Fairfield Medical Center

Rethinking the Standard of Care:

GLP-1, Beta-Blockers, and the Rhythm-Integrated Cardiology

A 2025 Review of Landmark Cardiovascular Trials — SELECT, SUMMIT, SOUL, REBOOT-CNIC, BETAMI-DANBLOCK and OPTION Trials

Michael Reinig, DO, FACC
FHP Cardiology

Obesity in the United States: Scope and Cardiovascular Impact

Epidemiology

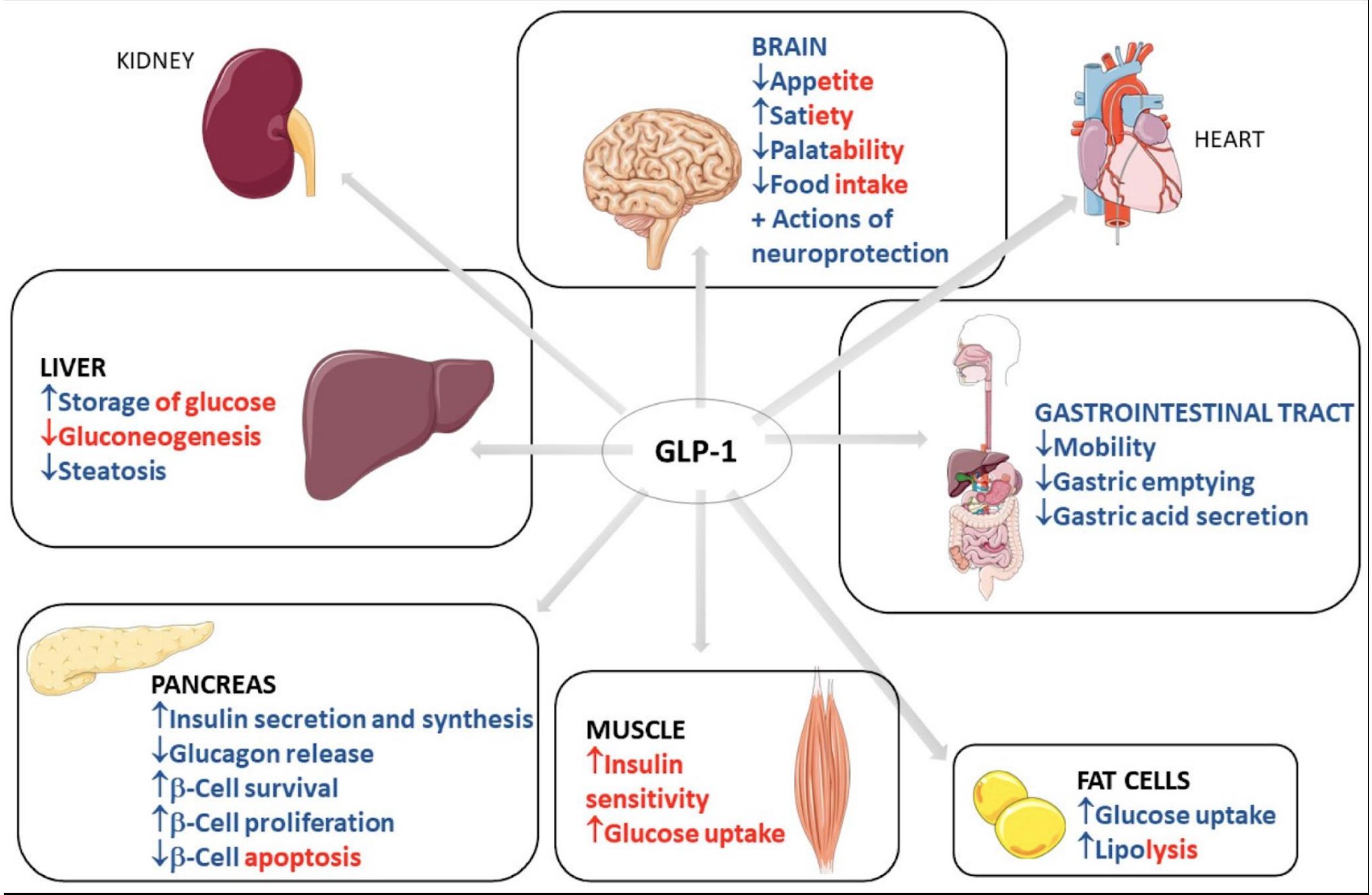
- ~42% of U.S. adults are obese ; ~9% have severe obesity (BMI ≥40 kg/m²)
- Rates have tripled since 1980

Pathophysiologic Effects on the Heart

- ↑ Blood volume & cardiac output → LV hypertrophy → diastolic dysfunction → HFpEF
- LA enlargement & fibrosis → ↑ AF and ventricular arrhythmia risk
- Obesity doubles risk of MI and stroke (core of metabolic syndrome)

Clinical Impact

- Shortens life expectancy by 5–10 years, mainly due to CVD
- Worsens HTN control, HF progression, procedural outcomes (PCI, ablation, device)


KIDNEY
BRAIN
↓Appetite
↑Satiety
↓Palatability
↓Food intake
+ Actions of
neuroprotection
HEART
LIVER
↑Storage of glucose
↓Gluconeogenesis
↓Steatosis
GLP-1
GASTROINTESTINAL TRACT
↓Mobility
↓Gastric emptying
↓Gastric acid secretion
PANCREAS
↑Insulin secretion and synthesis
↓Glucagon release
↑β-Cell survival
↑β-Cell proliferation
↓β-Cell apoptosis
MUSCLE
↑Insulin
sensitivity
↑Glucose uptake
FAT CELLS
↑Glucose uptake
↑Lipolysis

SELECT Trial

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Semaglutide and Cardiovascular Outcomes in Obesity without Diabetes

A. Michael Lincoff, M.D., Kirstine Brown-Frandsen, M.D., Helen M. Colhoun, M.D., John Deanfield, M.D., Scott S. Emerson, M.D., Ph.D., Sille Esbjerg, M.Sc., Søren Hardt-Lindberg, M.D., Ph.D., G. Kees Hovingh, M.D., Ph.D., Steven E. Kahn, M.B., Ch.B., Robert F. Kushner, M.D., Ildiko Lingvay, M.D., M.P.H., Tugce K. Oral, M.D., Marie M. Michelsen, M.D., Ph.D., Jorge Plutzky, M.D., Christoffer W. Tornøe, Ph.D., and Donna H. Ryan, M.D., for the SELECT Trial Investigators*

The SELECT Trial

Semaglutide and Cardiovascular outcomes in obesity without diabetes

Lincoff et al, New England Journal of medicine, 2023

Question

Can Semaglutide reduce Cardiovascular risk associated with overweight and obesity without diabetes?

Inclusion Criteria

- Age≥ 45
- BMI≥ 27
- Established Cardiovascular disease

Exclusion Criteria

- History of Diabetes
- HbA1c≥ 6.5%
- On Glucose lowering medication or GLP-1 Agonist within the previous 90 days
- NYHA class IV heart failure
- ESRD or on Dialysis

Methods

multi-center, double blind, randomized, placebo controlled, event driven superiority trial, 804 clinical sites in 41 countries

Semaglutide 8803 **1:1** Placebo 8801

Duration 34.2±13.7 months
Follow up 39.8±9.4 months

Primary End Point

Death from cardiovascular causes, non-fatal MI, non-fatal stroke

6.5% vs 8% (HR~0.8 P-value<0.001)

Secondary End Point

Death from cardiovascular causes

2.5% vs 3% (HR~0.85 P-value<0.07)

Death from heart failure

HR~0.82

Death from any cause

HR~0.81

Mean Change in Body Weight

-9.39% vs -0.88%

Adverese events leading to permanent discontinuation of trial product

16.6% vs 8.2% (P-Value<0.001)

Conclusion

Weekly subcutaneous Semaglutide 2.4 mg was superior to placebo in reducing the incidence of death in cardiovascular causes, nonfatal MI, or nonfatal stroke at a mean follow up 39.8 months in patients with preexisting cardiovascular disease and overweight or obesity but without diabetes. The incidence of adverse events was lower among patients who received semaglutide.

SELECT Trial Dosing Strategy

Titration Protocol:

- **Week 0:** 0.24 mg SC weekly
- **Week 4:** 0.5 mg
- **Week 8:** 1.0 mg
- **Week 12:** 1.7 mg
- **Week 16:** 2.4 mg (maintenance dose)

Tolerability Adjustment:

- Slower up titration permitted if GI side effects occurred.
- Lower maintenance doses allowed if unable to tolerate 2.4 mg.

Duration:

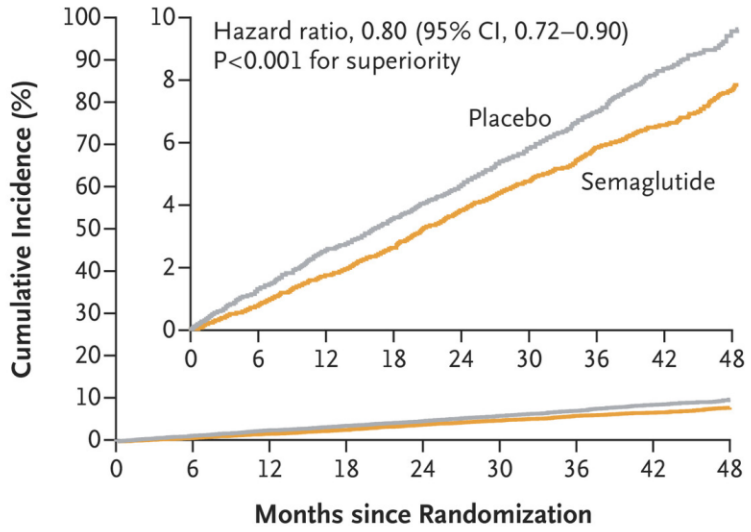
- Participants were followed for a median of **~40 months** (mean treatment ~2 years).

