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HbA1c and hypoglycaemia in intensively treated type 2 diabetes: a retrospective cohort study in primary care

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Abstract

Objective: To establish whether low HbA1c is associated with clinical hypoglycaemia among people with type 2 diabetes prescribed insulins or sulphonylureas.

Design: Retrospective cohort study using routine electronic GP health records collected between January 2013 and December 2015.

Setting: Three east London Clinical Commissioning Groups.

Participants: Two cohorts of adults with type 2 diabetes prescribed either (i) insulins with or without other oral antidiabetic medication (n = 6788, 36.4%) or (ii) sulphonylureas with or without other oral antidiabetic medications excluding insulins (n = 11,840, 63.6%).

Main outcome measures: First clinically recorded hypoglycaemia and all-cause mortality. Hazard ratios (HR) adjusting for age, ethnicity, renal function and comorbidities were calculated using Cox regression models.

Results: Compared with an HbA1c of 53–63 mmol/mol, the adjusted HR of hypoglycaemia in those with a low HbA1c, below 53 mmol/mol, in the insulin and sulphonylurea cohorts were 1.26 (95% CI, 0.97 to 1.62) and 1.54 (95% CI, 1.27 to 1.87), respectively. Adjusted HRs of all-cause mortality from low HbA1c in the insulin and sulphonylurea cohorts were 1.54 (95% CI, 1.15 to 2.07) and 1.42 (95% CI, 1.11 to 1.81), respectively. Increasing age and renal impairment were also associated with increased hypoglycaemic risk in both cohorts.

Conclusions: HbA1c below 53 mmol/mol was associated with episodes of clinical hypoglycaemia among people with type 2 diabetes prescribed sulphonylureas, and all-cause mortality in those prescribed insulins and sulphonylureas. These findings support the need for reviewing glycaemic targets and the intensities of treatment in those with low HbA1c prescribed insulins or sulphonylureas to reduce the risk of hypoglycaemia.

Keywords

type 2 diabetes mellitus, hypoglycaemia, glycosylated haemoglobin A, hypoglycaemic agents, primary health care

Introduction

Type 2 diabetes mellitus therapy focuses on reducing hyperglycaemia and its sequelae. Increasingly, intensive treatments have been employed to achieve tighter control of blood glucose. Sulphonylureas and insulin regimens are recommended as second and third line agents respectively for people with poorly controlled type 2 diabetes, and an HbA1c target of 53 mmol/mol is recommended for individuals on these medications.[1] These strategies have been supported by studies showing an association between reduced glycaemia and fewer microvascular complications of diabetes or non-fatal cardiovascular outcomes.[2–4] However, meta-analysis of trial data has shown no significant difference in all-cause or cardiovascular mortality between those with intensive glycaemic control versus conventional glycaemic control. Furthermore, intensive glycaemic control substantially increases the risk of hypoglycaemia.[5]

Hypoglycaemia is a major clinical consequence of intensive glucose-lowering therapy and is associated with falls, fractures and road traffic accidents.[6–11] However, episodes requiring medical assistance account for only a minority of cases, with up to 85% medically unreported.[12,13] Due to the possible harms of intensive treatments, recent national and international guidance has recommended more relaxed, individualised targets for glycosylated haemoglobin (HbA1c) in people with type 2 diabetes at risk of hypoglycaemia such as the frail, elderly or those with multiple comorbidities.[1,14,15] However, the relationship between hypoglycaemia and HbA1c is not clear. The early Diabetes Control and Complications Trial and UK Prospective Diabetes Study (UKPDS) suggested an inverse relationship between hypoglycaemic risk and HbA1c.[3,16] However, subsequent studies identified that poor glycaemic control, with high HbA1c values, was also

associated with hypoglycaemia.[12,17–21] Currie et al. found that post-index mean HbA1c exhibited a U-shaped association with all-cause mortality: study subjects with the lowest HbA1c had significantly higher risk for both those on oral therapies including sulphonylureas and those prescribed insulins.[22]

Our aim was to establish whether low HbA1c below 53 mmol/mol was prospectively associated with hypoglycaemia in each of these treatment groups. Our secondary aim was to identify whether low HbA1c below 53 mmol/mol was prospectively associated with higher rates of all-cause mortality among people with type 2 diabetes in east London prescribed insulins and/or sulphonylureas.

