Obesità e malattie cardiovascolari: fisiopatologia e evidenze dalla letteratura

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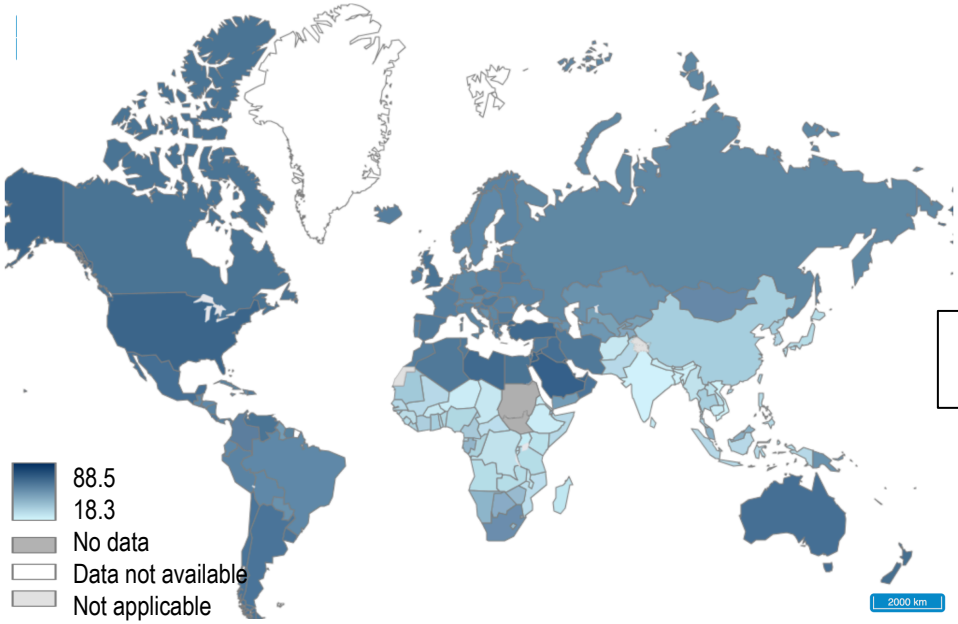
The pathophysiology of obesity in cardiovascular diseases is multifactorial, involving hemodynamic, metabolic, neurohormonal, and inflammatory mechanisms that collectively drive structural and functional changes in the heart and vasculature.

Why should cardiologists care about overweight and obesity?

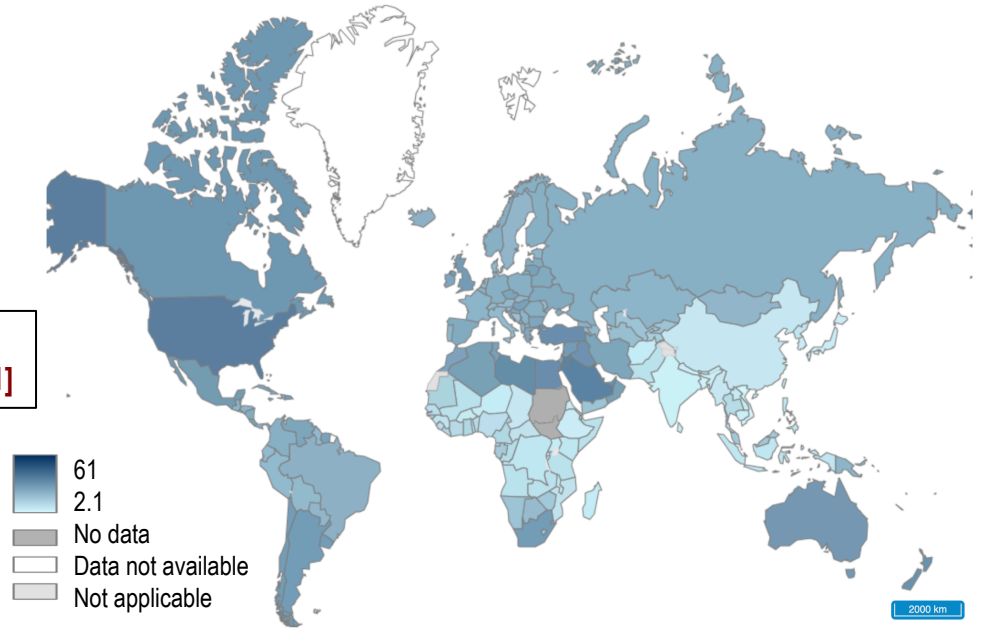
Prevalence* (%) of overweight (BMI ≥ 25) adults , 2016



Italy = 58.5 [54.2-62.5]

Mean BMI in Italy
25.6 kg/m^2 [25.1-26.1]

Prevalence* (%) of obese (BMI ≥ 30) adults , 2016



Italy = 19.9 [16.6-23.4]

*age-standardized estimate

World Health Organization

- Worldwide obesity has nearly tripled since 1975.
- In 2016, more than **1.35 billion** adults were overweight and **650 million** were obese.
- **39%** of adults were **overweight** in 2016, and **13% were obese**.
- 39 million children under the age of 5 were overweight or obese in 2020.
- Over 340 million children and adolescents aged 5-19 were overweight or obese in 2016.

World Health Organization. Obesity and overweight. June 9, 2021 (https://www.who.int/news-room/fact-sheets/detail/obesity -and-overweight).

International Journal of Cardiology 418 (2025) 132601

Clinical profile and management of patients with acute myocardial infarction admitted to cardiac care units: The EYESHOT-2 registry

the EYESHOT-2 Investigators[1]

Baseline clinical characteristics.

	Overall $n = 2806$	STEMI $n = 1329$	NSTEMI $n = 1477$	*P* value
BMI, kg/m^2 (mean ± SD)	27 ± 4	27 ± 4	27 ± 5	0.50
BMI > 30 kg/m^2 [a], n(%) *(data available for 2702 pts)*	539 (20.0)	243 (19.0)	296 (20.8)	0.27
Diabetes mellitus[b]	754 (26.9)	275 (20.7)	479 (32.4)	<0.0001

International Journal of Cardiology 433 (2025) 133290

LDL-cholesterol levels and lipid lowering therapy in secondary prevention. Baseline data from the BRING-UP prospective registry

Baseline characteristics and comorbidities in the total population and by setting of enrollment.

	Total population (n. 4790)	Discharge from hospitalizations (n. 2500)	Outpatients/day hospital (n. 2290)	P
BMI >27 kg/m^2, n. (%)	2044 (42.7)	1070 (42.8)	947 (42.5)	0.85
BMI ≥30 kg/m^2, n. (%)	945 (19.7)	493 (19.7)	452 (19.7)	0.99
Diabetes, n. (%)	1317 (27.5)	699 (27.5)	618 (27.0)	0.03
Type 1	28 (2.1)	15 (2.1)	13 (2.1)	
Type 2	1246 (94.6)	663 (94.9)	583 (94.3)	
Unknown	43 (3.3)	21 (3.0)	22 (3.6)	

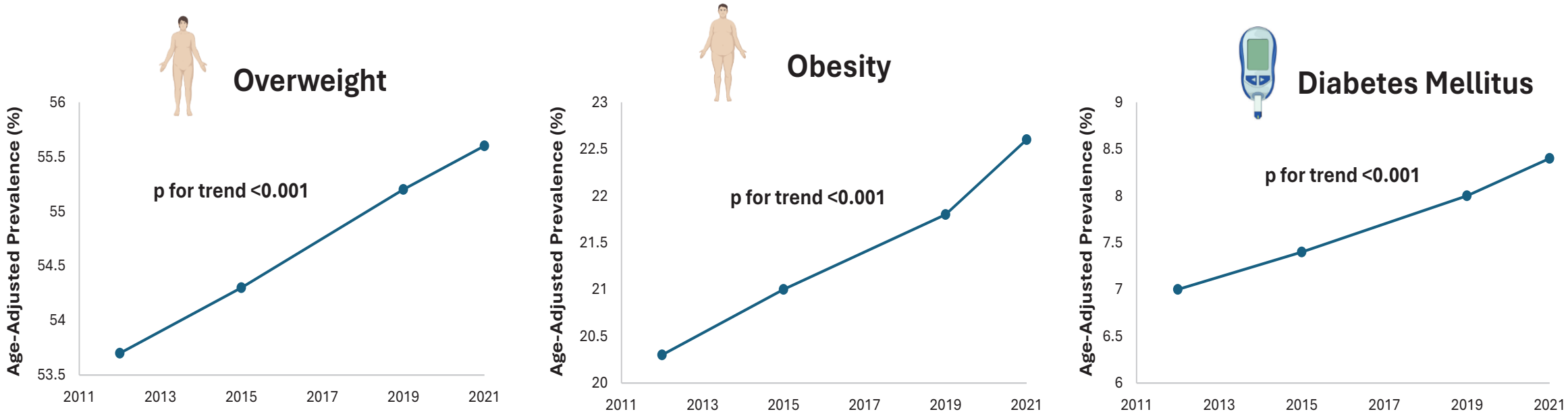
BRING-UP Prevention[1]

European Journal of Heart Failure (2025)

Heart failure-attributed mortality in Europe, 2012–2021

Marco Zuin[1,2,3*†], Pier Luigi Temporelli[4†], Marco Metra[5], Gianluigi Savarese[6], Gianluca Rigatelli[3], Claudio Bilato[7], and Fabrizio Oliva[8]

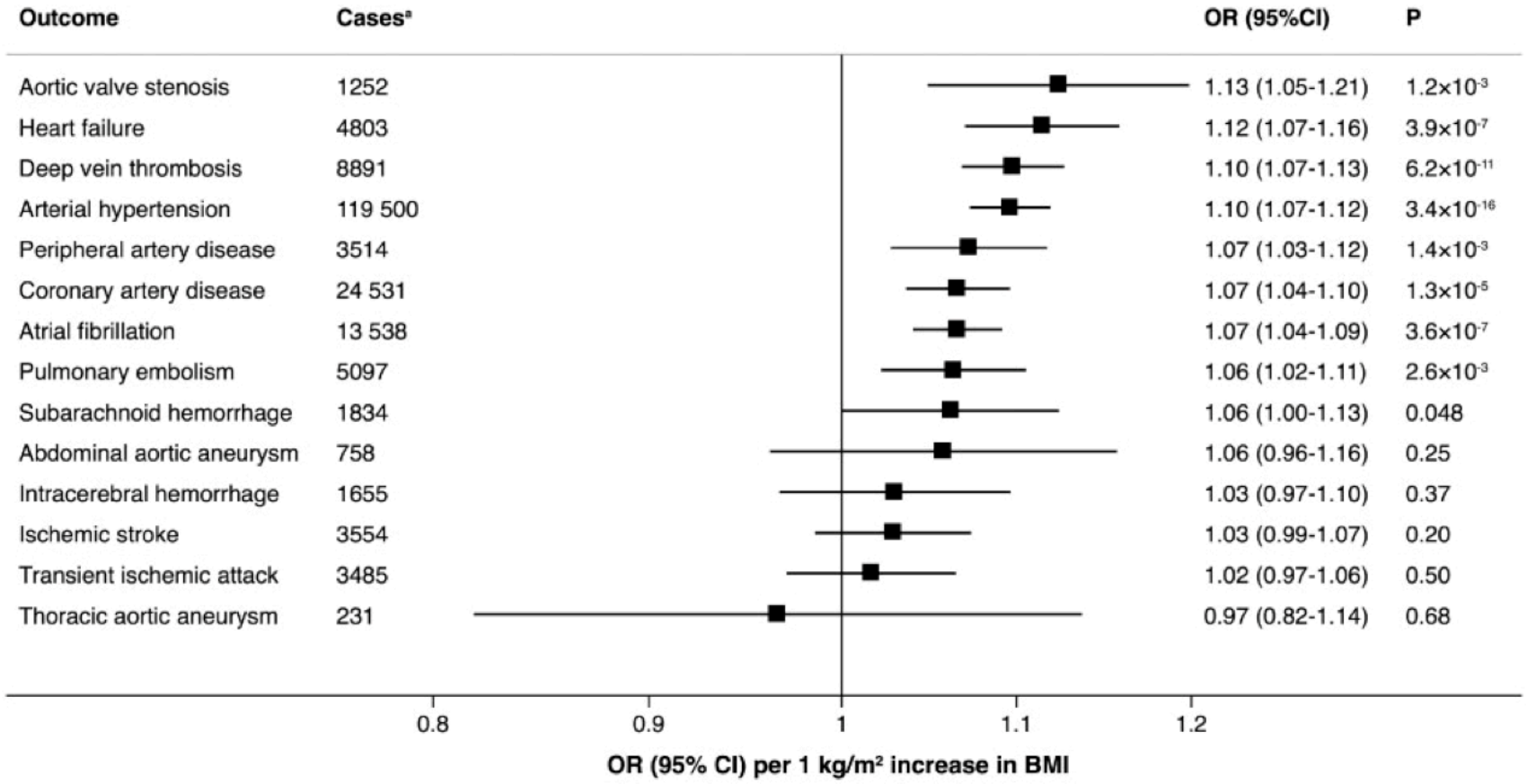
Changes of some major cardiometabolic risk factors for heart failure-attributable mortality in Europe from 2012 to 2021



Estimates were determined using the World Health Organization non-communicable diseases dataset: from 2012 to 2021, 42 178 659 individuals (20 312 867 men and 21865792 women) died in the considered European countries. HF was listed as the primary cause of death in 4 872 634 (2 084 521 men and 2788113 women), equating to 11522 deaths 100000 population

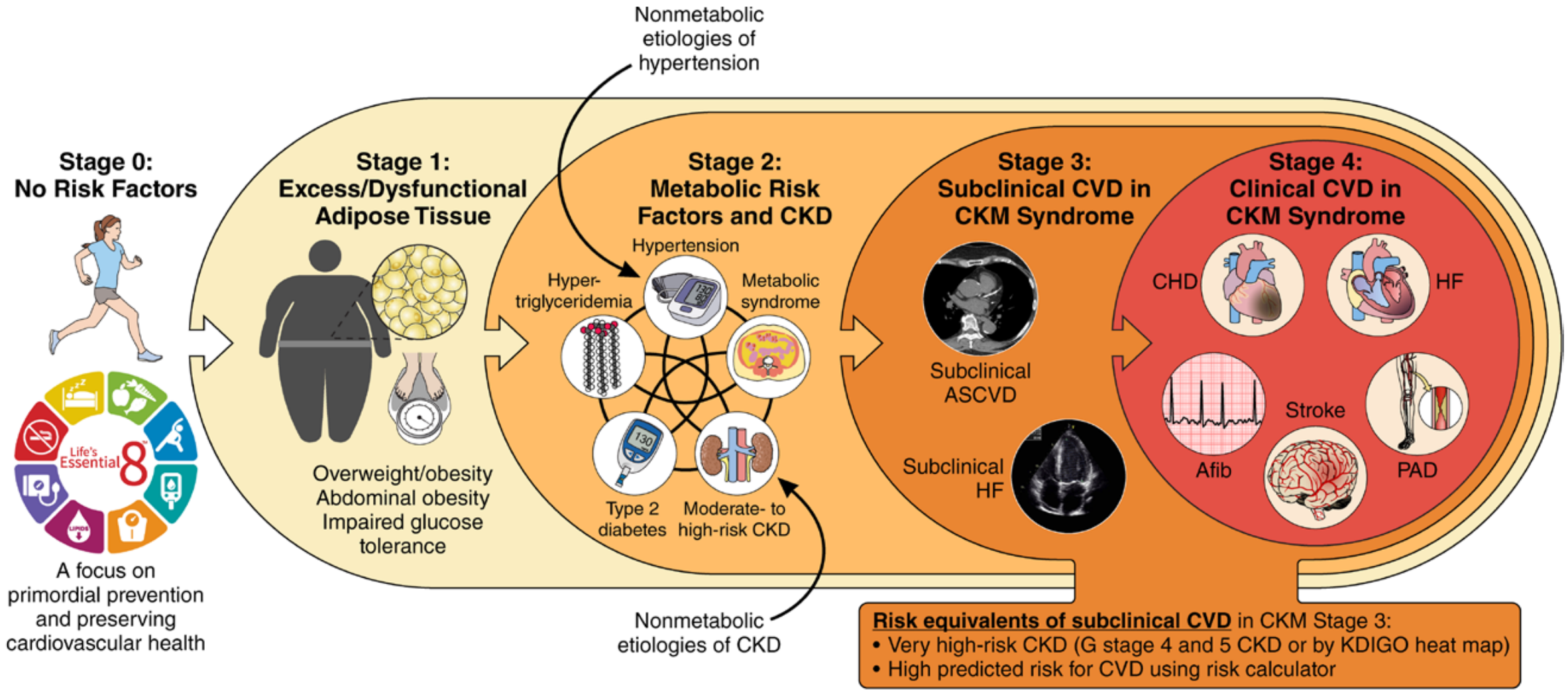
European Heart Journal (2020) **41**, 221–226

