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ARTICLE

Short-term impact of HbA_{1c} on morbidity and all-cause mortality in people with type 2 diabetes: a Danish population-based observational study

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Abstract
Aims/hypothesis In a population-based setting, we investigated whether diabetes-related morbidity and all-cause mortality within 2 years of HbA_{1c} measurement were associated with that HbA_{1c} level in individuals with type 2 diabetes. The main objective was to compare outcomes in those with HbA_{1c} ≥ and <7% (53 mmol/mol).
Methods Individuals with type 2 diabetes from Aarhus County, Denmark, were identified from public data files in a 3 year period (2001–2003). Stratifying the 17,760 individuals by HbA_{1c}, we estimated HRs for diabetes-related morbidities and all-cause mortality using Cox regression. Results were also stratified by treatment modality.
Results In total, 1,805 individuals experienced at least one diabetes-related morbidity and 1,859 individuals died. In general, the HRs in adjusted analyses of diabetes-related morbidity and mortality were increased for HbA_{1c} ≥7% (53 mmol/mol): morbidity, HR 1.48 (95% CI 1.34, 1.63); and mortality, HR 1.26 (95% CI 1.15, 1.39). On grouping individuals according to HbA_{1c} <5% (31 mmol/mol), 5.0–5.9% (31–41 mmol/mol), 6.0–6.9% (42–52 mmol/mol), 7.0–7.9% (53–63 mmol/mol), 8.0–8.9% (64–74 mmol/mol) and ≥9% (75 mmol/mol), the HRs for mortality formed a U shape, with HbA_{1c} 6.0–6.9% (42–52 mmol/mol) at the lowest point. For diabetes-related morbidity, a dose–response pattern appeared (lowest for HbA_{1c} <5% [31 mmol/mol]). Patterns of HR differed with treatment modality.
Conclusions/interpretation An HbA_{1c} level ≥7% (53 mmol/mol) was associated with increased morbidity and mortality. Both high and very low levels of HbA_{1c} were associated with increased mortality. A dose–response pattern appeared for morbidity. The impact of HbA_{1c} level on morbidity and mortality depended on treatment modality.

Keywords All-cause mortality · HbA_{1c} · Morbidity · Type 2 diabetes mellitus

Abbreviations

AMI	Acute myocardial infarction
DNPR	Danish National Patient Register
ICD-10	International Classification of Diseases version 10

Introduction

Chronic hyperglycaemia (assessed by HbA_{1c} level) is documented to be associated with microvascular complications [1–4]. For cardiovascular events, a meta-analysis in 2004 concluded that a 1% point increase in HbA_{1c} was associated with an 18% increase in the risk of cardiovascular events [5]. Two more recent meta-analyses concluded that intensive glycaemic control, measured by HbA_{1c}, had a significant beneficial effect on major cardiovascular events [6, 7]. However, except for two small studies included in the 2004 meta-analysis [8, 9], all the studies included in the three meta-analyses consisted of selected study populations, which may not have been representative of the general population. For instance, people with concomitant severe diseases were excluded, and participants were primarily self-selecting volunteers. Even a large registry-based study

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conducted in a primary care setting [10] only included people with type 2 diabetes who had a specific escalation of their diabetes treatment and who received oral blood-glucose-lowering drugs or insulin. This may, in part, explain its finding that both high and low HbA_{1c} levels were associated with increased mortality for people with type 2 diabetes.

To our knowledge, no large population-based registry studies that have included all people with type 2 diabetes, independent of their comorbid conditions and treatment status, have investigated the relationship between HbA_{1c} and cardiovascular events.

Since 2003, the Danish Department of Health, in accordance with international guidelines [11], has recommended that individuals with type 2 diabetes are offered intensive hyperglycaemic treatment aimed at reducing HbA_{1c} to <7% (53 mmol/mol) [12]. The primary aim of this study was to investigate whether, in an unselected population of individuals with type 2 diabetes, diabetes-related morbidity and/or all-cause mortality is lower at HbA_{1c} <7% (53 mmol/mol) vs ≥7% (53 mmol/mol). A secondary aim was to identify the range of HbA_{1c} levels associated with minimal diabetes-related morbidity and/or all-cause mortality.

Methods

Study design Individuals with type 2 diabetes were identified from public data files in Aarhus County, Denmark, using a dedicated validated algorithm described in detail elsewhere [13, 14]. Briefly, the algorithm is designed to identify people with type 2 diabetes in Aarhus County, Denmark, and has a sensitivity of 96% and a positive predictive value of 89%. Among other things it retrieves information on age, sex, laboratory results and redeemed prescriptions. Information on diabetes duration was gathered by a questionnaire sent to all individuals with diabetes in 2002 and by a questionnaire sent to general practitioners in 2003. In this study, individuals who were known to have type 2 diabetes by 31 December 2001, 2002 or 2003 and had at least one HbA_{1c} measurement were identified. Of the 18,515 individuals with type 2 diabetes identified, 17,760 had at least one HbA_{1c} measurement and constituted the study population.

