Improvement of glycemic control in type 2 diabetes: A systematic review and meta-analysis of randomized controlled trials

Matteo Monami [a,*], Riccardo Candido [b], Basilio Pintaudi [c], Giovanni Targher [d], Edoardo Mannucci [a] on behalf of the SID-AMD joint panel for Italian Guidelines on Treatment of Type 2 Diabetes[1]

[a] *Diabetology, Careggi Hospital and University of Florence, Italy*
[b] *Diabetes Centre District 3, Azienda Sanitaria Universitaria Integrata di Trieste, Via Puccini 48/50, 34100, Trieste, Italy*
[c] *SSD Diabetes Unit, Niguarda Ca' Granda Hospital, Milan, Italy*
[d] *Endocrinology, Diabetes and Metabolism, University of Verona, Italy*

Abstract *Aim:* Different guidelines provide similar, but not identical, therapeutic targets for HbA1c in type 2 diabetes. These targets can also depend from the different pharmacological strategies adopted for intensifying glycemic control.

Data synthesis: This meta-analysis includes randomized trials adopting any pharmacological regimen for intensifying glycemic control in T2DM (versus standard of care/placebo), with a trial duration ≥2 years and a between-group HbA1c difference≥0.5%. The primary outcome was to assess the effects of the improvement of glycemic control on major cardiovascular events (MACE), ocular and renal complications, and severe hypoglycemia. Mantel-Haenszel odds ratios (MH−OR) with 95% Confidence Intervals were calculated for all the outcomes considered.

We included 13 trials fulfilling the inclusion criteria. The improvement of glycemic control was associated with a lower risk of MACE (MH−OR:0.89 [95%CI 0.85−0.94]) and renal adverse events (MH−OR 0.73 [0.65−0.82]), but not all-cause mortality (MH−OR 0.95 [0.88−1.01]) and ocular adverse complications (MH−OR 0.94 [0.72−1.22]). For glucose-lowering drugs inducing hypoglycemia, a protective effect on the risk of microvascular complications, but not of MACE and all-cause mortality, was observed only for HbA1c ≤ 48 mmol/mol, but with higher risk of severe hypoglycaemia (MH−OR 2.72 [1.79−4.13]). Drugs not inducing hypoglycaemia were associated with a reduction of MACE, renal adverse events, and all-cause mortality, for HbA1c< 7% (no data for lower targets).

Conclusions: The present meta-analysis show that the improvement of glycemic control with drugs not inducing hypoglycemia is associated with a reduction in the risk of long-term chronic vascular and renal complications, and all-cause mortality.

* Corresponding author. Azienda Ospedaliero-Universitaria Careggi, Largo Brambilla 3, 50134, Florence, Italy.
E-mail address: matteo.monami@unifi.it (M. Monami).

[1] The Panel is composed of: Edoardo Mannucci; Riccardo Candido; Basilio Pintaudi; Giovanni Targher, Lina Delle Monache; Marco Gallo; Andrea Giaccari; Maria Luisa Masini; Fulvia Mazzone; Gerardo Medea; Marina Trento; and Giuseppe Turchetti.

Introduction

Different scientific guidelines provide similar, but not identical, therapeutic targets for hemoglobin A1c (HbA1c) levels in people with type 2 diabetes (T2DM). For example, the American Diabetes Association guidelines [1] recommend pursuing and maintaining HbA1c levels below 7% (<53 mmol/mol). Conversely, the National Institute for Clinical Excellence guidelines [2] recommend a HbA1c target <6.5% (<48 mmol/mol), if attainable with drugs not inducing hypoglycemia, or <7% (<53 mmol/mol) when using insulin therapy and/or sulfonylureas. These different recommendations can be the result of differences in methods for guideline development, established goals and priorities, or choice of evidence on which clinical decisions should be based.

For the latter point, information on desirable HbA1c targets can be derived either from observational cohort studies [2], or from randomized clinical trials (RCTs). The use of observational cohort studies allows the collection of large amounts of data, but it implies the risk of confounding bias. On the other hand, RCTs, although providing more reliable results, have the disadvantage of excluding a relevant fraction of the target population, such as very old patients or those with multiple comorbidities.

