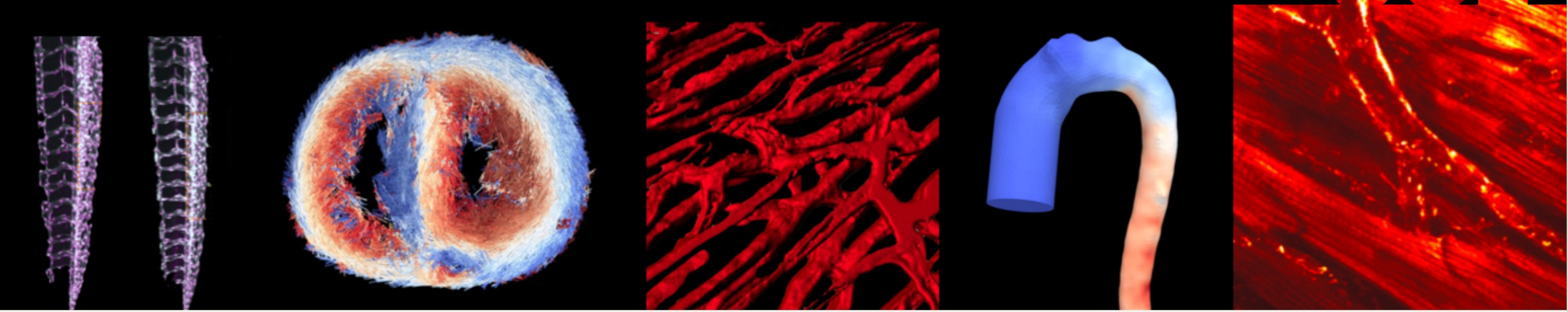
UCL INSTITUTE OF CARDIOVASCULAR SCIENCE



Personalised Medicine in Cardiovascular Disease

Cardiomyopathy UK
the heart muscle charity

Barts Health NHS
NHS Trust

Queen Mary
University of London

British Heart Foundation

NHS
National Institute for Health Research

wellcome

ACT
Funding cardiac research to save young lives

Declaration of interest

Consultancies/Ad Board:

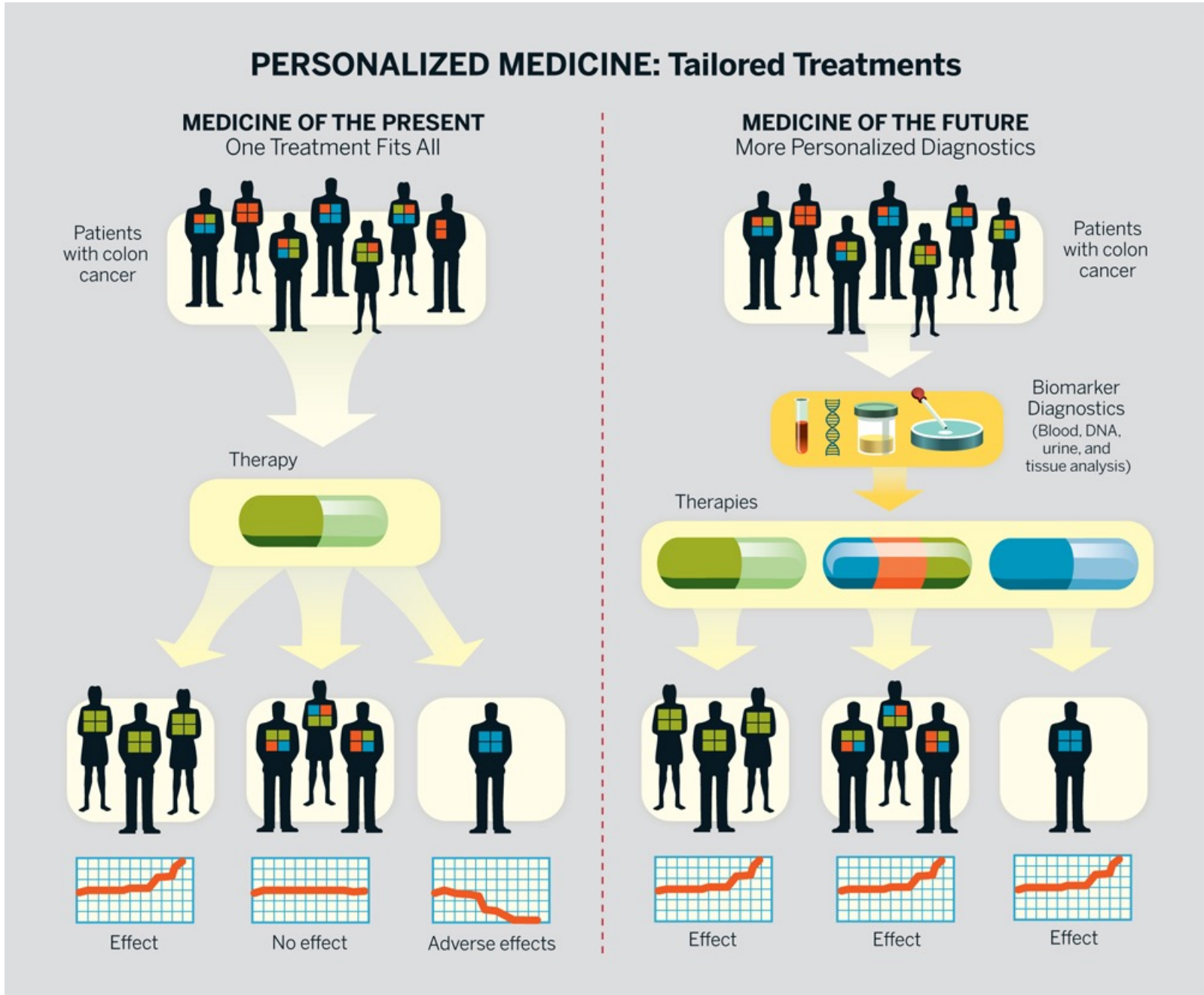
- MyoKardia (BMS)
- Pfizer
- Sanofi-Genzyme
- DinaQor
- Astra Zeneca
- Sarepta
- Freeline
- Biomarin
- Cardior
- Novo Nordisk

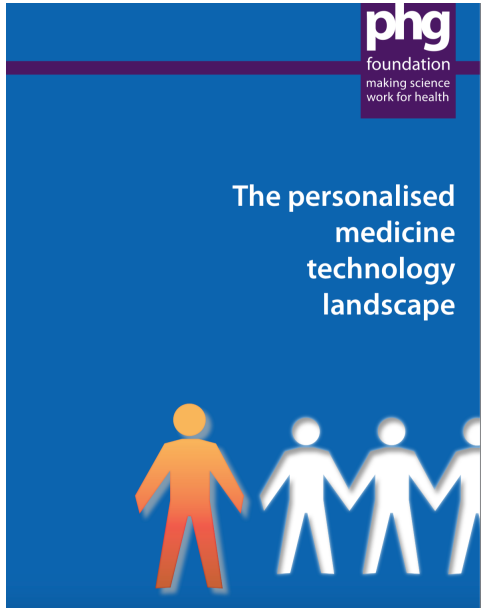

BRACE YOURSELVES
PERSONALIZED MEDICINE
IS COMING
quickmeme.com

What is personalised medicine?

"Stratified medicine is based on identifying subgroups of patients with distinct mechanisms of disease, or particular responses to treatments. This allows us to identify and develop treatments that are effective for particular groups of patients. Ultimately stratified medicine will ensure that the right patient gets the right treatment at the right time."

http://www.mrc.ac.uk/research/initiatives/stratified-medicine/


PERSONALIZED MEDICINE: Tailored Treatments
MEDICINE OF THE PRESENT
One Treatment Fits All
Patients with colon cancer
Therapy
Effect
No effect
Adverse effects
MEDICINE OF THE FUTURE
More Personalized Diagnostics
Patients with colon cancer
Biomarker Diagnostics
(Blood, DNA, urine, and tissue analysis)
Therapies
Effect
Effect
Effect

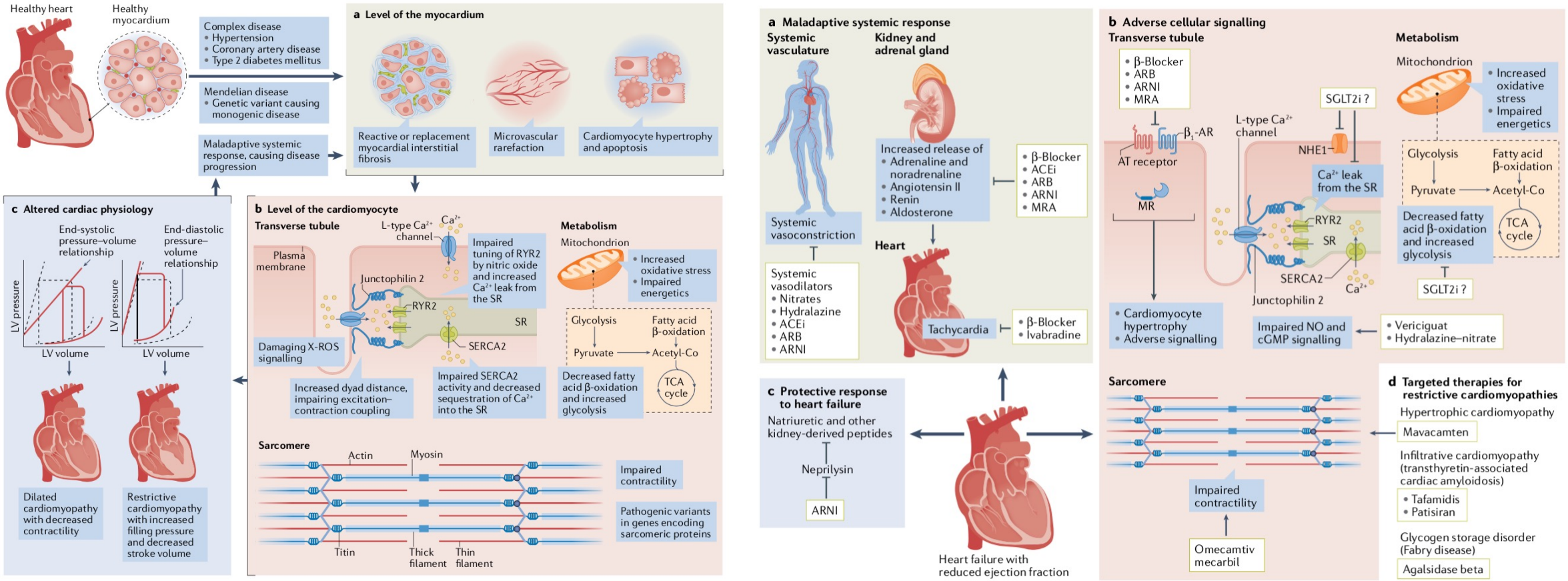


Microbiome analysis	Epigenomics	3D imaging and printing	Consumer m-health apps	Wearables and sensors
Metabolomics	Proteomics	Genome editing /therapy	Implantable biosensors	Point of care testing devices
ctDNA	Single cell 'omics	Stem cell therapy	EPR dependent technologies	Microfluidics
Pathogen Genomics	Transcriptomics	Robotics	Internet of things	Synthetic biology
Genomics	Pharmaco-genomics	Virtual and augmented reality	Machine learning	Nanomedicine

- Technologies for greater molecular level characterisation
- Technologies for personalised therapeutic interventions
- Technologies for personalised disease and health monitoring
- Underpinning and enabling technologies

Towards precision medicine in heart failure

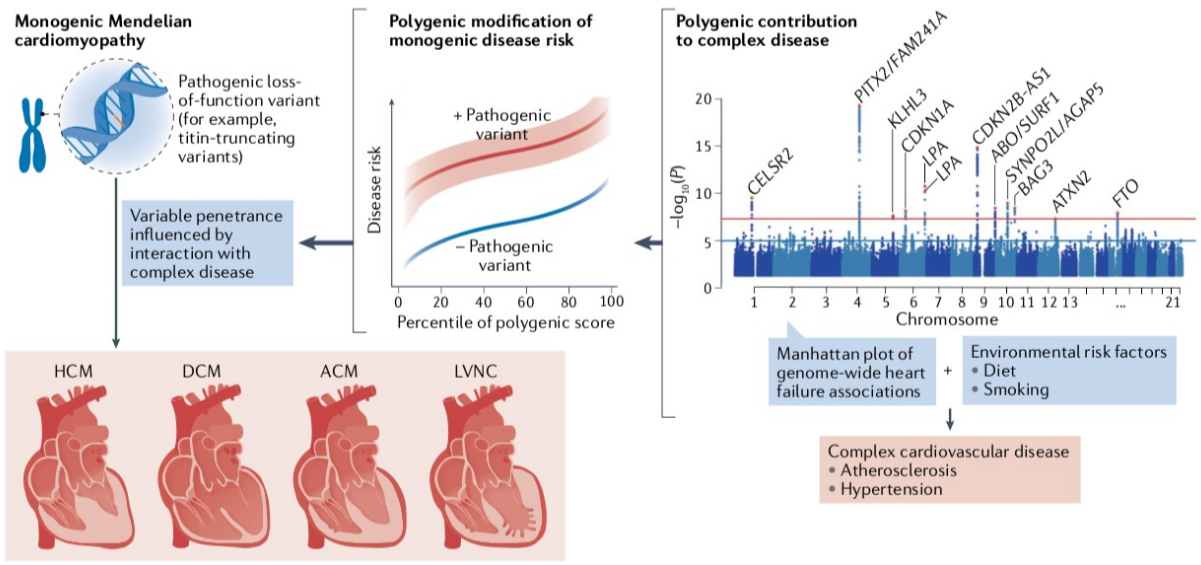
Chad S. Weldy [1,2] *and Euan A. Ashley* [1,2] ✉



Weldy CS, Ashley EA. Towards precision medicine in heart failure. Nat Rev Cardiol. 2021 Nov;18(11):745-762.

Towards precision medicine in heart failure

Chad S. Weldy[1,2] *and Euan A. Ashley*[1,2]✉



a Genetics

Heart failure and myocardial structure GWAS

Upstream contributors to coronary artery disease or atrial fibrillation
- *PITX2–FAM241A*
- *CDKN2B–AS1*
- *LPA*

Sarcomeric genes
- *TTN*
- *TTNT2*
- *ACTN2*

Developmental genes
- *TBX3*
- *HAND1*
- *GOSR1*
- *MTSS1*

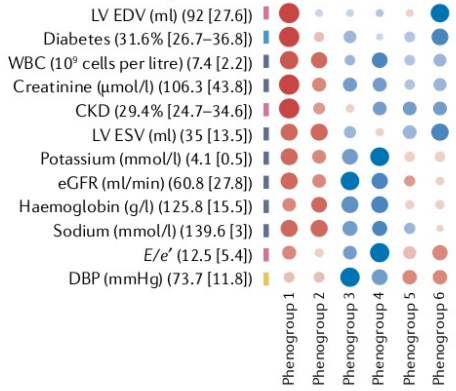
Cell signalling and survival genes
- *PLN*
- *BAG3*
- *CDKN1A*
- *KLHL3*

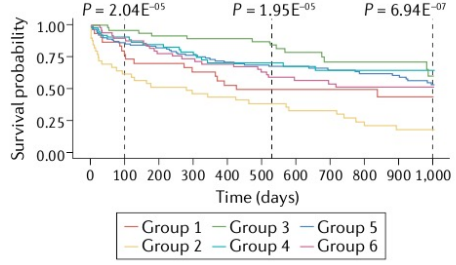
b Pharmacogenomics
- Angiotensin receptors
- β-Adrenergic receptors
- G-protein-coupled receptor kinases
- Orexin

c Proteomics
- Inflammation
- Matrix remodelling
- Coagulation system
- Oxidative stress
- Angiogenesis

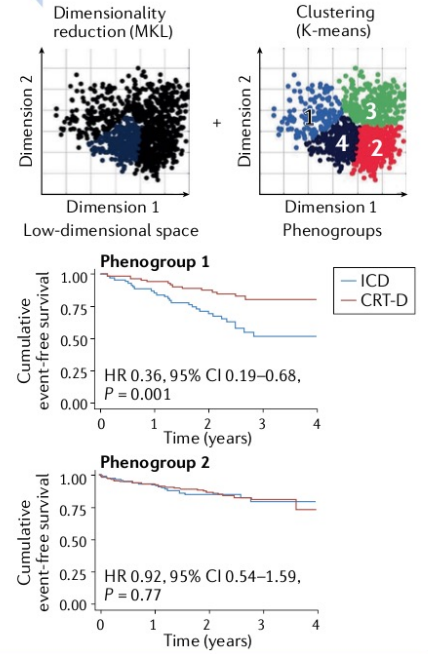
d Machine learning

Electronic health record data and proteomic data





Expanded machine learning to guide precision treatment for heart failure
- Polygenic risk
- Pharmacogenomic background
- Proteomic signature
- Electronic health record data



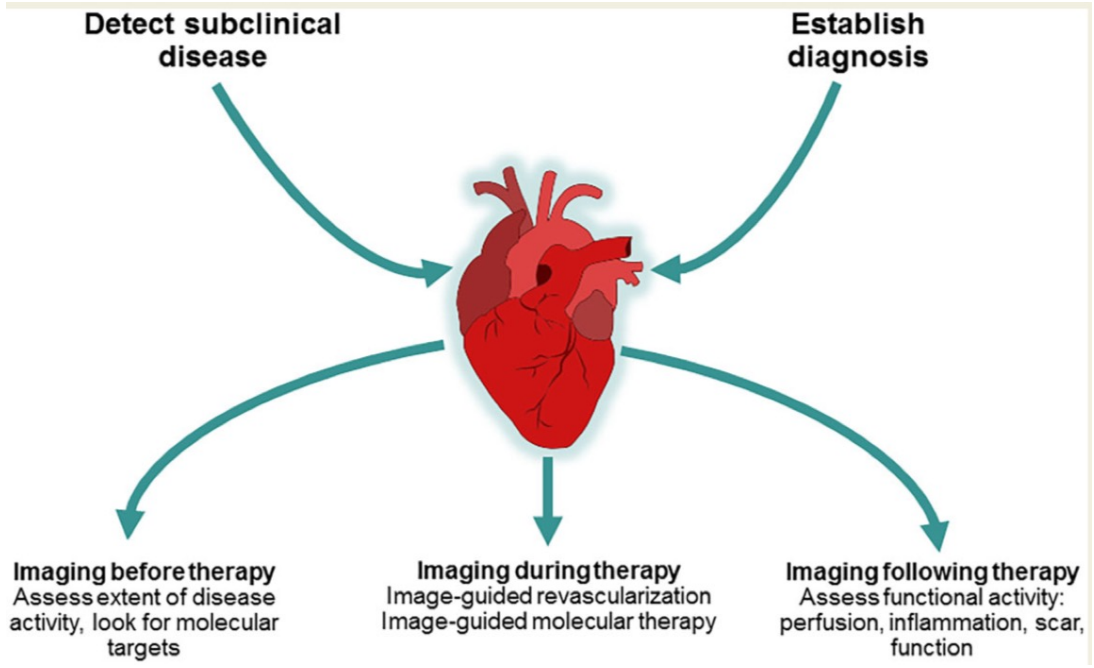
Differential response to cardiac resynchronization therapy determined by machine learning-based phenomapping

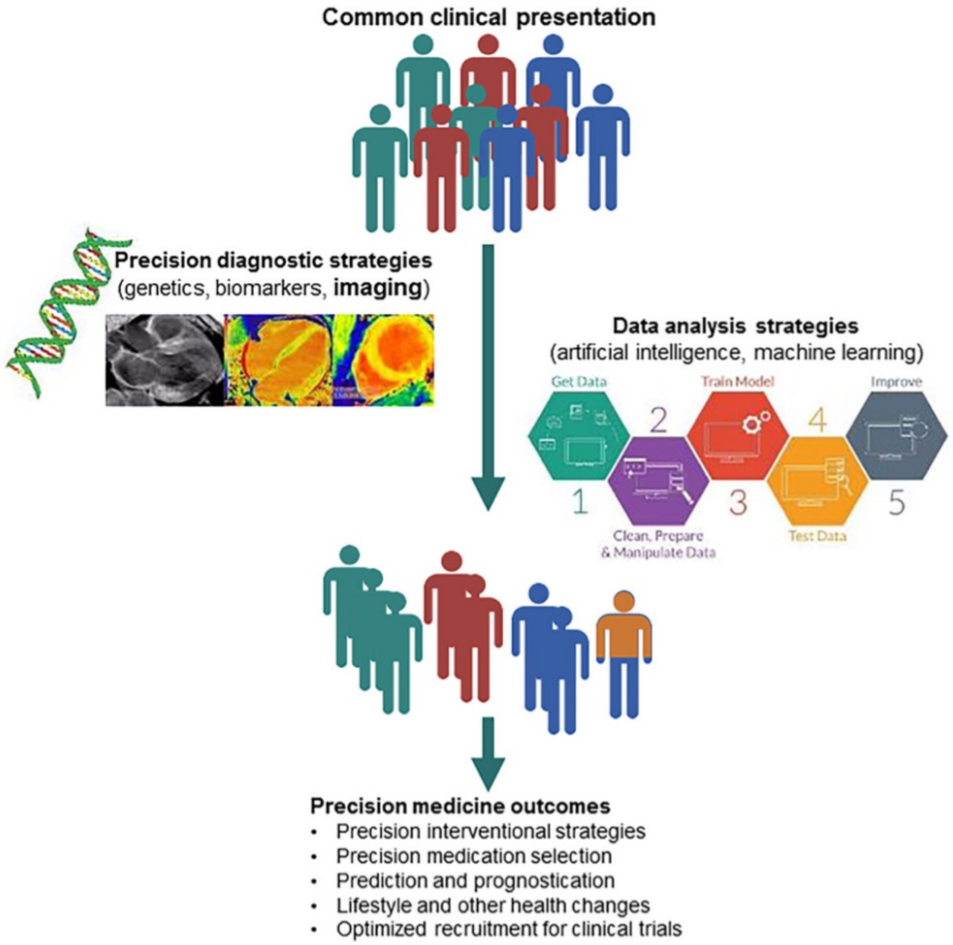
Precision medicine targeted to individual patients by selecting therapies and interventions based on causal biology

Weldy CS, Ashley EA. Towards precision medicine in heart failure. Nat Rev Cardiol. 2021 Nov;18(11):745-762.

