The relationship between glycaemic control and heart failure in 83,021 patients with type 2 diabetes

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Abstract

Aims/hypothesis The aim of this study was to examine the relationship between glycaemic control and hospitalisation for heart failure in patients with type 2 diabetes.

Methods Patients included in the Swedish National Diabetes Register (NDR) during 1998–2003 were followed until hospitalisation for heart failure, death or 31 December 2009. Unadjusted and adjusted incidence rates for heart failure were estimated by Poisson regression and relative risk was estimated by Cox regression.

Results In 83,021 patients with type 2 diabetes, 10,969 (13.2%) were hospitalised with a primary or secondary diagnosis of heart failure during a mean follow-up of 7.2 years. The incidence increased by male sex ($p<0.001$), older age ($p<0.001$) and longer diabetes duration ($p<0.001$). In Cox regression adjusting for risk factors of heart failure the HR per each percentage unit higher HbA_{1c}

(10 mmol/mol) for heart-failure hospitalisation was 1.12 (95% CI 1.10, 1.14). By category of HbA_{1c} the HR for heart failure hospitalisation was: HbA_{1c} 6.0 to <7.0% (42 to <53 mmol/mol), 0.91 (95% CI 0.84, 0.98); HbA_{1c} 7.0 to <8.0% (53 to <64 mmol/mol), 0.99 (95% CI 0.91, 1.07); HbA_{1c} 8.0 to <9.0% (64 to <75 mmol/mol), 1.10 (95% CI 1.01, 1.20); HbA_{1c} 9.0 to <10.0% (75 to <86 mmol/mol), 1.27 (95% CI 1.15, 1.41); HbA_{1c} ≥10.0% (≥86 mmol/mol), 1.71 (1.51, 1.93) (reference HbA_{1c} <6% [42 mmol/mol]). The HR for patients with HbA_{1c} 7.0 to <8.0% (53 to <64 mmol/mol) compared with patients with HbA_{1c} 6.0 to <7.0% (42 to <53 mmol/mol) was 1.09 (95% CI 1.03, 1.14).

Conclusions/interpretation Poor glycaemic control (HbA_{1c} >7% [53 mmol/mol]) is associated with an increased risk of hospitalisation for heart failure in patients with type 2 diabetes.

Keywords Glycaemic control · HbA_{1c} · Heart failure · Incidence · Risk estimation · Type 1 diabetes · Type 2 diabetes

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Abbreviations

ACCORD	Action to Control Cardiovascular Risk in Diabetes
ADVANCE	Action in Diabetes and Vascular Disease
CVD	Cardiovascular disease
ICD	International Classification of Diseases
NDR	National Diabetes Registry
NGSP	National Glycohemoglobin Standardization Program
OHA	Oral hypoglycaemic agent
UKPDS	UK Prospective Diabetes Study
VADT	Veterans Affairs Diabetes Trial

Introduction

Type 2 diabetes mellitus is associated with an increased risk of micro- and macrovascular complications and a

shorter life expectancy compared with the general population [1, 2]. The predominant cause of death in type 2 diabetes is cardiovascular disease (CVD), accounting for approximately 35% of total mortality [3]. Myocardial infarction, the most common manifestation of CVD in type 2 diabetes, has been shown to be reduced by intensive glycaemic control, improved blood lipids and reduction in BP [4–6].

Heart failure is a rapidly increasing CVD condition and a major cause for hospitalisation, with costs comprising 1–2% of the total health budget in many developed countries [7, 8]. A recent meta-analysis of clinical trials, including 4–5 years of follow-up, demonstrated that intensive glycaemic control did not prevent heart failure in type 2 diabetes [9]. To better understand the relationship between heart failure and glycaemic control, we studied a large population-based sample of patients with type 2 diabetes with long-term follow-up.

Methods

The Swedish National Diabetes Registry (NDR) was initiated in 1996 and managed by the Centre of Registers in Region Västra Götaland, Gothenburg, Sweden [10]. Information is collected by trained nurses and physicians during patient visits to hospital outpatient and primary care clinics nationwide, with reporting performed annually. The number of patients included in the registry has increased over time, primarily due to an increase in the number of participating primary care clinics. Type 2 diabetes in the registry is defined as treatment with diet only, diet combined with oral hypoglycaemic agents (OHA), insulin only or OHA combined with insulin. For patients treated with insulin, with or without OHA, type 2 diabetes was defined only in patients ≥ 40 years of age at the time of diabetes diagnosis. Data from the NDR was linked with the Swedish national discharge and mortality registries, with mandatory information on all principal and secondary discharge diagnoses, deaths and causes of deaths [11, 12]. This study was approved by the regional ethics review board at the University of Gothenburg, Gothenburg, Sweden.