The present meta-analysis was performed in the process of developing the Italian guidelines for the treatment of T2DM. Those guidelines, which have been promoted by the Italian Society of Diabetology (SocietàItaliana di Diabetologia, SID) and the Italian Association of Clinical Diabetologists (Associazione Medici Diabetologi, AMD), are being developed for the inclusion in the Italian National Guideline System (INGS), designed as a standard reference for clinical practice in Italy. In order to be included in the INGS, guidelines need to be formulated following the Grading of Recommendations Assessment, Development and Evaluation (GRADE) procedure, and to obtain a high rating on the Appraisal of Guidelines for Research and Evaluation (AGREE) instrument [3].

The definition of optimal HbA1c targets for T2DM patients treated either with or without drugs inducing hypoglycemia was identified by the guideline Panel as a relevant clinical issue. The critical outcomes defined for answering this question were the occurrence of major cardiovascular adverse events (MACE), microvascular complications, and mortality, as well as the occurrence of severe hypoglycaemia only for glucose-lowering drugs inducing hypoglycemia, i.e. sulfonylureas and insulin [4–6]. RCTs were chosen as the source of information for the aforementioned clinical outcomes. The present meta-analysis was performed for providing the appropriate evidence based for the formulation of recommendations about intensification of glycemic treatment in people with T2DM.

Methods

This meta-analysis is reported following the criteria of Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [7].

Search strategy and inclusion criteria

This meta-analysis has been registered on Open Science Framework registry (osf.io/gn4mf) [8].

A Medline, Embase, and Cochrane Library search, up to December 1st, 2020, was performed using the search string reported in Supplementary Materials (Table 2S). References of retrieved articles were manually searched for further studies. To search also the so-called "grey literature", an attempt to retrieve further articles was made by searching the following databases: Bielefeld Academic Search Engine (https://www.base-search.net/) and Open Grey (http://www.opengrey.eu/).

Search terms included

T2DM, cardiovascular, microvascular, macrovascular, retinopathy, nephropathy, and mortality. The search strategy is shown in Table 1S (Supplementary Materials).

We included all RCTs performed on patients with T2DM, adopting any pharmacological regimen for intensifying glycemic control, fulfilling the following criteria:

1) duration of treatment ≥2 years
2) between-group HbA1c difference ≥0.5% (≥6 mmol/mol)
3) primary or secondary endpoints, including at least one of the following events:
   a. Major cardiovascular events (MACE): nonfatal myocardial infarction, nonfatal stroke, and cardiovascular mortality
   b. Nonfatal myocardial infarction and/or nonfatal stroke and/or cardiovascular mortality
   c. Ocular adverse events: defined as a composite of requirement for retinal photocoagulation therapy or vitrectomy, development of proliferative retinopathy (new blood vessels on the disc or elsewhere, vitreous hemorrhage, preretinal hemorrhage, or fibrous proliferations on the disc or elsewhere), or progression of retinopathy by at least three steps on the Early Treatment of Diabetic Retinopathy Study (ETDRS) severity scale
   e. Renal adverse events: defined as a composite of end-stage kidney disease (dialysis or renal transplantation), renal death, development of an estimated glomerular filtration rate (e-GFR) of less than 30 mL/min/1·73 m^2 (calculated on at least two consecutive visits post-randomization using the Modification of Diet in Renal Disease [MDRD]study equation), or development of overt diabetic nephropathy (normoalbuminuria or microalbuminuria to sustained macroalbuminuria— i.e., an albumin-to-creatinine ratio>300 mg albumin per gram of creatinine recorded on at least two consecutive visits post-randomization)
   f. Severe hypoglycemia: defined as an episode requiring third-party assistance.

Only human studies were included, whereas no language or date restriction was imposed. Trials on diabetes other than type 2 were also excluded.

Outcomes

The primary outcome of the present meta-analysis was to assess the effects of improvement of glycemic control in comparison with standard care on the risk of MACE, eye and kidney adverse events, or severe hypoglycemia. Secondary outcomes included the risk of individual components of MACE and all-cause mortality.

Study selection

ENDNOTE X9 literature management software was used to manage the literature search records. These searches and the selection of studies were independently performed by two authors (M.M and E.M.) and conflicts resolved by a third investigator (R.C.).

