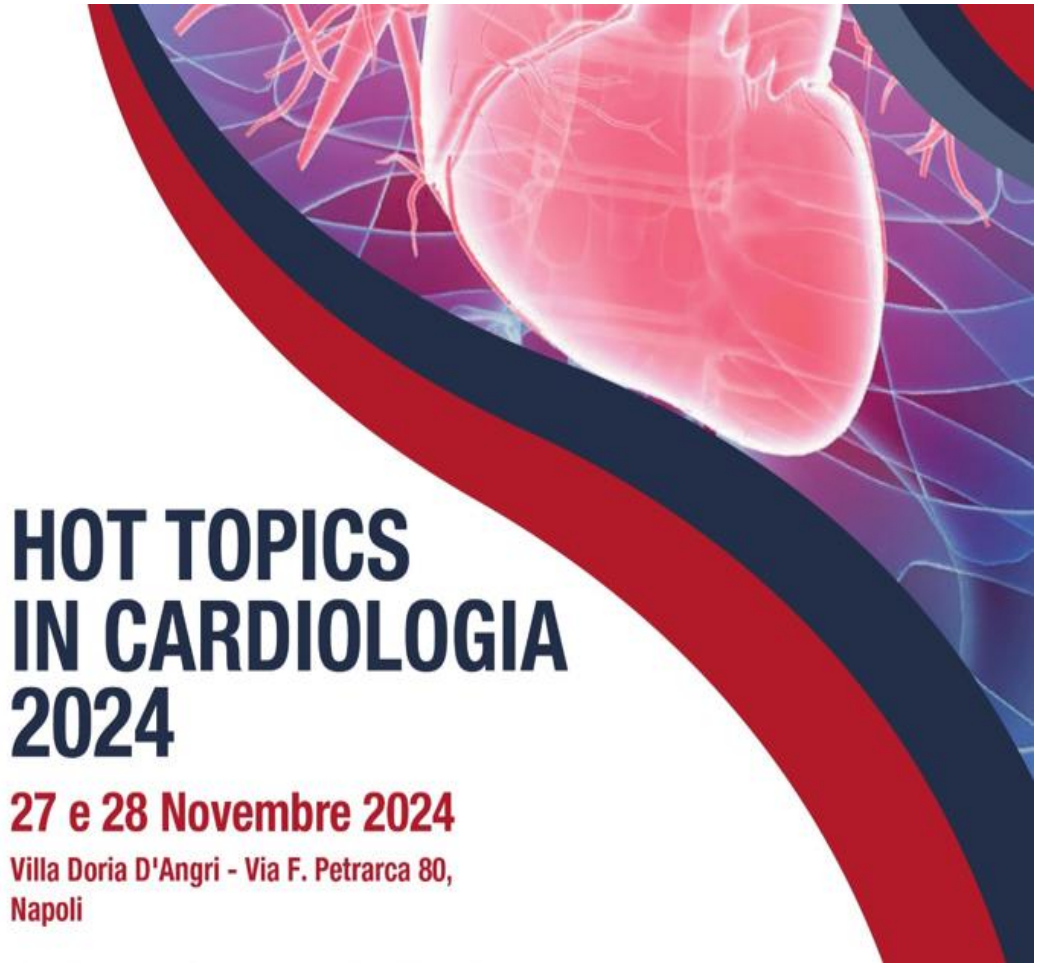

TITOLO: CARDIOMIOPATIE GENETICHE E RARE

RELATORE: GIUSEPPE LIMONGELLI

Link
profitable solutions

Disclosures

Giuseppe Limongelli

Università della Campania Luigi Vanvitelli
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Centro Europeo (ERN) Malattie rare del Cuore
Centro Coordinamento Malattie Rare - Regione Campania

Pfizer, Amicus, Sanofi, Takeda, BMS, Alnylam, Chiesi RD, Novartis

ESC European Society of Cardiology

European Heart Journal (2023) **44**, 3503–3626
https://doi.org/10.1093/eurheartj/ehad194

ESC GUIDELINES

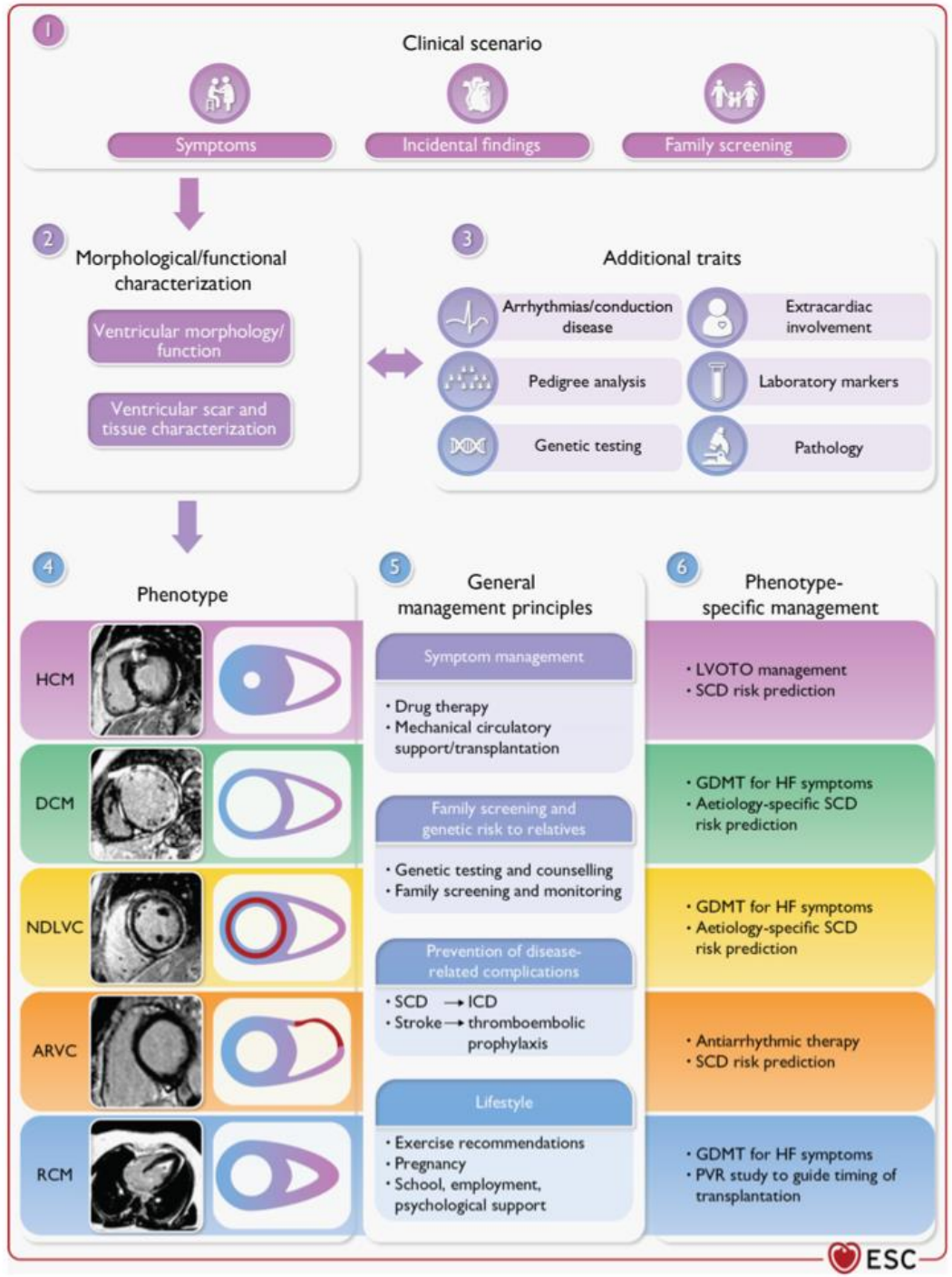
2023 ESC Guidelines for the management of cardiomyopathies

Developed by the task force on the management of cardiomyopathies of the European Society of Cardiology (ESC)

Authors/Task Force Members: Elena Arbelo *†, (Chairperson) (Spain), Alexandros Protonotarios ‡, (Task Force Co-ordinator) (United Kingdom), Juan R. Gimeno ‡, (Task Force Co-ordinator) (Spain), Eloisa Arbustini (Italy), Roberto Barriales-Villa (Spain), Cristina Basso (Italy), Connie R. Bezzina (Netherlands), Elena Biagini (Italy), Nico A. Blom[1] (Netherlands), Rudolf A. de Boer (Netherlands), Tim De Winter (Belgium), Perry M. Elliott (United Kingdom), Marcus Flather (United Kingdom), Pablo Garcia-Pavia (Spain), Kristina H. Haugaa (Sweden), Jodie Ingles (Australia), Ruxandra Oana Jurcut (Romania), Sabine Klaassen (Germany), Giuseppe Limongelli (Italy), Bart Loeys[2] (Belgium), Jens Mogensen (Denmark), Iacopo Olivotto (Italy), Antonis Pantazis (United Kingdom), Sanjay Sharma (United Kingdom), J. Peter Van Tintelen (Netherlands), James S. Ware (United Kingdom), Juan Pablo Kaski *†, (Chairperson) (United Kingdom), and ESC Scientific Document Group

