The Incidence of Congestive Heart Failure in Type 2 Diabetes

An update

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OBJECTIVE — The aims of this study were to update previous estimates of the congestive heart failure (CHF) incidence rate in patients with type 2 diabetes, compare it with an age- and sex-matched nondiabetic group, and describe risk factors for developing CHF in diabetic patients over 6 years of follow-up.

RESEARCH DESIGN AND METHODS — We performed a retrospective cohort study of 8,231 patients with type 2 diabetes and 8,845 nondiabetic patients of similar age and sex who did not have CHF as of 1 January 1997, following them for up to 72 months to estimate the CHF incidence rate. In the diabetic cohort, we constructed a Cox regression model to identify risk factors for CHF development.

RESULTS — Patients with diabetes were much more likely to develop CHF than patients without diabetes (incidence rate 30.9 vs. 12.4 cases per 1,000 person-years, rate ratio 2.5, 95% CI 2.3–2.7). The difference in CHF development rates between persons with and without diabetes was much greater in younger age-groups. In addition to age and ischemic heart disease, poorer glycemic control (hazard ratio 1.32 per percentage point of HbA_{1c}) and greater BMI (1.12 per 2.5 units of BMI) were important predictors of CHF development.

CONCLUSIONS — The CHF incidence rate in type 2 diabetes may be much greater than previously believed. Our multivariate results emphasize the importance of controlling modifiable risk factors for CHF, namely hyperglycemia, elevated blood pressure, and obesity. Younger patients may benefit most from risk factor modification.

Diabetes Care 27:1879–1884, 2004

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Received for publication 26 January 2004 and accepted in revised form 19 April 2004.

G.A.N., C.M.G., and J.B.B. receive funding from several firms that manufacture drugs marketed to treat diabetes (GlaxoSmithKline, Eli Lilly, and Wyeth) and may, in the future, receive support from other companies in these markets. All of this research group's contracts explicitly specify their right to publish any and all research results arising from commercial funding, without approval from the funder.

This research group's study site, Kaiser Permanente Northwest Region (KPNW), is a nonprofit group-model prepaid medical care organization. The Center for Health Research (CHR) is an affiliated not-for-profit organization dedicated to producing public-domain research in the public interest. The CHR is scientifically and professionally independent of the larger Kaiser Permanente organization. Apart from an annual charitable contribution from KPNW, CHR scientists set their own research agendas and secure their research funding from external sources, usually the National Institutes of Health. KPNW neither reviews nor approves the publications of CHR scientists.

Abbreviations: CHF, congestive heart failure; ESRD, end-stage renal disease; ICD-9-CM, International Classification of Diseases, 9th Revision, Clinical Modification; KPNW, Kaiser Permanente Northwest; UKPDS, U.K. Prospective Diabetes Study.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

As the leading cause of hospitalization for individuals aged 65 years and older (1), congestive heart failure (CHF) is emerging as a major public health concern. The CHF problem is magnified in individuals with diabetes, in whom incidence rates are two to five times greater than those in the general population (2–8). Nonetheless, heart failure has recently been termed "the frequent, forgotten, and often fatal complication of diabetes" (9), in part because estimates of the association between diabetes and CHF have been established primarily in studies that include diabetes as a potential risk factor in general populations (2,5,7,10).

To date, four studies have provided estimates of CHF incidence in large, exclusively diabetic populations. The U.K. Prospective Diabetes Study (UKPDS) reported heart failure incidence rates of 2.3–11.9 per 1,000 patient-years over 10 years of follow-up. This estimate was based on 4,585 subjects with newly diagnosed diabetes younger than 65 years at diagnosis (mean age 53 years)—a population not representative of all individuals with diabetes (11). The Type 2 Diabetes, Hypertension, Cardiovascular Events and Ramipril study examined the incidence of CHF requiring hospitalization in 4,912 subjects with diabetes (mean age 71 years), estimating an annual incidence rate of 1.0% (12). This study excluded patients treated with insulin or ACE inhibitors. Another recent study of heart failure in a population of more than 48,000 subjects with diabetes (mean age 58 years) found incidence rates of 4.5–9.2 per 1,000 person-years (13). However, the outcome measured was hospitalizations for which CHF was the primary diagnosis, thereby excluding less severe cases. Also, the study had a relatively short follow-up period (median 2.2 years). Finally, we recently used ambulatory and discharge diagnoses to estimate substantially higher CHF incidence (33 cases per 1,000 subjects) in a population of 8,460 persons with diabetes (mean age

63 years) followed for a maximum of 30 months (3).