Methods

Setting

The east London boroughs of Tower Hamlets, Newham and City & Hackney are among the most ethnically diverse in the UK with high levels of social deprivation. In April 2013, all 147 general practices in these localities provided primary care to 953,163 registered people.[23]

Approximately 50% of the local populations are from black African/Caribbean (14%) and South Asian ethnic groups (33%).[24] In 2013, the number of adults registered with diabetes in the three localities was 47,331 with an estimated prevalence of 6.4%.[23]

As in the rest of the UK, diabetes care is largely delivered in primary care settings by general practitioners and practice nurses, with all routine care parameters and prescribing recorded in the electronic health record.

Study design

Using a retrospective cohort study design, we analysed the electronic health records of patients from 139 out of 147 general practices in three co-terminous east London Clinical Commissioning Groups (Tower Hamlets, Newham and City & Hackney) between 1 January 2013 and 31 December 2015. Data from eight practices were not available for technical reasons.

We securely extracted non-identifiable patient-level data from the electronic health records of patients registered with participating practices on 9 September 2016, using pre-specified search terms. The criteria for selection of participants included in the study is detailed in Figure 1.

Those included formed two cohorts: (i) individuals prescribed insulins with or without other antidiabetic medication including sulphonylureas; and (ii) those prescribed sulphonylureas with or without other antidiabetic drugs excluding insulins, in the six months prior to 1 January 2013. Participants were followed from 1 January 2013 until they experienced an episode of hypoglycaemia, died, left the GP practice list, stopped medication for six months or the study period ended on 31 December 2015. Subjects in the sulphonylurea cohort who started using insulins during the study period were censored on the date insulins were commenced.

The primary outcome of the study was the first record in the primary care electronic health record of hypoglycaemia during the study period, defined by one of several specified Read codes for hypoglycaemia, hypoglycaemic coma or a documented blood glucose level below 3.9 mmol/L. The secondary outcome was death from any cause as defined by a coded registration status of 'deceased' in the primary care electronic health record (see supplementary material for complete code lists).

The exposure of interest was the last recorded HbA1c in mmol/mol, in the year prior to 1 January 2013. We defined a low HbA1c as below 53 mmol/mol, optimal HbA1c as 53–63 mmol/mol and increased HbA1c in three categories 64–74, 75–85 and >86 mmol/mol.

