Quarterly Medication Review Deprescribing Focus

LONG TERM CARE

Optimizing Diabetes Medications & Insulin

July to Sept 2023

- Residents with diabetes in LTC may often have issues with undernutrition, overly aggressive glycemic control with A1C levels below recommended target (less than 7%) and polypharmacy[2]
- Diabetes treatment in LTC should focus on:
  - Preventing **hypoglycemia** which may result in impaired cognitive and physical function, falls, fractures, seizures, emergency department visits, hospitalization and mortality
  - Preventing and controlling **symptomatic hyperglycemia** which may result in polydipsia, polyuria, dehydration, fatigue, falls, and renal insufficiency
- Intensive glucose control with A1C less than 6% is associated with higher mortality in the aging population[2]
- Given the long timeframe (approximately 8 years) to achieve theorized benefits of intense control, glycemic targets should reflect resident goals, health status, and life expectancy[1]

For the quarterly medication reviews from July to September 2023, reassess all residents on treatment for diabetes.

- Review A1C and blood glucose targets and assess if within targets recommended by Diabetes Canada for older adults[2] (see Table 1: *Glycemic Targets In Older People with Diabetes* on page 2). Assess if there have been any changes in clinical status that may necessitate adjustment of glycemic targets.
- Assess consistency of food intake, particularly if using insulin or sulfonylurea and consult the dietitian as required
- Assess the resident's current diabetes treatment for opportunities to deprescribe[3] (see page 8) and including the resident's ability to take medications and their goals of treatment
  - ◊ Assess for any contraindications and precautions for each class of antihyperglycemic agents
  - ◊ Assess renal function; modify dosages of antihyperglycemic agents or asses if medication needs to be stopped
  - ◊ Assess if the resident is having any side effects caused by their antihyperglycemic agents and if there are any interventions that can be taken to reduce side effects (e.g. slower titration of medications or dose reduction)
- When considering adding new medications for diabetes treatment and cardiovascular or renal benefits, consider time-to-benefit and the resident's life expectancy
  - ◊ Use a risk stratified approach (e.g., see BMJ tool on page 6) when considering SGLT-2 inhibitors and GLP-1 receptor agonists for residents with type 2 diabetes. Shared decision making is needed so the resident and family are aware of the relative benefit and potential risk of side effects.
- If a new antihyperglycemic agents has been started, monitor effectiveness (e.g. A1C, blood glucose values, symptoms of hyper - or hypoglycemia). If no or limited benefit seen within 3-6 months[3,4], consider modifying treatment
- If taking insulin, assess for:
  - ◊ Is the resident being over basalized?
  - ◊ Is the resident using basal and rapid-acting insulin versus NPH and regular insulin?
  - ◊ Are lower doses (e.g. 10 units or less per dose) still required?
  - ◊ Does the resident have sliding scale (reactive) or correction (supplemental) insulin orders?
  - ◊ Can the insulin regimen be simplified?

QMR Contents:

Attachments included with QMR: Non-Insulin Pharmacotherapy

Interlake-Eastern Regional Health Authority
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Optimizing Diabetes Medications

Glycemic Targets In Older People with Diabetes

- In the older person with diabetes and multiple comorbidities and/or frailty, strategies should be used to prevent hypoglycemia [1,2]

Table 1: Glycemic Targets In Older People with Diabetes[2,41]

Status	Functionally Dependent	Frail and/or with Dementia	End of Life
Clinical Frailty Index (based on Clinical Frailty Scale)	**4-5**	**6-8**	**9**
A1C Target - Low Risk Hypoglycemia (therapy does not include insulin or sulfonylureas)	8.0% or less	Less than 8.5%	A1C measurement not recommended. Avoid symptomatic hyperglycemia or any hypoglycemia
A1C Target - Higher Risk Hypoglycemia (therapy does include insulin or sulfonylureas)	7.1-8%	7.1-8.5%	
Capillary Blood Glucose Monitoring (CBGM) Preprandial: Postprandial:	 5—8 mmol/L 12 mmol/L or less	 6—9 mmol/L 4 mmol/L or less	Individualized
Continuous/Flash Glucose Monitoring[41]	Time within range greater than 60% (more than 14 h per day)	Time within range greater than 50% (more than 12 hours per day)	

- Although the correlation between A1C values and mean glucose values derived from continuous/flash glucose monitoring is much less in the elderly than younger patient populations, the two measures may be used in a complementary manner to assess glycemic control[3]
- It is important to remember that A1C is a surrogate marker for diabetes. For more on "*The Limitations and Potential Hazards of Using Surrogate Markers*"[5] see: https://www.ti.ubc.ca/2015/02/03/the-limitations-and-potential-hazards-of-using-surrogate-markers/
- A1C measurement may be falsely elevated. Consider if the resident has anemia (iron, vitamin B12, folate deficiency), conditions that impact red blood cell life span such as chronic kidney disease, recent blood transfusions, erythropoietin treatment, recent acute illness or hospitalization, chronic liver disease, and chronic opioid use [6,7]

Selection of Diabetes Medications

Per Diabetes Canada, all antihyperglycemic agents have Grade A evidence for effectiveness in reducing blood glucose levels[3].

Consider the following factors when determining which antihyperglycemic agent to use or which to add to the current treatment for an individual with type 2 diabetes:

- Degree of hyperglycemia (e.g. is treatment required based on Diabetes Canada recommendations for older people)
- Individual's preference, frailty, goals of care, and life expectancy
- Need for blood glucose monitoring required for the antihyperglycemic agent and acceptability by the resident
- Consistency of eating patterns
- Polypharmacy
- Concomitant medical conditions, especially cardiovascular risk and renal disease
- Contraindications or precautions with each class of antihyperglycemic agent and the side effect profile
- Renal function
  - Glycemic efficacy of sodium-glucose co-transporter-2 (SGLT-2) inhibitors is reduced with lower eGFR
  - Impaired renal function may prevent the use of some antihyperglycemic agents
- Costs and coverage; see attached resource *Non-Insulin Pharmacotherapy*

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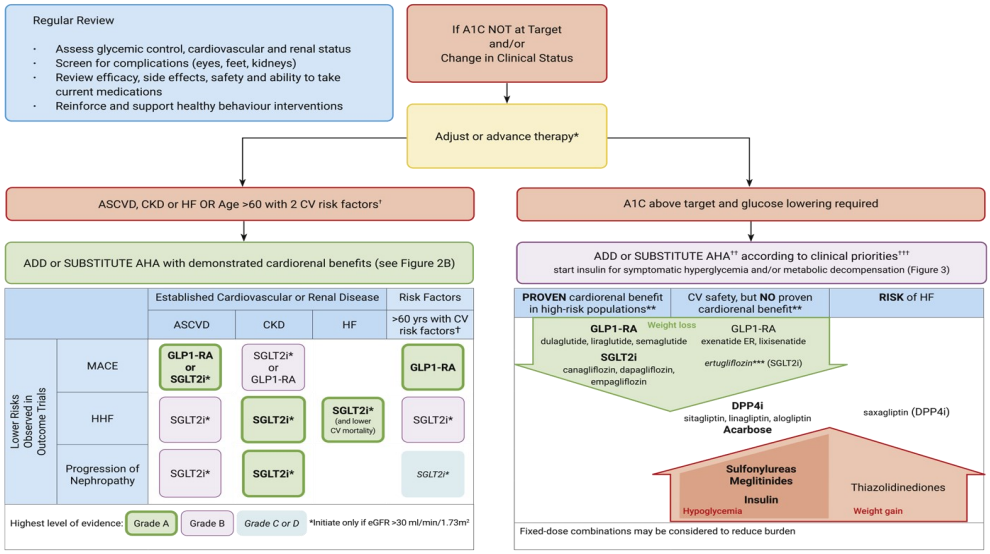
Optimizing Diabetes Medications



