CLASS conference learning and scientific sharing program

at the European Association for the Study of Diabetes
50th Annual Meeting
September 15-19, 2014
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Speaker Conflict of Interest Disclosure

- Consultant or speaker for:
  - NovoNordisk, Eli Lilly, Merck, Astra Zeneca, Sanofi, BD, Servier, Janssen.

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- Received financial support from Novo Nordisk Canada Inc to attend the 50th annual meeting of the European Association for the Study of Diabetes in Vienna, Austria, September 15-19, 2014
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A Majority of Women with GDM Could Benefit from Oral Hypoglycemic Agents: Successful glycemic control in > 60% of women taking mild doses of metformin-glyburide, with neonatal outcomes comparable to women on insulin therapy.

**PS 093-1094** – Gestational Diabetes Mellitus: The First Prospective Randomised-controlled Study of Metformin-Glyburide vs. Insulin

**By** Ardilouze J-L, Ménard J, Hivert M-F, et al

**Objective(s):** To assess maternal glycemic control and neonatal issues in a group of GDM women treated with metformin-glyburide combination vs. insulin

GDM = gestational diabetes mellitus
### Results at Study Entry

<table>
<thead>
<tr>
<th>At study entry*</th>
<th>Met–Gly (n = 35)</th>
<th>Insulin (n = 33)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weeks of gestation</td>
<td>29.3 ± 3.8</td>
<td>30.1 ± 3.1</td>
</tr>
<tr>
<td>Age (years)</td>
<td>31.1 ± 4.7</td>
<td>30.7 ± 4.4</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>85.3 ± 17.5</td>
<td>85.3 ± 22.9</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>32.0 ± 5.4</td>
<td>32.2 ± 7.2</td>
</tr>
<tr>
<td>A1C (%)</td>
<td>5.5 ± 0.4</td>
<td>5.3 ± 0.3</td>
</tr>
<tr>
<td>Gravida/Para/Aborta</td>
<td>3 / 1 / 1</td>
<td>3 / 1 / 1</td>
</tr>
<tr>
<td>Glycemic control 2 weeks prior to study entry (mmol/L)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fasting</td>
<td>5.3 ± 0.7</td>
<td>5.3 ± 0.6</td>
</tr>
<tr>
<td>2-hr pc breakfast</td>
<td>6.3 ± 0.8</td>
<td>6.3 ± 0.7</td>
</tr>
<tr>
<td>2-hr pc lunch</td>
<td>6.6 ± 0.8</td>
<td>6.4 ± 0.6</td>
</tr>
<tr>
<td>2-hr pc supper</td>
<td>6.8 ± 0.8</td>
<td>6.8 ± 0.9</td>
</tr>
</tbody>
</table>

*All *p* = NS

Met-Gly = metformin-glyburide; BMI = body mass index; NS = not significant


Reviewed by Dr. Joanne Liutkus
## Results at Delivery

<table>
<thead>
<tr>
<th>At delivery*</th>
<th>Met–Gly (n = 35)</th>
<th>Insulin (n = 33)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glycemic control 2 weeks prior to study entry (mmol/L)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fasting</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2-hr pc breakfast</td>
<td>4.7 ± 0.3</td>
<td>4.8 ± 0.3</td>
</tr>
<tr>
<td>2-hr pc lunch</td>
<td>5.8 ± 0.4</td>
<td>5.9 ± 0.5</td>
</tr>
<tr>
<td>2-hr pc supper</td>
<td>5.8 ± 0.5</td>
<td>5.9 ± 0.5</td>
</tr>
<tr>
<td>6.0 ± 0.5</td>
<td>6.1 ± 0.5</td>
<td></td>
</tr>
<tr>
<td>Hypoglycemias (&lt; 3.3) (n and %)</td>
<td>11 (32.4)</td>
<td>2 (6.3)</td>
</tr>
<tr>
<td>Weight gain (kg)</td>
<td>12.4 ± 6.4</td>
<td>12.9 ± 4.5</td>
</tr>
<tr>
<td>Insulin doses (units)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Breakfast</td>
<td>7.0 ± 4.2</td>
<td>11.3 ± 9.0</td>
</tr>
<tr>
<td>Lunch</td>
<td>8.5 ± 4.9</td>
<td>9.6 ± 8.1</td>
</tr>
<tr>
<td>Supper</td>
<td>11.0 ± 4.2</td>
<td>10.3 ± 6.8</td>
</tr>
<tr>
<td>Bedtime</td>
<td>11.0 ± 7.1</td>
<td>18.7 ± 15.1</td>
</tr>
</tbody>
</table>

*All p = NS except for hypoglycemias p < 0.01

Reviewed by Dr. Joanne Liutkus
Medications of Women in the Met–Gly Group at Delivery

