Coronary Heart Disease Risk Equivalence in Diabetes Depends on Concomitant Risk Factors

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OBJECTIVE — Diabetes has been defined as a coronary heart disease (CHD) risk equivalent, and more aggressive treatment goals have been proposed for diabetic patients.

RESEARCH DESIGN AND METHODS — We studied the influence of single and multiple risk factors on the 10-year cumulative incidence of fatal and nonfatal CHD and cardiovascular disease (CVD) in diabetic and nondiabetic men and women, with and without baseline CHD or CVD, in a population ($n = 4{,}549$) with a high prevalence of diabetes.

RESULTS — In both sexes, diabetes increased the risk for CHD (hazard ratio 1.99 and 2.93 for men and women, respectively). Diabetic men and women had a 10-year cumulative incidence of CHD of 25.9 and 19.1%, respectively, compared with 57.4 and 58.4% for nondiabetic men and women with previous CHD. The pattern was similar when only fatal events were considered. Diabetic individuals with one or two risk factors had a 10-year cumulative incidence of CHD that was only 1.4 times higher than that of nondiabetic individuals (14%). However, the 10-year incidence of CHD in diabetic subjects with multiple risk factors was >40%, and the incidence of fatal CHD was higher in these subjects than in nondiabetic subjects with previous CHD. Data for CVD showed similar patterns, as did separate analyses by sex.

CONCLUSIONS — Our results and comparisons with other available data show wide variation in the rate of CHD in diabetes, depending on the population and existing risk factors. Most individuals had a 10-year cumulative incidence >20%, but only those with multiple risk factors had a 10-year cumulative incidence that was equivalent to that of patients with CHD. Until more data are available, it may be prudent to consider targets based on the entire risk factor profile rather than just the presence of diabetes.

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An epidemic of diabetes is occurring in the U.S. and throughout the world (1,2). The major cause of death in diabetic individuals is cardiovascular disease (CVD), and virtually all prospective studies have shown that diabetic individuals have a two- to threefold increased risk of CVD (3).

Despite the increased CVD morbidity and mortality among diabetic individuals, only recently has there been a major focus on preventing CVD and controlling CVD risk factors in this population. The American Diabetes Association (4) and the American Heart Association (5) recently released guidelines for the prevention of CVD in diabetic patients. In addition, the National Cholesterol Education Program Adult Treatment Panel III (ATP III) placed a major emphasis on diabetes (6). In its report, the ATP III panel defined diabetes as a coronary heart disease (CHD) risk equivalent (i.e., an individual having a 10-year risk >20%). This decision was stimulated by findings from a Finnish cohort (7) that showed CHD event rates in diabetic individuals without known CHD were as high as those in nondiabetic individuals with prior CHD and supported by other data showing poor postevent survival in diabetic patients. A recent report of mortality in a population in western Scotland provided similar conclusions in a long-term analysis based on death certificates (8). Although a similar analysis of the Dubbo population data (9) on CHD did not support this equivalence, no separate examination has been reported of CHD event rates in diabetic individuals without known CHD versus those with established CHD in a population-based study in the U.S.

Understanding the extent of CHD risk of diabetic patients is important. Several recent secondary prevention studies in high-risk patients have shown that lowering current LDL cholesterol targets is associated with improved outcomes in diabetic and nondiabetic individuals (10–12). In addition, the results of two studies using statin therapy in high-risk diabetic patients (13,14) suggest that further reduction in CVD events can be achieved by lowering LDL cholesterol even further.

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Abbreviations: ATP III, Adult Treatment Panel III; CABG, coronary artery bypass graft; CHD, coronary heart disease; CVD, cardiovascular disease; IFG, impaired fasting glucose; MI, myocardial infarction; PTCA, percutaneous transluminal coronary angioplasty; SHS, Strong Heart Study.

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

See accompanying editorial, p. 457.

These studies have raised questions about appropriate targets for LDL cholesterol reduction in patients with known CHD and patients with diabetes (15). To make a decision about appropriate targets, it is important to understand absolute CHD and CVD risk and their relation to LDL cholesterol levels for diabetic individuals compared with nondiabetic individuals with prior events.

