The Ominous Octet
Type 2 Diabetes
To treat is to understand:
The potential of SGLT2 inhibitors

Lori Berard RN CDE
www.pinkpearls.ca
Learning Objectives

- Are there really 8 defects in diabetes?
  - Revisit the pathophysiology of T2DM
- Treat to failure?
  - Discuss achieving target glucose control
  - (WHERE DO SGLT2is FIT?)
- Designer therapy?
  - Explore the benefits of non-insulin diabetes therapy
Diabetes in Canada

<table>
<thead>
<tr>
<th>KEY STATISTICS</th>
<th>2016</th>
<th>2026</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes and prediabetes prevalent cases (rate)</td>
<td>11 million (29%)</td>
<td>13.9 million (33%)</td>
</tr>
<tr>
<td>Diabetes prevalent cases (rate)</td>
<td>3.5 million (9.2%)</td>
<td>4.9 million (11.6%)</td>
</tr>
<tr>
<td>Cost of diabetes to health-care system</td>
<td>$3.4 billion</td>
<td>$5 billion</td>
</tr>
<tr>
<td>2006 to 2016: estimated increase in diabetes prevalence</td>
<td></td>
<td>72%</td>
</tr>
<tr>
<td>2016 to 2026: estimated increase in diabetes prevalence</td>
<td></td>
<td>41%</td>
</tr>
</tbody>
</table>

Source: Canadian Diabetes Association Diabetes Charter Backgrounder October 2016
• Diabetes is a leading cause of several chronic diseases:
  • 30% of stroke victims,
  • 40% of people suffering a heart attack,
  • 50% of those on kidney dialysis, and
  • 70% of those with non-traumatic lower-limb amputations live with the disease.

• Compared to the general population, people with diabetes are
  • over three times more likely to be hospitalized with cardiovascular disease;
  • 12 times more likely to be hospitalized with end-stage renal disease and;
  • over 20 times more likely to be hospitalized for a non-traumatic lower limb amputation

• It is also one of the leading causes of blindness.

Source: Canadian Diabetes Association Annual Report 2015
Impact

30% of people with diabetes have clinically relevant depressive symptoms; individuals with depression have an approximately 60% increased risk of developing type 2 diabetes.

Diabetes reduces lifespan by 5–15 years.

25% of Canadians with diabetes indicated their treatment adherence was affected by cost.

Foot ulceration affects an estimated 15%–25% of people with diabetes in their lifetime.

33% of Canadians with type 2 diabetes do not feel comfortable disclosing their diabetes to others.

Source: Canadian Diabetes Association Diabetes Charter Backgrounder October 2016
Drugs with Different Mechanisms of Action are Required to Address the Numerous T2DM Pathophysiological Defects

The ominous octet


HGP, hepatic glucose production
Drugs with Different Mechanisms of Action are Required to Address the Numerous T2DM Pathophysiological Defects

The ominous octet

Don’t Lose Sight of What Matters…

- Insulin Resistance
- Insulin Insufficiency
- Hyperglycemia (Leaky Liver)
The Toolbox... while expanding is still not getting the job done
REMEMBER
How are we Doing?

DM-SCAN was a 2012 survey of 5,103 Canadians living with type 2 diabetes for a mean of 9.2 years.

50% of Canadian patients living with type 2 diabetes not at target AIC <7% were maintained only on monotherapy.

1 in 4 patients with at least one microvascular or macrovascular complication.
Joey wants to know...

WHAT IS THE PROBLEM?

It’s not usually hard to find solutions once you understand the problem. by Carl Christman
Lifestyle intervention is the cornerstone of Management for type 2 diabetes

ALL PEOPLE WITH DIABETES WHO ARE ABLE SHOULD BE TAUGHT HOW TO SELF-MANAGE THEIR DIABETES*

Clinical Practice Guidelines...
Friend or Foe
Physicians Adopt a Sequential Approach

- Average slope = 0.75% per 5 years
- Potential treatment changes on average every 5 years
- Goal: HbA1c ≤7%

~20 years


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*a*According to the ADA/EASD
ADA, American Diabetes Association; EASD, European Association for the Study of Diabetes
Delay in treatment intensification increases the risks of cardiovascular events in patients with type 2 diabetes

Sanjoy K Paul1,*, Keren Naftail Klein1, Brian L Thorsted2, Michael L Woinder2 and Kamlesh Khunti2*

Abstract

Background: The aim of the study was to evaluate the association of HbA1c levels with cardiovascular disease, and 7.1% experienced HbA1c consistently above 7.7% (53/58 patients) at the time of diagnosis.

