Synchronized strategies to improve glycemic outcome in type 2 diabetes
Sequential vs early combination treatment

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Need for an early and intensive approach to type 2 diabetes management

• At diagnosis of type 2 diabetes:
  • 50% of patients already have complications\(^1\)
  • up to 50% of β-cell function has already been lost\(^2\)

• Current management:
  • two-thirds of patients do not achieve target HbA\(_{1c}\)\(^3,4\)
  • majority require polypharmacy to meet glycemic goals over time\(^5\)

Maintaining glycemic targets can be difficult to achieve.

A significant number of patients with T2D have poor glycemic control \(^1\)

Glycemic control tends to decline over time with monotherapy \(^2\)

Target HbA\(_{1c}\) 6.5–7%*

*Glycemic targets should be individualised \(^3,4\)

Improving Glycemic Control in T2DM Achieving Glycemic Goals Sooner May Reduce the Risk of Complications \textsuperscript{1,2}

Conservative vs. proactive management: (A) traditional stepwise approach and (B) early combination approach. OAD, oral antidiabetic drug

Up-titrating monotherapy to the maximum recommended dose may not provide benefit.

Early Combination Therapy for T2DM Management

• Ensure Prompter and Better Glycemic Control
• Improving patient’s Adherence to Treatment
• Possibly Reducing Clinical Inertia
• More Opportunity to Address Individual Needs
• Reducing Risk of Diabetes Complications

Guidelines: initial combination therapy recommendations

If A1C values are ≥ 7.5-9 % ¹

If A1C values are ≥1.5-2% above target ³

Initial Combination of Empagliflozin and Metformin
OBJECTIVE:
This study compared the efficacy and safety of initial combinations of empagliflozin + metformin with empagliflozin and metformin monotherapy in patients with type 2 diabetes
Change from Baseline in HbA1c\textsuperscript{1}

![Graph showing changes in HbA1c levels with different treatments.](image)

Change from Baseline in Weight

Conclusions

- Initial combinations of empagliflozin + metformin for 24 weeks significantly reduced HbA1c versus empagliflozin once daily and metformin twice daily, without increased hypoglycemia, reduced weight versus metformin twice daily, and were well tolerated.
Combination of Linagliptin and Metformin
Linagliptin Reduces HbA1c Significantly Regardless of Level of Renal Impairment

<table>
<thead>
<tr>
<th></th>
<th>Normal</th>
<th>Mild RI</th>
<th>Moderate RI</th>
<th>Severe RI</th>
</tr>
</thead>
<tbody>
<tr>
<td>eGFR</td>
<td>≥90</td>
<td>≥69 to &lt;89</td>
<td>≥45 to &lt;59</td>
<td>&lt;30</td>
</tr>
</tbody>
</table>

**5 mg OD**

Pooled analysis of three Phase III trials:

- **At 24 weeks**
  - Normal: -0.63 (p<0.0001)
  - Mild RI: -0.67 (p<0.0001)
  - Moderate RI: -0.53 (p<0.01)

- **At 52 weeks**
  - Severe RI: -0.72 (p<0.0001)

Mean baseline HbA1c (%)

- Normal: 8.1
- Mild RI: 8.0
- Moderate RI: 8.2
- Severe RI: 8.2

1- Diabetes Obes Metab 2014;16(6):560-568. 2-Diabetes Care 2013;36:237-244. 3- Linagliptin drug Information, UpToDate drug Database, Feb 2021
Linagliptin clinical profile

Efficacy
- Meaningful and reliable efficacy across complete range of oral diabetes therapies
- Sustained efficacy in longer term treatment up to 2 years

Safety & Tolerability
- Overall safety profile similar to placebo:
  - No clinically relevant weight gain
  - Very low risk of hypoglycemia
  - Not associated with an increase in CV risk

Convenience
- Once-daily
- With or without food

No dose adjustment in renal or hepatic impairment

Renal excretion = 5%

Primarily excreted via bile & gut

1- Linagliptin Drug Information, UpToDate Drug Database, Accessed Feb 2021
Aims:
To evaluate the efficacy and safety of initial combination therapy with linagliptin plus metformin versus linagliptin or metformin monotherapy in patients with type 2 diabetes.
The primary efficacy endpoint was:
1. The mean change in HbA1c from baseline to week 24

Secondary endpoints assessed at week 24 included:
1. Mean change in FPG from baseline
2. Mean change from baseline in HbA1c and FPG over time, and
3. The proportion of patients requiring rescue therapy after failing to achieve pre-specified glycaemic targets or discontinuing because of lack of efficacy.

