Manuscript

Title: **Relationship between HbA_{1c} and All-cause Mortality in Older Patients with Insulin treated Type 2 Diabetes: Results of a Large UK Cohort Study**

Article Type: Clinical Research Study

Keywords: Insulin, HbA_{1c}, Mortality, Type 2 diabetes, Older

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Conflict of Interest: None

Abstract

Background: Our aim was to study the relationship between HbA_{1c} and cardiovascular morbidity and all-cause mortality among older insulin-treated patients with type 2 diabetes after adjustment for multiple confounders.

Methods: Data for 4589 adults with type 2 diabetes (>65yrs) on insulin treatment were sourced from 532 UK General Practices via the Health Improvement Network (THIN) database. Cox proportional hazard models and Kaplan-Meier estimators were fitted to derive the hazards of all-cause mortality by HbA_{1c} categories (less than 6.5%, 6.5-7.4%, 7.5-8.4%, 8.5-9.4%, 9.5%-10.4%, 10.5-11.4%; and 11.5% and above) after 5-yrs of follow-up following insulin initiation.

Results: We observed a U-shaped relationship between all-cause mortality and HbA_{1c}, with the lowest risk seen in the HbA_{1c} range of 6.5 - 7.4% and marked increased in risk with HbA_{1c} >11%. The highest mortality risks of 31% and 40% were significantly associated with the lowest (less than 6.5%) and highest (11.5% and above) HbA_{1c} categories: aHR: 1.31; (95%CI: 1.10 – 1.56; p = 0.002) and aHR: 1.40; (95%CI: 1.01 – 1.96; p = 0.039) respectively.

Conclusions: Both low and high HbA_{1c} were associated with increased all-cause mortality, among older patients with insulin-treated type 2 diabetes. This cohort study supports the need for individualisation of care and suggests better outcomes with HbA_{1c} levels around 6.5 - 7.4%, and markedly excess risk with HbA_{1c} >11%

Key messages

What is already known about this subject?

- Older patients account for a larger proportion of patients with type 2 diabetes.
- Recent guideline have emphasised the need to individualised HbA_{1c} target for patients with type 2 diabetes.
- The optimal HbA_{1c} target for older patients on insulin, which takes into account the risk benefit of insulin is unknown.

What does this study add?

- There is a U-Shape association between HbA_{1c} and risk of mortality among older (age >65 years) insulin-treated patients with Type 2 diabetes.

How might this impact on clinical practice

In older patients with insulin-treated Type 2 diabetes, very tight and very poor glucose control is associated with excess mortality. This suggest the need to take into account the risk and benefit of insulin therapy when used in older people with type 2 diabetes.

Introduction

More than 25% of all patients with type 2 diabetes (T2D) are aged over 65 years [1], and the risk-benefit balance for anti-hyperglycaemic therapies can vary considerably in older compared with younger age groups. The UK Prospective Diabetes Study (UKPDS) excluded patients >65 yrs [2] and more recent outcome trials in T2D [3,4,5], have failed to provide a clear consensus on the optimal HbA_{1c} target for older patients, especially those who are on insulin therapy.

Outcomes modelling suggests that the cardiovascular and mortality benefits of lowering HbA_{1c} can take 2 or more decades to manifest [6]. Thus, when treatments have limited or delayed benefits, the risk-benefit balance changes with increasing age. This is particularly so with the use of insulin treatment in older patients in whom the benefits of HbA_{1c} lowering may be offset by the increased risks of hypoglycaemia, frailty, cardiovascular disease, cognitive impairment and falls [7]. Indeed large epidemiological studies have observed a dose-response relationship between increasing insulin exposure and all-cause mortality [8-10].

International guidelines emphasise the importance of individualising HbA_{1c} targets and recommend a less stringent approach in older patients with longer duration diabetes [11-13]. Nevertheless, failing to adequately treat hyperglycaemia in older patients may increase the risk of acute metabolic events [14] morbidity and mortality [15]. We therefore sought to evaluate the relationship between all-cause mortality and a 2-point composite of cardiovascular events vs. HbA_{1c} among a large UK cohort of older patients with insulin-treated T2D under routine care.

