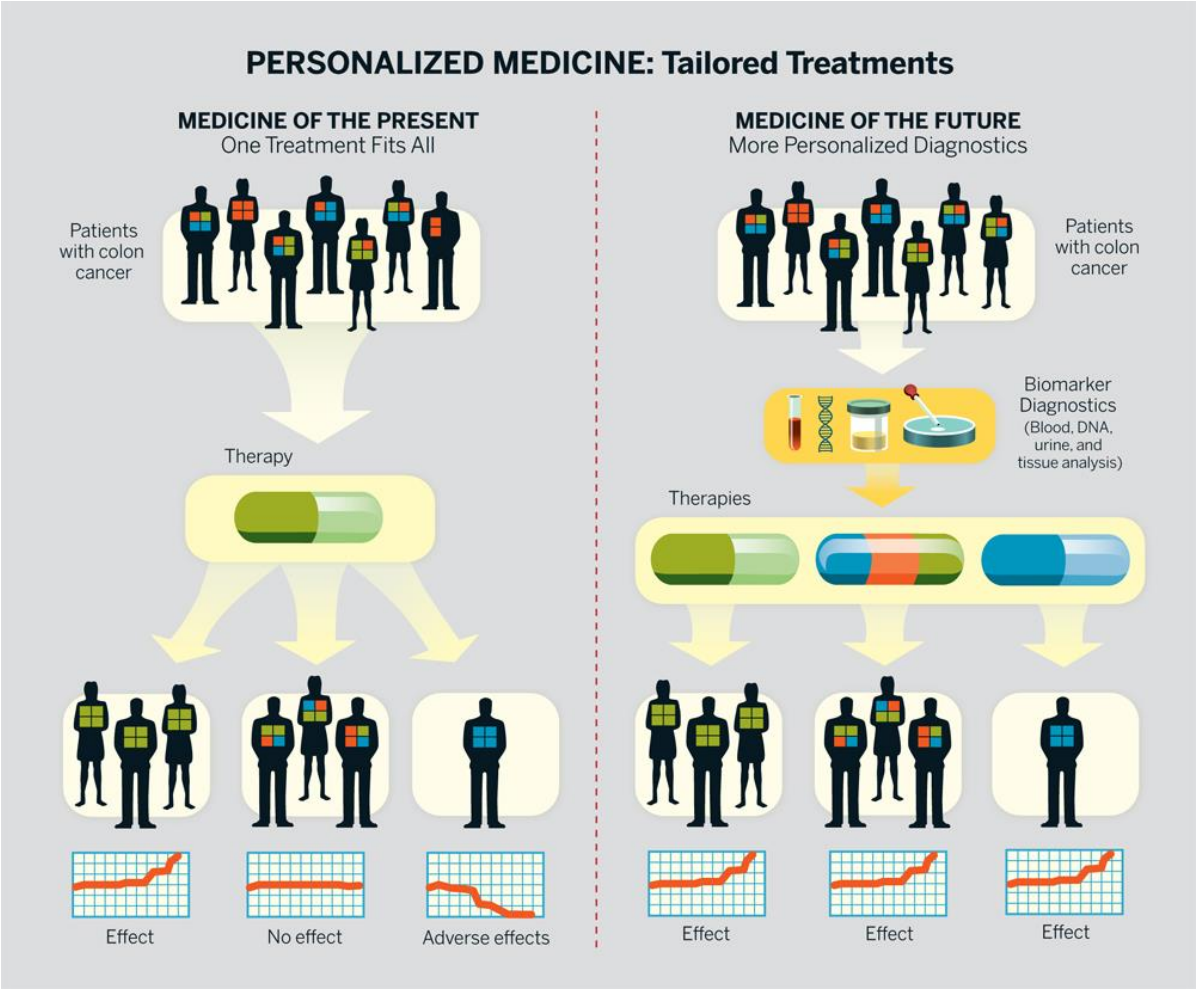
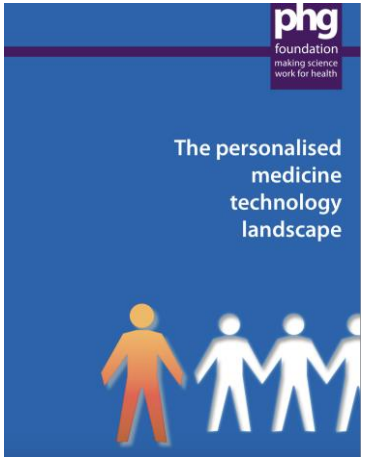
Personalised Medicine in Cardiovascular Disease

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."

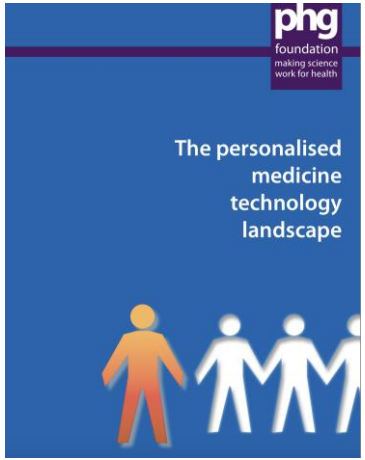
http://www.mrc.ac.uk/research/initiatives/stratified-medicine/


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

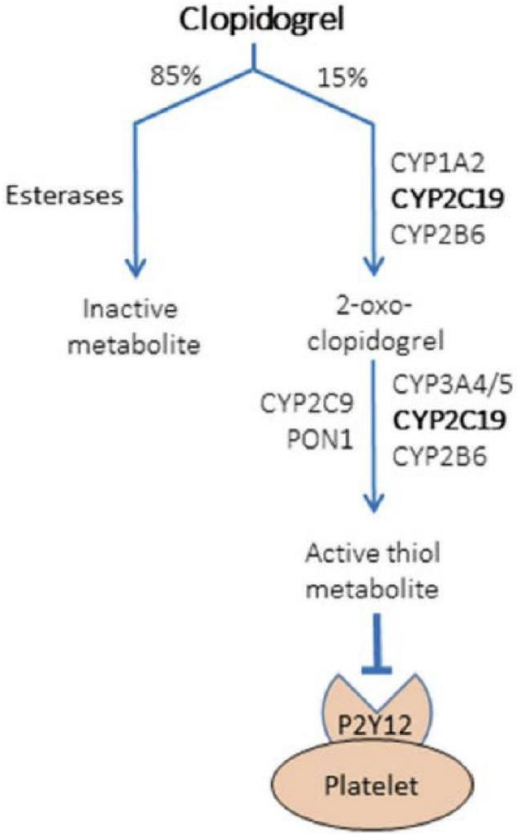


ctDNA*	→	Therapy selection in cancer	Genome editing /therapy†	→	Regenerative medicine applications
Pharmaco-genomics†	→	Genotype guided medicine optimisation	Stem cell therapy†	→	Regenerative medicine applications
Transcriptomics*	→	Gene expression based prognostics and therapy selection	3D imaging and printing*	→	Surgical planning and personalised implants
Pathogen Genomics*	→	WGS for disease outbreak detection and TB management	Machine learning†	→	Advanced image analysis through digital histopathology

AMERICAN COLLEGE of CARDIOLOGY

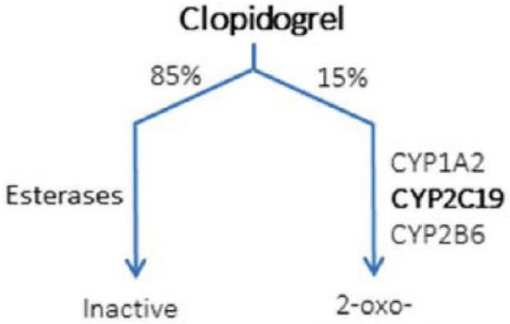
A Debate: Argument in Support of Personalized and Digital Medicine is the Answer

Nov 20, 2017 | Dr. Robert Roberts, MD, MACC



AHA: Gene Test Predicts Who Won't Benefit From Blood Thinner Plavix

By the American Heart Association



FDA (2017) Drug Label for Clopidogrel. Warning: Diminished Antiplatelet Effect in Patients with 2 Loss-of-Function Alleles of the *CYP2C19* Gene.

Phenotype	Recommendations
CYP2C19 poor metabolizer	Consider use of another platelet P2Y12 inhibitor in patients identified as CYP2C19 poor metabolizers

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

AMERICAN COLLEGE of CARDIOLOGY

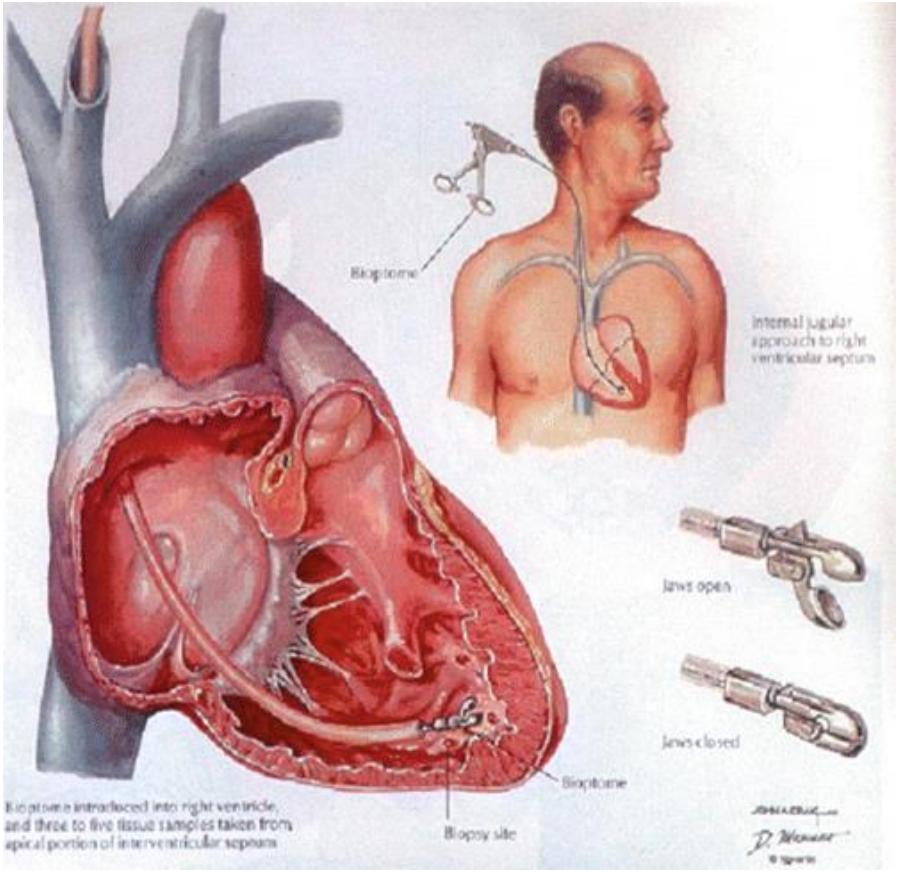
Precision Medicine: A Second Opinion

Nov 20, 2017 | Michael J Joyner, MD

Expert Analysis

the relative risks associated with a given variant are small, with values of 1.5 or less, and they explain a tiny fraction of the phenotypic variance.

