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Contemporary risk estimates of three HbA_{1c} variables in relation to heart failure following diagnosis of type 2 diabetes

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ABSTRACT

Background We evaluated the association between glycaemic control and the risk of heart failure (HF) in a contemporary cohort of persons followed after diagnosis of type 2 diabetes (T2D).

Methods and results Persons with T2D diagnosed between 1998 and 2012 were retrieved from the Clinical Practice Research Data Link in the UK and followed from diagnosis until the event of HF, mortality, drop out from the database due to any other reason, or the end of the study on 1 July 2015. The association between each of three different haemoglobin A_{1C} (HbA_{1c}) metrics and HF was estimated using adjusted proportional hazard models. In the overall cohort (n=94 332), the increased risk for HF per 1% (10 mmol/mol) increase in HbA_{1c} was 1.15 (95% CI 1.13 to 1.18) for updated mean HbA_{1c}, and 1.06 (1.04 to 1.07) and 1.06 (1.04 to 1.08) for baseline HbA_{1c} and updated latest HbA_{1c}, respectively. When categorised, the hazard risk (HR) for the updated mean HbA_{1c} in relation to HF became higher than for baseline and updated latest HbA_{1c} above HbA_{1c} levels of 9%, but did not differ at lower HbA_{1c} levels. The updated latest variable showed an increased risk for HbA_{1c} <6% (42 mmol/mol) of 1.16 (1.07 to 1.25), relative category 6–7%, while the HRs for updated mean and baseline HbA_{1c} showed no such J-shaped pattern.

Conclusions Hyperglycaemia is still a risk factor for HF in persons with T2D of similar magnitude as in earlier cohorts. Such a relationship exists for current glycaemic levels, at diagnosis and the overall level but the pattern differs for these variables.

INTRODUCTION

The global burden of diabetes has risen dramatically over the last two decades, and it is expected to affect over 500 million adults worldwide by 2030, with the majority having type 2 diabetes (T2D).[1] Persons with T2D have a shorter life expectancy, and heart failure (HF) is one of the most common causes of the excess risk of death in these patients.[2 3]

Whether T2D should be considered a causal factor or a comorbidity in HF is unclear.[4 5] In addition, studies of intensive glycaemic control in preventing cardiovascular (CV) events in persons with T2D have shown somewhat differing results. Three large clinical trials, conducted over a period of 3–5 years, failed to demonstrate clearly beneficial effects of intensive glycaemic control on CV outcomes.[6] However, the longer follow-up of the United Kingdom Prospective Diabetes Study (UKPDS) showed an association between intensive glucose control and reduced CV risk,[7] and the recent empagliflozin CV outcomes trial (CVOT) showed a reduction in the overall CV death (38%) as well as a markedly preventive effect on HF-related events (35%) by this glucose-lowering agent.[8]

Observational studies have generally shown a lesser risk of HF at lower glycaemic levels.[9–13] However, few population-based real-world studies have evaluated the importance of glycaemic control on the development of HF beginning at diagnosis of T2D, and contemporary estimates are sparse.[14] Recently, we found that the estimates of glycaemic control in relation to myocardial infarction varied over time with less strong associations during more recent time periods.[15]

The most commonly used measure of glycaemia is haemoglobin A_{1c} (HbA_{1c}).[16] However, a deeper understanding of the statistical application of repeated measures of HbA_{1c} is needed. When evaluating risk factors for cardiovascular disease (CVD) events in a statistical model, the most appropriate method to account for repeated measurements is not obvious. Consequently, various metrics of HbA_{1c} have been used in studies of diabetic complications.[15 17] Most commonly used have been the baseline HbA_{1c} and the updated mean HbA_{1c} (which at the time point for each new registration is the mean of all measurements taken thus far).

Therefore, following a similar comparative HbA_{1c} metric approach,[15] we sought in this study to evaluate HbA_{1c} in relation to HF in a large contemporary population of persons with T2D and compared three distinct methods using HbA_{1c} measurements from diabetes diagnosis and onwards.

METHODS

Data were obtained from the Clinical Practice Research Data Link (CPRD), where primary healthcare practitioners in the UK record patient information captured through Electronic Health Record IT systems and updated on regular intervals. CPRD has compiled patients' electronic health records since 1987 and currently collects data for approximately 8% of the UK population. CPRD provides researchers with access to high-quality anonymous healthcare data that include demographic,

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laboratory, prescribed drug and diagnosis.[18] The CPRD also provides linkage to external data sources which form part of the UK Health System such as the Hospital Episode Statistic (HES) data collected on a subset of patients from England and for whom GP consent for the data linkage has been obtained. Ethical approval was granted by the CPRD scientific committee and the National Information Governance Board of Ethics and Confidentiality Committee.

