GET TO TARGET

Considerations for adding long-acting GLP-1 RAs

GLP-1 RAs, glucagon-like peptide-1 receptor agonists

Faculty/presenter disclosure

- **Faculty:** Sorin Beca
- **Relationships with financial sponsors:**
  - Grants/Research Support: none
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  - Sorin Beca has received payment/funding from Novo Nordisk Canada Inc. AND/OR organization whose product(s) are being discussed in this program
  - Novo Nordisk Canada Inc. developed products that will be discussed in this program

Mitigating potential bias

- Bias in this program has been mitigated using independent content validation as follows:
  - All content has been reviewed by a physician and pharmacist steering committee, expert reviewers, the College of Family Physicians of Canada, and the Fédération des Médecins Omnipraticiens du Québec
  - All data has been sourced from evidence that is clinically accepted
  - All support used in justification of patient care recommendations conform to generally accepted standards and 2018 Diabetes Canada Clinical Practice Guidelines (CPG), as well as the most recently available clinical data
  - Sorin Beca will receive an honorarium from the College of Family Physicians of Canada (CFPC) for this talk

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CCRN Canadian Collaborative Research Network

Program objectives

After attending this program, participants will be able to:

- Recognize the key features of long-acting GLP-1 RAs and their potential role in diabetes management within a primary-care setting
- Reflect on a Diabetes Canada 2018 guideline-based approach to using the GLP-1 RA class to manage type 2 diabetes
- Integrate practical tips for initiating long-acting GLP-1 RA therapy based on patient characteristics

GLP-1 RAs, glucagon-like peptide-1 receptor agonists

Patient Case: Sandra

- **Age:** 49 years old
- **Gender:** Female
- **Occupation:** Accountant (with private coverage)

Newly diagnosed with type 2 diabetes

Medical status/history:

- **A1C:** 8.8%
- **eGFR:** 81 mL/min
- **ACR:** 1.7 mg/mmol
- **BMI:** 31.5 kg/m^2
- **BP:** 150/92 mmHg
- **LDL:** 3.6 mmol/L
- **HDL:** 1.1 mmol/L
- **Other:** Family history of stroke

Medications:

- **Added:**
  - Rosuvastatin 20 mg QD
  - Metformin 500 mg BID

Sandra was also referred to a local diabetes education clinic

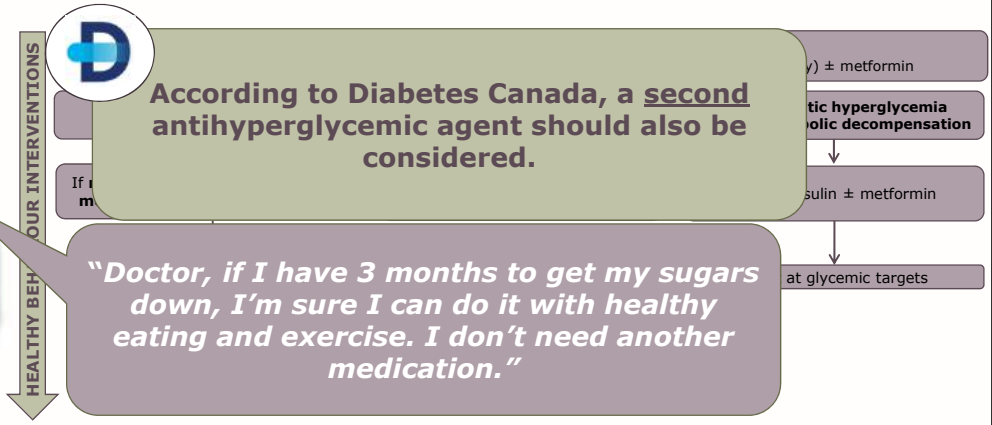
A1C, glycated hemoglobin

Diabetes Canada Clinical Practice Guidelines Expert Committee. Diabetes Canada 2018 Clinical Practice Guidelines for the Prevention and Management of Diabetes in Canada. Can J Diabetes. 2018;42(Suppl 1):S1-S325.

Patient Case: Sandra

According to Diabetes Canada, a <u>second</u> antihyperglycemic agent should also be considered.

"Doctor, if I have 3 months to get my sugars down, I'm sure I can do it with healthy eating and exercise. I don't need another medication."



A1C, glycated hemoglobin; AHA, antihyperglycemic agents

Diabetes Canada Clinical Practice Guidelines Expert Committee. Diabetes Canada 2018 Clinical Practice Guidelines for the Prevention and Management of Diabetes in Canada. Can J Diabetes. 2018;42(Suppl 1):S1-S325.

