Title: Efficacy and Safety of Intensive versus Conventional Glucose Targets in people with type 2 diabetes: A Systematic Review with Meta-analysis.

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SHORT TITLE: Intensive glycaemic control in elderly or frail patients with type 2 diabetes

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Abstract

Objectives: Intensive glucose control in type 2 diabetes (T2D) reduces the risks of long-term complications but may be associated with potential adverse metabolic and cardiovascular effects. The risk-benefits of intensive glucose control in the context of multi-factorial interventions to optimize HbA_{1c} target however remains unclear. This study re-evaluated the latest evidence on the efficacy and safety of intensive glycaemic control in adults with T2D.

Materials and Methods: We developed a search strategy to identify randomised control trials comparing standard glucose targets to intensive glucose targets pre-specified HbA_{1c} level within four databases: Ovid MedLine, Embase, Cochrane, and CINHAL. Subgroup analysis was also performed to account for the inclusion of glucose only versus multifactorial intervention trials. Results are reported as risk ratio (RR) and 95% confidence interval (CI).

Results: Fifty-seven publications including 19 trials were included in the current study. Compared to conventional glycemic control, intensive glycemic control decreased the risk of non-fatal myocardial infarction (0.8, [0.7, 0.91]), macroalbuminuria (0.72 [0.59, 0.87]), microalbuminuria (0.67 [0.52, 0.85]), major amputation (0.6 [0.38, 0.96]), retinopathy (0.75 [0.63, 0.9]), and nephropathy (0.78 [0.63, 0.97]). The risk of hypoglycemia increased with intensive glycemic control than conventional treatment (2.04 [1.34, 3.1]). No reduction in all-cause or cardiovascular mortality was observed. However, in the context of multi-factorial intervention, intensive glucose control was associated with significant reduction in all-cause mortality compared with conventional strategy (0.74 [0.57, 0.95]).

Conclusion: Intensive glycemic control decreased the risk of long-term diabetes complications at the expense of doubling in the risk of hypoglycemia. Multifactorial intervention with intensive lowering conferred reduction in the risk of all-cause mortality. Therefore, targeting HbA_{1c} levels should be individualised based on the clinical status, balancing risks and benefits and potential risk for developing these complications.

1. INTRODUCTION

Type 2 diabetes (T2D) is a highly prevalent chronic condition, characterized by β-cell dysfunction and insulin resistance as result of multiple genetic, biological environmental or lifestyle factors (1). Poor glucose control is associated with an increased risks of macrovascular, microvascular, and neurological complications (2, 3), which can lead to higher rates of developing blindness complications such as blindness, end-stage renal failure requiring dialysis or premature death from cardiovascular diseases. (4-6). Clinical guidelines have therefore been established for the treatment of people with T2D including behavior change, lifestyle modification, and often poly-pharmacotherapy (7) with an emphasis of achieving intensive glucose control with multifactorial interventions.

The association between elevated blood glucose levels, as assessed using glycated haemoglobin A1c (HbA_{1c}), with an increased microvascular complications (8, 9), all-cause mortality (10, 11), sensory neuropathy (9, 12), myocardial infarction (8, 13), stroke (14), and macrovascular mortality (10, 15) was previously reported. For each 1% mmol/mol increase in HbA_{1c} (after adjustment for other factors) there is an associated 18% rise in the risk of cardiovascular events (16), a 12 to 14% rise in mortality risks (17, 18), and a 37% rise in the risk of retinopathy or renal failure (18). There is debate on what "intensive control" should represent with existing studies and treatment guidelines using different targets for intensive and standard treatments. The intensive treatment target was HbA_{1c} ≤6% in the Veterans Affairs Diabetes Trial (VADT) (19), and the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial (20) compared with a target of HbA_{1c} below 6.5% in the Action in Diabetes and Vascular Disease—Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE) trial (21). The American Diabetes Association and the European Association for the Study of Diabetes meanwhile recommends an HbA_{1c} level of less than 7.0% as the standard glycaemic treatment goal (22), whereas the International Diabetes Federation recommends a level of less than 6.5% (23).

Because of inconsistent and varied definitions of intensive control, the impact of intensive glycemic control on diabetes and its individual complications are conflicting. Diabetes Control and Complications Study (DCCT) (24) and the United Kingdom Prospective Diabetes Study (UKPDS) (25) reported a causal relationship between high blood glucose and microvascular

complications. Guo et al. meanwhile reported the importance of intensive multifactorial intervention to optimize HbA_{1c}, lipid and blood pressure levels amongst newly diagnosed patients with T2D to reduce macrovascular events (26). Conversely, the ACCORD study found that the intensive treatment group had a higher all-cause mortality rate and a higher cardiovascular mortality rate than the standard treatment group (20).

The overall impact and risk-benefits of intensive glucose control therefore remains a matter of debate and ongoing uncertainty. While previous systematic reviews and meta-analysis (27-30) have provided cumulative evidence in this context, these were not analyzed in the context of multifactorial intervention. In addition, further trials investigating the impact of intensive interventions have since been published (31-33). To address this, we undertook this updated systematic review and meta-analysis to re-examine the relationship between intensive HbA_{1c} control and key outcomes considering the impact of multifactorial intervention. Further, we determined the impact of intensive glycemic control on all-cause and cardiac mortality, hypoglycemia, and its association with the risks of developing individual macro-and microvascular complications.

2. METHODS

This systematic review and meta-analysis follows the guidance of the "Cochrane handbook for systematic reviews of interventions" (34) and the "preferred reporting items for systematic review and meta-analysis" (PRISMA statement) (35).This systematic review and mate analysis version protocol was registered with PROSPERO with the registration number CRD42020151347.

2.1 Literature search

A comprehensive search strategy was developed and performed using Ovid MedLine, Embase, Cochrane, and CINHAL. Search terms included the following keywords: type 2 diabetes, T2D, intensive glycemic control, conventional glycemic control, hemoglobin A1c (HbA_{1c}), and randomised control trials, RCTs. We dated the search from January 1990 to January 2022. Hand searching of reference lists of the identified studies, and relevant grey literature search was also performed.

