Prevention of Heart Failure (HFrEF and HFpEF)

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15th Annual Orange County
Symposium for Cardiovascular
Disease Prevention

Disclosures:

- none

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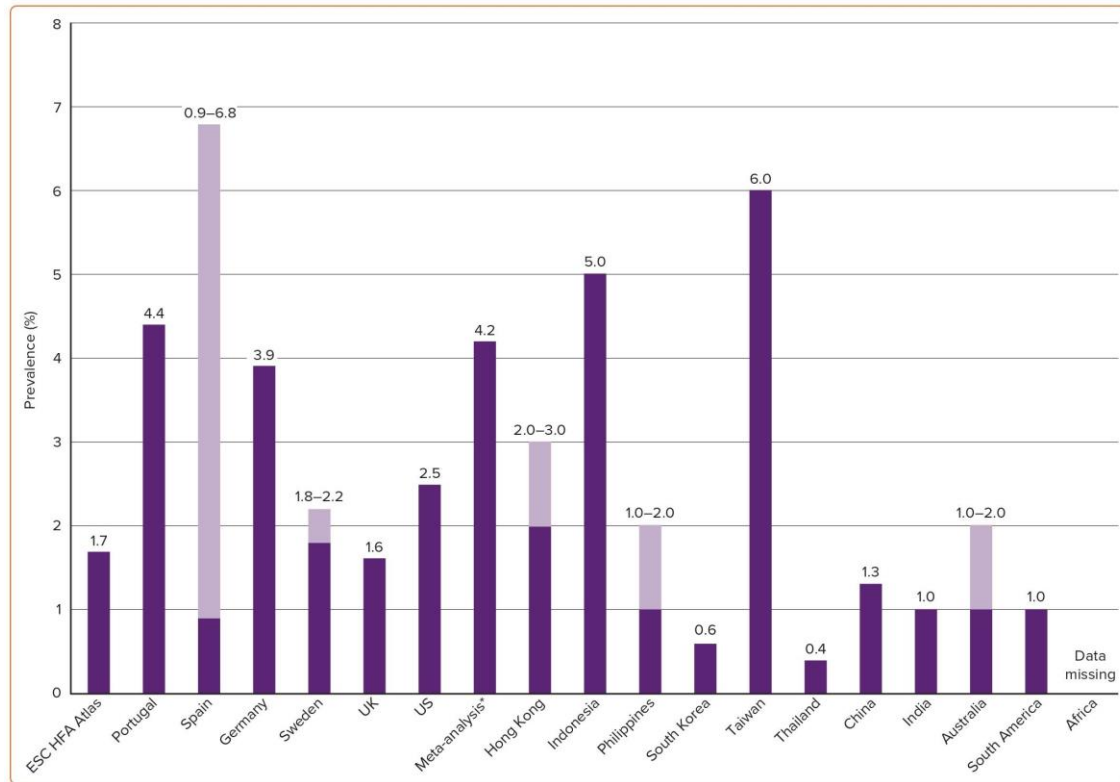Symposium for Cardiovascular
Disease Prevention

Definition of Heart Failure

"A pathophysiological state in which an abnormality of cardiac function is responsible for the failure of the heart to pump blood at a rate commensurate with the requirements of the metabolising tissues" (E Braunwald, 1980)
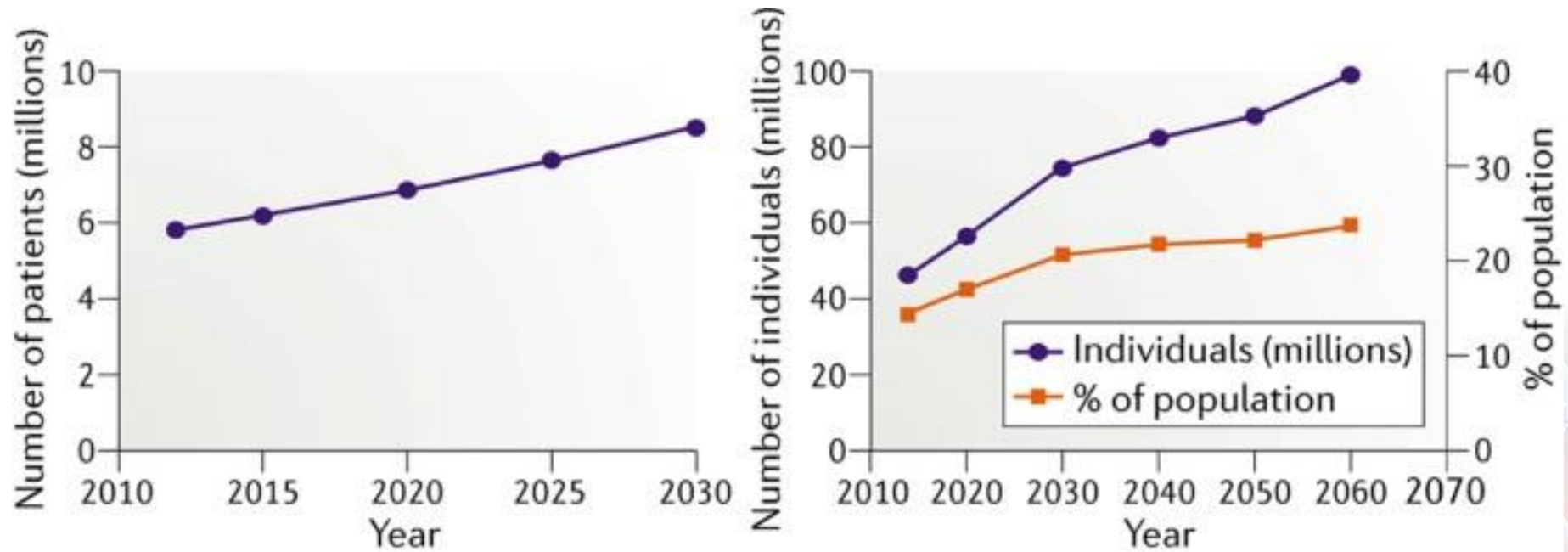
Epidemiology of Heart Failure

*Meta-analysis of studies from developed countries using echocardiographic case validation. ESC = European Society of Cardiology; HFA = Heart Failure Association.

Shahim B. Global public health burden of heart failure: an updated review. Published online October 5, 2023.

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Epidemiology of Heart Failure

Nature Reviews | Cardiology

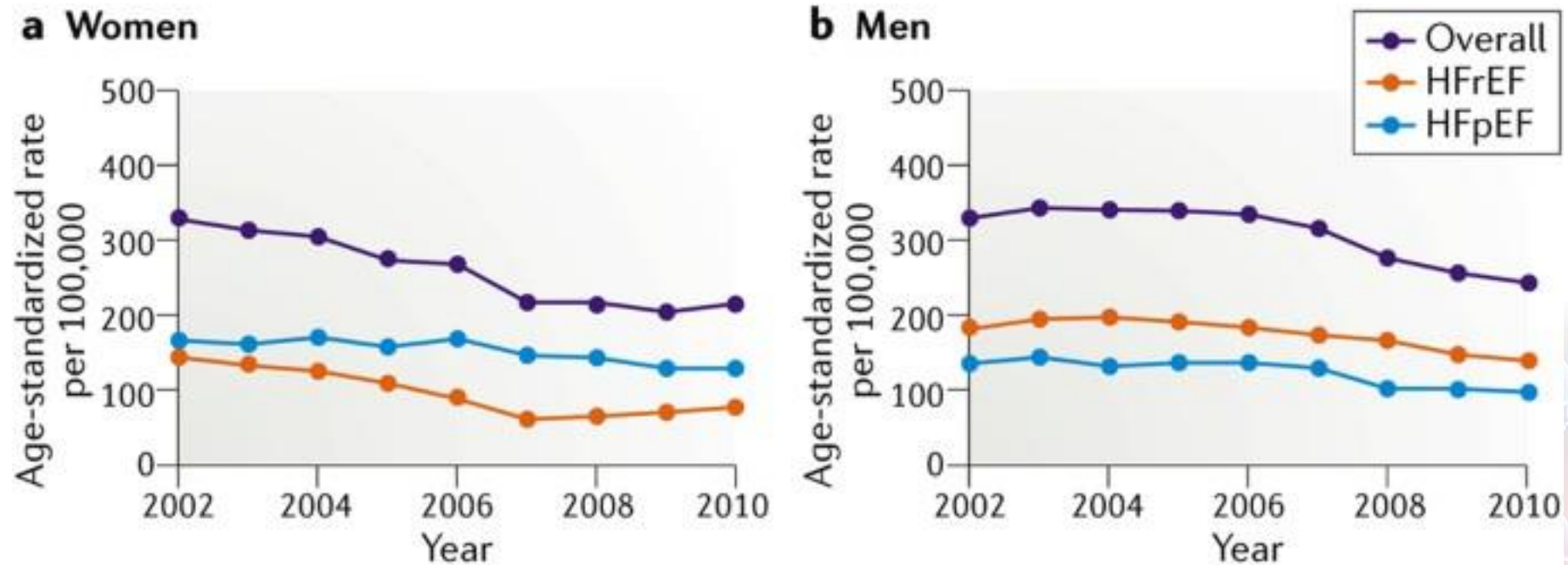Dunlay SM, Roger VL, Redfield MM. Epidemiology of heart failure with preserved ejection fraction. Nat Rev Cardiol. 2017;14(10):591-602.