Methods

Study Design and Data Sources

We conducted a retrospective cohort study using data obtained from UK Primary Care practices via The Health Improvement Network (THIN). THIN contains anonymised longitudinal records for more than 10.5 million patients (derived from 532 UK General Practices) which are representative of the whole UK population in terms of demography, mortality rates and the prevalence of major health conditions [16,17] and validated for diabetes-related outcomes. [18,19] Ethical approval for the present study was obtained from the South East Research Ethics Committee.

Study Population

This comprised older patients with T2D, aged 65 years and above and first ever initiated insulin therapy in their lifetime, between January 2007 and January 2013, irrespective of use of other antidiabetic drug combinations. Subsequently, they must have been on insulin therapy for at least 180 days, from index date to be eligible for inclusion in the study. For analysis of composite non-fatal MI and stroke, we excluded patients with previous cardiovascular events at baseline.

Covariates

Baseline covariates were extracted within 90 days of initiation of insulin. These consist of clinical and biochemical parameters such as body weight, body mass index (BMI) and blood pressure (systolic and diastolic); baseline HbA_{1c}, serum albumin creatinine ratio, estimated glomerular filtration rate (eGFR) total cholesterol levels, low-density lipoprotein (LDL), high-density lipoprotein (HDL) and triglycerides. Additionally, baseline demographic parameters (e.g. age, sex, socioeconomic deprivation score, alcohol and smoking status), medications, e.g. statins, aspirin, antihypertensive drugs and non-insulin antidiabetic drugs; co-morbidities; as well as the duration of diabetes, duration of insulin treatment and the overall duration of diabetes treatment were also included.

Procedure

Glycaemic control was measured by post-index mean HbA_{1c}. This was calculated as the mean of all recorded post-insulin HbA_{1c} values from the index date to earliest of the

following – mortality, loss to follow-up, discontinuation of insulin (i.e. no records of insulin prescription for a continuous period greater than 6 months) or end of the study period at 5 years. These mean HbA_{1c} were categorised into the following 7 categories: Less than 6.5%, 6.5-7.4%, 7.5-8.4%, 8.5-9.4%, 9.5%-10.4%, 10.5-11.4%; and 11.5% and above.

The hazard of all-cause mortality and a two-point composite of non-fatal stroke and MI was explored in each HbA_{1c} categories and compared to the HbA_{1c} range: 6.5 to 7.4%. Both endpoints must have occurred at least 180 days after the index date

Statistical Analyses

The primary outcome was all-cause mortality while the secondary outcome was a 2-point composite of non-fatal MI and stroke. The mean, frequency distribution and differences between the measured baseline covariates between the HbA_{1c} categories were calculated and summarized. Using the HbA_{1c} categories, the baseline covariates of the cohort were assessed independently using linear regression or as trend Pearson's Chi-square test.

Crude and adjusted Kaplan–Meier estimates of survival functions were obtained. We used the log-rank test to compare the equality of the survival curves between the categories of HbA_{1c}. From these survival functions, the absolute reduction in the probability of an event occurring within a 5-year follow-up was calculated.

We fitted a Cox proportional hazard model to estimate the marginal hazard ratios, to enable us to quantify the adjusted hazard of mortality in all the HbA_{1c} categories, using the HbA_{1c} range of 6.5 to 7.4% as the reference. This is because 7.5% is current NICE threshold for insulin treatment while 6.5% is the target HbA_{1c} for newly diagnosed diabetes.

In the adjusted model, all the covariates which showed significant association with both the exposure and outcome in our univariate analyses and changed the effect size by ≥10% were included alongside a priori confounders (i.e. mean age and diabetes duration) [18,19]. Proportional hazards assumptions were confirmed through Schoenfeld residuals test. Point estimates with 95% confidence intervals (CI) at the conventional statistical significance level of 0.05 were used in the regression models.

We observed that 11%, 13%, 17%, 17% and 16% of the patients did not have baseline HbA_{1c}, weight, systolic and diastolic BP, and BMI respectively. These missing data were computed using multiple imputations using the chained equation (MICE) model.

