Erfelijke Cardiomyopathieën

Nationale Hartfalendag 2018

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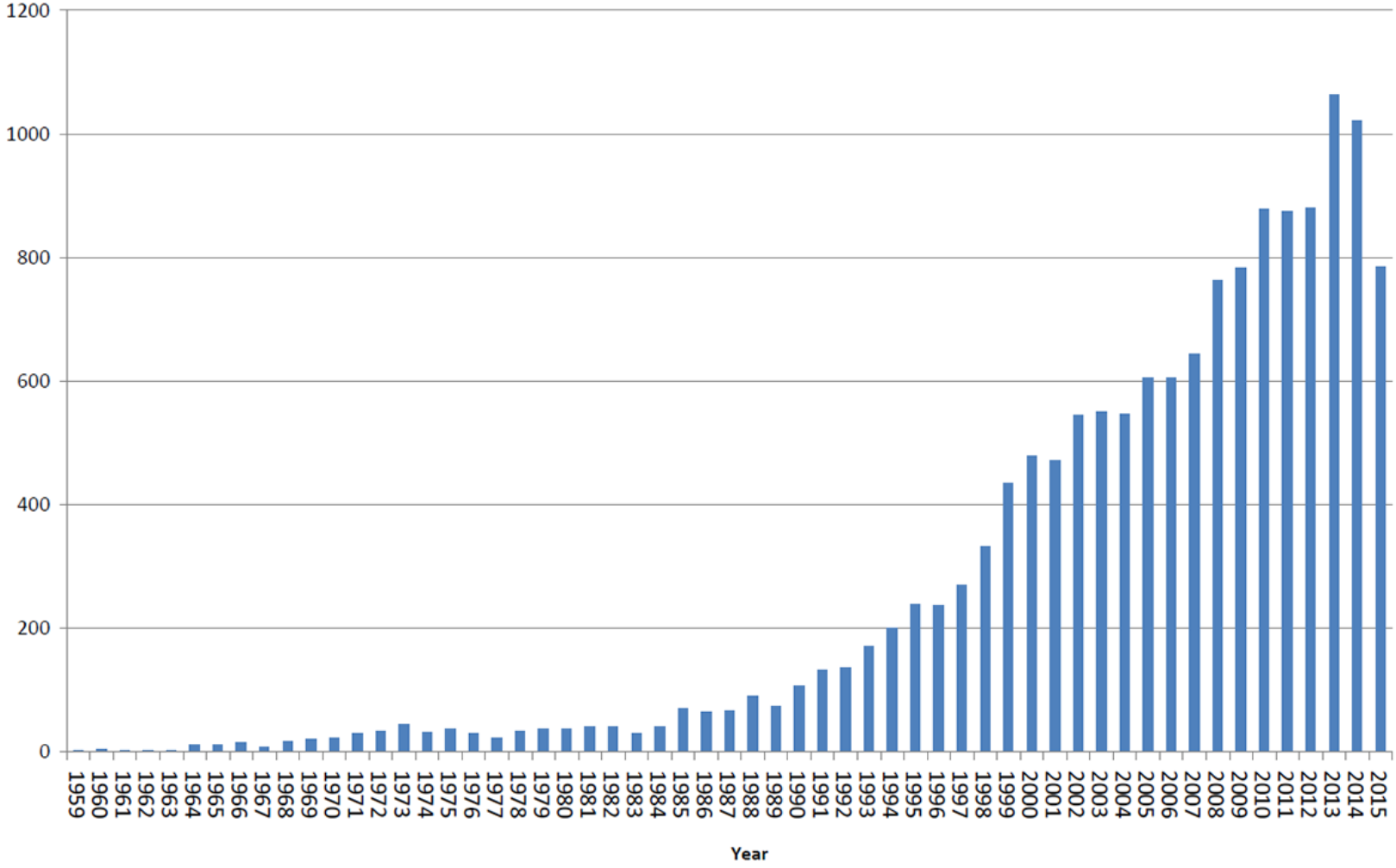
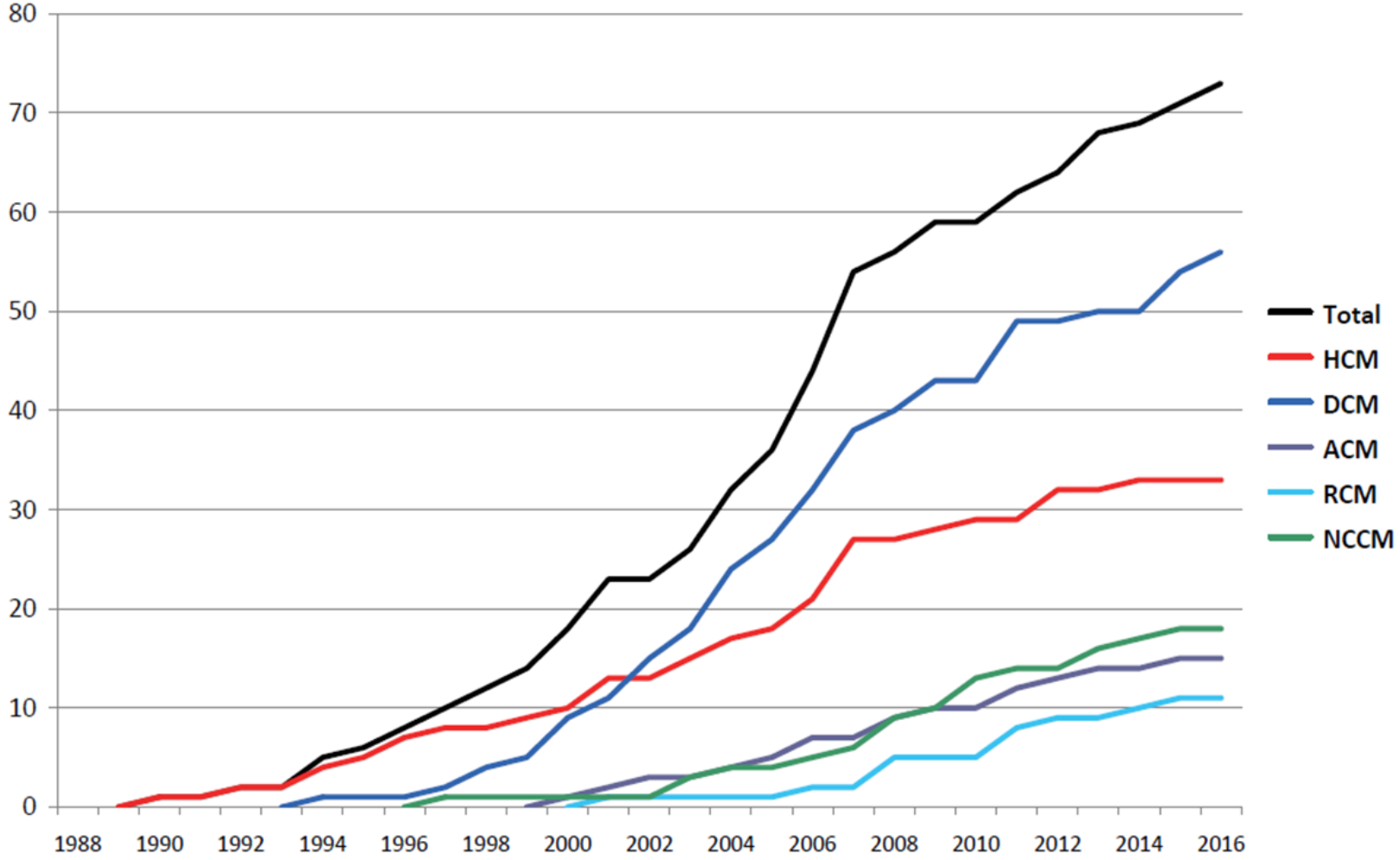
Disclosure belangen spreker [Naam] [Affiliation]