Patient Case: Sandra

- **Age:** 49 years old
- **Gender:** Female
- **Occupation:** Accountant (with private coverage)

3 months later

Medical status/history:
- **A1C:** 8.2%
- **eGFR:** 81 mL/min
- **ACR:** 1.7 mg/mmol
- **BMI:** 30.5 kg/m^2
- **BP:** 148/88 mmHg
- **LDL:** 1.9 mmol/L
- **HDL:** 1.1 mmol/L
- **Other:** Family history of stroke

Medications:
- Rosuvastatin 20 mg QD
- **Changed to:**
  - Metformin XR 2,000 mg QD
- **Added:**
  - Ramipril 5 mg QD

Patient Case: Sandra

- **Age:** 49 years old
- **Gender:** Female
- **Occupation:** Accountant (with private coverage)

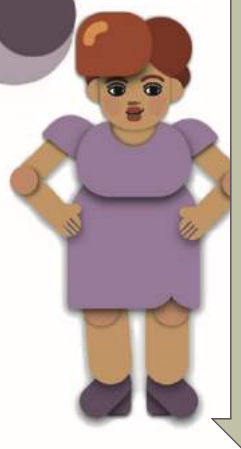
3 months later (6 months post- diagnosis)

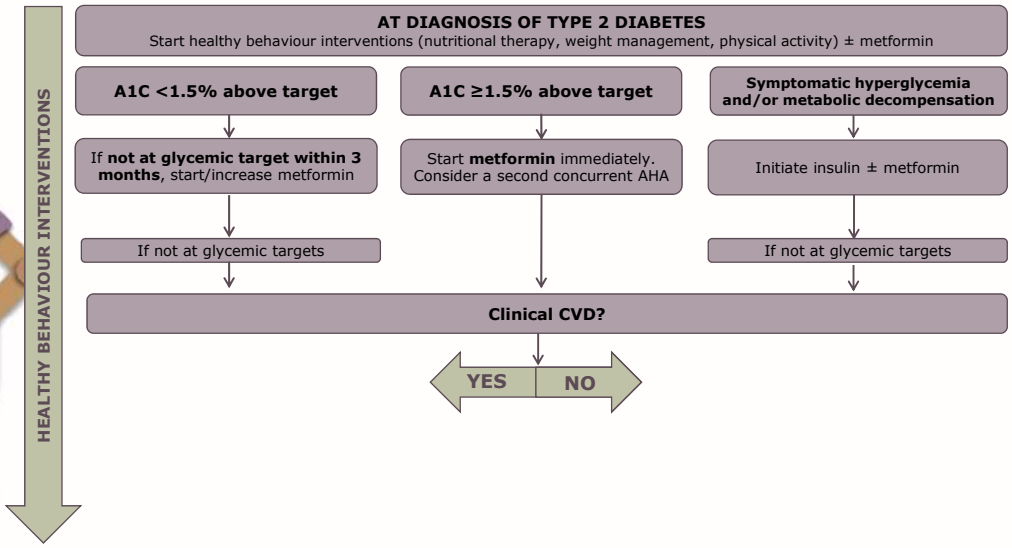
Medical status/history:
- **A1C:** 8.0%
- **eGFR:** 81 mL/min
- **ACR:** 1.7 mg/mmol
- **BMI:** 31.5 kg/m^2
- **BP:** 134/84 mmHg
- **LDL:** 1.9 mmol/L
- **HDL:** 1.1 mmol/L
- **Other:** Family history of stroke

Medications:
- Rosuvastatin 20 mg QD
- Metformin XR 2,000 mg QD
- Ramipril 5 mg QD

What are the next steps, according to the 2018 Diabetes Canada guidelines?

2018 Diabetes Canada recommendations





A1C, glycated hemoglobin; AHA, antihyperglycemic agents

Diabetes Canada Clinical Practice Guidelines Expert Committee. Diabetes Canada 2018 Clinical Practice Guidelines for the Prevention and Management of Diabetes in Canada. Can J Diabetes. 2018;42(Suppl 1):S1-S325.

2018 Diabetes Canada recommendations…cont'd

Add additional antihyperglycemic agent best suited to the individual based on the following	
CLINICAL CONSIDERATIONS	**CHOICE OF AGENT**
Avoidance of hypoglycemia and/or weight gain with adequate glycemic efficacy	DPP-4 inhibitor, GLP-1 receptor agonist or SGLT2 inhibitor
Other considerations: Reduced eGFR and/or albuminuria Clinical CVD or CV risk factors Degree of hyperglycemia Other comorbidities (CHF, hepatic disease) Planning pregnancy Cost/coverage Patient preference	see Renal Impairment Appendix

2018 Diabetes Canada recommendations for pharmacotherapy in type 2 diabetes

If metformin and healthy behaviour changes are not enough to control blood glucose, **other antihyperglycemic agent (AHA) options** should be added

Next-line treatment for patients not reaching target:

With CV disease

Add: AHA with CV benefit

Options: empagliflozin, liraglutide or canagliflozin*

Without CV disease

Add: Incretin agent and/or SGLT2i, if concerned about hypoglycemia and weight gain

Options: GLP-1 RA or DPP-4i and/or an SGLT2i

(If hypoglycemia and weight are not of concern, SUs, TZDs, and glinides can be considered)

On non-insulin AHAs

Add: once-daily basal insulin over premixed or bolus insulin

Options: NPH insulin, insulin degludec, insulin detemir or insulin glargine

On insulin

Add: GLP-1 RA, DPP-4i or SGLT2i before adding or intensifying prandial insulin therapy

* Avoid in people with prior lower extremity amputation. CV, cardiovascular; RA, receptor agonist; DPP-4i, DPP-4 inhibitor; SGLT2i, SLGT2 inhibitor

Diabetes Canada Clinical Practice Guidelines Expert Committee. Diabetes Canada 2018 Clinical Practice Guidelines for the Prevention and Management of Diabetes in Canada. Can J Diabetes. 2018; 42:S1-S325.

