Cardio-RM. Il paradosso di una metodica di riferimento per la disgnosi di una cardiopatia potenzialmente mortale ma sostanzialmente negata ai cardiologi

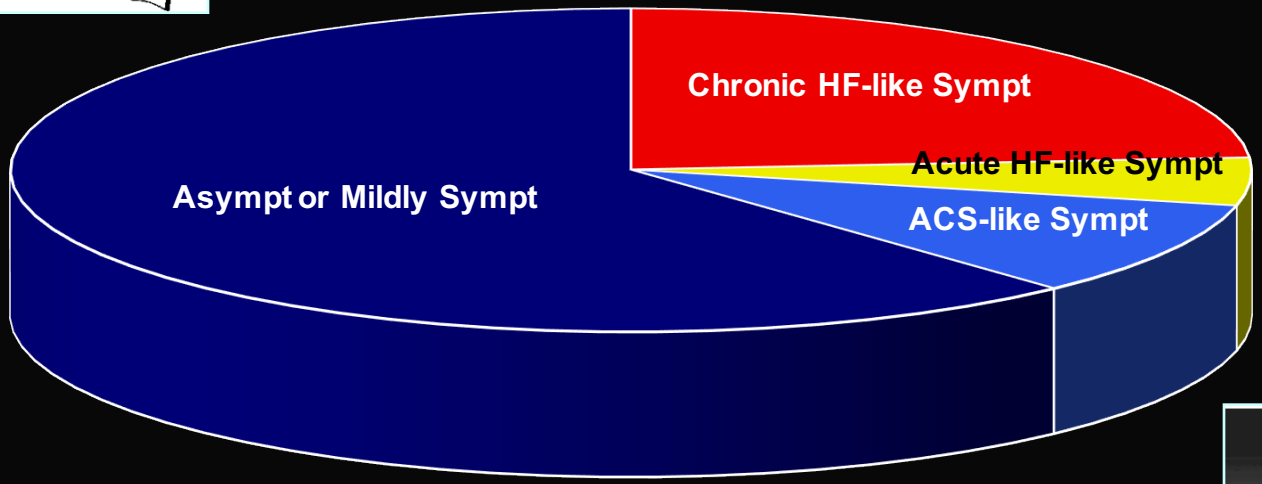
Santo Dellegrottaglie, MD – PhD

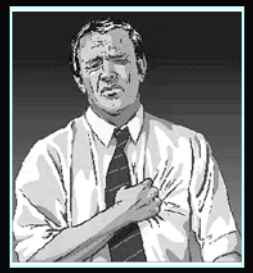
Laboratorio di RM Cardiovascolare
Divisione di Cardiologia
Ospedale Medico-Chirurgico Accreditato Villa dei Fiori
Acerra (Napoli)

Variable Clinical Presentation in Adult Patients with Acute or Chronic Myocarditis

Data from the European Study of Epidemiology and Treatment of Cardiac Inflammatory Diseases

True incidence is difficult to determine since clinical presentation varies widely and only 10% of cases leads to clinical symptoms!





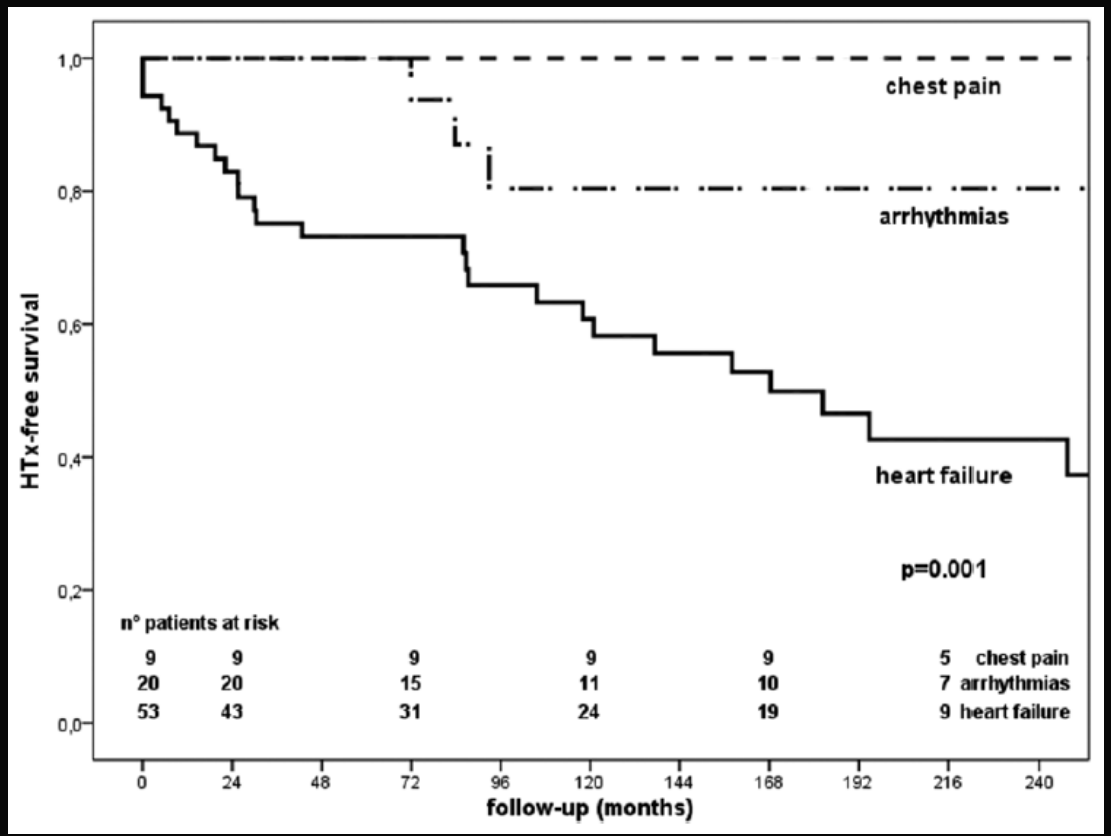
Hufnagel G et al. *Herz* 2000

Long-Term Evolution and Prognostic Stratification of Biopsy-Proven Active Myocarditis

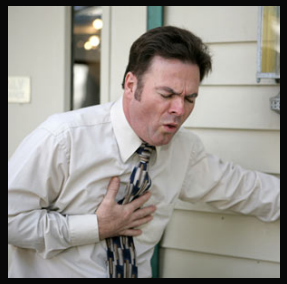
Marco Anzini, MD; Marco Merlo, MD; Gastone Sabbadini, MD; Giulia Barbati, PhD; Gherardo Finocchiaro, MD; Bruno Pinamonti, MD; Alessandro Salvi, MD; Andrea Perkan, MD; Andrea Di Lenarda, MD; Rossana Bussani, MD; Jozef Bartunek, MD, PhD; Gianfranco Sinagra, MD, FESC

(*Circulation*. 2013;128:2384-2394.)

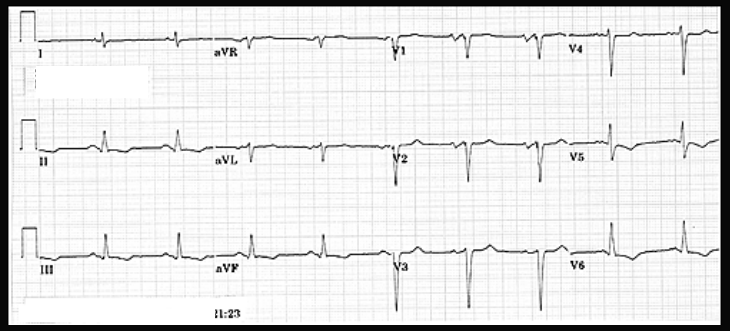
N = 82 pts. with EMB-proven acute myocarditis



Limited Accuracy of the Traditional Diagnostic Approaches to Myocarditis

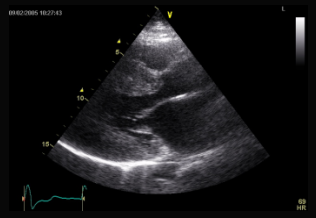


	Findings
	Sensitivity
Chest pain	30%
ECG abnormalities	50%
Troponin elevation	35-50%
Regional/global LV dysfunction	65%
	global dysfunction
Histological study	Cellular infiltration, Edema, necrosis



Lab results:

- ↑ Erythrocyte sedimentation rate
- ↑ C-reactive protein
- ↑ Leukocyte count
- ↑ Biomarkers of myocardial injury



The diagnosis of myocarditis is often based merely on suspicion!

Management of Myocarditis and Lack of an Accurate Diagnostic Modality

- Uncertainty of diagnosis at presentation
- Difficulties in monitoring disease course
- Poor capability of risk stratification
- Weakness of trial design for the evaluation of specific treatment regimens

Diagnosis of Myocarditis by EMB

Death of Dallas Criteria

Baughman KL, *Circulation* 2006

- Sampling error (low sensitivity)
- Variation in expert interpretation
- Variance of traditional histopathological findings with other markers of viral infection and immune activation in the heart
- Importance of immunohistological and molecular biological techniques on biventricular samples

Contribution and Risks of Left Ventricular Endomyocardial Biopsy in Patients With Cardiomyopathies

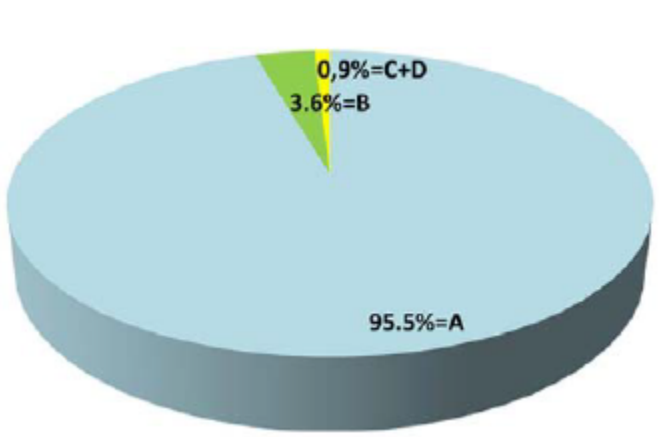
A Retrospective Study Over a 28-Year Period

Cristina Chimenti MD, PhD; Andrea Frustaci MD

(*Circulation*. 2013;128:1531-1541.)

N = 4221 pts. submitted to EMB (1983-2010)

Selective RV EMB (671; 15.9%)
Selective LV EMB (1153; 27.3%)
Biventricular EMB (2396; 56.8%)



A: Lymphocytic

B: Eosinophilic

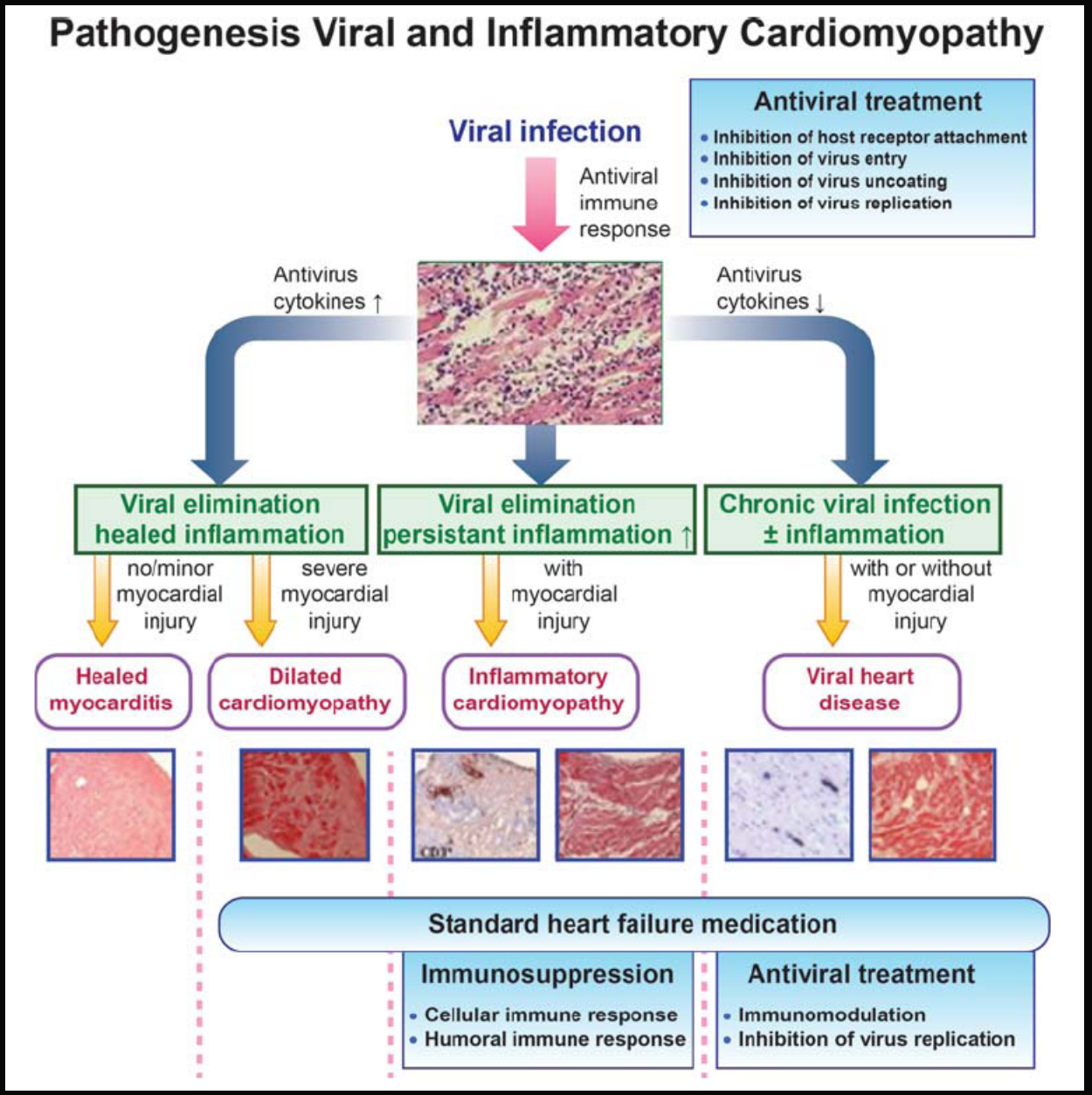
C: Giant cell

D: Sarcoid

	LVEMB (n=3549), n (%)	RVEMB (n=3068), n (%)	*P* Value
Major complication			
Perforation with cardiac tamponade	3 (0.08)	9 (0.29)	0.033
Pericardial effusion without pericardiocentesis	1 (0.028)	5 (0.16)	0.069
Brain embolization with transient cerebral ischemia	8 (0.22)	0	0.007
Pulmonary embolization	0	0	1.0
Permanent AV block	0	0	1.0
Death	0	0	1.0
Overall	12 (0.33)	14 (0.45)	0.116

By Echo	Isolated LV Involvement				Isolated RV Involvement				Biventricular Involvement			
Diagnosis	Total, n	n	%	*P* Value	Total, n	n	%	*P* Value	Total, n	n	%	*P* Value
Myocarditis	706			<0.001	43			<0.001	439			NS
LVEMB+		676	95.7			27	62.8			424	96.6	
RVEMB+		382	54.1			40	93.0			422	96.1	

Pathogenesis Viral and Inflammatory Cardiomyopathy



Schultheiss H et al. *Eur Heart J* 2011

Diagnosis of Myocarditis by EMB

Death of Dallas Criteria

Baughman KL, *Circulation* 2006

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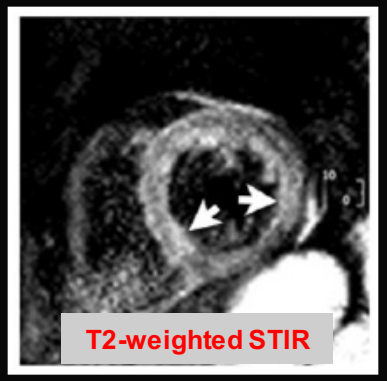
- Variation in expert interpretation
- Variance of traditional histopathological findings with other markers of viral infection and immune activation in the heart
- Importance of immunohistological and molecular biological techniques on biventricular samples

Cardiovascular Magnetic Resonance in Myocarditis

Friedrich M.G. et al. for the International Consensus Group on CMR in Myocarditis, *J Am Coll Cardiol* 2009

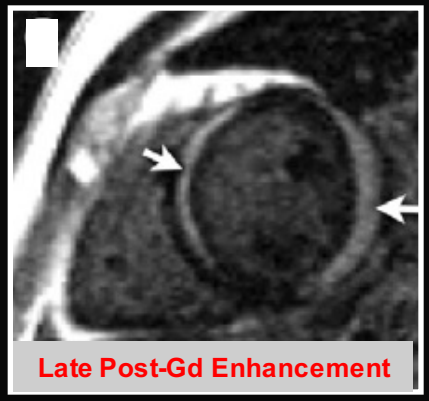
Tissue pathology in active myocarditis

- Edema/inflammation



- Hyperemia/capillary leakage

- Necrosis/fibrosis



Diagnostic Accuracy of CMR Tissue Criteria in Detecting Myocarditis

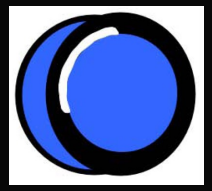
Friedrich M.G. et al. for the International Consensus Group on CMR in Myocarditis, *J Am Coll Cardiol* 2009

	Sensitivity (%)	Specificity (%)	Accuracy (%)	PPV (%)	NPV (%)
T2W STIR	70	71	70	77	63
Early Post-Gd Enhancement	74	83	78	86	70
Late Post-Gd Enhancement	59	86	68	89	53
Combination (any 2 of 3)	**67**	**91**	**78**	**91**	**69**

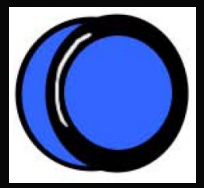
Proposed Diagnostic CMR Criteria for Myocarditis

(≥2 criteria need to be satisfied)

1. Regional or global ↑ SI in T2W STIR images
2. ↑ myocardium/skeletal muscle SI ratio in early post-Gd T1W images
3. ≥1 focal area of nonischemic enhancement in late post-Gd T1W images