Body mass index and body composition in relation to 14 cardiovascular conditions in UK Biobank: a Mendelian randomization study



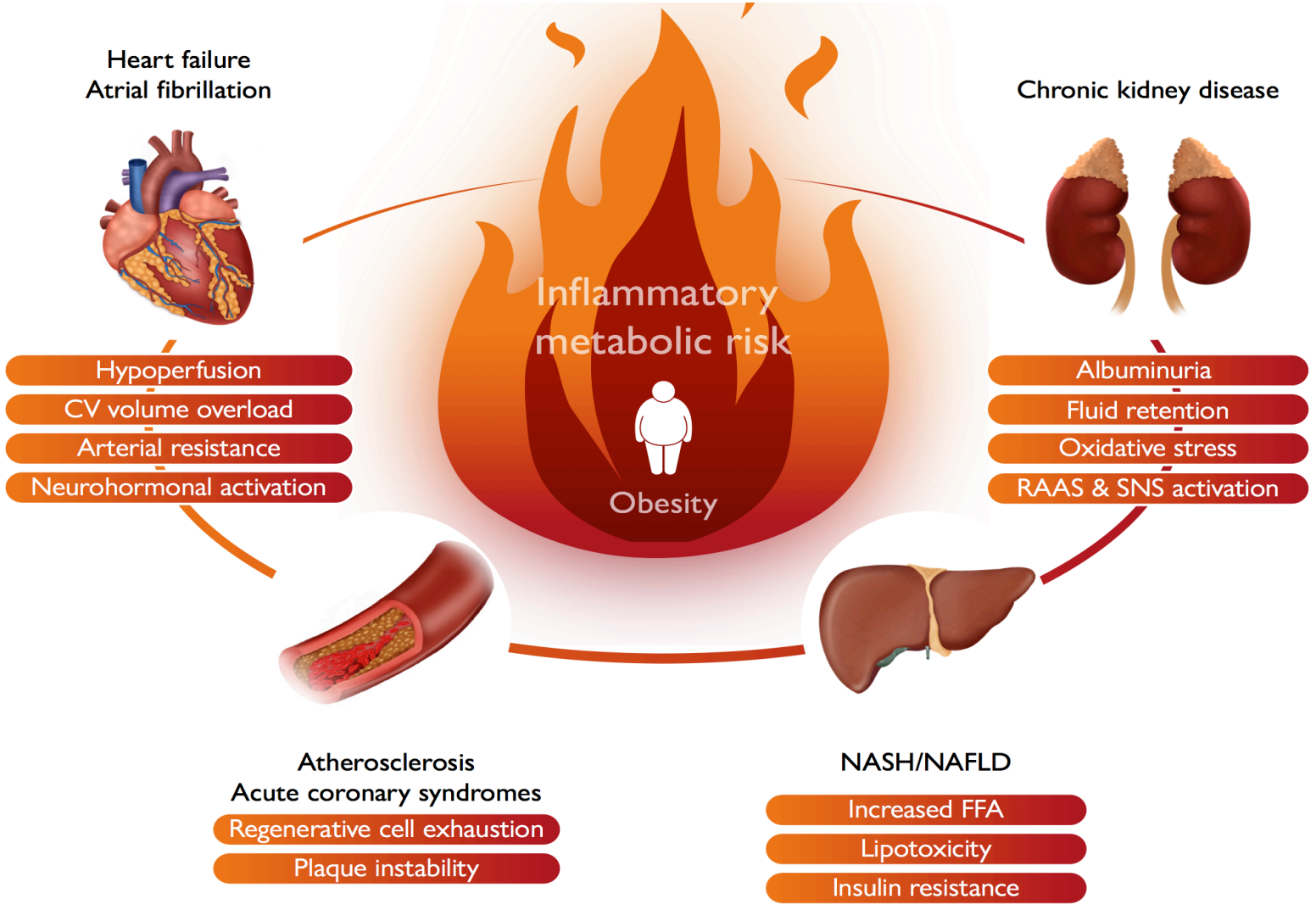
- **Associations of genetically predicted 1 kg/ m^2 increase in BMI with 14 CV conditions in UK Biobank (n=367 703).**
- Single-nucleotide polymorphisms associated with BMI and fat mass and fat-free mass indices were used as instrumental variables to estimate the associations with CV conditions
- After correcting for multiple testing, genetically predicted BMI was significantly positively associated with eight outcomes, including and with decreasing magnitude of association: aortic valve stenosis, heart failure, deep vein thrombosis, arterial hypertension, peripheral artery disease, coronary artery disease, atrial fibrillation, and pulmonary embolism.

Health disorder attributable to connections among obesity, diabetes, CKD, and CVD, including HF, AF, CHD, stroke, and PAD



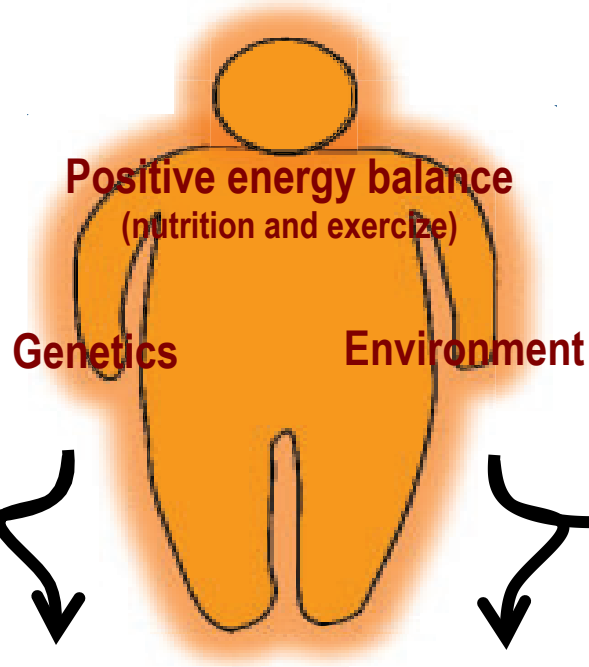
Circulation. 2023;148:00–00.

Obesity, particularly ectopic fat accumulation, has been linked to chronic inflammation and insulin resistance, which are linked to multiple pathways of cardiovascular risk

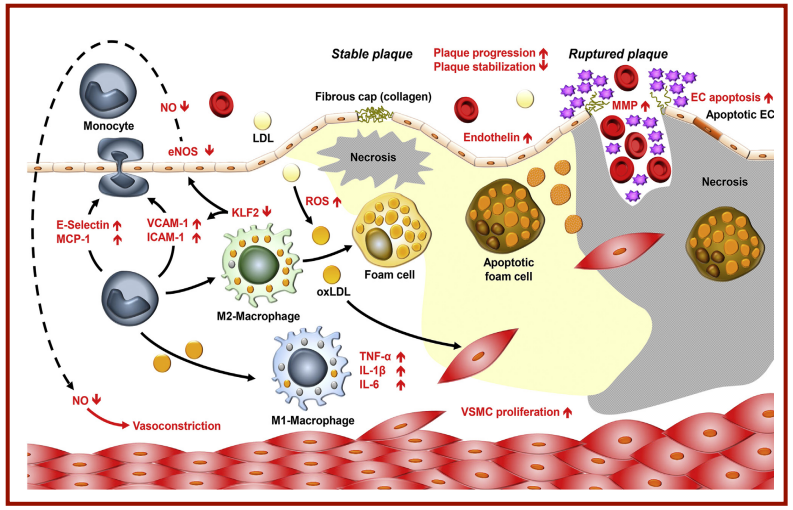


European Heart Journal (2023) **44**, 4141–4156

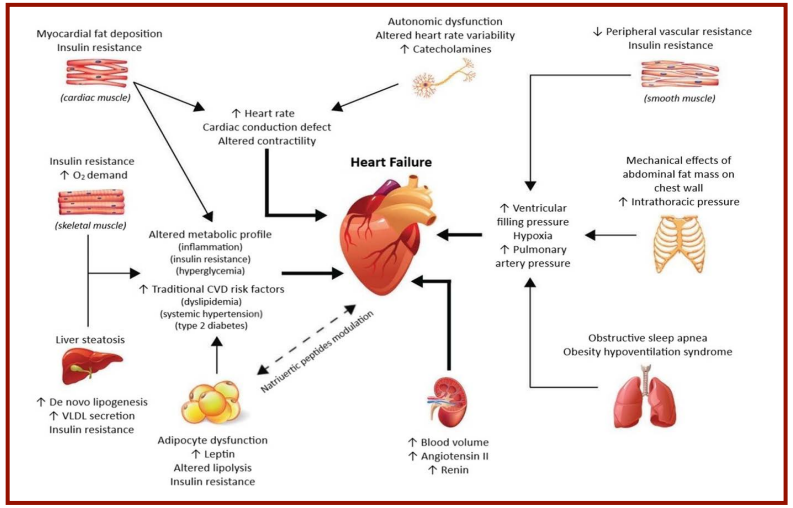
Sick fat Disease
(dysfunctional adipose tissue)



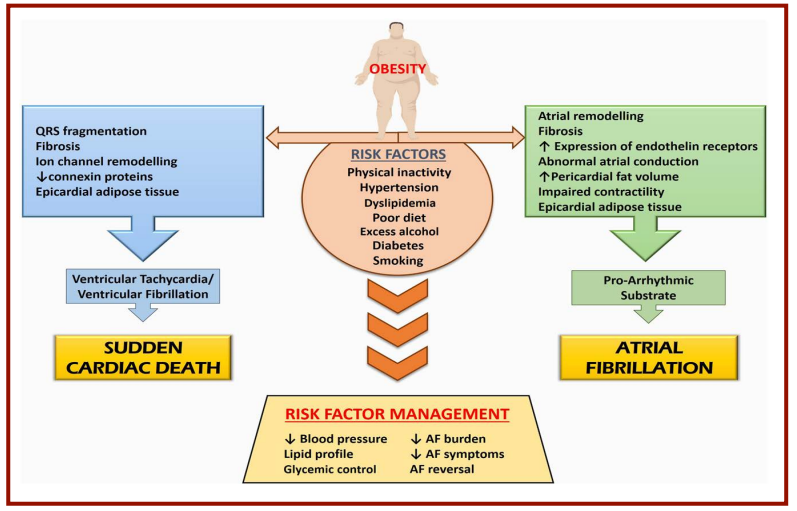
Fat mass Disease
(biomechanical abnormalities)



Atherosclerosis

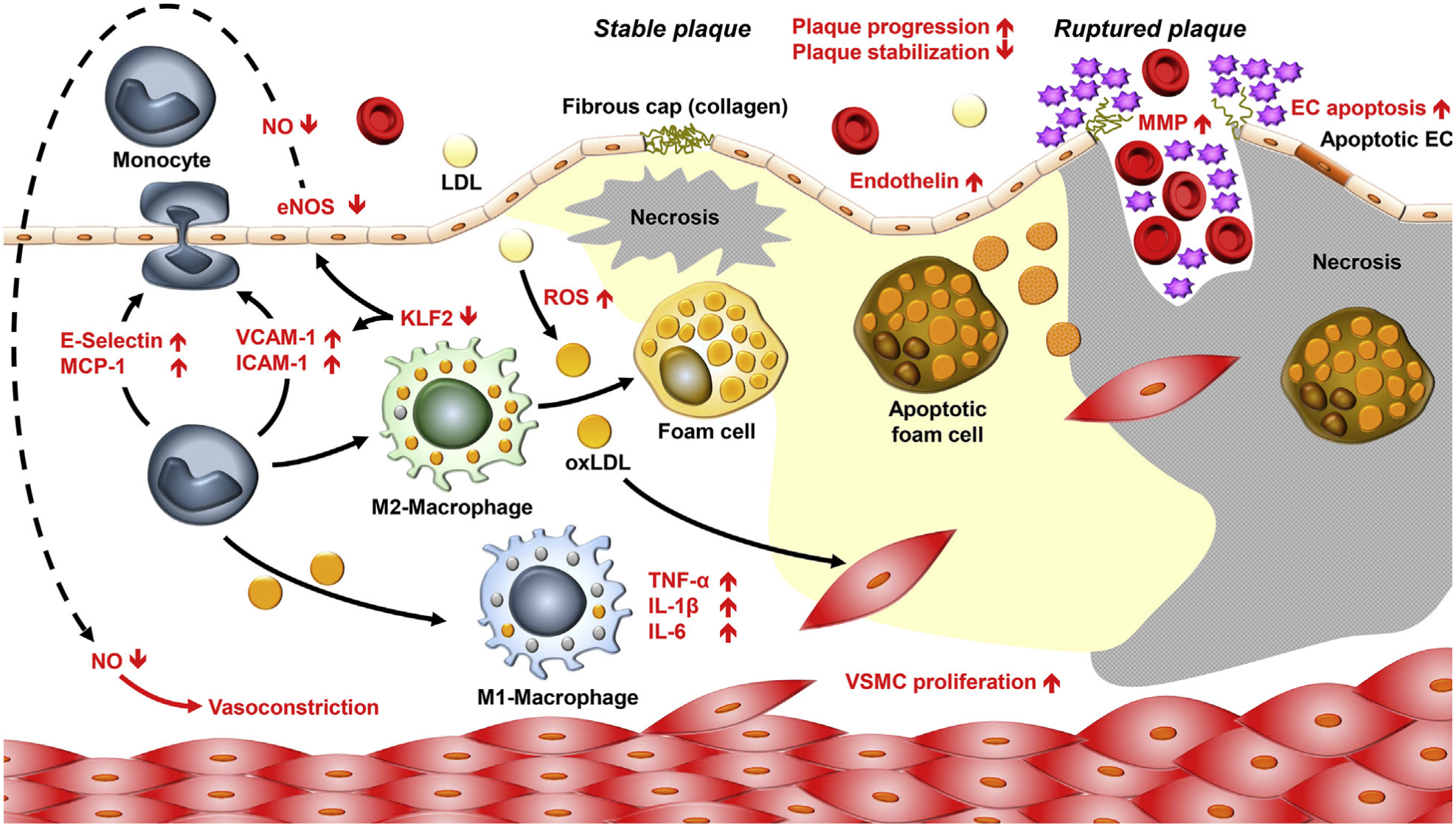


Heart failure



Arrhythmyas

Mechanisms driving the development of atherosclerosis in insulin resistent patients