Methods: In the cohort of 105,477 patients with type 2 diabetes and cardiovascular disease, 7.1% experienced HbA1c consistently above 7.7% (53/58 patients) at the time of diagnosis.

Results: In the cohort of 105,477 patients with type 2 diabetes and cardiovascular disease, 7.1% experienced HbA1c consistently above 7.7% (53/58 patients) at the time of diagnosis.

Conclusions: Among patients with newly diagnosed type 2 diabetes, 26% were not treated with insulin within 2 years of diagnosis.

Keywords: Type 2 diabetes, Delay in treatment intensification

Clinical inertia with regard to intensifying therapy in people with type 2 diabetes treated with basal insulin

K. Khunti1,*, A. Nikolajsen2, B. L. Thorsted2, M. Andersen3, M. J. Davies1 and S. K. Paul1,4

1Diabetes Research Centre, University of Liverpool, Liverpool, UK
2Novo Nordisk A/S, Bagsvaerd, Denmark
3Danish Diabetes Association, Copenhagen, Denmark
4Clinical Research Unit for Diabetes, University of Exeter Medical School, Exeter, UK

Aims: To investigate whether clinical inertia, the failure to intensify treatment regimens when required, exists in people with type 2 diabetes treated with basal insulin.

Methods: This was a retrospective cohort study involving patients with type 2 diabetes treated with basal insulin.

Results: A total of 11,608 patients were included in the analysis. Among all patients, 30.5% had their treatment intensified during the study period.

Conclusions: Clinical inertia was observed in patients with type 2 diabetes treated with basal insulin. Strategies should be developed to increase the number of patients undergoing therapy intensification and to reduce the delay in intensifying therapy for suitable patients on basal insulin. Initiatives to support patients continuing on insulin are also required.

Keywords: Basal, glargine, type 2 diabetes
Proportion of Patients with Drug Regimen Intensification in Response to Poor Glycemic Control: Specialist Vs Primary Care

**Graph Description:**
- **Any Drug Intensification:**
  - Specialist Care (591 patients): 45.1%, $P=0.009$
  - Primary Care (1911 patients): 37.4%
- **Adding new OAH Drug:**
  - Specialist Care (591 patients): 21.7%, $P=0.7$
  - Primary Care (1911 patients): 20.7%
- **Increasing Dose of OAH:**
  - Specialist Care (591 patients): 21.7%, $P=0.2$
  - Primary Care (1911 patients): 18.6%
- **Adding Insulin:**
  - Specialist Care (591 patients): 8.6%, $P<0.0001$
  - Primary Care (1911 patients): 1.7%

**Legends:**
- O AHA: Oral Antihyperglycemic Agent

Shah BR et al. Diabetes CARE 28:600-606, 2005
Start metformin immediately
Consider initial combination with another antihyperglycemic agent

A1C <8.5%
A1C ≥8.5%
Symptomatic hyperglycemia with metabolic decompensation

Start lifestyle intervention (nutrition therapy and physical activity) +/- Metformin
If not at glycemic target (2-3 mos)
Start / Increase metformin
If not at glycemic targets

Add another agent best suited to the individual by prioritizing patient characteristics:

<table>
<thead>
<tr>
<th>PATIENT CHARACTERISTIC</th>
<th>CHOICE OF AGENT</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PRIORITY: Clinical Cardiovascular Disease</strong></td>
<td>Anti-hyperglycemic agent with demonstrated CV Clinical Cardiovascular Disease outcome benefit (empagliflozin, liraglutide)</td>
</tr>
<tr>
<td>Degree of hyperglycemia</td>
<td>Consider relative A1C lowering</td>
</tr>
<tr>
<td>Risk of hypoglycemia</td>
<td>Rare hypoglycemia</td>
</tr>
<tr>
<td>Overweight or obesity</td>
<td>Weight loss or weight neutral</td>
</tr>
<tr>
<td>Cardiovascular disease or multiple risk factors</td>
<td>Effect on cardiovascular outcome</td>
</tr>
<tr>
<td>Comorbidities (renal, CHF, hepatic)</td>
<td>See therapeutic considerations, consider eGFR</td>
</tr>
<tr>
<td>Preferences &amp; access to treatment</td>
<td>See cost column; consider access</td>
</tr>
</tbody>
</table>

See next page…

2016
What Comes After Metformin? Depends…

<table>
<thead>
<tr>
<th>Patient characteristics</th>
<th>Agent characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Degree of hyperglycemia</td>
<td>BG lowering efficacy &amp; durability</td>
</tr>
<tr>
<td>Risk of hypoglycemia</td>
<td>Risk of inducing hypoglycemia</td>
</tr>
<tr>
<td>Weight</td>
<td>Effect on weight</td>
</tr>
<tr>
<td>Comorbidities (renal, cardiac, hepatic)</td>
<td>Contraindications &amp; side effects</td>
</tr>
<tr>
<td>Access to treatment</td>
<td>Cost and coverage</td>
</tr>
<tr>
<td>Patient preferences</td>
<td>Other</td>
</tr>
</tbody>
</table>
Joey wants to know... WHY AND WHEN WOULD YOU CHOSE...
Targeting Hyperglycemia: Insulin-Dependent vs Insulin-Independent Approaches

**Insulin-Dependent Mechanisms**

**Insulin action**
- TZDs
- Metformin

**Insulin release**
- Sulfonylureas
- GLP-1R agonists
- DPP-4 inhibitors
- Meglitinides

**Insulin replacement**
- Insulin

**Insulin-Independent Mechanism**

- Insulin-independent
- SGLT2

Adipose Tissues
Muscles
Liver
Pancreas

renal
Mechanism of action: SGLT2 inhibitors

Filtration of glucose

Glomerulus

Proximal tubule

S1

SGLT1

Distal tubule

Loop of Henle

Collecting tubule

Glucose reabsorption

Inhibition

Reduction in A1C and weight

Glycosuria

No glycosuria

70 -119g/day = 280-476calories/day

SGLT= Sodium/Glucose co-Transporter


Product monograph, INVOKANA® (canagliflozin), Janssen Inc., 2014

Nair S & Wilding J. J Clin Endocrinol Metab. 2010;95:34-42.
Comparison of SU, SGLT2i's and DPP4i's

<table>
<thead>
<tr>
<th></th>
<th>Sulfonylureas</th>
<th>DPP4 inhibitors</th>
<th>SGLT2 inhibitors</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>A1C Reduction</strong></td>
<td></td>
<td></td>
<td>to</td>
</tr>
<tr>
<td><strong>BP Reduction</strong></td>
<td>NO</td>
<td>NO</td>
<td></td>
</tr>
<tr>
<td><strong>Weight Loss</strong></td>
<td></td>
<td>Neutral to</td>
<td></td>
</tr>
<tr>
<td><strong>Hypo Risk</strong></td>
<td>YES</td>
<td>Rare</td>
<td>Rare</td>
</tr>
</tbody>
</table>

Adapted from the CDA - CPG

The “Composite Endpoint” of Diabetes

AIC
Hypoglycemia
Weight

But there are so many more things....
The risks associated with hypoglycemia can be significant...
What does 476 kcal look like?
To burn 476 Kcal’s a 200 lb person would need to...

