Glucose Lowering Medications for Type 2 Diabetes

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Background

In Canada, there are currently eight separate drug classes and approximately 20 different non insulin medications approved to lower glucose in type 2 diabetes. Clinical practice guidelines addressing the management of type 2 diabetes are available and provide treatment recommendations. In order to provide supplementary information, this education session focuses on current knowledge of the benefits and harms of non insulin glucose lowering medications, with an emphasis on clinical drug information.

During each PAD session, participants will have the opportunity to discuss:

- What the evidence says about the efficacy and safety of non insulin glucose lowering medications in terms of their effect on diabetes related morbidity and mortality;
- What the evidence says about how an intensive glucose lowering strategy compares to a less intensive strategy;
- What impact increasing the dose of non insulin glucose lowering medications has on hemoglobin A1C (A1C);
- What are important contraindications, precautions, adverse events and drug interactions to be aware of when prescribing and/or monitoring patients on non insulin glucose lowering medications.

Drug Information Scope (Oral Medications and Non Insulin Injectables)

- **Biguanide:** Metformin (Glucophage)
- **Sulfonylureas:** Glyburide (Diabeta), Gliclazide (Diamicron), Glimepiride (Amaryl)
- **Meglitinide:** Repaglinide (GlucoNorm)
- **Alpha Glucosidase Inhibitor:** Acarbose (Glucobay)
- **Thiazolidinediones (TZDs):** Pioglitazone (Actos), Rosiglitazone (Avandia)
- **Dipeptidyl Peptidase 4 (DPP4) Inhibitors:** Saxagliptin (Onglyza), Linagliptin (Trajenta), Sitagliptin (Januvia), Alogliptin (Nesina)
- **Sodium Glucose Cotransporter 2 (SGLT2) Inhibitors:** Canagliflozin (Invokana), Dapagliflozin (Forxiga), Empagliflozin (Jardiance)
- **Glucagon Like Peptide 1 (GLP1) Agonists:** Liraglutide (Victoza), Exenatide (Byetta)

The evidence for glucose lowering medications in type 2 diabetes

Systematic reviews are unable to draw conclusions that confidently inform glucose lowering medication choices in terms of their effect on diabetes related morbidity and mortality, due to insufficient, low quality or absent evidence.[1-18]

- The diabetes literature describes that a strategy of glucose lowering reduces the risk of microvascular outcomes (e.g., retinopathy, nephropathy) in persons with type 2 diabetes but that the impact on macrovascular outcomes (e.g., cardiovascular events) is uncertain.[19-28]
- Fewer randomized controlled trials (RCTs) have investigated diabetes related morbidity or mortality as their primary outcome compared to those investigating surrogate endpoints.[29]
- For regulatory approval, a statistically significant reduction in hemoglobin A1C (A1C) when compared to placebo must be demonstrated in monotherapy or combination therapy RCTs (generally over 24 weeks).[25-28]
- Glucose lowering medications can be approved without direct evidence they reduce the risk of diabetes related morbidity or mortality.[25-28]
- Since 2008, the U.S. Food and Drug Administration (FDA) has required pre-approval evidence that serves to exclude an 80% relative increase in cardiovascular risk.[27] Post-approval exclusion of a 30% relative increase in cardiovascular risk is required.[27]
- Postmarketing investigation into safety signals identified during the preapproval review is also necessary. Details can be found in publicly accessible U.S. FDA drug approval letters.[30-38]

To demonstrate that a strategy of glucose lowering reduces the risk of microvascular outcomes in persons with type 2 diabetes, UKPDS 33 is often the principal reference described.[39,40]

- Initiated in 1977 and published in 1998, UKPDS 33 tested an open label strategy of intensive glucose lowering in 3867 newly diagnosed type 2 diabetics, enrolled on the basis of a fasting plasma glucose (FPG) > 6 mmol/L.[39,40] Their average A1C at baseline was 7% and participants were followed for a median of 10 years.[39]
- Participants were randomized to an intensive glucose lowering strategy where insulin or a sulfonylurea was initiated immediately and modified over time, aiming for a target FPG < 6 mmol/L.[39,40]
- In the less intensive strategy, insulin or a sulfonylurea was initiated if FPG exceeded 15 mmol/L or if participants became symptomatic (thirst, polyuria) with diet intervention alone. The aim was to maintain a FPG < 15 mmol/L without symptoms of hyperglycemia.[39,40]
- Over 10 years, the median A1C achieved in the intensive group was 7.0% compared to 7.9% in the less intensive group.[39]
- A reduction in the risk of a secondary composite of microvascular outcomes is reported: reduced from 11.4 events per 1000 patient years to 8.6 events per 1000 patient years with the intensive strategy.[39] This composite included retinopathy requiring photocoagulation, vitreous hemorrhage, and fatal or nonfatal renal failure; investigators noted that the benefit was mostly the result of fewer patients requiring retinal photocoagulation.[39]
- The trial was not designed to inform conclusively of the impact of intensive glucose lowering on the risk of premature death, cardiovascular events, end stage renal disease, blindness, or amputation.[39-42]

Biguanide = metformin (Glucophage);
Sulfonylureas = glyburide (Diabeta), gliclazide (Diamicron), glimepiride (Amaryl); **Meglitinides** = repaglinide (GlucoNorm), nateglinide (Starlix);
AG Inhibitor = acarbose (Glucobay); **Thiazolidinediones (TZDs)** = pioglitazone (Actos), rosiglitazone (Avandia);
DPP4 Inhibitors = saxagliptin (Onglyza), linagliptin (Trajenta), sitagliptin (Januvia), alogliptin (Nesina);
SGLT2 Inhibitors = canagliflozin (Invokana), dapagliflozin (Forxiga), empagliflozin (Jardiance);
GLP1 Agonists = liraglutide (Victoza), exenatide (Byetta)

