Novel antidiabetic drugs: The story of the trees and the forest; has their position crystallized?

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Diabetes and its Novel Interventions: Antidiabetic Drugs

- Effect of glucose-lowering on cardiovascular events
- „Novel“ oral antidiabetic drugs
- Cardiovascular outcome trials with novel antidiabetic drugs
UKPDS: glucose control and incidence of myocardial infarction

Myocardial infarction
(p=0.052)

Intensive treatment (n=2729)
Conventional treatment (n=1138)

UKPDS-Group, Lancet 1998; 352:837-853
# UKPDS

## Intensive vs. control

<table>
<thead>
<tr>
<th></th>
<th></th>
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<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Any diabetes related endpoint</td>
<td>12%</td>
<td>0.029</td>
<td>9%</td>
<td>0.04</td>
</tr>
<tr>
<td>Microvascular disease</td>
<td>25%</td>
<td>0.0099</td>
<td>24%</td>
<td>0.001</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>16%</td>
<td>0.052</td>
<td>15%</td>
<td>0.014</td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>6%</td>
<td>0.44</td>
<td>13%</td>
<td>0.007</td>
</tr>
</tbody>
</table>

Effect of intensive glucose lowering on micro- and macrovascular events

ADVANCE study

11140 patients with type 2 diabetes

Intensive therapy
Target HbA1c: < 6.5%

Standard therapy
Target HbA1c: According to local guidelines

Follow-up: 4.3 years

Combined endpoint of micro- and macrovascular events
Effect of intensive glucose lowering on micro- and macrovascular events

ADVANCE study

Mean HbA$_1c$ at final visit
7.3 %
6.5%
Effect of intensive glucose lowering on micro- and macrovascular events

ADVANCE study

Macrovascular events (CV death, MI, Stroke)

- HbA1c 7.3%
- HbA1c 6.5%

Microvascular events (Nephropathy, retinopathy)

- HbA1c 7.3%
- HbA1c 6.5%

ACCORD: cardiovascular safety

Total mortality

HR (CI) 1.22 (1.01, 1.46)  
$p=0.04$

Effect of glucose-lowering on cardiovascular events

• Early intensive glucose control in patients without CV disease may reduce CV events and CV mortality after \( \sim 20 \) years.

• Hypoglycemia and weight gain should be avoided.

• In patients with a longer duration of diabetes (and a history of CV disease) an intensive glucose control regimen does not reduce CV events within a few years.

• An intensive glucose control regimen reduces microvascular complications in patients with type 2 diabetes.
Diabetes and its Novel Interventions: Antidiabetic Drugs

• Effect of glucose-lowering on cardiovascular events
• „Novel“ oral antidiabetic drugs:
  – DPP-IV inhibitors
  – SGLT2 inhibitors
• Cardiovascular outcome trials with novel antidiabetic drugs
Oral antidiabetic drugs

Insulin secretion ↓
Glucagon secretion ↑

Hyperglycemia

α-Glucosidase-inhibitors

Lipolysis ↑
Glucose uptake ↓

Sulfonylureas

DPP-IV-inhibitors

Metformin

Hepatic glucose production ↑

Glucose uptake ↓

Glucose reabsorption ↑

SGLT2 inhibitors

Glitazones

Glutazones

Incretin effect ↓

GLP-1 - metabolism

$T_{1/2} = 1-2$ min

- Sitagliptin
- Saxagliptin
- Alogliptin
- Linagliptin
Glucagon secretion decreased (α-cells)
Insulin secretion increased (β-cells)
Glucose uptake ↑
Blood glucose ↓
Glucose production ↓

GLP-1=Glukagon-like peptide-1; GIP=Glucose-dependent insulinotropic Polypeptide
Linagliptin significantly lowers HbA$_1c$ as add-on to metformin

Efficacy and safety of linagliptin vs. placebo added to metformin background therapy in patients with type 2 diabetes

<table>
<thead>
<tr>
<th></th>
<th>Placebo (n=175)</th>
<th>Linagliptin 5mg + Metformin (n=513)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>8.09%</td>
<td>8.02%</td>
</tr>
<tr>
<td>Week 6</td>
<td>7.93%</td>
<td>8.01%</td>
</tr>
<tr>
<td>Week 12</td>
<td>7.65%</td>
<td>7.95%</td>
</tr>
<tr>
<td>Week 18</td>
<td>7.50%</td>
<td>7.90%</td>
</tr>
<tr>
<td>Week 24</td>
<td>7.45%</td>
<td>7.85%</td>
</tr>
</tbody>
</table>

Significant placebo-corrected improvement in mean HbA$_1c$ of -0.64% observed at Week 24 after treatment with linagliptin (P<0.0001)

Note: Baseline HbA$_1c$: 8.09% linagliptin-treated group; 8.02% placebo group; Full analysis set (FAS), Last observation carried forward (LOCF)

Multiple effects of GLP-1

after Baggio, Gatroenterology, 2007;132:2131–2157
Effect of DPP-IV inhibitors on lesion development in ApoE-deficient mice

ApoE -/- Mice

High fat diet plus DPPIV-Inhibitor Sitagliptin

8 weeks old: Start of high fat feeding

High fat diet only

20 weeks old: Analysis
Sitagliptin increases plaque collagen content in lesions of ApoE-/- mice.

