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Optimal Target Level of Glycosylated Hemoglobin (HbA1c) for Reducing Cardiovascular Mortality in Patients with Diabetic Nephropathy: A Systematic Review

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ABSTRACT

Adverse cardiovascular (CVD) complications drive increased mortality in diabetic nephropathy (DN) patients. Glycemic control is the primary management approach in patients with diabetes. However, no specific thresholds have been reported for reducing CVD in DN patients. A systematic literature review was conducted in adherence with the PRISMA guidelines to synthesise evidence published from January 1990 to June 2024. The objective of this systematic literature review was to explore optimal glycemic control levels to reduce CVD complications in patients with diabetic nephropathy. A pre-defined study selection criterion was employed to conduct a targeted search of academic databases to yield relevant literature. Ten studies that met the eligibility criteria were synthesised to generate evidence-based findings. Findings revealed a linear correlation between glycosylated haemoglobin (HbA1c) levels and both cardiovascular mortality and the progression of nephropathy to end-stage renal disease (ESRD) and renal-related death. As the renal disease progressed, lower HbA1c values lost their predictive abilities and were associated with increased CVD risk. New glycemic controls, such as Glycated Albumin or the Haemoglobin Glycation Index, have shown potential to reflect glycemic levels accurately but require further validation to predict CVD mortality in DN patients. Our study identified a lack of research on CVD-specific mortality in DN patients, while accounting for heterogeneity in exposure and outcome domains. Future research should focus on long-term monitoring of HbA1c levels in DN and their influence on CVD mortality.

INTRODUCTION

Diabetes mellitus (DM) is one of the most prevalent chronic illnesses with significant mortality and morbidity. Globally, approximately 537 million people were living with diabetes in 2021 (10% of the global population), placing a healthcare burden of $966 billion (Magliano & Boyko, 2021). It is further predicted to rise to $1054 billion by 2045. Moreover, the epidemic rate of growth in DM is projected to increase to 643 million (11.3%) by 2030 and 783 million (12.2%) by 2045 (Ong *et al.*, 2023; Magliano & Boyko, 2021). The high morbidity and mortality burden of DM is associated with its microvascular complications, including retinopathy, nephropathy, and neuropathy, while macrovascular complications encompass myocardial infarction, stroke, peripheral vascular disease, and diabetic foot (Sosale *et al.*, 2014; Kharroubi & Darwish, 2015).

The most debilitating microvascular complication of DM is diabetic nephropathy (DN), affecting individuals diagnosed with both type 1 diabetes (T1D) and Type 2 diabetes (T2D), while being the leading cause of end-stage renal disease (ESRD) in developing countries. Diabetic nephropathy is characterised by persistent albuminuria resulting in the decline of glomerular filtration rate (GFR) along with hypertension, impaired kidney structure and functions, and proteinuria (Rout *et al.*, 2025). Cardiovascular disease (CVD) risk is increased by both diabetes and nephropathy (Borch-Johnsen & Kreiner, 1987). A recent study reported that diabetic kidney disease (DKD) exerts higher CVD risks in comparison to those diabetic patients who do not develop kidney disease. Furthermore, CVD risk is exacerbated in both the presence and absence of reduced eGFR and of urinary albumin-to-creatinine ratio (UACR) (Janota-Sosińska *et al.*, 2025). Studies report that diabetic patients with CKD complications were 1.8 times more likely at-risk for CVD mortality (Chou *et al.*, 2024). The risk of CVD mortality in diabetic nephropathy patients is compounded due to uremic toxins (El Chamieh *et al.*, 2022), chronic inflammation (Hasheminasabgorji & Jha, 2021), and accelerated atherosclerosis (Hasheminasabgorji & Jha, 2021), which collectively add to the synergistic risk. Strict glycemic control is essential in overcoming the development and progression of long-term DM complications. It involves monitoring glycated haemoglobin (HbA1c) levels over the past 2-3 months in blood glucose, making it a gold standard for clinical monitoring of glycemic control (McGuire *et al.*, 2016). HbA1c levels influence both microvascular and macrovascular complications in diabetic patients (Sartore *et al.*, 2023). The benefit of glycemic control in reducing end-organ complications has been reported in clinical trials such as the Diabetes Control and Complications Trial (DCCT) and the United Kingdom Prospective Diabetes Study (UKPDS) (UKPDS, 1998; Nathan *et al.*, 1993). While the DCCT demonstrated reduced risk of retinopathy, nephropathy, and neuropathy by 35-70%

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using intensive insulin therapy (Nathan *et al.*, 1993), the UKPDS reported a 25% risk reduction in microvascular complications (UKPDS, 1998).

