Perspective in Diabetes Drug Treatment

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Sackler School of Medicine Tel Aviv University
Conflicts of Interest

- Consulting
  MSD, BI, SANOFI, NOVONORDISK, ASTRazenca, PFIZER, TEVA, NOVARTIS

- Lecture
  MSD, BI, SANOFI, NOVONORDISK, ASTRazenca, PFIZER, TEVA, NOVARTIS, DEXON
The History of Treatment for T2D

Adapted from: Kahn et al. Lancet, 2014
Glucose control remains a major focus in the management of patients with T2D. However, this should always be in the context of a comprehensive cardiovascular risk factor program...including blood pressure control, lipid management and, in some circumstances, anti-platelet therapy.”

“The impact of glucose control on cardiovascular complications remains uncertain; a more modest benefit is likely to be present, but probably emerges only after many years of improved control.”

“More long-term data regarding the cardiovascular impact of our glucose-lowering therapies will be available over the next 1–3 years. Information from these will further assist us in optimizing treatment strategies.”

DPP-4i, dipeptidyl peptidase-4 inhibitor; GLP-1RA, glucagon-like peptide-1 receptor agonist; HbA1c, glycosylated haemoglobin; SGLT2i, sodium-glucose cotransporter-2 inhibitor; SU, sulphonylurea; T2D, type 2 diabetes; TZD, thiazolidinedione

Inzucchi SE et al. Diabetologia 2015;58:429–442
Second-line therapy for T2D in patients with established ASCVD or heart failure

What is the background for the changes?
Major adverse cardiovascular events

<table>
<thead>
<tr>
<th>LEADER¹</th>
<th>SUSTAIN 6²</th>
</tr>
</thead>
<tbody>
<tr>
<td>MACE</td>
<td>0.87 (0.78; 0.97)</td>
</tr>
<tr>
<td>CV death</td>
<td>0.78 (0.66; 0.93)</td>
</tr>
<tr>
<td>Non-fatal MI</td>
<td>0.88 (0.75; 1.03)</td>
</tr>
<tr>
<td>Non-fatal stroke</td>
<td>0.89 (0.72; 1.11)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>EMPA-REG OUTCOME³</th>
<th>CANVAS Program⁴</th>
</tr>
</thead>
<tbody>
<tr>
<td>MACE</td>
<td>0.86 (0.74; 0.99)</td>
</tr>
<tr>
<td>CV death</td>
<td>0.62 (0.49; 0.77)</td>
</tr>
<tr>
<td>Non-fatal MI</td>
<td>0.87 (0.70; 1.09)</td>
</tr>
<tr>
<td>Non-fatal stroke</td>
<td>1.24 (0.92; 1.67)</td>
</tr>
</tbody>
</table>

ASCVD, atherosclerotic cardiovascular disease; CI, confidence interval; CV, cardiovascular; MACE, major adverse cardiovascular event; MI, myocardial infarction; T2D, type 2 diabetes
Second-line therapy for T2D in patients with established ASCVD or HF

What is the background for the changes?
Hospitalisation for HF

EMP-A-REG OUTCOME

**HR: 0.65**
(95% CI: 0.50; 0.85)
*p*=0.002

![Graph showing EMP-A-REG OUTCOME](chart1)

CANVAS Program

**HR: 0.67**
(95% CI: 0.52; 0.87)

![Graph showing CANVAS Program](chart2)

LEADER

**HR: 0.87**
(95% CI: 0.73; 1.05)
*p*=0.14

![Graph showing LEADER](chart3)

SUSTAIN 6

**HR: 1.11**
(95% CI: 0.77; 1.61)
*p*=0.57

![Graph showing SUSTAIN 6](chart4)

ASCVD, atherosclerotic cardiovascular disease; CI, confidence interval; HF, heart failure; HR, hazard ratio; T2D, type 2 diabetes

### Considerations related to chronic kidney disease

**What is the background for the changes?**

**MACE in patients with and without CKD**

<table>
<thead>
<tr>
<th>Study</th>
<th>Hazard ratio (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>LEADER</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total population</td>
<td>0.87 (0.78; 0.97)</td>
<td></td>
</tr>
<tr>
<td>eGFR &lt;60 mL/min/1.73 m²</td>
<td>0.69 (0.57; 0.85)</td>
<td></td>
</tr>
<tr>
<td>eGFR ≥60 mL/min/1.73 m²</td>
<td>0.94 (0.83; 1.07)</td>
<td>0.01</td>
</tr>
<tr>
<td>Micro/macroalbuminuria*</td>
<td>0.83 (0.71; 0.97)</td>
<td></td>
</tr>
<tr>
<td>Normoalbuminuria*</td>
<td>0.92 (0.79; 1.07)</td>
<td>0.36</td>
</tr>
</tbody>
</table>

**EMPA-REG OUTCOME**

<table>
<thead>
<tr>
<th>Hazard ratio (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total population</td>
<td>0.86 (0.74; 0.99)</td>
</tr>
<tr>
<td>eGFR ≥90 mL/min/1.73 m²</td>
<td>1.10 (0.77; 1.57)</td>
</tr>
<tr>
<td>eGFR 60 to &lt;90 mL/min/1.73 m²</td>
<td>0.76 (0.61; 0.94)</td>
</tr>
<tr>
<td>eGFR &lt;60 mL/min/1.73 m²</td>
<td>0.88 (0.69; 1.13)</td>
</tr>
<tr>
<td>UACR &lt;30 mg/g</td>
<td>0.89 (0.72; 1.16)</td>
</tr>
<tr>
<td>UACR ≥30 to 300 mg/g</td>
<td>0.89 (0.69; 1.16)</td>
</tr>
<tr>
<td>UACR &gt;300 mg/g</td>
<td>0.69 (0.49; 0.96)</td>
</tr>
</tbody>
</table>

**SUSTAIN 6**

<table>
<thead>
<tr>
<th>Hazard ratio (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total population</td>
<td>0.74 (0.58; 0.95)</td>
</tr>
<tr>
<td>eGFR &lt;30 mL/min/1.73 m²</td>
<td>0.73 (0.27; 1.97)</td>
</tr>
<tr>
<td>eGFR ≥30 mL/min/1.73 m²</td>
<td>0.74 (0.57; 0.95)</td>
</tr>
<tr>
<td>eGFR &lt;60 mL/min/1.73 m²</td>
<td>0.84 (0.57; 1.25)</td>
</tr>
<tr>
<td>eGFR ≥60 mL/min/1.73 m²</td>
<td>0.67 (0.48; 0.92)</td>
</tr>
</tbody>
</table>

**CANVAS Program**

<table>
<thead>
<tr>
<th>Hazard ratio (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total population</td>
<td>0.86 (0.75; 0.97)</td>
</tr>
<tr>
<td>eGFR &lt;45 mL/min/1.73 m²</td>
<td>0.65 (0.41; 1.03)</td>
</tr>
<tr>
<td>eGFR 45 to &lt;60 mL/min/1.73 m²</td>
<td>0.71 (0.53; 0.95)</td>
</tr>
<tr>
<td>eGFR &lt;60 to 90 mL/min/1.73 m²</td>
<td>0.95 (0.80; 1.13)</td>
</tr>
<tr>
<td>eGFR ≥90 mL/min/1.73 m²</td>
<td>0.84 (0.62; 1.13)</td>
</tr>
</tbody>
</table>

*Only patients with albuminuria measurements at baseline (n=9137) included in albuminuria group.

