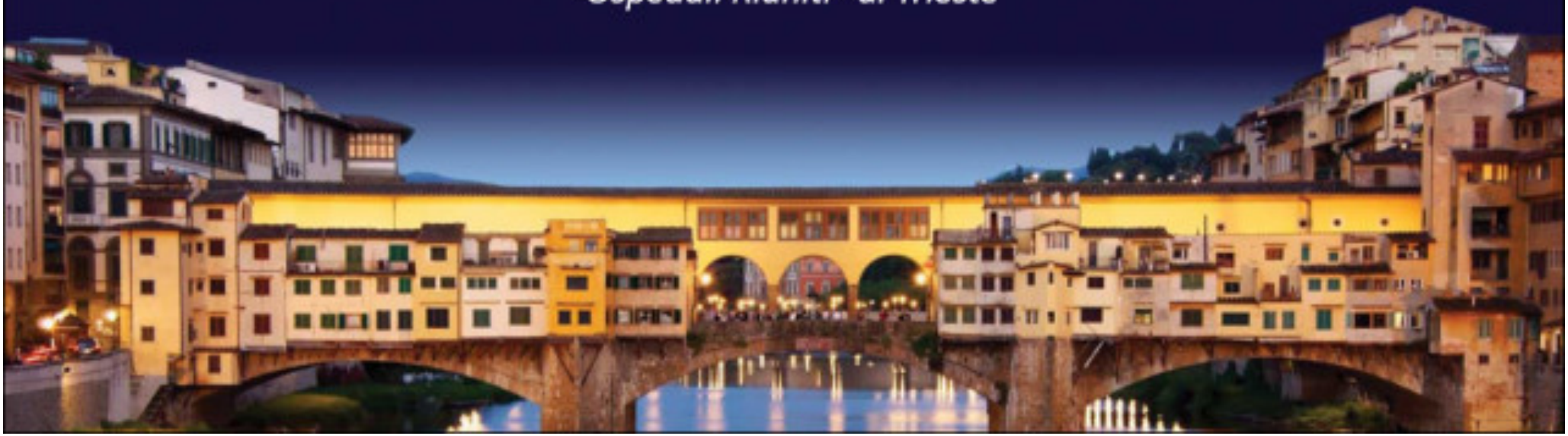
Conoscere e Curare il Cuore 2016

COM'È CAMBIATA LA STORIA NATURALE DELLA CARDIOMIOPATIA DILATATIVA ?

Gianfranco Sinagra

Dipartimento Cardiovascolare
Azienda Ospedaliero - Universitaria
"Ospedali Riuniti" di Trieste



HEART MUSCLE DISEASE REGISTRY OF TRIESTE (HMDR) (UPDATE – 15/02/2016)

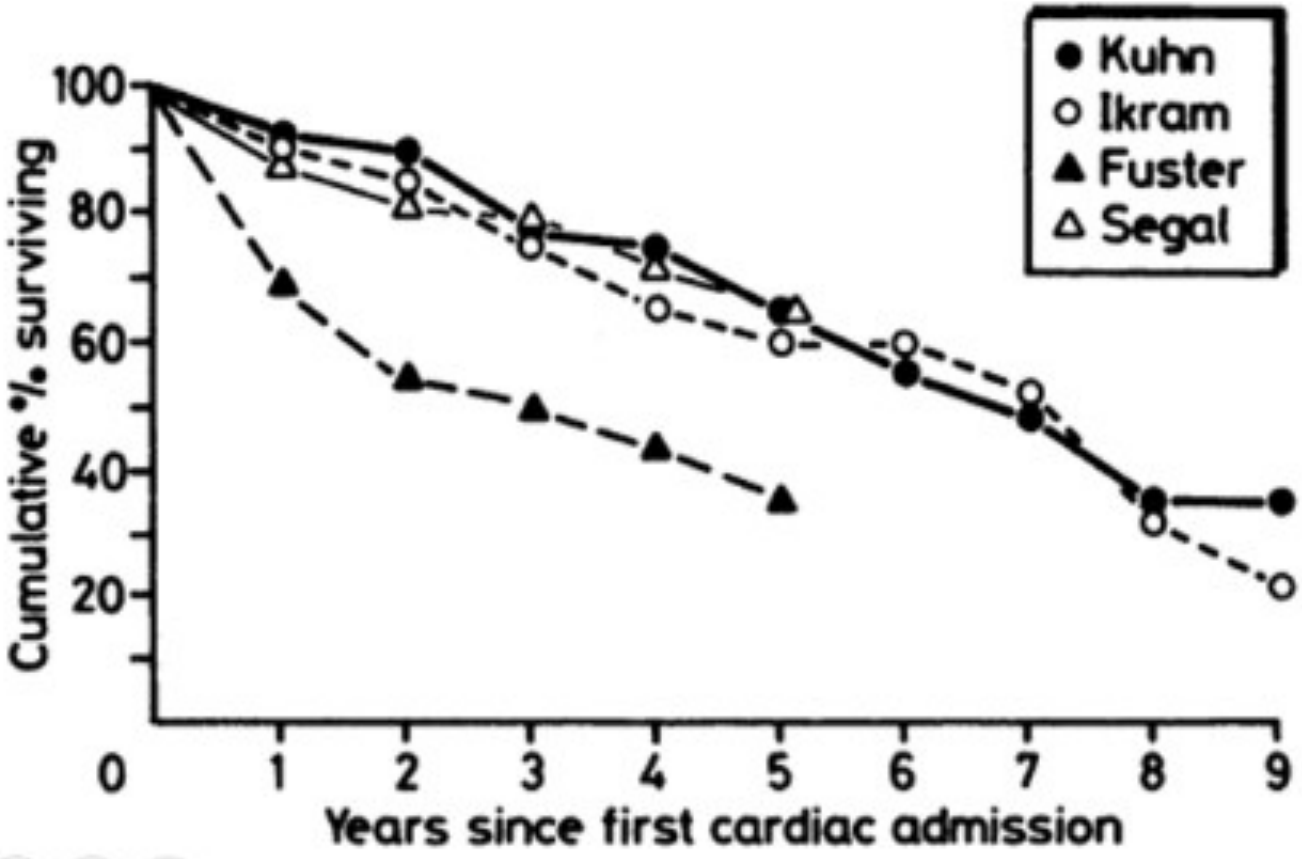
	DCM	HCM	ARVD	MYOC.	OTHERS
N° of pts	**1143**	295	127	113	240 (56 Amyloidosis)
Mean age (years)	**45±15**	41±20	54±15	38±16	50±14
Males (%)	**70**	64	69	70	66
Follow-up (months)	**110±83**	79±90	139±115	97±67	44±20
Years of enrolment	**1978-2016**	1983-2016	1976-2016	1981-2016	1980-2016
N° Follow-up (approx.)	**7300**	900	600	400	320

Br Heart J 1987;57:521–7

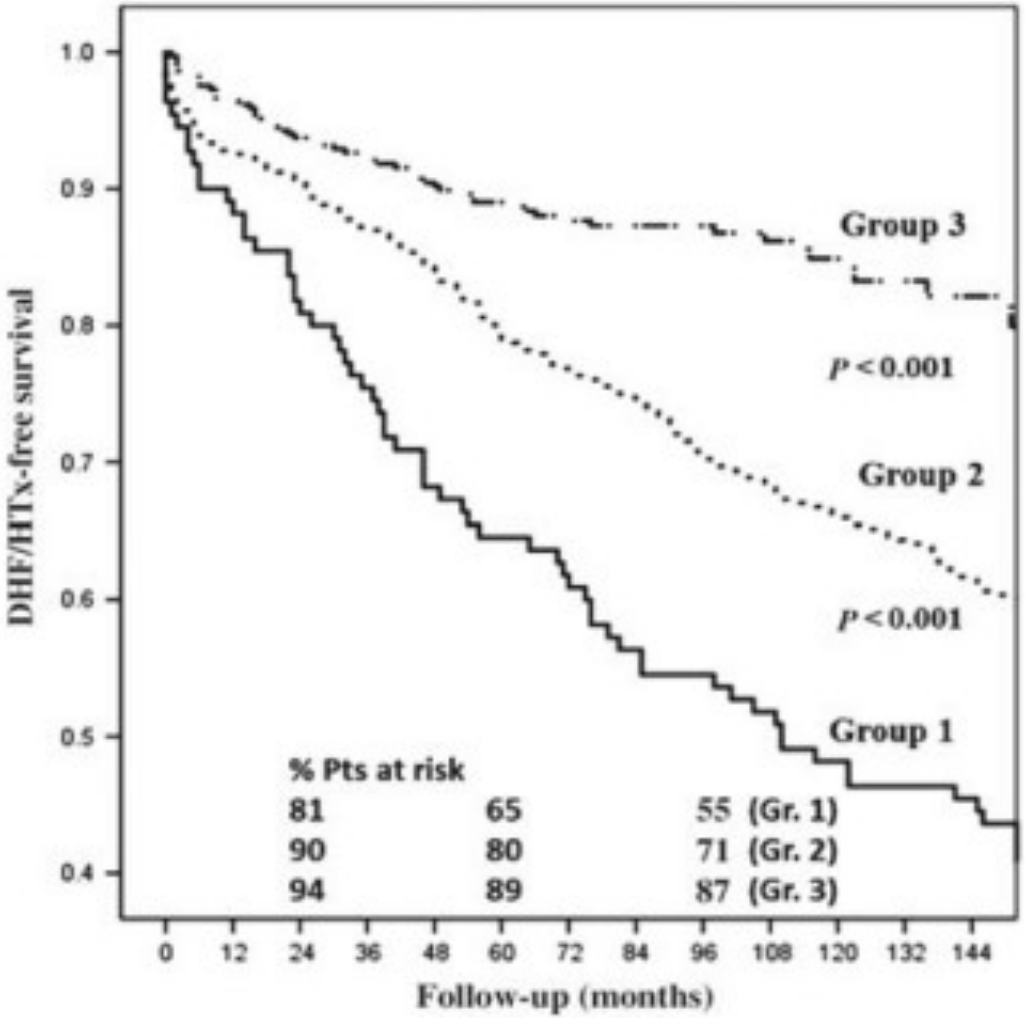
The course of idiopathic dilated cardiomyopathy in New Zealand

HAMID IKRAM, HAMMOND G WILLIAMSON, MICHAEL WON, IAN G CROZIER, ELIZABETH J WELLS

From the Departments of Cardiology and Community Medicine, The Princess Margaret Hospital, Christchurch, New Zealand

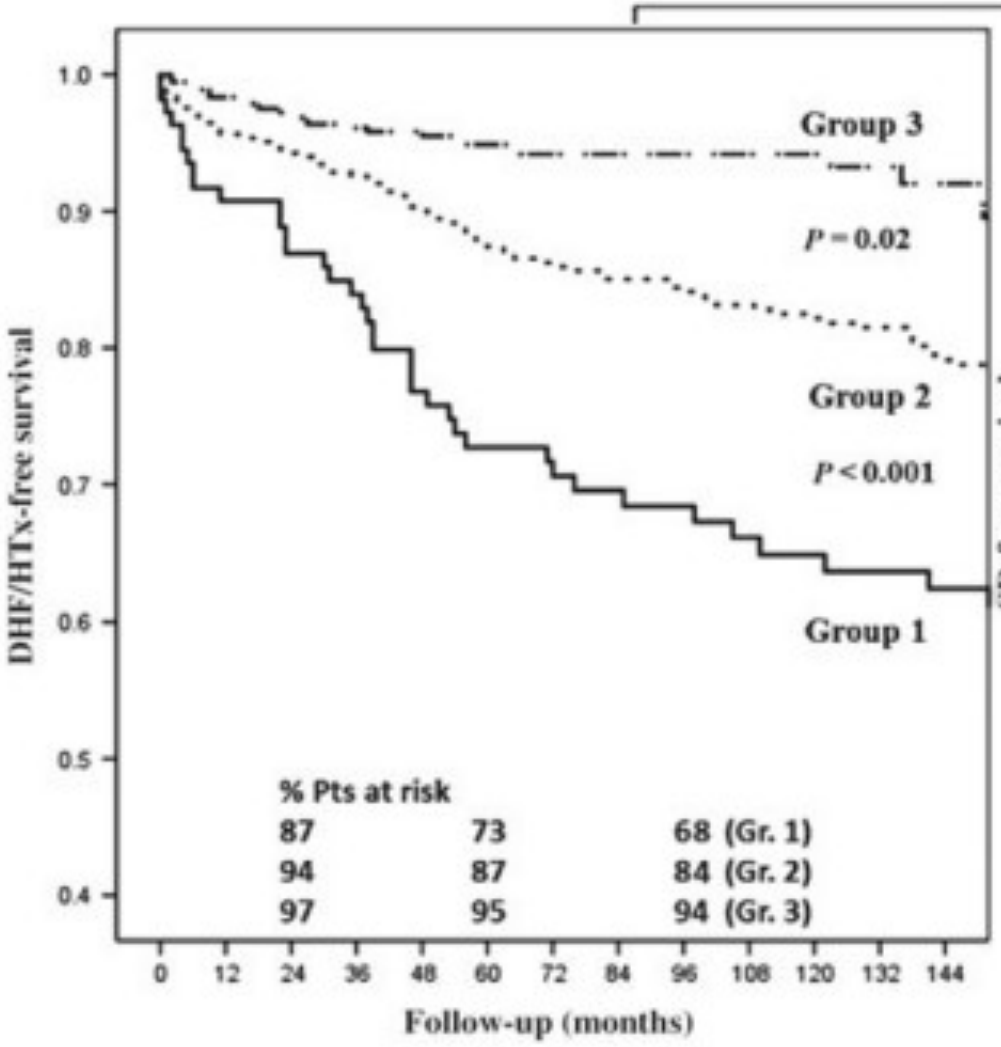


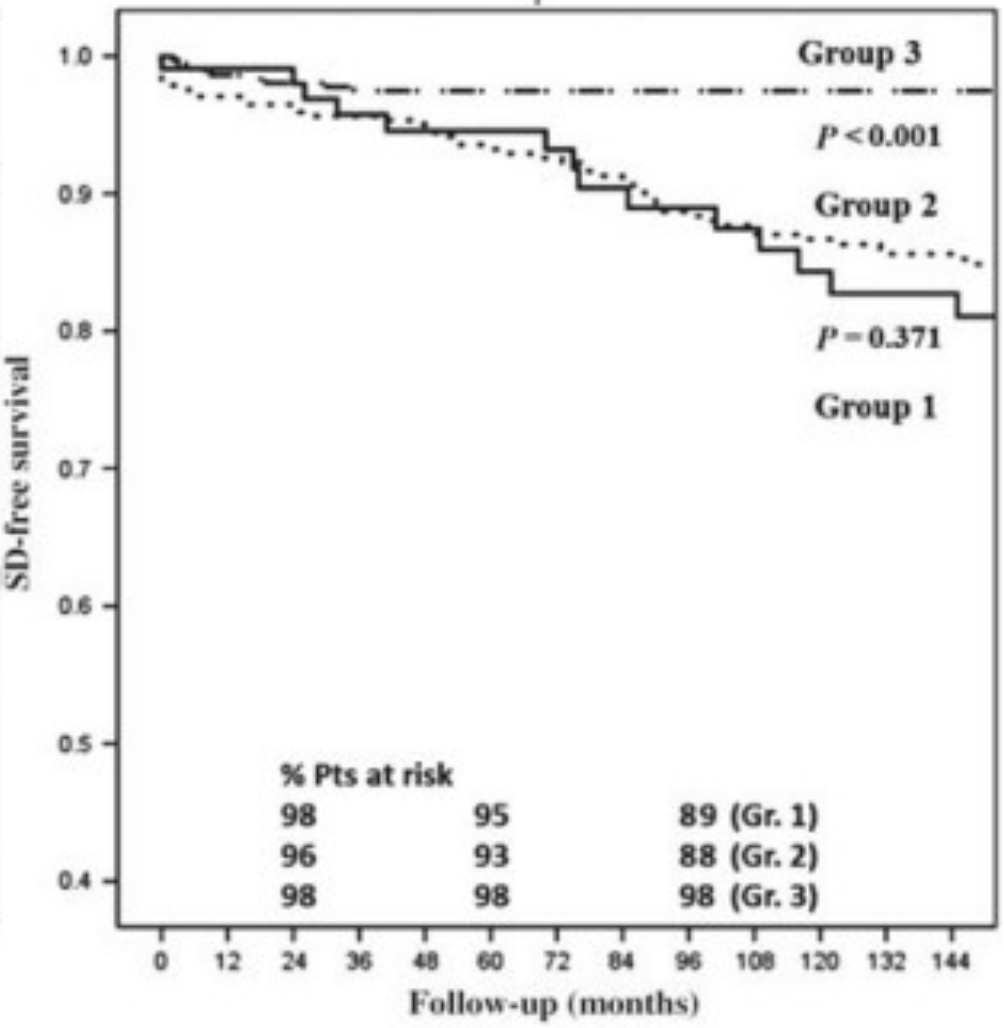
Long-term prognostic impact of therapeutic strategies in patients with idiopathic dilated cardiomyopathy: changing mortality over the last 30 years



Merlo M. Sinagra G et al; European Journal of Heart Failure (2014) **16**, 317–324

Long-term prognostic impact of therapeutic strategies in patients with idiopathic dilated cardiomyopathy: changing mortality over the last 30 years





Merlo M. Sinagra G et al; European Journal of Heart Failure (2014) 16, 317–324

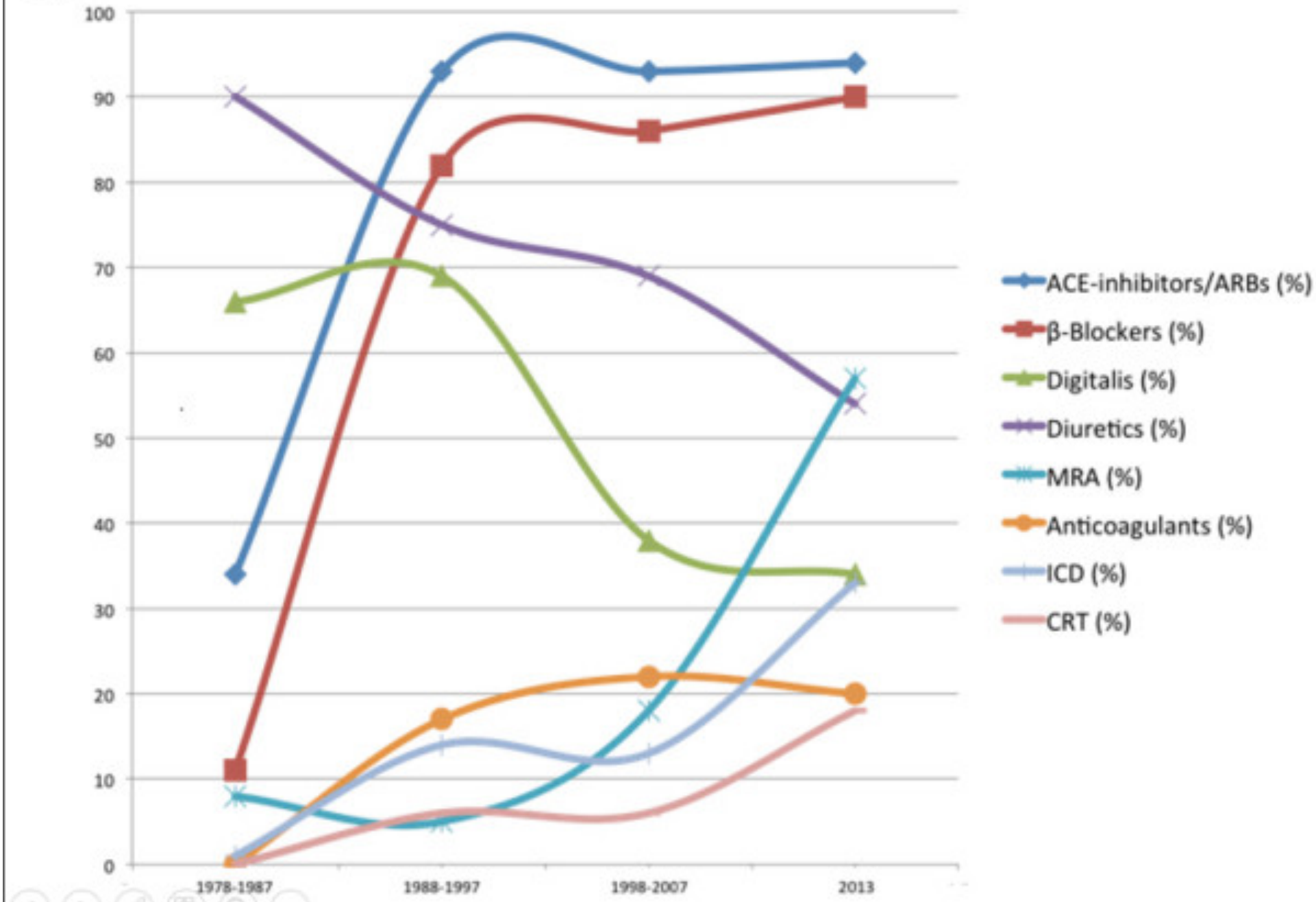
Long-term prognostic impact of therapeutic strategies in patients with idiopathic dilated cardiomyopathy: changing mortality over the last 30 years

