Dapagliflozin and Outcomes in Patients with Peripheral Artery Disease: Insights from DECLARE-TIMI 58

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for the DECLARE – TIMI 58 Investigators
American College of Cardiology
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Diabetes and peripheral artery disease (PAD) are frequently comorbid conditions

SGLT2 inhibitors:

• Reduce heart failure and renal complications in patients with diabetes

• Have been associated with amputation risk with 1 available agent but not the other 2; however, trials thus far have not been designed to evaluate amputation or limb ischemic events

• To date, a detailed examination of all limb ischemic events in high-risk subpopulations has not been performed
**Trial Design**

17,160 with Type 2 DM and Established CV Disease (6974 incl **1025 w/PAD**) or MRF (10186)

*PAD Inclusion Criteria:*
Current claudication + ABI < 0.90 or history of peripheral revascularization or amputation for ischemia

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**DAPAGLIFLOZIN 10 mg DAILY**

**PLACEBO**

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

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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

Median follow up 4.2 years

Wiviott SD, Raz I…Sabatine MA, AHJ 2018
Primary Endpoints

**CVD/HHF**
- 4.9% vs 5.8%
- HR 0.83 (0.73-0.95)
- P(Superiority) 0.005

**MACE**
- 8.8% vs 9.4%
- HR 0.93 (0.84-1.03)
- P(Noninferiority) <0.001
- P(Superiority) 0.17

Wiviott SD, Raz I...Sabatine MA, NEJM 2019; 380:347-357
Methods

Cardiac Events:
• MACE: composite of CV death, MI or ischemic stroke
• HHF: Hospitalization for heart failure

Renal Events:
• Renal primary: ≥ 40% decrease in eGFR to < 60 ml/minute/1.73 m² of BSA, new ESRD or death from renal or CV causes

Limb outcomes:
• Limb ischemic AEs with subset of:
  • Acute limb ischemia (ALI)
  • Chronic critical limb ischemia (CLI)
• Amputations, primary etiology, contributing where multifactorial
• Non-coronary revascularizations (urgent and elective)
• Major adverse limb events (MALE) – defined as composite of ALI, CLI, amputation for ischemia or urgent revascularization
Methods

1. **To compare the risk** of cardiac, renal and limb events in **patients with vs. w/o known PAD (in placebo arm)**

2. To evaluate the **efficacy of dapagliflozin** vs. placebo for cardiac and renal events **in patients with and w/o PAD**

3. **To evaluate the safety of dapagliflozin** vs. placebo for limb ischemic events and amputations in:
   - All patients
   - High risk subgroups including known PAD
## Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>PAD N=1,025</th>
<th>No PAD N=16,135</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age, median (IQR)</strong></td>
<td>62 (57, 68)</td>
<td>64 (60, 68)</td>
</tr>
<tr>
<td><strong>Female sex, %</strong></td>
<td>32</td>
<td>38</td>
</tr>
<tr>
<td><strong>Body Mass Index, median (IQR)</strong></td>
<td>31 (28, 35)</td>
<td>31 (28, 36)</td>
</tr>
<tr>
<td><strong>Caucasian, %</strong></td>
<td>84</td>
<td>79</td>
</tr>
<tr>
<td><strong>History Hypertension, %</strong></td>
<td>85</td>
<td>90</td>
</tr>
<tr>
<td><strong>Current Smoker, %</strong></td>
<td>23</td>
<td>14</td>
</tr>
<tr>
<td><strong>Duration of Diabetes (yrs), median (IQR)</strong></td>
<td>12 (7, 18)</td>
<td>10 (6, 16)</td>
</tr>
<tr>
<td><strong>Hemoglobin A1C, % (IQR)</strong></td>
<td>8 (8, 9)</td>
<td>8 (7, 9)</td>
</tr>
<tr>
<td><strong>Insulin, %</strong></td>
<td>52</td>
<td>40</td>
</tr>
<tr>
<td><strong>Estimated GFR (CKD-EPI) &lt; 60, %</strong></td>
<td>11</td>
<td>7</td>
</tr>
<tr>
<td><strong>History of Ischemic Heart Disease, %</strong></td>
<td>46</td>
<td>32</td>
</tr>
<tr>
<td><strong>History of Myocardial Infarction, %</strong></td>
<td>27</td>
<td>20</td>
</tr>
<tr>
<td><strong>History of Cerebrovascular Disease, %</strong></td>
<td>15</td>
<td>7</td>
</tr>
<tr>
<td><strong>History of CHF, %</strong></td>
<td>14</td>
<td>10</td>
</tr>
</tbody>
</table>