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Epidemiology of Heart Failure

Nature Reviews | Cardiology

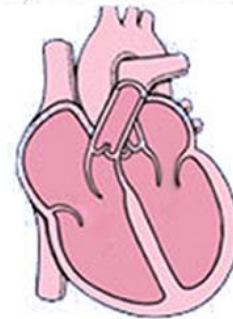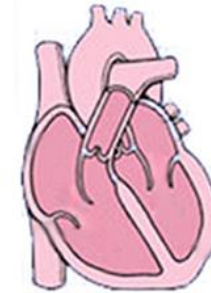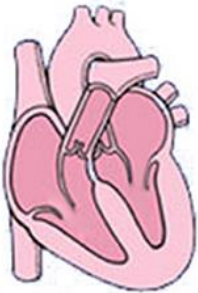15th Annual Orange County Symposium for Cardiovascular Disease Prevention

Dunlay SM, Roger VL, Redfield MM. Epidemiology of heart failure with preserved ejection fraction. Nat Rev Cardiol. 2017;14(10):591-602.

Epidemiology of Heart Failure

Characteristics	HFrEF	HFmrEF	HFpEF
Age	↑	↑↑	↑↑↑
Women	↓↓	↓	↑
Ischaemic heart disease	↑↑↑	↑↑↑	↑
AF	↑	↑↑	↑↑↑
Hypertension	↑	↑↑	↑↑↑
Diabetes	↑↑↑	↑↑↑	↑↑↑
Chronic kidney disease	↑↑	↑↑	↑↑↑
Natriuretic peptide levels	↑↑↑	↑	↑

HFrEF
(LVEF<40%)

HFmrEF
(LVEF 40-49%)

HFpEF
(LVEF≥50%)

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Epidemiology of Heart Failure

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Definition of Heart Failure

STAGE A:
At-Risk for Heart Failure

Patients at risk for HF but without current or previous symptoms/signs of HF and without structural/ functional heart disease or abnormal biomarkers

Patients with hypertension, CVD, diabetes, obesity, exposure to cardiotoxic agents, genetic variant for cardiomyopathy, or family history of cardiomyopathy

STAGE B:
Pre-Heart Failure

Patients without current or previous symptoms/signs of HF but evidence of 1 of the following:

Structural heart disease

Evidence of increased filling pressures

Risk factors and
• increased natriuretic peptide levels or
• persistently elevated cardiac troponin
in the absence of competing diagnoses

STAGE C:
Symptomatic Heart Failure

Patients with current or previous symptoms/signs of HF

STAGE D:
Advanced Heart Failure

Marked HF symptoms that interfere with daily life and with recurrent hospitalizations despite attempts to optimize GDMT

Heidenreich PA, et al. *Circulation.* 2022

Definition of Heart Failure

STAGE A: At-Risk for Heart Failure 22.4%	STAGE B: Pre-Heart Failure 34.1%	STAGE C: Symptomatic Heart Failure 23.6%	STAGE D: Advanced Heart Failure 0.2%
Patients at risk for HF but without current or previous symptoms/signs of HF and without structural/functional heart disease or abnormal biomarkers	Patients without current or previous symptoms/signs of HF but evidence of 1 of the following:	Patients with current or previous symptoms/signs of HF	Marked HF symptoms that interfere with daily life and with recurrent hospitalizations despite attempts to optimize GDMT
	Structural heart disease		
	Evidence of increased filling pressures		
Patients with hypertension, CVD, diabetes, obesity, exposure to cardiotoxic agents, genetic variant for cardiomyopathy, or family history of cardiomyopathy	Risk factors and • increased natriuretic peptide levels or • persistently elevated cardiac troponin in the absence of competing diagnoses		

Heidenreich PA, et al. *Circulation*. 2022
Ammar KA, et al. *Circulation*. 2007.

Definition of Heart Failure

STAGE A:
At-Risk for Heart Failure
22.4%

Patients at risk for HF but without current or previous symptoms/signs of HF and without structural/ functional heart disease or abnormal biomarkers

Patients with hypertension, CVD, diabetes, obesity, exposure to cardiotoxic agents, genetic variant for cardiomyopathy, or family history of cardiomyopathy

STAGE B:
Pre-Heart Failure
34.1%

Patients without current or previous symptoms/signs of HF but evidence of 1 of the following:

Structural heart disease

Evidence of increased filling pressures

Risk factors and
• increased natriuretic peptide levels or
• persistently elevated cardiac troponin
in the absence of competing diagnoses

STAGE C:
Symptomatic Heart Failure
23.6%

Patients with current or previous symptoms/signs of HF

STAGE D:
Advanced Heart Failure
0.2%

Marked HF symptoms that interfere with daily life and with recurrent hospitalizations despite attempts to optimize GDMT

Heidenreich PA, et al. *Circulation.* 2022
Ammar KA, et al. *Circulation.* 2007.

At Risk for HF (Stage A)

Patients with hypertension	→	Optimal control of BP (1)
Patients with type 2 diabetes and CVD or high risk for CVD	→	SGLT2i (1)
Patients with CVD	→	Optimal management of CVD (1)
Patients with exposure to cardiotoxic agents	→	Multidisciplinary evaluation for management (1)
First-degree relatives of patients with genetic or inherited cardiomyopathies	→	Genetic screening and counseling (1)
Patients at risk for HF	→	Natriuretic peptide biomarker screening (2a)
Patients at risk for HF	→	Validated multivariable risk scores (2a)

Pre-HF (Stage B)

Patients with LVEF ≤40%	→	ACEi (1)
Patients with a recent MI and LVEF ≤40%	→	ARB if ACEi intolerant (1)
Patients with LVEF ≤40%	→	Beta blocker (1)
Patients with LVEF ≤30%; >1 y survival; >40 d post MI	→	ICD (1)
Patients with nonischemic cardiomyopathy	→	Genetic counseling and testing (2a)

Continue lifestyle modifications and management strategies implemented in Stage A, through Stage B
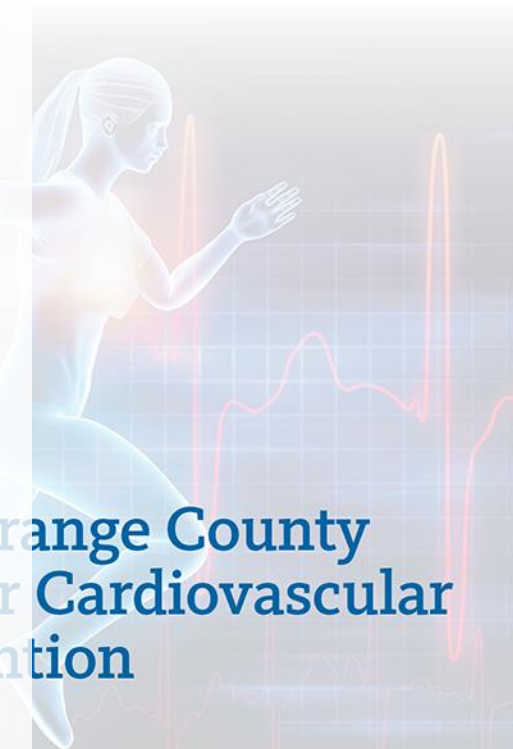
Lifestyle for Prevention of HF

1. Eat better
2. Be more active
3. Quit tobacco
4. Get healthy sleep – new in 2022
5. Manage weight
6. Control cholesterol
7. Manage blood sugar
8. Manage blood pressure

Life's Essential 8™

Heart.org

Ogunmoroti O, et al. Life's simple 7 and incident HF: MESA. JAHA. 2017

The American Heart Association's "Life's Simple 7"