* Changes in clinical status may necessitate adjustment of glycemic targets and/or deprescribing.
† Tobacco use; dyslipidemia (use of lipid-modifying therapy or a documented untreated low-density lipoprotein (LDL) ≥3.4 mmol/L, or high-density lipoprotein-cholesterol (HDL-C) <1.0 mmol/L for men and <1.3 mmol/L for women, or triglycerides ≥2.3 mmol/L); or hypertension (use of blood pressure drug or untreated systolic blood pressure [SBP] ≥140 mmHg or diastolic blood pressure [DBP] ≥95 mmHg).
†† All antihyperglycemic agents (AHAs) have Grade A evidence for effectiveness to reduce blood glucose levels.
††† Consider degree of hyperglycemia, costs and coverage, renal function, comorbidity, side effect profile and potential for pregnancy.
** In CV outcome trials performed in people with atherosclerotic cardiovascular disease (ASCVD), chronic kidney disease (CKD), heart failure (HF) or at high cardiovascular (CV) risk.
*** VERTIS (CV outcome trial for ertugliflozin) presented at American Diabetes Association (ADA) June 2020 showed noninferiority for major adverse CV events (MACE). Manuscript not published at time of writing.
A1C, glycated hemoglobin; *DPP4i*, dipeptidyl peptidase-4 inhibitors; *eGFR*, estimated glomerular filtration rate; *GLP1-RA*, glucagon-like peptide-1 receptor agonists; *exenatide ER*, exenatide extended-release; *HHF*, hospitalization for heart failure; *SGLT2i*, sodium-glucose cotransporter 2 inhibitors; *yrs*, years.

Figure 1: Reviewing, Adjusting, or Advancing Therapy in Type 2 Diabetes, consider the following:

- These recommendations are not specific to older individuals who require less stringent glycemic control and/or may not experience benefit for atherosclerotic cardiovascular disease (ASCVD), chronic kidney disease (CKD), major adverse cardiovascular events (MACE), or heart failure (HF) due to their shorter life expectancies
- While a SGLT2 inhibitor or a GLP-1 receptor agonist with proven cardiovascular benefit has been recommended for persons aged 60 and older with at least two cardiovascular risk factors by Diabetes Canada[3] these recommendations should be considered in conjunction with clinical practice guidelines specific for managing diabetes in older people[2,3]
- For residents requiring antihyperglycemic treatment optimization, agents with a lower risk of hypoglycemia such as DPP-4 inhibitors should be considered before an insulin secretagogue (sulfonylurea)[3]
- Pharmacare EDS criteria may not align with these recommendations (see attached resource *Non-Insulin Pharmacotherapy*)
- If the algorithm indicates a SGLT2 inhibitor or a GLP-1 receptor agonist can be used, if EDS criteria is met, there are no contraindications and renal function permits, **preference is to be given to a SGLT2 inhibitor** based on available evidence[20,21] and because of the substantially higher cost of GLP-1 receptor agonists compared to SGLT2 inhibitors. See *Cardiovascular & Renal Benefits of SGLT2 Inhibitors and GLP1 Receptor Agonists* on page 6

Oral Diabetes Medications

Metformin:

- Still considered a first line medication if there are no contraindications (e.g. advanced renal insufficiency). Use with caution in patients with impaired hepatic function or congestive heart failure (increase the risk of lactic acidosis)[33]
- Inexpensive, has few side effects, and provides durable glycemic control compared with sulfonylureas[9]
- Slow titration to the target dose is recommended to ease GI adverse effects. When carefully titrated, up to 95% of patients may be able to tolerate metformin[10]
- Monitor for GI intolerance, reduction in appetite, weight loss, vitamin B12 deficiency, serum creatinine at baseline and regularly
- The majority of participants in outcome trials demonstrating cardiorenal benefits for specific drugs/classes were taking other antihyperglycemic agents, including metformin, as background medications[3]
- Adjust dose with declining renal function[11]: eGFR 30-45 mL/min: 500-1000 mg/day, eGFR 15-30 mL/min: 500 mg/day (if eGFR is stable)

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Optimizing Diabetes Medications

Oral Diabetes Medications continued...

Sulfonylureas:

- Gliclazide and glimepiride are preferred over glyburide in the elderly because they are associated with a lower frequency of hypoglycemia [4,11]
- Consistent food intake is required to prevent hypoglycemia
- Monitor serum creatinine and liver function tests at baseline and regularly. Adjust dose with declining renal function

DPP-4 Inhibitors (e.g., alogliptin, linagliptin, saxagliptin and sitagliptin):

- Improved postprandial control and well tolerated option in older adults [12]
- DPP-4 inhibitors should be used over sulfonylureas as second-line therapy to metformin because of a lower risk of hypoglycemia [Grade B, Level 2][2]
- *Common side effects:* infections (URTI, UTI), headache, nausea, constipation and diarrhea, acute kidney injury
- Similarly effective and safe in young and older people with diabetes, cause minimal hypoglycemia when used alone (or with metformin) and do not result in weight gain [2,12]
- Risk of heart failure (HF) may be increased with saxagliptin (increase HF hospitalizations NNH=143/2.1 yrs, risk highest among patients with elevated levels of natriuretic peptides, previous heart failure, or chronic kidney disease)[13]
- Monitor for symptoms of HF, serum creatinine and liver function tests at baseline and regularly (especially for alogliptin)
- All but linagliptin require renal dosing adjustments[3]

Thiazolidinediones (e.g., rosiglitazone, pioglitazone):

- Use cautiously when eGFR less than 60 mL/min [3]
- In a population-based study of older patients with diabetes, rosiglitazone primarily was associated with an increased risk of congestive heart failure, acute myocardial infarction, and mortality when compared with other combination oral hypoglycemic agent treatments in individuals aged 66 years or older with diabetes[14]
- Other side effects include fractures, diarrhea and other GI side effects[3]

Focus on Newer Diabetes Medications

SGLT2 Inhibitors (e.g., canagliflozin, dapagliflozin, empagliflozin):

- *Contraindications*: type 1 diabetes, history of diabetic ketoacidosis (DKA), dialysis
- Renal dosing adjustment required for all SGLT2 inhibitors
- Hold SGLT2 inhibitors during illness or dehydration to prevent acute kidney injury (see SADMANS on page 7)
- Concomitant sulfonylurea or insulin increases hypoglycemia risk. When initiating, consider current level of glycemic control and hypoglycemia history to assess need to reduce or discontinue sulfonylurea or insulin[17]
- SGLT2 inhibitors are less effective at improving glycemic control once CrCl drops below 60mL/min[12]
  - For glycemic control, recommended to use if eGFR 45 mL/min or greater[40]
  - Clinical outcome trials enroll participants with eGFR down to 20-30 mL/min and demonstrate improvements in CVD, CKD, and HF patient outcomes [17]
  - Health Canada: do not initiate empagliflozin or canagliflozin if eGFR less than 30 mL/min; dapagliflozin if eGFR less than25 mL/min[17]
- Caution in residents using insulin to not reduce insulin doses too quickly due to the risk of diabetic ketoacidosis [37]
- Canagliflozin: discontinue if active foot ulcer, lower extremity infection, ischemic limb and consider risk factors that may increase risk of amputation before initiating (e.g., prior amputation, peripheral vascular disease, neuropathy, foot ulcers)[17]
- In the EMPA-REG trial empagliflozin 10mg per day performed similarly to 25mg per day.[42] Dividing the 25mg pill to 12.5mg per day results in significant cost savings**.** Empagliflozin 10 mg & 25 mg = $2.84/tab and Empagliflozin 12.5 mg = 1/2 x 25 mg tab = $1.42/tab. Refer to Therapeutics Letter: Pill Splitting (March 2020)

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Optimizing Diabetes Medications

SGLT2 inhibitors (e.g., canagliflozin, dapagliflozin, empagliflozin) continued...

