Memorial

BENEFIT OF GLP-1 RECEPTOR AGONISTS ON CARDIOVASCULAR HEALTH

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Objectives

Memorial

1. Explain the mechanism of action of glucagon-like peptide 1 receptor agonists (GLP-1 RA)
2. Discuss the current FDA approved indications for GLP-1 RAs
3. Provide an overview of the GLP-1 RA cardiovascular outcome trials (CVOTs)
4. Summarize the most recent ACC/AHA guideline recommendations
5. Discuss other relevant GLP-1 RA and glucose-dependent insulinotropic polypeptide (GIP)/GLP-1 RA CV trials

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GLP-1 RA Mechanism of Action

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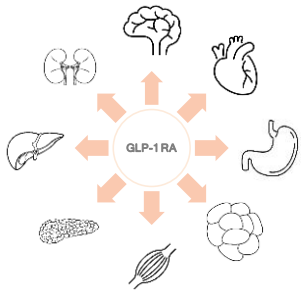

See references at end of presentation [1,2,3,4,5,6]

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FDA Indications for GLP-1 RAs

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- **Adults with type 2 diabetes**
  - semaglutide (injection, oral), dulaglutide, liraglutide, exenatide, tirzepatide
- **Reduce the risk of major cardiovascular events in adults with type 2 diabetes and known heart disease**
  - semaglutide (injection, oral), dulaglutide, liraglutide
- **Worsening of kidney disease and cardiovascular death in adults with type 2 diabetes and chronic kidney disease (CKD)**
  - semaglutide (injection)
- **Adults with obesity for chronic weight management**
  - tirzepatide, semaglutide (injection), liraglutide
- **Adults with moderate-severe obstructive sleep apnea and obesity**
  - tirzepatide
- **Adults with obesity or overweight with established cardiovascular disease**
  - semaglutide (injection)

See references at end of presentation [7,8,9,10,11,12,13,14]

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GLP-1 RA CVOTs Timeline

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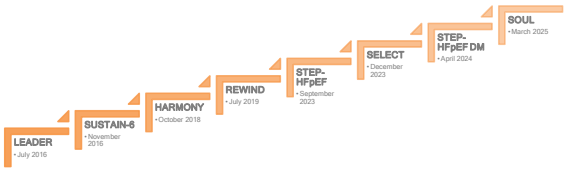

Rivera FB, Cruz LLA, Magalong JV, et al. Cardiovascular and renal outcomes of glucagon-like peptide 1 receptor agonists among patients with and without type 2 diabetes mellitus: A meta-analysis of randomized placebo-controlled trials. *Am J Prev Cardiol.*

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CVOTs

Memorial

Liraglutide and Cardiovascular Outcomes in Type 2 Diabetes (LEADER)

- Cardiovascular (CV) effect of liraglutide in patients with type 2 diabetes
- Liraglutide 1.8 mg daily (or max tolerated dose) vs placebo
- Primary composite outcome: first occurrence of death from CV causes, nonfatal myocardial infarction (MI), or nonfatal stroke

End Point	Liraglutide (N = 4668)	Placebo (N = 4672)	Hazard Ratio (95% CI)	P Value
	no. of patients (%)	no. of patients (%)		
Primary composite outcome	608 (13.0)	694 (14.9)	0.87 (0.78-0.97)	0.01
Expanded composite outcome	948 (20.3)	1062 (22.7)	0.88 (0.81-0.96)	0.005
Death from any cause	381 (8.2)	447 (9.6)	0.85 (0.74-0.97)	0.02
Death from CV causes	219 (4.7)	278 (6.0)	0.78 (0.66-0.93)	0.007

Marso SP, Daniels GH, Brown-Frandsen K, et al. Liraglutide and Cardiovascular Outcomes in Type 2 Diabetes. *N Engl J Med.*

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Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes (SUSTAIN-6)

- CV effects of semaglutide in patients with type 2 diabetes
- Semaglutide 0.5 mg or 1 mg once weekly vs placebo
- Primary composite outcome: first occurrence of CV death, nonfatal MI, or nonfatal stroke

End Point	Semaglutide (N = 1648)	Placebo (N = 1649)	Hazard Ratio (95% CI)	P Value
	no. of patients (%)	no. of patients (%)		
Primary composite outcome	108 (6.6)	146 (8.9)	0.74 (0.58-0.95)	<0.001 noninferiority; 0.02 superiority
Expanded composite outcome	199 (12.1)	264 (16.0)	0.74 (0.62-0.89)	0.002
All-cause death, nonfatal MI, or nonfatal stroke	122 (7.4)	158 (9.6)	0.77 (0.61-0.97)	0.03
Nonfatal stroke	27 (1.6)	44 (2.7)	0.61 (0.38-0.99)	0.04

Marso SP, Bain SC, Consoli A, et al. Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes. *N Engl J Med*.

