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IMPACT OF INTENSIVE GLYCEMIC CONTROL ON MICROVASCULAR AND MACROVASCULAR OUTCOMES IN TYPE 2 DIABETES: A SYSTEMATIC REVIEW AND META-ANALYSIS WITH IMPLICATIONS ON MIDDLE EASTERN AND UAE POPULATIONS

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Abstract

Background:

The idea of intensive glycemic control as an intervention to minimize the risk of microvascular and macrovascular complications has been suggested in patients with type 2 diabetes mellitus (T2DM). Nevertheless, there is still inconsistent evidence concerning its usefulness, especially when it comes to long-term results and whether it can be applied to the Middle Eastern populations.

Objective:

To assess the effect of intensive glucose control on microvascular and macrovascular complications in those with T2DM and its relevance to the Middle East and United Arab Emirates (UAE).

Methods:

The systematic review and meta-analysis were carried out as per PRISMA 2020 guidelines. An extensive literature review was used to find original research on intensive versus standard glycemic control in adults with T2DM. Included were 11 studies and 6 reports from 4 randomized controlled trials (ACCORD,

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ADVANCE, VADT, and UKPDS), which were suitable for quantitative pooling. Results with comparable effect measures were pooled using a random-effects model were grouped into meta-analysis using random effects. The I^2 statistic was used to determine heterogeneity, and results that could not be pooled were synthesized using narrative.

Results:

The small and near-significant decrease in major macrovascular events was observed with intensive glycemic control (HR 0.91; 95% CI 0.84-0.99; I^2 = 0). There was no impact on overall mortality (HR 1.05; 95% CI 0.88-1.27; I^2 = 66.3%) with the heterogeneity being driven by greater mortality in the ACCORD trial. A modest benefit was observed for overall microvascular outcomes (HR 0.90; 95% CI 0.82–1.00; I^2 = 30.2%). The most significant effect was the decrease in the nephropathy outcomes (HR 0.75; 95% CI 0.66-0.85; I^2 = 0%). There was an inconsistent effect on retinopathy and neuropathy. The long-term results were not consistent, as there was a legacy effect in UKPDS and no long-term benefit in ADVANCE-ON.

Conclusion:

Intensive glycemic control in T2DM offers limited benefits in decreasing microvascular disease, especially nephropathy, but has no significant effect on macrovascular disease or death. The results suggest personalized glycemic goals, as opposed to standardized intensive control interventions, particularly in heterogeneous populations like Middle East and UAE.

INTRODUCTION

One of the most significant global health issues and a significant cause of morbidity and mortality is type 2 diabetes mellitus (T2DM) because it is associated with both microvascular and macrovascular complications. Chronic hyperglycemia is also a key factor in the occurrence of complications like diabetic retinopathy, nephropathy, and neuropathy and cardiovascular disease, which is the leading cause of mortality in patients with T2DM [23]. These complications are progressive and have a significant effect on the quality of life and healthcare systems in all parts of the world, especially in places where diabetes is rapidly increasing, like the Middle East and the United Arab Emirates (UAE) [3, 4].

Microvascular complications represent one of the first signs of T2DM and are closely related to the exposure to glycemia in the long term. Diabetic retinopathy has been a significant cause of avoidable blindness, whereas diabetic nephropathy is a significant cause of end-stage renal disease [16, 25]. Also, neuropathy is associated with high morbidity, such as pain, sensory loss, and risks of foot ulcers and amputations [2]. These complications tend to be interconnected with one another, and there have been indications that the occurrence of one microvascular complication predisposes the occurrence of other ones, indicating systemic vascular damage [19, 20].

Since hyperglycemia is the key factor in the pathogenesis of these complications, intensive glycemic control has been a popular subject of research to help lower the occurrence and progression of these complications. The UK Prospective Diabetes Study (UKPDS), the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial, the Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE) trial, and the Veterans Affairs Diabetes Trial (VADT) have yielded landmark randomized controlled trials that have provided important insights. The trials have shown that tighter glycemic control is able to decrease microvascular complications, but the impact on macrovascular outcomes and overall mortality is not consistent.