An additional 42 months of follow-up are now available to augment our previously published 30-month analysis, thus providing estimates of CHF incidence over 6 years of follow-up. We also explore risk factors that predict CHF development in diabetes.

RESEARCH DESIGN AND METHODS

— The study population consisted of 9,591 individuals in whom type 2 diabetes was diagnosed before 1 January 1997 and an age- and a sex-matched comparison group of the same number of individuals without diagnosed diabetes. All subjects were members of Kaiser Permanente Northwest (KPNW), a not-for-profit group-model health maintenance organization serving ~450,000 members in the vicinity of Portland, Oregon. Individuals in whom CHF was diagnosed as of 1 January 1997 were excluded from the analysis (1,131 subjects with diabetes and 435 subjects without diabetes). We also excluded 229 diabetic subjects who were determined not to have diabetes after review by an endocrinologist and 311 nondiabetic subjects in whom diabetes developed during the follow-up period. These exclusions were applied after the initial one-to-one age and sex matching, so the final study population included 8,231 diabetic patients and 8,845 nondiabetic patients. These 17,076 patients were followed from 1 January 1997 through 31 December 2002 or until they experienced CHF, died, or left the health plan, whichever came earlier.

Data sources and variables

KPNW maintains comprehensive electronic health care utilization data on all its members. The electronic medical record, in use since 1996, allows the attending clinician to record as many as 20 International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) coded diagnoses at each ambulatory patient contact and up to nine discharge diagnoses for inpatient hospital admissions. An electronic problem list, also coded in ICD-9-CM, is available to the clinician at each contact. In addition, all KPNW laboratory tests are performed by a single regional laboratory, and the results are stored in a searchable electronic database. A pharmacy is located in each medical office, and most members have a pharmacy benefit, helping to ensure complete capture of pharmaceutical dispenses in the KPNW pharmacy database.

We defined CHF as the first occurring inpatient or outpatient diagnosis of CHF. However, if the diagnosis occurred solely in an outpatient setting, we required that the diagnosis be coded in at least two separate occurrences. KPNW clinicians have access to online guidelines for assessment of heart failure to assist in making the diagnosis. The guidelines state that when symptoms (e.g., orthopnea, dyspnea, paroxysmal nocturnal dyspnea, jugular venous distension, or edema) suggest heart failure, a careful examination in conjunction with a chest x-ray and electrocardiography is indicated. Heart failure is diagnosed when there is evidence of valvular dysfunction, systolic or diastolic dysfunction, or pericardial disease. More than 90% of subjects with CHF had undergone echocardiography, electrocardiography, or chest X-ray just before the diagnosis, ensuring that most of our patients probably had definitive CHF (3). The closed group-model structure of KPNW also encourages primary care clinicians to consult both formally and informally with cardiac specialists. Approximately 35% of patients with CHF were seen by cardiologists.

We also used the medical records to determine the presence of ischemic heart disease (ICD-9-CM codes 410.xx–414.xx). Blood pressure and body weight, measured at most outpatient contacts, were averaged over the observation period.

Antihyperglycemic therapy was identified at baseline from pharmacy dispensings. From laboratory data, we identified subjects with microalbuminuria, defined as an albumin excretion rate between 30 and 300 mg/day, or gross proteinuria (albumin excretion rate >300 mg/day or serum creatinine >1.5 mg/dl or 24-h urine protein >165 mg/day). End-stage renal disease (ESRD) was defined as referral for kidney dialysis or transplantation. We did not allow subjects to appear in more than one of the four stages of renal disease (none, microalbuminuria, proteinuria, or ESRD). We also extracted and averaged all HbA_{1c} values (Diamat high-performance liquid chromatography assay; Bio-Rad, Hercules, CA) available during the observation period (1997–2002 or when patients experienced CHF, died, or disenrolled).