2.2 Eligibility criteria and study selection

Randomised control trials and cluster-randomised controlled trials that compared intensive glycemic control to standard treatment modalities were included in this study. Studies including adults (age ≥ 18 years) with T2D were eligible for inclusion without language restriction. Exclusion criteria were as follows: non-randomised design, other types of diabetes where a sub-group analysis for people with T2D was not available and studies without a pre-defined glycemic target.

The identification of eligible studies was performed by two independent researchers (RA & TC). A third person (II) was available for arbitration in the event of any conflict or dispute.

2.3 Data extraction

Data extracted from the studies included the baseline features of the study population (age, sex, duration of diabetes), number of participants in each arm of the trial, duration of intervention and follow-up, the medications utilised (specifically whether this included insulin therapy), and the target of HbA_{1c}, fasting plasma glucose levels, or both.

Primary outcomes were event rates of macrovascular complications: non-fatal myocardial infarction, non-fatal stroke, and cardiovascular death. Secondary outcomes included: microvascular complications (neuropathy, retinopathy, nephropathy); other complications

(macroalbuminuria, microalbuminuria, major amputation, photocoagulation, revascularization); adverse events of intensive glycemic control in the form of hypoglycemia; and all-cause mortality.

Some trials, such as the United Kingdom Prospective Diabetes Study (UKPDS), have yielded multiple publications and subgroup analyses. Accordingly, we obtained data from the original manuscripts of these studies. However, we retrieved all potentially relevant data from other versions of such trials, not to miss any relevant outcomes. It should be noted that overlapping datasets were avoided, and whenever overlapping, we only used the primary dataset.

2.4 Quality Assessment

The quality of the studies included in this review were assessed using the Cochrane Risk of Bias tool provided in the Cochrane handbook for systematic reviews of interventions (34). Using six assessment domains provided by Cochrane handbook, studies were judged to have a low, high, or unclear risk of bias.

2.5 Data synthesis

Data were analysed using review manager 5.4 software and are presented as risk ratio (RRs) with 95% confidence interval (CI). We employed the random-effects model from the start and performed a "leaving one out" sensitivity analysis by excluding the study causing heterogeneity if possible. Heterogeneity was assessed and reported using I^2 statistics. We also conducted subgroup analysis of single factor (intensive vs conventional) and multifactorial comparisons (intensive multifactorial vs conventional multifactorial). These studies adopted a multifactorial approach used, in addition to glucose levels, other combined factors including hyperlipidemia or hypertension to determine their association with patients' outcomes.

3. Results

3.1 Literature search results

The literature search retrieved a total of 10,180 records; 8,201 remained after duplicate removal. Title and abstract screening excluded 7881 records. After full-text screening, we excluded 263 articles for specific reasons, including animal studies, protocols, papers with irrelevant outcomes, or designs other than RCTs. Fifty-seven publication were included and referenced in this review

(18, 21, 26, 31-33, 36-86). Many studies had multiple publications; therefore, 19 trials were included for data extraction and meta-analysis (18, 26, 31, 32, 36-50). The flow of study selection (PRISMA flow diagram) is shown in **Figure 1.**

3.2 Characteristics of included studies

A total of 34,536 people were included across all RCTs that compared intensive and conventional glycemic control with a predefined glycemic target were included. The participants' age ranged from 50 to 66.1 years in the intensive group and from 50.5 to 68.2 years in the conventional group. Females ranged from 3% to 71% in the intensive group and from 3% to 68% in the conventional group. The largest trial included an overall population of 11,140 patients and the smallest one included 43 only. At baseline, the mean HbA_{1c} ranged from 6.5 to 11.5 (mmol/mol) in the intensive group and from 6.5 to 12.2 (mmol/mol) in the conventional group. At the end of follow-up, the mean HbA_{1c} ranged from 6.25 to 9.2 (mmol/mol) and 6.42 to 12.1 (mmol/mol) for intensive and conventional groups, respectively. Three trials included recently diagnosed people with T2D, four trials gave no information on the duration of the diseases, and the rest included old diabetic patients with various durations. Follow-up duration ranged from 4 to 160 months. The baseline characteristics and the summary of included studies are shown in **Tables 1 and 2**.

3.3 Quality assessment

The quality of included trials ranged from moderate to high quality. Twelve studies had a low risk of bias regarding the random sequence generation domain, and nine trials were low biased regarding the allocation concealment domain. Blinding participants in such trials could not be easily applied, so ten trials were highly biased regarding the blinding domain. Blinding of assessors of outcomes occurred in ten trials, so this domain was judged as low biased. Twelve and thirteen trials were low biased regarding attrition and reporting bias, respectively. Most trials included a source of bias rather than the previously mentioned domains, such as funds from pharmaceutical companies. The details of each quality assessment domain and risk of bias graph are presented in **Supplementary Figure.**

3.4 Macrovascular complications

3.4.1 Nonfatal myocardial infarction

Nine studies reported on the outcome of nonfatal myocardial infarction (18, 32, 36, 38, 39, 41, 42, 47). The overall estimate demonstrated a reduced risk of nonfatal MI with lower glucose targets compared to conventional targets (RR =0.8, 95% CI [0.7, 0.91], p = 0.0006), with limited heterogeneity (p =0.27, I^2 =20%). This effect estimate holds true with subgroup analysis of single factor (intensive vs conventional) (RR= 0.84, 95% CI [0.75, 0.94], p = 0.003; I^2=0%) and multifactorial comparisons (intensive multifactorial vs conventional multifactorial) (RR= 0.61, 95% CI [0.43, 0.87], p= 0.003; I^2=27%). **Figure.2**

