Do We All Look the Same Age?

Professor Rick Steeds

Cardiologist, Queen Elizabeth Hospital, Birmingham UK

Queen Elizabeth Hospital Birmingham

University of Birmingham

The City of Birmingham

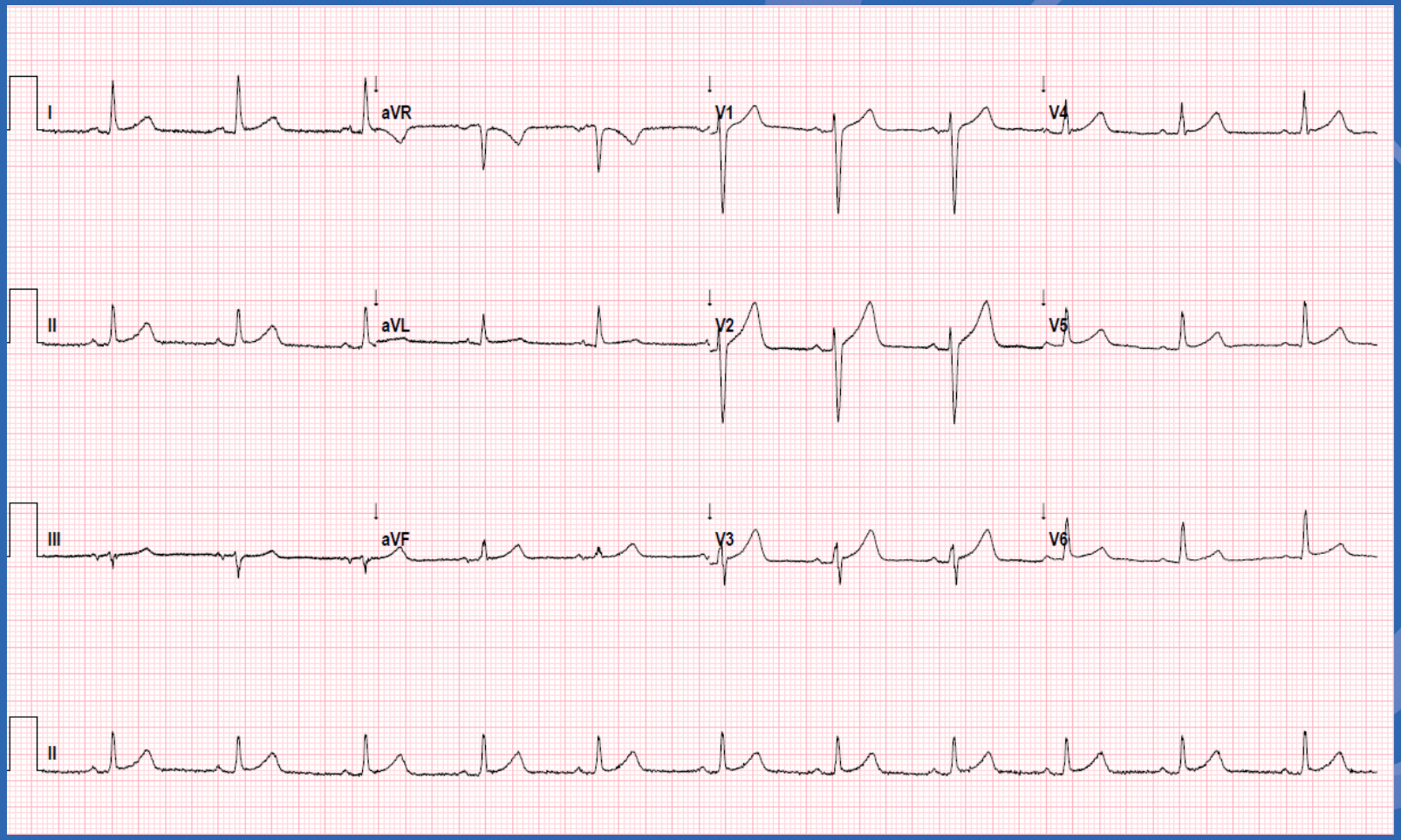
A City of Leisure and Culture

Friendly Locals!

Outline

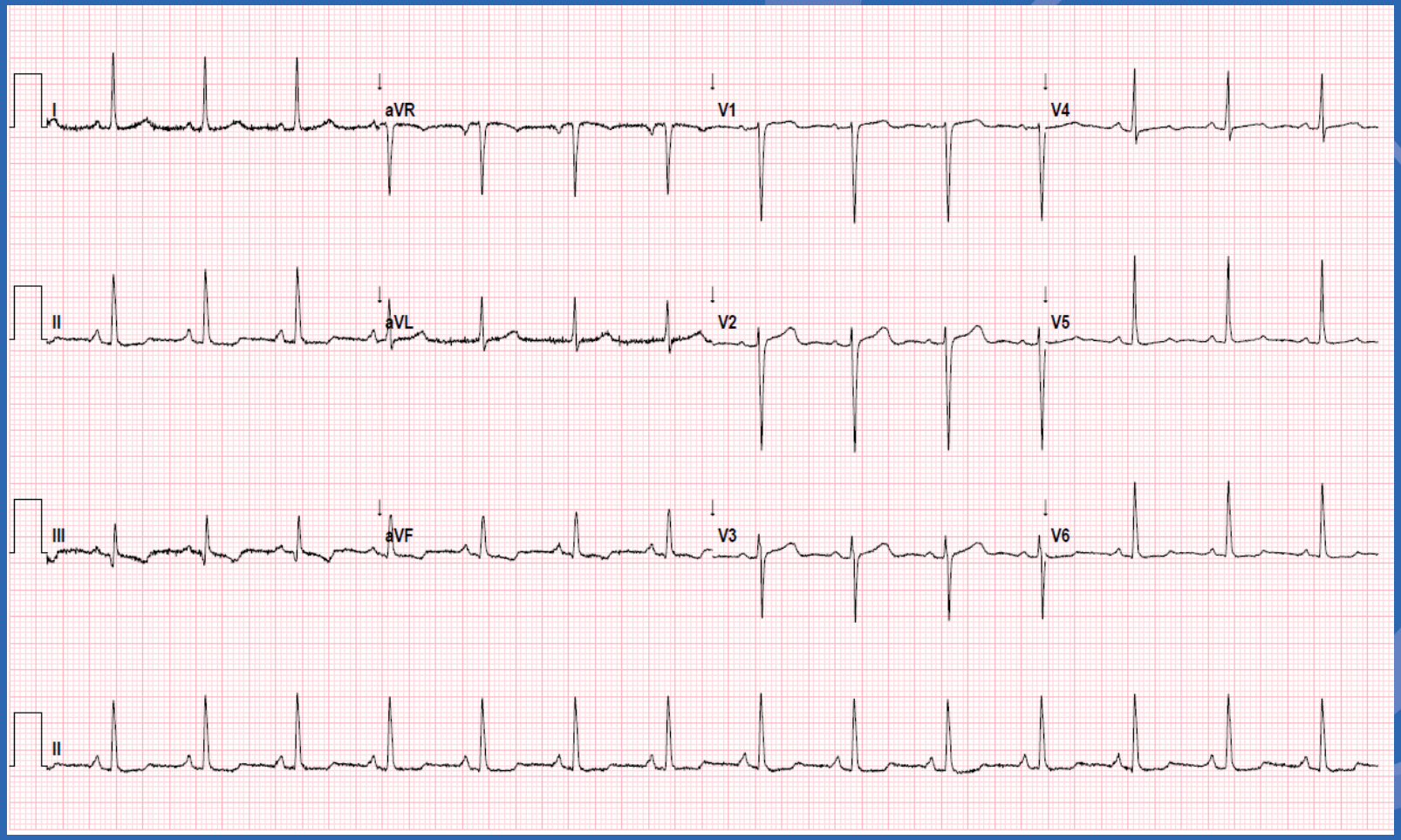
- What abnormalities should you look out for?
- Current treatments
- The pathophysiology of cardiomyopathy in AS
- A different perspective…

12-Lead Electrocardiogram (EKG)



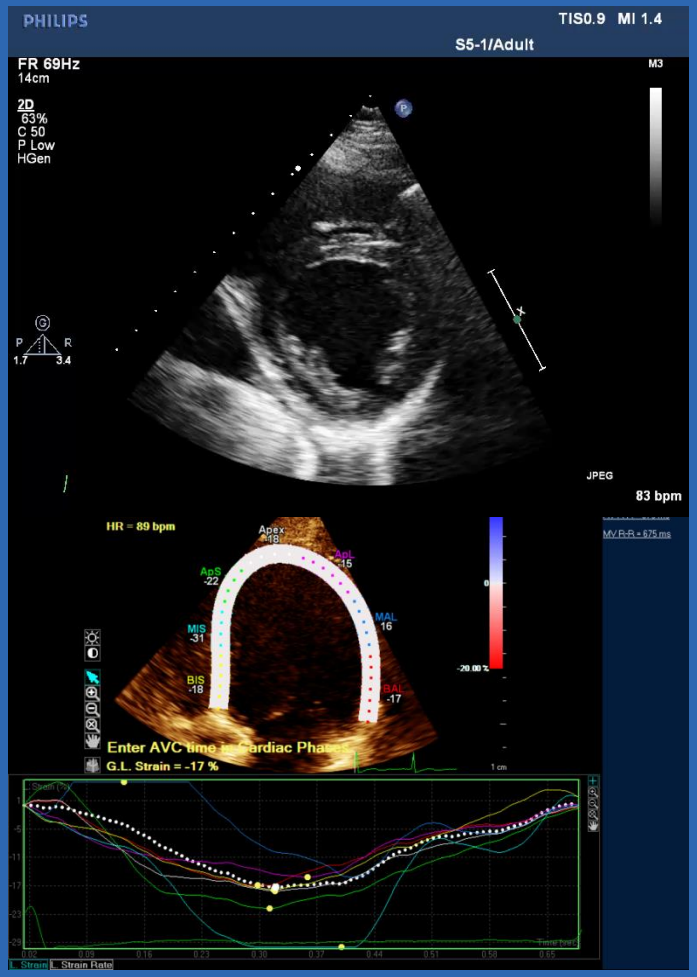
12-lead ECG is normal in 38-62% adults with AS

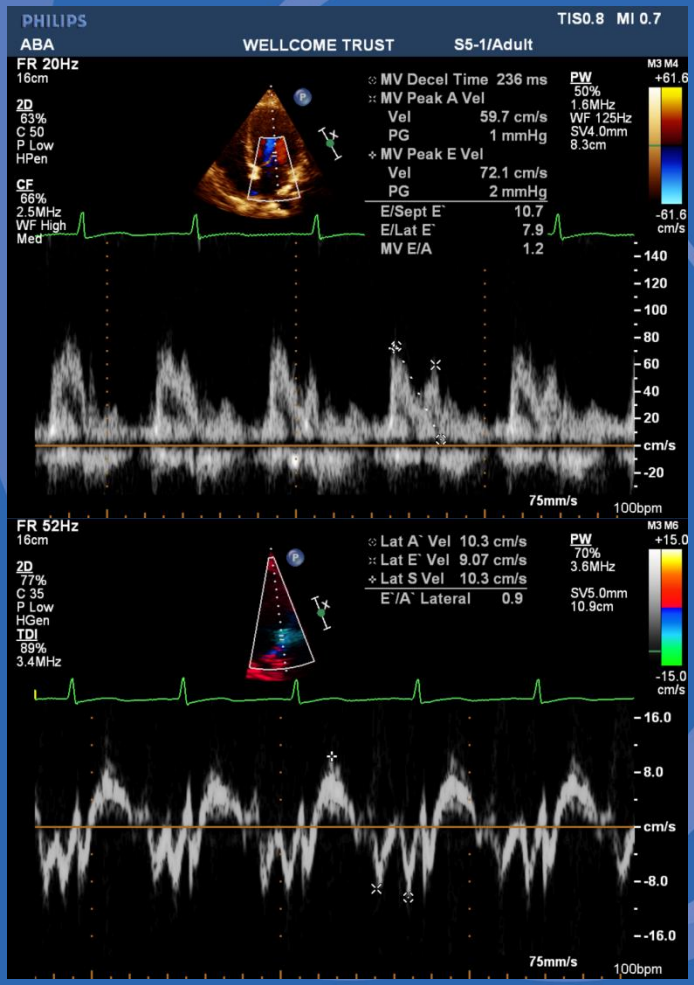
12-Lead Electrocardiogram (EKG)