Non-invasive imaging as the cornerstone of cardiovascular precision medicine

Stephan Achenbach [1]*, Friedrich Fuchs[2], Alexandra Goncalves[3,4], Claudia Kaiser-Albers[5], Ziad A. Ali[6], Frank M. Bengel[7], Stefanie Dimmeler [8], Zahi A. Fayad [9], Alexandre Mebazaa[10], Benjamin Meder[11], Jagat Narula[12], Amil Shah[13], Sanjay Sharma [14], Jens-Uwe Voigt[15], and Sven Plein [16]





European Heart Journal - Cardiovascular Imaging (2022) 23, 465–475

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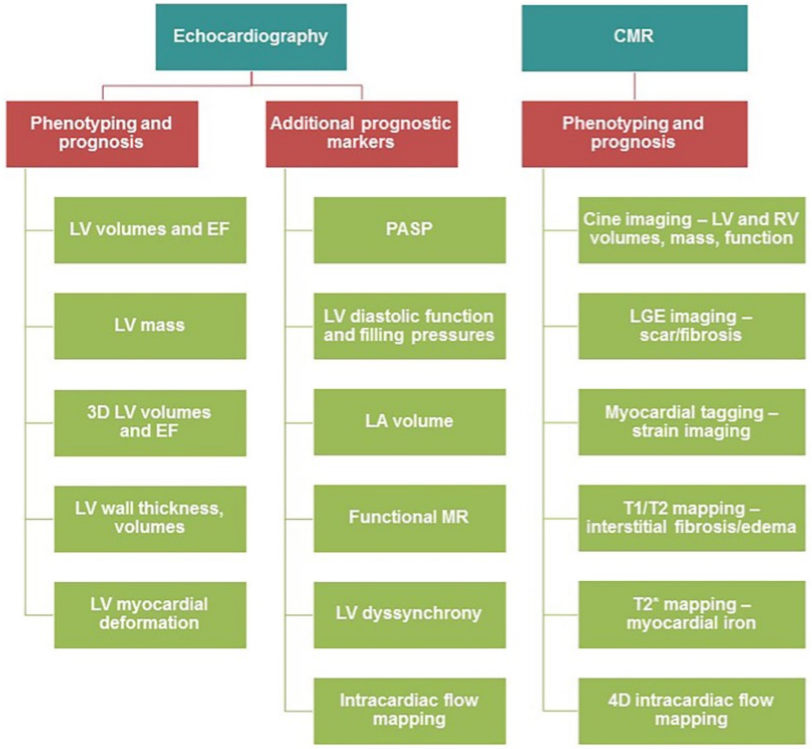
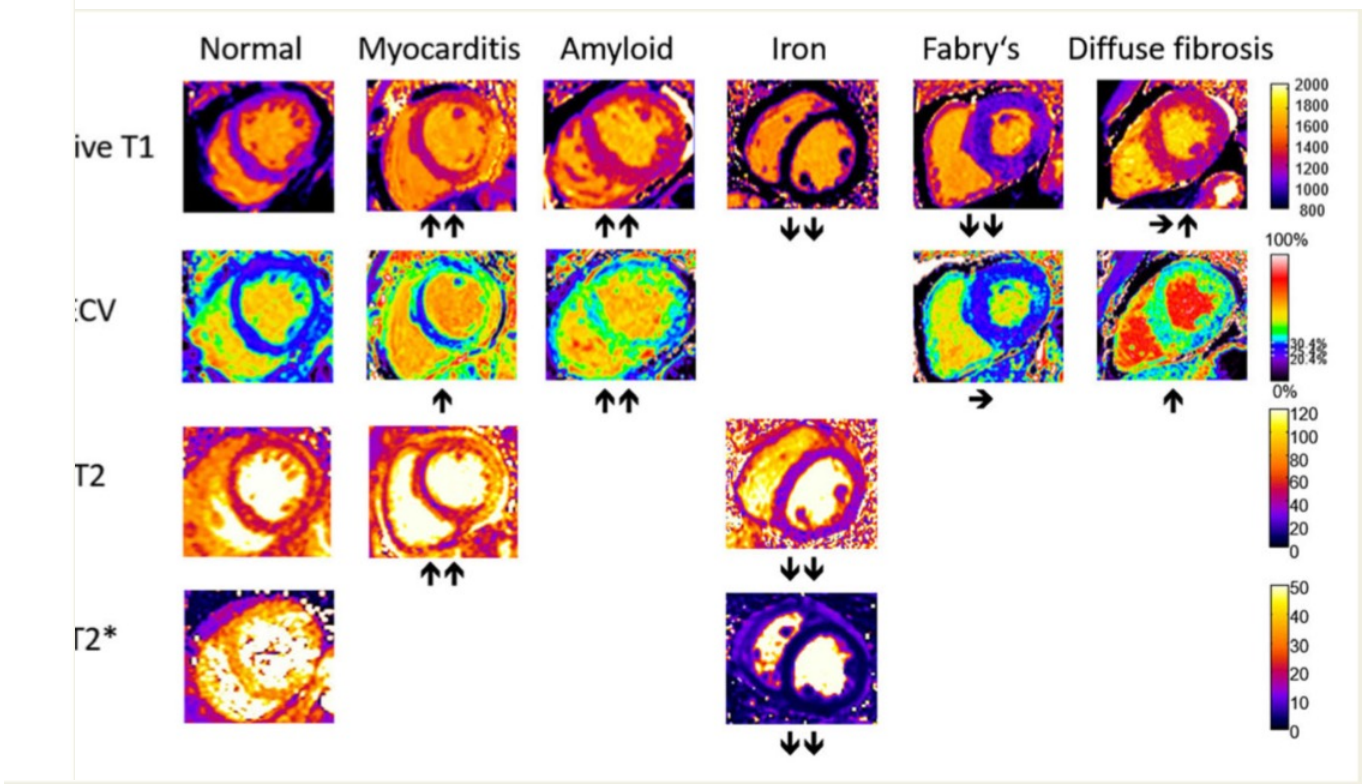
Stephan Achenbach [1]*, Friedrich Fuchs[2], Alexandra Goncalves[3,4], Claudia Kaiser-Albers[5], Ziad A. Ali[6], Frank M. Bengel[7], Stefanie Dimmeler [8], Zahi A. Fayad [9], Alexandre Mebazaa[10], Benjamin Meder[11], Jagat Narula[12], Amil Shah[13], Sanjay Sharma [14], Jens-Uwe Voigt[15], and Sven Plein [16]





European Heart Journal - Cardiovascular Imaging (2022) 23, 465–475

EDITORIAL

nature medicine

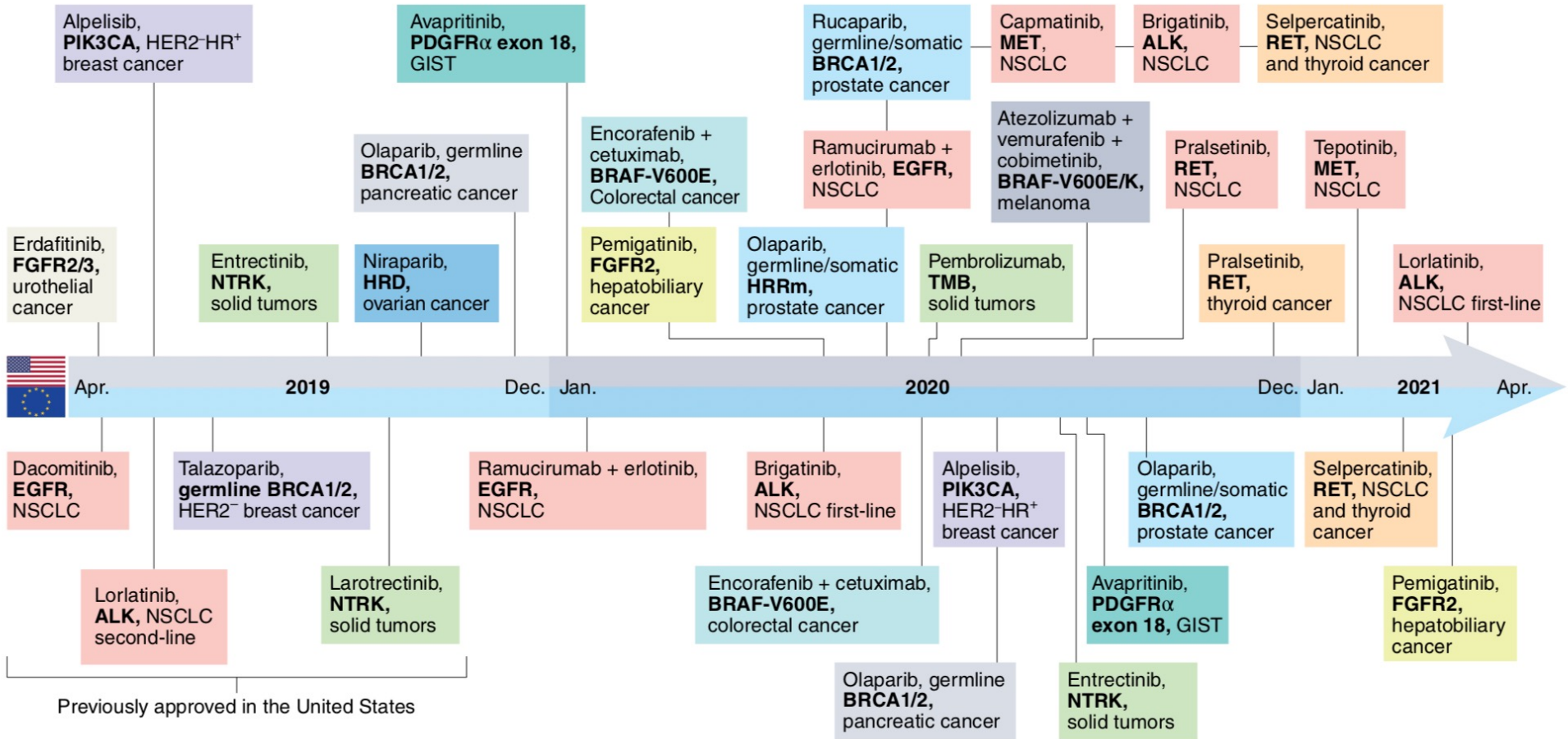
Taking personalized medicine to heart

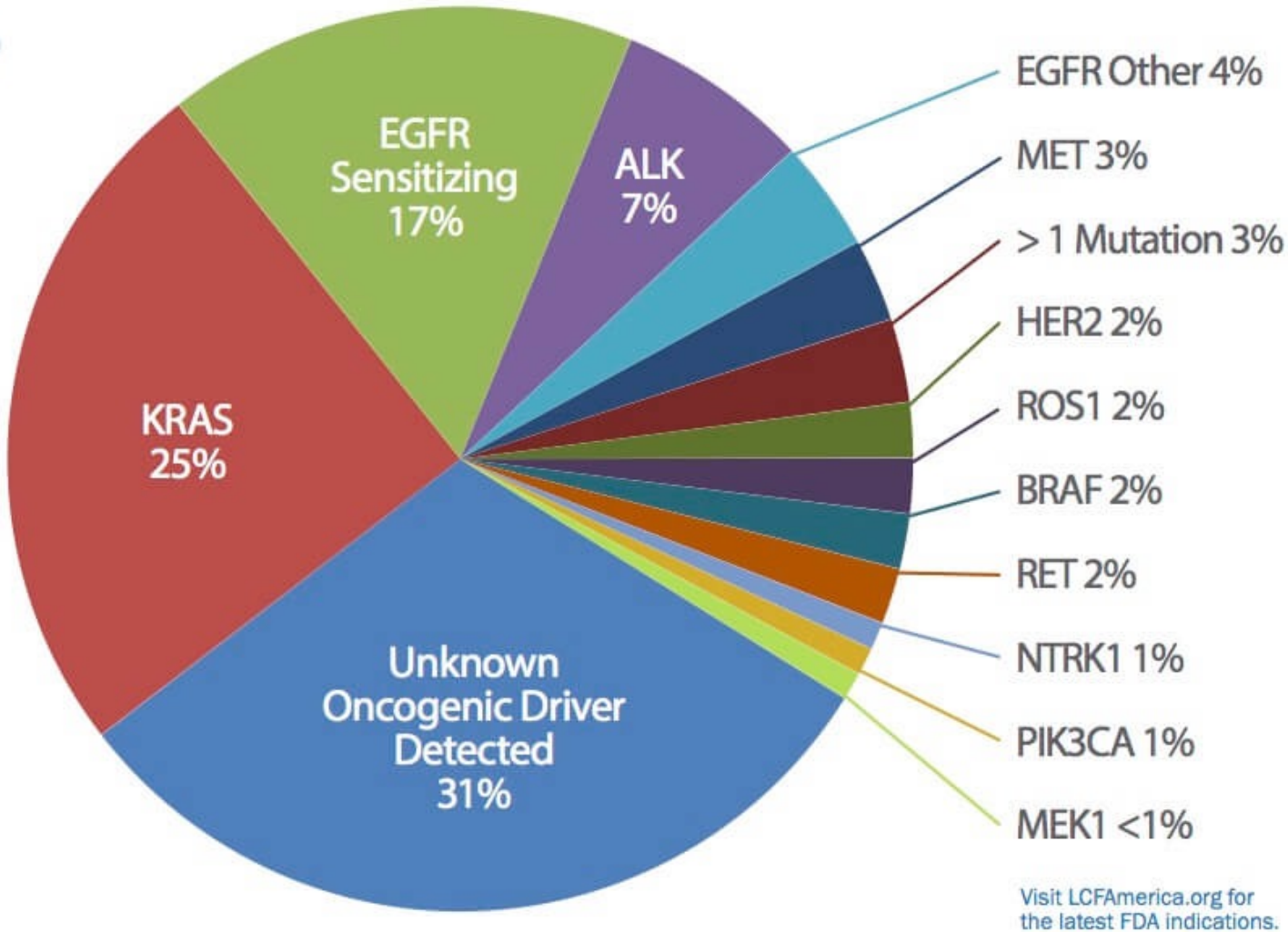
Tailoring treatment to the individual patient has revolutionized cancer therapy, but personalized medicine has yet to make much headway in the treatment of cardiovascular disease. With emerging insight into disease mechanisms and new treatment options, the time is now ripe for the cardiovascular field to adopt a more personalized approach to therapy.

NATURE MEDICINE VOLUME 24 | NUMBER 2 | FEBRUARY 2018

Delivering precision oncology to patients with cancer

Joaquin Mateo[1,18], Lotte Steuten[2,3,18], Philippe Aftimos[4], Fabrice André[5], Mark Davies[6], Elena Garralda[1], Jan Geissler[7], Don Husereau[8], Iciar Martinez-Lopez[9], Nicola Normanno[10], Jorge S. Reis-Filho[11], Stephen Stefani[12], David M. Thomas[13], C. Benedikt Westphalen[14,15,19] and Emile Voest[16,17,19] ✉





Visit LCFAmerica.org for the latest FDA indications.

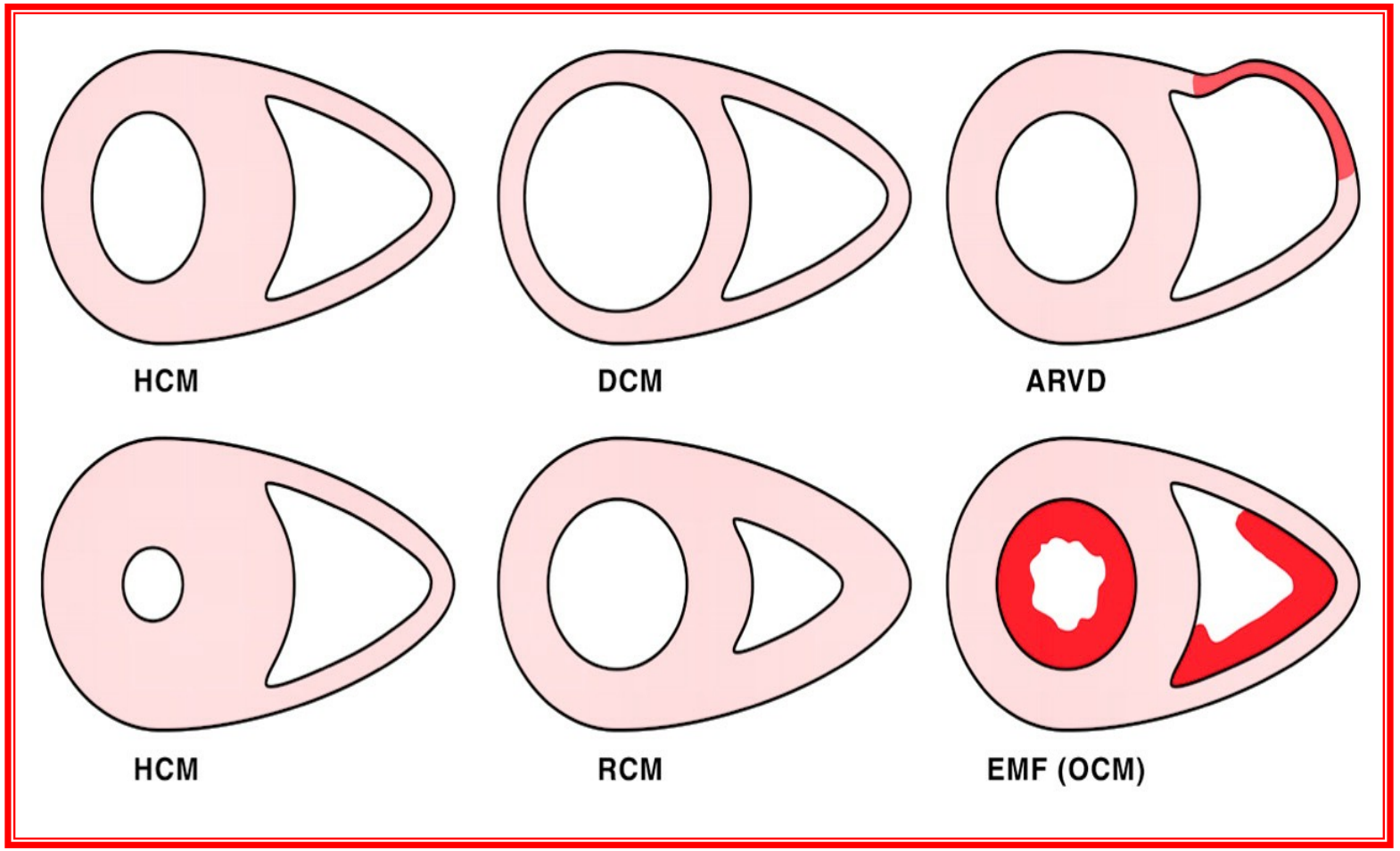
Cardiomyopathies?

Cardiomyopathy: Definition

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

ESC Working Group on Myocardial Pericardial Diseases (Elliott P et al. EHJ 2007)

Classification of Cardiomyopathies



Davies M. Heart 2000;83:469-474

Contemporary and Future Approaches to Precision Medicine in Inherited Cardiomyopathies

JACC Focus Seminar 3/5

Diane Fatkin, MD,[a,b,c] Hugh Calkins, MD,[d] Perry Elliott, MBBS, MD,[e,f] Cynthia A. James, PhD, CGC,[d] Stacey Peters, MBBS,[g,h] Jason C. Kovacic, MBBS, PhD[a,b,c,i]

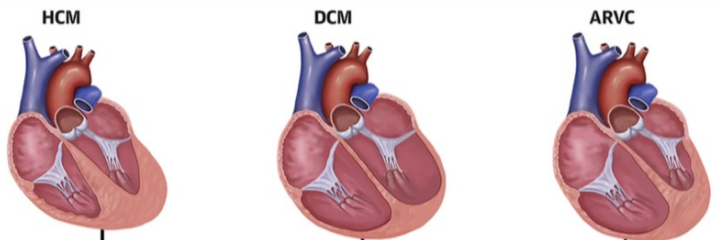
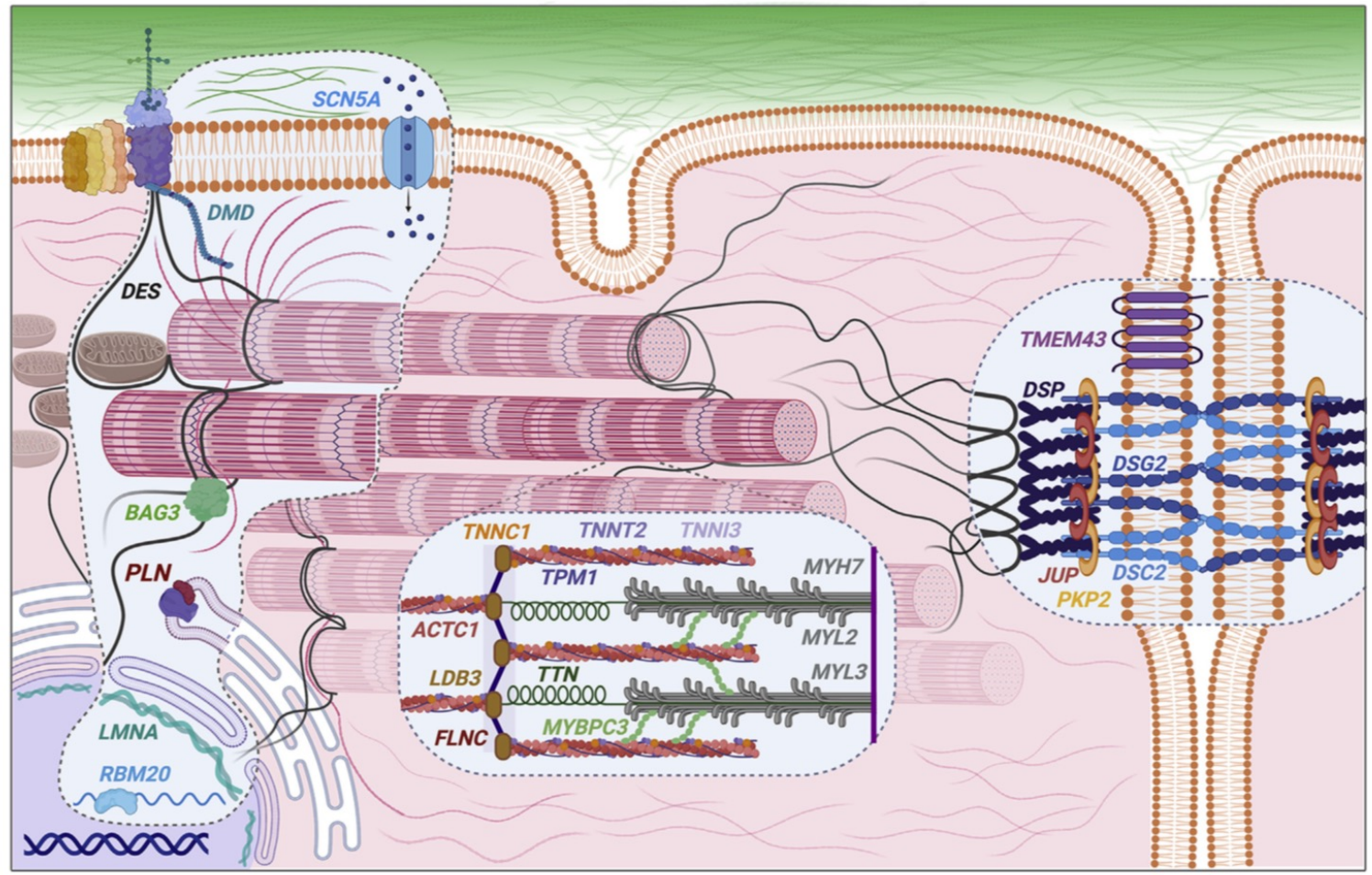


FIGURE 1 Location of Cardiomyopathy Disease Genes



J Am Coll Cardiol 2021;77:2551–72

Minor hypertrophic cardiomyopathy genes, major insights into the genetics of cardiomyopathies

