Oral Semaglutide for Type 2 Diabetes: Effectiveness and Value

Public Meeting — November 14, 2019

ICER
INSTITUTE FOR CLINICAL AND ECONOMIC REVIEW

WIFI: Brown-Guest
Password: not required

Why are we here today?

It is really hard to live with diabetes. I have to watch what I eat and I’m worried that my arms and legs and feet will never be back to normal. Only muscle relaxers make me able to walk. I will do anything to try to prevent the damage.

Steven Hadfield

Why are we here today?

When I was diagnosed in 2016, I immediately felt discouraged, and like I wasn't being heard. I was handed a few bottles of medication and insulin, without much explanation of what they would do and told to come back in three months, without understanding my targets, or even how to take an insulin injection. Naturally, I failed. My A1c barely budged, and I was frustrated about having diabetes without much guidance.

Mila Buckley

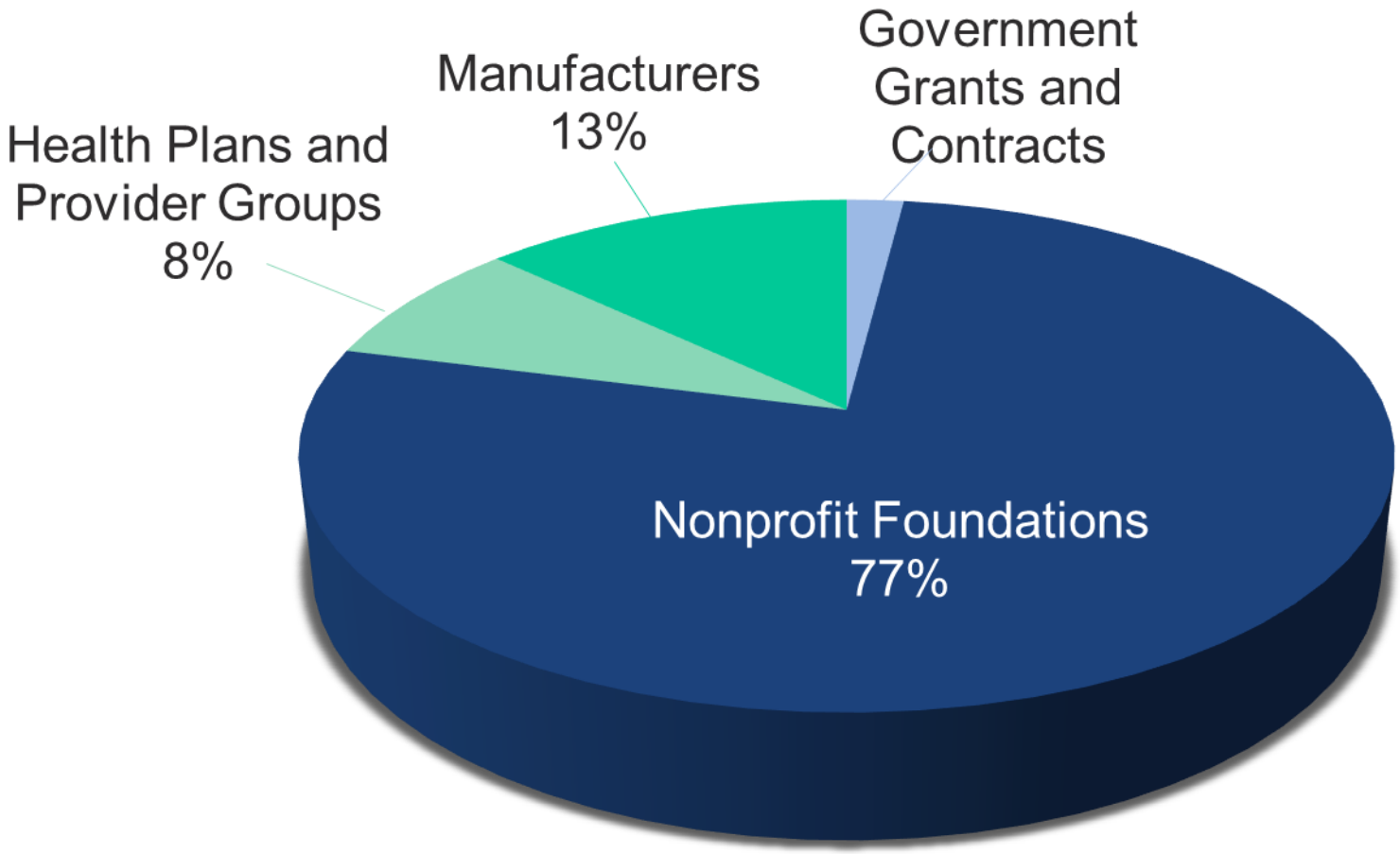
Why Are We Here Today?

- What happens the day these treatments are approved by the FDA?
- The historical context and the challenge we all face today
- Patients can have difficulty accessing drugs
- The goals for today's meeting

Organizational Overview

- New England Comparative Effectiveness Public Advisory Council
- The Institute for Clinical and Economic Review (ICER)

2019 Funding Sources

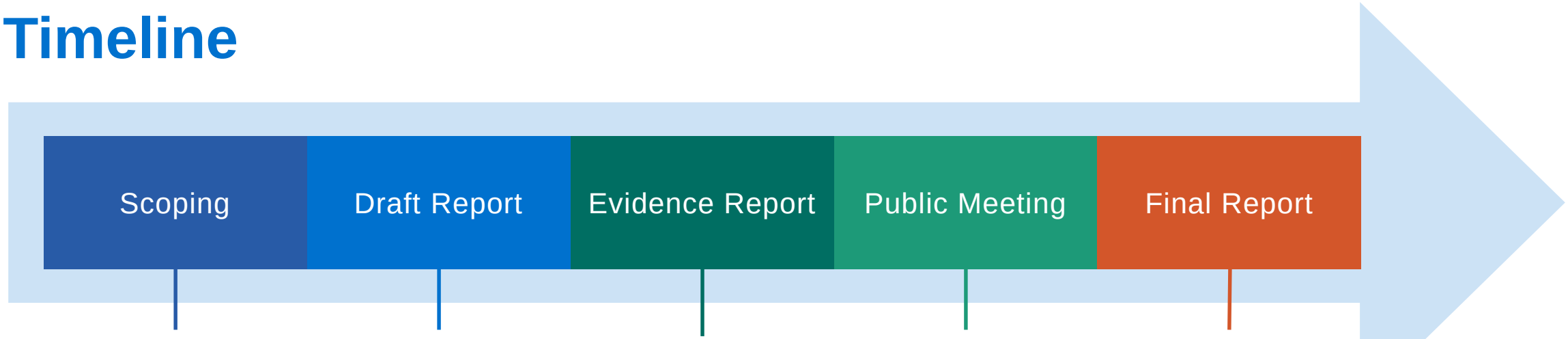


ICER Policy Summit and Non-Report activities only

How was the ICER report developed?

- Scoping with guidance from patient groups, clinical experts, manufacturers, and other stakeholders
- Internal ICER staff evidence analysis
- University of Washington cost-effectiveness modeling
- Public comment and revision
- Expert reviewers
  - Samar Hafida, MD, Staff Endocrinologist, Joslin Diabetes Center
  - Joanna Mitri, MD, MS, Staff Endocrinologist, Joslin Diabetes Center
  - Elizabeth Murphy, MD, DPhil, Chief, Division of Endocrinology and Metabolism, San Francisco General Hospital, UCSF
- How is the evidence report structured to support CEPAC voting and policy discussion?

Timeline



Introductory scoping calls with manufacturers, clinical experts, patient groups, clinical societies and insurers.

Public comment period after draft scope is posted.

Posting of model analysis plan.

Individual discussion calls with manufacturers.

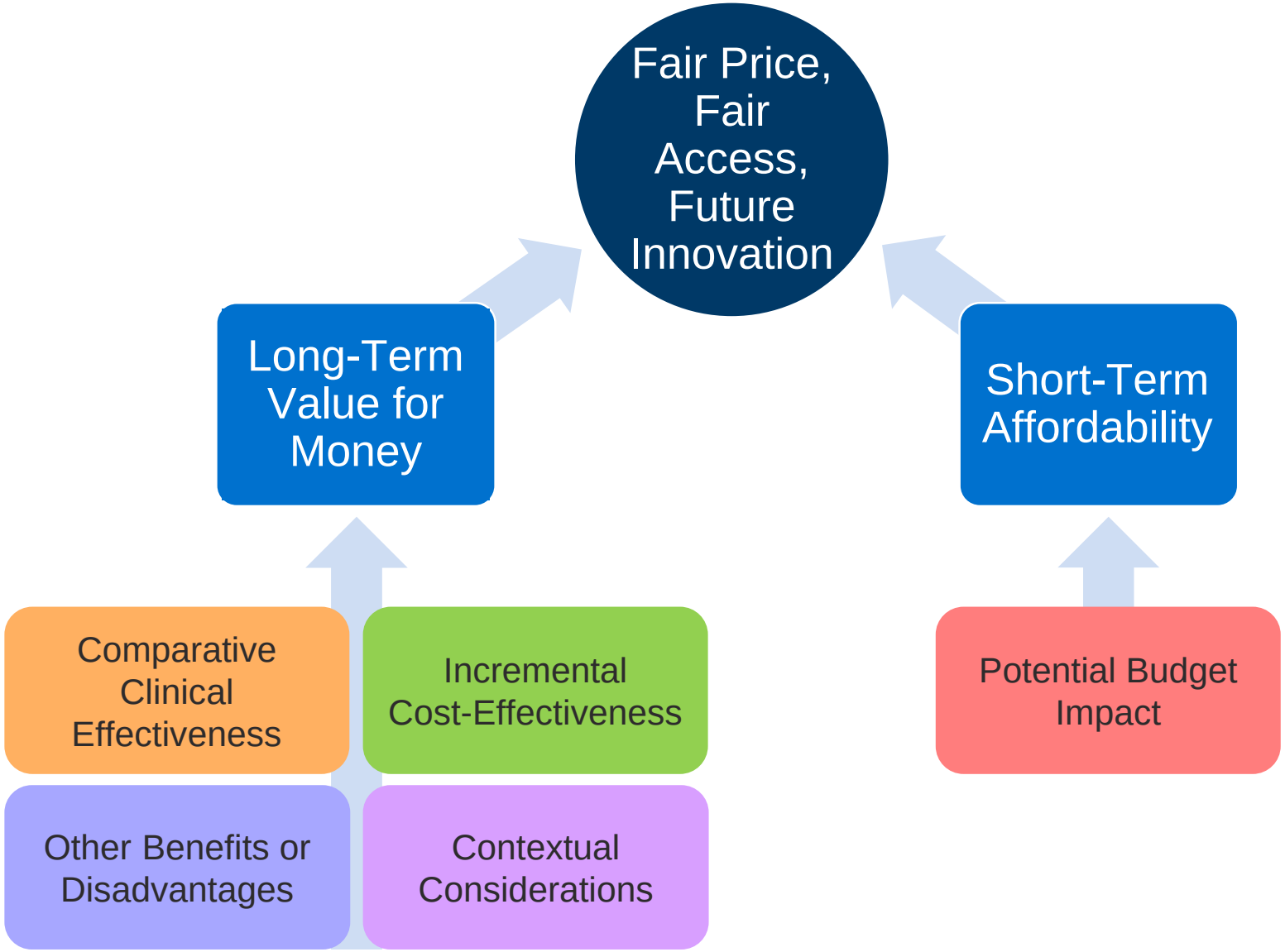
Opportunity for public comment.

Revision of review based on public input.

Deliberation of cost-effectiveness evidence to the public.

CEPAC panel votes on cost-effectiveness.

Final report is posted.



