Disclosures

<table>
<thead>
<tr>
<th>Speakers Bureau</th>
<th>none</th>
</tr>
</thead>
<tbody>
<tr>
<td>Research Funding</td>
<td>Novo Nordisk, Merck, Pfizer, Mylan, Gan &amp; Lee, Novartis, GI Dynamics</td>
</tr>
<tr>
<td>Consulting/Advising/Steering Committee</td>
<td>Novo Nordisk, Sanofi, Eli Lilly, Boeringer-Ingelheim, Astra Zeneca, Intarcia, Valeritas, TARGETPharma, Mannkind, Janssen</td>
</tr>
</tbody>
</table>
Timeline of Glucose Lowering Medications in USA

Number of medications & classes

19 18 17 16 15 14 13 12 11 10 9 8 7 6 5 4 3 2 1

Iletin insulin
PZI insulin
NPH insulin
Ultralente, Lente & Semilente insulin
Human insulin: Regular, NPH & U500

Millipore, glipizide, glyburide

glimepiride
metformin
acarbose
lispro
miglitol
troglitazone
repaglinide
rosiglitazone
pioglitazone
glargine
nateglinide
aspart
gluulisine
detemir
exenatide
pramlintide
sitagliptin
colesevelam
saxagliptin
bromocriptine
liraglutide
linagliptin
exenatide weekly
empagliflozin
inhaled insulin
albiglutide
dapagliflozin
dulaglutide
glargine U300
degludec
FDap
basaglar
erugenflomin
semaglutide

Distinct Classes
Agents
Products

Goals of Treatment

I. Metformin

II. Co-existing comorbidities/complications (ASCVD/ HF/ CKD)

III. Glycemic control
   - Weight control
   - Hypoglycemia
   - Cost

Davies et al, Diabetes Care 2019
**Goals of Treatment**

- **Maintain/improve Quality of Life**
  - Asymptomatic
  - Prevent acute complications
  - Manageable side effects
  - Practical
    - Route
    - Frequency of administration
    - Cost
  - Co-manage weight

- **Prevent/Manage Macrovascular Disease**
  - Other SOC (Statins/β-blockers/ACEI...)
  - Targeted interventions
    - GLP-1 RAs
    - SGLT2 inh

- **Prevent/Manage Microvascular Disease**
  - Tight glycemic (and BP) control
  - Targeted interventions
    - Anti-VEGF therapy (retinopathy, DME)
    - SGLT2 inhibitors (nephropathy)

---

**GLUCOSE-LOWERING MEDICATION IN TYPE 2 DIABETES: OVERALL APPROACH**

First-line therapy is metformin and comprehensive lifestyle (including weight management and physical activity) (Davies et al, Diabetes Care 2019)

---

**Davies et al, Diabetes Care 2019**
GLP-1 Receptor Agonists (GLP-1 RA)

The Incretin Effect

- GLP-1
- GIP
- PYY
- Cholecystokinin
- Oxyntomodulin
- VIP
- Secretin
- Ghrelin
- ...

Nauck MA. J Clin Endocrinol Metab. 1986;63:492-498
GLP-1 RAs: Metabolic Actions

![Diagram showing metabolic actions of GLP-1 RAs](Saraiva_FK_Cardiovascular_Diabetology_2014;13:142)

### GLP-1 RA Class

<table>
<thead>
<tr>
<th>Agent</th>
<th>Brand Name</th>
<th>Half Life</th>
<th>Route</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exenatide</td>
<td>Byetta</td>
<td>2.4 hrs</td>
<td>SQ</td>
<td>Twice Daily</td>
</tr>
<tr>
<td>Lixisenatide</td>
<td>Adlyxin*</td>
<td>3 hrs</td>
<td>SQ</td>
<td>Daily</td>
</tr>
<tr>
<td>Liraglutide</td>
<td>Victoza</td>
<td>13 hrs</td>
<td>SQ</td>
<td>Daily</td>
</tr>
<tr>
<td>Albiglutide</td>
<td>Tanzeum*</td>
<td>5 Days</td>
<td>SQ</td>
<td>Weekly</td>
</tr>
<tr>
<td>Dulaglutide</td>
<td>Trulicity</td>
<td>5 Days</td>
<td>SQ</td>
<td>Weekly</td>
</tr>
<tr>
<td>Exenatide</td>
<td>Bydureon/ Bcise</td>
<td>7-14 Days</td>
<td>SQ</td>
<td>Weekly</td>
</tr>
<tr>
<td>Semaglutide</td>
<td>Ozempic</td>
<td>7 Days</td>
<td>SQ</td>
<td>Weekly</td>
</tr>
<tr>
<td>Semaglutide</td>
<td>Rybelsus</td>
<td>7 Days</td>
<td>PO</td>
<td>Daily</td>
</tr>
</tbody>
</table>