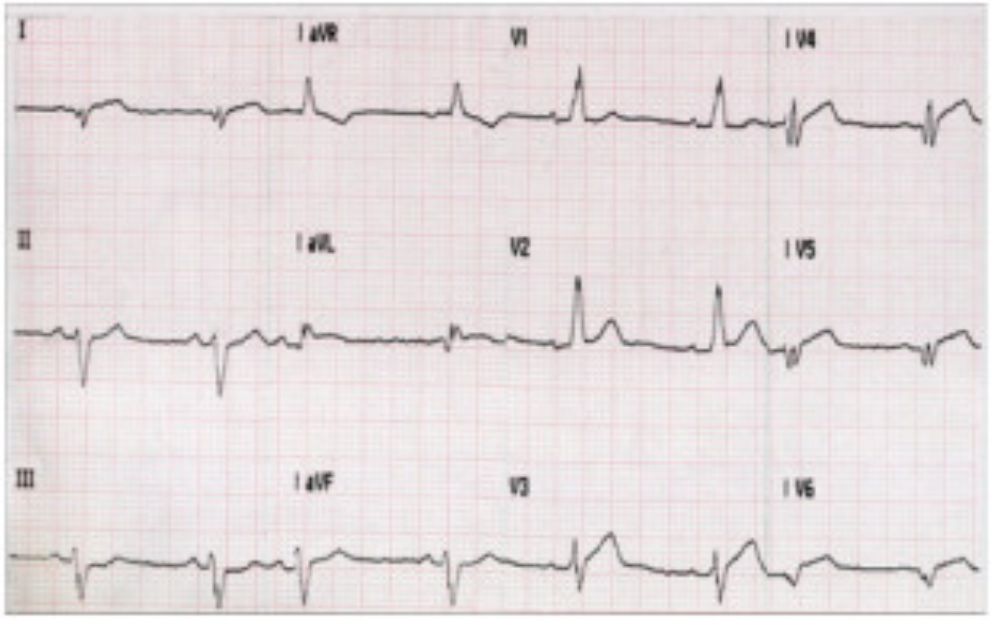
	1st decade (1978–1987) (110 patients)	2nd decade (1988–1997) (376 patients)	3rd decade (1998–2007) (367 patients)
Mean follow-up (months)	151 ± 29	153 ± 82	93 ± 41
All-cause mortality/heart transplant, *n* (%)	77 (70)	178 (47)	53 (14)
Incidence (events/100 patients/year)	5.6	3.9	1.9
Unexpected sudden death, *n* (%)	16 (15)	51 (14)	9 (3)
Incidence (events/100 patients/year)	1.2	1.1	0.3

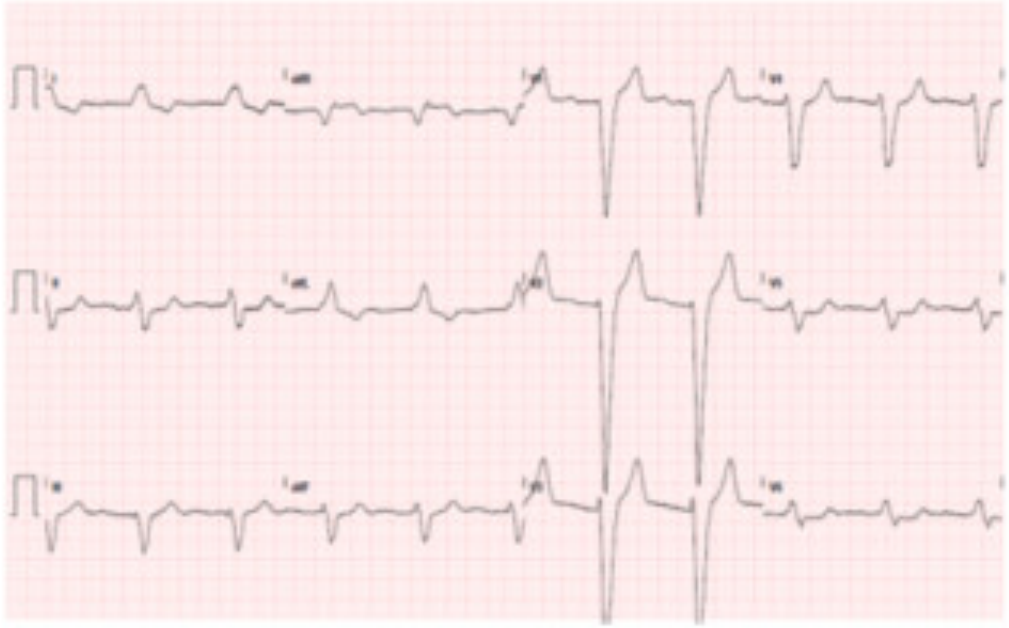
Merlo M. Sinagra G et al; European Journal of Heart Failure (2014) **16**, 317–324

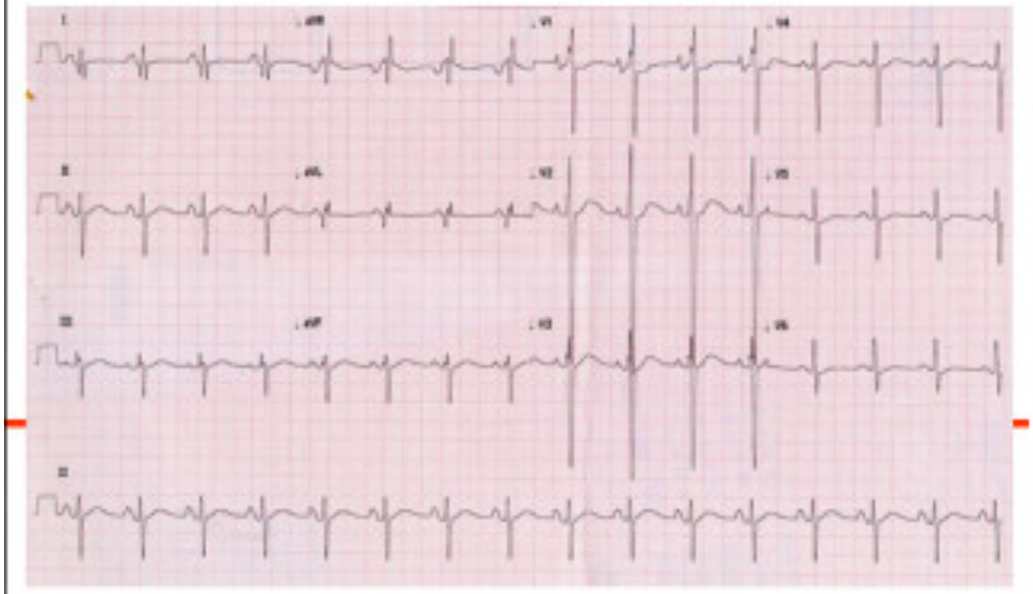
Registro CMPD Trieste: 1978-2013

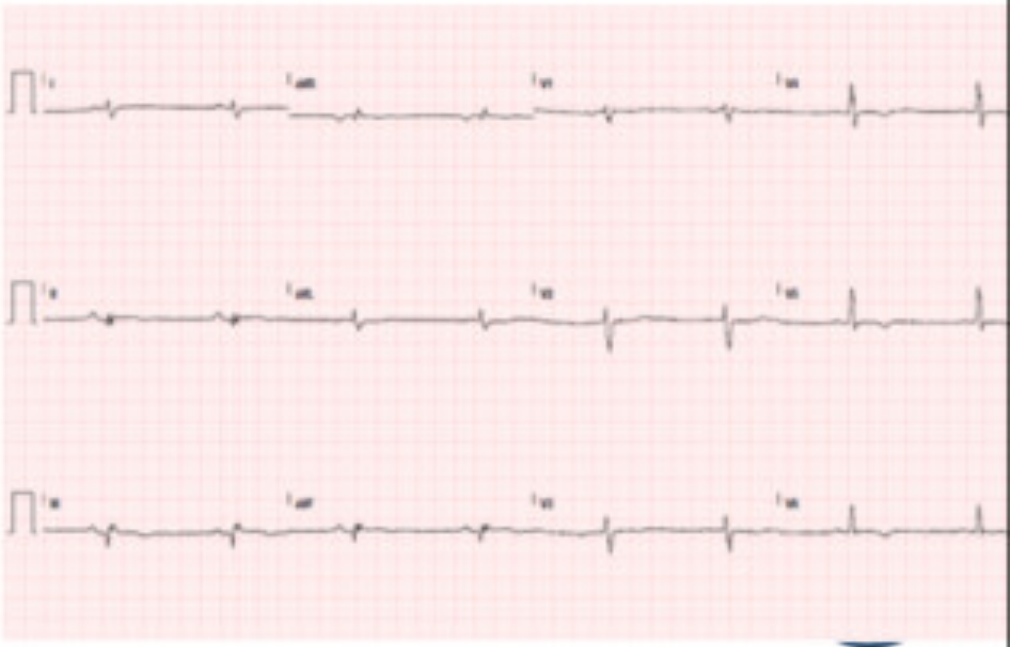
Azienda Ospedaliero - Universitaria
Ospedali Riuniti di Trieste