Key Point:

- Gradual escalation to target 2.4 mg mitigated GI intolerance while maintaining cardiovascular risk reduction benefits.

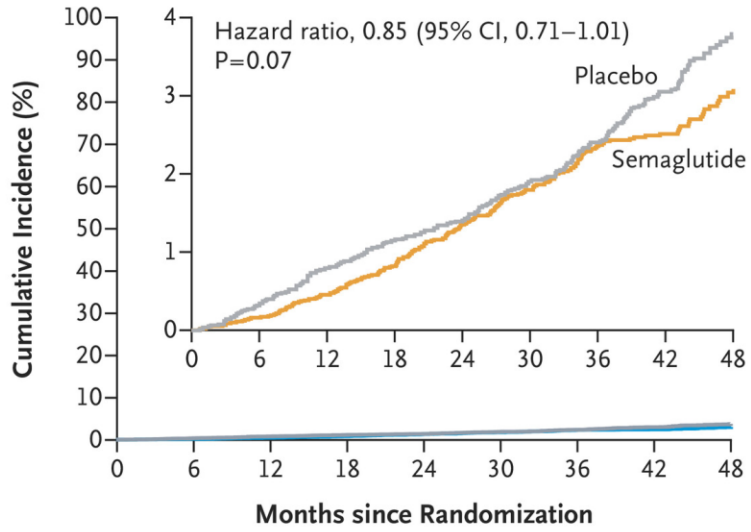
SELECT Trial – *N Engl J Med*, 2023;389:2095–2107

A Primary Cardiovascular Composite End Point



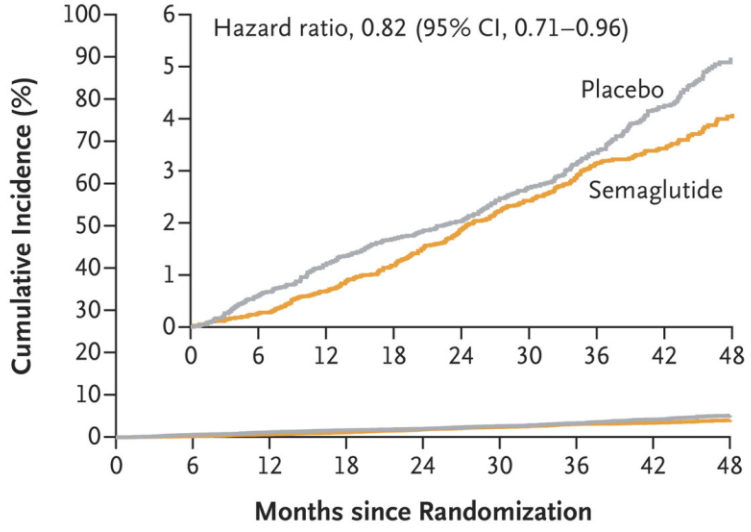
No. at Risk									
Placebo	8801	8652	8487	8326	8164	7101	5660	4015	1672
Semaglutide	8803	8695	8561	8427	8254	7229	5777	4126	1734

B Death from Cardiovascular Causes



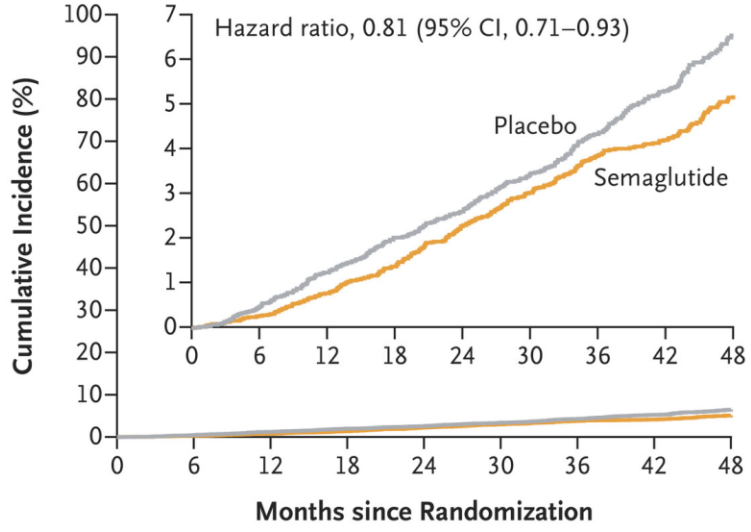
No. at Risk									
Placebo	8801	8733	8634	8528	8430	7395	5938	4250	1793
Semaglutide	8803	8748	8673	8584	8465	7452	5988	4315	1832

C Heart Failure Composite End Point



No. at Risk									
Placebo	8801	8711	8601	8485	8381	7341	5885	4198	1766
Semaglutide	8803	8740	8654	8557	8425	7409	5944	4277	1816

D Death from Any Cause

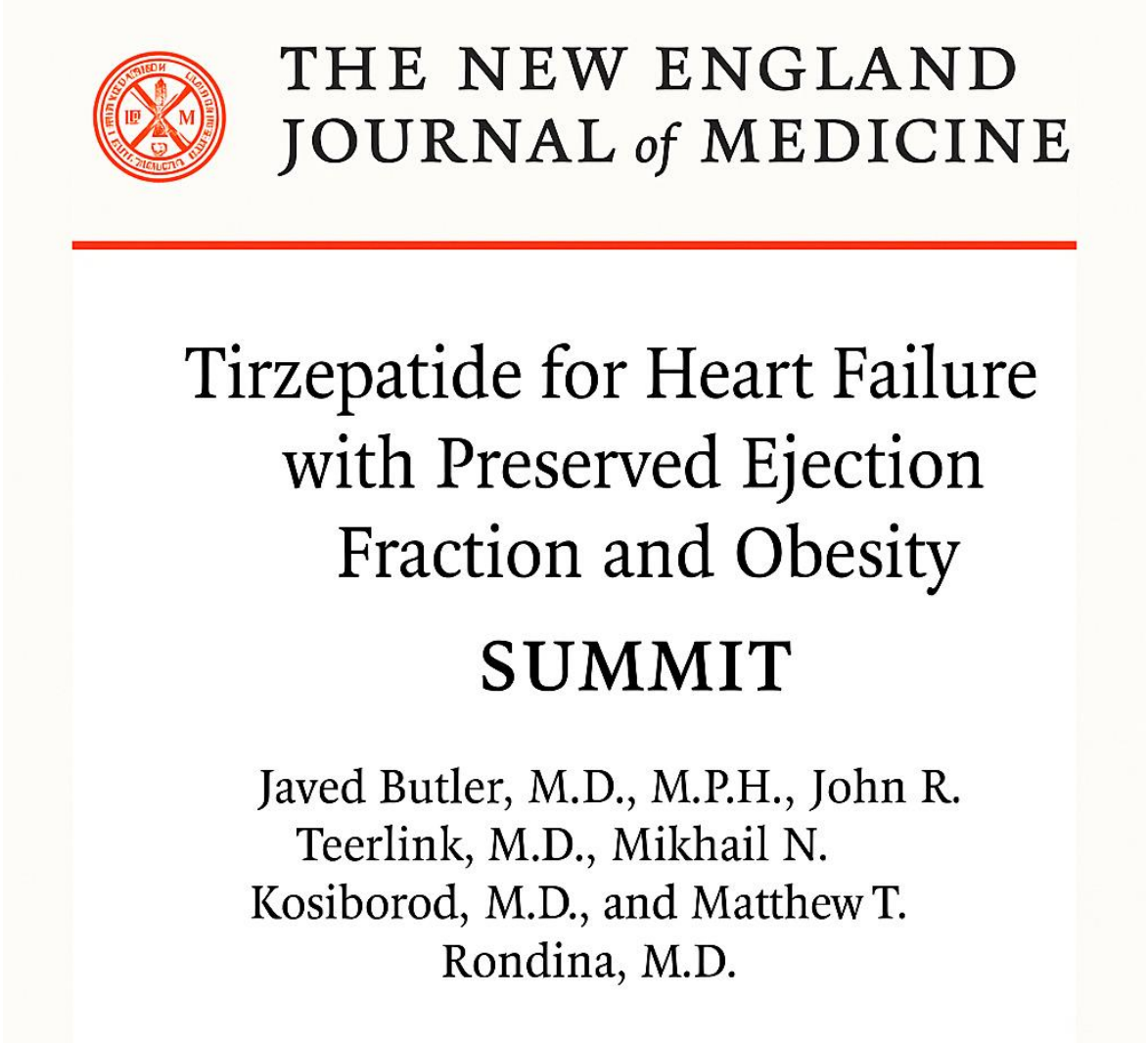


No. at Risk									
Placebo	8801	8733	8634	8528	8430	7395	5938	4250	1793
Semaglutide	8803	8748	8673	8584	8465	7452	5988	4315	1832

Key Takeaways

- SELECT is the **first trial** showing CV event reduction in **non-diabetic obese patients** with ASCVD.
- **20% reduction** in MACE; significant mortality benefit.
- Reframes obesity as a **treatable cardiovascular condition.**
- Sets stage for future GLP-1 use in **primary prevention** populations.

SUMMIT Trial



THE NEW ENGLAND JOURNAL of MEDICINE

Tirzepatide for Heart Failure with Preserved Ejection Fraction and Obesity

SUMMIT

Javed Butler, M.D., M.P.H., John R. Teerlink, M.D., Mikhail N. Kosiborod, M.D., and Matthew T. Rondina, M.D.