Analytic methods

All analyses were performed using SAS statistical software (SAS Institute, Cary, NC). Bivariate associations were tested using Student's *t* test for continuous measures and the χ^2 statistic for dichotomous variables. We used the Kaplan-Meier procedure to estimate the survival curves and Cox regression analysis to calculate the hazard ratios for predictors of incident CHF. To estimate the potential effect of obesity on CHF incidence, we limited the Cox regression analysis to the 79% of subjects (n = 6,496) for whom BMI values were available. Because of the high correlation between systolic and diastolic blood pressures, we used only diastolic blood pressure in the model because of its greater predictive power.

RESULTS

— The demographic characteristics of the diabetic cohort and the nondiabetic comparison group stratified by incident CHF are shown in Table 1. There were no statistically significant differences between the two groups in age or sex distribution. In both groups, subjects in whom CHF developed were significantly older than those who did not develop CHF. Patients with diabetes in whom CHF developed were, on average, 5.5 years younger than the nondiabetic subjects in whom CHF developed ($P <$ 0.001). Because follow-up was terminated after CHF was diagnosed, length of follow-up is longer for those who remained free of CHF but was very similar overall for the diabetic and nondiabetic groups.

Figure 1 displays Kaplan-Meier curves of CHF incidence for the diabetic and nondiabetic cohorts. The slope of the curve for the diabetic cohort is steeper, indicating an increased rate of CHF development compared with that for the nondiabetic cohort.

Table 2 displays the overall CHF incident rates per 1,000 person-years of follow-up for the diabetic cohort compared with the nondiabetic cohort, stratified by 10-year age-groups. Overall, diabetic patients experienced CHF at 2.5 times the rate of nondiabetic comparison subjects (30.9 vs. 12.4 cases per 1,000 person-years, $P < 0.001$). The absolute incidence rate of CHF increased steadily with age for both cohorts. However, the relative rate declined with increasing age, from a high of 11.0 (95% CI 5.6–21.8) for those

Table 1—*Demographic characteristics of subjects with and without diabetes*

	Incident					
	Subjects with diabetes			Subjects without diabetes		
	No CHF	CHF	Total	No CHF	CHF	Total
n	7,064	1,167	8,231	8,319	526	8,845
Baseline age*	62.0 ± 11.8	69.3 ± 10.5	63.1 ± 11.9	62.9 ± 11.9	74.8 ± 9.3	63.6 ± 12.1
Age distribution*						
<45 years	6.4	0.9	5.7	5.9	0.2	5.6
45–54 years	23.3	8.7	21.2	21.5	2.5	20.4
55–64 years	28.5	21.9	27.6	27.7	11.2	26.7
65–74 years	25.2	33.9	26.5	26.3	30.2	26.5
75–84 years	13.9	28.7	16.0	15.8	42.2	17.3
85–94 years	2.4	5.7	2.9	2.8	12.9	3.4
95+ years	0.2	0.2	0.2	0.1	0.8	0.2
Percentage women	47.7	48.0	47.8	49.1	45.6	48.9
Years of follow-up	4.9 ± 1.8	2.7 ± 1.7	4.6 ± 2.0	4.9 ± 1.8	2.7 ± 1.8	4.8 ± 1.9

Data are means ± SD or percent. *Age is not statistically significantly different between the diabetic and nondiabetic cohorts; however, within both cohorts age is significantly different between those who did and did not experience incident CHF ($P < 0.001$).

younger than 45 years to 1.8 (1.6–2.2) for those aged 75–84 years.