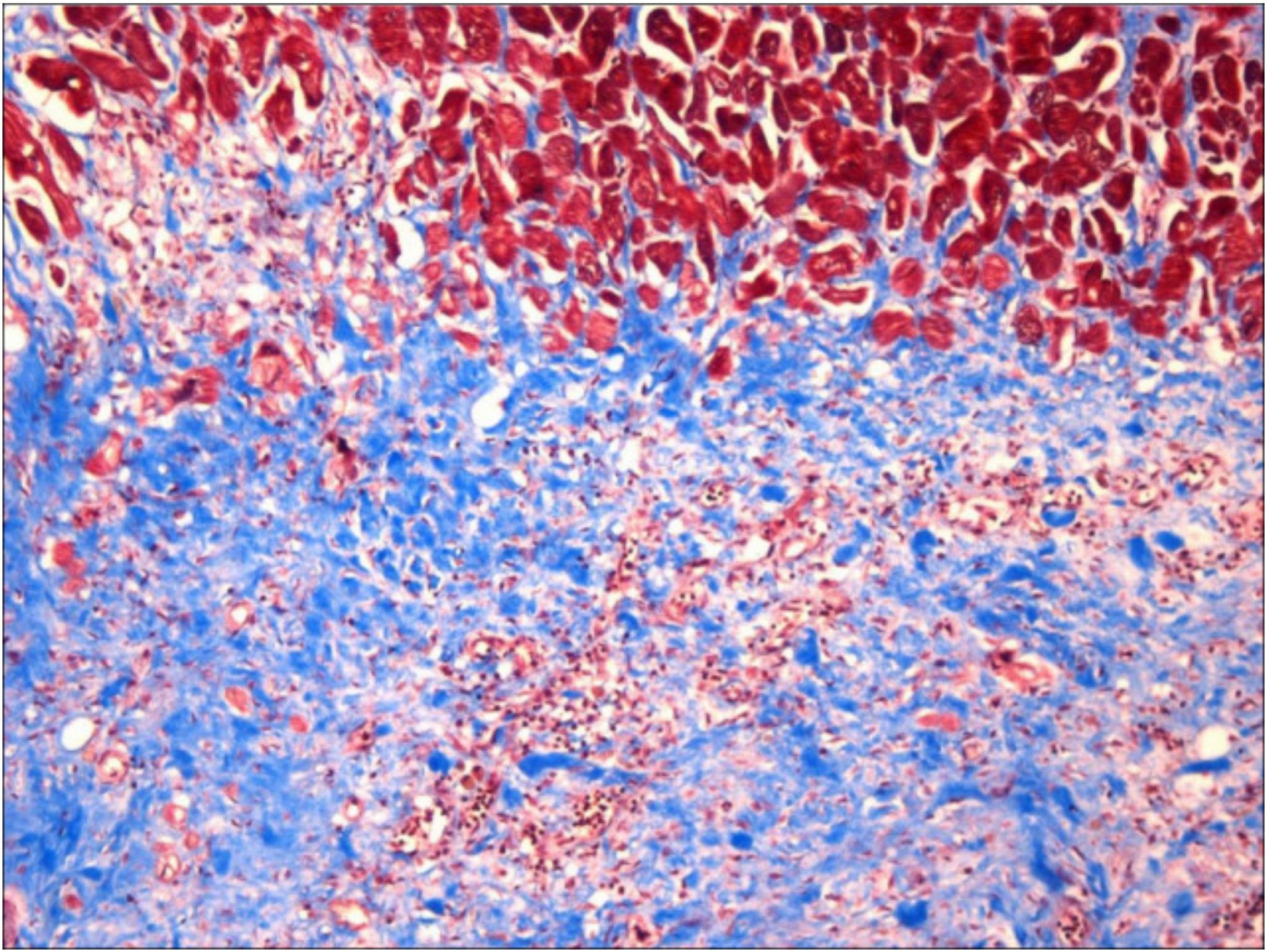


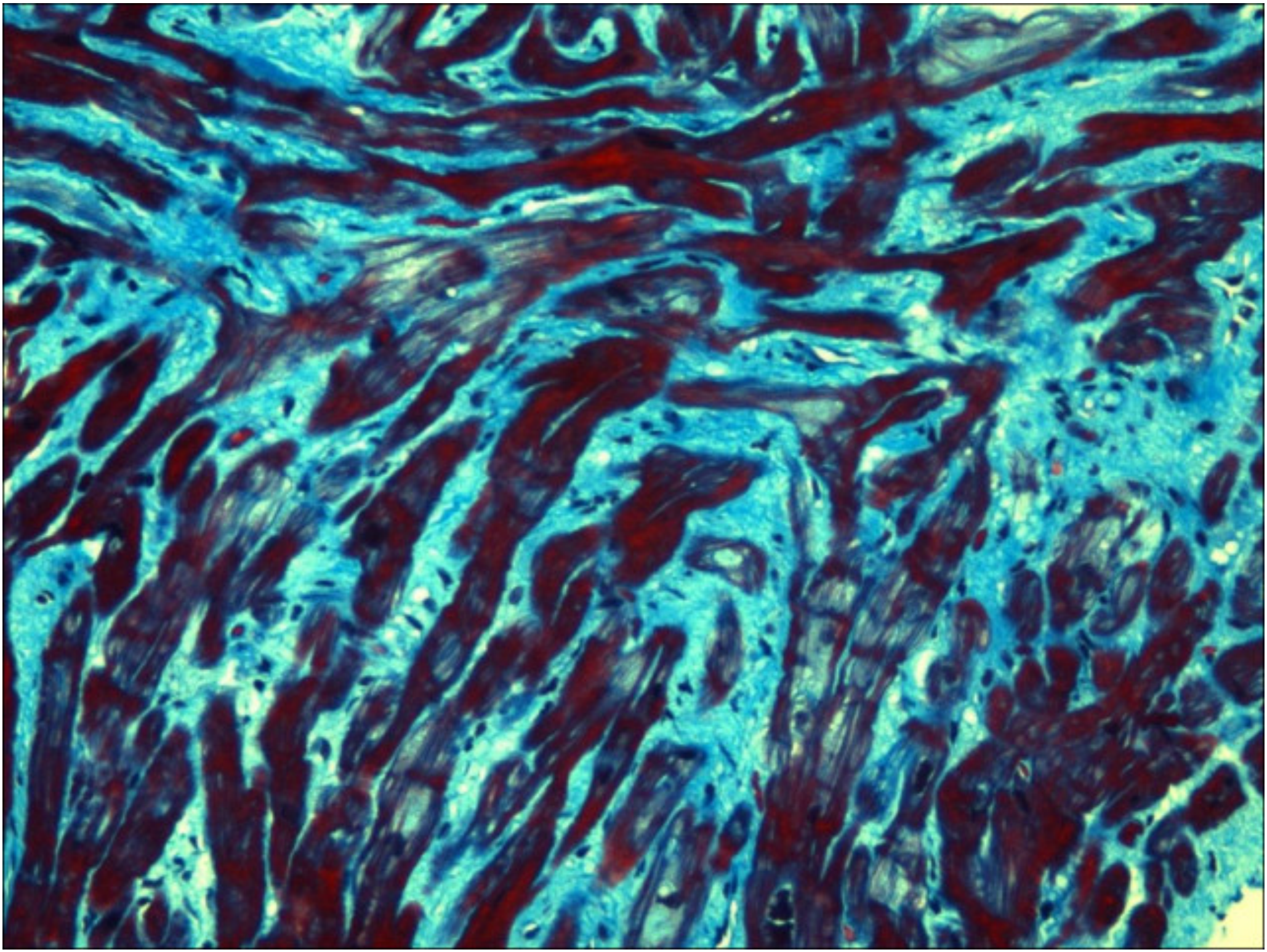

I
I aVR
V1
I V4
II
I aVL
V2
I V5
III
I aVF
V3
I V6

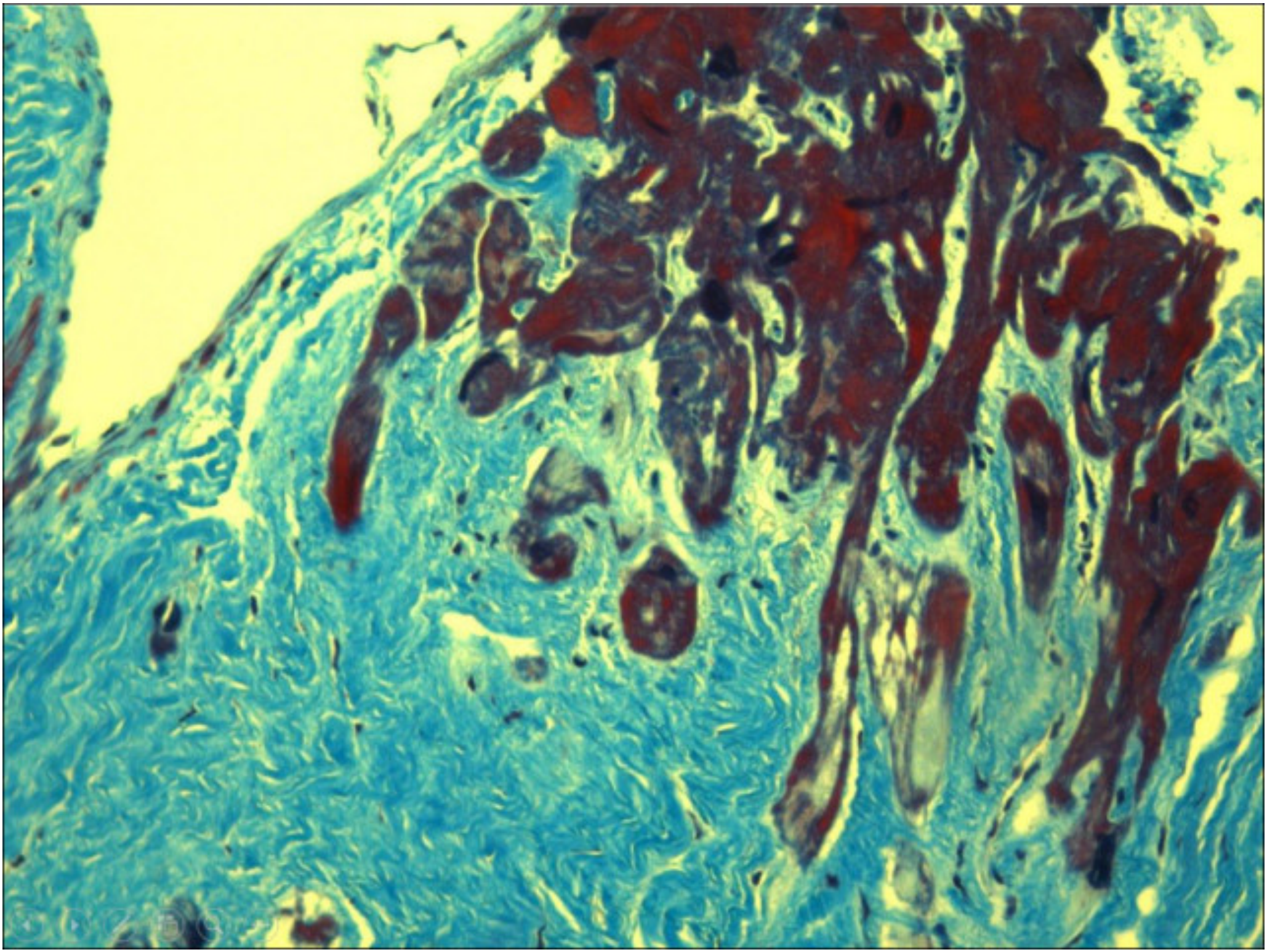










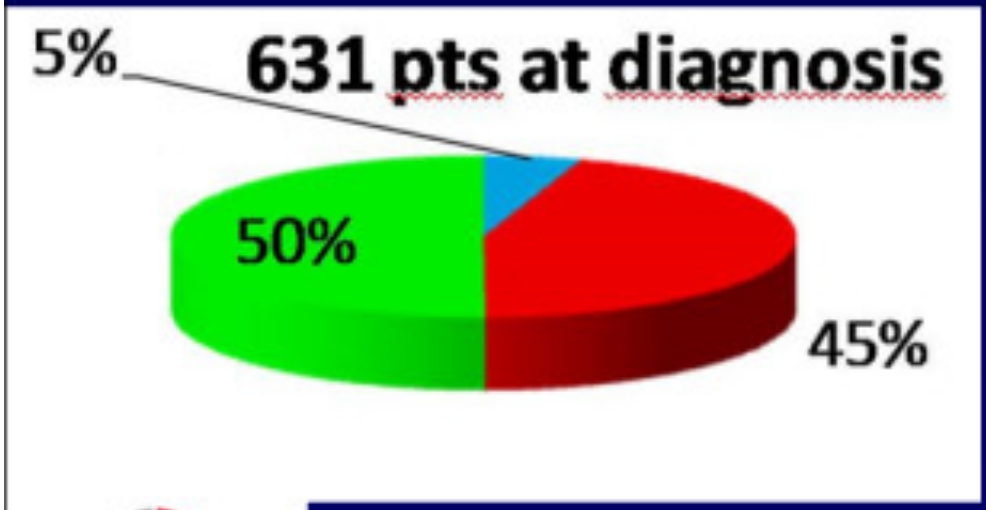


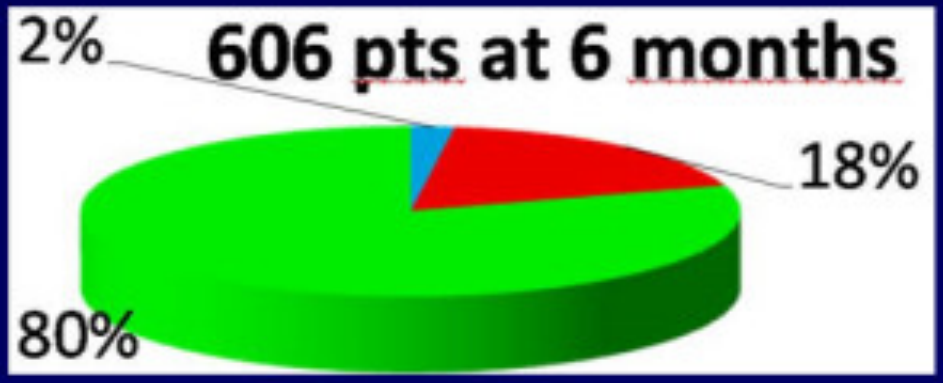
How Can Optimization of Medical Treatment Avoid Unnecessary Implantable Cardioverter-Defibrillator Implantations in Patients With Idiopathic Dilated Cardiomyopathy Presenting With "SCD-HeFT Criteria?"

Massimo Zecchin, MD[a,*], Marco Merlo, MD[a], Alberto Pivetta, MD[a], Giulia Barbati, PhD[b], Cristina Lutman, MD[a], Dario Gregori, PhD[b], Laura Vitali Serdoz, MD[a], Stefano Bardari, MD[a], Silvia Magnani, MD[a], Andrea Di Lenarda, MD[c], Alessandro Proclemer, MD[d], and Gianfranco Sinagra, MD[a]

THE TRIESTE CARDIOMYOPATHIES REGISTRY 1988-2006; DCM N=631 PTS; LVEF 30±10%

EF<35 NYHA IV | EF <35 NHYA II-III | NYHA I and/or EF>35





Zecchin et al Am J Cardiol 2012;109:729-35

Persistent Recovery of Normal Left Ventricular Function and Dimension in Idiopathic Dilated Cardiomyopathy During Long-Term Follow-up: Does Real Healing Exist?

Marco Merlo, MD; Davide Stolfo, MD; Marco Anzini, MD; Francesco Negri, MD; Bruno Pinamonti, MD; Giulia Barbati, PhD; Federica Ramani, PhD; Andrea Di Lenarda, MD; Gianfranco Sinagra, MD, FESC

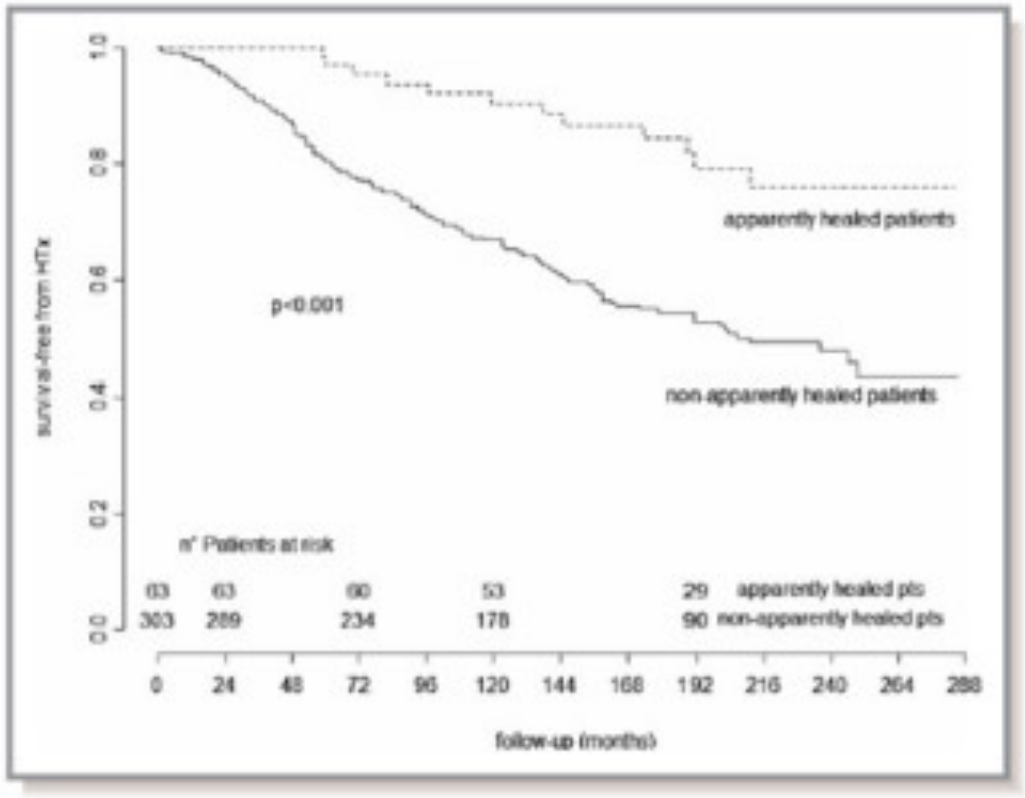


Figure 1. Kaplan–Meier curves for very long-term heart transplant-free survival of patients who were apparently healed and not apparently healed and alive at mid-term. Dotted lines represent apparently healed patients; solid lines represent patients who were not apparently healed. HTx indicates heart transplant.

Persistent apparent healing was defined as left ventricular ejection fraction ≥50% and indexed left ventricular end-diastolic diameter ≤33 mm/m2 at both mid-term (19±4 months) and long-term (103±9 months) follow-up.

J Am Heart Assoc. 2015 Jan; 4(1): e001504.

Persistent Recovery of Normal Left Ventricular Function and Dimension in Idiopathic Dilated Cardiomyopathy During Long-Term Follow-up: Does Real Healing Exist?

Marco Merlo, MD; Davide Stolfo, MD; Marco Anzini, MD; Francesco Negri, MD; Bruno Pinamonti, MD; Giulia Barbati, PhD; Federica Ramani, PhD; Andrea Di Lenarda, MD; Gianfranco Sinagra, MD, FESC

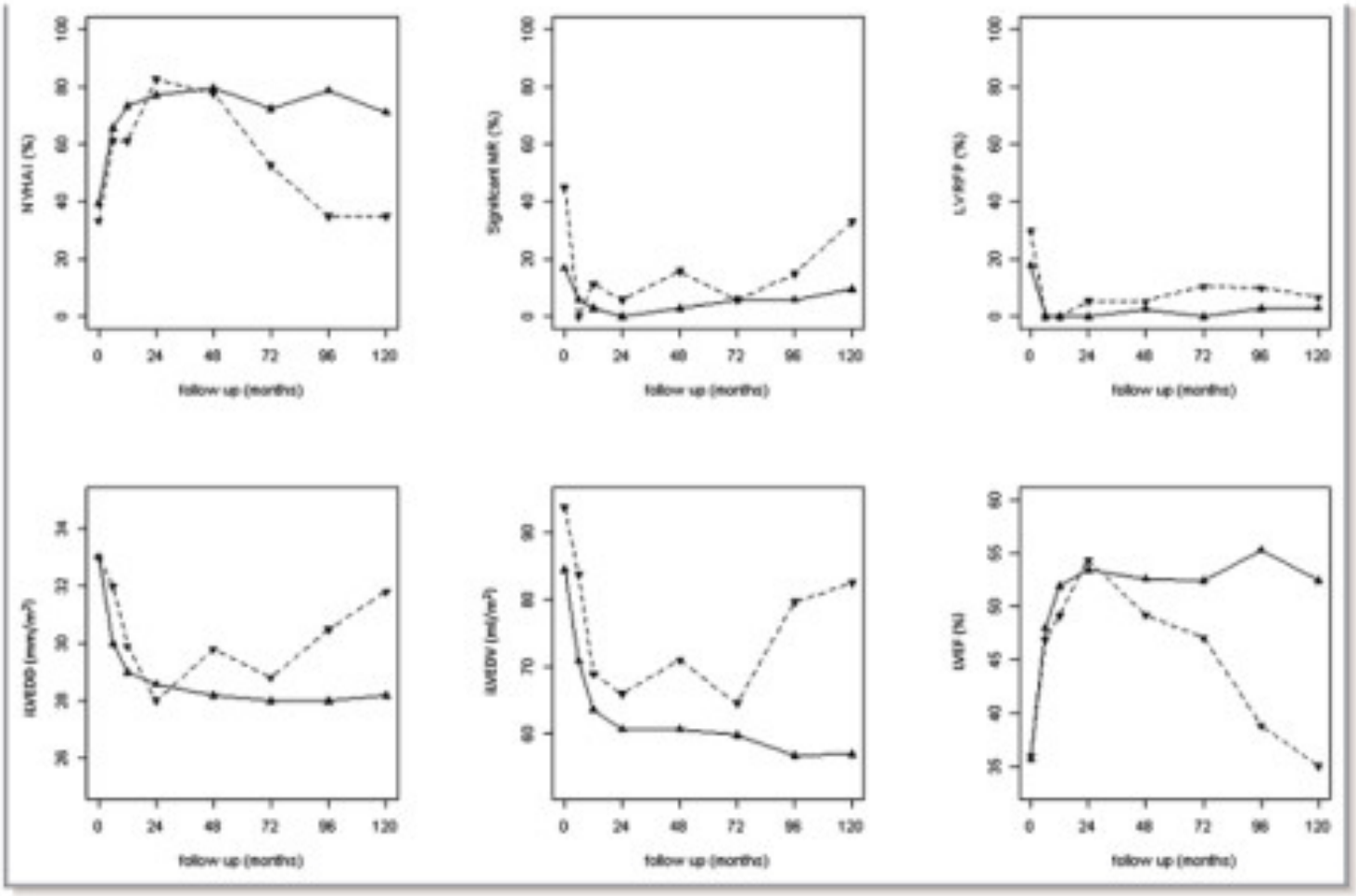


Figure 3. Longitudinal long-term trends of main clinical and laboratory features in patients who were persistently apparently healed and nonpersistently apparently healed. All analyzed patients underwent a complete echocardiographic evaluation at each follow-up. Solid lines represent persistently apparently healed patients; broken lines represent nonpersistently apparently healed patients. iLVEDD indicates indexed left ventricular end-diastolic diameter; iLVEDV, indexed left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; LVRFP, left ventricular restrictive filling pattern; MR, mitral regurgitation; NYHA, New York Heart Association.

J Am Heart Assoc. 2015 Jan; 4(1): e001504.

Persistent Recovery of Normal Left Ventricular Function and Dimension in Idiopathic Dilated Cardiomyopathy During Long-Term Follow-up: Does Real Healing Exist?

Marco Merlo, MD; Davide Stolfo, MD; Marco Anzini, MD; Francesco Negri, MD; Bruno Pinamonti, MD; Giulia Barbati, PhD; Federica Ramani, PhD; Andrea Di Lenarda, MD; Gianfranco Sinagra, MD, FESC

