

Glycemic Control and Heart Failure Among Adult Patients With Diabetes

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Background—Glycemic control is associated with microvascular events, but its effect on the risk of heart failure is not well understood. We examined the association between hemoglobin (Hb) A_{1c} and the risk of heart failure hospitalization and/or death in a population-based sample of adult patients with diabetes and assessed whether this association differed by patient sex, heart failure pathogenesis, and hypertension status.

Methods and Results—A cohort design was used with baseline between January 1, 1995, and June 30, 1996, and follow-up through December 31, 1997 (median 2.2 years). Participants were 25 958 men and 22 900 women with (predominantly type 2) diabetes, ≥ 19 years old, with no known history of heart failure. There were a total of 935 events (516 among men; 419 among women). After adjustment for age, sex, race/ethnicity, education level, cigarette smoking, alcohol consumption, hypertension, obesity, use of β -blockers and ACE inhibitors, type and duration of diabetes, and incidence of interim myocardial infarction, each 1% increase in Hb A_{1c} was associated with an 8% increased risk of heart failure (95% CI 5% to 12%). An Hb A_{1c} ≥ 10 , relative to Hb A_{1c} < 7 , was associated with 1.56-fold (95% CI 1.26 to 1.93) greater risk of heart failure. Although the association was stronger in men than in women, no differences existed by heart failure pathogenesis or hypertension status.

Conclusions—These results confirm previous evidence that poor glycemic control may be associated with an increased risk of heart failure among adult patients with diabetes. (*Circulation*. 2001;103:2668-2673.)

Key Words: heart failure ■ diabetes mellitus ■ glycemia ■ hemoglobin

The level of hemoglobin A_{1c} (Hb A_{1c}) is an index of metabolic control of diabetes.¹ Elevated levels of Hb A_{1c} indicate poor metabolic control and are associated with microvascular and neuropathic complications.^{2,3} Furthermore, lowering Hb A_{1c} effectively delays the onset and slows the progression of these complications in patients with type 1⁴ and type 2^{5,6} diabetes.

Poor glycemic control may also predict macrovascular complications, including coronary heart disease among patients with type 2 diabetes.^{7,8} Furthermore, recent evidence from the UK Prospective Diabetes Study (UKPDS), a clinical trial sample, suggests that glycemic control is associated with increased risk of heart failure among patients with type 2 diabetes.⁹ Heart failure is a chronic condition closely linked to diabetes¹⁰ whose prevalence is increasing in the United States.¹¹

The aims of this study were 3-fold: first, to investigate the association between Hb A_{1c} levels and heart failure incidence in a large, population-based sample of adult patients with diabetes; second, to examine whether the association is

independent of established coronary and diabetes-related factors; and third, to ascertain whether the association of interest differed by patient sex, heart failure pathogenesis (ie, prior history of ischemic event[s]), and presence of hypertension.

Methods

Study Cohort

The Kaiser Permanente Medical Care Program of Northern California maintains a Diabetes Registry that includes all members of the health plan with diabetes mellitus. The Registry started in 1994 by identifying patients with diabetes mellitus from multiple automated databases and has a false-positive rate of 2.4%.¹² During 1994 through mid-1997, 94 024 Diabetes Registry members ≥ 19 years old received a health survey that included questions about behavioral, demographic, and clinical data.^{12,13} Obesity was defined as a body mass index ≥ 30 kg/m². Hypertension was ascertained by self-report. LDL cholesterol was estimated by the Friedewald equation,¹⁴ and HDL cholesterol was measured by an enzymatic colorimetric test (PEG-modified enzyme and sulfated cyclodextrin). Hb A_{1c} levels were measured from January 1, 1995, through October 31, 1995, by high-performance liquid chromatography (Diamat, Biorad Laborato-

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ries) and by turbidimetric inhibition immunoassay (Boehringer Mannheim) between November 1, 1995, and June 30, 1996. The 2 methods were highly correlated ($r=0.98$).¹⁵