Diseases included in Charlson's comorbidity index [15] were used to adjust for possible confounding from comorbidities, although excluding diabetes without complications. Diagnoses were obtained from record linkage with the Danish National Patient Register (DNPR), which covers all hospitalisations in Denmark. As an association between low HbA_{1c} and mortality/morbidity might be due to reverse causality, we identified all individuals who, prior to inclusion, had been hospitalised with diseases known to decrease HbA_{1c} [16]. We included information on prior hospitalisations with renal insufficiency within 1 year prior to HbA_{1c} measurement, and with haemolytic anaemia, familial erythrocytosis or secondary polycythaemia within 10 years prior to HbA_{1c} measurement (the International Classification of Diseases version 10 [ICD-10] codes [www.who.int/classifications/icd/en/] are shown in the electronic supplementary material [ESM] Table 1). Hereafter, this group of diseases is referred to as 'HbA_{1c}-lowering diseases'.

Information on the outcome measures was obtained by record linkage with either the nationwide Danish Civil Registration System (mortality) or the DNPR (morbidity). We included the following as diabetes-related morbidities: arteriosclerosis, acute complications of diabetes, retinopathy, nephropathy, acute myocardial infarction (AMI), stroke and neuropathy (ICD-10 codes are shown in ESM Table 2). Individual migration history was obtained from the Civil Registration System. Dates were available for all events.

Statistical analysis The HbA_{1c} level of an individual was defined as the average of all HbA_{1c} measurements recorded in the year of the first registered HbA_{1c} measurement. Individuals were stratified into two groups, according to HbA_{1c} level: <7% (53 mmol/mol) and ≥7% (53 mmol/mol). Prior cardiovascular disease and the number of non-cardiovascular diseases were defined on the basis of diseases included in Charlson's comorbidity index. Myocardial infarction, congestive heart failure, peripheral vascular disease and cerebrovascular disease represented prior cardiovascular disease. The number of prior non-cardiovascular diseases was the number of different diseases for which each individual was hospitalised, from: dementia, chronic pulmonary disease, connective tissue disease, ulcer disease, mild liver disease, hemiplegia, moderate to severe renal disease, diabetes with end-organ damage, any tumour, leukaemia, lymphoma, moderate or severe liver disease, metastatic solid tumour and AIDS. Responders and non-responders to questionnaires concerning type 2 diabetes might have had different illness perceptions, mortalities and diabetes-related morbidities. Therefore, the analysis included an indicator variable for response status, i.e. whether or not the questionnaire was filled in and returned.

Unadjusted survival was estimated by the Kaplan–Meier method and Cox proportional hazard models were used to adjust for covariates. Adjustment was made for age, sex, response status, prior cardiovascular disease and the number of non-cardiovascular diseases. A subgroup analysis was performed for individuals with positive response status, as these were the individuals for whom information on diabetes duration was available. In this analysis, adjustment for response status was replaced by diabetes duration (0–2 years,

3+ years). Stratified analyses were performed according to diabetes treatment (diet, tablet, insulin [± tablet]). Individuals were stratified according to the treatment they were using (according to redeemed prescriptions) in the same year as their HbA_{1c} level was assessed. Finally, individuals were stratified based on their HbA_{1c} level: <5% (31 mmol/mol), 5.0–5.9% (31–41 mmol/mol), 6.0–6.9% (42–52 mmol/mol), 7.0–7.9% (53–63 mmol/mol), 8.0–8.9% (64–74 mmol/mol) and ≥9% (75 mmol/mol), using HbA_{1c} level 6.0–6.9% (42–52 mmol/mol) as the reference group. To address the possibility of reverse causality, these analyses were performed both with and without individuals who had been hospitalised with an HbA_{1c}-lowering disease and with a dataset that excluded all individuals dying within the first 6 months after inclusion. Similar analyses were performed stratified by diabetes treatment.

In secondary analyses we explored the possible impact of adjustment for preventive pharmacological treatment of cardiovascular diseases, longer follow-up time and stratification by diabetes duration (when available). To explore whether prior cardiovascular diseases or number of other diseases might be part of the causal pathway from HbA_{1c} level to morbidity and/or mortality, we conducted analyses in which these variables were excluded.

The proportionality assumption was assessed graphically and tested using Schoenfeld residuals [17]. The following categorical variables were included: sex (male, female), previous cardiovascular disease (yes, no), response status (yes, no) and diabetes duration (0–2 years, 3+ years). Time since 1 January of the year after the first registered HbA_{1c} measurement was used as the time scale. As information regarding changes in HbA_{1c}, comorbidity or treatment during follow-up was not available for the current study, we restricted follow-up to 2 years to limit the impact of changes in these variables. Each person was followed until death or morbidity outcome, emigration (censoring), 31 August 2010 or 2 years after inclusion, whichever came first. All estimates are accompanied by 95% CIs. Analyses were performed using Stata version 10.1 (StataCorp, College Station, TX, USA).

Results

Baseline characteristics are shown in Table 1. The median follow-up time per individual was 730 days and did not differ between groups. In total, 936 deaths occurred in individuals with HbA_{1c} <7% (53 mmol/mol) and 923 in individuals with HbA_{1c} ≥7% (53 mmol/mol). Among individuals with HbA_{1c} <7% (53 mmol/mol), 665 (8%) had at least one hospitalisation for a diabetes-related morbidity; for individuals with HbA_{1c} ≥7% (53 mmol/mol), the number was 1,140 (12%).

