



The long-term impact of early HbA1c control on nephropathy, neuropathy, and retinopathy in type 2 diabetes: Findings from a large UK observational study

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ABSTRACT

Introduction: The evidence remains contradictory regarding the optimal glycaemic targets needed to address the long-term effects of hyperglycaemia in people with diabetes mellitus (T2DM). We examined the association between HbA1c levels and the risk of individual microvascular complications among people with T2DM.

Methods: We used the Clinical Practice Research Datalink (CPRD) GOLD database for a prospective cohort study, following patients ≥ 18 years old from diagnosis of T2DM between January 2007 and December 2017. Neuropathy included foot ulcers, peripheral arterial disease, gangrene, and amputation. Nephropathy was classified by chronic kidney disease stages, and retinopathy included blindness and macular oedema. The risk of each complication in five HbA1c intervals [1.0%] intervals compared to 48.0–57.9 mmol/mol (6.5–7.5%) was assessed using a multivariate time-varying Cox regression adjusted by various patients' characteristics. Subgroup analyses were performed according to age, hypertension, and the use of antihypertensive medications.

Results: Our study included 172,869 patients (mean age 62.6 years and, 54.6% women). The risks were the highest in HbA1c levels >81.0 mmol/mol ($>9.6\%$) (HR 1.27, 95%CI 1.17–1.39 for nephropathy; 1.55, 1.27–1.47 for neuropathy; 1.66, 1.41–1.96 for retinopathy). The lowest risks observed in levels 48.0–57.9 mmol/mol (6.5–7.5%) for nephropathy and in levels <48.0 mmol/mol ($<6.5\%$) for neuropathy (0.98, 0.88–1.09) and for retinopathy (0.89, 0.79–0.99). In the subgroup analysis, higher HbA1c levels were associated with an increased risk of nephropathy, particularly in individuals over 60, those with hypertension, and those using antihypertensive medications. For neuropathy, being over 60 was associated with an increased risk across all HbA1c levels. In retinopathy, hypertension and the use of antihypertensive medications were associated with lower risk across all HbA1c levels, while individuals under 60 were associated with higher risks at elevated HbA1c levels compared to those over 60.

Conclusion: The risk of retinopathy and neuropathy was lowest in individuals with HbA1c levels within the non-diabetic range <48.0 mmol/mol ($<6.5\%$) and increased progressively with higher HbA1c levels. In contrast, the lowest risk of nephropathy was observed in individuals with HbA1c levels between 48.0 and 57.9 mmol/mol (6.5–7.5%). These findings underscore the importance of a personalized approach to diabetes management that considers multiple risk factors and incorporates novel therapeutic strategies beyond glucose control.

1. Introduction

Type 2 diabetes mellitus (T2DM) is a chronic condition characterized by elevated blood glucose levels, which, if left uncontrolled, can lead to

severe complications.¹ Among these, retinopathy, nephropathy, and neuropathy are particularly concerning due to their significant impact on patients' quality of life and their contribution to increased morbidity and mortality rates.¹ Glycated hemoglobin (HbA1c) is a key biomarker

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used to monitor long-term blood glucose control in T2DM patients, serving as a crucial measure to prevent or delay these complications.² Elevated HbA1c levels have been directly linked to the development and progression of microvascular complications, making its control a critical aspect of diabetes management.³ A DISCOVER observational cohort study conducted from 2014 to 2016 revealed an increasing incidence of these complications, with neuropathy affecting 7.7%, chronic kidney injury affecting 5%, and albuminuria affecting 4.3% of patients.⁴

The importance of maintaining target HbA1c levels is underscored by landmark clinical trials, such as Diabetes Control of Complications Trial (DCCT),⁵ the United Kingdom Prospective Diabetes Study (UKPDS),⁶ Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation (ADVANCE),⁷ Glucose Control and Vascular Complications in Veterans with Type 2 diabetes (VADT),⁸ and Action to Control Cardiovascular Risk in Diabetes (ACCORD)⁹ which have all demonstrated the significant impact of intensive glucose control on reducing the risk of nephropathy, retinopathy, and neuropathy in individuals with T2DM. As a result of the compelling evidence from these trials, current clinical guidelines recommend targeting HbA1c levels between 48 and 57 mmol/mol (6.5–7.5%) for most patients with T2DM. This glycaemic target range aims to strike a balance between minimizing the risk of individuals microvascular complications and avoiding hypoglycaemia (low blood sugar), ensuring the best possible outcomes for patients.

These Landmark trials have shaped current HbA1c targets, but recent studies lack the long-term follow-up from diagnosis needed to fully understand the impact of tight glycaemic control on individuals microvascular complications, with the ACCORD trial raising concerns about its safety.⁹ The discrepancy in findings may be due to the failure to differentiate between the benefits in newly diagnosed versus long-standing T2DM patients, highlighting the importance of the “legacy effect” of early glycaemic control and the need for further research considering the advent of newer diabetes medications with vascular protective effects.

Also, patient-specific factors such as age, hypertension, and concomitant medications can influence the optimal HbA1c target for minimizing microvascular complications¹⁰; however, research on individualised glycaemic targets remains limited. Contemporary clinical guidelines are advocating for a less glucocentric, individualised approach to diabetes management, emphasising multifactorial risk reduction and the utilisation of novel therapies with demonstrated efficacy independent of glucose-lowering. The lack of long-term studies tracking intensive glycaemic control from the time of diabetes diagnosis emphasises the need for more research to understand its lasting effects on small blood vessel complications in this population.

We therefore aim to investigate the most appropriate HbA1c target associated with decreased risk of individual microvascular complications following patients from the date of diagnosis and considering various patient characteristics such as age, comorbidities, and medication usage.

2. Methods

2.1. Design and study source

We used data from the UK's Clinical Practice Research Datalink (CPRD GOLD) database to perform prospective cohort study. GOLD is a database of anonymised, routinely collected primary care electronic health records, linked to Hospital Episode Statistics (HES) and the Office for National Statistics (ONS). These linkages facilitate the determination of hospital admissions and mortality. It has information from about 17 million people from roughly 674 UK medical facilities, making it trustworthy, valid to represent patients in the UK, high-quality, and suitable for use in conducting observational research.^{11,12} CPRD studies are approved by the Independent Scientific Advisory Committee (ISAC) of CPRD and the Medicines and Health products Regulatory Authority

(Protocol 19_202R). The data were collected by the NHS as part of patient care and support. The interpretation and conclusions contained in this study are those of the authors alone.

