Congestive Heart Failure in Type 2 Diabetes

Prevalence, incidence, and risk factors

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OBJECTIVE — To estimate the prevalence and incidence of congestive heart failure (CHF) in populations with and without type 2 diabetes and to identify risk factors for diabetes-associated CHF.

RESEARCH DESIGN AND METHODS — We searched the inpatient and outpatient electronic medical records of 9,591 individuals diagnosed with type 2 diabetes before 1 January 1997 and those of an age- and sex-matched control group without diabetes for a diagnosis of CHF. Among those without a baseline diagnosis of CHF, we searched forward for 30 months for incident cases of CHF. We constructed multiple logistic regression models to identify risk factors for both prevalent and incident CHF.

RESULTS — CHF was prevalent in 11.8% (n = 1,131) of diabetic subjects and 4.5% (n = 435) of control subjects at baseline. We observed incident cases of CHF in 7.7% of diabetic subjects free of CHF at baseline (650 of 8,460) and in 3.4% of control subjects (314 of 9,156). In diabetic subjects, age, diabetes duration, insulin use, ischemic heart disease, and elevated serum creatinine were independent risk factors for both prevalent and incident CHF. Better glycemic control at baseline, and improved glycemic and blood pressure control at follow-up predicted the development of CHF.

CONCLUSIONS — Despite controlling for age, duration of diabetes, presence of ischemic heart disease, and presence of hypertension, insulin use was associated with both prevalent and incident CHF. Why insulin use and better glycemic control both at baseline and follow-up independently predicted CHF deserves further study.

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The Framingham Heart Study (FHS) first demonstrated an increased risk of congestive heart failure (CHF) in patients with diabetes over 20 years ago (1). Although diabetes is frequently cited as a risk factor for CHF (2–9), CHF has not been well described in contemporary populations with type 2 diabetes. Recent therapeutic advances have increased coronary artery disease (CAD) survival. As a result, CAD has replaced hypertension and valvular heart disease as the primary cause of CHF (10,11). In addition, because CHF is an age-related condition, incidence and prevalence of CHF (and diabetes) can be expected to increase as the population ages (12,13). The objectives of this study were *1*) to estimate prevalence and incidence of CHF in a representative contemporary population of individuals with type 2 diabetes and in an age- and sex-matched population without diabetes and *2*) to identify current risk factors for CHF in diabetes.

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Abbreviations: CAD, coronary artery disease; CHF, congestive heart failure; FHS, Framingham Heart Study; OR, odds ratio; KPNW, Kaiser Permanente Northwest Division; UKPDS, U.K. Prospective Diabetes Study; VA CSDM, Veterans Affairs Cooperative Study in Type 2 Diabetes Mellitus.

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

RESEARCH DESIGN AND METHODS

Research setting and population

The subjects of this study were members of a long-established, not-for-profit, group-model health maintenance organization, Kaiser Permanente Northwest Division (KPNW). KPNW provides comprehensive, prepaid coverage to ~20% of the Portland, Oregon, population (~430,000 people during the period of this study). Subscribers resemble the area population as a whole (14).

All members of KPNW have access to the complete range of medically necessary clinical services. The organization maintains administrative and clinical electronic databases containing information on inpatient admissions, pharmacy dispenses, outpatient visits, laboratory tests, and outside claims and referrals. All of these databases are linked through the unique health record number that is given to each member at the time of initial enrollment in the health plan.

The KPNW Diabetes Registry was initially developed in 1989 and has been described in detail elsewhere (15,16). For this study, we selected all 9,591 registrants who had their diabetes diagnosed while members of KPNW before 1 January 1997 (baseline) and who had at least 1 month of eligibility during a 30-month follow-up observation period (1 January 1 1997 to 30 June 1999). For most subjects, a full 30 months of follow-up data were available (mean follow-up time was 28 months). KPNW's excellent member retention rate allowed for follow-up on 92.6% of registrants eligible in the year before baseline. We randomly selected an identical number of KPNW members without diabetes to use as a control group,

matching them with diabetic subjects on year of birth, sex, and health plan eligibility.

