------|------------------------|---------------------------------|-------|
| JUP       | +                      | +                     | -                      | Cardiocutaneous syndrome        | 4     |
| DSP       | -                      | +                     | +                      | Cardiocutaneous syndrome        | 25    |
| PKP2      | +                      | +                     | -                      |                                 | 6,26  |
| DSG2      | +                      | +                     | +                      |                                 | 8,26  |
| DSC2      | +                      | +                     | -                      |                                 | 9,26  |
| TGFB3     | +                      | Unknown               | Unknown                |                                 | 27    |
| TMEM43    | +                      | +                     | -                      |                                 | 28    |
| TTN       | +                      | +                     | +                      |                                 | 19,29 |
| DES       | -                      | +                     | +                      |                                 | 10    |
| Lamin A/C | -                      | +                     | +                      | Conduction disease              | 11    |
| PLN       | -                      | +                     | +                      |                                 | 16,26 |
| CTNNA3    | +                      | +                     | -                      |                                 | 14    |
| CDH2      | +                      | +                     | -                      |                                 | 13    |
| SCN5A     | -                      | +                     | +                      | Electrical > structural disease | 12,29 |
| FLNC      | -                      | +                     | +                      |                                 | 15    |
| RBM20     | Unknown                | Unknown               | +                      |                                 | 30    |
| BAG3      | Unknown                | Unknown               | +                      |                                 | 31    |



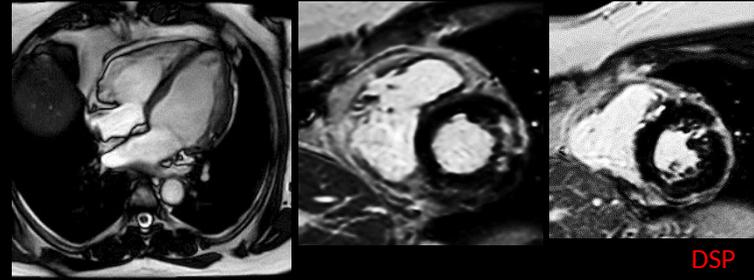
FLNC



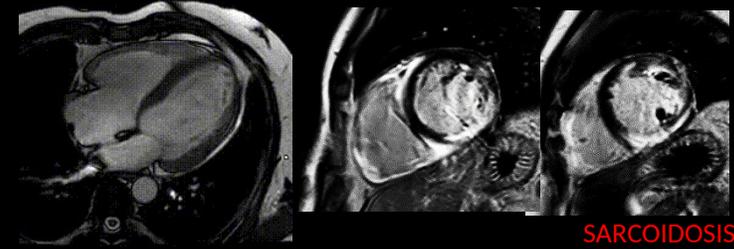
NO PATHOGENIC MUTATION



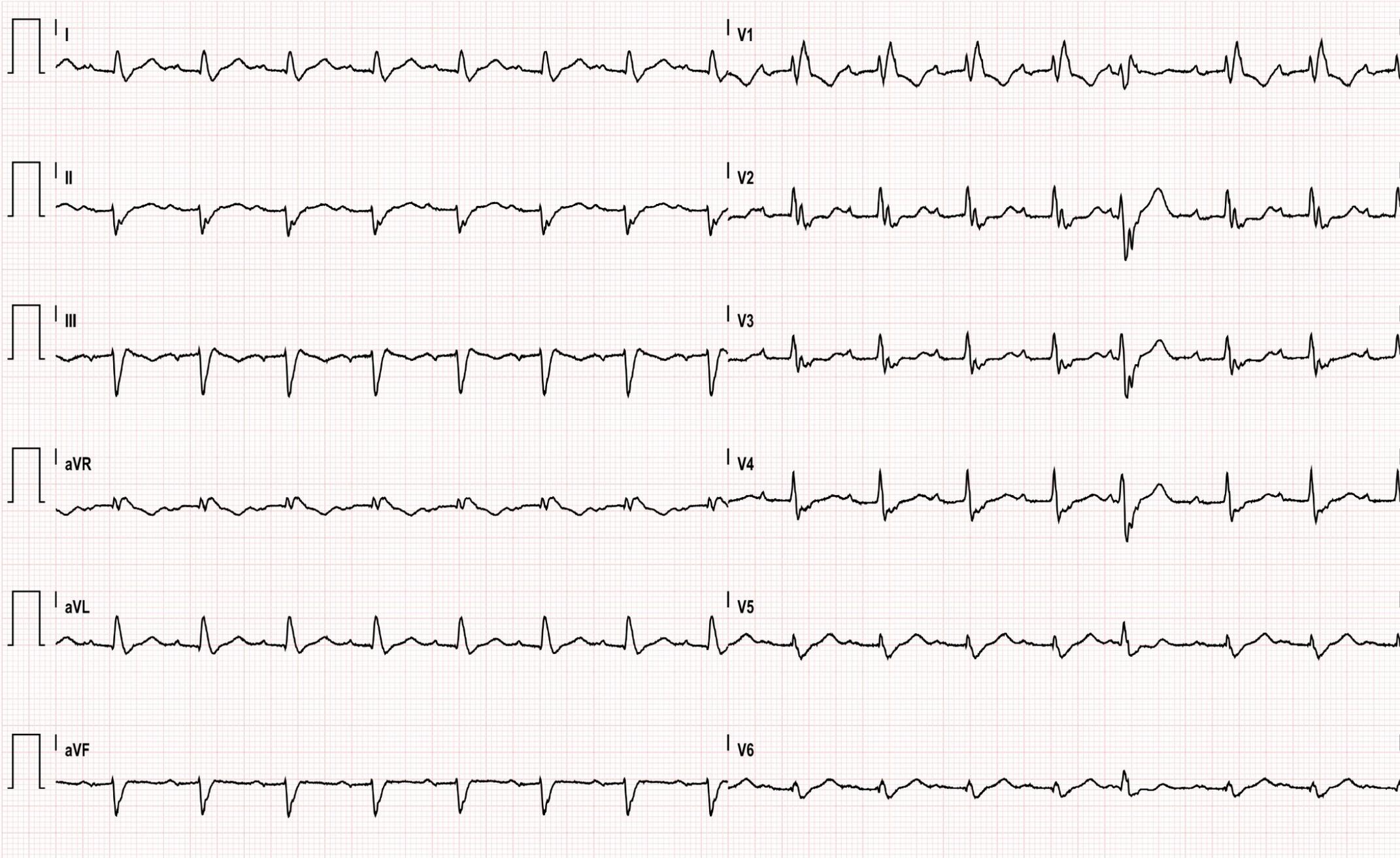
DSP



DSP

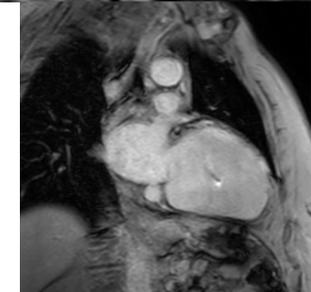
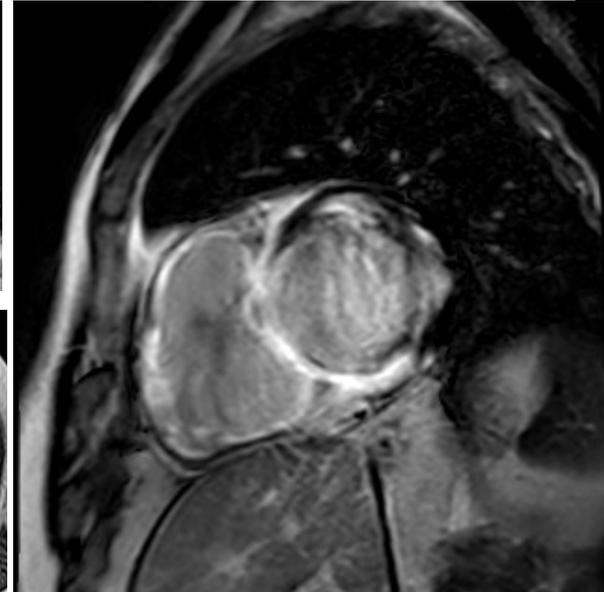
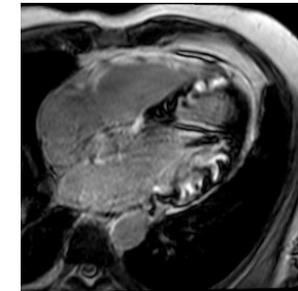
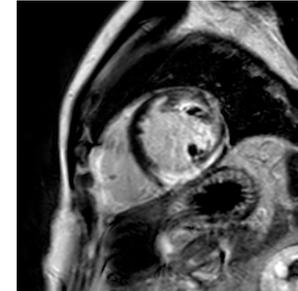


SARCOIDOSIS

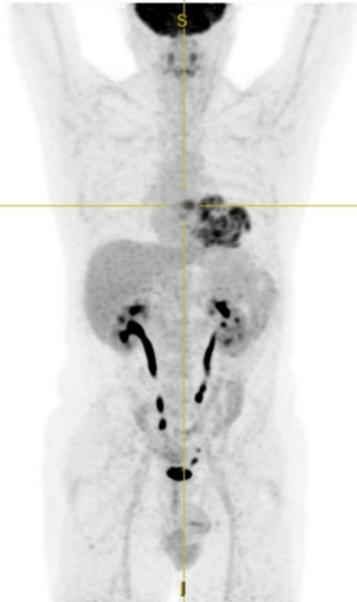




| Dati monodimensionali |    |         | Dati funzionali |       |           |
|-----------------------|----|---------|-----------------|-------|-----------|
|                       | mm | Normale | Vent. sinistro  | ml/mq | Normale i |
| Atrio destro          | 29 |         | FE %            | 23    | 58-76     |
| Atrio sinistro        | 21 |         |                 |       |           |
| A. Polmonare          | 24 | 16-33   | GCI             | 28    | 41-65     |
| A. Polm. Sn.          | 19 | 12-23   | VTDi            | 121   | 62-97     |
| A. Polm. Ds.          | 19 | 12-23   | Massa g/i       |       |           |
| Ao. Ascendente        | 35 | 22-38   | Vent. Destro    |       |           |
| Ao. Discendente       | 24 | 14-26   |                 |       |           |
| Setto Bas. Ant.       | 11 | 06-12   | FE %            | ---   | 53-79     |
| Diam. TDV Sn          | 61 | 37-54   | Gci             | ---   | 38-70     |
| Parete Lat Vent.      | 10 | 05-11   | VTDi            | ---   | 59-105    |

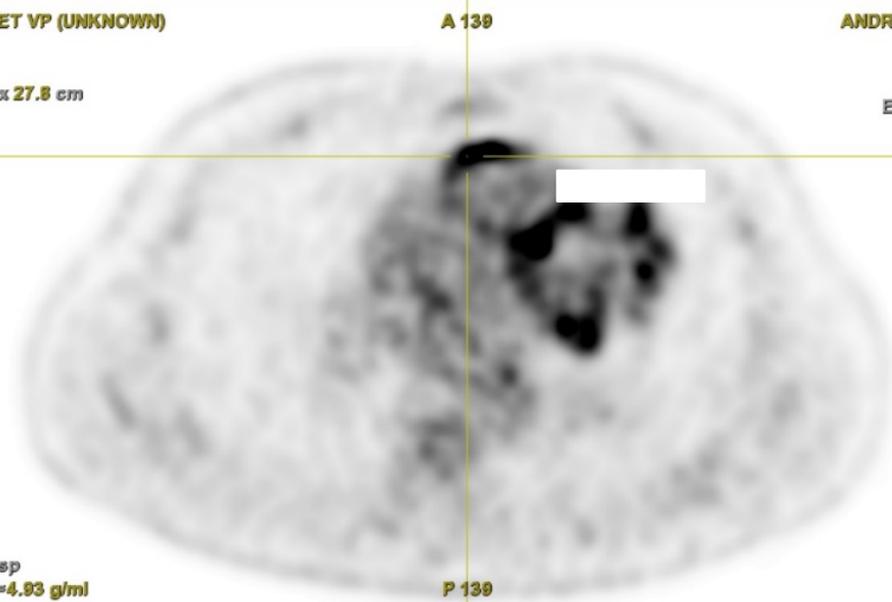


3D WB PET VP (UNKNOWN)  
HD MIP No cut  
DFOV 178.8 x 95.4 cm



ANDREUSSI MAURO  
Ex: May 26 2021

Axial WB PET VP (UNKNOWN)  
I: 294.9  
Im: 97  
DFOV 52.0 x 27.8 cm



A 139 ANDREUSSI MAURO  
Ex: May 26 2021

R  
P

L  
A

R  
2  
6  
0

L  
2  
6  
0

No VOI  
3.3mm /3.3sp  
m=0.00 M=10.00 g/ml

V=6.89

3.3  
3.3mm /3.3sp  
m=-0.01 M=4.93 g/ml

V=6.89

P 139

Axial CT FUSIONE  
I: 294.9  
Im: 97  
DFOV 52.0 x 27.8 cm  
STND/SS40/M No Filter

