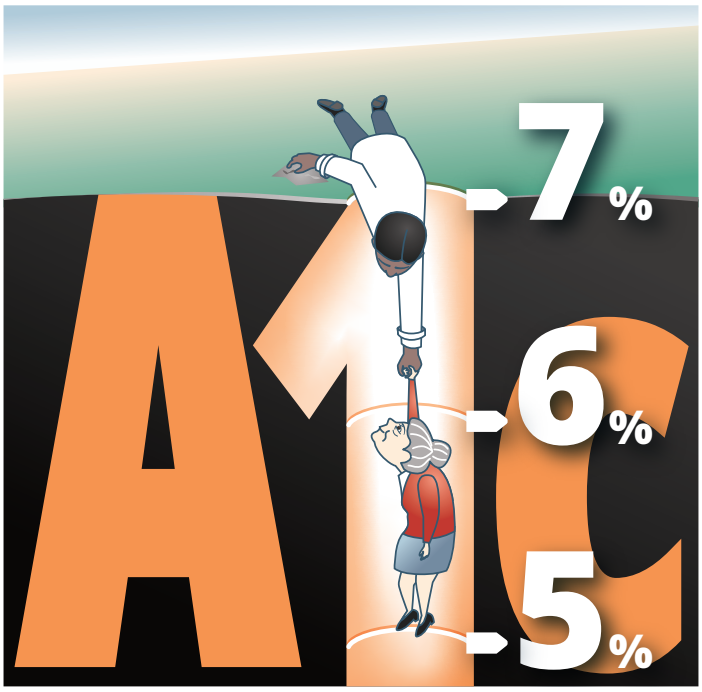
Therapeutics Initiative
Better prescribing. Better health.

THERAPEUTICS LETTER 151
September - October 2024

Safe diabetes treatment for older adults



PLAIN LANGUAGE SUMMARY

BOTTOM LINE

For most older adults (65 years or older) with type 2 diabetes who have an A1c below 7%, sulfonylureas or insulin do more harm than good.

Type 2 diabetes drugs for older adults

As people age, they are more likely to experience side effects from drugs. People with multiple health problems who take many medications are at even higher risk of harm from side effects. For diabetes medications, one of the most important side effects is low blood sugar. Sulfonylureas and insulins are the drugs most likely to cause low blood sugar.

Isn't a low A1c always good?

Experiments involving tens of thousands of patients looked at the effects of achieving an A1c below 7% for older adults. These trials show:

- There is no benefit of having an A1c below 7%, compared with a more relaxed value around 7.5% or 8.0%.
- Achieving an A1c below 7% raises the chances of dangerously low blood sugar.

Most older adults in these trials were taking sulfonylureas or insulin. These results show why using sulfonylureas or insulin to achieve an A1c below 7% is not recommended.

Reviewing diabetes medications is good practice

People change over time. Regular medication review is a good idea to determine if changes are needed. Changing medication makes sense if:

- a person has an A1c below 7% and is taking a sulfonylurea or insulin. This could mean reducing the dose of the drug, gradually reducing the dose with an aim to stop it, or stopping outright. Patients and prescribers should work together to decide and plan what to do, and how to monitor the results.
- a person is experiencing frequent or dangerous low blood sugars. In this case it almost always makes sense to reduce or stop a drug that lowers blood sugar.

ABSTRACT

Background: In older adults with type 2 diabetes (T2DM), tight glycemic control (HbA1c <7%) can result in more harm than benefit, especially when using insulin or sulfonylureas. Older adults are at higher risk for adverse drug events, especially hypoglycemia, which may cause falls, confusion, and hospitalizations.

Aims: This Therapeutics Letter evaluates the risks of tight glycemic control in older adults with T2DM, focusing on deprescribing diabetes medications in those over 65, especially those with multimorbidities and polypharmacy. It assesses the evidence from clinical trials and guidelines, with a focus on preventing hypoglycemia and improving patient-centered care through relaxed HbA1c targets.

Recommendations: Large RCTs show that intensive glycemic control (HbA1c ≤7%) does not reduce cardiovascular risk but increases hypoglycemia and mortality, particularly in older adults. Instead, glycemic targets should be adjusted based on the patient's overall health and life expectancy. Deprescribing may be considered, starting with drugs most likely to cause hypoglycemia (sulfonylureas or insulin). Regular reassessment and patient involvement in creating individualized treatment plans are essential.

