VIA MEDICA
REVIEW ARTICLE
ISSN 2450–7458
e-ISSN 2450–8187

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Randomized Controlled Trials Dedicated to Older Patients with Type 2 Diabetes: A Systematic Review

ABSTRACT

Objective: Older adults with type 2 diabetes (T2D) comprise a very diverse population regarding their age, comorbidities, and frailty status, and their treatment goals may be different from those typical of younger patients. The objective of this study was to assess participants' characteristics and the primary endpoints of randomized controlled trials (RCTs) dedicated to older adults with T2D.

Materials and methods: This study was a systematic review of RCTs enrolling solely patients with T2D aged 60 years or older published from 1994 through 2023. Eligible trials were searched for in PubMed, Embase, and Cochrane Central.

Results: The review included 35 RCTs (9068 participants). The weighted mean age of RCT participants was 71.4 years (co-primary outcome). The proportion of patients aged 75 years or older was reported in 11 (31%) RCTs; it was 27%. Proportion of patients with frailty was reported in 2 (6%) trials (co-primary outcome). The proportion of patients with different burden of comorbidities was provided in one (3%) RCT (co-primary outcome). The primary endpoints mostly (n = 25; 71%) involved HbA1c. A composite primary endpoint (reduction of HbA1c without significant hypoglycemia) was used in 2 (6%) trials. The results for the primary endpoints were generally positive.

Conclusions: Most of the analyzed RCTs did not report the key participants characteristics. The primary endpoints did not involve outcome measures particularly relevant to older patients. Modifications of the design and reporting of RCTs should be considered to translate their results into optimal clinical care of older adults with T2D.

Prospero identifier: CRD42023490827

Keywords: diabetes mellitus, type 2 diabetes, randomized controlled trial, frailty, comorbidities, elderly, older adult

Introduction

Diabetes is one of the most common diseases affecting older adults worldwide [1]. For instance, in the USA, the prevalence of diabetes and prediabetes in persons aged 65 years or older was 30% and 50%, respectively [2]. Similar values were reported by the authors of a national cross-sectional study performed in China [3]. Furthermore, it is estimated that between 2005 and 2025 the prevalence of diabetes will increase twofold in persons aged 65–74 years and fourfold in individuals aged 75 years or older [4]. Diabetes has

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Clinical Diabetology 2024
DOI: 10.5603/cd.100313
Received: 18.04.2024 Accepted: 25.05.2024
Early publication date: 11.07.2024

serious consequences to older patients; for example, it increases the risk of physical disability and cognitive impairment [5, 6]. Also, diabetes can reduce the quality of life of older individuals [7]. The vast majority of older adults with diabetes have type 2 diabetes (T2D) [1, 4].

Older persons with T2D comprise a highly heterogeneous population [8, 9]. The key factors that need to be considered here include not only the chronological age of the patient, but also his/her comorbidities, which are particularly common in older individuals with T2D [10, 11]. Another important problem in older patients is frailty — a state of increased vulnerability to physiological decompensation after a stressor event. Frailty is associated with higher risk of adverse health outcomes including mortality and is the key factor determining the prognosis for older adults with diabetes; furthermore, glycemic control targets and the choice of glucose-lowering drugs should vary according to the frailty level. Treatment escalation/de-escalation plans and decisions regarding switching to other drugs in older adults should also be made considering the frailty level. Because frailty is a dynamic state, its level in older patients should be assessed annually and within 3 months of the use of any new therapeutic intervention [12].

The highest-level evidence of the efficacy and the safety of new therapeutic interventions is provided by randomized controlled trials (RCTs). Unfortunately, older patients have been traditionally underrepresented in RCTs of glucose-lowering treatments [13, 14]. Therefore, separate trials to investigate the potential benefits and harms of antidiabetic drugs in older adults have been performed; by using relevant age limits, these trials have been designed to enroll solely geriatric patients [15]. However, to the best of our knowledge, no study has yet been performed to analyze these trials in a systematic way.

The primary objective of this systematic review was to characterize participants of RCTs dedicated to older adults with T2D. In particular, we were interested whether the characteristics of the participants reflect the heterogeneity of the population of older adults with T2D. Moreover, we analyzed the primary endpoints.