SUMMIT

Tirzepatide For Heart Failure With Preserved Ejection Fraction (HFpEF) and Obesity

OBJECTIVE

Evaluate the long-term effects of tirzepatide on major adverse HF outcomes

STUDY METHGDS

Mean BMI = 38 kg/m², mean probability of HFpEF >50%, substantial limitations on health and exercise capacity

STUDY DESIGN

Randomized 1:1 to receive tirzepatide up to 15 mg subcutaneously weekly or placebo for median of 104 weeks

TIRZEPATIDE (N=364)

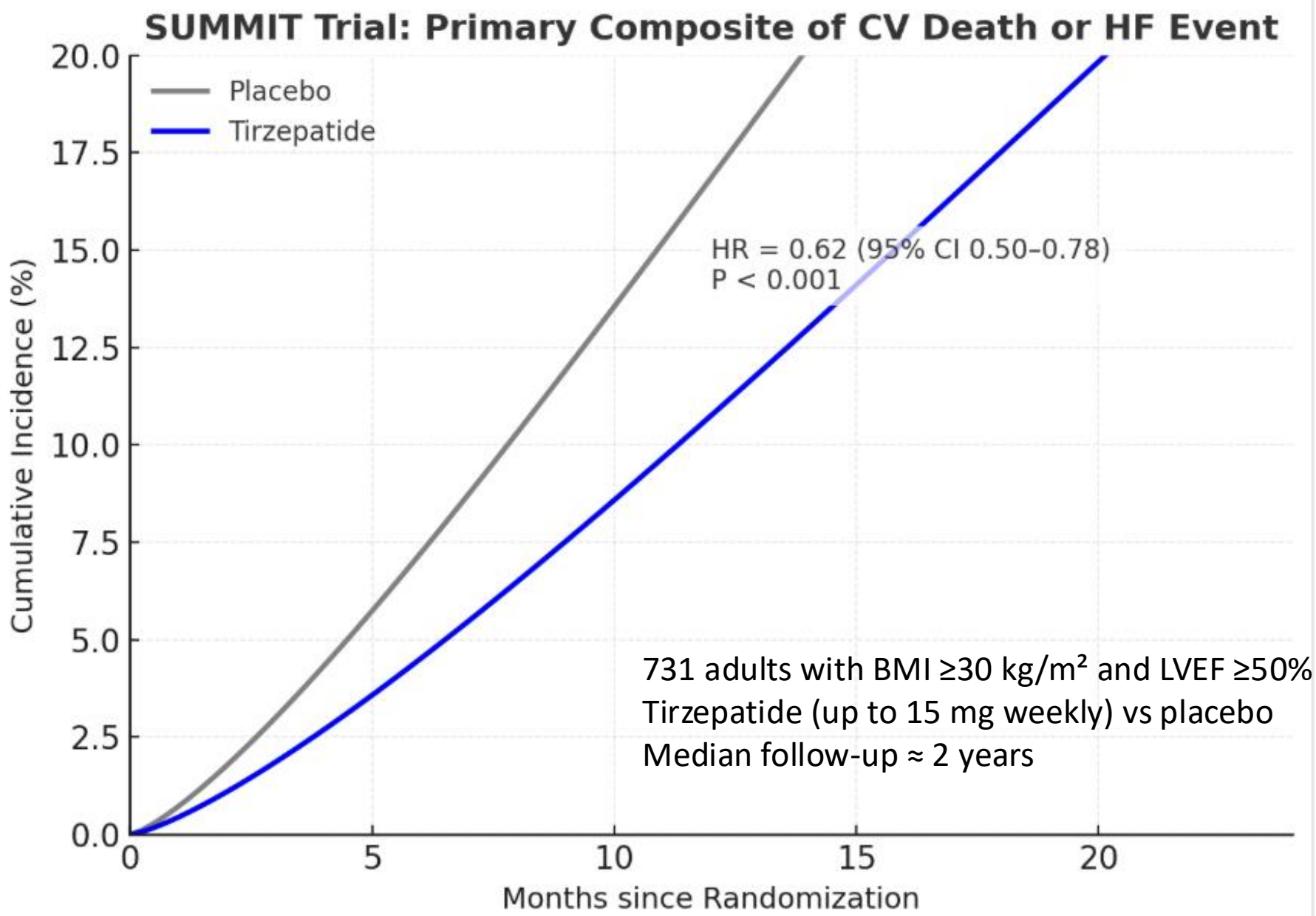
PLACEBO (N=367)

PRIMARY ENDPOINTS

Fewer worsening HF events in tirzepatide group vs placebo (Hazard Ratio 0.34–0.85), with no difference in cardiovascular death

CONCLUSION

Tirzepatide reduced the risk of cardiovascular death or worsening HF and improved health


SUMMIT Trial: Primary Composite of CV Death or HF Event
Placebo
Tirzepatide
HR = 0.62 (95% CI 0.50–0.78)
P < 0.001
731 adults with BMI ≥30 kg/m² and LVEF ≥50%
Tirzepatide (up to 15 mg weekly) vs placebo
Median follow-up ≈ 2 years
Cumulative Incidence (%)
Months since Randomization
0.0
2.5
5.0
7.5
10.0
12.5
15.0
17.5
20.0
0
5
10
15
20

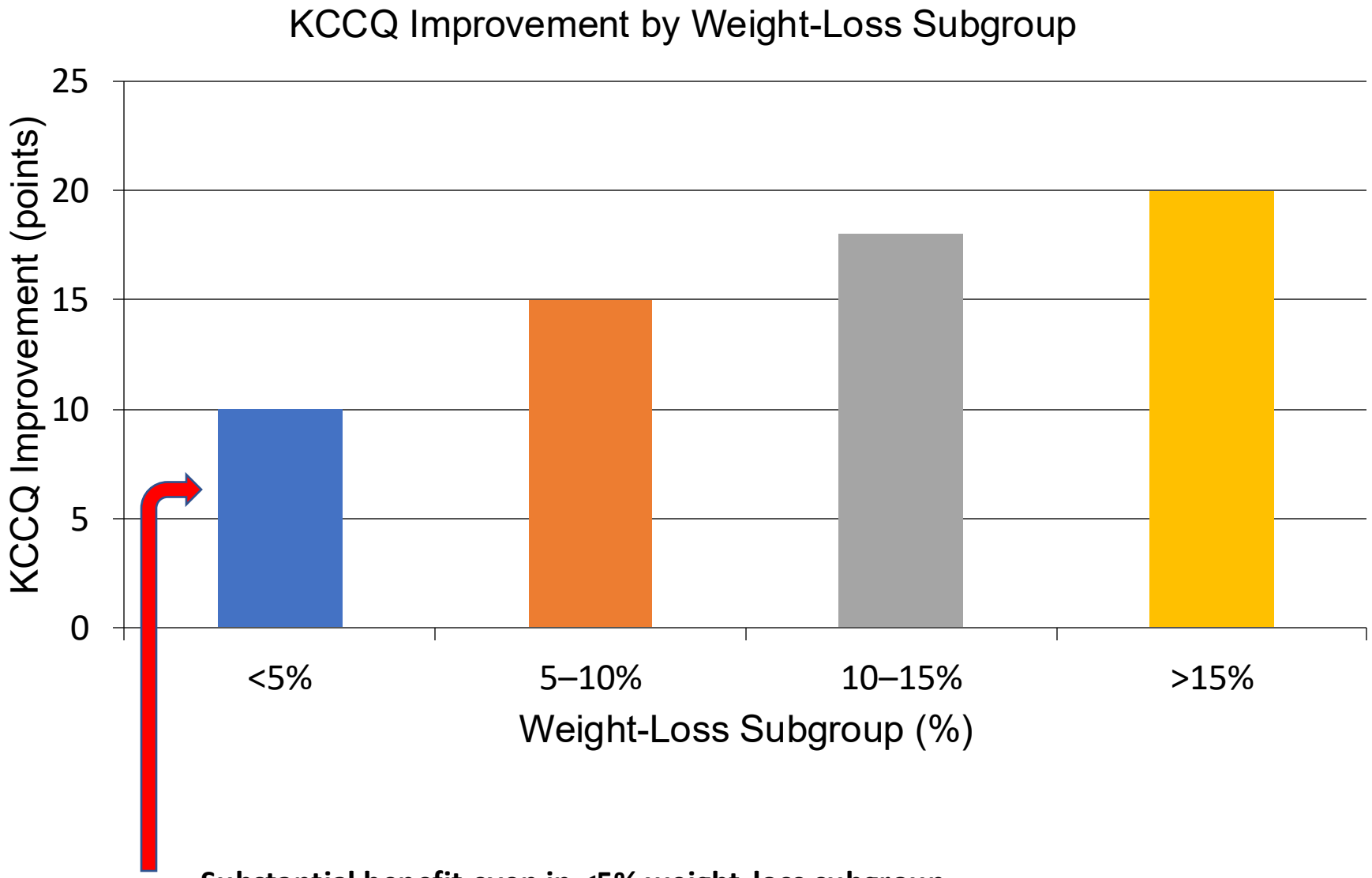
Key Results: SUMMIT Trial

Outcome	Tirzepatide	Placebo	Effect
CV death or worsening HF	**9.9%**	**15.3%**	**HR 0.62**, *p = 0.026*
Worsening HF events	**8.0%**	**14.2%**	**HR 0.54**
Δ KCCQ-CSS	—	—	**+6.8 points**, *p < 0.001*
Weight loss	**−13.9%**	**−2.2%**	*p < 0.001*

Secondary endpoints

- 6-min walk: +24.6 m improvement
- NT-proBNP ↓ 23%
- ↓ LV mass (−11 g), ↓ pericardial fat (−45 mL)