Patient and clinical characteristics

Variables assessed were age (years), sex, diabetes duration, HbA_{1c}, BMI, systolic and diastolic BP, smoking, antihypertensive medication use, glucose-lowering medication use, ischaemic heart disease, myocardial infarction, heart valve surgery, atrial fibrillation and microalbuminuria. LDL-cholesterol and HDL-cholesterol, which were systematically registered in the NDR from the year 2002 and onwards,

were included in a subgroup analysis. In the NDR, the Swedish standard for recording BP was the mean value of two supine readings (Korotkoff 1–5), using an appropriately sized cuff and after at least 5 min of rest. Standards for measuring and registering HbA_{1c}, BP, tobacco use and hypertensive medications have been described in previous studies [13]. Since diabetes clinics in Sweden used HbA_{1c} methods calibrated to the HPLC Mono-S method until September 2010, all HbA_{1c} values were converted to NGSP (National Glycohemoglobin Standardization Program) levels (DCCT-standard) [14]. HbA_{1c} values have also been reported by IFCC (International Federation of Clinical Chemistry)-standard in parenthesis.

Follow-up and endpoint definitions

In general, the principal diagnosis is the main cause of hospitalisation. A principal diagnosis of heart failure has been shown to have 95% validity according to criteria established by the European Heart Association, whereas an 82% validity has been reported irrespective of position of diagnosis [15]. Patients were followed from first inclusion in the NDR between 1998 and 2003 until a primary or secondary discharge diagnosis of heart failure, death or the end of follow-up on 31 December 2009. The ICD-10 discharge code (www.who.int/classifications/icd/en/) of I50 was used to define heart failure, irrespective of whether the heart failure was a principal or secondary diagnosis. Discharge codes for prior or intervening comorbid conditions were acute myocardial infarction (I21), atrial fibrillation (I48), valve disease (I05–I09 and I34–I36) and ischaemic heart disease (I20, I22, I24.8, I24.9 and I25). HbA_{1c} was examined in relation to hospitalisation for heart failure as dependent variable adjusting for variables significantly related to hospitalisation for heart failure.

Statistical analysis

A similar statistical methodology has been used in other studies of relationships between HbA_{1c} and diabetic complications [13, 16].

Incidence rates categorised by HbA_{1c} Unadjusted incidence rates for heart failure were calculated by dividing the number of patients with heart failure by the number of patient years of follow-up in a particular HbA_{1c} category, and reported as events per 1,000 years of follow-up. Studied categories were estimated using updated mean HbA_{1c}, and classified as <6.0%, 6.0–7.0%, 7.0–8.0%, 8.0–9.0%, 9.0–10.0% and >10.0%, (in mmol/mol <42, 42 to <53, 53 to <64, 64 to <75, 75 to <86 and ≥ 86). The updated mean HbA_{1c} was defined as the mean value, updated for each new measurement of HbA_{1c} (for example, when the third

measurement from baseline was performed, the updated mean HbA_{1c} was the mean of the first three values). Incidence rates adjusted for age, sex and diabetes duration were estimated using Poisson regression and reported per 1,000 patient years of follow-up.

Risk estimates A Cox proportional hazards model was constructed to study potential relationships between HbA_{1c} and hospitalisation for heart failure while adjusting for other potential risk factors. Updated means of HbA_{1c}, systolic BP, diastolic BP and BMI were calculated based on all patient registrations from inclusion until heart failure, death or end of the study, and included as time-dependent covariates. Age, sex and diabetes duration were used as baseline variables. Atrial fibrillation, valve surgery, ischaemic heart disease and myocardial infarction were recorded as either absent or present from 1987 onward. Smoking status was divided into four categories according to the percentage of registrations of each patient as a smoker during follow-up (none, <50%, ≥50% and unknown). Smoking status was defined as unknown if at least 50% of a patient's smoking registrations were missing. A categorical variable for BP medication was defined in the same way as smoking status. Glucose-lowering treatment was categorised by diet, oral medication only or insulin therapy.