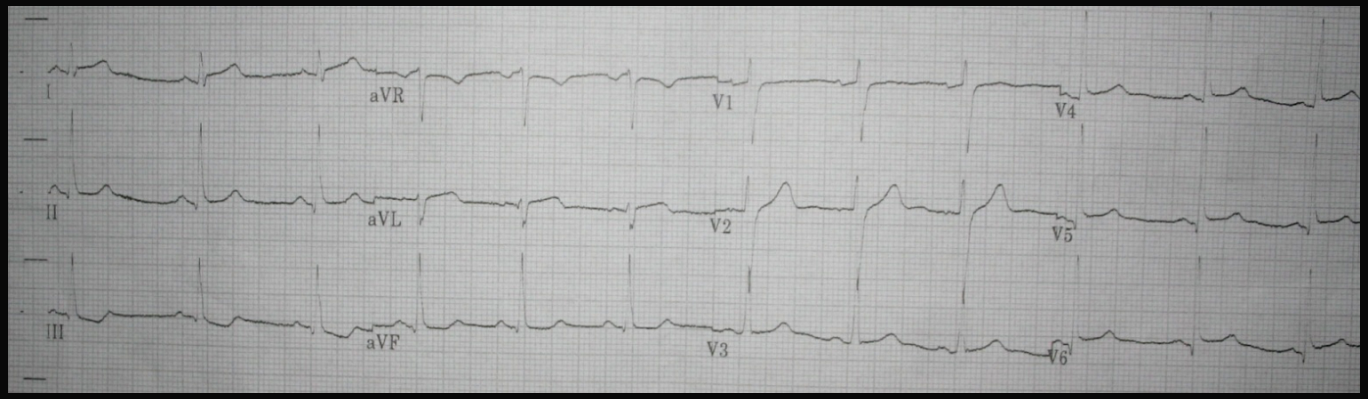


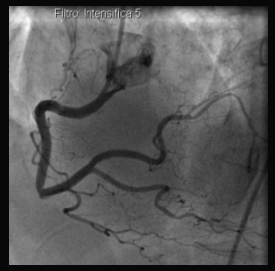
Ischemia

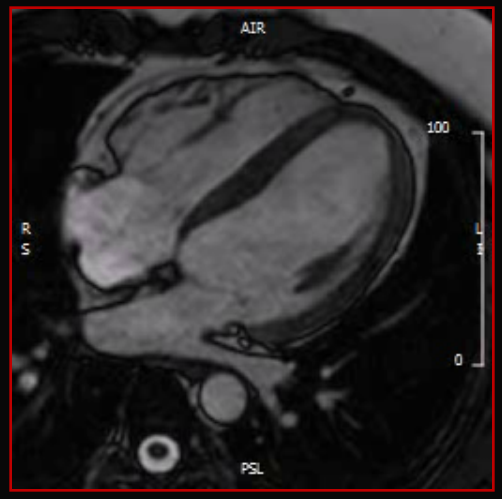


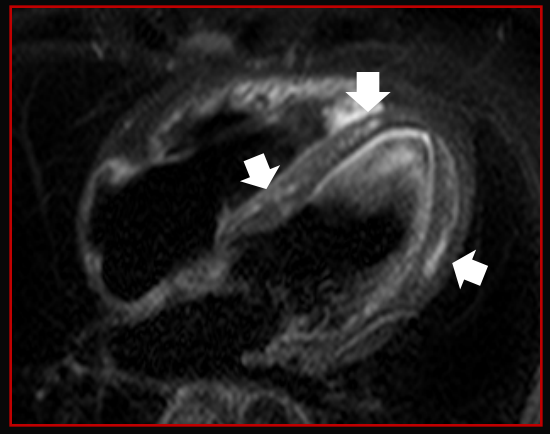
Myocarditis

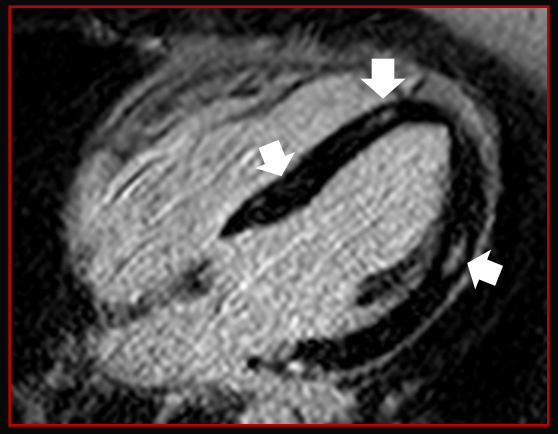
T.R.
36 year-old male
Intense chest pain after 3 days with fever (zenith = 39.1° C)
No CV risk factors
TnI = 5.18 ng/dl
Echo unremarkable
Coronary angiography –











Cine

(Function)

T2 STIR

(Edema/Inflammation)

Late Enhancement

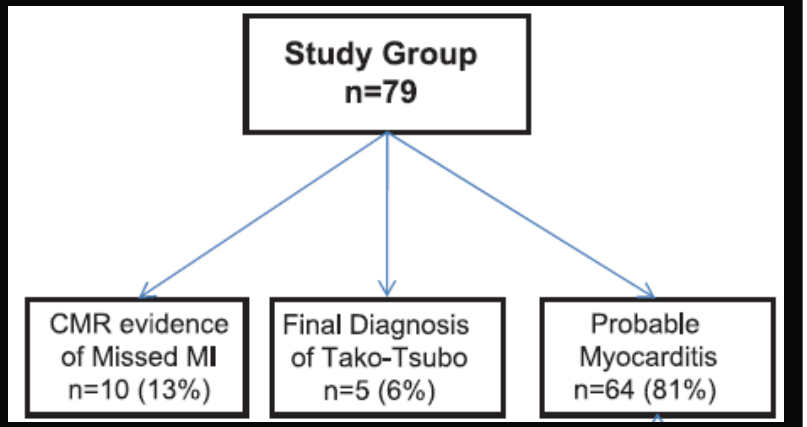
(Necrosis/Fibrosis)

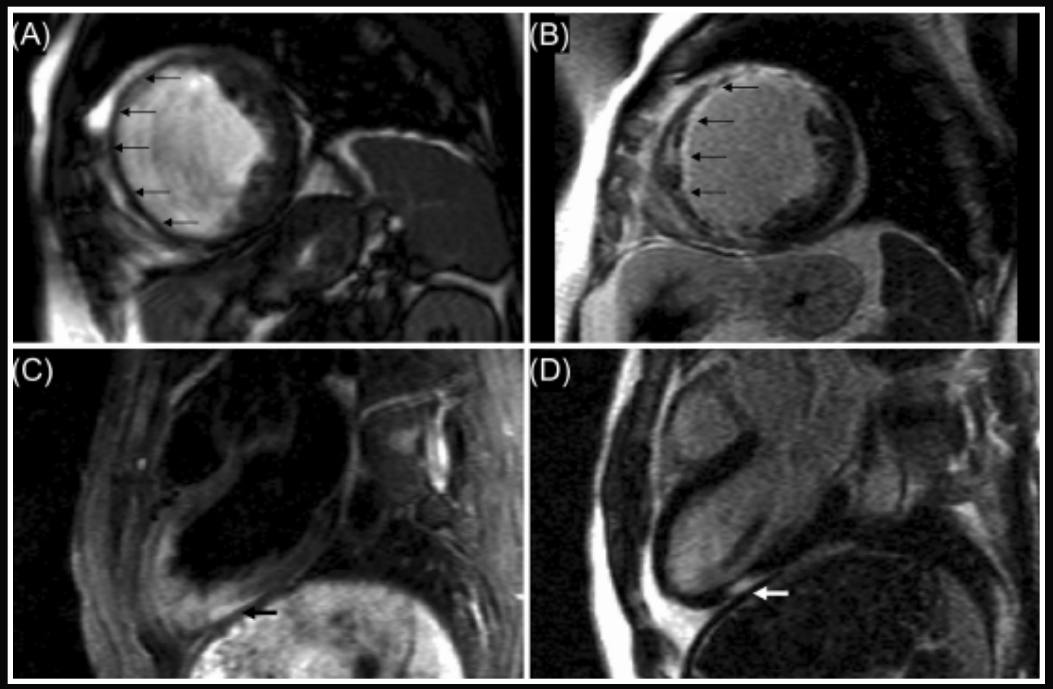
Role of CMR in Patients Presenting with Chest Pain, Raised Troponin, and Unobstructed Coronary Arteries

N= 79 pts resting chest pain, ↑ Tn and CAD (–) by cath

92% with abnormal ECG on presentation (40% with ↑ST)

Median symptoms-CMR interval = 15 days





Assomull RG et al. *Eur Heart J* 2007

Monney PA et al. *Heart* 2011

Systematic Review of Patients Presenting With Suspected Myocardial Infarction and Nonobstructive Coronary Arteries

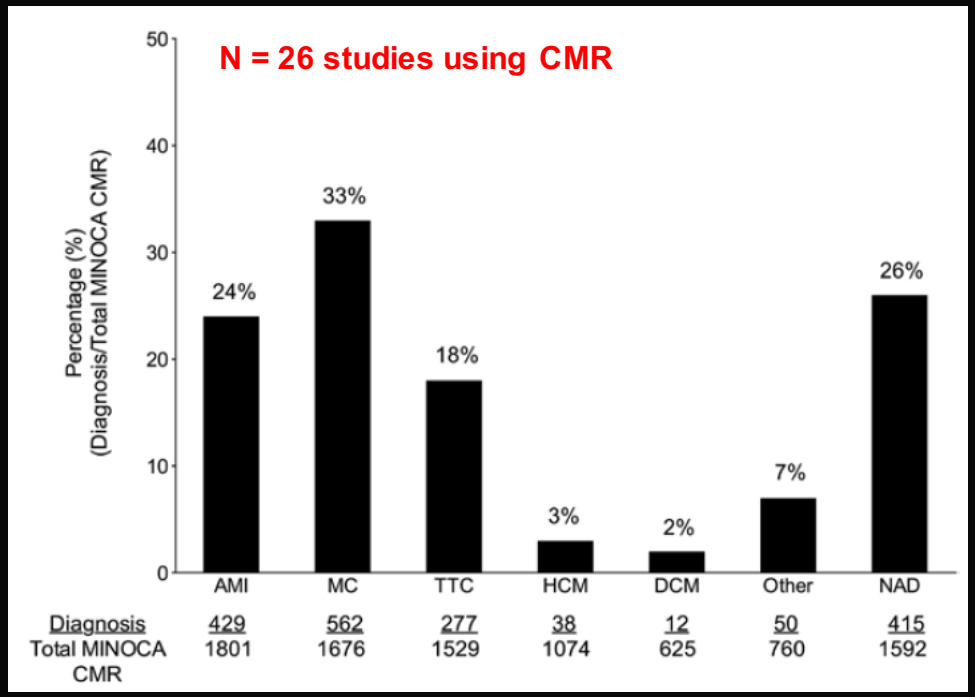
Sivabaskari Pasupathy, BSc(Hons); Tracy Air, BA (Hons), M.Biostatistics; Rachel P. Dreyer, BSc(Hons), PhD; Rosanna Tavella, BSc(Hons), PhD; John F. Beltrame, BSc, BMBS, PhD

Circulation. 2015;131:861-870.

Overall prevalence of MINOCA = 6%

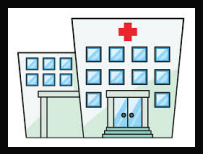
Table 2. All-Cause Mortality in Patients With MINOCA or MI-CAD

All-Cause Mortality	Comparative Studies: MI-CAD % (95% CI)	Comparative Studies: MINOCA % (95% CI)	Comparative Studies: OR (95% CI) *P* Value	All MINOCA Studies
In-hospital	3.2% (1.8%, 4.6%)	1.1% (-0.1%, 2.2%)	0.37 (0.2–0.67) *P*=0.001	0.9% (0.5%, 1.3%)
12-month	6.7% (4.3%, 9.0%)	3.5% (2.2%, 4.7%)	0.59 (0.41–0.83) *P*=0.003	4.7% (2.6%, 6.9%)

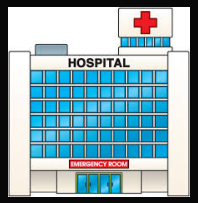


Routine evaluation of MINOCA should include CMR imaging, together with provocative spasm testing, and thrombophilia assessment

Hub-Spoke Model for Cardiac MRI



Cardiac MRI



Laboratorio
RM Cardiaca
Clinica Villa dei Fiori
(Acerra, Napoli)

~5% in ambulanza
da altri Ospedali

The Role of Endomyocardial Biopsy in the Management of Cardiovascular Disease: A Scientific Statement From the American Heart Association, the American College of Cardiology, and the European Society of Cardiology

Leslie T. Cooper, Kenneth L. Baughman, Arthur M. Feldman, Andrea Frustaci, Mariell Jessup, Uwe Kuhl, Glenn N. Levine, Jagat Narula, Randall C. Starling, Jeffrey Towbin, Renu Virmani and Endorsed by the Heart Failure Society of America and the Heart Failure Association of the European Society of Cardiology

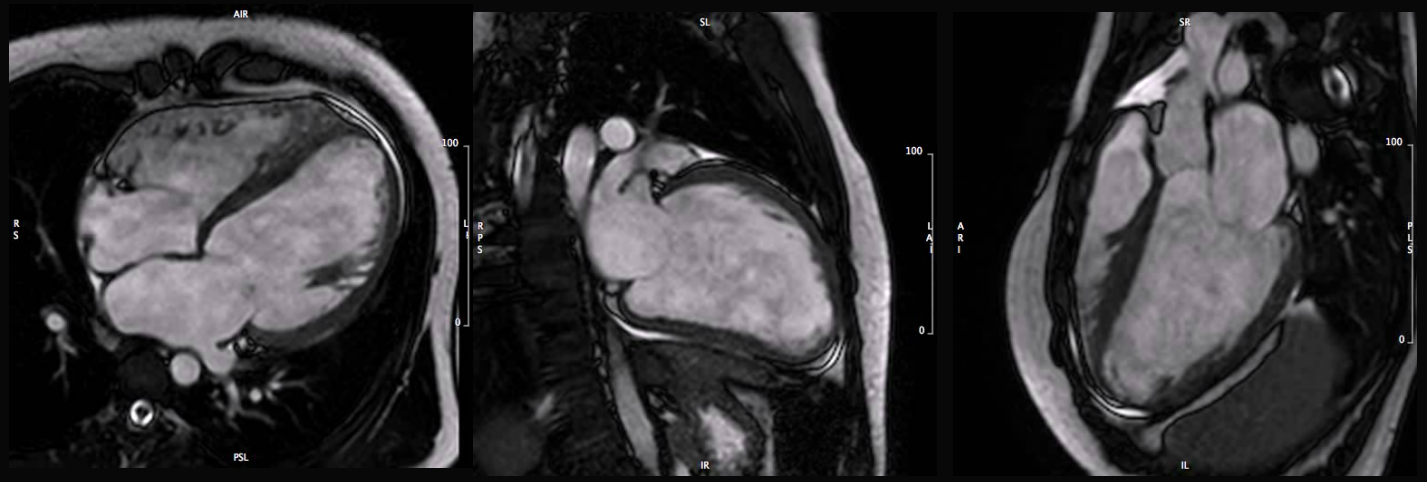
Circulation 2007;116;2216-2233; originally published online Oct 24, 2007;

Scenario Number	Clinical Scenario	Class of Recommendation (I, IIa, IIb, III)	Level of Evidence (A, B, C)
1	New-onset heart failure of *<2 weeks'* duration associated with a normal-sized or dilated left ventricle and hemodynamic compromise	I	B
2	New-onset heart failure of *2 weeks' to 3 months'* duration associated with a dilated left ventricle and new ventricular arrhythmias, second- or third-degree heart block, or failure to respond to usual care within 1 to 2 weeks	I	B
3	Heart failure of *>3 months'* duration associated with a dilated left ventricle and new ventricular arrhythmias, second- or third-degree heart block, or failure to respond to usual care within 1 to 2 weeks	IIa	C
4	Heart failure associated with a DCM of any duration associated with suspected allergic reaction and/or eosinophilia	IIa	C
5	Heart failure associated with suspected anthracycline cardiomyopathy	IIa	C
6	Heart failure associated with unexplained restrictive cardiomyopathy	IIa	C
7	Suspected cardiac tumors	IIa	C
8	Unexplained cardiomyopathy in children	IIa	C
9	New-onset heart failure of *2 weeks' to 3 months'* duration associated with a dilated left ventricle, without new ventricular arrhythmias or second- or third-degree heart block, that responds to usual care within 1 to 2 weeks	IIb	B
10	Heart failure of *>3 months'* duration associated with a dilated left ventricle, without new ventricular arrhythmias or second- or third-degree heart block, that responds to usual care within 1 to 2 weeks	IIb	C
11	Heart failure associated with unexplained HCM	IIb	C
12	Suspected ARVD/C	IIb	C
13	Unexplained ventricular arrhythmias	IIb	C
14	Unexplained atrial fibrillation	III	C

L. L.

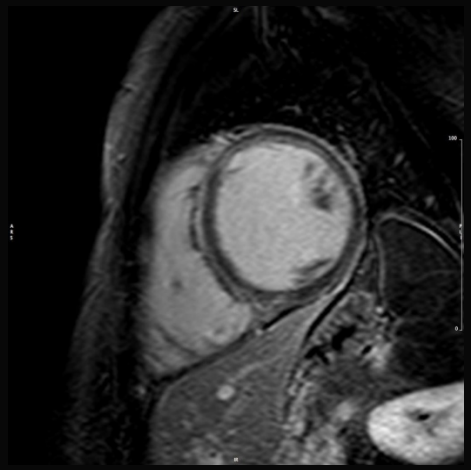
Maschio; 15 anni

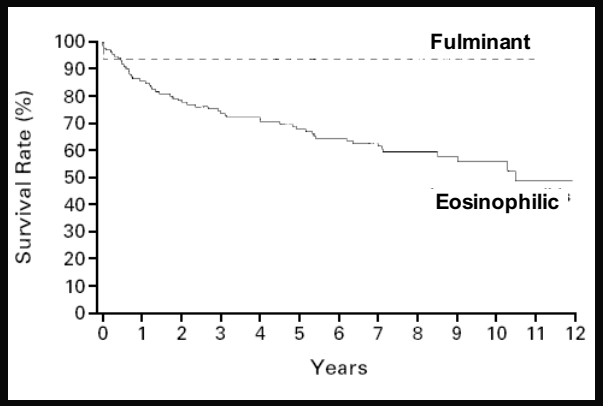
Scompenso cardiaco acuto → assistenza ventricolare → trapianto cardiaco

