Multinational Patterns of Second-line Antihyperglycaemic Drug Initiation Across Cardiovascular Risk Groups: Federated Pharmacoepidemiological Evaluation in LEGEND-T2DM

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(for the LEGEND-T2DM investigators)
Type 2 Diabetes Mellitus (T2DM)

1st line agent: Metformin

Blood sugar still elevated

2nd line agents:
- DPP4 inhibitors (DPP4i)
- Sulfonylureas (SU)
- GLP-1 Receptor Agonists (GLP-1 RA)
- SGLT2 inhibitors (SGLT2i)

Cardiovascular outcome RCTs:
- Neutral effect
- Not evaluated
- Reduced cardiovascular risk
- MI, Death
- Reduced cardiovascular risk
- MI, Death, Heart Failure

Elevated blood sugar
Multinational Serial Cross-sectional Study
2011-2021

- IBM MarketScan® Commercial Claim and Encounters Data (CCAE)
- IBM Health MarketScan® Multistate Medicaid Database (Medicaid)
- IBM Health MarketScan® Medicare Supplemental and Coordination of Benefits Database (Medicare)
- Optum Clinformatics Extended Data Mart - Date of Death (Optum CEDM)
- Optum® de-identified Electronic Health Record Dataset (Optum EHR)
- US Open Claims

US National Databases

- US Health System Databases
  - Columbia University Irving Medical Center
  - Johns Hopkins Medicine
  - Stanford Medicine
  - Department of Veterans Affairs Healthcare System

- UK-IQVIA Medical Research Data (UK)
- HIC, University of Dundee (Scotland)
- Information System for Research in Primary Care (Spain)
- France Longitudinal Patient Database (France)
- Germany Disease Analyser (Germany)
- Hong Kong Hospital Authority (Hong Kong)
- Australia Longitudinal Patient Database (Australia)
Inclusion Criteria

- Age ≥ 18 years
- Presence of T2DM
- Prior metformin use
- No prior second-line anti-hyperglycemic agent use

4.6 million patients across 17 data sources

Outcomes

- Calendar-year trends for proportionate initiation 2nd line agents
- Comparison of annualized change in initiation of GLP-1 RA and SGLT2i in patients with and without CVD

Exposures

- Presence of established cardiovascular disease
- Calendar Years
Proportionate Incident Use of Second-line Anti-hyperglycemic Agents in 2021

• Across US databases, initiation of cardioprotective agents ranged from 35% at the VA health system to 68% at Columbia University.

• Across non-US databases, initiation of cardioprotective agents ranged from 15% in France to 55% in Scotland in 2021
GLP-1 RA Uptake in Patients with Established CVD

- Initiation of GLP-1 RAs increased to 20-25% across most US populations

- Initiation was <5% in the VA

- Initiation was low across non-US databases, reaching a maximum of 14% in France in 2021
SGLT2i Uptake in Patients with Established CVD

- Initiation of SGLT2is increased to ~35% across US populations

- In the non-US databases, the initiation of SGLT2is was higher in most databases, reaching up to 54% in Scotland in 2021

- In France, the initiation was lower, reaching only to 6% in 2021
Slope Interaction for Annualized Change in Cardioprotective Agent Initiation in Patients with and without CVD (2016-2021)

### Representative Examples for GLP-1 RA Initiation

<table>
<thead>
<tr>
<th>Data Source</th>
<th>With-CVD Slope</th>
<th>Without-CVD Slope</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CCAE</td>
<td>0.019 (0.011 to 0.026)</td>
<td>0.068 (0.037 to 0.099)</td>
<td>0.003</td>
</tr>
<tr>
<td>Columbia</td>
<td>0.017 (0.011 to 0.023)</td>
<td>0.031 (0.016 to 0.047)</td>
<td>0.040</td>
</tr>
<tr>
<td>Medicare</td>
<td>0.051 (0.009 to 0.092)</td>
<td>0.051 (0 to 0.102)</td>
<td>0.986</td>
</tr>
<tr>
<td>France</td>
<td>0.003 (0.001 to 0.006)</td>
<td>0.014 (0.004 to 0.023)</td>
<td>0.024</td>
</tr>
<tr>
<td>Spain</td>
<td>0.003 (-0.001 to 0.006)</td>
<td>0.010 (0.001 to 0.019)</td>
<td>0.062</td>
</tr>
</tbody>
</table>

### Representative Examples for SGLT2i Initiation

<table>
<thead>
<tr>
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<th>With-CVD Slope</th>
<th>Without-CVD Slope</th>
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</tr>
</thead>
<tbody>
<tr>
<td>CCAE</td>
<td>0.014 (0.006 to 0.023)</td>
<td>0.035 (0.011 to 0.059)</td>
<td>0.053</td>
</tr>
<tr>
<td>Columbia</td>
<td>0.037 (0.022 to 0.052)</td>
<td>0.024 (0.013 to 0.034)</td>
<td>0.074</td>
</tr>
<tr>
<td>Medicare</td>
<td>0.092 (0.011 to 0.172)</td>
<td>0.056 (0.008 to 0.104)</td>
<td>0.325</td>
</tr>
<tr>
<td>France</td>
<td>0.001 (-0.001 to 0.003)</td>
<td>0.005 (-0.001 to 0.011)</td>
<td>0.132</td>
</tr>
<tr>
<td>Spain</td>
<td>0.033 (0.016 to 0.049)</td>
<td>0.065 (0.017 to 0.112)</td>
<td>0.115</td>
</tr>
</tbody>
</table>
Conclusion

• LEGEND-T2DM is the largest multinational pharmacoepidemiology study of anti-hyperglycemic therapy.

• Despite increased uptake, there is vast variation in use of cardioprotective therapies uses across populations with CVD.

• The uptake of these has been lower in the US, relative to other countries, particularly in patients with established CVD.

• Lack of selective use in CVD patients despite specific benefit in the population.
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Thank you for your attention!

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