A subgroup analysis based on all patients with at least one measurement of LDL- and HDL-cholesterol was carried out and included 77% of the cohort (63,986 patients). Variables representing HDL- and LDL-cholesterol were calculated as the mean values over all registrations during follow-up.

Results

Demographics

Among 83,021 patients with type 2 diabetes, 10,969 (13.2%) were hospitalised with a primary or secondary diagnosis of heart failure. Baseline characteristics for the total cohort and by category of HbA_{1c} are shown in Table 1. The mean HbA_{1c} was 7.4% (57 mmol/mol), mean BMI was 28.9 kg/m², and mean systolic/diastolic BP was 146/80 mmHg. Among all patients 13,445 (16.2%) had a history of myocardial infarction. The percentage of patients with myocardial infarction was greater among patients with higher HbA_{1c} levels (Table 1).

Heart failure incidence rates

The unadjusted incidence rates of heart failure per 1,000 person-years increased significantly, from 13.8 (95% CI

12.9, 14.8) for patients with HbA_{1c} <6.0% (<42 mmol/mol) to 25.8 (23.5–28.4) for patients with HbA_{1c} ≥10.0% (≥86 mmol/mol). Unadjusted incidence rates and 95% CIs by category of HbA_{1c} are shown in Table 2. Poisson regression demonstrated a significant increase in risk of hospitalisation for heart failure by male sex ($p<0.001$), older age ($p<0.001$) and longer diabetes duration (all $p<0.001$, Fig. 1).

Risk estimates for heart failure hospitalisation In Cox regression with HbA_{1c} included as a linear effect, the HR for heart-failure hospitalisation by each percentage unit (10 mmol/mol) increase in HbA_{1c} was 1.12 (95% CI 1.10, 1.14) after adjustment for age, sex, diabetes duration, BMI, smoking, systolic and diastolic BP, myocardial infarction, atrial fibrillation, ischaemic heart disease, heart valve disease, glucose-lowering therapy, antihypertensive medication, and microalbuminuria. Table 3 shows HRs and 95% CIs for heart-failure hospitalisation by HbA_{1c} category and stepwise adjustment for heart-failure risk factors. All variables adjusted for when relating HbA_{1c} to hospitalisation for heart failure were significantly ($p<0.05$) related to hospitalisation for heart failure. For HbA_{1c} ≥10.0% (≥86 mmol/mol), as compared with <6.0% (42 mmol/mol), the HR was 2.47 (95% CI 2.09, 2.65) after adjustment for age, sex and diabetes duration. This estimate decreased to 2.16 (95% CI 1.92, 2.43) after further adjustment for smoking, BMI and systolic and diastolic BP, and decreased to 1.71 (95% CI 1.51, 1.93) after additional adjustment for comorbidities (including baseline or intervening myocardial infarction), microalbuminuria, glucose-lowering therapy and BP medication. After adjustment for all covariates, patients with mean HbA_{1c} 6.0 to <7.0% (42 to <53 mmol/mol) had significantly lower risk for heart-failure hospitalisation than patients with HbA_{1c} <6.0% (<42 mmol/mol; HR 0.91, 95% CI 0.84, 0.98), with numerically similar risk for patients with HbA_{1c} 7.0 to <8.0% (53 to <64 mmol/mol) and HbA_{1c} <6.0% (<42 mmol/mol). However, the HR for patients with HbA_{1c} 7.0 to <8.0% (53 to <64 mmol/mol) vs patients with HbA_{1c} 6.0 to <7.0% (42 to <53 mmol/mol) showed a small but significantly increased risk (HR 1.09, 95% CI 1.03, 1.14). At levels of HbA_{1c} >8.0% (>64 mmol/mol), risk of heart failure increased progressively and significantly, compared with patients with HbA_{1c} <6.0% (<42 mmol/mol) (Table 3). Use of only a primary diagnosis of heart failure as the dependent variable showed no significant changes in risk for HbA_{1c} in categories of 6.0–7.0% (42 to <53 mmol/mol) and 7.0–8.0% (53 to <64 mmol/mol) compared with HbA_{1c} <6.0% (42 mmol/mol) for heart-failure hospitalisation (Table 3). There was no interaction between sex and HbA_{1c} in relation to hospitalisation for heart failure ($p=0.25$). In 63,986 (77%) of patients with information on LDL- and HDL-cholesterol, the HRs for heart-failure