Keywords: Aged; Deprescriptions; Diabetes Mellitus; Drug-Related Side Effects and Adverse Reactions; Glucagon-Like Peptide-1 Receptor Agonists; Glycemic Control; Hypoglycemic Agents; Medication Therapy Management; Polypharmacy; Sodium-Glucose Transporter 2 Inhibitors.

THE UNIVERSITY OF BRITISH COLUMBIA

Therapeutics Initiative
The University of British Columbia
Department of Anesthesiology, Pharmacology & Therapeutics
2176 Health Sciences Mall, Vancouver, BC, Canada V6T 1Z3

T +1 604.822.0700
F +1 604.822.0701
E info@ti.ubc.ca

ISSN 2369-8691

Safe diabetes treatment for older adults

For most people 65 years or older with type 2 diabetes and an A1c below 7%

Taking sulfonylureas or insulins does more harm than good

Therapeutics Initiative

THE UNIVERSITY OF BRITISH COLUMBIA

Image designed by Freepik

Multiple experts and primary care clinicians reviewed the draft of this Therapeutics Letter for factual accuracy, and to ensure it is relevant to clinicians.

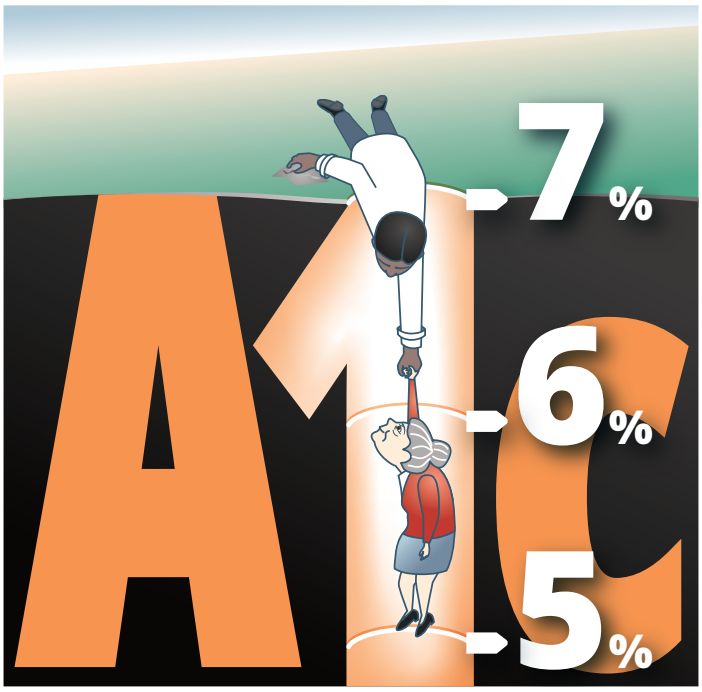
The UBC TI is funded by the BC Ministry of Health to provide evidence-based information about drug therapy. We neither formulate nor adjudicate provincial drug policies.

ISSN 2369-8691

Therapeutics Initiative
Better prescribing. Better health.

THERAPEUTICS LETTER 151
September - October 2024

Minimizing harms of tight glycemic control in older people with type 2 diabetes



Vignette: *Your 81-year-old patient has a new hemoglobin A1c result of 6.6%. He has had type 2 diabetes for 15 years, and he also has chronic obstructive pulmonary disease, osteoarthritis, hypertension, and had a myocardial infarction 10 years ago. He takes 12 daily medications, including metformin, sitagliptin, and glyburide. Having ordered the A1c test,* ***how do you respond to the result?***

Summary and conclusions

- **An A1c below 7% is likely associated with more harm than benefit in older adults (≥65 years) with type 2 diabetes taking sulfonylureas or insulin.**
- **Deprescribing is appropriate when A1c is <7% for older adults with type 2 diabetes taking sulfonylureas or insulin. Stop, gradually taper, or reduce drug dose(s) and monitor with clinical follow-up within 1 to 2 weeks.**