The Strong Heart Study (SHS) (16,17) contains the largest population-based cohort of diabetic individuals in the U.S. under continuous surveillance. This population has a high prevalence of diabetes-associated CVD (18), and data from this study have been shown to be relevant to other populations with rapidly increasing rates of diabetes. Our analysis examined rates of CHD and CVD in diabetic and nondiabetic members of the SHS population with the aim of providing data that could be useful in formulating therapeutic guidelines.

RESEARCH DESIGN AND METHODS

RESEARCH DESIGN AND METHODS — The SHS is a cohort study of CVD in 13 American Indian tribes or communities in three study centers in southwestern Oklahoma, central Arizona, and North and South Dakota (16,17). A total of 4,549 subjects participated in the baseline exam, which was conducted in 1989–1992. A follow-up exam was conducted in 1993–1995 and another in 1998–1999; each participant is contacted yearly for morbidity and mortality surveillance. The design, survey methods, and laboratory techniques have been previously described (16,17). Participants ranged in age from 45 to 74 years at baseline. The cohort had been followed for up to 12.6 years by the end of 2001. The 1st quartile, median, and 3rd quartile of follow-up for these participants were 9.0, 10.7, and 11.6 years, respectively.

During a personal interview with each subject, information was collected on demographic factors, medical history, medication use, and health-related habits (i.e., physical activity, smoking, alcohol consumption). A 12-lead electrocardiogram and a medical history that included the Rose questionnaire for angina pectoris were collected during each exam. Fasting blood samples and anthropometric measures were collected, and a 75-g oral glucose tolerance test was performed. Blood pressure was measured three consecutive times using standard mercury sphygmomanometers with the patient in the seated position and having rested for 5 min. The mean of the second and third measures was used as the recorded systolic and diastolic blood pressure. Hypertension was defined as systolic blood pressure ≥140 mmHg, diastolic blood pressure ≥90 mmHg, or current use of antihypertensive medication (19). Diabetes was defined by a fasting glucose ≥126 mg/dl, the taking of an oral hypoglycemic agent or insulin, or a report of physician-diagnosed diabetes (20). Impaired fasting glucose (IFG) was defined as a fasting glucose of 100–125 mg/dl.

Outcome variables

Prevalent CVD at enrollment was defined as prior myocardial infarction (MI), prior coronary revascularization (by percutaneous transluminal coronary angioplasty [PTCA] or coronary artery bypass graft [CABG]), previous angiographic documentation of coronary stenoses or pathologic Q waves on the electrocardiogram, or documentation of a previous stroke at the baseline examination. Incident CHD and CVD included fatal and nonfatal events between the date of the baseline survey and 31 December 2001. Deaths were identified through tribal and Indian Health Service hospital records and contact with participants and their families. Nonfatal events were identified at the examination or between examinations by annual surveillance. Medical records were extracted and events were adjudicated by standardized methods, as previously reported (16,17,21,22). Nonfatal CHD was defined as MI and cardiac interventions (i.e., PTCA or CABG) or new angiographic documentation of significant coronary artery stenosis. Nonfatal CVD events included CHD and stroke, and fatal CHD was defined as fatal MI, sudden death due to CHD, or fatal CHD. Fatal CVD events included fatal CHD or stroke or death due to aortic/peripheral arterial disease.

Data analysis

The incidence of fatal and nonfatal events is expressed as a rate (events per 1,000 person-years) and as the 10-year cumulative incidence (in percent). We chose this time frame because clinical risk assessment of individuals is often expressed in 10-year increments. Cumulative incidence was calculated as the number of new events over 10 years divided by the number of participants at risk at baseline. Cumulative incidence was age adjusted by the direct method using the age distribution of the entire SHS sample.

