NEWS BRIEFING
Diabetes and Cardiovascular Disease

*Moderated by:*
Robert Eckel, MD
University of Colorado
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A Cost Analysis of Intensified Versus Conventional Multifactorial Treatment of Type 2 Diabetes

The Steno-2 Study
ADA Congress 2018

Joachim Gaede
University of Copenhagen, Denmark
The Steno-2 Study was funded by unrestricted grants from Novo Nordisk
What is the Steno-2 Study?

High-risk type 2 diabetes patients (n=160) were randomized to either conventional or intensified multifactorial intervention.

### Intervention
- **Conventional multifactorial treatment**
- **Intensified multifactorial treatment**

### Follow-up
- **Intensified multifactorial treatment**
- **Intensified multifactorial treatment**

Timeline (years):
- 0
- 4
- 8
- 13
- 21

Endpoint:
- Kidney, eyes and nerves
- Heart attack, stroke, amputation
- Death
- Life span & Health economy

**Intensified multifactorial intervention**
- Structured risk factor intervention with predefined strict targets resembling current ADA guidelines
- Intensified pharmaceutical intervention + life style intervention

n=24
Patient years = 1,108

n=42
Patient years = 1,310
Steno-2
Intensified versus conventional multifactorial treatment

Major clinical outcomes in type 2 diabetes patients who were treated with the intensified multifactorial approach

~ 50% relative risk reduction in kidney, eye and nerve complications after 4 years (Lancet 353:617-622, 1999)


7.9 years of life gained after 21 years (Diabetologia 59: 2298-2307, 2016)
During 1993-2014, patients in the conventionally treated group had twice the number of organ damage events compared to the intensively treated patients.
Cumulative Costs for Health Care During 1993-2014

- Increase in costs after 8 years in the conventional group
- Increasing costs in the intensified treatment group after 15 years, mirroring the event curve
- Declining costs after 18 years in the conventional group caused by reduced number of patients, who were alive
### Cumulative Costs and Costs Per Patient Year

<table>
<thead>
<tr>
<th></th>
<th>Years</th>
<th>Intensive</th>
<th>Conventional</th>
<th>Difference</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>All direct medical costs (€)</strong></td>
<td>1993-2014</td>
<td>11,016,440</td>
<td>10,404,298</td>
<td>612,142</td>
<td>0.5</td>
</tr>
<tr>
<td></td>
<td>1996-2014</td>
<td>9,850,964</td>
<td>9,304,795</td>
<td>546,169</td>
<td>0.6</td>
</tr>
<tr>
<td><strong>Costs per patient year (€)</strong></td>
<td>1993-2014</td>
<td>8,172</td>
<td>9,047</td>
<td>-875</td>
<td>0.2</td>
</tr>
<tr>
<td></td>
<td>1996-2014</td>
<td>8,725</td>
<td>10,091</td>
<td>-1,366</td>
<td>0.045</td>
</tr>
</tbody>
</table>

We found no difference in total costs between the two groups, but a reduction in costs per patient year in the intensified treatment group.
Key point

• An intensified multifactorial approach to treatment of type 2 diabetes increased the lifespan of patients by a median of 7.9 years without any additional total health care costs over 21.2 years of follow-up

(More money spent on drugs; less money spent on complications)
Supplements
## Healthcare Expenses (1)

<table>
<thead>
<tr>
<th></th>
<th>Intensive</th>
<th>Conventional</th>
<th>Difference</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Outpatient</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiovascular disease</td>
<td>92</td>
<td>136</td>
<td>-44</td>
<td>0.09</td>
</tr>
<tr>
<td>Not cardiovascular disease</td>
<td>1,177</td>
<td>1,211</td>
<td>-34</td>
<td>1.0</td>
</tr>
<tr>
<td>Total (from 1996)</td>
<td>1,269</td>
<td>1,347</td>
<td>-78</td>
<td>0.9</td>
</tr>
<tr>
<td><strong>Prescription drugs</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prescription drugs (from 1996)</td>
<td>2,680</td>
<td>2,387</td>
<td>293</td>
<td>0.0006</td>
</tr>
</tbody>
</table>