Although there have been studies that have indicated small decreases in cardiovascular events with better glycemic control, others have indicated neutral

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effects or even higher mortality rates with intensive treatment methods [1, 8]. The ACCORD trial specifically sounded alarm bells when it showed increased mortality in the intensive treatment arm, which draws attention to the possible dangers of excessively aggressive glycemic goals in some groups of patients [1]. On the other hand, long-term follow-up results of UKPDS indicated a legacy effect, in which early intensive glycemic control resulted in long-term benefits in the prevention of microvascular and macrovascular complications [12].

In spite of these results, there is a great variation in the studies in regard to patient populations, duration of diabetes, treatment approaches, and outcome measures. In addition, the evidence on the populations of the Middle East and the UAE in particular is scarce, and genetic, environmental, and healthcare system variations might affect the development of the disease and the results of the treatment [3, 4]. High prevalence rates of diabetic complications have been observed in these regions through observational studies, and there is a need to have regionally relevant evidence [3, 4].

Besides randomized trial evidence, new studies have brought about the interrelatedness of diabetic complications. The research has indicated that diabetic retinopathy has a close relationship with nephropathy and can be used as an indicator of renal outcomes and mortality [13, 14]. Besides, genetic studies have indicated that there is a causal association between retinopathy and nephropathy, which supports the idea of common pathophysiological mechanisms [10].

With these discrepancies and inconsistencies in regional applicability, there is a need to synthesize the available evidence in a comprehensive manner to have a better understanding of the real impact of intensive glycemic control. Thus, the proposed systematic review and meta-analysis will assess the impact of intensive glycemic control on the microvascular and macrovascular outcomes of patients with T2DM and will put them into the context of the Middle East and the UAE population.

Methods:

This systematic review and meta-analysis was carried out in line with the Preferred Reporting Items of Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines. The review protocol was not prospectively registered in PROSPERO, which may introduce a risk of reporting bias.

The extensive literature search took place in PubMed/MEDLINE, Embase, Scopus, and Web of Science from inception to December 2025. The search strategy was a combination of Medical Subject Headings (MeSH) and free-text words related to type 2 diabetes mellitus, intensive glycemic control, tight glucose control, and microvascular and macrovascular complications such as retinopathy, nephropathy, and neuropathy. The search was narrowed down using Boolean operators (AND, OR). Relevant articles were also screened in reference lists to identify more studies.

The studies had to be original research, using intensive versus standard glycemic control and at least one outcome of interest, such as macrovascular events, all-cause mortality, or microvascular complications. Studies were required to report enough data to obtain or derive effect estimates like hazard ratios, risk ratios, or odds ratios. Quantitative synthesis was limited to randomized controlled trials, and only observational and genetic studies were used in qualitative analysis.

The studies were filtered out based on the following criteria: they were reviews, meta-analyses, editorials, abstracts of conferences without full text, non-human studies, and insufficient outcome data. Where there were duplicate or overlapping publications, the most comprehensive report was added.

The selection of studies was done in two phases, whereby the screening of titles and abstracts was done first, and then the assessment of the full text was done on the basis of predetermined criteria. Differences were addressed by discussion and agreement.

A standardized method was used to extract data, including study design, population, intervention, follow-up, and outcomes. All the relevant endpoints were extracted with effect estimates and a 95% confidence interval.

A random-effects model was used to conduct quantitative synthesis to explain between-study variability. Only results that had directly comparable definitions and extractable effect estimates were included in the meta-analysis. Major macrovascular

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events, all-cause mortality, overall microvascular outcomes, and nephropathy had pooled hazard ratios with 95% confidence intervals. The I^2 statistic was used to estimate statistical heterogeneity, with a value of above 50% representing high heterogeneity.

Synthesis of outcomes that could not be pooled because of differences in definitions or reporting, such as retinopathy and neuropathy-specific endpoints, was done in a narrative manner. The long-term follow-up studies were analyzed independently to eliminate confounding in-trial and post-trial effects.