Comparisons focused on CHD and CVD cumulative incidence in diabetic individuals with no prior CHD or CVD events versus nondiabetic individuals with prior events. Baseline risk factors, based on previous analyses, included sex, LDL cholesterol >100, albuminuria >300 mg/g creatinine, hypertension, HDL cholesterol <40, triglycerides >150, current smoking, 4th quartile of fibrinogen (>352 mg/dl), and diabetes duration >20 years. Triglyceride levels, the only continuous variable not normally distributed, was log transformed for analysis and back transformed for data presentation. In Table 1, the SD for triglycerides is reported as the coefficient of variation. Student's t and χ^2 tests were used to compare continuous and categorical variables, respectively. The Cox proportional hazard model was used to calculate age-adjusted hazard ratios (HRs).

RESULTS — Diabetes status could be assessed in 4,465 of the 4,549 men and women age 45–74 years who underwent the baseline examination. Of those, 2,124 had diabetes and 2,341 were nondiabetic (n = 995 [42.5%] with normal fasting glucose and 1,346 [57.5%] with IFG). In the diabetic individuals, 98 (4.6%) had CHD at baseline and 116 (5.5%) had CVD. Among nondiabetic individuals, 47 (2.0%) had baseline CHD and 58 had baseline CVD (2.5%). Diabetic participants with baseline CHD or CVD were older and were more likely to be male, have albuminuria, and have higher blood pressure, LDL cholesterol, triglycerides, and fibrinogen levels and lower HDL concentrations than those without baseline CHD or CVD (Table 1).

Figure 1 shows the 10-year age-adjusted cumulative incidence of CHD by sex, diabetes status, and baseline CHD status. In those without baseline CHD, diabetes increased the risk for CHD in both men and women (age-adjusted HR 1.95 [95% CI 1.57–2.42] and 2.82 [2.25–3.53], respectively). Diabetic men exceeded a 10-year cumulative incidence of 20% (25.9%), and diabetic women had an age-adjusted 10-year incidence of 19.1%. HRs were not substantially different when those with IFG were eliminated from the analyses (2.06 [1.53–2.78] and 3.12 [2.24–4.34] in men and women, respectively). If cases of newly diagnosed diabetes were excluded (18% of men and 12% of women), the 10-year incidences of nonfatal and fatal CHD were 15.77 and

Table 1—*Characteristics of diabetic participants at baseline*

	No previous CVD	Previous CVD	P
n	2,008	116	—
Age (years)	57 ± 8	61 ± 8	<0.0001
Sex (% female)	64	37	<0.0001
Systolic blood pressure (mmHg)	131 ± 21	135 ± 21	0.039
Diastolic blood pressure (mmHg)	77 ± 10	78 ± 11	0.54
BMI (kg/m^2)	32 ± 7	31 ± 6	0.10
HDL cholesterol (mg/dl)	43 ± 12	39 ± 9	0.0002
LDL cholesterol (mg/dl)	103 ± 32	110 ± 34	0.028
Triglycerides (mg/dl)*	143 ± 180	166 ± 201	0.011
Fibrinogen (mg/dl)	325 ± 86	310 ± 76	0.075
Fasting glucose (mg/dl)	208 ± 82	180 ± 64	0.0004
2-h glucose (mg/dl)	297 ± 122	267 ± 115	0.126
Duration of diabetes (years)	9.3 ± 9.3	11.8 ± 10.6	0.0118
HbA_{1c} (%)	8.5 ± 2.5	8.0 ± 2.1	0.020
Current smoking (%)	27	24	0.560
Urinary albumin/creatinine (%)			
Normal	49	46	0.422†
Microalbuminuria	31	32	—
Macroalbuminuria	20	23	—

Data are means ± SD unless otherwise indicated. Student's *t* test and χ^2 tests were used to compare continuous and categorical variables, respectively. *Triglyceride data were log transformed for analyses and back transformed for report. The triglyceride SD is reported as the coefficient of variation; the values are the geometric means. †χ^2 test with 2 degrees of freedom.