Roddy Walsh[1]✉, Joost A. Offerhaus[1], Rafik Tadros[2] and Connie R. Bezzina[1]

a

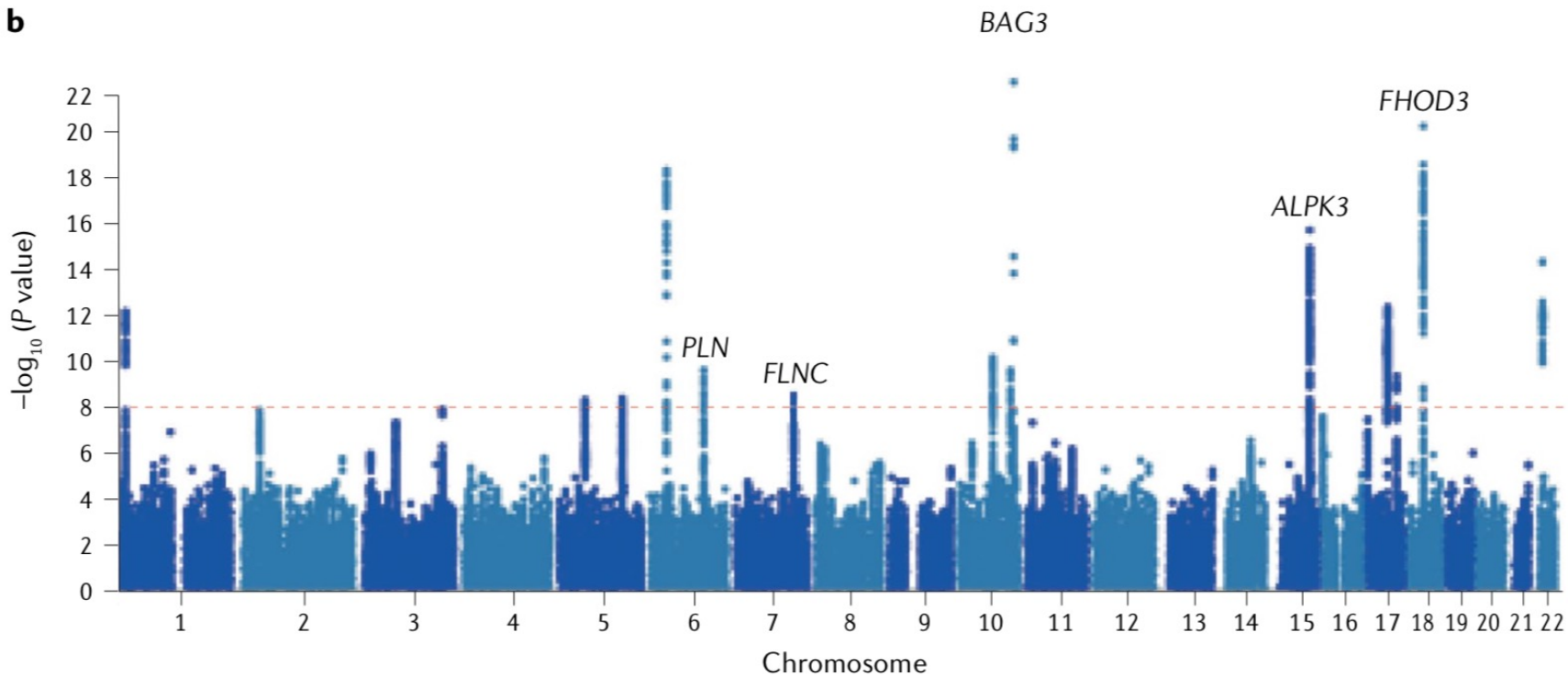
HCM
Case–control GWAS

Study	Cases	Controls
Tadros et al.	1,733	5,521
Harper et al.	2,780	47,486

UK Biobank
LV traits on up to 36,041 individuals

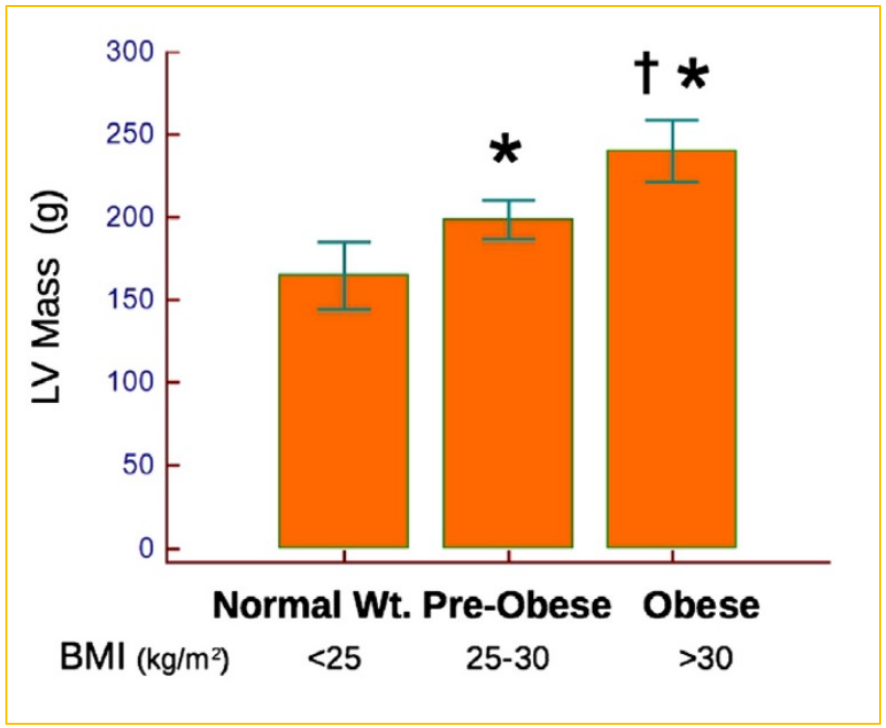
	EDV	ESV	EF	WT	Mass	Conc	Strain
HCM	NS	–	+	+	+	+	+
DCM	+	+	–	NS	NS	–	–

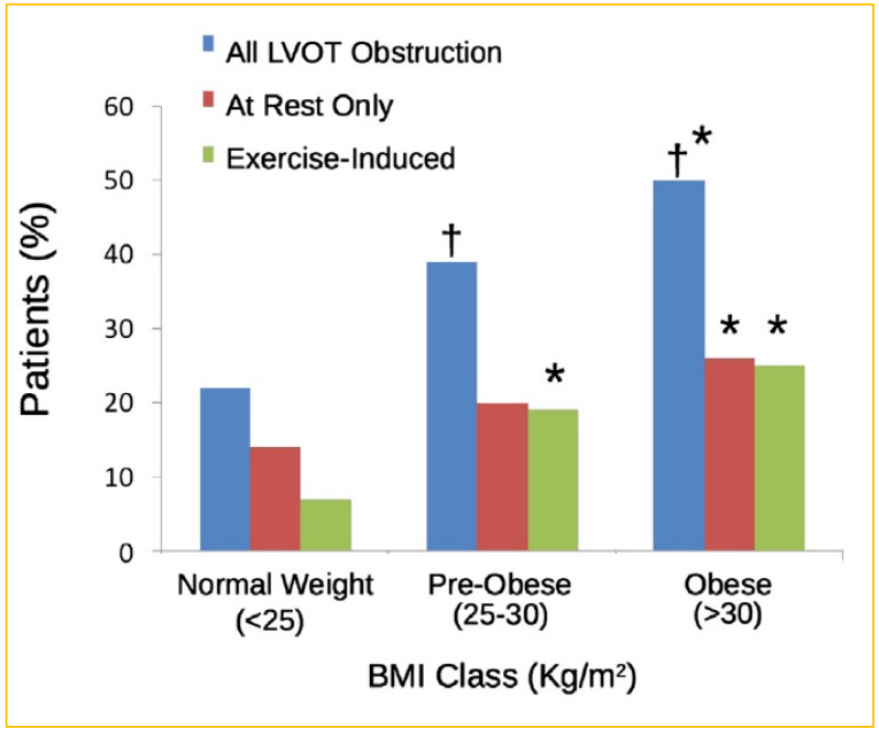
b



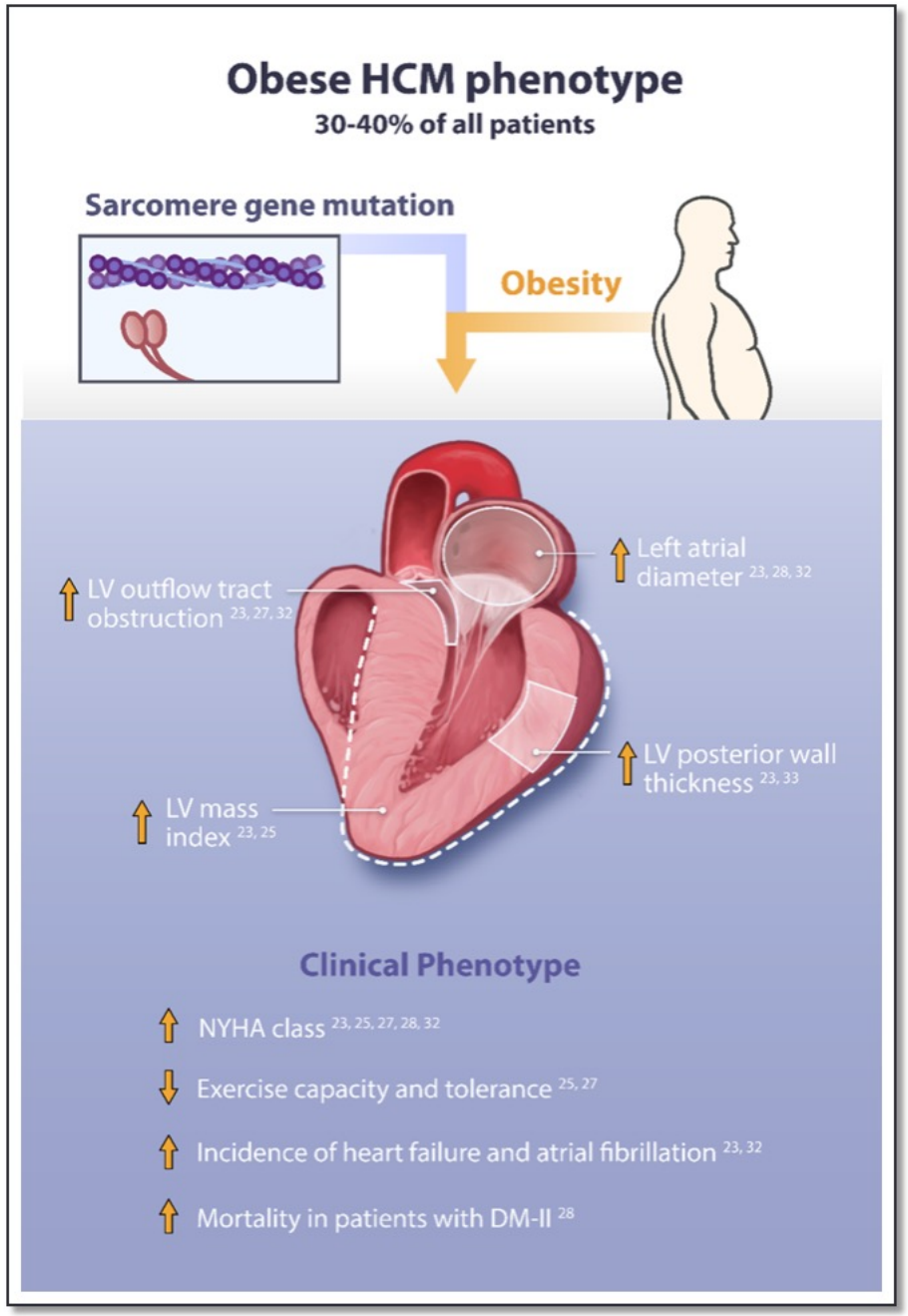
Obesity and its Association to Phenotype and Clinical Course in Hypertrophic Cardiomyopathy

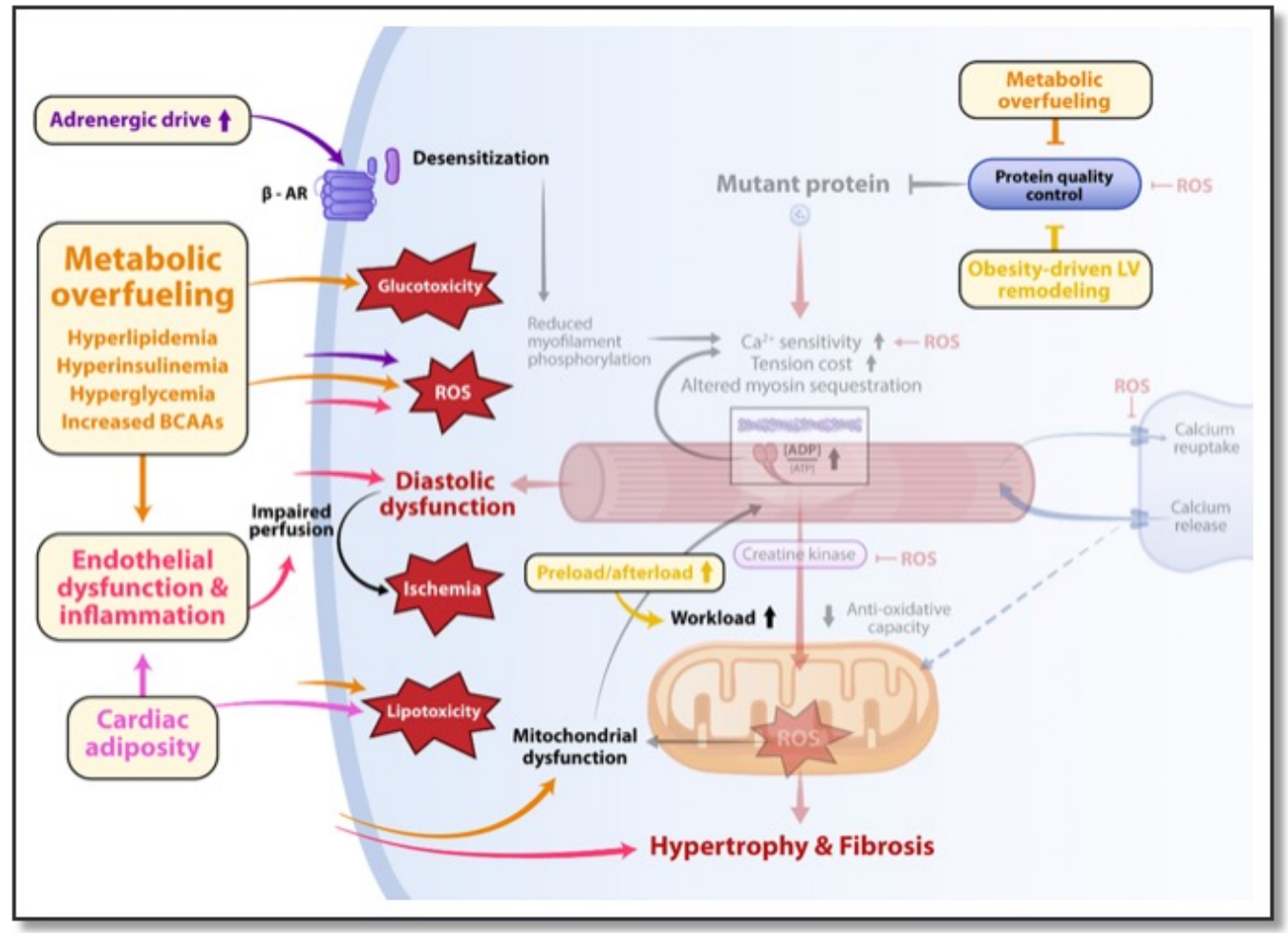
Iacopo Olivotto, MD,* Barry J. Maron, MD,† Benedetta Tomberli, MD,* Evan Appelbaum, MD,‡§ Carol Salton, AB,‡§ Tammy S. Haas, RN,† C. Michael Gibson, MD,‡§ Stefano Nistri, MD,* Eleonora Servettini, MD,* Raymond H. Chan, MD,§ James E. Udelson, MD,‖ John R. Lesser, MD,† Franco Cecchi, MD,* Warren J. Manning, MD,‡§ Martin S. Maron, MD‖





J Am Coll Cardiol 2013;62:449–57)





J Am Heart Assoc. 2020;9:e018641.

Contemporary and Future Approaches to Precision Medicine in Inherited Cardiomyopathies

JACC Focus Seminar 3/5

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FIGURE 5 Factors That Contribute to Cardiomyopathy Phenotypes

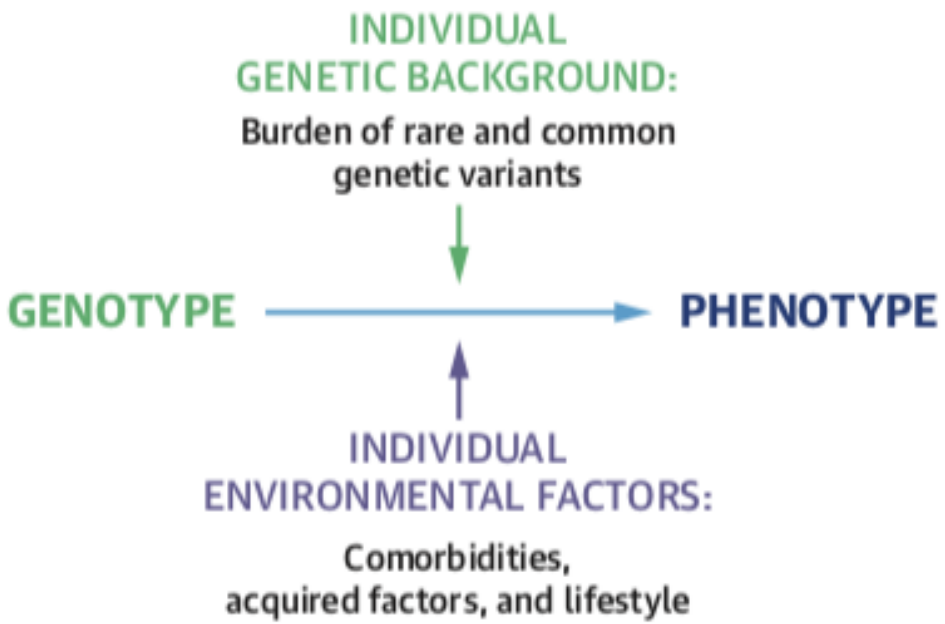
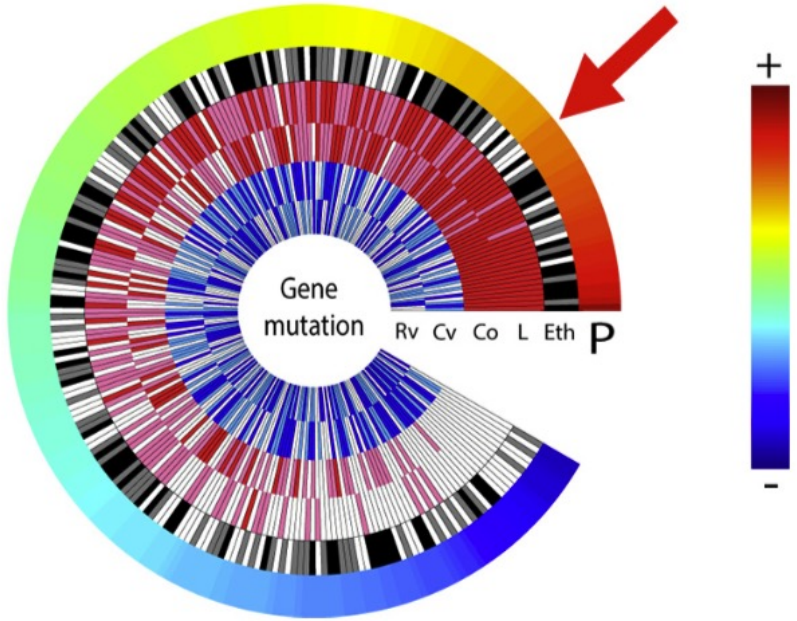
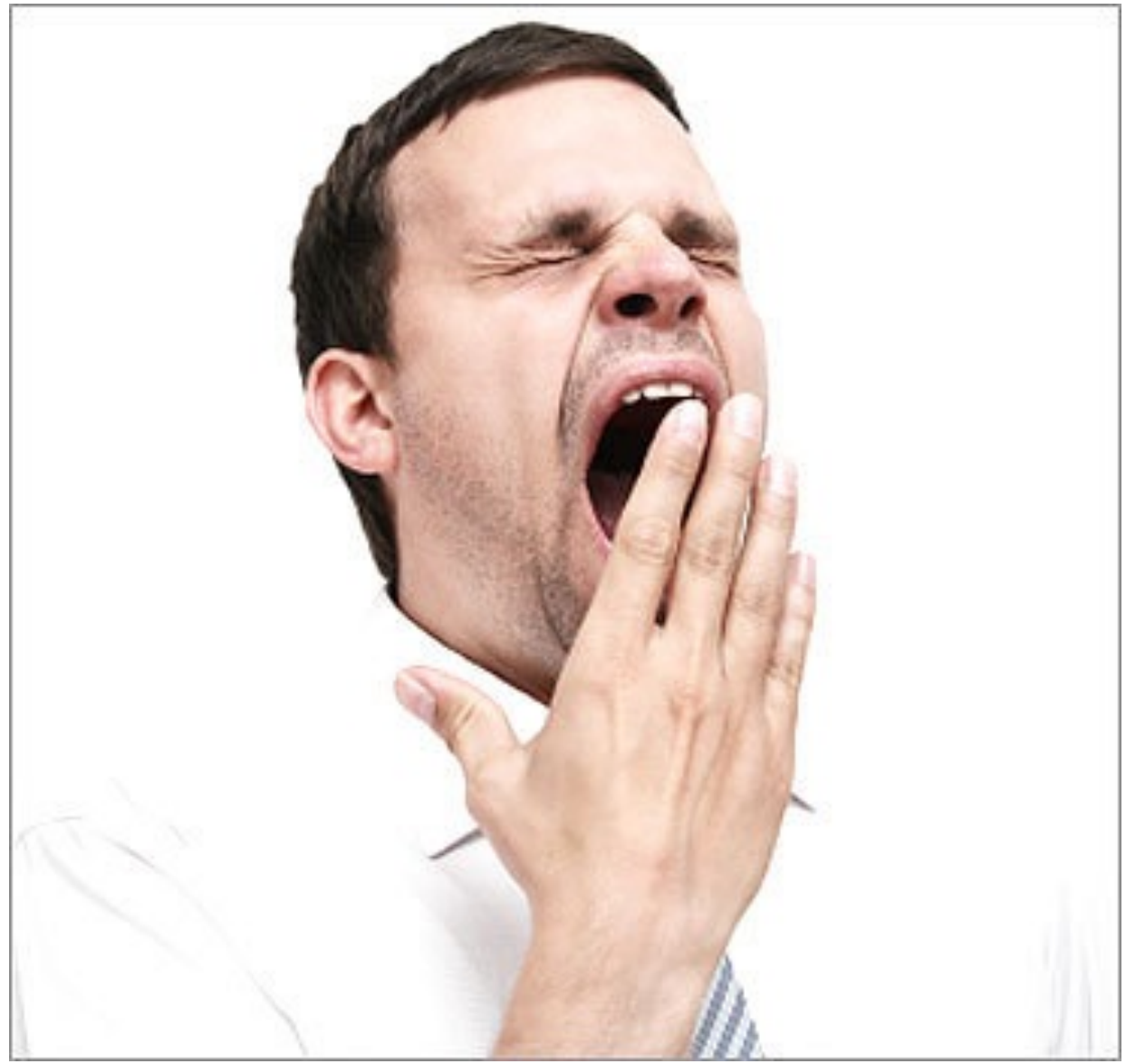


FIGURE 6 Myocardial Phenotype "Wheel of Fortune"

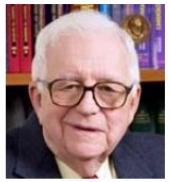


Cardiomyopathy phenotypes (P) such as left ventricular ejection fraction or wall thickness are continuous variables **(outer colored circle)**. Inner circles represent variable effects **(gradations of color)** of background rare variants (Rv), common variants (Cv), comorbidities (Co), lifestyle factors (L), and ethnicity (Eth). For any given value of P **(arrow)**, the relative contributions of a primary gene mutation and modifying factors will differ in individual patients.