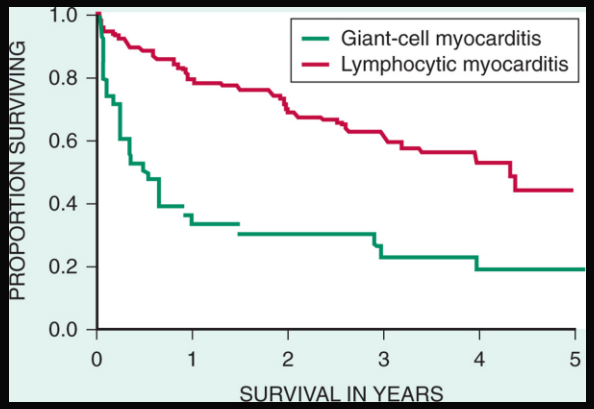


FE VSx = 18%

FE VDx = 24%







Braunwald's Heart Disease: A Textbook of Cardiovascular Medicine, 8th ed

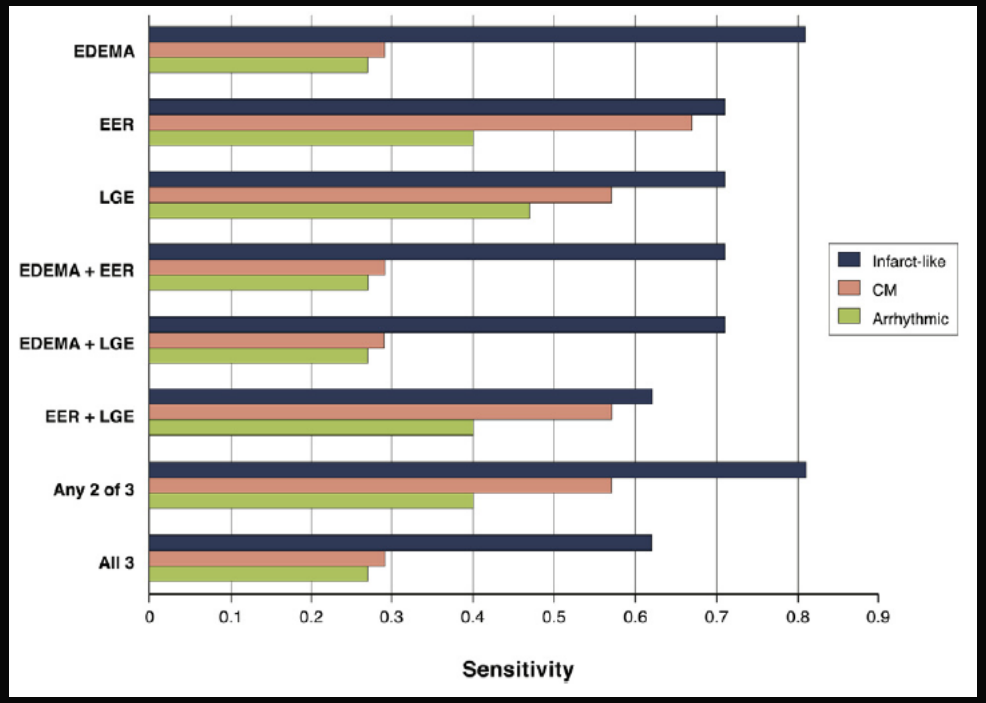
CMR Sensitivity Varies With Clinical Presentation and Extent of Cell Necrosis in Biopsy-Proven Acute Myocarditis

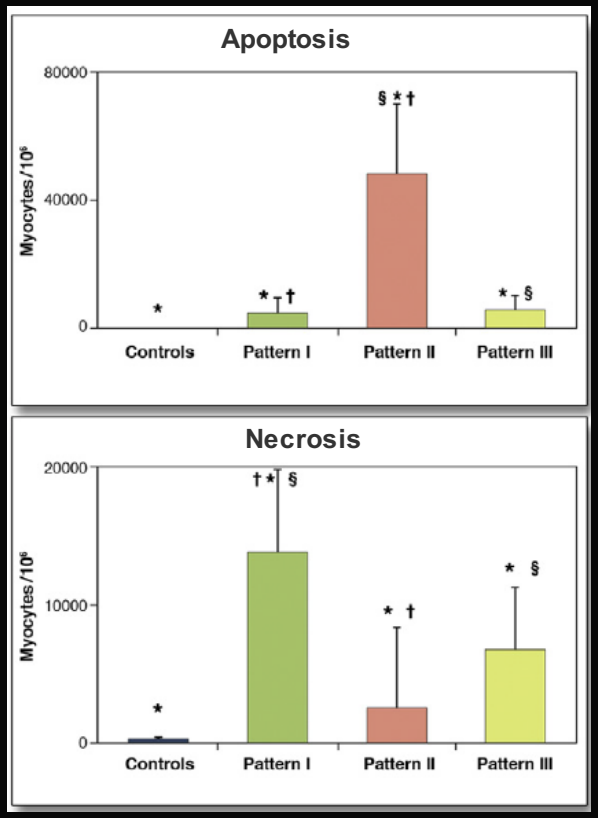
Marco Francone, MD, PHD,* Cristina Chimenti, MD, PHD,†‡ Nicola Galea, MD,* Fernanda Scopelliti, PHD,§ Romina Verardo, PHD,§ Roberto Galea, MD,‖ Iacopo Carbone, MD,* Carlo Catalano, MD,* Francesco Fedele, MD,† Andrea Frustaci, MD†§

Rome, Italy

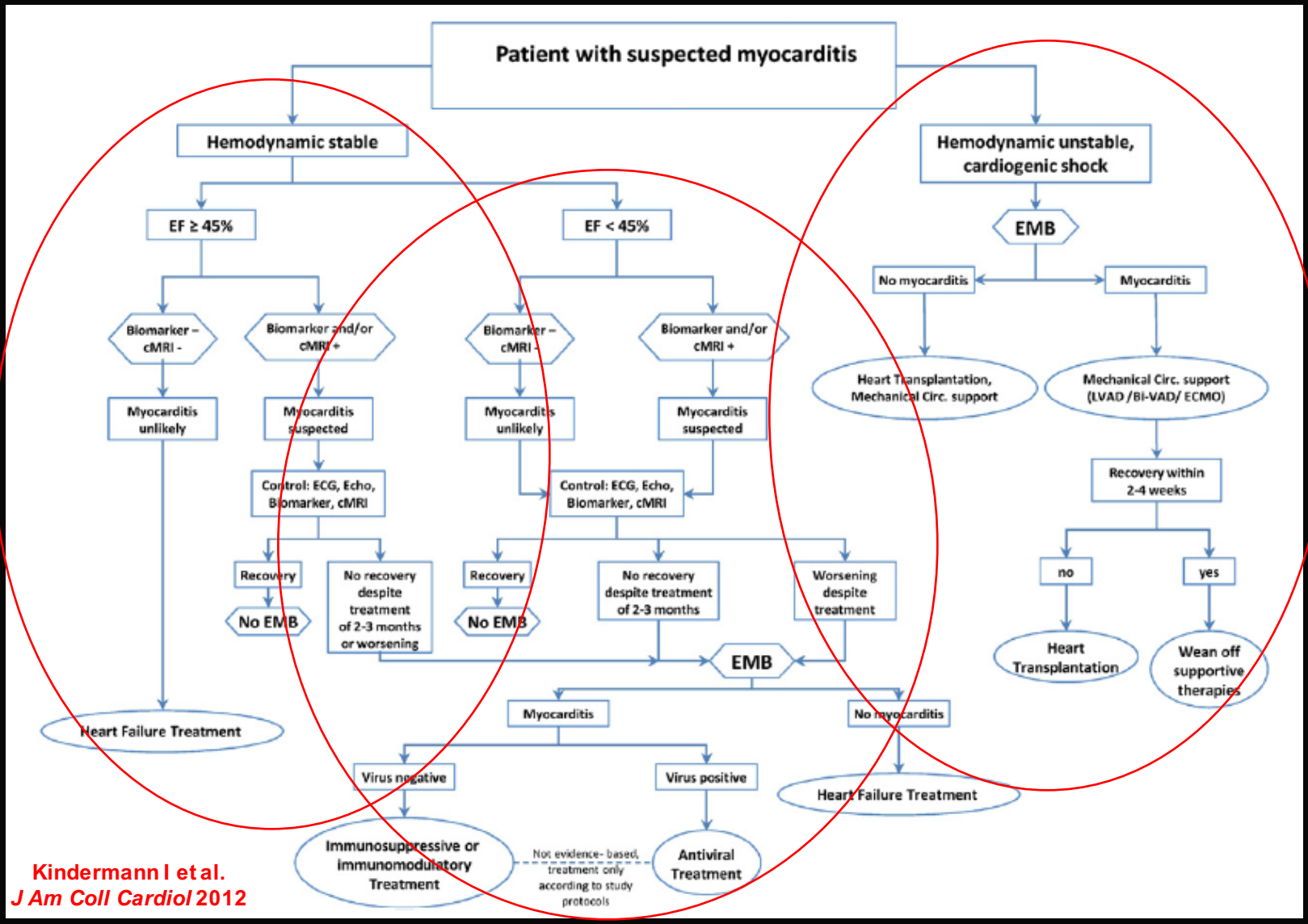
(J Am Coll Cardiol Img 2014;7:254–63)

N = 57 pts with lymphocytic acute myocarditis by EMB

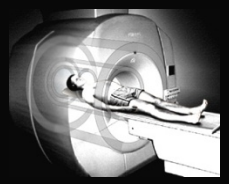




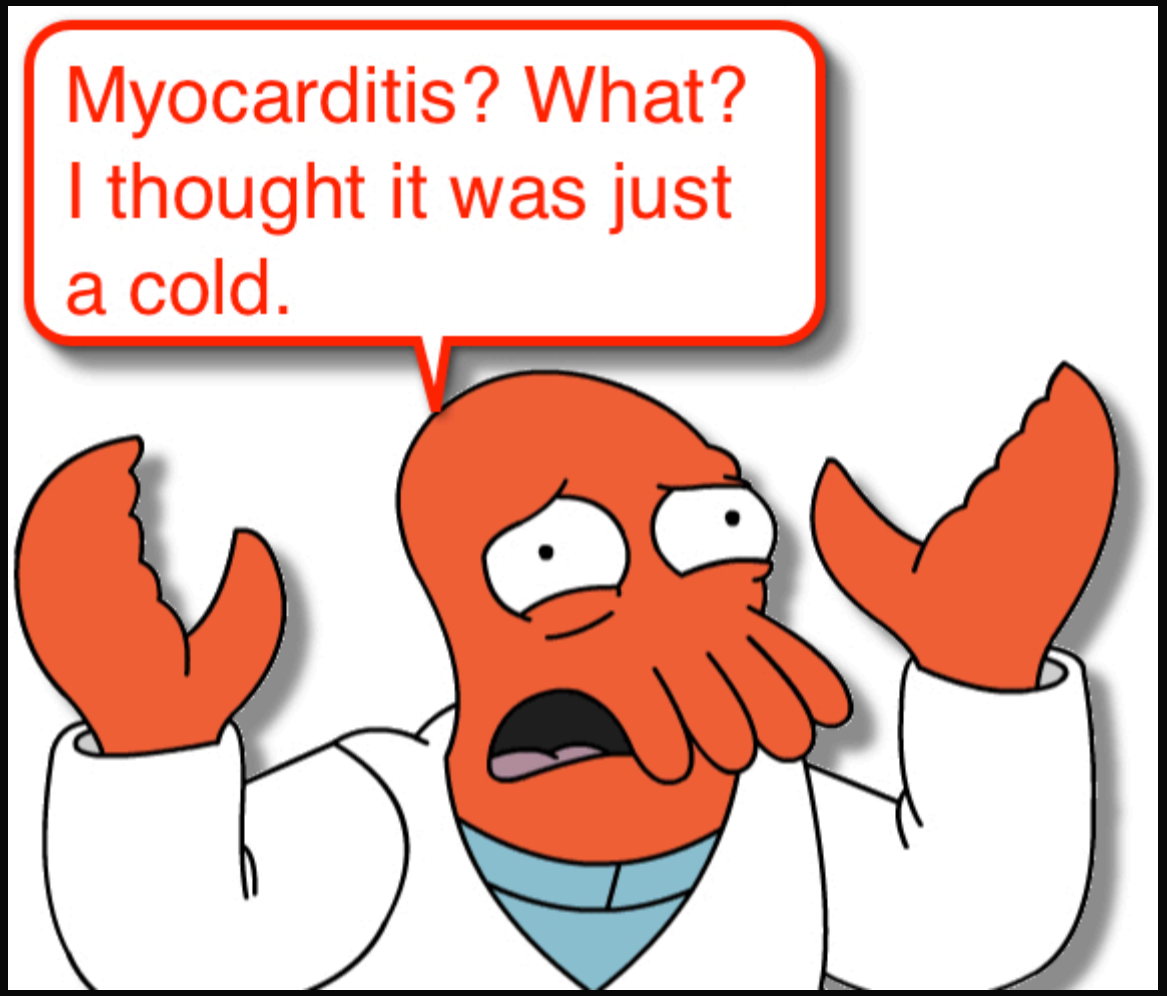
Proposed Diagnostic and Therapeutic Algorithm for Suspected Myocarditis

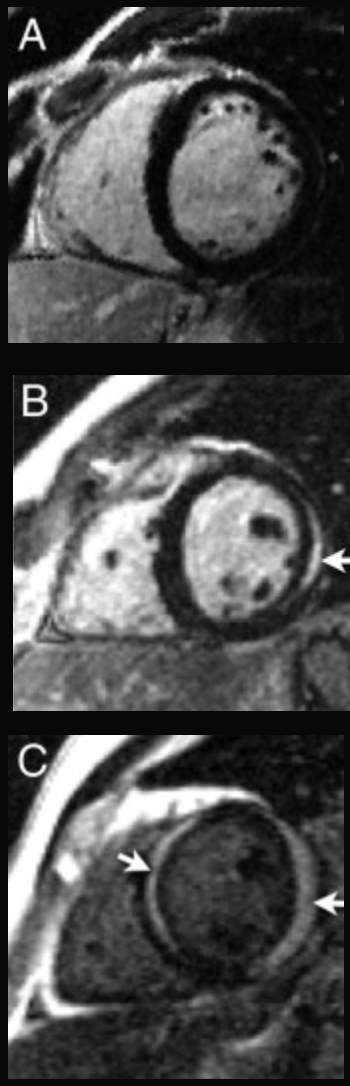


Kindermann I et al.
J Am Coll Cardiol 2012



Prognostic Significance of LGE Areas in Patients with Suspected Myocarditis

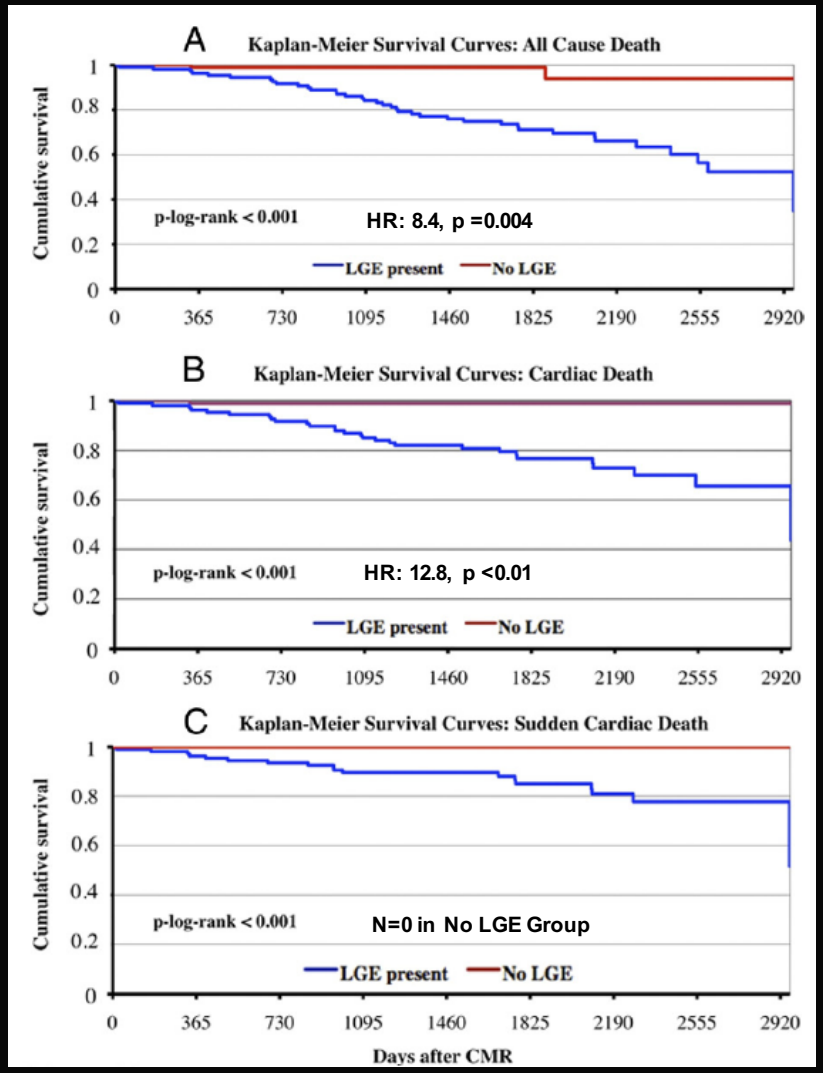




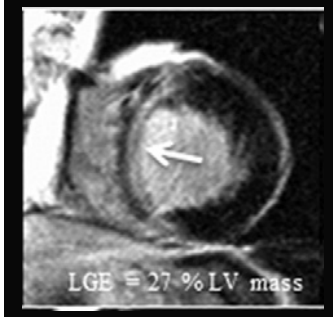
Long-Term Follow-Up of Biopsy-Proven Viral Myocarditis Predictors of Mortality and Incomplete Recovery

Grün S. et al. *J Am Coll Cardiol* 2012

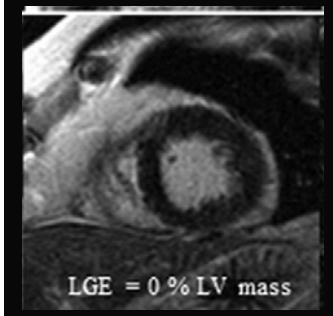
All patients with follow-up	203 (91.5)
Time to follow-up, days (4.7 years)	1,685 (1,267–2,102)
Female	63 (31.0)
Age, yrs	52 (40–54)
BMI, kg/m^2	26.3 (24.0–29.1)
BSA, m^2	2.0 (1.8–2.1)
Primary clinical presentation	
Symptoms of ACS	74 (36.5)
Subacute new-onset HF	62 (30.5)
Reoccurring episodes of overt HF	18 (8.9)
Combination of palpitations, fatigue, dyspnea on exertion	49 (24.1)
Aborted SCD	0
Initial NYHA functional class	
I	48 (23.6)
II	64 (31.5)
III	71 (35.0)
IV	20 (9.9)
Virus type by endomyocardial biopsy	
PVB19	113 (55.7)
HHV6	49 (24.1)
PVB19/HHV6	35 (17.2)
EBV	2 (1.0)
PVB19/HHV6/EBV	1 (0.5)
PVB19/EBV	2 (1.0)
HHV6/EBV	1 (0.5)
Blood testing	
Troponin positive	46 (22.7)
BNP, pg/ml	190 (39–652)
NT-proBNP, pg/ml	1,938 (220–8822)
CMR imaging parameter	
LVEF, %	45 (31–60)
EF indexed, %/m^2	23.7 (15.9–31.2)
LVEDV, ml	167 (129–210)
LVESV, ml	90 (47–144)
LGE present	108 (53.2)
LGE mass, g	5.3 (3.2–18.6)
LGE, % of LV mass	4.2 (2.3–9.3)
Event	
All-cause death	39 (19.2)
Cardiac death	29 (15.0)
SCD	18 (9.9)



LGE Present



No LGE



Cardiovascular magnetic resonance risk stratification in patients with clinically suspected myocarditis