Mortality was increased for individuals with an HbA_{1c} level ≥7% (53 mmol/mol), as was most diabetes-related morbidity, with the highest HR for nephropathy (HR 3.00 [95% CI 1.94, 4.62]) (Table 2). Inclusion of diabetes duration slightly lowered the excess risks. HRs were highest for microvascular diabetes-related morbidities (retinopathy, nephropathy, neuropathy) and no excess risk was found for AMI (HR 1.13 [95% CI 0.93, 1.38]) or stroke (HR 1.09 [95% CI 0.91, 1.30]). Stratification by treatment modality showed similar trends (Table 3), though we found no impact on mortality with HbA_{1c} ≥7% (53 mmol/mol) for individuals receiving oral blood-glucose-lowering drugs or insulin.

For individuals with HbA_{1c} levels <5% (31 mmol/mol), 5.0–5.9% (31–41 mmol/mol), 7.0–7.9% (53–63 mmol/mol), 8.0–8.9% (64–74 mmol/mol) or ≥9% (75 mmol/mol), the HRs of mortality relative to individuals with HbA_{1c} 6.0–6.9% (42–52 mmol/mol) formed a U shape, with the lowest mortality in the reference group (HbA_{1c} 6.0–6.9% [42–52 mmol/mol]) (Table 4). An HbA_{1c} <5% (31 mmol/mol) yielded HR 1.75 (95% CI 1.14, 2.69), and an HbA_{1c} ≥9% (75 mmol/mol) an HR of 1.44 (95% CI 1.24, 1.66). For diabetes-related morbidity, a dose–response pattern appeared, with the lowest morbidity in individuals with HbA_{1c} <5% (31 mmol/mol) (HR 0.79 [95% CI 0.41, 1.54]) and the highest in those with HbA_{1c} ≥9.0% (75 mmol/mol) (HR 1.79 [95% CI 1.57, 2.05]). Few of the individuals included had an HbA_{1c}-lowering disease: none (0%) with HbA_{1c} <5% (31 mmol/mol), 33 (1.4%) with HbA_{1c} 5.0–5.9% (31–41 mmol/mol), 78 (1.4%) with HbA_{1c} 6.0–6.9% (42–52 mmol/mol), 65 (1.6%) with HbA_{1c} 7.0–7.9% (53–63 mmol/mol), 32 (1.3%) with HbA_{1c} 8.0–8.9% (64–74 mmol/mol) and 25 (0.8%) with HbA_{1c}≥9.0% (75 mmol/mol). In total, 517 individuals died within 6 months of study inclusion. The results were similar when individuals with an HbA_{1c}-lowering disease were removed from the analyses (ESM Table 3) and when analysis was restricted to those who were alive 6 months after inclusion (ESM Table 4). When stratified by treatment, HRs for mortality formed a U shape for those receiving no glucose-lowering therapy, with the lowest mortality in the reference group (HbA_{1c} 6.0–6.9% [42–52 mmol/mol]) (Table 5), whereas the HRs for those receiving oral blood-glucose-lowering drugs or insulin formed an L shape, with the highest mortality among the very few individuals with HbA_{1c} <5% (31 mmol/mol), and with the elbow at HbA_{1c} 5.0–5.9% (31–41 mmol/mol) and 6.0–6.9% (42–52 mmol/mol), respectively. For diabetes-related morbidity, a dose–response pattern appeared (not statistically significant) for individuals receiving no glucose-lowering therapy, with lowest morbidity for individuals with HbA_{1c} <5% (31 mmol/mol) (HR 0.50 [95% CI 0.19, 1.36]). For those receiving glucose-lowering therapy no clear patterns could be

Table 1 Characteristics of individuals included

Characteristic	HbA_{1c}	
	<7% (53 mmol/mol)	≥7% (53 mmol/mol)
n	8,248	9,512
Age (years)	67 (57–77)	65 (56–74)
Women (%)	49.6	46.1
Duration of diabetes (years)[a]	2 (0–5)	4 (1–10)
HbA_{1c}		
Average value	0.064 (0.059–0.066)	0.082 (0.075–0.093)
Number of measurements (stratified by average HbA_{1c} value)		
<5%	2 (2–3)	–
5–5.9%	2 (1–3)	–
6–6.9%	2 (1–3)	–
7–7.9%	–	2 (1–4)
8–8.9%	–	3 (2–4)
≥9%	–	2 (1–4)
Prior cardiovascular disease, *n* (%)	2,020 (24.5)	2,315 (24.3)
Number of prior non-cardiovascular diseases	0 (0–1)	0 (0–1)
Preventive therapy for cardiovascular disease, *n* (%)	5,693 (69.0)	6,383 (67.1)
Follow-up to death or emigration (days)		
Median (min–max)	730 (2–730)	730 (2–730)
Total, years	15,498	18,018
Morbidity/mortality during follow-up		
Deaths, *n* (%)	936 (11.3)	923 (9.7)
Arteriosclerosis, *n* (%)	46 (0.6)	93 (1.0)
Acute complication of diabetes, *n* (%)	49 (0.6)	141 (1.5)
Retinopathy, *n* (%)	124 (1.5)	337 (3.5)
Nephropathy, *n* (%)	26 (0.3)	116 (1.2)
AMI, *n* (%)	194 (2.4)	228 (2.4)
Stroke, *n* (%)	244 (3.0)	264 (2.8)
Neuropathy, *n* (%)	34 (0.4)	94 (1.0)
At least one of the above morbidities, *n* (%)	665 (8.1)	1,140 (12.0)

HbA_{1c} categories in IFCC units: <31 mmol/mol, 31–41 mmol/mol, 42–52 mmol/mol, 53–63 mmol/mol, 64–74 mmol/mol, ≥75 mmol/mol

Values are median (quartiles) unless otherwise indicated

[a]Self-reported: information from 4,367 (53%) with HbA_{1c} <7% (53 mmol/mol) and from 7,380 (78%) with HbA_{1c} ≥7% (53 mmol/mol)

identified, although a tendency towards a dose–response pattern appeared, with higher morbidity for higher HbA1c. However, among those receiving insulin the highest morbidity was found in the four individuals with HbA_{1c} <5% (31 mmol/mol) (HR 7.58 [95% CI 1.82, 31.5]).