…the oculogenomic rhyme is just starting?


Bioptome
Internal jugular approach to right ventricular septum
Jaws open
Jaws closed
Bioptome
Biopsy site
Bioptome introduced into right ventricle, and three to five tissue samples taken from apical portion of interventricular septum

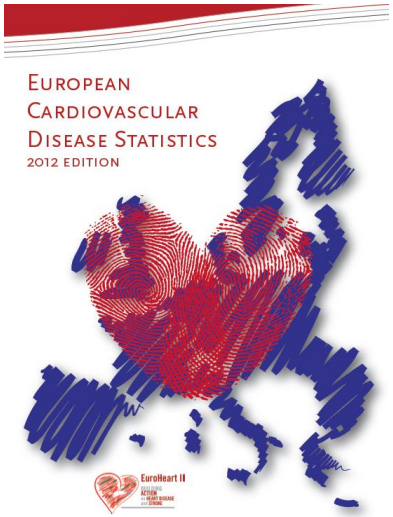


Figure 1.4a **Age-standardized death rates from CHD, men aged under 65, latest available year, Europe**

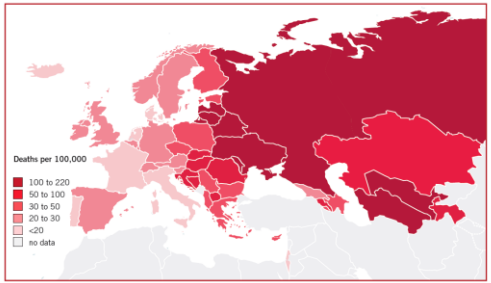
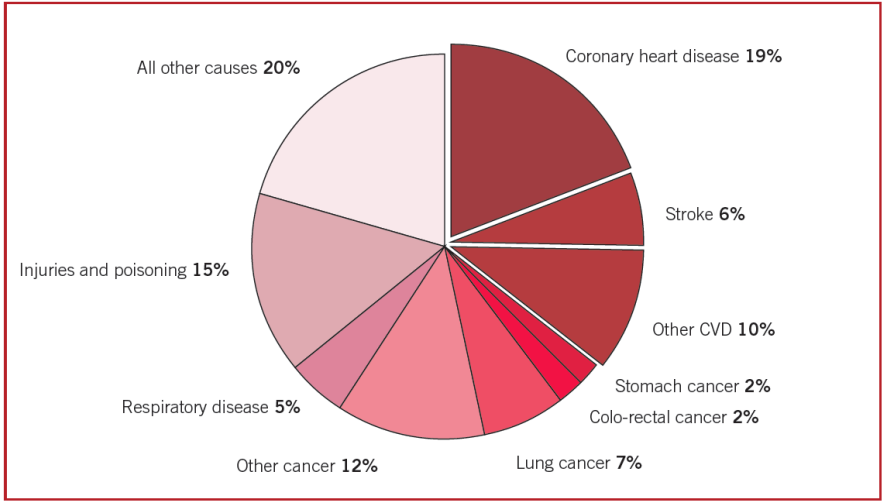


Figure 1.2a **Deaths under 75 by cause, men, latest available year, Europe**



Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): case-control study

*Salim Yusuf, Steven Hawken, Stephanie Ôunpuu, Tony Dans, Alvaro Avezum, Fernando Lanas, Matthew McQueen, Andrzej Budaj, Prem Pais, John Varigos, Liu Lisheng, on behalf of the INTERHEART Study Investigators**

9 risk factors accounted for 90% of the PAR in men and

94% in women.

Lancet 2004; 364: 937–52

Risk factor	Sex	Control (%)	Case (%)	Odds ratio (99% CI)	PAR (99% CI)
Current smoking	F	9·3	20·1	2·86 (2·36–3·48)	15·8% (12·9–19·3)
	M	33·0	53·1	3·05 (2·78–3·33)	44·0% (40·9–47·2)
Diabetes	F	7·9	25·5	4·26 (3·51–5·18)	19·1% (16·8–21·7)
	M	7·4	16·2	2·67 (2·36–3·02)	10·1% (8·9–11·4)
Hypertension	F	28·3	53·0	2·95 (2·57–3·39)	35·8% (32·1–39·6)
	M	19·7	34·6	2·32 (2·12–2·53)	19·5% (17·7–21·5)
Abdominal obesity	F	33·3	45·6	2·26 (1·90–2·68)	35·9% (28·9–43·6)
	M	33·3	46·5	2·24 (2·03–2·47)	32·1% (28·0–36·5)
Psychosocial index	F	–	–	3·49 (2·41–5·04)	40·0% (28·6–52·6)
	M	–	–	2·58 (2·11–3·14)	25·3% (18·2–34·0)
Fruits/veg	F	50·3	39·4	0·58 (0·48–0·71)	17·8% (12·9–24·1)
	M	39·6	34·7	0·74 (0·66–0·83)	10·3% (6·9–15·2)
Exercise	F	16·5	9·3	0·48 (0·39–0·59)	37·3% (26·1–50·0)
	M	20·3	15·8	0·77 (0·69–0·85)	22·9% (16·9–30·2)
Alcohol	F	11·2	6·3	0·41 (0·32–0·53)	46·9% (34·3–60·0)
	M	29·1	29·6	0·88 (0·81–0·96)	10·5% (6·1–17·5)
ApoB/ApoA1 ratio	F	14·1	27·0	4·42 (3·43–5·70)	52·1% (44·0–60·2)
	M	21·9	35·5	3·76 (3·23–4·38)	53·8% (48·3–59·2)

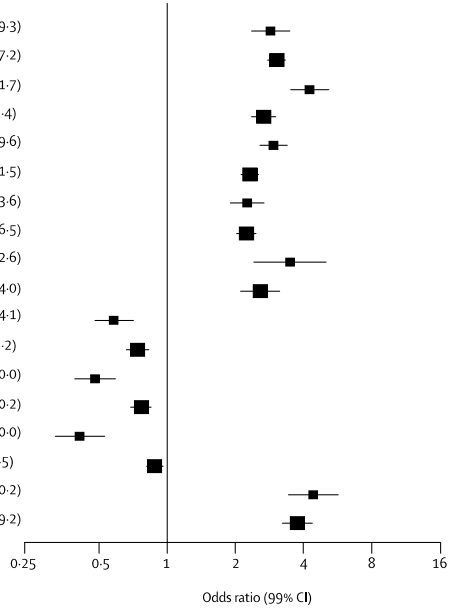
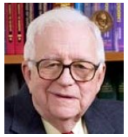


Figure 4: **Association of risk factors with acute myocardial infarction in men and women after adjustment for age, sex, and geographic region**
For this and subsequent figures, the odds ratios are plotted on a doubling scale. Prevalence cannot be calculated for psychosocial factors because it is derived from a model.



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

Impact

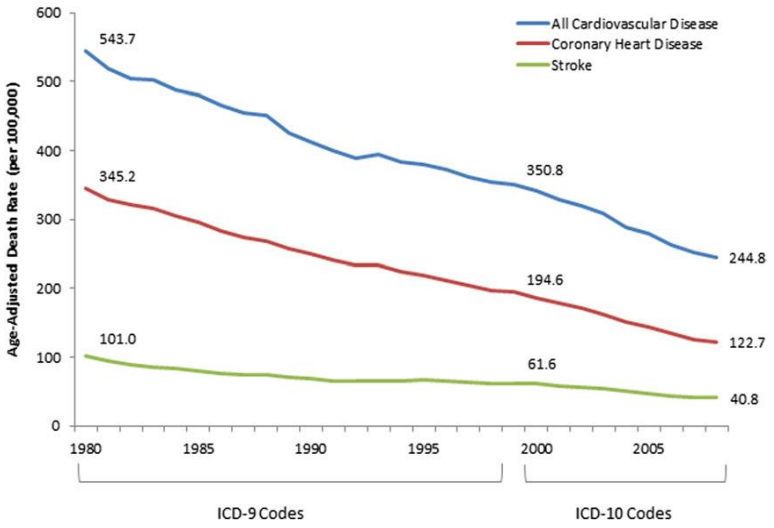
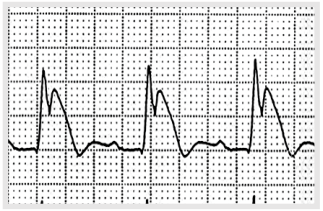
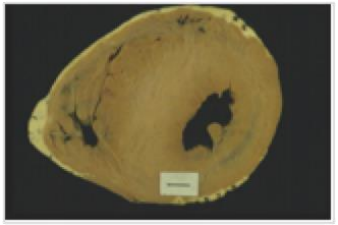


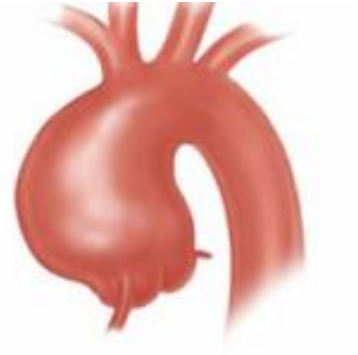
Figure 46 **Age-Adjusted Death Rates for Cardiovascular Disease, Coronary Heart Disease, and Stroke, 1980 to 2008**

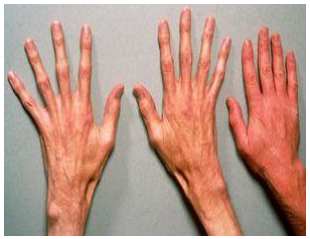
Blue line = all cardiovascular disease; **red line** = coronary heart disease; and **green line** = stroke. ICD = International Classification of Diseases. Source: National Institutes of Health, National Heart, Lung and Blood Institute. Morbidity and Mortality: 2012 Chart Book on Cardiovascular, Lung, and Blood Diseases. Available at: http://www.nhlbi.nih.gov/resources/docs/2012_ChartBook_508.pdf.

