

Glycaemic control in the elderly: What should we be aiming for?

Andrew McGovern

Diabetes is very common in older people, who are at high risk of diabetes-related complications. Overtreatment in the elderly is a particular concern, with increased risks of adverse medication effects and hypoglycaemia. Overambitious glycaemic targets may also increase mortality risk. However, undertreatment may increase the risk of death, cardiovascular disease, renal and eye disease, and even infection. Given these complexities, it is unclear what level of glycaemic control clinicians should aim for in the older population. This article discusses the current evidence for glycaemic targets in the elderly, with regard to clinical trials and observational studies. In light of this evidence, the current guidelines are discussed. The risks and benefits of tight glycaemic control are considered in view of the risks of hypoglycaemia, micro- and macrovascular disease, and infection. All these factors should be considered when devising an individualised target for the older person with diabetes.

Diabetes is very common in older people, and particularly among people in long-term care, among whom it can affect up to 25% (Fagot-Campagna et al, 2005). Even in the oldest age groups, the burden of diabetes-related disease is high and substantially reduces life expectancy. Evidence from high-quality diabetes studies and randomised controlled trials in the elderly is very limited, and the optimum level of glycaemic control in older people is unknown. Overtreatment is associated with the dangers of hypoglycaemia and medication side effects, including risks from polypharmacy. Undertreatment, however, may increase the risk of renal, eye and cardiovascular disease, and is associated with a higher incidence of infections. Hyperglycaemia also causes diuresis, leading to dehydration, visual impairment and confusion. This article discusses these risks, benefits and key considerations for glycaemic control in older adults.

Evidence for a glycaemic target

The evidence for specific glycaemic targets in the elderly are extremely limited. Despite the high burden of diabetes in this population, the majority of trials conducted to date exclude older people and those with multiple comorbidities. The first large randomised controlled trial to demonstrate a reduction in microvascular disease with tight glycaemic control excluded people aged 65 years and over (UK Prospective Diabetes Study Group, 1998). Subsequently, three trials were undertaken to explore the impact of tight glycaemic control on cardiovascular events in middle-aged and older people: ACCORD (Action to Control Cardiovascular Risk in Diabetes), ADVANCE (Action in Diabetes and Vascular Disease: Preterax and Diamicon MR Controlled Evaluation) and the VADT (Veterans Affairs Diabetes Trial). These three trials randomised people to HbA_{1c} targets of <42 mmol/mol (6.0%) or <48 mmol/mol (6.5%).

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Article points

1. There is little evidence on which to base glycaemic targets in older people with diabetes; however, overtreatment is a serious concern.
2. Tight glycaemic control increases the risk of hypoglycaemia and falls, and is unlikely to have microvascular and macrovascular benefits unless over the longer term.
3. Control of other risk factors, such as blood pressure, cholesterol, smoking and infection, along with regular screening for retinal and renal disease, should be the focus of care.
4. Glycaemic targets should be individualised based on multiple factors, including frailty, comorbidities and life expectancy. Diabetes medications should be very carefully selected and regularly reviewed.

Key words

- Frailty
- Glycaemic control
- Older people

Authors

Andrew McGovern is Clinical Researcher at the University of Surrey.

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1. Prospective and observational studies show little benefit from achieving tight glycaemic control in older people, and excessively tight control is even associated with increased mortality.
2. Recent guidelines emphasise the need for an individualised approach, with NICE recommending relaxation of blood glucose targets in older, frail people as well as those in end-of-life care and those for whom hypoglycaemia poses a particularly high risk.
3. The ADA and EASD recommend relaxing glycaemic targets to 58–64 mmol/mol (7.5–8.0%) in older people, and transitioning to even higher targets as age and vulnerability increase.

The ACCORD trial was terminated early owing to an excess risk of death in the intensive control group (Gerstein et al, 2008). This was predominantly in participants aged under 65 years. Whilst the increased risk was not demonstrated in the over-65s, there were more medication side effects and hypoglycaemic episodes in this older group (Miller et al, 2010). The ADVANCE trial and VADT both found no overall differences in the rates of cardiovascular events or death (Patel et al, 2008; Duckworth et al, 2009). These trials, therefore, show no benefit, and an increased risk of side effects, from very tight control in older people.