CI, confidence interval; eGFR, estimated glomerular filtration rate; HR, hazard ratio; MAC, major adverse cardiovascular event; UACR, urinary albumin-to-creatinine ratio.

Summary of the efficacy and safety findings in SGLT-2i CVOTs

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>DECLARE¹</th>
<th>EMPA-REG²</th>
<th>CANVAS³</th>
</tr>
</thead>
<tbody>
<tr>
<td>MACE Non-inferiority</td>
<td>✔️</td>
<td>✔️</td>
<td>✔️</td>
</tr>
<tr>
<td>hHF/CV Death</td>
<td>✔️</td>
<td>Nominal</td>
<td>Nominal</td>
</tr>
<tr>
<td>MACE Superiority</td>
<td>✗</td>
<td>✔️</td>
<td>✔️</td>
</tr>
<tr>
<td>Renal Composite</td>
<td>Nominal</td>
<td>Nominal</td>
<td>Nominal</td>
</tr>
<tr>
<td>Amputations</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Fractures</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Bladder cancer</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Genital infections</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>DKA</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
</tbody>
</table>

- ✔️ Statistically significant
- ✗ Not statistically significant
- No No imbalance
- Yes Imbalance observed
- Nominal
- Not formally significant as pre-specified in statistical analysis plan

CV, cardiovascular; CVOT, CV outcome trials; DKA, diabetic ketoacidosis; hHF, hospitalizations for heart failure; MACE, major adverse CV events; SGLT-2i, sodium-glucose co-transporter 2 inhibitor; T2D, type 2 diabetes

While earlier studies with diabetes treatments did not definitively show benefit for CV disease and HF, GLP-1 RAs are shown to have CV benefits driven by less atherosclerotic events.

<table>
<thead>
<tr>
<th></th>
<th>LEADER¹</th>
<th>SUSTAIN-6²</th>
<th>EXSCEL³ ⁴</th>
<th>HARMONY⁵</th>
</tr>
</thead>
<tbody>
<tr>
<td>MACE</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death from CV causes</td>
<td>0.87 (0.78, 0.97)</td>
<td>0.74 (0.58, 0.95)</td>
<td>0.91 (0.83, 1.00)</td>
<td>0.78 (0.68, 0.90)</td>
</tr>
<tr>
<td>Nonfatal MI</td>
<td>0.78 (0.66, 0.93)</td>
<td>0.98 (0.65, 1.48)</td>
<td>0.88 (0.76, 1.02)</td>
<td>0.93 (0.73, 1.19)</td>
</tr>
<tr>
<td>Nonfatal stroke</td>
<td>0.88 (0.75, 1.03)</td>
<td>0.74 (0.51, 1.08)</td>
<td>0.95 (0.84, 1.09)</td>
<td>0.75 (0.61, 0.0)²</td>
</tr>
<tr>
<td>Hosp. for heart failure</td>
<td>0.87 (0.73, 1.05)</td>
<td>1.11 (0.77, 1.61)</td>
<td>0.94 (0.78, 1.13)</td>
<td>0.85 (0.70, 1.04)⁴</td>
</tr>
<tr>
<td>Renal endpoint</td>
<td>0.78 (0.67, 0.92)²</td>
<td>0.64 (0.46, 0.88)³</td>
<td>0.85 (0.74, 0.98)⁵ ⁶</td>
<td></td>
</tr>
</tbody>
</table>

Favors liraglutide | Favors placebo | Favors semaglutide | Favors placebo | Favors exenatide QW | Favors placebo |

Favors placebo | Favors albiglutide | Favors placebo |

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²New onset of macroalbuminuria or a doubling of the serum creatinine level and an eGFR of ≤45 ml/min/1.73 m², the need for continuous renal-replacement therapy, or death from renal disease; ²New or worsening nephropathy includes persistent macroalbuminuria, persistent doubling of the serum creatinine level and a creatinine clearance of less than 45 ml/min/1.73 m² (according to the Modification of Diet in Renal Disease criteria), or the need for continuous renal-replacement therapy; ²40% eGFR decline, renal replacement, renal death, or new-onset macroalbuminuria; ²Adjusted for age, sex, ethnicity, race, region, duration of diabetes, prior history of CV event, insulin use, baseline glycated hemoglobin, eGFR, and body-mass index included fasting and nonfasting events; ²Composite of CV death or hospitalization for heart failure. CI, confidence interval; CV, cardiovascular; eGFR, estimated glomerular filtration rate; GLP-1 RA, GLP-1 receptor agonists; HR, hazard ratio; MACE, major adverse cardiovascular events; MI, myocardial infarction; QW, once weekly

Management of hyperglycaemia in type 2 diabetes – 2018 version

Key points to emphasise

Update informed by evidence generated in the past two years*

Greater focus on lifestyle interventions, with increased emphasis on weight loss and obesity management, incl. metabolic surgery

Greater focus on patient-related issues and self-management, which have a major impact on success of any pharmacological interventions

Preferred choices of glucose-lowering agents driven by the new evidence from CVOTs and consideration of major clinical need

*Between 1 January 2014 and 28 February 2018
ADA, American Diabetes Association; CVOT, cardiovascular outcomes trial; EASD, European Association for the Study of Diabetes
Management of hyperglycaemia in type 2 diabetes – 2018 version

Overall approach

Overall diabetes regimen
Based on patient preferences and clinical characteristics

Goals of diabetes care
Prevent complications and optimise quality of life

Fit for real-world use
Access, treatment cost, and insurance coverage should all be considered when selecting glucose-lowering medications
Decision cycle for patient-centred glycaemic management in type 2 diabetes

ASSESS KEY PATIENT CHARACTERISTICS
- Current lifestyle
- Comorbidities, i.e. ASCVD, CKD, HF
- Clinical characteristics, i.e. age, HbA1c, weight
- Issues such as motivation and depression
- Cultural and socio-economic context