All analyses were conducted using Stata Software, version 15. Statistical significance was put at a p-level of 0.05. The study was reported using the STROBE criteria for reporting observational studies.

Results

Patient Characteristics

There were 4,589 eligible patients that met the inclusion criteria. Figure 1 outlines the selection process for these study cohort. At baseline, the overall median age was 73.2 yrs (SD: 6.1); mean HbA_{1c}: 8.5% (SD: 1.8); 52.5% were females; while the mean BMI was 31.9±6.6 kg/m^2 and the average duration of insulin treatment was 3.4±1.2 years. Supplement 1 summarises the baseline characteristics of our study cohort by HbA_{1c} groups. Significant differences between the HbA_{1C} categories were observed in socio-economic status (p = 0.05), gender (p = 0.021), history of alcohol intake (p = 0.048) and use of lipid-lowering agents (p = 0.001) within the HbA_{1c} categories.

The median follow up period for the cohort was 3.6 years (IQR: 2.3–4.8), representing a total follow-up period of 26,023 person-years.

Primary Outcome – All-cause Mortality

A total of 1445 of all-cause mortality was recorded with a crude incidence rate of 56 per 1,000 person-years (95%CI: 52.7–58.5). The lowest proportion of deaths (4.7%) occurred in ≥11.5% HbA_{1c} category, while the highest (33%) occurred in the <6.5% category (Supplement 2). The 5-year probability of survival differed significantly between the HbA_{1c} categories. This fell from 98% in all categories at the first year to 74% and 76% at 5 years in the lowest (<6.5%) and highest (≥11.5%) HbA_{1c} categories respectively (log-rank test p-value = 0.046) (Figure 2).

In the adjusted Cox regression model, the risk of all-cause mortality was highest in the lowest and highest HbA_{1c} categories – a 31% significant increase in the hazard of death in the <6.5% HbA_{1c} category (tight glycaemic control) - HR: 1.31, 95%CI: 1.10–1.56; p=0.002 and a 40% (HR: 1.40, 95%CI: 1.01–1.96; p=0.039) increase in the HbA_{1c} ≥11.5% category (poor glycaemic control); thus giving a U-shaped association between post-insulin mean HbA_{1c} and all-cause mortality (Figure 3A).

Secondary Outcome – Composite Cardiovascular Events

A total of 982 composite events of non-fatal MI and stroke events occurred within the follow-up period. The crude incidence rate was 35 per 1,000 person-years (95%CI: 33.2–37.7). The least proportion (19.1%) was in the highest mean HbA_{1c} category, followed by 20.3% in the least mean HbA_{1c} category. The 5-year probability of survival for composite cardiovascular events differed significantly between the HbA_{1c} categories (log-rank test p-value = 0.009) (Figure 2B).

The risk of the 2-point composite cardiovascular event (Figure 3B), did not show the classical U-shaped pattern seen in all-cause mortality (Figure 3A). In the adjusted cox model, the risk increased further away from the comparator HbA_{1c} group of 6.5 to 7.4% in a consistent pattern (Supplement 2) except in the 8.5 to 9.4% HbA_{1c} category.. Also, there was no significant association between post-insulin mean HbA_{1c} and the hazard of 2-point composite cardiovascular events in all the HbA_{1c} groups except in the lowest (<6.5%) HbA_{1c} category in which the risk was 34% greater (aHR: 1.34; 95%CI: 1.08 – 1.66; p=0.007). Generally, compared to the 6.5 to 7.4% HbA_{1c} group, the risk of composite cardiovascular events was 4, 2, 12 and 13% higher in the 7.5-8.4%, 9.5-10.4%, 10.5-11.4% and ≥11.5% HbA_{1c} groups respectively (Supplement 2).

We tested for violations of the proportional hazards assumptions using Schoenfeld residuals test, in which we examined the null hypothesis that the hazard ratio is constant over time and we found no evidence (p=0.342) to reject this assumption of proportional hazards for the HbA_{1c} categories. .

