# Myocarditis - Dilated Cardiomyopathies: The Role of Endomyocardial Biopsy

## Diagnostic, Prognostic and Therapeutic Implications

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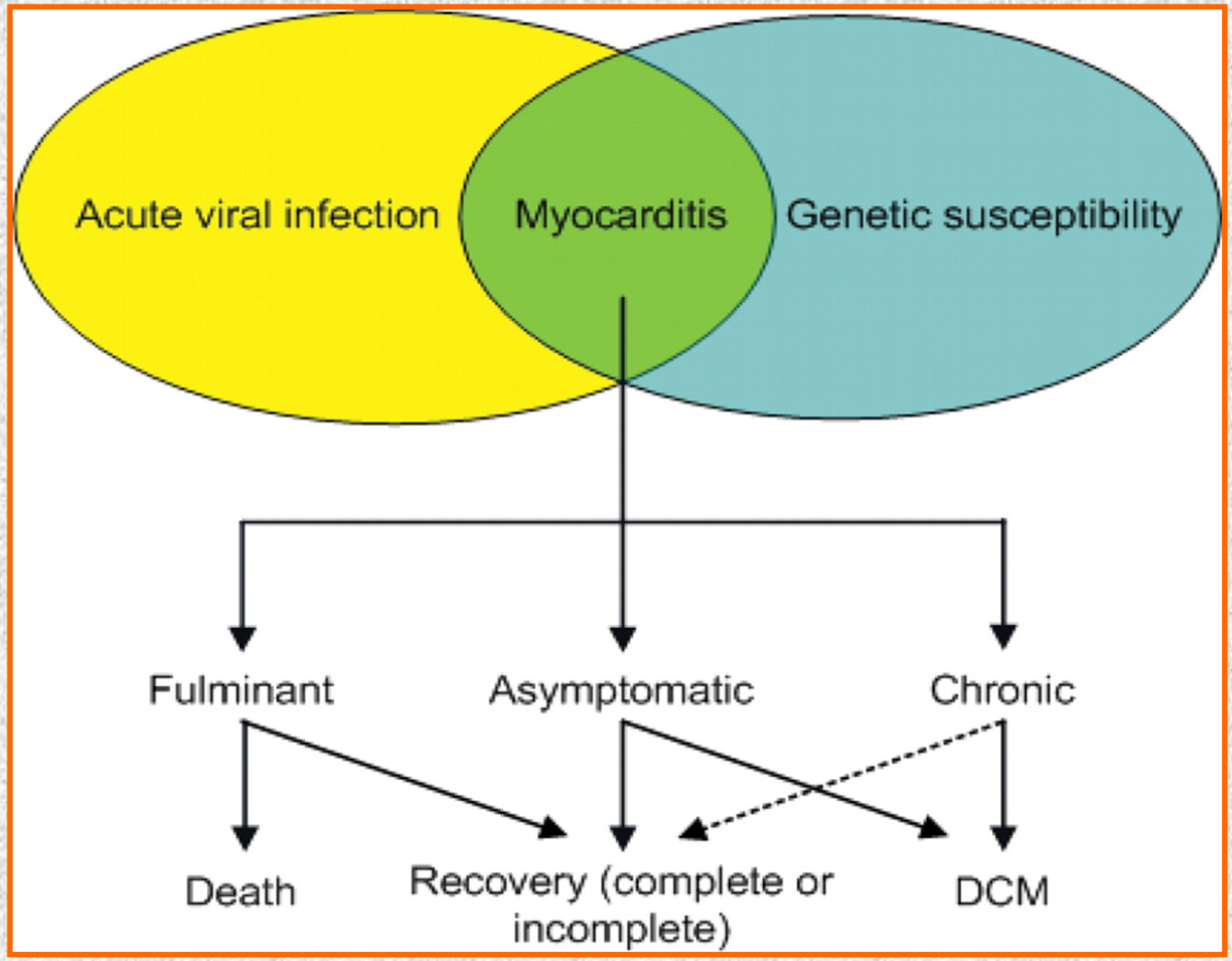
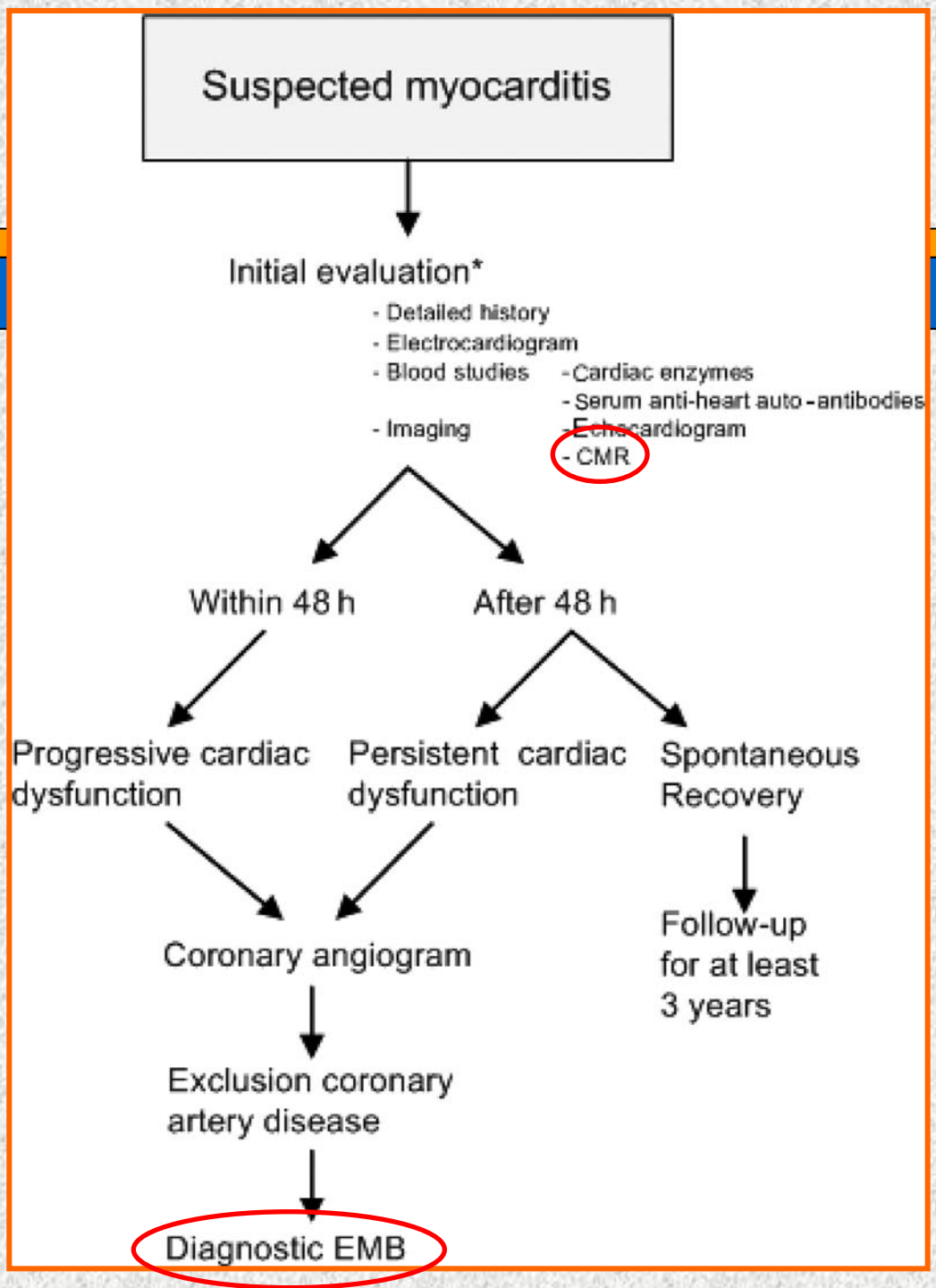
# Evolution of Acute Viral Myocarditis

*R Dennert et al, Eur Heart J 2008, July 9*



# Proposal of Diagnostic Approach for Patients with Suspected Myocarditis

**Persistent or Increasing Cardiac Dysfunction**




*R Dennert et al,*
*Eur Heart J 2008, July 9*

# The Role of Endomyocardial Biopsy in the Management of Cardiovascular Disease

## AHA/ACC/ESC scientific statement, Eur Heart Journal 2007, October 24

✓ **Clinical scenario 1**

**EMB should be performed in the setting of unexplained new-onset HF of <2 weeks' duration associated with normal-sized or dilated left ventricle in addition to hemodynamic compromise *(dd: lymphocytic vs GCM vs necrotizing eosinophilic)* (Class I, Evidence B)**

✓ **Clinical scenario 2**

**EMB should be performed in the setting of unexplained new-onset HF of 2 weeks' to 3 months' duration associated with a dilated left ventricle and new ventricular arrhythmias, Mobitz type II 2nd- or 3rd-degree AV heart block, or failure to respond to usual care within 1 to 2 weeks *(exclude GCM)* (Class I, Evidence B)**

✓ **Clinical scenario 4**

**EMB is reasonable in unexplained HF associated with a DCM of any duration with suspected allergic reaction in addition to eosinophilia (Class IIa, Evidence C)**

✓ **Clinical scenario 9**

**EMB may be considered in the setting of unexplained, new-onset HF of 2 weeks' to 3 months' duration associated with a dilated LV, without new ventricular arrhythmias, Mobitz type II 2nd- or 3rd-degree AV heart block that responds to usual care within 1 to 2 weeks (Class IIb, Evidence B)**

# Complication Rate of RV Endomyocardial Biopsy via Femoral Approach

## 3048 Diagnostic Procedures over an 11-Year Period

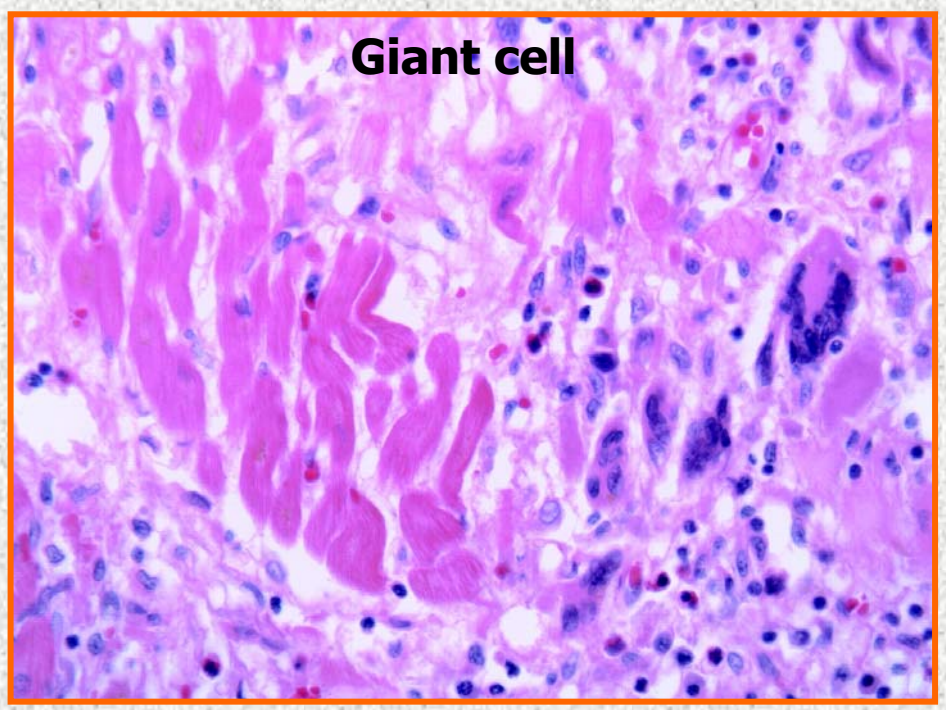
**Table 2. Major Complications of 2505 Retrospective and 543 Prospective EMB Procedures**

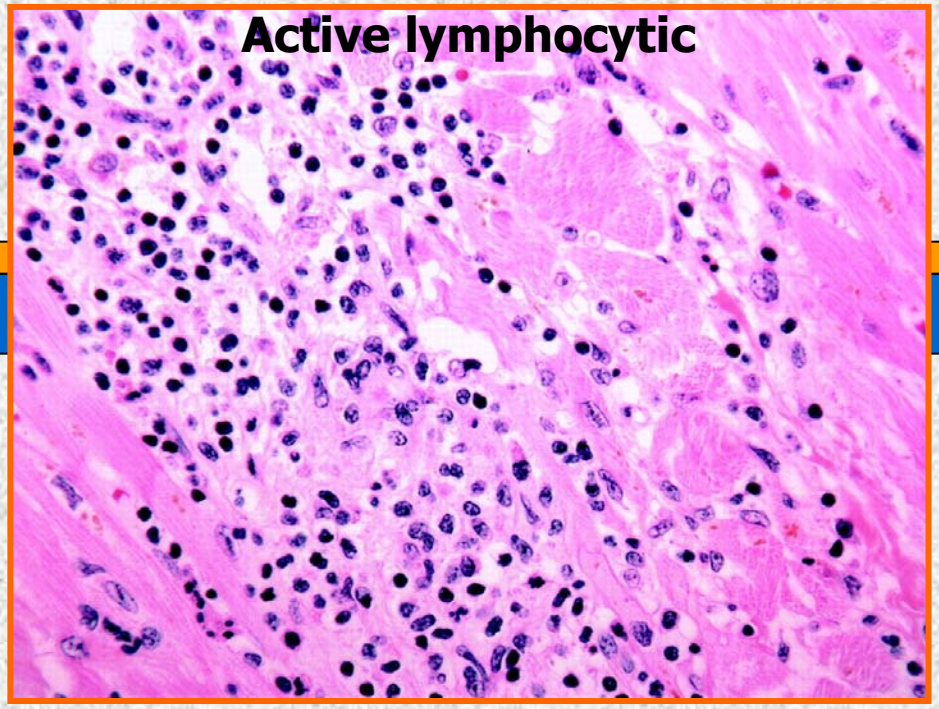
| Major Complications of EMB Procedures | Retrospective, Absolute/% | Prospective, Absolute/% |
|---|---|---|
| Pericardial tamponade with pericardiocentesis | 2/0.08 | 0/0 |
| Permanent complete AV block with permanent pacemaker required | 1/0.04 | 0/0 |
| Urgent cardiac surgery | 0/0 | 0/0 |
| Advanced cardiac life support | 0/0 | 0/0 |
| Hemothorax or pneumothorax | 0/0 | 0/0 |
| Death | 0/0 | 0/0 |

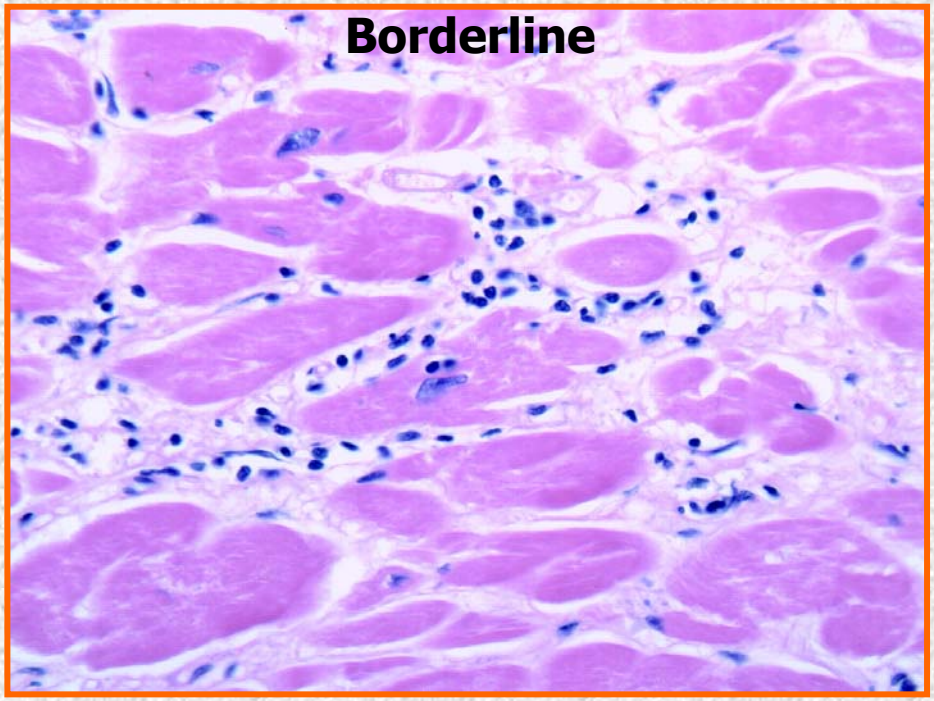
*M Holzmann et al, Circulation 2008, August 5*

# Myocarditis

## Current Trends in Diagnosis and Treatment

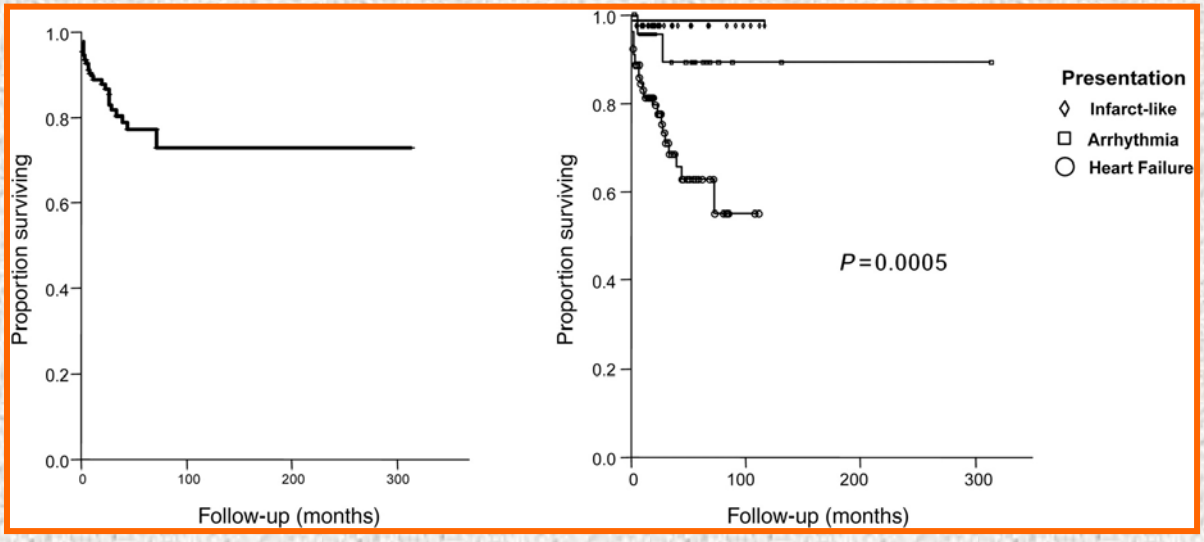


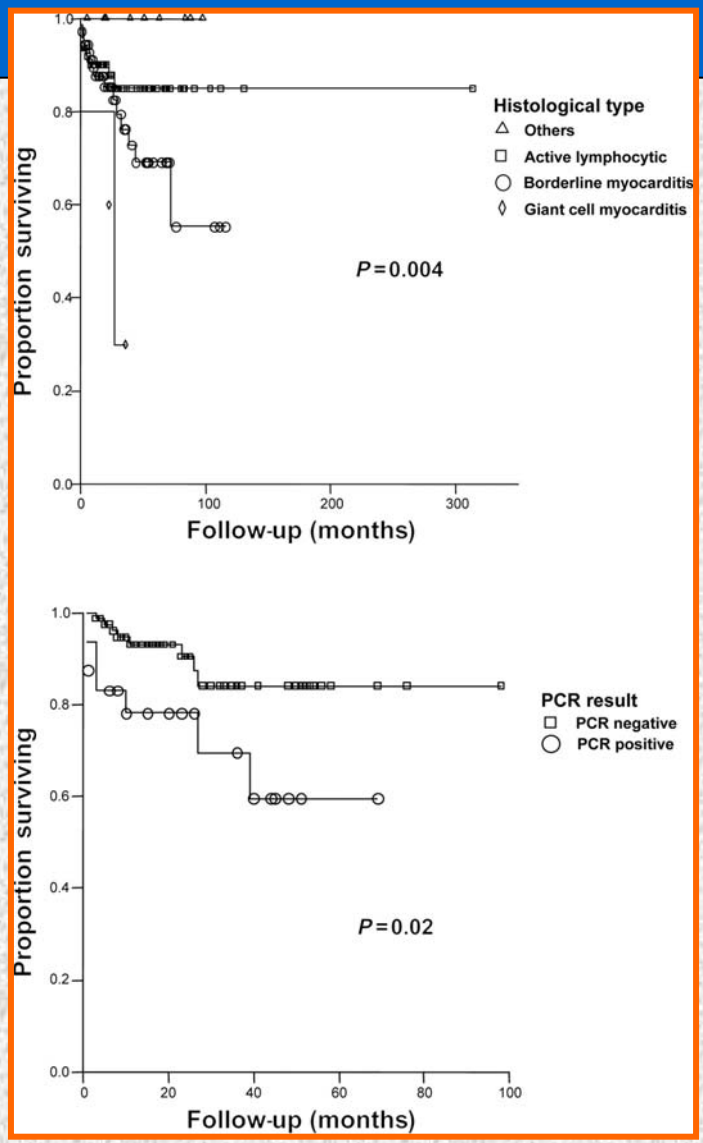




*JW Magnani and GW Dec*
*Circulation 2006, February 14*

# Probability for Myocarditis Patients of Remaining Free from Death or Transplantation According to Clinical and Histological Presentation

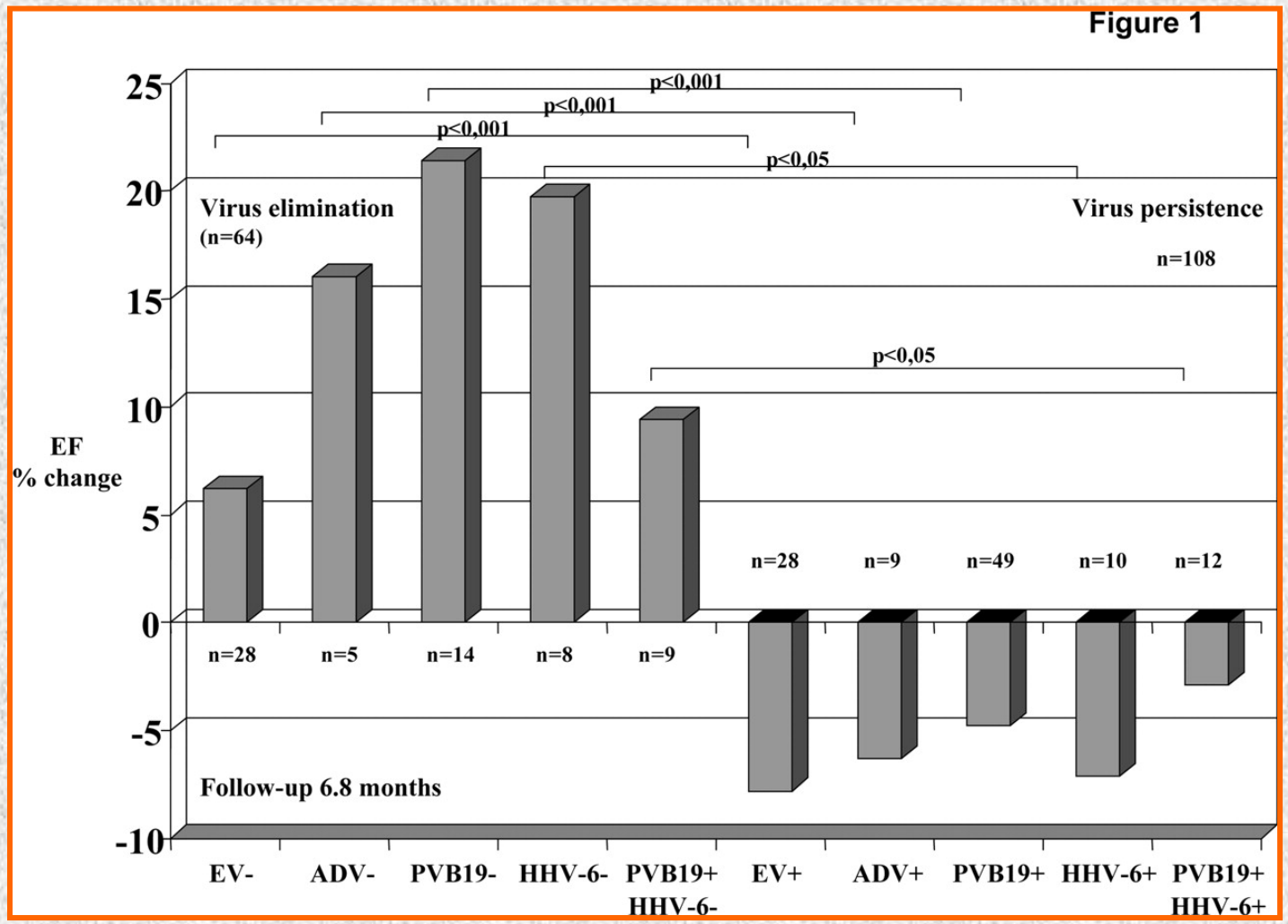


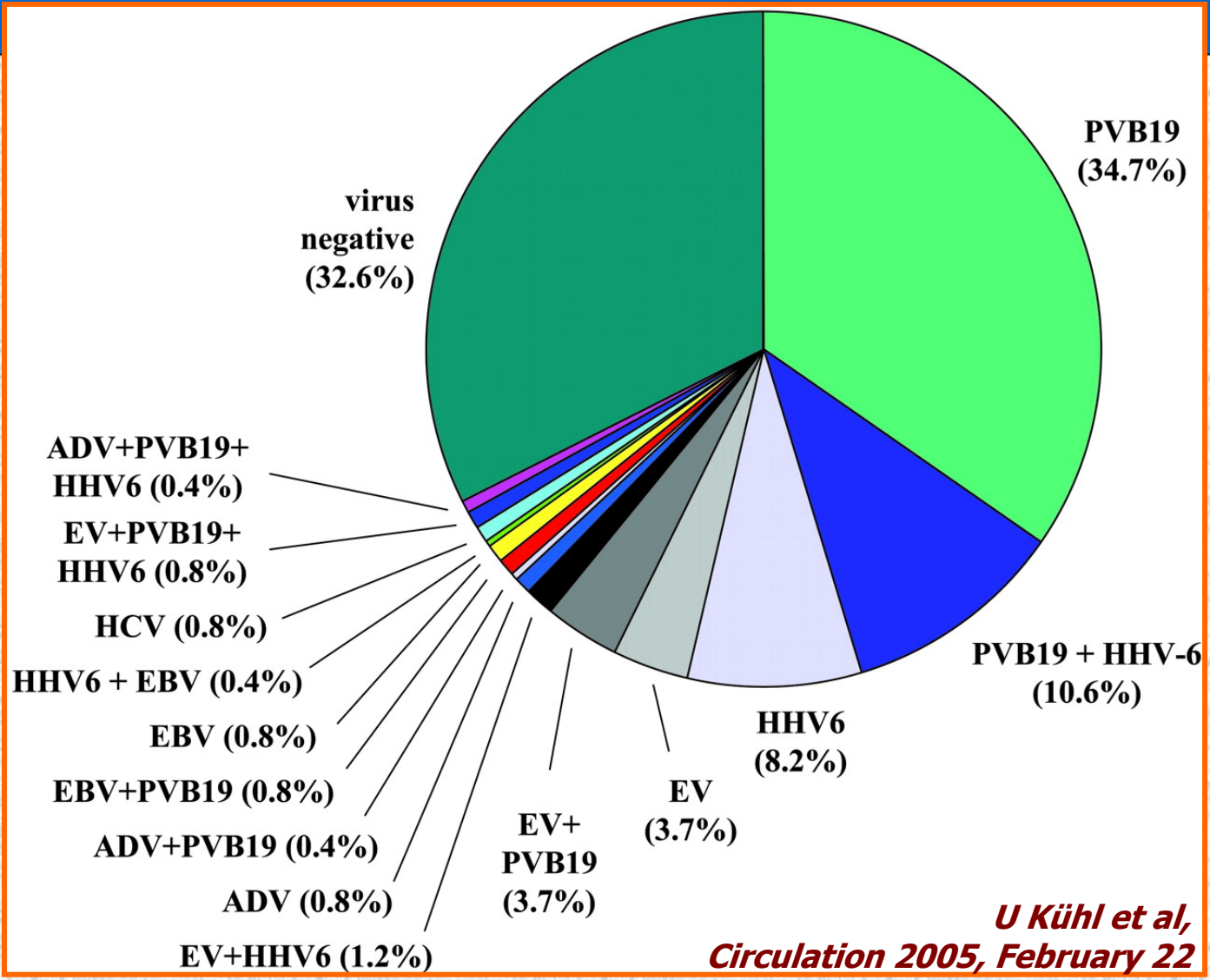

*ALP Caforio et al, Eur Heart J 2007;28:1326-1333*

# Viral Persistence in the Myocardium is Associated with Progressive Cardiac Dysfunction

*U Kühl et la, Circulation 2005;112:1965-1970*



# High Prevalence of Viral Genomes and Multiple Viral Infections in the Myocardium of Adults with "Idiopathic" Left Ventricular Dysfunction