Table 1 Characteristics of all 83,021 patients with type 2 diabetes and by baseline categories of HbA_{1c} at first inclusion in the register from 1998 to 2003

Characteristic	HbA _{1c} category, % (mmol/mol)						
	All	<6 (<42)	6.0 to <7.0 (42 to <53)	7.0 to <8.0 (53 to <64)	8.0 to <9.0 (64 to <75)	9.0 to <10.0 (75 to <86)	≥10.0 (≥86)
Number	83,021	10,953	25,685	22,341	14,205	6,003	3,834
HbA _{1c} , %, mean (SD)	7.37 (1.33)	5.65 (0.31)	6.52 (0.26)	7.40 (0.27)	8.41 (0.28)	9.37 (0.26)	10.9 (0.90)
HbA _{1c} , mmol/mol, mean	57.0	38.3	47.8	57.4	68.4	78.9	95.6
Men	45,887 (55.3)	6,214 (56.7)	14,106 (54.9)	12,341 (55.2)	7,837 (55.2)	3,300 (55.0)	2,089 (54.5)
Women	37,134 (44.7)	4,739 (43.3)	11,579 (45.1)	10,000 (44.8)	6,368 (44.8)	2,703 (45.0)	1,745 (45.5)
Age, years, mean (SD)	65.8 (11.7)	64.6 (12.7)	66.6 (11.8)	66.7 (11.4)	65.6 (11.2)	64.1 (11.4)	62.7 (11.6)
Diabetes duration, years, median (Q1,Q3)	5.0 (2.0,11.0)	2.0 (1.0,6.0)	4.0 (1.0,8.0)	7.0 (3.0,12.0)	9.0 (4.0,14.0)	9.0 (5.0,15.0)	8.0 (4.0,14.0)
BMI, mean (SD)	28.9 (5.04)	28.3 (4.93)	28.8 (4.92)	29.0 (4.95)	29.2 (5.08)	29.5 (5.39)	29.7 (5.71)
Systolic BP, mmHg, mean (SD)	145.9 (19.3)	143.7 (19.4)	145.5 (19.2)	146.6 (19.2)	146.9 (19.3)	146.9 (19.6)	145.9 (20.1)
Diastolic BP, mmHg, mean (SD)	79.8 (9.55)	79.3 (9.46)	79.4 (9.54)	79.6 (9.46)	80.2 (9.48)	80.9 (9.71)	81.5 (9.93)
Smoking registered at baseline or on any subsequent occasion							
Unknown	6,680 (8.05)	1,014 (9.26)	2,135 (8.31)	1,775 (7.95)	1,044 (7.35)	434 (7.23)	278 (7.25)
None registered	61,452 (74.0)	8,148 (74.4)	19,140 (74.5)	16,760 (75.0)	10,494 (73.9)	4,286 (71.4)	2,624 (68.4)
≥1 registration	14,889 (17.9)	1,791 (16.4)	4,410 (17.2)	3,806 (17.0)	2,667 (18.8)	1,283 (21.4)	932 (24.3)
CVD/medication registered at baseline or on any subsequent occasion							
Myocardial infarction	13,445 (16.2)	1,282 (11.7)	3,949 (15.4)	3,867 (17.3)	2,549 (17.9)	1,111 (18.5)	687 (17.9)
Atrial fibrillation	8,064 (9.71)	991 (9.05)	2,632 (10.25)	2,164 (9.69)	1,361 (9.58)	571 (9.51)	345 (9.0)
Valve disease	1,695 (2.04)	241 (2.20)	533 (2.08)	459 (2.05)	265 (1.87)	124 (2.07)	73 (1.90)
Ischaemic disease	22,345 (26.9)	2,232 (20.4)	6,642 (25.9)	6,444 (28.8)	4,150 (29.2)	1,761 (29.3)	1,116 (29.1)
Microalbuminuria							
Yes	8,079 (9.73)	740 (6.76)	2,043 (7.95)	2,350 (10.5)	1,656 (11.7)	790 (13.2)	500 (13.0)
No	47,377 (57.1)	6,282 (57.4)	14,780 (57.5)	12,799 (57.3)	8,087 (56.9)	3,331 (55.5)	2,098 (54.7)
Unknown	27,565 (33.2)	3,931 (35.9)	8,862 (34.5)	7,192 (32.2)	4,462 (31.4)	1,882 (31.4)	1,236 (32.2)
Antihypertensive drugs	66,445 (80.0)	8,249 (75.3)	20,623 (80.3)	18,225 (81.6)	11,529 (81.2)	4,826 (80.4)	2,993 (78.1)
Diabetes treatment							
Diet only	23,626 (28.5)	6,368 (58.1)	10,716 (41.7)	4,316 (19.3)	1,388 (9.77)	466 (7.76)	372 (9.7)
OHA only	31,567 (38.0)	2,824 (25.8)	9,809 (38.2)	9,974 (44.6)	5,586 (39.3)	2,096 (34.9)	1,278 (33.3)
Insulin ^a	27,828 (33.5)	1,761 (16.1)	5,160 (20.1)	8,051 (36.0)	7,231 (50.9)	3,441 (57.3)	2,184 (57.0)

