

# Management Strategies According to Different Severity & Types of Myocarditis

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[www.hfresearch.eu](http://www.hfresearch.eu)

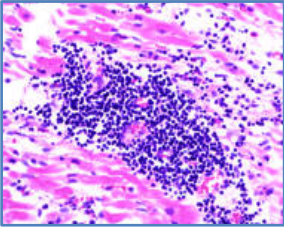


**Maastricht UMC<sup>+</sup>**



# Different severity/types of myocarditis

## Acute Myocarditis



- Smaller group
- Symptoms, ECG  $\Delta$ , troponine  $\uparrow$ ,
- EMB: pronounced inflammation
- CMR: increased T1/T2/LGE inflammation
- 80-90 % spontaneously recover

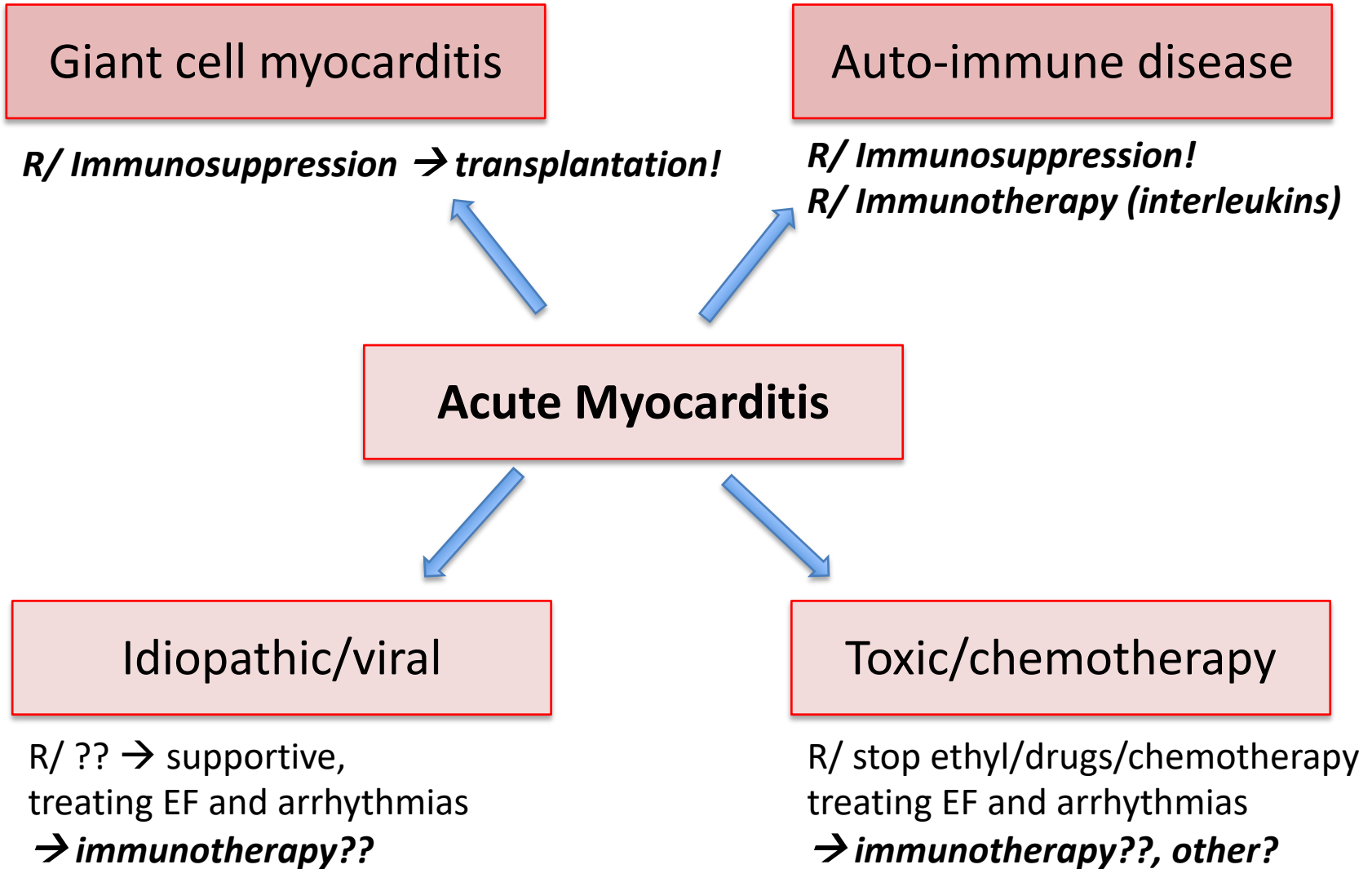
## Chronic Myocarditis



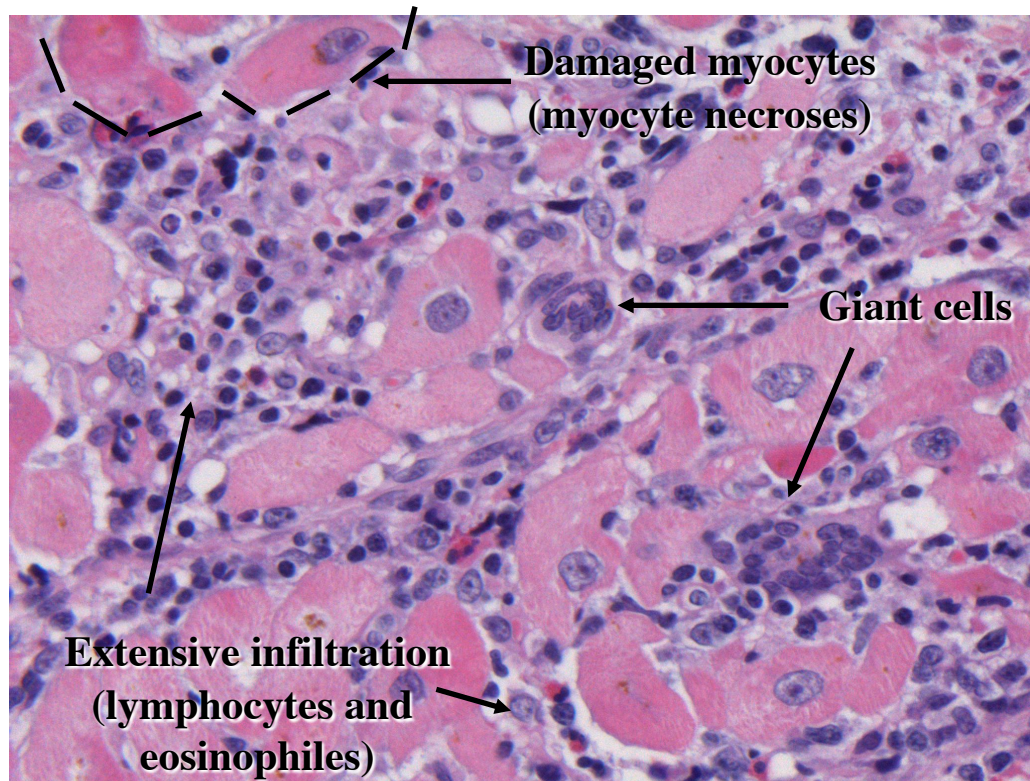
- Larger group (DCM), “mixed bag”
- Low EF, dilated heart
- EMB: subtle increase of T-cells
- CMR: T1/T2 mostly negative
- Less responsive to optimal HF therapy



# Acute Myocarditis

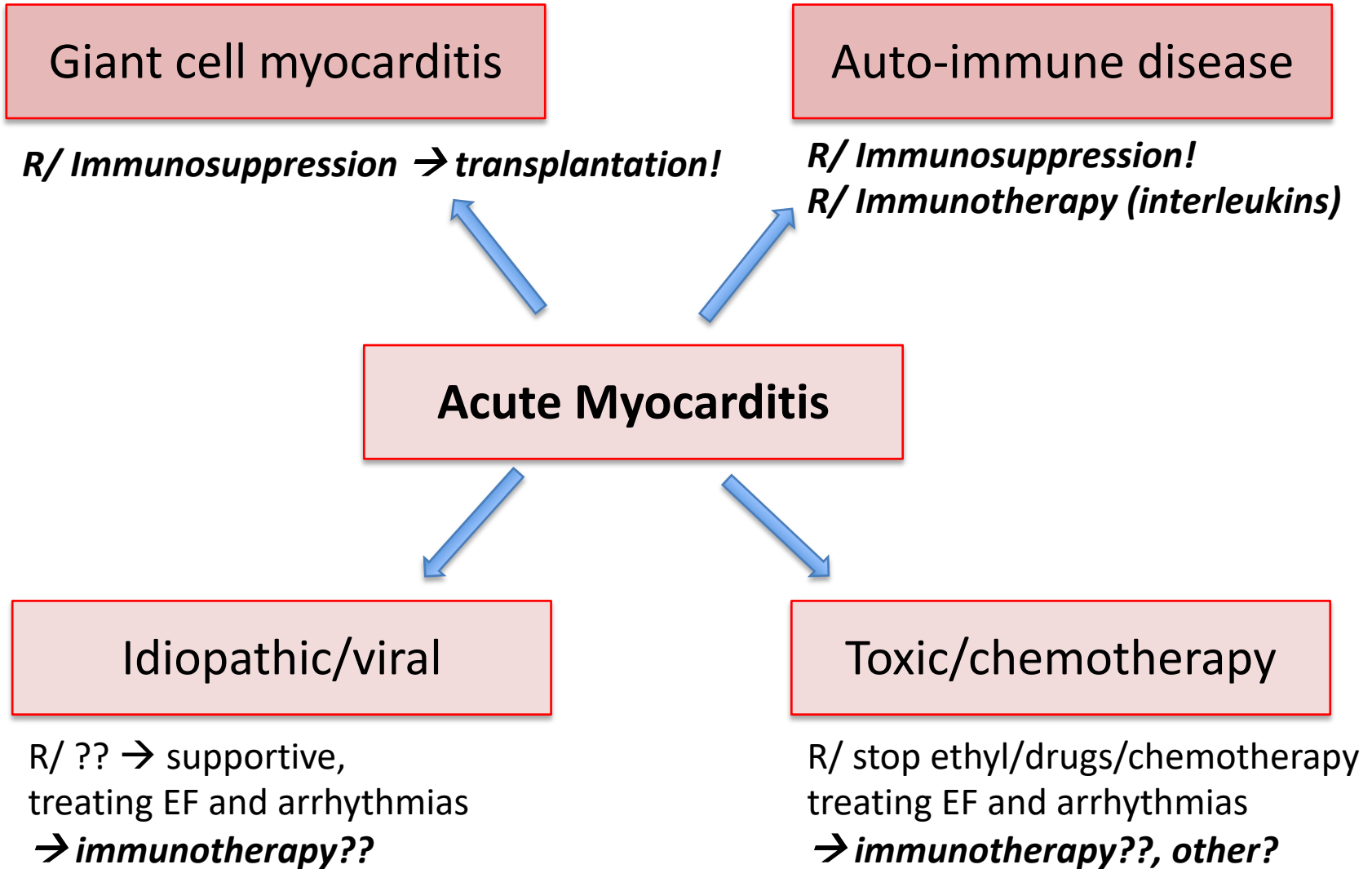


# Acute giant cell myocarditis



35 yrs old female, symptoms, EF 45% → 20% in a few days  
**Triple immunosuppressive therapy + cardiac transplantation !!**