*no longer marketed
GLP-1 RAs in T2D: HbA1c

- Long acting agents more effective than short acting
- GLP-1 RA class has the greatest glucose lowering efficacy (similar to insulin)

**“Equivalent” Doses Amongst GLP-1 RA**

**Glycemic effect**

<table>
<thead>
<tr>
<th>Product</th>
<th>Frequency</th>
<th>Equivalent dose*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exenatide (Bydureon)</td>
<td>QW</td>
<td>2 mg</td>
</tr>
<tr>
<td>Dulaglutide (Trulicity)</td>
<td>QW</td>
<td>0.75 mg 1.5 mg</td>
</tr>
<tr>
<td>Semaglutide (Ozempic)</td>
<td>QW</td>
<td>0.25 mg 0.5 mg 1 mg</td>
</tr>
<tr>
<td>Liraglutide (Victoza)</td>
<td>QD</td>
<td>0.6 mg 1.2 mg 1.8 mg</td>
</tr>
<tr>
<td>Lixisenatide (Adlyxin)</td>
<td>QD</td>
<td>10 µg 20 µg</td>
</tr>
<tr>
<td>Oral semaglutide (Rybelsus)</td>
<td>QD</td>
<td>3 mg 7 mg 14 mg</td>
</tr>
<tr>
<td>Exenatide (Byetta)</td>
<td>BID</td>
<td>5 µg 10 µg</td>
</tr>
</tbody>
</table>

*Equivalency based on clinical trials and expert opinion.

Almanoz et al. Clinical Diabetes, in press
Oral semaglutide (GLP-1 RA) vs sitagliptin (DPP IV inh): Hypoglycemia by SU background

• GLP-1 RAs have low risk of hypoglycemia
• glucose-dependent mechanism of action
• Hypoglycemia risk increased when co-administered with SU or INS

GLP-1 RAs in T2D: weight

GLP-1 RA class has by far the greatest weight lowering effect
Sema>lira>dula>exenatide>lixisenatide

BID, twice daily; BW, body weight; GLP-1 RA, glucagon-like peptide-1 receptor agonist; OD, once daily; QW, once a week; T2D, type 2 diabetes.

Overview of results from CVOT in T2D
Status as of June 2019

<table>
<thead>
<tr>
<th>Study</th>
<th>HR (95% CI)</th>
<th>N</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ELIXA</td>
<td>1.02 (0.89, 1.17)</td>
<td>6,068</td>
<td>0.81</td>
</tr>
<tr>
<td>EXCEL</td>
<td>0.91 (0.83, 1.00)</td>
<td>14,742</td>
<td>0.06</td>
</tr>
<tr>
<td>LEADER</td>
<td>0.87 (0.78, 0.97)</td>
<td>9,340</td>
<td>0.01</td>
</tr>
<tr>
<td>SUSTAIN 6</td>
<td>0.74 (0.58, 0.95)</td>
<td>3,297</td>
<td>0.02</td>
</tr>
<tr>
<td>PIONEER 6</td>
<td>0.79 (0.57, 1.11)</td>
<td>3,183</td>
<td>0.17</td>
</tr>
<tr>
<td>HARMONY</td>
<td>0.78 (0.68, 0.90)</td>
<td>9,463</td>
<td>0.0006</td>
</tr>
<tr>
<td>REWIND</td>
<td>0.88 (0.79, 0.99)</td>
<td>9,901</td>
<td>0.026</td>
</tr>
</tbody>
</table>

