EVERYTHING YOU WANTED TO KNOW ABOUT DIABETES DRUGS
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Objectives

- Discuss the indications, contraindications & modes of action of medications used to control increased blood glucose
- Discuss briefly the CDA 2013 guidelines & updates pertaining specifically to the medication used in T1DM & T2DM to control blood glucose
  - Focus on recent medication releases
- Discuss briefly other medications used in patients with T1DM & T2DM
- Explain the considerations & rationale for therapeutic choices in diabetes
- Discuss medication cost/coverage issues as they impact patient care
Diabetes: Complications

**Macrovascular**
- Stroke
- Heart disease & hypertension
  - 2-4 x increased risk
- Peripheral vascular disease
- Foot problems

**Microvascular**
- Diabetic eye disease (retinopathy & cataracts)
- Renal disease
- Erectile Dysfunction
- Peripheral Neuropathy

Key Challenges Of T1DM

- Patient unable to produce own endogenous insulin
- Insulin is lifesaving pharmacological therapy for people with T1DM
- Insulin use increases the risk of hypoglycemia
- Risk of DKA with uncontrolled BGs
- Micro- & Macrovascular disease
Key Challenges Of T2DM

- Diabetes is a progressive disease
  - Declining β-cell function
  - Deteriorating blood glucose control
  - Increased risk of CV disease
  - Difficulty controlling after meal glucose & glucose fluctuations
  - Complications & co-morbidities

- Diabetes treatments
  - Increased risk of low blood glucose with some therapies
  - Weight gain with some therapies
  - Complex treatment regimens
  - Increased requirement for self-monitoring of blood glucose
Glycemic Control Over Time In T2DM

Control erodes with time: only 38% of patients who have had type 2 diabetes for 15+ years are well controlled.

Non-Medication Management

- **Activity/Exercise**
  - Aerobic
    - 150 minutes per week
  - Resistance

- **Nutrition**
  - CDA recommends counseling by a dietitian for T2DM
  - Can ↓ A1c by 1.0% to 2.0%

Adapted from: CDA CPG 2013
Medication Management

- Usually more than one medication is required to achieve blood glucose goals
- On average, Canadians with diabetes take 8 prescription medications daily
  - Blood sugar
  - Blood pressure
  - Kidney protection
  - Cholesterol
  - Stroke/heart attack prevention
  - Pain control
Considerations For Medication Selection

- Efficacy & safety
- Dosing regimen
- Use with other agents
- Co-morbid conditions
- Cost (patient & institution)
- Monitoring
- Barriers to adherence
The “Perfect” Diabetes Drug

- Effective blood glucose lowering
- Low risk of hypoglycemia
- Simple dosing
- No weight gain
- Complimentary mechanism of action with other therapies
- Durability of action
- Well tolerated
- Long term safety
- Inexpensive
- Added value
  - Lipids
  - β-cell function
  - CVD
In Our Current Arsenal...

- **Oral medications**
  - Metformin
  - Sulfonylureas
  - Glitinides
  - α-glucosidase inhibitors
  - DPP-4 inhibitors
  - TZDs
  - SGLT-2 inhibitors

- **Non-insulin injectables**
  - GLP-1 analogues
    - Daily or BID
    - Weekly

- **Insulin**
  - Human
  - Analogues
  - Biosimilars
Sites Of Action

- **Liver**
  - ↓ glucose production
    - • TZDs
    - • Metformin
    - • Insulin
    - • Incretin agents

- **Intestine**
  - ↓ glucose absorption
    - • α-glucosidase inhibitors

- **Pancreas**
  - ↑ secretion of insulin or replace insulin & ↓ glucagon
    - • Insulin
    - • Secretagogues
    - • Incretin agents

- **Muscle/Adipose**
  - ↑ peripheral glucose uptake & utilization
    - • TZDs
    - • Metformin

- **Kidney**
  - ↑ excretion of glucose from kidneys
    - • SGLT-2 inhibitors
Non-Insulin Medications
Non-Insulin Medication Classes

- **Sensitizers**
  - Biguanides
    - Metformin
  - TZDs
    - Pioglitazone
    - Rosiglitazone

- **Secretagogues**
  - Sulfonylureas
    - Gliclazide
    - Glimepiride
    - Glyburide
  - Meglitinides
    - Repaglinide

- **α-glucosidase inhibitors**
  - Acarbose

- **Incretins**
  - DPP-4 inhibitors
    - Alogliptin
    - Linagliptin
    - Saxagliptin
    - Sitagliptin
  - GLP-1 analogues
    - Albiglutide*
    - Dulaglutide
    - Exenatide
    - Liraglutide