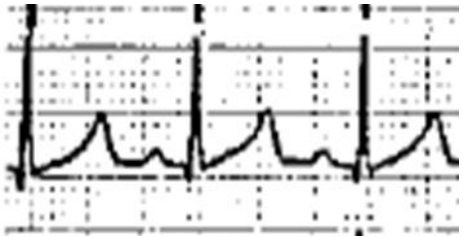
Spectrum of Genetic Disease

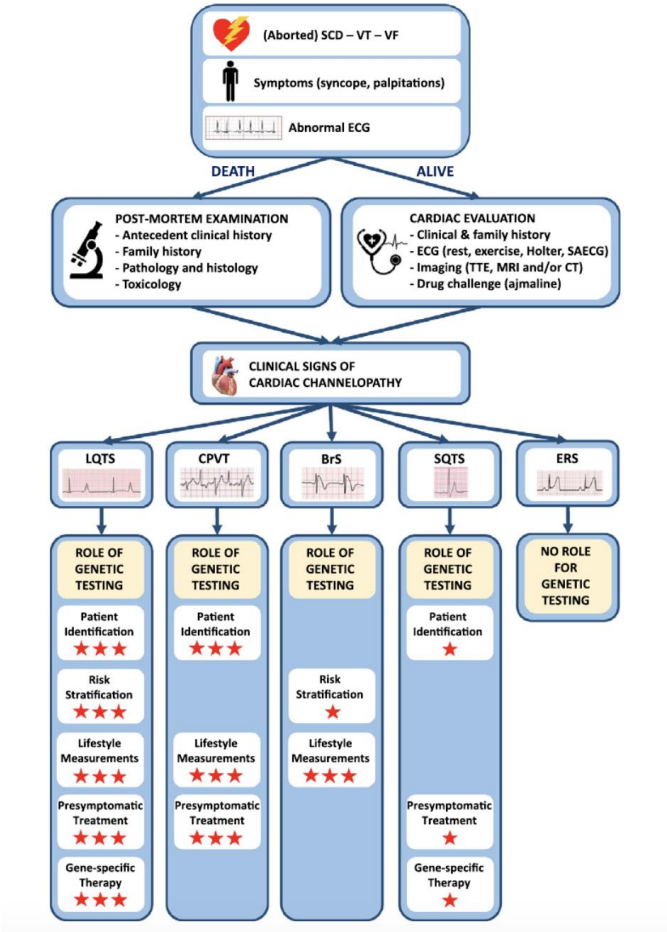












Inherited Arrhythmia Syndromes

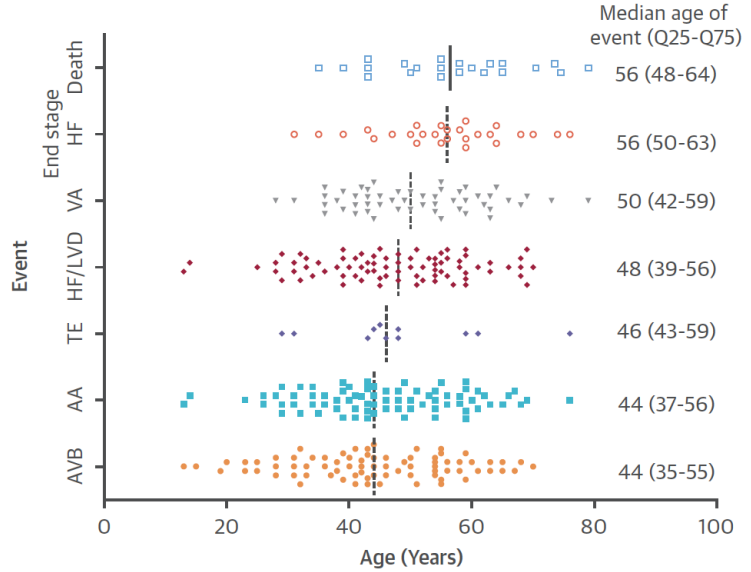
Wilde & Amin. International Journal of Cardiology 237 (2017) 53–55

Long-Term Arrhythmic and Nonarrhythmic Outcomes of Lamin A/C Mutation Carriers

Saurabh Kumar, BSc(Med)/MBBS, PhD,[a] Samuel H. Baldinger, MD,[b] Estelle Gandjbakhch, MD, PhD,[c] Philippe Maury, MD,[d] Jean-Marc Sellal, MD,[e,f,g,h] Alexander F.A. Androulakis, MD,[i] Xavier Waintraub, MD,[c] Philippe Charron, PhD,[c,j,k] Anne Rollin, MD,[d] Pascale Richard, PhD,[l] William G. Stevenson, MD,[a] Ciorsti J. Macintyre, MD,[a] Carolyn Y. Ho, MD,[a] Tina Thompson, RN,[m] Jitendra K. Vohra, MD,[n] Jonathan M. Kalman, MBBS, PhD,[n] Katja Zeppenfeld, MD,[i] Frederic Sacher, MD,[e,f,g] Usha B. Tedrow, MD, MSc,[a] Neal K. Lakdawala, MD[a]

122 patients with LMNA mutations from 87 families; genetic diagnosis 1998-2015:

FIGURE 1 Clinical Events



The median age at which clinical events occurred demonstrated a stepwise increment as disease intensified. AA = atrial arrhythmia; AVB = atrioventricular block; HF = heart failure; LVD = left ventricular dysfunction; TE = thromboembolism; VA = ventricular arrhythmia.

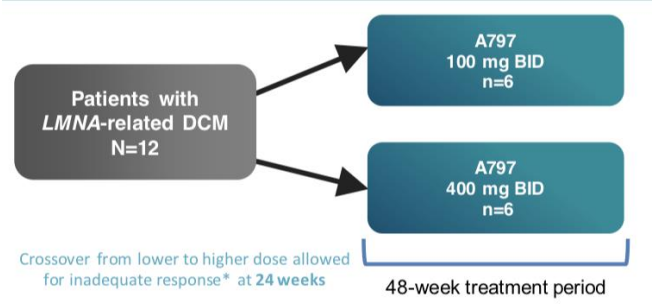
J Am Coll Cardiol 2016;68:2299–3

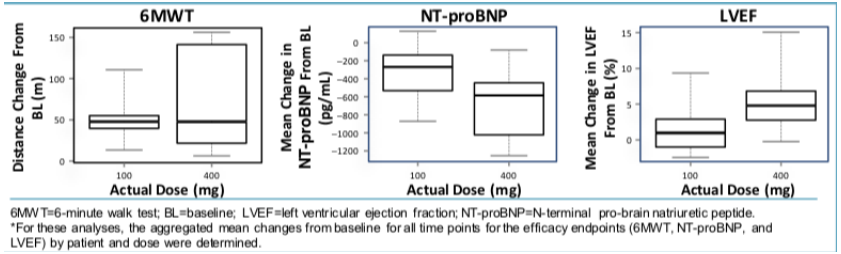
P4981

European Society of Cardiology Congress August 27–31, 2016 Rome, Italy

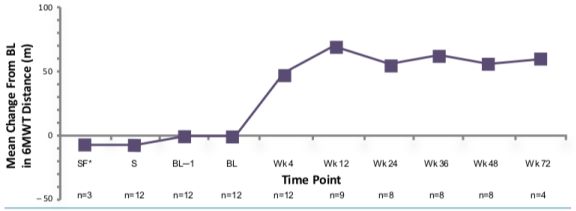
Phase 2 Study of A797, an Oral, Selective p38 Mitogen-Activated Protein Kinase Inhibitor, in Patients With *Lamin A/C*–Related Dilated Cardiomyopathy

Calum A. MacRae,[1] Matthew R. G. Taylor,[2] Luisa Mestroni,[2] John R. Moses,[3] Euan A. Ashley,[4] Matthew T. Wheeler,[4] Neal K. Lakdawala,[1] Ray E. Hershberger,[5] Mieke Ptaszynski,[6] Victor Sandor,[6] Michael E. Saunders,[6] Colleen Oliver,[6] Patrice A. Lee,[6] Daniel P. Judge[7]

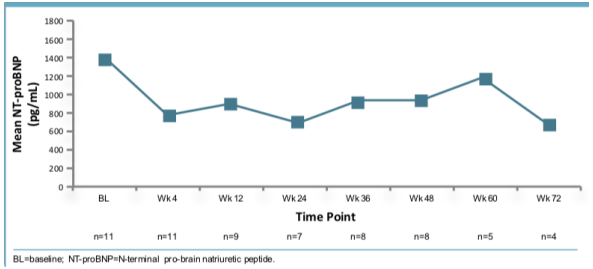




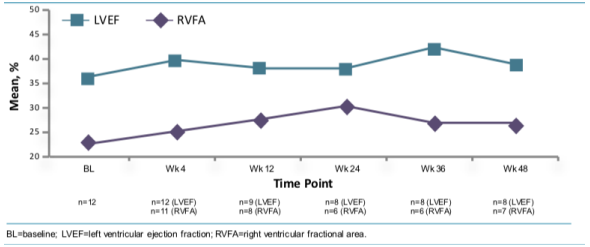
6MWT=6-minute walk test; BL=baseline; LVEF=left ventricular ejection fraction; NT-proBNP=N-terminal pro-brain natriuretic peptide.
*For these analyses, the aggregated mean changes from baseline for all time points for the efficacy endpoints (6MWT, NT-proBNP, and LVEF) by patient and dose were determined.



6MWT=6-minute walk test; BL=baseline; BL–1=day –1 (1 day before BL); S=screening; SF=screen fail.
*3 patients who failed screening were allowed to rescreen for this study. Their data are represented above in the "SF" group.

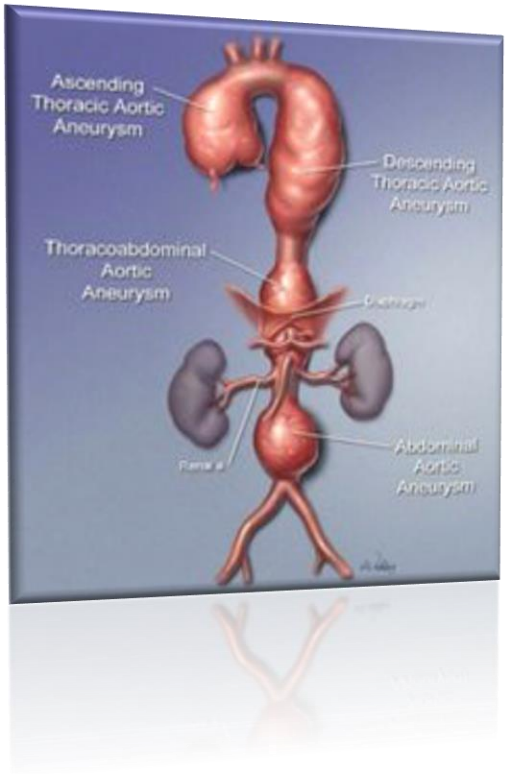


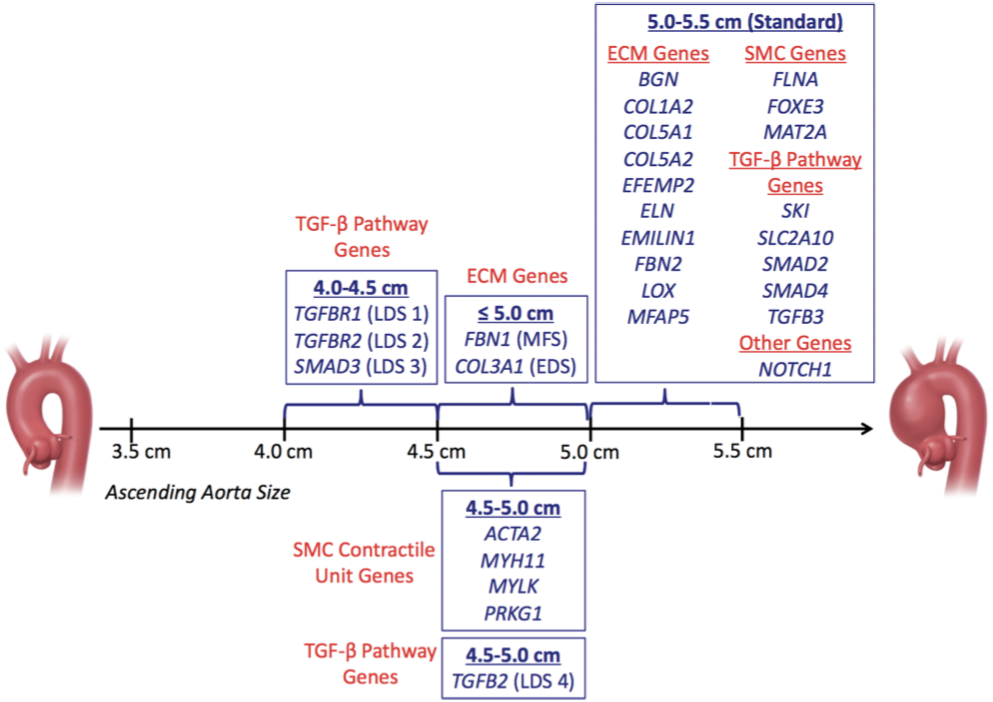
BL=baseline; NT-proBNP=N-terminal pro-brain natriuretic peptide.