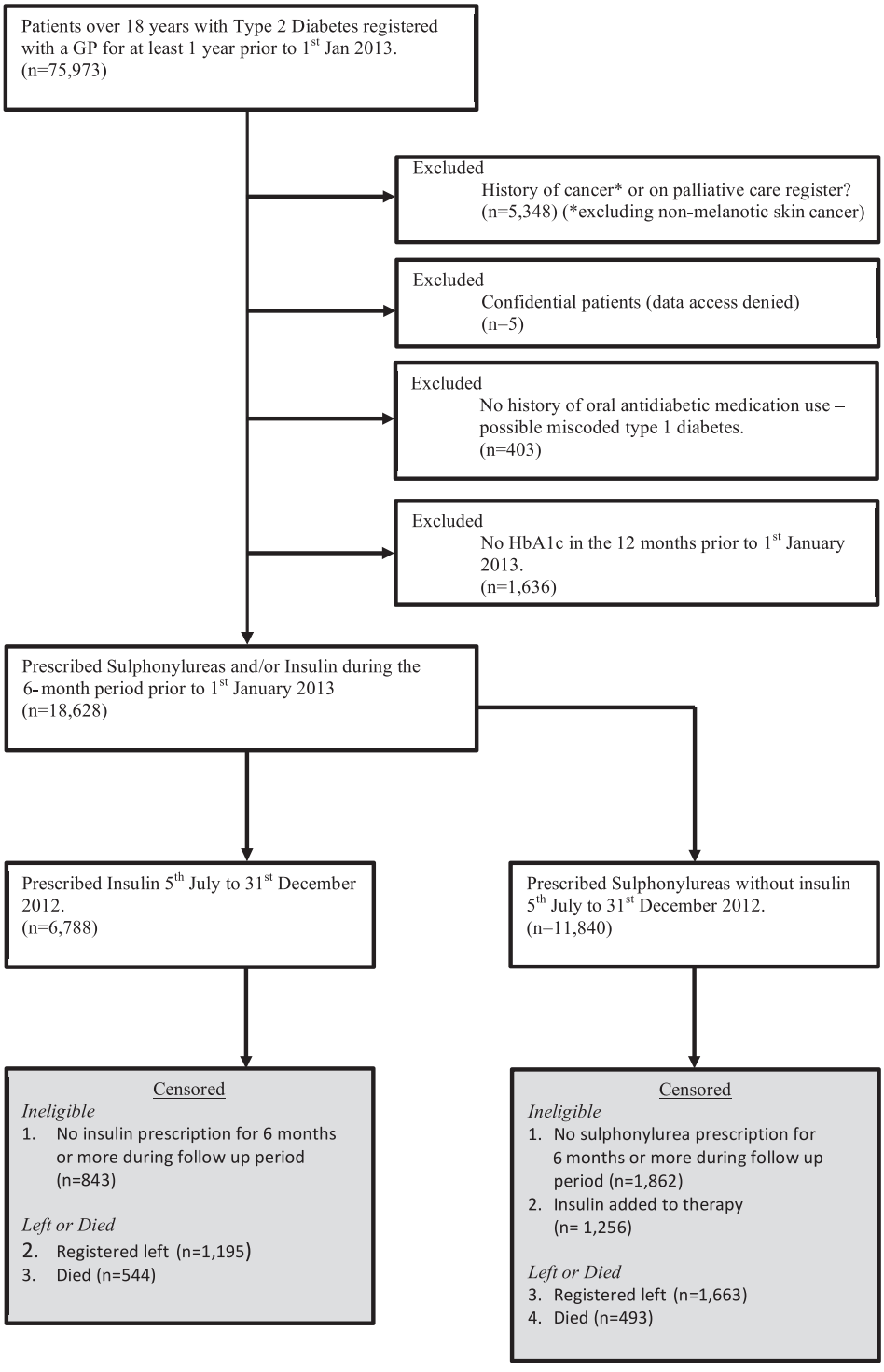
Data on other potential risk factors for hypoglycaemia as of 1 January 2013 were collected, including age, gender, renal function defined by last recorded estimated glomerular filtration rate (eGFR, ml/min/1.73 m^2) in the year prior to 1 January 2013, ethnicity, body mass index (kg/m^2), comorbidities defined using the Read codes in the Quality and outcomes Framework ruleset (ischaemic heart disease, stroke, hypertension, atrial fibrillation, heart failure, chronic obstructive pulmonary disease, dementia, severe mental illness, learning disability), duration of type 2 diabetes mellitus and cohort drug use (insulins or sulphonylureas).[25]

Statistical analysis

We calculated crude incidence rates of the first recorded episode of hypoglycaemia with 95% confidence intervals per 1000 patient-years across five HbA1c categories (<53, 53–63, 64–74, 75–85 and ≥86 mmol/mol) and by each co-variable, in each cohort. Using Cox proportional hazard modelling, unadjusted and adjusted hazard ratios for hypoglycaemia in each HbA1c category were calculated using 53–63 mmol/mol (optimal glycaemic control) as the reference category.

The proportional hazards assumption was tested using formal tests of interaction between HbA1c category and time bands of the follow-up period for each

Figure 1. Patients selected for inclusion in the study analysis.



cohort using likelihood ratio tests (LRT). The time bands were generated by splitting the study period according to tertiles of outcome events across the entire study period. The proportional hazards assumption was not violated for either outcome in both cohorts.

All other co-variables (age, gender, ethnicity, eGFR, body mass index, comorbidities, duration of

type 2 diabetes and duration of cohort drug use) were then included in the adjusted Cox regression models.

We calculated unadjusted and adjusted hazard ratios of insulin-use versus sulphonylureas without insulin for each outcome. We then examined the presence of any interaction between HbA1c, insulins and sulphonylureas on the risk of hypoglycaemia by testing the suitability of an interaction term in an adjusted Cox regression model combining the two cohorts, using likelihood ratio testing.

There were no large discrepancies in missing values between the two cohorts and thus all co-variables were included in the full model. Therefore, participants with missing values were excluded from the full Cox regression models.

HbA1c categories were tabulated among those lost to follow-up or censored to look for potential discrepancies that might lead to bias in the study's findings.

The stated analysis was then repeated for the secondary outcome, all-cause mortality.