- **SGLT-2 inhibitors**
  - Canagliflozin
  - Dapagliflozin
  - Empagliflozin

* - approved but not currently marketed in Canada
Metformin

- What it does
  - ↓ liver glucose production
  - ↑ insulin sensitivity
- A1c reduction
  - 1-1.5%
- Hypoglycemia risk
  - Negligible as monotherapy
- Coverage
  - ODB – 500mg
  - NIHB – 500mg & 850mg
- Cost
  - $-$-$-$

- What you should know
  - Metallic taste
  - GI side effects
  - Vitamin B₁₂/folate deficiency
  - Caution with kidney or liver problems
  - Weight neutral
  - Improved lipid profile
  - Caution with contrast media
  - Low risk of lactic acidosis

Adapted from: RxFiles.ca; Therapeutic Choices 2014;  CDA CPG 2013; CPS 2015
Thiazolidinediones (TZDs)

- **What they do**
  - ↑ insulin sensitivity
  - ↓ liver glucose production
- **A1c reduction**
  - 0.8%
- **Hypoglycemia risk**
  - Negligible as monotherapy
- **Coverage**
  - ODB – EAP (TRS)
  - NIHB – requires pre-approval
- **Cost**
  - $$

- **What you should know**
  - 6-12 weeks for full effect
  - Weight gain
  - Mild ↓ BP
  - Sustained BG ↓
  - May cause edema & fluid retention
  - Contraindicated patients with or history of CHF
  - Fractures; macular edema; MI (rosi); bladder CA (pio)

Adapted from: RxFiles.ca; Therapeutic Choices 2014; CDA CPG 2013; CPS 2015
Sulfonylureas

- **What they do**
  - Stimulate release of insulin from β-cells
- **A1c reduction**
  - 0.8%
- **Hypoglycemia risk**
  - glyburide – significant
  - glimepiride – moderate
  - gliclazide/gliclazide MR – minimal/moderate
- **Coverage**
  - ODB – gliclazide; gliclazide MR; glyburide
  - NIHB – gliclazide; gliclazide MR; glyburide
- **Cost**
  - $

- **What you should know**
  - Rapid BG lowering
  - Weight gain
  - Consider other classes in patients with high risk of low blood glucose
  - Small chance of allergic reaction if allergic to sulfa drugs
  - Caution with kidney or liver problems
  - Possible photosensitivity

Adapted from: RxFiles.ca; Therapeutic Choices 2014; CDA CPG 2013; CPS 2015
Meglitinides

- What they do
  - Stimulate release of insulin from β-cells
- A1c reduction
  - 0.7%
- Hypoglycemia risk
  - minimal/moderate
- Coverage
  - ODB – EAP
  - NIHB – full coverage
- Cost
  - $$

- What you should know
  - Rapid onset
  - Short-acting
  - Less risk of low blood glucose than SU
  - Weight gain (less than SU)
  - Safe for all stages of renal function
  - Need to be taken with every meal
    - If you skip a meal, don’t take the pill for that meal

Adapted from: RxFiles.ca; Therapeutic Choices 2014; CDA CPG 2013; CPS 2015
Acarbose

- What it does
  - Delays CHO absorption
- A1c reduction
  - 0.6%
- Hypoglycemia risk
  - Negligible as monotherapy
- Coverage
  - ODB – LU 175 or 176
  - NIHB – full coverage
- Cost
  - $$

What you should know
- GI side effects
  - Gas, bloating & flatulence
- Treat lows with dextrose, honey or milk only
- Weight neutral
- Take with 1st bite of meal

Adapted from: RxFiles.ca; Therapeutic Choices 2014; CDA CPG 2013; CPS 2015
Role Of Incretins In Glucose Control

Active GLP-1 and GIP
- Increased glucose uptake by muscles
- Decreased blood glucose
- Decreased appetite
- Increased satiety
- Decreased gut motility

Inactive DPP-4

Pancreas
- Increased glucose-dependent insulin release, increased ß-cell regeneration (GLP-1 & GIP)
- Decreased glucose-dependent glucagon release from α-cells (GLP-1)

Adapted from Drucker DJ. Cell Metab. 2006;3(3):153-165.
The Incretin Effect In Healthy Subjects

DPP-4 Inhibitors

- What they do
  - ↑ insulin secretion
  - ↓ glucagon secretion
- A1c reduction
  - 0.7%
- Hypoglycemia risk
  - Negligible as monotherapy
- Coverage
  - ODB – covered (including combos with metformin; alogliptin products not covered)
  - NIHB – requires prior approval (including combos with metformin; alogliptin products not covered)
- Cost
  - $$

- What you should know
  - Weight neutral
  - Glucose-dependent action
    - No action if BG low
  - Don’t impair normal glucagon response to low blood glucose
  - Caution in history of pancreatitis
  - Caution in kidney problems
    - Dose reductions required for alogliptin, sitagliptin & saxagliptin
    - No dose reduction needed for linagliptin