Agenda

10:00	Meeting Convened and Opening Remarks
10:15	Presentation of the Evidence
11:20	Manufacturer Public Comments and Discussion
11:50	Public Comments and Discussion
12:00	Lunch
1:00	New England CEPAC Panel Deliberation and Vote
2:15	Break
2:30	Policy Roundtable Discussion
3:45	Reflections from New England CEPAC Panel
4:00	Meeting Adjourned

Clinical and Patient Experts

Susan Weiner, MS, RDN, CDE, FAADE

Scientific Council Member, Beyond Type 2

Disclosures
- *No conflicts of interest to disclose.*

Elizabeth Murphy, MD

Chief, Division of Endocrinology and Metabolism, San Francisco General Hospital, UCSF

Disclosures
- *No conflicts of interest to disclose.*

Joanna Mitri, MD

Staff Endocrinologist, Joslin Diabetes Center

Disclosures
- *Received research support and non-branded speaking support from the National Dairy Council, as well as research support from the National Institutes of Health, Kowa Pharmaceutical Co., and the Juvenile Diabetes Research Foundation.*

Evidence Review

David M. Rind, MD

Chief Medical Officer

ICER

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Key Collaborators

- **Katherine Fazioli**, Research Lead, ICER
- **Eric Borrelli**, Evidence Synthesis Intern, ICER

Disclosures:

We have no conflicts of interest relevant to this report.

Prevalence

- In the US, ~30 million people with diabetes mellitus, 95% with type 2 DM
  - Estimated annual cost in 2012: $245 billion
  - Estimated hospitalizations in patients with DM in 2014: 7.2 million

What is Diabetes?

- “Diabetes mellitus” → excessive sweet urine
- Symptomatic condition with weight loss, electrolyte abnormalities, and death
- Yet, in type 2 DM:
  - Many patients without increased urine
  - Many patients not “spilling” sugar: A1c of almost 9% before blood glucose above 200 mg/dL
  - Many patients asymptomatic

Type 2 Diabetes

- Can be a condition with symptoms from very elevated glucose
- For many patients, though, it is a risk factor:
  - Macrovascular disease
    - Coronary disease and angina and myocardial infarction
    - Cerebrovascular disease and stroke
    - Peripheral vascular disease and claudication, infections, and amputations
  - Microvascular disease
    - Renal disease leading to end stage disease requiring dialysis and transplant
    - Retinal disease leading to blindness
    - Neurologic disease leading to numbness, injury, infection, and pain

Diagnosing and Monitoring Diabetes

- Diabetes is defined by various measures of blood glucose:
  - Fasting blood glucose (BG) ≥126 mg/dL
  - Glycated hemoglobin (percentage A1c) ≥6.5%
- BG and A1c also used to monitor treatment effectiveness
- Both are surrogate outcomes in asymptomatic patients with T2DM
  - Therapies could decrease glucose and increase risk (and risk factors such as weight gain)
  - Therapies that do not lower glucose as much could decrease risk

Cardiovascular Risk and Treatment for Diabetes

- Thiazolidinediones raised concerns about increased cardiac events, highlighting issues of surrogate outcomes
- In 2008, FDA mandated cardiovascular outcomes trials (CVOTs) with “hard” endpoints for new anti-diabetes treatments
- Intent was to ensure these agents were safe
- Result was that some agents found to lower risk of patient-important outcomes out of proportion to A1c reductions

What Does It Mean to Have T2DM?

- For many patients, initial impact is around being diagnosed and treated
  - Fears
  - Frequent testing
  - Multiple medications
  - Costs
- Over time, the severe macrovascular and microvascular complications of diabetes may dominate

Management

- First line management is based on “lifestyle changes” involving increased physical activity and changes in diet
- First line medication is generally metformin: does not lead to weight gain or hypoglycemia when used as single agent
- Additional options include:
  - Oral agents: sulfonylureas (SU); thiazolidinediones (TZD); **sodium-glucose cotransporter 2 inhibitors (SGLT-2i)**; **dipeptidyl peptidase-4 inhibitors (DPP-4i)**
  - Injectable agents: **glucagon-like peptide 1 receptor agonists (GLP-1 RA)**; insulin

2019 ADA Guidelines

- For second line medication therapy after metformin:
  - SGLT-2i or GLP-1 RA for patients with CVD
  - SLGT-2i followed by GLP-1 RA for patients with HF or CKD
  - SGLT2i or GLP-1 RA if need to promote weight loss
  - If no CVD or CKD and need to minimize hypoglycemia, anything except a SU
  - SU or TZD if cost is a major issue

Cost is a Major Issue

- 2019 report from the CDC
  - Reviewed surveys covering 2017-2018
  - 13% of adults did not take medication as prescribed to reduce drug costs
  - 24% asked their doctors for a lower cost medication

Insights from Discussions with Patients

- Financial toxicity was reiterated; one older patient described working many hours per week to qualify for employer-based insurance
- Complexity of treatment regimens is difficult, particularly with complex insulin regimens
- Stress of monitoring dietary intake and monitoring blood glucose
- Discomfort of frequent glucose monitoring and of injections
- Fear of organ damage from diabetes
- Pain of living with neuropathy

Scope of Review

- New GLP-1 RA: oral semaglutide
  - Injectable semaglutide available since 2017
- Semaglutide is the first oral GLP-1 RA
  - All other classes (except insulin) are oral
- Compare with:
  - Injectable GLP-1 RA
  - SGLT-2i
  - DPP-4i

Clinical Evidence

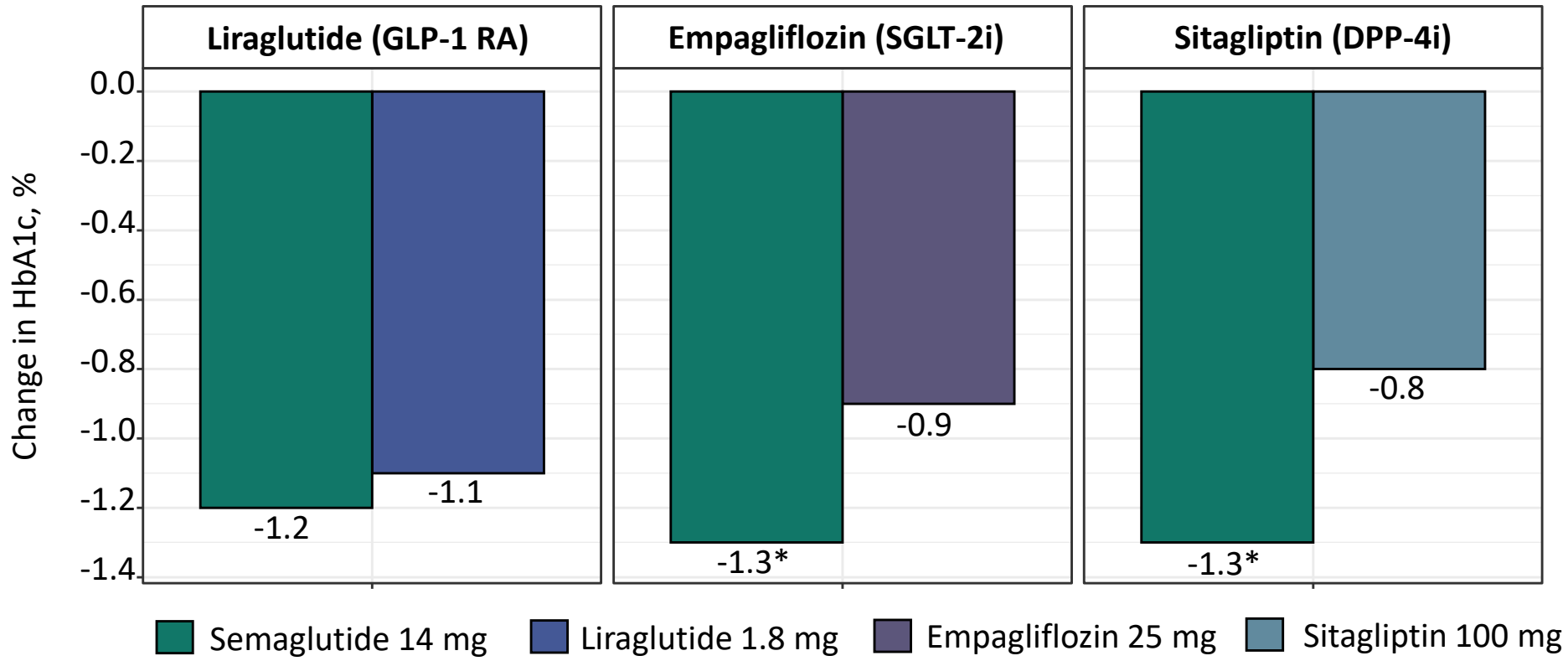
Available Evidence

- PIONEER program studying oral semaglutide
  - Comparators include:
    - Liraglutide (daily injectable GLP-1 RA)
    - Sitagliptin (DPP-4i)
    - Empagliflozin (SGLT-2i)
    - Placebo
- CVOTs of all agents and also injectable semaglutide
  - CVOT of oral semaglutide was short (1.3 years)

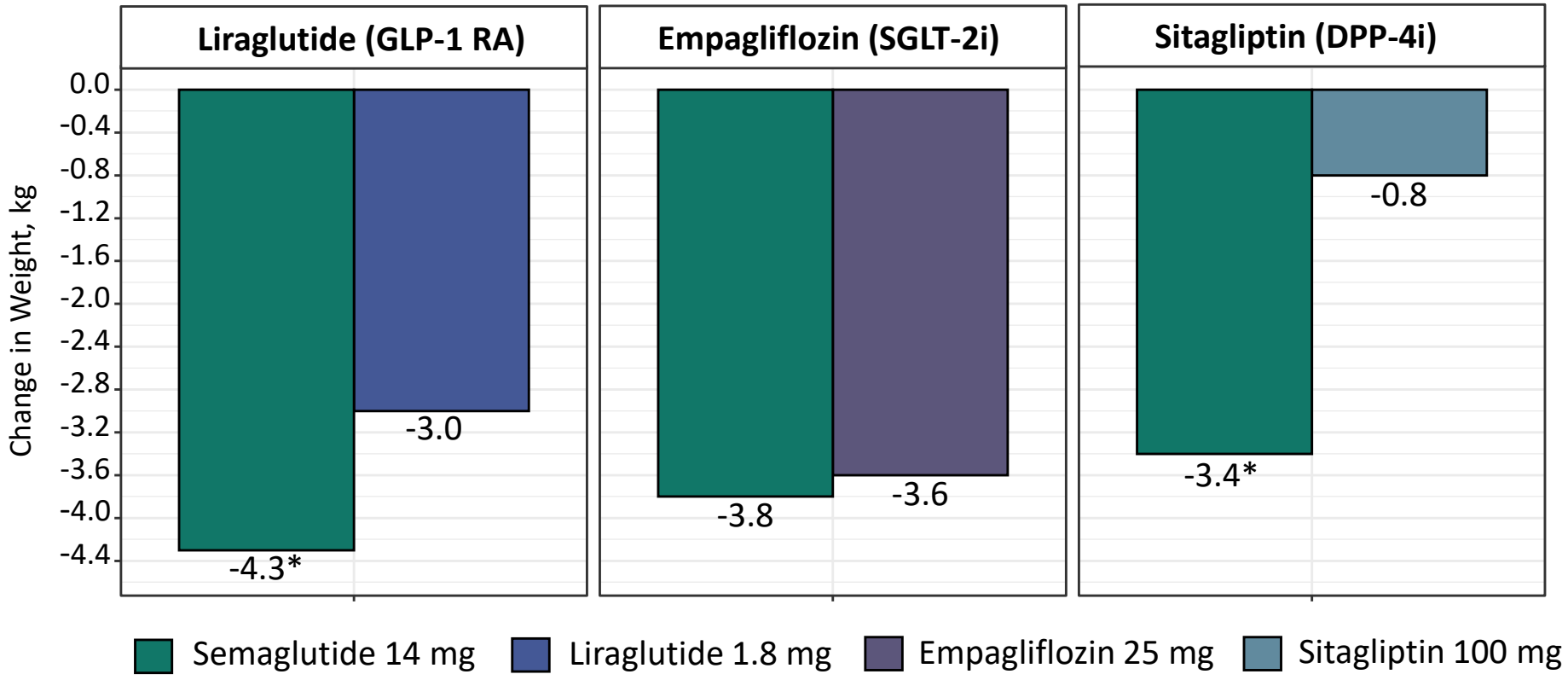
Outcomes

- Head-to-head clinical trials
  - Glycemic control
  - Weight change
  - Adverse events
- CVOTs
  - Cardiac and CV outcomes
  - Renal outcomes
  - Indirect requiring NMA
    - NMA combined oral and injectable semaglutide