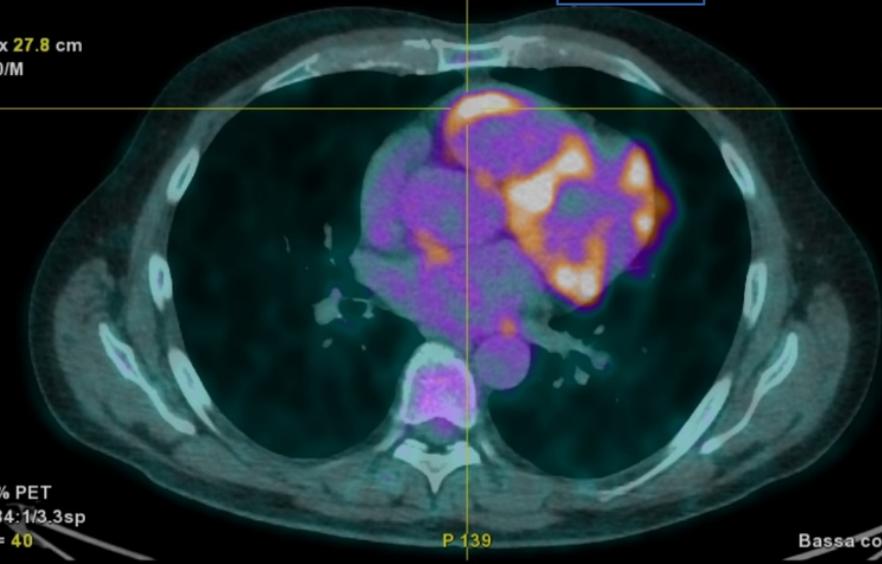
A 139

ANDREUSSI MAURO  
Ex: May 26 2021

Axial CT FUSIONE->WB PET VP (UNKNOWN)  
I: 294.9  
Im: 97  
DFOV 52.0 x 27.8 cm  
STND/SS40/M

A 139

ANDREUSSI MAURO  
Ex: May 26 2021



R  
2  
6  
0

L  
2  
6  
0

R  
2  
6  
0

L  
2  
6  
0

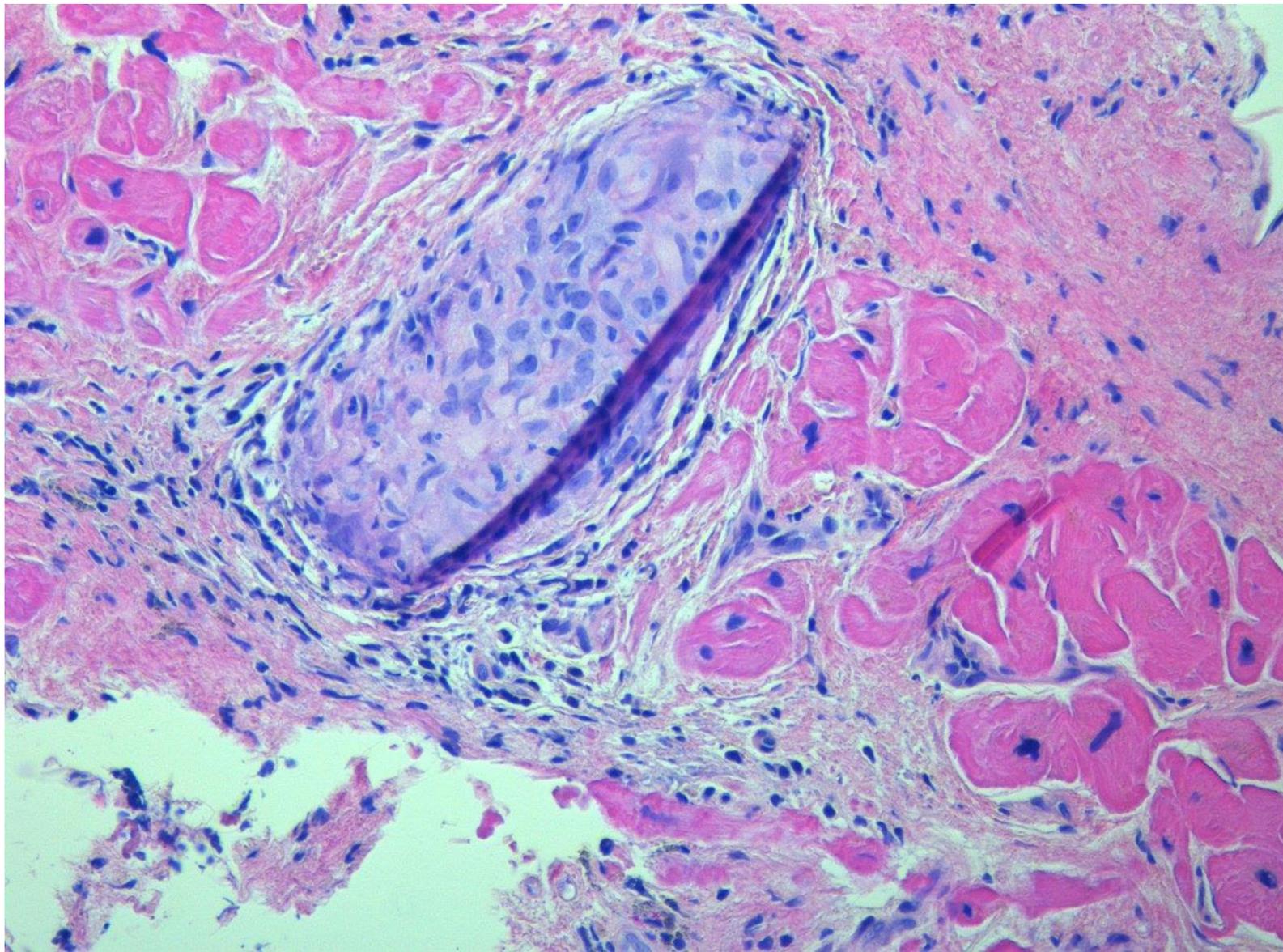
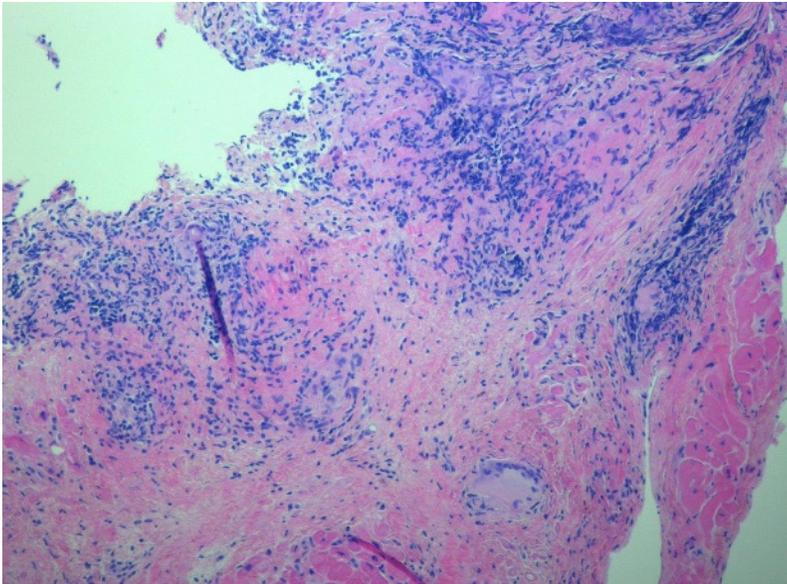
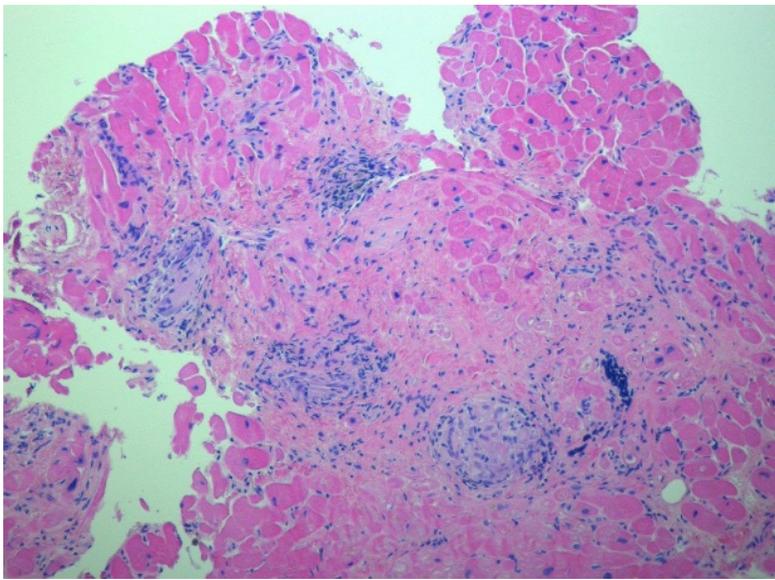
3.3  
kV 120  
3.8mm 0.984:1/3.3sp  
W = 400 L = 40

P 139

3.3  
kV 120 50 % PET  
3.8mm 0.984:1/3.3sp  
W = 400 L = 40

P 139

Bassa con perdita (15:1)



**“Quadro morfoistopatologico ed immunofenotipico coerente con processo sarcoidosico a localizzazione cardiaca con fibrotizzazione miocardica”**

## High prevalence of subtle systolic and diastolic dysfunction in genotype-positive phenotype-negative relatives of dilated cardiomyopathy patients

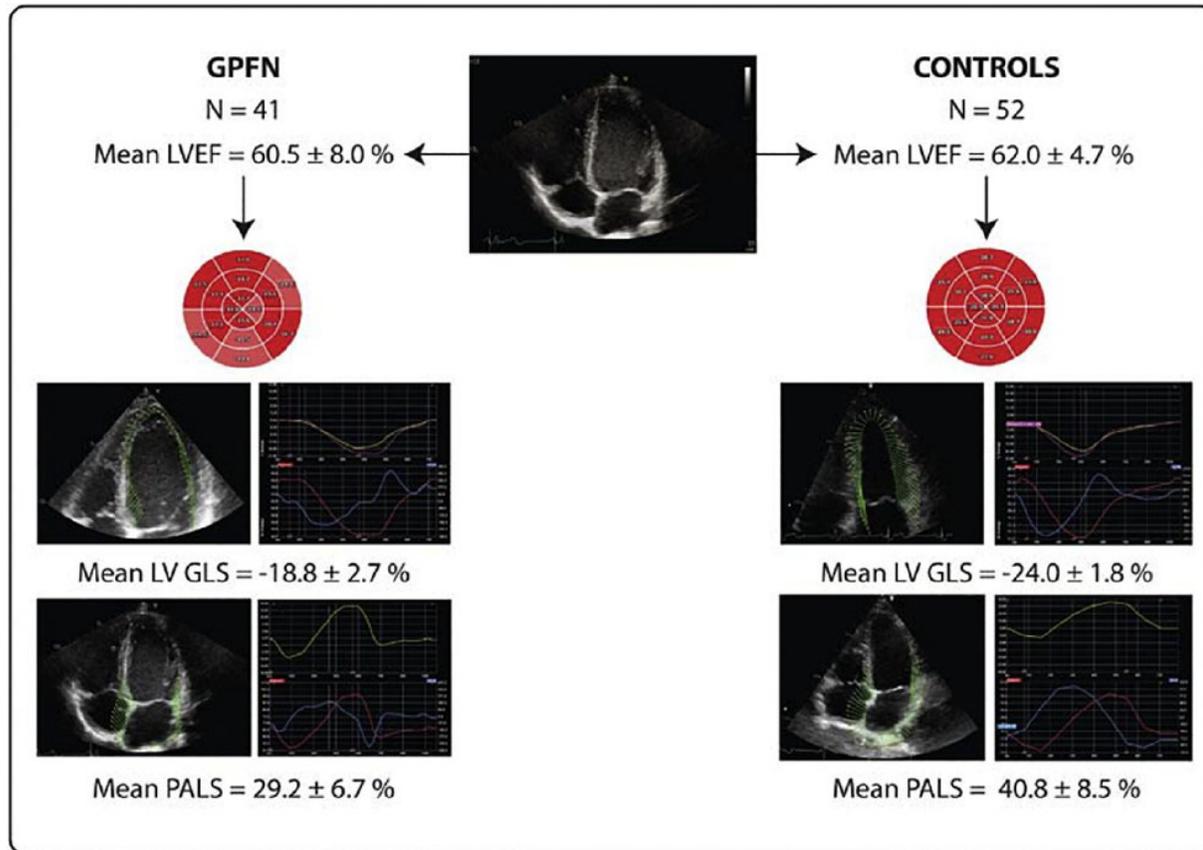
Alessia Paldino <sup>a,1,2</sup>, Giulia De Angelis <sup>a,1,2</sup>, Matteo Dal Ferro <sup>a,1,2</sup>, Giorgio Faganello <sup>b,2</sup>, Aldostefano Porcari <sup>a,2</sup>, Giulia Barbati <sup>c,2</sup>, Renata Korcova <sup>a,2</sup>, Piero Gentile <sup>a,2</sup>, Jessica Artico <sup>a,2</sup>, Antonio Cannatà <sup>a,2</sup>, Marta Gigli <sup>a,2</sup>, Bruno Pinamonti <sup>a,2</sup>, Marco Merlo <sup>a,3,2</sup>, Gianfranco Sinagra <sup>a,2</sup>

<sup>a</sup> Cardiothoracic Department, Azienda Sanitaria Universitaria Giuliano Isontina, Trieste, Italy

<sup>b</sup> Cardiovascular Center, Azienda Sanitaria Universitaria Giuliano Isontina, Trieste, Italy

<sup>c</sup> Biostatistics Unit, Department of Medical Sciences, University of Trieste, Trieste, Italy

International Journal of Cardiology (2020)



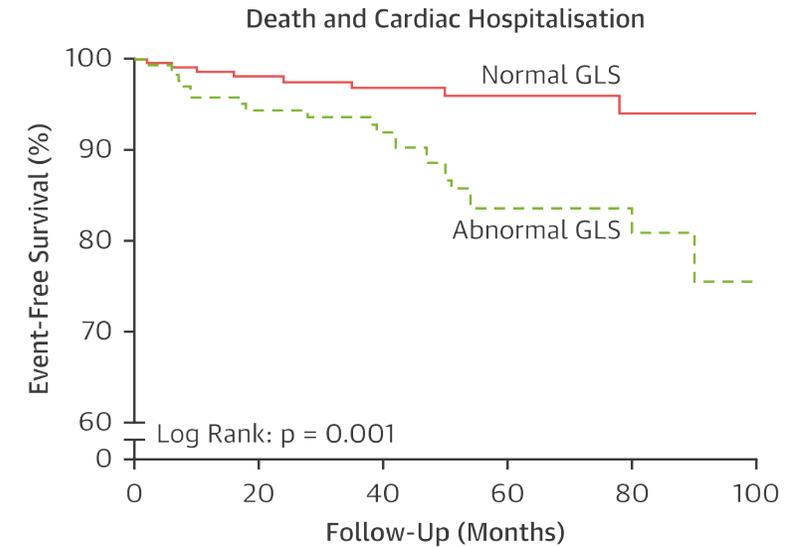
## Value of Speckle Tracking-Based Deformation Analysis in Screening Relatives of Patients With Asymptomatic Dilated Cardiomyopathy

Verdonschot et al.

Value of Echocardiographic GLS in DCM Relatives

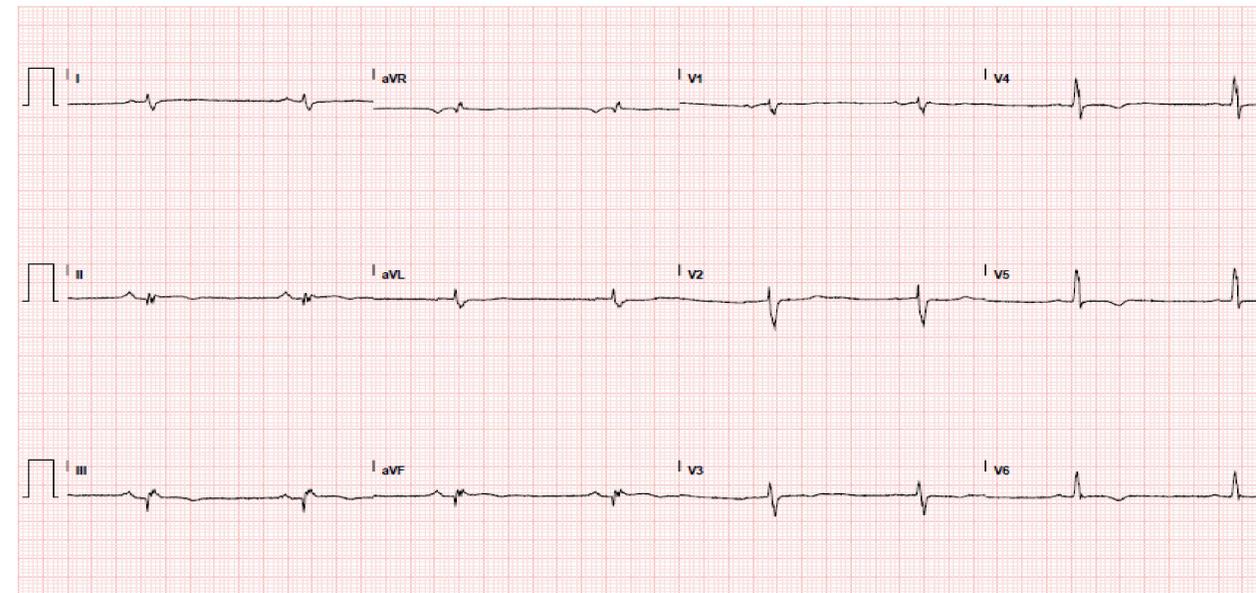
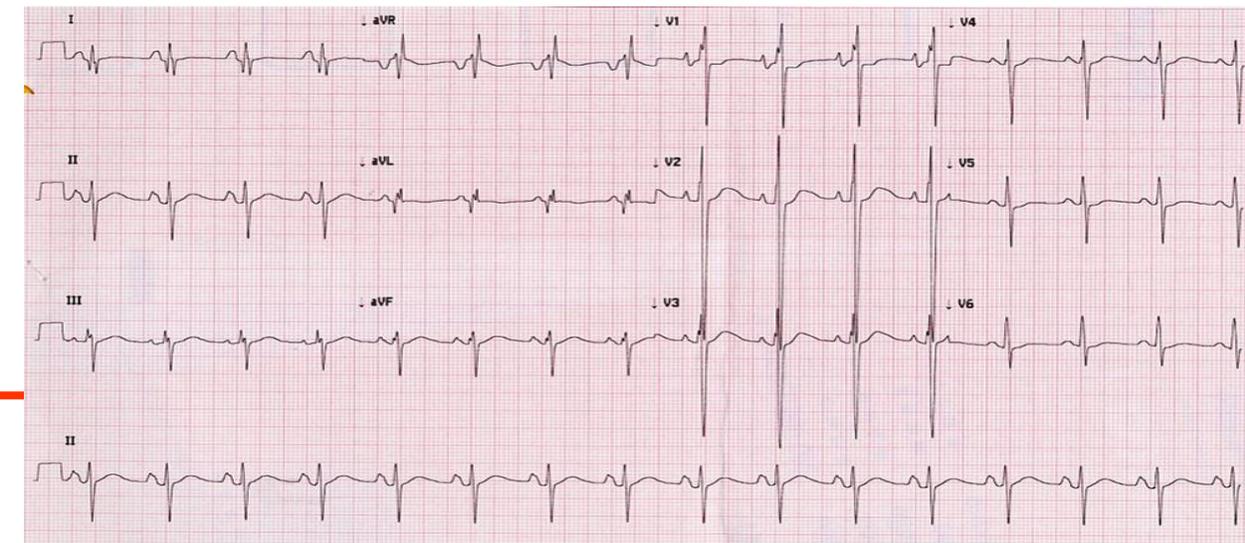
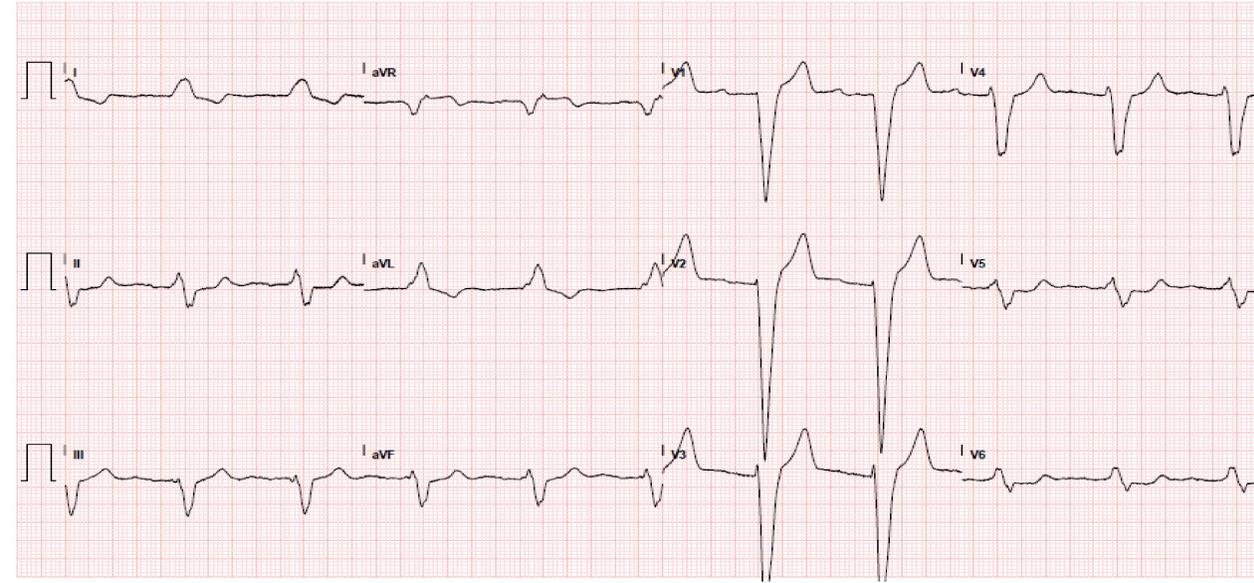
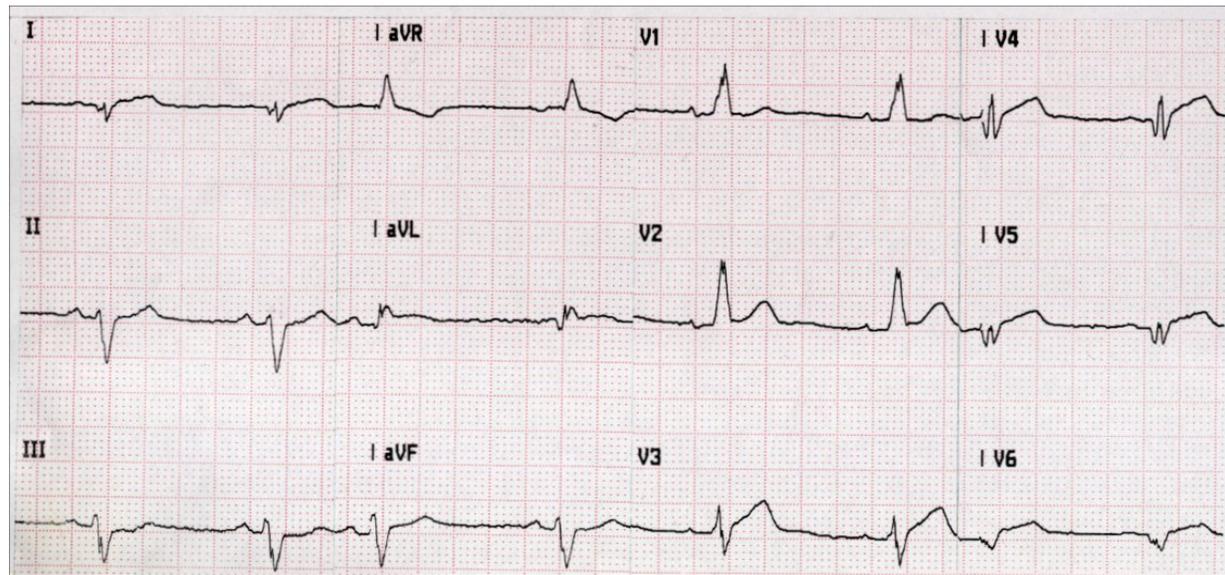
JACC: CARDIOVASCULAR IMAGING, VOL. ■, NO. ■, 2019

