INCRETIN THERAPY ROUNDTABLE:
Putting recommendations into practice

Program guide

TABLE OF CONTENTS

OBJECTIVES

After attending this program, participants will be able to:

1. Summarize relevant updates to the 2013 CDA guideline recommendations for the management of type 2 diabetes.
2. Differentiate between DPP-4 inhibitors and GLP-1 receptor agonists.
3. Explain how to optimally incorporate DPP-4 inhibitors and GLP-1 receptor agonists into clinical practice for better patient outcomes.

CASE STUDY

MEET WILLIAM

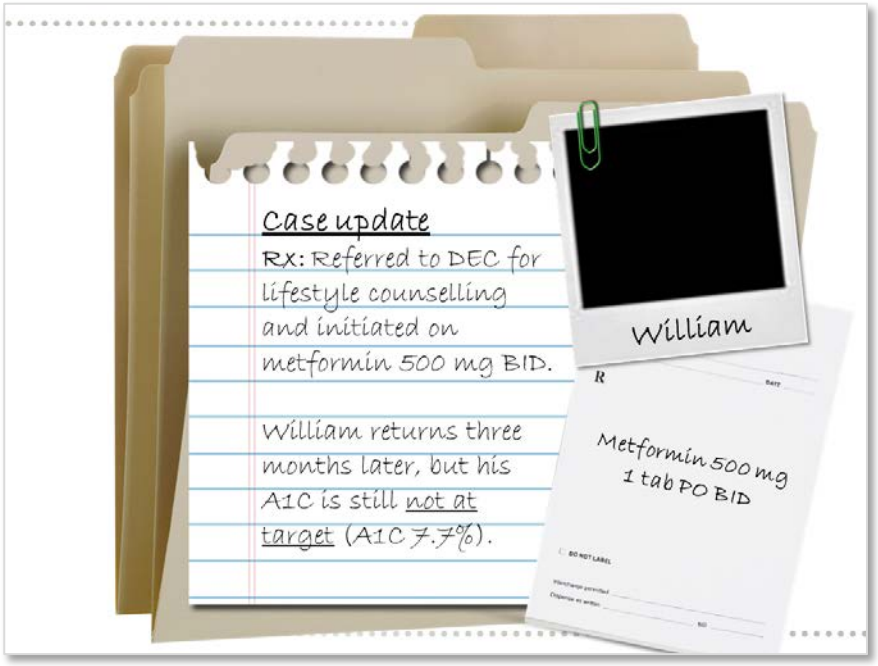
Initiating treatment

1. ***What should William's target A1C be?*** [page 2, slide 1]

2. ***Would you initiate a lifestyle intervention alone or lifestyle plus metformin?*** [page 2, slides 2-4; page 3, slide 5]

Additional notes:

CASE UPDATE



Next steps for William

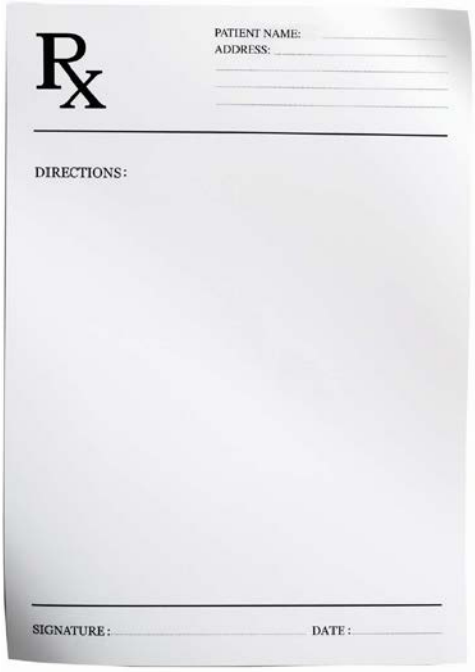
1. ***Would you uptitrate metformin or add a second antihyperglycemic agent?*** [page 3, slides 6 & 7]

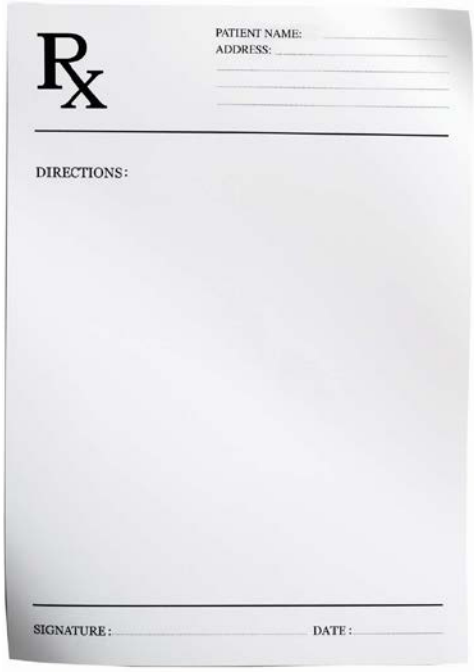
2. ***What are William's second-line treatment options and how do you individualize the treatment choice?*** [page 3, slide 8; page 4, slide 9]