J Am Coll Cardiol 2021;77:2551–72



What has all this to do with me?



Eugene Braunwald MD

Professor, Harvard Medical School and Chairman, TIMI Study Group

1. Electrocardiography
2. Cardiac catheterisation
3. Cardiovascular surgery
4. Coronary angiography
5. Invasive cardiology
6. The Coronary Care Unit
7. Cardiovascular Drugs
8. Preventative Cardiology
9. Echocardiography
10. Pacemakers & ICDs

European Society of Cardiology: cardiovascular disease statistics 2021

European Heart Journal (2022) 43, 716–799

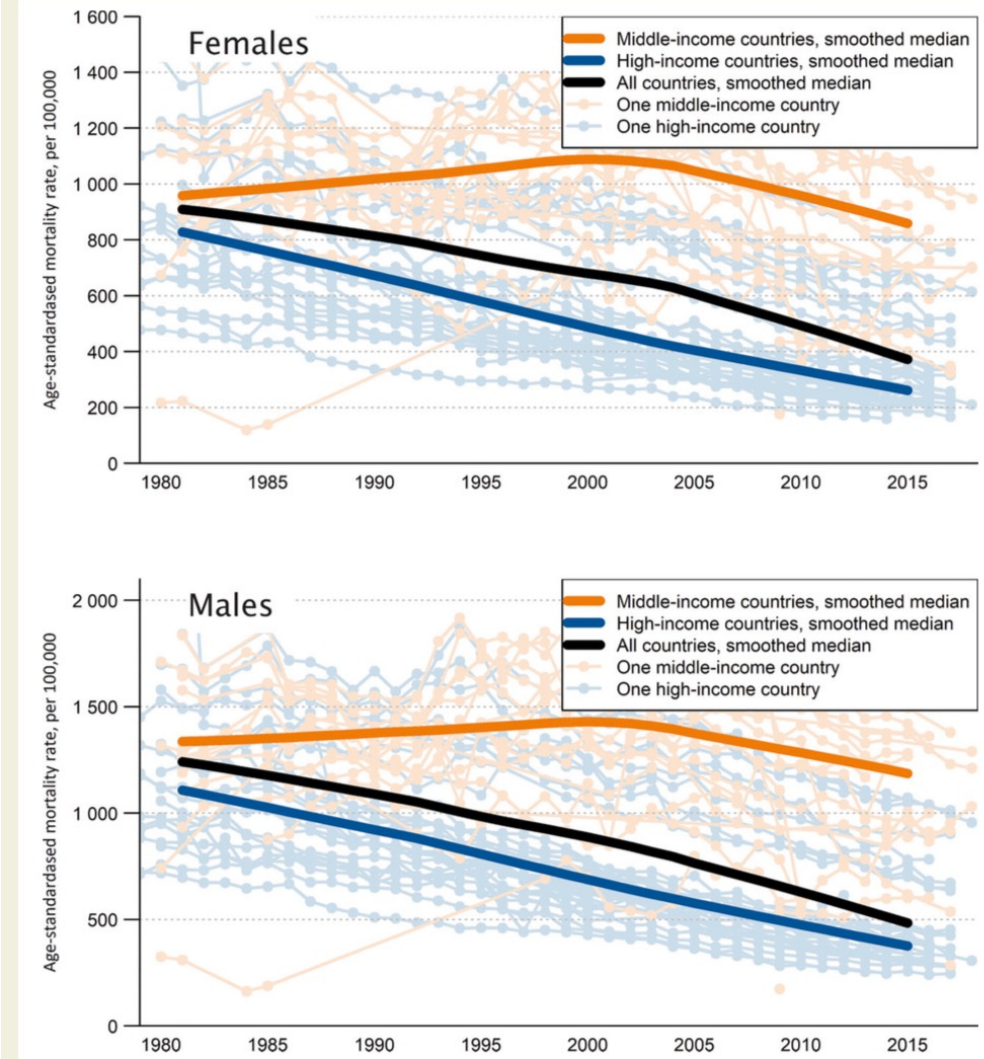


Figure 49 Time series: age-standardized mortality rate from cardiovascular disease per 100 000 people in females and males in European Society of Cardiology member countries (1980–2017).

European Heart Journal (2016) 37, 2129–2200
doi:10.1093/eurheartj/ehw128

2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure

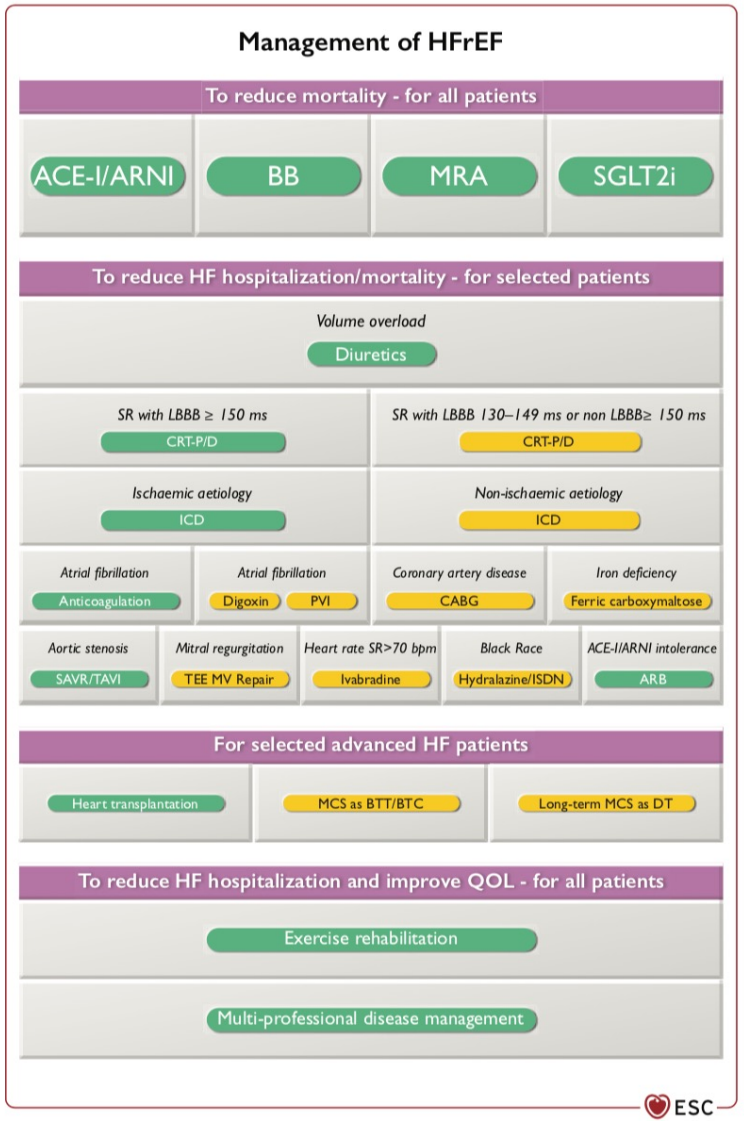
The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC)

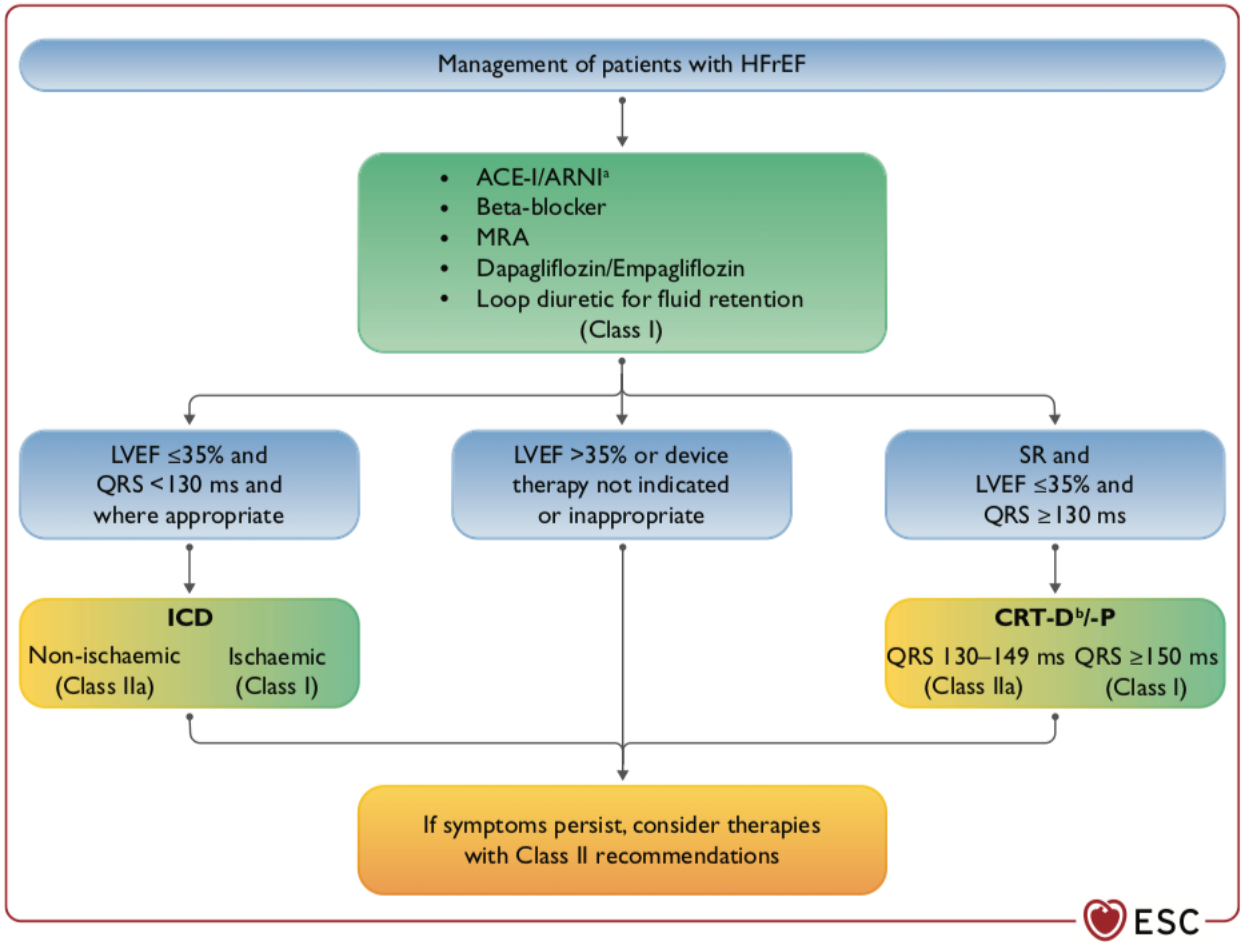
Developed with the special contribution of the Heart Failure Association (HFA) of the ESC

"The main terminology used to describe HF is historical and is based on measurement of the LVEF"

Type of HF		HFrEF	HFmrEF	HFpEF
CRITERIA	1	Symptoms ± Signs[a]	Symptoms ± Signs[a]	Symptoms ± Signs[a]
	2	LVEF <40%	LVEF 40–49%	LVEF ≥50%
	3	–	1. Elevated levels of natriuretic peptides[b]; 2. At least one additional criterion: a. relevant structural heart disease (LVH and/or LAE), b. diastolic dysfunction (for details see Section 4.3.2).	1. Elevated levels of natriuretic peptides[b]; 2. At least one additional criterion: a. relevant structural heart disease (LVH and/or LAE), b. diastolic dysfunction (for details see Section 4.3.2).

2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure

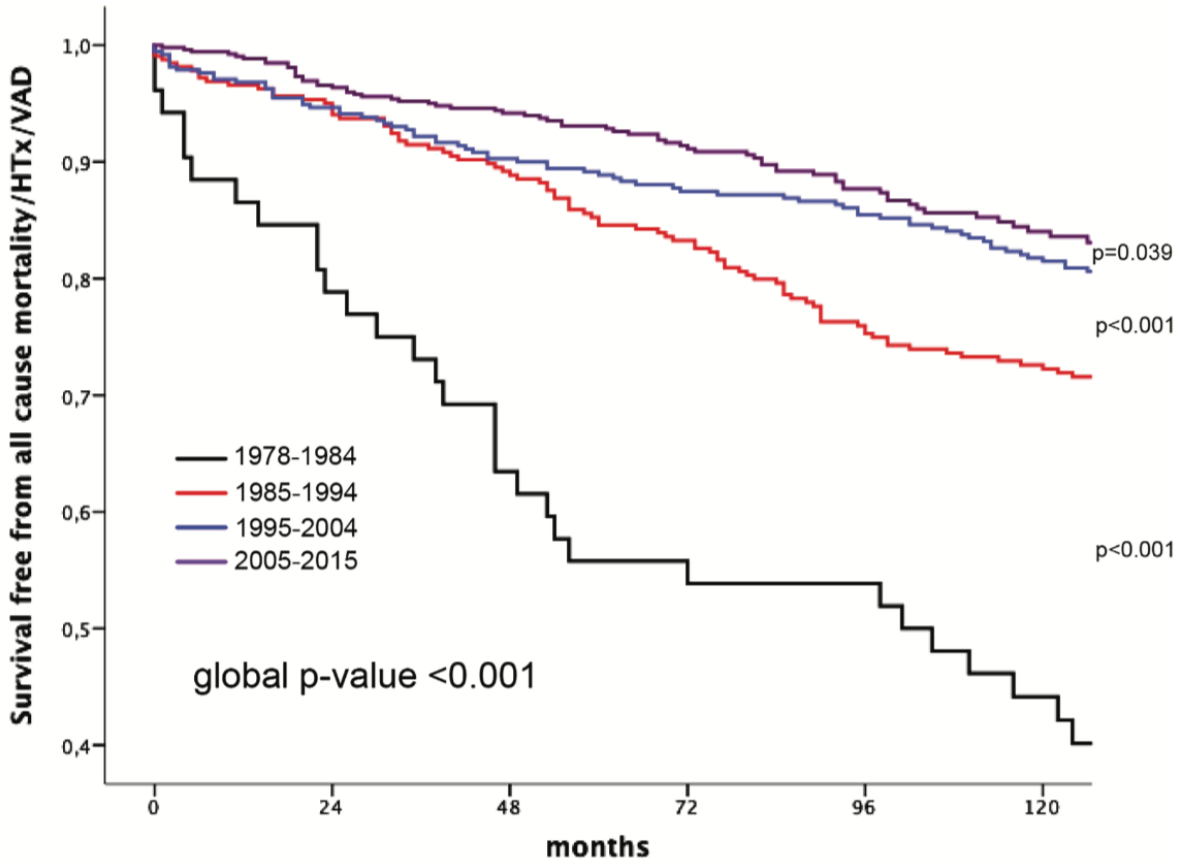




European Heart Journal (2021) 42, 3599-3726

Contemporary survival trends and aetiological characterization in non-ischaemic dilated cardiomyopathy

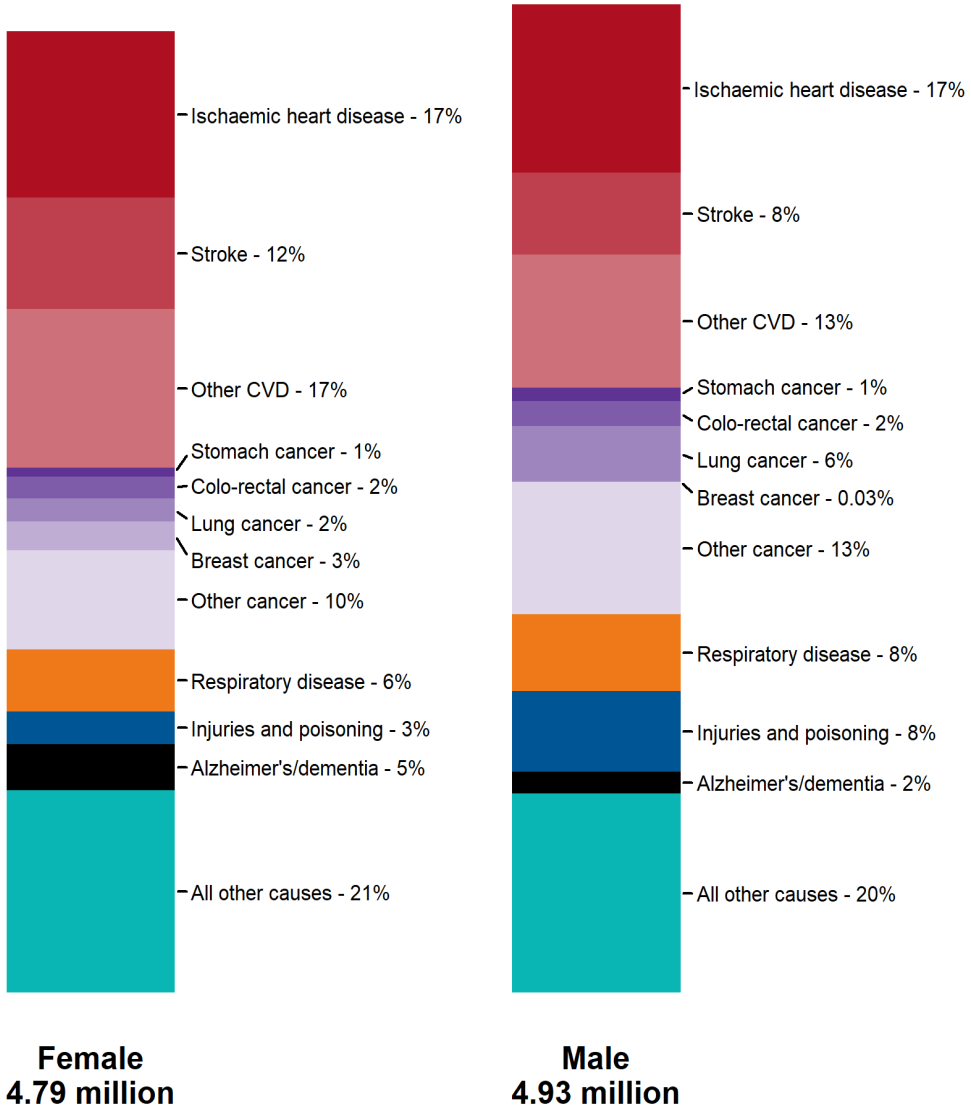
Marco Merlo[1*†], Antonio Cannatà[1,2†], Carola Pio Loco[1], Davide Stolfo[1], Giulia Barbati[3], Jessica Artico[1], Piero Gentile[1], Valerio De Paris[1], Federica Ramani[1], Massimo Zecchin[1], Marta Gigli[1], Bruno Pinamonti[1], Renata Korcova[1], Andrea Di Lenarda[4], Mauro Giacca[2], Luisa Mestroni[5], Paolo G. Camici[6], and Gianfranco Sinagra[1]



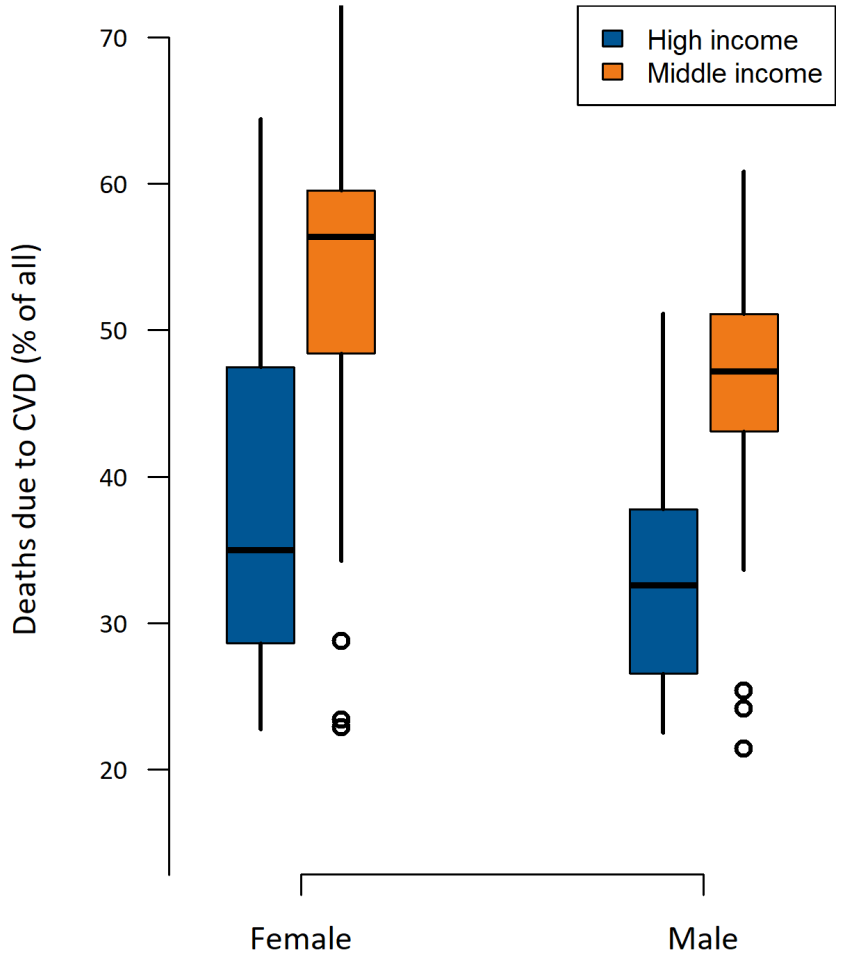
European Journal of Heart Failure (2020)22,1111–1121

What has all this to do with me?