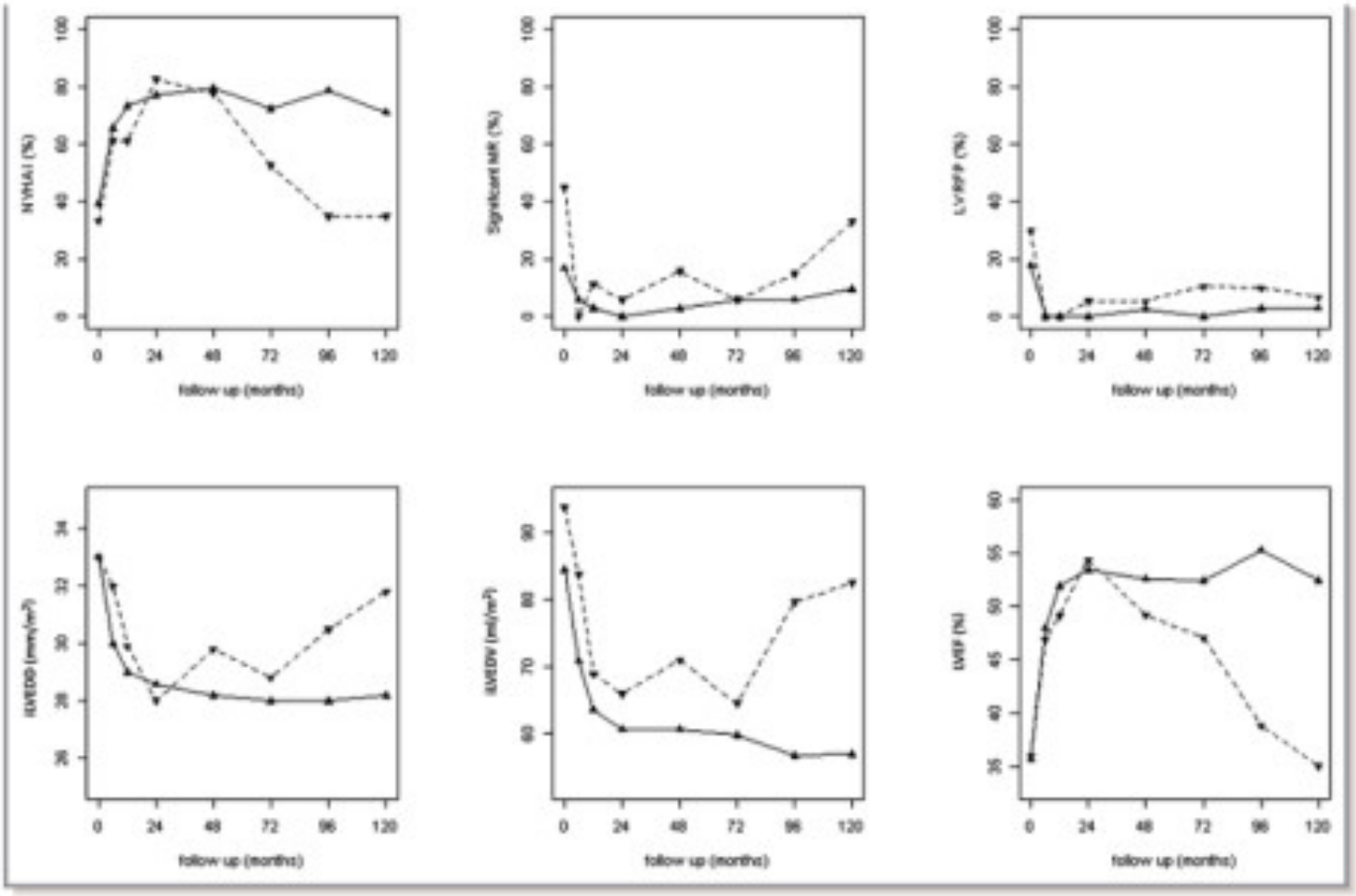


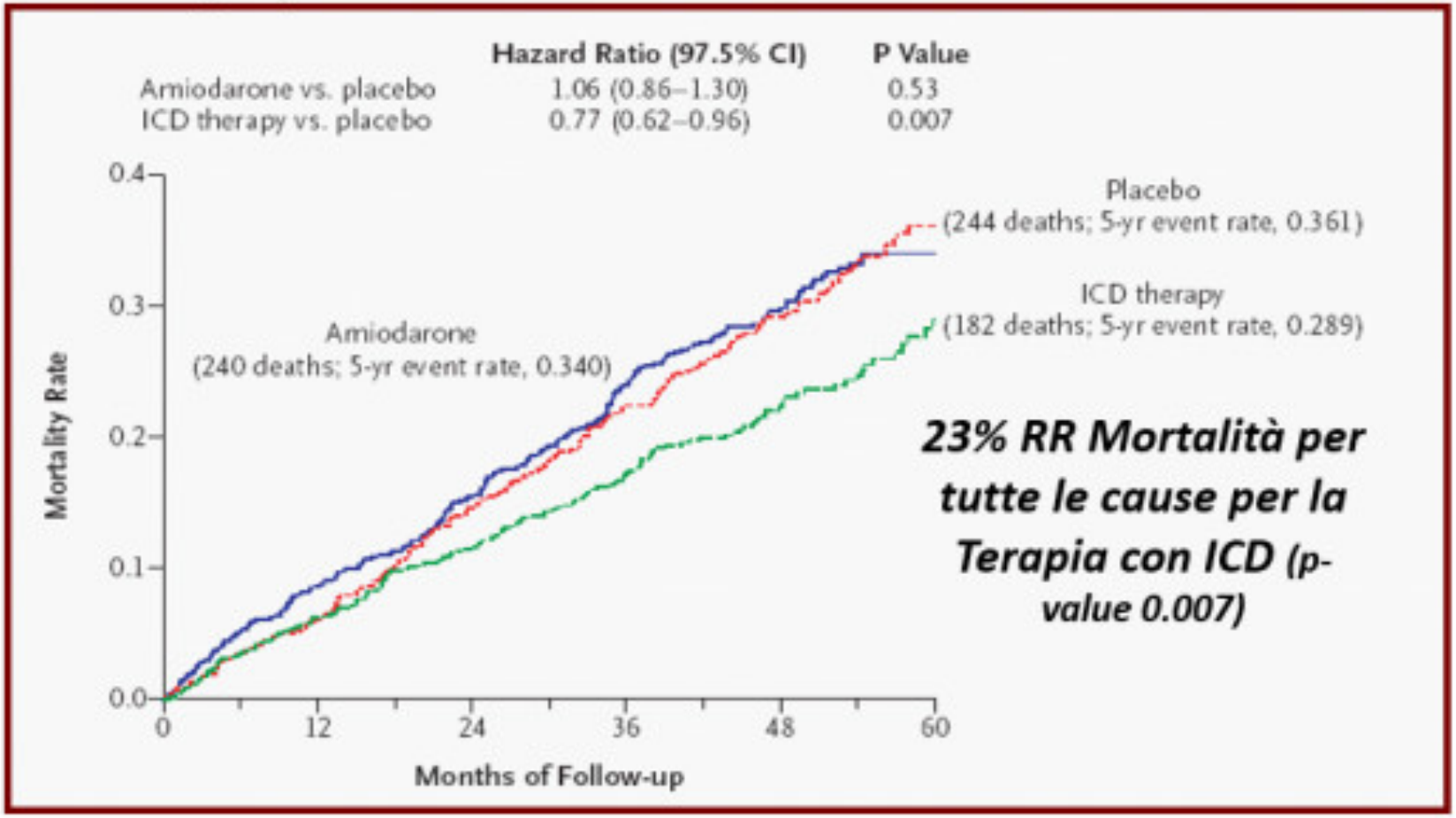
Figure 3. Longitudinal long-term trends of main clinical and laboratory features in patients who were persistently apparently healed and nonpersistently apparently healed. All analyzed patients underwent a complete echocardiographic evaluation at each follow-up. Solid lines represent persistently apparently healed patients; broken lines represent nonpersistently apparently healed patients. iLVEDD indicates indexed left ventricular end-diastolic diameter; iLVEDV, indexed left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; LVRFP, left ventricular restrictive filling pattern; MR, mitral regurgitation; NYHA, New York Heart Association.

J Am Heart Assoc. 2015 Jan; 4(1): e001504.

PREVENZIONE PRIMARIA

I TRIALS : SCDHEFT

Mortality by Intention-to-treat



Bardy GH, Lee KL, Mark DB, et al. Amiodarone or an implantable cardioverter-defibrillator for congestive heart failure. *N Engl. J Med.* 2005; 352:225-237.

Factors potentially predicting SD

LVEF
NYHA class
LVEDD
RV function
VE arrhythmias
Induced VE arrhythmias
Atrial fibrillation
QRS duration
Late potentials
Fragmented QRS
LGE at MRI
T-wave alternans
HRV / Heart rate turbulence
Heart rate recovery and recovery ventricular ectopy
Baroreflex sensitivity
QT variability - QT dinamicity
Heart/Mediastinum (H/M) ratio of MIBG uptake
....

Recommendations for the use of implanted cardioverter defibrillators in patients with heart failure

Recommendations	Class[a]	Level[b]	Ref[c]
Secondary prevention An ICD is recommended in a patient with a ventricular arrhythmia causing haemodynamic instability, who is expected to survive for >1 year with good functional status, to reduce the risk of sudden death.	I	A	144–147
Primary prevention An ICD is recommended in a patient with symptomatic HF (NYHA class II–III) and an EF ≤35% despite ≥3 months of treatment with optimal pharmacological therapy, who is expected to survive for >1 year with good functional status, to reduce the risk of sudden death			
(i) Ischaemic aetiology and >40 days after acute myocardial infarction	I	A	148, 149
(ii) Non-ischaemic aetiology	I	B	149

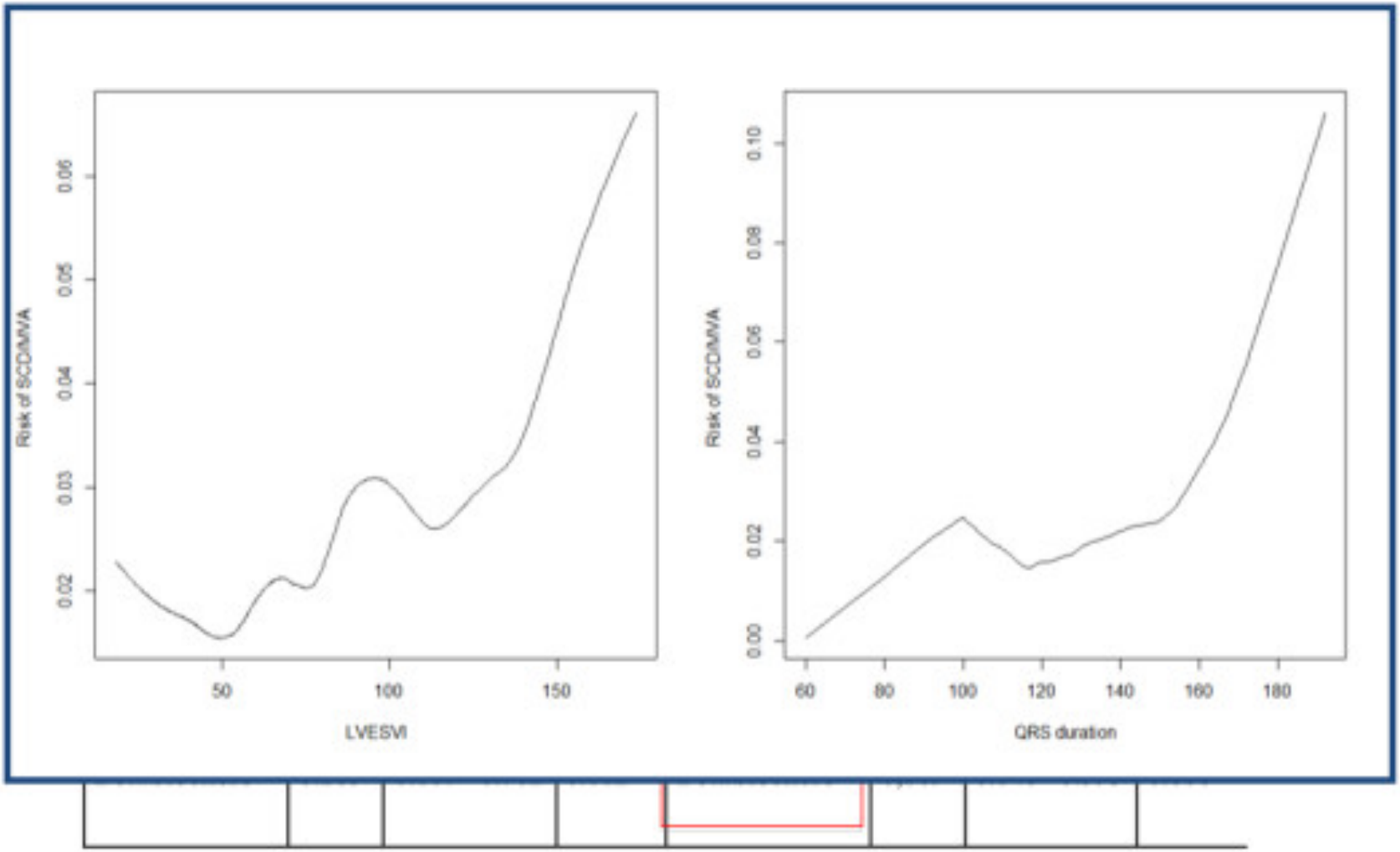
European Heart Journal (2012) **33**, 1787–1847

Early SCD/MVAs in DCM

Univariate variables				Multivariate variables			
Variables	**OR**	**CI 95%**	***p*-value**	**Variables**	**OR**	**CI 95%**	***p*-value**
NYHA III-IV	2.343	0.945 –5.81	0.066				
LVEDVI*	1.008	0.997 –1,018	0.152				
LVESVI*	1.01	0.999 –1,021	0.043	**LVESVI***	1.012	1.000 –1.024	0.043
LVEF*	0.965	0.923 –1.008	0.109				
LVEF≤35	0.853	0.333 –2.185	0.741	**LVEF≤35**	0.363	0.09 –1.30	0.147
QRS duration*	1.015	1.003 –1.026	0.011	**QRS duration***	1.017	1.003 –0.030	0.015
Betablockers	0.285	0.107 –0.762	0.012	**Betablockers**	0,169	0.048 –0.593	0.006

Losurdo P, Sinagra G et al. Under review

Early SCD/MVAs in DCM



Losurdo P, Sinagra G et al. Under review

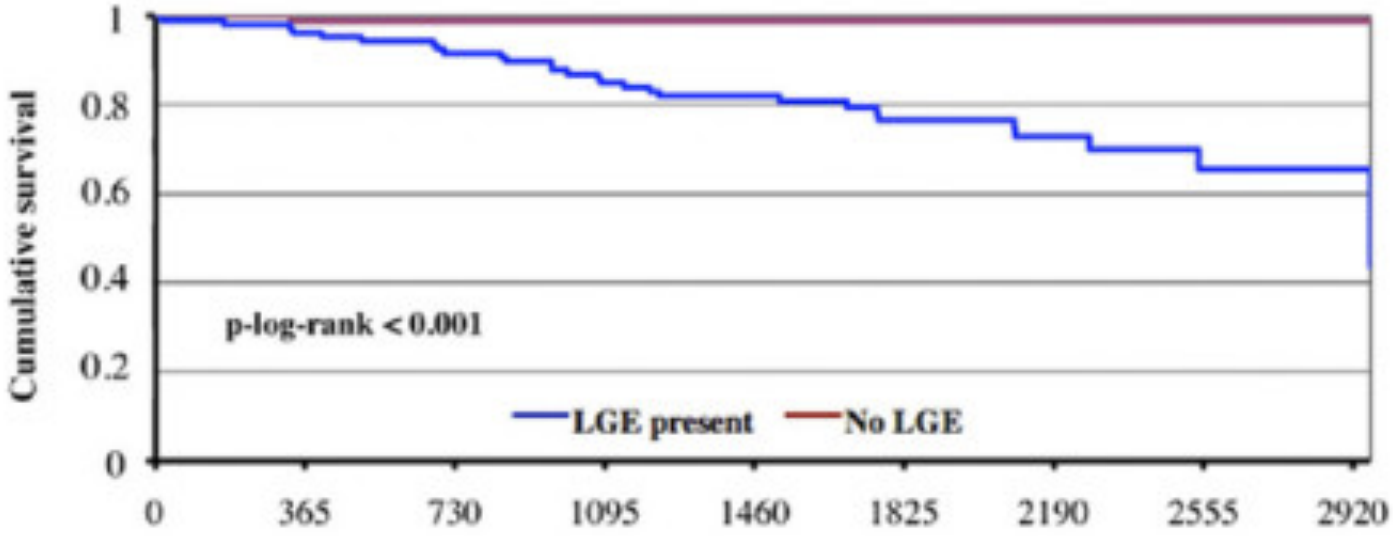
Ospedali Riuniti di Trieste

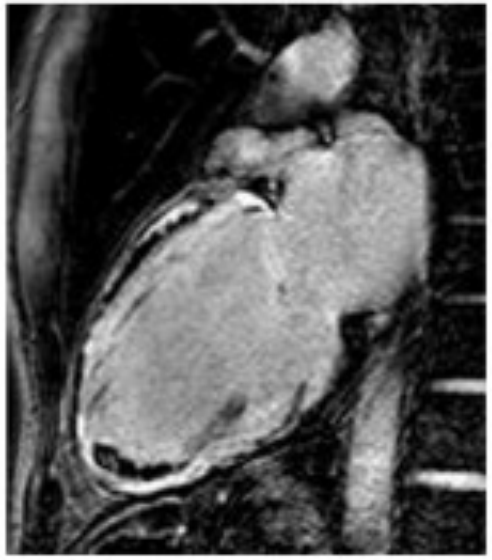
Long-Term Follow-Up of Biopsy-Proven Viral Myocarditis

Predictors of Mortality and Incomplete Recovery

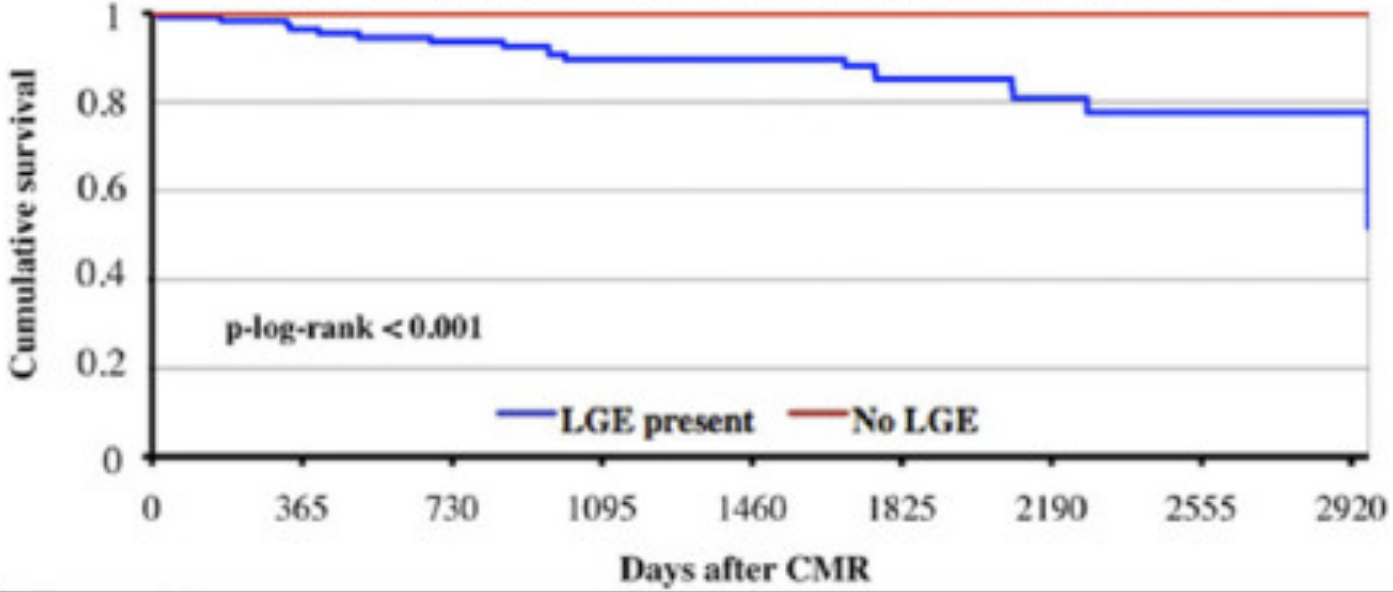
JACC Vol. 59, No. 18, 2012
May 1, 2012:1604–15

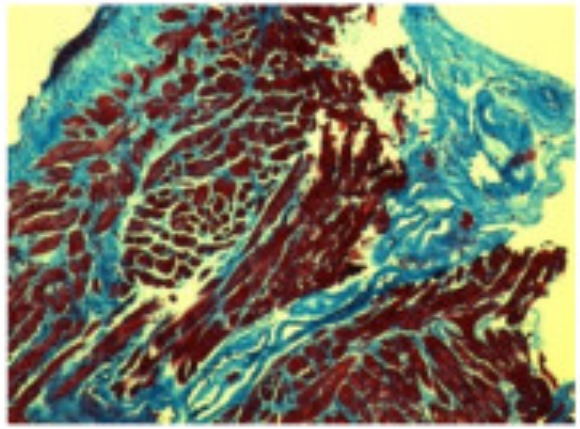
B Kaplan-Meier Survival Curves: Cardiac Death





C Kaplan-Meier Survival Curves: Sudden Cardiac Death



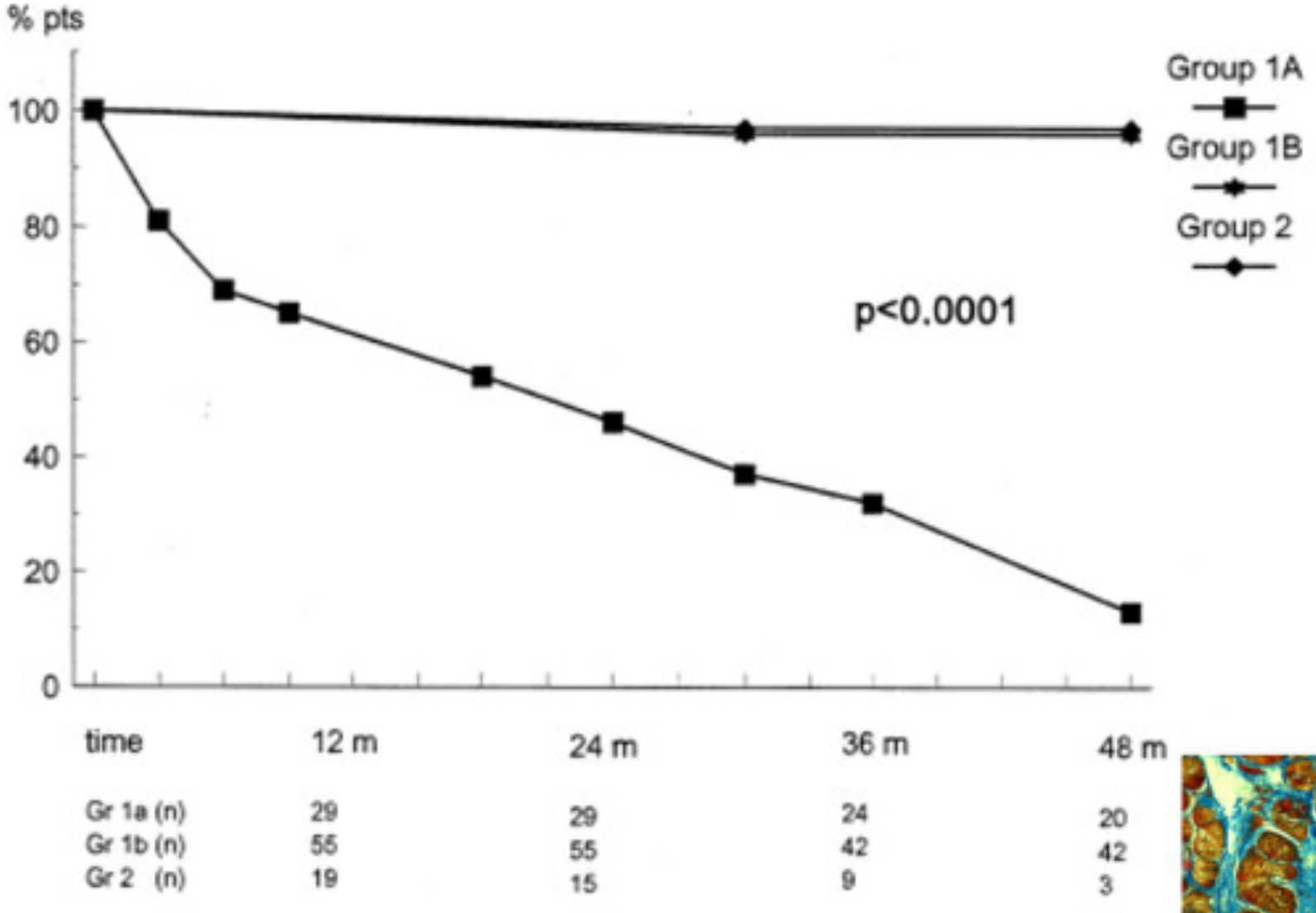


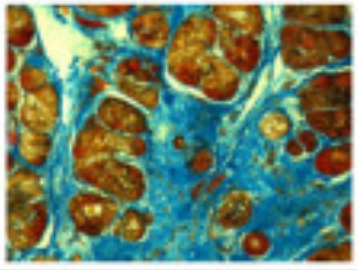
Persistence of Restrictive Left Ventricular Filling Pattern in Dilated Cardiomyopathy: An Ominous Prognostic Sign