CONSIDER SPECIFIC FACTORS THAT IMPACT ON CHOICE OF TREATMENT
- Individualised HbA1c target
- Impact on weight and hypoglycaemia
- Side-effect profile of medication
- Complexity of regimen i.e. frequency, mode of administration
- Choose regimen to optimise adherence and persistence
- Access, cost and availability of medication

Goals of care

• Prevent complications
• Optimise quality of life

AGREE MANAGEMENT PLAN

IMPLEMENT MANAGEMENT PLAN

ONGOING MONITORING AND SUPPORT

REVIEW & AGREE MANAGEMENT PLAN

ASCVD, atherosclerotic cardiovascular disease; CKD, chronic kidney disease; HbA1c, glycosylated haemoglobin; HF, heart failure
Glucose-lowering medication in type 2 diabetes: Overall approach

First-line therapy is metformin and comprehensive lifestyle (including weight management and physical activity) if HbA\(_1c\) above target proceed as below

**Established ASCVD or CKD**

- **ASCVD predominates**
  - GLP-1RA with proven CVD benefit*
  - SGLT-2i with proven CVD benefit* if eGFR adequate†

- **HF or CKD predominates**
  - PREFERABLY
    - SGLT-2i with evidence of reducing HF and/or CKD progression in CVOT if eGFR adequate‡
      - OR
    - If SGLT-2i not tolerated or contraindicated if eGFR less than adequate add GLP-1RA with proven CVD benefit*.

If HbA\(_1c\) above target

- Avoid TZD in the setting of HF
- Choose agents demonstrating CV safety:
  - Consider adding the other class (GLP-1RA and/or SGLT-2i) with proven CVD benefit
  - DPP-4i (not saxagliptin) in the setting of HF (if not on GLP-1RA)

If further intensification is required or patient is now unable to tolerate GLP-1RA and/or SGLT-2i, choose agents demonstrating CV safety:

- Consider adding the other class (GLP-1RA and/or SGLT-2i) with proven CVD benefit
- DPP-4i if not on GLP-1RA

**Without established ASCVD or CKD**

- **Compelling need to minimise hypoglycaemia**
  - DPP-4i
  - GLP-1RA
  - SGLT-2i
  - TZD

  - If HbA\(_1c\) above target
    - If HbA\(_1c\) above target
      - SGLT-2i
      - OR
      - GLP-1RA
      - OR
      - TZD

  - If HbA\(_1c\) above target
    - Continue with addition of other agents as outlined above

  - If HbA\(_1c\) above target
    - Consider the addition of SU** OR basal insulin:
      - Choose later generation SU with lower risk of hypoglycaemia*
      - Consider basal insulin with lower risk of hypoglycaemia*

- **Compelling need to minimise weight gain or promote weight loss**
  - GLP-1RA with good efficacy for weight loss**
  - OR
  - SGLT-2i

  - If HbA\(_1c\) above target
    - If HbA\(_1c\) above target
      - SGLT-2i
      - OR
      - GLP-1RA
      - OR
      - TZD

  - If HbA\(_1c\) above target
    - If HbA\(_1c\) above target
      - GLP-1RA
      - OR
      - TZD

  - If HbA\(_1c\) above target
    - If HbA\(_1c\) above target
      - SGLT-2i
      - OR
      - GLP-1RA

Cost is a major issue†††

- **Established ASCVD or CKD**
  - Insulin therapy:
    - Basal insulin with lowest acquisition cost
    - OR
    - Consider DPP-4i OR SGLT-2i with lowest acquisition cost†‡‡

- **Without established ASCVD or CKD**
  - Basal insulin:
    - OR
    - Consider the addition of SU** OR basal insulin:
      - Choose later generation SU with lower risk of hypoglycaemia
      - Consider basal insulin with lower risk of hypoglycaemia*

*Proven CVD benefit means it has label indication of reducing CVD events. For GLP-1RA strongest evidence for lixisenatide > exenatide extended release. For SGLT-2i evidence modestly stronger for empagliflozin > canagliflozin. **Be aware that SGLT-2i vary by region and individual agent with regard to indicated level of eGFR for initiation and continued use. †Both empagliflozin and canagliflozin have shown reduction in HF and reduction in CKD progression in CVOTs. ‡Degludec or U100 glargine have demonstrated CVD safety. §Low dose may be better tolerated though less well studied for CVD effects. ¶Choose later generation SU with lower risk of hypoglycaemia. †Degludec / glargine U300/glargine U100 / detemir = NPH insulin. **Semaglutide > liraglutide > dulaglutide > exenatide > lixisenatide. §§If no specific comorbidities (i.e. no established CVD, low risk of hypoglycaemia and lower priority to avoid weight gain or no weight-related comorbidities). ||Consider country- and region-specific cost of drugs. In some countries, TZDs relatively more expensive and DPP-4i relatively cheaper.

Without established ASCVD or CKD

If HbA\(_1c\) above target

- If HbA\(_1c\) above target
  - PREFERABLY
    - DPP-4i (if not on GLP-1RA)
  - Basal insulin
  - TZD
  - SU**

If triple therapy required or SGLT-2i and/or GLP-1RA not tolerated or contraindicated use regimen with lowest risk of weight gain:

- PREFERABLY
  - DPP-4i (if not on GLP-1RA)
  - Basal insulin
  - TZD
  - SU**
Glucose-lowering medication in type 2 diabetes: Overall approach

**Without established ASCVD or CKD**

- **Established ASCVD or CKD**
  - **ASCVD predominates**
    - **GLP-1RA with proven CVD benefit**
    - **SGLT-2i with proven CVD benefit**
    - **GLP-1RA or DPP-4i**
  - **HF OR CKD predominates**
    - **SGLT-2i with evidence of reducing HF and/or CKD progression in CVOT if eGFR adequate**
    - **GLP-1RA or DPP-4i**
  - **If HbA1c above target**
    - **Avoid TZD in the setting of HF**
    - **Consider adding the other class (GLP-1RA and/or SGLT-2i) with proven CVD benefit**
      - **DPP-4i if not on GLP-1RA**
      - **Basal insulin**
      - **TZD**

- **Compelling need to minimise hypoglycaemia and weight gain**
  - **If triple therapy required or SGLT-2i and/or GLP-1RA not tolerated or contraindicated or patient already on GLP-1RA**
    - **DPP-4i (if not on GLP-1RA)**
    - **SGLT-2i**
    - **GLP-1RA with good efficacy for weight loss**
    - **TZD**
    - **SUI**