Diabetic patients who developed CHF differed from patients who did not on a number of clinical characteristics (Table 3). Patients with incident CHF had longer duration of diabetes at baseline (6.1 vs. 4.4 years, $P < 0.001$) and were more likely to have ischemic heart disease (38.0 vs. 16.4%, $P < 0.001$) and more advanced renal disease (e.g., 29.8 vs. 18.2% had gross proteinuria, $P < 0.001$). Glycemic control (HbA_{1c}) and blood pressure were statistically but not clinically significantly different between those who did and those who did not develop CHF. BMI did not differ. Patients who experienced CHF were more likely to be using insulin (33.2 vs. 18.8%, $P < 0.001$) and metformin (15.9 vs. 13.3%, $P = 0.020$) at the start of follow-up.

The results of using Cox proportional hazards modeling to predict CHF incidence among the diabetic patients are shown in Table 4. Age at baseline was the strongest predictor of time to CHF, increasing the hazard by 40% for every 5 years of age (95% CI 1.35–1.45). The presence of ischemic heart disease more than doubled the risk of CHF (hazard ratio 2.36, 95% CI 2.06–2.69). Greater BMI (1.12 per 2.5 units of kg/m^2, 1.09–1.15) and poorer glycemic control (1.32 per HbA_{1c} percentage point, 1.23–1.41) were also strong predictors of more rapid development of CHF. Microalbuminuria seemed to reduce the risk of CHF (0.78, 0.65–0.93), but more severe renal disease increased the risk of CHF. Longer duration of diabetes and greater diastolic blood pressure also increased the hazard of experiencing CHF. Use of insulin was associated with an increased risk of CHF, but use of sulfonylureas or metformin was not. Female sex was not a significant predictor of CHF incidence.

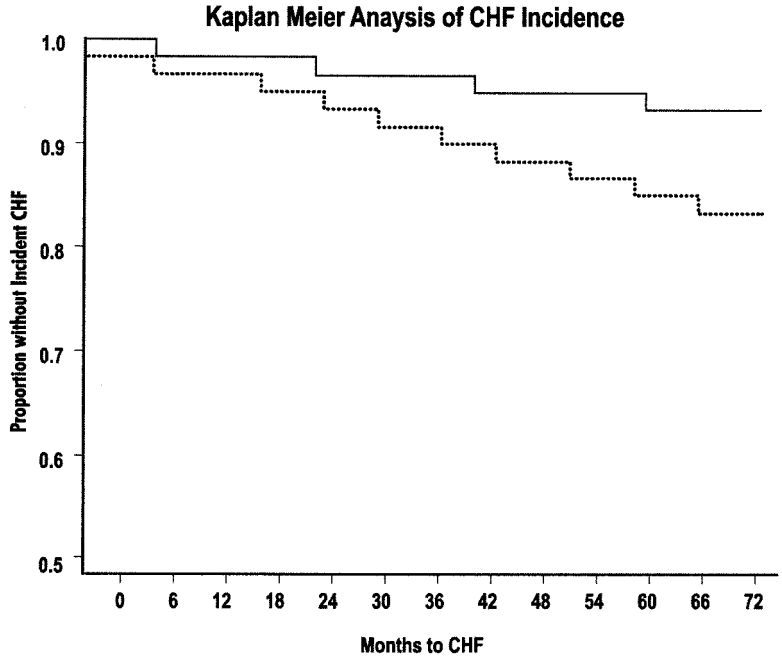

Figure 1—*Kaplan-Meier analysis of CHF incidence comparing the diabetic (- - -) and nondiabetic (—) cohorts. The cohorts are significantly different (P < 0.001).*

CONCLUSIONS— Our results, based on 8,231 patients of all ages and stages of diabetes followed for up to 6 years, indicate that the incidence of CHF in diabetes is 3–15 times greater than the previously reported 2–10 cases per 1,000 subjects (7,10–15). Published estimates of the incidence of CHF in patients with diabetes have relied on relatively small or unrepresentative samples, have been based on only patients with more severe CHF, or have been limited by relatively