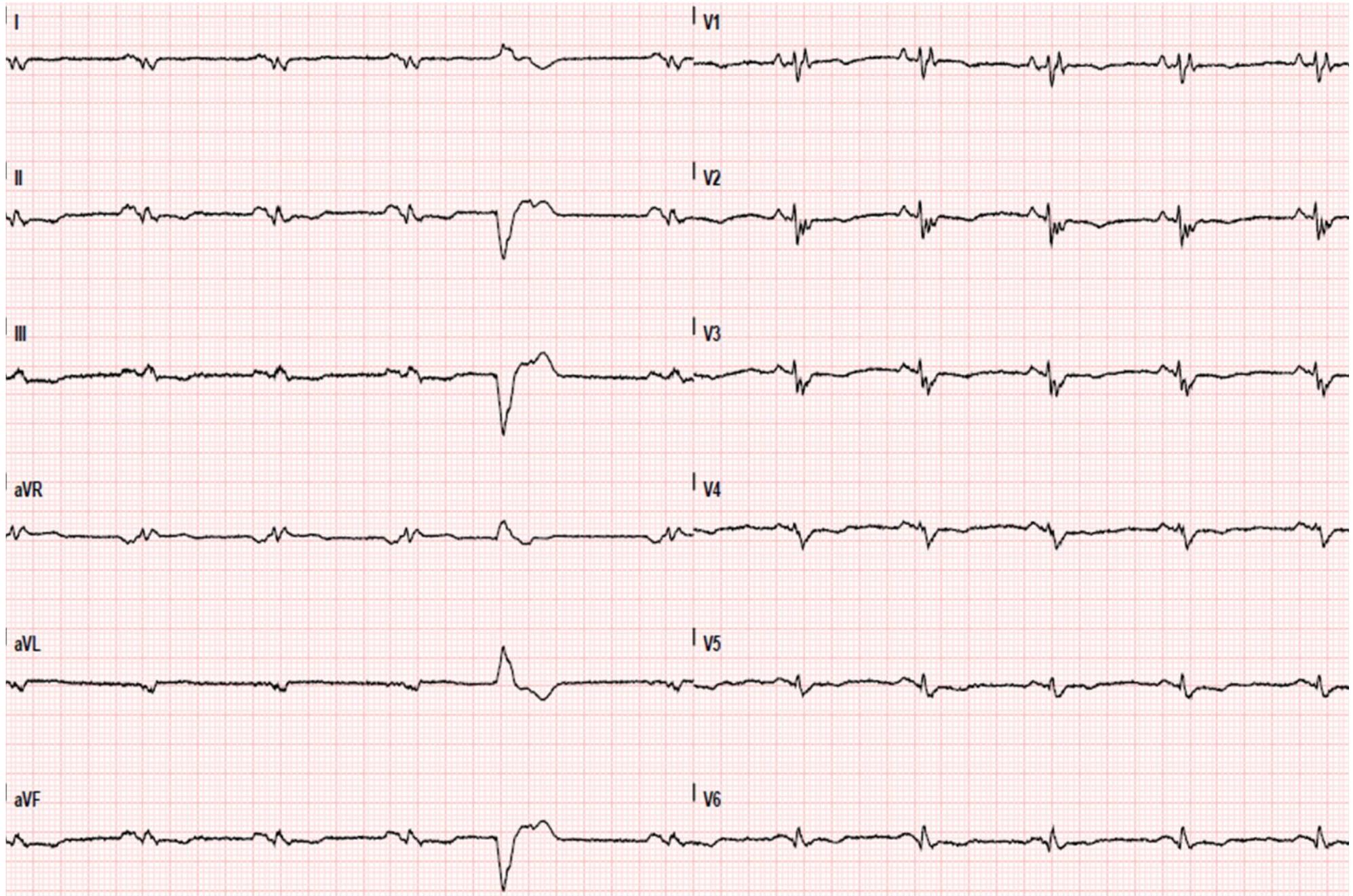
■ 2019 ■ ■



Number at risk

|               |     |     |     |    |    |    |
|---------------|-----|-----|-----|----|----|----|
| Abnormal GLS: | 203 | 133 | 109 | 63 | 26 | 6  |
| Normal GLS:   | 299 | 172 | 131 | 87 | 45 | 10 |



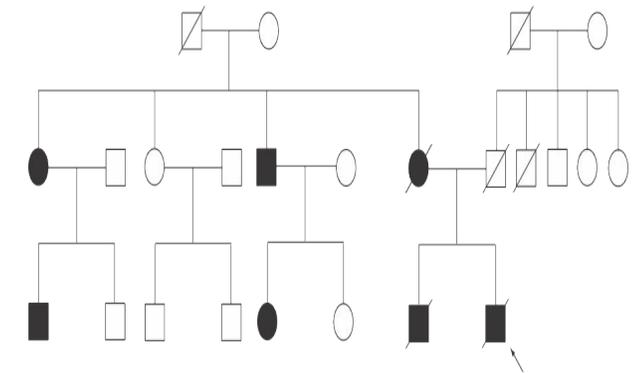
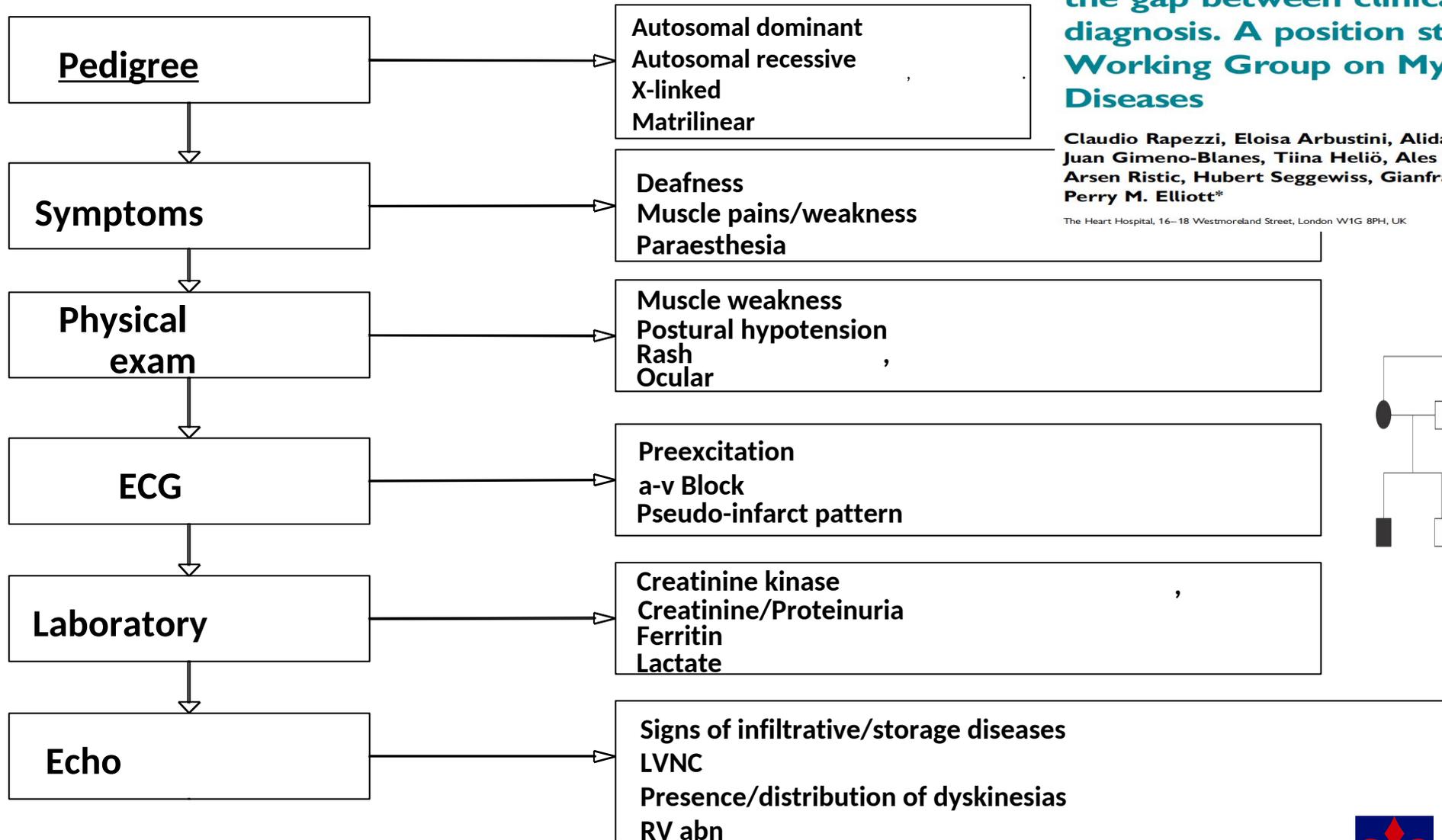


# “Red flags approach”

## Diagnostic work-up in cardiomyopathies: bridging the gap between clinical phenotypes and final diagnosis. A position statement from the ESC Working Group on Myocardial and Pericardial Diseases

Claudio Rapezzi, Eloisa Arbustini, Alida L. P. Caforio, Philippe Charron, Juan Gimeno-Blanes, Tiina Heliö, Ales Linhart, Jens Mogensen, Yigal Pinto, Arsen Ristic, Hubert Seggewiss, Gianfranco Sinagra, Luigi Tavazzi, and Perry M. Elliott\*

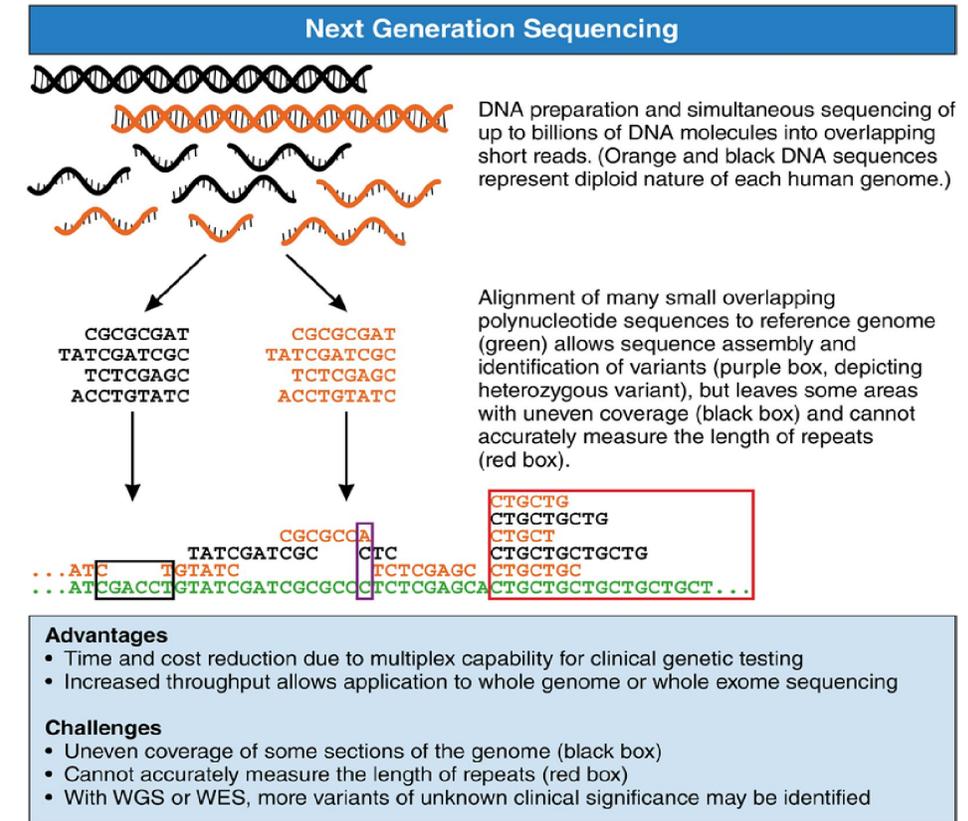
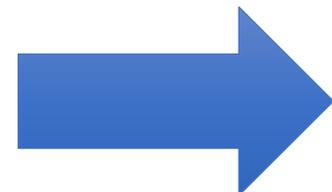
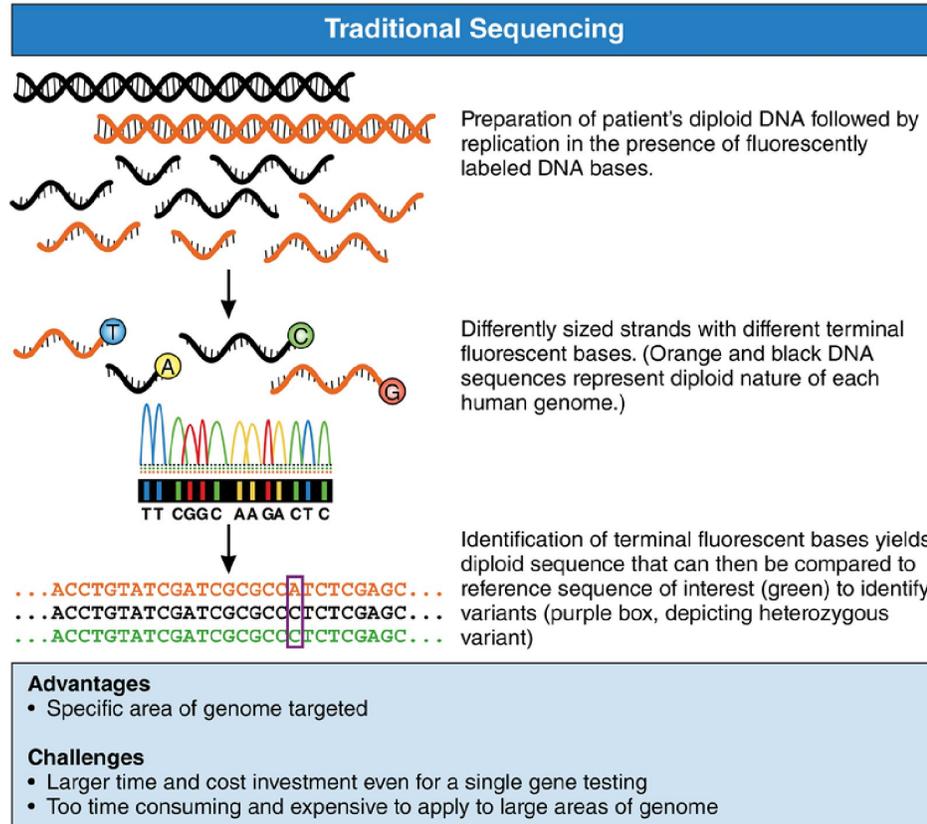
The Heart Hospital, 16–18 Westmoreland Street, London W1G 8PH, UK