2.2. Study population

We included adult patients (aged ≥ 18 years) with incident Type 2 Diabetes Mellitus (T2DM) newly diagnosed between January 1, 2007, and December 31, 2017. Cases were identified using specific Read codes (for primary care data in CPRD) and ICD-10 codes (for linked Hospital Episode Statistics) indicative of T2DM.¹³

The index date was defined as the date of the first recorded diagnostic code or the first prescription of an oral antidiabetic agent. To ensure the cohort included only incident cases, we applied strict exclusion criteria. We excluded patients who: (1) had any record of antidiabetic medication prescriptions prior to the index date; (2) had a recorded diagnosis of other diabetes types (e.g., Type 1 or secondary diabetes); (3) initiated insulin therapy within 12 months of diagnosis (to minimize misclassification of latent autoimmune diabetes); (4) had evidence of existing microvascular complications (nephropathy, neuropathy, or retinopathy) prior to the index date; or (5) had a follow-up duration of less than 12 months. The censoring date (end of follow-up) was defined as the earliest of: the date of death, the date the patient transferred out of the practice, or the study end date (December 31, 2017).

2.3. Outcomes and exposure

Nephropathy was defined according to the KDIGO guidelines¹⁴ as the development of either pathological albuminuria or sustained eGFR decline. Specifically, we identified albuminuria as the presence of micro- or macroalbuminuria (corresponding to KDIGO categories A2 and A3). Decreased eGFR was defined as an eGFR < 60 mL/min/1.73m², stratified into standard KDIGO categories: G3a (45–59), G3b (30–44), G4 (15–29), and G5 (< 15). The event date was defined as the first record of either albuminuria or an eGFR < 60 mL/min/1.73m². Neuropathy was defined as a composite endpoint capturing peripheral nerve damage and its severe clinical sequelae. This included diagnoses of peripheral neuropathy, diabetic foot ulceration, gangrene, and lower limb amputation. While we acknowledge that conditions such as gangrene and amputation involve a vascular component, they were included in the ‘neuropathy’ outcome to capture the full spectrum of the neuro-ischemic diabetic foot, where neuropathy acts as a primary precipitating factor for ulceration and tissue loss. Retinopathy was defined as a composite outcome including diagnoses of background or proliferative diabetic retinopathy, diabetic maculopathy, and macular oedema. We also included advanced complications such as vitreous haemorrhage and blindness, as well as procedural codes indicating active treatment (e.g., retinal laser photocoagulation).

HbA1c levels were our main exposure and categorised into five groups (< 48.0 mmol/mol; 48.0–57.9 mmol/mol; 58–69.9 mmol/mol; 70.0–80.9 mmol/mol, and ≥ 81 mmol/mol), with the 48.0–57.9 mmol/mol group (aligning with current guidelines) serving as the reference group.

2.4. Confounders

Quarterly intervals were used to extract a full set of patient parameters, clinical diagnoses, medications, and laboratory measurement *s.* Patients' demographics (age, gender, ethnicity), body-mass index (BMI), blood pressure, lifestyle factors (alcohol consumption, smoking status), and family history of heart disease were all taken into account. Clinical diagnoses included ischemic heart disease, atrial fibrillation, prior stroke, chronic renal disease, Parkinson's disease, peripheral arterial disease, heart failure, rheumatic diseases, hypertension, serious mental health disorders, and HIV/AIDS. Lipid-lowering drugs,

antihypertensives, and a wide range of anti-diabetic treatments were identified. The laboratory data of importance included HbA1c, eGFR, full lipid profile (low- and high-density lipoprotein, total cholesterol, triglycerides), and urine albumin creatinine ratio. These variables were included based on their established or biologically plausible roles as confounders in the relationship between glycaemic control and microvascular complications. Factors such as BMI, blood pressure, lipid profile, and smoking status are integral components of metabolic health and are independently associated with the development of microvascular disease. Similarly, comorbid conditions like chronic kidney disease, cardiovascular disease, and mental health disorders may influence both glycaemic regulation and susceptibility to complications. Including these covariates helps to account for the broader clinical context in which HbA1c levels may affect outcomes.¹⁵

2.5. Statistical analysis

Descriptive analyses were performed for baseline and demographic data which were represented in number and frequency in the case of categorical variables and mean and standard deviation (SD) in the case of contentious variables. The incidence rate of each complication was presented by the Kaplan-Meier curves and calculated based on the numbers with the outcome and the person years of follow-up. Multiple imputation using multiple chained equations was used to manage missing data for HbA1c, weight, body mass index, systolic and diastolic blood pressure, low- and high-density lipoprotein, total cholesterol, triglycerides, smoking status, and alcohol use, which were assumed to be missing at random. Rubin's method was utilised for all analyses on imputed data in order to get combined effect estimates.¹⁶

Multivariate time-varying Cox regression analysis was used to investigate the association between HbA1c levels and individual microvascular outcomes, accounting for confounding variables. The findings were reported quarterly, every 91 days, and were represented as hazard ratio (HR) with 95% confidence interval (CIs). Proportional hazard assumptions and covariate distributions were evaluated. Age, sex, BMI, smoking status, alcohol use, and the use of antidiabetic, antihypertensive, and lipid-lowering medications were included as covariates in the main models. Any included variables violating these assumptions were used as stratas, while continuous variables were modelled using fractional polynomials.

We employed stepwise selection to develop an optimal model for each outcome, considering a model optimal only if the Akaike's Information Criteria (AIC)¹⁷ decreased by less than two. The model's calibration was evaluated using both Royston's D and Harrell's C statistics.

The primary analysis explored the association between HbA1c categories and risk, using HbA1c levels of 6.5–7.5% (48.0–57.9 mmol/mol) as the reference. To further illustrate risk trends, we also present estimates based on specific HbA1c values, using 7% (53 mmol/mol) as the reference. These findings underscore the gradual changes in risk across the HbA1c levels.

Additionally, subgroup analyses were conducted to assess the individual microvascular complications in patients with health conditions, prescribed treatments, and those who were at least 60 years old at baseline. Each covariate was examined through two distinct analyses: one focusing on patients with the given condition or prescription, and another on individuals aged 60 and above. Stata version 17.0 was used for data preparation and analysis.

3. Results

3.1. Cohort characteristics

The study cohort included 172,869 individuals newly diagnosed with T2DM, selected from the CPRD population as illustrated in the flowchart Supplementary Fig. 1. During the study period, 14,302 (8.4%) individuals developed nephropathy, 3995 (2.3%) developed

neuropathy, and 2535 (1.5%) developed retinopathy. The average age of participants was 62.6 years, with a standard deviation (SD) of 14 years. Their average body mass index (BMI) was 31.9 (SD 6.6), and their average HbA1c level was 52.6 mmol/mol (SD 13.3). Most participants (54.6%) were female. A more detailed breakdown of patients' characteristics at the start of the study can be found in Table 1.

Median follow-up durations were 3.6 years for nephropathy, and 3.8 years for both neuropathy and retinopathy analyses (Range: <1 to 10 years for all outcomes), reflecting the continuous recruitment of incident cases over the study period. Total person-time at risk was 702,960 person-years for nephropathy, 727,101 for neuropathy, and 738,206 for retinopathy.