Unless otherwise stated, values are numbers (percentage)

^aWith or without OHA

hospitalisation by category of HbA_{1c} also showed a similar risk pattern as in the other models (Table 3). The HR for patients with HbA_{1c} 7.0 to <8.0% (53 to <64 mmol/mol) compared with patients with HbA_{1c} 6.0 to <7.0% (42 to <53 mmol/mol) was 1.08 (95% CI 1.02, 1.15).

Discussion

In this nationwide study evaluating hospitalisation for heart failure in patients with type 2 diabetes, hyperglycaemia was an independent predictor of hospitalisation for heart

failure. However, when studied by category of HbA_{1c}, risk of heart-failure hospitalisation was only increased in patients with poor glycaemic control (HbA_{1c} >7.0% [53 mmol/mol]), and there was no further reduction in risk in patients with HbA_{1c} <6% (42 mmol/mol) compared with those with HbA_{1c} 6 to <7% (42 to <53 mmol/mol). Of the three models used, the model adjusting for the most possible confounders did in fact demonstrate an increased risk for hospitalisation for heart failure in patients with HbA_{1c} <6% (42 mmol/mol), but this was not confirmed in other models, or when analysing a primary diagnosis of heart failure separately. The incidence for heart-failure hospitalisation

Table 2 First hospitalisation for heart failure per 1,000 patient-years by updated HbA_{1c} categories with 95% CIs estimated using Poisson regression

Admission data	Updated mean HbA _{1c} category, % (mmol/mol)						
	All	<6.0 (<42)	6.0 to <7.0 (42 to <53)	7.0 to <8.0 (53 to <64)	8.0 to <9.0 (64 to <75)	9.0 to <10.0 (75 to <86)	≥10.0 (≥86)
Patient-years	593,314	58,996	187,240	189,288	103,563	37,347	16,879
No. of cases	10,969	816	3,021	3,659	2,198	839	436
Cases per 1,000 patient-years		13.8	16.1	19.3	21.2	22.5	25.8
95% CIs		(12.9, 14.8)	(15.6, 16.7)	(18.7, 20.0)	(20.5, 22.1)	(21.0, 24.0)	(23.5, 28.4)

was high (13% over 7 years) and increased with male sex, older age and longer diabetes duration.

In a recent meta-analysis comprising over 20,000 individuals with type 2 diabetes in the Action to Control Cardiovascular Risk in Diabetes (ACCORD), Action in Diabetes and Vascular Disease (ADVANCE), Veterans Affairs Diabetes Trial (VADT) and UK Prospective Diabetes Study (UKPDS) trials [9], no effect of intensive therapy in preventing heart failure was found. The follow-up period was 4–5 years, with the UKPDS being truncated at this time point to keep the study lengths consistent. In the ACCORD, ADVANCE and VADT intensive glycaemic control was directed towards achieving glucose levels close to normal levels. The current study further supports the premise that aiming for close to normal glucose levels might not lead to further risk reductions in preventing heart failure in type 2 diabetes, but supports the notion that achieving an HbA_{1c}