Older adults with type 2 diabetes are more vulnerable to medication harms

About 1 in 5 older Canadians (≥65) have diabetes, mostly type 2 (T2DM).[1] Many are healthy, with excellent functional status. However, older adults with T2DM often have several other chronic health problems, functional limitations, frailty, and polypharmacy. This increases risk of adverse drug events,[2] especially hypoglycemia – an important cause of falls, confusion, emergency department visits, and hospitalization.[3–5] During 2022, a sulfonylurea, an insulin, or repaglinide was dispensed to over 82,300 British Columbians age 65 or older (about 8% of BC's population in this age group). During the first half of 2024, at least one of these drugs was dispensed to over 71,000 BC residents ≥65, the vast majority type 2 diabetics. These numbers do not include beneficiaries of the First Nations Health Benefit Plan and federally insured residents, and include only prescriptions dispensed at a community pharmacy.

Lower glycemic targets unnecessary but harmful for older adults

There is no evidence to specify "ideal" A1c targets in older adults. Aiming for a specific number or threshold is complicated by the continuous variability of A1c in a population (similar to hemoglobin, creatinine, or body weight). Individuals also show day-to-day biological variability and measurement error in A1c.[6]

Large randomized controlled trials (RCTs) examined the effects of treating to intensive glycemic targets (e.g., A1c ≤7% or ≤6.5%), versus treating to relaxed targets (~7.5–8.5%) among people with longstanding type 2 diabetes.[7–9] These RCTs were conducted in groups whose mean age ranged from 60 to 66 years. They mainly tested the use of metformin in combination with sulfonylureas or insulin to achieve targets. Aiming for intensive glycemic targets did not reduce the risk of cardiovascular (CV) events versus more relaxed A1c targets.[7–9] But compared with a relaxed target, achieving A1c ≤7% **increased risk of severe hypoglycemia**[7–9] and it **increased risk of premature mortality** in the ACCORD trial.[8]

Targeting an A1c ≤7%, especially with sulfonylureas or insulin, is now widely considered "overtreatment" for older adults.[10–12] If choosing a target-based approach, current organizational guidelines consistently recommend **relaxed glycemic targets for most older adults with T2DM, and avoidance of SUs or insulin.**[10–12] For example, Choosing Wisely Canada provides the following reasonable glycemic targets:

- 7.0 – 7.5% in healthy older adults with long life expectancy;
- 7.5 – 8.0% for moderate comorbidity and a life expectancy <10 years;
- 8.0 – 8.5% for multiple morbidities and shorter life expectancy.[12]

Preventing hypoglycemia should be a central clinical goal of T2DM management in older adults.[10–12]

Recent evidence raises further questions about the appropriateness of treating to intensive A1c targets. Large RCTs of sodium/glucose cotransporter-2 inhibitors (SGLT2i) and glucagon-like peptide-1 receptor agonists (GLP1RA) for type 2 diabetes showed that cardiovascular events were

THE UNIVERSITY OF BRITISH COLUMBIA

Therapeutics Initiative
The University of British Columbia
Department of Anesthesiology, Pharmacology & Therapeutics
2176 Health Sciences Mall, Vancouver, BC, Canada V6T 1Z3

T +1 604.822.0700
F +1 604.822.0701
E info@ti.ubc.ca

ISSN 2369-8691

reduced with achieved A1c values in the mid 7% range, among patients with a mean age in the early 60s.[13,14] This suggests that cardiovascular benefits may be independent of A1c lowering. Offering SGLT2i or GLP1RA to older people with type 2 diabetics reflects the clinical goal of reducing cardiovascular morbidity, instead of a surrogate number. Increasingly, SGLT2i and GLP1RA are covered by provincial drug benefit formularies, improving access. Costs of SGLT2i can sometimes be reduced by dose-splitting.[15]

However, very limited evidence is available about the effectiveness and safety of SGLT2i or GLP1RA in people ≥75, or who have multimorbidity or frailty. In RCTs of SGLT2i or GLP1RA that included patients with type 2 diabetes, about 10% of participants were ≥75.[13,14,16,17,18,19] Thus, even sub-analyses of landmark trials that claim safety in older adults **included few people older than 75**.[19–22] In frail older people, relevant adverse effects of SGLT2i include dehydration, urinary tract infection, euglycemic diabetic ketoacidosis, and orthostatic hypotension; and from GLP1RA, weight loss or gastrointestinal adverse effects.[11]