Adapted from: RxFiles.ca; Therapeutic Choices 2014; CDA CPG 2013; CPS 2015
GLP-1 Agonists

- **What They Do**
  - ↑ insulin secretion
  - ↓ glucagon secretion
  - Central satiety
- **A1c reduction**
  - 1%
- **Hypoglycemia risk**
  - Negligible as monotherapy
- **Coverage**
  - ODB – not covered
  - NIHB – not covered
- **Cost**
  - $$$$$

- **What you should know**
  - SC injection
  - BID to Qweekly
  - ↓ weight (5.5kg/2y)
  - Glucose-dependent action
  - Delay gastric emptying (feel full)
  - Nausea & vomiting
  - Reports of pancreatitis
    - Association, not causality
  - Caution with kidney problems
  - Parafollicular cell hyperplasia
  - Contraindicated in history of MTC or MEN-2

Adapted from: RxFiles.ca; Therapeutic Choices 2014; CDA CPG 2013; CPS 2015
# GLP-1 Receptor Agonist Drugs

<table>
<thead>
<tr>
<th></th>
<th>Daily</th>
<th>Weekly</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Exenatide* (Byetta)</td>
<td>Dulaglutide (Trulicity)</td>
</tr>
<tr>
<td></td>
<td>Liraglutide (Victoza)</td>
<td>Exenatide-LAR (Bydureon)</td>
</tr>
<tr>
<td>Half-life</td>
<td>2-5h (exenatide)</td>
<td>Several days</td>
</tr>
<tr>
<td></td>
<td>12h (liraglutide)</td>
<td></td>
</tr>
<tr>
<td>Fasting BG</td>
<td>Modest reduction</td>
<td>Strong reduction</td>
</tr>
<tr>
<td>A1c</td>
<td>Modest reduction</td>
<td>Strong reduction</td>
</tr>
<tr>
<td>Postprandial</td>
<td>Strong reduction</td>
<td>Modest reduction</td>
</tr>
<tr>
<td>hyperglycemia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gastric emptying rate</td>
<td>Decrease</td>
<td>No effect</td>
</tr>
<tr>
<td>Blood pressure</td>
<td>Reduction</td>
<td>Reduction</td>
</tr>
<tr>
<td>Body weight reduction</td>
<td>1–5 kg</td>
<td>2–5 kg</td>
</tr>
</tbody>
</table>

* - BID

# GLP-1R Agonists Vs DPP-4 Inhibitors

<table>
<thead>
<tr>
<th>Property/Effect</th>
<th>GLP-1 Agonists</th>
<th>DPP-4 Inhibitors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mechanism of action</td>
<td>Pharmacologic agonist of GLP-1R</td>
<td>Inhibitor of incretin degradation</td>
</tr>
<tr>
<td>Route of administration</td>
<td>Subcutaneous</td>
<td>Oral</td>
</tr>
<tr>
<td>A1c lowering (dose dependent)</td>
<td>Up to 1.5%</td>
<td>Up to 1%</td>
</tr>
<tr>
<td>Slows gastric emptying</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Promotes satiety</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Weight</td>
<td>Decreased</td>
<td>Neutral</td>
</tr>
</tbody>
</table>

Drucker DJ. Cell Metab. 2006 Mar;3(3):153-165.
Kidney & Glucose Homeostasis

- Kidney
  - Produces glucose
  - Uses glucose
  - Filters glucose
  - Reabsorbs glucose

Adapted from: CDA CPG 2015
Mechanism of Action

SGLT-2 inhibitors lower plasma glucose levels in patients with T2DM by inhibiting renal glucose reabsorption.

Glomerulus  Proximal tubule  Distal tubule  Collecting duct

Glucose filtration

Decreased glucose reabsorption

SGLT-2i

Increased glucose secretion

Rossetti et al J Clin Invest 1987;79:1510-1515;
Renal Threshold

![Graph showing the relationship between plasma glucose and urinary glucose excretion. The graph illustrates the normal threshold, SGLT-2 inhibition, and diabetes threshold.](image-url)
SGLT-2 Inhibitors

- **What they do**
  - Block glucose reabsorption in kidney
- **A1c reduction**
  - 0.7-1%
- **Hypoglycemia risk**
  - Low risk of hypoglycemia
- **Coverage**
  - ODB – covered (combos with metformin not covered)
  - NIHB – requires prior approval (combos with metformin not covered)
- **Cost**
  - $$$

- **What you should know**
  - ↓ BP ~6/3 mmHg
  - Weight loss
    - Removes 50-80g/day
  - ↑ urination; transient
  - Risk of UTI/genital infections
  - Ketoacidosis
  - Dehydration/electrolyte imbalance (osmotic diuresis)
    - ↑ K⁺
  - Acute decrease in eGFR
  - Slight increase in LDL
  - Caution with kidney problems
  - Bladder/prostate/breast cancer?

