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Research Article

The Impact of Intensive Versus Standard Control of Glycemia on the Risk of Poor Kidney Outcomes and Mortality in Patients with Type 2 Diabetes: A Meta-Analysis of Randomized Studies

Doaa Mohammed Shaaban Mohammed[1]*, Ibrahim Abdraboh Alhazmi[2], Nalah Yahya Al-Mani[2], Abdulrahman Mohammed Al-Sawidan[2], Jumanah Ali Bafail[3], Norah Hussain Alameri[4], Aisha Abutaleb Alhassani[4], Hanan Ibrahim Alhassani[4], Hisham Mohmed Abdullah AlHindi[5] and Wafa Adel Toonsi[3]

[1]*General Practitioner, Ministry of Interior, Jeddah, Saudi Arabia*

[2]*Medical Intern, College of Medicine, Najran University, Najran, Saudi Arabia*

[3]*Medical Intern, College of Medicine, King Abdulaziz University, Jeddah, Saudi Arabia*

[4]*Medical Intern, College of Medicine, Umm al-Qura University, Al-Qunfudhah, Saudi Arabia*

[5]*Resident Internal Medicine, Ministry of Health, King Abdulaziz Hospital, Jeddah, Saudi Arabia*

***Corresponding Author:** Doaa Mohammed Shaaban Mohammed, General Practitioner, Ministry of Interior, Jeddah, Saudi Arabia.

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Abstract

Background: The impact of targeting intensive glycemic control on the risk of developing renal complications in type 2 diabetes (T2DM) is controversial and an updated evidence is required from randomized clinical trials (RCTs).

Objectives: To conduct a meta-analysis of the effects of intensive versus standard glycemic control interventions on the risk of developing renal complications and death in T2DM.

Methods: Three scientific databases were searched for eligible RCTs and their updated post-hoc analyses to identify the impact of intensive glycemic control on the risk of incident microalbuminuria (MA) and doubling of serum creatinine (primary outcomes) as well as macroalbuminuria, ESRD, renal death and all-cause mortality (secondary outcomes). Pooled effect estimates and 95% confidence intervals (95% CIs) were computed based on risk ratios (RRs) and time-to-event data (hazard ratios [HRs]).

Results: A total of 13 articles (corresponding to eight RCTs) were included (31,111 patients, 61.23% males). The risks of MA, doubling of serum creatinine, ESRD, death from kidney disease, and all-cause mortality were not changed by intensive glucose control. However, the risk of macroalbuminuria decreased with the tight control compared to standard interventions (RR = 0.73, 95%CI, 0.66 to 0.80, $p < 0.001$ and HR = 0.71, 95%CI, 0.61 to 0.81, $p < 0.001$). Performance bias was evident in six trials (75%).

Conclusion: There was a 27% reduced risk of macroalbuminuria with intensive glucose control despite the lack of effects on other clinically meaningful outcomes of overt nephropathy. Future randomized studies should report renal outcomes based on large sample sizes, long-term follow-up periods, and using novel and reliable biomarkers of nephropathy.

Keywords: *Diabetes Mellitus; Blood Glucose; HbA1c; Randomized Clinical Trials*

Abbreviations

ACR: Albumin/Creatinine Ratio; CI: Confidence Interval; ESRD: End-Stage Renal Disease; FPG: Fasting Plasma Glucose; HR: Hazard Ratio; MA: Microalbuminuria; PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-analyses; RCTs: Randomized Clinical Trials; RR: Relative Risk; T2DM: Type 2 Diabetes Mellitus

Introduction

Type 2 diabetes mellitus (T2DM) is a significant public health problem and the leading cause of non-traumatic lower extremity amputations, blindness, peripheral neuropathy and end-stage renal disease (ESRD) worldwide. In 2017, T2DM affected more than 460 million individuals, representing 6.82% of the total population worldwide [1,2]. Evidence indicates that T2DM prevalence is projected to increase to more than 7,000 individuals per 100,000 in 2030 and the total number to 200 million by 2040 [1,3]. The disease is increasingly prevalent owing to increased consumption of unhealthy diets and sedentary lifestyles, leading to significant morbidity, premature mortality and increased healthcare expenditure [4]. These unfavorable consequences are primarily attributable to T2DM-related complications, including macrovascular and microvascular complications. Of the latter, diabetic nephropathy can develop due to inflammation and endothelial dysfunction. Diabetic nephropathy takes place in about 20 - 40% of all diabetics [5] and it is the leading cause of ESRD in multiple countries, including the United States [6]. Clinically, albuminuria or reduced glomerular filtration rate, or both are indicative of nephropathy. In randomized studies, a doubling of serum creatinine, changes in proteinuria, or the development of ESRD are frequently used as renal endpoints to assess the efficacy of diabetes management and glycemic control [7].