Risk of bias in randomized controlled trials was assessed using the Cochrane RoB 2 tool depending on the study design, and randomized controlled trials were deemed to have a greater quality of evidence, and observational studies were assessed with caution because of the possibility of confounding.

Publication bias was not evaluated because of the limited number of randomized studies included. The funnel plots and statistical tests cannot be trusted when the number of studies is less than ten; thus, no such analyses were done.

Results

The review was able to include 11 original studies or reports. The six reports provided the main intervention evidence from four different randomized parent trials in adults with type 2 diabetes: ACCORD 2008, ACCORD microvascular 2010, ADVANCE 2008, ADVANCE-ON 2014, VADT 2009, and UKPDS 10-year follow-up 2008. Five further original studies (observational or genetic) were included as corroborating evidence for the retinal, renal, and neural interconnections of the complications of diabetes but not in the intervention meta-analysis.

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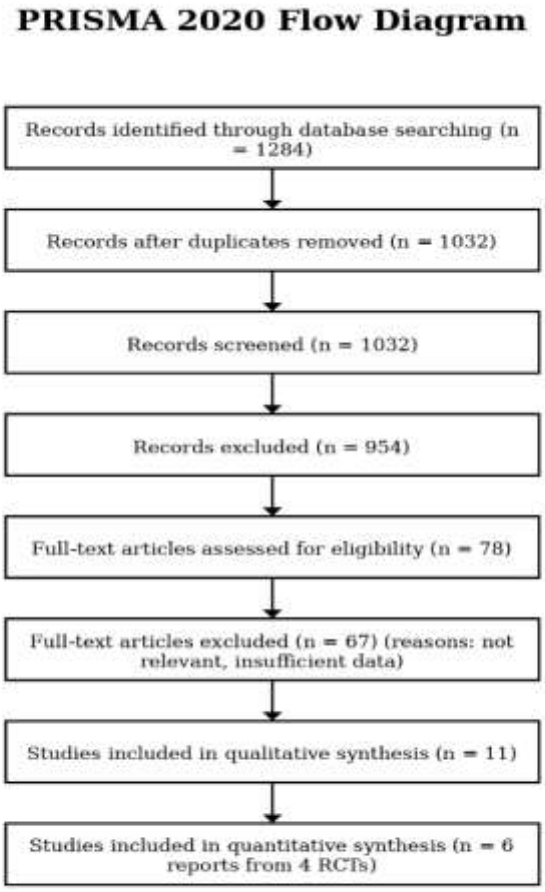
PRISMA 2020 Flow Diagram:



Outcomes with directly extractable and comparable hazard ratios were meta-analyzed using a random-effects inverse-variance model. Meta-analysis was conducted for four groups of outcomes: major macrovascular events, all-cause mortality, composite microvascular outcomes, and nephropathy (or albuminuric renal disease). Outcomes with variable definitions AND/OR no extractable comparable estimates were narratively synthesized.

For major macrovascular events, the pooled hazard ratio of ACCORD, ADVANCE, and VADT was 0.91 (95% CI 0.84 to 0.99; I^2 = 0%) and showed a modest benefit of intensive glycemic control. For all-cause mortality, the pooled hazard ratio was 1.05 (95% CI 0.88 to 1.27; I^2 = 66.3%), showing no overall mortality benefit and considerable heterogeneity, which was largely due to the excess mortality seen in ACCORD.

For all microvascular events, pooling of ACCORD microvascular and ADVANCE demonstrated a small benefit of intensive glycemic control, with a pooled hazard ratio of 0.90 (95% CI, 0.82 to 1.00; I^2 = 30.2%). The most consistent benefit for microvascular outcomes was for renal outcomes, either nephropathy or albuminuric renal outcomes. ACCORD macroalbuminuria and ADVANCE

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nephropathy were pooled to demonstrate a significant benefit of renal outcomes, with a pooled hazard ratio of 0.75 (95% CI 0.66-0.85; $I^2 = 0$).