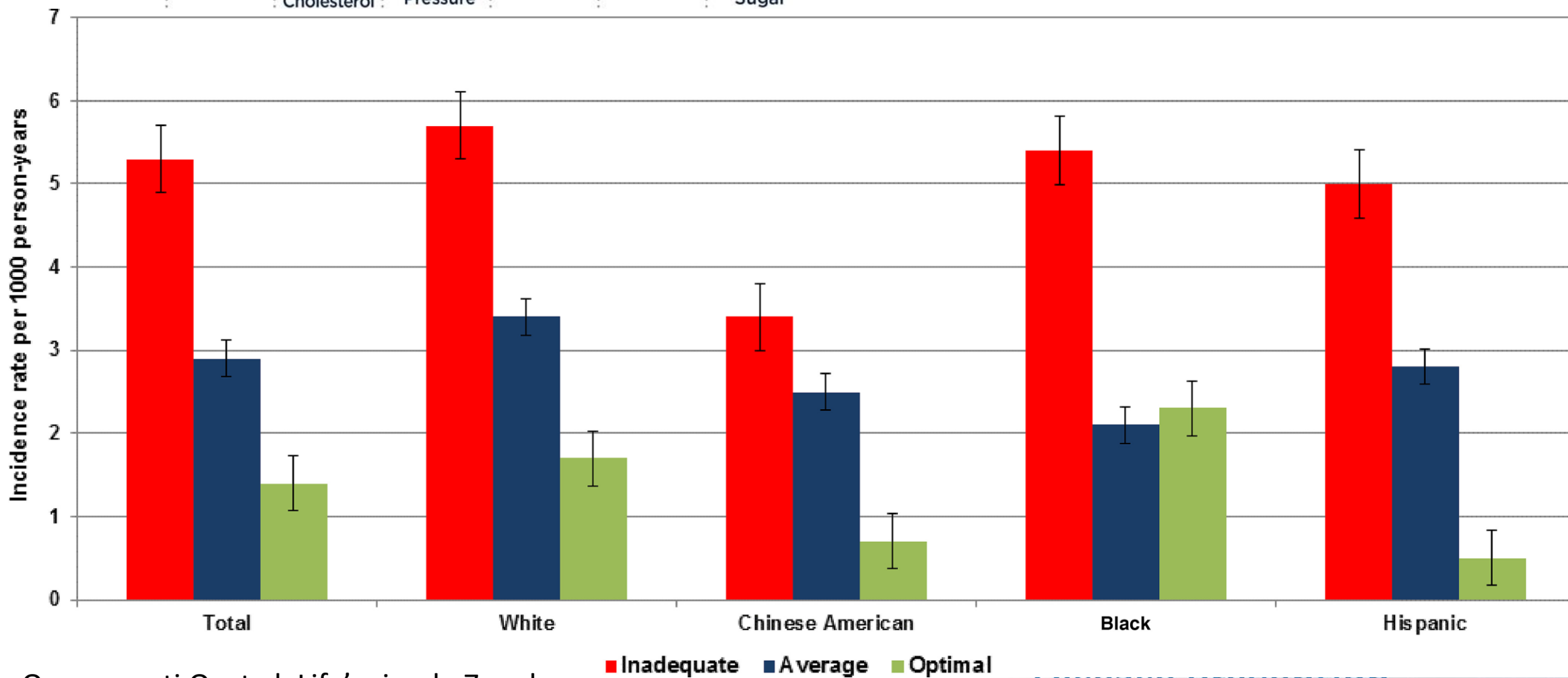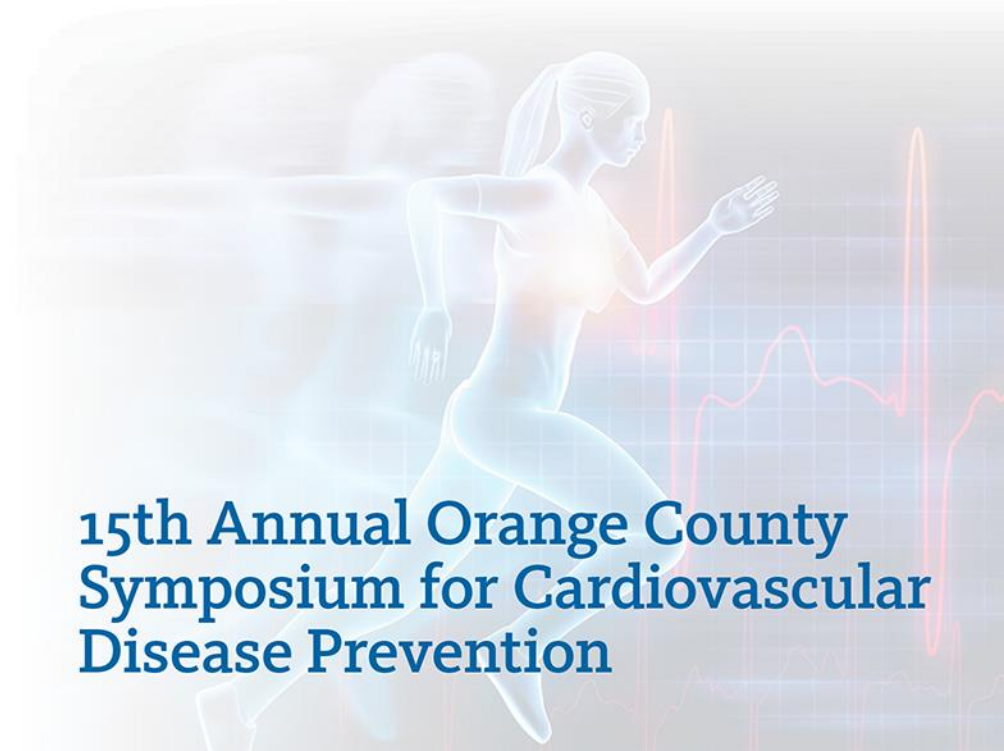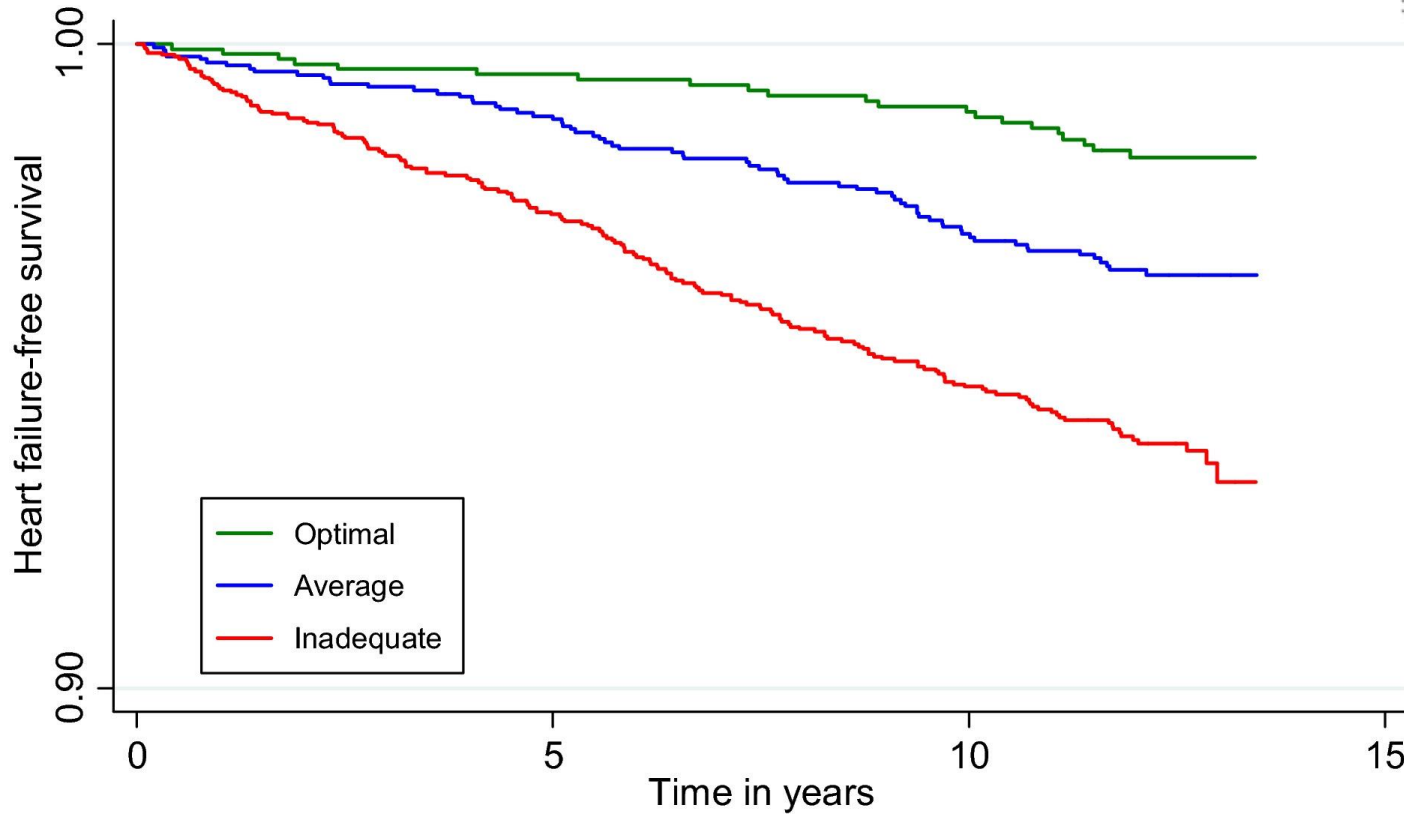Stop Smoking · Get Active · Control Your Cholesterol · Manage Blood Pressure · Eat Healthy · Lose Weight · Reduce Blood Sugar

Heart failure-free survival vs. Time in years

Legend:
- Optimal
- Average
- Inadequate

Ogunmoroti O, et al. Life's simple 7 and incident HF: MESA. JAHA. 2017

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Obesity and HF

- Obesity is a prevailing epidemic (38% of US population) and is associated with multiple CVD states

- Multiple studies demonstrate an association with obesity and the development of heart failure