After exclusion of 3722 known false-positives, 83% [74 993/ (94 024–3722)] of noninstitutionalized, living, active Diabetes Registry members responded to the survey. The study cohort consisted of a subset of 69% of survey responders ($n=51\ 680$) who had ≥ 1 measurement of Hb A_{1c} between January 1, 1995, and June 30, 1996. For patients with >1 measurement of Hb A_{1c} in that period, only the last measurement was used. Those who had a previous hospitalization with primary or secondary diagnosis of heart failure during the 5 years before baseline were excluded from the analysis ($n=2822$). The final sample for analysis comprised 48 858 adult patients with diabetes (25 958 men and 22 900 women). Follow-up for heart failure hospitalizations and for mortality from any cause was complete through December 31, 1997 (median 2.2 years; range <1 year to 2.9 years). The study protocol was approved by the Kaiser Foundation Institutional Review Board.

Study End Point

The primary study end point was a composite of hospitalization for heart failure or death with heart failure as underlying cause. Incident hospitalizations were captured by use of automated hospital primary discharge diagnosis of heart failure (*International Classification of Diseases, 9th revision* [ICD-9] codes 428.x) or hypertensive heart disease with heart failure (402.01, 402.11, 402.91) in all health plan hospitals. Mortality from any cause, including death by heart failure (same codes as hospitalizations), was ascertained by use of the California Automated Mortality Linkage System.¹⁶

Previous ischemic event(s) during the 5 years before baseline were ascertained through a search of hospitalizations and/or outpatient diagnoses for ischemic heart disease (410.x to 414.x) and/or ischemic stroke (433.x to 438.x) and/or revascularization procedures, including coronary artery bypass graft surgery (36.1x), percutaneous transluminal coronary angioplasty (36.0x), and carotid endarterectomy (38.12).

To determine the validity of the primary discharge diagnosis of heart failure in our hospitalization database, we randomly selected 200 hospital charts of study participants and determined the extent to which these cases met major and minor Framingham criteria for heart failure.¹⁷ The most frequently encountered major criteria for heart failure were rales (86.5%), radiographic cardiomegaly (73%), and acute pulmonary edema (55%), and the most frequent minor criteria were bilateral ankle edema (77.5%) and dyspnea on ordinary exertion (96%). Overall, 92.5% of cases met ≥ 2 major and 1 minor heart failure criteria; 89% met ≥ 1 major and 2 minor criteria; and 97% met either of the 2 definitions above. Thus, the positive predictive value of heart failure ascertainment by hospital discharge codes was 97%, and the false-positive rate was 3%. Because we did not review charts of patients without heart failure, the sensitivity, specificity, and negative predictive value of the ascertainment method by discharge diagnosis codes could not be determined.

Because atherosclerotic cardiovascular disease is a common cause of heart failure, we also determined the extent to which hospitalization for heart failure was accompanied by either unstable angina (411.1, 411.81, and 411.89) or acute myocardial infarction (410.x).

Statistical Methods

Poisson regression was used to estimate sex-specific, age-adjusted incidence rates of heart failure (per 1000 person-years) according to the Hb A_{1c} categories used before: $<7\%$, 7% to $<8\%$, 8% to $<9\%$, 9% to $<10\%$, and $\geq 10\%$.⁹ Follow-up time was calculated for each person from baseline to the time of heart failure hospitalization (2%), death (5%), termination of health plan membership (9%), or closing date (December 31, 1997) (84%). Estimation of relative risks associated with categories of Hb A_{1c} (to assess threshold effects and nonlinear associations) and for a 1 SD linear increase in Hb A_{1c} and control for potential confounders were done by sequential Cox proportional-hazards

