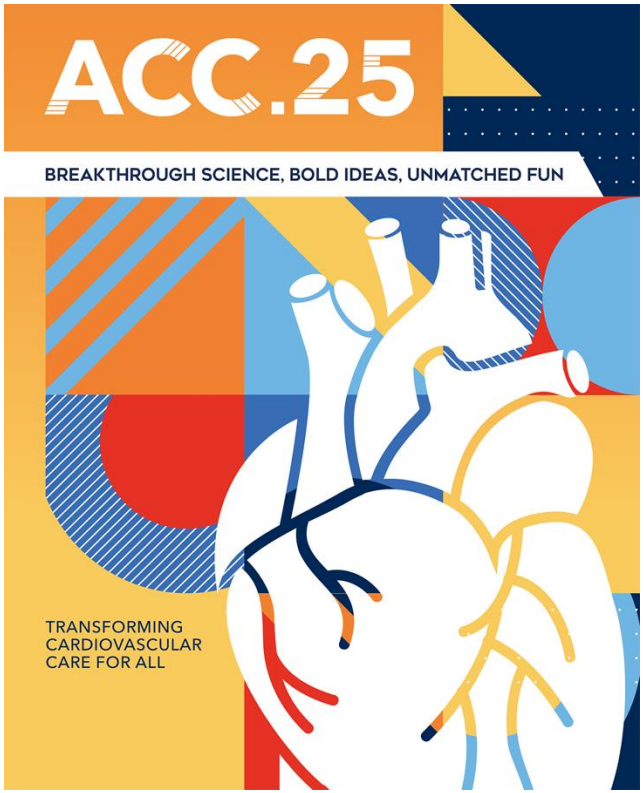
ACC.25 Trials Overview



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Objectives

- Summarize the key findings from key clinical trials presented at ACC.25
- Evaluate the clinical relevance of new trial data and how these findings may influence or update current CV guidelines and practice
- Compare and contrast emerging therapies or interventions with current standard-of-care treatments
- Foster critical appraisal skills and discussion

Case #1

- 67-year-old male with T2DM, Obesity, CKD, and hypertension admitted to CTU with new onset dyspnea and volume overloaded. Diagnosed with AHF and ECHO shows LVEF of 51% with LVH and moderate diastolic dysfunction.
- He receives effective diuresis and is transitioned to oral Lasix. He receives diet and lifestyle recommendations with plan to follow-up with Cardiology as an outpatient.

Which medications would you like to discharge the patient home on for his HFpEF?

HFpEF Management

Recommendations for HF With Preserved Ejection Fraction* Referenced studies that support the recommendations are summarized in the Online Data Supplements.		
COR	**LOE**	**Recommendations**
1	C-LD	1. Patients with HFpEF and hypertension should have medication titrated to attain blood pressure targets in accordance with published clinical practice guidelines to prevent morbidity.[1–3]
2a	B-R	2. In patients with HFpEF, SGLT2i can be beneficial in decreasing HF hospitalizations and cardiovascular mortality.[4]
2a	C-EO	3. In patients with HFpEF, management of AF can be useful to improve symptoms.
2b	B-R	4. In selected patients with HFpEF, MRAs may be considered to decrease hospitalizations, particularly among patients with LVEF on the lower end of this spectrum.[5–7]
2b	B-R	5. In selected patients with HFpEF, the use of ARB may be considered to decrease hospitalizations, particularly among patients with LVEF on the lower end of this spectrum.[8,9]
2b	B-R	6. In selected patients with HFpEF, ARNi may be considered to decrease hospitalizations, particularly among patients with LVEF on the lower end of this spectrum.[10,11]
3: No-Benefit	B-R	7. In patients with HFpEF, routine use of nitrates or phosphodiesterase-5 inhibitors to increase activity or QOL is ineffective.[12,13]

Any other therapies you would consider for management of the patient's HFpEF?