12.03% for men and 13.02 and 9.59% for women. The 10-year cumulative incidence of CHD in nondiabetic participants with previous CHD was much higher (57.4 and 58.4% in men and women, respectively), and rates in diabetic individuals with previous CHD were only slightly greater in men and equal in women (61.1 and 58.1%, respectively). The pattern was similar if only fatal events were considered (Fig. 1, darker portion of bars). Fatal CHD in participants without previous CHD occurred more often in diabetic than in nondiabetic individuals (10.5 vs. 4.0% in men and 7.7 vs. 2.0% in women). These 10-year values were not as high as in nondiabetic individuals who had previous CHD (17.3% in men and 11.6% in women).

Data using CVD rather than CHD showed similar patterns. In diabetic men and women without prevalent CVD, the 10-year cumulative incidences were 34.0 and 24.3%, respectively (age-adjusted HR 1.86 [1.52–2.26] and 2.89 [2.36–3.54]). Much higher 10-year incidences were observed in men and women with prevalent CVD without (61.7 and 62.7%, respectively) and with (65.6 and 66.7%, respectively) diabetes.

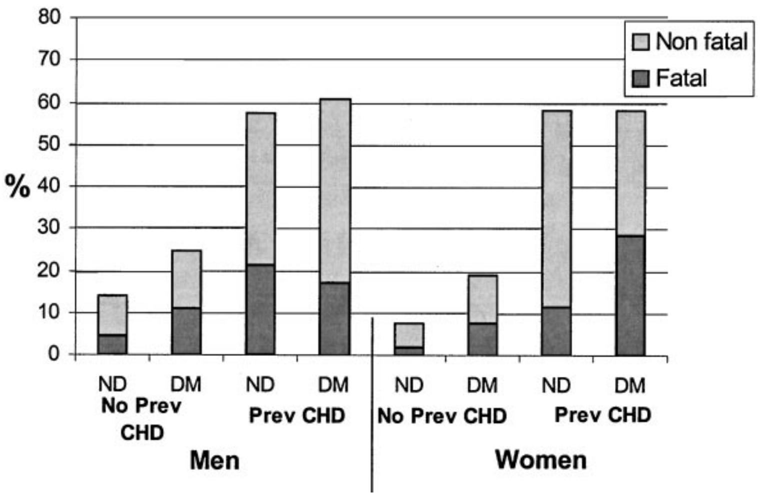

Figure 1—*The 10-year cumulative incidence of CHD in men and women by diabetes status and previous CHD. Data are 10-year cumulative incidences. Corresponding data for incidence rates (per 1,000 person-years) for men for total CHD were 16.9 (1.0 reference group) and 33.9 (HR 2.0 [95% CI 1.6–2.5]) in nondiabetic (ND) and diabetic (DM) men without previous (Prev) CHD and 104.8 (HR 4.7 [3.0–7.3]) and 138.3 (6.4 [4.5–9.2]) in nondiabetic and diabetic men with previous CHD. For women, the total CHD rates/1,000 person-years were 6.8 (1.0 reference group) and 24.6 (HR 3.5 [2.8–4.5]) in nondiabetic and diabetic women without previous CHD and 98.0 (12.8[5.1–32.0]) and 116.3 (14.5 [8.7–24.0]) in nondiabetic and diabetic women with previous CHD. The rates per 1,000 person-years for fatal CHD in men were 5.2 (1.0 reference group) and 15.0 (HR 1.6 [1.2–2.1]), 39.3 (2.2 [1.1–4.5]), and 45.0 (1.6 [1.0–2.6]) and 1.4 (1.0 reference group), 10.3 (HR 2.1 [1.3–3.4]), 39.2 (2.7 [0.6–12.7]), and 64.0 (4.1 [1.9–8.9]) in women.*