The evidence for glucose lowering strategies in type 2 diabetes

Systematic reviews have demonstrated that a less intensive glucose lowering strategy has a lower risk of severe hypoglycemia compared to an intensive strategy.[1,2] The evidence is less certain for other clinical outcomes.[1-3]

A recent systematic review identified 28 clinical trials (including UKPDS 33) which contribute data on 34,912 participants with type 2 diabetes.[1] The intensive glucose targets varied between trials. In the two RCTs contributing the majority of data, intensive strategies targeted an A1C < 6% (ACCORD) and ≤ 6.5% (ADVANCE).[4,5] This involved a greater number of glucose lowering medications, increasing medication doses, and more frequent medication changes compared to the less intensive strategy.[4,5] The less intensive targets also varied between RCTs with the larger trials generally achieving A1C values between 7% and 8%.[4-7]

When **targeting intensive glucose lowering** rather than a less intensive strategy as part of the care of persons with type 2 diabetes:

- The effect on their risk of **premature death, fatal cardiovascular event, stroke, end stage renal disease, neuropathy, visual deterioration or blindness** is uncertain (there was no statistically significant increase or decrease).[1-3]

- **Nonfatal myocardial infarction:** 4.1% rather than 4.8% of people might experience a nonfatal myocardial infarction after 5 years, approximately 99 out of 100 would have the same outcome (ARR 0.7%, NNTB ≈ 160 over 5 years).[1]

- **Amputation of lower extremity:** 0.9% rather than 1.3% of people might experience amputation of a lower extremity after approximately 5 years (ARR 0.4%, NNTB ≈ 220 over ≈ 5 years).[1]

- **Microvascular event:** 10.1% rather than 11.6% of people might experience a microvascular event after approximately 5 years, approximately 98 out of 100 people would have the same outcome (ARR 1.5%, NNTB ≈ 72 over ≈ 5 years).[1]

- **Serious adverse event** (e.g., events resulting in death, disability, hospitalization): 23.0% rather than 21.6% of people might experience a serious adverse event after approximately 5 years, approximately 99 out of 100 people would have the same outcome (ARI 1.4%, NNTH ≈ 77 over ≈ 5 years).[1]

- **Severe hypoglycemia** (e.g., hypoglycemic episode that requires assistance): 6.4% rather than 2.9% of people would experience an episode of severe hypoglycemia over 12 months (ARI 3.5%, NNTH 29 over 12 months).[1]

The evidence for severe hypoglycemia was judged as high quality, indicating the reviewers' confidence in the estimate of harm.[1] The evidence is less certain for other clinical outcomes due in part to: methodological limitations of the included studies, insufficient data for some outcomes, use of a microvascular composite outcome that includes both severe and less severe outcomes, and because the effect on some outcomes is weighted by a study (ACCORD) which was stopped early due to an increased risk of mortality with the intensive glucose lowering strategy.[1-4,8]

ARR = absolute risk reduction; **NNTB** = number needed to treat for an additional beneficial outcome (estimate)
ARI = absolute risk increase; **NNTH** = number need to treat for an additional harmful outcome (estimate)

Magnitude of Hemoglobin A1C Lowering and Dose Response

Systematic reviews consider the glycemic efficacy of most non insulin glucose lowering medications to be generally similar, reducing A1C by approximately 1% on average as monotherapy.[1,2] Two-drug combinations reduce A1C by approximately 1% more than monotherapy (e.g., range 0.64% to 0.96% when added to metformin).[1-4] The results of glycemic efficacy RCTs may not be precisely applicable to all persons with type 2 diabetes.

- The average participant generally is middle aged, Caucasian, without significant comorbidity, and has a baseline A1C between 7 to 10% (RCTs generally exclude participants who are more severely hyperglycemic).[1-8]
  - *Example:* In a meta analysis of DPP4 Inhibitors (30,563 participants), the baseline A1C of participants ranged from 7.20% to 9.48% across 62 RCTs.[9]
- Glycemic efficacy RCTs generally follow patients for a period of weeks or months, rather than years.[1-8]
  - *Example:* In a systematic review of GLP1 Agonists, 62 RCTs were identified that followed patients for < 12 weeks, 50 that followed patients for 12 to 51 weeks, and 8 that followed patients for ≥ 52 weeks.[10]
  - U.S. FDA reviews noted that maximum to near maximum A1C lowering generally occurred by 12 weeks for several newer glucose lowering medications.[11-19]
- The A1C lowering effect may vary across RCTs.
  - *Example:* In a systematic review of SGLT2 Inhibitors, A1C was reduced on average by 0.66% from baseline compared to placebo (0.79% in monotherapy RCTs and 0.61% in combination therapy RCTs).[6] The A1C lowering effect ranged from 0.12% to 1.17% across 26 RCTs.[6]

For many glucose lowering medications, standard or starting doses will generally yield similar hemoglobin A1C reductions compared to higher or maximum doses.[5,8,11-23]

Dose response relationships are often not characterized in a systematic manner. The literature does however provide the following examples:

- Metformin: doses ≥ 2000 mg per day reduced A1C by an additional 0.26% compared to lower doses (1000 to 1500 mg per day)[20]
- Metformin plus Glyburide: a combination of glyburide 5 mg plus metformin 500 mg (mean dose glyburide 17 mg/metformin 1740 mg per day) did not reduce A1C more than a combination of glyburide 2.5 mg plus metformin 500 mg (mean dose 8.8 mg glyburide/metformin 1760 mg per day)[21]
- Glimepiride: higher doses of glimepiride (e.g., 4 or 8 mg per day) did not reduce A1C significantly more than lower doses (e.g., 1 mg per day)[22]
- Acarbose: no evidence of an additional A1C reduction with doses greater than acarbose 150 mg per day[5,23]
- Saxagliptin: differences in A1C lowering between saxagliptin 5 mg per day and 2.5 mg per day ranged from 0.02% to 0.27% across RCTs reviewed by the U.S. FDA; there was no evidence of an additional A1C reduction with 10 mg per day (note, 10 mg is not an approved dose)[11]
- Linagliptin: there was no evidence of an additional A1C reduction with linagliptin 10 mg per day compared to 5 mg per day in RCTs reviewed by the U.S. FDA (note, 10 mg is not an approved dose)[12]
- Sitagliptin: sitagliptin 200 mg per day did not consistently reduce A1C compared to 100 mg per day in RCTs reviewed by the U.S. FDA (note, 200 mg is not an approved dose)[13]
- Alogliptin: alogliptin 25 mg per day and 12.5 mg per day were generally similar in reducing A1C across RCTs reviewed by the U.S. FDA[14]
- Canagliflozin: differences in A1C lowering between canagliflozin 300 mg per day and 100 mg per day ranged from 0.09% to 0.25% across RCTs reviewed by the U.S. FDA[15]
- Dapagliflozin: differences in A1C lowering between dapagliflozin 10 mg per day and 5 mg per day ranged from 0.08% to 0.19% across RCTs reviewed by the U.S. FDA[16]
- Empagliflozin: differences in A1C lowering between empagliflozin 25 mg per day and 10 mg per day ranged from 0.06% to 0.13% across RCTs reviewed by the U.S. FDA[17]
- Liraglutide: liraglutide 1.8 mg per day and 1.2 mg per day were generally similar in reducing A1C across studies reviewed by the U.S. FDA;[18] a systematic review found no significant difference between liraglutide 1.8 mg per day and 1.2 mg per day in reducing A1C[8]
- Exenatide: differences in A1C lowering between exenatide 10 mcg BID and 5 mcg BID ranged from 0.22% to 0.40% across RCTs reviewed by the U.S. FDA[19]

Risk of Hypoglycemia with Glucose Lowering Medications

Quantifying the risk of hypoglycemia attributable to glucose lowering medications in a precise and clinically meaningful manner is not possible. Short term glycemic efficacy RCTs define hypoglycemia variably, typically exclude older patients with multimorbidity or a history of severe hypoglycemia and they rarely report severe hypoglycemic events.[1-10] Reaching firm conclusions regarding the comparative safety between and within glucose lowering classes is also challenging when comparisons do not give consideration to the intensity of the glucose lowering strategy or doses of comparator medicines used.

- *Example:* A systematic review comparing sulfonylureas with metformin in patients with type 2 diabetes found that the relative risk of severe hypoglycemia was increased with sulfonylurea therapy relative to metformin (RR 5.64, 95%CI 1.22 to 26.00).[9] Uncertainty is reflected however in the small number of events: 13 severe hypoglycemic events reported in 3801 participants, with only 5 of 14 RCTs reporting this outcome.[9]

Recent comparative systematic reviews, excluding SGLT2 Inhibitors, identified data for overall hypoglycemia, but the evidence was too limited to evaluate severe hypoglycemia:[1,2]

When added to metformin:[1]

- **Sulfonylureas** (OR 7.5, 95%CrI 4.4 to 13.7), **Meglitinides** (OR 8.3, 95%CrI 3.3 to 23.4), **Basal Insulin** (OR 4.1, 95%CrI 1.7 to 10.7), **Biphasic Insulin** (OR 7.0, 95%CrI 2.8 to 18.1) ↑ the risk of hypoglycemia compared to metformin alone
- Acarbose, TZDs, DPP4 Inhibitors, GLP1 Agonists did not significantly increase the risk hypoglycemia

When added to metformin plus a sulfonylurea:[2]

- **TZDs** (OR 5.6, 95%CI 2.8 to 11.3), **DPP4 Inhibitors** (OR 2.5, 95%CI 1.0 to 6.6), **GLP1 Agonists** (OR 2.1, 95%CI 1.5 to 2.8), **Basal Insulin** (OR 2.0, 95%CI 1.2 to 3.6) ↑ the risk of hypoglycemia

In a separate systematic review of **SGLT2 Inhibitors**, the risk of hypoglycemia was OR 1.28 (95%CI 0.99 to 1.65) compared with placebo.[4]

Effect of Glucose Lowering Medications on Body Weight

The clinical significance of body weight changes associated with glucose lowering medications, in terms of longer term diabetes related morbidity and mortality, is unclear.[1-3] These body weight change estimates are derived from short term RCTs (i.e., generally less than one year), therefore how and whether these changes persist in the long term is not known.[1-4]

A recent comparative systematic review, excluding SGLT2 inhibitors, found:[1]

When added to metformin:[1]

- **Sulfonylureas** (2.1 kg gain, 95%CrI 1.3 kg to 2.9 kg gain), **Meglitinides** (1.8 kg gain, 95%CrI 0.5 kg to 3.1 kg gain), **TZDs** (2.7 kg gain, 95%CrI 1.9 kg to 3.5 kg gain), **Basal Insulin** (1.7 kg gain, 95%CrI 0.3 kg to 3.1 kg gain), and **Biphasic Insulin** (3.1 kg gain, 95%CrI 1.5 kg to 4.7 kg gain) ↑ body weight on average compared to metformin alone
- Acarbose and DPP4 Inhibitors did not significantly affect body weight
- **GLP1 Agonists** ↓ body weight on average (1.8 kg loss, 95%CrI 0.8 kg to 2.9 kg loss) compared to metformin alone