However, the UKPDS did not find an effect of HbA1c on macrovascular complications (UKPDS, 1998). In chronic conditions like DM, literature reports a "legacy effect" which encompasses long-term benefits or harms associated with past euglycemia or hyperglycemia, respectively, and long-term follow-up of trials like DCCT/ECID and UKPDS revealed intensive control was related to improved macrovascular outcomes over time (Control *et al.*, 2016; Holman *et al.*, 2008). In comparison to these early studies, later trials included long-term TD2 patients with a history of risk factors or vascular complications (Group, 2008; Patel *et al.*, 2008; Duckworth *et al.*, 2009) to evaluate the impact of intensive control on CVD risk. Trials like Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial and Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE) in their follow-up reported no significant effect of intensive glycemic control on CVD events (Wong *et al.*, 2016), however, ADVANCE trial reported sustained reduced end-stage renal disease (ESRD) values (HR 0.54 [95% CI 0.34, 0.85]; p = 0.007) (Gerstein *et al.*, 2011).

One of the significant drawbacks of intensive diabetic treatment includes the risk of hypoglycemia (Gubitosi-Klug *et al.*, 2017). Studies report hypoglycemia to cause arrhythmias and other CVD-related complications and mortality while its causal linkages are being explored (Li *et al.*, 2023). Similarly, severe hypoglycemia and CKD are reported to exhibit synergistic properties leading to increased all-cause mortality, particularly in T2D patients (Kong *et al.*, 2014). The prognostic value of HbA1c becomes critically unreliable in the presence of uremic disturbances, anaemia, or altered RBC survival (NGSP, 2021). However, a recent study reported that in T2D patients with advanced CKD and reduced glycemic control, there was no influence on HbA1c or major adverse kidney events (MAKE) (Navarro-Blackaller *et al.*, 2025). These further underscore the unreliability of HbA1c in diabetic nephropathy. Guidelines for diabetic patients with CKD have evolved over the years, and now, instead of only managing for glycemic levels, they recommend a more personalised approach. This includes HbA1c levels ranging from 6.5% to 8.0% in patients with diabetic nephropathy, depending on clinical factors such as comorbidities and an increased risk of hypoglycemia (Khunti *et al.*, 2021).

Given the recognition of personalised glycemic levels, a critical research gap exists. These guidelines are based on data from studies that are either focused on the general diabetic population or report increased CVD risk. There is a lack of focus on assessing the association between HbA1c levels and critical CVD events leading to mortality in a severely vulnerable group comprising diabetic nephropathy patients (Caturano *et al.*, 2025). This warrants the synthesis of current evidence to evaluate optimal HbA1c levels to reduce CVD mortality in high-risk diabetic nephropathy patients.

This systematic literature review aims to assess the HbA1c levels required to reduce CVD burden in the high-risk subgroup with diabetic nephropathy. This literature review will investigate the optimal glycemic value associated with decreased CVD mortality in DN patients categorised by kidney disease severity and albuminuria status.

MATERIALS AND METHODS

Study Design

A systematic research review methodology was employed to synthesise the current scholarship on the association between different HbA1c target levels and cardiovascular mortality in patients with diabetic nephropathy. The literature review will be conducted in accordance with PRISMA guidelines, ensuring a transparent, reproducible, and robust review process.

Eligibility Criteria

A pre-defined eligibility criterion was curated using the PICO (Population, Intervention, Comparator, and Outcome) framework for article evaluation (Table 1). The publication timeline for eligible studies spanned from January 1990 to June 2024. Only studies published in English were included.

Table 1: PICO Framework for Selection of Eligible Studies

Category	Inclusion Criteria	Exclusion Criteria
Population	Adult human patients (≥ 18 years). Diagnosed with diabetic nephropathy/ diabetic kidney disease (DKD). DKD is defined by the presence of any one of the following: - Persistent albuminuria (e.g., UACR ≥30 mg/g). - Reduced eGFR (e.g., <60 mL/min/1.73m²). - Diabetic kidney disease staging (e.g., KDIGO categories G1-G5, A1-A3). - A clinical diagnosis as per study criteria. Diabetes Type: Type 1 or Type 2 diabetes mellitus.	- Studies where the population includes individuals without diabetic nephropathy, or where DKD patients form an unanalysable subgroup. - Studies focusing solely on non-diabetic kidney disease. - Studies involving pediatric or adolescent populations (<18 years).