Data extraction

Summary estimates of the variables of interest were extracted from the principal publication, when available; whenever needed, secondary publications and clinicaltrials.gov registry were used for retrieval of missing tion, in the hierarchical order reported above. Data extraction was performed independently by two authors (E.M. and M.M.), and conflicts resolved by a third investigator (R.C.). The following parameters/information were extracted: first author, publication year, National Clinical Trial (NCT) number or other registration identifiers/acronyms, investigational drugs and comparisons, sample size, duration of the trial, age, baseline body mass index (BMI), and HbA1c levels.

Data on HbA1c levels, and rates of MACE, ocular and renal adverse events, and severe hypoglycemia at the endpoint were also extracted.

Risk of bias assessment

The risk of bias was assessed using the Cochrane risk of bias tool forRCTs [9]. The risk of bias was assessed in seven specific domains: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other bias. The results of these seven domains were graded as 'low' risk of bias, 'high' risk of bias, or 'uncertain' risk of bias.

The assessment of risk of bias was performed independently by two reviewers (M.M. and E.M.), and conflicts were resolved by a third reviewer (R.C.).

Data analysis

Mantel-Haenszel odds ratios (MH−OR) with 95% confidence intervals (95% CI) were calculated for all the outcomes considered, on an intention-to-treat basis, excluding RCTs with zero clinical events, using a random-effects model. The fixed-effect model was used only for the sensitivity analyses, due to the intrinsic clinical heterogeneity of the eligible RCTs.

Separate analyses were performed for subgroups of RCTs with different mean HbA1c levels in the intensified treatment arm. In addition, separate subgroup analyses were also performed on RCTs that used or not hypoglycemia-inducing drugs (i.e., insulin, sulfonylureas or glinides) for the intensification of therapy in the intensified regimen arm.

The study heterogeneity was assessed using the I^2-statistics. To estimate the existence of possible publication/disclosure biases, we examined funnel plots for risk of both 3-point MACE and all-cause mortality. The Egger's regression test was not calculated, because its sensitivity appears to be low when the number of studies included in a meta-analysis is small [10].

The GRADE methodology [3]was used to assess the overall quality of the eligible RCTs, using the GRADEpro GDT software (GRADEpro Guideline Development Tool. McMaster University, 2015. Available from https://gradepro.org/cite/gradepro.org).

Analyses were performed using Review Manager (RevMan), Version 5.3 (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014).

Results

The trial flow summary is reported in Fig. 1S.A total of 5310 studies were initially identified after removing duplicate publications. The principal characteristics of the 13 RCTs fulfilling the inclusion criteria were reported in Table 1. The UKPDS 33 and 34 were considered as a single trial in the principal analysis and therefore analyses were conducted on 12 RCTs. The 12 RCTs included in the meta-analysis enrolled a total of 42,589 and 36,527 patients with T2DM in the intensive and standard therapy arms, respectively. None of these eligible RCTs enrolled patients over 75 years of age. The overall quality of the included RCTs was generally high for all items of the Cochrane tool (Fig. 2S).

Out of 12RCTs, 11, 12,11, 11, 10, 8, 7, and 11 reported information on the risk of MACE, all-cause mortality, nonfatal myocardial infarction, nonfatal stroke, cardiovascular mortality, ocular adverse events, renal adverse events, or severe hypoglycemia.

Risk of 3-point MACE

All RCTs reported detailed information on 3-point MACE, with the exception of one RCT [11], which was therefore excluded from the primary analysis. Funnel plot (Fig. 3S) did not reveal any relevant publication bias.

As shown in Fig. 1, intensified glycemic treatment was associated with a significantly lower risk of 3-point MACE (MH−OR 0.89 [95% CI 0.85−0.94]), with evidence of a low heterogeneity (I^2: 24%). This result was further confirmed in a sensitivity analysis using a fixed-effect model (MH−OR 0.90 [0.86−0.94]).

Intensification of glycemic control was associated with a significant reduction of MACE in RCTs that used drugs not inducing hypoglycaemia (MH−OR: 0.85 [0.78−0.93];

Table 1 Baseline characteristics of the RCTsincluded in the meta-analysis.