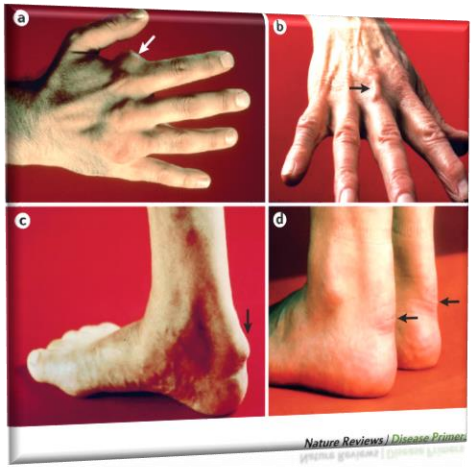
BL=baseline; LVEF=left ventricular ejection fraction; RVFA=right ventricular fractional area.

ARRAY

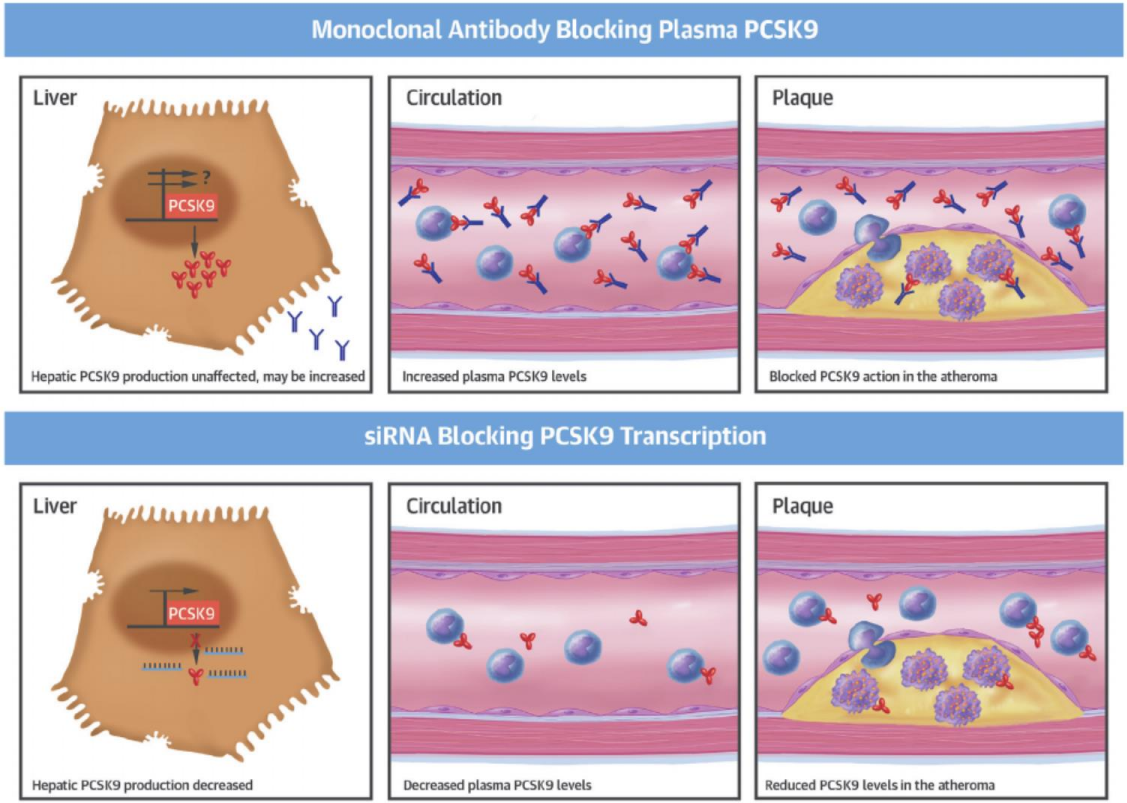




AORTA, February 2017, Volume 5, Is



Defesche, J. C. *et al.* (2017) Familial hypercholesterolaemia
Nat. Rev. Dis. Primers doi:10.1038/nrdp.2017.93



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

ESC GUIDELINES

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

HEART FAILURE

HF is a clinical syndrome characterized by typical symptoms (e.g. breathlessness, ankle swelling and fatigue) that may be accompanied by signs (e.g. elevated jugular venous pressure, pulmonary crackles and peripheral oedema) caused by a structural and/or functional cardiac abnormality, resulting in a reduced cardiac output and/or elevated intracardiac pressures at rest or during stress

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).

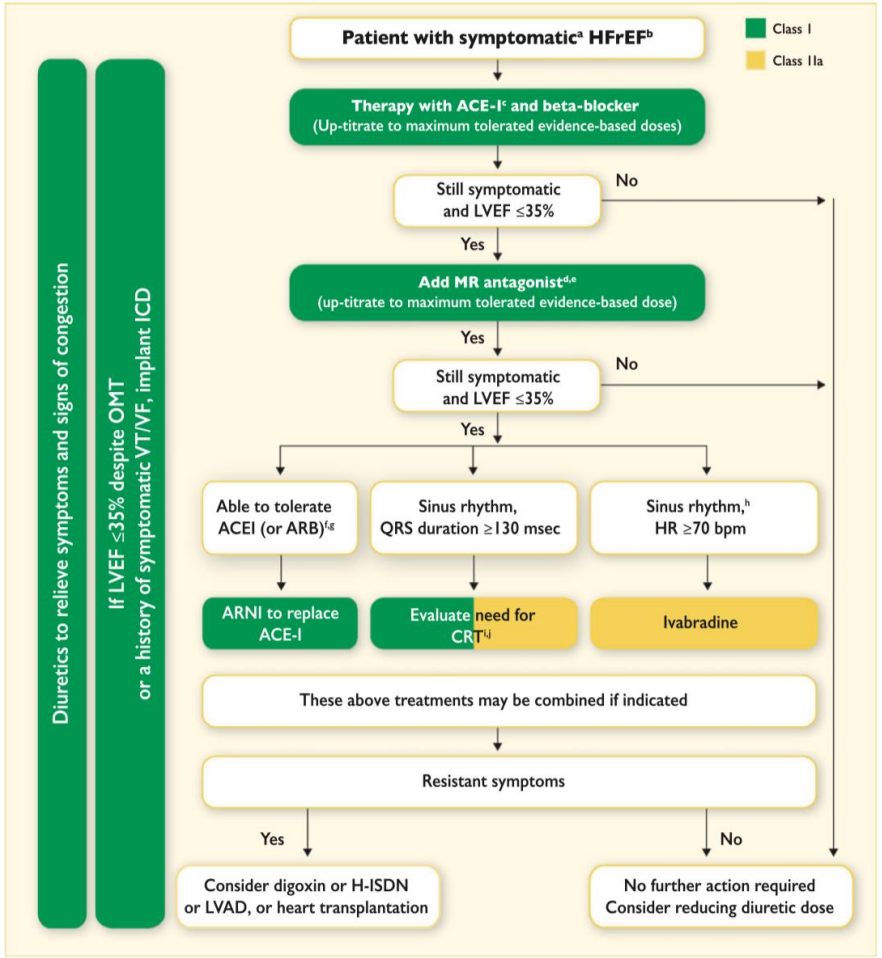
European Heart Journal (2016) **37**, 2129–2200
doi:10.1093/eurheartj/ehw128

ESC GUIDELINES

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



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

ESC GUIDELINES

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

Where is all the cardiomyopathy?

- In clinical practice, a clear distinction between acquired and inherited cardiomyopathies remains challenging.

- In most patients with a definite clinical diagnosis of HF, there is no confirmatory role for routine genetic testing...

Case One

- Male age 49 years
- DCM in 2016 breathlessness, tiredness

PMH:

- bilateral operation for varicose veins in both legs
- Spinal fusion surgery 2015