All analyses were undertaken using Stata 14 (StataCorp., Texas, USA).[26] Two-sided p values below 0.05 were considered statistically significant.

Results

A total of 18,628 subjects were included in the study (Figure 1). Of these, 6788 (36.4%) were prescribed insulins with or without other antidiabetic medication and 11,840 (63.6%) sulphonylureas with or without other diabetic medication excluding insulins at baseline. Among the insulin cohort, 90.1% were prescribed analogue insulins, 9.9% human insulins. Of those prescribed analogue insulins, 40.1% were on basal agents. For those in the sulphonylurea cohort, 93.7% were prescribed second-generation sulphonylureas, 2.7% first-generation and 3.6% third-generation agents. Of the 11,091 on second-generation sulphonylureas, 97.0% were prescribed Gliclazide.

During the three-year study period, 2858 (15.3%) participants left the study population, 1195 (17.6%) from the insulin cohort and 1663 (14.3%) from the sulphonylurea cohort. Additionally, 843 (12.4%) of the insulin cohort and 1862 (16.0%) of the sulphonylurea cohort were ineligible for further follow-up when six months or more had elapsed between their last prescription and the end of the study period. Finally, 1256 (10.8%) of the sulphonylurea cohort were censored because insulin therapy was commenced during the study period (Figure 1). The mean length of follow-up was 2.32 years in the insulin cohort and 2.22 in the sulphonylurea cohort.

Table 1 shows the baseline characteristics of the study population and each cohort. The distribution of baseline HbA1c across those lost to follow-up or censored can be found in the supplementary materials.

Hypoglycaemia

Of the participants entering the study, 1315 (7.1%) had a clinically recorded episode of hypoglycaemia during the three-year study period, 675 (9.9%) of the insulin cohort and 640 (5.4%) of those prescribed sulphonylureas without insulin (Table 2).

After adjusting for all other covariables, the hazard ratio of first recorded hypoglycaemia from low HbA1c (<53 mmol/mol) in the insulin and sulphonylurea cohorts were 1.26 (95% CI, 0.97 to 1.63) and 1.54 (95% CI, 1.27 to 1.87), respectively (Figure 2).

We found evidence of interaction between insulin-use versus sulphonylureas and baseline HbA1c (LRT $p < 0.01$). Insulin use was associated with a higher relative risk of hypoglycaemia versus sulphonylureas at all levels of HbA1c, with increasing risk in higher HbA1c categories: hazard ratio 1.27 (95% CI, 1.01 to 1.60) in those with HbA1c < 53 mmol/mol; HbA1c 53–63, hazard ratio 1.55 (95% CI, 1.23 to 1.95); HbA1c 63–74, hazard ratio 2.59 (95% CI, 1.83 to 3.67); HbA1c 75–85, hazard ratio 2.18 (95% CI, 1.38 to 3.45); HbA1c ≥ 86, hazard ratio 2.22 (95% CI, 1.51 to 3.26).

Online supplementary tables show the risk of hypoglycaemia for the remaining covariables in the adjusted models for each cohort. In both cohorts, increasing age, impaired renal function and Black African/Caribbean ethnicity were associated with higher risks of clinical hypoglycaemia. Cognitive impairment was associated with higher hypoglycaemic risk in the sulphonylurea cohort.

Mortality

There were 1037 deaths among participants during the study period (5.6%). The adjusted Cox model demonstrated the highest mortality risks in the lowest and highest HbA1c categories in both cohorts: HbA1c < 53 mmol/mol, hazard ratio 1.54 (95% CI, 1.15 to 2.07) in those prescribed insulin, hazard ratio 1.42 (95% CI, 1.11 to 1.81) in the sulphonylurea cohort; and HbA1c ≥ 86 mmol/mol, hazard ratio 1.81 (95% CI, 1.37 to 2.39) for insulin users and hazard ratio 2.06 (95% CI, 1.41 to 3.02) for sulphonylureas without insulin (Table 2).

After adjusting for all other covariables, insulin-use was associated with increased mortality risk relative to sulphonylureas: hazard ratio 1.36 (95% CI, 1.16 to 1.58). There was no evidence of interaction between cohort medication and baseline HbA1c (likelihood ratio test $p = 0.98$).

Table 1. Baseline characteristics of the insulin and sulphonylurea cohorts.