Trial	Investigational drug	Sample size (n)	Comparator	Sample size (n)	Trial dur. (years)	Age (years)	$HbA1_c$ (%)	BMI (kg/m^2)	HbA1c end-(%)	Severe hypos (ID/C)
ACCORD [32]	Multiple drugs	5128	Multiple drugs	5123	3.5	62	8.3	32.2	6.4	830/261
ADVANCE [16]	Gliclazide	5571	Multiple drugs	5569	5.0	66	7.5	28.0	6.5	150/81
CANVAS [31]	Canagliflozin	5795	Placebo	4345	5.7	63	8.2	32.0	8.0	NR/NR
EXSCEL [30]	Exenatide LAR	7356	Placebo	7396	3.2	62	8.0	31.7	7.7	247/219
KUMAMOTO [11]	Insulin	52	Insulin	50	6.0	49	9.1	20.5	7.0	2/1
PROACTIVE [33]	Pioglitazone	2605	Placebo	2633	2.9	62	7.8	30.8	7.0	29/16
REWIND [29]	Dulaglutide	4949	Placebo	4952	5.4	66	7.3	32.3	6.9	64/74
SUSTAIN-6 [28]	Semaglutide	1648	Placebo	1649	2.1	65	8.7	32.8	7.3	369/350
UKPDS 33–34 [12,13]	Multiple drugs	3071	None	1138	11,1	54	6.2	27.5	7.0	301/13
VACSDM [34]	Insulin	75	Insulin	78	2.2	60	9.3	31.0	7.1	5/2
VADT [14]	Multiple drugs	892	Multiple drugs	8990	6.3	60	9.4	31.3	6.9	187/90
VERTIS-CV [27]	Ertugliflozin	5499	Placebo	2745	3.5	64	8.2	32.0	7.6	284/162

ID: Investigational Drug; C: Comparator; dur.: duration; end.: endpoint; hypos: hypoglycaemia; BMI: Body Mass Index. Multiple drugs: including sulfonylureas/glinides and/or insulin.

Fig. 4S), but only with a marginal reduction of MACE in those using drugs potentially inducing hypoglycaemia (MH–OR: 0.92 [0.84–1.00], p = 0.050; Fig. 5S). The risk reduction of MACE was statistically significant in RCTs with mean HbA1c levels in the intensified treatment arm 7.1–7.5 and 6.6–7.0%, but not in those with HbA1c ≤ 6.5% (Fig. 6S). With drugs not inducing hypoglycemia, a significant reduction of MACE was observed in RCTs in which mean HbA1c in the intensified treatment arm was 7.1–7.5 and 6.6–7.0%; no RCTs with those drugs were available reporting HbA1c in the intensified arm below 6.6% (Fig. 4S). No significant effect on risk of MACE of drugs inducing hypoglycemia was observed in different subgroups of RCTs divided for mean HbA1c in the intensified treatment arm (Fig. 6S).

Risk of nonfatal myocardial infarction, stroke, and cardiovascular mortality

Cases of nonfatal myocardial infarction were 1985 and 1811 in intensive treatment and comparator arms, respectively. As shown in Fig. 7S, intensive treatment was associated with a significant reduction of nonfatal myocardial infarction (MH–OR 0.90 [0.84–0.96]). I^2-statistics did not show any significant heterogeneity across the studies (I^2: 5%).

Cases of nonfatal stroke were 1161 and 1086 in intensive treatment and comparator arms, respectively. Fig. 8S showed a significant reduction of nonfatal stroke in patients allocated in the intensive treatment arm (MH–OR 0.89 [0.81–0.98]).

Cardiovascular deaths were 2011 and 1,718 in intensive treatment and comparator arms, respectively. The intensification of glycemic control was associated with a borderline (non-significant) reduction of cardiovascular mortality (MH–OR0.93 [0.85–1.01]; p = 0.08; I^2: 29%), as shown in Fig. 9S.