Social history

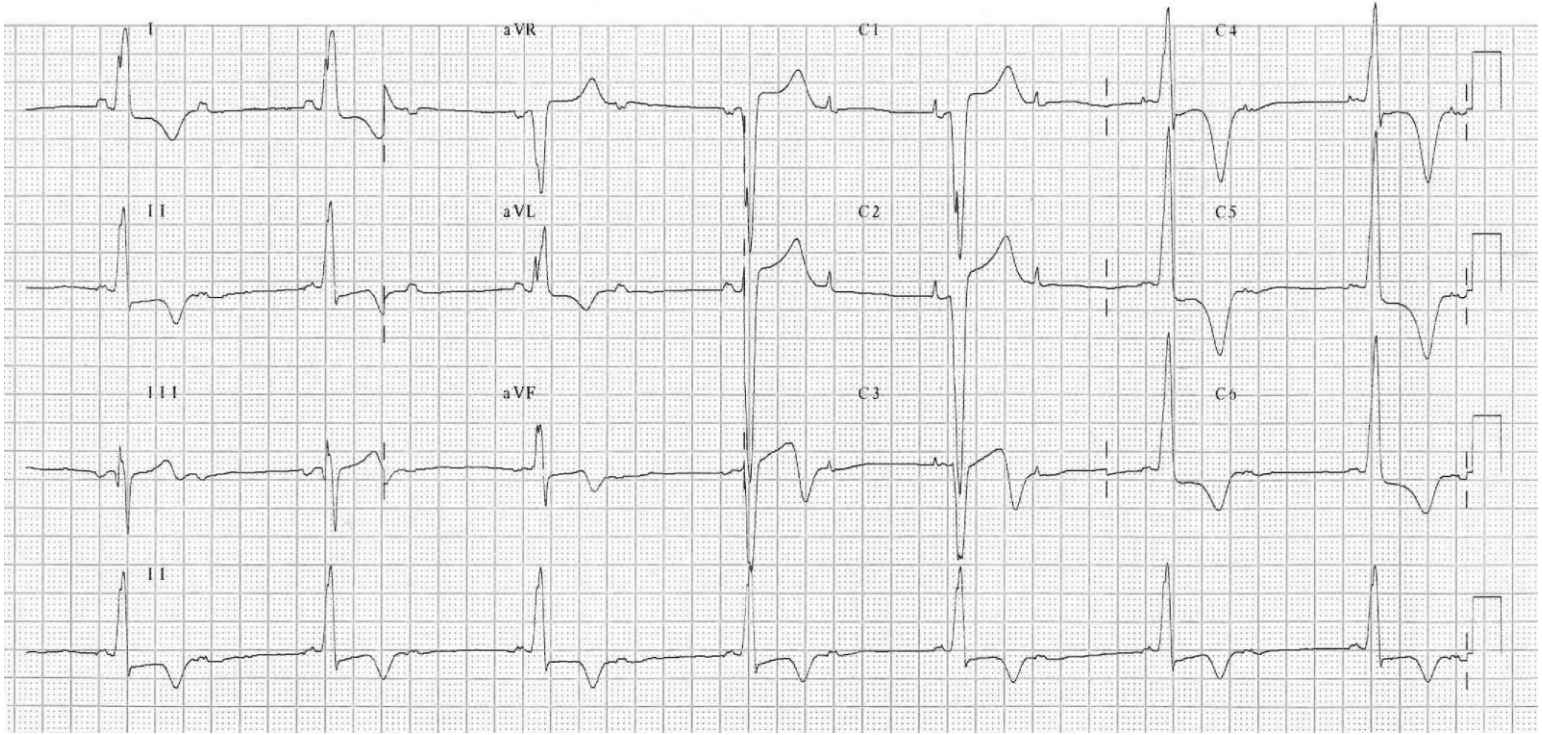
- Chef, drinks 1 beer after work, 1 bottle of wine+2 beers during the weekend
- Ex-smoker (15 years)

Investigations

- Echo/CMR: Dilated LV, EF 35%, myocardial scar
- Holter: 13337 PVCs, 320 couplets, 6 triplets, 1 SVT 5 beats

Case Two

- 38 year old woman
- Hypertension
- Presented with cellulitis in UK and then referred on to cardiology due to low heart rate
- Tubal ligation in India abandoned after 2:1 heart block
- Asymptomatic – no syncope or shortness of breath
- Ramipril 5mg, Amlodipine 5mg
- Systems enquiry unremarkable. Routine bloods normal.


I
aVR
C1
C4
I I
aVL
C2
C5
I I I
aVF
C3
C6
I I

Case 3

49y Afro-Caribbean male

Past Medical History

- Alpha Thalassaemia Trait

Family history

- Nil

Social history

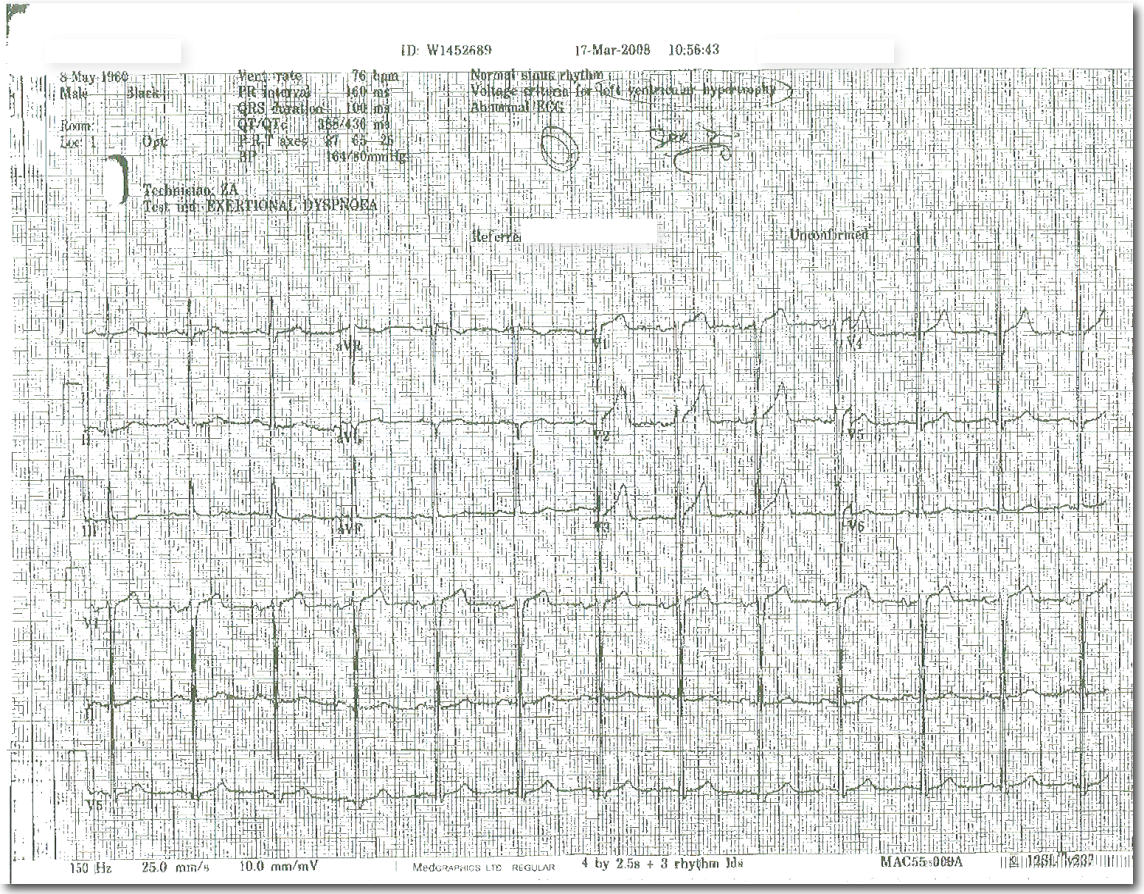
- Ex-smoker of 40 cigarettes per day up to 2002
- Up to 8 Units per night up to 5 years ago

Case 3

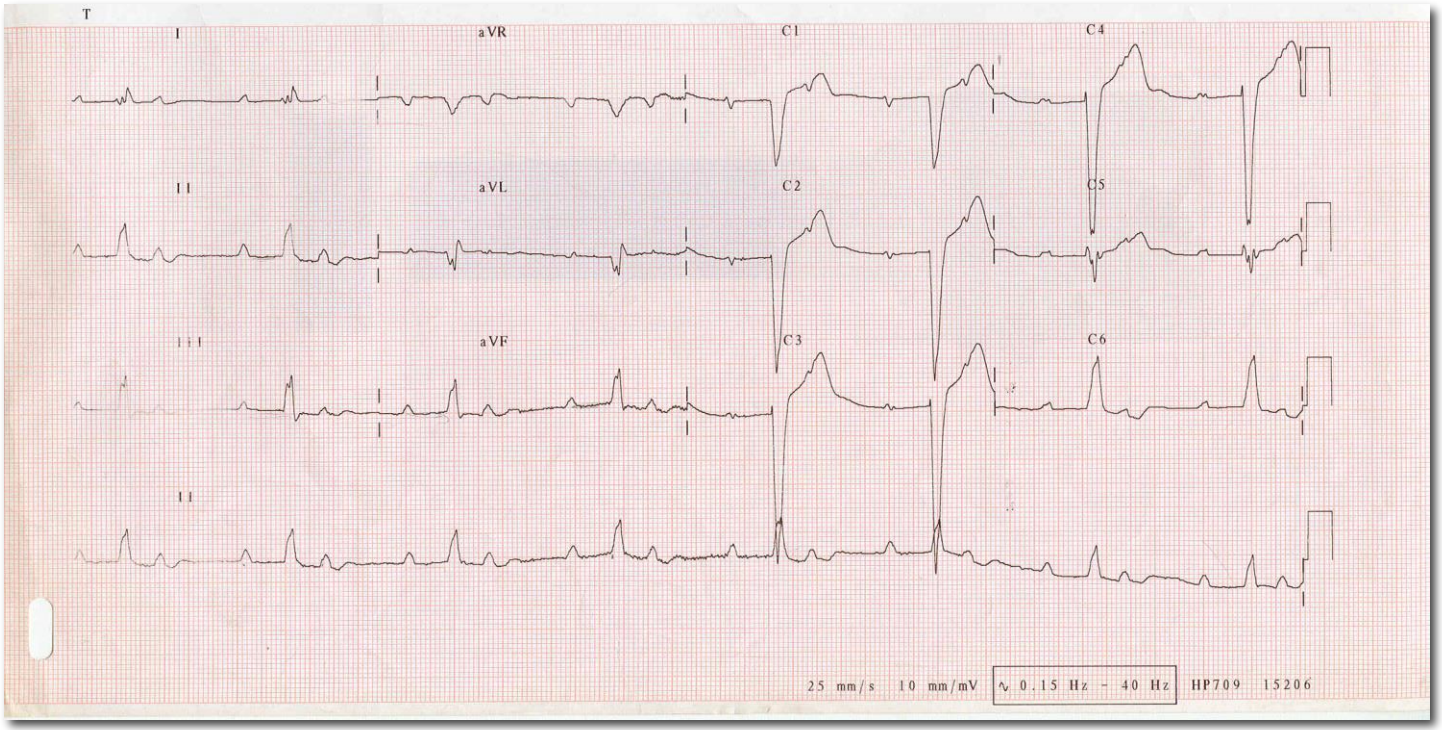
March 2008: Investigated for dyspnoea

Diagnosis:

- Hypertension
- Asthma



Case



October 2008:

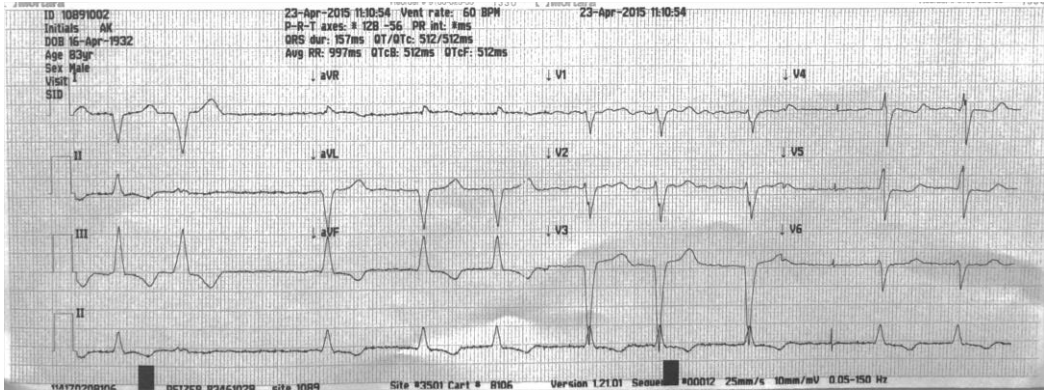
Presented to A&E following an episode of syncope