Julia Schumm[1†], Simon Greulich[1†], Anja Wagner[2], Stefan Grün[1], Peter Ong[1], Kerstin Bentz[1], Karin Klingel[3], Reinhard Kandolf[3], Oliver Bruder[4], Steffen Schneider[4], Udo Sechtem[1] and Heiko Mahrholdt[1*]

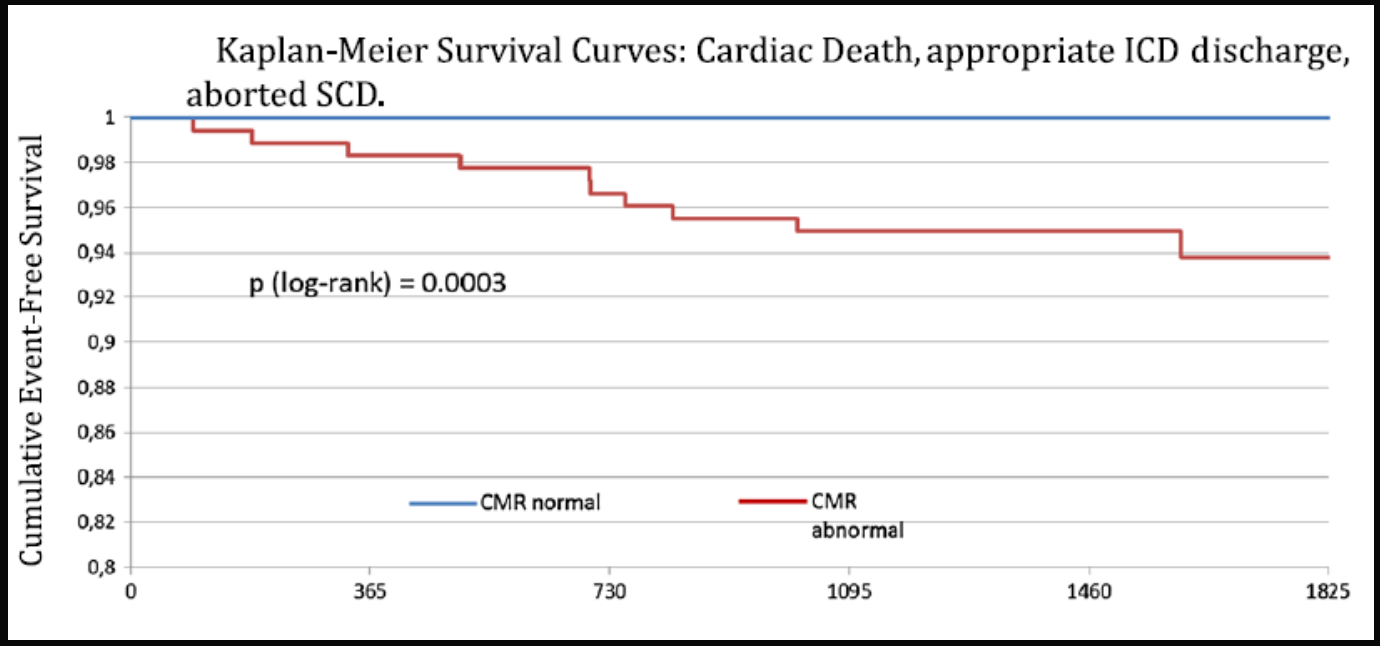
Journal of Cardiovascular Magnetic Resonance 2014, **16**:14

N = 405 pts undergoing CMR for clinically suspected myocarditis (2007-2008)

Symptoms = chest pain (53.6%); dyspnea (33.8%); palpitations (22.7%)

Median follow-up = 1591 days

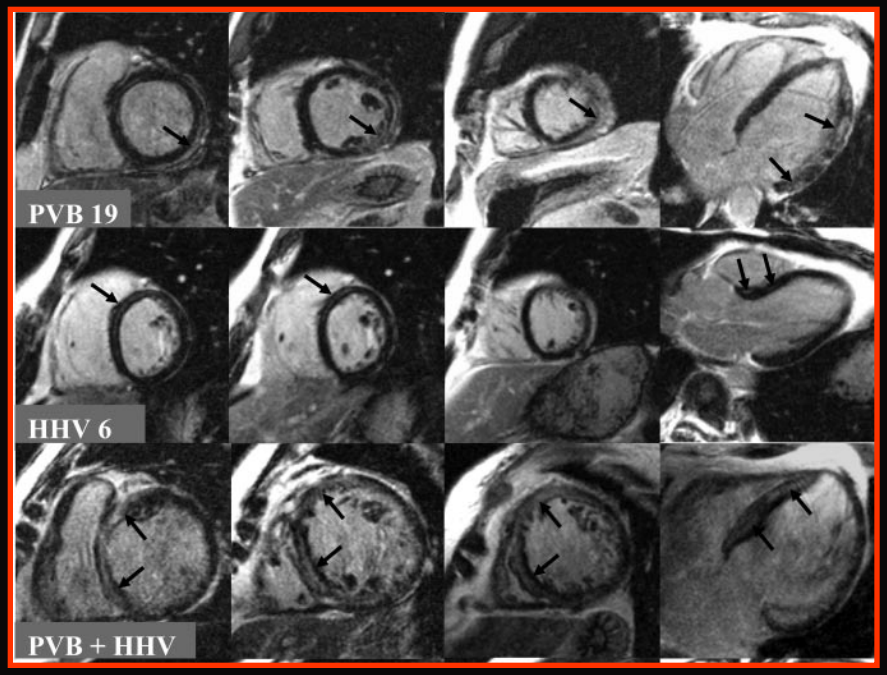
Normal CMR = normal LV volumes and EF, no LGE



Presentation, Patterns of Myocardial Damage, and Clinical Course of Viral Myocarditis

Mahrholdt H et al. *Circulation* 2006

N= 87 pts with clinically-defined myocarditis
CMR study first and then EMB



	Presentation	LGE Patterns	Clinical Course
Parvovirus B19 (PVB19)	ACS-like	Subepicardial lateral wall	Recovery
Human herpes virus 6 (HHV6)	Heart failure	Intramyocardial spetum	CHF
PVB19 + HHV6	Heart failure	Intramyocardial septum	CHF

ITAlian CMR on MYocarditis (ITAMY)

Studio retrospettivo multicentrico

9 Centri RM cardiaca

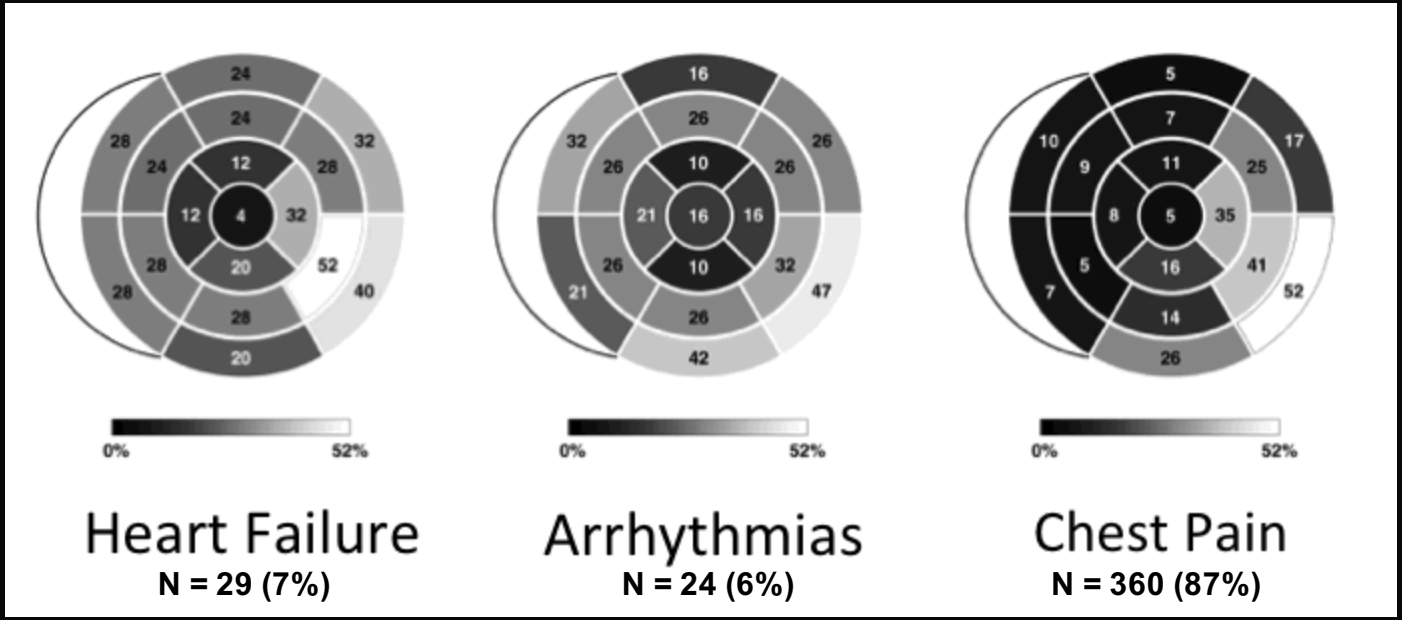
N = 413 pz consecutivi con sospetta miocardite acuta (confermata alla RM)

Eventi = 26 eventi

Di Bella G, Aquaro GD, Monti L, Camastra G, Dellegrottaglie S, Pepe A, Pontone G, Perrazolo M, Lanzillo C, C Moro. On behalf of the working group "Applicazioni della Risonanza Magnetica" of the Italian Society of Cardiology

ITAlian CMR on MYocarditis (ITAMY)

- Preliminary Results

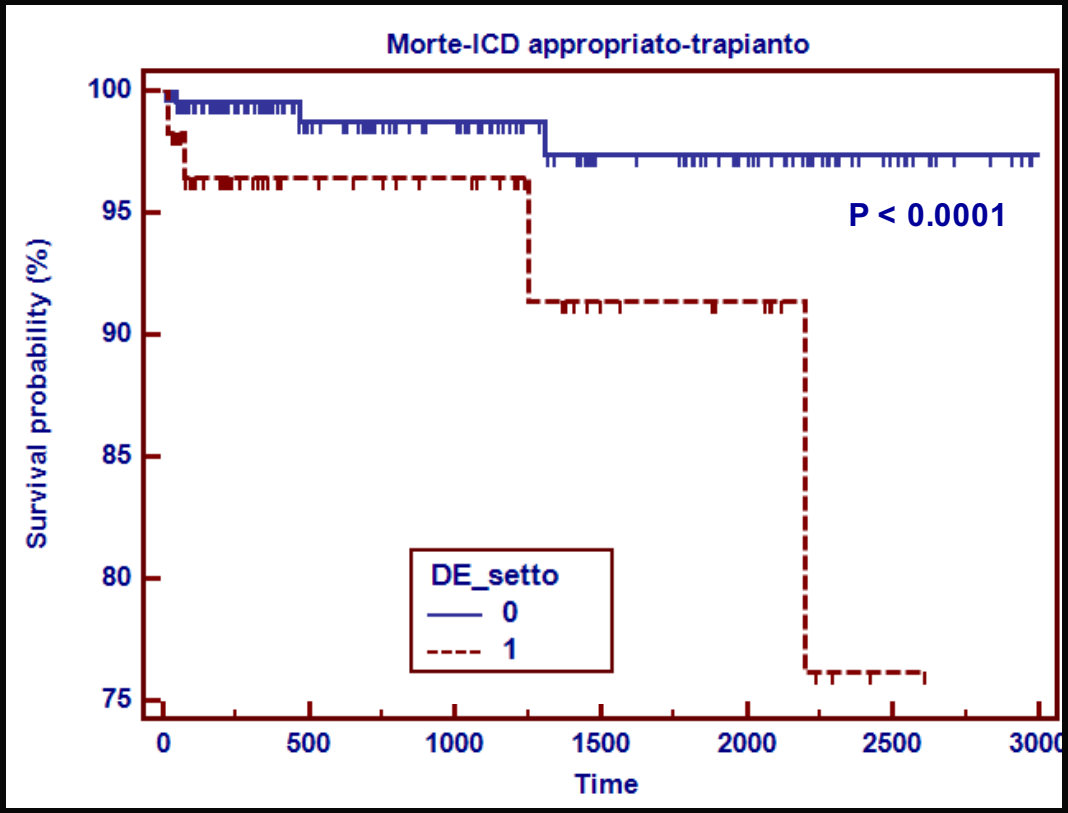


Di Bella G et al on behalf of the working group "Applicazioni della Risonanza Magnetica"
Of the Italian Society of Cardiology

ITAlian CMR on MYocarditis (ITAMY)

- Preliminary Results

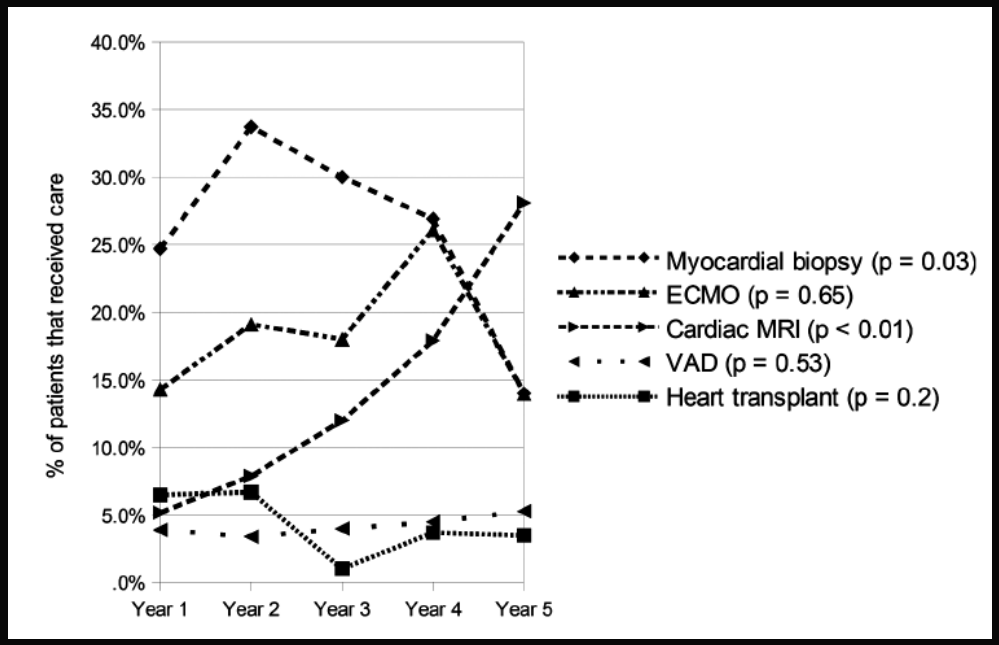
LGE Septum



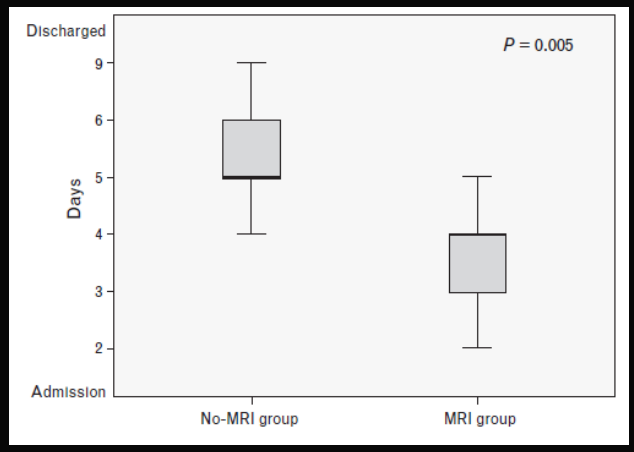
Di Bella G et al on behalf of the working group "Applicazioni della Risonanza Magnetica"
Of the Italian Society of Cardiology

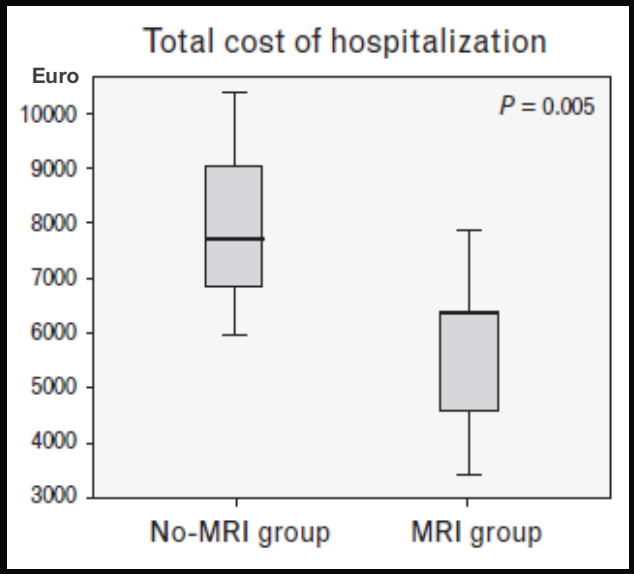
Clinical Use and Utility of CMR in Patients with Suspected Myocarditis

Demographics, Trends, and Outcomes in Pediatric Acute Myocarditis in the United States, 2006 to 2011



Ghelani SJ et al. *Circ Cardiovasc Qual Outcomes* 2012





Di Bella G et al. *J Cardiov Med* 2011

Radiologists and Cardiologists for Cardiac MRI: Fight or Collaboration?

