ACC 2025 Updates - Cardiometabolic Disorders

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Semaglutide Cardiovascular Outcomes Trial - SOUL

SOUL Trial - Overview

Objective: Evaluate **CV efficacy** of once-daily **oral semaglutide** in patients with **T2DM + ASCVD and/or CKD**

Study Design:

- **Phase 3b**, multicenter (444 sites, 33 countries)
- **9,650** participants (1:1 semaglutide vs placebo)
- **Median follow-up**: 49.5 months
- Dose escalation: 3 mg → 7 mg → 14 mg
- Background: Standard glucose-lowering & CV care per guidelines

Patient Profile:

- **Mean age**: 66.1 years | **Female**: 28.9%
- **Inclusion**:
  - Age ≥50 years, T2DM (HbA1c 6.5–10%)
  - ASCVD (CAD, CVD, PAD) and/or CKD
- **Exclusion**: ESRD, long-term dialysis

SOUL Trial Results & Interpretation

Primary Outcome – 3-point MACE:

(all-cause death, nonfatal MI, or nonfatal stroke)

- **Semaglutide**: 12.0%
- **Placebo**: 13.8%

Risk Reduction

- **14% reduction** in MACE with oral semaglutide
- No increase in serious adverse events

Secondary Outcomes

- Major kidney events, limb events: **No significant difference**
- Safety profile: **Well tolerated**

Clinical Implications:

What This Means

- Oral semaglutide offers **proven CV protection** in **high-risk T2DM** patients
- Suitable for those with **ASCVD, CKD**, or both
- **Alternative to injectable GLP-1 RAs** for needle-averse patients

- Strengthens the **risk-benefit profile** of oral GLP-1 therapy
- Reinforces the role of **oral semaglutide in CV risk reduction**

Presented by Dr. Darren K. McGuire at the American College of Cardiology Annual Scientific Session (ACC.25), Chicago, IL, March 29, 2025.

STRIDE Trial: Effects of Semaglutide in Patients With Peripheral Artery Disease

STRIDE Trial – Semaglutide in PAD + T2DM

Objective:

Evaluate the impact of **semaglutide 1 mg weekly** on **functional capacity** in patients with **PAD + type 2 diabetes**

Study Design:

- Design: Randomized controlled trial, 52 weeks
- Patients: **N = 792**, PAD + T2DM
- Intervention: Semaglutide 1 mg vs. placebo
- Focus: Functional improvements beyond glycemic control

Primary Outcome:

- ↑ **Treadmill Walking Distance**: ~13% increase (~26–40 meters gain)
- Improved Quality of Life
- **Reduced Revascularization or Death**: 54% relative risk reduction

Bonaca, Marc P., et al. "Semaglutide and walking capacity in people with symptomatic peripheral artery disease and type 2 diabetes (STRIDE): a phase 3b, double-blind, randomised, placebo-controlled trial." *The Lancet* 405.10489 (2025): 1580-1593.

STRIDE Trial – Semaglutide in PAD + T2DM

Mechanistic Insights:

Benefits persisted post-treatment, suggesting:

- Direct vascular effect
- Independent of weight loss

Multi-System Benefits:

- ↓ Inflammation
- Improved vascular tone & perfusion
- Potentially cardioprotective & renoprotective

Clinical Implications:

- Semaglutide may become **standard adjunct** therapy in PAD patients with T2DM
- Adds to evidence for **GLP-1 RAs** in cardiometabolic care
- **Mobility + CV risk + QoL** improvement = **Triple benefit**

Ideal for:

- PAD + T2DM patients struggling with walking capacity
- High CV risk patients seeking functional improvement

Bonaca, Marc P., et al. "Semaglutide and walking capacity in people with symptomatic peripheral artery disease and type 2 diabetes (STRIDE): a phase 3b, double-blind, randomised, placebo-controlled trial." The Lancet 405.10489 (2025): 1580-1593.