Kaplan-Meier survival curves (Supplementary Fig. 2) illustrate the cumulative incidence of nephropathy (Fig. 2a), retinopathy (Fig. 2b), and neuropathy (Fig. 2c) across HbA1c categories. Higher HbA1c levels were consistently associated with increased risk of all microvascular complications and lower survival probabilities across all outcomes.

3.2. Nephropathy

The risk of developing nephropathy showed a continuous increase across all HbA1c categories, with the highest risk observed in individuals with HbA1c levels ≥ 81.0 mmol/mol (Hazard Ratio: 1.27, 95% Confidence Interval: 1.17 to 1.39). The reference group had the lowest risk (48.0–57.9 mmol/mol 6.5–7.5%), followed by individuals with HbA1c <48.0 mmol/mol (<6.5%) (HR: 1.07, 95% CI: 1.03 to 1.12), as illustrated in Fig. 1.

Fractional polynomial modeling (Fig. 1) revealed a non-linear relationship between HbA1c and nephropathy risk, with a noticeable increase in risk beyond HbA1c levels of 53 mmol/mol. The steepness of the curve highlights the progressive nature of risk elevation, which is associated with broader confidence intervals, likely due to increased estimate variability. The hazard ratios for covariates, Royston's D and Harrell's C statistics are provided in Supplementary Table 1.

In subgroup analysis, for individuals aged <60 years, the lowest risk of nephropathy was observed in the reference group with HbA1c levels of 48.0–57.9 mmol/mol (6.5–7.5%). This was followed by those with HbA1c levels <48 mmol/mol (<6.5%) (HR 1.08, 95% CI 1.03–1.12). The highest risk in this age group was seen in individuals with HbA1c levels ≥ 81 mmol/mol ($\geq 9.6\%$) (HR 1.22, 95% CI 1.11–1.35). Among individuals aged ≥ 60 years, the reference group also showed the lowest risk, followed by individuals with HbA1c levels <48 mmol/mol (<6.5%) (HR 1.04, 95% CI 0.99–1.09), and the highest risk was observed in those with HbA1c levels ≥ 81 mmol/mol ($\geq 9.6\%$) (HR 1.11, 95% CI 0.98–1.25) (Supplementary Fig. 3a).

For individuals without hypertension, the reference group (HbA1c 48.0–57.9 mmol/mol) (6.5–7.5%) showed the lowest risk of nephropathy. This was followed by a slightly elevated risk for those with HbA1c levels <48 mmol/mol (<6.5%) (HR 1.07, 95% CI 1.03–1.12), while the highest risk was observed among those with HbA1c levels ≥ 81 mmol/mol ($\geq 9.6\%$) (HR 1.20, 95% CI 1.07–1.35). Conversely, among individuals with hypertension, the reference group again showed the lowest risk, followed by those with HbA1c levels <48 mmol/mol (<6.5%) (HR 1.05, 95% CI 0.91–1.21), and the highest risk was seen in individuals with HbA1c levels ≥ 81 mmol/mol ($\geq 9.6\%$) (HR 1.31, 95% CI 1.10–1.57). Supplementary Fig. 3b.

For individuals taking antihypertensive medication, the lowest risk of nephropathy was in the reference group (HbA1c 48.0–57.9 mmol/mol) (6.5–7.5%). The next lowest risk was for those with HbA1c levels <48 mmol/mol (<6.5%) (HR 1.06, 95% CI 0.86–1.31), and the highest risk was observed for individuals with HbA1c levels ≥ 81 mmol/mol ($\geq 9.6\%$) (HR 1.46, 95% CI 1.13–1.88). Among those not taking antihypertensive medication, the reference group again had the lowest risk, followed by individuals with HbA1c levels <48 mmol/mol (<6.5%), while the highest risk was noted for those with HbA1c levels ≥ 81 mmol/mol ($\geq 9.6\%$) (HR 2.37, 95% CI 1.84–3.06) Supplementary Fig. 3c.

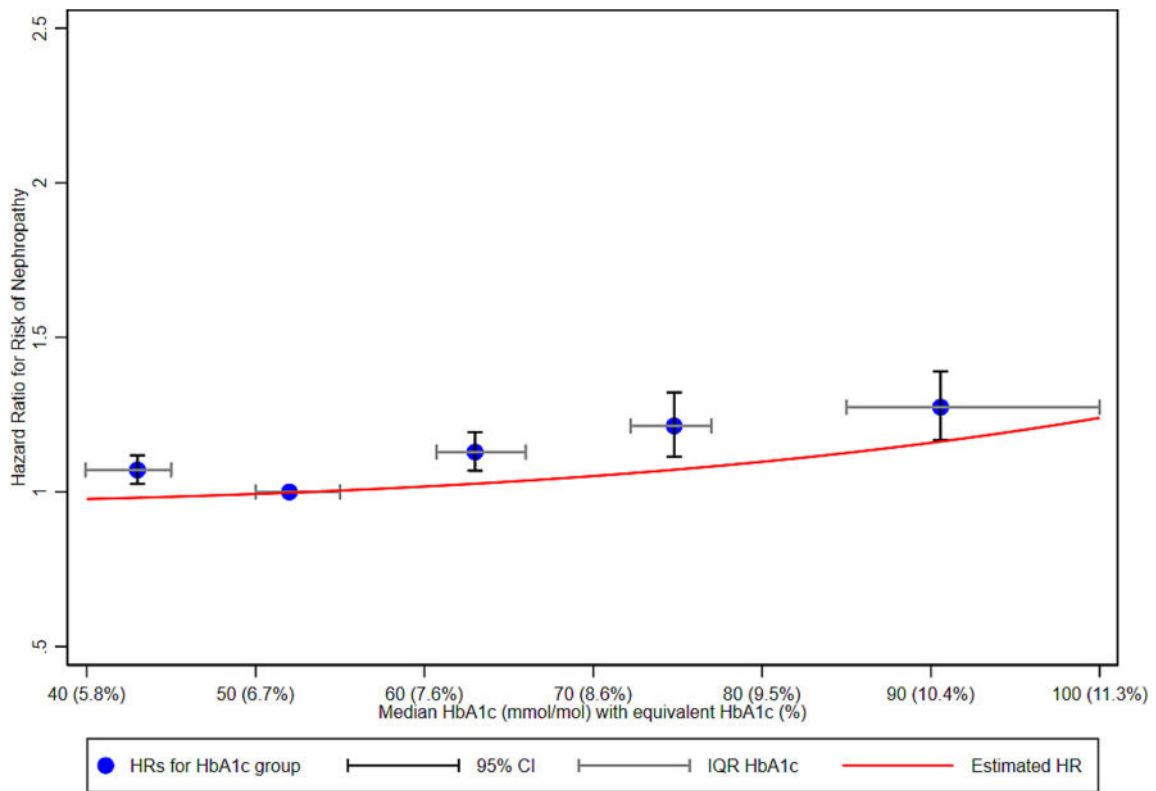


Fig. 1. The risk of Nephropathy Outcome across different levels of HbA1c (Reference: 6.5–7.5% [48.0–57.9 mmol/mol]).