Dulaglutide and Cardiovascular Outcomes in Type 2 Diabetes (REWIND)

- Major adverse CV events (MACE) of dulaglutide in patients with type 2 diabetes with and without previous CV disease
- Dulaglutide 1.5 mg once weekly vs placebo
- Primary composite outcome: first occurrence of non-fatal MI, non-fatal stroke, or death from CV causes

End Point	Dulaglutide (N = 4949)	Placebo (N = 4952)	Hazard Ratio (95% CI)	P Value
	no. of patients (%)	no. of patients (%)		
Primary composite outcome	594 (12.0)	663 (13.4)	0.88 (0.79-0.99)	0.026
Stroke	158 (3.2)	205 (4.1)	0.76 (0.62-0.94)	0.010
Nonfatal stroke	135 (2.7)	175 (3.5)	0.76 (0.61-0.95)	0.017

Gerstein HC, Colhoun HM, Dagenais GR, et al. Dulaglutide and cardiovascular outcomes in type 2 diabetes (REWIND): a double-blind, randomised placebo-controlled trial. *Lancet*.

Semaglutide in Patients with Heart Failure with Preserved Ejection Fraction and Obesity (STEP-HFpEF)

- Effects of semaglutide on function and symptoms in patients with obesity-related HFpEF
- Semaglutide 2.4 mg once weekly vs placebo
- Dual primary end points: change from baseline in the Kansas City Cardiomyopathy Questionnaire clinical summary score (KCCQ-CSS) and change in body weight

End Point	Semaglutide (N = 263)	Placebo (N = 266)	Hazard Ratio (95% CI)	P Value
Change in KCCQ-CSS from baseline to week 52 (points)	16.6	8.7	7.8 (4.8 to 10.9)	<0.001
% change in body weight from baseline to week 52	-13.3	-2.6	-10.7 (-11.9 to -9.4)	<0.001
Change from baseline to week 52 in 6-minute walk distance (m)	21.5	1.2	20.3 (8.6 to 32.1)	<0.001
Change from baseline to week 52 in CRP level (%)	-43.5	-7.3	0.61 (0.51 to 0.72)	<0.001

Kosiborod MN, Abildstrøm SZ, Borlaug BA, et al. Semaglutide in Patients with Heart Failure with Preserved Ejection Fraction and Obesity. *N Engl J Med*.

Semaglutide and Cardiovascular Outcomes in Obesity without Diabetes (SELECT)

- CV effects of semaglutide in overweight or obese patients without diabetes
- Semaglutide 2.4 mg once weekly vs placebo
- Primary composite end point: death from CV causes, nonfatal MI, or nonfatal stroke

End Point	Semaglutide (N = 8803)	Placebo (N = 8801)	Hazard Ratio (95% CI)	P Value
	no. of patients (%)	no. of patients (%)		
Primary composite end point	569 (6.5)	701 (8.0)	0.80 (0.72-0.90)	<0.001

Lincoff AM, Brown-Frandsen K, Colhoun HM, et al. Semaglutide and Cardiovascular Outcomes in Obesity without Diabetes. *N Engl J Med*.

Semaglutide in Patients with Obesity-Related Heart Failure and Type 2 Diabetes (STEP-HFpEF DM)

- Effects of semaglutide on function and symptoms in patients with obesity-related HFpEF and type 2 diabetes
- Semaglutide 2.4 mg once weekly vs placebo
- Primary end points: change from baseline in the Kansas City Cardiomyopathy Questionnaire clinical summary score (KCCQ-CSS) and change in body weight

End Point	Semaglutide (N = 310)	Placebo (N = 306)	Hazard Ratio (95% CI)	P Value
Change in KCCQ-CSS from baseline to week 52 (points)	13.7	6.4	7.3 (4.1 to 10.4)	<0.001
% change in body weight from baseline to week 52	-9.8	-3.4	-6.4 (-7.6 to -5.2)	<0.001
Change from baseline to week 52 in 6-minute walk distance (m)	12.7	-1.6	14.3 (3.7 to 24.9)	0.008
Change from baseline to week 52 in CRP level (%)	-42.0	-12.8	0.67 (0.55 to 0.80)	<0.001

Kosiborod MN, Petrie MC, Borlaug BA, et al. Semaglutide in Patients with Obesity-Related Heart Failure and Type 2 Diabetes. *N Engl J Med*.

