

# Diabetes Canada Clinical Practice Guidelines 2018 Update

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# Presenter Disclosure

- ▶ *I have no current or past relationships with commercial entities.*
- ▶ *I have received no speaker's fee for this learning activity.*

# Commercial Support Disclosure

- ▶ *This learning activity has received no financial or in-kind support from any commercial or other organization.*

# Learning Objective

- ▶ To identify major changes within the **2018 Diabetes Canada Clinical Practice Guidelines**<sup>1</sup> pertinent to pharmacists working with adult patients with type 2 diabetes mellitus (T2DM).

# Presentation Outline

- ▶ **Targets for Glycemic Control**
  - ▶ A1c & Plasma Glucose Targets
  - ▶ Monitoring of Glycemic Control
- ▶ **Antihyperglycemic Therapy**
- ▶ **Pharmacotherapy for Cardiovascular Protection**
- ▶ **Additional Topics**
  - ▶ Weight Management
  - ▶ Sick Day Management
  - ▶ Hyperglycemic Emergencies in Adults
  - ▶ Pre-Diabetes
  - ▶ Complementary & Alternative Medicine
  - ▶ Diabetes & Driving
- ▶ **Online Tools for Practitioners**

# Topics Not Covered

- ▶ Chapter 10: Physical Activity & Diabetes
- ▶ Chapter 11: Nutrition Therapy
- ▶ Chapter 12: Glycemic Management of Type 1
- ▶ Chapter 16: In-Hospital Management
- ▶ Chapter 18: Diabetes & Mental Health
- ▶ Chapter 19: Influenza & Other Vaccinations
- ▶ Chapter 20: Diabetes & Transplantation
- ▶ Chapter 24: Screening for the Presence of CVD
- ▶ Chapter 27: Management of Acute Coronary Syndromes
- ▶ Chapter 28: Treatment of Diabetes in People with Heart Failure
- ▶ Chapter 30: Retinopathy
- ▶ Chapter 31: Neuropathy
- ▶ Chapter 32: Foot Care
- ▶ Chapter 33: Sexual Dysfunction & Hypogonadism
- ▶ Chapter 34: Type 1 in Children & Adolescents
- ▶ Chapter 35: Type 2 in Children & Adolescents
- ▶ Chapter 36: Pregnancy
- ▶ Chapter 38: Type 2 Diabetes in Indigenous People

# Targets for Glycemic Control

A1c & Plasma Glucose (PG)

# Targets for Glycemic Control

A1c Target	Patient Population
≤ 6.5 %	Adults with type 2 diabetes (T2DM) at low risk of hypoglycemia, to reduce the risk of chronic kidney disease (CKD) and retinopathy
≤ 7.0 %	Most adults with T2DM
7.1 → 8.5%	<p><b><u>7.1 - 8.0%</u></b> <b>Functionally dependent patients</b></p> <p><u>7.1 - 8.5%</u> <i>At-risk patients with:</i></p> <ul style="list-style-type: none"><li>• <i>Recurrent severe hypoglycemia and/or hypoglycemia unawareness</i></li><li>• <i>Limited life expectancy</i></li><li>• <i>Frail elderly and/or with dementia</i></li></ul> <p><i>[Grade D, Consensus]</i></p>
<p><b>End of life: A1C measurement not recommended. Avoid symptomatic hyperglycemia and any hypoglycemia. [Grade D, Consensus]</b></p>	



# Targets for Glycemic Control

Patient Population	A1c (%)	Preprandial PG (mmol/L)	2h Postprandial PG (mmol/L)
Most patients	$\leq 7.0$	4.0 - 7.0	5.0 - 10.0
If A1c $\leq 7.0$ % is not achieved despite achieving above targets		<b>4.0 - 5.5</b> <i>[Grade D, Level 4]</i>	<b>5.0 - 8.0</b>

# Monitoring of Glycemic Control

## ▶ Continuous Glucose Monitoring (CGM) Systems

- ▶ **2013 Guidelines:** CGM is recommended for patients with T1DM to improve A1c and reduce episodes of hypoglycemia

## ▶ Flash Glucose Monitoring (FGM)

### ▶ Freestyle Libre®

- ▶ *Only flash glucose monitor available in Canada*

- ▶ **New recommendation: FGM** may be offered to people with diabetes to **decrease time spent in hypoglycemia.**<sup>4,5</sup>

- ▶ *[Grade B, Level 2 for type 1 diabetes; Grade B, Level 2 for T2DM]*

3. Berard LD, Siemens R, Woo V. *Diabetes Canada 2018 Clinical Practice Guidelines for the Prevention and Management of Diabetes in Canada: Monitoring Glycemic Control.* Can J Diabetes 2018;42(Suppl 1):S47-S53.

4. Bolinder J, Antuna R, Geelhoed-Duijvestijn P, et al. Novel glucose-sensing technology and hypoglycaemia in type 1 diabetes: A multicentre, non-masked, randomised controlled trial. Lancet 2016;388:2254-63.

5. Haak T, Hanaire H, Ajjan R, et al. Flash glucose-sensing technology as a replacement for blood glucose monitoring for the management of insulin-treated type 2 diabetes: A multicenter, open-label randomized controlled trial. Diabetes Ther 2017;8:55-73.