Material and methods

RCT selection and data extraction

To be eligible for inclusion in our review, a trial had to: 1) be an RCT of an antidiabetic drug or a biological administered systemically; 2) enroll solely older adults with T2D (for the purposes of this study, an older adult was defined as an individual aged 60 years or older; we included trials with a lower age limit of 60 years or higher and trials without a lower age limit in which the age of the youngest participant was higher than 60 years); 3) have the primary endpoint related to the efficacy or safety of the investigational drug in treating diabetes or its microvascular or macrovascular complications (trials with the primary endpoint concerning the prevention of diabetes complications were also included); and 4) be published in 1994 or later.

We excluded from our analysis non-interventional (observational) studies, nonrandomized trials, phase 1 trials, trials enrolling patients with type 1 diabetes, gestational diabetes, secondary diabetes, or prediabetic state, trials enrolling solely healthy volunteers, trials enrolling patients younger than 60 years of age, trials of interventions other than drugs or biologicals (including vitamins and dietary supplements), trials of interventions applied locally, and secondary analyses of previously published RCTs.

The literature search was performed on December 20, 2023. Eligible RCTs were searched for in Embase, PubMed, and Cochrane Central Register of Controlled Trials (CENTRAL) using search terms concerning T2D and older patients. Search algorithms used for individual databases are presented in Supplementary File 1. Records of all studies were imported into an Endnote library, and duplicate entries were removed. The titles and abstracts of all articles were screened to identify studies potentially meeting the eligibility criteria. Next, full texts of all potentially eligible articles were reviewed. Moreover, we manually searched the reference lists of all included articles. From each of the included publications we extracted RCT characteristics (the general characteristics, the eligibility criteria, and the primary endpoints) and patient characteristics.

The search in Embase, PubMed, and Cochrane was complemented by searching the World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP; https://trialsearch.who.int/). We used the ICTRP to identify the results of trials meeting the eligibility criteria listed above, but whose results were not available in Pubmed, Embase, and Cochrane. The search algorithm for the WHO ICTRP is provided in Supplementary File 1; the platform was searched on December 21, 2023.

Study selection was performed by 2 independent reviewers (D.K. and J.B.). Data extraction was performed using a standardized Excel form by one reviewer (M.S.), and the concordance of the extracted data with the data in the included publications was performed by another reviewer (J.B.). All discrepancies between the reviewers during RCT selection and data extraction were resolved through consensus.

The review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)

standards (http://www.prisma-statement.org/?AspxAutoDetectCookieSupport=1) and was registered with Prospero (CRD42023490827). It did not involve a meta-analysis, and therefore we did not perform risk of bias assessment [16, 17].

Primary and secondary outcomes

The review had 3 coprimary outcomes: 1) Weighted mean age of RCT participants (years); 2) Proportion of patients with different extent of comorbidities among RCT participants [as determined by a validated clinical scale such as Charlson Comorbidity Index or Total Illness Burden Index (TIBI); %]; and 3) Proportion of patients with frailty among RCT participants (%). The secondary outcomes included the following: 1) The proportion of participants aged 75 years or older (%); 2) The proportion of RCTs with a subgroup analysis to compare the effects of the investigational treatment between younger and older patients (%); 3) The proportion of RCTs with an analysis to compare the effects of the investigational treatment between subgroups of patients with different levels of frailty (%); 4) The proportion of RCTs reporting the representation of participants with renal function impairment (%); 5) The proportion of RCTs with an analysis to compare the effects of the investigational treatment between subgroups of patients with different degrees of renal function impairment (%); 6) The proportion of RCTs reporting the representation of patients with comorbidities of the cardiovascular system (%); 7) The proportion of women among RCT participants (%); and 8) The proportion of RCTs with different types of primary endpoint (%).