Geen (potentiële) belangenverstrengeling	Geen
Voor bijeenkomst mogelijk relevante relaties:	Bedrijfsnamen
Sponsoring of onderzoeksgeld	
Honorarium of andere (financiële) vergoeding	
Aandeelhouder	
Andere relatie, namelijk …	



Pubmed hits “cardiomyopathy” and “genetics”



Number of implicated genes

Cardiomyopathy - definition

"Cardiomyopathy: a myocardial disorder in which the heart is structurally and functionally abnormal, in the absence of coronary artery disease, hypertension, valvular heart disease and congenital heart disease sufficient to cause the observed myocardial abnormality

Cardiomyopathy can be part of systemic disease (e.g. amyloidosis) or syndrome (e.g. Noonan syndrome) or muscular disease (e.g. limb girdle MD) or
isolated cardiac disorder (e.g. HCM)

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

Elliott EHJ 2008

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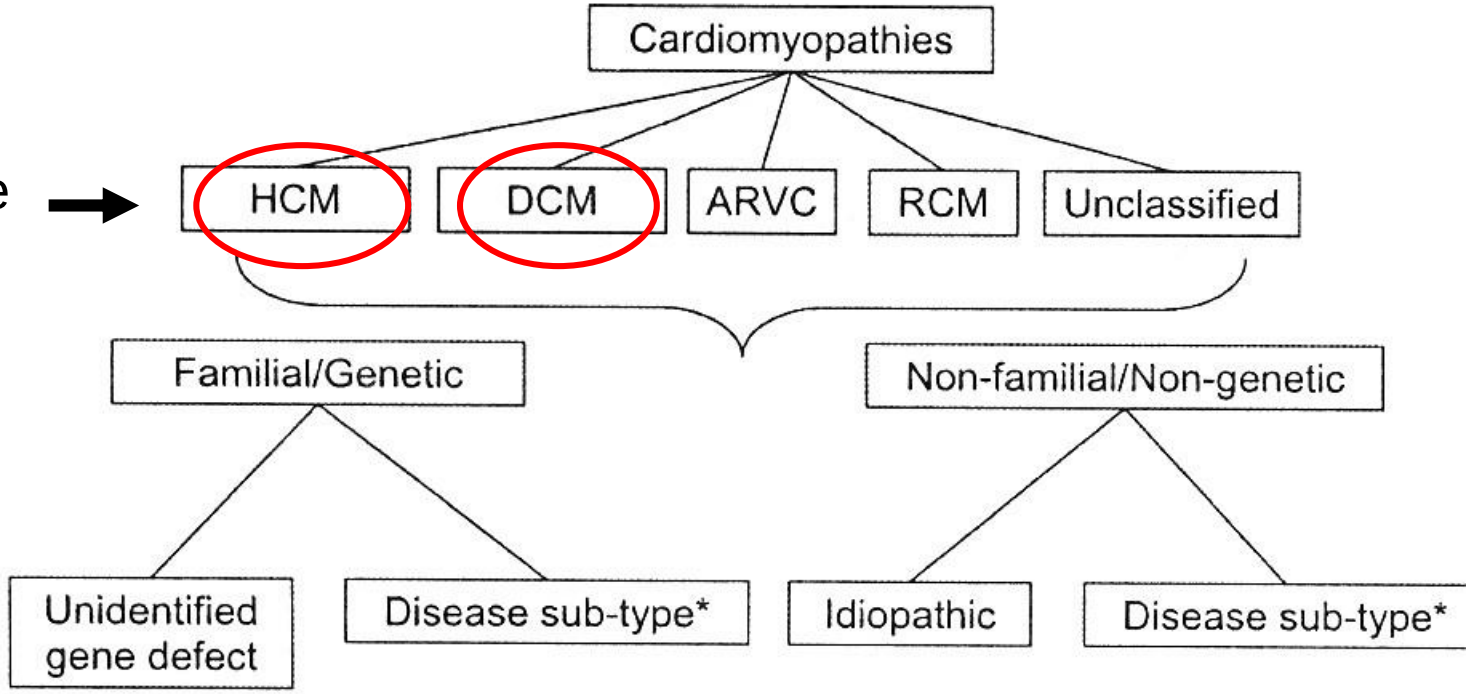
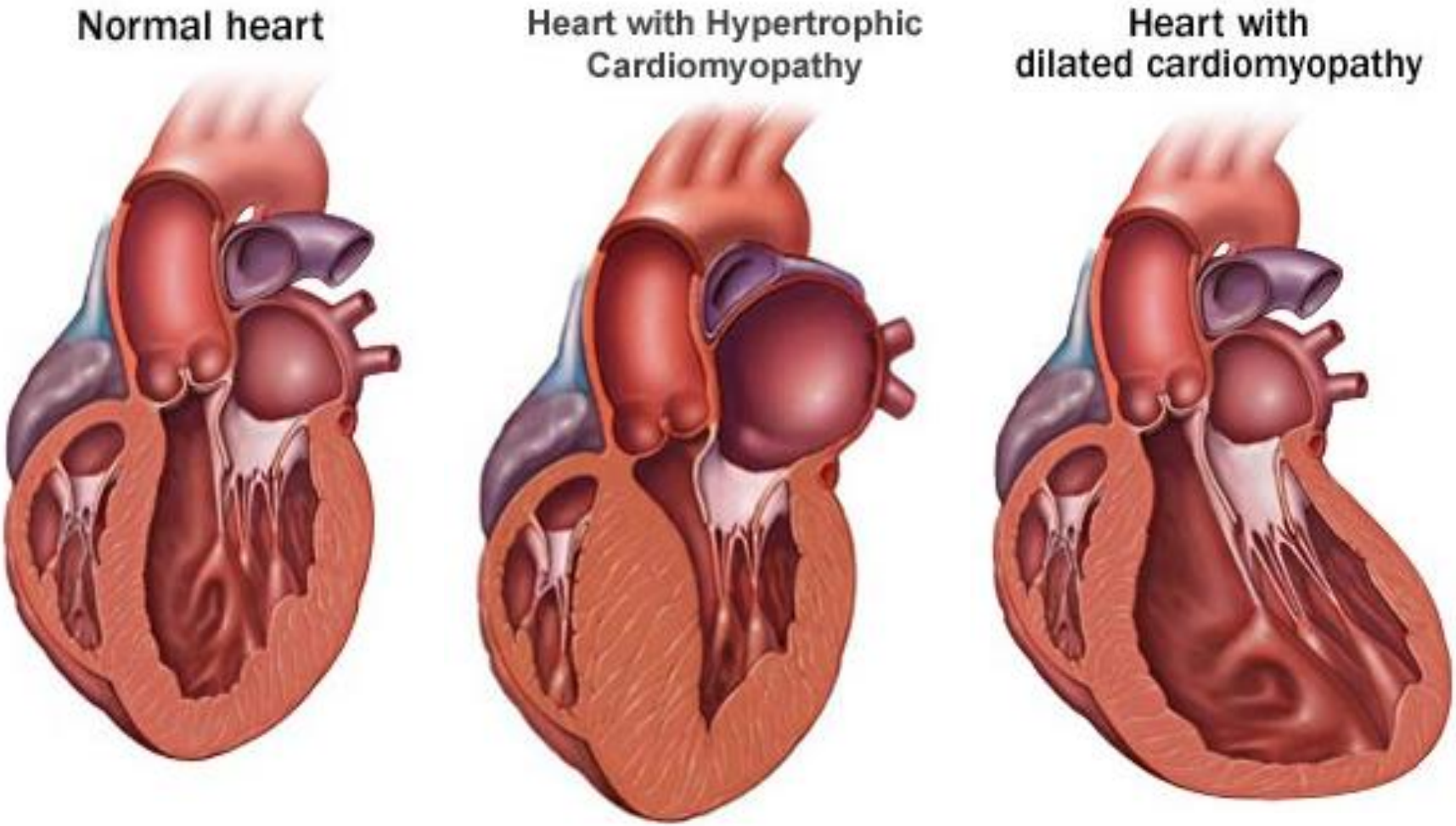
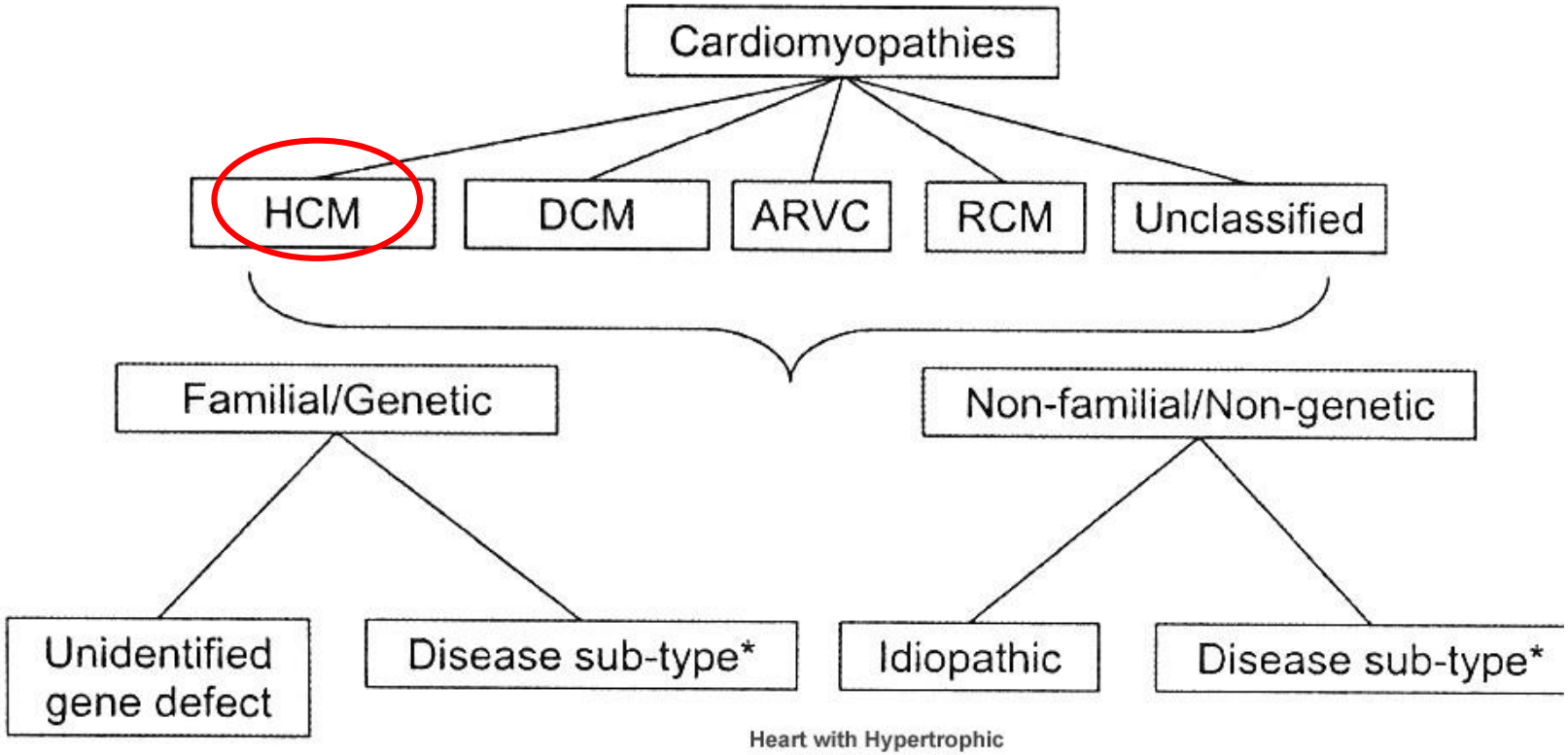
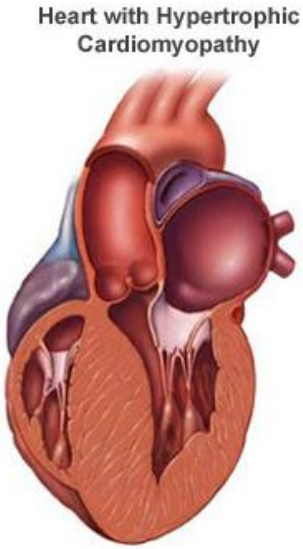
phenotype →