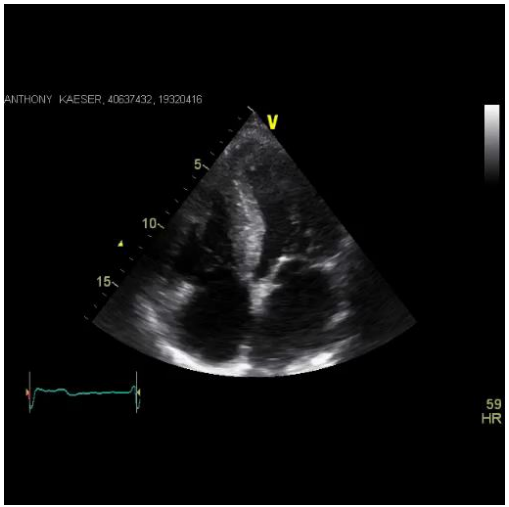
Case 4:

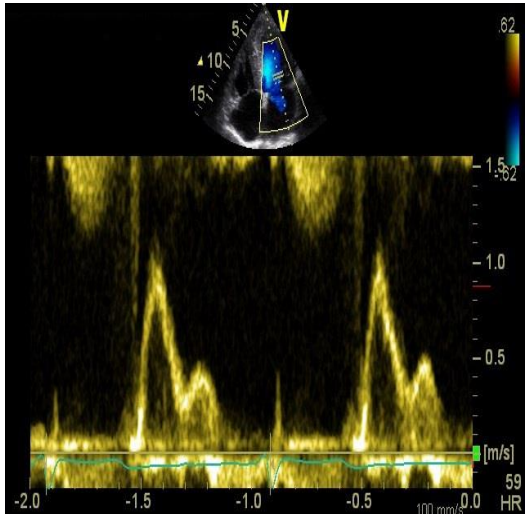
72 year old male

Previous CABG & AVR

New onset AF







Management

CASE ONE (DCM)

- Ramipril 5 mg bd, bisoprolol 3.75 mg, spironolactone 25 mg, furosemide 40 mg

CASE TWO (HCM, AV block)

Pacemaker

CASE THREE (normal LV, AV block)

Pacemaker

CASE FOUR (AF, mild LVH, diastolic dysfunction)

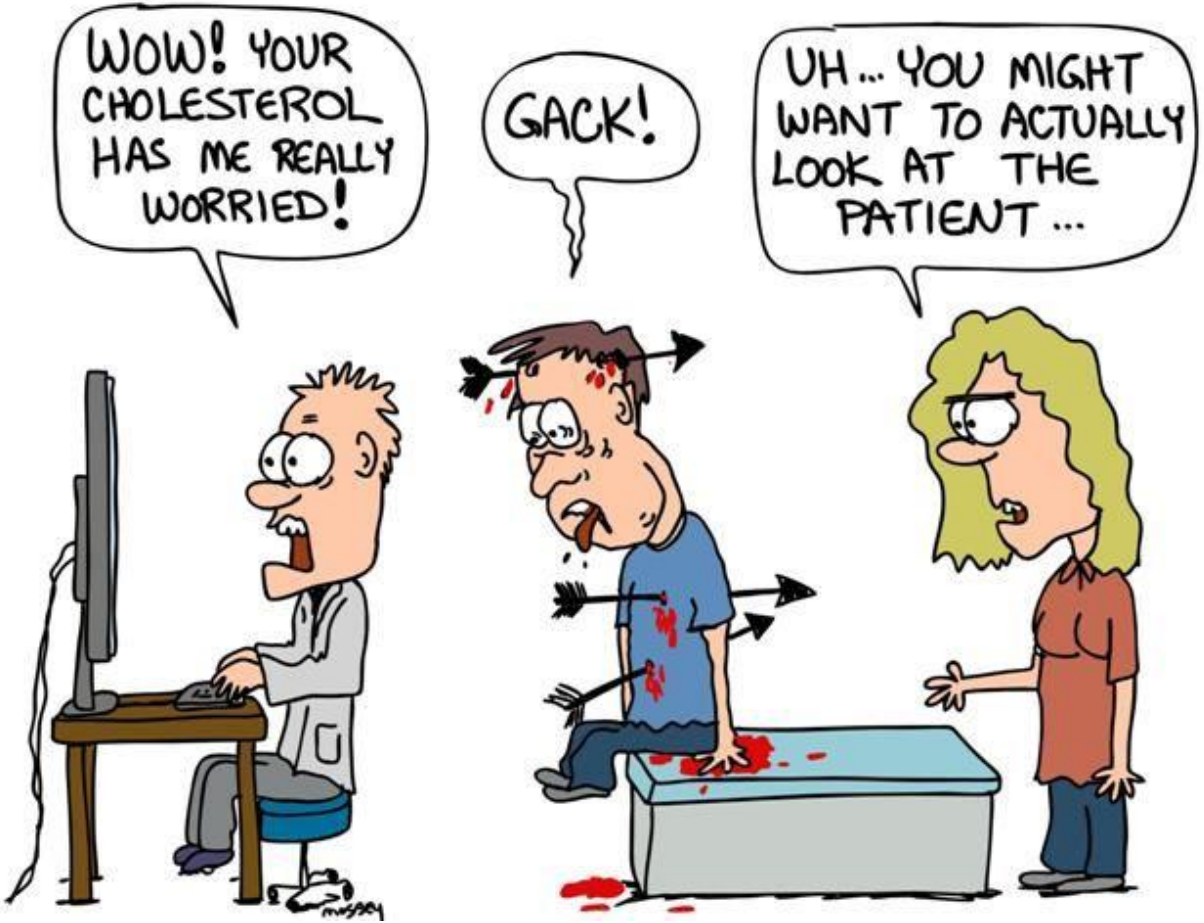
HFPeF: DCCV, Anticoagulate, Manage risk factors

ESC Guidelines

Anti-intellectualism in Clinical Cardiovascular Medicine

… concern with understanding clinical syndromes has been replaced by formulae for their treatment.

J Cohn. Journal of Cardiac Failure Vol. 6 No. 4 2000


WOW! YOUR CHOLESTEROL HAS ME REALLY WORRIED!
GACK!
UH... YOU MIGHT WANT TO ACTUALLY LOOK AT THE PATIENT...

Clinical Cardiology:

Heart Failure

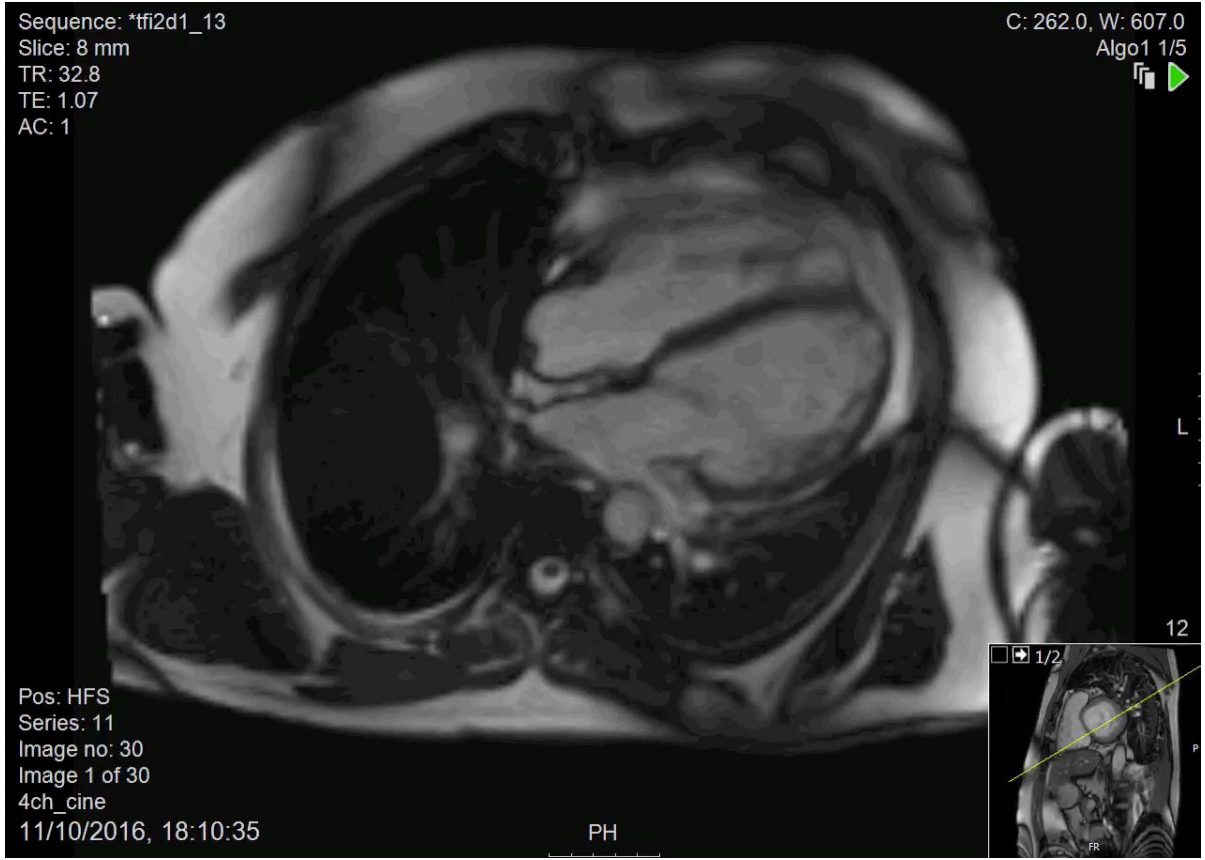
Atherosclerosis

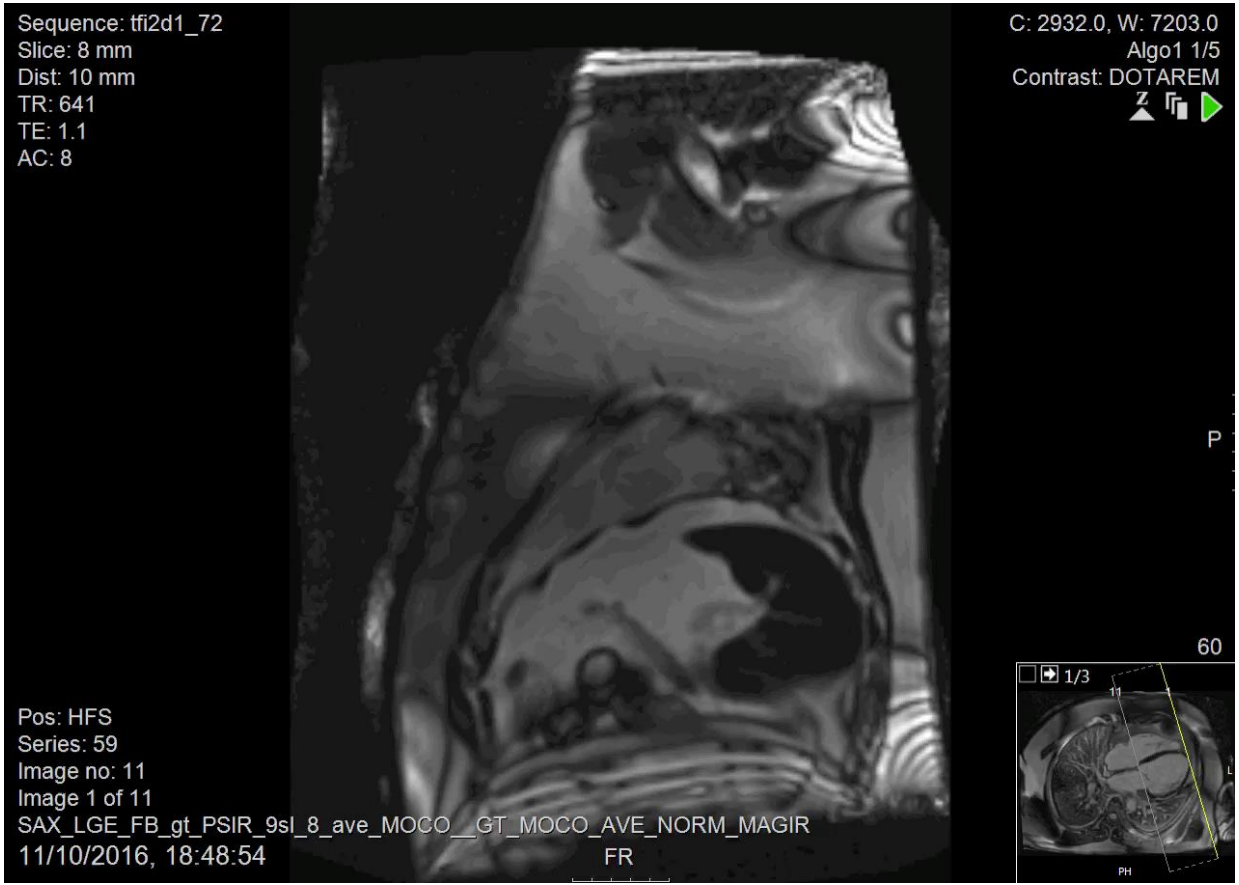
Atrial Fibrillation

What about the cases?

Case 1

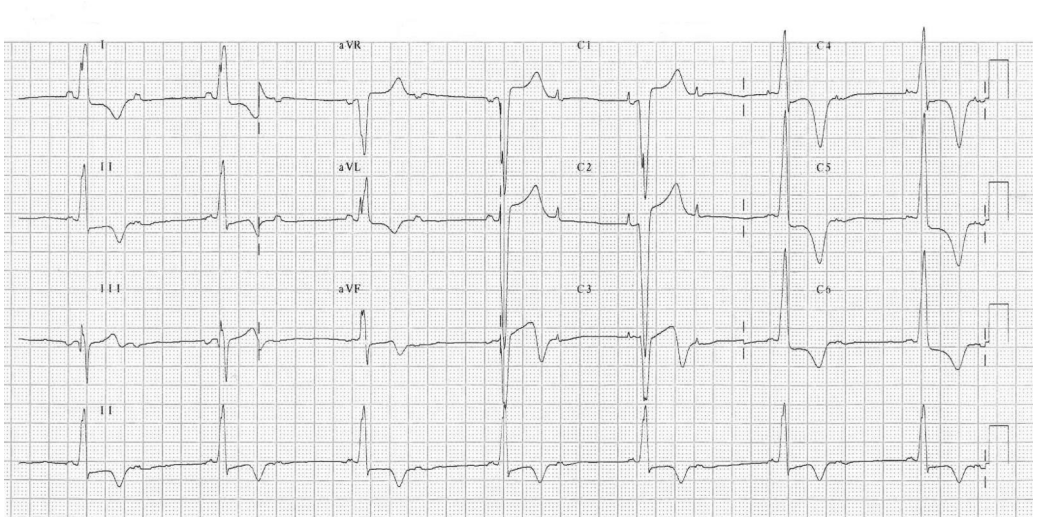
First days of November 2016 collapsed while walking in Paris-chest compressions from a bystander->ICD implantation.

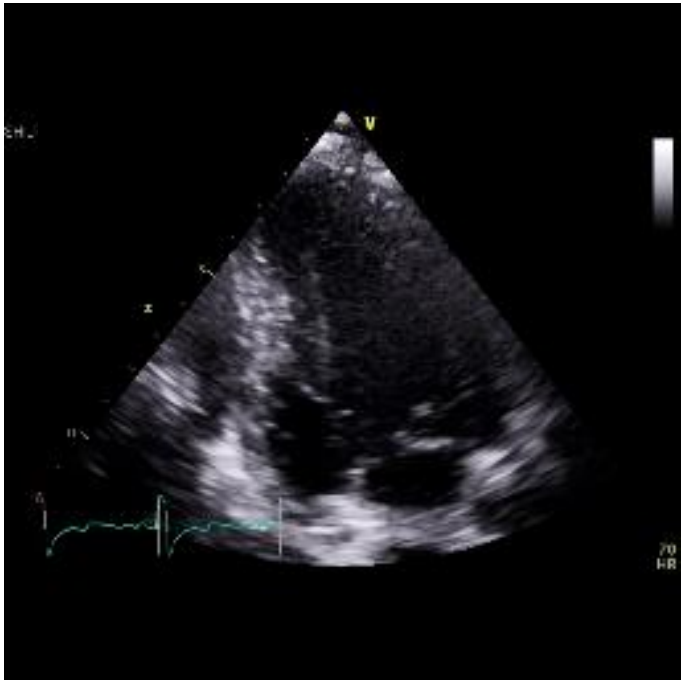

Sequence: *tfi2d1_13
Slice: 8 mm
TR: 32.8
TE: 1.07
AC: 1
C: 262.0, W: 607.0
Algo1 1/5
L
12
1/2
P
FR
Pos: HFS
Series: 11
Image no: 30
Image 1 of 30
4ch_cine
11/10/2016, 18:10:35
PH