<table>
<thead>
<tr>
<th>N (%) of women</th>
<th>Met (mg/day)</th>
<th>Gly (mg/day)</th>
<th>Insulin (units)</th>
</tr>
</thead>
<tbody>
<tr>
<td>8 (22.9)</td>
<td>844 ± 268</td>
<td></td>
<td></td>
</tr>
<tr>
<td>14 (40.0)</td>
<td>1,179 ± 153</td>
<td>3.9 ± 1.9</td>
<td></td>
</tr>
<tr>
<td>10 (28.6)</td>
<td>1,333 ± 250</td>
<td>8.6 ± 2.2</td>
<td>12.7 ± 9.9</td>
</tr>
<tr>
<td>3 (8.6)</td>
<td></td>
<td>9.4 ± 4.4</td>
<td></td>
</tr>
</tbody>
</table>

- In the 13 women taking insulin (37.2%), injections were started 4.2 ± 2.1 weeks after initiation of Met–Gly treatment.
# Neonatal Issues

<table>
<thead>
<tr>
<th>Neonatal issues*</th>
<th>Met (n = 35)</th>
<th>Insulin (n = 33)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Caesarean sections (n)</td>
<td>9</td>
<td>8</td>
</tr>
<tr>
<td>Neonates’ weight (g)</td>
<td>3,360 ± 389</td>
<td>3,227 ± 570</td>
</tr>
<tr>
<td>Gestational age (weeks)</td>
<td>38.7 ± 1.1</td>
<td>38.4 ± 1.5</td>
</tr>
<tr>
<td>Hypoglycemias (n and %)</td>
<td>21 (60)</td>
<td>15 (45)</td>
</tr>
</tbody>
</table>

*All p = NS
Discussion & Implications

• Take-home messages:
  – evidence for alternatives to insulin for women with GDM
  – cost implications: OADs, insulin, OADs + insulin
  – increased risk of hypoglycemia with Met-Gly combination: clinical significance?

• Consider:
  – timing of delivery for obstetricians
  – home births
  – midwife-assisted deliveries
  – long-term effects of Met-Gly

OADs = oral antidiabetic drugs
Assessing the Impact of Diabetes on Heart Failure with Preserved Ejection Fraction (HFpEF)

**Objective(s):** To investigate the impact of diabetes on long-term prognosis in patients with heart failure and preserved left ventricular function from an everyday life perspective
Heart Failure Preserved Ejection Fraction (HFpEF): Background

- In the general population, prevalence of heart failure is 2% (10% after 70 years old), diabetes is 8% \(^1\)
- prevalence of 30% of patients with HF have type 2 diabetes

Clinical characteristics:
- High age
- Female gender
- Hypertension
- Obesity
- Diabetes

Diagnostic criteria:
1. Symptoms
2. Signs
3. Normal/mildly reduced left ventricular EF (≥ 40 or ≥ 50%)
4. Relevant structural heart disease* and/or diastolic dysfunction

\(^1\)McMurray JJ et al. Eur Heart J 2012; 33(14):1787-847
Heart Failure in Diabetes

• Causes of heart failure in diabetes:
  – co-morbidities
  – diabetes cardiomyopathy
    • more myocardial fibrosis and hypertrophy
    • different myocardial metabolism

Johansson I, et al. OP 08-045, presented at the 2014 EASD
Reviewed by Dr. Éric Poulin
Diabetes Cardiomyopathy

- Deranged metabolism:
  - FFA use (oxidation) 90% vs. 60% in patients without diabetes mellitus
  - glucose use (oxidation) 10% vs. 40% in patients without diabetes mellitus

- Many diabetes mellitus patients do not have artery stenosis more than 50%, but:
  - microangiopathy disease
  - platelet hypereactivity
  - endothelial dysfunction

*PDH = pyruvate dehydrogenase; FFA = free fatty acid; ATP = adenosine triphosphate

Johansson I, et al. OP 08-045, presented at the 2014 EASD
Reviewed by Dr. Éric Poulin
Prognosis in Diabetes Mellitus and HFpEF

• **Worse prognosis in T2DM, regardless of EF**
  – CHARM trial\(^1\): even with preserved EF, mortality at 3.5 years is 20% vs. 40% with reduced EF
    • n = 7,599; diabetes mellitus in 28%
    • diabetes mellitus: mortality predictor in HFpEF (HR 2.00)

• **In S-HFR, better survival in patients without diabetes mellitus:**
  – adjusted OR 1.39 (1.20–1.61)

T2DM = type 2 diabetes mellitus; HR = hazard ratio; OR = odds ratio
\(^1\)MacDonald et al. Eur Heart J 2008; 1377-85
S-HFR Conclusions