Results from Head-to-Head PIONEER Trials: Change in HbA1c at 26 Weeks



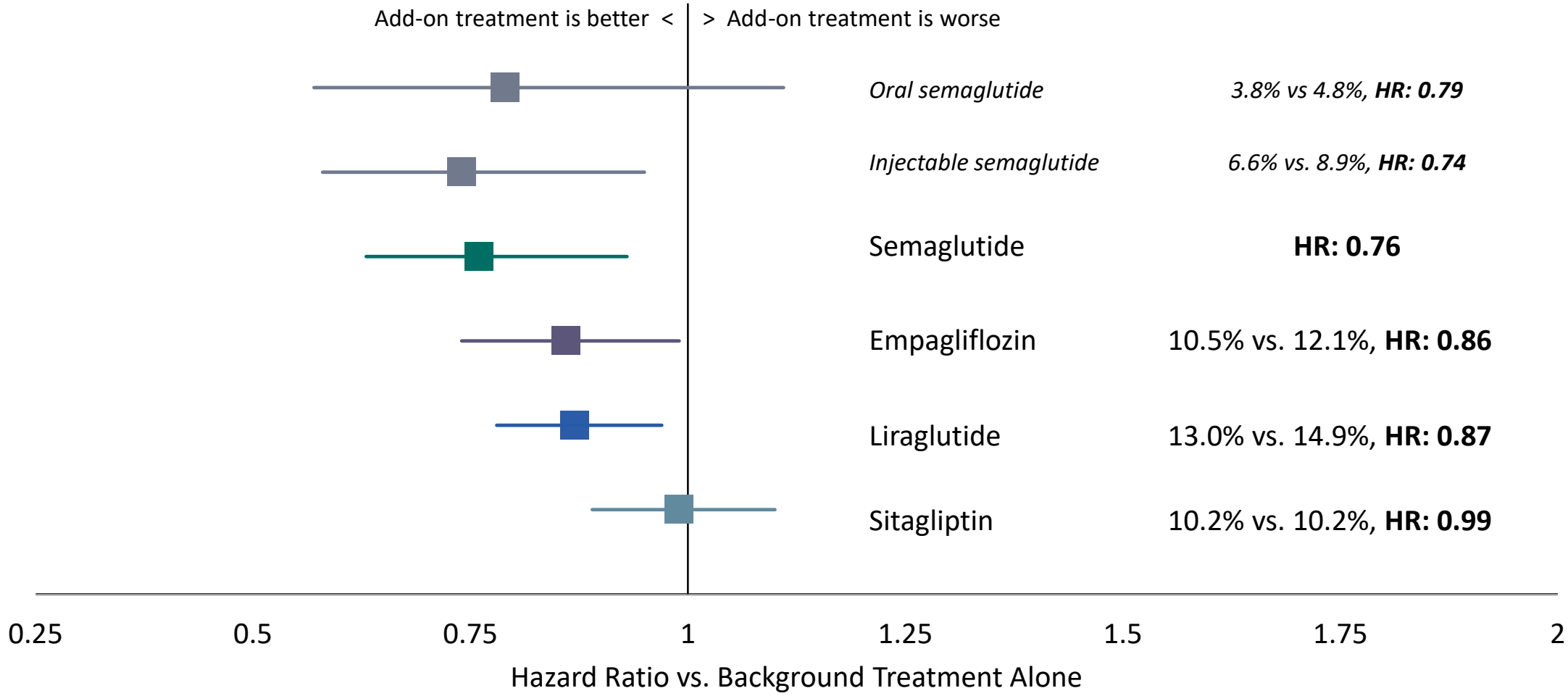
Results from Head-to-Head PIONEER Trials: Change in Weight at 52 Weeks



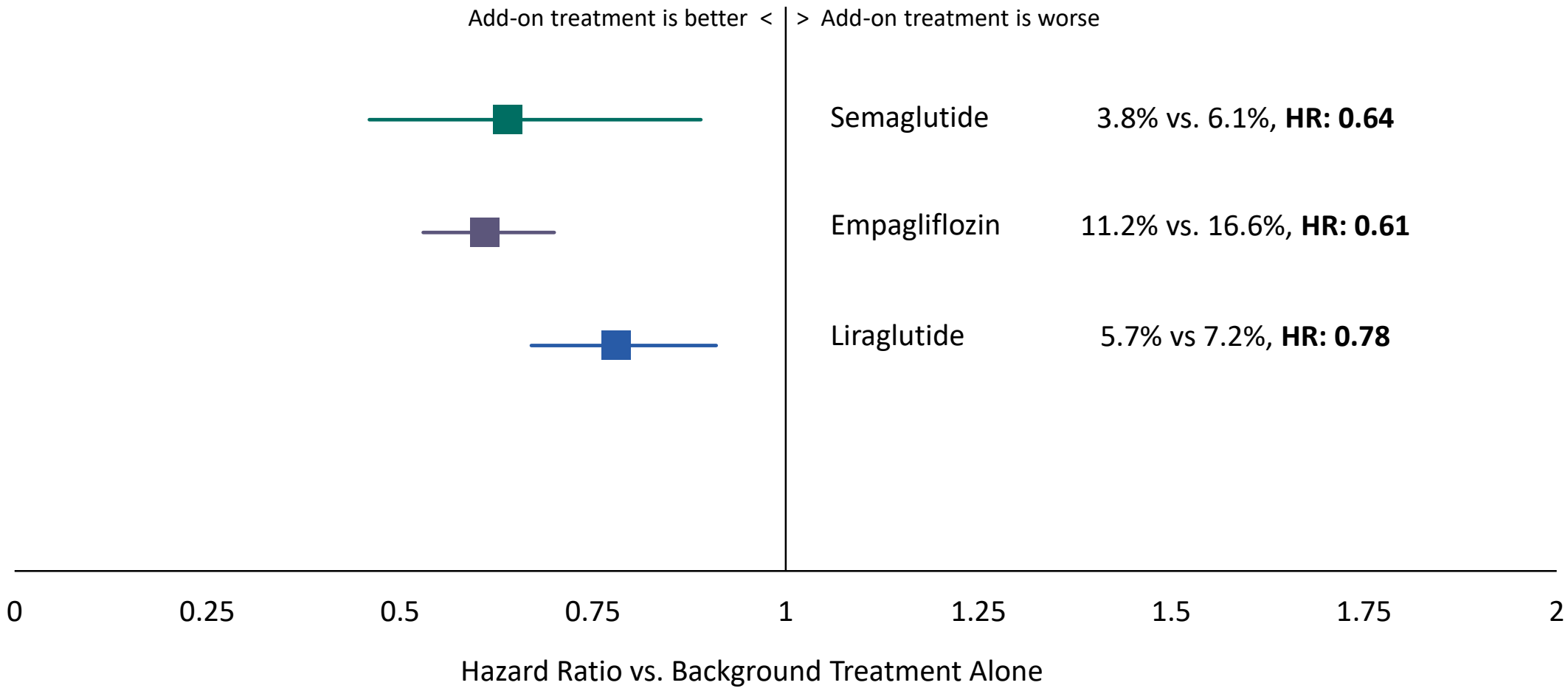
CVOTs

Drug	N	Median Follow-Up
Oral Semaglutide	3183	1.3 years
Injectable Semaglutide	3297	2.1 years
Liraglutide	9340	3.8 years
Empagliflozin	7020	3.1 years
Sitagliptin	14671	3.0 years

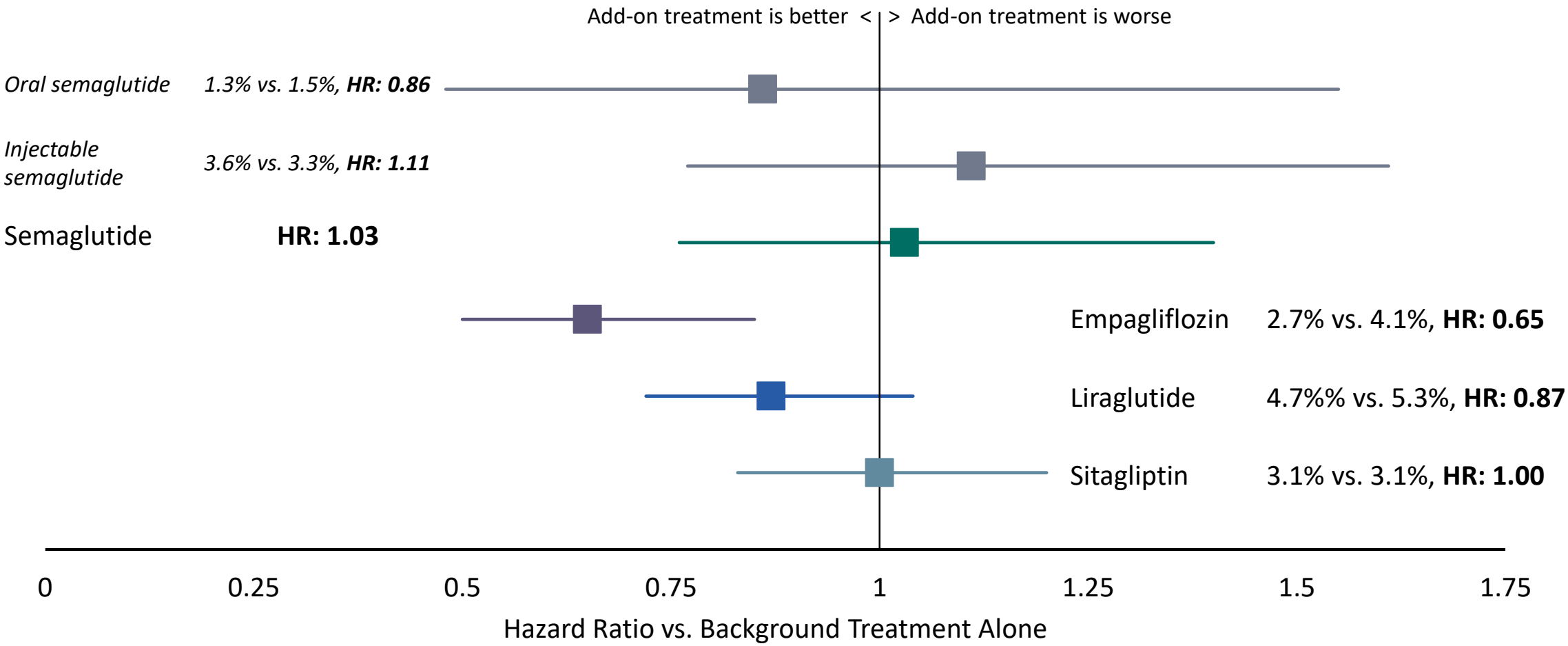
Rates and Hazard Ratios for 3-Point MACE



Rates and Hazard Ratios for Nephropathy



Rates and Hazard Ratios for Hosp. for Heart Failure



Limitations of NMA

- Wide confidence intervals where small differences may be important
- Combined oral and injectable semaglutide
- Entry and exclusion criteria not identical across trials
  - Is there effect modification?