3.3. Neuropathy

The risk of developing neuropathy varied continuously across HbA1c

levels, with the lowest risk observed in individuals with HbA1c <48.0 mmol/mol (<6.5%) (HR: 0.98, 95% CI: 0.88–1.09) and the highest risk in those with HbA1c ≥81.0 mmol/mol (≥9.6%) (HR: 1.55, 95% CI:

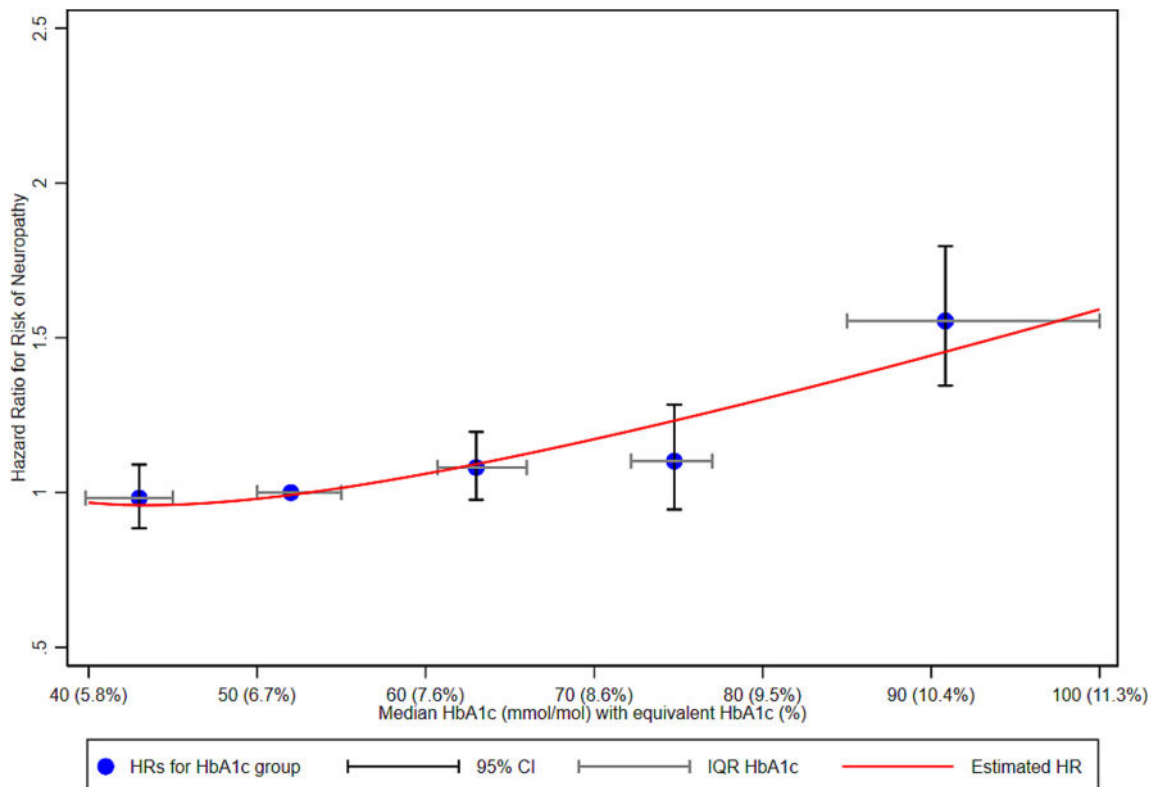


Fig. 2. The risk of first Neuropathy Outcome across different levels of HbA1c (Reference: 6.5–7.5% [48.0–57.9 mmol/mol]).

1.35–1.80), followed by individuals in the 70.0–80.9 mmol/mol (8.6–9.5%) category (HR: 1.10, 95% CI: 0.95–1.28), as shown in Fig. 2.

Fractional polynomial modeling (Fig. 2) demonstrated a non-linear association between HbA1c and neuropathy risk, with a noticeable increase in risk beyond 53 mmol/mol (~7.0%). The steepness of the curve highlights the dynamic nature of risk variation and may explain the relatively wide confidence intervals in certain HbA1c ranges. The hazard ratios for covariates, Royston's D and Harrel's C statistics are provided in Supplementary Table 2.

In subgroup analysis for neuropathy outcomes, among individuals aged <60 years, those with HbA1c levels <48 mmol/mol (<6.5%) showed a reduced risk compared to the reference (HR 0.84, 95% CI 0.65–1.07) and the other HbA1c categories. The highest risk was observed among those with HbA1c levels ≥81 mmol/mol (≥9.6%) (HR 1.56, 95% CI 1.24–1.97).

For individuals aged ≥60 years, the reference group (48.0–57.9 mmol/mol, 6.5–7.5%) demonstrated the lowest risk, while those with HbA1c levels <48 mmol/mol (<6.5%) showed a relatively higher risk (HR 1.03, 95% CI 0.93–1.14). The highest risk in this age group was again seen in individuals with HbA1c levels ≥81 mmol/mol (≥9.6%) (HR 1.42, 95% CI 1.18–1.71) (Supplementary Fig. 4a).

For individuals without hypertension, those with HbA1c levels <48 mmol/mol (<6.5%) showed the lowest risk of neuropathy (HR 0.93, 95% CI 0.80–1.08). The highest risk was observed in individuals with HbA1c levels ≥81 mmol/mol (≥9.6%) (HR 1.59, 95% CI 1.29–1.98). Conversely, among individuals with hypertension, the reference group (48.0–57.9 mmol/mol, 6.5–7.5%) remained the lowest-risk group. Those with HbA1c levels <48 mmol/mol (<6.5%) had a slightly elevated risk (HR 1.01, 95% CI 0.89–1.14), while the highest risk was observed in those with HbA1c levels ≥81 mmol/mol (≥9.6%) (HR 1.49, 95% CI 1.25–1.77) (Supplementary Fig. 4b).

For individuals taking antihypertensive medications, the reference group (48.0–57.9 mmol/mol, 6.5–7.5%) again showed the lowest risk of neuropathy. Those with HbA1c levels <48 mmol/mol (<6.5%)

displayed a modestly increased risk (HR 1.02, 95% CI 0.92–1.13), while the highest risk was seen in individuals with HbA1c levels ≥81 mmol/mol (≥9.6%) (HR 1.50, 95% CI 1.27–1.77). Among individuals not taking antihypertensive medications, those with HbA1c levels <48 mmol/mol (<6.5%) (HR 0.86, 95% CI 0.70–1.07) showed the lowest risk of neuropathy. The highest risk in this group was noted among those with HbA1c levels ≥81 mmol/mol (≥9.6%) (HR 1.63, 95% CI 1.25–2.13) (Fig. 4c).