Intervention / Exposure	Specific HbA1c target levels, categories of glycemic control, or achieved HbA1c levels. This includes: - Intensive glycemic control (e.g., targeting HbA1c <6.5%, <7.0%). - Standard glycemic control. - Studies reporting outcomes stratified across a range of HbA1c values (e.g., <7%, 7-8%, >8%). - Studies reporting the association between achieved HbA1c levels (as a continuous variable or in predefined categories) and cardiovascular mortality.	- Studies that do not specify HbA1c targets, do not stratify participants by HbA1c levels, and do not report an association between achieved HbA1c and the outcome. - Studies focusing only on mean HbA1c for a single cohort without any comparative analysis or association testing.
Comparator	A different HbA1c target level or category. Standard vs. intensive control, higher HbA1c targets (e.g., <8.0%) vs. lower targets (e.g., <7.0%), or any within-study comparison of different HbA1c strata.	Studies without a comparative group or analysis of different HbA1c levels/targets. Single-arm studies or those reporting only a single HbA1c value for the entire cohort without comparison.
Outcomes	Cardiovascular mortality (as defined by the study authors). This includes death attributable to atherosclerotic cardiovascular disease (e.g., MI, stroke), heart failure, sudden cardiac death, or other fatal cardiovascular events. OR A composite major adverse cardiovascular event (MACE) outcome that includes cardiovascular mortality as a component, provided cardiovascular mortality data is separately extractable. Measured at any time point during a minimum follow-up of 12 months.	- Studies that do not report cardiovascular mortality as a distinct outcome, and where it cannot be extracted from a composite endpoint. - Studies with a follow-up duration of less than 12 months. - Studies where cardiovascular mortality data cannot be extracted or calculated.
Study Type & Context	Randomised Controlled Trials (RCTs), prospective or retrospective cohort studies, case-control studies, and systematic reviews or meta-analyses that report original, stratified data on HbA1c and cardiovascular mortality in patients with diabetic nephropathy. Clinical studies conducted in any setting (e.g., primary care, tertiary hospital, clinical trial centres) that report on the association between HbA1c and cardiovascular mortality in the specified population.	In-vitro (laboratory-based) studies, animal studies, systematic reviews, or meta-analyses that do not provide extractable, stratified outcome data, narrative reviews, editorials, commentaries, case reports, case series, and studies published only as conference abstracts without sufficient methodological or results detail. Studies not published in English.

Search Strategy

The literature was searched across academic databases, including PubMed, Scopus, MEDLINE, the Cochrane Library, and EMBASE. The search strategy encompassed keyword combinations derived from database-specific vocabulary terms (e.g., MeSH terms for PubMed). These include "Diabetic Nephropathies," "Diabetic Kidney Disease," "Kidney Disease," "Diabetic," "Glycated Haemoglobin," "HbA1c," "Glycemic Control," "Glycaemic Control," "HbA1c Target," "Cardiovascular Mortality," "Cardiovascular Death," "Heart Disease Mortality," and "Mortality." The search strings used in different databases are presented in Table 2. The language filter was applied to include only English studies.

Study Selection

A total of 200 articles were extracted from electronic databases; 70 duplicates were identified and removed. In the initial screening phase, titles and abstracts were analysed, resulting in the exclusion of 50 irrelevant articles. The remaining 80 articles were then screened based on predefined eligibility criteria (PICO Framework: Table 1), and then the studies were assessed for eligibility and full-text availability; 70 studies were excluded for

Table 2: Search String for Literature Retrieval

Database	Controlled Vocabulary Terms	Search String (Adapted for each database's syntax)
PubMed	"Diabetic Nephropathies"[Mesh] "Glycated Hemoglobin"[Mesh] "Cardiovascular Diseases"[Mesh] "Mortality"[Mesh]	("Diabetic Nephropathies"[Mesh] OR "Diabetic Kidney Disease" OR "Diabetic Glomerulosclerosis") AND ("Glycated Haemoglobin"[Mesh] OR "HbA1c" OR "Glycated Haemoglobin A" OR "glycemic control" OR "glycaemic control" OR "HbA1c target") AND ("Cardiovascular Diseases"[MeSH] OR "Cardiovascular Mortality" OR "Cardiovascular Death" OR "Heart Disease Mortality") AND ("Mortality"[Mesh] OR "Death" OR "Survival")
EMBASE (via Ovid)	'diabetic nephropathy/exp 'hemoglobin a1c/exp 'cardiovascular mortality/exp 'mortality/exp	('diabetic nephropathy'/exp OR 'diabetic kidney disease' OR 'diabetic glomerulosclerosis') AND ('haemoglobin a1c'/exp OR 'hbA1c' OR 'glycated haemoglobin' OR 'glycemic control' OR 'glycaemic control') AND ('cardiovascular mortality'/exp OR 'cardiovascular death' OR 'heart disease mortality') AND ('mortality'/exp OR 'death' OR 'survival')
Scopus	None	("diabetic nephropathy" OR "diabetic kidney disease) AND ("hbA1c" OR "glycated haemoglobin" OR "glycemic control") AND ("cardiovascular mortality" OR "cardiovascular death")
Cochrane Library	None	("diabetic nephropathy" OR "diabetic kidney disease") AND ("HbA1c" OR "glycated haemoglobin" OR "glycemic control") AND ("cardiovascular mortality" OR "cardiovascular death") in Title, Abstract, or Keywords
MEDLINE (via Ovid)	"Diabetic Nephropathies"/ "Haemoglobin A, Glycosylated"/ "Cardiovascular Diseases"/ "Mortality"/	("Diabetic Nephropathies"/ OR "Diabetic Kidney Disease". OR "Diabetic Glomerulosclerosis" AND ("Haemoglobin A, Glycosylated"/ OR "HbA1c" OR "Glycated Haemoglobin A" OR "glycemic control". OR "glycaemic control") AND ("cardiovascular diseases"/ OR "Cardiovascular Mortality" OR "Cardiovascular Death". OR "Heart Disease Mortality") AND ("Mortality"/ OR "Death" OR "Survival")