Secondary analyses with longer follow-up times (last exit after 8.6 years) revealed statistically significant associations between HbA_{1c} >7% (53 mmol/mol) and AMI (HR 1.26 [95% CI 1.13, 1.42]) and stroke (HR 1.22 [95% CI 1.09, 1.35]) (ESM Table 5). All other results were similar to those reported in Tables 1 and 4. Analyses with further adjustment for preventive pharmacological treatment of cardiovascular diseases and stratification by diabetes duration (when available) produced similar results (ESM Tables 6 and 7), as did analyses performed without including information on prior cardiovascular diseases or number of other diseases (ESM Tables 8 and 9).

Discussion

In this population-based registry study of individuals with type 2 diabetes, individuals with an HbA_{1c} level >7% (53 mmol/mol) had higher mortality and higher diabetes-related morbidity compared with those with HbA_{1c} level <7%. The largest excess risk was found for microvascular complications (retinopathy, nephropathy and neuropathy), whereas no excess risk was found for AMI or stroke. Stratification by treatment modality showed no impact of HbA_{1c} ≥7% (53 mmol/mol) on mortality for individuals receiving oral blood-glucose-lowering drugs or insulin. Stratifying HbA_{1c} level into six groups revealed that both HbA_{1c} <5% (31 mmol/mol) and HbA_{1c} ≥7% (53 mmol/mol) increased mortality, whereas a trend towards a dose–response pattern was seen for diabetes-related morbidity, with the lowest morbidity for HbA_{1c} <5% (31 mmol/mol).

Table 2 HRs for mortality and morbidity for individuals with HbA_{1c} ≥7% (53 mmol/mol) compared with individuals with HbA_{1c} <7% (53 mmol/mol)

Mortality/morbidity	All included individuals (n=17,760)		Individuals with information on diabetes duration (n=11,747)	
	n	Adjusted[a] HR (95% CI)	n	Adjusted[b] HR (95% CI)
All-cause mortality	1,859	1.26 (1.15, 1.39)	611	1.15 (0.97, 1.36)
Arteriosclerosis	139	1.76 (1.23, 2.51)	90	1.71 (1.05, 2.78)
Acute complication of diabetes	190	2.13 (1.52, 2.97)	158	1.68 (1.16, 2.45)
Retinopathy	461	1.88 (1.52, 2.32)	398	1.55 (1.23, 1.94)
Nephropathy	142	3.00 (1.94, 4.62)	125	2.39 (1.50, 3.81)
AMI	422	1.13 (0.93, 1.38)	250	1.25 (0.95, 1.63)
Stroke	508	1.09 (0.91, 1.30)	287	1.00 (0.78, 1.27)
Neuropathy	128	1.89 (1.26, 2.82)	110	1.88 (1.19, 2.97)
At least one of the above morbidities	1,805	1.48 (1.34, 1.63)	1,272	1.43 (1.26, 1.61)

[a]Adjusted for age, sex, prior hospital admission for cardiovascular disease, number of prior diagnosed non-cardiovascular diseases and response status

[b]Adjusted for age, sex, prior hospital admission for cardiovascular disease, number of prior diagnosed non-cardiovascular diseases and duration of diabetes

Our finding of an elevated risk of overall diabetes-related morbidity for people with type 2 diabetes and HbA_{1c} ≥7% (53 mmol/mol) supports the findings of three meta-analyses [5–7], which all concluded that increasing levels of HbA_{1c} increased the risk of cardiovascular disease. Further, the results of a clear relationship between HbA_{1c} and microvascular events support previous findings [18, 19], though in our study the relationship was independent of willingness to participate and any comorbid conditions.

We found no statistically significant excess risk of stroke in the short follow-up period. This contradicts the finding, reported by Selvin et al [5], that a small increased risk was found in all the included studies [4, 20, 21] (RR 1.17 [95% CI 1.03, 1.3] RR 1.14 [95% CI 1.01, 1.28]; RR 1.17 [95% CI 1.05, 1.30]), but supports the findings of Ray et al [6] (pooled OR 0.93 [95% CI 0.81, 1.06]), in which none of the included studies showed a statistically significant effect of intensive glucose-lowering treatment on the risk of stroke. However, studies included by Ray et al had shorter average follow-up (between 2.9 and 10.1 years) compared with those included by Selvin et al (between 6 and 10 years). When using a longer follow-up time in the present study, we found a statistically significant excess risk of stroke. The divergent results found by Selvin et al and Ray et al may also reflect the different approaches to targeting a preventive approach for cardiovascular diseases over the years. The time period and the general preventive strategy for people with type 2 diabetes in our study match more closely with Ray et al than with Selvin et al.

