Dapagliflozin in Patients Hospitalized with COVID-19

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on behalf of DARE-19 Investigators
Disclosures

- Research Grants:
  - AstraZeneca, Boehringer Ingelheim

- Clinical Trial Leadership/Consultant:
  - AstraZeneca, Applied Therapeutics, Amgen, Bayer, Boehringer-Ingelheim, Eli Lilly, Janssen, Merck (Diabetes), Novo Nordisk, Sanofi, Vifor Pharma

- DARE-19 Trial was funded by AstraZeneca
Trial Leadership and Data Analysis

- Investigator-initiated Trial
  - Sponsored by Saint Luke’s Mid America Heart Institute
  - Performed in collaboration with AstraZeneca and George Clinical

- Executive Committee
  - Mikhail Kosiborod (Chair), Otavio Berwanger, Gary Koch, Felipe Martinez, Omar Mukhtar, Subodh Verma, Russell Esterline (AZ), Jan Oscarsson (AZ), Anna Maria Langkilde (AZ)

- Data Analysis
  - Fengming Tang, Kensey Gosh, Philip G. Jones (Saint Luke’s)
  - Samvel Gasparyan, Joan Buenconsejo, Olof Bengtsson (AZ)

- Independent Data and Safety Monitoring Board
  - James DeLemos (Chair), Robert Guigliano, Carolyn Lam, Ralph D’Agostino Jr
Background and Rationale

• Patients hospitalized with Covid-19 and cardiometabolic risk factors are at high risk for multi-organ failure and death
• There is a dearth of efficacious therapies that reduce the risk of major clinical events, and large unmet clinical need for additional treatment options
• SGLT2i provide organ protection in patients with chronic cardiometabolic conditions (T2D, HF, CKD) and favorably affect a number of pathophysiologic pathways disrupted during acute illness, such as Covid-19

CKD, chronic kidney disease; HF, heart failure; SGLT2i, sodium-glucose co-transporter-2 inhibitors; T2D, type 2 diabetes.
We hypothesized that dapagliflozin may reduce the risk of multi-organ failure and death, and improve recovery in patients that are hospitalized with Covid-19 and have cardiometabolic risk factors.
Key Inclusion Criteria
- Hospitalization with confirmed/suspected SARS-CoV-2 for \( \leq 4 \) days
- \( O_2 \) saturation of \( \geq 94\% \) on \( \leq 5 \) L/min
- CXR findings c/w Covid-19
- \( \geq 1 \) risk factor (HTN, Type 2 Diabetes, ASCVD, HF, CKD)

Key Exclusion Criteria
- Critical illness on presentation
- eGFR <25 mL/min/1.73m\(^2\)
- Type 1 Diabetes
- Prior diabetic ketoacidosis

ASCVD, atherosclerotic cardiovascular disease; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; HF, heart failure; HTN, hypertension.
Adult patients hospitalized with confirmed or strongly suspected COVID-19

1:1 randomization to dapagliflozin 10 mg/day or matching placebo, given in addition to standard of care treatment

Dapagliflozin 10 mg/day

Matching placebo daily

All patients have daily assessments until hospital discharge, death or end of 30-day treatment period*

Extended follow-up period after last dose. Patients contacted at Day 60 and Day 90

Screening

30-Day Treatment Period

60-Day Observational Follow-up

*Discharged patients asked to attend telephone visits at Day 15 and Day 30.
Dual Primary Endpoints

- **Prevention** - time to first major clinical event
  - Respiratory (invasive or non-invasive mechanical ventilation)
  - Cardiovascular (pressor, inotropes, new or worsened HF, sustained VT/VF, resuscitated cardiac arrest)
  - Kidney (doubling of creatinine or initiation of dialysis)
  - Death from any cause

- **Recovery** - hierarchical composite ranking each patient using the following order
  - Death
  - Organ failure
  - Clinical status if still hospitalized at Day 30
  - Time to hospital discharge before Day 30

HF, heart failure; VT/VF, ventricular tachycardia/ventricular fibrillation.
DARE-19 Trial
1250 Patients – 7 Countries – 95 Sites

North America:
- Canada: 4
- US: 287
- Mexico: 118

Western Europe:
- UK: 2

South America:
- Brazil: 762
- Argentina: 27

Asia:
- India: 50
Patient Disposition

1273 Patients Screened

- 23 patients did not qualify

1250 Patients Randomized

Dapagliflozin (n=625)

- 69 patients discontinued dapagliflozin

617 (99%) Completed Study

Placebo (n=625)