➢ Safety and tolerability data were collected at screening and throughout the study
Adjusted mean change in haemoglobin A1c (HbA1c) over time by prior OAD status in randomized patients. Treatment-naïve:
Adjusted mean change in haemoglobin a1c (HbA1c) over time by prior OAD status in randomized patients. Prior OAD treatment:
Mean Change in HbA1c

Patients (n)

- LIN 5 mg qd: 66, 69
- MET 500 mg bid: 68, 73
- MET 1000 mg bid: 74, 64
- LIN 2.5 mg + MET 500 mg bid: 63, 74
- LIN 2.5 mg + MET 1000 mg: 66, 74
- Open-label arm*: 66

Mean ± s.e. change in HbA1c (%)

- HbA1c <8.5%
- 8.5% ≤ HbA1c <11.0%
- HbA1c ≥11%
• Initial combination therapy with linagliptin plus metformin was superior to metformin monotherapy in improving glycaemic control, with a similar safety and tolerability profile, no weight gain and a low risk of hypoglycaemia
Linagliptin + Metformin significantly has superior glycemic control compared to linagliptin and metformin monotherapy, in terms of improving glycosylated hemoglobin, fasting and postprandial glucose levels.

An excellent tolerability profile, without promoting weight gain and hypoglycemic episodes.

Exert synergistic (complementary) pharmacodynamic effects, including an enhanced incretin effect, suppressed hepatic glucose production, and improved peripheral insulin sensitivity.

Address multiple defects of type 2 diabetes pathophysiology (pancreatic islet dysfunction, insulin resistance, increased hepatic glucose output), and most importantly, in the context of a safe, efficacious, flexible, and convenient therapeutic regimen.

Combination of Empagliflozin and Linagliptin
Combination of Empagliflozin and Linagliptin as Second-Line Therapy in Subjects With Type 2 Diabetes Inadequately Controlled on Metformin

DOI: 10.2337/dc14-2364
Objective & End point

Objective:
- To evaluate the efficacy and safety of empagliflozin/linagliptin in subjects with type 2 diabetes.

Primary end point:
- Change from baseline in HbA1c at week 24

Key Secondary end point:
- Change from baseline in FPG at week 24
- Change from baseline in body weight at week 24
- Proportion of subjects with baseline HbA1c ≥7% (≥ 53 mmol/mol) who had HbA1c <7% (< 53 mmol/mol) at week 24.

1. DeFronzo et al. (2015). Diabetes Care; 38:384
Study Design

1. DeFronzo et al. (2015). Diabetes Care; 38:384
Change from Baseline in HbA1c at Week 24

- EMPA 25 mg/LINA 5 mg (n=134): -1.19%
  - (95% CI: -0.58%, -0.75%, p<0.001)
- EMPA 10 mg/LINA 5 mg (n=135): -1.08%
  - (95% CI: -0.50%, -0.67%, p<0.001)
- EMPA 25 mg (n=140): -0.62%
- EMPA 10 mg (n=137): -0.66%
- LINA 5 mg (n=128): -0.70%

Adjusted mean (SE) change from baseline in HbA1c (%)

Mean baseline HbA1c (% [mmol/mol])

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Mean Baseline</th>
</tr>
</thead>
<tbody>
<tr>
<td>EMPA 25 mg</td>
<td>7.90 [63]</td>
</tr>
<tr>
<td>LINA 5 mg</td>
<td>7.95 [63]</td>
</tr>
<tr>
<td>EMPA 10 mg</td>
<td>8.02 [64]</td>
</tr>
<tr>
<td>LINA 5 mg</td>
<td>8.00 [64]</td>
</tr>
<tr>
<td>EMPA 25 mg</td>
<td>8.02 [64]</td>
</tr>
</tbody>
</table>

