

EDITORIAL

From burden to benefits: new promises of glucose-lowering treatments in older adults

Keywords: type 2 diabetes; older adults; evidence; glucose-lowering treatment; effectiveness; safety

Key Points

- To accompany: *Evaluation of glucose-lowering medications in older people: a comprehensive systematic review and network meta-analysis of randomised controlled trials* [13]
- Type 2 diabetes is a burden for patients and society, posing complex challenges for physicians
- GLP-1RAs and SGLT2 inhibitors, show benefits on cardiovascular and renal risks, with improved safety profiles suited to older adults
- As age advances, fewer treatments are often needed, supporting simplified regimens that minimise risks

Type 2 diabetes mellitus (T2D) is an increasing concern among older adults, posing considerable epidemiological and clinical challenges. The increase in the prevalence of T2D, which affects more than 20% of adults aged 65 and over in Europe, combined with global population ageing, is expected to put significant pressure on healthcare systems [1]. However, this chronic condition represents mainly a significant burden for patients. T2D mechanisms closely interact with the ageing process - ageing favours both the causes of glycaemic control dysregulation and the consequences and complications of T2D [2]. Consequently, T2D is associated with multiple comorbidities, as well as several age-related conditions, leading to increased frailty, reduced quality of life, and a shorter healthy life expectancy [2–7].

In addition to its burden on individuals and society, T2D also presents considerable treatment challenges. While glucose-lowering treatments (GLT) are often necessary for glycaemic control, they carry risks of adverse effects, such as hypoglycaemia, and serious clinical events, including mortality and hospitalisation. These adverse events are more commonly associated with older hypoglycaemic drugs (e.g. insulin, sulphonylureas (SU), and glinides), and particularly with intensive treatments, as older adults exhibit substantial health heterogeneity [8–11]. This is a compounded misfortune for older patients, who face risks from both the disease and its treatment. These challenges are further exacerbated by the marked gap of knowledge, as main pharmaceutical

trials and studies lacked to include representative older participants (i.e. including frail older patients - who are the most vulnerable to adverse effects of treatments), limiting the quality of evidence available for clinical guidelines [12].

The study by Pan et al. [13], which is the focus of this editorial, provides an appropriate window into this critical knowledge gap. Their high-quality systematic review and network meta-analysis includes 22 trials with 41 654 older participants, comparing the efficacy and safety of different glucose-lowering drug, focusing on cardiovascular, renal, and hypoglycaemic outcomes. The authors find that newer drugs, such as GLP-1 receptor agonists (GLP-1RAs) and sodium-glucose cotransporter-2 inhibitors (SGLT2i), offer significant benefits, particularly in reducing adverse cardiovascular and renal events, with GLP-1RAs, SGLT2i, metformin, SU and dipeptidyl-peptidase 4 inhibitors effectively restoring glycaemic control, while SU are associated with a higher risk of (severe) hypoglycaemia.

For clinicians and researchers, these results and conclusions raise promising insights. Firstly, it is reassuring to observe the relative safety of newer treatments compared with other drug classes - though weight loss requires careful consideration for many older patients [14]. Further, it is noteworthy that only SU are associated with a significant risk of hypoglycaemia and severe hypoglycaemia - even though insulin was not among the drug classes studied. Secondly, it reminds us that the new treatments (GLP1-RAs and SGLT2i) appear particularly well-suited for managing the renal and cardiovascular comorbidities commonly associated with T2D. This study underscores that these treatments offer benefits beyond glycaemic management, potentially slowing or preventing comorbidities and thereby reducing the overall disease burden. Thirdly, the observation that the number of treatments needed often decreases as age advances is especially relevant in the context of clinical practice. Simplifying therapeutic regimens, particularly for older adults with limited life expectancy or multiple comorbidities, aligns with efforts to minimise treatment burden while maintaining efficacy [15]. This reduction supports a shift towards optimising quality of life, reducing complications, and promoting patient-centred care as individual's age. Lastly, as highlighted by Pan et al. [13], this study provides valuable clues on personalised T2D treatment strategies in older adults,

supporting clinicians in choosing treatments that prioritise specific benefits or minimise risks (e.g. hypoglycaemia or loss of weight).

In conclusion, the study provides new high-quality evidence and highlights the anticipated benefits of newer glucose-lowering drugs in older people with T2D. As we approach a new era in diabetes management for older adults, it is essential to harness the potential of novel therapies. As suggested by Pan *et al.* [13], these results indicate that newer glucose-lowering drugs could legitimately replace certain higher-risks treatments, even for vulnerable patients, or at least encourage a greater emphasis on prescribing these new drugs. Despite these progresses, the field remained widely unexplored, and coordinated efforts are needed to shift from a burden-oriented model to one focussed on benefits in the treatment of T2D in older adults.

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