Statistical analysis

Descriptive statistics were used to characterize the included trials. Discrete variables were reported as numbers and percentages, and continuous variables were presented as medians with ranges. The weighted mean age of RCTs participants was determined based on the following formula:

$[(m_1*n_1) +\ldots+ (m_x*n_x)]/(n_1 +\ldots+ n_x)$, where:

m_1 = mean age of participants in the first RCT

m_x = mean age of participants in the last RCT

n_1 = number of participants in the first RCT

n_x = number of participants in the last RCT

Results

General characteristics of included trials

The initial literature search yielded 12,926 trials, of which 35 met all the eligibility criteria; the PRISMA flow diagram is shown in Figure 1. List of included RCTs is presented in Supplementary Appendix 2, and their detailed characteristics are reported in Table 1. Overall, the trials enrolled 9068 participants, the median number of participants being 192 (range, 54–1173). The investigational sites were commonly located in Asia (n = 11; 31%) and North America (n = 10; 29%). The investigational drugs were mostly dipeptidyl peptidase 4 (DPP-4) inhibitors (n = 14; 39%) followed by insulin (n = 10; 29%; Tab. 1). In 23 (66%) RCTs the effects of the investigational drug were compared with another antidiabetic drug, while 12 (34%) trials included placebo controls.

The lower age limits in most trials were set at 65 (n = 16; 48%) or 60 (n = 12; 36%) years. Upper age limits were used in only 7 (21%) trials; these were within range 80–90 years (median, 85 years).

Primary endpoints

The primary endpoints used in individual RCTs are listed in Table 2. Overall, the primary endpoints (secondary outcome) frequently (n = 25; 71%) involved assessment of HbA1c concentration. In each of these the specific outcome measure was change in HbA1c concentration. In addition, in one (3%) of these trials the coprimary outcome was the proportion of patients achieving certain HbA1c concentration. In 12 (34%) RCTs the primary endpoints were related to other indices of glycemic control, especially fasting plasma glucose (n = 7; 20%; some of these trials may have had more than one primary endpoint). Only 2 (6%) trials had a composite primary endpoint based on achieving target HbA1c concentration without 'clinically significant' [18] or 'confirmed/severe' [19] hypoglycemia. In addition, in 2 (6%) trials the rate of hypoglycemia was used as a coprimary outcome measure [20]. The median timeframe for the primary endpoint assessment was 24 weeks (range, 4–144 weeks).

The results for the primary endpoints were in most cases positive; for instance, in each of the placebo-controlled RCTs the investigational drugs showed significant antidiabetic effects (Tab. 2).

Participants' characteristics

All RCTs reported the mean age of the participants, the weighted mean age being 71.4 years (coprimary outcome). However, the representation of patients aged 75 years or older was reported in only 11 (33%) RCTs; it was 1120/4100 participants (27%; secondary outcome). Nine RCTs (27%) included subgroup analyses to assess the efficacy of the investigational treatments by the age of the participants (secondary outcome); in most cases (n=8; 24%) these focused on patients aged 75 years or older. The age of the oldest participant was reported in 9 (24%) trials; it was within range 79–97 years (median, 90).