within the range 6–7% (42–53 mmol/mol) is beneficial. It is also worth noting that a beneficial effect might have been seen in clinical trials if data based on a time period longer than 4–5 years had been considered and that different glucose-lowering agents might have different preventive effects when achieving close to normal levels (e.g. with respect to hypoglycaemia), but this remains to be clarified. Recent clinical guidelines from the ADA and EASD generally recommend a target HbA_{1c} of below 7% (53 mmol/mol) in patients with type 2 diabetes and have recommended targets for certain subgroups of patients (e.g. HbA_{1c} 6.0–6.5% [42–48 mmol/mol] in patients with long expected survival) [17].

The current findings support the recommendation that HbA_{1c} targets of <7.0% (53 mmol/mol) should be set for patients with type 2 diabetes whereas targets below 6.0% (42 mmol/mol) should not be generally recommended.

Fig. 1 Incidence rates and 95% CIs for heart failure by updated mean HbA_{1c} category, calculated using a Poisson regression model adjusted for age, sex and updated mean HbA_{1c} (a) and, additionally, diabetes duration (b, c). (a) The incidences for men (squares) and for women (circles) are shown for age classes 61–65 years (white squares and circles) and 71–75 years (black squares and circles). (b) Incidences for

men aged 66–70 years with diabetes duration of 0–5 years (white squares) and 11–15 years (black squares). (c) Incidences for women aged 66–70 years with diabetes duration of 0–5 years (white circles) and 11–15 years (black circles). The corresponding HbA_{1c} categories in mmol/mol are <42, 42 to <53, 53 to <64, 64 to <75, 75 to <86 and ≥86, respectively

Table 3 Adjusted HRs for the development of heart failure and 95% CIs for updated HbA_{1c} categories examined using Cox regression

HbA _{1c} category		Model 1		Model 2		Model 3		Model 3, primary diagnosis		Model 3+LDL, HDL and subgroup analysis lipids	
%	mmol/mol	HR	95 % CI	HR	95 % CI	HR	95 % CI	HR	95 % CI	HR	95 % CI
<6.0 (reference)	<42 (reference)	1		1		1		1		1	
6.0 to <7.0	42 to <53	1.07	(0.98, 1.14)	1.01	(0.94, 1.10)	0.91	(0.84, 0.98)	0.95	(0.83, 1.08)	0.90	(0.81, 1.00)
7.0 to <8.0	53 to <64	1.27	(1.17, 1.37)	1.19	(1.10, 1.29)	0.99	(0.91, 1.07)	1.05	(0.92, 1.20)	0.97	(0.88, 1.08)
8.0 to <9.0	64 to <75	1.53	(1.40, 1.66)	1.42	(1.31, 1.54)	1.10	(1.01, 1.20)	1.22	(1.06, 1.41)	1.07	(0.95, 1.20)
9.0 to <10.0	75 to <86	1.85	(1.68, 2.04)	1.70	(1.54, 1.88)	1.27	(1.15, 1.41)	1.50	(1.27, 1.77)	1.28	(1.12, 1.46)
≥10.0	≥86	2.47	(2.09, 2.65)	2.16	(1.92, 2.43)	1.71	(1.51, 1.93)	2.40	(1.99, 2.89)	1.90	(1.61, 2.24)

Model 1, adjusted for age, sex and diabetes duration

Model 2, additionally adjusted for smoking, BMI, systolic BP and diastolic BP

Model 3, as model 2, additionally adjusted for myocardial infarction, atrial fibrillation, ischaemic heart disease, heart valve surgery, glucose-lowering therapy, antihypertensive medication and microalbuminuria