An HbA_{1c} level ≥7% (53 mmol/mol) was not associated with risk of AMI in the short follow-up period in our study. All the studies included by Ray et al [6] and by Turnbull et al [7] showed a reduced risk of non-fatal myocardial infarction, ending up with pooled estimated reductions of 17% (95% CI 7%, 25%) or 15% (95% CI 6%, 24%), respectively, with more intensive glycaemic control. However, the studies included by Ray et al and by Turnbull et al had longer follow-up periods than the present study. When using a longer follow-up period, we found a statistically significant excess risk of AMI. Distinguishing non-fatal from fatal myocardial infarction was not possible in our study.

We found an elevated mortality for individuals with HbA_{1c} ≥7% (53 mmol/mol), which does not support the conclusion in the meta-analyses of no association for people with type 2 diabetes undergoing intensive glycaemic control as measured by HbA_{1c} [6, 7]. However, our finding that HbA_{1c} ≥7% (53 mmol/mol) had no impact on mortality in individuals receiving oral blood-glucose-lowering drugs or insulin support the findings of the two meta-analyses, and may imply that a stricter distinction between an HbA_{1c} level obtained without pharmaceutical treatment and an HbA_{1c} level obtained by glucose-lowering therapies should be maintained in future studies.

When stratifying individuals into six groups based on HbA_{1c} levels, a dose–response pattern was seen for diabetes-related morbidity, with the lowest morbidity with HbA_{1c} levels <5% (31 mmol/mol). The highest impact of HbA_{1c} level was on microvascular complications. This agrees with the established association between HbA_{1c} level and diabetes-related microvascular morbidity [1–4]. However, little is known about the association with lower levels of HbA_{1c}. Further stratification by treatment modality revealed a possible association between an HbA_{1c} <5% (31 mmol/mol) and an increased morbidity among individuals who received some form of glucose-lowering therapy. However, very few individuals received glucose-lowering therapy and had HbA_{1c} <5% (31 mmol/mol); of the 32 individuals who did, six had at least one diabetes-related morbidity. A dose–response pattern was seen for those who did not receive any glucose-lowering therapy. Among people without diabetes, and thereby with generally lower HbA_{1c} levels, a continuous increase in the risk of coronary heart

Table 3 HRs for individuals with HbA_{1c} ≥7% (53 mmol/mol) compared with individuals with HbA_{1c} <7% (53 mmol/mol), stratified by treatment modality

Treatment modality	All included individuals		Individuals with information on diabetes duration	
	n	Adjusted[a] HR (95% CI)	*n*	Adjusted[b] HR (95% CI)
No glucose-lowering therapy	7,842		3,728	
HbA_{1c} <7% (53 mmol/mol)	5,690		2,403	
HbA_{1c} ≥7% (53 mmol/mol)	2,152		1,325	
All-cause mortality	1,859	1.26 (1.15, 1.39)	611	1.15 (0.97, 1.36)
Morbidity				
Arteriosclerosis	139	1.76 (1.23, 2.51)	90	1.71 (1.05, 2.78)
Acute complication of diabetes	190	2.13 (1.52, 2.97)	158	1.68 (1.16, 2.45)
Retinopathy	461	1.88 (1.52, 2.32)	398	1.55 (1.23, 1.94)
Nephropathy	142	3.00 (1.94, 4.62)	125	2.39 (1.50, 3.81)
AMI	422	1.13 (0.93, 1.38)	250	1.25 (0.95, 1.63)
Stroke	508	1.09 (0.91, 1.30)	287	1.00 (0.78, 1.27)
Neuropathy	128	1.89 (1.26, 2.82)	110	1.88 (1.19, 2.97)
At least one of the above	1,805	1.48 (1.34, 1.63)	1,272	1.43 (1.26, 1.61)
Oral glucose-lowering treatment	7,095		5,520	
HbA_{1c} <7% (53 mmol/mol)	2,139		1,607	
HbA_{1c} ≥7% (53 mmol/mol)	4,956		3,913	
All-cause mortality	657	0.85 (0.73, 1.00)	254	0.90 (0.70, 1.17)
Morbidity				
Arteriosclerosis	57	2.12 (1.09, 4.10)	41	1.95 (0.90, 4.25)
Acute complication of diabetes	66	0.91 (0.54, 1.51)	48	0.86 (0.47, 1.55)
Retinopathy	197	1.75 (1.22, 2.50)	165	1.76 (1.18, 2.61)
Nephropathy	71	2.14 (1.15, 3.98)	60	1.68 (0.89, 3.17)
AMI	163	1.12 (0.80, 1.57)	116	1.38 (0.90, 2.11)
Stroke	191	0.95 (0.70, 1.29)	139	0.99 (0.69, 1.41)
Neuropathy	57	1.69 (0.88, 3.28)	53	1.51 (0.77, 2.94)
At least one of the above	726	1.29 (1.09, 1.52)	561	1.35 (1.12, 1.64)
Insulin	2,775		2,469	
HbA_{1c} <7% (53 mmol/mol)	400		334	
HbA_{1c} ≥7% (53 mmol/mol)	2,375		2,135	
All-cause mortality	392	0.83 (0.65, 1.07)	241	0.94 (0.67, 1.33)
Morbidity				
Arteriosclerosis	41	3.47 (0.84, 14.4)	34	2.70 (0.64, 11.3)
Acute complication of diabetes	104	0.99 (0.57, 1.71)	96	0.99 (0.55, 1.78)
Retinopathy	137	1.27 (0.75, 2.14)	128	1.17 (0.69, 1.99)
Nephropathy	52	1.61 (0.64, 4.07)	52	1.51 (0.60, 3.82)
AMI	81	1.01 (0.54, 1.86)	69	0.91 (0.48, 1.75)
Stroke	84	1.05 (0.57, 1.94)	65	1.14 (0.54, 2.39)
Neuropathy	39	2.18 (0.66, 7.13)	38	2.00 (0.61, 6.60)
At least one of the above	473	1.23 (0.94, 1.62)	422	1.17 (0.87, 1.57)

