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REVIEW ARTICLE

Evaluating glucose-lowering treatment in older people with diabetes: Lessons from the IMPERIUM trial

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Abstract

Understanding the benefits and risks of treatments to be used by older individuals (≥65 years old) is critical for informed therapeutic decisions. Glucose-lowering therapy for older patients with diabetes should be tailored to suit their clinical condition, comorbidities and impaired functional status, including varying degrees of frailty. However, despite the rapidly growing population of older adults with diabetes, there are few dedicated clinical trials evaluating glucose-lowering treatment in older people. Conducting clinical trials in the older population poses multiple significant challenges. Despite the general agreement that individualizing treatment goals and avoiding hypoglycaemia is paramount for the therapy of older people with diabetes, there are conflicting perspectives on specific glycaemic targets that should be adopted and on use of specific drugs and treatment strategies. Assessment of functional status, frailty and comorbidities is not routinely performed in diabetes trials, contributing to insufficient characterization of older study participants. Moreover, significant operational barriers and problems make successful enrolment and completion of such studies difficult. In this review paper, we summarize the current guidelines and literature on conducting such trials, as well as the learnings from our own clinical trial (IMPERIUM) that assessed different glucose-lowering strategies in older people with type 2 diabetes. We discuss the importance of strategies to improve study design, enrolment and attrition. Apart from summarizing some practical advice to facilitate the successful conduct of studies, we highlight key gaps and needs that warrant further research.

KEYWORDS

antidiabetic drug, clinical trial, diabetes complications, glycaemic control, hypoglycaemia

1 | INTRODUCTION

The growing diabetes pandemic coupled with significant improvements in medical care has resulted in a rise in an older population with diabetes (≥65 years old). The International Diabetes Federation estimated a global diabetes prevalence of 9.6% in people older than 65 years.[1] It is much higher in some countries such as the United States where 25% of adults ≥65 years of age were diagnosed with diabetes and about 48% with prediabetes as of 2015.[2] This prevalence is estimated to increase 4.5-fold from 2005 to 2050 in those ≥65 years of age.[3]

Older people with diabetes comprise a heterogeneous population with unique medical, psychological and social needs. They often have a number of geriatric syndromes such as frailty, cognitive impairment, depression, urinary incontinence, falls and fractures, vision and hearing

impairment, and persistent pain, which add to the complexity and burden of diabetes.[4] Frailty is of particular relevance because frail older individuals have lower functional reserves and are more vulnerable to comorbidities, adverse events and mortality. Frailty may also change the course and natural history of diabetes and trigger the need for modifications of glucose-lowering treatment. Weight loss, which is typically associated with frailty, may reverse the tendency to hyperglycaemia, promote normoglycaemia and increase the risk of hypoglycaemic episodes with or without pharmacological therapy.[5]

Older patients with diabetes may also have several comorbidities such as cardiovascular disease and microvascular complications.[4] This increases the use of prescription and over-the-counter medications, resulting in higher rates of polypharmacy in older adults.[6] In 2011, >85% of people in the United States aged 62-85 years used at least one, and more than one-third of them used five or more prescription medicines.[7] Polypharmacy increases the risk of drug interactions and adverse events.[8] Other age-related phenomena such as impairment of renal or hepatic excretory function might result in altered pharmacokinetics of the drugs, making older patients more vulnerable to adverse events, including hypoglycaemia, than younger patients.

Hypoglycaemia in older people receiving glucose-lowering therapy may carry a significant risk of morbidity and mortality.[9,10] The consequences of hypoglycaemia range from life-threatening cardiovascular events triggered by severe hypoglycaemia episodes to physical and cognitive dysfunction, frailty, disability and mortality resulting from repeated non-severe episodes.[11]

Acknowledging the differences between older and younger patients, the International Conference on Harmonization (ICH) guideline on geriatrics (E7)[12] called for the inclusion of representative older patients with concomitant therapies and comorbidities in drug development trials (Table 1). The ICH guideline has been adopted by regulatory bodies including the European Medicines Agency (EMA)[14] and the US Food and Drug Administration (FDA) and six other ICH member countries.[15] Table 1 provides a summary of requirements set by the ICH and EMA regarding the inclusion of older patients in drug development clinical trials.

Besides pharmacokinetics, pharmacodynamics, safety and efficacy of the drug, other aspects of drug therapy such as patient acceptability, dosage and route of administration, dosing frequency, formulations, excipients, container closures, devices, technologies, product information, medication management and recognition might be very relevant for older drug users and have been discussed in the reflection paper on the pharmaceutical development of medicines for use in the older population published by the EMA.[14]

This review summarizes current literature and guidelines on conducting clinical trials evaluating glucose-lowering therapies in older patients with diabetes. We also share our experience with regards to the planning, designing, implementing and reporting of clinical trials involving older patients in need of glucose-lowering therapy based on our learnings from the randomized clinical trial entitled, "Individualized treatMent aPproach for oldER vulnerable patIents; a randomized, controlled stUdy in type 2 diabetes Mellitus" (IMPERIUM study; NCT02072096).[16] This was the first study conducted in vulnerable adults ≥65 years of age with type 2 diabetes, which aimed at evaluating different treatment strategies to lower blood glucose in frail older patients.