- **3 Beers**
- **3 Colas**
- **9 Cookies**
- **1.6 Cheeseburgers**
- **43 Sugar Packets (2.8g ea)**

- **RUN (8km/hr)** for 36 minutes
- **WALK (3.2km/hr)** for 1.9 hours
- **SWIM laps** for 54 minutes
## Proportion of Diabetic Complications Attributable to Hypertension

<table>
<thead>
<tr>
<th>Complication</th>
<th>Proportion attributable to hypertension</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stroke</td>
<td>75%</td>
</tr>
<tr>
<td>End stage renal disease</td>
<td>50%</td>
</tr>
<tr>
<td>Coronary Artery Disease</td>
<td>35%</td>
</tr>
<tr>
<td>Eye disease</td>
<td>35%</td>
</tr>
<tr>
<td>Leg amputation</td>
<td>35%</td>
</tr>
</tbody>
</table>
Benefits of BP Lowering in Diabetes

- Meta-analysis of 27 randomized trials showed intense BP reduction (i.e., by 6/4.6 mmHg) resulted in:
  - 36% reduction in stroke
  - 27% reduction in total mortality
  - 25% reduction in major cardiovascular events
### Not indicated for type 1 diabetes

<table>
<thead>
<tr>
<th>SGLT2 inhibitor</th>
<th>Monotherapy</th>
<th>Dual Combination</th>
<th>Triple Combination</th>
<th>Add-On to INSULIN</th>
<th>Add-On to Sitagliptin</th>
<th>Combo with METFORMIN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Canagliflozin</td>
<td>😊</td>
<td>😊</td>
<td>😊</td>
<td>😊</td>
<td>😊</td>
<td>😊</td>
</tr>
<tr>
<td>Dapagliflozin</td>
<td>😊</td>
<td>😊</td>
<td>😊</td>
<td>😊</td>
<td>😊</td>
<td>😊</td>
</tr>
<tr>
<td>Empagliflozin</td>
<td>😊</td>
<td>😊</td>
<td>😊</td>
<td>😊</td>
<td>😊</td>
<td>😊</td>
</tr>
</tbody>
</table>

*Not to be used with insulin mix*

Clinical considerations before starting SGLT2 inhibitors

- **eGFR**: eGFR must be ≥ 60 mL/min/1.73m² to initiate
- **A1c**: If A1c close to normal: dose adjustments for SU or insulin may be required
- **BP**: If optimal BP with antihypertensives: Reduction or withdrawal of other antihypertensive agents may be required
- **Other**: History of yeast infections should be explored

What to do during times of illness (SADMAN)
### SGLT2 Inhibitors:
Dose guide based on eGFR

<table>
<thead>
<tr>
<th>CKD Stage eGFR mL/min</th>
<th>≥ 60</th>
<th>≥ 45 to &lt; 60</th>
<th>&lt; 45</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Canagliflozin</strong></td>
<td>100 mg</td>
<td>100 mg*</td>
<td>Contraindicated</td>
</tr>
<tr>
<td></td>
<td>300 mg</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Empagliflozin</strong></td>
<td>10 mg</td>
<td>10 mg</td>
<td>Contraindicated</td>
</tr>
<tr>
<td></td>
<td>25 mg</td>
<td>25 mg</td>
<td></td>
</tr>
<tr>
<td><strong>Dapagliflozin</strong></td>
<td>5 mg</td>
<td>Contraindicated</td>
<td></td>
</tr>
<tr>
<td></td>
<td>10 mg</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- eGFR must be ≥ 60 mL/min for initiation of SGLT2i therapy.
- *In patients tolerating canagliflozin whose eGFR persistently falls below 60 mL/min, the dose of canagliflozin should be adjusted to or maintained at 100 mg once daily.

