Canadian Diabetes Association Clinical Practice Guidelines

Pharmacologic Management of Type 2 Diabetes

Chapter 13

(Updated March 2016)

William Harper, Maureen Clement, Ronald Goldenberg, Amir Hanna, Andrea Main, Ravi Retnakaran, Diana Sherifali,Vincent Woo, Jean-François Yale

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Pharmacotherapy in T2DM Checklist

- ✓ **CHOOSE** initial therapy based on **glycemia**
- ✓ **START** with **Metformin** +/- others
- ✓ **INDIVIDUALIZE** your therapy choice based on characteristics of the **patient** and the **agent**
- ✓ **REACH TARGET** within **3-6 months** of diagnosis

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GET TO TARGET WITHIN

3-6 MONTHS

OF DIAGNOSIS

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Initial Choice of Therapy Depends on Glycemia

Initial A1C <8.5%	→	Start metformin OR Reassess in 2-3 months then decide on starting metformin
Initial A1C ≥8.5%	→	Start metformin AND Consider combo therapy to achieve ≥1.5% A1C reduction

Initial Choice of Therapy Depends on Glycemia

Symptomatic Hyperglycemia

+

Metabolic Decompensation

- Polyuria
- Polydipsia
- Weight loss
- Volume depletion

Concern about Insulin Deficiency

INSULIN +/- Metformin

CHOICE OF AGENT AFTER INITIAL METFORMIN NEEDS TO BE INDIVIDUALIZED

2016

Add another agent best suited to the individual by prioritizing patient characteristics:

PATIENT CHARACTERISTIC	CHOICE OF AGENT
PRIORITY: Clinical Cardiovascular Disease →	SGLT2 inhibitor with demonstrated CV outcome benefit
Degree of hyperglycemia Risk of hypoglycemia Overweight or obesity CV disease or multiple risk factors Comorbidities (renal, CHF, hepatic) Preferences & access to treatment	Consider relative A1C lowering Rare hypoglycemia Weight loss or weight neutral Effect on cardiovascular outcome See therapeutic considerations See cost column; consider access