Vittone et al.; Diabetologia 2012; 55:2267-2275
Oral antidiabetic drugs

**Incretin effect ↓**

**Insulin secretion ↓**
**Glucagon secretion ↑**

**DPP-IV-inhibitors**

**Metformin**

**Hyperglycemia**

**α-Glucosidase-inhibitors**

**Glucose uptake ↓**

**Lipolysis ↑**
**Glucose uptake ↓**

**Sulfonylureas**

**Hepatic glucose production ↑**

**Glucagon secretion ↑**

**Glucose reabsorption ↑**

**Glitazones**

**SGLT2 inhibitors**

**Glucose uptake ↓**

---
Renal glucose reabsorption in healthy individuals

Glucose

SGLT1

~10%

SGLT2

~90%

SGLT = sodium-glucose cotransporter

Renal glucose reabsorption in patients with diabetes

Glucose

SGLT1
~10%

SGLT2
~90%

SGLT=sodium-glucose cotransporter

Urinary glucose excretion
Increased SGLT2 expression and renal glucose reabsorption

SGLT = sodium-glucose cotransporter

SGLT2 inhibitor effect: increased urinary glucose excretion
Changes in HbA1c in SGLT2 inhibitor treated patients

- Placebo
- Dapagliflozin 2.5 mg
- Dapagliflozin 5 mg
- Dapagliflozin 10 mg

HbA1c - baseline (%)
- Placebo (n=228) 7.91 %
- Empagliflozin 10 mg (n=224) 7.87 %
- Empagliflozin 25 mg (n=224) 7.86 %

Changes in body weight in SGLT2 inhibitor treated patients

Canagliflozin (placebo adjusted values)
12 wk study (n = 451)

Empagliflozin
12 wk study (n = 495)

Seman L et al. Presented at EASD Annual Meeting, Lisbon 12-16 September 2011; abstract #147
Changes in blood pressure in SGLT2 inhibitor treated patients

Mean systolic blood pressure at week 12

Tikkanen I, et al. (AHA) Scientific Sessions, November 16-20, 2013, Dallas, USA (Poster 2091).
„Novel“ oral antidiabetic drugs

DPP-IV inhibitors
- reduce blood glucose levels glucose-dependent
- do not induce hypoglycemia or weight gain

SGLT2 inhibitors
- reduce blood glucose levels insulin-independent
- do not increase the risk for hypoglycemic events
- reduce weight and blood pressure
Diabetes and its Novel Interventions: Antidiabetic Drugs

- Effect of glucose-lowering on cardiovascular events
- „Novel“ oral antidiabetic drugs:
  - DPP-IV inhibitors
  - SGLT2 inhibitors
- Cardiovascular outcome trials with novel antidiabetic drugs
Cardiovascular outcome trials

Traditional CV Outcome Trials

Designed to Demonstrate CV Benefit

Diabetes CV Safety Trials

Designed to Demonstrate CV Safety (non-inferiority)
Guidance for Industry
Diabetes Mellitus — Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes

“….If upper bound of two-sided 95% CI for HR is between 1.3 and 1.8, a postmarketing full CV safety trial will be required to definitively assess whether upper bound is <1.3…."

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
December 2008
Clinical/Medical

OR 1.64
95% CI 0.98-2.74
P=0.06

Nissen, Wolski; N Engl J Med 2007 (356), 2457-2471

Myocardial infarction
OR 1.43
95% CI 1.03-1.98
P=0.03

CV death
39
22
Cardiovascular outcome trials

Traditional CV Outcome Trials

Diabetes CV Safety Trials

Designed to Demonstrate CV Benefit

Designed to Demonstrate CV Safety (non-inferiority)
<table>
<thead>
<tr>
<th>Traditional CV Outcome Trials</th>
<th>Diabetes CV Safety Trials Primarily Designed to Demonstrate CV Safety</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Lower CV risk vs placebo or active comparator</strong></td>
<td><strong>No increased CV risk vs placebo as part of standard care</strong></td>
</tr>
<tr>
<td>Initiation of blinded treatment or placebo</td>
<td>Initiation of blinded treatment or placebo</td>
</tr>
<tr>
<td><strong>No adjustment to maintain HbA(_1c) levels the same in both groups</strong></td>
<td>Adjustment to maintain HbA(_1c) levels the same in both groups</td>
</tr>
<tr>
<td><strong>Difference in HbA(_1c) between treatment and placebo</strong></td>
<td><strong>Small or no difference in HbA(_1c) between treatment and placebo</strong></td>
</tr>
<tr>
<td><strong>CV benefit of treatment demonstrated by significant reduction in CV outcomes</strong></td>
<td><strong>No increased CV risk (CV safety) of treatment demonstrated by noninferiority</strong></td>
</tr>
</tbody>
</table>
Cardiovascular outcome trials
DPP-IV inhibitors