Quality of Life and Other Patient Reported Outcomes

- Variable reporting across the trials
- No consistent QoL benefits for semaglutide versus comparators

Harms

- Gastrointestinal side effects common with GLP-1 RAs
  - Discontinuation for GI AE higher with semaglutide than for empagliflozin (8% vs. 0.7%) or sitagliptin (6.9% vs. 2.6%)
- May be more AEs related to diabetic retinopathy with semaglutide than placebo (7.1% vs. 6.3%)
- SGLT-2i increase rates of minor genitourinary infection in women

Controversies and Uncertainties

- Imprecision in NMA results, particularly comparing semaglutide and empagliflozin on MACE and nephropathy
- Do the comparators represent the underlying classes?
- Adherence in clinical trials is better than in the real world
  - Semaglutide has GI side effects
  - Oral semaglutide has complex initiation regimen and must be taken on an empty stomach
- Rare harms may affect decision making
  - Genitourinary infections, DKA, and limb amputations with SGLT-2i
  - Thyroid tumors with GLP-1 RA

Potential Other Benefits and Contextual Considerations

- Oral GLP-1 RA
  - No pain of injection
  - Treatment for patients who refuse injections
  - Does not require refrigeration like many injectable treatments for T2DM

Public Comments Received

- Real world adherence
- Uncertainties in results
- Variation in individual CVOT outcomes between oral and injectable semaglutide

Summary of Oral Semaglutide Comparisons

- Injectable GLP-1 RA (Liraglutide)
  - Seems to reduce A1c and weight more than liraglutide
  - Point estimates on MACE favor semaglutide but with wide confidence intervals.
  - **“P/I”: Promising but inconclusive**
- SGLT-2i (Empagliflozin)
  - Reduces A1c more than empagliflozin
  - Both drugs have similar effects on weight
  - MACE reduction may be better than empagliflozin but with wide confidence intervals
  - Empagliflozin reduces hospitalization for HF more than semaglutide
  - Both drugs seem to have similar effects on nephropathy
  - Discontinuation higher with semaglutide and GI side effects much more common
  - Rare, severe genitourinary infection risk with empagliflozin could affect patient decision making
  - **“I”: Insufficient**

Summary of Oral Semaglutide Comparisons (continued)

- DPP-4i (Sitagliptin)
  - Reduces A1c, weight, MACE, and probably nephropathy more than sitagliptin
  - Sitagliptin is better tolerated
  - **“B+”: Incremental or better**
- Background therapy
  - Reduces A1c, weight, MACE, and probably nephropathy compared with continued background therapy
  - **“A”: Superior**

Questions?

Cost-Effectiveness

Greg Guzauskas, MSPH, PhD

Senior Research Scientist

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Disclosures:

Financial support was provided to the University of Washington from the Institute for Clinical and Economic Review.

University of Washington researchers have no conflicts to disclose defined as more than $10,000 in health care company stock or more than $5,000 in honoraria or consultancies relevant to this report during the previous year from health care technology manufacturers or insurers.

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Objective

To estimate the lifetime cost-effectiveness of oral semaglutide (Rybelsus®, Novo Nordisk) added to background treatment for the treatment of type 2 diabetes mellitus (T2DM) versus:

- Sitagliptin (Januvia®, Merck) added to ongoing background treatment
- Empagliflozin (Jardiance®, Boehringer Ingelheim and Eli Lilly) added to ongoing background treatment
- Liraglutide (Victoza®, Novo Nordisk) added to ongoing background treatment
- Ongoing background antihyperglycemic treatment (e.g., metformin with or without sulfonylureas) alone

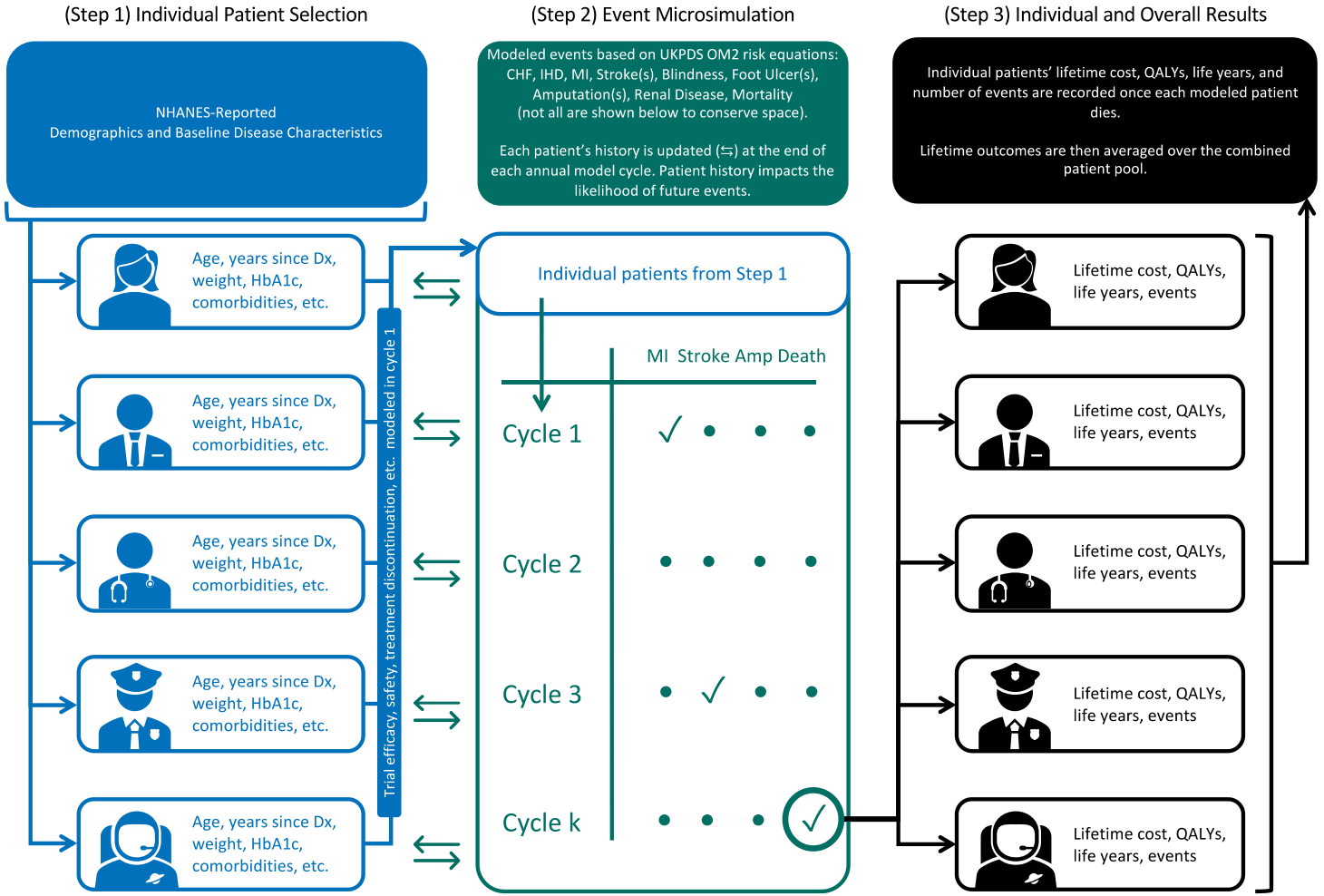
Methods in Brief

Methods Overview

- **Model**: Microsimulation adaptation of UKPDS OM2[1,2]
- **Population:** T2DM patients with inadequately HbA1c (≥7%)
- **Setting**: United States
- **Perspective**: Health care sector
- **Time Horizon**: Lifetime
- **Discount Rate**: 3% per year (costs and outcomes)
- **Cycle Length**: 1 year
- **Primary Outcomes**: Cost per quality-adjusted life year (QALY) gained
  Cost per life year (LY) gained
  Cost per major adverse cardiovascular event (MACE) avoided

1. Hayes AJ, et al. Diabetologia. 2013;56(9):1925-1933.
2. Laiteerapong N, et al. Ann Intern Med. 2018;168(3):170-178.

Model Schematic



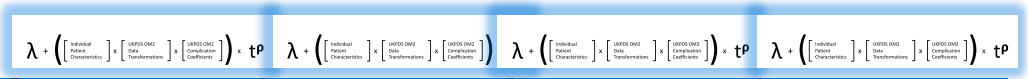
T2DM Outcomes and Mortality: UKPDS OM2[1]

$$\lambda + \left(\left[\begin{array}{c} \text{Individual} \\ \text{Patient} \\ \text{Characteristics} \end{array} \right] \times \left[\begin{array}{c} \text{UKPDS OM2} \\ \text{Data} \\ \text{Transformations} \end{array} \right] \times \left[\begin{array}{c} \text{UKPDS OM2} \\ \text{Complication} \\ \text{Coefficients} \end{array} \right] \right) \times t^{\rho}$$

- 13 T2DM complications equations
  - heart failure, ischemic heart disease, first MI for females, first MI for males, subsequent MI, first stroke, subsequent stroke, blindness, foot ulcer, first amputation without prior ulcer, first amputation with prior ulcer, subsequent amputation, and end stage renal disease
- 4 mortality equations
  - death without history of clinical event(s), death in the year of a clinical event, death with history of clinical event(s), and death in subsequent year of prior event(s)

1. Hayes AJ, et al. Diabetologia. 2013;56(9):1925-1933.

Microsimulation Demonstration



Patient Characteristic	Patient at Baseline	Tracked Patient
Age		
BMI		
HbA1c		
MI History		
Renal History		
Ulcer History		
Dead		

Model Year	MI	Nephropathy	Ulcer	Death
Year 1				
Year 2				
Year 3				
Year 4				
Year 5				
Year 6				
Year 7…				

Microsimulation Demonstration

0 = No, 1 = Yes

Patient Characteristic	Patient at Baseline	Tracked Patient
Age	55	
BMI	34.6	
HbA1c	8.5%	
MI History	0	
Renal History	0	
Ulcer History	0	
Dead	**0**	

Model Year	MI	Nephropathy	Ulcer	Death
Year 1				
Year 2				
Year 3				
Year 4				
Year 5				
Year 6				
Year 7…				

Microsimulation Demonstration

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Year 2				
Year 3				
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Year 5				
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Year 7…				

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Dead	**0**	

Model Year	MI	Nephropathy	Ulcer	Death
Year 1 	0	0	1	0
Year 2				
Year 3				
Year 4				
Year 5				
Year 6				
Year 7…				

Microsimulation Demonstration

0 = No, 1 = Yes

Patient Characteristic	Patient at Baseline	Tracked Patient
Age	55	56
BMI	34.6	35.1
HbA1c	8.5%	8.7%
MI History	0	0
Renal History	0	0
Ulcer History	0	1
Dead	**0**	**0**

Model Year	MI	Nephropathy	Ulcer	Death
Year 1	0	0	1	0
Year 2				
Year 3				
Year 4				
Year 5				
Year 6				
Year 7…				

Microsimulation Demonstration

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Patient Characteristic	Patient at Baseline	Tracked Patient
Age	55	56
BMI	34.6	35.1
HbA1c	8.5%	8.7%
MI History	0	0
Renal History	0	0
Ulcer History	0	1
Dead	**0**	**0**

Model Year	MI	Nephropathy	Ulcer	Death
Year 1	0	0	1	0
Year 2 	0	0	0	0
Year 3				
Year 4				
Year 5				
Year 6				
Year 7…				