Variable Total	Sulphonylurea N (%) 11840 (100)	Insulin N (%) 6788 (100)
HbA1c (mmol/mol) (%)		
<53 (<7.0)	3630 (30.7)	998 (14.7)
53–63 (7.0–7.9)	3644 (30.8)	1679 (24.7)
64–74 (8.0–8.9)	2018 (17)	1502 (22.1)
75–85 (9.0–9.9)	1087 (9.2)	1079 (15.9)
≥86 (≥10.0)	1461 (12.3)	1530 (22.5)
Age (n, %)		
<55	3032 (25.6)	1456 (21.4)
55–64	3387 (28.6)	1878 (27.7)
65–74	2536 (21.4)	1650 (24.3)
≥75	2885 (24.4)	1804 (26.6)
Gender		
Male	6527 (55.1)	3400 (50.1)
Female	5313 (44.9)	3388 (49.9)
Ethnicity (%)		
White	2614 (22.1)	1776 (26.2)
South Asian	6056 (51.1)	3064 (45.1)
Black	2569 (21.7)	1654 (24.4)
Other	526 (4.4)	254 (3.7)
Not recorded	75 (0.6)	40 (0.6)
eGFR (ml/min/1.73 m^2)		
≥60	158 (1.3)	320 (4.7)
30–59	1406 (11.9)	1206 (17.8)
<30	8422 (71.1)	3998 (58.9)
Not recorded	1854 (15.7)	1264 (18.6)
BMI		
<25	2718 (23)	1158 (17.1)
25–30	4517 (38.2)	2458 (36.2)
30–34	2724 (23)	1819 (26.8)
≥35	1846 (15.6)	1321 (19.5)
Not recorded	35 (0.3)	32 (0.5)
Duration of diabetes		
< 5 years	2739 (23.1)	620 (9.1)
≥ 5 years	8877 (75)	5957 (87.8)
Unknown	224 (1.9)	211 (3.1)
Duration of study drug prescriptions		
< 6 months (N, %)	645 (5.4)	311 (4.6)
6–12 months (N, %)	598 (5.1)	325 (4.8)
≥12 months (N, %)	10597 (89.5)	6152 (90.6)
Comorbidities (%)		
Ischaemic heart disease	1607 (13.6)	1673 (24.6)
Stroke	636 (5.4)	595 (8.8)
Hypertension	7409 (62.6)	4696 (69.2)
Atrial fibrillation	322 (2.7)	260 (3.8)
Heart failure	403 (3.4)	570 (8.4)
COPD	2021 (17.1)	1388 (20.4)
Dementia	140 (1.2)	123 (1.8)
SMI	396 (3.3)	245 (3.6)
Learning disability	67 (0.6)	35 (0.5)

Discussion

Summary

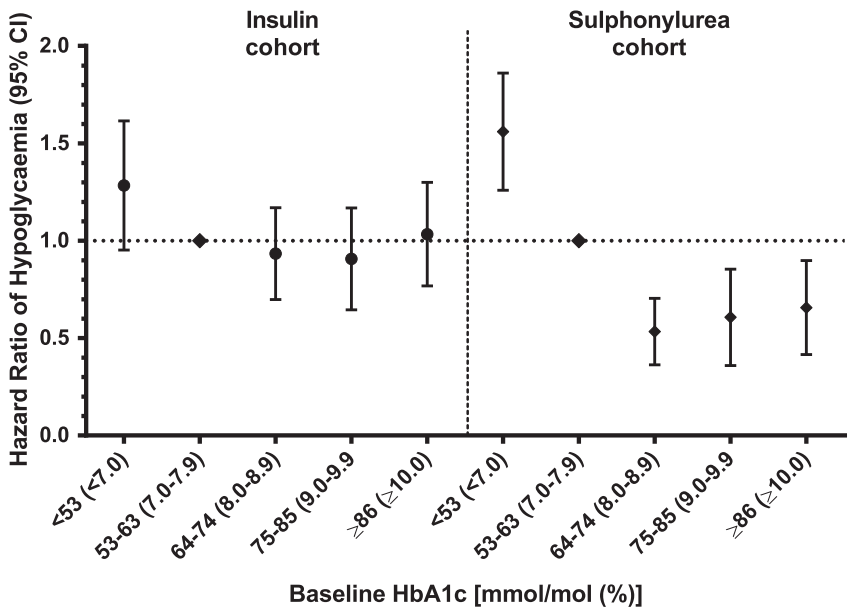
We found that in the routine use of both insulins and sulphonylureas, low HbA1c levels below 53 mmol/mol were associated with a significant increased risk of hypoglycaemia. After adjustment for other factors, this association remained independently associated with hypoglycaemia in those on sulphonylureas, while the increased risk among those on insulins was non-significant. At all levels of HbA1c, insulins were associated with a greater risk of hypoglycaemia compared to sulphonylureas, particularly among those with higher HbA1c values. All-cause mortality