We identified 102 747 patients with T2D in the CPRD diagnosed between 1 January 1998 and 30 June 2012. Index date was defined as the first recorded diagnosis of T2D. Patients aged 18 years or older were included if they had a record in the CPRD at least 3 years prior to diagnosis, and information on gender, age, blood pressure, CV drug use and at least one recorded baseline HbA_{1c} measurement.

Patients below 40 years of age using insulin at diagnosis and continuing with insulin as the only glucose-lowering medication were excluded due to potential misclassification of type 1 diabetes. Follow-up time was defined as the time from T2D diagnosis until the date of HF, death or dropout from the electronic health records for any other reason, or the end of the study on 1 July 2015, whichever came first. HF was identified using the earliest record from the CPRD or HES databases. From these, the following exclusions were implemented: unknown sex (3 subjects), date of death before index date (69 subjects), HF event registered within a 3-year time period prior to their index date (2957 subjects), 1 registration of HbA_{1c} which coincided with the date of death or HF date (47 subjects), only 1 registration of HbA_{1c} with a follow-up time longer than 2 years (364 subjects), no baseline information on blood pressure (1037 subjects) and no baseline information on body mass index (BMI) (3944 subjects). The remaining selected cohort consisted of 94 332 patients of whom 6068 (6.4%) experienced HF during follow-up. Medcodes in CPRD and International Classification of Disease version 10 (ICD-10) codes in HES were used to define HF events as listed in online supplementary table S1.

Three different HbA_{1c} variables were constructed: baseline, updated latest and updated mean. Baseline HbA_{1c} is the value recorded closest to the date of diagnosis within 90 days before and 30 days after diagnosis. Updated latest HbA_{1c} and updated mean HbA_{1c} are time-varying variables, which are recalculated each time a new HbA_{1c} measurement is recorded during the patient's follow-up. Updated latest HbA_{1c} is set to the most recently recorded value, which then represents the patient's HbA_{1c} until a new measurement is taken. Similarly, updated mean HbA_{1c} is the mean of all available HbA_{1c} measurements.

Baseline values for other risk factors were determined by taking the value closest to the T2D diagnosis date, within a 2-year interval consisting of 1 year before and 1 year after diabetes diagnosis. Smoking status was assigned 'yes' if the patient had at least once been recorded as smoker or ex-smoker, 'no' if all records indicated non-smoker and 'unknown' if no information was available. The use of statins, β blockers, ACE inhibitors (ACEi), angiotensin II receptor blockade (ARBs) and/or acetylsalicylic acid (ASA) was defined as an indicator of any CV drug prescription during the 2-year baseline interval.

Statistical analysis

Proportional hazards models were constructed to assess and compare the association between each HbA_{1c} variable and HF. Overall comparisons of the HbA_{1c} variables were based on the estimated linear effect HRs. To further investigate the shape of the risk curves associated with HF, models were fitted with each HbA_{1c} variable categorised as follows: <6% (42 mmol/mol), 6 to <7% (42–53) used as the reference category, 7 to <8% (53–64), 8 to <9% (64–75), 9 to <10% (75–86) and ≥10% (≥86). Each model (one for each HbA_{1c} variable) was stratified for time period (before and after 1 January 2004) in order to allow for different baseline hazard functions in the two time periods, where the incentives for registration of HbA_{1c} differed. Furthermore, all models were adjusted for sex, age, BMI, smoking, prior MI and prior stroke (counting events occurring 3 years prior to index date), systolic and diastolic blood pressure categorised into five classes each (for systolic <126, 126 to <135, 135 to <142, 142 to <155, ≥155 mm Hg, and for diastolic <72, 72 to <80, 80 to <83, 83 to <90, ≥90 mm Hg) and use of statins, β blockers, ACEi, ARBs and ASA at baseline. As the adjusting covariates changed very little between the three different HbA_{1c} models, only data from the model where HbA_{1c} is included as updated mean HbA_{1c} are presented in online supplementary table S2. All adjusting covariates are baseline measurements (ie, using the registration closest in time to the index date, but no more than ±1 year from index date). Potential deviations from model assumptions were evaluated based on the scaled Schoenfeld residuals, and penalised spline functions were used to check the functional form of continuous covariates.[19] Incidence rates of HF were estimated using a Poisson regression model allowing for overdispersion and with follow-up time included as an offset.

