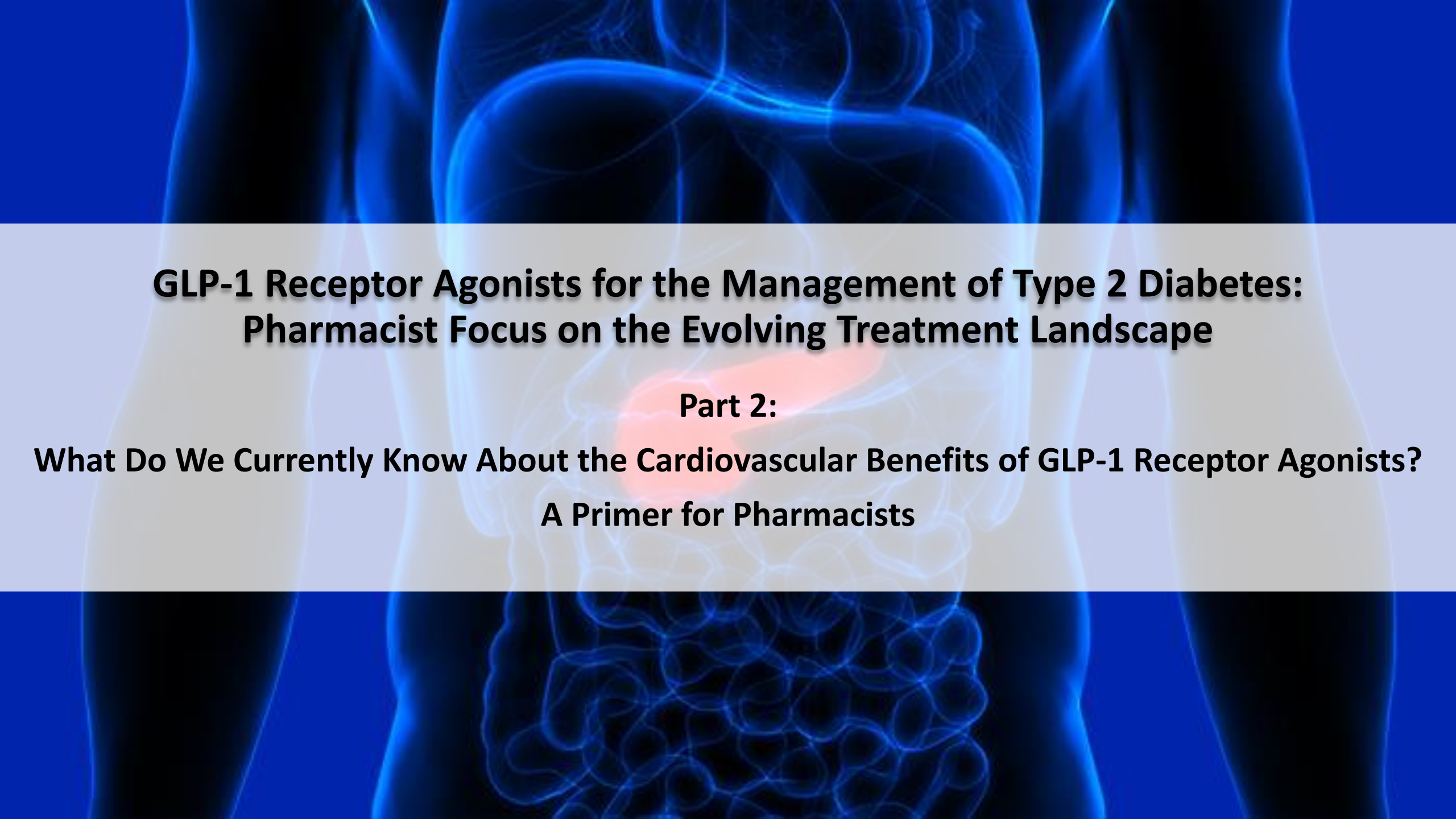

GLP-1 Receptor Agonists for the Management of Type 2 Diabetes: Pharmacist Focus on the Evolving Treatment Landscape

Part 2:

What Do We Currently Know About the Cardiovascular Benefits of GLP-1 Receptor Agonists?

A Primer for Pharmacists

This educational activity is sponsored by Postgraduate Healthcare Education, LLC and supported by an educational grant from Novo Nordisk Inc.

Faculty

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Heather P. Whitley, PharmD is an Associate Clinical Professor of Pharmacy Practice at the Auburn University Harrison School of Pharmacy. She holds a BS in Biochemistry from Clemson University and she earned her PharmD from the Medical University of South Carolina in 2004. She subsequently completed a Pharmacy Practice residency in 2005 and a Primary Care residency in 2006, both of which were ASHP-accredited residency programs. Dr. Whitley is also a Board-Certified Pharmacotherapy Specialist and a Certified Diabetes Educator.

Dr. Whitley has practiced in multiple locations in Alabama as a Clinical Pharmacy Diabetes Specialist, including family medicine practices in the rural Black Belt, FQHC facilities, and, most recently, a family medicine residency program in Montgomery, Alabama that is affiliated with Baptist Health System. For the duration of her career, she has been a faculty member of the Auburn University Harrison School of Pharmacy.

Dr. Whitley has published 30 manuscripts and presented at national and international levels, focusing predominantly on her diabetes-related research, which includes diagnostic measures, diabetes care and the chronic care model, and the scholarship of teaching and learning, particularly as it involves provision of care at camps for children with type 1 diabetes.

Disclosures

Dr. Whitley has no actual or potential conflicts of interest in relation to this program.

The clinical reviewer, Jennifer M. Trujillo, PharmD, FCCP, BCPS, CDE, BC-ADM has served as a consultant to BD, Sanofi, and Novo Nordisk.

Susanne Batesko, RN, BSN, Robin Soboti, RPh, as well as the planners, managers, and other individuals, not previously disclosed, who are in a position to control the content of Postgraduate Healthcare Education (PHE) continuing education activities hereby state that they have no relevant conflicts of interest and no financial relationships or relationships to products or devices during the past 12 months to disclose in relation to this activity. PHE is committed to providing participants with a quality learning experience and to improve clinical outcomes without promoting the financial interests of a proprietary business.

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- **UAN:** 0430-0000-19-117-L01-P
- **Credits:** 1.25 hour (0.125 ceu)
- **Activity Type:** Knowledge

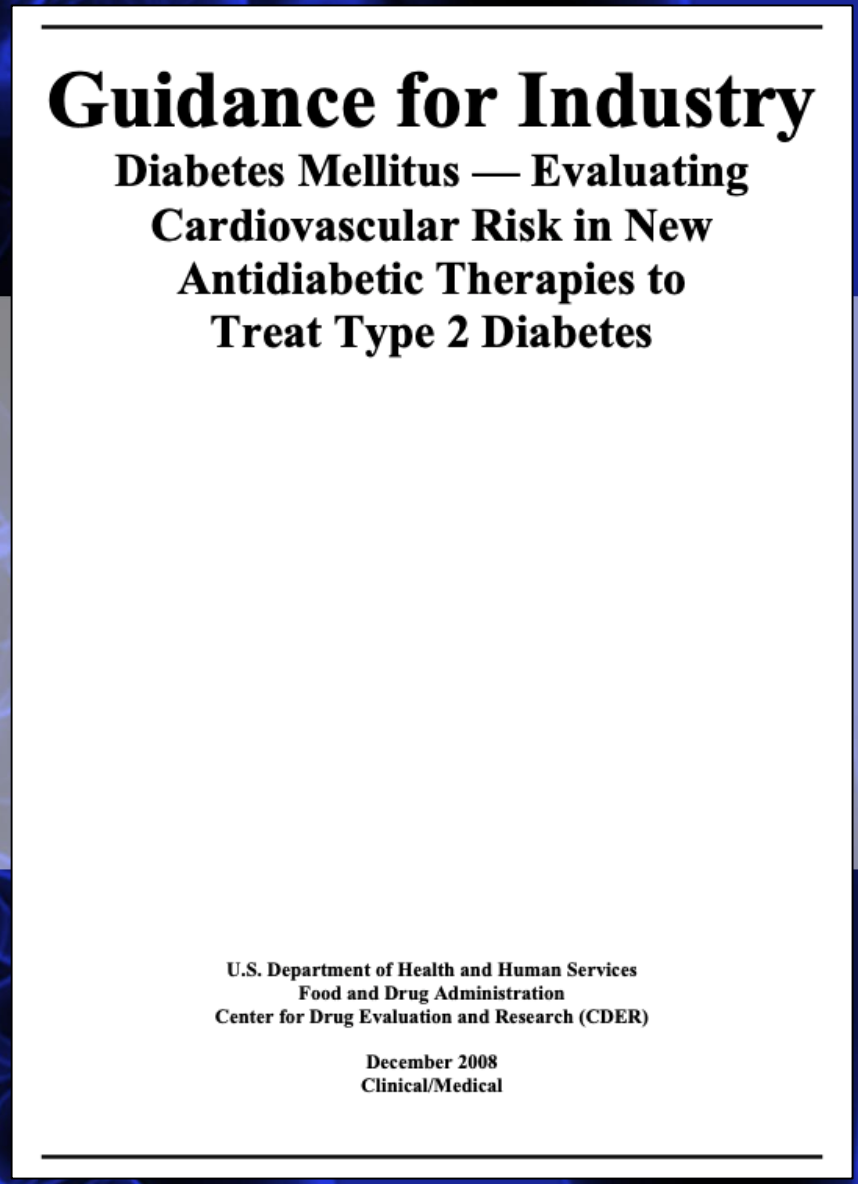
Learning Objectives

- **Evaluate** data from glucagon-like peptide (GLP)-1 receptor agonist (RA) cardiovascular outcome trials (CVOTs) and apply implications to patient care
- **Describe** proposed mechanisms by which GLP-1 RAs reduce cardiovascular risk in patients with type 2 diabetes mellitus (T2DM)
- **Recall** agent-specific GLP-1 RA indications for use in addition to improving glycemic control in the management of T2DM

Hirshberg, et al. *Diabetes Care*. 2011;34(Suppl 2):S101-6.; U.S. Department of HHS; FDA. *Guidance for industry. Diabetes mellitus – evaluating cardiovascular risk in new antidiabetic therapies to treat type 2 diabetes*. https://www.fda.gov/media/71297/download/. Published December 2008.

New FDA Requirement

Hirshberg, et al. *Diabetes Care*. 2011;34(Suppl 2):S101-6.; U.S. Department of HHS; FDA. *Guidance for industry. Diabetes mellitus – evaluating cardiovascular risk in new antidiabetic therapies to treat type 2 diabetes*. https://www.fda.gov/media/71297/download/. Published December 2008.



Guidance for Industry

Diabetes Mellitus — Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

December 2008
Clinical/Medical

Historic CVOTs in Diabetes and Their Implications[1]

		Microvascular		CVD		Mortality	
Study	**A1C**[a]	Initial trial	Long-term follow-up	Initial trial	Long-term follow-up	Initial trial	Long-term follow-up
UKPDS[2,3]	7.9 vs. 7.0	↓	↓	–	↓	–	↓
DCCT/EDIC[4,5]	9.1 vs. 7.0	↓	↓	–	↓	–	–
ACCORD[6,7]	7.5 vs. 6.4	?		–		↑	
ADVANCE[8]	7.3 vs. 6.5	↓		–		–	
VADT[9]	8.4 vs. 6.9	↓		–		–	

[a]Values presented are for conventional/standard therapy group vs. intensive therapy group at the end of initial trial

1. Bergenstal RM, et al. *Am J Med*. 2010;123(4):374.e9-18.; 2. UKPDS Group. *Lancet*. 1998;352(9131):854-65.; 3. Holman RR, et al. *N Engl J Med*. 2008;359(15):1577-89.; 4. DCCT. *N Engl J Med.* 1993;329(14):977-86.; 5. Nathan DM, et al. *N Engl J Med*. 2005;353(25):2643-53.; 6. ACCORD Study Group. *N Engl J Med*. 2008;358(24):2545-59.; 7. ACCORD Study Group. *N Engl J Med*. 2010;363(3):233-44.; 8. ADVANCE Collaborative Group. *N Engl J Med*. 2008;358(24):2560-72.; 9. Duckworth W, et al. *N Engl J Med*. 2009;360(2):129-39.

CVD, cardiovascular disease.

FDA Guidance for Industry

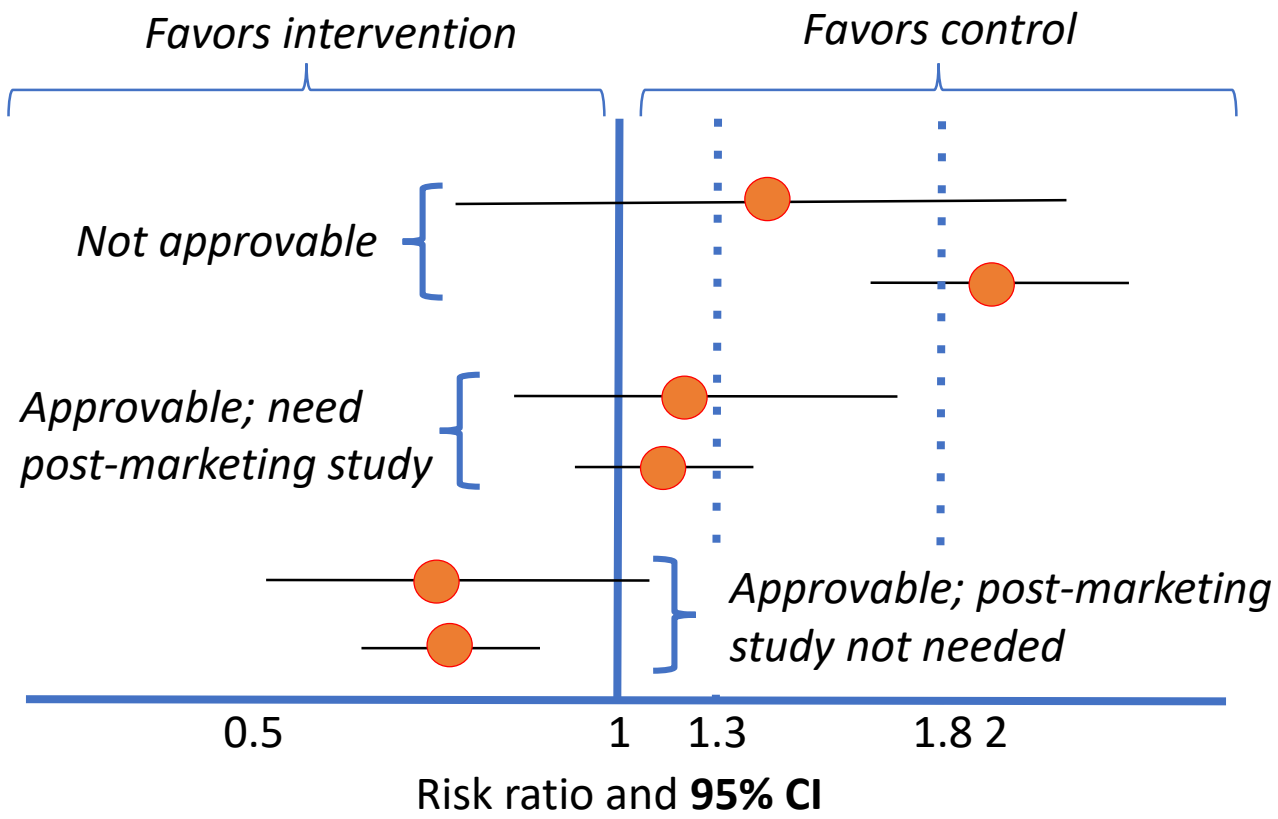
"To ensure that a new [antihyperglycemic] therapy does not increase cardiovascular risk to an unacceptable extent…."