Reassessing diabetes drugs

What if a patient has used the same diabetes medication(s) for years? As chronic conditions accrue, and susceptibility to adverse effects increases with age, overall health status may decline, requiring reassessment.[23] To assess whether medication changes are needed, consider:

- Is treatment to a target A1c congruent with outcomes important to this patient?
- How different is the actual A1c from what is medically appropriate for this individual?
- Are adverse effects from diabetes drugs present, or is there increased risk for hypoglycemia (previous hypoglycemia, hypoglycemia unawareness, malnutrition, cognitive impairment, impaired renal function)?
- Is the patient taking a sulfonylurea or insulin?
- Are any medications particularly burdensome or expensive?

Evidence and guidance for deprescribing

When a patient's diabetes medications do not align with health goals, or the harms outweigh benefits, **consider whether deprescribing is appropriate**. Three systematic reviews examined evidence on deprescribing of diabetes medications, primarily in people at risk for hypoglycemia.[24–26] Deprescribing does not appear to increase adverse events, nor risk clinically significant changes in glucose control. A clinical practice guideline and 2-page decision support tool from deprescribing.org can help guide decisions and plans.[27]

Practical considerations for deprescribing

Start with drugs most likely to cause hypoglycemia: sulfonylureas or insulin.[27] Develop individualized deprescribing plans together with patients. **Most people value being involved in planning**.[28] Decide whether to:

- stop a drug;
- gradually taper it to the minimum available dose before stopping;
- reduce the dose; or
- switch to a drug with a more favourable benefit/harm profile.

There is no evidence from RCTs to identify one best approach.[27] The most appropriate choice for any individual may depend on actual drug dose(s), patient context (e.g., baseline glycemic control, risk of harm), expected longevity, and patient goals and preferences. Even when clinicians consider deprescribing as desirable, some patients may view a therapeutic decision to relax glycemic targets as "giving up."[29] Explaining clearly the reasons to de-intensify diabetes treatment can help to engage patients and caregivers in a decision to deprescribe.[30]

Possible discussion points, depending on the patient's health context, include:[27,31]

- "Tight" glycemic control risks dangerous hypoglycemia, without compensatory benefits.
- Aging makes people more susceptible to adverse drug effects (e.g., confusion, falls and fractures caused by hypoglycemia). What worked well before may no longer be optimal.
- **Periodic re-evaluation of diabetes care is always good clinical practice**.

Patients value a clear monitoring and follow-up plan, and clinical support throughout the deprescribing process.[28] They want to know what to expect, and what to do if they experience problems. This includes understanding that they can restart a diabetes medication or switch to another drug, when clinically appropriate (e.g., if symptomatic hyperglycemia occurs).[28]

Blood glucose results can be monitored during follow-up, along with symptoms of hypo- or hyperglycemia. The deprescribing.org guideline for reducing diabetes medications suggests follow up 1 to 2 weeks after changes in therapy, to review capillary or venous blood glucose, and to assess for symptoms.[27] Because it equilibrates slowly with blood glucose, **re-testing A1c is inappropriate until at least 3 months after changes to drug therapy.**

Vignette resolution: *Your 81-year-old patient has an A1c of 6.6%. Reducing potentially dangerous or unnecessary diabetes drugs makes sense. Glyburide increases risk of hypoglycemia, while sitagliptin has not been shown to prevent any complication of diabetes. After discussion, you decide together to relax his A1c goal, stop glyburide first, re-check his A1c after 3 months, and then reconsider sitagliptin.*

Disclaimer

All inferences, opinions and conclusions drawn in this manuscript are those of the authors and do not reflect the opinions or policies of the data stewards.

Data References

The BC Ministry of Health approved access to and use of BC data. The following data source was used: PharmaNet.

Multiple experts and primary care clinicians reviewed the draft of this Therapeutics Letter for factual accuracy, and to ensure it is relevant to clinicians.

The UBC TI is funded by the BC Ministry of Health to provide evidence-based information about drug therapy. We neither formulate nor adjudicate provincial drug policies.