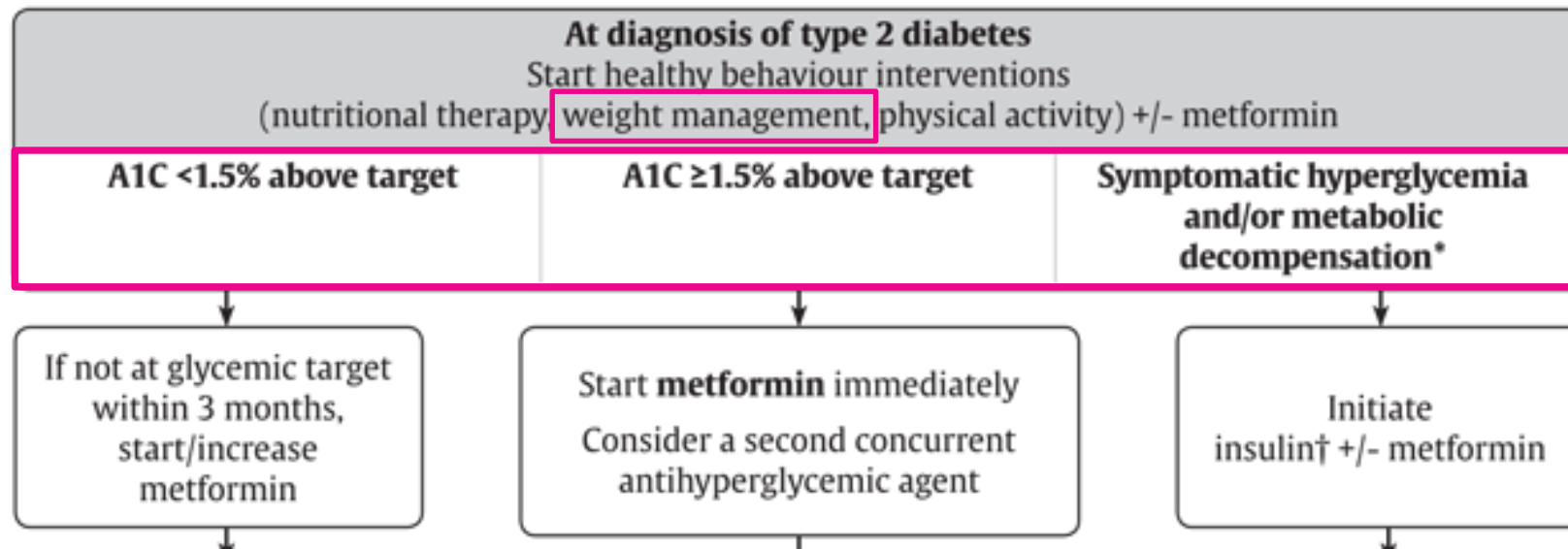
# Pharmacotherapy for T2DM

Antihyperglycemic Agents

# Initiation of Antihyperglycemic Agents

## Chapter 13 - Pharmacologic Glycemic Management of Type 2 Diabetes in Adults

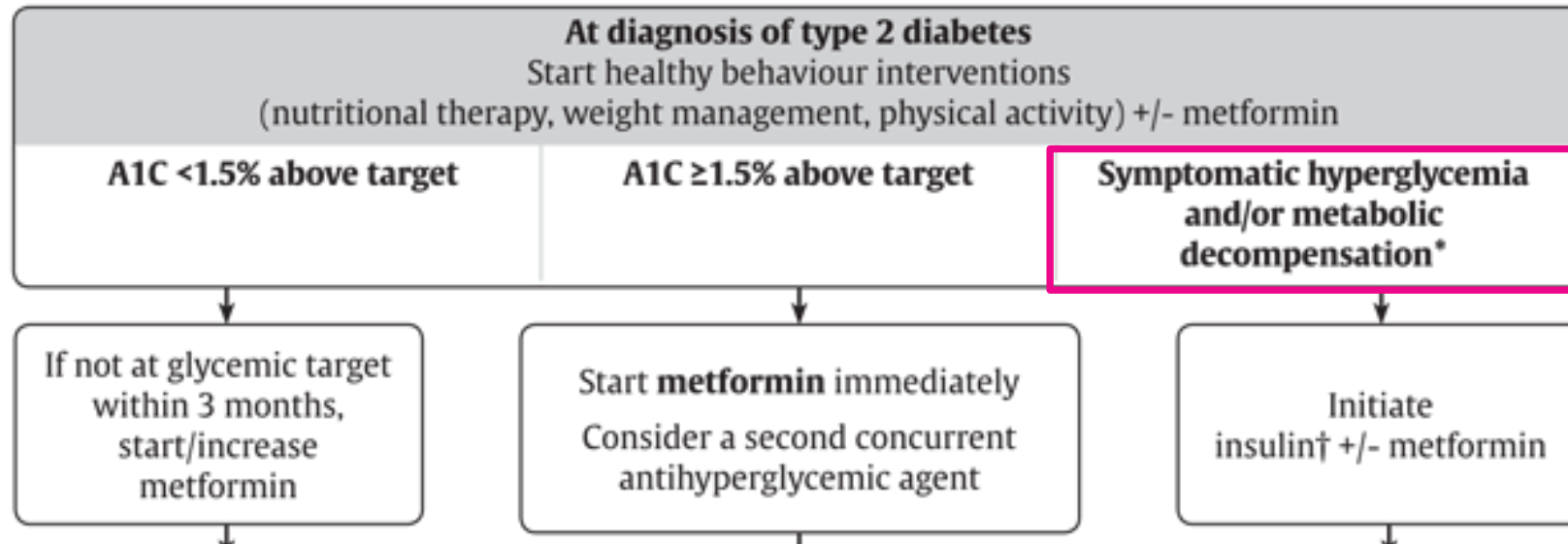
Figure 1. Management of hyperglycemia in type 2 diabetes



**Individualized targets**

- < 1.5 % above target vs < 8.5%

# Initiation of Antihyperglycemic Agents



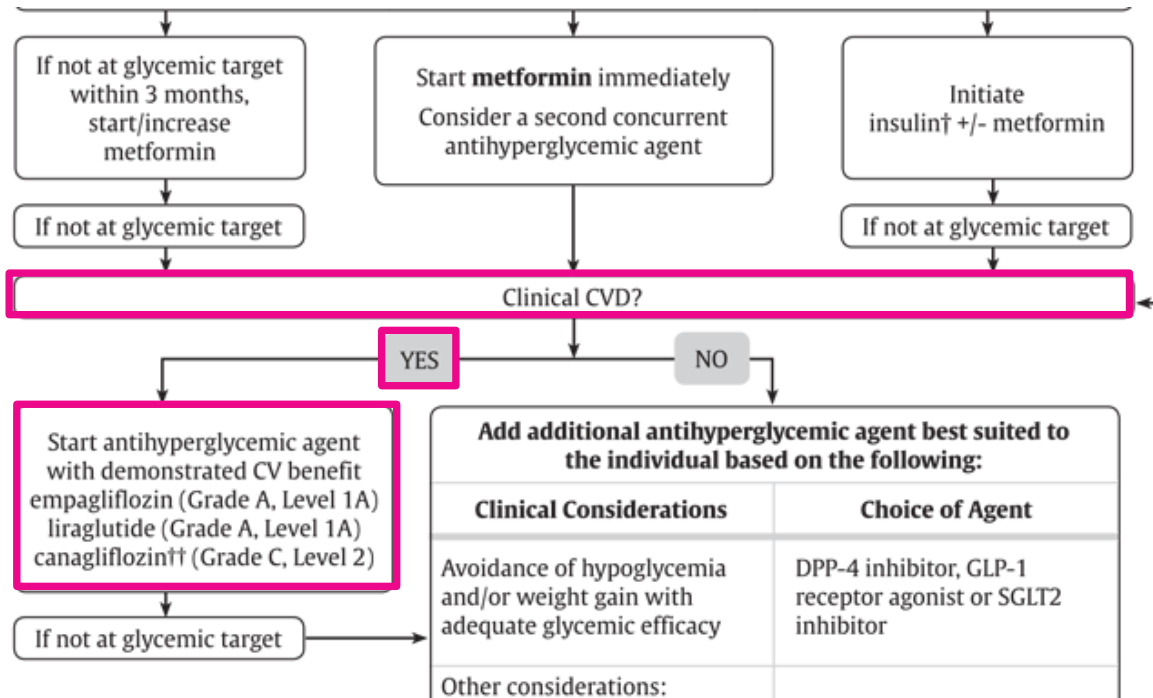
## Irrespective of A1c

This includes patients with:

- Dehydration
- Unintentional weight loss
- DKA
- HHS

*Insulin may be tapered or discontinued once stability is achieved.*

# Initiation of Antihyperglycemic Agents



+ semaglutide

Prioritize use of antihyperglycemic agents with **demonstrated CV benefit** in patients with **established CVD**.<sup>7,8,9</sup>

This includes:

- MI
- Established CAD on angiography
- Unstable angina
- Stroke
- PAD

6. Lipscombe L, Booth G, Butalia S, Dasgupta K, et al. *Diabetes Canada 2018 Clinical Practice Guidelines for the Prevention and Management of Diabetes in Canada: Pharmacologic Glycemic Management of Type 2 Diabetes in Adults*. Can J Diabetes 2018;42(Suppl 1):S88-S103.