*U Kühl et al,*
*Circulation 2005, February 22*

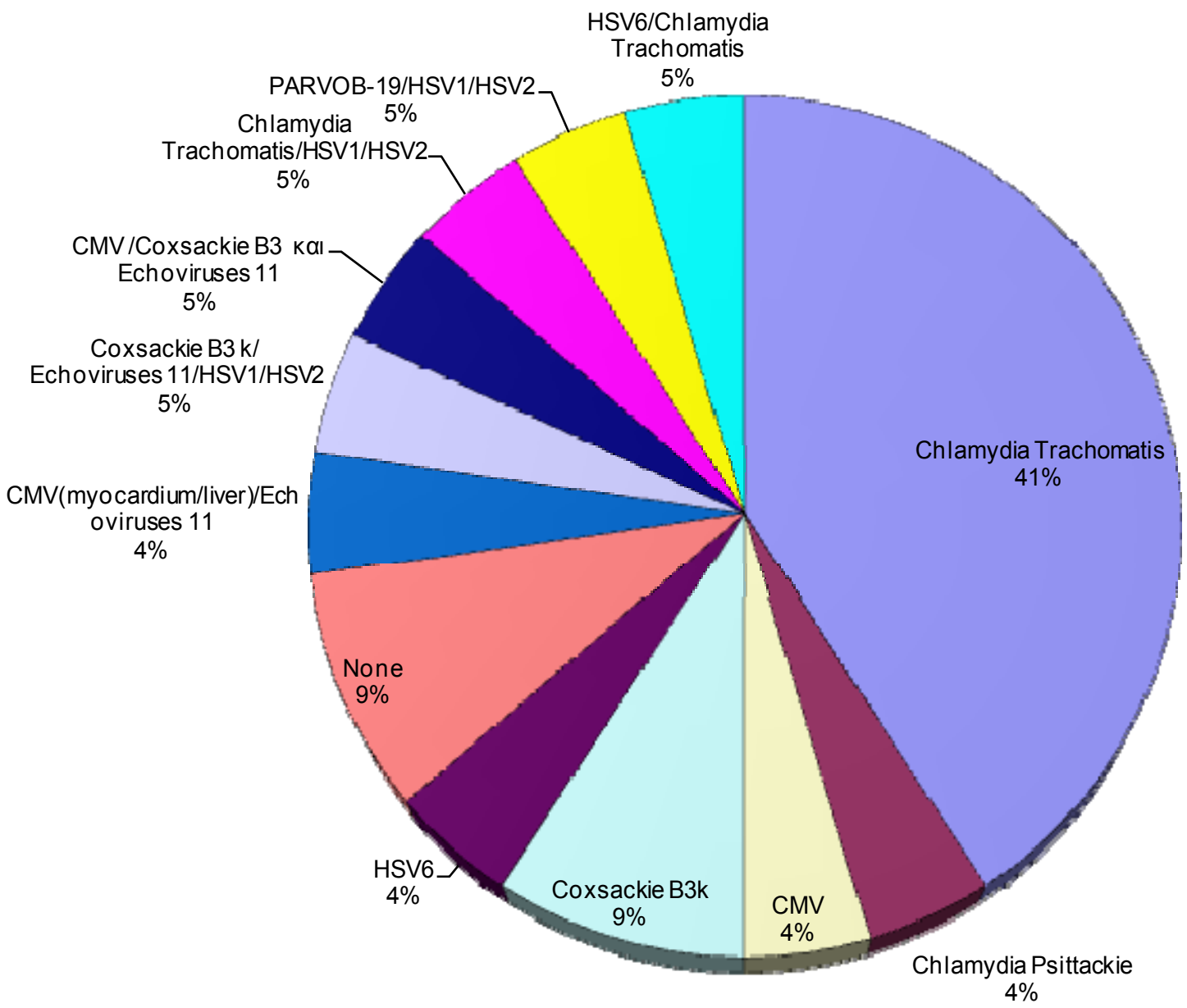
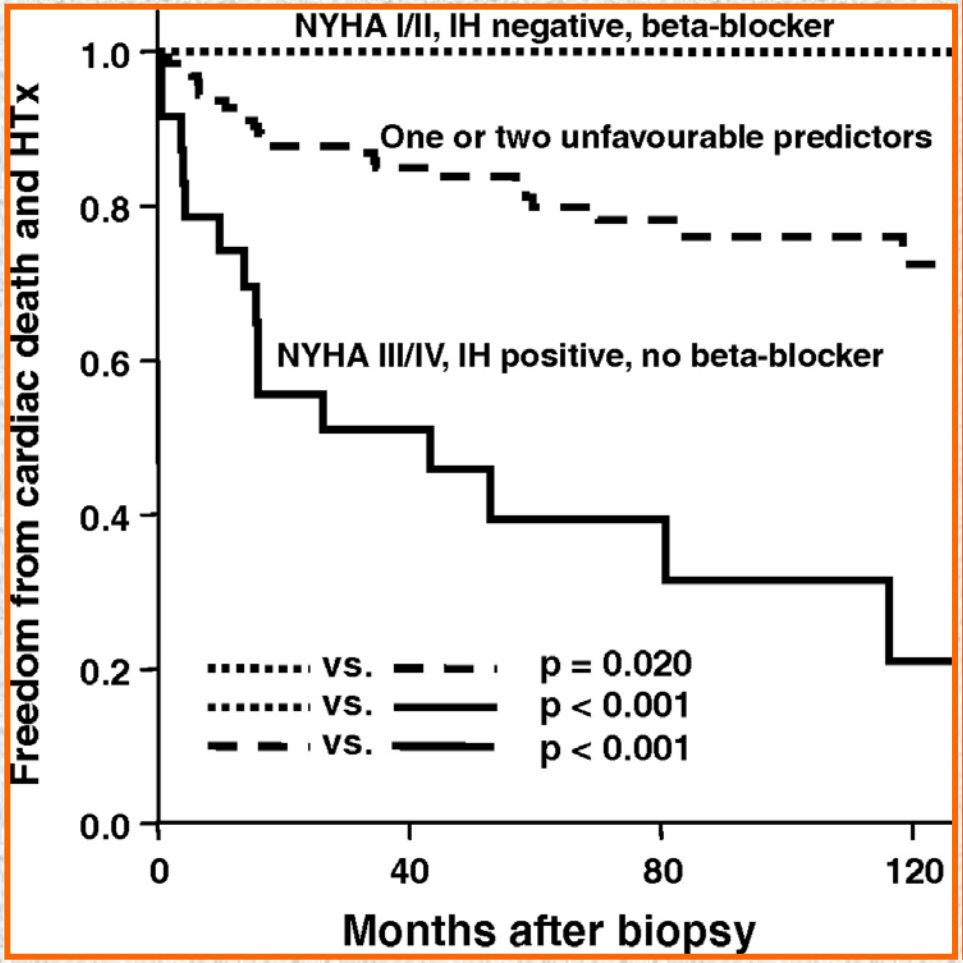
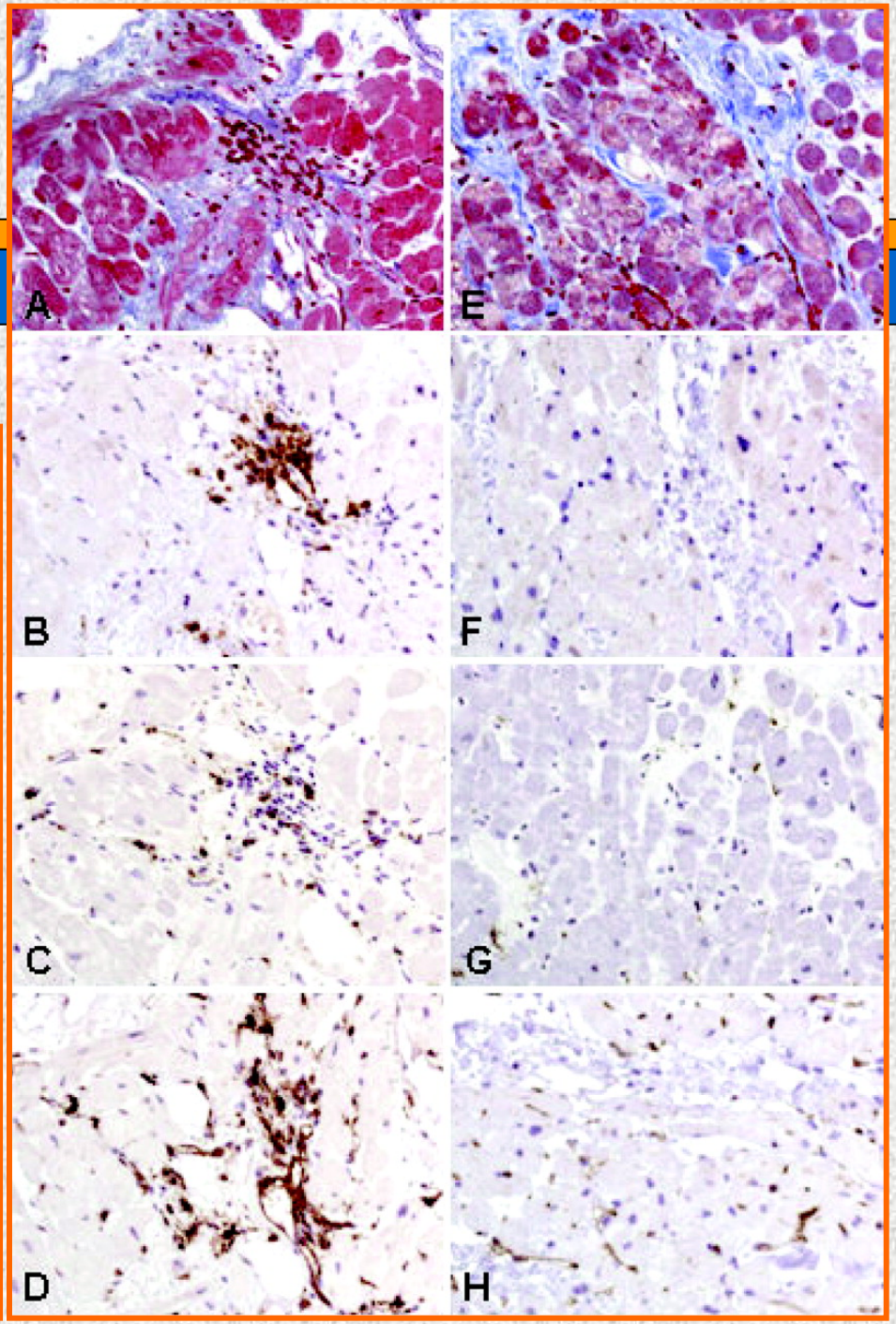


Chart Title
HSV6/Chlamydia Trachomatis 5%
PARVOB-19/HSV1/HSV2 5%
Chlamydia Trachomatis/HSV1/HSV2 5%
CMV /Coxsackie B3 και Echoviruses 11 5%
Coxsackie B3 k/ Echoviruses 11/HSV1/HSV2 5%
CMV(myocardium/liver)/Echoviruses 11 4%
None 9%
HSV6 4%
Coxsackie B3k 9%
CMV 4%
Chlamydia Psittackie 4%
Chlamydia Trachomatis 41%

# Predictors of Outcome in Patients with Suspected Myocarditis

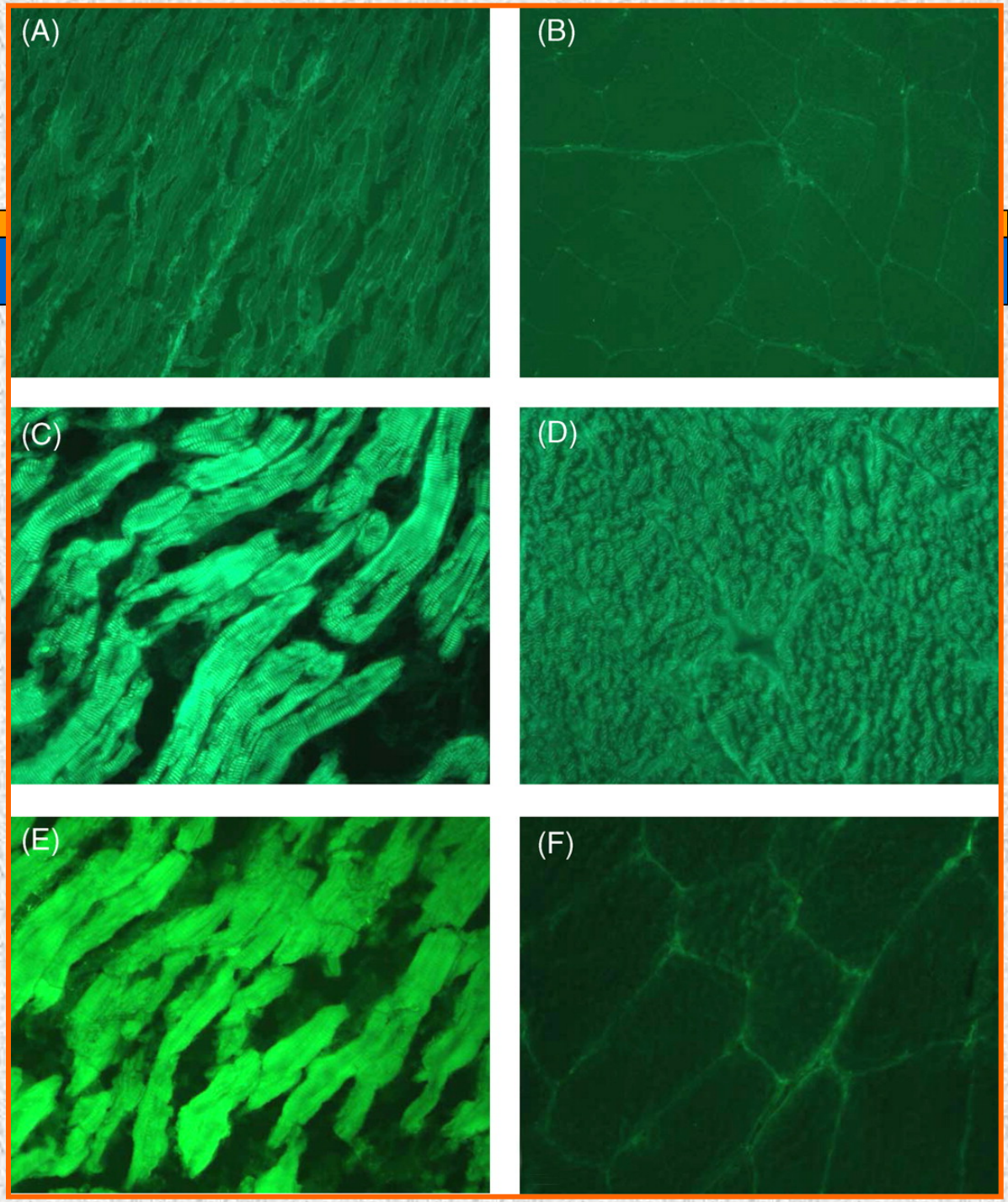
*I Kindermann et al, Circulation 2008, August 5*



# A Prospective Study of Biopsy-Proven Myocarditis

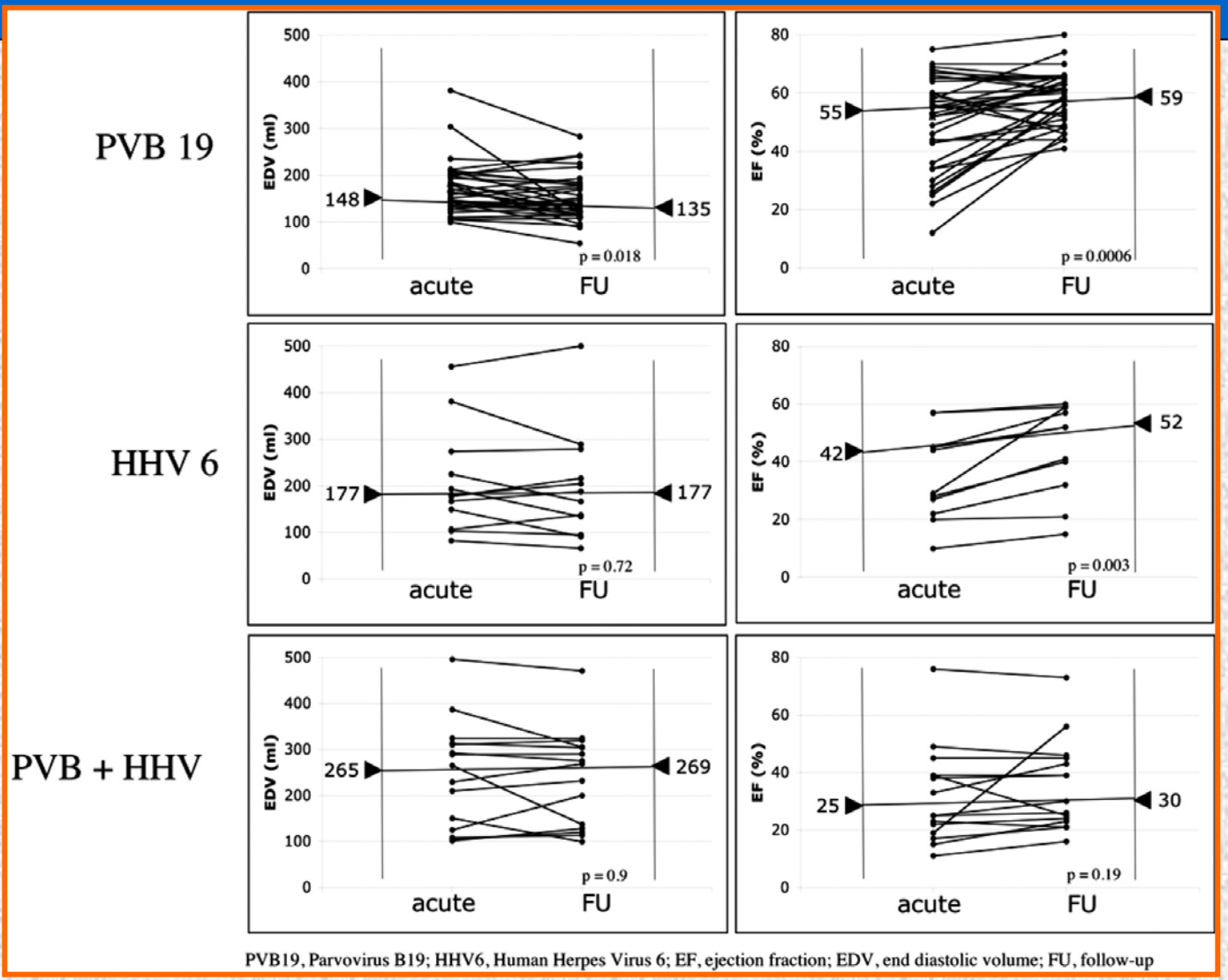
## Prognostic Relevance of Clinical and Aetiopathogenic Features at Diagnosis




*ALP Caforio et al,*
*Eur Heart J 2007;28:1326-1333*

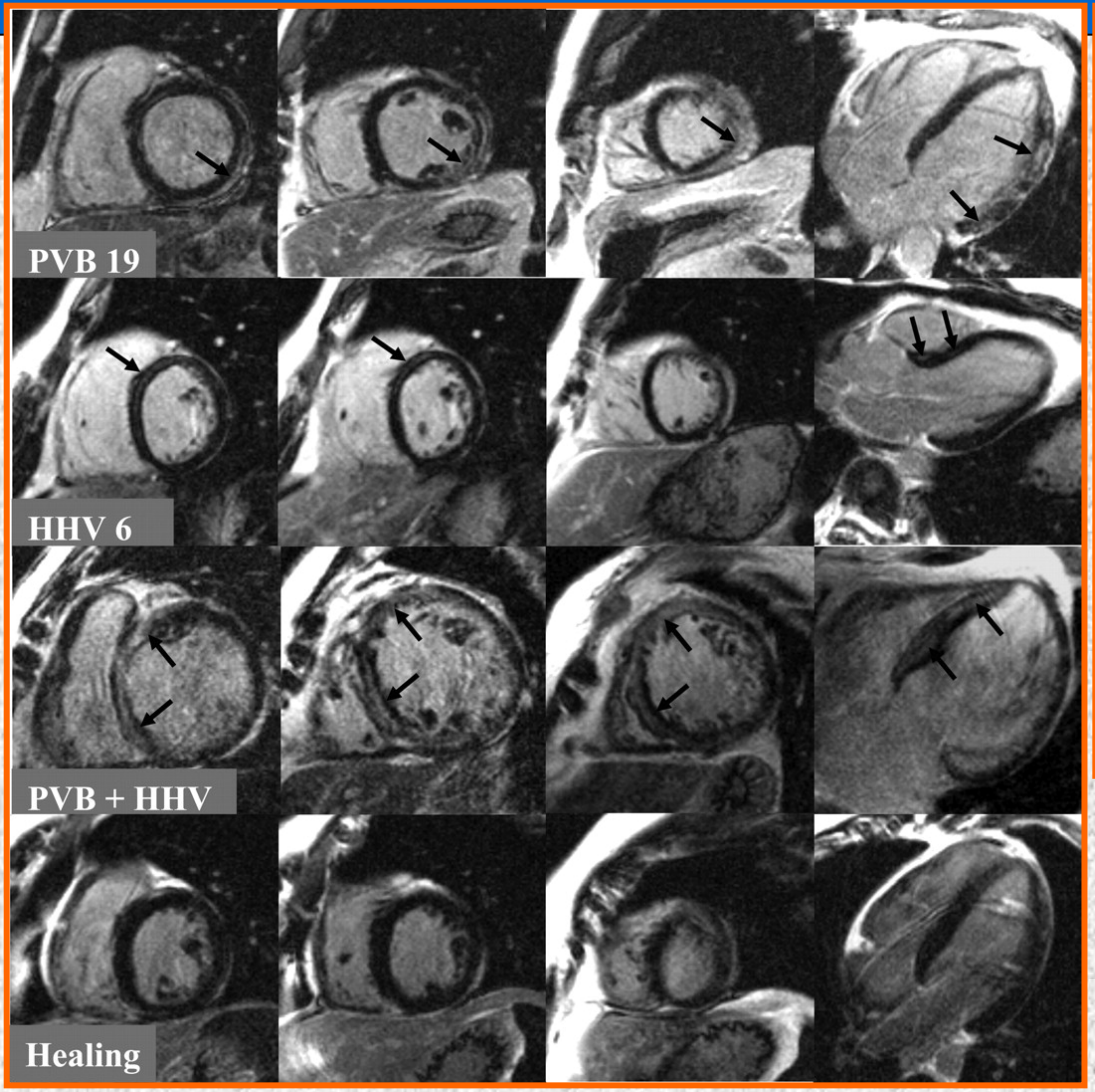
# Presentation, Patterns of Myocardial Damage and Clinical Course of Viral Myocarditis

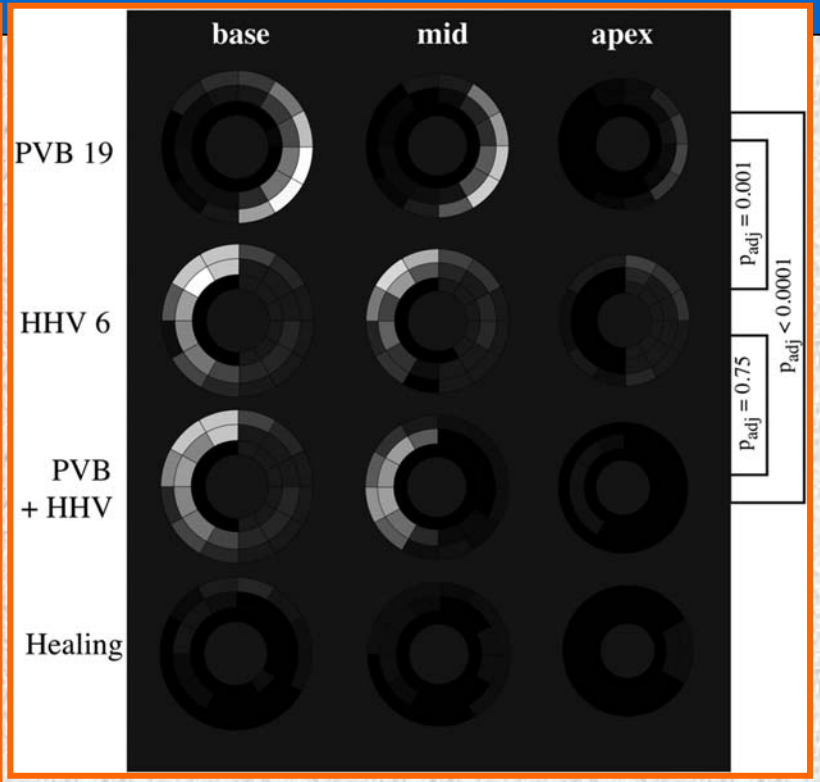
*H Mahrholdt et al, Circulation 2006;114:1581-1590*




PVB19, Parvovirus B19; HHV6, Human Herpes Virus 6; EF, ejection fraction; EDV, end diastolic volume; FU, follow-up

# Spatial Distribution of the Mean Values for Segmental Extent of LGE at Time of the Initial CMR Scan with Respect to the Viral Type



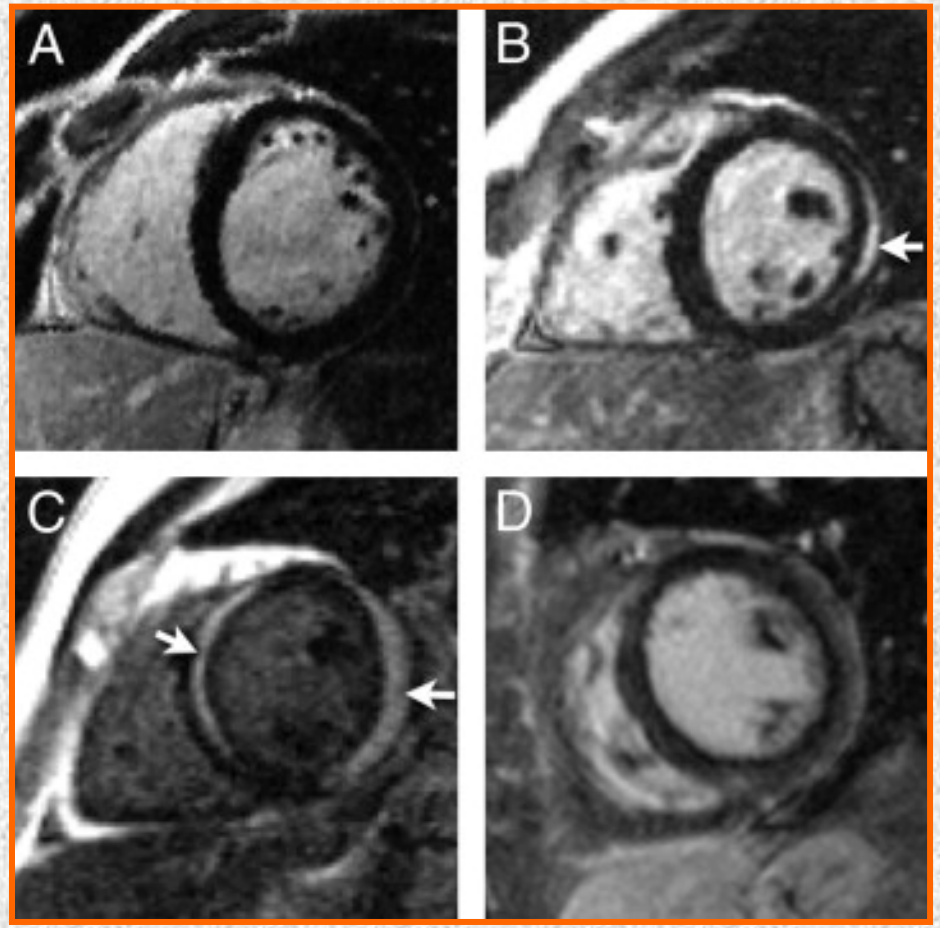




*H Mahrholdt et al, Circulation 2006;114:1581-1590*

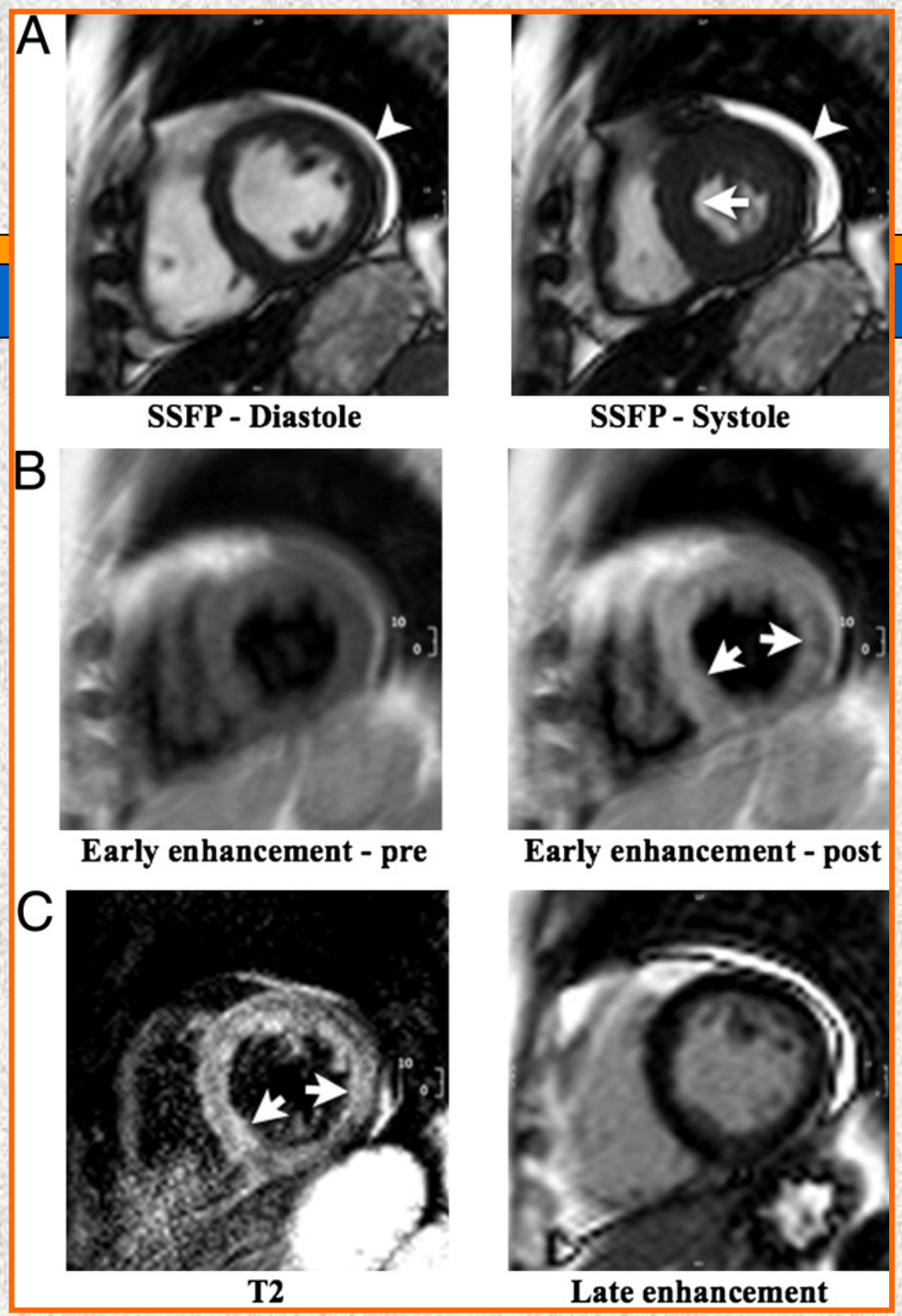
# Summary of Recommended Components for the CMR Study Report

| | |
|---|---|
| **LV volume and function** | LV end-diastolic volume and volume index<br>LV end-systolic volume and volume index<br>Ejection fraction<br>Cardiac index<br>LV mass and mass index |
| **Presence or absence of markers for inflammatory activity and injury** | T2 signal/edema (regional edema or global T2 ratio)<br>Calculated global myocardial early gadolinium enhancement ratio (hyperemia)<br>Myocardial late gadolinium enhancement with nonischemic regional distribution (necrosis) |
| **Conclusion** | On the basis of the presence or absence of 2 or more criteria, considering additional evidence by the presence of LV dysfunction and/or pericardial effusion |
| **Recommendation for follow-up** | Based on clinical setting<br>A follow-up 4 weeks after the onset of symptoms may have prognostic implications and thus is recommended. |