CV Composite in Prespecified Subgroups

<table>
<thead>
<tr>
<th>Subgroups</th>
<th>Dulaglutide</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Events/Total (%)</td>
<td>Rate/100 py</td>
<td>Events/Total (%)</td>
</tr>
<tr>
<td>History of CVD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prior CVD</td>
<td>280 /1560 (17.9)</td>
<td>3.7</td>
</tr>
<tr>
<td>No Prior CVD</td>
<td>277 /3093 (8.9)</td>
<td>1.7</td>
</tr>
</tbody>
</table>

Hazard Ratio 95% CI

Gerstein et al, REWIND, Lancet 2019: 121
GLP-1 RA: Potential Mechanisms for CVD Benefit


Rakipovski et al. JACC Basic Transl Sci 2018; 3: 844-857
GLP-1 RA & Heart Failure

<table>
<thead>
<tr>
<th>Study</th>
<th>Hospitalization for Heart Failure</th>
<th>HR (CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ELIXA</td>
<td></td>
<td>0.96 (0.75, 1.23)</td>
</tr>
<tr>
<td>LEADER</td>
<td></td>
<td>0.87 (0.73, 1.05)</td>
</tr>
<tr>
<td>SUSTAIN-6</td>
<td></td>
<td>1.11 (0.71, 1.61)</td>
</tr>
<tr>
<td>EXSCEL</td>
<td></td>
<td>0.94 (0.78, 1.13)</td>
</tr>
<tr>
<td>PIONEER 6</td>
<td></td>
<td>0.86 (0.48, 1.55)</td>
</tr>
<tr>
<td>REWIND</td>
<td></td>
<td>0.83 (0.77, 1.12)</td>
</tr>
</tbody>
</table>

- Favors GLP-1 RA
- Favors placebo
- HR approx. 0.81 HARMONY

Davies et al, Diabetes Care 2019
Renal Composite Outcome
New Macroalbuminuria, 30% fall in eGFR, or Renal Replacement Rx

Gerstein et al, REWIND, Lancet 2019: 121

Sustained eGFR Decline ≥ 30, 40 & 50%

Sensitivity Analyses

Gerstein et al, REWIND, Lancet 2019: 121
GLP-1 RA Side Effects

- **Gl issues (up to 40%)**:  
  - Nausea  
  - Vomiting  
  - Heartburn  
  - Diarrhea  
  - Constipation  
  - Cramping

- **Mitigating actions**:  
  - Decrease intake  
  - Only eat if hungry  
  - Eat slowly  
  - Increase fiber content  
  - Reassurance (resolves over time)  
  - OTC remedies (ginger, preggy pops, etc)  
  - Slow (back down) titration

- **Good to know**:  
  - Medullary Thyroid Carcinoma  
  - Retinopathy  
  - Pancreatitis  
  - Cholelithiasis

Oral Semaglutide: first oral GLP-1 RA

- **SNAC**: Sodium N-(8-(2-hydroxybenzoyl) amino) caprylate  
  - a small fatty acid derivative  

- SNAC causes a local increase of pH leading to higher solubility and protection from proteolytic degradation  
  - The effect is fully reversible  
  - Approximately 1% of semaglutide is absorbed, the rest is degraded in the GI tract

- **Maximum concentration after po intake**: 1 hr  
- **Half-life**: 1 weeks  
- **Steady state**: 4-5 weeks  
  - ≈5 wks to be eliminated after last dose  
- **Dosing conditions**:  
  - Fasting for 6 hrs  
  - Small amount of water only  
  - No intake for MINIMUM 30 minutes  

*Buckley ST et al. Sci Transl Med 2018*
Sodium GLucose Co-transporter 2 Inhibitors (SGLT2 inh)

Majority of glucose is reabsorbed by SGLT2 (90%)\(^1,2\)

Remaining glucose is reabsorbed by SGLT1 (10%)\(^1,2\)

Glucose filtration = 180 g/day\(^1,2\)