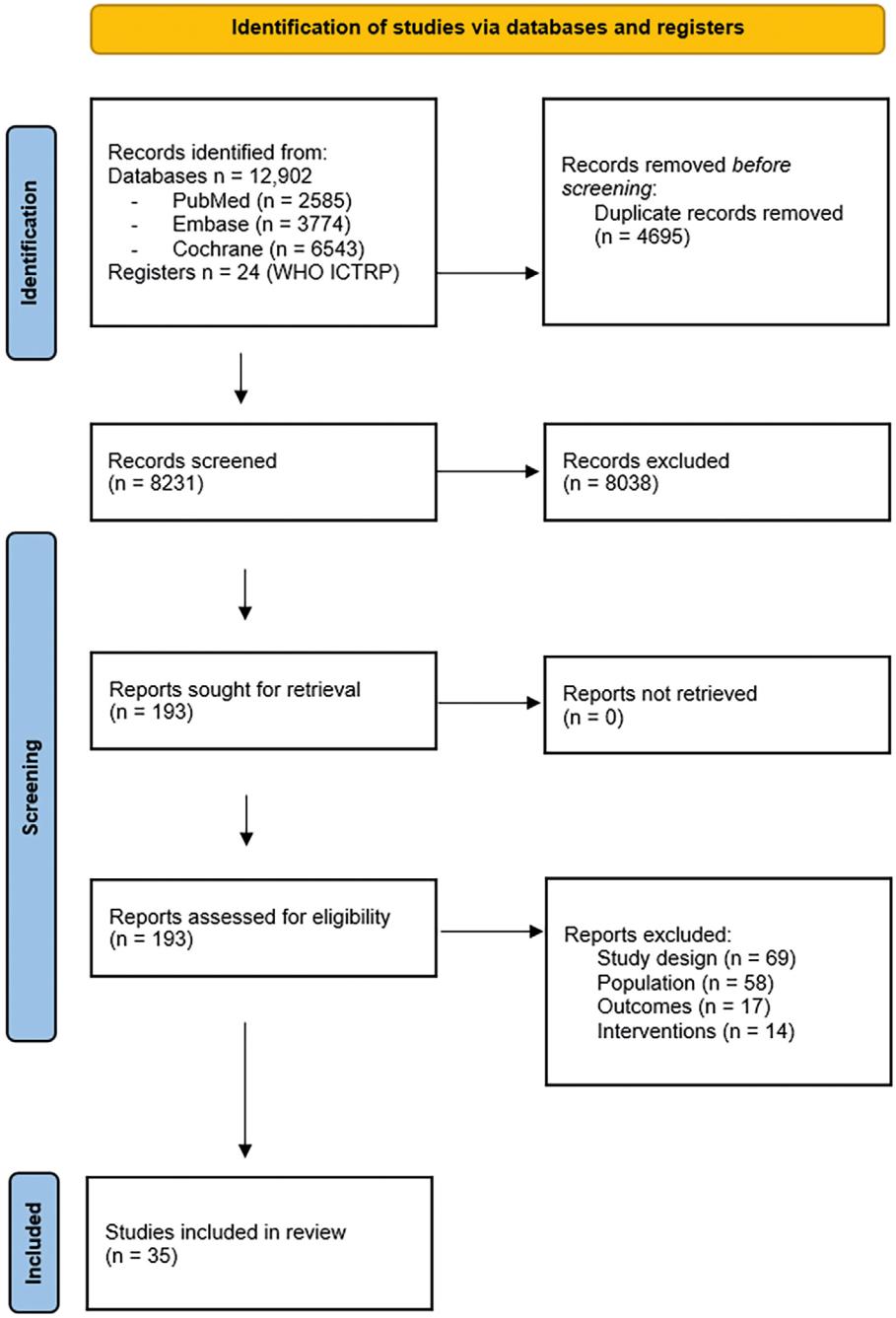

Figure 1. Selection of Randomized Controlled Trials Dedicated to Older Adults with Type 2 Diabetes

Only 2 (6%) RCTs reported the representation of patients with frailty (coprimary outcome). In the first trial 95% of the participants had frailty [18]. However, the vast majority of these individuals were patients with very mild frailty. Patients with mild and moderate frailty constituted 12.5% of trial participants. In the other RCT, the proportion of frail patients was 9% [21]; however, the investigators did not report the representation of patients with different levels of frailty. The efficacy data by the frailty status of the participants were presented by one (3%) trial [21] (secondary outcome).

The proportion of participants with different extents of comorbidities (coprimary outcome) was reported by only one (3%) RCT; the comorbidity burden in individual patients was expressed as the Total Illness Burden Index (TIBI); 35% of enrolled patients had a TIBI score of at least 5 [18]. None of the trials presented the results by the degree of patients' comorbidities (secondary outcome).

Table 1. Characteristics of Randomized Clinical Trials Dedicated to Older Patients with Type 2 Diabetes

	n	%
Investigational treatment		
DPP-4 inhibitors	14	40
Insulin	10	29
Meglitinides	3	9
Alpha-glucosidase inhibitors	2	6
Thiazolidinediones	2	6
GLP-1 agonists	1	3
SGLT2 inhibitors	1	3
Multiple	2	6
Sponsor		
Pharmaceutical industry	19	54
Non-commercial	6	17
Mixed	3	9
Undisclosed	7	20
Investigational site		
Asia	11	31
North America	10	29
Europe	5	14
Other	1	3
Transcontinental	8	23
Multicenter trials		
Yes	27	82
No	8	23

Percentages may not add up to 100% due to rounding error
DPP-4 — dipeptidyl peptidase 4; GLP-1 — glucagon-like peptide 1; SGLT2 — sodium-glucose co-transporter 2