Table 2. Number of events, incident rates, full and final adjusted hazard ratios of first recorded hypoglycaemia and all-cause mortality by HbA1c categories in the insulin and sulphonylurea cohorts.

		Insulins				Sulphonylureas			
	HbA1c (mmol/mol) (%)	Events (N [%])	IR per 1000PY (95% CI)	Unadj. HR (95% C.I.)	Adj. HR (95% C.I.)	Events (N [%])	IR per 1000PY (95% CI)	Unadj. HR (95% C.I.)	Adj. HR (95% C.I.)
Hypoglycaemia	Total	675 (100.0)	42.8 (39.7, 46.1)	–	–	640 (100.0)	24.3 (22.5, 26.3)	–	–
	<53 (<7.0)	132 (19.6)	61.8 (52.1, 73.3)	1.38** (1.10, 1.72)	1.26 (0.97, 1.62)	304 (47.5)	38.3 (34.3, 42.9)	1.66*** (1.39, 1.99)	1.54*** (1.27, 1.87)
	53–63 (7.0–7.9)	178 (26.4)	44.5 (38.4, 51.5)	1.00 (1.00, 1.00)	1.00 (1.00, 1.00)	197 (30.8)	22.8 (19.8, 26.2)	1.00 (1.00, 1.00)	1.00 (1.00, 1.00)
	64–74 (8.0–8.9)	144 (21.3)	40.6 (34.5, 47.8)	0.91 (0.73, 1.14)	0.91 (0.71, 1.18)	63 (9.8)	13.8 (10.8, 17.6)	0.60*** (0.45, 0.80)	0.52*** (0.37, 0.71)
	75–85 (9.0–9.9)	89 (13.2)	34.8 (28.3, 42.9)	0.78 (0.61, 1.01)	0.88 (0.66, 1.18)	33 (5.2)	14.2 (10.1, 20.0)	0.61** (0.42, 0.88)	0.57** (0.38, 0.87)
	≥86 (≥10.0)	132 (19.6)	37.3 (31.5, 44.3)	0.84 (0.67, 1.05)	1.01 (0.78, 1.31)	43 (6.7)	15.1 (11.2, 20.4)	0.64** (0.46, 0.89)	0.63* (0.43, 0.91)
Total in Cox model				6788	5318			11,839	9728
Death	Total	544 (100.0)	32.5 (29.9, 35.4)	–	–	493 (100.0)	18.2 (16.6, 19.8)	–	–
	<53 (<7.0)	110 (20.2)	47.3 (39.2, 57.0)	1.75*** (1.35, 2.28)	1.54** (1.15, 2.07)	215 (43.6)	25.7 (22.5, 29.4)	1.76*** (1.41, 2.19)	1.42** (1.11, 1.81)
	53–63 (7.0–7.9)	115 (21.1)	27 (22.5, 32.4)	1.00 (1.00, 1.00)	1.00 (1.00, 1.00)	130 (26.4)	14.6 (12.3, 17.3)	1.00 (1.00, 1.00)	1.00 (1.00, 1.00)
	64–74 (8.0–8.9)	111 (20.4)	29.6 (24.5, 35.6)	1.09 (0.84, 1.42)	1.28 (0.97, 1.70)	72 (14.6)	15.5 (12.3, 19.5)	1.06 (0.79, 1.41)	1.42* (1.03, 1.96)
	75–85 (9.0–9.9)	75 (13.8)	28 (22.4, 35.1)	1.04 (0.78, 1.39)	1.14 (0.82, 1.58)	28 (5.7)	11.9 (8.2, 17.2)	0.81 (0.54, 1.22)	1.24 (0.76, 2.01)
	≥86 (≥10.0)	133 (24.4)	35.9 (30.3, 42.5)	1.33* (1.04, 1.71)	1.81*** (1.37, 2.39)	48 (9.7)	16.7 (12.6, 22.1)	1.13 (0.81, 1.58)	2.06*** (1.41, 3.02)
Total in Cox model				6788	5318			11,839	9729