SGLT 2 inhibitor

↑glucosuria
↑natriuresis

SGLT 2 Inhibitors

<table>
<thead>
<tr>
<th>Agent</th>
<th>Brand Name</th>
<th>Dose</th>
<th>Route</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Empagliflozin</td>
<td>Jardiance</td>
<td>10 mg &amp; 25 mg</td>
<td>Oral</td>
<td>Daily</td>
</tr>
<tr>
<td>Canagliflozin</td>
<td>Invokana</td>
<td>100 mg &amp; 300 mg</td>
<td>Oral</td>
<td>Daily</td>
</tr>
<tr>
<td>Dapagliflozin</td>
<td>Farxiga</td>
<td>5 mg &amp; 10 mg</td>
<td>Oral</td>
<td>Daily</td>
</tr>
<tr>
<td>Ertugliflozin</td>
<td>Steglatro</td>
<td>5 mg &amp; 15 mg</td>
<td>Oral</td>
<td>Daily</td>
</tr>
</tbody>
</table>

The results of 12 studies are displayed. None of these were head-to-head studies and direct comparisons should not be made.

Empagliflozin (SGLT 2 Inh) vs Glimepiride (SU) – 4 yr F/u
Second Line Therapy after Metformin

Ridderstrale M. Diabetes Obes Metab. 2018;20(12):2768

3% vs 38% = 12.6 times higher!

SGLT 2 inh: Weight

SGLT-2 inhibitors are not indicated for weight management.

The results of 12 studies are displayed. None of these were head-to-head studies and direct comparisons should not be made.

SGLT 2 inhibitors: Proposed CV protection mechanisms

Proposed SGLT 2 inh Effects on Na/H Exchangers 1 (heart) & 3 (kidneys)

Blockade of the sodium-hydrogen exchanger by SGLT2 inhibitors

- Increased sodium excretion
- Decreased body weight
- Decreased blood pressure
- Hemoconcentration

Decreased cardiac injury
Decreased cardiac wall stress

Empagliflozin (SGLT 2 Inh) Elevates Ketone Bodies
Changing Cardiac Metabolism?

T2D (n=66)

- Baseline
- Acute dosing
- Chronic dosing

β-hydroxybutyrate (μmol/L)

Ferrannini et al, Diabetes 2016;65:1190-1195
SGLT 2 inh & MACE by CV Risk: 
*Preexistent CV Event or Risk Factors*

The Lancet 2019 393, 31-39DOI: (10.1016/S0140-6736(18)32590-X)

---

SGLT 2 inh and HHF/CV Death Outcomes

The Lancet 2019 393, 31-39DOI: (10.1016/S0140-6736(18)32590-X)
**DAPA-HF: SGLT 2 Inh in Heart Failure**

Age 66.2 yrs
67.7% NYHA II
LVEF 31.2%
DM 41.8%
HHF 47.8%

Mcmurray et al. NEJM 2019:1995 (DAPA-HF)

---

**Dedicated Heart Failure Studies**

<table>
<thead>
<tr>
<th></th>
<th>HFrEF</th>
<th>HFpEF</th>
</tr>
</thead>
<tbody>
<tr>
<td>GLP-1 RA</td>
<td></td>
<td>? (maybe)</td>
</tr>
<tr>
<td>SGLT2 inh</td>
<td></td>
<td>DAPA-HF</td>
</tr>
<tr>
<td></td>
<td>dapagliflozin</td>
<td>DELIVER</td>
</tr>
<tr>
<td></td>
<td>empagliflozin</td>
<td>empagliflozin</td>
</tr>
<tr>
<td>EMPEROR-Red</td>
<td>EMPEROR-Pres</td>
<td></td>
</tr>
<tr>
<td>SOLOIST-WHF</td>
<td></td>
<td>sotagliflozin</td>
</tr>
</tbody>
</table>
SGLT 2 Inh: Proposed Renal-protection Mechanisms

Heerspink HJL. Kidney Int. 2018; 94:26

CREDENCE: Renal Outcome Study for Canagliflozin (SGLT 2 Inh)

- DM 100%
- Age 63 yrs
- Diabetes duration 15.8 yr
- CVD 50.4%
- eGFR 56.2
- ACR 927

Perkovik et al. NEJM. 2019; 380(24):2301
CREDENDE: Renal Outcome Study for Canagliflozin (SGLT 2 Inh)