All p-values < 0.001 except BMI (p=0.0256)
PAD Characteristics

Fontaine Classification at Randomization, %

<table>
<thead>
<tr>
<th>Stage</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage I: Asymptomatic</td>
<td>25</td>
</tr>
<tr>
<td>Stage IIa: Mild claudication</td>
<td>49</td>
</tr>
<tr>
<td>Stage IIb: Moderate-severe claudication</td>
<td>21</td>
</tr>
<tr>
<td>Stage III or IV: Ischemia rest pain, ulceration or gangrene</td>
<td>6</td>
</tr>
</tbody>
</table>

Ankle Brachial Index Category, %

<table>
<thead>
<tr>
<th>Category</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 0.5</td>
<td>5</td>
</tr>
<tr>
<td>0.5-&lt;0.9</td>
<td>93</td>
</tr>
<tr>
<td>0.9-&lt;1.4</td>
<td>2</td>
</tr>
</tbody>
</table>

Hierarchically Defined:

- Amputation = any history of amputation regardless of current symptoms
- Revascularization = any history of revascularization but no history of amputation
- Claudication = claudication with no history of amputation or revascularization
Epidemiology of cardiac, renal and limb outcomes in patients with vs. w/o PAD randomized to placebo
Cardiovascular & Renal Risk by PAD in Placebo Patients

Adjust HR 1.23  
(0.97 – 1.56)

Adj HR 1.60  
(1.21 – 2.12)

Adj HR 1.51  
(1.13 – 2.03)

MACE  
9.0%  
15.9%  

CVD/HF  
5.4%  
12.1%  

Renal Primary  
5.3%  
10.9%  

Adjusted for age, sex, race, BMI, hypertension, dyslipidemia, smoking, duration of DM, A1c, eGFR, hx CAD, and hx cerebrovascular disease
Limb Outcomes by PAD Status in Placebo Patients

<table>
<thead>
<tr>
<th>Event</th>
<th>Adj HR</th>
<th>P-value</th>
<th>Any Limb Adverse Event</th>
<th>PAD</th>
<th>no PAD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute Limb Ischemia</td>
<td>19.69</td>
<td>&lt;0.01</td>
<td>2.1%</td>
<td>3.4%</td>
<td>0.1%</td>
</tr>
<tr>
<td>Critical Limb Ischemia</td>
<td>12.99</td>
<td>&lt;0.01</td>
<td>5.0%</td>
<td>5.0%</td>
<td>0.3%</td>
</tr>
<tr>
<td>Amputation</td>
<td>4.47</td>
<td>&lt;0.01</td>
<td>1.1%</td>
<td>1.1%</td>
<td>0.3%</td>
</tr>
<tr>
<td>Limb Infection</td>
<td>2.13</td>
<td>&lt;0.01</td>
<td>3.3%</td>
<td>3.3%</td>
<td>1.1%</td>
</tr>
</tbody>
</table>

Adjusted for age, sex, race, BMI, hypertension, dyslipidemia, smoking, duration of DM, A1c, eGFR, hx CAD, and hx cerebrovascular disease
Limb Outcomes by PAD Status in Placebo Patients

**Distribution of Amputation by Primary Etiology**

- **PAD**
  - **15, 35%**
  - **6, 14%**
  - **14, 10%**

- **No PAD**
  - **123, 85%**

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- **Any Limb Adverse Event**
  - **Adj HR 8.37, P<0.01**

- **Acute Limb Ischemia**
  - **Adj HR 19.69, P<0.01**
  - **2.1%, 3.4%**

- **Critical Limb Ischemia**
  - **Adj HR 12.99, P<0.01**
  - **0.1%, 0.3%**

- **Amputation**
  - **Adj HR 4.47, P<0.01**
  - **5.6%, 1.1%**

- **Limb Infection**
  - **Adj HR 2.13, P<0.01**
  - **8.2%, 3.3%**

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*Investigator Reported

**Adjusted for age, sex, race, BMI, hypertension, dyslipidemia, smoking, duration of DM, A1c, eGFR, hx CAD, and hx cerebrovascular disease**
Efficacy of Dapagliflozin in Patients with and without PAD
Consistent Benefit of Dapagliflozin in Patients with and without PAD