In a separate systematic review, **SGLT2 Inhibitors** resulted in an average ↓ in body weight of 1.74 kg (95% CI 1.45 kg to 2.03 kg loss) compared with placebo.[4]

RR = relative risk; **95%CI** = 95% confidence interval; **OR** = odds ratio; **95%CrI** = 95% credible interval from network meta-analysis

Biguanide = metformin (Glucophage);
Sulfonylureas = glyburide (Diabeta), gliclazide (Diamicron), glimepiride (Amaryl); **Meglitinides** = repaglinide (GlucoNorm), nateglinide (Starlix);
AG Inhibitor = acarbose (Glucobay); **Thiazolidinediones (TZDs)** = pioglitazone (Actos), rosiglitazone (Avandia);
DPP4 Inhibitors = saxagliptin (Onglyza), linagliptin (Trajenta), sitagliptin (Januvia), alogliptin (Nesina);
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Specific Considerations: Place in Therapy, Contraindications, Precautions, Adverse Events

Specific Considerations serves to emphasize current clinically relevant drug information in a rapidly evolving drug therapy topic; it is not intended to replace comprehensive prescribing information. **Renal** See Tables 1B, 2B for renal contraindications and dosing adjustments. **Health Canada Vigilance Adverse Reaction Reporting Form:** http://www.hc-sc.gc.ca/dhp-mps/medeff/report-declaration/ar-ei_form-eng.php

METFORMIN (Glucophage)

- **reasonable first line therapy** overall favourable or non harmful effect on surrogate outcomes (A1C, lipids), intermediate outcomes (body weight), safety (hypoglycemia, cardiovascular morbidity & mortality) and cost[1-7]
- **gastrointestinal** *dose related* diarrhea, nausea, vomiting, bloating, flatulence, anorexia, taste disturbance;[8] common during initiation & generally transient;[8] similar adverse event profile with the extended release formulation[9]
- **vitamin B12 deficiency** recommendation to assess every 1 to 2 years;[8] RCT comparing metformin 850 mg TID vs. placebo added to insulin, reported vitamin B12 deficiency (defined as less than 150 pmol/L), absolute risk increase 7.2% (95%CI 2.3 to 12.1), number needed to treat to harm ≈ 14 per 4 years[10]
- **lactic acidosis** 0.03 cases per 1000 patient years;[8] systematic review, in 24,739 patients prescribed metformin there were no cases of metformin associated lactic acidosis (literature search did not include case reports);[11] Canadian prescribing information advises avoiding the use of metformin in patients with decreased renal function, hypoxemia, hypoperfusion, excess alcohol intake, evidence of hepatic disease;[8] avoid maximum metformin dose in elderly patients;[8] perioperatively discontinue 2 days prior to surgical procedures if food & fluids restricted, restart when oral intake resumed & renal function confirmed normal[8]

REPAGLINIDE (GlucoNorm)

- **dosing strategy** emphasizes post prandial glucose levels (e.g., skip a dose if meal is skipped)[22]
- **insulin secretagogue** similar to sulfonylureas in glucose lowering mechanism;[23] combined use with sulfonylureas not recommended[23]
- **compared to sulfonylureas** systematic reviews could not confidently differentiate in terms of efficacy and safety due to insufficient comparative data[1,2]
- **age > 75** repaglinide use not recommended[22]

ACARBOSE (Glucobay)

- **gastrointestinal** *dose related* flatulence, diarrhea, abdominal pain;[24,25] contraindicated in inflammatory bowel disease, colonic ulceration, intestinal obstruction, chronic intestinal diseases associated with marked disorders of digestion or absorption[24]
- **hypoglycemia oral treatment** must use glucose (dextrose) not dietary sugar (sucrose)[24]

GLYBURIDE (Diabeta), **GLICLAZIDE** (Diamicron), **GLIMEPIRIDE** (Amaryl)

- **comparative safety & efficacy** current evidence does not confidently differentiate between these 3 sulfonylureas in terms of their efficacy and safety due to insufficient comparative data[12-17]
- **gastrointestinal** *dose related* nausea, vomiting, diarrhea, epigastric burning & fullness, gastric irritation[18-20]
- **history of sulfonamide allergy** a contraindication to sulfonylurea use as per Canadian prescribing information;[18-20] insufficient evidence to determine existence or absence of allergic cross reactivity between sulfonamide antibiotics & nonantibiotic sulfonamides[21]
- **hypersensitivity** pruritus, erythema, urticaria, maculopapular exanthems, allergic vasculitis, photosensitivity[18-21]
- **hematologic** case reports leukopenia, erythrocytopenia, agranulocytosis, thrombocytopenia, hemolytic anemia, aplastic anemia, pancytopenia[18-20]
- **glucose 6 phosphate dehydrogenase (G6PD) deficiency** increased risk of hemolytic anemia; sulfonylurea use not recommended[18-20]

PIOGLITAZONE (Actos), **ROSIGLITAZONE** (Avandia)