3.4. Retinopathy

The risk of developing retinopathy demonstrated a continuous pattern across HbA1c levels, with the lowest risk observed in individuals with HbA1c <48.0 mmol/mol (<6.5%) (HR: 0.89, 95% CI: 0.79–0.99) and the highest in those with HbA1c ≥81.0 mmol/mol (≥9.6%) (HR: 1.66, 95% CI: 1.41–1.96), followed by individuals in the 70.0–80.9 mmol/mol (8.6–9.5%) category (HR: 1.43, 95% CI: 1.41–1.70), as illustrated in Fig. 3.

Fractional polynomial modeling (Fig. 3) revealed a non-linear relationship between HbA1c and retinopathy risk, with an evident increase in risk at HbA1c levels above 53 mmol/mol (~7.0%). The shape of the curve underscores the gradual nature of risk escalation and may contribute to the wider confidence intervals at specific HbA1c ranges. The hazard ratios for covariates, Royston's D, and Harrel's C statistics are provided in Supplementary Table 3.

In subgroup analysis, individuals aged <60 years had the lowest incidence of retinopathy events when their HbA1c levels were <48.0 mmol/mol (<6.5%) (HR 0.79, 95% CI 0.59–1.04). Conversely, the highest risk in this age group was observed among those with HbA1c levels ≥81 mmol/mol (≥9.6%) (HR 2.20, 95% CI 1.47–2.29). For individuals aged ≥60 years, the lowest risk was also observed in those with HbA1c <48.0 mmol/mol (<6.5%) (HR 0.93, 95% CI 0.82–1.06), while the highest risk was seen in those with HbA1c levels of 70.0–80.9 mmol/mol (8.6–9.5%) (HR 1.09, 95% CI 0.48–1.41). Notably, younger

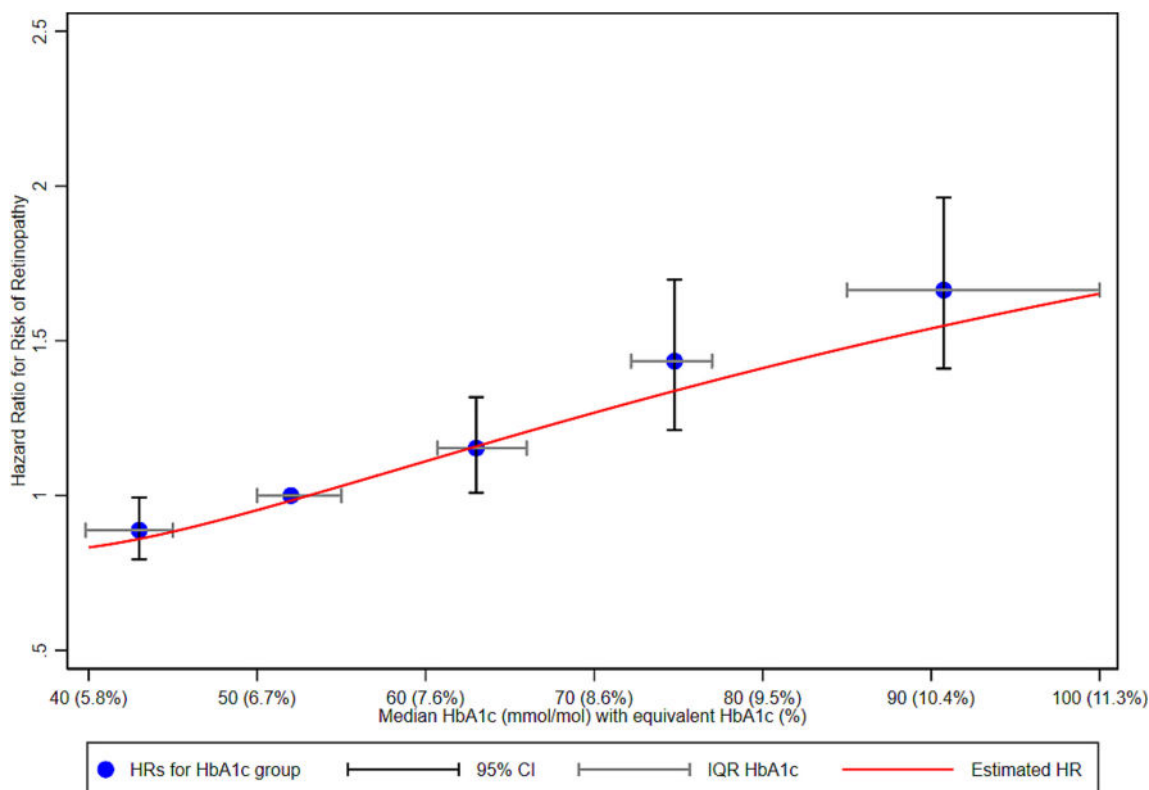


Fig. 3. The risk of first Retinopathy Outcome across different levels of HbA1c (Reference: 6.5–7.5% [48.0–57.9 mmol/mol]).

individuals appeared more susceptible to retinopathy as HbA1c increased, compared to older individuals (Fig. 5a).

Individuals without hypertension showed the lowest risk of retinopathy when HbA1c levels were <48 mmol/mol (<6.5%) (HR 0.85, 95% CI 0.69–1.06), while the highest risk was observed among those with HbA1c levels \geq 81.0 mmol/mol (\geq 9.6%) (HR 2.14, 95% CI 1.69–2.70). Conversely, among individuals with hypertension, the highest risk was seen in those with HbA1c \geq 81.0 mmol/mol (\geq 9.6%) (HR 1.31, 95% CI 1.03–1.68), while the lowest risk was observed in individuals with HbA1c levels of 48.0–57.9 mmol/mol (6.5–7.5%) (HR 0.90, 95% CI 0.78–1.03) (Fig. 5b).

Among individuals on antihypertensive medication, the lowest risk of retinopathy was observed in those with HbA1c <48 mmol/mol (<6.5%) (HR 0.92, 95% CI 0.81–1.05), followed by individuals with HbA1c levels of 58.0–69.9 mmol/mol (7.6–8.5%) (HR 1.06, 95% CI 0.89–1.25). The highest risk within this group was observed in those with HbA1c levels \geq 81 mmol/mol (\geq 9.6%) (HR 1.36, 95% CI 1.09–1.69). Conversely, among individuals not taking antihypertensive medication, the lowest risk was seen in those with HbA1c <48.0 mmol/mol (<6.5%) (HR 0.77, 95% CI 0.58–1.01), while the highest risk was noted in individuals with HbA1c \geq 81.0 mmol/mol (\geq 9.6%) (HR 2.37, 95% CI 1.84–3.07) (Fig. 5c).