Figure 2 shows the combined 10-year cumulative incidences of CHD in men and women. Diabetic participants without baseline CHD were separated into four strata based on the number of cardiovascular risk factors. The 10-year cumulative incidence differed markedly depending on the number of risk factors. Compared with nondiabetic individuals, diabetic participants with one or two risk factors (*n* = 430; 20.24%) had only a 1.4 times higher CHD rate (10-year incidence 14%). On the other hand, the 10-year CHD incidence in diabetic participants with 7–9 risk factors (*n* = 52; 2.5%) exceeded 40% but remained lower than that in nondiabetic individuals with previous CHD. When only fatal CHD was considered (Fig. 2, darker portion of bars), the incidence in those with 7–9 risk factors became higher than that in nondiabetic individuals with baseline CHD (30.0 vs. 20.3; *P* = 0.02). Similar patterns were observed using broader CVD criteria. Rates of CVD in diabetic individuals with no prevalent CVD were 17.5, 25.9, 42.1, and 50.0% in those with 1–2, 3–4, 5–6, and 7–9 risk factors, respectively, whereas event rates in individuals with previous disease were 60.3% in nondiabetic and 70.7% in diabetic individuals. For fatal CVD, the 10-year cumulative incidence in those with multiple risk factors was higher than in nondiabetic individuals with previous CVD (34.0 vs. 27.6%; *P* = 0.03; data not shown).

CONCLUSIONS

— Diabetic individuals without prevalent CHD at baseline had a two- to threefold higher incidence of CHD, with a 10-year cumulative incidence of 25.9 and 19.1% in men and

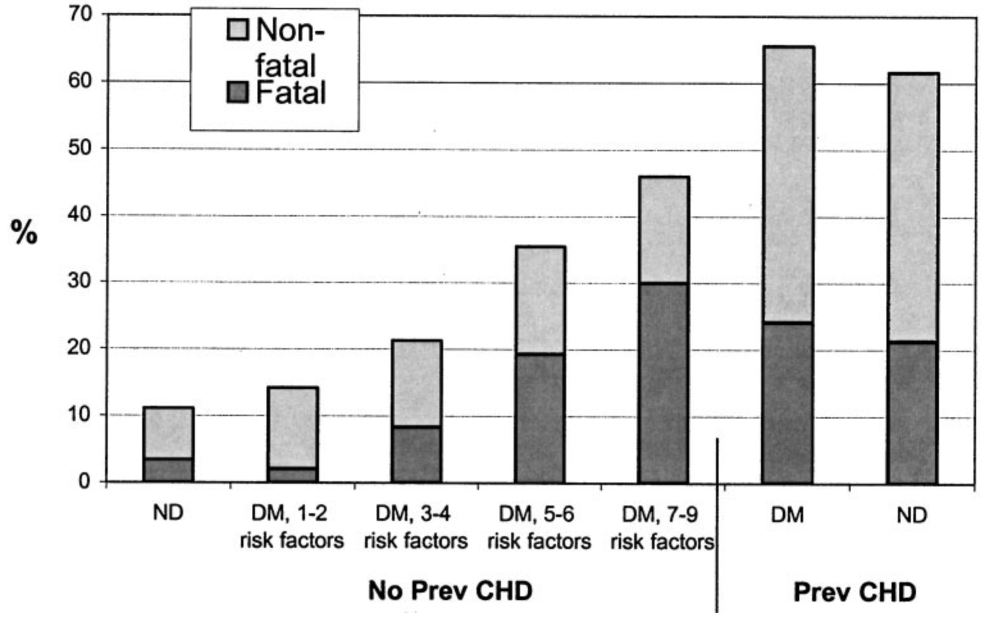

Figure 2—*The 10-year cumulative incidence of CHD by numbers of risk factors (men and women combined). Baseline risk factors include sex, LDL cholesterol >100 mg/dl, albuminuria (>300 mg/g creatinine), hypertension, HDL <40 mg/dl, triglycerides >150 mg/dl, current smoking, 4th quartile of fibrinogen (>352 mg/dl), and diabetes duration >20 years. DM, diabetes; ND, no diabetes; Prev, previous.*

women, respectively. The incidence of CHD in nondiabetic men and women with prior CHD, however, was 57.4 and 58.4%, respectively. Thus, in this population-based sample of diabetic individuals, although the 10-year cumulative incidence reached or exceeded the ATP III–defined level of CHD risk equivalence (>20%/10 years), the cumulative incidence in nondiabetic as well as in diabetic individuals with prior CHD (i.e., those who have been termed at high risk) (15) was considerably higher. The same pattern was observed when a broader category of CVD (CHD plus stroke) was considered as the end point.