POLL QUESTION

On average, which agent-specific characteristic has the greatest impact when you are choosing a secondary agent?

A. A1C reduction
B. Weight reduction
C. Risk of hypoglycemia
D. CV safety or protection
E. Impact on comorbidities (e.g., CKD, CHF, or microvascular complications)
F. Overall safety profile
G. Ease of use

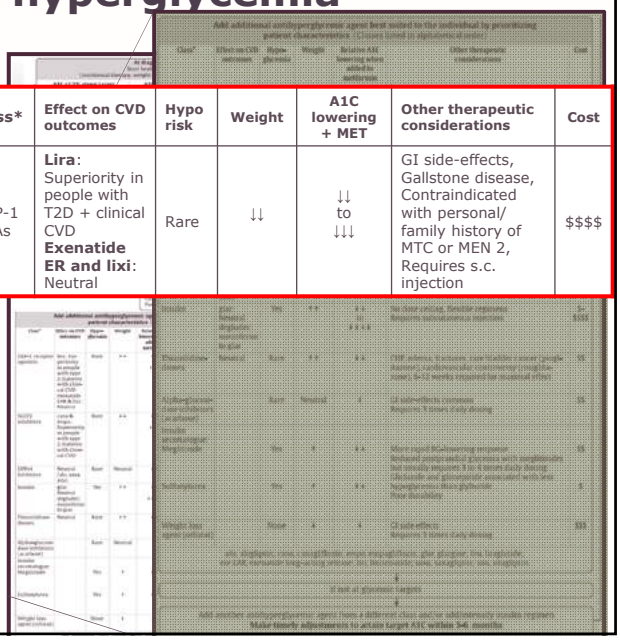
Overview of long-acting GLP-1 RAs

Guideline recommendations: Options to manage hyperglycemia

Per the 2018 Diabetes Canada guidelines, GLP-1 RAs are:

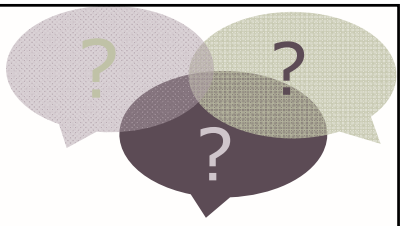
- **Recommended as a second-line treatment** option for glycemic control when weight gain and hypoglycemia are a concern

Class*	Effect on CVD outcomes	Hypo risk	Weight	A1C lowering + MET	Other therapeutic considerations	Cost
GLP-1 RAs	**Lira**: Superiority in people with T2D + clinical CVD **Exenatide ER and lixi**: Neutral	Rare	↓↓	↓↓ to ↓↓↓	GI side-effects, Gallstone disease, Contraindicated with personal/ family history of MTC or MEN 2, Requires s.c. injection	$$$$



* Listed by CV outcome data
GI, gastrointestinal; MEN 2, multiple endocrine neoplasia type 2; MTC, medullary thyroid cancer; s.c., subcutaneous
Diabetes Canada Clinical Practice Guidelines Expert Committee. Can J Diabetes. 2018;42 Suppl 1:S88-103.

GROUP DISCUSSION



What is your comfort level with using a GLP-1 RA at this stage of treatment?

Would a GLP-1 RA be appropriate for Sandra?

Currently available GLP-1 RAs for the treatment of type 2 diabetes

Molecule name	Brand name	Homology to human GLP-1	Main route of elimination	Half-life	Admin/ Route
Short-acting GLP-1 RAs					
Exenatide (Approved in 2011)	Byetta®	53% (Exendin-4)	Glomerular filtration	2.4 hours	BID/SC
Lixisenatide (Approved in 2017)	Adlyxine™	50% (Modified exendin-4)	Glomerular filtration	2–5 hours	QD/SC
Long-acting GLP-1 RAs					
Liraglutide (Approved in 2010)	Victoza®	97% (Modified human GLP-1)	Endogenously metabolized	8–13 hours	QD/SC
Dulaglutide (Approved in 2015)	Trulicity®	90% (Modified human GLP-1)	Endogenously metabolized	~5 days	QW/SC
Exenatide ER (Approved in 2015)	Bydureon®	53% (Exendin-4)	Glomerular filtration	7–14 days	QW/SC
Semaglutide (Approved in 2018)	Ozempic®	94% (Modified human GLP-1)	Endogenously metabolized	~7 days	QW/SC

Based on clinical response and after at least one week the dose can be increased to maximum dose to achieve maximum efficacy for glycemic control. † If additional glycemic control is needed after 4 weeks, dose may be increased to 1.0 mg once weekly. BID, twice daily; ER, extended release; QD, once daily; QW, once weekly; SC, subcutaneous
Byetta® Product Monograph, AstraZeneca Canada Inc., June 30, 2014; Adlyxine™ Product Monograph, Sanofi-Aventis Canada Inc., May 23, 2017; Victoza® Product Monograph, Novo Nordisk Canada Inc., November 17, 2017; Trulicity® Product Monograph, Eli Lilly Canada Inc., April 18, 2018; Bydureon® Product Monograph, AstraZeneca Canada Inc., May 17, 2017; Ozempic® Product Monograph, Novo Nordisk Canada, January 4, 2018; Lovshin JA. Can J Diabetes. 2017;41(5):524-535.