RESULTS

Median follow-up of the 94 332 patients was 5.8 years, men comprised 56% of the cohort, mean age was 62 years at diabetes diagnosis, mean systolic blood pressure was 141 mm Hg, 64% were on statins, 39% were on ACEi and 54% were smokers or ex-smokers at diagnosis (table 1). In total, there were 6068 HF events registered resulting in a cumulative incidence of 6.4% persons with T2D (table 1). The incidence rate of HF was significantly higher in men throughout all age intervals (tables 2 and 3). Figure 1 shows the estimated incidence rates per age quintile for men and women separately.

Relationship between HF and HbA_{1c}

Regardless of HbA_{1c} modelling, there was a significant association between HbA_{1c} and HF. The estimated overall risk increase per 1% (10 mmol/mol) increase in HbA_{1c} ranged from 6% for baseline HbA_{1c} to 15% for the updated mean HbA_{1c} (table 4). When categorised by HbA_{1c}, the latest variable showed a J-shaped increased risk for HbA_{1c} <6% (42 mmol/mol) of 1.16 (1.07 to 1.25), relative category 6–7%, which was not observed for the updated mean and baseline HbA_{1c} (table 4).

Comparisons of the three HbA_{1c} variables

According to the estimated linear effect HRs, baseline HbA_{1c} showed the lowest HR for HF, followed by updated latest and updated mean HbA_{1c} (table 4). By HbA_{1c} categories, there were discernible differences in the shape of the risk curves across HbA_{1c} levels (figure 2). Most notable was a significantly increased risk of 16% for the updated latest variable in HbA_{1c} <6%, relative to the reference category 6–7%, where the corresponding estimates of the baseline and updated mean HbA_{1c} showed no risk increase. The updated mean HbA_{1c} variable also notably indicated higher HRs at the upper end of HbA_{1c} categories versus baseline and latest. For the baseline HbA_{1c}, the HRs levelled out above the 8–9% HbA_{1c} category, while for the updated mean HbA_{1c} variable the HRs showed a monotonic increase with increasing HbA_{1c} category.