models.¹⁸ Four models were considered: Model 1 was age- and sex-adjusted. Model 2 was adjusted for age, sex, race/ethnicity (black, Hispanic, Asian/Pacific Islander, and other/unknown, versus white), level of education (less than high school, some college, and unknown, versus college education or higher), cigarette smoking (former, current, unknown, versus never), alcohol consumption (never, former, occasional, light, heavy, and unknown, versus moderate), self-reported hypertension, obesity, and cardioprotective medication use at baseline (ACE inhibitor and β -blockers). Adjustment for ACE inhibitors was performed because of trials among patients with heart failure of left ventricular dysfunction demonstrating reductions in the risk of death, myocardial infarction, or hospital admission for heart failure.^{19–22} Adjustment for β -blockers was done on the basis of recent trials showing that use of β -blockers in addition to standard therapy improved left ventricular function, reduced hospitalizations, and in the case of bisoprolol, long-acting metoprolol, and carvedilol, improved survival in patients with chronic heart failure.^{23,24} No adjustment was performed for LDL or HDL cholesterol because of the large proportion of missing data on these variables. However, we evaluated the effect of lipid adjustment in a subset of cohort members with complete LDL and HDL cholesterol values. Model 3 included additional covariates for diabetes type/treatment (type 1, type 2 on oral hypoglycemic agents, type 2 on insulin, and unknown type/treatment, versus type 2 on diet) and duration of diabetes (5 to 9 years, ≥ 10 years, and unknown, versus <5 years). To ascertain the degree to which the increased risk of heart failure associated with poor glycemic control might be due to an interim cardiac event, model 4 included a dichotomous variable that represented incidence of myocardial infarction during follow-up.

Formal tests for interaction in the Cox models were conducted to assess whether the relationship between Hb A_{1c} (as a continuous variable) and heart failure risk differed by patient sex, history of ischemic event(s), and presence of hypertension. Only the interaction with patient sex was statistically significant ($P=0.03$), so results stratifying by patient sex are also presented. All statistical analyses were performed with SAS 6.11 (SAS Institute Inc).

Results

The mean age of the cohort was 58 years; 52% of men and 49% of women were white (Table 1). Men had a slightly higher education level and a greater proportion of former cigarette smokers than women. More women than men reported never consuming alcohol, and more men than women reported either moderate or heavy alcohol consumption. The distribution of diabetes type and treatment and the duration of diabetes were similar between sexes.

The distribution of Hb A_{1c} levels was comparable in men and women: $\approx 22\%$ were in poor glycemic control (ie, Hb A_{1c} $\geq 10\%$). Women reported more hypertension and obesity and had a higher prevalence of high LDL than men, whereas HDL cholesterol was lower in men. Approximately 26% and 9% used ACE inhibitors and β -blockers, respectively. No evidence was found that those in poor glycemic control had greater ACE inhibitor or β -blocker use (data not shown). The number of nonfatal myocardial infarctions during follow-up, as ascertained by primary hospital discharge diagnosis codes 410.x, was 1103 (2.3%), 682 in men (2.6%) and 421 in women (1.8%).

After a median of 2.2 years of follow-up, 516 and 419 incident heart failure events were documented in men and women, respectively. In men, there were 501 hospitalizations with nonfatal heart failure, 9 hospitalizations with fatal heart failure, and 6 deaths by heart failure without hospitalization.

TABLE 1. Baseline Cohort Characteristics

Characteristics	Men (n=25 958)	Women (n=22 900)
Age, y	58±13	58±13
Race/ethnicity		
White	52	49
Black	9	12
Hispanic	11	12
Asian and Pacific Islander	11	11
Other and unknown	17	16
Level of education		
<High school	31	39
Some college	24	25
≥College	23	15
Unknown	22	20
Cigarette smoking		
Never	30	47
Former	38	24
Current	9	8
Unknown	23	20
Alcohol consumption		
Never	9	24
Former	21	21
≤1 drink/mo	17	20
<7 drinks/wk	20	9
7–19 drinks/wk	7	2
≥20 drinks/wk	2	0
Unknown	24	23
Diabetes/treatment type		
Type 1	4	5
Type 2 on insulin	15	19
Type 2 on oral hypoglycemic agents	45	41
Type 2 on diet	15	15
Unknown	20	19
Duration of diabetes, y	9±10	9±10
0–5	35	34
5–9	18	17
≥10	28	31
Unknown	19	18
Hemoglobin A _{1c} , %	8.5±1.9	8.6±1.9
<7	23	20
7 to <8	22	22
8 to <9	18	19
9 to <10	15	16
≥10	22	23
Hypertension		
No	28	25
Yes	40	44
Missing	32	31
Obesity		
No	50	40
Yes	27	37