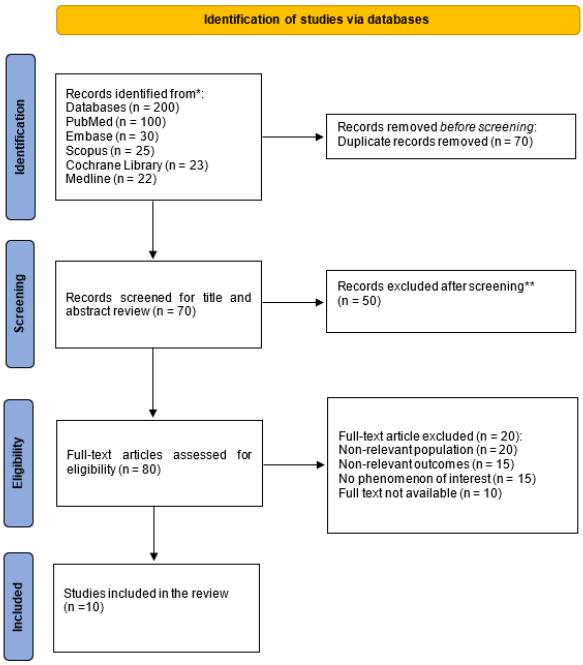

Figure 1: PRISMA Flowchart for Study Selection

non-adherence. Ten articles aligned rigorously with the defined criteria and were selected to be included in the final synthesis. Visual representation of the screening process is presented in the PRISMA flowchart in Figure 1.

Table 3: Summarised Data Extraction Variables

Category	Variables for Extraction
Study Identification & Characteristics	Author(s), Publication Year, Journal, Country of Study, Funding Source, Type of Study (e.g., RCT, Prospective Cohort, Retrospective Cohort)
Study Methodology	Primary Objective/ Aim, Study Design, Data Collection Period, Duration of Follow-up, Confounding Factors Adjusted For (e.g., age, sex, blood pressure, lipid levels, medication use), Conflict of Interest Statement
Population & Context	Total Sample Size, Sample Size per Comparison Group, Age Range & Mean Age, Proportion of Male/Female Participants, Type of Diabetes (Type 1, Type 2, or mixed), Diabetic Nephropathy Definition & Diagnostic Criteria, Baseline Renal Function (e.g., mean eGFR, albuminuria level), Clinical Setting, Inclusion/ Exclusion Criteria
Intervention / Exposure Details	HbA1c Target Levels or Categories Defined in the Study (e.g., <6.5%, 6.5-7.5%, >8.0%), Definition of Glycaemic Control Groups (e.g., intensive vs. standard), Method of HbA1c Measurement, Mean HbA1c Achieved in Each Group During Follow-up
Outcome Data: Primary	Cardiovascular Mortality: Definition used in the study, Number of Events, Incidence Rate, Hazard Ratio (HR), Risk Ratio (RR), or Odds Ratio (OR) with corresponding 95% Confidence Intervals and p-values. Raw data for calculating these measures (the number of events and the total number of participants in each group) will be extracted.
Outcome Data: Other	All-Cause Mortality, Time-to-Event Data, Any Reported Subgroup Analyses, Other Reported Cardiovascular Outcomes (e.g., MACE), Serious Adverse Events Related to Glycaemic Control (e.g., severe hypoglycaemia)
Authors' Conclusions & Relevance	The authors' main conclusions on the association between HbA1c and cardiovascular mortality, the study's strengths and limitations, future research needs, and Relevance to clinical practice and this review.