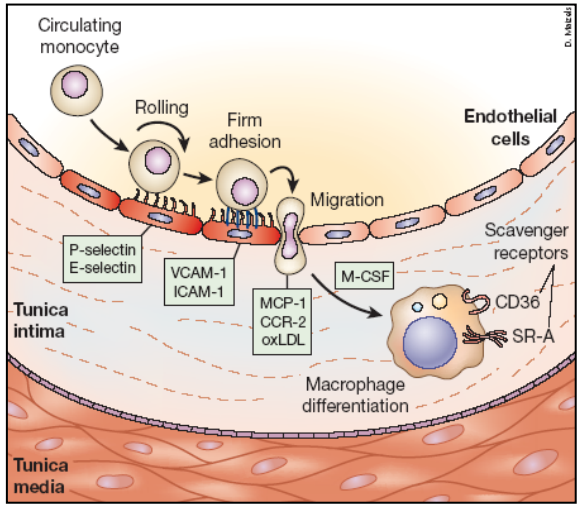


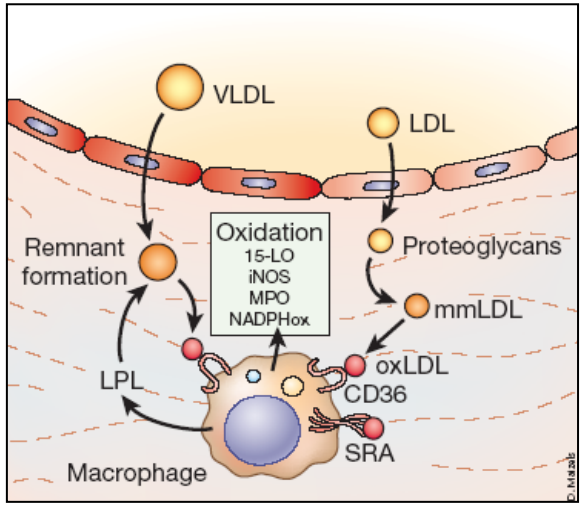
Excess weight promotes atherosclerosis

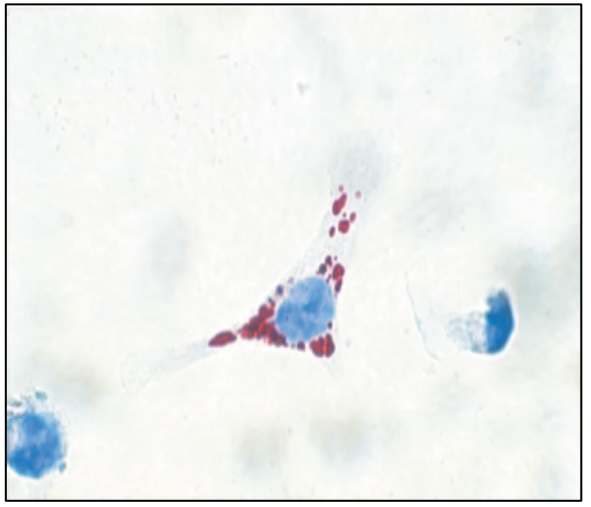
BMI

Risk factors contribute to:

- Blood pressure
- Serum glucose
- Insulin resistance
- Plasma lipids
- **Inflammation**







The New England Journal of Medicine
Volume 340 Number 2 January 14, 1999

Atherosclerosis — An Inflammatory Disease

Russell Ross, Ph.D.

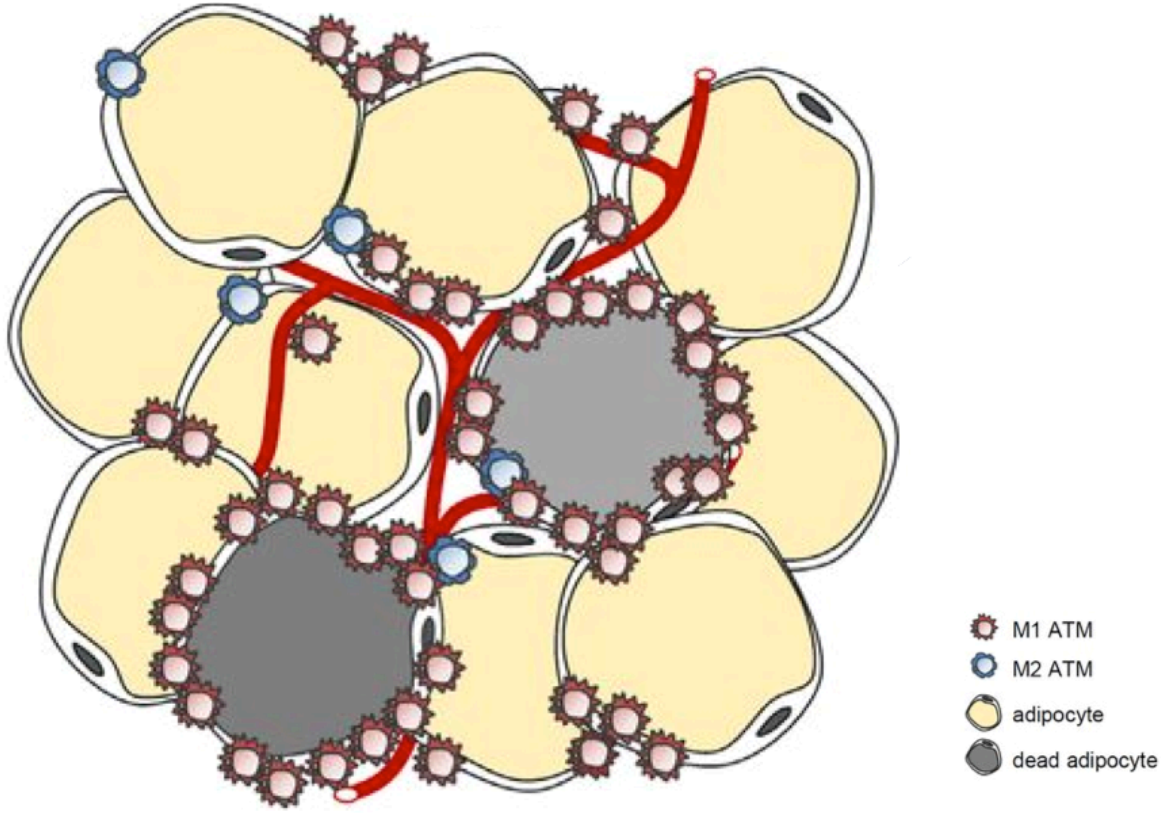
ATHEROSCLEROSIS is an inflammatory disease. Because high plasma concentrations of cholesterol, in particular those of low-density lipoprotein (LDL) cholesterol, are one of the principal risk factors for atherosclerosis,[1] the process of atherogenesis has been considered by many to consist largely of the accumulation of lipids within the artery wall; however, it is much more than that.

- **Five different signaling pathways** are dominant determinants of adipose tissue inflammation: increased circulating endotoxin due to dysregulation in the microbiota-gut-brain axis, systemic oxidative stress, macrophage accumulation, adipocyte death and **NLRP3 inflammasome activation**
- Release of several highly **active molecules (adipokines)** (leptin, resistin, adiponectin, visfatin) and classical **cytokines**, such as TNFα, IL-6, MCP-1 and IL-1.
- **Three metabolic pathways** are noteworthy in the development of adipose tissue inflammation: toll-like receptor 4/ phosphatidyl-inositol-3'-kinase/Protein kinase B signaling pathway, endoplasmic reticulum stress-derived unfolded protein response, and inhibitor of nuclear factor kappa-B kinase beta (IKKβ)-**nuclear factor kappa B (NF-κB) pathway**

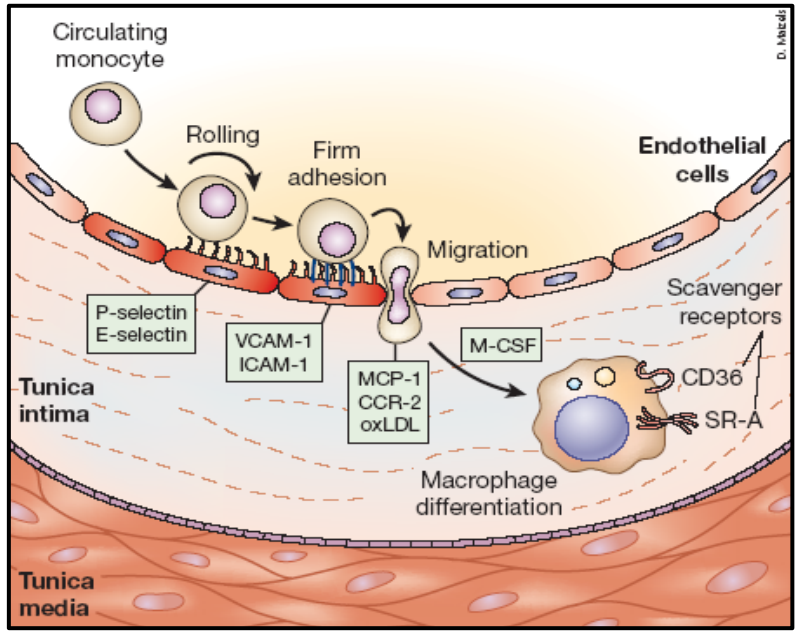
Obese state

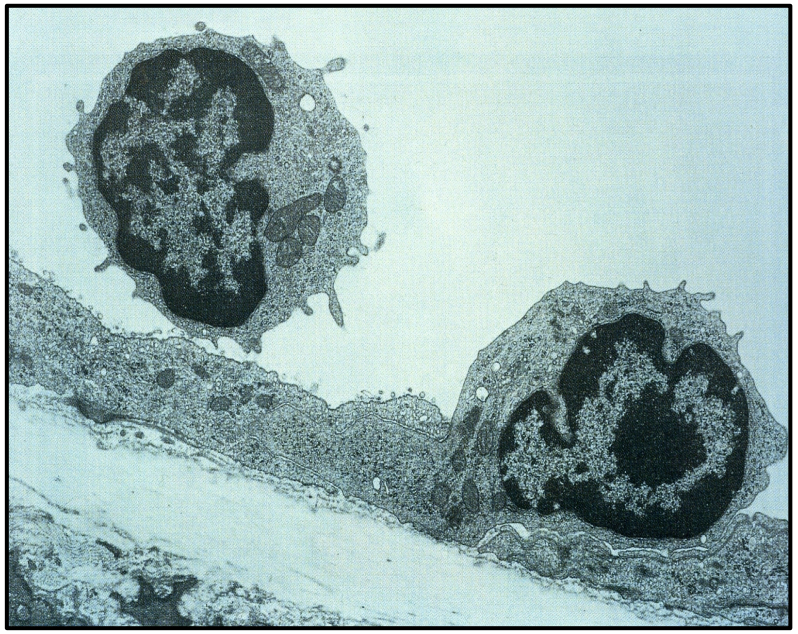
Hypertrophy
- cell size ↑
- FFA release ↑
- adiponectin ↓
- pro-inflammatory cytokines ↑
- immune cell recruitment ↑
- hypoxia and fibrosis ↑
- insulin sensitivity ↓

Dysfunctional

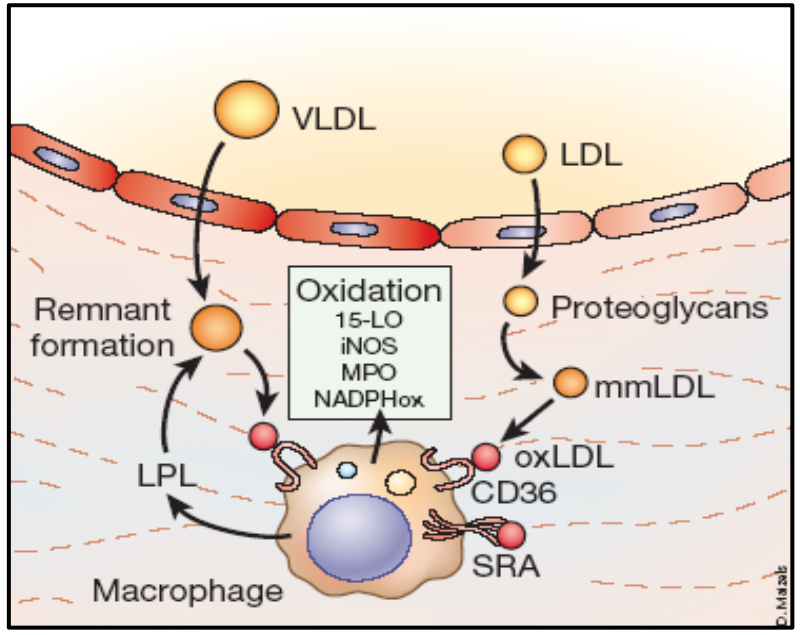


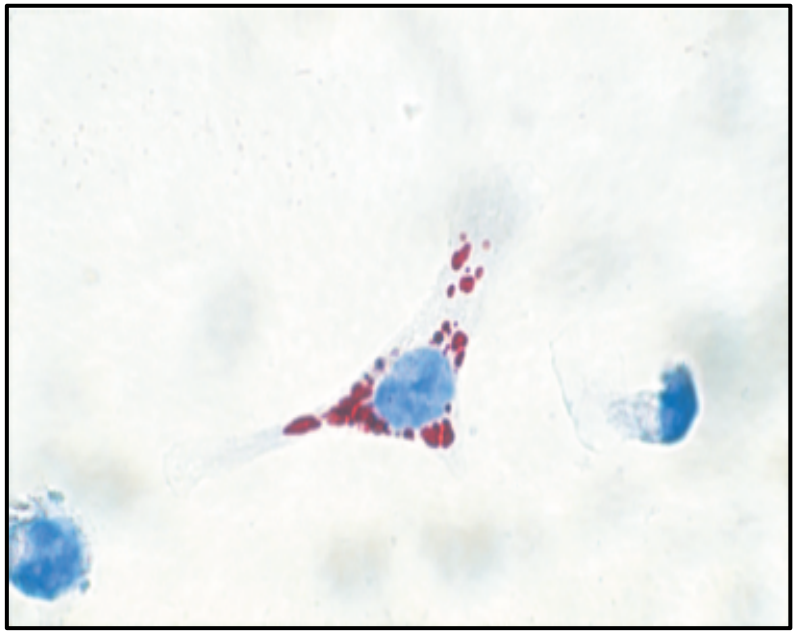
monocytes adhesion to “activated” endothelial cells