TABLE 1. Continued

Characteristics	Men (n=25 958)	Women (n=22 900)
Missing	23	23
Serum LDL, mmol/L	3.60±0.92	3.81±1.03
<4.14	22	17
≥4.14	7	10
Missing	71	73
Serum HDL, mmol/L	0.88±0.23	1.09±0.31
<0.91 in men, <1.16 in women	24	24
≥0.91 in men, ≥1.16 in women	17	14
Missing	59	62
β-Blockers	9	9
ACE inhibitors	27	26
Interim myocardial infarction, incidence per 100	2.6	1.8

Values are mean±SD or percent.

In women, there were 411 hospitalizations with nonfatal heart failure, 3 hospitalizations with fatal heart failure, and 5 deaths by heart failure without hospitalization. Of the 924 hospitalizations with heart failure as the principal diagnosis, 825 (89%) did not have unstable angina or acute myocardial infarction as secondary diagnosis, and 99 (11%) had either unstable angina or acute myocardial infarction as secondary diagnosis.

Age-adjusted incidence rates of heart failure increased with increasing levels of Hb A_{1c} in a monotonic fashion in both men (*P* for linear trend=0.0001) and women (*P* for linear trend=0.009) (Table 2). Only 2% (11/516) of incident heart failure events in men and 2% (10/419) in women occurred among patients with known type 1 diabetes.

After adjustment for age and sex, each 1% increase in Hb A_{1c} was associated with a 12% increased risk of heart failure (95% CI 8% to 16%) (Table 3). Also in age- and sex-adjusted analysis, a concentration of Hb A_{1c} ≥10, relative to Hb A_{1c} <7, was associated with a 1.83-fold (95% CI 1.48 to 2.25) greater risk of heart failure. Further adjustment for race/ethnicity, education level, cigarette smoking, alcohol consumption, hypertension, obesity, ACE inhibitors, β-blockers, diabetes type and duration, and interim myocardial infarction attenuated but did not explain the association.

Analysis stratifying by patient sex indicated that the association was stronger in men than in women (*P* for interaction=0.03) (Table 3). In the fully adjusted analysis (model 4), the relative risk associated with a 1% increase in Hb A_{1c} concentration was 1.12 (95% CI 1.07 to 1.18) in men and 1.04 (95% CI 0.98 to 1.09) in women; a concentration of Hb A_{1c} ≥10, relative to Hb A_{1c} <7, was associated with a 1.8-fold increased heart failure risk in men compared with a 1.3-fold increased heart failure risk in women. No significant interactions were found between Hb A_{1c} and having a history of ischemic event(s) (*P*=0.52) or between Hb A_{1c} and hypertension status (*P*=0.89).

Adjustment for LDL and HDL cholesterol among those with complete lipid information (n=13 806; 252 events)

TABLE 2. Number of Events, Persons, Person-Years, and Age-Adjusted Rates per 1000 Person-Years of Heart Failure Hospitalization and/or Death by Hemoglobin A_{1c} Concentration