References

1. Statistics Canada. *Diabetes, by age group Table: 13-10-0096-07.* Release date: 2023-11-06. DOI: 10.25318/1310009601-eng
2. Hilmer SN, McLachlan AJ, Le Couteur DG. *Clinical pharmacology in the geriatric patient.* Fundamental & Clinical Pharmacology. 2007; 21(3):217-230. DOI: 10.1111/j.1472-8206.2007.00473.x
3. Lee AK, Juraschek SP, Windham BG, et al. *Severe Hypoglycemia and Risk of Falls in Type 2 Diabetes: The Atherosclerosis Risk in Communities (ARIC) Study.* Diabetes Care. 2020; 43(9):2060-2065. DOI: 10.2337/dc20-0316
4. Lega IC, Campitelli MA, Austin PC, et al. *Potential diabetes overtreatment and risk of adverse events among older adults in Ontario: a population-based study.* Diabetologia. 2021; DOI: 10.1007/s00125-020-05370-7
5. Abdelhafiz AH, Rodríguez-Mañas L, Morley JE, Sinclair AJ. *Hypoglycemia in Older People - A Less Well Recognized Risk Factor for Frailty.* Aging & Disease. 2015; 6(2):156-167. DOI: 10.14336/AD.2014.0330
6. McCormack JP, Holmes DT. *Your results may vary: the imprecision of medical measurements.* BMJ. 2020; 368:m149. DOI: 10.1136/bmj.m149
7. Patel A, MacMahon S, Chalmers J, et al for The ADVANCE Collaborative Group. *Intensive Blood Glucose Control and Vascular Outcomes in Patients with Type 2 Diabetes.* New England Journal of Medicine. 2008; 358(24):2560-2572. DOI: 10.1056/NEJMoa0802987
8. Gerstein HC, Miller ME, Byington RP, et al for The Action to Control Cardiovascular Risk in Diabetes Study Group. *Effects of Intensive Glucose Lowering in Type 2 Diabetes.* New England Journal of Medicine. 2008; 358(24):2545-2559. DOI: 10.1056/NEJMoa0802743
9. Duckworth W, Abraira C, Moritz T, et al. *Glucose Control and Vascular Complications in Veterans with Type 2 Diabetes.* New England Journal of Medicine. 2009; 360(2):129-139. DOI: 10.1056/NEJMoa0808431
10. Diabetes Canada Clinical Practice Guidelines Expert Committee. *Diabetes Canada 2018 Clinical Practice Guidelines for the Prevention and Management of Diabetes in Canada.* Canadian Journal of Diabetes. 2018; 42(Supplement 1):A1-A18, S1-S326 https://www.sciencedirect.com/journal/canadian-journal-of-diabetes/vol/42/suppl/S1
11. American Diabetes Association Professional Practice Committee. *13. Older Adults: Standards of Medical Care in Diabetes—2022.* Diabetes Care. 2022; 45 (Supplement 1):S195-S207. DOI: 10.2337/dc22-S013
12. Choosing Wisely Canada. *Geriatrics: Eight Tests and Treatments to Question.* Published 2022. https://choosingwiselycanada.org/recommendation/geriatrics/
13. Zinman B, Wanner C, Lachin JM, et al. *Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes.* New England Journal of Medicine. 2015; 373(22):2117-2128. DOI: 10.1056/NEJMoa1504720
14. Marso SP, Daniels GH, Brown-Frandsen K, et al. *Liraglutide and Cardiovascular Outcomes in Type 2 Diabetes.* New England Journal of Medicine. 2016; 375(4):311-322. DOI: 10.1056/NEJMoa1603827
15. Therapeutics Initiative. *Pill splitting: Making the most of meds in a time of need.* Therapeutics Letter. Special Edition: March 2020. https://ti.ubc.ca/special-edition
16. Packer M, Anker SD, Butler J, et al. *Cardiovascular and Renal Outcomes with Empagliflozin in Heart Failure.* New England Journal of Medicine. 2020; 383(15):1413-1424. DOI: 10.1056/NEJMoa2022190
17. McMurray JJV, Solomon SD, Inzucchi SE, et al. *Dapagliflozin in Patients with Heart Failure and Reduced Ejection Fraction.* New England Journal of Medicine. 2019; 381(21):1995-2008. DOI: 10.1056/NEJMoa1911303