NOT MUCH



National causes of death in females and males in ESC member countries (latest year)



Proportions of deaths caused by CVD in ESC member countries stratified by sex and national income status (latest year)

European Heart Journal (2022) 43, 716–799

TALES FROM THE CLINIC (1)

Clinical History

42y, male

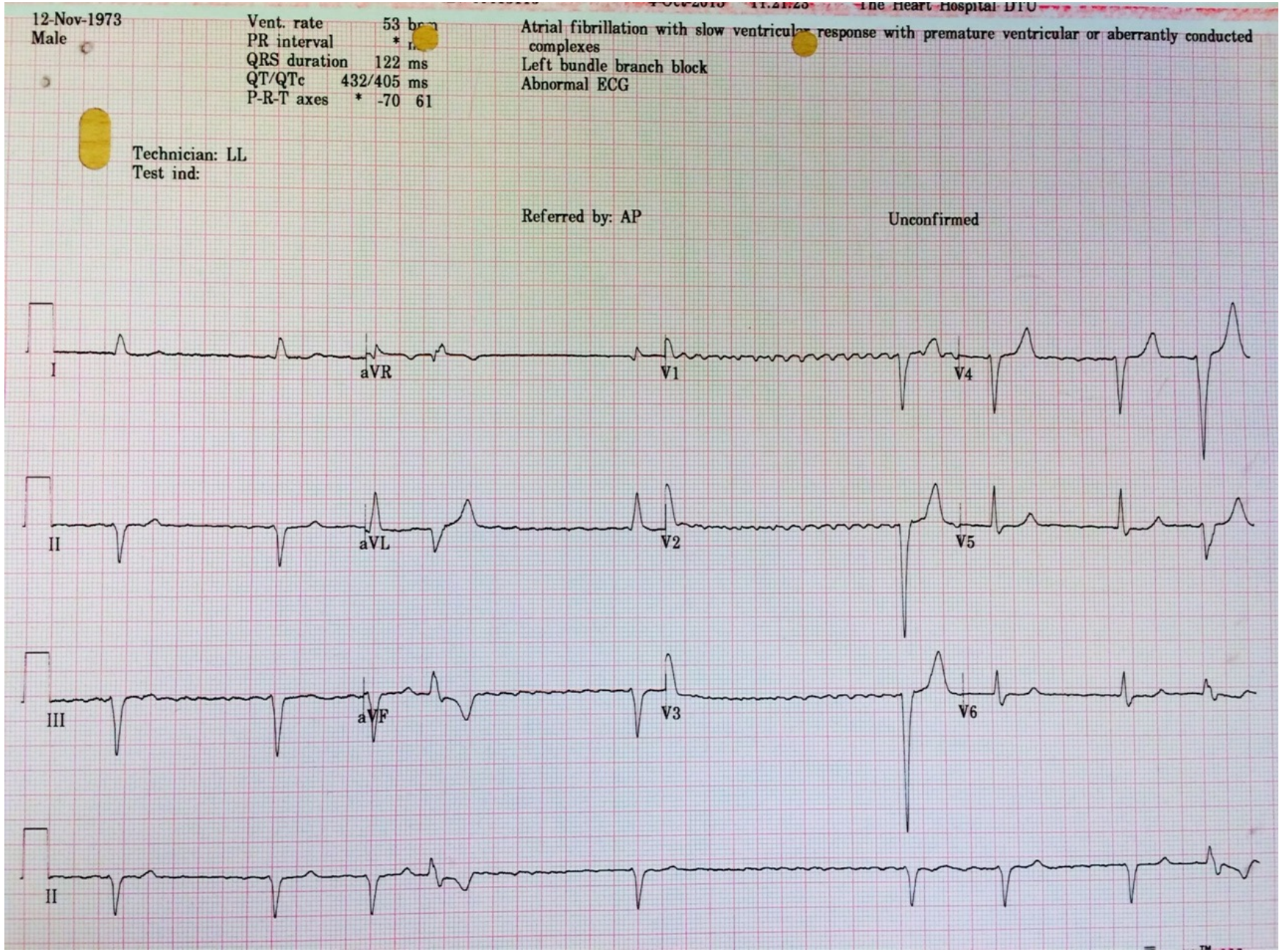
- AF 2007
  - Incidental finding
  - DCCV 2008
  - Medication: Aspirin 75mg
  - Holter: NSVT x 5 beats

- CMR: Mild impairment of LV function. Biatrial dilatation with LA diameter of 43mm.

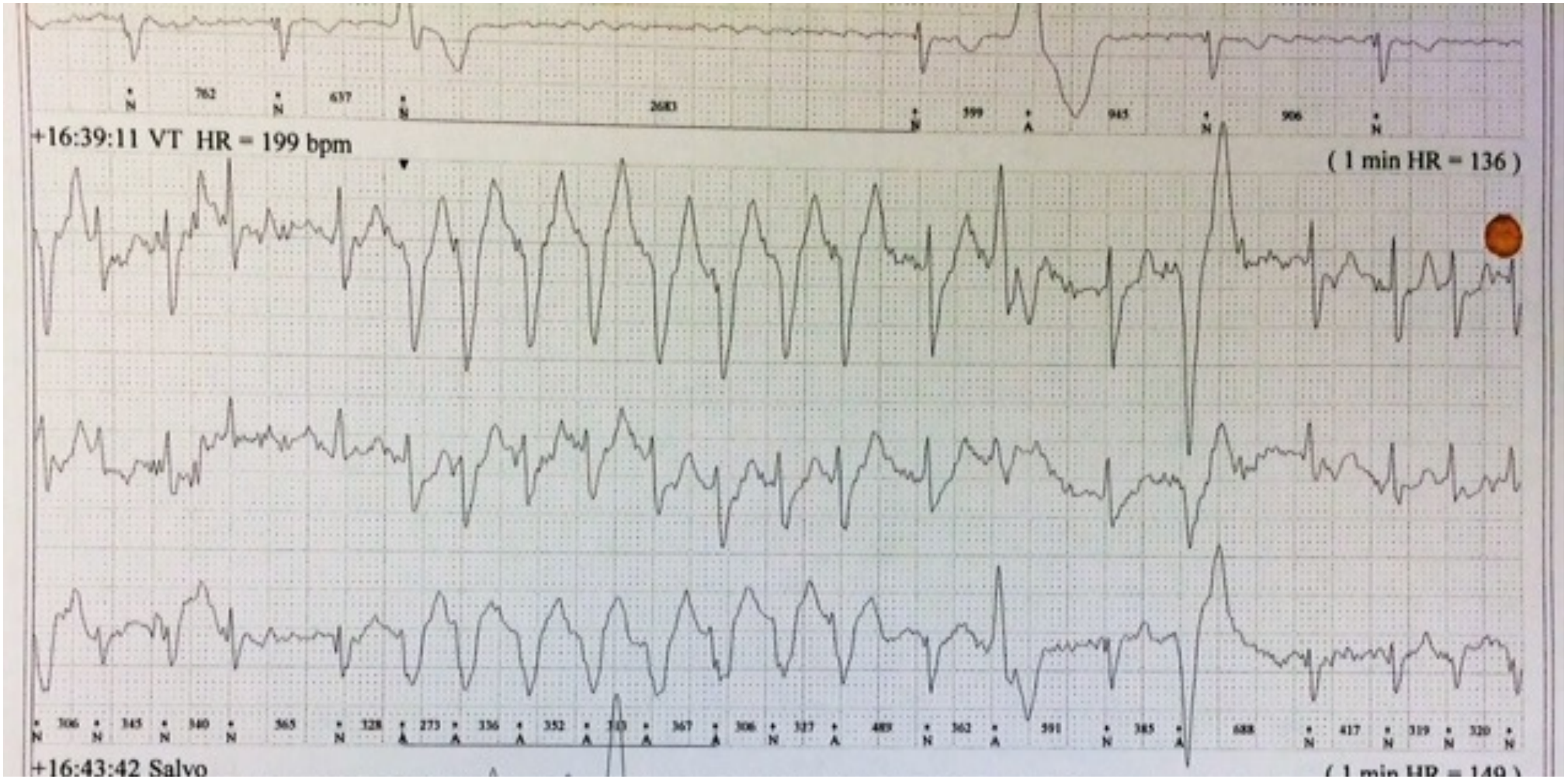
Clinical History

- Family History
  - Father:
    - AF
    - PPM – CHB
    - CRT-P 2011
    - RIP aged 63
  - Paternal grandfather:
    - AF and PPM
    - RIP aged 64 ?cause

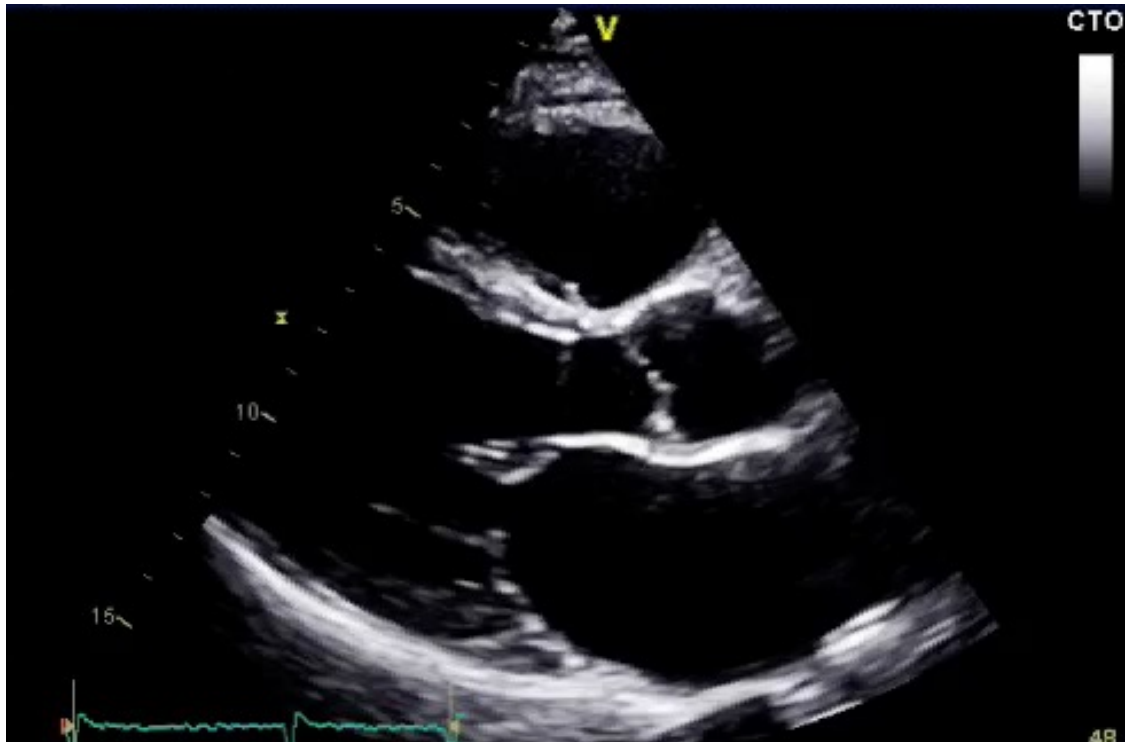
ECG

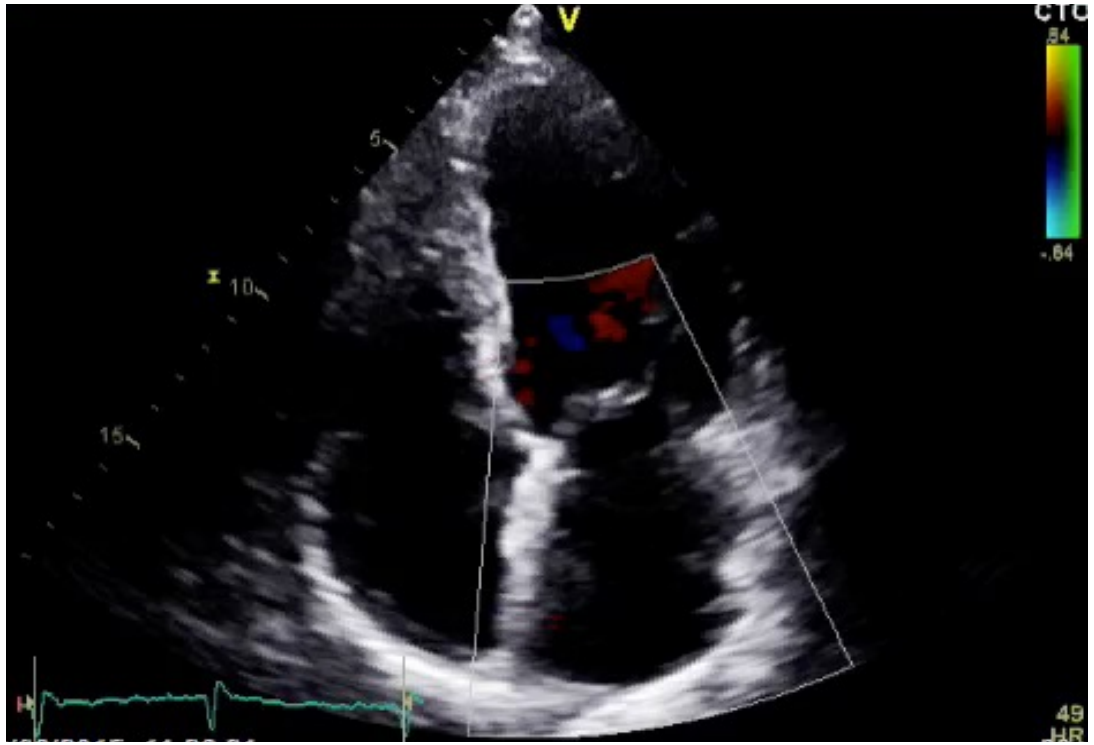

12-Nov-1973
Male
Vent. rate 53 bpm
PR interval * ms
QRS duration 122 ms
QT/QTc 432/405 ms
P-R-T axes * -70 61
Atrial fibrillation with slow ventricular response with premature ventricular or aberrantly conducted complexes
Left bundle branch block
Abnormal ECG
Technician: LL
Test ind:
Referred by: AP
Unconfirmed
I
aVR
V1
V4
II
aVL
V2
V5
III
aVF
V3
V6
II

24 hour Holter

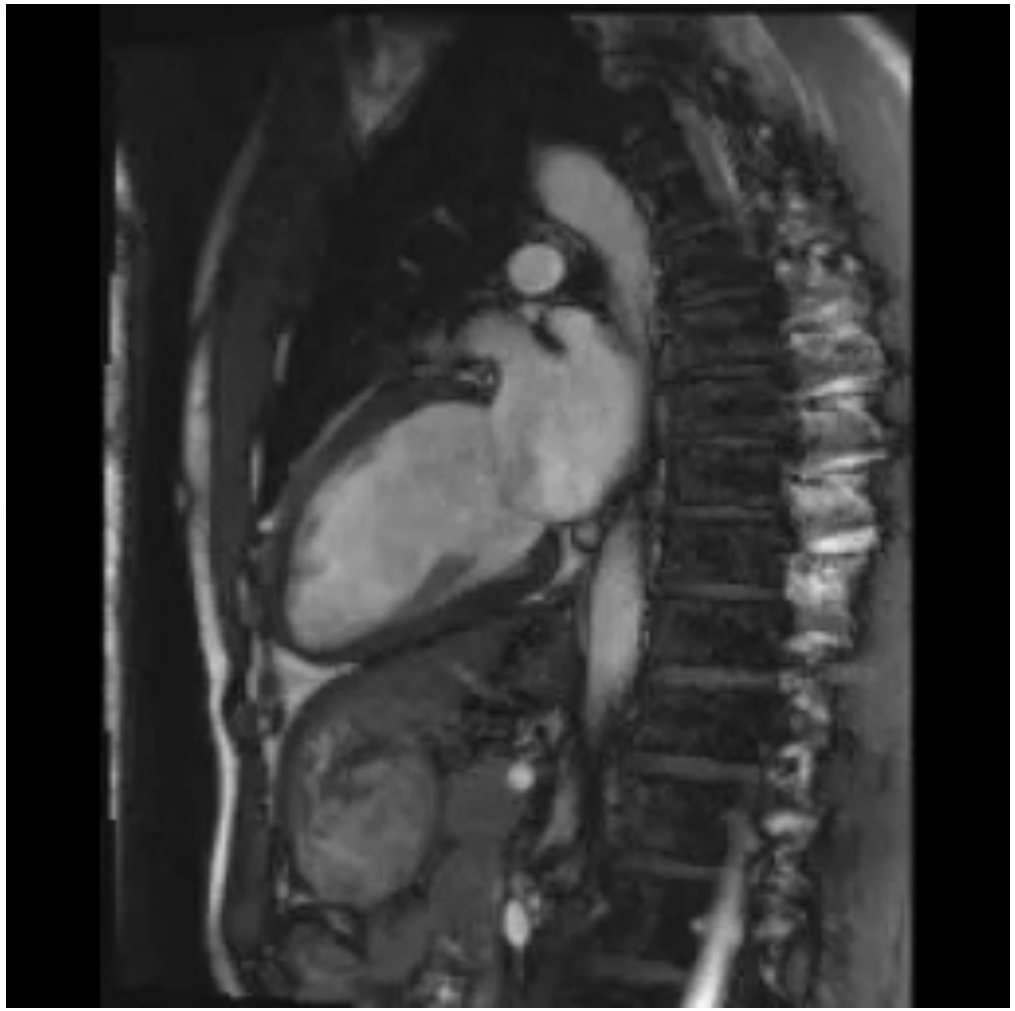


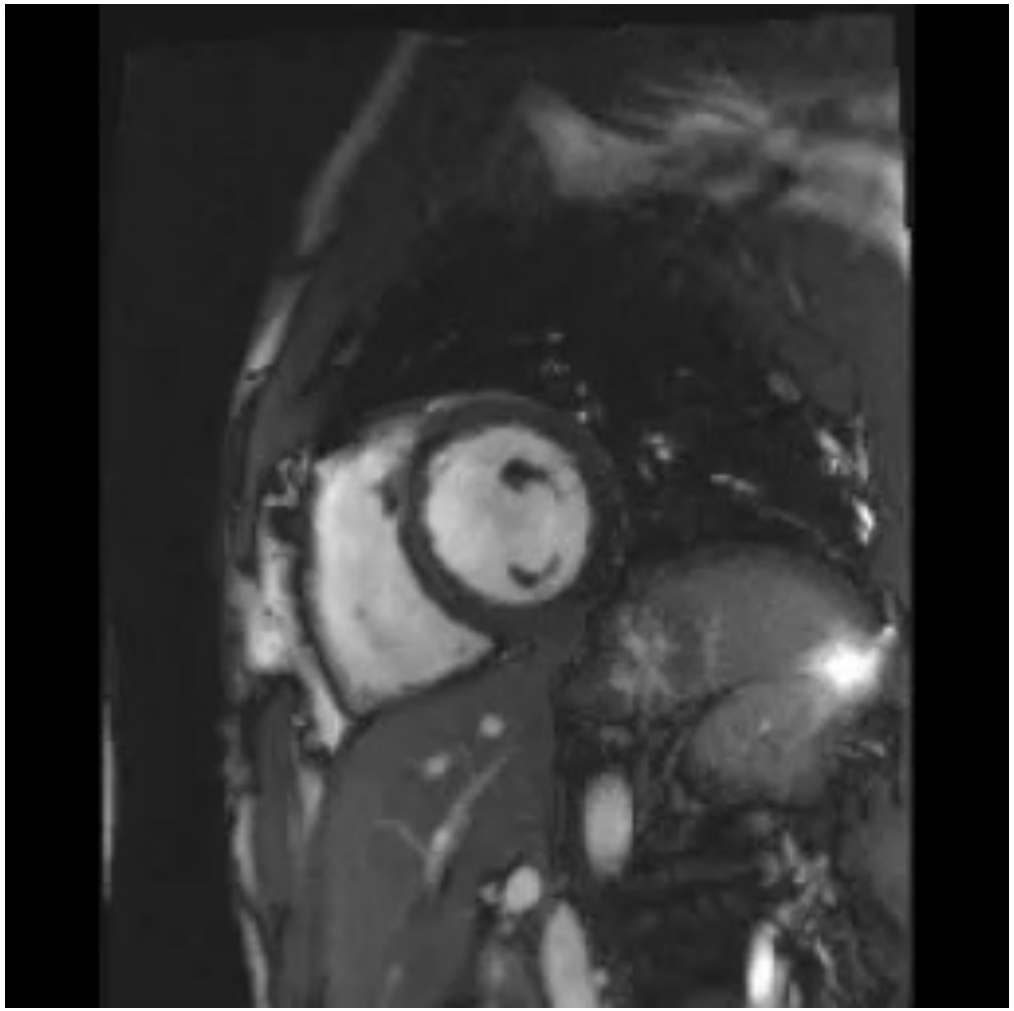
Echocardiogram





CMR





European Heart Journal (2016) 37, 2129–2200
doi:10.1093/eurheartj/ehw128

2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure

The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC)

Developed with the special contribution of the Heart Failure Association (HFA) of the ESC

"The main terminology used to describe HF is historical and is based on measurement of the LVEF"

Type of HF		HFrEF	HFmrEF	HFpEF
CRITERIA	1	Symptoms ± Signs[a]	Symptoms ± Signs[a]	Symptoms ± Signs[a]
	2	LVEF <40%	LVEF 40–49%	LVEF ≥50%
	3	–	1. Elevated levels of natriuretic peptides[b]; 2. At least one additional criterion: a. relevant structural heart disease (LVH and/or LAE), b. diastolic dysfunction (for details see Section 4.3.2).	1. Elevated levels of natriuretic peptides[b]; 2. At least one additional criterion: a. relevant structural heart disease (LVH and/or LAE), b. diastolic dysfunction (for details see Section 4.3.2).

The Phenotype

- Young
- Family History of AF, PM
- NSVT
- Mild LV impairment

- WHY?

Diagnosis

- **Genetic Testing**
  - **Lamin A/C : c.**1489-1 G>A

Risk Factors for Malignant Ventricular Arrhythmias in Lamin A/C Mutation Carriers

A European Cohort Study

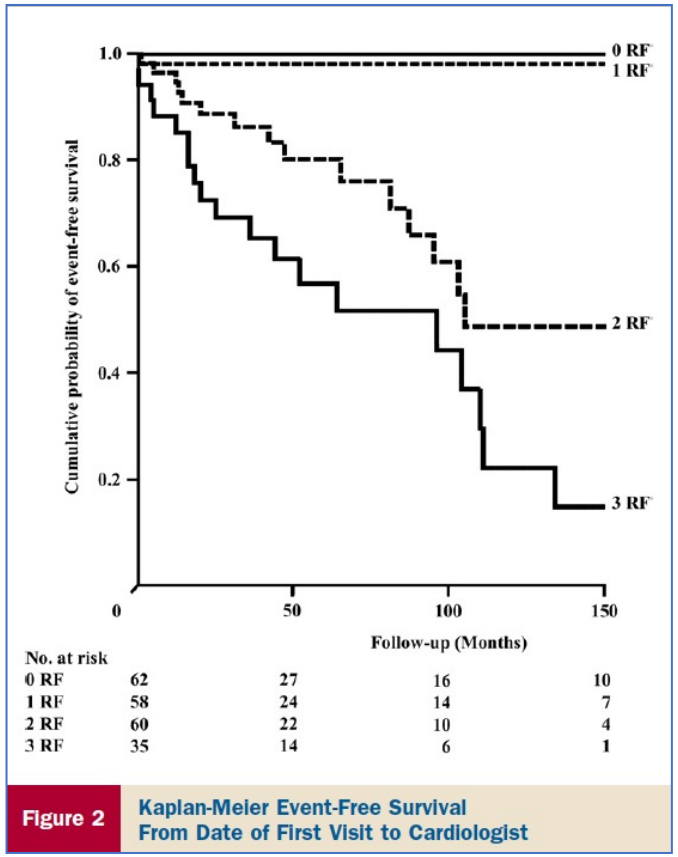


Figure 2 Kaplan-Meier Event-Free Survival From Date of First Visit to Cardiologist

NSVT, LVEF 45%, male

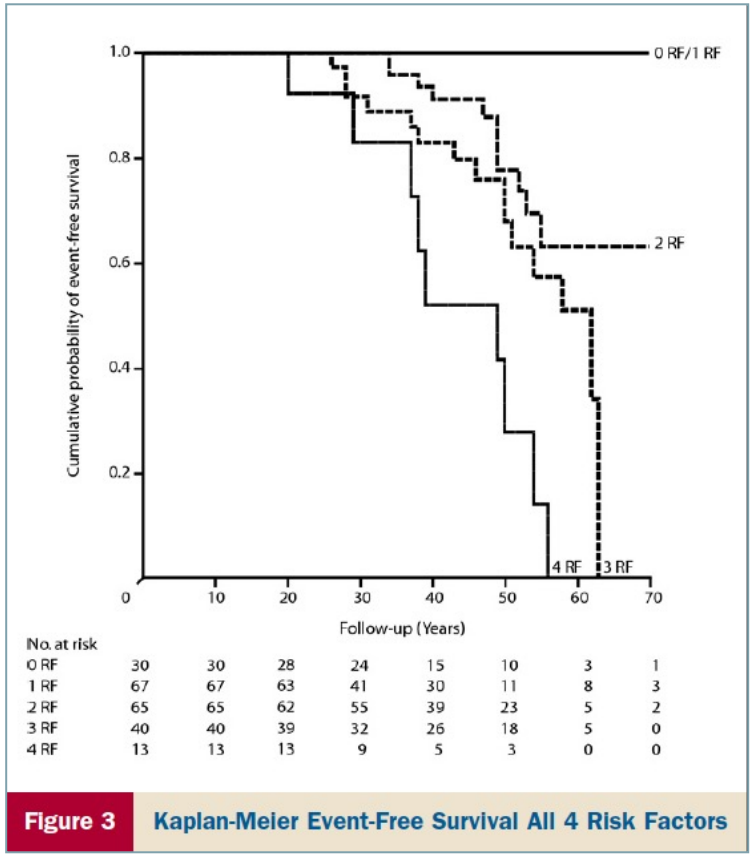


Figure 3 Kaplan-Meier Event-Free Survival All 4 Risk Factors

+ non-missense mutations (ins-del/truncating or mutations affecting splicing)