Criteria

1. Include patients at higher risk for CV events
   - Advanced disease
   - Elderly
   - Renal impairment

2. Sufficient size & duration
   - Minimum of 2 years

3. Endpoints
   - CV death, MI, stroke (MACE)
   - +/- other endpoints



CI, confidence interval; CV, cardiovascular; FDA, United States Food and Drug Administration; MACE, major adverse cardiovascular event; MI, myocardial infarction.

Hirshberg, et al. *Diabetes Care*. 2011;34(Suppl 2):S101-6.; U.S. Department of HHS; FDA. *Guidance for industry. Diabetes mellitus – evaluating cardiovascular risk in new antidiabetic therapies to treat type 2 diabetes*. https://www.fda.gov/media/71297/download/. Published December 2008.

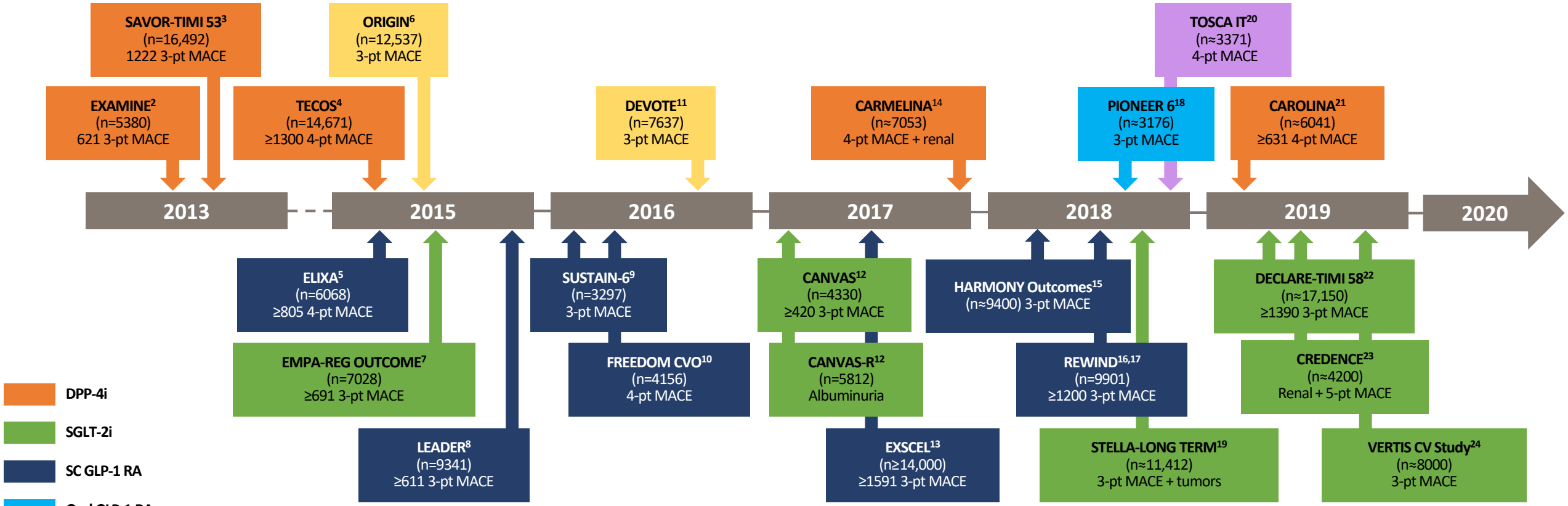
FDA-Approved GLP-1 RA Medications

Agent	Date of FDA approval	Formulations	Route	Dosing frequency
Exenatide	April 2005	5-mcg and 10-mcg pens	SC	Twice daily
Lixisenatide	July 2016	10-mcg and 20-mcg pens	SC	Daily
Liraglutide	January 2010	6-mg/mL (3 mL) pen	SC	Daily
Exenatide XR	October 2017	2-mg vial for reconstitution, 2-mg pen	SC	Weekly
Dulaglutide	September 2014	0.75-mg and 1.5-mg pens	SC	Weekly
Semaglutide	December 2017	0.25-mg, 0.5-mg, and 1-mg pens	SC	Weekly
Semaglutide	September 2019	3-mg, 7-mg, and 14-mg tablets	PO	Daily

PO, by mouth; SC, subcutaneously.

Adlyxin [package insert]. 2016.; Byetta [package insert]. 2015.; Bydureon [package insert]. 2018.; Trulicity [package insert]. 2017.; Ozempic [package insert]. 2017.; Rybelsus [package insert]. 2019.; Victoza [package insert]. 2017.

Timeline of Recent Type 2 Diabetes CVOTs[1]



DPP-4i, dipeptidyl peptidase 4 inhibitor; SGLT-2i, sodium glucose transport protein 2 inhibitor.; TZD, thiazolidinedione.

Note: Dates represent estimated completion dates according to ClinicalTrials.gov.

1. Johansen OE. *World J Diabetes.* 2015;6(9):1092-6.; 2. White WB, et al. *N Engl J Med.* 2013;369(14):1327-35.; 3. Scirica BM, et al. *N Engl J Med.* 2013;369(14):1317-26.; 4. Green JB, et al. *N Engl J Med.* 2015;373(3):232-42.; 5. Pfeffer MA, et al. *N Engl J Med.* 2015;373(23):2247-57.; 6. The ORIGIN Trial Investigators. *N Engl J Med.* 2012;367(4):319-28.; 7. Zinman B, et al. *N Engl J Med.* 2015;373(22):2117-28.; 8. Marso SP, et al. *N Engl J Med.* 2016;375(4):311-22.; 9. Marso SP, et al. *N Engl J Med.* 2016;375(19):1834-44.; 10. ClinicalTrials.gov. NCT01455896.; 11. Marso SP, et al. *N Engl J Med.* 2017;377(8):723-32.; 12. Neal B, et al. *N Engl J Med*. 2017;377(7):644-57.; 13. Holman RR, et al. *N Engl J Med.* 2017;377(13):1228-39.; 14. Rosenstock J, et al. *JAMA.* 2019;321(1):69-79.; 15. Hernandez AF, et al. *Lancet.* 2018;392(10157):1519-29.; 16. Gerstein HC, et al. *Lancet.* 2019;394(10193):121-30.; 17. Gerstein HC, et al. *Lancet.* 2019;394(10193):131-8.; 18. Husain M, et al. *N Engl J Med.* 2019;381(9):841-51.; 19. Nakamura I, et al. *Adv Ther.* 2019;36(4):923-49.; 20. ClinicalTrials.gov. NCT00700856.; 21. Rosenstock J, et al. *JAMA.* 2019.; 22. Wiviott SD, et al. *N Engl J Med.* 2019;380(4):347-57.; 23. Perkovic V, et al. *N Engl J Med.* 2019;380(24):2295-306.; 24. ClinicalTrials.gov. NCT01986881.

ARS Question 1

Which of the following is TRUE regarding conclusions from the published CVOTs for GLP-1 RAs?

A. All demonstrated at least CV safety compared to placebo
B. All demonstrated reduced CV risk of stroke compared to placebo
C. All demonstrated improved efficacy by reducing the risk of CV death
D. All demonstrated improved efficacy by reducing the risk of MACE

Overview of GLP-1 RA CVOTs

Study identifier	No. of patients	Study design	Primary endpoint	Results HR (95% CI)
ELIXA[1] ACS < 180 days; A1C 5.5%-11%	6068	Lixisenatide Placebo	4-pt MACE	**1.02 (0.89-1.17)** P<0.001 (non-inferiority) p=0.81 (superiority)
LEADER[2] CV risk/CVD; A1C ≥ 7.0%	9340	Liraglutide Placebo	3-pt MACE	**0.87 (0.78-0.97)** p=0.01 (superiority)
SUSTAIN 6[3] CVD; A1C ≥ 7.0%	3297	Semaglutide (SC) Placebo	3-pt MACE	**0.74 (0.58-0.95)** p=0.02 (superiority)
PIONEER 6[4] CVD or CKD	3183	Semaglutide (PO) Placebo	3-pt MACE	**0.79 (0.57-1.11)** P<0.001 (non-inferiority) P=0.17 (superiority)
EXSCEL[5] High CV risk/CVD; A1C 6.5%-10.0%	14,752	Exenatide ER Placebo	3-pt MACE	**0.91 (0.83-1.00)** P<0.001 (non-inferiority) p=0.06 (superiority)
REWIND[6] High CV risk; A1C ≤ 9.5%	9901	Dulaglutide Placebo	3-pt MACE	**0.88 (0.79-0.99)** p=0.026 (superiority)

CKD, chronic kidney disease; HR, hazard ratio.

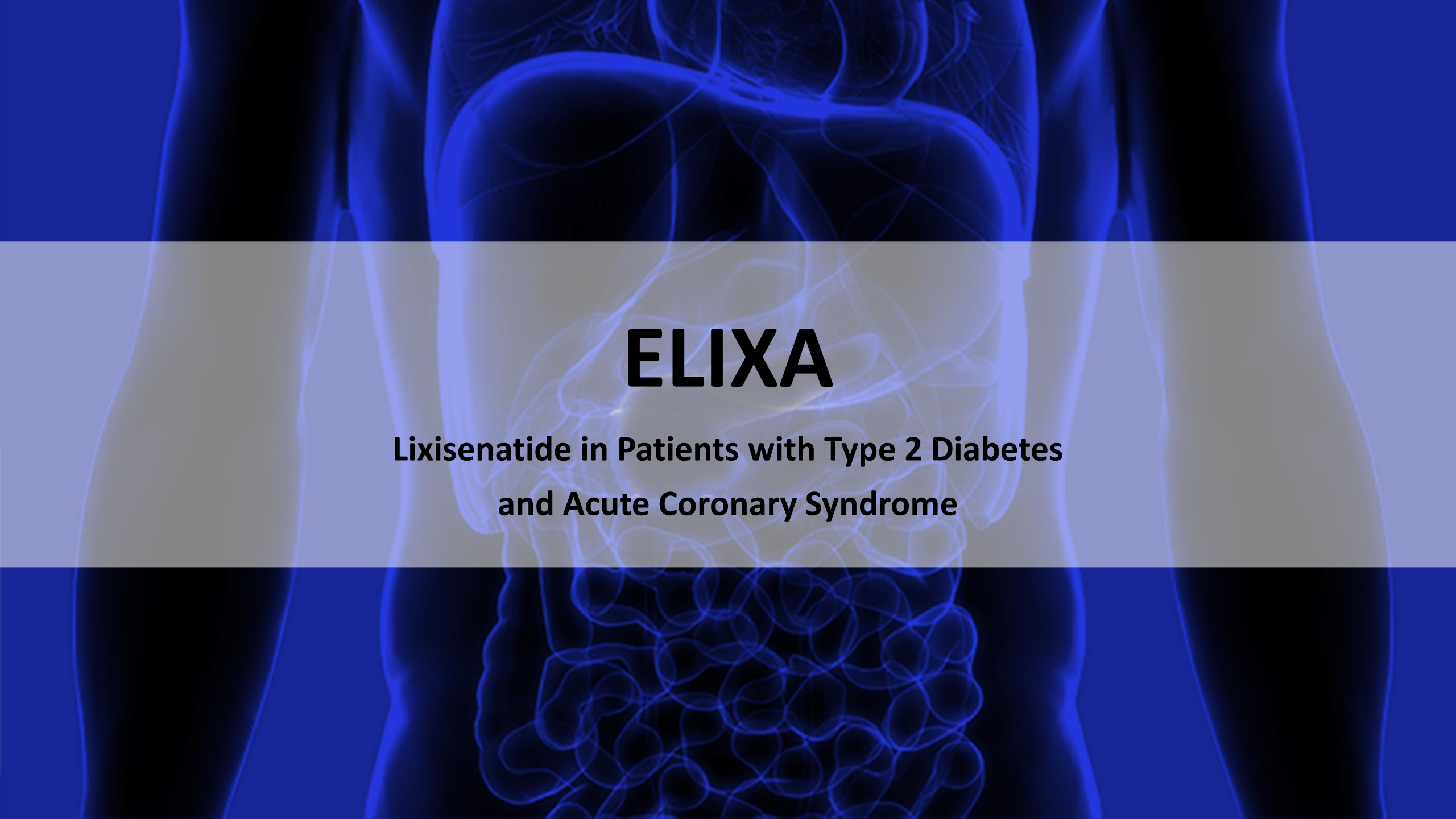
1. Pfeffer MA, et al. *N Engl J Med.* 2015;373(23):2247-57.; 2. Marso SP, et al. *N Engl J Med.* 2016;375(4):311-22.;3. Marso SP, et al. *N Engl J Med.* 2016;375(19):1834-44.; 4. Husain M, et al. *N Engl J Med.* 2019;381(9):841-51.; 5. Holman RR et al. *N Engl J Med* 2017;377(13):1228-39.; 6. Gerstein HC, et al. Lancet. 2019;394(10193):121-30.

GLP-1 RA FDA-Approved Cardiovascular Indications

Medication	CV FDA indication	Guideline recommendation
Liraglutide (Victoza)	"…reduce the risk of major adverse CV events in adults with type 2 diabetes and established CVD"	In people with T2D with ASCVD or increased risk for ASCVD, the addition of liraglutide decreased MACE and mortality…
Semaglutide (Ozempic)	None	…Semaglutide also had favorable effects on CV end points in high-risk subjects
Semaglutide (Rybelsus)	None	**GLP1-RA strongest evidence for:** Liraglutide > Semaglutide SC > Exenatide ER
Exenatide XR (Bydureon, Bydureon BCise)	None	
Dulaglutide (Trulicity)	None	

ASCVD, atherosclerotic cardiovascular disease.

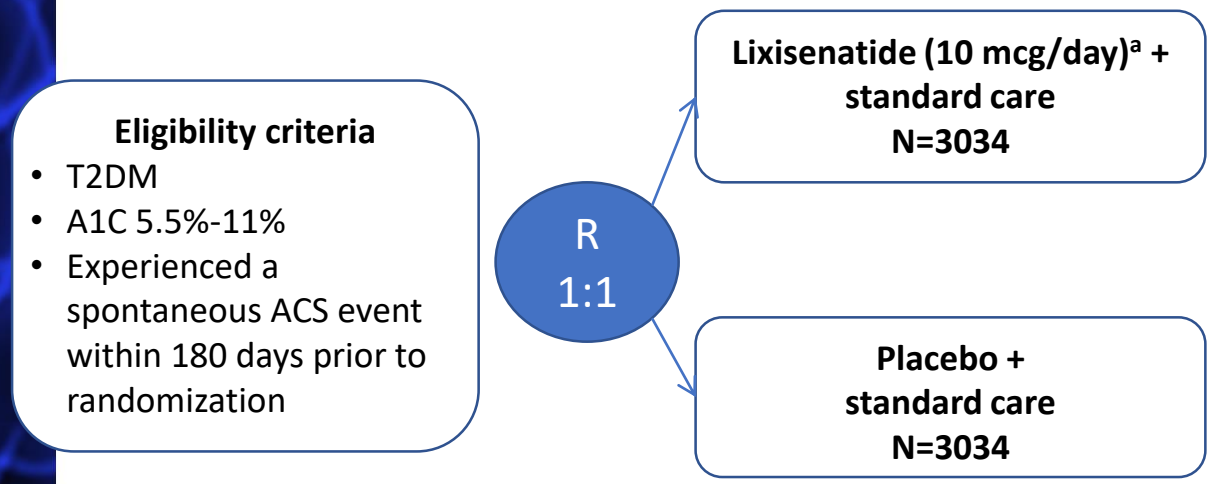
Adlyxin [package insert]. 2016; American Diabetes Association. *Diabetes Care*. 2019;42(Suppl. 1):S90-S102.; American Diabetes Association. *Diabetes Care.* 2019;42(Suppl 1):S94.; Bydureon [package insert]. 2018; Byetta [package insert]. 2015; Ozempic [package insert]. 2017.; Trulicity [package insert]. 2017; Victoza [package insert]. 2017.