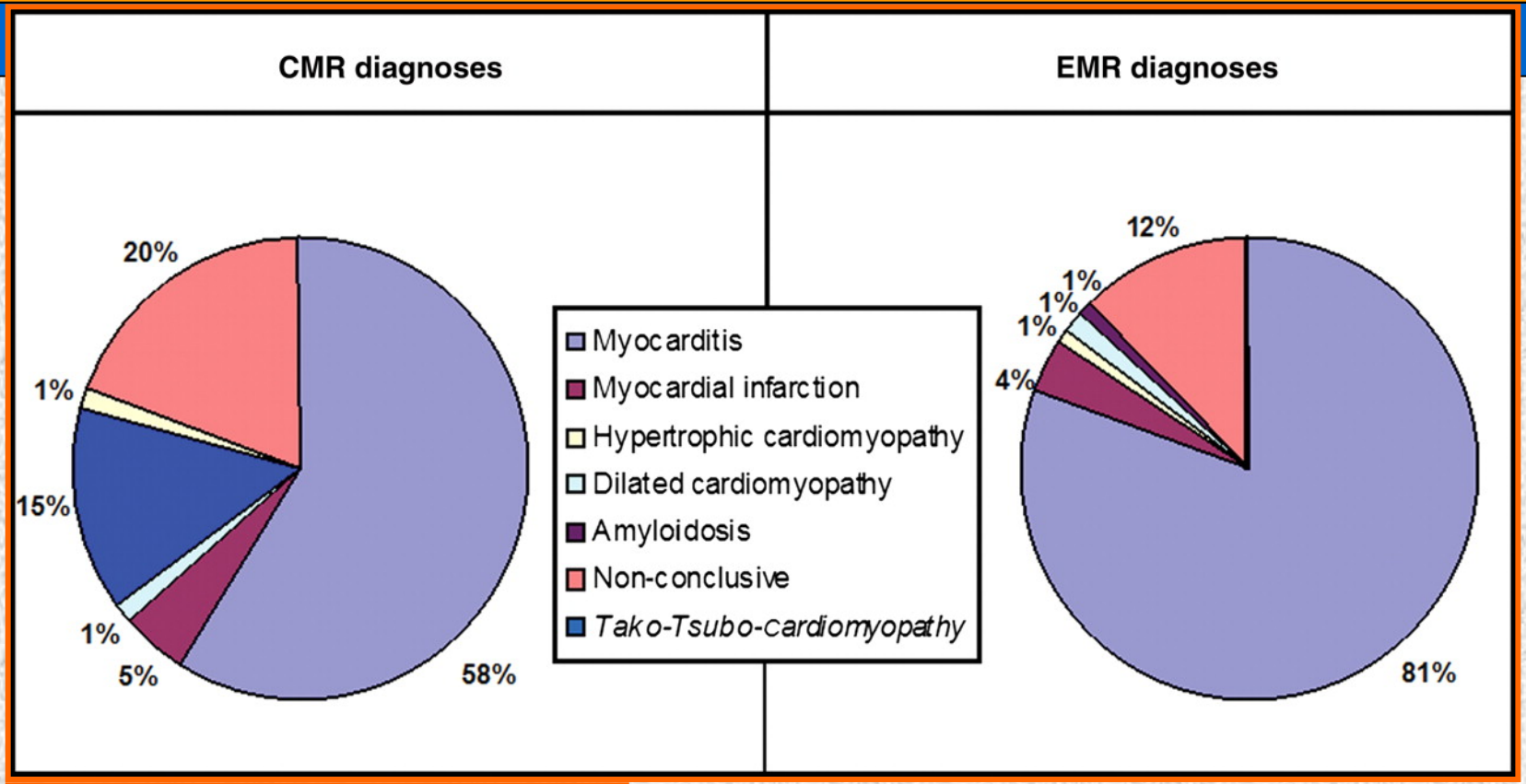
# Cardiovascular Magnetic Resonance in Myocarditis:
## A JACC White Paper

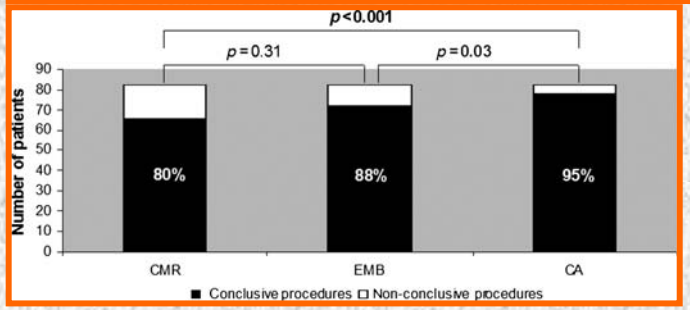



*MG Friedrich et al,*
*J Am Coll Cardiol 2009, April 28*



# Diagnostic Synergy of Non-Invasive Cardiovascular Magnetic Resonance and Invasive Endomyocardial Biopsy in Troponin-Positive Patients without Coronary Artery Disease




*H Baccouche et al,*
*Eur Heart J 2009, August 20*

# This CMR Image of a Patient with Remote Myocarditis Shows Chronic Multifocal, Partially Subendocardial Scarring

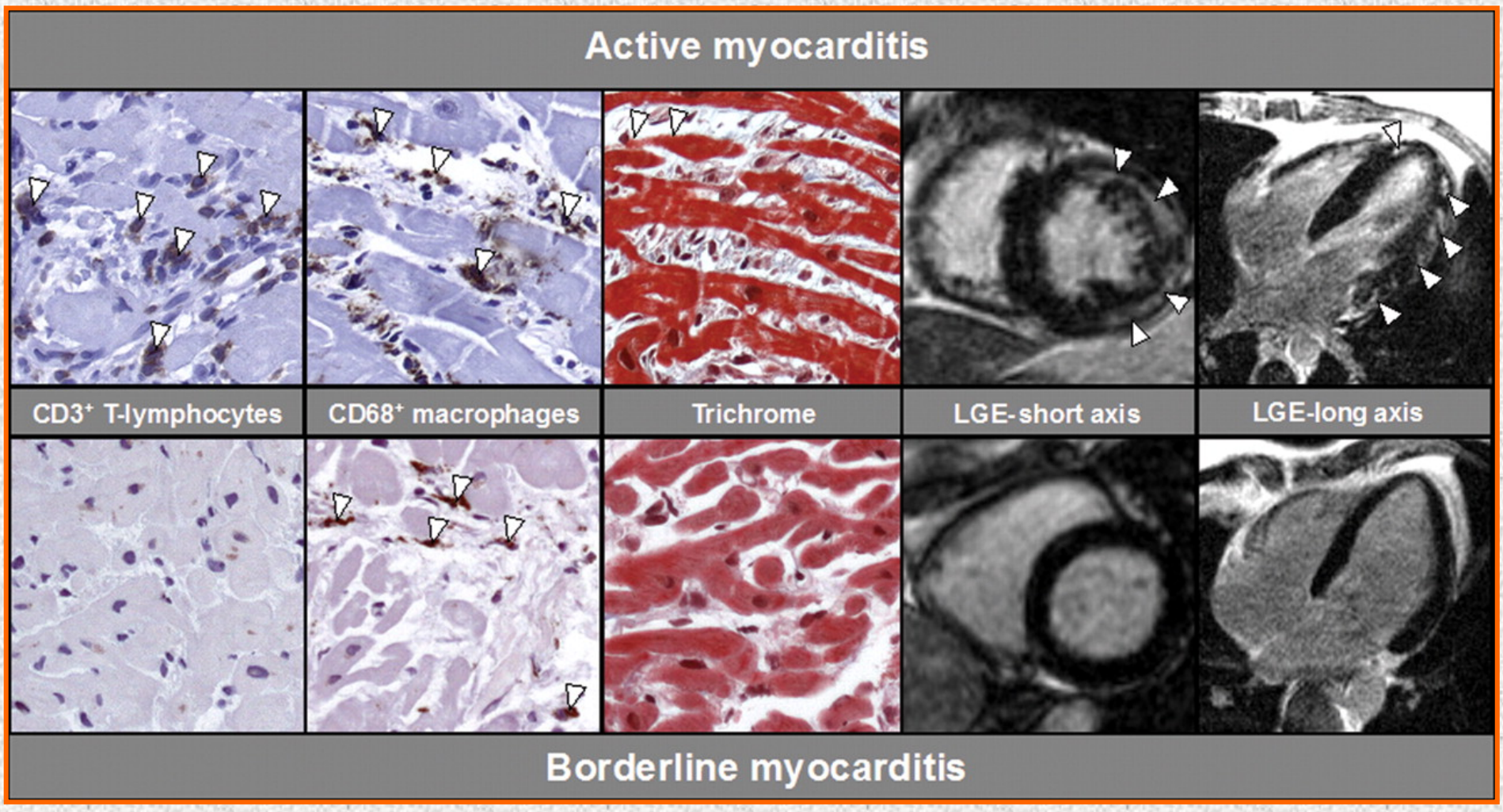
**The degree of *sampling error* depends on**

**(a) the number of biopsies taken per patient and**
**(b) the methods applied for *ex vivo* analysis**

***MG Friedrich: JACC Cardiovascular Imaging September 2008***

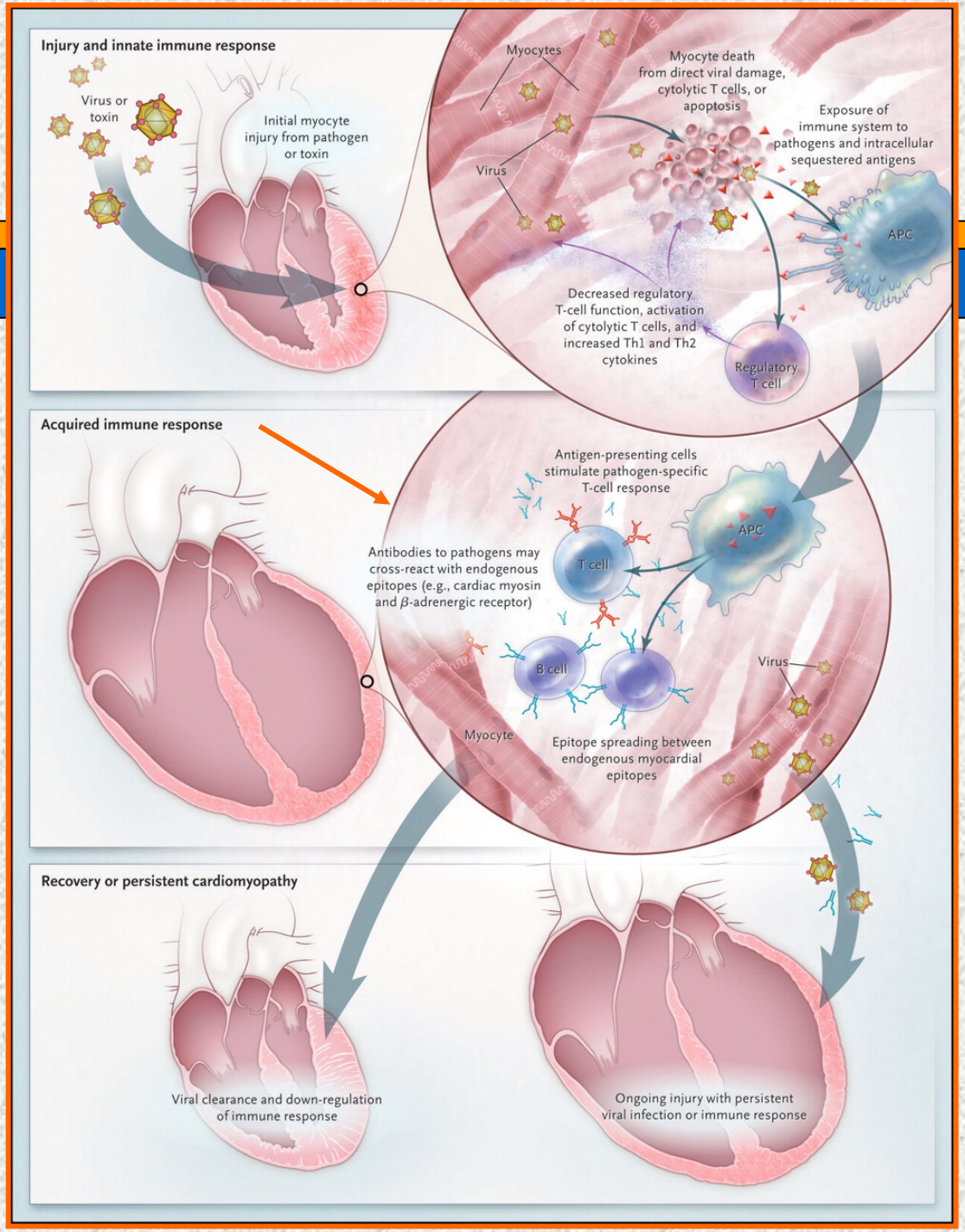
# Limitations and Failure of CMR

**...in the patient with borderline myocarditis cardiovascular magnetic resonance was not able to diagnose myocarditis due to low extent of inflammation...**

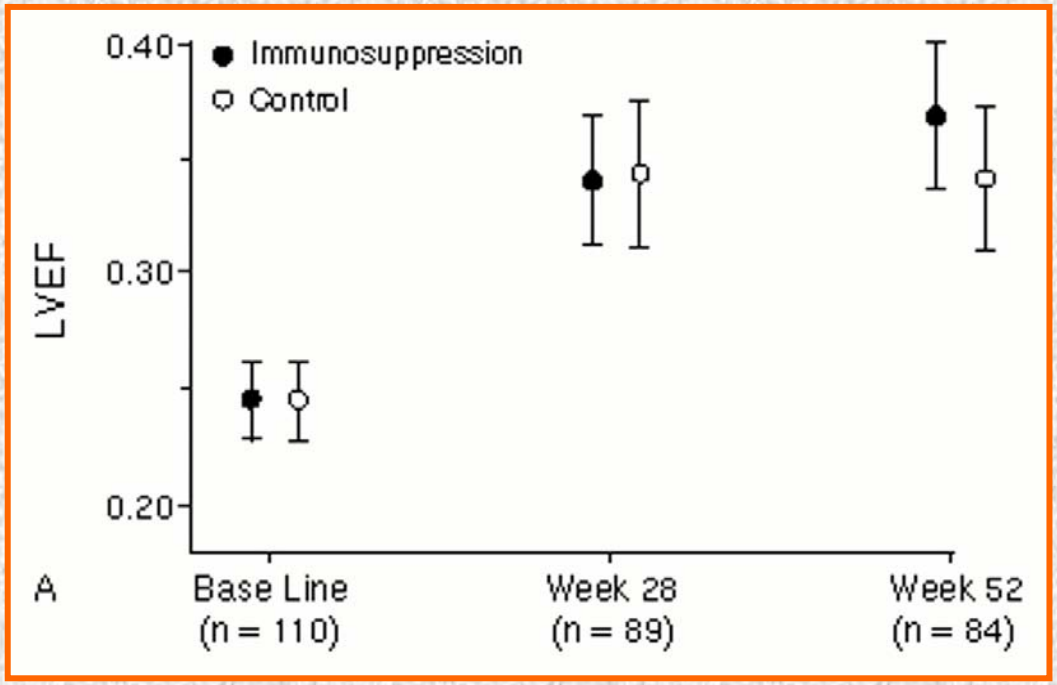


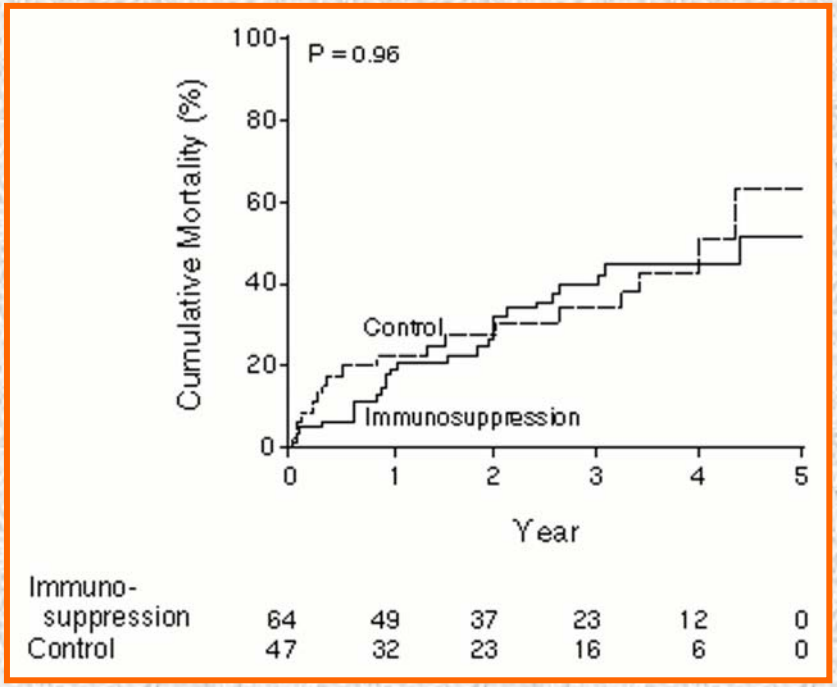
# Pathogenesis of Myocarditis

**The Progression from Acute Injury to Chronic Dilated Cardiomyopathy May Be Simplified into a Three-Stage Process**



# A Clinical Trial of Immunosuppressive Therapy for Myocarditis

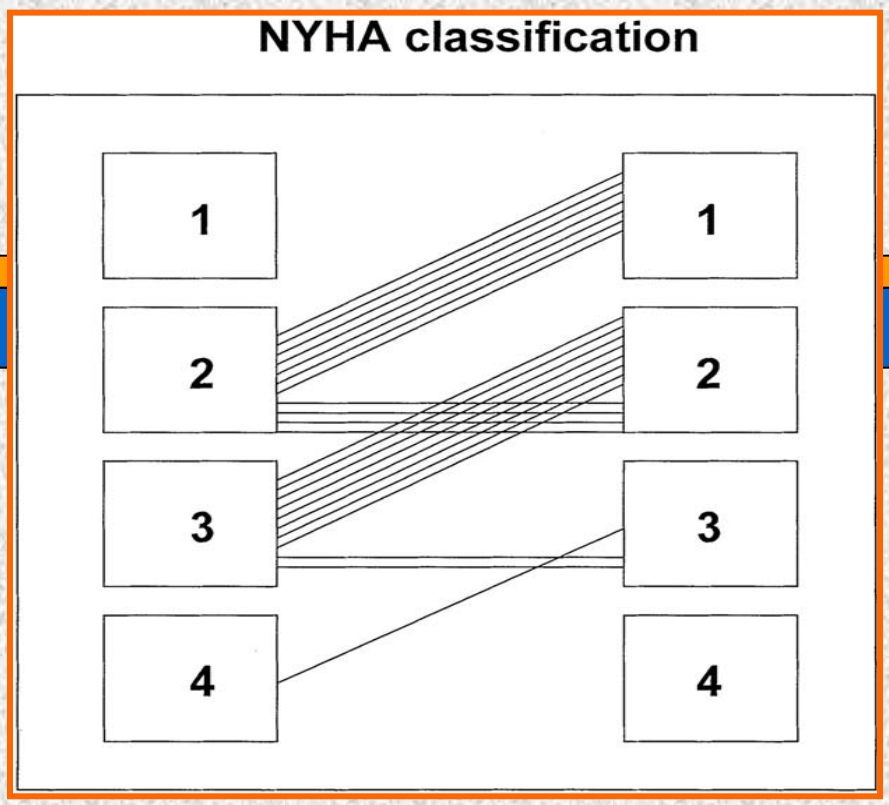


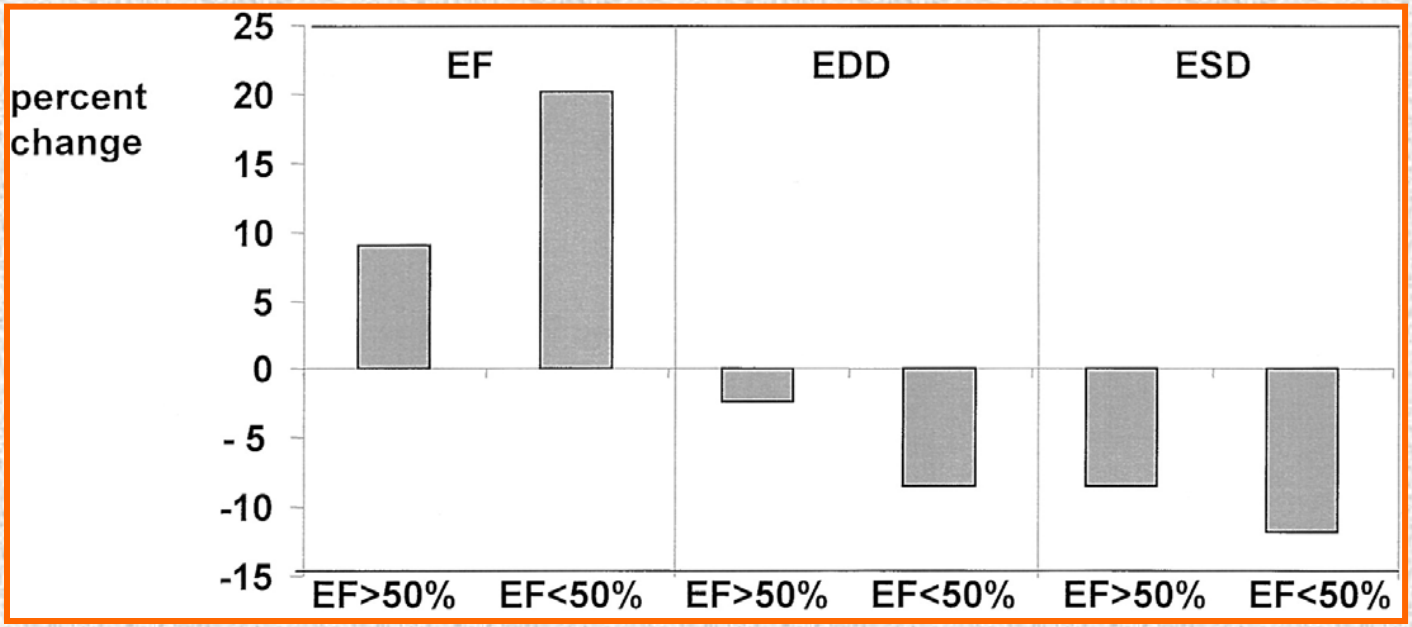




*J Mason et al, New Engl J Med 1995, August 3*
*for The Myocarditis Treatment Trial Investigators*

# Interferon-β Treatment Eliminates Cardiotropic Viruses and Improves LV Function in Patients with Myocardial Persistence of Viral Genomes and LV Dysfunction

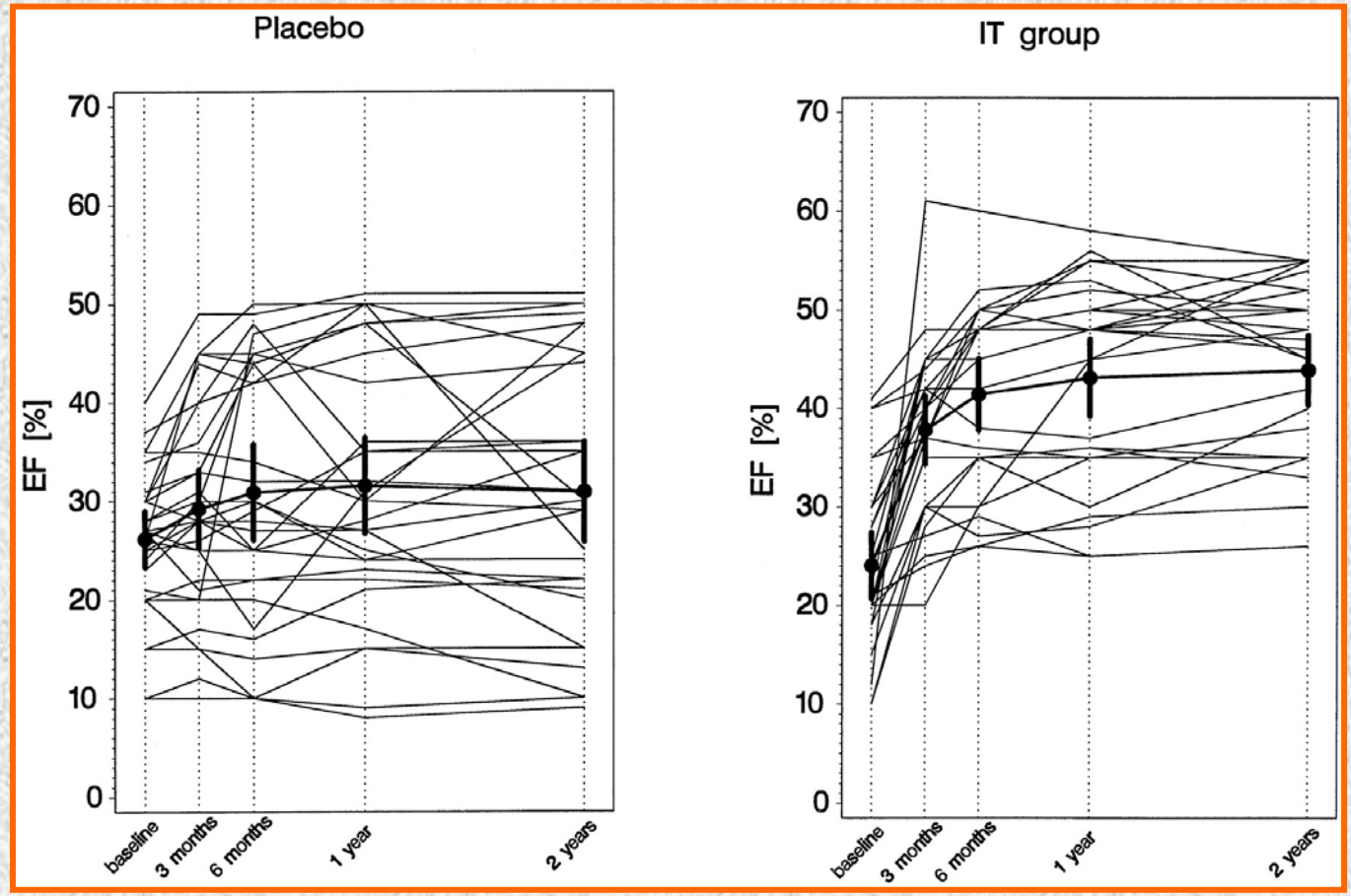
*U Kühl et al, Circulation 2003, June 10*



