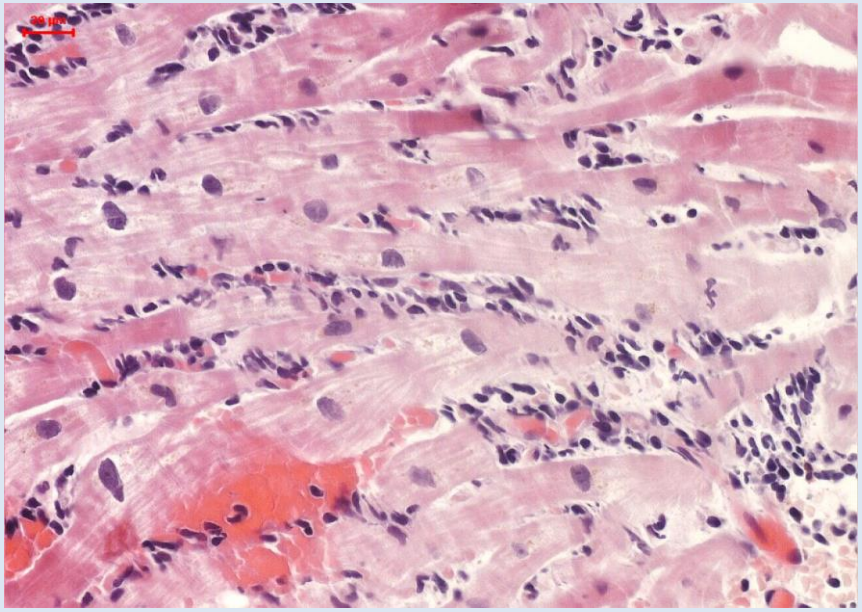
Myocarditis update

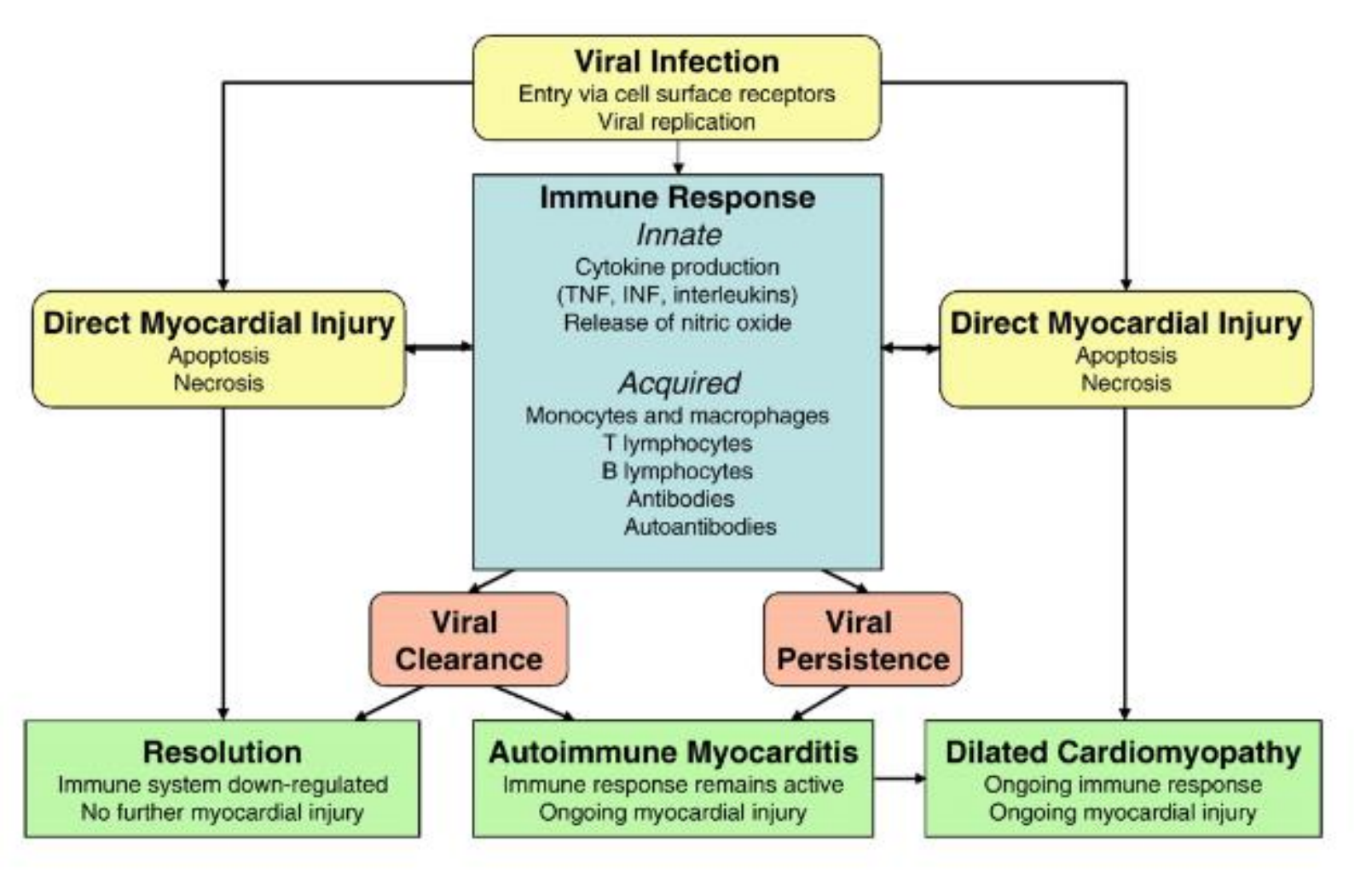
Standard therapy in 2017



Carsten Tschöpe, Berlin

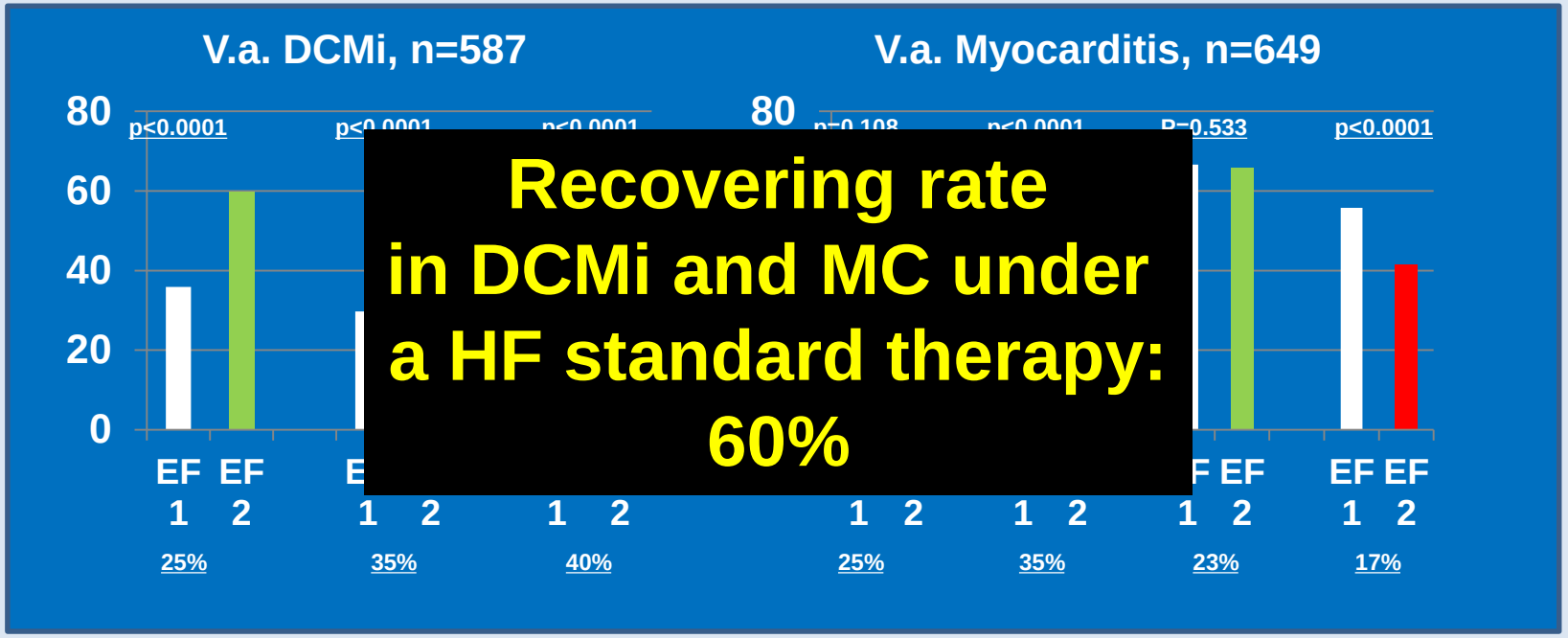
Charite, CVK

Pathogenesis of viral myocarditis



Spontaneous Course of biopsy proven MC/DCMi *

(mean follow-up: 4,5 Y (range 0,5-16 Y)



Conventional standard therapy

1. **ACEI/ARB**
2. **Beta Blocker**
3. **MRA** (EF < 35%)
4. **Diuretics**
5. **Ivabradine** (HF > 74 bpm)

Cafiero et al, Eur Heart J 2013

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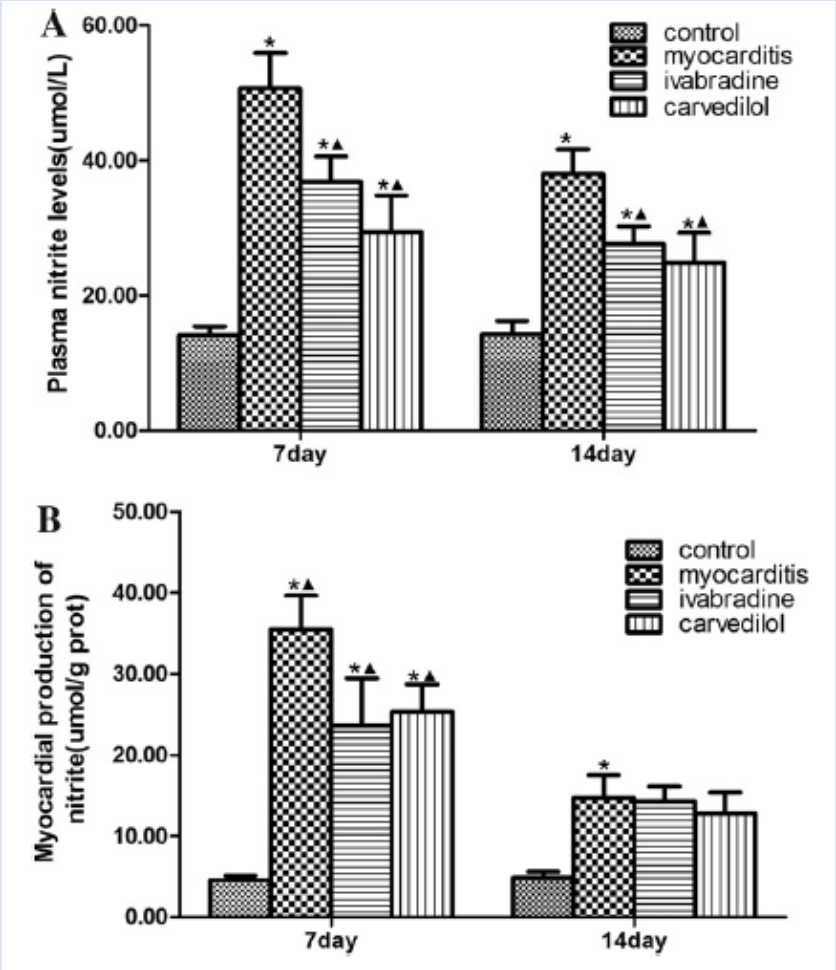

Conventional standard therapy

1. **ACEI/ARB**
2. **Beta Blocker**
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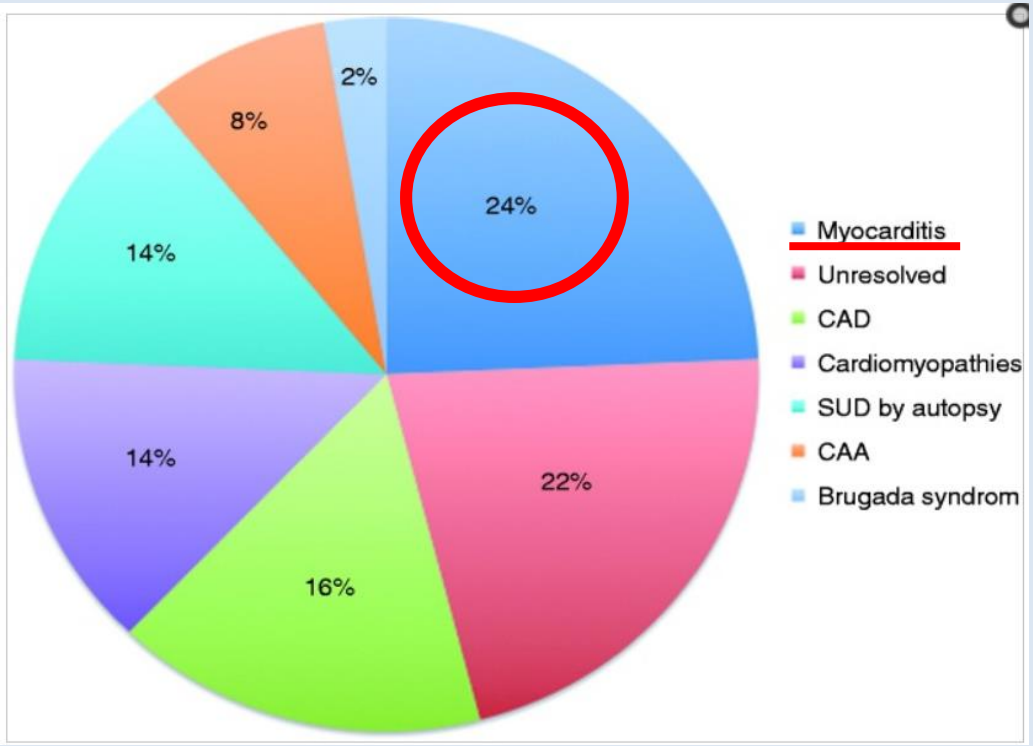
4. **Diuretics**
5. **Ivabradine** (HF > 74 bpm)
6. **No Sport**

Recommendation

20. Physical activity should be restricted during the acute phase of myocarditis and for at least 6 months in athletes and non-athletes. This recommendation is based upon expert opinion of this Task Force.