Hemoglobin A _{1c} , %	All (n=48 858)			Men (n=25 958)			Women (n=22 900)		
	n/N	P-Y	Rate per 10 ³ P-Y (95% CI)	n/N	P-Y	Rate per 10 ³ P-Y (95% CI)	n/N	P-Y	Rate per 10 ³ P-Y (95% CI)
<7	145/10 631	21 963	4.5 (2.9–7.0)	81/5969	12 329	4.5 (2.5–8.2)	64/4662	9634	4.5 (2.4–8.6)
7 to <8	197/10 692	23 417	5.8 (3.8–8.9)	107/5653	12 379	5.9 (3.2–10.6)	90/5039	11 038	5.6 (3.0–10.5)
8 to <9	181/9238	20 808	6.3 (4.1–9.7)	93/4847	10 926	6.0 (3.3–10.9)	88/4391	9882	6.6 (3.5–12.2)
9 to <10	172/7354	16 576	8.3 (5.5–12.6)	100/3817	8528	9.2 (5.2–16.4)	72/3537	8048	7.2 (3.9–13.4)
≥10	240/10 943	23 594	9.2 (6.2–13.8)	135/5672	12 059	10.3 (5.9–17.8)	105/5271	11 536	8.0 (4.4–14.5)
<i>P</i> for linear trend			0.0001			0.0001			0.009

n/N indicates events/persons; P-Y, person-years.

showed no attenuation of risk (data not shown). Furthermore, the predictive strength of Hb A_{1c} was maintained when the analysis was restricted to the 825 hospitalizations in which heart failure was the principal diagnosis and there was no secondary diagnosis of unstable angina or acute myocardial infarction (RR per 1% increase in Hb A_{1c} 1.09 [95% CI 1.05 to 1.13] and RR of Hb A_{1c} ≥10% versus <7% 1.61 [95% CI 1.29 to 2.03]).

Discussion

This study suggests an independent, graded association between glycemic control and incidence of hospitalization and/or death due to heart failure among adult patients with

diabetes and supports the recently published results in the UKPDS 35.⁹ Although the association was stronger in men than in women, we found a monotonic risk gradient in both sexes, with no evidence of a threshold level. The association persisted after adjustment for cardiovascular risk factors, use of β-blockers and ACE inhibitors at baseline, diabetes-related factors, and development of interim myocardial infarction during follow-up and was maintained in heart failure hospitalizations in which there was no secondary diagnosis of unstable angina or myocardial infarction.

Our findings are consistent with 2 interpretations. First, poor glycemic control may simply be a marker of worse

TABLE 3. Age-, Sex-, and Multivariate-Adjusted Association Between Hemoglobin A_{1c} and Heart Failure Hospitalization and/or Death

Hemoglobin A _{1c} , %	Model 1	Model 2	Model 3	Model 4
All (n=48 858; 935 events)				
<7	1	1	1	1
7 to <8	1.20 (0.97–1.48)	1.21 (0.98–1.50)	1.15 (0.92–1.42)	1.15 (0.93–1.43)
8 to <9	1.25 (1.01–1.56)	1.26 (1.01–1.57)	1.12 (0.89–1.39)	1.10 (0.88–1.38)
9 to <10	1.64 (1.31–2.04)	1.62 (1.30–2.03)	1.42 (1.13–1.78)	1.39 (1.11–1.74)
≥10	1.83 (1.48–2.25)	1.80 (1.45–2.22)	1.57 (1.27–1.95)	1.56 (1.26–1.93)
Per 1% difference	1.12 (1.08–1.16)	1.11 (1.07–1.15)	1.09 (1.05–1.13)	1.08 (1.05–1.12)
Men (n=25 958; 516 events)				
<7	1	1	1	1
7 to <8	1.22 (0.92–1.63)	1.24 (0.93–1.65)	1.17 (0.87–1.56)	1.18 (0.88–1.58)
8 to <9	1.23 (0.91–1.65)	1.23 (0.91–1.65)	1.08 (0.80–1.47)	1.07 (0.79–1.46)
9 to <10	1.85 (1.38–2.48)	1.85 (1.38–2.49)	1.62 (1.20–2.19)	1.61 (1.19–2.18)
≥10	2.11 (1.60–2.79)	2.06 (1.56–2.73)	1.79 (1.35–2.39)	1.80 (1.35–2.40)
Per 1% difference	1.16 (1.11–1.21)	1.15 (1.09–1.20)	1.12 (1.07–1.18)	1.12 (1.07–1.18)
Women (n=22 900; 419 events)				
<7	1	1	1	1
7 to <8	1.15 (0.84–1.59)	1.18 (0.86–1.63)	1.12 (0.81–1.54)	1.11 (0.80–1.53)
8 to <9	1.27 (0.92–1.75)	1.30 (0.94–1.80)	1.16 (0.83–1.61)	1.13 (0.81–1.57)
9 to <10	1.39 (0.99–1.95)	1.37 (0.98–1.93)	1.20 (0.85–1.69)	1.15 (0.81–1.63)
≥10	1.53 (1.11–2.09)	1.54 (1.12–2.11)	1.36 (0.98–1.87)	1.32 (0.95–1.82)
Per 1% difference	1.07 (1.02–1.13)	1.06 (1.01–1.12)	1.05 (0.99–1.10)	1.04 (0.98–1.09)