The most common abnormality is T wave inversion in 21/47 (45%)

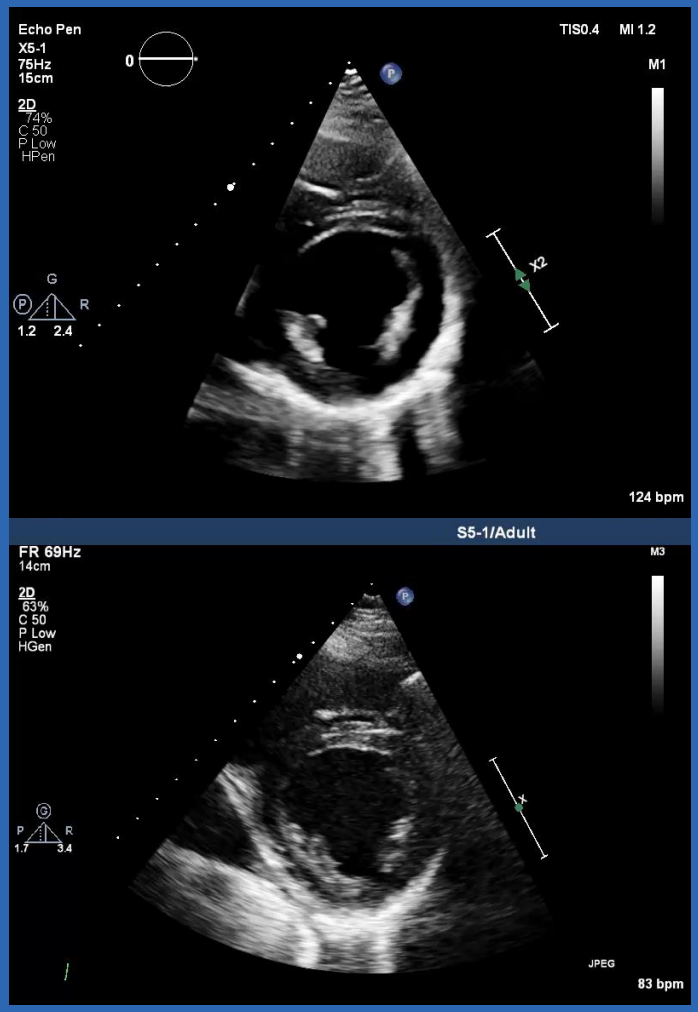
Echocardiography

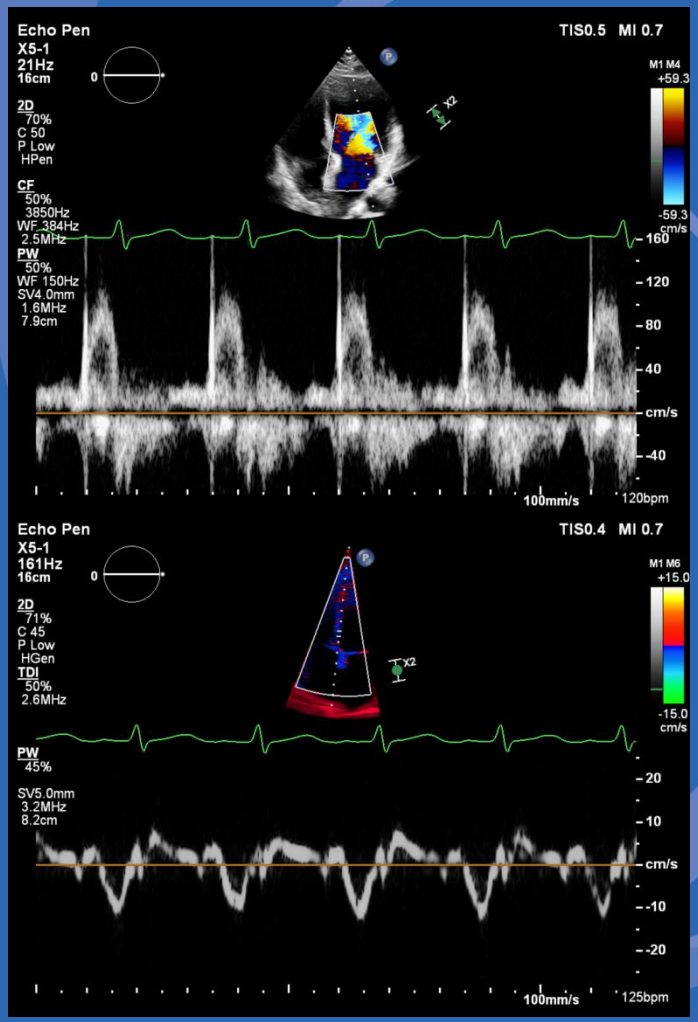




Transthoracic echocardiography is normal in 36-62% adults with AS

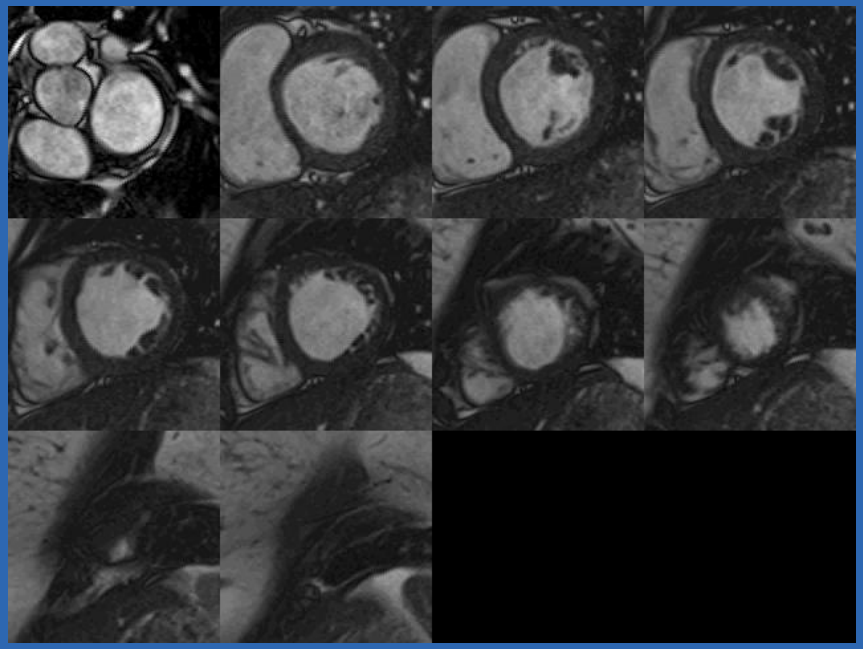
Echocardiography

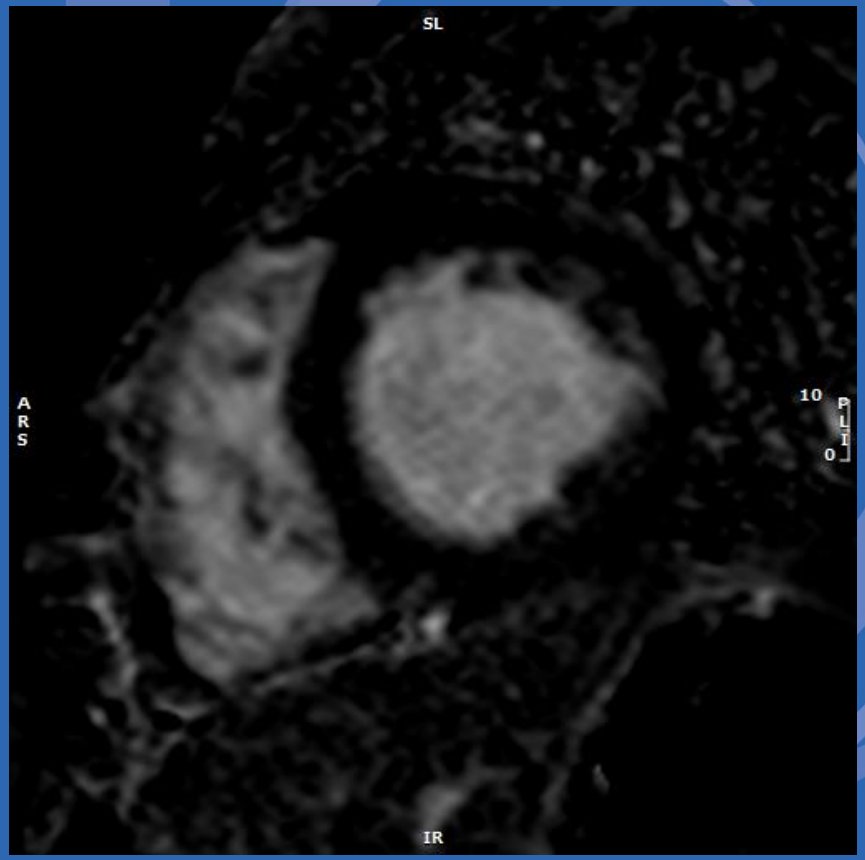




Most common abnormality is relaxation of the heart in 20/47 (43%)