Health Canada-approved indications for long-acting GLP-1 RA therapies

	In combination with diet and exercise*	Add-on to MET	Add-on to SU	Add-on to MET + SU	Combination with insulin	For cardioprotection in patients with CVD
GLP-1 RAs						
Dulaglutide	✓	✓		✓	Basal + MET Prandial + MET	
Exenatide ER	✓	✓	✓	✓	Not indicated	
Liraglutide	✓	✓		✓	Basal + MET	✓
Semaglutide†	✓	✓		✓	Basal + MET	

* In patients for whom metformin is inappropriate; † Refer to the speaker's notes for additional details.
CVD, cardiovascular disease; MET, metformin; SU, sulfonylurea
Dulaglutide Product Monograph, Eli Lilly Canada Inc., 2018; Exenatide ER Product Monograph, AstraZeneca Canada Inc., 2017; Liraglutide Product Monograph, Novo Nordisk Canada Inc., 2017; Semaglutide Product Monograph, Novo Nordisk Canada Inc., 2018.

Overview of available long-acting GLP-1 RAs

Dulaglutide, exenatide, liraglutide, semaglutide

Efficacy

- Substantial A1C reduction (1.0%–1.5% mean reduction)
- Significant weight loss (2.8 kg–5.5 kg mean reduction)
- Negligible risk for hypoglycemia

Safety

Warnings for:

- GI side effects (nausea, vomiting, diarrhea)
- Gallstone disease

Contraindication:

- Personal/family history of medullary thyroid cancer or MEN2

Diabetes Canada Clinical Practice Guidelines Expert Committee. Can J Diabetes. 2018;42 Suppl 1:S88-103; Dulaglutide Product Monograph, Eli Lilly Canada Inc., April 18, 2018; Exenatide ER Product Monograph, AstraZeneca Canada Inc., May 17, 2017; Liraglutide Product Monograph, Novo Nordisk Canada Inc., November 17, 2017; Semaglutide Product Monograph, Novo Nordisk Canada, January 4, 2018; Lovshin JA. Can J Diabetes. 2017;41(5):524-535.

Efficacy of long-acting GLP-1 RAs

Head-to-head GLP-1 RA clinical trials: Efficacy in glycemic control

AWARD-6
(N=599)

DULA vs LIRA

p (non-inferiority) <0.0001

DURATION 6
(N=911)

EXEN ER vs LIRA

p<0.02

SUSTAIN 3
(N=813)

SEMA vs EXEN ER

p<0.0001

SUSTAIN 7
(N=1,201)

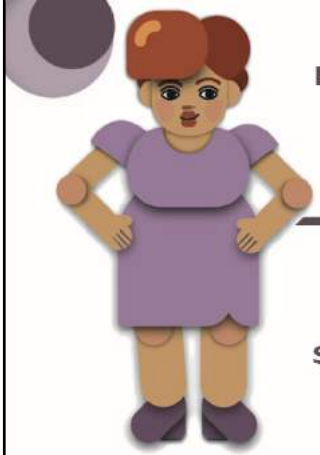
SEMA vs DULA

p<0.0001

DULA, dulaglutide; EXEN ER, exenatide extended-release; LIRA, liraglutide; SEMA, semaglutide

Trujillo JM, et al. Ther Adv Endocrinol Metab. 2015;6(1):19-28; Wysham C, et al. Diabetes Care. 2014;37:2159-2167; Ahmann A, et al. Diabetes. 2016;65(Suppl 1):A49; Ahmann AJ, et al. Diabetes Care. 2018;41(2):258-266; Pratley RE, et al. *Lancet Diabetes Endocrinol*. 2018;6(4):275-286.

Head-to-head GLP-1 RA clinical trials: Reductions in body weight



AWARD-6
(N=599)

DULA vs LIRA

p=0.011

DURATION 6
(N=911)

EXEN ER vs LIRA

p=0.0005

SUSTAIN 3
(N=813)

SEMA vs EXEN ER

p<0.05

SUSTAIN 7
(N=1,201)

SEMA vs DULA

p<0.0001

DULA, dulaglutide; EXEN ER, exenatide extended-release; LIRA, liraglutide; SEMA, semaglutide

Trujillo JM, et al. Ther Adv Endocrinol Metab. 2015;6(1):19-28; Wysham C, et al. Diabetes Care. 2014;37:2159-2167; Ahmann A, et al. Diabetes. 2016;65(Suppl 1):A49; Ahmann AJ, et al. Diabetes Care. 2018;41(2):258-266; Pratley RE, et al. Lancet Diabetes Endocrinol. 2018;6(4):275-286.