- **heart failure** pioglitazone, rosiglitazone use is contraindicated[26,27]
- **fluid retention** *dose related* edema, weight gain, macular edema with decrease in visual acuity; educate patients on signs and symptoms; risk increased when used with insulin or as triple therapy with metformin and a sulfonylurea (not approved indications)[26,27]
- **ischemic heart disease** pioglitazone, rosiglitazone use is not recommended;[26,27] rosiglitazone not recommended in patients treated with nitrates[27]
- **rosiglitazone Canadian prescribing restrictions** use only if all other oral glucose lowering medications are inadequate, contraindicated, or not tolerated & obtain patient's written informed consent[27,28]
- **fractures** increase in risk in women (OR 2.23, 95%CI 1.65 to 3.01);[29] predominantly upper limbs and distal lower limbs[26,27,29]
- **bladder cancer active or history** pioglitazone use is contraindicated; risk possibly related to duration of therapy and cumulative dose;[26,30] pioglitazone + dapagliflozin combination not recommended[31]
- **respiratory tract infection** increased risk of pneumonia or lower respiratory tract infection (RR 1.40, 95%CI 1.08 to 1.82)[32]

SAXAGLIPTIN (Onglyza), **LINAGLIPTIN** (Trajenta), **SITAGLIPTIN** (Januvia), **ALOGLIPTIN** (Nesina)

- **pancreas** acute and chronic, fatal and nonfatal pancreatitis, pancreatic cancer;[33] 2014 systematic review concludes that current evidence cannot firmly confirm or reject risk;[34] U.S FDA and European Medicines Agency have also not reached a conclusion regarding a causal relationship of incretin based drugs with pancreatitis and pancreatic cancer;[33] educate patients on signs and symptoms
- **arthralgia** U.S. FDA advises of case reports of joint pain; may be severe and disabling[35]
- **hypersensitivity** anaphylaxis, angioedema, urticaria, cutaneous vasculitis, exfoliative skin conditions[36-39]
- **renal** possibility of renal adverse events (e.g., renal impairment, decreased creatinine clearance, acute renal failure) noted for saxagliptin, sitagliptin, alogliptin[36,38,39]
- **heart failure** linagliptin, sitagliptin use currently not recommended;[37,38] saxagliptin caution warranted;[36] alogliptin caution NYHA functional classes III and IV[39]
- **insulin** linagliptin not currently indicated for use in combination with insulin due to possible increase in cardiovascular risk with this combination[37]
- **immunologic** *dose related* decrease lymphocyte count; review in setting of unusual or prolonged infection[36-38]

CANAGLIFLOZIN (Invokana), **DAPAGLIFLOZIN** (Forxiga), **EMPAGLIFLOZIN** (Jardiance)

- **reduced intravascular volume** use not recommended in patients who are volume depleted; *dose related* dehydration, hypovolemia, orthostatic hypotension, hypotension; risk increased in renal impairment, age ≥ 65, low systolic blood pressure, patients on antihypertensives (e.g., loop diuretics, angiotensin converting enzyme inhibitors, angiotensin receptor blockers)[31,40,41]
- **renal** *dose related* osmotic diuresis including increased urination; increase in serum creatinine, decrease in estimated glomerular filtration rate[31,40,41]
- **ketoacidosis** case reports Canada, U.S., Europe; serious & requiring hospitalization; some cases only moderately increased blood glucose levels[42-44]
- **fractures** U.S. FDA advises of increased risk with canagliflozin; fractures can occur as early as 12 weeks; more likely low trauma and of upper extremities[45]
- **genitourinary** genital mycotic infection (OR 3.50, 95%CI 2.46 to 4.99), urinary tract infection (OR 1.34, 95%CI 1.03 to 1.74)[46]
- **hyperkalemia** *dose related* increase in potassium observed with canagliflozin, dapagliflozin;[31,40] risk increased in renal impairment and with potassium sparing diuretics, angiotensin converting enzyme inhibitors, angiotensin receptor blockers[31,40]
- **older adults** increased risk of adverse events related to volume depletion & renal impairment;[31,40,41] increased risk of urinary tract infection;[41] decreased glycemic efficacy[40,41]
- **bladder cancer** active or history dapagliflozin use not recommended;[31] dapagliflozin + pioglitazone combination not recommended[31]
- **hematologic** increase in hemoglobin, hematocrit; caution/not recommended in patients with elevated hematocrit[31,40,41]
- **lipids** *dose related* increase in LDL-C[31,40,41]

LIRAGLUTIDE (Victoza), **EXENATIDE** (Byetta)

- **pancreas** acute and chronic, fatal and nonfatal pancreatitis, pancreatic cancer;[33] 2014 systematic review concludes that current evidence cannot firmly confirm or reject risk;[34] U.S FDA and European Medicines Agency also have not reached a conclusion regarding a causal relationship of incretin based drugs with pancreatitis and pancreatic cancer;[33]educate patients on signs and symptoms
- **gastrointestinal** *dose related* nausea, vomiting, diarrhea, dehydration, constipation, dyspepsia; decreased gastric emptying; not recommended in inflammatory bowel disease, diabetic gastroparesis[47,48]
- **renal** possibility of renal adverse events (e.g., increases in serum creatinine, worsened chronic renal failure, acute renal failure); risk may be increased in patients receiving concomitant medications affecting renal function and/or hydration[47,48]
- **thyroid** contraindicated if personal or family history of medullary thyroid cancer or in Multiple Endocrine Neoplasia syndrome type 2[47,48]
- **cardiac** increase in heart rate, PR interval prolongation; caution in patients with ischemic heart disease, tachyarrhythmias, conduction system abnormalities, or in combination with other medications that affect heart rate or PR interval[47,48]
- **hypersensitivity** anaphylaxis, angioedema, rash, pruritus[47,48]
- **injection site reactions** hematoma, bruising, pain, swelling, burning, pruritus[47,48]