- **If HbA1c above target**
  - **Consider DPP-4i with lowest acquisition cost or SU with lowest risk of weight gain or patient already on GLP-1RA**
    - **DPP-4i**
    - **SUI**

- **If HbA1c above target**
  - **Consider basal insulin with lowest risk of hypoglycaemia and weight gain**
    - **SUI**
    - **TZD**
    - **Basal insulin**

- **If DPP-4i not tolerated or contraindicated or patient already on GLP-1RA**
  - **Consider SU with lower risk of hypoglycaemia and weight gain**
    - **SUI**
    - **TZD**

- **Without established ASCVD or CKD**
  - **If HbA1c above target**
    - **Consider SU with lower risk of hypoglycaemia and weight gain**
      - **SU6• TZD5• Basal insulin**
  - **With lowest acquisition cost**
    - **GLP-1RA with good efficacy for weight loss**
    - **TZD with good efficacy for weight loss**
    - **SUI**

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**To avoid clinical inertia re-assess and modify treatment regularly (3–6 months)**

- **First-line therapy is Metformin and comprehensive lifestyle (including weight management and physical activity)**
  - **IF HbA1c ABOVE TARGET PROCEED AS BELOW**
  - **EITHER/ OR**
  - **SU with lowest risk of hypoglycaemia**
  - **DPP-4i if not on GLP-1RA**
  - **If triple therapy required or SGLT-2i**
  - **TZD**
  - **Insulin therapy**

**Cost is a major issue****

- **If HbA1c above target**
  - **Consider DPP-4i or SGLT-2i with lowest acquisition cost**
  - **SU with lowest risk of weight gain**
  - **TZD with good efficacy for weight loss**
  - **SUI**

---

- **CVD benefit**
  - **Proven CVD benefit means it has label indication of reducing CVD events. For GLP-1RA strongest evidence for liraglutide>semaglutide>exenatide extended release. For SGLT-2i evidence modestly stronger for empagliflozin>canagliflozin>ipragliflozin.**

---

- **Compelling need to minimise hypoglycaemia and weight gain**
  - **If HbA1c above target**
    - **Consider later generation SU with lower risk of hypoglycaemia and weight gain**
      - **SU6• TZD5• Basal insulin**

---

- **Avoid TZD in the setting of HF**
  - **Consider adding the other class with proven CVD benefit**
  - **DPP-4i if not on GLP-1RA**
  - **Basal insulin**
  - **TZD**

---

- **If further intensification is required or patient is now unable to tolerate GLP-1RA and/or SGLT-2i, choose agents demonstrating CV safety:**
  - **Consider adding the other class (GLP-1RA and/or SGLT-2i) with proven CVD benefit**
  - **DPP-4i if not on GLP-1RA**
  - **Basal insulin**
  - **TZD**
First-line therapy
First-line glucose-lowering medication for T2D
What are the changes?

General approach 2015:
Metformin remains the optimal drug for monotherapy

General approach 2018:
Metformin is the preferred glucose-lowering drug for most people with T2D

T2D, type 2 diabetes
First-line glucose-lowering medication for T2D

2018

- Metformin, on top of lifestyle intervention, remains as the recommended first line glucose-lowering medication for patients with T2D.
Patients with established ASCVD, CKD or HF

ASCVD, atherosclerotic cardiovascular disease; CKD, chronic kidney disease; HF, heart failure
Second-line therapy for T2D in patients with established ASCVD, CKD or HF

What are the changes?

General approach 2015:
Not any specific preferences

General approach 2018:
In patients with established ASCVD, CKD or HF a GLP-1RA or a SGLT-2i with proven CVD benefit is recommended

ASCVD, atherosclerotic cardiovascular disease; GLP-1RA, glucagon-like peptide-1 receptor agonist; HF, heart failure; SGLT-2i, sodium-glucose cotransporter-2 inhibitor
Second-line therapy for T2D in patients with established ASCVD or HF

**ASCVD predominates**

- **GLP-1RA with proven CVD benefit***

- **SGLT-2i with proven CVD benefit**, if eGFR adequate†

**If HbA1c above target**

If further intensification is required or patient is now unable to tolerate GLP-1RA and/or SGLT-2i, choose agents demonstrating CV safety:

- Consider adding the other class (GLP-1RA and/or SGLT-2i) with proven CVD benefit
- DPP-4i if not on GLP-1RA
- Basal insulin§
- TZD¶
- SU||

**HF OR CKD predominates**

**PREFERABLY**

- **SGLT-2i with evidence of reducing HF and/or CKD progression in CVOT if eGFR adequate‡**

**If SGLT-2i not tolerated or contraindicated or if eGFR less than adequate† add GLP-1RA with proven CV benefit***#

**If HbA1c above target**

Choose agents demonstrating CV safety:

- Consider adding the other class with proven CVD benefit*
- DPP-4i (not saxagliptin) in the setting of HF (if not on GLP-1RA)
- Basal insulin§
- SU||

*Proven CVD benefit means it has label indication of reducing CVD events. For GLP-1RA strongest evidence for liraglutide>semaglutide>exenatide extended release. For SGLT-2i evidence modestly stronger for empagliflozin>canagliflozin; †Be aware that SGLT-2i vary by region and individual agent with regard to indicated level of eGFR for initiation and continued use; ‡Both empagliflozin and canagliflozin have shown reduction in HF and reduction in CKD progression in CVOTs; §Degludec or U100 glargine have demonstrated CVD safety; ¶Low dose may be better tolerated though less well studied for CVD effects; ||Choose later generation SU with lower risk of hypoglycaemia; *Caution with GLP-1RA in ESRD
Choosing glucose-lowering medication

In patients with established ASCVD

**ASCVD predominates**

GLP-1RA with proven CVD benefit*

**EITHER/OR**

SGLT-2i with proven CVD benefit*, if eGFR adequate‡

If HbA₁c above target

If further intensification is required or patient is now unable to tolerate GLP-1RA and/or SGLT-2i, choose agents demonstrating CV safety:
- Consider adding the other class (GLP-1RA and/or SGLT-2i) with proven CVD benefit
- DPP-4i if not on GLP-1RA
- Basal insulin§
- TZD¶
- SU||

---

*Proven CVD benefit means it has label indication of reducing CVD events. For GLP-1RA strongest evidence for liraglutide>semaglutide>exenatide extended release. For SGLT-2i evidence modestly stronger for empagliflozin>canagliflozin; †Be aware that SGLT-2i vary by region and individual agent with regard to indicated level of eGFR for initiation and continued use; ‡Both empagliflozin and canagliflozin have shown reduction in HF and reduction in CKD progression in CVOTs; §Degludec or U100 glargine have demonstrated CVD safety; ¶Low dose may be better tolerated though less well studied for CVD effects; ||Choose later generation SU with lower risk of hypoglycaemia
Choosing glucose-lowering medication