---

Product Monograph, JARDIANCE (empagliflozin), Boehringer Ingelheim Ltd., 2016.
Product Monograph, FORXIGA (dapagliflozin), Astra Zeneca, 2016.
## SGLT2 Inhibitor Class

### Summary of Benefits and Risk Considerations

<table>
<thead>
<tr>
<th>Benefits</th>
<th>Risk Considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reduced A1c</td>
<td>Increased yeast infections</td>
</tr>
<tr>
<td>Insulin-independent mode of action</td>
<td>Reduced intravascular volume (in susceptible patients)</td>
</tr>
<tr>
<td>Low risk hypoglycemia</td>
<td>Increased LDL cholesterol</td>
</tr>
<tr>
<td>Reduced blood pressure</td>
<td>Not indicated with eGFR &lt; 45 mL/min</td>
</tr>
<tr>
<td>Reduced weight</td>
<td>SADMANS - euglycemic DKA (in susceptible patients)</td>
</tr>
<tr>
<td>Reduced triglycerides</td>
<td></td>
</tr>
<tr>
<td>Oral medication, once daily</td>
<td></td>
</tr>
</tbody>
</table>

Effects of SGLT2 Inhibitors on Infections

2. DAPA: Available at: www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/EndocrinologicandMetabolicDrugsAdvisoryCommittee/ucm252891.htm

*These are not head to head trials

**URINARY TRACT INFECTIONS**

<table>
<thead>
<tr>
<th></th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td>Canagliflozin 300 mg/d</td>
<td>[Graph]</td>
<td>[Graph]</td>
</tr>
<tr>
<td>Dapagliflozin 10 mg/d</td>
<td>[Graph]</td>
<td>[Graph]</td>
</tr>
<tr>
<td>Empagliflozin 25 mg/d</td>
<td>[Graph]</td>
<td>[Graph]</td>
</tr>
<tr>
<td>Placebo</td>
<td>[Graph]</td>
<td>[Graph]</td>
</tr>
</tbody>
</table>

**GENITAL MYCOTIC INFECTIONS**

<table>
<thead>
<tr>
<th></th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td>Canagliflozin 300 mg/d</td>
<td>[Graph]</td>
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<td>Dapagliflozin 10 mg/d</td>
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<td>[Graph]</td>
</tr>
<tr>
<td>Placebo</td>
<td>[Graph]</td>
<td>[Graph]</td>
</tr>
</tbody>
</table>
Time to first female genital mycotic infection

The highest rate of occurrence was observed during the first 4 months of treatment, followed by an attenuation. Less than 1% of patients discontinued for this reason.
Effects of SGLT-2 inhibitors on A1C levels in CKD

- In moderate renal failure, the A1c reduction is halved

<table>
<thead>
<tr>
<th>Drug</th>
<th>eGFR 30 to &lt;50</th>
<th>eGFR 30 to 59</th>
<th>eGFR 30 to &lt;60</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline mean A1C (%)</td>
<td>8.0</td>
<td>8.4</td>
<td>8.0</td>
</tr>
<tr>
<td>Baseline mean eGFR (mL/min/1.73m²)</td>
<td>39.4</td>
<td>44.6</td>
<td>≈ 43</td>
</tr>
</tbody>
</table>

![Graph showing effects of SGLT-2 inhibitors on A1C levels in CKD](image_url)

- **Canagliflozin**
  - eGFR 30 to <50 (N=269)
  - Baseline mean A1C: 8.0%
  - Baseline mean eGFR: 39.4 mL/min/1.73m²
  - Change from Baseline: -0.03 (±0.44)

- **Dapagliflozin**
  - eGFR 30 to <50 (N=252)
  - Baseline mean A1C: 8.4%
  - Baseline mean eGFR: 44.6 mL/min/1.73m²
  - Change from Baseline: -0.32 (±0.44)

- **Empagliflozin**
  - eGFR 30 to <60 (N=374)
  - Baseline mean A1C: 8.0%
  - Baseline mean eGFR: ≈ 43 mL/min/1.73m²
  - Change from Baseline: -0.05 (±0.37)

* p <0.001; †p <0.05.

eGFR Mean Change from Baseline Over Time

Active (Glimepiride)-controlled Add-on to Metformin Study (DIA3009) and Active (Sitagliptin)-controlled Add-on to Metformin

**DIA3009**
- Glimepiride (BL: 89.5)
- CANA 100 mg (BL: 89.7)
- CANA 300 mg (BL: 91.4)

**DIA3015**
- SITA 100 mg (BL: 87.76)
- CANA 300 mg (BL: 87.17)
Incident or worsening nephropathy – EMPA REG

Kaplan-Meier estimate in patients treated with ≥1 dose of study drug.
Hazard ratios are based on Cox regression analyses.
HR, hazard ratio; CI, confidence interval. Pre-specified analyses.
Doubling of serum creatinine*, initiation of renal replacement therapy, or death due to renal disease – EMPA REG

Kaplan-Meier estimate in patients treated with ≥1 dose of study drug. Hazard ratios are based on Cox regression analyses.

