Very Practical Tips for Managing Type 2 Diabetes

Jean-François Yale, MD, FRCPC
McGill University Health Centre, Montreal, Canada
Jean-francois.yale@mcgill.ca www.dryale.ca

OBJECTIVES

The participant will be able to:

- **Apply various strategies to reduce the impact of cost when considering antihyperglycemic strategies**
- **Adjust antihyperglycemic therapies to eGFR**
- **Decrease antihyperglycemic medications in elderly with type 2 diabetes when appropriate**

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DISCLOSURES

- **Advisory Boards**
  Sanofi, Merck, Eli Lilly, Boehringer-Ingelheim, Bayer, Novo-Nordisk, Astra Zeneca, Janssen, Takeda, Abbott
- **Lectures**
  Sanofi, Merck, Eli Lilly, Boehringer-Ingelheim, Bayer, Novo-Nordisk, Astra Zeneca, Janssen, Takeda, Abbott, Medtronic
- **Research Funds**
  Sanofi, Merck, Eli Lilly, Boehringer-Ingelheim, Mylan, Medtronic, Janssen, Astra Zeneca, Bayer

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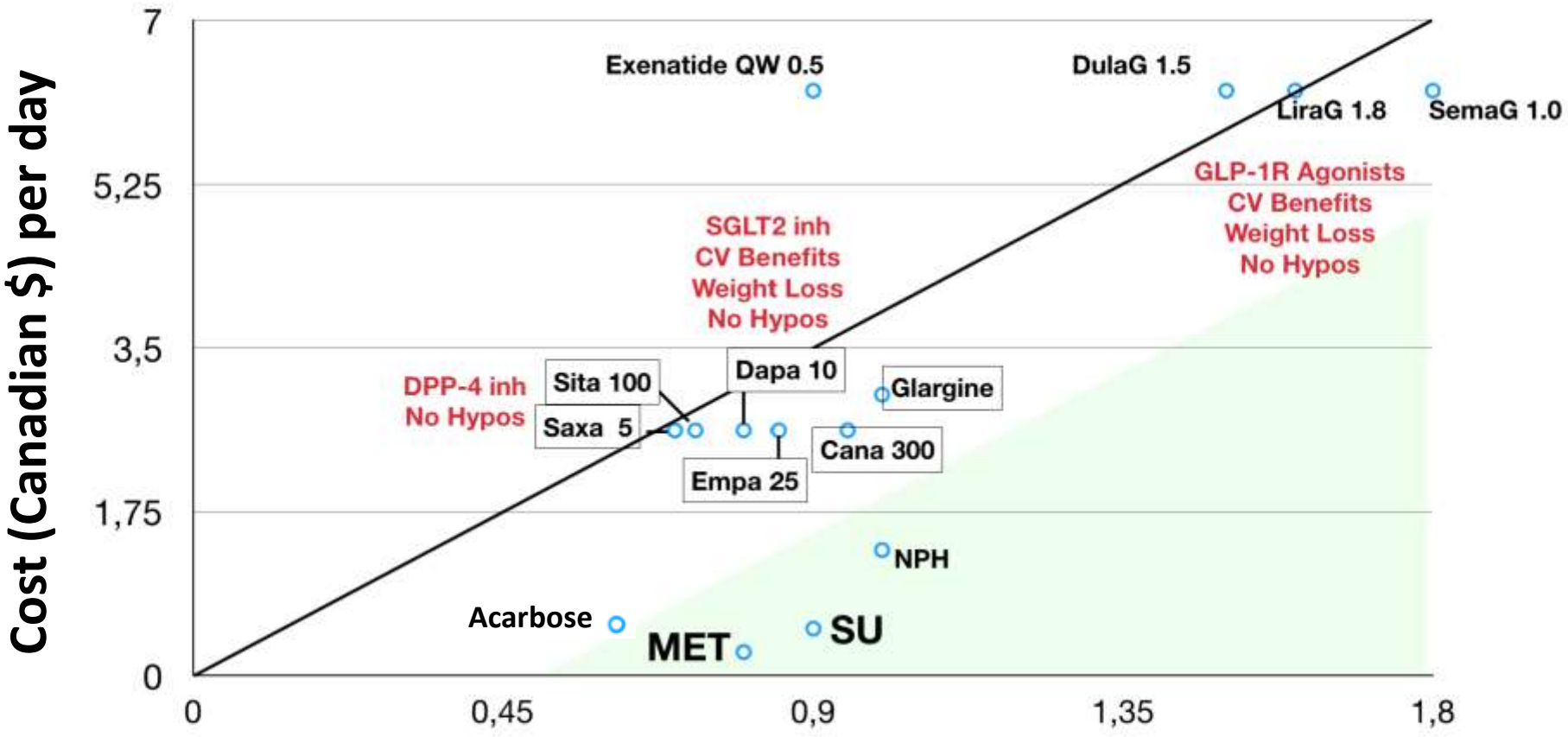
Cost of Antihyperglycemic Therapy by A1c Reduction