Table 1 Patient characteristics at baseline by HbA_{1c} categories

	HbA_{1c} at baseline						
	<6%	6%–7%	7%–8%	8%–9%	9%–10%	≥10%	All
n (%)	6610 (7.0)	26 851 (28)	20 253 (21)	11 071 (12)	7982 (8.5)	21 565 (23)	94 332
HF events	432 (6.5)	1652 (6.2)	1389 (6.9)	780 (7.0)	498 (6.2)	1317 (6.1)	6068 (6.4)
HbA_{1c} (%)	5.6 (0.3)	6.5 (0.3)	7.4 (0.3)	8.4 (0.3)	9.4 (0.3)	11.7 (1.2)	8.3 (2.2)
Men, n (%)	3582 (54)	13 982 (52)	10 859 (54)	6223 (56)	4745 (59)	13 131 (61)	52 522 (56)
Age (years)	64.5 (12.5)	64.5 (12.1)	63.0 (12.6)	60.7 (13.1)	58.9 (13.1)	58.6 (12.8)	61.9 (12.8)
SBP (mm Hg)	141 (19)	140 (18)	141 (18)	141 (19)	142 (19)	140 (19)	141 (19)
DBP (mm Hg)	80 (11)	80 (10)	81 (10)	82 (11)	83 (11)	83 (11)	82 (11)
BMI (kg/m^2)	30.0 (6.1)	31.6 (6.3)	32.3 (6.6)	32.3 (6.8)	32.2 (6.7)	31.0 (6.5)	31.7 (6.5)
HDL* (mmol/L)	1.3 (0.5)	1.2 (0.4)	1.2 (0.4)	1.2 (0.4)	1.2 (0.4)	1.2 (0.4)	1.2 (0.4)
LDL† (mmol/L)	2.9 (1.0)	2.9 (1.0)	2.9 (1.0)	3.0 (1.0)	3.1 (1.1)	3.2 (1.1)	3.0 (1.1)
TG‡ (mmol/L)	1.9 (1.3)	2.0 (1.3)	2.2(1.3)	2.4 (1.8)	2.6 (2.0)	2.9 (2.3)	2.3 (1.7)
Follow-up (years), median (IQR)	6.0 (3.7, 9.1)	5.4 (3.5, 8.2)	5.6 (3.5, 8.5)	6.0 (3.6, 9.2)	6.2 (3.7, 9.6)	6.1 (3.7, 9.3)	5.8 (3.6, 8.8)
Smoking							
Yes	3481 (53)	14 727 (55)	11 027 (54)	6077 (55)	4290 (54)	11 565 (54)	51 167 (54)
No	2681 (41)	10 810 (40)	8111 (40)	4242 (38)	3074 (38)	8455 (39)	37 373 (40)
Unknown	448 (6.8)	1314 (4.9)	1115 (5.5)	752 (6.8)	618 (7.7)	1545 (7.2)	5792 (6.1)
Prior MI	141 (2.1)	565 (2.1)	470 (2.3)	236 (2.1)	135 (1.7)	247 (1.1)	1794 (1.9)
Prior stroke	140 (2.1)	488 (1.8)	372 (1.8)	150 (1.4)	110 (1.4)	250 (1.2)	1510 (1.6)
β-Blockers	2384 (36)	8792 (33)	5787(29)	2774 (25)	1757 (22)	4191 (19)	25 685 (27)
ACEi	2828 (43)	11 789 (44)	8835 (44)	4575 (41)	3068 (38)	7737 (36)	38 832 (41)
ARBs	944 (14)	4118 (15)	2809 (14)	1288 (12)	691 (8.7)	1786 (8.3)	11 636 (12)
ASA	2632 (40)	10 716 (40)	7990 (40)	3903 (35)	2632 (33)	6670 (31)	34 543 (37)
Statins	4073 (62)	18 634 (69)	13 531 (67)	6760 (61)	4682 (59)	12 730 (59)	60 410 (64)
Diabetes treatment							
Diet	5600 (84.7)	20 185 (75.2)	10 063 (49.7)	3438 (31.1)	1887 (23.6)	3792 (17.6)	44 965 (47.7)
Metformin	877 (13.3)	6141 (22.9)	9195 (45.4)	6564 (59.3)	5109 (64.0)	14 084 (65.3)	41 970 (44.5)
1 OAD	29 (0.4)	80 (0.3)	126 (0.6)	92 (0.8)	75 (0.9)	221 (1.0)	623 (0.7)
≥2 OAD	27 (0.4)	193 (0.7)	483 (2.4)	561 (5.1)	530 (6.6)	2118 (9.8)	3912 (4.1)
Insulin	77 (1.2)	252 (0.9)	386 (1.9)	416 (3.8)	381 (4.8)	1350 (6.3)	2862 (3.0)

Numbers are mean (standard deviation) or n (%) if not else specified.
*18 212 (19%) of the subjects are missing high-density lipoprotein information.
†31 136 (33%) of the subjects are missing low-density lipoprotein information.
‡15 302 (16%) of the subjects are missing triglyceride (TG) information.
ACEi, ACE inhibitors; ARBs, angiotensin II receptor blockade; ASA, acetylsalicylic acid; DBP, distolic blood pressure; HbA_{1c}, haemoglobin A_{1C}; HF, heart failure; IQR, interquartile range; MI, myocardial infarction; OAD, oral antidiabetic drug; SBP, systolic blood pressure.

Table 2 Incidence rates (IR) of heart failure (HF) per 1000 patient years in a population with T2D

	Patients, n	HF events, n	Patient years	IR (95% CI)
All	94 332	6068	600 048	10.1 (9.48 to 10.8)
Men	52 522	3531	329 978	10.7 (9.84 to 11.6)
Women	41 810	2537	270 070	9.39 (8.51 to 10.4)

Table 3 Incidence rates (IR) of heart failure by sex and age per 1000 patient years in a population with T2D

Age, years	Men IR (95% CI)	Women IR (95% CI)
<51	2.06 (1.34 to 3.16)	1.47 (0.81 to 2.69)
51–58	5.19 (3.97 to 6.78)	3.21 (2.12 to 4.86)
59–65	8.61 (6.97 to 10.6)	6.12 (4.58 to 8.16)
66–72	14.6 (12.2 to 17.3)	10.7 (8.59 to 13.2)
≥73	28.9 (25.3 to 33.1)	22.9 (19.9 to 26.4)