German register of sport-related sudden deaths



Bohm et al Eu J Precv Cardiol 2016

Conventional standard therapy

1. **ACEI/ARB**
2. **Beta Blocker**
3. **MRA** (EF <35%)
4. **Diuretics**
5. **Ivabradine** (HF > 74 bpm)
6. **No Sport** (for 6 months)
7. **Devices**

   Chronic phase: GL

Management of ventricular arrhythmias in inflammatory heart disease

Anti-arrhythmic therapy should be considered in patients with symptomatic non-sustained or sustained VT during the acute phase of myocarditis.	**IIa**	**C**
The implant of an ICD or pacemaker in patients with inflammatory heart diseases should be considered after resolution of the acute episode.	**IIa**	**C**
In patients with haemodynamically compromising sustained VT occurring after the resolution of acute episodes, an ICD implantation should be considered if the patient is expected to survive >1 year with good functional status.	**IIa**	**C**
recovery or ICD implantation in patients after inflammatory heart diseases with residual severe LV dysfunction and/or ventricular electrical instability.	**IIa**	**C**

Conventional standard therapy

Management of ventricular arrhythmias in inflammatory heart disease

A wearable defibrillator should be considered for bridging until full recovery or ICD implantation in patients after inflammatory heart diseases with residual severe LV dysfunction and/or ventricular electrical instability.	IIa	C

Conventional standard therapy

Wearable Defibrillator by Myocarditis

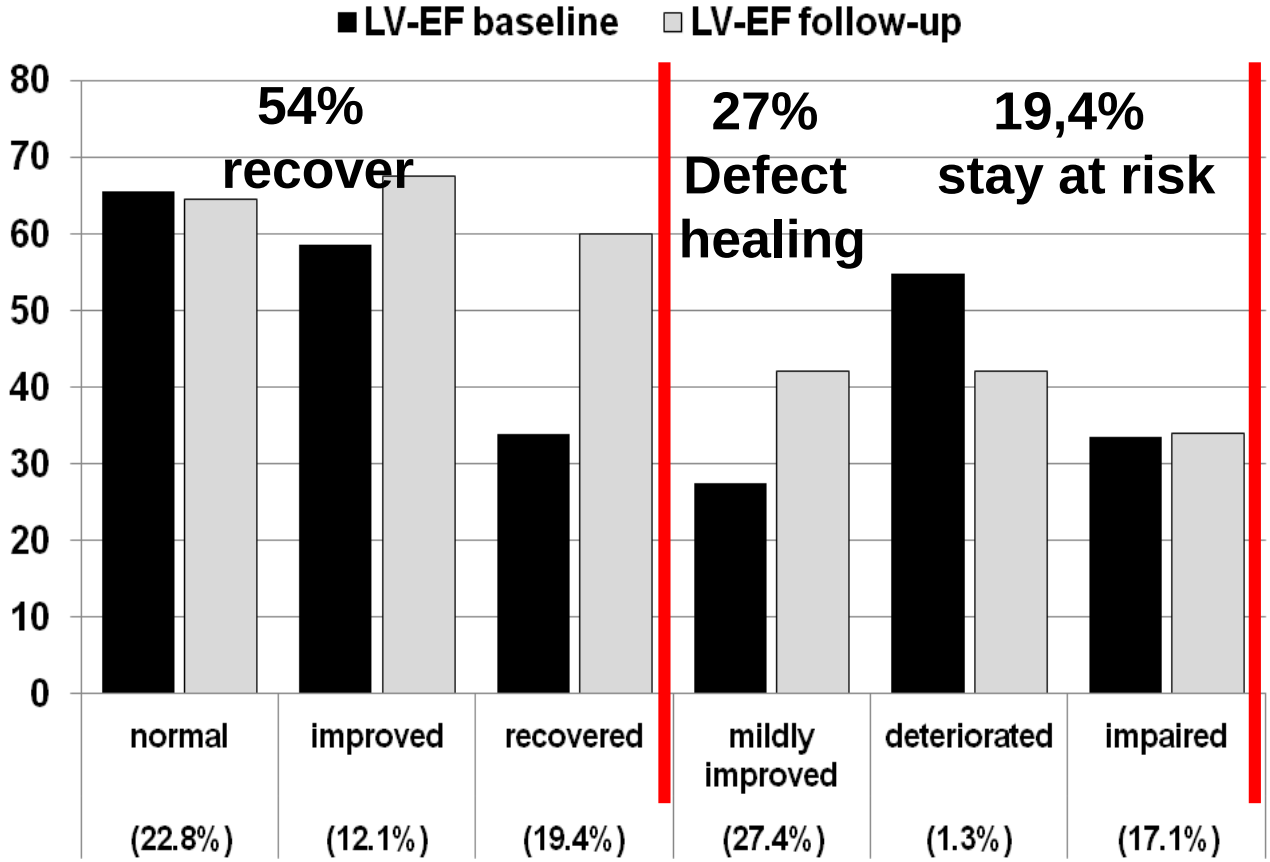
85 Pat with DCMi (EF< 35%) with Life Vest protected

0 Life saving event

25 Pat became in the follow up a permanent device incl. CRT if LSB

Despite HF standard therapy 45% will patients with MC/DCMi will not recover

Spontaneous Course of biopsy proven MC/DCMi * (clinical mean follow-up: 30 months, n=922)



* No specific treatment due to viral persistence

Determinates for failure of recover

The clinical recovery rate is dependent from :

1. Initial defect size

2. Type and phase of inflammatory response

3. Persistence and type of the virus

Determinates for failure of recover

The clinical recovery rate is dependent from :

1. Initial defect size

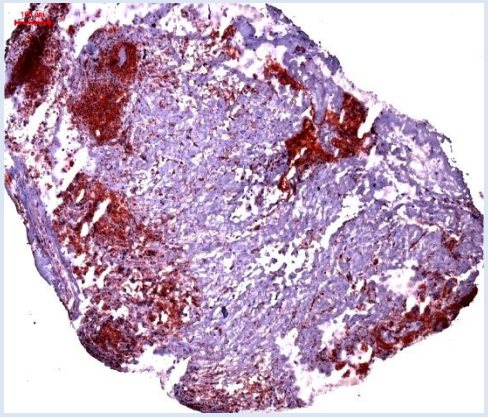
2. Type and phase of inflammatory response

3. Persistence and type of the virus

Initial defect size and type of inflammatory response

Severe unexplained acute new onset HF

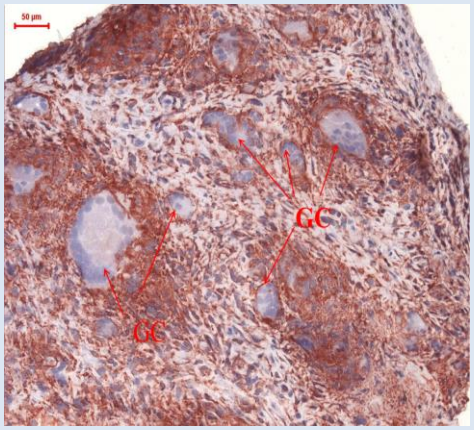
Fulminant Myocarditis



(EF: 32%)

Moderate Prognosis

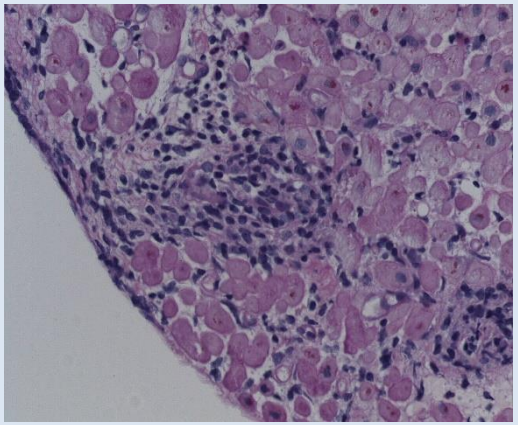
Giant cell Myocarditis



(EF: 32%)

Poor Prognosis

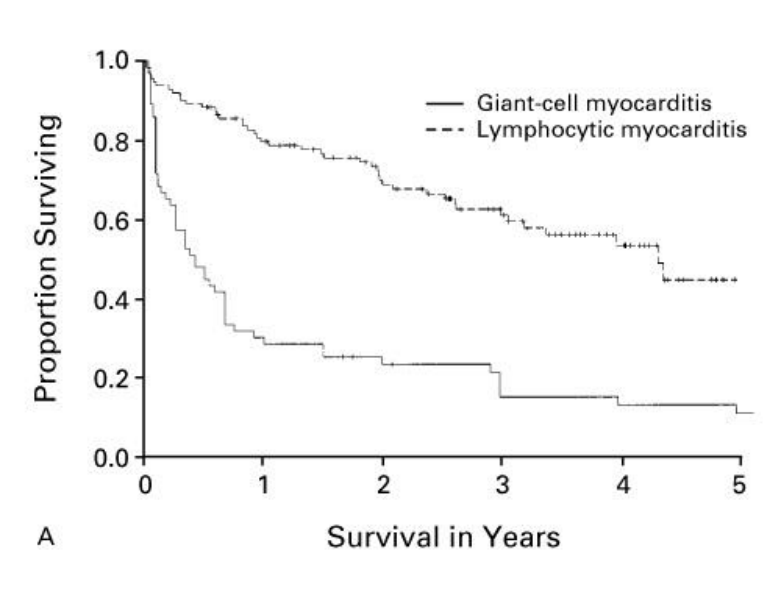
Eosinophilic Myocarditis



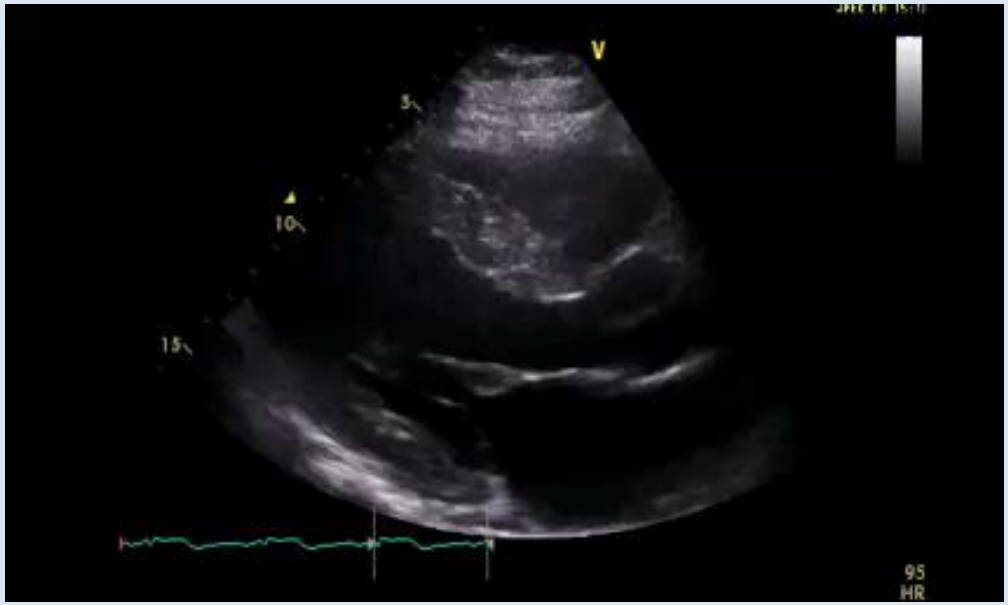
(EF: 30%,)

Poor Prognosis

Kaplan–Meier Survival Curves for Patients with Giant-Cell Myocarditis



Cooper LT Jr et al. N Engl J Med 1997



Tschöpe et al

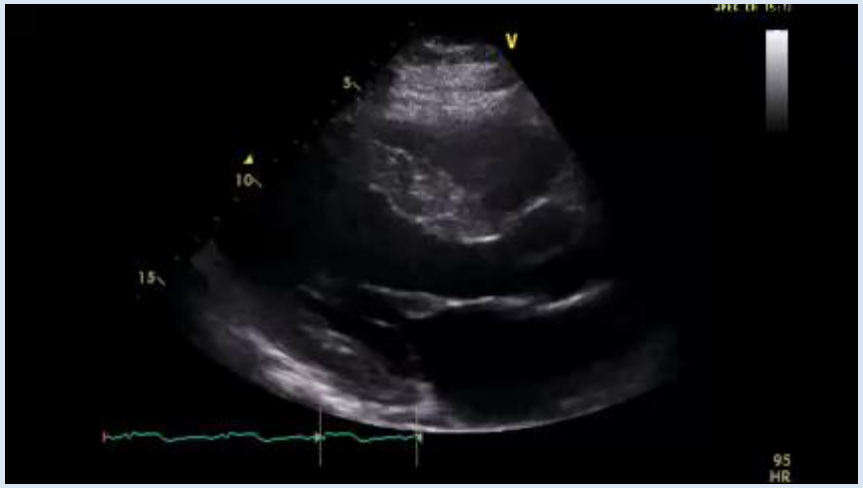
Current therapeutic options in Acute Giant Cell Myocarditis

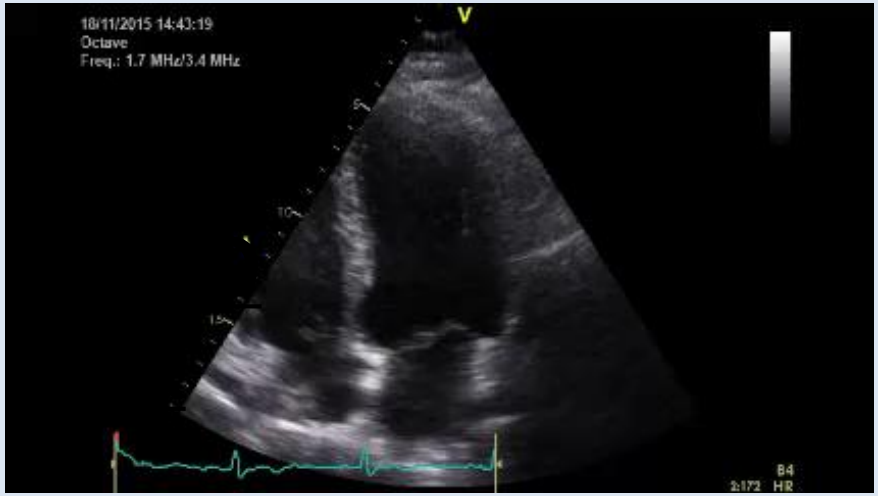
Giant cell myocarditis (Cooper et al[33,34])
Antithymoglobulin
275 mg in 500 mL 0.9% saline solution for 12 h/24 h
Days 1 to 5
Under cardiac monitoring
Ciclosporine
Start dose 200 mg/24 h (100 mg/12 h)
Targeted trough level: 100-120 μg/mL
1 year
Methylprednisolone
Initial dose: 1 mg/kg
After 4 weeks: decrease by 10 mg, and then another 10 mg every 2 weeks until 5-10 mg maintenance dose
1 year

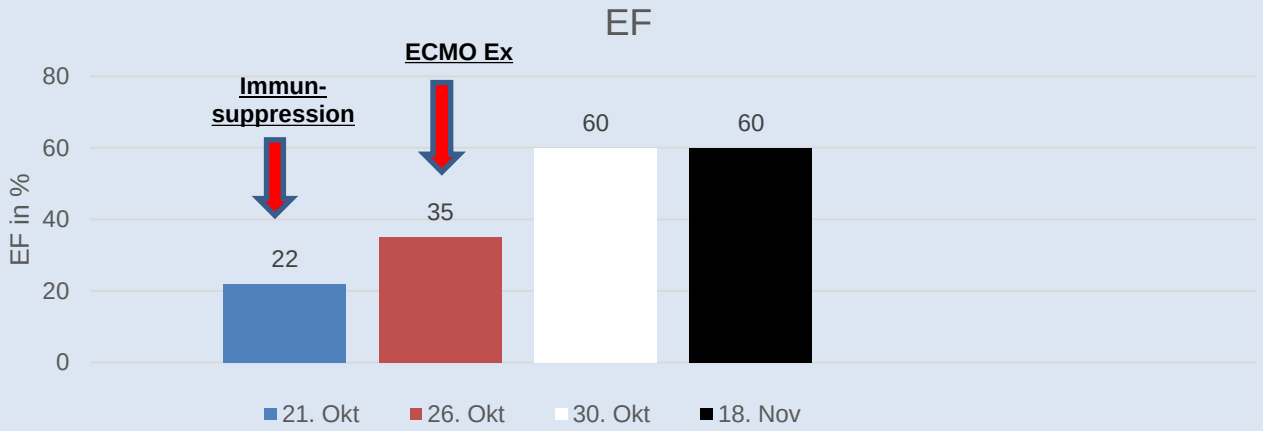
Dominguez F , Tschöpe et al, Rev. Esp Cardiol 2016

Caforio et al, Eur Heart J 2013

Course of the Giant cell myocarditis







Current Therapeutic Options in
Acute fulminant myocarditis forms

eosinophilic myocarditis (Frustaci et al[45])
Azathioprine
50 mg/12 h for 6 months
Weekly laboratory control with blood count/liver enzymes during the first month
Contemplate other alternatives if < 3000 leucocytes or < 1000 lymphocytes
Methylprednisolone
Initial dose: 1 mg/kg
After 4 weeks: decrease by 10 mg, and then another 10 mg every 3 weeks until 5-10 mg maintenance dose
6 months
Accompanying treatment in all cases pantoprazole/omeprazole 20 mg/24 h, calcium 1 g/24 h