SUMMIT Trial: Benefits Beyond Weight Loss



Substantial benefit even in <5% weight-loss subgroup

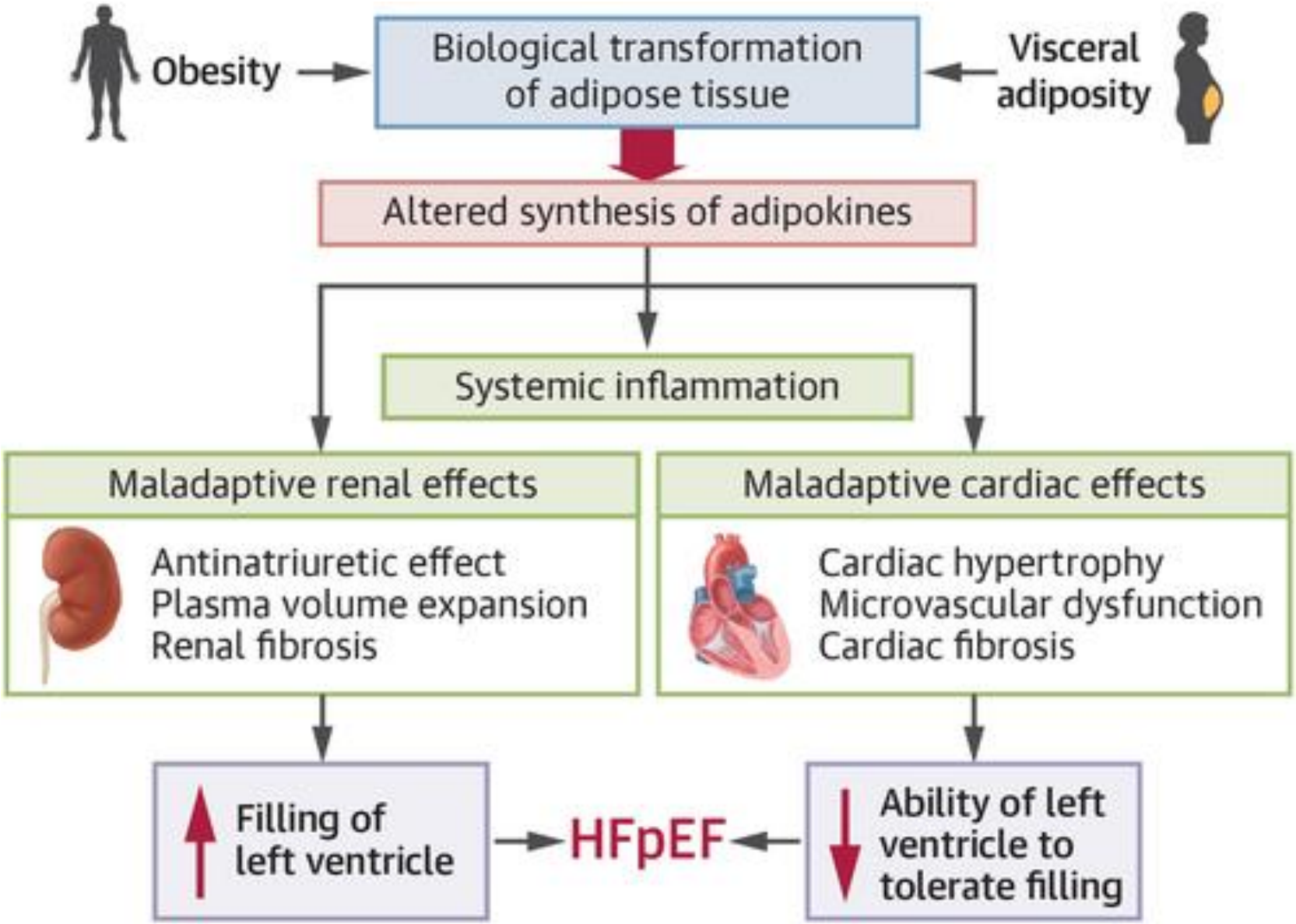
Key Takeaways: SUMMIT Trial

- First trial showing GLP-1/GIP agonist reduces HF events in obese HFpEF
- 38% RRR in HF hospitalizations
- Improved quality of life and exercise capacity
- SUMMIT confirms metabolic therapy can reduce HF events and improve QoL

SUMMIT Trial Substudy: Cardiac MRI

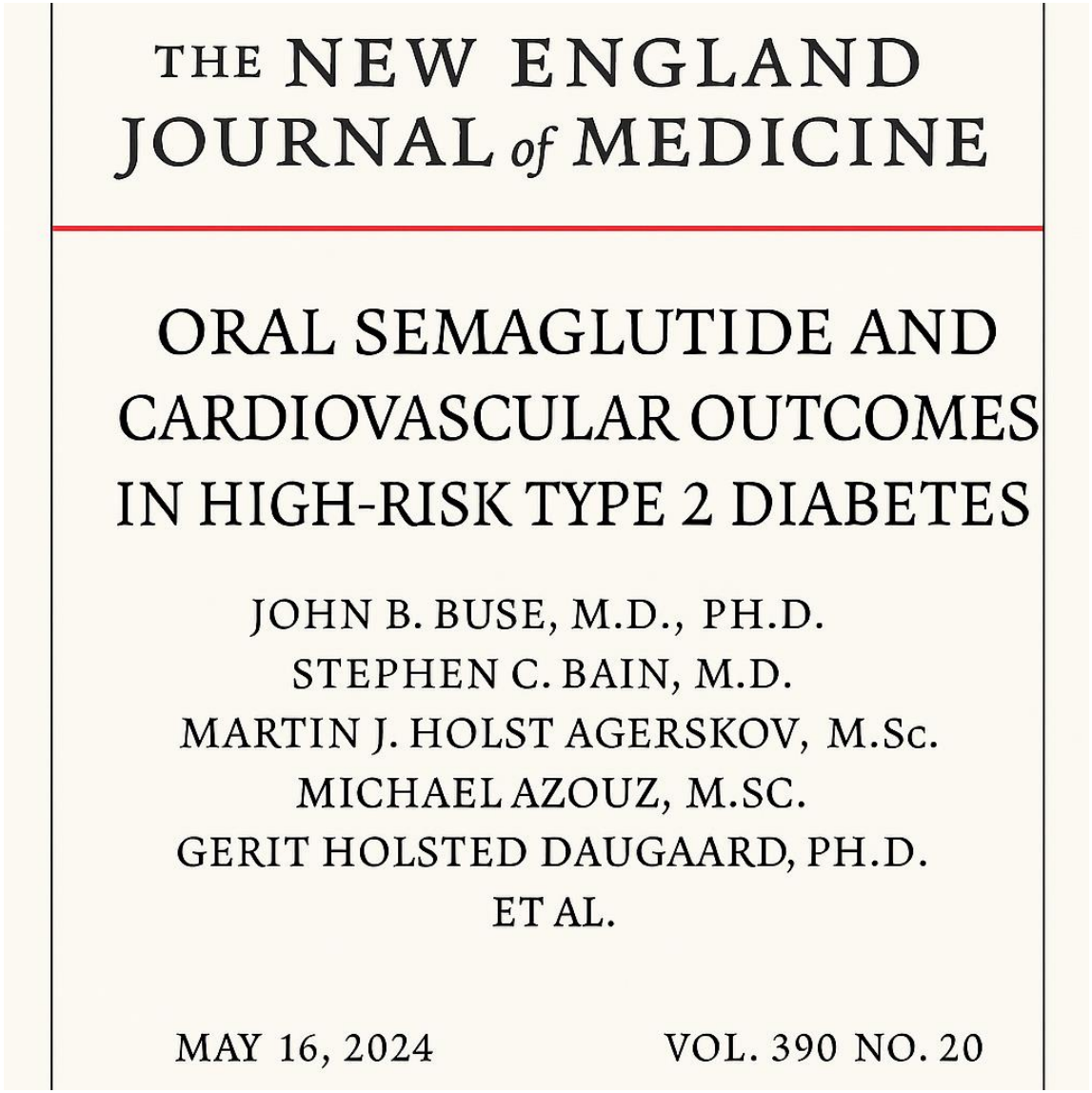
- Reduction in LV mass and paracardiac fat irrespective of Wt. loss
- Paracardiac adipose tissue may play key role in obesity related HFpEF
- Acts in Paracrine manner releasing proinflammatory and profibrotic adipocytes leading myocardial inflammation and fibrosis
- Exerts extrinsic restraint impairing ventricular relaxation
- Changes in LV Mass lead to elevated RA pressure & LV filling pressure

JACC Heart Failure 2020;8(8)657-666



JACC: 86(16) 1297 October 2025

SOUL Trial


THE NEW ENGLAND JOURNAL of MEDICINE
ORAL SEMAGLUTIDE AND CARDIOVASCULAR OUTCOMES IN HIGH-RISK TYPE 2 DIABETES
JOHN B. BUSE, M.D., PH.D.
STEPHEN C. BAIN, M.D.
MARTIN J. HOLST AGERSKOV, M.Sc.
MICHAEL AZOUZ, M.SC.
GERIT HOLSTED DAUGAARD, PH.D.
ET AL.
MAY 16, 2024
VOL. 390 NO. 20

The SOUL Trial

Oral Semaglutide and Cardiovasccular Outcomes

Hochberg et al., New England Journal of medicine, 2025

Question

Does oral semaglutide reduce cardiovascular risk in patients with type 2 diabetes?