- Risk Factors
- Stable CAD-CVD-PAD
- Post-ACS patients

SAVOR-Timi-Saxagliptin
EXAMINE-Alogliptin
TECOS-Sitagliptin

CAROMELINA - Linagliptin
CAROLINA - Linagliptin

Kidney disease
## Baseline characteristics

<table>
<thead>
<tr>
<th>Baseline Variables</th>
<th>SAVOR (Saxagliptin)</th>
<th>EXAMINE (Alogliptin)</th>
<th>TECOS (Sitagliptin)</th>
<th>CAROLINA (Linagliptin)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Participants (n)</td>
<td>16,500</td>
<td>5,400</td>
<td>14,724</td>
<td>6,046</td>
</tr>
<tr>
<td>Age (y)</td>
<td>65</td>
<td>61</td>
<td>66</td>
<td>64</td>
</tr>
<tr>
<td>Diabetes Duration (y)</td>
<td>12</td>
<td>7.2</td>
<td>9.4</td>
<td>~6</td>
</tr>
<tr>
<td>BMI (kg/m^2)</td>
<td>31</td>
<td>29</td>
<td>29</td>
<td>30</td>
</tr>
<tr>
<td>A1C (%)</td>
<td>8.0</td>
<td>8.0</td>
<td>7.3</td>
<td>7.2</td>
</tr>
<tr>
<td>Prior CVD (%)</td>
<td>78</td>
<td>~100</td>
<td>100</td>
<td>34</td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>81</td>
<td>83</td>
<td>86</td>
<td>84</td>
</tr>
<tr>
<td>Prior Insulin Use (%)</td>
<td>41</td>
<td>30</td>
<td>23</td>
<td>0</td>
</tr>
<tr>
<td>Comparator</td>
<td>Placebo</td>
<td>Placebo</td>
<td>Placebo</td>
<td>Glimepiride</td>
</tr>
</tbody>
</table>

DPP-4 inhibitors: CV outcome trials

SAVOR-TIMI53
DPP-4 inhibitor
Saxagliptin

EXAMINE
DPP-4 inhibitor
Alogliptin

16492 pat with diabetes and CAD or high CV risk
5380 pat with diabetes and ACS within the last 90 days

Duration:
2.1 years
18 months
DPP-4 inhibitors: CV outcome trials

SAVOR-TIMI53

Hazard ratio, 1.00 (95% CI, 0.89−1.12)
P<0.001 for noninferiority
P=0.99 for superiority

2yr Kaplan–Meier rate:
Saxagliptin, 7.3%
Placebo, 7.2%


EXAMINE

Hazard ratio, 0.96 (upper boundary of the one-sided repeated CI, 1.16)

Cardiovascular outcome trials
SGLT2 inhibitors

Risk Factors | Stable CAD-CVD-PAD | Post-ACS patients

- DECLARE-TIMI 58
  Dapagliflozin

- Canvas
  Canagliflozin

- EMPA-REG OUTCOME
  Empagliflozin
EMP A-REG OUTCOMEx™

• Multicenter, randomized, placebo-controlled trial
• 7034 patients with diabetes and high CV risk

Follow-up: event-driven min. 691 events

Primary endpoint:
CV death, MI, stroke

**Cardiovascular outcome trials**

**Baseline characteristics**

<table>
<thead>
<tr>
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<th>EXAMINE (Alogliptin)</th>
<th>EMPA-REG OUTCOME</th>
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<td>Participants (n)</td>
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<td>5,400</td>
<td>7,034</td>
</tr>
<tr>
<td>Age (y)</td>
<td>65</td>
<td>61</td>
<td>63</td>
</tr>
<tr>
<td>Diabetes Duration (y)</td>
<td>12</td>
<td>7.2</td>
<td>57% &gt; 10 y</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>31</td>
<td>29</td>
<td>31</td>
</tr>
<tr>
<td>A1C (%)</td>
<td>8.0</td>
<td>8.0</td>
<td>8.1</td>
</tr>
</tbody>
</table>

Current cardiovascular outcome trials examine whether novel antidiabetic drugs increase cardiovascular risk in patients with diabetes.

Diabetes and its Novel Interventions: Antidiabetic Drugs

- DPP-IV inhibitors as well as SGLT2 inhibitors reduce blood glucose without increasing the risk for hypoglycemic events

- Current cardiovascular safety trials examine whether these agents increase cardiovascular risk in patients with diabetes