Dominguez F et al. Rev Esp Cardiol 2016

Determinates for failure of recover

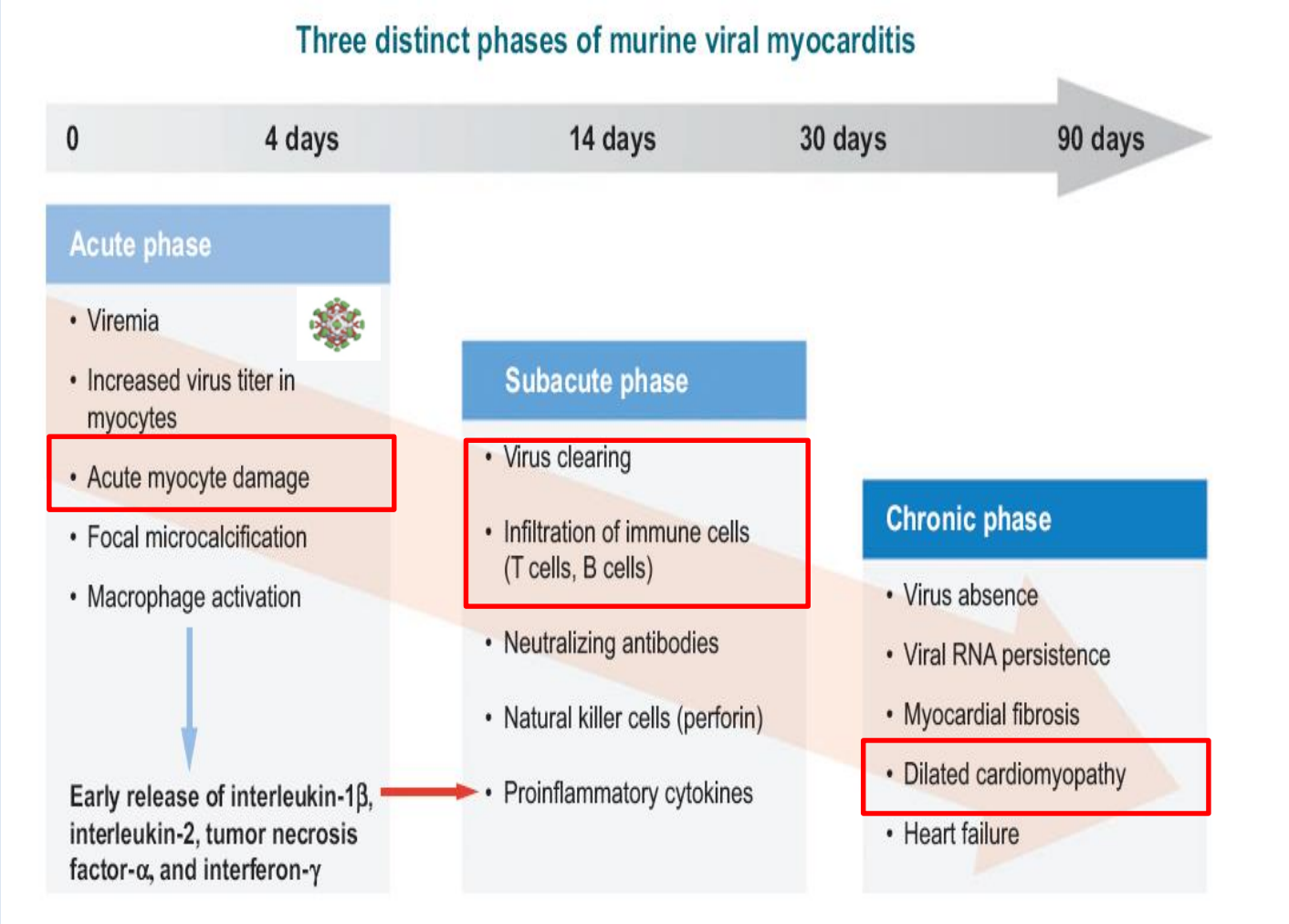
The clinical recovery rate is dependent from :

1. Initial defect size

2. Type and phase of inflammatory response

3. Persistence and type of the virus

Phase of myocarditis



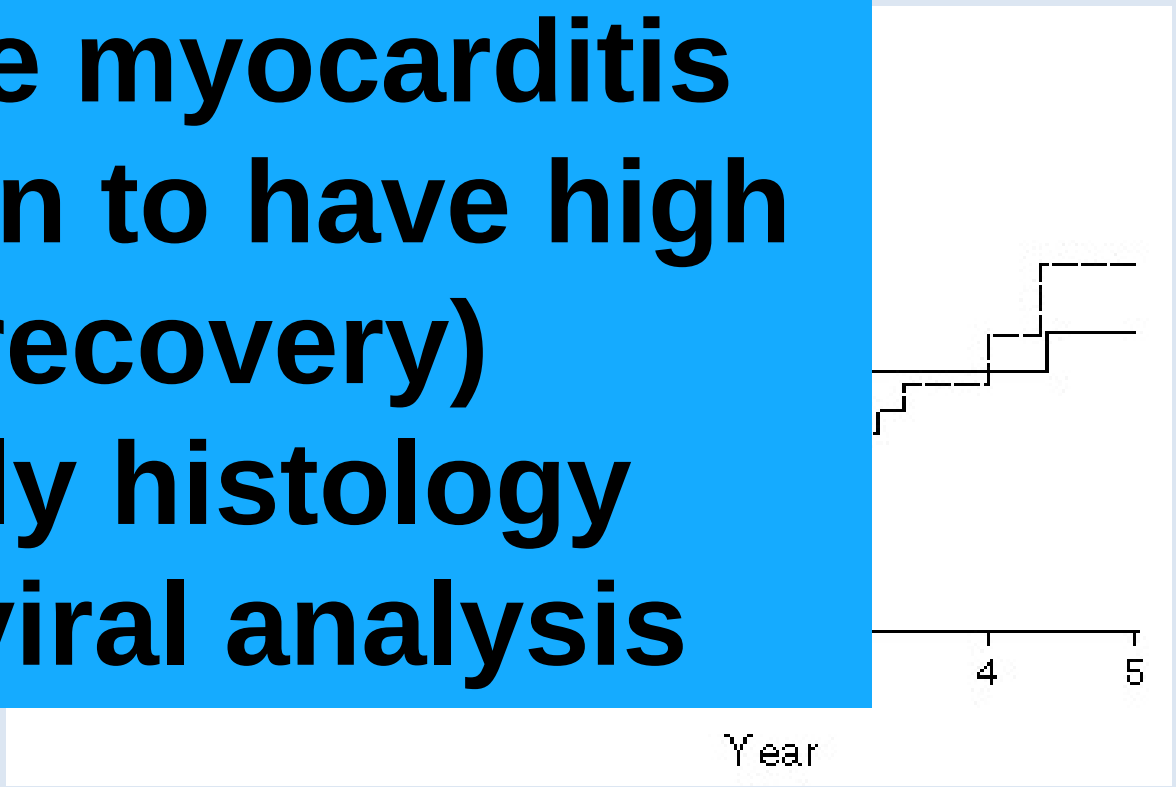
Esfandiarei et al. Annu. Rev. Pathol. Mech. Dis 2008

Dallas Criteria – Immunsuppression in acute myocarditis Negative US-Trail

Histology

Mortality
(Defined as deaths and Cardiac Transplantations)
in the immunosuppression and control group

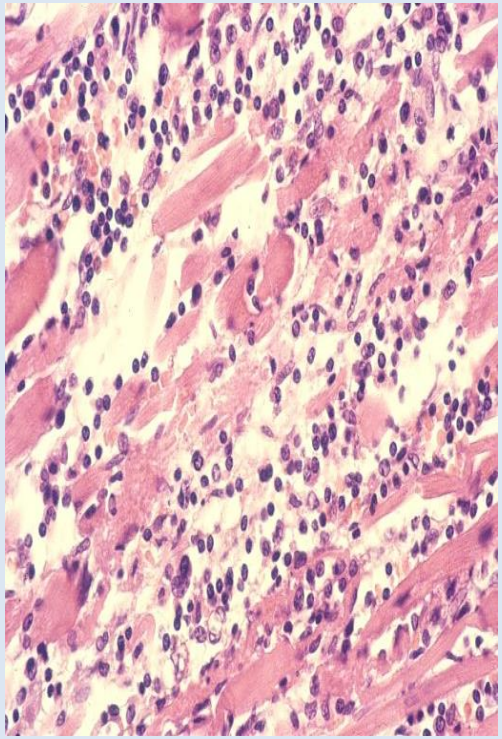
Acute myocarditis (known to have high recovery)
Only histology
No viral analysis