7. Zinman B, Wanner C, Lachin JM, et al. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. N Engl J Med 2015;373:2117-28.

8. Neal B, Perkovic V, Mahaffey KW, et al. Canagliflozin and cardiovascular and renal events in type 2 diabetes. N Engl J Med 2017 ;377(7):644-657.

9. Marso SP, Daniels GH, Brown-Frandsen K, et al. Liraglutide and cardiovascular outcomes in type 2 diabetes. N Engl J Med 2016;375:311-22.

# Canagliflozin

- ▶ Review conducted by an independent committee found the evidence for CV benefit to be **weaker** for canagliflozin
  - ▶ **Interim analysis** of CANVAS study data in 2012 → **unblinding** of study data
    - ▶ Unblinding of data = Potential threat to internal validity
  - ▶ Decision was made to **combine CANVAS with CANVAS-R data**
    - ▶ Increased power for CV outcomes
    - ▶ Revision of study protocol = Potential threat to internal validity
- ▶ No significant benefit for **individual outcomes**
- ▶ Increased risk of **fractures and amputations** with canagliflozin

# SGLT2is & Special Populations

## ▶ Chronic Kidney Disease & Heart Failure (HF)

▶ New recommendation: In adults with T2DM and **clinical CVD** in whom glycemic targets are not achieved with existing antihyperglycemic medication(s) and with an **eGFR >30 mL/min/1.73m<sup>2</sup>**, an **SGLT2i** may be added to:

▶ Reduce the risk of progression of **nephropathy**.<sup>8,9</sup>

▶ [Grade B, Level 2 for empagliflozin; Grade C, Level 3 for canagliflozin]

▶ Reduce the risk of **heart failure hospitalization**.<sup>7,8</sup>

▶ [Grade B, Level 2 for empagliflozin; Grade C, Level 2 for canagliflozin].

6. Lipscombe L, Booth G, Butalia S, Dasgupta K, et al. *Diabetes Canada 2018 Clinical Practice Guidelines for the Prevention and Management of Diabetes in Canada: Pharmacologic Glycemic Management of Type 2 Diabetes in Adults*. Can J Diabetes 2018;42(Suppl 1):S88-S103.

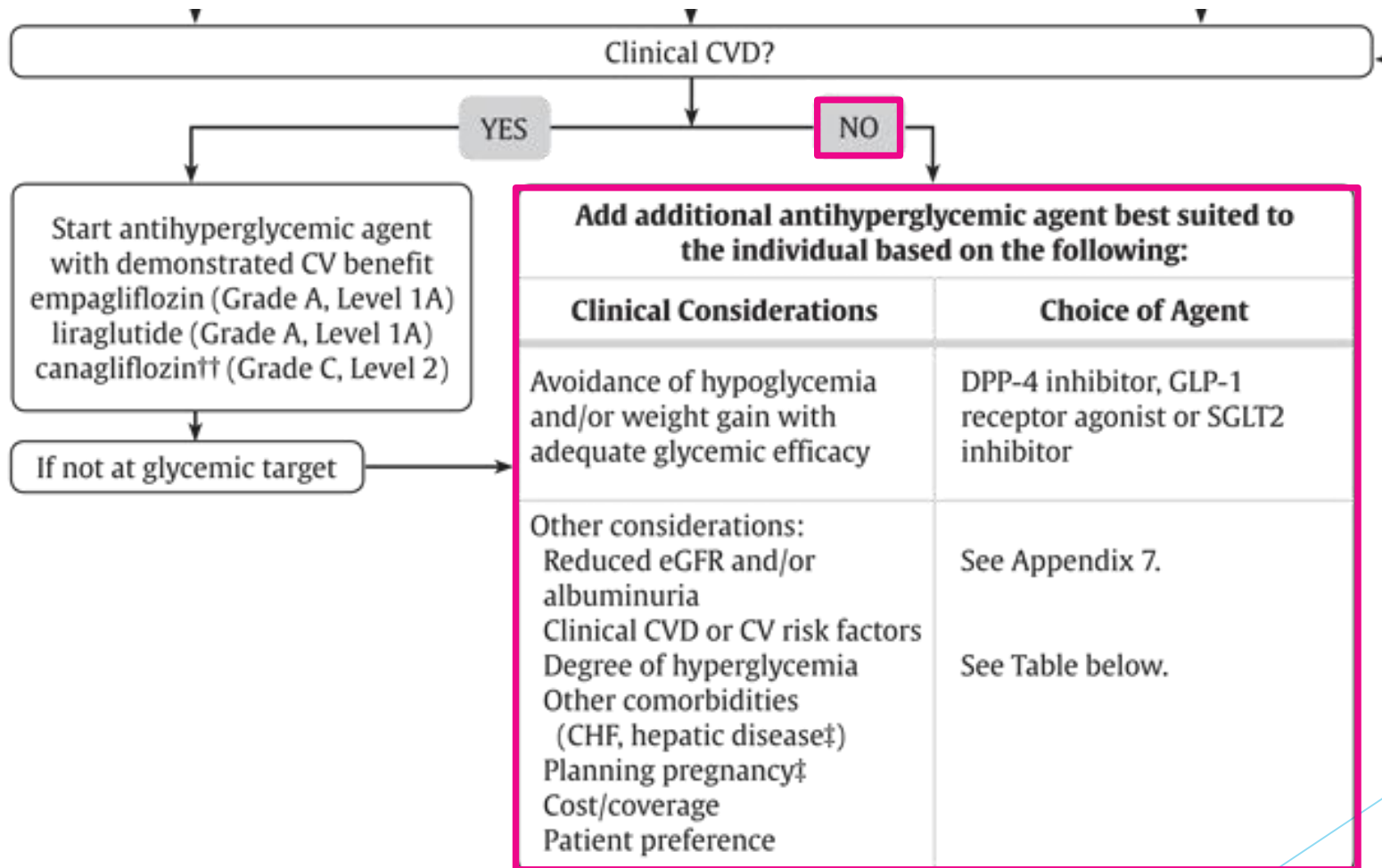
7. Zinman B, Wanner C, Lachin JM, et al. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. N Engl J Med 2015;373:2117-28.

8. Neal B, Perkovic V, Mahaffey KW, et al. Canagliflozin and cardiovascular and renal events in type 2 diabetes. N Engl J Med 2017 ;377(7):644-657.