2 | WHY IS IT DIFFICULT TO CONDUCT DIABETES TRIALS IN OLDER PATIENTS?

Despite significant progress in diabetes clinical research, information about outcomes of glucose-lowering treatments in older patients remains limited. Understanding the reasons behind such scarcity of data may help develop solutions for this problem.

2.1 | Conflicting perspectives on treatment goals

It is widely accepted that blood glucose should be lowered in older patients with diabetes while reducing or even avoiding the risk of hypoglycaemia.[1,4,17] The extent to which blood glucose should be

TABLE 1 Regulatory guidance on inclusion of older patients in clinical trials

	Guidance

ICH E7[12]	• Trial population should be representative of the population that will use the drug.
	  ○ Call for inclusion of patients that are ≥75 years old and receiving treatments or having medical problems common in geriatric populations.
	• Exclusion of patients based on upper age limits, comorbid conditions and concomitant illnesses is no longer justified (unless there is a reason to believe that inclusion may endanger them or lead to difficulties in interpreting study results).
	• Phase 2 and 3 trials should include a minimum meaningful number of older participants.
	  ○ For medicines intending to treat diseases present in older patients but not unique to them, at least 100 participants should be ≥65 years old (with the exception of uncommon diseases).
	  ○ For medicines intended for diseases associated with ageing, ≥50% of participants should be ≥65 years old.

EMA[13]	• Requires "reasonable" number of older patients (of age 65-74, 75-84 and 85+ years old) that will allow presentation of data for these age groups to confirm their consistency with results obtained from younger populations. • Calls for functional characterization of older patients participating in the trials to ensure that they truly represent the target patient population and include vulnerable (frail) geriatric patients. • Recommends use of the short physical performance battery or gait speed as the instruments that best fulfil criteria of the prognostic value, validation status, feasibility and ease of use, time needed, ease of investigator's training, and cost.

Abbreviations: EMA, European Medicines Agency; FDA, Food and Drug Administration; ICH, International Conference on Harmonisation.

lowered, the best ways to achieve glycaemic targets and the choice of glucose-lowering therapies are frequently extrapolated from studies conducted in younger individuals.

A belief that older patients may benefit from normalizing blood glucose levels may lead to setting overly ambitious glycaemic goals for participants of clinical trials and ultimately to their "overtreatment" in real-world clinical practice.[18-20] While there is an agreement that glycated haemoglobin (HbA1c) of ≤7% (≤53 mmol/mol) is a reasonable target for most adults, the assumption that lowering blood glucose reduces microvascular complications, as well as prevents cardiovascular events may not be true for patients with a short life expectancy.[21] The risk of adverse events with glucose-lowering treatment may outweigh the benefits of preventing microvascular complications in frail older patients. A range of alternative glycaemic targets have been proposed for older patients with diabetes, e.g., <7.5% (<59 mmol/mol), <8.0% (<64 mmol/mol), <8.5% (<69 mmol/mol) or 8.0%-9.0% (64-75 mmol/mol), depending on the overall health status, duration of diabetes, life expectancy, treatment burden and vulnerability to hypoglycaemia. However, none of the goals set for an older population have been validated in dedicated clinical trials, let alone cardiovascular outcome clinical trials. The UK Prospective Diabetes Study[21,22] excluded patients at the age of ≥65 years and the subgroup analysis of other trials (ACCORD, ADVANCE, VADT) evaluating the role of glycaemic control in the prevention of cardiovascular outcomes did not result in conclusive findings.[23-27] This lack of standardized treatment goals poses a challenge for those who design clinical trials. Investigators caring for older patients who have shorter life expectancy, comorbidities, polypharmacy, increased risk of complications and of adverse events, as well as geriatric syndromes such as memory impairment and frailty may be reluctant to follow stringent glycaemic goals set in a study.

While long-term benefits of lowering blood glucose have not been studied and hence are unproven in older adults, there is an agreement that detrimental effects of hypoglycaemia in older individuals are more pronounced and clinically relevant compared with those in younger individuals. Older age is a well-recognized predisposing factor for any type of hypoglycaemia in diabetes.[28,29] The consequences of hypoglycaemia in older patients may range from deteriorating quality of life, ambulatory difficulties, falls, fractures and cognitive impairment to grave life-threatening episodes of seizure, coma, cardiovascular events, arrhythmia and hospitalizations.[30,31] Therefore, balancing the potential benefits of improved glycaemic control and the risk of hypoglycaemia is an important goal of diabetes treatment for older patients.

2.2 | Acceptability of newer treatment options in older patients

Conventionally used glucose-lowering treatments such as insulins, sulphonylureas and meglitinides increase the risk of hypoglycaemia, which for decades has been considered a price to be paid for improved glycaemic control. Recent oral and injectable therapies that per se do not increase the risk of hypoglycaemia may be used as stand-alone or combination treatment.