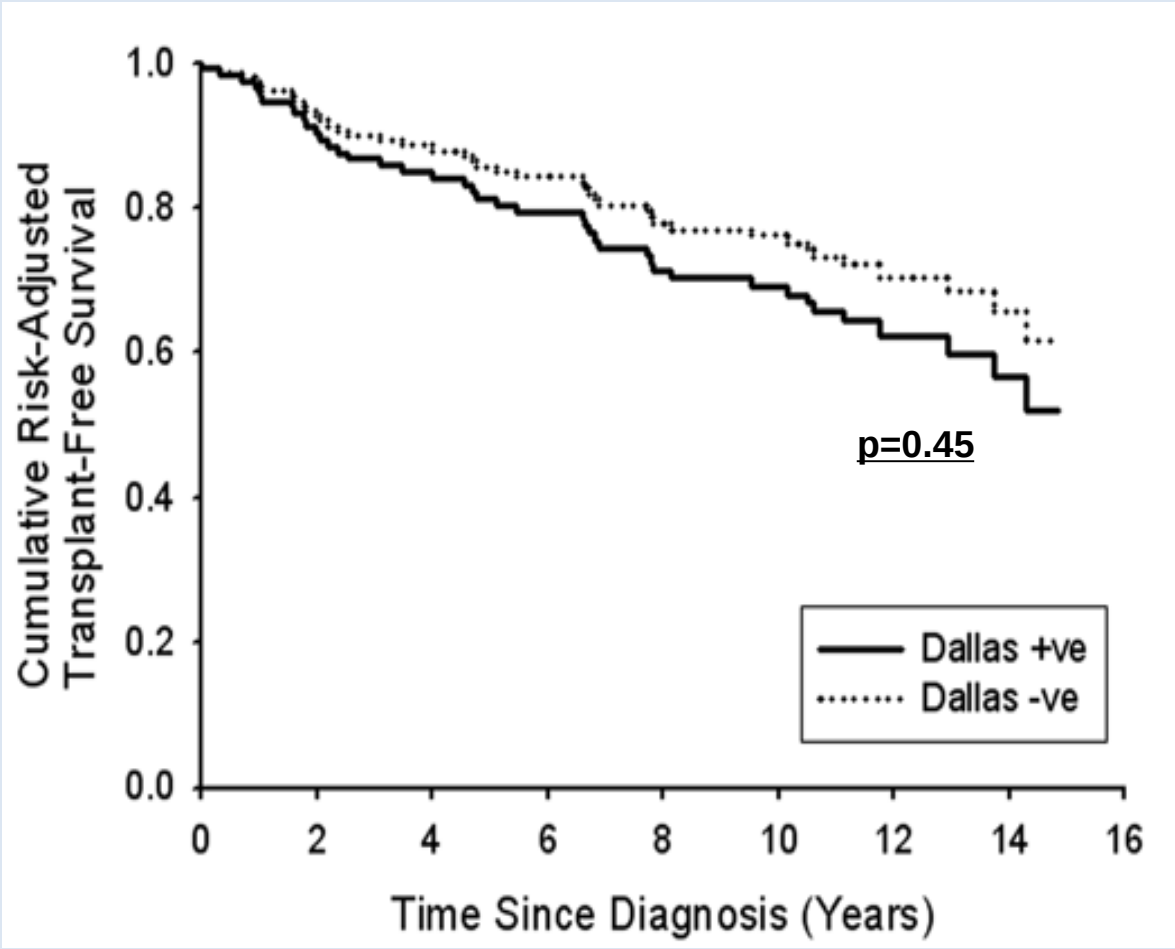


N=111

Histology - Dallas Criteria – Have no prognostic significance

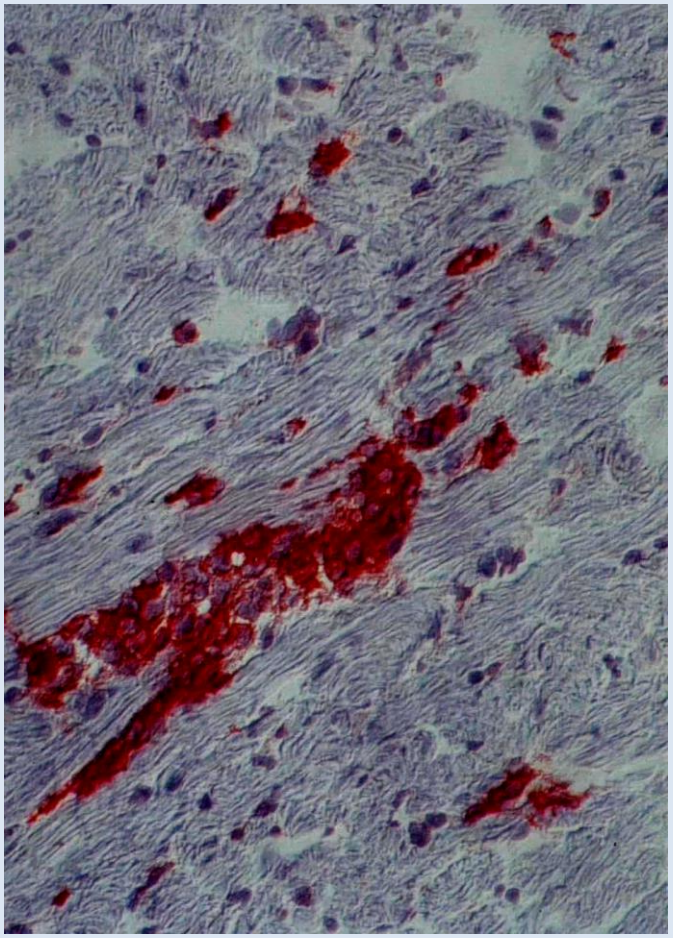
Histology

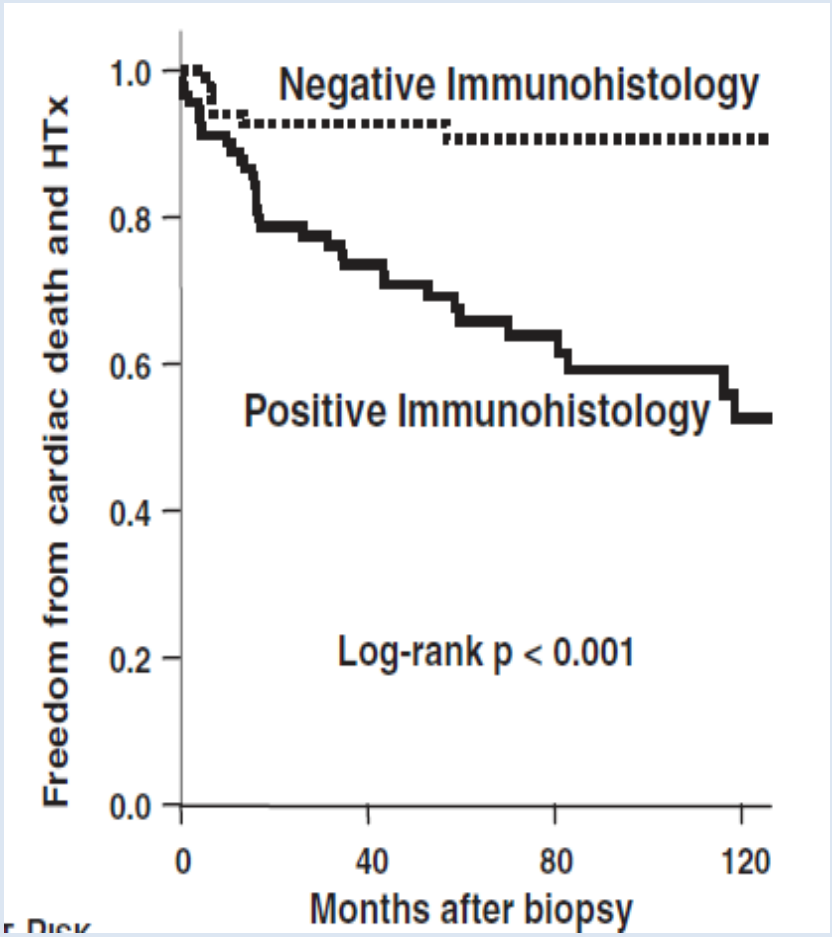




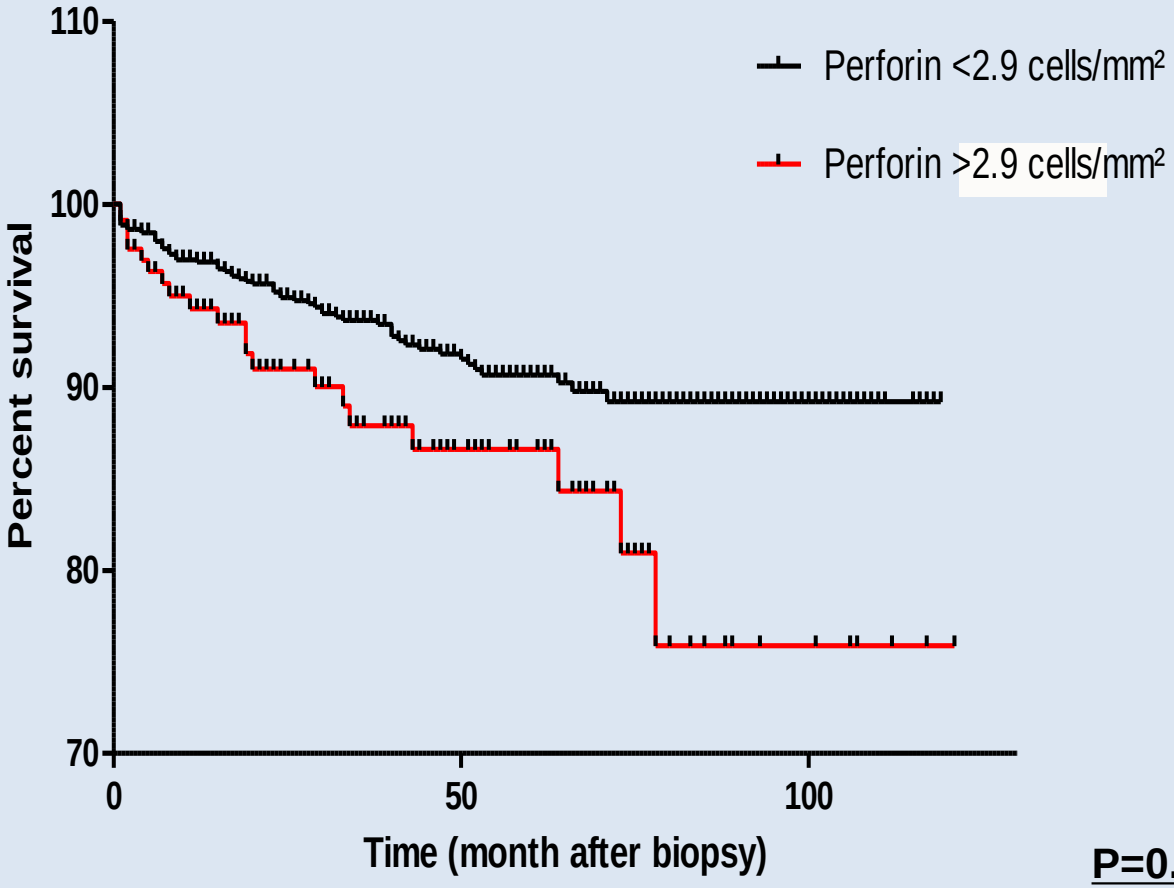
Grogan M et al. JACC 1995

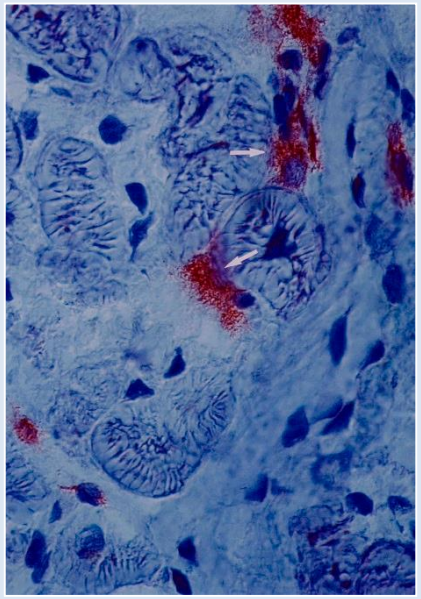
Immunohistology criteria – have a prognostic significance





Immunohistology criteria – Perforin has a prognostic significance





P=0.001

N = 2389

CHARITÉ UNIVERSITÄTSMEDIZIN BERLIN

Prof Carsten Tschöpe Cardiology

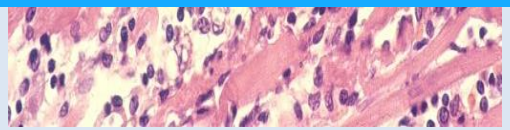
Escher et al.

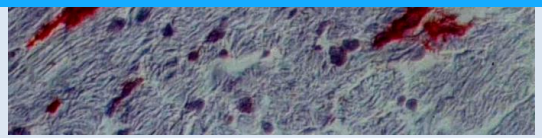
The requirement for a specific treatment strategy for myocarditis is a comprehensive diagnostic by an endomyocardial biopsy

Histology

Immuno-histology

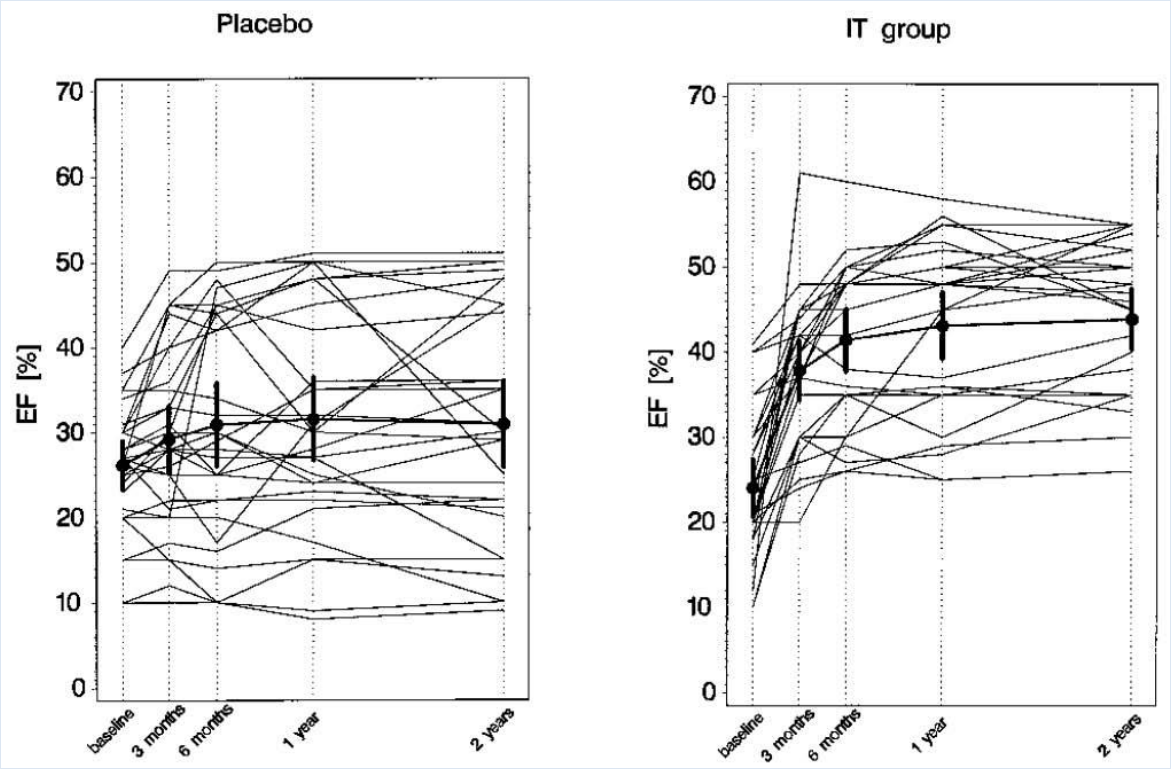
No interventional studies are available using immunohistolgical biopsy marker in acute myocarditis





Immunohistology Criteria (HLA pos) – Immun-suppression in the chronic phase of myocarditis

Serial EF in 58 patients with completed 2 years of follow-up. placebo (n = 30), immunosuppression (n =28)



Immunohistology Criteria – Immunosuppression in the chronic phase of myocarditis

21 responder after immunosuppressive therapy

		Baseline				After 6-Month IT*	
Pt	Age/Sex	EF, %	NYHA Class	Cardiac AutoAb	Months Since Disease Onset	EF, %	NYHA Class
1	37/M	23	IV	+	9	54	I
2	53/M	24	IV	+	8	39	II
3	50/M	24	IV	+	9	47	I
4	30/F	21	IV	+	10	40	II
5	34/M	32	III	+	8	45	I
6	49/M	32	III	–	9	45	II
7	53/M	30	III	–	9	44	II
8	19/M	28	III	+	8	48	I
9	18/M	23	IV	+	9	45	I
10	23/F	18	IV	+	7	49	I
11	36/F	25	IV	+	8	54	I
12	51/M	22	IV	+	10	41	II
13	35/M	24	IV	+	10	51	I
14	15/M	27	IV	+	8	44	II
15	33/F	29	IV	+	11	47	I
16	59/F	23	III	+	12	48	I
17	60/F	33	III	+	8	52	II
18	54/F	21	IV	+	9	53	I
19	50/M	26	IV	+	12	45	II
20	33/F	26	III	+	11	51	I
21	60/F	29	IV	+	10	50	I

IT indicates immunosuppressive treatment, Pt, patient; EF, ejection fraction; and AutoAb, autoantibodies.

20 non- responder after immunosuppressive therapy

		Baseline				After 6 Month IT	
Pt	Age/Sex	EF, %	NYHA Class	Cardiac AutoAb	Months Since Disease Onset	EF, %	NYHA Class
1	55/M	21	IV	–	8	16	IV
2	62/F	23	IV	–	9	22	IV
3	29/F	33	IV	–	10	29	IV
4	37/M	30	III	–	11	24	III
5	50/M	25	IV	–	12	20	IV
6	52/M	26	IV	–	8	24	IV
7	59/M	25	IV	–	9	17	III
8	54/M	33	IV	–	7	32	IV*
9	49/M	28	IV	–	10	27	III
10	37/M	32	III	–	11	28	IV*
11	59/M	30	III	–	9	15	IV*
12	25/M	21	IV	–	9	20	IV†
13	51/M	24	IV	–	8	24	IV*
14	41/M	31	III	–	10	26	IV*
15	48/M	31	IV	–	8	28	IV†
16	26/M	19	IV	–	9	18	III
17	34/M	25	IV	–	8	24	IV†
18	27/M	29	III	–	10	20	IV
19	57/F	32	III	–	10	28	III
20	56/M	27	IV	–	9	24	III

IT indicates immunosuppressive treat… patient; EF, ejection fraction; and AutoAb,

Immunohistology Criteria – Immunosuppression in the chronic phase of myocarditis

18/21 responder were virus - negative

17/20 non- responder were virus-positive

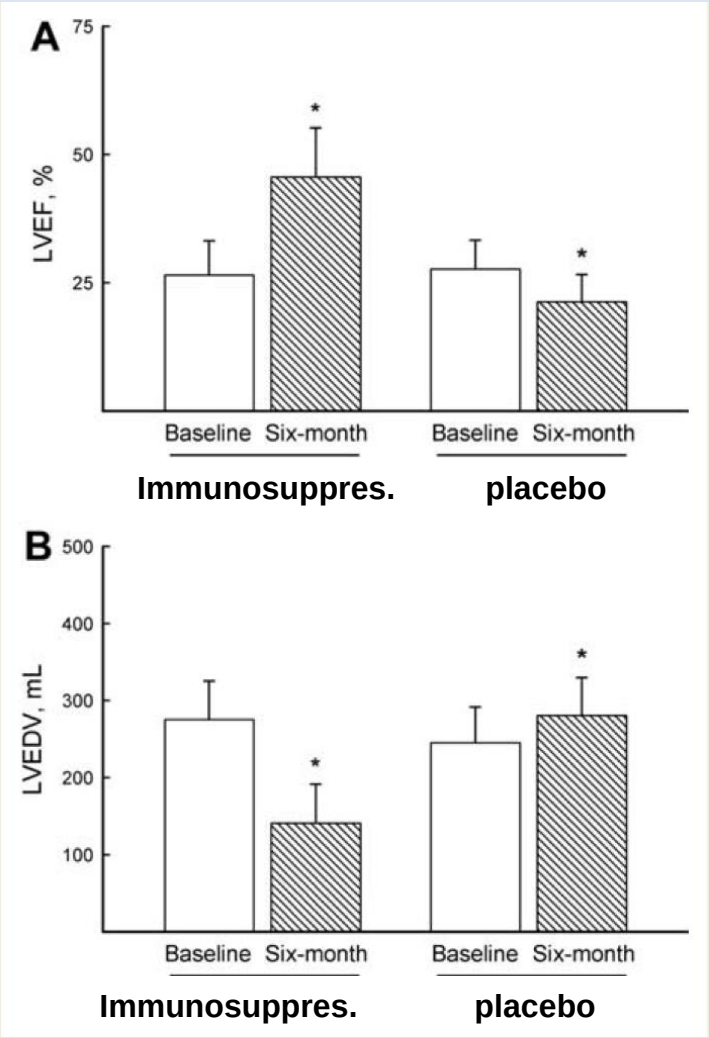
		Baseline					After 6-Month IT*	
Pt	Age/Sex	EF, %	NYHA Class	Viral Agent	Cardiac AutoAb	Months Since Disease Onset	EF, %	NYHA Class
1	37/M	23	IV	–	+	9	54	I
2	53/M	24	IV	–	+	8	39	II
3	50/M	24	IV	–	+	9	47	I
4	30/F	21	IV	–	+	10	40	II
5	34/M	32	III	–	+	8	45	I
6	49/M	32	III	–	–	9	45	II
7	53/M	30	III	–	–	9	44	II
8	19/M	28	III	–	+	8	48	I
9	18/M	23	IV	HCV	+	9	45	I
10	23/F	18	IV	–	+	7	49	I
11	36/F	25	IV	HCV	+	8	54	I
12	51/M	22	IV	–	+	10	41	II
13	35/M	24	IV	–	+	10	51	I
14	15/M	27	IV	–	+	8	44	II
15	33/F	29	IV	–	+	11	47	I
16	59/F	23	III	–	+	12	48	I
17	60/F	33	III	HCV	+	8	52	II
18	54/F	21	IV	–	+	9	53	I
19	50/M	26	IV	–	+	12	45	II
20	33/F	26	III	–	+	11	51	I
21	60/F	29	IV	–	+	10	50	I

IT indicates immunosuppressive treatment; Pt, patient; EF, ejection fraction; and AutoAb, autoantibodies.

