Questions You've Asked
T2DM –SGLT-2i & GLP-1a

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Academic Detailing Service

nova scotia health
Drug Evaluation Unit

Dalhousie Academic Detailing Conference 2023
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1

Disclosure

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Jennifer Fleming (BScPharm, ACPR, DEU Pharmacist, she/her)

No actual or potential conflict of interest with this topic or presentation.

This session is presented from Mi'kma'ki, the ancestral and unceded territory of the Mi'kmaq. We are all Treaty people.

2

Objectives

At the conclusion of this presentation, participants will be able to

- Explain the differences in safety & efficacy between high & low dose semaglutide in T2DM.
- Recognize the potential for severe GI-related adverse effects associated with GLP-1a use.
- Determine whether there is a known difference in incidence of SGLT-2i associated Fournier's gangrene between women and men.

3

1.

What is the value in using high dose semaglutide in T2DM?

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4

Semaglutide Indication (Ozempic)

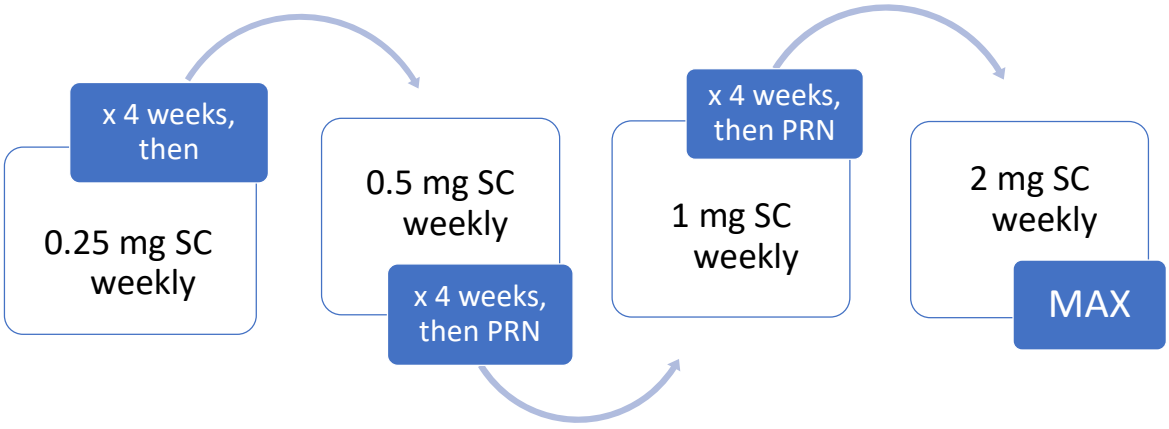
For once-weekly treatment of adults with T2DM ***to improve glycemic control***, in combination with:

- diet and exercise in patients for whom metformin (MET) is inappropriate due to CI or intolerance.
- MET, when diet and exercise plus maximal tolerated dose of MET do not achieve adequate glycemic control.
- MET and a SU, when diet and exercise plus dual therapy with MET and a SU do not achieve adequate glycemic control.
- MET or a SU and an SGLT2i, when diet and exercise plus MET or a SU, in addition to an SGLT2i, do not achieve adequate glycemic control.
- basal insulin with MET, when diet and exercise plus basal insulin with MET do not achieve adequate glycemic control

https://pdf.hres.ca/dpd_pm/00071939.PDF

5

Subcutaneous Semaglutide Dosage



https://pdf.hres.ca/dpd_pm/00071939.PDF

6

Evidence: Glycemic Control

Sustain Forte 2021 (N = 961)

40-week, MC, DB RCT

P	Adults, T2DM, A1C 8-10% on stable dose of metformin (100%) ± SU (53%); no other T2DM or obesity meds within 90 days of screening
I	Semaglutide 2 mg SC weekly
C	Semaglutide 1 mg SC weekly
O	1º Change in A1C from baseline to week 40

Lancet Diabetes Endocrinol 2021;9:563-74.

7

Evidence: Glycemic Control

Sustain Forte 2021 (N = 961): **Change in A1C**

Lancet Diabetes Endocrinol 2021;9:563-74.

8

Evidence: Glycemic Control

Step 2 2021 (N = 1210)

68-week, MC, DB RCT

P	Adults, T2DM (A1C 7-10%), BMI ≥ 27 kg/m^2, unsuccessful dietary effort to lose weight; treated with diet/exercise ± ≤ 3 po GLDs • Biguanides 92%, SU 26%, SGLT2 25%, TZD 5%
I	Semaglutide 2.4 mg SC weekly + lifestyle intervention
C	Semaglutide 1 mg SC weekly + lifestyle intervention
	Placebo + lifestyle intervention
O	Exploratory 2^o • Change in A1C from baseline to week 68

Lancet 2021; 397: 971–84.