SGLT 2 Inhibitors Renal Dosing Label

<table>
<thead>
<tr>
<th>eGFR</th>
<th>Canagliflozin</th>
<th>Empagliflozin</th>
<th>Dapagliflozin</th>
<th>Ertugliflozin</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;60</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>45-60</td>
<td>100mg only*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>30-45</td>
<td>ACR&gt;300</td>
<td>avoid use</td>
<td>avoid use</td>
<td></td>
</tr>
<tr>
<td>&lt;30</td>
<td>Do not start, may continue</td>
<td>contraindicated</td>
<td>contraindicated</td>
<td>contraindicated</td>
</tr>
<tr>
<td>Dialysis</td>
<td>contraindicated</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- CV benefits are independent of eGFR
- Glycemic benefits decrease with GFR and become negligible when eGFR <45

*if on UGT enzyme inducers avoid use when eGFR<60
Dedicated Renal Outcome Studies with Glucose Lowering Drugs

<table>
<thead>
<tr>
<th>Renal</th>
<th>FLOW</th>
<th>GLP-1 RA</th>
<th>semaglutide sq</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>SGLT2 inh</td>
<td>DAPA-CKD</td>
<td>dapagliflozin</td>
</tr>
<tr>
<td></td>
<td>EMPA-Kidney</td>
<td>empagliflozin</td>
<td></td>
</tr>
<tr>
<td></td>
<td>CREDENCE</td>
<td>canagliflozin</td>
<td></td>
</tr>
</tbody>
</table>

SGLT 2 Side Effects

- Mycotic genital infections
- Urinary tract infections
- Dehydration & AKI (esp in population with lower eGFR)
- Orthostasis
- Diabetic Ketoacidosis
- Increased LDL
- Lower limb amputations
- Bone fractures

Assess volume status
Manage diuresis

Assess prior occurrence
Ensure not type 1!

Examine feet
Do not start if open wound
Patient education re. foot exam
GLP-1 RA or SGLT2 inh: This IS the Question! (or maybe both...?)

GLP-1 RA vs SGLT2i: HbA$_1c$

<table>
<thead>
<tr>
<th>DURATION 8$^1$</th>
<th>PIONEER 2$^2$</th>
<th>SUSTAIN 8$^3$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intention-to-treat</td>
<td>On-treatment</td>
<td>On-treatment</td>
</tr>
<tr>
<td>52 weeks</td>
<td>52 weeks</td>
<td>52 weeks</td>
</tr>
<tr>
<td>Baseline: 9.3%</td>
<td>Baseline: 8.1%</td>
<td>Baseline: 8.3%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Drug</th>
<th>Exe 2 mg</th>
<th>Dapa 10 mg</th>
<th>Oral sema 14 mg</th>
<th>Empa 25 mg</th>
<th>Sema 1.0 mg</th>
<th>Cana 300 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Change in HbA$_1c$ (%)</td>
<td>$-1.4$</td>
<td>$-1.2$</td>
<td>$-1.3$</td>
<td>$-0.8$</td>
<td>$-1.0$</td>
<td>$-1.0$</td>
</tr>
</tbody>
</table>

'Change from baseline in HbA$_1c$, from the 'on-treatment' observation period was:
1.8% with Exe 2 mg + Dapa 10 mg, $-1.6\%$ with Exe 2 mg, and $-1.2\%$ with Dapa 10 mg

2. Rodbard et al. Diab Care, 2019; 2272
3. Lingwai I et al. Lanced D&E, 2019:834
**GLP-1 RA vs SGLT-2i: weight**

<table>
<thead>
<tr>
<th>DURATION 81</th>
<th>PIONEER 22</th>
<th>SUSTAIN 82</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intention-to-treat’ 52 weeks</td>
<td>On-treatment 52 weeks</td>
<td>On-treatment 52 weeks</td>
</tr>
<tr>
<td>Baseline: 91 kg</td>
<td>Baseline: 92 kg</td>
<td>Baseline: 90 kg</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Drug</th>
<th>Exe 2 mg</th>
<th>Dapa 10 mg</th>
<th>Oral sema 14 mg</th>
<th>Empa 25 mg</th>
<th>Sema 1.0 mg</th>
<th>Cana 300 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Change in body weight (kg)</td>
<td>-1.5</td>
<td>-2.3</td>
<td>-4.7</td>
<td>-3.8</td>
<td>-4.2</td>
<td></td>
</tr>
</tbody>
</table>