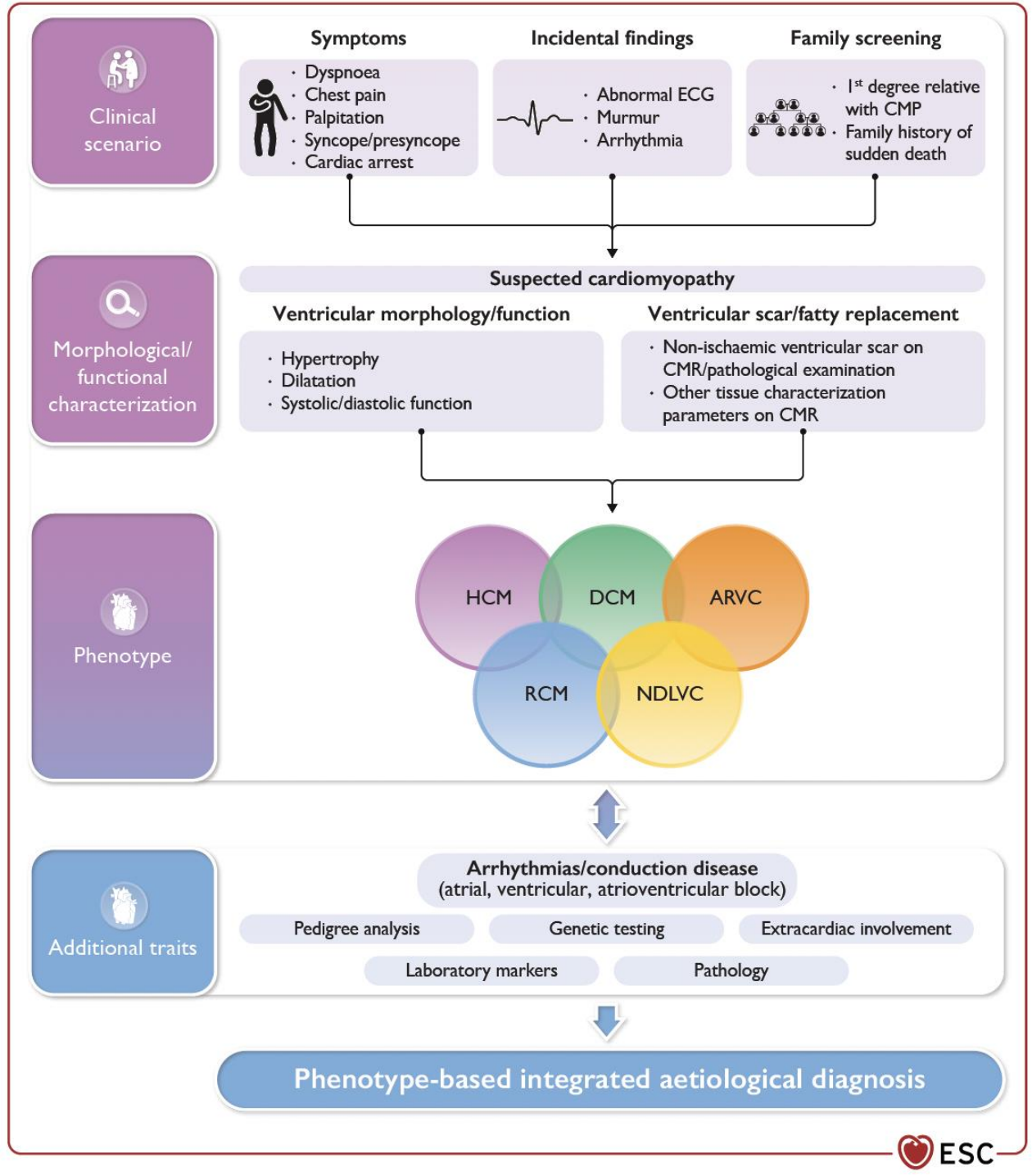
First Step

The Patient Pathway: clinical scenarios and definition of Phenotypes



Second Step

Systematic approach to cardiomyopathies: Aetiology definition



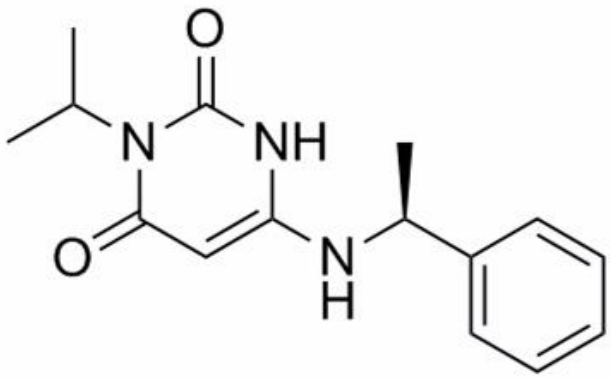
Phenotype

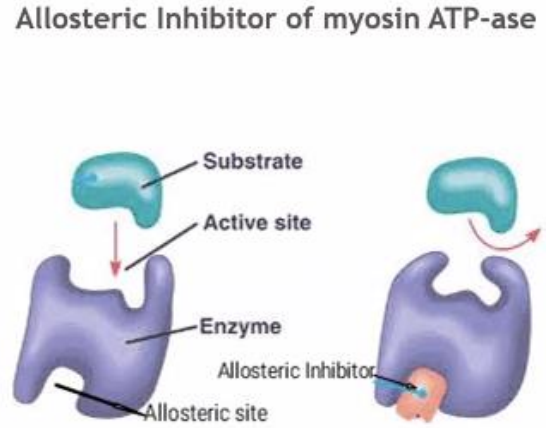
Aetiology

Management

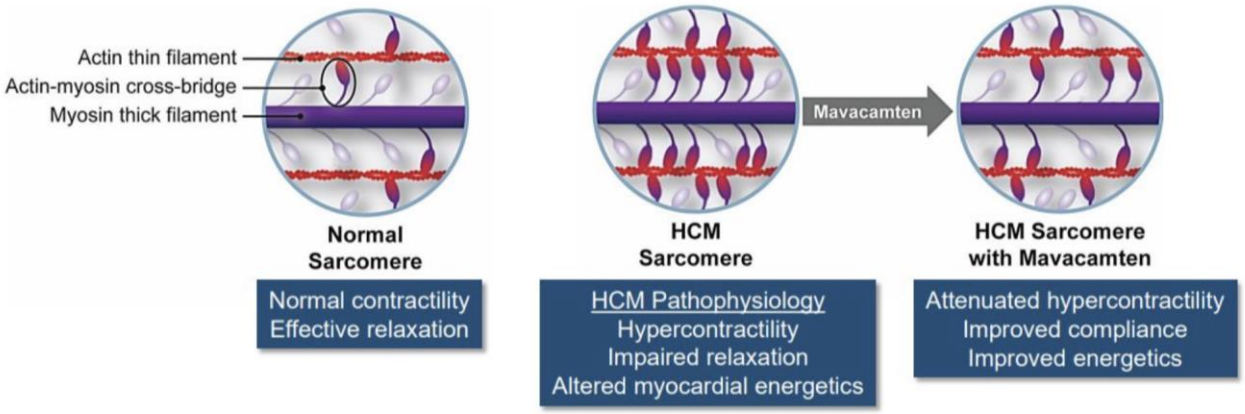
What is MAVACAMTEN?

Mavacamten is a small molecule, selective allosteric inhibitor of cardiac myosin





Mechanism of action?



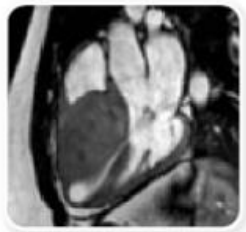
MYH7: SRX/DRX

From Bench to Bedside

Clinical studies

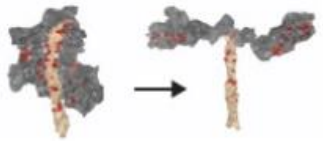
Hypercontractile LV

LVOT obstruction >> symptoms



Basic science

Gain of function MHY7 mutations

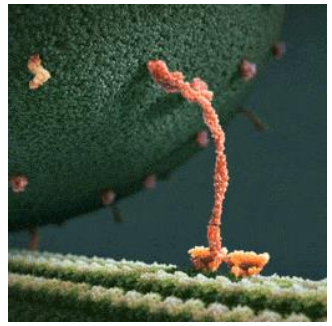


Targeted molecular approach

Myosin inhibitors
Mavacamten

Pre-clinical data

- ↓ Contractility
- ↑ Compliance
- ↑ Energetics
- ↓ LV hypertrophy
- ↓ Disarray
- ↓ Myocardial fibrosis



Can we use it in clinic?

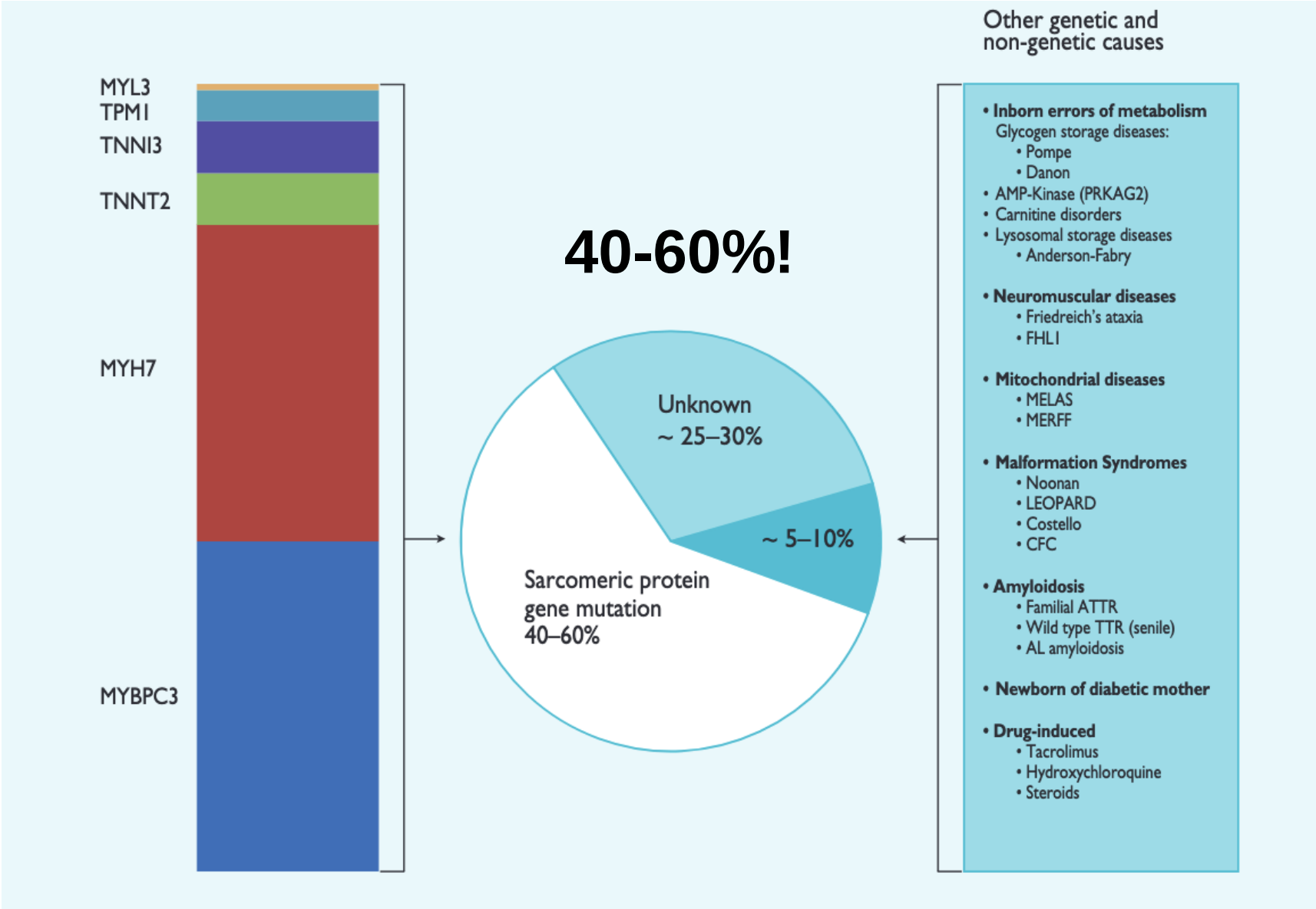
Mavacamten: a first-in-class myosin inhibitor for obstructive hypertrophic cardiomyopathy

Eugene Braunwald [1,2]*, Sara Saberi[3], Theodore P. Abraham[4], Perry M. Elliott[5], and Iacopo Olivotto[6]