SUMMIT Trial: Tirzepatide in HFpEF with Obesity

- Study Design
  - Phase 3, double blind, randomized, placebo-controlled trial
  - 731 patients with HFpEF (LVEF ≥50%) and BMI ≥30 kg/m²
  - Tirzepatide (up to 15 mg weekly) vs. Placebo
  - Median follow-up: 104 weeks

- Primary Endpoints
  - Change of CV death or worsening HF event
  - Change in KCCQ-CSS at 52 weeks

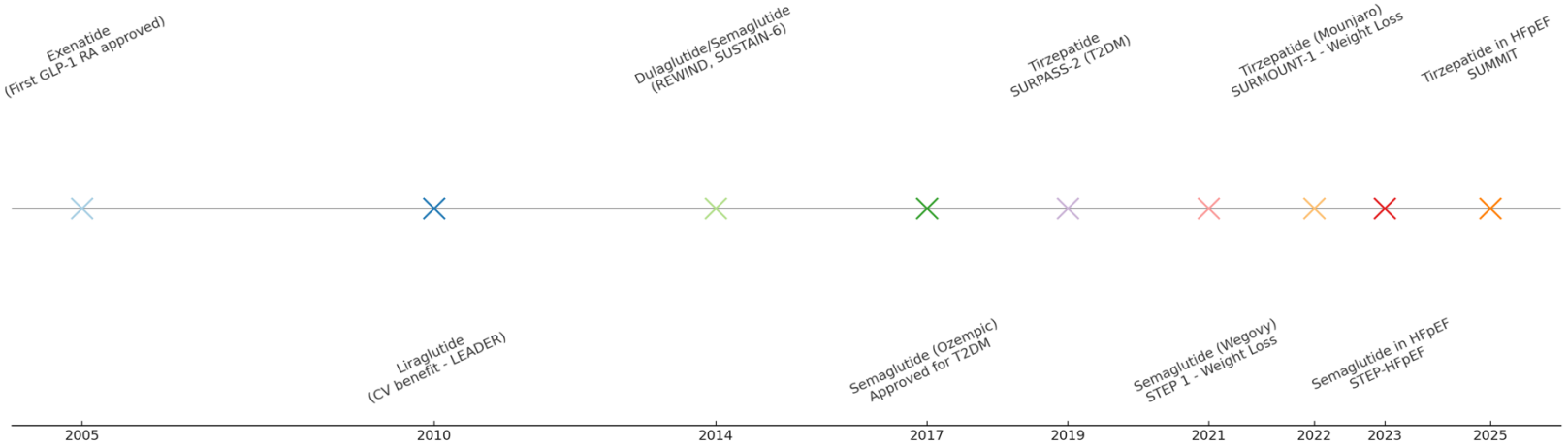
- Key Results
  - CV death or worsening HF event: 9.9% (Tirzepatide) vs. 15.3% (Placebo); HR 0.62; p=0.026
  - KCCQ-CSS improvement: +19.5 (Tirzepatide) vs. +12.7 (Placebo); Δ=6.9; p<0.001.
  - 6MWD increase: +26.0 m vs. +10.1 m; p<0.001
  - Weight loss: −13.9% vs. −2.2%; p<0.001
  - hsCRP reduction: −38.8% vs. −5.9%; p<0.001

- Conclusions
  - Tirzepatide reduced HF events and improved quality of life in patients with HFpEF and obesity.
  - Benefits included enhanced functional capacity, significant weight loss, and reduced systemic inflammation.

GLP-1 Agonists Drug Class

- First GLP-1 agonist was approved in 2005 (Exenatide)
- Expanded to include liraglutide, dulaglutide, semaglutide, and tirzepatide (dual GIP-GLP-1)
- MOA
  - Mimics endogenous GLP-1 leading to:
    - ↑ Insulin secretion from pancreatic β-cells → Only when glucose is elevated, reducing hypoglycemia risk
    - ↓ Glucagon secretion from pancreatic α-cells → Leads to reduced hepatic glucose output
    - Delayed gastric emptying → Slows postprandial glucose absorption and increases satiety
    - Central appetite suppression via hypothalamic receptors → Drives weight loss
  - Dual GIP/GLP-1 receptor agonists
    - GIP (Glucose-dependent Insulinotropic Polypeptide) is another incretin hormone
    - Synergistic insulinotropic effects
    - Enhanced satiety and adipose tissue modulation
- Indications
  - T2DM
  - Obesity
  - HFpEF (Obesity-related)