Microsimulation Demonstration

0 = No, 1 = Yes

Patient Characteristic	Patient at Baseline	Tracked Patient
Age	55	57
BMI	34.6	35.6
HbA1c	8.5%	9.1%
MI History	0	0
Renal History	0	0
Ulcer History	0	1
Dead	**0**	**0**

Model Year	MI	Nephropathy	Ulcer	Death
Year 1	0	0	1	0
Year 2	0	0	0	0
Year 3				
Year 4				
Year 5				
Year 6				
Year 7…				

Microsimulation Demonstration

0 = No, 1 = Yes

Patient Characteristic	Patient at Baseline	Tracked Patient
Age	55	57
BMI	34.6	35.6
HbA1c	8.5%	9.1%
MI History	0	0
Renal History	0	0
Ulcer History	0	1
Dead	**0**	**0**

Model Year	MI	Nephropathy	Ulcer	Death
Year 1	0	0	1	0
Year 2	0	0	0	0
Year 3 	1	0	0	0
Year 4				
Year 5				
Year 6				
Year 7…				

Microsimulation Demonstration

0 = No, 1 = Yes

Patient Characteristic	Patient at Baseline	Tracked Patient
Age	55	58
BMI	34.6	36.0
HbA1c	8.5%	9.3%
MI History	0	1
Renal History	0	0
Ulcer History	0	1
Dead	**0**	**0**

Model Year	MI	Nephropathy	Ulcer	Death
Year 1	0	0	1	0
Year 2	0	0	0	0
Year 3	1	0	0	0
Year 4				
Year 5				
Year 6				
Year 7…				

Microsimulation Demonstration

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Year 2	0	0	0	0
Year 3	1	0	0	0
Year 4	1	0	0	1
Year 5				
Year 6				
Year 7…				

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Year 3	1	0	0	0
Year 4	1	0	0	1
Year 5				
Year 6				
Year 7…				

Microsimulation Demonstration

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Age	55	58
BMI	34.6	36.0
HbA1c	8.5%	9.3%
MI History	0	1
Renal History	0	0
Ulcer History	0	1
Dead	**0**	**1**

Model Year	# of Complications	Cost	Life Years	QALYs
Year 1	0 1	$44,462	0.971	0.517
Year 2	0 0	$25,281	0.943	0.465
Year 3	1 1	$59,014	0.915	0.478
Year 4	1 1	$58,469	0.888	0.458
Year 5				
Year 6				
Year 7…				
	=	=	=	=
	3	**$187,226**	**3.717**	**1.918**

Microsimulation Demonstration

NHANES Patient	# of Complications	Cost	Life Years	QALYs
1	2	$253,978	5.417	2.357
2	3	$583,300	5.417	2.349
3	1	$171,928	13.166	7.332
4	1	$147,534	13.166	6.946
5	0	$81,938	7.020	4.078
6	**3**	**$187,226**	**3.717**	**1.918**

Microsimulation Demonstration

NHANES Patient	# of Complications	Cost	Life Years	QALYs
1	2	$253,978	5.417	2.357
2	3	$583,300	5.417	2.349
3	1	$171,928	13.166	7.332
4	1	$147,534	13.166	6.946
5	0	$81,938	7.020	4.078
6	3	$187,226	3.717	1.918
AVERAGE:	**1.4**	**$247,736**	**8.837**	**4.612**

Microsimulation Demonstration

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1	2	$253,978	5.417	2.357
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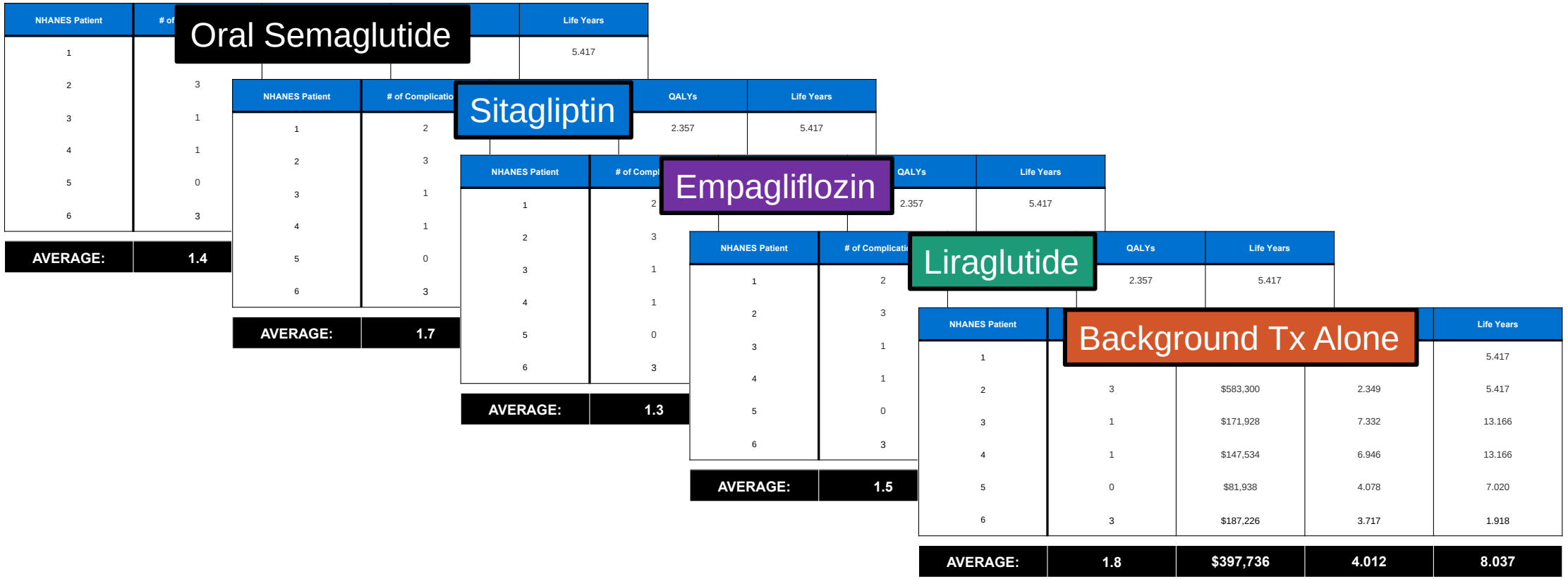
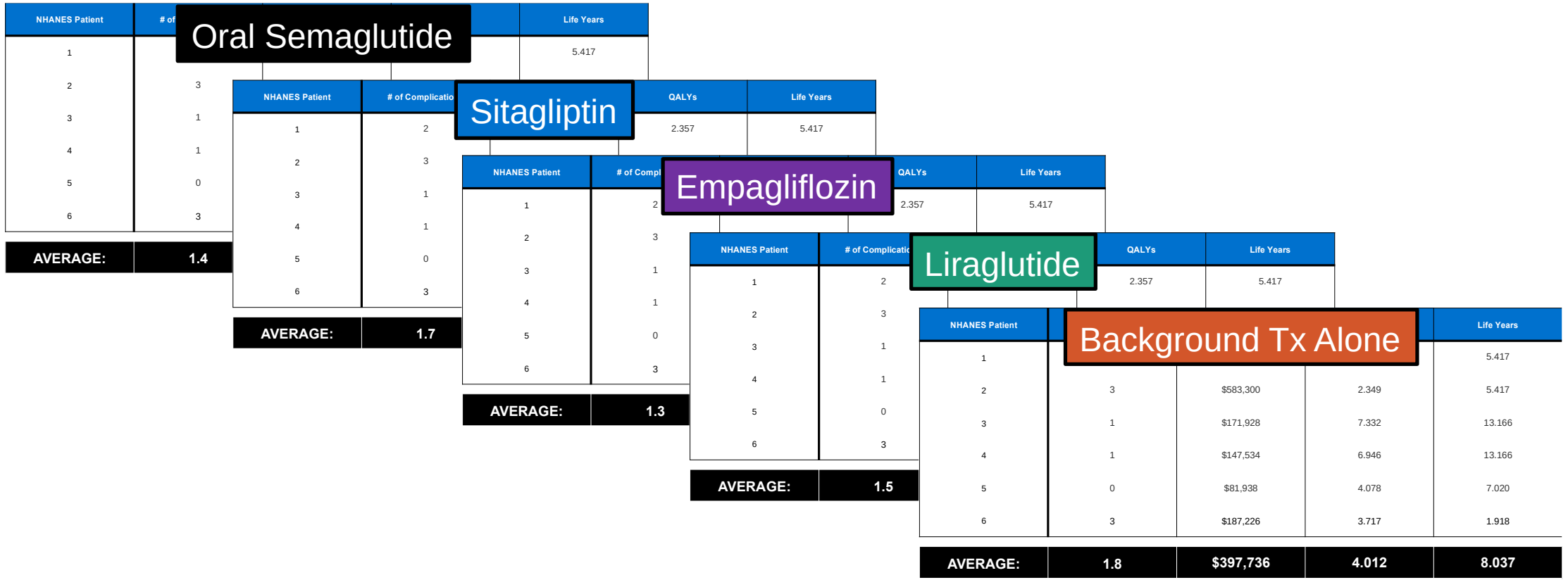
4	1	$147,534	13.166	6.946
5	0	$81,938	7.020	4.078
6	3	$187,226	3.717	1.918
AVERAGE:	**1.4**	**$247,736**	**8.837**	**4.612**

