# Diabetes in the frail elderly

## *Individualization of glycemic management*

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Older adults with diabetes who are otherwise healthy and who have considerable life expectancy (more than 10 years) should generally receive diabetes care with goals and targets similar to those for younger adults. However, it is important to individualize treatment goals for those frail elderly who have comorbidities, limited function, limited life expectancy, impaired cognition, or a high risk of adverse events from treatment.[1,2] In such individuals, treatment goals might need to be relaxed. When individualizing therapy, it is important to consider overall benefits and harms, and to avoid acute complications of hypoglycemia and hyperglycemia.

## Case 1

Mr B.H. is an 84-year-old retired farmer, new to your family practice and in the clinic for a medication review. He was recently assessed following a minor motor vehicle accident and diagnosed with vascular dementia (Montreal Cognitive Assessment score of 15 out of 30). Other medical problems include type 2 diabetes for more than 15 years, hypertension, coronary artery disease (coronary artery bypass graft 12 years ago), stable chronic heart failure, abdominal aortic aneurysm, chronic kidney disease (estimated glomerular filtration rate of 34 mL/min), benign prostatic hypertrophy, and chronic back pain. Medications include 5 mg of ramipril daily, 5 mg of amlodipine daily, 81 mg of acetylsalicylic acid daily, 20 mg of furosemide daily, 500 mg of metformin twice daily, 5 mg of glyburide twice daily, 10 mg of atorvastatin daily, and 500 mg of acetaminophen as needed. Mr B.H. lives with his elderly wife in their own home and is able to perform all basic activities of daily living. His appetite is adequate, but his wife and son note that in the past 6 months he forgets to eat regularly if not prompted. Laboratory results confirm good glycemic control with hemoglobin $A_{1c}$ ($HbA_{1c}$) measurements of 7.2% and 7.4% in the past 8 months.

## Bringing evidence to practice

- Mr B.H. would meet the criteria for "frail elderly." Frail describes patients who have an accumulation of multiple chronic illnesses with associated vulnerabilities such as dementia, functional decline, and geriatric syndrome including falls, impaired mobility, and polypharmacy.[3]
- Randomized controlled trials evaluating the benefits and harms of tight glycemic control have not included healthy or frail elderly patients.
- Randomized controlled trials evaluating the effects of tight glycemic control in people with type 2 diabetes mellitus (T2DM) have identified modest benefits as well as some harms (**Table 1**).[4-9]
- Benefits seen with intensive glycemic control have been mostly microvascular and require 5 to 10 years to be realized. Macrovascular benefits have been seen with metformin among obese patients with T2DM. In the UKPDS-33 (United Kingdom Prospective Diabetes Study), macrovascular benefit was not seen in the initial 10-year trial, but was seen in the intensive-control group in a 10-year follow-up analysis of the original trial (ie, 20 years after trial initiation).[4,6] Benefits have always been offset by the increased risk of severe hypoglycemia. In the ACCORD (Action to Control Cardiovascular Risk in Diabetes) trial, intensive treatment resulted in an increase in all-cause mortality.[9] Data from observational studies provide additional insight for elderly populations. The Cohort Study in Aging found that mortality risk formed a U-shaped curve that increased for $HbA_{1c}$ levels below 6.0% and above 9.0%. Risk of any complication increased with $HbA_{1c}$ levels above 8.0%.[10] Results were consistent across age groups, including for those aged 80 and older. A similar U-shaped curve has also been demonstrated for mortality risk in T2DM and chronic kidney disease.[11]
- The limited life expectancy of the frail elderly, together with the increased risk of hypoglycemia, warrants a less-aggressive approach to glucose management in this population.[1,12]
- Elderly people with diabetes, like Mr B.H., are at high risk of developing hypoglycemia (blood glucose [BG] below 4 mmol/L). Impaired liver and renal function due to aging and disease results in decreased gluconeogenesis. This can be compounded further by reduced renal clearance of hypoglycemic drugs such as sulfonylureas (eg, glyburide, gliclazide) and insulin. Autonomic neuropathy and decreased ß-receptor response might result in the absence of typical hypoglycemic symptoms such as sweating, tachycardia, and tremor. In the frail elderly this hypoglycemia unawareness is compounded by mental and physical inability to respond to or treat low BG levels.
- Hypoglycemia can lead to poor balance and increase the risk of falls. Severe hypoglycemia can cause seizures and death. Hypoglycemia in the elderly can be severe and prolonged, precipitating cardiovascular events.[3]