Notably, early studies suggested that tight diabetes control (HbA1c 6.0 - 6.5%) could reduce the risk of microvascular complications compared to the standard target (HbA1c of < 7%), and insulin injections could prevent urinary albumin secretion in diabetic patients [8,9]. On the other hand, without any intervention, approximately 30% of patients with baseline microalbuminuria (MA) experience diabetic nephropathy after 20 years of the disease onset. Actually, the incidence of MA has been considered an early marker of progression to irreversible macroalbuminuria and renal complications [10] and a predictor of cardiovascular disease in T2DM [7]. Therefore, optimal glycemic control may be a key factor that halts the development of renal complications. Indeed, previous meta-analyses have shown that the intensive control of glycaemia is an effective approach to decrease the burden of cardiovascular disease in T2DM [11,12]. Nevertheless, little is known about the risk of renal complications. The impact of tight glycemic control on renal complications might help tailor robust guidelines for patients at risk, particularly those with albuminuria detected early at diagnosis. Such guidelines can preferably be developed based on the combined outcomes of high-quality randomized clinical trials (RCTs). In the present study, we sought to conduct a meta-analysis of RCTs which have studies the effect of intensive diabetic control on the risk of developing renal complications via the relevant renal endpoints compared to the standard control of glycemia in patients with T2DM.

Methods

Eligibility criteria

A meta-analysis was outlined based on the guidelines of the Preferred Reporting Items for Systematic reviews and Meta-analyses (PRISMA) statement [13]. Eligible studies included English RCTs with at least two randomized arms of adult patients with T2DM who have received pharmacologic interventions to achieve intensive or standard control for glycemia. Such studies should have reported at least one of the primary renal outcomes. Studies reporting an extended follow-up of previously conducted RCTs (post-hoc analyses) were also included. Diabetes control should have been defined by specific HbA1c or fasting plasma glucose (FPG) targets, whenever applicable. Trials recruiting specific populations of patients, such as critically-ill patients and those undergoing renal transplantation were excluded. Additionally, the following studies were not eligible: retrospective investigations, narrative reviews, case reports, and meta-analyses.

Types of outcomes measures

The primary outcome measures were incident MA and/or doubled serum creatinine. Incident microalbuminuria is defined as the progression from normoalbuminuria to microalbuminuria (urine albumin/creatinine ratio [ACR] of 30 to 300 mg/g), whereas doubling of serum creatinine should have reached a threshold of ≥ 200 µmol/L. The development of macroalbuminuria (ACR > 300 mg/g), ESRD, kidney disease-related death, and all-cause mortality were all considered secondary outcomes.

Search strategy

The search process was carried out by two authors () across three scientific databases, including PubMed, Embase and he Cochrane Library with no specific limits for the date of publication of eligible trials. These databases were last accessed on October 24, 2020. A set of specific keywords and Boolean operators was used in the search process as demonstrated in appendix 1. Reference lists of eligible articles were also screened for other eligible studies.

#1 "intensive" AND ("normal" OR "standard")
#2 "creatinine" AND ("doubl*" OR "doubling" OR "doubled"
#3 "albuminuria" OR "microalbuminuria" OR "macroalbuminuria"
#4 "type 2 diabetes" OR ("diabetes" AND "T2DM")
#5 "random*" OR "randomized" OR "randomly" OR "trial"
#6 #1 AND #2 AND #3 AND #4 AND #5

Appendix 1: *The employed search strategy in the PubMed database.*

Study selection and data collection

All articles were meticulously screened against the assigned eligibility criteria. The obtained search records were uploaded to a reference management software (EndNote v. X9) to identify and exclude duplicate records. A specific dataset was designed in Microsoft Excel (v. 2016) for data collection, which was performed by two independent authors (). Any disagreement regarding study inclusion/exclusion was resolved by discussion. The following data was extracted from the full-article version of the included articles: 1) study data: the last name of the first author, year of publication, the name of the trial/study group, study setting, and the duration of follow-up; 2) patients' data: sample size, the number of allocated patients to each treatment arm (intensive and standard), gender, as well as group-based demographic data, including age, baseline HbA1c, and baseline serum creatinine; 3) defined targets of glycemic control based on HbA1c and/or FPG; 4) outcome data reported at the end of the follow-up period, including the number of patients who developed MA, doubling of serum creatinine, ESRD and death due to renal causes or any cause. The reported effects of glycemic control plans on renal endpoints using adjusted/unadjusted hazard ratios (HRs) were also collected for the subsequent analysis.