9. Wanner C, Inzucchi SE, Lachin JM, et al. Empagliflozin and progression of kidney disease in type 2 diabetes. N Engl J Med 2016;375:323-34.



# Initiation of Antihyperglycemic Agents



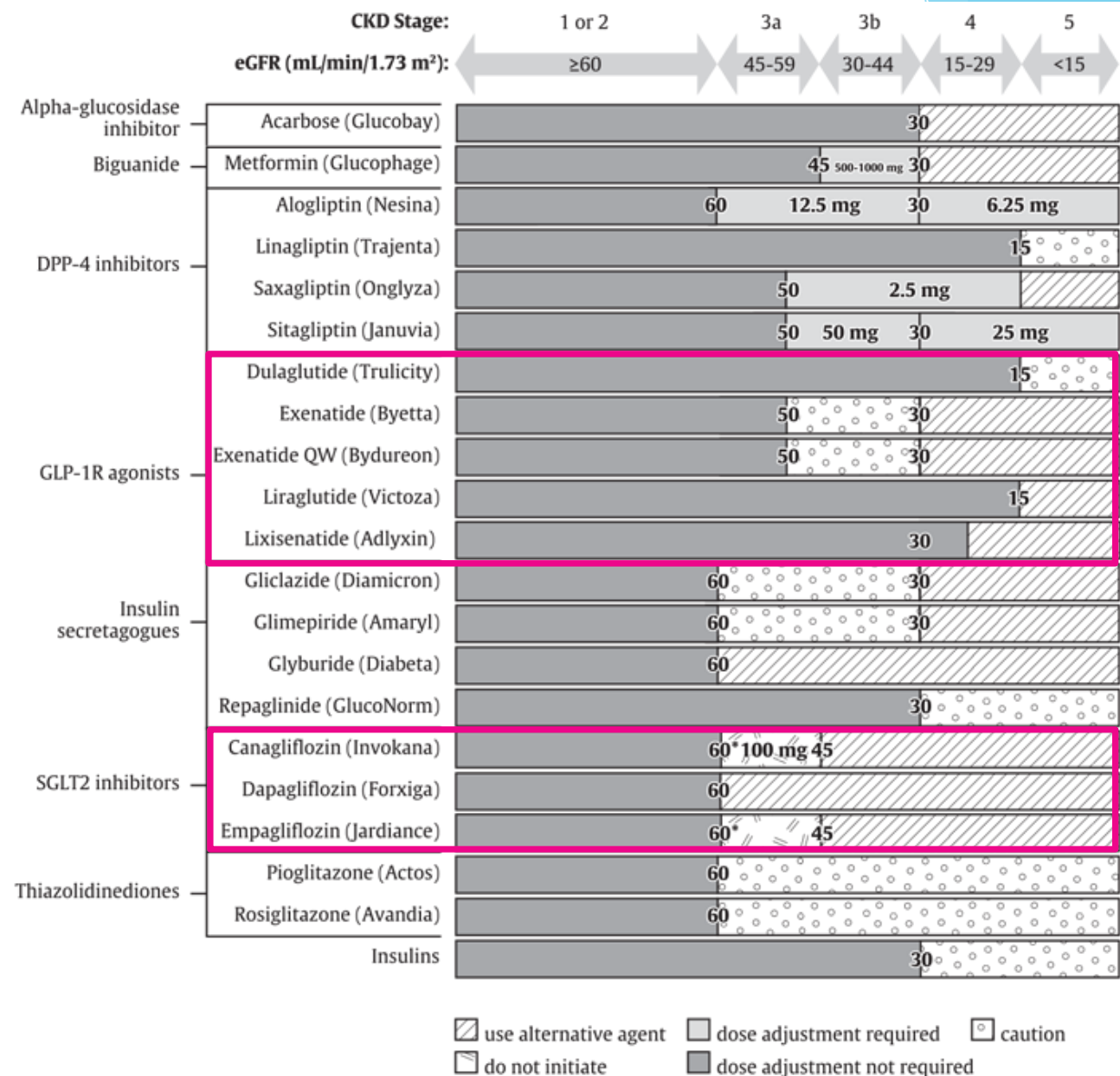
# Initiation of Antihyperglycemic Agents

Figure 1. Management of hyperglycemia in type 2 diabetes (*continued*)

Sulfonylurea	Yes	↑	↓↓	but usually requires 3 to 4 times daily dosing Gliclazide and glimepiride associated with less hypoglycemia than glyburide Poor durability	\$
Weight loss agent (orlistat)	None	↓	↓	GI side effects Requires 3 times daily dosing	\$\$\$
<p><i>alo</i>, alogliptin; <i>cana</i>, canagliflozin; <i>empa</i>, empagliflozin; <i>glar</i>, glargine; <i>lira</i>, liraglutide; <i>exe LAR</i>, exenatide long-acting release; <i>lixi</i>, lixisenatide; <i>saxa</i>, saxagliptin; <i>sita</i>, sitagliptin.</p>					
↓					
If not at glycemic targets					
↓					
<p><b>Add another antihyperglycemic agent from a different class and/or add/intensify insulin regimen</b>  <b>Make timely adjustments to attain target A1C within 3-6 months</b></p>					

# Renal Function

Figure 2. Antihyperglycemic medications and renal function



\* May be considered when indicated for CV and renal protection with eGFR <60 but >30 ml/min/1.73m<sup>2</sup>

# Insulin Recommendations

## New Recommendations

- ▶ In adults with T2DM treated with basal insulin therapy, consider the following options if reducing the risk of hypoglycemia is a priority:
  - ▶ **Insulin degludec may be considered over insulin glargine U-100**
    - ▶ Decreased risk of overall and nocturnal hypoglycemia<sup>10, 11</sup>
      - ▶ *[Grade B, Level 2 for patients with  $\geq 1$  risk factor for hypoglycemia; Grade C, Level 3 for others]*
    - ▶ Decreased risk of severe hypoglycemia in patients at high CV risk<sup>12</sup>
      - ▶ *[Grade C, Level 3]*
  - ▶ **Insulin glargine U-300 may be considered over insulin glargine U-100**
    - ▶ Decreased risk of overall and nocturnal hypoglycemia<sup>13</sup>
      - ▶ *[Grade C, Level 3]*

6. Lipscombe L, Booth G, Butalia S, Dasgupta K, et al. *Diabetes Canada 2018 Clinical Practice Guidelines for the Prevention and Management of Diabetes in Canada: Pharmacologic Glycemic Management of Type 2 Diabetes in Adults*. Can J Diabetes 2018;42(Suppl 1):S88-S103.

10. Ratner RE, Gough SC, Mathieu C, et al. Hypoglycaemia risk with insulin degludec compared with insulin glargine in type 2 and type 1 diabetes: A pre-planned meta-analysis of phase 3 trials. *Diabetes Obes Metab* 2013;15:175-84.