Antihyperglycemic Coverage by RAMQ

Class	Medication	$/day at max dose	MONO if SU and MET NT or CI	+ MET if SU CI,NT or INEFF	+ SU if Met CI, NT or INEFF	IF CVD + A1c>7	+ MET if DPP4i INEFF, NT or CI and BMI > 30 and high A1c	If other SU NT or INEFF
Biguanides	Metformin (Glucophage)	0.18						
α-Glucosidase Inhibitors	Acarbose (Glucobay)	1.03						
DPP-4 Inhibitors	Alogliptin (Nesina)	2.10	EN167	EN148 (EN150 Kazano)	EN149			
	Linagliptin (Trajenta)	2.25	EN167	EN148 (EN150Jentaduetto)				
	Saxagliptin (Onglyza)	2.30		EN148 (EN150 Komboglyze)	EN149			
	Sitagliptin (Januvia)	2.62	EN167	EN148 (EN150 Janumet et XR)				
SGLT2 Inhibitors	Canagliflozin (Invokana)	2.62	EN167	EN148	EN149			
	Dapagliflozin (Forxiga)	2.45		EN148 (EN199 Xigduo)	EN149			
	Empagliflozin (Jardiance)	2.62	EN167	EN148 (EN199 Synjardy)		EN179		
GLP-1R Agonists	Liraglutide (Victoza)	6.85					Form	
	Exenatide (Byetta)	2.49						
	Exenatide QW (Bydureon)	6.85						
	Dulaglutide (Trulicity)	6.85					Form	
	Semaglutide (Ozempic)	6.85						
Thiazolidine-diones	Pioglitazone (Actos)	1.05	EN121	EN118	EN119			
	Rosiglitazone (Avandia)	2.87	EN121	EN118 (EN81 Avandamet)	EN119			
Insulin Secretagogues	Gliclazide (Diamicron)	0.50						
	Glimepiride (Amaryl)	0.77						EN23
	Glyburide (Diabeta)	0.23						
	Repaglinide (GlucoNorm)	0.84						

Green = on general list: no code or form required **Orange** = Médicament d'exception: code or form required

NT=Not tolerated **INEFF**=Inefficacious **CI**=Contraindicated **SU**=Sulfonylurea **MET**=Metformin **Mono**=Monotherapy **Form**=Médicament d'exception form required

EN199 requires 3 month stability of each component x 3 months

JF Yale october 2018

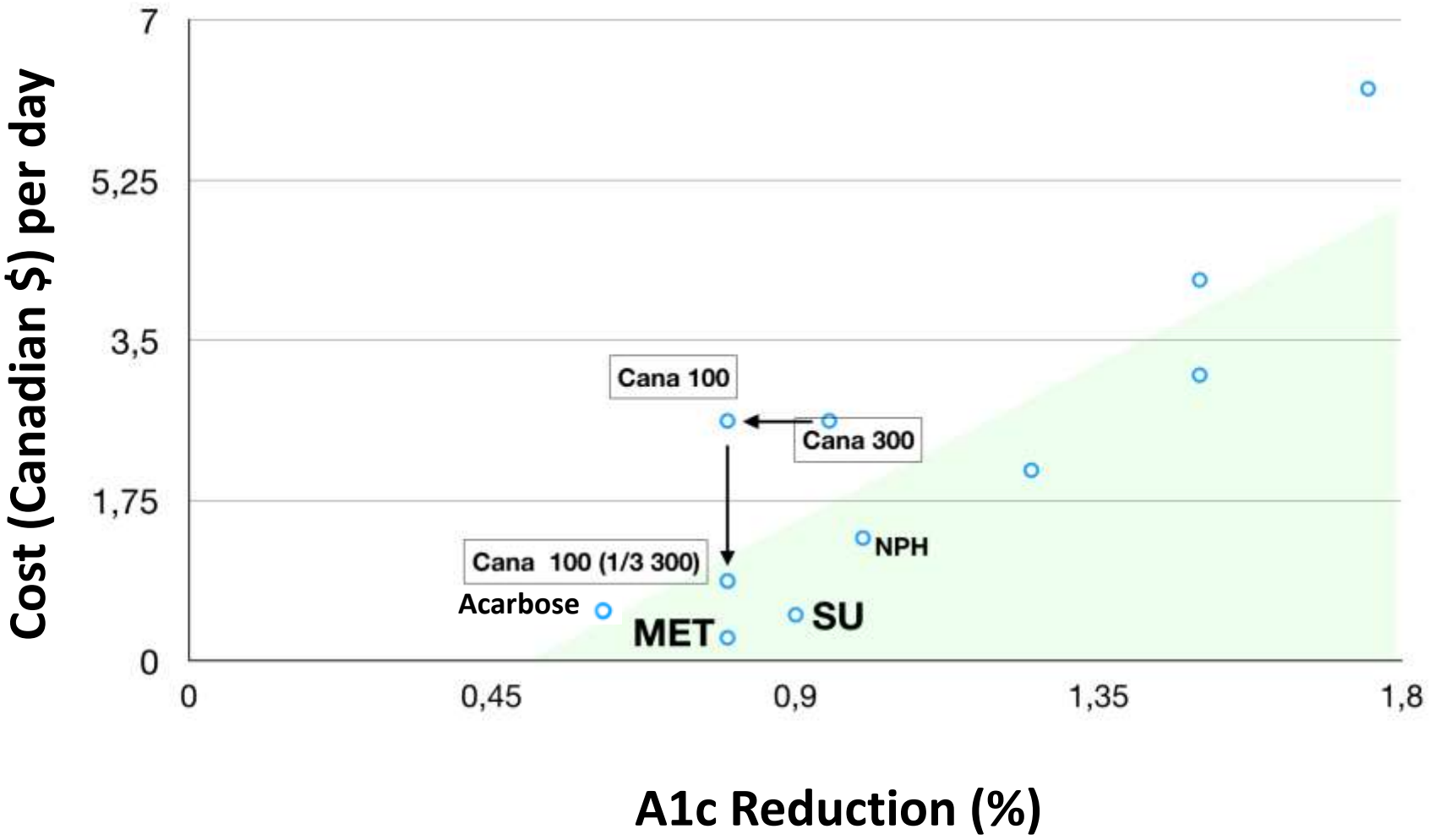
What is the price structure of your medication ?