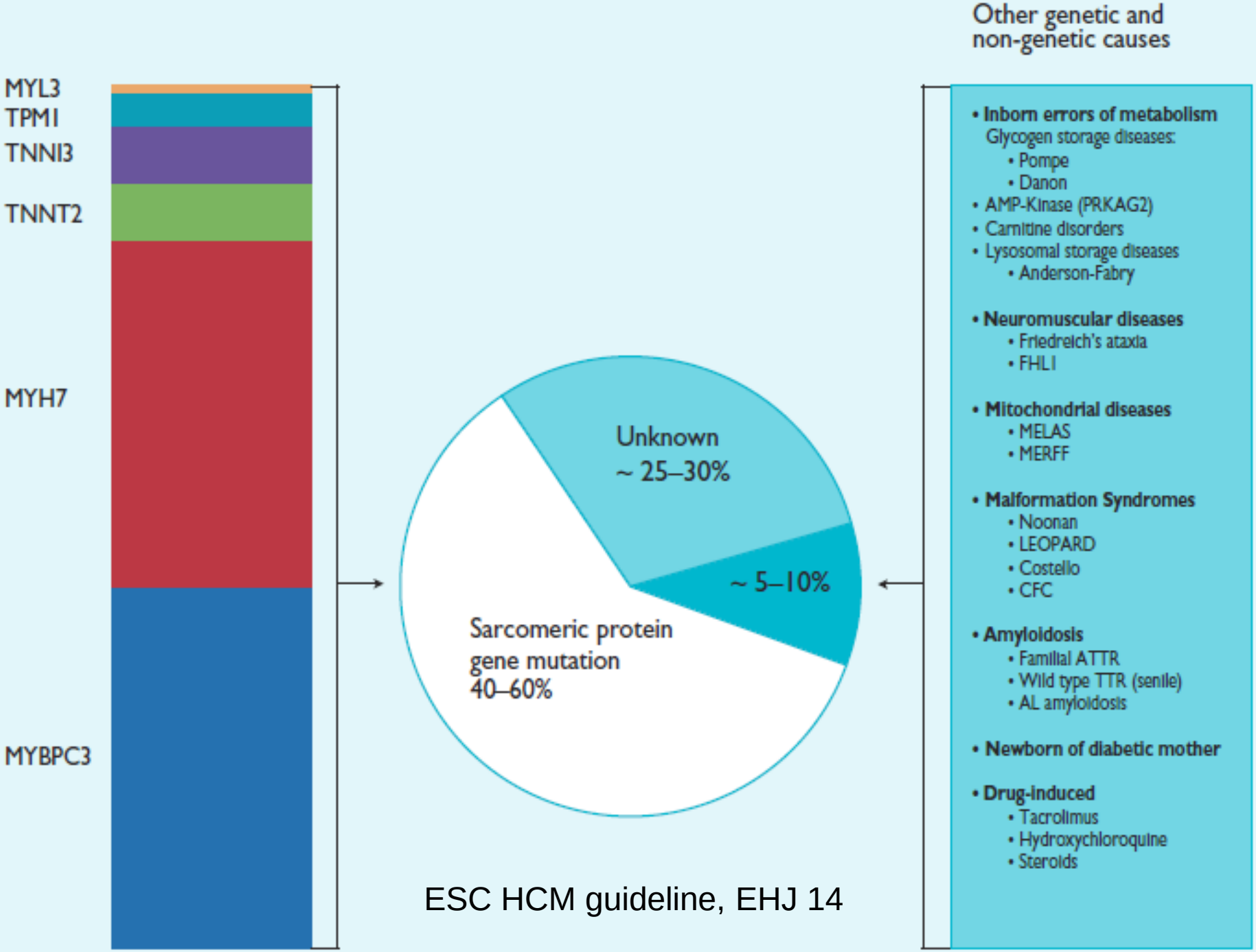



Normal heart
Heart with Hypertrophic Cardiomyopathy
Heart with dilated cardiomyopathy