• In 30,697 patients with T2DM, EF ≥ 50% (61% male, 39% female):
  – 25% of patients with HFpEF have type 2 diabetes
  – diabetes is an independent predictor of mortality even after adjustment of co-morbidities
  – co-morbidities common
    • 50% reported ischemic heart disease
    • 68% reported hypertension

Johansson I, et al. OP 08-045, presented at the 2014 EASD
Reviewed by Dr. Éric Poulin
Telephone Intervention May Enhance Adherence to Insulin Therapy by Offering the Opportunity to Customize Information to Individuals Under Real-world Conditions

**PS 075-941** – Adherence to Insulin Treatment in Insulin Naïve Type 2 Diabetic Patients: Results of Telephonic Intervention

**By** Gogas Yavuz D, Bilen H, Sancak S, et al

**Objective(s):** To assess the efficacy of phone-based support on insulin treatment adherence in insulin-naïve type 2 diabetic patients using different insulin treatment regimens (basal, basal-bolus and premix) in third-care medical centres in Turkey
Methods

• 12-week, open-label, randomized multicentre study
  – n = 1,456 insulin-naïve patients
• Randomized to standard of care of telephonic intervention (TI)
• Primary outcome: insulin treatment adherence
• TI group received 1 call every month with a detailed series of standardized questions
• Standard-of-care group received 1 call at the end of 12 weeks
Basal Demographic and Glycemic Parameters in Patients Adherent and Non-adherent to Insulin Treatment

<table>
<thead>
<tr>
<th></th>
<th>Adherent Group (n = 224)</th>
<th>Non-adherent Group (n = 1,232)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs)</td>
<td>57 ± 13</td>
<td>56 ± 11</td>
<td>0.7</td>
</tr>
<tr>
<td>Duration of diabetes (yrs)</td>
<td>4.9 ± 6.9</td>
<td>6.6 ± 6.2</td>
<td>0.0001</td>
</tr>
<tr>
<td>Insulin dosage (IU/d)</td>
<td>31.5 ± 18</td>
<td>31.5 ± 19</td>
<td>0.9</td>
</tr>
<tr>
<td>FPG (mg/dL)</td>
<td>231 ± 83</td>
<td>231.7 ± 85</td>
<td>0.9</td>
</tr>
<tr>
<td>PPG (mg/dL)</td>
<td>298 ± 96</td>
<td>300 ± 111</td>
<td>0.8</td>
</tr>
<tr>
<td>A1C (%)</td>
<td>10 ± 2</td>
<td>10.5 ± 2</td>
<td>0.01</td>
</tr>
</tbody>
</table>

IU = international unit; FPG = fasting plasma glucose; PPG = postprandial glucose
## Insulin Injection Drop-off Rates According to Insulin Treatment Regimen

<table>
<thead>
<tr>
<th>Drop off at least 1 injection in a week</th>
<th>n</th>
<th>Basal Bolus</th>
<th>Premix</th>
<th>Basal</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>yes</td>
<td>81</td>
<td>71</td>
<td>52</td>
<td>204</td>
<td></td>
</tr>
<tr>
<td></td>
<td>%</td>
<td>27.0%</td>
<td>15.0%</td>
<td>15.8%</td>
<td>18.5%</td>
</tr>
<tr>
<td>no</td>
<td>219</td>
<td>401</td>
<td>277</td>
<td>897</td>
<td></td>
</tr>
<tr>
<td></td>
<td>%</td>
<td>73.0%</td>
<td>85.0%</td>
<td>84.2%</td>
<td>81.5%</td>
</tr>
<tr>
<td>Total</td>
<td>300</td>
<td>472</td>
<td>329</td>
<td>1,101</td>
<td></td>
</tr>
</tbody>
</table>

\*p < 0.001 vs. premix and basal group

Reviewed by Lori Berard, RN
Reported Causes of Dropout for Insulin Therapy

Gogas Yavuz D, et al. PS 075-941, presented at the 2014 EASD
Reviewed by Lori Berard, RN
Discussion & Implications

• Take-home messages:
  – TI group compliance was 83.2% vs. 70.3% in standard group
  – in addition to a standardized education module, telephone support provided by trained nurses improved adherence to all insulin regimens
  – significant barriers to adherence include physician attitudes

• Consider:
  – phone sessions ~20 minutes, adherence self-reported
    • need to understand the 80-question survey
  – basal-bolus might be too difficult for some, even with support
  – demonstrates need for self-management support
  – may help form insulin support programs for DECs and industry, as insulin starts move to community

DEC = diabetes education centre

Gogas Yavuz D, et al. PS 075-941, presented at the 2014 EASD
Reviewed by Lori Berard, RN
Addition of GLP-1 Analogue May be Better than Initiating Insulin in Some Patients Failing Oral Agents