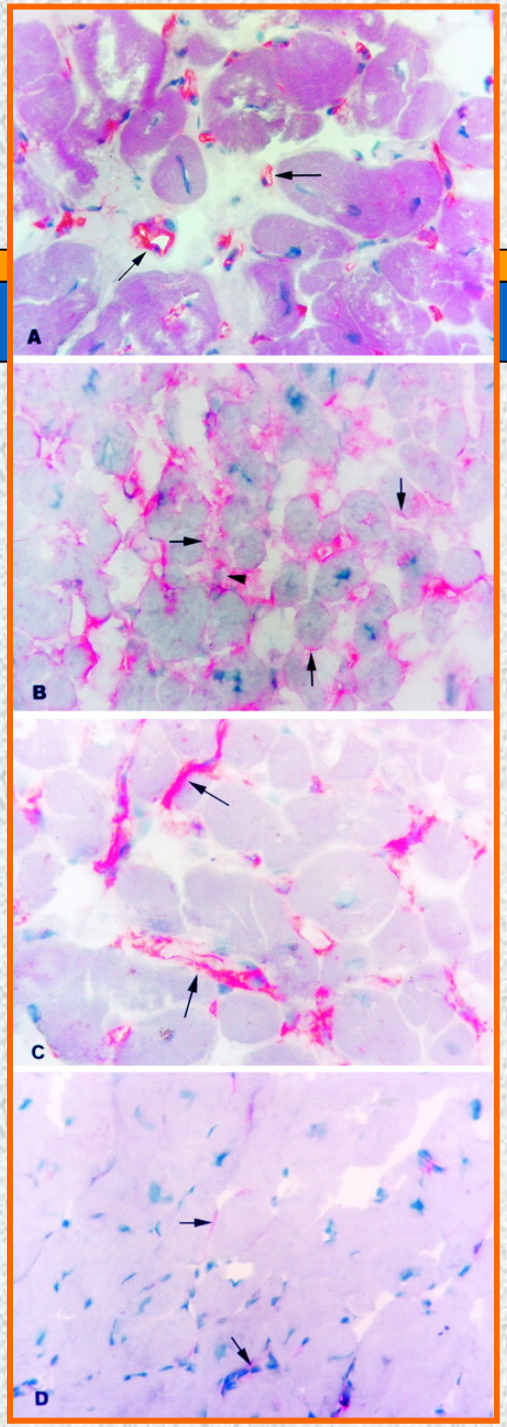



# Randomized, Placebo-Controlled Study for Immunosuppresive Treatment of Inflammatory Dilated Cardiomyopathy

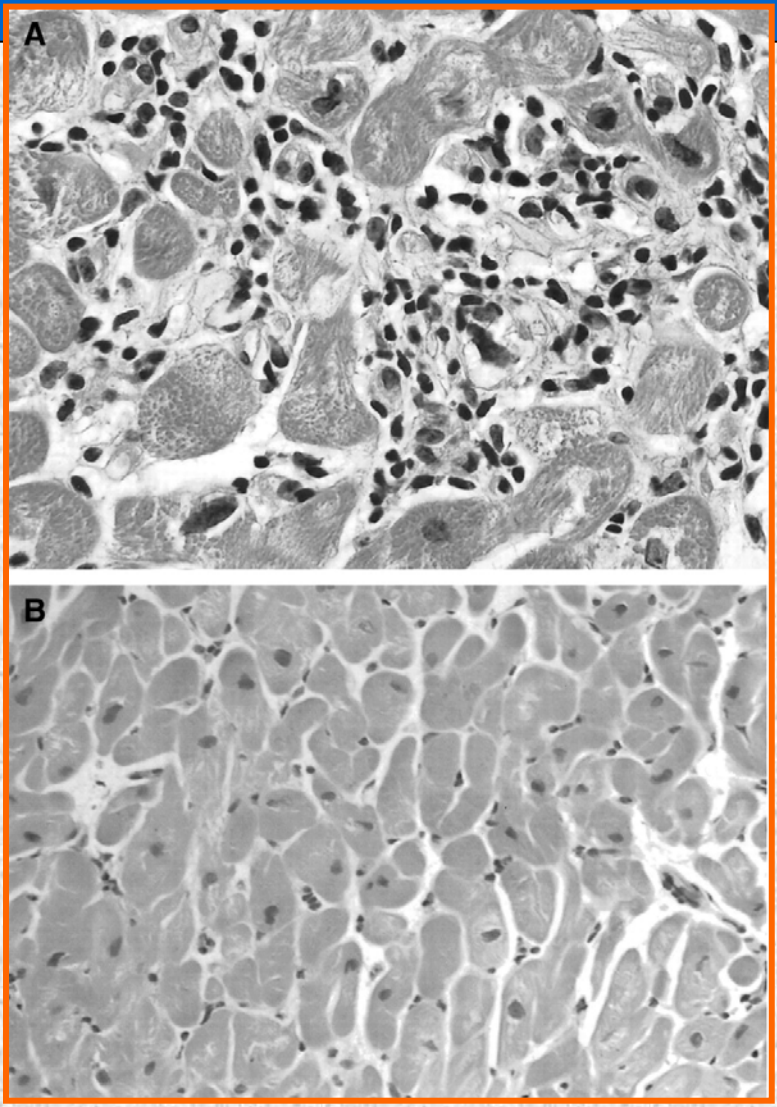
## Two-Year Follow-up Results




*R Wojnicz et al, Circulation 2001, July 3*

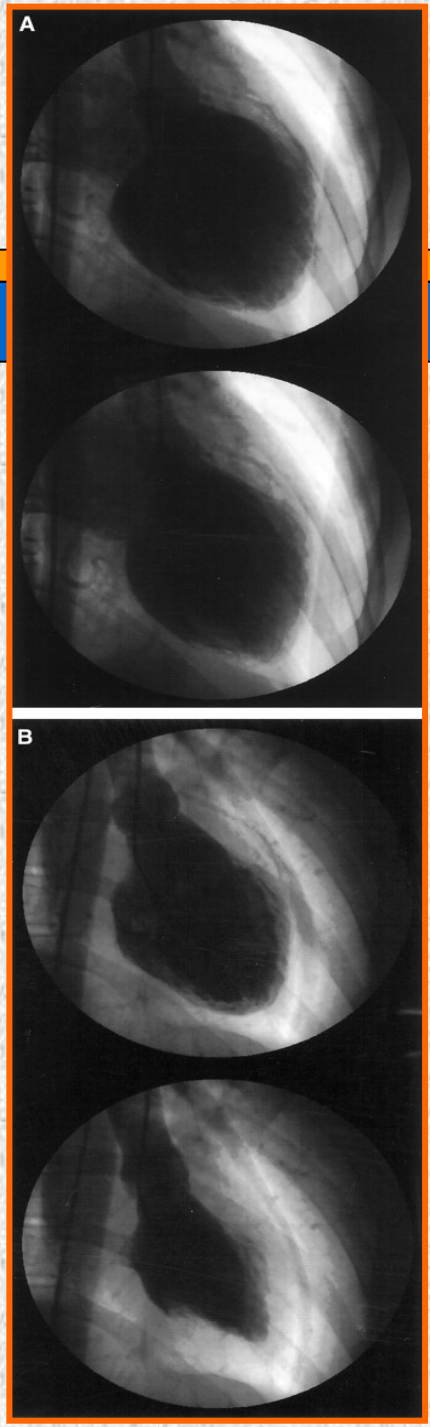


# Immunosuppressive Therapy for Active Lymphocytic Myocarditis



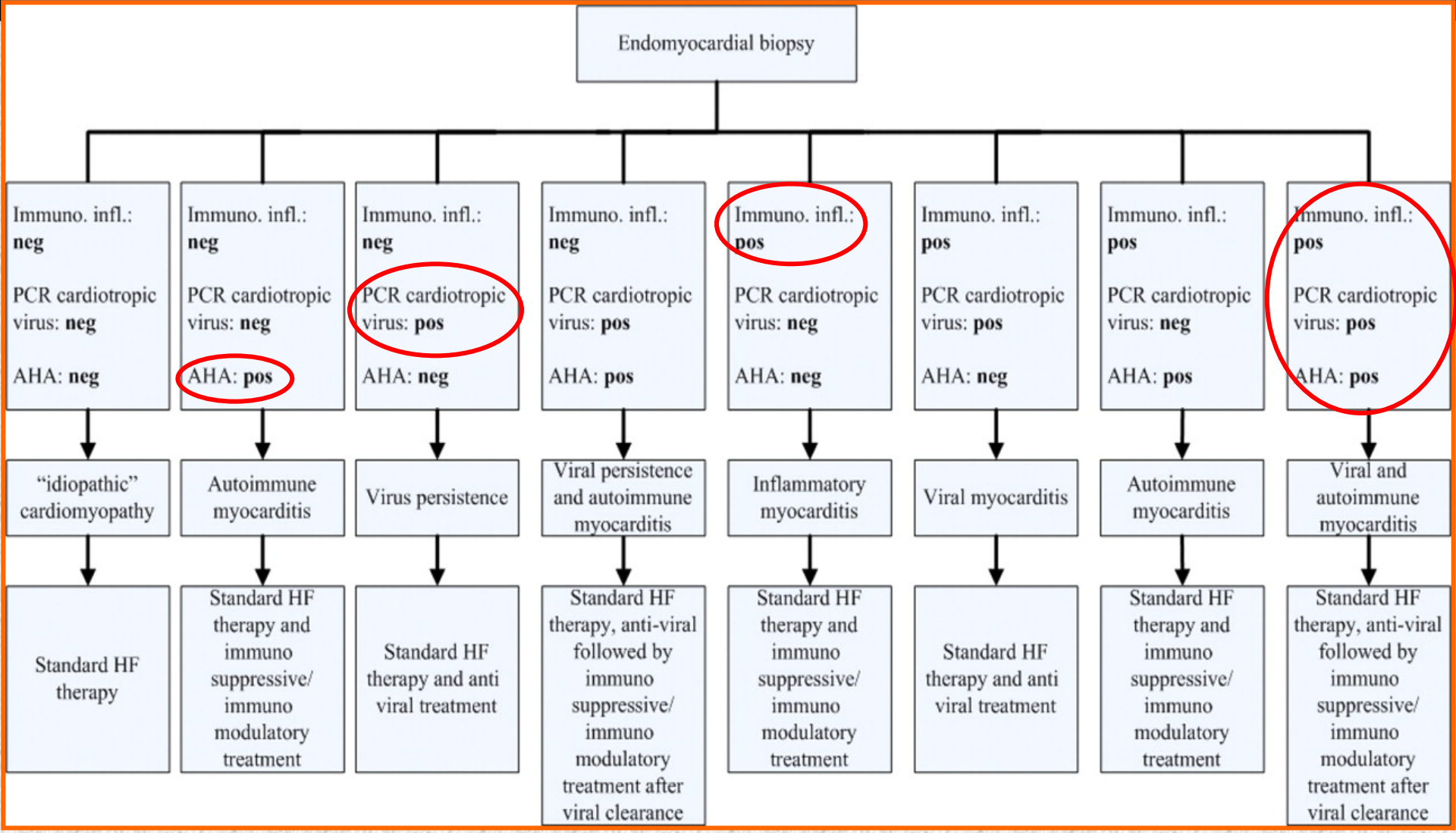

**Virological and Immunologic Profile of Responders vs Nonresponders**

*A Frustaci et al, Circulation 2003, February 18*



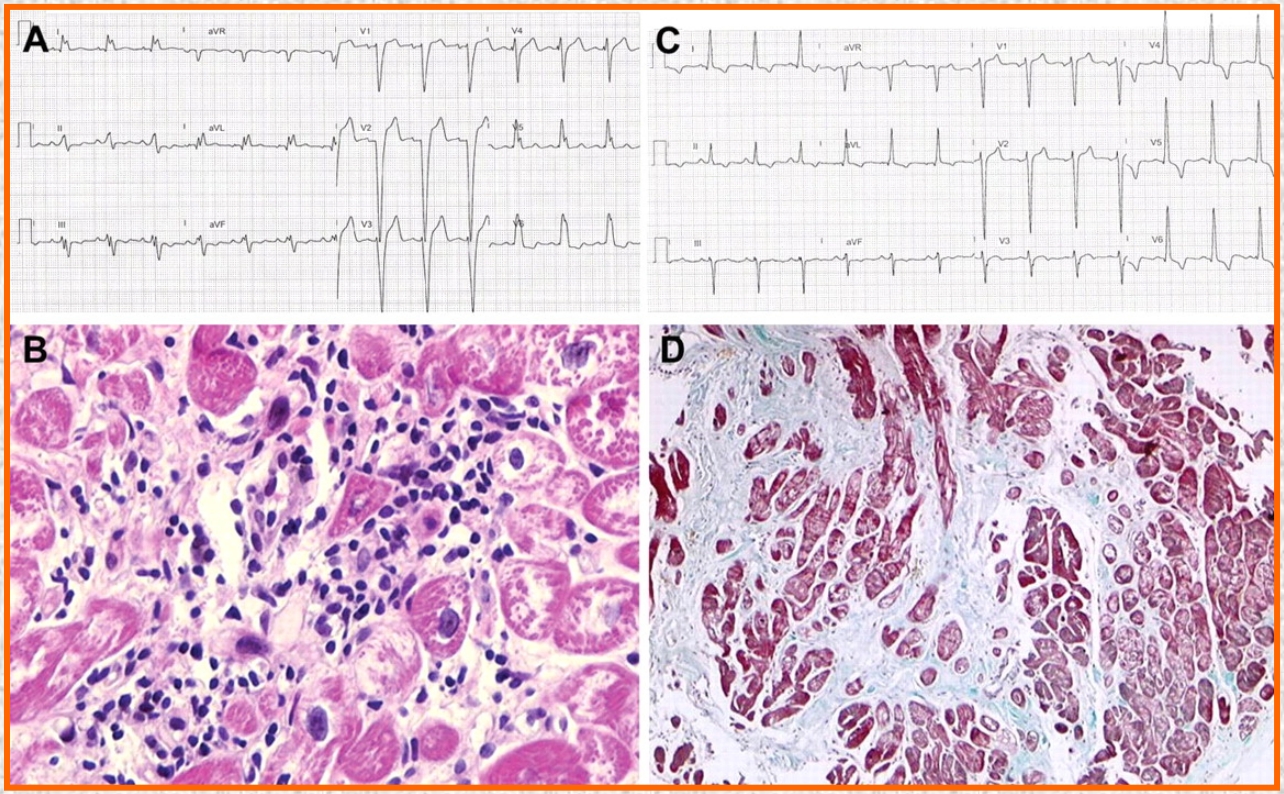
# Proposal of Treatment Algorithm Based on Endomyocardial Biopsy Results

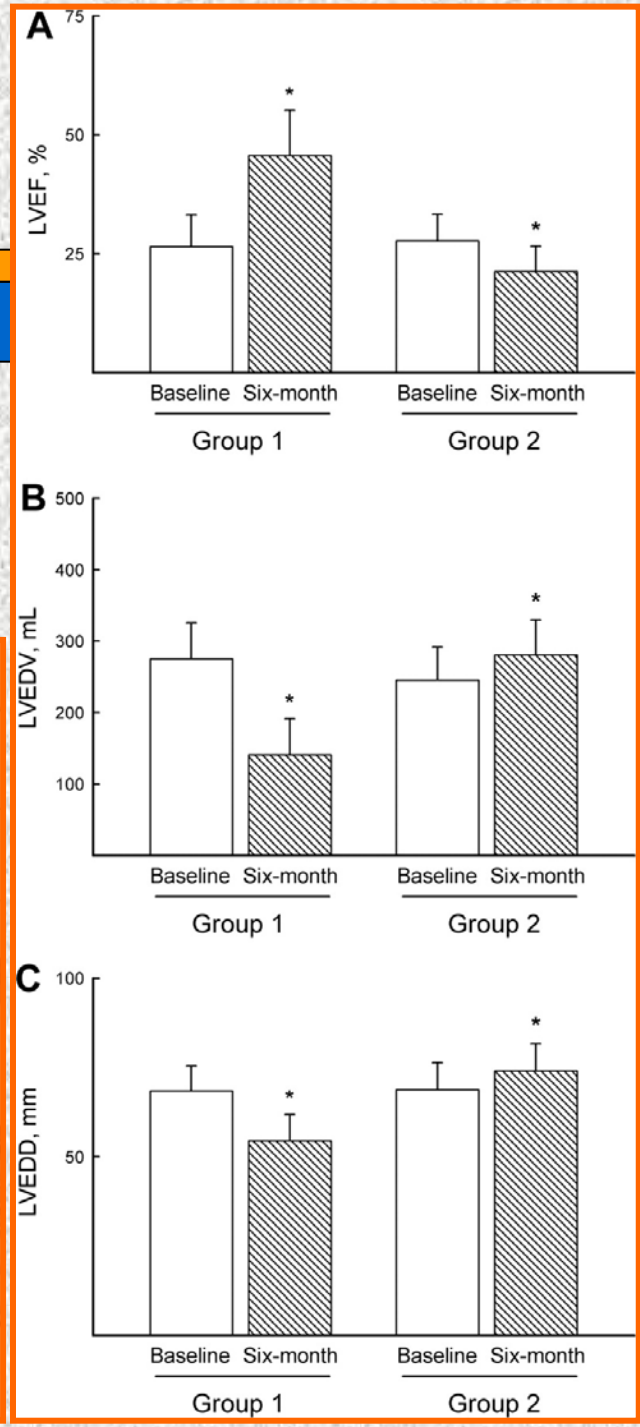
*R Dennert et al, Eur Heart J 2008, July 9*



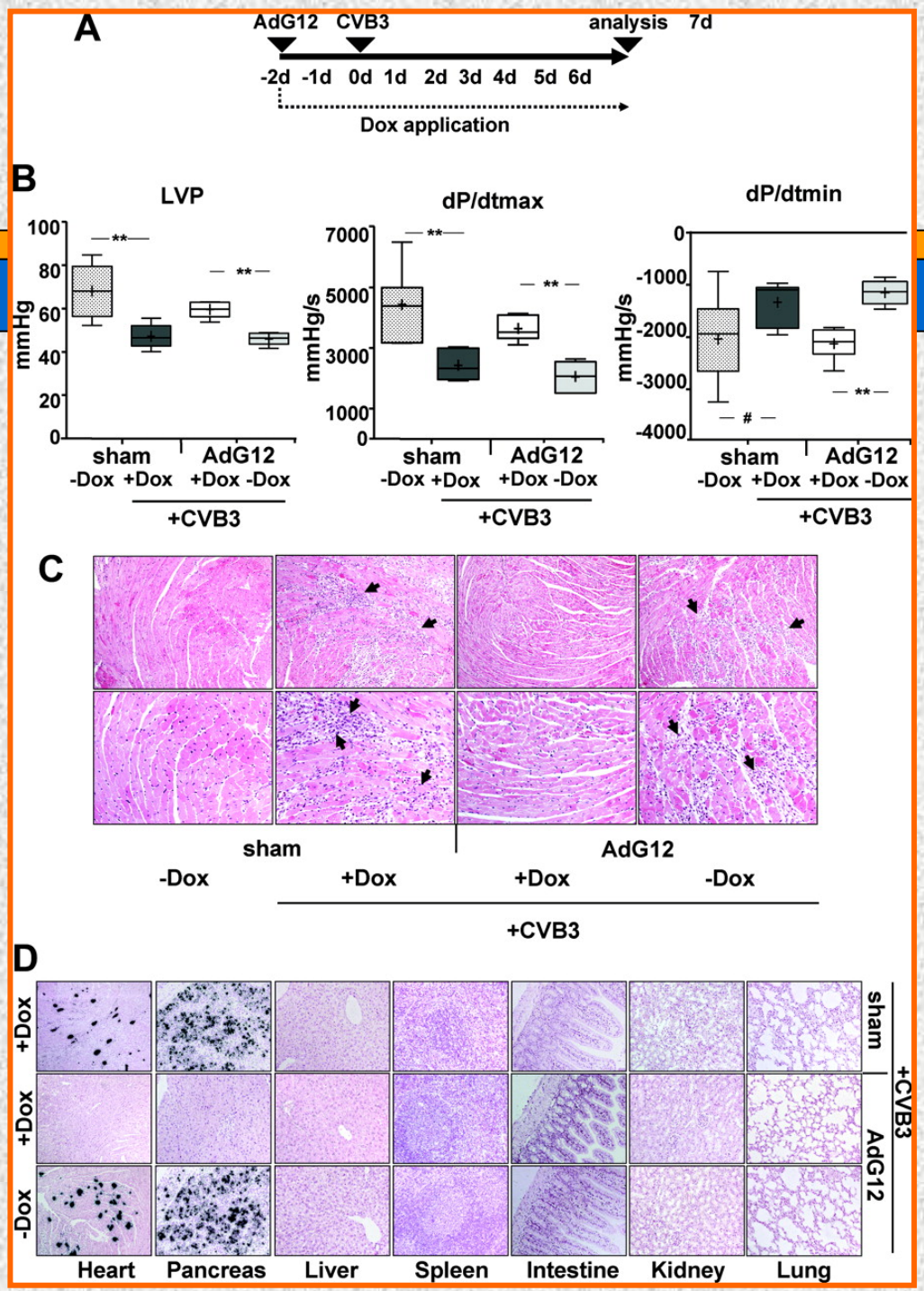
# Randomized Study on the Efficacy of Immunosuppressive Therapy in Patients with Virus-Negative Inflammatory Cardiomyopathy: the TIMIC Study

*Frustaci A et al, Eur Heart J 2009, August*



# Prevention of Cardiac Dysfunction in Acute Coxsackievirus B3 Cardiomyopathy by Inducible Expression of a Soluble Coxsackievirus-Adenovirus Receptor




*S Pinkert et al,*
*Circulation 2009, December 8*

# Myocarditis and Heart Failure

## Need for Better Diagnostic, Predictive and Therapeutic Tools

**"…A combined effort of clinicians, pathologists and immunologists must contribute to the development of new criteria of myocarditis, which should include clinical presentation, auto-antibodies, imaging and cardiac biopsies for detailed study of *inflammation*, *auto-immunity* and *virus presence*. These new criteria to be developed will help to better classify, treat and predict the prognosis of a given patient with myocarditis…"**

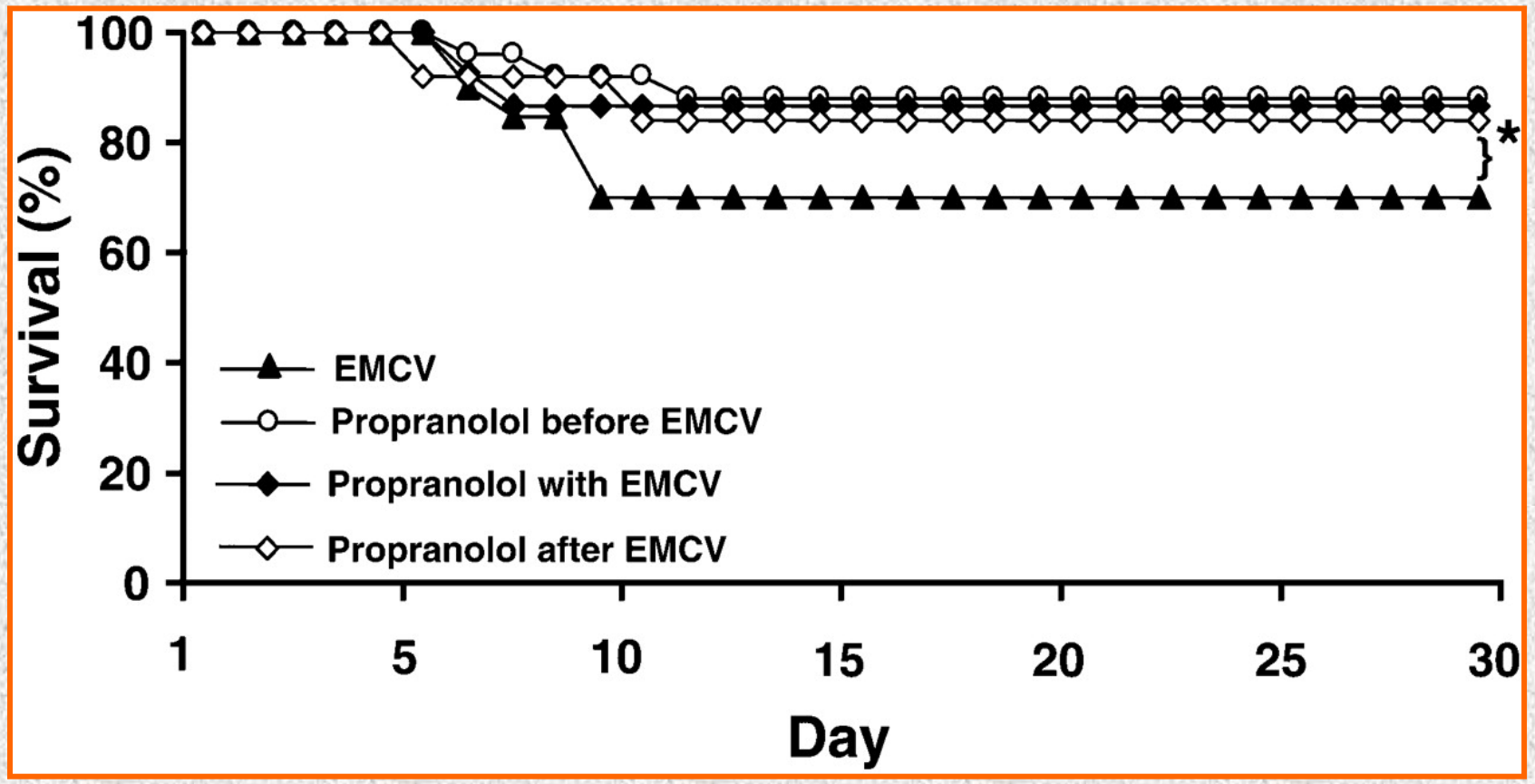
***S Heymans, Eur Heart Journal 2007, June - Editorial***

### The heat is off: immunosuppression for myocarditis revisited

**"…If the results of Frustaci and colleagues are replicated in a larger, multicentre designed trial with clinical endpoints such as death and heart transplantation, the class I indications for heart biopsy will expand to a much larger population…"**

***Leslie T. Cooper, Eur Heart J 2009, August - Editorial***

# Propranolol Ameliorates and Epinephrine Exacerbates Progression of Acute and Chronic Viral Myocarditis



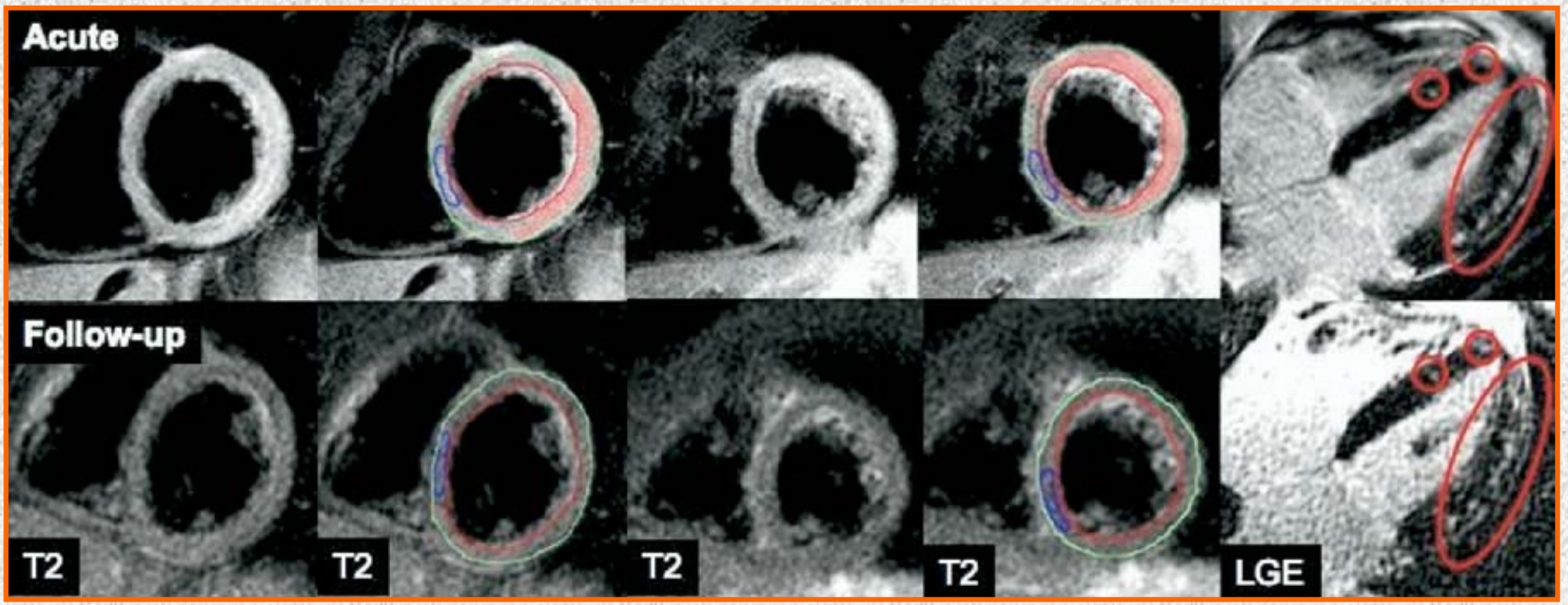

*Ju-Feng Wang et al, Am J Physiol 2005, May 27*

# Indications for Cardiovascular Magnetic Resonance in Patients With Suspected Myocarditis

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

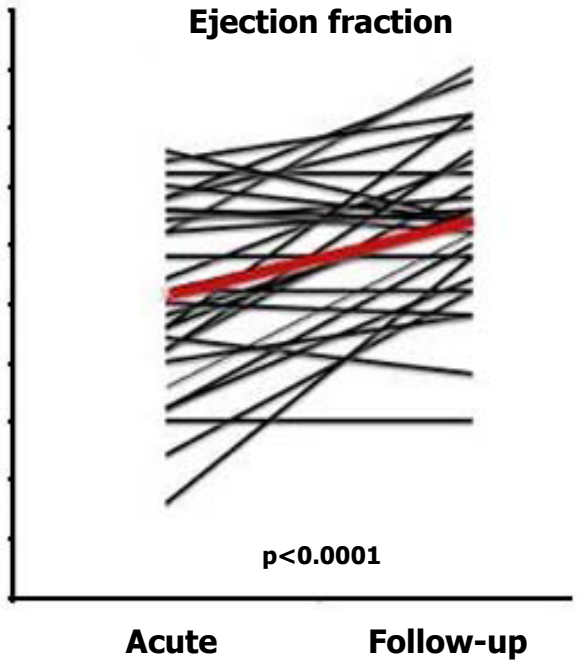
*MG Friedrich et al,*
*J Am Coll Cardiol 2009, April 28*

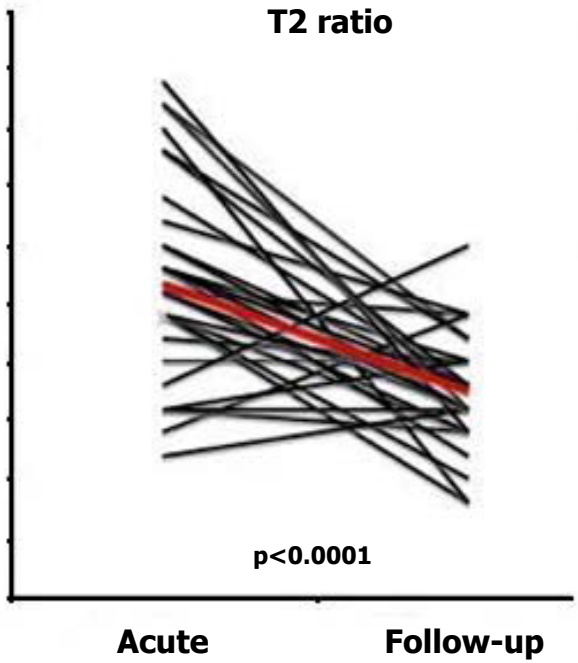
# Cardiac Magnetic Resonance Monitors Reversible and Irreversible Myocardial Injury in Myocarditis