- A systematic review on the use of SGLT2 inhibitors showed that they appear to be relatively safe in the older population if clinical considerations such as concomitant diuretic use are accounted for and adjusted appropriately[15] however it was concluded that a future randomized controlled trials evaluating the safety and tolerability of SGLT2 inhibitors in the elderly population are still warranted as they can increase the risks of [37]:
  - Genital infection (RR 3.75, 95% CI 3.00–4.67; P for drug effect <0.001)
  - Urinary tract infection (RR 1.07, 95% CI 0.99–1.15; *p* for drug effect = 0.074)
  - Volume depletion (RR 1.14, 95% CI 1.05–1.24; *p* for drug effect = 0.002)
  - Diabetic ketoacidosis (RR 2.57, 95% CI 1.53–4.31; P for drug effect <0.001)

Close and careful monitoring of SGLT2 inhibitors is required in the geriatric population [37]

- Monitor for the occurrence and frequency of genital infections and UTIs
- Assess for volume depletion and correct before initiating an SGLT2 inhibitors
  - Urine volume may increase and may require dose reduction of loop diuretics[15].
- Monitor for volume depletion throughout treatment. In frail elderly people and for those with cognitive impairment, there could be increased risk of dehydration, orthostatic hypotension, and renal impairment with reduced oral intake
  - Increased urinary frequency and volume may occur; recommended to take in the morning
- Measure lying & standing blood pressures and monitor for orthostatic hypotension
  - Watch for postural BP drop and reassess antihypertensive and/or diuretic doses if necessary[18]
- eGFR may decrease upon initiation (on average, a 3 mL/min/1.73 m2 decrease). An eGFR decrease greater than 30% from baseline warrants careful evaluation[17]
  - Check renal function and potassium at baseline, within 2 to 4 weeks of staring, and then periodically
- SGLT2 inhibitors have a Health Canada warning regarding the risk of euglycemic diabetic ketoacidosis

GLP-1 Receptor Agonists (e.g., semaglutide, liraglutide, dulaglutide, lixisenatide):

- *Contraindications:* type 1 diabetes , history of pancreatitis, concurrent DPP-4 inhibitors, personal or family history of medullary thyroid cancer, multiple Endocrine Neoplasia Syndrome Type 2 [12,17]
- *Caution:* history of tachyarrhythmias, atrioventricular block, concomitant use of other sympathomimetic drugs or drugs that prolong PR interval [17,19]. Severe gastrointestinal disease, including gastroparesis, a history of stomach/gastric surgery, or inflammatory bowel disease [19]
- No dosage adjustment required in renal impairment, but limited efficacy and safety data if eGFR less than 15 mL/min or dialysis [17]
- Concomitant sulfonylurea or insulin increases risk. When initiating consider current level of glycemic control and hypoglycemia history to assess need to reduce or discontinue sulfonylurea or insulin [12,17]
- Caution in residents using insulin to not reduce insulin doses too quickly due to the risk of diabetic ketoacidosis [19]

Close and careful monitoring of GLP-1 receptor agonists is required in the geriatric population

- GI side effects can be significant: nausea, vomiting, diarrhea, abdominal pain, decreased appetite, constipation, dyspepsia.[12,17] NNH = 18; 95% CI, 8 to 112)[20] especially at the beginning of treatment and increasing doses
- Monitor for reduced food intake, weight loss and volume depletion particularly in frail older people
- Monitor for deterioration in renal function if severe adverse gastrointestinal reaction
- Acute pancreatitis: discontinue GLP1 receptor agonist [17]
- Acute gallbladder disease: discontinue GLP1 receptor agonist (gallbladder studies if cholelithiasis suspected) [17]
- Monitor for progression of diabetic retinopathy in patients with retinopathy [19]
- Monitor for diabetic ketoacidosis[19]

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Optimizing Diabetes Medications

Cardiovascular & Renal Benefits of SGLT2 Inhibitors and GLP1 Receptor Agonists

- In people with type 2 diabetes who have atherosclerotic cardiovascular disease, guidelines [3,12,17,21] prioritize the use of SGLT2 inhibitors or GLP1 receptor agonists for diabetes treatment, and for those with type 2 diabetes and chronic kidney disease (CKD) or heart failure (HF) the use of SGLT2 inhibitors is prioritized [3,17]
- However the time-to-benefit and resident life expectancy needs to be taken into consideration
  - It may take up to 5 or more years to achieve microvascular benefits and 10 or more years to achieve macrovascular benefits of good glycemic control [22,23,24]
- In a systematic review and network meta-analysis of randomized controlled trials, it was found that the absolute benefits of these drugs vary substantially across patients from low to very high risk of cardiovascular and renal outcomes
  - For the lowest risk group there were only 5 fewer deaths per 1000 patients over five years and 48 fewer deaths per 1000 patients treated over five years in the highest risk group[20]
- As it was found that SGLT-2 inhibitors were superior to GLP-1 receptor agonists in improving cardiovascular and renal outcomes except for nonfatal stroke[20], the stratified recommendations did provide stronger recommendations for SGLT-2 inhibitors when treatment is recommended
  - GLP-1 receptor agonists were shown to improve mortality but to a lesser extent than SGLT-2 inhibitors; weak recommendations for use of GLP-1 receptor agonists are based on not being able to use a SGLT-2 inhibitor (e.g., due to contraindications)[20,21]
- Cardiovascular and CKD trials have not shown higher doses to result in greater vascular event reduction nor are there clinically important reductions in surrogate markers (e.g., HbA1c, weight loss) with higher versus lower doses[26]
- BMJ provides a tool for to assess the evidence of potential benefits and potential harms for the SGLT-2 inhibitors and GLP-1 receptor agonists and individual considerations[21]: https://doi.org/10.1136/bmj.n1091
- Also refer to the attached resource *Non-Insulin Pharmacotherapy* for trials showing cardiovascular and renal outcomes, the NNT and time required for benefit

Recommendation: Use a risk stratified approach (e.g., BMJ tool linked above) when considering SGLT-2 inhibitors and GLP-1 receptor agonists for residents with type 2 diabetes. Shared decision making is needed so the resident and family are aware of the relative benefit and potential risk of side effects.

Weight Loss with GLP-1 Receptor Agonists

- Semaglutide (Ozempic®) and Lixisenatide (Adlyxine®) are not indicated for weight loss and Pharmacare part 3 EDS does not include weight loss as an indication.
- A retrospective cohort study[34] among patients with type 2 diabetes initiating GLP-1 receptor agonists included individuals with a median body mass index was 41.2 kg/m2 (IQR 35.8, 46.4) showed a mean weight change at 12 months of 4.6 kg. It was concluded that patients may not frequently achieve clinically meaningful weight loss and suggests that lifestyle interventions, including diet, physical exercise, and psychological support, remain an important component of a weight management strategy in patients with type 2 diabetes.
- Other medications for diabetes including metformin and SGLT2 inhibitors also result in some weight loss and DPP-4 inhibitors are weight neutral. Pharmacological therapy alone is unlikely to help the majority of residents achieve clinically meaningful weight loss.
- For more information on weight loss associated with the various types of antihyperglycemic agent, see attached resource *Non-Insulin Pharmacotherapy.*

! If a new antihyperglycemic agents has been started, monitor efficacy (e.g., A1C, blood glucose values, symptoms of hyper or hypoglycemia). If no or limited efficacy seen or resident is within 3-6 months[3,4] or resident is experiencing adverse effects sooner, reassess treatment.