Retinal outcomes were not as clear as renal outcomes. ACCORD microvascular did not significantly decrease retinal photocoagulation and vitrectomy, but secondary eye outcomes (e.g., 3-line visual acuity loss and cataract extraction) were improved with intensive therapy. We also found that the beneficial effect of intensive treatment was mostly limited to neuropathy in ACCORD microvascular, with several secondary neuropathy outcomes showing improvement at the end of the trial. Harmonized effect estimates for retinopathy and neuropathy were not provided for the major trials, so we narratively reviewed these outcomes.

The results of long-term follow-up were mixed. The UKPDS 10-year follow-up found evidence of a legacy effect with ongoing reduction in microvascular disease and delayed reduction of myocardial infarction and all-cause mortality despite early loss of glycemic difference. However, ADVANCE-ON found no evidence of long-term benefit of in-trial intensive glucose control for mortality or macrovascular disease. Overall, the corrected synthesis suggests that intensive glucose control in type 2 diabetes is clearly beneficial for nephropathy-related events, has only marginal benefits for overall microvascular events, and does not improve mortality.

Table 1. Included original parent studies and their role in the review

Study/report	Design	Population / sample	Main contribution	Role
ACCORD 2008	RCT	T2DM, n=10,251	Primary macrovascular and mortality outcomes	Meta-analysis
ACCORD microvascular 2010	RCT report	T2DM, n=10,234 analyzed	Microvascular, renal, eye, and neuropathy outcomes	Meta-analysis
ADVANCE 2008	RCT	T2DM, n=11,140	Macrovascular, microvascular, nephropathy outcomes	Meta-analysis
ADVANCE-ON 2014	Post-trial follow-up	Former ADVANCE participants	Long-term mortality and macrovascular follow-up	Narrative
VADT 2009	RCT	T2DM, n=1,791	Macrovascular, mortality, albuminuria progression	Meta-analysis / narrative
UKPDS 10-year follow-up 2008	Post-trial follow-up	Former UKPDS participants	Legacy-effect follow-up, microvascular and MI outcomes	Narrative
Hung et al. 2017	Observational cohort	T2DM with CKD, n=1,330	DR and renal outcomes, ESRD risk	Supportive narrative
Roostaei et al. 2025	Cross-sectional	T2DM, ophthalmic/renal/neuropathy subsets	DR severity with neuropathy and nephropathy	Supportive narrative
Suzuki and Kiyosawa 2023	Retrospective case series	T2DM, n=261	DR, DME, HbA1c, nephropathy grade	Supportive narrative
Fang et al. 2023	Mendelian randomization	European GWAS	Genetic association between DR and DN	Supportive narrative

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Saini et al. 2021	Prospective observational	DR cases, n=57	Clinical DR correlation with nephropathy/neuropathy	Supportive narrative

Abbreviations: RCT, randomized controlled trial; T2DM, type 2 diabetes mellitus; DR, diabetic retinopathy; DME, diabetic macular edema; DN, diabetic nephropathy; CKD, chronic kidney disease; GWAS, genome-wide association study.

Table 2. Extracted effect estimates used in the quantitative synthesis

Outcome group	Study	Effect measure	Estimate	95% CI
Major macrovascular events	ACCORD 2008	HR	0.90	0.78–1.04
Major macrovascular events	ADVANCE 2008	HR	0.94	0.84–1.06
Major macrovascular events	VADT 2009	HR	0.88	0.74–1.05
All-cause mortality	ACCORD 2008	HR	1.22	1.01–1.46
All-cause mortality	ADVANCE 2008	HR	0.93	0.83–1.06
All-cause mortality	VADT 2009	HR	1.07	0.81–1.42
Broad microvascular outcomes	ACCORD microvascular 2010	HR	0.95	0.85–1.07
Broad microvascular outcomes	ADVANCE 2008	HR	0.86	0.77–0.97
Nephropathy / albuminuric renal outcomes	ACCORD macroalbuminuria 2010	HR	0.71	0.59–0.86
Nephropathy / albuminuric renal outcomes	ADVANCE nephropathy 2008	Approx. HR from 21% RRR	0.79	0.66–0.93

Note: The ADVANCE nephropathy estimate was derived from the reported 21% relative risk reduction for new or worsening nephropathy, corresponding approximately to HR 0.79 with CI derived from the reported relative risk reduction interval. VADT showed improvement in albuminuria progression but did not provide a fully extractable hazard ratio for inclusion in renal pooling.