[a]Adjusted for age, sex, prior hospital admission for cardiovascular disease, number of prior diagnosed non-cardiovascular diseases and response status

[b]Adjusted for age, sex, prior hospital admission for cardiovascular disease, number of prior diagnosed non-cardiovascular diseases and duration of diabetes

disease with increasing HbA_{1c} has been established [22]. In the present study, only 161 individuals had HbA_{1c} <5% (31 mmol/mol) (and nine of these had diabetes-related morbidities), and therefore the results of any association among individuals with very low levels of HbA_{1c} have to be confirmed in other studies.

Some new studies of the association between mortality and HbA_{1c} levels in people without type 2 diabetes have emerged. Selvin et al [22], supported by results from Carson et al [23], found a J-shaped association between HbA_{1c} level and all-cause mortality, with lowest mortality for people (without diabetes) with an HbA_{1c} level between

Table 4 HRs for mortality and morbidity at six HbA_{1c} levels

Outcome	All included individuals (n=17,760)		Individuals with information on diabetes duration (n=11,747)	
	n (events)	Adjusted[a] HR (95% CI)	n (events)	Adjusted[b] HR (95% CI)
Outcome: All-cause mortality				
HbA_{1c}				
<5%	161 (22)	1.75 (1.14, 2.69)	42 (7)	7.67 (3.57, 16.48)
5.0–5.9%	2,295 (275)	1.12 (0.97, 1.29)	1,111 (60)	1.37 (1.01, 1.86)
6.0–6.9%	5,792 (638)	1 (reference)	3,200 (131)	1 (reference)
7.0–7.9%	4,104 (428)	1.22 (1.08, 1.38)	3,000 (154)	1.14 (0.90, 1.44)
8.0–8.9%	2,415 (228)	1.37 (1.18, 1.60)	1,967 (119)	1.37 (1.06, 1.76)
≥9.0%	2,993 (268)	1.44 (1.24, 1.66)	2,427 (140)	1.44 (1.13, 1.83)
Outcome: At least one morbidity				
HbA_{1c}				
<5%	161 (9)	0.79 (0.41, 1.54)	42 (6)	1.99 (0.89, 4.48)
5.0–5.9%	2,295 (161)	0.86 (0.72, 1.03)	1,111 (88)	0.95 (0.75, 1.21)
6.0–6.9%	5,792 (492)	1 (reference)	3,200 (269)	1 (reference)
7.0–7.9%	4,104 (403)	1.14 (1.00, 1.30)	3,000 (297)	1.14 (0.96, 1.34)
8.0–8.9%	2,415 (310)	1.52 (1.32, 1.76)	1,967 (256)	1.48 (1.25, 1.76)
≥9.0%	2,993 (430)	1.79 (1.57, 2.05)	2,427 (356)	1.75 (1.49, 2.05)

HbA_{1c} categories in IFCC units: <31 mmol/mol, 31–41 mmol/mol, 42–52 mmol/mol, 53–63 mmol/mol, 64–74 mmol/mol, ≥75 mmol/mol

[a]Adjusted for age, sex, prior hospital admission for cardiovascular disease, number of prior diagnosed non-cardiovascular diseases and response status

[b]Adjusted for age, sex, prior hospital admission for cardiovascular disease, number of prior diagnosed non-cardiovascular diseases and duration of diabetes

5.0% and 5.5% (31 and 37 mmol/mol). A recent large study [24] found no evidence of such a J-shaped association, but rather a monotone relationship, with lowest risk for lowest HbA_{1c}. We found a trend towards a J shape, with lowest mortality for HbA_{1c} levels between 6.0% and 6.9% (42 and 52 mmol/mol). This supports the findings by Currie et al [10] of low and high HbA_{1c} increasing all-cause mortality, though study populations and the definition of optimal levels of HbA_{1c} differed. In the study by Currie et al, only people with type 2 diabetes who had a specific escalation of their diabetes treatment were included. On separating individuals into those receiving a combination therapy with oral blood-glucose lowering agents and those receiving insulin-based therapies, the optimal levels of HbA_{1c} were 7.0–8.0% (53–64 mmol/mol) and 7.5–8.0% (59–64 mmol/mol), respectively. We found no association between higher levels of HbA_{1c} and high mortality in those who received glucose-lowering therapy, but we did find an indication of higher mortality in individuals with low levels of HbA_{1c}. It remains unclear why HbA_{1c} <6% (42 mmol/mol) should increase mortality in individuals with type 2 diabetes. None of the individuals with an HbA_{1c} <5% (31 mmol/mol) had an HbA_{1c}-lowering disease and the results did not change after the exclusion of individuals with an HbA_{1c}-lowering disease or when restricting analyses to those who were alive after 6 months. Therefore, reverse causality does not appear to account for the association. It could be a random finding, or it could suggest that a low HbA_{1c} is actually harmful in itself or a marker of other underlying diseases, such as inflammation and impaired liver function, as suggested by Carson et al [23]. However, Turnbull et al [7] showed a significantly higher rate of major hypoglycaemic events in intensively treated individuals, and this may also be the case in our study. This area should be considered in future studies.