# Next-Generation Sequencing in Cardiovascular Disease

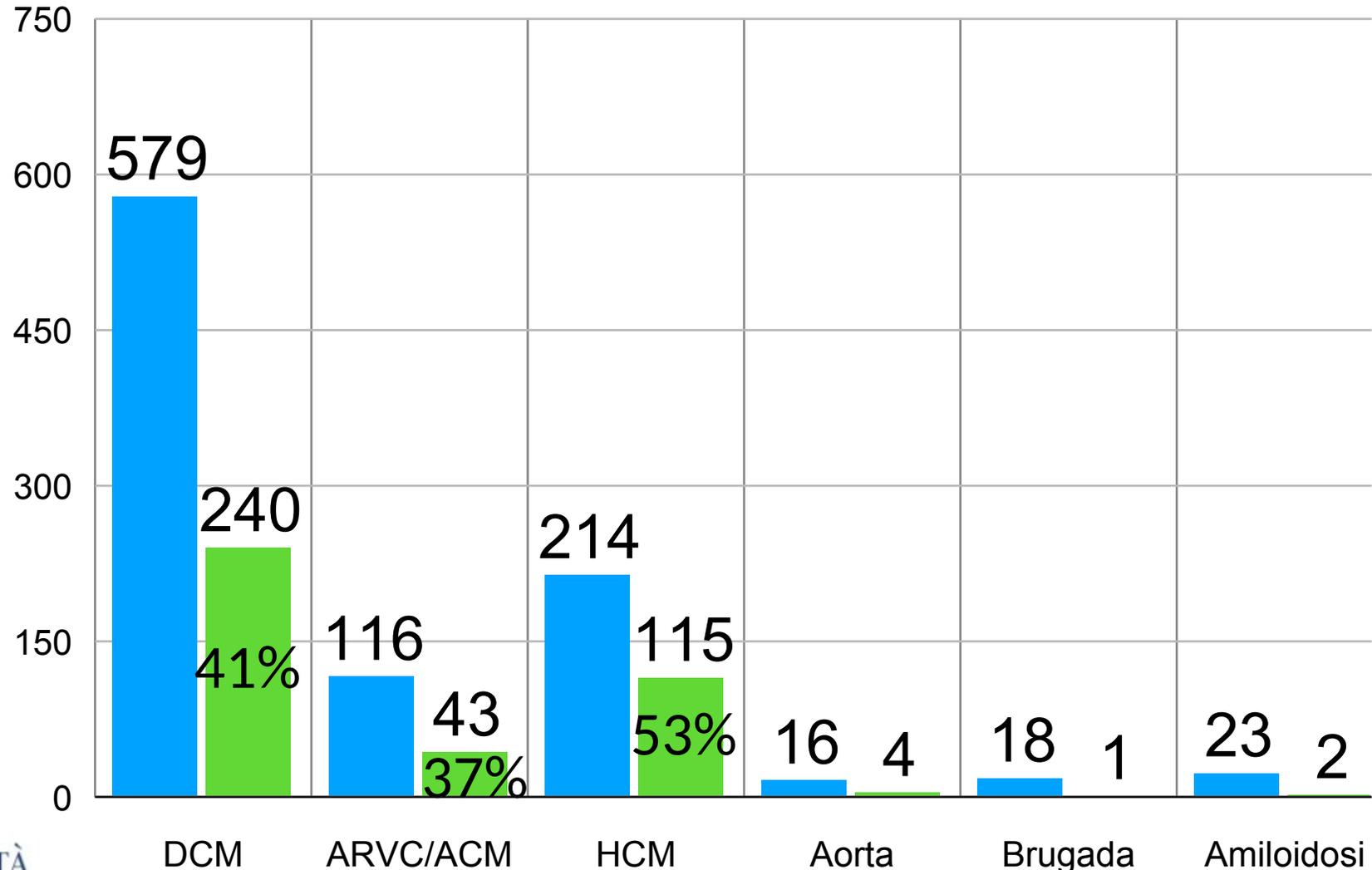
## Present Clinical Applications and the Horizon of Precision Medicine

Victoria N. Parikh, MD  
Euan A. Ashley, FRCP,  
DPhil

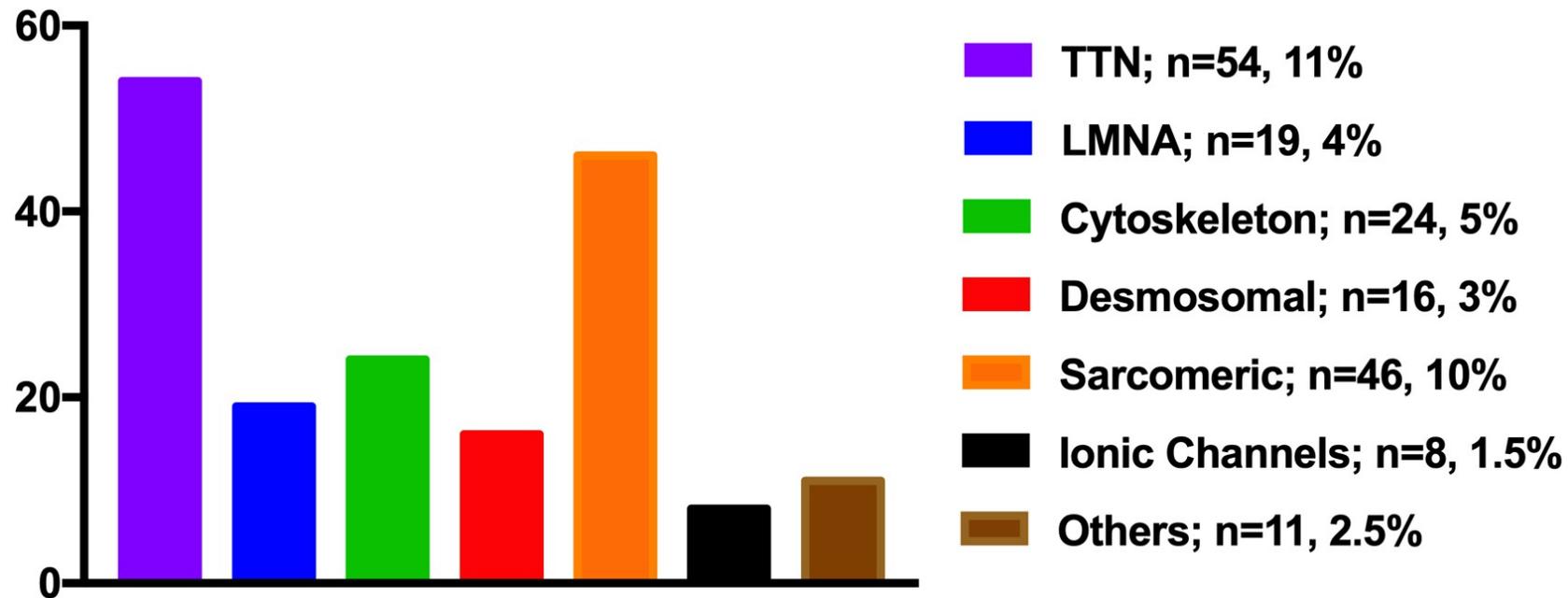


# Esito genotipizzazione per diagnosi - Registro Cardio-Trieste (2014 - 8/2021; probandi)

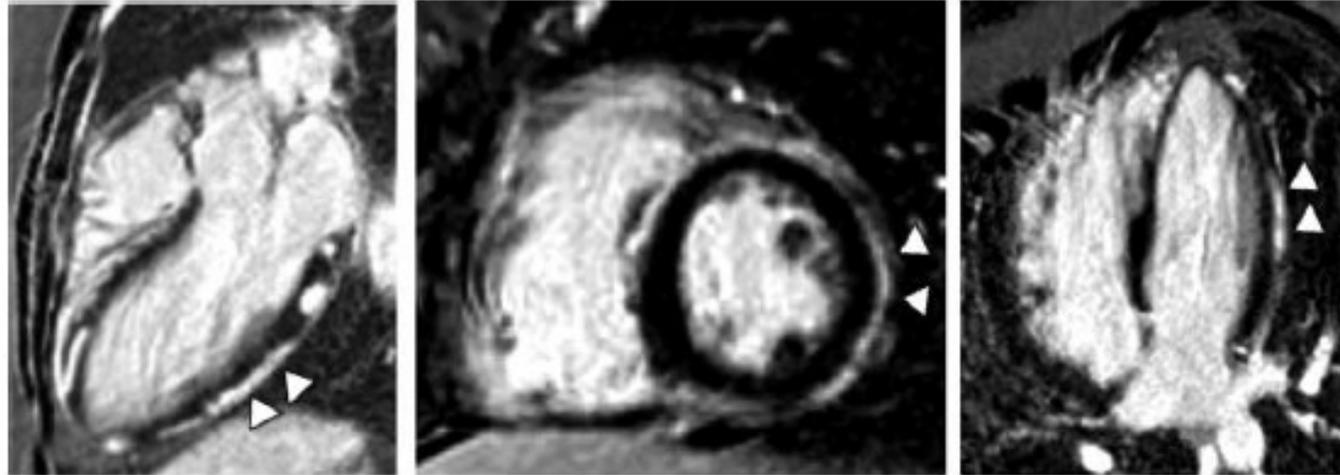
■ Genotipizzati ■ Referti LP



# DCM genetic heterogeneity

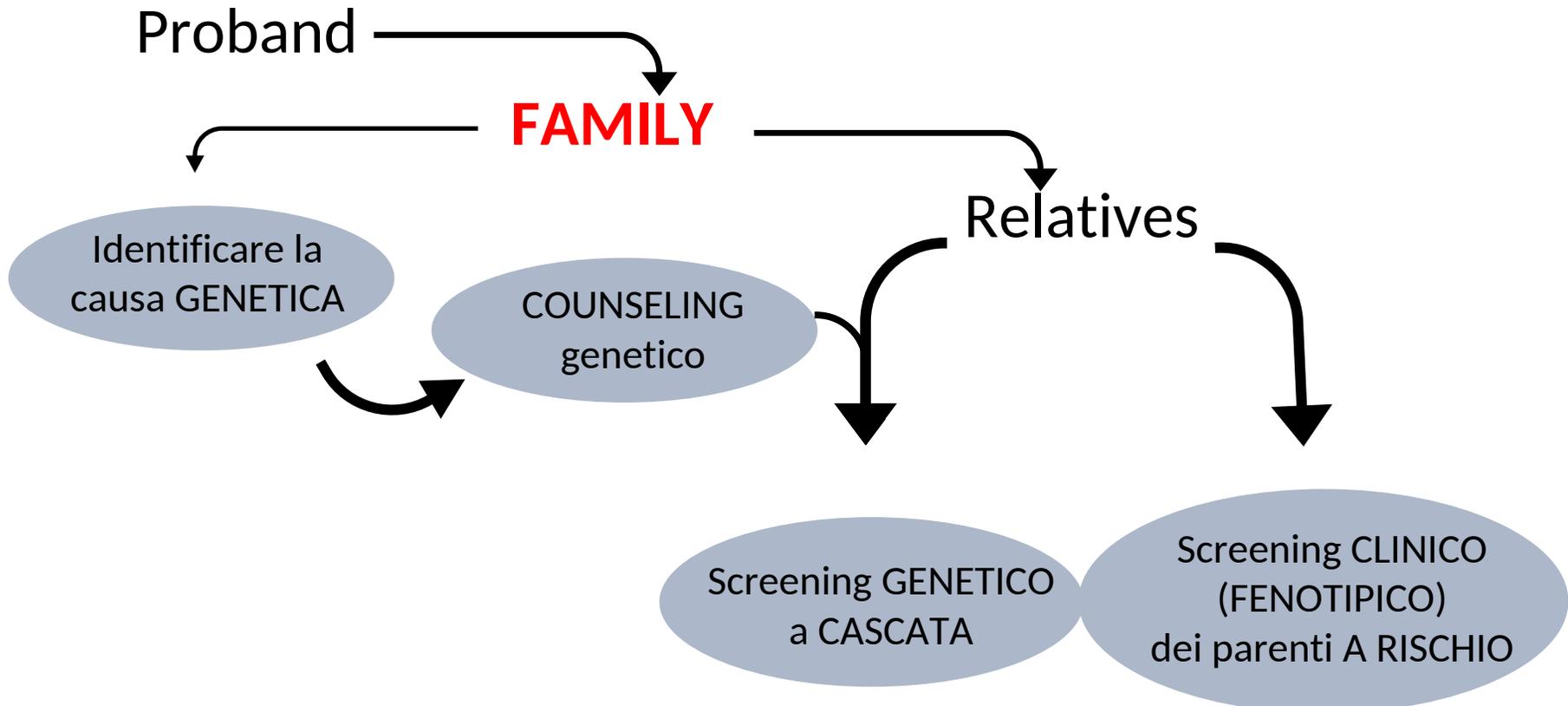
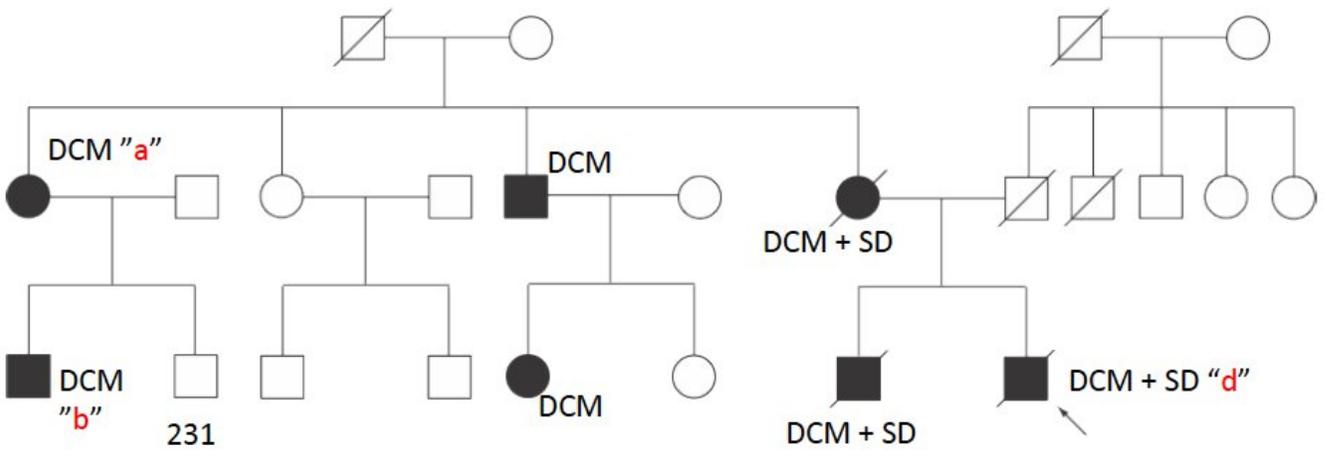


# Desmoplakin Cardiomyopathy, a Fibrotic and Inflammatory Form of Cardiomyopathy Distinct From Typical Dilated or Arrhythmogenic Right Ventricular Cardiomyopathy



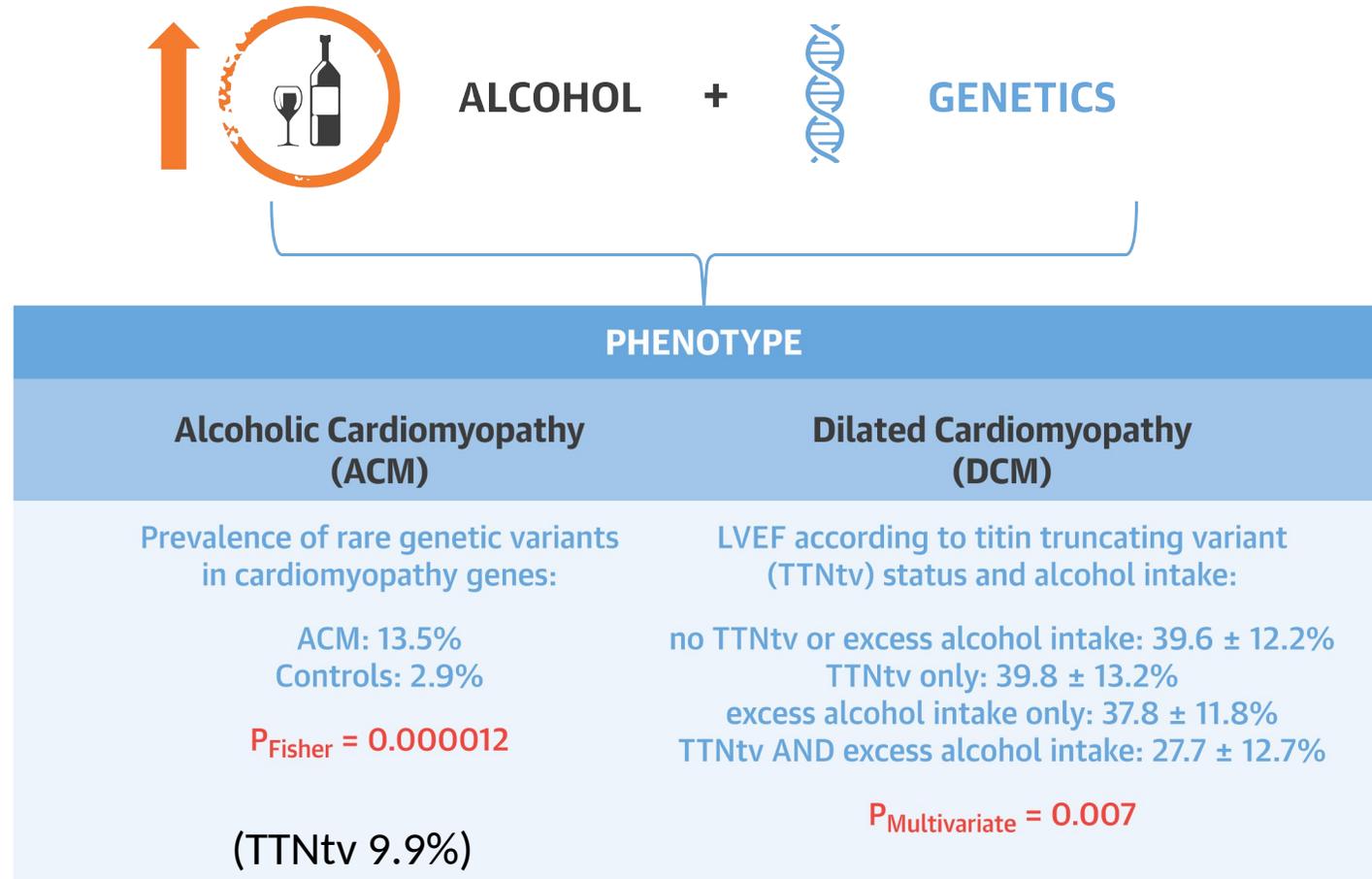
Acute myocardial injury and fibrosis preceding systolic dysfunction.