GROUP DISCUSSION

Do these data impact which medication you would recommend for Sandra? Why or why not?

Comparing long-acting GLP-1 RAs to other antihyperglycemic agents

How do long-acting GLP-1 RAs compare to DPP-4is?

Overview of available DPP-4is

Alogliptin, linagliptin, saxagliptin, sitagliptin

Efficacy

- A1C: 0.7% mean reduction
- Kg: Weight neutral
- H: Negligible risk for hypoglycemia

Safety

Warnings for:

- Pancreatitis
- Rare joint pain
- Not recommended in severe hepatic impairment due to no clinical experience
- Caution in patients with heart failure (saxagliptin)

Diabetes Canada Clinical Practice Guidelines Expert Committee. Can J Diabetes. 2018;42 Suppl 1:S88-103; Respective Product Monographs as of June 2018; Waldrop G, et al. J Am Coll Cardiol. 2016;67(12):1488-1496.

Head-to-head comparisons: GLP-1 RAs vs. DPP-4is

- **A1C** — **Superior glycemic control** with **long-acting GLP-1 RAs** compared to a DPP-4i (ΔA1C: ⬇ 0.4–1.1%)
- **Kg** — **Significantly greater weight loss** with long-acting GLP-1 RAs compared to a DPP-4i (ΔBody weight: ⬇ 1.1–4.2 kg)
- **H** — No major or severe episodes of hypoglycemia

Nauck M, et al. Diabetes Care. 2014;372149–2158; Bergenstal RM, et al. Lancet. 2010;376:431-9; Pratley RE, et al. Int J Clin Pract. 2011;65(4):397–407; Ahren B, et al. Lancet Diabetes Endocrinol. 2017;5(5):341–354.

GROUP DISCUSSION

How do these results apply to Sandra's treatment?

Recall Sandra's profile

3 months later (6 months post-diagnosis)

- **Age:** 49 years old
- **Gender:** Female
- **Occupation:** Accountant (with private coverage)

Medical status/history:

- **A1C:** 8.0%
- **eGFR:** 81 mL/min
- **ACR:** 1.7 mg/mmol
- **BMI:** 31.5 kg/m^2
- **BP:** 134/84 mmHg
- **LDL:** 1.9 mmol/L
- **HDL:** 1.1 mmol/L
- **Other:** Family history of stroke

Medications:

- Rosuvastatin 20 mg QD
- Metformin XR 2,000 mg QD
- Ramipril 5 mg QD

Major considerations between GLP-1 RAs and DPP-4is for Sandra

Level of glycemic control

Impact on weight

Route of administration

GROUP DISCUSSION

If you added a DPP-4i and Sandra was still not achieving her A1C target, would it be worth switching to a GLP-1 RA?

AHA, antihyperglycemic agent

Switching from DPP-4i to GLP-1 RAs

- **A1C** — **Significant and clinically relevant A1C reductions** when switching from sitagliptin to a long-acting GLP-1 RA (⬇A1C: 0.24–0.54%)
- **Kg** — **Greater weight loss** when switching **from sitagliptin to a long-acting GLP-1 RA** (⬇ body weight: 1.10–1.67 kg)
- **!** — Long-acting GLP-1 RAs generally well-tolerated, with mild-to-moderate nausea being the most frequent adverse event

Wysham C, et al. Diabet Med. 2011;28:705–714; Pratley RE, et al. Diabetes Care. 2012;35:1986–1993; Bailey TS, et al. Diabetes Obes Metab. 2016.18(12):1191-1198.

How do long-acting GLP-1 RAs compare to SGLT2is?

Overview of available SGLT2is

Canagliflozin, dapagliflozin, empagliflozin

Efficacy

- **A1C**: 0.7–1.0% mean reduction (reduced efficacy in patients with renal insufficiency)
- **Kg**: Significant weight loss (2.5kg–4.5 kg mean reduction)
- **H**: Negligible risk for hypoglycemia

Safety

Warnings for:

- Genital infections
- Urinary tract infections
- Dose-related increases in LDL-C
- Do not initiate if GFR<60 mL/min/1.73m² (canagliflozin and dapagliflozin)
- Discontinue use of eGFR<30 mL/min/1.73m² (empagliflozin)
- Diabetic ketoacidosis/type 1 diabetes
- Bladder cancer (dapagliflozin)
- Hypotension
- Fractures (canagliflozin)
- Lower-limb amputations (canagliflozin)

Diabetes Canada Clinical Practice Guidelines Expert Committee. Can J Diabetes. 2018;42 Suppl 1:S88-103; Respective Product Monographs as of June 2018; DeFronzo RA, Diabetes Obes Metab. 2017;19(10):1353-1362.