Over the last few years, studies for some of the hypoglycaemia-neutral sodium-glucose cotransporter-2 inhibitors (SGLT-2is) and glucagon-like peptide-1 receptor agonists (GLP-1 RAs) have shown an additional benefit of lowering cardiovascular events in patients with type 2 diabetes with cardiovascular disease[32-37] or without.[38] These trials have involved a large proportion of older patients, yet overall study populations were generally younger and may have had different characteristics than typical older patients. Demonstrating consistency of findings for the overall cardiovascular outcomes study population and older participant subgroups may support extrapolation of results.[38-40] However, despite evidence supporting use of newer hypoglycaemia-neutral treatments, in real world clinical practice, older patients including those at high risk of hypoglycaemia continue to use sulphonylureas and insulin for a variety of reasons.[20]

Cardiovascular benefits may become apparent in a long-term perspective and, therefore, may be irrelevant in the case of patients with limited life expectancy. On the other hand, rare adverse events of therapies may be of greater concern in older patients. Examples include volume depletion in older patients using SGLT-2is,[41,42] nausea and gastrointestinal adverse events with GLP-1 RAs,[43] or increased risk of fractures and heart failure with thiazolidinediones.[44,45] Weight loss, a benefit of SGLT-2i or GLP-1 RA therapy, may not be desirable for many older patients who are already lean. Finally, the higher costs of the novel diabetes treatments may prevent broader access to older individuals.

Thus, shorter life expectancy, comorbidities, polypharmacy, increased risk of complications and of adverse events, geriatric syndromes such as memory impairment and frailty, and lastly economic considerations make treatment goals and therapeutic choices in older patients different from those accepted as standard for treatment in younger patients.

2.3 | Issues with participation of older patients in clinical trials

Many clinical trials enrol participants who are considerably younger than a representative population of patients affected by the diseases studied. This problem has been reported across different therapeutic areas such as heart failure, hypertension, Alzheimer's disease, colorectal cancer and depression, as well as diabetes.[46,47] Older patients may be excluded from participation because of explicitly set age limits or, much more often, because inclusion and exclusion criteria indirectly limit their participation based on comorbidities, polypharmacy, cognitive impairment, short life expectancy and other factors.[14,47] Even if the enrolment and exclusion criteria allow participation of older people in clinical trials, relatively few might get enrolled even if their enrolment is desired. Barriers leading to their underrepresentation may be related to concerns about greater drug toxicity, poor compliance, mobility issues and reliance on assistance of caregivers. Even if they are enrolled, older study participants may not represent the

TABLE 2 Problems and issues in diabetes trials involving older patients

Problems and issues in diabetes trials involving older patients relevant to	Description	Potential solutions
Investigators	Lack of experience in assessment and care of older patients.	Additional training offered to the site staff including information about conducting trials with regards to communication, sensory, mobility and cognitive problems in older people.[46]
	Lack of suitable patients in typical trial centres.	Involvement of different types of sites (geriatric clinics, primary care, internal medicine, community-based clinics and services).
	Lack of motivation to recruit older patients if younger ones are eligible.	Setting age-specific enrolment targets.[46]
	Therapeutic inertia.	• Involvement of investigators and patient advocates in protocol development. • Simplification of the protocol. • Monitoring treatment decisions (e.g., in electronic database).
Study participants	Lack of interest or inability to participate in studies.	• Incentives for patients (e.g., reimbursement, meals, education). • Involving primary care practices rather than secondary. • Social interactions, addressing altruism as a factor improving participation.[46]
	Lack of awareness of trial.	Information, advertising through appropriate channels used by the intended age group.
	Concerns about safety of the study treatment.	• Understandable study treatment information, simplification of informed consent. • Additional time offered to older patients.
	Need assistance to get to the study sites or follow the protocol.	• Provision of care for those the patients are responsible for.[46] • Logistical support (transportation to the sites or study visits at home/institution where patients stay). • Home-based trials, visits, investigative procedures.[46] • Simplification of protocols, flexible time for the study visits. • Avoidance of additional visits, i.e., telephone visits, other indirect contacts.
	No functional characterization.	Introduction of simple user-friendly tools to assess comorbidities and functional status (frailty, cognitive function).
	Discontinuations.	Study sample size adjustments based on higher than expected dropouts.
Caregivers	Lack of motivation to ensure trial participation.	• Incentives for caregivers to motivate compliance with the protocol. • Providing incentives for transportation, parking, etc. • Providing caregiver with specific information and literature to support their critical role. • Collecting patient-reported outcomes from caregivers.
Facilities where patients stay	Need for acceptance from the institutions' leadership and staff. Informed consent from family, caregivers and not from a patient.	Establishing good communication and relationship with facility administration and staff including provision of study information brochures, published research and face-to-face communication.
	Mistrust of clinical research.	Building awareness and trust by explaining the need for clinical studies.
	Perception of additional workload and cost.	• Reimbursement and recognition for the facility staff. • Discussion of costs, informed consent, and other potential issues early. • Engaging facility management and staff at the time of enrolment. • Periodic follow-up meetings with the facility management and staff.