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Optimizing Diabetes Medications

Sick Days with Type 2 Diabetes

SADMANs

- The Canadian Diabetes Association[3] has developed a simple, memorable SADMANS pneumonic for the "Sick Day Medication List" highlighting the need to hold medications that are likely to cause adverse drug reactions (ADR) during short term illnesses which could preclude dehydration or during periods of acute kidney decline
- For residents unable to maintain adequate fluid intake and who are at risk of dehydration (e.g. experiencing an acute infectious illnesses such as influenza, pneumonia, COVID-19, who are experiencing nausea and/or vomiting) or experiencing a sudden decrease in renal function, assess if any medications need to be held to prevent further adverse drug reactions or renal decline
- Assess the resident's medications using the SADMANs mnemonic (*Table 2: Sick Day Medication List* below) with the PCH prescriber and obtain an order to hold medications as required. Medications can be resumed at the usual dose once resident is recovered
- The frequency of blood glucose checks may need to be increased to closely monitor the resident for glucose fluctuations
- If resident is using insulin, the amount of insulin being used may need to be increased or decreased. For example, bolus insulin at meal time may need to be paused in not eating

Table 2: Sick Day Medication List[3]

	Type of Medication	Comments
S	**Sulfonylureas, other Secretagogues (e.g. glyburide, gliclazide)**	Hold due to reduced clearance by the kidneys and increased risk of low blood sugars or hypoglycemia
A	ACE inhibitors (e.g., ramipril, enalapril etc.)	Hold due to increased risk for decline in kidney function
D	Diuretics* (e.g., chlorthalidone, eplerenone, furosemide, hydrochlorothiazide, indapamide, metolazone, spironolactone)	Hold due to increased risk for decline in kidney function **Special consideration whether or not to hold diuretics (especially furosemide) in heart failure with short term illness depends on heart failure and fluid retention status*
	Direct renin inhibitor (e.g., aliskiren)	Hold due to increased risk for decline in kidney function
M	**Metformin**	Hold due to a reduced clearance of the drug by the kidneys and increased risk for adverse effects (e.g. more stomach upset). Consider restarting at a lower dose if ongoing nausea and/or diarrhea
A	Angiotensin Receptor Blockers (ARBs e.g., losartan, valsartan etc.)	Hold due to increased risk for decline in kidney function
N	NSAIDs and COXIBS (e.g., ibuprofen, naproxen, celecoxib)	Hold due to increased risk for decline in kidney function. In most situations it is recommended to continue with low dose ASA during short term illnesses
S	**SGLT2 Inhibitors**	Hold due to increased risk for decline in kidney function

Diabetic Ketoacidosis (DKA) is a Medical Emergency!

- *Risk factors*: sudden reduction or omission of insulin, pancreatic disorders causing insulin deficiency (e.g., type 1 diabetes, pancreatitis, pancreatic surgery), long standing type 2 diabetes, latent autoimmune diabetes, acute serious illness or infection, major surgery or hospitalization, reduced caloric intake due to illness, surgery, ketogenic diet
- *Symptoms:* hyperglycemia, fast deep breathing, feeling short of breath, nausea or vomiting, stomach pain, loss of appetite, excessive thirst, unusual sleepiness or tiredness, confusion, slurred speech, rapid heart rate[17]
- **Euglycemic diabetic ketoacidosis (EDKA)** is a rare, acute, life-threatening emergency that is characterized by euglycemia, metabolic acidosis, and ketoacidosis. Unlike DKA, the diagnosis of EDKA is often overlooked because of the absence of hyperglycemia
- **If residents taking insulin, SGLT2 inhibitors, or GLP1 agonists are exhibiting signs of DKA or EDKA, they need to be assessed immediately.**

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Optimizing Diabetes Medications

Deprescribing of Antihyperglycemics

- As per the *Deprescribing Antihyperglycemic Agents in Older Persons evidence-based clinical practice guideline*[35], if the potential for harm from antihyperglycemic agents (e.g. hypoglycemia) outweighs the potential benefit of treatment, deprescribing antihyperglycemic treatment is recommended. The full guideline[35] is available at: http://www.cfp.ca/content/63/11/832?
- **Consider deprescribing in older individuals who are at risk of hypoglycemia due to:**
  - Multiple comorbidities
  - Recurrent episodes of hypoglycemia
  - Taking sulfonylureas (in particular glyburide) or insulin
  - Benefit of treatment is uncertain due to: limited life expectancy, frailty, dementia, extensive coronary artery disease and are at high risk of ischemia
  - Drug interactions contributing to hypoglycemia - some medications can cause or mask symptoms of hypoglycemia (e.g., anti-hyperglycemics, beta blockers, ACE inhibitors, ethanol, fluoroquinolones, salicylates [40]
  - Overly intense glycemic control targets in place
  - Impaired renal function
  - Unpredictable eating patterns
- **Recommended deprescribing strategies include:**
  - Reducing the dose(s) or stopping the agent(s) most likely to contribute to hypoglycemia such as a sulfonylurea or insulin. If an individual is experiencing hypoglycemia, or at high risk of hypoglycemia, and their A1C level is below target, consider discontinuing one agent at a time
  - Simplify insulin regimens (see page 12)

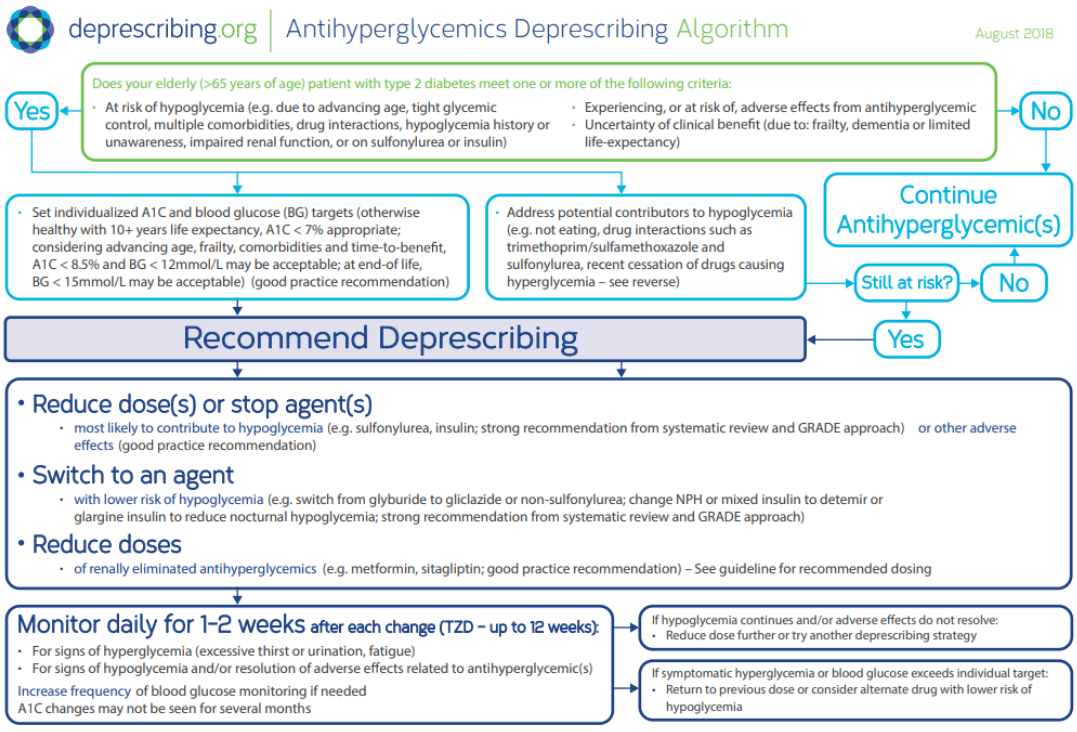

Figure 2: Antihyperglycemic Deprescribing Algorithm[35]