3.4.2 Nonfatal stroke

Six studies reported this outcome (18, 32, 36, 40-42). The intensive group did not show any difference over the conventional group (RR =0.87, 95% CI [0.61, 1.23]), and the analysis was heterogenous (p =0.04, I^2 =57%). This effect estimate kept true with subgroup analysis of single factor (RR= 1.11, 95% CI [0.87, 1.41], p=0.39; I^2=0%) and multifactorial comparisons (RR= 0.61, 95% CI [0.35, 0.1.06], p= 0.42; I^2=53%),

3.5 Microvascular complications

3.5.1 Macroalbuminuria

Two studies reported this outcome (31, 42) and the overall effect estimate showed a lower risk in intensive group over the conventional group (RR =0.72, 95% CI [0.59, 0.87], p= 0.0008), and the pooled analysis was homogenous (p= 0.55, I^2=0%). This effect estimate was kept true in subgroup analysis for single factor comparison (RR= 0.7, 95% CI [0.56, 0.86], p= 0.0009). While no significant difference was detected when comparing intensive multifactorial vs conventional multifactorial groups (RR= 0.82, 95% CI [0.51, 1.3], p= 0.4).

3.5.2 Revascularization

Analysis of association with revascularization was not analysed per single factor analysis in any of the included studies. On the other hand, three studies (32, 40, 41) used multifactorial approach and no difference was found (RR= 0.84 (95% CI [0.6, 1.17], p= 0.3), and the analysis was homogenous (p= 0.52, I^2= 0%).

3.5.3 Major amputation

Five studies reported this outcome (18, 32, 36, 40, 41). The effect estimate showed lower risk of major amputation in the overall intensive group compared with the overall conventional group (RR= 0.6, 95% CI [0.38, 0.96], *p* =0.03), and the pooled analysis was homogenous (*P*= 0.59, I^2= 0%). This effect estimate was true when comparing intensive multifactorial vs conventional multifactorial approach (RR= 0.44, 95% CI [0.2, 0.97] *p*= 0.04). While no significant difference was found when comparing intensive vs conventional approaches (RR= 0.71, 95% CI [0.4, 1.25], *p*= 0.24; I^2= 0%).

3.5.4 Microalbuminuri*a*

The overall estimate of four trials (36, 42, 48, 50) demonstrated a lower risk of microalbuminuria for the intensive group compared with the conventional group (RR= 0.67, 95% CI [0.52, 0.85], *p*= 0.001). The pooled analysis was heterogenous (*p*= 0.03, I^2= 65%). This effect estimate accords with subgroup analysis of single factor (RR= 0.57, 95% CI [0.33, 0.98], *p*= 0.04) and multifactorial comparisons (RR= 0.71, 95% CI [0.58, 0.87], *p*= 0.0008).

3.5.5 Neuropathy

Two trials reported this outcome (42, 48). The overall effect estimate showed no significant difference between the intensive and the conventional groups (RR= 0.95, 95% CI [0.89, 1.00], *p*= 0.05), and the pooled analysis was homogenous (*p*= 0.89, I^2= 0%). This effect estimate was kept true in subgroup analysis of single factor (RR= 0.95, 95% CI [0.89, 1.00], *p*= 0.05) and multifactorial comparisons (RR= 0.88, 95% CI [0.3, 2.54], *p*= 0.81).

3.5.6 Retinopathy

Seven trials reported this outcome (18, 36, 38, 39, 42, 47, 48). The intensive group appeared to have a lower risk compared with the conventional group (RR= 0.75, 95% CI [0.63, 0.9], *p*= 0.002), and the pooled analysis was heterogenous (*p*= 0.03, I^2= 58%). This effect estimate was kept true in subgroup analysis when comparing (RR= 0.58, 95% CI [0.32, 1.04], *p*= 0.07). However, no significant difference was detected when comparing intensive and conventional approaches (RR= 0.77, 95% CI [0.64, 0.93], *p*= 0.93; I^2= 62%).

3.5.7 Nephropathy

The overall estimate of seven trials (18, 36, 38, 39, 42, 47, 48) showed a lower risk in the intensive group over the conventional group (RR= 0.78, 95% CI [0.63, 0.97], *p*= 0.03), and the results were heterogenous (*p*= 0.0005, I^2=75%). This effect estimate was true in subgroup analysis of single factor (RR= 0.78, 95% CI [0.62, 0.98], *p*= 0.04). While no significant difference was found for the multifactorial subgroup (RR= 0.79, 95% CI [0.48, 1.27], *p*= 0.33).

3.5.8 Photocoagulation

Three trials reported this outcome (18, 39, 42) and the estimate showed no differences between intensive and conventional approaches (RR= 0.91, 95% CI [0.75, 1.11], *p*= 0.35), and the pooled analysis was heterogenous (*p*= 0.05, I^2= 67%). Heterogeneity was resolved after exclusion of UKPDS trial (*P*= 0.85, I^2=0%) and results still not statically significant.

3.6 Mortality risk

3.6.1 All-cause mortality

Seventeen trials reported this outcome (18, 26, 32, 36-44, 46-50). The overall effect estimate showed no difference in mortality risks between the groups (RR= 0.91, 95% CI [0.8, 1.03], *p*= 0.15). The pooled analysis was heterogenous in the overall estimate (*p*= 0.002, I^2= 62%). The effect estimate holds true in the subgroup analysis of single factor comparison (RR= 0.1, 95% CI [0.88, 1.14], *p*= 1, I^2= 54%). Intensive multifactorial intervention group however was associated with reduced all-cause mortality compared with conventional multifactorial group (RR= 0.74; 95% CI [0.57, 0.95], *p*= 0.02), **Figure.3**

3.6.2 Cardiovascular mortality

There was no difference for risk of cardiovascular death between intensive and conventional treatment groups aggregated from fifteen trials (18, 26, 36-44, 46, 47, 49, 50) (RR= 1.03, 95% CI [0.82, 1.3], *p*= 0.8). The pooled studies were heterogeneous (*p*= 0.02, I^2= 55%). The effect estimate was kept true with subgroup analysis of single factor (RR= 1.12, 95% CI [0.89, 1.41], *p*= 0.33, I^2= 52%) and multifactorial (RR= 0.68, 95% CI [0.32, 1.45], *p*= 0.32; I^2= 65%), **Figure.3**