Risk of bias

The methodological quality of the included trials was assessed using the Cochrane risk-of-bias tool for randomized trials [14] which is based on random sequence generation, allocation concealment, blinding (personnel, outcome assessors, and participants), selective outcome reporting, and other sources of bias. Quality assessment was performed by two authors (), and any discrepancy was resolved by discussion with a third author (). Data was recorded and depicted using Revman v 5.4 (the Cochrane Collaboration, Oxford, United Kingdom).

Statistical analysis

Statistical analysis was performed using R software (R i386 version 4.0.0). The quantitative synthesis of outcome data was generally based on two models. First, the frequency of patients who have experienced an event (primary or secondary outcomes) in each treatment arm was entered in a relative risk (RR) model. Aggregate data was analyzed and expressed as RR and their respective 95% confidence intervals (CIs) using the Mantel-Haenszel method in the *metabin* command. Second, the collected HRs and their 95% CIs from individual studies were entered in the HR model. The inverse variance method was used to compute pooled effect estimates using the *metagen* com-

mand. Statistical heterogeneity between the included trials was assessed using I^2 statistics. A random-effects model was applied when the statistical heterogeneity was significant ($I^2 \geq 50\%$); otherwise, a fixed-effects model was carried out. Subgroup analysis was performed for the outcomes with significant heterogeneity based on the sample size and the median follow-up periods. Publication bias was assessed visually by interpreting the funnel plots and statistically via an Egger's test based on the weighted linear regression of the effect size on its standard error. A p value of < 0.05 was considered to indicate statistical significance.

Results

Results of the search process

The initial search process revealed a total of 1492 records across different databases, of which 40 records were identified from the bibliographies of screened articles. After excluding duplicate records (n = 190), 18 studies met the predefined eligibility criteria and their full-text versions were downloaded. However, five studies were excluded owing to recruiting patients with microalbuminuria at baseline (the whole cohort) [15,16], including critically-ill patients [17], or the lack of primary outcomes [18,19]. Therefore, 13 articles (corresponding to eight RCTs) were eventually included in the meta-analysis (Figure 1) [8,20-31].

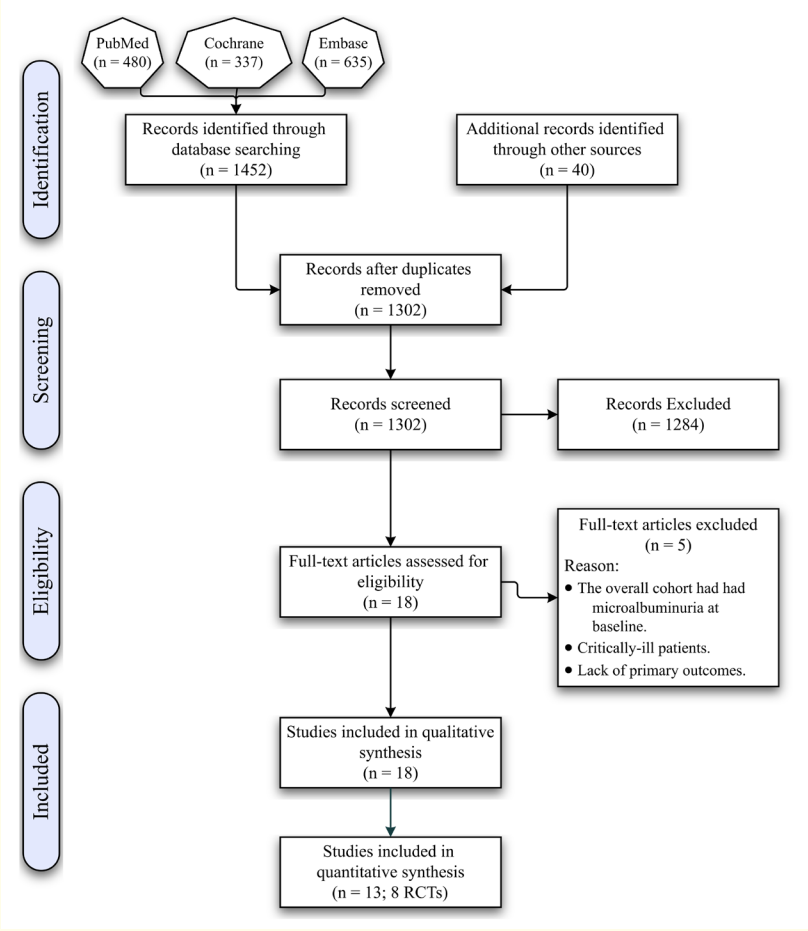


Figure 1: *A flowchart depicting the results of the search process in the current study.*

Characteristics of the included studies

The included articles were published between 1995 and 2020. These included 31,111 patients with T2DM (61.23% males; 52.93% were assigned to the intensive glycemic control arm). Five articles represented a follow-up of previously published trials [21,23,25,27,31]. Of the original RCTs (n = 8), three studies [20,22,30] were conducted at collaborating medical centers in multiple countries (in North America, Europe, and Asia). The remaining articles were single-center [8,29] or multi-center studies [24,26,28] held in a single country. The median follow-up periods across all studies ranged between 7.0 and 17.2 years (Table 1).