FLAT **Example: Canagliflozin 300 mg = $2.62 per day**
Canagliflozin 100 mg = $2.62 per day

Cutting the 300 mg pill in 3 pieces will bring the cost down to $0.87 per day

$640 savings per patient per year

Cost of Antihyperglycemic Therapy by A1c Reduction

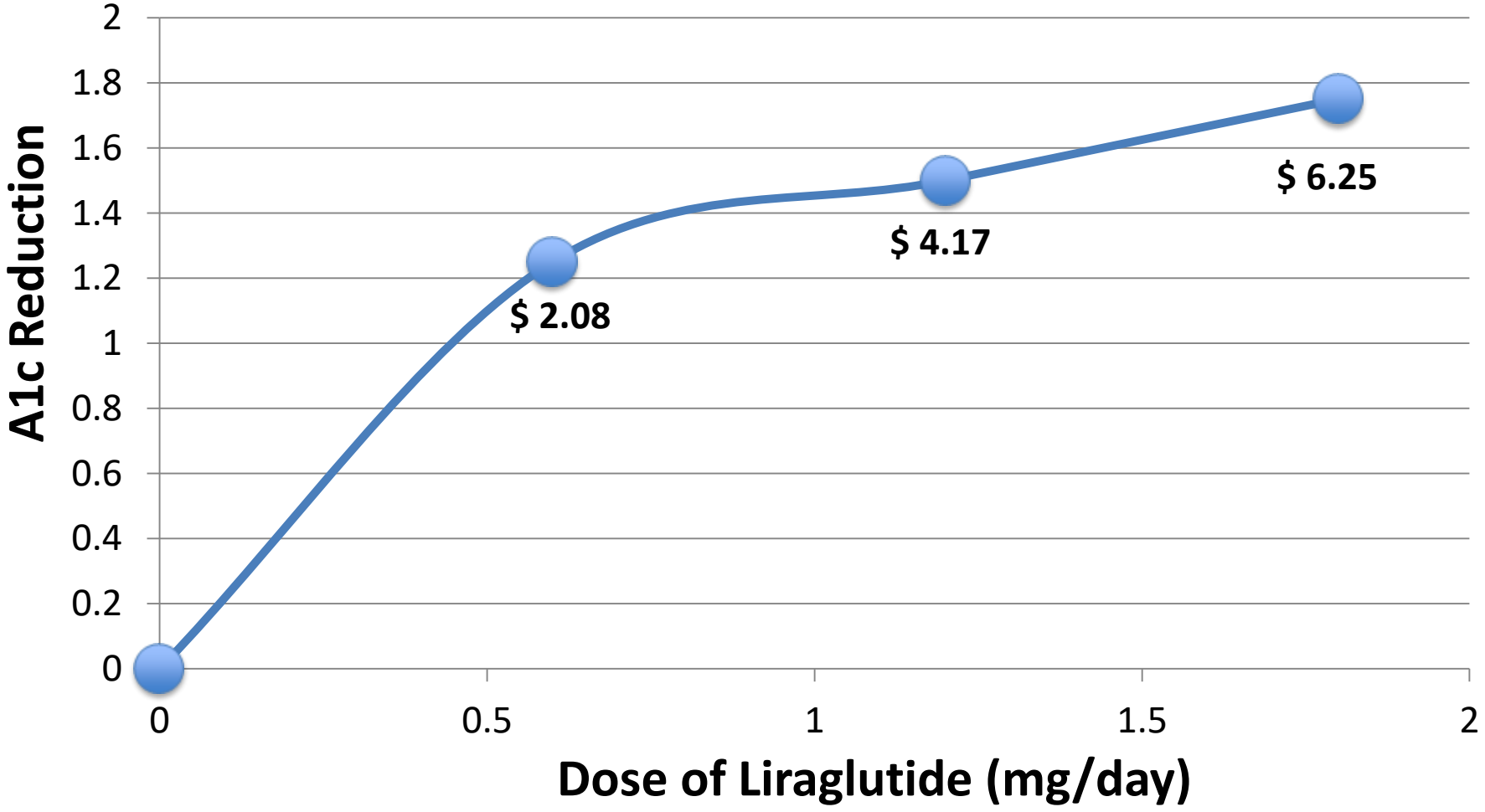


What is the price structure of your medication ?

LINEAR **Example: Liraglutide**

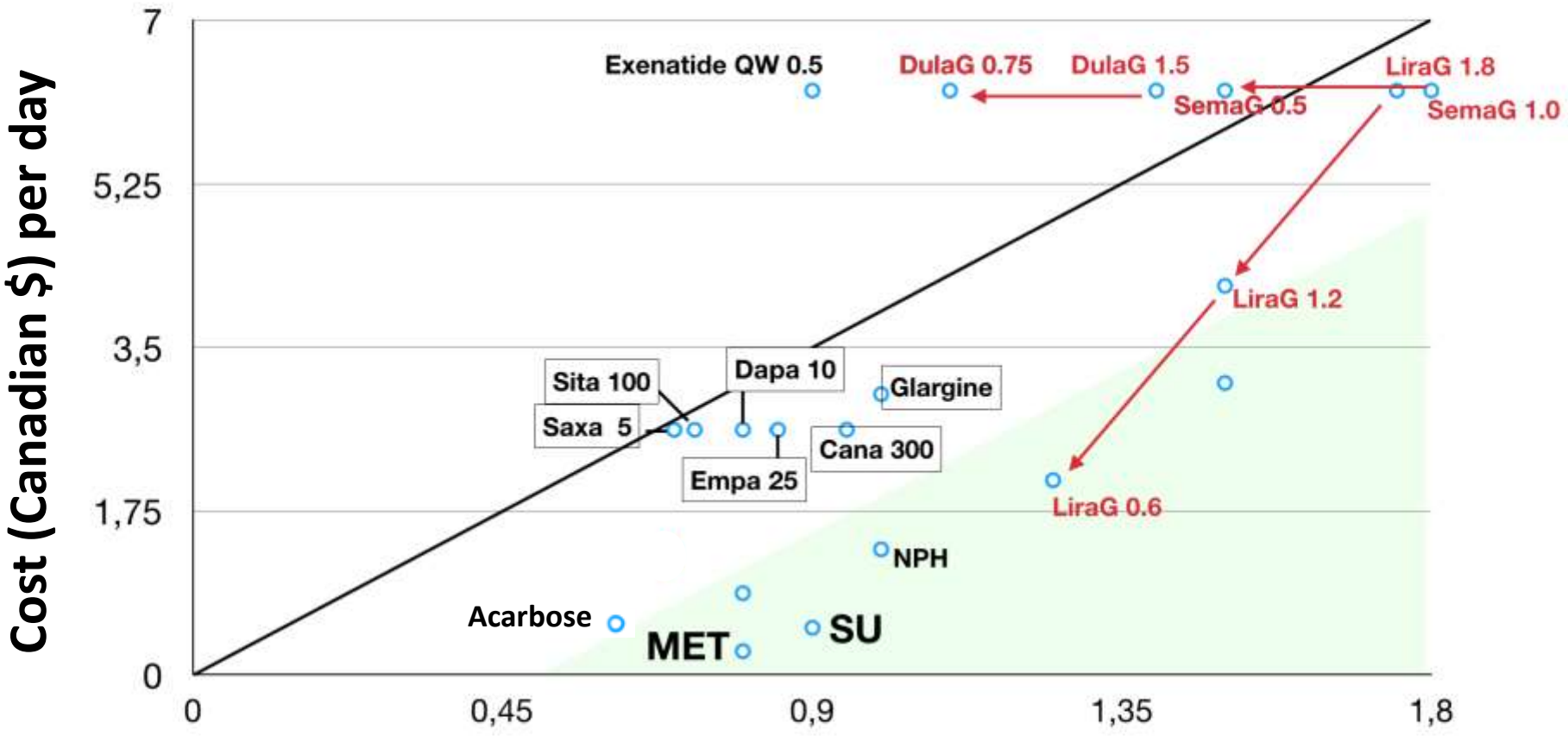
1.8 mg = $ 6.25
1.2 mg = $ 4.17
0.6 mg = $ 2.08