		Baseline					After 6 Month IT	
Pt	Age/Sex	EF, %	NYHA Class	Viral Agent	Cardiac AutoAb	Months Since Disease Onset	EF, %	NYHA Class
1	55/M	21	IV	–	–	8	16	IV
2	62/F	23	IV	EBV	–	9	22	IV
3	29/F	33	IV	INFA	–	10	29	IV
4	37/M	30	III	PVB19	–	11	24	III
5	50/M	25	IV	EBV	–	12	20	IV
6	52/M	26	IV	EBV	–	8	24	IV
7	59/M	25	IV	–	–	9	17	III
8	54/M	33	IV	AV	–	7	32	IV*
9	49/M	28	IV	–	–	10	27	III
10	37/M	32	III	EV	–	11	28	IV*
11	59/M	30	III	AV	–	9	15	IV*
12	25/M	21	IV	AV+EV	–	9	20	IV†
13	51/M	24	IV	EV	–	8	24	IV*
14	41/M	31	III	AV	–	10	26	IV*
15	48/M	31	IV	EV	–	8	28	IV†
16	26/M	19	IV	EBV	–	9	18	III
17	34/M	25	IV	EV	–	8	24	IV†
18	27/M	29	III	EV	–	10	20	IV
19	57/F	32	III	EBV	–	10	28	III
20	56/M	27	IV	AV	–	9	24	III

IT indicates immunosuppressive treatment; Pt, patient; EF, ejection fraction; and AutoAb,

Immunosuppression in virus-negative DCMi: 6 months Follow-up – TIMIC Study



Randomized, double-blind, placebo-controlled study

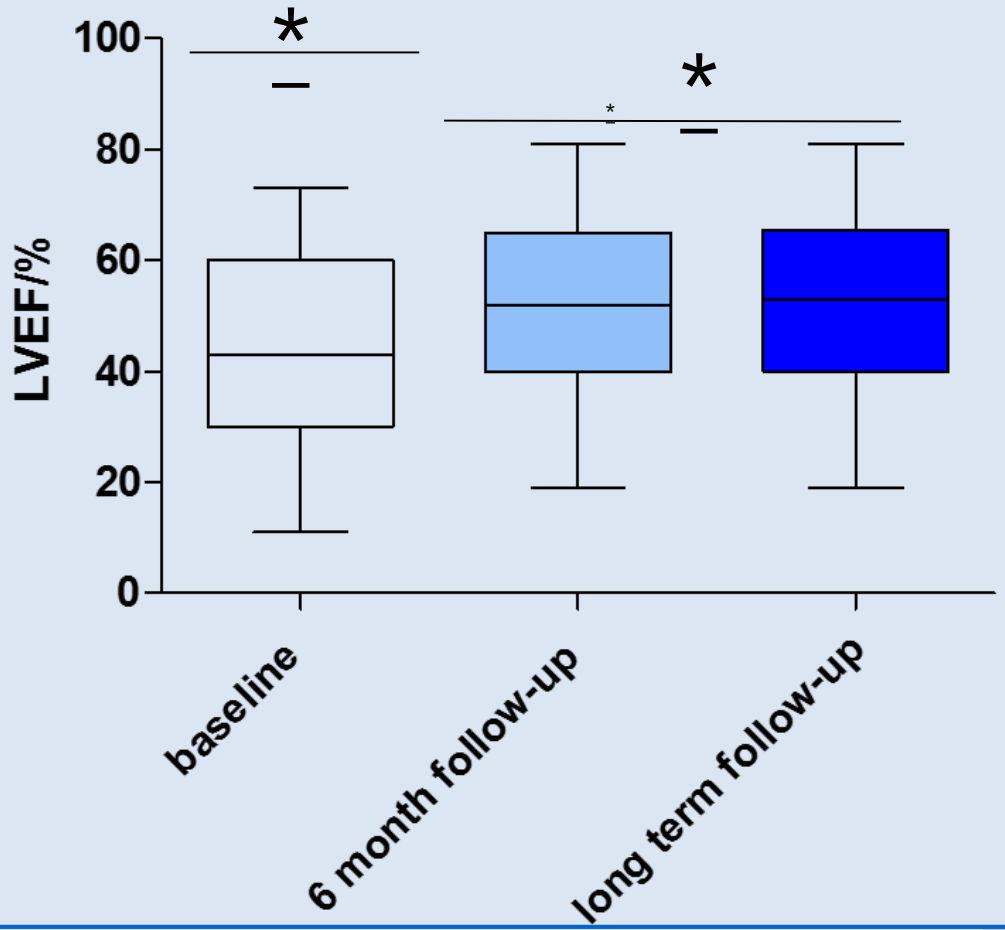
n=85 patients

Placebo: **n= 42 patients**
Immunosuppression: **n= 43 patients**
Prednisone / Azathioprine

* P<0.05

Frustaci et al. Eur Heart J 2009

Immunosuppression in immunohistology positive and viral negative chronic myocarditis in the long-term follow up (6Y)



*p<0.005

Time dependent response to immunomodulatory therapy

Data from 130 patients in 3 placecbo-controlled trials if immunomodulatory therapy in DCM were combined and prospectively analysed

Association of symptom duration with change in left ventricular ejection fraction

Symptom	Time after	LV-EF increase (%)	Wilcoxon rank sum test	
Duration (months)	Baseline (months)	Placebo	IT	*p* values
<6	6	13.3	14.3	0.8355
	12	15.2	14.8	0.7434
≥6	6	4.4	14.4	<0.001
	12	5.6	19.5	<0.001

LV-EF, left ventricular ejection fraction; IT, immunomodulatory therapy.

Stanton et al. Int J Cardiol 2008

Status of other discussed therapeutic Options
Chronic forms of myocarditis

Chronic/autoimmune myocarditis (inflammatory cardiomyopathy).

- Immunglobulins
- Immunadsorption
- ß1 receptor auto antibody antagonist/elimination

Under Investigation:

- CD20 Inhibition*
- Colchicine*
- Anti-Cytokines
- Mesenchymal stromal cell application*

Dominguez F et al. Rev Esp Cardiol 2016

* Tschöpe et al

Status of other discussed therapeutic Options
Chronic forms of myocarditis

Chronic/autoimmune myocarditis (inflammatory cardiomyopathy).

- **Immunglobulins**
- **Immunadsorption**
- **ß1 receptor auto antibody antagonist**

Under Investigation:

- **CD20 Inhibition***
- **Colchicine***
- **Anti-Cytokines**
- **Mesenchymal stromal cell application***

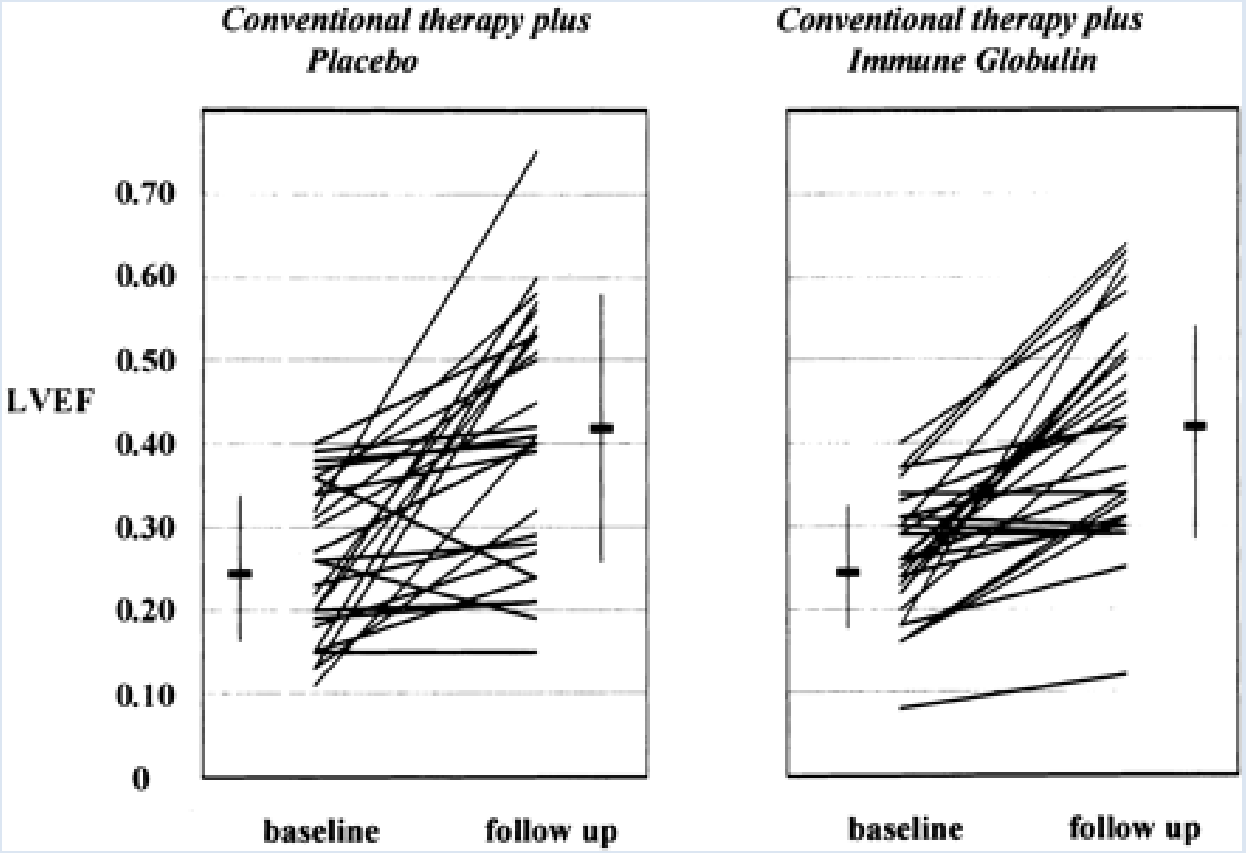
Dominguez F et al. Rev Esp Cardiol 2016

* Tschöpe et al

Clincal evidence

IMAC-Studie acute myocarditis or recent –onset DCM

Placebo-controlled application of 2 g/kg over a period of 2-4 days (n=62)
No biopsy proven study
-> No additional benefit in the IVIG group

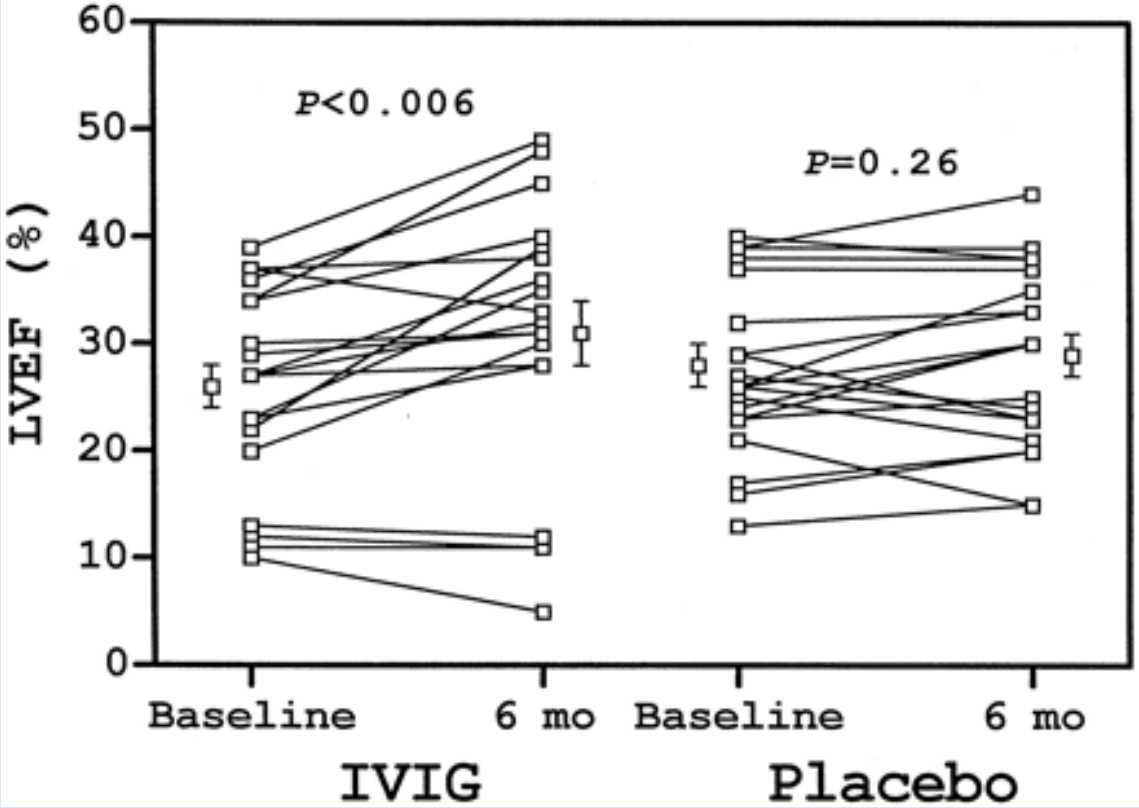


McNamara, et al Circulation 2001

Clincal evidence

First pilot study using IVIG patients with chronic DCMl

Pilotstudie: Placebo-controlled application of 2 g/kg over a period of 5 days and monthy infusions for 5 months in ICM or DCM patients (n=40)
-> additional benefit in the IVIG group of 5 units



Gullestad et al. Circulation 2001

Intravenous immunoglobulins (iv IG) in CHF

Summary

- Mechanisms poorly understood
- no effe
- Co acti stem
- Small s ts
- Different population (DCM,ICM; acute, chronic)
- Different protocols of application

No recommendation for Iv IG in myocarditis

Status of other discussed therapeutic Options
Chronic forms of myocarditis

Chronic/autoimmune myocarditis (inflammatory cardiomyopathy).

- **Immunglobulins**
- **Immunadsorption**
- **ß1 recepter auto antibody antagonism/elimination**

Under Investigation:

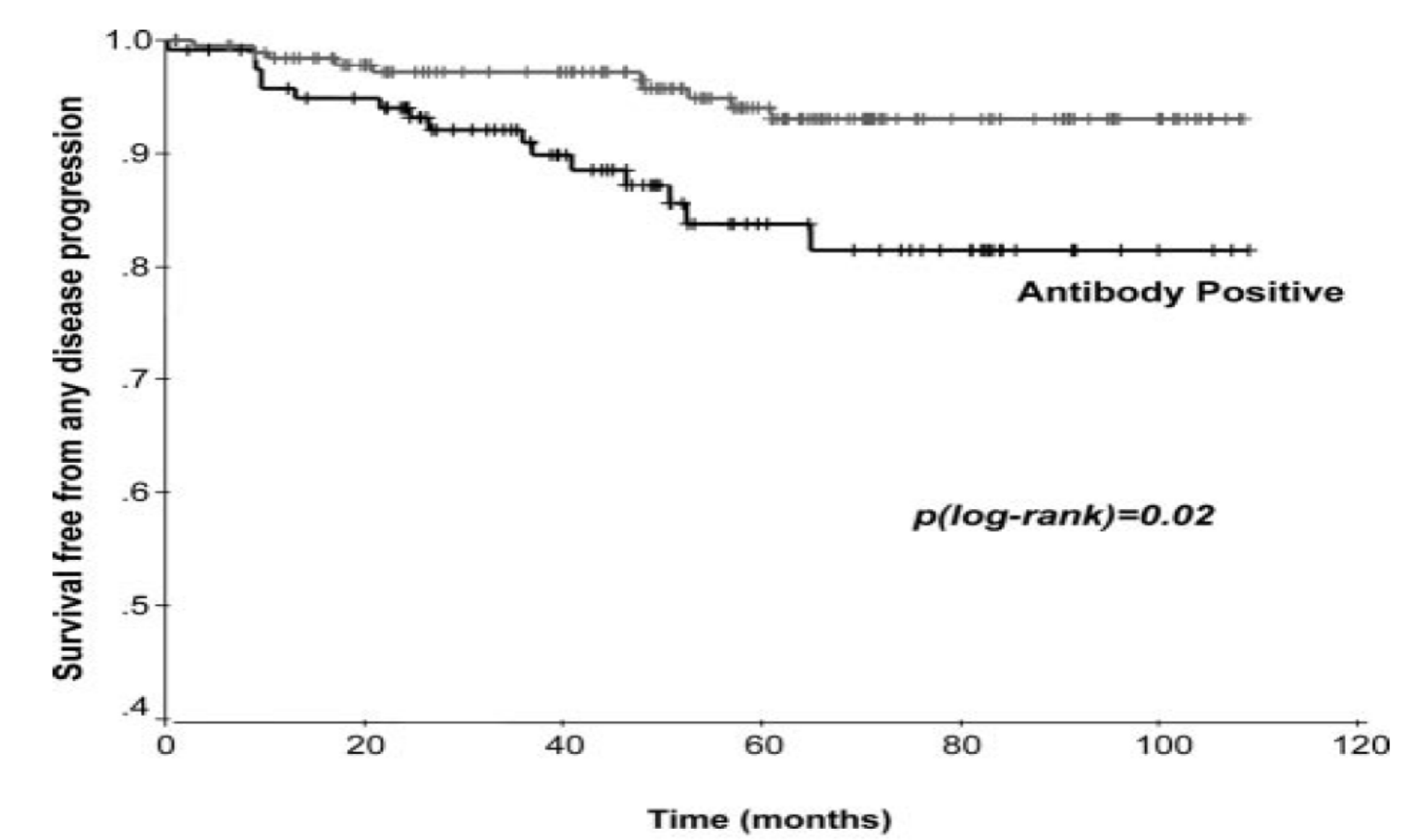
- **CD20 Inhibition***
- **Colchicine***
- **Anti-Cytokines**
- **Mesenchymal stromal cell application***