Trial Name	Location	Median follow-up (years)	Total (M/F)	Age*	Baseline HbA1C (%)*	Serum creatinine (µmol/L)*	Targets of glycemic control	Interventions
Kumamoto [8]	1 outpatient clinic in Japan	6	102 (49/53)	INT: 48 ± 11.1 STD: 50.5 ± 14.4	INT: 9.3 ± 1.8 STD: 9 ± 1.8	NR	INT: HbA1c < 7%, FPG < 140 mg/dL, mean MAGE < 100 mg/dL, and 2h PPG < 200 mg/dl STD: FPG < 140 mg/dL without symptoms of hyperglycemia	INT: insulin injections 3 or more times/d STD: 1 or 2 insulin injections/d
Shi., *et al*. 2020 [29]	1 center in China	7	150 (75/75)	INT: 49.8 ± 6.6 STD: 47.8 ± 8.1	INT: 8.9 ± 1.7 STD: 8.7 ± 1.7	NR	INT: FPG <7 mmol/L, HbA1c < 7% STD: FPG ≤ 7 mmol/L, HbA1c ≤ 8%	INT: metformin (BMI≥ 24 kg/m^2) or glipizide (24 kg/m^2). Acarbose or insulin was added to control blood glucose if needed. STD: dietary advice
ACCORD and ACCORDION [20,21]	77 centers in the US and Canada	8.8	10251 (6299/3952)	INT: 62.2 ± 6.8 STD: 62.2 ± 6.8	INT: 8.1 ± 0.2 STD: 8.1 ± 0.2	INT: 79.6 ± 2.4 STD: 79.6 ± 2.4	INT: HbA1c <6.0% STD: HbA1c 7.0-7.9%	The therapeutic interventions were individualized by study investigators on the basis of the allocated glycemic target.

ADVANCE and ADVANCE-ON [22,23]	215 centers in 20 countries	9.9	11140 (6407/4733)	INT: 66 ± 6 STD: 66 ± 6	INT: 7.5 ± 1.6 STD: 7.5 ± 1.5	INT: 86 ± 24 STD: 87 ± 27	INT: HbA1c ≤6.5% STD: based on local guidelines of each participating country	INT: gliclazide (30 - 120 mg daily); the dose may be increased with the addition of metformin, acarbose, or insulin to achieve the HbA1c target. STD: Patients who were using gliclazide were instructed to substitute the drug with another sulfonylurea.
ADDITION-Europe [30,31]	379 centers in Denmark, the Netherlands, and the UK	10	3057 (1771/1286)	INT: 60.3 ± 6.9 STD: 60.2 ± 6.8	INT: 7 ± 1.6 STD: 7 ± 1.5	INT: 83.4 ± 17.1 STD: 84.9 ± 18.6	INT: HbA1c < 6.5%	Different interventions in each country.
UKPDS 34 [28]	15 centers in the UK	10.7	753 (350/403)	INT: 53 ± 1.4 STD: 53 ± 1.5	INT: 7.3 ± 0.3 STD: 7.1 ± 0.3	INT: 78 ± 5.5 STD: 79 ± 5.4	INT: FPG <6 mmol/L	INT: metformin (a single 850 mg oral tablet daily). Glibenclamide was added if needed to achieve the glycemic target. Metformin dose was reduced if adverse events had developed. STD: dietary advice. Non-intensive pharmacological therapy was added if marked hyperglycemia developed.