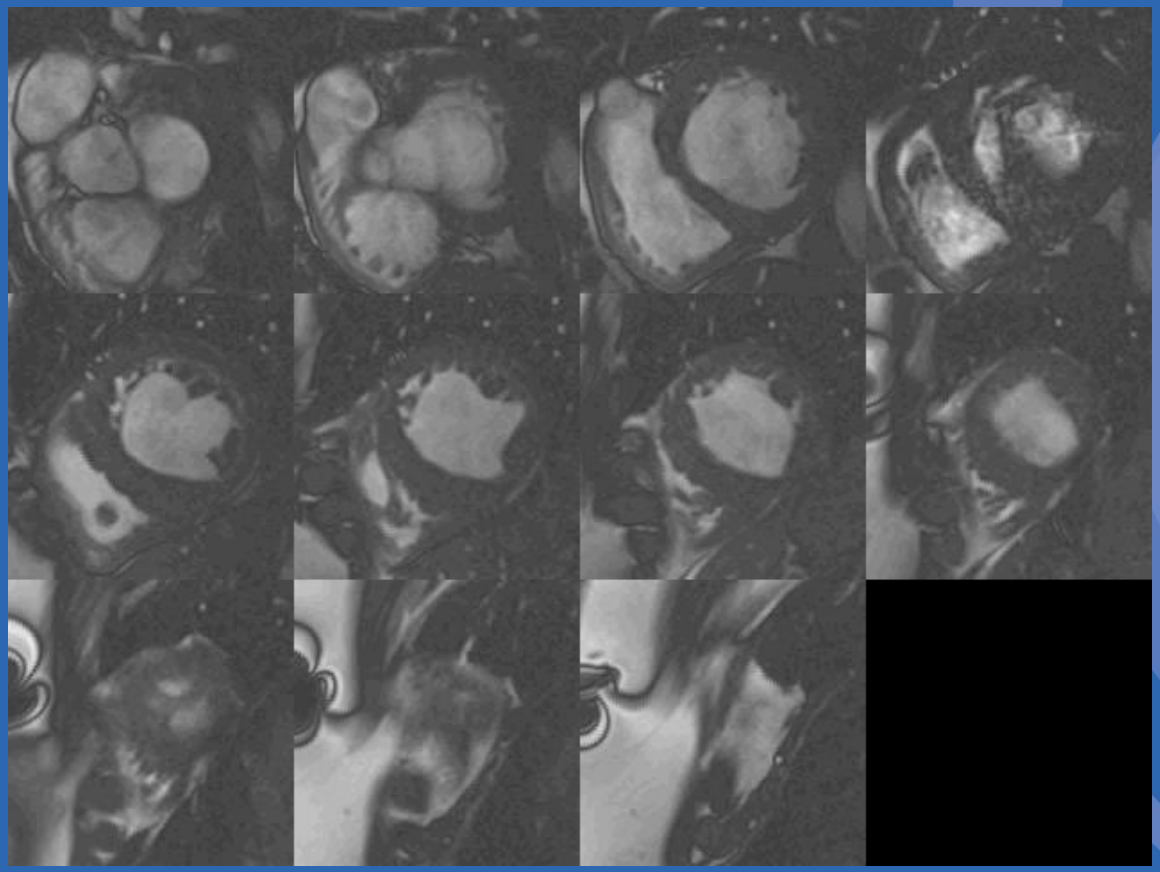
Magnetic Resonance Imaging

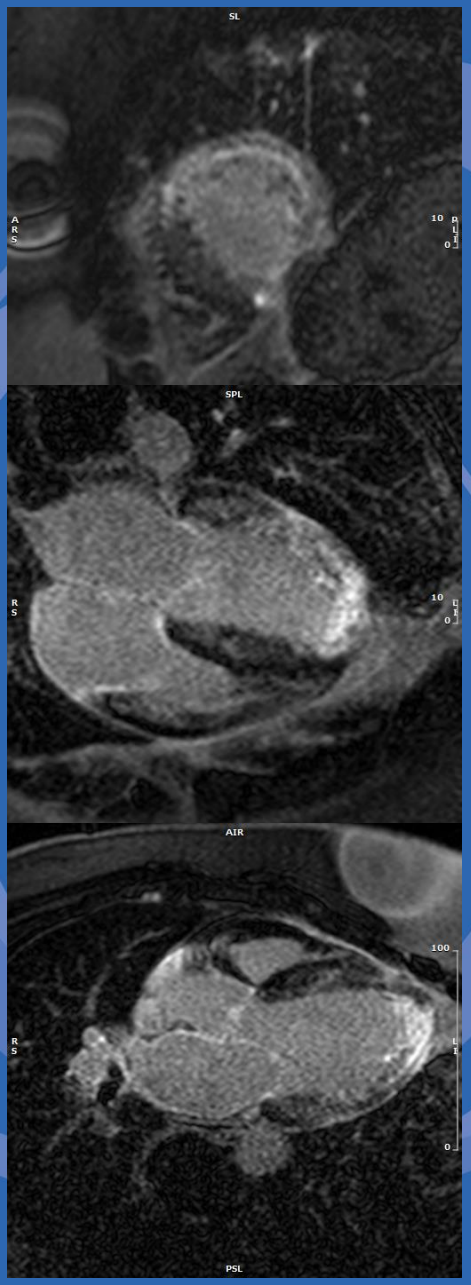




Cardiac MRI *normal* in 36-62%

Magnetic Resonance Imaging





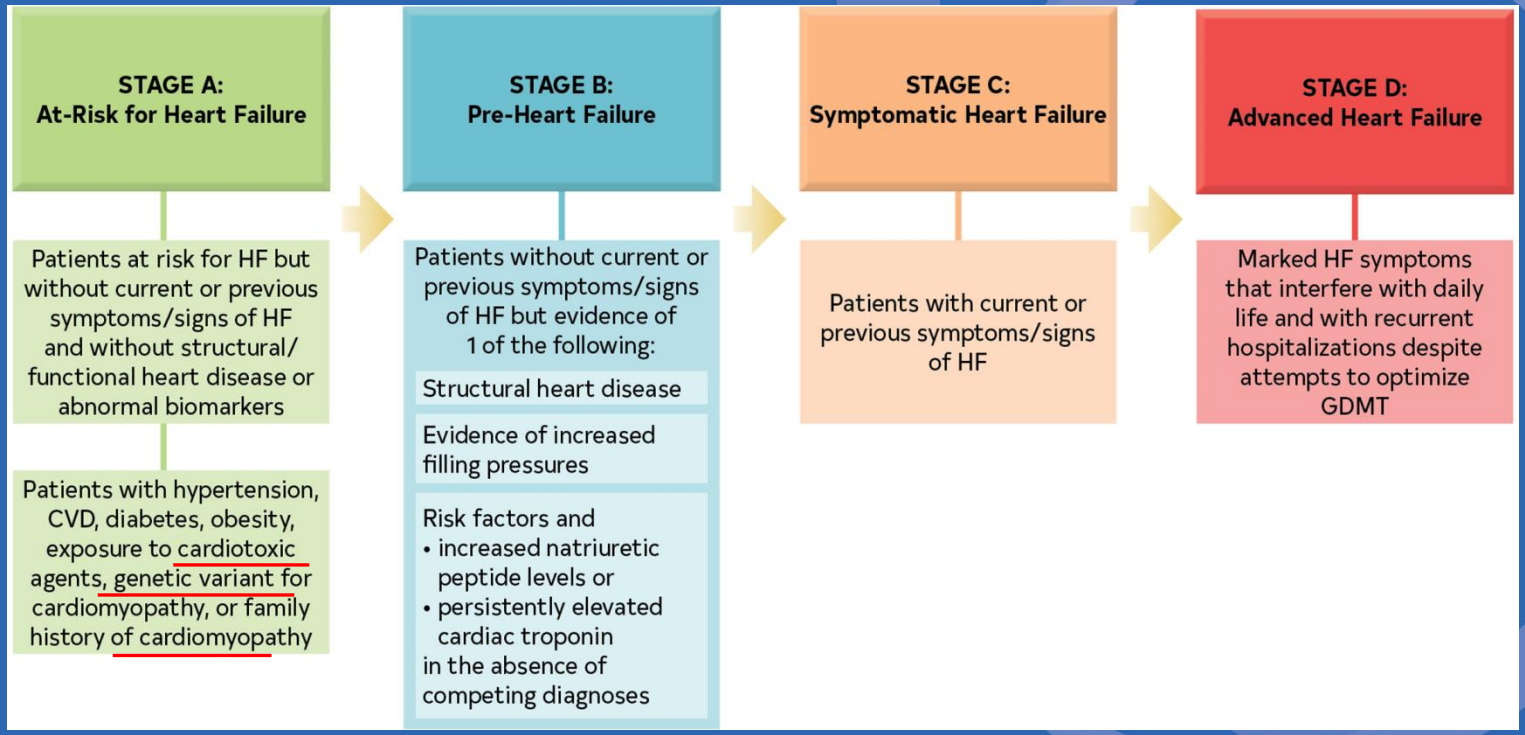
Most common abnormality is late gadolinium enhancement in 21/47 (45%)

Summary

- Cardiovascular disease not affect everyone with AS
- Standard tests picks up abnormalities in @ one third

Standard Therapies in AS Cardiovascular Disease

- No specific therapy for AS cardiomyopathy

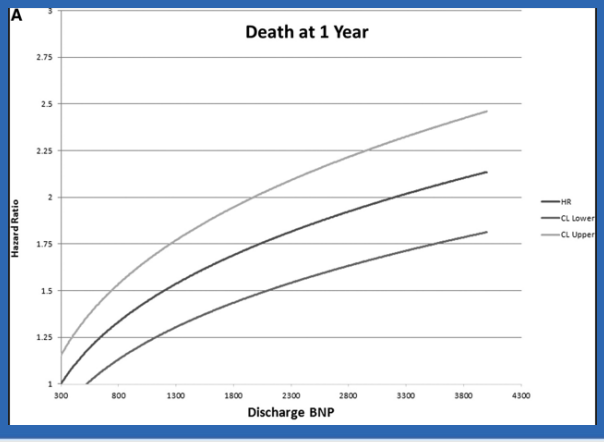


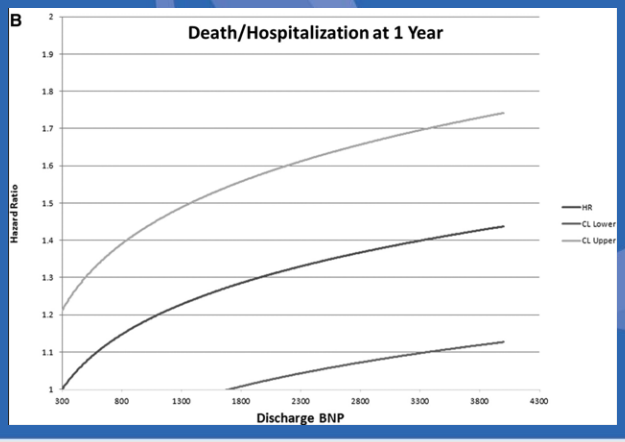
Risk factors: abnormal NTproBNP (49%) and HS Tn (34%) in AS

Heidenreich *Circulation* 2022

Determinants of Therapy

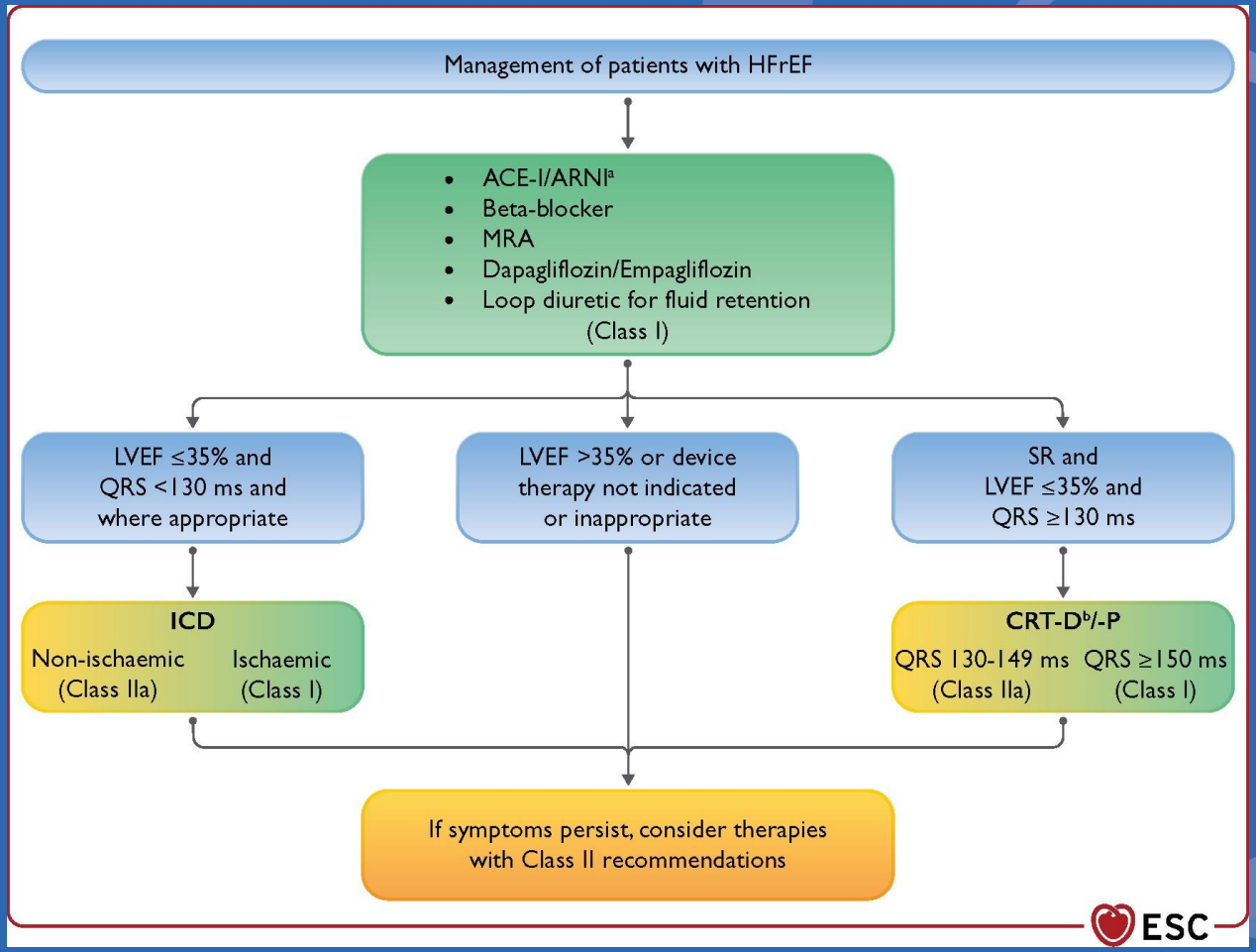
Type of HF		HFrEF	HFmrEF	HFpEF
CRITERIA	1	Symptoms ± Signs[a]	Symptoms ± Signs[a]	Symptoms ± Signs[a]
	2	LVEF ≤40%	LVEF 41–49%[b]	LVEF ≥50%
	3	–	–	Objective evidence of cardiac structural and/or functional abnormalities consistent with the presence of LV diastolic dysfunction/raised LV filling pressures, including raised natriuretic peptides[c]