Ndumele CE, et al. JAHA. 2016.
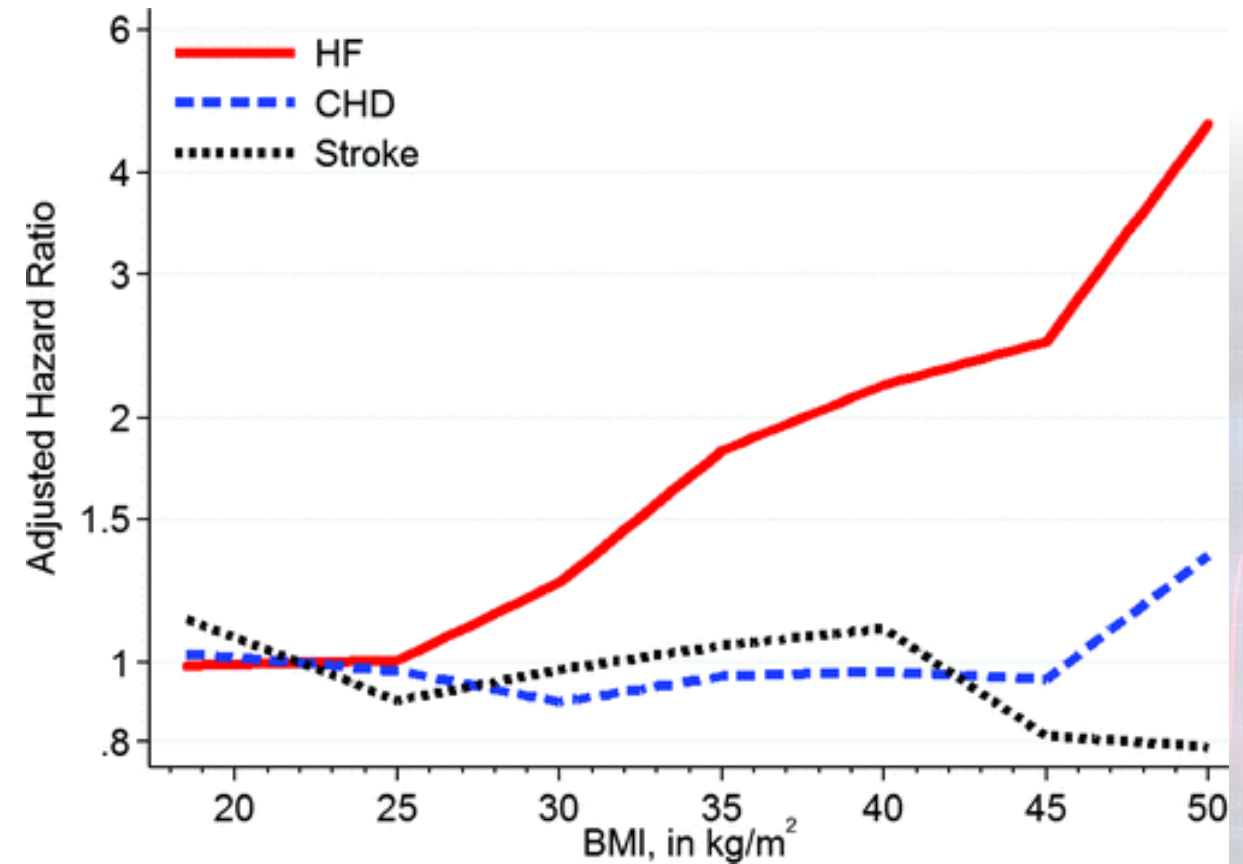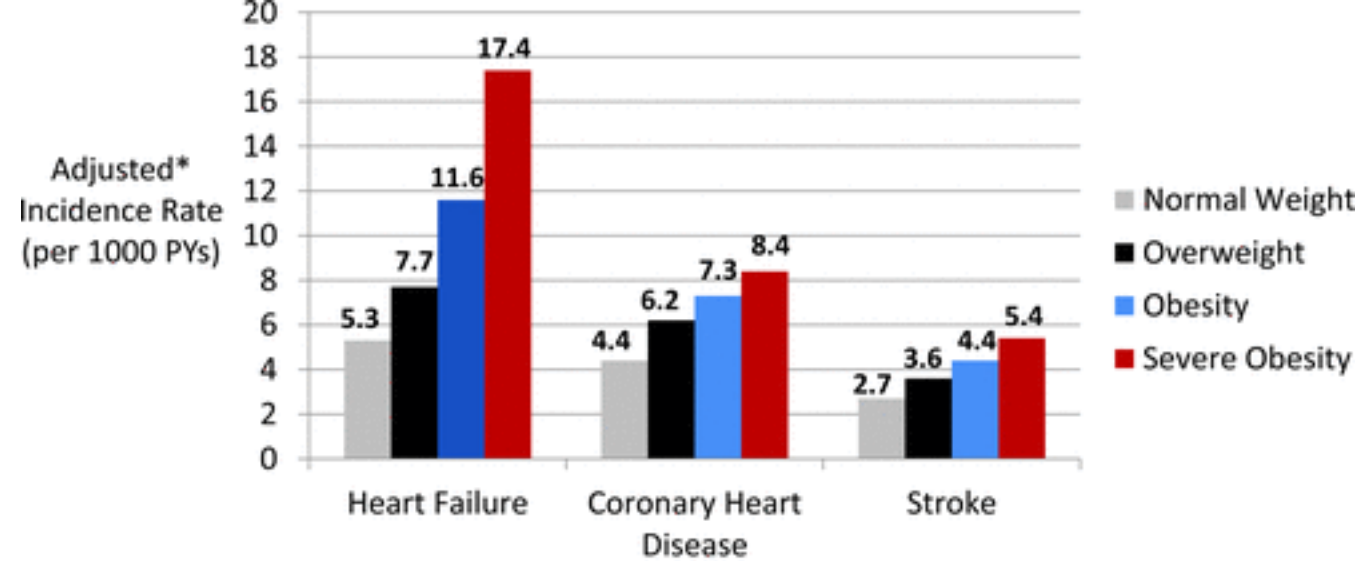
Obesity and HF

- Obesity is a prevailing epidemic (38% of US population) and is associated with multiple CVD states

- Multiple studies demonstrate an association with obesity and the development of heart failure

- Multivariate analysis adjusted for risk factors demonstrated 5% (men) and 7% (women) increased risk of developing HF per unit BMI

- Exercise and weight loss interventions may be beneficial in reducing HF risk

Kenchaiah S, et al. NEJM 2002.

II. Models with body-mass index and all covariates defined as time-dependent variables‡
A. Body-mass index as a continuous variable   1.06 (1.04–1.08)   <0.001
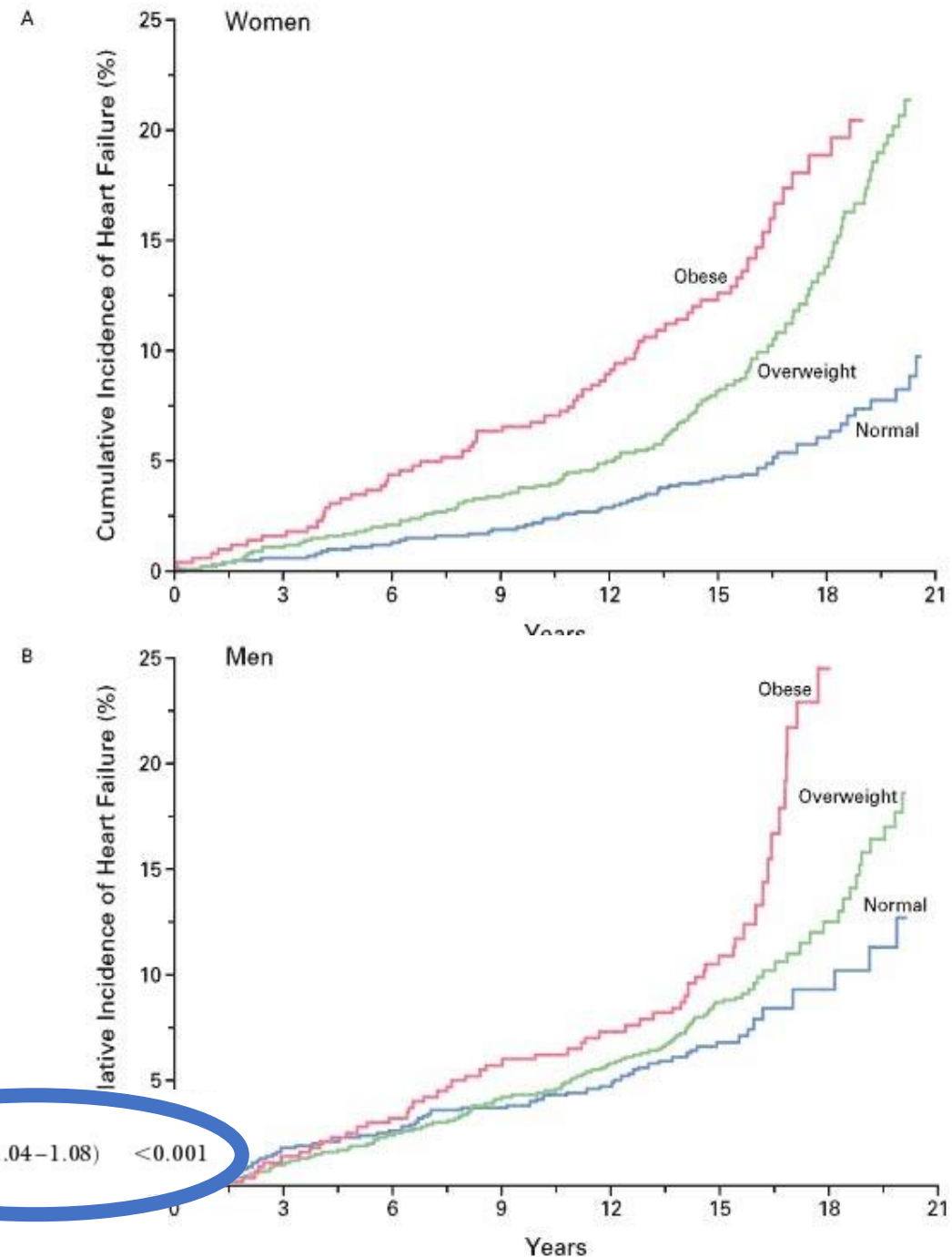
Obesity and HF

- STEP-HFpEF tested semaglutide in obese nondiabetic patients with HFpEF (elevated BNP, elevated LV pressure, or HF hospitalization)

- Co-Primary Endpoints :
  - KCCQ Symptom Score
  - Weight Loss

- Secondary endpoints :
  - 6 minute walk test
  - NT-pro BNP
  - CRP

- Demonstrated improvement in weight loss, symptoms, functional status and biomarkers