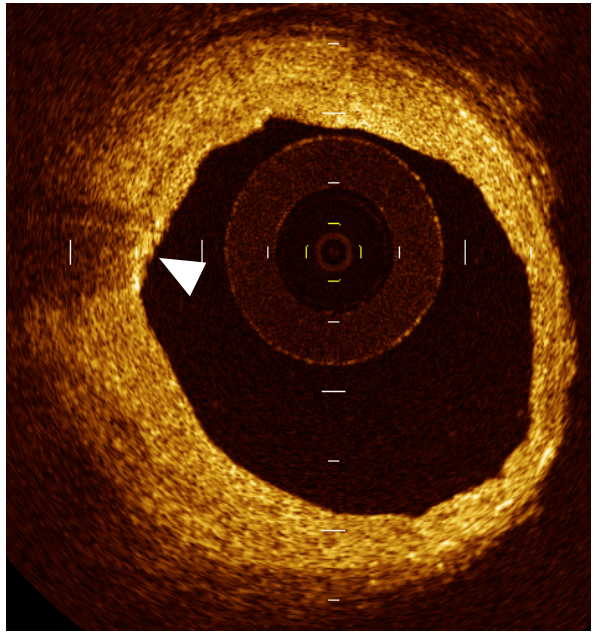
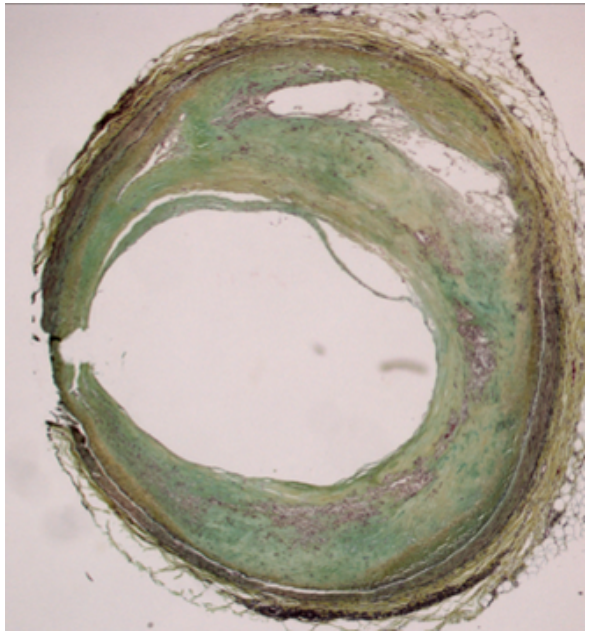
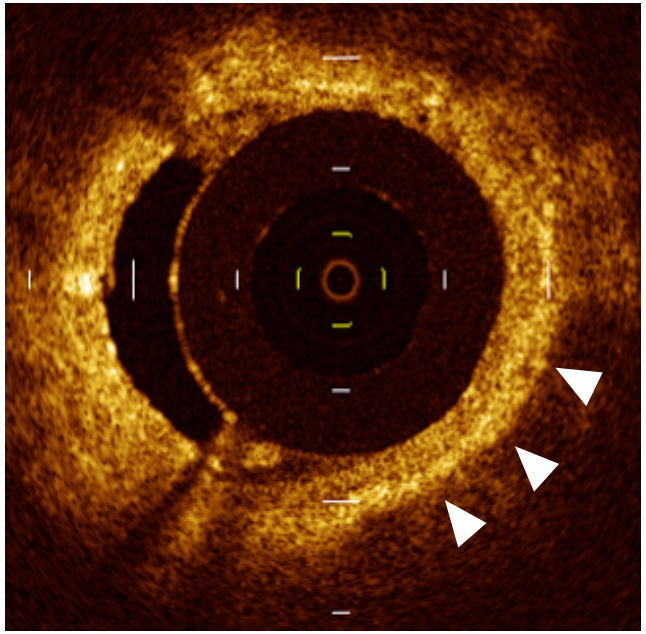
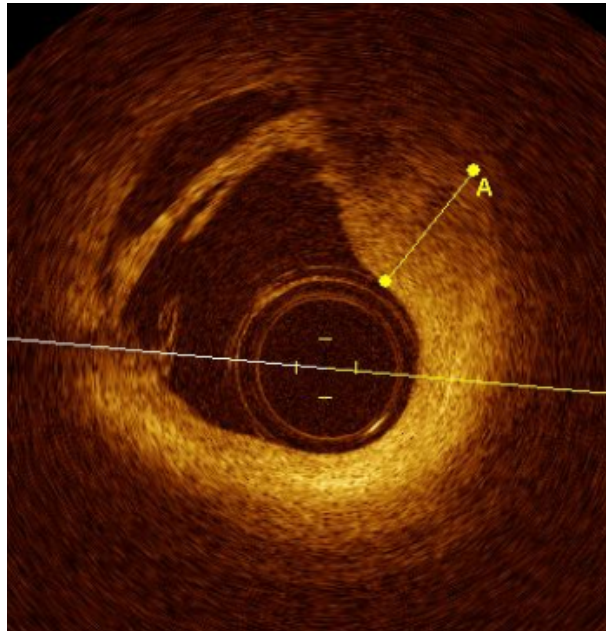