(J Am Coll Cardiol 2012;59:493–500)

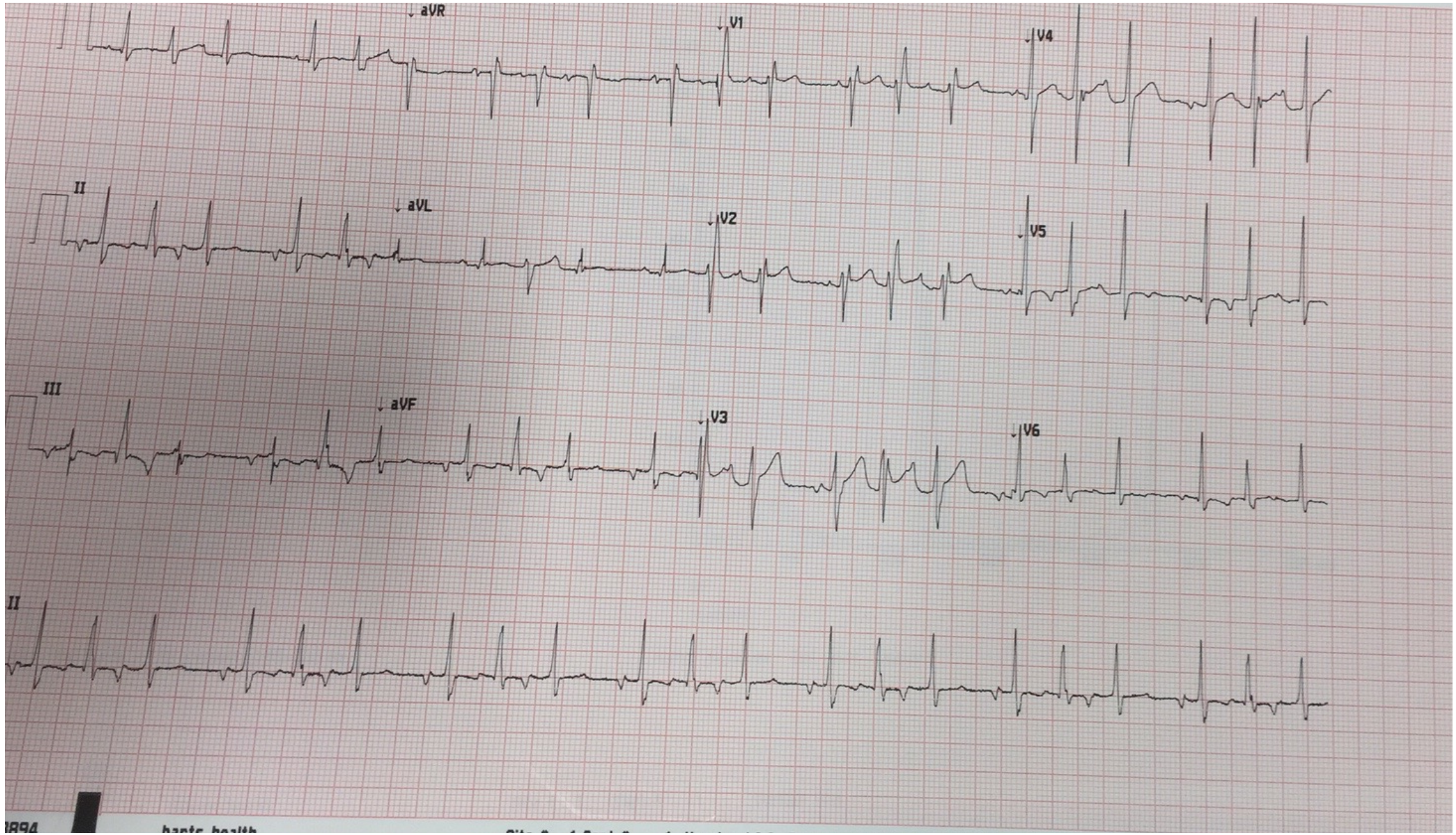
TALES FROM THE CLINIC (2)

Background

- 24 year old male
- 2006: Incidental diagnosis of junctional arrhythmias, supra- and ventricular multifocal ectopics
- Intermittently impaired LV/RV systolic function
- 2008: EPS and RV biopsy
  - Flecainide challenge negative
  - Normal coronaries
  - No ablation as too many foci
  - EMB: “The findings are in keeping with dilated cardiomyopathy but there are no specific features to indicate its cause.

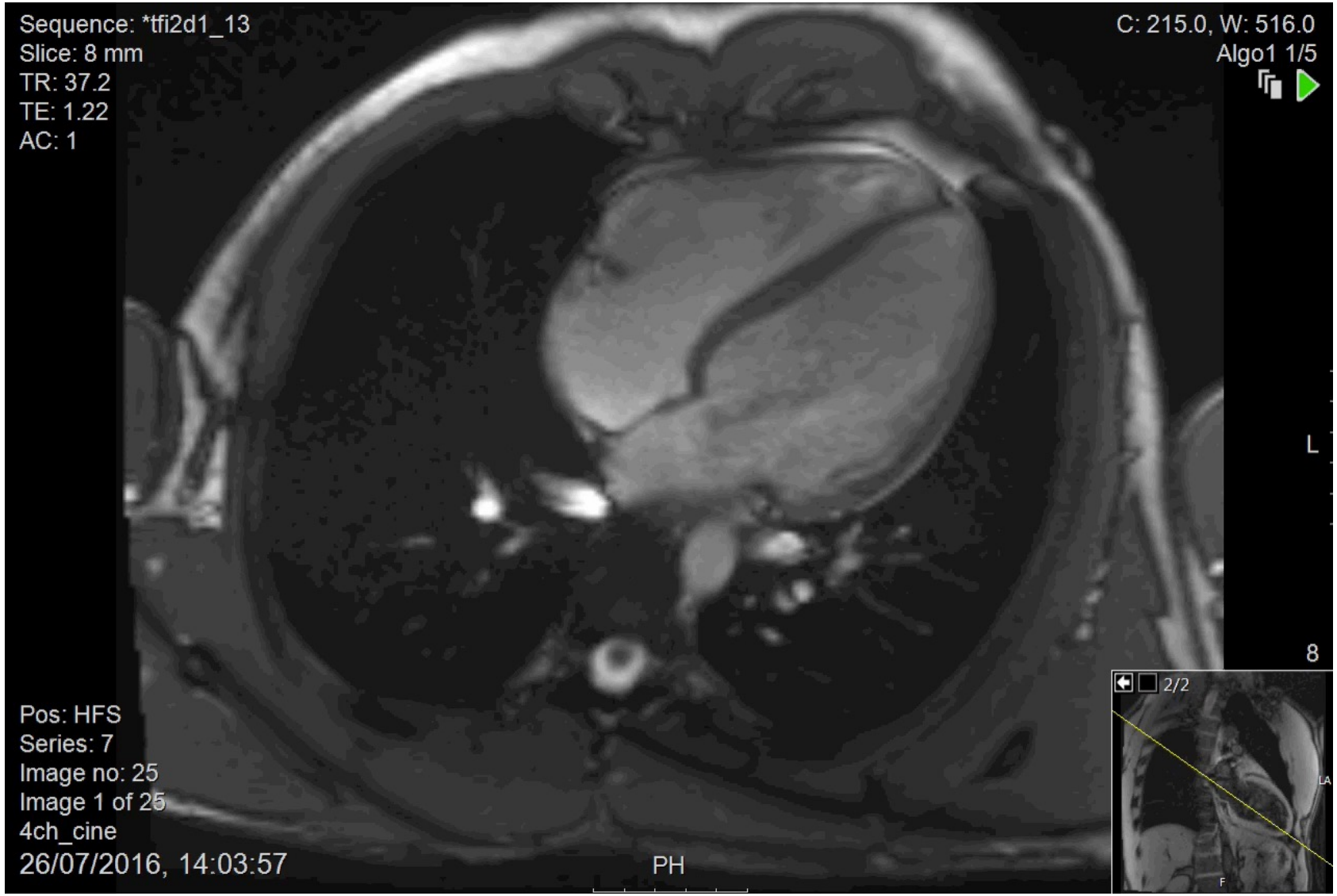
2017-18

- Carvedilol 25mg BD, Ramipril 2.5mg OD
- No symptoms except some occasional palpitations
- No syncope
- No SOB
- Very fit, into different sports, regular gym-attendance
- Works as accountant


aVR
V1
V4
II
aVL
V2
V5
III
aVF
V3
V6
II

Holter

- 47000 VES, 34% of total
- NSVTs, polymorphic and monomorphic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Slice: 8 mm
TR: 37.2
TE: 1.22
AC: 1
C: 215.0, W: 516.0
Algo1 1/5
L
8
Pos: HFS
Series: 7
Image no: 25
Image 1 of 25
4ch_cine
26/07/2016, 14:03:57
PH
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Genetics

Gene	Variant	Result	Pathogenicity	Population frequency	Number of references
SCN5A	**NP_932173.1:p.Arg222Gln NM_198056.2:c.665G>A NC_000003.11:g.38655272C>T**	Heterozygosis	**Pathogenic or disease-causing (+++)**	**Mutation (not found in controls)**	28
RBM20	NP_001127835.2:p.Ala387Val NM_001134363.2:c.1160C>T NC_000010.10:g.112541527C>T	Heterozygosis	Unknown clinical significance (?)	Mutation (not found in controls)	0

Clinical interpretation

The SCN5A mutation has been documented in several families affected with dilated cardiomyopathy and frequent ventricular arrhythmias (conduction disorders and supraventricular arrhythmias are also described). Sudden death and severe systolic dysfunction has been reported. Almost all affected were diagnosed before the age of 30. This variant may be used for predictive purposes, and we recommend its inclusion in the familial screening.

The RBM20 mutation is classified as of unknown clinical significance. The expected phenotype for pathogenic variants in this gene is dilated cardiomyopathy associated with arrhythmias; however, the mutation identified in this study is located outside the pathogenic regions (hotspots) in the gene. The use of this variant as part of the familial screening could be considered for research purposes only.

Functional study / Animal model

This mutation has been functionally characterized by several independent groups (obtaining similar results). These electrophysiological studies showed that this mutation leads to a gain of function. An activation curve shifted to negative potentials (earlier activation), with more accelerated kinetics, was observed. This produced an increase in the current window (typical of long QT). Interestingly, channel inactivation also occurred early, which is a mechanism that would cause a loss-of-function of the channel (typical of Brugada). An *in silico* model determined that the ectopic activity in the Purkinje system would occur or by an incomplete repolarization of these cells, and the disappearance of arrhythmias with quinidine or exercise was also observed.

Treatment

- January 2018: Quinidine
- March 2018: EF 62%; **3** VE in 24 hours

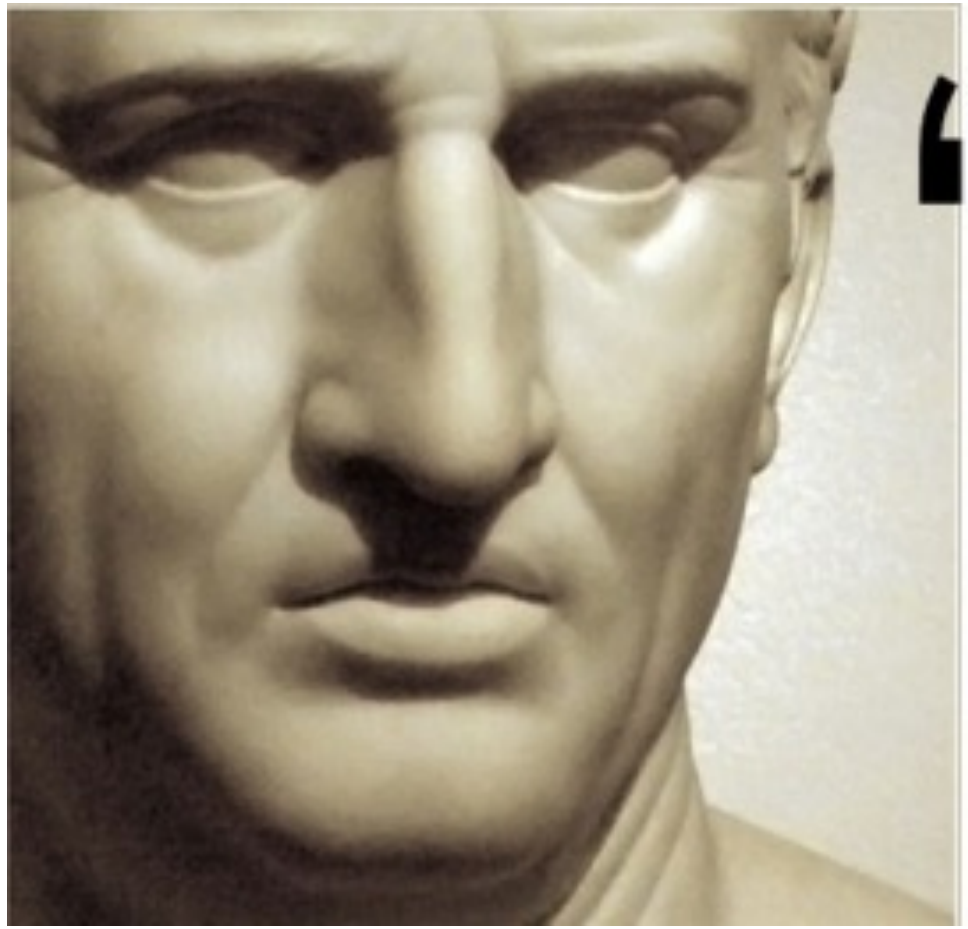
EDITORIAL

nature medicine

Taking personalized medicine to heart

Tailoring treatment to the individual patient has revolutionized cancer therapy, but personalized medicine has yet to make much headway in the treatment of cardiovascular disease. With emerging insight into disease mechanisms and new treatment options, the time is now ripe for the cardiovascular field to adopt a more personalized approach to therapy.

NATURE MEDICINE VOLUME 24 | NUMBER 2 | FEBRUARY 2018



"If you wish to persaude
me you must
think my thoughts,
feel my feelings and
speak my words."

Cicero, Roman Statesman

(1) Is this stuff real?

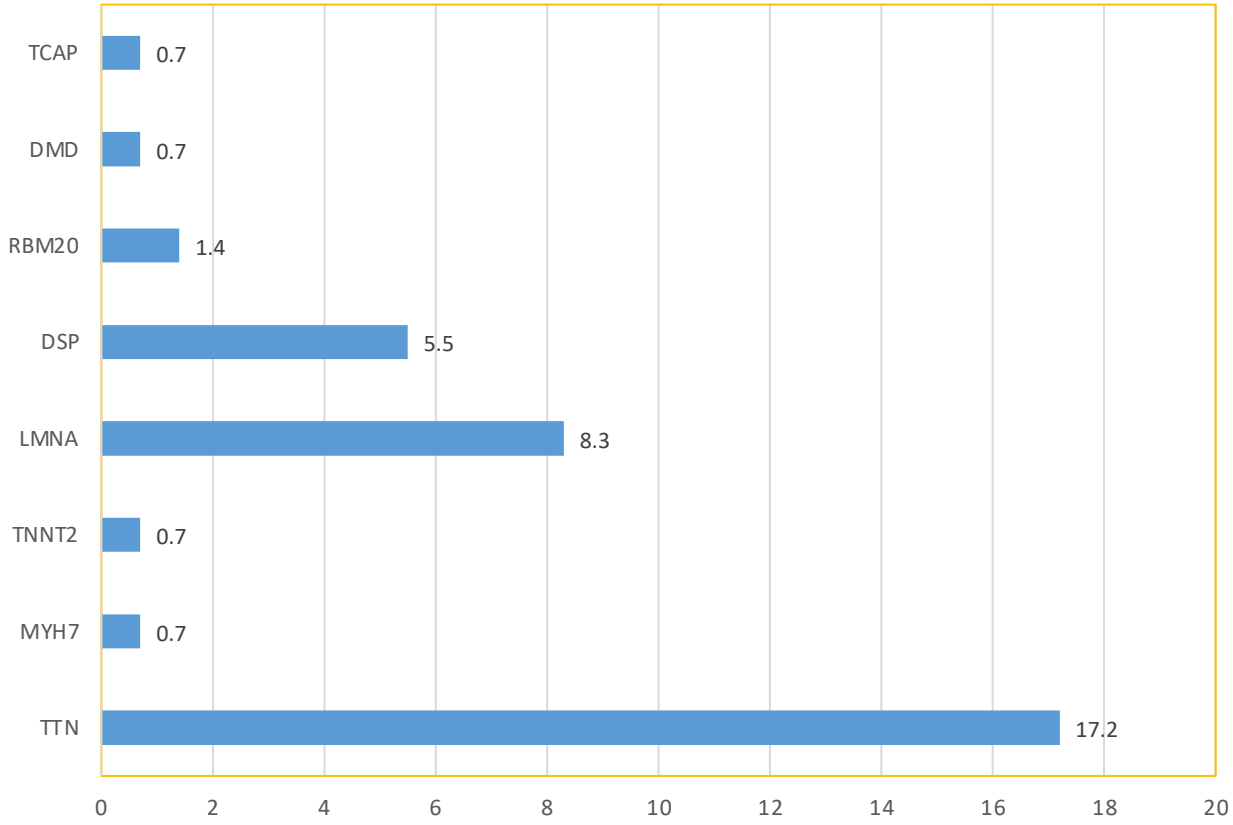
Genetics and genotype–phenotype correlations in Finnish patients with dilated cardiomyopathy

Oyediran Akinrinade[1,2†], Laura Ollila[3†], Sanna Vattulainen[1], Jonna Tallila[4], Massimiliano Gentile[4], Pertteli Salmenperä[4], Hannele Koillinen[5], Maija Kaartinen[3], Markku S. Nieminen[3], Samuel Myllykangas[2,4‡], Tero-Pekka Alastalo[1,4‡], Juha W. Koskenvuo[4,6,7‡*], and Tiina Heliö[3‡]

101 genes associated with cardiomyopathies in 145 unrelated Finnish patients with DCM

Familial (n=63)
48% mut +ve

Sporadic (n=82)
26% mut +ve



Eur Heart J. 2015 Sep 7;36(34):2327-37.

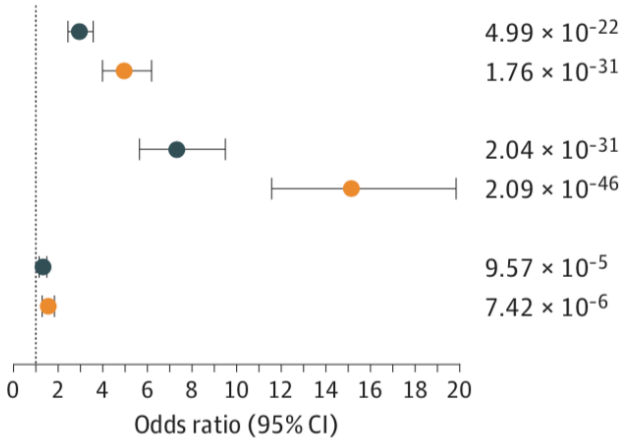
JAMA Cardiology | Original Investigation

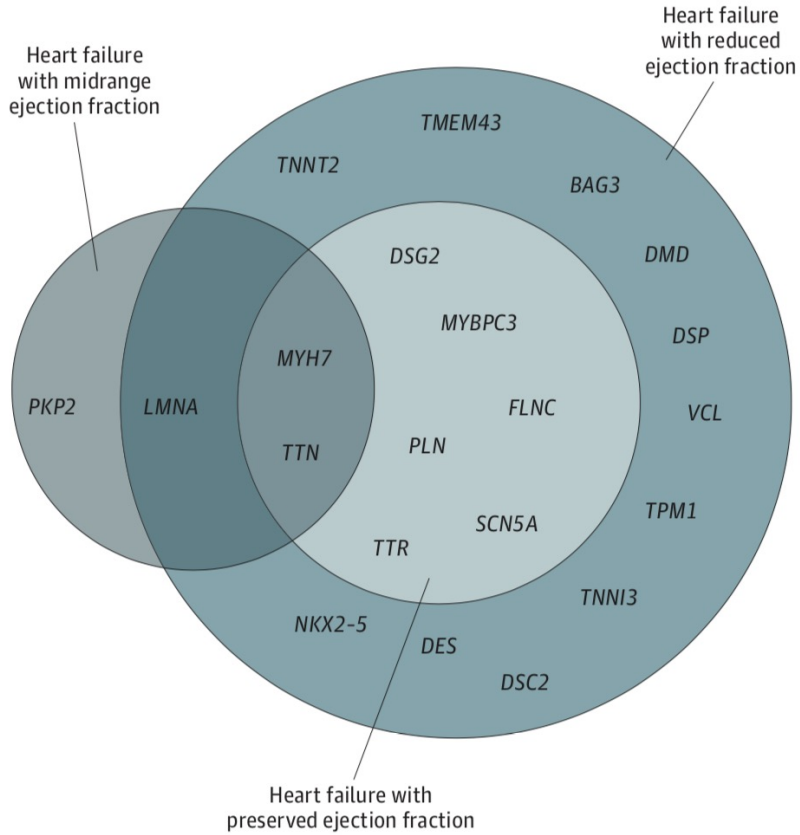
Assessing the Role of Rare Genetic Variation in Patients With Heart Failure

Gundula Povysil, MD, PhD; Olympe Chazara, PhD; Keren J. Carss, PhD; Sri V. V. Deevi, PhD; Quanli Wang, MSc; Javier Armisen, PhD; Dirk S. Paul, PhD; Christopher B. Granger, MD; John Kjekshus, MD, PhD; Vimla Aggarwal, MBBS; Carolina Haefliger, MD; David B. Goldstein, PhD

B Outcomes by *ICD-10* code

PSI filtering	Odds ratio (95% CI)	*P* value
Heart failure (I50)		
None	2.95 (2.44-3.57)	4.99×10^{-22}
>90%	4.97 (3.99-6.19)	1.76×10^{-31}
Cardiomyopathy (I42)		
None	7.32 (5.65-9.50)	2.04×10^{-31}
>90%	15.15 (11.57-19.84)	2.09×10^{-46}
Ischemic heart diseases (I20–I25)		
None	1.31 (1.15-1.49)	9.57×10^{-5}
>90%	1.53 (1.28-1.83)	7.42×10^{-6}