Inclusion Criteria

- Age ≥ 18 years
- Established cardiovascular disease

Exclusion Criteria

- Type 1 diabetes
- GLP-1 agonist use ≥30 days
- eGFR < 15 mL/min/1.73 m^2
- eGFR < 15 mL/min/1

Methods

1:1

Semagulide 9818

Placobo 9834

Duration 33.3±11m

Follow-up 3.4±0,9 y

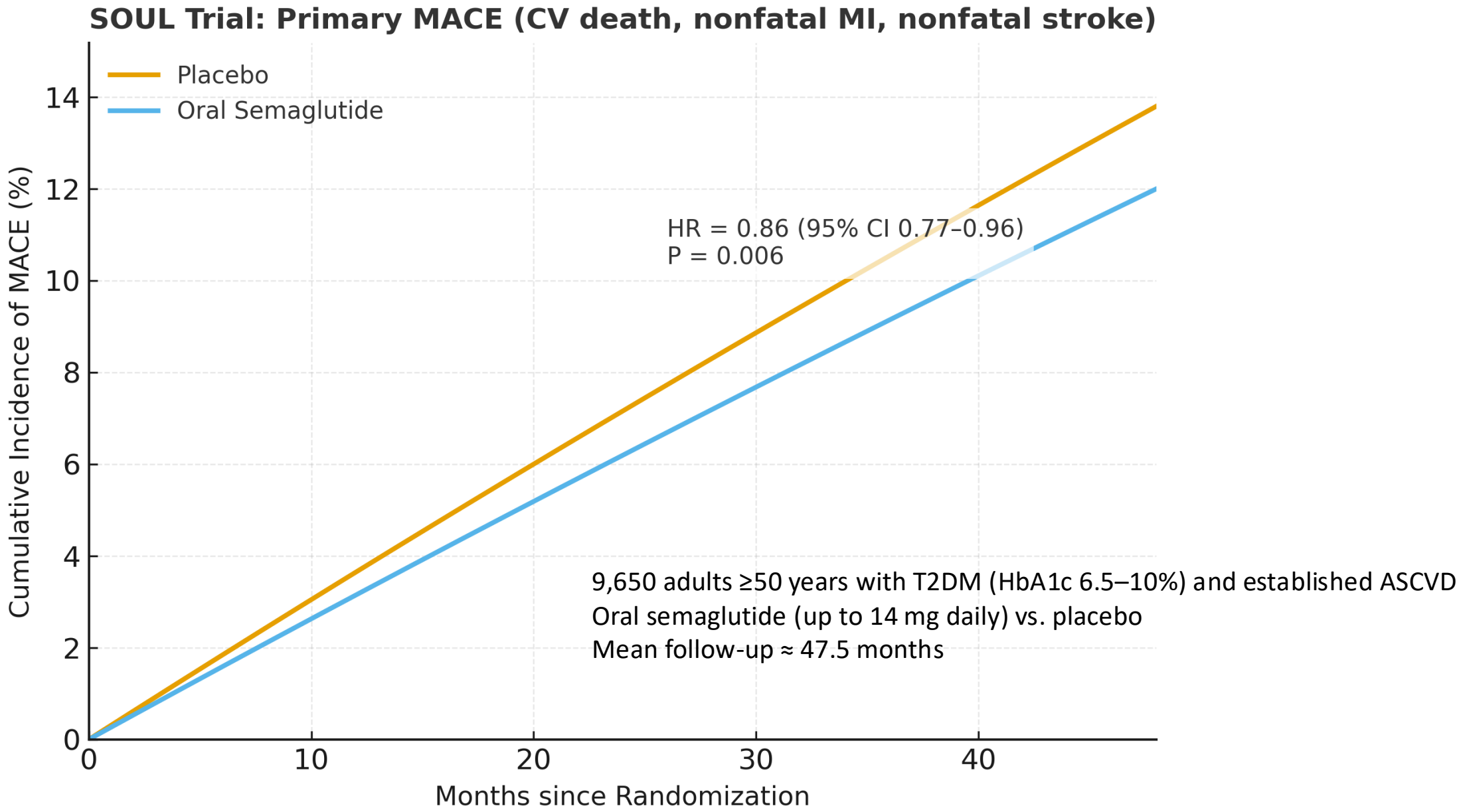
Primary End Point

Death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke

HR=0.80, p=0,80, p == 0,001

Conclusion

Once-daily oral semaglutide was superior to placebo in reducing the incidence of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke in patients with type 2 diabetes


SOUL Trial: Primary MACE (CV death, nonfatal MI, nonfatal stroke)
Placebo
Oral Semaglutide
HR = 0.86 (95% CI 0.77–0.96)
P = 0.006
9,650 adults ≥50 years with T2DM (HbA1c 6.5–10%) and established ASCVD
Oral semaglutide (up to 14 mg daily) vs. placebo
Mean follow-up ≈ 47.5 months
Cumulative Incidence of MACE (%)
0
2
4
6
8
10
12
14
0
10
20
30
40
Months since Randomization

GLP-1 Trials — Summary & Clinical Implications

SELECT:

- Semaglutide in patients with obesity and established CVD (no diabetes)
- Showed a **20% reduction in cardiovascular death, MI, or stroke**
- → **First proof that weight-loss therapy lowers CV events**

SUMMIT:

- Tirzepatide in obese patients with HFpEF
- **Reduced HF events and improved quality of life and exercise capacity**
- → **Demonstrates that treating obesity improves heart failure outcomes**

SOUL:

- Oral semaglutide in type 2 diabetes with ASCVD/CKD
- **Reduced major CV events by 14%**
- → **Shows oral GLP-1 therapy also provides cardiovascular protection**

Common heart attack drug doesn't work and may raise risk of death for some women, new studies say

UPDATED AUG 30, 2025

By Sandee LaMotte

Beta-Blockers After MI — Why Re-Examine an Old Standard?

Background

- Beta-blockers have been standard post-MI therapy since the 1970s–1980s (BHAT, TIMI).
- Early studies showed ~20–30% mortality reduction — but those were pre-reperfusion, pre-statin, pre-ACE inhibitor eras.
- Today's MI patients receive early PCI, statins, DAPT, and revascularization

The Question

- Do all post-MI patients still benefit from chronic beta-blockade, or only those with LV dysfunction or heart failure?
- Could routine therapy in patients with LVEF >40% and no HF be unnecessary or even harmful?

Clinical Rationale

Revisiting a long-standing dogma — asking whether 'routine beta-blockers for everyone' still holds true in the era of PCI, statins, and optimized secondary prevention.

REBOOT-CNIC Trial

The NEW ENGLAND JOURNAL of MEDICINE

Beta-Blockers after Myocardial Infarction without Reduced Ejection Fraction

Authors: Borja Ibanez, M.D., Ph.D., Roberto Latini, M.D., Ph.D., Xavier Rossello, M.D., Ph.D. , Alberto Dominguez-Rodriguez, M.D., Ph.D. , Felipe Fernández-Vazquez, M.D., Ph.D., Valentina Pelizzoni, M.D., Pedro L. Sánchez, M.D., Ph.D., +57 , for the REBOOT-CNIC Investigators* Author Info & Affiliations

Published August 30, 2025 | DOI: 10.1056/NEJMoa2504735 | Copyright © 2025

REBOOT–CNIC

Beta-Blockers After MI with Preserved LVEF > 40% and No Heart Failure

To compare the long-term clinical benefit of beta-blocker versus no beta-blocker in patients ater acute myocardial infarction with LVEF > 40 % in contemporary care

Primary Outcome

Composite of death + HF hospitalization

Inclusion criteria

- Acute MI (ST-segment elevation or non-ST)
- Invasive management of MI
- No discharge LVEF > 40 %
- No signs or history of heart failure

8,505 Patients

109 centers in Spain & Italy

Beta-blocker therapy

HR 1.04
(95 % CI 0,86-12)
P = 0,63

Key Results

Routine beta-blocker therapy post-MI offers no mortality or morbidity benefit with LVEF > 40 %

Study Design & Population

- n = 8,505 patients from 109 hospitals.
- Inclusion: Recent STEMI/NSTEMI, invasive management, LVEF >40%, no HF.
- Exclusion: LVEF ≤40%, chronic HF, or contraindications to beta-blockers.
- Follow-up: Median 3.7 years.
- Beta-blocker group: Standard doses of bisoprolol, carvedilol, or metoprolol.
- Control group: No beta-blocker therapy post-discharge.
- Background therapy: nearly universal DAPT, statins, ACEi/ARB, revascularization.

Baseline Characteristics

- Mean age: 61 years; 19% women.
- 10% prior MI; median LVEF 55%.
- 97% received PCI; >95% on statin and DAPT.
- *Represents well-treated modern MI population*.

Primary Endpoint Results

- Composite endpoint (death, reinfarction, HF hospitalization):
  - 22.5 vs 21.7 per 1,000 patient-years (Beta-blocker vs Control)
  - HR 1.04 (95% CI 0.89–1.22; p=0.63)
- No difference in all-cause mortality (HR 1.06).
- No reduction in recurrent MI or HF hospitalization.

Clinical Implications & Summary

- Beta-blockers *may not* be mandatory in MI patients with preserved EF.
- Reinforces evidence-based tailoring of post-MI therapy.
- Suggests individualized approach based on LV function, symptoms, arrhythmia risk
- Guidelines may evolve for routine use to LVEF ≤40% or symptomatic patients.
- REBOOT-CNIC redefines post-MI secondary prevention in the modern era.

BETAMI-DANBLOCK Trial

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Beta-Blockers after Myocardial Infarction in Patients without Heart Failure

Authors: John Munkhaugen, M.D., Ph.D., Anna Meta D. Kristensen, M.D., Sigrun Halvorsen, M.D., DM.Sc., Therese Holmager, Ph.D., Michael Hecht Olsen, M.D., DM.Sc., Arnhild Bakken, P.T., Ph.D., Thomas S.G. Sehested, M.D., Ph.D., +57 , for the BETAMI–DANBLOCK Investigators* Author Info & Affiliations

Published August 30, 2025 | DOI: 10.1056/NEJMoa2505985 | **Copyright © 2025**

BETAMI–DANBLOCK Trial

Ziff et al., JAMA 2024

Question

Do beta-blockers improve survival after an MI in patients without heart failure?