Discussion

We have shown that for older patients (aged >65 years) with Insulin-treated T2Ds, following adjustment for various confounders, very high and very low levels of HbA_{1c} were associated with higher risks of adverse outcomes. The highest mortality risks were observed at the lowest (< 6.5%) and highest (11.5% and above) levels of HbA_{1c}. Interestingly, however, this U-shaped association between HbA_{1c} and mortality was not observed in the subgroup of patients with no previous history of a cardiovascular event at baseline.

Intensive control of blood glucose levels in patients with T2D reduces the risk of long-term vascular complications leading to blindness, kidney failure, lower limb amputation and adverse cardiovascular events [2,15,20]. Previous observational studies, however, have provided conflicting evidence regarding the association between achieved HbA_{1c} levels and mortality among patients with T2D in routine care. Earlier studies s have reported a more linear relationship [21,22], whereas more recent studies have reported a U-shaped association between HbA_{1c} and mortality [23-25]. Of note, in a study by Currie et al [23], a U-shaped association was observed among insulin users, but not apparent among non-insulin treated patients. The discrepancies between older and more recent studies are likely to be attributable to the more aggressive glycaemic targets being adopted in response to recent national and international guidelines, as well as the greater use of combination therapies which include insulin.

A post-hoc analysis of the ACCORD trial has revealed a discordant HbA_{1c}-mortality relationship between the control arm and the intensively treated arm [26], indicating that aggressive use of glucose-lowering treatments might influence the HbA_{1c}-mortality relationship. In a more recent sub-analysis of that trial, regardless of intervention arm, the subgroup of older patients experienced higher annualized rates of severe hypoglycaemia [27]. Thus, the recommendation for individualization of HbA_{1c} targets for older people needs to be based on a variety of considerations including levels of frailty, presence of multiple comorbidities and the complexities and safety of polypharmacy. Yet, despite the well-recognised associations between intensive glucose control and the increased risk of hypoglycaemia, and the links between hypoglycaemia and enhanced sympathomimetic (adrenergic) drive [28], cardiac arrhythmias [29] and mortality [30], there is limited data on defining the appropriate HbA_{1c}-target range in older patients with insulin treated T2D.

Our analysis therefore advances current knowledge in several ways: (1) it assessed the association between HbA_{1c} and mortality specific to older patients with Insulin-treated T2D; (2) it utilised a large electronic record of individual patient-data among a cohort receiving routine care in UK General Practice; (3) we derived an association between HbA_{1c} range with reduction in the risk of mortality, and (4) observed no association between HbA_{1c} range with composite cardiovascular events

Our findings in older insulin treated patients with T2D are consistent with recent observational studies in patients with T2D which reported a strong U-shaped HbA_{1c} – mortality association. However, rather than aiming to achieve an HbA_{1c} target to below a certain value, our data suggests the need to control HbA_{1c} to a certain range (6.5 to 7.4%) in order to maximally reduce mortality. .

Unlike mortality, we did not observe a clear U-shaped association between cardiovascular events and HbA_{1c} in this group of patients, but rather a similar cardiovascular risk across all HbA_{1c} levels. This implies that this older patient cohort are generically at higher risk of cardiovascular events, irrespective of HbA_{1c} levels, and that other non- cardiovascular factors may influence mortality outcomes at high or low levels of HbA_{1c}. Older patients at low levels of HbA_{1c} may have poor nutritional status and are generally more frail, whereas those with higher HbA_{1c} may have a higher risk of dehydration, infection, electrolyte abnormalities and metabolic complications [7], all of which may contribute to an elevated mortality risk, independent of cardiovascular events. A discrepancy between mortality and cardiovascular outcomes was also observed in the ACCORD study where, despite an increase in mortality with intensive glucose control, the number of patients achieving the composite of non-fatal myocardial infarction, non-fatal stroke, or death from cardiovascular causes was lower in the intensive compared with the standard therapy groups. [3].