Data

The hospital discharge database, which contains up to nine ICD-9-CM diagnoses for each inpatient stay, was searched from 1 January 1987 to 30 June 1999 for evidence of CHF. We similarly searched the electronic medical record, which contains as many as 20 ICD-9-CM diagnoses for each ambulatory contact, from 1 January 1996 (when it first became available) to 30 June 1999. We defined prevalent CHF as any inpatient or outpatient diagnosis of CHF before 1 January 1997 (see APPENDIX for ICD-9-CM codes). For those with no evidence of prevalent CHF at baseline, we searched forward for new diagnoses of CHF and identified those found as incident cases. To calculate the incidence rate of CHF, we divided the number of new cases of CHF by the total number of months of health plan eligibility that occurred before the CHF diagnosis date or, if no CHF was diagnosed, until the end of the observation period.

Age and sex were extracted from membership records. We calculated duration of diabetes as time from the date of diabetes diagnosis to 1 January 1997. Measured body weight and blood pressure were obtained from the electronic medical record, and information on antidiabetic drug therapy was obtained from KPNW pharmacy records. We ascertained blood glucose control (HbA_{1c}) and serum creatinine levels from electronic laboratory records (all KPNW laboratory tests are performed by a single regional laboratory using standardized methods that are frequently recalibrated against reference samples). Follow-up values were those within 6 months preceding the occurrence of CHF or, in absence of CHF, up to 6 months before the end of follow-up. When multiple measurements were available, we used the value nearest to the follow-up date.

Analytic methods

To determine independent associations between age, sex, duration of diabetes, type of antidiabetic drug therapy, HbA_{1c}, serum creatinine, body weight, blood pressure, and the prevalence of CHF, we estimated a multiple logistic regression model. To study incident CHF, we used similar methods but used follow-up values of antidiabetic drug therapy and changes in body weight, HbA_{1c}, serum creatinine, and systolic blood pressure. We calculated change scores as follow-up minus baseline values. We also included dichotomous variables for the presence of ischemic heart disease and hypertension at baseline, and a second pair of dichotomous variables for new diagnoses of ischemic heart disease and hypertension that occurred during the follow-up period.

RESULTS — CHF was identified in 11.8% (n = 1,131) of diabetic subjects at baseline compared with 4.5% (n = 435) of control subjects. Of the 8,460 diabetic subjects who did not have CHF at baseline, 7.7% (n = 650) developed CHF over a 30-month follow-up period, an incidence rate of 3.33 events per 100 person-years. By comparison, 3.4% (n = 314) of the 9,156 control subjects free of CHF at baseline developed CHF during the follow-up period (1.52 events per 100 person-years). CHF was approximately two to eight times more prevalent in subjects with diabetes than in the age- and sex-matched control group, and incidence of CHF increased dramatically with age in both groups (Fig. 1). In subjects with diabetes, CHF approximately doubled from 33 cases per 1,000 for subjects aged 45–54 years to 68 cases per 1,000 for those aged 55–64 years; it then doubled again to 135 cases per 1,000 for subjects aged 65–74 years. Annual incidence of CHF was also age-related. Subjects with diabetes were two to five times more likely to develop CHF than subjects in the age- and sex-matched control group.

The characteristics of subjects with diabetes with and without prevalent CHF are compared in Table 1. Subjects with CHF were significantly older (73.2 vs. 63.0 years, $P < 0.001$), had a longer duration of diabetes (6.4 vs. 4.5 years, $P < 0.001$), and were more likely to have been using insulin (34.6 vs. 17.7%, $P < 0.001$). Women were more likely to have had CHF than men (53.8 vs. 47.8%, $P < 0.001$). Ischemic heart disease was much more prevalent in subjects with CHF than without (64.9 vs. 19.7%, $P < 0.001$), as was hypertension (75.3 vs. 49.1%, $P < 0.001$). Subjects with CHF also had lower body weight (186 vs. 203 lbs, $P < 0.001$), lower systolic (137 vs. 140 mmHg, $P < 0.001$) and diastolic (74 vs. 80 mmHg, $P < 0.001$) blood pressure, and higher levels of serum creatinine (1.39 vs. 1.03 mg/dl, $P < 0.001$). Glycemic control did not differ.