JACC

(J Am Coll Cardiol 1997;29:604–12)

BRUNO PINAMONTI, MD, MASSIMO ZECCHIN, MD, ANDREA DI LENARDA, MD,
DARIO GREGORI, MA, PHD, GIANFRANCO SINAGRA, MD, FULVIO CAMERINI, MD





The American Journal of Cardiology

Early Improvement of Functional Mitral Regurgitation in Patients With Idiopathic Dilated Cardiomyopathy

Davide Stolfo, MD[a,*], Marco Merlo, MD[a], Bruno Pinamonti, MD[a], Stefano Poli, MD[a], Marta Gigli, MD[a], Giulia Barbati, PhD[a,b], Enrico Fabris, MD[a], Andrea Di Lenarda, MD[b], and Gianfranco Sinagra, MD, FESC[a]

survival rate—free from Htx persistence/early development moderate-severe FMR 93%, 81%, and 66% vs 91%, 64%, and 52% at 1, 6, and 12 years p = 0.044

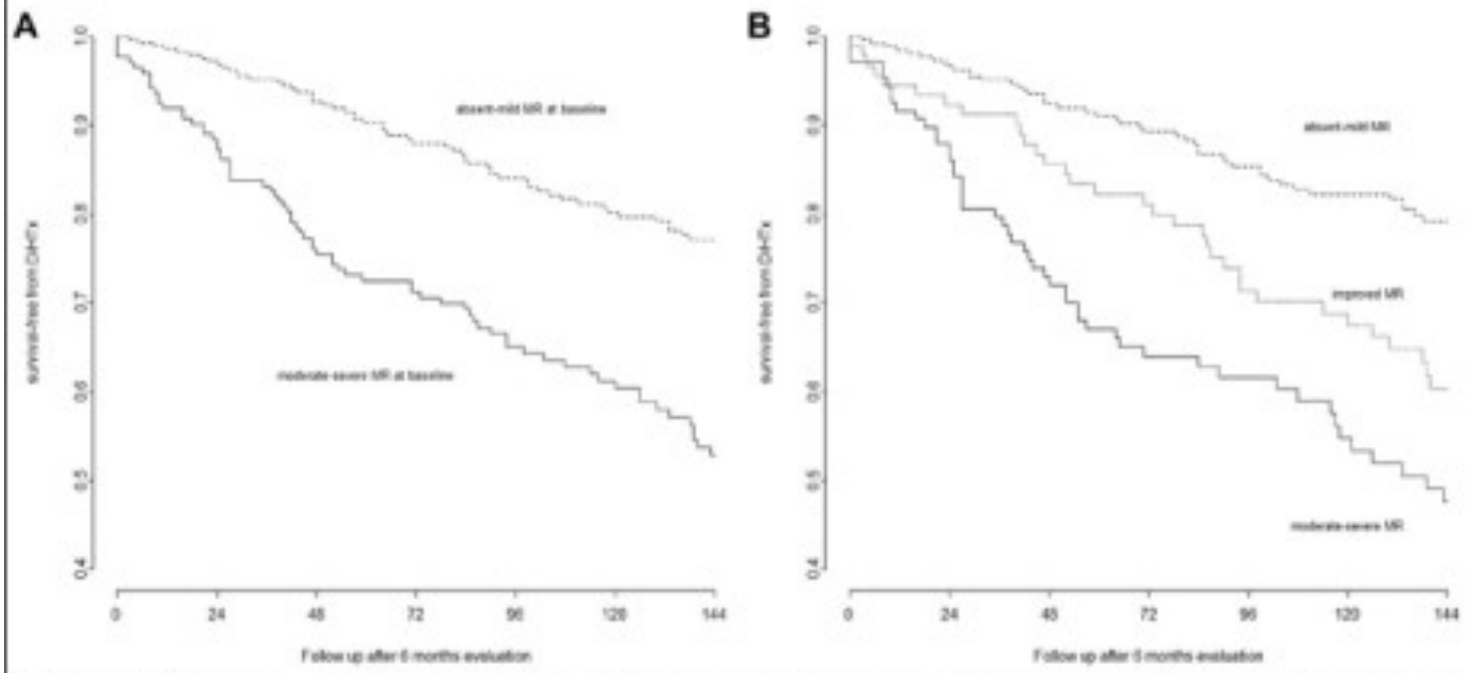
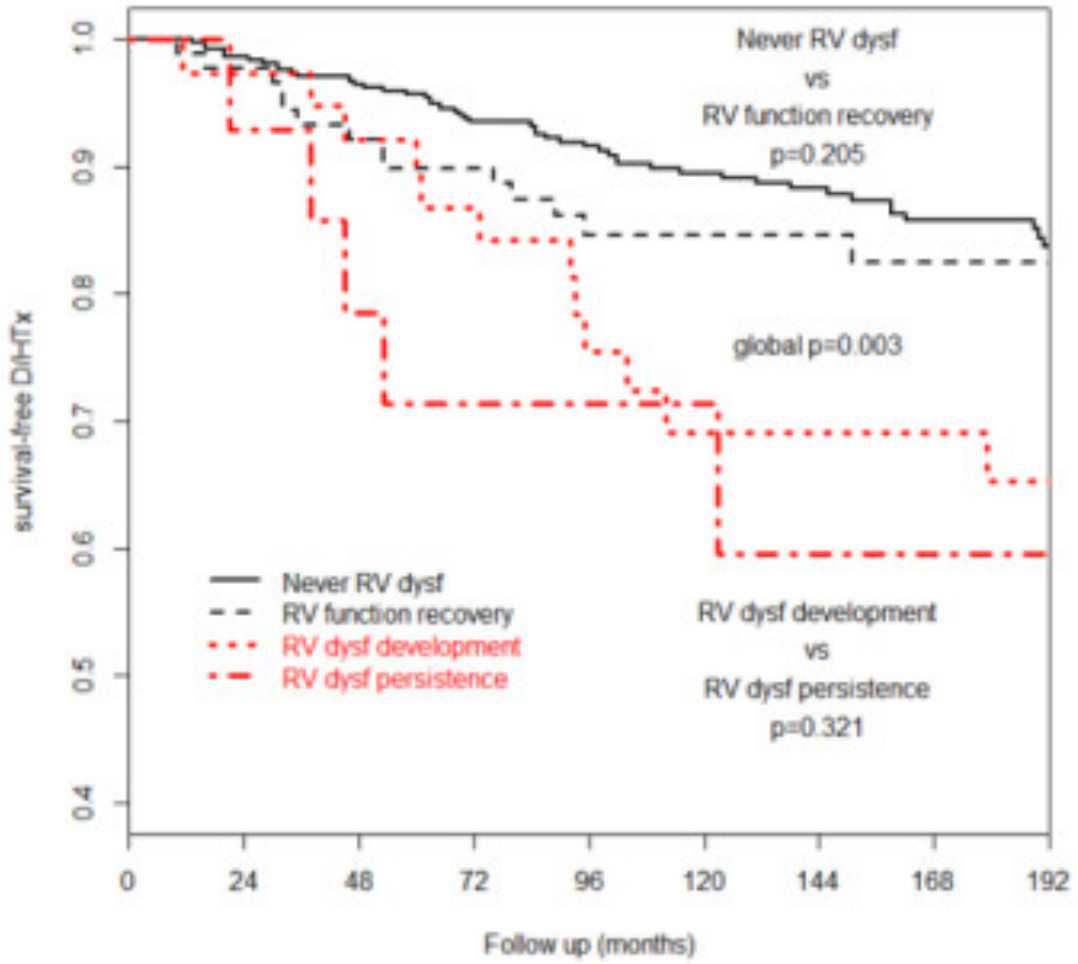


Figure 3. Kaplan-Meier curves—*(panel A)* survival free from death/heart transplantation in patients with IDC according to FMR degree at baseline; *(panel B)* survival free from death/heart transplantation in patients with IDC according to evolution of FMR. Abbreviations: D/heart transplantation = death/heart transplantation.

Am J Cardiol. 2015 Apr 15;115(8):1137-43

DCM – Right Ventricle, LVRR AND OUTCOME

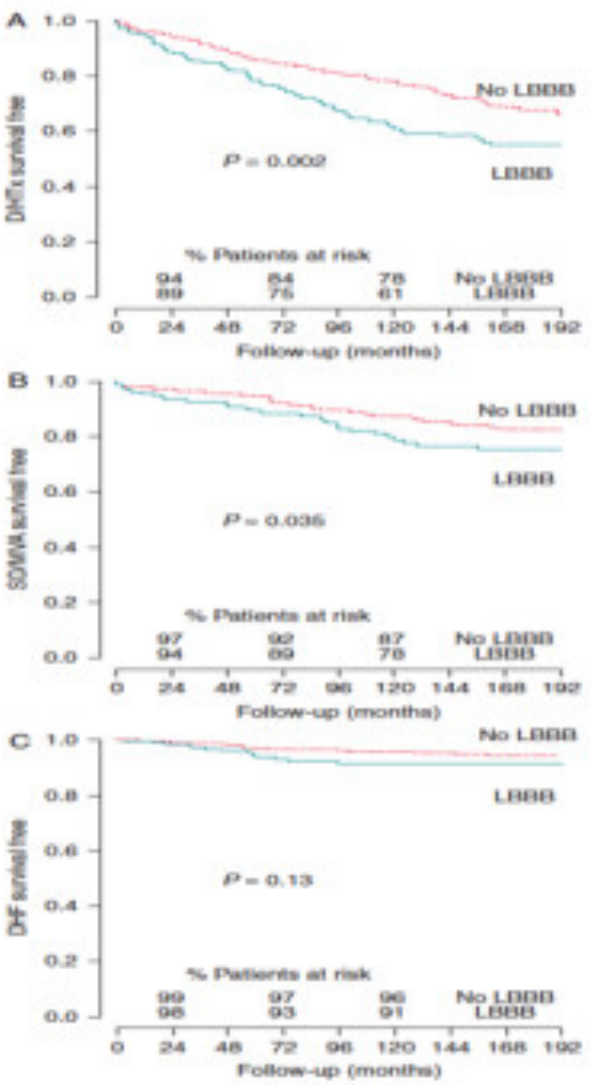


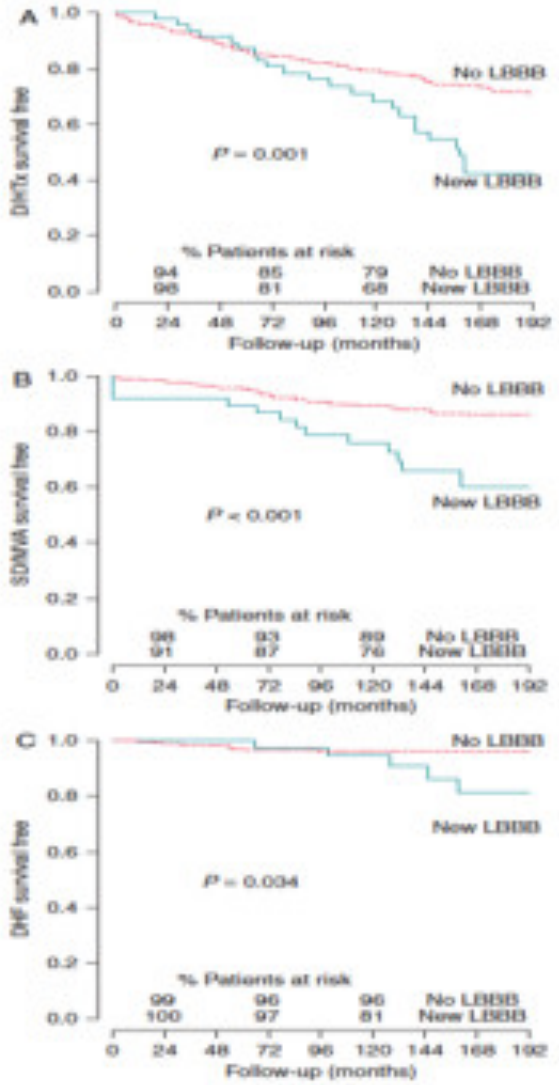
Merlo M, Sinagra G et al. JACC Cardiovasc Imag, 2016, in press

New-onset left bundle branch block independently predicts long-term mortality in patients with idiopathic dilated cardiomyopathy: data from the Trieste Heart Muscle Disease Registry

Europace (2014) **16**, 1450–1459

EUROPEAN SOCIETY OF CARDIOLOGY®





Europace (2014) **16**, 363–371
doi:10.1093/europace/eut339

Long-term outcome of 'super-responder' patients to cardiac resynchronization therapy

Massimo Zecchin[1]*, Alberto Proclemer[1], Silvia Magnani[1], Laura Vitali-Serdoz[1], Domenico Facchin[2], Daniele Muser[2], Andrea Nordio[1], Giulia Barbati[1], Ilaria Puggia[1], Gianfranco Sinagra[1], and Alessandro Proclemer[2]

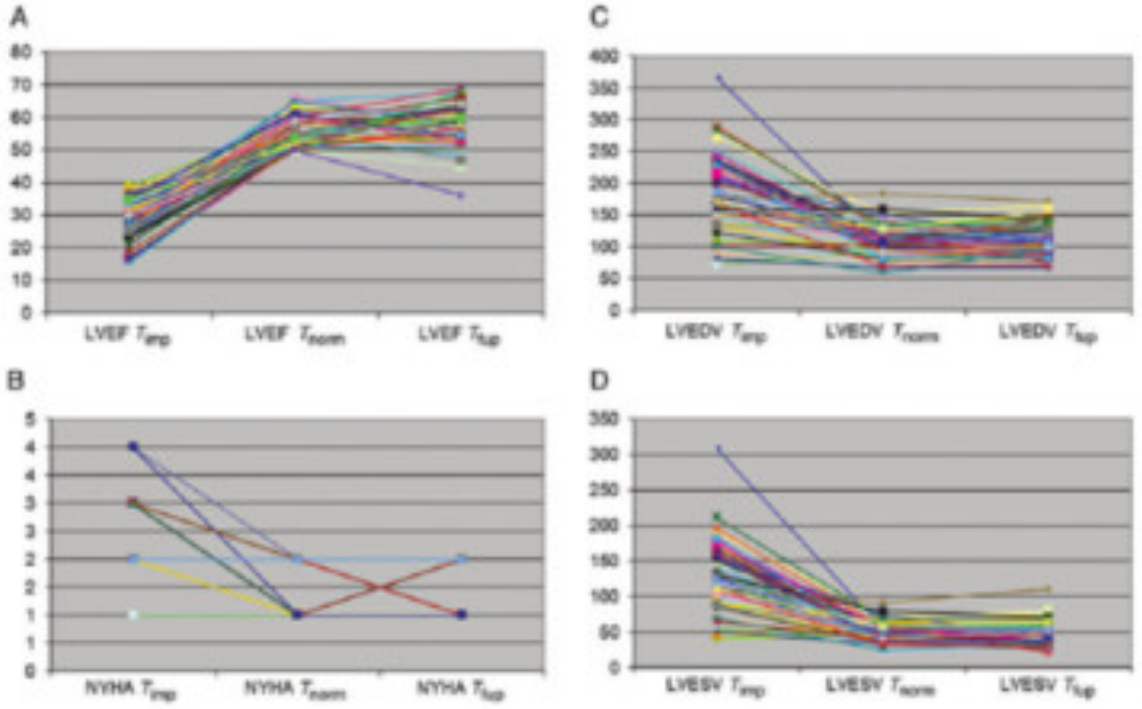
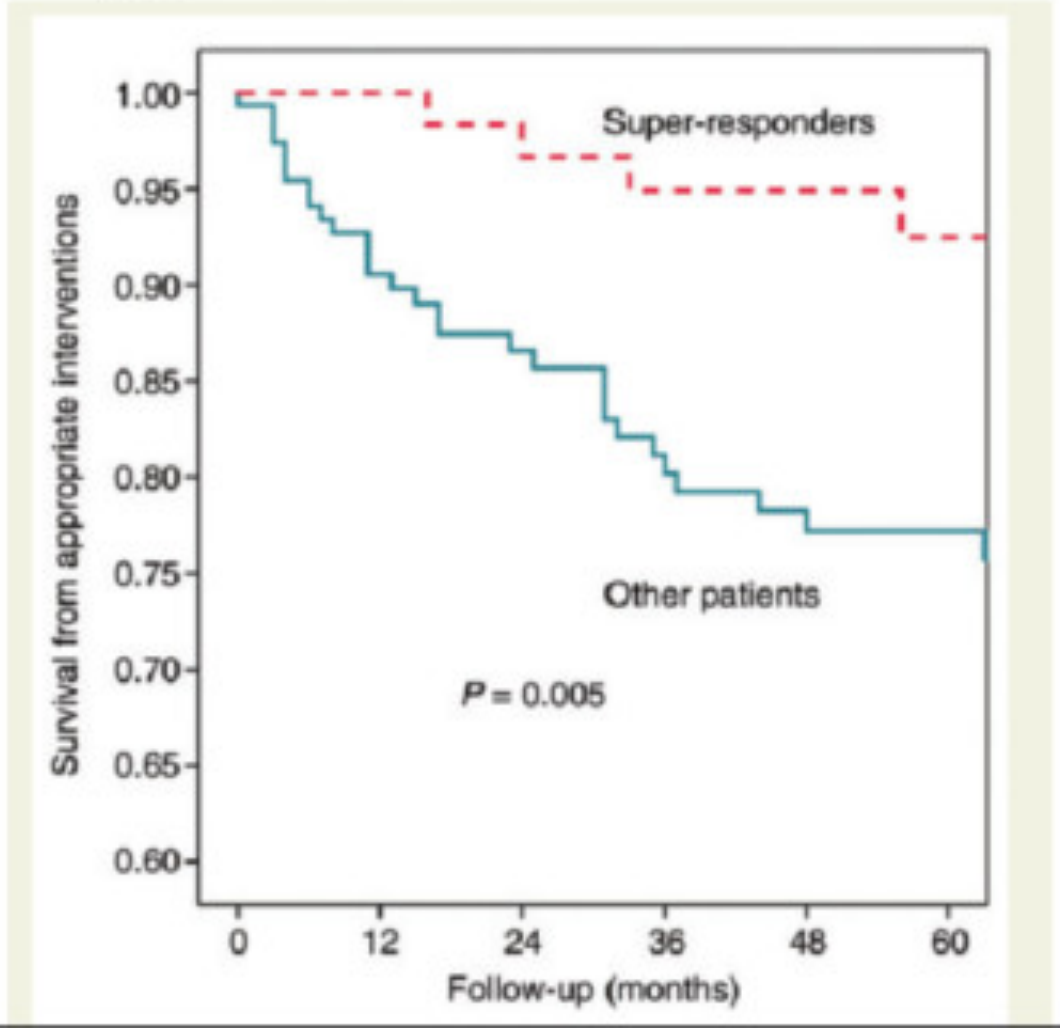


Figure 1 Clinical and echocardiographic data at implantation and during long-term follow-up. (*A*) LVEF at implantation (T_{imp}), after 1 or 2 years (T_{norm}) and at the last echocardiographic follow-up (T_{fup}) after 51 ± 27 months; (*B*) NYHA functional class at T_{imp}, T_{norm} and T_{fup}; (*C*) LVEDV at T_{imp}, T_{norm} and T_{fup}; (*D*) LVESV at T_{imp}, T_{norm} and T_{fup}. Legend: see Table 1.