Dominguez F et al. Rev Esp Cardiol 2016

* Tschöpe et al

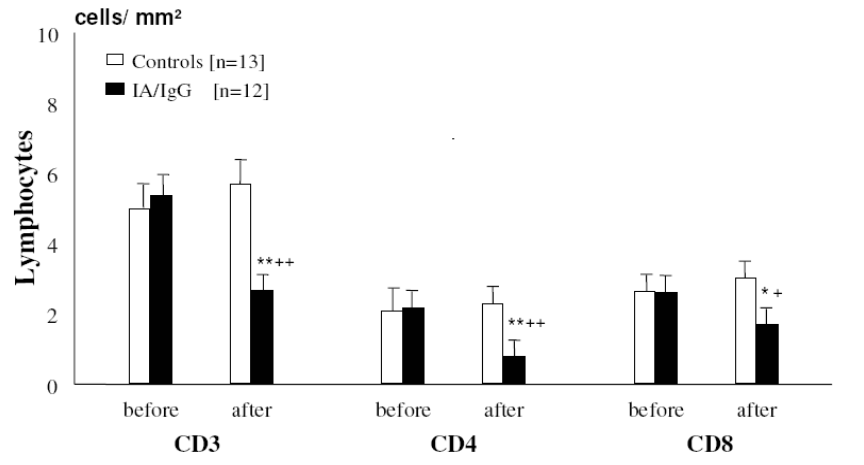
Autoantibodies in DCM

592 relatives of 169 consecutive DCM patients were investigated for having cardiac autoantibodies. When being antibody positive an increased risk for development of DCM

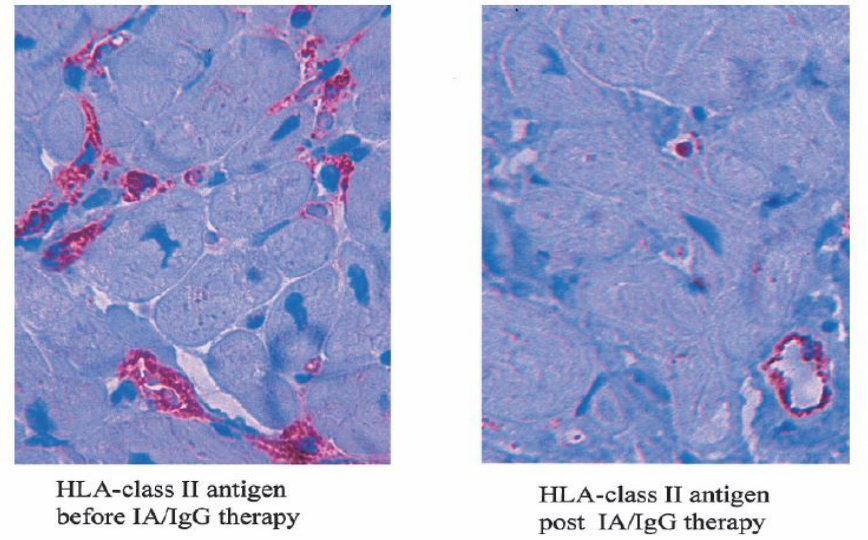


Caforio et al. Circulation 2007

Clincal evidence
Cardiac biopsy anlyzings after Immunadsorption



- Reduction of lymphocyt infiltration



HLA-class II antigen before IA/IgG therapy

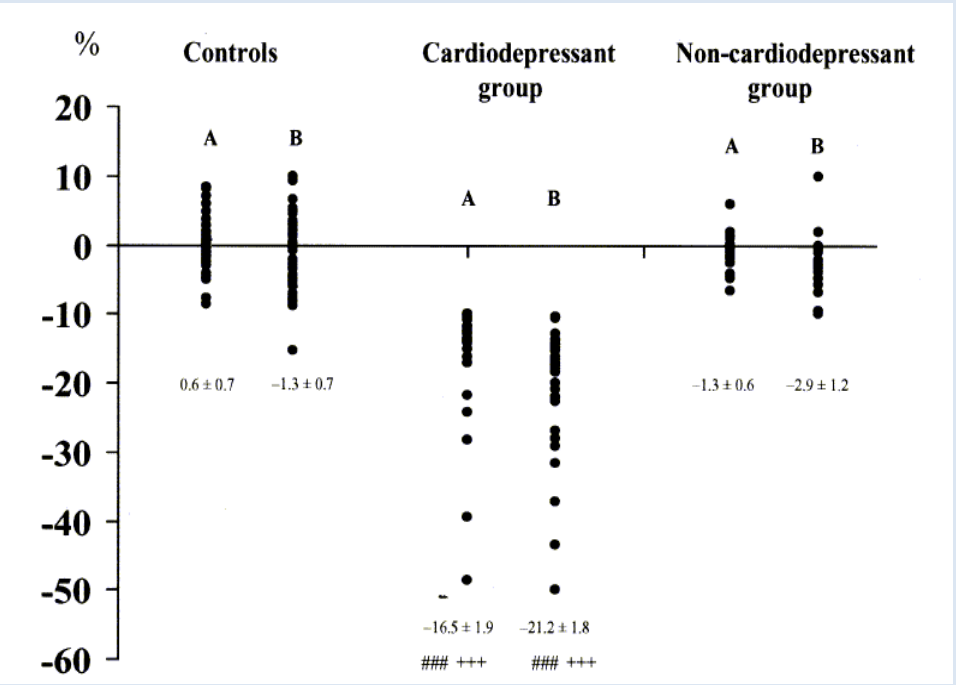
HLA-class II antigen post IA/IgG therapy

- Reduction of HLA Class II Expression

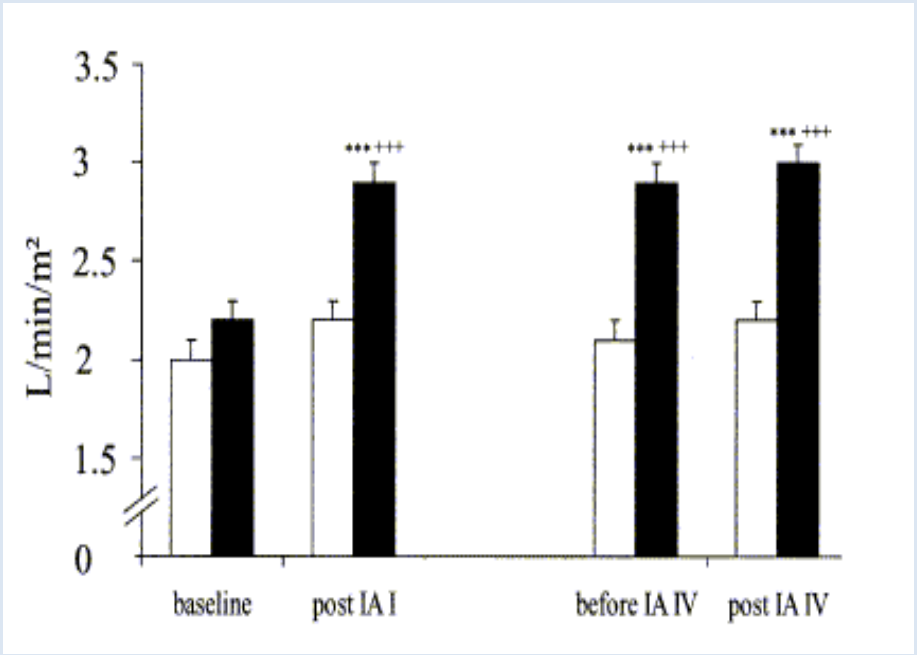
Clincal evidence

Relevance of cardiodepressant antibodies for the outcome of immunoadsorption in DCM

Changes of Ca-transient (A) and shortening (B) of isolated cells



Effect of IA in patient with depressant AB (black) vs. non-depressant AB (white)



Staudt A et al. JACC 2004

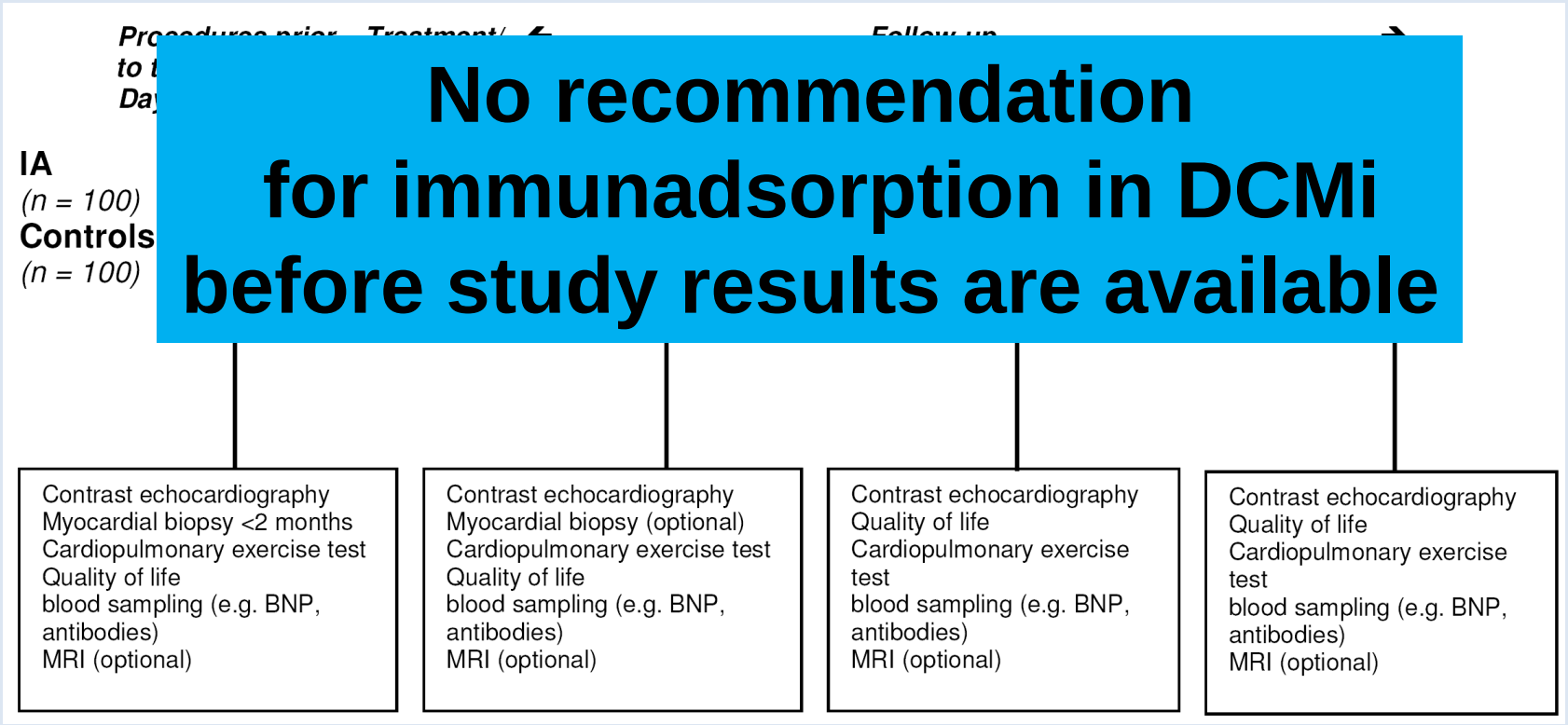
DCM Immunabsorption-Study

Placebo-controlled, multicenter, randomized prospective Study

EF < 40%

Prim. endpoint: Change in EF (after 6 Months)

Sec. endpoint: Total mortality and cardiac morbidity (after 24 Monate)



No recommendation for immunadsorption in DCMi before study results are available

Felix et al
Cardiol et al, Eur Heart J 2013

Current Therapeutic Options in Chronic forms of myocarditis

Chronic/autoimmune myocarditis (inflammatory cardiomyopathy).
Azathioprine
50 mg/12 h for 6 months
Weekly laboratory control with blood count/liver enzymes during the first month
Contemplat… < 1000 l…
Methylpredni…
Initial dose: … mg/kg
After 4 weeks: decrease by 10 mg, and then another 10 mg every 3 weeks until 5-10 mg maintenance dose
6 months
Accompanying treatment in all cases pantoprazole/omeprazole 20 mg/24 h, calcium 1 g/24 h

After Exclusion of viral persistence

Dominguez F et al. Rev Esp Cardiol 2016

Determinates for failure of recover

The clinical recovery rate is dependent from :

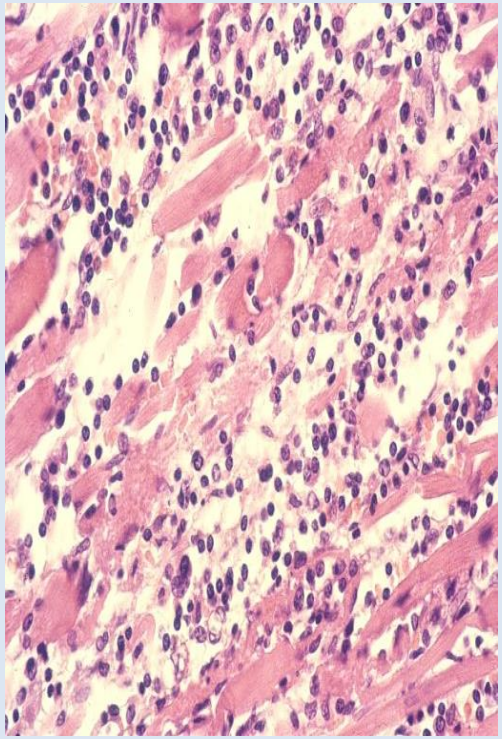
1. Initial defect size

2. Type and phase of inflammatory response

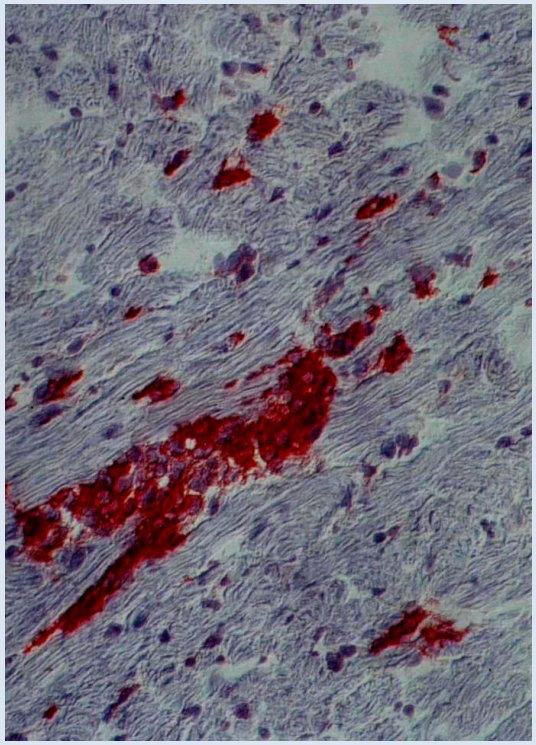
3. Persistence and type of the virus

The requirement for a specific treatment strategy for myocarditis is a comprehensive diagnostic by an endomyocardial biopsy