To provide a comparative overview, the incidence rates and hazard ratios for each microvascular outcome across HbA1c categories are summarized in Table 2.

4. Discussion

Our study revealed that nephropathy, neuropathy, and retinopathy risks were increased with increased HbA1c levels and the highest were especially in levels above 81.0 mmol/mol (9.6%), while the lowest risks were observed in levels less than 48.0 mmol/mol except for nephropathy the lowest risk was seen in 48.0–57.9 mmol/mol (6.5–7.5%) levels. In the subgroup analysis, increased nephropathy risk was associated with higher HbA1c levels, particularly in individuals over 60, those with hypertension, and those using antihypertensive medications. For neuropathy, age over 60 was consistently associated with increased risk across all HbA1c levels. In retinopathy, hypertension and the use of antihypertensive medications were generally associated lower risk across all HbA1c levels, while individuals under 60 years old had higher risks at elevated HbA1c levels compared to those over 60.

In nephropathy, we observed a J-shaped association, where risk was elevated at both extremes. The highest risk was observed in levels more than 81.0 mmol/mol (>9.6%), while the lowest risk was found in the group with HbA1c levels between 48.0 and 57.9 mmol/mol (6.5–7.5%) This distinct trajectory likely reflects the pathophysiology of diabetic kidney disease, where severe, sustained hyperglycemia drives the rapid change from normo- to albuminuria status. Once established, albuminuria acts as a potent accelerator of eGFR decline. Our findings were

consistent with a systematic review and meta-analysis, which incorporated large clinical trials such as VADT, ADVANCE, UKPDS, and ACCORD. These studies demonstrated that effective management of T2DM was associated with a 20% reduction in the incidence of macroalbuminuria, end-stage kidney disease, and mortality.¹⁸ Another cohort study in China found that the albumin to creatinine ratio had a positive association with increasing HbA1c level with an inflection point of 53 mmol/mol (7%) and this correlation remained after adjusting covariates.¹⁹ These results signified that the risk was increasing also among prediabetes patients and by increasing baseline HbA1c values, the risk of chronic kidney disease and end-stage kidney disease increased.^{20,21} Another study found that the kidney function (guided by glomerular filtration rate) was reduced by reaching the HbA1c level of 46 mmol/mol (6.4%).²² The underlying mechanism of diabetic nephropathy is basement membrane thickening, arteriosclerosis, and interstitial tissue fibrosis which starts with glomerular hyperfiltration and progresses gradually to loss of kidney functions.²³

Interestingly, we observed a J-shaped association for nephropathy, with increased risk in individuals with HbA1c < 48 mmol/mol (<6.5%). The most plausible driver for this elevated risk is hypoglycemia-induced renal injury. Hypoglycemia triggers profound sympathetic activation and hemodynamic shifts, leading to renal vasoconstriction and acute inflammatory injury. Repeated episodes of these acute insults can accelerate the decline in eGFR and progression to end-stage renal disease, as observed in other large national cohorts.^{24,25} Thus, for renal preservation, avoiding hypoglycemia may be as critical as lowering hyperglycemia, particularly in older adults.

Hypertensive patients were associated with an increased risk of diabetic nephropathy compared to non-hypertensive in all HbA1c groups which was supported by Wagnew 2018 et al. who found that kidney disease complications were increasing in hypertensive diabetic patients compared to non-hypertensive patients.²⁶ Another study found that hypertension had a significant role in the development of diabetic nephropathy.²⁷ This could be explained by increased inflammation, oxidative stress, and glomerular pressure associated with hypertension which leads to glomerular sclerosis and eventually chronic kidney disease.^{28,29} Therefore, tight control of blood pressure is a must to prevent progression of diabetic nephropathy; on the contrary, we found that using antihypertensive drugs was associated with increased risk of diabetic nephropathy; however, this can be explained as mostly the patients who were on antihypertensive medications had hypertension which in turn increased the risk as many clinical trials found that antihypertensive medications had a role in decreasing progression of diabetic nephropathy.^{30–32}

Our findings indicate that individuals over 60 years of age are at an increased risk of developing diabetic nephropathy. However, a previous study reported no statistically significant difference in the incidence of chronic kidney disease between older and middle-aged patients.³³ In contrast, another study identified age above 50 as a substantial risk

Table 2
Incidence rate and hazard ratio for microvascular complications by HbA1c levels.

HbA1c Group	Nephropathy Incidence Rate (per 1000 PY)	HR (95% CI)	Neuropathy Incidence Rate (per 1000 PY)	HR (95% CI)	Retinopathy Incidence Rate (per 1000 PY)	HR (95% CI)
<6.5% (ref)	21.4	1.07	5.49	0.98	3.43	0.89
<48 mmol/mol		(1.03–1.12)		(0.88–1.09)		(0.79–0.99)
6.5–7.5%		Reference		Reference		Reference
48–57.9 mmol/mol						
7.6–8.5%		1.13		1.08		1.15
58–69.9 mmol/mol		(1.07–1.19)		(0.98–1.20)		(1.01–1.32)
8.6–9.5%		1.21		1.10		1.43
70–80.9 mmol/mol		(1.11–1.32)		(0.95–1.28)		(1.21–1.70)
\geq 9.6%		1.27		1.55		1.66
\geq 81 mmol/mol		(1.17–1.39)		(1.27–1.47)		(1.41–1.96)

Table 1
Baseline characteristics of the cohort stratified by HbA1c at inclusion.