ELIXA

Lixisenatide in Patients with Type 2 Diabetes and Acute Coronary Syndrome

ELIXA:
Study Design, Objectives, and Enrolled Patients



Baseline characteristics

Median time to follow-up: 2.1 years
Mean age: 60 years
Mean BMI: 32.5 kg/m^2
Previous CVD: 100%
Mean duration of T2DM: 9.3 years
Mean A1C: 7.7%

- **Study design:** Multicenter, randomized, double-blind, parallel-group, placebo-controlled study
- **Primary objective:** To evaluate the effects of lixisenatide on CV morbidity and mortality (composite endpoint of CV death, nonfatal MI, nonfatal stroke, hospitalization for UA) compared to placebo in T2DM patients who recently experienced an ACS event

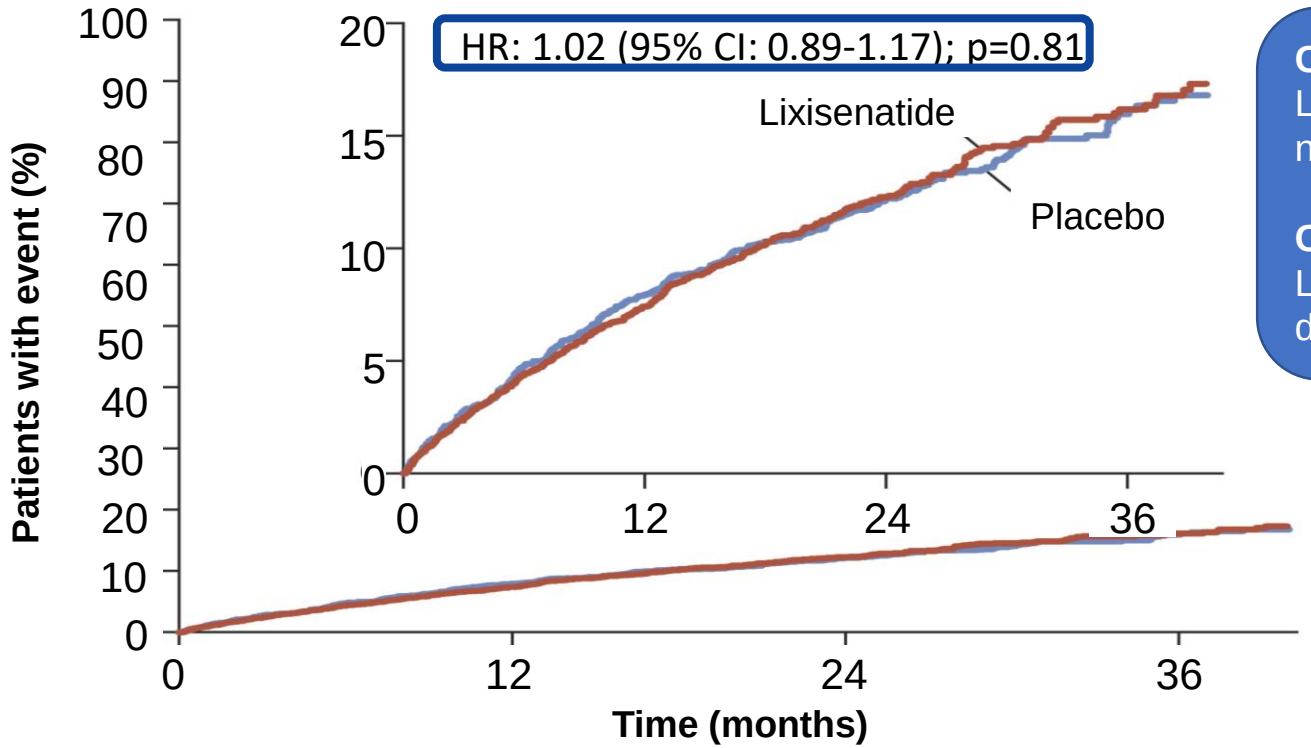
[a]Dose could be increased to a maximum of 20 mcg/day at the investigator's discretion

ACS, acute coronary syndrome; BMI, body mass index; UA, unstable angina.

Pfeffer MA, et al. *N Engl J Med.* 2015;373(23):2247-57.

ELIXA: Primary Outcome

First Occurrence of 4-Point MACE
(CV Death, Nonfatal MI, Nonfatal Stroke, or Unstable Angina)



No. at Risk:

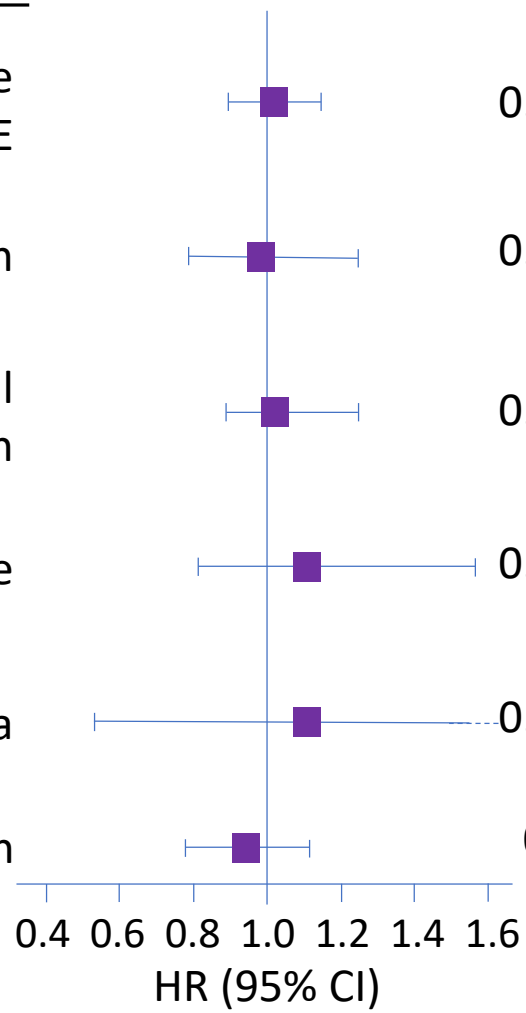
Lixisenatide	3034	2785	1558	484
Placebo	3034	2759	1566	476

CI upper limit < 1.3
Lixisenatide met the non-inferiority criterion

CI upper limit > 1.0
Lixisenatide did not demonstrate superiority

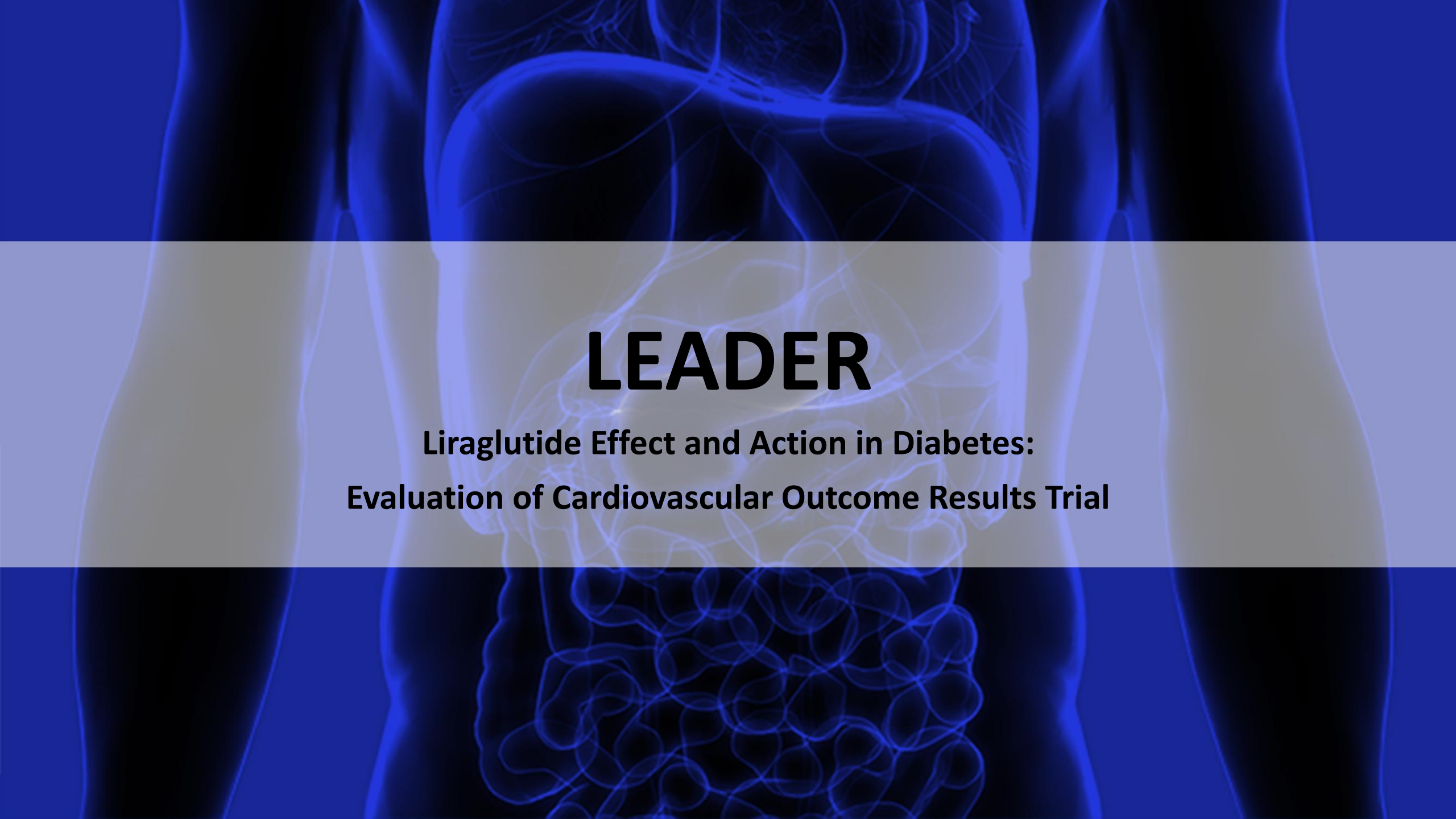
Pfeffer MA, et al. *N Engl J Med.* 2015;373(23):2247-57.

ELIXA: Individual Components of 4-Pt MACE



Outcome	*P*	*HR (95% CI)*
Primary composite 4-point MACE	0.81	1.02 (0.89-1.17)
CV death	0.85	0.98 (0.78-1.22)
Myocardial infarction	0.71	1.03 (0.87-1.22)
Stroke	0.54	1.12 (0.79-1.58)
Unstable angina	0.81	1.11 (0.47-2.62)
All-cause death	0.5	0.94 (0.78-1.13)

Pfeffer MA, et al. *N Engl J Med.* 2015;373(23):2247-57.



LEADER

Liraglutide Effect and Action in Diabetes:
Evaluation of Cardiovascular Outcome Results Trial

LEADER:
Study Design, Objectives, and Enrolled Patients

Selected eligibility criteria

- T2DM with A1C ≥ 7.0%
- Age ≥ 50 years with ≥ 1 coexisting CV condition
  or
- Age ≥ 60 years with ≥ 1 CV risk factor

R
1:1

Liraglutide (0.6-1.8 mg) + standard care
N=4668

Placebo + standard care
N=4672

Baseline characteristics

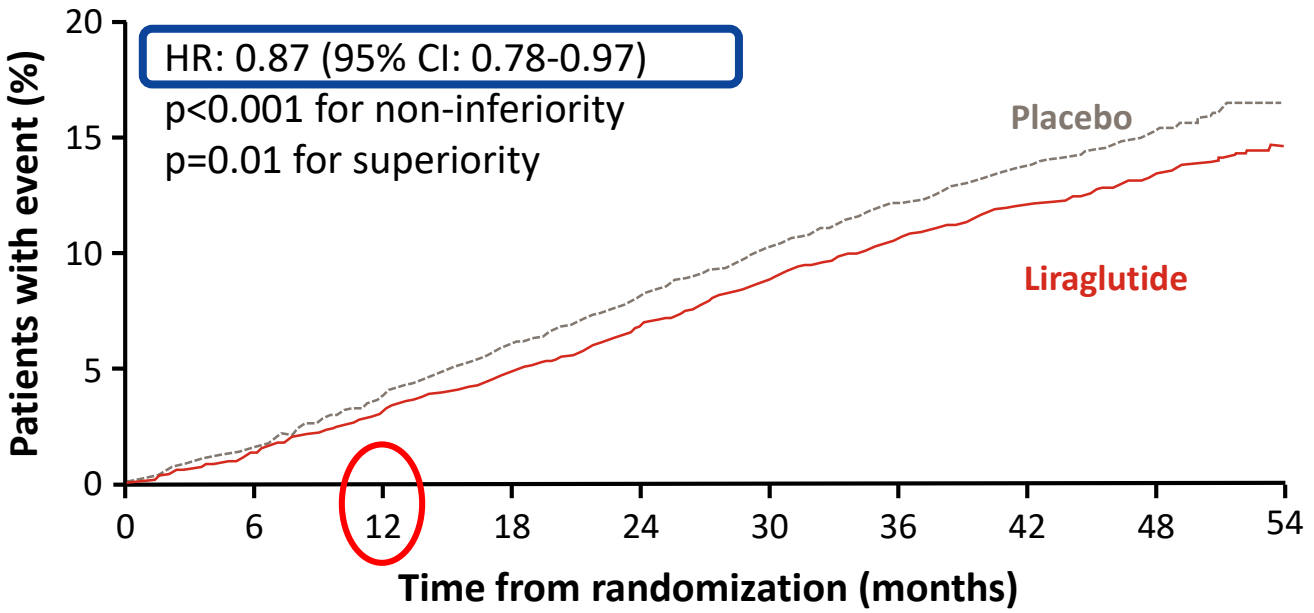
Median time to follow-up: 3.8 years
Mean age: 65 years
Mean BMI: 32.5 kg/m^2
Previous CVD: 81%
Mean duration of T2DM: 12.8 years
Mean A1C: 8.7%

- **Study design:** International, randomized, placebo-controlled study
- **Primary objective:** To evaluate the effect of liraglutide compared to placebo on the incidence of CV events in adults with T2DM

Marso SP, et al. *Am Heart J*. 2013;166:823-30.e5.

