Effect of Dapagliflozin on Atrial Fibrillation/Flutter in Patients with Type 2 Diabetes mellitus: Insights from the DECLARE-TIMI 58 trial

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On behalf of the DECLARE-TIMI 58 Investigators

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Conflicts of Interests

• Grants to Brigham and Women’s Hospital from AstraZeneca and Bristol-Myers Squibb

• Research grant from the Deutsche Forschungsgemeinschaft

• Lecture fees from AstraZeneca
Background

• AF/AFL are associated with both diabetes and its related comorbidities including hypertension, obesity, and HF.

• The pathophysiology that may causally link diabetes with AF/AFL include structural, electromechanical, mechanical myocardial remodeling, and an imbalance in the sympathetic-parasympathetic tone.

• SGLT2i have been shown to lower blood pressure, reduce weight, have salutary effects on left ventricular remodeling and reduce hospitalization for HF and cardiovascular death in patients with T2DM.
Background

- Dapagliflozin is a selective SGLT2 inhibitor that blocks glucose and Na\(^+\) reabsorption in the kidneys and thereby lowers HbA1c in patients with T2DM.
- In DECLARE-TIMI 58, dapagliflozin has been shown to significantly reduce the risk of CV death/HHF in T2DM, driven by a reduction in HHF, and was non-inferior with regard to MACE.

Zelniker TA, Braunwald E; JACC 2018
Wiviott SD et al.; NEJM 2018
Objective

➢ To investigate the effect of the SGLT2i dapagliflozin on the incidence and total burden of AF/AFL events in post-hoc analyses from the DECLARE-TIMI 58 trial

Methods

➢ AF/AFL events (new or worsening) were identified by search of MedDRA Preferred Terms: “atrial fibrillation” and “atrial flutter”
➢ AE & SAE included
➢ Cox regression models used for time to first event analysis
➢ Negative binomial regression models for analysis of total (i.e., first and recurrent) number of AF/AFL events
DECLARE-TIMI 58

17,160 with Type 2 DM
Established CV Disease (6974) or
Multiple Risk Factors (10186)

DAPAGLIFLOZIN
10 mg DAILY

RANDOMIZE 1:1 DOUBLE BLIND
All other DM Rx per treating MD

PLACEBO

Follow-up visits
In Person Q 6 mo/ telephone Q 3 mo

Primary EPs
Safety: MACE (CVD/MI/Ischemic Stroke)
Dual Efficacy: CVD/HHF, MACE

DURATION
EVENT DRIVEN
≥1390 MACE

Median follow up – 4.2 years

Wiviott SD, et al., AHJ 2018; Wiviott SD et al., NEJM 2019
AF/AFL

HR $0.81$, $95\%$ CI $0.68$ to $0.95$; $P=0.009$
### AF/AFL Outcomes by Major Subgroups

<table>
<thead>
<tr>
<th>Subgroups</th>
<th>Daplan (%)</th>
<th>Placebo (%)</th>
<th>HR (95%CI)</th>
<th>P interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>AF/AFL</td>
<td>264 (3.1)</td>
<td>325 (3.8)</td>
<td>0.81 (0.68, 0.95)</td>
<td></td>
</tr>
<tr>
<td>History of AF/AFL</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Hx of AF/AFL</td>
<td>68 (12.4)</td>
<td>86 (15.2)</td>
<td>0.79 (0.58, 1.09)</td>
<td>0.89</td>
</tr>
<tr>
<td>No Hx of AF/AFL</td>
<td>196 (2.4)</td>
<td>239 (3.0)</td>
<td>0.81 (0.67, 0.98)</td>
<td></td>
</tr>
<tr>
<td>ASCVD vs. MRF</td>
<td></td>
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</tr>
<tr>
<td>ASCVD</td>
<td>141 (4.1)</td>
<td>170 (4.9)</td>
<td>0.83 (0.66, 1.04)</td>
<td>0.72</td>
</tr>
<tr>
<td>MRF</td>
<td>123 (2.4)</td>
<td>155 (3.1)</td>
<td>0.78 (0.62, 0.99)</td>
<td></td>
</tr>
<tr>
<td>History of HF</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HF</td>
<td>55 (6.5)</td>
<td>70 (8.0)</td>
<td>0.78 (0.55, 1.11)</td>
<td>0.88</td>
</tr>
<tr>
<td>No HF</td>
<td>209 (2.7)</td>
<td>255 (3.3)</td>
<td>0.81 (0.68, 0.97)</td>
<td></td>
</tr>
</tbody>
</table>
AF/AFL Outcomes by Subgroups