11. Wysham C, Bhargava A, Chaykin L, et al. Effect of insulin degludec vs insulin glargine U100 on hypoglycemia in patients with type 2 diabetes. The SWITCH 2 Randomized Clinical Trial. *JAMA* 2017;318(1):45-56.

12. Marso SP, McGuire DK, Zinman B, et al. Efficacy and safety of degludec versus glargine in type 2 diabetes. *N Engl J Med* 2017; 377(8):723-732.

13. Ritzel R, Roussel R, Volli GB, et al. Patient-level meta-analysis of the EDITION 1, 2 and 3 studies: glycaemic control and hypoglycaemia with new insulin glargine 300 U/ml versus glargine 100 U/ml in people with type 2 diabetes. *Diabetes Obes Metab* 2015;17:859-67.

# Insulin & AHAs

## New Recommendations

### ▶ GLP-1 Receptor Agonists

- ▶ Consider as **add-on therapy**, before initiating bolus insulin or intensifying insulin
  - ▶ Weight loss and lower risk of hypoglycemia as compared to single or multiple boluses<sup>14-16</sup>
    - ▶ [Grade A, Level 1A]

### ▶ SGLT2 Inhibitors

- ▶ Consider as **add-on therapy to insulin**
  - ▶ Weight loss and lower risk of hypoglycemia as compared to additional insulin<sup>17,18</sup>
    - ▶ [Grade A, Level 1A]

### ▶ DPP-4 Inhibitors

- ▶ **May be considered as add-on therapy to insulin**
  - ▶ No weight gain and lower risk of hypoglycemia as compared to additional insulin<sup>19</sup>
    - ▶ [Grade A, Level 1A]

# Diabetes in Older People

- ▶ **New Recommendation: DPP-4 inhibitors should be used over sulfonylureas as second line therapy to metformin, because of a lower risk of hypoglycemia<sup>21</sup>**
  - ▶ *[Grade B, Level 2]*
- ▶ **Updated Recommendation: Insulin detemir, glargine U-100, **glargine U-300** and **degludec** may be used instead of NPH or human 30/70 insulin to lower the frequency of hypoglycemic events<sup>22,23</sup>**
  - ▶ *[Grade D, Consensus for degludec and glargine U-300]*

20. Meneilly GS, Knip A, Miller DB et al. *Diabetes Canada 2018 Clinical Practice Guidelines for the Prevention and Management of Diabetes in Canada: Diabetes in Older People*. Can J Diabetes 2018;42(Suppl 1):S283-S295.

21. Rosenstock J, Wilson C, Fleck P. Alogliptin versus glipizide monotherapy in elderly type 2 diabetes mellitus patients with mild hyperglycaemia: A prospective, double-blind, randomized, 1-year study. *Diabetes Obes Metab* 2013;15:906-14.

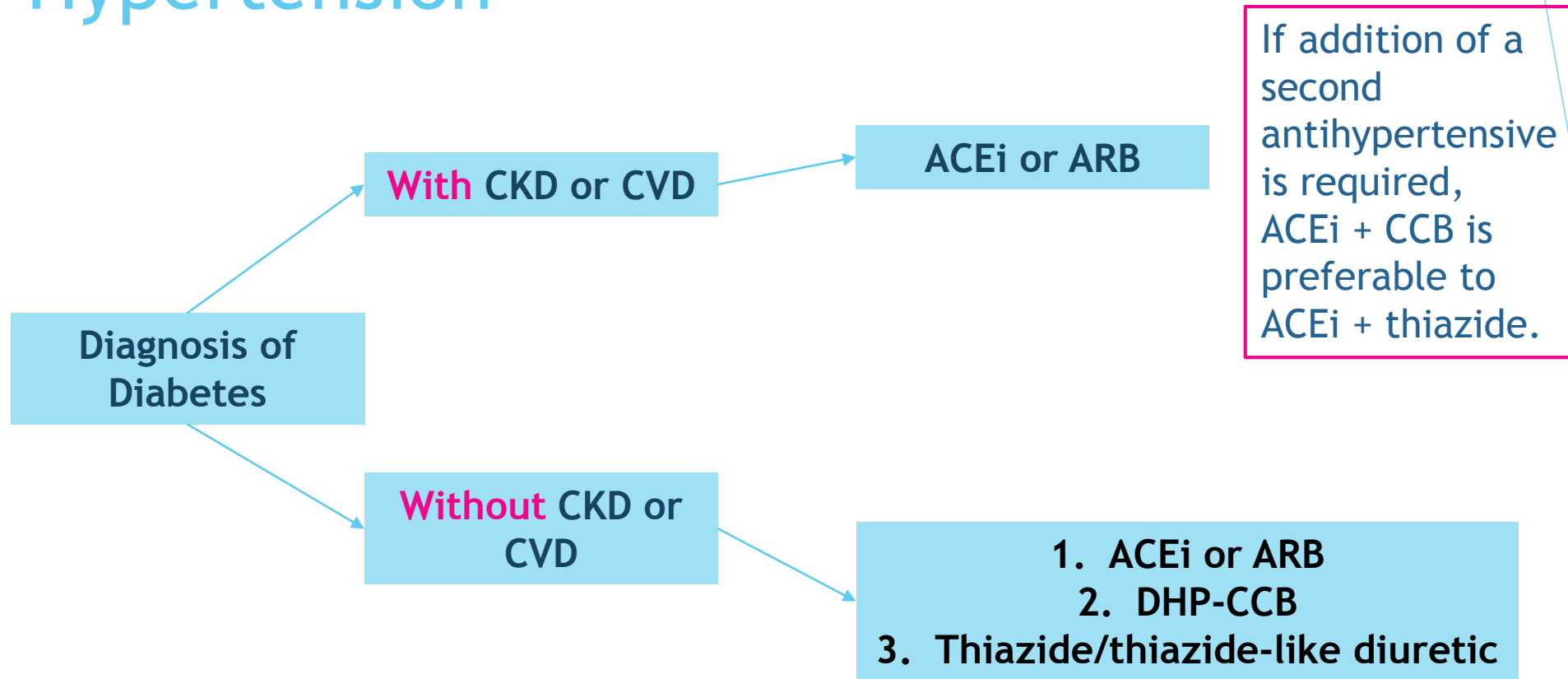
22. Janka HU, Plewe G, Busch K. Combination of oral antidiabetic agents with basal insulin versus premixed insulin alone in randomized elderly patients with type 2 diabetes mellitus. *J Am Geriatr Soc* 2007;55:182-8.

23. Garber AJ, Clauson P, Pedersen CB, et al. Lower risk of hypoglycemia with insulin detemir than with neutral protamine hagedorn insulin in older persons with type 2 diabetes: A pooled analysis of phase III trials. *J Am Geriatr Soc* 2007;55:1735-40.

# Pharmacotherapy for T2DM

Medications for CV Risk Reduction

# Hypertension



► Recommendations fully harmonized with Hypertension Canada Guidelines.