Dose Response of A1c with Liraglutide



Ingwersen SH et al. Diabetes Research and Clinical Practice 108:113-119, 2015

Cost of Antihyperglycemic Therapy by A1c Reduction



Semaglutide Pens

0.25/0.5 mg pen

0.5 mg per week = 6.50 CAD per day
2mg pen = 187.50$

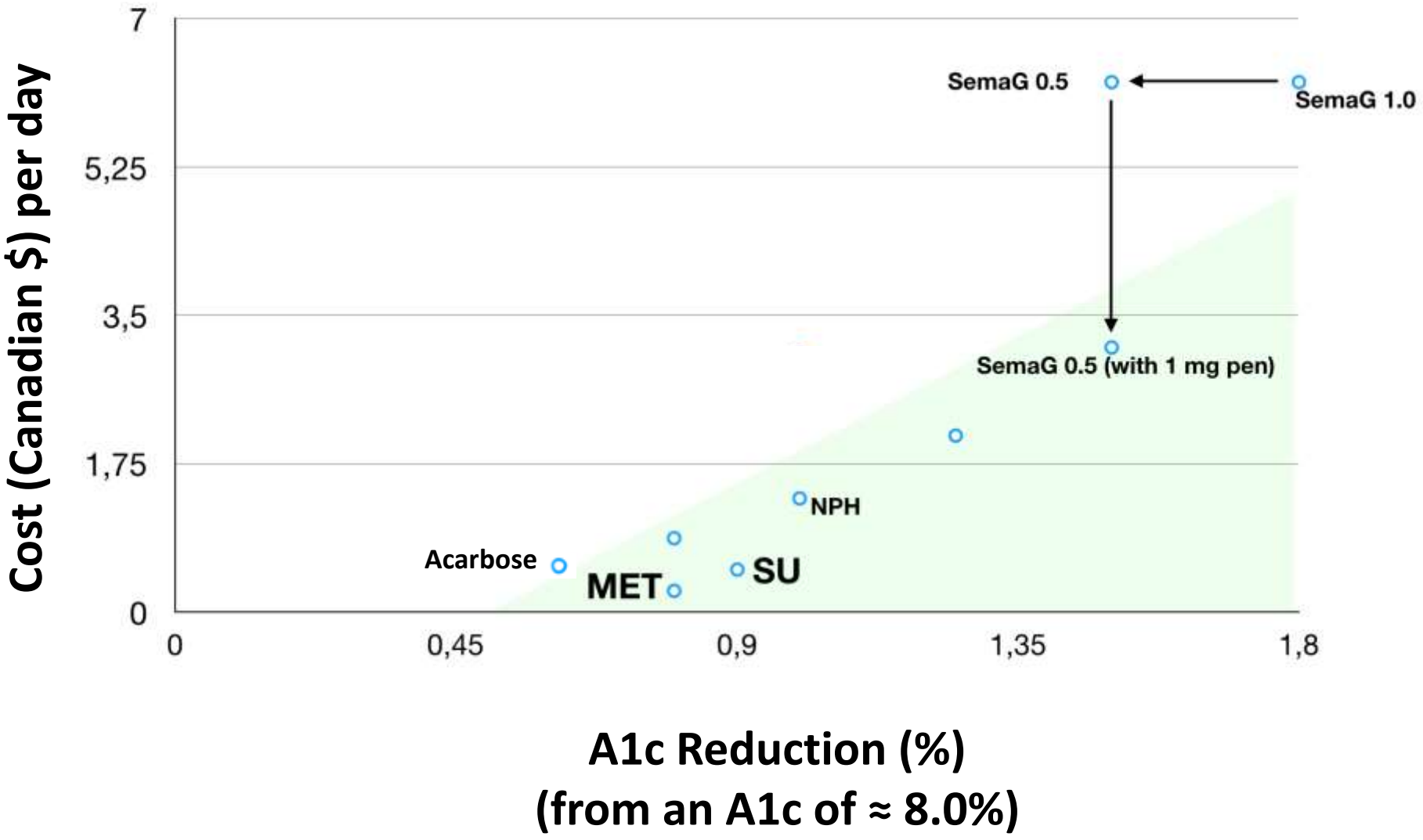
$1200 savings
per patient per year

1.0 mg pen

1.0 mg per week = 6.50 CAD per day
2 x 2 mg pen = 187.50$
2 mg pen = 93.75$

Using this pen to give 0.5 mg per week
brings the cost down to 3.25 per day
But you have to count the clicks… 36 clicks