Note: Adjusting variables in adjusted Cox regression models: age, gender, eGFR, ethnicity, body mass index, comorbidities (ischaemic heart disease, stroke, hypertension, atrial fibrillation, heart failure, chronic obstructive pulmonary disease, dementia, serious mental illness, learning disability), duration of type 2 diabetes and duration of cohort medication (insulins or sulphonylureas). Number included in adjusted Cox regression model: (i) insulin cohort = 5320; (ii) sulphonylurea cohort = 9727. Number in adjusted model experiencing hypoglycaemia: (i) insulin cohort = 524; (ii) sulphonylurea cohort = 551.
*$p < 0.05$, **$p < 0.01$, ***$p < 0.001$.

Figure 2. Hazard ratios of first recorded hypoglycaemic events by HbA1c category stratified by hypoglycaemic agent (adjusted Cox regression models).



was significantly increased in both the low and highest HbA1c categories, particularly among those prescribed insulins.

Strengths and limitations

Many prior studies examining the relationship of HbA1c and hypoglycaemia included only severe cases of hypoglycaemia that required third party assistance and/or hospital admission, usually with a blood glucose of less than 3.0 mmol/L or those who recovered after administration of glucose or glucagon.[3,17,19,20] We identified hypoglycaemia codes recorded in primary care electronic clinical records and/or primary care recorded blood glucose measurements below 3.9 mmol/L to capture all severities of hypoglycaemia. Furthermore, we did not exclude patients with previous hypoglycaemia. Therefore, our findings are likely to be generalisable to established populations with type 2 diabetes treated with either insulins or sulphonylureas.

It is likely that most hypoglycaemia was self-managed without healthcare involvement and thus not recorded at all.[12] By using coded data and laboratory measurements rather than free-text information from the patient records, we were unable to determine the clinical severity of the recorded hypoglycaemic events, whether asymptomatic, mild or requiring the assistance of others. We were also unable to access participants' hospital records and thus may have missed hospital episodes that were not recorded in the GP records. Given that only 4.7% of all instances of hypoglycaemia are reported to a medical professional, episodes leading to hospital attendance are likely to represent only a small proportion of cases.[12] This potential omission of more serious cases is likely to have led to an underestimation of the strength of association we observed between HbA1c and hypoglycaemia, but is unlikely to have influenced its direction.

During the study period, 15.3% of participants were censored because they left their respective practices. However, there were no major discrepancies in the distribution of baseline HbA1c among those who left their practices compared to those that remained. Larger proportions of subjects who stopped their medication for six months or more had lower baseline HbA1c than their respective cohorts at the start of the study. Reasons for stopping medication may have included side effects such as unreported hypoglycaemia, possibly underestimating the association of low HbA1c and hypoglycaemia.

This study is subject to the limitations of any routinely collected data where coding of information may have varied in quality and extent between clinicians. However, we think this is unlikely to have caused systematic biases that would have substantially influenced our results. Medication doses were

not available for this study, preventing analysis of the effect of insulin or sulphonylurea dosage. Additionally, we did not include participants' other concurrent medications in our analysis and were unable to account for any effect these might have had on our findings.

A limitation of this study is the use of a single baseline HbA1c measurement from which the risk estimates for both the primary and secondary outcomes were derived. Other similar studies have used a variety of methods to calculate mean HbA1c from multiple measurements to account for an individual's overall glycaemic control during the respective study periods.[22,27,28] We opted to use a single baseline exposure measurement to identify disparities in risk as a pragmatic decision because such an approach can be easily deployed in electronic health record-based risk prediction tools in primary care.

This study measured time to the first hypoglycaemic event and does not account for disparities in the frequency of hypoglycaemia by HbA1c experienced by subjects. Collecting data on multiple hypoglycaemic events during the study period and conducting a random effects Poisson regression analysis may provide more robust estimates of the associations between hypoglycaemia and HbA1c but there are challenges inherent to such an approach, most notably distinguishing discrete episodes from multiple recordings of the same event, particularly when using both clinical codes and laboratory measurements.