In patients with established HF or CKD

- SGLT-2is preferred over GLP-1RAs as significant, consistent reductions in hospitalisation for HF have been seen in SGLT-2i trials
- SGLT-2i
  - Empagliflozin, Canagliflozin, Dapagliflozin
- GLP-1RA
  - Liraglutide preferred

<table>
<thead>
<tr>
<th>HF OR CKD predominates</th>
<th>OR</th>
</tr>
</thead>
<tbody>
<tr>
<td>SGLT-2i with evidence of reducing HF and/or CKD progression in CVOT if eGFR adequate*</td>
<td>SGLT-2i not tolerated or contraindicated or if eGFR less than adequate† add GLP-1RA with proven CV benefit*#</td>
</tr>
</tbody>
</table>

- Avoid TZD in the setting of HF
- Choose agents demonstrating CV safety:
  - Consider adding the other class with proven CVD benefit*
  - DPP-4i (not saxagliptin) in the setting of HF (if not on GLP-1RA)
  - Basal insulin§
  - SU||

*Proven CVD benefit means it has label indication of reducing CVD events. For GLP-1RA strongest evidence for liraglutide>semaglutide>exenatide extended release. For SGLT-2i evidence modestly stronger for empagliflozin>canagliflozin; †Be aware that SGLT-2i vary by region and individual agent with regard to indicated level of eGFR for initiation and continued use; *Both empagliflozin and canagliflozin have shown reduction in HF and reduction in CKD progression in CVOTs; §Degludec or U100 glargine have demonstrated CVD safety; ||Choose later generation SU with lower risk of hypoglycaemia; #Caution with GLP-1RA in ESRD
The sodium-glucose cotransporter-2 (SGLT2) therapy
Normal glucose homeostasis

Net balance $\approx 0$ g/day

<table>
<thead>
<tr>
<th>Glucose input $\approx 250$ g/day:</th>
<th>Glucose uptake $\approx 250$ g/day:</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Dietary intake $\approx 180$ g/day</td>
<td>• Brain $\approx 125$ g/day</td>
</tr>
<tr>
<td>• Glucose production $\approx 70$ g/day</td>
<td>• Rest of the body $\approx 125$ g/day</td>
</tr>
<tr>
<td>• Gluconeogenesis</td>
<td></td>
</tr>
<tr>
<td>• Glycogenolysis</td>
<td></td>
</tr>
</tbody>
</table>

Net balance $\approx 0$ g/day:

- The kidney filters circulating glucose
  - Glucose filtered $\approx 180$ g/day
- The kidney reabsorbs and recirculates glucose
  - Glucose reabsorbed $\approx 180$ g/day

---

Glucose handling in Type 2 diabetes\textsuperscript{1,2}

Glucose input >280 g/day:
- Dietary intake >180 g/day
- Glucose production ~100 g/day
  - Gluconeogenesis\textsuperscript{*}
  - Glycogenolysis

Glucose uptake >250 g/day:
- Brain ~125 g/day
- Rest of the body >125 g/day

Average blood glucose concentration \textbf{150 mg/dL}
Kidney filters all circulating glucose

\textit{Glucose filtered} ~270 g/day

Increased reabsorption and recirculation of glucose

Above the renal threshold for glucose (~200 mg/dL), glucose is excreted in the urine (glucosuria)

\textsuperscript{*}Elevated glucose production in patients with Type 2 diabetes attributed to hepatic and renal gluconeogenesis.\textsuperscript{2}

Renal glucose reabsorption in healthy individuals

Filtered glucose load 180 g/day

SGLT2 ~90%

SGLT1 ~10%

The sodium-glucose cotransporter-2 (SGLT2) mechanism in the proximal tubule

Renal glucose reabsorption in patients with hyperglycaemia

When blood glucose increases above the renal threshold (>\sim 10 \text{ mmol/L} \text{ or } >180 \text{ mg/dL}), the capacity of SGLT’s is exceeded, resulting in urinary glucose excretion.

Empagliflozin increases urinary glucose excretion via SGLT2 inhibition

*Loss of ~ 80 g of glucose per day = 240 cal/day.

~ 80 g

SGLT, sodium glucose cotransporter.
*Filtering glucose load > 180 g/day
SGLT1 compensate
SGLT2 inhibitor
SGLT2 inhibitors reduce glucose reabsorption in the proximal tubule, leading to urinary glucose excretion* and osmotic diuresis

~ 80 g
### Mean difference and heterogeneity in meta-analyses of double blind, randomised controlled trials comparing SGLT2-i versus placebo.