DCM
Ventricular ectopy
Posterior wall scar

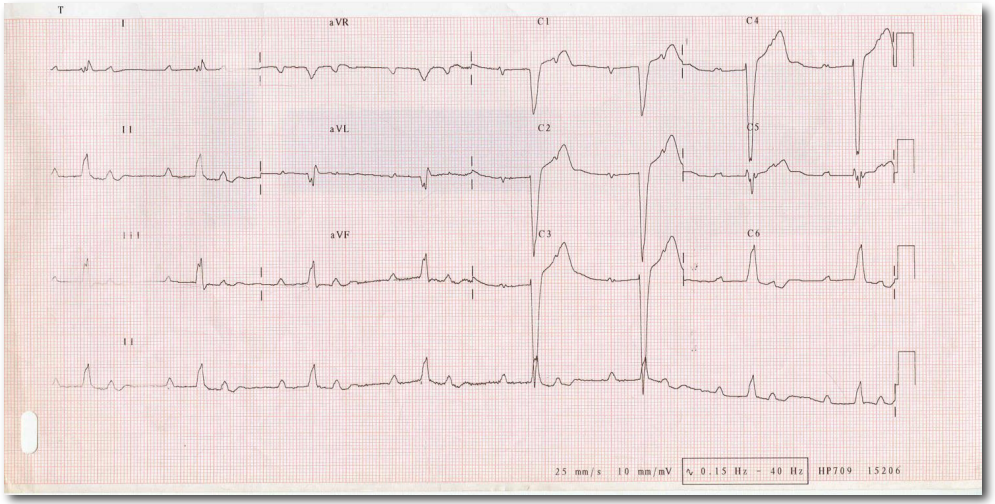
DSG2 mutation

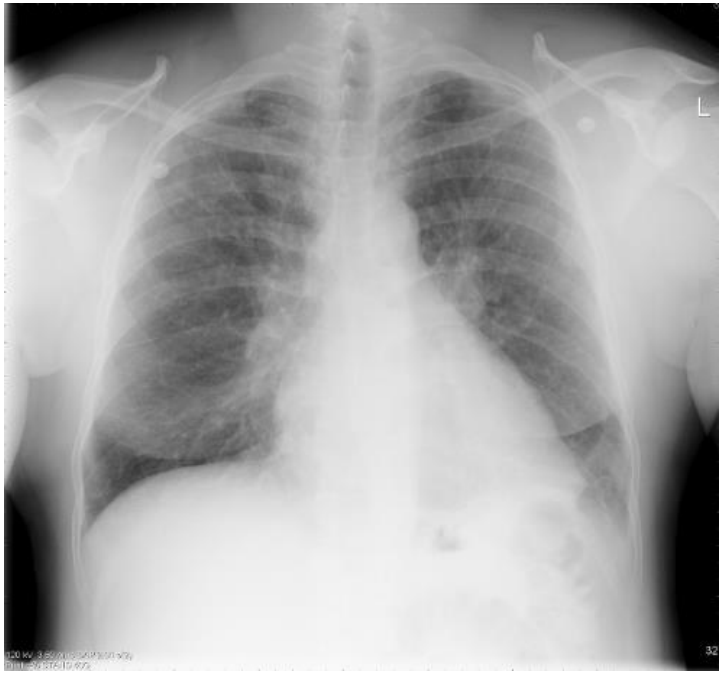




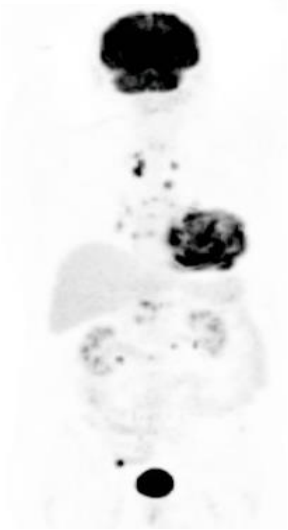
HCM, conduction disease, pre-excitation

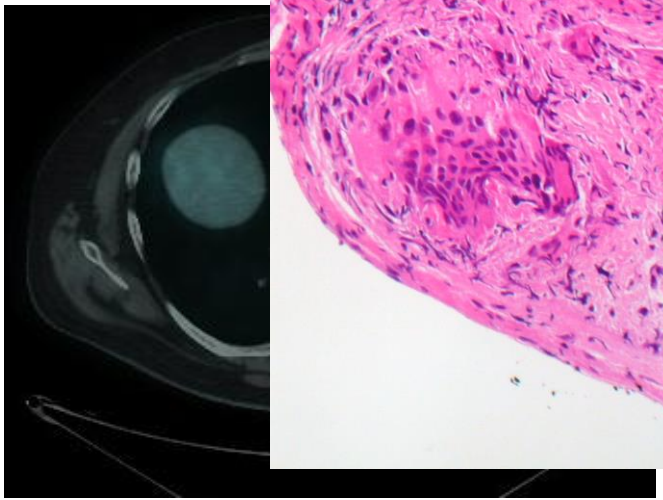
Mutation in PRKAG2





AV block, abnormal chest X-ray





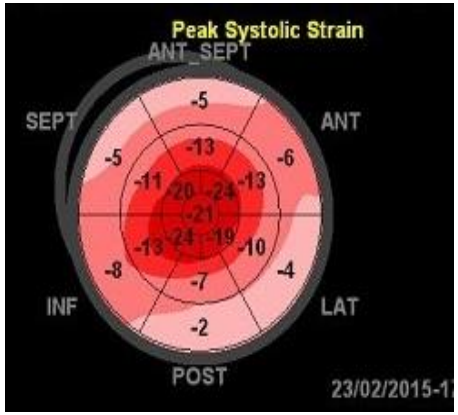
Sarcoidosis

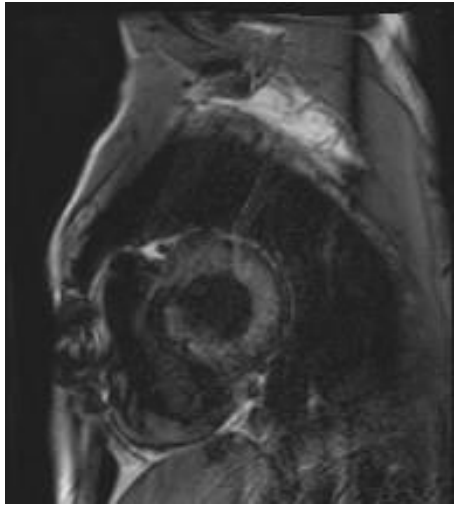
72 year old male

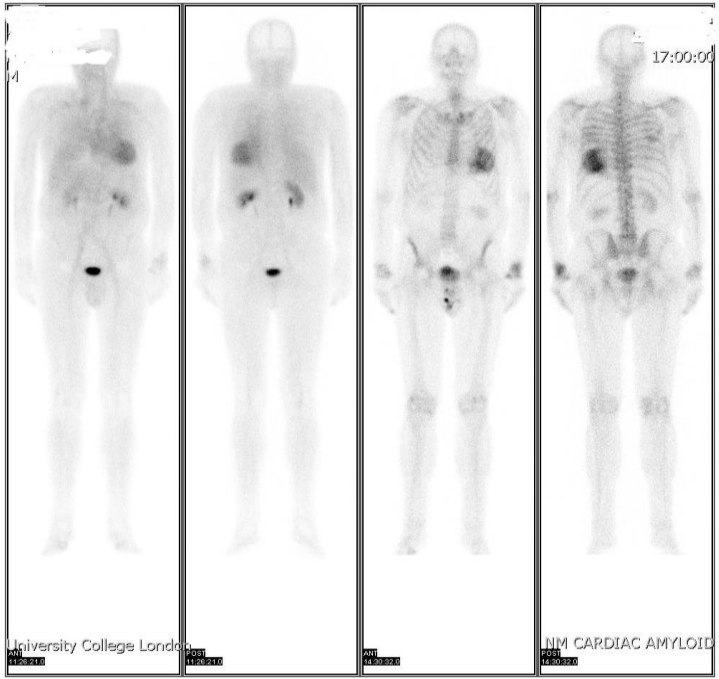
Proteinuria

Bilateral carpal tunnel syndrome

TTR AMYLOIDOSIS







Management

CASE ONE (Arrhythmogenic cardiomyopathy)

- High risk genetic mutation. Low threshold for ICD. Family screening

CASE TWO (PRKAG2)

- Family screening

CASE THREE (Sarcoidosis)

- Immunosuppressive therapy

CASE FOUR (TTR amyloidosis)

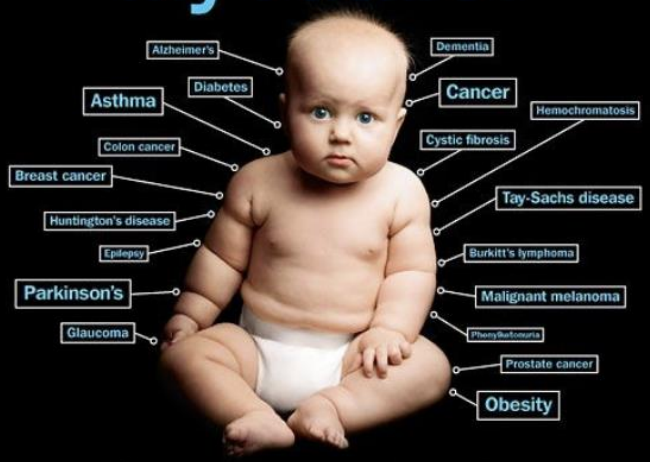
- TTR stabiliser

DECEMBER 24, 2012

Egypt Divided / Pot's Big Moment / Best of 2012 Movies, Music, Books & More

TIME

Want to Know My Future?

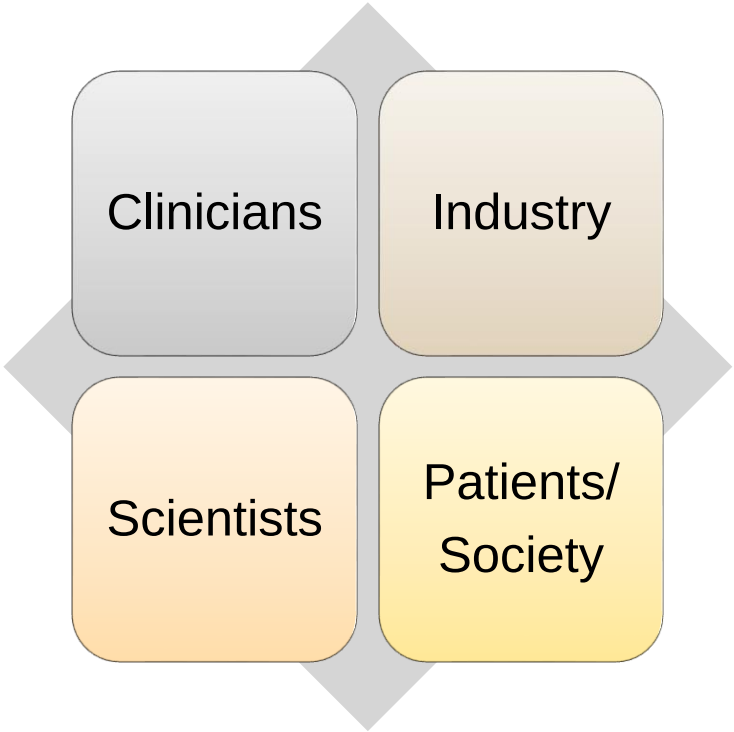


New genetic tests can point to risks—but not always a cure

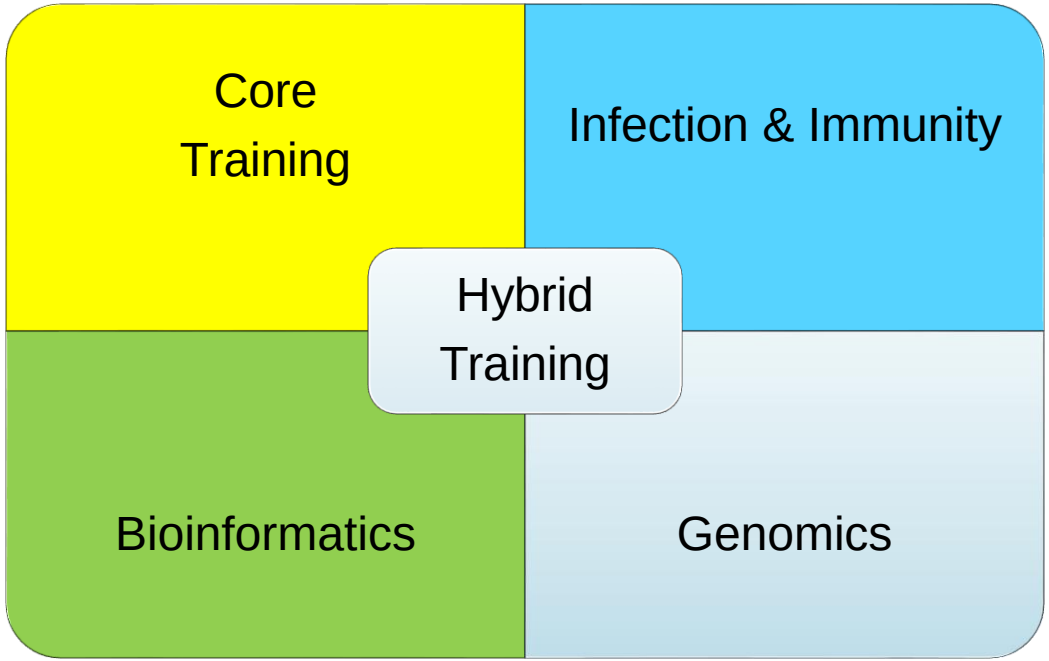
BY BONNIE ROCHMAN

www.time.com

Frontiers: New Partnerships

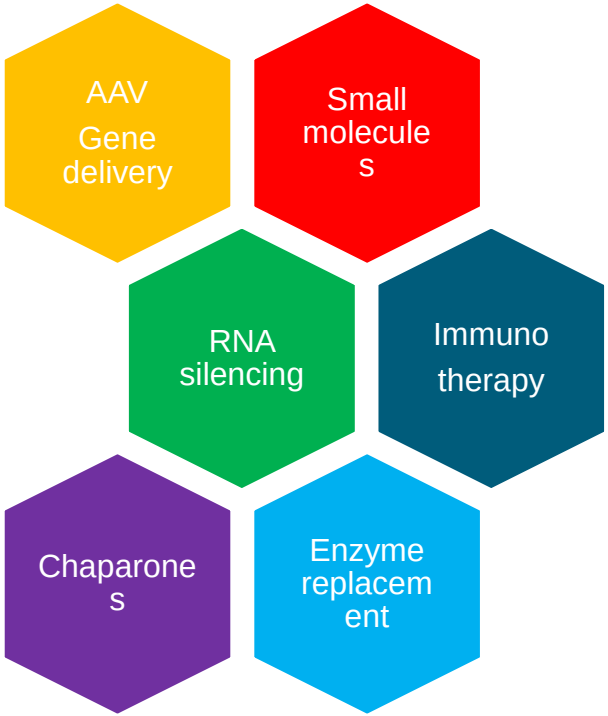


Frontiers: New Workforce



Frontiers: New Armoury

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



Anti-intellectualism in Clinical Cardiovascular Medicine

…it should not be necessary for us to sacrifice the traditional value of a better understanding of the diseases we are asked to treat

J Cohn. Journal of Cardiac Failure Vol. 6 No. 4 2000

AMERICAN COLLEGE of CARDIOLOGY

Treatment Spotlight: Personalized Medicine