**Table 1. Trials of intensive versus less-intensive BG lowering:** *No RCTs studying the effects of intensive glycemic control have included frail elderly patients.*

| RCT TRIAL | MEAN AGE, Y | TRIAL DURATION, Y | $HBA_{1c}$ ATTAINED, % | BENEFITS OR HARMS IN MORE-INTENSIVE GLUCOSE-LOWERING ARM (LOWER $HBA_{1c}$) VS LESS-INTENSIVE TREATMENT ARM |
|---|---|---|---|---|
| UKPDS-33[4] | 54 | 10 | 7.0 vs 7.9 | • No difference in major clinical outcomes* at 10 y†<br>• Benefits on surrogate outcomes (less microvascular disease after ≥ 6 y)<br>• Increase in serious hypoglycemia<br>• A follow-up study after 20 y saw decreased MI and all-cause death[6] |
| ADVANCE[7] | 66 | 5 | 6.5 vs 7.3 | • No difference in major clinical outcomes* at 5 y<br>• Decrease in microvascular end points (NNT = 67 at 5 y), mostly nephropathy surrogates<br>• Increase in serious hypoglycemia (NNH = 83 at 5 y) |
| VADT[8] (most participants had a history of CV problems) | 60 | 5.6 | 6.9 vs 8.4 | • No difference in major clinical outcomes* at 5.6 y<br>• Increased rate of serious adverse events (NNH = 15 at 5.6 y)<br>• Increase in serious hypoglycemia (NNH = 83 at 5.6 y) |
| ACCORD[9] (35% of participants had a history of CV problems) | 62 | 3.5 | 6.4 vs 7.5 | • More death with intensive treatment (NNH = 95 at 3.5 y) (any macrovascular benefit outweighed by increase in death)<br>• Increase in serious hypoglycemia (NNH = 9 at 3.5 y) |

ACCORD—Action to Control Cardiovascular Risk in Diabetes, ADVANCE—Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation, BG—blood glucose, CV–cardiovascular, $HbA_{1c}$—glycated hemoglobin $A_{1c}$, MI—myocardial infarction, NNT—number needed to treat for 1 additional person to benefit, NNH—number needed to treat for 1 additional person to be harmed, RCT—randomized controlled trial, T2DM—type 2 diabetes mellitus, UKPDS—United Kingdom Prospective Diabetes Study, VADT—Veterans Affairs Diabetes Trial.
*Major clinical outcomes included CV death, MI, stroke, end-stage renal disease, and blindness.
†The UKPDS-34[5] found a decrease in death (NNT = 14 at 10.7 y) and decrease in stroke (NNT = 48 at 10 y) when metformin specifically was used compared with standard treatment in obese patients with T2DM ($HbA_{1c}$ achieved was 7.4% vs 8.0%).

- Sustained hyperglycemia is also problematic, leading to polyuria and nocturia, which can result in dehydration, falls, and associated complications.
- Individualization of treatment is essential to provide reasonable glycemic control while avoiding hypoglycemia. In the frail elderly this will result in less-stringent glycemic targets.[13,14] For example, $HbA_{1c}$ levels below 8.0%, or even below 8.5%, and a random BG measurement of 7 to 14 mmol/L might be reasonable. Guidelines vary with regard to $HbA_{1c}$ recommendations for the elderly; however, all acknowledge the need for individualized and less-stringent treatment goals. More information is available in the *RxFiles Q&A: Glycemic Targets for the Frail Elderly*,[15] available from **CFPlus.***
- Metformin dosing should be adjusted for renal dysfunction when creatinine clearance is 60 mL/min or lower. Canadian and American diabetes guideline groups recommend that metformin be avoided in patients with creatinine clearance below 30 mL/min owing to the risk of lactic acidosis.[1,2] However, metformin-associated lactic acidosis is rare, estimated to be 1 to 9 cases per 100 000 patient years.[16] Some have suggested that the risk is coincidental, rather than causal. Because other antihyperglycemic drugs come with their own risks, and often less evidence for benefit, there is rationale for cautious use of metformin in patients with a greater degree of renal dysfunction.[16]
- Glyburide, with its long duration of action, is associated with a greater risk of hypoglycemia than regular-release gliclazide. However, whether this advantage is preserved with the once-daily, modified-release (MR) formulation is unknown. Severe hypoglycemia with gliclazide MR in combination therapies was a concern in the ADVANCE (Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation) trial (the number needed to harm was 83 at 5 years).[7] Current Canadian guidelines recommend gliclazide as the sulfonylurea of choice in the elderly.[1]

*The *RxFiles Q&A: Glycemic Targets for the Frail Elderly* is available at **www.cfp.ca.** Go to the full text of the article online and click on **CFPlus** in the menu at the top right-hand side of the page.

## Case 1 resolution

Metformin and glyburide are discontinued; Mr B.H. is started on 30 mg of gliclazide MR once daily. All other drug therapy remains unchanged. Care planning and the risks of overly tight diabetic control are discussed with the patient and his family. Home care nursing support is initiated for medication management and intermittent random BG testing. At a follow-up clinic

visit in 3 months, nursing reports document random BG values of 4.6 to 12.8 mmol/L; Mr B.H.'s $HbA_{1c}$ level is 7.9%. There have been no episodes of severe hypoglycemia, and Mr B.H. reports no concerns.