3. ***Do you think William could benefit from the early use of an incretin agent as add-on to metformin?*** [page 4, slide 9]

4. ***What are the similarities and differences between DPP-4 inhibitors and GLP-1 receptor agonists?*** [page 4, slides 10-12; page 5, slides 13, 14 & 16; page 6, 17]

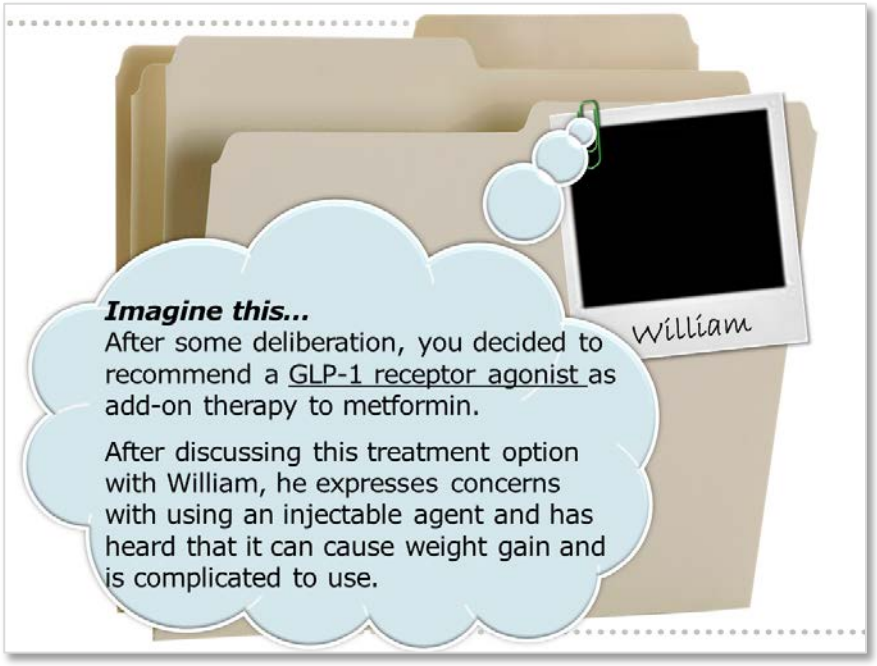
5. ***Using the prescription pads given, how would you prescribe a DPP-4 inhibitor? A GLP-1 receptor agonist?***





Additional notes:

CASE UPDATE (SCENARIO 1)

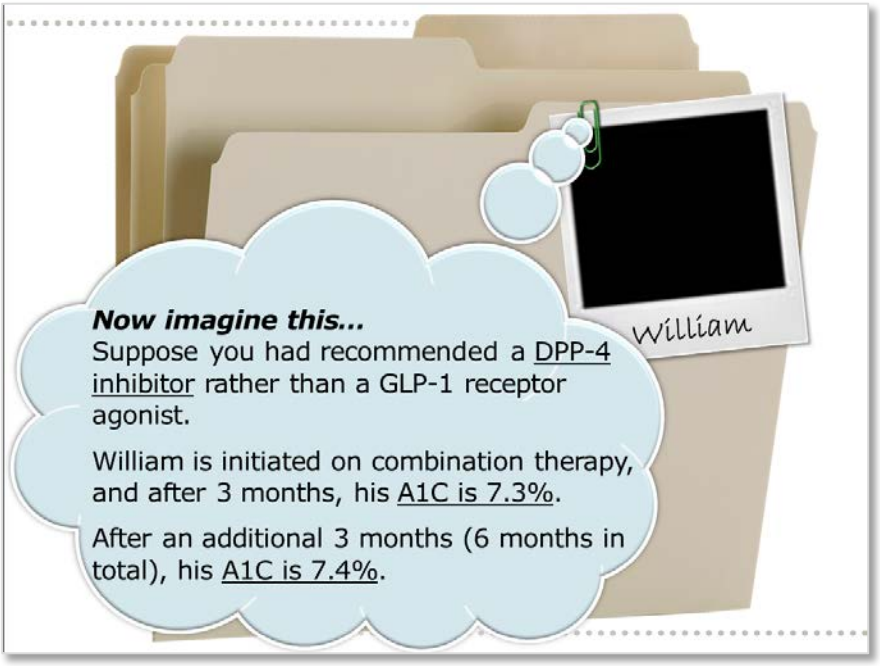


Overcoming objections to GLP-1 receptor agonists

1. ***What are some common patient barriers to initiating GLP-1 receptor agonists and how might you help manage these barriers?*** [page 6, slides 19 & 20]