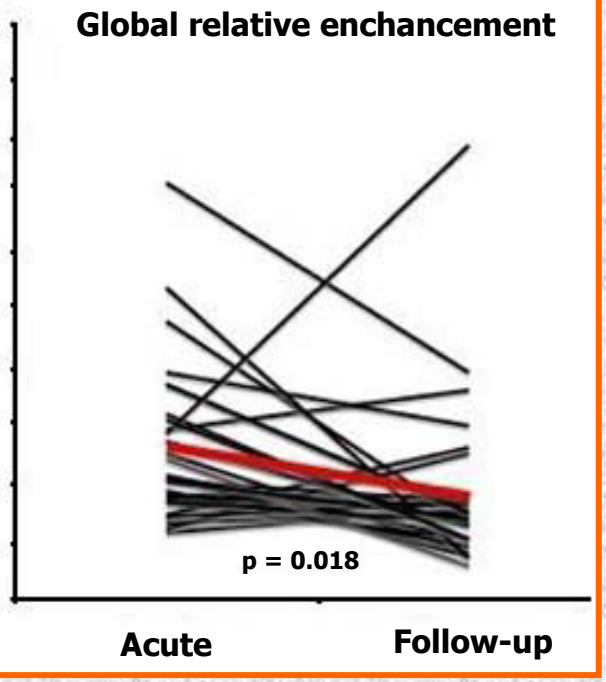



*A Zagrosek et al, JACC Cardiovascular Imaging 2009, February*

# Concordant Normalization of LV Global Function and Tissue Parameters of Acute Myocardial Injury in Myocarditis




*A Zagrosek et al, JACC Cardiovascular Imaging 2009, February*

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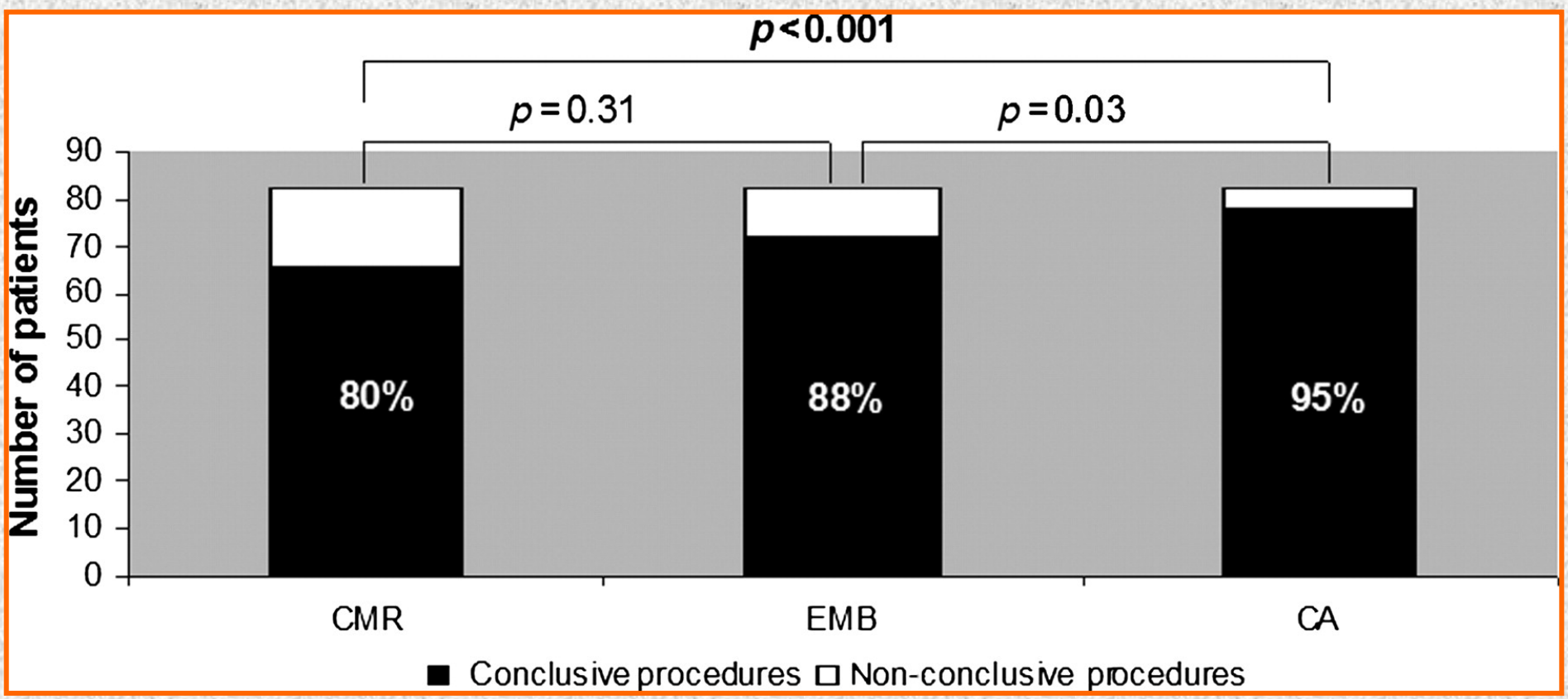
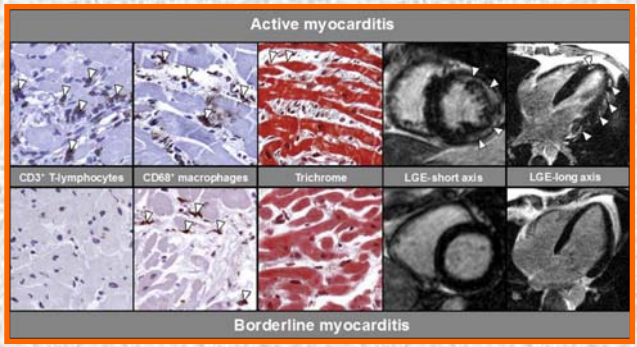



*H Baccouche et al, Eur Heart J 2009, August 20*

# Conclusions

## Diagnostic synergy of non-invasive cardiovascular magnetic resonance and invasive endomyocardial biopsy




i) **EMB is superior to LGE-CMR in diagnosing myocarditis because of its ability to capture minor forms of myocarditis**

ii) **The value of LGE in the CMR-based diagnosis of myocarditis is related to the histological degree and extent of inflammation as detected on EMB**

iii) **The degree of *sampling error* depends on**
**(a) the number of biopsies taken per patient and**
**(b) the methods applied for *ex vivo* analysis**

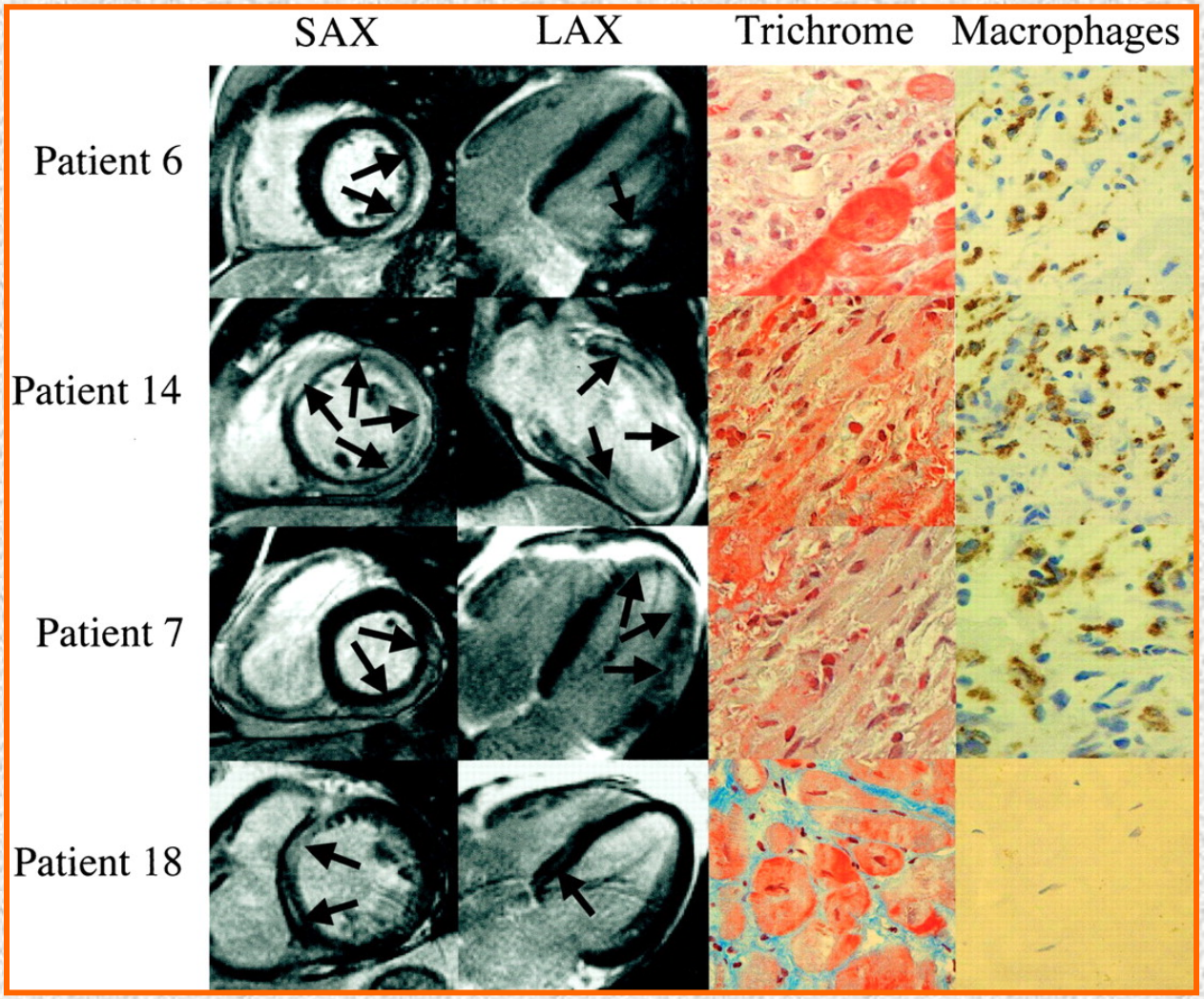
iv) **The combined approach seems superior to each single technique and can overcome some of the well-known limitations of CMR and EMB as individually applied techniques**

v) **The use of CMR only to establish the diagnosis of myocarditis will result in less detailed information about the degree of inflammation, the presence of special forms of myocarditis (such as *giant cell or eosinophilic myocarditis*), or the presence and type of *virus***

# Cardiovascular MRI Assessment of Human Myocarditis

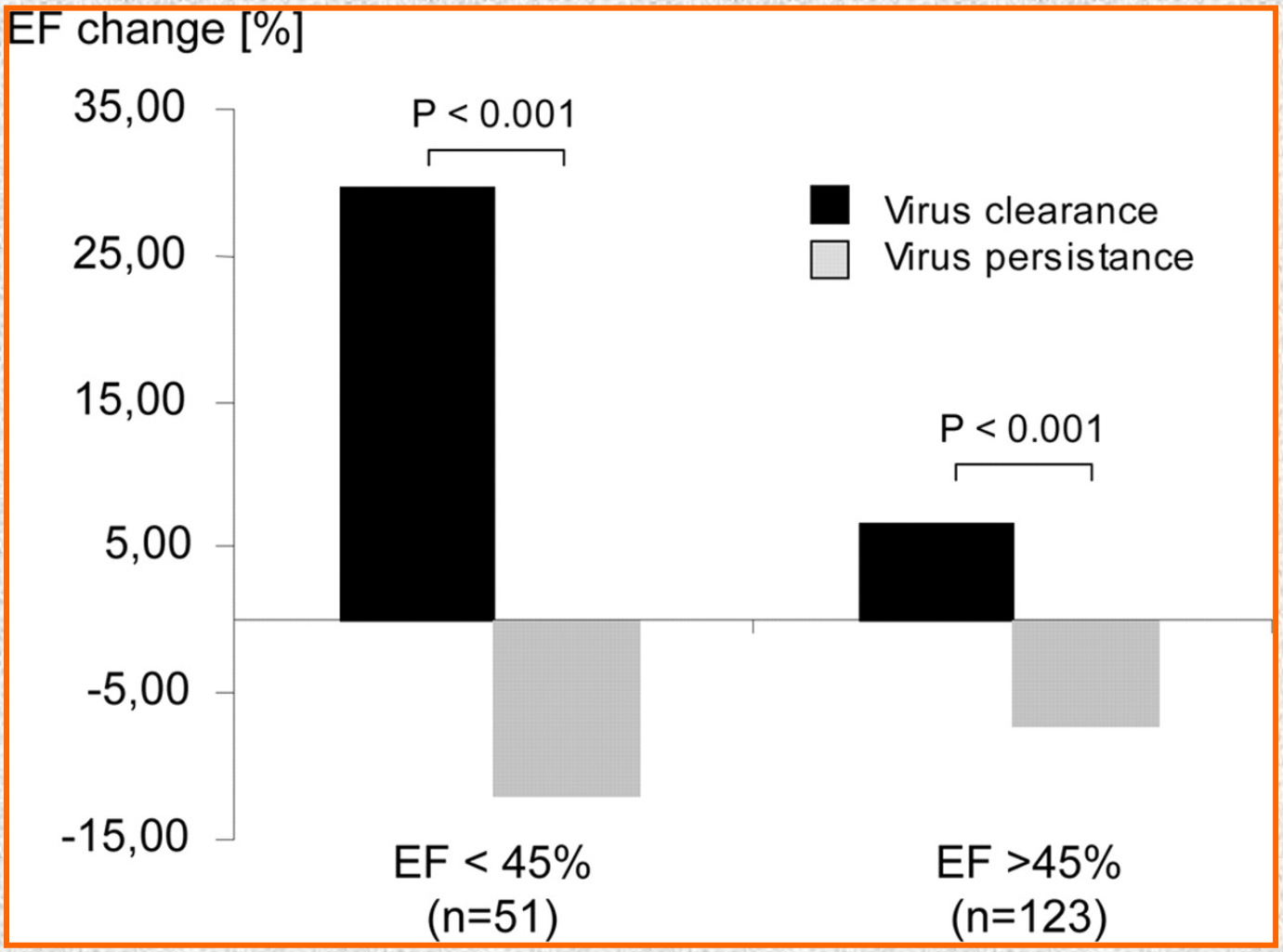
## A Comparison to Histology and Molecular Pathology

*H Mahrholdt et al, Circulation 2004;109:1250-1258*



# Viral Persistence in the Myocardium is Associated with Progressive Cardiac Dysfunction

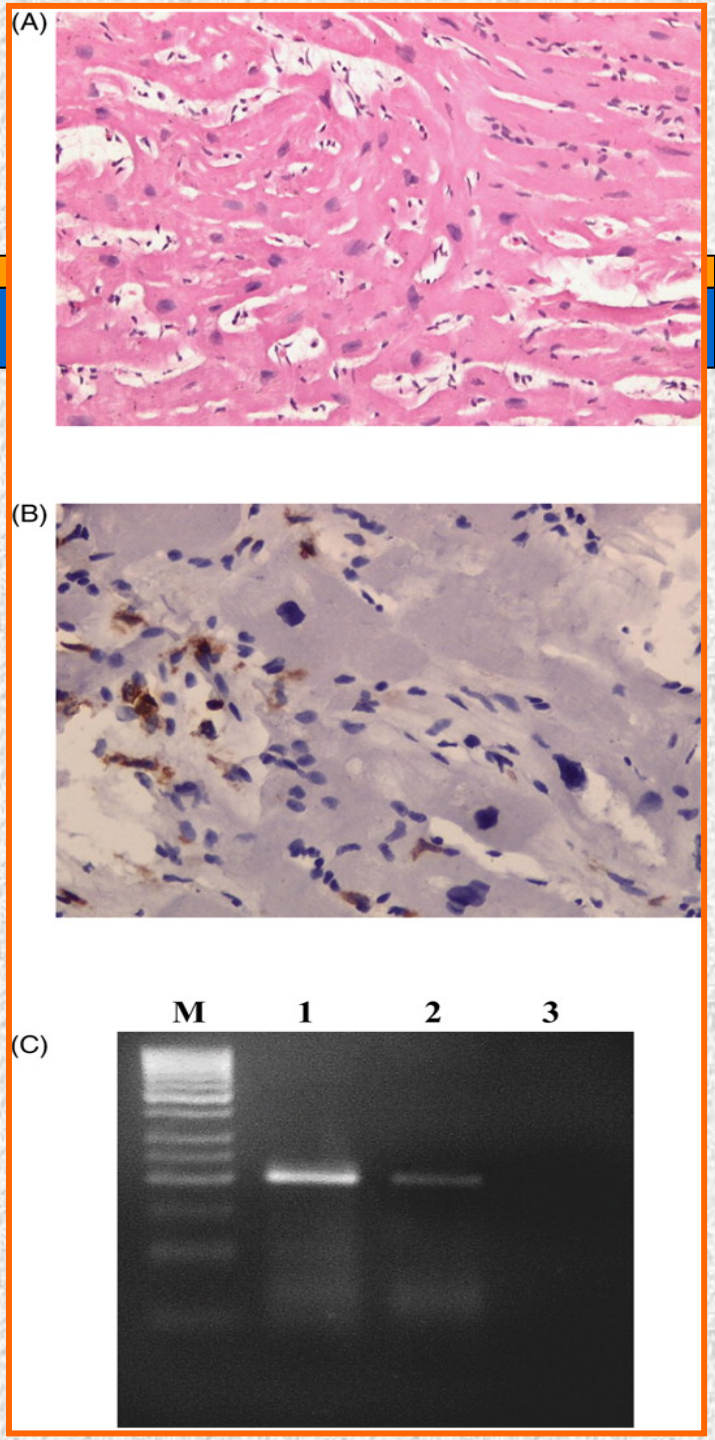
*U Kühl et la, Circulation 2005;112:1965-1970*



# Myocarditis in Hypertrophic Cardiomyopathy Patients Presenting Acute Clinical Deterioration

**Recognition can potentially affect disease prognosis and treatment**

*A Frustaci et al,*
*Eur Heart J 2007;28:733-740*



# Εμφάνιση Νόσου

- **27 ετών Ιταλός**
  Αμυγδαλίτιδα σε αποδρομή (αντιβίωση)
- **Νοσοκομείο Κερκύρας**
  προκάρδιο άλγος, ↑ ST-T $V_2$-$V_6$
  θετική ενζυμική κίνηση, περικαρδιακή συλλογή και LVEF:25%
- **Διακομιδή Νοσοκομείο Ιωαννίνων**
  Αιμοδυναμικά ασταθής, χορήγηση ινοτρόπων (Dopamine –Dobutamine )
  → διακομιδή ΩΚΚ
- **Εργαστηριακός Έλεγχος**
  WBC: 27.400, CRP:559, CPK:1083, CPK-MB:69, RCTNI :11
  **Υποπληθυσμοί Λεμφοκυττάρων**
  **$CD_3$: 796 (960-2570) - $CD_4$: 541 (544-1660) - $CD_8$: 260 (350-900)**
  **$CD_4/CD_8$: 2,1 (0.93-3,50) - $CD_{19}$: 147 (122-350)**
  **NK: 49 (250-650)**
- **CxR: εικόνα πνευμονικού οιδήματος (συμφόρηση)**
- **Echo: LV: 62/44, LVEF:25%, MR:$2^+/4^+$, Διάχυτη υποκινησία**

# Πορεία Νόσου

- ✓ **Αιμοδυναμικός έλεγχος**
  **CAA, Δεξιός καθετηριασμός + βιοψία**
  **PA: 46/29/38, PCWP: 38/37/35**
  **LVEF:25%, MR:$2^{+}/4^{+}$**
- ✓ **PCR σε μυοκαρδιακό ιστό και αίμα**
  **CMV (+)**
  **CMV Copies : 4809/ml αίματος ή 601 copies/$10^{6}$ WBC**
- ✓ **Θεραπεία**
  **Valgancyclovir 900 mg**
  **↑LVEF: 45%**
  **Αφαίρεση IABP, ↓CMV copies (327 copies/ml αίματος ή 45 copies/$10^{6}$ WBC)**
- ✓ **Νοσηλεία 15 ημερών**
- ✓ **LVEF (εξόδου): 60%**

# Clinical Scenario 12

**AHA/ACC/ESC scientific statement, Eur Heart Journal 2007, October 24**

- ✓ **EMB may be considered in the setting of suspected ARVD/C**

***Class of Recommendation IIb, Level of Evidence C***

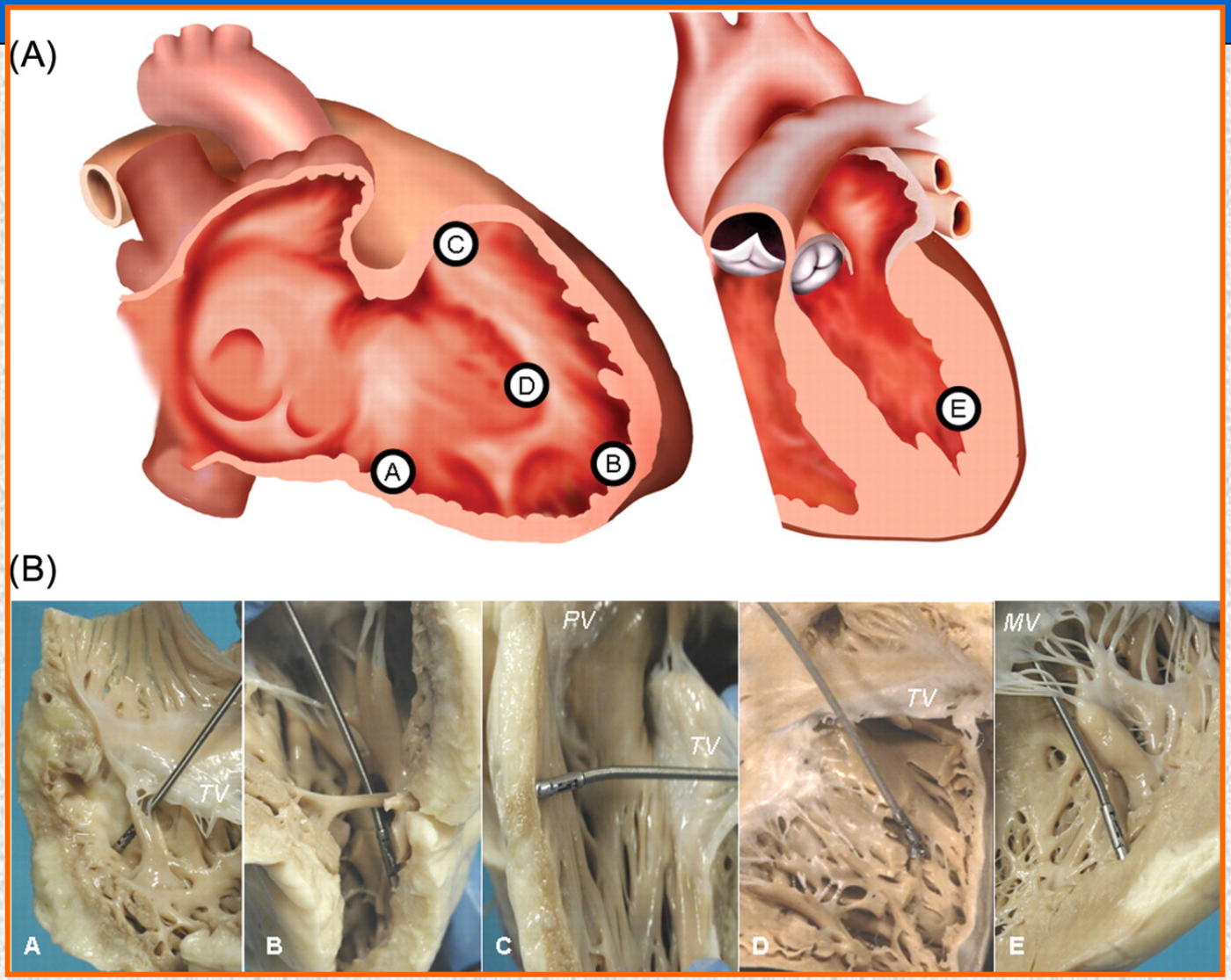
# Clinical Scenario 6

**AHA/ACC/ESC scientific statement, Eur Heart Journal 2007, October 24**

- ✓ **EMB is reasonable in the setting of heart failure associated with unexplained restrictive cardiomyopathy**

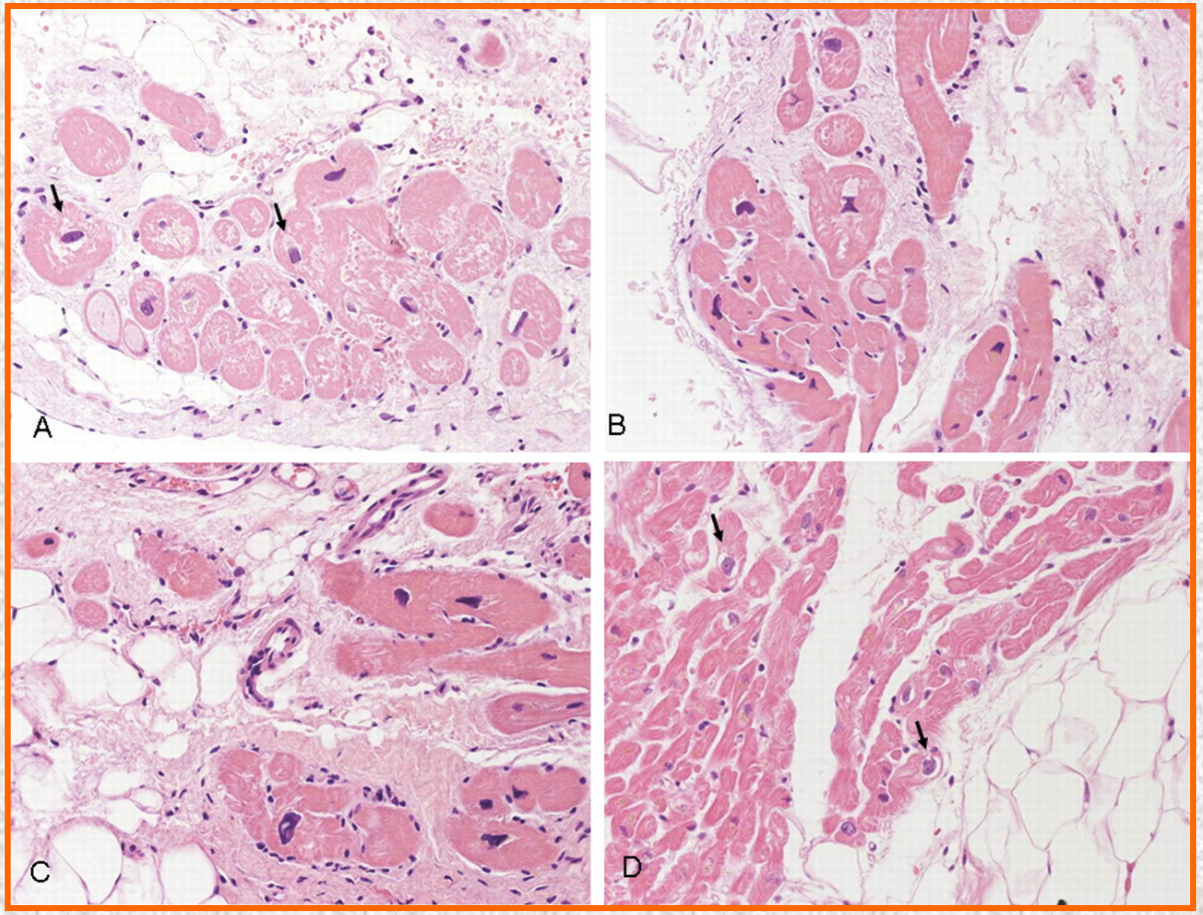
***Class of Recommendation IIa, Level of Evidence C***

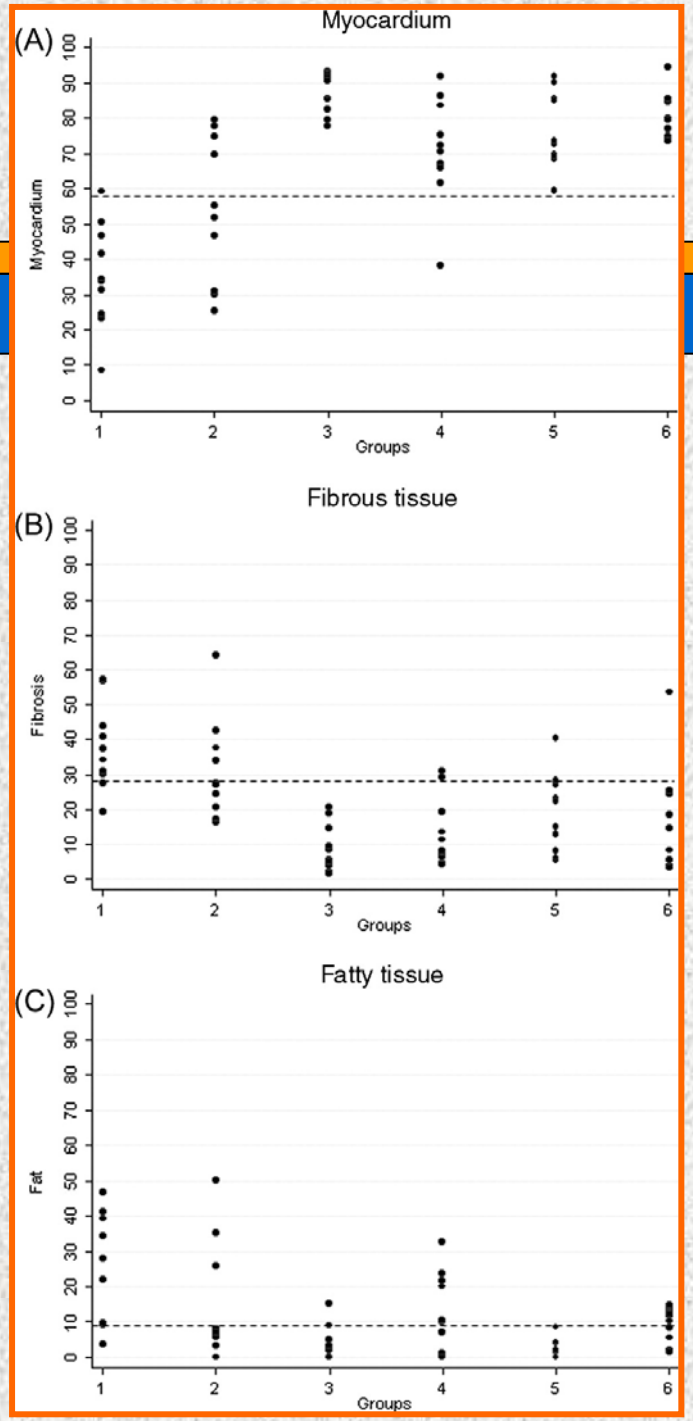
# Quantitative Assessment of Endomyocardial biopsy in Arrhythmogenic Right Ventricular Cardiomyopathy/ Dysplasia: an *in Vitro* Validation of Diagnostic Criteria