The SELECT Trial

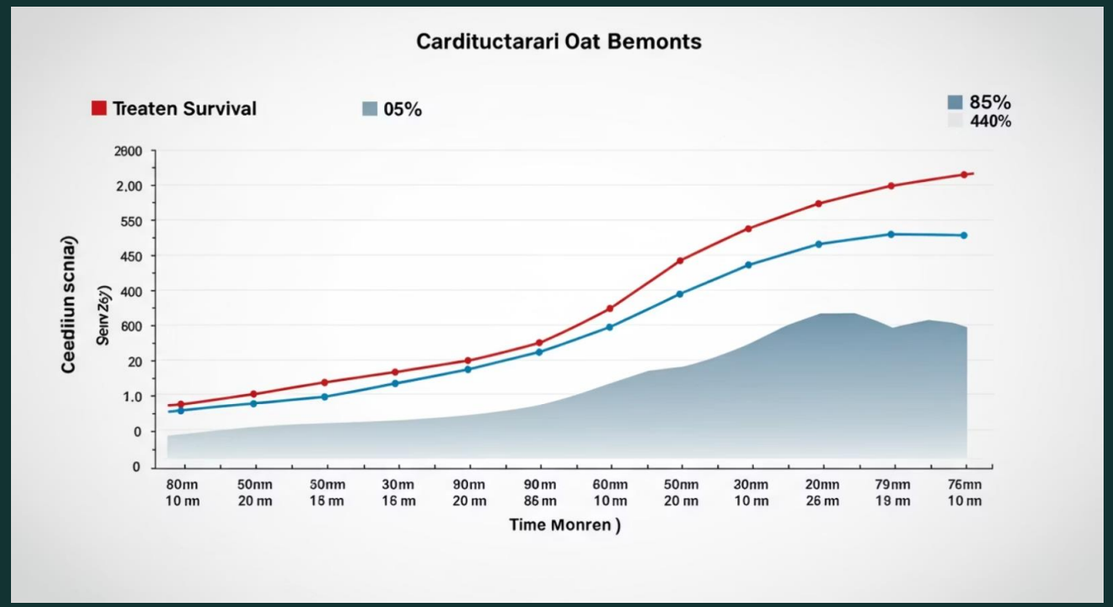
The SELECT Trial: Groundbreaking Evidence

Trial Design

- 17,000+ participants with obesity and established CVD
- No history of diabetes
- Randomized to semaglutide 2.4mg weekly or placebo

Primary Outcome

20% reduction in CV death, nonfatal MI, and nonfatal stroke with semaglutide.



Additional Benefits

- Improved renal outcomes
- Decreased all-cause mortality
- 35% reduction in inflammatory markers (CRP)

Mechanism and Clinical Implications

Anti-inflammatory Effects

Cardiovascular protection appears independent of weight loss and HbA1c improvement.

Marked reduction in inflammatory markers suggests novel mechanism.

Safety Profile

No increase in major adverse effects including pancreatitis.

Higher discontinuation rates due to gastrointestinal side effects.

Future Direction

Dual agonists like tirzepatide (GLP-1 + GIP) may offer enhanced benefits.

Cardiovascular outcome trials for newer agents pending.

A Study of Tirzepatide in Participants With Heart Failure With Preserved Ejection Fraction (HFpEF) and Obesity - SUMMIT

SUMMIT Trial: Interpretation & Clinical Relevance

Objective: The SUMMIT trial showed that among obese patients with HFpEF, once weekly subcutaneous Tirzepatide was superior to placebo in improving the composite endpoint of CV death and HF-related events over 104 weeks of follow-up.

Study Design:

- Phase 3, randomized, double-blind trial
- **N = 731** (Tirzepatide: 364; Placebo: 367)
- **Follow-up:** Median 104 weeks
- Dose escalation: 2.5 mg → 15 mg by week 20
- Stratified by BMI, recent HF decompensation, and T2DM status

Inclusion Highlights:

- HFpEF (LVEF ≥50%) + Obesity (BMI ≥30)
- Elevated NT-proBNP
- Functional limitation (6MWD 100–425m, KCCQ-CSS ≤80)
- Stable HF therapy for ≥4 weeks

Packer M, Zile MR, Kramer CM, et al., for the SUMMIT Trial Study Group. Interplay of Chronic Kidney Disease and the Effects of Tirzepatide in Patients With Heart Failure, Preserved Ejection Fraction, and Obesity, The SUMMIT Trial. JACC. Published online March 31, 2025. Epublished DOI: 10.1016/j.jacc.2025.03.009. Presented by Dr. Milton Packer at the American College of Cardiology Annual Scientific Session (ACC.25), March 31, 2025.