Risk of all-cause mortality

As shown in Fig. 10S, no significant publication bias was detected. Total deaths were 3317 and 2812 in intensive and

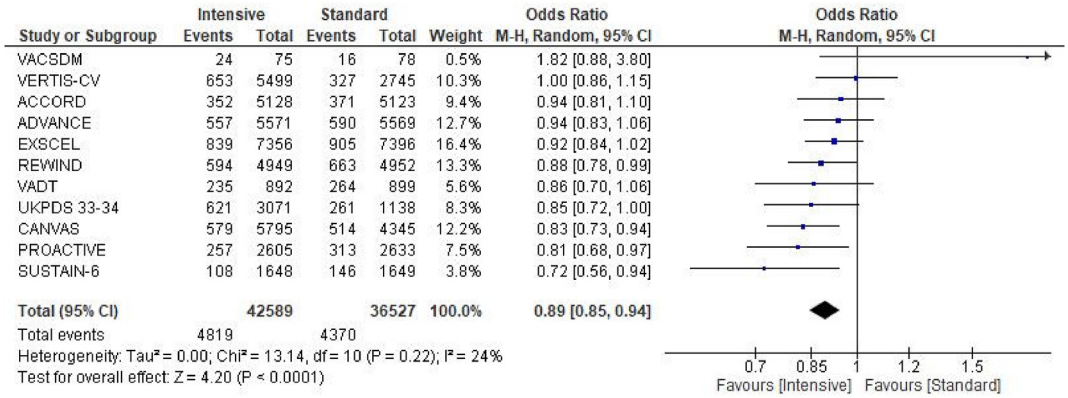

Figure 1 Risk of major adverse cardiovascular events (MACE) in T2DM patients allocated in the intensive versus standard care arms (MH–OR, 95% CI: Mantel-Haenzel Odds Ratio, with 95% of Confidence Intervals).

standard care arms, respectively. As shown in Fig. 2, intensification of glycemic control was associated with a borderline (non-significant) reduction of all-cause mortality (MH−OR 0.95 [0.88−1.01], p = 0.10), which reached statistical significance in a sensitivity analysis using a fixed-effect model (MH−OR 0.94 [0.89−0.99], p = 0.01). I^2-statistics (I^2: 29%) showed a moderate heterogeneity across the studies. In RCTs with drugs not inducing hypoglycemia, the intensification of treatment was associated with a significant reduction of all-cause mortality (Fig. 11S), whereas no significant difference was observed in RCTs with hypoglycemia-inducing drugs (Fig. 12S). Intensification of treatment was associated with a significant reduction of all-cause mortality in RCTs in which mean HbA1c in the intensified regimen was 7.6−8%, whereas no statistically significant effects were observed in other HbA1c categories (Fig. 13S).

Risk of ocular and renal adverse events

Figs. 14S and 15S did not show any relevant publication bias. The intensification of glycemic control did not significantly reduce the risk of ocular adverse events in comparison with standard care, as shown in Fig. 3 panel A (MH−OR 0.94 [0.72−1.22], I^2: 78%); whereas a significant reduction in favour of intensive treatment was observed for renal adverse events (MH−OR 0.73 [0.65−0.82], I^2: 27%), which was further confirmed in a sensitivity analysis, using a fixed-effect model (MH−OR: 0.74 [0.68−0.81]).

However, the reduction of ocular adverse events was statistically significant in RCTs with mean HbA1c in the intensified treatment arm≤6.5% (Fig. 16S). When analysing separately RCTs with drugs not inducing hypoglycemia, no significant reduction was observed in the risk of ocular adverse events for any HbA1c subgroup; no RCT with those drugs was available reporting HbA1c in the intensified arm below 6.6% (Fig. 17S). A significant reduction of the risk of ocular adverse events with the use of drugs inducing hypoglycemia was observed only in RCTs with mean HbA1c in the intensified treatment arm≤6.5% (Fig. 18S). Conversely, the reduction of renal adverse events in the intensified glycemic treatment arm was significant across all HbA1c targets (Fig. 19S); similar results were obtained when considering only RCTs using hypoglycemia-inducing agents (Fig. 21S), whereas in RCTs using drugs not inducing hypoglycaemia a significant reduction of the risk of kidney adverse events was observed only for HbA1c levels between 7.6 and 8.0% (Fig. 20S).