2. ***Do you or your patients have any other major safety concerns with the use of GLP-1 receptor agonists? How do you address these concerns in your practice?*** [page 7, slides 21 & 22]

CASE UPDATE (SCENARIO 2)



Next steps post DPP-4 inhibitor

1. ***What are the common adverse events reported with DPP-4 inhibitors?*** [page 7, slide 23]

2. ***Are there any cardiovascular safety data on DPP-4 inhibitors or GLP-1 receptor agonists?*** [page 7, slide 24]

3. ***What are the recommendations for prescribing DPP-4 inhibitors in moderate or severe renal impairment? GLP-1 receptor agonists?*** [page 8, slide 25]

4. ***Do you think William could benefit from being switched to a GLP-1 receptor agonist? Why or why not?*** [page 8, slide 26]

5. ***Would you add a third antihyperglycemic agent to William's metformin plus DPP-4 inhibitor, or would you switch the DPP-4 inhibitor to a GLP-1 receptor agonist? Discuss the advantages and disadvantages of your preferred approach.*** [page 4, slide 9]

Additional notes:

TOP 5 CLINICAL TIPS

In the space provided below, record your top 5 take-home clinical tips from this educational program.

1

2

3

4

5

Summary of key learnings

- Target A1C ≤7% is appropriate for *most* patients
- Early, aggressive glycemic control, ideally without weight gain or hypoglycemia is essential to minimizing the risk of diabetes complications – incretin therapies can help to safely achieve this
- Adding a second antihyperglycemic agent to submaximal metformin is more effective and will have fewer side effects than uptitrating metformin
- Consider key characteristics when selecting a second-line therapy (including A1C effect, and impact on body weight and hypoglycemia risk)
- Incretin therapies can and should be used early in the treatment continuum if target A1C is not being achieved
- GLP-1 receptor agonists, in particular, are more effective than DPP-4 inhibitiors at reducing A1C and body weight, and can help patients (including those near target) reach glycemic goals when added on to or switched from existing antihyperglycemic therapy
- Objections to GLP-1 receptor agonists are readily manageable and can be overcome

INCRETIN THERAPY ROUNDTABLE:
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Resource guide

REFERENCE MATERIAL

CDA 2013 guidelines: Individualizing A1C targets

Target A1C:

≤6.5% — May be considered in some patients with type 2 diabetes to further lower the risk of nephropathy and retinopathy

≤7.0% — **Most patients** with type 1 and type 2 diabetes

7.1-8.5% — Consider if:

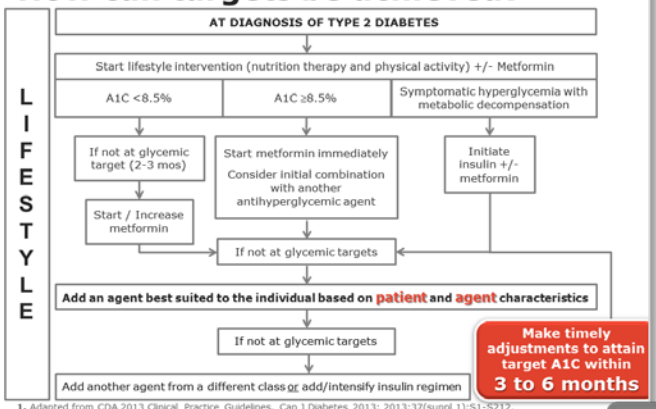
- Limited lifetime expectancy
- High level of functional dependency
- Extensive vascular disease
- Multiple co-morbidities
- Recurrent severe hypoglycemia
- Hypoglycemia unawareness
- Long standing diabetes for whom it is difficult to achieve A1C ≤7.0%*

*Effective doses of multiple antihyperglycemic agents including intensified basal-bolus insulin therapy have been tried.

Adapted from: **1.** CDA 2013 Clinical Practice Guidelines. Can J Diabetes 2013; 2013;37(suppl 1):S1-S212.