The proportion of patients with renal function impairment was reported by 19 (55%) RCTs (secondary outcome). In most cases (n = 13; 39%) these data included the GFR value. In 9 (27%) of these, the reported parameter was the proportion of patients with different values of GFR per arm, while 4 trials (12%) presented the mean value of GFR per arm. Moreover, 5 (15%) trials provided the data on the proportion of patients with 'nephropathy' per arm, whereas the value of the creatinine clearance (CrCl) was reported in only one (3%) trial. Very few trials included a subgroup analysis to assess the effects of the investigational drug by renal function (secondary outcome); in 6 (18%) trials these analyses concerned the efficacy of the drug, while 2 (6%) trials reported the incidence of hypoglycemia by renal function.

Seventeen (52%) RCTs provided the data on different comorbidities of the cardiovascular system (secondary outcome). These mostly included ischemic heart disease (n=10; 30%) and hypertension (n=8; 24%). The quality of the reporting of these data was in many cases suboptimal. Firstly, only 11 (33%) of the trials reported the proportion of patients with cardiovascular diseases per arm; 4 (12%) RCTs presented the general proportion of patients with cardiovascular diseases in the trial; 3 (9%) RCTs presented other data on cardiovascular disease (e.g. the mean value of blood pressure); and 4 (12%) trials referred to unspecified cardiovascular diseases. The proportion of patients with cerebrovascular disease/stroke per arm was reported by only 4 (12%) trials. Also, 3967/9068 (44%) participants were women (secondary outcome).

Discussion

Most of the analyzed RCTs reported positive results for the primary endpoints. However, a very important problem that should be considered when interpreting these results is great heterogeneity of the population of older patients with T2D [8, 9]. One of the key factors that can affect the efficacy and safety of the investigational glucose-lowering treatments is frailty [9, 12]. Therefore, the representation of participants with frailty should be provided in publications reporting the results of RCTs dedicated to older adults with diabetes [15]. Unfortunately, the proportion of participants with frailty was reported in only 2 trials from our sample [18, 21]. However, it should also be noted that only 2 trials had the eligibility criteria limiting the enrollment of patients with inadequate functional status [22, 23]. Thus, most RCTs may have included a number of frail individuals, but their actual proportion was not reported.

As was the case with the frailty status, the reporting of participants' comorbidities was also in most cases inadequate. First, only one trial [18] provided the proportion of patients with different extents of comorbidities. Also, many RCTs did not report important data on specific comorbidities. For instance, information on renal function of trial participants was reported only by 49% of the RCTs. Thus, in more than half of the trials it is impossible to draw conclusions about the efficacy of the investigational treatments in patients with chronic kidney disease (CKD). This is an important problem because CKD is one of the most common comorbidities in patients with T2D including older individuals [24]. CKD in patients with diabetes can have a range of serious consequences such as risk of adverse health outcomes (including frailty), reduced quality of life, and premature mortality [25]. Furthermore, renal function is an important factor affecting the safety of glucose-lowering treatments [26].

We also showed that the reporting of the data on the participants' ages was in many cases suboptimal. While all trials reported the mean age of the participants, only 31% of the RCTs provided the proportion of patients aged 75 years or older. Subgroup analyses assessing

Table 2. Primary Endpoints and Results of Randomized Controlled Trials Dedicated to Older Patients with Type 2 Diabetes