Table 1A: Glucose Lowering Medications, Dosage Forms, and Dosing

Metformin[1-6]	**Sulfonylureas**[1,7-10]	**Repaglinide**[1,11,12]	**Acarbose**[1,13]
Generic Name (Brand Names)			
metformin (Glucophage, generics) **metformin extended release** (Glumetza)	**glyburide** (Diabeta, generics) **gliclazide** (Diamicron, generics) **gliclazide modified release** (Diamicron MR, generics) **glimepiride** (Amaryl, generics)	**repaglinide** (GlucoNorm, generics)	**acarbose** (Glucobay)
Suggested Glucose Lowering Mechanism			
biguanide: increases hepatic and peripheral insulin sensitivity	insulin secretagogues: increase release of insulin from pancreatic beta cells	insulin secretagogue, meglitinide analogue: increases release of insulin from pancreatic beta cells	alpha glucosidase inhibitor: delays digestion and absorption of glucose
Dosage Forms			
metformin tabs 500, 850 mg [500 mg scored] **metformin extended release (ER) tabs** 500, 1000 mg [do not break or crush] **extended release formulation** similar glycemic efficacy & adverse event profile as immediate release[6]	**glyburide tabs** 2.5, 5 mg [both doses scored] **gliclazide tabs** 80 mg [scored] **gliclazide modified release (MR) tabs** 30, 60 mg [60 mg scored] **glimepiride tab** 1, 2, 4 mg [all doses scored]	**repaglinide tabs** 0.5, 1, 2 mg	**acarbose tabs** 50, 100 mg [both doses scored]
Adult Dose → For many glucose lowering medications, standard or starting doses will generally yield similar hemoglobin A1C reductions as higher or maximum doses.			
metformin initial 500 mg PO BID or 850 mg once a day; **titrate** may ↑ by 500 mg weekly or by 850 mg every 2 weeks; **max** 2500 to 2550 mg per day; preferably given with food **metformin ER initial** 1000 mg PO once a day with evening meal; **titrate** may ↑ by 500 mg weekly; **max** 2000 mg per day; administer with food to ensure adequate absorption	**glyburide initial** 1.25 to 5 mg PO once a day with first meal of the day (max initial dose 2.5 mg if age > 60); **titrate** may ↑ by 2.5 mg weekly; **max** 20 mg per day & 10 mg per dose **gliclazide initial** 80 mg PO BID with meals; **max** 320 mg per day **gliclazide MR initial** 30 mg PO once a day; **titrate** may ↑ by 30 mg every 2 weeks; **max** 120 mg per day **glimepiride initial** 1 mg PO once a day; **titrate** may ↑ by 1 mg per day at 1 to 2 week intervals; **max** 8 mg per day	**repaglinide initial** 1 to 2 mg PO preprandially BID to QID (0.5 mg initial preprandial dose if treatment naïve or A1C < 8%); **titrate** minimum 1 week between dose increases; **max** 4 mg per dose, 16 mg per day; administer 30 minutes or immediately preceding meal; skip dose if meal is missed	**acarbose initial** 50 mg PO once a day with main meal; **titrate** may ↑ every 1 to 2 weeks to BID then TID; **max** 100 mg TID
PO oral administration; **ER** extended release; **MR** modified release			

Potential risk factors for hypoglycemia: Targeting intensive glucose lowering, combinations of glucose lowering medications, advanced age, hepatic impairment, renal impairment, debility, malnutrition, alcohol intake, beta blockers (i.e., it may be more difficult to recognize signs and symptoms of hypoglycemia).[1-18]

Table 1B: Renal Considerations, Drug Interactions, Cost

Metformin[1-6]	Sulfonylureas[1,7-10]	Repaglinide[1,11,12]	Acarbose[1,13]
Renal → All classes of non insulin glucose lowering medications require attention to renal function, including assessment at baseline and periodically thereafter.			
metformin Canadian prescribing information advises assessing renal function every 6 months: do not titrate to maximum dose if decreased renal function; temporarily discontinue during or if possibility of acute decline in renal function; metformin contraindicated if **CrCl < 60 mL/min; U.K. guidance** advises reviewing metformin dose if **eGFR < 45 mL/min**; discontinue if **eGFR < 30 mL/min**[5]	**sulfonylureas** conservative initial dosing, titration, maintenance doses; all 3 sulfonylureas are contraindicated in severe renal impairment	**repaglinide** caution with dose increases	**acarbose CrCl < 25 mL/min** use not recommended
Hepatic			
All classes of non insulin glucose lowering medications identify hepatic impairment as either a precaution or a contraindication.			
Select Drug Interactions → Some examples of combinations that are best avoided or where therapy modification would be considered. Always refer to a current drug interaction resource. The possible impact of medications which strongly induce or inhibit metabolism or transport should be considered when added or withdrawn.			
cimetidine, intravascular iodinated contrast agents, topiramate possible ↑ risk lactic acidosis	**thiazolidinediones (TZDs), DPP4 inhibitors, SGLT2 inhibitors, GLP1 agonists, strong CYP2C9 inhibitors** consider ↓ sulfonylurea dose; **bosentan** + glyburide ↑ risk elevated transaminases; **strong CYP2C9 inducers**	**gemfibrozil, clopidogrel** ↑ repaglinide concentration; **strong CYP2C8 inhibitors or inducers**; **strong CYP3A4 inducers**	**metformin, sulfonylurea, insulin** consider ↓ metformin, sulfonylurea, or insulin dose
Approximate Annual Medication Cost *(PharmaCare Coverage)* **→ Annual medication costs range from approximately $35 per year to $3200 per year.**			
metformin generic *(regular benefit)* $35 500 mg (@ 2 tabs per day) $48 850 mg (@ 2 tabs per day) $70 500 mg (@ 4 tabs per day) **metformin ER brand** *(non benefit)* $464 1000 mg (@ 1 tab per day)	**glyburide generic** *(regular benefit)* $45 5 mg (@ 2 tabs per day) **gliclazide generic** *(limited coverage)* $74 80 mg (@ 2 tabs per day) **gliclazide MR generic** *(limited coverage)* $74 30 mg (@ 2 tabs per day) **glimepiride generic** *(non benefit)* $193 any strength (@ 1 tab per day)	**repaglinide generic** *(non benefit)* $289 2 mg (@ 3 tabs per day)	**acarbose brand** *(non benefit)* $319 50 mg (@ 3 tabs per day)