1

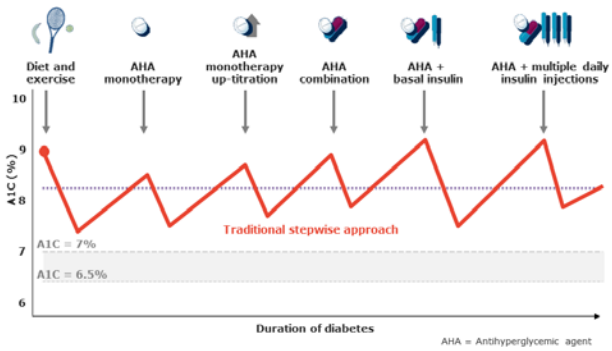
How can targets be achieved?



1. Adapted from CDA 2013 Clinical Practice Guidelines. Can J Diabetes 2013; 2013;37(suppl 1):S1-S212.

2

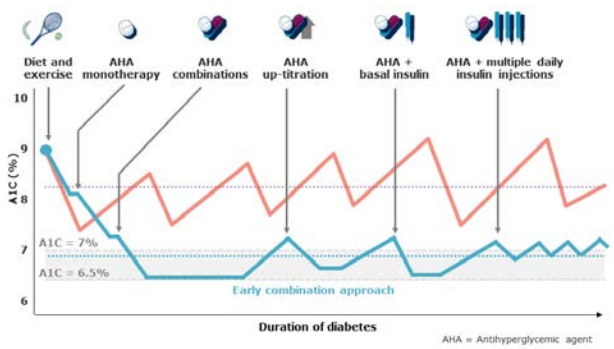
Glycemic control deteriorates over time, despite treatment



Adapted from: **1.** Del Prato S. Int J Clin Pract 2005;59:1345-1355.

3

Proactive management can help achieve targets earlier



Adapted from: **1.** Del Prato S. Int J Clin Pract 2005;59:1345-1355.

4

Benefits of early, aggressive A1C reduction

Relative risk reduction*

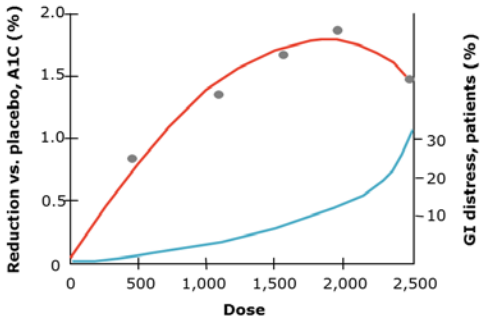
- 9% Any diabetes-related endpoint
- 13% All-cause mortality
- 15% Myocardial infarction
- 24% Microvascular disease

*At the end of post-trial follow-up (median 8.5 years). Significant reduction on intensive therapy vs. conventional therapy.

1. Holman et al. NEJM. 2008;359:1577-89.

5

Metformin dose-response curve



Metformin dose-response curve showing A1C reductions and GI-related effects according to dose.

1. Riddle M. Am J Med 2000; 108(6A):15S-22S.

6

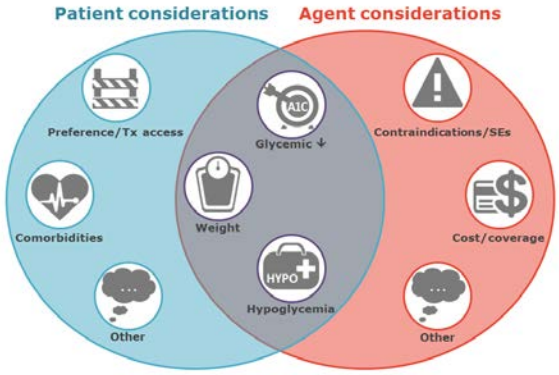
CDA 2013 guidelines: Combination therapy

The initial use of combinations of submaximal doses of antihyperglycemic agents produces more rapid and improved glycemic control and fewer side effects compared to monotherapy at maximal doses. Furthermore, many patients on monotherapy with the late addition of another antihyperglycemic agent may not readily attain target BG levels.

1. CDA 2013 Clinical Practice Guidelines. Can J Diabetes 2013;37(suppl 1):S1-S212.

7

Key considerations for selecting a second-line therapy



1. CDA 2013 Clinical Practice Guidelines. Can J Diabetes 2013; 2013;37(suppl 1):S1-S212.

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How do available agents address patient and agent characteristics?