<table>
<thead>
<tr>
<th>SGLT2-I</th>
<th>Total n</th>
<th>Mean difference (confidence interval)</th>
<th>I²(Q) %</th>
<th>Sub group differences</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fasting plasma glucose (mg/dL)</td>
<td>8,914</td>
<td>-28.1 (-31.1; -25.1)</td>
<td>79.1</td>
<td>P = 0.04</td>
</tr>
<tr>
<td>Body weight (kg)</td>
<td>9,612</td>
<td>-2.1 (-2.3; -1.9)</td>
<td>44.5</td>
<td>P &lt; 0.01</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>9,336</td>
<td>-3.9 (-4.6; -3.3)</td>
<td>33.6</td>
<td>P = 0.03</td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg)</td>
<td>7,402</td>
<td>-2.0 (-2.4; -1.6)</td>
<td>6.3</td>
<td>P = 0.82</td>
</tr>
<tr>
<td>Heart rate (bpm)</td>
<td>4,587</td>
<td>-0.6 (-1.3; 0.0)</td>
<td>48.4</td>
<td>P = 0.04</td>
</tr>
<tr>
<td>HDL cholesterol (mmol/L)</td>
<td>4,696</td>
<td>0.05 (0.04; 0.07)</td>
<td>31.0</td>
<td>P = 0.03</td>
</tr>
<tr>
<td>Triglycerides (mmol/L)</td>
<td>4,704</td>
<td>-0.09 (-0.16; 0.02)</td>
<td>29.8</td>
<td>P &lt; 0.01</td>
</tr>
<tr>
<td>LDL cholesterol (mmol/L)</td>
<td>5,431</td>
<td>0.09 (0.04; 0.14)</td>
<td>55.5</td>
<td>P &lt; 0.01</td>
</tr>
<tr>
<td>Alanine aminotransferase (U/L)</td>
<td>3,719</td>
<td>-2.8 (-4.0; -1.7)</td>
<td>44.3</td>
<td>P = 0.59</td>
</tr>
<tr>
<td>Creatinine (umol/L)</td>
<td>5,445</td>
<td>0.6 (0.1; 1.1)</td>
<td>11.3</td>
<td>P = 0.05</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Dapagliflozin</th>
<th>Total n</th>
<th>MD (CI)</th>
<th>I²(Q) %</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Fasting plasma glucose (mg/dL)</td>
<td>3,844</td>
<td>-24.6 (-28.7; -20.4)</td>
<td>74</td>
<td></td>
</tr>
<tr>
<td>Body weight (kg)</td>
<td>4,432</td>
<td>-2.0 (-2.2; -1.8)</td>
<td>24</td>
<td></td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>3,943</td>
<td>-3.0 (-4.3; -2.7)</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg)</td>
<td>2,699</td>
<td>-2.1 (-2.9; -1.3)</td>
<td>9</td>
<td></td>
</tr>
<tr>
<td>Heart rate (bpm)</td>
<td>2,148</td>
<td>-0.7 (-2.1; 0.7)</td>
<td>63</td>
<td></td>
</tr>
<tr>
<td>HDL cholesterol (mmol/L)</td>
<td>1,75</td>
<td>0.09 (-0.03; 0.21)</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>Triglycerides (mmol/L)</td>
<td>1,75</td>
<td>0.00 (-0.12; 0.12)</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>LDL cholesterol (mmol/L)</td>
<td>1,75</td>
<td>-0.15 (-0.32; 0.02)</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>Alanine aminotransferase (U/L)</td>
<td>1,817</td>
<td>-2.1 (-3.8; -0.5)</td>
<td>30</td>
<td></td>
</tr>
<tr>
<td>Creatinine (umol/L)</td>
<td>2,335</td>
<td>0.3 (-0.4; 1.0)</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Empagliflozin</th>
<th>Total n</th>
<th>MD (CI)</th>
<th>I²(Q) %</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Fasting plasma glucose (mg/dL)</td>
<td>2,855</td>
<td>-29.5 (-33.1; -25.9)</td>
<td>60</td>
<td></td>
</tr>
<tr>
<td>Body weight (kg)</td>
<td>3,063</td>
<td>-2.0 (-2.2; -1.7)</td>
<td>9</td>
<td></td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>3,185</td>
<td>-3.2 (-4.2; -2.3)</td>
<td>11</td>
<td></td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg)</td>
<td>3,185</td>
<td>-1.9 (-2.5; -1.2)</td>
<td>31</td>
<td></td>
</tr>
<tr>
<td>Heart rate (bpm)</td>
<td>1,103</td>
<td>0.5 (-0.7; 1.6)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>HDL cholesterol (mmol/L)</td>
<td>2,417</td>
<td>0.04 (0.02; 0.06)</td>
<td>27</td>
<td></td>
</tr>
<tr>
<td>Triglycerides (mmol/L)</td>
<td>2,435</td>
<td>0.00 (-0.09; 0.08)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>LDL cholesterol (mmol/L)</td>
<td>3,173</td>
<td>0.06 (0.01; 0.10)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Alanine aminotransferase (U/L)</td>
<td>673</td>
<td>-3.4 (-6.1; -0.6)</td>
<td>46</td>
<td></td>
</tr>
<tr>
<td>Creatinine (umol/L)</td>
<td>1,872</td>
<td>0.3 (-0.6; 1.1)</td>
<td>15</td>
<td></td>
</tr>
</tbody>
</table>

Storgaard H, PLOS ONE November 11, 2016
What is SGLT2 doing?

**SGLT2** may produce changes in metabolism, sodium and volume to unburden the diabetic heart and kidney.

### The diabetic heart and kidney

- Glucose
- Salt
- Water

### Possible mechanisms driving the cardio-renal effects of empagliflozin

- Glucose
- Salt
- Water

### EMPA-REG OUTCOME®

- 3P-MACE ↓14%
- CV death ↓38%
- All-cause mortality ↓32%
- HHF ↓35%
- Incident or worsening nephropathy ↓39%
Possible CV and renal mechanisms of SGLT2

SGLT2i  Mechanism  Possible cardio–renal effects  CV/renal outcomes observed in EMPA–REG OUTCOME®

Volume  Cardiac function  Preload  Cardiac efficiency  CV death

Metabolism  Arrhythmia

Sodium  Arterial wall structure/function  Renal function

UNa  REG

REG, removal of excess glucose; UNa, urinary sodium
Empagliflozin may improve arterial wall structure/function, and cardiac and renal function, by reducing glucose toxicity.

The available evidence to support the hypothesis may be incomplete; specific evidence for empagliflozin may not be available for the hypothesis or parts thereof.

IC, intracellular; REG, removal of excess glucose
Empagliflozin may influence cardiac and renal function via changes in energy supply

The available evidence to support the hypothesis may be incomplete; specific evidence for empagliflozin may not be available for the hypothesis or parts thereof.

FFA, free fatty acids; REG, removal of excess glucose
Empagliflozin may reduce glomerular pressure by activating tubuloglomerular feedback

The available evidence to support the hypothesis may be incomplete; specific evidence for empagliflozin may not be available for the hypothesis or parts thereof.

MD, macula densa; UNa, urinary sodium
Hyperfiltration in diabetic nephropathy and reduction of hyperfiltration by SGLT2 inhibitors

Sanjay K, Adv Ther (2016)
The Glucagon Like Peptide-1 (GLP-1) Receptor Analog therapy
Islet cell dysfunction leads to abnormal insulin and glucagon dynamics in type 2 diabetes

The incretin hormones play a crucial role in a healthy insulin response

• Insulin response is greater following oral glucose than iv glucose, despite similar plasma glucose concentration

**Nauck et al. Diabetologia 1986;29:46–52, healthy volunteers (n=8)**
The absolute incretin effect is reduced in type 2 diabetes

Healthy (n = 8)

Type 2 diabetes (n = 14)

Nauck et al. Diabetologia 1986;29:46–52, healthy volunteers (n=8)
Native GLP-1 is rapidly degraded by DPP-4

Double immunohistochemical staining for DPP-4 (red) and GLP-1 (green) in the human ileum

Adapted from: Hansen et al. Endocrinology 1999;140:5356–63
Proposed routes of action of GLP-1 in the central regulation of feeding and glucose metabolism
GLP-1RAs have multifactorial effects
GLP-1 action in the central nervous system.