*C Basso et al, Eur Heart J 2008, September 26*

# Quantitative Assessment of EMB in ARVC/D: an *in Vitro* Validation of Diagnostic Criteria

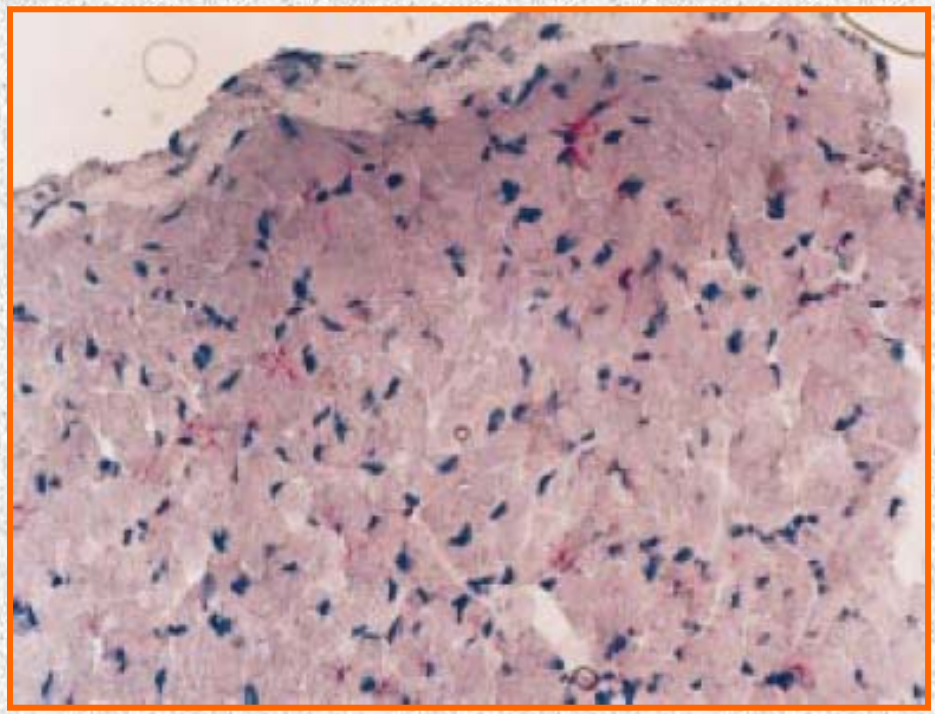


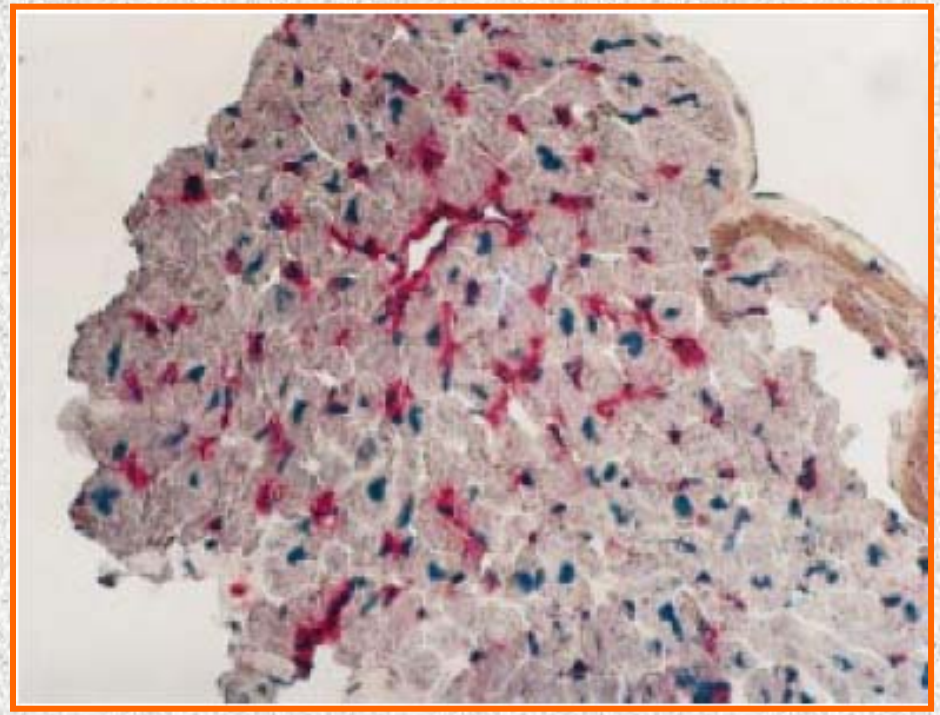




*C Basso et al, Eur Heart J 2008, September 26*

# Immunohistological Diagnosis of Myocarditis

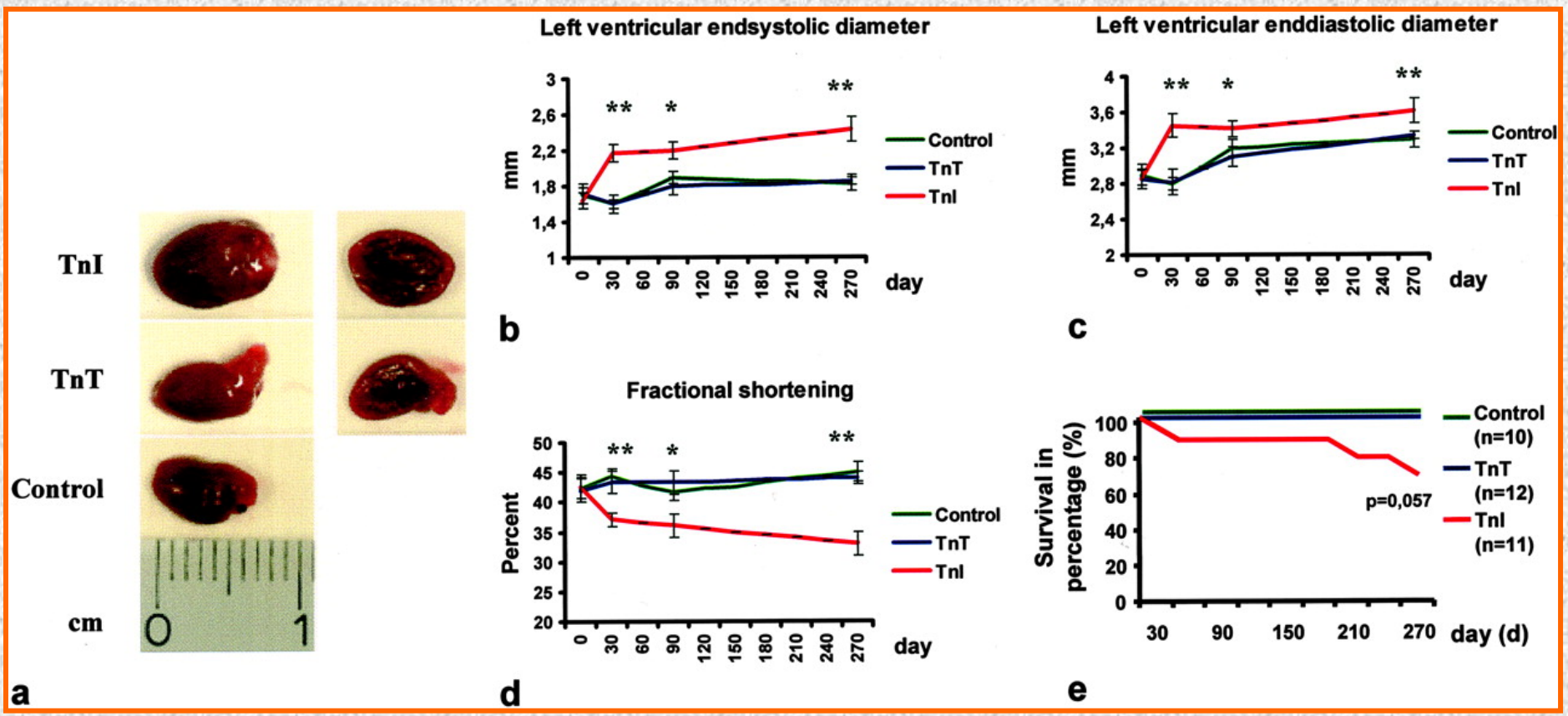
## Potential Role of Sarcolemmal Induction of the MCH and ICAM-1 in the Detection of Autoimmune Mediated Myocyte Injury





*R Wojnicz et al, Eur Heart Journal 1998;19:1564-1572*

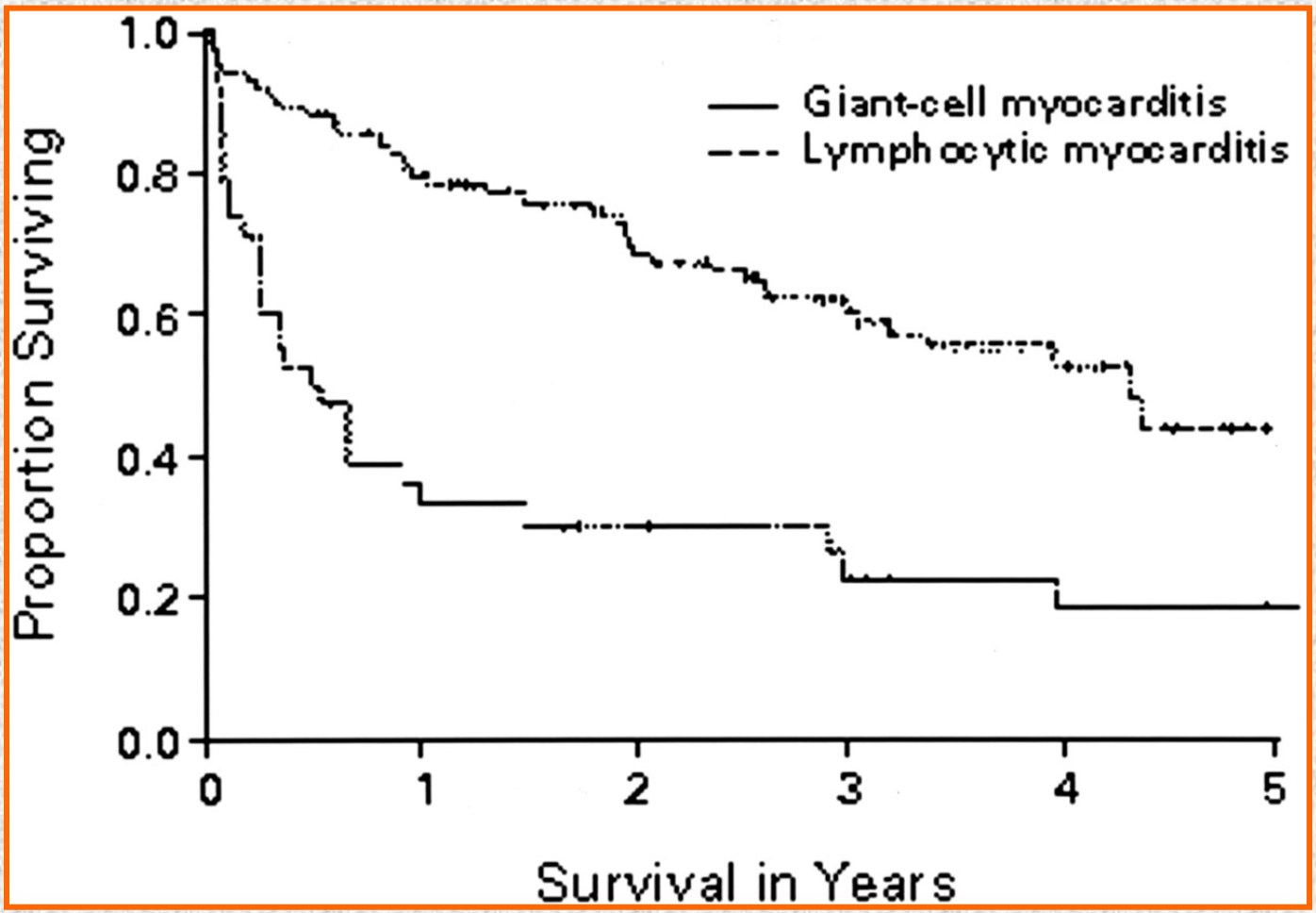
# Cardiac Troponin I but not Cardiac Troponin T Induces Severe Autoimmune Inflammation in the Myocardium




*S Göser et al, Circulation 2006;114:1693-1702*

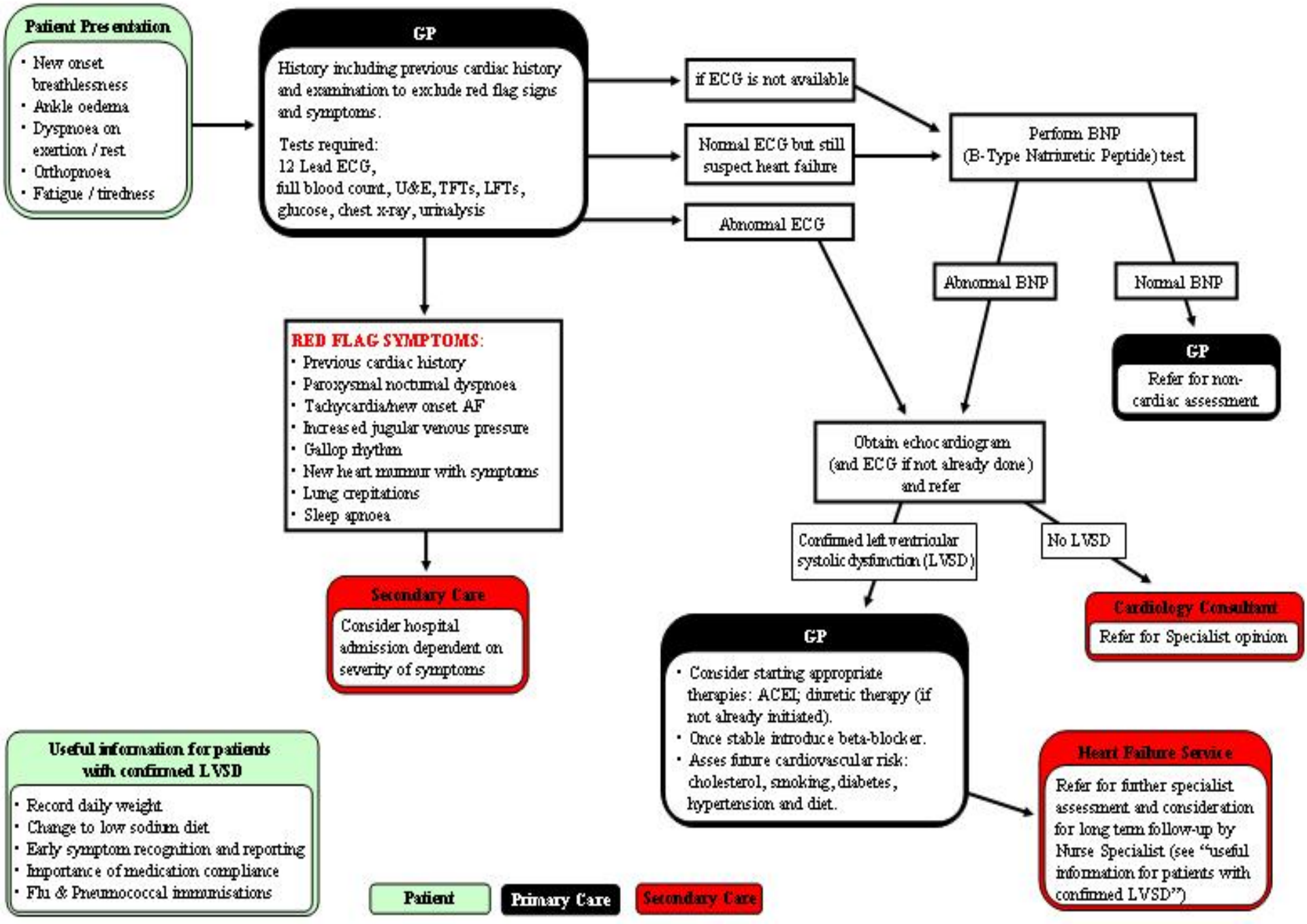
# Myocarditis

## Current Trends in Diagnosis and Treatment




*JW Magnani and GW Dec. Circulation 2006, February 14*

# Cardiology – Suspected NEW Heart Failure



# Criteria for Diagnosis of Heart Failure

| ***HISTORY*** | ***Points*** |
|---|---|
| rest dyspnea | 4 |
| orthopnea | 4 |
| PND | 3 |
| dyspnea walking on level | 2 |
| dyspnea on climbing | 1 |

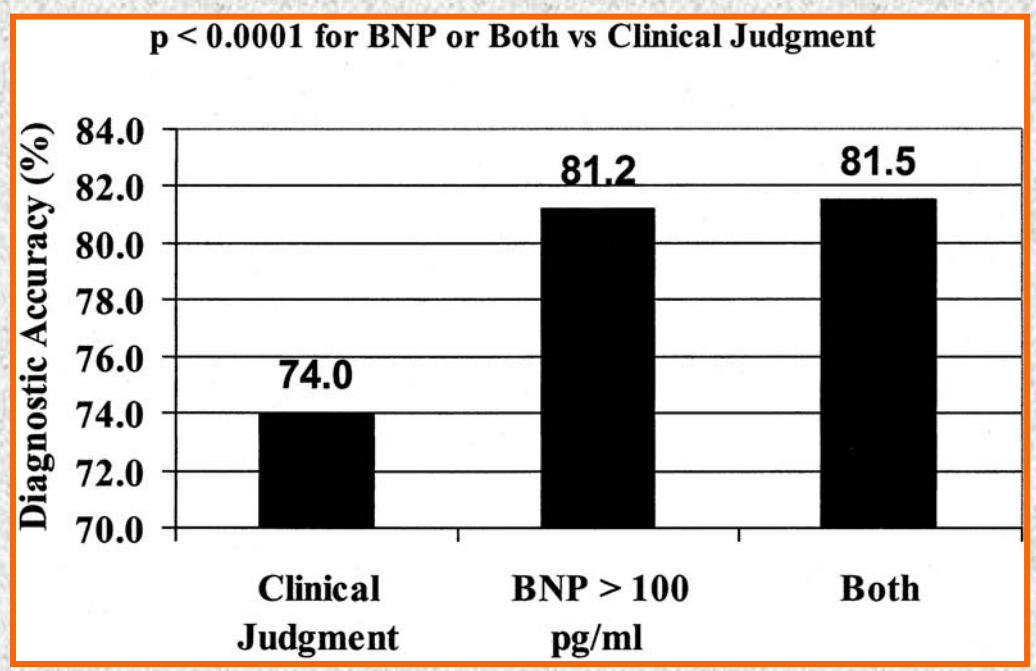
| ***CHEST X-Ray*** | |
|---|---|
| alveolar pulmonary edema | 4 |
| interstitial pulmonary edema | 3 |
| bilateral pleural effusion | 3 |
| CT ratio > 0.50 | 3 |
| flow redistribution | 2 |

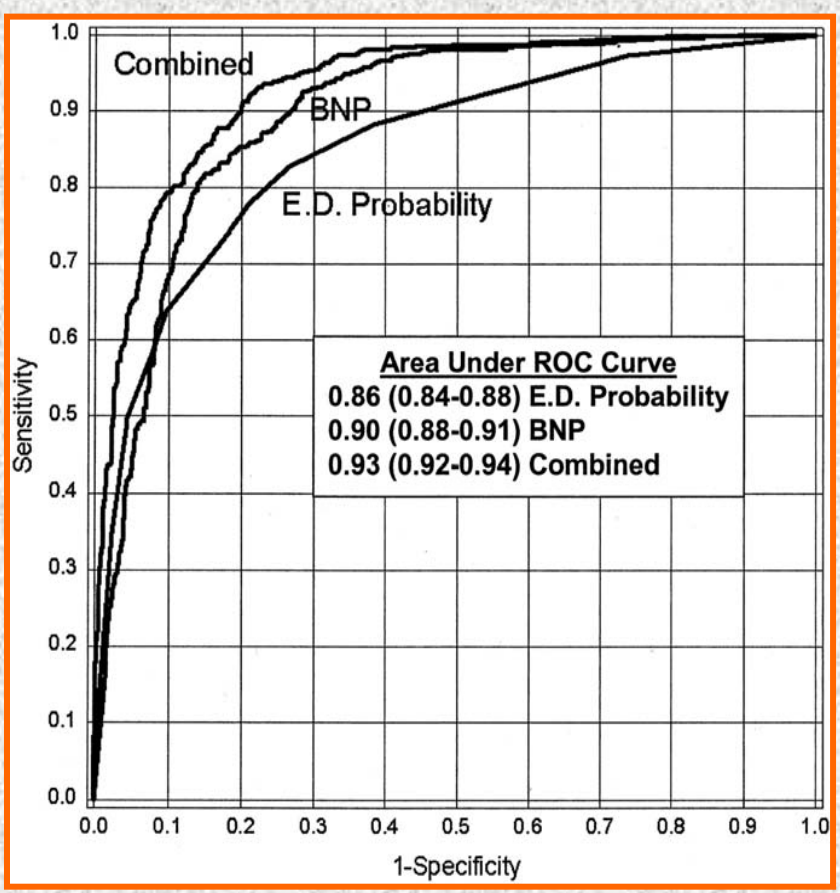
| ***PHYSICAL*** | ***Points*** |
|---|---|
| HR 91-110 | 1 |
| HR > 110 | 2 |
| JVP > 6 cm | 2 |
| JVP > 6 cm & hepatomeg | 3 |
| lung crackles in base | 1 |
| lung crackles above base | 2 |
| wheezing | 3 |
| S3 | 3 |

**8-12 points - definite CHF**
**5-7 points - possible CHF**
**< 5 points - unlikely CHF**

# B-Type Natriuretic Peptide and Clinical Judgement in Emergency Diagnosis of Heart Failure

## Analysis from BNP Multinational Study




*PA McCullough et al, Circulation 2002;106:416*

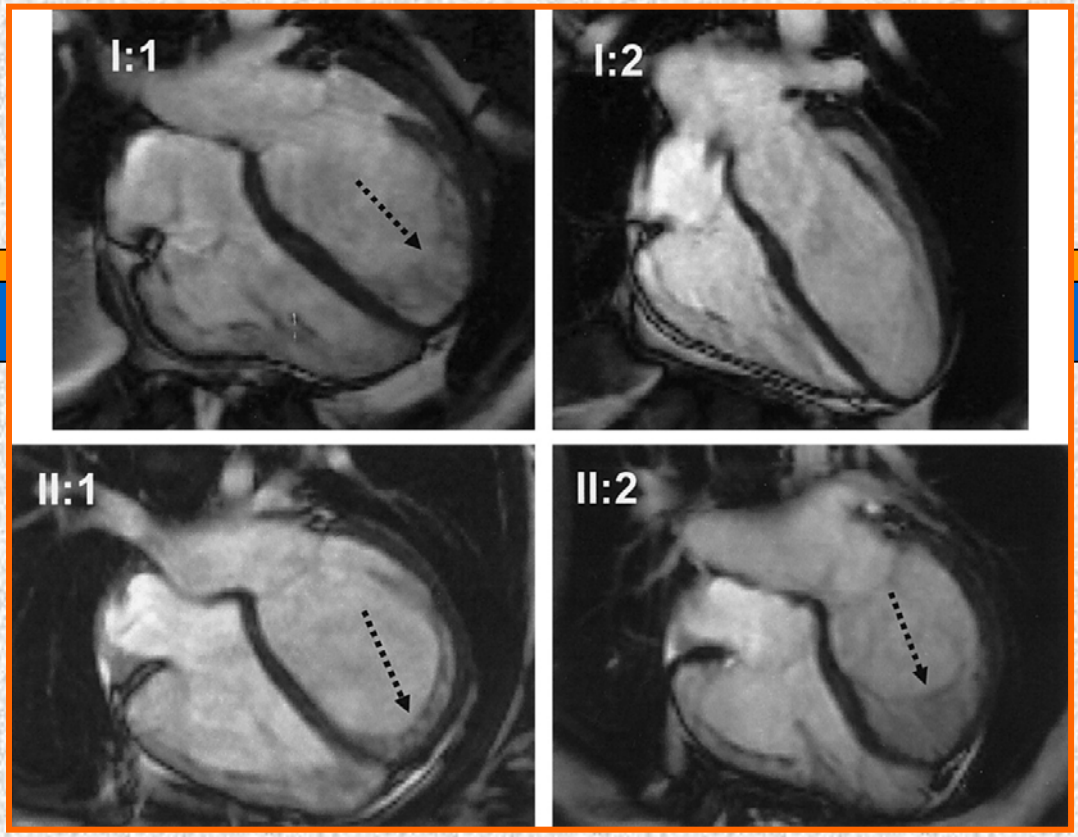
# Indications for Coronary Angiography in New Onset Cardiomyopathy

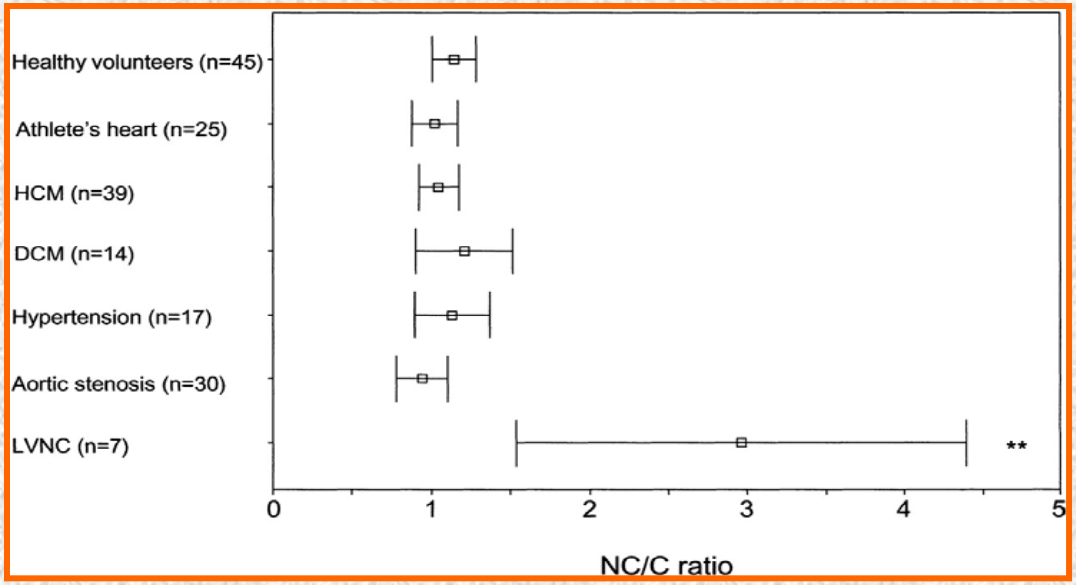
**ACC/AHA CONSENSUS GUIDELINES** *(Hunt SA, et al. Circulation 2001;104:2996)*

- ✓ **Patients with Known Coronary Artery Disease/Angina Pectoris**
  - **Revascularization recommended in vast majority of such individuals with multivessel disease; little role for non-invasive testing**
  - **Coronary angiography considered (Class I, Evidence: B)**
- ✓ **Patients with Known Coronary Artery Disease Who Lack Angina**
  - **No controlled trials have examined whether coronary revascularization can improve outcomes in this population**
  - **Many centers first evaluate patient for myocardial hibernation**
  - **Coronary angiography considered (Class IIa, Evidence: C)**
- ✓ **Patients with or without Chest Pain in Whom Coronary Artery Disease has not Been Evaluated**
  - **Approximately 35% of patients with IDCM will report angina-like pain**
  - **Coronary angiography should be considered (Class IIa, Evidence: C)**