*Accompanied by eGFR (MDRD) ≤45 ml/min/1.73m².

HR, hazard ratio; CI, confidence interval. Post-hoc analyses.
Possible Mechanism of Renal Protection Testing in CANVAS R CREDENCE DELIGHT OTHERS...

**Possible Mechanism of Renal Protection Testing in CANVAS R CREDENCE DELIGHT OTHERS...**

**A.**
- **Pharmacological Actions:**
  - SGLT2 inhibition
  - Afferent constriction

- **Hemodynamic effects & clinical implications:**
  - Decreased intraglomerular pressure due to increased afferent resistance in T1D-H patients
  - Decreased hyperfiltration

**B.**
- RAAS blockade
- Efferent dilation

- **Hemodynamic effects & clinical implications:**
  - Decreased intraglomerular pressure due to decreased afferent resistance
  - Decreased hyperfiltration
  - Proven renal protection in clinical trials

**C.**
- SGLT2 inhibition + RAAS blockade
- Afferent constriction + Efferent dilation

- **Hemodynamic effects & clinical implications:**
  - Normalization of intraglomerular pressure due to increased afferent + decreased efferent resistance?
  - Additive intraglomerular pressure reduction?
  - Potential for long-term renal protection?
  - Role in other conditions with intraglomerular hypertension (obesity, diabetes, hypertension, etc.)

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Health Canada Update: Invokana & Forxiga
Evaluation of a Potential Risk of Acute Kidney Injury

October 16, 2015

• HC initiated safety review of two SGLT2i (Invokana and Forxiga) considering serious reports of acute kidney injury, acute renal failure and renal failure (severe renal impairment). Jardiance was not included in the review due to its recent approval - however, it already contains wording in its labelling for acute kidney failure (acute renal failure).

• At the time of the review, Health Canada had received two reports of acute kidney injury in Invokana users. Additional international reports of kidney injury suspected to be linked with either Invokana or Forxiga were provided by their Canadian manufacturers.

• At the time of the review, the product information for both Invokana and Forxiga already included some warnings on the use of these products in patients who have severe kidney problems or are on dialysis. The product labeling also reports the occurrence of decreased kidney function in patients treated with SGLT2 inhibitors.

• Health Canada is working with the manufacturers on an update to the Canadian prescribing information of Invokana and Forxiga to reflect the risk of acute kidney injury and will notify Canadians when changes have occurred.
What Causes AKI?

- Acute kidney injury has three main causes: A sudden, serious drop in blood flow to the kidneys. Heavy blood loss, an injury, or a bad infection called sepsis can reduce blood flow to the kidneys. Not enough fluid in the body (dehydration) also can harm the kidneys.
DKA and SGLT2 Inhibitors

Recommendations:

1. SGLT2 inhibitors are not indicated for patients with Type 1 diabetes or with a history of DKA

2. Be aware of risk factors for DKA in patients on SGLT2 inhibitors: Misdiagnosed Type 1 or LADA, the post-operative period, caloric restriction, reduction of insulin dose, alcohol intake

3. If a patient exhibits signs and symptoms of DKA even with normal glucose values an evaluation should be done and if DKA is present the use of an SGLT2 inhibitor should be discontinued

Review Article

SGLT2 Inhibitor–associated Diabetic Ketoacidosis: Clinical Review and Recommendations for Prevention and Diagnosis

Ronald M. Goldenberg, MD; Lori D. Berard, RN, CDE; Alice Y.Y. Cheng, MD; Jeremy D. Gilbert, MD; Subodh Yemna, MD, PhD; Vincent C. Woo, MD; and Jean-François Yale, MD