**CV Death, MI or Ischemic Stroke**

- **No PAD – N=16135**
  - CV Death or Hosp. for Heart Failure
    - 0.83
  - Renal Primary
    - 0.76

- **PAD – N=1025**
  - CV Death or Hosp. for Heart Failure
    - 0.93
  - Renal Primary
    - 0.76

**n/N (%)**

- **Pbo**
  - CV Death or Hosp. for Heart Failure
    - 9.0%
  - Renal Primary
    - 15.9%

- **Dapa**
  - CV Death or Hosp. for Heart Failure
    - 8.3%
  - Renal Primary
    - 16.9%

- **ARR**
  - CV Death or Hosp. for Heart Failure
    - 1.3%
  - Renal Primary
    - 1.4%

**P-interaction**

- CV Death, MI or Ischemic Stroke
  - 0.42

- CV Death or Hosp. for Heart Failure
  - 0.79

- Renal Primary
  - 0.84

**Favors**

- **Dapagliflozin**
  - No PAD – N=16135
  - PAD – N=1025
  - Overall

- **Placebo**
  - No PAD – N=16135
  - PAD – N=1025
  - Overall
Safety of Dapagliflozin vs. Placebo for Limb Outcomes in All Patients
Dapagliflozin and Limb Outcomes
All Patients

Any limb ischemic AE
MALE
Acute Limb Ischemia
Critical Limb Ischemia
Urgent Revascularization
Elective Revascularization

MALE Defined as ALI, CLI, amputation for ischemia or Urgent Revascularization for Ischemia
Dapagliflozin and Amputations
All Patients

All p-values > 0.05

<table>
<thead>
<tr>
<th>Condition</th>
<th>DAPA</th>
<th>Placebo</th>
<th>HR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amputation</td>
<td>1.43%</td>
<td>1.32%</td>
<td>1.09</td>
<td>0.84 – 1.40</td>
</tr>
<tr>
<td>Amputation for ALI</td>
<td>0.12%</td>
<td>0.12%</td>
<td>0.99</td>
<td>0.41 – 2.39</td>
</tr>
<tr>
<td>Amputation for CLI</td>
<td>0.30%</td>
<td>0.26%</td>
<td>1.18</td>
<td>0.67 – 2.08</td>
</tr>
<tr>
<td>Amputation for Infection</td>
<td>1.12%</td>
<td>0.98%</td>
<td>1.14</td>
<td>0.85 – 1.53</td>
</tr>
</tbody>
</table>

n/N: 8574/8569
Safety of Dapagliflozin vs. Placebo for Amputation and Other Limb Events in High Risk Subgroups
Dapagliflozin and Amputation in Key Subgroups

- Age < 65 years
  - Diabetes Duration ≤ 5 yrs: 1.19
  - Diabetes Duration >5 - 10 yrs: 1.24
  - Diabetes Duration >10 - ≤ 15 yrs: 1.23
   - Diabetes Duration >15 - ≤ 20 yrs: 0.80

- Age ≥ 65 years
  - Diabetes Duration > 20 yrs: 1.24

- Diabetes Duration > 20 yrs
  - Diabetes Duration >5 - 10 yrs: 0.92
  - Diabetes Duration >10 - ≤ 15 yrs: 1.24
  - Diabetes Duration >15 - ≤ 20 yrs: 0.80