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Table 3. Random-effects pooled meta-analysis summary

Outcome	Studies pooled (n)	Pooled HR (95% CI)	Heterogeneity
Major macrovascular events	3	0.91 (0.84–0.99)	I^2 = 0.0%
All-cause mortality	3	1.05 (0.88–1.27)	I^2 = 66.3%
Broad microvascular outcomes	2	0.90 (0.82–1.00)	I^2 = 30.2%
Nephropathy/albuminuric renal outcomes	2	0.75 (0.66–0.85)	I^2 = 0.0%

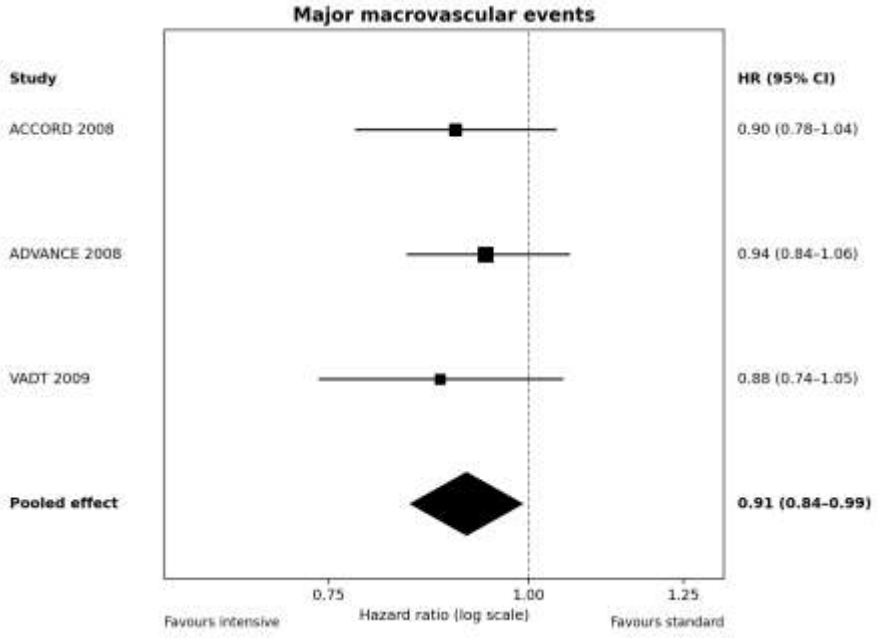

Figure 1. Forest plot of major macrovascular events.