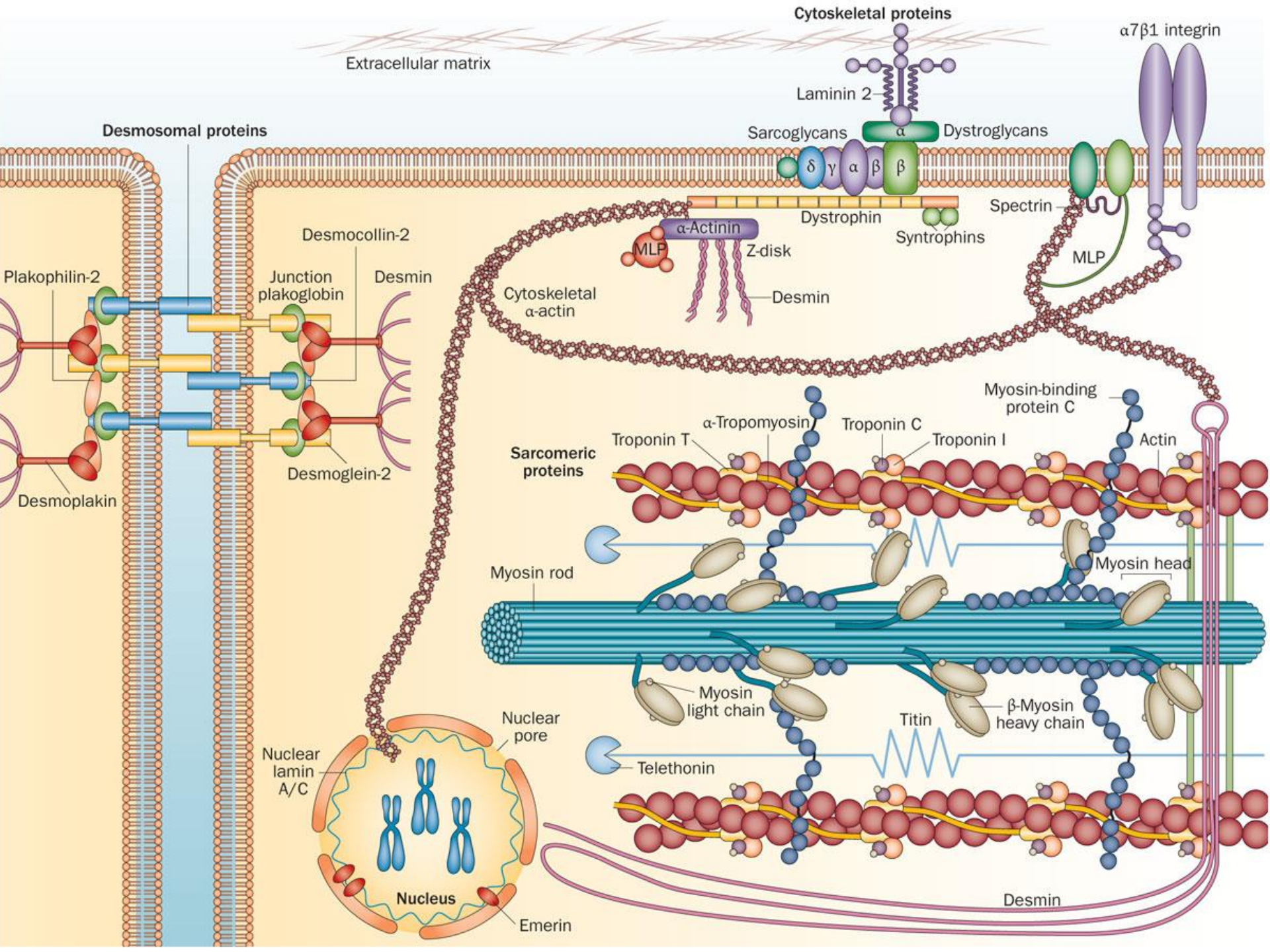


phenotype : “LVH”





ESC HCM guideline, EHJ 14


Cytoskeletal proteins
α7β1 integrin
Extracellular matrix
Laminin 2
Sarcoglycans
α
Dystroglycans
δ
γ
α
β
β
Desmosomal proteins
Spectrin
Dystrophin
Syntrophins
α-Actinin
MLP
Z-disk
MLP
Desmocollin-2
Plakophilin-2
Junction plakoglobin
Desmin
Cytoskeletal α-actin
Desmin
Myosin-binding protein C
α-Tropomyosin
Troponin C
Troponin T
Troponin I
Actin
Sarcomeric proteins
Desmoglein-2
Desmoplakin
Myosin rod
Myosin head
Myosin light chain
β-Myosin heavy chain
Titin
Nuclear pore
Nuclear lamin A/C
Telethonin
Nucleus
Emerin
Desmin

Hypertrofische (obstructieve) cardiomyopathie

- LVH, m.n. septum (≥15 mm), ev. obstructie
- Plotse dood, risk calculator
- Hartfalen – HFpEF
- BF, TEC
- Familiair, autosomaal dominant
- Mutatie in sarcomeergenen: MYH7, MYBPC3
- NB founder-mutaties
- Behandeling? BB, CA, septumreductie, ICD

Geen “HCM”? Red flags

Echo:	concentrische LVH
	LV hypokinesie
	Betrokkenheid RV, kleppen, IAS
	Pericardvocht
ECG:	Lage voltages, extreme voltages, extreme as
	AV-blok
	Korte PR-tijd/pre-excitatie
Extracardiaal:	Spierziekte
	Doofheid, mentale retardatie
	Huidafwijkingen

Rapezzi, Eur Heart J 2013

Amyloidose

Echo: "LVH"

- Goede systolische functie
- Diastolische dysfunctie
- ook RV, ev. kleppen, IAS
- Pericardvocht
- Sparkling

ECG:

- Lage voltages
- Geleidingsstoornissen

Amyloidose

Stapeling verkeerd gevouwen eiwitten -> amyloidfibrillen, neerslag in organen/weefsels

Vormen:

- AA-amyloidose, bv RA
- AL-amyloidose, bv Kahler
- Transthyretine-amyloidose (ATTR)

Transthyretin amyloidosis (ATTR)

- **Genetic**: *TTR* mutations
  - Netherlands: >10 families, >100 carriers
  - UMCG: referral center

- **Wild type**:
  - Natural transthyretin
  - Senile amyloidosis, including cardiac amyloidosis

  - Oorzaak HFpEF?