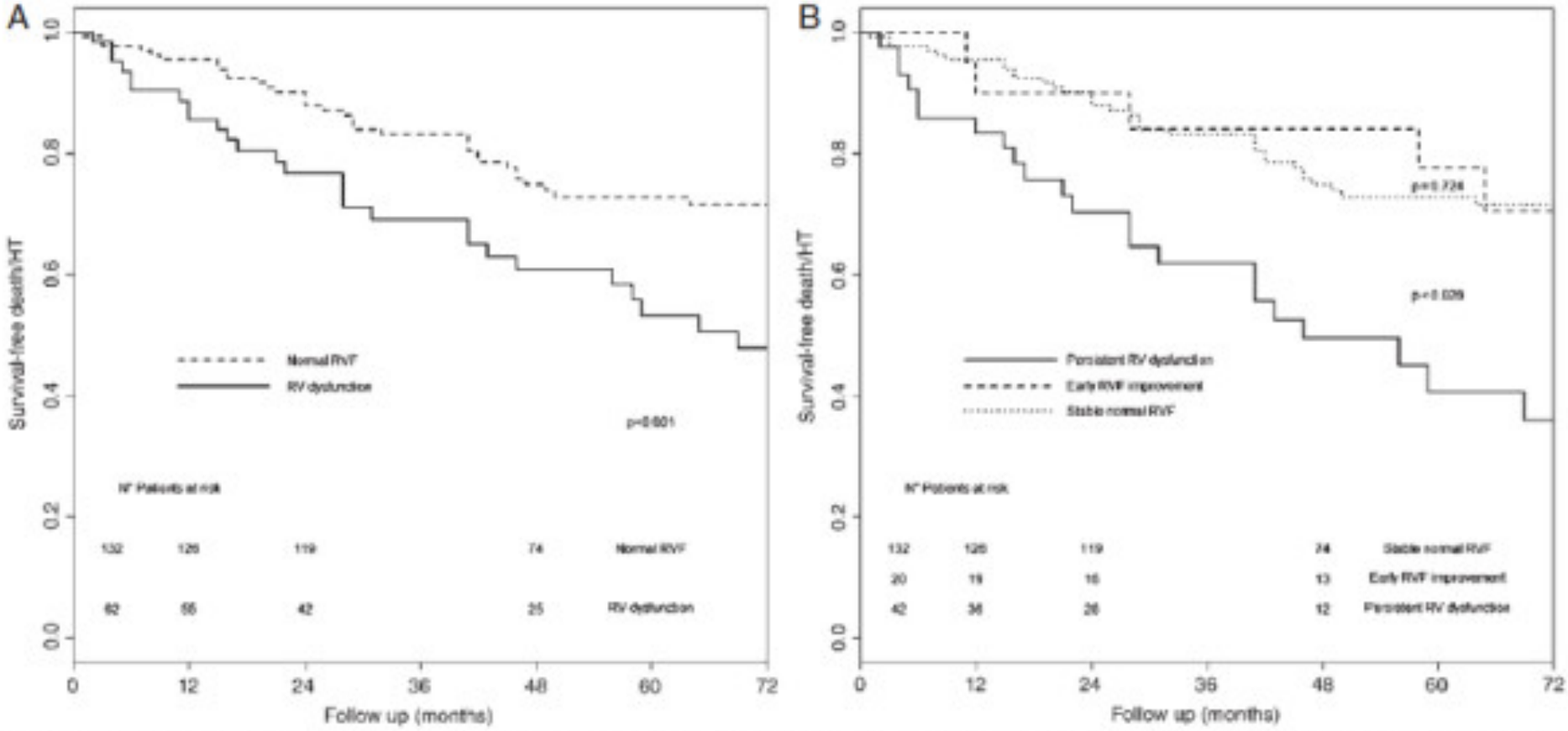
Europace (2014) 16, 363–371
doi:10.1093/europace/eut339

Long-term outcome of 'super-responder' patients to cardiac resynchronization therapy

Massimo Zecchin[1]*, Alberto Proclemer[1], Silvia Magnani[1], Laura Vitali-Serdoz[1], Domenico Facchin[2], Daniele Muser[2], Andrea Nordio[1], Giulia Barbati[1], Ilaria Puggia[1], Gianfranco Sinagra[1], and Alessandro Proclemer[2]



Early right ventricular response to cardiac resynchronization therapy: impact on clinical outcomes

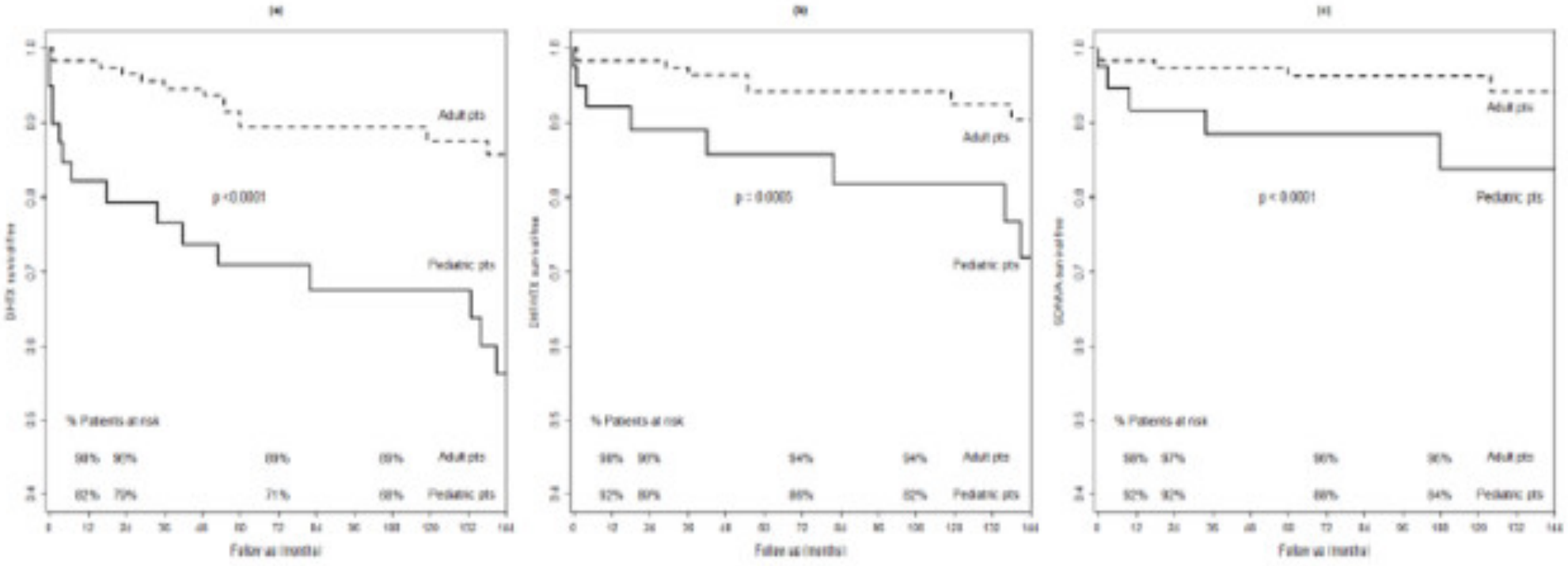


Kaplan–Meier curves for survival free from death/heart transplantation (HT) according to pre-implantation right ventricular (RV) dysfunction (A) and post-implantation changes in RV function (RVF) (B).

European Journal of Heart Failure (2016) **18**, 205–213

Natural History of Dilated Cardiomyopathy in Children

Manuscript Submission and Peer Review System

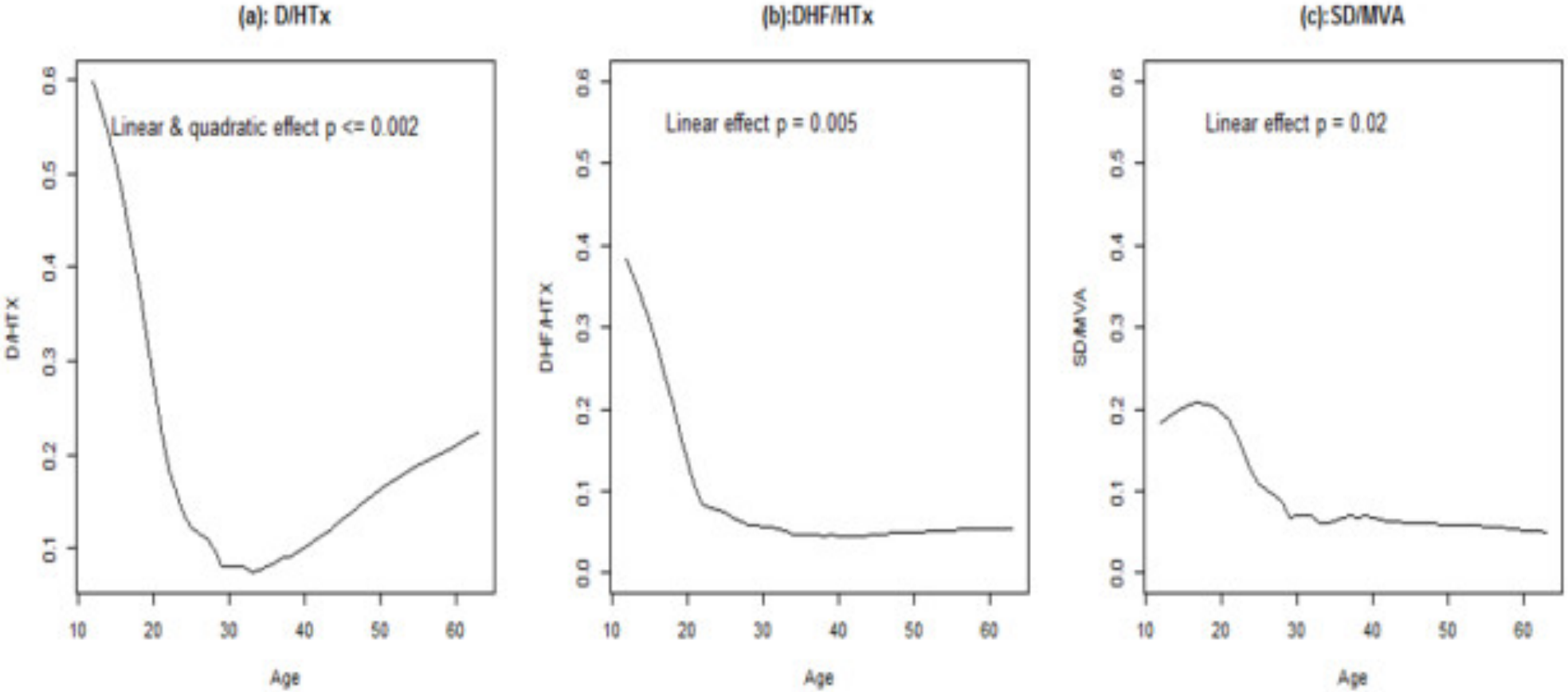


Long term survival rate free from heart transplantation (a), from pump failure death or heart transplantation (b) and long term survival rates free from SD/MVA (c) in 47 paediatric (solid line) vs. sample of 141 adult patients(dotted line) matched in a 1:3 ratio after adjustment for baseline differences between the two subgroups.

Puggia I, Sinagra G et al; JAHA, submitted

Natural History of Dilated Cardiomyopathy in Children

Manuscript Submission and Peer Review System



Effect of age on outcome measurements. Paediatric age (i.e.<18 years) was associated with increasing risk of all major events (D/HTx [a], DHF/HTx [b], SD/MVA [c]).

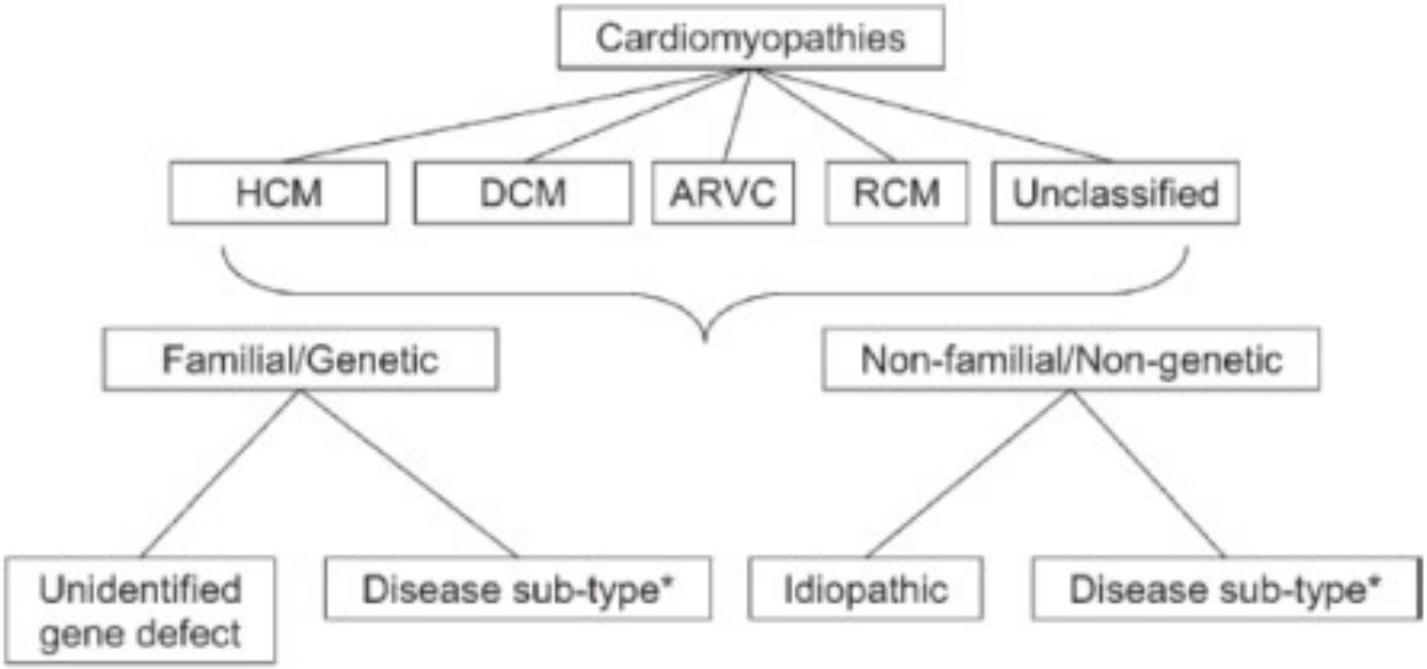
Puggia I, Sinagra G et al; JAHA, submitted

European Heart Journal (2008) 29, 270–276
doi:10.1093/eurheartj/ehm342

ESC REPORT

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

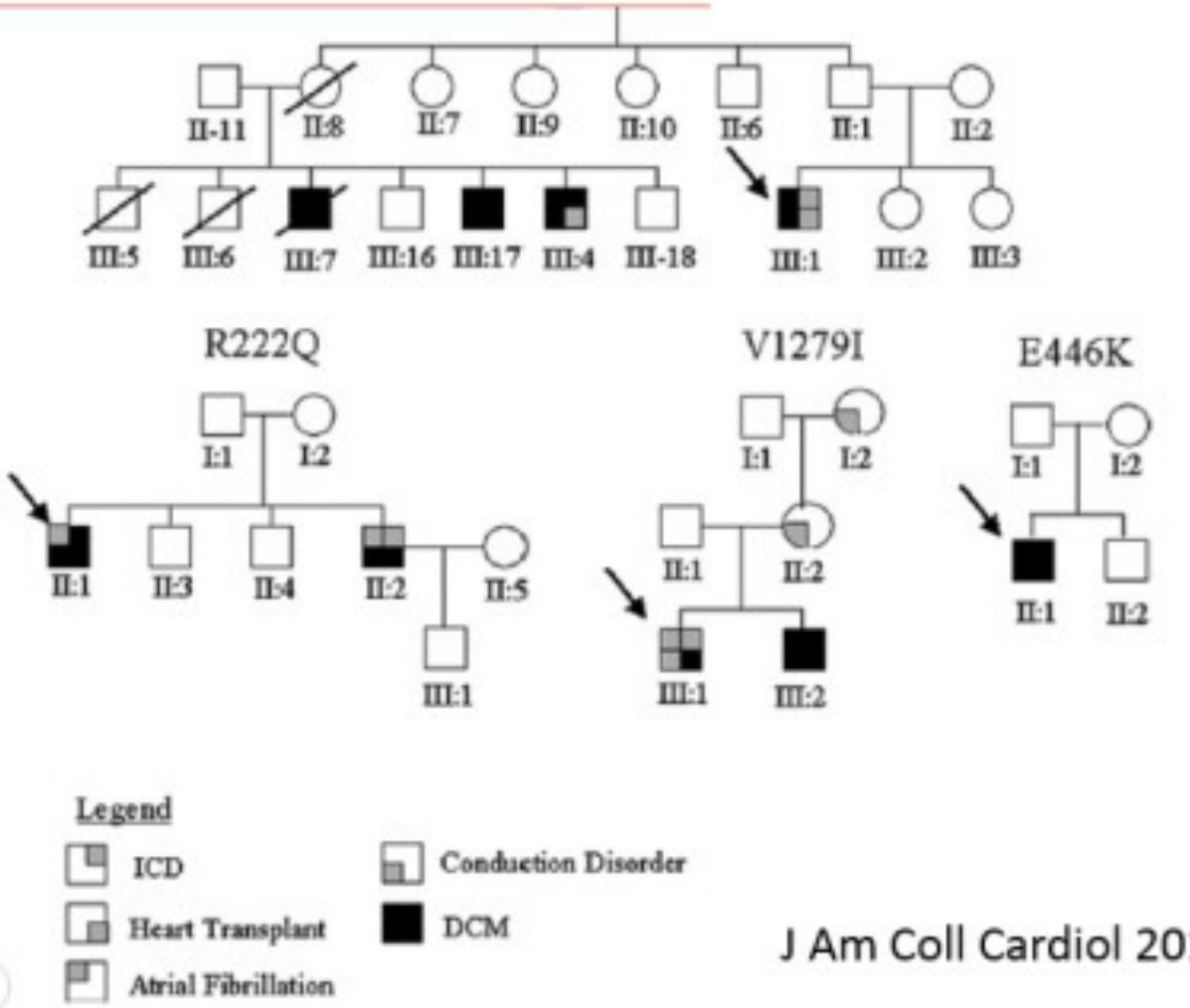
Perry Elliott, Bert Andersson, Eloisa Arbustini, Zofia Bilinska, Franco Cecchi, Philippe Charron, Olivier Dubourg, Uwe Kühl, Bernhard Maisch, William J. McKenna, Lorenzo Monserrat, Sabine Pankuweit, Claudio Rapezzi, Petar Seferovic, Luigi Tavazzi, and Andre Keren*