# Acute Myocarditis



# Acute myocarditis due to auto-immune disease

Infectious	
Viral	Parvovirus B19, human herpes virus-6, Epstein-Barr virus, enteroviruses, (coxsackievirus, adenovirus), CMV, HHV-8, HSV-1, HSV-2
Others	<i>Borrelia</i> , <i>Coccidioides immitis</i>
Systemic disease	
Auto-immune and others	Sarcoidosis, giant cell myocarditis, eosinophilic myocarditis, rheumatoid arthritis, rheumatic disease
Toxic	
Medications	Immune check point inhibitors, anthracyclines, clozapine, adrenergic drugs, 5-fluorouracil
Other agents	Alcohol, amphetamines, cocaine

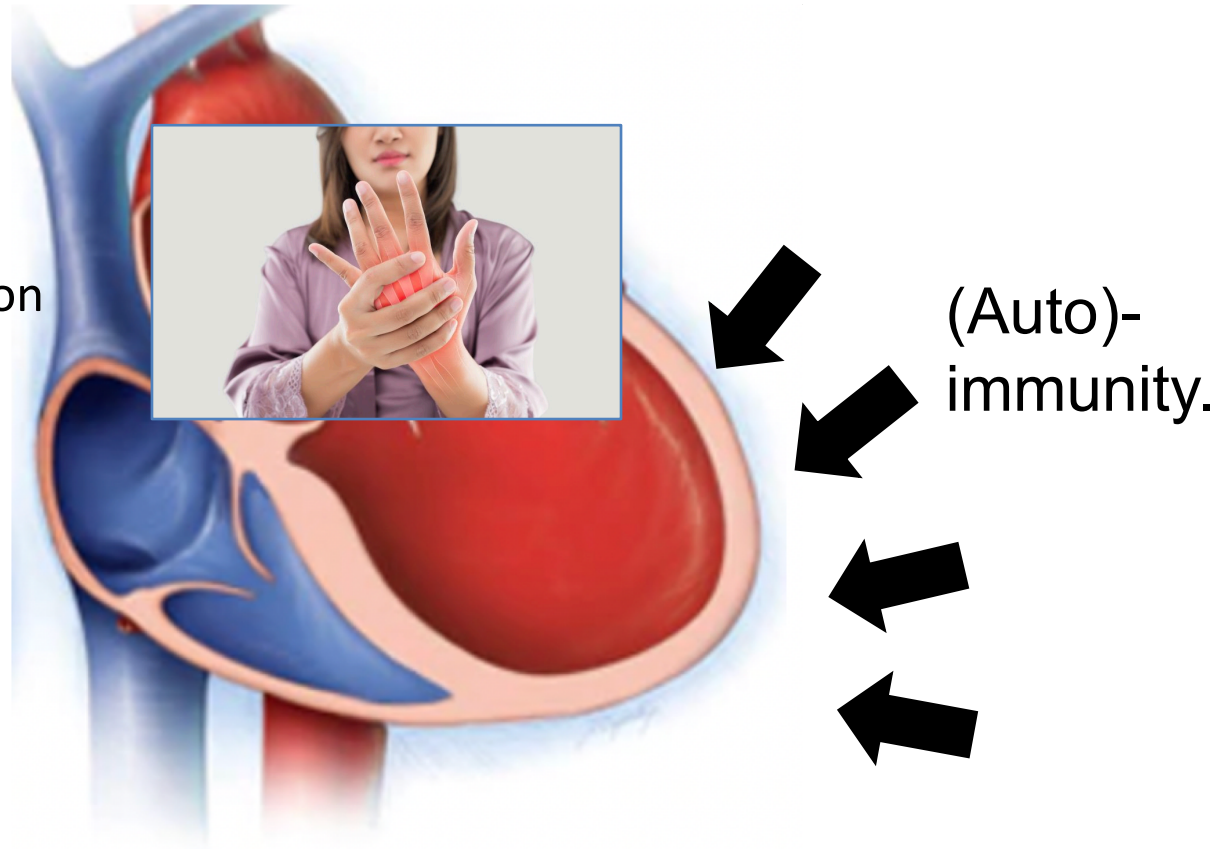
Systemic disease	
Auto-immune and others	Sarcoidosis, giant cell myocarditis, eosinophilic myocarditis, SLE, ANCA-positive vasculitis, rheumatoid arthritis, any other auto-immune disease