3.7 Hypoglycemia

This outcome was reported by five trials (31, 38, 42, 45, 50) and the overall estimate demonstrated two-fold higher risk in the intensive group compared with conventional group (RR= 2.04, 95% CI [1.34, 3.1], *p*= 0.0009). The pooled analysis was heterogenous in the total estimate (*p*< 0.00001, I^2= 97%). This effect estimate was kept true in subgroup analysis of single factor (RR= 2.17, 95% CI [1.13, 4.15], *p*= 0.02) and multifactorial (RR= 1.84, 95% CI [1.63, 2.08], *p*< 0.00001)**, Figure.4**

4. Discussion

This systematic review and meta-analysis assessed the latest evidence on the efficacy and safety of intensive glycemic control compared to conventional glycemic control. Moreover, we conducted subgroup analysis separating the overall estimate into single factor and multifactorial interventions. The overall analysis showed that intensive glycemic control was associated with a lower risk of nonfatal myocardial infarction, macroalbuminuria, microalbuminuria, major amputation, retinopathy, and nephropathy and a higher risk of hypoglycemia. No significant differences were seen on the risks of non-fatal stroke, cardiovascular death, neuropathy, revascularization, photocoagulation, and all-cause mortality by all-factor analysis. Subgroup analysis showed that multifactorial glycemic control produced significant reductions in all-cause mortality compared to single factor glycemic control.

With uncertainties regarding safety and efficacy of intensive glucose control on cardiovascular death, the results of overall and subgroup analysis of our study were consistent with those of previous studies (27, 28, 30) showing no effect of intensive glycemic control on cardiovascular mortality. On the other hand, the ACCORD trial was terminated with an unexpected rise in the cardiovascular mortality after intensive glycemic control, which is difficult to explain. Regarding all-cause mortality, no difference in risks in our study in the whole and single-factor analysis which was consistent with findings of previous studies (27, 28, 32, 87). Interestingly, multifactorial analysis showed that intensive glycemic control significantly reduced the risk of all-cause mortality. Contrary, the ACCORD study (33) reported an increased risk of all-cause mortality after intensive glycemic control. The trial was terminated after a mean of 3.5 years of follow-up due to unexpected high mortality -257 out of 5128 dead patients in the intensive group and 203 out of 5123 deceased patients in the conventional group- and significant hypoglycemia among patients in the intensive group with no clear explanation about the real cause of this high mortality (42). This can be justified by different factors, including the resultant HbA_{1c} levels in both groups, which was 6.4% in the intensive group compared to 7.5% in the conventional treatment group, and the magnitude and speed of reducing HbA_{1c} levels, which was 1.4% in the intensive group compared to 0.6% in the conventional group within the first four months after randomization. Other explanations might also include factors influencing hypoglycaemia, as

differences in medication regimens and their differential risks of hypoglycaemia. However, it should be noted that the explanations provided are still theoretical and no evidence regarding the high mortality rate was provided. Therefore, these factors should be considered when interpreting the data of current studies as they are not usually considered in the analysis and can represent a significant bias.

For nonfatal myocardial infarction however, the outcome is clear - targeting a lower glucose level led to benefits over conventional treatment, whether in isolation or as part of a multifactorial approach. These results are consistent with many previous meta-analyses (27-29) and clinical trials (32, 33). Our results differed from the work by Hemmingsen et al. (27, 28), but as the authors noted their results were limited by imprecision and possible selective reporting bias, and called for more trials to confirm these findings. On the other hand, the updated meta-analysis by Hemmingsen et al. (88) showed that the risk of nonfatal myocardial infarction was significantly reduced in the intensive glycemic control group. This adds to the significance reported in the current meta-analysis and implies the beneficial association between intensive glycemic control- in both overall and subgroup analysis- and nonfatal myocardial infarction. For nonfatal stroke, previous meta-analyses showed no difference in the risks between intensive glycemic control and conventional treatment (27, 28, 41). Stettler et al., however, concluded that improved glycemic levels might reduce the incidence of macrovascular complications such as stroke and peripheral vascular events (89).

The risk of hypoglycemia in the overall and subgroup analysis was higher with intensive glycemic control compared to conventional glycemic control. Several previous studies reported similar results (27, 28), despite variable definitions of hypoglycemia in trials. Hanefeld et al. (90) concluded that intensive glycemic control in patients with newly diagnosed T2D was not associated with an increased risk of hypoglycemia, but they targeted normal fasting glucose levels. Fasting glucose levels might be strong predictors of hypoglycemia and excursion of post-prandial glucose levels. This can influence clinicians to set-up strict normalization strategies and prepare their patients to normalize blood glucose levels against excursions and fluctuations. Moreover, we could not identify whether the development of severe hypoglycemia has an impact

on cardiovascular and all-cause mortality due to unavailability of sufficient data, which should be addressed in future studies.

Intensive glycemic control significantly reduced the risk or both micro- and macroalbuminuria – important precursors to progressive diabetic nephropathy. Our findings support the results by Slinin et al. (87) and Coca et al. (91). We also found that intensive glycemic control seemed to considerably reduce the risk of amputation compared to conventional control, similarly to Hemmingsen et al. (27). We noticed that the approach with exclusive glycemic target showed insignificant results, unlike a multifactorial approach. Regarding retinopathy, several studies also found a significant reduction of retinopathy by intensive glycemic control (27, 28). Newly diagnosed patients with diabetes (18) showed a higher retinopathy rate than patients with more advanced diseases (39). However, the need for photocoagulation was not associated with the intensive glycemic control compared to conventional glycemic control, either before or after sensitivity analysis.

The intensive glycemic control showed a significant reduction in nephropathy, consistent with a previous meta-analysis (27). Moreover, the definition and diagnosis of nephropathy differed across studies, causing considerable heterogeneity (38, 42). Our results also showed non-significant difference of intensive multifactorial glucose control on revascularization, which are consistent with the results of other studies (27, 28, 32, 41).