cholesterol crystal-induced activation of NLRP3 inflammasome in foam cells

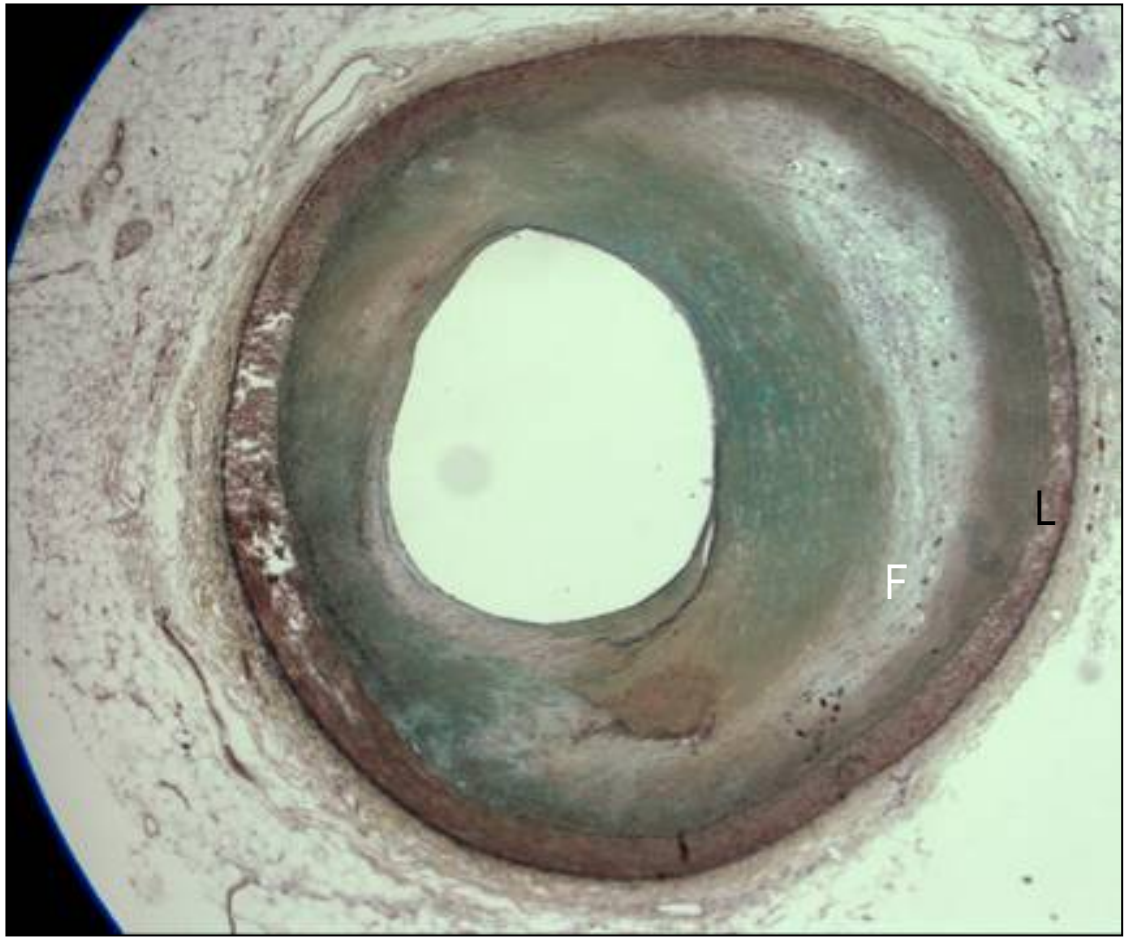




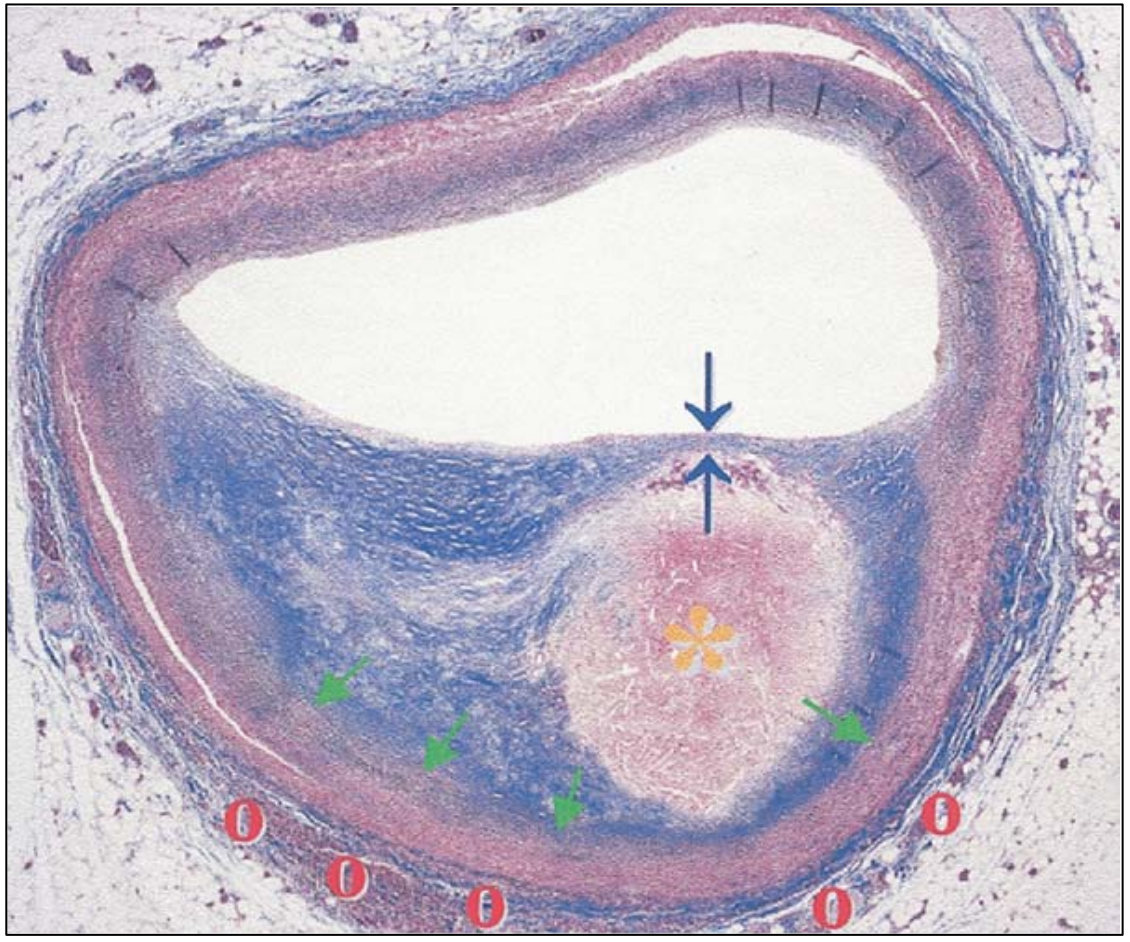
Atheromas at early stages

Fatty streaks	Cluster of foam cells		Lipid pool
			

Stable plaque

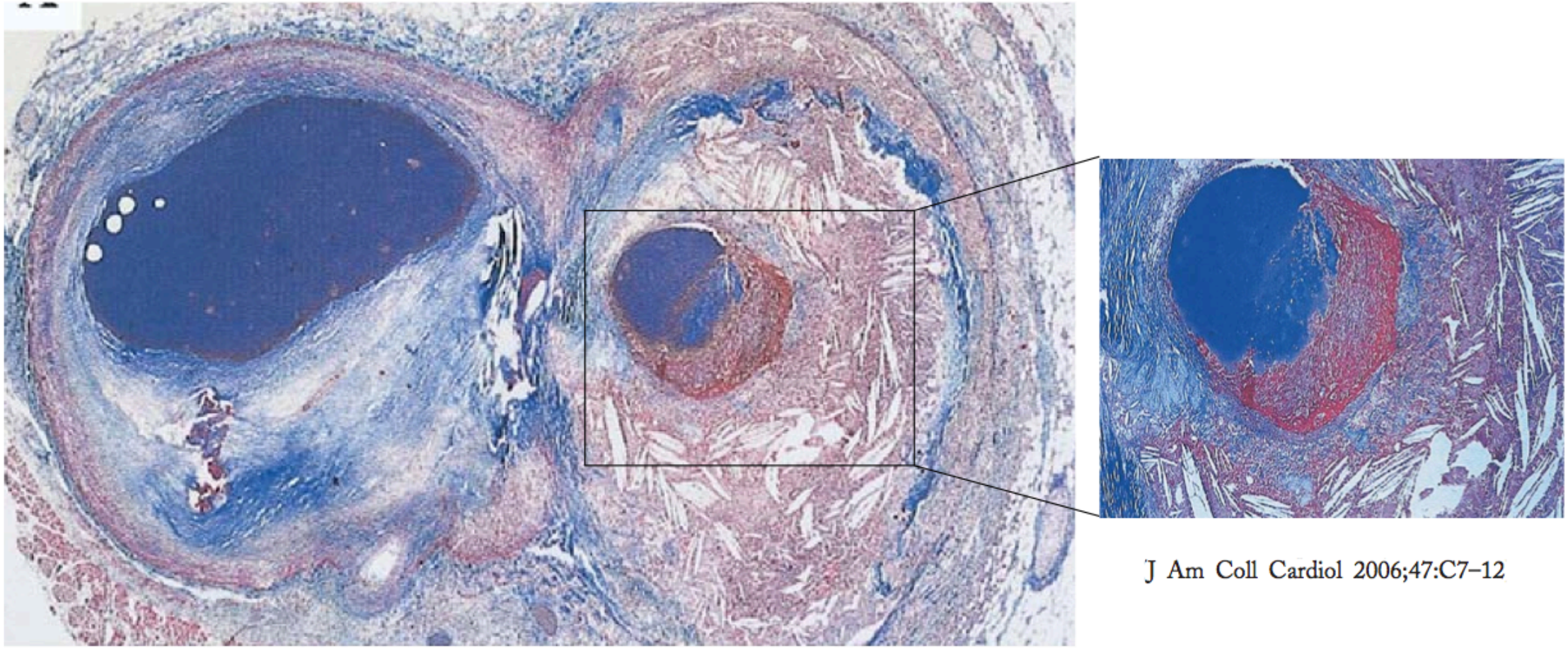


Vulnerable plaque



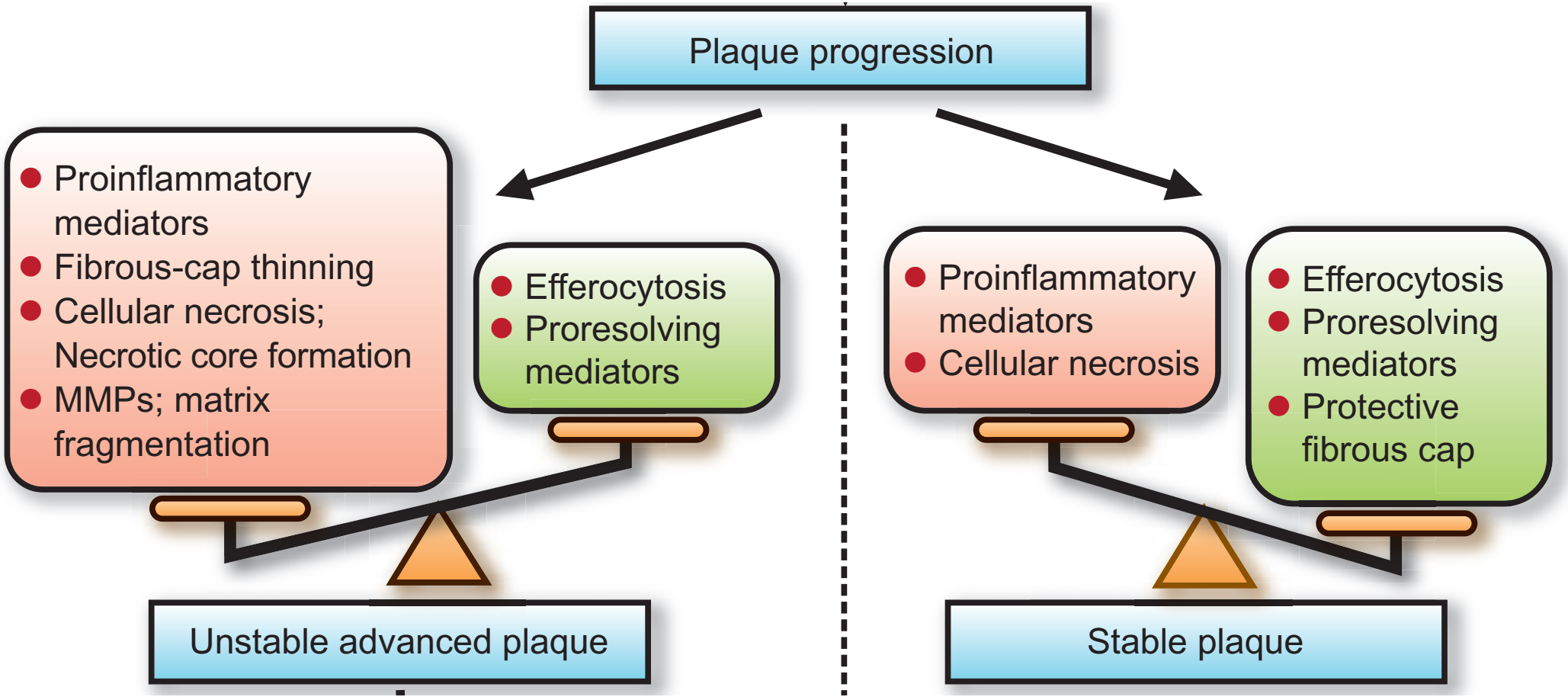
Vulnerability features: thin fibrous cap (<65 μm), a necrotic core more than 30% of the total plaque, haemorrhage, infiltration of inflammatory cells, low VSMC density

Towards stability (healing) or towards clinical event?



J Am Coll Cardiol 2006;47:C7–12

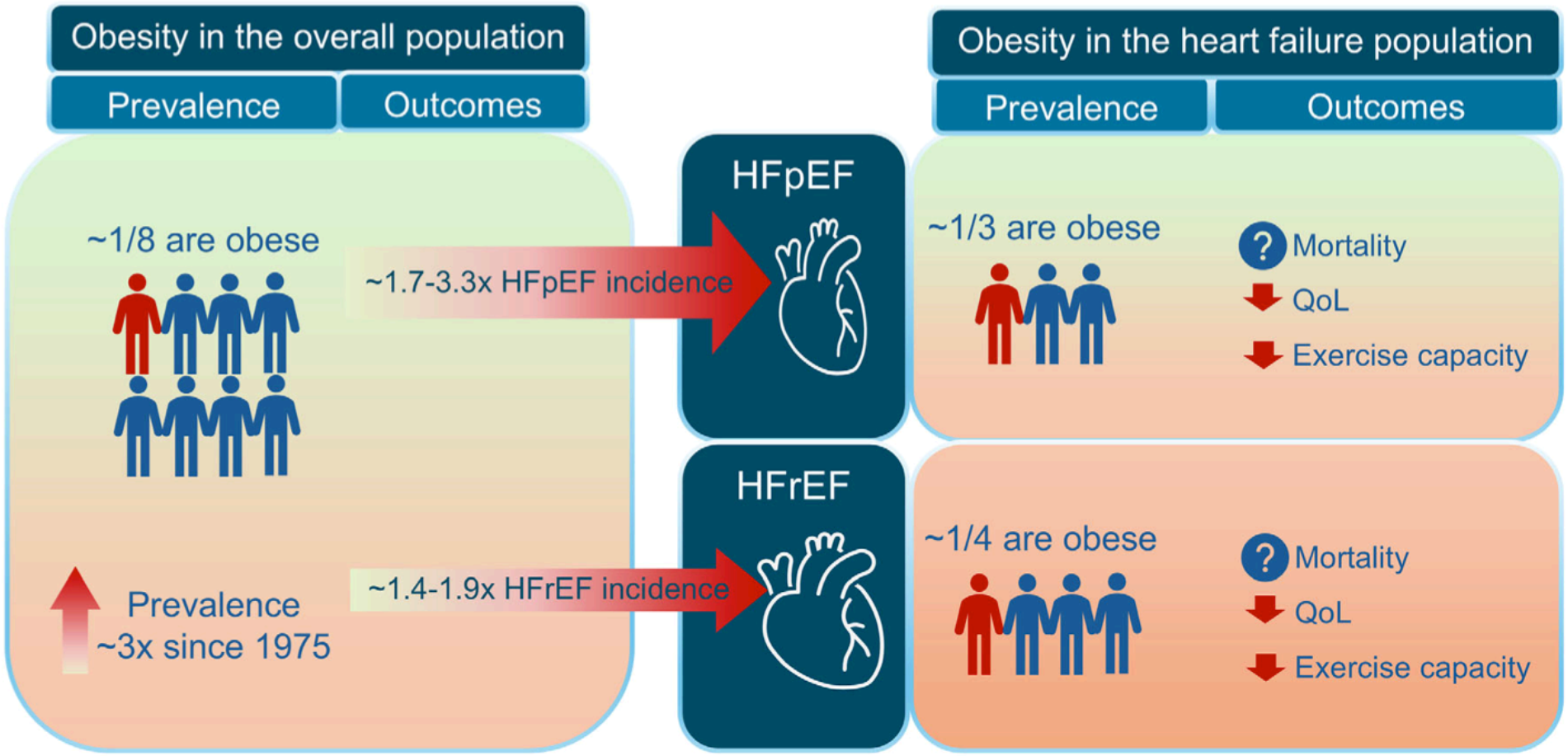
Towards stability (healing) or towards clinical event?



European Journal of Heart Failure (2025) **27**, 1273–1293

Heart failure and obesity: Translational approaches and therapeutic perspectives. A scientific statement of the Heart Failure Association of the ESC

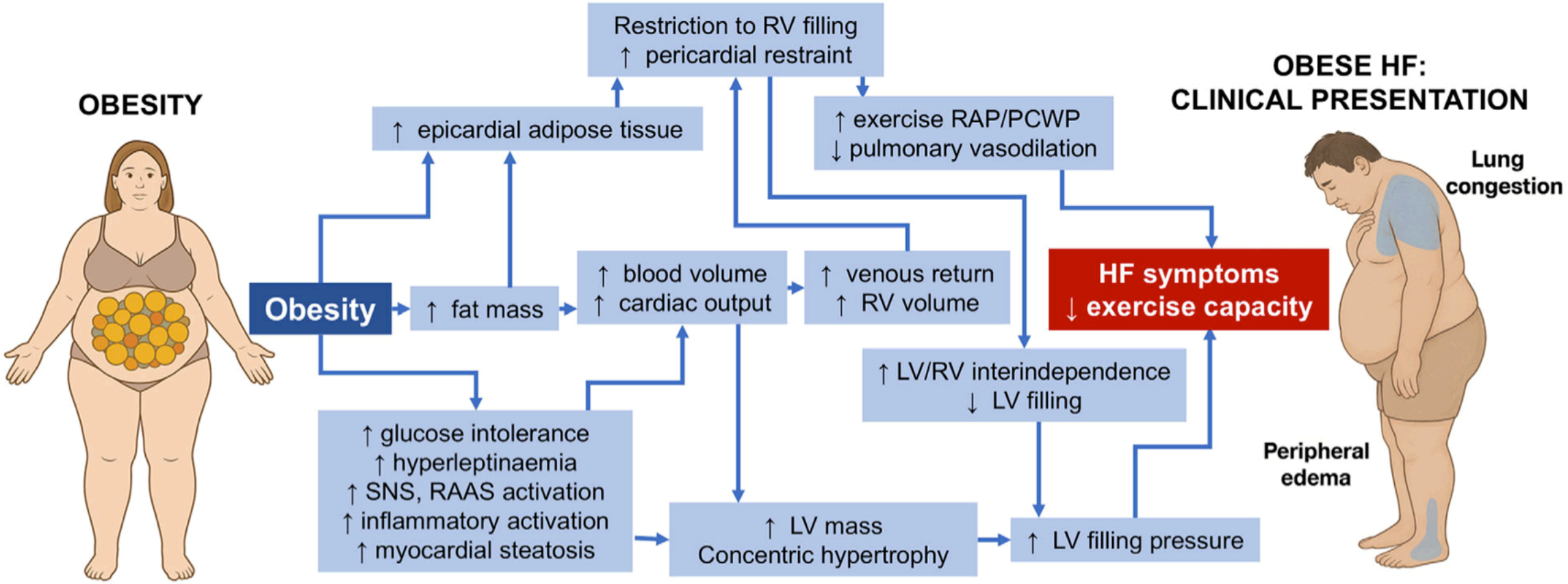
Obesity prevalence in the overall population, and risk of and complications in HFrEF and HFpEF



European Journal of Heart Failure (2025) **27**, 1273–1293

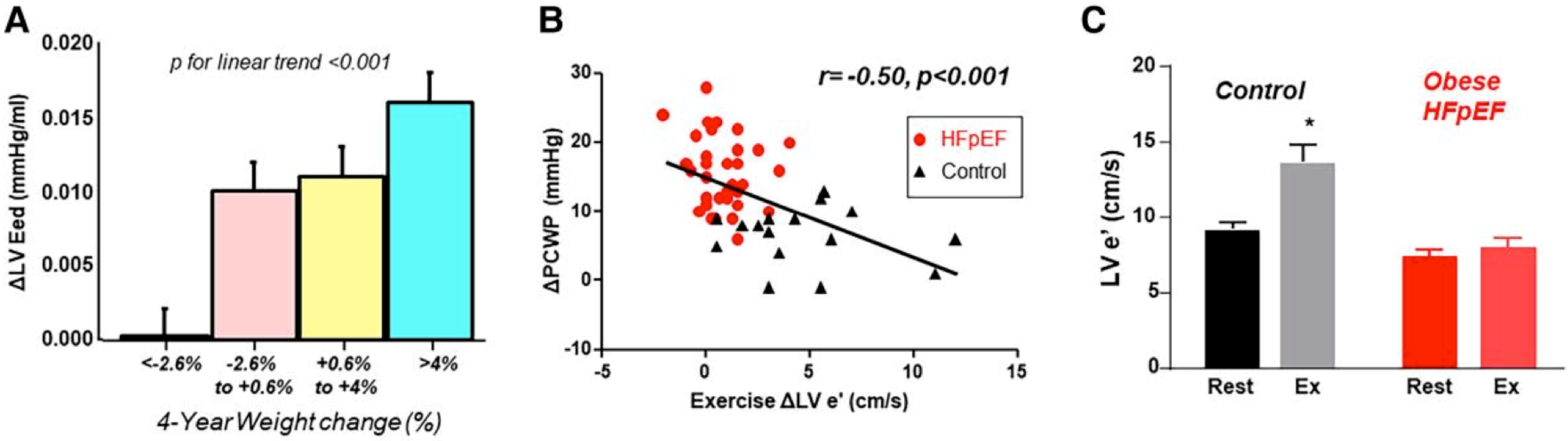
Heart failure and obesity: Translational approaches and therapeutic perspectives. A scientific statement of the Heart Failure Association of the ESC

Pathophysiological link between obesity and heart failure



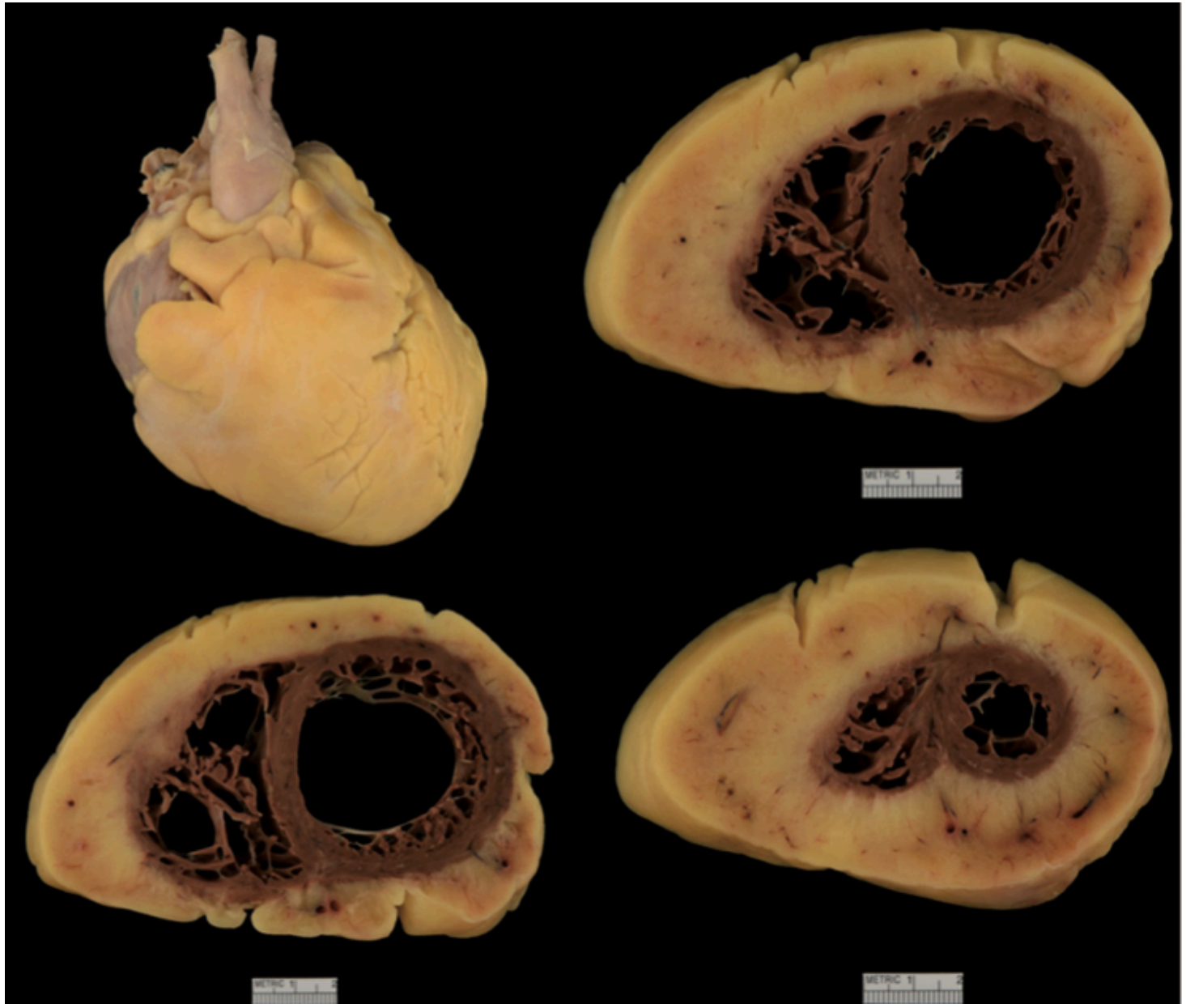
Cardiovascular Research (2022) **118**, 3434–3450