Characteristic		<48 mmol/ mol <6.5%	48–57.9 mmol/ mol 6.5–7.5%	58.0–69.9 mmol/mol 7.5–8.5%	70.0–80.9 mmol/ mol 8.5–9.6%	≥81.0 mmol/mol ≥9.6%	Total	P Value
Age (Years)	mean (SD)	63.91 (12.88)	64.50 (12.33)	61.82 (12.87)	58.65 (13.22)	61.50 (15.54)	62.73 (14.01)	<0.001
Weight (kg)	mean (SD)	88.21 (19.61)	90.13 (20.00)	94.18 (21.06)	96.75 (22.17)	92.20 (22.17)	90.84 (20.89)	<0.001
BMI (kg/m ²)	mean (SD)	30.86 (6.06)	31.69 (6.30)	32.82 (6.66)	33.39 (6.95)	32.40 (7.05)	31.84 (6.58)	<0.001
Systolic BP (mmHg)	mean (SD)	132.47 (14.25)	133.32 (14.29)	134.31 (14.90)	135.35 (15.03)	134.45 (16.11)	133.70 (15.12)	<0.001
Diastolic BP (mmHg)	mean (SD)	75.82 (9.09)	76.33 (9.14)	77.81 (9.26)	79.25 (9.96)	77.42 (10.07)	76.84 (9.57)	<0.001
Total Cholesterol (mmol/L)	mean (SD)	4.44 (1.06)	4.48 (1.05)	4.57 (1.09)	4.70 (1.15)	4.69 (1.18)	4.52 (1.09)	<0.001
HDL (mmol/L)	mean (SD)	1.28 (0.38)	1.24 (0.35)	1.18 (0.33)	1.13 (0.33)	1.24 (0.47)	1.24 (0.38)	<0.001
LDL (mmol/L)	mean (SD)	2.50 (0.95)	2.50 (0.96)	2.57 (0.99)	2.67 (1.10)	2.68 (1.05)	2.54 (0.98)	<0.001
HbA1c (mmol/mol)	mean (SD)	42.26 (3.70)	51.77 (2.78)	62.53 (3.31)	74.54 (3.07)	95.71 (13.82)	52.60 (13.35)	<0.001
Gender								
Female	n (%)	17,829 (43.8%)	18,325 (44.5%)	6133 (41.6%)	1781 (37.5%)	34,486 (48.2%)	78,554 (45.4%)	<0.001
Ethnicity								
Unknown	n (%)	25,885 (63.6%)	25,566 (62.1%)	9281 (63.0%)	2894 (60.9%)	46,002 (64.4%)	54,356 (31.4%)	<0.001
White	n (%)	374 (0.9%)	364 (0.9%)	121 (0.8%)	54 (1.1%)	767 (1.1%)	109,628 (63.4%)	
Black	n (%)	1041 (2.6%)	1429 (3.5%)	505 (3.4%)	179 (3.8%)	2447 (3.4%)	1680 (1%)	
Asian	n (%)	329 (0.8%)	339 (0.8%)	134 (0.9%)	49 (1.0%)	753 (1.1%)	5601 (3.2%)	
Other	n (%)	13,079 (32.1%)	13,486 (32.7%)	4699 (31.9%)	1575 (33.2%)	21,517 (30.1%)	1604 (0.9%)	
Alcohol Intake								
None	n (%)	3633 (27.5%)	3786 (29.4%)	1310 (30.4%)	437 (33.1%)	3877 (32.0%)	13,043 (29.7%)	
Trivial	n (%)	4744 (35.9%)	4846 (37.7%)	1609 (37.3%)	459 (34.7%)	3970 (32.8%)	15,628 (35.6%)	
Light	n (%)	1937 (14.6%)	1801 (14.0%)	523 (12.1%)	150 (11.3%)	1477 (12.2%)	5888 (13.4%)	
Moderate	n (%)	1466 (11.1%)	1221 (9.5%)	402 (9.3%)	137 (10.4%)	1406 (11.6%)	4632 (10.6%)	
Heavy	n (%)	459 (3.5%)	340 (2.6%)	114 (2.6%)	37 (2.8%)	429 (3.5%)	1379 (3.1%)	<0.001
Very Heavy	n (%)	225 (1.7%)	161 (1.3%)	80 (1.9%)	20 (1.5%)	212 (1.7%)	698 (1.6%)	
Previous	n (%)	760 (5.7%)	716 (5.6%)	275 (6.4%)	82 (6.2%)	745 (6.1%)	2578 (5.9%)	
Smoking								
Never	n (%)	10,014 (45.6%)	9633 (44.5%)	3240 (43.3%)	991 (41.7%)	12,155 (42.6%)	36,033 (43.9%)	
Ex-Smoker	n (%)	8734 (39.7%)	8317 (38.4%)	2828 (37.8%)	878 (37.0%)	10,435 (36.6%)	31,192 (38.0%)	
Current smoker (light)	n (%)	1500 (6.8%)	1736 (8.0%)	646 (8.6%)	247 (10.4%)	3004 (10.5%)	7133 (8.7%)	<0.001
Current smoker (moderate)	n (%)	950 (4.3%)	1129 (5.2%)	429 (5.7%)	141 (5.9%)	1609 (5.6%)	4258 (5.2%)	
Current smoker (heavy)	n (%)	784 (3.6%)	836 (3.9%)	336 (4.5%)	119 (5.0%)	1314 (4.6%)	3389 (4.1%)	
Diabetes medications								
DPP4 inhibitor	n (%)	539 (1.3%)	1147 (2.8%)	1027 (7.0%)	511 (10.8%)	1860 (2.6%)	5084 (2.9%)	<0.001
GLP1 receptor agonist	n (%)	78 (0.2%)	129 (0.3%)	120 (0.8%)	78 (1.6%)	347 (0.5%)	752 (0.4%)	<0.001
Metformin	n (%)	16,647 (40.9%)	22,845 (55.5%)	10,906 (74.0%)	3757 (79.1%)	32,293 (45.2%)	86,448 (50.0%)	<0.001
Other diabetes medications	n (%)	43 (0.1%)	61 (0.1%)	57 (0.4%)	20 (0.4%)	139 (0.2%)	320 (0.2%)	<0.001
SGLT2 inhibitor	n (%)	63 (0.2%)	146 (0.4%)	189 (1.3%)	97 (2.0%)	239 (0.3%)	734 (0.4%)	<0.001
Sulphonylurea	n (%)	2613 (6.4%)	4180 (10.1%)	2943 (20.0%)	1372 (28.9%)	7307 (10.2%)	18,415 (10.7%)	<0.001
Thiazolidinediones	n (%)	416 (1.0%)	796 (1.9%)	566 (3.8%)	224 (4.7%)	1211 (1.7%)	3213 (1.9%)	<0.001
Other medications								
Lipid lowering drugs	n (%)	26,152 (64.2%)	28,778 (69.9%)	9995 (67.8%)	2966 (62.4%)	41,916 (58.6%)	109,807 (63.5%)	<0.001
Steroids	n (%)	9651 (23.7%)	10,355 (25.1%)	3675 (24.9%)	1081 (22.8%)	19,189 (26.8%)	43,951 (25.4%)	<0.001
Antihypertensives	n (%)	28,136 (69.1%)	28,672 (69.6%)	9644 (65.4%)	2817 (59.3%)	47,502 (66.4%)	116,771 (67.5%)	<0.001

factor for nephropathy, with an odds ratio (OR) of 3.8 (95% CI: 2.21–6.53), suggesting that advancing age may play a crucial role in disease progression.³⁴

The risk of neuropathy was seen in our study to be the lowest in those with HbA1c level <48.0 mmol/mol (<6.5%) and increased by increasing the HbA1c level to reach the highest risk at the level above 81 mmol/mol (9.6%) which was supported by Lai 2019 et al. who found that the severity of diabetic neuropathy was associated with poor glycaemic control and HbA1c variability.³⁵ Also, another study found that each increase in HbA1c level was associated with an increased risk of neuropathy by 10 to 15%.³⁶ This could be explained by increased exposure to hyperglycaemia results in nerve ischemia, axonal degeneration, and demyelination.³⁷

Age is one of the diabetic neuropathy risk factors as we found which was supported by many studies.^{38,39} It can result from being exposed to diabetes as the incidence of diabetic neuropathy was increased in patients with a history of diabetes for more than 15 years compared to those with only less than five years.⁴⁰ Also, increasing age could be associated with increasing cellular ageing and neuronal degeneration.^{38,41}

The association between diabetic neuropathy and hypertension is not clear in the literature, some studies did not find an association^{42,43} and others found a significant association^{44–46}; however, a recent systematic review concluded a significant association between both.⁴⁷ In our study, we could not confirm an association between both factors as we found that neuropathy risk was the lowest at a level less than 48 mmol/mol (<6.5%) non-hypertensive patients and 48.0–57.9 mmol/mol (6.5–7.5%) for hypertensive patients and the highest risk was at a level more than 81 mmol/mol (6.9%) in both and non-hypertensive patients.