**OP 07-038** – Efficacy and Safety of Once Weekly Dulaglutide vs Insulin Glargine in Combination with Metformin and Glimepiride in Type 2 Diabetes Patients (AWARD-2)

**By** Giorgino F, Benroubi M, Sun J-H, et al

**Objective(s):** To compare efficacy and safety of 2 doses of dulaglutide with insulin glargine in type 2 diabetes inadequately controlled with maximally tolerated doses of metformin and glimepiride

Dulaglutide is not approved for use in Canada
## Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>DU 1.5 mg n = 273</th>
<th>DU 0.75 mg n = 272</th>
<th>Glargine n = 262</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex, F, %</td>
<td>47</td>
<td>50</td>
<td>49</td>
</tr>
<tr>
<td>Age, years</td>
<td>56 (10)</td>
<td>57 (9)</td>
<td>57 (9)</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>31 (5)</td>
<td>32 (5)</td>
<td>32 (6)</td>
</tr>
<tr>
<td>Duration of diabetes, years</td>
<td>9 (6)</td>
<td>9 (6)</td>
<td>9 (6)</td>
</tr>
<tr>
<td>A1C %</td>
<td>8.2 (1)</td>
<td>8.1 (1)</td>
<td>8.1 (1)</td>
</tr>
<tr>
<td>mmol/mol</td>
<td>66 (11)</td>
<td>65 (11)</td>
<td>65 (11)</td>
</tr>
<tr>
<td>Fasting serum glucose, mmol/L</td>
<td>9.2 (2.7)</td>
<td>9.0 (2.7)</td>
<td>9.1 (2.7)</td>
</tr>
<tr>
<td>Treatment at screening, %</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 OAM</td>
<td>16.5</td>
<td>15.4</td>
<td>16.2</td>
</tr>
<tr>
<td>≥ 2 OAMs</td>
<td>83.5</td>
<td>84.6</td>
<td>83.8</td>
</tr>
<tr>
<td>At randomization</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metformin dose, mg/day</td>
<td>2,379 (480)</td>
<td>2,412 (495)</td>
<td>2,419 (475)</td>
</tr>
<tr>
<td>Glimepiride dose, mg/day</td>
<td>6.3 (1.7)</td>
<td>6.3 (1.6)</td>
<td>6.2 (1.6)</td>
</tr>
</tbody>
</table>

Values shown are for mean (standard deviation [SD]) unless otherwise noted; intention to treat (ITT)
Dulaglutide is not approved for use in Canada
DU = dulaglutide; BMI = body mass index; OAM = oral antidiabetic medication

Giorgino F, et al. OP 07-038, presented at the 2014 EASD
Reviewed by Dr. Hasnain Khandwala
A1C Targets at 52 and 78 Weeks

**A1C < 7.0%**
(53 mmol/mol)

**A1C ≤ 6.5%**
(47.5 mmol/mol)

- *p < 0.05 vs. glargine; **p < 0.001 vs. glargine*
- ITT logistic regression using last observation carried forward (LOCF) analysis
- Dulaglutide is not approved for use in Canada

Giorgino F, et al. OP 07-038, presented at the 2014 EASD
Reviewed by Dr. Hasnain Khandwala
Body Weight Change Over Time

Baseline weight = 86.3 kg

Data presented are least squares [LS] means ± standard error [SE]

**p < 0.001 vs. glargine
Dulaglutide is not approved for use in Canada
ITT, Mixed-effect Model Repeated Measure (MMRM) analysis

Giorgino F, et al. OP 07-038, presented at the 2014 EASD
Reviewed by Dr. Hasnain Khandwala
## Cumulative Adverse Events Events Through 78 Weeks

|                                | DU 1.5 mg  
n = 273 | DU 0.75 mg  
n = 272 | Glargine  
n = 262 |
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Any adverse event, n (%)</td>
<td>201 (73.6)</td>
<td>188 (69.1)</td>
<td>192 (73.3)</td>
</tr>
<tr>
<td>GI adverse event, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>42 (15.4)##</td>
<td>21 (7.7)##</td>
<td>4 (1.5)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>29 (10.6)</td>
<td>25 (9.2)</td>
<td>15 (5.7)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>18 (6.6)#</td>
<td>10 (3.7)</td>
<td>3 (1.1)</td>
</tr>
<tr>
<td>Severe hypoglycemia, n (%)</td>
<td>2 (0.7)</td>
<td>0 (0.0)</td>
<td>2 (0.8)</td>
</tr>
<tr>
<td>Injection-site reactions, n (%)</td>
<td>2 (0.7)</td>
<td>2 (0.7)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Adjudicated pancreatitis, n (%)</td>
<td>2 (0.7)</td>
<td>1 (0.4)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Pancreatic cancer, n</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