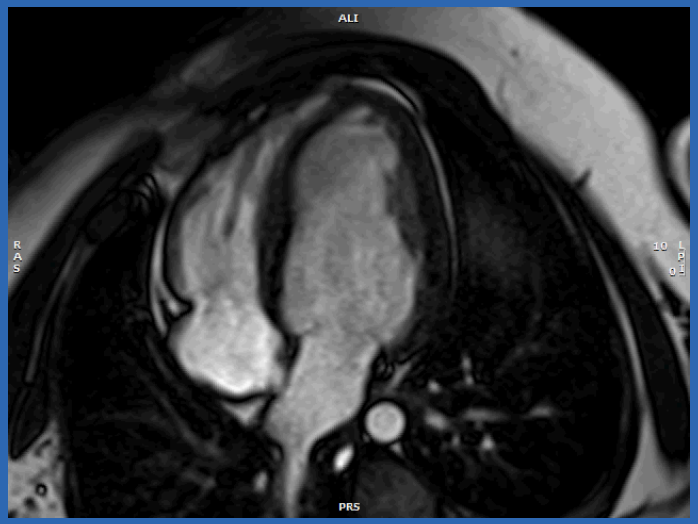
Kociol *Circ HF* 2011

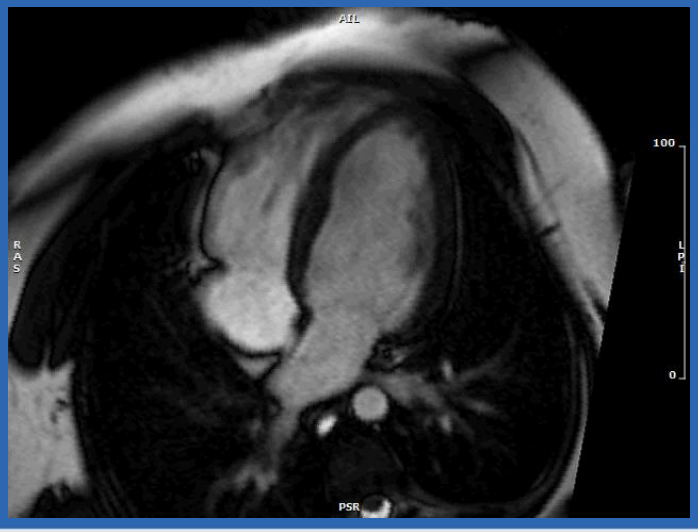
Standard Evidence-Based Therapy for HFrEF

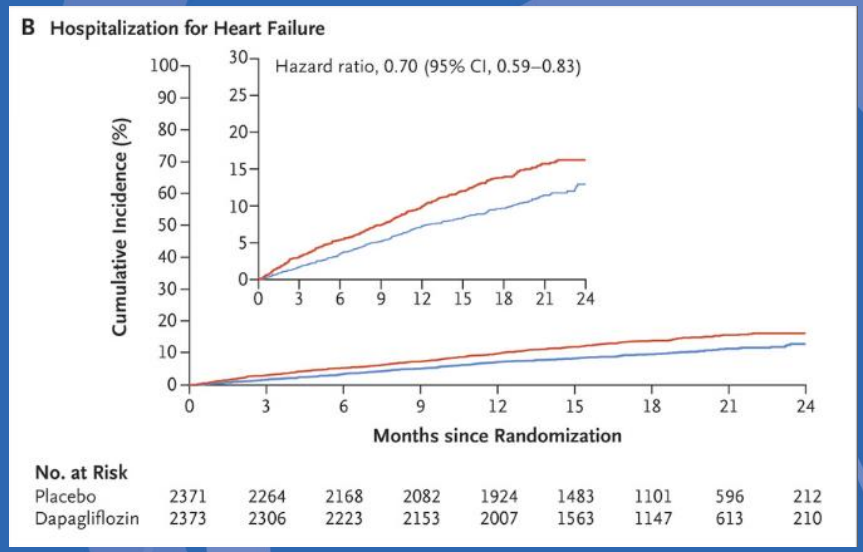


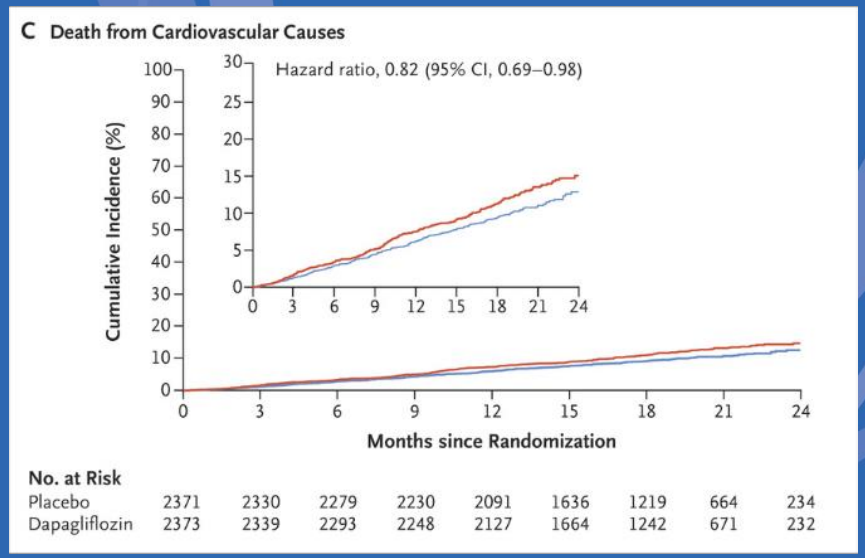
Consider restricting dietary sodium; no proven benefit vitamins, iron, thiamine

Response to Therapy



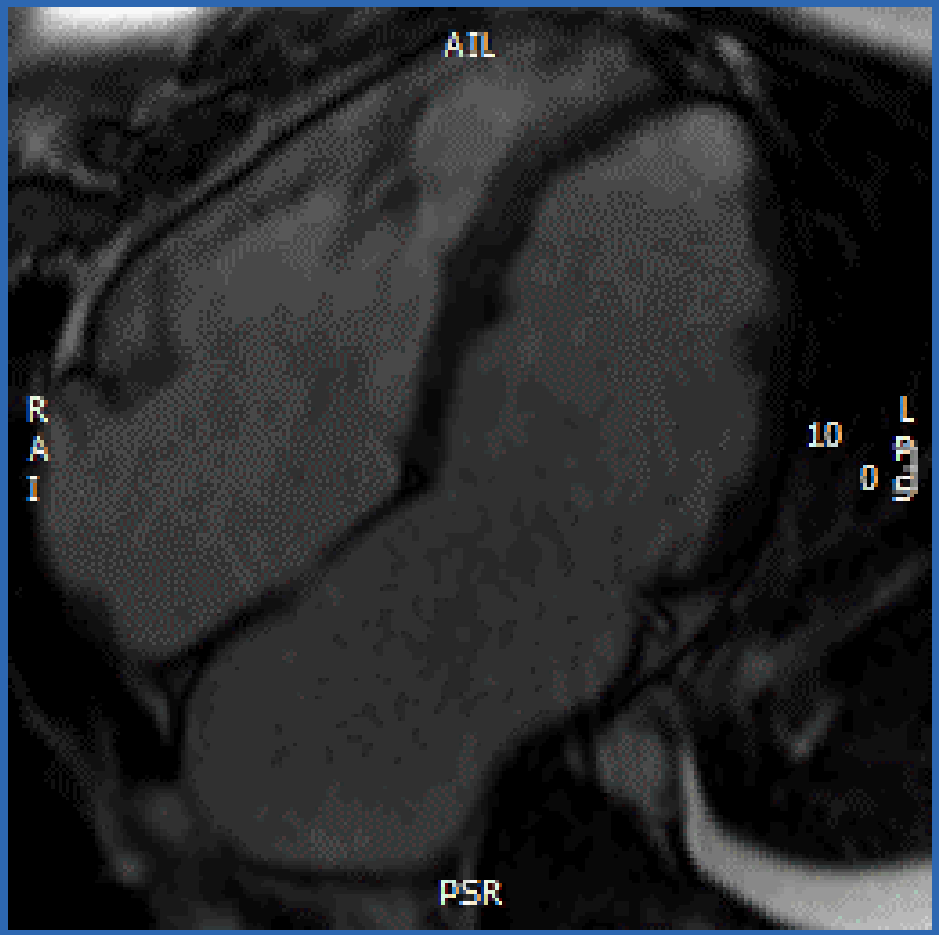


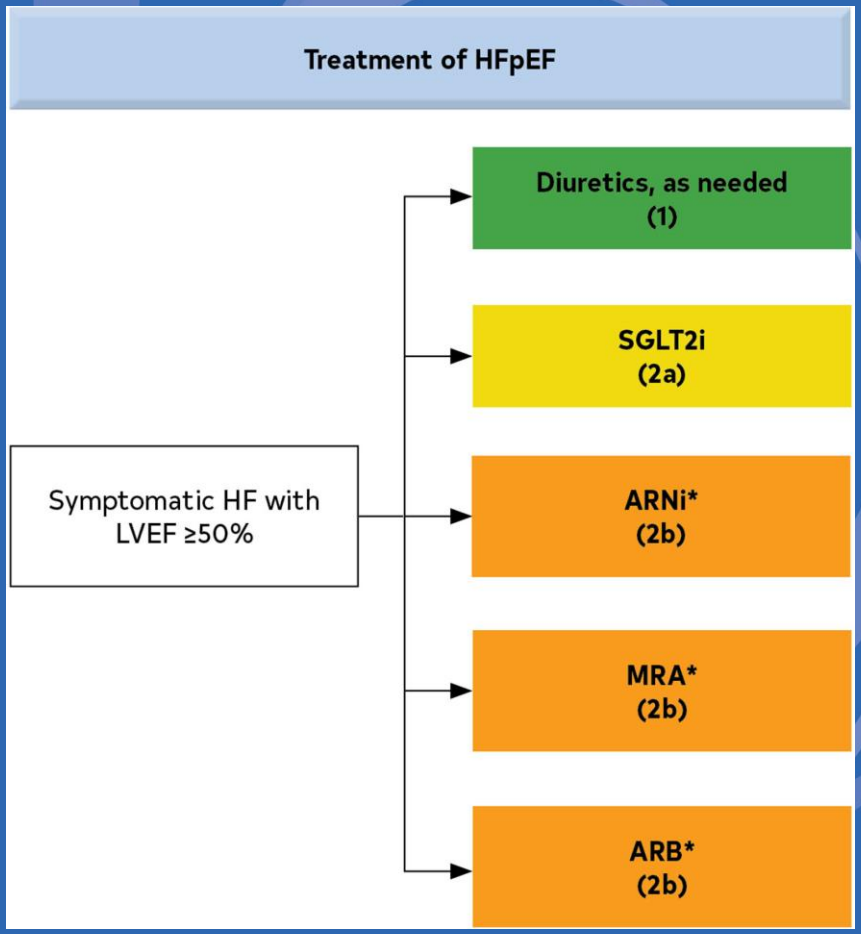




McMurray *NEJM* 2019

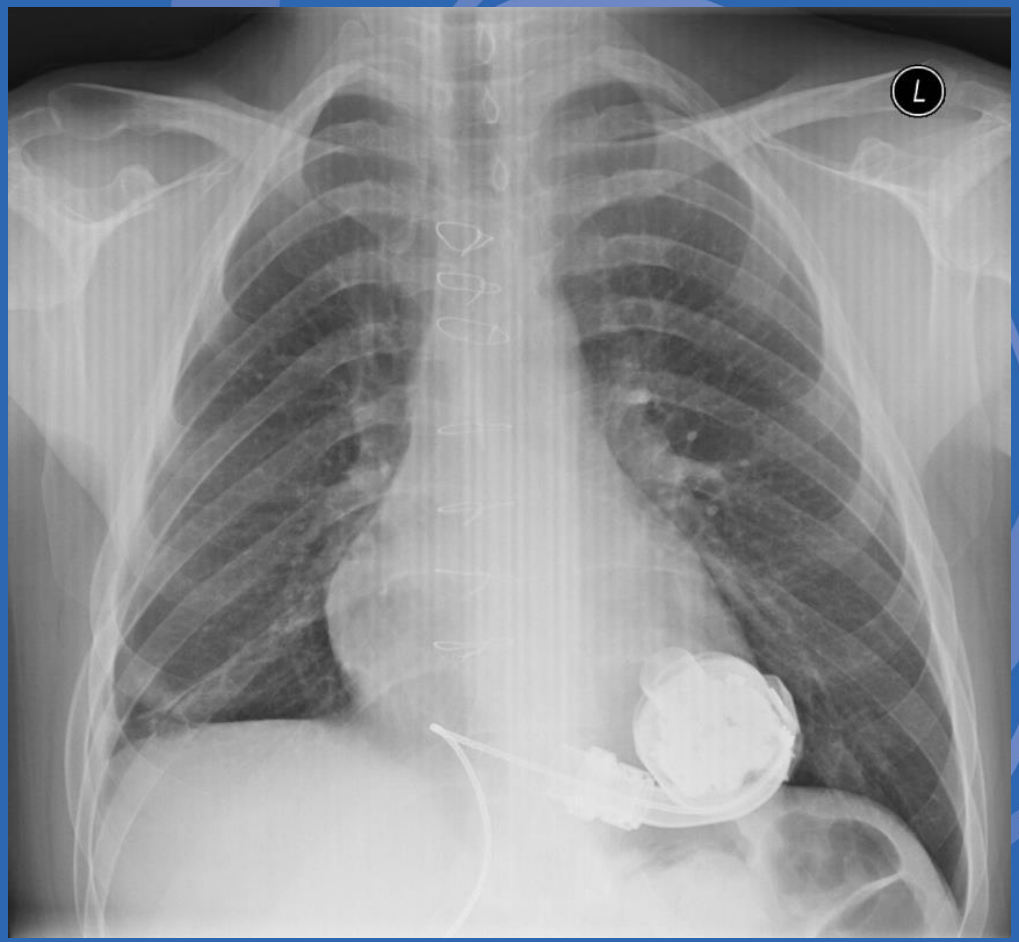
Standard Evidence-Based Therapy for HFpEF