Table 1 **Mavacamten trial characteristics and outcomes**

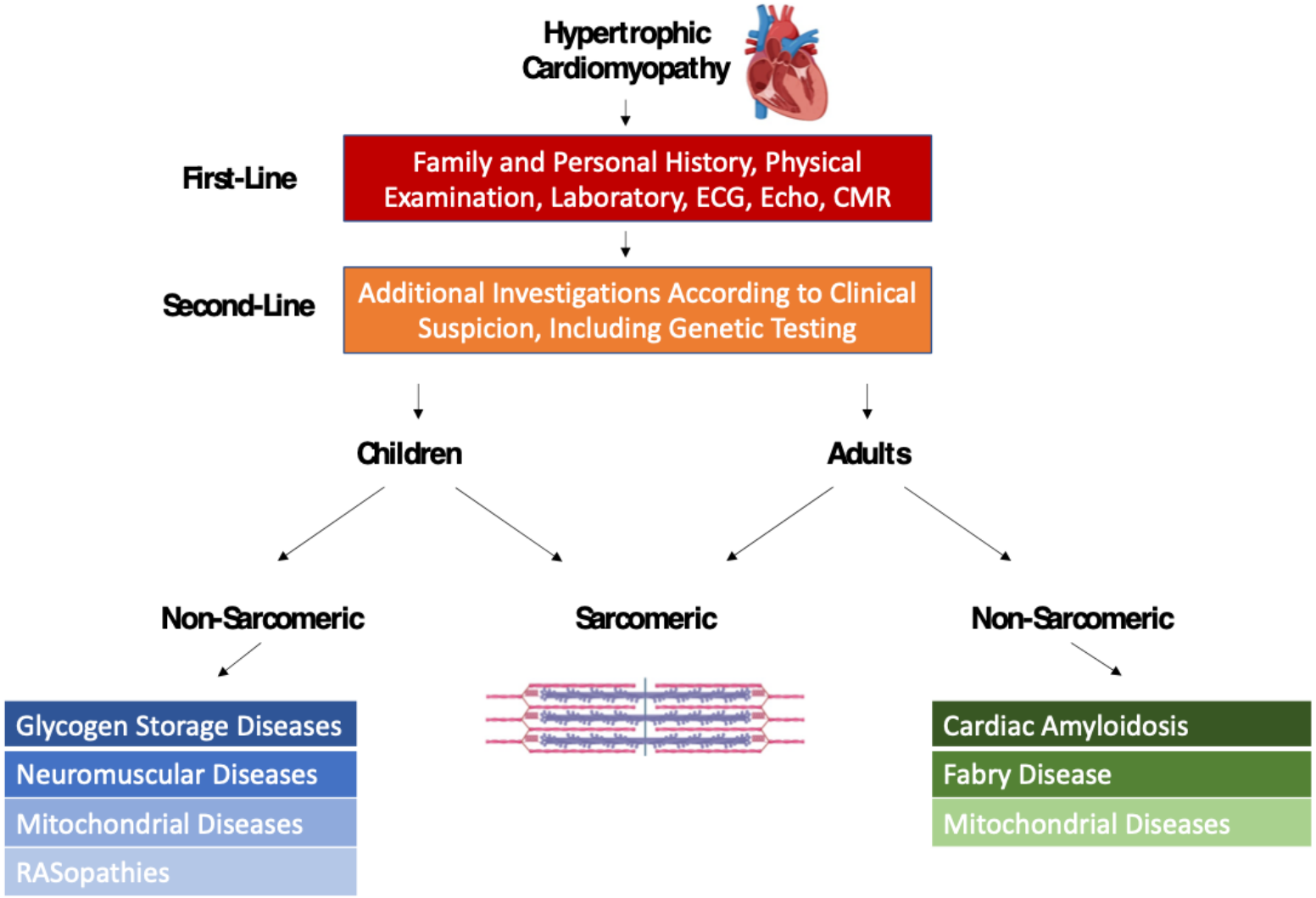
Title (reference)	PIONEER HCM[41,42]	EXPLORER HCM[36,37]	VALOR-ACH[43]
Design	Open-label Non-randomized	Double-blind randomized	Double-blind Randomized
N	21	251 (123 vs 128)	112 (56 vs 56)
Duration (weeks)	12	30	16
NYHA class	II/III	II/III	III/IV
Dose (mg/day)	2–20	2.5–15	2.5–15
Primary endpoint	Change in post-exercise LVOT gradient	Exercise capacity symptom burden	Continued eligibility for SRT
OUTCOMES	↓ LVOT gradients	↓ LVOT gradients	↓ eligibility for SRT
	Improved exercise capacity and ventilatory efficiency	Improved exercise capacity	↓ LVOT gradients
	↓ NYHA class	↓ NYHA class	↓ NYHA class
	↓ NRS dyspnoea score	↓ NT-proBNP and hs-cTnI	↓ NT-proBNP and hs-cTnI
	Improved health status	Improved diastolic function	Improved health status

Genetics in HCM – Aetiological Diagnosis



Elliott et al. ***Eur Heart J*** 2014

Diagnostic Work – Phenocopies/Genocopies

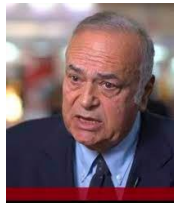


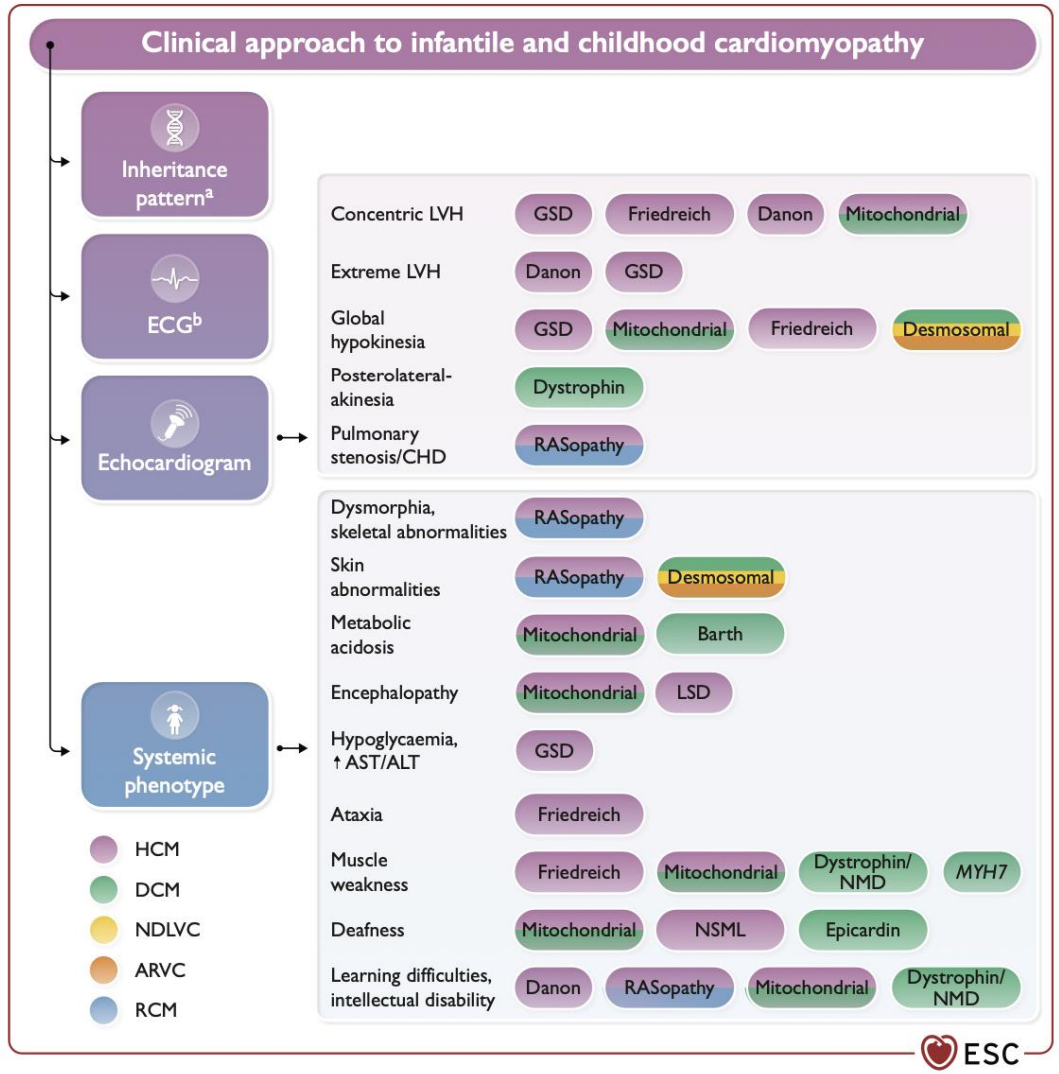
Monda et al. ***Circ Heart Fail*** 2023

Looking for Pheno-Genocopies: CMP mindset and the RF approach!

The red flags approach

Pedigree	Autosomal dominant Autosomal recessive X-linked Matrilinear
Symptoms	Deafness Muscle pains/weakness Paraesthesia
Physical exam	Muscle weakness Postural hypotension Rash Ocular
ECG	Preexcitation a-v Block Pseudo-infarct pattern
Laboratory	Creatinine kinase Creatinine/Proteinuria Ferritin Lactate
Echo	Signs of infiltrative/storage diseases LVNC Presence/distribution of dyskinesias





Rapezzi C, Eur Heart J. 2013 May;34(19):1448-58

Third Step

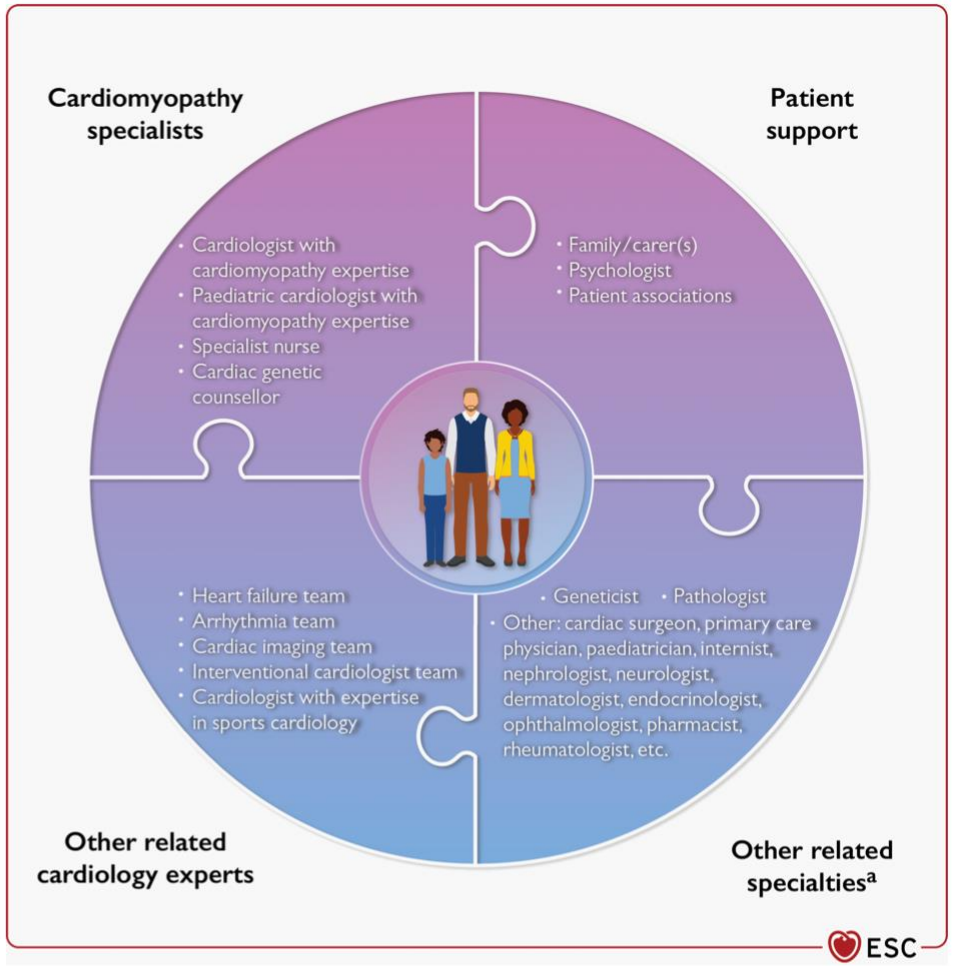
CMP mindset - Multidisciplinary Approach

Recommendation Table 1 — Recommendations for the provision of service of multidisciplinary cardiomyopathy teams

Recommendations	Class[a]	Level[b]
It is recommended that all patients with cardiomyopathy and their relatives have access to multidisciplinary teams with expertise in the diagnosis and management of cardiomyopathies.	I	C
Timely and adequate preparation for transition of care from paediatric to adult services, including joint consultations, is recommended in all adolescents with cardiomyopathy.[58,59]	I	C

© ESC 2023

[a]Class of recommendation.
[b]Level of evidence.