Quality Assessment

All of the included studies were critically appraised for their methodological robustness, risk of bias, and to ensure the synthesis of evidence is of high quality. Studies were grouped by study type, and an appropriate quality assessment tool was used. Appraisal tools are employed according to their respective study types. Since the majority of the included studies were prospective and retrospective cohorts, the Newcastle-Ottawa Scale (NOS) was employed. An adapted version of the Cochrane Risk of Bias Tool was used to appraise the only post hoc analysis of the RCT included. The studies were ranked "Good", "Fair", or "Poor" based on their individual assessment. Conclusively, the selected evidence base demonstrated intense rigour, with the majority of studies rated "Good" and prioritised in synthesising the evidence. Studies with "Fair/Poor" ratings will be cautiously presented. Consolidated quality appraisal ratings are presented in Table 4.

Table 4: Consolidated Quality Appraisal

Study (Year)	Design	Tool	Overall Rating
Huang *et al.* (2024)	Prospective Cohort	Newcastle-Ottawa Scale (NOS)	Good
Rhee *et al.* (2017)	Retrospective Cohort	Newcastle-Ottawa Scale (NOS)	Good
Shurraw *et al.* (2011)	Retrospective Cohort	Newcastle-Ottawa Scale (NOS)	Good
Williams *et al.* (2010)	Retrospective Cohort	Newcastle-Ottawa Scale (NOS)	Fair
Kalantar-Zadeh *et al.* (2007)	Retrospective Cohort	Newcastle-Ottawa Scale (NOS)	Good
Okada *et al.* (2007)	Prospective Cohort	Newcastle-Ottawa Scale (NOS)	Fair
Morioka *et al.* (2001)	Prospective Cohort	Newcastle-Ottawa Scale (NOS)	Fair
Wu *et al.* (1997)	Retrospective Cohort	Newcastle-Ottawa Scale (NOS)	Poor
Tzamaloukas *et al.* (1993)	Retrospective Cohort	Newcastle-Ottawa Scale (NOS)	Poor
Papademetriou *et al.* (2015)	Post-hoc RCT Analysis	Cochrane ROB 2.0 (adapted)	Good

RESULTS AND DISCUSSONS

Study Characteristics

Adherence to predefined eligibility criteria led to the selection of 10 studies, of which the majority were observational (n=9), and only one was a post hoc analysis of a randomised controlled trial. The lack of RCTs is a significant research gap. Geographically, most of the studies were conducted in the USA (n=5), followed by Japan (n=2), Canada (n=1), and Taiwan (n=1). Collectively, the pooled sample size accounted for 180,000 participants who were diagnosed with various stages of DKD, which spanned from stage 3 CKD to end-stage renal disease (ESRD). Across studies, sample sizes ranged from 78 to more than 82,000 participants, who were followed for 1 year to 9 years. Furthermore, all of the studies assessed correlations between glycemic control and cardiovascular mortality; however, due to the scarcity of evidence, the exposure (HbA1c criteria) and outcomes (CVD-specific or MACE) reported were not uniform. Study characteristics are summarised in Table 5.

Table 5: Study Characteristics Table

Study (Year)	Huang *et al.* (2024)	Rhee *et al.* (2017)	Papademetriou *et al.* (2015)	Shurraw *et al.* (2011)	Williams *et al.* (2010)
Country	USA	USA	USA/Canada	Canada	USA
Design	Prospective Cohort	Retrospective Cohort	Post-hoc RCT Analysis	Retrospective Cohort	Retrospective Cohort
Population (DKD Stage)	DKD (eGFR <60 or ACR >30)	Diabetic CKD transitioning to ESRD	T2D + CKD Stage I-III (ACCORD)	DM + CKD Stage 3-4	DM on hemodialysis
Sample Size	1,057	17,819	10,136	23,296	24,751
Exposure / Glycemic Measure	Haemoglobin Glycation Index (HGI) tertiles	Mean HbA1c in pre-ESRD year (categories: <5% to ≥9%)	Intensive (HbA1c <6.0%) vs. Standard (7.0-7.9%) therapy	HbA1c categories (<7%, 7-9%, >9%)	Time-updated HbA1c categories (≤5.0% to ≥11.0%)
Outcome (CV Mortality)	CVD death (ICD-10 codes)	CV death (USRDS)	CV death (ACCORD def.)	Composite CV events (MI, stroke, HF, revasc)	All-cause mortality (CV not separated)
Key Adjusted Confounders	Age, sex, race, SES, comorbidities, diabetes meds, HEI, eGFR, Hb, HbA1c	Age, sex, race, CCI, BMI, labs (albumin, Hb, eGFR)	Age, sex, BMI, HbA1c, SBP, smoking, CVD history, med use	Age, sex, income, comorbidity, eGFR, distance to nephrologist	Age, sex, race, vintage, access, labs (albumin, Hb, Kt/V)
Follow-up Duration	Median 6.67 years	1 year post-ESRD	Median 3.4 years (up to 8)	Median 46 months	Up to 3 years