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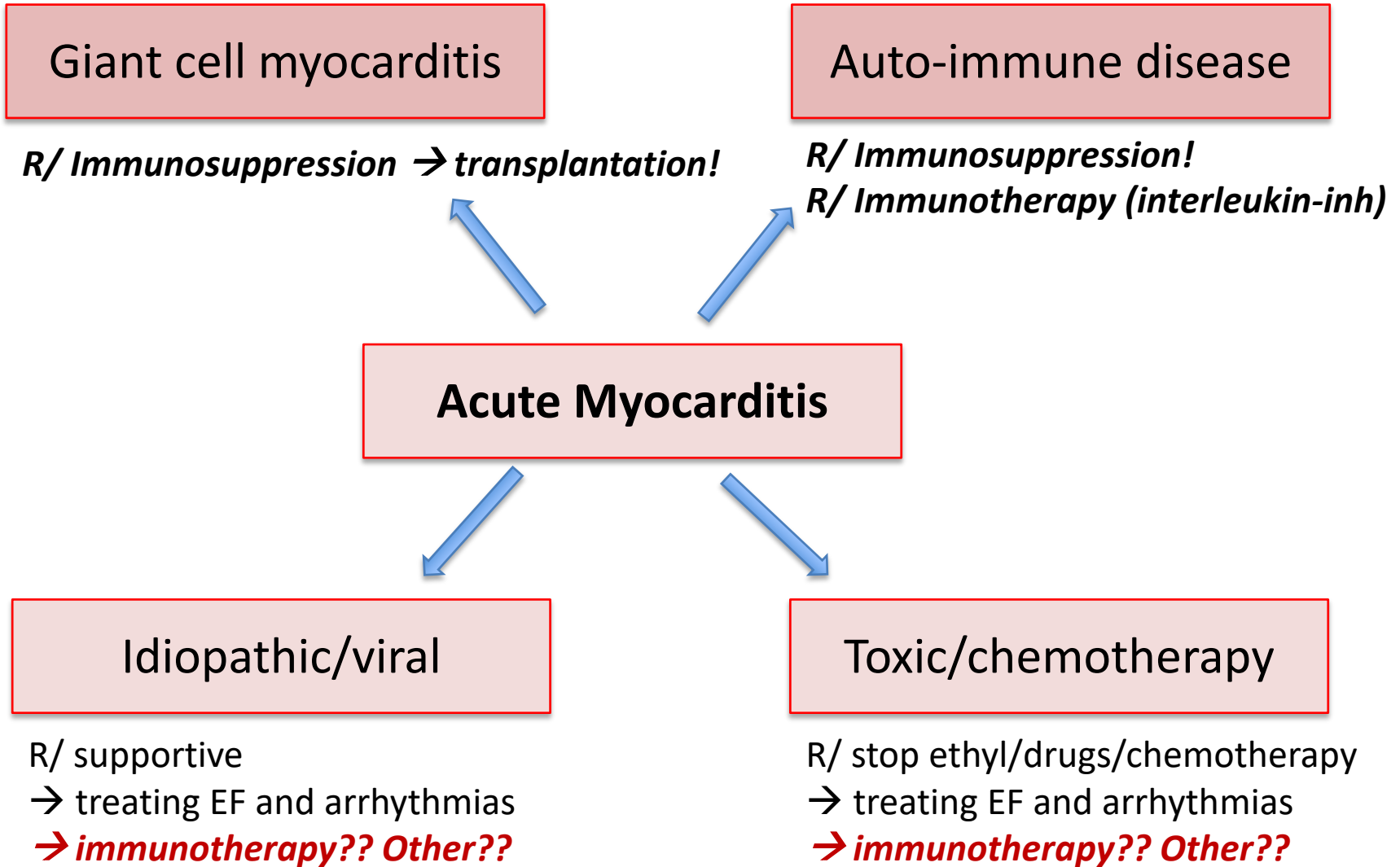
# Auto-immune diseases → myocarditis & dilated CMP

- Female 41 yrs
- Vasculitis in remission
- EF 40 %





# Acute Myocarditis



# Acute myocarditis: chemotherapy

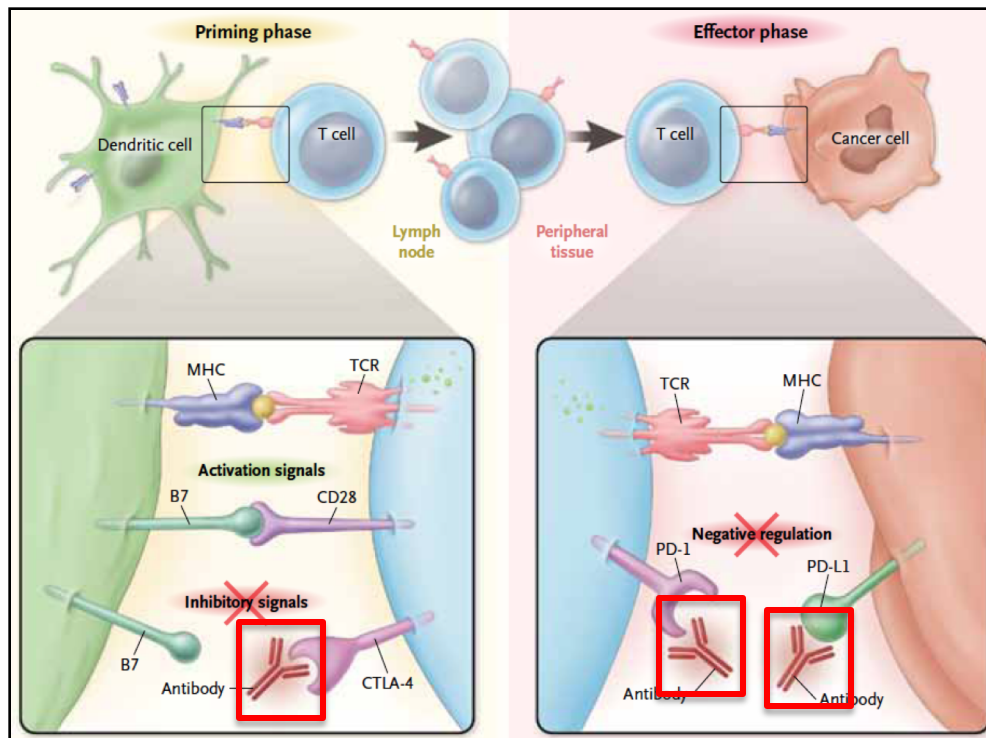
Infectious	
Viral	Parvovirus B19, human herpes virus-6, Epstein-Barr virus, enteroviruses, (coxsackievirus, adenovirus), CMV, HIV, SARS-CoV-2
Others	<i>Borrelia</i> , <i>Coxiella burnetii</i> (Q-fever)
Systemic disease	
Auto-immune and others	Sarcoidosis, myositis, rheumatoid disease
Toxic	
Medications	Immune check point inhibitors, anthracyclines, clozapine, adrenergic drugs, 5-fluorouracil
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Toxic	
Medications	<u>Immune check point inhibitors</u> , anthracyclines, clozapine, adrenergic drugs, 5-fluorouracil