DISCUSSION

In this contemporary population study of 94 332 persons followed from diagnosis of T2D, we found that hyperglycaemia remains as an essential risk factor for HF events of similar magnitude as that demonstrated in earlier studies. An association between hyperglycaemia and HF was apparent when measures of glycaemic control were taken at the time of diagnosis of T2D, for the current levels of glycaemic control as well as for the overall control since the diagnosis of T2D. The risk increase for HF per 1% (10 mmol/mol) increase in HbA_{1c} was 15% for the updated mean HbA_{1c}, whereas it was only 6% for baseline HbA_{1c} and the latest HbA_{1c} variables. The risk pattern of HF in relation to the updated mean HbA_{1c} diverged when compared with the other variables mainly at HbA_{1c} levels above 9%, whereas no major differences were found below this level. Also noteworthy, at HbA_{1c} lower than 6% (42 mmol/mol) the updated latest HbA_{1c} variable showed an increased risk of HF compared with the referent HbA_{1c} 6–7% (42–52 mmol/mol), whereas the two other variables showed no such J-shaped association.

The risk increase of HF of 15% by 1% (10 mmol/mol) higher updated mean HbA_{1c} is in line with earlier studies.[7 10–13] To our knowledge, risk associations between the updated latest

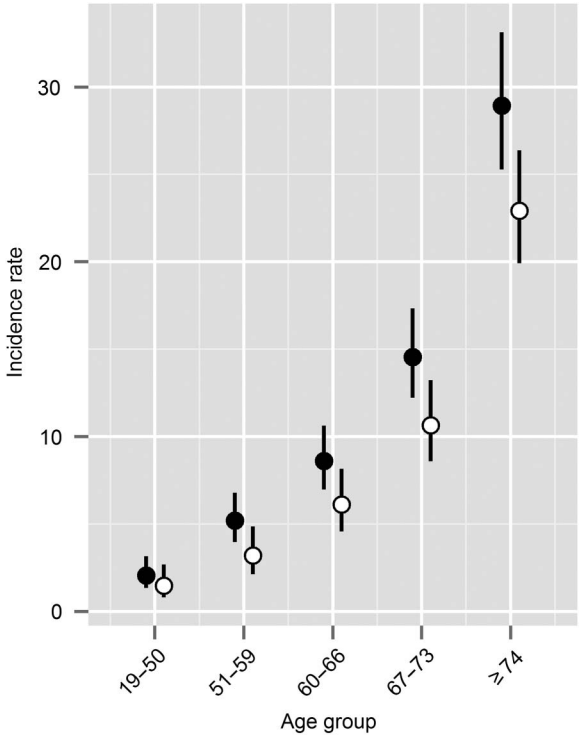

Figure 1 Incidence heart failure rates per 1000 patient years with 95% CIs, for men (squares) and women (circles) across age categories.

HbA_{1c} value and HF have not been evaluated previously in large population-based studies although recently a smaller population-based study found a U-shaped association between mean HbA_{1c} and mortality in chronic HF subjects with T2D.[20] In a meta-analysis of four randomised trials of intensive glycaemic control, no preventive effect on HF could be shown.[21] It is noteworthy that three of these studies were relatively short and that the effects of intensive therapy on HF may act over longer time periods. Furthermore, in three of these studies the intervention of intensive CV therapy was generally initiated many years after the diagnosis of T2D and, therefore, the effects of CV treatment initiation may differ between early and later stages of the disease. However, the recent empagliflozin CVOT showed a clear preventive effect on HF in persons with T2D and CV disease, which may be due to contributing effects of the medication beyond its glucose-lowering factors.[8]

In the light of few existing clinical trials of patients with T2D where intensive glycaemic control was initiated at diagnosis and preventive effects on HF were investigated, it is essential that we confirm that a strong association exists between hyperglycaemia and HF in this contemporary population-based study following persons from diagnosis. This finding implies that good glycaemic control is likely essential in preventing HF in persons with T2D and that early as well as overall control is essential. Based on preventive effects by metformin in the UKPDS study,[7] metformin is still a first-line option at diagnosis of T2D. The sodium glucose cotransporter 2 inhibitors may from the recent findings in the empagliflozin CVOT be especially efficient in preventing HF, but it will be valuable to further confirm that this is the case also in a more general population of persons with T2D, without known CVD morbidity. The clinical trials of incretin-based therapies have not so far shown any preventive effect on CVD but were generally designed to show non-inferiority and may have preventive effects over longer time periods.[22–24]