- eGFR < 60
- eGFR 60-90
- eGFR ≥ 90

- HgbA1C < 7%
- HgbA1C 7% - < 8%
- HgbA1C 8% - < 9%
- HgbA1C ≥ 9%

- PAD
- No PAD

Overall

Favors
Dapagliflozin
Pbo
P-interaction
Favors
Placebo

<table>
<thead>
<tr>
<th>Condition</th>
<th>Dapagliflozin</th>
<th>Placebo</th>
<th>P-interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &lt; 65 years</td>
<td>75/4626</td>
<td>62/4619</td>
<td>0.3895</td>
</tr>
<tr>
<td>Age ≥ 65 years</td>
<td>48/3948</td>
<td>51/3950</td>
<td>0.5922</td>
</tr>
<tr>
<td>Diabetes Duration ≤ 5 yrs</td>
<td>20/1883</td>
<td>14/1948</td>
<td></td>
</tr>
<tr>
<td>Diabetes Duration &gt;5 - 10 yrs</td>
<td>20/2373</td>
<td>22/2354</td>
<td></td>
</tr>
<tr>
<td>Diabetes Duration &gt;10 - ≤ 15 yrs</td>
<td>27/2014</td>
<td>21/1936</td>
<td></td>
</tr>
<tr>
<td>Diabetes Duration &gt;15 - ≤ 20 yrs</td>
<td>33/1246</td>
<td>25/1186</td>
<td></td>
</tr>
<tr>
<td>Diabetes Duration &gt; 20 yrs</td>
<td>23/1058</td>
<td>31/1144</td>
<td>0.6920</td>
</tr>
<tr>
<td>eGFR &lt; 60</td>
<td>11/604</td>
<td>15/658</td>
<td></td>
</tr>
<tr>
<td>eGFR 60-90</td>
<td>55/3836</td>
<td>46/3890</td>
<td></td>
</tr>
<tr>
<td>eGFR ≥ 90</td>
<td>57/4133</td>
<td>52/4021</td>
<td>0.5495</td>
</tr>
<tr>
<td>HgbA1C &lt; 7%</td>
<td>4/771</td>
<td>4/772</td>
<td></td>
</tr>
<tr>
<td>HgbA1C 7% - &lt; 8%</td>
<td>35/3314</td>
<td>29/3306</td>
<td></td>
</tr>
<tr>
<td>HgbA1C 8% - &lt; 9%</td>
<td>30/2190</td>
<td>24/2324</td>
<td></td>
</tr>
<tr>
<td>HgbA1C ≥ 9%</td>
<td>54/2297</td>
<td>56/2163</td>
<td>0.0926</td>
</tr>
<tr>
<td>No PAD</td>
<td>79/8053</td>
<td>85/8067</td>
<td></td>
</tr>
<tr>
<td>PAD</td>
<td>44/521</td>
<td>28/502</td>
<td></td>
</tr>
</tbody>
</table>

BRIGHAM AND WOMEN'S HOSPITAL
HARVARD MEDICAL SCHOOL
TEACHING HOSPITAL
Dapagliflozin and Limb Outcomes
PAD Patients

N=1025    All p-values > 0.05

<table>
<thead>
<tr>
<th>Event</th>
<th>DAPA</th>
<th>Placebo</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any limb ischemic AE</td>
<td>19.4%</td>
<td>20.3%</td>
<td>0.93 (0.71 – 1.23)</td>
</tr>
<tr>
<td>MALE</td>
<td>9.6%</td>
<td>10.2%</td>
<td>0.92 (0.62 – 1.35)</td>
</tr>
<tr>
<td>Acute Limb Ischemia</td>
<td>2.9%</td>
<td>3.4%</td>
<td>0.84 (0.42 – 1.69)</td>
</tr>
<tr>
<td>Critical Limb Ischemia</td>
<td>5.8%</td>
<td>5.0%</td>
<td>1.12 (0.66 – 1.91)</td>
</tr>
<tr>
<td>Urgent Revascularization</td>
<td>4.0%</td>
<td>5.0%</td>
<td>0.79 (0.44 – 1.42)</td>
</tr>
<tr>
<td>Elective Revascularization</td>
<td>12.1%</td>
<td>14.1%</td>
<td>0.84 (0.60 – 1.19)</td>
</tr>
<tr>
<td>Amputation</td>
<td>8.4%</td>
<td>5.6%</td>
<td>1.51 (0.94 – 2.42)</td>
</tr>
</tbody>
</table>

MALE Defined as ALI, CLI, amputation for ischemia or Urgent Revascularization for Ischemia
1. Patients with PAD were at heightened risk of cardiac, renal and limb complications vs. those without

2. The efficacy of dapagliflozin for CVD/HF and renal outcomes was consistent regardless of PAD status but with greater absolute benefits in PAD

3. There was no significant excess risk of amputations or limb ischemic events with dapagliflozin in the overall population

4. There was no consistent pattern of risk or benefit related to limb events in patients with PAD or other high-risk subgroups