Current Situation

Category[a]	Performed by Radiologists (%)	Performed by Cardiologists (%)	Performed by Surgeons (%)	Performed by Other Physicians (%)
Cardiac MR imaging (*n* = 1,017)	85.7	13.6	0.0	0.7
MR angiography (*n* = 154,764)	95.3	0.0	0.1	4.5
Cardiovascular nuclear medicine (*n* = 3,045,452)	37.8	53.8	0.1	8.2
Echocardiography (*n* = 12,207,754)	1.6	79.8	0.2	18.4
Vascular sonography (*n* = 3,835,014)	44.8	11.3	23.8	20.0

Levin DC et al. *Am J Roentgenol* 2002

Cardiac MRI: an Underused Modality

Radiologist's Faults

- Scarce propensity for collaboration with cardiologists (bad experiences with invasive angio and echo in the past)
- Limited interest in developing strong cardiac MRI services (low revenue)
- On average, inadequate knowledge of CV pathophysiology and capacity to put imaging findings in the right clinical context

Cardiologist's Faults

- Cardiac MRI is poorly represented in residency programs (inadequate knowledge of indications and how to use imaging information)
- Self-referral possibility favors other imaging modalities (echo, SPECT)
- No MRI scanners in cardiology departments

Bruder *et al. Journal of Cardiovascular Magnetic Resonance* 2013, **15**:9
http://www.jcmr-online.com/content/15/1/9

Journal of Cardiovascular Magnetic Resonance

RESEARCH Open Access

European cardiovascular magnetic resonance (EuroCMR) registry – multi national results from 57 centers in 15 countries

Oliver Bruder[1], Anja Wagner[2], Massimo Lombardi[3], Jürg Schwitter[4], Albert van Rossum[5], Günter Pilz[6], Detlev Nothnagel[7], Henning Steen[8], Steffen Petersen[9], Eike Nagel[10], Sanjay Prasad[11], Julia Schumm[12], Simon Greulich[12], Alessandro Cagnolo[3], Pierre Monney[4], Christina C Deluigi[1], Thorsten Dill[13], Herbert Frank[14], Georg Sabin[1], Steffen Schneider[15] and Heiko Mahrholdt[12*]

Reader		
Cardiologist	70.7%	19589/27703
Team of cardiologist and radiologist	26.7%	7398
Radiologist	2.6%	716
Primary indication for CMR		
Myocarditis/cardiomyopathies	32.2%	8950/27767
Suspected CAD/ischemia in known CAD	34.2%	9508
Myocardial viability	14.6%	4048
Valvular heart disease	5.4%	1495

All	100%
Completely new diagnosis not suspected before	8.7%
Therapeutic consequences	
Change in medication	25.0%
Invasive procedure	16.8%
Hospital discharge	10.2%
Hospital admission	1.4%
Impact on patient management (new diagnosis and/or therapeutic consequence)	61.8%

Conclusions

1- CMR imaging offers a unique combination of safety, feasibility and accuracy in detecting myocarditis

2- CMR-based diagnostic criteria for myocarditis have been recently defined

3- Data from large multicenter trials with standardized protocols comparing CMR studies to biopsy-derived criteria are lacking

4- The prognostic value of CMR criteria for myocarditis begins to be defined

5- Compared with EMB, information about the degree of inflammation, the presence of special forms of myocarditis [e.g., giant cell or eosinophilic myocarditis, which require specific therapies], or the presence and type of virus is not provided

6- Probably, CMR has already become the major diagnostic tool to rule out myocarditis

Laboratorio RM Cardiaca

Ospedale Medico-Chirugico Accreditato Villa dei Fiori

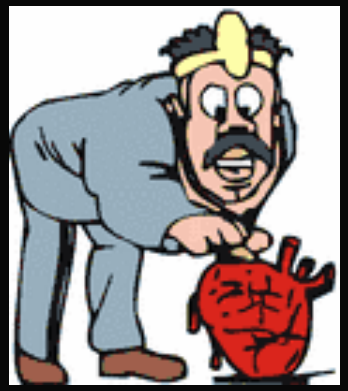
Acerra (Napoli)

Cardio-RM. Il paradosso di una metodica di riferimento per la disgnosi di una cardiopatia potenzialmente mortale ma sostanzialmente negata ai cardiologi

Santo Dellegrottaglie, MD – PhD

Laboratorio di RM Cardiovascolare
Divisione di Cardiologia
Ospedale Medico-Chirurgico Accreditato Villa dei Fiori
Acerra (Napoli)

Limited Scanner/Operator Availability for Cardiac MRI



Cardiologist

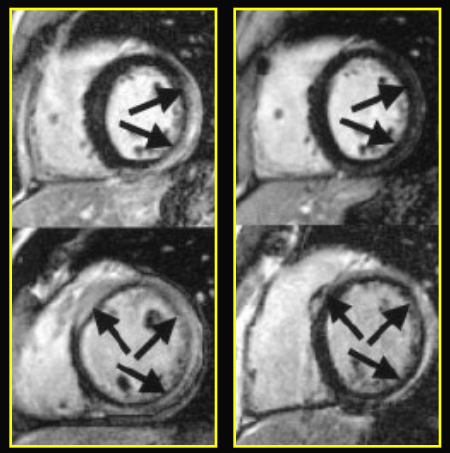
Radiology Oriented Imager

General Imaging Sessions

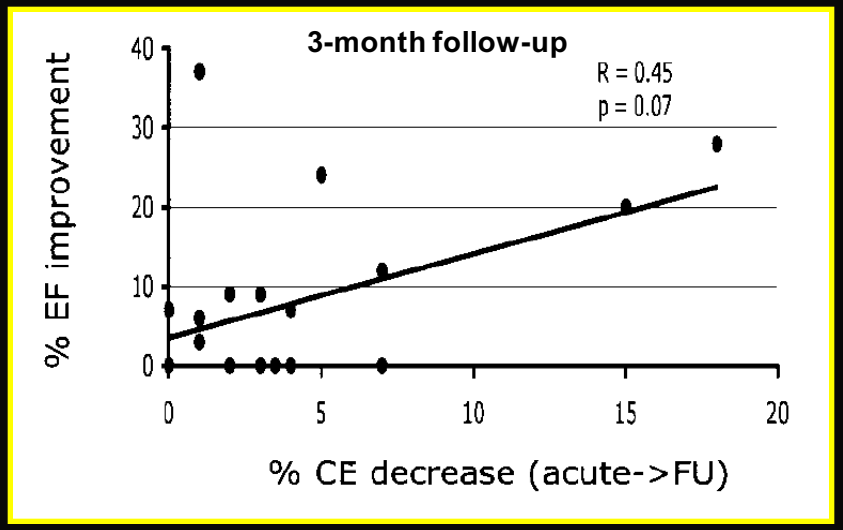
Cardiology Oriented Imager

Dedicated Imaging Sessions

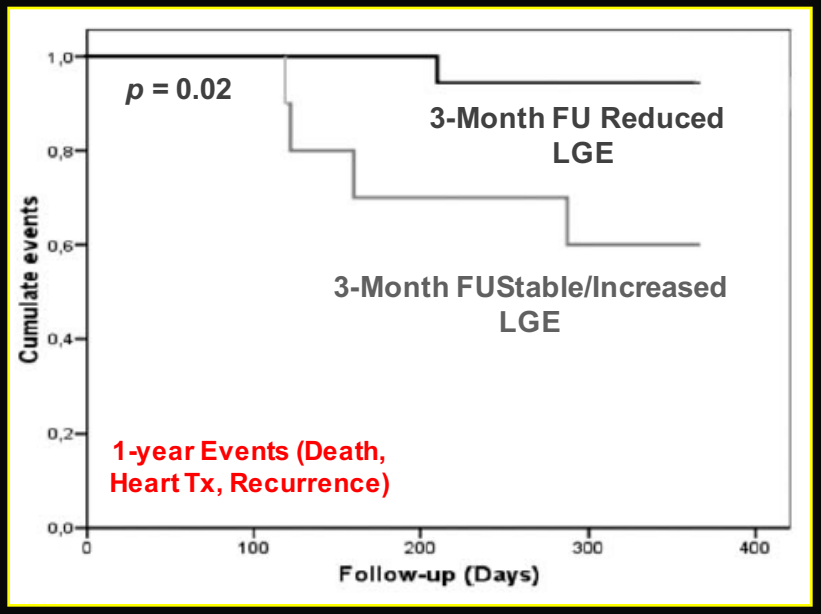
Relationship of Cardiac MR Findings to Clinical Outcome in Patients with Myocarditis



Late Gadolinium Enhancement



Mahrholdt H et al. *Circulation* 2004



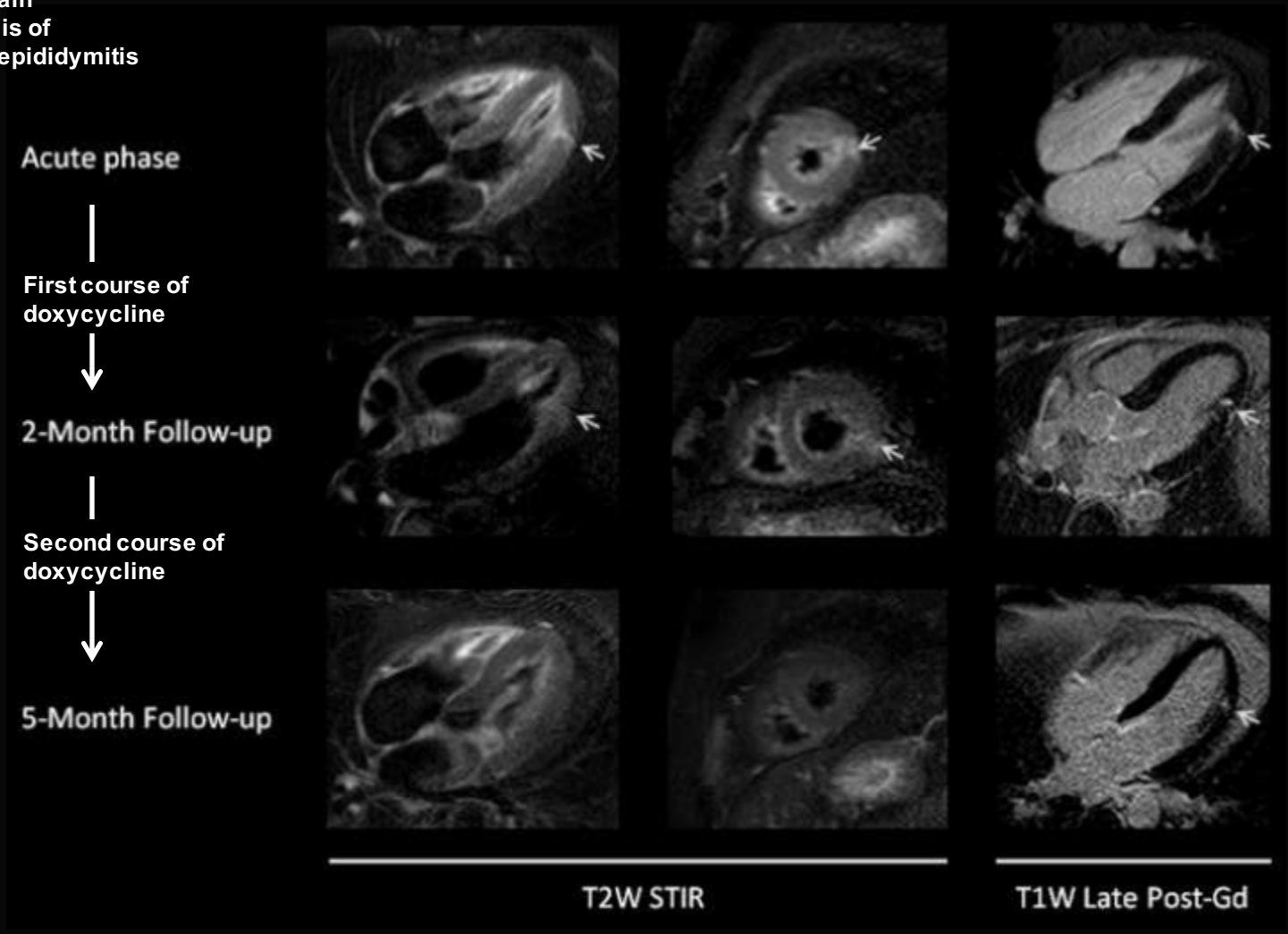
Barone-Rochette G et al. *J Magn Res Imag* 2013

A case of acute myocarditis associated with *Chlamydia trachomatis* infection: role of cardiac MRI in the clinical management

S. Dellegrottaglie · G. Russo · M. Damiano · P. Pagliano · L. Ferrara · C. De Simone · P. Guarini

Infection 2014;42:937-940

32 year-old male
Intense chest pain
Recent diagnosis of
C. trachomatis epididymitis
TnI = 2.28 ng/dl



Histopathological, Immunohistological and Molecular Biological Findings in Hearts of Patients With Myocarditis

Kindermann I et al. *J Am Coll Cardiol* 2012

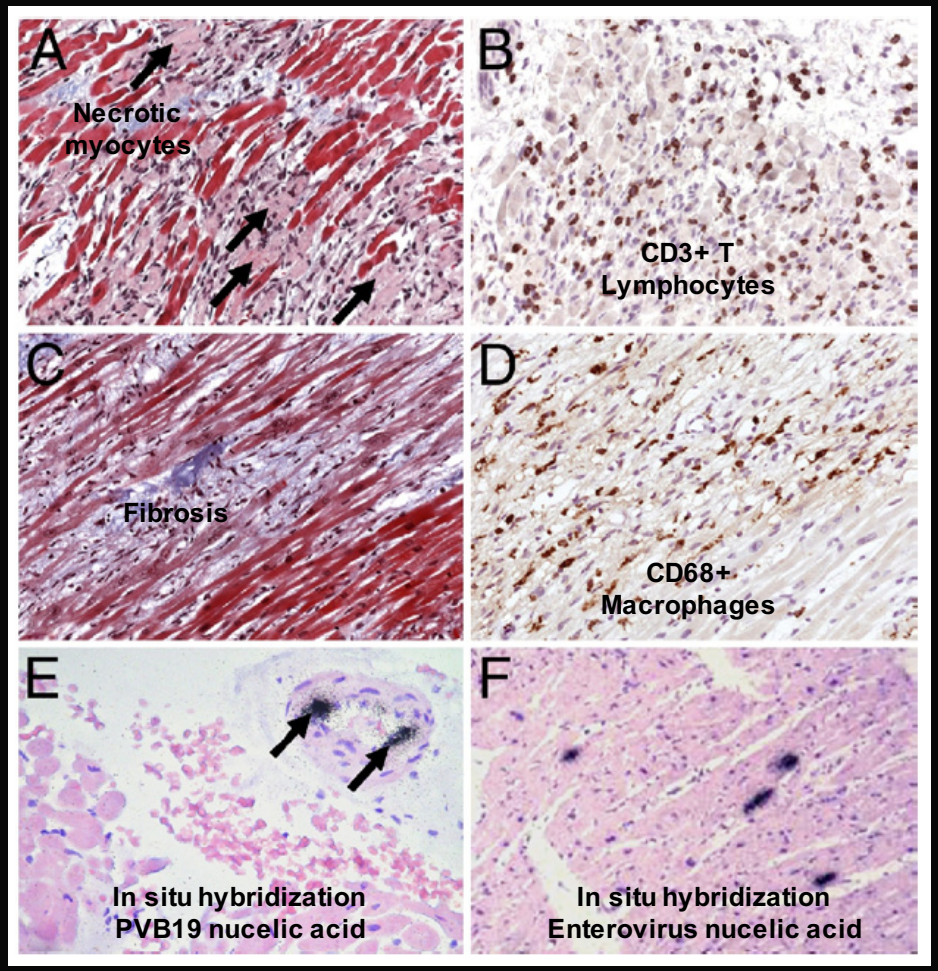
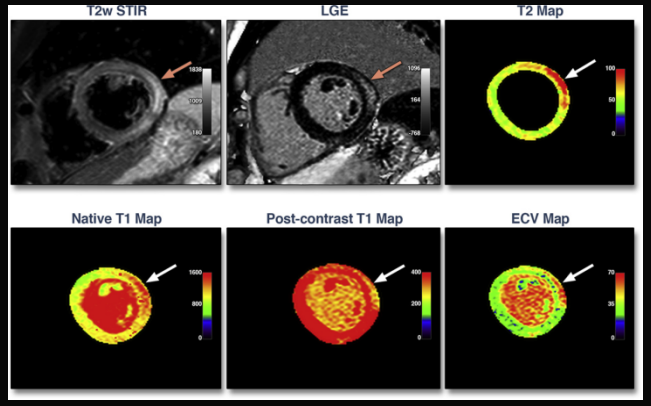


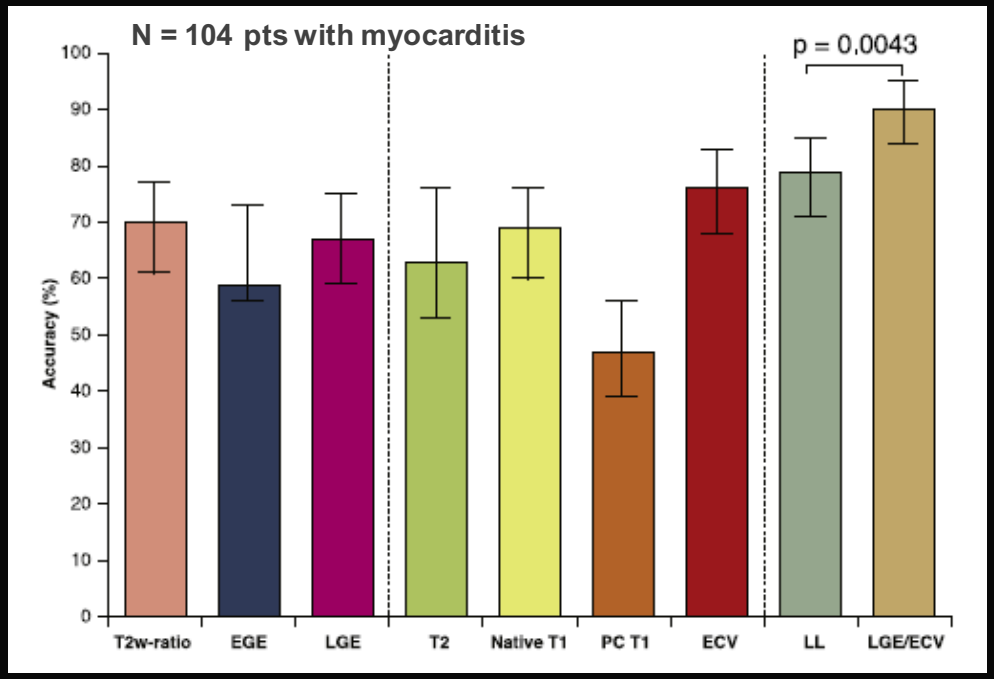
Table 2. HR for the Primary End Point: Time to Cardiac Death or Heart Transplantation (N=181 pts with suspected myocarditis)

	Univariate Analysis		Multivariate Analysis	
Variable	HR (95% CI)	*P*	HR (95% CI)	*P*
Age, y	1.00 (0.98–1.03)	0.693		
Male sex	0.91 (0.48–1.75)	0.782		
NYHA functional class III/IV	3.43 (1.73–6.77)	<0.001	3.20 (1.36–7.57)	0.008
LV end-diastolic dimension index, mm/m	1.05 (1.01–1.10)	0.027	1.05 (0.97–1.15)	0.207
LV ejection fraction, %	0.98 (0.96–1.00)	0.026	1.01 (0.97–1.04)	0.651
LV end-diastolic pressure, mm Hg	1.05 (1.00–1.09)	0.030	1.00 (0.95–1.05)	0.983
Positive immunohistology	4.54 (2.01–10.28)	<0.001	3.46 (1.39–8.62)	0.008
Dallas-positive histopathology*	1.51 (0.81–2.80)	0.195		
Evidence of viral genome	0.96 (0.51–1.80)	0.893		
β-Blocker medication	0.50 (0.26–0.95)	0.034	0.43 (0.21–0.91)	0.027

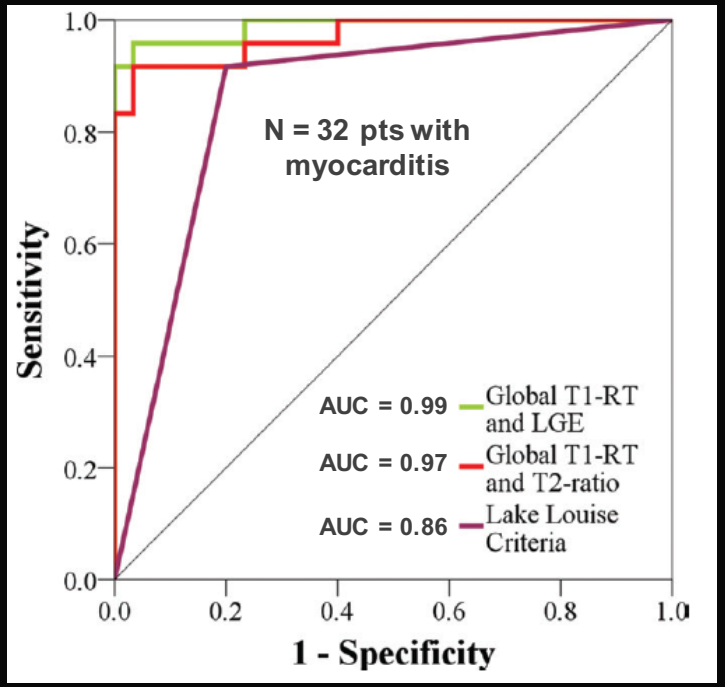
Kindermann I et al. *Circulation* 2008

T1 Mapping in Patients with Suspected Myocarditis

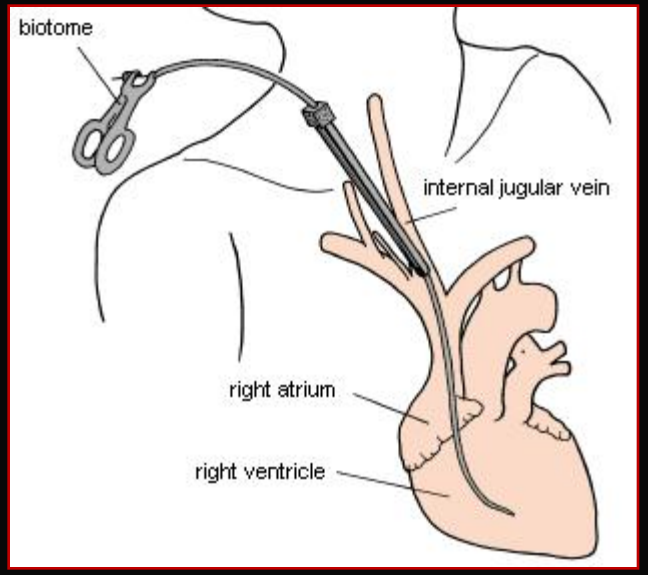




Radunski UK et al. *J Am Coll Cardiol Img* 2014



Luetkens JA et al. *Radiology* 2014



In a group of 755 pts. the major complication rate for LV-EMB was 0.64% and for RV-EMB 0.82%.