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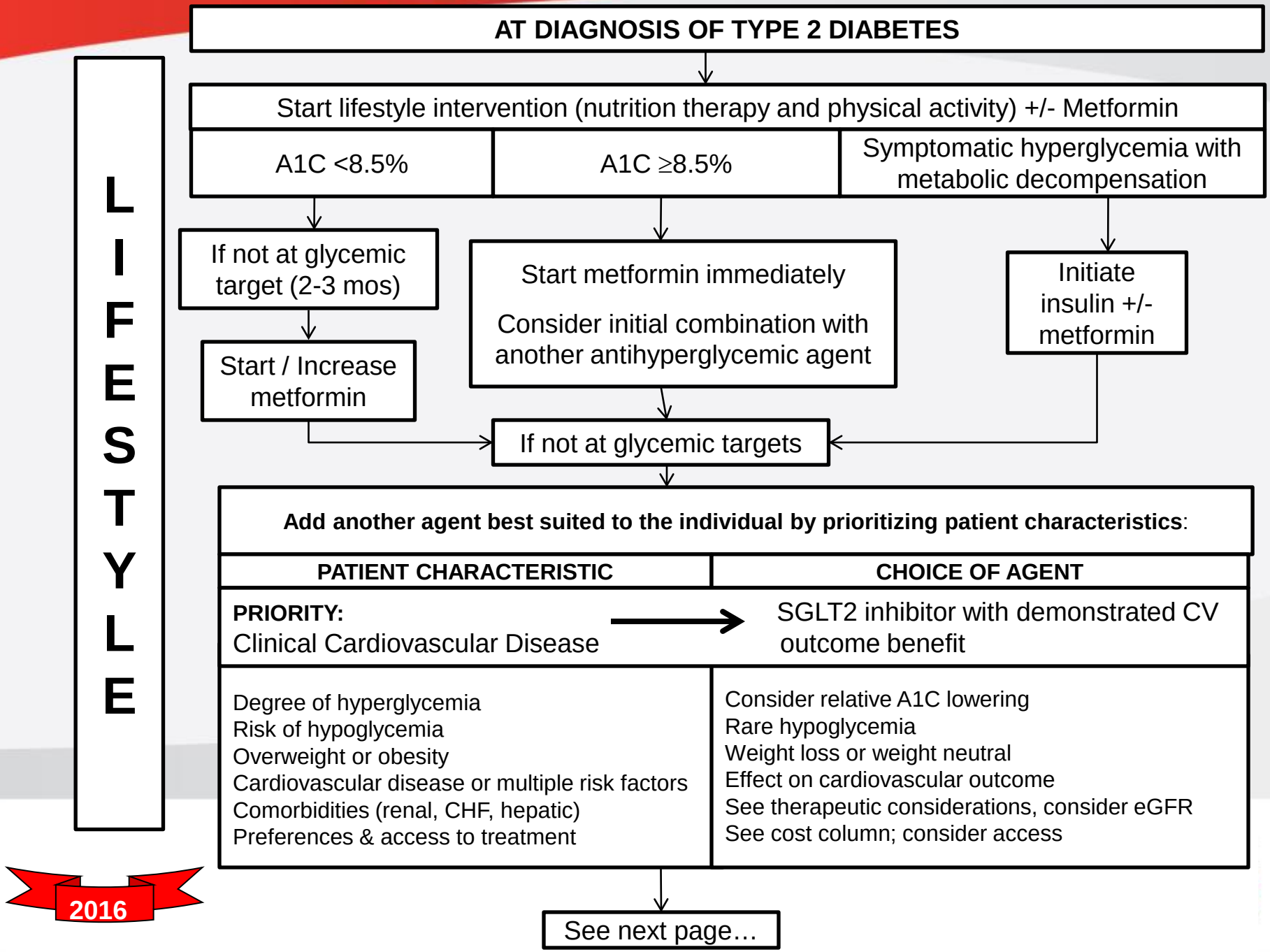
Add another class of agent best suited to the individual (*agents listed in alphabetical order*):						
Class	**Relative A1C Lowering**	**Hypo-glycemia**	**Weight**	**Effect in Cardiovascular Outcome Trial**	**Other therapeutic considerations**	**Cost**
α-glucosidase inhibitor (acarbose)	↓	Rare	neutral to ↓		Improved postprandial control, GI side-effects	$$
Incretin agents: DPP-4 Inhibitors GLP-1R agonists	 ↓↓ ↓↓ to ↓↓↓	 Rare Rare	 Neutral to ↓ ↓↓	 Neutral (alo, saxa, sita) Neutral (lixi)	 Caution with saxagliptin in heart failure GI side-effects	 $$$ $$$$
Insulin	↓↓↓	Yes	↑↑	Neutral (glar)	No dose ceiling, flexible regimens	$-$$$$
Insulin secretagogue: Meglitinide Sulfonylurea	 ↓↓ ↓↓	 Yes Yes	 ↑ ↑		 Less hypoglycemia in context of missed meals but usually requires TID to QID dosing Gliclazide and glimepiride associated with less hypoglycemia than glyburide	 $$ $
SGLT2 inhibitors	↓↓ to ↓↓↓	Rare	↓↓	Superiority (empa in T2DM patients with clinical CVD)	Genital infections, UTI, hypotension, dose-related changes in LDL-C, caution with renal dysfunction and loop diuretics, dapagliflozin not to be used if bladder cancer, rare diabetic ketoacidosis (may occur with no hyperglycemia)	$$$
Thiazolidinediones	↓↓	Rare	↑↑	Neutral	CHF, edema, fractures, rare bladder cancer (pioglitazone), cardiovascular controversy (rosiglitazone), 6-12 weeks required for maximal effect	$$
Weight loss agent (orlistat)	↓	None	↓		GI side effects	$$$

alo=alogliptin; glar=glargine; saxa=saxagliptin; sita=sitagliptin; lixi=lixisenatide; empa=empagliflozin


AT DIAGNOSIS OF TYPE 2 DIABETES
Start lifestyle intervention (nutrition therapy and physical activity) +/- Metformin
A1C <8.5%
A1C ≥8.5%
Symptomatic hyperglycemia with metabolic decompensation
If not at glycemic target (2-3 mos)
Start / Increase metformin
Start metformin immediately
Consider initial combination with another antihyperglycemic agent
Initiate insulin +/- metformin
If not at glycemic targets
Add another agent best suited to the individual by prioritizing patient characteristics:
PATIENT CHARACTERISTIC
CHOICE OF AGENT
PRIORITY:
Clinical Cardiovascular Disease
SGLT2 inhibitor with demonstrated CV outcome benefit
Degree of hyperglycemia
Risk of hypoglycemia
Overweight or obesity
Cardiovascular disease or multiple risk factors
Comorbidities (renal, CHF, hepatic)
Preferences & access to treatment
Consider relative A1C lowering
Rare hypoglycemia
Weight loss or weight neutral
Effect on cardiovascular outcome
See therapeutic considerations, consider eGFR
See cost column; consider access
LIFESTYLE
2016
See next page…

From prior page…

LIFESTYLE

Add another class of agent best suited to the individual (classes listed in alphabetical order):