VADT and VADT-F [24, 25]	20 centers in USA	11.8	1791 (1739/52)	INT: 60.5 ± 9 STD: 60.3 ± 9	INT: 9.4 ± 2 STD: 9.4 ± 2	INT: 88.4 ± 17.7 STD: 88.4 ± 17.7	INT: HbA1c <6% STD: HbA1c <9%	Metformin plus rosiglitazone (BMI ≥ 27) or glimepiride plus rosiglitazone (BMI < 27). INT: maximal doses and STD: half the maximal doses. Insulin was added if needed.
UKPDS 33 [26]	23 centers in the UK	17.2	3867 (2359/1508)	INT: 53.2 ± 8.6 STD: 53.4 ± 8.6	INT: 7.1 ± 1.5 STD: 7.1 ± 1.4	INT: 82.8 ± 4.7 STD: 81.8 ± 5.1	INT: FPG <6 mmol/L (premeal FPG of 4-7 mmol/L in insulin-treated patients) STD: FPG <15 mmol/L without symptoms of hyperglycemia	INT: Insulin or sulphonylurea STD: diet

Table 1: *Baseline characteristics of the included RCTs/participants (sorted based on the median follow-up period in each trial). *Results are expressed as means ± standard deviations; 2h PPG: 2-h postprandial glucose concentration; ACCORD: The Action to Control Cardiovascular Risk in Diabetes trial; ADDITION: Intensive Treatment In People with Screen Detected Diabetes in Primary Care; ADVANCE: The Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation; BMI: Body Mass Index; F: Female; FPG: Fasting Plasma Glucose; HbA1c : Glycated Hemoglobin; INT: The Intensive Treatment Arm; M: Male; MAGE: Mean Amplitude of Glycemic Excursions; NR: Not Reported; STD: The Standard Treatment Arm; UKPDS: The University Group Diabetes Program; VADT: Veterans Affairs Diabetes Trial; VADT-F: The Veterans Affairs Diabetes Trial Follow-Up Study.*

Risk of bias

Figure 2 depicts the summary of risk of bias judgements. Random sequence generation was not merely mentioned in one trial; thus, such a domain was judged as unclear. The risk of bias due to the lack of blinding of participants was high in six trials [8,22,20,24,29,30], because participants were unblinded to the interventions. In all trials, outcome assessment was performed by independent assessors who were blinded to group assignment. Regarding the publication bias, visual analysis of the primary outcomes showed symmetrical funnel shapes, indicating a lack of publication bias. This was confirmed by the results of the Eggers regression test ($p > 0.05$). However,

focusing on the secondary outcomes, published studies were unevenly scattered around the mean effect estimates for incident macroalbuminuria (Figure S1B) and death from renal causes (Figure S1E) which was corroborated by the results of the Eggers regression test (p = 0.049 and p = 0.017, respectively).

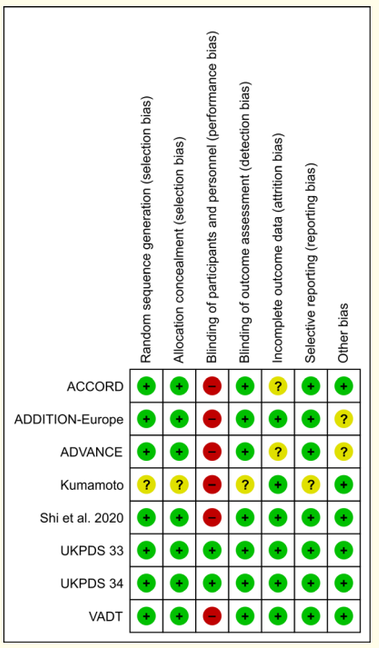
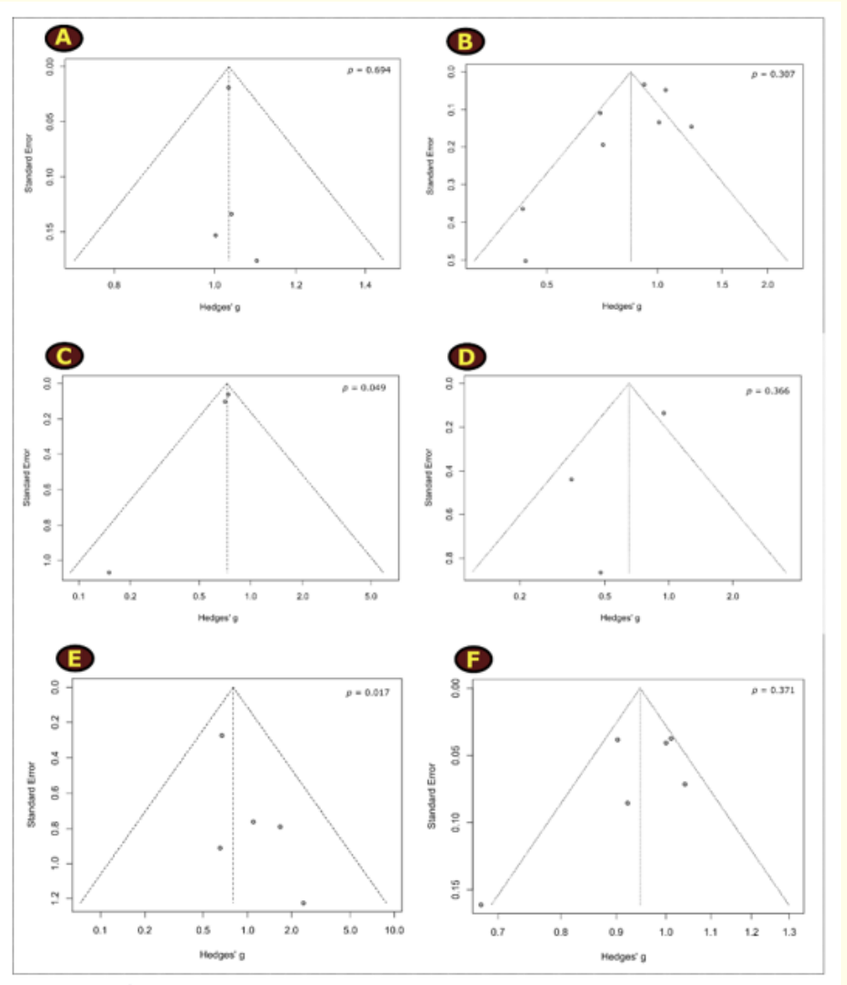