	Relative A1C lowering	Change in body weight	Overall risk of hypoglycemia	Cost
Alpha glucosidase inhibitor (acarbose)	↓	Neutral to ↓	Rare	$$
DPP-4 inhibitors	↓↓	Neutral to ↓	Rare	$$$
GLP-1 receptor agonists	↓↓ to ↓↓↓	↓↓	Rare	$$$$
Insulin	↓↓↓	↑↑	Yes	$-$$$$
Meglitinides	↓↓	↑	Yes	$$
Sulfonylureas	↓↓	↑	Yes	$
TZDs	↓↓	↑↑	Rare	$$
Weight loss agent (orlistat)	↓	↓	None	$$$

SGLT2 inhibitors are now available, but are currently not in the guidelines.

Second-line therapies are covered by most private plans

DPP-4=dipeptidyl peptidase-4; GLP-1=glucagon-like peptide 1; SGLT2=sodium glucose cotransporter 2;TZDs=thiazolidinediones
1. Adapted from CDA 2013 Clinical Practice Guidelines. Can J Diabetes 2013; 2013:37(suppl 1):S1-S212.

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Approved indications for DDP-4 inhibitors and DPP-4 inhibitors/metformin FDC

	Mono-therapy	Add-on to AHA					Combination with insulin
		MET	MET + SU	SU	PIO	PIO + MET	
Linagliptin (TRAJENTA®) (5 mg QD)	✓	✓	✓	✓			Not indicated
Linagliptin/MET (JENTADUETO™) (2.5 mg/500 mg, 2.5 mg/850 mg & 2.5 mg/1000 mg BID)	✓			✓			Not indicated
Saxagliptin (ONGLYZA®) (2.5 mg & 5 mg QD)		✓	✓	✓			Basal or premix ± MET
Saxagliptin/MET (KOMBOGLYZE™) (2.5mg/500mg, 2.5mg/850mg & 2.5mg/1000mg BID)	✓			✓			Basal or premix
Sitagliptin (JANUVIA®) (20 mg, 50 mg & 100 mg QD)	✓	✓	✓		✓	✓	Basal or premix ± MET
Sitagliptin/MET (JANUMET®; JANUMET® XR) (50 mg/500 mg, 50 mg/850 mg & 50 mg/1000 mg BID; 50 mg/500 mg, 50 mg/1000 mg & 100 mg/1000 mg QD)	✓			✓	✓		Basal or premix

AHA=antihyperglycemic agents; FDC=fixed-dose combination; MET=Metformin; PIO=pioglitazone; SU=sulfonylurea.
1. Saxagliptin Product Monograph, Bristol Myers Squibb/Astra Zeneca, 2013. **2.** Sitagliptin Product Monograph, Merck Frosst, 2013. **3.** Linagliptin Product Monograph, Boehringer Ingelheim (canada) Ltd., 2014.

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Approved indications for GLP-1 receptor agonists

	Mono-therapy	Add-on to AHA					Combination with insulin
		MET	MET + SU	SU	PIO	PIO + MET	
Exenatide (BYETTA®) (5 µg & 10 µg BID)		✓	✓	✓			Glargine ± MET
Liraglutide (VICTOZA®) (1.2 mg & 1.8 mg QD)		✓	✓				Basal + MET

AHA=antihyperglycemic agnets; MET=Metformin; PIO=pioglitazone; SU=sulfonylurea.
1. Liraglutide Product Monograph, Novo Nordisk Canada, 2014. **2.** Exenatide Product Monograph, Bristol Myers Squibb, 2013.

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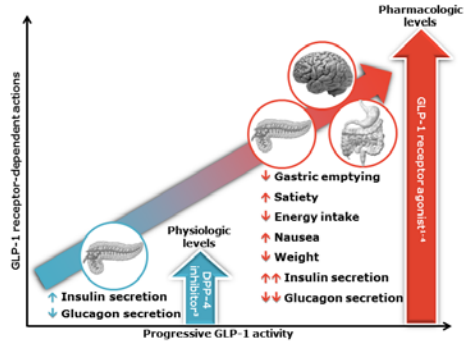
Incretin therapies reduce A1C by impacting GLP-1 levels differently



1. Wajchenberg BL. Endocr Rev. 2007;28(2):187-218. **2.** Drucker DJ. Diabetes Care. 2003;26(10):2929-2940. **3.** Baggio LL, Drucker DJ. Gastroenterology. 2007;132(6):2131-2157. **4.** Drucker DJ, Nauck MA. Lancet. 2006;368(9548):1696-1705. **5.** Kendall DM, et al. Am J Med. 2009;122(6 Suppl):S37-S50.