- 66 patients discontinued placebo

620 (99%) Completed Study
# Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Dapagliflozin (N=625)</th>
<th>Placebo (N=625)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age, years</td>
<td>61</td>
<td>62</td>
</tr>
<tr>
<td>Female, %</td>
<td>42</td>
<td>44</td>
</tr>
<tr>
<td>Inclusion risk factors, %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Type 2 diabetes</td>
<td>50</td>
<td>52</td>
</tr>
<tr>
<td>Heart failure</td>
<td>7</td>
<td>7</td>
</tr>
<tr>
<td>Hypertension</td>
<td>84</td>
<td>85</td>
</tr>
<tr>
<td>ASCVD</td>
<td>15</td>
<td>17</td>
</tr>
<tr>
<td>CKD</td>
<td>6</td>
<td>7</td>
</tr>
<tr>
<td>Mean heart rate, beats/min</td>
<td>79</td>
<td>80</td>
</tr>
<tr>
<td>Mean systolic blood pressure, mm/Hg</td>
<td>127</td>
<td>127</td>
</tr>
<tr>
<td>Mean oxygen saturation, %</td>
<td>96</td>
<td>95</td>
</tr>
<tr>
<td>Positive SARS-CoV-2 test, %</td>
<td>93</td>
<td>92</td>
</tr>
<tr>
<td>Medication at screening, %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACEi/ARB</td>
<td>36</td>
<td>35</td>
</tr>
<tr>
<td>Statin</td>
<td>20</td>
<td>23</td>
</tr>
<tr>
<td>Insulin</td>
<td>36</td>
<td>35</td>
</tr>
<tr>
<td>Remdesivir</td>
<td>18</td>
<td>18</td>
</tr>
<tr>
<td>Systemic Steroids</td>
<td>29</td>
<td>31</td>
</tr>
</tbody>
</table>

ACEi/ARB, angiotensin-converting enzyme inhibitor/angiotensin receptor blocker; ASCVD, atherosclerotic cardiovascular disease; CKD, chronic kidney disease.
Primary Outcome of Prevention:
Organ Failure or Death from Any Cause
Time to Organ Failure or Death

Hazard ratio, 0.80 (95% CI, 0.58–1.10)  
$p=0.168$

Placebo: 86 events (13.8%)
Dapagliflozin: 70 events (11.2%)

<table>
<thead>
<tr>
<th>No. at Risk</th>
<th>Days since Randomization</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dapagliflozin</td>
<td>625</td>
</tr>
<tr>
<td>Placebo</td>
<td>625</td>
</tr>
</tbody>
</table>
**Primary Outcome of Prevention - Components**

<table>
<thead>
<tr>
<th>Outcome, n</th>
<th>Dapagliflozin (N=625)</th>
<th>Placebo (N=625)</th>
<th>Hazard ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary composite outcome</td>
<td>70</td>
<td>86</td>
<td>0.80 (0.58, 1.10)</td>
</tr>
<tr>
<td>New or worsening organ dysfunction</td>
<td>64</td>
<td>80</td>
<td>0.80 (0.57, 1.11)</td>
</tr>
<tr>
<td>Respiratory decompensation*</td>
<td>58</td>
<td>70</td>
<td>0.85 (0.60, 1.20)</td>
</tr>
<tr>
<td>Cardiac decompensation†</td>
<td>47</td>
<td>58</td>
<td>0.81 (0.55, 1.19)</td>
</tr>
<tr>
<td>Kidney decompensation‡</td>
<td>24</td>
<td>35</td>
<td>0.65 (0.38, 1.10)</td>
</tr>
<tr>
<td>Death from any cause</td>
<td>41</td>
<td>54</td>
<td>0.77 (0.52, 1.16)</td>
</tr>
</tbody>
</table>

*Respiratory decompensation requiring initiation of mechanical ventilation, and/or initiation of extracorporeal membrane oxygenation. †Includes new or worsening congestive heart failure, requirement for vasopressor therapy and/or inotropic or mechanical circulatory support, or ventricular tachycardia or fibrillation. ‡Doubling of s-Creatinine or initiation of renal-replacement therapy.
Primary Outcome: Recovery
Primary Outcome of Recovery (Hierarchical Composite Endpoint)

Win ratio, 1.09 (95% CI 0.97, 1.22); p=0.14

- **Improvement**
  - Discharge (0-3 days): 25.3 Dapagliflozin, 31.7 Placebo
  - Discharge (3-6 days): 17.4 Dapagliflozin, 16.6 Placebo
  - Discharge (6-9 days): 6.4 Dapagliflozin, 5.8 Placebo
  - Discharge (9-12 days): 3.7 Dapagliflozin, 3.0 Placebo
  - Discharge (12-15 days): 2.6 Dapagliflozin, 2.4 Placebo
  - Discharge (15-30 days): 0.5 Dapagliflozin, 0 Placebo