Primary Endpoint

- All-cause mortality or MI

Inclusion Criteria

- Age ≤ 80 years
- LVEF ≥ 50%
- No heart failure

Beta-blocker 2,505

No beta-blockes 2,505

Methods

Two trials combined (BETAMI and DANBLOC

~5,020 patients

Exclusion Criteria

- Persistent ischemia
- Important bradycardia
- Class I indication for a beta-blocker

Methods

Two trials combined (BETAMI and DANBLOCK)

~5,020 patients

Results

No difference (P=0,58)

Conclusion

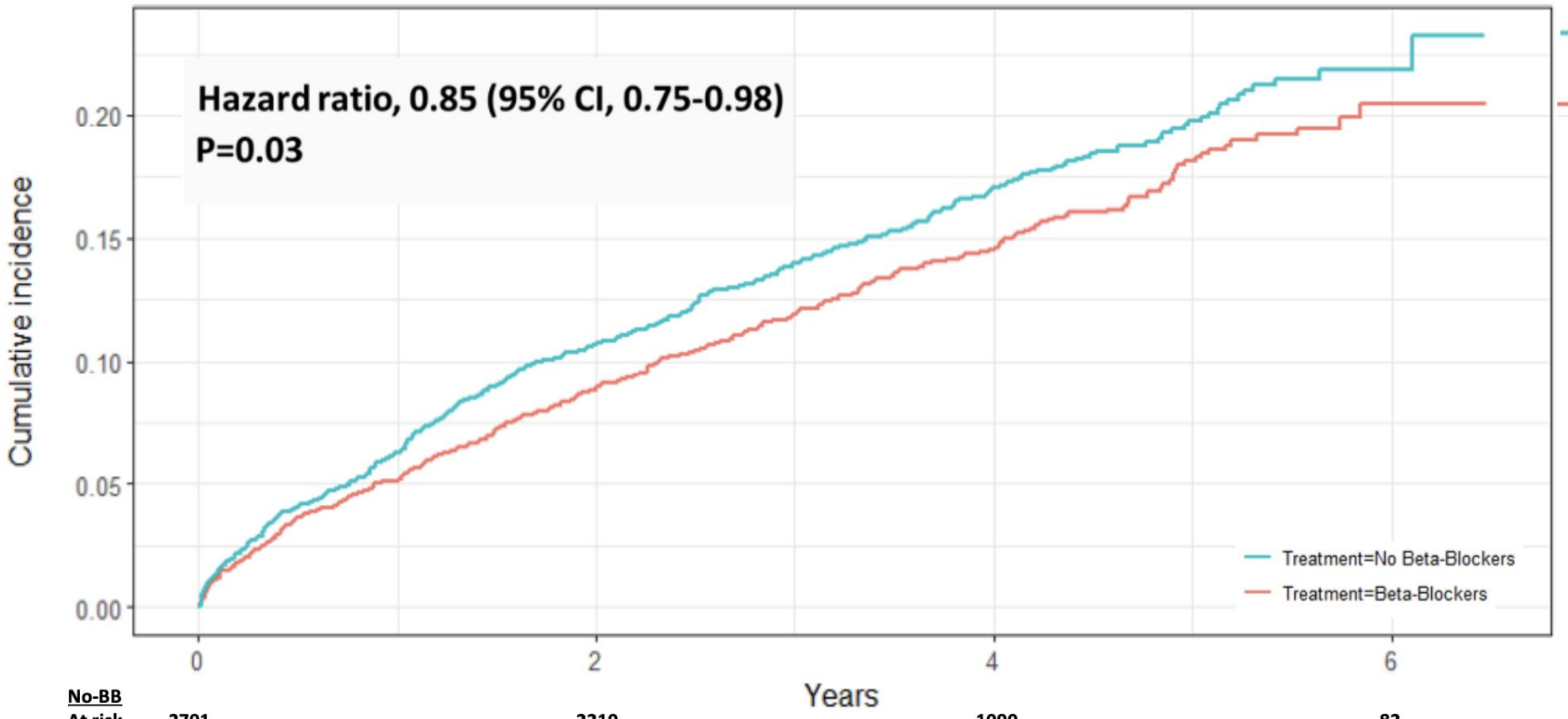
Routine use of beta-blockers post-MI in patients without heart failure did not reduce risk

BETAMI Study
BEta-Blocker Treatment after Acute Myocardial Infarction

BETAMI-DANBLOCK - PRIMARY RESULT

DANBLOCK

All-cause Mortality or MACE



No BB

BB

Median follow-up 3.5 years

No-BB				
At risk	2791	2210	1090	82
BB				
At risk	2783	2241	1114	95

ESC Congress 2025 Madrid

REDUCE-AMI Trial

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Beta-Blockers after Myocardial Infarction and Preserved Ejection Fraction

Authors: Troels Yndigegn, M.D., Bertil Lindahl, Ph.D., Katarina Mars, M.D., Joakim Alfredsson, Ph.D., Jocelyne Benatar, Ph.D., Lisa Brandin, Ph.D., David Erlinge, Ph.D., +12 , for the REDUCE-AMI Investigators* Author Info & Affiliations

Published April 7, 2024 | N Engl J Med 2024;390:1372-1381 | DOI: 10.1056/NEJMoa2401479 | VOL. 390 NO. 15

Fairfield Medical Center

REDUCE-AMI:
Beta-blockers after Myocardial Infarction and Preserved Ejection Fraction

RESULTS: In patients with AMI with preserved LVEF, long-term use of beta-blockers didn't lower the risk of death or new heart attacks compared to those who didn't take beta-blockers.

PURPOSE: To examine if long-term oral beta-blocker use in patients with acute myocardial infarction (AMI) and preserved preserved left ventricular ejection fraction (LVEF) reduces the risk of death or new heart attacks compared to not using beta-blockers.

TRIAL DESIGN: Registry-based, prospective, randomized, open-label, parallel group clinical trial (n=5020).

	Beta-Blockers (N=2508)	No Beta-Blockers (N=2512)	Hazard Ratio (95%CI)	P value
Primary endpoint				
All-cause death or myocardial infarction, no (%)	199 (7.9)	208 (8.3)	0.96 (0.79 - 1.16)	0.64
Secondary endpoints				
All-cause death, no (%)	97 (3.9)	103 (4.1)	0.94 (0.71 – 1.24)	
Death from cardiovascular causes	38 (1.5)	33 (1.3)	1.15 (0.72 – 1.84)	
Myocardial infarction	112 (4.5)	117 (4.7)	0.96 (0.74 – 1.24)	

Key Takeaways: Starting oral beta-blocker treatment early after a heart attack in patients with normal heart function didn't result in a lower combined occurrence of death or new heart attacks.

Beta-Blockers Post-MI in the Modern Era
Summary and Clinical Implications

REBOOT-CNIC • BETAMI-DANBLOCK • REDUCE-AMI

🧠 Do beta-blockers still help after MI in patients with preserved EF?

- Modern PCI era
- Preserved EF (≥50%)
- On full GDMT

REBOOT-CNIC (NEJM 2024)
5,020 pts, LVEF ≥50%
❌ No reduction in death, MI, or HF hosp.

REDUCE-AMI (NEJM 2024)
5,020 pts, LVEF ≥50%
❌ No benefit on death or recurrent MI

BETAMI-DANBLOCK (Circulation 2023)
3,500 pts, LVEF >40%
❌ No difference in death or MI

Routine β-blocker therapy not beneficial in revascularized, preserved-EF post-MI.
Continue only if EF ≤40%, HF, or arrhythmia risk.

OPTION Trial

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Left Atrial Appendage Closure after Ablation for Atrial Fibrillation

Authors: Oussama M. Wazni, M.D., Walid I. Saliba, M.D., Devi G. Nair, M.D., Eloi Marijon, M.D., Ph.D., Boris Schmidt, M.D., Troy Hounshell, D.O., Henning Ebelt, M.D., +22 , for the OPTION Trial Investigators* Author Info & Affiliations

Published November 16, 2024 | N Engl J Med 2025;392:1277-1287 | DOI: 10.1056/NEJMoa2408308

VOL. 392 NO. 13 | Copyright © 2024

Background & Rationale

- AF ablation does not eliminate long-term stroke risk
- OAC reduces stroke but increases bleeding
- LAAC may offer similar stroke prevention with less bleeding
- OPTION trial tested LAAC vs continued OAC post-ablation

Prospective, randomized, multi-center, global investigation to determine if left atrial appendage closure with the WATCHMAN FLX Device is a reasonable alternative to oral anticoagulation in patients after AF ablation.*

1,600 Patients Randomized 1:1

AF Ablation + WATCHMAN FLX (N = 803 ITT)

AF Ablation + OAC (N = 797 ITT)

3-Year Follow-up

*Thermal AFib ablation only.