LEADER: Primary Outcome

First Occurrence of MACE (CV Death, Nonfatal MI, or Nonfatal Stroke)



CI upper limit < 1.3
Liraglutide met the non-inferiority criterion

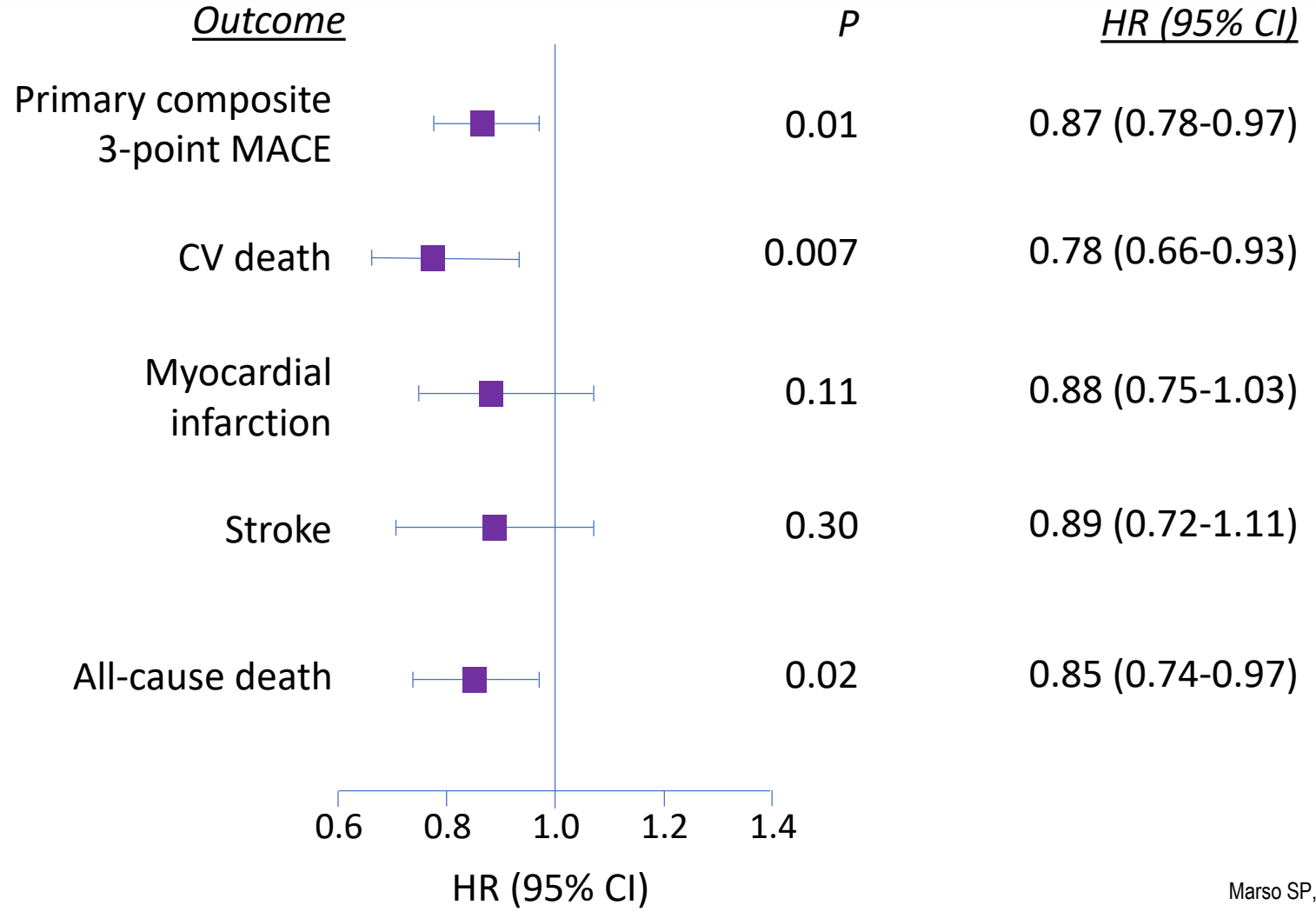
CI upper limit < 1.0
Liraglutide demonstrated superiority vs. placebo

No. at risk

Liraglutide	4668	4593	4496	4400	4280	4172	4072	3982	1562	424
Placebo	4672	4588	4473	4352	4237	4123	4010	3914	1543	407

Marso SP, et al. *N Engl J Med.* 2016;375(4):311-22.

LEADER: Individual Components of 3-Pt MACE



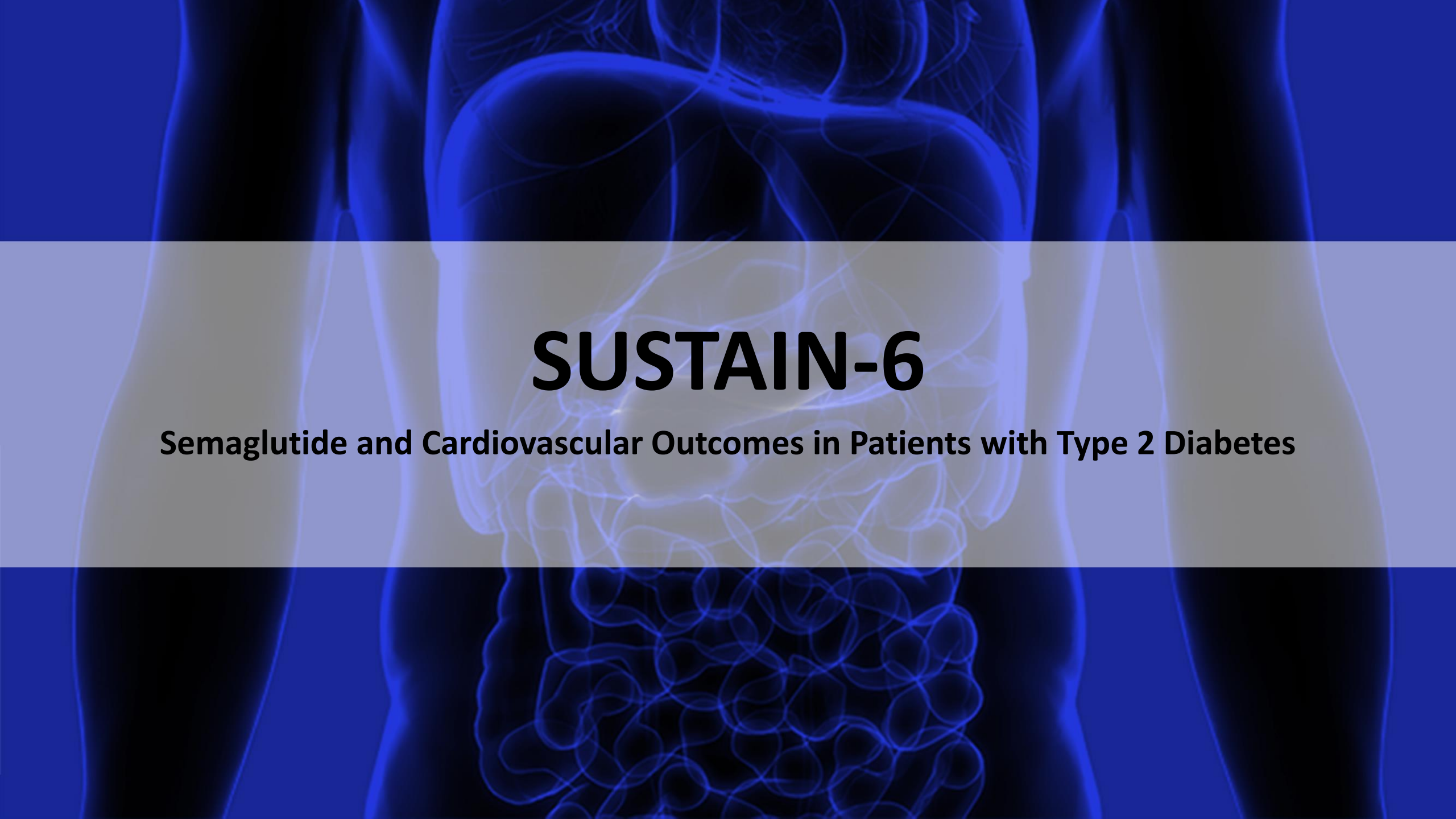
Marso SP, et al. *N Engl J Med.* 2016;375(4):311-22.

LEADER: Microvascular Outcomes

Outcome	Liraglutide (N=4668) n (%)	Liraglutide (N=4668) Incidence rate	Placebo (N=4672) n (%)	Placebo (N=4672) Incidence rate	HR (95% CI)	p-value
Microvascular composite	355 (7.6)	2.0	416 (8.9)	2.3	0.84 (0.73-0.97)	0.02
Retinopathy*	106 (2.3)	0.6	92 (2.0)	0.5	1.15 (0.87-1.52)	0.33
Nephropathy^	268 (5.7)	1.5	337 (7.2)	1.9	0.78 (0.67-0.92)	0.003

*Retinopathy defined as the need for retinal photocoagulation or treatment with intravitreal agents, vitreous hemorrhage, or the onset of diabetes-related blindness.
^Nephropathy defined as the new onset of macroalbuminuria or a doubling of the serum creatinine level and an estimated glomerular filtration rate of ≤ 45 mL/min/1.73 m^2, the need for continuous renal-replacement therapy, or death from renal disease.

Marso SP, et al. *N Engl J Med.* 2016;375(4):311-22.



SUSTAIN-6

Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes

SUSTAIN-6:
Study Design, Objectives, and Enrolled Patients

Eligibility Criteria:
- T2DM with A1C ≥ 7.0%
- Age ≥ 50 years with evidence of CVD
  or
- Age ≥ 60 years with subclinical evidence of CVD
- Drug naïve or treated with 1-2 OADs or insulin

R
1:1:1:1

Semaglutide
(0.5 mg or 1.0 mg once a week)
+ standard care
(N=1648)

Volume-matched placebo
+ standard care
(N=1649)

Baseline characteristics

Median time to follow-up: 2.1 years
Mean age: 64.6 years
Mean BMI: 32.8 kg/m^2
Previous CVD: 83%
Mean duration of T2DM: 13.9 years
Mean A1C: 8.7%

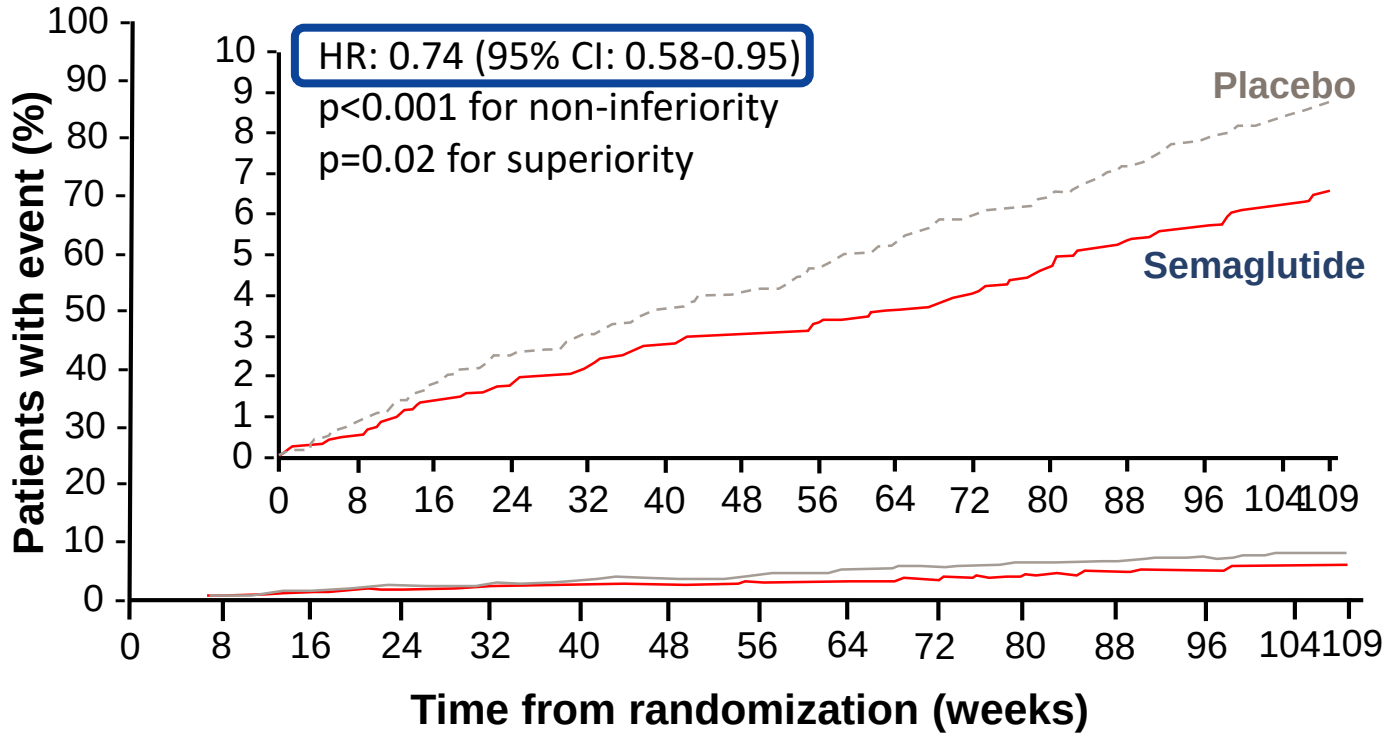
- **Study design:** Multicenter, randomized, placebo-controlled, double-blind study
- **Primary objective:** To evaluate CV and other long-term outcomes with semaglutide in subjects with T2DM

OAD, oral antidiabetic drug.

Marso SP, et al. *N Engl J Med.* 2016;375(19):1834-44.

SUSTAIN-6: Primary Outcome

First Occurrence of MACE (CV Death, Nonfatal MI, or Nonfatal Stroke)



No. at risk

Semaglutide	1648	1619	1601	1584	1568	1543	1524
Placebo	1649	1616	1586	1567	1534	1508	1479

CI upper limit < 1.3
Semaglutide met the non-inferiority criterion

CI upper limit < 1.0
Semaglutide demonstrated superiority vs. placebo

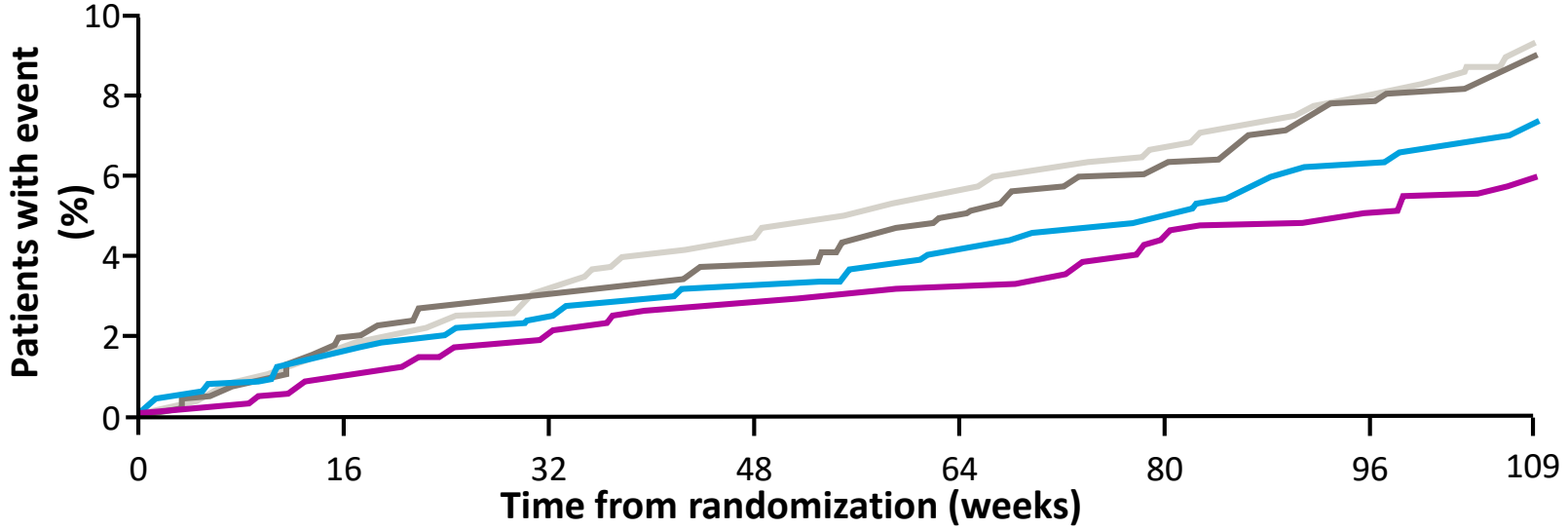
Marso SP, et al. *N Engl J Med.* 2016;375(19):1834-44.