Study[1]	Drug name	Control	Primary endpoint (unit)	Timeframe for primary endpoint assessment (weeks)	Results[2]
Araki et al. (2012)	Multiple	Multiple	Incidence of fatal and non-fatal events [%][3]	144	No significant difference between the groups ($p > 0.05$)
Bae et al. (2022)	Teneligliptin	Placebo	HbA1c change from baseline [%]	12	Placebo-adjusted mean change in HbA1c with teneligliptin −0.76% ($p < 0.001$)
Barnett et al. (2013)	Linagliptin	Placebo	HbA1c change from baseline [%]	24	Placebo-adjusted mean change in HbA1c with linagliptin −0·64% ($p < 0.0001$)
Barzilai et al. (2011)	Sitagliptin	Placebo	HbA1c change from baseline [%]	24	Placebo-adjusted mean change in HbA1c with sitagliptin −0.7% ($p < 0.001$)
Chien et al. (2011)	Sitagliptin	Multiple	HbA1c change from baseline [%]	24	Mean change in HbA1c −1.14% with sitagliptin and 0.0% in control ($p < 0.0001$)
Coscelli et al. (1995)	Insulin (pens)	Insulin (syringes)	Rate of hypoglycemia [number of episodes/patient/week]	12	No statistically significant difference between the groups ($p > 0.05$)
Gao et al. (2020)	Linagliptin + metformin	Metformin	HbA1c change from baseline [%]; FPG change from baseline [mmol/L]	12	Mean change in HbA1c −2.42% with linagliptin+metformin and −1.26% in control ($p < 0.05$); mean change in FBG −4.19 mmol/L with linagliptin and −2.48 mmol/L in control ($p < 0.05$)
Hartley et al. (2015)	Sitagliptin	Glimepiride	HbA1c change from baseline [%]	30	Mean change in HbA1c −0.32% with sitagliptin and −0.51% with glimepiride (non-inferiority of sitagliptin relative to glimepiride)
Heller et al. (2018)	Multiple (glucose-dependent treatments)	Multiple (non-glucose-dependent treatments)	Achieving individualized HbA1c target without clinically significant hypoglycemia [%]	24	No statistically significant difference between the groups (64.5% vs. 54.9%; $p = 0.19$)
Herman et al. (2005)	Insulin (CSII)	Insulin (MDI)	HbA1c change from baseline [%]	48	Mean change in HbA1c −1.7% with insulin CSII and −1.6% with insulin MDI ($p = 0.20$)
Herz (2002)	Insulin	Glyburide	HbA1c change from baseline [%]; rate of hypoglycemia [number of episodes/patient/30 days]	16	Mean change in HbA1c −1.14% with insulin and −0.36% with glyburide ($p = 0.001$); no statistically significant difference in hypoglycemia rate between insulin and glyburide ($p = 0.07$)
Johnson et al. (2011)	Insulin (MDI)	Insulin (CSII)	Glycemic variability[4]	48	Comparable improvement in both groups
Johnston et al. (1998)	Miglitol	Placebo	HbA1c change from baseline [%]	48	Placebo-adjusted mean change in HbA1c −0.41% ($p = 0.01$)
Josse et al. (2003)	Acarbose	Placebo	HbA1c change from baseline [%]	48	Placebo-adjusted mean change in HbA1c −0.6% ($p < 0.05$)
Kumar et al. (1998)	Troglitazone	Placebo	FPG change from baseline [mmol/L]	12	Mean placebo-adjusted FPG change −2.6 mmol/L to −3.2 mmol/L with troglitazone (depending on dose; $p < 0.001$)
Ledesma et al. (2019)	Linagliptin	Placebo	HbA1c change from baseline [%]	24	Placebo-adjusted mean change in HbA1c −0.63% ($p = 0.0001$)
Liu et al. (2022)	Repaglinide+ metformin	Metformin	FPG change from baseline [mmol/L]	12	Mean FPG change −3.15 mmol/L with repaglinide+metformin and −2.54 mmol/L in control ($p = 0.0007$)
Machry et al. (2021)	Insulin (pens)	Insulin (syringes)	HbA1c change from baseline [%]	24	Mean change in HbA1c −1.95% for pens and −1.05 for syringes ($p = 0.101$)
Meneilly et al. (2016)	Lixisenatide	Placebo	HbA1c change from baseline [%]	24	Placebo-adjusted mean change in HbA1c −0.51% ($p < 0.0001$)