Also displayed in Table 1 are the characteristics of subjects with diabetes who did and did not develop CHF during the follow-up period. Older age (70.2 vs. 62.4 years, $P < 0.001$), longer diabetes duration (5.9 vs. 4.4 years, $P < 0.001$), and more insulin use (31.0 vs. 18.4%, $P < 0.001$) characterized subjects who developed CHF. Ischemic heart disease was more likely to be present at baseline (40.9 vs. 18.0%, $P < 0.001$) and more likely to be diagnosed during follow-up (18.6 vs. 5.7%, $P < 0.001$) among those who developed CHF. Hypertension was also more likely to be present at baseline (66.9 vs. 47.6%, $P < 0.001$), but somewhat less likely to be newly identified during follow-up (8.9 vs. 11.6%, $P < 0.05$). Although HbA_{1c} at baseline did not differ, those who developed CHF had lower HbA_{1c} at follow-up (7.5 vs. 7.8%, $P < 0.001$). Serum creatinine levels were greater at both baseline (1.24 vs. 1.01 mg/dl, $P < 0.001$) and follow-up (1.36 vs. 0.98 mg/dl, $P < 0.001$) in incident CHF cases. Higher systolic blood pressure at baseline (143 vs. 139 mmHg, $P < 0.001$) was associated with incident CHF, but follow-up systolic blood pressures did not differ. Diastolic blood pressure was lower for those who developed CHF at both baseline (77 vs. 80 mmHg, $P < 0.001$) and follow-up (75 vs. 78 mmHg, $P < 0.001$).

To isolate independent predictors of prevalent CHF, we estimated a multiple logistic regression model (Table 2). Older age (odds ratio [OR] = 1.05, 95% CI 1.04–1.06), female sex (1.35, 1.13–1.61), longer diabetes duration (1.04, 1.01–1.07), insulin use (1.47, 1.17–1.85), presence of ischemic heart disease (4.44, 3.74–5.26), and hypertension (1.69, 1.40–2.05) emerged as important predictors of prevalent CHF. Body weight, which was inversely associated with CHF in the bivariate analysis, was nonsignificant after controlling for other factors. Serum creatinine was a strong predictor of CHF (1.73, 1.49–2.01), but HbA_{1c} was not.

We constructed a second multiple logistic regression model to identify independent risk factors for incident CHF (Table 3). Older age (OR 1.05, 95% CI 1.03–1.06), longer diabetes duration (1.04, 1.01–1.08), insulin use (1.66, 1.26–2.20), use of an oral agent (1.28,