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Summary of incretin-based therapies

DPP-4 inhibitors
- GLP-1 in physiological range
- Limited by endogenous secretion of GLP-1
- Relative A1C lowering: ↓↓
- No weight change
- Well tolerated
- Oral
- Low risk of hypoglycemia

GLP-1 receptor agonists
- Pharmacological levels of GLP-1
- Not limited by endogenous secretion of GLP-1
- Relative A1C lowering: ↓↓ to ↓↓↓
- Weight loss
- GI side effects
- Injection
- Low risk of hypoglycemia

DPP-4=dipeptidyl peptidase-4; GI=gastrointestinal; GLP-1=glucagon-like peptide.

1. CDA 2013 Clinical Practice Guidelines. Can J Diabetes 2013; 2013;37(suppl 1):S1-S212.

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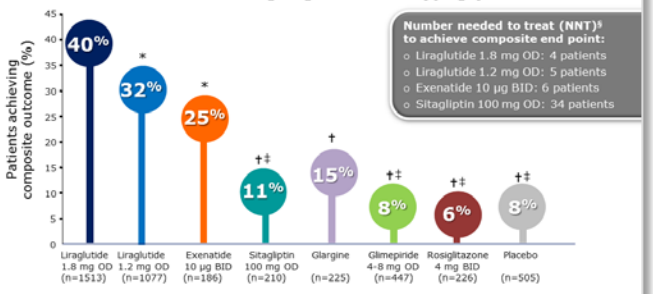
Incretin therapies can help achieve the composite goal

Composite outcome:

A1C <7.0% + NO weight gain + NO hypoglycemia



Number needed to treat (NNT)§ to achieve composite end point:
- Liraglutide 1.8 mg OD: 4 patients
- Liraglutide 1.2 mg OD: 5 patients
- Exenatide 10 µg BID: 6 patients
- Sitagliptin 100 mg OD: 34 patients

*p<0.001 vs. liraglutide 1.8 mg; †p<0.0001 vs. liraglutide 1.8 mg; ‡p<0.0001 vs. liraglutide 1.2 mg.
§NNT: calculated as 1 divided by absolute risk reduction.

1. Zinman B et al. *Diabetes, Obesity and Metabolism* 2012;14:77–82.

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A significant proportion of Canadians with type 2 diabetes are just above target A1C

Proportion of Canadians with:*

A1C ≤7% **50%**

A1C 7% to ≤9% **41%**

A1C >9% **9%**

Can incretin therapies help these patients reach target A1C?

*≤7.0% was the goal set by physicians for 81% of patients.
DM-SCAN survey of 5103 Canadians with type 2 diabetes in November 2012.

1. Leiter et al. Can J Diabetes. 2013;37:82-89.

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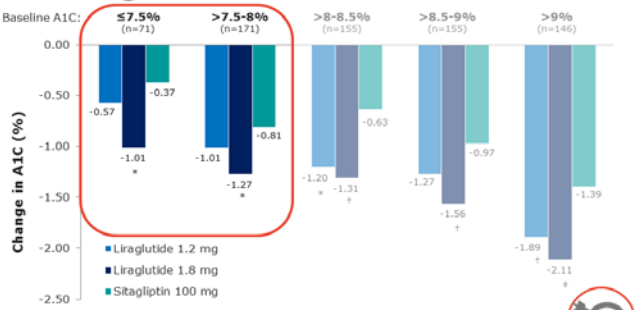
Regardless of baseline A1C, incretin therapies can provide effective A1C lowering



*p<0.05 vs. sitagliptin, †P≤0.01 vs. sitagliptin, ‡p≤0.001 vs. sitagliptin
As of February 2014, no sub-analyses by baseline A1C are available to our knowledge for exenatide or saxagliptin added to metformin

1. Pratley R et al. Int J Clin Pract 2011;65(4):397-407.

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Incretin therapies minimize weight gain and hypoglycemia risk

DPP-4 INHIBITORS			GLP-1 RECEPTOR AGONISTS	
Linagliptin[1,2] (5 mg QD)	Saxagliptin[3,4] (5 mg QD)	Sitagliptin[5,6] (100 mg QD)	Exenatide[7,8] (5 µg & 10 µg BID)	Liraglutide[9-11] (1.2 mg & 1.8 mg QD)

Mean change in weight from baseline with MET combination therapy

NO significant change | NO significant change | NO significant change | -1.3 kg to -2.6 kg | -2.6 kg to -3.4 kg

Weight neutral | Weight loss

Low risk of hypoglycemia

Significant difference in weight loss and hypoglycemia between GLP-1 receptor agonists has not been demonstrated.
MET=metfromin.