9

Evidence: Glycemic Control

Step 2 2021 (N = 1210): **Change in A1C**

2^o OC	**Sema 2.4 mg**	**Sema 1 mg**	**ETD (95% CI)**
A1C at week 68 (%)	6.4	6.6	-
Change in A1C from baseline to week 68 (%)	-1.6%	-1.5%	-0.2 (-0.3 to 0.0)

Lancet 2021; 397: 971–84.

10

Evidence: Clinical Outcomes

Sustain-6 2016 (N = 3,297)

MC, DB, RCT, Follow-up median 2.1 years

P	Adults, T2DM, high CV risk
I	Semaglutide 0.5 or 1 mg mg SC weekly
C	Placebo 0.5 or 1 mg SC weekly

O	1º MACE
	• Sema *not worse than* pbo (P < 0.001)
	  • Sema 6.6% vs pbo 8.9%, HR 0.74 (95% CI 0.58-0.95), ARR 2.3%, NNT 44 (95% CI 25-210)
	  • *Post-hoc* testing for superiority also SS (P = 0.02)

SIMILAR RESULTS BETWEEN DOSES

Sema 0.5 mg:
HR 0.77 (95% CI 0.55-1.08), P = 0.13

Sema 1 mg:
HR 0.71 (95% CI 0.49-1.02), P = 0.06

N Engl J Med 2016; 375:1834-1844

11

Evidence: Clinical Outcomes

- Higher Doses

12

Evidence: Metabolic Outcomes (BW)

STEP 2 2021 (N = 1210)

- Additional baseline characteristics
  - Mean BW 99.9 kg (2.4 mg) vs 99 kg (1 mg) vs 100.5 kg (pbo)
  - Mean BMI 35.9 kg/m^2 (2.4 mg) vs 35.3 kg/m^2 (1 mg) vs 35.9 kg/m^2 (pbo)

Co-primary OCs	Sema 2.4 mg	Sema 1 mg	Result (95% CI)
% change in BW from baseline to week 68	-9.64%	-6.99%	ETD -2.65 (-3.66 to -1.64)
≥ 5% BW reduction to week 68	68.8%	57.1%	OR 1.62 (1.21 to 2.18)

Lancet 2021;397:971-84.

13

Evidence: Metabolic Outcomes (BW)

SUSTAIN FORTE 2021 (N = 961)

- Additional baseline characteristics
  - Mean BW 100.1 kg (2 mg) vs 98.6kg (1 mg)
  - Mean BMI 34.8 kg/m^2 (2 mg) vs 34.4 kg/m^2 (1 mg)

2^o OC	Sema 2 mg	Sema 1 mg	ETD (95% CI)
Change in BW from baseline to week 40	-6.4 kg	-5.6 kg	-0.77 kg (-1.55 to 0.01)

Lancet Diabetes Endocrinol 2021;9:563-74.

14

Adverse Effects

Sustain Forte 2021

Outcome	Sema 1 mg	Sema 2 mg
Treatment-emergent AEs	52%	57%
GI AE		
Overall	31%	34%
Mild	25%	28%
Moderate	11%	10%
Severe	2%	3%

Step 2 2021

Outcome	Sema 1 mg	Sema 2.4 mg
Any AE	81.8%	87.6%
SAE	7.7%	9.9%
GI AE		
Nausea	32.1%	33.7%
Vomiting	13.4%	21.8%
Diarrhea	22.1%	21.3%
Constipation	12.7%	17.4%

Lancet Diabetes Endocrinol 2021;9:563-74.
Lancet 2021;397:971-84.

15

Cost

Semaglutide SC Dose	Cost for Four Week Supply	
	NS Pharmacare	McKesson
0.5 mg weekly	$203.94	$221.28
1 mg weekly	$203.94	$219.75
2 mg weekly	Not listed	Not listed

16

The Verdict

17

2.

Should I tell my patients to hold GLP1a two weeks before surgery?

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18

Evidence – Perioperative GI Events

- Case series and case reports[1-5]
  - 11 people
    - Age 31 to 62
    - Female 73%
    - T2DM 27%
    - Obesity 91%
    - Overweight 9%
    - Exposure
      - 1 pt - Semaglutide 0.25 mg SC weekly *x 1 mo**
      - 1 pt - Semaglutide 0.5 mg SC weekly *x 5 mo**
      - 1 pt - Semaglutide 1 mg *x 1 week**
      - 1 pt - Semaglutide 1.7 mg SC weekly *x 2 mo**
      - 1 pt - Liraglutide 1.2 mg SC daily*
      - 5 pts - Liraglutide 3 mg SC daily *x 3 to 9 mo*
      - 1 pt – Liraglutide (dose NR)

1. Cureus. 2023 Jul 19;15(7):e42153.
2. Can J Anesth 2023;70:1397–1400.
3. Can J Anesth 2023;70:1394–1396.
4. Obesity Surgery (2018) 28:2113–2116.
5. Am J Med. 2023 Aug 9:S0002-9343(23)00499-0.