Primary diagnosis, 76,164 patients, 4,112 cases of heart failure

Subgroup analysis lipids, 63,986 patients, 6,847 cases of heart failure

In three previous observational studies, an increased risk of hospitalisation for heart failure was found with higher HbA_{1c} for patients with type 2 diabetes [16, 18, 19]. In two of these studies heart failure was analysed in relation to category of HbA_{1c}; however, these studies included fewer patient-years of follow-up and numbers of events [16, 18], making conclusive analyses more difficult for subgroups of patients categorised by HbA_{1c}. In type 1 diabetes a recent study showed a very strong relationship between HbA_{1c} and the incidence of heart failure, with a 30% increase in risk for each percentage unit (10 mmol/mol) increase in HbA_{1c}, from the same register as in the present study [13]. This can be compared with the 12% increased risk of heart failure with each percentage unit (10 mmol/mol) increase in HbA_{1c} found in this study of patients with type 2 diabetes. Hence, the relationship between HbA_{1c} and hospitalisation for heart failure in type 1 diabetes seems to be much stronger than in type 2 diabetes. Although only speculative, the reason for this relationship may be due to longer exposure to hyperglycaemia among patients with type 1 diabetes than in those with type 2 diabetes. Since HbA_{1c} levels are often relatively stable in patients with diabetes [20], it is likely that those patients with type 1 diabetes who have poor glycaemic control have been exposed to pronounced dysglycaemia over a much longer time period, possibly adding to the risk of heart failure. Another possible explanation could be that risk factors such as hypertension and obesity are more common in type 2 diabetes, therefore reducing the relative influence of hyperglycaemia for risk of heart failure.

The current findings contradict two studies that examined HbA_{1c} as a risk factor for mortality in patients with diabetes

in general and in patients with diabetes and heart failure, respectively, which both showed a U-shaped relationship, with the lowest risk at a median HbA_{1c} of 7.5% (58 mmol/mol) and in the interval 7.1–7.8% (54–62 mmol/mol), respectively [21, 22]. However, a previous analysis from the Swedish NDR of type 2 diabetes found no U- or J-shaped relationship for fatal or non-fatal myocardial infarction or for total mortality but a progressively lower risk with HbA_{1c} <7% (53 mmol/mol) [10]. Analyses of the association between HbA_{1c} and diabetic complications in the UKPDS also showed no indication of increased risks of diabetic complications for patients with low HbA_{1c} levels [16]. The discussion about whether obtaining glycaemic control close to normal levels is associated with increased risk of mortality originates from the ACCORD trial where the trial was stopped due to more deaths occurring in patients undergoing intensive therapy aimed at obtaining close to normal HbA_{1c} levels [23, 24]. However, post hoc analyses of the ACCORD trial have shown that the excess mortality in intensively treated patients was observed in those patients with high HbA_{1c} levels, but not in those obtaining close to normal glycaemic control, indicating that some factor other than the glycaemic control per se contributed to the excess mortality in patients receiving intensive therapy [25]. Moreover, in the ADVANCE trial, reaching similar HbA_{1c} levels as in the ACCORD trial, intensive therapy had no harmful effect with respect to mortality or cardiovascular disease and a beneficial effect on renal complications was found, also indicating that HbA_{1c} levels per se close to normal levels do not contribute to increased risks of mortality or complications [26].

Limitations of the present study include the unavailability of data in patients who had heart failure but who were not

hospitalised. The non-randomised design implies that it is unknown whether good-to-moderate glycaemic control prevents hospitalisation for heart failure, although the reduced risks shown seem to indicate this. Strengths of this study include the population-based design, large size and long follow-up, thus enabling accurate risk estimations. Further, detailed information on other heart-failure risk factors were retrieved, some of which have not been adjusted for in previous studies of glycaemic control and heart failure [16, 18, 19]. Another strength is that, for the first time, the same analyses have been performed in two large cohorts of type 1 and type 2 diabetes from the same background population and same follow-up period [13], making it possible to compare the results between type 1 and type 2 diabetes.

In conclusion, poor glycaemic control ($\text{HbA}_{1c} > 7\%$ [53 mmol/mol]) is an independent risk factor for heart-failure hospitalisation in patients with type 2 diabetes, whereas no further risk reductions seem to exist at $\text{HbA}_{1c} < 6\%$ (42 mmol/mol). Further, in the present era, the incidence of hospitalisation for heart failure remains high among patients with type 2 diabetes. Men, older patients and those with longer duration of type 2 diabetes have an increased incidence of heart failure, and hyperglycaemia is a stronger risk factor for heart-failure hospitalisation in type 1 than type 2 diabetes.

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Contribution statement ML, IB, SG, AS, and AR designed the study protocol. IB and ML performed literature reviews. ML and MO designed the statistical analysis and MO performed the analysis. All authors provided support in the interpretation of results. ML performed the main writing of the manuscript and all authors reviewed the manuscript.

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