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Optimizing Insulin

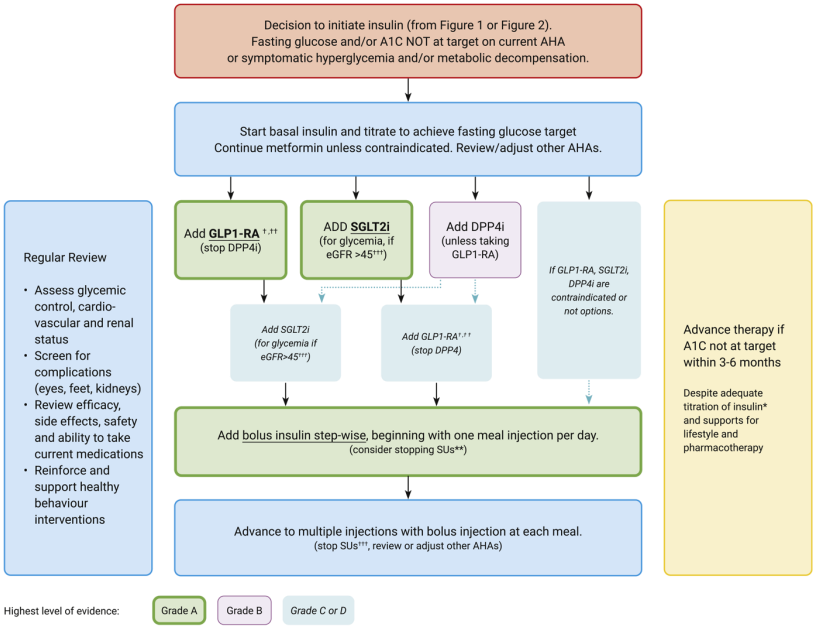
Basal Insulin

Basal Insulin versus Intermediate Insulin (e.g. NPH)[27,28,29]

- Insulin NPH action peaks between 4 to 10 hours which may lead to hypoglycemia in some patients, particularly nocturnal hypoglycemia following an evening dose. Insulin NPH may require twice daily dosing compared to
- In a CADTH meta-analysis, overall hypoglycemia results were 55.9% for NPH and 47.2% for insulin glargine NNT = 12 over 6-12 months[28]
- Patients with chronic kidney disease stages 3 and 4 had a lower incidence of hypoglycemia when receiving insulin glargine versus NPH insulin[29]
- Insulin glargine reduces overall and nocturnal hypoglycemia compared with insulin NPH[27]
- Consider switching from insulin NPH to long-acting basal insulin 100 unit /mL analogues in adults who have risk factors for severe hypoglycemia including: any previous episode of severe hypoglycemia, hypoglycemia unawareness, long duration of insulin use (5 years or longer), eGFR less than 45 mL/min, autonomic neuropathy, cognitive impairment, extensive coronary artery disease or heart failure[39]
- When transitioning from insulin NPH to a long acting basal 100 units/mL insulin, switch on a unit to unit basis unless taking twice daily NPH, then reduce the total insulin dose by 20%[39,40]

When is the right time to give basal insulin in older adults?

- Dosing basal insulin in the morning may lower the risk of early morning hypoglycemia if given in the evening. This allows the use of higher doses of insulin in the morning compared to bedtime, and doses can be titrated to fasting glucose levels[26]



* Titration of basal insulin to achieve FPG target without hypoglycemia.
† And titrate dose of GLP1-RA, as tolerated.
†† Or fixed-ratio combination.
††† If eGFR >30 ml/min/1.73m^2, may be used for cardiorenal benefit.
** Sulfonylureas or meglitinides.
AHAs, antihyperglycemic agents; A1C, glycated hemoglobin; DPP4i, dipeptidyl peptidase-4 inhibitors; eGFR, estimated glomerular filtration rate; GLP1-RA, glucagon-like peptide-1 receptor agonists; SGLT2i, sodium-glucose cotransporter 2 inhibitors; SU, sulfonylureas.

Figure 3: Starting or Advancing Insulin in Type 2 Diabetes[3]:

- This algorithm is not specific to older individuals who require less stringent glycemic control
- Pharmacare EDS criteria may not align with these recommendations (see attached resource *Non-Insulin Pharmacotherapy*)
- For residents requiring antihyperglycemic treatment optimization, agents with a lower risk of hypoglycemia such as DPP-4 inhibitors should be assessed and considered before insulin[3]
- While a SGLT2 inhibitor or a GLP-1 receptor agonist with proven cardiovascular benefit has been recommended for persons aged 60 and older with at least two cardiovascular risk factors by Diabetes Canada[3] these recommendations should be considered in conjunction with clinical practice guidelines specific for managing diabetes in older people[2,3]
- For residents with cardiovascular considerations, if there are no contraindications and renal function permits, **preference is to be given to a SGLT2 inhibitor** based on available evidence[20,21] and the lower cost compared to GLP-1 receptor agonists. See *Cardiovascular & Renal Benefits of SGLT2 Inhibitors and GLP1 Receptor Agonists* on page 6

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Winnipeg Regional Health Authority Caring for Health
Office régional de la santé de Winnipeg À l'écoute de notre santé

Quarterly Medication Review Deprescribing Focus

LONG TERM CARE

Optimizing Insulin

Basal Insulin continued...

Overbasalization of Insulin in Type 2 Diabetes[30]

- Overbasalization is when the basal insulin is titrated beyond an appropriate dose in an effort to achieve glycemic targets
- Although fasting blood glucose targets have been achieved, basal insulin doses are increased further leading to hypoglycemia during the day or evening with persistent postprandial hyperglycemia
- Exogenous basal insulin is a "background" insulin and cannot release a bolus of insulin to manage postprandial hyperglycemia

Identification in Clinical Practice

- **Basal insulin dose greater than 0.5 units/kg/day**
- Fasting blood glucose can be in target but the A1C level is elevated
- Blood glucose value taken two hours after a meal (post prandial) is 3 mmol/L or higher than the value taken before that same meal (pre-prandial)
- The blood glucose taken in the bedtime is 2.8 mmol/L or higher than the morning blood glucose values
- Resident may experience hypoglycemia symptoms overnight, on waking, or when meals delayed/skipped. The resident may have to snack between meals or before bed *("feeding insulin")*
- Weight gain

To decrease postprandial hyperglycemia:

- Increase insulin action at mealtimes by adding an non-insulin antihyperglycemic agent (e.g. metformin, DPP-4 inhibitors, SGLT2 inhibitors
- Add rapid acting bolus insulin at meal times where the postprandial value is 3 mmol/L or higher than the pre-prandial value
- Consider reducing basal insulin dose - increasing basal insulin to more than 0.5 units/kg has been shown to not improve A1C and is associated with weight gain
- It has been suggested that postprandial glucose values are a better predictor of outcomes in older people with diabetes than A1C or pre-prandial glucose values. Older people with type 2 diabetes who have survived an acute myocardial infarct (MI) may have a lower risk for a subsequent CV event with targeting of postprandial vs. fasting/preprandial glycemia [3]

