The Significant Effect of Diabetes Duration on Coronary Heart Disease Mortality

The Framingham Heart Study

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OBJECTIVE — The risk of coronary heart disease (CHD) in type 2 diabetes is two- to threefold higher than in the general population, but the effect of diabetes duration on CHD risk has not been well characterized. We hypothesized that duration of diabetes is an important predictor of incident CHD among people with diabetes.

RESEARCH DESIGN AND METHODS — The duration of diabetes (fasting glucose ≥126 mg/dl, random glucose ≥200 mg/dl, or use of an oral hypoglycemic agent or insulin) was assessed in participants with diabetes in the original and offspring cohorts of the Framingham Heart Study. Only subjects with diabetes diagnosed between the ages of 30 and 74 years, without a history of ketoacidosis, and free of cardiovascular disease at the baseline evaluation were included. Cox proportional hazards models were used to estimate the hazard ratio of incident CHD events and mortality over a 12-year follow-up period; models were adjusted for known CHD risk factors.

RESULTS — Among 588 person-exams with diabetes (mean age 58 ± 9 years, 56% men), there were 86 CHD events, including 36 deaths. After adjustment for age, sex, and CHD risk factors, the risk of CHD was 1.38 times higher for each 10-year increase in duration of diabetes (95% CI 0.99–1.92), and the risk for CHD death was 1.86 times higher (1.17–2.93) for the same increase in duration of diabetes.

CONCLUSIONS — Duration of diabetes increases the risk of CHD death independent of coexisting risk factors. Further research is necessary to understand the pathophysiology of this increased risk.

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Type 2 diabetes confers a two- to threefold increase in the risk of cardiovascular disease (CVD) (1). Nearly 11 million Americans with diabetes will develop CVD (2,3), and two-thirds will die from coronary heart disease (CHD) (2).

It has been suggested that the duration of diabetes may be a CVD risk factor. The results of previous studies that have examined this association have been inconclusive. Some reports have noted an association between type 2 diabetes disease duration and the development of CVD (4–9), whereas others have not (10,11).

Many prior studies were unable to reliably identify the onset of diabetes due to lack of antecedent measures of glycemia. The Framingham Heart Study has measured blood glucose every 2–4 years, enabling an accurate inception of diabetes. Thus, we sought to assess the effect of diabetes duration on incident CHD morbidity and mortality, hypothesizing that there would be an association between diabetes duration and the development of CHD.

RESEARCH DESIGN AND METHODS

— The subjects from this study were drawn from the original and offspring cohorts of the Framingham Heart Study. Beginning in 1948, 5,209 men and women aged 28–62 years were enrolled in the original cohort study. Starting in 1971, offspring and spouses of offspring or the original cohort were enrolled in the study. The selection criteria and study design have been described elsewhere (12,13). The standard clinic examination included an interview, a physical examination, and laboratory tests. Cardiovascular events, including all major hospitalizations and deaths, were documented throughout follow-up. Original cohort subjects were invited to attend examinations every 2 years, and offspring subjects were invited to attend examinations every 4 years.

We selected three original cohort examinations, ~12 years apart (1954–1958, 1968–1972, and 1981–1984), and two offspring examinations, 12 years apart (1979–1983 and 1991–1995), from which to draw participants; the study design is schematically represented in Fig. 1. Examination dates were chosen to be nonoverlapping with respect to follow-up. Participants could contribute diabetes duration information at more than one examination provided that they reached the next examination free of a CVD event. For example, a 60-year-old diabetic subject with 5 years of diabetes duration attending an examination in 1956 could contribute information over

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Abbreviations: CABG, coronary artery bypass graft; CHD, coronary heart disease; CVD, cardiovascular disease.