Values are hazard ratio (95% CI). See methods for covariates included in each model.

patient compliance with blood pressure and lipid medication and of less rigorous physician care. Second, poor glycemic control may be a true risk factor for heart failure.

Poor glycemic control and associated hyperglycemia may be causally related to the development of heart failure by 2 mechanisms: through promotion of atherosclerosis and ensuing coronary artery disease, and through development of a specific diabetic cardiomyopathy (ie, direct damage to the heart muscle).

Hyperglycemia may be linked to atherogenesis through modification of LDL lipoproteins by advanced glycosylation end products,²⁵ endothelial dysfunction,²⁶ increased plasminogen activator inhibitor 1, von Willebrand factor and platelet aggregation,²⁷ and dyslipidemia with increased production of VLDL, low plasma HDL, and high plasma levels of small, dense LDL.²⁸

Clinical-pathological work has described a specific form of cardiomyopathy in patients with diabetes, thought to be caused by microangiopathy²⁹ and by cellular changes in calcium transport and fatty acid metabolism.³⁰ Also, several studies have demonstrated abnormalities of left ventricular mechanical function (primarily diastolic) in patients with diabetes without known coronary artery disease.³¹

Our study has several limitations. First, the follow-up time was relatively short, but this was compensated by a large sample size. Because the progression to clinical heart failure may be longer than 2 years, it is likely that some diabetic patients in the study had preclinical heart failure at baseline. The likelihood of bias due to disease at baseline was minimized, however, by the exclusion of patients with documented heart failure up to 5 years before baseline. Second, because of the small number of events among them, we were unable to make inferences about the association between glycemic control and heart failure among patients with type 1 diabetes. Third, because the ascertainment of outcome was based on hospitalization and/or death, less severe or subclinical heart failure (ie, not requiring hospitalization or showing asymptomatic left ventricular dysfunction) were not considered. Fourth, the analysis was based on a single measurement of Hb A_{1c}, although Hb A_{1c} is indicative of the time-averaged blood glucose concentration over the past 3 months.¹ Fifth, we were unable to characterize the severity of heart failure in terms of left ventricular function (ie, ejection fraction) or functional status (ie, New York Heart Association class), because this information was not available in our clinical databases. Finally, the proportion of participants with missing data for lipid values was quite high; nonetheless, adjustment for LDL and HDL cholesterol in subset analysis had only a marginal effect.

Our findings may have important clinical and public health implications. First, although it is yet to be determined by clinical trials, our results suggest that tight glycemic control may potentially reduce the incidence of heart failure. Second, because no Hb A_{1c} threshold could be identified, our data suggest that it might be desirable to achieve levels of glycemia as close to the normoglycemic range as possible (ie, Hb A_{1c} <7%). This potential benefit of tight metabolic control of diabetes should be weighed against existing barriers to

glycemic control, including fear of hypoglycemia and, in women, weight gain.³²

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