CrCl creatinine clearance; **eGFR** estimated glomerular filtration rate; **ER** extended release; **MR** modified release. **Annual cost:** estimated annual medication cost without markup and professional fee; calculated using the British Columbia PharmaCare Formulary Search: https://pcbl.hlth.gov.bc.ca/pharmacare/benefitslookup/ and McKesson Canada: https://www.mckesson.ca/ (accessed July 3, 2015)
Limited coverage: Special Authority Criteria available from: http://www2.gov.bc.ca/gov/content/health/practitioner-professional-resources/pharmacare/prescribers/special-authority

Table 2A: Glucose Lowering Medications, Dosage Forms, and Dosing

Thiazolidinediones (TZDs)[1,14-16]	DPP4 Inhibitors[1,17-24]	SGLT2 Inhibitors[1,25-27]	GLP1 Agonists[1,28,29]
Generic Name (Brand Names)			
pioglitazone (Actos, generics) **rosiglitazone** (Avandia), with metformin (Avandamet)	**saxagliptin** (Onglyza), with metformin (Komboglyze) **linagliptin** (Trajenta), with metformin (Jentadueto) **sitagliptin** (Januvia), with metformin (Janumet), with extended release metformin (Janumet XR) **alogliptin** (Nesina), with metformin (Kazano)	**canagliflozin** (Invokana) **dapagliflozin** (Forxiga) **empagliflozin** (Jardiance)	**liraglutide injection** (Victoza) **exenatide injection** (Byetta)
Suggested Glucose Lowering Mechanism			
increases hepatic and peripheral insulin sensitivity; decreases hepatic glucose production	potentiates incretin pathway: increases insulin release; decreases glucagon secretion	decreases renal glucose reabsorption; increases urinary excretion of glucose	potentiates incretin pathway: increases insulin release; decreases glucagon secretion; delays gastric emptying
Dosage Forms → See footnote below for dosage forms in combination with metformin.			
pioglitazone tabs 15, 30, 45 mg **rosiglitazone tabs** 2, 4, 8 mg	**saxagliptin tabs** 2.5, 5 mg **linagliptin tabs** 5 mg **sitagliptin tabs** 25, 50, 100 mg **alogliptin tabs** 6.25, 12.5, 25 mg	**canagliflozin tabs** 100, 300 mg **dapagliflozin tabs** 5, 10 mg **empagliflozin tabs** 10, 25 mg	**liraglutide 6 mg/mL** 3 mL multidose pen provides 30 doses of 0.6 mg, 15 doses of 1.2 mg, 10 doses of 1.8 mg **exenatide 250 mcg/mL** 1.2 mL multidose pen provides 60 doses of 5 mcg; 2.4 mL multidose pen provides 60 doses of 10 mcg
Adult Dose → For many glucose lowering medications, standard or starting doses will generally yield similar hemoglobin A1C reductions as higher or maximum doses.			
pioglitazone initial 15 or 30 mg PO once a day; **max** 45 mg once day **rosiglitazone initial** 4 mg PO per day (once or divided BID); **max** may ↑ to 8 mg per day after 8 to 12 weeks following clinical evaluation for fluid retention; **max** 4 mg per day if used in combination with a sulfonylurea	**saxagliptin initial & max** 5 mg PO once a day **linagliptin initial & max** 5 mg PO once a day **sitagliptin initial & max** 100 mg PO once a day **alogliptin initial & max** 25 mg PO once a day	**canagliflozin initial** 100 mg PO once a day preferentially before first meal in the morning; **max** may ↑ to 300 mg once a day if tolerating *and* eGFR ≥ 60 mL/min *and* low risk of reduced intravascular volume **dapagliflozin initial** 5 mg PO once a day; **max** may ↑ to 10 mg once a day **empagliflozin initial** 10 mg PO once a day; **max** may ↑ to 25 mg once a day	**liraglutide initial** 0.6 mg subcut once a day; **titrate** may ↑ after one week to 1.2 mg once a day; **max** 1.8 mg once a day; given without regard to meals **exenatide initial** 5 mcg subcut BID; **max** may ↑ after one month to 10 mcg BID; dose within 60 minute period prior to two main meals of the day (at least 6 hours or more apart)
Dosage forms available with metformin: rosiglitazone 2, 4 mg with 500, 1000 mg metformin IR; **saxagliptin** 2.5 mg with 500, 850, 1000 mg metformin IR; **linagliptin** 2.5 mg with 500, 850, 1000 mg metformin IR; **sitagliptin** 50 mg with 500, 850, 1000 mg metformin IR and with 1000 mg metformin ER; **alogliptin** 12.5 mg with 500, 850, 1000 mg metformin IR			
DPP4 dipeptidyl peptidase 4; **SGLT2** sodium glucose cotransporter 2; **GLP1** glucagon like peptide 1; **PO** oral administration; **subcut** subcutaneous administration; **eGFR** estimated glomerular filtration rate; **IR** immediate release; **ER** extended release			