Diagnostic EMB results were achieved significantly more often in those patients who underwent biventricular EMBs (79.3%) compared to those who underwent either selective LV-EMB or selective RV-EMB (67.3%; *P<0.001).*

Yilmaz A et al. *Circulation* 2010

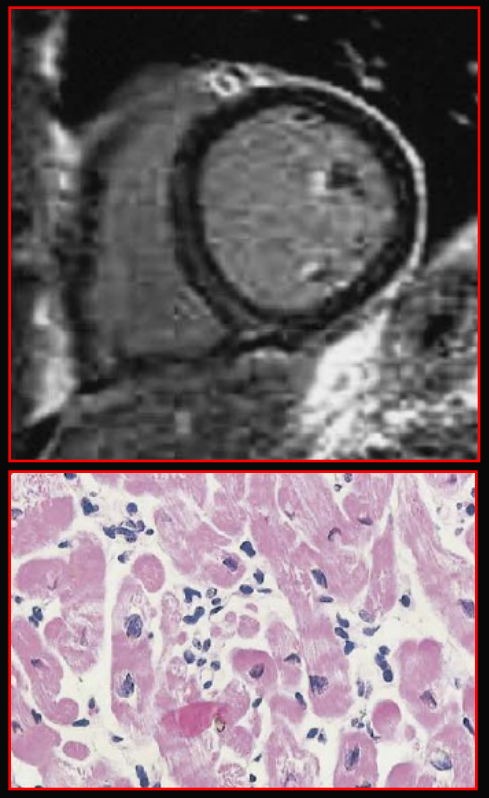
DE-CMR in Patients With Chronic Myocarditis Presenting With Heart Failure or Recurrent Arrhythmias

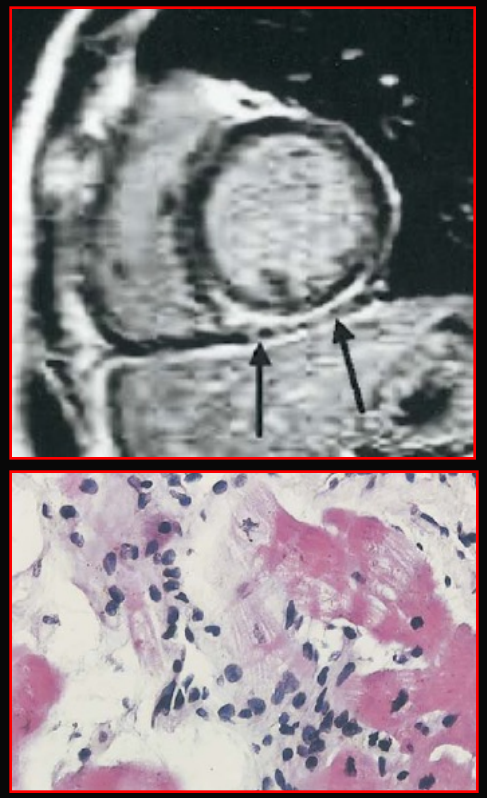
De Cobelli F, Pieroni M, Esposito A et al. *J Am Coll Cardiol* 2006

N= 23 pts with chronic myocarditis defined as
>6 months CHF and/or repetitive ventricular arrhythmias
+ non history of recent infection
+ acute/borderline myocarditis by biventricular EMB

LE + = 70% of pts

Mid-wall LE (62.5%)





Sub-epicardial LE (37.5%)

A.G.

Maschio; 46 anni

Diagnosi cardiomiopatia dilatativa (2009)

FE VSx = 23%

Coronarie esenti da stenosi (2009)

UNIVERSITA' LA SAPIENZA
FACOLTA' DI MEDICINA E CHIRURGIA
POLICLINICO UMBERTO I
DIPARTIMENTO DI SCIENZE CARDIOVASCOLARI E RESPIRATORIE

SIG. [redacted] **D.NASC.** [redacted]

DATA ESAME 03/07/2010 **N° SEQ.** 38-10

SEDE ESPLORATA: VSx [✓] VDx [ ]

DESCRIZIONE ISTOLOGICA:

Si osservano tre frammenti di buone dimensioni consistenti in fibre miocardiche normo-orientate ipertrofiche e con evidenza di attenuazione.
L'interstizio è aumentato per fibrosi intercellulare, perivascolare, focali aree di sostituzione fibrosa e frequenti infiltrati infiammatori linfomonucleari focalmente associati a necrosi dei cardiociti adiacenti. Nei frammenti in esame sono contenute tre normali arteriole.
L'endocardio è moderatamente ispessito con prominenza di fibrocellule muscolari lisce.

CONCLUSIONI:
Miocardite con fibrosi e focale evidenza di attivita' in ipertrofia dilatazione ventricolare sinistra.
In considerazione della negativita' della PCR per virus cardiotropi(vedi referto allegato) puo' essere indicata la terapia immunosoppressiva (in aggiunta alla terapia di supporto) nel caso di una progressiva e rilevante compromissione della funzione ventricolare sinistra.

DR. CRISTINA CHIMENTI

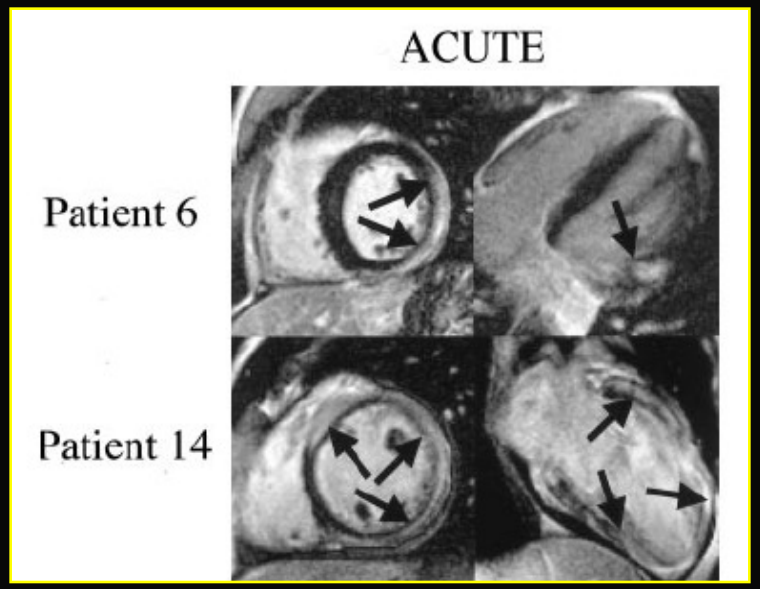
PROF. A. FRUSTACI

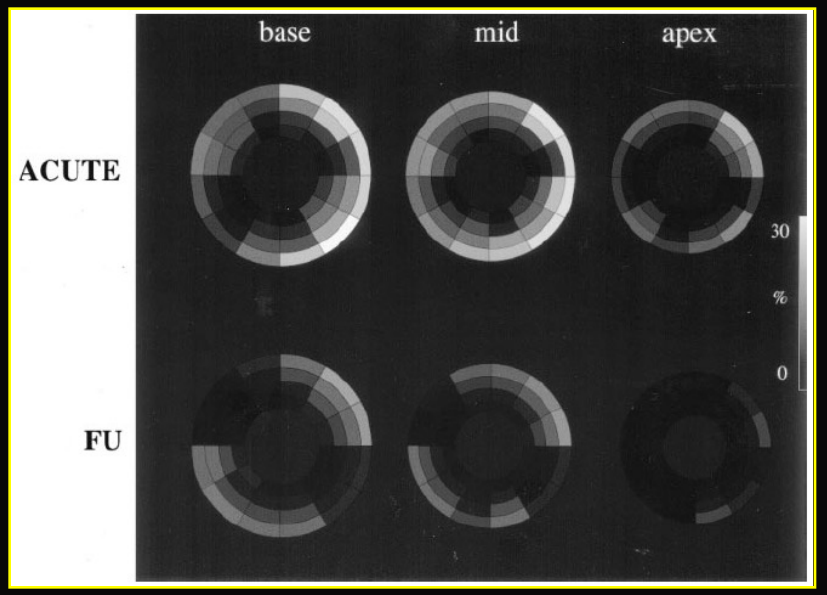
CMR Assessment of Human Myocarditis
A Comparison to Histology and Molecular Pathology

Mahrholdt H et al. *Circulation* 2004

N= 32 pts with clinically-defined myocarditis
CMR study first and then EMB

Areas of LE in 88% of patients!!!





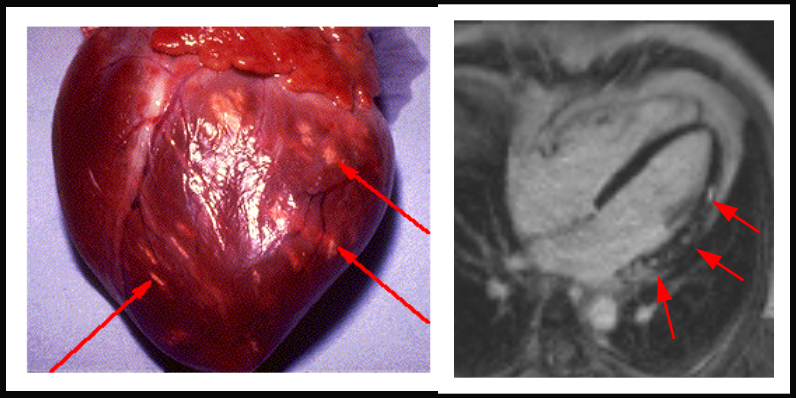
19/21 (90%) Positive EMB in LE (+) sites

1/11 (9%) Positive EMB in LE (–) sites

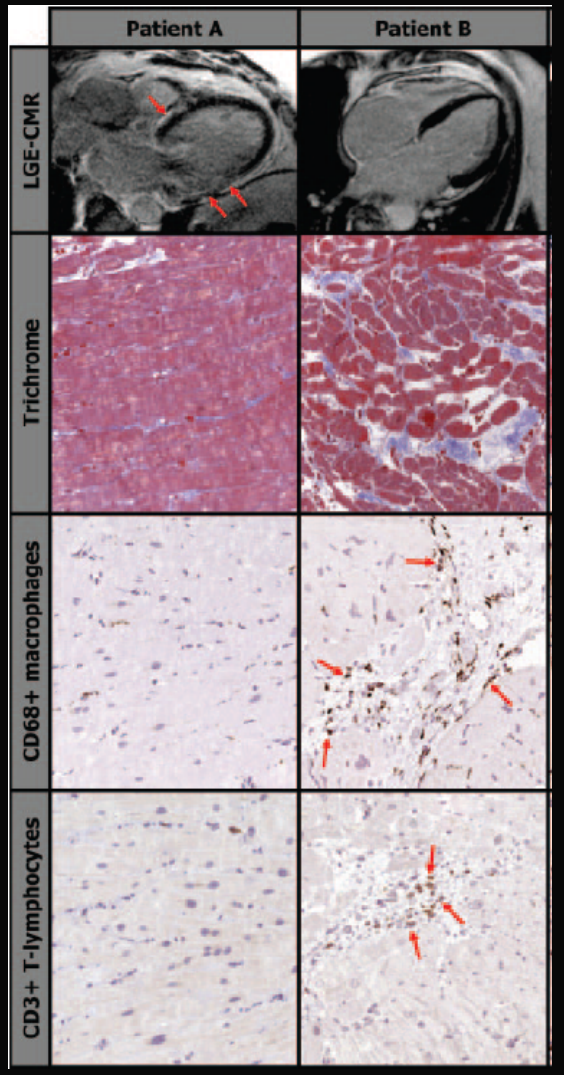
Comparative Evaluation of LV and RV Endomyocardial Biopsy: Differences in Complication Rate and Diagnostic Performance

Yilmaz A et al. *Circulation* 2010

N= 292 pts with biventricular EMB for suspected myocarditis
LE-CMR only

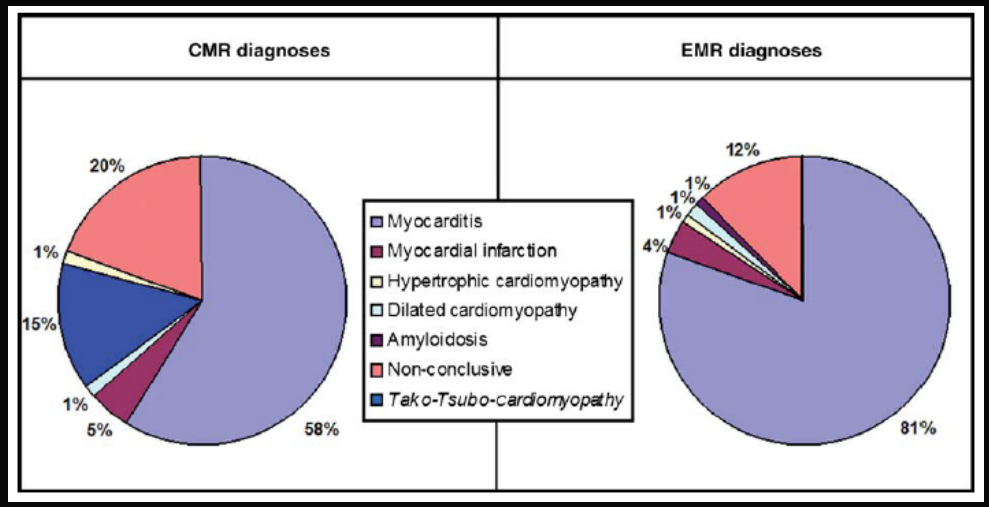


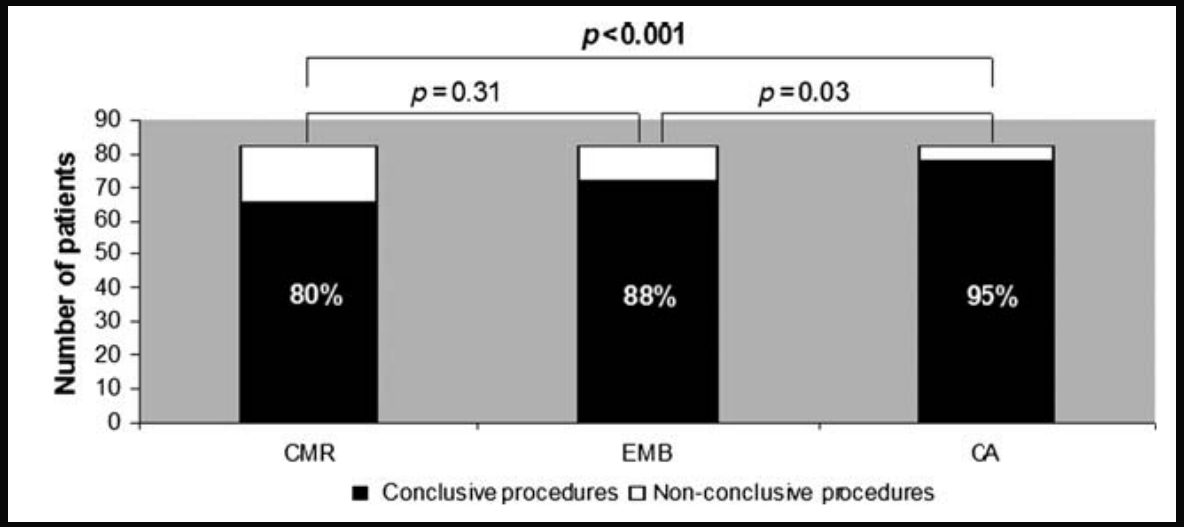
There were no differences in the number of positive EMB findings when related to the site of CMR– based LE



Diagnostic Synergy of Cardiac MR and EMB in Troponin-positive Patients Without CAD

- N= 82 pts. with TnI-positive acute chest pain
- No significant coronary disease
- CMR with LE imaging only
- RV and/or LV EMB guided by CMR with dectection of viral genomes