1. DeFronzo et al. (2015). Diabetes Care;38:384
Patients with HbA1c ≥7% at baseline who had HbA1c <7% at week 24

1. DeFronzo et al. (2015). Diabetes Care ;38:384
Patients with HbA1c ≥7% at baseline who had HbA1c <7% at week 52

DeFronzo et al. (2015). Diabetes Care; 38:384
Change in HbA\textsubscript{1c} at Week 24 in Patients with HbA\textsubscript{1c} $\geq$ 8.5\%\textsuperscript{1}

\begin{table}[h]
\centering
\begin{tabular}{|c|c|c|c|c|}
\hline
 & EMPA 25 mg/ & EMPA 10 mg/ & EMPA 25 mg/ & EMPA 10 mg/ & LINA 5 mg/ \\
& LINA 5 mg & LINA 5 mg & LINA 5 mg & LINA 5 mg & (n=128) \\
& (n=134) & (n=135) & (n=140) & (n=137) & \\
\hline
Adjusted mean (SE) change from baseline in HbA\textsubscript{1c} (%) & -1.84 & -1.61 & -1.22 & -1.29 & -0.99 \\
\hline
\end{tabular}
\end{table}

Mean baseline HbA\textsubscript{1c} (% [mmol/mol])
\begin{tabular}{|c|c|c|c|c|}
\hline
\hline
\end{tabular}

1. DeFronzo et al. (2015). Diabetes Care; 38:384
Combination of Empagliflozin+Linagliptin Demonstrates Early and Durable Achievement of Goal

* ADA recommends an A1C target of <7%. Individual goal of patient should be determined by their physician. Change from baseline vs individual components, p<0.0001.

1. DeFronzo et al. (2015). Diabetes Care;38:384 2. ADA Standards of Medical Care 2021
# Change from Baseline in FPG at Week 24

<table>
<thead>
<tr>
<th>Group</th>
<th>Adjusted Mean (SE) Change from Baseline in FPG (mg/dl)</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>EMPA 25 mg/LINA 5 mg (n=134)</td>
<td>-35.30</td>
<td>(-40.0, -30.6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>EMPA 10 mg/LINA 5 mg (n=135)</td>
<td>-32.20</td>
<td>(-37.0, -27.4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>EMPA 25 mg/LINA 5 mg (n=140)</td>
<td>-18.80</td>
<td>(-23.4, -14.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>EMPA 10 mg/LINA 5 mg (n=137)</td>
<td>-20.80</td>
<td>(-25.6, -16.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LINA 5 mg (n=128)</td>
<td>-13.10</td>
<td>(-18.0, -8.2)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

**Mean baseline FPG [mg/dl]**

<table>
<thead>
<tr>
<th>Group</th>
<th>Mean baseline FPG [mg/dl]</th>
</tr>
</thead>
<tbody>
<tr>
<td>EMPA 25 mg/LINA 5 mg (n=134)</td>
<td>154.6</td>
</tr>
<tr>
<td>EMPA 10 mg/LINA 5 mg (n=135)</td>
<td>156.7</td>
</tr>
<tr>
<td>EMPA 25 mg/LINA 5 mg (n=140)</td>
<td>159.9</td>
</tr>
<tr>
<td>EMPA 10 mg/LINA 5 mg (n=137)</td>
<td>161.6</td>
</tr>
<tr>
<td>LINA 5 mg (n=128)</td>
<td>156.4</td>
</tr>
</tbody>
</table>

1. DeFronzo et al. (2015). Diabetes Care; 38:384
Change from baseline in body weight at Week 24

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Adjusted Mean (SE) Change from Baseline (kg)</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>EMPA 25 mg/LINA 5 mg</td>
<td>-3.0 (0.2 kg)</td>
<td>-0.7 to 1.0</td>
<td>0.660</td>
</tr>
<tr>
<td>EMPA 10 mg/LINA 5 mg</td>
<td>-2.6</td>
<td>-3.2 to -1.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>EMPA 25 mg/LINA 5 mg</td>
<td>-2.5</td>
<td>-3.2 to -1.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>EMPA 10 mg/LINA 5 mg</td>
<td>-2.3 (0.1 kg)</td>
<td>-2.9 to -1.4</td>
<td>0.876</td>
</tr>
<tr>
<td>EMPA 25 mg/LINA 5 mg</td>
<td>-1.9 (0.0 kg)</td>
<td>-2.8 to -1.1</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Mean baseline body weight (kg)

|                      | 78.6 | 79.0 | 79.9 | 80.2 | 77.7 |

1. DeFronzo et al. (2015). Diabetes Care; 38:384
Change from baseline in BP (mmHg) at Week 52

1. DeFronzo et al. (2015). Diabetes Care; 38:384
Conclusion

• Combinations of empagliflozin/linagliptin as second-line therapy for 52 weeks significantly reduced HbA1c compared with the individual components and were well tolerated.
Thanks for your attention