Geloneze B, Drugs (2017)
**GLP-1RAs for the treatment of T2D**

<table>
<thead>
<tr>
<th>Exendin-4 based</th>
<th>Human-based</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Small</td>
</tr>
<tr>
<td><strong>Exenatide</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>Liraglutide</strong></td>
</tr>
<tr>
<td></td>
<td><strong>Semaglutide</strong></td>
</tr>
<tr>
<td><strong>Lixisenatide</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Dulaglutide</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Albiglutide</strong></td>
<td></td>
</tr>
</tbody>
</table>

*Albiglutide will be withdrawn by July 2018 for commercial reasons.*

GLP-1RA, glucagon-like peptide-1 receptor agonist; IgG4 Fc, immunoglobulin-G4 fragment crystallisable.

Typical GLP-1RA PK profiles at steady state by dosing frequency

BID, twice daily; GLP-1RA, glucagon-like peptide-1 receptor agonist; PK, pharmacokinetics.

Summary: pharmacokinetic profiles of approved GLP-1RAs and semaglutide

<table>
<thead>
<tr>
<th>Agent</th>
<th>$t_{1/2}$</th>
<th>$t_{max}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exenatide BID$^1$</td>
<td>2.4 h</td>
<td>0.6 h</td>
</tr>
<tr>
<td>Lixisenatide OD$^2$</td>
<td>3 h</td>
<td>1–3.5 h</td>
</tr>
<tr>
<td>Liraglutide OD$^3$</td>
<td>13 h</td>
<td>8–12 h</td>
</tr>
<tr>
<td>Dulaglutide QW$^4$</td>
<td>~4 days</td>
<td>24–48 h</td>
</tr>
<tr>
<td>Albiglutide QW$^5*$</td>
<td>~5 days</td>
<td>3–5 days</td>
</tr>
<tr>
<td>Exenatide QW$^6$</td>
<td>7–14 days</td>
<td>6–7 weeks</td>
</tr>
<tr>
<td>Semaglutide QW$^7,8$</td>
<td>~7 days</td>
<td>1–3 days</td>
</tr>
</tbody>
</table>

*Albiglutide will be withdrawn by July 2018 for commercial reasons.

The PK profile of semaglutide at steady state makes it suitable for once-weekly dosing

In this trial investigating the effects of semaglutide on different aspects of beta-cell function (study 3635), assessment of plasma semaglutide level was conducted after 12 weeks of treatment at 1.0 mg steady state in subjects with T2D (n=37). Data are presented as mean (standard deviation). Dashed line indicates lower limit of quantification.

PK, pharmacokinetic; $t_{1/2}$, half-life.

Semaglutide treatment increases first- and second-phase insulin secretion

INTRAVERSEOUS GLUCOSE TOLERANCE TEST

Mean insulin response to the intravenous glucose tolerance test (25 g glucose bolus load) before and after 12 weeks of treatment with semaglutide or placebo. p<0.0001 for both first- and second-phase semaglutide vs placebo. Values are means (± standard errors) from a mixed model for repeated measurements analysis using ‘on-treatment without rescue medication’ data from subjects in the full analysis set. Subject 101069 has been removed from all IVGTT statistical analysis due to incorrect amount of glucose infused. IVGTT, intravenous glucose tolerance test.

The signal of semaglutide$^{750}$ in the brain is GLP-1R-dependent

Maximum intensity projection of average (n=4–5) semaglutide$^{750}$ distribution in wild-type C57BL/6 mice (left) and Glp-1r$^{-/-}$ mice (right).

AP, area postrema; ARH, arcuate hypothalamic nucleus; NTS, nucleus of the solitary tract; OV, vascular organ of the lamina terminalis; SF, septofimbrial nucleus; SFO, subfornical organ; VL, lateral ventricle.

Jensen CB et al. Presented at the 77th American Diabetes Association Scientific Sessions, 9–13 June 2017, San Diego, CA, USA. Poster Presentation 1145-P.
Changes in A1C values with glucagon-like peptide 1 receptor agonists (GLP-1 RAs) in head-to-head clinical studies.
Changes in weight with glucagon-like peptide 1 receptor agonists (GLP-1 RAs) in head-to-head clinical studies.
Summary: GLP-1 RA mechanism of action

1. Glp-1RA increases insulin secretion and beta-cell responsiveness, and suppresses hepatic glucose output in a glucose-dependent manner\textsuperscript{1,2}

2. Energy intake, food consumption and body weight are reduced with semaglutide vs placebo\textsuperscript{3}

3. Glp-1RA e attenuates plaque lesion progression in atherosclerotic mouse models\textsuperscript{4}

Summary: GLP-1 RA mechanism of action

Drucker DJ. *Cell Metab* 2016;24:15–30
The Multiple Agonist
Gut hormone polyagonists for the treatment of type 2 diabetes

Improves:
- Body weight
- Energy Expenditure
- Glycemic control
- Cholesterol

GLP-1/Glucagon co-Agonist

Improves:
- Glycemic control
- Body weight
- Lipolysis
- Cholesterol

GLP-1/GIP co-Agonist

Improves:
- Body weight
- Glycemic control
- Hepatosteatosis
- Cholesterol
- Energy Expenditure
- Lipolysis

GLP-1/GIP/Glucagon Tri-Agonist

Brandt SJ Peptides 2018
Schematic demonstrating the qualitative metabolic effects of GLP-1, glucagon and GIP on systems metabolism,
Schematic demonstrating the qualitative metabolic effects of GLP-1/glucagon dual agonist on systems metabolism,

Brandt SJ Journal of Endocrinology 2018
Dual AG lowers body weight and food intake via activation of GLP1R and GCGR

Pocai A, Diabetes 2009
Metabolic actions of GLP-1R agonists and GcgR agonists on key organs

**GLP-1 effects**

**Glucagon effects**

**GLP-1/glucagon effects**

- ↑↑ Satiety
- ↓↓ Food intake
- ↑ Leptin sensitivity
- ↑↑ Energy expenditure
- ↑↑ Lipolysis
- ↑↑ FAO
- ↑↑ Insulin sensitivity
- ↑ GSIS
- ↓↓ Body weight
- ↓↓ Fat mass
- ↑↑ Lipolysis
- ↑↑ Oxygen consumption
Coadministration of Glucagon-Like Peptide-1 During Glucagon Infusion in Humans Results in Increased Energy Expenditure and Amelioration of Hyperglycemia

Tan TM, Diabetes 2013
Coadministration of Glucagon-Like Peptide-1 During Glucagon Infusion in Humans Results in Increased Energy Expenditure and Amelioration of Hyperglycemia