Studying various HbA_{1c} metrics offers clinicians compound perspectives on this biomarker with potentially differing purposes and utilities. The baseline HbA_{1c} provides the clinician with information on whether the glycaemic control at diagnosis already has a predictive value on complications at later stages. However, when meeting patients in the clinic, the current HbA_{1c} value is the main focus from a treatment perspective and may therefore also be so in prognosis. On the other hand, the overall glycaemic control from diagnosis, measured as a mean value, is likely to be a better prognostic marker. This is also essential to account for when estimating the magnitude of hyperglycaemia as a contributing factor to HF, which is crucial in health-economic models and risk-engines used in clinical practice.[25–29] However, being able to use the updated mean HbA_{1c} in risk engines requires that the risk engine is incorporated in the electronic medical record system, since it will be burdensome for the clinician to insert multiple historical HbA_{1c} values. Nonetheless, this is an essential point from our findings since the HRs described by 1% higher HbA_{1c} differ greatly depending on the HbA_{1c} metric used. It is noteworthy that in accordance with our recent analysis of HbA_{1c} in relation to MI (15), there was a J-shaped pattern for the latest HbA_{1c} variable. Although this finding is repeated here for another CV complication and it could be inferred that very tight glycaemic control, for example, HbA_{1c} close to normal levels may be harmful, it should be interpreted with caution since patients with HbA_{1c} <6% (42 mmol/mol) have a glycaemic control lower than general targets. There may be characteristics essential for this patient group, which are difficult to control for in the current analyses.

A strength of the present study is the large population studied, which we believe to be the largest observational study of glycaemic control and HF in patients with T2D. The size is essential for obtaining adequately precise risk estimates to compare different HbA_{1c} variables and whether patterns of the associations differ at different HbA_{1c} levels. We also adjusted for the main risk factors but it should be noted that residual confounding cannot be excluded due to the observational nature of

Table 4 HR estimates (95% CI) of the association between heart failure and HbA_{1c}, based on the linear effect model (increase per 1% HbA_{1c}) and categorised HbA_{1c} variables

		Categories of HbA_{1c}				
HbA_{1c} variable	Increase per 1% HbA_{1c}	<6%	7%–8%	8%–9%	9%–10%	≥10%
Baseline	1.06 (1.04 to 1.07)	0.98 (0.88 to 1.09)	1.16 (1.08 to 1.25)	1.30 (1.19 to 1.41)	1.26 (1.14 to 1.39)	1.36 (1.26 to 1.46)
Latest	1.06 (1.04 to 1.08)	1.16 (1.07 to 1.25)	1.06 (1.00 to 1.14)	1.36 (1.24 to 1.49)	1.30 (1.14 to 1.49)	1.41 (1.24 to 1.60)
Updated mean	1.15 (1.13 to 1.18)	1.02 (0.92 to 1.15)	1.21 (1.14 to 1.29)	1.48 (1.36 to 1.60)	1.64 (1.46 to 1.84)	1.84 (1.60 to 2.13)

The reference value for the categorical HbA_{1c} variables was 6 to <7%. All HR estimates were adjusted for sex, age, BMI, smoking, prior MI, prior stroke, blood pressure, use of medications (statins, β-blockers, ACEi, ARBs and ASA).
ACEi, ACE inhibitors; ARBs, angiotensin II receptor blockade; ASA, acetylsalicylic acid; HbA_{1c}, haemoglobin A_{1C}.

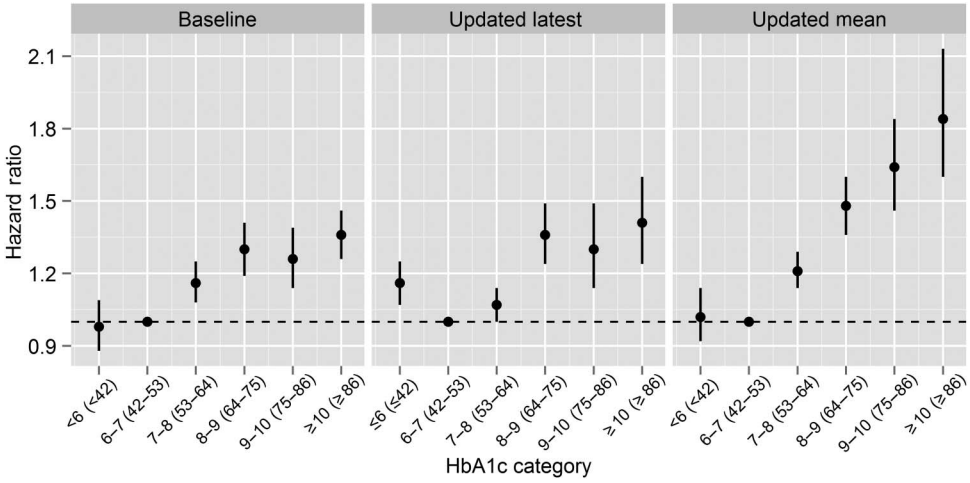

Figure 2 Estimated HRs with 95% CI for each of the three HbA_{1c} variables, across categories of HbA_{1c} level for heart failure events. Reference category is 6%–<7% (42–53 mmol/mol). The dashed line indicates HR=1.