Last Step

Management - Treatment

	Etiology	Novel Therapies		
Sarcomeric HCM	Mutations in Sarcomeric Genes Responsible for an Hypercontractility Phenotype	Myosin Inhibitors	→	Mavacamten Aficamten
		Gene Therapy		
RASopathy	LVH Caused by Upregulation of RAS-MAPK or PI3K-AKT-mTor Patway	MEK1 Inhibitors (in NS)	→	Trametinib
		mTor Inhibitors (in NSML)	→	Everolimus
Pompe Disease	Mutations in *GAA* Gene Responsible for Abnormal Lysosomal Glycogen Accumulation	Enzyme Replacement Therapy	→	Aglucosidase Alpha
Danon Disease	Mutations in *LAMP* Gene Responsible for Abnormal Glycogen Accumulation	Gene Therapy		
Friedreich Ataxia	LVH Caused by Mitochondria Proliferation and Iron Accumulation	NRF2 Agonists	→	Omaveloxolone

	Etiology	Novel Therapies		
Sarcomeric HCM	Mutations in Sarcomeric Genes Responsible for an Hypercontractility Phenotype	Myosin Inhibitors	→	Mavacamten Aficamten
		Gene Therapy		
Fabry Disease	Mutations in *GLA* Gene Responsible for Gb3 and LysoGb3 Accumulation	Enzyme Replacement Therapy	→	Agalsidase Alpha Agalsidase Beta Pegunigalsidase
		Chaperone Therapy	→	Migalastat
		Substrate Reduction Therapy	→	Lucerastat Venglustat
Cardiac Amyloidosis	Abnormal Amyloid Fibrils Formation and Deposition	Antisense Oligonucleotides	→	Inotersen Eplotersen
		Small Interfering RNA	→	Patisiran Vutrisiran
		Tetramer Stabilizers	→	Tafamidis Acoramidis
		Clearance of Amyloid Deposits	→	Antibodies

Monda et al. Circ HF 2023

…a journey toward "precision medicine"…

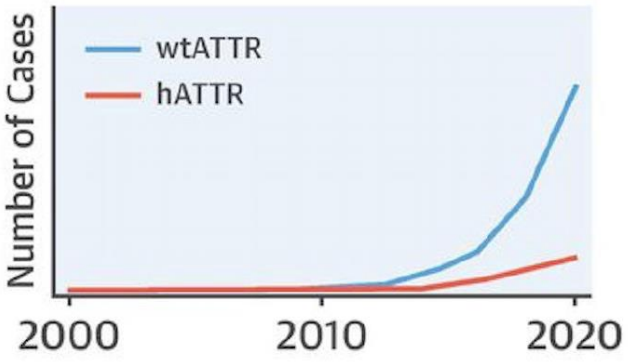
AMYLOIDOSYS: One name, many disease…

Terminology and Classification of Amyloidoses

Amyloid protein	Precursor	Syndrome or involved tissue
AL	**immunoglobulin light chain**	**Primary / Myeloma associated**
ATTR	**Transthyretin**	**Familial (PAF)** **Senile (wilde type TTR)**
AA	Serum AA	Secondary, reactive
A $ß_2$M	$ß_2$ microglobulin	Hemodyalisis associated
AApo AII AFib Alys	Apolipoprotein AII Fibrinogen α chain Lysozyme	Familial Familial Familial
…. Aß APrP	…. Aß protein precursor Prion protein	…. Alzheimer's desease, aging Spongioform encephalopathies

-More than 30 different types of Amyloidosis (each due to a specific protein)

-Cardiac Amyloidosis: AL + ATTr (up to 95%)



J Am Coll Cardiol 2019;73:2872-91

Mayo

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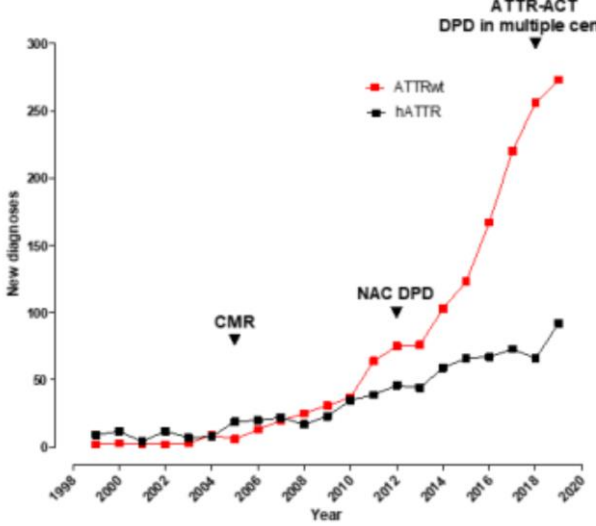


ESC European Society of Cardiology — European Journal of Heart Failure (2022) doi:10.1002/ejhf.2504 — RESEARCH ARTICLE

Unmasking the prevalence of amyloid cardiomyopathy in the real world: results from Phase 2 of the AC-TIVE study, an Italian nationwide survey

Marco Merlo[1†], Linda Pagura[1†], Aldostefano Porcari[1], Matteo Camelli[2], Giuseppe Vergaro[3], Beatrice Musumeci[4], Elena Biagini[5], Marco Canepa[6,7], Lia Crotti[8,9], Massimo Imazio[10,11], Cinzia Forleo[12], Francesco Cappelli[13,14], Federico Perfetto[14], Stefano Favale[12], Gianluca Di Bella[15], Franca Dore[16], Francesca Girardi[16], Daniela Tomasoni[17], Rita Pavasini[18], Valeria Rella[8], Giuseppe Palmiero[19], Martina Caiazza[19], Maria Cristina Carella[12], Andrea Igoren Guaricci[12], Giovanna Branzi[8], Angelo Giuseppe Caponetti[5], Giulia Saturi[5], Giovanni La Malfa[6], Andrea Carlo Merlo[6], Alessandro Andreis[10], Francesco Bruno[10], Francesca Longo[1], Maddalena Rossi[1], Guerino Giuseppe Varrà[1], Riccardo Saro[1], Luca Di Ienno[18], Giuseppe De Carli[2], Elisa Giacomin[2], Chiara Arzilli[20], Giuseppe Limongelli[19], Camillo Autore[4], Iacopo Olivotto[13], Luigi Badano[8,9], Gianfranco Parati[8,9], Stefano Perlini[21], Marco Metra[17], Michele Emdin[3], Claudio Rapezzi[18,22*], and Gianfranco Sinagra[1*]

The AC-tive Study

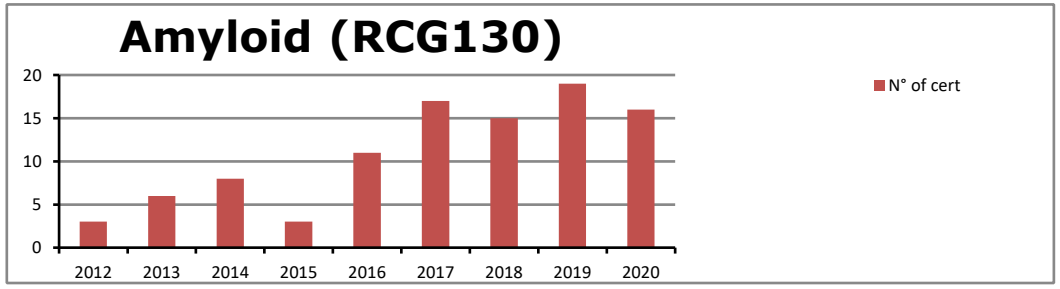
Rare or Overlooked?

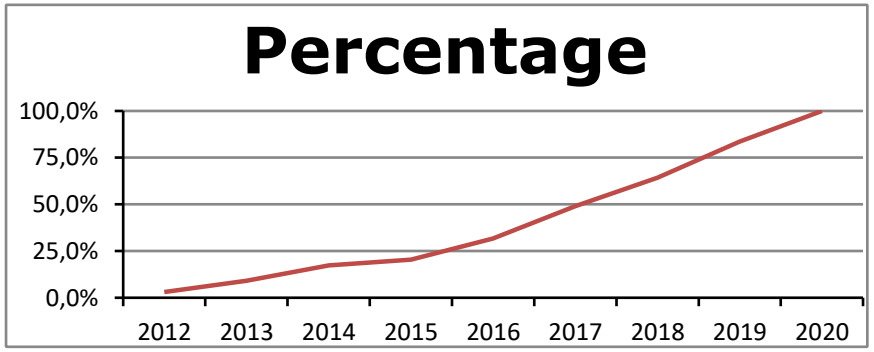
ESC European Society of Cardiology — European Journal of Preventive Cardiology (2024) 00, 1–8 https://doi.org/10.1093/eurjpc/zwae093 — FULL RESEARCH PAPER *Heart failure and cardiomyopathies*

Wild-type transthyretin cardiac amyloidosis is not rare in elderly subjects: the CATCH screening study

Alberto Aimo[1,2†], Giuseppe Vergaro[1,2†], Vincenzo Castiglione[1,2], Iacopo Fabiani[2], Andrea Barison[1,2], Francesco Gentile[1,2], Yu Fu Ferrari Chen[2], Assuero Giorgetti[2], Dario Genovesi[2], Gabriele Buda[3], Maria Franzini[4], Massimo Piepoli[5], Stefano Moscardini[6], Claudio Rapezzi[7,8‡], Marianna Fontana[9], Claudio Passino[1,2], and Michele Emdin[1,2*]

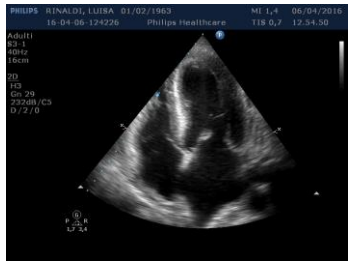
Catch Study





When to suspect Cardiac Amyloidosis?

Left Ventricular Wall Thickness ≥ 12 mm

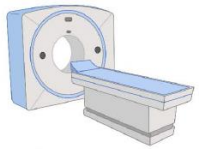


+ ≥1 of

- Heart failure in ≥ 65 years
- Aortic stenosis in ≥ 65 years
- Hypotension or normotensive if previously hypertensive
- Sensory involvement, autonomic dysfunction
- Peripheral polyneuropathy
- Proteinuria
- Skin bruising
- Bilateral carpal tunnel syndrome
- Ruptured biceps tendon
- Subendocardial/transmural LGE or increased ECV
- Reduced longitudinal strain with apical sparing
- Decreased QRS voltage to mass ratio
- Pseudo Q waves on ECG
- AV conduction disease
- Possible family history

Garcia-Pavia et al. 2021 EHJ

Prevalence of AMY in HF?