# Dyslipidemia

- ▶ Treatment targets **fully harmonized** with Canadian Cardiovascular Society dyslipidemia guidelines.
- ▶ New Recommendation: Fasting or **non-fasting lipid profiles** are both appropriate.
  - ▶ If triglycerides > 4.5 mmol/L, recommend fasting lipid profile.
    - ▶ *[Grade D, Consensus]*
- ▶ New Recommendation: In patients with clinical CVD, **ezetimibe** or **evolocumab** may be used to further reduce CV events.<sup>23,24</sup>
  - ▶ *[Grade A, Level 1 for ezetimibe; Grade A, Level 1 for evolocumab]*

22. Mancini GBJ, Hegele RA, Leiter LA et al. *Diabetes Canada 2018 Clinical Practice Guidelines for the Prevention and Management of Diabetes in Canada: Dyslipidemia*. Can J Diabetes 2018;42(Suppl 1):S178-S185.

23. Cannon CP, Blazing MA, Giugliano RP, et al. Ezetimibe added to statin therapy after acute coronary syndromes. N Engl J Med 2015;372:2387-97.

24. Cardiovascular safety and efficacy of the PCSK9 inhibitor evolocumab in patients with and without diabetes and the effect of evolocumab on glycaemia and risk of new-onset diabetes: A prespecified analysis of the FOURIER randomised controlled trial. Lancet Diabetes Endocrinol. 2017 Dec;5(12):941-950

# Cardiovascular Protection

- ▶ **New Recommendation: ACE inhibitor or ARB**, at doses that have demonstrated vascular protection, should be used to **reduce CV risk** in adults with diabetes with any of the following:
  - ▶ **Clinical CVD** <sup>26,27</sup>
    - ▶ [Grade A, Level 1]
  - ▶ **Age ≥55 years with an additional CV risk factor** (Total cholesterol >5.2 mmol/L, HDL-C <0.9 mmol/L, hypertension, albuminuria, smoking) **or end organ damage** (albuminuria, retinopathy, left ventricular hypertrophy) <sup>26,27</sup>
    - ▶ [Grade A, Level 1]
  - ▶ **Microvascular complications**
    - ▶ [Grade D, Consensus]
- ▶ Doses that have demonstrated vascular protection include:
  - ▶ Perindopril 8 mg once daily<sup>28</sup>
  - ▶ Ramipril 10 mg once daily<sup>26</sup>
  - ▶ Telmisartan 80 mg once daily<sup>27</sup>

25. Stone JA, Houlden RL, Lin P et al. *Diabetes Canada 2018 Clinical Practice Guidelines for the Prevention and Management of Diabetes in Canada: Cardiovascular Protection in People with Diabetes*. Can J Diabetes 2018;42(Suppl 1):S162-S169.

26. The Heart Outcomes Prevention Evaluation Study Investigators, Yusuf S, Sleight P, et al. Effects of an angiotensin-converting-enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients. *New Engl J Med* 2000;342:145-53.

27. ONTARGET Investigators, Yusuf S, Teo KK, et al. Telmisartan, ramipril, or both in patients at high risk for vascular events. *N Engl J Med* 2008;358:1547-59.

28. Daly CA, Fox KM, Remme WJ, et al. The effect of perindopril on cardiovascular morbidity and mortality in patients with diabetes in the EUROPA study: Results from the PERSUADE substudy. *Eur Heart J* 2005;26:1369-78.

# Additional Topics

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# Weight Management

- ▶ **New Recommendation: Weight management medication** may be considered in people with diabetes who are overweight or obese to promote weight loss and improve glycemic control.
  - ▶ **Liraglutide**<sup>30</sup>
    - ▶ [Grade A, Level 1A]
  - ▶ **Orlistat**<sup>31</sup>
    - ▶ [Grade A, Level 1A]

**Table 5**  
Medications approved for the treatment of obesity in type 2 diabetes

Class	Relative weight loss	Side effects	Therapeutic considerations	Cost
Gastrointestinal lipase inhibitor	↓	Loose stools, GI upset, rare liver failure	Oral medication, decreases fat absorption, may require vitamin supplementation	\$\$\$
GLP-1 receptor agonist	↓↓	Nausea, GI upset, rare gallstones and pancreatitis	Subcutaneous injectable, increases satiety	\$\$\$\$

GLP-1, Glucagon-like peptide-1.

29. Wharton S, Pedersen S, Lau DCW, Sharma AM. *Diabetes Canada 2018 Clinical Practice Guidelines for the Prevention and Management of Diabetes in Canada: Weight Management in Diabetes*. Can J Diabetes 2018;42(Suppl 1):S124-S129.

30. Davies MJ, Bergenstal R, Bode B, et al. Efficacy of liraglutide for weight loss among patients with type 2 diabetes: The SCALE diabetes randomized clinical trial. JAMA 2015;314:687-99.

31. Hollander PA, Elbein SC, Hirsch IB, et al. Role of orlistat in the treatment of obese patients with type 2 diabetes. A 1-year randomized double-blind study. Diabetes Care 1998;21:1288-94.

# Sick Day Management

- ▶ Previous sick day management recommendations have been updated to include **SGLT2is**.
  - ▶ **Updated Recommendation:** Metformin, insulin secretagogues and **SGLT2is** should be **temporarily withheld** during **acute illnesses** associated with reduced oral intake or dehydration.
    - ▶ *[Grade D, Consensus]*
  - ▶ **New Recommendation:** **SGLT2is** should be **temporarily withheld** prior to major surgical procedures, and during acute infections and serious illness to reduce the risk of **ketoacidosis**.
    - ▶ *[Grade D, Consensus]*

# Hyperglycemic Emergencies in Adults

- ▶ **Diabetic Ketoacidosis & SGLT2 Inhibitors**
  - ▶ SGLT2is can precipitate euglycemic DKA
  - ▶ **New recommendation:** Individuals treated with SGLT2is with symptoms of DKA should be assessed for this condition even if BG is not elevated.
    - ▶ *[Grade D, Consensus]*
- ▶ **Precipitating factors:**
  - ▶ *Insulin dose reduction or omission*
    - ▶ *May occur at time of introduction of SGLT2i*
  - ▶ *Surgery or infection*
  - ▶ *Exercise*
  - ▶ *Low carbohydrate or reduced food intake*

# Other Topics

## ▶ Pre-Diabetes

- ▶ **No new recommendations** regarding the use of pharmacotherapy to help reduce the risk of T2DM in patients with **pre-diabetes**.
  - ▶ *Emerging evidence to support the use of liraglutide<sup>30</sup>*

## ▶ Complimentary and Alternative Medicine

- ▶ **No new recommendations** regarding the use of **CAM** in patients with diabetes
  - ▶ Insufficient evidence to support the use of any natural health products (NHPs)
    - ▶ *Updated list of NHPs that have been evaluated*

33. Prebtani APH, Bajaj HS, Goldenberg R, Mullan Y. *Diabetes Canada 2018 Clinical Practice Guidelines for the Prevention and Management of Diabetes in Canada: Reducing the Risk of Developing Diabetes*. Can J Diabetes 2018;42(Suppl 1):S20-S26.