*p < 0.05 vs. glargine; **p < 0.001 vs. glargine

Dulaglutide is not approved for use in Canada

GI = gastrointestinal
Discussion & Implications

• **Take-home messages:**
  - insulin is generally considered to be best option for patients failing oral agents
  - in this study, addition of 0.75 mg dulaglutide QW is as effective as insulin glargine; 1.5 mg is superior to insulin glargine
    - both doses cause less hypoglycemia
  - insulin glargine is associated with weight gain, whereas both doses of dulaglutide caused weight loss
  - dulaglutide treatment was well tolerated with no significant increase in overall adverse reactions
  - addition of a GLP-1 analogue may be a better option than initiating insulin therapy in some patients failing oral agents
  - QW formulation of dulaglutide may be more acceptable to patients and may improve compliance
  - further studies are needed to show if effects on glycemic control, weight etc, compared to insulin are sustained

Dulaglutide is not approved for use in Canada
QW = once weekly; GLP-1 = glucagon-like peptide-1
Once-weekly Dulaglutide 1.5 mg Demonstrates Noninferior Glycemic Control Compared to Once-daily Liraglutide 1.8 mg, with a Similar Safety and Tolerability Profile

OP 07-040 – Efficacy and Safety of Once Weekly Dulaglutide Versus Once Daily Liraglutide in Type 2 Diabetes (AWARD-6)

By Tofé Povedano S, Dungan KM, Forst T, et al

Objectives: To compare the efficacy and safety of once-weekly dulaglutide (DU) 1.5 mg with once-daily liraglutide (LIRA) 1.8 mg in metformin-treated (≥ 1,500 mg) patients with type 2 diabetes

Dulaglutide is not approved for use in Canada
Study Design

- Key inclusion criteria:
  - type 2 diabetes
  - A1C ≥ 7.0% (≥ 53 mmol/mol) and ≤ 10.0% (≤ 86 mmol/mol)
  - stable dose of metformin (≥ 1,500 mg/day) for ≥ 3 months

---

Dulaglutide 1.5 mg once weekly

Liraglutide 1.8 mg once daily

Screening/lead-in

Treatment period

Background therapy

Safety follow-up

Follow-up

Week

-2 0 2 26 30

Randomization

Liraglutide titration period

Final endpoint

---

*Patients received metformin ≥ 1,500 mg/day throughout the study; *b*Patients randomized to liraglutide were initiated at a dose of 0.6 mg/day in Week 1 then up-titrated to 1.2 mg/day in Week 2 and 1.8 mg/day in Week 3.

Patients who could not tolerate the full dose for the treatment duration were required to discontinue study drug.

Dulaglutide is not approved for use in Canada.

Dungan et al. Lancet 2014 (ahead of print)
A1C Change from Baseline at 26 Weeks

Baseline A1C = 8.1% (65 mmol/mol)

Data presented are LS mean ± SE; †p < 0.001, noninferiority vs. liraglutide; aTreatment difference (nominal 95% CI), ITT, MMRM analysis
Dulaglutide is not approved for use in Canada
LS = least squares; SE = standard error; CI = confidence interval; ITT = intention to treat; MMRM = Mixed-effect Model Repeated Measure
Dungan et al. Lancet 2014 (ahead of print)

Tofé Povedano S, et al. OP 07-040, presented at the 2014 EASD
Reviewed by Dr. Irene Hramiak
Body Weight Change Over Time

Baseline weight = 94.1 kg

Data presented are LS means ± SE; #p < 0.05 vs. dulaglutide; ITT, MMRM analysis
Dulaglutide is not approved for use in Canada
Dungan et al. Lancet 2014 (ahead of print)

Tofé Povedano S, et al. OP 07-040, presented at the 2014 EASD
Reviewed by Dr. Irene Hramiak
### Cumulative Adverse Events Through 26 Weeks

<table>
<thead>
<tr>
<th>Event</th>
<th>DU 1.5 mg n = 299</th>
<th>LIRA 1.8 mg n = 300</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any AE, n (%)</td>
<td>185 (61.9)</td>
<td>189 (63.0)</td>
</tr>
<tr>
<td>GI adverse events, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>107 (35.8)</td>
<td>107 (35.7)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>61 (20.4)</td>
<td>54 (18.0)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>21 (7.0)</td>
<td>25 (8.3)</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>36 (12.0)</td>
<td>36 (12.0)</td>
</tr>
<tr>
<td></td>
<td>24 (8.0)</td>
<td>18 (6.0)</td>
</tr>
<tr>
<td>Study/study drug discontinuations for GI AE</td>
<td>9 (3.0)</td>
<td>13 (4.3)</td>
</tr>
<tr>
<td>Hypoglycemia (≤ 3.9 mmol/L ± symptoms)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total (events/pt/year), mean (SD)</td>
<td>0.02 (0.08)</td>
<td>0.03 (0.17)</td>
</tr>
<tr>
<td>Severe hypoglycemia</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Injection-site reactions, n (%)</td>
<td>1 (0.3)</td>
<td>2 (0.7)</td>
</tr>
<tr>
<td>Adjudicated pancreatitis, n</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Pancreatic cancer, n</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Dulaglutide is not approved for use in Canada