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# Targeting Immune Checkpoints for Cancer Treatment → unchain the T-cells in the heart



- **CTLA-4 Inhibitors**
  - Ipilimumab (Yervoy)
- **PD-1 Inhibitors**
  - Nivolumab (Opdivo)
  - Pembrolizumab (Keytruda)
- **PDL-1 Inhibitors**
  - Atezolizumab (Tecentriq)
  - Durvalumab (FDA breakthrough designation)
- **Combination Therapy**

Adapted from Ribas A. *New England Journal of Medicine*, 2012.

# Rapid Increase in Reporting of Fatal ICI-Associated Myocarditis

**Table: Characteristics of patients with immune checkpoint inhibitor associated myocarditis (n=101)**

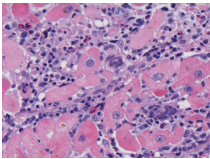
Characteristic	Percent (%)
<b>Male gender</b>	66
<b>Cancer</b>	
Melanoma	40
NSCLC	30
Renal	7
Other*	23
<b>Concomitant medications</b>	
Aspirin	11
Statin	11
Beta blocker	7
ACE/ARB	12
Diabetes medication	9
<b>No CV/Diabetes medications</b>	<b>75</b>
<b>Regimen</b>	
Anti-PD-1 monotherapy	
- Nivolumab	43
- Pembrolizumab	15
Anti-PD-L1 monotherapy*	3
Anti-CTLA-4 (Ipilimumab) monotherapy	5
Combination anti-PD-1/PD-L1 + anti-CTLA-4	27
Combination anti-PD-1/PD-L1 + anti-CTLA-4 + ...	2
<b>Timing (median, range)</b>	<b>25 days (5-120)</b>
<b>Concomitant events</b>	
Myositis/rhabdomyolysis	25
Myasthenia gravis	10
Colitis	4
Severe cutaneous events†	4
Other‡	5
<b>Fatal outcome</b>	<b>52</b>
<b>Reporting year</b>	
2010 – 2014	3
2015	6
2016	15
<b>2017 (through Dec. 6)</b>	<b>76</b>

- > 2 % of all treated
- Fatality rates:
  - Anti-PD-1/PD-L1 plus anti-CTLA-4: 78%
  - Anti-PD-1/PD-L1 monotherapy: 42%
- In part (in)dependent of CV risk factors
- 25 days (5-120 days)

# Acute Myocarditis

Giant cell myocarditis

R/ Immunosuppression → transplantation!



Auto-immune disease

R/ Immunosuppression!  
R/ Immunotherapy (interleukins)



•use sledgehammers to crack nuts

Acute Myocarditis

Idiopathic/viral

R/ ?? → supportive,  
treating EF and arrhythmias  
→ immunotherapy??

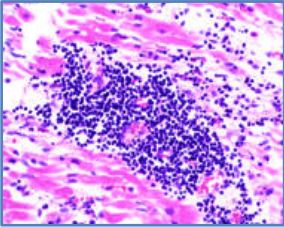
Toxic/chemotherapy

R/ stop ethyl/drugs/chemotherapy  
treating EF and arrhythmias  
→ immunotherapy??, other?



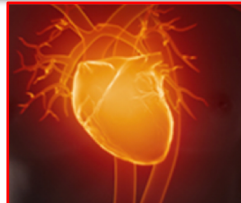
# Different severity/types of myocarditis