| Overall Cohort Characteristics         |              |             |         |
|--|--------------|-------------|---------|
|  | DSP, n=107   | PKP2, n=81  | P Value |
| Female                                 | 69%          | 51%         | 0.01    |
| Age at evaluation, y                   | 36±16        | 39±20       | 0.24    |
| Proband                                | 41%          | 42%         | 1.0     |
| Normal ventricular function            | 36% (37/103) | 60% (47/79) | 0.002   |
| RV predominant                         | 14% (14/103) | 40% (32/79) | <0.001  |
| LV predominant                         | 51% (52/103) | 0% (0/79)   | <0.001  |
| Palmoplantar keratoderma or curly hair | 55% (54/98)  | 2% (1/46)   | <0.001  |
| Moderate/intense exercise              | 53% (42/80)  | NA          | NA      |
| Truncating mutation                    | 98%          | 100%        | 0.51    |
| TFC definite ARVC                      | 34% (35/103) | 49% (39/79) | 0.036   |
| TFC borderline ARVC                    | 28% (29/103) | 14% (11/79) |         |
| TFC possible ARVC                      | 38% (39/103) | 37% (29/79) |         |
| Episodic chest pain                    | 21%          | 4%          | 0.001   |
| Troponin elevation                     | 15%          | 0%          | <0.001  |
| T wave inversions V1-V2                | 15% (15/101) | 13% (10/76) | 0.83    |
| T wave inversions V1-V3                | 8% (8/101)   | 50% (38/76) | <0.001  |
| T wave inversions V4-V6                | 21% (20/96)  | 22% (17/76) | 0.85    |
| Left bundle-branch block               | 1% (1/96)    | 0% (0/76)   | 1.0     |
| Right bundle-branch block              | 2% (2/96)    | 1% (1/76)   | 1.0     |
| Frequent PVCs (>500/24 h)              | 56% (32/57)  | 61% (23/38) | 0.83    |
| LV LGE                                 | 40% (23/57)  | 10% (5/51)  | <0.001  |
| LVEF, %                                | 46±14, n=103 | 59±8, n=79  | <0.001  |
| VT outcome                             | 28%          | 30%         | 0.87    |



# Genetic Etiology for Alcohol-Induced Cardiac Toxicity

**CENTRAL ILLUSTRATION** Alcohol Consumption and Genetic Background Act in Concert to Determine Cardiac Phenotype



Ware, J.S. et al. J Am Coll Cardiol. 2018;71(20):2293-302.

# Genetic Variants Associated With Cancer Therapy–Induced Cardiomyopathy

**Table 2.** Burden Analysis of 9 DCM Genes in CCM Cohorts

| Gene                | Cohort A<br>(n=99) | Cohort B<br>(n=73) | Cohort C<br>(n=41) | All CCM<br>(n=213) | TCGA*<br>Breast/<br>Lung<br>(n=2053) | HVOL†<br>(n=445) | P Values Comparisons of |                        |                        |   |
|---------------------|--------------------|--------------------|--------------------|--------------------|--------------------------------------|------------------|-------------------------|------------------------|------------------------|---|
|                     |                    |                    |                    |                    |                                      |                  | All CCM Versus          |                        |                        | NFE§ CCM<br>(n=170)<br>Versus NFE<br>gnomAD |
|                     |                    |                    |                    |                    |                                      |                  | TCGA                    | HVOL                   | gnomAD‡                |   |
| BAG3                | 1 (1.0%)           | 2 (2.7%)           | 0 (0.0%)           | 3 (1.4%)           | 18 (0.9%)                            | 4 (0.9%)         | 0.44 (1)                | 0.69 (1)               | 0.44 (1)               | 0.37 (1)                                    |
| DSP                 | 0 (0.0%)           | 0 (0.0%)           | 0 (0.0%)           | 0 (0.0%)           | 4 (0.2 %)                            | 0 (0.0%)         | 1 (1)                   | 1 (1)                  | 1 (1)                  | 1 (1)                                       |
| LMNA                | 0 (0.0%)           | 1 (1.4%)           | 0 (0.0%)           | 1 (0.5%)           | 16 (0.8%)                            | 2 (0.4%)         | 1 (1)                   | 1 (1)                  | 1 (1)                  | 1 (1)                                       |
| MYH7                | 3 (3.0%)           | 0 (0.0%)           | 0 (0.0%)           | 3 (1.4%)           | 35 (1.7%)                            | 5 (1.1%)         | 1 (1)                   | 0.72 (1)               | 1 (1)                  | 0.75 (1)                                    |
| SCN5A               | 0 (0.0%)           | 0 (0.0%)           | 0 (0.0%)           | 0 (0.0%)           | 3 (0.2%)                             | 1 (0.2%)         | 1 (1)                   | 1 (1)                  | 1 (1)                  | 1 (1)                                       |
| TCAP                | 1 (1.0%)           | 0 (0.0%)           | 1 (2.4%)           | 2 (0.9%)           | 2 (0.1%)                             | 0 (0.0%)         | 0.05 (0.45)             | 0.10 (0.90)            | 0.07 (0.62)            | 1 (1)                                       |
| TNNC1               | 0 (0.0%)           | 0 (0.0%)           | 0 (0.0%)           | 0 (0.0%)           | 1 (0.1%)                             | 0 (0.0%)         | 1 (1)                   | 1 (1)                  | 1 (1)                  | 1 (1)                                       |
| TNNT2               | 0 (0.0%)           | 1 (1.4%)           | 0 (0.0%)           | 1 (0.5%)           | 7 (0.3%)                             | 0 (0.0%)         | 0.55 (1)                | 0.32 (1)               | 0.50 (1)               | 0.34 (1)                                    |
| TTN                 | 10 (10.0%)         | 4 (5.5%)           | 2 (4.9%)           | 16 (7.5%)          | 22 (1.1%)                            | 3 (0.7%)         | 7.36e−08<br>(6.62e−07)  | 3.42e−06<br>(3.08e−05) | 5.87e−14<br>(5.28e−13) | 2.03e−10<br>(1.82e−09)                      |
| 8 genes<br>(no TTN) | 5 (5.1%)           | 4 (5.5%)           | 1 (2.4%)           | 10 (4.7%)          | 86 (4.2%)                            | 12 (2.7%)        | 0.72                    | 0.25                   | 0.01                   | 0.21  |
| 9 genes             | 15 (15.1%)         | 8 (11%)            | 3 (7.3%)           | 26 (12.2%)         | 108 (5.3%)                           | 15 (3.4%)        | 1.98e−04                | 3.90e−05               | 1.78e−06               | 6.98e−06                                    |

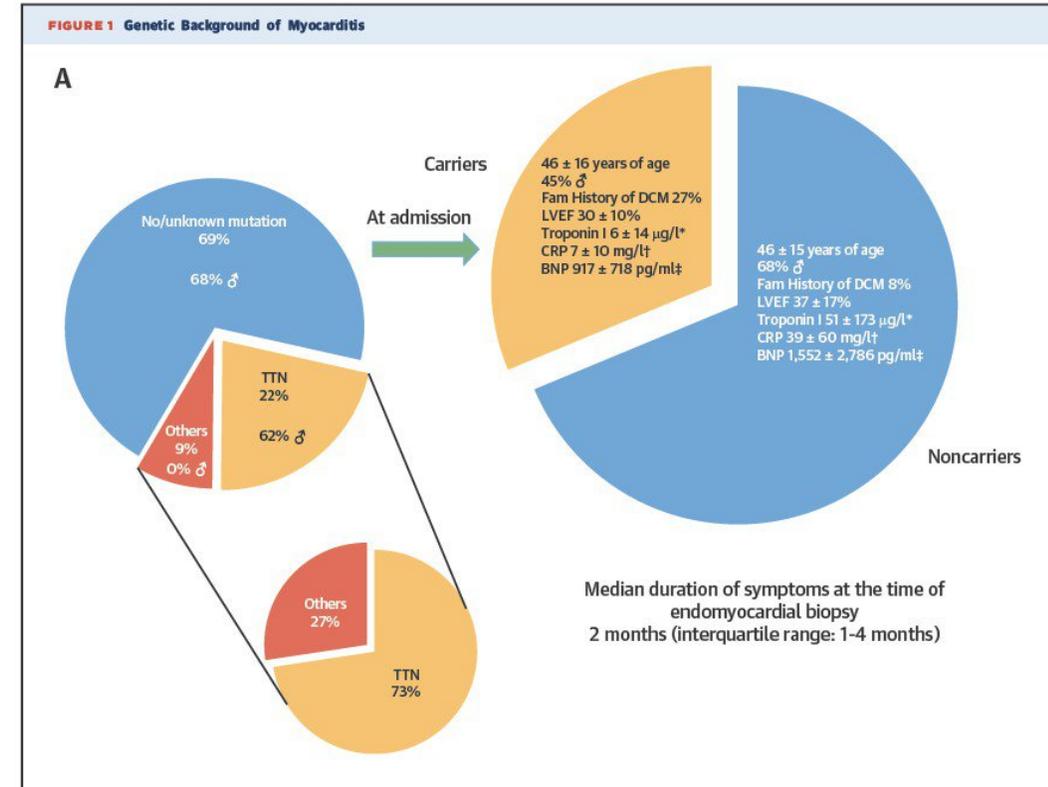
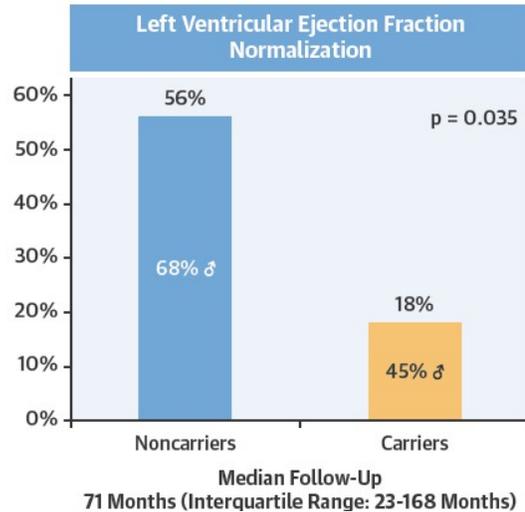
*Circulation.* 2019;140:31–41. DOI: 10.1161/CIRCULATIONAHA.118.037934



# Environment and genetics

## Inflammation (myocarditis)

Genetic predisposition to DCM should be ruled out in some cases of myocarditis, especially (1) in the setting of known familial Cardiomyopathy, (2) in the presence of LV dysfunction and remodeling associated with only mild histological inflammation, or, (3) in cases of persistent LV dysfunction despite immunosuppressive therapy, and, finally, (4) in particular cases of recurrent myocarditis - SCA like presentation, no or mild LV dysfunction, arrhythmia



**Lymphocytic Myocarditis**

**Artico, Merlo, Sinagra et al**  
 VOL. 75, NO. 24, 2020  
 ISSN 0735-1097/\$36.00

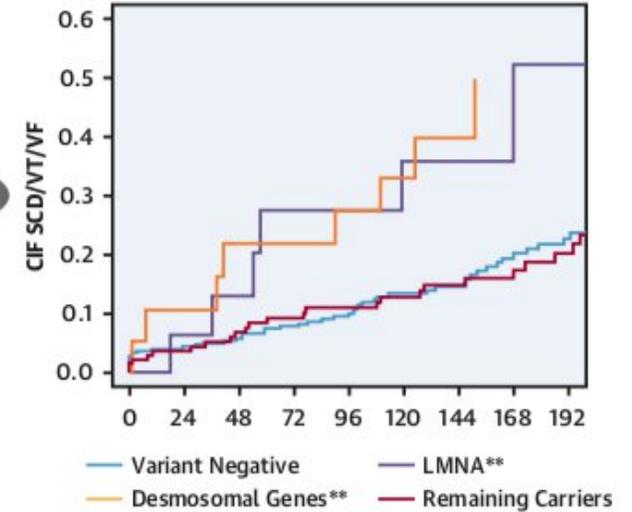
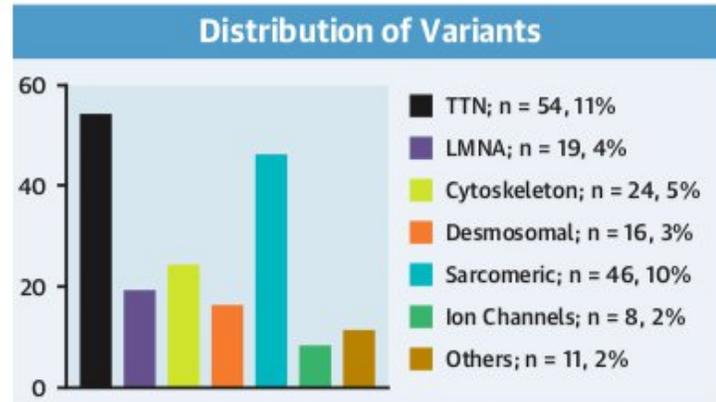
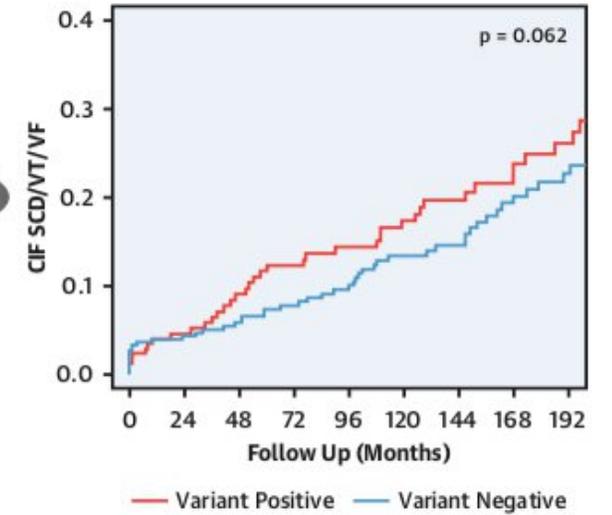
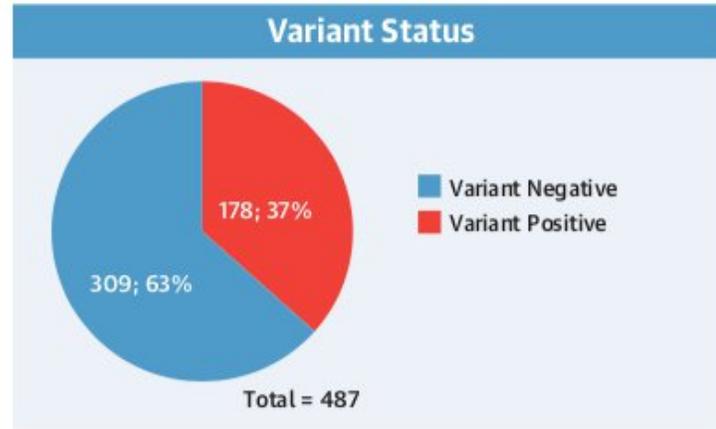
**A Genetically Predisposed Disease?**