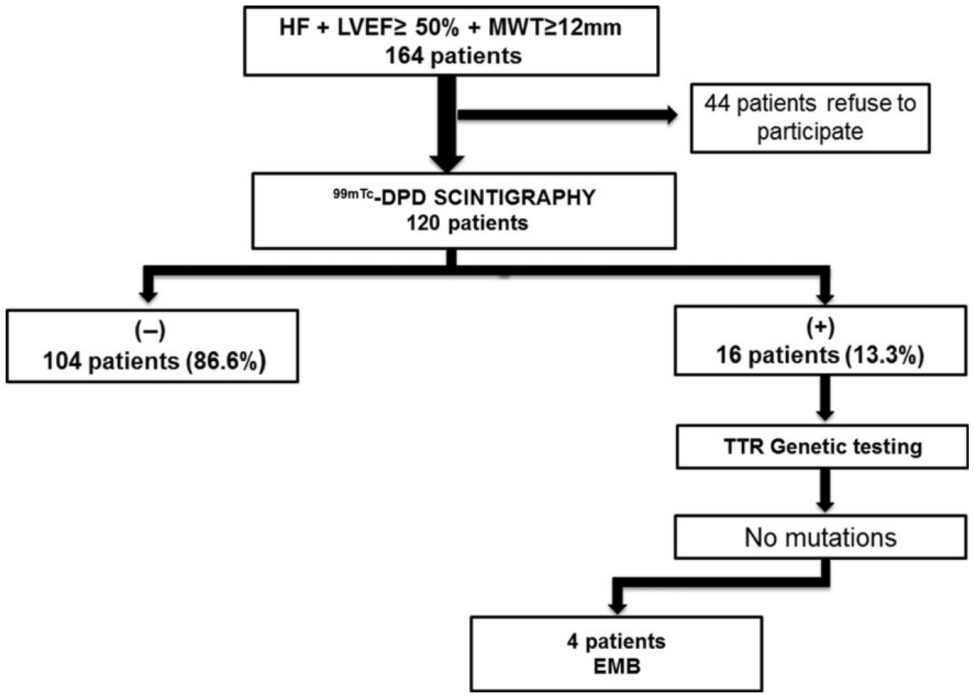


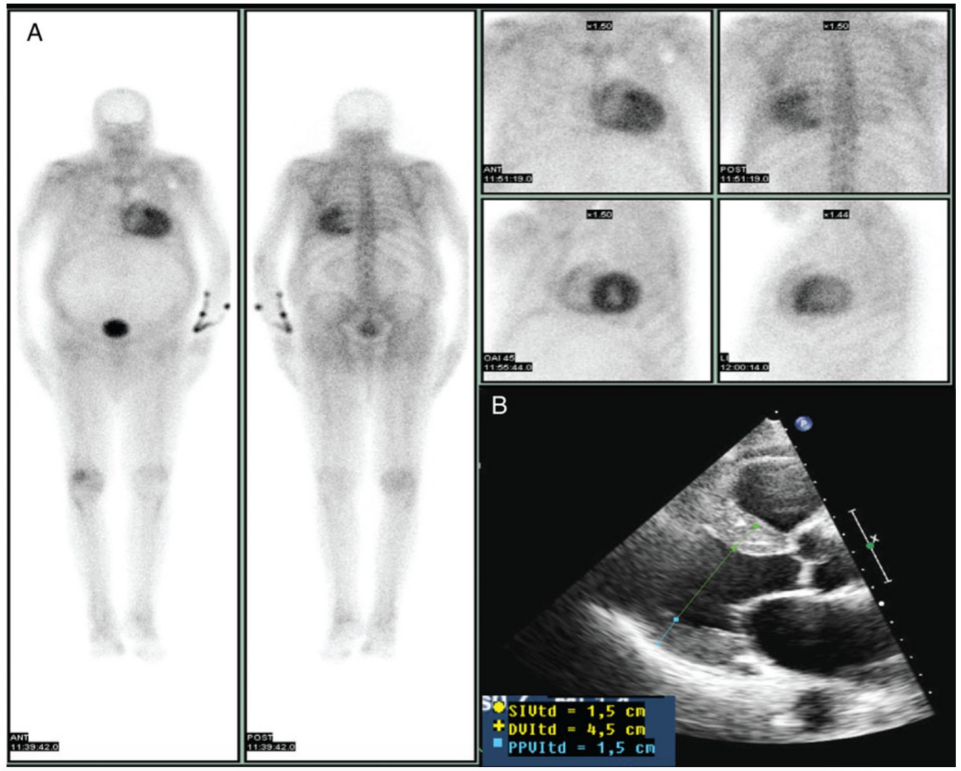
Candesartan in Heart Failure-Assessment of Reduction in Mortality and Morbidity (CHARM) and Controlled Rosuvastatin Multinational Trial in Heart Failure (CORONA) clinical trials.

JAMA Cardiol. 2021;6(4):379-386

Wild-type transthyretin amyloidosis as a cause of heart failure with preserved ejection fraction

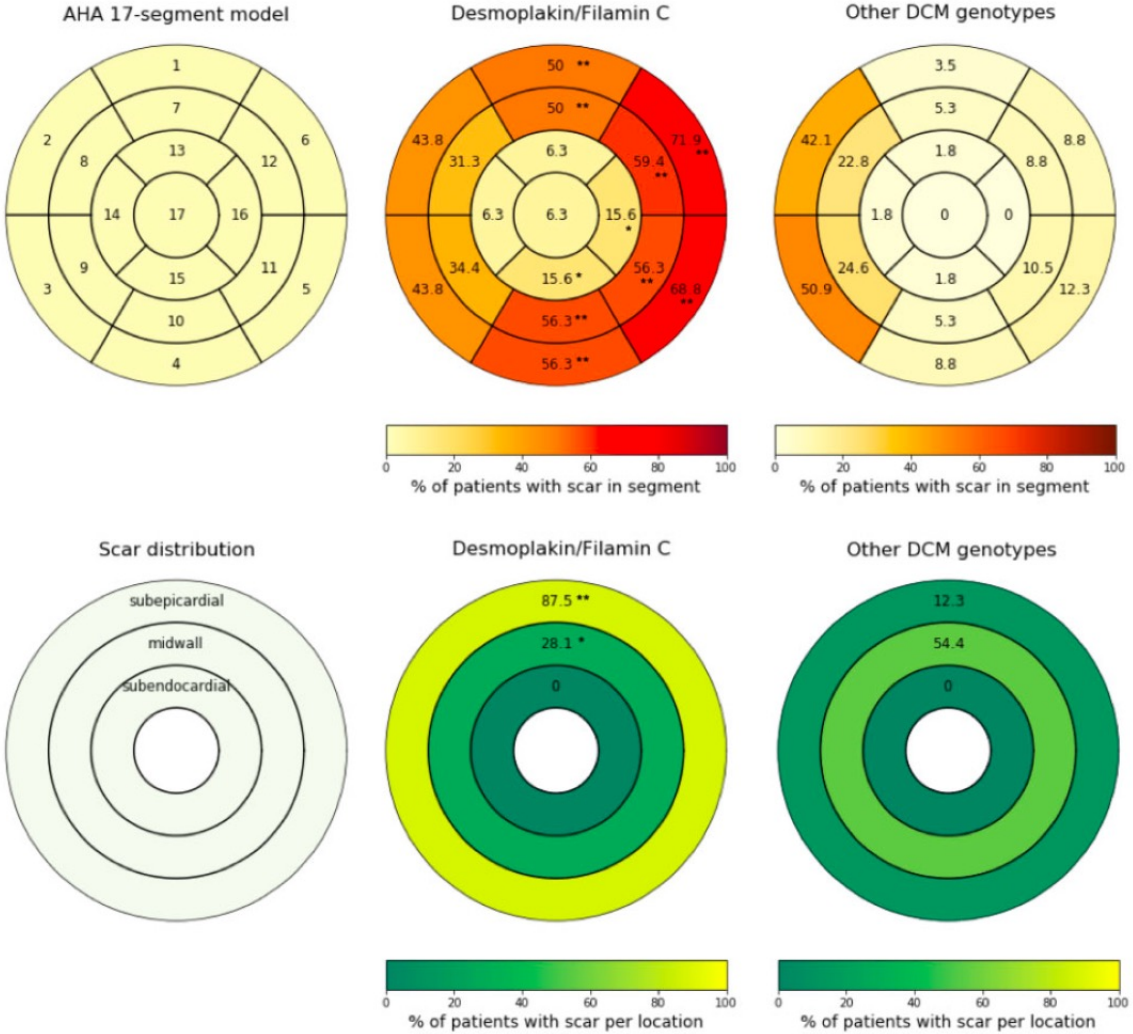
Esther González-López[1], Maria Gallego-Delgado[1], Gonzalo Guzzo-Merello[1], F. Javier de Haro-del Moral[2], Marta Cobo-Marcos[1], Carolina Robles[1], Belén Bornstein[3,4,5], Clara Salas[6], Enrique Lara-Pezzi[7], Luis Alonso-Pulpon[1], and Pablo Garcia-Pavia[1,7]*

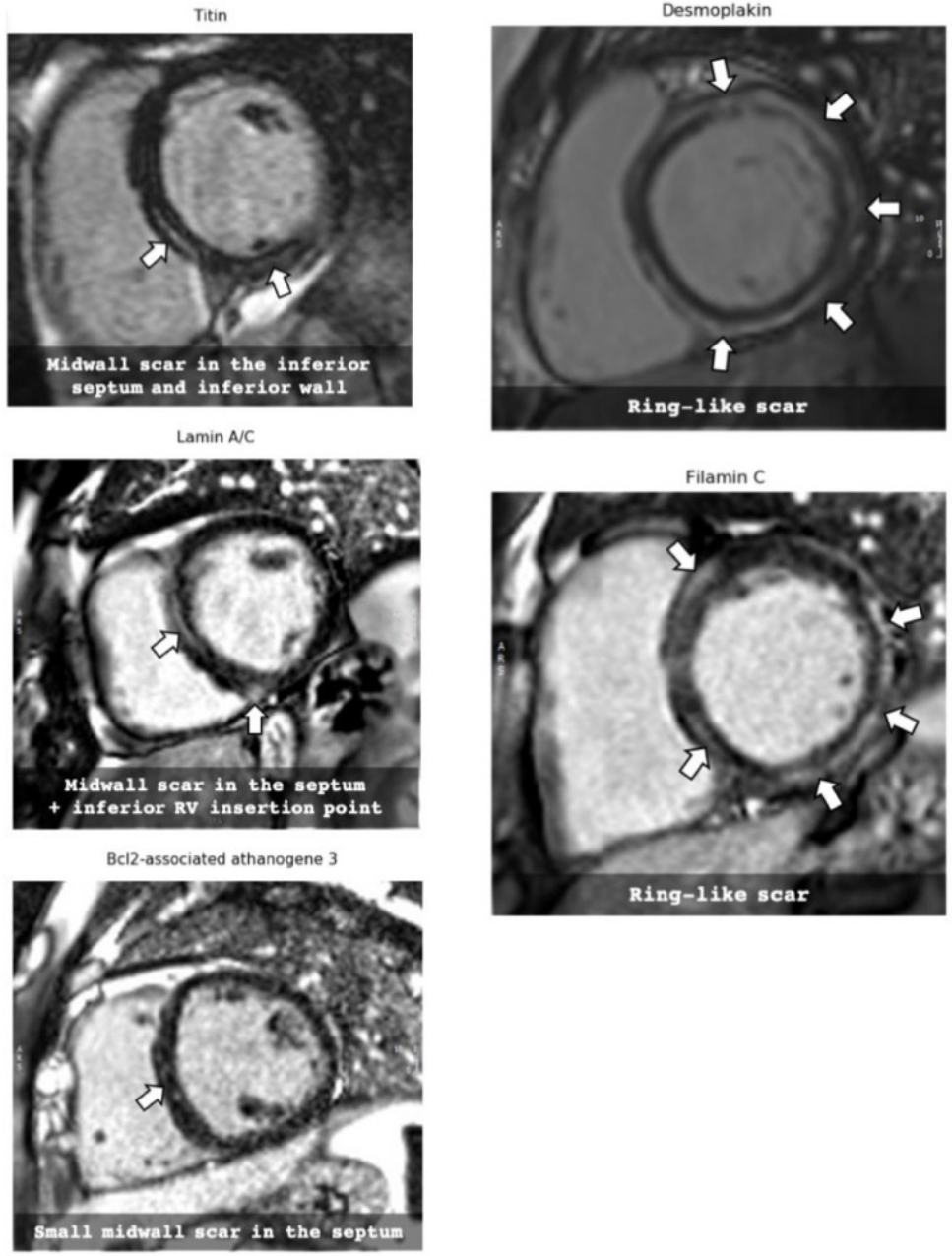




European Heart Journal (2015) 36, 2585–2594

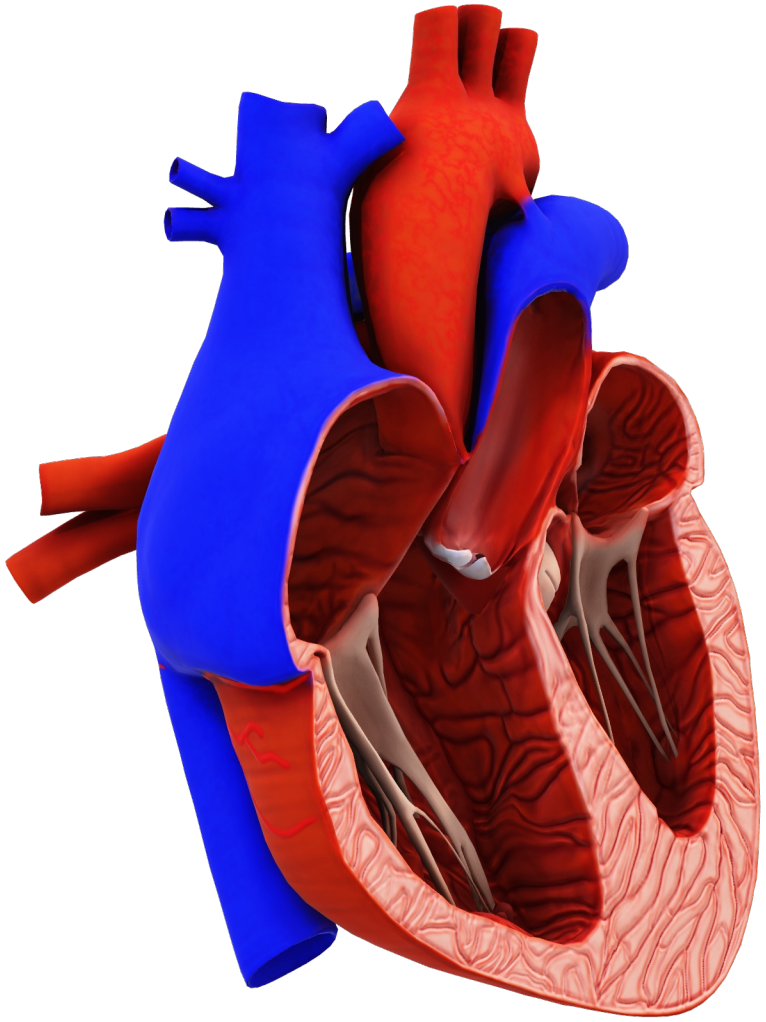
Dilated cardiomyopathy and arrhythmogenic left ventricular cardiomyopathy: a comprehensive genotype-imaging phenotype study



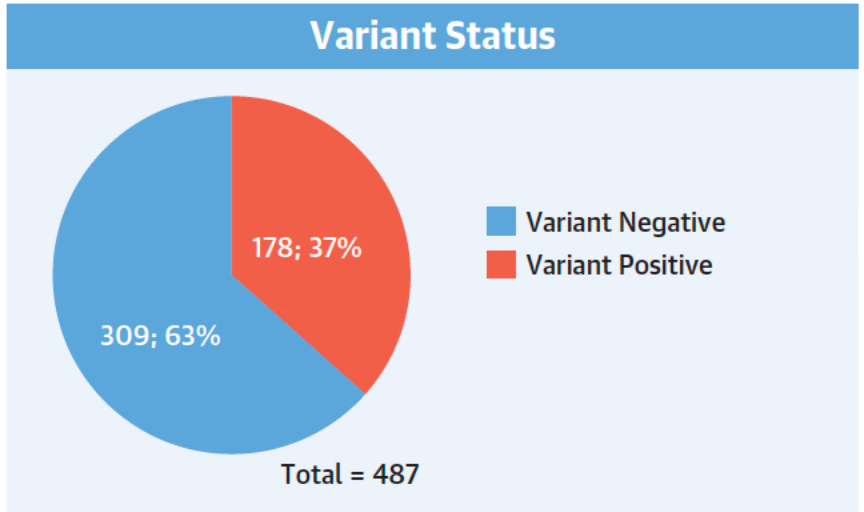


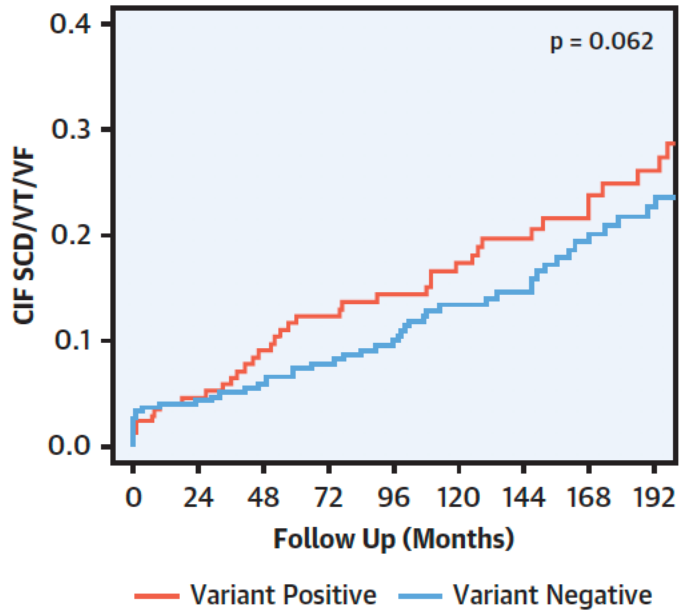
European Heart Journal - Cardiovascular Imaging (2019) 0, 1–11

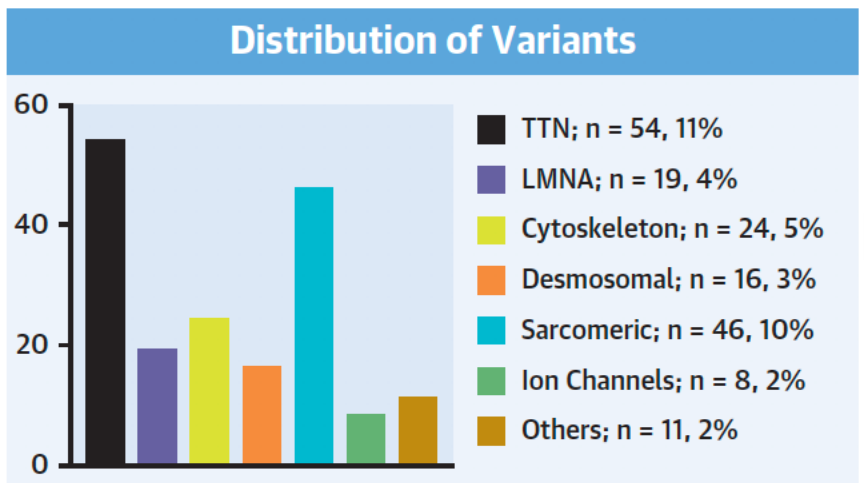
(2) Actionability?

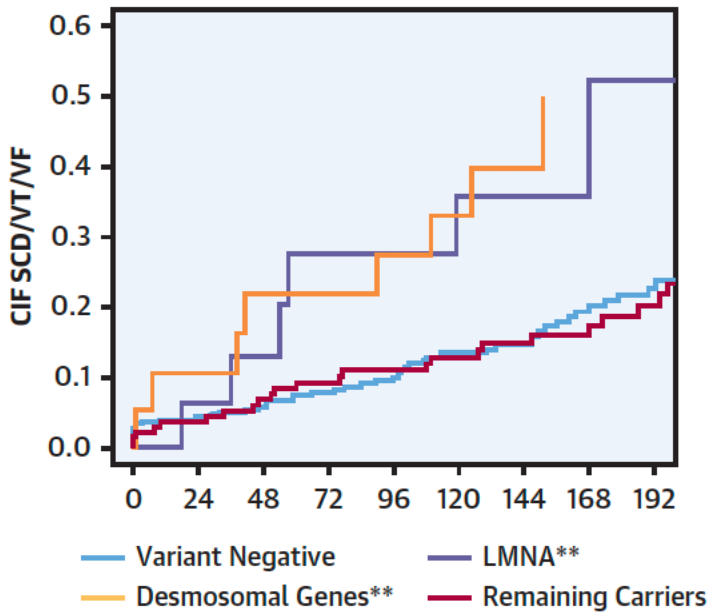


Atrial arrhythmia	Antiarrhythmics, DOAC, ablation
Ventricular arrhythmia	Antiarrhythmics, Ablation, ICD
Heart failure	ACE, MRA, BB, SGLT2, ARNI, transplant, VAD
Valve disease	TEER









Gigli, M. et al. J Am Coll Cardiol. 2019;74(11):1480-90.

2013 ESC Guidelines on cardiac pacing and cardiac resynchronization therapy

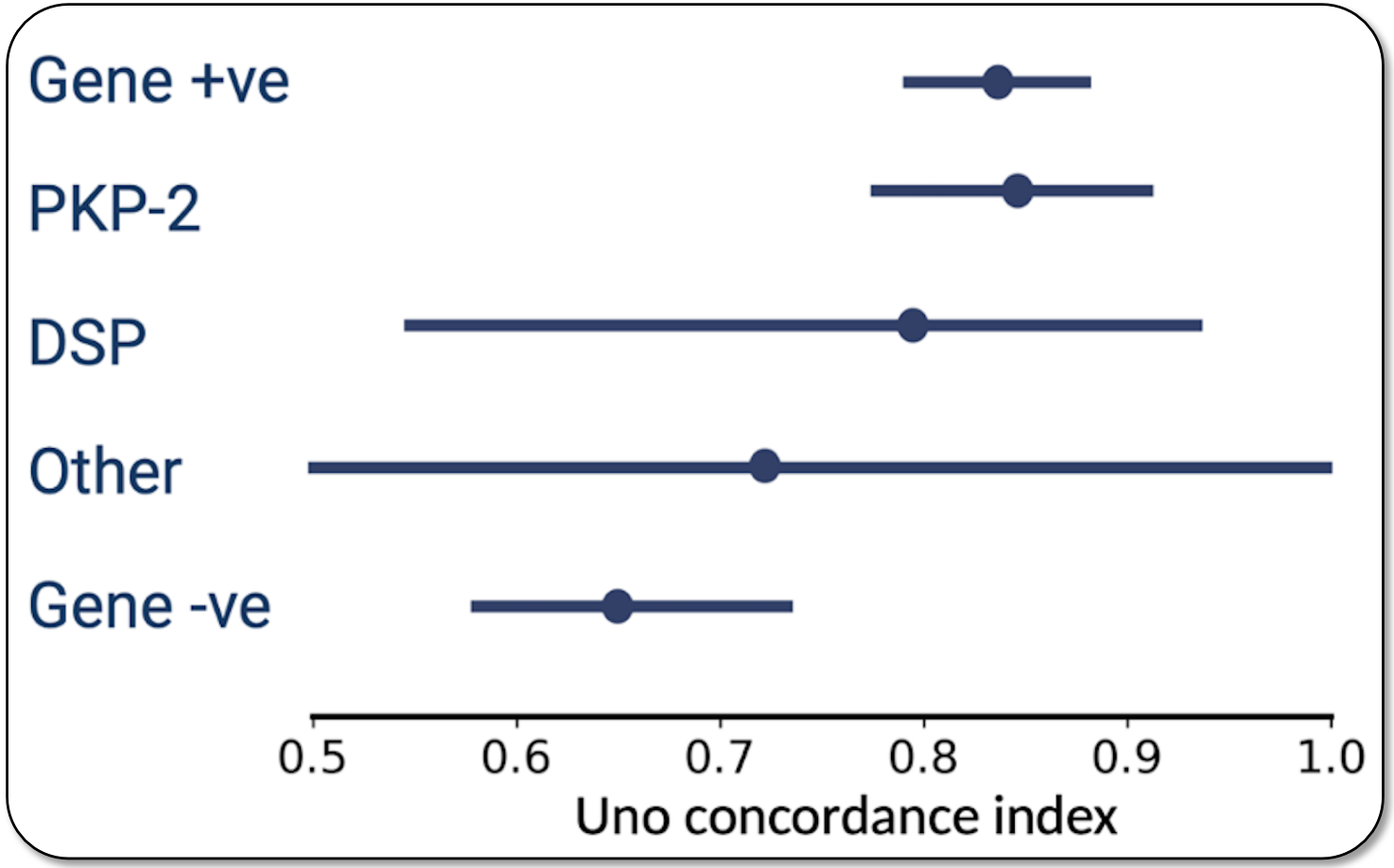
The Task Force on cardiac pacing and resynchronization therapy of the European Society of Cardiology (ESC). Developed in collaboration with the European Heart Rhythm Association (EHRA).