## Acute Myocarditis



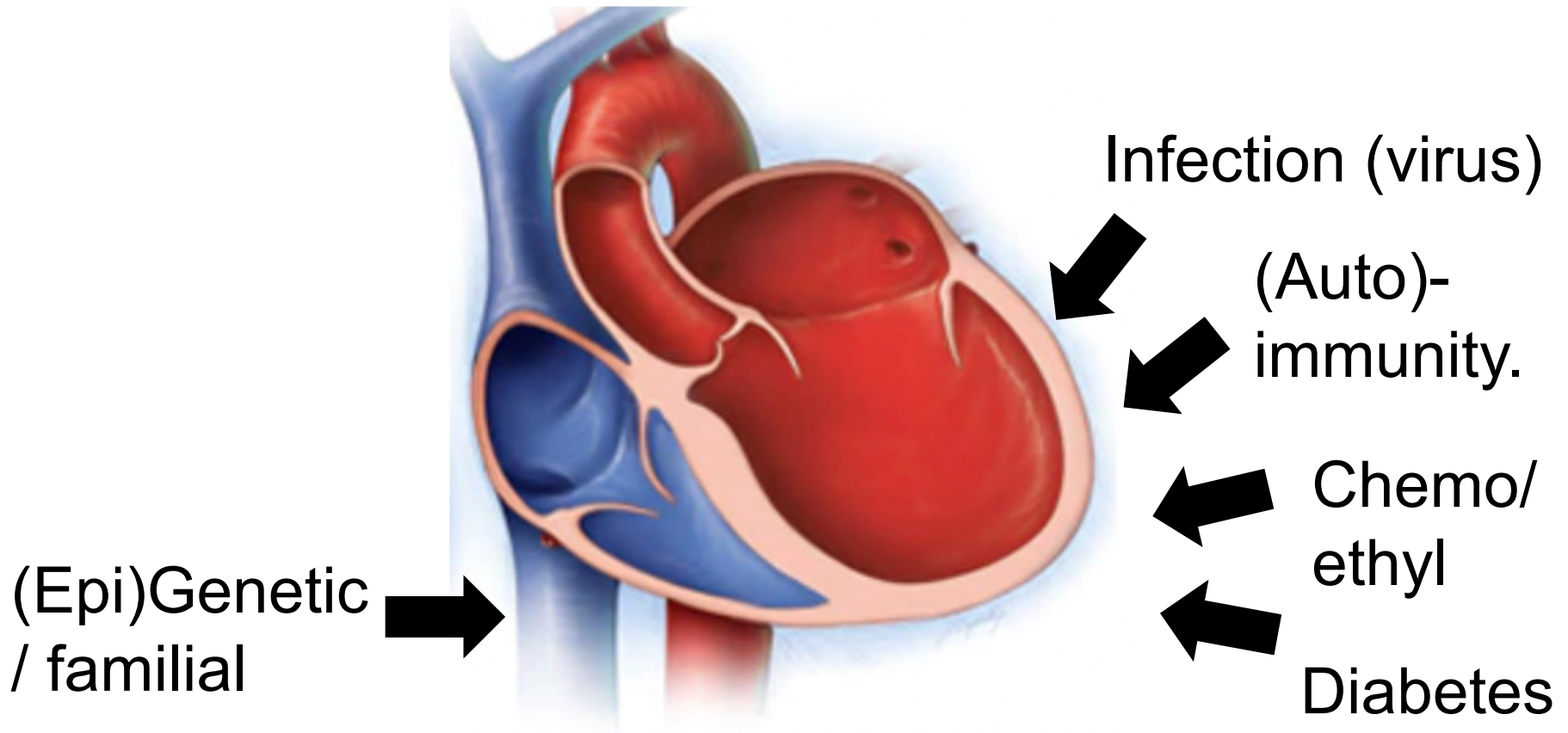
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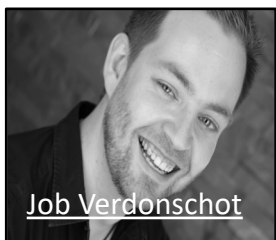
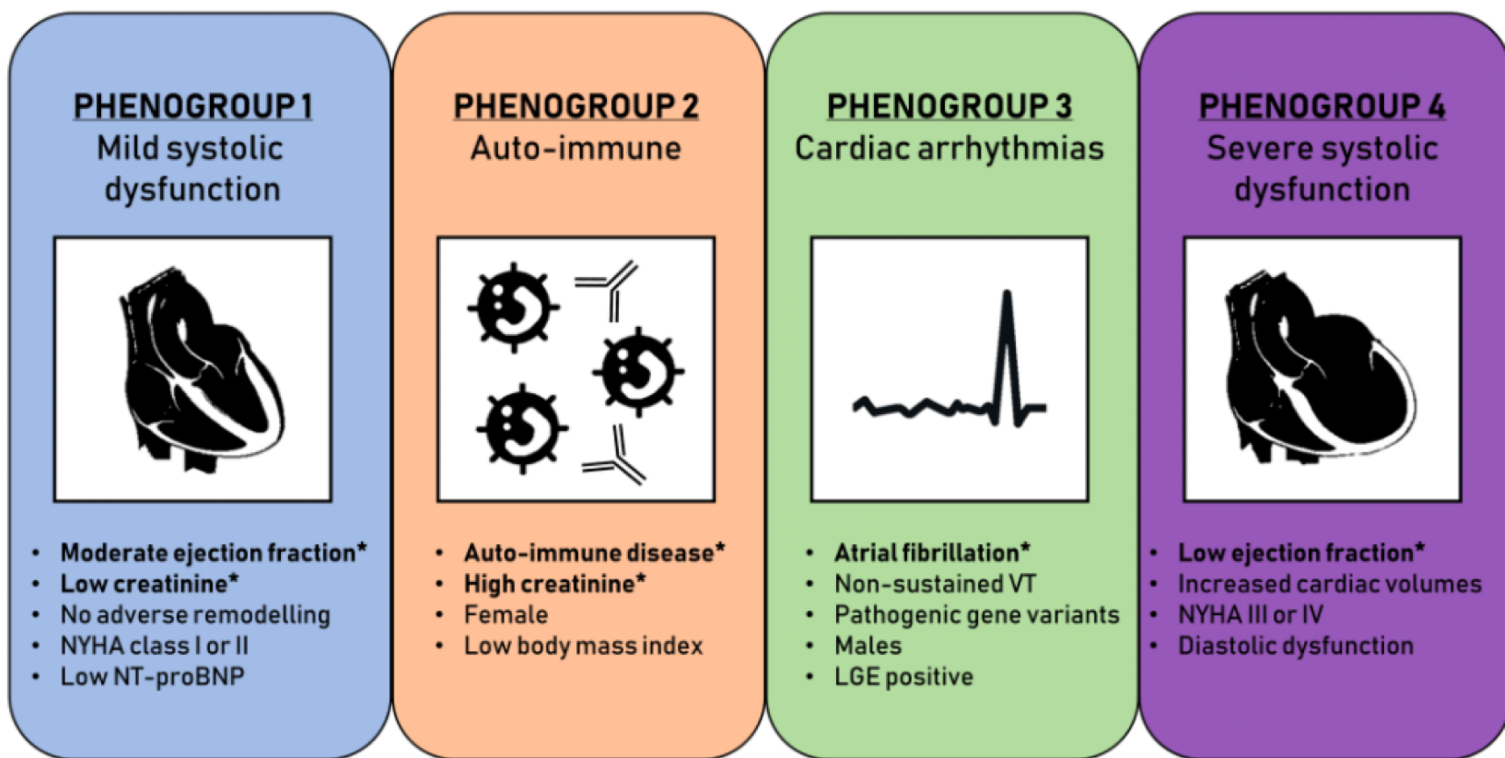


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# Dilated cardiomyopathies: Genetics-acquired diseases!