Timeline of GLP-1: From T2DM to HFpEF



Year	Drug/Intervention	Key Trial(s)	Indication / Outcome
2005	Exenatide	AMIGO	First GLP-1 RA approved (T2DM)
2010	Liraglutide	LEADER	CV outcome benefit in T2DM
2014	Dulaglutide/Semaglutide	REWIND, SUSTAIN-6	CV safety shown in T2DM
2017	Semaglutide (Ozempic)	Approved for T2DM	Expanded use for T2DM
2019	Tirzepatide	SURPASS-2	Effective glucose control in T2DM
2021	Semaglutide (Wegovy)	STEP 1	Weight loss in obesity (non-T2DM)
2022	Tirzepatide (Mounjaro)	SURMOUNT-1	Significant weight loss (obesity)
2023	Semaglutide in Obesity	SELECT	CV benefit in obesity without DM
2023	Semaglutide in HFpEF	STEP-HFpEF	QoL and functional gains in HFpEF
2025	Tirzepatide in HFpEF	SUMMIT	HF events, weight, QoL in HFpEF

SUMMIT Trial Appraisal

- Strengths
  - Robust design: Large, multicenter, randomized, double-blind, placebo-controlled trial.
  - Clinically meaningful endpoints: Patient-centered outcomes (KCCQ-CSS, 6MWD) and hard CV outcomes (CV death or HF events)
  - Longer duration of follow-up (~2 years)
  - Consistent benefit seen across subgroups: Effects seen across NYHA classes, sex, and baseline BMI
  - Specifically targeted the obese HFpEF phenotype, a group with limited treatment options

- Limitations
  - High rate of GI side effects limits tolerability
  - Weight loss as a confounder: Difficult to disentangle whether improvements were due to direct cardiac effects or weight loss alone
  - Generalizability: May not apply to HFpEF patients without obesity (BMI <30), or those with diabetes not well-represented

SUMMIT Trial Mechanistic Insights

- Cardiac Remodeling
  - Cardiac MRI substudy showed reductions in LV mass by 11g and paracardiac adipose tissue by 45 mL with Tirzepatide
  - Suggests favorable cardiac remodeling—possibly through reduced wall stress and improved myocardial efficiency
- Volume Status
  - Tirzepatide reduced circulatory volume expansion, potentially decreasing cardiac filling pressures
- Anti-inflammatory Effects
  - Marked reduction in hsCRP (a ~43% drop) supports a systemic anti-inflammatory effect, which may reduce myocardial inflammation and stiffness—a key contributor to HFpEF pathophysiology

SUMMIT Trial Clinical Insights

- Tirzepatide reduced heart failure events and improved quality of life in patients with HFpEF and obesity.
- Benefits included enhanced functional capacity (↑ KCCQ, ↑ 6MWD), significant weight loss, and reduced systemic inflammation (↓ hsCRP).
- Mechanisms likely include favorable cardiac remodeling, volume status improvement, and anti-inflammatory effects.
- Highlights the evolving role of metabolic modulation in HFpEF—particularly for the obese phenotype with T2DM or insulin resistance.
- GLP-1 and dual GIP/GLP-1 receptor agonists (e.g., tirzepatide) represent a promising new class for obesity-related HFpEF, though currently not guideline-endorsed for this indication.
- Tirzepatide is not currently covered by pharmacare
- Semaglutide (Ozempic) is only covered by pharmacare for those with T2DM

Case #2

- 57-year-old male with T2DM, HTN, and is a smoker presents to the ED with an 8 hours history of chest pain. ECG shows anterior-septal ST-elevation with Q-waves. Code STEMI is activated, and he receive x2 DES to the LAD and staged PCI with x1 DES to the LCx. He is started on DAPT and ECHO shows a severely reduced systolic function (LVEF 25%) with akinesis of the anterior wall, apex, and apical septum. DEFINITY® Contrast ECHO is performed with shows a LV thrombus. You plan to start him on GDMT

The CCU Attending asks you how would you like to treat his LV thrombus?