(Continues)

TABLE 2 (Continued)

Problems and issues in diabetes trials involving older patients relevant to	Description	Potential solutions
Study design, goals and endpoints	Lack of accepted standards of treatment and treatment goals in older patients.	Need for earlier involvement of stakeholders (clinicians, patients, caregivers, and payers), at the stage of study design development.
	Need for individualization of therapy goals (no "one size fits all" endpoints).	Individualization of glycaemic targets.
	Enrolled patients may not represent real-life population.	Conducting clinical trials in primary care centres rather than in specialty care.[46]
Study sponsors	High costs and complexity of the trials because of higher numbers of patients, costs associated with support for patients and caregivers (e.g., transportation).	Setting evidence-based minimal requirements for participation of older patients and specific subgroups by regulatory agencies and ethical review boards; providing regulatory incentives for successful inclusion of older patients.

real-world geriatric population in terms of functional status and comorbidities as relatively fit individuals are more likely to participate in clinical trials. Functional characterization of the older study participants and assessment of frailty remains exceptional rather than a routine procedure in diabetes clinical research.

Older patients with diabetes typically attend different types of clinics than the typical diabetes and endocrine clinical research sites. They may receive diabetes care from their primary care clinics, geriatricians, internal medicine clinics or institutional health care professionals (Table 2). Many receive their care through assisted living services while in nursing homes or chronic care facilities. Older patients commonly have multiple comorbidities and thus conflicting priorities, and limited time and interest in participation. They may not be able to reach the sites or require caregiver assistance to get to the site for study visits. It is particularly difficult for protocols with multiple and long study visits, e.g., in case of multiple tests or procedures that require remaining at the investigative sites for hours. Telephone discussions, which are common for protocols requiring frequent monitoring and treatment adjustments such as insulin titrations, may address this problem to some extent. However, frequent calls continue to be a burden as common age-related sensory or memory impairments can make telephone discussions difficult.

Investigators and site staff may lack expertise in managing older patients and may be reluctant to pursue glycaemic targets that may be perceived as ambitious and treatments that require therapy adjustments. Thus, in trials requiring changes or intensification of therapy such as insulin titration studies, we observe the phenomenon of so-called "clinical inertia", where the treatment decisions are delayed, or the protocol guidance is not fully followed. Inertia in clinical trials probably reflects conflict of the protocol with the usual clinical practice to "start low and go slow" in older participants. On the other hand, study participants themselves may be non-compliant with the protocol. Increasing age and a variety of other factors may increase risk of non-adherence to the clinical study protocols among older participants, and sponsors might consider implementation of preventive measures to help patients at risk to complete the trial successfully.[48]

Researchers should also consider strategies to prevent dropouts or discontinuations,[49] as the likelihood of discontinuation because of adverse events might be higher among older patients. Demanding protocols that are manageable in younger populations might turn out to be too burdensome for older patients, particularly in longer studies.[50] Sample size calculations should account for dropouts higher than those observed in "typical" populations. It might be necessary to offer incentives for both patients and their caregivers to ensure their continued interest in study participation through increasing the benefit-risk ratio for participating in the clinical trial.[49]

2.4 | Difficulties in proper characterization of patients

Older patients are inherently heterogeneous and require characterization depending on the underlying trial objectives.[51] This characterization should ensure that the enrolled patients resemble a real-world population of patients. Two of the most important elements of characterization are the functional status and comorbidities of the patient. Frailty has a major impact on treatment decisions in the real world, yet we are not aware of any study where this has been captured (except in IMPERIUM, as will be discussed in Section 3). Comorbidities and frailty should essentially be assessed at baseline to understand the characteristics of the study participants. In many instances, functional status should be evaluated throughout the trial to understand if the study treatment might impact it. Significant changes in functional status [measured by the Short Physical Performance Battery (SPPB)] in older participants with diabetes are evident after 1 year of follow-up when the intervention was resistance exercise, nutritional education, and optimizing glycaemic and blood pressure control.[52] However, a longer period of trial duration may be required to see changes in functional status if the intervention was solely linked to blood glucose regulation.