Class	Relative A1C Lowering	Hypo-glycemia	Weight	Effect in Cardiovascular Outcome Trial	Other therapeutic considerations	Cost
Alpha-glucosidase inhibitor (acarbose)	↓	Rare	Neutral to ↓		Improved postprandial control, GI side-effects	$$
Incretin agents: DPP-4 Inhibitors	↓↓	Rare	Neutral to ↓	Neutral (alo, saxa, sita)	Caution with saxagliptin in heart failure	$$$
GLP-1R agonists	↓↓ to ↓↓↓	Rare	↓↓	Neutral (lixi)	GI side effects	$$$$
Insulin	↓↓↓	Yes	↑↑	Neutral (glar)	No dose ceiling, flexible regimens	$-$$$$
Insulin secretagogue: Meglitinide	↓↓	Yes	↑		Less hypoglycemia in context of missed meals but usually requires TID to QID dosing	$$
Sulfonylurea	↓↓	Yes	↑		Gliclazide and glimepiride associated with less hypoglycemia than glyburide	$
SGLT2 inhibitors	↓↓ to ↓↓↓	Rare	↓↓	Superiority (empa in T2DM patients with clinical CVD)	Genital infections, UTI, hypoten-sion, dose-related changes in LDL-C, caution with renal dysfunction and loop diuretics, dapagliflozin not to be used if bladder cancer, rare diabetic ketoacidosis (may occur with no hyperglycemia)	$$$
Thiazolidinediones	↓↓	Rare	↑↑	Neutral	CHF, edema, fractures, rare bladder cancer (pioglitazone), cardiovascular controversy (rosiglitazone), 6-12 weeks required for maximal effect	$$
Weight loss agent (orlistat)	↓	None	↓		GI side effects	$$$

alo=alogliptin; empa=empagliflozin; glar=glargine; lixi=lixisenatide; saxa=saxagliptin; sita=sitagliptin

If not at glycemic target

- Add another agent from a different class
- Add/Intensify insulin regimen

Make timely adjustments to attain target A1C within 3-6 months

2016

Add another class of agent best suited to the individual (*agents listed in alphabetical order*):						
Class	**Relative A1C Lowering**	**Hypo-glycemia**	**Weight**	**Effect in Cardiovascular Outcome Trial**	**Other therapeutic considerations**	**Cost**
α-glucosidase inhibitor (acarbose)	↓	Rare	neutral to ↓		Improved postprandial control, GI side-effects	$$
Incretin agents: DPP-4 Inhibitors GLP-1R agonists	 ↓↓ ↓↓ to ↓↓↓	 Rare Rare	 Neutral to ↓ ↓↓	 Neutral (alo, saxa, sita) Neutral (lixi)	 Caution with saxagliptin in heart failure GI side-effects	 $$$ $$$$
Insulin	↓↓↓	Yes	↑↑	Neutral (glar)	No dose ceiling, flexible regimens	$-$$$$
Insulin secretagogue: Meglitinide Sulfonylurea	 ↓↓ ↓↓	 Yes Yes	 ↑ ↑		 Less hypoglycemia in context of missed meals but usually requires TID to QID dosing Gliclazide and glimepiride associated with less hypoglycemia than glyburide	 $$ $
SGLT2 inhibitors	↓↓ to ↓↓↓	Rare	↓↓	Superiority (empa in T2DM patients with clinical CVD)	Genital infections, UTI, hypotension, dose-related changes in LDL-C, caution with renal dysfunction and loop diuretics, dapagliflozin not to be used if bladder cancer, rare diabetic ketoacidosis (may occur with no hyperglycemia)	$$$
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Types of Insulin