- Further trials ongoing

Kosiborod MN, et al. Semaglutide in patients with heart failure with preserved ejection fraction and obesity. N Engl J Med. 2023
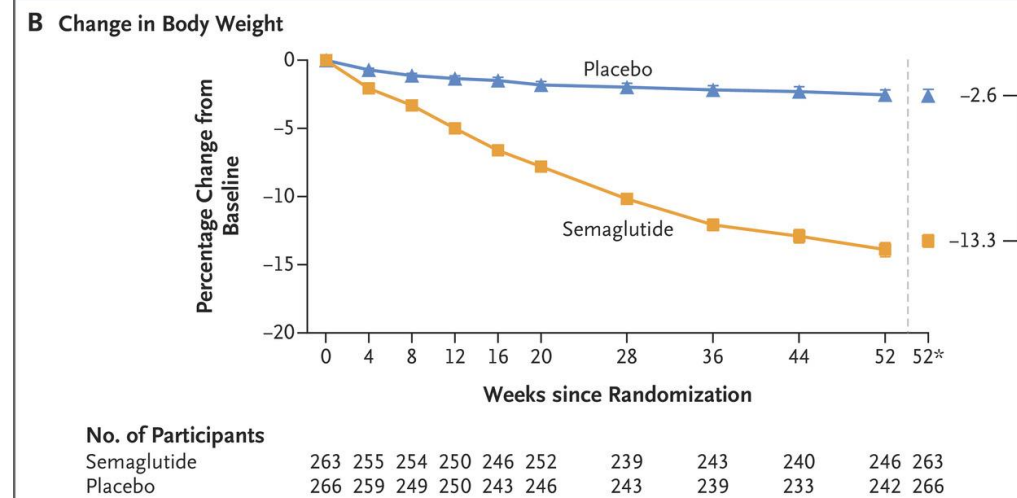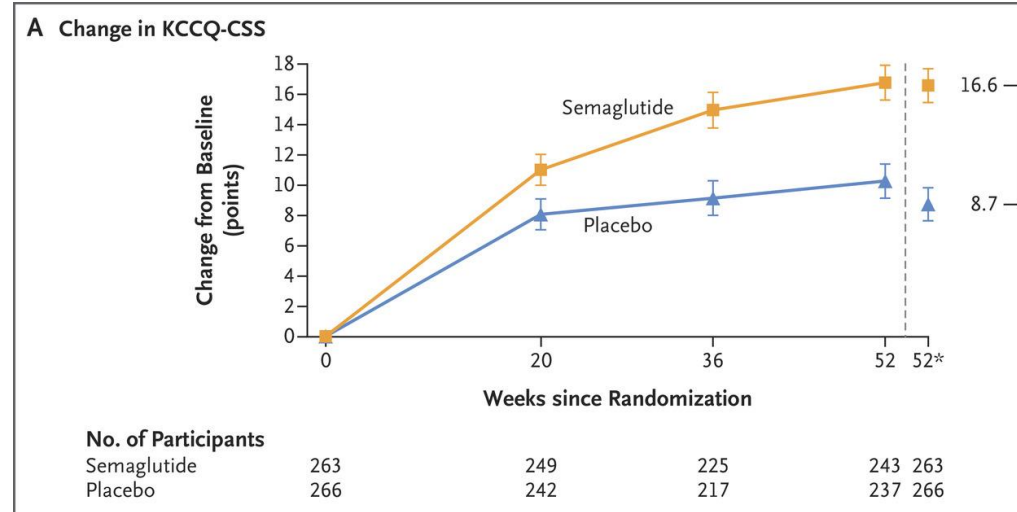
Hypertension and heart failure

- Elderly patients recruited in the 1990s were enrolled in the Cardiovascular Heart Study and Health Aging and Body Composition Study

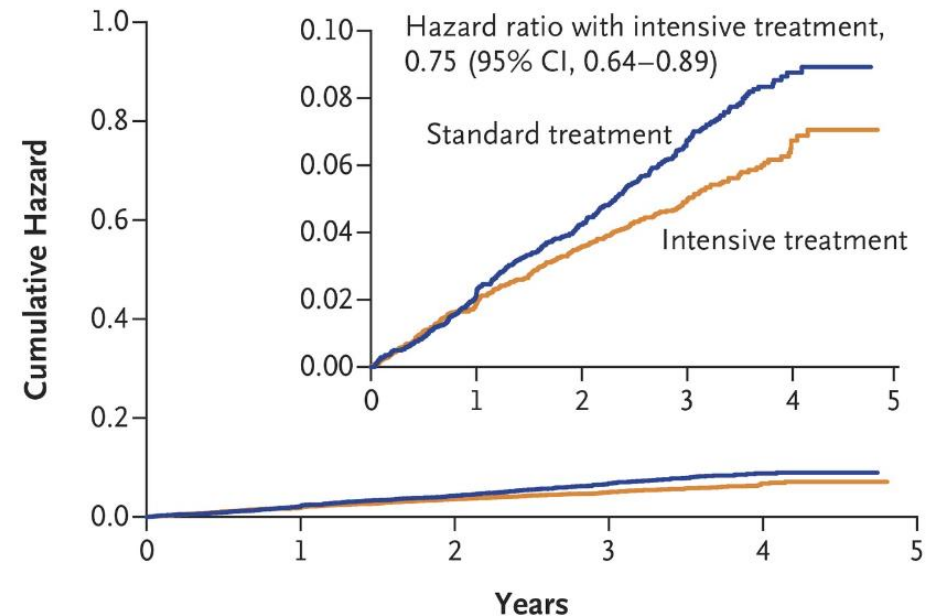- 11% of patients developed heart failure, with escalating risk over SBP > 120 mmHg
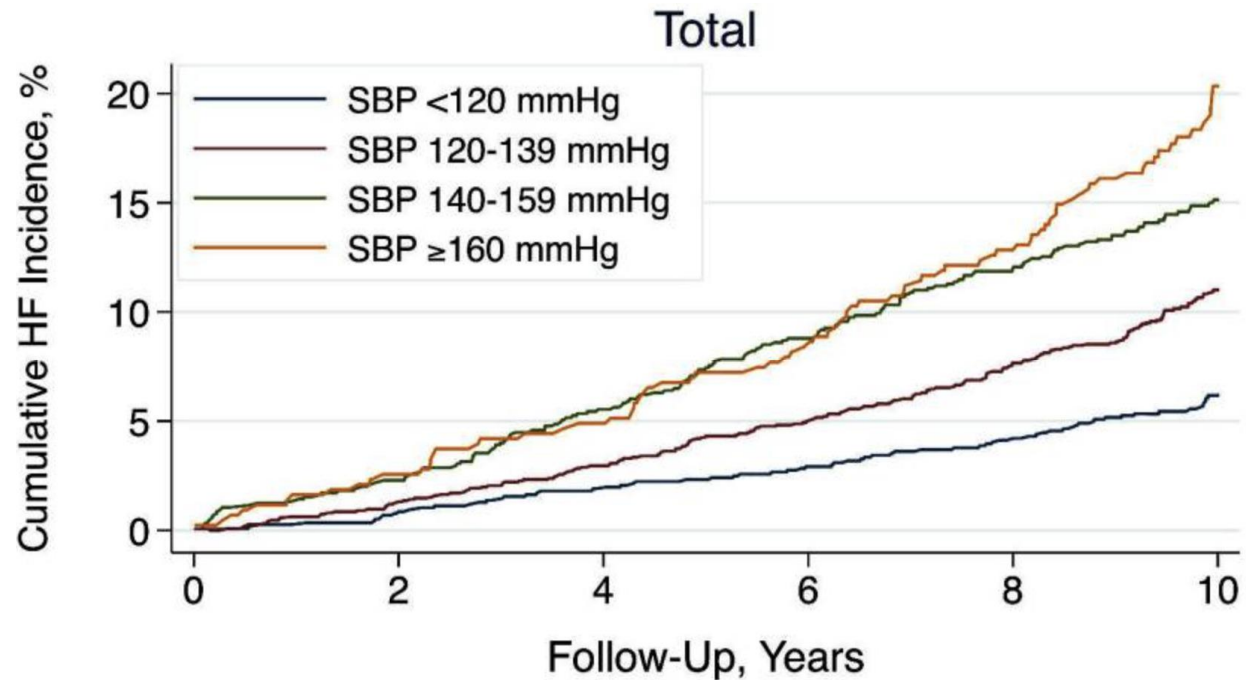
Butler J, et al. The CHS and Health-ABC. Heart. 2011.

Hypertension and heart failure

- SPRINT trial demonstrated substantial benefit with intensive blood pressure control (120 mmHg vs 140 mmHg) in reducing CV and all cause mortality in high-risk nondiabetic adults

- Intensive BP control was associated with lower heart failure risk over 5 years (1.3% vs 2.1% p=0.002)


A **Primary Outcome**

Hazard ratio with intensive treatment, 0.75 (95% CI, 0.64–0.89)

Standard treatment

Intensive treatment

Cumulative Hazard

Years

No. at Risk

|					
Standard treatment	4683	4437	4228	2829	721
Intensive treatment	4678	4436	4256	2900	779

The SPRINT Research Group. NEJM. 2015.