1. Linagliptin Product Monograph, Boehringer Ingelheim (Canada) Ltd. 2014. 2. Taskinen M-R et al. Diabetes, Obes, Metab 2011;13:65-74. 3. Saxagliptin Product Monograph, Bristol Myers Squibb/Astra Zeneca, 2013. 4. DeFronzo R et al. Diabetes Care 2009;32:1649-55. 5. Sitagliptin Product Monograph, Merck Frosst, 2013. 6. Charbonnel B et al. Diabetes Care 2006;29:2638-43. 7. Exenatide Product Monograph, Bristol Myers Squibb 2013. 8. DeFronzo R et al. Diabetes Care 2005;28(5):1092-100. 9. Liraglutide Canadian Product Monograph, Novo Nordisk Canada, 2013. 10. Nauck M et al. Diabetes Care 2009;32:84-90. 11. Pratley RE et al. Lancet 2010;375:1447-56.

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Potential role of incretin therapy in the treatment type 2 diabetes

Add incretin therapy to....

Diet and exercise → MET → MET + AHA(s) → MET + AHA(s) + insulin

Why consider adding an incretin agent **AFTER** metformin?[1]

Help achieve... A1C + + HYPO

A1C <7.0% | NO weight gain | NO hypoglycemia

AHA=antihyperglycemic agent; MET=metformin.

1. Saxagliptin Product Monograph, Bristol Myers Squibb/Astra Zeneca, 2013. 2. Sitagliptin Product Monograph, Merck Frosst, 2013. 3. Linagliptin Product Monograph, Boehringer Ingelheim (canada) Ltd., 2014. 4. Liraglutide Product Monograph, Novo Nordisk Canada, 2014. 5. Exenatide Product Monograph, Bristol Myers Squibb, 2013. 6. CDA 2013 Clinical Practice Guidelines. Can J Diabetes 2013; 2013;37(suppl 1):S1-S212.

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Top clinical tips for initiating injectable therapies

1. Start with an open discussion
2. Show the pen and needle size
3. Demonstrate how to use the pen
4. Have patients do their first injection

Identify and utilize available **community resources** to assist and support you in the management of your patient.

Adapted from: 1. Ross SA. Am J Med. 2013 Sep;126(9 Suppl 1):S38-48 2. Davies et al. Diabet Med 2011;28;333–37.

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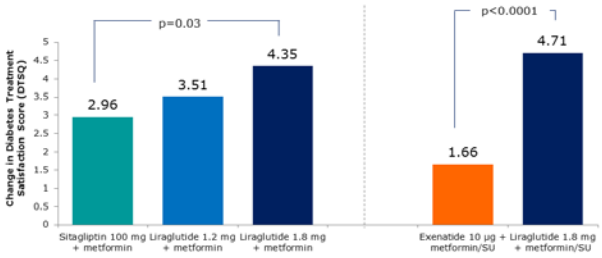
Patient treatment satisfaction is not reduced by the injectable format

Mean change in treatment satisfaction from baseline at 26 weeks[1,2]



Improved treatment satisfaction with injectable incretin therapies is driven by effect on glycemic control and body weight.

1. Davies et al. Diabet Med 2011;28;333–37. 2. Schmidt WE et al. Diabet Med 2011;28(6):715-23.

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The truth about nausea with GLP-1 receptor agonists

Risk of mild to moderate, transient nausea

Most common adverse event reported with GLP-1 receptor agonists

- *Nausea with GLP-1 receptor agonists was mild to moderate and transient in nature (less persistent with liraglutide vs. exenatide)*
- *Initiating liraglutide at 0.6 mg and exenatide at 5 µg may help reduce the incidence of nausea during initial titration*

TIPS TO COMBAT NAUSEA:
- ✓ Eat slower and more frequent, smaller amounts
- ✓ Avoid spicy and fatty foods
- ✓ Keep well hydrated

1. Liraglutide Product Monograph, Novo Nordisk Canada Inc., 2014. 2. Exenatide Product Monograph, Eli Lilly Canada, 2011. 3. Buse JB, et al. Lancet. 2009;374:39-47.