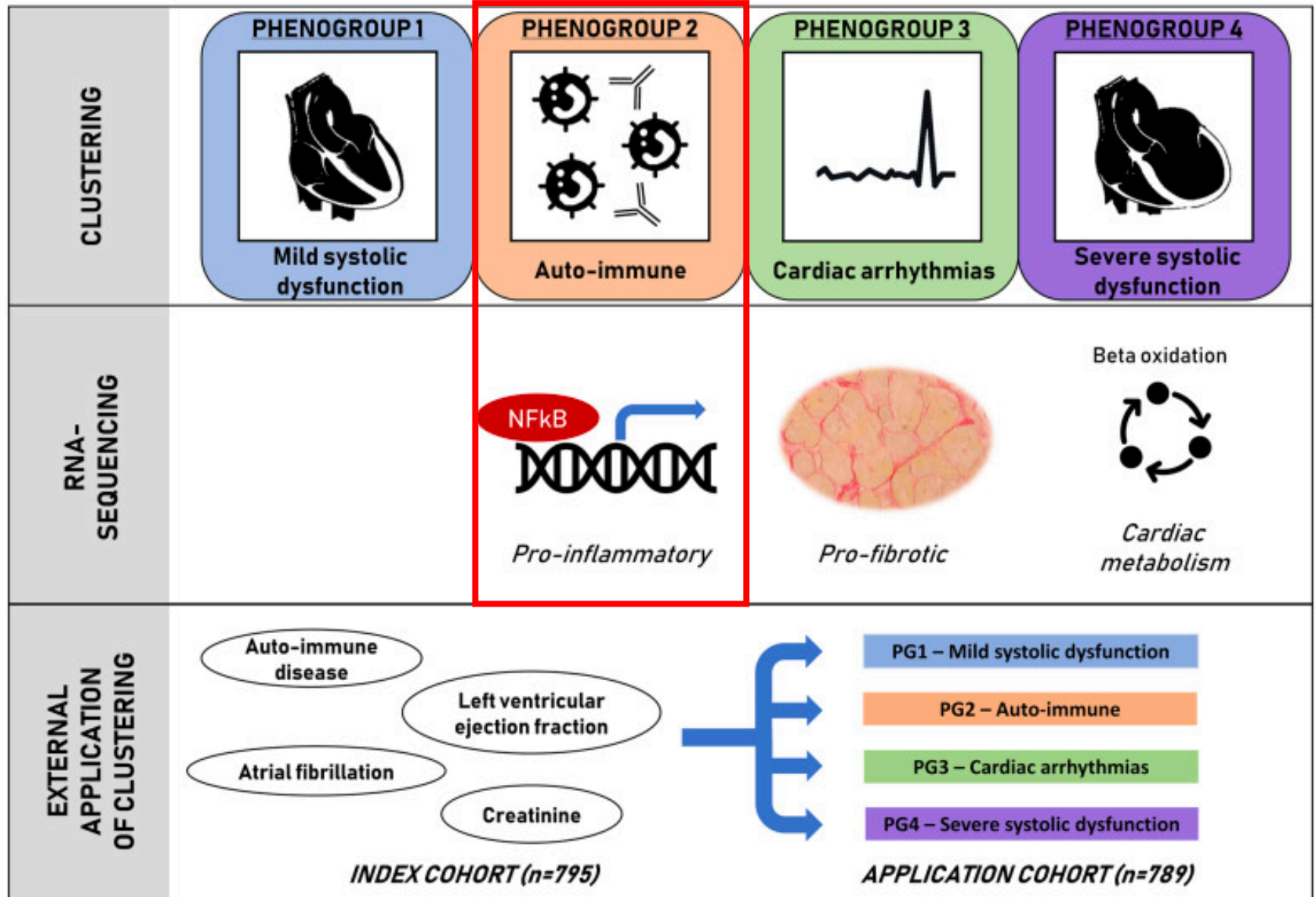


# Phenocustering: clinics + genetics + biopsies (27 common parameters)



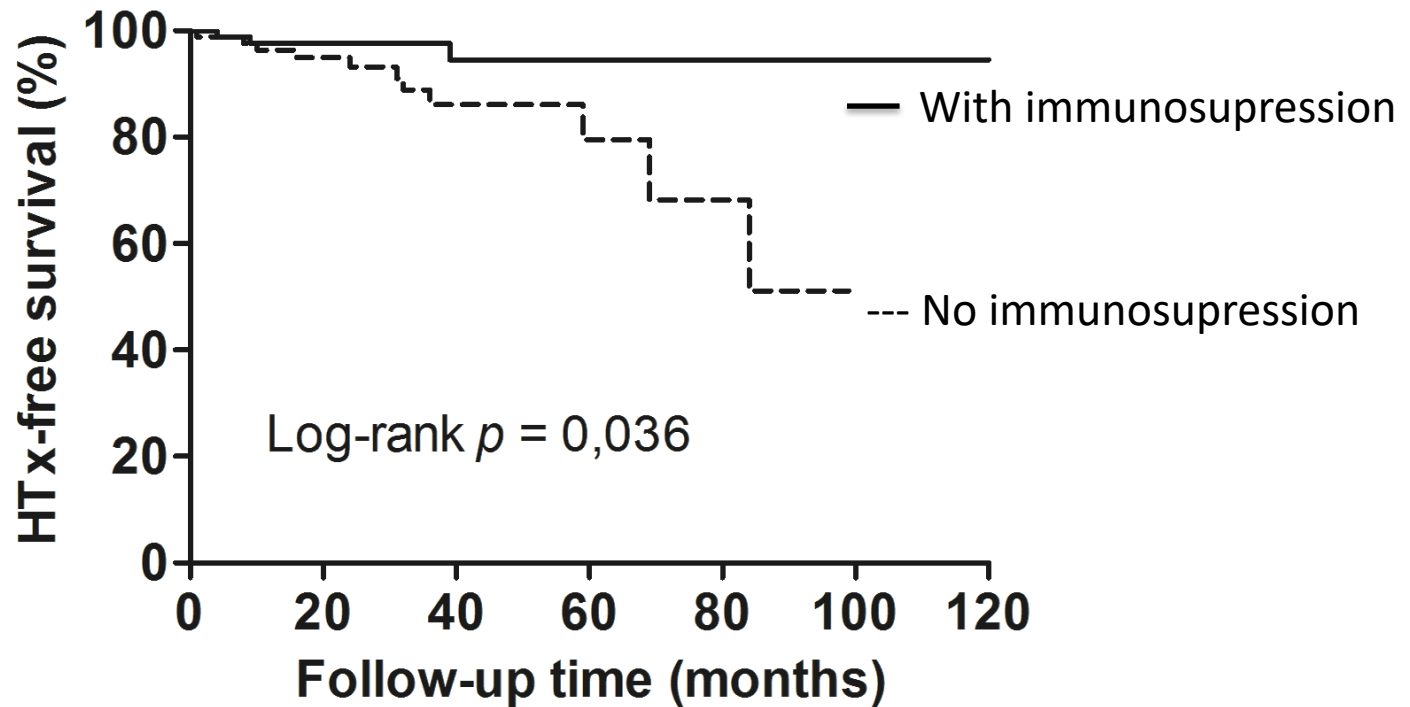
**n=795 DCM patients.** Unsupervised machine learning 47 parameters + random forest tree analysis (supervised)

# DILATED CARDIOMYOPATHY



# Immuno-suppression is beneficial in chronic myocarditis **in retrospective!**

Virus negative (< 250 copies/ug DNA), CD45/CD3+positive (ESC)



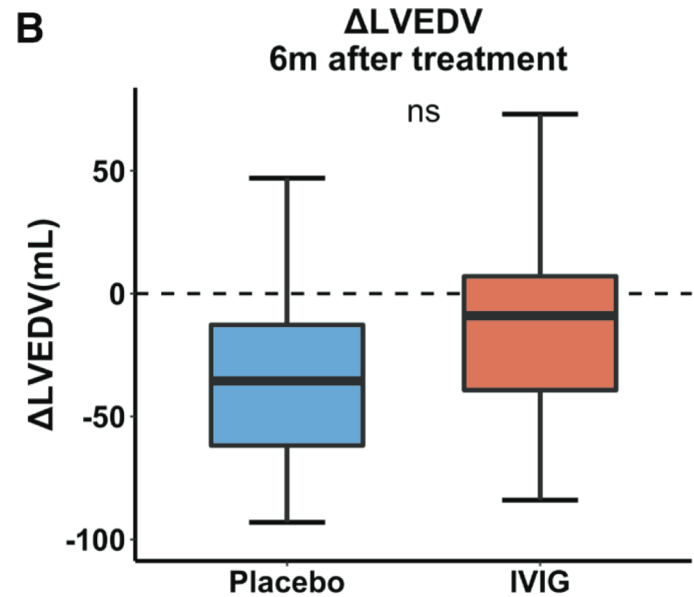
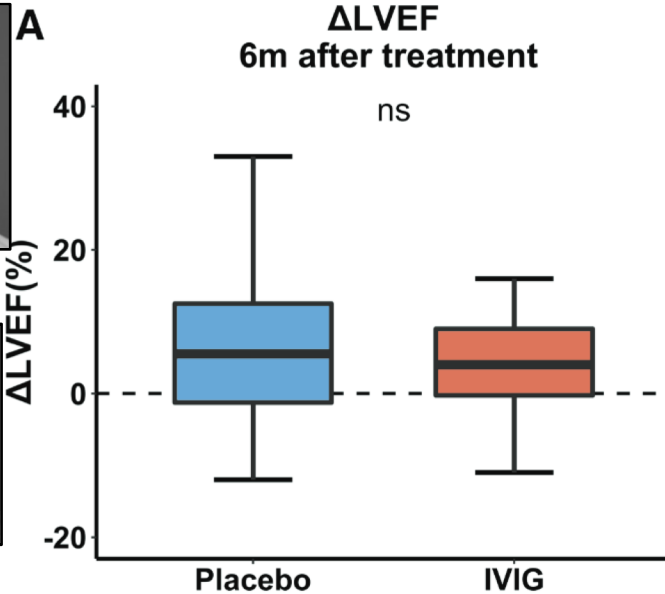
Immuno+	90	61	28	10	3	2	1
Immuno-	90	55	29	12	4	2	0

= using sledgehammers to crack nuts



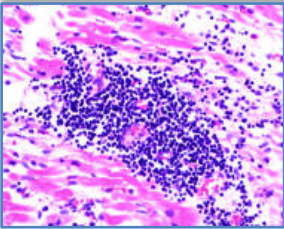
# Intravenous immunoglobulin therapy in parvovirus B19-related DCM: neutral outcome.

- A prospective, double-blind, randomized, placebo-controlled trial.
- n=55, PVB19 > 200 copies/ug DNA



# Future treatment options in different severity/types of myocarditis?

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**Any immunotherapy in idiopathic/viral or toxic myocarditis ??**

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**Inflammatory RNA/protein profiling in heart/circulation of DCM subgroups!!**