However, observational data suggest that even aiming for the more modest target of <48 mmol/mol (6.5%), used as the less intensive treatment group in these studies, is harmful. A large observational study using the UK General Practice Research Database of 47 970 people with type 2 diabetes aged ≥50 years found a U-shaped relationship between HbA_{1c} and all-cause mortality: both high and low HbA_{1c} were associated with increased mortality (Currie et al, 2010). The lowest risk of death was in those with an HbA_{1c} around 58 mmol/mol (7.5%). Another observational study of 71 092 people with type 2 diabetes aged ≥60 years, in California, demonstrated a similar U-shaped association between HbA_{1c} and mortality (Huang et al, 2011). This study also investigated the relationship between HbA_{1c} and diabetes complications in the older population. The authors found that increasing HbA_{1c} was associated with an increased risk of microvascular and cardiovascular events, with the lowest risk in those with an HbA_{1c} <42 mmol/mol (6.0%).

The limitations of these observational studies should be highlighted. It is possible that some additional factor other than glucose control was responsible for the apparent relationship between low HbA_{1c} and mortality. Lower HbA_{1c} levels may be associated with poor nutritional status and other factors that are also risk factors for mortality. Additionally, in most cases, current HbA_{1c} is a reasonable indicator of glucose control over a number of years, and the observed associations may be a result of long-term glycaemic trends. If this is the case, the excess risk will not be amenable to intervention with glucose-lowering medications.

Current recommendations

A wide range of HbA_{1c} targets have been recommended for the elderly: 53–64 mmol/mol (7.0–8.0%; Sinclair, 2011), 64–69 mmol/mol (8.0–8.5%; Kirkman et al, 2012), and even up to 75 mmol/mol (9.0%; Mallery et al, 2013). However, as discussed earlier, the evidence base for these recommendations is very limited.

In recent years, guidelines have shifted towards a more individualised approach to setting glycaemic targets. Recommendations in both the NICE (2015) guideline and the American Diabetes Association/European Association for the Study of Diabetes (ADA/EASD) joint position statement on hyperglycaemia management (Inzucchi et al, 2012) include specific recommendations for older adults with type 2 diabetes.

The ADA/EASD joint position statement recommends that:

“...glycemic targets for elderly with long-standing or more complicated disease should be less ambitious than for the younger, healthier individuals. If lower targets cannot be achieved with simple interventions, an HbA_{1c} of <7.5–8.0% may be acceptable, transitioning upward as age increases and capacity for self-care, cognitive, psychological and economic status, and support systems decline.”

NICE do not provide any specific targets in their recommendations for the elderly:

“Consider relaxing the target HbA_{1c} level on a case-by-case basis, with particular consideration for people who are older or frail, for adults with type 2 diabetes:

- *who are unlikely to achieve longer-term risk-reduction benefits, for example, people with a reduced life expectancy*
- *for whom tight blood glucose control poses a high risk of the consequences of hypoglycaemia, for example, people who are at risk of falling*

[...]

- *for whom intensive management would not be appropriate, for example, people with significant comorbidities.”*

Hypoglycaemia

Hypoglycaemic episodes are extremely common

in older people with diabetes; in one study of people aged ≥ 80 years with type 2 diabetes who were admitted to hospital, severe hypoglycaemia (requiring intravenous glucose) occurred in around 25% (Greco and Angileri, 2004). In older people, hypoglycaemic symptoms also tend to be more related to the impact of low glucose levels on neurons (e.g. confusion, dizziness) rather than the release of adrenaline and related hormones that occurs in younger people (e.g. sweating, tremor, palpitations). This may limit the ability of the older person to self-treat or to communicate the need for treatment to others. Hypoglycaemia can also lead to falls and loss of confidence in the elderly. Furthermore, it may worsen cognitive impairment, particularly if recurrent. The risks of hypoglycaemia are of particular concern in those who live alone, in whom a single episode can be fatal.

For these reasons, hypoglycaemia avoidance is critical in the elderly. Hypoglycaemia is also more common in those with polypharmacy, renal and liver impairment, and excessive alcohol intake. Careful questioning about hypoglycaemic events and assessment of risk factors for hypoglycaemia are an important part of the diabetes assessment in the elderly. In those with the highest risk, medications that have the highest predisposition for hypoglycaemia should be avoided and glycaemic targets relaxed.

Microvascular disease

The elderly are at higher risk of eye disease, renal impairment and neuropathy. Age over 80 years is also the strongest population-level predictor of falls and fractures (Rafiq et al, 2014), and poor vision and neuropathy both compound this risk. Early identification and treatment of these microvascular complications are, therefore, particularly important in this population.

As well as diabetic retinopathy, older people are at high risk of glaucoma, cataracts and age-related macular degeneration. This means the benefit of an annual complete eye examination is probably greater in this group than in younger people with diabetes, as these comorbid conditions can also be recognised and treated early. Poor vision can also lead to difficulties with medication use, particularly with injectable therapies, and

difficulty reading blood glucose meters. Vigilance is needed to identify these factors.