SCN5A Mutations Associate With Arrhythmic Dilated Cardiomyopathy and Commonly Localize to the Voltage-Sensing Mechanism

William P. McNair, PhD,* Gianfranco Sinagra, MD,§ Matthew R. G. Taylor, MD, PhD,*†
Andrea Di Lenarda, MD,§ Debra A. Ferguson, MS, ANP,* Ernesto E. Salcedo, MD,*
Dobromir Slavov, PhD,* Xiao Zhu, BS,* John H. Caldwell, PhD,‡ Luisa Mestroni, MD,*†
and the Familial Cardiomyopathy Registry Research Group

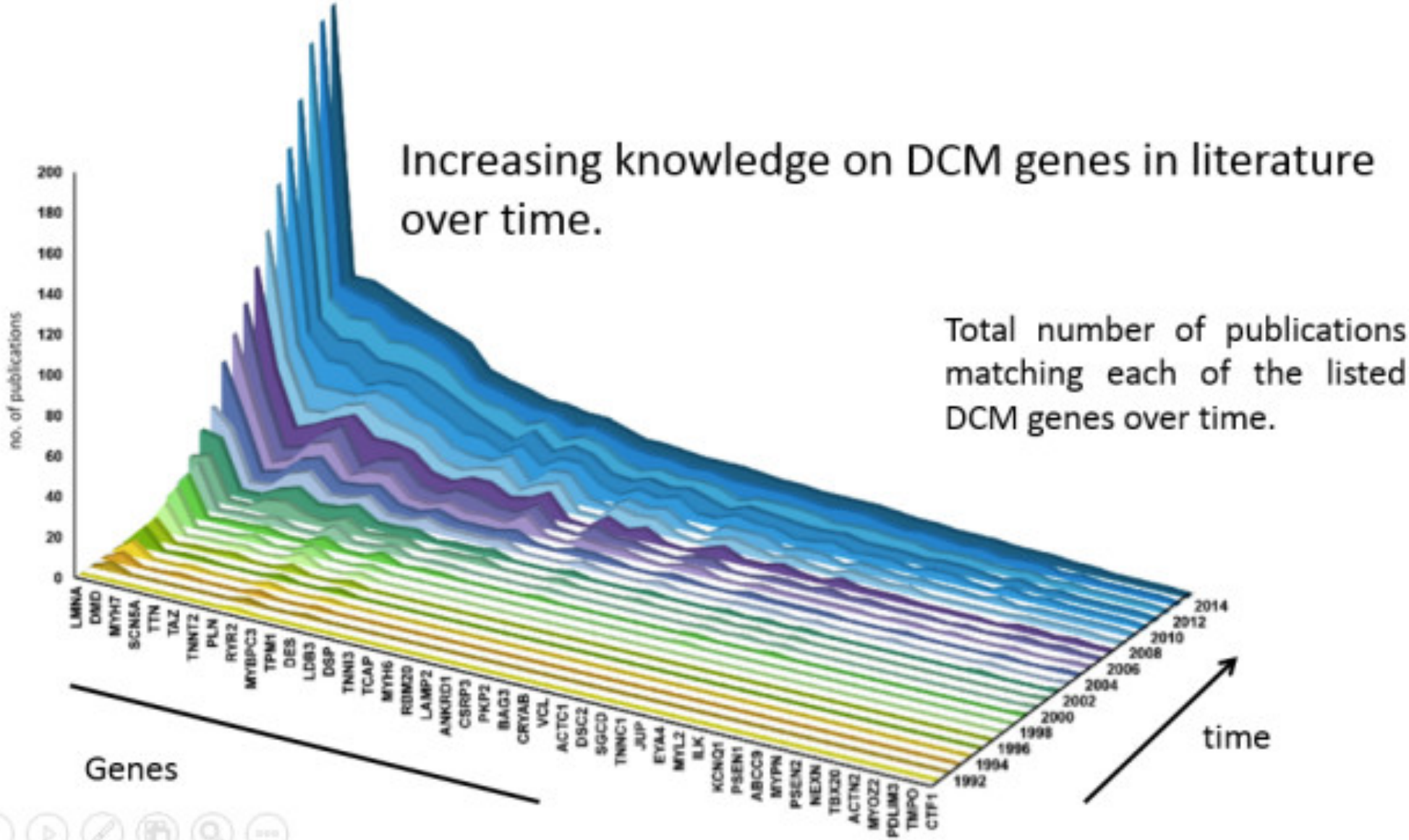
Aurora, Colorado; and Trieste, Italy



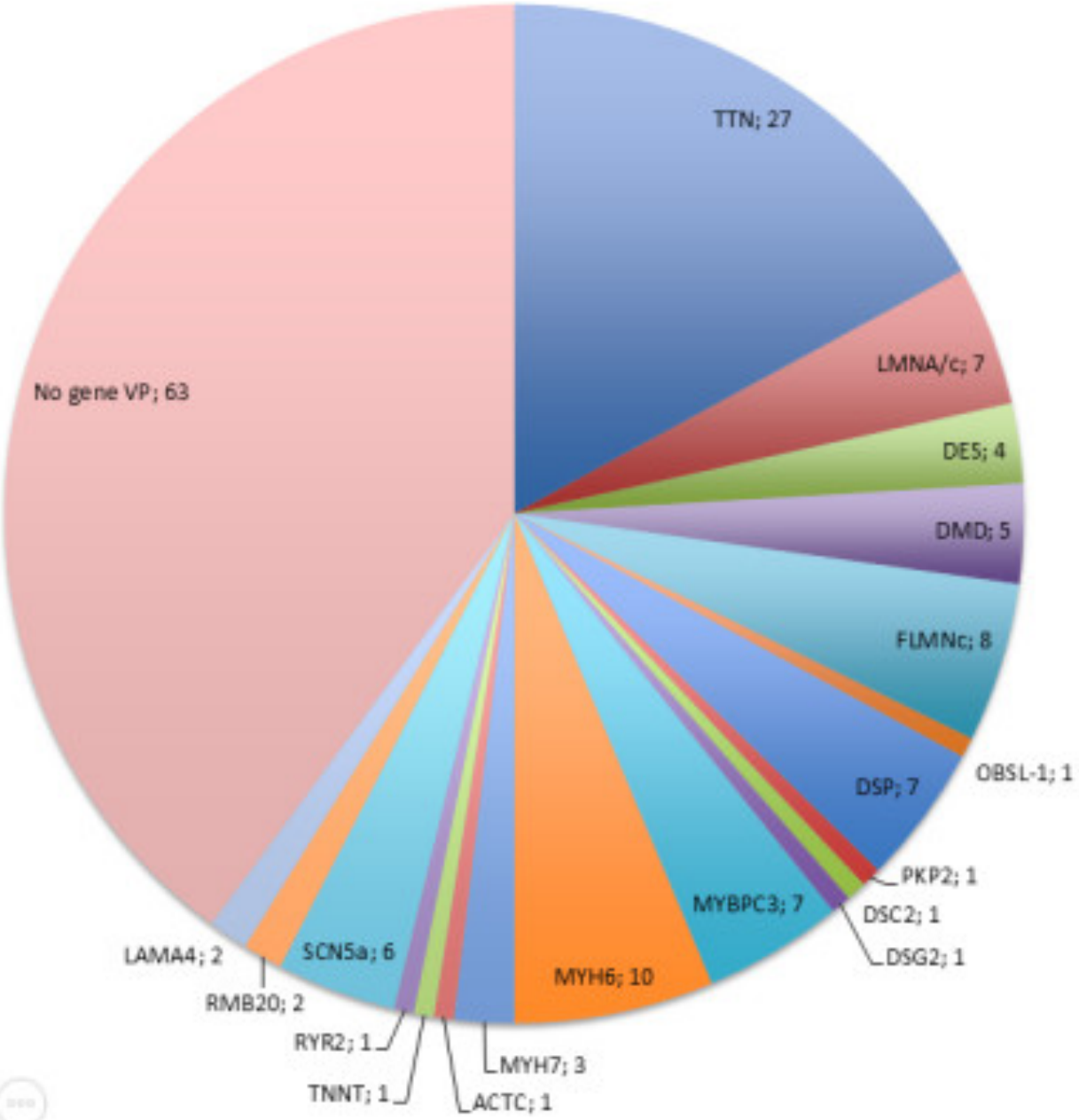
J Am Coll Cardiol 2011;57:2160-8.

Epidemiology of dilated cardiomyopathy

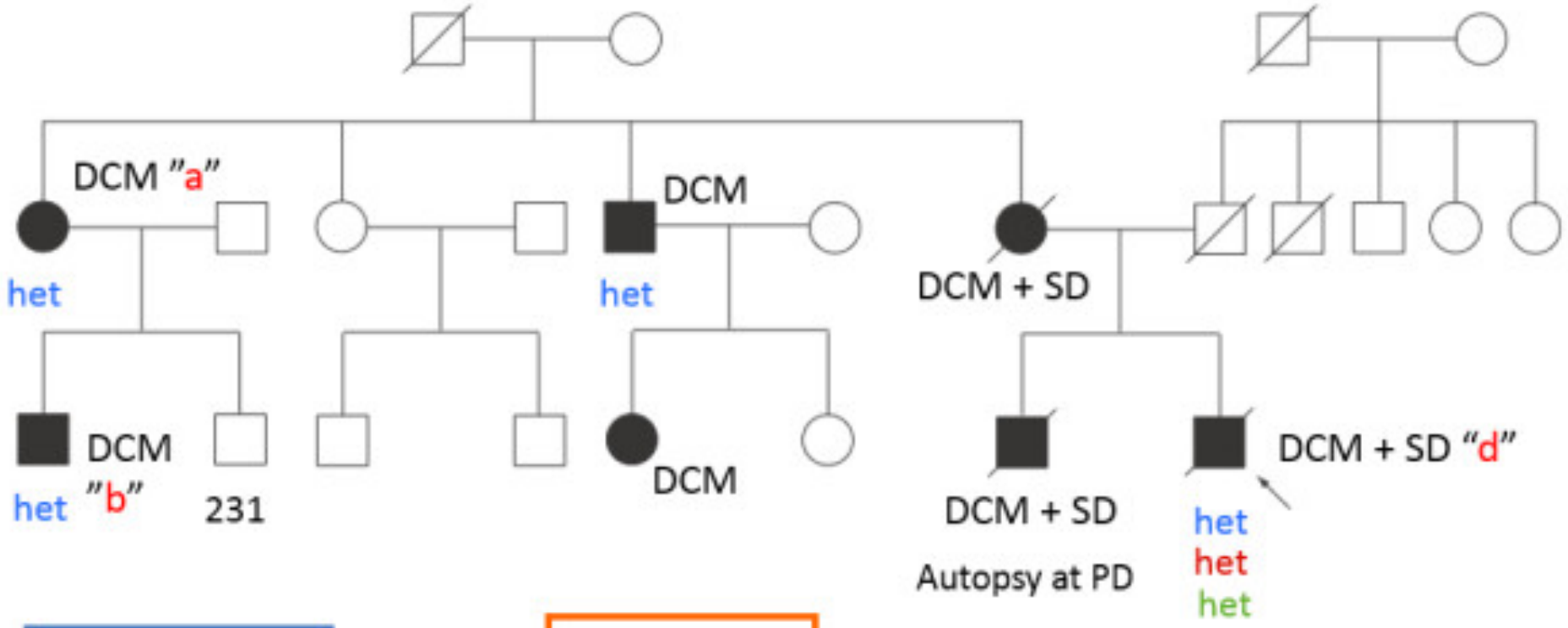
Prevalence of DCM is ~ 1/250 and is increasing in the last decades due mostly to higher ability in diagnosing this disease.



DCM genes (pathogenic variants; 194 probands)



FAM#225:
DCM – Sudden death



FLNC splicing exon skipping

DSP non syn Rs200250096

CAV3 non syn Rs116840776

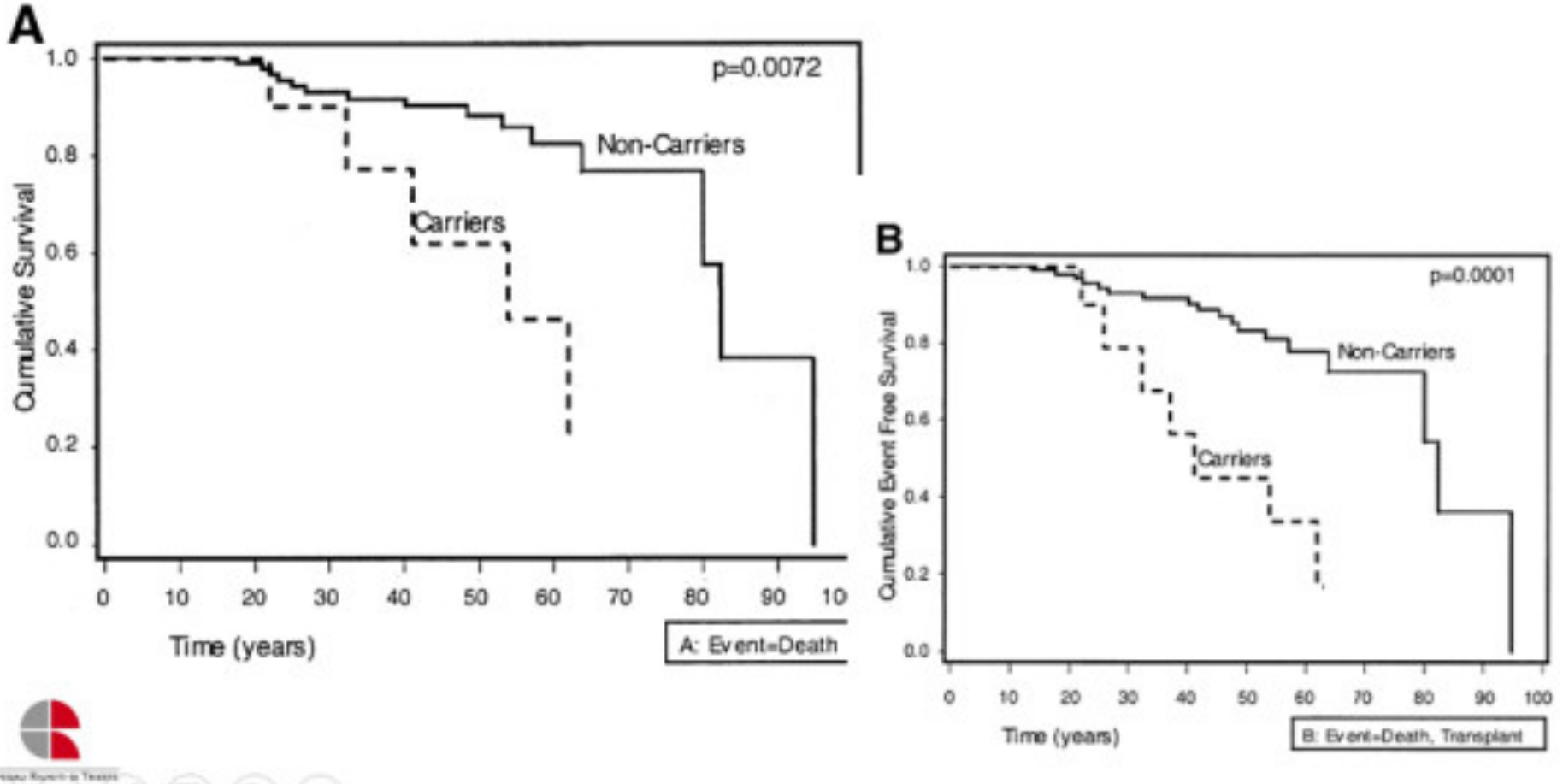
Journal of the American College of Cardiology
© 2003 by the American College of Cardiology Foundation
Published by Elsevier Science Inc.

Vol. 41, No. 5, 2003
ISSN 0735-1097/03/$30.00
doi:10.1016/S0735-1097(02)02954-6

Natural History of Dilated Cardiomyopathy Due to Lamin A/C Gene Mutations

Matthew R. G. Taylor, MD,* Pamela R. Fain, PHD,*†‡ Gianfranco Sinagra, MD, FESC,§ Misi L. Robinson,‖ Alastair D. Robertson, PHD,* Elisa Carniel, MD,§ Andrea Di Lenarda, MD, FESC,§ Teresa J. Bohlmeyer, MD,* Debra A. Ferguson, MS,* Gary L. Brodsky, PHD,* Mark M. Boucek, MD,*¶ Jean Lascor, MS,¶ Andrew C. Moss, BA,* Wai-Lun P. Li, BS,*† Gary L. Stetler, PHD,† Francesco Muntoni, MD, FRCPCH,# Michael R. Bristow, MD, PHD, FACC,* Luisa Mestroni, MD, FACC, FESC,* Familial Dilated Cardiomyopathy Registry Research Group

Denver, Colorado; Trieste, Italy; Omaha, Nebraska; and London, United Kingdom



LMNA mutations in Dilated Cardiomyopathy

Study design:

- multicenter cohort of **269** *LMNA* mutation carriers

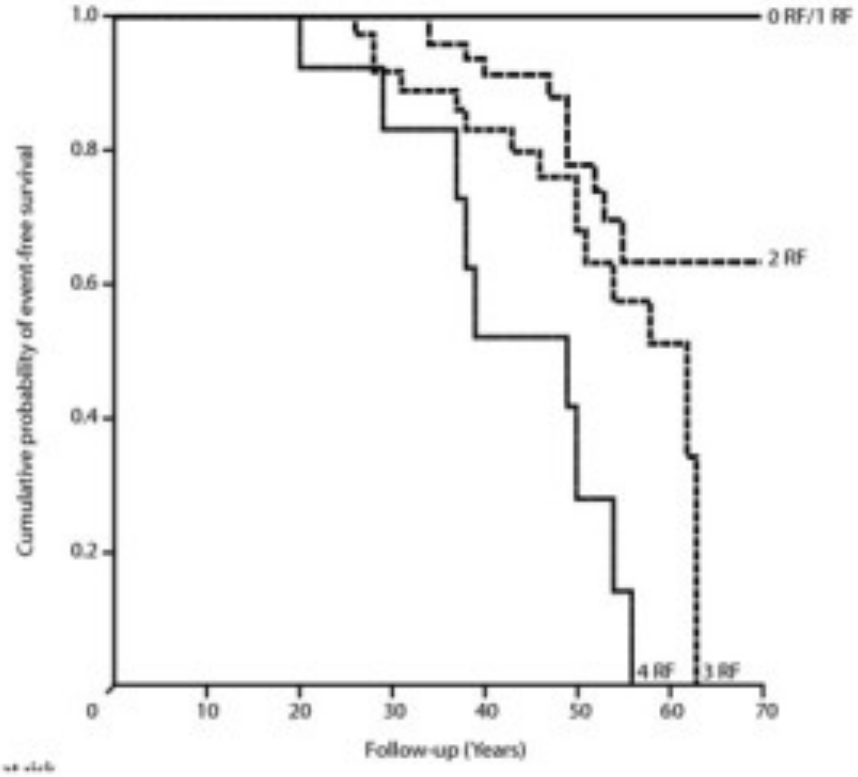
Results:

LMNA carriers with MVA: 18%

- 11 cardiopulmonary resuscitation
- 25 appropriate ICD treatment
- 12 SD

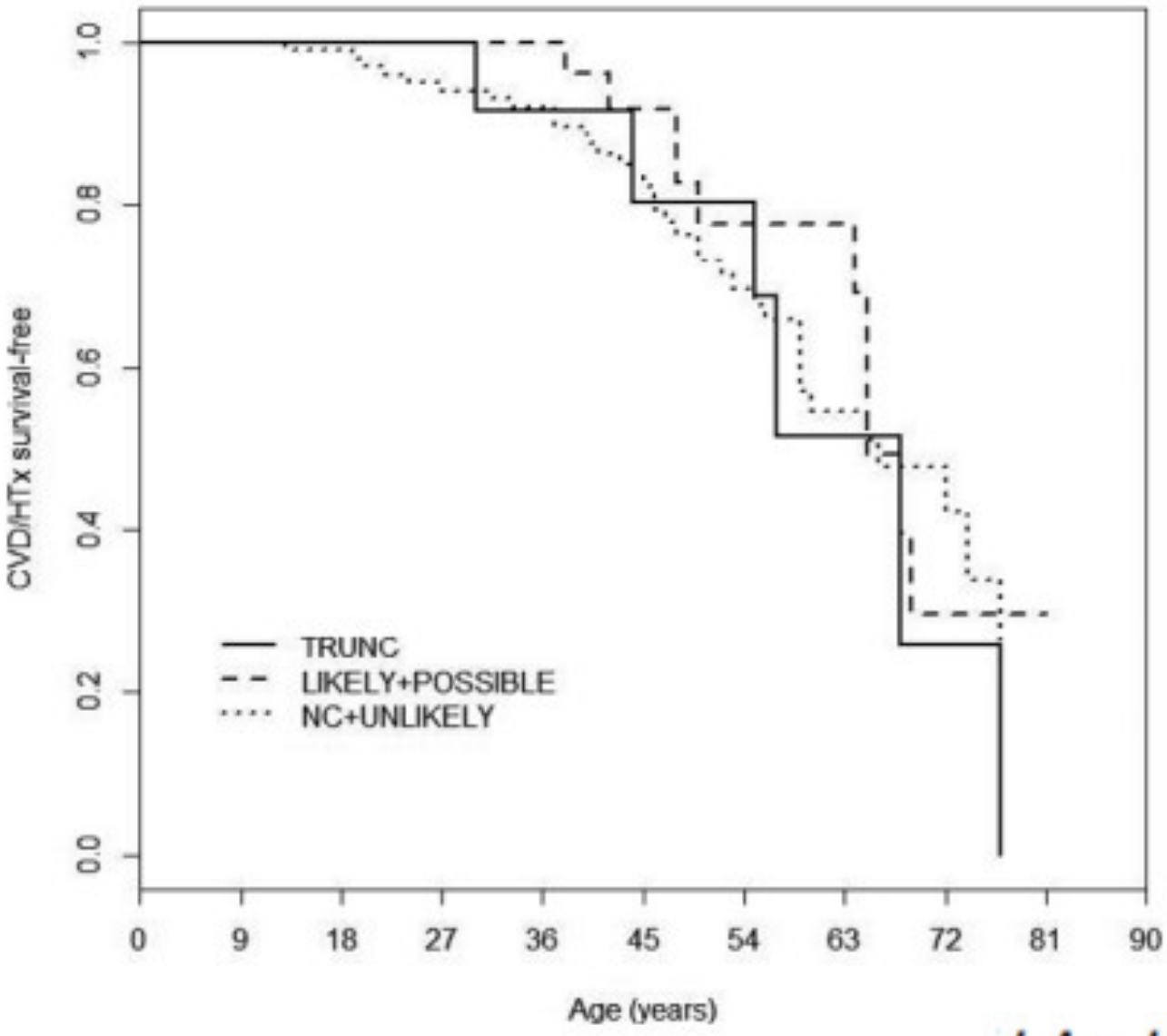
4 independent Risk Factors, cumulative risk:

- nonsustained ventricular tachycardia
- LVEF < 45%
- Male gender
- Truncating mutations



Rijsingen et al., J Am Coll Cardiol 2012;59:493–500

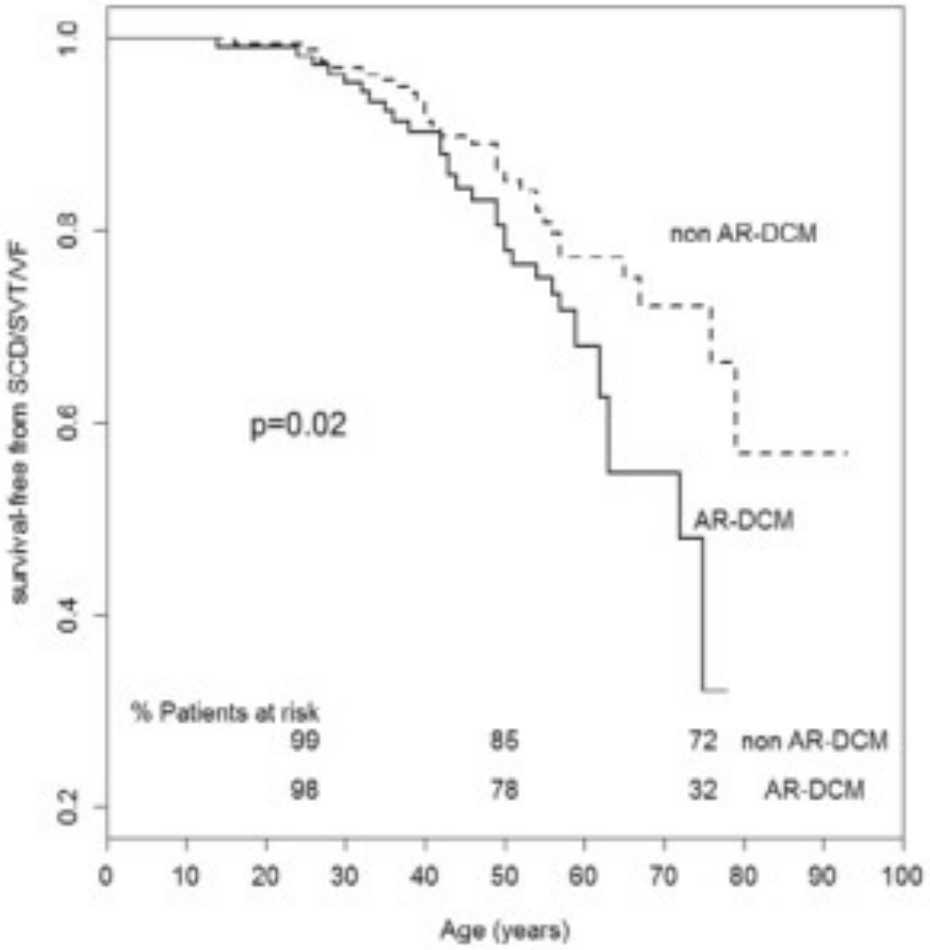
Role of Titin Missense Variants in Dilated Cardiomyopathy

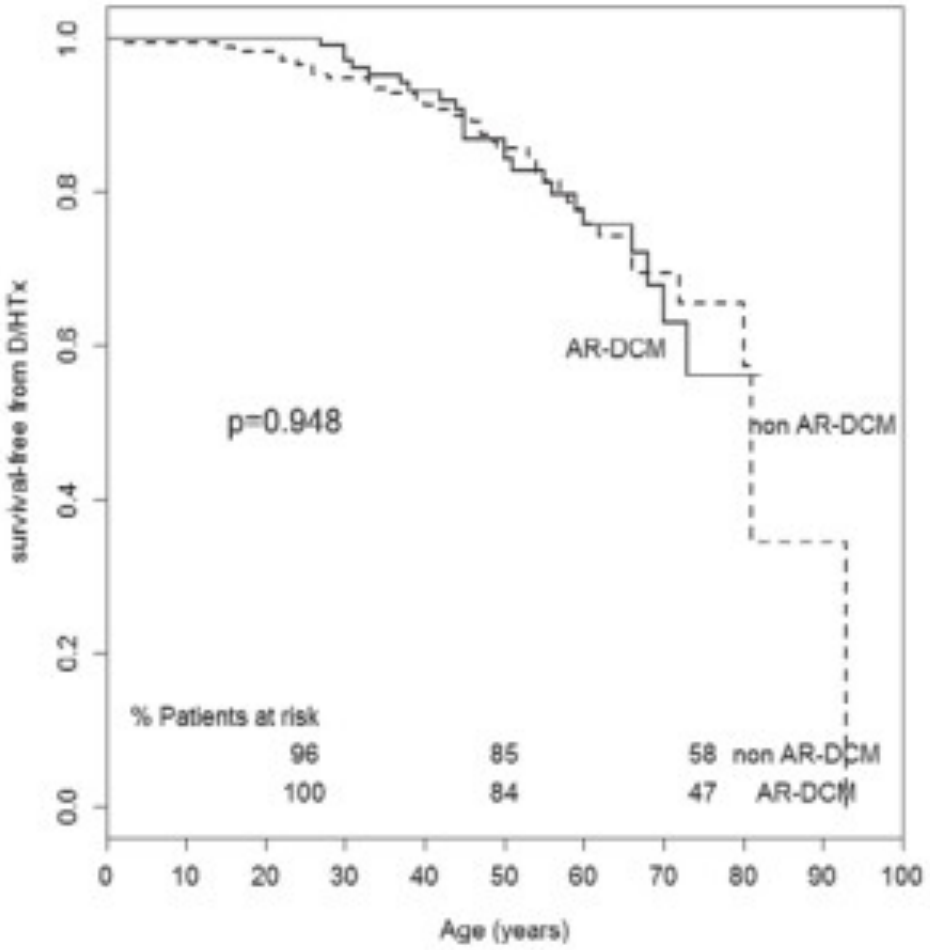


Begay, Mestroni, Sinagra et al

***J Am Heart Assoc.* 2015;4:e002645**

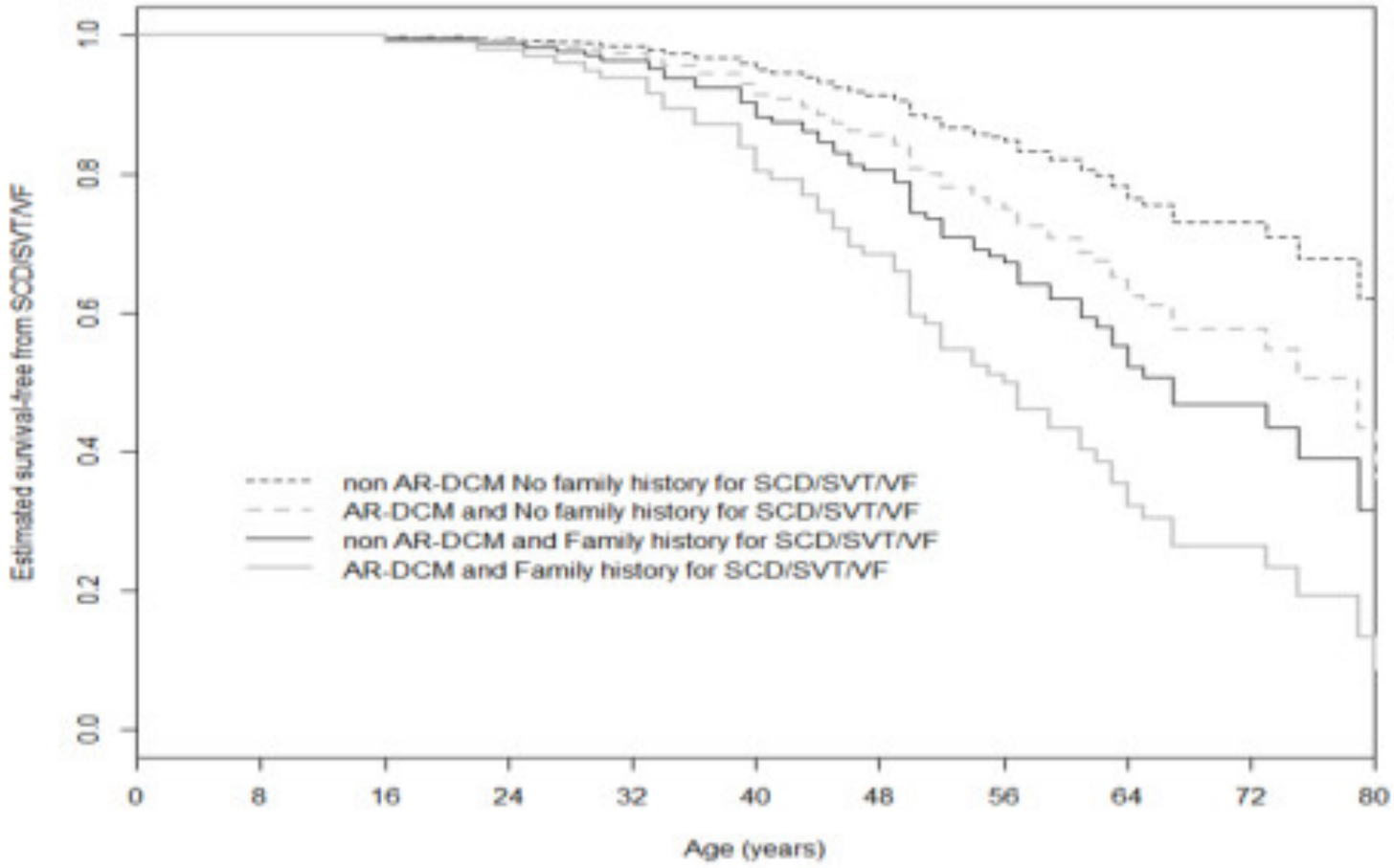
Arrhythmogenic Phenotype in Dilated Cardiomyopathy: Natural History and Predictors of Life-Threatening Arrhythmias





J Am Heart Assoc . 2015;4:e002149

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



	Univariable Analysis			Multivariable Analysis		
	HR	95% CI	P Value*	HR	95% CI	P Value*
AR-DCM	1.77	1.08–2.91	0.024	1.81	1.13–2.91*	0.013
Family history of SCD/SVT/VF	2.11	1.30–3.42	0.048	1.77	1.09–2.86	0.020
Male sex	1.66	0.97–2.87	0.102			
LVEF, %	0.98	0.97–1.02	0.214			
LVEDD, mm	1.02	0.99–1.04	0.233			
Inverted T waves in leads I, II, V5	0.51	0.25–0.78	0.050			
QRS >110 ms in leads II, V5	0.73	0.44–1.22	0.233			
Family history of SCD	1.38	0.83–2.32	0.223			
Family history of AR-DCM	1.72	0.82–3.63	0.171			
Complex QRS	0.81	0.34–1.91	0.211			
Complex NSVT	0.98	0.57–1.68	0.936			

J Am Heart Assoc . 2015;4:e002149

European Heart Journal (2012) 33, 1564–1570
doi:10.1093/eurheartj/ehs112

REVIEW

Frontiers in cardiovascular medicine

Personalized medicine: hope or hype?

Keyan Salari[1], Hugh Watkins[2], and Euan A. Ashley[3]*

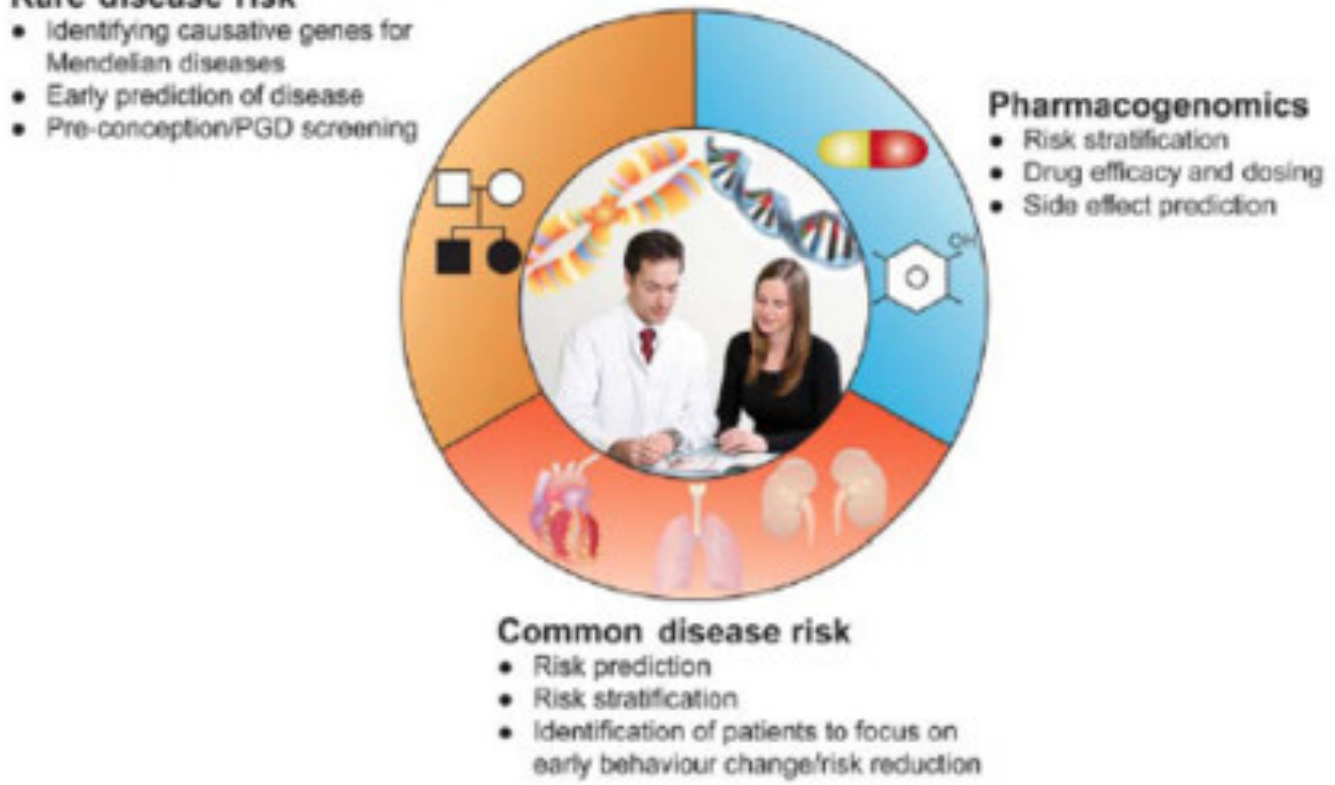


Figure 1 Domains of personalized medicine.

Take Home Message

- **La storia naturale della CMPD è migliorata grazie all'ottimizzazione dei trattamenti, sistematizzazione del follow up e stringente caratterizzazione eziologica;**
- **alcuni pattern fenotipici e di severità (familiarità, coesistenti condizioni rimuovibili, geometria e funzione Vsin e Vdx, fibrosi RM, RVFP, IM, aritmie VE, tolleranza ai farmaci) possono guidare nella stratificazione del rischio e timing procedurale;**
- **alcuni genotipi appaiono prognosticamente rilevanti e possono orientare scelte aggressive in alcuni sottogruppi, in particolare nella prevenzione della SD**