Adapted from: RxFiles.ca; eTherapuetics +; CPS 2015
Insulin
Principles Of Insulin Therapy

- **Goal**
  - Mimic the body’s normal insulin secretion

- **Practical**
  - Mimic the body’s normal insulin secretion as closely as possible

- **Individualize**
  - Match insulin action to patient’s lifestyle & eating patterns
Insulin

- What it does
  - Replaces/supplements body’s insulin supply
  - Allows body to use glucose in the blood

- A1c reduction
  - > 2%

- Hypoglycemia risk
  - Significant

- Coverage*
  - ODB – covered (NovoRapid – LU: 388, 389, 390; Basaglar, Fiasp & Toujeo not covered)
  - NIHB – covered (NovoMix 30, Humalog u200, Basaglar, Fiasp & Toujeo not covered)

- What you should know
  - Greatest ↓ A1c & no maximum dose
  - Immediate onset
  - Weight gain
  - Can use with oral meds in T2DM
  - All common types available without a prescription (OTC)
  - May need to adjust dose with worsening kidney function
  - Absorption rate can be affected by exercise or rubbing of injection site
  - Usually requires dose adjustment to reach target blood glucose
  - Should test BGs regularly

* -newer formulations awaiting coverage

Adapted from: RxFiles.ca; Therapeutic Choices 2014; CDA CPG 2016 update; CPS 2015
## Types Of Insulin - Mealtime

<table>
<thead>
<tr>
<th>Insulin Type (trade name)</th>
<th>Onset</th>
<th>Peak</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Bolus (prandial) Insulins</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rapid-acting insulin analogues (clear):</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Insulin aspart (<em>Fiasp</em>®)</td>
<td>4 - 5 min</td>
<td>45 - 60 min</td>
<td>3 - 5 h</td>
</tr>
<tr>
<td>• Insulin aspart (<em>NovoRapid</em>®)</td>
<td>10 - 15 min</td>
<td>1 - 1.5 h</td>
<td>3 - 5 h</td>
</tr>
<tr>
<td>• Insulin glulisine (<em>Apidra</em>™)</td>
<td>10 - 15 min</td>
<td>1 - 1.5 h</td>
<td>3 - 5 h</td>
</tr>
<tr>
<td>• Insulin lispro (<em>Humalog</em>®)</td>
<td>10 - 15 min</td>
<td>1 - 2 h</td>
<td>3.5 - 4.75 h</td>
</tr>
<tr>
<td>• Insulin lispro 200u/mL (<em>Humalog</em>®)</td>
<td>10 - 15 min</td>
<td>1 - 2 h</td>
<td>3.5 - 4.75 h</td>
</tr>
<tr>
<td><strong>Short-acting insulins (clear):</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Insulin regular (<em>Humulin</em>®-R)</td>
<td>30 min</td>
<td>2 - 3 h</td>
<td>6.5 h</td>
</tr>
<tr>
<td>• Insulin regular (<em>Novolin</em>® ge Toronto)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Adapted from: CDA CPG 2016 Update
## Types Of Insulin - Basal

<table>
<thead>
<tr>
<th>Insulin Type (trade name)</th>
<th>Onset</th>
<th>Peak</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Basal Insulins</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intermediate-acting insulins (cloudy):</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Insulin NPH (Humulin®-N)</td>
<td>1 - 3 h</td>
<td>5 - 8 h</td>
<td>Up to 18 h</td>
</tr>
<tr>
<td>• Insulin NPH (Novolin® ge NPH)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Long-acting basal insulin analogues (clear):</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Insulin degludec (Tresiba®) *</td>
<td>90 min</td>
<td>Not applicable</td>
<td>&gt; 42 h</td>
</tr>
<tr>
<td>• Insulin detemir (Levemir®)</td>
<td>90 min</td>
<td></td>
<td>16-24 h</td>
</tr>
<tr>
<td>• Insulin glargine (Basaglar®)</td>
<td>90 min</td>
<td></td>
<td>Up to 24 h</td>
</tr>
<tr>
<td>• Insulin glargine (Lantus®)</td>
<td>90 min</td>
<td></td>
<td>Up to 24 h</td>
</tr>
<tr>
<td>• Insulin glargine 300u/mL (Toujeo®)</td>
<td>Up to 6 h</td>
<td></td>
<td>Up to 30 h</td>
</tr>
</tbody>
</table>

* - not available in Canada, yet

Adapted from: CDA CPG 2016 Update
## Types Of Insulin - Premixes

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

Adapted from: CDA CPG 2016 Update
Insulin Action Profile – Premixed

Adapted from: CDA CPG 2016 Update
Now What?
Consider...