TABLE 3 Tools to assess frailty, functional status and comorbidities

Tool	Information provided	Clinical research and practice use
Functional status including frailty		
Fried Score[53]	It is originally based on 5 components of physical frailty (3 questions and 2 procedures). Questions are based on weight loss, exhaustion and low physical activity; and procedures measure gait speed and hand grip strength. It is scored out of 5: 0 (robust/not frail); 1-2 (pre-frail), and 3-5 (frail).	It is less frequently used as it involves 2 practical measures/procedures. It is also seen as a physical frailty measure only.
CSHA Clinical Frailty Scale[54]	It categorizes frailty as: very fit, well, well with treated comorbid disease, apparently vulnerable, mildly frail, moderately frail or severely frail.	Visual representation and description in 7 categories; easy to apply; and good for encouraging clinicians to think of frailty in clinical settings.
CSHA frailty index[54,55]	Original model calculates relative frailty, fitness and severity based on 70 deficits that include presence and severity of current diseases, ability in ADLs, and physical signs from clinical and neurologic exams.	It is not practical to use in clinical setting unless it is represented by the shorter electronic frailty index, which can be captured on electronic primary care databases in some countries using routine clinical data.
FRAIL Scale[56]	It is based on 5 components: fatigue, resistance, ambulation, illness and loss of weight. It is scored from 0 to 5, with 3-5 termed as frail, 1-2 as pre-frail, and 0 as robust. It has high predictive value for future disability.	It does not require face-to-face consultation. It is now becoming measure of choice in many clinical settings and clinical trials. It is validated in multiple populations.
Short Physical Performance Battery (SPPB)[57]	It is an evaluation tool for lower limb function that combines gait speed, chair stands and balance tests. It has high predictive ability for mortality, care home admission and future disability.	It requires little training. It is a quick assessment that is becoming a standard objective measure of functional change in clinical trials involving older people.
Gait Speed[58]	It uses gait speed as a measure of functional capacity and predictor of health outcomes. Low gait speed can predict higher risk of hospitalization and need for a caregiver.	This is one of the three domains of evaluation in the SPPB. It is easy to measure and there are population-based reference values available.
Electronic frailty index (eFI)[59]	It categorizes presence of frailty as mild, moderate or severe based on existing electronic health records in primary care in the UK without additional assessments being required. It uses 36 deficits based on 2171 read codes.	It is not a diagnostic tool, but a risk stratification tool. When the score is high (indicating probable presence of frailty), direct clinical evaluation is required for diagnosis.
CSHA functional scale	It scores based on 12 ADLs as 0 (independent in carrying the ADL), 1 (needs assistance), or 2 (incapable).	–
Comorbidity		
Cumulative illness rating scale (CIRS)[60]	A measure of multimorbidity and particularly of the burden of chronic medical illness. It has 14 individual system scores, giving a score of 0-56.	After previous training, the CIRS has good inter- and intra-rater reliability. It can be used in community/family practice.
Charlson comorbidity index (CCI) and its adaptations (Deyo CCI, Romano CCI, D'Hoore CCI, Ghali CCI, Quan CCI)[61,62]	It predicts the 1-year mortality for an individual with a range of comorbidities.	It is a widely used and a recommended index when outcome of interest is mortality.
Elixhauser comorbidity index (EI)[63]	It uses a comprehensive set of 30 comorbidities to predict mortality. These are based on the international classification of diseases (ICD).	It is used to predict in-hospital resource use and/or mortality.
Index of coexisting disease (ICED)[64]	Each condition or limitation experienced by the patient has a score based on its severity and level of physical impairment.	It was initially shown as a strong predictor of death in dialysis patients.
Chronic disease score (CDS)[65]	It uses medications to identify comorbidities.	–
RxRisk and RxRisk-V[66]	It is an all-age risk assessment using outpatient pharmacy database to identify chronic diseases and predict future health care costs.	It is recommended when evaluating health care utilization.

(Continues)

TABLE 3 (Continued)

Tool	Information provided	Clinical research and practice use
Cognitive function screening		
Mini-Mental State Examination (MMSE)[67]	It is usually scored out of 30, with a score less than 24 indicative of "cognitive impairment".	It is commonly used and highly validated in different populations and languages. It can be a disadvantage in poorly educated people or those with poor vision. It is now copyrighted and may require a fee to be paid for use.
Mini cog[68]	It consists of a 3-step test: Registration of 3 words, a clock test and then the recall of the 3 words.	It takes 3 min to complete; has varied scoring systems, but easy to employ with minimal training; less affected by language or education. It has been validated in patients with diabetes in primary care.
Montreal cog (MoCA)[69]	This is a rapid screening instrument for mild cognitive impairment. It scores out of 30 points and assesses attention and concentration, executive functions, memory, language, visuo-constructional skills, conceptual thinking, calculations and orientation. A score of 26 is rated as normal.	Is available in more than 40 languages/dialects but not all versions have been validated. Now requires a fee to have researchers trained in its use.

Abbreviations: ADL, activity of daily living; CSHA, Canadian Study of Health and Aging.

There are no gold standard tools established to assess either functional status or comorbidities that could be consistently used in clinical diabetes trials but we do list some of the widely used tools (see Table 3). Recently, EMA provided guidance on the characterization of older patients in a reflection paper that recommends SPPB as the instrument that best fulfils criteria for the prognostic value, validation status, feasibility and ease-of-use, time needed, ease of investigator training and cost.[13,57] The geriatric assessment tool, Gait Speed, was recommended as an alternative when SPPB use is not feasible in clinical trials.[58]

While not a standard procedure in diabetes clinical trials, assessment of the metabolic phenotype might help to understand better the probable disease progression, treatment modalities, intensity and goals of therapy of study participants.[57] A recent analysis identified different subtypes of adult-onset diabetes based on the clustering of clinical characteristics.[57] One phenotype was found to be typical for older people whose disease seems to have the mildest clinical course.[51] However, not all elements of phenotyping, which is based on body mass index, age at onset of diabetes, homoeostasis model assessment estimates of β-cell function (HOMA2-B) and insulin resistance (HOMA2-IR) and glutamic acid decarboxylase antibodies, are used routinely in diabetes trials or clinical practice.