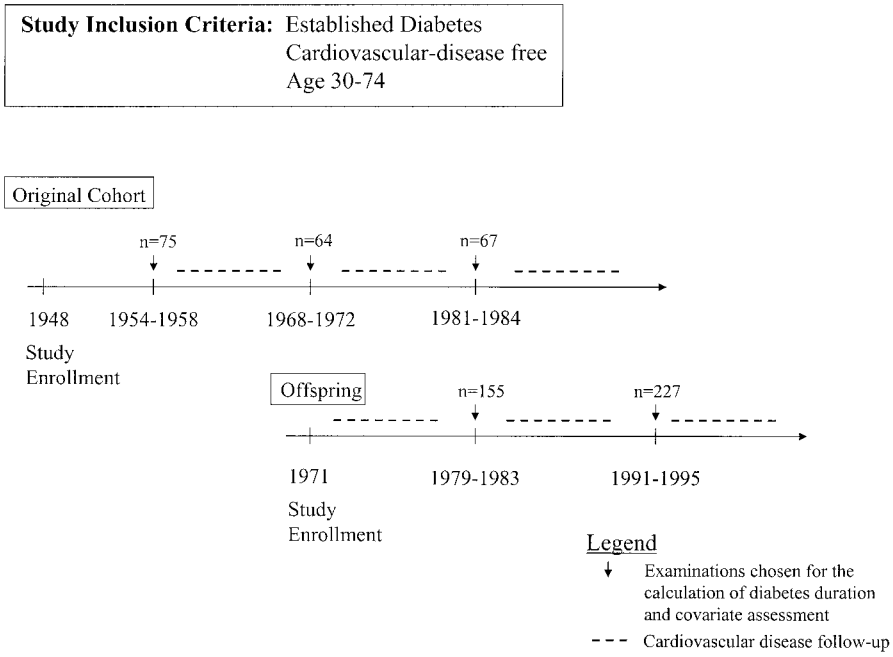

Figure 1—*Schematic representation of study design.*

the next 12 years for this diabetes duration. If this subject was free of CVD in 1968, the subject could provide additional diabetes duration as a 72-year-old with 17 years of diabetes duration. The majority of subjects contributed only one person-exam (n = 379), 103 individuals contributed two person-exams, and only 1 subject contributed three person-exams. Altogether there are 483 individuals in the analytic sample and 588 person-exams. Follow-up information was available on 100% of the 588 person-exams.

Diabetes diagnosis and diabetes duration

Diabetes was diagnosed by either a fasting plasma glucose ≥126 mg/dl, a nonfasting plasma glucose ≥200 mg/dl, or treatment with either insulin or an oral hypoglycemic agent. Subjects with a history of ketoacidosis or age at onset <30 years old were excluded; subjects with an age at onset >74 years old were also excluded. Diabetes duration, the exposure variable in this study, was determined by identifying the date of onset of diabetes as the midpoint of the interval during which the subject was free of diabetes and then developed diabetes. Charts were reviewed to determine the date of diagnosis of subjects who entered the study with diabetes or who did not return for a follow-up examination within an 8-year period. The duration of diabetes was determined at each of the five examinations. All subjects with preexisting CVD were excluded.

Ascertainment of CVD outcomes

A panel of three physicians reviewed each cardiovascular event according to preestablished criteria. CHD included myocardial infarction and sudden and nonsudden CHD death; this outcome is often referred to as "hard" CHD. CHD death included deaths attributable to myocardial infarction and sudden and nonsudden CHD deaths. CVD included CHD, as well as angina, coronary insufficiency (unstable angina with ischemic electrocardiogram changes), congestive heart failure, and atheroembolic brain infarction; CVD death included deaths attributable to these causes.

Details regarding the methods of risk factor measurement and laboratory analysis have been described elsewhere (14). Each examination included CVD assessment, 12-lead electrocardiogram, and blood testing. Measured covariates were assessed at each of the five examinations. Subjects with a systolic blood pressure ≥140 mmHg, diastolic blood pressure ≥90 mmHg (average of two readings taken by the examining physician), or on antihypertensive medication were defined as hypertensive. Lipid measures included total cholesterol. Smoking status was defined as number of cigarettes smoked per day in the year preceding the exam. BMI was defined as weight (in kilograms) divided by the square of height (in meters). Covariate assessment was made at the time of the examination.

Statistical analysis

Cox proportional hazards survival models were developed to examine the risk of increasing diabetes duration on development of CHD, CHD death, CVD, CVD death, total mortality, and non-CVD mortality, each considered separately. Descriptive statistics were generated on all study variables, including means and SDs for continuous measures and percentages for discrete measures. Statistics were generated for the total sample and then by 5-year increments in duration of diabetes. Diabetic subjects from the selected baseline examinations were pooled, and diabetes duration entered the model as a continuous variable. Subjects were followed for 12 years to ascertain outcome status. In the Cox models, the outcome time axis utilized was time to event, including CVD, CVD death, CHD, CHD death, total mortality, or non-CVD mortality, depending on the specific outcome used in the Cox models. In the Cox models, the exposure variable used was diabetes duration as a continuous variable. Crude, age- and sex-adjusted, and multivariable (age, sex, systolic blood pressure, hypertension treatment, total cholesterol, BMI, smoking status, and electrocardiogram left ventricular hypertrophy) models were estimated. Hazard ratios (HRs) are presented as the risk of CVD or all-cause mortality per 10-year increase in the duration of diabetes. To examine whether the effect of duration of diabetes on morbidity and mortality was linear, we estimated Cox models with linear and quadratic terms for duration of diabetes. The quadratic terms failed to reach statistical significance, suggesting that the risk of diabetes duration has a linear effect on morbidity and mortality.