Table 2B: Renal Considerations, Drug Interactions, Cost

Thiazolidinediones (TZDs)[1,14-16]	DPP4 Inhibitors[1,17-24]	SGLT2 Inhibitors[1,25-27]	GLP1 Agonists[1,28,29]
Renal → All classes of non insulin glucose lowering medications require attention to renal function, including assessment at baseline and periodically thereafter.			
pioglitazone no dose adjustments recommended **rosiglitazone** **CrCl < 30 mL/min** caution	**saxagliptin** **CrCl ≤ 50 mL/min** 2.5 mg; **severe impairment** caution; **ESRD** use not recommended **linagliptin** no dose adjustment recommended; **ESRD** caution **sitagliptin** **CrCl 30 to 49 mL/min** 50 mg; **CrCl < 30 mL/min or ESRD** 25 mg **alogliptin** **CrCl 30 to 50 mL/min** 12.5 mg; **CrCl < 30 mL/min or ESRD** 6.25 mg	**canagliflozin** **eGFR < 60 mL/min** do not initiate; **eGFR < 45 mL/min** contraindicated; consider 300 mg dose only if eGFR ≥ 60 mL/min **dapagliflozin** **eGFR < 60 mL/min** contraindicated **empagliflozin** **eGFR < 60 mL/min** do not initiate; **eGFR < 45 mL/min** contraindicated	**liraglutide** **CrCl < 50 mL/min** use not recommended **exenatide** **CrCl 30 to 50 mL/min** caution when initiating or if increasing dose; **CrCl < 30 mL/min** contraindicated
Hepatic			
All classes of non insulin glucose lowering medication identify hepatic impairment as either a precaution or a contraindication.			
Select Drug Interactions → Some examples of combinations that are best avoided or where therapy modification would be considered. Always refer to a current drug interaction resource. The possible impact of medications which strongly induce or inhibit metabolism or transport should be considered when added or withdrawn.			
insulin ↑ risk fluid retention & heart failure (combination not indicated); **sulfonylurea + metformin** (i.e., triple therapy) ↑ risk fluid retention & heart failure (combination not indicated); **sulfonylurea** consider ↓ sulfonylurea dose; **dapagliflozin** + pioglitazone uncertain bladder cancer risk; **strong CYP2C8 inhibitors or inducers**	**sulfonylurea or insulin** consider ↓ sulfonylurea or insulin dose; **strong CYP3A4 inhibitors** + saxagliptin; **strong CYP3A4 and/or P-glycoprotein inducers** + linagliptin	**sulfonylurea or insulin** consider ↓ sulfonylurea or insulin dose; **loop diuretics** ↑ intravascular volume depletion; **pioglitazone** + dapagliflozin uncertain bladder cancer risk; **UDP-glucuronosyl transferase enzyme inducers** + canagliflozin; **digoxin** + canagliflozin	**sulfonylurea or insulin** consider ↓ sulfonylurea or insulin dose; **sympathomimetics** caution other medications that ↑ heart rate, ↑ PR interval; **exenatide** caution oral medications that require rapid absorption or have a narrow therapeutic index; **oral contraceptives** administer one hour before exenatide dose
Approximate Annual Medication Cost *(PharmaCare Coverage)* **→ Annual medication costs range from approximately $35 per year to $3200 per year.**			
pioglitazone generic *(limited coverage)* $257 30 mg (@ 1 tab per day) **rosiglitazone brand** *(non benefit)* $851 4 mg (@ 1 tab per day)	**saxagliptin brand** *(limited coverage)* $934 2.5 mg (@ 1 tab per day) $1119 5 mg (@ 1 tab per day) **linagliptin brand** *(limited coverage)* $887 5 mg (@ 1 tab per day) **sitagliptin brand** *(non benefit)* $1175 any strength (@ 1 tab per day) **alogliptin brand** *(non benefit)* $1032 any strength (@ 1 tab per day)	**canagliflozin brand** $1033 any strength (@ 1 tab per day) **dapagliflozin brand** $1033 any strength (@ 1 tab per day) **empagliflozin brand** $1033 any strength (@ 1 tab per day)	**liraglutide brand** *(non benefit)* $1070 0.6 mg daily $2139 1.2 mg daily $3208 1.8 mg daily **exenatide brand** *(non benefit)* $1808 any strength BID

CrCl creatinine clearance; **ESRD** end stage renal disease; **eGFR** estimated glomerular filtration rate. **Annual cost** estimated annual medication cost without markup and professional fee; calculated using the British Columbia PharmaCare Formulary Search: https://pcbl.hlth.gov.bc.ca/pharmacare/benefitslookup/ and McKesson Canada: https://www.mckesson.ca/ (accessed July 3, 2015)
Limited coverage: Special Authority Criteria available from: http://www2.gov.bc.ca/gov/content/health/practitioner-professional-resources/pharmacare/prescribers/special-authority

Evidence Summary

- **Systematic reviews are unable to draw conclusions that confidently inform glucose lowering medication choices in terms of their effect on diabetes related morbidity and mortality.**
- **Systematic reviews have demonstrated that a less intensive glucose lowering strategy has a lower risk of severe hypoglycemia compared to an intensive strategy. The evidence is less certain for other clinical outcomes.**
- **For many glucose lowering medications, standard or starting doses will generally yield similar hemoglobin A1C reductions compared to higher or maximum doses.**

References available upon request.

Materials are designed to be used in conjunction with an academic detailing session provided by PAD pharmacists. For more information, or to schedule an academic detailing session, please contact:

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