SUSTAIN-6: Primary Outcome by Dose

First Occurrence of MACE
(CV Death, Nonfatal MI, or Nonfatal Stroke)

Semaglutide 0.5 mg
HR: 0.77 (95% CI: 0.55-1.08); p=0.13

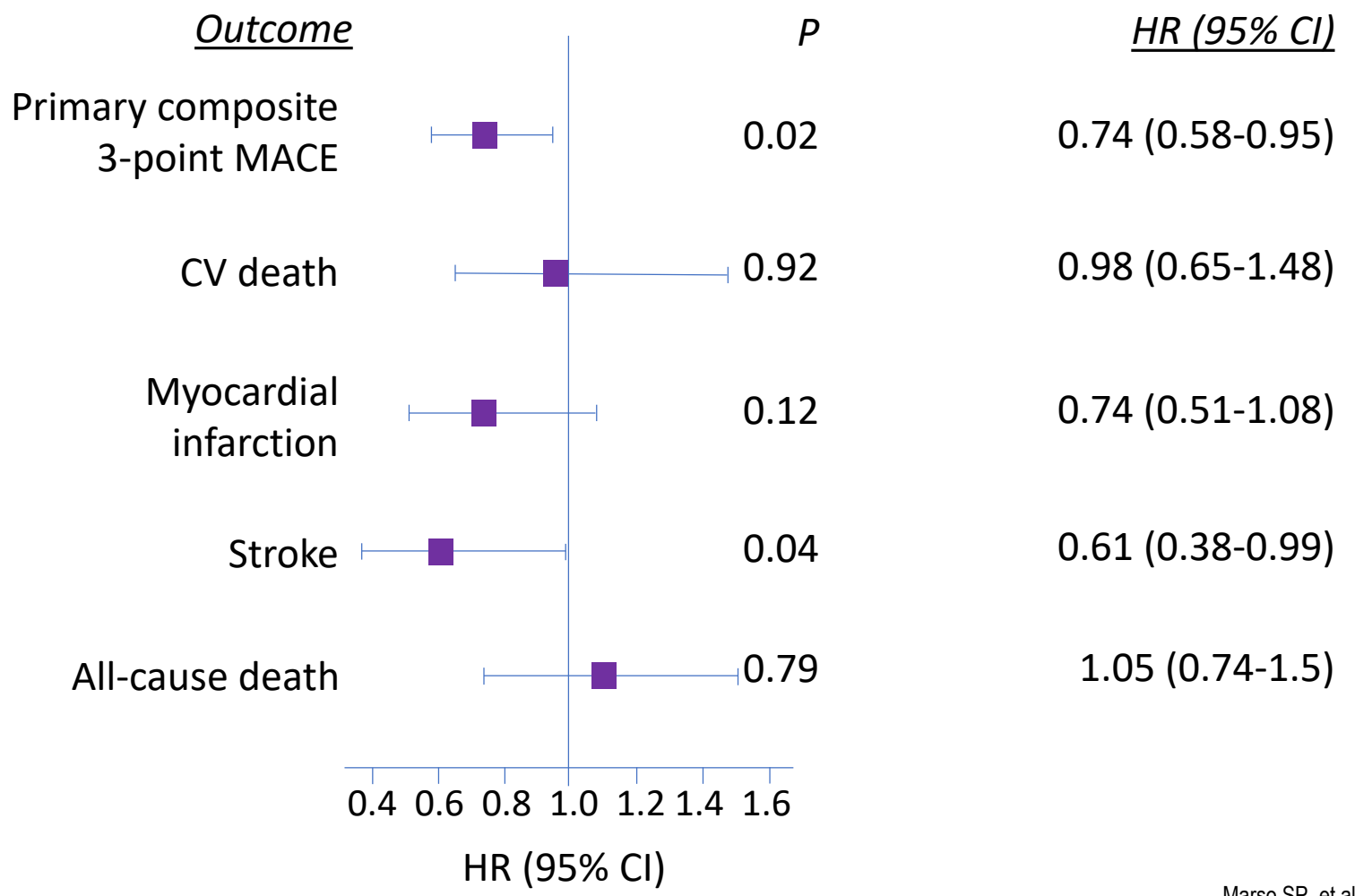
Semaglutide 1.0 mg
HR: 0.71 (95% CI: 0.49-1.02); p=0.06



No. at risk							
Sema 0.5 mg	826	811	803	794	783	769	759
Sema 1.0 mg	822	808	798	790	785	774	765
PBO 0.5 mg	824	809	791	778	760	746	732
PBO 1.0 mg	825	807	795	789	774	762	747

Marso SP, et al. *N Engl J Med.* 2016;375(19):1834-44.

SUSTAIN-6: Individual Components of 3-Pt MACE



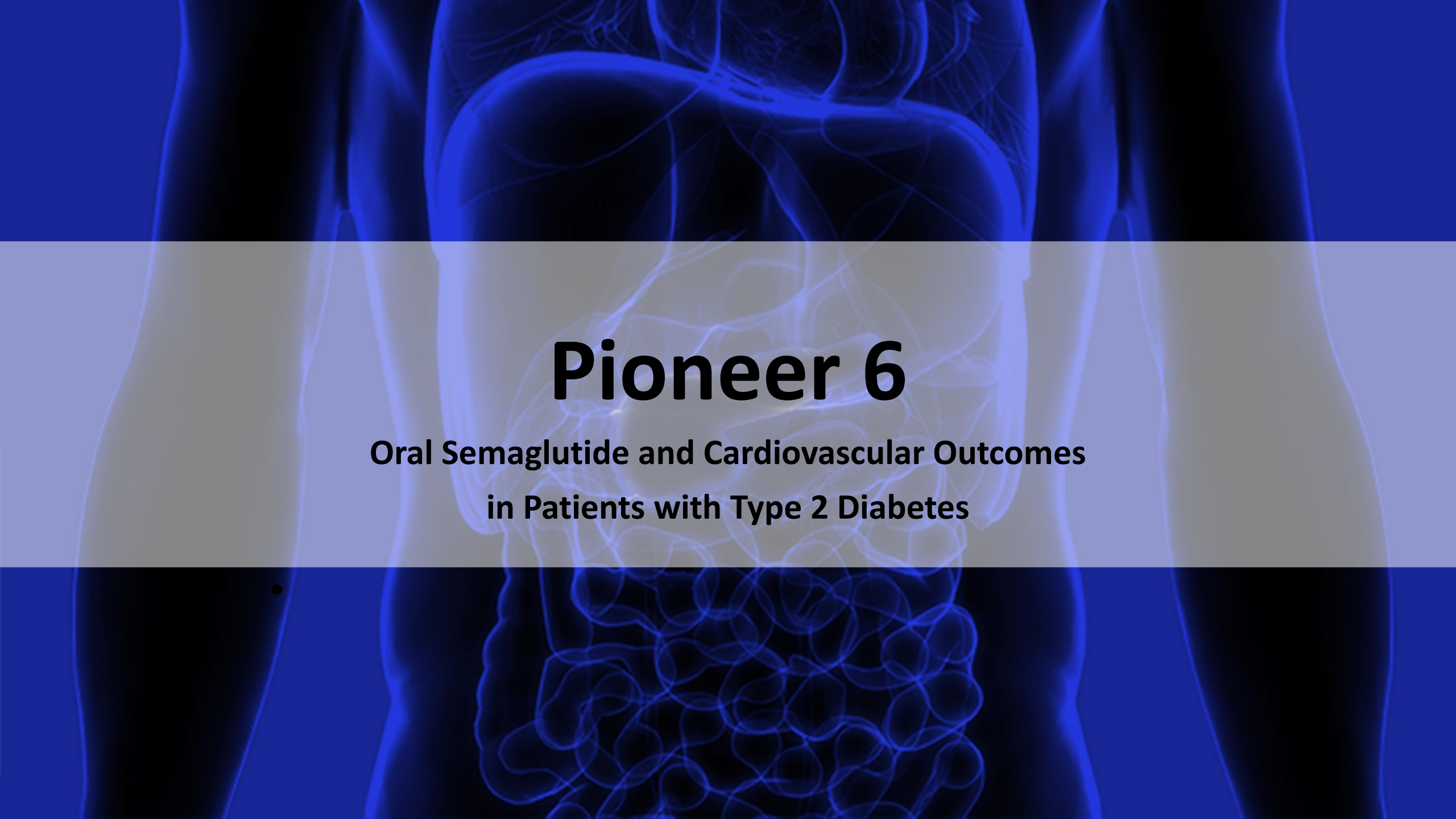
Marso SP, et al. *N Engl J Med.* 2016;375(19):1834-44.

SUSTAIN-6: Microvascular Outcomes

	Semaglutide (N=1648)		Placebo (N=1649)			
Outcome	**n (%)**	**Incidence rate[a]**	**n (%)**	**Incidence rate**	**HR (95% CI)**	**p-value**
Retinopathy complications*	50 (3.0)	1.49	29 (1.8)	0.86	1.76 (1.11-2.78)	0.02
New or worsening nephropathy^	62 (3.8)	1.86	100 (6.1)	3.06	0.64 (0.46-0.88)	0.005

*Retinopathy complications include vitreous hemorrhage, onset of diabetes-related blindness, and the need for treatment with an intravitreal agent or retinal photocoagulation.
^New or worsening nephropathy includes persistent macroalbuminuria, persistent doubling of the serum creatinine level and a creatinine clearance of less than 45 ml per minute per 1.73 m^2 of body-surface area (according to the Modification of Diet in Renal Disease criteria), or the need for continuous renal-replacement therapy

Marso SP, et al. *N Engl J Med.* 2016;375(19):1834-44.



Pioneer 6

Oral Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes

PIONEER-6:
Study Design, Objectives, and Enrolled Patients

Eligibility criteria

- T2DM
- Age ≥ 50 years with CVD or CKD

or

- Age ≥ 60 years with ≥ 1 CV risk factor
- Excluded patients with previous retinopathy

R
1:1

Oral semaglutide (14-mg tablet PO daily) + standard of care (N=1591)

Placebo + standard of care (N=1592)

Baseline characteristics

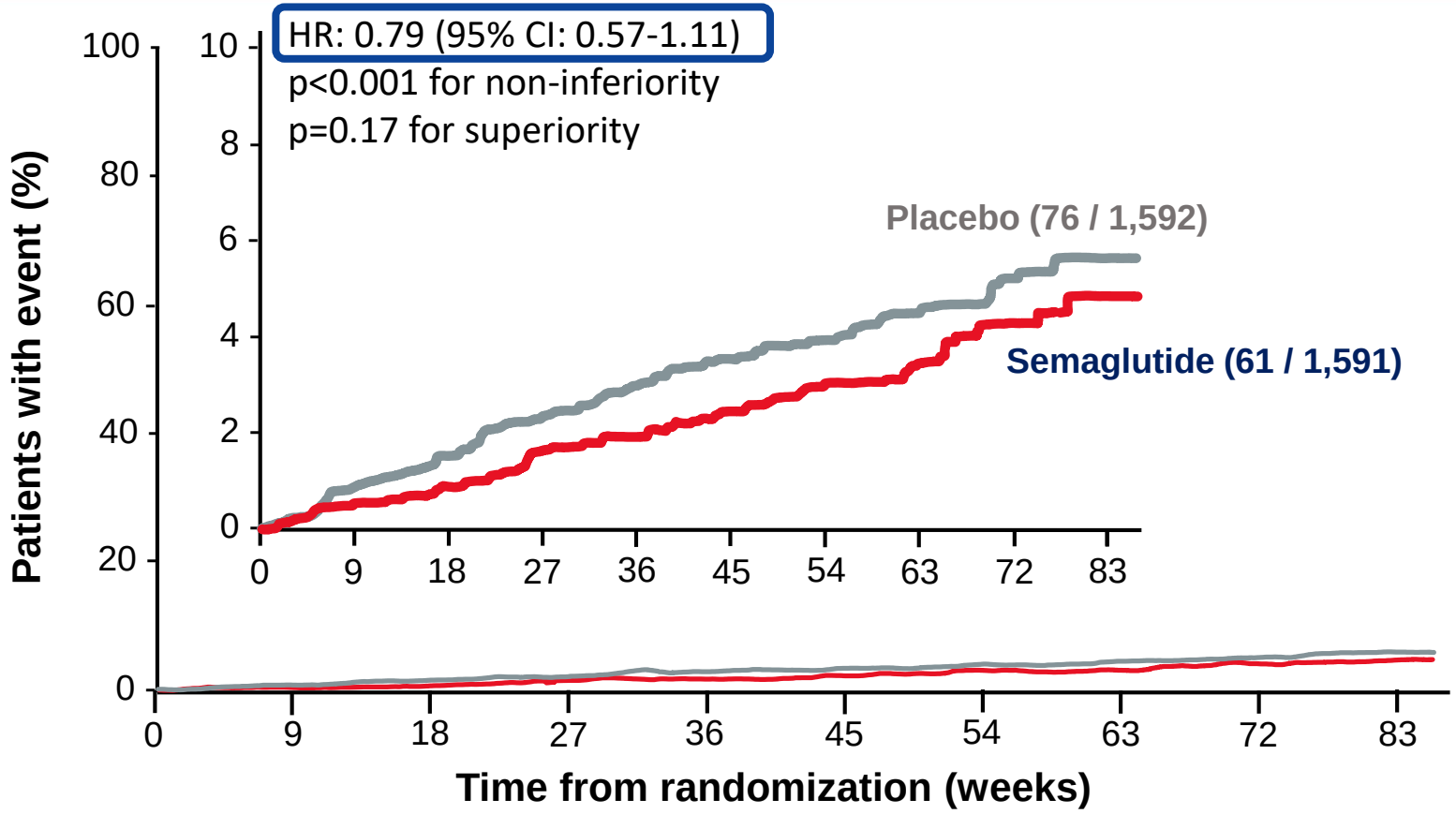
Median time to follow-up: 1.3 years
Mean age: 66 years
Mean BMI: 32.6 kg/m^2
Previous CVD: 84.7%
Mean duration of T2DM: 14.9 years
Mean A1C: 8.2%

- **Study design:** Randomized, double-blind, placebo-controlled study
- **Primary objective:** To investigate the CV safety of oral semaglutide in subjects with T2DM

Husain M, et al. *N Engl J Med.* 2019;381(9):841-51.