Insulin Glargine Versus Insulin Degludec:

- SWITCH 2 trial randomized patients with type 2 diabetes and at least one risk factor for hypoglycemia (e.g., history of hypoglycemia, longer than 5 years of insulin therapy, hypoglycemia unawareness or moderate chronic renal failure) to insulin degludec or insulin glargine 100 units/mL. After 32 weeks of treatment, insulin degludec was associated with a significantly lower rate of the primary endpoint of overall symptomatic hypoglycemic episodes (rate ratio 0.70, 95% CI 0.61–0.80). The proportions of patients with hypoglycemic episodes were 9.7% and 14.7% for insulin degludec and insulin glargine 100 units/ml, respectively [31]
- Insulin degludec or insulin glargine administered once daily provided similar improvements in long-term glycemic control and nocturnal hypoglycemia rate was found to be reduced by 49% (P = 0.004) with degludec relative to glargine [38]
- Consider switching to insulin degludec if:
  - Resident experiences hypoglycemia while taking insulin glargine 100 units/mL and/or
  - Resident needing to use BID insulin glargine or is using daily glargine and daily insulin NPH. Giving a BID regimen of a long acting insulin can result in overlap of the insulin effect from both doses and result in hypoglycemia. This may signify that a once daily glargine insulin is not lasting the full 24 hours but giving a once daily larger dose of glargine insulin may cause hypoglycemia.
  - If switching from insulin glargine to insulin degludec, use a 20% dose reduction to prevent hypoglycemia[40]
  - As the activity profiles of insulin glargine and insulin degludec are similar for most people (see *Figure 4: Action Profiles of Insulin)* and insulin degludec is more expensive that insulin glargine, insulin glargine is the preferred basal insulin for new starts. Insulin degludec (Tresiba FlexTouch) = $6.30/mL; insulin glargine = $4.47/mL

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Rapid Acting Insulins

Rapid Acting Insulin versus "Regular" Insulin:

- Rapid acting insulin mimics the physiological action of insulin in the body
  - Rapid acting insulin (e.g. insulin lispro) has an onset of action of 5 to 15 minutes, a peak effect of 1 to 2 hours and a duration of action that lasts 4-6 hours
  - Regular insulin has an onset of action of 30 to 60 minutes, peak effect of 2 to 4 hours and a duration of action up to 6 to 8 hours
- Compared to regular insulin, rapid acting insulin has been shown to lower postprandial glucose levels two hours after meals [37]
- Using insulin lispro instead of regular insulin at meal time may improve glycemic control with reduced number of hypoglycemic episodes in LTC residents[2]

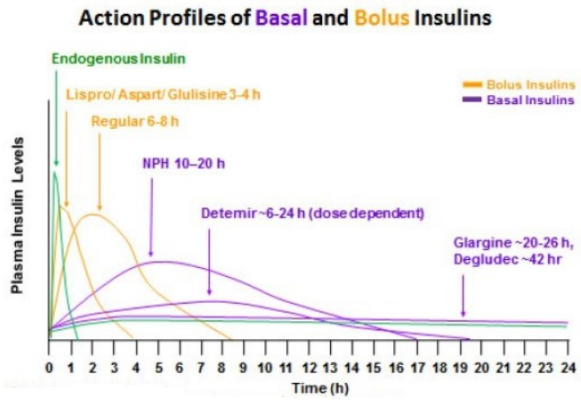

Figure 4: Action Profiles of Insulin [37]

- Rapid acting insulin is the preferred prandial insulin to be given for residents who do not eat consistent meals as it can be taken with the first bite of food once nursing is certain that the resident will eat their meal
  - Can be injected at the start of the a meal (up to 2 minutes before meal) or within 20 minutes after starting the meal[12]
  - The possibility of administration of rapid acting insulins immediately after meals is another important benefit, as it may not always be possible to predict how much food the resident will eat[37]
- The longer action of regular insulin may increase the resident's risk of experiencing hypoglycemia for up to 6 to 8 hours if they did not eat an adequate amount at their meal time, in particular nocturnal hypoglycemia[37], if an inadequate amount of supper was eaten.

Practice Point: If the resident has a scheduled bolus insulin order and an prn order for correction insulin at meal time (e.g. extra insulin given based on pre-prandial blood glucose), typically the same type of insulin should be used for the scheduled and correction dose (e.g. use rapid acting insulin for both the scheduled and correction dose if needed). If frequent correction doses need to be given, the scheduled dose should be modified to reflect the increase insulin required. Using the same type of insulin reduces wastage and prevents the correction insulin from expiring if being used infrequently.

Premixed insulins[33]:

- Long-acting basal analogues are associated with a lower frequency of hypoglycemia than premixed insulin in older adults
- Premixed insulin provide less dosing flexibility compared to basal and basal-bolus regimens
- Mixed insulins require fixed meal schedules and a consistent food intake to prevent hypoglycemia throughout the day

Sliding Scale Insulin (SSI)

- Choosing Wisely recommends[45]: ***Don't use SSI for long-term diabetes management for individuals residing in the nursing home.***
  - SSI is a reactive way of treating hyperglycemia after it has occurred rather than preventing it. Good evidence exists that SSI is neither effective in meeting the body's physiologic insulin needs nor is it efficient in the LTC setting in medically stable individuals. Use of SSI is associated with more frequent glucose checks and insulin injections, leads to greater resident discomfort and increased nursing time and resources. With SSI regimens, residents may be at risk of wide glucose fluctuations or hypoglycemia when insulin is given and food intake is erratic.
- In observational studies, the degree of glycemic control varies widely between different LTC centers, adherence to clinical practice guidelines is poor, and SSI (correction insulin only) are used frequently despite lack of evidence for their effectiveness[2]

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Sliding Scale Insulin (SSI) continued...

- The utilization of SSI is prevalent in LTC and is associated with poorer glycemic control and higher frequency of capillary blood glucose (CBG) monitoring and hypoglycemia[2]
- The American Geriatrics Society 2023 Beers Criteria for Potentially Inappropriate Medication Use in Older Adults[44] recommends avoiding sliding scales for insulin (moderate evidence, strong recommendation)
    - Higher risk of hypoglycemia without improvement in hyperglycemia management regardless of care setting.
    - Avoid insulin regimens that include only short- or rapid-acting insulin dosed according to current blood glucose levels without concurrent use of basal or long-acting insulin.

Recommendation: Sliding scale (reactive) and correction (supplemental) insulin protocols should be avoided in elderly LTC residents with diabetes to prevent worsening glycemic control [Grade C, Level 3][3]

Simplification of Insulin Regimens:

- It has been demonstrated that simplification of the insulin regimen in older people with type 2 diabetes by switching multiple-dose insulin regimens to once-a-day insulin glargine 100 units/mL with or without noninsulin antihyperglycemic agents results in equivalent glycemic control and a reduced risk of hypoglycemia[32]
- Simplification of the insulin regimen has been shown to reduce hypoglycemia without worsening glycemic control[33]
- Reassess if bolus insulin doses of 10 units or less can be discontinued and a non-insulin medication started[33]