## Genetic Risk of Arrhythmic Phenotypes in Patients With Dilated Cardiomyopathy

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



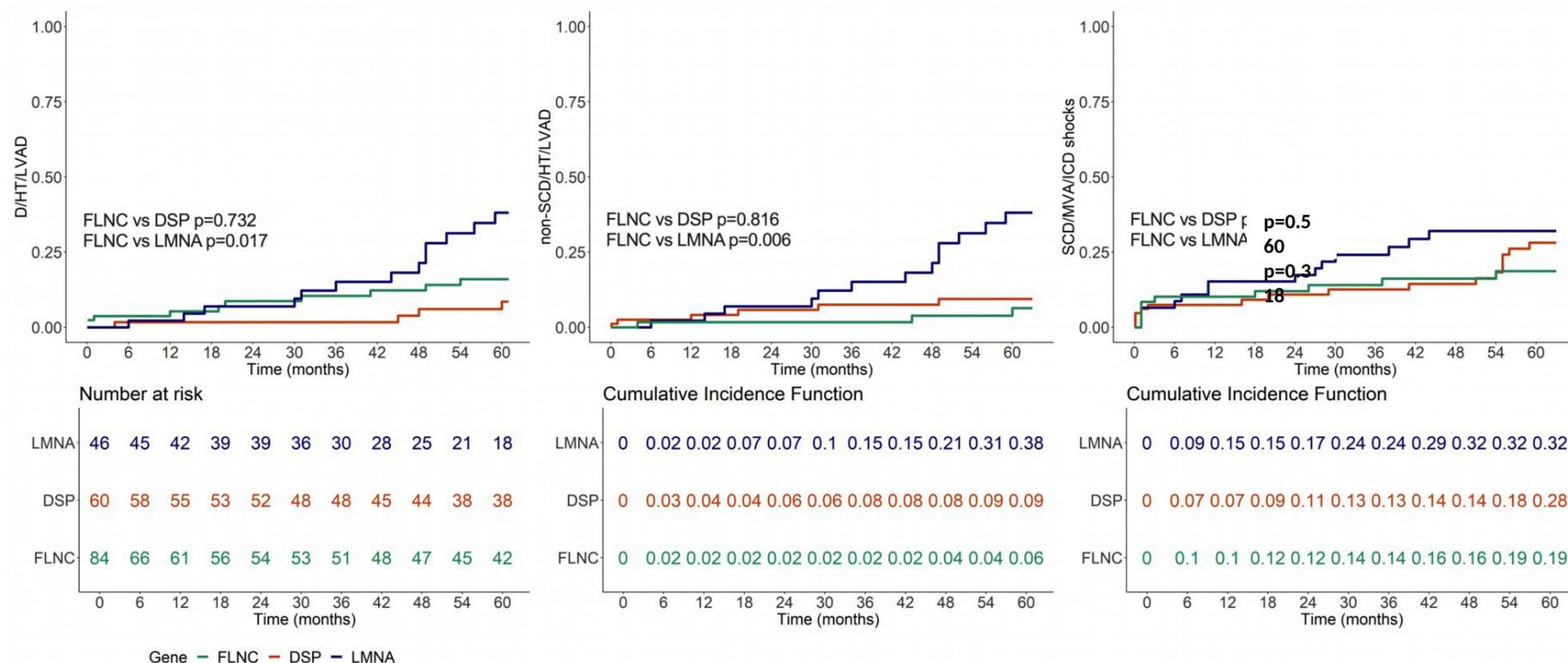
### CENTRAL ILLUSTRATION Effect of Genotype on Outcome in Dilated Cardiomyopathy



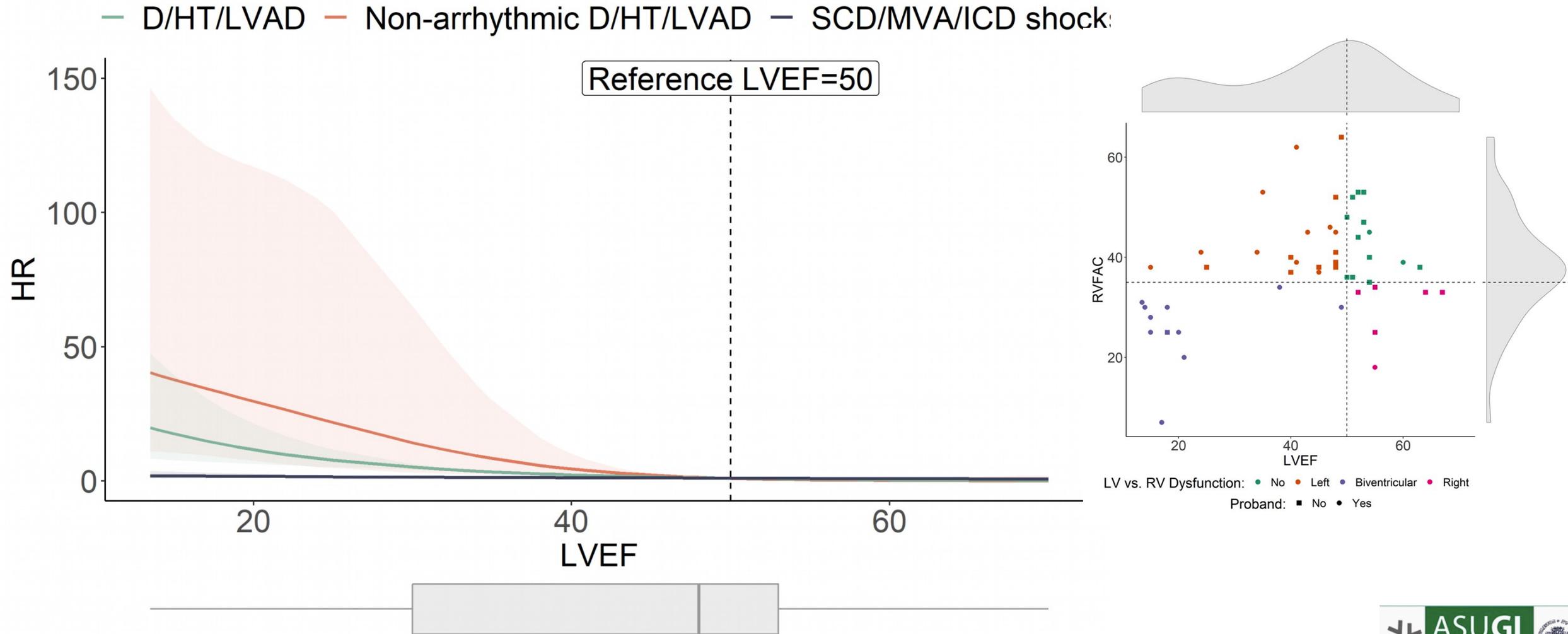
Gigli, M. et al. J Am Coll Cardiol. 2019;74(11):1480-90.

## ORIGINAL RESEARCH ARTICLE

## Phenotypic Expression, Natural History, and Risk Stratification of Cardiomyopathy Caused by Filamin C Truncating Variants



# Phenotypic Expression, Natural History and Risk Stratification of Cardiomyopathy Caused by Filamin C Truncating Variant



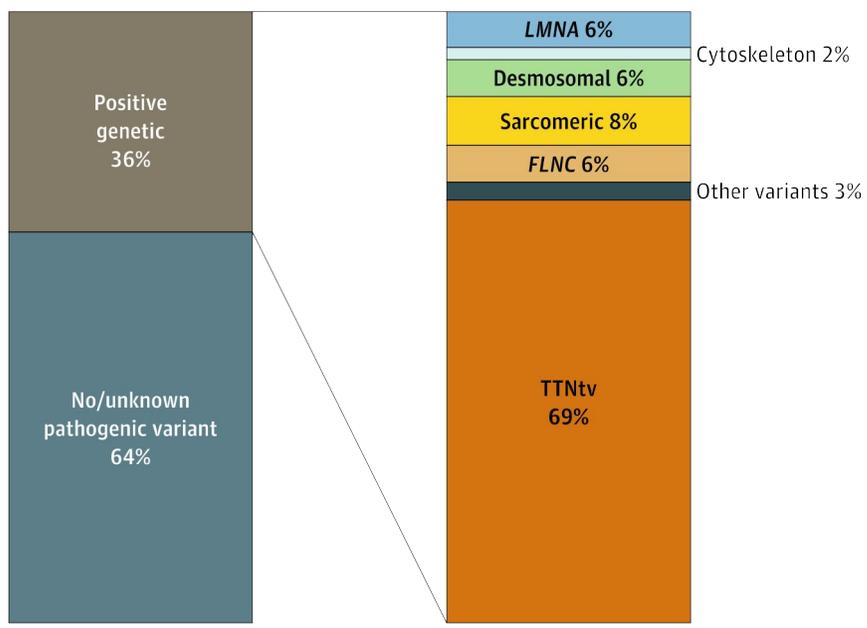


# Association of Titin Variations With Late-Onset Dilated Cardiomyopathy

Antonio Cannatà, MD; Marco Merlo, MD; Matteo Dal Ferro, MD; Giulia Barbati, PhD; Paolo Manca, MD; Alessia Paldino, MD; Sharon Graw, PhD; Marta Gigli, MD; Davide Stolfo, MD; Renee Johnson, PhD; Darius Roy, MD; Kevin Tharratt, MD; Daniel I. Bromage, MD, PhD; Jean Jirikowic, MSGC; Antonio Abbate, MD, PhD; Allison Goodwin, MD; Krishnasree Rao, MD; Amr Marawan, MD; Gerry Carr-White, MD; Leema Robert, MD; Victoria Parikh, MD, PhD; Euan Ashley, MD, PhD; Theresa McDonagh, MD; Neal K. Lakdawala, MD; Diane Fatkin, MD; Matthew R. G. Taylor, MD, PhD; Luisa Mestroni, MD; Gianfranco Sinagra, MD

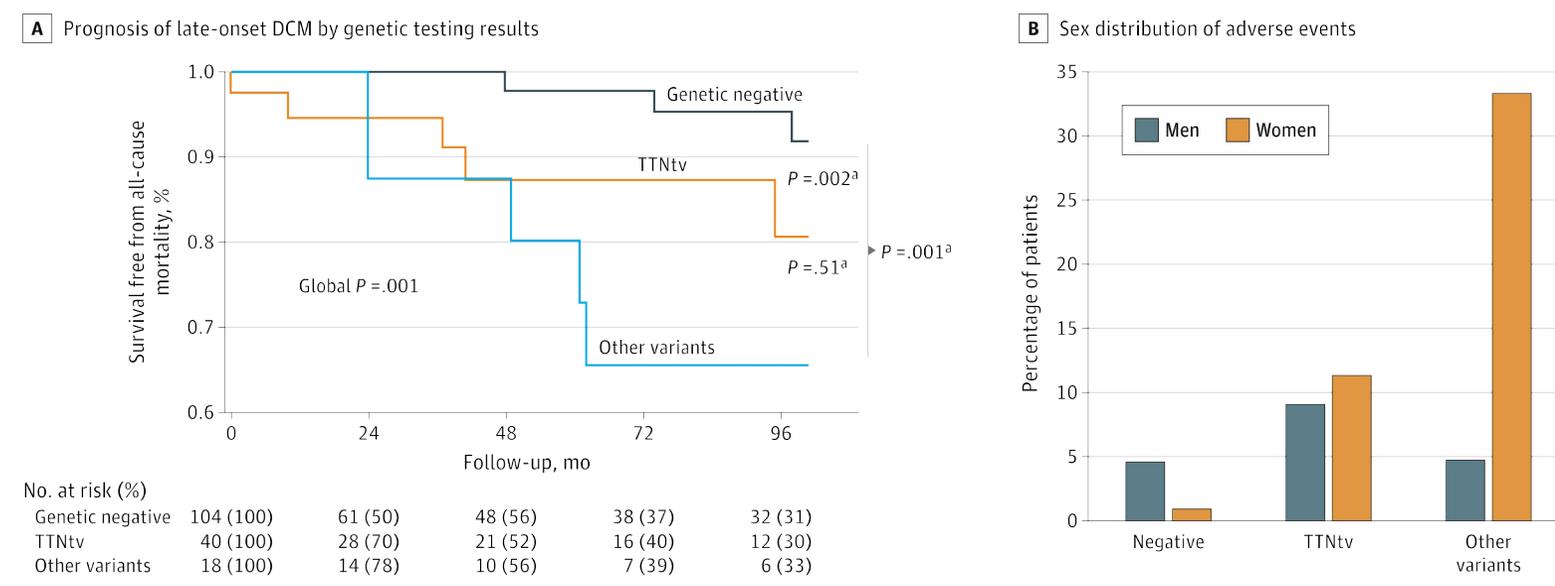
JAMA Cardiology Published online February 9, 2022

Figure 1. Diagnostic Yield and Genetic Landscape in the Late-Onset Dilated Cardiomyopathy Population



FLNC indicates filamin C; LMNA, lamin A/C; TTNtv, *titin*-truncating variants.

Figure 3. Long-term Prognosis of Late-Onset Dilated Cardiomyopathy (DCM) According to Genetic Testing Results and Sex Distribution of Adverse Events

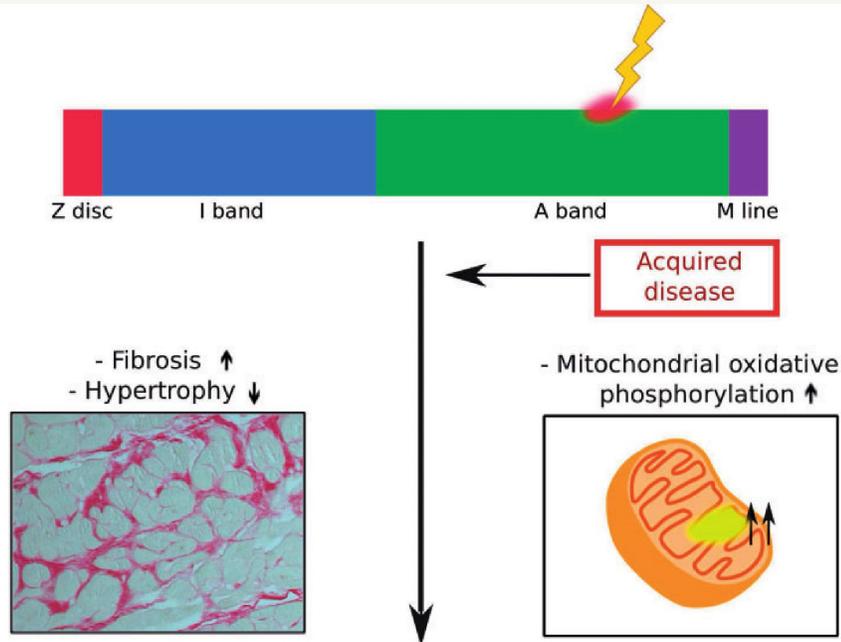


TTNtv indicates *titin*-truncating variants.

<sup>a</sup> Significant after Bonferroni correction.

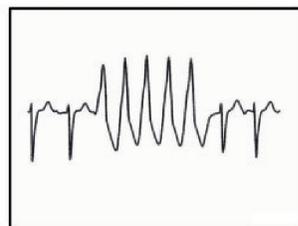
# Titin cardiomyopathy leads to altered mitochondrial energetics, increased fibrosis and long-term life-threatening arrhythmias