AE = adverse event; GI = gastrointestinal; SD = standard deviation

Dungan et al. Lancet 2014 (ahead of print)
Discussion & Implications

• **Take-home messages:**
  - liraglutide is the current comparator for GLP-1 trials of QW products
  - dulaglutide has shown non-inferiority for glycemic control
  - liraglutide provides better weight loss
  - advantage of once-daily GLP-1 for patient compliance remains to be established

• **Consider:**
  - will probably have 2 QW analogues in next 12 months
  - some QW analogue preparations require reconstitution and special injection techniques

Dulaglutide is not approved for use in Canada
GLP-1 = glucagon-like peptide-1; QW = once weekly

Tofé Povedano S, et al. OP 07-040, presented at the 2014 EASD
Reviewed by Dr. Irene Hramiak
Empagliflozin Improves Glucose Variability in Type 1 Diabetes

**Objective:** To assess how 8 weeks’ treatment with empagliflozin as adjunct to insulin therapy in T1DM impacts diurnal CGM patterns, as well as time spent in hyper- and hypoglycemia

Empagliflozin is not approved for use in Canada

CGM = continuous glucose monitoring
Study Design

- Proof-of-concept study, 2 months in duration

1 week

Screening

2 weeks

Run-in

8 weeks

Open-label empagliflozin 25 mg qd

2 weeks

Follow-up

2-week CGM analysis

2-week CGM analysis

2-week CGM analysis

2-week CGM analysis

Insulin titration†

CGM

†Basal and bolus insulin doses were reduced at onset of treatment with empagliflozin as recommended by the investigator and adjusted thereafter

Empagliflozin is not approved for use in Canada
## Study Cohort Characteristics

<table>
<thead>
<tr>
<th>Clinical characteristics, n = 40</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Male sex (%)</td>
<td>20 (50)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>24.3 ± 5.1</td>
</tr>
<tr>
<td>Diabetes duration (years)</td>
<td></td>
</tr>
<tr>
<td>&gt; 1 to 5</td>
<td>4 (10)</td>
</tr>
<tr>
<td>&gt; 5</td>
<td>36 (90)</td>
</tr>
<tr>
<td>Insulin regimen</td>
<td></td>
</tr>
<tr>
<td>Insulin pump</td>
<td>26 (65)</td>
</tr>
<tr>
<td>MDI</td>
<td>14 (35)</td>
</tr>
<tr>
<td>Total daily insulin (U)</td>
<td>54.7 ± 20.4</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>24.5 ± 3.2</td>
</tr>
<tr>
<td>Urine albumin to creatinine ratio (mg/mmol)</td>
<td>1.2 ± 0.9</td>
</tr>
<tr>
<td>GFR\textsubscript{INULIN} (mL/min/1.73 m²)</td>
<td>154 ± 33</td>
</tr>
<tr>
<td>A1C (%)</td>
<td>8.0 ± 0.9</td>
</tr>
</tbody>
</table>

Data are mean ± standard deviation (SD) or n (%)
Empagliflozin is not approved for use in Canada
MDI = multiple dose insulin; BMI = body mass index; GFR = glomerular filtration rate

Perkins B, et al. PS 076-956, presented at the 2014 EASD
Reviewed by Dr. Sorin Beca
The visual AGP display (for a single subject) represents data collapsed over 24 hours where the median (black line) and percentiles are indicated (25th and 75th percentile in solid red, 10th and 90th in dotted red).

Empagliflozin is not approved for use in Canada.