Nagao et al. (2023)	Sitagliptin	Multiple	HbA1c change from baseline [%]	48	Mean change in HbA1c −0.61% with sitagliptin and −0.29% in control ($p < 0.01$)
Omori et al. (2018)	Repaglinide	Sulfonylureas	HbA1c change from baseline [%]	12	Mean change in HbA1c −0.07% with repaglinide and 0.02% in control ($p > 0.05$)
Papa et al. (2008)	Insulin	Multiple	HbA1c change from baseline [%]	24	Mean change in HbA1c −1.5% with insulin and −0.6% in control ($p = 0.38$)
Pasquel et al. (2015)	Insulin	Multiple	Mean fasting and daily plasma glucose [mg/dL]	26	Mean FPG 131 mg/dL with insulin and 123 mg/dl in control ($p = 0.06$); mean daily plasma glucose 163 mg/dL with insulin and 138 mg/dL in control ($p < 0.001$)
Ritzel et al. (2018)	Insulin (300 units/ml)	Insulin (100 units/ml)	HbA1c change from baseline [%]	26	Mean change in HbA1c −0.89% with higher insulin dose and −0.91% with lower insulin dose ($p < 0.01$)
Rosenstock et al. (2006)	Rosiglitazone	Placebo	Proportion of participants reaching FPG≥10 mmol/l [%]	96	Primary endpoint reached in 2% of participants receiving rosiglitazone and 28.7% of participants from control group ($p < 0.0001$)
Rosenstock et al. (2013)	Alogliptin	Glipizide	HbA1c change from baseline [%]	52	Mean change in HbA1c −0.14% for alogliptin and −0.09% for glipizide (non-inferiority of alogliptin relative to glipizide)
Schernthaner et al. (2015)	Saxagliptin	Glimepiride	Proportion of participants with HbA1c < 7% without confirmed/severe hypoglycemia [%]	52	Primary endpoint achieved in 37.9% of participants receiving saxagliptin and 38.2% of participants from control group ($p = 0.94$)
Schwarz et al. (2008)	Nateglinide	Placebo	HbA1c change from baseline [%]	12	Placebo-adjusted mean change in HbA1c with linagliptin −0·5% ($p = 0.004$)
Schweizer et al. (2009)	Vildagliptin	Metformin	HbA1c change from baseline [%]	24	Mean change in HbA1c -0.64% with vildagliptin and −0.75% with metformin (non-inferiority of vildagliptin relative to metformin)
Strain et al. (2013)	Vildagliptin	Placebo	Proportion of participants reaching investigator-defined HbA1c target [%]; HbA1c change from baseline [%]	24	Proportion of participants reaching HbA1c target 52.6% and 27% with vildagliptin and in control, respectively ($p < 0.0001$); placebo-adjusted mean change in HbA1c with vildagliptin-0.6% ($p < 0.0001$)
Sun et al. (2014)	Insulin + acarbose	Insulin	FPG change from baseline [mmol/l]; 2hPBG change from baseline [mmol/l]; HbA1c change from baseline [%]	32	Mean change in FBG −1.94 mmol/L with insulin+ acarbose and −1.75 mmol/L in control ($p < 0.05$); mean change in 2hPBG −10.56 mmol/L with insulin + acarbose and 10.16 mmol/L in control ($p < 0.05$); mean change in HbA1c −1.54% with insulin + acarbose and −1.39% in control ($p < 0.05$)
Terauchi et al. (2017)	Sitagliptin	Glimepiride	HbA1c change from baseline [%]	52	Mean change in HbA1c −0.66% with sitagliptin and −0.77% with glimepiride (non-inferiority of sitagliptin relative to glimepiride)
Wang et al. (2015)	Saxagliptin	Acarbose	HbA1c change from baseline [%]; FPG change from baseline [mmol/L]; SDBG and LAGE change from baseline [mmol]	40	Mean change in HbA1c −0.82% with saxagliptin and −0.7% in control ($p = 0.04$); mean change in FBG −2.21 mmol/L with saxagliptin and −1.99 mmol/L in control ($p = 0.02$); mean change in SDBG −0.11 with saxagliptin and −0.12 in control ($p > 0.05$); mean change in LAGE −1.95 mmol/L with saxagliptin and −2.3 mmol/L in control ($p > 0.05$)
Warren et al. (2004)	Insulin (preprandial)	Insulin (postprandial)	Mean plasma glucose concentration during 4-h meal test [mg/dL]	4	Mean plasma glucose 161 mg/dL with postprandial insulin and 153 mg/dl with preprandial insulin ($p > 0.05$)
Yabe et al. (2023)	Empagliflozin	Placebo	HbA1c change from baseline [%]	52	Placebo-adjusted mean change in HbA1c with empagliflozin −0.57% ($p < 0.0001$)

