Comparative efficacy and safety of Fenofibrate/Pravastatin/Ezetimibe therapy and Simvastatin/Ezetimibe therapy in Type 2 Diabetic patients with combined hyperlipidemia and cardiovascular disease

Michel Farnier\textsuperscript{1}, Kjetil Retterstøl\textsuperscript{2}, Mirosław Dłuzniewski\textsuperscript{3}, Albert Császár\textsuperscript{4}, Armin Steinmetz\textsuperscript{5}

\textsuperscript{1}Dijon, France; \textsuperscript{2}Oslo, Norway; \textsuperscript{3}Warsaw, Poland; \textsuperscript{4}Budapest, Hungary; \textsuperscript{5}Andernach, Germany
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Patients with type 2 diabetes (T2D) and cardiovascular disease (CVD) are classified in a “very high-risk” category.

In diabetic patients with CVD, statin therapy should be initiated regardless of baseline LDL-C, with a treatment target of < 70-77 mg/dL (< 1.8-2.0 mmol/L) (ESC/EASD guidelines).

For patients with high triglycerides (TG), non-HDL-C is considered as a secondary target (< 100 mg/dL) (NCEP guidelines).

Very high-risk patients with T2D and CVD often require combination therapy to achieve recommended LDL-C and non-HDL-C goals.
Objective

To evaluate the efficacy and safety of Fenofibrate (F) 160 mg / Pravastatin (P) 40 mg fixed dose combination and Ezetimibe (E) 10 mg compared to Simvastatin (S) 20 mg and Ezetimibe (E) 10 mg in T2D patients with CVD and not at goals on Simvastatin (S) 20 mg
Comparison of F/P + E triple therapy and S + E combined therapy in patients with T2D and CVD

**Study design**

- **273 patients**
  - **Open-label**
    - S20mg + E10mg (n=136)
  - **Double-blind**
    - F160mg / P40mg + E10mg (n=137)
  - **Open-label**
    - F160mg / P40mg + E10mg

**Selection**

- V1 V2 V3 V4 V5 V6 V7
  - Weeks: -7 -6 -1 0 6 12 18 24

**Run-in period**

- S20mg plus diet

**Efficacy phase**

- F160mg / P40mg + E10mg

**Safety phase**

- S20mg + E10mg

**Multicenter, randomized, double-blind, parallel group study conducted at 73 European centers**
Comparison of F/P + E triple therapy and S + E combined therapy in patients with T2D and CVD

Study Patients

- T2D patients with CVD and documented mixed hyperlipidemia
- randomized after a 6-week run-in period on S20 mg if:
  - non-HDL-C ≥ 100 mg/dL or LDL-C ≥ 70 mg/dL
    - (2.59 mmol/L) (1.8 mmol/L)
  - and
  - TG 150 – 600 mg/dL (1.7 – 6.8 mmol/L)

Main Exclusion criteria

- AST or ALT > 2 x ULN
- CK > 3 x ULN
- abnormal renal function:
  - creatinine clearance < 60 ml/min and
  - plasma creatinine > 15 mg/L
- uncontrolled diabetes (HbA1c > 8.5%) or diabetes requiring insulin
Comparison of F/P + E triple therapy and S + E combined therapy in patients with T2D and CVD

- **Primary endpoint**: % change in non-HDL-C (ITT analysis)

- **Secondary endpoints**: % changes in LDL-C, HDL-C, TG, ApoA1, ApoB, … % of patients achieving LDL-C and non-HDL-C goals (ITT analysis)

- **Safety**
Demographics and Patients characteristics at baseline (safety randomized population)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>F160/P40+E10 group (n = 137)</th>
<th>S20+E10 group (n = 135)</th>
<th>Total (n = 272)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs) &lt; 65 yrs old</td>
<td>61.7 ± 8.4 (66 %)</td>
<td>60.6 ± 7.5 (71 %)</td>
<td>61.1 ± 7.9 (68 %)</td>
</tr>
<tr>
<td>Men</td>
<td>45.3 %</td>
<td>48.1 %</td>
<td>46.7 %</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>31.6 ± 5.1</td>
<td>31.5 ± 4.6</td>
<td>31.6 ± 4.8</td>
</tr>
<tr>
<td>Waist circ. (cm)</td>
<td>105.7 ± 11.8</td>
<td>106.6 ± 12.3</td>
<td>106.2 ± 12.0</td>
</tr>
<tr>
<td>Duration of T2D (yrs)</td>
<td>5.7 ± 5.8</td>
<td>4.3 ± 3.4</td>
<td>5.0 ± 4.8</td>
</tr>
</tbody>
</table>

Data are mean ± SD
Baseline lipid profiles (on S20 mg) (ITT population)