AGP = ambulatory glucose profile

Perkins B, et al. PS 076-956, presented at the 2014 EASD
Reviewed by Dr. Sorin Beca
Time Spent at Various Glycemic Levels (%)

Glucose Variability

Data are mean standard deviation (SD). Proportion of individual values for entire period. *p < 0.05 vs. baseline. Similar pattern as for % < 70 mg/dL was seen for % < 60 mg/dL in all categories with ranges: Total: 2.4–2.6%, MDI: 3.2–5.7%, CSII: 1.1–1.8%

Empagliflozin is not approved for use in Canada

IQR = interquartile range; CSII = continuous subcutaneous insulin infusion

Perkins B, et al. PS 076-956, presented at the 2014 EASD
Reviewed by Dr. Sorin Beca
Discussion & Implications

• Take-home message:
  – empagliflozin x 8 weeks improved glycemic control, reduced incidence of hypoglycemic events, reduced insulin doses and weight, and improved glycemic variability in T1DM patients

• Considerations, limitations:
  – proof-of-concept, single-arm, open-label pilot study: short duration, small sample size
  – improved night-time glycemia more prominent than daytime

• Clinical implications:
  – too early to assess clinical impact in Canada
  – future research needed to prove safety
    • *e.g.*, degree of basal/short-acting insulin adjustment upon initiation/interruption of empagliflozin

Empagliflozin is not approved for use in Canada

Perkins B, et al. PS 076-956, presented at the 2014 EASD
Reviewed by Dr. Sorin Beca
Fixed-dose Combination of Empagliflozin/Linagliptin as Add-on to Metformin in T2DM Lowers A1C More than Either Agent Alone

**OP 01-001** – Fixed-dose Combinations of Empagliflozin/Linagliptin for 52 Weeks as Add-on to Metformin in Subjects with Type 2 Diabetes

**By** De Fronzo RA, Lewin A, Patel S, et al

**Objectives:** To evaluate the efficacy and safety of fixed-dose combinations of empagliflozin/linagliptin as add-on to metformin in subjects with type 2 diabetes mellitus (T2DM)

Empagliflozin is not approved for use in Canada
**Study Design**

- Phase III, double-blind, RCT in T2DM, BMI < 45 kg/m², eGFR > 60 mL/min/1.73 m², on metformin ≥ 1,500 mg/day

Screening (n = 1,179) → 2-week placebo run-in → Randomization (n = 677)

- Empagliflozin 25 mg / linagliptin 5 mg (n = 137)
- Empagliflozin 10 mg / linagliptin 5 mg (n = 136)
- Empagliflozin 25 mg (n = 135)
- Empagliflozin 10 mg (n = 134)
- Linagliptin 5 mg (n = 135)

52 weeks

Empagliflozin is not approved for use in Canada

RCT = randomized control trial; BMI = body mass index; eGFR = estimated glomerular filtration rate
Change from Baseline in A1C at Week 52

Mean baseline 7.90 7.95 8.02 8.00 8.02

Adjusted mean (SE) change from baseline

-0.2  -0.4  -0.6  -0.8  -1.0  -1.5  -1.4

-1.21  -1.05 **  -0.64  -0.69  -0.48

*Significantly better (p < 0.001) vs empa 25 mg or lina 5 mg
**Significantly better (p < 0.001) vs empa 10 mg or lina 5 mg

ANCOVA in full analysis set with last observation carried forward (LOCF) imputation
Empagliflozin is not approved for use in Canada
SE = standard error; CI = confidence interval

De Fronzo RA, et al. OP 01-001, presented at the 2014 EASD
Reviewed by Dr. David Shu
## Selected Adverse Events

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Empagliflozin 25 mg/linagliptin 5 mg (n = 137)</th>
<th>Empagliflozin 10 mg/linagliptin 5 mg (n = 136)</th>
<th>Empagliflozin 25 mg (n = 141)</th>
<th>Empagliflozin 10 mg (n = 140)</th>
<th>Linagliptin 5 mg (n = 132)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urinary tract infection&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Male 14 (10.2) 2 (2.7) 12 (18.8)</td>
<td>Male 13 (9.6) 2 (2.4) 11 (21.2)</td>
<td>Male 19 (13.5) 2 (3.0) 17 (22.7)</td>
<td>Male 16 (11.4) 3 (3.7) 13 (22.0)</td>
<td>Male 20 (15.2) 3 (4.5) 17 (26.2)</td>
</tr>
<tr>
<td></td>
<td>Female 12 (9.6) 2 (2.7) 11 (21.2)</td>
<td>Female 12 (9.6) 3 (3.0) 17 (22.7)</td>
<td>Female 19 (13.5) 3 (3.7) 17 (22.7)</td>
<td>Female 20 (15.2) 3 (4.5) 17 (26.2)</td>
<td>Female 20 (15.2) 3 (4.5) 17 (26.2)</td>
</tr>
<tr>
<td>Genital infection&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Male 3 (2.2) 2 (2.7) 1 (1.6)</td>
<td>Male 8 (5.9) 2 (2.4) 6 (11.5)</td>
<td>Male 12 (8.5) 3 (4.5) 9 (12.0)</td>
<td>Male 11 (7.9) 5 (6.2) 6 (10.2)</td>
<td>Male 3 (2.3) 2 (3.0) 1 (1.5)</td>
</tr>
<tr>
<td></td>
<td>Female 2 (2.7) 1 (1.6) 1 (1.6)</td>
<td>Female 11 (8.5) 3 (4.5) 10 (19.0)</td>
<td>Female 11 (7.9) 5 (6.2) 6 (10.2)</td>
<td>Female 2 (2.3) 2 (3.0) 1 (1.5)</td>
<td>Female 2 (2.3) 2 (3.0) 1 (1.5)</td>
</tr>
<tr>
<td>Volume depletion&lt;sup&gt;c&lt;/sup&gt;</td>
<td>1 (0.7)</td>
<td>2 (1.5)</td>
<td>2 (1.4)</td>
<td>1 (0.7)</td>
<td>4 (3.0)</td>
</tr>
<tr>
<td>Hypersensitivity reactions&lt;sup&gt;d&lt;/sup&gt;</td>
<td>1 (0.7)</td>
<td>1 (0.7)</td>
<td>0</td>
<td>0</td>
<td>1 (0.8)</td>
</tr>
<tr>
<td>Pancreatitis&lt;sup&gt;e&lt;/sup&gt;</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1 (0.8)</td>
</tr>
</tbody>
</table>