18. Husain M, Birkenfeld AL, Donsmark M, et al. *Oral Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes.* New England Journal of Medicine. 2019; 381(9):841-851. DOI: 10.1056/NEJMoa1901118
19. Karagiannis T, Tsapas A, Athanasiadou E, et al. *GLP-1 receptor agonists and SGLT2 inhibitors for older people with type 2 diabetes: A systematic review and meta-analysis.* Diabetes Research & Clinical Practice. 2021; 174:108737. DOI: 10.1016/j.diabres.2021.108737
20. Monteiro P, Bergenstal RM, Toural E, et al. *Efficacy and safety of empagliflozin in older patients in the EMPA-REG OUTCOME® trial.* Age & Ageing. 2019; 48(6):859-866. DOI: 10.1093/ageing/afz096
21. Cahn A, Mosenzon O, Wiviott SD, et al. *Efficacy and Safety of Dapagliflozin in the Elderly: Analysis From the DECLARE–TIMI 58 Study.* Diabetes Care. 2020; 43(2):468-475. DOI: 10.2337/dc19-1476
22. Evans M, Morgan AR, Davies S, Beba H, Strain WD. *The role of sodium-glucose co-transporter-2 inhibitors in frail older adults with or without type 2 diabetes mellitus.* Age & Ageing. 2022; 51(10). DOI: 10.1093/ageing/afac201
23. Raghavan S, Matlock D. *Diabetes Mellitus Treatment Deintensification: When Well-Controlled Diabetes Mellitus Becomes Overcontrolled.* Circulation Cardiovascular Quality & Outcomes. 2017; 10(4). DOI: 10.1161/CIRCOUTCOMES.117.003706
24. Deng Z, Thompson W, Korenvain C, et al. *Benefits and Harms of Deprescribing Antihyperglycemics for Adults With Type 2 Diabetes: A Systematic Review.* Canadian Journal of Diabetes. 2022; 46(5):473-479. DOI: 10.1016/j.jcjd.2022.01.009
25. Seidu S, Kunutsor SK, Topsever P, et al. *Deintensification in older patients with type 2 diabetes: A systematic review of approaches, rates and outcomes.* Diabetes Obesity & Metabolism. 2019; 21(7):1668-1679. DOI: 10.1111/dom.13724
26. Oktora MP, Kerr KP, Hak E, Denig P. *Rates, determinants and success of implementing deprescribing in people with type 2 diabetes: A scoping review.* Diabetic Medicine. 2021; 38(2):e14408. DOI: 10.1111/dme.14408
27. Farrell B, Black C, Thompson W, et al. *Deprescribing antihyperglycemic agents in older persons: Evidence-based clinical practice guideline.* Canadian Family Physician. 2017; 63(11):832-843. https://www.cfp.ca/content/63/11/832
28. Reeve E, To J, Hendrix I, et al. *Patient barriers to and enablers of deprescribing: A systematic review.* Drugs & Aging. 2013; 30(10):793-807. DOI: 10.1007/s40266-013-0106-8
29. Pilla SJ, Jalalzai R, Tang O, et al. *A National Survey of Physicians' Views on the Importance and Implementation of Deintensifying Diabetes Medications.* Journal of General Internal Medicine. 2023; DOI: 10.1007/s11606-023-08506-8
30. Farrell B, Mangin D. *Deprescribing Is an Essential Part of Good Prescribing.* American Family Physician. 2019; 99(1):7-9. http://www.ncbi.nlm.nih.gov/pubmed/30600973
31. Green AR, Aschmann H, Boyd CM, Schoenborn N. *Assessment of Patient-Preferred Language to Achieve Goal-Aligned Deprescribing in Older Adults.* JAMA Network Open. 2021; 4(4):e212633. DOI: 10.1001/jamanetworkopen.2021.2633

Multiple experts and primary care clinicians reviewed the draft of this Therapeutics Letter for factual accuracy, and to ensure it is relevant to clinicians.

The UBC TI is funded by the BC Ministry of Health to provide evidence-based information about drug therapy. We neither formulate nor adjudicate provincial drug policies.