- Degree of hyperglycemia
- Risk of hypoglycemia
- Overweight or obese
- Cardiovascular disease or multiple risk factors
- Comorbidities
  - Renal
  - CHF
  - Hepatic
- Preference of patient
  - Route
  - Frequency
  - “Pill burden”
- Access to treatment
  - Costs/coverage
Individualizing A1c Target

A target A1C ≤6.5% may be considered in some patients with type 2 diabetes to further lower the risk of nephropathy and retinopathy which must be balanced against the risk of hypoglycemia.

Most patients with type 1 and type 2 diabetes

Consider 7.1-8.5% if:
- Limited life expectancy
- High level of functional dependency
- Extensive coronary artery disease at high risk of ischemic events
- Multiple co-morbidities
- History of recurrent severe hypoglycemia
- Hypoglycemia unawareness
- Longstanding diabetes for whom it is difficult to achieve an A1C ≤7%, despite effective doses of multiple antihyperglycemic agents, including intensified basal-bolus insulin therapy.
# Antihyperglycemic Agents & Renal Function

**CKD Stage:**
- **5:** <15
- **4:** 15–29
- **3:** 30–59
- **2:** 60–89
- **1:** ≥90

**eGFR (mL/min/1.73 m²):**
- <15
- 15–29
- 30–59
- 60–89
- ≥90

### Alphaglucosidase Inhibitor
- **Acarbose**
  - Stage 1, 2, 3: Safe
  - Stage 4, 5: Caution and/or reduce dose
  - Not recommended

### Biguanide
- **Metformin**
  - Stage 1, 2, 3: Safe
  - Stage 4, 5: Caution and/or reduce dose
  - Not recommended

### DPP-4 inhibitors
- **Alogliptin**
  - Stage 1, 2, 3: Safe
  - Stage 4, 5: Caution and/or reduce dose
  - Not recommended

### GLP-1R agonists
- **Linagliptin**
  - Stage 1, 2, 3: Safe
  - Stage 4, 5: Caution and/or reduce dose
  - Not recommended

### GLP-1R agonists
- **Saxagliptin**
  - Stage 1, 2, 3: Safe
  - Stage 4, 5: Caution and/or reduce dose
  - Not recommended

### GLP-1R agonists
- **Sitagliptin**
  - Stage 1, 2, 3: Safe
  - Stage 4, 5: Caution and/or reduce dose
  - Not recommended

### Biguanide
- **Albiglutide**
  - Stage 1, 2, 3: Safe
  - Stage 4, 5: Caution and/or reduce dose
  - Not recommended

### Biguanide
- **Dulaglutide**
  - Stage 1, 2, 3: Safe
  - Stage 4, 5: Caution and/or reduce dose
  - Not recommended

### SGLT2 inhibitors
- **Exenatide (BID/QW)**
  - Stage 1, 2, 3: Safe
  - Stage 4, 5: Caution and/or reduce dose
  - Not recommended

### SGLT2 inhibitors
- **Liraglutide**
  - Stage 1, 2, 3: Safe
  - Stage 4, 5: Caution and/or reduce dose
  - Not recommended

### Biguanide
- **Gliclazide/Glimepiride**
  - Stage 1, 2, 3: Safe
  - Stage 4, 5: Caution and/or reduce dose
  - Not recommended

### Biguanide
- **Glyburide**
  - Stage 1, 2, 3: Safe
  - Stage 4, 5: Caution and/or reduce dose
  - Not recommended

### Insulin Secretagogues
- **Repaglinide**
  - Stage 1, 2, 3: Safe
  - Stage 4, 5: Caution and/or reduce dose
  - Not recommended

### SGLT2 inhibitors
- **Canagliflozin**
  - Stage 1, 2, 3: Safe
  - Stage 4, 5: Caution and/or reduce dose
  - Not recommended

### SGLT2 inhibitors
- **Dapagliflozin**
  - Stage 1, 2, 3: Safe
  - Stage 4, 5: Caution and/or reduce dose
  - Not recommended

### SGLT2 inhibitors
- **Empagliflozin**
  - Stage 1, 2, 3: Safe
  - Stage 4, 5: Caution and/or reduce dose
  - Not recommended

### Biguanide
- **Thiazolidinediones**
  - Stage 1, 2, 3: Safe
  - Stage 4, 5: Caution and/or reduce dose
  - Not recommended

