Background

- SGLT2 inhibitors reduce blood glucose by blocking reabsorption of glucose in the proximal tubule, excreting excess glucose in the urine.
- Approved for treatment of Type 2 Diabetes.
- Medications in SGLT2 inhibitor class include: Invokana (canagliflozin), Farxiga (dapagliflozin) & Jardiance (empagliflozin).
- Recommended by the American Diabetes Association, American Association of Clinical Endocrinologist, and American College of Endocrinology as adjunct therapy after Metformin.

Objective

To analyze the difference between clinical trial results of sodium-glucose cotransporter-2 (SGLT2) inhibitors and available, published real world evidence with regard to clinical indicators such as hemoglobin A1c, weight, cardiovascular effects, and significant adverse events.

Method

- Literature analysis to identify randomized clinical trials of SGLT2 inhibitors and published real world evidence, case reports, and evidence-based guidelines.
- Literature published between March 2013 and December 2018.
- Compare clinical differences between individuals taking the medication short-term during clinical trials and long-term as part of their regular diabetic management plan.

Results

- 15 articles were reviewed to compare clinical trial results to clinical practice.
- Outcomes reviewed from 2013 through 2018.

<table>
<thead>
<tr>
<th>Clinical Trial</th>
<th>Clinical Practice</th>
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<tbody>
<tr>
<td>HbA1c Reduction</td>
<td>0.4-1.1%</td>
</tr>
<tr>
<td>Weight Loss</td>
<td>1.6-3 kg</td>
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</table>

- Clinical Practice
  - Cardiovascular Effects
  - Real world data for all three SGLT2 inhibitors found lower hospitalization rates for heart failure (HR = 0.61; 95% CI, 0.51-0.73) and death (HR = 0.49; 95% CI, 0.41-0.57).
  - Genital Infections
  - FDA warning issued for Fournier’s gangrene, which has occurred in 12 people.

Results (continued)

- Lower extremity amputation
- Large observational studies have been conducted in an attempt to refute or confirm the link between SGLT2 inhibitors and amputation event. The results are conflicting; some showed a higher (non-statistically significant) rate of amputations and some did not.
- The OBSERVE-4D study analyzed patient-level data from 4 U.S. administrative claims databases, including data from more than 700,000 patients, and found no increased risk of lower extremity amputations with canagliflozin when compared to dapagliflozin and empagliflozin.

Limitations

- Limited Real World Evidence currently available on primary outcome and side effects.
- Difficult to know if adverse events are due to SGLT2 inhibitors or the disease progression of diabetes.
- Many outcomes may be under-reported.

Conclusions

SGLT2 inhibitors are useful in reducing blood glucose as adjunct therapy to Metformin. They result in a reduction of the HbA1c as well as weight. More research with real world evidence needs to be conducted to determine the prevalence and significance of harmful adverse events.

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