Table 2—*Six-year CHF incidence per 1,000 person-years by age-group*

Age	Diabetic patients	Nondiabetic patients	Rate ratio	95% CI
<45 years	4.5	0.4	11.0	5.6–21.8
45–54 years	11.9	1.4	8.6	6.4–11.4
55–64 years	23.6	5.0	4.7	3.9–5.8
65–74 years	38.7	13.7	2.8	2.4–3.3
75–84 years	63.9	34.7	1.8	1.6–2.2
85–94 years	97.8	78.8	1.2	0.8–1.8
95+ years	59.5	110.4	0.5	0.1–2.2
All	30.9	12.4	2.5	2.3–2.7

short follow-up (3,7,10–15). These limitations may have led to underestimations of CHF in patients with diabetes. In addition, our results may arise, in part, from increasing rates of CHF over time that are related to increased survival of patients with diabetes. The most recent Framingham data contain follow-up through 1996 (14), and other estimates of CHF are based on data from similar or earlier time periods. The current results include follow-up through 2002—data that are more contemporary than previous studies (7,13,14). Finally, comparisons of studies with differing mean ages are especially difficult in age-dependent diseases such as CHF, which may account for some of the difference we report.

Although CHF incidence rates increase with age and are higher in diabetic patients than in nondiabetic subjects across all age-groups, the difference in CHF rate ratios decreases with increasing age. Therefore, it seems that diabetes not only increases the risk of CHF but also accelerates its occurrence. These results are consistent with a similar finding we previously reported across all types of cardiovascular disease (16) and with a recent study demonstrating that patients in whom diabetes is diagnosed at younger ages are at much greater risk for cardiovascular disease (17).

Our previously published multivariate model of CHF incidence over a 30-month follow-up period included both lower baseline HbA_{1c} and a reduction in HbA_{1c} at follow-up as predictor variables (3). In the current study, using the same population but with a longer, 72-month follow-up period, higher average HbA_{1c} emerged as a strong predictor of CHF incidence. Although we again found that patients with CHF had a lower average HbA_{1c} value before CHF than at baseline (data not shown), it was not a significant predictor in the new multivariate model. However, when HbA_{1c} measurements were averaged over the entire observation period, higher values were predictive of CHF. These results suggest that cumulative glycemic burden, rather than glycemic control at a given point in time, is the more important CHF risk factor, underscoring the importance of maintaining good glycemic control throughout the course of diabetes. This is also consistent with results from the UKPDS, which used an updated mean of annual measurements to demonstrate a similar relationship between HbA_{1c} and risk of heart failure (11).

Table 3—*Clinical characteristics of subjects with diabetes, by incident CHF status*

	No CHF	Incident CHF	*P*
n	7,064	1,167	
Duration of diabetes at baseline (years)	4.4 ± 3.5	6.1 ± 3.8	0.001
HbA_{1c} during observation (%)	7.9 ± 1.1	8.1 ± 1.2	0.001
Ischemic heart disease (%)*	16.4	38.0	0.001
Renal function*			
Normal (%)	60.0	49.9	0.001
Microalbuminuria (%)	20.4	17.6	
Gross proteinuria (%)	18.2	29.8	
ESRD (%)	1.4	2.7	
Systolic blood pressure during observation (mmHg)	139 ± 12.8	143 ± 14.8	0.001
Mean diastolic blood pressure during observation (mmHg)	79 ± 7.1	77 ± 8.0	0.001
BMI† (kg/m^2)	32.3 ± 6.8	32.5 ± 7.0	0.599
Use of sulfonylurea (%)	74.5	77.0	0.076
Use of metformin (%)	13.3	15.9	0.020
Use of insulin (%)	18.8	33.2	0.001

Data are means ± SD unless otherwise indicated. *At end of observation (date of CHF, death, termination from health plan, or 31 December 2002); †available for 79% of subjects.

The relationships between diabetes, heart disease, and obesity are well established. However, even within a study population that had an average BMI >32 kg/m^2, we found that each additional 2.5 BMI units increased CHF risk by 12%. This is probably due to the increased insulin resistance and hypertension associated with obesity and the corresponding risk of cardiovascular disease (18–20). Obesity rates in the U.S. are continuing to increase (21). Our results suggest that a corresponding increase in CHF can be expected even if other risk factors are well managed.