Obesity and heart failure with preserved ejection fraction: new insights and pathophysiological targets



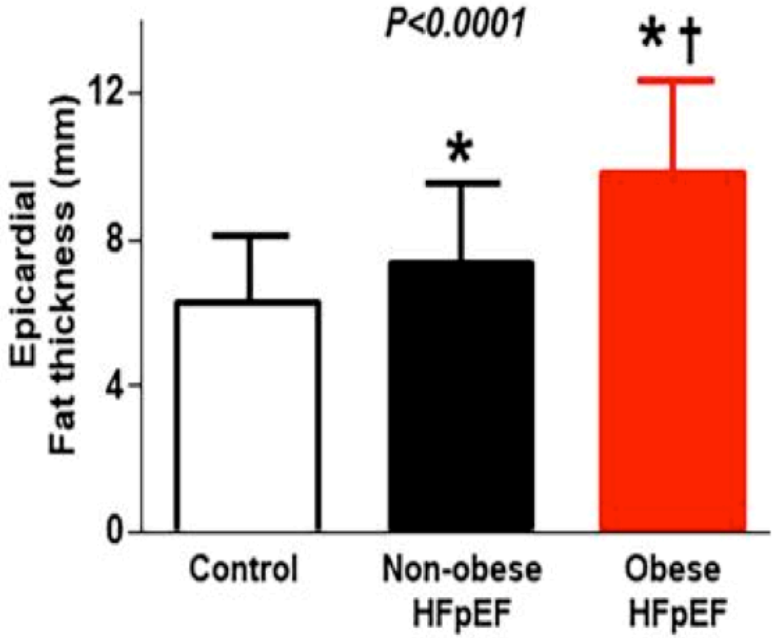
(A) Increasing **weight gain** is associated with progressively greater **increases in estimated LV end diastolic chamber stiffness** (ΔLV Eed) over time in community-dwelling adults, predisposing to HFpEF. (B) **Impairments** in the ability to enhance **LV early diastolic relaxation velocity** (ΔLV e') with exercise are associated with greater i**ncreases in pulmonary capillary wedge pressure** (PCWP), and enhancement in LV e' with exercise is substantially blunted in obese HFpEF (C)

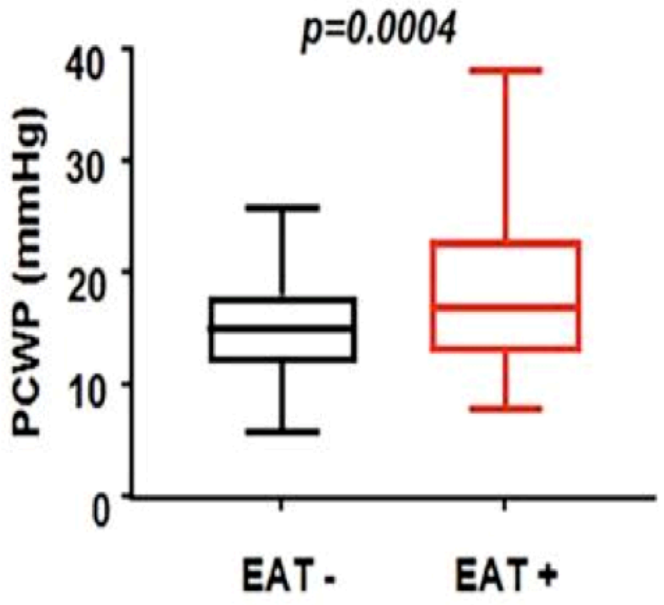
- An 82-year-old woman with HFpEF, recurrent hospitalizations (in the last 12 months), obesity, AF, diabetes, and CKD presented with worsening dyspnoea and oedema.
- LVEF 57%, normal LV mass, mild left atrial enlargement, a dilated inferior vena cava, and PAPS of 48 mmHg.
- Parenteral diuretics and antibiotics were administered, but symptoms worsened and died 4 days later.
- At autopsy, total heart weight upon removal from the chest was **758 g**, with marked circumferential epicardial fat deposition.
- Following dissection of epicardial fat, the heart weighed 415g (expected weight 241g). Thus, **epicardial fat accounted for 343 g, 46%**of the total heart mass.
- Cause of death was established as sepsis complicated by congestive heart failure.

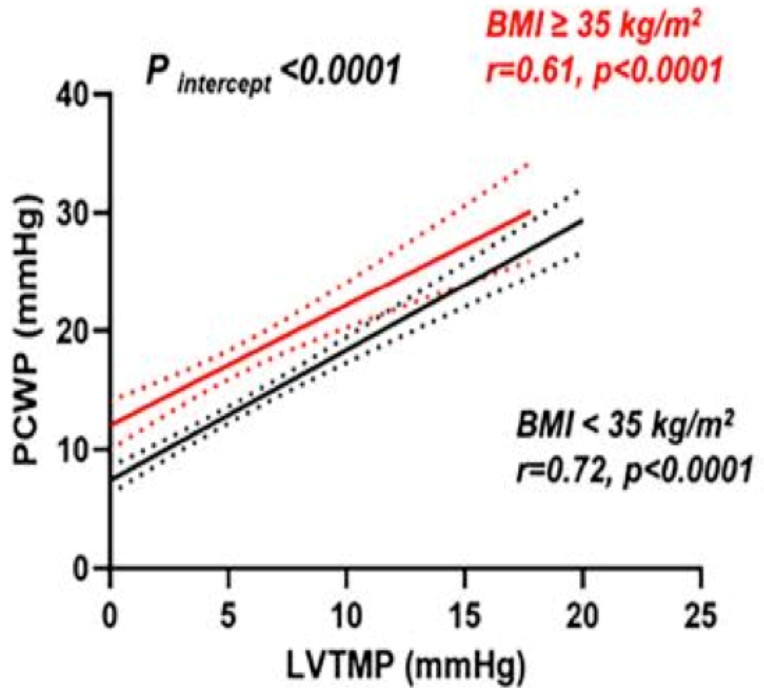


Cardiovascular Research (2022) **118**, 3434–3450

Obesity and heart failure with preserved ejection fraction: new insights and pathophysiological targets





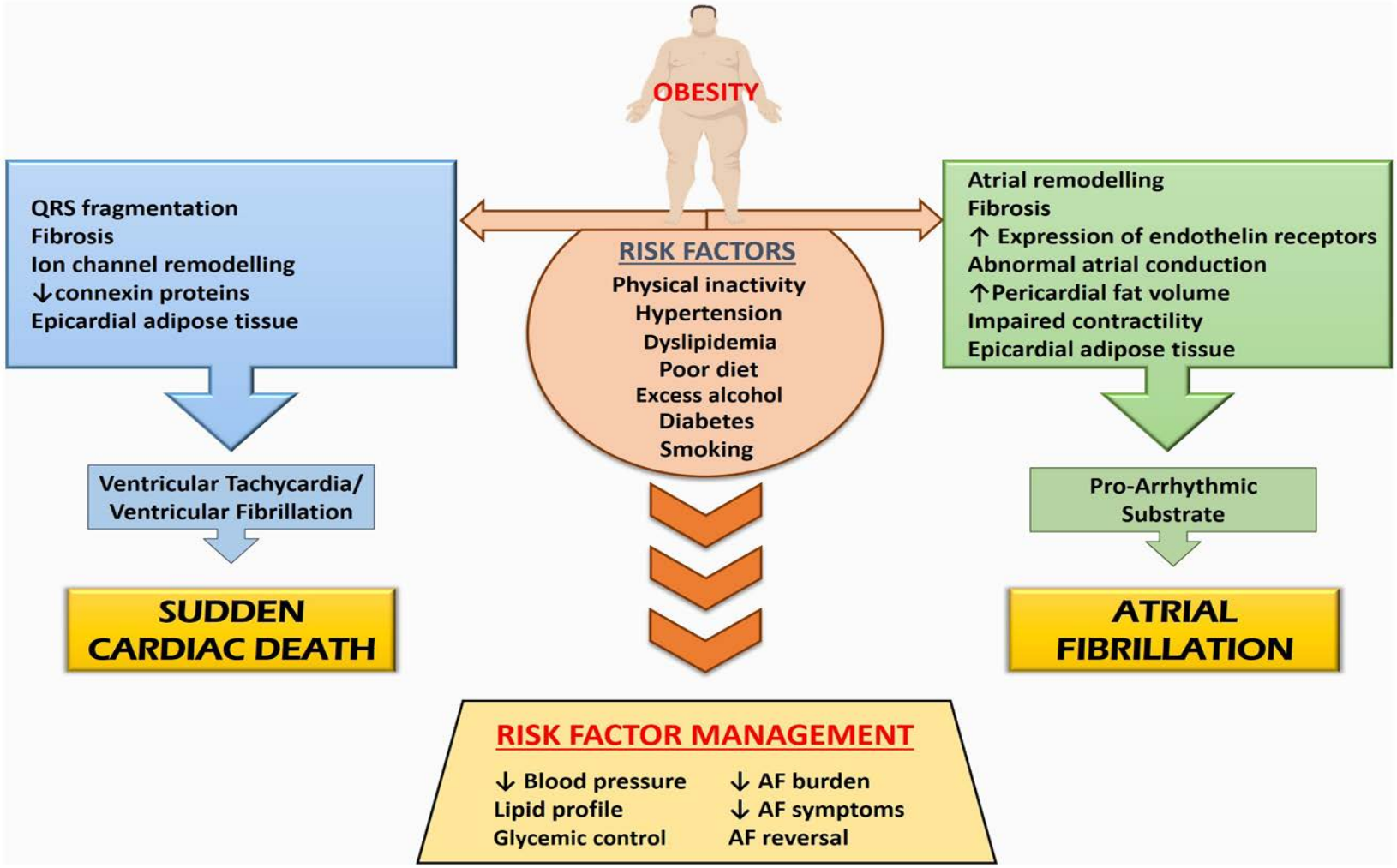


When compared with healthy controls and non-obese HFpEF, **patients with obese HFpEF display increased epicardial fat thickness**, which is associated with **higher pulmonary capillary wedge pressures** (PCWP). The increase in external constraint on the heart in patients with obesity results in a higher PCWP for any LV transmural distending pressure (LVTMP).

Circulation. 2021;143:e984–e1010.

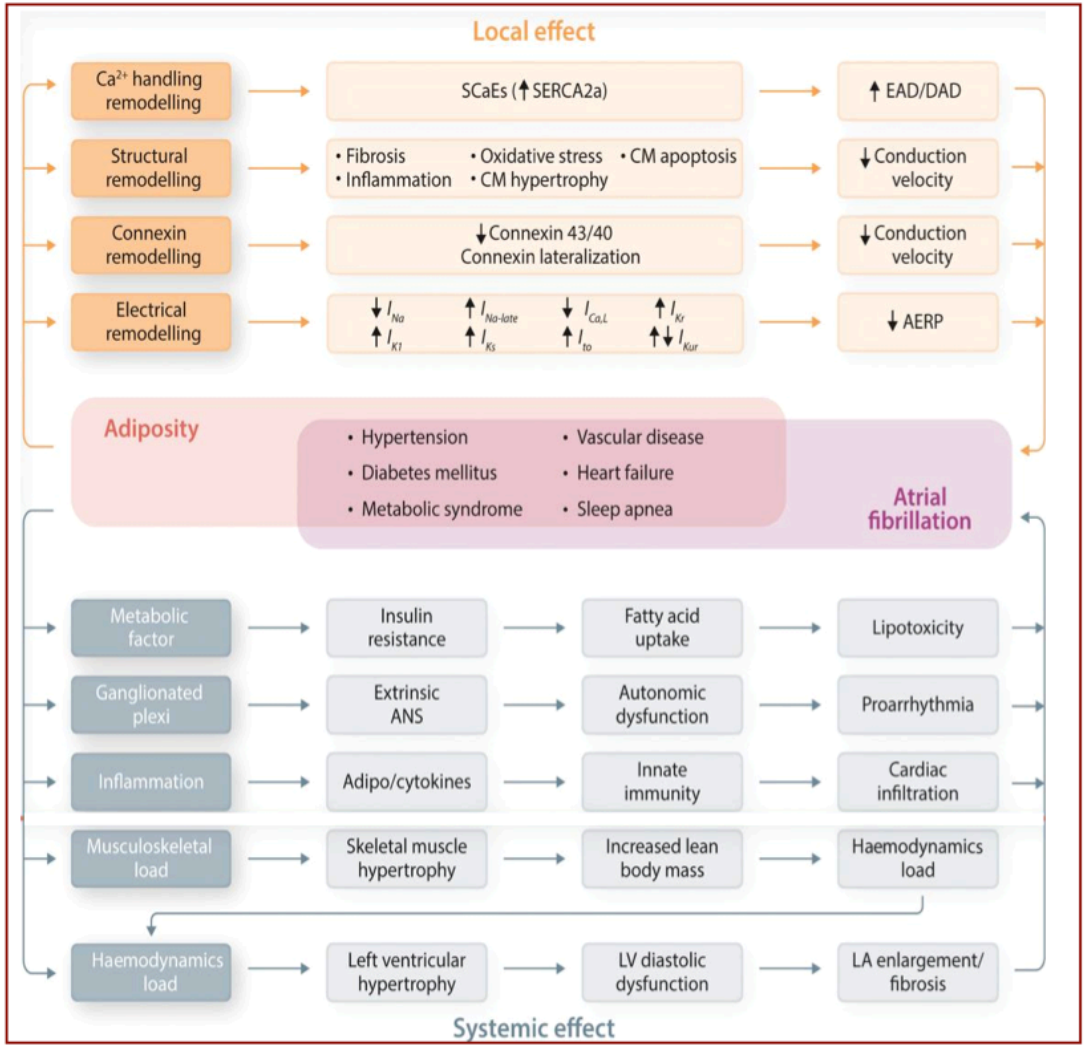
Obesity and Cardiovascular Disease

A Scientific Statement From the American Heart Association



Cardiovascular Research (2023) **119**, 614–630

Adiposity-associated atrial fibrillation: molecular determinants, mechanisms, and clinical significance