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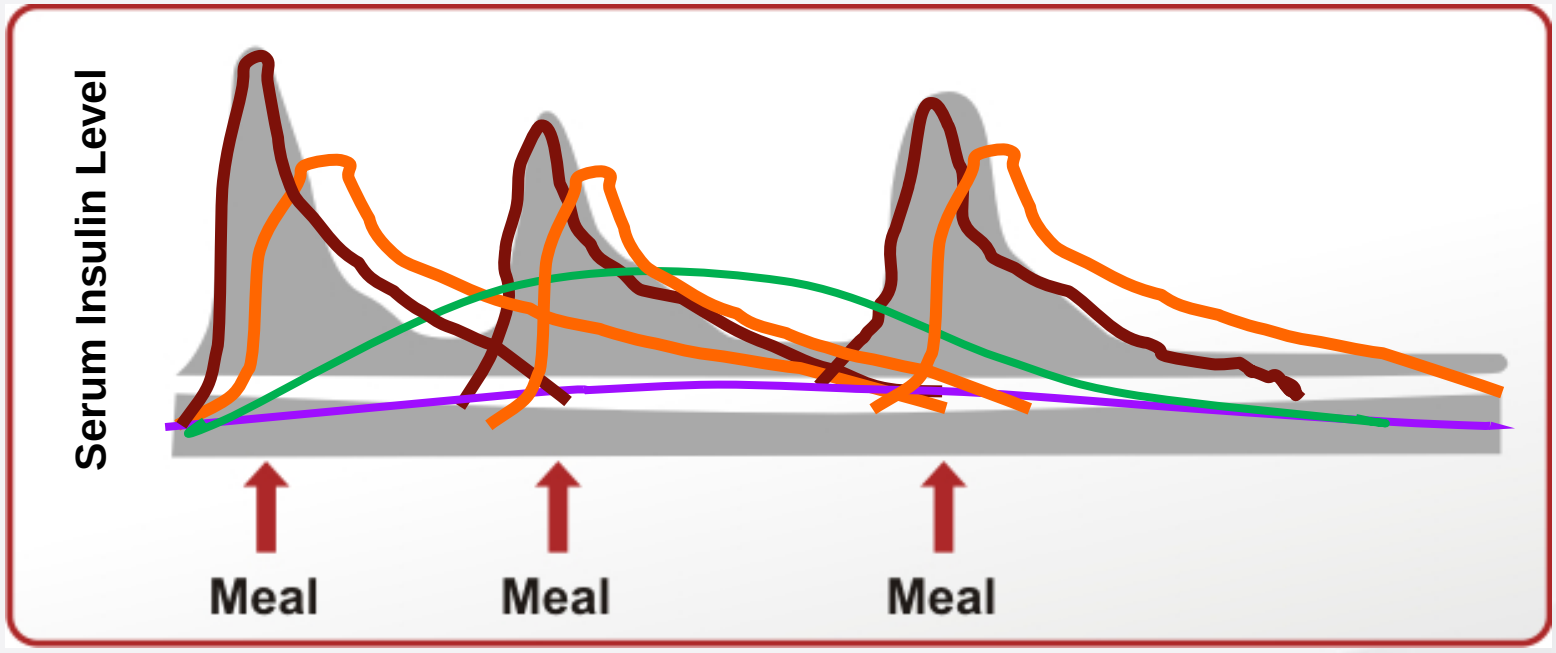
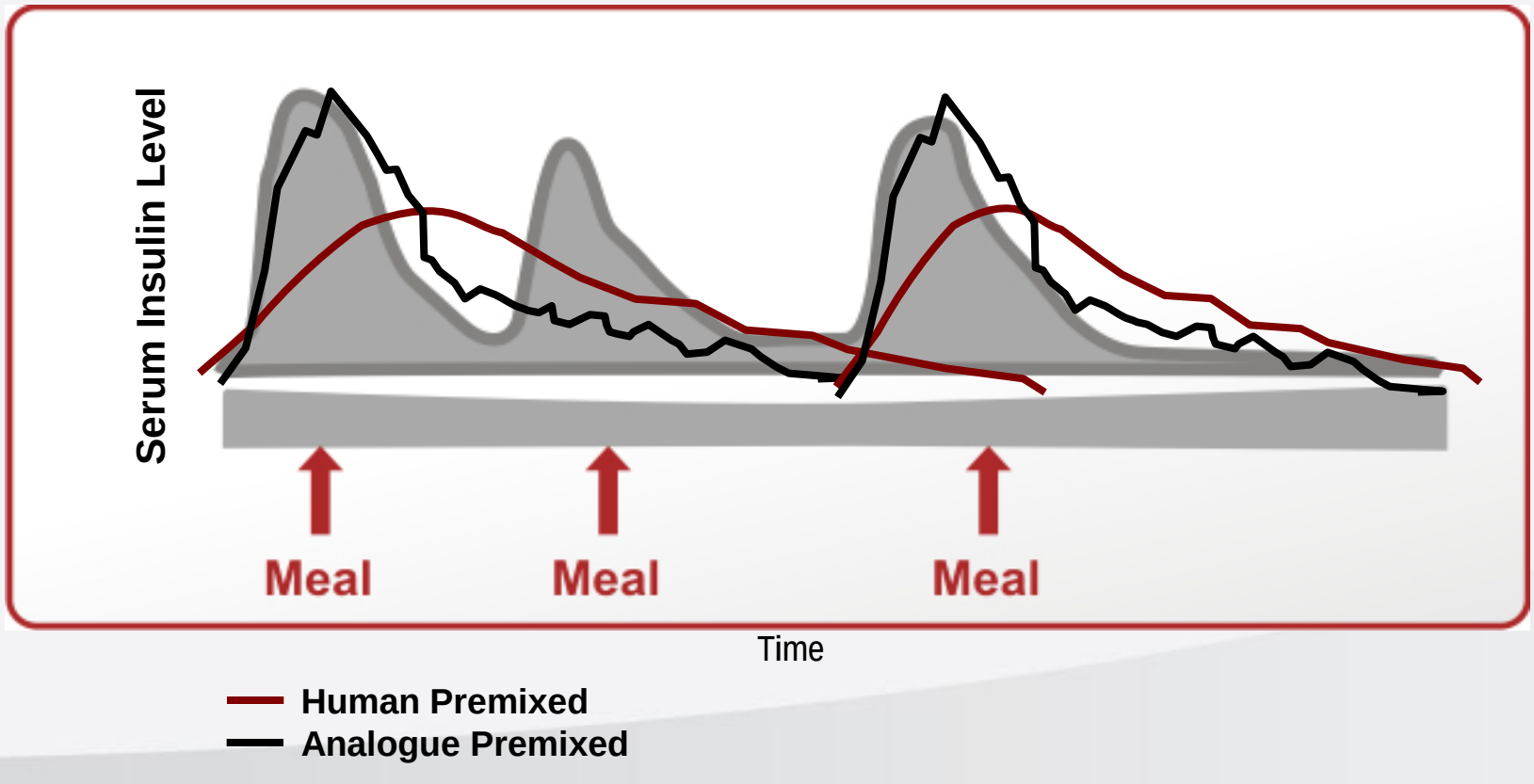
Insulin Type (trade name)	Onset	Peak	Duration
Bolus (prandial) Insulins			
Rapid-acting insulin analogues (clear): • Insulin aspart (NovoRapid®) • Insulin glulisine (Apidra™) • Insulin lispro (Humalog®) • Insulin lispro U200 (Humalog® 200 units/mL)	 10 - 15 min 10 - 15 min 10 - 15 min 10 - 15 min	 1 - 1.5 h 1 - 1.5 h 1 - 2 h 1 - 2 h	 3 - 5 h 3 - 5 h 3.5 - 4.75 h 3.5 - 4.75 h
Short-acting insulins (clear): • Insulin regular (Humulin®-R) • Insulin regular (Novolin®geToronto)	30 min	2 - 3 h	6.5 h
Basal Insulins			
Intermediate-acting insulins (cloudy): • Insulin NPH (Humulin®-N) • Insulin NPH (Novolin®ge NPH)	1 - 3 h	5 - 8 h	Up to 18 h
Long-acting basal insulin analogues (clear) • Insulin detemir (Levemir®) • Insulin glargine (Lantus®) • Insulin glargine U300 (Toujeo®) • Insulin glargine (Basaglar™)	 90 min 90 min Up to 6 h 90 min	 Not applicable	 Up to 24 h (detemir 16-24 h) Up to 24 h (glargine 24 h) Up to 30 h Up to 24 h (glargine 24 h)