Heidenreich *Circulation* 2022

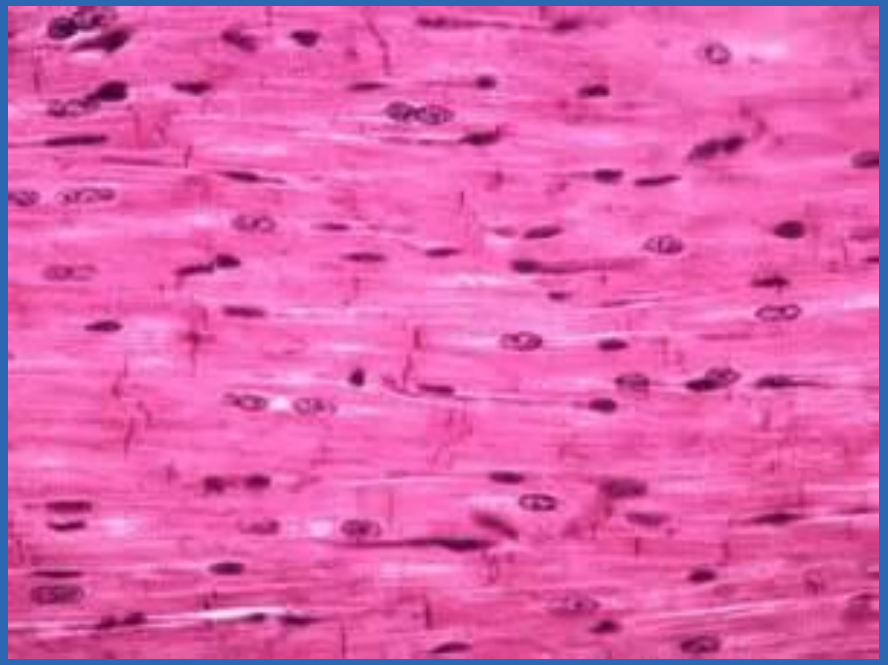
Circulatory Support and Transplant



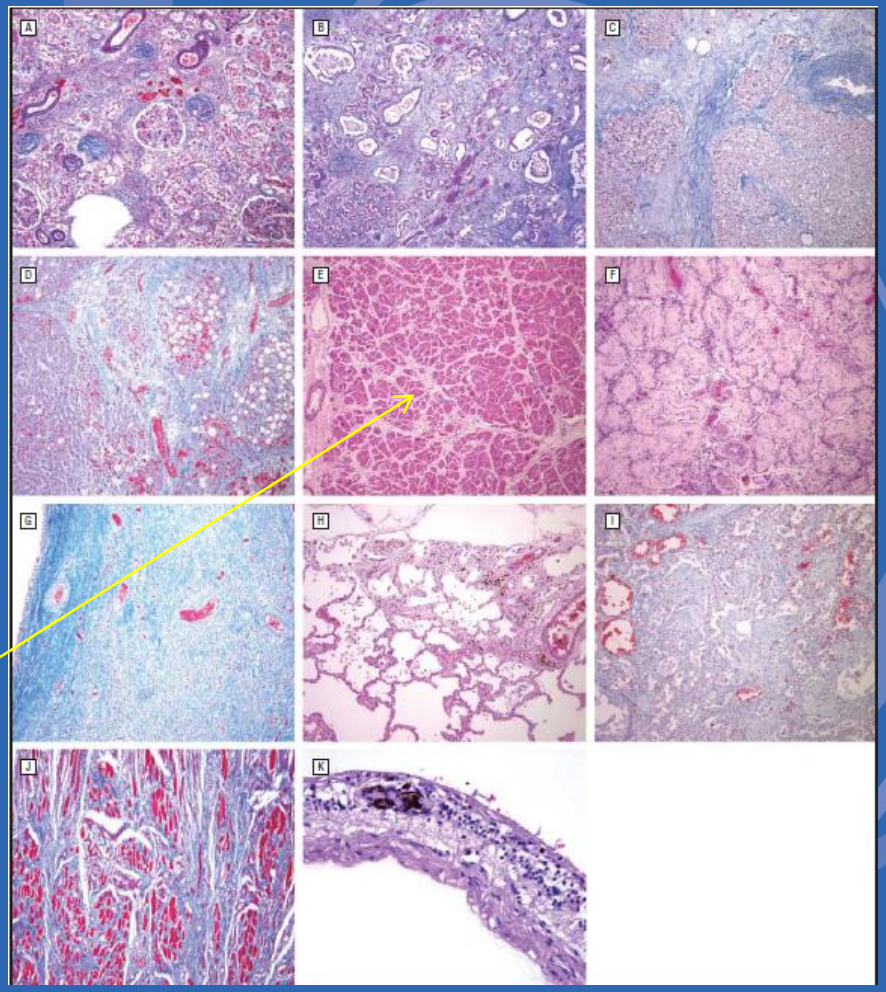
Summary

- Cardiovascular disease not affect everyone with AS
- Standard tests picks up abnormalities in @ one third
- There is no specific therapy to AS cardiomyopathy but current standard therapies are available and help
- These are not curative and there is residual risk to impaired quality of life and life expectancy

The Myocardium



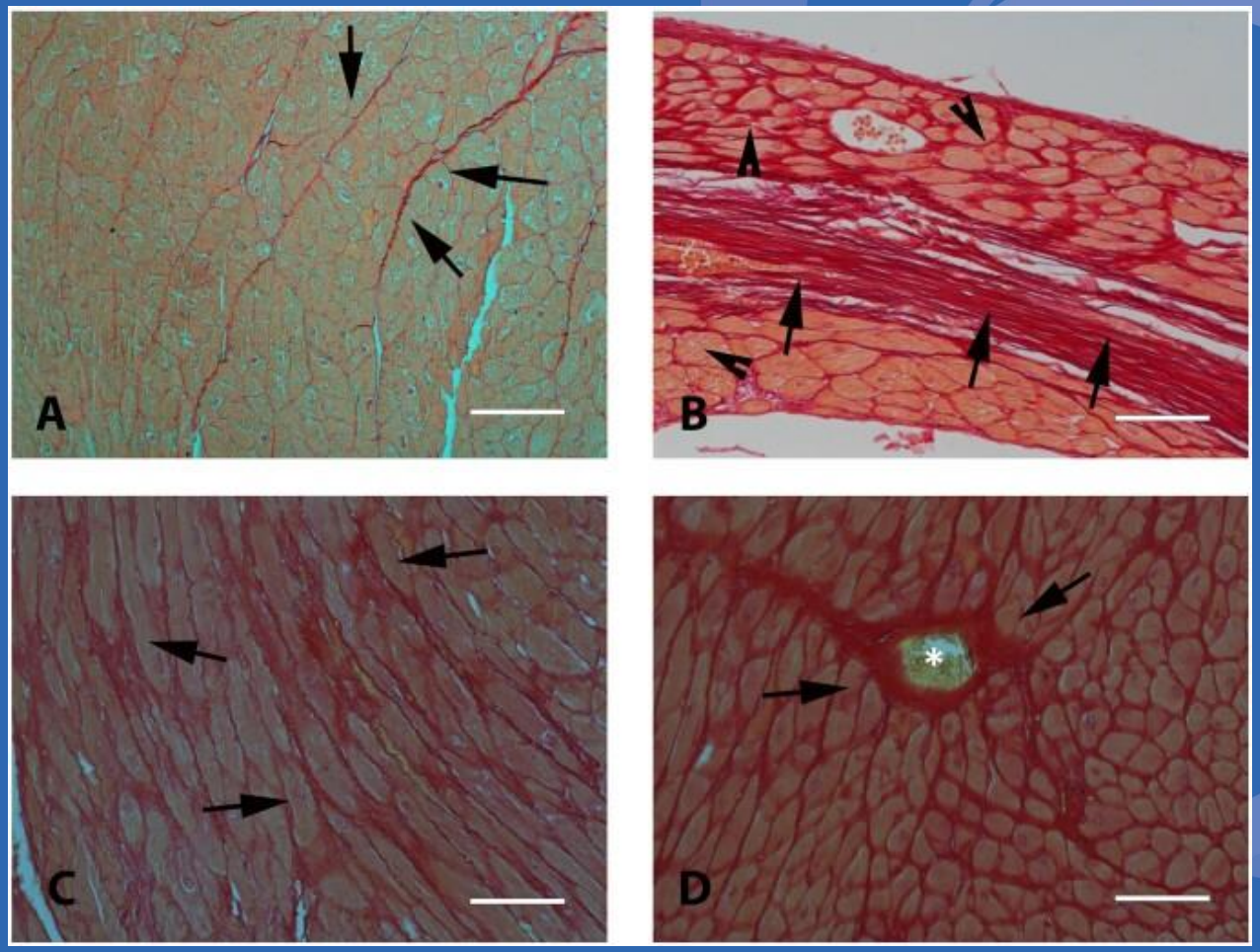
‘Collagen fibres between the cardiac muscle fibres, some of which are enlarged’