Subgroups | P interaction | Subgroups | P interaction
--- | --- | --- | ---
Age | 0.66 | HbA1c | 0.54
  - Age < 70 | | HbA1c < 8%
  - Age ≥ 70 | | HbA1c ≥ 8%
Sex | 1.00 | BMI | 0.75
  - Male | | BMI ≥ 30 kg/m²
  - Female | | BMI < 30 kg/m²
SBP | 0.20 | eGFR | 0.88
  - SBP < 135 | | eGFR ≥ 90 ml/min/1.73m²
  - SBP ≥ 135 | | eGFR 60-90 ml/min/1.73m²
  - SBP ≥ 135 | | eGFR < 60 ml/min/1.73m²

Favors Dapagliflozin ← → Favors Placebo
Sensitivity Analyses

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Dapagliflozin</th>
<th>Placebo</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AF/AFL</td>
<td>264 (3.1)</td>
<td>325 (3.8)</td>
<td>0.81 (0.68, 0.95)</td>
</tr>
<tr>
<td>Only SAE's</td>
<td>132 (1.5)</td>
<td>166 (1.9)</td>
<td>0.79 (0.63, 0.99)</td>
</tr>
<tr>
<td>Hospitalization for AF/AFL</td>
<td>141 (0.9)</td>
<td>194 (1.3)</td>
<td>0.73 (0.59, 0.91)</td>
</tr>
<tr>
<td>No HHF within 14 days of AF/AFL</td>
<td>238 (2.8)</td>
<td>288 (3.4)</td>
<td>0.82 (0.69, 0.97)</td>
</tr>
<tr>
<td>AF/AFL among those who never experienced HHF</td>
<td>215 (2.6)</td>
<td>246 (3.0)</td>
<td>0.86 (0.72, 1.03)</td>
</tr>
</tbody>
</table>

Favors Dapagliflozin ← → Favors Placebo
Number of Events Per Patient

Total: 769 events in 589 pts

Counts

Number of Events

- 1: 589 (77%)
- 2: 124 (16%)
- 3: 36
- 4: 12
- 5: 6
- 6: 1
- 7: 1
Total # of Events

Total Events
IRR 0.77, 95% CI 0.64 to 0.92, P=0.005

Additional Events
IRR 0.67 (0.44-1.01)

1st Event
HR 0.81 (0.68-0.95)

Placebo
325
107

Dapagliflozin
264
73
Limitations

1. Post-hoc analyses

2. AF/AFL events were not prespecified outcomes and determined by local investigators

3. ECGs were not systematically collected
Conclusion

Dapagliflozin appears to reduce both the first as well as the total number of AF/AFL events in high-risk patients with T2DM. This effect was consistent regardless of the patients’ prior history of AF/AFL, ASCVD, or HF.

Slides available at www.timi.org
Possible Mechanisms How SGLT2i May Reduce AF/AFL

**Indirect Cardiac Effects**
- Decongestive Effect
- BP Lowering
- Weight Loss
- HbA1c↓

**Direct Cardiac Effects**
- Cardiac Remodeling
- Reduction of the sympathetic overdrive
- Oxidative Stress↓
- Inflammation↓
- Epicardial fat ↓

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