- **Stable**
  - Hospitalized without oxygen support: 0.2 Dapagliflozin, 0.5 Placebo

- **Deterioration**
  - Hospitalized with high flow oxygen support: 0.2 Dapagliflozin, 0 Placebo
  - One organ dysfunction: 2.6 Dapagliflozin, 3.0 Placebo
  - Multiple organ dysfunction: 2.1 Dapagliflozin, 2.2 Placebo
  - Death: 6.6 Dapagliflozin, 8.6 Placebo

DAPagliflozin in Rspiratory failure in patients with COVID-19
Key Secondary Outcomes
Composite Kidney Endpoint

Hazard ratio, 0.74 (95% CI, 0.50–1.07)

Placebo: 65 events (10.4%)
Dapagliflozin: 48 events (7.7%)

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<tr>
<th>No. at Risk</th>
<th>Days since Randomization</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dapagliflozin</td>
<td>625 618 612 603 594 585 576 570 568 565 564</td>
</tr>
<tr>
<td>Placebo</td>
<td>625 619 608 599 585 577 567 563 560 558 555</td>
</tr>
</tbody>
</table>
All-cause Mortality

Hazard ratio, 0.77 (95% CI, 0.52–1.16)

Cumulative Incidence (%)

Days since Randomization

No. at Risk
Dapagliflozin: 625 624 622 617 612 606 595 586 586 584 581
Placebo: 625 623 620 617 604 595 587 580 578 575 572

Placebo: 54 events (8.6%)
Dapagliflozin: 41 events (6.6%)

DARE-19
DApagliflozin in REspiratory failure in patients with COVID-19
<table>
<thead>
<tr>
<th>Events, n</th>
<th>Dapagliflozin (N=613)</th>
<th>Placebo (N=616)</th>
<th>Risk difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any severe AE*</td>
<td>65</td>
<td>82</td>
<td>-2.71 (-6.37, 0.93)</td>
</tr>
<tr>
<td>AE with the outcome of death</td>
<td>32</td>
<td>48</td>
<td>-2.57 (-5.41, 0.19)</td>
</tr>
<tr>
<td>Discontinuation due to AE</td>
<td>44</td>
<td>55</td>
<td>-1.75 (-4.85, 1.31)</td>
</tr>
<tr>
<td>Acute kidney injury</td>
<td>21</td>
<td>34</td>
<td>-2.09 (-4.52, 0.23)</td>
</tr>
<tr>
<td>Diabetic ketoacidosis</td>
<td>2</td>
<td>0</td>
<td>0.33 (-0.30, 1.18)</td>
</tr>
</tbody>
</table>

*Including death
AE, adverse event.
Summary and Conclusions

- In DARE-19 Trial which evaluated patients hospitalized with Covid-19 and cardiometabolic risk factors, treatment with dapagliflozin did not achieve statistical significance for the dual primary endpoints.

- Numerically fewer patients treated with dapagliflozin experienced organ failure and death - consistent across components (respiratory, cardiovascular, kidney complications and death).

- Dapagliflozin was well tolerated, with numerically fewer serious adverse events than placebo.
Practice Implications

- DARE-19 - first trial that evaluated SGLT2i in patients with acute illness, patient population with the highest risk ever tested with this class
- Given the lack of data, there were concerns that using SGLT2i in Covid-19 could increase the risk of AKI and ketoacidosis
- This fueled recommendations from some groups to stop SGLT2i in patients with Covid-19, even if they had conditions in which this class has been proven to produce substantial benefits (T2D, HF)
- In DARE-19, rates of serious adverse events (including AKI) were numerically lower with dapagliflozin than placebo, and only two non-severe events of DKA were reported
- Our results do not support discontinuation of SGLT2i in a setting of Covid-19, as long as patients are monitored

AKI, acute kidney injury; CKD, chronic kidney disease; DKA, diabetic ketoacidosis; HF, heart failure; SGLT2i, sodium-glucose co-transporter-2 inhibitors; T2D, type 2 diabetes.
Research Implications

- DARE-19 raises a hypothesis that SGLT2i may afford organ protection in other types of acute illness

- This should be evaluated in future trials
We thank all patients, investigators and their teams, and collaborators for their participation in the trial and extraordinary efforts under the most difficult of circumstances due to the ongoing pandemic.