Farmaci Antidiabetici e Rischio Cardio-Nefro-Vascolare

Il Fatto
A. Giaccari
CONGRESSO PERIFERICO AMD - SID

LA CLINICA DEL DIABETE INCONTRO TRA ESPERIENZE MULTIDISCIPLINARI
Tivoli, 30 settembre 2017

Il dr. GIACCARI dichiara di aver ricevuto negli ultimi due anni compensi o finanziamenti dalle seguenti Aziende Farmaceutiche e/o Diagnostiche:

- ASTRazeneca, Lilly, Takeda
  Sanofi, MSD
A1c Predicts CV Risk
prospective study of 229 Finnish type 2 diabetic patients without previous vascular disease


A1c = glycosylated hemoglobin; CHD = coronary heart disease.

*P<0.01 vs lowest tertile; †P<0.05 vs lowest tertile.
Effects of Intensive Glucose Lowering in Type 2 Diabetes

The Action to Control Cardiovascular Risk in Diabetes Study Group*

Intensive Blood Glucose Control and Vascular Outcomes in Patients with Type 2 Diabetes

The ADVANCE Collaborative Group*

Glucose Control and Vascular Complications in Veterans with Type 2 Diabetes
ACCORD: HbA1c

Time (years)

<table>
<thead>
<tr>
<th>Year</th>
<th>Standard therapy</th>
<th>Intensive therapy</th>
</tr>
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<tbody>
<tr>
<td>6</td>
<td>9.0</td>
<td>8.5</td>
</tr>
<tr>
<td>5</td>
<td>8.5</td>
<td>8.0</td>
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<td>4</td>
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<td>7.5</td>
</tr>
<tr>
<td>3</td>
<td>7.5</td>
<td>7.0</td>
</tr>
<tr>
<td>2</td>
<td>7.0</td>
<td>6.5</td>
</tr>
<tr>
<td>1</td>
<td>6.5</td>
<td>6.0</td>
</tr>
<tr>
<td>0</td>
<td>6.0</td>
<td>5.5</td>
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</tbody>
</table>

ACCORD: CV Events were non-significantly reduced by intensive treatment.

HR 0.90 (0.78-1.04)  
P = 0.16
ACCORD: all cause mortality was significantly increased by intensive treatment.

HR 1.22 (1.01-1.46)  
P = 0.04

# Impact of Intensive Therapy for Diabetes: Summary of Major Clinical Trials

<table>
<thead>
<tr>
<th>Study</th>
<th>Microvasc</th>
<th>CVD</th>
<th>Mortality</th>
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<tbody>
<tr>
<td><strong>VADT</strong></td>
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<td><strong>ADVANCE</strong></td>
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<td><strong>ACCORD</strong></td>
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</tr>
</tbody>
</table>

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Kendall DM, Bergenstal RM. © International Diabetes Center 2008
PROACTIVE: primary outcome

Dormandy JA et al.: Lancet 366:1279, 2005
RECORD primary endpoint
CV events and hospitalizations

rosiglitazone: the final meta-analysis for MI

promised to save β-cells
executed on charges of murder
the burdening clinical point

can the reduction of HbA1c prevent CV events?

NO!
they might even be dangerous
CV outcome trials for new drugs

<table>
<thead>
<tr>
<th>Year</th>
<th>Trial</th>
<th>Drug</th>
<th>Sponsor</th>
<th>Start Date</th>
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</thead>
<tbody>
<tr>
<td>2012</td>
<td>SAVOR TIMI 53</td>
<td>Saxagliptin</td>
<td>AZ/BMS</td>
<td>7/13</td>
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<tr>
<td>2013</td>
<td>EXAMINE</td>
<td>Alogliptin</td>
<td>Takeda</td>
<td>12/13</td>
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<tr>
<td>2014</td>
<td>TECOS</td>
<td>Sitagliptin</td>
<td>Merck</td>
<td>12/14</td>
</tr>
<tr>
<td>2015</td>
<td>ELIXA</td>
<td>Lixisenatide</td>
<td>Sanofi</td>
<td>5/14</td>
</tr>
<tr>
<td>2016</td>
<td>LEADER</td>
<td>Liraglutide</td>
<td>Novo</td>
<td>1/16</td>
</tr>
<tr>
<td>2017</td>
<td>SUSTAIN 6</td>
<td>Semaglutide</td>
<td>Novo</td>
<td>1/16</td>
</tr>
<tr>
<td>2018</td>
<td>CANVAS (interim)</td>
<td>Canagliflozin</td>
<td>J&amp;J</td>
<td>(6/18)</td>
</tr>
<tr>
<td>2019</td>
<td>CANVAS</td>
<td>Canagliflozin</td>
<td>J&amp;J</td>
<td>(15)</td>
</tr>
<tr>
<td>2020</td>
<td>CAROLINA</td>
<td>Linagliptin</td>
<td>BI/Lilly</td>
<td>(9/18)</td>
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<tr>
<td></td>
<td>REWIND</td>
<td>Dulaglutide</td>
<td>Lilly</td>
<td>(4/19)</td>
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<tr>
<td></td>
<td>HARMONY</td>
<td>albiglutide</td>
<td>GSK</td>
<td>(7/20)</td>
</tr>
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</table>