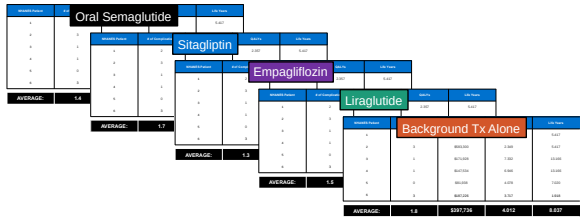
Microsimulation Demonstration



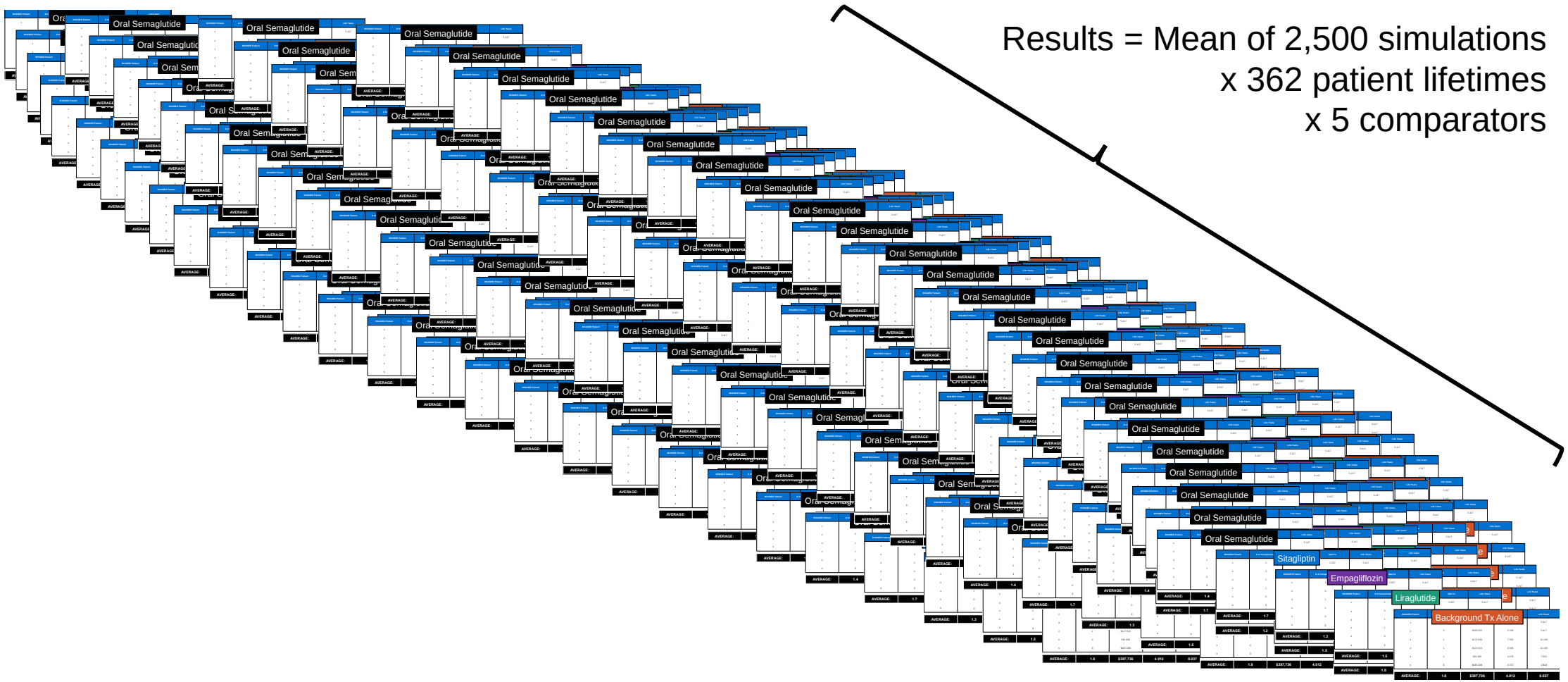
Microsimulation Demonstration



Microsimulation Demonstration



Microsimulation Demonstration



Results = Mean of 2,500 simulations
x 362 patient lifetimes
x 5 comparators

Key Model Assumptions

- The incremental rate of MACE, HF, and kidney function decline is independent of patient characteristics.
- Hazard ratio adjustment of UKPDS OM2 risk estimates for MACE, HF and kidney function decline, based on NMA results, was maintained over each patient's lifetime.
- Patients who discontinue treatment and/or reach HbA1c of 8.5% or above receive insulin therapy. No additional drugs are modeled.

NHANES Patient Characteristics (n = 362)[1]

Age (years), mean (SD)	61.8 (12.6)
Female, %	45.3%
Black Race, %	45.0%
Current Smoker, %	34.5%
Duration of Diabetes (years), mean (SD)	13.1 (9.5)
Body Mass Index (kg/m^2), mean (SD)	34.4 (7.7)
Estimated Glomerular Filtration Rate (ml/min/m^2), mean (SD)	80.6 (31.4)
HbA1c (%), mean (SD)	8.7 (1.8)
History of Myocardial Infarction, %	11.6%
History of Stroke, %	8.0%
History of Heart Failure, %	10.5%
History of Ischemic Heart Disease, %	12.4%
History of Angina, %	5.8%
History of Renal Complications, %	22.7%

*Only patients with HbA1c ≥7% were included

1. Centers for Disease Control and Prevention (CDC). National Center for Health Statistics (NCHS). National Health and Nutrition Examination Survey Data. U.S. Department of Health and Human Services, Centers for Disease Control and Prevention. https://wwwn.cdc.gov/nchs/nhanes/ContinuousNhanes/Default.aspx?BeginYear=2015. Published Survey Years: 2013-14, 2015-16. Accessed August 20, 2019.

T2DM Outcomes and Mortality: UKPDS OM2[1]

$$\lambda + \left(\left[\begin{array}{c} \text{Individual} \\ \text{Patient} \\ \text{Characteristics} \end{array} \right] \times \left[\begin{array}{c} \text{UKPDS OM2} \\ \text{Data} \\ \text{Transformations} \end{array} \right] \times \left[\begin{array}{c} \text{UKPDS OM2} \\ \text{Complication} \\ \text{Coefficients} \end{array} \right] \right) \times t^{\rho}$$

- 13 T2DM complications equations
  - heart failure, ischemic heart disease, first MI for females, first MI for males, subsequent MI, first stroke, subsequent stroke, blindness, foot ulcer, first amputation without prior ulcer, first amputation with prior ulcer, subsequent amputation, and end stage renal disease
- 4 mortality equations
  - death without history of clinical event(s), death in the year of a clinical event, death with history of clinical event(s), and death in subsequent year of prior event(s)

1. Hayes AJ, et al. Diabetologia. 2013;56(9):1925-1933.

T2DM Outcomes and Mortality: UKPDS OM2[1]

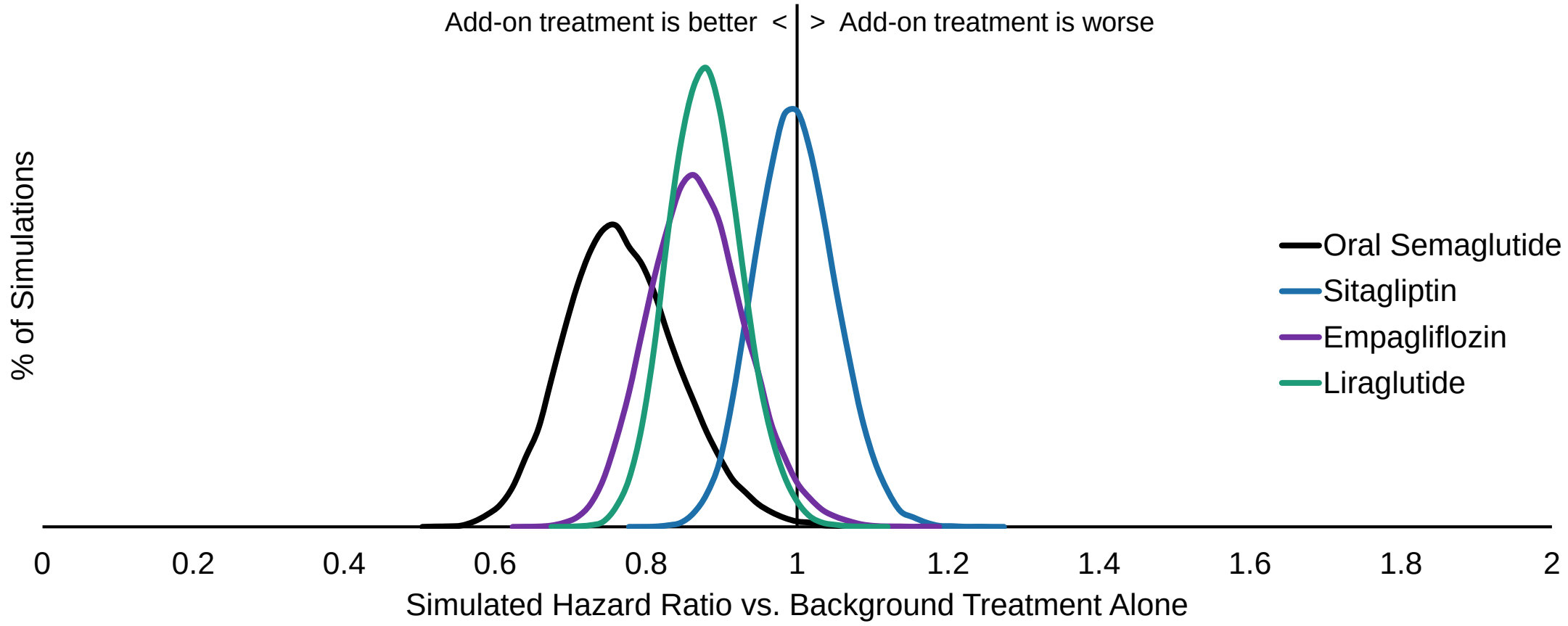
$$\lambda + \left(\left[\begin{array}{l} \text{Individual} \\ \text{Patient} \\ \text{Characteristics} \end{array} \right] \times \left[\begin{array}{l} \text{UKPDS OM2} \\ \text{Data} \\ \text{Transformations} \end{array} \right] \times \left[\begin{array}{l} \text{UKPDS OM2} \\ \text{Complication} \\ \text{Coefficients} \end{array} \right] \right) \times t^{\rho}$$

- 13 T2DM complications equations
  - heart failure, ischemic heart disease, first MI for females, first MI for males, subsequent MI, first stroke, subsequent stroke, blindness, foot ulcer, first amputation without prior ulcer, first amputation with prior ulcer, subsequent amputation, and end stage renal disease
- 4 mortality equations
  - death without history of clinical event(s), death in the year of a clinical event, death with history of clinical event(s), and death in subsequent year of prior event(s)

NMA hazard ratios applied

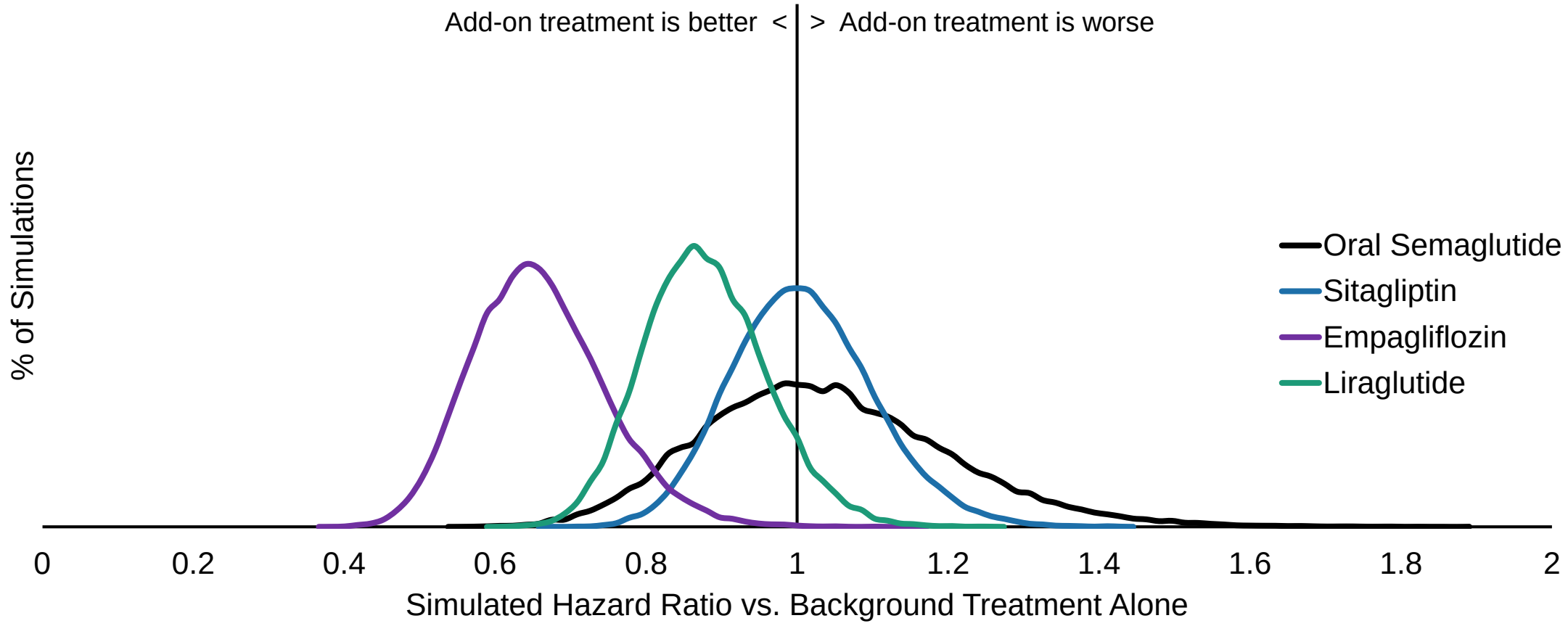
1. Hayes AJ, et al. Diabetologia. 2013;56(9):1925-1933.