Risk of severe hypoglycemia

Improvement of glycemic control was associated with a significantly higher risk of severe hypoglycaemia in comparison with standard care (MH−OR 1.84 [1.20, 2.82], p = 0.005; I^2: 96%). The difference was significant in trials using hypoglycemia-inducing agents for intensification of treatment (MH−OR 2.72 [1.79−4.13], Fig. 22S), with evidence of high heterogeneity (I^2: 89%); this association achieved a statistical significance only in RCTs with HbA1c in the intensified arm ≤ 6.5%, but not 6.6%−7.5% (Fig. 22S). Conversely, no significant increase of severe hypoglycemia was observed in trials with drugs not inducing hypoglycaemia (MH−OR 1.03 [0.88, 1.20], Fig. 23S), irrespective of endpoint HbA1c levels.

Quality of evidence

Using the GRADE algorithm [3], the overall quality of evidence for risk of MACE, all-cause mortality, renal and ocular adverse events, or severe hypoglycaemia is reported in Tables 4S and 5S The results were subdivided on the basis of the glycemic targets and the type of glucose-lowering drug used (inducing or not inducing hypoglycemia).

Discussion

Specifically designed long-term RCTs [12−16] had already shown that the improvement of glycemic control in T2DM is associated with a significant reduction in the risk of development and progression of microvascular complications. Although individual RCT data did not reach statistical

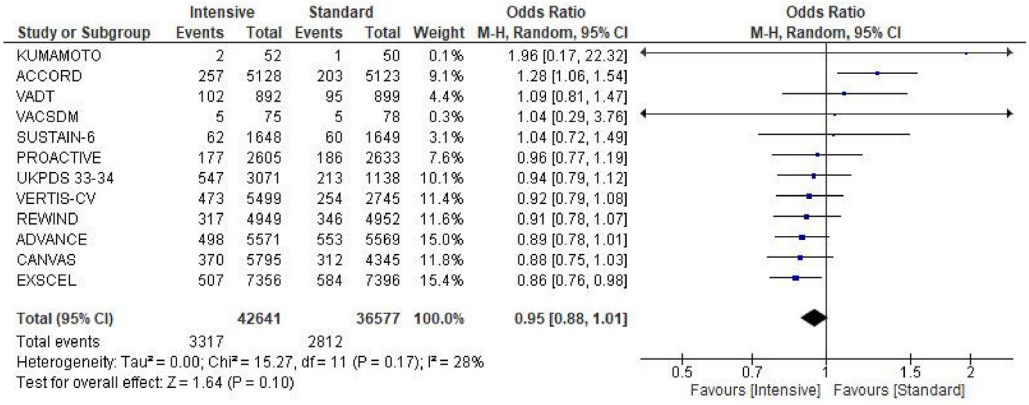

Figure 2 Risk of all-cause mortality in T2DM patients allocated in the intensive versus standard care arm (MH−OR, 95% CI: Mantel-Haenzel Odds Ratio, with 95% of Confidence Intervals).