5. Strengths and limitations

Our study utilised a robust methodology derived from the Cochrane handbook and the PRISMA checklist. We included all relevant articles, making the current population sample the largest in the literature. Moreover, we included articles, regardless of their country, language or outcomes. This is also the first study, to our knowledge, to assess single factor glucose and multifactorial interventions separately. Although many meta-analyses were previously published, ours represent the most updated evidence, in addition to analyzing our outcomes according to one factor and multifactorial strategies.

There are some limitations to our work. Firstly, the participants in the trials widely varied in their characteristics such as age, body mass index, duration of the disease, presence or absence of co-

morbidities, progressive nature of the disease, associated complications, and its degree, and pharmacological treatment options. Moreover, diagnostic criteria, definitions of outcomes, anti-diabetic treatment regimens used, and the measuring method of the glycemic target also differed and produced high heterogeneity. While including a more defined group of patients would be ideal, this would affect the sample size, the quality of our analysis and generalizability of our findings. Treating such differences in clinical research and practice is therefore difficult and implies that the nature of diabetes care is remarkably different across countries due to differences in access to most efficacious treatment regimens and healthcare facilities. Finally, definition of targeted and achieved HbA_{1c} levels differs remarkably for intensive and conventional treatment groups among the included trials, which remains the case in treatment guidelines for routine clinical practice. However, our current findings are still highly representative, probably having the most reliable evidence in the current literature, despite the reported heterogeneities and limitations. Accordingly, studying the impact of certain anti-diabetic regimens, quality of care, and the effect of certain interventions could not be conducted on the current analysis because of the nature of current data. Therefore, further future investigations are encouraged to overcome these limitations.

6. Current implications and future recommendations

Current findings indicate that intensive glycemic control reduces the risk of long-term diabetes complications, at the expense of doubling the risk of hypoglycaemia, but not cardiovascular death. When intensive glucose control is applied in conjunction with intensive multifactorial intervention, a reduction in the risk of all-cause mortality compared to the conventional interventions was observed. Severe hypoglycemia is associated with a high risk of death, (52), regardless of the intensive or conventional control. The magnitude of risk and benefits provided from this meta-analysis would allow a more objective balance of risk and benefits to be undertaken in routine practice, to facilitate individualizing of Hba1c targets in patients with T2D in the context of multifactorial intervention.

This meta-analysis emphasizes the need for high-quality future research with larger and more representative cohorts, with a focus on following the newest guidelines for diabetes diagnosis and management. This can help discover the best management practices and high-yield

interventions that might overcome the current association between cardiovascular death and other complications and lead to better outcomes. Whilst randomised control trials may achieve this, with access to large electronic datasets now readily available observational designs are likely to yield informative results moving forwards.

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FIGURE LEGENDS

Figure 1 PRISMA Flow chart for study

Figure 2 Effects of intensive glucose intervention on non-fatal myocardial infarction – single factor approach and multi-factorial intervention approach

Figure 3 Effects of Intensive glucose control on cardiovascular death and total mortality. – single factor approach and multi-factorial intervention approach

Figure 4 Effects of Intensive glucose control on hypoglycaemia events - single factor approach and multi-factorial intervention approach

Table 1: Baseline characteristics of the included studies.