Similarly, annual screening for renal impairment is of high importance in the elderly, and regular review of all diabetes medications in those with renal impairment is mandatory. Preventing progression of renal impairment with angiotensin-converting enzyme inhibitors or angiotensin receptor blockers is likely to be of benefit in those with a life expectancy of more than a few years.

The prevalence of diabetic neuropathy is over 50% in the elderly (Young et al, 1993). Foot care is key to preventing the development of ulcers and subsequent infections and amputations in any person with diabetes. This should not be neglected in the elderly population.

Functional decline may limit older people's ability to attend for screening. Every clinical encounter should be considered as an opportunity to screen for microvascular disease and its impact. As already discussed, there is little evidence for the benefit of tight glycaemic control in the elderly and there are no agreed glycaemic targets for those with established microvascular disease. Ensuring regular screening and careful consideration and management of complications when they arise is probably more important than focusing on tight glycaemic control.

Cardiovascular disease

Cardiovascular disease is a major cause of death and morbidity in the elderly and, therefore, it is important to consider. However, the cardiovascular benefits from glucose lowering are small and may only occur up to a decade after improvements in glucose control (Holman et al, 2008). Thus, it is unlikely that clinically relevant cardiovascular risk reduction can be achieved through glycaemic control in the elderly. Other cardiovascular risk factors, such as blood pressure, cholesterol and smoking, should be the focus of care, in preference over glycaemic control, in this high-risk group.

Infection risk

The impact of glycaemic control on infection risk is a somewhat neglected topic in both research and clinical practice. A slowly growing body of evidence from randomised controlled trials and observational studies suggests that hyperglycaemia

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1. Hypoglycaemia is of particular concern in older people. It is more common in those with polypharmacy, renal and liver impairment, and excessive alcohol intake.
2. Careful assessment of hypoglycaemia risk is important, and antidiabetes therapy may need to be changed or reduced in those at high risk.
3. Annual eye examinations can be particularly beneficial in older people, and foot care is crucial to prevent ulceration, especially given the high rate of neuropathy in this population.
4. Annual screening for renal disease is also important, along with review of medications that may be affected by renal impairment.
5. Tight glycaemic control is unlikely to improve cardiovascular risk unless over the long term; therefore, other risk factors, such as blood pressure, cholesterol and smoking, should be the focus of care.

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1. Although relaxed glycaemic control reduces the risk of hypoglycaemia and falls, it is also associated with an increased risk of infection. Therefore, caution and regular follow-up is needed when relaxing glucose targets in those at highest risk of infection.
2. Clinicians should follow the “start low and go slow” maxim when prescribing diabetes medication for older people. Regular medication reviews are essential.

is associated with increased risk of a wide range of infections, including meningitis, pneumonia, urinary tract infections, cellulitis, infected diabetic foot, bone and joint infections, and fungal infections (Pearson-Stuttard et al, 2016). People with diabetes are at increased risk of death from pneumonia and other infectious diseases (Seshasai et al, 2011), and the elderly are especially vulnerable.

A recent retrospective, observational study of 19 456 people with diabetes aged ≥65 years (mean age, 75.3 years) assessed the association between glycaemic control and the risk of three clinically important infections: pneumonia, urinary tract infections and skin infections, including cellulitis (McGovern et al, 2016). The incidence of these infections was assessed using GP records over a one-year period after stratifying for the most recent HbA_{1c} reading. The risk of all three infection types was found to be increased in those with an HbA_{1c} >69 mmol/mol (8.5%). No significant increase in risk was identified below this HbA_{1c} threshold, although there was a trend towards higher infection rates (Figure 1). Of particular concern

was the increased risk of pneumonia in those with the poorest control: approximately double that of people with good glycaemic control.

More research is needed before these results are translated into clinical recommendations, but the findings do suggest that caution should be exercised when considering relaxing glycaemic targets in those most vulnerable to infection.

Use of specific agents

Diabetes medication needs to be carefully considered in the elderly, in view of the risks of hypoglycaemia, falls, fractures, renal impairment, infections and heart failure. The major considerations for the different drug classes in this patient group are outlined in Table 1. Drug metabolism in the elderly is often slower; therefore, as with all medications in the elderly, the axiom of “start low and go slow” should always be borne in mind (Kezerle et al, 2014). Regular medication reviews to minimise polypharmacy and ensure there are no difficulties in taking medications, as well as reviews of adverse effects, are mandatory in this group.