RESULTS — There were 588 person-exams (329 men and 259 women) with diabetes, with a mean age of 58 years. Mean duration of diabetes was 7.8 years, ranging from 0.3–44.5 years; five person-exams had a duration of >25 years. When baseline characteristics were examined by 5-year increments of duration, those with

Table 1—*Baseline characteristics of study participants by duration of diabetes*

	Overall	<5 years	5–10 years	>10 years
n	588	262	159	167
Age (years)	58 ± 9	57 ± 9	58 ± 8	61 ± 8
Men (%)	56	56	58	53
Systolic blood pressure (mmHg)	141 ± 21	141 ± 22	139 ± 20	143 ± 22
Hypertension (%)	49	51	43	53
Hypertension treatment (%)	31	29	26	40
Total cholesterol (mg/dl)	219 ± 44	218 ± 40	225 ± 47	217 ± 48
BMI (kg/m^2)	29 ± 6	30 ± 6	29 ± 5	29 ± 5
Current tobacco use (%)	26	26	31	19
ECG left ventricular hypertrophy (%)	2	2	1	3

Data are means ± SD, unless noted otherwise. ECG, electrocardiogram.

longer duration were older, more likely to be hypertensive, and less likely to smoke (Table 1). Morbidity and mortality rates per 1,000 person-years by 5-year category of diabetes duration are presented in Table 2.

There were 193 CVD events, including 55 deaths. In crude models, the risk of CVD was 1.23 times higher for each 10-year increase in duration of diabetes (95% CI 0.98–1.54; $P = 0.07$). These results were not different in age- and sex-adjusted and multivariable-adjusted models (Table 3). In fully adjusted models, the risk of diabetes duration on CVD death was not significant (odds ratio [OR] 1.44, 95% CI 0.97–2.15; $P = 0.07$). Overall, there were 86 CHD events, including 36 deaths. In crude models, the risk of CHD was 1.33 times higher for each 10-year increase in diabetes duration (0.96–1.84; $P = 0.08$). These results persisted in age-, sex-, and multivariable-adjusted models (Table 3).

There were 36 CHD deaths. In crude models, the risk of CHD was 1.83 times higher for each 10-year increase in diabetes duration (95% CI 1.18–2.83; $P < 0.007$). These results persisted in age- and sex-adjusted models and multivariable-adjusted models (HR 1.86, 95% CI 1.17–2.93; $P < 0.008$) (Table 3). Overall, there were 125 deaths. For each 10-year increase in diabetes duration, there was no increase in the risk of all-cause mortality (1.21, 0.91–1.60; $P = 0.19$) (Table 3).

There were 70 non-CVD deaths. The multivariable-adjusted HR per decade of diabetes was 0.87 (95% CI 0.58–1.31; $P = 0.50$) (Table 3).

CONCLUSIONS — Among people with type 2 diabetes, duration of diabetes is significantly and positively related to the risk of CHD mortality. For each decade of duration of diabetes, the 10-year risk of CHD death was 86% greater. Duration of diabetes was not related to CHD morbidity or CVD morbidity or mortality, suggesting a mechanism of action that is specific to CHD death.

The association between duration of type 2 diabetes and the development of CVD is controversial. Some studies have noted an association (4–9), whereas others have not (10,11). In the reports with a significant association, many have used CHD death as an end point (4,5,7,8), suggesting that a unique mechanism may exist between type 2 diabetes and coronary death.

Indeed, an autopsy study demonstrated an association between diabetes duration and the extent of atherosclerosis and myocardial lesions (15). Clinically, patients with diabetes have been shown to have less development of coronary collateral vessels (16). Together, these observations may explain why mortality following a myocardial infarction in patients with diabetes is higher than in patients without diabetes (17).

Further insights regarding the association between diabetes and cardiovascular death may be explained by the Bypass Angioplasty Revascularization Investigation trial. Among participants with diabetes, the trial demonstrated a survival benefit for coronary artery bypass graft (CABG) surgery as compared with percutaneous transluminal coronary angioplasty (18). To elucidate the mechanism for this differential survival benefit, mortality rates from subsequent Q-wave myocardial infarctions were compared. Patients with diabetes who underwent CABG had a lower Q-wave myocardial infarction mortality rate in comparison with diabetic participants who had not undergone CABG (19). Detre et al. hypothesized that this difference may be due to greater vessel patency in patients with diabetes following CABG compared with percutaneous transluminal coronary angioplasty. Indeed, those who underwent CABG had nearly half as many remaining significant lesions (19). It is possible that the positive relation between diabetes duration and CHD death in our study was mediated in a similar way. A greater number of atherosclerotic lesions may exist in those with longer duration of diabetes, thereby increasing the risk of CHD death in the setting of a coronary event. This mechanism may also explain why duration of diabetes was associated with an increased risk for CHD death, but not nonfatal events.