- No difference in costs of outpatient services between the groups
- Slightly higher costs for prescription drugs in the intensified treatment group
## Healthcare Expenses (2)

<table>
<thead>
<tr>
<th></th>
<th>Intensive</th>
<th>Conventional</th>
<th>Difference</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Inpatient</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiovascular disease</td>
<td>1,331</td>
<td>2,213</td>
<td>-882</td>
<td>0.002</td>
</tr>
<tr>
<td>Not cardiovascular disease</td>
<td>3,079</td>
<td>3,281</td>
<td>-202</td>
<td>0.6</td>
</tr>
<tr>
<td><strong>Total (1993-2014)</strong></td>
<td>4,410</td>
<td>5,494</td>
<td>-1,084</td>
<td>0.04</td>
</tr>
<tr>
<td><strong>Primary health sector</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary health care sector (from 1993)</td>
<td>433</td>
<td>514</td>
<td>-81</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

- Lower costs associated with intensified treatment in inpatient health services. Specifically related to cardiovascular disease.
- Lower costs in the primary health sector in the intensified treatment group.
Canagliflozin Versus Other Antihyperglycemic Agents on the Risk of Below-Knee Lower Extremity Amputation (BKLE) for Patients with Type 2 Diabetes Mellitus: Results of the OBSERVE-4D Study, a Real-World Analysis of >700,000 U.S. Patients

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Chapel Hill, NC
Presenter Disclosures

• **Consultant:** None

• **Employee:** None

• **Research Support:** AstraZeneca, Boehringer Ingelheim, Johnson & Johnson, Lexicon, Novo Nordisk, Sanofi, Theracos, and vTv Therapeutics

• **Speaker’s Bureau:** None

• **Stock Options:** Mellitus Health, PhaseBio Pharmaceuticals

• **Other (advisor under contract with employer):** Adocia, AstraZeneca, Dexcom, Elcelyx Therapeutics, Eli Lilly, Intarcia Therapeutics, Lexicon, Metavention, NovaTarg, Novo Nordisk, Sanofi, Senseonics, and vTv Therapeutics
Introduction to OBSERVE-4D

- OBSERVE-4D is the largest, most comprehensive, retrospective real-world observational study to evaluate the risk of below-knee lower extremity (BKLE) amputation and hospitalized heart failure (HHF) among the individual sodium glucose cotransporter 2 inhibitor (SGLT2i) medicines.

- OBSERVE-4D compared Canagliflozin vs. other SGLT2i therapies, and non-SGLT2is across a broad type 2 diabetes (T2D) population of more than 700,000 patients in the United States.

- Some SGLT2is have reported a CV benefit. Findings from other clinical trials and prior observational studies on the risk of BKLE amputation with SGLT2is have been mixed.
  - An increased risk of amputation was identified with Canagliflozin in the CANVAS Program.
  - A potential risk of BKLE amputation is reported in the label of the SGLT2i ertugliflozin.

- Up until now, no real-world study has shown head-to-head comparative evidence of HHF and BKLE amputation among individual SGLT2i medicines.
Methods

• De-identified patient-level data were extracted from four U.S. administrative claims databases:
  o Truven MarketScan®: Commercial Claims and Encounters, Multi-state Medicaid, Medicare Supplemental Beneficiaries and OptumInsight’s Clinformatics® Datamart

• The risks of HHF and BKLE amputation were compared for:
  o Canagliflozin versus non-SGLT2i (any dipeptidyl peptidase-4 inhibitor, glucagon-like peptide-1 receptor agonist, thiazolidinedione, sulfonylurea, insulin, or acarbose, bromocriptine, miglitol, nateglinide, or repaglinide)
  o Canagliflozin versus other SGLT2is (dapagliflozin and empagliflozin)

• Risk was characterized in the overall population and the sub-group with established CV disease

• Propensity score adjustment was performed to reduce confounding due to imbalances in baseline covariates

• A set of negative control outcomes were used to control for systematic bias
Reduced Risk of Hospitalized Heart Failure

- The internal validity of OBSERVE-4D is confirmed by the detection of a similar reduction in HHF as seen in randomized clinical trials, other real-world evidence studies, and across the SGLT2i class.
- New users of Canagliflozin had a lower risk of HHF compared with new users of non-SGLT2is; similar reductions observed among the SGLT2i class.