Figure 2: *The results of authors' judgement of the risk of bias of the included randomized clinical trials.*



Supplementary Figure: *Funnel plots showing an assessment of the risk of publication bias in studies reporting doubling of serum creatinine (A), incident microalbuminuria (B), incident macroalbuminuria (C), ESRD (D), death from renal causes (E), and all-cause mortality (F).*

Clinical primary and secondary outcomes

Doubling of creatinine was reported in four trials. The pooled results showed that intensive diabetic control did not increase the risk of creatinine doubling based on relative risk estimates (RR = 1.03, 95%CI, 1.00 to 1.07, p = 0.089, Figure 3A) and adjusted hazard ratios (HR = 1.04, 95%CI, 0.99 to 1.10, p = 0.117, Figure 3B). Similarly, the risk of developing MA was not significant based on the reported outcomes of both parameters (RR = 0.85, 95%CI, 0.64 to 1.11, p = 0.149, Figure 3C and HR = 0.86, 95%CI, 0.73 to 1.02, p = 0.083, Figure 3D).

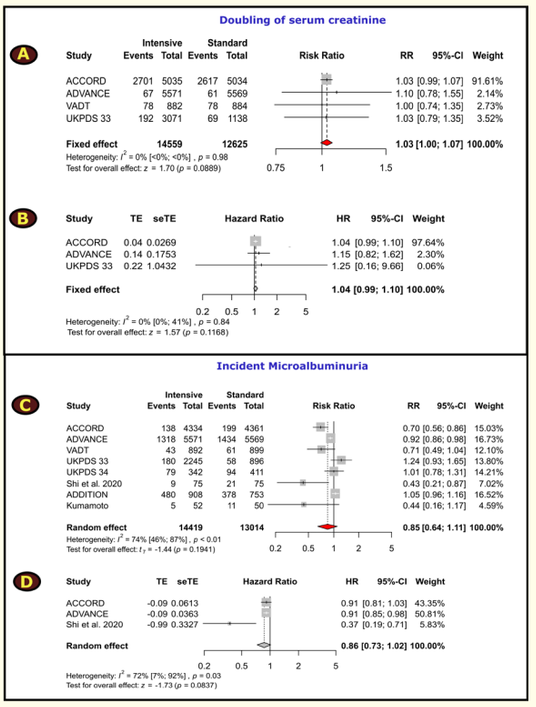


Figure 3: *Forest plots showing the outcomes of doubling of serum creatinine, including the risk ratio (panel A) and hazard ratio (panel B), as well as incident microalbuminuria, including the risk ratio (panel C) and hazard ratio (panel D).*

Regarding the secondary outcomes, results revealed that the intensive control of diabetes reduced the risk of macroalbuminuria (RR = 0.73, 95%CI, 0.66 to 0.80, p < 0.001), and reduced the rate of its incidence over the follow-up periods across studies (HR = 0.71, 95%CI, 0.61 to 0.81, p < 0.001, Figure 4A). However, the risks of ESRD, renal-related death, and all-cause mortality did not change with intensive diabetic control compared to a standard therapy (Figure 4B-4D).