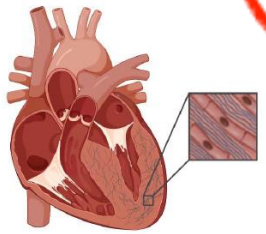


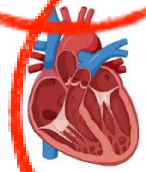
Bone scintigraphy
for non-cardiac reasons:
≥81 years: ~1.3% M, ~0.4% W

Autopsy in unselected
elderly individuals: 21%
(95% CI 7-39%)

HFpEF: 12%
(95% CI 6-20%)
M 73% (39-100%)
77 years (66-86)
AL-CA 10% (0-40%)

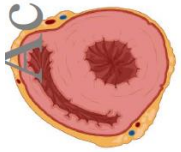
Aortic stenosis: 8%
(95% CI 5-13%)
M 67% (50-89%)
84 years (75-88)
AL-CA 2% (0-6%)





HFrEF/HFmrEF: 10%
(95% CI 6-15%)
M 100%
81 years (76-85)
AL-CA 0%

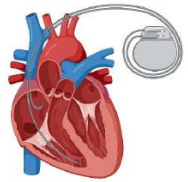
Prevalence of cardiac amyloidosis in screening studies



HCM: 7%
(95% CI 5-9%)
M 80% (73-87%)
74 years
AL-CA 0-9%

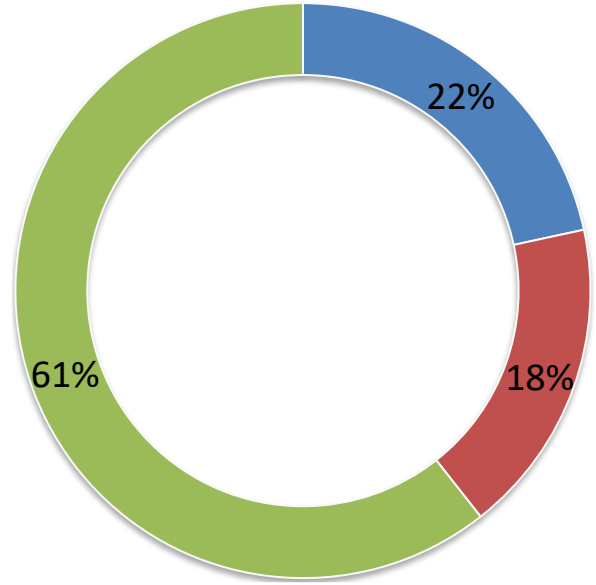
Surgery for carpal tunnel
syndrome: 7%
(95% CI 5-10%)
M 64% (33-100%)
76 years (73-79)
AL-CA 18% (0-33%)

Conduction disorders: 2%
(95% CI 0-4%)
M 50%
90 years
AL-CA 0%



Aimo et al. 2022 EJHF

Prevalence of HF in AMY?



Transthyretin cardiac amyloid: Broad heart failure phenotypic spectrum and implications for diagnosis

Mileydis Alonso[1], Radhika K. Neicheril[2], Yosef Manla[3], Malcolm L. McDonald[1], Alejandro Sanchez[1], Gabrielle Lafave[2], Yelenis Seijo De Armas[1], Antonio Lewis Camargo[1], Dipan Uppal[1], David Wolinsky[1], Nina Thakkar-Rivera[1], Mauricio Velez[1], David A. Baran[1], Jerry D. Estep[1] and David Snipelisky[1]*

ESC HEART FAILURE
ESC Heart Failure (2024)

OSPEDALI DEI COLLI
MONALDI - COTUGNO - C.T.O.
"AZIENDA OSPEDALIERA SPECIALISTICA DEI COLLI"
Monaldi - Cotugno - C.T.O.

The Patient Clinical Pathway in Amyloidosis

ESC European Heart Journal (2021) 42, 1554–1568 doi:10.1093/eurheartj/ehab072
SPECIAL ARTICLE
Heart failure and cardiomyopathies

Diagnosis and treatment of cardiac amyloidosis: a position statement of the ESC Working Group on Myocardial and Pericardial Diseases

Pablo Garcia-Pavia[1,2,3*], Claudio Rapezzi[4,5], Yehuda Adler[6], Michael Arad[7], Cristina Basso[8,9,9], Antonio Brucato[10], Ivana Burazor[11], Alida L.P. Caforio[2,12], Thibaud Damy[3,13], Urs Eriksson[14], Marianna Fontana[15], Julian D. Gillmore[15], Esther Gonzalez-Lopez[1,3], Martha Grogan[16], Stephane Heymans[17,18,19], Massimo Imazio[20], Ingrid Kindermann[21], Arnt V. Kristen[22,23], Mathew S. Maurer[24], Giampaolo Merlini[25,26], Antonis Pantazis[27], Sabine Pankuweit[28], Angelos G. Rigopoulos[29], and Ales Linhart[30]

Signs & symptoms, ECG, echo or CMR suggestive of cardiac amyloidosis

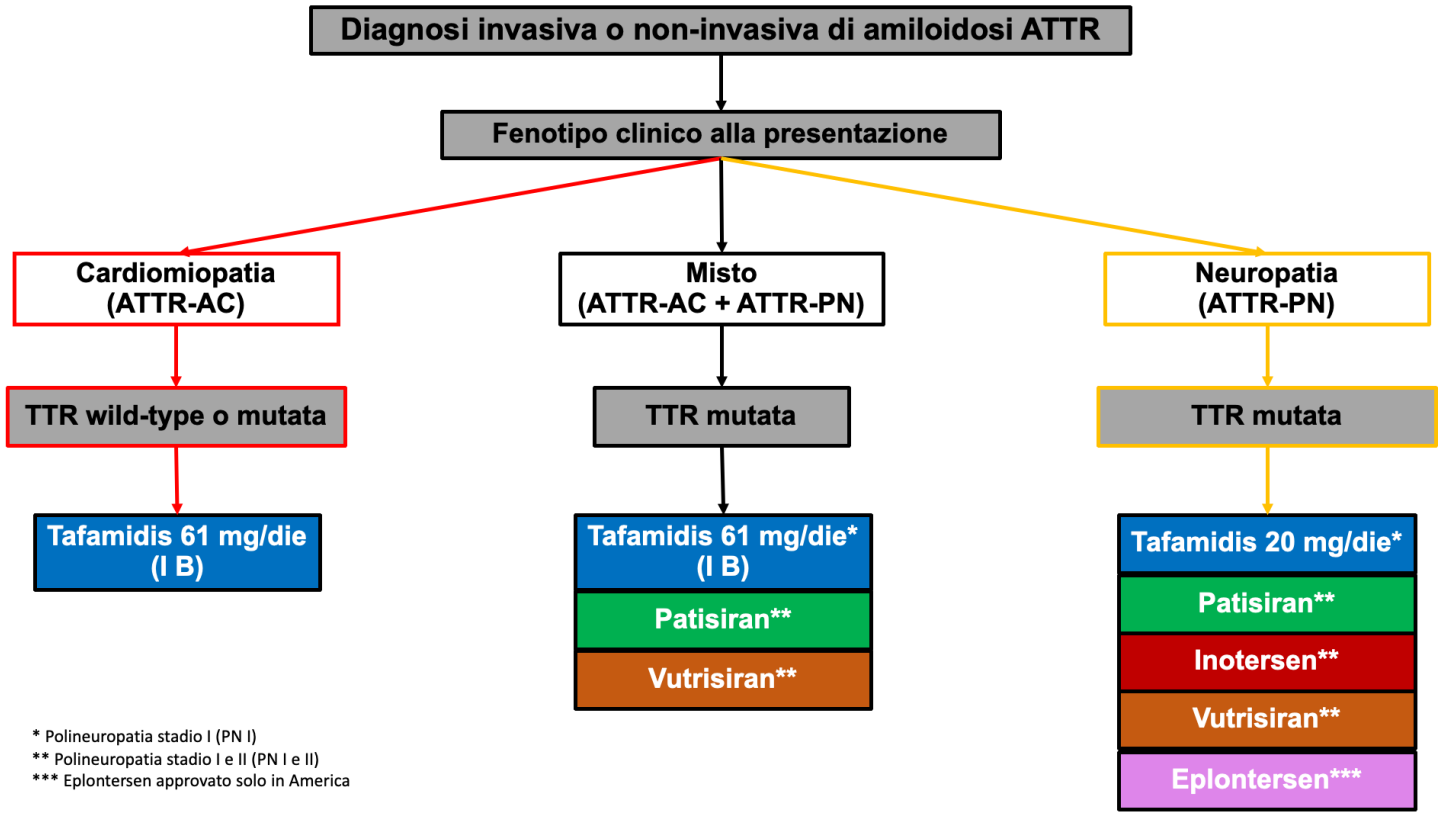
^{99m}Tc-DPD/PYP/HMDP Scintigraphy with SPECT &

Haematologic tests (serum free-light chain quantification & serum and urine immunofixation)

Scintigraphy grade 0 Haematologic tests -	Scintigraphy grade 1-3 Haematologic tests -		Scintigraphy grade 0 Haematologic tests +	Scintigraphy grade 1-3 Haematologic tests +
AL/ATTR cardiac amyloidosis unlikely	Grade 2-3 **Cardiac ATTR amyloidosis**	Grade 1 Histological confirmation (cardiac/extracardiac) **to diagnose**	AL amyloidosis?	Histological confirmation (usually cardiac) **to subtype**
If suspicion persists consider CMR followed by biopsy	TTR genetic testing ATTRwt / ATTRv		CMR negative: Amyloidosis unlikely CMR + or inconclusive: Histological confirmation (cardiac/extracardiac) **to diagnose**	

Percorsi Diagnostico-Terapeutico-Assistenziali (PDTA) per Pazienti con Amiloidosi Cardiaca - Position Paper SIC e ANMCO

A cura della Rete Italiana dell'Amiloidosi Cardiaca (RIAC)

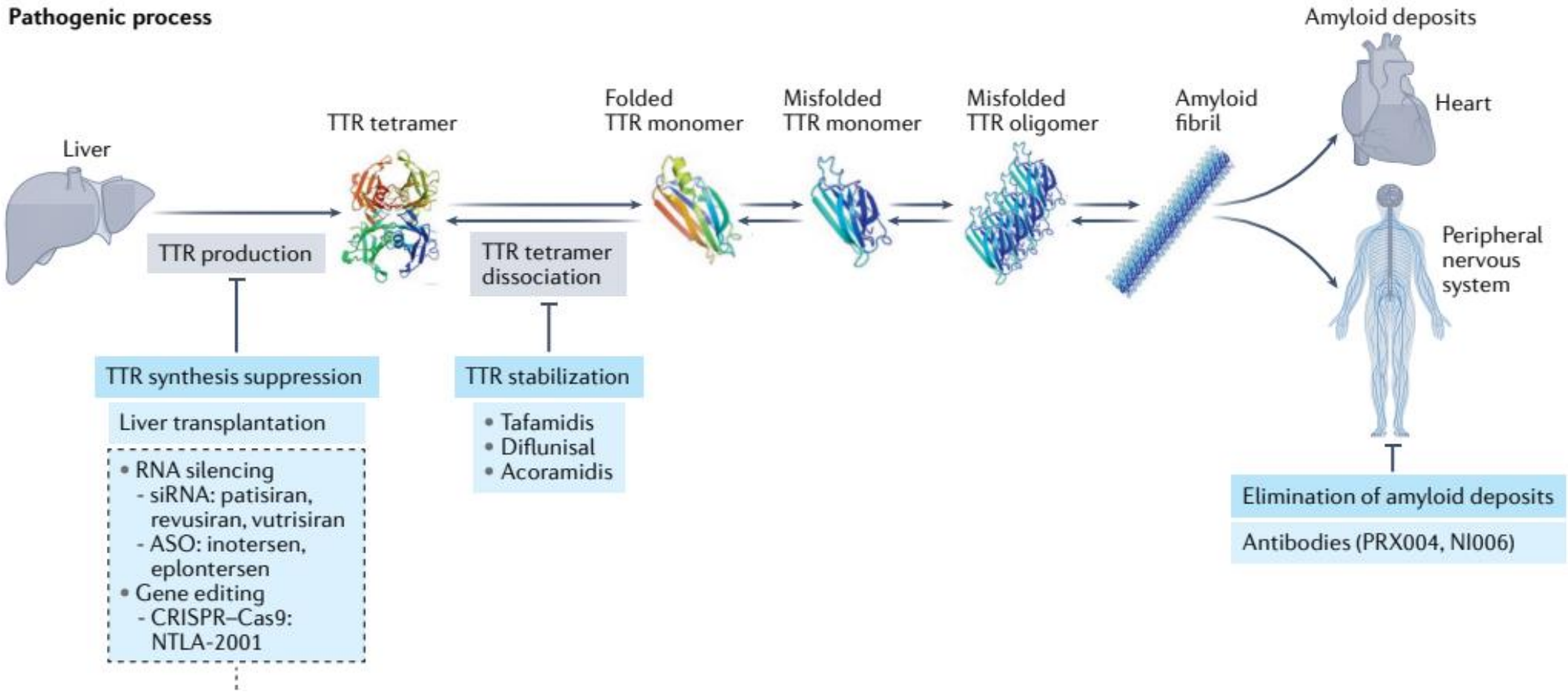


"Alla luce del frequente coinvolgimento cardiaco, ***il Cardiologo è sempre più protagonista dalle fasi di sospetto di malattia alla conferma diagnostica, rappresentando una figura di riferimento e di convergenza tra specialisti di differenti ambiti*** *medici come Nefrologo, Neurologo, Ematologo, Medico Internista, Geriatra, Chirurgo Plastico ed Ortopedico.*

Il Cardiologo si pone in continuità con il Medico Nucleare, l'Anatomo-Patologo ed il Medico Genetista per raggiungere una diagnosi di certezza ed eziologica, e orientare il successivo iter per i pazienti, e, in caso di forme ereditarie, per i loro familiari"

Porcari et al.