---

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

No dose adjustment but close monitoring of renal function

# Diabetes Drugs & Associated Risk Factors

<table>
<thead>
<tr>
<th>Drug</th>
<th>Weight</th>
<th>Blood Pressure</th>
<th>Dyslipidemia</th>
<th>Hypoglycemia Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>α-glucosidase inhibitors</td>
<td>Neutral</td>
<td>Improved</td>
<td>Neutral/Improved</td>
<td>Low</td>
</tr>
<tr>
<td>DPP-4 inhibitors</td>
<td>Loss/Neutral</td>
<td>Neutral</td>
<td>Improved</td>
<td>Low</td>
</tr>
<tr>
<td>GLP-1 agonists</td>
<td>Loss</td>
<td>Improved</td>
<td>Improved</td>
<td>Low</td>
</tr>
<tr>
<td>Insulin</td>
<td>Gain</td>
<td>Neutral</td>
<td>Improved</td>
<td>High</td>
</tr>
<tr>
<td>Meglitinides</td>
<td>Gain</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Moderate</td>
</tr>
<tr>
<td>Metformin</td>
<td>Loss/Neutral</td>
<td>Neutral</td>
<td>Improved</td>
<td>Low</td>
</tr>
<tr>
<td>SGLT2 inhibitors</td>
<td>Loss</td>
<td>Improved</td>
<td>Increased LDL</td>
<td>Low</td>
</tr>
<tr>
<td>Sulfonylureas</td>
<td>Gain</td>
<td>Neutral</td>
<td>Variable</td>
<td>Moderate</td>
</tr>
<tr>
<td>TZD</td>
<td>Gain</td>
<td>Improved</td>
<td>Mixed</td>
<td>Low</td>
</tr>
</tbody>
</table>
T1 Diabetes
Medications In T1DM

- Insulin
  - Basal/bolus or MDI
    - Long-acting analogue/rapid-acting analogue
  - Continuous subcutaneous insulin infusion (CSII)
    - Insulin pump
    - Rapid-acting analogue (aspart or lispro)

- Hypoglycemia
  - Counsel about the risk, prevention & treatment of low blood glucose
  - Hypoglycemia unawareness
    - Increased frequency of blood glucose monitoring, including occasional overnight testing
    - Less strict blood glucose targets

- Oral meds?
T2 Diabetes
AT DIAGNOSIS OF TYPE 2 DIABETES

Start lifestyle intervention (nutrition therapy and physical activity) +/- Metformin

<table>
<thead>
<tr>
<th>A1C &lt;8.5%</th>
<th>A1C ≥8.5%</th>
<th>Symptomatic hyperglycemia with metabolic decompensation</th>
</tr>
</thead>
</table>

If not at glycemic target (2-3 mos)

Start / Increase metformin

Start metformin immediately
Consider initial combination with another antihyperglycemic agent

If not at glycemic targets

Initiate insulin +/- metformin

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

PATIENT CHARACTERISTIC

Prioritize:
Clinical Cardiovascular Disease

Degree of hyperglycemia
Risk of hypoglycemia
Overweight or obesity
Cardiovascular disease or multiple risk factors
Comorbidities (renal, CHF, hepatic)
Preferences & access to treatment

CHOICE OF AGENT

Antihyperglycemic agent with demonstrated CV outcome benefit (empagliflozin, liraglutide)
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

See next page…
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
Add another class of agent best suited to the individual (agents listed in alphabetical order):

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

11/2016
Special Populations

Children
Pregnancy
Elderly
Children With T2DM

- In children with T2DM, if glycemic targets are not achieved within 3 to 6 months using lifestyle modifications alone, 1 of the following should be initiated:
  - Metformin
  - Glimepiride
  - Insulin

- Metformin may be used at diagnosis in those children presenting with an A1C >7.0%

Adapted from: CDA CPG 2013
Pregnancy

- **Preconception care**
  - Aim for A1c ≤ 7%
  - Stop ACEi, ARB & statins
  - Switch from OADs to insulin

- **Blood glucose control during pregnancy**
  - FPG < 5.3 mmol/L
  - 1h PPPG < 7.8 mmol/L
  - 2h PPPG < 6.7 mmol/L

- May use rapid acting analogues
  - No difference in baby outcomes

- May use glyburide or metformin during pregnancy for T2DM women who are non-adherent to or who refuse insulin
  - Likely safe BUT no long-term data
  - need discussion with patient

Adapted from: CDA CPG 2013
Elderly

- Assess for level of functional dependency (frailty)
- Individualize glycemic targets based on the above (A1c ≤ 8.5% for frail elderly) but if otherwise healthy, use the same targets as younger people
- Avoid hypoglycemia
  - Especially in cognitive impairment
- Choose antihyperglycemic therapy carefully
  - Caution with
    - Sulfonylureas - hypoglycemia
    - Thiazolidinediones - fractures; heart failure
  - Caution with renal dysfunction
- Basal analogues instead of NPH or human 30/70 insulin
- Premixed insulins instead of mixing insulins separately
- Prefilled pens vs. refillable pens or syringes
- Regular diets instead of “diabetic diets” or nutritional formulas in nursing homes

Adapted from: CDA CPG 2013
Coming Soon...
Future Medications/Treatments...