Study ID	Reference	Age, years: intensive; conventional	Female, %: intensive; conventional	Previous microvascular disease, %: intensive; conventional	Previous macrovascular disease, % intensive; conventional	Mean HbA1c at baseline, % (mmol/mol) mean (SD): intensive; conventional	Mean HbA1c at end of follow-up, % (mmol/mol) mean (SD): intensive; conventional	Fasting blood glucose at baseline (mmol/L), mean (SD) for total sample	Fasting blood glucose at follow-up (mmol/L), mean (SD) for total sample	Previous cardiovascular disease, intensive/conventional (No)
ACCORD 2008	(42)	62.2 (6.8); 62.2 (6.8)	38.7; 38.4	NR	35.6; 34.8	8.3 (1.1); 8.3 (1.1)	6.5 (0.67); 7.5 (0.82)	9.5 (2.68); 9.4 (2.71)	NR	1826/1783
ADVANCE 2008	(38)	65.7 (6.5); 65.8 (6.4)	42.4; 42.7	10.3; 10.6	32.2; 32.1	7.4 (1.5); 7.4 (1.5)		8.5 (2.7); 8.4 (2.8)	NR	1794/1796
Bagg 2001	(37)	57.2 (7.4); 54.5 (9.2)	57; 57	62; 59	9.5; 9	10.8 (0.24); 10.47 (0.23)[#]	8.02 (0.25); 10.23 (0.23)[#]	13.7 (0.64); 13.2 (0.62)[#]	8.7 (0.71); 11.1 (0.62)[#]	2/2
Griffin 2011	(41)	60.3 (6.9); 60.2 (6.8)	41.5; 42.7	NR	NR	7 (1.6); 7 (1.5)	6.6 (0.95); 6.7 (0.95)	NR	NR	109/79
IDA 2009	(43)	66 (59-72); 62 (59-68)[*]	26; 24	NR	10; 12	6.5 (5.8-7.7); 6.5 (5.8-7.6)[*]	6.3 (5.3-7.2); 6.6 (5.9-7.1)	7 (6-8.5); 7.3 (6.5-8.7)	7 (6.2-8.2); 7.1 (6-8.8)	39/43
Jaber 1996	(44)	59 (12); 65 (12)	71; 68	NR	NR	11.5 (2.9); 12.2 (3.5)	9.2 (2.1); 12.1 (3.7)	11.1 (4); 12.7 (4.7)	8.5 (2.3); 11 (3.9)	NR
Kumamoto 1995	(47)	48 (15.5); 50.5 (14.5)	50; 54	50; 50	NR	9.3 (1.8); 8.95 (1.85)	7.1 (1.1); 9.4 (1.5)	NR	NR	NR
REMBO 2008	(46)	64 (55- 71); 64 (58; 68)[*]	24; 35	NR	NR	7.1 (6.52, 8.2); 7.17 (6.57, 8.52)	6.73 (6.41, 7.6); 6.74 (6.19, 7.78)	6.45 (5.37, 7.1); 6.58 (5.76, 8.28)	6.94 (5.41, 8.54); 6.8 (5.82-8.25)	41/40
Sasso 2021	(32)	66.1 (9); 68.2 (8.8)	50.2; 45.9	NR	NR	7.5 (1.1); 7.3 (1.1)	6.9 (0.6); 7.4 (1.1)	NR	147.4 (39.4); 153.6 (44.8)	NR
Steno 2008	(40)	54.9 (7.2); 55.2 (7.2)	NR	NR	NR	8.4 (1.6); 8.8 (1.7)	7.7 (1.2); 8 (1.4)	182 (56); 189 (54)[$]	160 (55); 170 (61)[$]	NR
Ueki 2020	(31)	58.9 (6.4); 59.1 (6.3)	38.2; 37.8	NR	NR	8.01 (1.05); 7.98 (1.05)	NR	159.6 (41.5); 158.7 (39.4)	NR	146/142
UKPDS 2008	(18)	53.2 (8.6); 53.4 (8.6)	40; 38	NR	NR	7.09 (1.54); 7.05 (1.42)	NR	8.1 (7.1-9.8); 8 (7.1-9.6)	NR	NR
VA CSDM 1995	(36)	60.4 (6.4); 59.9 (6.7)	NR	NR	NR	9.28 (1.81); 9.52 (1.46)	NR	11.4; 12.6	NR	31/72
VADT 2009	(39)	60.5 (9); 60.3 (9)	2.89; 2.91	NR	NR	9.4 (2); 9.4 (2)	6.9 (1-0.6); 8.3 (0.6-1.2)[*]	NR	NR	355/368
Webb 2019	(48)	59.3 (9.9); 59.6 (10)	43.7; 41.1	NR	NR	7.2 (1.5); 7.3 (1.8)	NR	NR	NR	NR
Zhang 2011	(50)	67.8 (5.03); 66.6 (4.82)	33.3; 38.8	6; 4	19; 16	7.44 (1.3); 7.44 (1.29)	6.32 (0.65); 7.02 (0.66)	7.8 (2.13): 7.8 (2.37)	5.71 (1.4); 6.43 (0.94)	NR
Guo 2008	(26)	NR	41.8; 41.8	NR	NR	7.14 (1.87); 7.72 (2.45)	6.3 (0.9); 7.1 (1.91)	8.16 (2.63); 8.99 (2.48)	7.05 (1.7); 8.33 (2.62)	NR
Yang 2007	(49)	50 (8); 53 (9)	NR	NR	NR	7.41 (1.67); 6.85 (1.17)	6.25 (0.63); 6.41 (0.77)	7.15 (1.7); 7.33 (1.86)	6.54 (1.12); 6.81 (1.37)	NR
Johansen 2017	(45)	53.6 (9.1); 56.6 (8.1)	48; 47	NR	NR	6.65 (0.8); 6.74 (0.9)	NR	131.5 (115.3 - 152.3); 140.5 (124.3 - 171.2)[*$]	NR	NR

[*]Median (Interquartile range); [#]Mean (standard error of means); [$]mg/dl; SD, Standard deviation; NR, No results; NO, Number; ACCORD, The Action to Control Cardiovascular Risk in Diabetes Study Group; ADVANCE, The Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation; IDA, The Insulin Diabetes Angioplasty; REMBO, Rational ENective Multicomponent Therapy in the Struggle Against DiaBetes Mellitus in Patients With COngestve Heart Failure; UKPDS, The UK Prospective Diabetes Study; VA CSDM, Veterans Affairs Cooperative Study on Glycemic Control and Complications in Type II Diabetes; VADT, Veterans Affairs Diabetes Trial.

Table 2: Summary of the included studies.