LV Thrombus Management

- AHA Scientific Statement (2022):
  - "In patients with heart failure and left ventricular thrombus, anticoagulation with a vitamin K antagonist for at least 3 months is reasonable to reduce the risk of thromboembolism"
  - "Repeat TTE or CMR in 3 months to assess thrombus resolution"

- DOACs are not currently guideline-endorsed as first line, but increasingly used off-label based on emerging observational data
  - AHA Statement notes that a DOAC may be considered if warfarin is contraindicated or poorly tolerated, on a case-by-case basis

RIVAWAR Trial

- Study Design
  - Single-center, open-label, randomized controlled trial
  - 261 patients (mean age 54.5 years; 20.7% female) with LV thrombus diagnosed within 7 days of STEMI or NSTEMI
  - Randomization to rivaroxaban or warfarin for 12 weeks
  - Echocardiography at 4 and 12 weeks
- Endpoints
  - Primary
    - Complete resolution of LV thrombus at 3 months, assessed by echocardiography
  - Secondary
    - All-cause mortality
    - Ischemic stroke
    - Major bleeding events
- Key Results
  - 95% thrombus resolution in both rivaroxaban and warfarin groups at 3 months
  - No significant differences in all-cause mortality, ischemic stroke, or major bleeding between groups
- Conclusions
  - Rivaroxaban is as effective and safe as warfarin for resolving LV thrombus post-MI
  - Rivaroxaban offers practical advantages, such as predictable dosing and no need for INR monitoring

RIVAWAR Appraisal

- Strengths
  - Direct clinical relevance: Addresses a real-world management dilemma (warfarin vs. DOAC for LV thrombus)
  - High thrombus resolution rates in both study arms: >95%, showing non-inferiority of rivaroxaban
  - Simplified anticoagulation: DOAC use removes need for INR monitoring, potential for better patient adherence

- Limitations
  - Single center study and thus limits generalizability to broader populations
  - Open-label design: Potential for performance and detection bias
  - Small sample size (n=261) and thus trial may be underpowered for rare but critical outcomes (ie, embolic events, major bleeding)
  - Unclear applicability to non-post-MI LV thrombus or NICM

RIVAWAR Clinical Insights

- Warfarin remains the guideline-recommended therapy for LV thrombus, but the RIVAWAR trial supports the potential use of DOACs in post-MI patients
- Rivaroxaban showed similar efficacy to warfarin in thrombus resolution at 3 months, with no increase in stroke, bleeding, or mortality.
- DOACs offer practical benefits such as fixed dosing, no INR monitoring, and potentially improved adherence.
- Consider rivaroxaban in patients who are post-MI with LV thrombus when warfarin is contraindicated or poorly tolerated.
- Clinical judgment is essential as DOACs remain off-label for this indication; guideline updates may follow as more evidence emerges.

Case #3

- 51-year-old female with hypertension, ACS, and HFrEF (LVEF 36%) on GDMT. She was recently admitted to hospital for an AHF episode believed secondary to medication non-compliance. She was diuresed in hospital and pharmacy was able to get her coverage for all her medications prior to discharge. You are seeing her in outpatient clinic follow-up.

What diet and lifestyle recommendations do you have, specifically should she be limiting her fluid intake?

Diet & Lifestyle Management in Heart Failure

- CCS & AHA/ACC/HFSA guidelines recommend treating CV risk factors
- Exercise is recommended to improve functional capacity in HF
- Sodium restriction based on low-quality evidence
  - AHA recommends reduction of sodium intake to <2.3 g/day for general CV health promotion, but no trials to support this restriction in patients with HF
  - Sodium restriction can result in low diet quality with inadequate macronutrient and micronutrient intake
  - 2022 SODIUM-HF trial compared a low sodium diet (<1.5 g/d) to standard care (~2.0-2.5 g/d), demonstrated no composite reduction in all-cause mortality, CV hospitalizations, or ED visits
- No specific guideline recommendation exists for fluid restriction