- DPP-4 inhibitors
- GLP-1 analogues
- Insulins (injection; inhalation; oral)
- Insulin biosimilars
- SGLT-2 inhibitors
- Dopamine receptor agonists
- Bile acid sequestrants
- G-protein receptor agonists
- Monoclonal antibodies
- Fructose 1,6-bisphosphatase inhibitors
- Salicylate derivatives
- Glucokinase activators
- Serine proteinase inhibitor
- iBAT inhibitors
- Leptin analogues
- mTOT modulator
- GLUT4 stimulant
- Ghrelin Receptor Agonist
- Glucagon receptor antagonists
- Protein Tyrosine Phosphatase-1b inhibitors
- Camitine-Palmitoyltransferase -1 inhibitors
- Acetyl COA Carboxylase inhibitors
- Hydroxysteroid Dehydrogenase-1 inhibitors
- Human pro-islet peptide
- MTP inhibitors
- Bromocriptine
- Closed-loop insulin pumps/artificial pancreas
Glucokinase Activators

- **Glucokinase**
  - High impact on glucose homeostasis
  - Glucose sensor role in pancreatic β-cells
  - Rate-controlling enzyme for hepatic glucose clearance & glycogen synthesis

- **Glucokinase activators**
  - Stimulate insulin biosynthesis & secretion
  - Augment glucose metabolism in glucokinase-expressing cells
  - Work by enhancement of β-cell function

- **Side effects**
  - Rare
  - Hypoglycemia
  - Fatty liver
  - Hyperlipidemia
Monoclonal Antibodies

- Treat diabetes by inducing immune tolerance via monoclonal antibodies

- Otelixizumab
  - Anti-CD3 monoclonal antibody
  - Known to stimulate C-peptide levels & reduce insulin requirement in T1DM

- Teplizumab has shown similar results

- Other monoclonal antibodies being investigated
  - Anti-CD20
  - Anti-CTGF
  - Anti-IL-1β
G-prtein Receptor Stimulators

- GPR119 is expressed in the pancreas & GI tract in rodents & humans, as well as in the brain of rodents.
- Activation of the receptor has been shown to cause a reduction in food intake & body weight gain in rats.
- GPR119 has also been shown to regulate incretin & insulin secretion.
Other Considerations
Other Meds To Consider In T2DM

- **Blood Pressure/Vascular Protection**
  - ACEIs ("-prils")
  - ARBs ("-sartans")
  - Thiazides
  - Calcium channel blockers
  - Beta blockers ("-olols”)

- **Cholesterol/lipids**
  - HMG-CoA reductase inhibitors ("-statins”)
  - Fibrates
  - Cholesterol absorption inhibitor
  - PCSK9 inhibitors (injectable)

- **Weight Loss Agents**
  - Orlistat (Xenical)
  - Liraglutide (Saxenda)

- **Cardiovascular**
  - ECASA
  - Clopidrogrel
  - Other anti-platelets

- **Neuropathic Pain**
  - Anticonvulsants
  - Antidepressants
  - Opioid analgesics
  - Local anesthetics
Vascular Protection Checklist

- A1c – optimal glycemic control (usually ≤7%)
- BP – optimal blood pressure control (<130/80)
- Cholesterol – LDL ≤2.0 mmol/L if decided to treat
- Drugs to protect the heart
  - A – ACEi or ARB
  - S – Statin
  - A – ASA if indicated
- Exercise / Eating healthy – regular physical activity, achieve and maintain healthy body weight
- Smoking cessation

Adapted from: CDA CPG - 2013
Who Should Receive ACEi or ARB Therapy?

- ≥55 years of age OR
- Macrovascular disease OR
- Microvascular disease

- Regardless of baseline blood pressure
- At doses that have shown vascular protection [perindopril 8 mg daily (EUROPA), ramipril 10 mg daily (HOPE), telmisartan 80 mg daily (ONTARGET)]
- Among women with childbearing potential, ACEi or ARB should only be used in the presence of proper preconception counseling & reliable contraception
  - Stop ACEi or ARB either prior to conception or immediately upon detection of pregnancy

Adapted from CDA CPG 2013
ONTARGET study investigators. NEJM. 2008;358:1547-59
Hypertension Checklist

- Assess for hypertension (≥ 130/80 mmHg)
- Treat to target < 130/80 mmHg
- Use multiple antihypertensive medications if needed to achieve target (often necessary)
- Use initial combination therapy if
  - systolic blood pressure > 20 mmHg OR
  - diastolic blood pressure > 10 mmHg above target

Adapted from: CDA CPG - 2013
Pharmacotherapy For Hypertension in Patients With Diabetes

With Nephropathy, CVD or CV risk factors

ACE Inhibitor or ARB

With the above

1. ACE Inhibitor or ARB or
2. Thiazide diuretic or DHP-CCB

Combination of 2 first line drugs may be considered as initial therapy if the blood pressure is ≥20 mmHg systolic or ≥10 mmHg diastolic above target

> 2-drug combinations

• Monitor serum K⁺ & SCr in patients with CKD prescribed an ACEi or ARB
• Combinations of an ACEi with an ARB are specifically not recommended in the absence of proteinuria
• More than 3 drugs may be needed to reach target values
• If SCr > 150 µmol/L or CrCl < 30 ml/min, a loop diuretic should be substituted for a thiazide diuretic if control of volume is desired

Adapted from: CDA CPG - 2013
Who Should Receive Statins?