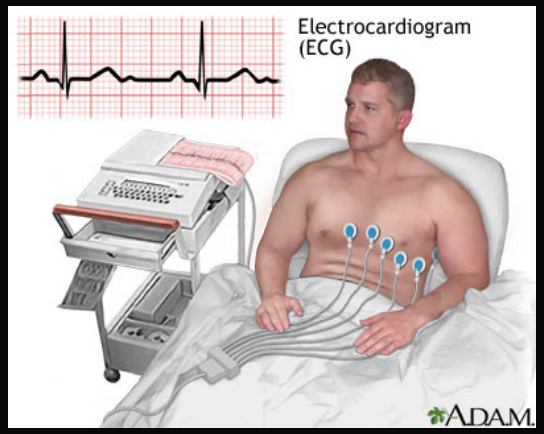


Baccouche H, et al. *Eur Heart J* 2009

Indications for CMR in Patients With Suspected Myocarditis

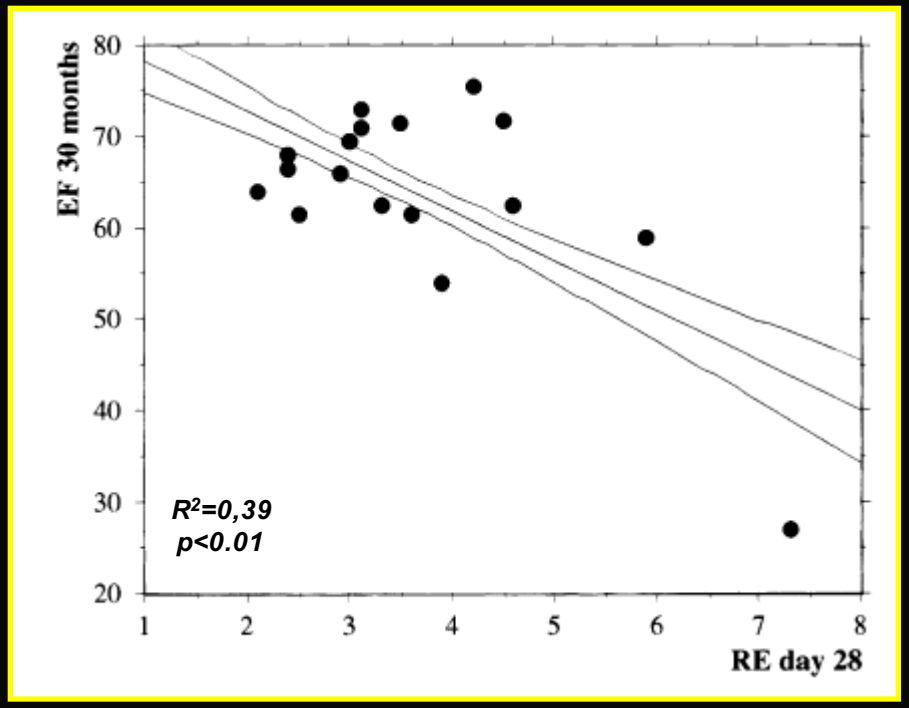
Friedrich M.G. et al. for the International Consensus Group on CMR in Myocarditis, *J Am Coll Cardiol* 2009

New Onset or Persisting Symptoms Suggestive of Myocarditis	Plus	Evidence for Recent/Ongoing Myocardial Injury	Plus	Suspected Viral Etiology
Dyspnea *or* orthopnea *or* palpitations *or* effort intolerance/malaise *or* chest pain		Ventricular dysfunction *or* new or persisting ECG abnormalities *or* elevated troponin		History of recent systemic viral disease or previous myocarditis *or* absence of risk factors for coronary artery disease or age <35 yrs *or* symptoms not explained by coronary stenosis on coronary angiogram *or* recent negative ischemic stress test



Relationship of Cardiac MR Findings to Long-Term Outcome in Patients with Myocarditis

Early Post-Gd Enhancement



R=-0,30
p<0.001

Wagner A et al. *MAGMA* 2003

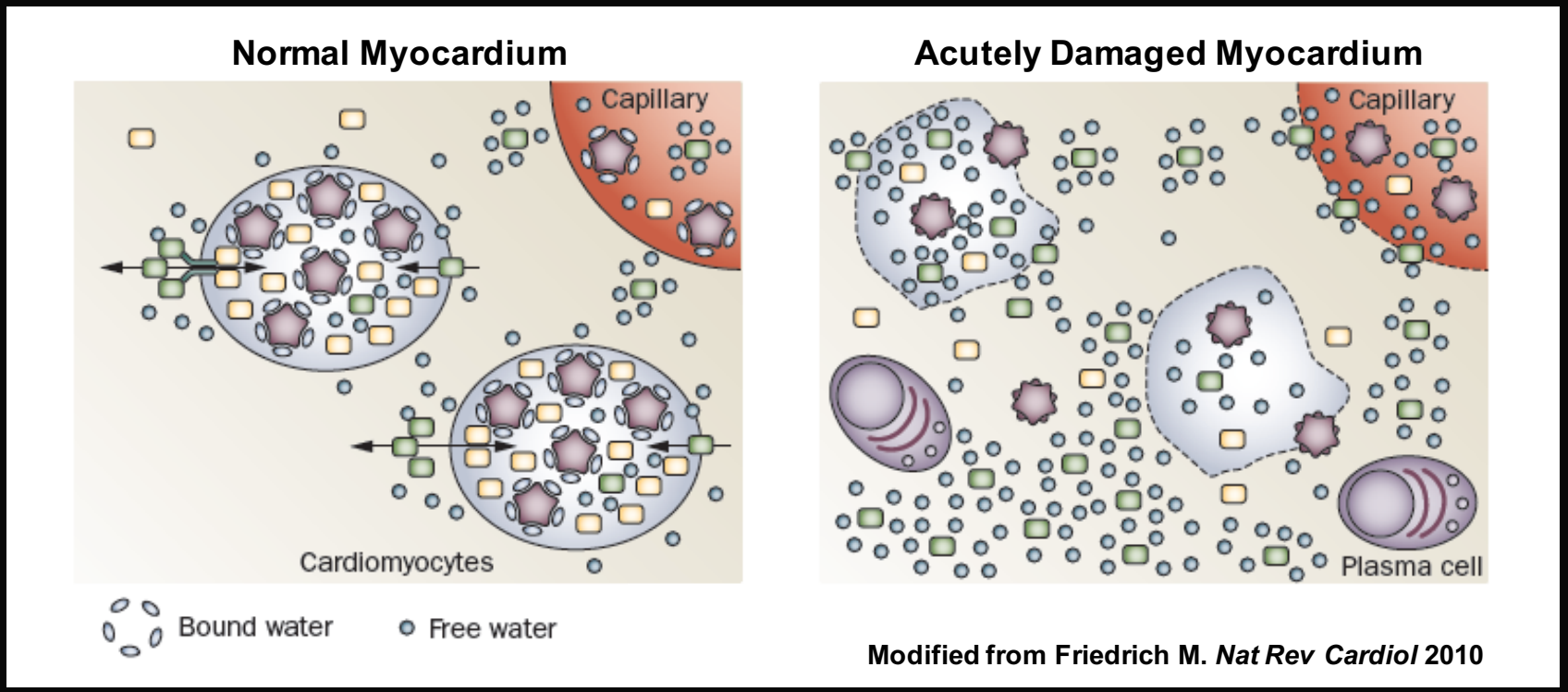
The Prognostic Implications of Cardiovascular Magnetic Resonance

Flett AS et al. *Circ Cardiovasc Imaging* 2009

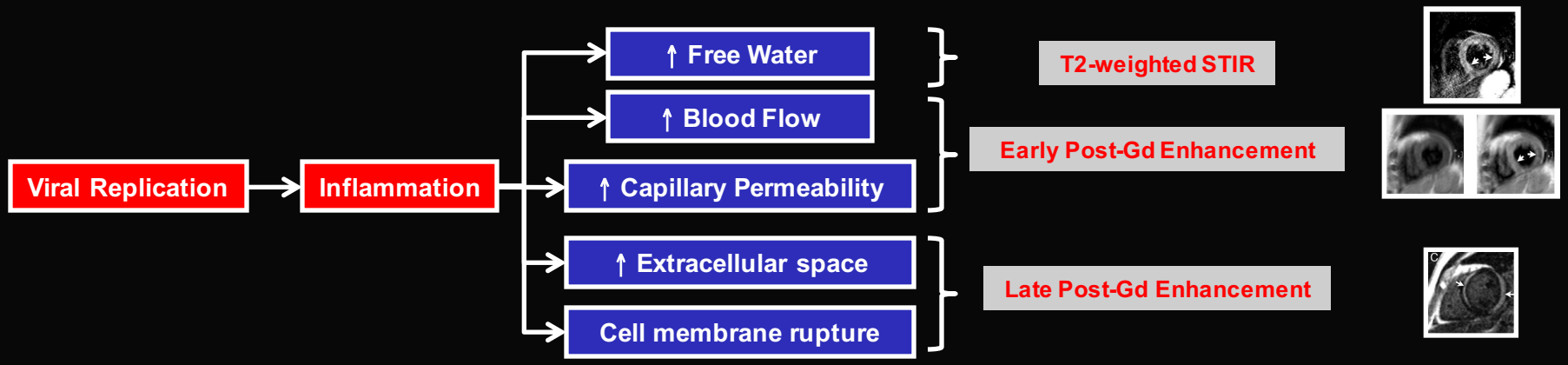
Table. Prognostic Evidence Base of CMR

Disease	Technique	Studies	End Point, n, (Patient-Years)	Reference
ACS chest pain	Adenosine stress	1	MACE, 131, (168)	Ingkanisorn et al, 2006[7]
Infarction	Infarct size	1	MACE/mortality, 122, (244)	Wu et al, 2007[10]
	MVO	4	MACE, 405, (378)	Wu et al, 1998[13], Hombach et al, 2005[14], Cochet et al, 2008[15]*, Bruder et al, 2008[16]
	Peri-infarct zone	1	Mortality, 144, (346)	Yan et al, 2006[20]
	Silent MI	3	MACE/mortality, 682, (1210)	Kwong et al, 2006[28], Kwong et al, 2008[29], Valle et al, 2008[48]*
Chronic IHD	Extent of LGE	2	MACE/mortality, 1486, (3801)	Cao et al, 2008[25], Chan et al, 2008[24]
Postsurgical	New LGE	1	MACE/mortality, 152, (441)	Rahimi et al, 2008[31]*
Normal LV	Dobutamine stress	2	MACE/mortality, 578, (1063)	Hundley et al, 2002[37], Kuijpers et al, 2004[39]
	Mixed stress	1	MI/mortality, 513, (1180)	Jahnke et al, 2007[41]
	Adenosine stress	2	Mortality, 1220, (2823)	Bingham and Hachamovitch, 2008[44], Pilz et al, 2008[42]
	Dipyridamole stress	1	MACE/mortality, 420, (483)	Bodi et al, 2007[43]
Impaired LV	Dobutamine stress	1	MI/mortality, 200, (1000)	Dall'Armellina et al, 2008[40]
	LGE	2	MACE, mortality, 435, (1050)	Yokota et al, 2008[32], Kwon et al, 2009[33]
	LGE pre-CRT	1	Heart failure, nonresponse, mortality, 62, (126)	Chalil et al, 2007[34]
	CMR TSI pre-CRT	1	MACE/mortality, 77, (161)	Chalil et al, 2007[35]
DCM	LGE	2	MACE/mortality, 166, (274)	Assomull et al, 2006[46], Wu et al, 2008[47]
HCM	LGE	1	Mortality, 424, (1201)	Rubinshtein et al, 2008[56]
	Apical aneurysms	1	MACE, mortality, 1299, (5326)	Maron et al, 2008[50]†
Amyloid	Gd kinetics	1	Mortality, 29, (49)	Maceira et al, 2008[62]
PAH	Volumes	1	Mortality, 64, (64)	Van Wolferen et al, 2007[63]
Congenital	RV morphology	1	MACE, 88, (370)	Knauth et al, 2008[69]
Stroke	Carotid plaque	1	Stroke, 154, (490)	Takaya et al, 2006[71]

Imaging Myocardial Damage with Cardiac MRI



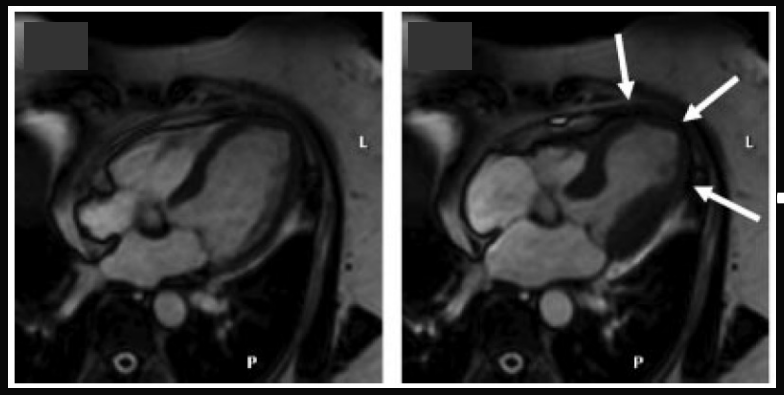
Modified from Friedrich M. *Nat Rev Cardiol* 2010



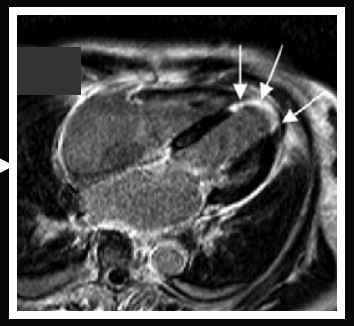
Differential Diagnosis of Suspected Apical Ballooning Syndrome Using Contrast-Enhanced MRI

Eitel I. et al. *Eur Heart J* 2008

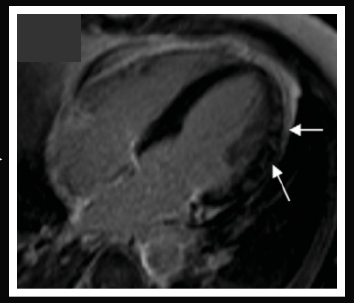
N= 59 ACS pts with normal coronary vessels and apical ballooning by cath
(suspected Tako-Tsubo based on Mayo Clinic Criteria)



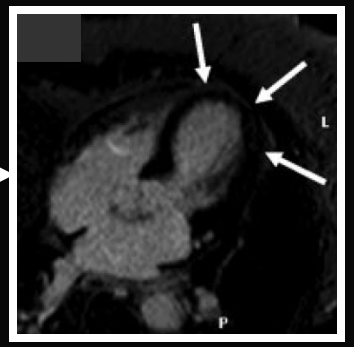
End-diastole End-systole



MI (13, 22%)



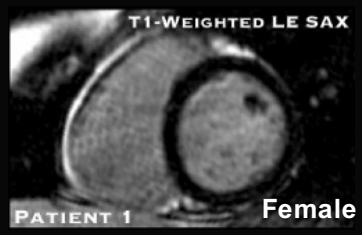
Myocarditis (8, 14%)

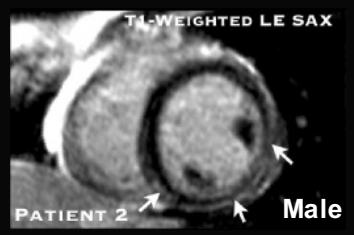


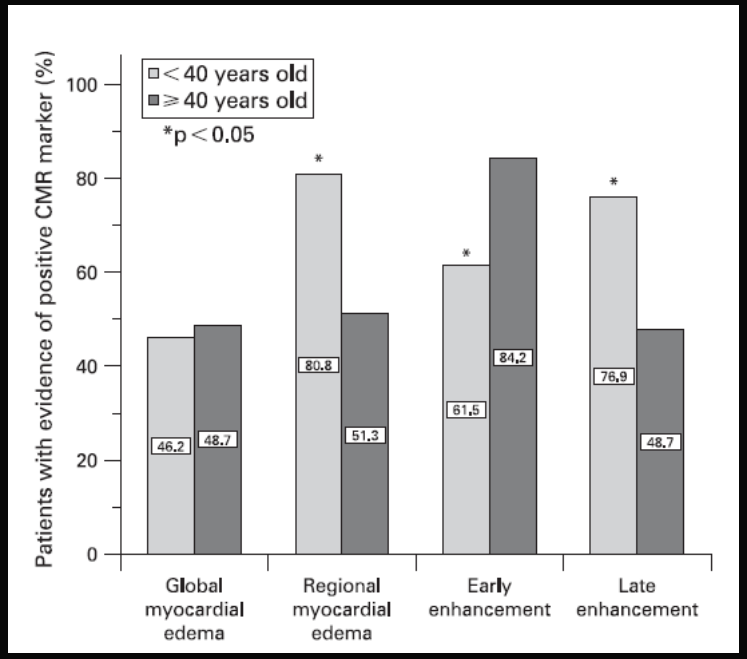
Takotsubo (38, 64%)

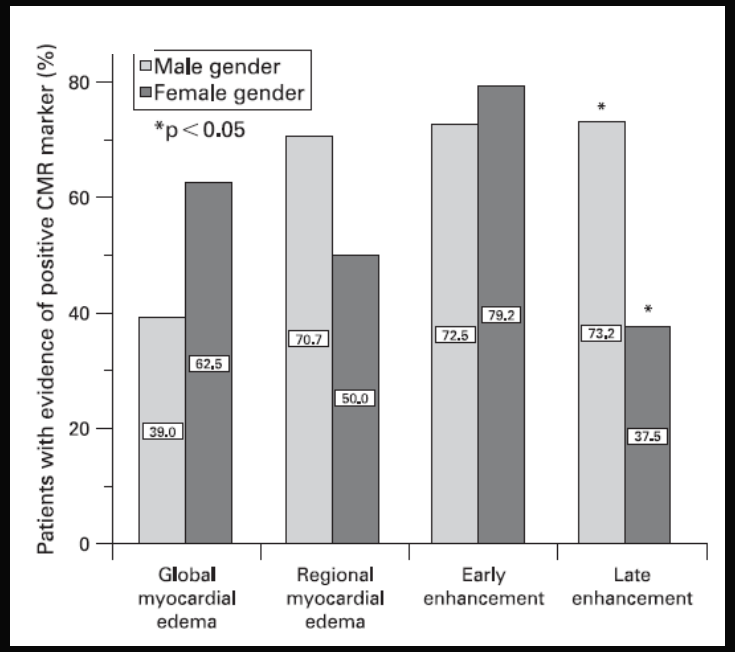
Age and Gender Effects on the Extent of Myocardial Involvement in Acute Myocarditis