<table>
<thead>
<tr>
<th></th>
<th>F160/P40+E10 group (n = 133)</th>
<th>S20+E10 group (n = 133)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-HDL-C (mg/dL)</td>
<td>145.9 ± 33.0</td>
<td>152.8 ± 38.6</td>
</tr>
<tr>
<td>LDL-C (mg/dL)</td>
<td>109.4 ± 30.7</td>
<td>114.2 ± 33.0</td>
</tr>
<tr>
<td>TG (mg/dL)</td>
<td>247.6 ± 92.4</td>
<td>262.9 ± 97.6</td>
</tr>
<tr>
<td>ApoB (mg/dL)</td>
<td>94 ± 21</td>
<td>97 ± 22</td>
</tr>
<tr>
<td>HDL-C (mg/dL)</td>
<td>44.5 ± 9.7</td>
<td>43.3 ± 9.1</td>
</tr>
<tr>
<td>ApoA-I (mg/dL)</td>
<td>140 ± 20</td>
<td>137 ± 20</td>
</tr>
</tbody>
</table>

Data are mean ± SD
Comparison of F/P + E triple therapy and S + E combined therapy in patients with T2D and CVD

Changes in non-HDL-C (primary endpoint)

-21.2
-24.7

*p < 0.0001 vs baseline

p=0.089
Comparison of F/P + E triple therapy and S + E combined therapy in patients with T2D and CVD

Changes in other lipid parameters

<table>
<thead>
<tr>
<th></th>
<th>LDL-C</th>
<th>TG</th>
<th>ApoB</th>
</tr>
</thead>
<tbody>
<tr>
<td>F160/P40+E10</td>
<td>-19.8</td>
<td>-22.8</td>
<td>-8.2</td>
</tr>
<tr>
<td>S20+E10</td>
<td>-25.1</td>
<td>-22.8</td>
<td>-15.7</td>
</tr>
</tbody>
</table>

* * * p < 0.0001 vs baseline

* p = 0.007

* p = 0.05

* p = 0.149
Comparison of F/P + E triple therapy and S + E combined therapy in patients with T2D and CVD

Changes in other lipid parameters

** p=0.03, + p=0.01 vs baseline

p=0.066

p=0.063

** LS means % change

F160/P40+E10
S20+E10

HDL-C
ApoA-I
Comparison of F/P + E triple therapy and S + E combined therapy in patients with T2D and CVD

Achievement of LDL-C and non-HDL-C goals

<table>
<thead>
<tr>
<th></th>
<th>Number (%) of patients at goal</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>F160/P40+E10 group</strong></td>
<td></td>
</tr>
<tr>
<td>non-HDL-C&lt;100 mg/dL</td>
<td>56 (42.1%)</td>
</tr>
<tr>
<td>LDL-C&lt;70 mg/dL</td>
<td>50 (37.6%)</td>
</tr>
<tr>
<td>non-HDL-C&lt;100 and LDL-C&lt;70 mg/dL</td>
<td>46 (34.6%)</td>
</tr>
<tr>
<td><strong>S20+E10 group</strong></td>
<td></td>
</tr>
<tr>
<td>non-HDL-C&lt;100 mg/dL</td>
<td>54 (40.6%)</td>
</tr>
<tr>
<td>LDL-C&lt;70 mg/dL</td>
<td>54 (40.6%)</td>
</tr>
<tr>
<td>non-HDL-C&lt;100 and LDL-C&lt;70 mg/dL</td>
<td>48 (36.1%)</td>
</tr>
</tbody>
</table>

Legend:
- Red: non-HDL-C<100 mg/dL
- Yellow: LDL-C<70 mg/dL
- Green: non-HDL-C<100 and LDL-C<70 mg/dL
### Safety results

<table>
<thead>
<tr>
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<th>F160/P40+E10 group (n = 137)</th>
<th>S20+E10 group (n = 135)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>n (%) of patients</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All AEs</td>
<td>20 (14.6%)</td>
<td>19 (14.1%)</td>
</tr>
<tr>
<td>Treatment related AEs</td>
<td>9 (6.6%)</td>
<td>4 (3.0%)</td>
</tr>
<tr>
<td>Serious AEs</td>
<td>3 (2.2%)</td>
<td>1 (0.7%)</td>
</tr>
<tr>
<td>Discontinued due to AE</td>
<td>5 (3.6%)</td>
<td>2 (1.5%)</td>
</tr>
<tr>
<td>Rhabdomyolysis or Myopathy</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>CK &gt; 5 ULN</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>AST or ALT &gt; 3 ULN</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>
Limitations of this study

- short duration
- lack of power to clinical outcomes

however, the ACCORD trial lipid arm has supported the use of fenofibrate-statin combination therapy in type 2 diabetic patients with high TG / low HDL-C.
Conclusions (1)

- A combination therapy of lipid-lowering drugs is frequently required to reach the recommended lipid goals for T2DM patients in secondary prevention.

- Simvastatin/Ezetimibe dual therapy and Fenofibrate/Pravastatin + Ezetimibe triple therapy have the same complementary beneficial effect on non-HDL-C for patients not at goals on Simvastatin monotherapy (effect on LDL-C greater with Simvastatin/Ezetimibe combination therapy).
The triple therapy has induced more beneficial effects on TG, with a trend to a greater increase on HDL-C and ApoA-I.

The same proportions of patients have reached LDL-C and/or non-HDL-C goals with the 2 tested strategies.

Long-term clinical trials are necessary to determine what therapeutic option should be selected for these very high-risk patients.