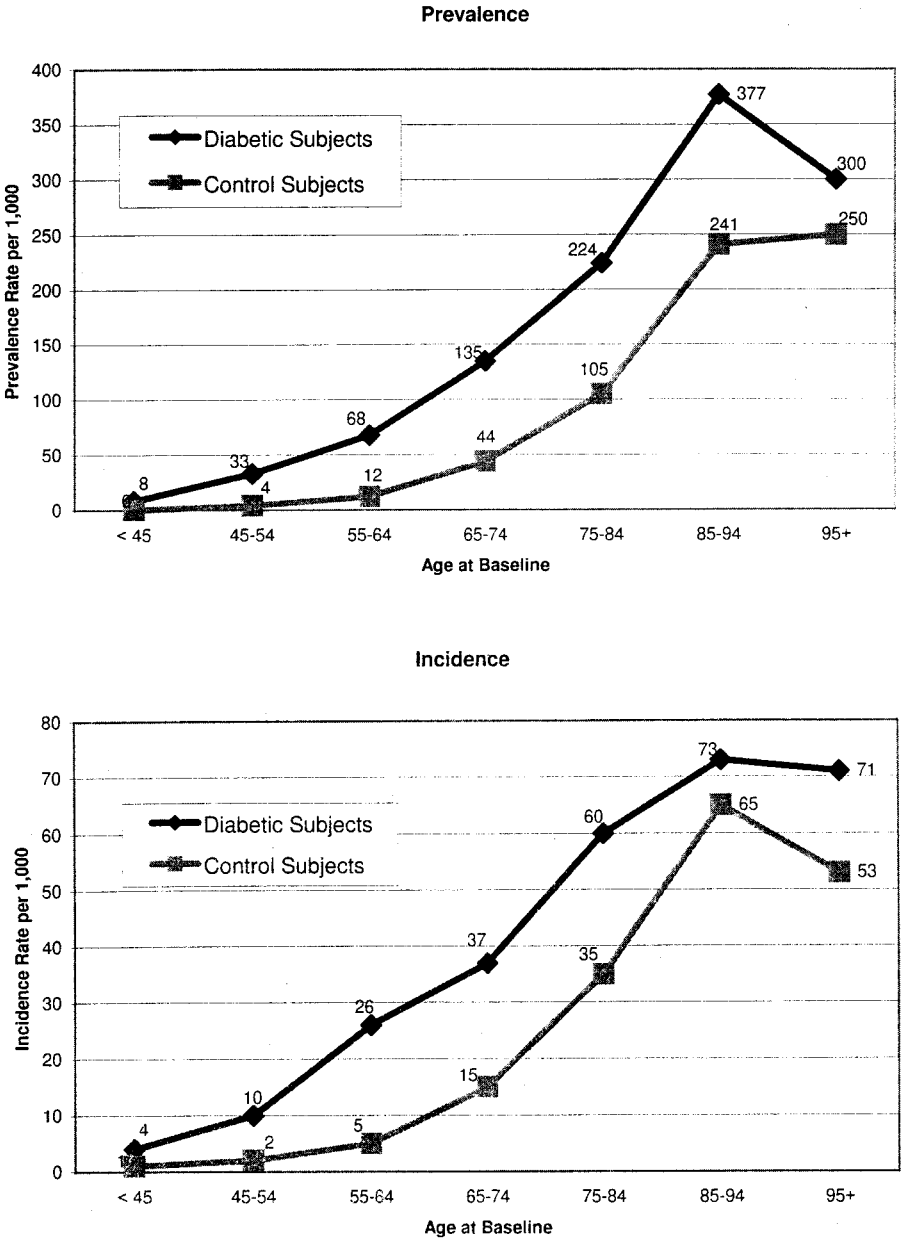

Figure 1—*Prevalence and annual incidence rates of CHF per 1,000 people.*

1.01–1.62), ischemic heart disease at baseline (2.73, 2.17–3.43), and new ischemic heart disease at follow-up (4.31, 3.19–5.81) all predicted incident CHF. Reduction in HbA_{1c} from baseline to follow-up (0.86, 0.79–0.94) and reduction in systolic blood pressure (0.99, 0.99–1.00) were also independently associated of incident CHF, as was lower baseline HbA_{1c} (0.91, 0.83–1.00) and greater baseline body weight (1.00, 1.00–1.01). Higher baseline serum creatinine levels (1.78, 1.43–2.21) and an increase in serum creatinine at follow-up (1.74, 1.41–2.16) strongly predicted incident CHF. A hypertension diagnosis, either at baseline or during follow-up, was not statistically significant in the multivariate model.