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Safety considerations when selecting an incretin therapy

Risk of pancreatitis

Not recommended in patients with history of pancreatitis

- *Incretin agents have been associated with isolated cases of pancreatitis in trials and post-marketing reports (causal relationship not established)*

2014 UPDATE
FDA/EMA did not find evidence to support an increased overall risk in independent analyses

Risk of c-cell carcinoma

GLP-1RA not recommended in patients with personal or familial history of medullary thyroid cancer/MEN2

- *Increased risk of medullary thyroid cancer or C-cell adenomas suggested in rodents (no evidence in humans)*

1. Garg R et al. Diabetes Care 2010;33:2359-54. 2. Liraglutide Product Monograph, Novo Nordisk Canada Inc., 2014. 3. Linagliptin Product Monograph, Boehringher Ingelheim (Canada) Ltd., 2014. 4. Egan AG, et al. N Engl J Med 2014;370:794-7. DOI: 10.1056/NEJMp1314078. 5. Bjerre Knudsen et al. Endocrinology 2010; DOI: 10.1210/en.2009-1272. 6. Exenatide Product Monograph, Eli Lilly Canada, 2011. 7. Hegedus L et al. J Clin Endocrinol Metab 2011;96(3):853-60.

22

Low infection risk with DPP-4 inhibitors

Low risk of infection

Most common adverse event reported with DPP-4 inhibitors

- *Reported infection rates with DPP-4 inhibitors were low and occurred at similar rates to each other**

*Indirect comparison based on individual product monographs.

1. Sitagliptin Product Monograph, Merck Frosst Canada Ltd., 2013. 2. Saxagliptin Product Monograph, Bristol Myers Squibb, Astra Zeneca, 2013. 3. Linagliptin Product Monograph, Boehringher Ingelheim (Canada) Ltd, 2014.

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CV outcomes of incretin therapies are being assessed in ongoing trials

	Risk Factors	Stable CAD-CVD-PAD	ACS Patients	Results
SAVOR-Timi-Saxagliptin	✓	✓		Available
TECOS-Sitagliptin		✓		Dec 2014
EXAMINE-Alogliptin*		✓	✓	Available
CAROLINA-Linagliptin	✓	✓		Sep 2018
CARMELINA-Linagliptin	✓	✓		Jan 2018
LEADER-Liraglutide	✓	✓		Oct 2015
EXSCEL-Exenatide LAR	✓	✓		Apr 2018

For the most part, available results have been neutral (no increased CV risk vs. placebo); though, further investigation is warranted
- ***SAVOR: ↑ rate of hospitalization for heart failure (p<0.007 vs. placebo)***

*Not an approved therapy in Canada.

1. Adapted from clinicaltrials.gov.ca May 2014. 2. Scirica BM et al N Engl J Med 2013;369:1317-1326.. 3. White WB et al. N Engl J Med 2013;369:1327-1335.

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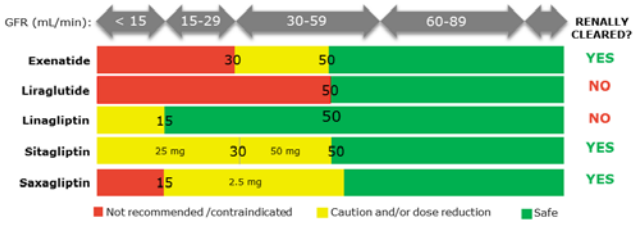
Consider renal function when selecting an incretin therapy



Adapted from: **1.** Product Monographs as of March 1, 2013. **2.** CDA 2013 Clinical Practice Guidelines. Can J Diabetes 2013;37(suppl 1):S1-S212. **3.** Yale JF, J Am Soc Nephrol 2005; 16:S7-S10.

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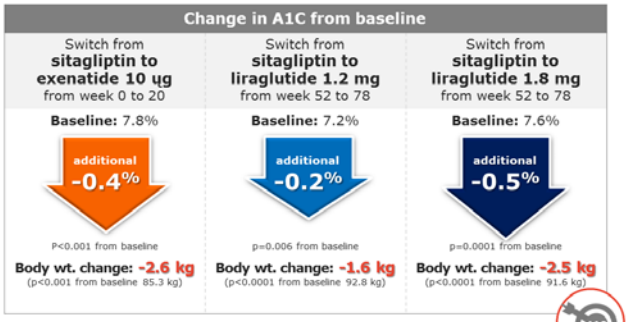
Switching from DPP-4 inhibitor to a GLP-1 receptor agonist may provide additional A1C reduction



A1C and body weight reductions were maintained for patients who continued on liraglutide 1.2 mg and liraglutide 1.8 mg through 78 weeks.

1. Violante R et al, Diabet Med 2012;29:e417–e424. **2.** Pratley RE et al, Diabetes Care 2012;35(10):1986-93.

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