*Change from baseline in body weight in the ‘on-treatment’ observation period was –3.3% with Exe 2 mg + Dapa 10 mg, –1.5% with Exe 2 mg, and –2.3% with Dapa 10 mg. 1. Jabbour SA et al. Diabetes Care 2018;41:2136–46; 2. Novo Nordisk. Data on file.*

---

**GLP-1 RA OR SGLT 2 INHIBITOR: THIS IS THE QUESTION!**

<table>
<thead>
<tr>
<th></th>
<th>GLP-1 RAs</th>
<th>SGLT 2 inhibitors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Administration</td>
<td>SQ (or PO)</td>
<td>PO</td>
</tr>
<tr>
<td>Frequency</td>
<td>Weekly (or daily)</td>
<td>daily</td>
</tr>
<tr>
<td>Glucose lowering</td>
<td>+++</td>
<td>+ (dependent on baseline HbA1c &amp; eGFR)</td>
</tr>
<tr>
<td>Weight lowering</td>
<td>+++</td>
<td>+</td>
</tr>
<tr>
<td>MACE</td>
<td>+++</td>
<td>+</td>
</tr>
<tr>
<td>HHF (reduced EF)</td>
<td>Neutral</td>
<td>++++</td>
</tr>
<tr>
<td>HFpEF</td>
<td>?</td>
<td>Pending</td>
</tr>
<tr>
<td>Renal outcomes</td>
<td>Pending</td>
<td>Likely, confirmed for CANA (for eGFR&gt;30)</td>
</tr>
<tr>
<td>eGFR &lt;30</td>
<td>Yes</td>
<td>Not indicated</td>
</tr>
<tr>
<td>Main AE</td>
<td>GI</td>
<td>Infections</td>
</tr>
</tbody>
</table>
Pathophysiology of CVD in Diabetes

Diabetes

Oxidative Stress → Inflammation → Insulin Resistance → Vasculopenia

Atherosclerotic (MACE) Events → Heart Failure Events → CV Death

CV, cardiovascular; CVD, cardiovascular disease; MACE, major adverse cardiovascular events.
Renal Effects of SGLT 2 inh and GLP1 RAs

**Broad kidney endpoint:** New macroalbuminuria, doubling of creatinine, 40% decline in eGFR, ESKD, renal death

Renal Effects of SGLT 2 inh and GLP1 RAs

**Kidney endpoint w/o albuminuria:** doubling of creatinine, 40% decline in eGFR, ESKD, renal death
SGLT2 inh & GLP-1 RA: Ideal Partnership?

**DURATION 8**
- Exenatide 2mg + Dapagliflozin 10 mg
  - Baseline HbA1c 9.3%
  - 28 wks f/u

**UTHSCSA**
- Liraglutide 1.8mg + Canagliflozin 300 mg
  - Baseline HbA1c 8.2%
  - 16 wks f/u

Change in HbA1c

Abdul-Ghani et al. Diabetes 2018 (Supl 1)
GLP-1 RA added to SGLT-2i: HbA<sub>1c</sub>

**AWARD 10**
- On-treatment
- 24 weeks
- Baseline: 8.0%

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Change in HbA&lt;sub&gt;1c&lt;/sub&gt; (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dula 1.5 mg</td>
<td>-1.34</td>
</tr>
<tr>
<td>Dula 0.75 mg</td>
<td>-1.2</td>
</tr>
<tr>
<td>PBO</td>
<td>-0.5</td>
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</tbody>
</table>

**SUSTAIN 9**
- On-treatment
- 30 weeks
- Baseline: 8.0%

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Change in HbA&lt;sub&gt;1c&lt;/sub&gt; (%)</th>
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</thead>
<tbody>
<tr>
<td>Sema 1.0 mg</td>
<td>-1.1</td>
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</table>