Hyperlipidemia and HF

- Acute coronary syndromes are a common cause of HF

- High intensity statins have demonstrated benefit in reducing HF post-ACS. This benefit persists in high-risk groups (BNP>80)

- Metanalyses confirm benefit in this patient population

Scirica BM, et al. PROVE-IT TIMI-22. JACC. 2006.
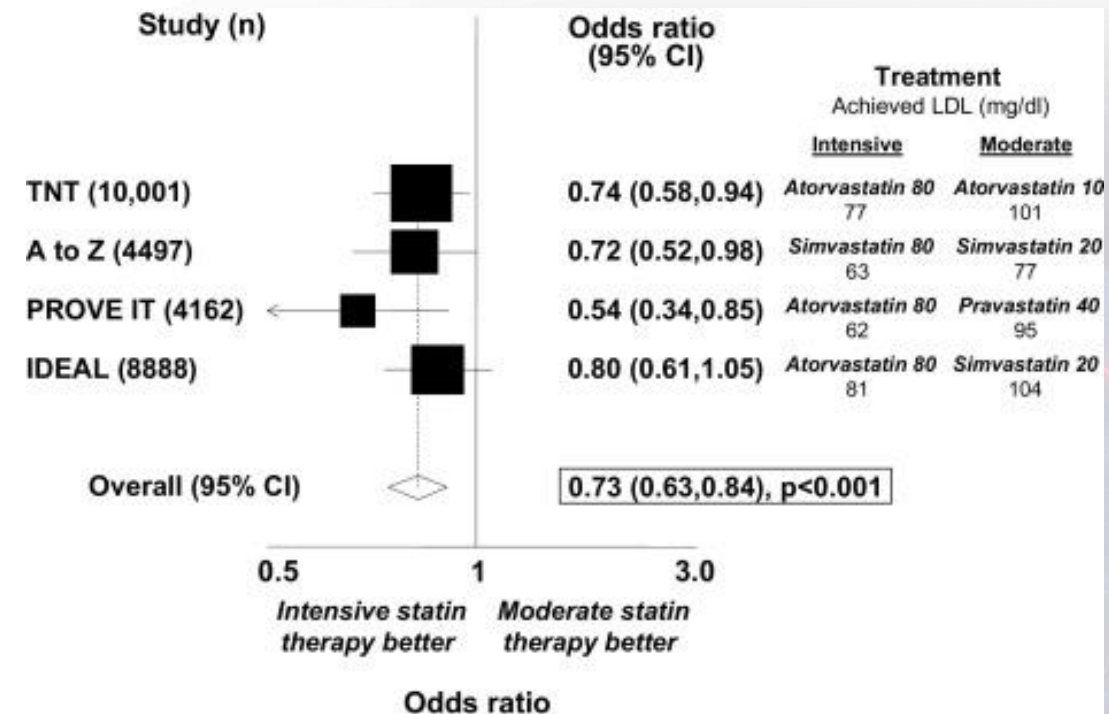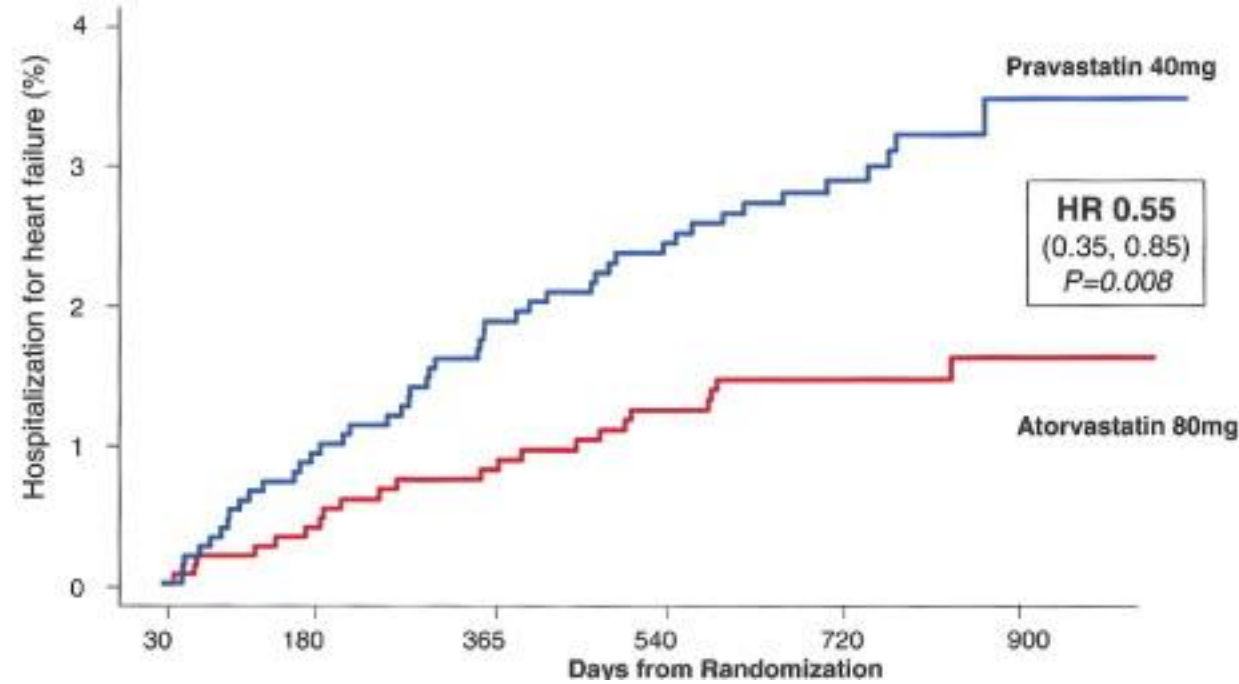
Lipoprotein(a) and HF

- Prior studies have suggested risk of HF associated with Lp(a)

- Effect appears to be associated with antecedent MI. When MI excluded from analyses, there is no difference in the incidence of HF in regard to Lp(a).

- Prevention of MI and ACS is key!
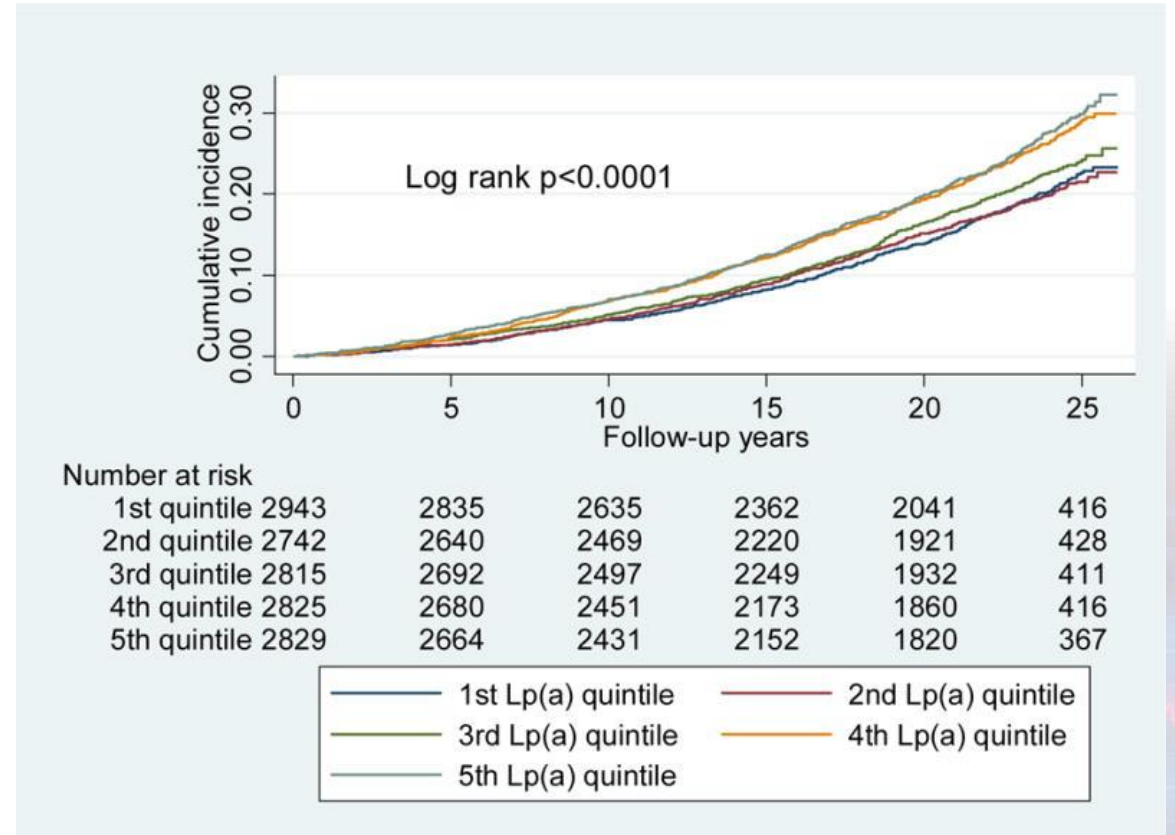
Agarwala A, et al. Lp(a) with incident CHF hospitalization. *Atherosclerosis*. 2017

Diabetes and heart failure

- Historically: no cardiovascular benefit with diabetes medications

- Recent pharmacologic developments include SGLT2 inhibitors and GLP-1 RAs, both of which have demonstrated substantial ASCVD benefits in DM patients in cardiovascular outcomes trials