Our analyses were subject to some limitations inherent to observational studies, such as coding errors, unlisted comorbidities or missing data. In addition, our exposure data relates to prescriptions so we cannot be certain that the patients were completely compliant with their medication. However, should there be any over-estimation of exposure to the medications in our analysis, such a misclassification would be non-differential and only bias results towards unity. Furthermore, other factors apart from HbA_{1c} may also influence the decision to intensify treatment by starting insulin, such as tolerability, safety, cost and a patient's preference. . Although we could not account for potential residual confounders such

as indications for intensification of treatment, censuring influenced by patients' condition or differences in doses, we were able to account for differences in the observed covariates and we used robust analytical techniques to control confounding that may bias the results of the estimated treatment effects. Nonetheless, the issue of unmeasured confounding does persist, e.g. the relationship between severity of risk factors and clinical outcomes or differences in the time-varying relationship for each risk factor with individual outcomes.

Recent local and international guidelines have emphasised the importance of individualised HbA_{1c} targets to take into account patient factors such as age, body mass index, comorbidities or duration of diabetes. This is particularly relevant when determining the safety profile of insulin treatment in older patients. Our data supports a strong U-shaped association between HbA_{1c} and mortality with minimum safe and high HbA_{1c} values identified to reduce the risks of mortality in this high risk group of patients in routine care. The observational data presented here therefore provide important guidance to the management of the rapidly growing number of older patients with T2D who require insulin therapy to manage their hyperglycaemia and symptoms.

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Legend

Tables

Supplement 1: Baseline Characteristics of Study Cohort

Supplement 2: Events and Rates and Hazard Ratio of All-cause Mortality and composite Cardiovascular (CV) events in older T2D on Insulin Therapy

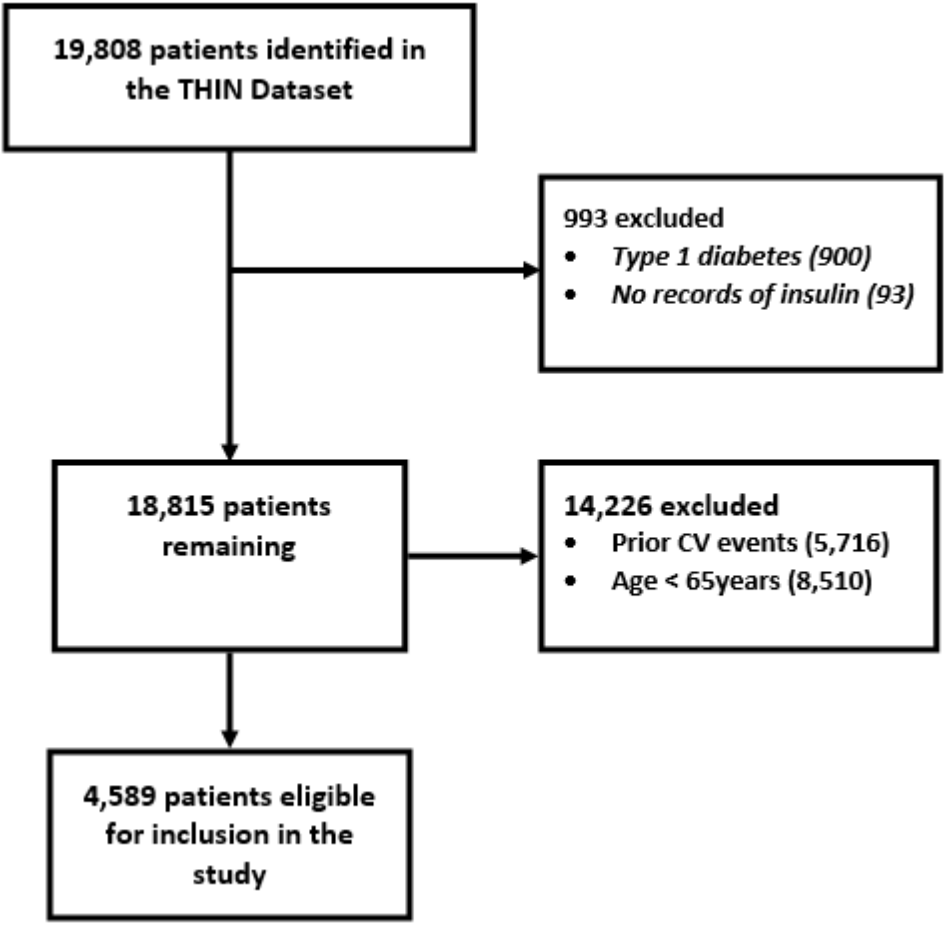
Figures:

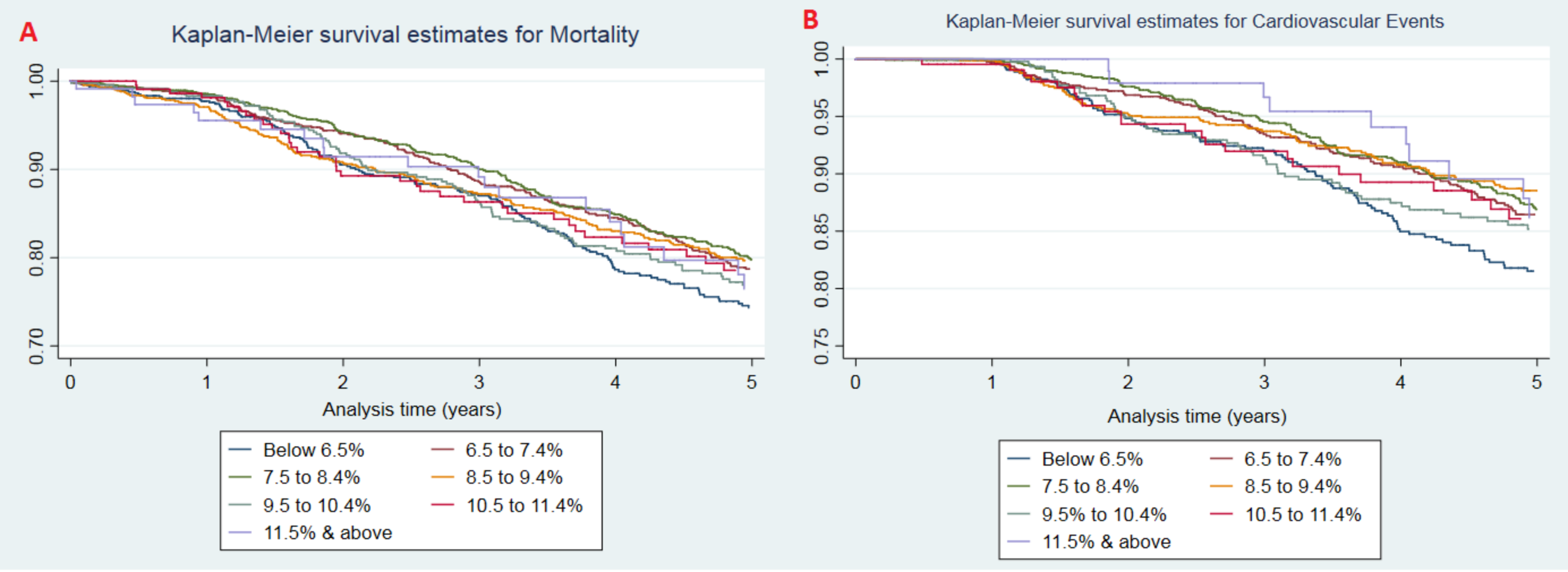
Figure 1: Flow diagram of selection of study participants