Reviews and network meta-analyses: GLP-1 RAs vs. SGLT2i

- Currently, there are **no head-to-head trials** comparing GLP-1 RAs to SGLT2i

A1C — GLP-1 RAs may be more efficacious at achieving **improved glycemic control** vs. SGLT2i[1]

A1C — **Significantly greater A1C reductions** in a meta-analysis comparing semaglutide to SGLT2i[2]

Kg — **Significantly better weight loss with semaglutide** vs. SGLT2i[2]

1. Gurgle HE, et al. Vasc Health Risk Manag. 2016;12:239-249; 2. Kanters S et al. Poster: OP-0013 presented at International Diabetes Federation 2017 Congress, 4–8 December 2017, Abu Dhabi, United Arab Emirates.

GROUP DISCUSSION

How does this information affect your choice of treatment for Sandra?

Recall Sandra's profile

- **Age:** 49 years old
- **Gender:** Female
- **Occupation:** Accountant (with private coverage)

3 months later (6 months post-diagnosis)

Medical status/history:

- **A1C:** 8.0%
- **eGFR:** 81 mL/min
- **ACR:** 1.7 mg/mmol
- **BMI:** 31.5 kg/m^2
- **BP:** 134/84 mmHg
- **LDL:** 1.9 mmol/L
- **HDL:** 1.1 mmol/L
- **Other:** Family history of stroke

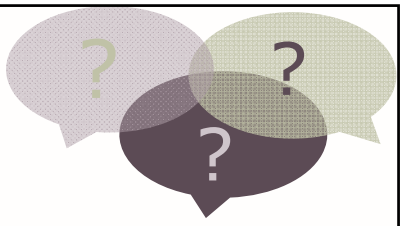
Medications:

- Rosuvastatin 20 mg QD
- Metformin XR 2,000 mg QD
- Ramipril 5 mg QD

Major considerations between GLP-1 RAs and SGLT2i for most patients with T2D

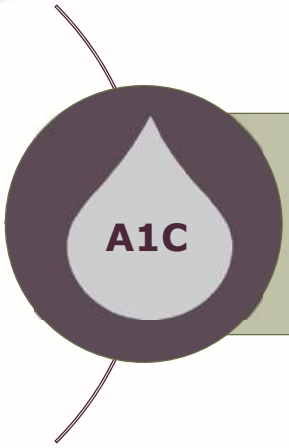
Level of glycemic control | **Impact on weight** | **Renal function** | **Safety profile**

GROUP DISCUSSION



What if Sandra was later in her treatment journey and already on an SGLT2i + metformin, but still not achieving target?
Could you add a GLP-1 RA?

Adding a GLP-1 RA to an SGLT2i



Significant and clinically meaningful improvements in glycemic control with **long-acting GLP-1 RAs** (dulaglutide and exenatide ER) as add-on therapy to SGLT2i

Frías JP, et al. Lancet Diabetes Endocrinol. 2016;4(12):1004-1016; Ludvik B, et al. Lancet Diabetes Endocrinol. 2018;6(5):370-381.

How do long-acting GLP-1 RAs compare to basal insulins?

"What if" scenario:
What if Sandra was later in her treatment journey and already on a DPP-4i or SGLT2i, but still not achieving her A1C target?

Head-to-head comparisons: GLP-1 RAs vs. basal insulins

GLP-1 RA could be a viable long-term injectable treatment for patients who have not yet started taking insulin

Aroda VR, et al. Lancet Diabetes Endocrinol. 2017;5(5):355-366; Giorgino F, et al. Diabetes Care. 2015;38(12):2241-2249; Diamant M, et al. Lancet Diabetes Endocrinol. 2014;2(6):464-473; D'Alessio D, et al. Diabetes Obes Metab. 2015;17(2):170-8; Russell-Jones D, et al. Diabetologia. 2009;52(10):2046-55.

GLP-1 RA therapy in patients with or at risk of cardiovascular disease

Recall Sandra's profile

- **Age:** 49 years old
- **Gender:** Female
- **Occupation:** Accountant (with private coverage)

3 months later (6 months post-diagnosis)

Medical status/history:

- **A1C:** 8.0%
- **eGFR:** 81 mL/min
- **ACR:** 1.7 mg/mmol
- **BMI:** 31.5 kg/m^2
- **BP:** 134/84 mmHg
- **LDL:** 1.9 mmol/L
- **HDL:** 1.1 mmol/L
- **Other:** Family history of stroke

Medications:

- Rosuvastatin 20 mg QD
- Metformin XR 2,000 mg QD
- Ramipril 5 mg QD

"What if" scenario:
What if Sandra presented with cardiovascular disease?

Recall the 2018 Diabetes Canada recommendations

HEALTHY BEHAVIOUR INTERVENTIONS

AT DIAGNOSIS OF TYPE 2 DIABETES
Start healthy behaviour interventions (nutritional therapy, weight management, physical activity) ± metformin

A1C <1.5% above target	**A1C ≥1.5% above target**	**Symptomatic hyperglycemia and/or metabolic decompensation**
If **not at glycemic target within 3 mo**…start/increase metformin	Start **metformin** immediately. Consider a second concurrent AHA	Initiate insulin ± metformin

…nic targets

"…in people with clinical CVD in whom A1C targets are not achieved… an AHA with demonstrated CV benefit should be added…"

Start antihyperglycemic agent with demonstrated CV benefit
empagliflozin (Grade A, Level 1A)
liraglutide (Grade A, Level 1A)
canagliflozin* (Grade C, Level 2)

A1C, glycated hemoglobin; AHA, antihyperglycemic agent
Diabetes Canada Clinical Practice Guidelines Expert Committee. Diabetes Canada 2018 Clinical Practice Guidelines for the Prevention and Management of Diabetes in Canada. Can J Diabetes. 2018;42(Suppl 1):S1-S325.