In addition to a possible direct effect of diabetes duration on atherosclerotic lesion formation, several additional mechanisms may be uniquely related to the development of CVD in the setting of longer diabetes duration. Diabetes duration has been shown to increase the risk of microalbuminuria (20,21), and the risk of CHD in the setting of nephropathy has been shown to be markedly influenced by diabetes duration (22). Microalbuminuria is a potent risk factor for CVD among patients with diabetes (23), suggesting an additional mechanism of action to explain

Table 2—*Age- and sex-adjusted 10-year morbidity and mortality rates per 1,000 person-years by 5-year category of diabetes duration*

Outcome	<5 years	5–10 years	>10 years
CVD	308	284	354
CHD	127	127	163
CVD death	59	112	103
CHD death	25	78	76
All-cause mortality	145	207	158
Non-CVD mortality	88	108	66

Table 3—*Risk of events for each 10-year increase in duration of diabetes*

Outcome	Events (*n*)	Crude		Age and sex adjusted		Multivariable adjusted*	
		HR	95% CI	HR	95% CI	HR	95% CI
CVD	193	1.23	0.98–1.54	1.13	0.91–1.41	1.25	0.99–1.57
CHD	86	1.33	0.96–1.84	1.22	0.89–1.67	1.38	0.99–1.92
CVD death	55	1.50†	1.02–2.21	1.30	0.89–1.90	1.44	0.97–2.15
CHD death	36	1.83‡	1.18–2.83	1.59†	1.04–2.42	1.86‡	1.17–2.93
All-cause mortality	125	1.21	0.91–1.60	1.06	0.80–1.39	1.09	0.83–1.46
Non-CVD mortality	70	0.98	0.65–1.48	0.87	0.59–1.30	0.87	0.58–1.31

*Multivariable adjustment includes age, sex, systolic blood pressure, hypertension treatment, total cholesterol, BMI, tobacco use, and electrocardiogram left ventricular hypertrophy; †$P < 0.05$; ‡$P < 0.01$.

the impact of diabetes duration on CHD death.

Vascular reactivity, a marker of impaired endothelial dysfunction, has been shown to be diminished in long-term type 1 diabetes (24), and impaired vascular reactivity may coexist among subjects with early onset coronary artery disease (25). Thus, one may speculate that longer exposure to hyperglycemia may increase the risk of endothelial dysfunction, increasing the risk of CVD.

Other potential mechanisms may exist as well. Heart rate variability has been shown to be reduced among those with diabetes (26). Reduced heart rate variability increases the risk of cardiovascular events (27) and sudden cardiac death among subjects with known heart failure (28). It is possible that a longer duration of diabetes might be associated with autonomic neuropathy and reduced heart rate variability, increasing the risk of cardiovascular death. Additionally, abnormalities in clotting mechanisms have been shown to be associated with diabetes (29,30), suggesting the possibility for an increased risk of acute thrombosis. Lastly, diabetes has been shown to be associated with systemic oxidative stress (31), and long-term exposure to increased amounts of oxidative stress may explain another mechanism for the increased risk of CHD death among diabetic patients.

This analysis is complicated by the observation that longer duration of diabetes is also associated with older age. If our findings were primarily due to confounding by age, we would expect to see similar results in both cardiac and noncardiac causes of death. However, duration of diabetes does not appear to be related to noncardiac death, suggesting that the association between increasing age and duration does not explain our observed association between duration and CHD death.

This study has strengths over prior studies that have examined the relation between diabetes duration and CVD risk. Serial screening of serum glucose enabled the early detection of diabetes. In fact, diabetes is often present 4–7 years before its eventual diagnosis (32). Additionally, we excluded subjects who presented with signs and symptoms that suggested type 1 diabetes. In our analyses, covariate assessment was made contemporaneously with the diagnosis of diabetes. Lastly, all CHD outcomes were adjudicated by a three-member physician panel.

Certain limitations of our study deserve mention. The Framingham Heart Study is neither ethnically nor geographically representative of the U.S. However, the relations of risk factors to CHD outcomes observed in the Framingham Heart Study have recently been validated in six ethnically and geographically diverse cohorts and were found to be applicable in other populations (33). We were also limited in our definition of diabetes, as members of the original cohort of the Framingham Heart Study did not have fasting measures of glucose. Instead, we had to rely on nonfasting glucose ≥200 mg/dl to diagnose diabetes. Indeed, this operational definition of diabetes may be less sensitive for the diagnosis of diabetes and is likely to identify those with more severe diabetes. Lastly, failure to reach statistical significance in some of our analyses may be due to small sample size. Assuming the event rates we observed here, in order to detect HRs on the order of 1.25 (approximately the effects we observed for CVD, CHD, and total mortality) we would need at least 1,060, 2,400, and 1,600 subjects per comparison group, respectively, to ensure 80% power in two-sided analysis with a 5% level of significance.

In conclusion, duration of diabetes increases the risk of CHD death independent of coexisting risk factors. Further research is necessary to understand the pathophysiology of this increased risk.

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