this study and lack of availability of recognised prognostic HF biomarkers such as N-terminal pro b-type natriuretic peptide (NT-pro-BNP). Previous studies that have validated HF diagnoses and HF risk assessment methods have found the CPRD to have good levels of accuracy and completeness.[30] We are, therefore, confident in our outcomes.

In conclusion, hyperglycaemia remains a strong risk factor for HF in persons with T2D, of similar magnitude as in earlier cohorts. Such a relationship exists both for current glycaemic levels, at diagnosis and the overall level but the patterns differ for these variables.

Key messages

What is already known on this subject?
Observational studies have generally shown a lesser risk of heart failure (HF) at lower glycaemic levels. However, there are few contemporary population-based real-world studies that have evaluated the importance of glycaemic control on the development of HF from the beginning at diagnosis of T2D. Also, it is not known which metric of HbA_{1c} is best suited to estimate the glycaemic hazard risk on HF.

What might this study add?
In a large contemporary population-based real-world study, we demonstrate that all studied metrics of HbA1c (baseline, updated latest and updated mean) confer a risk increase for HF in incident T2D and thus that hyperglycaemia continues to be a strong risk factor for HF in persons with T2D. Of the studied HbA1c metrics, the updated mean HbA1c showed higher hazard risk estimates than the others, indicating that the average long-term glycaemic control is of clinical importance to reduce HF outcomes. Also by only estimating risk based on baseline or latest HbA1c, the impact of glycemic control can be underestimated.

How might this impact on clinical practice?
Hyperglycaemia continues to be a strong risk factor of HF in persons with T2D, and the higher risk estimates for the updated mean HbA1c indicate that there is clinically significant benefit on reducing HF outcomes by implementing glycaemic control.

Contributors All authors took part in the design of the study and interpretation of results. MO conducted the statistical analysis. SS and ML wrote the manuscript. VS retrieved the data from CPRD and reviewed and contributed to writing of the manuscript. CC and MO reviewed and contributed to writing of the manuscript. SS is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Competing interests MO, VS, CC and SS are employed by AstraZeneca. ML has been consultant or received honoraria from AstraZeneca, Medtronic, Novo Nordisk and Pfizer and received research grants from Abbot Scandinavia, AstraZeneca, DexCom, Novo Nordisk, Pfizer and participated in advisory boards for Novo Nordisk.

Ethics approval Ethical approval for this study has been obtained from the ISAC (Independent Scientific Advisory Committee) for MHRA Database Research for the Clinical Practice Research Datalink (CPRD).

Provenance and peer review Not commissioned; externally peer reviewed.

REFERENCES

1 Whiting DR, Guariguata L, Weil C, *et al*. IDF diabetes Atlas: global estimates of the prevalence of diabetes for 2011 and 2030. *Diabetes Res Clin Pract* 2011;94:311–21.
2 Gottdiener JS, Arnold AM, Aurigemma GP, *et al*. Predictors of congestive heart failure in the elderly: the Cardiovascular Health Study. *J Am Coll Cardiol* 2000;35:1628–37.
3 Peterson LR, McKenzie CR, Schaffer JE. Diabetic cardiovascular disease: getting to the heart of the matter. *J Cardiovasc Transl Res* 2012;5:436–45.
4 MacDonald MR, Petrie MC, Hawkins NM, *et al*. Diabetes, left ventricular systolic dysfunction, and chronic heart failure. *Eur Heart J* 2008;29:1224–40.
5 Voors AA, van der Horst IC. Diabetes: a driver for heart failure. *Heart* 2011;97:774–80.
6 Skyler JS, Bergenstal R, Bonow RO, *et al*., American Diabetes Association; American College of Cardiology Foundation. American Heart Association. Intensive glycemic control and the prevention of cardiovascular events: implications of the ACCORD, ADVANCE, and VA diabetes trials: a position statement of the American Diabetes Association and a scientific statement of the American College of Cardiology Foundation and the American Heart Association. *Circulation* 2009;119:351–7.
7 Holman RR, Paul SK, Bethel MA, *et al*. 10-year follow-up of intensive glucose control in type 2 diabetes. *N Engl J Med* 2008;359:1577–89.
8 Zinman B, Wanner C, Lachin JM, *et al*., EMPA-REG OUTCOME Investigators. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. *N Engl J Med* 2015;373:2117–28.