CONCLUSIONS — To date, the best estimates of prevalent and incident CHF are based on the largely nondiabetic population of the FHS. Published estimates of prevalence range between 1% (aged 50–59 years) and 10% (aged 80–89 years), and age-related incidence ranges between 1 and 85 cases per 1,000 (17). Although our CHF rates are somewhat higher, FHS investigators believe their estimates are understated because they were based on major and minor clinical factors that were "rather severe, and did not include subjects with impaired subclinical cardiac function now detectable by noninvasive technology" (17,18). Our higher rates of CHF may also reflect improved CAD survival.

A potential limitation of our study is that some unknown proportion of our cases may be suspected but not confirmed. Using objective measures (electrocardiography, chest radiography, and transthoracic echocardiography), Cowie et al. (19) found that a panel of cardiologists confirmed just 25% of new cases of heart failure suspected by primary physicians. Although we could not access imaging results, radiology visit data indicate that 92.5% of our diagnosed subjects received an echocardiogram, electrocardiogram, or chest X-ray before the CHF diagnosis. Thus, the vast majority of our cases appears to have been diagnosed objectively. Furthermore, diagnostic errors would not bias comparisons between the diabetic and control groups. Indeed, the relative incidence and prevalence rates between the diabetic and control groups that we report are similar to those found in the FHS over two decades ago (1).

Prior research has established diabetes as a risk factor for CHF (2–9), so we were not surprised to find that CHF was more common in subjects with diabetes than in an age- and sex-matched control group. Interestingly, however, the slopes of the increasing prevalence and incidence of CHF across age groups were very similar for subjects with and without diabetes. This suggests that diabetes adds a more or less constant risk of CHF, independent of age. We also observed an approximate doubling of prevalence with each decade of age—a phenomenon reported in the FHS (17).

The role of insulin as a cardiovascular risk factor in type 2 diabetes remains controversial. Although much of the debate has centered on endogenous hyperinsulinemia (20–32), several prospective studies, with contradictory results, have investigated the association between exogenous insulin therapy and CVD. The first such study, the University Group Diabetes Program (UGDP) failed to find a difference in cardiovascular disease risk between those receiving diet or insulin therapy (33). The U.K. Prospective Dia-

Table 1—*Characteristics of members with diabetes with and without prevalent CHF at baseline and with and without incident CHF at follow-up*

	Prevalence			Incidence		
	CHF at baseline	No CHF at baseline	Total	CHF at follow-up	No CHF at follow-up	Total
n	1,131	8,460	9,591	650	7,810	8,460
Proportion of population (%)	11.8	88.2	100.0	7.7	92.3	100.0
Mean age (years)	73.2*	63.0	64.2	70.2*	62.4	63.0
% Female	53.8*	47.8	48.5	46.2	48.0	47.8
Mean duration of diabetes (years)	6.4*	4.5	4.8	5.9*	4.4	4.5
Ischemic heart disease diagnosed (%)						
Prior to baseline	64.9*	19.7	25.1	40.9*	18.0	19.7
Between baseline and follow-up (%)	—	—	—	18.6	5.7	6.7
Hypertension diagnosed						
Prior to baseline	75.3*	49.1%	52.2%	66.9*	47.6	49.1
Between baseline and follow-up	—	—	—	8.9†	11.6	11.4
Diabetes therapy (%)						
Oral antihyperglycemic agents	46.5*	58.9	57.5	52.2	56.0	55.7
Insulin (alone or in combination)	34.6*	17.7	19.7	31.1*	18.4	19.4
Baseline Measures:						
HbA_{1c} (%)	7.7	7.7	7.7	7.7	7.7	7.7
Serum creatinine (mg/dl)	1.39*	1.03	1.08	1.24*	1.01	1.03
Systolic blood pressure (mmHg)	137*	140	139	143*	139	140
Diastolic blood pressure (mm Hg)	74*	80	79	77*	80	80
Weight (lbs.)	186*	203	201	199	203	203
Follow-up measures						
HbA_{1c} (%)				7.5*	7.8	7.8
Serum creatinine (mg/dl)				1.36*	0.98	1.02
Systolic blood pressure (mmHg)				138	139	140
Diastolic blood pressure (mmHg)				75*	78	78
Weight (lbs.)				199	202	203