Tan TM, Diabetes 2013
Coadministration of Glucagon-Like Peptide-1 During Glucagon Infusion in Humans Results in Increased Energy Expenditure and Amelioration of Hyperglycemia

Tan TM, Diabetes 2013
GLP-1/GcgR Dual Analog

<table>
<thead>
<tr>
<th>Compound</th>
<th>Company/Institution</th>
<th>Phase</th>
<th>Administration</th>
</tr>
</thead>
<tbody>
<tr>
<td>SAR425899</td>
<td>Sanofi-Aventis</td>
<td>Phase 1</td>
<td>SC, daily</td>
</tr>
<tr>
<td>LY2944876/TT-401</td>
<td>Eli Lilly</td>
<td>Phase 2</td>
<td>SC, weekly</td>
</tr>
<tr>
<td>HM12525A</td>
<td>Hanmi Pharmaceuticals</td>
<td>Phase 1</td>
<td>SC, weekly</td>
</tr>
<tr>
<td>ZP2929</td>
<td>Zealand</td>
<td>Phase 1</td>
<td>SC, daily</td>
</tr>
<tr>
<td>MEDI0382</td>
<td>MedImmune</td>
<td>Phase 1</td>
<td>SC</td>
</tr>
<tr>
<td>VPD-107</td>
<td>Spitfire Pharma</td>
<td>Preclinical</td>
<td>SC, weekly</td>
</tr>
<tr>
<td>MOD-6031</td>
<td>OPKO Biologics</td>
<td>Phase 1</td>
<td>SC, monthly</td>
</tr>
<tr>
<td>Liraglutide + NN9030</td>
<td>Novo Nordisk</td>
<td>Phase 1</td>
<td>SC</td>
</tr>
</tbody>
</table>

Sanchez-Garrido MA, Diabetologia (2017)
Schematic demonstrating the qualitative metabolic effects of GLP-1/GIP dual agonist on systems metabolism,

Brandt SJ. Journal of Endocrinology 2018
What is LY3298176?

- A 39 amino-acid synthetic peptide (4.8 kDa) with a C20 fatty diacid moiety connected to lysine residue at position 20 via a linker that prolongs the duration of action, allowing once-weekly subcutaneous administration.

- Its structure is primarily based on the GIP amino acid sequence with agonist activity at both the GIP and GLP-1 receptors.

- Equipotent to native GIP and less potent than native GLP-1.

GIP, gastric inhibitory polypeptide; GLP-1, glucagon-like peptide-1.
The rationale for developing a GLP-1/GIP dual agonist

- GLP-1RAs improve glucose control by enhancing glucose-stimulated insulin secretion,\textsuperscript{1,2} delaying gastric transit,\textsuperscript{3,4} decreasing plasma glucagon levels,\textsuperscript{5} and reducing body weight by activating anorexigenic pathways in the brain\textsuperscript{6} through activation of GLP-1R signalling.

- The GLP-1R is expressed in pancreatic beta cells, cells of the gastric antrum/pylorus, and neurons in the central and peripheral nervous systems\textsuperscript{7}

- Despite the broad metabolic benefits of GLP-1RAs, many patients do not achieve glycaemic targets,\textsuperscript{8} and weight loss with these agents is less than what can be attained with bariatric surgery\textsuperscript{9,10}

Proposed mode of action of GLP-1/GIP dual agonists

Proposed Direct Effects:
- ↑ Insulin Secretion
- ↓ Glucagon Secretion
- ↓ Food Intake
- ↑ Energy Expenditure?
- ↑ Glucose Uptake
- □ Delayed Gastric Emptying
- □ Altered Lipid Metabolism

Proposed Indirect Effects:
- □ CV Protection?
- □ Improved Renal Function?
- □ Improved NASH?
- ↑ Insulin Sensitivity
- ↓ Plasma triglycerides

CV, cardiovascular; GIP, gastric inhibitory polypeptide; GLP-1, glucagon-like peptide-1; NASH, non-alcoholic steatohepatitis.

Efficacy and safety of LY3298176, a novel dual GIP and GLP-1 receptor agonist, in patients with type 2 diabetes: a randomised, placebo-controlled and active comparator-controlled phase 2 trial

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LY3298176 phase 2 trial design

318 subjects with T2D
- Age 18–75 years
- HbA$_{1c}$ 7.0–10.5%
- BMI 23–50 kg/m$^2$
- Diet and exercise ± metformin

Randomisation 1:1:1:1:1:1

Placebo (n=51)
LY 1 mg (n=52)
LY 5 mg (n=55)
LY 10 mg (n=51)
LY 15 mg (n=53)
Dulaglutide 1.5 mg (n=54)

Treatment duration 26 weeks
Follow-up 4 weeks

All treatments were administered once-weekly. Stratified randomisation based on: baseline HbA$_{1c}$ (<8.5% or ≥8.5%), metformin use (yes or no), BMI (<30 kg/m$^2$ or ≥30 kg/m$^2$). BMI, body mass index; LY, LY3298176. Frias JP et al. Lancet 2018. doi: 10.1016/S0140-6736(18)32260-8. [Epub ahead of print].
Change in HbA$_{1c}$ from baseline to week 26

*\(p<0.05\) vs placebo; †\(p<0.05\) vs dulaglutide 1.5 mg. Data presented are LS mean ± SE. MMRM on treatment analysis.

LS, least squares; LY, LY3298176; MMRM, mixed-effect model repeated measure; SE, standard error.

Figure adapted from Frias JP et al. Lancet 2018. doi: 10.1016/S0140-6736(18)32260-8. [Epub ahead of print].
Change in body weight from baseline to week 26

*\( p < 0.05 \) vs placebo; †\( p < 0.05 \) vs dulaglutide 1.5 mg. Data presented are LS mean ± SE. MMRM on treatment analysis.

LS, least squares; LY, LY3298176; MMRM, mixed-effect model repeated measure.

Figure adapted from Frias JP et al. Lancet 2018. doi: 10.1016/S0140-6736(18)32260-8. [Epub ahead of print].
Dose–response modelling for HbA1c

Bayesian dose–response model with interpolated dose levels. Data are posterior mean, with SD error bars. mITT, modified intention-to-treat; SD, standard deviation.

Dose–response modelling for weight

Bayesian dose–response model with interpolated dose levels; Data are posterior mean, with SD error bars.
mITT, modified intention-to-treat; SD, standard deviation.
Schematic demonstrating the qualitative metabolic effects of GLP-1/glucagon/GIP triple agonist on systems metabolism

Brandt SJ. Journal of Endocrinology 2018
A rationally designed monomeric peptide triagonist corrects obesity and diabetes in rodents

Finan B. nature medicine 2014
Thank You