# Left Ventricular Non-Compaction

## Insights from Cardiovascular MRI

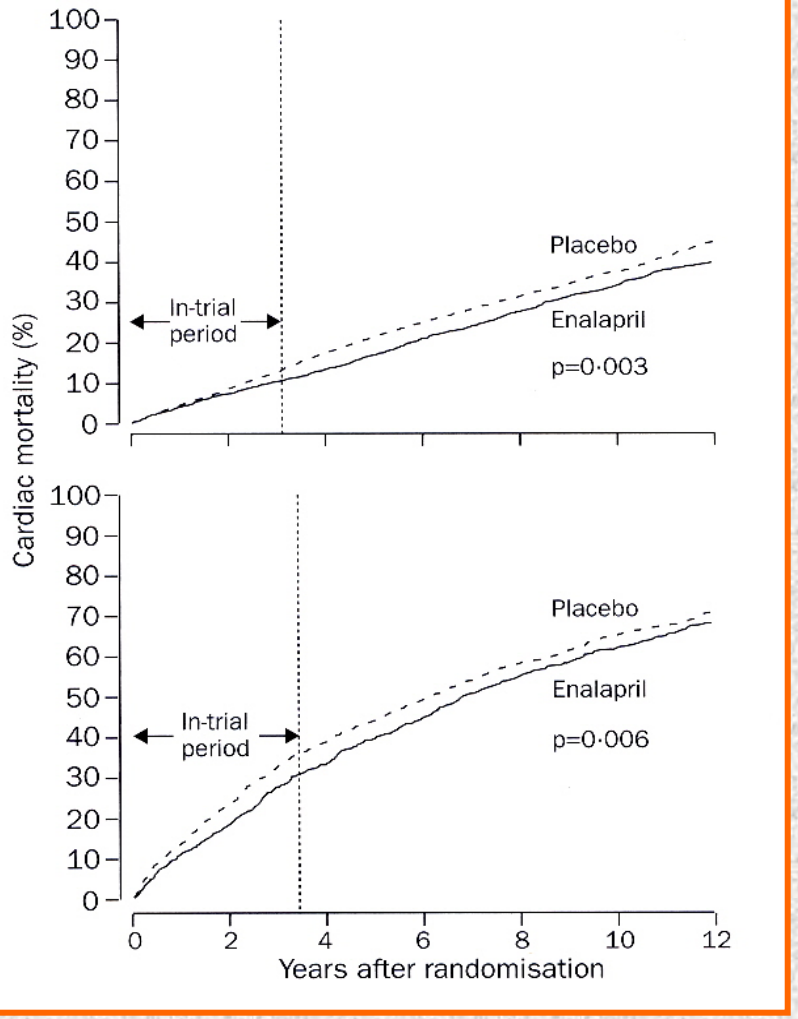



*SE Petersen et al,*
*J Am Coll Cardiol 2005;46:101-105*

# ACE Inhibitors
# Asymptomatic LV Dysfunction

EF <35%

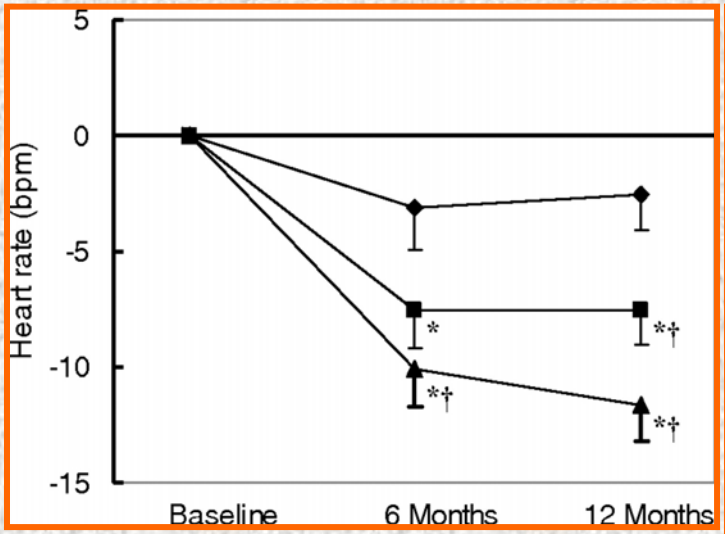


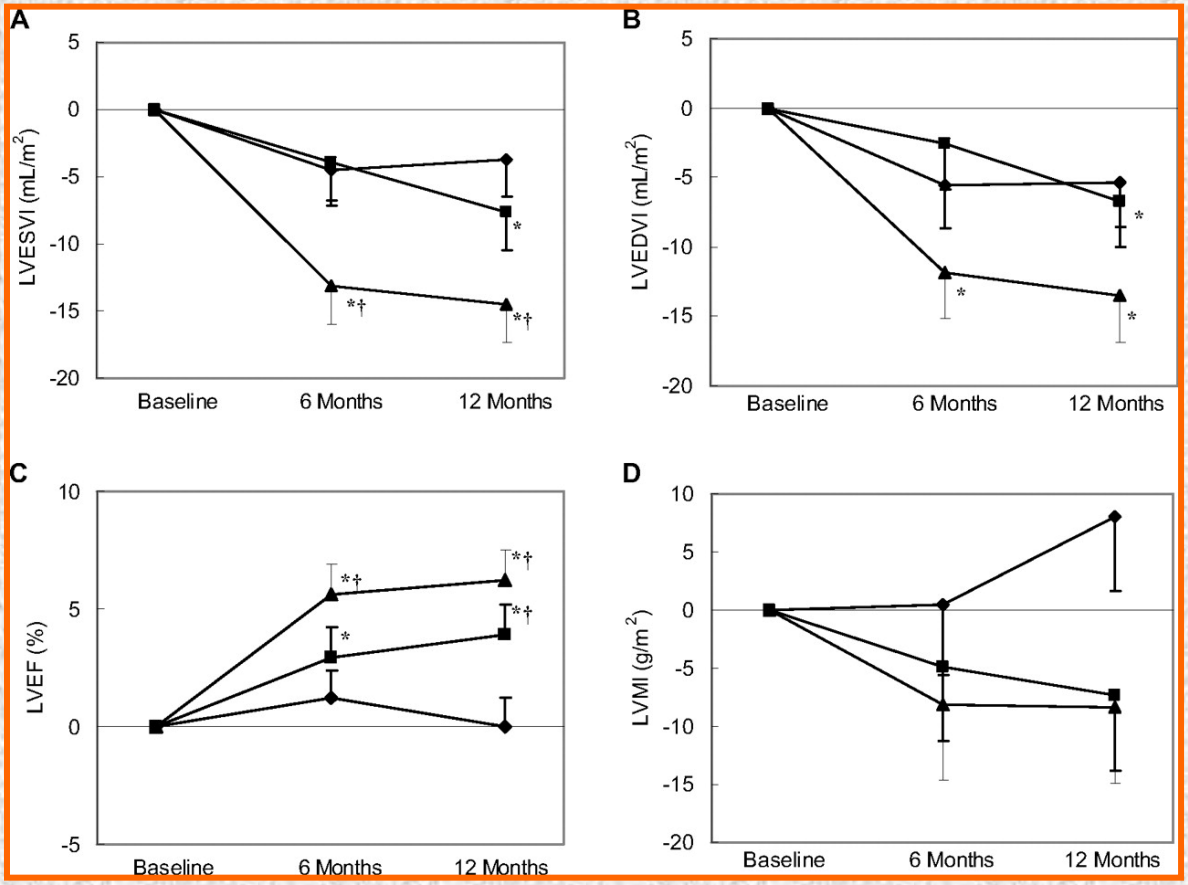

**SOLVD (prevention)**
**12-year survival and life expectancy**

***Lancet 2003;361:1843-48***

# Metoprolol Reverses Left Ventricular Remodeling in Patients with Asymptomatic Systolic Dysfunction

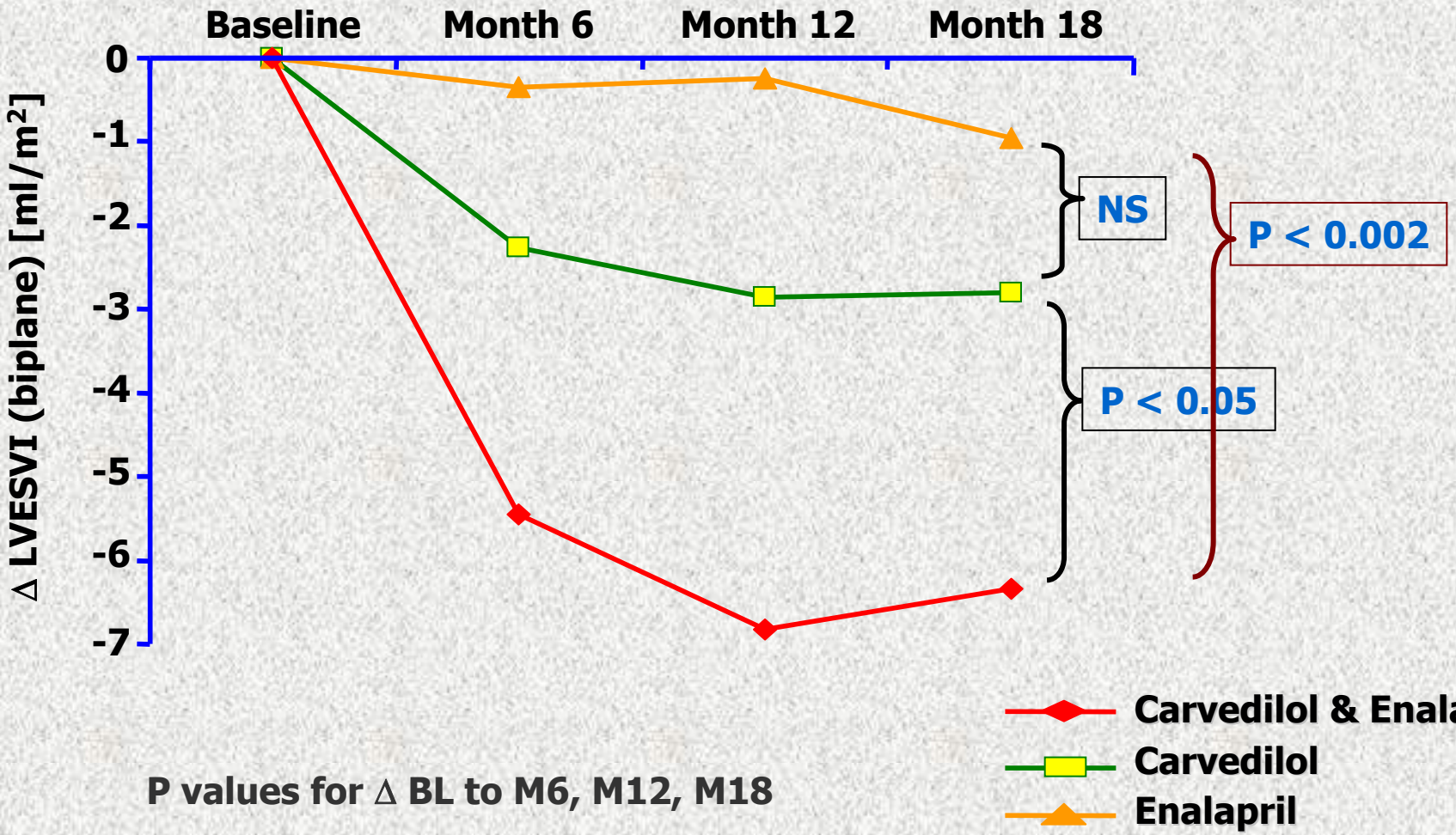
## REVERT Trial



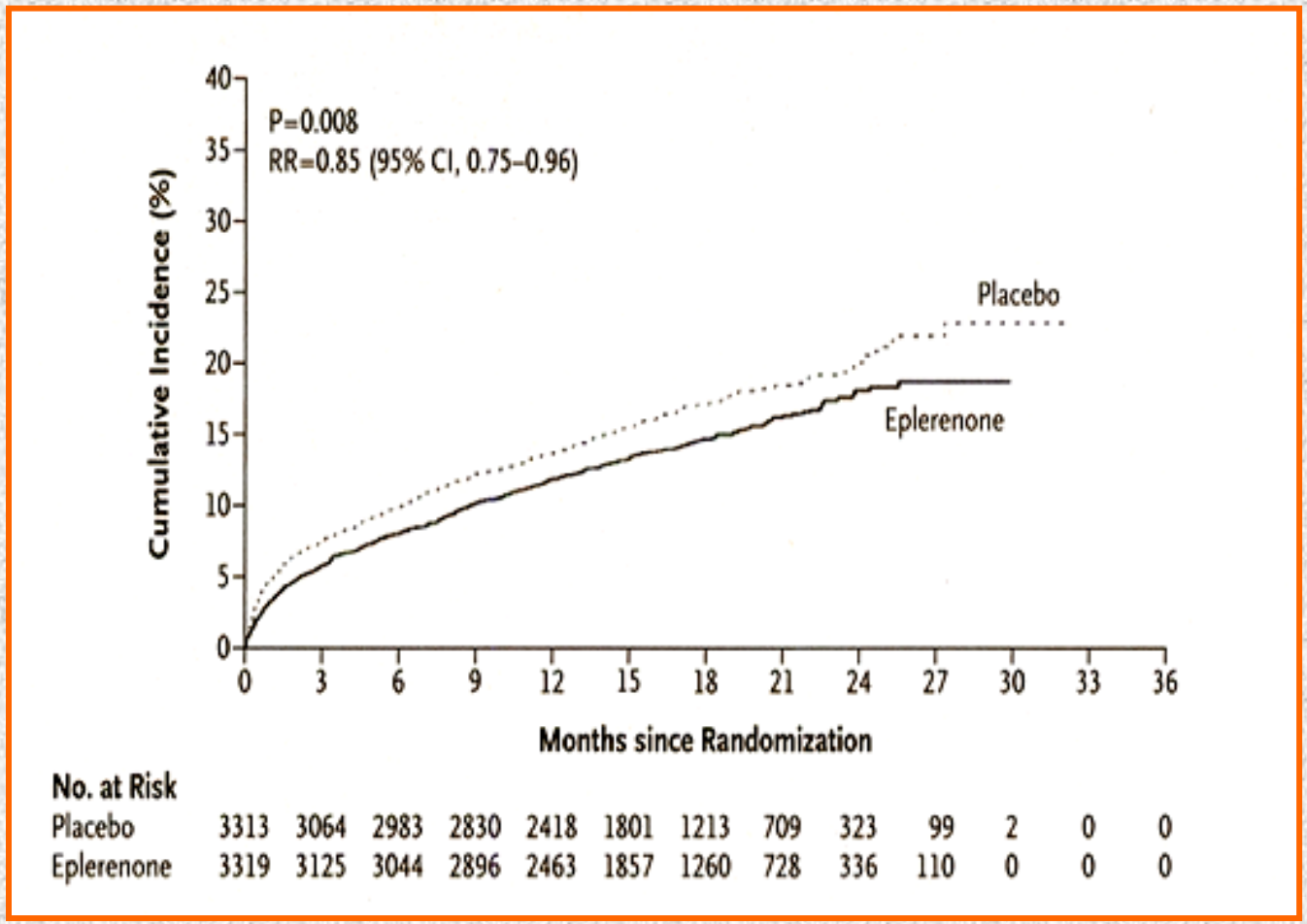

*WS Colucci et al, Circulation 2007, June 18*

# Primary Endpoint: LVESVI
# Comparison Between Treatments (CARMEN Study)

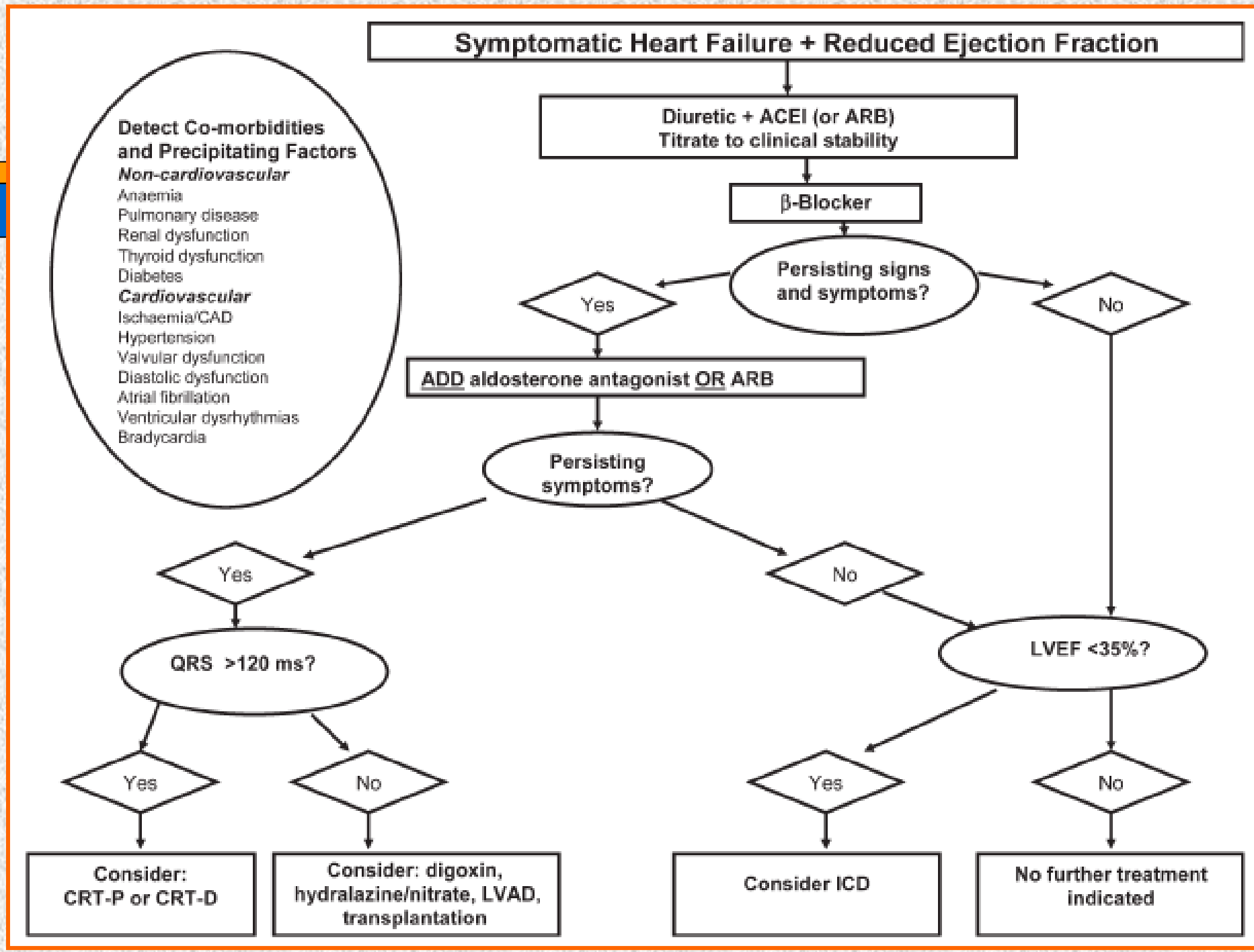



P values for Δ BL to M6, M12, M18

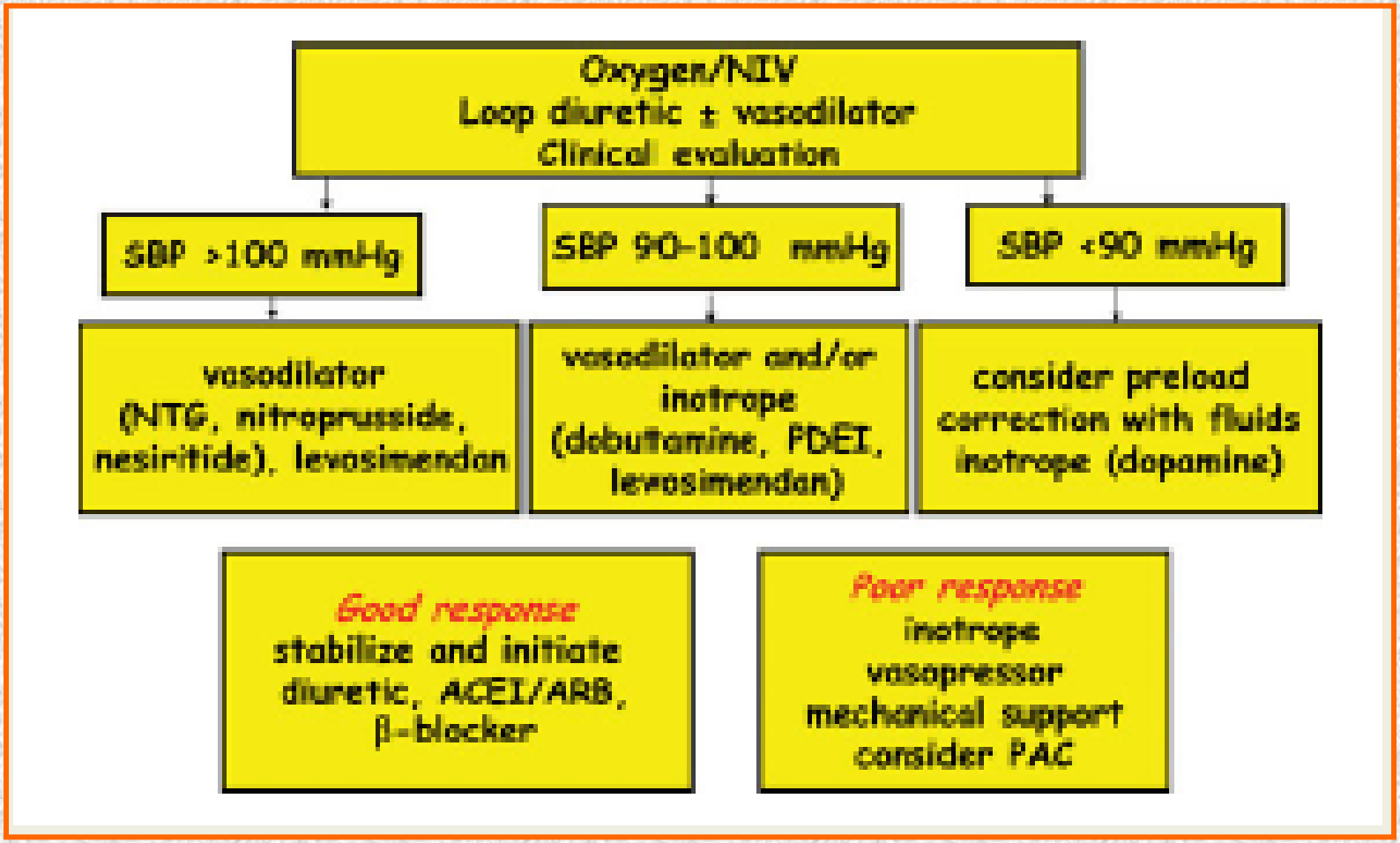
# Eplerenone, a Selective Aldosterone Blocker, after Myocardial Infarction (EPHESUS TRIAL)

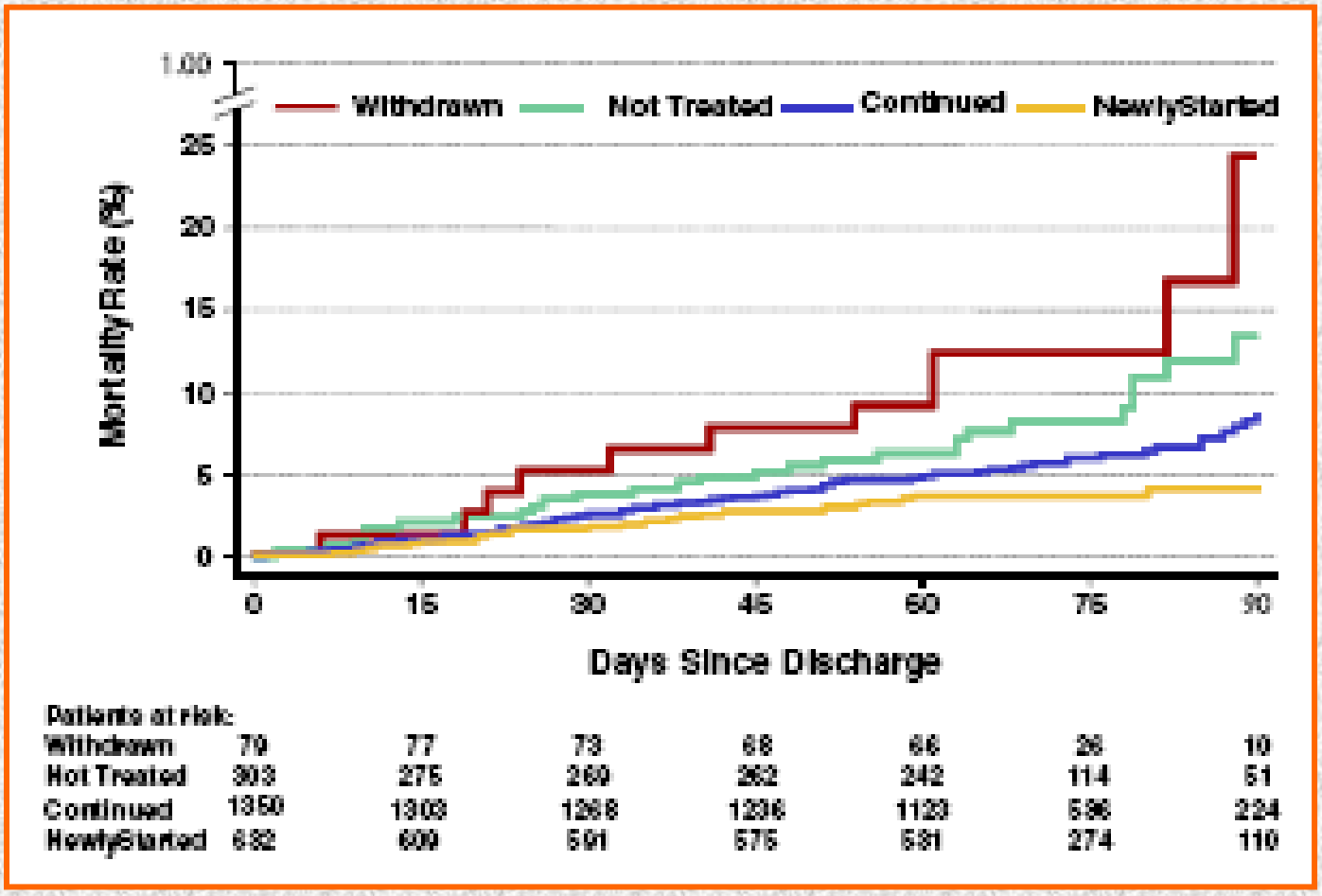



*B Pitt et al, N Engl J Med 2003, April 3*


Symptomatic Heart Failure + Reduced Ejection Fraction
Diuretic + ACEI (or ARB)
Titrate to clinical stability
β-Blocker
Persisting signs and symptoms?
Yes
No
ADD aldosterone antagonist OR ARB
Persisting symptoms?
Yes
No
QRS >120 ms?
Yes
No
LVEF <35%?
Yes
No
Consider: CRT-P or CRT-D
Consider: digoxin, hydralazine/nitrate, LVAD, transplantation
Consider ICD
No further treatment indicated
Detect Co-morbidities and Precipitating Factors
Non-cardiovascular
Anaemia
Pulmonary disease
Renal dysfunction
Thyroid dysfunction
Diabetes
Cardiovascular
Ischaemia/CAD
Hypertension
Valvular dysfunction
Diastolic dysfunction
Atrial fibrillation
Ventricular dysrhythmias
Bradycardia

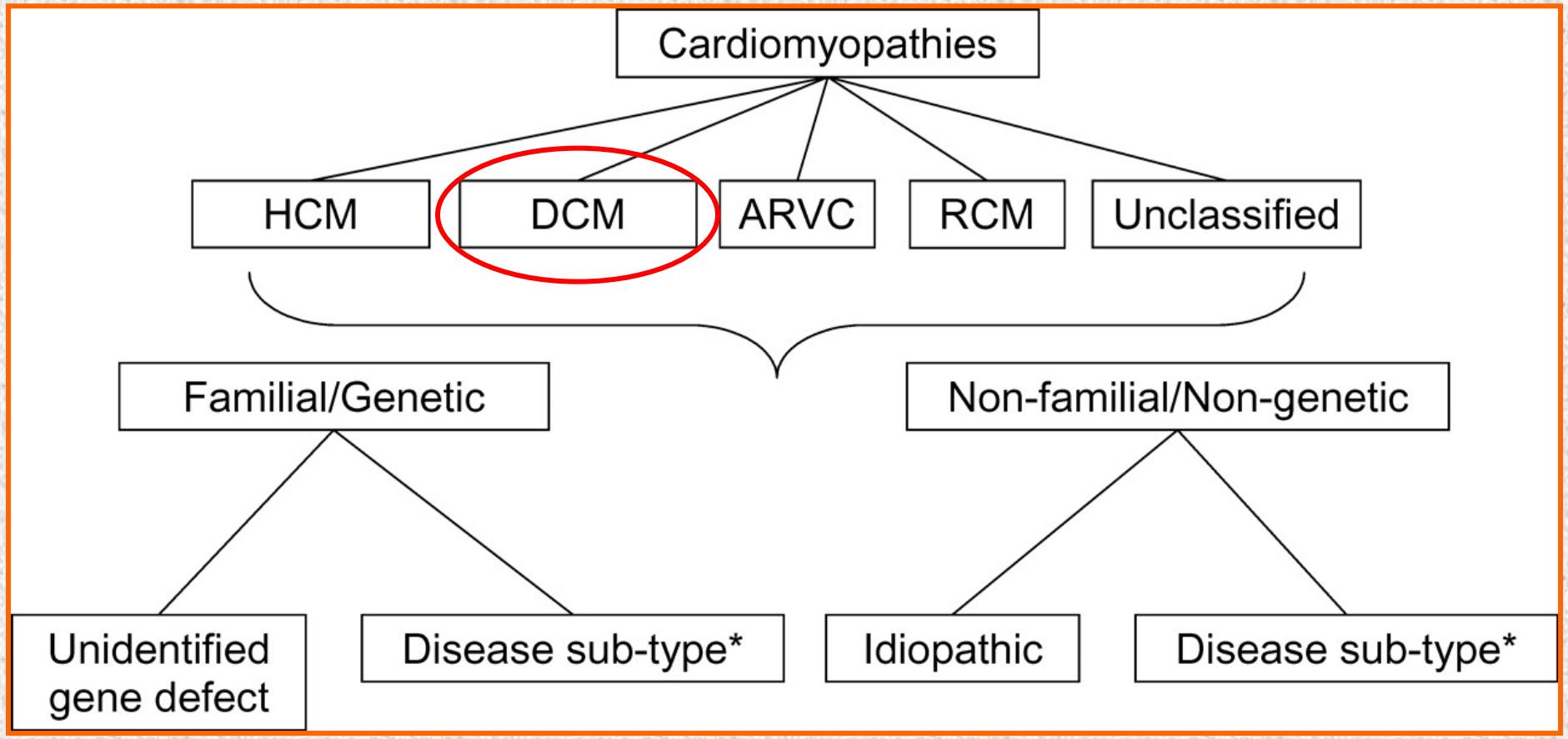
# ESC Guidelines



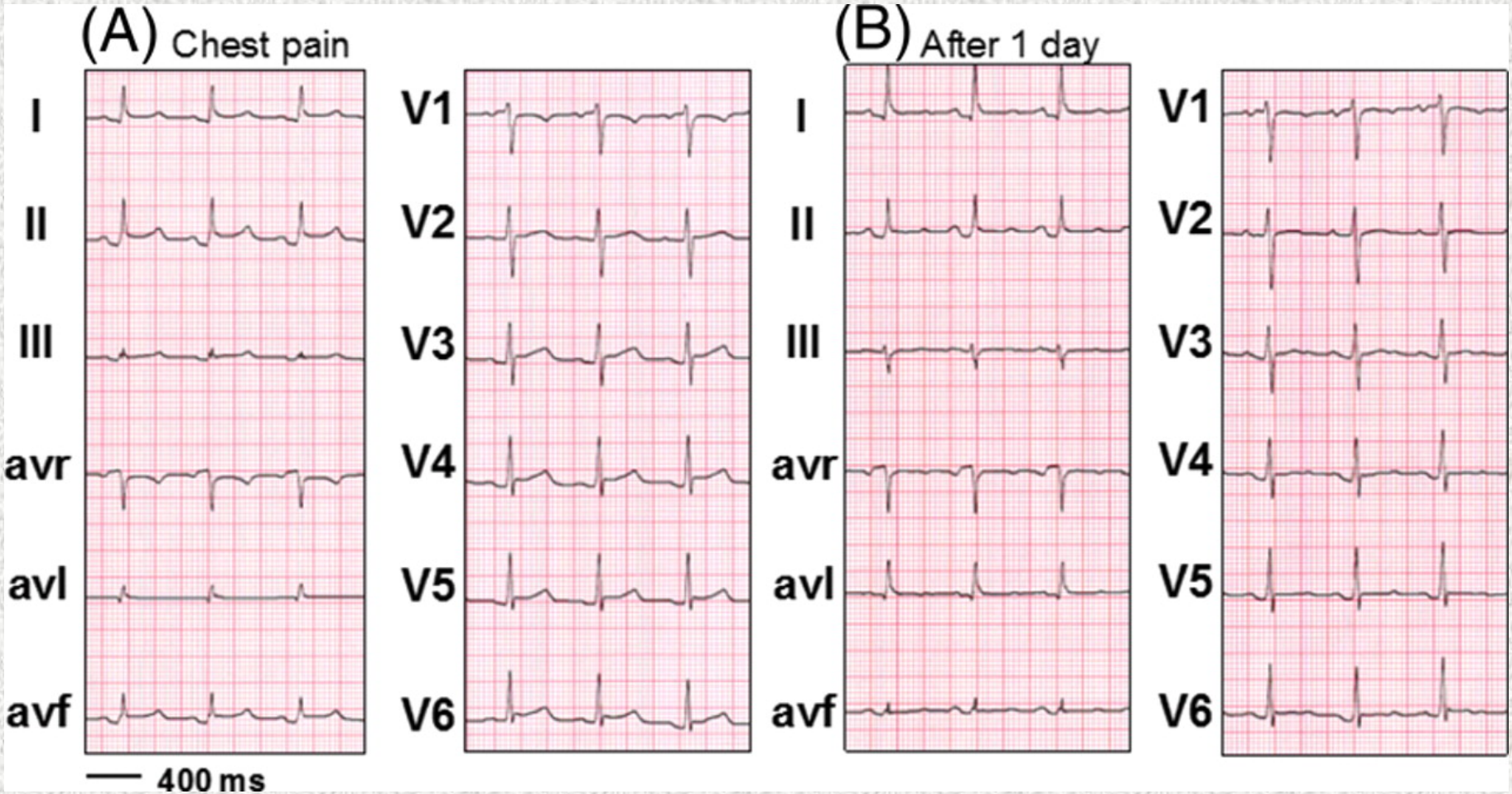

Withdrawn
Not Treated
Continued
NewlyStarted
Mortality Rate (%)
1.00
25
20
15
10
5
0
0
15
30
45
60
75
90
Days Since Discharge
Patients at risk:
Withdrawn 79 77 73 68 66 26 10
Not Treated 303 275 269 262 242 114 51
Continued 1359 1303 1268 1236 1123 536 224
NewlyStarted 682 609 591 575 531 274 110