Mohammed et al. JACC 2014
Left ventricular amyloid deposition in patients with heart failure and preserved ejection fraction

Obductiestudie: 109 HFpEF (antemortem), 131 controles

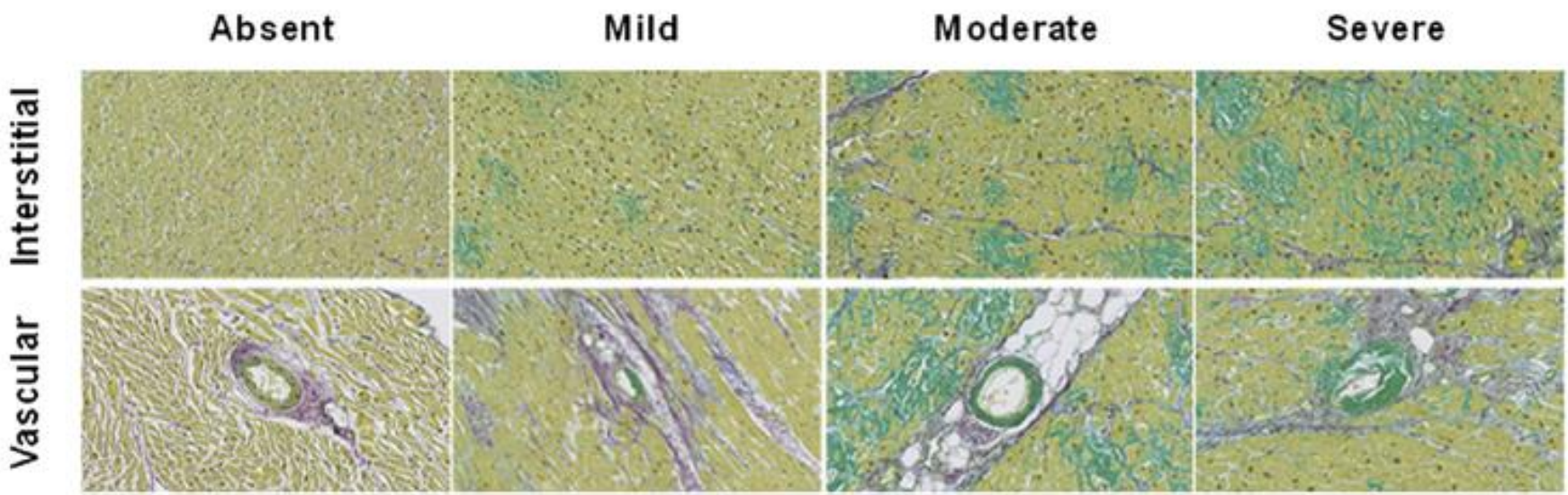