The significant strengths of this study are its large population-based setting, with the inclusion of all individuals with type 2 diabetes, independent of their willingness to participate, comorbid conditions and glucose-lowering treatment status. Other strengths are the completeness of information on deaths, emigrations and hospitalisations, and the ability to adjust for comorbidity.

This study also has some limitations. We have no information about changes in HbA_{1c} during follow-up, but as follow-up was restricted to 2 years, we expect the impact on morbidity and mortality of any changes to be small. The study is observational, and hence the main concern is the possibility of confounding by severity, and the dynamic interaction between HbA_{1c} level and treatment modality. We do not know the reasons for initiating treatment in some and not in others, but it seems likely that HbA_{1c} level, together with the general condition of the patient, will have influenced the treatment decision. Once initiated, treatment is likely to have influenced the HbA_{1c} level. We consider that the basis of the decision would be similar in each stratum when individuals are stratified by treatment modality. However, the group of individuals with HbA_{1c} level ≥7% (53 mmol/mol) and who did not receive any pharmacological treatment most

Table 5 HRs for mortality and morbidity at six different HbA_{1c} levels, stratified by treatment modality

Outcome by treatment modality	All included individuals		Individuals with information on diabetes duration	
	n (events)	Adjusted[a] HR (95% CI)	*n* (events)	Adjusted[b] HR (95% CI)
No glucose-lowering therapy	7,842		3,728	
Outcome: All-cause mortality				
HbA_{1c}				
<5%	126 (12)	1.34 (0.75, 2.39)	23 (2)	6.66 (1.59, 27.95)
5.0–5.9%	1,612 (179)	1.14 (0.96, 1.37)	621 (25)	1.70 (1.03, 2.81)
6.0–6.9%	3,948 (410)	1 (reference)	1,757 (40)	1 (reference)
7.0–7.9%	1,425 (154)	1.24 (1.03, 1.49)	825 (31)	1.45 (0.91, 2.32)
8.0–8.9%	390 (37)	1.51 (1.08, 2.13)	257 (11)	2.49 (1.28, 4.87)
≥9.0%	341 (16)	1.05 (0.64, 1.74)	245 (6)	1.74 (0.74, 4.14)
Outcome: At least one morbidity				
HbA_{1c}				
<5%	126 (4)	0.50 (0.19, 1.36)	23 (1)	0.68 (0.09, 4.84)
5.0–5.9%	1,612 (102)	0.85 (0.68, 1.07)	621 (41)	0.92 (0.64, 1.30)
6.0–6.9%	3,948 (307)	1 (reference)	1,757 (130)	1 (reference)
7.0–7.9%	1,425 (114)	1.02 (0.82, 1.27)	825 (60)	0.98 (0.72, 1.33)
8.0–8.9%	390 (35)	1.31 (0.92, 1.86)	257 (26)	1.47 (0.96, 2.24)
≥9.0%	341 (39)	1.83 (1.31, 2.57)	245 (26)	1.62 (1.06, 2.48)
Oral glucose-lowering treatment	7,095		5,520	
Outcome: All-cause mortality				
HbA_{1c}				
<5%	28 (7)	3.42 (1.60, 7.29)	17 (4)	10.19 (3.68, 28.22)
5.0–5.9%	566 (70)	0.90 (0.68, 1.19)	401 (22)	1.03 (0.63, 1.67)
6.0–6.9%	1,532 (179)	1 (reference)	1,180 (65)	1 (reference)
7.0–7.9%	2,083 (186)	0.85 (0.69, 1.04)	1,649 (73)	0.88 (0.63, 1.23)
8.0–8.9%	1,313 (99)	0.80 (0.63, 1.03)	1,058 (46)	1.04 (0.71, 1.52)
≥9.0%	1,573 (116)	0.87 (0.69, 1.10)	1,215 (44)	0.98 (0.66, 1.44)
Outcome: At least one morbidity				
HbA_{1c}				
<5%	28 (3)	1.46 (0.46, 4.60)	17 (3)	2.51 (0.79, 7.94)
5.0–5.9%	566 (46)	0.90 (0.65, 1.26)	401 (35)	1.09 (0.74, 1.60)
6.0–6.9%	1,532 (138)	1 (reference)	1,180 (98)	1 (reference)
7.0–7.9%	2,083 (201)	1.10 (0.88, 1.36)	1,649 (159)	1.22 (0.95, 1.56)
8.0–8.9%	1,313 (154)	1.36 (1.08, 1.72)	1,058 (119)	1.44 (1.10, 1.89)
≥9.0%	1,573 (184)	1.46 (1.16, 1.82)	1,215 (147)	1.67 (1.29, 2.16)
Insulin	2,775		2,469	
Outcome: All-cause mortality				
HbA_{1c}				
<5%	4 (3)	3.32 (1.02, 10.77)	2 (1)	11.75 (1.57, 87.90)
5.0–5.9%	102 (26)	1.60 (0.99, 2.58)	82 (13)	1.48 (0.76, 2.89)
6.0–6.9%	291 (49)	1 (reference)	247 (26)	1 (reference)
7.0–7.9%	591 (87)	0.99 (0.70, 1.41)	521 (49)	1.03 (0.64, 1.65)
8.0–8.9%	710 (91)	0.98 (0.69, 1.39)	651 (62)	1.04 (0.65, 1.64)
≥9.0%	1,077 (136)	0.96 (0.69, 1.33)	966 (90)	1.13 (0.93, 1.76)
Outcome: At least one morbidity				
HbA_{1c}				
<5%	4 (2)	7.58 (1.82, 31.54)	2 (2)	10.28 (2.46, 43.00)