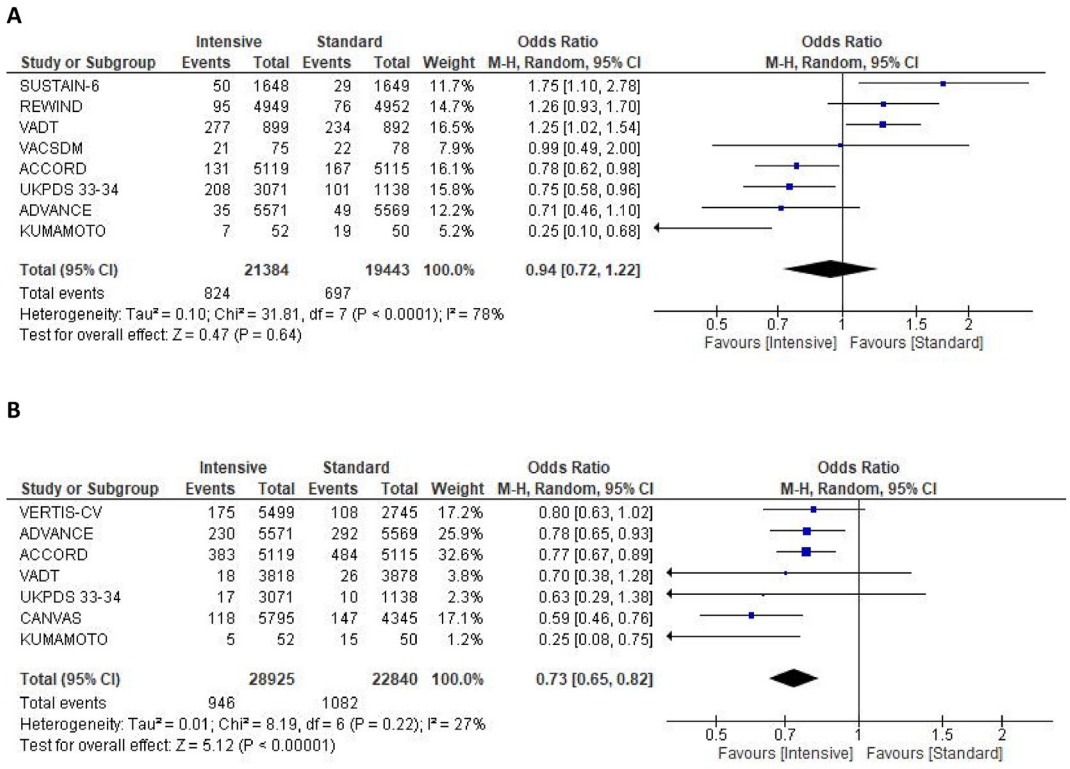

Figure 3 Risk of ocular (panel A) and renal adverse events (panel B) in T2DM patients allocated in the intensive versus standard care arms (MH—OR, 95% CI: Mantel-Haenzel Odds Ratio, with 95% of Confidence Intervals).

significance, the combined analysis of these same trials had also shown a significant reduction of MACE, with no effect on all-cause mortality [17]. More recently, a large number of cardiovascular outcome trials performed for regulatory requirements provided additional data on the effect of the improvement of glycemic control on mortality, MACE and other chronic vascular complications of diabetes. In fact, although many recent RCTs were designed to verify the cardiovascular safety of newer glucose-lowering drugs, minimizing between-group differences in HbA1c, in some of those RCTs the actual difference in glycemic control between the active treatment and placebo arms was remarkable.

When considering all available RCTs, we found that the improvement of HbA1c determines a significant reduction in the risk of both micro- and macro-vascular complications (including also MACE), with no effect on all-cause mortality risk. This result confirms the findings of previous meta-analyses of patient-level [17] and trial-level [18]data, but on a much larger data set.

The effect of the improvement of glycemic control on long-term clinical outcomes depends, at least partly, on the strategies adopted for such intensification. It is quite obvious that the risk of hypoglycemia is higher with insulin therapy or insulin secretagogues than with other glucose-lowering agents. In addition, when RCTs intensifying treatment with drugs inducing or not inducing hypoglycemia are analyzed separately, the former seem to produce a greater improvement of microvascular diabetic outcomes, and the latter of cardiovascular events and all-cause mortality. Severe hypoglycemia, which is frequent when attempting to reach near-normal glycemia with insulin therapy or insulin secretagogues [15], could have a detrimental effect on cardiovascular disease and mortality [6,19] because of adrenergic activation and thrombotic tendency [20]. On the other hand, some of the effects on cardiovascular disease and mortality of drugs not inducing hypoglycemia, and of metformin, glucagon-like peptide 1 (GLP-1) receptor agonists and sodium-glucose cotransporter-2 (SGLT2) inhibitors in particular [21—24], could partly depend on mechanisms different from the improvement of plasma glucose levels. In addition, it is possible to assume that a detrimental effect of sulfonylureas on mortality [6]blunted the possible benefits of the improvement of glycemic control in RCTs using hypoglycemia-inducing drugs. It should also be noted that in many cardiovascular outcome trials using non-hypoglycemia-inducing drugs, the HbA1c levels in intensified treatment arms were considerably higher than those reported in trials using hypoglycemia-inducing drugs. Thus, it is possible to hypothesize that the reduction of hyperglycemia reduces the risk of cardiovascular events and mortality only above a threshold far from normoglycemia, being ineffective for lower glucose levels. However, epidemiological data in the general population seem to exclude this hypothesis, showing the lowest levels of mortality for HbA1c values in the 5—5.5% range [25,26]. At the first glance, the apparent lack of any significant effect of the improvement of glycemic control with drugs not-inducing hypoglycemia on microvascular complications could appear surprising.