2.5 | Choice of clinical trial endpoints

In addition to endpoints such as HbA1c change, proportions of patients meeting HbA1c targets, weight change, change in fasting plasma glucose, or adverse events, other clinical trial endpoints reflecting changes relevant from patients' and caregivers' perspective may be useful for diabetes trials involving older people. When assessing efficacy of glucose-lowering therapy, clinical trial sponsors should consider the need to individualize glycaemic goals and avoid hypoglycaemia. Composite endpoints such as achievement of HbA1c goal of ≤7.0% (≤53.0 mmol/mol) without hypoglycaemia have been used in diabetes trials over the years.[70,71] However, individualization of therapy goals remains unaddressed. We are aware of one dipeptidyl peptidase-4 inhibitor study that adopted individual glycaemic targets for older patients,[72] but no detailed information is available about specific targets and the decision process in choosing them for individual patients.

2.6 | Hypoglycaemia as a study endpoint

It is not clear which category of hypoglycaemia is most suitable as an endpoint or for inclusion in the composite primary endpoint relevant for older patients. A growing body of evidence supports the notion that all episodes of hypoglycaemia with blood glucose levels <3.0 mmol/L (54.0 mg/dL) are relevant.[73] Apart from conferring risk of morbidities, such episodes negatively affect quality of life, result in reluctance to advance therapy and affect adherence to diabetes therapies.[74,75] The most complete understanding of hypoglycaemia risk might come from continuous glucose monitoring studies that so far have rarely been performed in older patients with type 2 diabetes because of technical complexity and added burden of clinical trial procedures. Availability of novel continuous glucose monitoring systems and flash glucose monitoring may broaden the opportunity for use in older patients and detect otherwise overlooked episodes of hypoglycaemia, e.g., nocturnal episodes and episodes that patients are unaware of.[76]

However, considering only hypoglycaemia episodes (irrespective of severity) does not reflect the impact hypoglycaemia has on patients and caregivers. Assessment of discomfort and disruption created by hypoglycaemia is of importance for older patients. Thus, further study

is needed to investigate outcome measures best suited for older patients, which would reflect the individual success of therapy and burden of associated hypoglycaemia. Patient-reported outcomes, measures of quality of life, costs of treatment and caregiver-reported outcomes may help to understand the full impact of the disease and treatment.

Because of limitations and problems encountered in randomized clinical trials, other types of clinical research may be better suited to evaluate certain aspects of glucose-lowering treatments among older individuals. Real-world evidence (RWE) studies that collect evidence in real clinical care, home or community settings may create the way to involve study participants who otherwise are not enrolled in clinical trials conducted at academic centres and research sites.[77] In addition, RWE research offers greater external validity in comparison with randomized clinical trials as they involve patients with coexisting illnesses and concomitant therapies.[77] Drawbacks of RWE research include the innate risk of study bias, inability to control variability, and limited ways to assure completeness and quality of data collected. These problems may be addressed to some extent through pragmatic studies that aim at preserving a real-world practice setting by minimizing inclusion and exclusion criteria and reducing the burden on participants by limiting the number and complexity of study visits and procedures.[78] However, pragmatic studies typically assess interventions delivered to randomized populations in an unblinded fashion. The unobtrusive collection of data makes pragmatic trials suitable for the collection of adverse events that are important for patients, such as cardiovascular events, death, disability or hospitalizations, but may limit possibilities of assessment of minor adverse events, signs, symptoms and quality of life. Importantly, RWE and pragmatic studies provide limited opportunities for functional characterization of study participants. Another important limitation of these studies is low sensitivity to detect hypoglycaemia. Studies based on retrospective collection of hypoglycaemia events using medical records or questionnaires may miss many hypoglycaemic episodes, leading to the underestimation of hypoglycaemia risk.[79] Reports of hypoglycaemic episodes that require hospital admission or emergency room visit may be considered reliable, as they are recorded and create a memorable and reportable experience.[80] However, these episodes account for only a minority of overall episodes.

3 | LEARNINGS FROM THE IMPERIUM TRIAL

3.1 | The IMPERIUM trial

We conducted the IMPERIUM randomized controlled trial[16] to address the knowledge gap related to the use of novel glucose-lowering therapies that per se do not increase risk of hypoglycaemia ("glucose-dependent mode of action") in older patients with type 2 diabetes. We enrolled vulnerable (moderately ill and/or frail) patients aged ≥65 years. While use of agents such as dipeptidyl peptidase-4 inhibitors and GLP-1 RAs seems to be justified in older patients who are more vulnerable to hypoglycaemia, these patients are frequently treated with agents that are "non-glucose dependent" in their blood glucose lowering action such as sulphonylureas and insulin. We compared two treatment strategies using several marketed oral antihyperglycaemic medications (OAMs) and injectable treatments (either GLP-1RA or insulin glargine). Strategy A adopted "glucose-dependent" therapies with non-sulphonylurea OAMs and GLP-1RAs if injectable therapy was needed. Strategy B reflected a more traditional treatment approach with sulphonylureas as a preferred OAM used either in monotherapy or in combination, and insulin glargine (100 units/mL) as a first-line injectable treatment, if needed. The trial assessed the relative success of Strategy A as compared with Strategy B in achieving and sustaining glycaemic control in the absence of episodes of clinically significant hypoglycaemia.