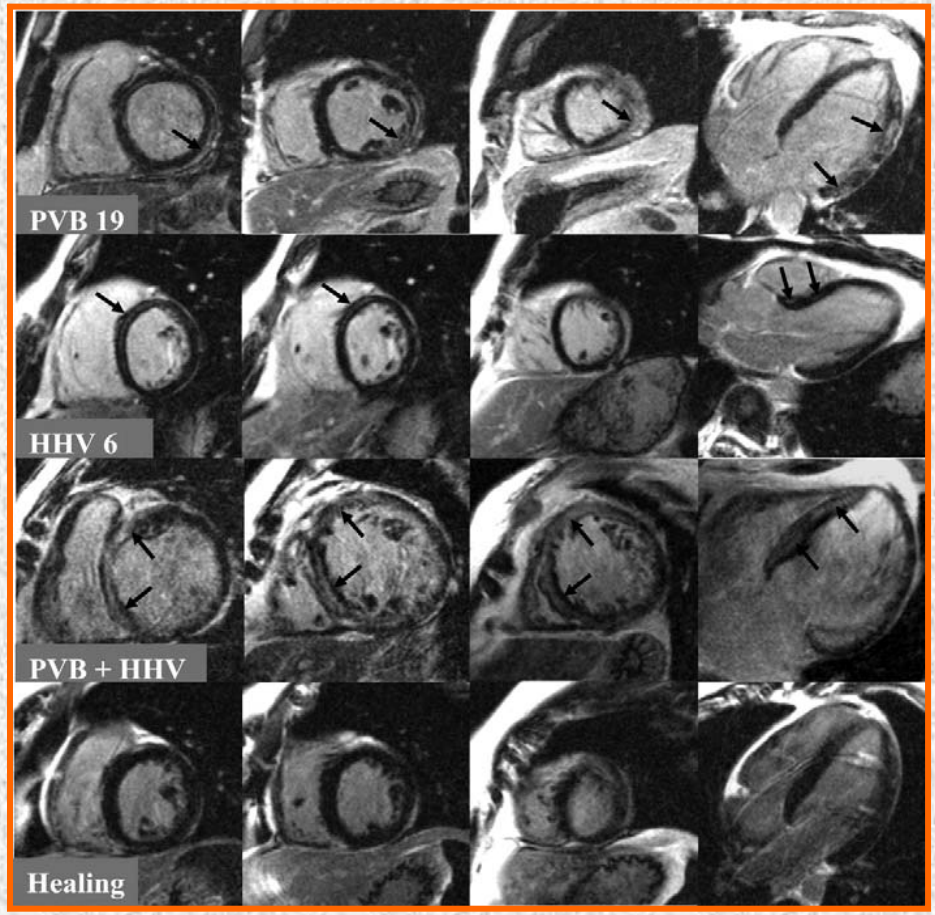
| Educational topics | Skills and self-care behaviours |
|---|---|
| Definition and aetiology of heart failure | Understand the cause of heart failure and why symptoms occur |
| Symptoms and signs of heart failure | Monitor and recognize signs and symptoms<br>Record daily weight and recognize rapid weight gain<br>Know how and when to notify healthcare provider<br>Use flexible diuretic therapy if appropriate and recommended |
| Pharmacological treatment | Understand indications, dosing, and effects of drugs<br>Recognize the common side-effects of each drug prescribed |
| Risk factor modification | Understand the importance of smoking cessation<br>Monitor blood pressure if hypertensive<br>Maintain good glucose control if diabetic<br>Avoid obesity |
| Diet recommendation | Sodium restriction if prescribed<br>Avoid excessive fluid intake<br>Modest intake of alcohol<br>Monitor and prevent malnutrition |
| Exercise recommendations | Be reassured and comfortable about physical activity<br>Understand the benefits of exercise<br>Perform exercise training regularly |
| Sexual activity | Be reassured about engaging in sex and discuss problems with healthcare professionals<br>Understand specific sexual problems and various coping strategies |
| Immunization | Receive immunization against infections such as influenza and pneumococcal disease |
| Sleep and breathing disorders | Recognize preventive behaviour such as reducing weight of obese, smoking cession, and abstinence from alcohol<br>Learn about treatment options if appropriate |
| Adherence | Understand the importance of following treatment recommendations and maintaining motivation to follow treatment plan |
| Psychosocial aspects | Understand that depressive symptoms and cognitive dysfunction are common in patients with heart failure and the importance of social support<br>Learn about treatment options if appropriate |
| Prognosis | Understand important prognostic factors and make realistic decisions<br>Seek psychosocial support if appropriate |

# Classification of the Cardiomyopathies: a Position Statement from the ESC Working Group on Myocardial and Pericardial Diseases

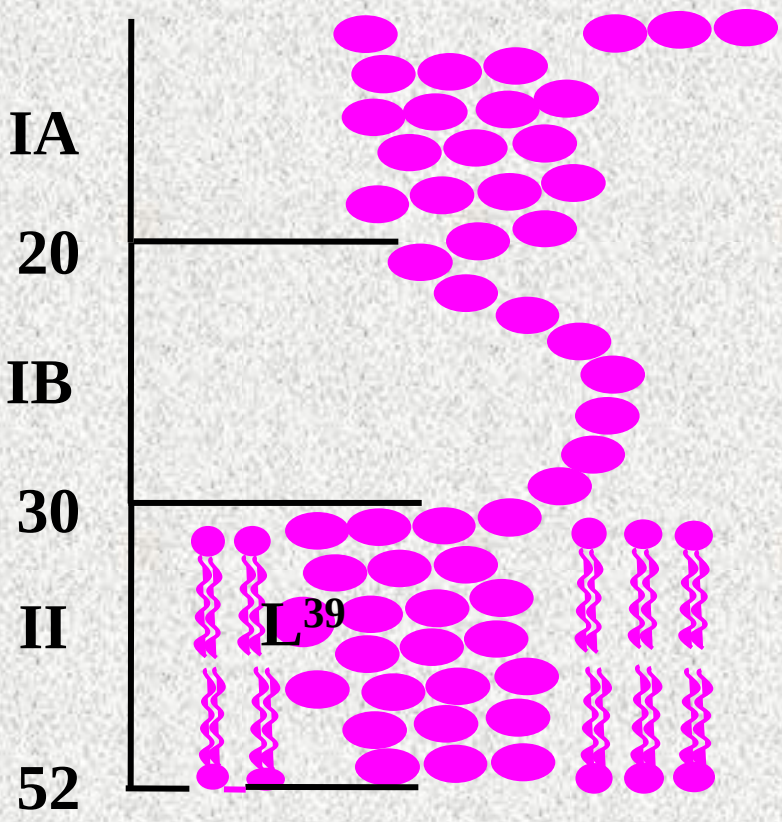


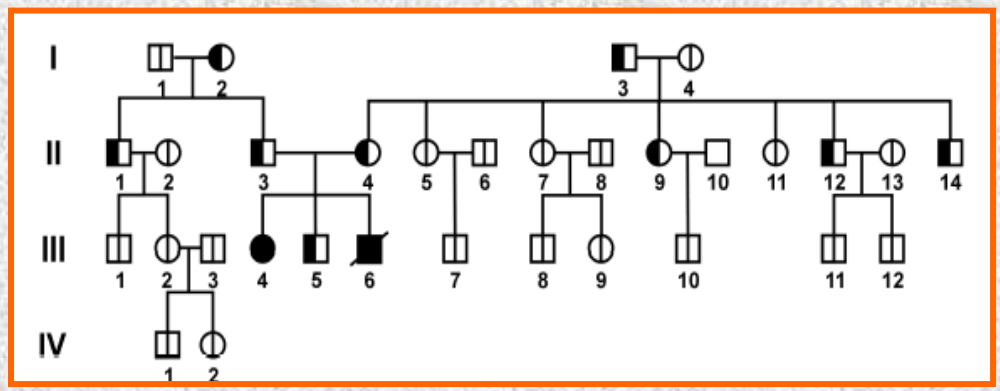

*P Elliot et al, Eur Heart Journal 2007, October 4*


(A) Chest pain
I
II
III
avr
avl
avf
V1
V2
V3
V4
V5
V6
400 ms
(B) After 1 day
I
II
III
avr
avl
avf
V1
V2
V3
V4
V5
V6


PVB 19
HHV 6
PVB + HHV
Healing

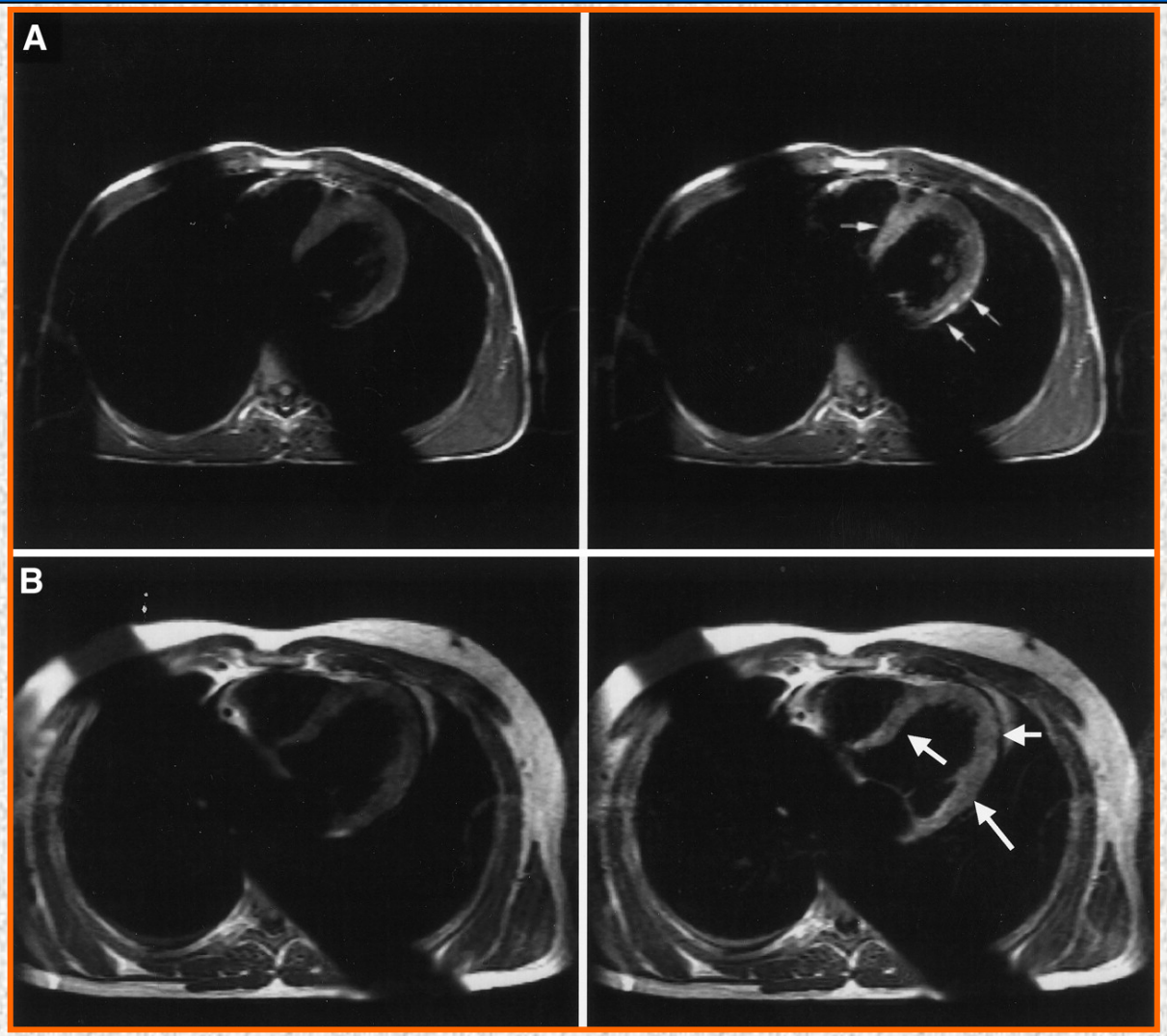
# Human Phospholamban Mutation and Dilated Cardiomyopathy



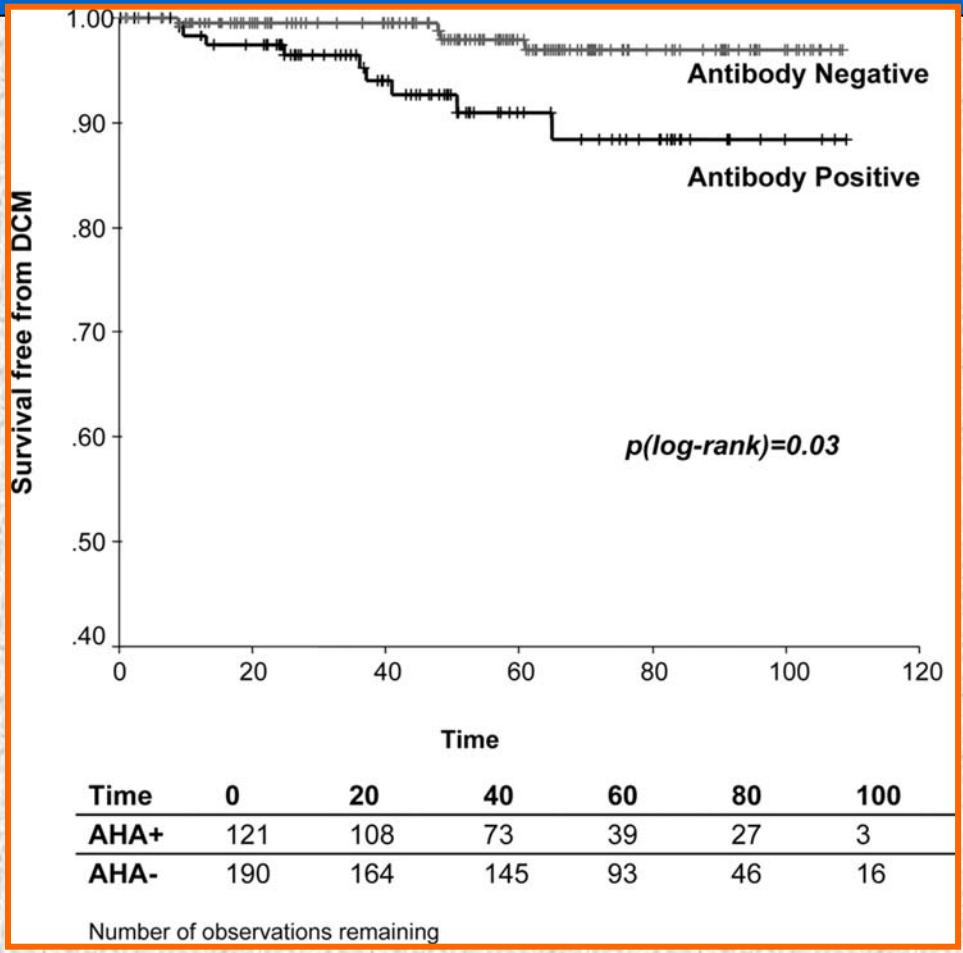

*Leu$^{39}$ → Stop Codon:TTA$^{39}$ → TGA*

*Haghighi et al, J Clin Invest March 2003*


A
B

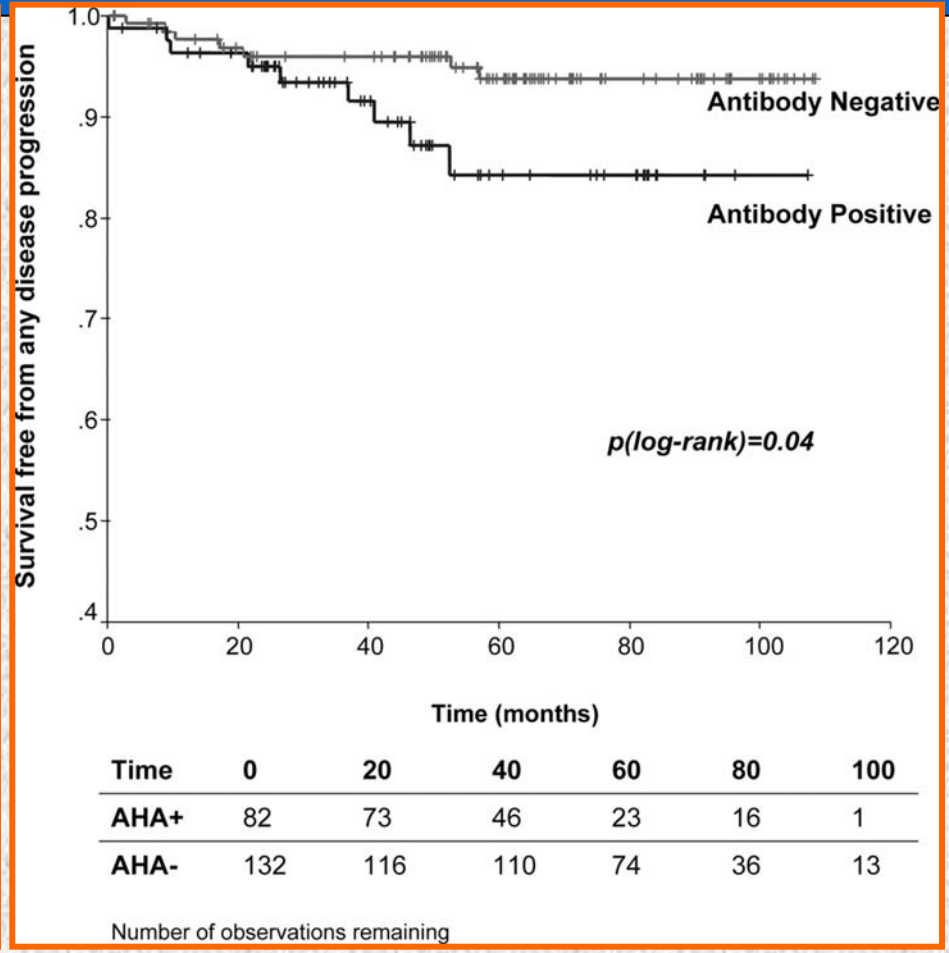
# Prospective Familial Assessment in DCM

## Cardiac Autoantibodies Predict Disease Development in Asymptomatic Relatives




| Time | 0 | 20 | 40 | 60 | 80 | 100 |
|---|---|---|---|---|---|---|
| AHA+ | 121 | 108 | 73 | 39 | 27 | 3 |
| AHA- | 190 | 164 | 145 | 93 | 46 | 16 |

Number of observations remaining



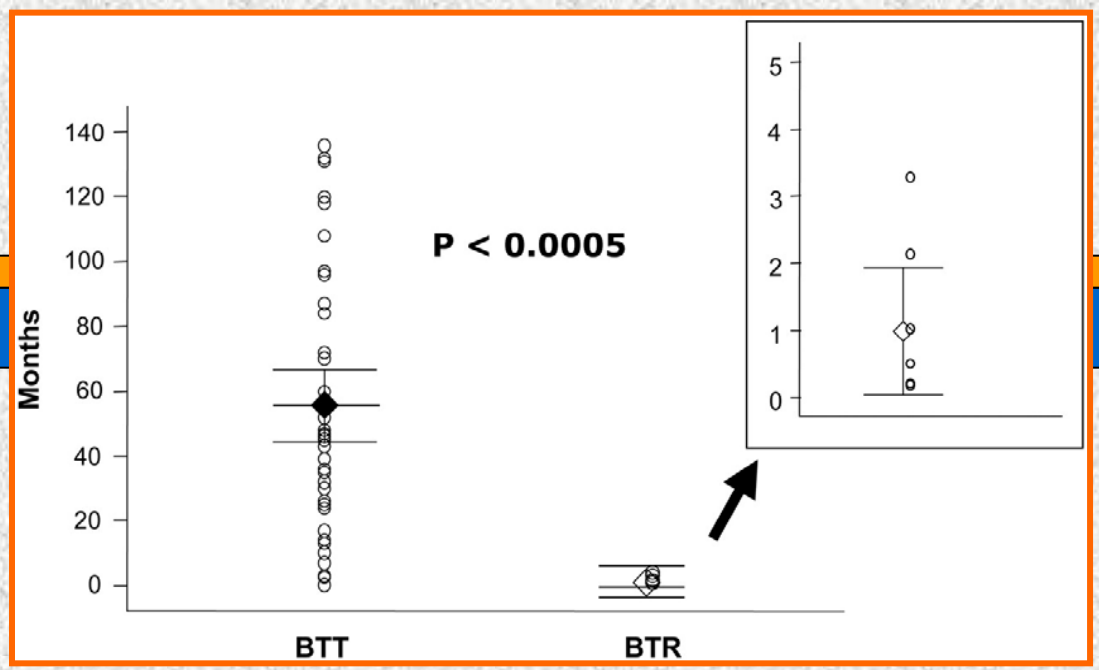

| Time | 0 | 20 | 40 | 60 | 80 | 100 |
|---|---|---|---|---|---|---|
| AHA+ | 82 | 73 | 46 | 23 | 16 | 1 |
| AHA- | 132 | 116 | 110 | 74 | 36 | 13 |

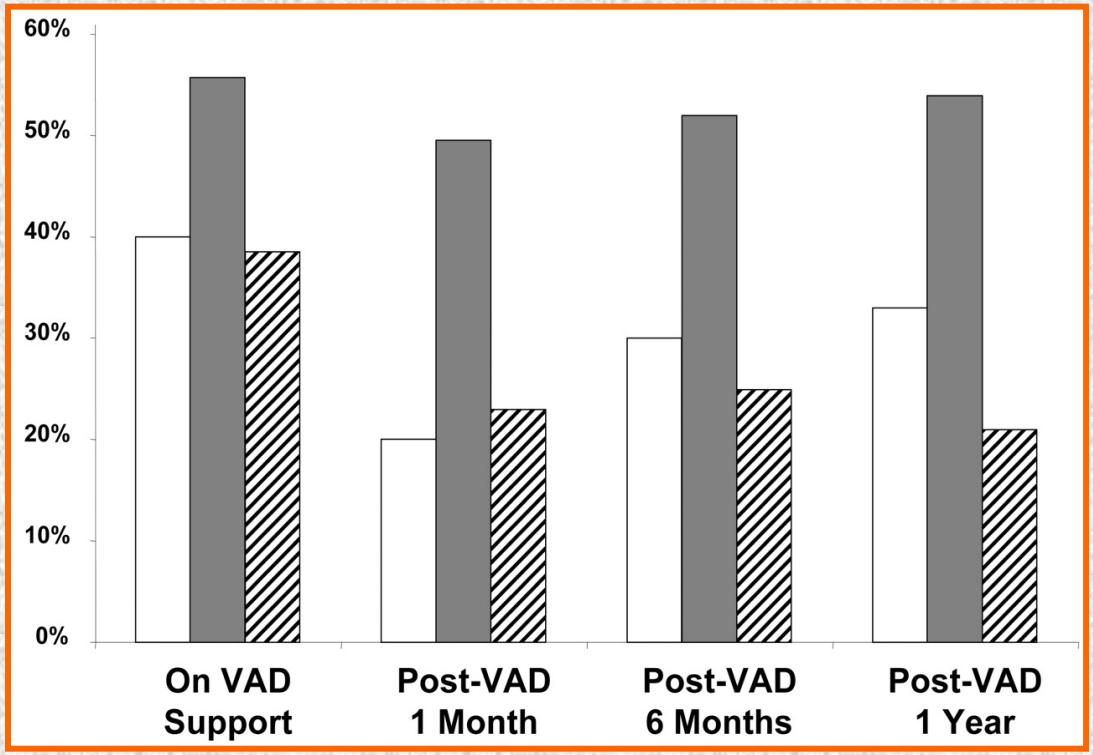
Number of observations remaining

*ALP Caforio et al, Circulation 2007, January2/9*

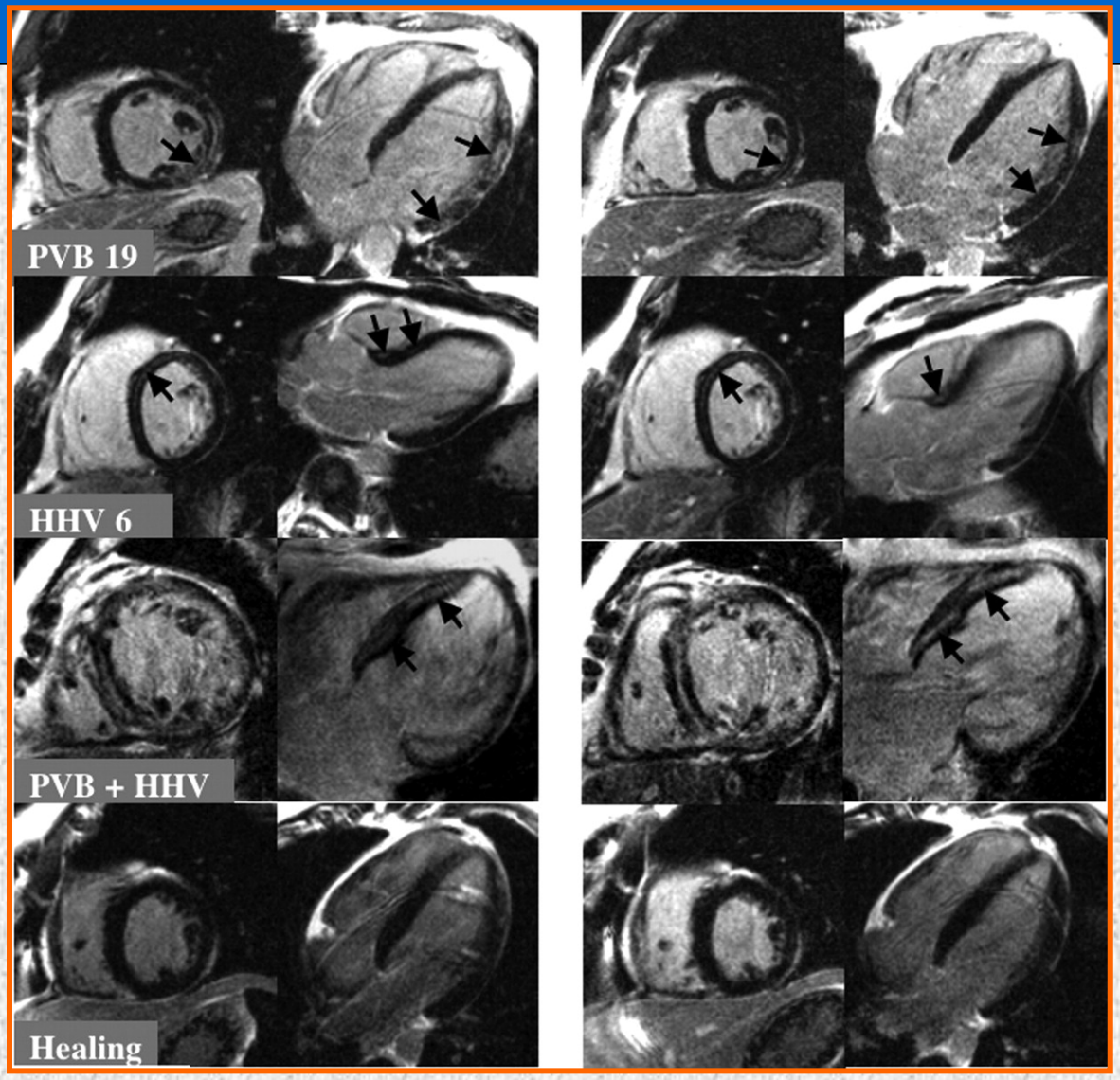
# Myocardial Recovery Using Ventricular Assist Devices

*MA Simon et al,*
*Circulation 2005, August 30*



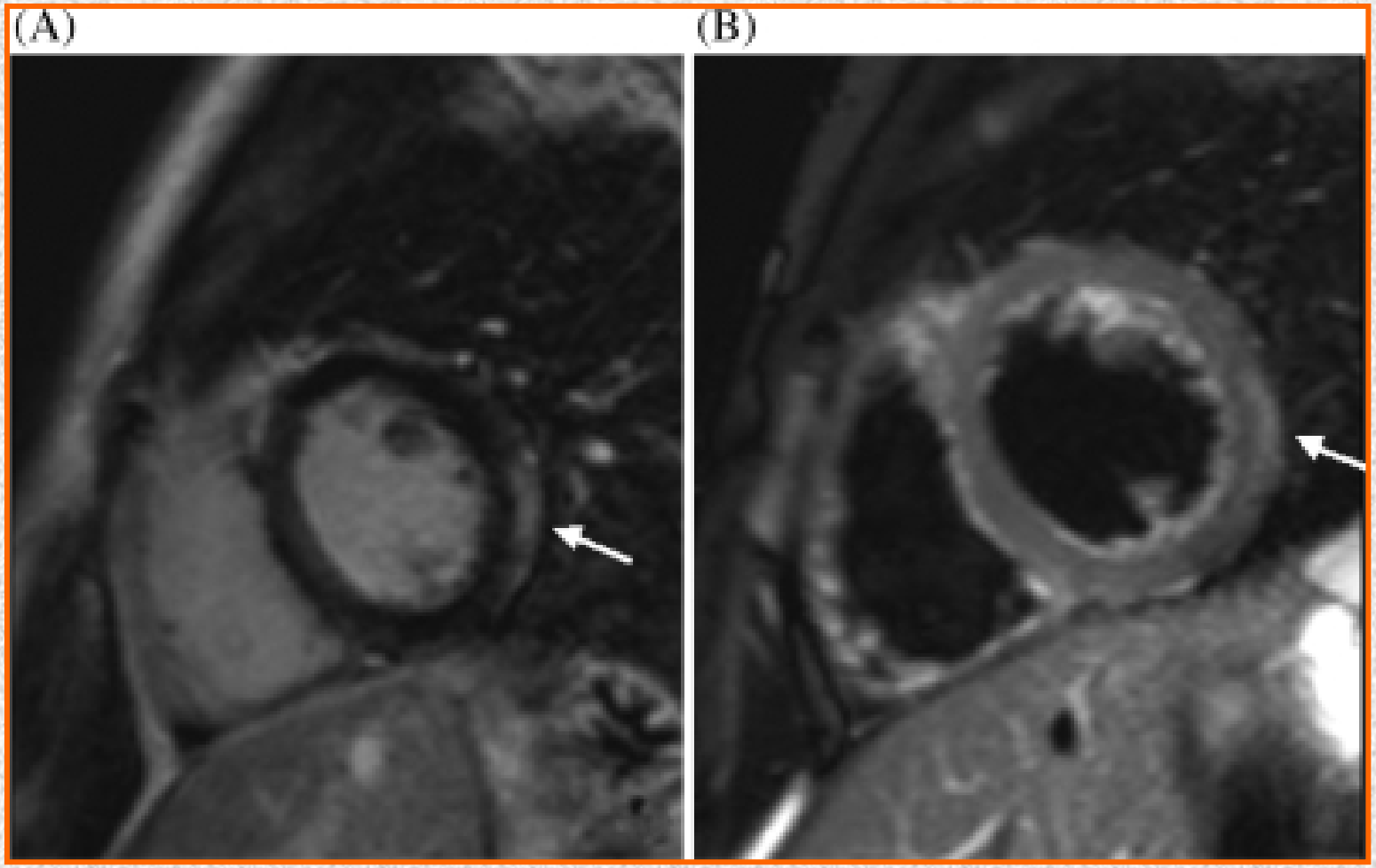



# Presentation, Patterns of Myocardial Damage and Clinical Course of Viral Myocarditis




*H Mahrholdt et al,*
*Circulation 2006;114:1581-1590*

# Cardiac Magnetic Resonance Imaging of a Patient with Acute Myocarditis




*R Dennert et al, Eur Heart J 2008, July 9*