Types of Insulin (continued)

Insulin Type (trade name)	Time action profile
Premixed Insulins	
Premixed regular insulin – NPH (cloudy): • 30% insulin regular/ 70% insulin NPH (Humulin® 30/70) • 30% insulin regular/ 70% insulin NPH (Novolin®ge 30/70) • 40% insulin regular/ 60% insulin NPH (Novolin®ge 40/60) • 50% insulin regular/ 50% insulin NPH (Novolin®ge 50/50)	A single vial or cartridge contains a fixed ratio of insulin (% of rapid-acting or short-acting insulin to % of intermediate-acting insulin)
Premixed insulin analogues (cloudy): • 30% Insulin aspart/70% insulin aspart protamine crystals (NovoMix® 30) • 25% insulin lispro / 75% insulin lispro protamine (Humalog® Mix25®) • 50% insulin lispro / 50% insulin lispro protamine (Humalog® Mix50®)	





Appendix 3

Examples of Insulin Initiation and Titration Regimens in People with Type 2 Diabetes

All people starting insulin should be counseled about the recognition, prevention and treatment of hypoglycemia. Consider a change in type or timing of insulin administration if glycemic targets are not being reached.

Example A: Basal insulin (Humulin®-N, Lantus®, Levemir®, Novolin®ge NPH) added to oral antihyperglycemic agents

- Insulin should be titrated to achieve target fasting BG levels of 4.0 to 7.0 mmol/L.
- Individuals can be taught self-titration, or titration may be done in conjunction with a healthcare provider.
- Suggested starting dose is 10 units once daily at bedtime.
- Suggested titration is 1 unit per day until target is reached.
- A lower starting dose, slower titration and higher targets may be considered for elderly or normal weight subjects.
- In order to safely titrate insulin, patients must perform SMBG at least once a day fasting.
- Insulin dose should not be increased if the individual experiences 2 episodes of hypoglycemia (BG <4.0 mmol/L) in 1 week or any episode of nocturnal hypoglycemia.
- For fasting BG levels consistently <5.5 mmol/L, a reduction of 1 to 2 units of insulin may be considered to avoid nocturnal hypoglycemia.
- Oral antihyperglycemic agents (especially secretagogues) may need to be reduced if daytime hypoglycemia occurs.

Example B: Basal Plus Strategy - Adding bolus (prandial) insulin (Apidra®, Humalog®, NovoRapid®) once daily to optimized basal insulin therapy

- When intensification of insulin therapy is necessary, start one injection of meal time insulin to either main meal or breakfast.
- Starting dose is 2 to 4 units and patient can be taught self titration or dose increase can be done by HCP.
- To safely increase dose, glucose levels should be measured at least prior to insulin dose then titrated by 1 unit daily to either of the following targets.
  - 2 hour post meal glucose of 10.0 mmol/L (or ≤ 8.0 mmol/L in certain cases)
  - pre-meal glucose of the next meal of 4.0 to 7.0 mmol/L.
- Important to keep carbohydrate intake constant. Oral antihyperglycemic agents (especially secretegogues) may need to be reduced or stopped particularly if daytime hypoglycemia occurs.

Example C: Basal-Bolus Insulin - Intensive insulin therapy

- Calculate total daily dose of 0.3 to 0.5 units/kg then distribute as follows:
  a. 40% of total insulin dose as basal insulin (Humulin®-N, Lantus®, Levemir®, Novolin®ge NPH).
  b. 20% of total insulin as bolus (prandial) insulin 3 times per day using either rapid-acting insulin analogue (Apidra®, Humalog®, NovoRapid®) or short-acting insulin (Humulin®, Novolin®ge Toronto).

Example D: Premixed insulin (Humulin® 30/70, Novolin® 30/70, Humalog® Mix 25 or Humalog® Mix 50, NovoMix® 30,) added to oral antihyperglycemic agents

- Suggested starting dose is 5 to 10 units once or twice daily (prebreakfast and/or presupper).
- Suggested titration is 1 to 2 units added to prebreakfast dose and/or presupper dose daily until target BG values are reached based on prebreakfast and presupper BG readings.
- Prebreakfast premixed insulin achieves presupper target BG value (4.0 to 7.0 mmol/L).
- Presupper premixed insulin achieves target fasting BG value (4.0 to 7.0 mmol/L).
- 30/70 premixed insulin should be given 30 to 45 minutes before meals.
- Humalog® Mix 25 or NovoMix® 30 premixed insulin should be given immediately before eating.
- Stop increasing insulin when both target BG levels are reached.
- If both BG targets are not reached, continue to increase the relevant dose until both targets achieved.
- The individual needs to self-monitor BG at least twice daily to safely titrate insulin.
- Insulin dose should not be increased if the individual experiences 2 or more episodes of hypoglycemia (BG <4.0 mmol/L) in 1 week or any episode of nocturnal hypoglycemia.
- Oral antihyperglycemic agents (especially secretagogues) may need to be reduced or stopped at the start of this regimen or when daytime hypoglycemia occurs.

Sample Instructions for Patients With Type 2 Diabetes Who Are Starting and Adjusting Basal Insulin

You will be taking insulin _____ at _____.
It is important that you continue to take your other diabetes medications as prescribed unless you have been told to change the dose or stop them.

How to adjust your insulin dose

- Your target fasting blood glucose level is _____ mmol/L.
- You will inject _____ units of _____ at _____.
- You will continue to increase your insulin dose by _____ unit(s) every _____ day(s) until your fasting blood glucose level is _____ mmol/L.
- Do not increase your insulin when your fasting blood glucose is _____ mmol/L.
- You should call for further instructions when your blood glucose reaches _____ mmol/L for 3 or more days: phone number _____.
- A side effect of insulin is low blood glucose (hypoglycemia); low blood glucose can occur with too much insulin, increased activity or not enough food.

