ACP Northern California Chapter Annual Regional Scientific Meeting

Update in General Medicine

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Background

- Type 2 DM is the leading cause of kidney failure in the U.S.

- Standard approach to prevent DM nephropathy is with blockade of the renin-angiotensin-aldosterone system (i.e. with ACE-I or ARB)
CREDENCE Trial

“Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation” trial

Canagliflozin and Renal Outcomes in Type 2 Diabetes and Nephropathy

Background

SGLT2 Inhibitors

Currently 4 SGLT2 inhibitors are approved in the US:
- Canagliflozin (Invokana)
- Dapagliflozin (Farxiga)
- Empagliflozin (Jardiance)
- Ertugliflozin (Steglatro)
Background

• In CV trials of SGLT2 inhibitors, results have suggested that these drugs may improve renal outcomes in patients with type 2 DM
Clinical Question

- **Population** – patients with type 2 diabetes AND albuminuric CKD AND treated with renin-angiotensin system blockade

- **Intervention** – canagliflozin 100mg daily

- **Comparison** – placebo

- **Outcomes** –
  - ESRD
  - Doubling of the serum creatinine level
  - Death from renal or CV causes
Trial Participants

• Inclusion Criteria
  – Men and women at least 30 years of age
  – Diagnosis of type 2 diabetes with an HbA1c of 6.5% to 12.0%
  – Diagnosis of CKD (eGFR of 30 to <90 ml) and albuminuric (urinary albumin-to-creatinine ratio >300 to 5000)
  – Treatment with a stable dose of ACE-I OR ARB for at least 4 weeks

• Exclusion Criteria
  – Suspected non-diabetic kidney disease or type 1 diabetes
  – Treatment with immunosuppression for kidney disease
  – History of dialysis or kidney transplantation
  – Dual-agent treatment with ACE-I and ARB, a direct renin inhibitor, or a mineralocorticoid-receptor antagonist
## Results

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Canagliflozin (N=2202)</th>
<th>Placebo (N=2199)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age – yr</td>
<td>62.9 ± 9.2</td>
<td>63.2 ± 9.2</td>
</tr>
<tr>
<td>Female sex – no. (%)</td>
<td>762 (34.6)</td>
<td>732 (33.3)</td>
</tr>
<tr>
<td>Glycated hemoglobin - %</td>
<td>8.3 ± 1.3</td>
<td>8.3 ± 1.3</td>
</tr>
<tr>
<td>Estimated GFR – ml/min/1.73 m2</td>
<td>56.3 ± 18.2</td>
<td>56.0 ± 18.3</td>
</tr>
<tr>
<td>Median urinary albumin to creatinine ratio</td>
<td>923 (459-1794)</td>
<td>931 (473-1868)</td>
</tr>
</tbody>
</table>
Results

A Primary Composite Outcome

Hazard ratio, 0.70 (95% CI, 0.59–0.82)
P = 0.00001

- Placebo: 340
- Canagliflozin: 245

Patients with an Event (%) vs. Months since Randomization
Results

C  End-Stage Kidney Disease

Hazard ratio, 0.68 (95% CI, 0.54–0.86)
P=0.002

Placebo

Canagliflozin

Patients with an Event (%) vs. Months since Randomization
## Results

<table>
<thead>
<tr>
<th>Secondary Outcomes</th>
<th>Canagliflozin</th>
<th>Placebo</th>
<th>HR</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hospitalization for heart failure</td>
<td>89/2202</td>
<td>141/2199</td>
<td>0.61</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(0.47-0.80)</td>
<td></td>
</tr>
<tr>
<td>CV death, MI, stroke</td>
<td>217/2202</td>
<td>269/2199</td>
<td>0.80</td>
<td>0.01</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(0.67-0.95)</td>
<td></td>
</tr>
</tbody>
</table>
Results

• Rates of lower limb amputations and fractures were similar in the two groups
• Rates of DKA were low, but higher in the canagliflozin group than in the placebo group

<table>
<thead>
<tr>
<th></th>
<th>n/N</th>
<th>Event rate per 1000 patient-years</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Canagliflozin</td>
<td>Placebo</td>
</tr>
<tr>
<td>Diabetic Ketoacidosis</td>
<td>11/2200</td>
<td>1/2197</td>
</tr>
<tr>
<td></td>
<td>2.2</td>
<td>0.2</td>
</tr>
<tr>
<td></td>
<td>10.80</td>
<td>1.39-83.65</td>
</tr>
</tbody>
</table>
Study Limitations

• Stopped early
• Excluded patients with advanced CKD (eGFR < 30)
• Excluded patients with nonalbuminuric or microalbuminuric kidney disease
Practical Implications

Patient with type 2 DM and A1c not at goal

Metformin and comprehensive lifestyle change?

CKD (but eGFR > 45) and urine albumin/Cr > 300?

ACE-I or ARB?

Consider starting canagliflozin 100mg once daily
FDA Approves Invokana (canagliflozin) to Treat Diabetic Kidney Disease (DKD) and Reduce the Risk of Hospitalization for Heart Failure in Patients with Type 2 Diabetes and DKD

RARITAN, N.J., Sept. 30, 2019 /PRNewswire/ -- The Janssen Pharmaceutical Companies of Johnson & Johnson announced today that the U.S. Food and Drug Administration (FDA) approved a new indication for Invokana (canagliflozin) to reduce the risk of end-stage kidney disease (ESKD), worsening of kidney function, cardiovascular (CV) death, and hospitalization for heart failure in adults with type 2 diabetes.
Practical Implications

• Side effects:
  – Hypotension
  – Increased urination
  – Increased rate of genitourinary infections
Practical Implications

Canagliflozin (Invokana) is an expensive drug used to treat type 2 diabetes. It helps to control blood sugar. This drug is more popular than comparable drugs. There are currently no generic alternatives to Invokana. It is covered by most Medicare and insurance plans, but some pharmacy coupons or cash prices may be lower. The lowest GoodRx price for the most common version of Invokana is around $493.20, 16% off the average retail price of $606.96. Compare SGLT2 inhibitors.

Insurance Coverage: Many major insurance plans no longer cover Invokana as of 2019. Learn More

Prices and coupons for 30 tablets of Invokana 100mg

- Costco: $497.76 with free coupon
- Ralphs: $512.69 with free coupon
- Safeway: $519.38 with free coupon
- Vons Pharmacy: $519.38 with free coupon
Thank you!
References