Oral Semaglutide and Cardiovascular Outcomes in High-Risk Type 2 Diabetes (SOUL)

- CV efficacy of oral semaglutide in patients with type 2 diabetes and atherosclerotic cardiovascular disease, chronic kidney disease, or both
- Oral semaglutide 14 mg daily (or max tolerated dose) vs placebo
- Primary outcome: major adverse CV events
  - Composite of death from CV causes, nonfatal MI, or nonfatal stroke

End Point	Oral Semaglutide (N = 4825)	Placebo (N = 4825)	Hazard Ratio (95% CI)	P Value
	no. of patients (%)	no. of patients (%)		
Primary composite outcome	579 (12.0)	668 (13.8)	0.86 (0.77-0.96)	0.006

McGuire DK, Marx N, Mulvagh SL, et al. Oral Semaglutide and Cardiovascular Outcomes in High-Risk Type 2 Diabetes. *N Engl J Med*.

ACC/AHA Guideline Recommendations

Memorial

- **2023 AHA/ACC Guideline for the Management of Patients with Chronic Coronary Disease (CCD)**
  - In patients with type 2 diabetes and CCD, use of GLP-1 RA or sodium-glucose cotransporter 2 (SGLT2) inhibitor with proven CV benefit is recommended to reduce risk of MACE (recommendation 1A)
  - GLP-1 RA shown beneficial in addition to diet and physical activity in patients with CCD and overweight or obesity for further weight reduction (recommendation 2A)
- **2024 ACC Expert Consensus Decision Pathway for Treatment of Heart Failure With Reduced Ejection Fraction**
  - Data to suggest symptomatic benefit of GLP-1 RA in HFpEF when used for treatment of obesity
- **2024 AHA/ASA Guideline for the Primary Prevention of Stroke**
  - In patients with diabetes and high CV risk or established CVD and hemoglobin A1c ≥7%, GLP-1 RA effective to reduce the risk of stroke (recommendation 1A)

See references at end of presentation [13,24,26]

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STRIDE Trial

Memorial

Semaglutide and Walking Capacity in People with Symptomatic Peripheral Artery Disease (PAD) and Type 2 Diabetes (STRIDE)

- Primary outcome: ratio to baseline of maximum walking distance at week 52
- Semaglutide 1 mg once weekly vs placebo

Primary End Point	Semaglutide (N = 396)	Placebo (N = 396)	Estimate (95% CI)	P Value
Median maximum walking distance at week 52, ratio to baseline	338; 1.21 (0.95 to 1.55)	345; 1.08 (0.86 to 1.36)	1.13 (1.06 to 1.21)	0.0004

Bonaca MP, Catarig AM, Houlind K, 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. *Lancet*.

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SUMMIT Trial

Memorial

Tirzepatide for Heart Failure with Preserved Ejection Fraction and Obesity (SUMMIT)

- Primary outcomes:
  - Composite of adjudicated death from CV causes or a worsening heart failure event
  - Change from baseline to 52 weeks in the KCCQ-CSS
- Tirzepatide (up to 15 mg once weekly) vs placebo

Primary End Points	Tirzepatide (N = 364)	Placebo (N = 367)	Hazard Ratio or Difference (95% CI)	P Value
	Value	Value		
Adjudicated death from CV causes or a worsening heart failure event – no.(%)	36 (9.9)	56 (15.3)	0.62 (0.41 to 0.95)	0.026
Change at 52 weeks in KCCQ-CSS	19.5±1.2	12.7±1.3	6.9 (3.3 to 10.6)	<0.001

Packer M, Zile MR, Kramer CM, et al. Tirzepatide for Heart Failure with Preserved Ejection Fraction and Obesity. *N Engl J Med*.

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Upcoming GLP-1 RA & GIP/GLP-1 RA Trials

Memorial

Trial	Drug	Disease State
SURPASS-CVOT	tirzepatide	CV outcomes
SURMOUNT-MMO	tirzepatide	CV outcomes
EVOKE	semaglutide	Alzheimer disease

Pilla P, Modanessi T. GLP1RAs in Clinical Practice: Therapeutic Advances and Safety Perspectives - American College of Cardiology. American College of Cardiology.

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