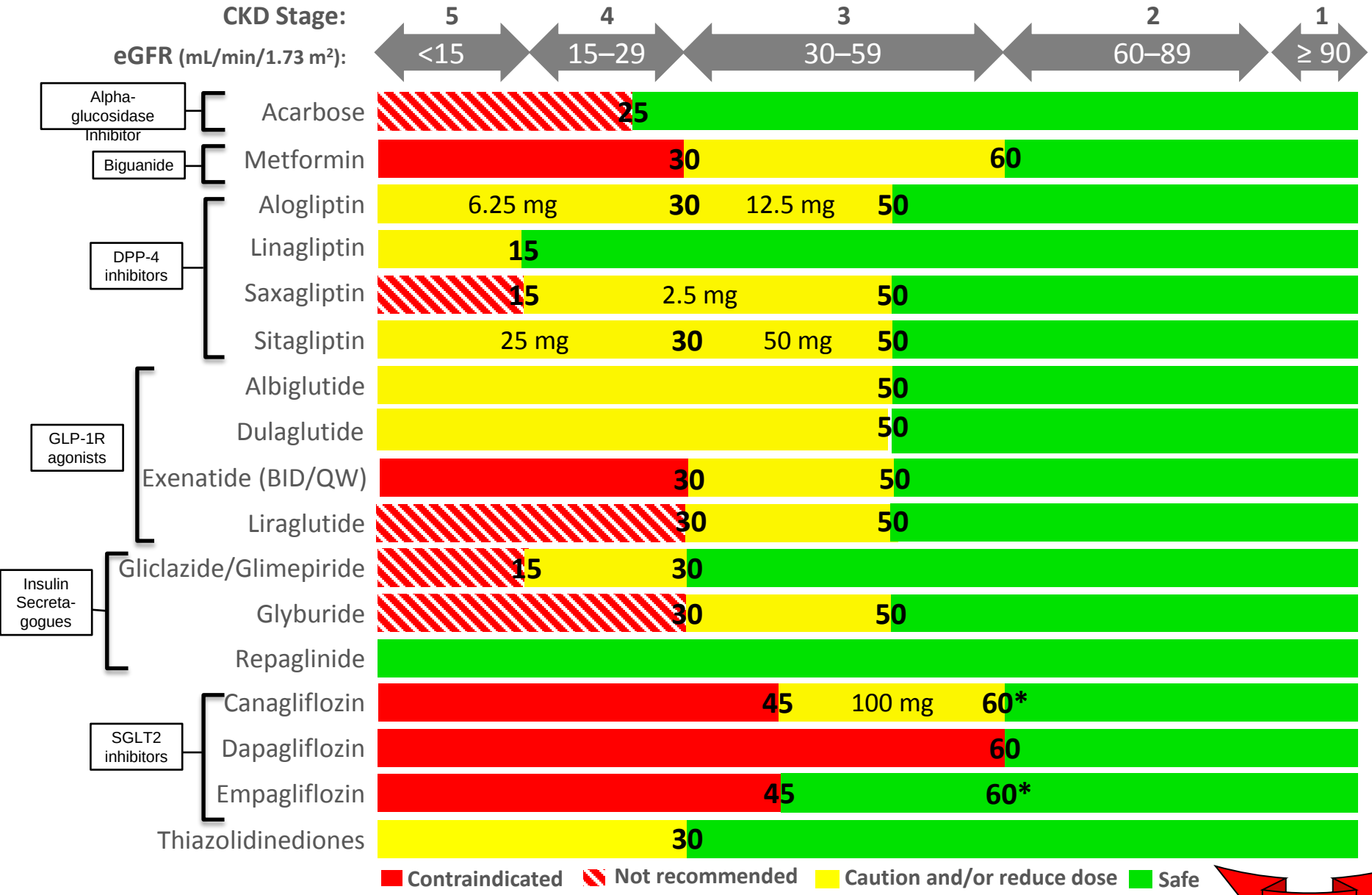
Monitoring your blood glucose

- It is important to test your blood glucose while your insulin treatment is being modified.
- You should test your blood glucose and record the value every day before breakfast and _____.
- Test before each meal, unless you are instructed differently.
- It is important to record your blood glucose values and any changes in activity or food in your diary and bring this to your next appointment; this information helps us to understand your diabetes control.
- Unless otherwise instructed, you are trying to reach a target blood glucose of 4.0 to 7.0 mmol/L before meals, and 5.0 to 10.0 mmol/L after meals.
- If you think your blood glucose is low, check it and record that information in your diary.

Instructions for taking your diabetes medications

Current medications	Dose	Time of day	Special instructions

Antihyperglycemic agents and Renal Function



* = do not initiate if eGFR <60 ml/min

2016

Adapted from: Product Monographs as of March 2016
Harper W et al. Can J Diabetes 2015;39:440.