GLP-1 RA added to SGLT-2i: weight

**AWARD 10**
- On-treatment
- 24 weeks
- Baseline: 91.5 kg

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<thead>
<tr>
<th>Treatment</th>
<th>Change in body weight (kg)</th>
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<tr>
<td>Dula 1.5 mg</td>
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<tr>
<td>Dula 0.75 mg</td>
<td>-2.6</td>
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<tr>
<td>PBO</td>
<td>-2.1</td>
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**SUSTAIN 9**
- On-treatment
- 30 weeks
- Baseline: 91.7 kg

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<tr>
<td>Sema 1.0 mg</td>
<td>-3.4</td>
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</table>

Ludvik B et al. Lancet Diabetes Endocrinol 2018:370  
Zinman B et al. Lancet Diabetes and Endocrinology 2019
SGLT2 Inhibitors added to GLP 1 RA

CANVAS Study – patients on GLP-1 RA

Fulcher G. DiabObesMetab 2016 18:82

SGLT2 Inhibitors added to GLP 1 RA

CANVAS Study – patients on GLP-1 RA

Fulcher G. DiabObesMetab 2016 18:82
GLP-1 RA + SGLT2 = Match Made in Heaven?

Looking to the Future

Martinez R et al. Diabetes 2019:1182
# Cardiovascular Outcome Studies (CVOTs)

<table>
<thead>
<tr>
<th>GLP-1 RA</th>
<th>TECOS</th>
<th>CAROLINA</th>
<th>CARAMELINA</th>
<th>EXAMINE</th>
<th>SAVOR-TIMI</th>
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<tbody>
<tr>
<td></td>
<td>Sitagliptin</td>
<td>Linagliptin*</td>
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<td>Alogliptin</td>
<td>Saxagliptin</td>
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<td>PIONEER 6</td>
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<td>LEADER</td>
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<td>Semaglutide PO</td>
<td>Exenatide ER</td>
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<tr>
<td>Dual Agonists</td>
<td>SURPASS-CVOT</td>
<td>Semaglutide SQ</td>
<td>Semaglutide SQ</td>
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<td>SGLT 2 Inh</td>
<td>EMPA-REG</td>
<td>DECLARE</td>
<td>CANVAS</td>
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<td>Degludec*</td>
<td>Degludec*</td>
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</table>

*active comparator

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# Related Outcome Studies with Glucose Lowering Drugs

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<thead>
<tr>
<th>HFrEF</th>
<th>HFP EF</th>
<th>Nephropathy</th>
<th>Retinopathy</th>
<th>Obesity CVOT</th>
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<tbody>
<tr>
<td>GLP-1 RA</td>
<td>?</td>
<td>FLOW</td>
<td>FOCUS</td>
<td>SELECT</td>
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<tr>
<td>SGLT 2 Inh</td>
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<td>DELIVER</td>
<td>DAPA-CKD</td>
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<td>dapagliflozin</td>
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<td>EMPEROR-Pres</td>
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<td>SOLOIST-WHF</td>
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</table>
Dual and Triple Agonists

Tirzepetide – dual GIP-GLP-1 Agonist - phase 2 study
Tirzepetide – dual GIP-GLP-1 Agonist - phase 2 study

Therapeutic Areas Investigated for Incretin Therapy

- Type 2 Diabetes
- Obesity
- Cardiovascular event reduction
- NASH
- Diabetic Kidney Disease
- Diabetic Retinopathy
- Mental Health (Alzheimer, dementia, addiction)
CONCLUSIONS

• Diabetes treatment guidelines are progressing:
  • Cardiovascular and renal protection are taking a higher priority
  • Glycemic control still important, but a secondary goal

• SGLT 2 inhibitors have proven efficacy in preventing:
  • heart failure hospitalizations and CV death – in high risk patients (ASCVD or HFrEF)
  • progression of kidney disease – in patients with diabetic nephropathy (eGFR 30-90 and ACR>300)

• GLP-1 RAs have proven efficacy in:
  • preventing major cardiovascular events – in high and medium risk patient
  • weight management
  • Are safe and effective in more advanced renal dysfunction (eGFR<45)

• Combination therapy is tempting, data supporting it are limited at this time
• Research Volunteers
• Research Staff
• Collaborators
• Colleagues
• Fellows and Trainees
• Funders