*$P < 0.001$ compared with no CHF; †$P < 0.05$ compared with no CHF.

betes Study (UKPDS) also did not find an association between treatment with insulin and macrovascular outcomes among subjects newly diagnosed with diabetes (34) and, in the Diabetes Mellitus, Insulin Glucose Infusions in Acute Myocardial Infarction (DIGAMI) Study, Malmberg (35) reported that intensive insulin treatment after acute myocardial infarction improved long-term survival. However, the Feasibility Trial of the Veterans Affairs Cooperative Study in Type 2 Diabetes Mellitus (VA CSDM) initially found a significant increase in cardiovascular events among older veterans with established type 2 diabetes who received intensive insulin treatment (36). Subsequently, though, the VA CSDM study group reported in a follow-up study that intensive insulin treatment did not affect left ventricular function (37). Finally, the recent Atherosclerosis Risk in Communities (ARIC) Study found an association between coronary heart disease and treatment with insulin (38).

We found a strong relation between exogenous insulin use and both prevalent and incident CHF after the inclusion of variables to control for the progression and severity of diabetes. In addition, interaction terms of insulin use with age and duration of diabetes were not statistically significant in this model. Thus, our results

Table 2—*Risk factors for prevalent CHF in multivariate modeling using logistic regression*

Variable	β	SE	*P*	OR	95% Cl
Age	0.318	0.005	0.001	1.05	1.04–1.06
Female sex	0.082	0.090	0.001	1.35	1.13–1.61
Duration of diabetes	0.077	0.014	0.005	1.04	1.01–1.07
Use of oral agent	−0.055	0.096	0.032	0.82	0.68–0.98
Use of insulin	0.088	0.117	0.001	1.47	1.17–1.85
HbA_{1c}	−0.006	0.029	0.799	0.99	0.94–1.05
Serum creatinine	0.154	0.076	0.001	1.73	1.49–2.01
Systolic blood pressure	−0.090	0.002	0.001	0.99	0.99–1.00
Diastolic blood pressure	−0.107	0.004	0.001	0.98	0.97–0.99
Weight	−0.004	0.001	0.879	1.00	1.00–1.00
Ischemic heart disease	0.365	0.087	0.001	4.44	3.74–5.26
Hypertension	0.143	0.098	0.001	1.69	1.40–2.05

Table 3—*Risk factors for incident CHF in multivariate modeling using logistic regression*

Variable	β	SE	*P*	OR	95% CI
Age (baseline)	0.279	0.006	0.001	1.05	1.03–1.06
Duration of diabetes	0.081	0.017	0.012	1.04	1.01–1.08
Use of insulin	0.121	0.142	0.001	1.66	1.26–2.20
Use of oral agent	0.066	0.122	0.044	1.28	1.01–1.62
Baseline HbA_{1c}	−0.081	0.049	0.052	0.91	0.83–1.00
Baseline serum creatinine	0.125	0.110	0.001	1.78	1.43–2.21
Baseline systolic blood pressure	−0.019	0.003	0.589	1.00	0.99–1.00
Baseline weight	0.071	0.001	0.037	1.00	1.00–1.01
Change* in HbA_{1c}	−0.143	0.046	0.001	0.86	0.79–0.94
Change* in serum creatinine	0.125	0.110	0.001	1.74	1.41–2.16
Change* in systolic blood pressure	−0.091	0.003	0.007	0.99	0.99–1.00
Change* in weight	0.047	0.002	0.148	1.00	1.00–1.01
Baseline ischemic heart disease	0.230	0.117	0.001	2.73	2.17–3.43
Follow-up ischemic heart disease	0.217	0.153	0.001	4.31	3.19–5.81

*Change is calculated as follow-up measurement minus baseline measurement, so a negative coefficient represents a reduction in value from baseline follow-up.

are consistent with the hypothesis that insulin therapy is a risk factor for CHF. We stress, however, that our results derive from observational, not randomized, data. They do not prove a causal effect of insulin use on CHF.