However, all data on glucose-lowering drugs not inducing hypoglycemia, with only one exception [12], derive from RCTs specifically designed for testing the effects on cardiovascular, and not microvascular, outcomes; as a consequence, the quality of such results could be questionable.

Some further limitations of our meta-analysis should be mentioned. Although the difference in HbA1c between treatment arms was considerable, several RCTs included in the meta-analysis were not specifically designed for assessing the benefits of the improvement of diabetes treatment, but for verifying the safety of newer glucose-lowering drugs; this difference in study aims affects trial design, possibly influencing final results. Notably, in cardiovascular safety trials, the study protocol aimed at minimizing between-group differences on glycemic control; however, such aim was often missed, with relevant differences in HbA1c across treatment arms. The present meta-analysis includes only trials with a between-group HbA1c difference greater than 0.5%.One of the usual problems in performing meta-analyses is the heterogeneity across the eligible RCTs of criteria used for the definition of clinical outcomes different from all-cause mortality. In this case, the diagnostic criteria adopted for defining MACE and severe hypoglycemia were comparable across the trials, but those adopted for defining ocular and renal adverse events were more problematic. Another issue is the use of concomitant treatments affecting cardiovascular outcomes (e.g., lipid-lowering or anti-hypertensive drugs, etc.). Although randomization avoids major differences between the treatment arms in concurrent therapy, in some of the older RCTs therapeutic attitudes could have been different from those recommended by the more recent guidelines [1,2]. In addition, although the overall number and size of available RCTs was remarkable, the number of studies for each subgroup was limited when separate analyses were performed for different HbA1c levels reached with drugs inducing or not inducing hypoglycemia. Notably, in none of the available RCTs using drugs not inducing hypoglycemia the HbA1c level in the intervention arm was below 6.6% (49 mmol/mol). Therefore, to date, there is no direct evidence of the effect of attaining non-diabetic HbA1c levels with glucose-lowering drugs not inducing hypoglycemia. Another important limitation of the meta-analysis is represented by the selection of patients included in the eligible RCTs, who cannot be entirely considered representative of the population with T2DM attending the outpatient diabetes services. In particular, RCTs designed for assessing cardiovascular safety of newer drugs included only or mainly T2DM patients with prior cardiovascular events and/or at very high cardiovascular risk. Furthermore, most of the available RCTs, with few exceptions [27–31], did not include patients aged more than 75 years; therefore, there is no information available for this subset of patients.

In conclusion, the results of this meta-analysis of RCTs show that in people with T2DM the improvement of glycemic control with drugs not inducing hypoglycemia is associated with a reduction in the risk of long-term chronic vascular complications (MACE and renal adverse events) and all-cause mortality, at least for HbA1c levels above 7%. The reduction of HbA1c below that threshold could have some favorable effects, but there is no available direct evidence in this respect. When the reduction of HbA1c is achieved with drugs inducing hypoglycemia, a progressive reduction of complications and an increase in the risk of severe hypoglycemia is observed. Therefore, the choice of the most adequate HbA1c target for each patient with T2DM should be made considering an appropriate risk/benefit ratio.

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This research was performed independently of any funding, as part of the institutional activity of the investigators. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Contributors

MM and **EM** were involved in each of the following points:

1. Design
2. Data Collection
3. Analysis
4. Writing manuscript

RC, BP, and **GT** were involved in each of the following points:

1. Manuscript revision

Research involving human participants and/or animals

This article does not contain any studies with human participants or animals performed by any of the authors.

Declaration of competing interest

MM has received speaking fees from Astra Zeneca, Bristol Myers Squibb, Boehringer-Ingelheim, Eli-Lilly, Merck, Novo Nordisk, and Sanofi; **RC, BP, and GT** has no relevant conflicts of interest to declare. **EM** has received consultancy fees from Merck and Novartis speaking fees from Astra Zeneca, Bristol Myers Squibb, Boehringer-Ingelheim, Eli-Lilly, Merck, Novo Nordisk, Sanofi, and Novartis and research grants from Merck, Novartis, and Takeda.

All the authors approved the final version of this manuscript. Dr. Edoardo Mannucci is the person who takes full responsibility for the work as a whole, including the study design, access to data, and the decision to submit and publish the manuscript.

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