1 LMC Diabetes & Endocrinology, Thornhill, Ontario, Canada; 2 Winnipeg Regional Health Authority Health Sciences Centre, University of Manitoba, Diabetes Research Group, Winnipeg, Manitoba, Canada; 3 Division of Endocrinology and Metabolism, St. Michael’s Hospital, Department of Medicine, University of Toronto, Toronto, Ontario, Canada; 4 Division of Endocrinology and Metabolism, Sunnybrook Health Sciences Centre, Department of Medicine, University of Toronto, Toronto, Ontario, Canada; 5 Division of Cardiac Surgery, St. Michael’s Hospital, Departments of Surgery and Pharmacology and Toxicology, University of Toronto, Toronto, Ontario, Canada; 6 Section of Endocrinology and Metabolism, Health Sciences Centre, University of Manitoba, Winnipeg, Manitoba, Canada; and 7 Division of Endocrinology and Metabolism, McGill University Health Centre, McGill University, Montreal, Quebec, Canada
Perspective

- DKA is a medical emergency affecting people with diabetes
- Type 1 diabetes – prevalence has been found to be 4.6 to 8.0 per 1000 patient-years.
- DKA is not exclusive to those with type 1 diabetes.
- Data from a Swedish population study indicated that DKA in persons with type 2 diabetes may account for as much as one third of all DKA cases, with a rate of 0.5 per 1000 patient-years.
- Type 2 diabetes clinical trial programs for canagliflozin, dapagliflozin, and empagliflozin have all reported episodes of DKA.
- To date, these trials have accumulated 44,000 patient-years of exposure to SGLT2 inhibitors.
- DKA incidence rates varying from 0.16 to 0.76 event per 1000 patient-years.
- Excluding the cases of autoimmune diabetes, incidence rates were 0.13 and 0.38 per 1000 patient-years with canagliflozin 100 mg and 300 mg, respectively.
- Among canagliflozin treated patients developing DKA in the clinical trial program, 8 of 10 were treated with insulin, and most had a precipitating factor such as surgery, infection, and insulin reduction or omission, but only 1 of 10 did not have hyperglycemia.
The most effective means of preventing SGLT2 inhibitor–associated DKA is to ensure that SGLT2 inhibitors are appropriately prescribed and are withheld during any situation that might precipitate DKA:

- eg, acute illness, surgery, dehydration, excessive alcohol intake

Given that the half-life of the SGLT2 inhibitors ranges from 11 to 13 hours, and the SGLT2 inhibitor effect can persist for at least a few days after discontinuation, these agents should be discontinued 3 days before major surgical procedures.
Table. Precipitants for sodium-glucose cotransporter 2 (SGLT2) inhibitor-associated diabetic ketoacidosis and actions to prevent its occurrence.

The insulin dose should be maintained, and supplemental insulin may be necessary

<table>
<thead>
<tr>
<th>Precipitant</th>
<th>Action(s) Regarding SGLT2 Inhibitor</th>
</tr>
</thead>
</table>
| Acute illness (e.g., infection, gastroenteritis, myocardial infarction/stroke) | Hold at onset  
 Restart when feeling well and able to eat and drink |
| Bariatric surgery                                     | Hold while on preoperative low-carbohydrate diet  
 Reevaluate postoperatively                            |
| Major surgical procedures                            | Hold 3 days* before surgery  
 Restart when feeling well and able to eat and drink |
| Risk of dehydration (e.g., extensive exercise, preparing for colonoscopy) | Hold until able to maintain hydration  
 Hold until normal diet resumes  
 Stop immediately  
 Reassess at a later date |
| Low-carbohydrate diet                                  |                                                          |
| Excessive alcohol intake                               |                                                          |

*Empirical based on 5 half-lives.
To safely use SGLT2i

Figure 2. Prescribing sodium-glucose cotransporter 2 inhibitors (SGLT2i) and prevention of diabetic ketoacidosis (UKA). CHO = carbohydrate; HbA1c = glycated hemoglobin; BMI = body mass index; LADA = latent autoimmune diabetes in adulthood; T1DM = type 1 diabetes mellitus; T2DM = type 2 diabetes mellitus.
Bone Fractures: A Diabetes Complication Often Ignored

By Beth W. Orenstein
Reviewed by Pat F. Bass, III, MD, MPH

Many people aren't aware of the connection between diabetes and bone fractures. Find out how you can protect your bones and guard against this complication of diabetes.
Bone Fracture Incidence
An Update that is really necessary??