CENTRAL ILLUSTRATION: Diversity of Physiologic Effects of SGLT2i and GLP1RA

Wilcox, T. et al. J Am Coll Cardiol. 2020;75(16):1956–74.
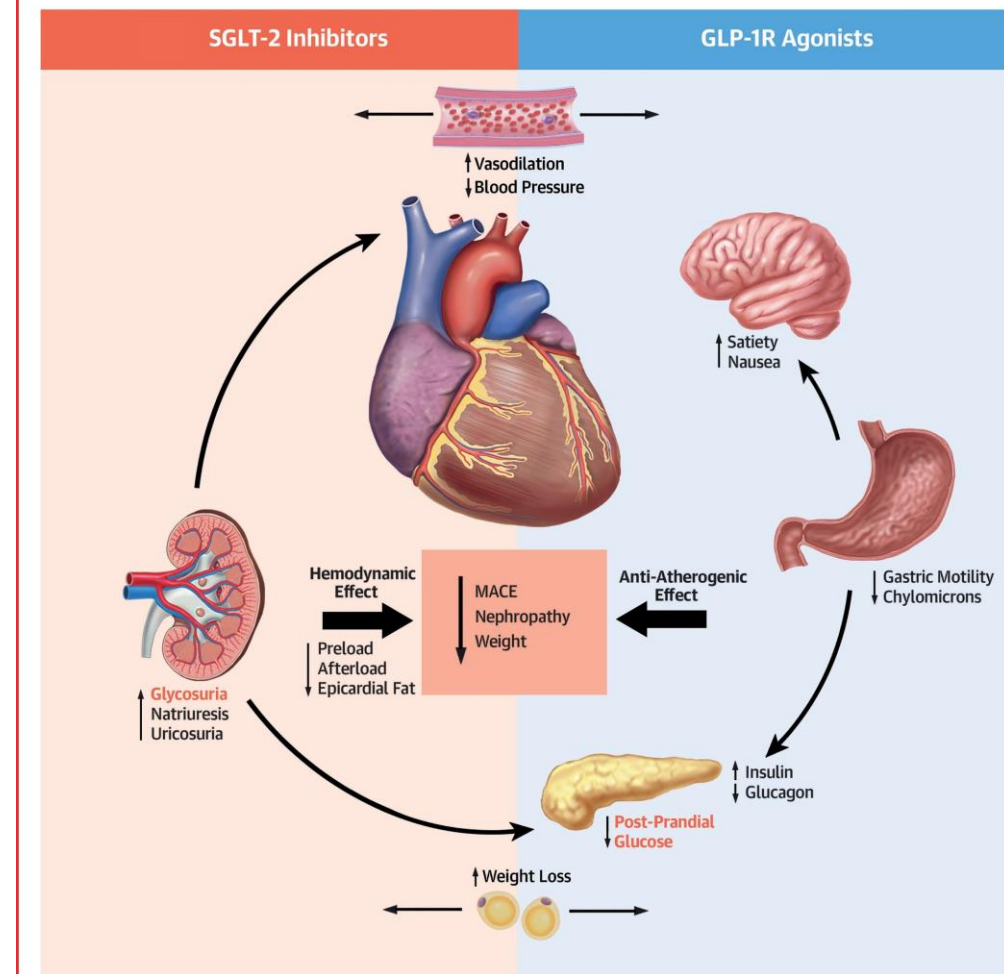
Diabetes and heart failure

- CV outcome trial for empagliflozin (EMPA-REG OUTCOMES) demonstrated substantial benefit in CV death, HF hospitalization and all cause mortality
- Significant benefit in reduction of heart failure hospitalization

A **Primary Outcome**

D **Hospitalization for Heart Failure**

Hazard ratio, 0.65 (95% CI, 0.50–0.85)
P=0.002
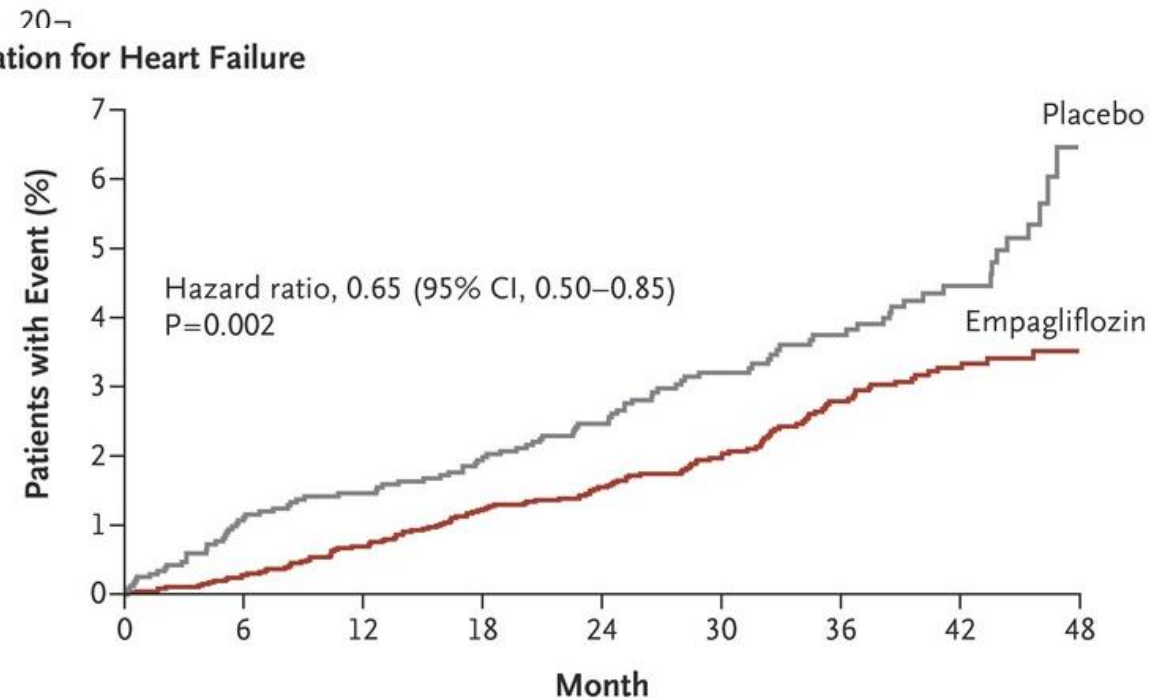
No. at Risk

Empagliflozin	4687	4614	4523	4427	3988	2950	2487	1634	395
Placebo	2333	2271	2226	2173	1932	1424	1202	775	168

Diabetes and heart failure

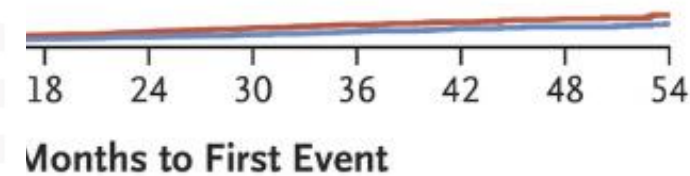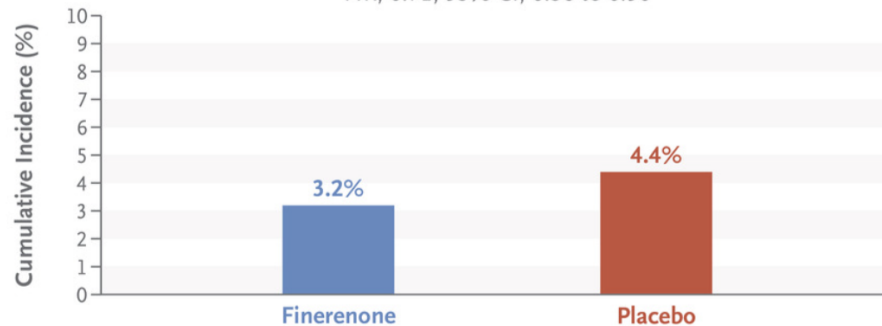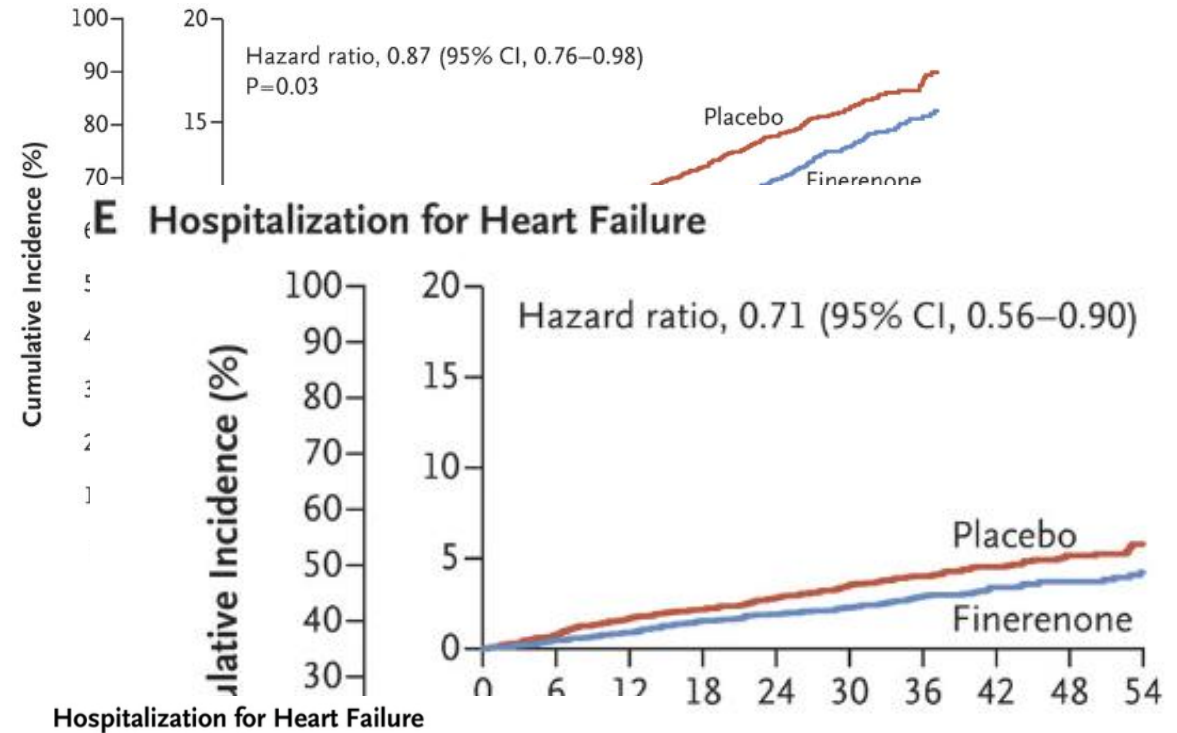- Meta-analysis of three pivotal SGLT2 inhibitors demonstrate significant reduction in HF hospitalization for patients with ASCVD and trend towards reduction in high-risk patients

- SGLT2 inhibitors now first line therapy for heart failure as well

	Patients		Events	Events per 1000 patient-years		Weight (%)	HR	HR (95% CI)
	Treatment (n)	Placebo (n)		Treatment	Placebo			
Patients with atherosclerotic cardiovascular disease								
EMPA-REG OUTCOME	4687	2333	463	19·7	30·1	30·9		0·66 (0·55–0·79)
CANVAS Program	3756	2900	524	21·0	27·4	32·8		0·77 (0·65–0·92)
DECLARE-TIMI 58	3474	3500	597	19·9	23·9	36·4		0·83 (0·71–0·98)
Fixed effects model for atherosclerotic cardiovascular disease (p<0·0001)								0·76 (0·69–0·84)
Patients with multiple risk factors								
CANVAS Program	2039	1447	128	8·9	9·8	30·2		0·83 (0·58–1·19)
DECLARE-TIMI 58	5108	5078	316	7·0	8·4	69·8		0·84 (0·67–1·04)
Fixed effects model for multiple risk factors (p=0·0634)								0·84 (0·69–1·01)

0·35   0·50   1·00   2·50

← Favours treatment   Favours placebo →

Zelniker TA, et al. *Lancet*. 2019.