7.1.2. Dietary Sodium Restriction

Recommendation for Dietary Sodium Restriction		
COR	**LOE**	**Recommendation**
2a	**C-LD**	1. For patients with stage C HF, avoiding excessive sodium intake is reasonable to reduce congestive symptoms.[1–6]

7.1.3. Management of Stage C HF: Activity, Exercise Prescription, and Cardiac Rehabilitation

Recommendations for Management of Stage C HF: Activity, Exercise Prescription, and Cardiac Rehabilitation Referenced studies that support the recommendations are summarized in the Online Data Supplements.		
COR	**LOE**	**Recommendations**
1	**A**	1. For patients with HF who are able to participate, exercise training (or regular physical activity) is recommended to improve functional status, exercise performance, and QOL.[1–9]
2a	**B-NR**	2. In patients with HF, a cardiac rehabilitation program can be useful to improve functional capacity, exercise tolerance, and health-related QOL.[1,2,5,6,8]

8.2. Nonpharmacological Management: Advanced HF

Recommendation for Nonpharmacological Management: Advanced HF		
COR	**LOE**	**Recommendation**
2b	**C-LD**	1. For patients with advanced HF and hyponatremia, the benefit of fluid restriction to reduce congestive symptoms is uncertain.[1–4]

FRESH-UP Trial

- Study Design
  - Multicenter, open-label, randomized controlled trial
  - 504 outpatients with chronic heart failure (NYHA class II–III)
  - Randomization to:
    - Liberal fluid intake: No restriction
    - Restricted fluid intake: 1,500 mL/day
  - Follow-up at 3 months and conducted in 9 outpatient HF clinics across the Netherlands
- Endpoints
  - Primary
    - Change in Kansas City Cardiomyopathy Questionnaire Overall Summary Score (KCCQ-OSS)
  - Secondary
    - Thirst distress score (TDS-HF), Heart failure hospitalization, & Mortality
- Key Results
  - No significant difference in KCCQ-OSS at 3 months (74.0 vs 72.2; $p = 0.06$)
  - Liberal intake group had less thirst distress (TDS-HF: 16.9 vs 18.6; $p < 0.001$)
  - No difference in HF hospitalization or mortality
- Conclusions
  - Fluid restriction to 1.5L/day did not improve QoL in stable HF outpatients
  - Liberal fluid intake may improve patient comfort without compromising safety

FRESH-UP Appraisal

- Strengths
  - Randomized controlled design: Minimizes bias and enhances internal validity
  - Patient-centered primary outcome: Use of KCCQ-OSS, a validated quality-of-life tool specific to HF.
  - Good adherence: Fluid intake monitoring showed >80% adherence, strengthening the validity of intervention comparisons
  - Real-world applicability: Included stable, ambulatory HF patients commonly seen in outpatient practice

- Limitations
  - Open-label design: Could introduce performance and response bias, especially with subjective outcomes like QoL and thirst.
  - Short duration (3 months): May not capture long-term outcomes or delayed effects of fluid management.
  - Exclusion of more severe HF patients: Results may not apply to patients with advanced HF (e.g., NYHA IV or recent hospitalization).
  - Limited ethnic diversity: Conducted in the Netherlands; applicability to broader populations may be constrained

FRESH-UP Clinical Insights

- Routine fluid restriction in stable outpatients with CHF is not supported by recent evidence
- Reinforce individualized care:
  - Fluid restriction may still be useful in advanced HF (e.g., refractory congestion, hyponatremia), but not routinely needed in stable NYHA II–III patients
  - No strong evidence to support regular fluid restriction in patients admitted with AHF
- Prioritize evidence-based interventions:
  - Start patients on GDMT
  - Exercise
  - Lifestyle risk factor modification
- Address patient comfort and adherence:
  - Liberal fluid intake may enhance quality of life and improve adherence in selected patients without compromising safety.
- Guideline-consistent messaging:
  - No formal recommendation for fluid restriction in stable HF from ACC/AHA/CCS; apply clinical judgment case-by-case.

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Thank you for listening!

Questions and Discussion