- ≥40 yrs old OR
- Macrovascular disease OR
- Microvascular disease OR
- DM >15 yrs duration and age >30 years OR
- Warrants therapy based on the 2012 Canadian Cardiovascular Society lipid guidelines

- Regardless of baseline LDL-C
- Among women with childbearing potential, statins should only be used in the presence of proper preconception counseling & reliable contraception
  - Stop statins prior to conception

Adapted from: CDA CPG - 2013
Lipid Checklist

- Target LDL ≤ 2.0 mmol/L
- 2nd line
  - Bile acid sequestrants
    - ↓ LDL
    - Colesevelam: A1c ↓ effect
    - Can ↑ TG
    - GI upset
  - Cholesterol absorption inhibitors
    - ↓ LDL
  - Fibrates
    - ↓ TG; variable effect on LDL & HDL
    - Use if TG > 10 mmol/L
  - Nicotinic acid
    - ↓ TG & LDL; ↑ HDL
    - Dose related deterioration in blood glucose control

Adapted from: CDA CPG - 2013
Weight Loss

- Goal is to prevent weight gain, promote weight loss & prevent weight re-gain

- Weight loss of only 5-10% improves:
  - Insulin sensitivity
  - Glycemic control
  - Blood pressure
  - Lipid levels

Adapted from: CDA CPG - 2013
Weight Loss Strategies

- **Lifestyle**
  - Limited
  - Slow & difficult?

- **Medications**
  - Few options
  - Not permanent solution
  - Consider weight effect of current medications

- **Bariatric surgery**
  - Permanent cure?
## Effect On Weight

<table>
<thead>
<tr>
<th>Weight Gain</th>
<th>Weight Effect (kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insulin</td>
<td>+4.5 to 5.0</td>
</tr>
<tr>
<td>Thiazolidenediones (TZDs)</td>
<td>+4.2 to 4.8</td>
</tr>
<tr>
<td>Sulfonylureas</td>
<td>+1.6 to 2.6</td>
</tr>
<tr>
<td>Meglitinides</td>
<td>+ 0.7 to 1.8</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Weight Neutral or Decrease Weight</th>
<th>Weight Effect (kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metformin</td>
<td>-4.6 to 0.4</td>
</tr>
<tr>
<td>α-Glucosidase inhibitors</td>
<td>+0.0 to 0.2</td>
</tr>
<tr>
<td>Dipeptidyl peptidase-4 (DPP-4) inhibitors</td>
<td>+0.0 to 0.4</td>
</tr>
<tr>
<td>Glucagon-like peptide-1 (GLP-1) receptor agonists</td>
<td>-1.3 to 3.0</td>
</tr>
</tbody>
</table>

CDA CPG 2013; Hollander, P. Diabetes Spectrum 2007; 20(3): 159-165
Reducing Progression Of Diabetic Nephropathy

- Optimal glycemic control in T1 & T2DM shown to reduce the development & progression of nephropathy
- Optimal blood pressure control
- ACE-inhibitor (ACEi) or Angiotensin Receptor Blocker (ARB)

Adapted from: CDA CPG - 2013
Neuropathic Pain

Preferred Options

- **Anticonvulsants**
  - pregabalin
  - gabapentin
  - valproate

- **Antidepressants**
  - tricyclics
    - amitriptyline
    - desipramine
    - nortriptyline
  - SNRIs
    - duloxetine
    - venlafaxine

Other Options

- **Opioid**
  - dextromethorphan
  - hydromorphone ER
  - morphine ER
  - oxycodone ER
  - tapentadol ER
  - tramadol ER

- **Cannabinoids**

- **Other anticonvulsants**

- **SSRIs**

- **Topicals**
  - nitrate spray
  - capsaicin cream

Adapted from: CDA CPG – 2013
Treatment of painful diabetic neuropathy – American Academy of Neurology.
CAM is not recommended for glycemic control for individuals with diabetes, as there is not sufficient evidence regarding safety & efficacy.

Individuals with diabetes should be routinely asked if they are using CAM.
Formulating A Management Plan: Collaboration

- People are the experts in their own lives
- Health professionals are the experts in clinical aspects of diabetes
- 99% of diabetes care is self care
- Behavior change takes place as health professionals help people make informed decisions about their self care
- Not all patients will be primary decision makers in their own care
Questions...

"It wasn’t really insulin. You don’t have diabetes yet. It was just a warning shot."

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