Table 5 (continued)

Outcome by treatment modality	All included individuals		Individuals with information on diabetes duration	
	n (events)	Adjusted[a] HR (95% CI)	*n* (events)	Adjusted[b] HR (95% CI)
5.0–5.9%	102 (10)	0.61 (0.31, 1.21)	82 (9)	0.64 (0.31, 1.33)
6.0–6.9%	291 (46)	1 (reference)	247 (40)	1 (reference)
7.0–7.9%	591 (87)	0.93 (0.65, 1.33)	521 (77)	0.90 (0.61, 1.32)
8.0–8.9%	710 (121)	1.10 (0.78, 1.54)	651 (111)	1.06 (0.74, 1.52)
≥9.0%	1,077 (207)	1.26 (0.92, 1.74)	966 (183)	1.23 (0.87, 1.73)

HbA_{1c} categories in IFCC units: <31 mmol/mol, 31–41 mmol/mol, 42–52 mmol/mol, 53–63 mmol/mol, 64–74 mmol/mol, ≥75 mmol/mol

[a] Adjusted for age, sex, prior hospital admission for cardiovascular disease, number of prior diagnosed non-cardiovascular diseases and response status

[b] Adjusted for age, sex, prior hospital admission for cardiovascular disease, number of prior diagnosed non-cardiovascular diseases and duration of diabetes

likely comprises individuals for whom it is believed (either by the general practitioner or by the individual) that behavioural changes are sufficient and individuals for whom pharmacological treatment has been deselected. Therefore, the results might be biased by severity. However, in the analysis we have adjusted for age, other diseases and diabetes duration (when available).

Secondary analyses with adjustment for preventive pharmacological treatment of cardiovascular diseases, longer follow-up time, and stratification by diabetes duration (when available) showed similar results, and hence we consider that we captured most of the possible confounding factors.

Treatment modality was based on the treatment status of each person in the same year as of that of their HbA_{1c} level. Over the 2-year period, people receiving oral blood-glucose-lowering drugs rose from 26% to 29% in the group with HbA_{1c} <7% (53 mmol/mol), and declined from 52% to 49% in the group with HbA_{1c} ≥7% (53 mmol/mol). The percentage of people receiving insulin rose from 5% to 5.5% for those with HbA_{1c} <7% (53 mmol/mol) and from 25% to 31% for HbA_{1c} ≥7% (53 mmol/mol). Among individuals without glucose-lowering therapy at inclusion, 967 (12%) were receiving oral glucose-lowering therapy 1 year after inclusion and 88 (1%) were receiving insulin (±oral glucose therapy). By 2 years after inclusion, the respective numbers were 1,537 (20%) and 163 (2%). Whether the changes affected the results of the stratified analyses is unknown. We did not have complete information on other potential confounders. For instance, we lacked information on diabetes duration for some of the individuals included; for those for whom this information was available, it was primarily self-reported and therefore it might not have been accurate. The overall conclusion did not change significantly when including the available information on diabetes duration, so we consider it unlikely that omission of duration has introduced substantial bias. However, it is unknown whether duration would have affected the results if the 'true' durations had been available for analysis. Further, we did not have access to information on smoking habits.

Some of the included individuals did not have type 2 diabetes or were not aware that they had been characterised as having type 2 diabetes. To address the issue of non-awareness and the possible bias introduced in behavioural changes, we included information on whether each person responded to the questionnaire sent to them. Regarding the inclusion of people without type 2 diabetes, they would most likely have been included in the database because they had two HbA_{1c} measurements within one calendar year, and would have been grouped to HbA_{1c} level <7% (53 mmol/mol). This might have biased towards lower mortality and diabetes-related morbidity for HbA_{1c} level <7% (53 mmol/mol). The positive predictive value of the database used is estimated at 89% [14], so approximately 11% of the individuals included did not have diabetes. In a worst case scenario all of these would have been included in the group with HbA_{1c} <7% (53 mmol/mol). Because of the new suggested diagnostic criteria [25] we decided, in a worst case scenario, to consider only people with HbA_{1c} <6.5% (48 mmol/mol) as not having diabetes. If we remove a random 11% of the total population of individuals who were alive with no diabetes-related morbidity after 2 years, and who had HbA_{1c} level <6.5% (48 mmol/mol), the impact of HbA_{1c} ≥7% (53 mmol/mol) is somewhat different, with HR 0.99 (95% CI 0.90, 1.09) for mortality and 1.11 (95% CI 1.01, 1.23) for the occurrence of at least one morbidity.

In conclusion, among individuals with type 2 diabetes, those with HbA_{1c} <7% (53 mmol/mol) had lower mortality and lower diabetes-related morbidity (especially microvascular) than those with a level ≥7% (53 mmol/mol). Both high and low levels of HbA_{1c} were associated with increased mortality, whereas a dose–response pattern appeared for diabetes-related morbidity. However, the impact of different HbA_{1c} levels on morbidity and mortality

seems to depend on whether individuals receive glucose-lowering therapies.

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