Cardiovascular Diabetology (2023) 22:192

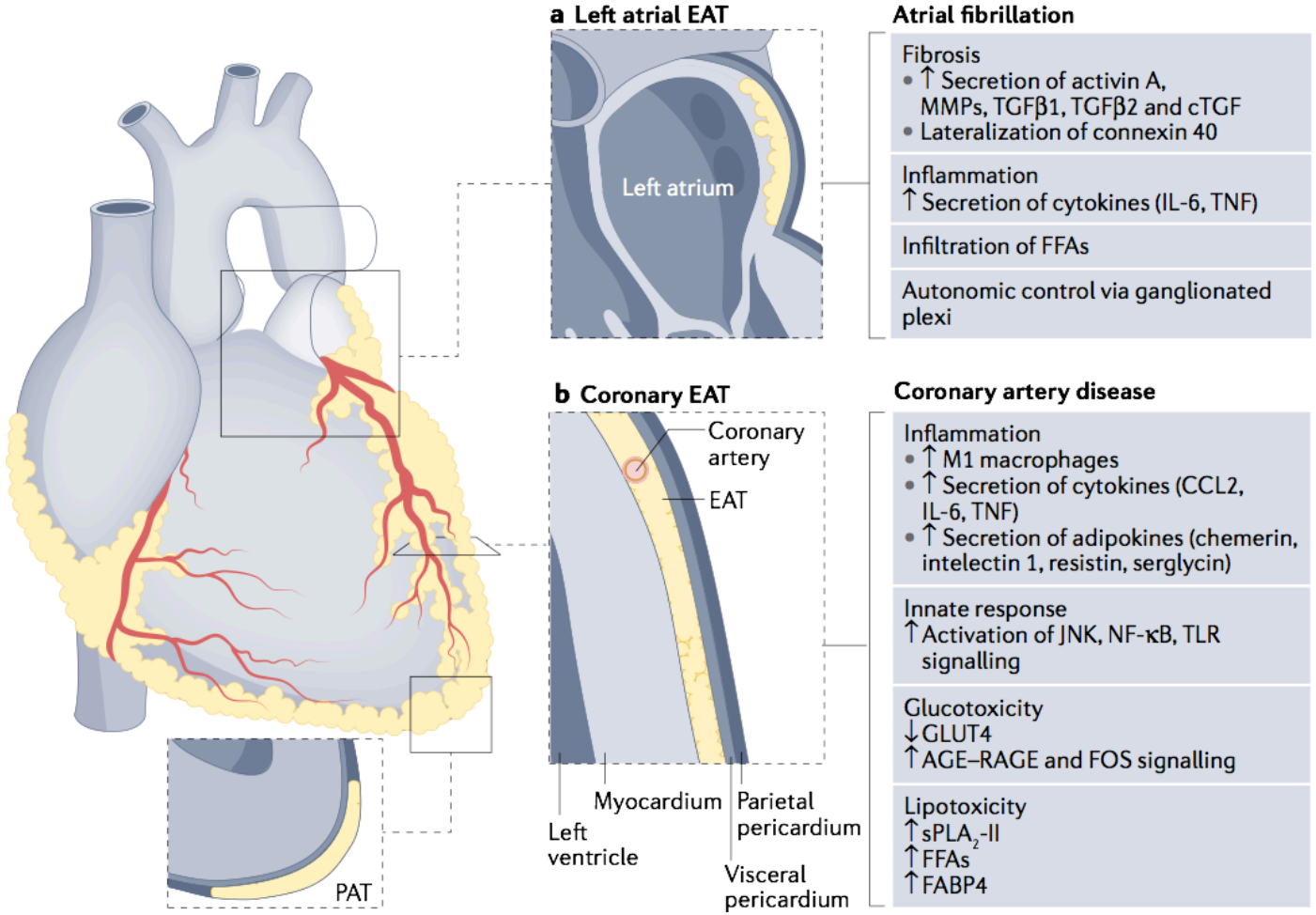
Obesity and atrial fibrillation: a narrative review from arrhythmogenic mechanisms to clinical significance

Adjusted risk (obesity vs. normal weight)	AF	Follow up (years)	Definition of obesity	Total	Study
HR 1.54 (male); HR 1.46 (female)	526	13.7	BMI ≥ 30 kg/m^2	5282	Wang et al. 2004
HR 2.35 (male); HR 1.99 (female)	533	5.7	BMI ≥ 30 kg/m^2	47,589	Frost et al. 2005
HR 1.36	1810	10	BMI > 30 kg/m^2	8051	Zacharias et al.2005
HR 1.65	834	12.9	BMI ≥ 30 kg/m^2	34,309	Tedrow et al. 2010
HR 2.04	110	4.6	BMI ≥ 30 kg/m^2	271,203	Karasoy et al. 2013
HR 2.9	287	1.5	BMI ≥ 30 kg/m^2	7169	Grundvold et al. 2015
HR 2.41	288	6	BMI ≥ 30 kg/m^2	18,290	Berkovitch et al. 2016
HR 1.2	5106	7.5	BMI ≥ 25 kg/m^2	389,321	Lee et al. 2017
OR 1.4	1511	8	BMI > 30 kg/m^2	67,278	Foy et al. 2018
HR 1.24	1959	4.95	BMI ≥ 25 kg/m^2	17,134	Lim et al.2019
HR 1.327	196,136	8.17	BMI ≥ 30 kg/m^2	9,797,418	Kim et al. 2019

NATURE REVIEWS | CARDIOLOGY VOLUME 19 | SEPTEMBER 2022

Epicardial adipose tissue in contemporary cardiology

- Epicardial adipose tissue (EAT) has **anatomical and functional interactions with the heart** owing to shared circulation and absence of muscle fascia separating the two organs.
- **Regional distribution** of EAT is important because pericoronary EAT and left atrial EAT differently affect the risk of CAD and atrial fibrillation, respectively.
- EAT has a role in the development of several cardiovascular diseases through **complex mechanisms**, including gene expression profile, pro-inflammatory and profibrotic proteome, neuromodulation, and glucose and lipid metabolism.



NATURE REVIEWS | CARDIOLOGY VOLUME 19 | SEPTEMBER 2022

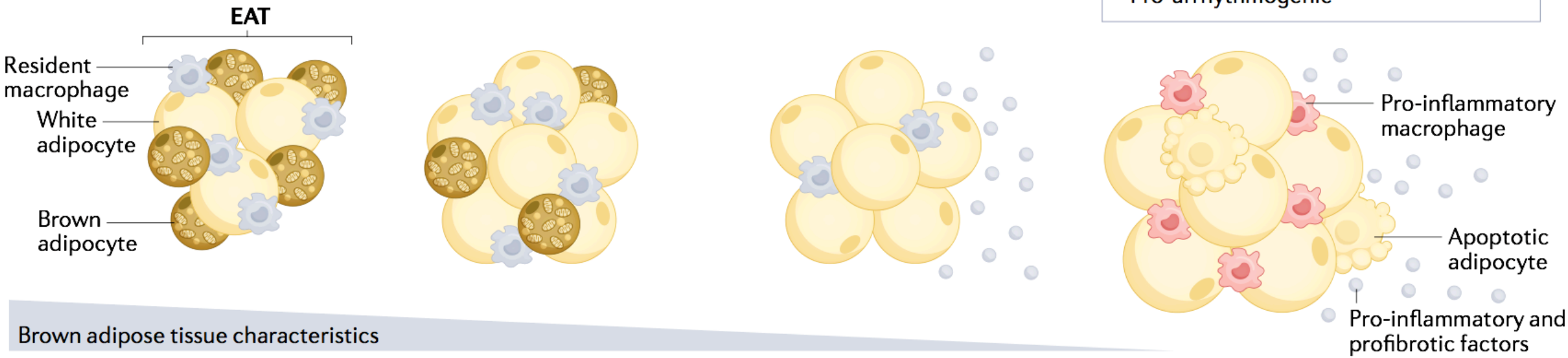
Epicardial adipose tissue in contemporary cardiology

Neonate and early years of life
- Cardioprotective
- Thermogenic

Childhood to adulthood
- Cardioprotective
- Fuel for the myocardium

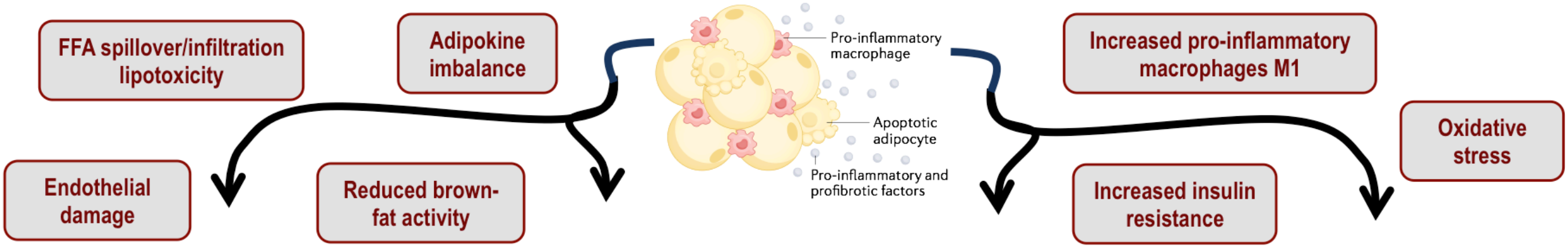
Old age
↓Thermogenic function
↑ Profibrotic and pro-apoptotic factors

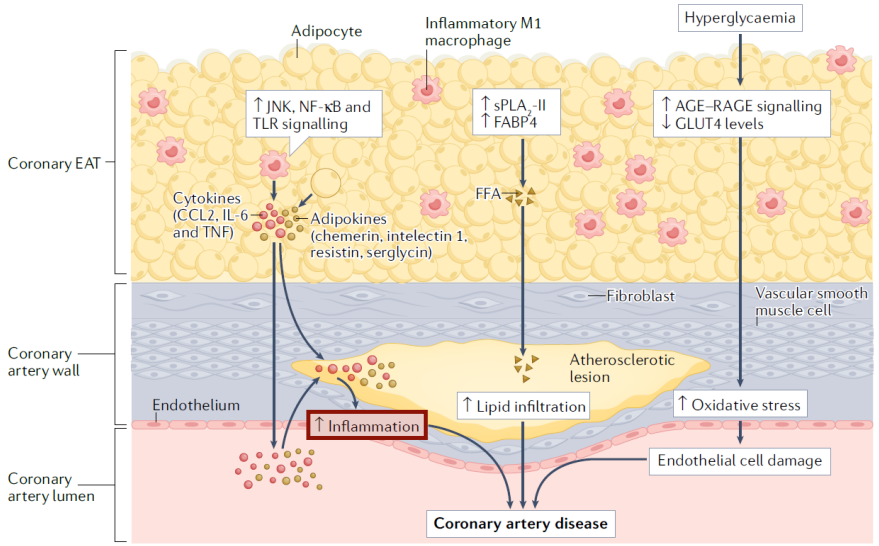
Pathological conditions
Atrial fibrillation, coronary artery disease, diabetes mellitus, heart failure, obesity
- Pro-atherogenic
- Pro-arrhythmogenic

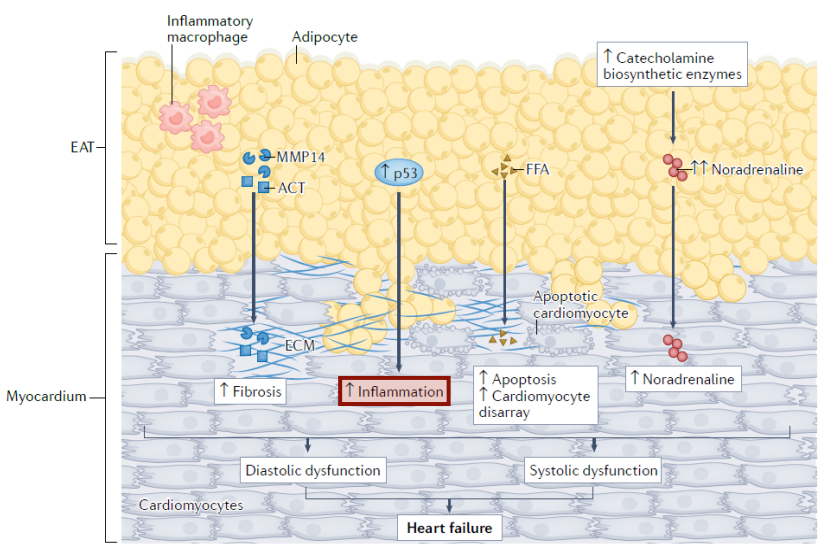


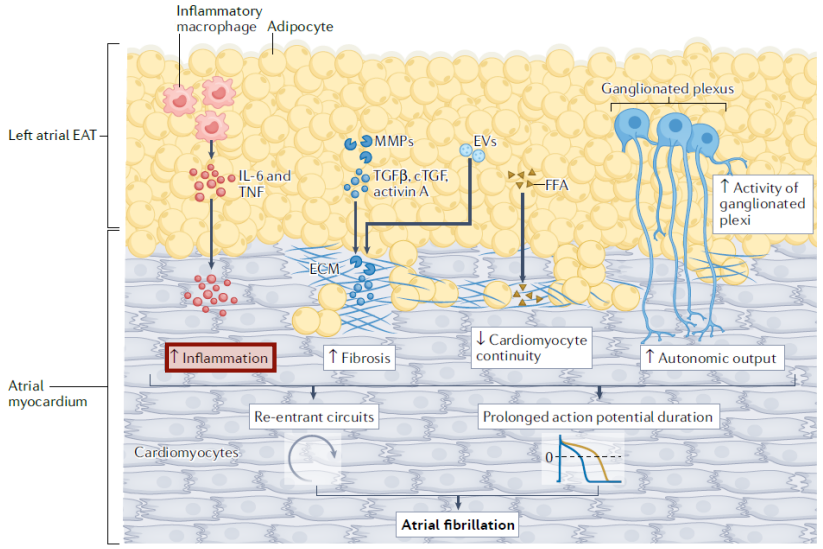
EAT changes with age and in pathological conditions. In the neonate and early years of life, EAT is morphologically and functionally similar to brown adipose tissue. The brown fat-like properties of EAT rapidly decrease with age, from childhood to adulthood. However, EAT maintains cardioprotective functions such as providing a source of energy and heat to the heart. In pathological conditions, such as CAD, DM, HF and AF, EAT becomes pro-atherogenic and pro-arrhythmogenic.

Epicardial adipose tissue in contemporary cardiology







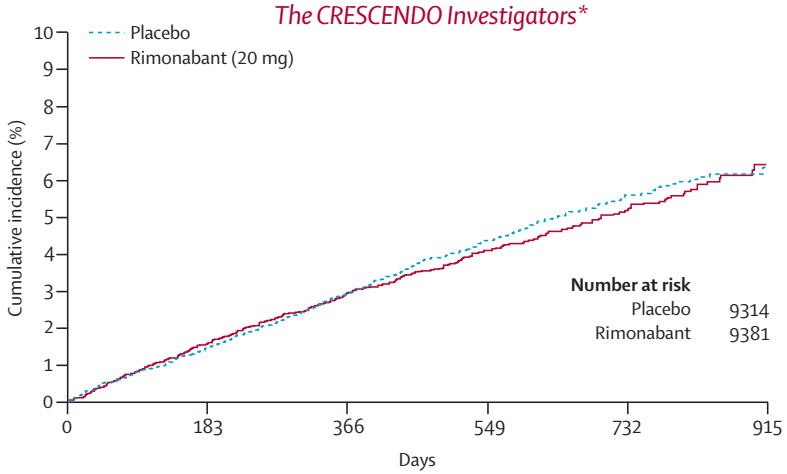


Atherosclerosis | **Heart failure** | **Arrhythmyas**

www.thelancet.com Vol 376 August 14, 2010

Rimonabant for prevention of cardiovascular events (CRESCENDO): a randomised, multicentre, placebo-controlled trial