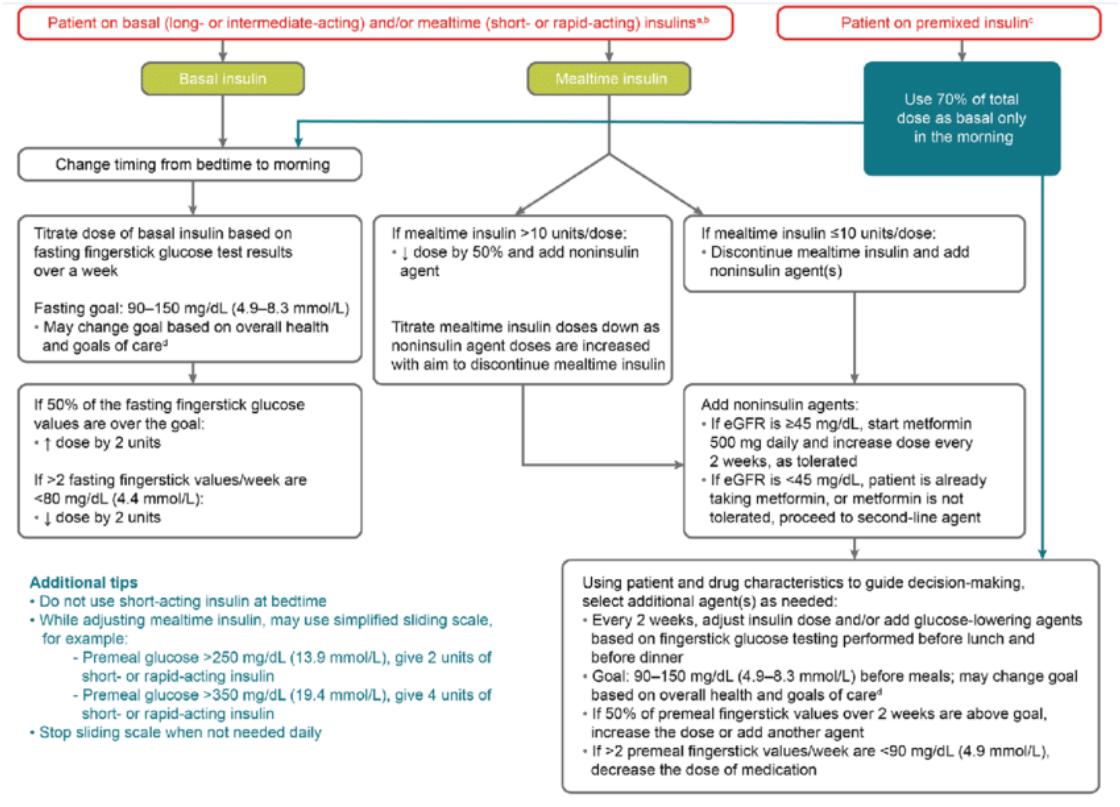

Figure 5: Simplification of Complex Insulin Therapy[33]

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Optimizing Diabetes Medications & Insulin