<table>
<thead>
<tr>
<th>Comparison</th>
<th>Population</th>
<th>Exposure (n/PY)</th>
<th>Outcomes, n</th>
<th>HR (95% CI)</th>
<th>Calibrated P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>CANA</td>
<td>Comparator</td>
<td>CANA</td>
<td>Comparator</td>
</tr>
<tr>
<td>Overall</td>
<td>Overall</td>
<td>111,332/53,116</td>
<td>445,367/255,504</td>
<td>124</td>
<td>2,979</td>
</tr>
<tr>
<td></td>
<td>Established CV disease</td>
<td>32,384/14,692</td>
<td>135,006/79,292</td>
<td>95</td>
<td>2,234</td>
</tr>
<tr>
<td>CANA vs all non-SGLT2i</td>
<td>Overall</td>
<td>69,554/31,363</td>
<td>98,169/41,667</td>
<td>56</td>
<td>73</td>
</tr>
<tr>
<td></td>
<td>Established CV disease</td>
<td>19,596/8,584</td>
<td>26,993/10,952</td>
<td>34</td>
<td>44</td>
</tr>
</tbody>
</table>

Meta-analytic estimate in the on-treatment population.
No Increased Risk of Below-Knee Amputation

• OBSERVE-4D found no increased risk of amputation with Canagliflozin in the general type 2 diabetes patient population or in patients with established CV disease

• These findings were consistent across all SGLT2is

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<th>Exposure (n/PY)</th>
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<td></td>
<td>CANA</td>
<td>Comparator</td>
<td>CANA</td>
<td>Comparator</td>
</tr>
<tr>
<td>Overall</td>
<td>111,332/53,125</td>
<td>445,367/256,646</td>
<td>60</td>
<td>481</td>
<td>0.75 (0.40-1.41)</td>
</tr>
<tr>
<td>Established CV disease</td>
<td>32,384/14,702</td>
<td>135,006/80,176</td>
<td>33</td>
<td>271</td>
<td>0.72 (0.34-1.51)</td>
</tr>
<tr>
<td>CANA vs all non-SGLT2i</td>
<td></td>
<td>CANA</td>
<td>Comparator</td>
<td>CANA</td>
<td>Comparator</td>
</tr>
<tr>
<td>Overall</td>
<td>69,554/31,369</td>
<td>98,169/41,666</td>
<td>40</td>
<td>53</td>
<td>1.14 (0.67-1.93)</td>
</tr>
<tr>
<td>Established CV disease</td>
<td>19,596/8,584</td>
<td>26,993/10,951</td>
<td>23</td>
<td>35</td>
<td>1.08 (0.63-1.82)</td>
</tr>
</tbody>
</table>
Key Conclusions

• The OBSERVE-4D study shows that in the general T2D population, and in those with established CV disease, there is no increased risk of below-knee lower extremity amputation with Canagliflozin in clinical practice in the United States.

• The amputation risk observed with Canagliflozin was similar compared to other SGLT2is and other classes of diabetes medications.

• The number of patients with long-duration (>6 months) exposure is limited and further study will be required to fully understand the issue.

• Canagliflozin can also have an important and positive impact on reducing a patient’s risk of HHF.