N= 65 pts with clinically acute myocarditis





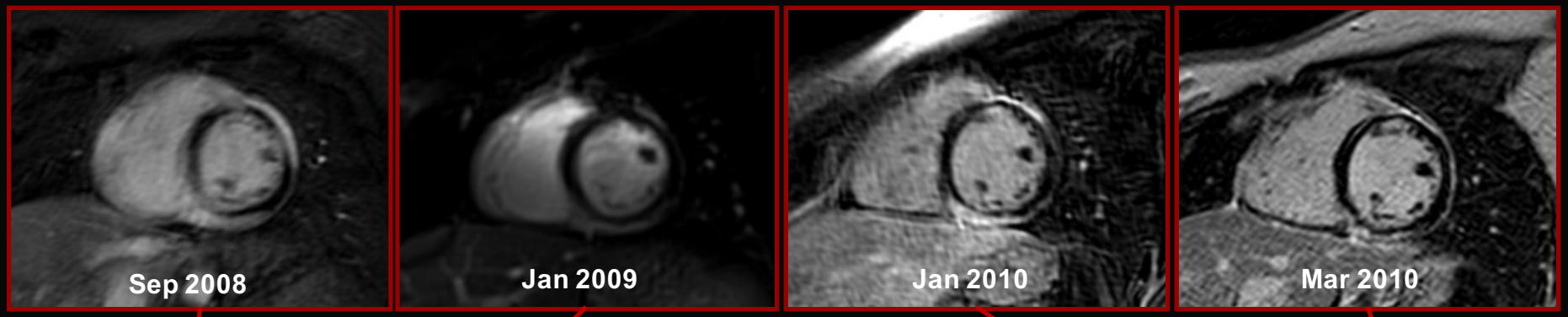


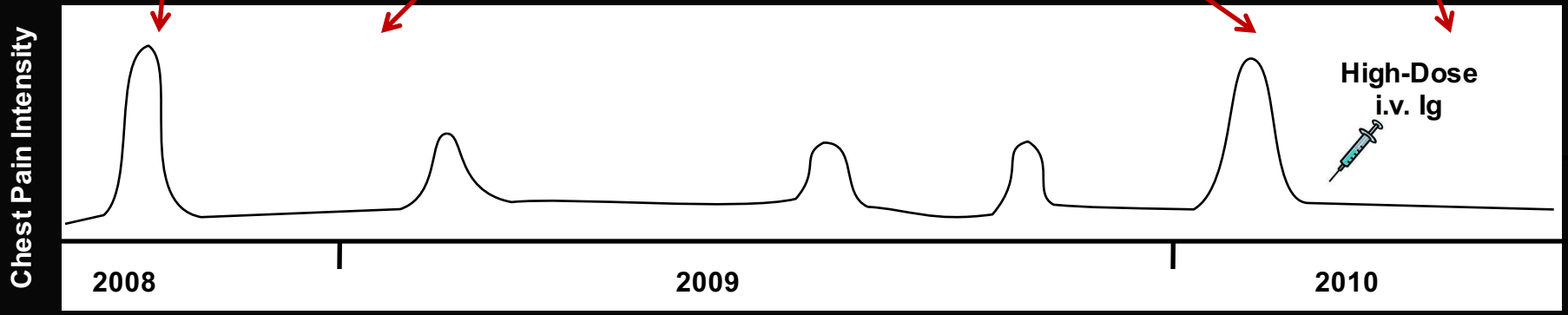


Cocker M.S. et al. *Heart* 2009

Monitoring Effects of Therapy at the Myocardial Level by Cardiac MR in Patients with Myocarditis

M.L.
17 year-old female
Acute viral myocarditis





EuroCMR Registry

Results of the German Pilot Phase

Bruder O. et al. *J Am Coll Cardiol* 2009

Baseline Characteristics	N= 11,040 from 20 Centers
All	100 (11,040)
Male	63.7% (7,020/11,017)
Female	36.3% (3,997/11,017)
Age (yrs)	60 (47–70)
BMI (kg/m^2)	26.2 (23.7–29.4)
Field	
1.0-T	1.1% (116/11,002)
1.5-T	98.2% (10,801)
3.0-T	0.8% (85)
Stress	
No stress	68.5% (7,565/11,040)
Adenosine	20.9% (2,309)
Dobutamine	10.6% (1,166)
Reader	
Cardiologist	78.2% (8,619)
Team of cardiologist and radiologist	20.1% (2,215)
Radiologist	1.7% (187)
Primary indication for CMR	
Myocarditis/cardiomyopathies	31.9% (3,511/11,026)
Suspected CAD/ischemia in known CAD	30.8% (3,399)
Myocardial viability	14.7% (1,626)
Valvular heart disease	4.8% (531)
Aortic disease	3.4% (372)
Congenital heart disease	1.6% (181)
Ventricular thrombus	1.4% (154)
Cardiac masses	1.2% (129)
Pulmonary vessels	1.1% (126)
Coronary vessels	0.2% (25)
Other than above	8.8% (972)

Impact of CMR on Patient Management by Indication

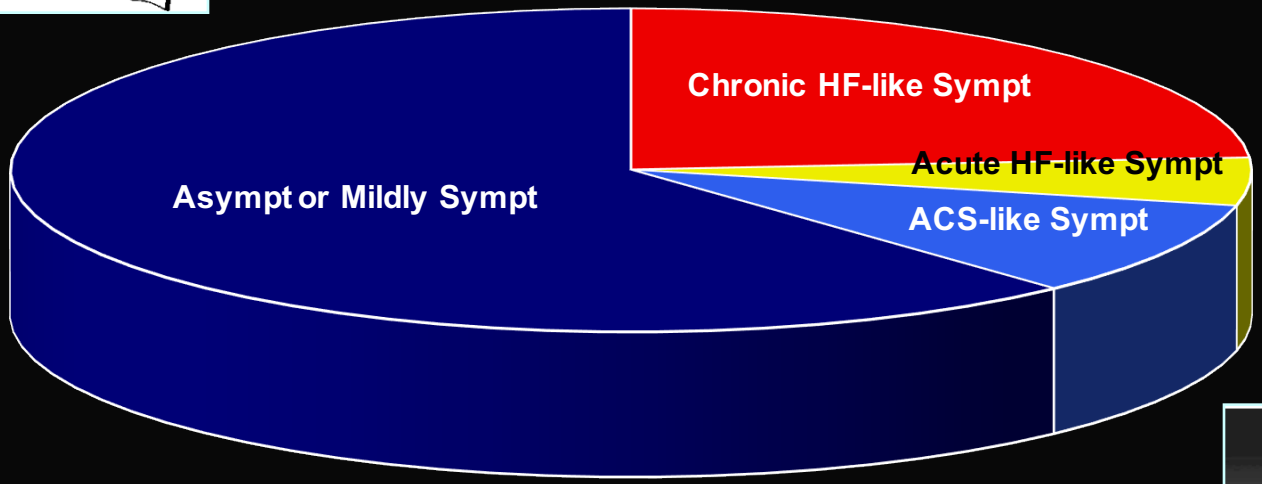
	Myocarditis/CMP
All (from n = 11,040)	31.8%
Completely new diagnosis not suspected before	21%
Therapeutic consequences	
Change in medication	22.7%
Intervention/surgery	2.9%
Invasive angiography/biopsy	6.3%
Hospital discharge	1.7%
Hospital admission	0.4%
Impact on patient management (new diagnosis and/or therapeutic consequence)	55.0%

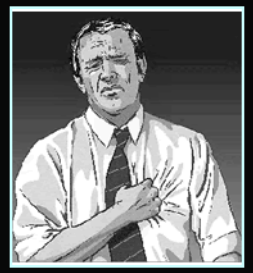
From April 2007 and January 2009

Variable Clinical Presentation in Adult Patients with Acute or Chronic Myocarditis

Data from the European Study of Epidemiology and Treatment of Cardiac Inflammatory Diseases

True incidence is difficult to determine since clinical presentation varies widely and only 10% of cases leads to clinical symptoms!





Hufnagel G et al. *Herz* 2000

Published Controlled Studies on Cardiovascular Magnetic Resonance in Myocarditis

Friedrich M.G. et al. *J Am Coll Cardiol* 2009

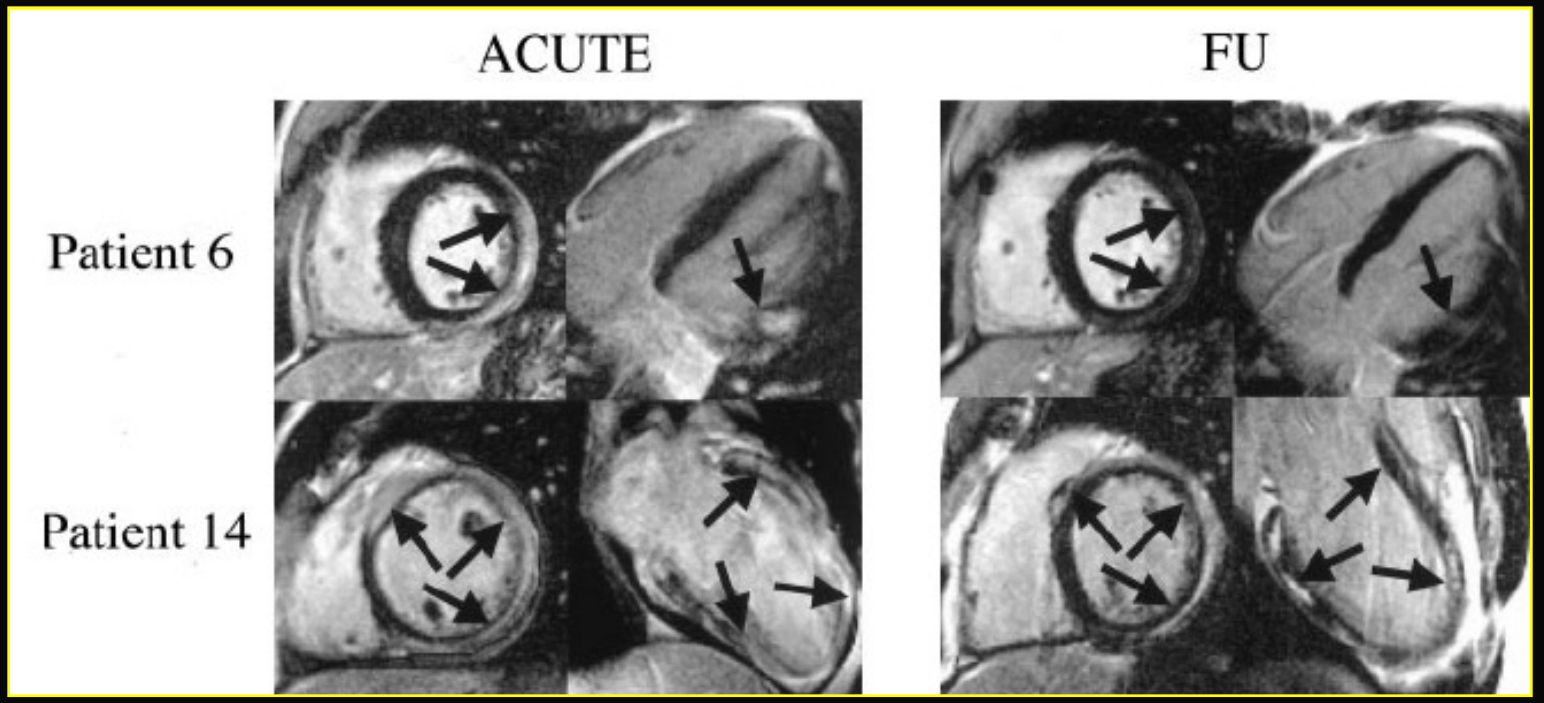
	Validation	No. of Patients	No. of Control Patients
Friedrich et al., *Circulation* 1998 (9)	Clinical	19	18
Laissy et al., *Chest* 2002 (11)	Clinical	20	7
Rieker et al., *Rofo* 2002 (36)	Clinical	11	10
Laissy et al., *Radiology* 2005 (37)*	Clinical	24	31
Abdel-Aty et al., *J Am Coll Cardiol* 2005 (13)	Clinical	25	22
Mahrholdt et al., *Circulation* 2006 (40)	Histology	87	26
Gutberlet et al., *Radiology* 2008 (34)†	Histology	48	35
Yilmaz et al., *Heart* 2008 (43)†	Histology	55	30
Total		289	179

CMR Assessment of Human Myocarditis

A Comparison to Histology and Molecular Pathology

Mahrholdt H et al. *Circulation* 2004

N= 32 pts with clinically-defined myocarditis
CMR study first and then EMB



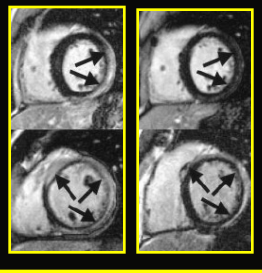
Relationship of Cardiac MR Findings to Clinical Outcome in Patients with Myocarditis

TABLE 7. Predictors of Clinical Outcome: Multiple Linear Model for LVEF at Follow-Up

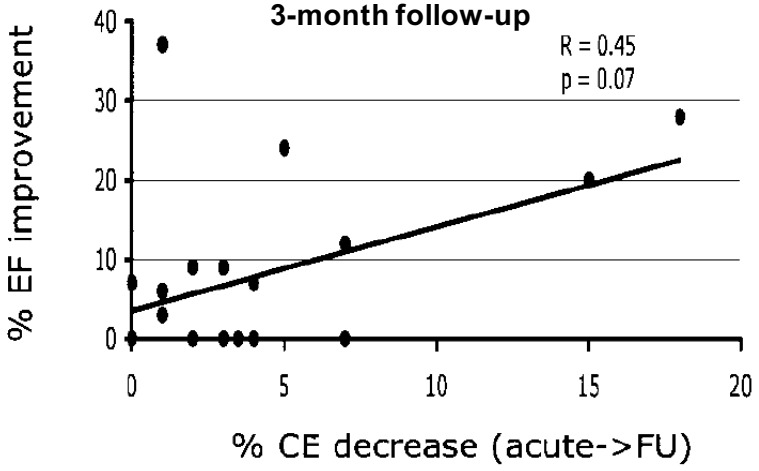
			P	
Variable	Estimate	SE	Wald	F
(Intercept)	38.51	5.58	<0.0001	
EDV acute	0.48	0.072	<0.0001	<0.0001
Virus				
HHV6+PVB19	−8.14	3.066	0.003	<0.01
Symptom				
Heart failure	−2.78	3.072	0.37	
Other	−10.06	3.89	0.012	
LGE, %LV	−0.751	0.211	0.029	<0.05
LGE septal	−0.56	0.22	0.012	0.012

LGE indicates late gadolinium enhancement. Residual SE=7.925 on 60 *df*. Multiple R^2=0.7663, adjusted R^2=0.7469. F statistic: 39.36 on 5 and 60 *df*, $P=2.2e^{-16}$.

Mahrholdt H et al. *Circulation* 2006



Late Gadolinium Enhancement

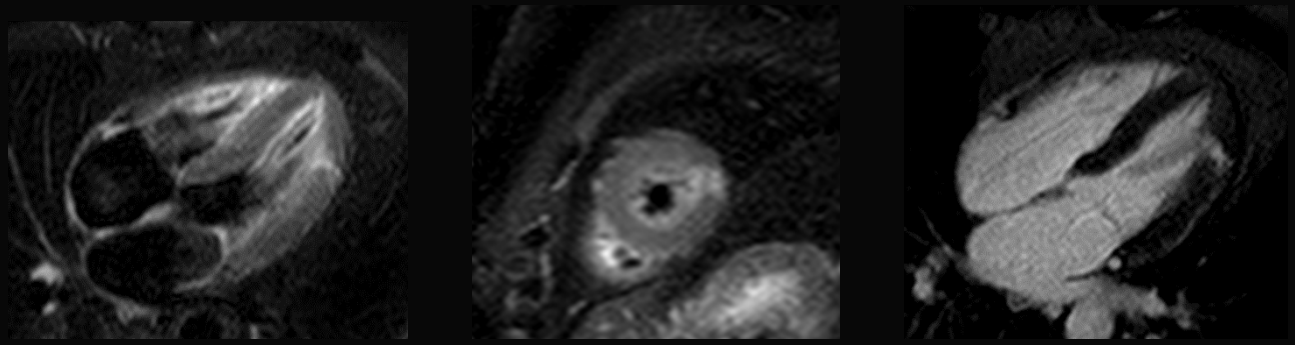


Mahrholdt H et al. *Circulation* 2004

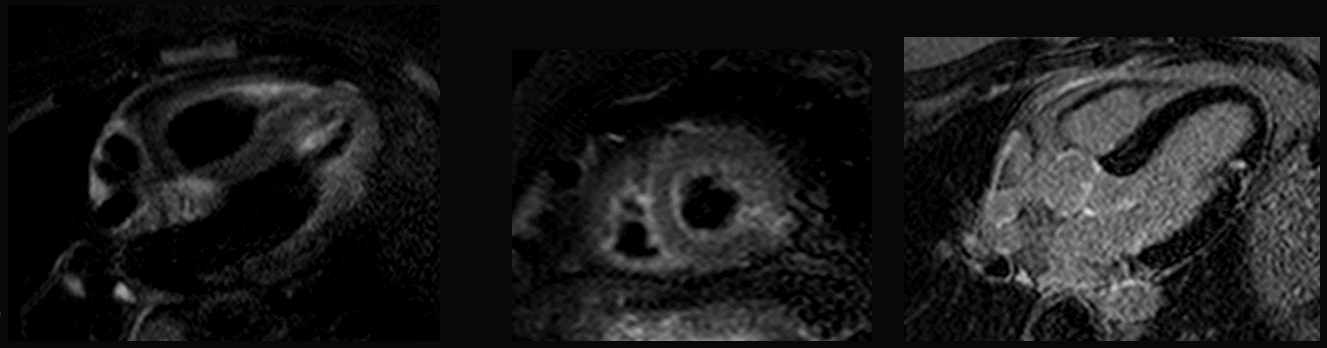
G. T.
32 year-old male
Intense chest pain
Recent diagnosis of C. trachomatis epididymitis
TnI = 2.28 ng/dl

A Case of Acute Myocarditis Associated with *Clamydia Trachomatis* Infection: Role of Cardiac MRI in the Clinical Management

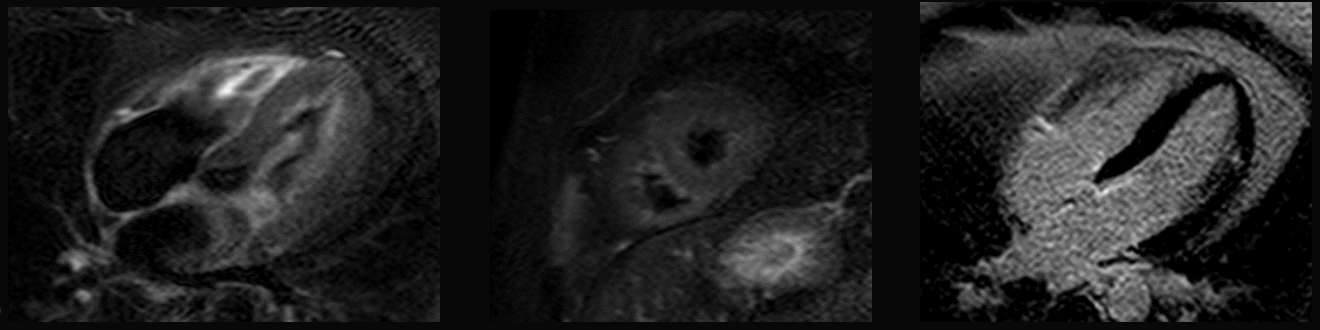
Acute phase



2-Month Follow-up



5-Month Follow-up



Dellegrottaglie S, Russo G, Damiano M, Pagliano P, Ferrara L, De Simone C, Guarini P (Submitted)

the three musketeers