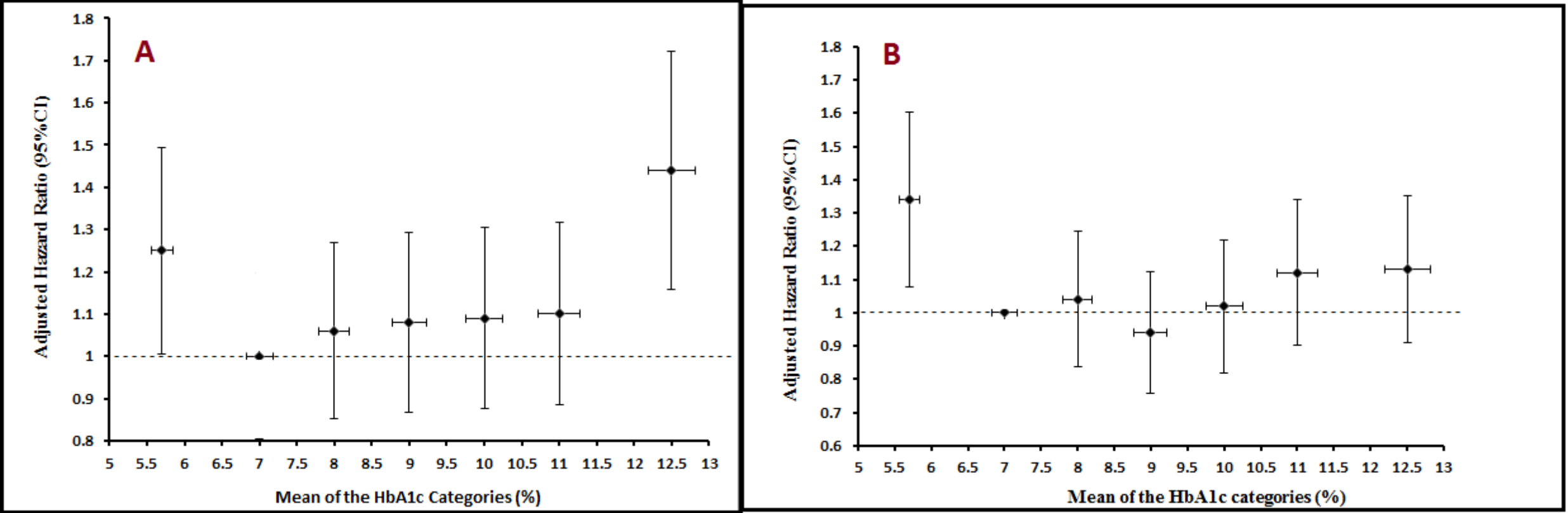
Figure 2: Kaplan-Meier Survival analysis plot for (A) All-cause Mortality (log-rank test p value = 0.046). (B) 2-point composite Cardiovascular (non-fatal MI and stroke) events (log-rank test p value = 0.009)

Figure 3: Graph of Adjusted Hazard Ratios for All-cause mortality (A) and 2-point composite Cardiovascular (non-fatal MI and stroke) events (B) *(The vertical bars show 95% CI while the horizontal bars show the mean HbA_{1c} range. * Shows truncation of range at the upper and/or lower range limit).*

Supplement figure 1 HbA1c categories calculated as mean of all values, yearly mean, accumulative mean,.


19,808 patients identified in the THIN Dataset
993 excluded
Type 1 diabetes (900)
No records of insulin (93)
18,815 patients remaining
14,226 excluded
Prior CV events (5,716)
Age < 65years (8,510)
4,589 patients eligible for inclusion in the study


A
Kaplan-Meier survival estimates for Mortality
1.00
0.90
0.80
0.70
0
1
2
3
4
5
Analysis time (years)
Below 6.5%
6.5 to 7.4%
7.5 to 8.4%
8.5 to 9.4%
9.5 to 10.4%
10.5 to 11.4%
11.5% & above
B
Kaplan-Meier survival estimates for Cardiovascular Events
1.00
0.95
0.90
0.85
0.80
0.75
0
1
2
3
4
5
Analysis time (years)
Below 6.5%
6.5 to 7.4%
7.5 to 8.4%
8.5 to 9.4%
9.5% to 10.4%
10.5 to 11.4%
11.5% & above