Figure 2 Semiquantitative Characterization of Severity of Amyloid Deposition in SAB Stained LV Sections

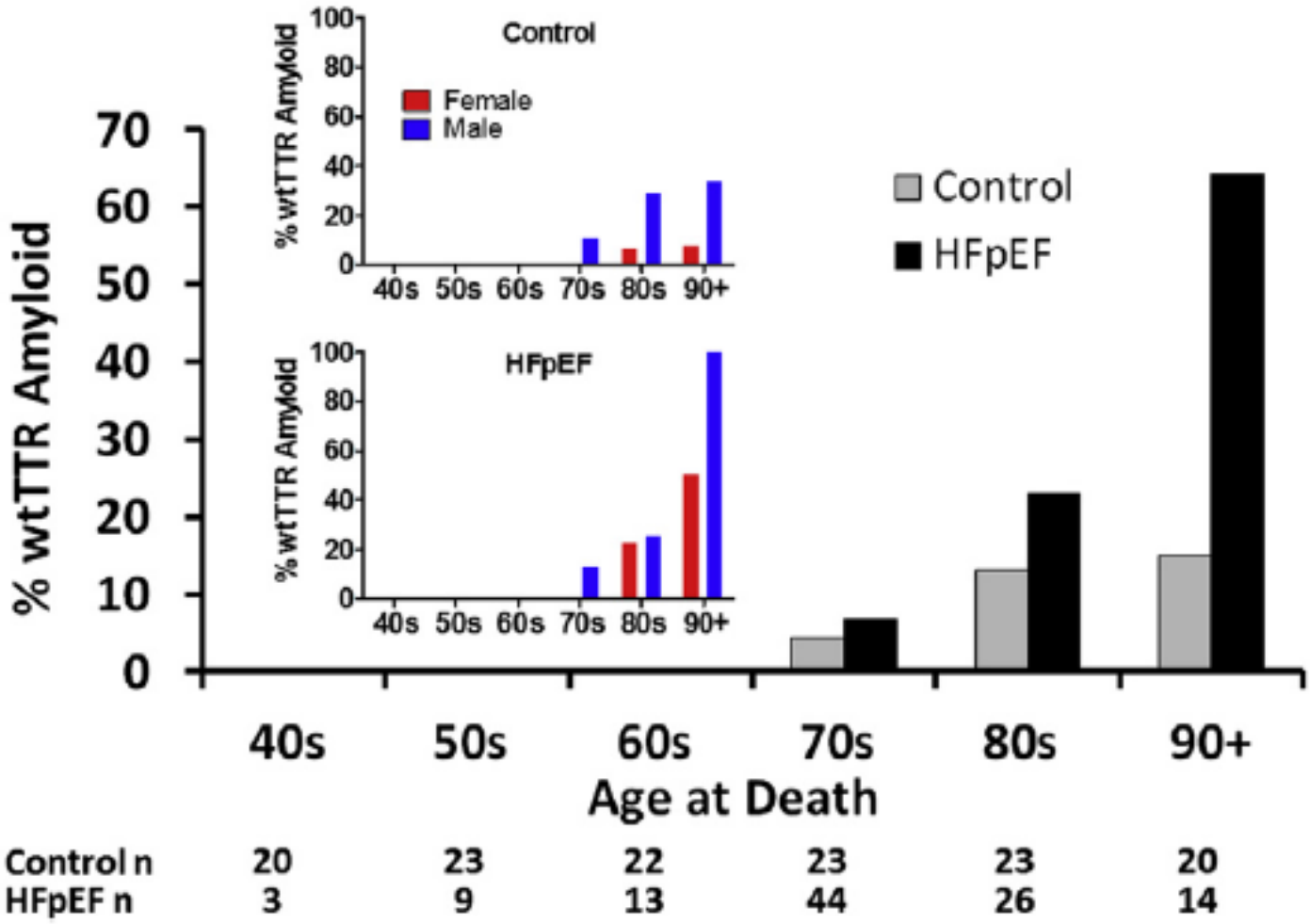
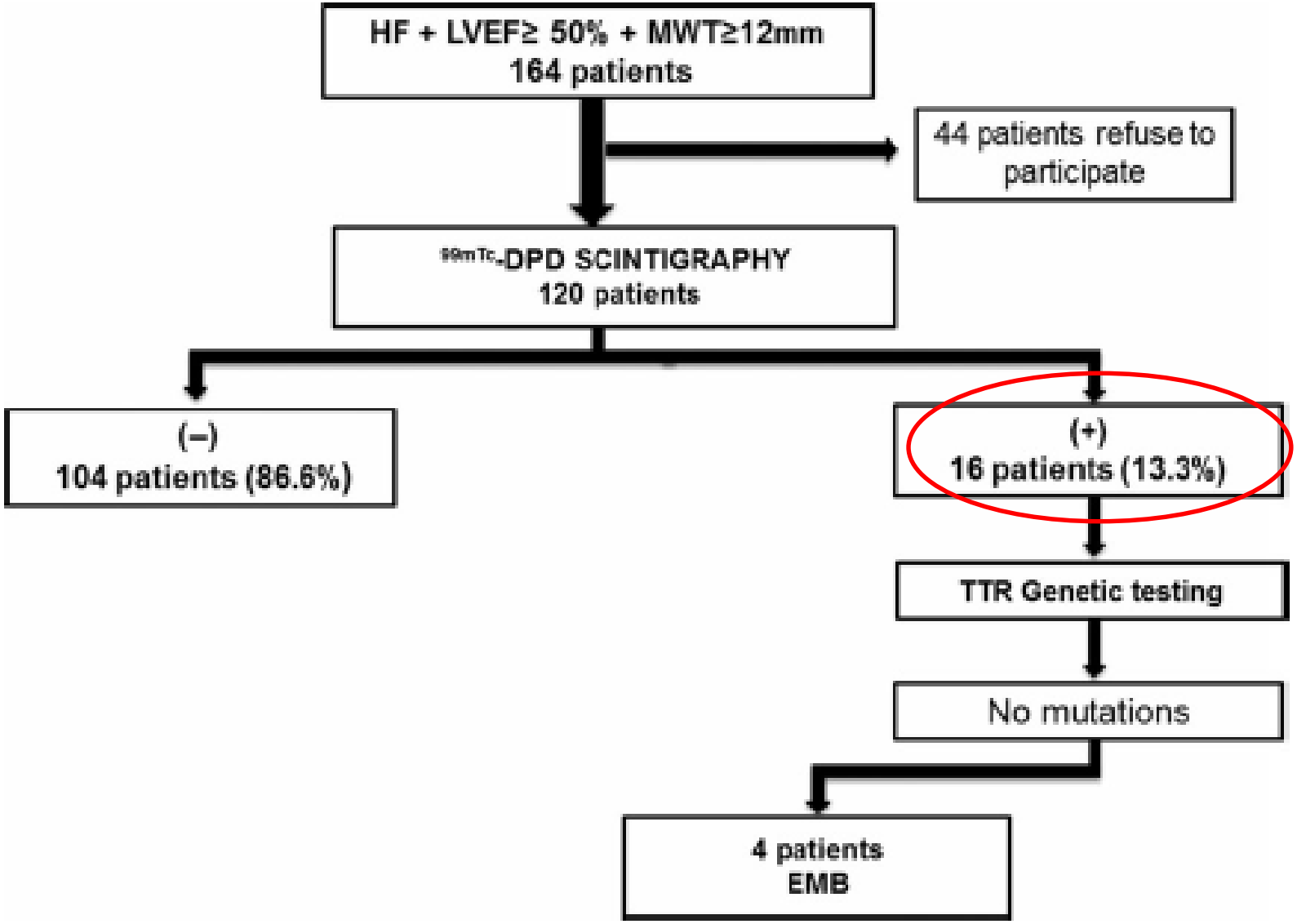
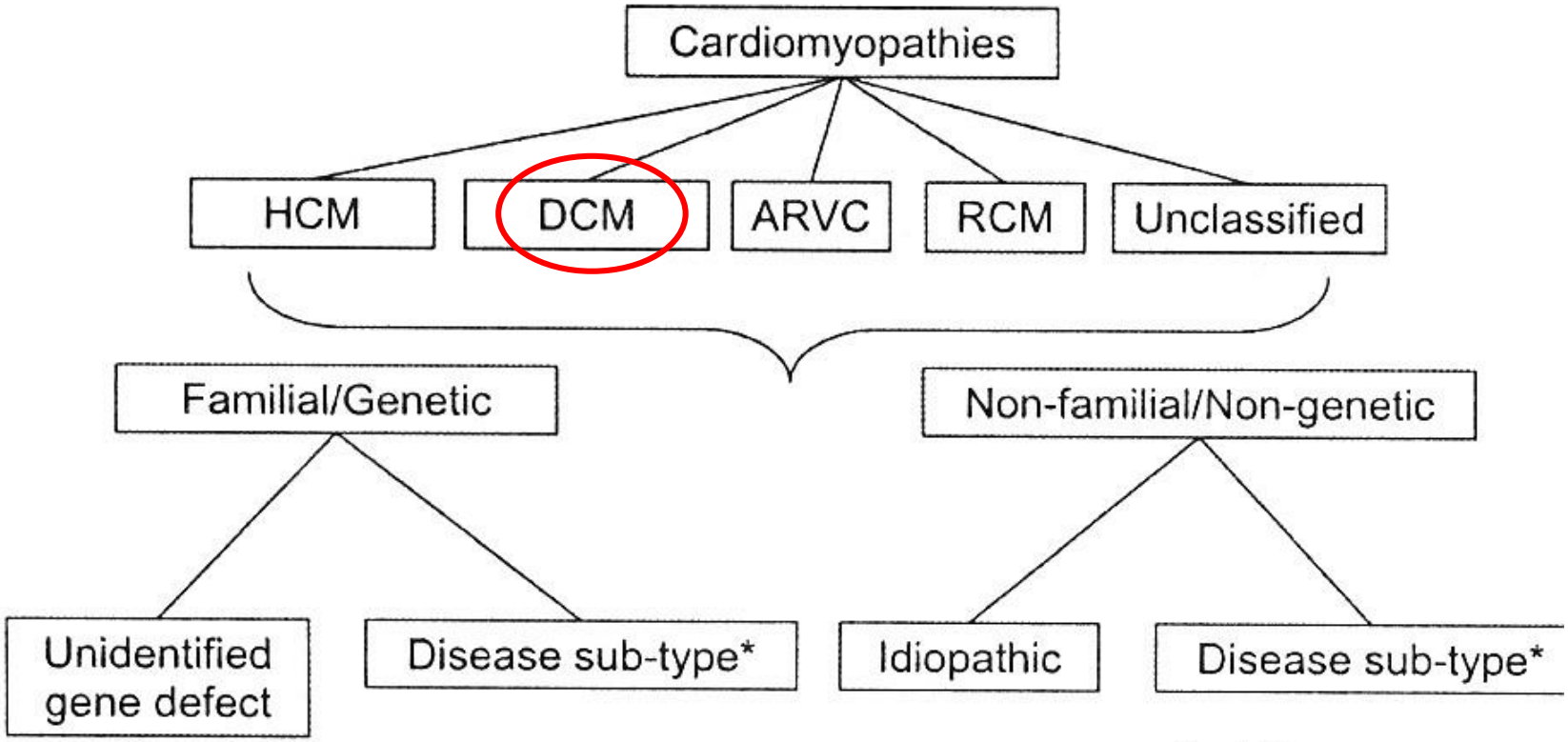