Microalbuminuria is recognized as a risk factor for cardiovascular disease in diabetes (22,23) and has been shown to be a risk factor for CHF as well (12). In our model, microalbuminuria seemed to reduce the risk of CHF. However, because patients with microalbuminuria are immediately treated with ACE inhibitors in the KPNW system, it may merely be serving as a marker for more aggressive treatment, and the apparent reduced risk may be representing the beneficial effects of ACE inhibitors on CHF. As renal dysfunction became more severe, the risk of CHF increased considerably (25% for gross proteinuria and 54% for ESRD). Whether impaired renal function is an early manifestation of preclinical CHF or is itself a cause of CHF cannot be established from these data. Nevertheless, impaired renal function seems to be an "early warning sign" for possible impending CHF development.

The UKPDS demonstrated that tight blood pressure control reduces macrovas-

Table 4—*Cox regression analysis for development of CHF for patients with type 2 diabetes*

	Hazard ratio	95% CI	*P*
Age at baseline (per 5 years)	1.40	1.35–1.45	0.001
Ischemic heart disease*	2.36	2.06–2.69	0.001
BMI (per 2.5 units)	1.12	1.09–1.15	0.001
Mean HbA_{1c} (per percentage point)	1.32	1.23–1.41	0.001
Duration of diabetes (per year)	1.05	1.03–1.07	0.001
Microalbuminuria*	0.78	0.65–0.93	0.006
Gross proteinuria*	1.25	1.08–1.46	0.004
ESRD*	1.54	1.04–2.30	0.032
Mean diastolic blood pressure (per 5 mmHg)	1.10	1.04–1.16	0.001
Use of insulin*	1.25	1.06–1.48	0.007
Use of sulfonylurea*	0.99	0.85–1.17	0.892
Use of metformin*	1.02	0.86–1.22	0.849
Female sex*	0.97	0.85–1.10	0.656

*Dichotomous variables, where hazard ratio represents risk if variable is present.

cular disease risk in type 2 diabetes (24). In our data, elevated blood pressure was predictive of incident CHF, suggesting that the benefits of blood pressure control might also extend to risk of CHF.

One important limitation of the current study is the use of electronic data to define CHF, which may result in our overstating the true incidence of CHF. However, we used methods that mirrored those recently reported by McCullough et al. (25), in which 83% of automated ICD-9-CM diagnoses of CHF were validated with medical record review. We previously found that 92.5% of our CHF patients were diagnosed after echocardiography, electrocardiography, or chest X-ray (3). Additionally, 82% of our CHF cases were found in the inpatient medical record, where diagnoses are more likely to be objectively confirmed. Unlike another study in a similar setting (13), we allowed the inpatient CHF discharge diagnosis to occur in any position, not just the first listed. Finally, just 18% of our cases were found only in the outpatient medical record, alleviating any concern that primary care clinicians may be coding CHF too aggressively in the medical office.

In our previous report, use of insulin and oral agents was strongly predictive of CHF incidence (3). In line with our previous findings, use of insulin at the start of follow-up was predictive of CHF. However, we did not find use of sulfonylurea or metformin to be predictive of CHF in the present study. Controversy surrounding the negative cardiac effects of sulfonylureas remains, although our findings are consistent with the UKPDS, which did not find increased mortality in the sulfonylurea-treated group (15). Studies specifically designed to estimate the potential effects of antidiabetic agents on CHF incidence, accounting for the high rate of antidiabetic medication switching and addition in the diabetic population, are needed. The choice of antidiabetic medication is strongly correlated with glycemic control, making it very hard to separate the independent effects of each of these factors on the risk of CHF development.

The high incidence of CHF among the diabetic population emphasizes the need for early recognition and aggressive treatment of modifiable risk factors for CHF. Our results confirm that tight glycemic and blood pressure control as well as weight loss and treatment of renal disease are essential to the long-term health of people with diabetes. Given the substantially larger CHF rate ratios and the greater life expectancy of patients younger than 65 years, younger persons may benefit most from intensive risk factor modification.

Acknowledgments— This research was sponsored by GlaxoSmithKline, Inc.

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