1. Expected dates for completion of primary endpoint (source: clinicaltrials.gov, accessed 04/2016)
2. Interims data ~2016; 2nd Linagliptin CV outcomes trial vs PBO (CARMELINA) expected to start in 2013, per primary CI (tbc) results in 2018
3. Per Janssen commentary at FDA ACM, next CV meta-analysis planned after 500 events- expected in 2015
4. per Novo interims analysis possible in 2014/15 if required for review of obesity sNDA
SAVOR-TIMI: MACE cumulative incidence

Hazard ratio, 1.00 (95% CI, 0.89–1.12)
P<0.001 for non inferiority

EXAMINE: MACE cumulative incidence

White WB et al. NEJM 369:1327; 2013
TECOS: Primary CV Outcome PP Analysis for Non-inferiority

* CV death, nonfatal MI, nonfatal stroke, hospitalization for unstable angina
Green JB et al. NEJM 2015
gliflozins reduce CV deaths
(EMPAREG secondary endpoint)

HR 0.62
(95% CI 0.49, 0.77)
p<0.0001
risk reduced by 38%

patients with event (%)

months

empagliflozin
placebo

Zinman B et al.: NEJM 373:2117, 2015
The primary composite outcome in the time-to-event analysis was the first occurrence of death from cardiovascular causes, non-fatal myocardial infarction, or non-fatal stroke. The cumulative incidences were estimated with the use of the Kaplan–Meier method, and the hazard ratios with the use of the Cox proportional-hazard regression model. The data analyses are truncated at 54 months, because less than 10% of the patients had an observation time beyond 54 months. CI: confidence interval; CV: cardiovascular; HR: hazard ratio.
EMPA-REG OUTCOME Study

The BI10773 (Empagliflozin) Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients (EMPA-REG OUTCOME) was a randomized, double-blind trial that assessed the effect of empagliflozin, a SGLT2 inhibitor, versus placebo and standard care, on cardiovascular outcomes in patients with type 2 diabetes and existing cardiovascular disease. Study participants had a mean age of 63 years, 57% had diabetes for more than 10 years, and 99% had established cardiovascular disease. EMPA-REG OUTCOME showed that over a median follow-up of 3.1 years, treatment reduced the composite outcome of MI, stroke, and cardiovascular death by 14% (absolute rate 10.5% vs. 12.1% in the placebo group) and cardiovascular death by 38% (absolute rate 3.7% vs. 5.9%) (29). The FDA recently added a new indication for empagliflozin, to reduce the risk of cardiovascular death in adults with type 2 diabetes and cardiovascular disease. Whether other SGLT2 inhibitors will have the same effect in high-risk patients and whether empagliflozin or other SGLT2 inhibitors will have a similar effect in lower-risk patients with diabetes remains unknown.
CANVAS primary MACE outcome
CV Death, Nonfatal Myocardial Infarction or Nonfatal Stroke

EMPAREG, Zinman B et al.: NEJM 373:2117, 2015
CANVAS, Neal B et al.: NEJM Jun 12, 2017
CANVAS & EMPAREG

primary MACE outcome
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CANVAS & EMPAREG
primary MACE outcome
CV Death, Nonfatal Myocardial Infarction or Nonfatal Stroke

EMPAREG, Zinman B et al.: NEJM 373:2117, 2015
CANVAS, Neal B et al.: NEJM Jun 12, 2017
Primary outcome
All-cause death, non-fatal MI - including silent MI, non-fatal stroke, urgent coronary revascularization

HR=0.96 (95% CI, 0.74-1.26)
P=0.79
Key secondary outcome, on treatment population

Sudden death, fatal and non-fatal MI (including silent MI), fatal and non-fatal stroke, major leg amputation (above the ankle), coronary, leg or carotid arteries revascularization

HR = 0.67 (95% CI, 0.47-0.96)

P = 0.03
CVD-REAL: Health Records

Truven MarketScan Claims & Encounters and linked Medicare

National full-population registries

National full-population registries

Clinical Practice Research Datalink (CPRD) and The Health Improvement Network (THIN)

Diabetes Patienten Verlaufsdocumentation (DPV) initiative

propensity match

SGLT-2i

search a patient similar for 42 different criteria

other glucose lowering drugs

compared 1:1
CVD-REAL: all cause death
primary analysis (N=215,622)

<table>
<thead>
<tr>
<th>database</th>
<th>N</th>
<th>events</th>
<th>HR (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>US</td>
<td>143,264</td>
<td>250</td>
<td>0.38 (0.29, 0.50)</td>
</tr>
<tr>
<td>Norway</td>
<td>25,050</td>
<td>364</td>
<td>0.55 (0.44, 0.68)</td>
</tr>
<tr>
<td>Denmark</td>
<td>18,468</td>
<td>323</td>
<td>0.46 (0.37, 0.57)</td>
</tr>
<tr>
<td>Sweden</td>
<td>18,378</td>
<td>317</td>
<td>0.47 (0.37, 0.60)</td>
</tr>
<tr>
<td>UK</td>
<td>10,462</td>
<td>80</td>
<td>0.73 (0.47, 1,15)</td>
</tr>
<tr>
<td>Total</td>
<td>215,622</td>
<td>1334</td>
<td>0.49 (0.41, 0.57)</td>
</tr>
</tbody>
</table>

in conclusione ...

- in prevenzione secondaria alcuni farmaci sono efficaci nel ridurre eventi CV.
- non è (né sarà mai) possibile stabilire differenze in prevenzione primaria.
- i risultati in prevenzione secondaria sono estrapolabili alla primaria?