Key Model Inputs:
MACE Outcomes Efficacy vs. Background Treatment[1-4]



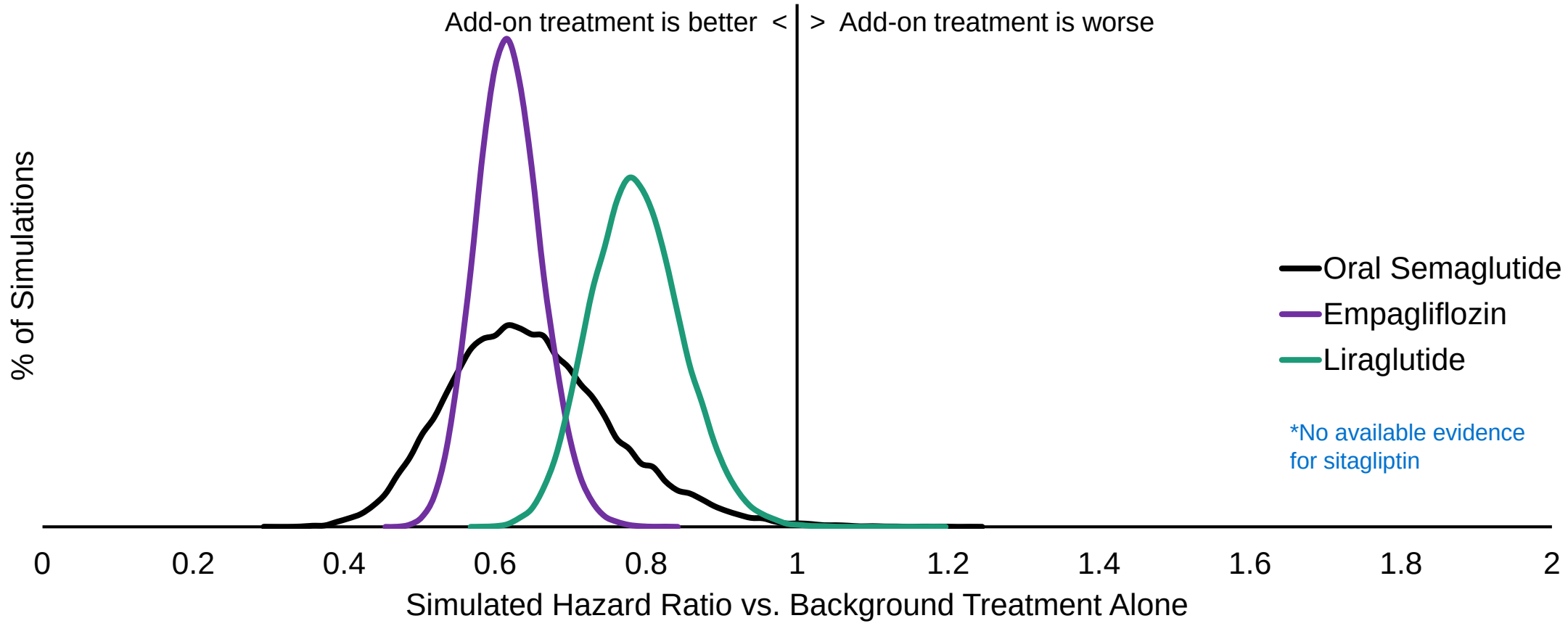
1. Husain M, et al. *N Engl J Med.* 2019.
2. Marso SP, et al. *New Engl J Med.* 2016;375(4):311-322.
3. Green JB, et al. *New Engl J Med.* 2015;373(3):232-242.
4. Zinman B, et al. *New Engl J Med.* 2015;373(22):2117-2128.

Key Model Inputs:
HF Outcome Efficacy vs. Background Treatment[1-4]



1. Husain M, et al. *N Engl J Med.* 2019.
2. Marso SP, et al. *New Engl J Med.* 2016;375(4):311-322.
3. Green JB, et al. *New Engl J Med.* 2015;373(3):232-242.
4. Zinman B, et al. *New Engl J Med.* 2015;373(22):2117-2128.

Key Model Inputs:
Renal Outcome Efficacy* vs. Background Treatment[1-4]



1. Husain M, et al. *N Engl J Med.* 2019.
2. Marso SP, et al. *New Engl J Med.* 2016;375(4):311-322.
3. Green JB, et al. *New Engl J Med.* 2015;373(3):232-242.
4. Wanner C, et al. New Engl J Med. 2016;375(4):323-334.

Key Model Inputs: Estimated Treatment Costs

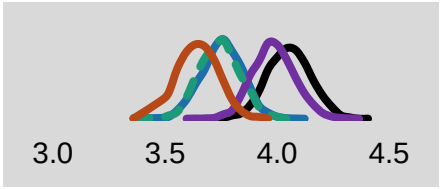
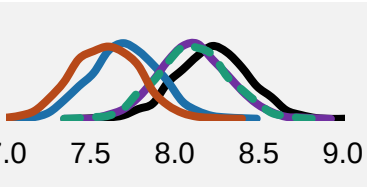
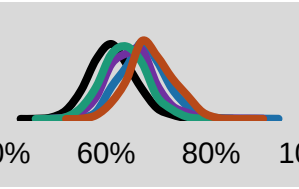
Drug	WAC per Bottle/Pen[1]	Discount From WAC[2]	Net Price per Month	Net Price per Year
Oral Semaglutide (Rybelsus®), 30-Tablet Bottle*	$772.43	35.10%	$508.62	**$6,103.45**
Sitagliptin (Januvia®), 30-Tablet Bottle	$451.20	72.60%	$125.42	**$1,505.07**
Empagliflozin (Jardiance®), 30-Tablet Bottle	$492.85	65.20%	$174.01	**$2,088.13**
Liraglutide (Victoza®), 18 mg/3mL Pen†	$307.26	28.60%	$667.74	**$8,012.85**

*WAC price published September 20, 2019; for net price, we assumed the same discount from WAC as that for injectable semaglutide.
† Prices for liraglutide are per 3 ml pen, and the annual price calculation assumes a 1.8 mg (0.3ml)/day dosage.

1. Truven Health Analytics. Red Book Online Search. http://www.micromedexsolutions.com. Accessed October 1, 2019.
2. SSR Health L. https://www.ssrhealth.com/. Accessed October 1, 2019.

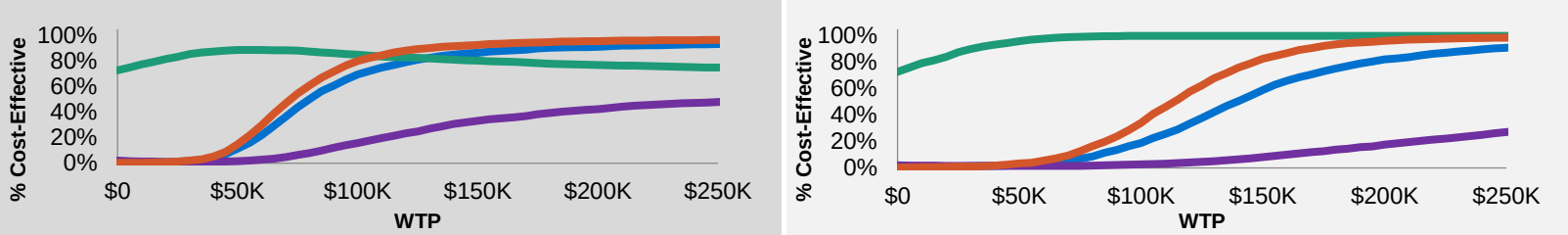
Results

Estimated Base-Case Results

				
Drug	**Cost**	**QALYs**	**Life Years**	**MACE**
Oral semaglutide ●	$295,000	4.03	8.18	59.9%
Sitagliptin ●	$254,000	3.73	7.66	65.8%
Empagliflozin ●	$263,000	3.97	8.07	63.4%
Liraglutide ●	$305,000	3.72	8.06	62.2%
Background Tx ●	$250,000	3.63	7.55	67.2%

Tx: treatment; QALYs: quality-adjusted life year; MACE: major adverse cardiovascular event

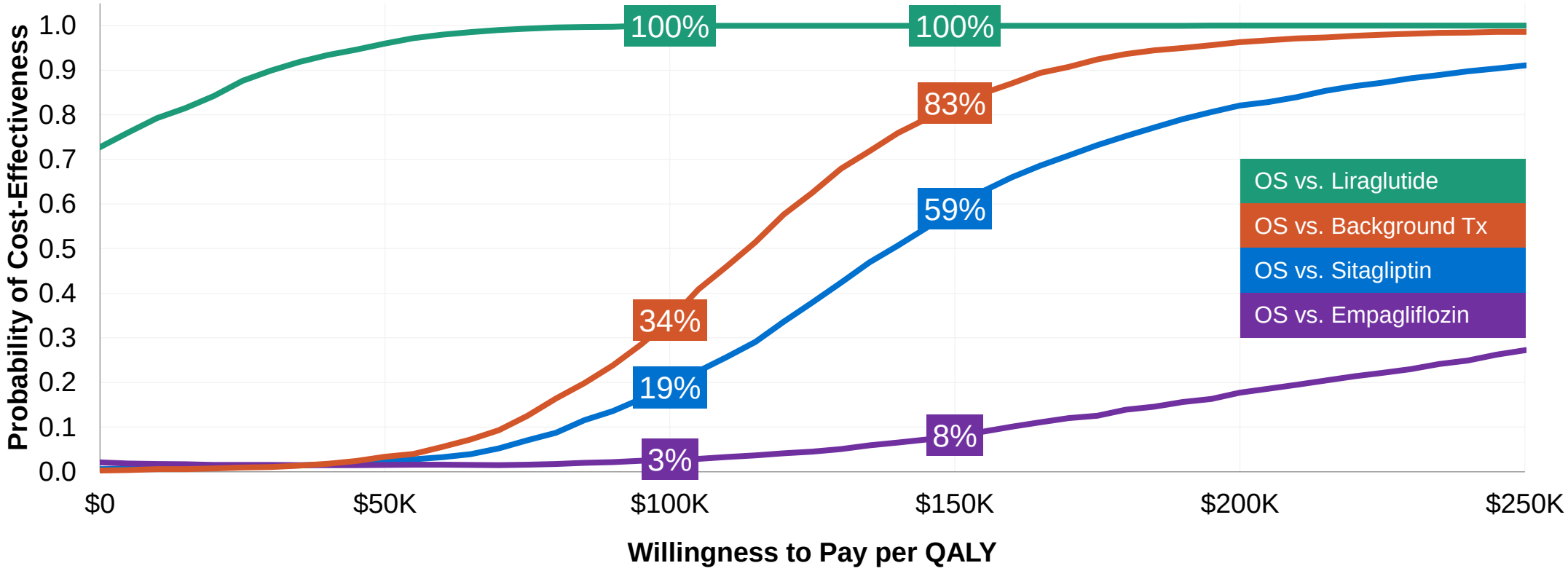
Estimated Base-Case Incremental Results



Oral Semaglutide vs. Comparator:	Cost per Life Year Gained	Cost per QALY Gained
Sitagliptin	$80,000	$140,000
Empagliflozin	$290,000	$480,000
Liraglutide	Cost-Saving	Cost-Saving
Background Tx	$70,000	$110,000

Tx: treatment; QALYs: quality-adjusted life year; MACE: major adverse cardiovascular event

Probabilistic Sensitivity Analysis:
Percentage of Simulations Meeting Cost-Effectiveness Thresholds