PIONEER-6: Primary Outcome

First Occurrence of MACE
(CV Death, Nonfatal MI, or Nonfatal Stroke)



CI upper limit < 1.3
Semaglutide met the non-inferiority criterion

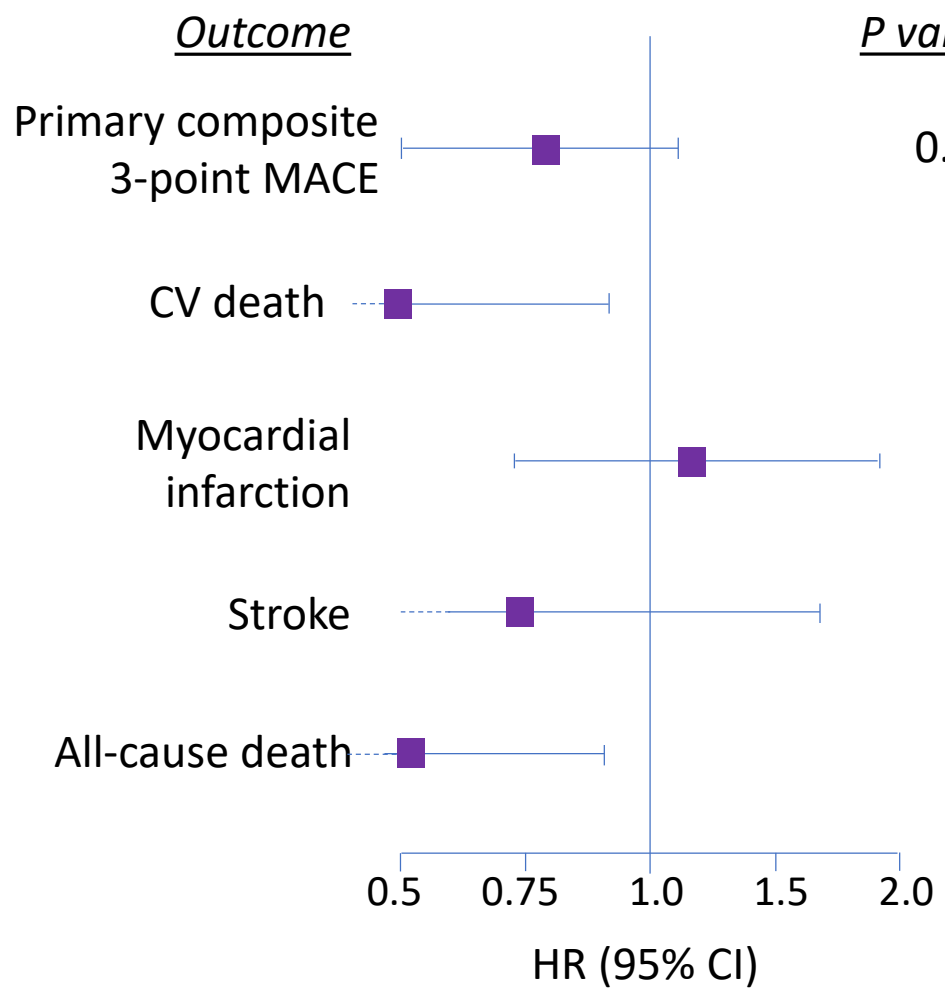
CI upper limit > 1.0
Semaglutide did not demonstrate superiority vs. placebo

No. at risk

Semaglutide	1591	1583	1575	1564	1557	1547	1512	1062	735	16
Placebo	1592	1577	1565	1551	1538	1528	1489	1032	713	11

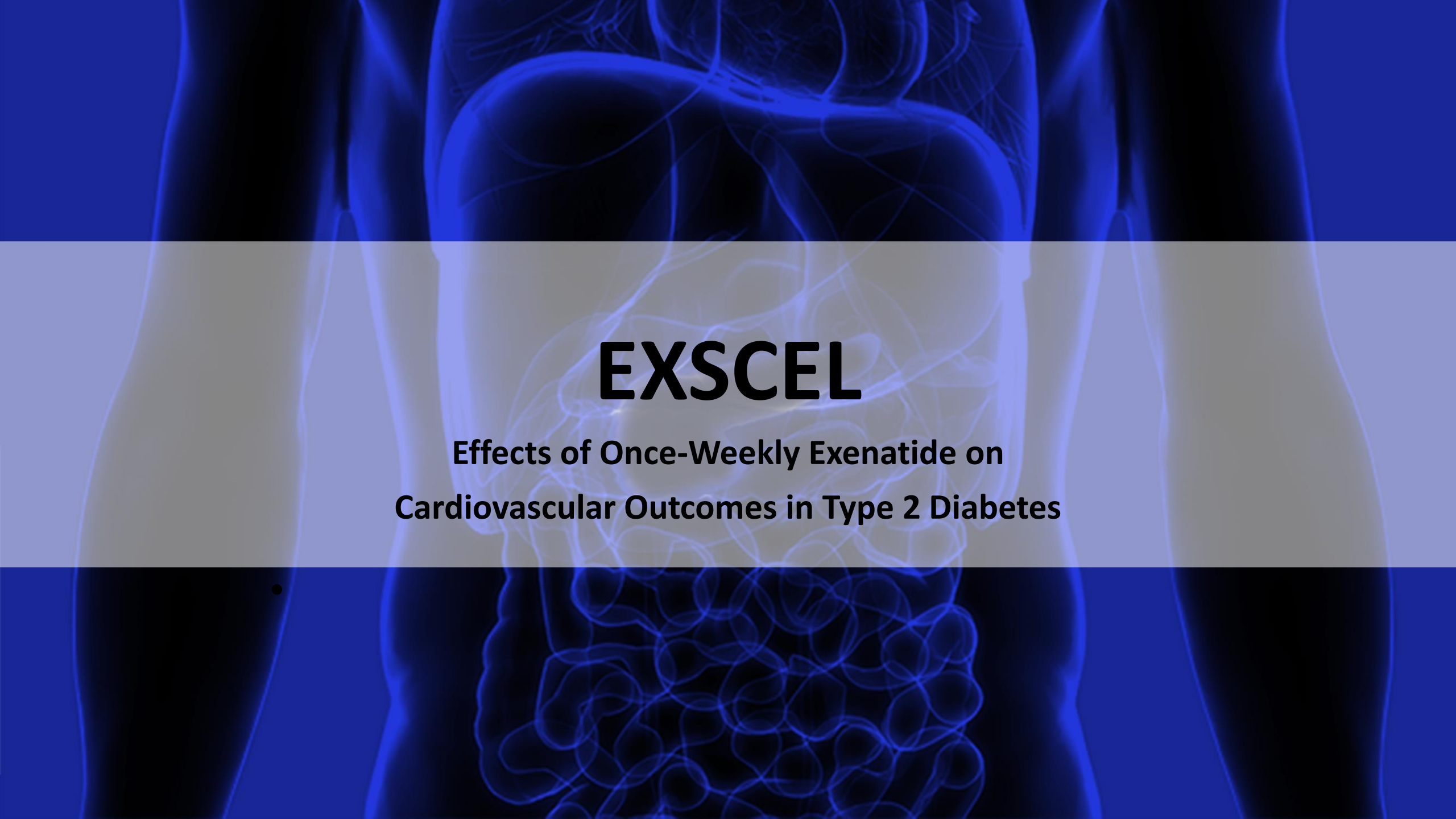
Husain M, et al. *N Engl J Med.* 2019;381(9):841-51.

PIONEER-6: Individual Components of 3-Pt MACE



*Not controlled for multiple comparisons; interpreted as exploratory

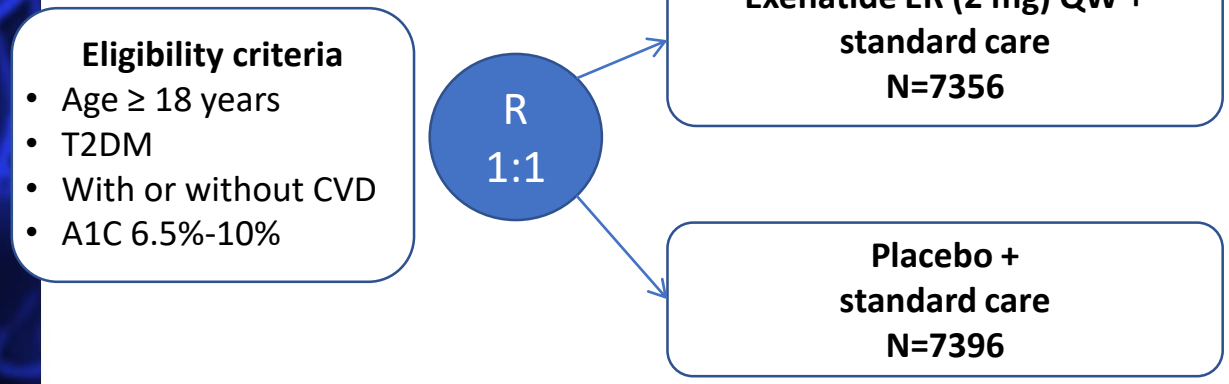
Husain M, et al. *N Engl J Med.* 2019;381(9):841-51.



EXSCEL

Effects of Once-Weekly Exenatide on Cardiovascular Outcomes in Type 2 Diabetes

EXSCEL:
Study Design, Objectives, and Enrolled Patients



Baseline characteristics

Median time to follow-up: 3.2 years
Mean age: 62 years
Mean BMI: 31.8 kg/m^2
Previous CVD: 73% (27% without)
Mean duration of T2DM: 12 years
Mean A1C: 8%

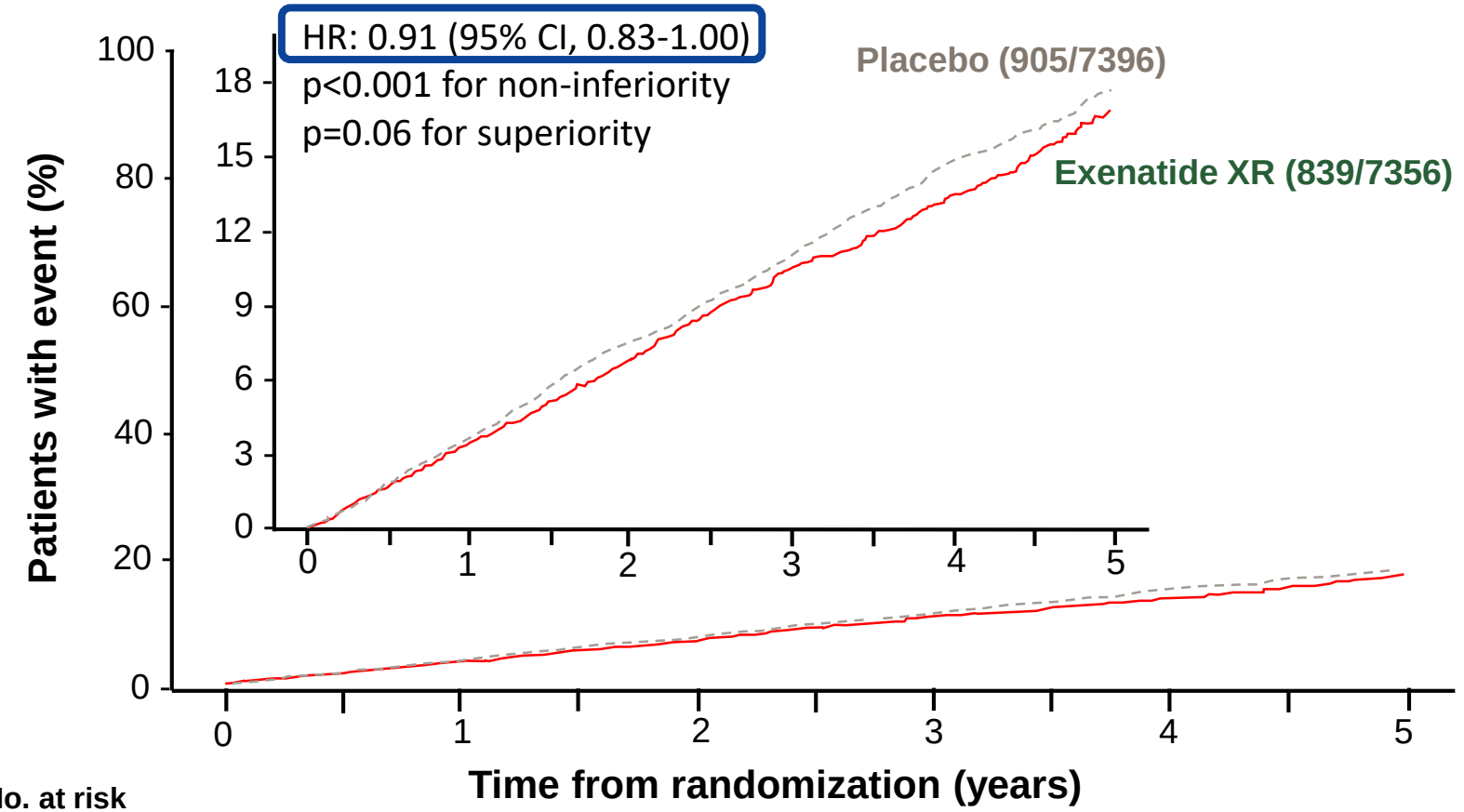
- **Study design:** International, randomized, placebo-controlled pragmatic study
- **Primary objective:** To evaluate the long-term CV safety and efficacy of once-weekly exenatide in adults with T2DM with a wide range of CV risks
- **Rate of non-completers:** 43% exenatide, 45.2% placebo
- **Outcomes resulted in change of the delivery device used to BCise**

QW, weekly.

Holman RR, et al. *N Engl J Med*. 2017;377(13):1228-39.

EXSCEL: Primary Outcome

First Occurrence of MACE
(CV Death, Nonfatal MI, or Nonfatal Stroke)



CI upper limit < 1.3
Exenatide met the non-inferiority criterion

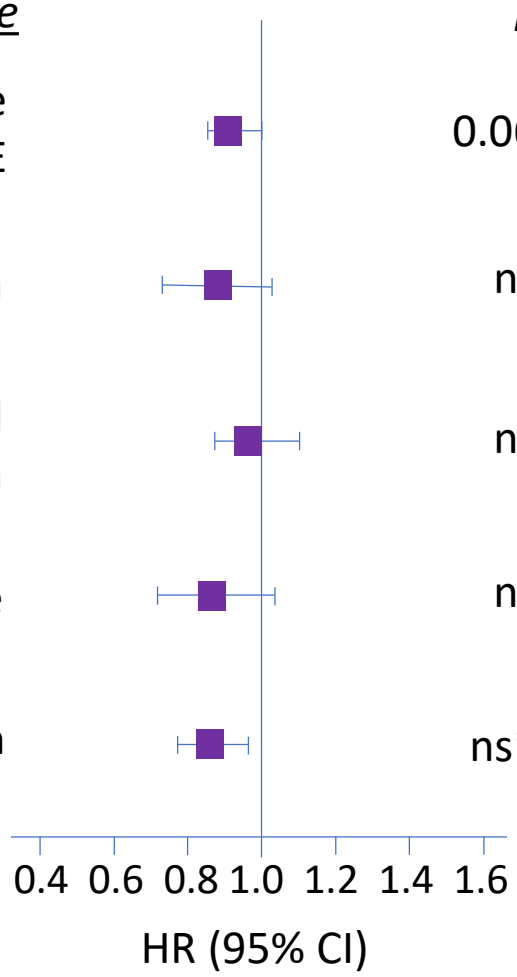
CI upper limit > 1.0
Exenatide did not demonstrate superiority vs. placebo

No. at risk											
Exenatide	7356	7101	6893	6580	5912	4475	3595	3053	2281	1417	727
Placebo	7396	7120	6897	6565	5908	4468	3565	2961	2209	1366	687

Holman RR, et al. *N Engl J Med*. 2017;377(13):1228-39.