We did not find poor glycemic control to be associated with prevalent CHF, in accord with the UKPDS, which also found no association between heart failure and glycemic control (34). However, the mean HbA_{1c} in this population was 7.7%, and 83% of the population had values <9%. With so few poorly controlled subjects, it may have been difficult to detect an association.

We did, however, find that a reduction in HbA_{1c} coupled with a lower baseline HbA_{1c} predicted incident CHF in a multivariate model. HbA_{1c} averaged 7.7% at baseline, and follow-up measurements, which were taken before the CHF diagnosis, averaged 7.5% for those who developed CHF. Although it is possible that a reduction of HbA_{1c} in patients with incident CHF was the result of greater attention being paid to sicker patients, we do not believe this possibility contributes to our finding. Subjects with diabetes in KPNW receive much more guideline-adherent care than typical for other patients, and consequently they achieve lower-than-usual risk factor levels (16). Nearly 90% of KPNW's diabetes registrants receive at least one HbA_{1c} measurement each year (mean = 2.8) and average 14 ambulatory visits annually. It seems unlikely that patients who were about to be diagnosed with CHF suddenly received sufficient additional attention to lower their glycemic levels. However, those with incident CHF were somewhat more likely to have had a follow-up HbA_{1c} test than those free of CHF (90.0 vs. 81.6%, $P < 0.001$). The extent to which this testing rate difference biased our results is unknown. Nonetheless, the persistence of the significance of the reduction of HbA_{1c} while controlling for duration of diabetes, use of insulin, presence of ischemic heart disease, and impaired renal function further suggests that reduction in HbA_{1c} may be an independent risk factor for developing CHF.

That tighter glycemic control was independently associated with developing CHF raises the possibility that aggressive glycemic control is potentially dangerous in older patients with ischemic heart disease. Acute hypoglycemia increases cardiac workload (39), which could result in ischemia in those with cardiovascular disease. We lack data to determine frequency or severity of hypoglycemic episodes and their relation to incident CAD or CHF. The current Action to Control Cardiovascular Complications in Diabetes (ACCORD) trial, sponsored by the National Heart, Lung and Blood Institute, will address this crucial issue.

We also found a reduction in systolic blood pressure to be associated with the onset of CHF. The UKPDS has previously shown experimentally that tighter blood pressure control reduces risk of heart failure (40). However, based on our observational data, we cannot determine whether the reduction in blood pressure was a cause or a result of CHF.

Prevalence and incidence of type 2 diabetes and CHF can be expected to rise as the population ages and lives longer. We hope that our data on the prevalence and incidence of CHF, and their associated risk factors, increase the attention paid to CHF in diabetes and contribute to a re-evaluation of strategies for preventing and treating heart failure and cardiovascular disease in type 2 diabetes.

APPENDIX A

ICD-9-CM diagnosis codes

CHF

401.91: Hypertensive renal disease, unspecified, with CHF
402.01: Malignant hypertensive heart disease with CHF
402.11: Benign hypertensive heart disease with CHF
402.91: Hypertensive heart disease with CHF
404.01: Malignant hypertensive heart and renal disease with CHF
404.03: Malignant hypertensive heart and renal disease with CHF and renal failure
404.11: Benign hypertensive heart and renal disease with CHF
404.13: Benign hypertensive heart and renal disease with CHF and renal failure
404.93: Hypertensive heart and renal disease, unspecified, with CHF
428.0: CHF

Ischemic heart disease

410.xx: Acute myocardial infarction
411.xx: Other acute and subacute forms of ischemic heart disease
412.xx: Old myocardial infarction
413.xx: Angina pectoris
414.xx: Other forms of chronic ischemic heart disease

Hypertension

401.1: Essential hypertension, benign
401.9: Essential hypertension, unspecified

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