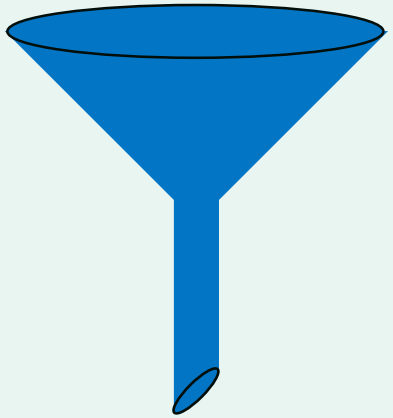
OS: oral semaglutide; Tx: treatment; QALY: quality-adjusted life year

Scenario Analyses

Scenario	Alteration from Base Case	Impact
Modified societal perspective	Age-specific annual estimates of productivity costs for T2DM patients added to all comparators	Similar cost-effectiveness ratios
Declining MACE and renal effectiveness	Adjusted the relative effect of oral semaglutide versus background treatment alone by annually increasing the MACE and nephropathy hazard ratios by 5%& 10% per year	Cost-effectiveness ratios tended to increase

Limitations

T2DM Complexity



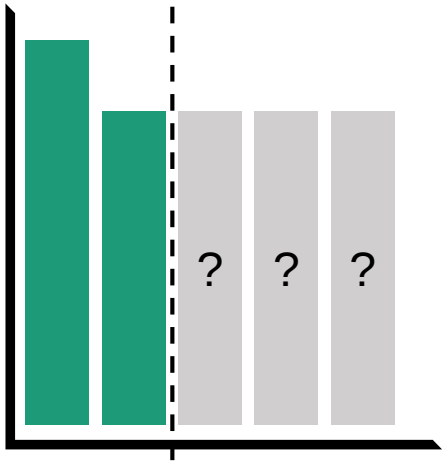
UKPDS OM2 Equations

NHANES Population

≈

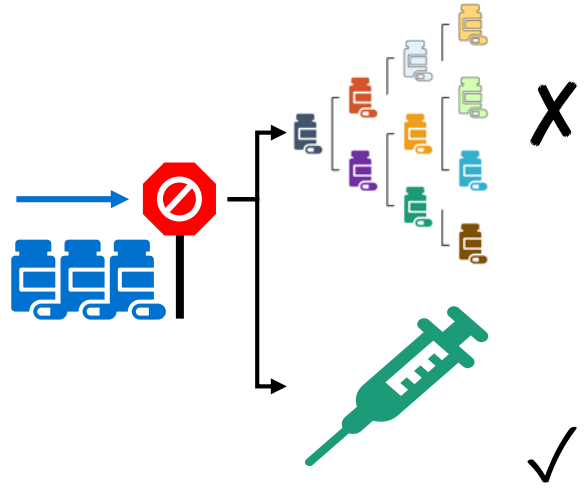
PIONEER Populations

Trial



Long-term

Treatment Cascade



✗

✓

Insulin

Comments Received

1. Patient cohort selection (NHANES) not representative of PIONEER trials

2. Model outcomes were lower/higher than expected
   - Model share agreements with manufacturers

3. Excessive amount of uncertainty

Conclusions for Oral Semaglutide (OS)

Health Outcomes

OS > Sitagliptin

OS ≈ Empagliflozin

OS > Liraglutide

OS > Background tx

Cost Outcomes

OS > Sitagliptin

OS > Empagliflozin

OS < Liraglutide

OS > Background tx

Takeaways

- Potentially cost-effective vs. sitagliptin and background tx at a $100K-$150K/QALY threshold
- Dominant vs. liraglutide
- Not cost-effective vs. empagliflozin
  - ↑ Depends on price ↑

Questions?

Manufacturer Public Comment and Discussion

Manufacturer Public Commenters

Speaker	Title	Affiliation
Todd Hobbs, MD	Vice President, Chief Medical Officer of North America, Novo Nordisk	Full-time employee of Novo Nordisk
Swapnil Rajpathak, MD, MPH, PhD	Executive Director, Center for Observational and Real World Evidence, Merck	Full-time employee of Merck
Leo Seman, MD, PhD	Director, Clinical Development and Medical Affairs, Boehringer Ingelheim	Full-time employee of Boehringer Ingelheim

Public Comment and Discussion

Susan Weiner, MS, RDN, CDE, FAADE
Scientific Council Member, Beyond Type 2

Conflicts of Interest:

- *No conflicts to disclose.*

Lunch

Meeting will resume at 1:00p

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Voting Questions

WIFI: Brown-Guest
Password: none

Test Question: What does the Providence metropolitan area have more of (per capita) than any other US city?

A. Chinese restaurants

B. Doughnut shops

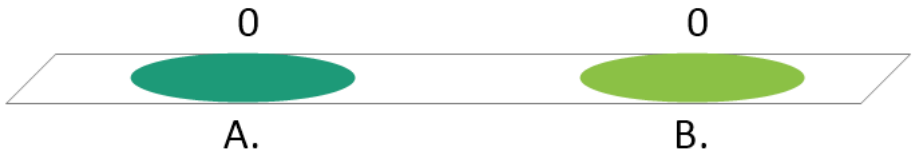
C. Pharmacies

D. Art supply shops

1. Is the evidence adequate to demonstrate that adding oral semaglutide (Rybelsus®) to ongoing background therapy provides a positive net health benefit?

A. Yes

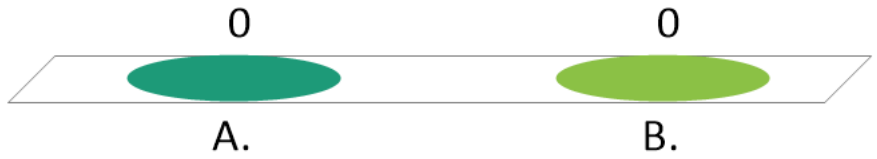
B. No



2. Is the evidence adequate to demonstrate that the net health benefit of adding oral semaglutide is superior to that provided by adding sitagliptin (Januvia®)?

A. Yes

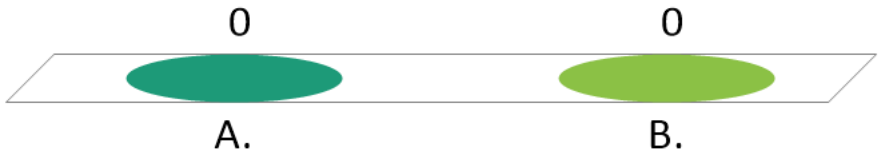
B. No



3. Is the evidence adequate to demonstrate that the net health benefit of adding oral semaglutide is superior to that provided by adding liraglutide (Victoza®)?

A. Yes

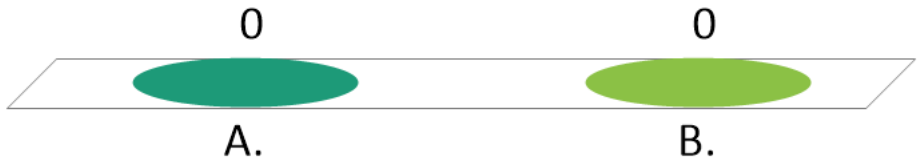
B. No



4. Is the evidence adequate to distinguish the net health benefit of adding oral semaglutide from that provided by adding empagliflozin (Jardiance®)?

A. Yes

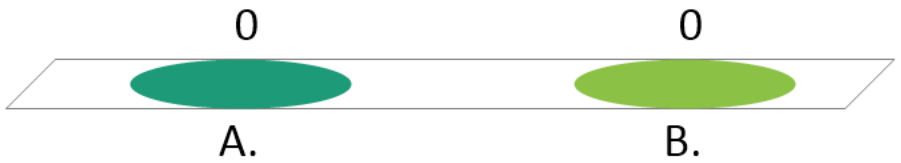
B. No



If yes:
4a. Which treatment provides greater net health benefit?

A. Oral semaglutide

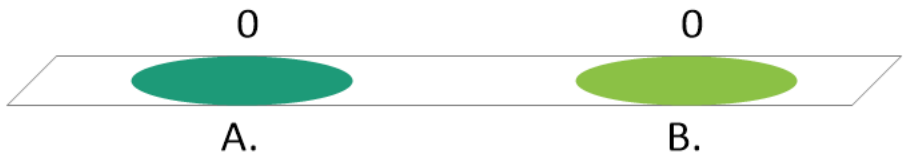
B. Empagliflozin



5. For patients currently receiving ongoing background therapy, does adding treatment with oral semaglutide offer one or more of the following potential "other benefits or disadvantages." (select all that apply)

A. This intervention offers reduced complexity compared to liraglutide that will significantly improve patient outcomes.

B. There are other important benefits or disadvantages that should have an important role in judgments of the value of this intervention: _____



6. Are any of the following contextual considerations important in assessing the long-term value for money of oral semaglutide? (select all that apply)

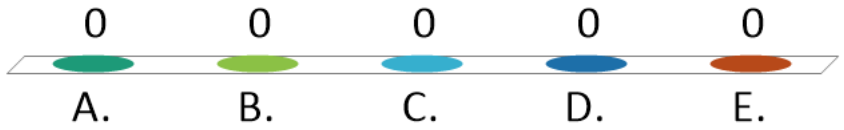
A. This intervention is intended for the care of individuals with a condition of particularly high severity in terms of impact on length of life and/or quality of life.

B. This intervention is intended for the care of individuals with a condition that represents a particularly high lifetime burden of illness.

C. There is significant uncertainty about the long-term risk of serious side effects of this intervention.

D. There is significant uncertainty about the magnitude or durability of the long-term benefits of this intervention.

E. There are additional contextual considerations that should have an important role in judgments of the value of this intervention: _____.

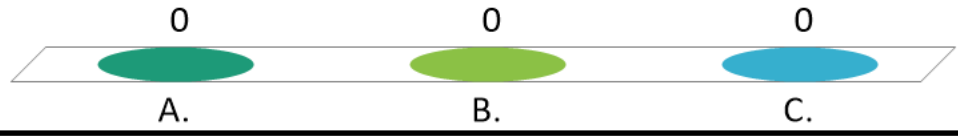


7. Given the available evidence on comparative effectiveness and incremental cost effectiveness, and considering other benefits, disadvantages, and contextual considerations, what is the long-term value for money of treatment with oral semaglutide versus ongoing background therapy alone?

A. Low long-term value for money at current pricing

B. Intermediate long-term value for money at current pricing

C. High long-term value for money at current pricing



Break

Meeting will resume at 2:30pm

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Policy Roundtable

Policy Roundtable

Participant	Affiliation	Conflict of Interest
Jeff Casberg, MS	Director of Clinical Pharmacy, IDP Analytics	Owns Anthem, Cigna, CVS, and McKesson stock shares
Bonnie Donato, MA, PhD	Executive Director of Primary Care, Health Economics, and Outcomes Research, Boehringer Ingelheim	Full-time employee of Boehringer Ingelheim
Todd Hobbs, MD	Vice President, Chief Medical Officer of North America, Novo Nordisk	Full-time employee of Novo Nordisk
Joanna Mitri, MD, MS	Staff Endocrinologist, Joslin Diabetes Center	Received support from the National Dairy Council, National Institutes of Health, Kowa, and the Juvenile Diabetes Research Foundation
Lisa Murphy, MD, DPhil	Chief, Division of Endocrinology and Metabolism, San Francisco General Hospital, University of California, San Francisco	No conflicts of interest to disclose
David Strutton, PhD	Vice President, Global Pharmaceuticals & Policy Research, Center for Observational and Real-World Evidence, Merck	Full-time employee of Merck
Susan Weiner, MS, RDN, CDE, FAADE	Scientific Council Member, Beyond Type 2	No conflicts of interest to disclose.

New England CEPAC Reflections

Next Steps

- Meeting recording posted to ICER website next week
- Final Report published on or around December 9, 2019
  - Includes description of New England CEPAC votes, deliberation, policy roundtable discussion
- Materials available at: https://icer-review.org/topic/type-2-diabetes/

Adjourn

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