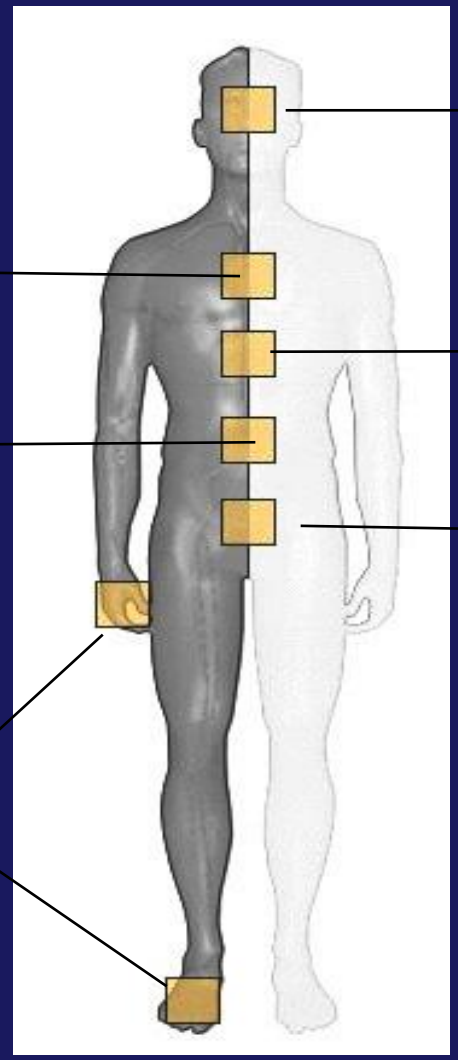
TTR treatment target



Aimo, A. et al *Nat Rev Cardiol* **19**, 655–667

Anderson Fabry Cardiomyopathy

- Rare, X linked
- alpha-Gal deficit
- GB3 storage



Eyes

Celebrovascular disease

Heart

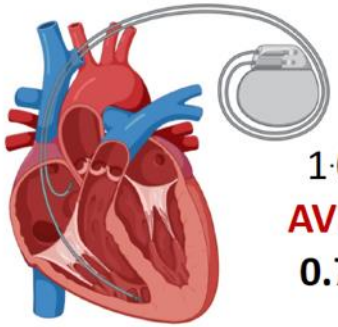
Gastrointestinal involvement

Kidney

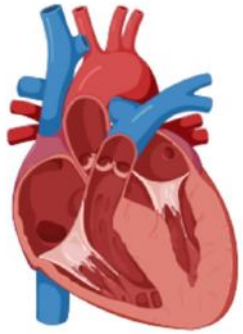
Skin

Acroparesthesia

15 Studies including
1·108·793 Patients Screened
Newborns:
0.01% (95%CI 0.002-0.079)



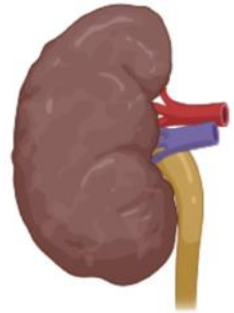
3 Studies including
1·033 Patients Screened
AVB/SND Requiring PMK:
0.70% (95%CI 0.30-1.40)



26 Studies including
10·080 Patients Screened
Hypertrophic Cardiomyopathy
1.20% (95%CI 0.80-1.80)

Prevalence of Fabry disease in Screening Studies

3 Studies including
904 Patients Screened
Small-Fiber Neuropathy:
1.00% (95%CI 0.30-3.40)



38 Studies including
62·050 Patients Screened
End-Stage Renal Disease:
0.30% (95%CI 0.20-0.40)

25 Studies including 15·295
Patients Screened
Stroke:
0.70% (95%CI 0.50-1.00)

Monda E, et al. Circ Genomic Precis Medicine 2023

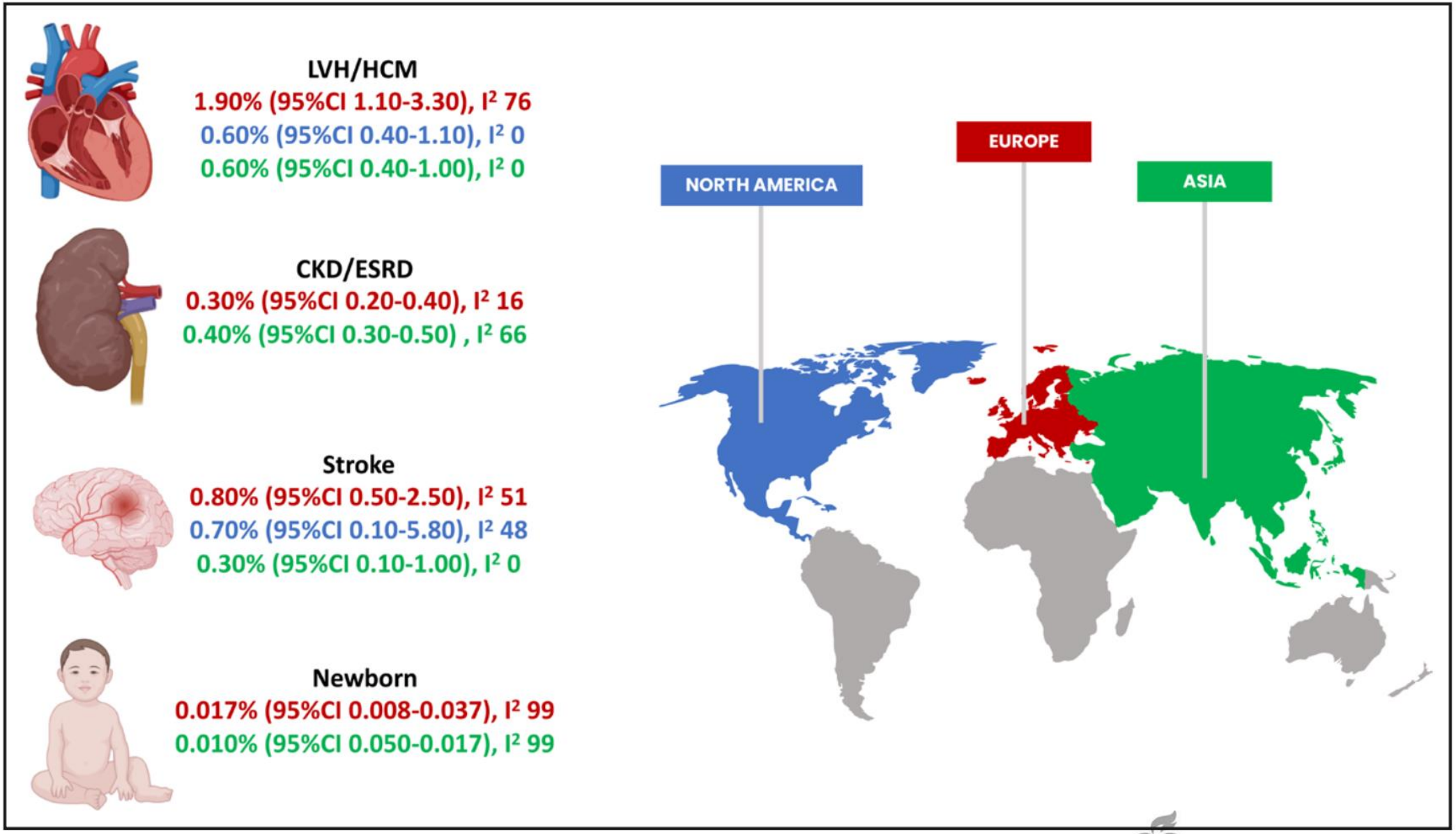


Figure 4. Continent-specific subanalysis. The continent-specific pooled prevalence of the Fabry disease within each setting (red, Europe; green, Asia; blue, North America; and grey, prevalence in these continents not available).

Monda E, et al. Circ Genomic Precis Medicine 2023

When to suspect Fabry CMP?

Left Ventricular Wall Thickness ≥ 12 mm

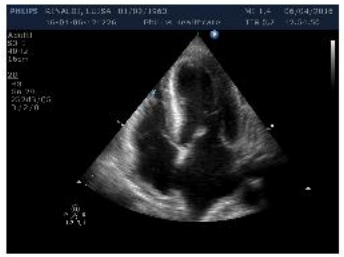
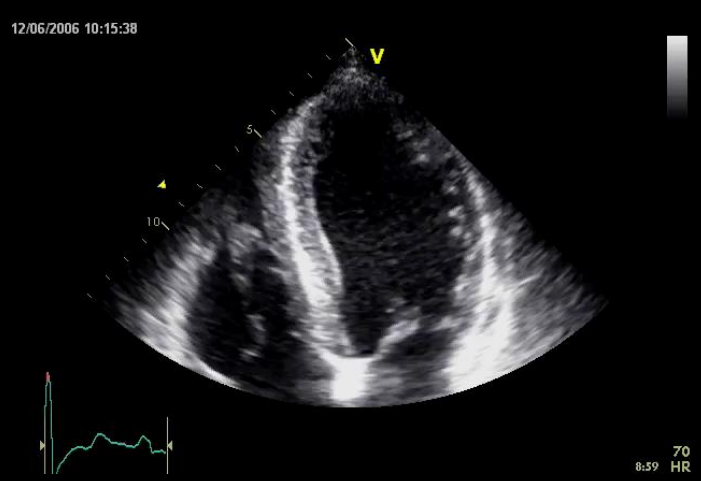


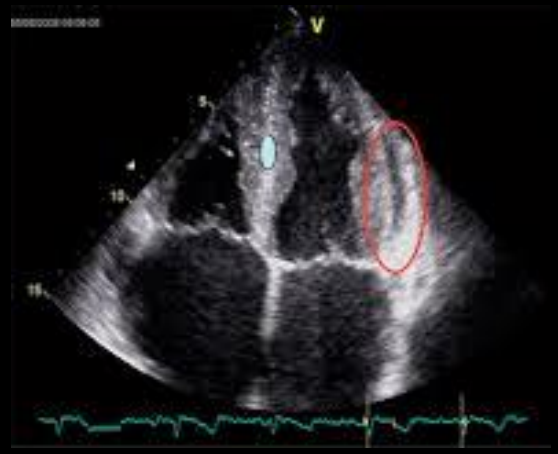
FIGURE 1 Fabry Disease Red Flags for Differential Diagnosis