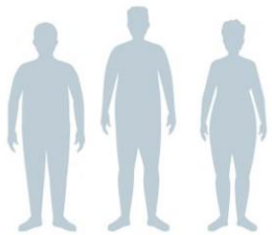
The NEW ENGLAND JOURNAL of MEDICINE

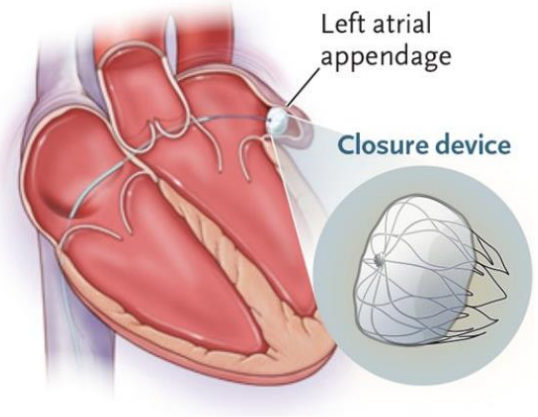
Left Atrial Appendage Closure after Ablation for Atrial Fibrillation

A Research Summary based on Wazni OM et al. | 10.1056/NEJMoa2408308 | Published on November 16, 2024

Patients

- 1600 adults
- Mean age: 70 years
- Men: 66%; Women: 34%





Left Atrial Appendage Closure

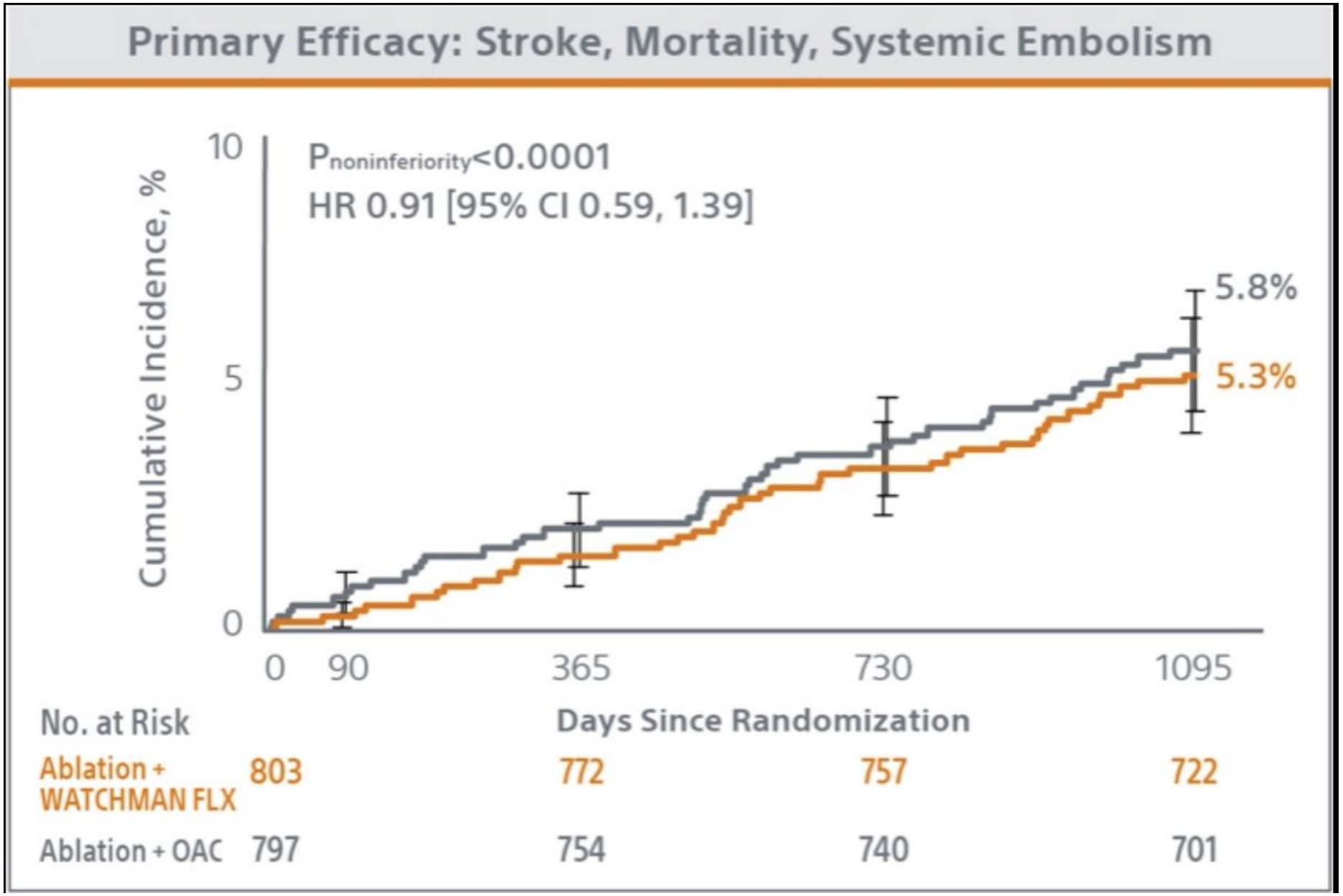
N = 803

Oral Anticoagulation

N = 797

Procedural Outcomes

- Device success: 98.8%
- Concomitant LAAC with ablation common
- Periprocedural complication rate ≈2.7%
- Imaging confirmed closure in >95% at follow-up

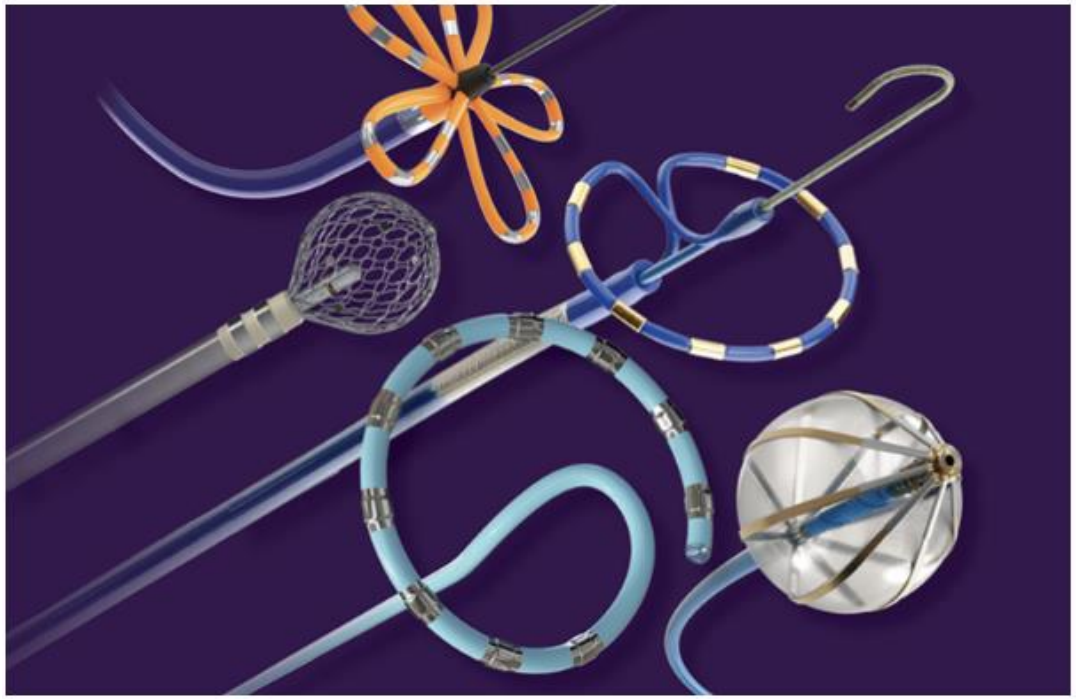


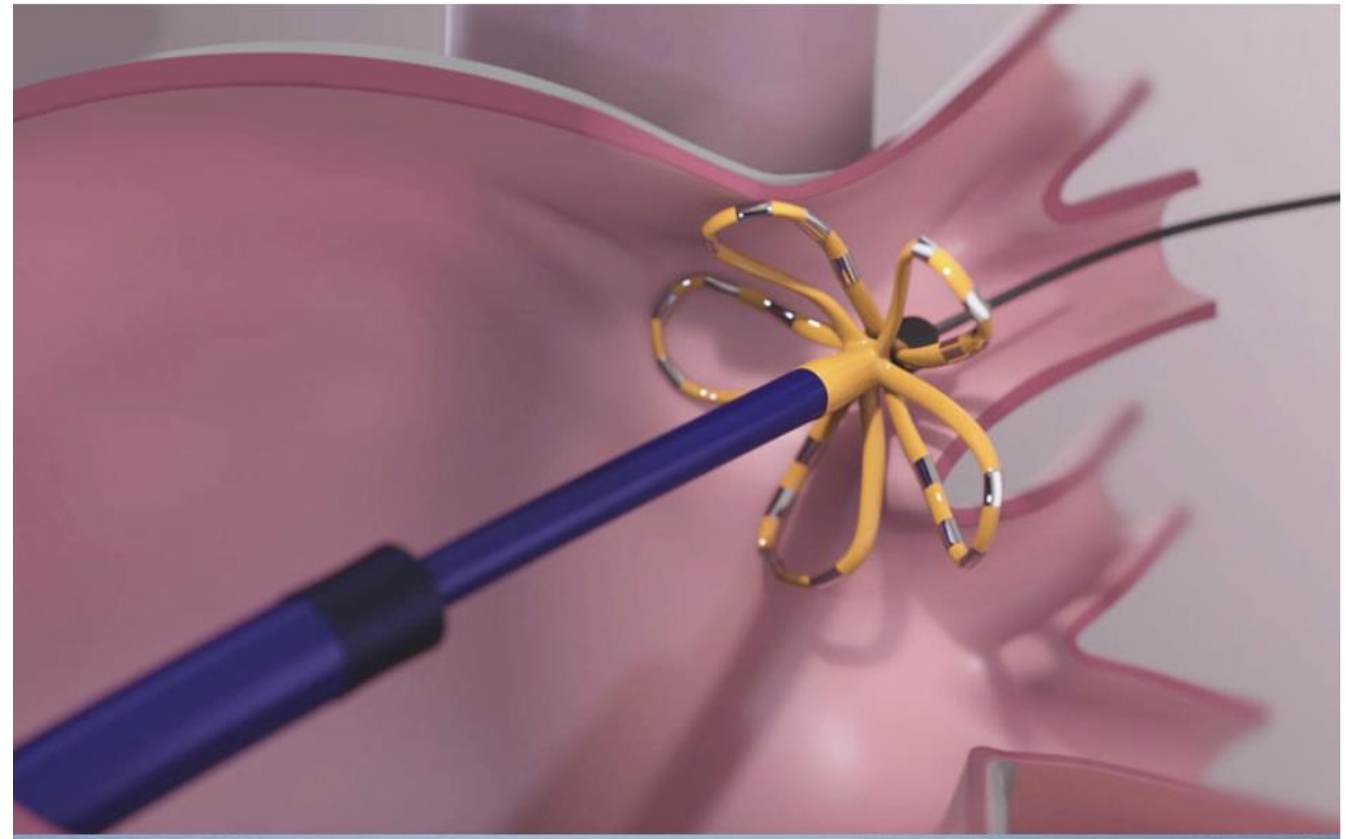
- 1,600 patients
- CHA_2DS_2-VASc ≥2 (men), ≥3 (women)
- Watchman FLX LAAC (concomitant or staged) vs DOAC
- 36 months