Marshall *Arch Intern Med* 2005

Variation in Cardiac Fibrosis

Normal



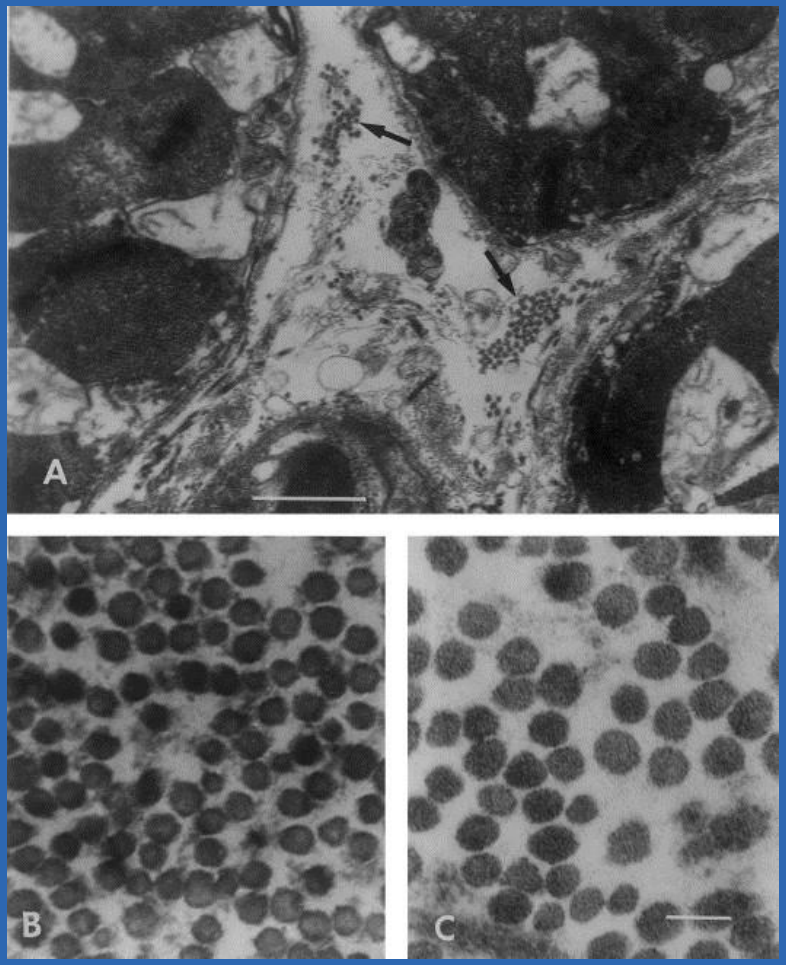
Reparative

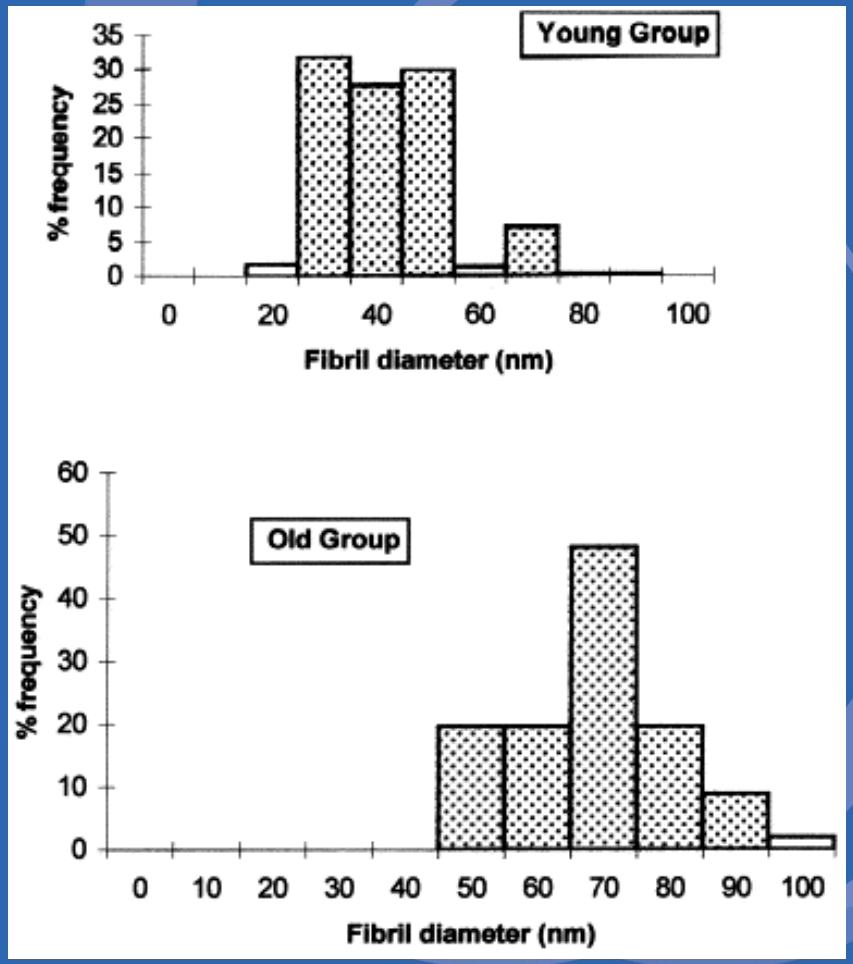
Interstitial

Perivascular

Frangiogiannis *Cardiovasc Res* 2021

Ageing and Cardiac Fibrosis



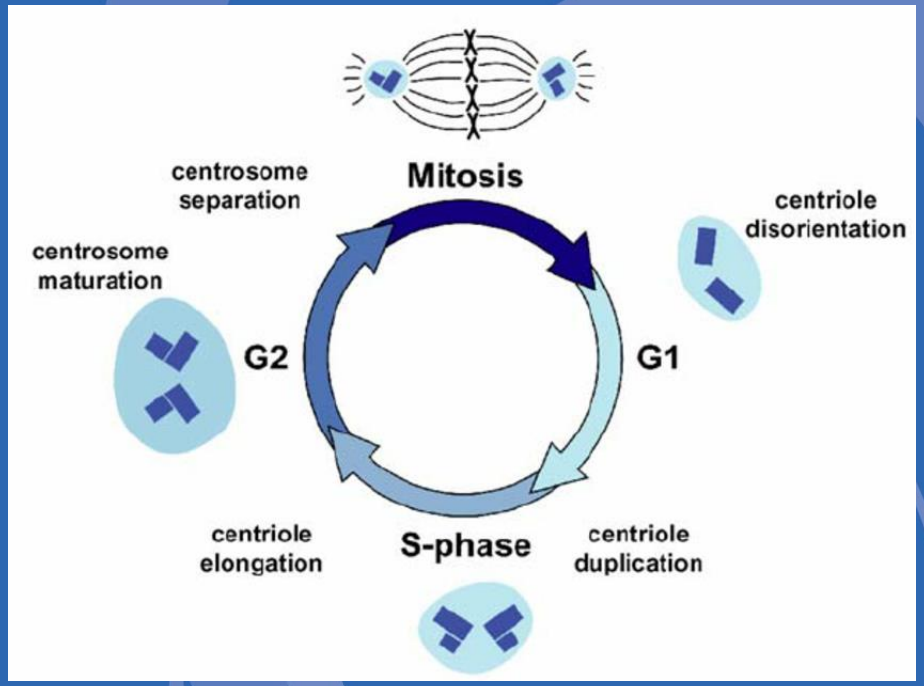


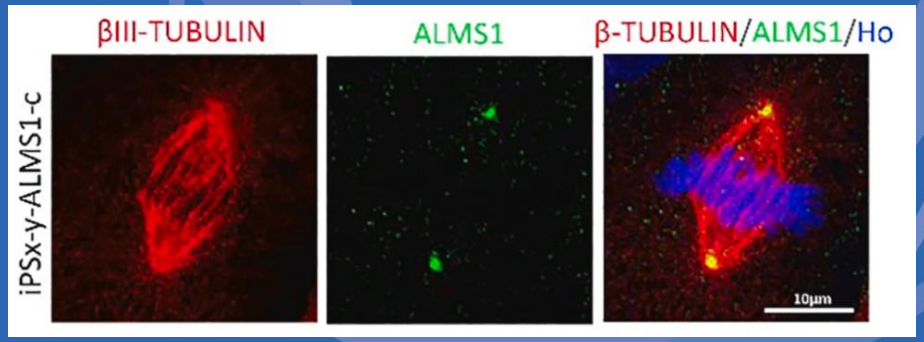
Common feature of ageing is progressive increase in collagen density and thickness

Debessa *Mech Ageing Dev* 2001

Role of ALMS1

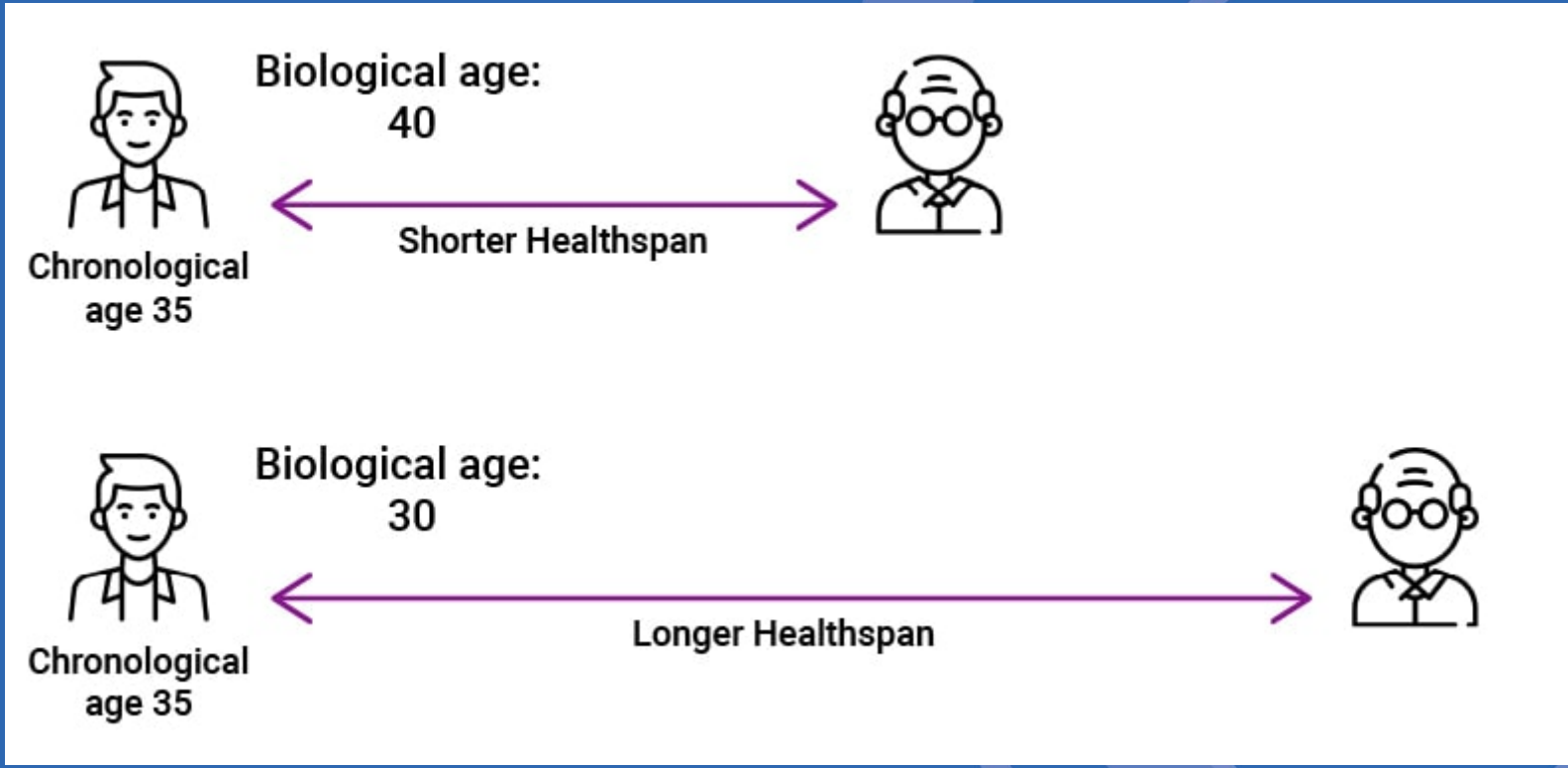
- *ALMS1* is a component of the centrosome, organizing microtubules and providing structure to cells.
- Proposed role of *ALMS1* in cell cycle arrest of cardiomyocytes
- Dysregulation of the cell cycle to cell senescence, and often progressive with age.





Ji *Stem Cell Research* 2020

Phenoage and Chronological Age

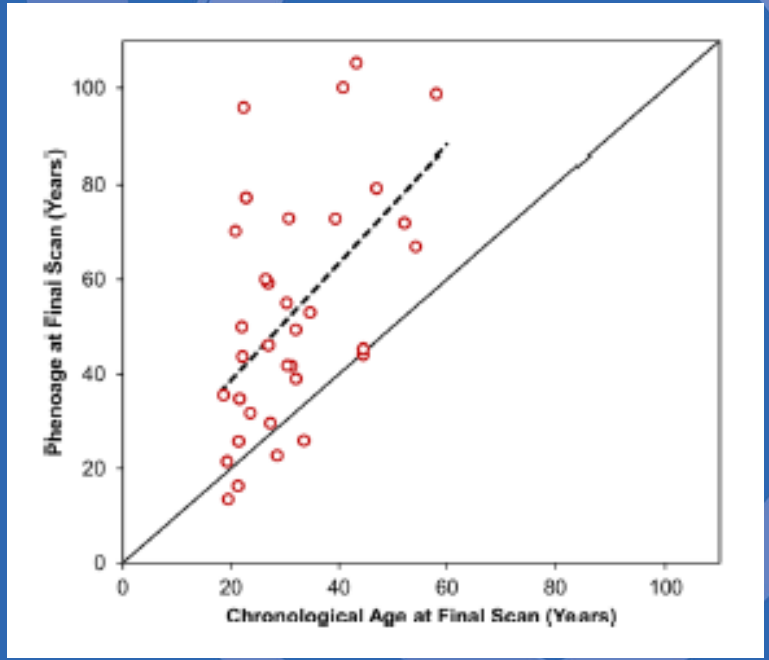


Phenoage is a reliable measure of biological ageing that outperforms other measures for all-cause mortality, risk of cancer, healthspan, physical functioning, dementia