## Truncating TTN Mutation

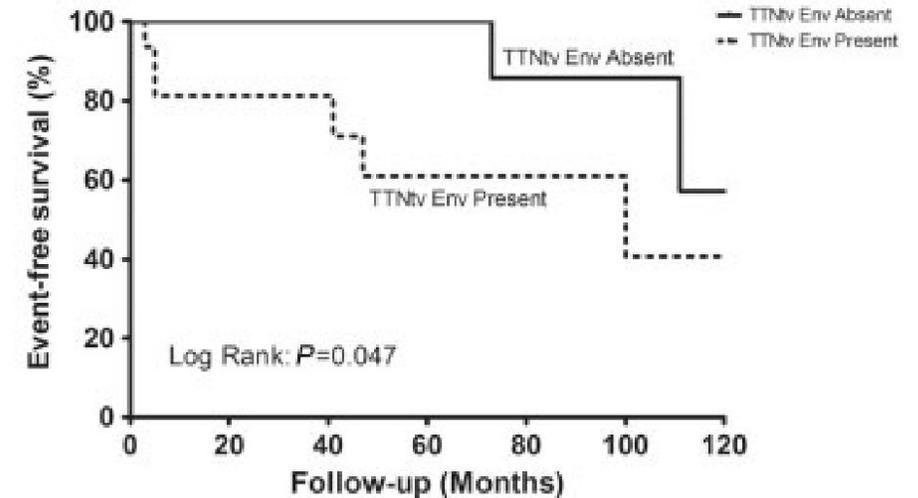


## Dilated Cardiomyopathy

- Ventricular arrhythmias ↑



Life-threatening arrhythmia in TTNtv according to environmental factors

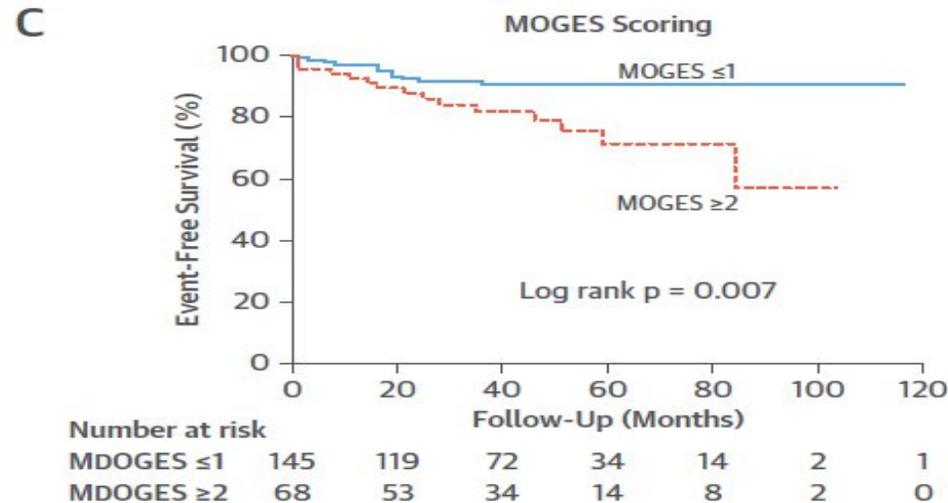
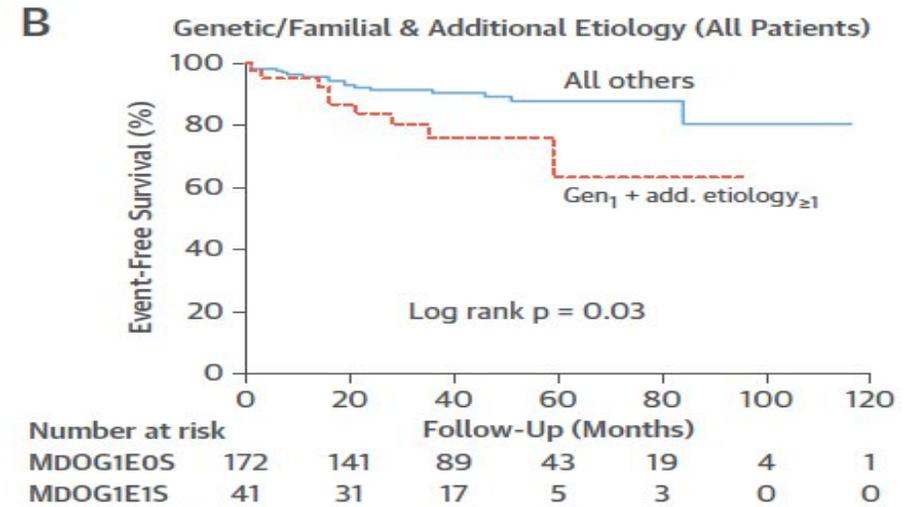
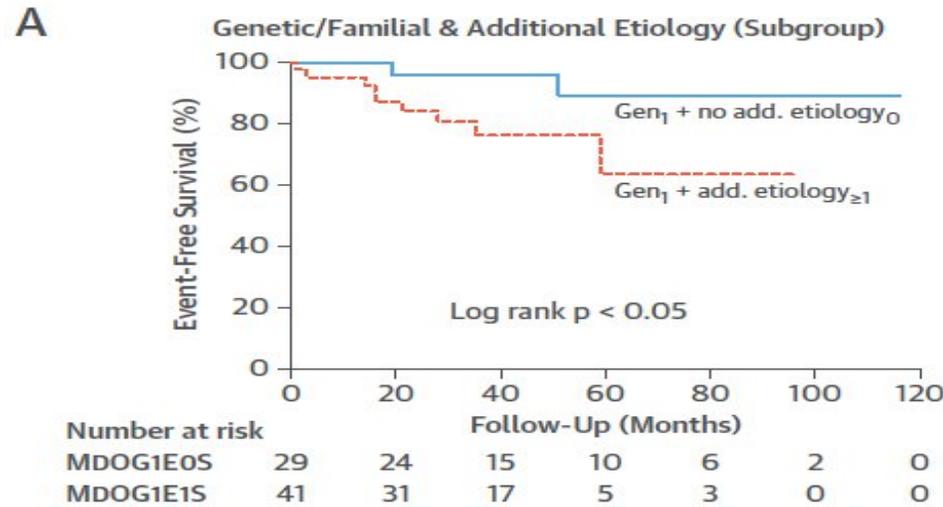


Number at risk

|                    |    |    |   |   |   |   |   |
|--------------------|----|----|---|---|---|---|---|
| TTNtv Env absent:  | 21 | 15 | 9 | 8 | 3 | 2 | 1 |
| TTNtv Env present: | 17 | 12 | 8 | 6 | 5 | 3 | 2 |

# Prognostic Relevance of Gene-Environment Interactions in Patients With Dilated Cardiomyopathy

## Applying the MOGE(S) Classification



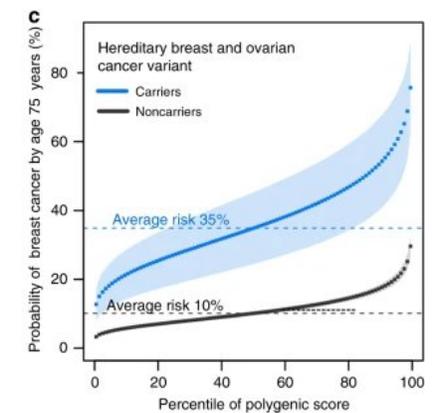
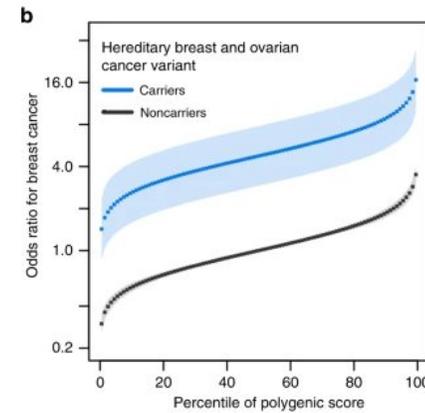
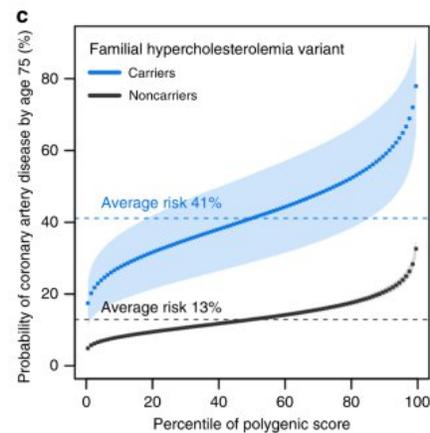
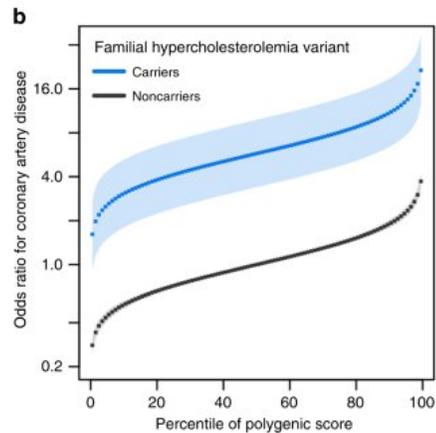
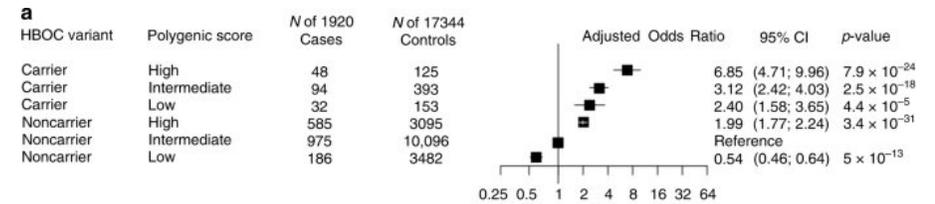
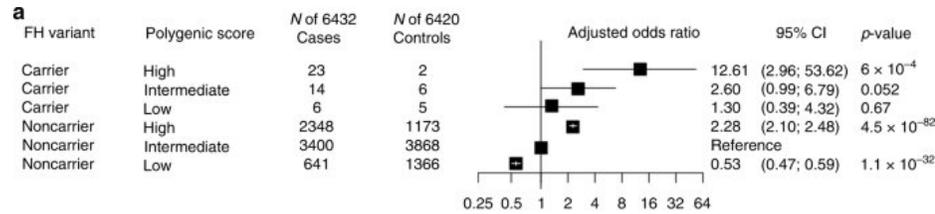
ARTICLE

<https://doi.org/10.1038/s41467-020-17374-3> OPEN



# Polygenic background modifies penetrance of monogenic variants for tier 1 genomic conditions

Akl C. Fahed<sup>1,2,3,4,5,13</sup>, Minxian Wang<sup>4,5,13</sup>, Julian R. Homburger<sup>6,13</sup>, Aniruddh P. Patel<sup>1,2,3,4,5</sup>, Alexander G. Bick<sup>1,3,4,5</sup>, Cynthia L. Neben<sup>6</sup>, Carmen Lai<sup>6</sup>, Deanna Brockman<sup>1,4,5</sup>, Anthony Philippakis<sup>4,5</sup>, Patrick T. Ellinor<sup>2,3,4,5</sup>, Christopher A. Cassa<sup>7</sup>, Matthew Lebo<sup>8</sup>, Kenney Ng<sup>9</sup>, Eric S. Lander<sup>4,5,10,11</sup>, Alicia Y. Zhou<sup>6</sup>, Sekar Kathiresan<sup>2,3,5,12</sup> & Amit V. Khera<sup>1,2,3,4,5</sup>✉



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

## Recommendations for an implantable cardioverter-defibrillator in patients with heart failure

### 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  $\geq 3$  months of OMT, provided they are expected to survive substantially longer than 1 year with good functional status.<sup>161,165</sup>

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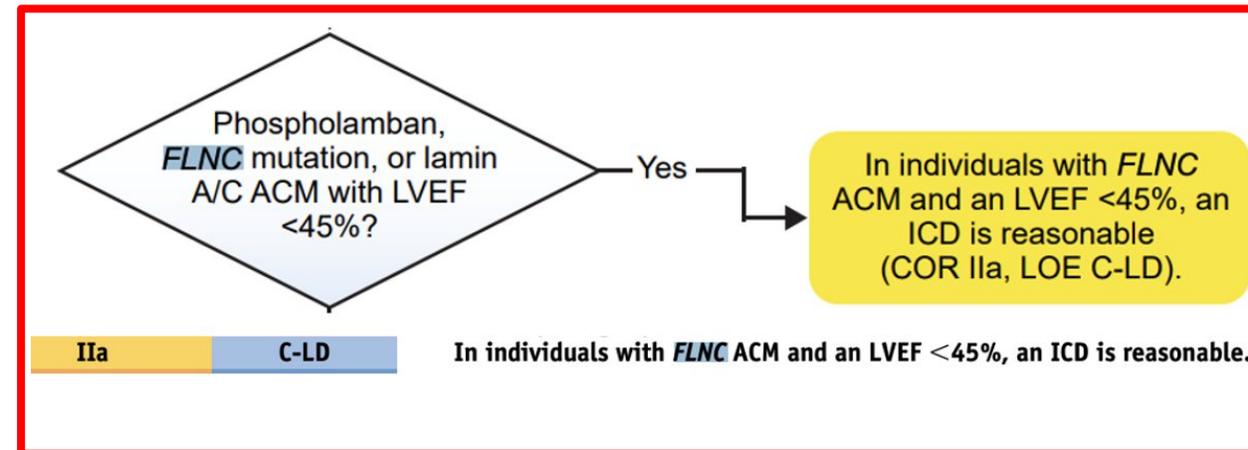
An ICD should be considered to reduce the risk of sudden death and all-cause mortality in patients with symptomatic HF (NYHA class II–III) of a non-ischaemic aetiology, and an LVEF  $\leq 35\%$  despite  $\geq 3$  months of OMT, provided they are expected to survive substantially longer than 1 year with good functional status.<sup>161,166,167</sup>

IIa

A

## 2019 HRS expert consensus statement on evaluation, risk stratification, and management of arrhythmogenic cardiomyopathy: Executive summary

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



# 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 ≤35% despite ≥3 months of OMT, provided they are expected to survive substantially longer than 1 year with good functional status. <sup>161,165</sup> | 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 ≤35% despite ≥3 months of OMT, provided they are expected to survive substantially longer than 1 year with good functional status. <sup>161,166,167</sup>   | 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 ≤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. <sup>1–9</sup> |

«...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.»

|  |  |
|--|--|
| <b>Value Statement:<br/>High Value (A)</b> | 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. <sup>10–15</sup> |
|--|--|

## Post-discharge arrhythmic risk stratification of patients with acute myocarditis and life-threatening ventricular tachyarrhythmias

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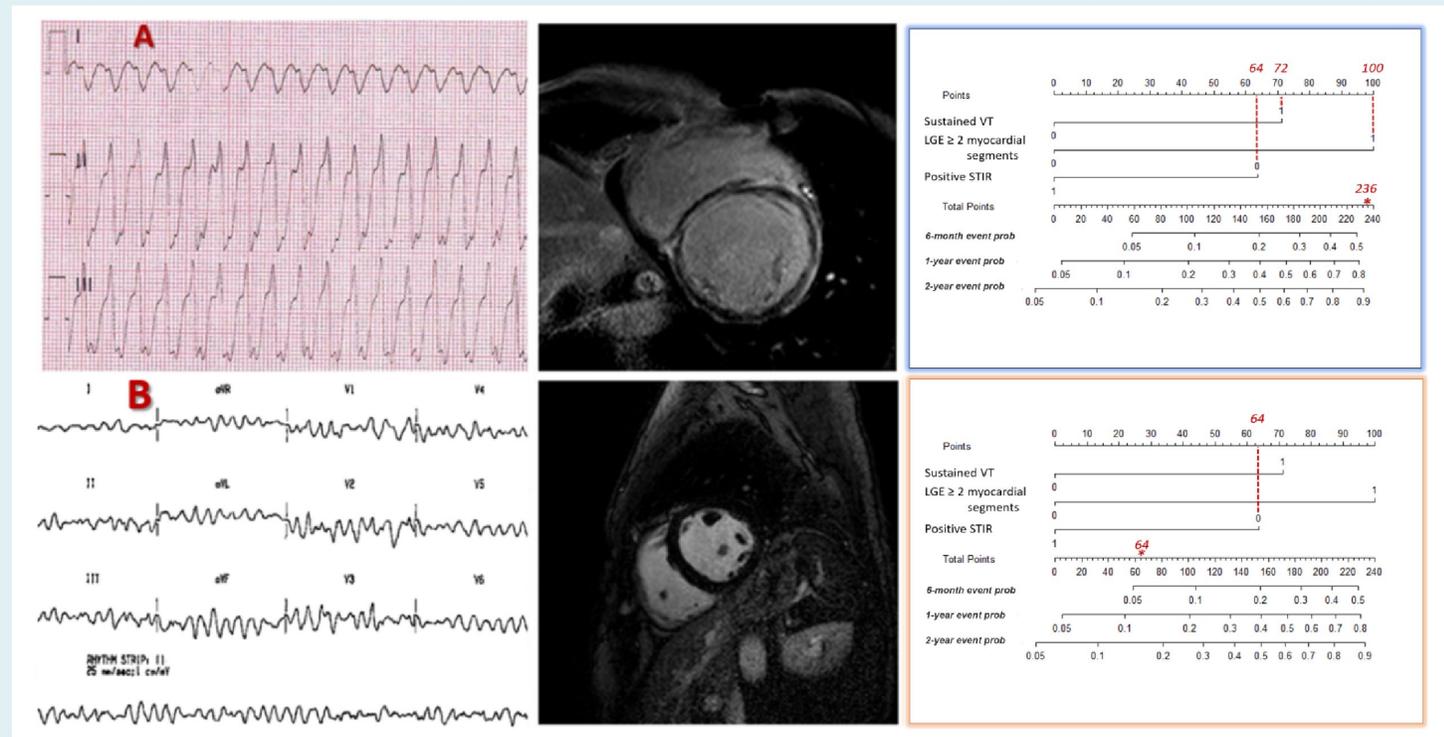
**Table 2** Univariable and multivariable analysis for baseline prediction model of major arrhythmic events at follow-up

|   | HR (95% CI) for MAEs <sup>a</sup> |                  |                  |                  |
|---|-----------------------------------|------------------|------------------|------------------|
|   | Unadjusted HR                     | P-value          | Adjusted HR      | P-value          |
| Epoch of enrolment (1995–2004 vs. 2005–2019)      | 0.18 (0.03–1.32)                  | 0.09             |                  |                  |
| Male sex  | 0.38 (0.18–0.81)                  | 0.012            |                  |                  |
| Family history of cardiomyopathy                  | 2.31 (1.04–5.15)                  | 0.04             |                  |                  |
| Sustained ventricular tachycardia at presentation | 2.24 (1.20–4.17)                  | <b>0.011</b>     | 2.90 (1.38–6.11) | <b>0.005</b>     |
| LVEDV   | 1.01 (0.99–1.01)                  | 0.07             |                  |                  |
| LGE involving ≥2 myocardial segments at CMR       | 3.56 (1.75–7.23)                  | <b>&lt;0.001</b> | 4.51 (2.39–8.53) | <b>&lt;0.001</b> |
| Absence of positive STIR at CMR                   | 1.90 (1.05–3.44)                  | <b>0.033</b>     | 2.59 (1.40–4.79) | <b>0.002</b>     |
| Cardiac sarcoidosis                               | 12.95 (2.69–62.34)                | 0.001            |                  |                  |

All tested variables with P-values >0.1 are not shown.

CI, confidence interval; CMR, cardiac magnetic resonance; HR, hazard ratio; LGE, late gadolinium enhancement; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; MAE, major arrhythmic event; STIR, short-tau inversion recovery.

<sup>a</sup>The independent predictors of MAEs during follow-up were studied in the population with available CMR data (n = 117/156, 75%; 44 events).