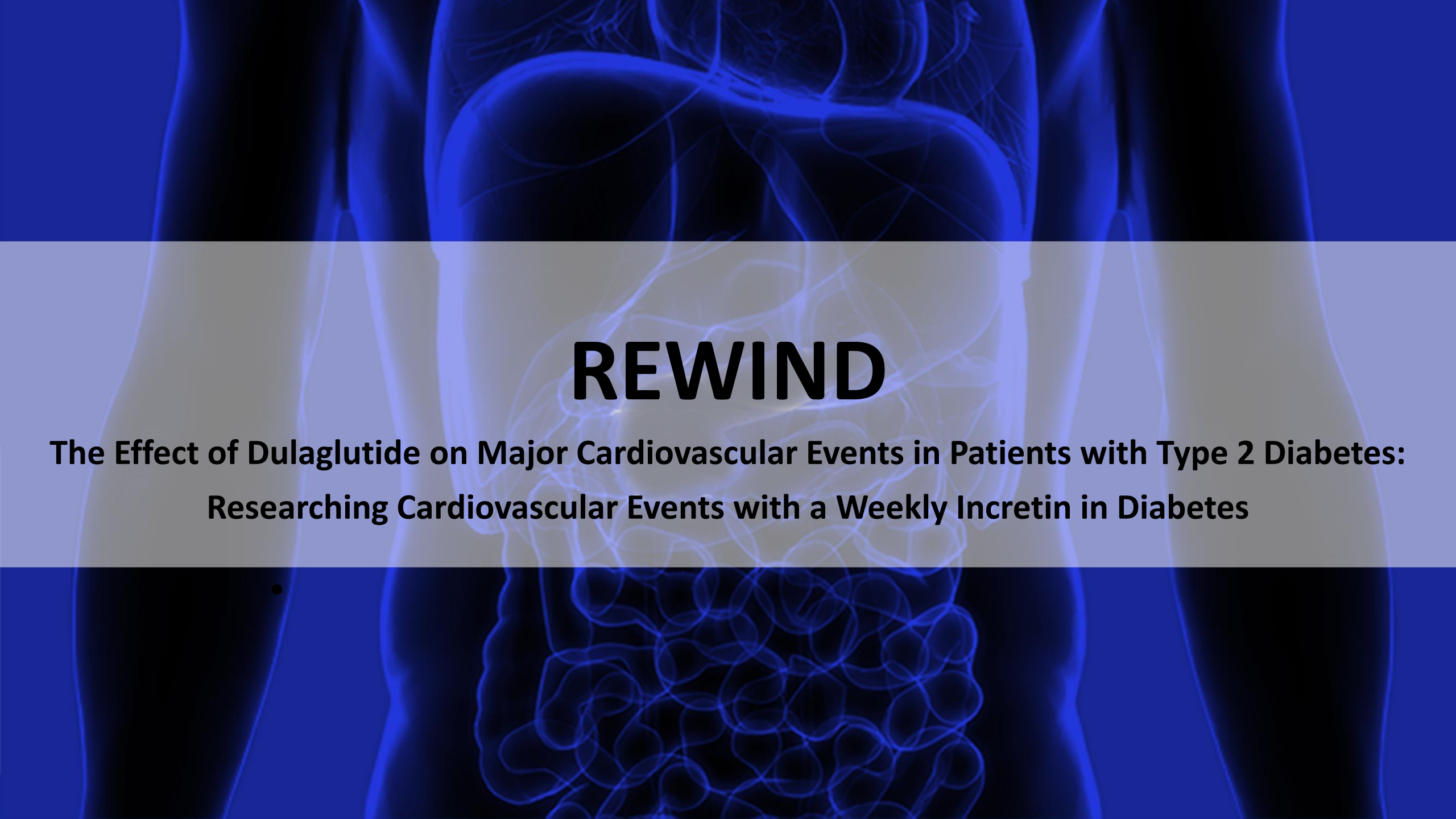
EXSCEL: Individual Components of 3-Pt MACE

Outcome	*P*	*HR (95% CI)*
Primary composite 3-point MACE	0.06	0.91 (0.83-1.00)
CV death	ns	0.88 (0.78-1.02)
Myocardial infarction	ns	0.97 (0.85-1.10)
Stroke	ns	0.85 (0.70-1.03)
All-cause death	ns*	0.86 (0.77-0.97)*



*Not statistically significant due to hierarchical testing

Holman RR, et al. *N Engl J Med*. 2017;377(13):1228-39.



REWIND

The Effect of Dulaglutide on Major Cardiovascular Events in Patients with Type 2 Diabetes: Researching Cardiovascular Events with a Weekly Incretin in Diabetes

REWIND:
Study Design, Objectives, and Enrolled Patients

Eligibility criteria

- Age ≥ 50 years
- CVD or risk factors
- T2DM
- A1C ≤ 9.5%
- Without CV or CVA event within previous 2 months
- eGFR ≥ 15 mL/min/1.73 m^2
- Excluded patients on dialysis

R
1:1

N=9901

Dulaglutide (1.5 mg) QW + standard care

Placebo + standard care

Baseline characteristics

Median time to follow-up: 5.4 years
Mean age: 66.2 years
Mean BMI: 32.3 kg/m^2
Previous CVD: 31% (69% without)
Mean duration of T2DM: 10 years
Mean A1C: 7.3%

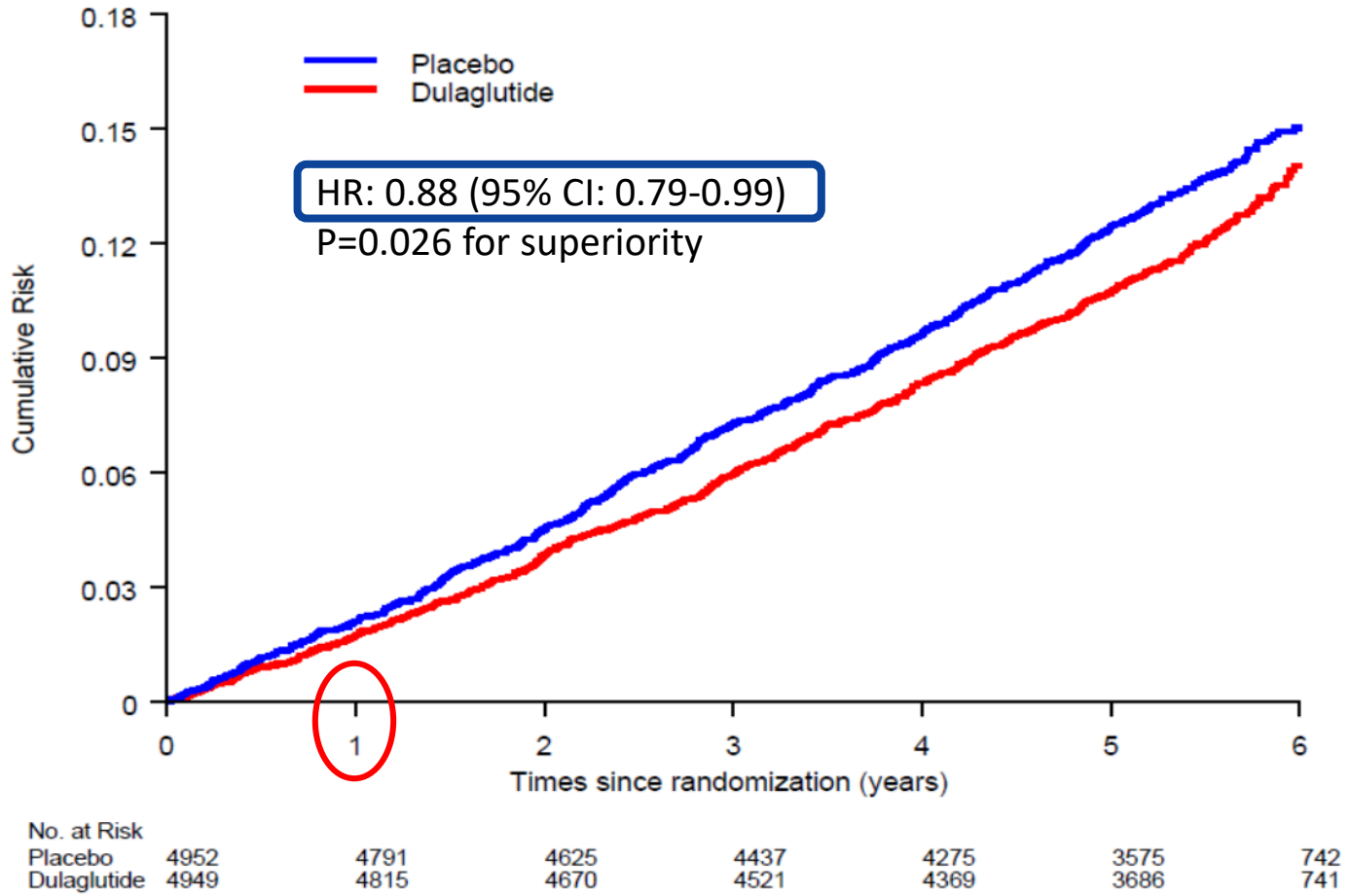
- **Study design:** International, multicenter, randomized, placebo-controlled study
- **Primary objective:** To evaluate the long-term CV safety and efficacy of once-weekly dulaglutide in adults with T2DM with a wide range of CV risks

CVA, cerebrovascular; eGFR, estimated glomerular filtration rate.

Gerstein HC, et al. *Diabetes Obes Metab*. 2018;20(1):42-9.;
Gerstein HC, et al. *Lancet*. 2019;394(10193):121-30.

REWIND: Primary Outcome

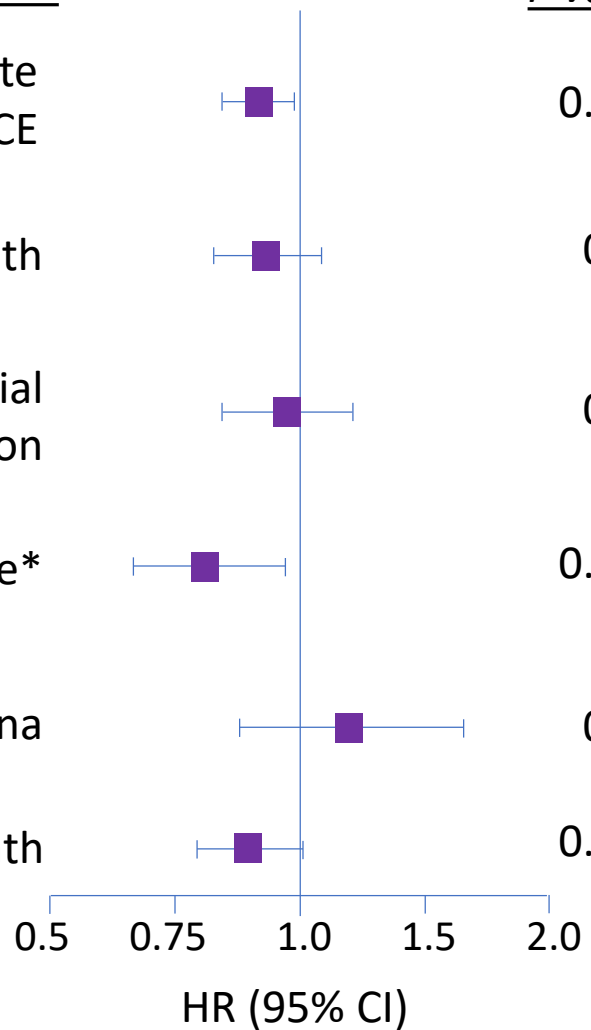
First Occurrence of MACE (CV Death, Nonfatal MI, or Nonfatal Stroke)



Gerstein HC, et al. *Lancet*. 2019;394(10193):121-30.

REWIND: Individual Components of 3-Pt MACE

Outcome	*P value*	*HR (95% CI)*
Primary composite 3-point MACE	0.026	0.88 (0.79-0.99)
CV death	0.21	0.91 (0.78-1.06)
Myocardial infarction	0.63	0.96 (0.79-1.16)
Stroke*	0.010	0.76 (0.61-0.95)
Unstable angina	0.41	1.14 (0.84-1.54)
All-cause death	0.067	0.90 (0.8-1.01)



*Not statistically significant due to alpha spreading and distribution of the p-value among secondary endpoints

Gerstein HC, et al. *Lancet*. 2019;394(10193):121-30.

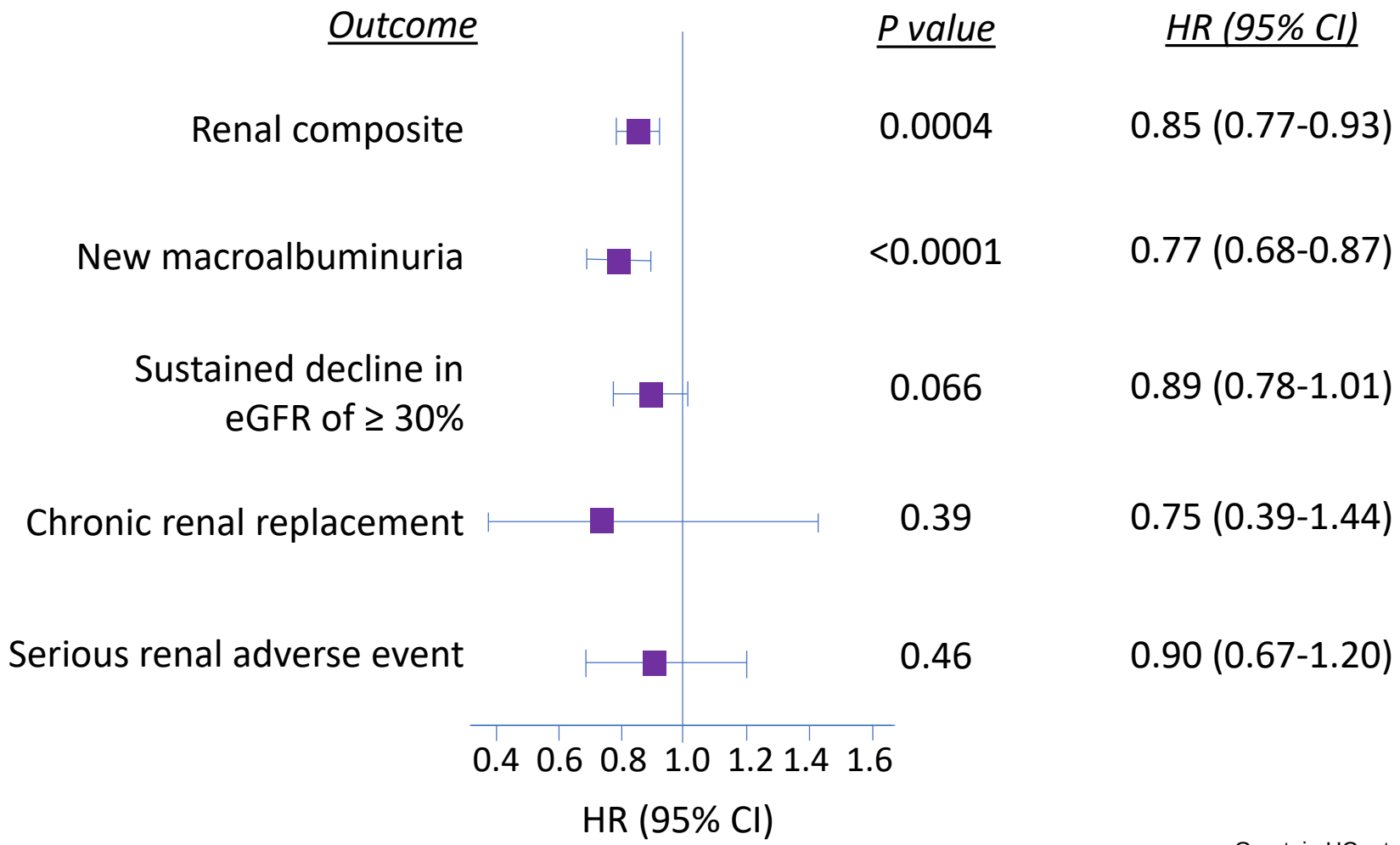
REWIND: Microvascular Outcomes

Outcome	Dulaglutide (N=4949) n (%)	Dulaglutide (N=4949) Incidence rate[a]	Placebo (N=4952) n (%)	Placebo (N=4952) Incidence rate	HR (95% CI)	p-value
Eye outcome*	95 (1.9)	0.37	76 (1.5)	0.30	1.24 (0.92-1.68)	0.16
Renal outcome^	848 (17.1)	3.47	970 (19.6)	4.07	0.85 (0.77-0.93)	0.0004

*Diabetic retinopathy defined as photocoagulation, anti-vascular endothelial growth factor therapy, or vitrectomy.
^Renal disease defined as development of a urinary albumin-to-creatinine ratio centration, a sustained 30% or greater decline in eGRF, or chronic renal replacement therapy.