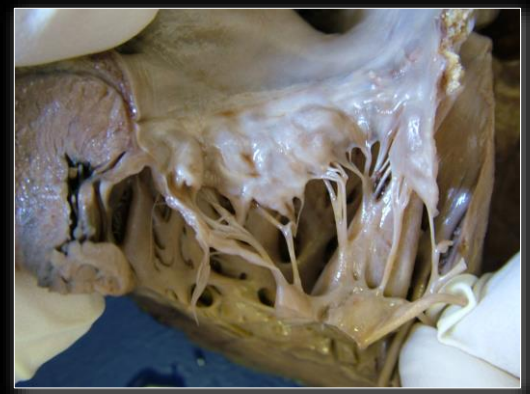
Presenting Decades of Age	Extra-Cardiac Red Flags		Cardiac Red Flags		Diagnostic Tool
	Any time	Family history of renal failure and/or stroke	Family history of LVH, particularly if no evidence of male-to-male transmission	History	
	1–2	Neuropathic pain			
	1–2	Gastrointestinal symptoms	Short PQ interval†	Electrocardiography	
	1–2	Angiokeratomas	Bradycardia		
	1–2	Cornea verticillata*	Chronotropic incompetence		
	1–2	Hypohidrosis, heat/cold, and exercise intolerance	Atrioventricular blocks†		
	1–2	Albuminuria	LVH with normal systolic function	2D-echocardiography	
	3–4	Juvenile and/or cryptogenic TIA/stroke	Reduced global longitudinal strain		
	3–4	Hearing loss (either progressive or sudden)	Mild-to-moderate aortic root dilation		
	3–4	Dolichoectrasia of the basilar artery, chronic white matter hyperintensities at brain MRI	Mitral and aortic valve thickening with mild-to-moderate regurgitation		
	3–4	Proteinuria	Hypertrophy of papillary muscles	Cardiac Magnetic Resonance	
	3–4	Renal failure	Mid-layer posterolateral late gadolinium enhancement		
	3–4	Lymphedema	Low native T1		

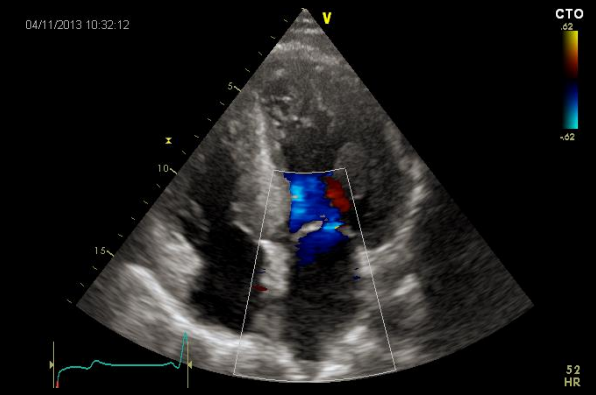
Fabry disease red flags for differential diagnosis of patients with idiopathic left ventricular hypertrophy (LVH) and/or hypertrophic cardiomyopathy. *In the absence of iatrogenic causes (chloroquine/amiodarone). †Short PQ interval in early stages; atrioventricular and bundle branch blocks are more common in advanced disease. 2D-echo = 2-dimensional echocardiography; MRI = magnetic resonance imaging; TIA = transient ischemic attack.

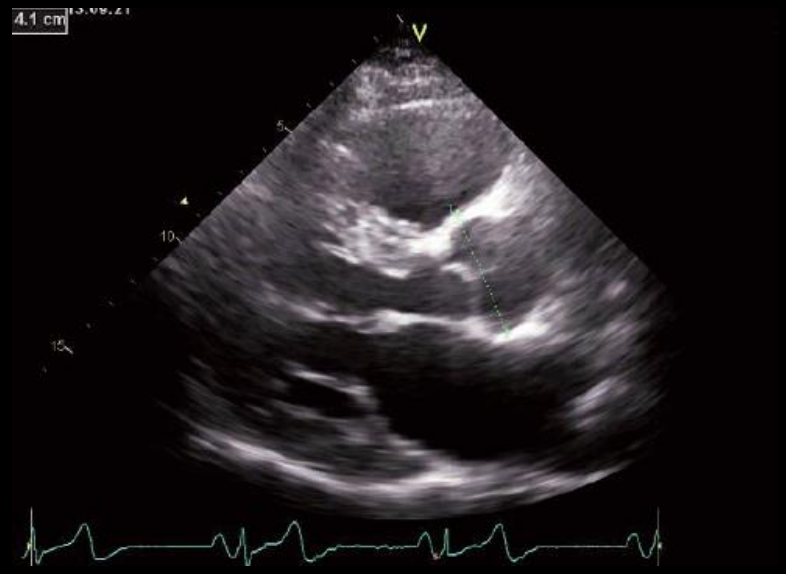
www.cardiogenetics.it

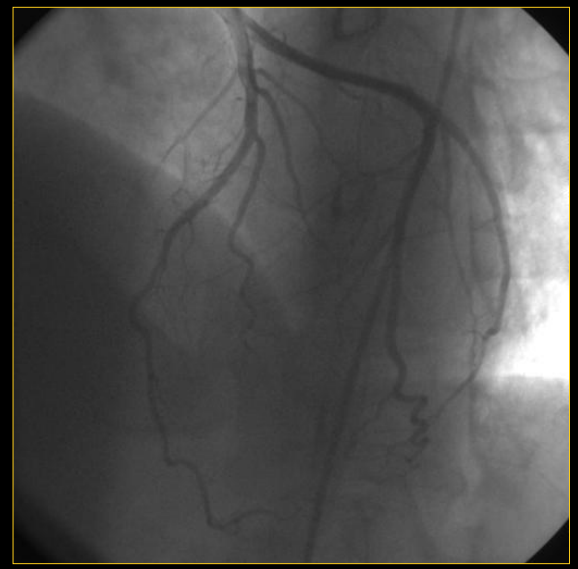


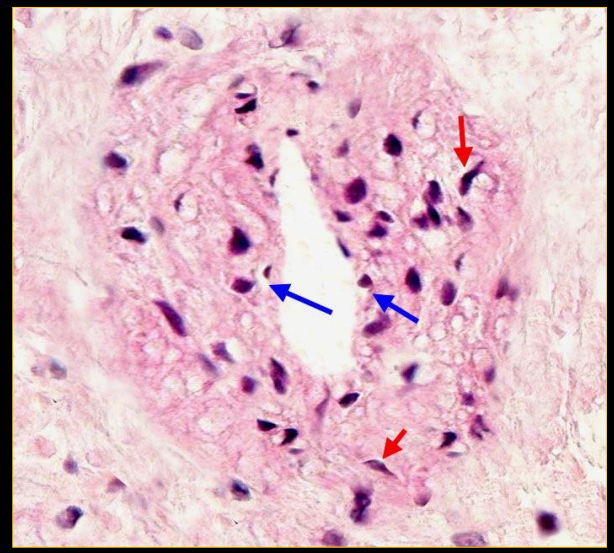












Nieman M, Weidemann F. Cardiogenetics 2013; 3:e3.

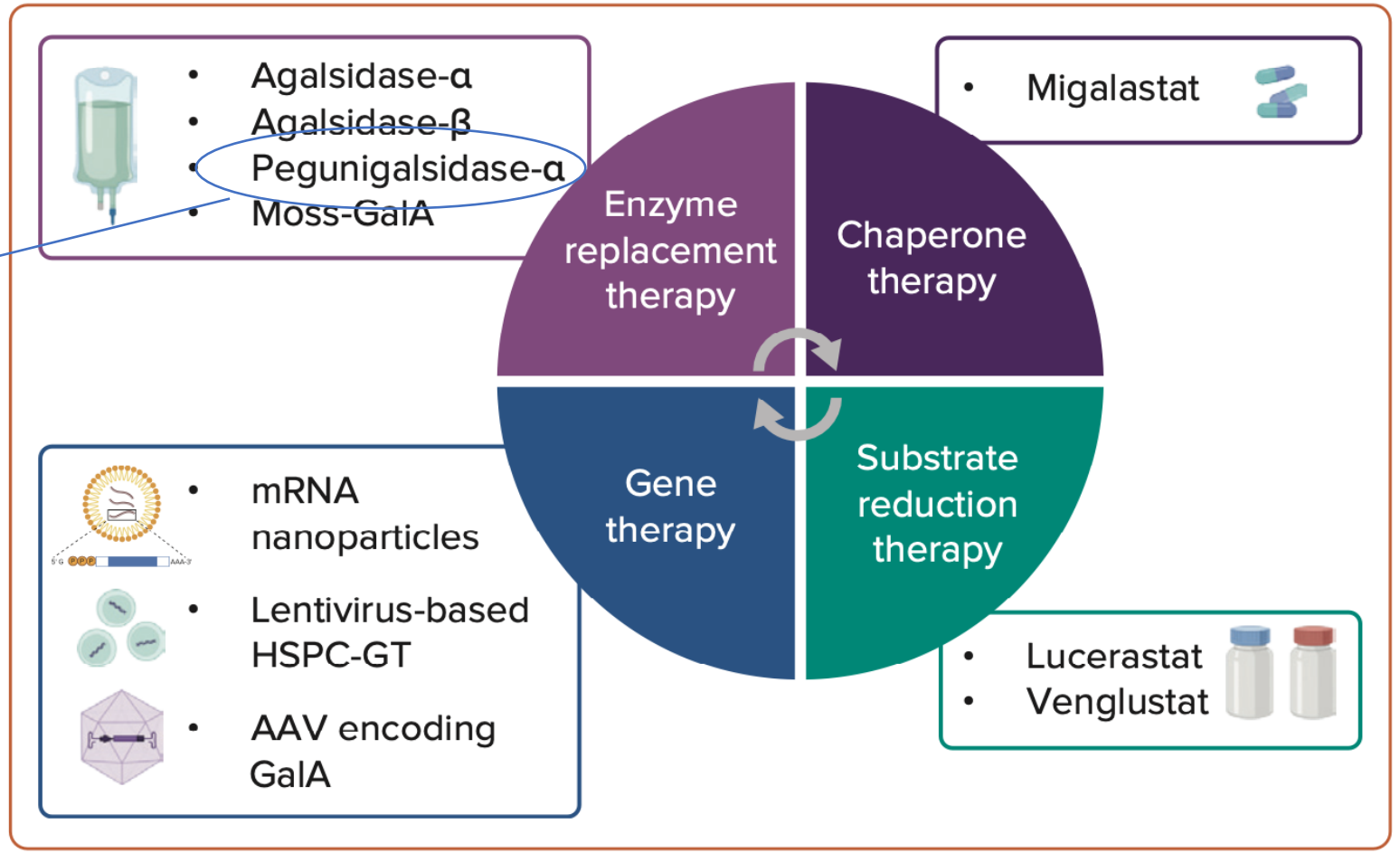
Table 1: Imaging Features of Cardiac Involvement According to FD Stage

	Early Stage	Advanced Stage
ECG	Short PR interval	Atrioventricular block High QRS voltages Negative T waves
Echocardiography	No LVH Reduced GLS in basal posterolateral segment Radial strain impairment	LVH Reduced GLS Papillary muscles hypertrophy Diastolic dysfunction
CMR	Reduced native T1 values	Normal native T1 value Diffuse LGE

CMR = cardiac MRI; FD = Fabry's disease; GLS = global longitudinal strain; LGE = late gadolinium enhancement; LVH = left ventricular hypertrophy.