**Figure 3** Probability of experiencing major arrhythmic events (MAEs) after discharge according the combination of variables identified at multivariable analysis. A nomogram taking into account the competing risk setting was estimated from the multivariable model to calculate the individual probability of experiencing relapse of MAEs during follow-up. (A) A patient with sustained ventricular tachycardia (VT) at presentation (72 points), late gadolinium enhancement (LGE) involving ≥2 myocardial segments (100 points) without positive short-tau inversion recovery (STIR) (64 points), and the respective nomogram shows a total score of 236 points and a probability of MAE relapse of 54%, 83%, and 91% at 6 months, 1 year, and 2 years, respectively. (B) A patient with ventricular fibrillation (VF) at presentation (0 points), focal LGE (0 points) and absence of positive STIR (64 points) at cardiac magnetic resonance, and the respective nomogram showing a probability of MAE relapse of 6%, 12%, and 16% at 6 months, 1 year, and 2 years, respectively.



### Presentation with:

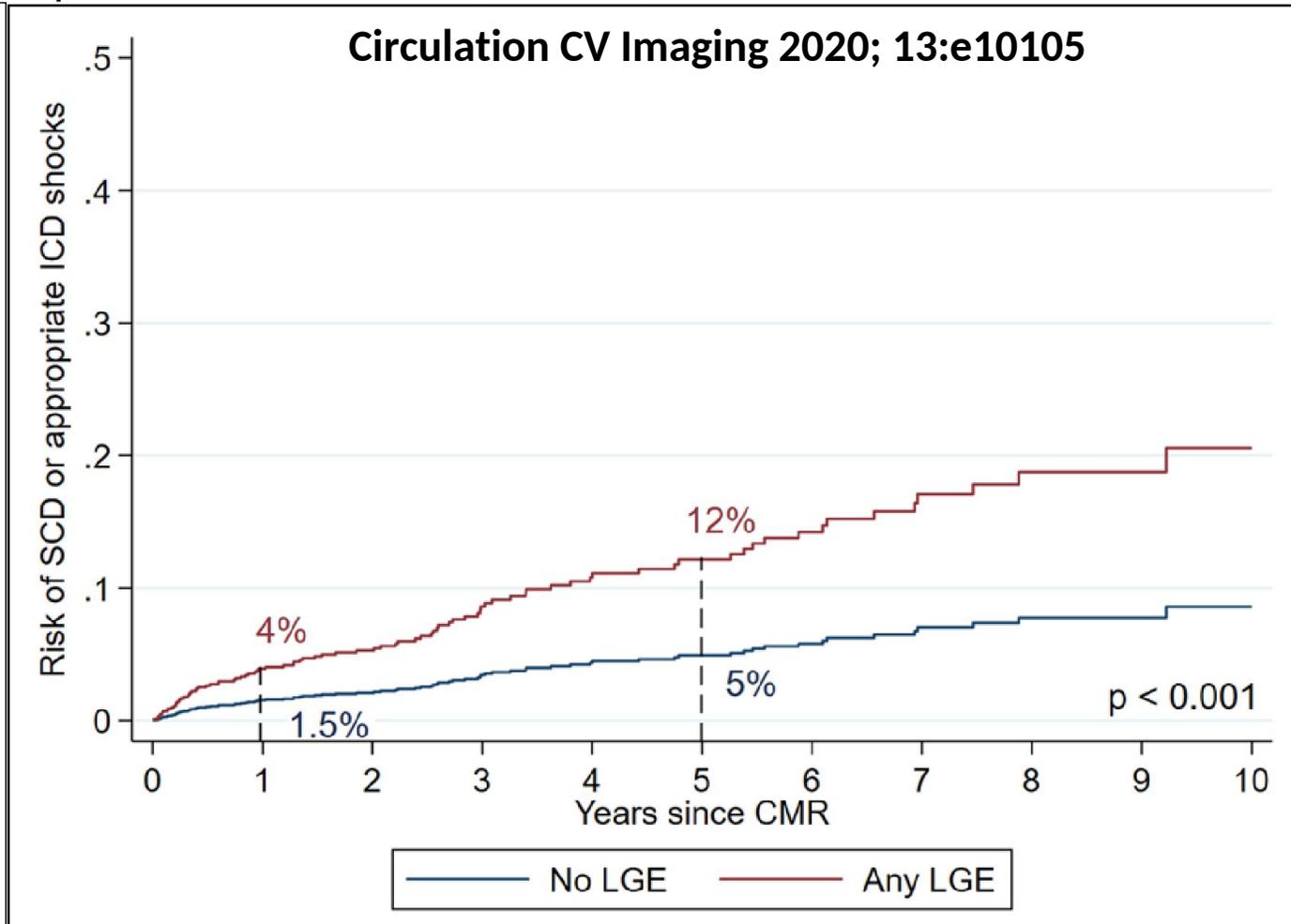
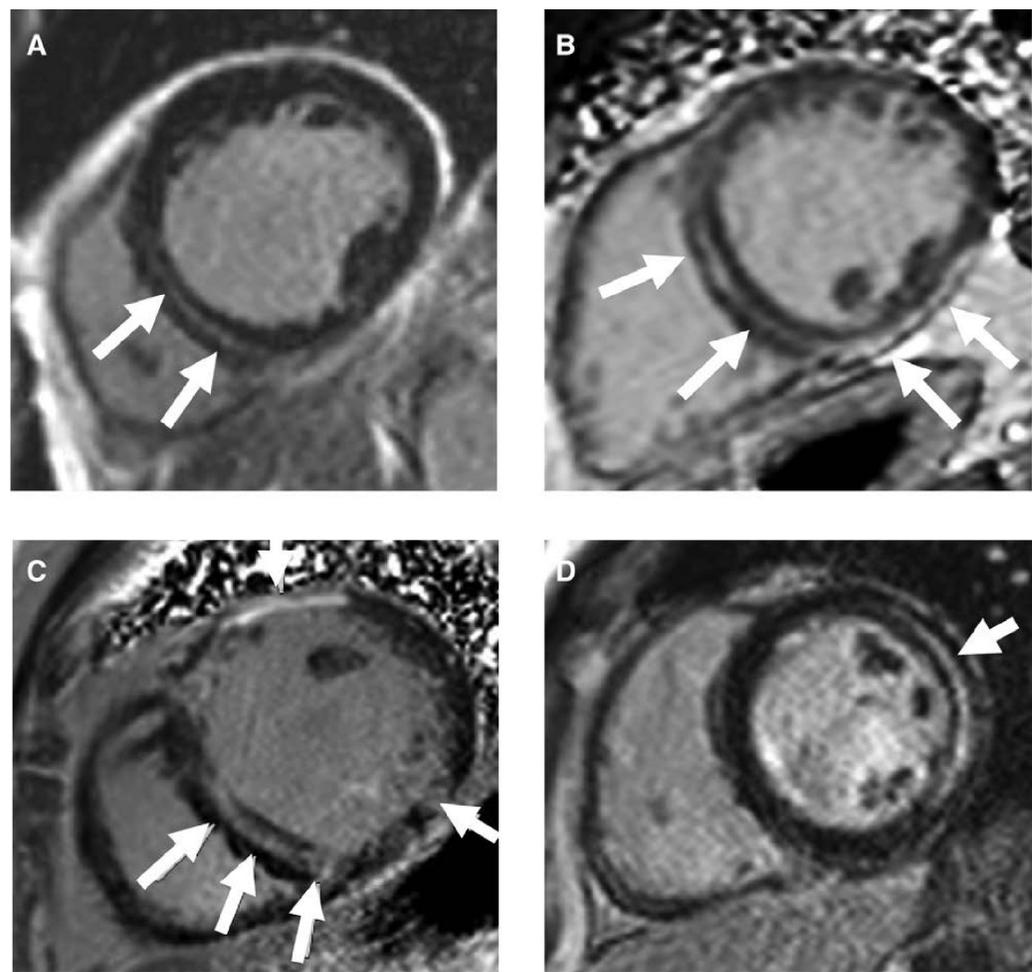
- Sustained Ventricular Tachycardia
  - LGE involving ≥ 2 myocardial segments
  - Absence of positive STIR
- Arrhythmic risk +++

ORIGINAL ARTICLE

# Prognostic Value of Late Gadolinium Enhancement for the Prediction of Cardiovascular Outcomes in Dilated Cardiomyopathy

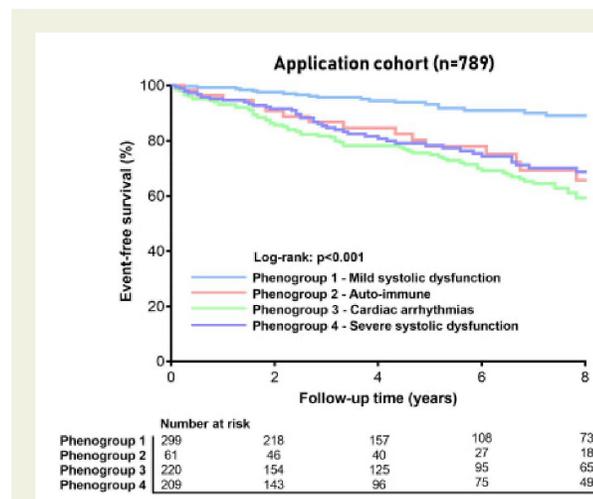
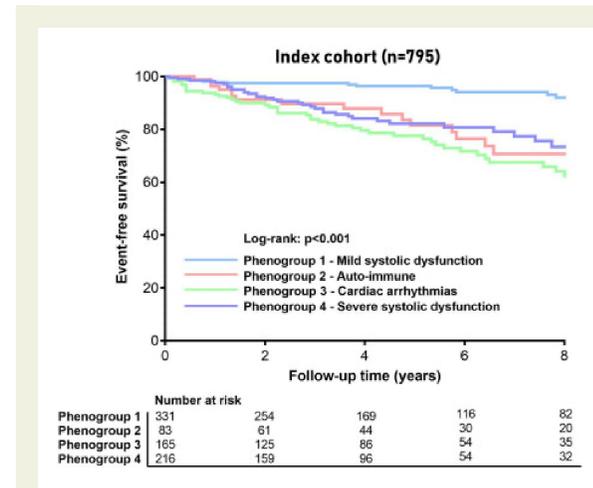
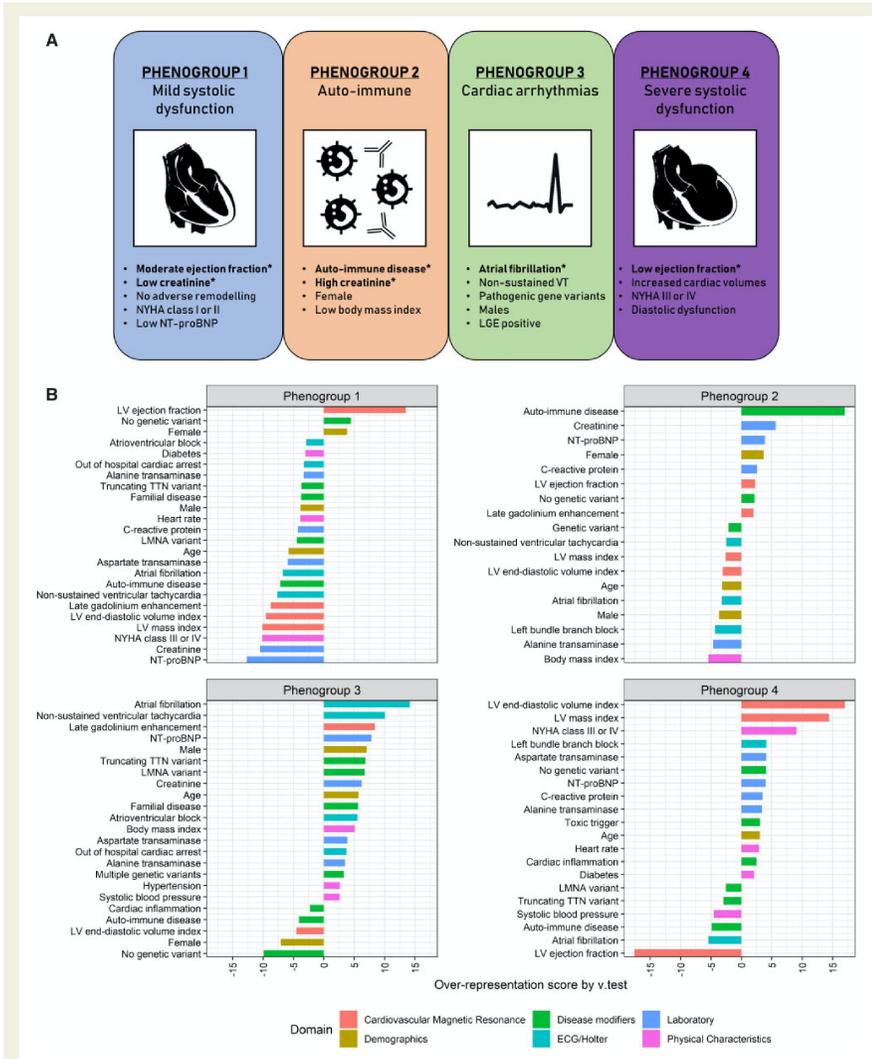
An International, Multi-Institutional Study of the MINICOR Group

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## Phenotypic clustering of dilated cardiomyopathy patients highlights important pathophysiological differences

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# Precision Medicine in the Management of Dilated Cardiomyopathy

JACC State-of-the-Art Review

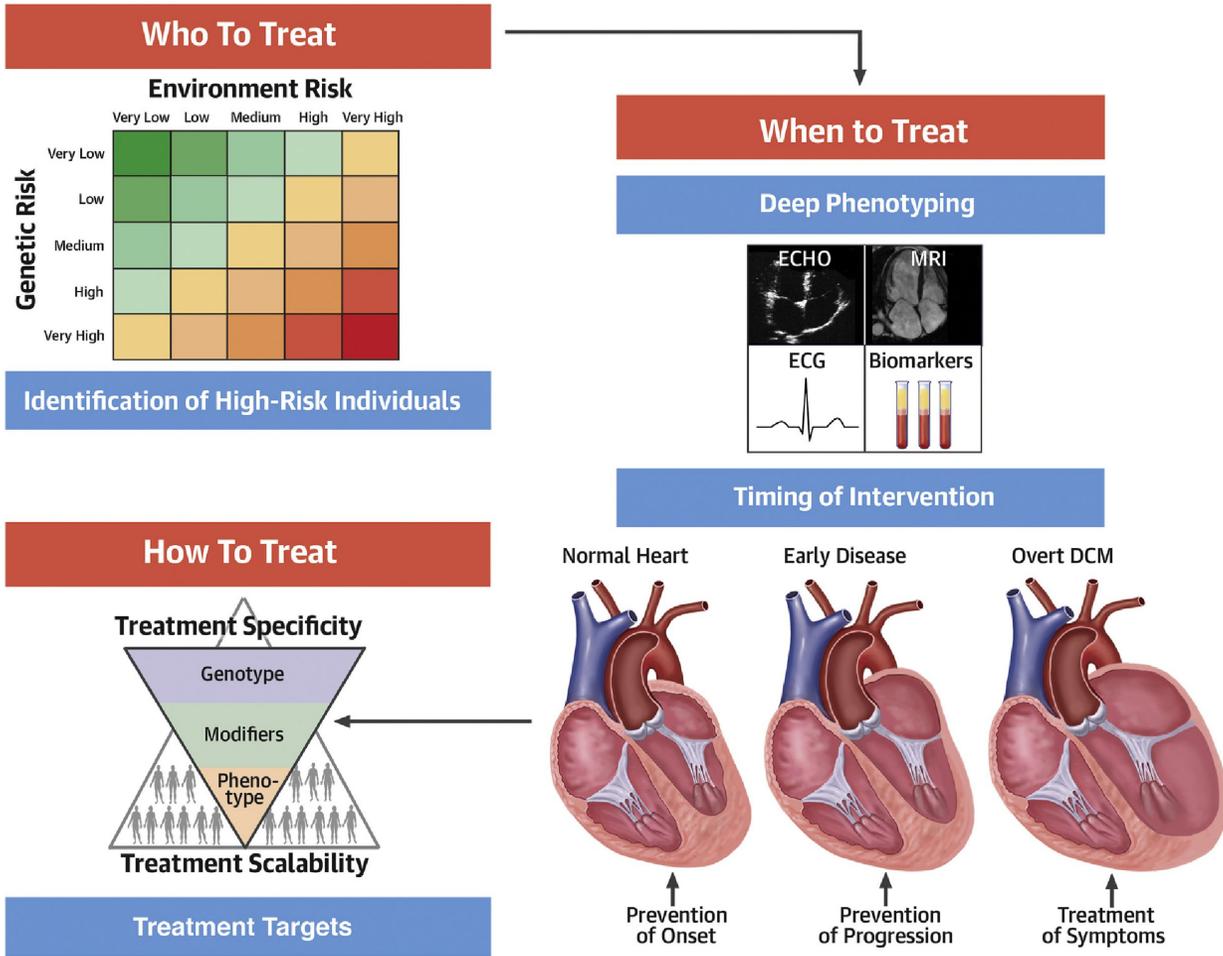
Fatkin *et al.*

Precision Medicine in Dilated Cardiomyopathy

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**CENTRAL ILLUSTRATION** Precision Medicine for Dilated Cardiomyopathy



Fatkin, D. et al. J Am Coll Cardiol. 2019;74(23):2921-38.