Study ID	Year of publication	Total participants (NO)	Participants: intensive; conventional (NO)	Treatment definition (glycemic target), intensive	Treatment definition (glycemic target), conventional	Duration of disease, years (mean): intensive; convention	Drugs used in intensive group	Drugs used in standard group	Follow up	Primary outcomes
ACCORD	2008	10251	5128; 5123	HbA1c <6.0% (42 mmol/mol)	HbA1c= 7.0-7.9% (53-63 mmol/mol)	10; 10	Anti-hyperglycemic Agents (biguanides, insulin secretagogues, thiazolidinediones, alpha-glucosidase inhibitors and insulins)	Standard glycemic glucose-lowering approach; diet and lifestyle advice	3.5 years	First occurrence of non-fatal MI or non-fatal stroke or death from cardiovascular causes
ADVANCE	2008	11140	5571; 5569	HbA1c <6.5% (48 mmol/mol)	HbA1c <local guidelines	7.9; 8	Modified-release gliclazide (30 to 120 mg daily) (Diamicron MR, Servier), other glucose-lowering drugs as required and were required to discontinue any other sulphonylurea	Standard, guideline-based glucose lowering (modified release gliclazide) when they entered the study were required to substitute this drug with another sulphonylurea	5 years	Major macrovascular events and major microvascular events
Bagg	2001	43	21; 22	HbA1c <7.0% (53 mmol/mol)	Avoid symptomatic hyperglycemia; fortnightly fasting capillary glucose tests of >17mmol/L	7.9; 5.9	Oral hypoglycaemic agents before commencing insulin	Diet and nursing advice only	20 weeks	Weight change
Griffin	2011	3057	1678; 1379	HbA1c <7.0% (53 mmol/mol)	Standard diabetes care	NR	Intensive multifactorial approach including lifestyle advice (smoking cessation, physical activity 30 min./day and healthy diet) and pharmacological treatment	Standard diabetes care	5.3 years	First cardiovascular event including cardiovascular mortality, cardiovascular morbidity (non-fatal myocardial infarction and non-fatal stroke), revascularisation, and nontraumatic amputation
IDA	2009	93	39; 43	HbA1c<6.5%, FBG =5.0–7.0 mmol/L and a preprandial blood glucose <10.0 mmol/L.	Standard treatment	6.4; 6.5	Intensified insulin-based glucose control	Ongoing glucose-lowering treatment (i.e. insulin, oral agents or combinations)	2 weeks and at 1, 3 and 6 months	Restenosis rate after PCI
Jaber	1996	45	17; 22	FBG ≤6.6 mmol/L and 2-hour postprandial blood glucose concentrations of <10.0 mmollL «180 mg/dL) or to reach maximum daily doses of the sulfonylurea agent.	Standrad medical care	6.8; 6.2	Pharmacological treatment was provided to patients in the intervention group that was similar to but wider than that reported by Helper and Strand; advice about diabetes and lifestyle	Continue receiving normal treatment from their primary care physicians	4 months	Fasting plasma glucose and glycated hemoglobin concentrations
Kumamoto	1995	110	55; 55	HbA1c ~7.0% (53 mmol/mol), 2 hour postprandial glucose <200 mg/dL; mean amplitude of glycaemic excursions <100 mg/dL	FBG close to <140 mg/dL with no symptoms of hypoglycemia	8.2; 8.5	Insulin 3 or more times daily (rapidacting insulin at each meal and intermediate-acting insulin at bedtime) (multiple insulin injection therapy (MIT))	One or two daily injections of intermediate-acting insulin	10 years	Retinopathy and the progression of diabetic microvascular complications
REMBO	2008	81	41; 40	HbA1c <7.0% in participants receiving sulfonylurea; HbA1c <6.5% in participants receiving insulin	Not specified standard care	5; 6	Gliclazide; metformine; and ACE inhibitors	Previously selected hypoglycemic therapy (glibenclamide; repaglinide; glimepiride; metformine) and coronary heart failure therapy	12 months	Any diabetes related endpoint
Sasso	2021	395	207; 188	HbA1c <7.0% (53 mmol/mol)	Conventional therapy	NR	Multifactorial interventions with a prespecified algorithm for management of hypertension, glycol-metabolic control and dyslipidemia, including non-pharmacological and pharmacological treatment; physical activity and low sodium diet	Standard care usually administered at their diabetic outpatient for the management of blood pressure, glycaemic and lipid control, and antiplatelet treatment	13 years	Major fatal/non-fatal cardiovascular events
Steno	2008	160	80; 80	HbA1c <6.5%	Conventional multifactorial treatment	NR	Multifactorial intervention (oral hypoglycaemic agent; metformin (maximum, 1 gm twice daily); gliclazide (maximum, 160 mg twice daily; neutral protamine Hagedorn (NPH) insulin at bedtime was recommended	Conventional therapy according to the 1988 recommendations of the Danish Medical Association	13.3 years	Time to death from any cause

Ueki	2020	2540	1269; 1271	HbA1c <6.2%	Conventional therapy	8.58; 8.47	Multifactorial intervention; all patients continued to receive their pre-registration anti-diabetic medication, anti-hypertensive medication; lipid lowering medications; as well as their prescribed diet and exercise regimens	Conventional therapy	8.5 years	Major macrovascular events, major microvascular events, and all-cause mortality
UKPDS	2008	3867	2729; 1138	FPG <6.0 mmol/L	FBG <15 mmol/L	Newly diagnosed	Intensive therapy with insulin; sulphonylureas: chlorpropamide 100-500 mg, glibenclamide 2.5-20 mg or glipizide 2.5-40 mg; and metformin up to 2550 mg	Conventional therapy primarily with diet; or insulin therapy; or metformin	UKPDS 33: 10.0 years; UKPDS 34: 10.7 years	Any diabetes related endpoint
VA CSDM	1995	153	75; 78	HbA1c <7.5%	Avoid excessive hyperglycaemia or symptoms of excessive glucosuria, ketonuria, or hypoglycaemia	8; 7.7	One injection of evening intermediate or long-acting insulin; continued evening insulin combined with daytime glipizide in step increments of 2.5-5.0 mg/week until HbA1c goal or maximum dose is reached; two injections of insulin alone, no glipizide; multiple daily insulin injections, no glipizide	Avoiding excessive hyperglycaemia, or symptoms of excessive glycosuria, ketonuria, or hypoglycaemia; one injection of intermediate or long-acting insulin per day	27 months	Any diabetes related endpoint
VADT	2009	1791	892; 899	Reduce HbA1c by 1.5% (16.4 mmol/mol)	Wellbeing, avoidance of deterioration of HbA1c, keeping levels at 8-9%, and preventing symptoms of glycosuria, hypoglycaemia, and ketonuria	11.5; 11.5	(1) metformin 500 mg to 2000 mg BID, and rosiglitazone 4 mg BID; (2) initiate insulin, or if already on insulin, adjust to one evening injection of an intermediate or long-acting preparation targeted to normal fasting glucose (i.e., 80–115 mg/dl); (3) add morning insulin and may add alpha glucosidase inhibitors; (4) multiple daily insulin injections with retention of oral agents (at least one oral sensitizer); and (5) any necessary combination	(1) metformin 500 mg and up to 1000 mg, and rosiglitazone 4 mg; (2) for patients who have not been on insulin previously, add intermediate or long-acting insulin, 1 U/9 lb; (3) increase metformin dosage to 1000 mg BID; (3) increase rosiglitazone dose to 8 mg/day; (4) increase insulin dose (may include alpha glucosidase inhibitors); (5) any combination that may be required,	5.6 years	Major macrovascular events and major microvascular events.
Webb	2019	336	144; 192	HbA1c ≤7.0% or 53 mmol/mol	HbA1c ≤7.5 % (58 mmol/mol)	NR	Intensive multifactorial interventions	Standard multifactorial interventions	5 years	Diabetes related complications
Zhang	2011	97	48; 49	HbA1c <6.5% (48 mmol/mol)	Local diabetes control guidelines	8; 8.9	Gliclazide sustained-release tablets 30–120 mg/d and stopped taking other sulfonylureas.	Standard care; antihyperglycaemic agents except gliclazide sustained-release tablets; and non-mandatory home blood glucose monitoring	5 years	Glucose control
Guo 2008	2008	220	166; 54	HbAlc <7.0%	Routine outpatient service	Newly diagnosed	Education on diet, physical exercise, hypoglycemic agents; Glipizide (maximum of 15 mg daily), Metformin (maximum of 2250 mg daily) and α Glucosidase inhibitors, Glucobay, maximum of 150 mg daily; Captopril; and Simvastatin	Traditional or routine outpatient service	NR	Carotid intima-media thickness
Yang 2007	2007	66	57; 19	HbA1c <7.0%	Routine outpatient service	Newly diagnosed	Multiple subcutaneous insulin injections	Routine outpatient service	NR	Carotis intima thickness
Johansen 2017	2017	98	64; 34	HbA1c <6.5%	Standard diabetes care	5; 6	Intensive lifestyle intervention, 5 to 6 weekly aerobic sessions (duration 30-60 minutes), and 2 to 3 sessions of resistance training	Standard diabetes care	1 year	Change in HbA1c level