Gerstein HC, et al. *Lancet*. 2019;394(10193):121-30.

Exploratory REWIND Renal Components



Gerstein HC, et al. *Lancet*. 2019;394(10193):131-8.

ARS Question 2

How can data from GLP-1 RA CVOTs best be applied to patient care?

A. Consider the enrolled population for achieving the desired outcome
B. Identify the desired outcome of interest
C. Recommend the GLP-1 RA with the most robust primary endpoint
D. Compare the numbers needed to treat and harm (NNT and NNH) when choosing the best GLP-1 RA

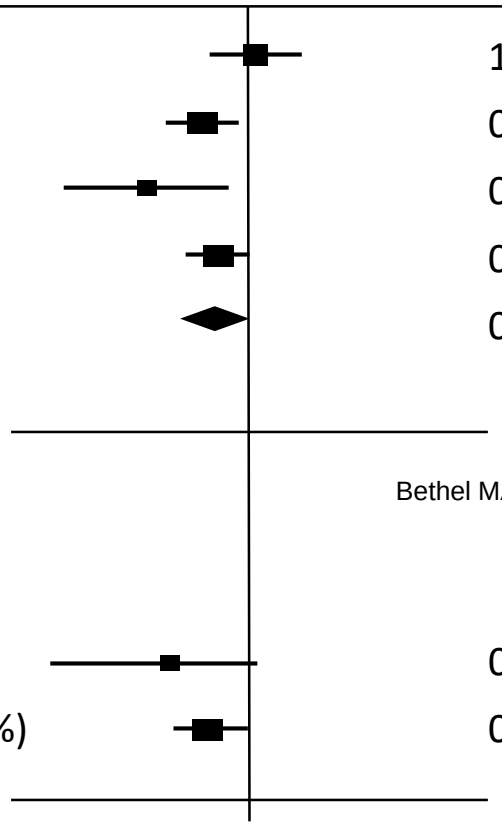
Summary of CVOTs for GLP-1 RAs

TRIAL Drug	ELIXA[1] Lixisenatide	LEADER[2] Liraglutide	SUSTAIN 6[3] Semaglutide	PIONEER 6[4] Semaglutide	EXSCEL[5] Exenatide ER	REWIND[6] Dulaglutide
Median follow-up time, y	2.1	3.8	2.1	1.3	3.2	5.4
Trial participants, n	6068	9340	3297	3183	14752	9901
Mean age, y	60.3	64.3	64.6	66	62	66
Female sex, n (%)	2894 (30.7)	3337 (35.7)	1295 (39.3)	1007 (31.6)	5603 (38.0)	4589 (46.3)
Established ASCVD, n (%)	6068 (100)	6775 (72.5)	2735 (83.0)	2695 (84.7)	10,782 (73.1)	3114 (31.5)
History of heart failure, n (%)	1922 (20.3)	1667 (17.8)	777 (23.6)	388 (12.2)	2389 (16.2)	853 (8.6)
eGFR < 60 mL/min/1.73 m^2, n (%)	1407 (23.2)	2158 (23.1)	939 (28.5)	875 (27.5)	3191 (21.6)	2199 (22.6)
Mean duration of diabetes, y	9.3	12.9	13.9	14.9	12.0	10.0
Mean baseline A1C, %	7.7	8.7	8.7	8.2	8.0	7.3

1. Pfeffer MA et al. *N Engl J Med.* 2015;373(23):2247-57.; 2. Marso SP, et al. *N Engl J Med.* 2016;375(4):311-22.; 3. Marso SP, et al. *N Engl J Med.* 2016;375(19):1834-44.;
4. Husain M, et al. *N Engl J Med.* 2019;381(9):841-51.; 5. Holman RR, et al. *N Engl J Med.* 2017;377(13):1228-39.; 6. Gerstein HC, et al. *Lancet*. 2019;394(10193):121-30.

Primary Outcome Comparison Among GLP-1 RA CVOTs

	GLP-1 RA	Placebo	MACE	HR (95% CI)	P-value
ELIXA	400/3034 (13%)	392/3034 (13%)		1.02 (0.98, 1.17)	0.776
LEADER	608/4668 (13%)	694/4672 (15%)		0.87 (0.78, 0.97)	0.015
SUSTAIN 6	108/1648 (7%)	146/1649 (9%)		0.74 (0.58, 0.95)	0.016
EXSCEL	839/7356 (11%)	905/7396 (12%)		0.91 (0.83, 1.00)	0.061
Overall				0.90 (0.82, 0.99)	0.033
Test for heterogeneity: p=0.11, I^2=50%					
PIONEER 6	61/1591 (3.8%)	78/1592 (4.8%)		0.79 (0.57, 1.11)	0.17
REWIND	594/4949 (12%)	663/4952 (13.4%)		0.88 (0.79, 0.99)	0.026

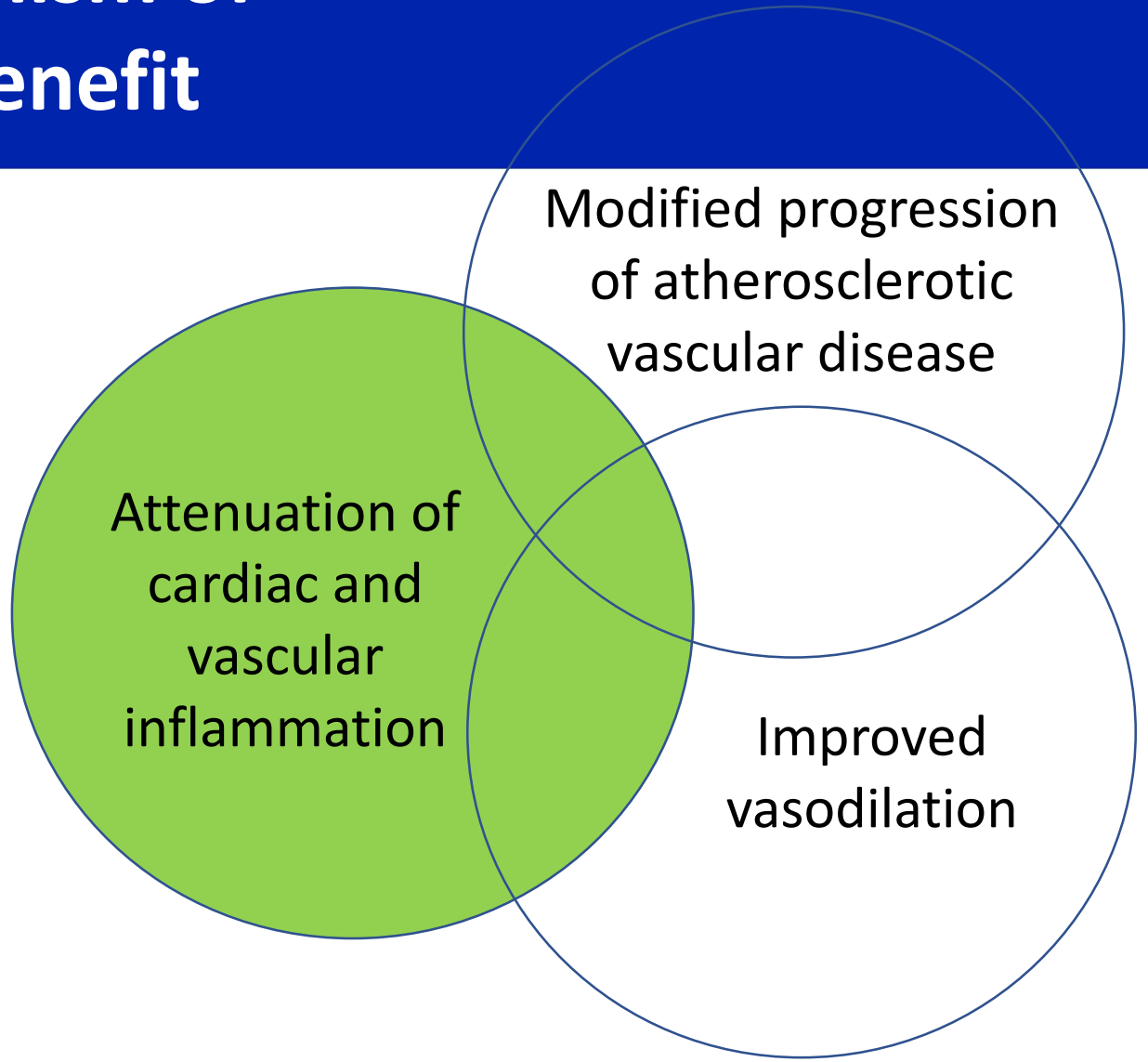


Bethel MA, et al. *Lancet Diabetes Endocrinol*. 2018;6(2):105-13.

Gerstein HC, et al. *Lancet*. 2019;394(10193):121-30.;
Husain M, et al. *N Engl J Med.* 2019;381(9):841-51.

Proposed Mechanism of GLP1-RA on CV Benefit

Time to benefit: approximately 12 months



Drucker DJ. *Cell Metab*. 2016;24(1):15-30.;
Nauck MA, et al. *Circulation*. 2017;136(9):849-70.;
Zhang Z, et al. *Cardiovasc Diabetol*. 2017;16(1):31.

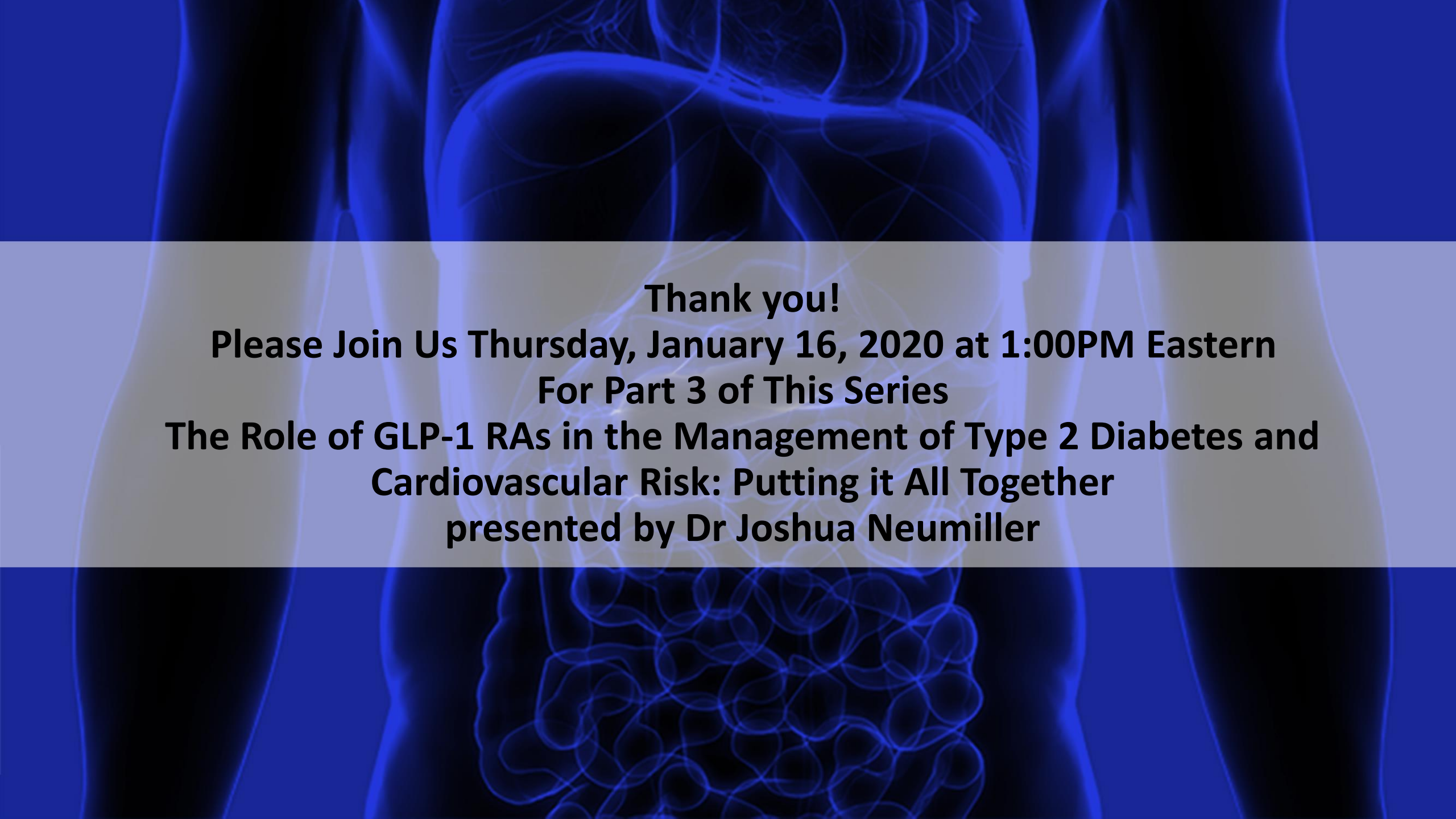
GLP-1 RAs in CVOTs: Overall Summary

- Near double risk of CVD in those living with diabetes mellitus
- Shift in trial focus from glycemic control to CV safety for new T2DM medications
- Studied populations expanded to include:
  - Longer-standing T2DM
  - Higher baseline CV risk
  - Decreased renal function
- ALL CVOTs for GLP-1 RAs have proven CV safety
- Some GLP-1 RAs associated with improved lower CV event risk in studied populations
  - Liraglutide (Victoza)
    - New FDA indication
  - Semaglutide (Ozempic)
  - Dulaglutide (Trulicity)
- Selective GLP-1 RA use provides benefit
  - Improved glycemic control
  - Reduced risk of MACE
  - Possibly provide improved renal protection

Conclusions

- Clear benefit of CV risk reduction in patients with T2DM — *with and without ASCVD* — in addition to glycemic benefit
- In-depth analysis of CVOT allows for connecting the patient in the study to YOUR patient
- What comes next…
  - Will class effects on CV safety/benefit be concluded for long-acting GLP-1 RA?
  - Will other GLP-1 RAs gain FDA-approved CV indications?
  - What is the impact of combining SGLT2 inhibitor and GLP-1 RA therapy?
  - Will there be more oral GLP-1 RAs or possibly new oral GLP-1 RA combination medications?
  - How will patient preference influence use of oral versus injectable GLP-1 RAs?
  - Will there be a role for these medications in patients with type 1 diabetes and ASCVD?
  - How will the new CVOT data impact guidelines?


Question & Answer



Thank you!

Please Join Us Thursday, January 16, 2020 at 1:00PM Eastern

For Part 3 of This Series

The Role of GLP-1 RAs in the Management of Type 2 Diabetes and Cardiovascular Risk: Putting it All Together

presented by Dr Joshua Neumiller