Guidelines
Executive Summary
Full Guidelines
Quick Reference Guide

Key Messages
Screening & Diagnosis
Vascular Protection
Blood Glucose Lowering
Self-Management Education
Team & Organizing Care
Special Populations

For Healthcare Providers
Healthcare Provider Tools
Slides and Videos

For Patients
Patient Resources

Other Langua
Ressources françaises

Canadian Diabetes Association is helping you provide patient-centred diabetes care and chronic disease management.

NEW: 2015 Interim Update to the Guidelines 2015

Quick Access

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SCREENING FOR AND DIAGNOSING DIABETES

SELF-MONITORING BLOOD GLUCOSE

REDUCING VASCULAR RISK

INDIVIDUALIZING YOUR PATIENT'S A1C TARGET

2015
PHARMACOTHERAPY FOR TYPE 2 DIABETES

CPG CHAPTER SLIDES & VIDEOS

News & Highlights

2015 Interim Update to the Guidelines
New addition to the Pharmacologic Management of Type 2 Diabetes

Tip of the Week
Healthcare provider Q&A

Pharmacotherapy for Type 2 Diabetes

Print

By Agent and Patient Characteristics

▼ STEP 1: Inital Pharmacotherapy

At diagnosis of type 2 diabetes: Start lifestyle intervention (nutrition therapy and physical activity) +/- Meformin

Which of the following applies to your patient?

- A1C <8.5%
- A1C ≥8.5%
- Symptomatic hyperglycaemia with metabolic decompensation

Get Recommendation

▼ STEP 2: Individualize and Sort Results

Please complete step 1

Recommendation 1

1. In people with a **new diagnosis** of type 2 diabetes:
   - **i.** **Metformin** may be used **at time of diagnosis**, in conjunction with lifestyle management [Grade D, consensus]
   - ii. If **A1C ≤8.5%** and glycemic targets are not achieved using lifestyle management within 2-3 months, antihyperglycemic agent therapy with metformin should be initiated [Grade A, level 1].

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Recommendation 1 (continued)

iii. If **A1C ≥8.5%**, antihyperglycemic agents should be **initiated concomitantly** with lifestyle management, and consideration should be given to initiating **combination therapy with two agents**, one of which may be insulin (Grade D, consensus)

iv. Individuals with **symptomatic hyperglycemia** and **metabolic decompensation** should receive an initial antihyperglycemic regimen containing **insulin** with or without metformin [Grade D, Consensus]

Recommendation 2

2. **Metformin** should be the **initial** drug used in monotherapy [(Grade A, Level 1) for overweight patients; (Grade D, consensus) for non-overweight patients]

Recommendation 3

3. Other classes of antihyperglycemic agents, including insulin, should be added to metformin, or used in combination with each other, if glycemic targets are not met, taking into account the information in Figure 1 and Table 1 [Grade D, consensus] and these adjustments to and/or additions of antihyperglycemic agents should be made in order to **attain target A1C within 3-6 months** [Grade D, consensus]

Recommendation 4

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4. In people with **clinical cardiovascular disease** in whom glycemic targets are not met, a **SGLT2 inhibitor with demonstrated cardiovascular outcome benefit** should be added to antihyperglycemic therapy to reduce the risk of cardiovascular and all-cause mortality [Grade A, Level 1A for empagliflozin].

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Recommendation 5 2016

5. Choice of additional pharmacological agents should be individualized taking into consideration *[Grade D, consensus]*

Patient Characteristics

- Degree of hyperglycemia
- Risk of hypoglycemia
- Overweight or obesity
- Clinical cardiovascular disease
- Co-morbidities (renal, CHF, hepatic)
- Patient preferences and access

Agent Characeristics

- BG lowering efficacy and durability
- Risk of inducing hypoglycemia
- Effect on weight
- Effect on cardiovascular outcomes
- Side effects
- Contraindications
- Cost and coverage

Recommendation 6

6. When **basal** insulin is added to antihyperglycemic agents, **long-acting analogues** (detemir or glargine) may be used instead of intermediate-acting NPH to reduce the risk of nocturnal and symptomatic hypoglycemia [Grade A, Level 1A]

Recommendation 7

7. When **bolus** insulin is added to antihyperglycemic agents, **rapid-acting analogues** (insulin aspart, glulisine, or lispro) may be used instead of regular insulin to improve glycemic control [Grade B, Level 2] and to reduce the risk of hypoglycemia [Grade D, Consensus]

Recommendation 8

8. All individuals with type 2 diabetes currently using, or starting therapy with **insulin** or **insulin secretagogues**, should be counseled about the prevention, recognition, and treatment of drug-induced **hypoglycemia** [Grade D, Consensus]

CDA Clinical Practice Guidelines

http://guidelines.diabetes.ca – for professionals

1-800-BANTING (226-8464)

http://diabetes.ca – for patients