Cost of Antihyperglycemic Therapy by A1c Reduction



Example of Cost-Driven Strategies

Classical Approach 1:	Cost per day
Metformin 1000 mg BID	$0,18
Gliclazide MR 120 mg OD	$0.50
Monitoring 1 strip a day	$0.70
TOTAL:	**$1.38**

Classic Approach 2:	**Cost per day**
Metformin 1000 mg BID	$0.18
Sitagliptin 100 mg OD	$2.62
No strips	
TOTAL:	**$2.80**

SGLT2 Approach 1	Cost per day
Metformin 1000 mg BID	$0.18
Canagliflozin 100 mg OD	$2.62
No strips	
TOTAL:	**$2.80**

SGLT2 Approach 2:	Cost per day
Metformin 1000 mg BID	$0.18
Canagliflozin 100 mg OD (as 1/3 of Cana 300 at 2.62$)	$0.87
No strips	
TOTAL:	**$1.05**

Even less expensive than sulfonylureas !

Example of Cost-Driven Strategies

Classical Approach:	Expected A1C Drop	Cost per day ($ CAD)
Metformin 1000 mg BID	-0.80	0.18
Gliclazide MR 120 mg OD	-0.90	0.50
Sitagliptin 100 mg OD	-0.70	2.62
Monitoring 1 strip a day		0.70
TOTAL:		**4.00**

Cost-Driven Strategy:

Metformin 1000 mg BID	-0.80	0.18
Empagliflozin 1/2 of 25 mg OD	-0.80	1.31
Liraglutide 0.6 mg SC OD	-1.25	2.08
No test strips		
TOTAL:		**3.57**

+ CV Protection + No risk of hypoglycemia + 2-5 Kg weight loss

Conclusions

1. Newer, more-expensive drugs, bring unique advantages over conventional drugs: absence of hypoglycemia, weight loss, and cardiovascular and renal benefits.

2. Simple strategies exist that allow reducing substantially the cost of these newer therapies

Antihyperglycemic Agents and Renal Failure

Yale JF, version May 2018
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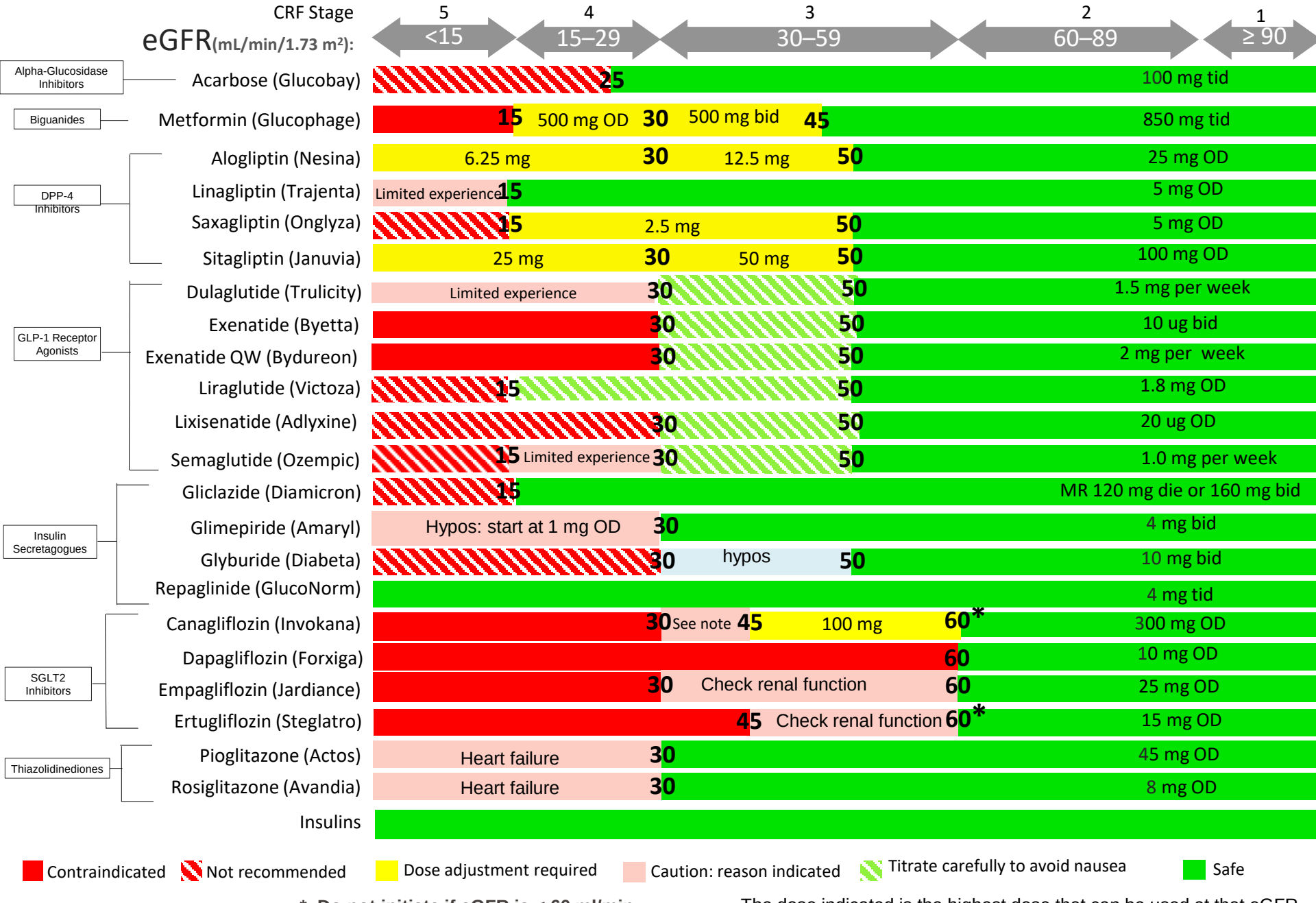