Comparison with existing literature

Our findings support those of previous studies that found increased risks of hypoglycaemia with low HbA1c. Chan et al., who pooled data from three randomised controlled trials comparing insulin preparations combined with metformin, demonstrated a statistically significant relationship of low HbA1c and hypoglycaemia.[29] Subjects in the UK Prospective Diabetes Study trial treated with insulins or sulphonylureas who achieved lower median HbA1c experienced more hypoglycaemia.[16] In contrast, the ACCORD study found higher HbA1c at baseline was associated with an increased risk of hypoglycaemia in both the intensive and standard treatment arms.[20] However, the ACCORD study aimed to reduce HbA1c rapidly predominantly using insulin. Those in whom HbA1c did not fall quickly were at higher risk of hypoglycaemia, which the authors postulate may have been due to unsuccessful further intensifications of therapy.

The Diabetes and Aging Study suggested a U-shaped trend of raised hypoglycaemic risk with both low and high glycosylated haemoglobin, but we found no significant evidence of such a relationship (Figure 2).[21]

In line with previous research, we found higher incidence rates of hypoglycaemia in the insulin cohort compared to those on sulphonylureas.[7,16] However, we found a significant interaction of risk between insulin-use relative to sulphonylureas and baseline HbA1c, in which the relative risk of hypoglycaemia associated with insulin use was greater at higher HbA1c levels. Such individuals with poorly controlled diabetes are likely to be treated with higher insulin doses and thus at greater hypoglycaemic risk.[12] This may also account for the findings of the ACCORD study in which most patients were prescribed insulins.[20]

Like Currie et al. who examined a national General Practice database, our analysis demonstrated higher mortality in both those with low and highest HbA1c in both the insulin and sulphonylureas cohorts.[22] The mortality risk from low HbA1c was slightly higher among those prescribed insulins but was also significantly raised in those in the sulphonylurea cohort, in contrast to the findings of Monami et al.[27] Theirs was a smaller nested case-control study, which found HbA1c below 6.5% (48 mmol/mol) to be associated with significantly higher mortality risk in those treated with insulins, adjusting for metformin exposure and renal insufficiency only.

Implications for clinical practice and research

Identifying patients with a HbA1c below 53 mmol/mol prescribed insulins or sulphonylureas, particularly the elderly, those with renal and cognitive impairment for medicines review may provide an opportunity to optimise glycaemic control to more relaxed targets that reduce both hypoglycaemic and mortality risk.

This study explored disparities in time to first recorded hypoglycaemic event by a single baseline HbA1c. Further research using linked primary and secondary care health records is needed to examine the effect of HbA1c on the risk of multiple hypoglycaemic events using analysis methods that accurately account for the time-varying nature of HbA1c.

Conclusion

Individuals with type 2 diabetes on sulphonylureas or insulin with low HbA1c < 53 mmol/mol were at increased risk of experiencing episodes of clinical hypoglycaemia in comparison to those with more optimal levels of HbA1c, though only significantly so in the sulphonylurea cohort. Mortality exhibited a U-shaped curve, with the greatest risk associated with low and highest HbA1c categories in users of

both insulins and sulphonylureas. Insulin users were at higher overall risk of both hypoglycaemia and mortality than those on sulphonylureas. In people with low HbA1c at increased hypoglycaemic risk, more relaxed glycaemic targets and de-intensification of insulins and/or sulphonylureas may reduce hypoglycaemia and mortality.

Declarations

Competing Interests: None declared.

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Ethics approval: This is a secondary analysis of non-identifiable routine primary care data, which is covered by an existing data sharing agreement between the research institution (Clinical Effectiveness Group, Queen Mary University of London) and each General Practice providing routinely collected data. Ethics approval for this study was not required. The data used in this study was anonymised primary care data extracted from a computer terminal connected to the encrypted NHS network in a room protected by a combination-locked door. The non-identifiable dataset was then transferred via an encrypted university electronic file sharing service to the password-enabled personal computer of the corresponding author only.

Guarantor: MM.

Contributorship: MM performed the relevant literature search. MM, JR, SK and RM co-designed the study and all contributed to the development and writing of the study protocol. MM extracted the data and performed the data analysis with support from SK and RM. MM holds full responsibility for conduct of this study. He had full access to the data used in the study and is responsible for the integrity and accuracy of the data and data analysis, and fully controlled the decision to publish. All authors contributed to the manuscript and approved the final submission of the report.

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