- Annualized incidence of fractures based on updated data is similar to incidence included in original approved labeling
- Relative risk increase of fractures based on updated data is similar to relative risk increase in the original approved labeling
- Location (upper extremity) and type (low trauma) of fracture based on updated data is similar to location and type of fracture in original approved labeling

<table>
<thead>
<tr>
<th></th>
<th>Comparator</th>
<th>CANA 100 mg</th>
<th>CANA 300 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Updated labeling, fracture incidence per 100 patient-years</td>
<td></td>
<td>1.1</td>
<td>1.4</td>
</tr>
<tr>
<td>Original approved labeling, fracture incidence per 100 patient-years</td>
<td>1.4</td>
<td>1.9</td>
<td>1.8</td>
</tr>
</tbody>
</table>
Amputations

The preventable diabetes complication...

Diabetes and foot care: A patient’s checklist

Many people with diabetes have problems with their feet. You can prevent serious problems by following these basic guidelines. Ask your doctor to explain your risk factors for foot problems.

<table>
<thead>
<tr>
<th>DO...</th>
<th>DON'T...</th>
</tr>
</thead>
<tbody>
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<td></td>
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</table>
Health Authorities Update

<table>
<thead>
<tr>
<th>Health Canada¹</th>
<th>FDA²</th>
<th>EMA-PRAC³</th>
</tr>
</thead>
<tbody>
<tr>
<td>October 26, 2016</td>
<td>May 18, 2016</td>
<td>February 10, 2017</td>
</tr>
</tbody>
</table>

- Product monograph was updated to reflect increased risk of lower limb amputation, primarily of the toe from the CANVAS trial, with the imbalance occurring as early as the first 26 weeks of therapy
- A Drug Safety Communication (DSC) was issued based on an interim safety analysis from the ongoing CANVAS study that signaled an increased risk of lower limb amputations, mostly affecting the toes, in patients treated with canagliflozin
- Prescribing information updated with increased risk of lower limb amputation (mostly affecting the toes)
- A warning will also be included for other SGLT2 medicines, highlighting the importance of routine preventative foot care
- Doctors should also consider stopping treatment with canagliflozin if patients develop significant foot complications such as infection or skin ulcers

The Independent Drug Monitoring Committee (IDMC) observed an increase of lower-limb amputation, mostly affecting toes.

The IDMC has also reported that CANVAS-R trial, has not shown the same risks of increased leg and foot amputations (average follow-up of 9 months)

The possibility that canagliflozin increases lower-limb amputations (toe) is currently not confirmed.

The IDMC has recommended that the CANVAS trial should continue.
Incidence of amputations with SGLT2 inhibitors: data from RCT

- MEDLINE, www.clinicaltrials.gov, and Medical Reviews from FDA were searched for amputations reported as serious adverse events in controlled trials, meeting the following criteria:
  - treatment duration >12 weeks
  - patients with type 2 diabetes
  - SGLT2 inhibitor (dapagliflozin, empagliflozin, canagliflozin, ipragliflozin, ertugliflozin, luseogliflozin, or tofogliflozin) compared to placebo or active comparator

- Serious adverse events were available in 74/81 trials
  - 2 trials with empagliflozin listed:
    - leg amputation: no cases reported
    - finger amputation: one case each in the active treatment group

Last but certainly not least...

What about the “CV” stuff

- CANVAS and CANVAS R
  - ADA 2017
- DECLARE
  - Expected 2018/19
  - EASD 2017 meta analysis of all cause mortality and ??
- VERITAS
  - 2020

And you know...there will be more to learn, to discuss, to debate, and to integrate.