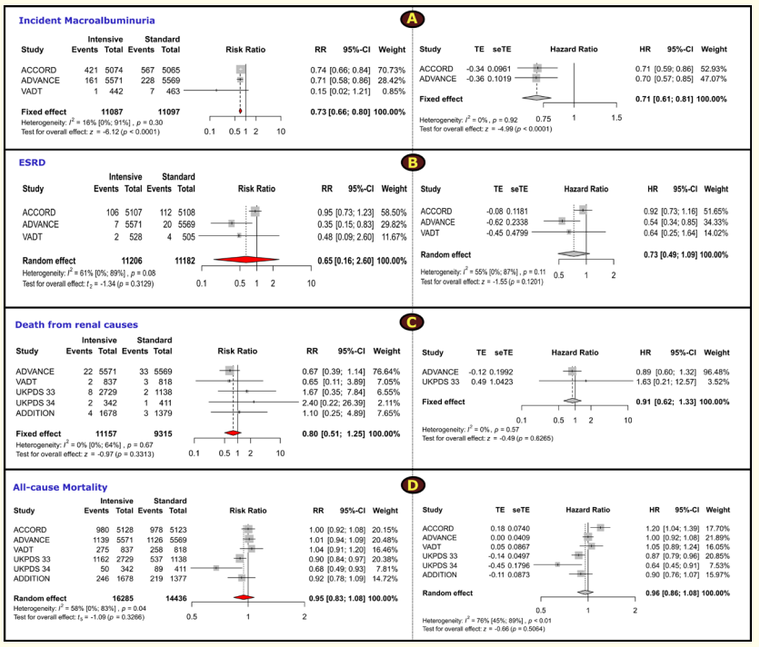


Figure 4: *Forest plots of the secondary outcomes showing the risk ratios and hazard ratios of incident macroalbuminuria (panel A), ESRD, (panel B), death from renal causes (panel D), and all-cause mortality (panel D).*

Notably, the between-study heterogeneity was significant for the outcomes of incident MA (I^2 = 74%), ESRD (I^2 = 61%), and all-cause mortality (I^2 = 58%, Figure 3 and 4). Subgroup analysis indicated that the heterogeneity disappeared in the all-cause mortality outcome for the studies with large sample sizes (> 10,000 patients) and relatively short median follow-up periods (< 10 years). However, effect estimates of the impact of glycemic control were not changed in all outcomes (Table S1).

Parameter	Category	Number of patients		No. of studies	Effect estimate (95% CI)	Heterogeneity	
		INT	STD			%	p
Incident microalbuminuria							
Sample size	> 10,000	9905	9930	2	0.82 (0.15 to 4.6)	83	0.02
	< 10,000	4998	3326	6	0.85 (0.54 to 1.32)	67	0.01
Median follow-up	< 10 years	10032	10055	4	0.69 (0.4 to 1.19)	75	< 0.001
	≥ 10 years	4871	3201	4	1.02 (0.71 to 1.45)	52	0.1
ESRD							
Sample size	> 10,000	10070	10677	2	0.63 (0.01 to 313.63)	79	0.03
	< 10,000	528	505	1	0.48 (0.09 to 2.6)	NA	NA
Median follow-up	< 10 years	10070	10677	2	0.63 (0.01 to 313.63)	79	0.03
	≥ 10 years	528	505	1	0.48 (0.09 to 2.6)	NA	NA
All-cause Mortality							
Sample size	> 10,000	10699	10692	2	1.01 (0.94 to 1.07)	0	0.86
	< 10,000	5586	3744	4	0.9 (0.7 to 1.16)	57	0.07
Median follow-up	< 10 years	10699	10692	2	1.01 (0.94 to 1.07)	0	0.86
	≥ 10 years	5586	3744	4	0.9 (0.7 to 1.16)	57	0.07

Table S1: *Subgroup analysis of the outcomes with substantial heterogeneity.*

CI: Confidence Interval; ESRD: End-Stage Renal Disease; INT: The Intensive Treatment Arm; STD: The Standard Treatment Arm.

Discussion

Nephropathy is an important microvascular complication and a significant source of morbidity and mortality in T2DM. Recent evidence showed a correlation between hyperglycemia and deficits in ATP production in mesangial and proximal tubular cells, which could contribute to cellular damage and nephrotic changes [32]. Therefore, the clinical implications of glycemic control on subsequent renal complications have been assessed in the current study. Meta-analysis of all available cases and hazard ratio data showed no statistically significant effects of intensive glycemic control on the major kidney outcomes, including the development of microalbuminuria, doubling of serum creatinine, or ESRD. Additionally, renal death and all-cause mortality were not influenced by the intensified approach. However, there was a significantly reduced risk of macroalbuminuria favoring intensive glycemic control in both case analysis and adjusted hazard ratio analysis.