Monda et al. 2023

Figure 2: Therapeutic Options for Patients with Fabry's Disease



AGENZIA ITALIANA DEL FARMACO
DETERMINA 5 luglio 2024
Riclassificazione del medicinale per uso umano «Elfabrio», ai sensi dell'articolo 8, comma 10, della legge 24 dicembre 1993, n. 537. (Determina n. 174/2024). (24A03622)
(GU n.169 del 20-7-2024)

Possible aetiological therapies include enzyme replacement therapy, chaperone therapy, substrate reduction therapy and gene therapy. AAV = adeno-associated virus; GalA = galactosidase A; HSPC-GT = haematopoietic stem/progenitor cell gene therapy. Created with BioRender.com.

Can we answer open questions/gaps of knowledge?

OSPEDALI DEI COLLI
MONALDI - COTUGNO - C.T.O.
"AZIENDA OSPEDALIERA SPECIALISTICA DEI COLLI"
Monaldi - Cotugno - C.T.O.

Università degli Studi della Campania *Luigi Vanvitelli*

MALATTIE GENETICHE E RARE CARDIOVASCOLARI

CENTRO COORDINAMENTO MALATTIE RARE REGIONE CAMPANIA

European Reference Network
for rare or low prevalence complex diseases
Network Heart Diseases (ERN GUARD-HEART)
Member AORN Colli — Italia

Fonte: Presentazione C. CHIMENTI

Rete Italiana ANMCO-SIC Centri Amiloidosi: Survey

ANMCO 2024

Rete Italiana Centri Amiloidosi: Survey

152 Centri in 19 Regioni

Nord ---------- **46%**

Piemonte, Valle d'Aosta, Lombardia, Trentino Alto Adige, Veneto, Friuli Venezia Giulia, Liguria, Emilia Romagna

Centro ---------- **29%**

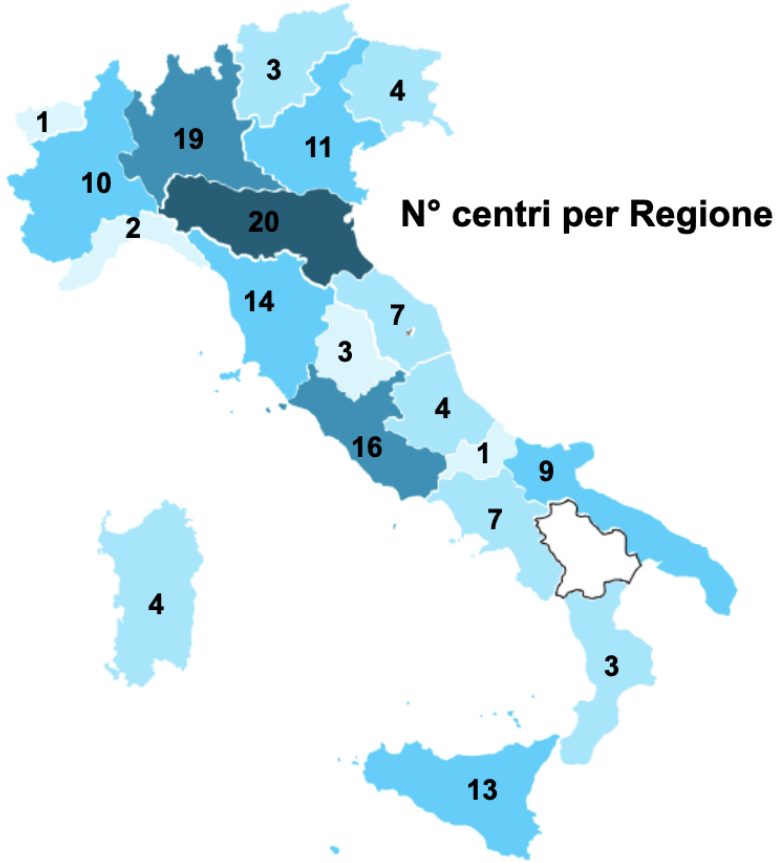
Toscana, Umbria, Marche, Lazio, Abruzzo

Sud ---------- **13%**

Molise, Campania, Puglia, Calabria

Isole ---------- **11%**

Sicilia e Sardegna



- Pazienti con varie forme di Amiloidosi seguiti periodicamente: **6386**
- Nuove diagnosi di Amiloidosi nel 2021-2022: **3992**

ESC European Society of Cardiology

European Heart Journal - Quality of Care and Clinical Outcomes (2024) **0**, 1–5
https://doi.org/10.1093/ehjqcco/qcae052

COHORT PROFILE

The Italian Fabry Disease Cardiovascular Registry (IFDCR)

Giuseppe Limongelli[1,2,*,†], Elena Biagini[2,3,†], Francesco Cappelli[4], Francesca Graziani[2,5], Emanuele Monda[1,2], Iacopo Olivotto[6], Vanda Parisi[2,3], Maurizio Pieroni[7], Marta Rubino[1,2], Serena Serratore[8], Gianfranco Sinagra[2,9], Ciro Indolfi[8], and Pasquale Perrone Filardi[10], on behalf of the Italian Fabry Disease Cardiovascular Registry promoted by the Italian Society of Cardiology (SIC)

Vai alla pag

Table 2 **Specific objectives of the Fabry Disease Italian Cardiovascular Registry**

Specific objectives
Assess the epidemiology of cardiovascular manifestations of FD in Italy (e.g. incidence of heart failure, atrial fibrillation, brady- and tachyarrhythmias, cardiovascular hospitalizations, and cardiovascular death)
Assess the role of clinical, ECG, imaging, and laboratory parameters useful for the early diagnosis of FD
Evaluate the natural history of untreated patients (e.g. female without organ involvement or patients carrying late-onset *GLA* variants)
Evaluate the genotype–phenotype correlations for rare *GLA* variants
Assess the role of clinical, ECG, imaging, and laboratory parameters (e.g. lyso-Gb3) for monitoring cardiovascular involvement progression in treated and untreated patients
Identify risk factors of major arrhythmic events (i.e. sudden cardiac death, sustained ventricular arrhythmias, ICD appropriate shock) and develop a tailored risk model
Assess the indications for ICD and pacemaker implantation and the factors driving the choice
Identify risk factors of atrial fibrillation and develop a tailored risk model
Assess the incidence and risk factors of systemic embolism in patients with atrial fibrillation
Assess the use of oral anticoagulation or non-pharmacological therapies for the prevention of atrial fibrillation-related embolic events and assess the factors driving the choice
Assess the role of conventional heart failure pharmacological therapies on clinical, imaging, and biochemical parameters, quality of life, and clinical outcomes
Evaluate the prevalence, clinical significance, and impact on treatment efficacy of anti-drug antibodies in patients treated with enzyme replacement therapy
Assess the role of artificial intelligence models applied to early diagnosis, management, outcome prediction, and response to therapy

Abbreviations: ECG, electrocardiography; FD, Fabry disease; ICD, implantable cardioverter-defibrillator.

Figure 1 The IFDCR participating centres.

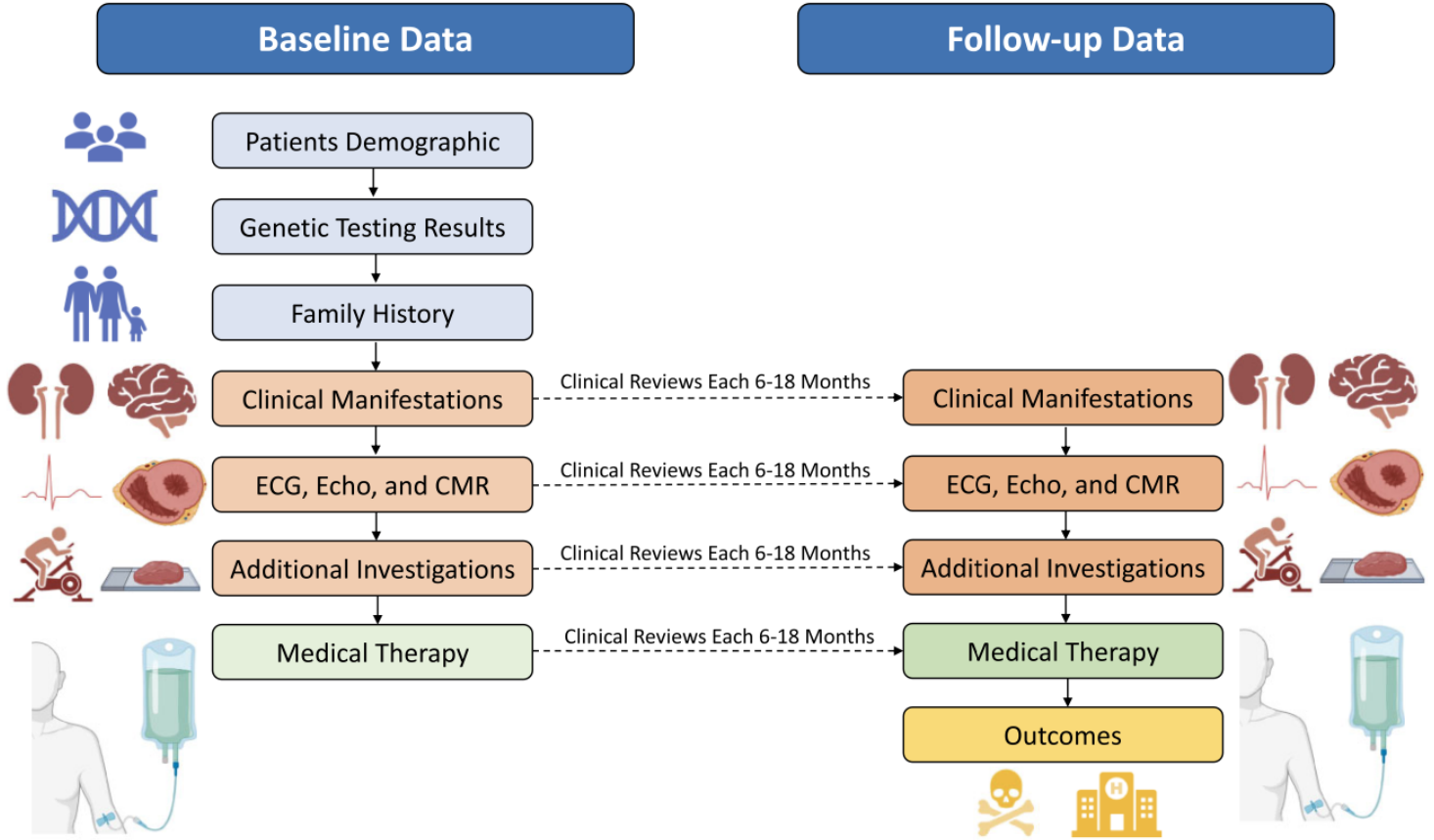


Figure 2 Baseline and follow-up data collection.

ESC European Society of Cardiology
European Heart Journal - Quality of Care and Clinical Outcomes (2024) **0**, 1–5
https://doi.org/10.1093/ehjqcco/qcae052
COHORT PROFILE

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The recruitment period consists of two parts. The prospective patient enrolment period in the study spans from January 2024 to December 2031. Additionally, retrospective data from January 1981 to December 2023 have been collected in 35 of the 50 centres included, corresponding to 753 patients (63% females [$n = 476$]), and will be collected in the remaining 15 centres. Participating centres will be requested to consecutively enrol all eligible FD patients and plan a systematic periodic follow-up.


Thank you for
your attention