Summary: GLP-1 RA CVOTs

STATUS	RISK FACTORS	STABLE CAD-CVD-PAD	ACS PATIENTS
Completed		✓ LEADER: Liraglutide	
Completed	≈ EXSCEL: Exenatide ER		
Completed		✓ SUSTAIN 6: Semaglutide*	
Ongoing	REWIND: Dulaglutide		

≈ Neutral for MACE
✓ Superior for MACE

*Achieved non-inferiority; superiority was not a pre-specified assessment
ACS, acute coronary syndrome; CAD, coronary artery disease; CVD, cerebrovascular disease; CVOTs, cardiovascular outcome trials; PAD, peripheral artery disease
Adapted from clinicaltrials.gov; Pfeffer MA, et al. N Engl J Med. 2015; Marso SP, et al. N Engl J Med. 2016; Marso SP, et al. *N* Engl J Med. 2016;375(19):1834-1844; Holman RR, et al. N Engl J Med. 2017;377(13):1228-1239.

GROUP DISCUSSION

Which GLP-1 RA might you consider if Sandra had a history of CVD?

What factors could explain the differences in CV data within the GLP-1 RA class?

Summary

- Mechanism of action results in **pharmacologic** levels of GLP-1 activity
- One of the **most efficacious** second-line options for reducing A1C and weight
- **Negligible risk** for hypoglycemia
- Most common side effects are **GI in nature** and **transient**
- Demonstrated **CV safety*** (liraglutide and semaglutide showed CV benefits)
- Indicated for use across the diabetes treatment **continuum**

CV, cardiovascular; GI, gastrointestinal
* CVOT study with dulaglutide is not yet available

Key takeaways

GLP-1 RAs are one of the many classes to choose from across the treatment continuum

Consider your patient's individual needs to select the most appropriate treatment

Practical tips for initiating GLP-1 RA therapy

Practical solutions for initiating GLP-1 RA therapy

Strategies for troubleshooting cost and coverage gaps

- Direct the patient towards support groups and reimbursement programs (e.g., innoviCares)
- Encourage the patient to advocate for themselves if their insurance claim is initially denied
- Ask the patient to weigh upfront drug costs against potential for:
  - A1C reductions
  - Weight loss
  - CV risk reduction
- Explain that diabetic complications, like CVD, can significantly increase out-of-pocket expenses and affect quality of life

CVD, cardiovascular disease
Adapted from Iuga AO, et al. *Risk Manag Healthc Policy*. 2014;7:35-44; Ross SA. *Am J Med*. 2013;126(9 Suppl 1):S38-48.

For patients: Overcoming fear of injections

Demonstrate how to self-inject

- "Dry" injection training increases confidence and reduces patient anxiety
- Proper injection technique may lead to less pain

Use a smaller needle

- Needle size is positively correlated with injection pain

Dosing frequency

- Patients may prefer longer-acting QW options

Hidden needles

- Patients with needle anxiety, although easily managed, may prefer not handling needles

Consult the Forum for Injection Technique (FIT) Recommendations

- A website developed to establish and promote best practice in injection technique for all involved in diabetes care (www.fit4diabetes.com)

Agent	Needle size/gauge	Dosing frequency	Hidden needle
Dulaglutide	5 mm 29 gauge	QW	✓
Exenatide ER	7 mm 23 gauge	QW	✘
Liraglutide	4 mm 32 gauge	QD	✘
Semaglutide	4 mm 32 gauge	QW	✘

Larger gauge=**smaller** diameter

Arendt-Nielsen L, Egekvist H, Bjerring P. Somatosens Mot Res. 2006;23:37-43; Dulaglutide Product Monograph, Eli Lilly Canada Inc., 2018; Exenatide ER Product Monograph, AstraZeneca Canada Inc., 2017; Lange J, et al. Med Devices (Auckl). 2015;8:255-264; Liraglutide Product Monograph, Novo Nordisk Canada Inc., 2017; Lixisenatide Product Monograph, Sanofi-Aventis Canada Inc., 2017; Ross SA. Am J Med. 2013;126(9 Suppl 1):S38-48; Semaglutide Product Monograph, Novo Nordisk Canada Inc., 2018.