Many aspects of the design and study conduct were novel; therefore, we decided to begin the trial planned to last 72 weeks with an internal pilot phase involving approximately 20% of the full study population treated for at least 24 weeks. The results of this pilot study did not show a significant difference between the two treatment strategies ($P = 0.67$). The conditional power for statistical significance of the primary outcome indicated low probability of the study success (conditional power = 0.05), and hence the study was terminated after the interim analysis. While the study is considered as "failed", the learnings from it might inform future research of this kind and are worthy of reporting to the clinical research community.

3.2 | Enrolling patients and characterizing study participants

Enrolment of patients at typical diabetes trial sites represented significant challenges, leading to extension of the enrolment period and searching for suitable patients at other endocrine/diabetes and primary care sites. One of the unique features of the trial was the attempt to characterize health and functional status of the enrolled patients to ensure that study participants not only met age criteria, but also were representative of the older population, i.e., they had comorbidities and/or were frail. We adopted the Total Illness Burden Index (TIBI) to assess comorbidities and Clinical Frailty Scale (CFS) Index to confirm eligibility criteria. While use of CFS is easier and intuitive, adoption of TIBI required more effort. In the IMPERIUM trial, TIBI was calculated by a clinician based on the patients' responses to 15 questions. Scores calculated during the study were sent to the coordinating centre for validation. These tools helped to identify vulnerable patients, but we found that mean TIBI and CFS scores were relatively low; mean ± SD of TIBI = 3.8 ± 2.4 and CFS = 4.1 ± 0.6, with only one-third of the study subjects at least moderately ill and frail. Thus, we had enrolled patients who were healthier and functioning better than we expected. Interestingly, we did not note differences between patients with high and low TIBI and CFS scores in terms of likelihood of reaching treatment target, developing hypoglycaemia or decreasing HbA1c. We noted that investigators tended to assign a higher HbA1c target (7.5%-7.9%, 59-63 mmol/mol)

to patients with a higher CFS at baseline (≥5). Based on this experience, we recommend that future trials should seek sites that are able to enrol more study participants who are ill and frail. Researchers should seek study sites other than diabetes and endocrine clinics. Primary care practices, geriatric clinics, community-based clinics and services, and long-care facilities might offer greater access to potential study participants. Identifying such centres and establishing collaboration poses additional challenges. Table 2 provides suggestions to help establish such new research sites. We strongly recommend functional characterization of study participants either with CSF or another simple tool. We also suggest setting stringent eligibility criteria related to the health and functional status, otherwise healthier and fitter study participants are likely to be enrolled.

3.3 | Choosing individualized treatment goals

Investigators in our study had a choice of allocating three different target HbA1c values to patients: 7.5%-7.9% (59-63 mmol/mol); 7.0%-7.4% (53-57 mmol/mol); and <7.0% (<53 mmol/mol). Treatment was to be adjusted, either uptitrated or intensified if actual HbA1c was higher than the target value. Investigators could choose a specific target based on their best clinical judgement; however, some guidance was provided in the protocol. Assessment criteria included patients' dependence on others, cognitive and functional status, risk of hypoglycaemia, duration of diabetes, presence of complications and comorbidities, and life expectancy. Overall, the most stringent goal of HbA1c <7.0% (<53 mmol/mol) was chosen in approximately 50% of trial participants, while the highest HbA1c goal was chosen for approximately 12%; consistent with the overall better than expected health of enrolled patients. We tried to evaluate the impact of patient characteristics on the selection of individualized treatment targets.

Of several determinants, high baseline HbA1c (≥8.5% or ≥69 mmol/mol) and CFS score of ≥5 positively correlated with the choice of the highest target HbA1c values. There was no correlation between the target HbA1c chosen and gender, body mass index <35 kg/m^2, previous sulphonylurea use, TIBI score or presence of renal disease. This might reflect lack of understanding among investigators on how frailty or comorbidities should impact treatment choice.

3.4 | Treatment strategies versus specific treatments

The IMPERIUM study evaluated treatment strategies rather than specific treatments. We believe that such studies are needed, taking into consideration the growing variety of therapeutics available to patients and clinicians. While clinical trials sponsored by pharmaceutical companies typically investigate specific drugs, studies evaluating more real-life scenarios are presumably clinically more relevant. Another advantage was that the investigators had freedom to use multiple drugs from the same therapeutic class at variable doses. This was possible as study participants were provided prescription cards rather than dispensing drugs. However, it also turned out to be difficult for the clinical study staff, who are more accustomed to simple and straightforward treatment requirements.