NR, No results; NO, Number; ACCORD, The Action to Control Cardiovascular Risk in Diabetes Study Group; ADVANCE, The Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation; IDA, The Insulin Diabetes Angioplasty; REMBO, Rational ENective Multicomponent Therapy in the Struggle Against DiaBetes Mellitus in Patients With COngestve Heart Failure; UKPDS, The UK Prospective Diabetes Study; VA CSDM, Veterans Affairs Cooperative Study on Glycemic Control and Complications in Type II Diabetes; VADT, Veterans Affairs Diabetes Trial.

Table 3: Summary of the results of each outcome before subgrouping.

Outcome	Number of studies	Pooled RR	95% CI	P-value	I^2 heterogeneity
Nonfatal myocardial infarction	9	0.8	[0.7, 0.91]	0.0006	20%
Nonfatal stroke	6	0.87	[0.61, 1.23]	0.42	57%
Cardiovascular death	15	1.03	[0.82, 1.3]	0.8	55%
Macroalbuminuria	2	0.72	[0.59, 0.87]	0.0008	0%
Revascularization	3	0.84	[0.6, 1.17]	0.3	0%
Major amputation	5	0.6	[0.38, 0.96]	0.03	0%
Microalbuminuria	4	0.67	[0.52, 0.85]	0.001	65%
Neuropathy	2	0.95	[0.89, 1.00]	0.05	0%
Retinopathy	7	0.75	[0.63, 0.9]	0.002	58%
Nephropathy	7	0.78	[0.63, 0.97]	0.03	75%
Photocoagulation	3	0.91	[0.75, 1.11]	0.35	67%
All-cause mortality	17	0.91	[0.8, 1.03]	0.15	62%
Hypoglycemia	5	2.04	[1.34, 3.1]	0.0009	97%

RR, Risk ratio; CI, Confidence interval.

Table 4: Results of the single factor subgroup.

Outcome	Pooled RR	95% CI	P-value	I2 heterogeneity	I^2 heterogeneity after sensitivity analysis	The excluded study
Nonfatal myocardial infarction	0.84	[0.75, 0.94]	0.003	0%		
Nonfatal stroke	1.11	[0.87, 1.41]	0.39	0%		
Cardiovascular death	1.12	[0.89, 1.41]	0.33	52%	0%	ADVANCE 2008 trial
Macroalbuminuria	0.7	[0.56, 0.86]	0.0009	Not estimable		
Major amputation	0.71	[0.4, 1.25]	0.24	0%		
Microalbuminuria	0.57	[0.33, 0.98]	0.04	75%	0%	ADVANCE 2008 trial
Neuropathy	0.95	[0.89, 1.00]	0.05	Not estimable		
Retinopathy	0.77	[0.64, 0.93]	0.93	62%	20%	Kumamoto 2000 trial
Nephropathy	0.78	[0.62, .98]	0.04	78%	Not resolved	
Photocoagulation	0.91	[0.75, 1.11]	0.35	67%	0%	UKPDS trial
All-cause mortality	0.1	[0.88, 1.14]	1	54%	0%	ACCORD 2008 trial
Hypoglycemia	2.17	[1.13, 4.15]	0.02	98%	41%	ACCORD 2008 trial

RR, Risk ratio; CI, Confidence interval; ACCORD, The Action to Control Cardiovascular Risk in Diabetes Study Group; ADVANCE, The Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation; UKPDS, The UK Prospective Diabetes Study.

Table 5: Results of the multifactorial subgroup.

Outcome	Pooled RR	95% CI	P-value	I2 heterogeneity	I2 heterogeneity after sensitivity analysis	The excluded study
Nonfatal myocardial infarction	0.61	[0.43, 0.87]	0.003	27%		
Nonfatal stroke	0.61	[0.35, 0.1.06]	0.42	53%		
Cardiovascular death	0.68	[0.32, 1.45]	0.32	65%	Not resolved	
Macroalbuminuria	0.82	[0.51, 1.3]	0.4	Not estimable		
Revascularization	0.84	[0.6, 1.17]	0.3	0%		
Major amputation	0.44	[0.2, 0.97]	0.04	0%		
Microalbuminuria	0.71	[0.58, 0.87]	0.0008	Not estimable		
Neuropathy	0.88	[0.3, 2.54]	0.81	Not estimable		
Retinopathy	0.58	[0.32, 1.04]	0.07	Not estimable		
Nephropathy	0.79	[0.48, 1.27]	0.33	Not estimable		
All-cause mortality	0.74	[0.57, 0.95]	0.02	52%		
Hypoglycemia	1.84	[1.63, 2.08]	<0.00001	Not estimable		

RR, Risk ratio; CI, Confidence interval.