For HCPs: Overcoming injection therapy reluctance

Avoid assumptions about patient preference

- Studies suggest that opposition to injectable GLP-1 RA therapies may be more perceived than real
- Patients may be less averse to injectable therapies than their physicians assume

Emphasize benefit of potential weight loss

- Weight benefit in addition to the added effects on A1C and low risk of hypoglycemia (i.e., differentiate GLP-1 RAs from insulin)

Demonstrate how to use the device

- Use support staff (e.g., nurse, CDE, pharmacists) if time is a constraint

Provide ongoing support and education

- Lack of knowledge may lead to erroneous perceptions and interpretations of injectable therapy

CDE, certified diabetes educator
Ross SA. Am J Med. 2013;126(9 Suppl 1):S38-48; Tella SH, Rendell MS. Ther Adv Endocrinol Metab 2015;6(3):109-34.

Mitigating GI side effects

- Set appropriate treatment expectations
  - While common, GI side effects are manageable and transient (typically resolves after 4–8 weeks)
- Use a slow dose escalation
  - Starting at a lower dose and titrating upward can also reduce the incidence of nausea (agent-dependent)
- Respect satiety
  - Recommend eating small meals throughout the day
  - Avoid consuming high-fat foods
  - Patients might find that nausea is more tolerable if they have an empty stomach at the time of dosing (e.g., before bed)

Agent	Slow–dose escalation
Dulaglutide	✘
Exenatide ER	✘
Liraglutide	✓
Semaglutide	✓

Dulaglutide Product Monograph, Eli Lilly Canada Inc., 2018; Exenatide ER Product Monograph, AstraZeneca Canada Inc., 2017; Liraglutide Product Monograph, Novo Nordisk Canada Inc., 2017; Lixisenatide Product Monograph, Sanofi-Aventis Canada Inc., 2017; Meier JJ. Nat Rev Endocrinol. 2012;12:728-42; Ross SA. Am J Med. 2013;126(9 Suppl 1):S38-48; Semaglutide Product Monograph, Novo Nordisk Canada Inc., 2018; Tella SH, Rendell MS. *Ther Adv Endocrinol Metab* 2015;6(3):109-34.

Diabetic retinopathy

- Diabetic retinopathy is a major diabetic microvascular complication that can lead to decreased visual acuity and blindness
  - Prevalence rate of retinopathy in the adult population with type 2 diabetes is ~40.3%
- Although rapid A1C improvement has been associated with a temporary worsening of retinopathy, long-term glycemic control is associated with improvement in this measure

Diabetes Canada Clinical Practice Guidelines Expert Committee. Can J Diabetes. 2018;42 Suppl 1:S210-216; Feldman-Billard S, et al. Diabetes Metab. 2017; Kang YM, et al. Endocrinol Metab (Seoul). 2017;32(3):316-325; Nathan DM, et al. Diabetes Care. 2014;37(1):9-16.

Semaglutide diabetic retinopathy considerations

Semaglutide product monograph: Diabetic retinopathy

- In a 2-year trial involving patients with T2D and high CV risk, more events of diabetic retinopathy complications with semaglutide (3.0%) compared to placebo (1.8%)
- Absolute risk increase for diabetic retinopathy complications was larger among patients with a history of diabetic retinopathy
- Long-term glycemic control may decrease the risk of diabetic retinopathy
- Patients with a history of diabetic retinopathy should be monitored for progression of diabetic retinopathy

FDA briefing book: Ophthalmologist conclusion

"It is better to reduce HbA1c as soon as possible, regardless of whether or not it results in an initial increase in the progression of retinopathy."
"There is no reason to restrict semaglutide with respect to population or dosing schedule. There is also no reason to require any more or less ophthalmic follow-up."

Semaglutide Product Monograph. Novo Nordisk Canada Inc. January 4, 2018; Semaglutide FDA Briefing Document. Endocrinologic and Metabolic Drugs Advisory Committee Meeting October 18, 2017. Retrieved from: https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/EndocrinologicandMetabolicDrugsAdvisoryCommittee/UCM580460.pdf.

Diabetes Canada recommendations: Screening for retinopathy

- Screening is important for early detection of treatable disease
- **Tight glycemic control reduces the onset and progression of sight-threatening diabetic retinopathy**
- Multiple therapeutic options are available to reduce the risk of significant visual loss

Table 1
Screening for retinopathy

When to initiate screening
- Type 1 diabetes: 5 years after diagnosis in all individuals ≥15 years
- Type 2 diabetes: children, adolescents and adults at diagnosis

Screening methods
- 7-standard field, stereoscopic-colour fundus photography with interpretation by a trained reader (gold standard)
- Direct ophthalmoscopy or indirect slit-lamp fundoscopy through dilated pupil
- Digital fundus photography

If retinopathy is present
- Diagnose retinopathy severity and establish appropriate monitoring intervals (1 year or less)
- Treat sight-threatening retinopathy with laser, pharmacological or surgical therapy
- Review glycemic, BP and lipid control, and adjust therapy to reach targets as per guidelines*
- Screen for other diabetes complications

If retinopathy is not present
- Type 1 diabetes: rescreen annually
- Type 2 diabetes: rescreen every 1 to 2 years
- Review glycemic, BP and lipid control, and adjust therapy to reach targets as per guidelines*
- Screen for other diabetes complications

Diabetes Canada Clinical Practice Guidelines Expert Committee. Can J Diabetes. 2018;42 Suppl 1:S210-216.