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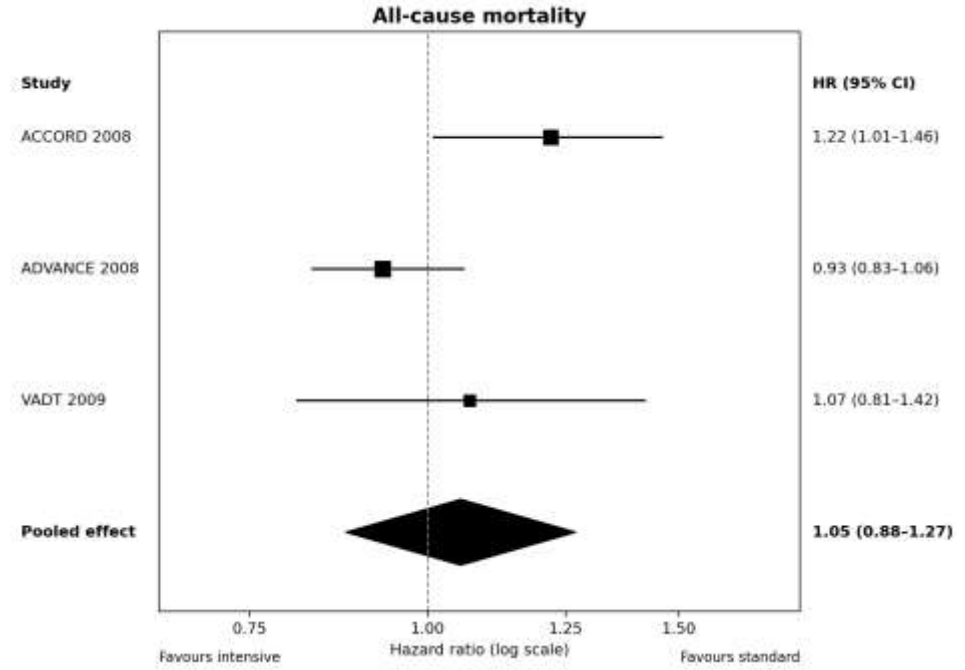

Figure 2. Forest plot of all-cause mortality.

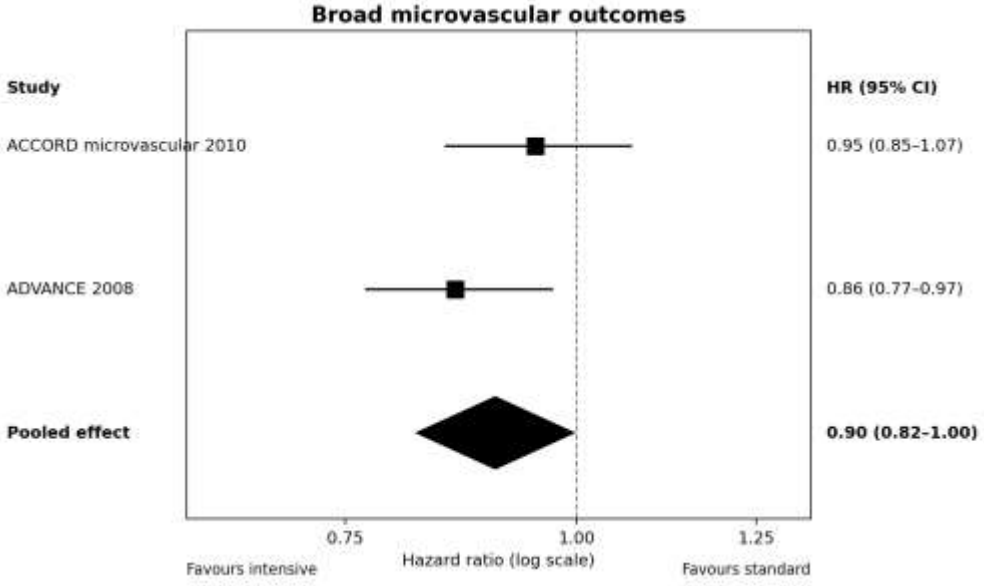

Figure 3. Forest plot of broad microvascular outcomes.