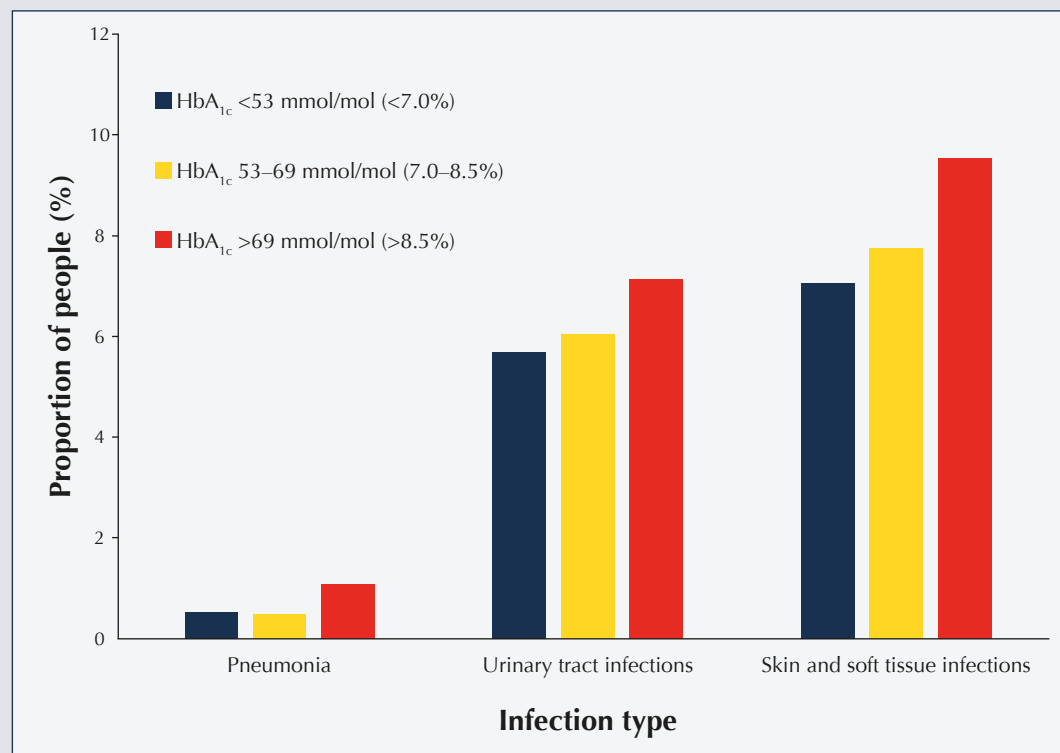


Figure 1. Infection rates in older adults stratified by glycaemic control. The lowest infection rates occur in those with the best glycaemic control (blue) and the highest rates in those with the worst control (red). Data from McGovern et al (2016).

Conclusions

The benefits of tight glycaemic control on microvascular and macrovascular disease in the elderly are likely to be small. The risks associated with overtreatment also increase with age and frailty. However, hyperglycaemia probably increases the risk of infections in this very vulnerable group. Glycaemic targets should, therefore, be individualised based on multiple factors, including frailty, comorbidities and life expectancy. Diabetes medications should be very carefully selected and regularly reviewed in the older adult with diabetes, and vigilance should be maintained in screening for and managing complications. ■

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Table 1. Major antidiabetes medication considerations in older people.

Medication	Major considerations in older people
Metformin	Use with caution in renal impairment. Avoid if eGFR is <30 mL/min/1.73 m ² .
Sulfonylureas (e.g. gliclazide, glipizide)	High risk of hypoglycaemia. In the elderly, short-acting agents (e.g. glipizide) should be preferred over long-acting agents (e.g. chlorpropamide and glyburide)
Thiazolidinediones (e.g. pioglitazone)	Can worsen heart failure and decrease bone density, resulting in increased fracture risk. Can be used in renal impairment and does not increase risk of hypoglycaemia
Alpha-glucosidase inhibitors (e.g. acarbose)	Not as effective as other agents and commonly cause flatulence and diarrhoea. Good safety profile and no hypoglycaemia risk
DPP-4 inhibitors (e.g. alogliptin, linagliptin, saxagliptin, sitagliptin, vildagliptin)	Generally well tolerated, although not as effective as other agents
SGLT2 inhibitors (e.g. canagliflozin, dapagliflozin, empagliflozin)	Low incidence of hypoglycaemia. Increased risk of genital candidiasis and urinary tract infections may limit use in the elderly
GLP-1 receptor agonists (e.g. exenatide, liraglutide, lixisenatide)	Weight loss effects may be beneficial in some elderly patients and detrimental in others. No hypoglycaemia risk. Nausea and vomiting may limit use in some elderly people
Insulin	Use may be limited by risk of hypoglycaemia and difficulty of administration. Dose reduction may be required in renal impairment to minimise hypoglycaemia

DPP-4=dipeptidyl peptidase-4; eGFR=estimated glomerular filtration rate; GLP-1=glucagon-like peptide-1, SGLT2=sodium–glucose cotransporter 2.

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