Tzamaloukas *et al.* (1993)	Wu *et al.* (1997)	Morioka *et al.* (2001)	Okada *et al.* (2007)	Kalantar-Zadeh *et al.* (2007)
USA	Taiwan	Japan	Japan	USA
Retrospective Cohort	Retrospective Cohort	Prospective Cohort	Prospective Cohort	Retrospective Cohort
DM on dialysis (Type I & II)	T2D starting HD	DM starting HD	T2D ESRD on HD	Diabetic MHD patients
226	137	150	78	23,618
Glycemic control (Good vs. Poor by glucose range & HbA1c)	Pre-HD glycemic control (Good vs. Poor by HbA1c & glucose)	HbA1c at HD start (<7.5% vs. ≥7.5%)	HbA1c & Glycated Albumin (median split)	HbA1c categories (<5% to ≥10%)
CV death (listed as cause)	Cardiac death	CV death (cardiac, cerebrovascular, PVD)	CV death (sudden death, HF, MI, stroke)	CV death (MI, arrest, HF, CVA)
None (unadjusted comparisons)	Age, serum albumin, cholesterol, glycemic control	Age, sex	Age, sex, dialysis vintage, BMI, SBP, albumin, hematocrit, Kt/V	Case-mix + MICS-adjusted (BMI, albumin, ferritin, Hb, etc.)
Not specified (1976-1991)	Up to 5 years	Median 2.69 years	Mean 35 months	3 years

Abbreviations: ACR = Albumin-to-creatinine ratio; CCI = Charlson Comorbidity Index; CKD = Chronic Kidney Disease; CV = Cardiovascular; CVA = Cerebrovascular Accident; DM = Diabetes Mellitus; DKD = Diabetic Kidney Disease; eGFR = estimated Glomerular Filtration Rate; ESRD = End-Stage Renal Disease; HD = Hemodialysis; HEI = Healthy Eating Index; HF = Heart Failure; HGI = Hemoglobin Glycation Index; MHD = Maintenance Hemodialysis; MI = Myocardial Infarction; MICS = Malnutrition-Inflammation Complex Syndrome; PVD = Peripheral Vascular Disease; RCT = Randomized Controlled Trial; SES = Socioeconomic Status; SBP = Systolic Blood Pressure; T2D = Type 2 Diabetes; USRDS = United States Renal Data System.

Synthesis of Findings

The evidence was limited to observational studies, and this was further compounded by increased methodological and clinical heterogeneity, which precluded a meta-analysis. It included variability of exposures, characterisation of populations, and uncertainty across studies. Given the limitations, a narrative review was appropriate, which classified the affected population by several stages of DKD, as presented in Table 6.

The noteworthy aspect highlighted across the studies was the non-linearity of the correlation between HbA1c and cardiovascular mortality in diabetic nephropathy patients, which modulated significantly depending on the progression stage of kidney disease.

Initially, at stages 3-4 of CKD, when patients are not dependent on dialysis, the relationship between HbA1c and cardiovascular mortality was reported to be U- or J-shaped, indicating that both high and low HbA1c values were associated with increased cardiovascular mortality. Their values across studies differed significantly, where one study reported CV mortality was predicted via Haemoglobin Glycation Index (Huang *et al.*, 2024), while CV events were reported at HbA1c level >9% while this risk was simultaneously associated with lower HbA1c levels at <6.5% (Shurraw *et al.*, 2011). Papademetriou *et al.* (2015) reported a 41% higher risk of CV mortality in patients with CKD who were on intensive glycemic control (HbA1c <6.0%) compared with those without