Figure 1 Prevalence of LV wtTTR Amyloid in Control (n = 131) and HFpEF (n = 109) Patients by Age

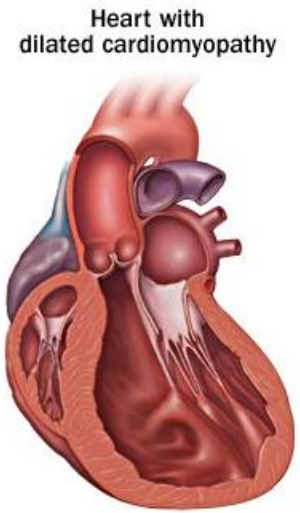


Conclusie: onverklaarde HFpEF op hoge leeftijd, denk aan amyloidose. Overweeg botscan



Phenotype:

Dilatation: LVEDD >2.7 cm/m2
Dysfunction: LV ejection fraction <45%



DCM ≠ diagnosis

causes DCM (n=1230)
Felker, New Engl J Med 2000

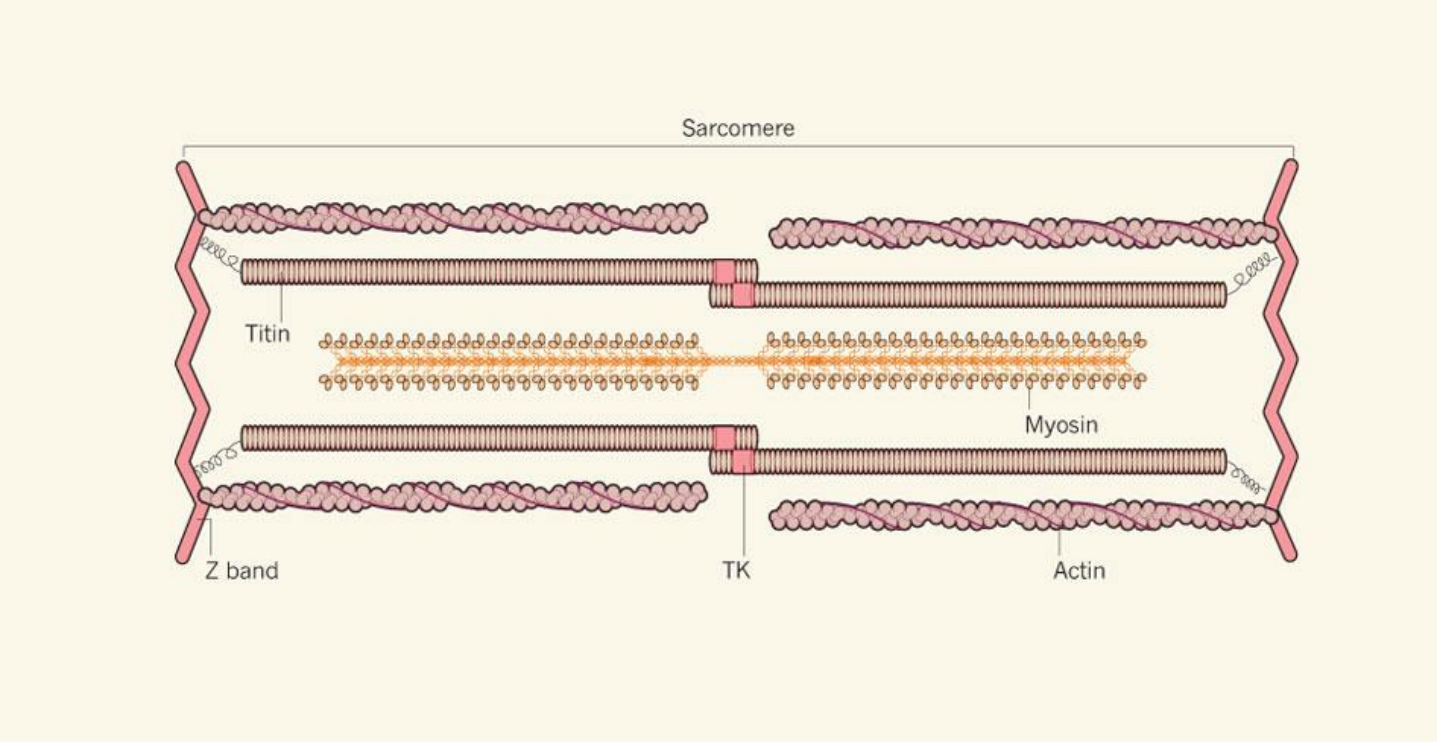
- ischemic heart disease 7%
- hypertension 4%
- myocarditis 9%
- HIV 4%
- infiltrative disease 5%
- peripartum 4%
- connective tissue disease 3%
- alcohol/cocaine 3%
- cytostatics 1%
- others 10%
- idiopathic 50% ← 1/3 familiair

Familial dilated cardiomyopathy

1p32	NEXN		10q25	RBM20
1q21	lamin A/C	nuclear env.	10q26	PDLIM
1q31	PSEN2		11p11.2	MyBPC3
1q32	TNNT2		11p15	CSRP3
1q42	ACTN2		11p15	ILK
2q31	titin	sarcomere	11q22	CRYAB
2q35	desmin	cytoskeleton	12p12	ABCC9
3p14	TNNC1		12q22	TMPO
3p21	SCN5A	ion channel	14q12	MYH6
5p15	SDHA		14q12	MYH7
5q33	δ- sarcoglycan		14q24	PSEN1
6q21	LAMA4		15q14	ACTC1
6q22	phospholamban	calcium	15q22	TPM1
6q23	EYA4		17q12	Tcap/telethonin
9q31	FKTN		19q13	TNNI3
10p13	Nebulette		Xq28	TAZ
10q21	MYPN		Xq28	emerin
10q22	metavinculin		Xp21	dystrophin
10q22	LDB3			
10q23	ANKRD1			

2018 >50 genes!

Herman, NEJM 2012:
Truncations of titin causing dilated cardiomyopathy



titine: grootste human eiwit, >27 k aminozuren,
“moleculaire veer”, elasticiteit en stabiliteit sarcomeer

Table 1. Subjects with *TTN* Truncating Variants, According to Cohort.

Type of Mutation	Subjects with Dilated Cardiomyopathy (N = 312)	Subjects with Hypertrophic Cardiomyopathy (N = 231)	Controls (N = 249)	P Value*	
				All Subjects	Selected Subjects
	number of subjects				
Nonsense†	28	0	0	1×10^{-10}	5×10^{-11}
Frameshift	19	2	2	0.0004	1×10^{-5}
Splicing†	19	1	5	0.001	4×10^{-6}
Copy number	1	0	0	NA	NA
Any mutation	67	3	7	$<2\times10^{-16}$	$<2\times10^{-16}$

Familial cases 25%, sporadic cases 18%

Conclusion:
TTN mutations are a common cause of iDCM

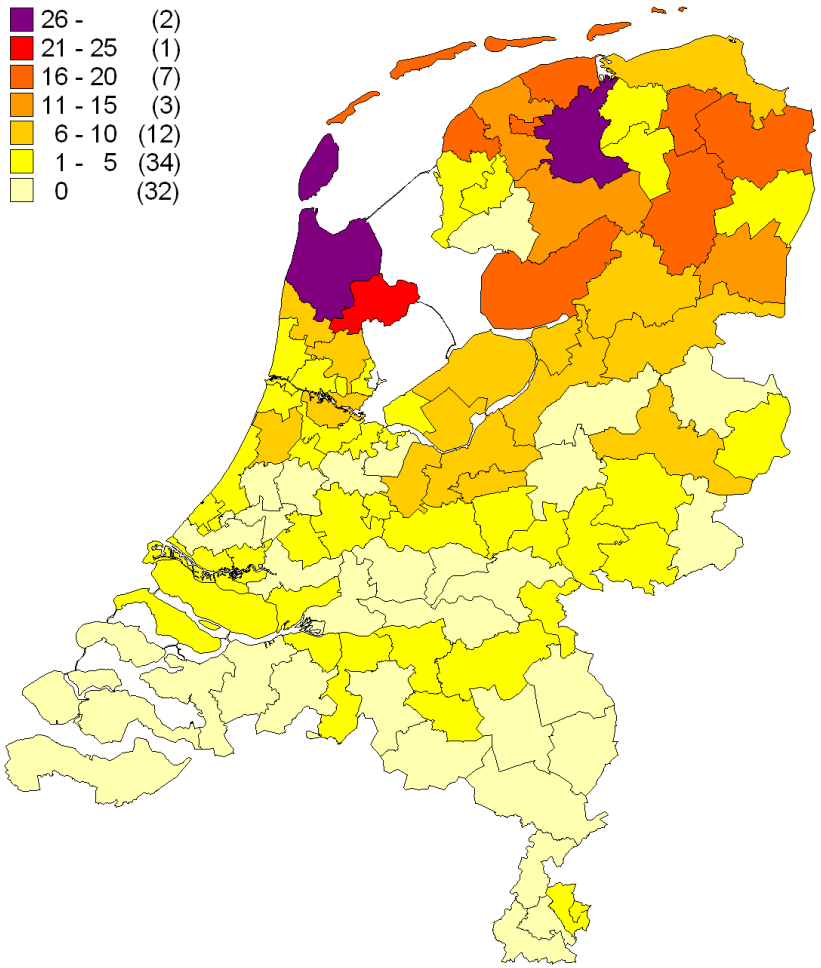
NB1 overlap met HCM
NB2 ook mutaties bij controles

Phospholamban cardiomyopathy

2018
Including family screening:
>1000 mutation carriers!
www.phorecast.nl

City of Groningen:
Prevalence ~0.1%

Founder mutation:
estimated to be
575-825 years old



Phenotype - summary

Arrhythmogenic cardiomyopathy:

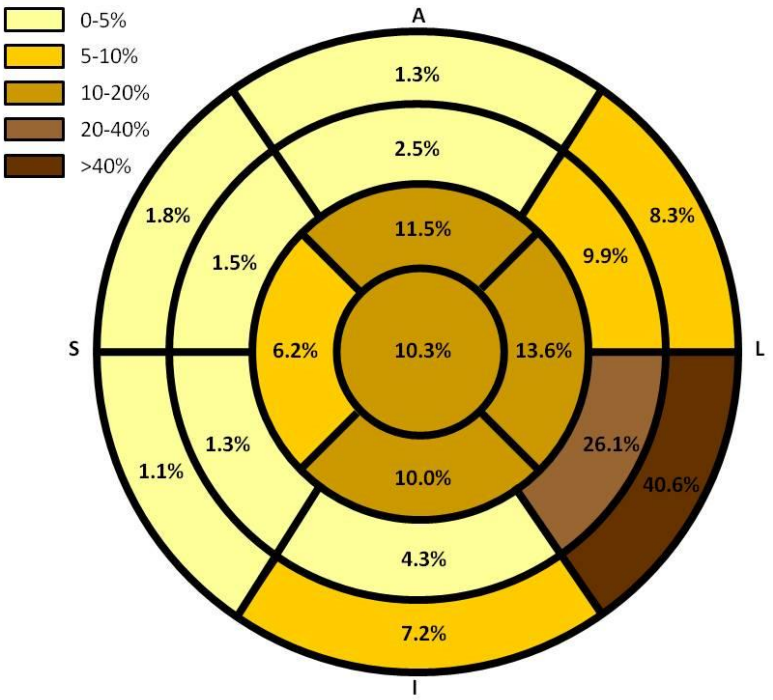
features of both ARVC of DCM – overlap syndrome:

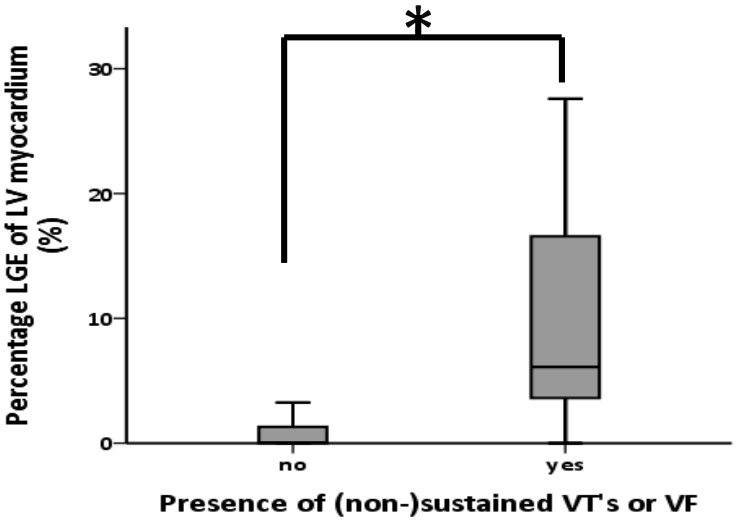
-malignant arrhythmias (early)

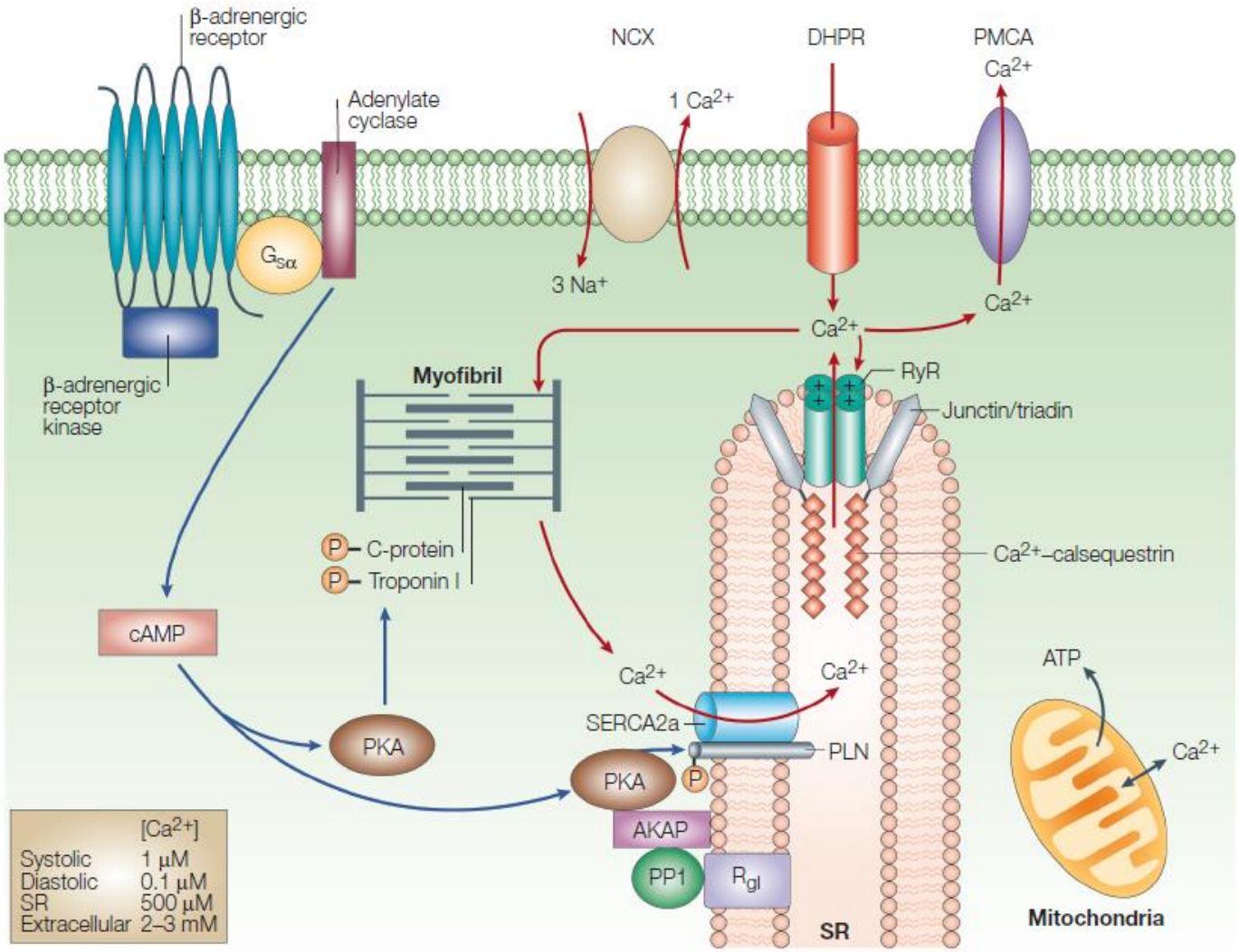
-heart failure (later)

-low voltage

-MRI: extensive fibrosis, inferolateral


0-5%
5-10%
10-20%
20-40%
>40%
A
S
L
I
1.3%
2.5%
1.8%
1.5%
8.3%
9.9%
11.5%
6.2%
10.3%
13.6%
1.3%
1.1%
26.1%
40.6%
10.0%
4.3%
7.2%


*
Percentage LGE of LV myocardium (%)
30
20
10
0
no
yes
Presence of (non-)sustained VT's or VF



PLN R14del: superinhibition SERCA (gain of function)
→ diastolic cytoplasmic calcium-overload → cell-death, fibrosis

Conclusions

Points to keep in mind in a patient who presents with a “cardiomyopathy”:

- characterize phenotype: HCM, DCM, ARVC, RCM, LVNC
- most common: HCM ~ HFpEF
  DCM ~ HFpEF (HF Guidelines)
- identify underlying causes; exclude other cardiac disease
- idiopathic cardiomyopathies are often genetic, family history?

- send patient to cardiogenetics center!