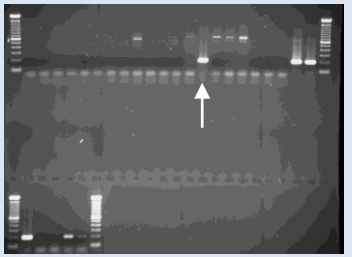
Histology



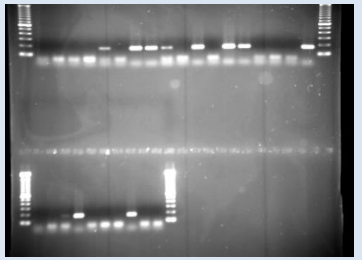
Immuno-Histology



Molecular-biology



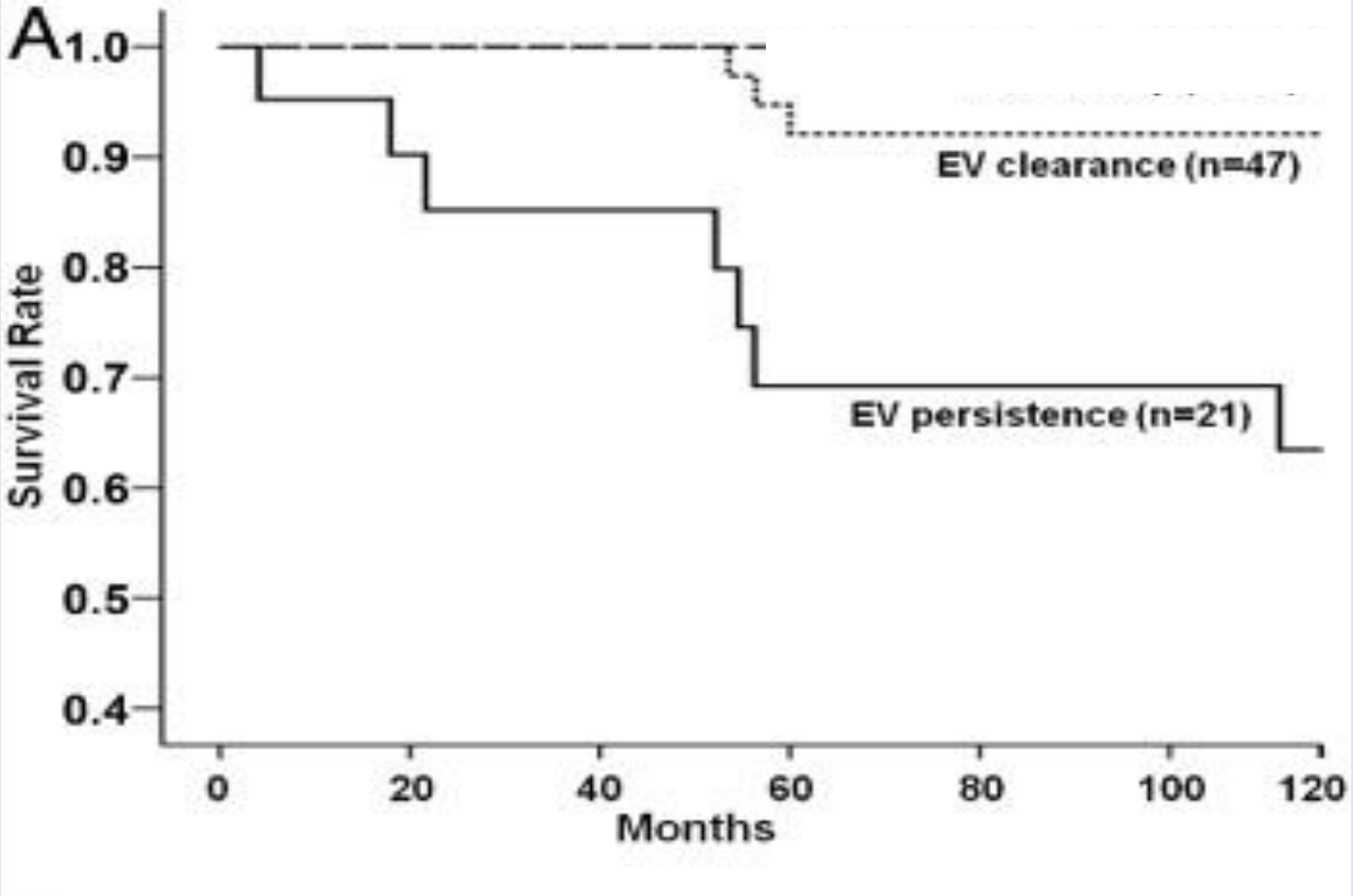
Coxsackie



Parvovirus B19

Caforio et al. Eur Heart J 2013

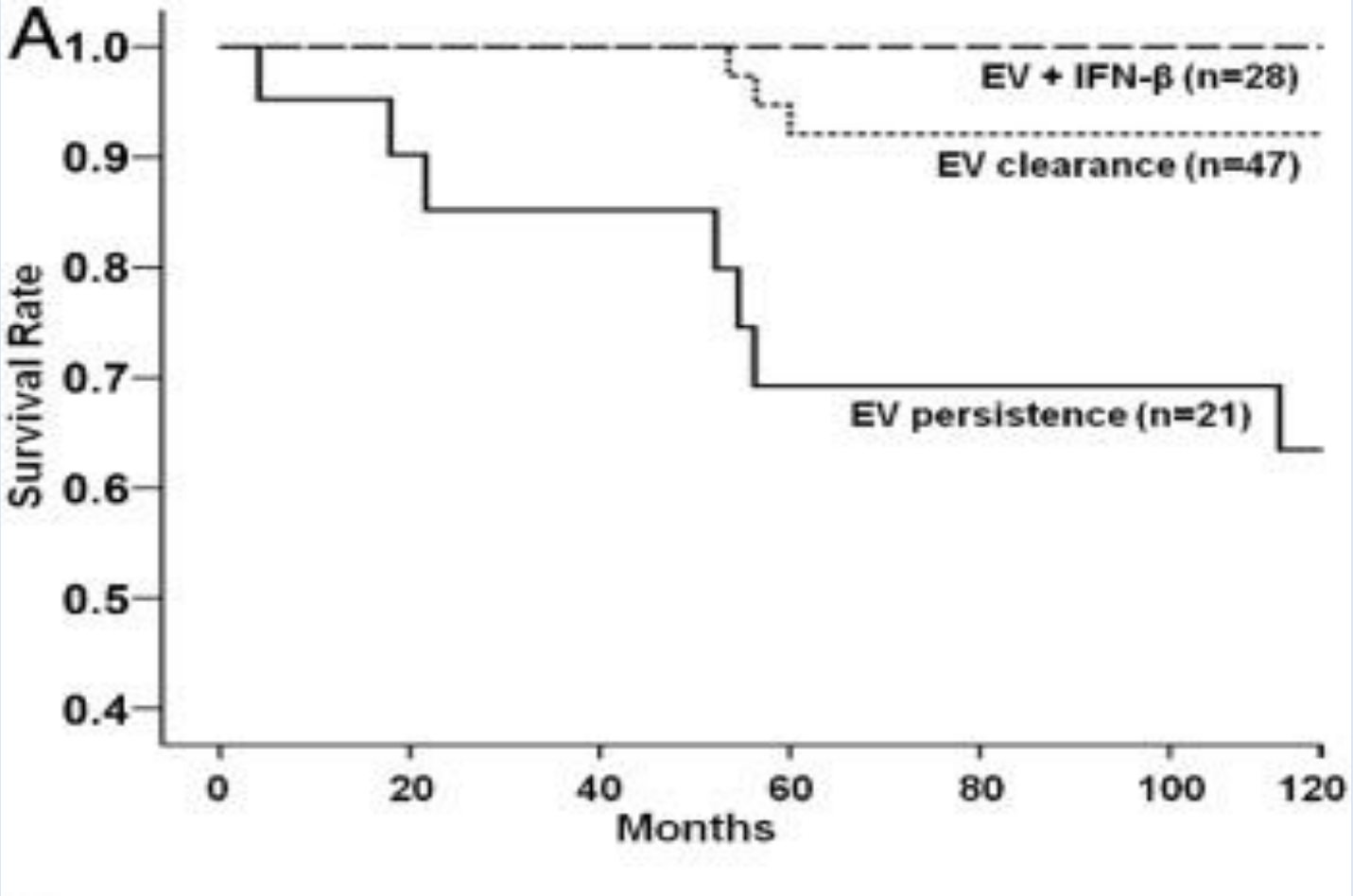
Cardiac Coxsacki virus persistence and prognosis



50% EV Spontan-elimination

Kühl et al. JACC, 2012

Cardiac Coxsacki virus persistence and prognosis



50% EV Spontan-elimination

Kühl et al. JACC, 2012

ß-Interferon in Chronic Viral Cardiomyopathy RCT Phase II – BICC Study

Response variable	Adeno/enterovirus (stratum 1, $n = 15$)		Parvovirus (stratum 2, $n = 128$)		Differences between strata	
	Placebo ($n = 6$)	IFN-β-1b ($n = 9$)	Placebo ($n = 42$)	IFN-β-1b ($n = 86$)	p (two-sided)	p treatment effect (interaction test)
Overall response (virus elimination/reduction, primary)	1 (16.7 %)	4 (44.4 %)	8 (19.0 %)	29 (33.7 %)	0.646	0.652
NYHA improvement	($n = 5$)	($n = 7$)	($n = 37/39$)	($n = 80$)		
Week 0–12	1 (20.0 %)	6 (85.7)	7 (18.9 %)	29 (36.3 %)	**0.039**	0.160
Week 0–24	1 (20.0 %)	6 (85.7)	11 (28.2 %)	31 (38.8 %)	0.100	0.094
Randomised untreated patients	3		3			

ESC recommendation of the Working group

Current state of knowledge on aetiology, diagnosis, management, and therapy of myocarditis: a position statement of the European Society of Cardiology Working Group on Myocardial and Pericardial Diseases

Alida L. P. Caforio[1†*], Sabine Pankuweit[2†], Eloisa Arbustini[3], Cristina Basso[4], Juan Gimeno-Blanes[5], Stephan B. Felix[6], Michael Fu[7], Tiina Heliö[8], Stephane Heymans[9], Roland Jahns[10], Karin Klingel[11], Ales Linhart[12], Bernhard Maisch[2], William McKenna[13], Jens Mogensen[14], Yigal M. Pinto[15], Arsen Ristic[16], Heinz-Peter Schultheiss[17], Hubert Seggewiss[18], Luigi Tavazzi[19], Gaetano Thiene[4], Ali Yilmaz[20], Philippe Charron[21], and Perry M. Elliott[13]

Anti-viral therapies

There is still no approved antiviral-therapy for the treatment of enteroviral infections. Vaccines may be an option in the future.[166] Treatment with acyclovir, gancyclovir, and valacyclovir may be considered in patients with herpes virus infection,[167] although their efficacy is unproven in myocarditis. Preliminary data on interferon-beta treatment suggest that it eliminates enteroviral and adenoviral genomes in patients with left ventricular dysfunction,[168] is associated with improvement in NYHA functional class,[169] and, specifically in enteroviral infection, with a better 10-year prognosis.[152] In general,

ESC recommendation of the Working group

European Heart Journal (2013) **34**, 2636–2648
doi:10.1093/eurheartj/eht210

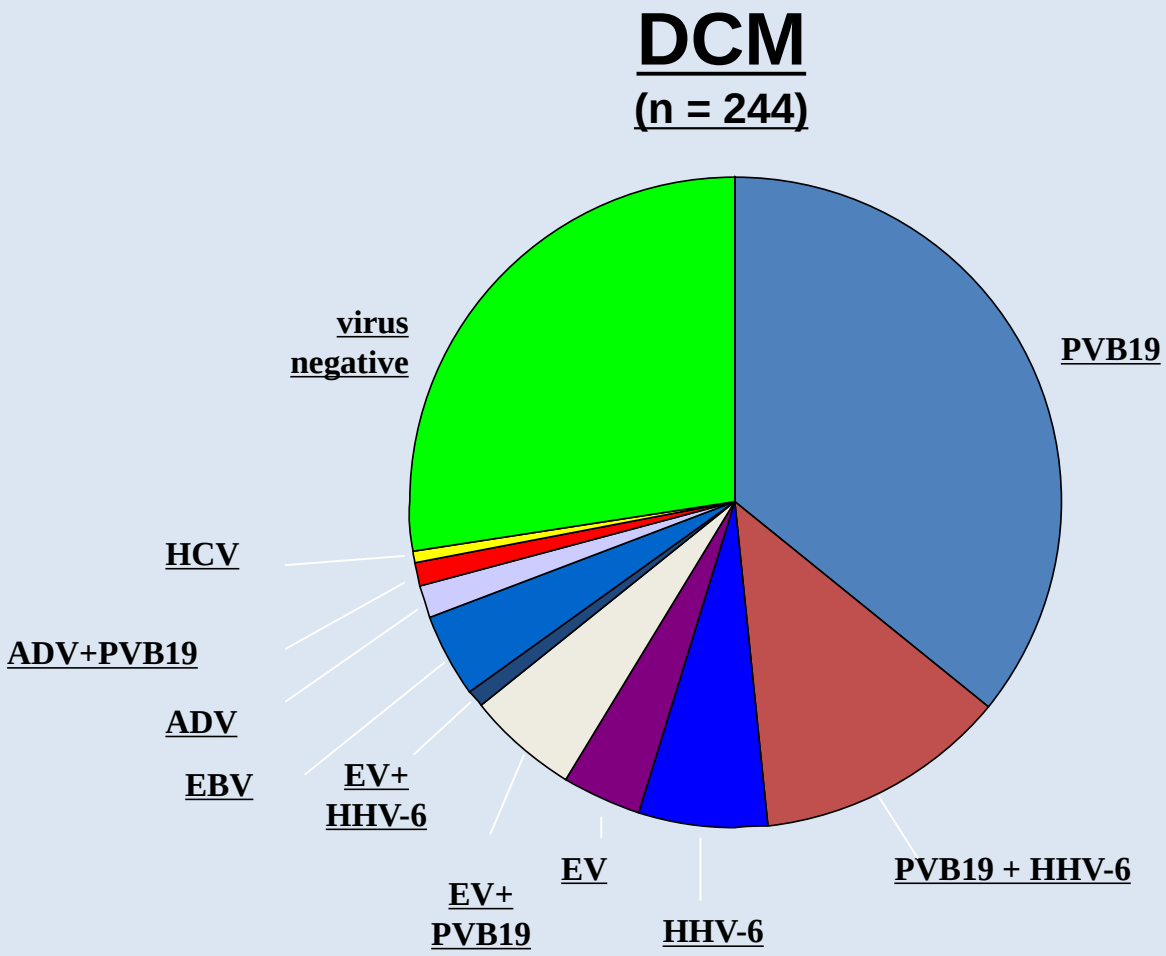
ESC REPORT

Current state of knowledge on aetiology, diagnosis, management, and therapy of myocarditis:

Immunsuppression after exclusion of viral persistence!