SUMMIT Trial: Interpretation & Clinical Relevance

Key Insights:

- ↓ **CV death + HF events**, mainly driven by fewer HF hospitalizations
- Significant gains in:
  - Quality of life (**KCCQ-CSS**)
  - Functional status (**6MWD**)
  - **~14% weight loss**
- Supports GLP-1/GIP agonists in **cardiometabolic HFpEF** care

Mechanistic Insights:

- Benefits went **beyond weight loss**
  - ↓ inflammation (**hsCRP**)
  - ↑ **EQ-5D-5L**, ↓ BP, ↑ renal markers
- Points to a **direct vascular or anti-inflammatory effect**

Subgroup Insights:

- **CKD patients**: similar HF & QoL benefit despite worse baseline profile
- Consistent results across:
  - **Obesity classes**
  - **NYHA II–IV**
  - With/without **AF**

Packer M, Zile MR, Kramer CM, et al., for the SUMMIT Trial Study Group. Interplay of Chronic Kidney Disease and the Effects of Tirzepatide in Patients With Heart Failure, Preserved Ejection Fraction, and Obesity, The SUMMIT Trial. JACC. Published online March 31, 2025.

SUMMIT Trial: Interpretation & Clinical Relevance

Limitations & Considerations:

- Only **17% were on SGLT2 inhibitors** → underrepresentation of modern HF therapy
- Unclear if benefits are **reproducible in non-obese HFpEF**
- Mechanism still partly attributed to **weight loss vs. independent effect.**

Conclusion:

- SUMMIT is a **landmark trial** in obese HFpEF population, offering **a new therapeutic avenue** through cardiometabolic modulation
- Complementary to **STEP-HFpEF** results with semaglutide, it strengthens the case for **metabolic-centric HF care.**

Packer M, Zile MR, Kramer CM, et al., for the SUMMIT Trial Study Group. Interplay of Chronic Kidney Disease and the Effects of Tirzepatide in Patients With Heart Failure, Preserved Ejection Fraction, and Obesity, The SUMMIT Trial. JACC. Published online March 31, 2025. Epublished DOI: 10.1016/j.jacc.2025.03.009. Presented by Dr. Milton Packer at the American College of Cardiology Annual Scientific Session (ACC.25), March 31, 2025.

DAPA-TAVI: Dapagliflozin Safe and Effective in Older Adults With HF Undergoing TAVI

DAPA-TAVI Trial – Interpretation & Key Findings

Objective: To evaluate the **efficacy and safety** of **dapagliflozin 10 mg** in reducing **all-cause mortality or worsening heart failure** in older adults with heart failure undergoing **TAVI** for severe aortic stenosis.

Key Interpretation:

- **Dapagliflozin** significantly reduced the risk of **all-cause death or worsening HF** in elderly patients undergoing TAVI, with a **28% relative risk reduction**
- The benefit was primarily driven by a **37% reduction in worsening HF events**

Why It Matters:

- **First trial** testing an **SGLT2 inhibitor in valvular heart disease**: specifically severe aortic stenosis post-TAVI
- Contradicts the old notion that "TAVI fixes everything"; shows **SGLT2i offers additive benefit**
- Expands the role of SGLT2 inhibitors to a **new high-risk, elderly population** often underrepresented in trials

Study Design:

- **Type**: Randomized, double-blind, controlled trial
- **Population**: 1,222 patients with **severe aortic stenosis** post-TAVI, median age 82.4 years

Raposeiras-Roubin S, Amat-Santos IJ, Rossello X, et al. Dapagliflozin in patients undergoing transcatheter aortic-valve implantation. NEJM. Published online March 29, 2025. Doi: 10.1056/NEJMoa2500366

DAPA-TAVI Trial – Clinical Relevance & Practice Implications

Subgroup and Safety Insights:

- Benefits **consistent across** age, sex, renal function, and diabetes status
- Even **very elderly patients (>80 years)** experienced improved outcomes
- Higher incidence of **genital infections (1.8%)** and **hypotension (6.6%)** seen with dapagliflozin, but manageable

Clinical Takeaway:

- DAPA-TAVI supports **routine use of dapagliflozin post-TAVI**, especially in patients with concurrent HF
- Reinforces **SGLT2i as foundational therapy** across heart failure phenotypes—even in valvular heart disease
- Encourages clinicians to **avoid therapeutic inertia** in older adults and confidently prescribe SGLT2i post-procedure

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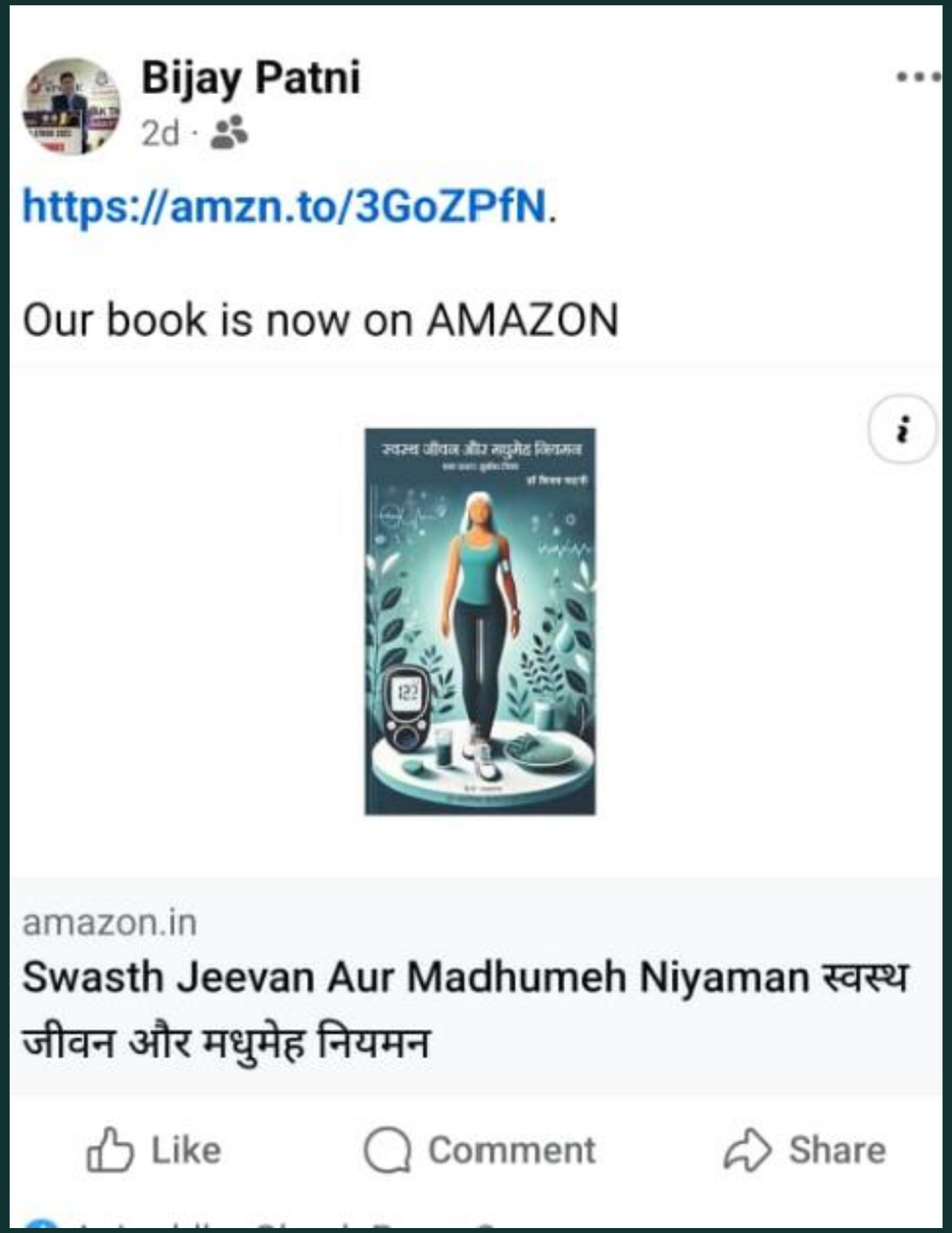

THANK YOU

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