*=Do not initiate if eGFR is < 60 ml/min

The dose indicated is the highest dose that can be used at that eGFR

Explanatory Notes for the Renal Failure and antihyperglycemic Agents Table

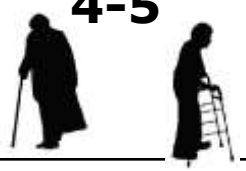
Medications for which the Recommendations in the Table Differ from the Product Monograph

Metformin	The Health Canada product monograph states « Contraindicated in presence of an eGFR < 60 ml/min. » The FDA revised its recommendations in 2016 to allow its use down to an eGFR of 30 ml/min. A recent study assessed the use of adjusted dosages down to eGFR of 15 ml/min. The recommendations in this table are based on that study. With these dosages, the circulating levels of metformin are similar to those of usual dosages with normal renal function. (Lalau JD et al. Diabetes Care 2018; 41: 547-553).
Glyburide	The Canadian product monograph states: «In patients with renal insufficiency, the initial dosing, dose increments, and maintenance dosage should be conservative to avoid hypoglycemic reactions. ». In fact, glyburide is metabolized by the liver into ACTIVE metabolites that are then excreted by the kidneys. There is therefore a risk of accumulation. Glyburide causes many hospitalisations for hypoglycemia, and should be used with caution at eGFR between 30 and 50 ml/min, and should probably be avoided with eGFR under 30 ml/min considering the available alternatives..
Canagliflozin	The Canadian product monograph states: « Contraindication: Renally impaired patients with eGFR less than 45 mL/min/1.73 m2, end-stage renal disease or patients on dialysis. » However, the CANVAS program demonstrated renal benefits in patients with an eGFR above 30 ml/min. Consequently, in patient with cardiovascular disease and an A1c above target, canagliflozin can be used safely above 30 ml/min according to Diabetes Canada guidelines. Since there have been cases of hyperkalemia with the 300 mg dose in patients with an eGFR between 30 and 60 ml/min, it is recommend to restrict the dosing to 100 mg at these eGFR values.
Pioglitazone	The Canadian product monograph states: : « No dose adjustment in patients with renal dysfunction is recommended. ». This is because the circulating levels of pioglitazone are not affected by renal function. However, pioglitazone tends to increase fluid retention and edema. In patients with renal failure, this led to more cases of heart failure and extreme caution is therefore recommended if used with an eGFR below 30 ml/min.