This controversy was also been for the role of antihypertensive drugs in term of the association as neuropathy risk was lowest at HbA1c levels below 48 mmol/mol (<6.5%) for those that not in antihypertensive drug and highest at levels above 81 mmol/mol (>9.6%), regardless of antihypertensive medication use; however, ACEIs were found to have some benefits in diabetic neuropathy and hypertensive patients which could be explained by that hyperglycaemia potentiates the angiotensin II action which in turn increases the vasoconstriction, inflammation, and thrombosis, therefore, blocking this cascade by ACEIs or ARBs could have benefits in decreasing the risk of neuropathy.^{47–50}

The risk of retinopathy was increasing by increasing HbA1c levels as we found which was supported by Poshtchaman 2023 et al.⁵¹ Also, a direct relationship was found between retinopathy severity and HbA1c levels.⁵² Another study found that keeping HbA1c levels below 53.0 mmol/mol (7%) could prevent retinopathy progression and development.⁵³

Unexpectedly, we observed a higher rate of retinopathy in patients without a recorded diagnosis of hypertension compared to those with a diagnosis. This likely reflects the presence of undiagnosed or masked hypertension in the 'no diagnosis' group, who consequently remain untreated and exposed to vascular damage. Conversely, diagnosed patients benefit from regular surveillance and pharmacotherapy, particularly RAS inhibitors (ACE inhibitors or ARBs), which have established microvascular protective effects beyond blood pressure lowering. Thus, this finding highlights the protective value of diagnosis and active management rather than contradicting the established risks of hypertension."

The relation between age and developing diabetic retinopathy is not clear in the literature.⁵⁴ Stratton et al. reported that while increasing age beyond 65 years was associated with the progression of diabetic retinopathy, it did not significantly impact its incidence.⁵⁵ Furthermore, the severity of diabetic retinopathy has been linked to the age at diagnosis and the duration of diabetes, with increased severity and progression observed in individuals diagnosed at 30 years old.^{56,57}

Our findings align with these observations, demonstrating variations in diabetic retinopathy risk across different age groups and HbA1c levels. Specifically, among patients with HbA1c levels above 58 mmol/

mol (7.6%), older individuals showed a higher risk of diabetic retinopathy. However, for HbA1c levels above 58.0 mmol/mol (7.6%), younger patients showed a higher risk of retinopathy, with the highest hazard ratio observed in the >81.0 mmol/mol (9.6%) category. This suggests that the risk of diabetic retinopathy is more strongly influenced by the age at diabetes onset and the duration of exposure to hyperglycemia rather than chronological age alone. These findings highlight the need for targeted screening strategies that account for both age and metabolic control to mitigate disease progression.

Antihypertensive drugs may have a role in decreasing the risk of retinopathy in T1DM as found by using ACEIs⁵⁸; however, their role in T2DM is questionable as the DIRECT-Protect 2 trial found that they had no role in decreasing the risk of retinopathy in T2DM.⁵⁹ Moreover, Lin 2015 et al. found that ACEIs, ARBs, and calcium channel blockers were associated with an increased risk of diabetic retinopathy compared to beta blockers.⁶⁰ Our results found that using antihypertensive drugs was associated with decreased risks of retinopathy compared to no use of antihypertensive drugs in all HbA1c levels except less than 48.0 mmol/mol (<6.5%), therefore, more studies are needed to solve this controversy.

4.1. Strength and limitations

Our primary strength lies in utilising a high-quality population dataset, which includes a large sample size, enhancing the robustness and generalizability of our findings. Also, it is the first study to perform subgroup analysis for all microvascular complications separately and study the specific risk factors like age, antihypertensive drugs, and hypertension; however, there are some limitations like being an observational study which increased the risk of some biases due to unmeasured confounders. To mitigate potential bias from missing data, we utilised multiple imputation methods. Nevertheless, residual confounding might still exist due to unmeasured variables such as diet and lifestyle, which could influence the relationship between HbA1c levels and outcomes. Also, our follow-up duration may not be very sufficient for developing microvascular complications, therefore, more studies with longer follow-ups are needed. The risk associated with the use of antihypertensive medications may be influenced by the presence of hypertension, as our study observed similar findings between hypertensive patients and those on antihypertensive drugs. This similarity suggests that individuals with hypertension are likely to be on antihypertensive medications, which could explain the comparable results in these two groups. Also, in the subgroup analysis, we could not look for the risk of microvascular complications by specification of each type of antihypertensive medication, therefore, it is important to investigate the role of using each type of antihypertensive medications and their role in influencing microvascular complications in both the presence and absence of hypertension.

5. Conclusion

Our study provides critical insights into the relationship between HbA1c levels and individuals microvascular complications. We observed that retaining HbA1c levels below 48 mmol/mol (6.5%), within the normal glycaemic range, is associated to a lower risk of neuropathy and retinopathy outcomes. On the other hand, higher HbA1c levels associated with an increased risk of these complications, reaching a peak when levels exceed 81.0 mmol/mol (9.6%). These findings underscore the importance of an individualised approach to diabetes management, focusing on reducing multifactorial risk factors and incorporating new therapies that demonstrate efficacy independent of glucose-lowering effects. Therefore, further studies are warranted to confirm the associations between the use of various medications, the management of comorbidities, and the risk of microvascular complications.

CRedit authorship contribution statement

Rami Aldafas: Writing – review & editing, Writing – original draft, Methodology, Investigation, Formal analysis. **Yana Vinogradova:** Writing – review & editing, Supervision, Methodology, Investigation, Formal analysis, Data curation. **Thomas S.J. Crabtree:** Writing – review & editing, Methodology, Investigation, Formal analysis, Data curation. **Jason Gordon:** Writing – review & editing, Supervision, Methodology, Investigation, Formal analysis, Conceptualization. **Iskandar Idris:** Writing – review & editing, Visualization, Supervision, Resources, Project administration, Methodology, Investigation, Funding acquisition, Data curation, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.jdiacomp.2026.109292>.

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