Alida L. P. Caforio[1†*], Sabine Pankuweit[2†], Eloisa Arbustini[3], Cristina Basso[4], Juan Gimeno-Blanes[5], Stephan B. Felix[6], Michael Fu[7], Tiina Heliö[8], Stephane Heymans[9], Roland Jahns[10], Karin Klingel[11], Ales Linhart[12], Bernhard Maisch[2], William McKenna[13], Jens Mogensen[14], Yigal M. Pinto[15], Arsen Ristic[16], Heinz-Peter Schultheiss[17], Hubert Seggewiss[18], Luigi Tavazzi[19], Gaetano Thiene[4], Ali Yilmaz[20], Philippe Charron[21], and Perry M. Elliott[13]

Viral genoms in myocardial biopsies



ESC recommendation of the Working group

European Heart Journal (2013) **34**, 2636–2648
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ESC REPORT

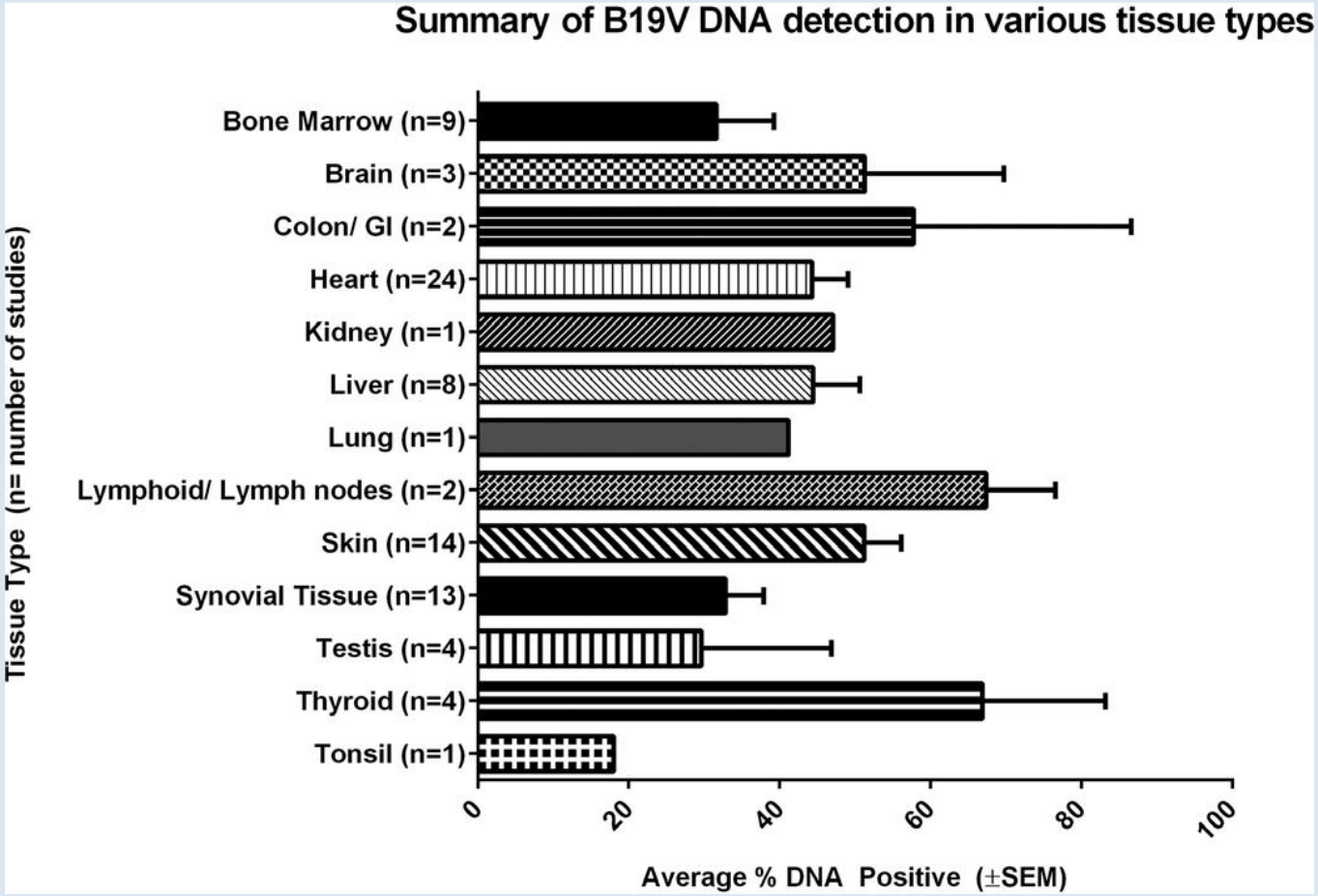
Current state of knowledge on aetiology, diagnosis, management, and therapy of myocarditis:

No word about the parvovirus!

and Pericardial Diseases

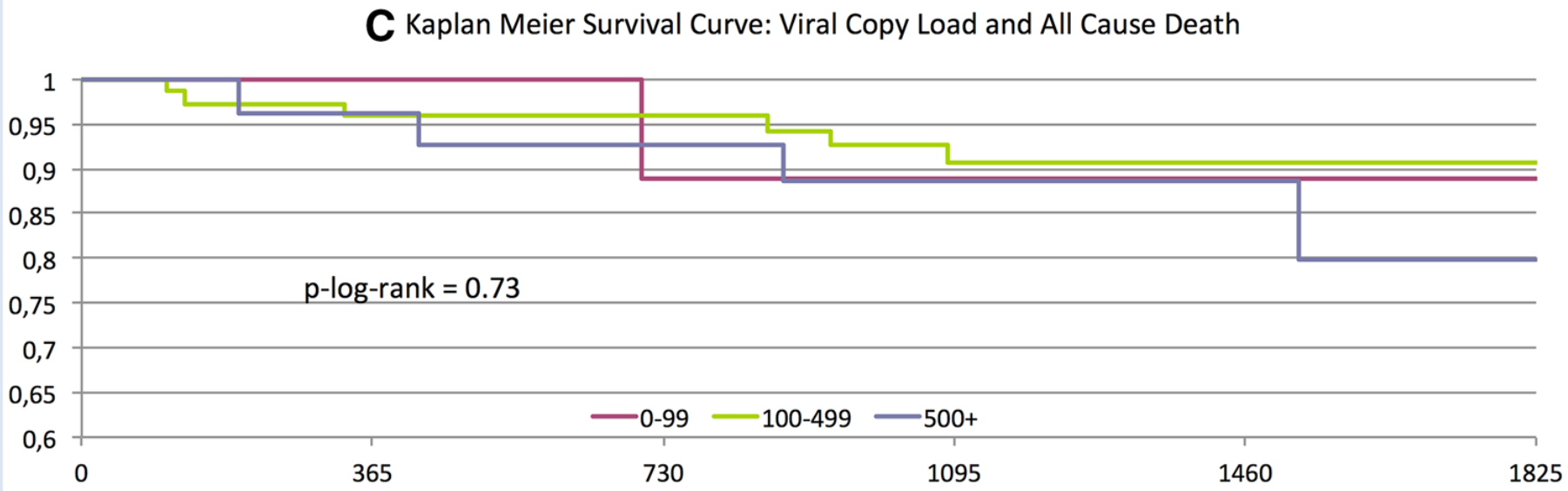
Alida L. P. Caforio[1†*], Sabine Pankuweit[2†], Eloisa Arbustini[3], Cristina Basso[4], Juan Gimeno-Blanes[5], Stephan B. Felix[6], Michael Fu[7], Tiina Heliö[8], Stephane Heymans[9], Roland Jahns[10], Karin Klingel[11], Ales Linhart[12], Bernhard Maisch[2], William McKenna[13], Jens Mogensen[14], Yigal M. Pinto[15], Arsen Ristic[16], Heinz-Peter Schultheiss[17], Hubert Seggewiss[18], Luigi Tavazzi[19], Gaetano Thiene[4], Ali Yilmaz[20], Philippe Charron[21], and Perry M. Elliott[13]

Persistent B19V DNA in non-erythroid tissues: possible role in inflammatory and disease process



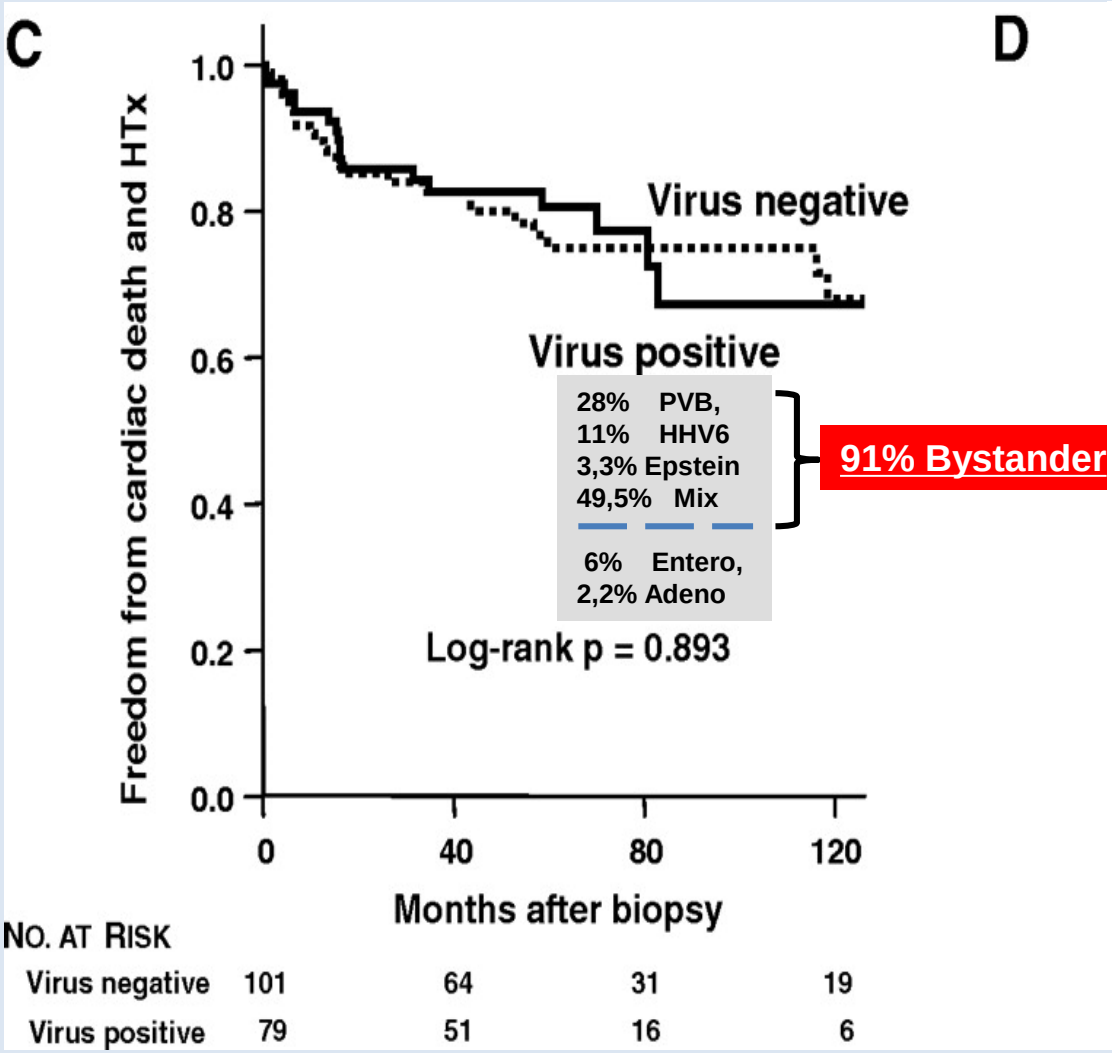
Adlowitz-Small L A et al. Virus Research 2014

No impact of B19V DNA load in EMBs on survival of DCMi patients



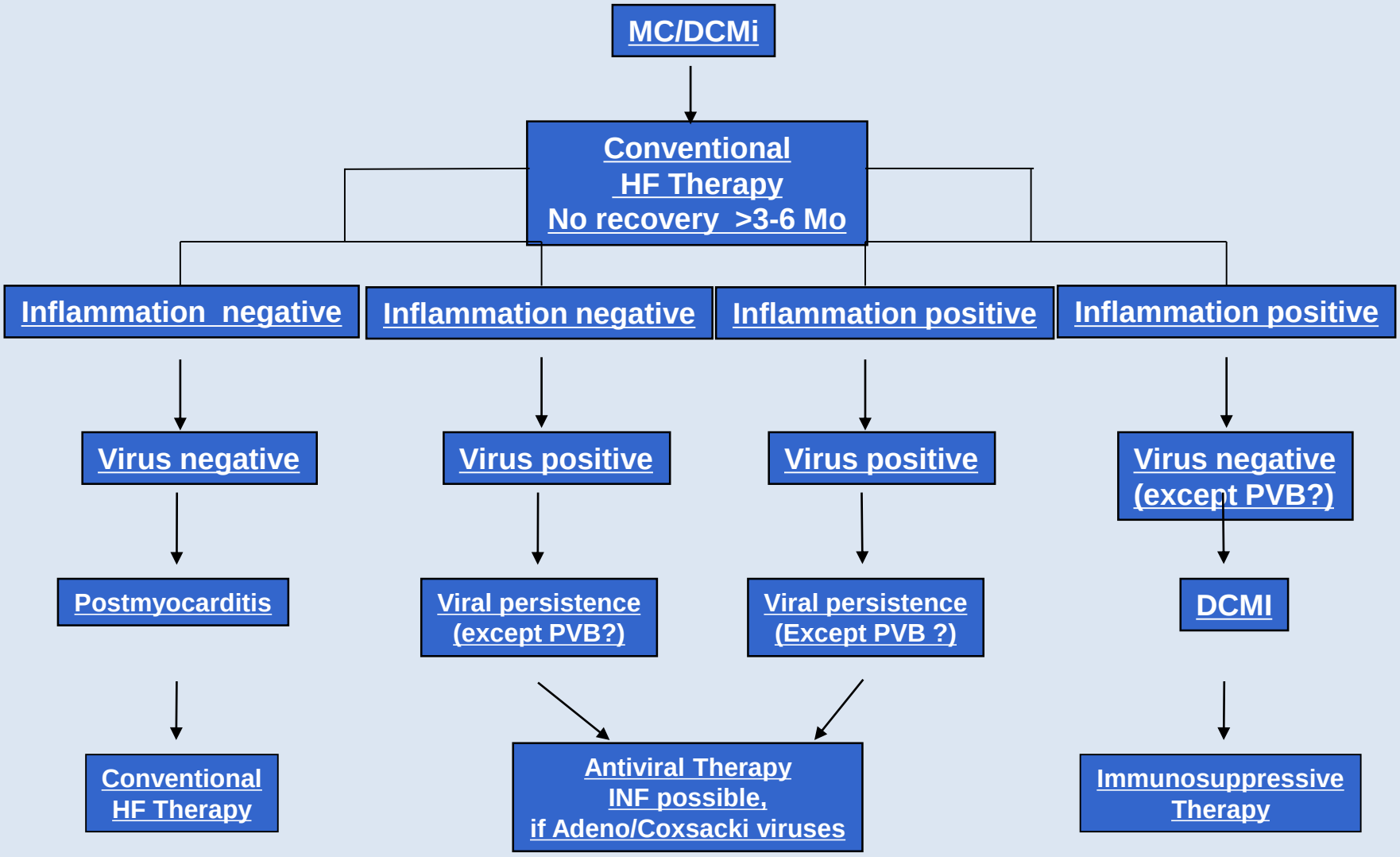
Patients at risk					
Copy Load 0-99	9	8	6	5	2
Copy Load 100-499	69	69	45	19	4
Copy Load > 500	26	25	21	11	1

Unadjusted survival free from cardiac death and heart transplantation according to the findings of endomyocardial biopsy.



Kindermann et al. Circulation. 2008;118:639-648

Biopsie-based Therapy options



Summary of treatment options in myocarditis

1. **Initiation of HF standard therapy in stable acute MC and a follow up based on the high recovery rate is recommend**
2. **Immunosuppressive therapy in cardiogenic pre/shock after biopsy proven existence of inflammation**
3. **Biopsy based therapy indication in MC/DCMi > 3-6 Mo after onset, when chance of recovery becomes low.**

Summary of treatment options in myocarditis

1. Initiation of HF standard therapy in stable acute MC and a follow up based on the high recovery rate is recommend
2. Immunosuppressive therapy in cardiogenic pre/shock after biopsy proven existence of inflammation
3. Biopsy based therapy indication in MC/DCMi > 3-6 Mo after onset, when chance of recovery becomes low.
4. Immunosuppression after exclusion of Coxsacki und adeno viruses
5. Interferonß by Coxsacki/adenoviruses possible – not approved
6. Role of parvovirus as well as herpes virus as known bystander is unclear.

Single centre experience: treat inflammation despite bystanders