3.5 | Clinical inertia

Despite the familiarity with OAMs and injectable treatments used in the trial, and that all treatments were to be used in accordance with the product labels, we noted the problem of clinical inertia within the trial. The trial investigators tended to delay the decision to uptitrate and/or intensify the treatment despite the patient not reaching the individual HbA1c target at consecutive visits. As pursuing glycaemic goals was pivotal for the success of the study that meant to provide a conclusive answer to the main hypothesis tested, we had to implement additional monitoring of the trial decisions. Investigators were contacted and reminded about the action needed (dose adjustment of existing treatment or prescribing next line therapy) if no change of treatment was recorded at two consecutive visits at which HbA1c remained above the individualized target value. Overall, approximately 60% of patients achieved their HbA1c target value at the last study visit (65.3% with Strategy A and 59.1% with Strategy B). Within each treatment group, patients with HbA1c ≥8.5% (≥69 mmol/mol) at baseline probably experience more clinical inertia than those who had lower HbA1c (Strategy A: $P = 0.049$; Strategy B: $P = 0.048$).

3.6 | Defining hypoglycaemia, the right way

The primary endpoint of the trial was a composite outcome of achieving and maintaining target HbA1c while avoiding clinically relevant hypoglycaemia. We defined clinically relevant hypoglycaemia as episodes of severe hypoglycaemia; repeated episodes of hypoglycaemia as confirmed by blood glucose level of ≤70 mg/dL (≤3.9 mmol/L) causing significant disruption of the patient's activity; or repeated episodes of hypoglycaemia with blood glucose level of <54 mg/dL (<3.0 mmol/L). While the composite endpoint aimed to reflect clinically meaningful problems of treatment risk-benefit balance, this definition of clinically relevant hypoglycaemia was found to be too stringent. It disregarded a clear majority of hypoglycaemia episodes as "not relevant", leading to the conclusion that both treatment strategies were similar in terms of clinical outcomes. The lower risk of total, documented symptomatic and asymptomatic hypoglycaemia with Strategy A was not considered during the decision to terminate the trial even though these findings are highly relevant for clinical practice. Very few "clinically relevant hypoglycaemia" episodes were reported in our trial despite the significant improvement in mean HbA1c. Adoption of less stringent definitions in future research might help in capturing all clinically relevant episodes. The recent position statement, proposed by the International Hypoglycaemia Study Group and adopted by the ADA, EASD and EMA among others, offers a more useful endpoint for future trials.[73]

4 | CONCLUSIONS AND FUTURE PERSPECTIVES

In conclusion, we believe that assessment of efficacy and safety of glucose-lowering treatments among older patients with diabetes remains suboptimal. With the growing population of older people with diabetes, it becomes an urgent and relevant challenge that needs to be addressed in future clinical research. To identify appropriate glucose-lowering treatments or treatment regimens, a paradigm shift is warranted in conducting clinical trials in older adults. Studies that are more thorough, conducted in patients with comorbidities and impaired functional status, and with various degrees of frailty are necessary to understand fully the risk-benefit ratio of therapies used in older individuals. While conducting diabetes clinical trials in older people poses significant operational challenges, including the need to reach atypical research sites, it is nevertheless a broad societal responsibility to ensure that such trials take place. Successful completion of trials requires new strategies to improve enrolment, study design and adoption of study endpoints to ensure retention of patients in the trials and compliance with the protocol. More research is needed for informed therapy goal-setting, to allow individualization of treatment targets and to adopt clinical trial endpoints representing benefits and risks that are most relevant from the perspective of older patients and their caregivers.

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CONFLICT OF INTEREST

S.A.J. has received personal fees from Eli Lilly and Merck. H.S.R. has received fees from Novo Nordisk, Sanofi Aventis, Zealand Pharma, and Eli Lilly for advisory board meetings and consultancy; and personal and speaker fees from Novo Nordisk. R.E.P. reports consulting fees from Boehringer-Ingelheim, Eisai, Inc., GlaxoSmithKline, Glytec, LLC, Pfizer, Janssen and Mundipharma; grants from Lexicon Pharmaceuticals; speaker and consulting fees from AstraZeneca; grants and consulting fees from Ligand Pharmaceuticals, Inc., Eli Lilly, Sanofi and Merck; grants, speaker fees and consulting fees from Novo Nordisk and Takeda; personal consulting fees from Sanofi US Services, Inc., outside the submitted work. Except for consulting fees in February 2018 and June 2018 from Sanofi US Services, Inc., services by R.E.P. were paid for directly to AdventHealth, a nonprofit organization. A.F. has served on advisory boards for Boehringer Ingelheim, Eli Lilly, Astra Zeneca; as a consultant for Eli Lilly, Sanofi, Boehringer-Ingelheim, MSD, and on speaker bureaus for Astra Zeneca, Boehringer Ingelheim, Eli Lilly, and Sanofi. R.J.H. and J.K. are employees and stockholders of Eli Lilly and Company, USA, while R.D. is a former employee of Eli Lilly and Company, USA.

AUTHOR CONTRIBUTIONS

All the authors have contributed towards the conception of the review article and the generation of review outline and all subsequent drafts. All authors participated in the writing, critical reviewing, and approval of the final draft for submission.

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