• The overall benefit-risk profiles of Canagliflozin and the SGLT2i class are positive and physicians should feel comfortable and confident in prescribing the class to their patients.
Alirocumab and Cardiovascular Outcomes in Patients with Acute Coronary Syndrome (ACS) and Diabetes

Prespecified Analyses of ODYSSEY OUTCOMES

Kausik K. Ray, MD
Imperial College, London
Presenter Disclosures

- **Research grants:** Amgen, Sanofi, Regeneron, MSD, Pfizer
- **Consultancy:** Amgen, Sanofi, Regeneron, MSD, Pfizer, Astra Zeneca, Lilly, The Medicines Company, Kowa, IONIS, Takeda, Novo Nordisk, Boehringer Ingelheim, Esperion, Cipla, Algorithm, Abbvie, Resverlogix, Cerenis

The trial was funded by **Sanofi** and **Regeneron Pharmaceuticals**
Background and Goals

• A majority of patients with ACS have a glucometabolic abnormality (prediabetes or diabetes)
• ACS patients with diabetes are at higher risk for recurrent ischemic CV events than ACS patients without diabetes, and derive greater absolute benefit from high-intensity statin therapy or ezetimibe + statin
• Genetic loss of function in PCSK9 is associated with increased risk of new-onset diabetes (NOD)\(^1\)
• Evolocumab (FOURIER) in chronic atherosclerotic CV disease\(^2\) showed greater absolute benefit in patients with diabetes than in those without diabetes. Neither FOURIER nor the Phase 3a alirocumab program (4974 patients) showed an increased risk of NOD\(^3\)

In this prespecified analysis from the ODYSSEY OUTCOMES trial, we compared the CV efficacy and glucometabolic safety of alirocumab or placebo among people with diabetes, prediabetes, or normoglycemia

Treatment Assignment

Post-ACS patients (1 to 12 months)

Run-in period of 2–16 weeks on high-intensity or maximum-tolerated dose of atorvastatin or rosuvastatin

At least one lipid entry criterion met

Randomization

Alirocumab SC Q2W

Placebo SC Q2W

Patient and investigators remained blinded to treatment and lipid levels for the entire duration of the study

Relative and Absolute Risk Reduction with Alirocumab By Glucometabolic Status

Relative risk reduction

\[ P_{\text{interaction}} = 0.98 \]

Absolute risk reduction

\[ P_{\text{interaction}} = 0.0019 \]

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>MACE Incidence</th>
<th>Relative risk reduction</th>
<th>Absolute risk reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Alirocumab n/N (%)</td>
<td>Placebo n/N (%)</td>
<td>HR (95% CI)</td>
</tr>
<tr>
<td>Overall</td>
<td>903/9462 (9.5)</td>
<td>1052/9462 (11.1)</td>
<td>0.85 (0.78, 0.93)</td>
</tr>
<tr>
<td>Normoglycemia</td>
<td>192/2639 (7.3)</td>
<td>220/2595 (8.5)</td>
<td>0.85 (0.70, 1.03)</td>
</tr>
<tr>
<td>Prediabetes</td>
<td>331/4130 (8.0)</td>
<td>380/4116 (9.2)</td>
<td>0.86 (0.74, 1.00)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>380/2693 (14.1)</td>
<td>452/2751 (16.4)</td>
<td>0.84 (0.74, 0.97)</td>
</tr>
</tbody>
</table>

Median (Q1, Q3) follow-up: 2.8 (2.3, 3.4) years
Analysis method for A1c and fasting glucose: repeated-measures mixed effects model; random effects = slope, intercept; fixed effects = treatment, baseline value, and time. Only post-randomization values prior to initiation of diabetes medication were included in the analysis.
*Without diabetes = prediabetes or normoglycemia.
Conclusions

Among people with diabetes at baseline:
• Risk of recurrent ischemic events after ACS is high, despite intensive statin treatment
• Using alirocumab to target LDL-C levels of 25–50 mg/dL:
  o Produces a similar relative risk reduction to those without diabetes
  o Produces a greater absolute risk reduction compared to those without diabetes

Among people without diabetes at baseline, over the duration of this study:
• No evidence of increased fasting serum glucose or A1c with alirocumab, compared with placebo
• No overall increase in new-onset diabetes with alirocumab, compared with placebo
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• For interviews with any of the presenters, please contact Michelle Kirkwood or a member of the Press Office team.
MEDIA CONTACT

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