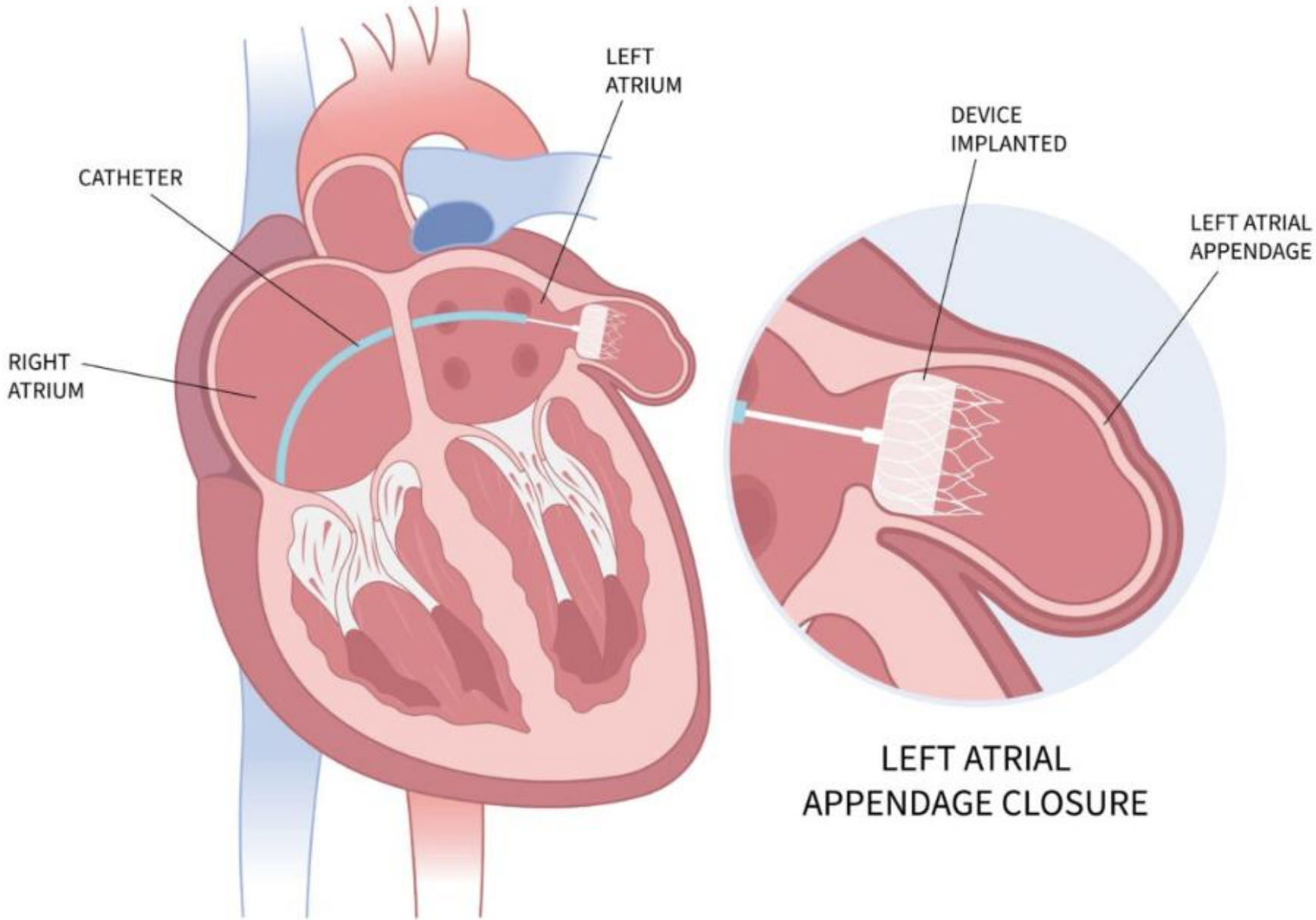
Primary Results

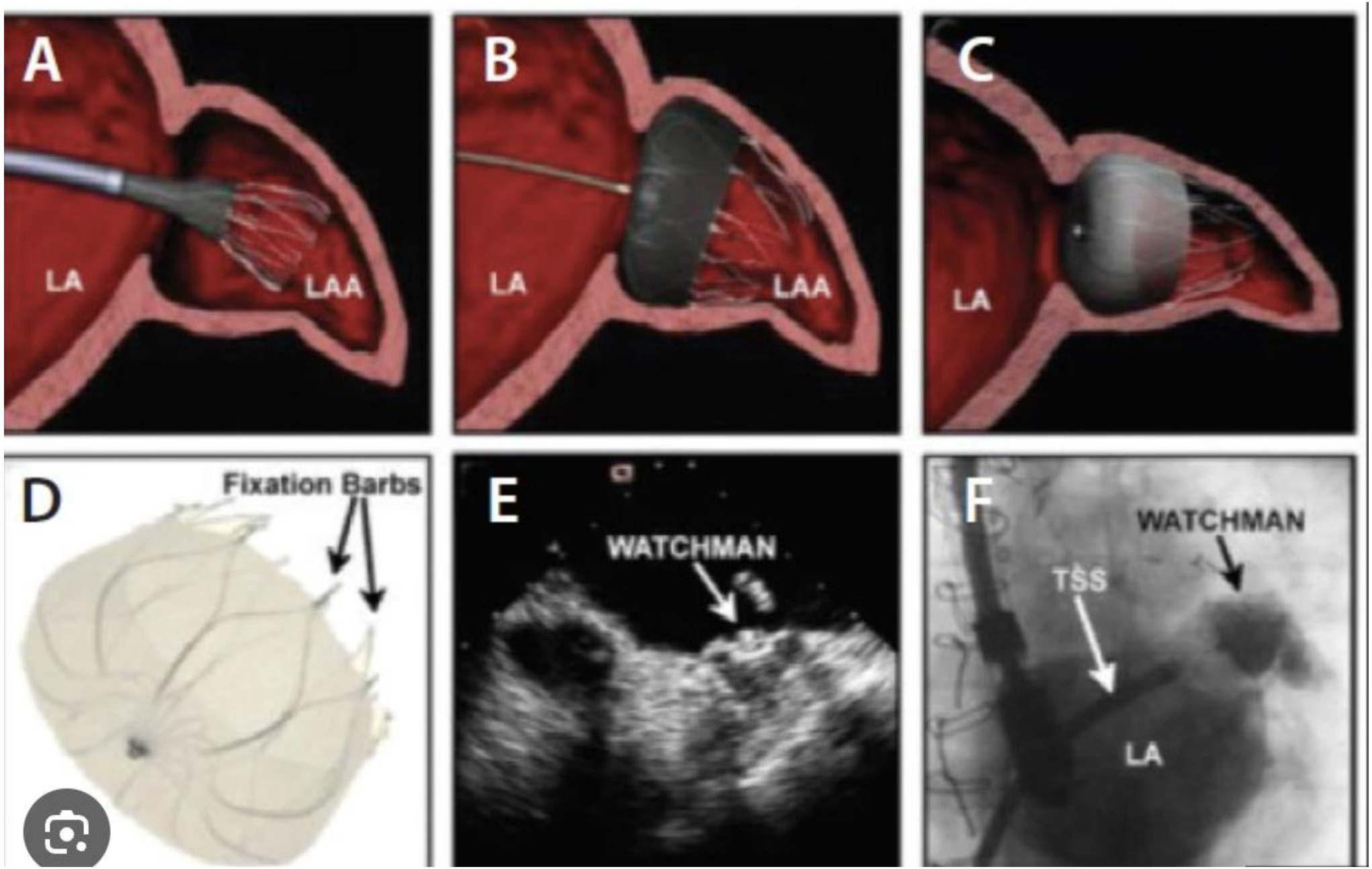
- Efficacy endpoint: 5.3% (LAAC) vs 5.8% (OAC)
- Non-inferior for death/stroke/systemic embolism
- Ischemic stroke: 1.2% vs 1.3%
- Equivalent thromboembolic protection

- Major + clinically relevant non-major bleeding: 8.5%(LAAC) vs 18.1%(OAC)
- 55% relative reduction in bleeding
- Fewer late bleeds; no increase in thrombotic events






LEFT
ATRIUM
CATHETER
RIGHT
ATRIUM
DEVICE
IMPLANTED
LEFT ATRIAL
APPENDAGE
LEFT ATRIAL
APPENDAGE CLOSURE


A
LA
LAA
B
LA
LAA
C
LA
D
Fixation Barbs
E
WATCHMAN
F
WATCHMAN
TSS
LA

OPTION Trial
Summary & Clinical Implications

- LAAC offers stroke prevention comparable to OAC with less bleeding
- Appropriate for post-ablation patients with bleeding risk or OAC intolerance
- Low procedural risk with experienced operators
- OPTION broadens indication for Watchman FLX
- Shared decision-making essential

Thank You