34. Grossman LD, Roscoe R, Shack AR. *Diabetes Canada 2018 Clinical Practice Guidelines for the Prevention and Management of Diabetes in Canada: Complementary and Alternative Medicine*. Can J Diabetes 2018;42(Suppl 1):S154-S161.

# Diabetes & Driving

- ▶ **New Chapter**
- ▶ Reviews recommendations for reporting of unfit drivers
- ▶ **Hypoglycemia Monitoring**
  - ▶ Drivers with diabetes treated with insulin secretagogues and/or insulin:
    - ▶ Measure BG level immediately before and at least every 4 hours while driving
    - ▶ Should not drive when BG level is  $< 4.0$  mmol/L
    - ▶ If BG level is  $< 4.0$  mmol/L, they should not drive until at least **40 minutes** after their BG level has risen to  $> 5.0$  mmol/L
    - ▶ Refrain from driving immediately if they experience severe hypoglycemia while driving, and notify their HCP



# Online Tools for Practitioners

- ▶ **Diabetes Canada Clinical Practice Guidelines Website: <http://guidelines.diabetes.ca/>**



**Reduce the Risk of Diabetes Complications**



**Keep People with Diabetes Safe**



**Support Self-management**

## Clinical Decision Support Tools

**SCREENING FOR  
GDM**

**PHYSICAL ACTIVITY  
DECISION TOOL**

**SCREENING FOR AND  
DIAGNOSING DIABETES**

**SELF-MONITORING  
BLOOD GLUCOSE**

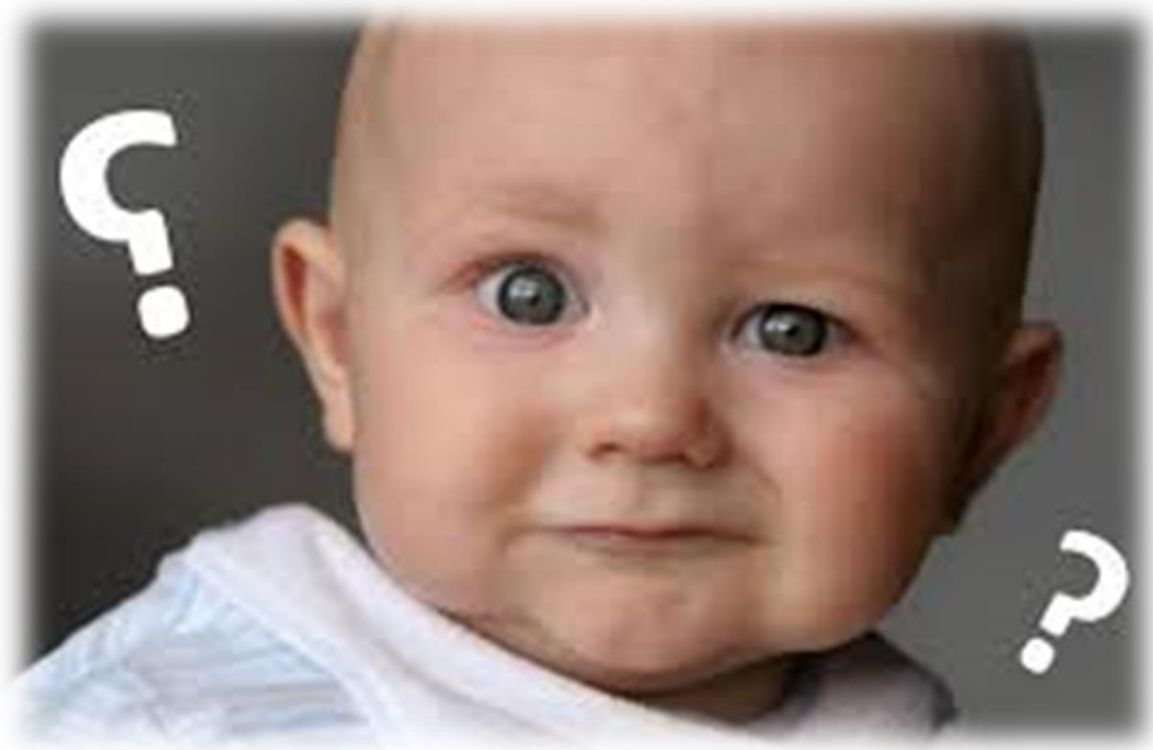
**REDUCING  
VASCULAR RISK**

**PHARMACOTHERAPY  
FOR TYPE 2 DIABETES**

**INDIVIDUALIZING YOUR  
PATIENT'S A1C TARGET**

**INSULIN  
ORDER SETS**

Questions?



# References

- ▶ 1. 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.
- ▶ 2. Imran SA, Agarwal G, Bajaj HS, Ross S. *Diabetes Canada 2018 Clinical Practice Guidelines for the Prevention and Management of Diabetes in Canada: Targets for Glycemic Control*. Can J Diabetes 2018;42(Suppl 1):S42-S46.
- ▶ 3. Berard LD, Siemens R, Woo V. *Diabetes Canada 2018 Clinical Practice Guidelines for the Prevention and Management of Diabetes in Canada: Monitoring Glycemic Control*. Can J Diabetes 2018;42(Suppl 1):S47-S53.
- ▶ 4. Bolinder J, Antuna R, Geelhoed-Duijvestijn P, et al. Novel glucose-sensing technology and hypoglycaemia in type 1 diabetes: A multicentre, non-masked, randomised controlled trial. *Lancet* 2016;388:2254-63.
- ▶ 5. Haak T, Hanaire H, Ajjan R, et al. Flash glucose-sensing technology as a replacement for blood glucose monitoring for the management of insulin-treated type 2 diabetes: A multicenter, open-label randomized controlled trial. *Diabetes Ther* 2017;8:55-73.
- ▶ 6. Lipsombe L, Booth G, Butalia S, Dasgupta K, et al. *Diabetes Canada 2018 Clinical Practice Guidelines for the Prevention and Management of Diabetes in Canada: Pharmacologic Glycemic Management of Type 2 Diabetes in Adults*. Can J Diabetes 2018;42(Suppl 1):S88-S103.
- ▶ 7. Zinman B, Wanner C, Lachin JM, et al. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. *N Engl J Med* 2015;373:2117-28.
- ▶ 8. Neal B, Perkovic V, Mahaffey KW, et al. Canagliflozin and cardiovascular and renal events in type 2 diabetes. *N Engl J Med* 2017; 377(7):644-657.
- ▶ 9. Marso SP, Daniels GH, Brown-Frandsen K, et al. Liraglutide and cardiovascular outcomes in type 2 diabetes. *N Engl J Med* 2016;375:311-22.
- ▶ 10. Ratner RE, Gough SC, Mathieu C, et al. Hypoglycaemia risk with insulin degludec compared with insulin glargine in type 2 and type 1 diabetes: A pre-planned meta-analysis of phase 3 trials. *Diabetes Obes Metab* 2013;15:175-84.
- ▶ 11. Wysham C, Bhargava A, Chaykin L, et al. Effect of insulin degludec vs insulin glargine U100 on hypoglycemia in patients with type 2 diabetes. *The SWITCH 2 Randomized Clinical Trial*. *JAMA* 2017;318(1):45-56.
- ▶ 12. Marso SP, McGuire DK, Zinman B, et al. Efficacy and safety of degludec versus glargine in type 2 diabetes. *N Engl J Med* 2017; 377(8):723-732.
- ▶ 13. Ritzel R, Roussel R, Volli GB, et al. Patient-level meta-analysis of the EDITION 1, 2 and 3 studies: glycaemic control and hypoglycaemia with new insulin glargine 300 U/ml versus glargine 100 U/ml in people with type 2 diabetes. *Diabetes Obes Metab* 2015;17:859-67.