Table 6: Synthesis of Findings from Selected Studies

Study (Year)	Population (DKD Stage)	Glycemic Exposure / Comparison	Main Finding Related to CV Mortality	Key Reported Effect Measure (HR, 95% CI)
Non-Dialysis Dependent CKD (Stages 3-4)				
Huang *et al.* (2024)	DKD (CKD 1-4)	HGI Tertiles (Q3: High vs. Q2: Mid)	J-shaped association. High HGI is associated with increased CV mortality, independent of HbA1c.	HR 2.06 (1.13–3.77), P-trend=0.03
Shurraw *et al.* (2011)	CKD Stage 3-4	HbA1c >9% vs. <7%	U-shaped association. HbA1c >9% associated with a higher risk of CV events. Excess mortality is also at HbA1c <6.5%.	HR for All-Cause Mortality (Stage 3): 1.35 (1.20–1.53)
Papademetriou *et al.* (2015)	CKD Stage I-III (ACCORD)	Intensive (A1c<6%) vs. Standard (7-7.9%)	Intensive control increased CV mortality in CKD patients. No significant effect in non-CKD patients.	HR 1.41 (1.05–1.89), P=0.02
Transition to ESRD / Pre-ESRD				
Rhee *et al.* (2017)	Pre-ESRD (Transition)	HbA1c ≥9% vs. 6-<7%	Higher pre-ESRD HbA1c (≥8-9%) is associated with higher post-ESRD CV death risk.	Significant association per case-mix model (Specific HR in Suppl.)
Wu *et al.* (1997)	Pre-ESRD (Start of HD)	Poor vs. Good Control (Pre-HD)	Poor pre-dialysis glycemic control predicted higher cardiac mortality on dialysis.	Multivariate HR for Good Control: 0.37 (0.18–0.80), P<0.01
ESRD on Dialysis				
Kalantar-Zadeh *et al.* (2007)	HD Patients	HbA1c ≥10% vs. 5-5.9%	Higher HbA1c incrementally associated with higher CV death, after adjusting for MICS.	MICS-adj. HR 1.73 (1.44–2.08), P<0.001
Okada *et al.* (2007)	HD Patients	HbA1c (continuous)	HbA1c (as a continuous variable) is not a significant predictor of CV mortality in ESRD.	Adj. HR per 1%: 1.13 (1.03–1.25), P=0.012
Note: This was for all-cause mortality; CV-specific was NS.				
Morioka *et al.* (2001)	HD Patients (Initiation)	HbA1c ≥7.5% vs. <7.5%	Higher HbA1c at HD start was associated with worse survival, but the difference in CV deaths was not significant.	Adj. HR per 1% incr. (All-cause): 1.13 (1.03–1.25), P=0.012
Williams *et al.* (2010)	HD Patients	HbA1c >11% vs. 5-5.9%	U-shaped association with mortality. High HbA1c (>11%) is weakly associated with a higher risk.	Case-mix+lab HR for >11%: ~1.21 (P<0.05)
Tzamaloukas *et al.* (1993)	HD Patients	Poor vs. Good Control	Poor control is associated with higher CV mortality, but no adjusted analysis was performed.	Not provided (unadjusted)

Abbreviations: Adj. = Adjusted; CV = Cardiovascular; DKD = Diabetic Kidney Disease; ESRD = End-Stage Renal Disease; HD = Hemodialysis; HGI = Hemoglobin Glycation Index; HR = Hazard Ratio; MICS = Malnutrition-Inflammation Complex Syndrome; NS = Not Significant.

CKD (Papademetriou *et al.*, 2015). Glycemic control in patients with ESRD, where the initial transition to dialysis was increasingly associated with exhibiting a legacy effect. Findings from Rhee *et al.* (2017) and Wu *et al.* (1997) were significant for increased CV mortality risk in advanced stages of ESRD due to poorly controlled glycemic levels at the initiation of dialysis. This corresponds to the long-term impact caused by pre-dialysis hyperglycemia.

For patients at the advanced stages of dialysis in ESRD, the association between glycated haemoglobin levels and CVD mortality risk is mixed and highly influenced by other factors. For example, Kalanta-Zadeh *et al.* (2007) reported, in their larger cohort, that high HbA1c levels (e.g., >10%) were associated with increased CV mortality. While contradicting this association, Okada *et al.* (2007) deemed HbA1c an "unreliable" factor in high-risk diabetic nephropathy patients, as both the higher and lower ends of HbA1c levels correspond to significant risk and, subsequently, catastrophic outcomes (Okada *et al.*, 2007). However, Williams *et al.* (2010) attribute these associations to the Malnutrition-Inflammation Complex Syndrome (MICS), providing a plausible explanation for HbA1c to influence disease severity or catabolism rather than facilitate reasonable glycemic control in such circumstances (Williams *et al.*, 2010).

Conclusively, the impact of HbA1c levels on CVD mortality in patients with diabetic nephropathy is highly variable across the several stages of DKD. In advanced stages, strict glycemic control was life-threatening, while in the initial stages, it was compromised by higher uncontrolled glycemic levels.

field.