1. Canadian Geriatrics Society. Eight tests and treatments to question. Updated November 2022 [accessed July 12, 2023] https://choosingwiselycanada.org/recommendations/geriatrics/
2. Graydon, S., Meneilly G, Knip A, Miller, D, et al. *Diabetes Canada 2018 Clinical Practice Guidelines for the Prevention and Management of Diabetes in Canada*: Diabetes in Older Adults. Can J Diabetes 2018;42 (Suppl 1):S283-S295.
3. Lipsombe L, Butalia S, Dasgupta K, et al. *Diabetes Canada 2018 Clinical Practice Guidelines for the Prevention and Management of Diabetes in Canada*: Pharmacologic Glycemic Management of Type 2 Diabetes in Adults:2020 Update. Can J Diabetes 44 (2020):S575-S591.
4. Fernando K, Bain S, Holmes P, Jones P, Patel D. Glucagon-Like Peptide 1 Receptor Agonist Usage in Type 2 Diabetes in Primary Care for the UK and Beyond: A Narrative Review. Diabetes Ther (2021) 12:2267–2288 https://doi.org/10.1007/s13300-021-01116-9
5. Therapeutics Initiative. The Limitations and Potential Hazards of Using Surrogate Markers. Therapeutics Letter October-December 2014 [accessed July 17, 2023] https://www.ti.ubc.ca/2015/02/03/the-limitations-and-potential-hazards-of-using-surrogate-markers/
6. Berard LD, Siemens R, Woo V. Monitoring glycemic control. Canadian journal of diabetes. 2018 Apr 1;42:S47-53. 19.
7. Radin MS. Pitfalls in hemoglobin A1c measurement: when results may be misleading. J Gen Intern Med. 2014;29(2):388-394. doi:10.1007/s11606-013-2595-x
8. Raz I, Ceriello A, Wilson PW, et al. Post hoc subgroup analysis of the HEART2D trial demonstrates lower cardiovascular risk in older patients targeting postprandial versus fasting/premeal glycemia. Diabetes Care 2011;34:1511–13
9. Regier L , LeBras M, Trischuk,T Diabetes Treatment: Glycemic Management in T2DM. July 2023 [accessed July 17, 2023] https://www.rxfiles.ca/RxFiles/uploads/documents/members/cht-diabetes.pdf
10. Jadzinsky M, Pfützner A, Paz-Pacheco E, Xu Z, Allen E, Chen R, CV181-039 Investigators. Saxagliptin given in combination with metformin as initial therapy improves glycaemic control in patients with type 2 diabetes compared with either monotherapy: a randomized controlled trial. Diabetes, Obesity and Metabolism. 2009 Jun;11(6):611-22.
11. Regier L , LeBras M, Trischuk,T Anti-Hyperglycemia Type2 Diabetes Agents: Drug Comparison Table. July 2023 [accessed July 16, 2023] https://www.rxfiles.ca/RxFiles/uploads/documents/members/cht-diabetes-agents.pdf
12. Centre for Effective Practice. (June 2023). Type 2 diabetes: Non-insulin pharmacotherapy: Ontario. Toronto: Centre for Effective Practice. [accessed July 17, 2023] https://tools.cep.health/tool/type-2-diabetes-non-insulin-pharmacotherapy-2/
13. SAVOR-TIMI 53 Scirica BM, Bhatt DL, Braunwald E, et al., on behalf of the SAVOR-TIMI 53 Steering Committee and Investigators. Saxagliptin and cardiovascular outcomes in patients with type 2 diabetes mellitus. *N Engl J Med* 2013;369:1317-26.
14. Lipscombe LL, Gomes T, Lévesque LE, Hux JE, Juurlink DN, Alter DA. Thiazolidinediones and Cardiovascular Outcomes in Older Patients With Diabetes. *JAMA.* 2007;298(22):2634–2643. doi:10.1001/jama.298.22.2634
15. Edwards S, Lam, C, Thomas L. Evaluation of the Safety and Tolerability of Sodium-Glucose Co-Transporter 2 Inhibitors in the Older Population: A Systemic Review. The Senior Care Pharmacist, Volume 28, Number 7, 1 July 2023, pp. 276-287(12)
16. Zelniker TA et al. SGLT2 inhibitors for primary and secondary prevention of cardiovascular and renal outcomes in type 2 diabetes: a systematic review and meta-analysis of cardiovascular outcome trials. The Lancet. 2019; 393(10166):31-39
17. B.C. Provincial Academic Detailing (PAD) Service. Type 2 Diabetes Focused Update: SGLT2 Inhibotirs and GLP1 Agonists. (July 2023) [accessed July 18, 2023]. https://www2.gov.bc.ca/assets/gov/health/practitioner-pro/provincial-academic-detailing-service/pad2021_sglt2-inhibitors-glp1-agonists_handout.pdf
18. Getting the most from your Sodium Glucose Co-transporter-2 Inhibitors (SGLT2i). Imperial College Healthcare NHS Trust. February 2023. Accessed June 21, 2023.
19. Fernando K, Bain S, Holmes P, Jones P, Patel D. Glucagon-Like Peptide 1 Receptor Agonist Usage in Type 2 Diabetes in Primary Care for the UK and Beyond: A Narrative Review. Diabetes Ther (2021) 12:2267–2288 https://doi.org/10.1007/s13300-021-01116-9
20. Palmer SC, Tendal B, Mustafa RA, et al. Sodium-glucose cotransporter protein-2 (SGLT-2) inhibitors and glucagon-like peptide-1 (GLP-1) receptor agonists for type 2 diabetes: Systematic review and network meta-analysis of randomised controlled trials. BMJ 2021;372:m4573.
21. Li S, Vandvik P O, Lytvyn L, Guyatt G H, Palmer S C, Rodriguez-Gutierrez R et al. SGLT-2 inhibitors or GLP-1 receptor agonists for adults with type 2 diabetes: a clinical practice guideline *BMJ 2021; 373 :n1091 doi:10.1136/bmj.n1091*
22. ADVANCE. ADVANCE Collaborative Group, Patel A, MacMahon S, Chalmers J, Neal B, Billot L, Woodward M, Marre M, Cooper M, Glasziou P, Grobbee D, Hamet P, Harrap S, Heller S, Liu L, Mancia G, Mogensen CE, Pan C, Poulter N, Rodgers A, Williams B, Bompoint S, de Galan BE, Joshi R, Travert F. Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. N Engl J Med. 2008 Jun 12;358 (24):2560-72
23. UKPDS-33. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). UK Prospective Diabetes Study (UKPDS) Group. Lancet. 1998 Sep 12;352(9131):837-53. 10.
24. UKPDS-34. Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). UK Prospective Diabetes Study (UKPDS) Group. Lancet. 1998 Sep 12;352(9131):854-65.
25. Shi FH, Li H, Shen L, et al. High-dose sodium-glucose co-transporter-2 inhibitors are superior in type 2 diabetes: A meta-analysis of randomized clinical trials. *Diabetes Obes Metab*. 2021;23(9):2125-2136. doi:10.1111/dom.14452
26. Leung E, Wongrakpanich S, Munshi MN. Diabetes Management in the Elderly. Diabetes Spectr. 2018 Aug;31(3):245-253. doi: 10.2337/ds18-0033. PMID: 30140140; PMCID: PMC6092888
27. LeBras M, Laubscher T. Hypoglycemia in type 2 diabetes: It is common, so what strategies can minimize the risk? Can Fam Physician. 2021 Jan;67(1):35-38. doi: 10.46747/cfp.670135. PMID: 33483395; PMCID: PMC7822618.
28. Canadian Agency for Drugs and Technologies in Health Long-acting insulin analogues for the treatment of diabetes mellitus: meta-analyses of clinical outcomes. Ottawa, ON: Canadian Agency for Drugs and Technologies in Health; 2008.
29. Betônico CC, Titan SMO, Lira A, Pelaes TS, Correa-Giannella MLC, Nery M, Queiroz M. Insulin Glargine U100 Improved Glycemic Control and Reduced Nocturnal Hypoglycemia in Patients with Type 2 Diabetes Mellitus and Chronic Kidney Disease Stages 3 and 4. Clin Ther. 2019 Oct;41(10):2008-2020.e3. doi: 10.1016/j.clinthera.2019.07.011. Epub 2019 Aug 2. PMID: 31383366.
30. Cowart K. Overbasalization: Addressing Hesitancy in Treatment Intensification Beyond Basal Insulin. Clin Diabetes. 2020 Jul;38(3):304-310. doi: 10.2337/cd19-0061. PMID: 32699482; PMCID: PMC7364465.
31. Wysham C, Bhargava A, Chaykin L, et al. Effect of insulin degludec vs insulin glargine U100 on hypoglycemia in patients with type 2 diabetes. The SWITCH 2 Randomized Clinical Trial. JAMA 2017;318(1):45–56.
32. Munshi MN, Slyne C, Segal AR, et al. SImplification of insulin regimen in older adults and risk of hypoglycemia. JAMA Intern Med 2016;176:1023–6.
33. American Diabetes Association Professional Practice Committee; 13. Older Adults: *Standards of Medical Care in Diabetes—2022. Diabetes Care* 1 January 2022; 45 (Supplement_1): S195–S207. https://doi.org/10.2337/dc22-S013
34. Weiss T, Yang L, Carr RD, *et al*. Real-world weight change, adherence, and discontinuation among patients with type 2 diabetes initiating glucagon-like peptide-1 receptor agonists in the UK. *BMJ Open Diab Res Care* 2022;10:e0025
35. Farrell B, Black C, Thompson W, et al. 2017. Deprescribing antihyperglycemic agents in older persons Evidence-based clinical practice guideline. Can Fam Physician. 63 (11): 832-843.
36. Qiu M, Ding LL, Zhang M, Zhou HR. Safety of four SGLT2 inhibitors in three chronic diseases: A meta-analysis of large randomized trials of SGLT2 inhibitors. Diab Vasc Dis Res. 2021 Mar-Apr;18 (2):14791641211011016. doi: 10.1177/14791641211011016. PMID: 33887983; PMCID: PMC8481734.
37. Melo, K.F.S., Bahia, L.R., Pasinato, B. *et al.* Short-acting insulin analogues versus regular human insulin on postprandial glucose and hypoglycemia in type 1 diabetes mellitus: a systematic review and meta-analysis. *Diabetol Metab Syndr* **11**, 2 (2019). https://doi.org/10.1186/s13098-018-0397-3
38. Zinman B, Philis-Tsimikas A, Cariou B, Handelsman Y, Rodbard HW, Johansen T, Endahl L, Mathieu C; NN1250-3579 (BEGIN Once Long) Trial Investigators. Insulin degludec versus insulin glargine in insulin-naive patients with type 2 diabetes: a 1-year, randomized, treat-to-target trial (BEGIN Once Long). Diabetes Care. 2012 Dec;35(12):2464-71. doi: 10.2337/dc12-1205. Epub 2012 Oct 5. PMID: 23043166; PMCID: PMC3507614.
39. LeBras M, Trischuk,T Insulin Initiation, Titration and Follow up in T2M. May 2023 [accessed July 18, 2023] https://www.rxfiles.ca/RxFiles/uploads/documents/members/cht-insulin-initiation-titration.pdf
40. Centre for Effective Practice. (April 2021). Type 2 Diabetes: Insulin Therapy. Ontario. Toronto: Centre for Effective Practice. [accessed July 17, 2023] https://tools.cep.health/wp-content/uploads/2022/03/CEP_InsulinTherapy_March11.pdf
41. Battelino T, Danne T, Bergenstal RM. et al. Clinical targets for continuous glucose monitoring data interpretation: Recommendations from the international consensus on time in range. *Diabetes Care. 2019;42:1593–603.*
42. Therapeutics Initiative. *Pill Splitting: making the most of meds in time of need.* Therapeutics Letter. Special Edition: March 2020. SE. ti.ubc.ca/2020/03/23/special-edition-march-2020-pill-splitting/
43. Powerpak. Module 6: Understanding Insulin Therapy. (May 2019) [accessed July 21, 2023]. https://www.powerpak.com/course/content /118201
44. 2023 American Geriatrics Society Beers Criteria® Update Expert Panel. 2023. American Geriatrics Society 2023 Updated AGS Beers Criteria® for Potentially Inappropriate Medication Use in Older Adults. J Am Geriatr Soc.2023;712052-2081.
45. AMDA – The Society for Post-Acute and Long-Term Care Medicine. Fifteen Things Physicians and Patients Should Question. Updated July 28, 2022 [accessed July 21, 2023] https://res.cloudinary.com/paltc/image/upload/v1666280559/docs/AMDA_Choosing_Wisely_Statements_10_xtww3e.pdf