An ICD should be considered in patients with DCM and a confirmed disease-causing *LMNA* mutation and clinical risk factors.[d]	IIa	B

2015 ESC Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death

The Task Force for the Management of Patients with Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death of the European Society of Cardiology (ESC)

Importance of genotype for risk stratification in arrhythmogenic right ventricular cardiomyopathy using the 2019 ARVC risk calculator



Eur Heart J. 2022 Aug 21;43(32):3053-3067. doi: 10.1093/eurheartj/ehac235.

The NEW ENGLAND JOURNAL of MEDICINE

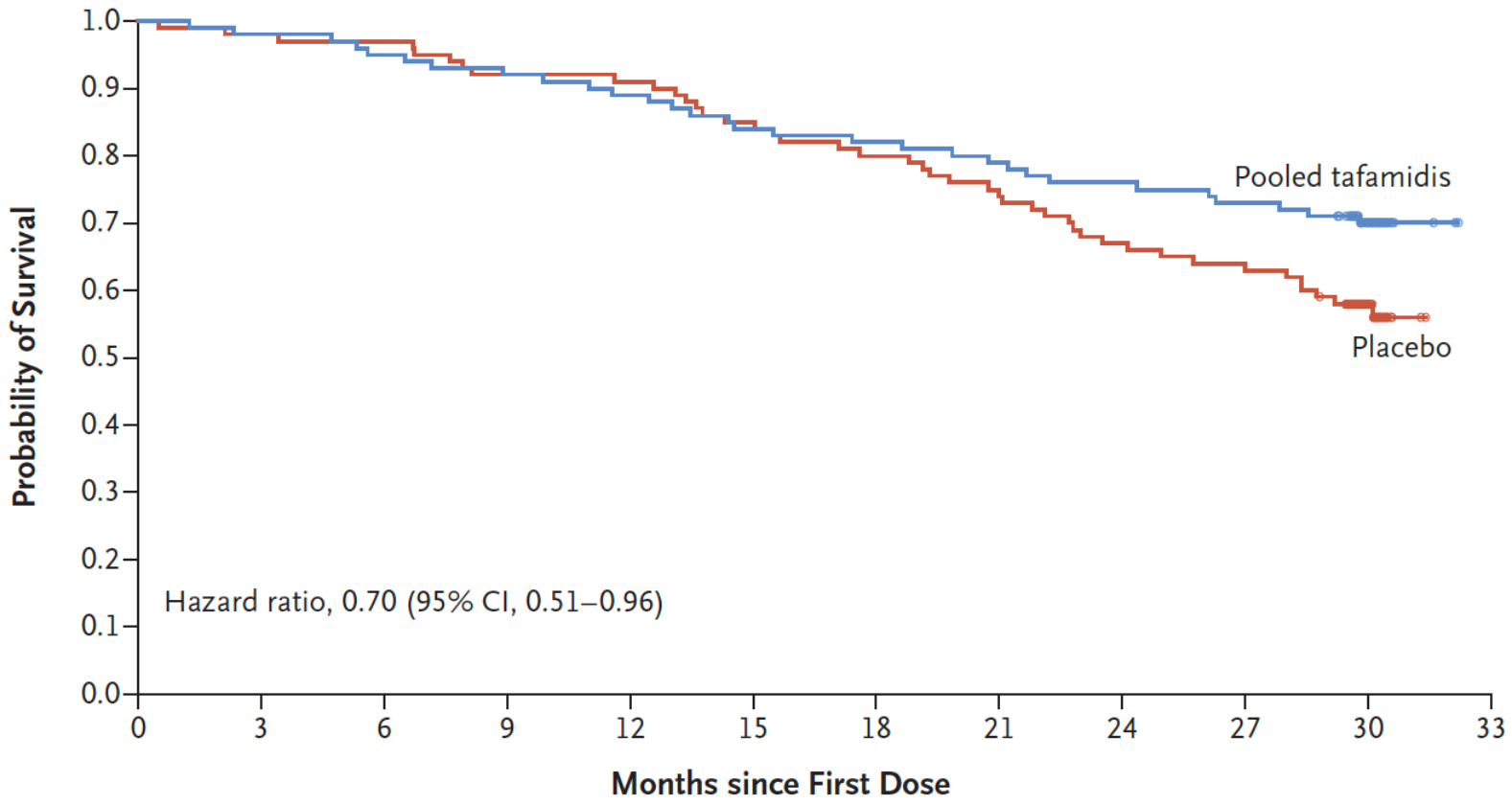
ESTABLISHED IN 1812 SEPTEMBER 13, 2018 VOL. 379 NO. 11

Tafamidis Treatment for Patients with Transthyretin Amyloid Cardiomyopathy

Mathew S. Maurer, M.D., Jeffrey H. Schwartz, Ph.D., Balarama Gundapaneni, M.S., Perry M. Elliott, M.D., Giampaolo Merlini, M.D., Ph.D., Marcia Waddington-Cruz, M.D., Arnt V. Kristen, M.D., Martha Grogan, M.D., Ronald Witteles, M.D., Thibaud Damy, M.D., Ph.D., Brian M. Drachman, M.D., Sanjiv J. Shah, M.D., Mazen Hanna, M.D., Daniel P. Judge, M.D., Alexandra I. Barsdorf, Ph.D., Peter Huber, R.Ph., Terrell A. Patterson, Ph.D., Steven Riley, Pharm.D., Ph.D., Jennifer Schumacher, Ph.D., Michelle Stewart, Ph.D., Marla B. Sultan, M.D., M.B.A., and Claudio Rapezzi, M.D., for the ATTR-ACT Study Investigators*

N Engl J Med 2018;379:1007-16.

B **Analysis of All-Cause Mortality**



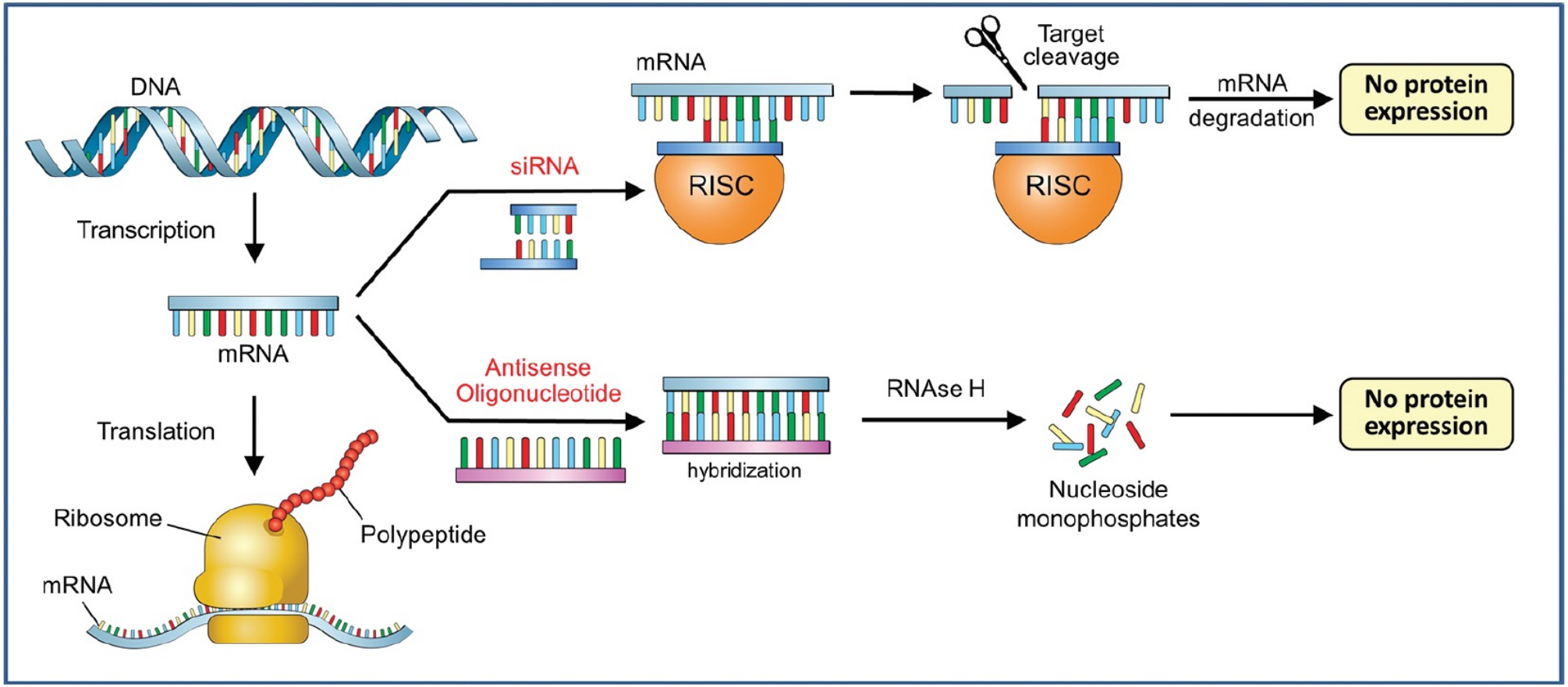
No. at Risk (cumulative no. of events)

Pooled tafamidis	264 (0)	259 (5)	252 (12)	244 (20)	235 (29)	222 (42)	216 (48)	209 (55)	200 (64)	193 (71)	99 (78)	0 (78)
Placebo	177 (0)	173 (4)	171 (6)	163 (14)	161 (16)	150 (27)	141 (36)	131 (46)	118 (59)	113 (64)	51 (75)	0 (76)

N Engl J Med 2018;379:1007-16

Amyloid heart disease: genetics translated into disease-modifying therapy

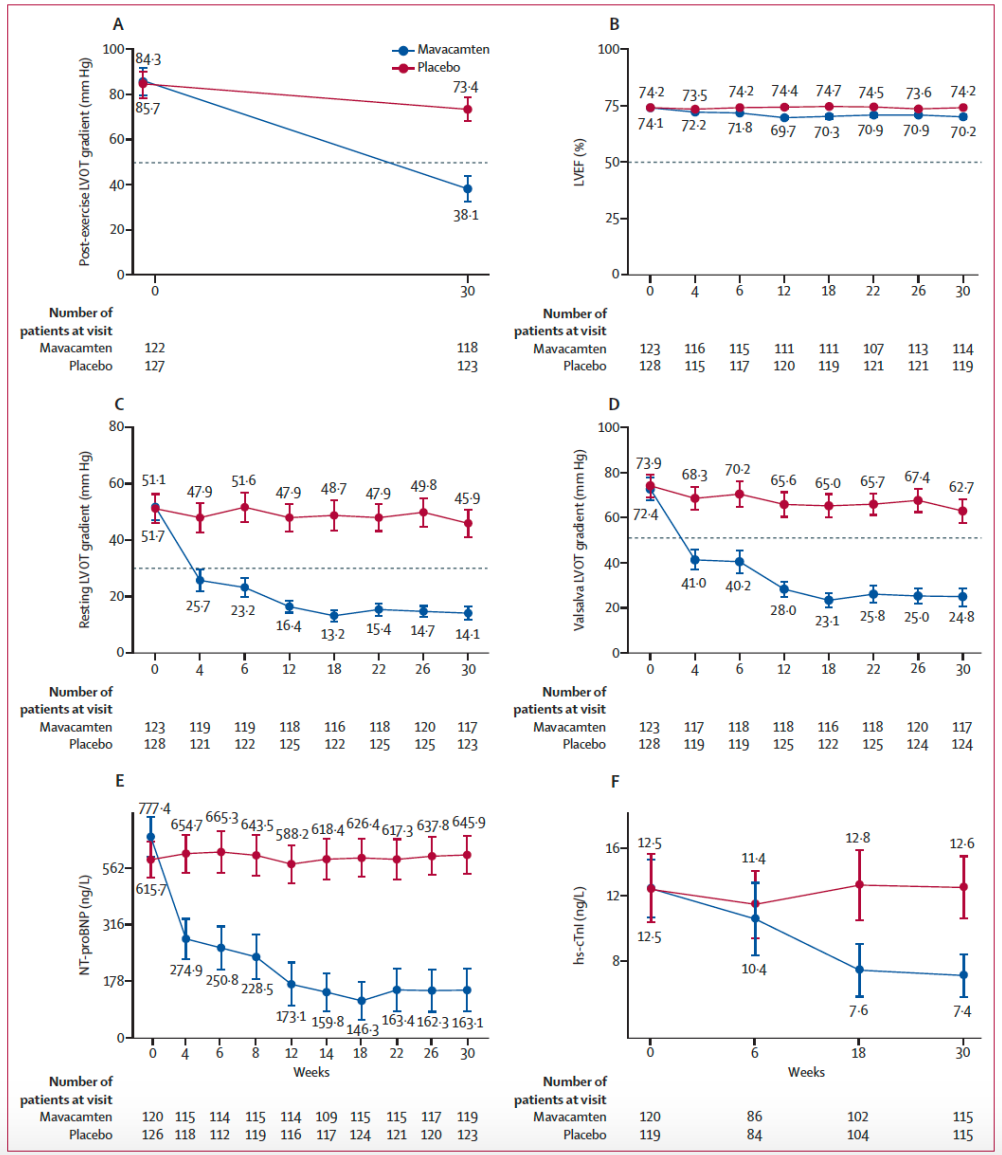
Brett W Sperry,[1] W. H. Wilson Tang[2,3]



Sperry BW, Tang WHW. Heart 2017;103:812–817.

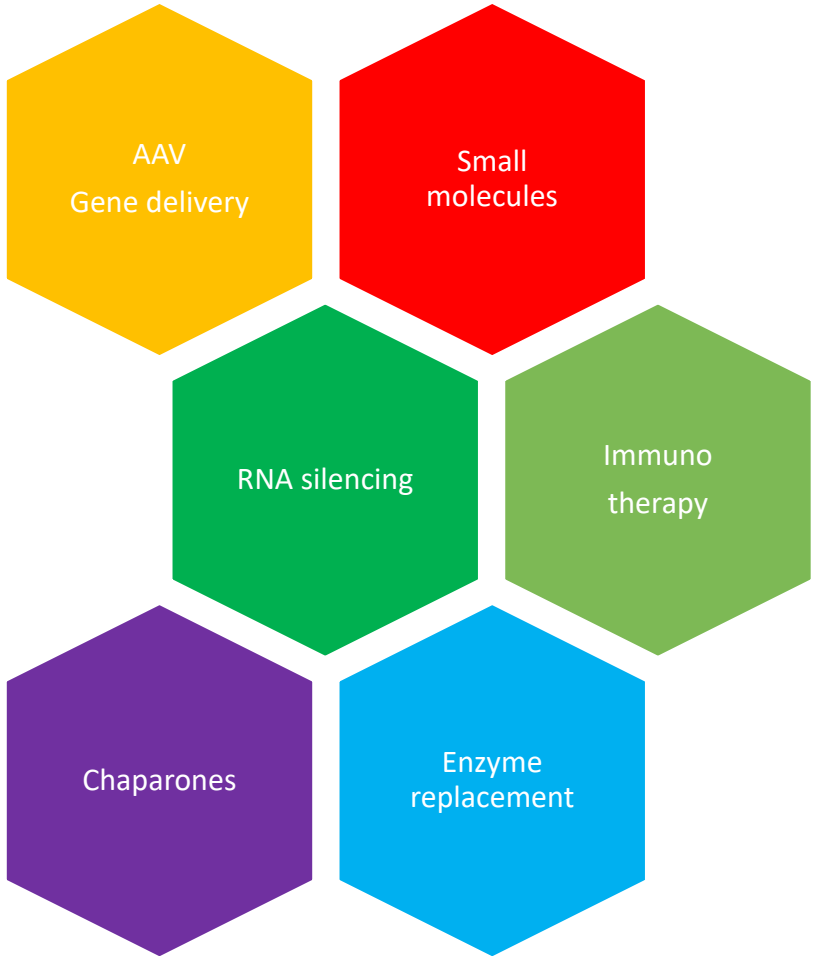
Mavacamten for treatment of symptomatic obstructive hypertrophic cardiomyopathy (EXPLORER-HCM): a randomised, double-blind, placebo-controlled, phase 3 trial

*Iacopo Olivotto, Artur Oreziak, Roberto Barriales-Villa, Theodore P Abraham, Ahmad Masri, Pablo Garcia-Pavia, Sara Saberi, Neal K Lakdawala, Matthew T Wheeler, Anjali Owens, Milos Kubanek, Wojciech Wojakowski, Morten K Jensen, Juan Gimeno-Blanes, Kia Afshar, Jonathan Myers, Sheila M Hegde, Scott D Solomon, Amy J Sehnert, David Zhang, Wanying Li, Mondira Bhattacharya, Jay M Edelberg, Cynthia Burstein Waldman, Steven J Lester, Andrew Wang, Carolyn Y Ho, Daniel Jacoby, on behalf of EXPLORER-HCM study investigators**

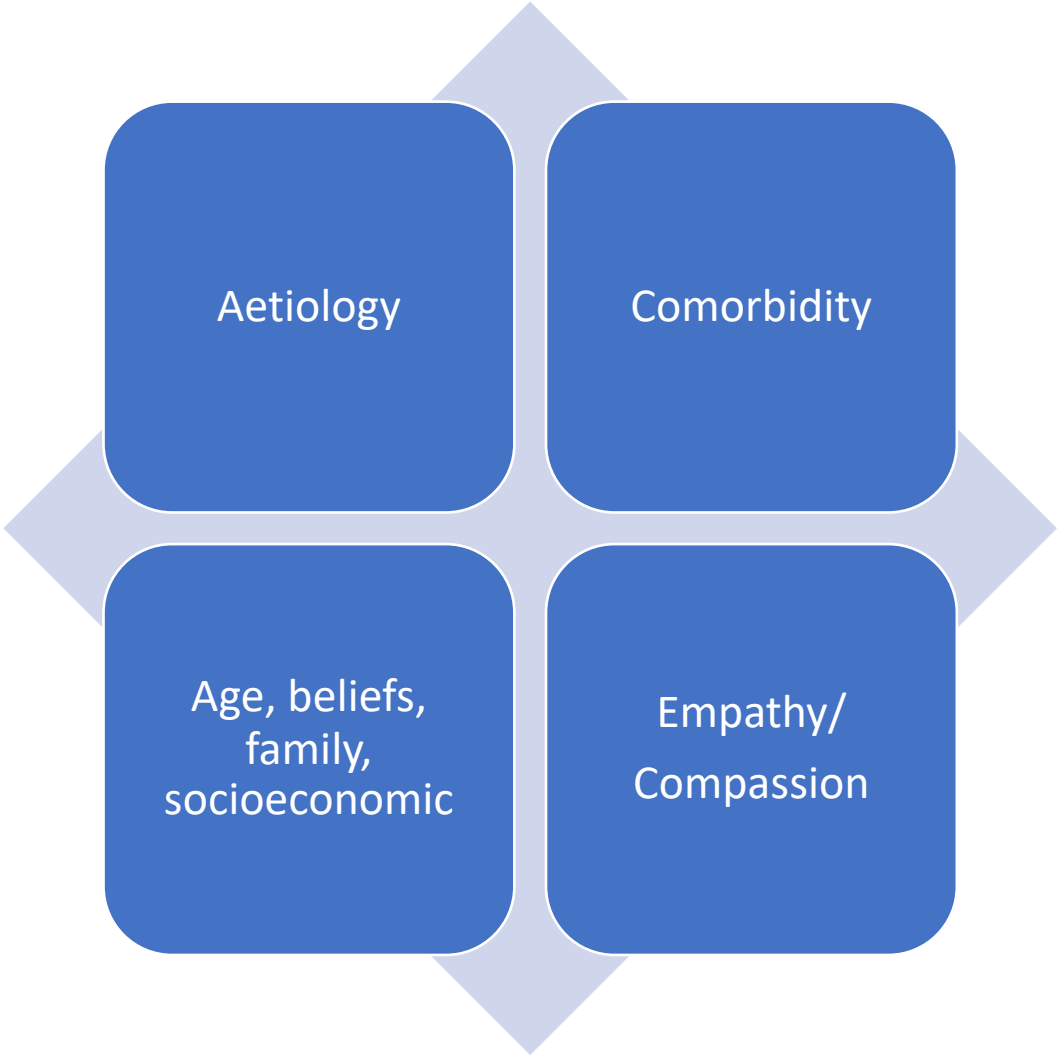


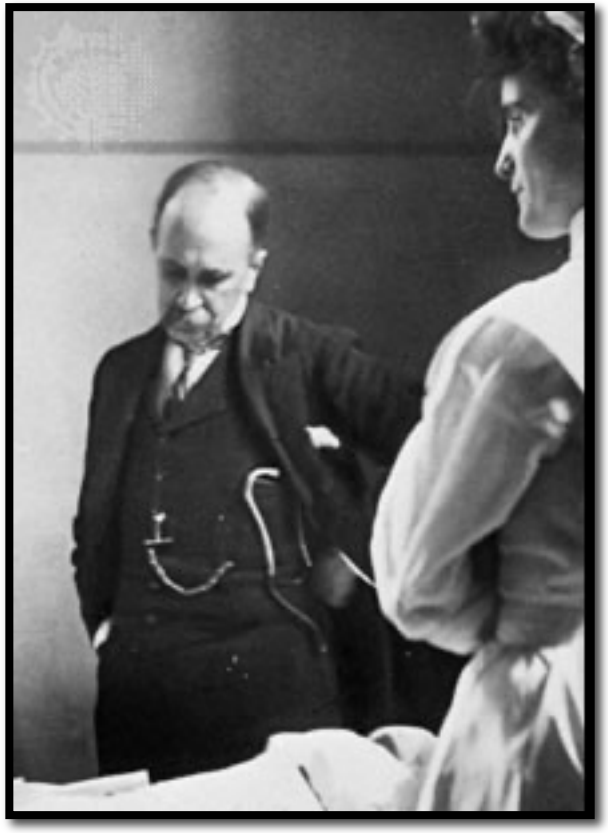
Frontiers: New Armoury

- ß-blockers
- RAAS inhibitors
- Statins
- Vasodilators
- Antiplatelets
- Anticoagulants
- Devices



Different Facets of Personal/Precision Medicine





“If it were not for the great variability among individuals, medicine might as well be a science and not an art”

Sir William Osler, 1892

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