## Case 2

Mrs D.G. is a 79-year-old woman residing in a long-term care home after being hospitalized for a hip fracture that was treated surgically with arthroplasty. It has been 3 weeks since her surgery, and she is recovering well. Her family physician is contacted because the nurse is concerned about Mrs D.G.'s blood sugar levels, which have ranged from 3.3 mmol/L before lunch and supper to 10.6 mmol/L after some meals. Twice in the past week Mrs D.G. has required fruit juice to treat hypoglycemia. She has advanced rheumatoid arthritis with multiple joint deformities and decreased mobility. Other medical conditions include type 2 diabetes of more than 20 years' duration, obesity (she weighs 80 kg and her body mass index is 31.2 kg/m$^2$), hypertension, stable angina, chronic kidney disease (estimated glomerular filtration rate of 48 mL/min), osteoporosis, diabetic peripheral neuropathy, and early retinopathy. Mrs D.G.'s current diabetes therapy is 16 units of neutral protamine Hagedorn (NPH) insulin twice daily and 5 units of insulin lispro (Humalog) before meals (total daily insulin dose is 47 units per day). Before hospitalization, Mrs D.G. was taking 500 mg of metformin daily, 120 mg of gliclazide MR daily, and 20 units of NPH insulin at bedtime. Her diabetes control was "suboptimal" before the hip fracture ($HbA_{1c}$ measurement taken 4 months ago was 8.2%), and she attributed this to the "excellent meals" provided in the assisted-living complex where she used to reside.

## Bringing evidence to practice

- It is important to individualize BG targets for Mrs D.G. given her limited life expectancy (less than 10 years), comorbidities, and risk of hypoglycemia. Hypoglycemia presents an acute danger for Mrs D.G., and any benefit of tight glycemic control would take years to achieve.
- For the acute management of hypoglycemia, glucose or dextrose tablets (15 g) or sugar (3 tsp) dissolved in water are the preferred choice for treatment because these are absorbed more quickly than orange juice or glucose gels.[1] Glucose and dextrose tablets might be difficult to chew or swallow.[3] Glucose gels are generally not recommended because they must be swallowed to be effective and are slowly absorbed.
- Following a hypoglycemic event, factors that might have contributed to the hypoglycemia should be assessed (inadequate carbohydrate intake at meals, increased physical activity, too much oral antihyperglycemic agent or insulin), and treatment should be adjusted accordingly.
- Mrs D.G. is likely experiencing excessive insulin effect before lunch and supper from the morning NPH dose. With twice-daily dosing of NPH insulin, rapid or short-acting insulin might not be required before lunch. A BG of 10.6 mmol/L following meals (postprandial) is acceptable for Mrs D.G. To avoid hypoglycemia, it might be safer to decrease her insulin and aim for random BG levels in the range of 7 to 14 mmol/L.
- While titrating the insulin dose to effect, more-frequent BG monitoring will be useful. Less-frequent BG monitoring will be suitable once glycemic control has stabilized.[1,17,18]
- Once the appropriate total daily insulin dose is determined, consider changing to twice-daily premixed insulin for patients like Mrs D.G. While premixed insulins are often not first-line choices for these sorts of patients, they require less nursing time and fewer needle pokes, and are likely to be effective owing to the fixed mealtimes and predictable routine in long-term care homes. Premixed human insulin provides similar control and is less expensive than premixed analogue insulin.[19]
- Metformin has evidence for benefit including reduced mortality. It can be used with insulin to overcome insulin resistance and reduce the insulin dose required by about 20% to 25%.[20]
- Metformin dosing should be adjusted for renal dysfunction. Lower doses can be used for creatinine clearance below 60 mL/min,[1,21] as discussed in Case 1. Additional precautions might be necessary for patients with reduced renal function; specifically, the metformin dose should be held if patients encounter acute episodes of illness, dehydration, acute heart failure, contrast media, etc.[16]
- Sulfonylureas and incretins are unlikely to have much effect in some elderly patients with T2DM in view of the duration of their diabetes and reduced pancreatic β-cell insulin production. Glitazones such as pioglitazone can be used in patients with reduced renal dysfunction; however, they are associated with increased edema, heart failure, weight gain, and fractures.

## Case 2 resolution

Metformin is resumed at 250 mg twice daily. The insulin dose is initially reduced to 8 units of NPH in the morning and at bedtime (0.2 units/kg/day), and 3 units of Humalog before breakfast and supper. Regular BG monitoring is implemented with further adjustment of insulin doses as needed, fixing lows first. With the reintroduction of metformin and a change in diet, Mrs D.G. requires less insulin than when in hospital. Her blood sugar levels are in the range of 8 to 12 mmol/L, and she has had no further

episodes of hypoglycemia. The option of converting to a 30/70 premix (eg, Humulin 30/70, 10 units twice daily) is being considered.

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