19

Other Observational Data

- Nakatani et al 2017[1] (N = 14, T2DM)
  - Lira causes delayed gastric emptying & inhibits duodenal & small intestine motility
    - Effect may be decreased or absent in people with DN-associated dysautonomia
- Kobori et al 2023[2]
  - Japanese case-control study, 205 pairs (GLP1a +/-) matched for age, sex, insulin treatment, A1C; all had T2DM and fasted ≥ 12 hours prior to EGD
    - Gastric residue during EGD**: GLP1a 5.4% vs no GLP1a 0.49%,** P = 0.004
      - Confirmed cases were taking
        - Liraglutide 1.8 mg daily (n = 2)
        - Dulaglutide 0.75 mg weekly (n = 5)
        - Semaglutide 0.5 mg weekly (n = 2)
        - Semaglutide 1 mg weekly (n = 2)

1. Diabetes & Metabolism 43 (2017) 430–437.
2. J Diabetes Investig 2023; 14: 767–773.

20

Other Observational Data

- 4 published studies[1-4]:
  - Variable designs
  - ± T2DM
  - GLPa dosed for T2DM (but not consistently reported)
  - Evaluation by ultrasound or endoscopy
  - Results
    - GLP1a associated with delayed gastric emptying or higher risk of gastric residuals in all but one study[4] in which a numerical increased risk of residual was observed, but NS

1. BJS Open. 2023 Jan 6;7(1):zrac169.
2. Can J Anesth/J Can Anesth (2023) 70:1300–1306.
3. J Clin Anesth. 2023 Aug;87:111091.
4. Ann Pharmacother. 2022 Aug;56(8):922-926.

21

What are the experts saying?

June 29, 2023

Day or week before procedure:
- **Daily GLP1a -** Hold day of procedure
- **Weekly GLP1a -** Hold week prior to procedure

"Consider consulting an endocrinologist for bridging the antidiabetic therapy to avoid hyperglycemia."

Day of procedure:
- **Continue with procedure if:** GLP1a held & no GI symptoms.
- **Consider delaying the procedure if:** severe nausea/vomiting/retching, abdominal bloating or pain.
  - Discuss concerns of potential regurgitation and aspiration.
- **Use precaution if:** GLP1a not held.
  - Assess gastric contents by ultrasound if possible. Otherwise, assume full stomach & consider delaying procedure or proceeding with full stomach precautions.

https://www.asahq.org/about-asa/newsroom/news-releases/2023/06/american-society-of-anesthesiologists-consensus-based-guidance-on-preoperative

22

What are the experts saying? Canadian Anesthesiologists' Society

June 2023

- Inquire re: GLP1a use preoperatively
- Consider possibility patient has a full stomach despite fasting
- If prolonged holding of GLP1a not feasible, consider aspiration risk reduction strategies
- US to assess gastric residuals may be helpful
- Report incidents to ISMP Canada or local hospital-based systems (forwarded to HC, Vanessa's Law)

23

What are the experts saying?

Editorial – Can J Anesth (2023) 70:1281-1286.

- GLP1a for weight loss → consider holding for at least 3 half-lives (e.g. 3 weeks for Semaglutide)
- GLP1a for T2DM → "consider consultation with an endocrinologist"
- Prolonged fasting unlikely required (or reasonable)
- If hold x at least 3 half-lives is not possible,
  - Consider RSI for GA & techniques to minimize risk of regurgitation
  - Metoclopramide??
- POC US? But potential false + and –
- Research required

24

The Verdict

25

3.

Is there a difference in rates of Fournier's gangrene between women and men on SGLT2i?

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26

Canada Vigilance Adverse Reaction Database

Fournier's Gangrene

SGLT-2i	Total # Cases	# Females	# Males
Empagliflozin (Jardiance)	39	11	28
Canagliflozin (Invokana)	9	3	6
Dapagliflozin (Forxiga)	12	5	7
TOTAL	**60**	**19**	**41**

(January 2015 to March 2023)

Canada Vigilance Program: https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-database.html Accessed 2023/07/28.

27

FDA Drug Safety Communication 2018

- Warning about rare occurrences of FG with SGLT2i inhibitors for diabetes
- FAERS database (March 2013 – Feb 2018) & medical lit search
  - 12 cases FG in people taking SGLT2i
    - 7 men
    - 5 women

https://www.fda.gov/drugs/drug-safety-and-availability/fda-warns-about-rare-occurrences-serious-infection-genital-area-sglt2-inhibitors-diabetes Accessed 2023/07/26.

28

Primary Literature

- RCTs, SR & MAs not helpful **X**
- 2 promising observational studies
  - Fisher et al 2020 **X**
  - Patil et al 2023 **X**

Am J Cardiol 2023;201:281–293.

Diabetes Obes Metab 2020; 22(9): 1648-1658.

29

The Verdict

30