N (%) in subjects who received ≥ 1 dose of study drug

<sup>a</sup>Based on 77 preferred terms; <sup>b</sup>Based on 89 preferred terms; <sup>c</sup>Based on 8 preferred terms; <sup>d</sup>Based on 3 Standardized MedDRA Queries (SMQs); <sup>e</sup>Based on SMQ and 1 preferred term

Empagliflozin is not approved for use in Canada
Discussion & Implications

• Take-home messages:
  – combination therapy with empagliflozin/linagliptin 5 mg:
    • lowered A1C more than either as monotherapy
    • provides a simple, well-tolerated therapy that effectively lowers A1C, with minimal hypoglycemia and weight loss

Empagliflozin is not approved for use in Canada
Type II diabetes is a complex progressive disease involving many different disease pathways that requires early onset of novel combination therapy in order to maximize lowering of A1c while at the same time reducing the risk of hypoglycemia and weight gain.

Is there a role for early combination therapy in the management of patients with Type 2 diabetes?

By B. Zinman (CA)

Objectives: 1. To review the specific reasons why early combination therapy may be beneficial in Type 2 diabetes and 2. To review the evidence regarding effectiveness of different combination therapies.
Specific reasons why early combination therapy may be beneficial in Type 2 diabetes

- Early robust lowering of A1c
- Avoidance of clinical inertia associated with a stepwise approach to therapy
- Potential for early combination therapy to impact Beta-cell function
- Initiation of a therapeutic intervention with a complementary mechanism of action
- Potential to use less than maximal doses of individual agents, minimizing side effect.

Key Findings

1. The vast majority of patients with Type 2 diabetes eventually require combination therapy: 50% of patients at 3 years; 75% of patients at 9 years

2. There is significant clinical inertia in response to inadequate glycemic control (A1c >8%): specialist and primary care physicians similar except when initiating insulin therapy

3. Secondary failure of metformin monotherapy is increased when initial A1c is >8%: approximately 19% per year.

B. Zinman. Astra Zeneca Symposium presented at the 2014 EASD
Reviewed by Dr. Joanne F. Liutkus
Combination Therapy vs. each as monotherapy

1. Metformin + SU: Hypoglycemia, weight gain, lack of durability.

2. Saxagliptin + Metformin: superior glycemic control

3. Saxagliptin + Dapagliflozin + Metformin = superior

4. Sitagliptin + metformin: plus lower post meal glucose levels.

5. Linagliptin + Metformin
   Hack T et al. Diab Obes Metab 2012; 14: 565-74

6. Metformin XR + Dapagliflozin: plus weight loss

7. Exenatide BID + Metformin
   DeFronzo RA et al. Diabetes Care 2005; 28: 1092-100

8. Saxagliptin + Dapagliflozin
   Rosenstock J et al. presented at the ADA Congress 2014. Abstract #127-LB

9. Dapagliflozin + Insulin: reduction of insulin dosage by 20 units

B. Zinman. Astra Zeneca Symposium presented at the 2014 EASD
Reviewed by Dr. Joanne F. Liutkus
Discussion & Implications

• **Take-home messages:**
  – Good evidence that initiating dual therapy for new onset diabetes results in:
    • Improved glycemic control
    • Less hypoglycemia
    • Weight loss or no weight gain
    • Improved adherence
    • Cost effective
    • Reduced number of pills per day
    • Fewer SFX
  – No threshold for A1c as to when combination therapy should be initiated.
  – Need to educate both specialists and primary care providers of the importance of early, aggressive glycemic control

• **Consider:**
  – Impact on Canadian health care system.
Questions, comments?