[1]Full bibliographic details for each study are provided in Supplementary file 2; [2]Results for the primary endpoints; [3]Including but not limited to ACS, stroke, coronary revascularization, and death due to renal failure; [4]Glycemic variability in this trial was determined based on several different parameters. hPBG — 2-h postprandial blood glucose; ACS — acute coronary syndrome; CSII — continuous subcutaneous insulin infusion; FPG — fasting plasma glucose; LAGE — largest amplitude of glycemic excursions; MDI— multiple daily injection; SDBG — standard deviation of blood glucose

the efficacy of the investigational treatments in these patients were presented in 27% of the publications. This is an important problem because patients aged 75 years and older have been particularly underrepresented in registrational trials of glucose-lowering treatments [27]. Furthermore, according to recent estimates, the prevalence of diabetes is growing rapidly in individuals aged over 75 years [4]. Therefore, such patients should be particularly encouraged to participate in clinical trials dedicated to geriatric patients, and the data on their representation should be reported in publications.

Overall, inadequate reporting of the key participants' characteristics hinders assessment of the generalizability of RCT results to 'real-world' geriatric patients with T2D, many of whom are older than 75 years and have multiple comorbidities including CKD, and frailty.

In most RCTs the primary endpoint was related to HbA1c. While HbA1c concentration is an established outcome measure in clinical trials of glucose-lowering treatments, other outcomes may be more relevant to RCTs dedicated to older patients. In particular, a composite endpoint involving reduction of HbA1c concentration without significant hypoglycemia should be considered in this context [15]. This results from the fact that hypoglycemia occurs more frequently in older adults and can have serious consequences [28]. Unfortunately, only 2 of the analyzed RCTs [18, 19] included assessment of hypoglycemia as a component of the primary endpoint. Admittedly, the investigational drugs assessed in some trials (e.g., linagliptin or sitagliptin) did not have high potential to induce hypoglycemia. However, hypoglycemia was not used as a component of the primary endpoint also in trials of insulin (n = 10) or oral glucose-lowering drugs with a relatively high potential for causing hypoglycemia (e.g., gliclazide).

We propose several recommendations that will enable the investigators to improve the generalizability of RCTs dedicated to older patients with T2D. Firstly, the participants should be better characterized regarding frailty and comorbidities. Apart from providing the data on common comorbidities occurring in older adults (e.g., CKD and diseases of the cardiovascular system), ideally the comorbidity burden in individual participants should be assessed at baseline and expressed using a validated measure. Given the importance of both frailty and comorbidities to older patients with T2D, subgroup analyses should be performed to investigate (at least preliminarily) how these affect the efficacy and safety of the investigational treatments. Moreover, in view of the importance of hypoglycemia to older patients with diabetes, it should be used more frequently as a component of a composite outcome along with reduction in HbA1c.

The strength of our study is that it is the first to provide a comprehensive analysis of RCTs dedicated to older persons with T2D. We show significant shortcomings of most trials, which may provide a starting point for designing future RCTs whose generalizability will be easier to evaluate. The main limitation is that we focused on RCTs dedicated to older adults and did not assess other types of studies (e.g., 'real-world' studies and secondary analyses of RCTs enrolling both younger and older patients) that may also provide important insights into the efficacy and the safety of glucose-lowering treatments. These should be analyzed in future systematic reviews. Another limitation is that we used a strict cut-off value of the participants age (60 years); therefore, some trials enrolling a substantial proportion of older patients may have been excluded from our review.

Conclusions

Most of the analyzed RCTs failed to report the key participants' characteristics, which are essential to translate their results into optimal clinical care of older patients with T2D. The recommendations formulated in this article will aid in achieving the full potential of clinical trials dedicated to older patients.

Article information

Supplementary material

Supplementary materials for this article can be found at https://journals.viamedica.pl/clinical_diabetology/article/view/100313.

Funding

This publication was prepared without any external source of funding.

Author contribution

All authors made substantial contributions to the conception and design, acquisition of data, or analysis and interpretation of data, were involved in drafting the article or reviewing it critically for important intellectual content, and approved the version to be published.

Conflict of interest

The authors declare no conflict of interest.

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