# References

- ▶ 14. Mathieu C, Rodbard HW, Cariou B, et al. A comparison of adding liraglutide versus a single daily dose of insulin aspart to insulin degludec in subjects with type 2 diabetes (BEGIN: VICTOZA ADD-ON). *Diabetes Obes Metab* 2014;16:636-44.
- ▶ 15. Rosenstock J, Guerci B, Hanefeld M, et al. Prandial options to advance basal insulin glargine therapy: Testing lixisenatide plus basal insulin versus insulin glulisine either as basal-plus or basal-bolus in type 2 diabetes: The GetGoal Duo-2 Trial. *Diabetes Care* 2016;39:1318-28.
- ▶ 16. Eng C, Kramer CK, Zinman B, et al. Glucagon-like peptide-1 receptor agonist and basal insulin combination treatment for the management of type 2 diabetes: A systematic review and meta-analysis. *Lancet* 2014;384:2228-34.
- ▶ 17. Rosenstock J, Jelaska A, Frappin G, et al. Improved glucose control with weight loss, lower insulin doses, and no increased hypoglycemia with empagliflozin added to titrated multiple daily injections of insulin in obese inadequately controlled type 2 diabetes. *Diabetes Care* 2014;37:1815-23.
- ▶ 18. Wilding JP, Woo V, Rohwedder K, et al. Dapagliflozin in patients with type 2 diabetes receiving high doses of insulin: Efficacy and safety over 2 years. *Diabetes Obes Metab* 2014;16:124-36.
- ▶ 19. Zinman B, Ahren B, Neubacher D, et al. Efficacy and cardiovascular safety of linagliptin as an add-on to insulin in type 2 diabetes: A pooled comprehensive post hoc analysis. *Can J Diabetes* 2016;40:50-7.
- ▶ 20. Meneilly GS, Knip A, Miller DB et al. *Diabetes Canada 2018 Clinical Practice Guidelines for the Prevention and Management of Diabetes in Canada: Diabetes in Older People.* *Can J Diabetes* 2018;42(Suppl 1):S283-S295.
- ▶ 21. Sheldon WT, Gilbert RE, Jones C et al. *Diabetes Canada 2018 Clinical Practice Guidelines for the Prevention and Management of Diabetes in Canada: Treatment of Hypertension.* *Can J Diabetes* 2018;42(Suppl 1):S186-S189.
- ▶ 22. Mancini GBJ, Hegele RA, Leiter LA et al. *Diabetes Canada 2018 Clinical Practice Guidelines for the Prevention and Management of Diabetes in Canada: Dyslipidemia.* *Can J Diabetes* 2018;42(Suppl 1):S178-S185.
- ▶ 23. Cannon CP, Blazing MA, Giugliano RP, et al. Ezetimibe added to statin therapy after acute coronary syndromes. *N Engl J Med* 2015;372:2387-97.
- ▶ 24. Cardiovascular safety and efficacy of the PCSK9 inhibitor evolocumab in patients with and without diabetes and the effect of evolocumab on glycaemia and risk of new-onset diabetes: A prespecified analysis of the FOURIER randomised controlled trial. *Lancet Diabetes Endocrinol.* 2017 Dec;5(12):941-950
- ▶ 25. Stone JA, Houlden RL, Lin P et al. *Diabetes Canada 2018 Clinical Practice Guidelines for the Prevention and Management of Diabetes in Canada: Cardiovascular Protection in People with Diabetes.* *Can J Diabetes* 2018;42(Suppl 1):S162-S169.
- ▶ 26. The Heart Outcomes Prevention Evaluation Study Investigators, Yusuf S, Sleight P, et al. Effects of an angiotensin-converting-enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients. *New Engl J Med* 2000;342:145-53.
- ▶ 27. ONTARGET Investigators, Yusuf S, Teo KK, et al. Telmisartan, ramipril, or both in patients at high risk for vascular events. *N Engl J Med* 2008;358:1547-59.

# References

- ▶ 28. Daly CA, Fox KM, Remme WJ, et al. The effect of perindopril on cardiovascular morbidity and mortality in patients with diabetes in the EUROPA study: Results from the PERSUADE substudy. *Eur Heart J* 2005;26:1369-78.
- ▶ 29. Wharton S, Pedersen S, Lau DCW, Sharma AM. *Diabetes Canada 2018 Clinical Practice Guidelines for the Prevention and Management of Diabetes in Canada: Weight Management in Diabetes*. *Can J Diabetes* 2018;42(Suppl 1):S124-S129.
- ▶ 30. Davies MJ, Bergenstal R, Bode B, et al. Efficacy of liraglutide for weight loss among patients with type 2 diabetes: The SCALE diabetes randomized clinical trial. *JAMA* 2015;314:687-99.
- ▶ 31. Hollander PA, Elbein SC, Hirsch IB, et al. Role of orlistat in the treatment of obese patients with type 2 diabetes. A 1-year randomized double-blind study. *Diabetes Care* 1998;21:1288-94.
- ▶ 32. Goguen J, Gilbert J. *Diabetes Canada 2018 Clinical Practice Guidelines for the Prevention and Management of Diabetes in Canada: Hyperglycemic Emergencies in Adults*. *Can J Diabetes* 2018;42(Suppl 1):S109-S114.
- ▶ 33. Prebtani APH, Bajaj HS, Goldenberg R, Mullan Y. *Diabetes Canada 2018 Clinical Practice Guidelines for the Prevention and Management of Diabetes in Canada: Reducing the Risk of Developing Diabetes*. *Can J Diabetes* 2018;42(Suppl 1):S20-S26.
- ▶ 34. Grossman LD, Roscoe R, Shack AR. *Diabetes Canada 2018 Clinical Practice Guidelines for the Prevention and Management of Diabetes in Canada: Complementary and Alternative Medicine*. *Can J Diabetes* 2018;42(Suppl 1):S154-S161.
- ▶ 35. Houlden RL, Berard L, Lakoff JM. *Diabetes Canada 2018 Clinical Practice Guidelines for the Prevention and Management of Diabetes in Canada: Diabetes and Driving*. *Can J Diabetes* 2018;42(Suppl 1): S150-S153.