The results of the primary outcomes are concordant to other systematic reviews and meta-analyses. Based on four RCTs, Herrera-Gómez., *et al*. [33] have also found no significant differences in the pooled of estimates of clinical renal endpoints, including doubling of serum creatinine, incident MA, and ESRD with targeting a tight glycemic control compared to the standard control. However, they demonstrated that the odds of renal death has significantly decreased with the intensive intervention. While these results were based on a small

number of studies (n = 2) [33], death from renal causes in our review was estimated based on the reported results of five trials and two trials in the RR and HR models, respectively. Moreover, Boussageon., *et al*. [11] demonstrated significantly reduced risks of MA with the intensive targets; however, the authors have combined the data of new and worsening MA, and the significant risk difference disappeared after excluding low-quality studies.

Interestingly, it is important to note that the risk of MA as a surrogate marker of nephropathy was lower with the implementation of the intensive approach in three included trials [20,22,29]. The ADVANCE trial included the largest sample size (n = 11,140), accounting for one third of the total number of patients included in our meta-analysis [22]. The outcomes of such a trial showed a significant risk reduction in the incident MA with targeting intensive control of glycemia. The UKPDS study showed also a decrease in the composite retinal-renal outcome in the intensive blood glucose control arm by either sulphonylureas or insulin [26]. However, as indicated in our review, statistical significance was not evident in the pooled random-effects models of both case-based and HR-based analyses. Using a random-effects model (due to the substantial heterogeneity between studies) might have led to the lack of statistical significance. Statistical heterogeneity might have affected by the inherent differences in study designs and cohort characteristics. For example, patients recruited in the UKPDS cohort were studied from the time of diabetes diagnosis, received treatment for 11 years, followed-up for longer periods and attained higher HbA1c targets than the intensive group of the ACCORD study (Table 1).

Another important observation is that the impact of intensive glycemic control may be evident on the composite microvascular outcome rather than the exclusive outcomes of nephropathy [8,22,26,28]. Observational data from the ADVANCE and the UKPDS 33 trials revealed 14% and 25% risk reductions of microvascular outcomes when targeting intensive glycemic control [22,26]. Additionally, in the present study, the analysis of secondary outcomes revealed that the risk of macroalbuminuria decreased by 27% based on the combined analysis of three major trials [20,22,24] and the pooled adjusted HR decreased by 29% by intensive compared to standard glycemic control. Macroalbuminuria is an important marker of overt diabetic nephropathy which frequently takes place within 5 - 10 years of the onset of MA [34]. Such a state of persistent albuminuria is highly predictive of renal failure [35]. However, the concurrent lack of a significant effect of intensive glycemic control on other clinically-important renal outcomes, including doubling of serum creatinine and ESRD, is conflicting. The variation in the follow-up period may partly explain these observations. Indeed, this raises the need to employ alternative surrogate biomarkers for early renal impairment in diabetes [7]. In addition, investigating hard renal outcomes which are clinically meaningful to indicate the development of diabetic nephropathy should be stressed in future trials to conclude reliable evidence that could be included in the relevant treatment guidelines.

Strengths and Limitations

We provided an updated review of the available RCTs. In our analysis, we sought to utilize RR and HR, which are frequently used to define the probability of developing renal complications in a specified time period [36]. In contrast, the authors of the most recently published meta-analysis [33] used pooled odds ratio as an effect estimate for renal outcomes. We have also provided the results based on a large number of patients. However, the obtained outcomes may be limited by multiple factors. The substantial heterogeneity between studies was significant in the results of important outcomes, such as incident MA and ESRD, and we could not explain the source of heterogeneity. The variation in the outcomes may be attributable to study-level reasons, such as the introduction of glycemic control interventions at late stages of diabetes, inadequate statistical power to reveal a significant difference, and the variation in the glycemic targets. The small number of trials which have reported distinct outcomes may represent another limitation, particularly for hard renal outcomes, such as macroalbuminuria and ESRD. Future studies and *post-hoc* analyses are therefore required to report important kidney-related results to help conclude evidence-based outcomes in order to support the efforts aiming at reducing risk of future complications in a significant proportion of T2DM patients.

Conclusion

In conclusion, compared to standard glycemic control targets, intensive glycemic control had no significant effect on the risk of nephropathy as indicated by the available surrogate biomarkers of early diabetic kidney disease (incident MA) as well as the indicators of overt diabetic nephropathy (doubling of serum creatinine and ESRD). However, targeting a tight control of glycemia reduced the risk of developing persistent albuminuria (macroalbuminuria). Future large-sized studies and *post-hoc* analyses of the established trials are needed to further elucidate the prospected difference in renal complications. The use of novel and reliable biomarkers for early renal impairment is warranted in future RCTs.

Conflict of Interest

The authors declare no conflicts of interest.

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