Diabetes, CKD, and Heart Failure

- Finerenone is a novel nonsteroidal mineralocorticoid receptor antagonist

- Recent trials demonstrated benefit in diabetic kidney disease in reducing CKD progression and CV events

- This agent appears to reduce the development of HF and hospitalization

Pitt B, et al. NEJM. 2021

Cancer and HF

- Heart disease and cancer share similar lifestyle and health risk factors
  - diabetes, obesity, hypertension, tobacco use
- Cancer death rates for middle aged US adults have declined from 1999 to 2017
- Heart disease rates for the same patient group have declined from 1999 to 2011 but increased from 2011 onwards. This is thought to be due to obesity, cardiometabolic diseases, and heart failure
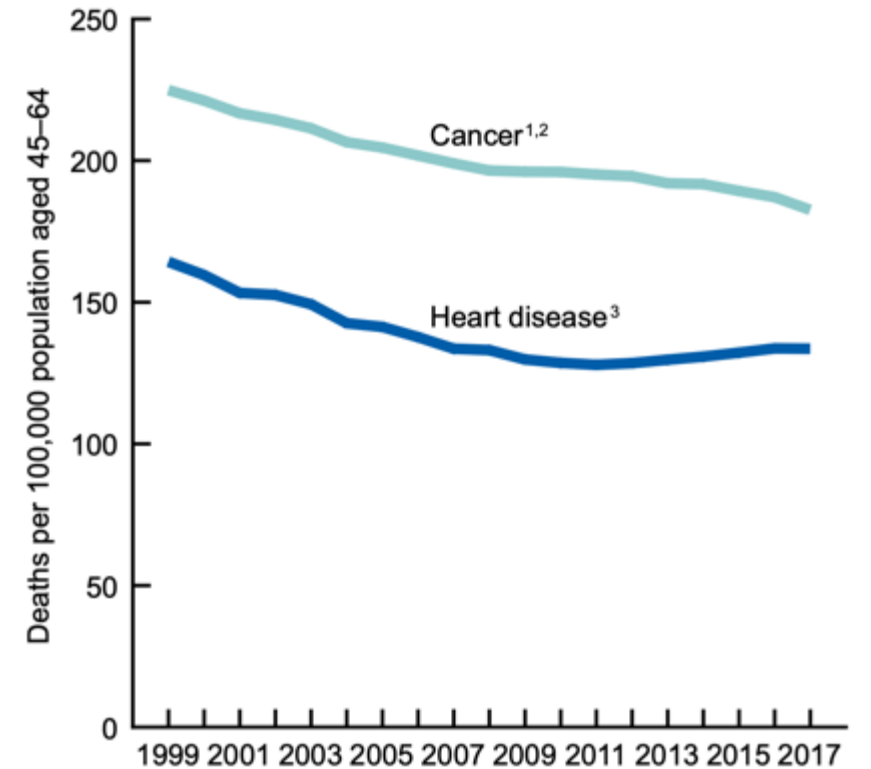
Curtin SC, Trends in Cancer and Heart Disease Death Rates Among Adults Aged 45–64: United States, 1999–2017National Vital Statistics Report, May 2019
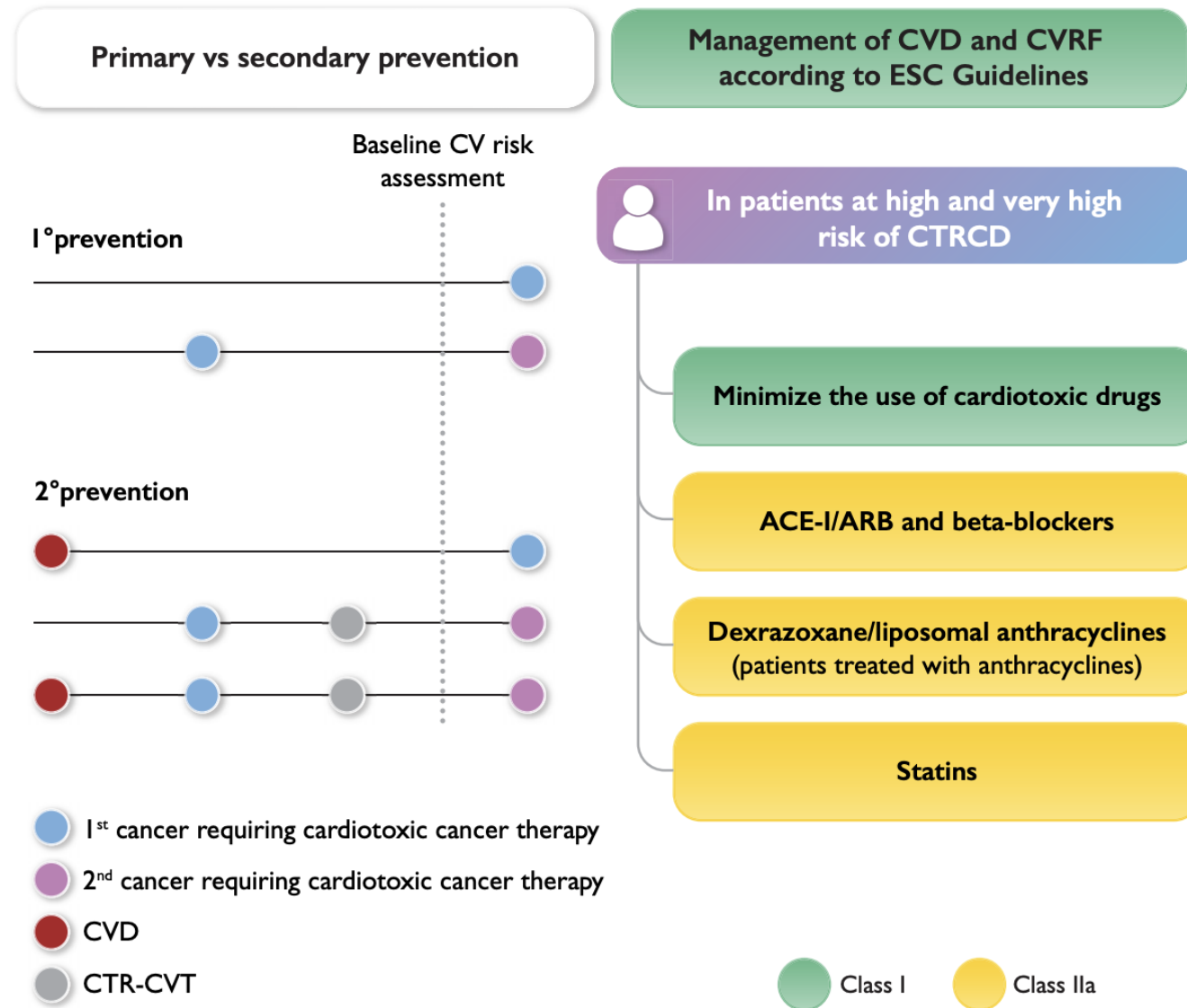
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Cancer and HF

- The next frontier of preventative cardiology may focus on treatment of cardiovascular risks in patients with comorbid cancer
- Growing evidence for surveillance and treatment benefit

Primary and secondary cancer-therapy related CV toxicity prevention strategies

Primary vs secondary prevention

Baseline CV risk assessment

1°prevention

2°prevention

- 1st cancer requiring cardiotoxic cancer therapy
- 2nd cancer requiring cardiotoxic cancer therapy
- CVD
- CTR-CVT

Management of CVD and CVRF according to ESC Guidelines

In patients at high and very high risk of CTRCD

Minimize the use of cardiotoxic drugs

ACE-I/ARB and beta-blockers

Dexrazoxane/liposomal anthracyclines (patients treated with anthracyclines)

Statins

Class I   Class IIa

Lyon AR, et al. ESC Cardio-oncology Guidelines. *Eur Heart J.* 2022.

Prevention of Heart Failure

- HFrEF and HFpEF affect different populations and preventative strategies may differ
- Lifestyle optimization is the foundation for cardiovascular disease prevention, including heart failure
- HFrEF incidence has decreased due to targeted treatment of hypertension and atherosclerosis
- Targeting other comorbidities earlier in life may prevent HFpEF
- New and exciting diabetes interventions provide future HF prevention strategies
- Cardiovascular disease prevention in cancer patients will be the next frontier of preventative cardiology

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