DISCUSSION

The primary objective of this study was to explore optimal glycemic levels that will aid in reducing the associated cardiovascular mortality risk in patients diagnosed with diabetic nephropathy. The noteworthy finding of our research is that the relationship between HbA1c and CVD risk is highly variable and driven by renal decline involving progression of CKD to its various stages. While tight glycemic control might be harmful in advanced CKD, this variability is more complex in ESRD. Historically, the importance of intensive glycemic control in reducing microvascular complications was actively investigated in diabetes-related trials such as the Diabetes Control and Complications Trial (DCCT) and the United Kingdom Prospective Diabetes Study (UKPDS), which, in the long run, also reported sustained benefits for macrovascular complications. However, they had one critical limitation: the participants in the study were either diagnosed with T1D/T2D or had normal renal function. The onset of micro- and macro-vascular complications was primarily attributed to consistent hyperglycemic exposure. The next generation of trials, including ACCORD, ADVANCE, and VADT, recruited a higher-risk group of individuals diagnosed with a long-term CV or diabetes. It is worth noting that these trials reported increased CV mortality when intensive HbA1c targets (e.g., <6.0%) were used. However, inclusion of DKD as a subgroup in another later trial (ACCORD) highlighted their role as an effect modifier. In this subgroup, higher mortality was reported, further highlighting diabetic kidney disease as a significant disruptor for intense glycemic control. These findings are consistent with the "legacy" foundations laid by the UKPDS population, whose defining characteristic was a lower baseline rate of adverse renal complications.

Competing risks are increasingly being explored, and the fact that intensive glycemic controls lead to higher CVD mortality risk, particularly in advanced DN, makes them a crucial factor. When patients are faced with declining glomerular filtration rate (GFR), it increases the likelihood of severe hypoglycemia caused by the treatment, ultimately resulting in impaired insulin and sulfonylurea pharmacokinetics, renal gluconeogenesis, and anorexia. Hypoglycemia is known in the literature for its impact on arrhythmias, myocardial ischemia, and subsequently increased CV mortality. Collectively, these findings underscore that the threat of hypoglycemia will have negative consequences on the long-term benefits of reduced HbA1c.

Our study points to another critical aspect: a U-shaped association between HbA1c and mortality, especially in the ESRD population. This association is known as the "risk-factor paradox," a well-known phenomenon among dialysis patients. The main instigator identified in our findings is Malnutrition-Inflammation Complex Syndrome (MICS) (Kalantar-Zadeh *et al.*, 2007). Deceased HbA1c levels in conditions like ESRD do not necessarily reflect strict glycemic controls; they are more driven by anaemia of chronic disease, and compromised RBC life-cycle, etc. Contrary to these findings, low HbA1c reiterates its role as an identifier of severe inflammation, catabolism, or frailty, which ultimately drives CV mortality. These findings are critical for interpreting the findings of Williams *et al.* (2010), in which, in unadjusted analyses, low HbA1c values were associated with increased mortality risk. This highlights the importance of markers of nutrition and inflammation in modulating the likelihood of further crises. Another study further explained it included in our analysis that adjusting for potential confounders like MICS will help establish a dose-response relationship, which will ultimately increase CV mortality associated with increased HbA1c (Kalantar-Zadeh *et al.*, 2007). These findings highlight that hyperglycemia's impact may fade into the background amid the manifestations of systemic illness, rendering unadjusted HbA1c a misleading measure.

This unreliability of HbA1c in late-stage CKD or ESRD has led to the exploration of new glycemic markers, such as Glycated Albumin (GA), which has a reduced half-life and is independent of erythrocyte dynamics. In the work of Okada *et al.* (2007), GA was acknowledged as a reliable predictor of CVD in comparison to HbA1c for the ESRD population. However, its limitations included

the inability to accurately predict mortality. In contrast, Huang *et al.* (2024) employed the Haemoglobin Glycation Index, which works on the principle of the intrinsic glycolytic phenotype. Using HGI leads to independent CV mortality risk predictions in DKD. The ability of an individual to glycate proteins, regardless of glycemic level, may lead to potential complications. This explains how severe complications are manifested despite adequate HbA1c targets.

Despite these valuable findings, this study possesses some limitations. There is a wider gap in the literature regarding RCTs specifically conducted in DN/DKD patients to assess HbA1c targets or comparators linked to CVD mortality. CVD-specific outcomes in the literature were minimal. Most studies were observational, limiting our ability to establish causal inference. Furthermore, data heterogeneity also necessitates a more in-depth synthesis without the support of meta-analysis. Future research should address these identified gaps and conduct long-term studies to evaluate optimal glycemic control and its role in reducing CVD mortality in patients with DN. Novel glycemic markers should also be integrated into future research to account for variability across the DN disease spectrum.

field.

CONCLUSIONS

This study explored optimal glycemic targets to reduce CVD mortality in patients with DN. However, the findings revealed that, rather than a fixed range, glycemic levels should be individualised for each patient, as they align with the kidney disease stage. It is essential to balance the non-significant impacts of intensive glycemic control in certain DN conditions, particularly when there is increased risk of hypoglycemia or a possibility of confounding by a malnutrition-inflammation state. Literature is scarce on CVD-specific mortality outcomes in DN patients and on optimal glycemic comparator levels. Future research should focus on conducting individualised HbA1c targeting studies with newer glycemic control interventions to account for the evolving DN disease spectrum.

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