Comments Specific to Some Antihyperglycemic Classes

SGLT2 Inhibitors	Because their action requires glomerular filtration of glucose, the antihyperglycemic efficacy of SGLT2 inhibitors decreases with eGFR. Under 60 ml/min, the effect on glycemia and weight (but not blood pressure) is half of what can be seen at higher eGFR. However, the EMPAREG trial revealed impressive cardiovascular and renal benefits, equivalent at doses of 10 and 25, and equivalent whether the eGFR was between 30 and 60 ml/min or greater than 60 ml/min. On that basis, Health Canada now allows the use of empagliflozin at eGFR above 30 ml/min. During the first weeks of treatment, the eGFR can be expected to drop by 4-8 ml/min, followed by a stability over time, in contrast to the gradual decline seen in people with diabetes without empagliflozin. Albuminuria will decrease by half very rapidly.
GLP-1 Receptor Agonists	Some GLP-1 receptor agonists are excreted by the kidneys and can accumulate in case of renal failure (lixisenatide, exenatide and exenatide QW). The other GLP-1R agonists are not excreted through the kidneys and do not accumulate (liraglutide, dulaglutide, semaglutide). However, all these agents can cause nausea and/or vomiting, particularly at initiation. In presence of renal failure, dehydration resulting from vomiting could cause acute renal failure (pre-renal). In those circumstances, it is therefore important to titrate very slowly the dosages to avoid nausea.

Glycemic Targets in Older People with Diabetes

Status	Functionally independent	Functionally dependent	Frail and/or with dementia	End of Life
Clinical Frailty Index	1-3 	4-5 	6-8 	9 
A1c Target *low risk of hypoglycemia* (i.e. therapy does not include insulin or SU)	≤ 7.0%	< 8.0%	< 8.5 %	A1c measurement not recommended. Avoid symptomatic hyperglycemia or any hypoglycemia
A1c Target higher risk of hypoglycemia (i.e. therapy includes insulin or SU)		7.1-8.0 %	7.1-8.5 %	
CBGM preprandial postprandial	4-7 mmol/L 5-10 mmol/L	5-8 mmol/L < 12 mmol/L	6-9 mmol/L < 14 mmol/L	Individualized

Diabetes Canada 2018 Clinical Practice Guidelines

Putting it all together

- Age and employment: 75 contract worker
- Insurance: RAMQ
- Type 2 diabetes x 5 years
  - Cardiovascular history: NO
  - Current medication:
    - Metformin/Sitagliptin 1000/50 bid
    - Gliclazide MR 120 die
    - Statin
    - Angiotensin receptor blocker
- Problems with his medication ? hypoglycemia

  - BMI: 36
  - Blood pressure: 138/88
  - A1c: 8.0%
  - eGFR: > 60 ml/min
  - LDL Cholesterol: 1.95

A1c Goal ?
Less than 7.0%

Avoid hypoglycemia:

Replace gliclazide by:
SGLT2 inhibitor
and/or
weekly GLP-1R agonist

A1c to expect
Stop gliclazide: +0.7
Add SGLT2i: -0.9
Add GLP-1R agonist: -1.4
Stop Sitagliptin : +0.7
Total: -0.9

BW change to expect:
Stop gliclazide: -2 Kg
Add SGLT2i: -3 Kg
Add GLP-1R agonist : -6 Kg
Total : -11 Kg

BP change to expect:
Add SGLT2i: -4
Add GLP-1R agonist: -2

Putting it all together

- Age and employment: 79 retired
- Insurance: RAMQ
- Type 2 diabetes x 25 years
  - Cardiovascular history: YES
  - Early cognitive problems, lives alone
  - Current medication:
    - Novolin NPH 38 units at bedtime
    - NovoRapid 10 units before each meal
- Problems with his medication ? hypoglycemia
  - BMI: 33
  - Blood pressure: 129/84
  - A1c: 8.2%
  - eGFR: 54

A1c Goal ?
7.1-8.0%

Avoid hypoglycemia:

Replace NPH by glargine
Reduce insulin dosages

Consider replacing
rapid-acting insulin
by other modalities

Add metformin 500 bid
Add a DPP-4 inhibitor
(step towards a GLP-1R agonist)

Stop the DPP-4i and
add a GLP-1R agonist

Consider adding a
low dose of SGLT2 inhibitor

Ultimate goal is to stop the
rapid-acting insulin,
and possibly the basal as well

Putting it all together

A1c Goal ?
7.1-8.5%

- Age and employment: 84 Long-term care
- Insurance: RAMQ
- Type 2 diabetes x 25 years
  - Cardiovascular history: YES
  - Current medication:
    - Metformin/Sitagliptin 500/50 bid
    - Gliclazide 60 mg die
- Problems with his medication ?
  hypoglycemia with variable glucose depending on food ingested at each meal
  - BMI: 21
  - Blood pressure: 138/88
  - A1c: 7.9%
  - eGFR: 46
  - LDL Cholesterol: 1.95

Avoid hypoglycemia:

Reduce Gliclazide, or replace with Repaglinide

Reduce sitagliptin to 50 mg per day, and possibly metformin if low appetite (from bid to die at supper)

Accept an increase in A1c in order to reduce hypoglycemia

Avoid drugs that would induce weight loss
SGLT2 inhibitor
(or use low dose)
GLP-1R agonist

Thank you !

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