Levine *Ageing* 2018

Phenoage and AS

- 45 participants with AS
- Median phenoage 48yrs (IQR 35-72) cf median chronological age 29yrs (IQR 22-39)
- Phenoage older in 85%
- Median difference +18 yrs
- Looked at echo findings over 10 yrs: gradual ↓ LV size, ↑ wall thickness, ↓ GLS, ↑ E/A

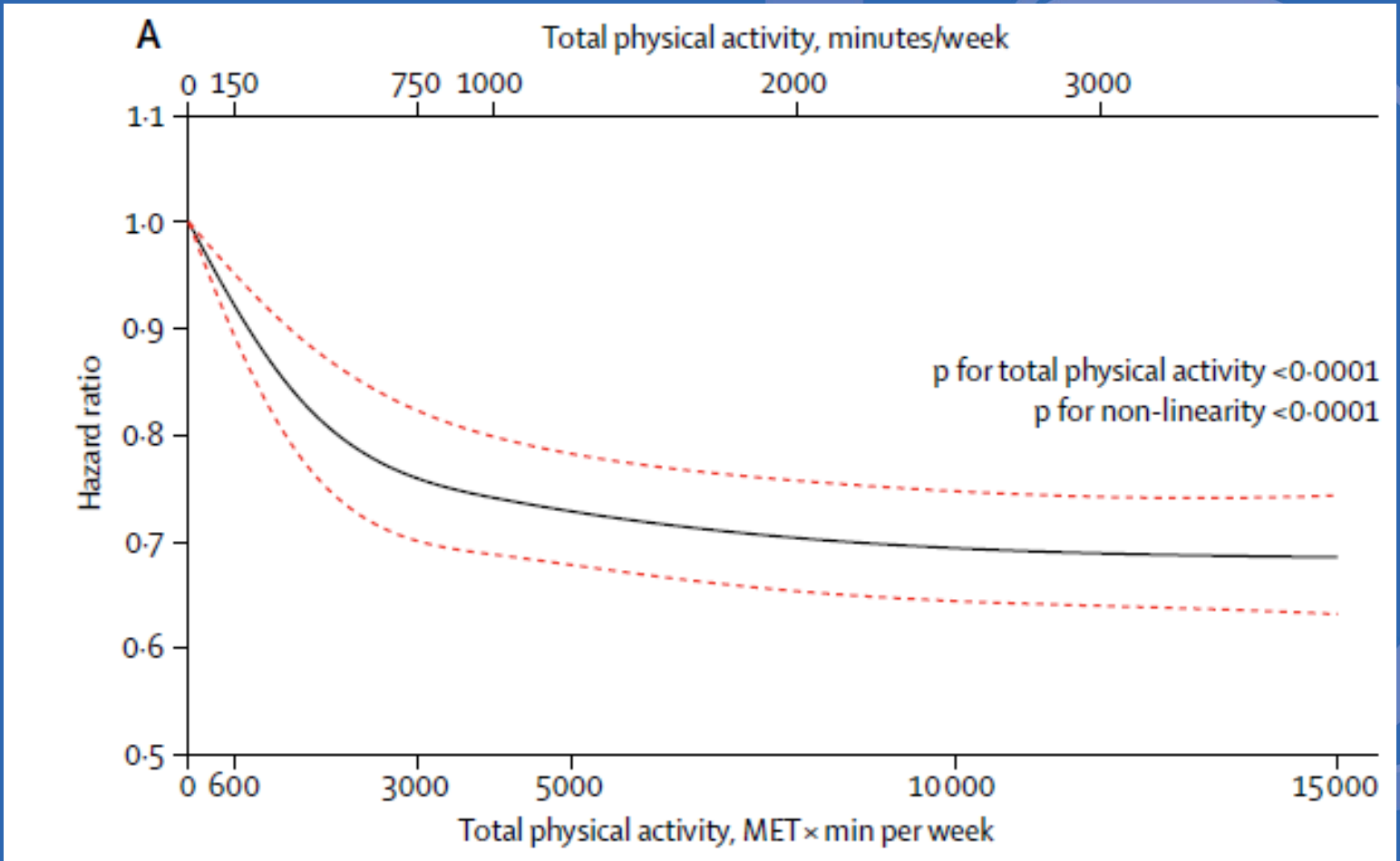


Patel *Geroscience* 2023

Summary

- Cardiovascular disease not affect everyone with AS
- Standard tests picks up abnormalities in @ one third
- There is no specific therapy to AS cardiomyopathy but current standard therapies are available and help
- These are not curative and there is residual risk to impaired quality of life and life expectancy
- Fibrosis is a core feature of pathogenesis of AS cardiomyopathy on PM and imaging
- Phenoage is advanced in AS – does this offer insights?

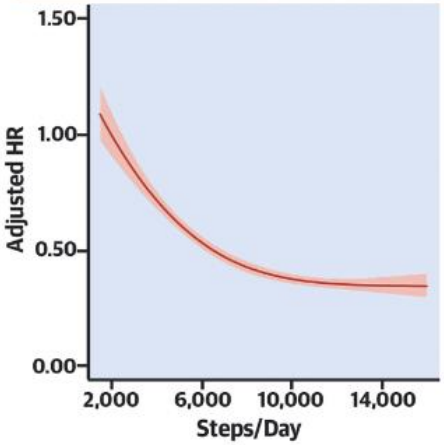
The effect of physical activity on mortality and cardiovascular disease in 130 000 people from 17 high-income, middle-income, and low-income countries: the PURE study



Counting Your Steps…

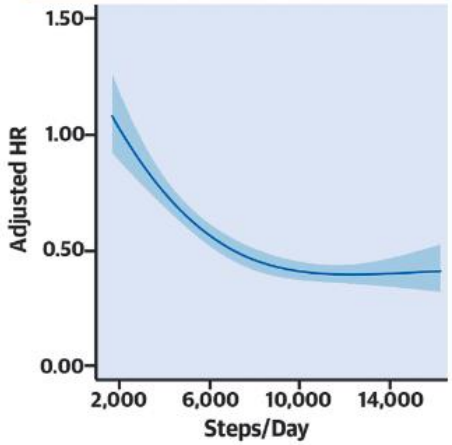
This systemic review and meta-analysis of 12 cohorts including 111,309 individuals from the general population identified minimal and optimum step count targets for reducing adverse health outcomes.

All-Cause Mortality



	Steps/day	Adjusted HR (95% CI)
Minimum dose	2,517	0.92 (0.84-0.99)
Optimum dose	8,763	0.40 (0.38-0.43)
Risk reduction at 16,000 steps	16,000	0.35 (0.30-0.40)

Incident CVD (Fatal and Nonfatal)



	Steps/day	Adjusted HR (95% CI)
Minimum dose	2,735	0.89 (0.79-0.99)
Optimum dose	7,126	0.49 (0.45-0.55)
Risk reduction at 16,000 steps	16,000	0.42 (0.33-0.53)

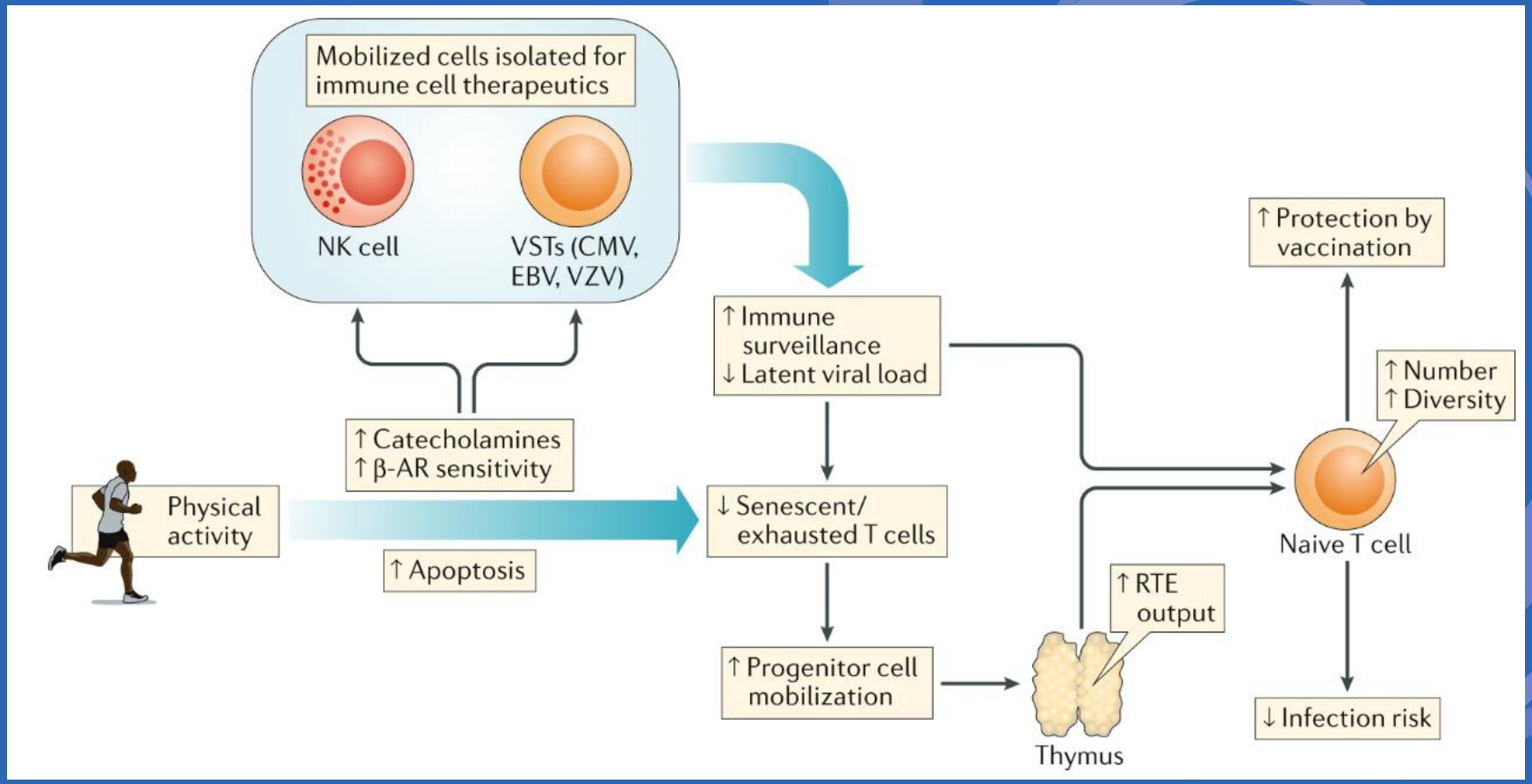
Step count targets were independent of:

Sex

Device wear location (wrist vs hip)

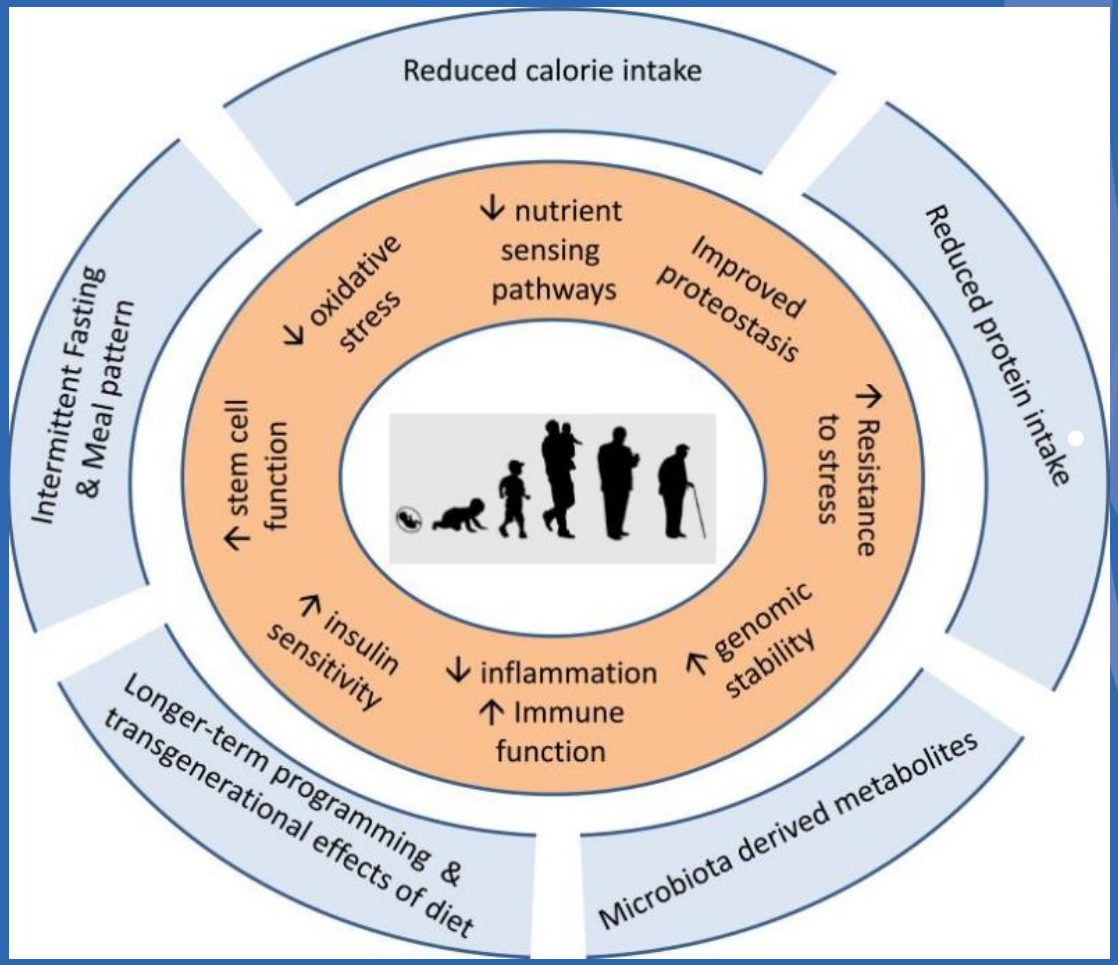
Additional health benefits with higher step cadence, irrespective of total step count