A
Adjusted Hazard Ratio (95%CI)
1.8
1.7
1.6
1.5
1.4
1.3
1.2
1.1
1
0.9
0.8
5 5.5 6 6.5 7 7.5 8 8.5 9 9.5 10 10.5 11 11.5 12 12.5 13
Mean of the HbA1c Categories (%)
B
Adjusted Hazard Ratio (95%CI)
1.8
1.7
1.6
1.5
1.4
1.3
1.2
1.1
1
0.9
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0.7
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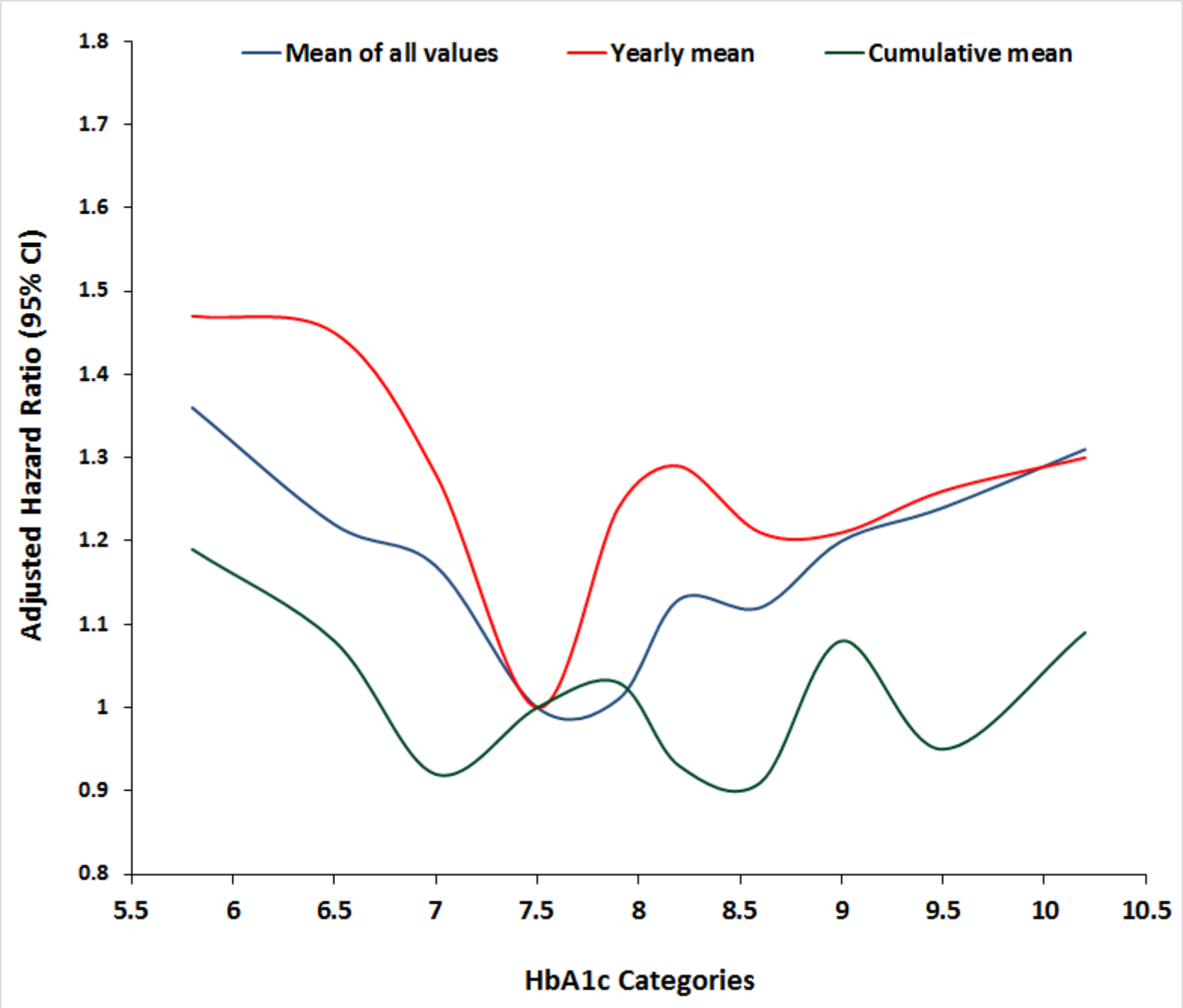
5 5.5 6 6.5 7 7.5 8 8.5 9 9.5 10 10.5 11 11.5 12 12.5 13
Mean of the HbA1c categories (%)


Mean of all values
Yearly mean
Cumulative mean
Adjusted Hazard Ratio (95% CI)
1.8
1.7
1.6
1.5
1.4
1.3
1.2
1.1
1
0.9
0.8
5.5
6
6.5
7
7.5
8
8.5
9
9.5
10
10.5
HbA1c Categories