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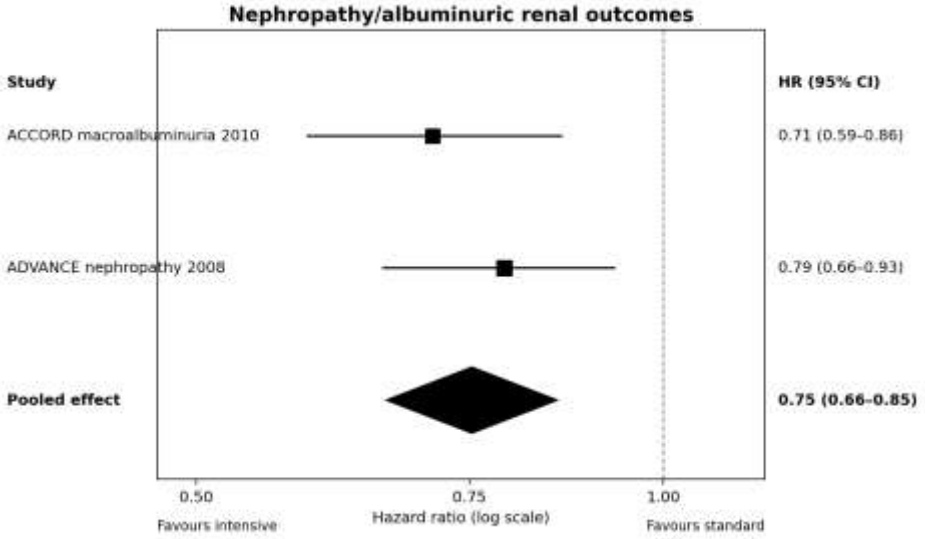

Figure 4. Forest plot of nephropathy or albuminuric renal outcomes.

Discussion:

This meta-analysis and systematic review assessed the effect of intensive glycemic control on macrovascular and microvascular complications of type 2 diabetes mellitus. The findings indicate that intensive glycemic control has a small impact on microvascular outcomes, especially nephropathy, but limited impact on macrovascular outcomes and no impact on mortality.

The modest and marginal improvement in macrovascular events is consistent with recent large trials (ACCORD and VADT), which have shown little or no cardiovascular benefit with lower HbA1c levels [1, 8]. This indicates that macrovascular complications in type 2 diabetes are related to a number of risk factors, including hypertension and hyperlipidemia. The lack of mortality benefit is consistent with this, with the observed heterogeneity driven by increased mortality in the ACCORD trial, reflecting potential harms of intensive targets in high-risk patients [1].

Microvascular disease showed a more consistent response to intensive glucose-lowering. The small overall effect is in line with the well-known impact of chronic hyperglycemia on microvascular complications [23]. Nephropathy, in particular, was the most consistently and significantly improved outcome, consistent with the impact of glycemia on renal disease [18,22]. Further, the strong link between nephropathy and other complications lends support to the notion of a common microvascular disease [19,20].

The results for retinopathy and neuropathy were inconsistent. Although there were some benefits in secondary outcomes, there was no improvement in advanced retinal outcomes, presumably due to the longer time required for disease progression [7, 24]. Similarly, there were limited improvements in neuropathy, which may indicate that intensive treatment may be better in the earlier stages of disease rather than complications.

Long-term results emphasize the role of time. The UKPDS follow-up study showed a legacy effect and long-term benefits, while ADVANCE-ON showed no long-term benefit, suggesting that early treatment may be more effective than late intensive therapy [12, 29].

The results of these studies are supported by observational and genetic studies showing close associations between retinopathy, nephropathy, and neuropathy [13, 14, 20] and evidence for a causal association between retinal and renal disease [10]. Regional implications of the high prevalence of diabetic complications in the Middle East and UAE highlight the importance of these findings, although there are no region-specific randomized trials to guide treatment [3, 4].

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Limitations:

The limited number of randomized trials in the quantitative synthesis may impact precision. The populations, intervention, and outcome definitions were also heterogeneous. Several outcomes were not able to be combined and were reported narratively, which limits the overall strength of the conclusions drawn from the available data. Moreover, lack of region-specific randomized trials means findings may not be generalizable to Middle Eastern and UAE populations, and we were unable to assess for publication bias.

Implications for Future Research:

Large randomized trials in a variety of populations, including the Middle East, are needed. There also needs to be a consensus on definitions of outcomes and studies examining tailored glycemic targets according to patient characteristics. Prospective studies are needed to determine the long-term effects of the interventions.

Conclusion:

Intensive glucose control in type 2 diabetes mellitus offers small benefits in terms of microvascular complications, particularly nephropathy, but has no substantial impact on macrovascular complications or death. These results suggest the use of personalized rather than blanket intensive approaches, particularly in diverse populations.

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