Tip 1: Exercise Reduces Your Biological Age



Duggal *Nature Reviews Imm* 2019

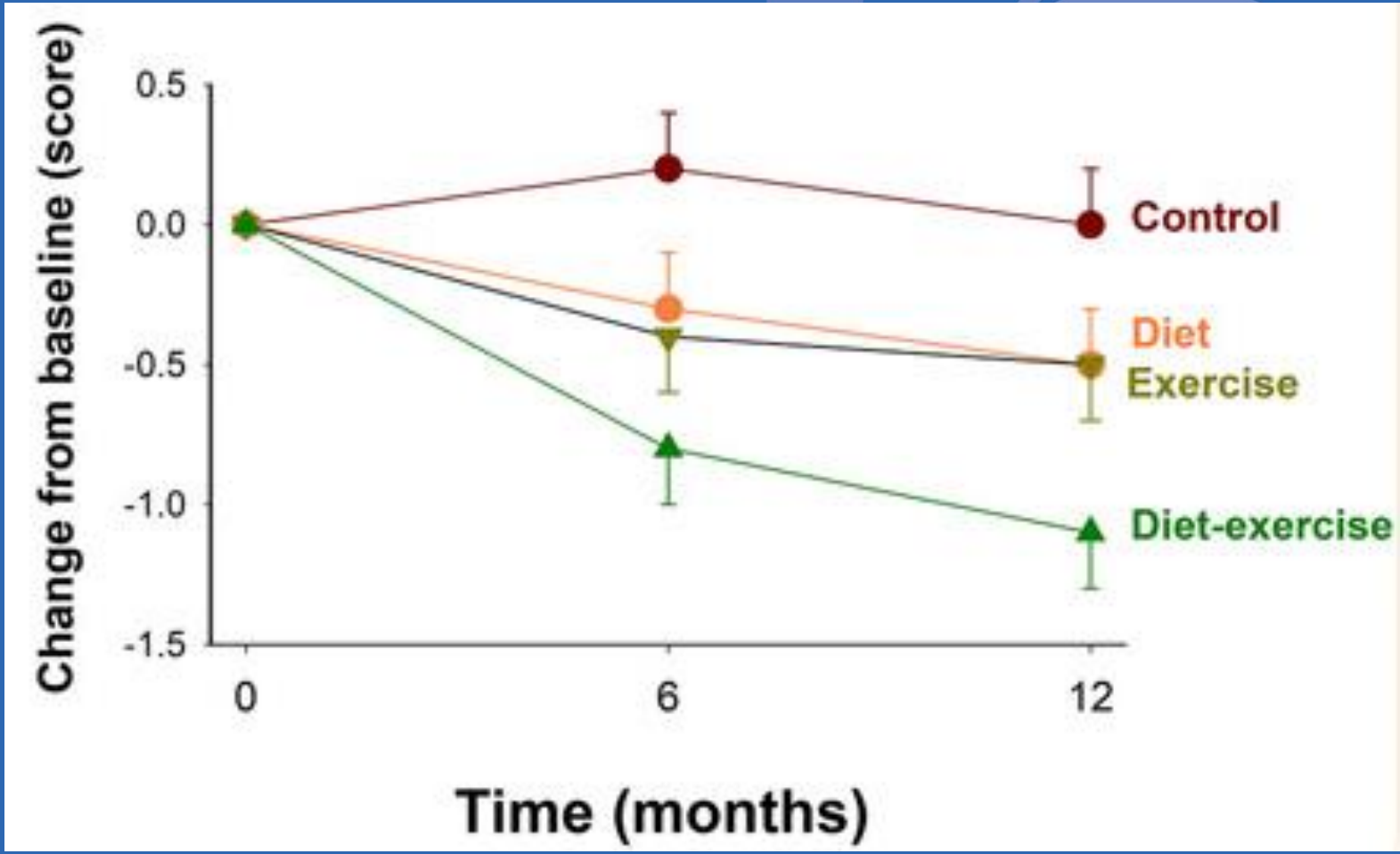
Tip 2: Diet reduces Your Biological Age



- 10-50% reduced CI
- Intermittent fasting:
  - 5:2 diet
  - Time limited to 4-12hrs
- Specific nutrients:
  - Protein? Increase
  - Methionine
- Microbiota:
  - Mixed intake
  - Vegetable and fruits

Fontana *Cell* 2015

A Combination?



Ho *J Nutr Health Ageing* 2023

Tip 3: Do NOT Smoke

Smoker!

Okada *Plastic and Recon Surg* 2013

Tip 3: Do NOT Smoke

Smoker!

Okada *Plastic and Recon Surg* 2013

Tip 3: Do NOT Smoke

Smoker! Smoker!

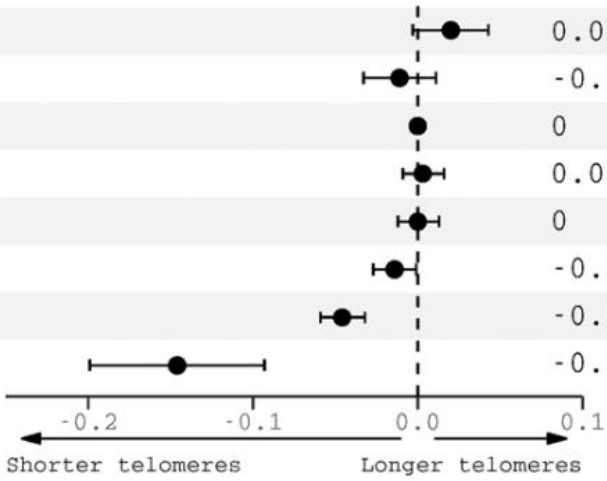
But 14 years longer!

Okada *Plastic and Recon Surg* 2013

Tip 4: Take Care with Alchohol

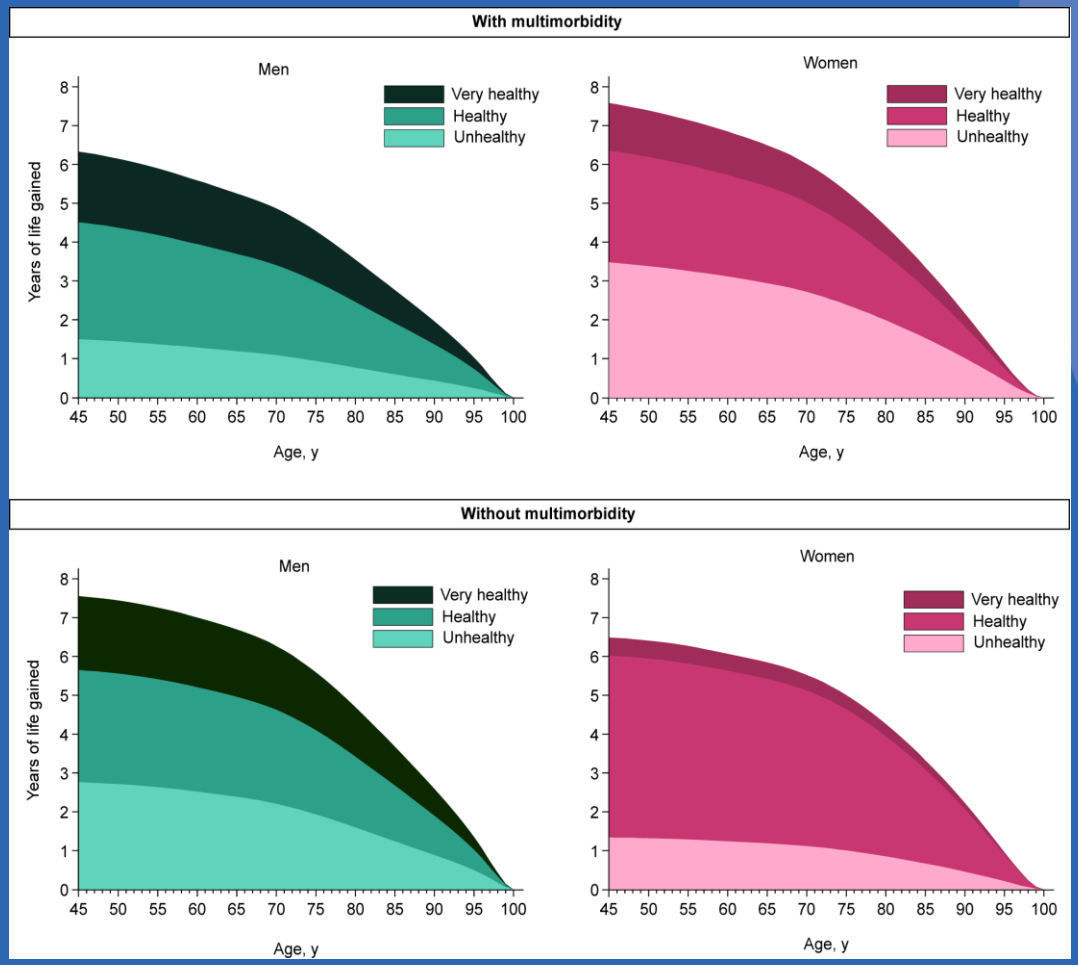
- Telomere length is a potential biomarker of ageing
- Repetitive nucleotide sequences act as cap at ends of chromosomes but 50-100 lost at each cell division
- Telomere shortening therefore occurs with cell ageing

Alcohol.intake.weekly	N	Estimate	LCI	UCI	p.value
Never drinker	8240	0.02	-0.003	0.043	0.081
Previous drinker	9393	-0.011	-0.033	0.011	0.332
<6 units	42279	0	0	0	0
6- <11 units	43536	0.003	-0.009	0.016	0.598
11- <17 units	46237	0	-0.012	0.013	0.948
17- <29 units	48291	-0.014	-0.027	-0.001	0.034
29+ units	47378	-0.046	-0.059	-0.032	2.36e-11
Alcohol use disorder	1301	-0.146	-0.199	-0.093	6.14e-08



Topiwala *Mol Psychiatry* 2022

Tip 5: Ideally Do It ALL!



- Life expectancy at 45yrs in the healthiest was ♂ 7.6yrs and 6.5yrs♀ more
- Healthiest:
  - >150mins/week
  - ≥5 fruit and/or veg/day
  - Non-smoker
  - Alcohol ≤14U/week
- Co-morbidity included:
  - Hypertension
  - Diabetes

Potential Factors

Summary

- Cardiovascular disease not affect everyone with AS
- Standard tests picks up abnormalities in @ one third
- There is no specific therapy to AS cardiomyopathy, but current standard therapies are available and help
- These are not curative and there is residual risk to impaired quality of life and life expectancy
- Fibrosis is a core feature of pathogenesis of AS cardiomyopathy on PM and imaging
- Phenoage is advanced in AS – does this offer insights?
- Biological ageing can be modified: people with AS can do things that help