9 Stratton IM, Adler AI, Neil HA, *et al*. Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study. *BMJ* 2000;321:405–12.
10 Iribarren C, Karter AJ, Go AS, *et al*. Glycemic control and heart failure among adult patients with diabetes. *Circulation* 2001;103:2668–73.
11 Nichols GA, Gullion CM, Koro CE, *et al*. The incidence of congestive heart failure in type 2 diabetes: an update. *Diabetes Care* 2004;27:1879–84.
12 Lind M, Olsson M, Rosengren A, *et al*. The relationship between glycaemic control and heart failure in 83,021 patients with type 2 diabetes. *Diabetologia* 2012;55:2946–53.
13 Zhao W, Katzmarzyk PT, Horswell R, *et al*. HbA1c and heart failure risk among diabetic patients. *J Clin Endocrinol Metab* 2014;99:E263–7.
14 Parry HM, Deshmukh H, Levin D, *et al*. Both high and low HbA_{1c} predict incident heart failure in type 2 diabetes mellitus. *Circ Heart Fail* 2015;8:236–42.
15 Olsson M, Schnecke V, Cabrera C, *et al*. Contemporary risk estimates of three HbA_{1c} variables for myocardial infarction in 101,799 patients following diagnosis of type 2 diabetes. *Diabetes Care* 2015;38:1481–6.
16 Jeffcoate SL. Diabetes control and complications: the role of glycated haemoglobin, 25 years on. *Diabet Med* 2004;21:657–65.
17 Lind M, Odén A, Fahlén M, *et al*. A systematic review of HbA_{1c} variables used in the study of diabetic complications. *Diabetes Metab Syndr Clin Res Rev* 2008;2:282–93.
18 The Clinical Database Research Datalink http://www.cprd.com/intro.asp
19 Therneau TM, Grambsch PM. *Modeling survival data: extending the cox model*. New York: Springer-Verlag, 2000:107–11.
20 Elder DH, Singh JS, Levin D, *et al*. Mean HbA_{1c} and mortality in diabetic individuals with heart failure: a population cohort study. *Eur J Heart Fail* 2016;18:94–102.
21 Turnbull FM, Abraira C, Anderson RJ, *et al*. Intensive glucose control and macrovascular outcomes in type 2 diabetes. *Diabetologia* 2009;52:2288–98.
22 Scirica BM, Bhatt DL, Braunwald E, *et al*., SAVOR-TIMI 53 Steering Committee and Investigators. Saxagliptin and cardiovascular outcomes in patients with type 2 diabetes mellitus. *N Engl J Med* 2013;369:1317–26.
23 Green JB, Bethel MA, Armstrong PW, *et al*., TECOS Study Group. Effect of sitagliptin on cardiovascular outcomes in type 2 diabetes. *N Engl J Med* 2015;373:232–42.
24 Pfeffer MA, Claggett B, Diaz R, *et al*., ELIXA Investigators. Lixisenatide in patients with type 2 diabetes and acute coronary syndrome. *N Engl J Med* 2015;373:2247–57.
25 Stevens RJ, Kothari V, Adler AI, *et al*. The UKPDS risk engine: a model for the risk of coronary heart disease in type II diabetes (UKPDS 56). *Clin Sci* 2001;101:671–9.
26 Zethelius B, Eliasson B, Eeg-Olofsson K, *et al*. A new model for 5-year risk of cardiovascular disease in type 2 diabetes, from the Swedish National Diabetes Register (NDR). *Diabetes Res Clin Pract* 2011;93:276–84.
27 Bagust A, Hopkinson PK, Maslove L, *et al*. The projected health care burden of Type 2 diabetes in the UK from 2000 to 2060. *Diabet Med* 2002;19(Suppl 4):1–5.
28 McKinlay J, Marceau L. US public health and the 21st century: diabetes mellitus. *Lancet* 2000;356:757–61.
29 Bagust A, Hopkinson PK, Maier W, *et al*. An economic model of the long-term health care burden of Type II diabetes. *Diabetologia* 2001;44:2140–55.
30 Hippisley-Cox J, Coupland C. Development and validation of risk prediction equations to estimate future risk of heart failure in patients with diabetes: a prospective cohort study. *BMJ Open* 2015;5:e008503.