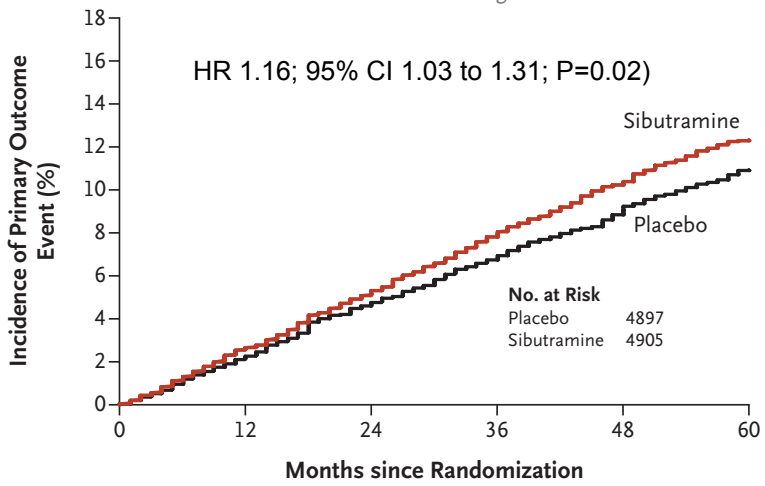
*The CRESCENDO Investigators**



N ENGL J MED 363;10 NEJM.ORG SEPTEMBER 2, 2010

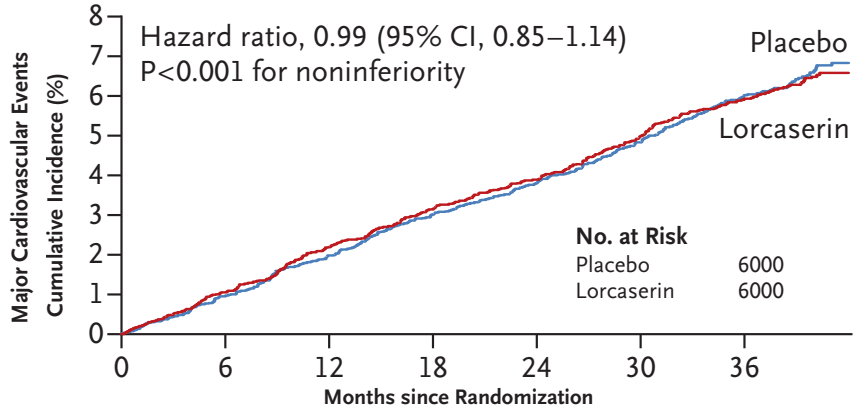
Effect of Sibutramine on Cardiovascular Outcomes in Overweight and Obese Subjects

the SCOUT Investigators*



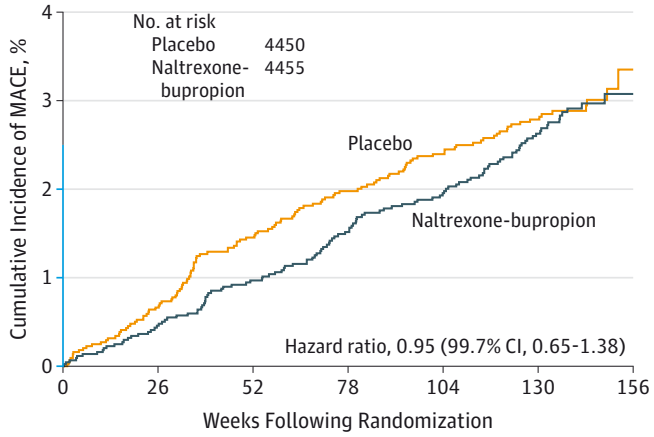
N ENGL J MED 379;12 NEJM.ORG SEPTEMBER 20, 2018

Cardiovascular Safety of Lorcaserin in Overweight or Obese Patients



JAMA March 8, 2016 Volume 315, Number 10

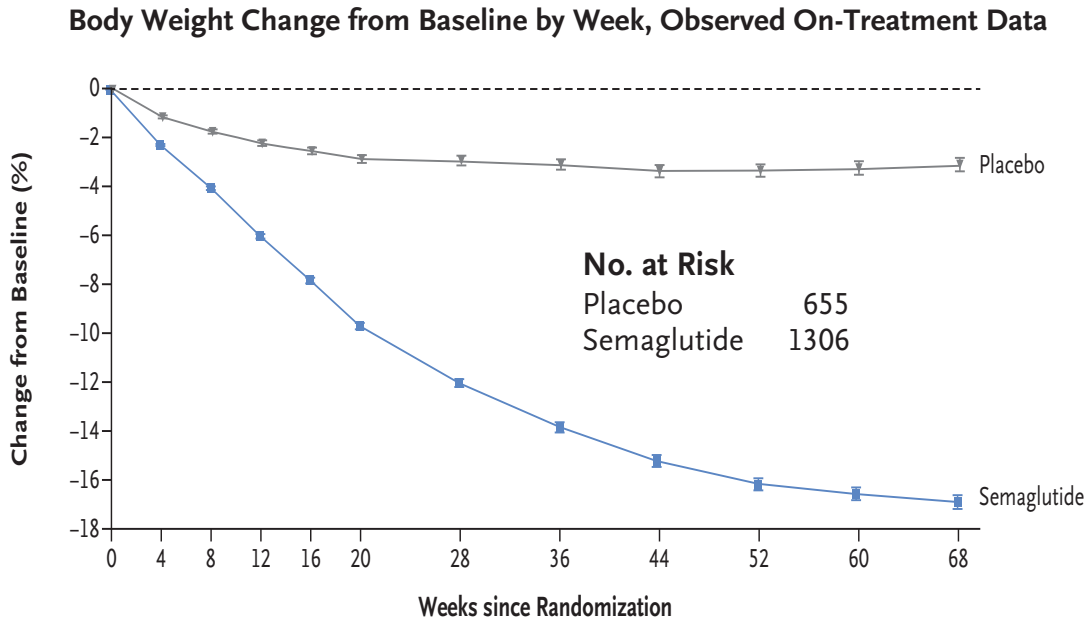
Effect of Naltrexone-Bupropion on Major Adverse Cardiovascular Events in Overweight and Obese Patients With Cardiovascular Risk Factors



The NEW ENGLAND JOURNAL of MEDICINE

Once-Weekly Semaglutide in Adults with Overweight or Obesity

the STEP 1 Study Group*

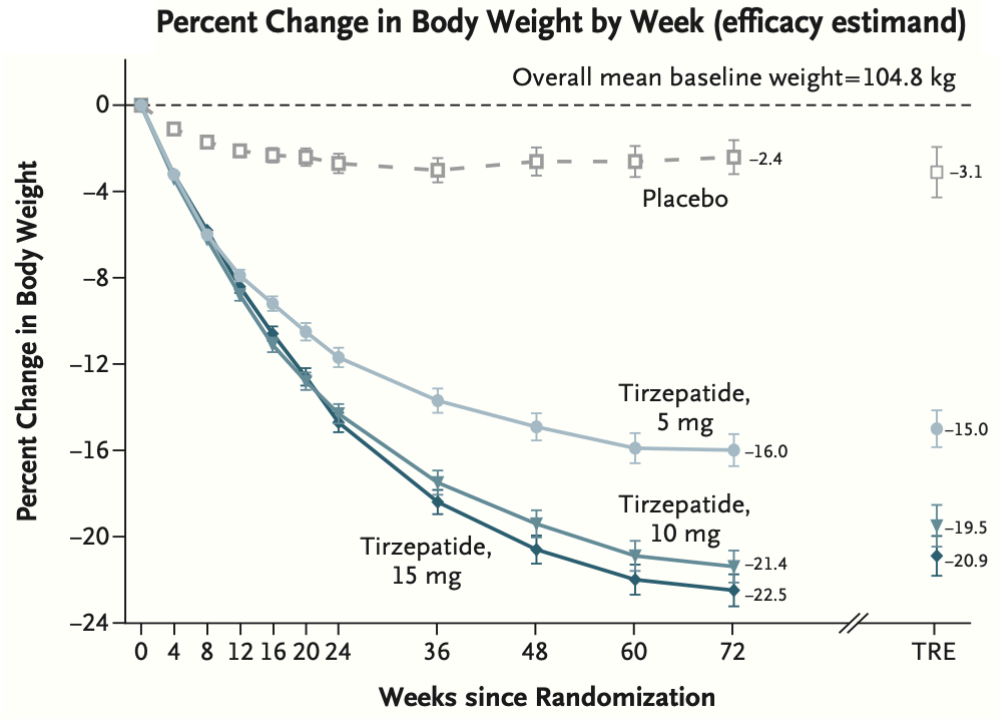


- Double-blind trial, enrolling 1961 adults with a BMI ≥ 30 or greater (≥27 if ≥1 weight-related coexisting condition), and no diabetes, randomly assigned, in a 2:1 ratio, to 68 weeks of once-weekly subcutaneous semaglutide (2.4 mg) or placebo, plus lifestyle intervention.
- Coprimary end points were % change in body weight and weight reduction >5%.
- The mean change in body weight from baseline to week 68 was −14.9% in the semaglutide group as compared with −2.4% with placebo

The NEW ENGLAND JOURNAL of MEDICINE

Tirzepatide Once Weekly for the Treatment of Obesity

SURMOUNT-1 Investigators*

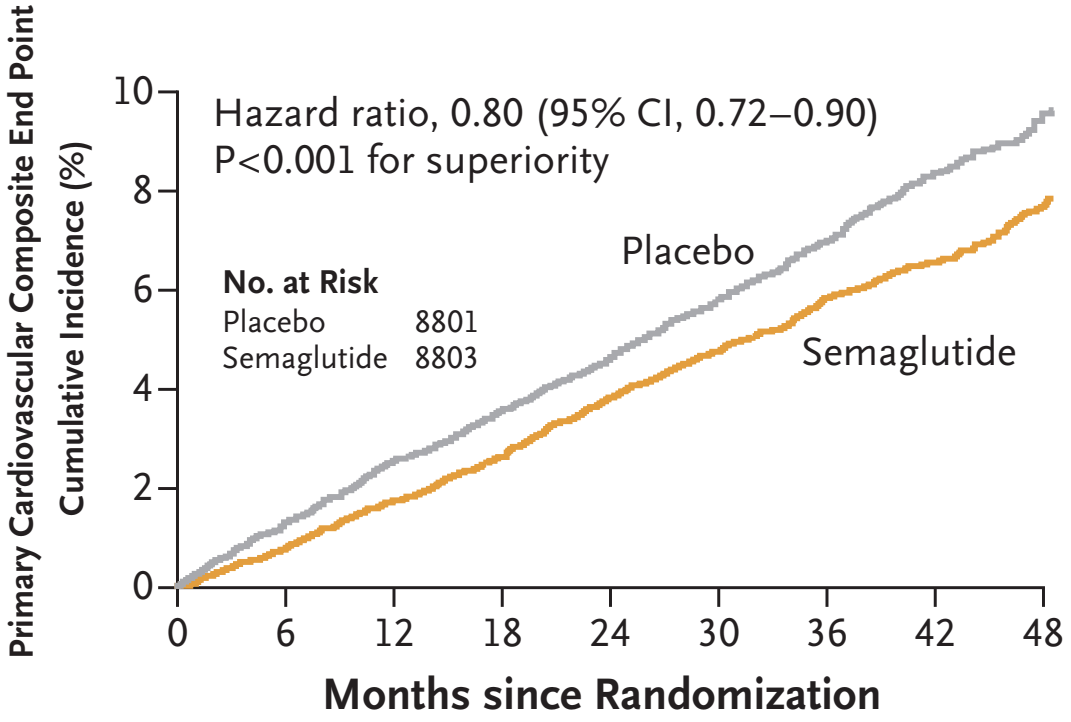


- phase 3 double-blind, randomized, controlled trial, enrolling 2539 adults with BMI ≥ 30 (≥ 27 and if ≥ 1weight-related complication) and no diabetes, in a 1:1:1:1 ratio to receive once-weekly, subcutaneous tirzepatide (5, 10 or 15 mg) or placebo for 72 weeks, including a 20-week dose-escalation period.
- Coprimary end points were % change in weight and a weight > 5%

The NEW ENGLAND JOURNAL of MEDICINE

Semaglutide and Cardiovascular Outcomes in Obesity without Diabetes

the SELECT Trial Investigators*

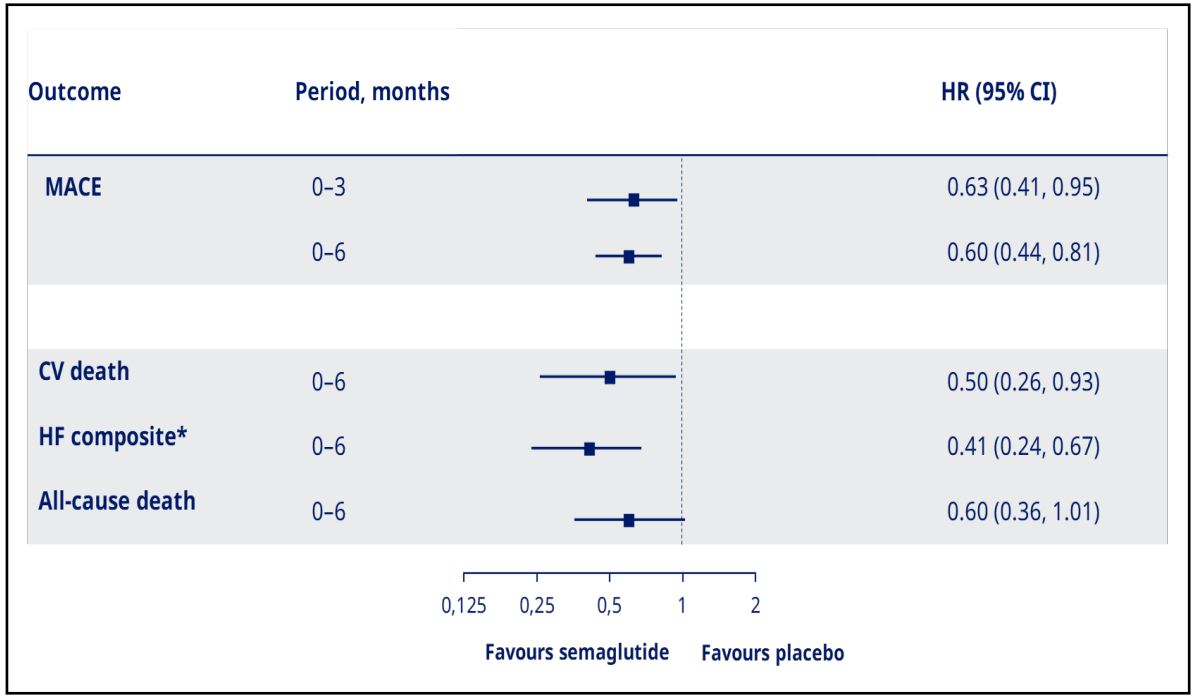


- Multicenter, double-blind, randomized, placebo-controlled, event-driven superiority trial on 17,604 patients ≥ 45 years , with CVDs and BMI ≥ 27 but no diabetes, randomly assigned (1:1) to 2.4 mg s.c. semaglutide once-weekly or placebo.
- Primary end point was a composite of death from CV causes, nonfatal MI or stroke in a time-to-first-event. Mean (SD) duration of exposure to semaglutide or placebo was 34.2±13.7 mo., and mean duration of follow-up was 39.8±9.4 mo.

Presented on November 10th, 2023 AHA sessions

Obes Facts 2025;18(suppl 1):1–656

Early Clinical Benefit of Semaglutide in Adults with Overweight or Obesity and Cardiovascular Disease: A Secondary Analysis of the SELECT Trial



At the planned trial visits, the treatment difference (semaglutide - placebo) in mean body weight was −1.1% (95% CI −1.2, −1.1) at week 4 and −3.6% (95% CI −3.7, 3.5) at week 12.

An official website of the United States government Here's how you know

National Library of Medicine
National Center for Biotechnology Information

PRS Login

ClinicalTrials.gov

Find Studies | Study Basics | Submit Studies | Data and API | Policy | About | My Saved Studies (0)

Home > Search Results > Study Record

Active, not recruiting

A Study of Tirzepatide (LY3298176) on the Reduction on Morbidity and Mortality in Adults With Obesity (SURMOUNT-MMO)

ClinicalTrials.gov ID NCT05556512

Sponsor Eli Lilly and Company

Information provided by Eli Lilly and Company (Responsible Party)

Last Update Posted 2025-11-24

Grazie 1000!!!

claudio.bilato@aulss8.veneto.it