When diabetic individuals were stratified by the number of risk factors, wide variation was seen in CHD and CVD events. This is consistent with many reports of the role of CVD risk factors in diabetic individuals from our study (SHS) (4,5,17,18,23–26). In diabetic individuals with one or two additional risk factors, the 10-year cumulative incidence was only 1.4-fold higher than in those without diabetes and thus would not be considered consistent with ATP III CHD risk equivalence. On the other hand, CHD rates increased markedly with an increasing number of risk factors, exceeding the 20% threshold in the groups with multiple risk factors. Although the rates for nonfatal events did not approach those of nondiabetic individuals with prior CHD or CVD, both CHD and CVD mortality in diabetic individuals with multiple risk factors was equivalent to that of individuals with prior CVD or CHD. The cumulative effect of risk factors in diabetic patients was similar to that shown in analyses from the Atherosclerosis Risk in Communities (27) and Framingham (28) studies, and this heterogeneity of risk in diabetic individuals has long been described in publications focusing on individual risk factors in diabetic individuals (4,5,25,26).

This study is a population-based sample, and the relative homogeneity of the population, the high rates of diabetes, and the minimal loss to follow-up ensure comprehensive data collection. The earlier age of diabetes onset in this population makes the data more reflective of the full age range of diabetic individuals and not just those who develop diabetes in later years. However, the question arises concerning the ability to generalize these analyses, which came from a specific ethnic group. We compared our incidence rates with published data for CHD and CVD in nondiabetic and diabetic individuals with and without prior disease from population-based studies (7–9,29–31) as well as from the placebo groups of recent primary and secondary prevention trials (13,14,32–38). In making comparisons across studies, it is important to note that end point definitions vary, with some studies including interventions and others only fatal and nonfatal MIs for CHD. In the current therapeutic climate of implementing early intervention before permanent ischemia ensues, it is reasonable to include individuals undergoing PTCA or CABG in the CHD category. Other studies included angina as well as CHD and stroke for CVD.

Despite these differences, the incidence rates for those with and without diabetes and no prior vascular disease in our analyses were comparable with those for other populations (7,9,27,29–31), with most studies (9,27,29–31) showing an approximately two- to threefold increased incidence in diabetic individuals. Although trials are not optimal studies to assess CHD risk, our CHD rates were somewhat lower than those of some of the placebo groups of the primary prevention trials (32,34), where patients at high-risk were selected. When comparing the incidence rates for individuals with prior disease, more variation is seen. Rates in this study for individuals without diabetes but with prior disease were higher than the rates from the study in the Finnish population (7) but comparable with rates from most other studies (9,13,29,35–38). Rates in diabetic individuals with previous disease in most secondary prevention trials were similar to or even higher than in this study (13,35,37,38). It should be emphasized that variations in health care access in diverse populations may contribute to variability in rates of recurrent events. Of particular importance is that there may be varied use of statins, ACE inhibitors, and other agents (e.g., aspirin) that may influence CVD rates depending on the study population and year of baseline exam. The impact of using these agents, which was not common practice at the time of the study's baseline but would have become increasingly common over the course of follow-up, must be considered in making comparisons of contemporary to earlier studies. It also is important to note that most publications analyze events with a follow-up of ≤10 years, whereas the long-term effects of diabetes and the amplification of risk factors may magnify over time. Results from a study in Scotland support this assertion, although that population differs from the U.S. population and the diabetes was underascertained and thereby skewed toward greater severity (8).

In conclusion, recent evidence of benefit from trials that achieved LDL cholesterol targets lower than the current recommended 100 mg/dl have led to discussion about more aggressive targets for lowering LDL cholesterol. The recent update of the APT III guidelines (15) suggests that a goal of <70 mg/dl could be appropriate in populations who are at very high risk. Because diabetes had been classified as a CHD risk equivalent, the question was raised as to whether this target would be appropriate for all diabetic individuals. This issue has been the focus of several thoughtful commentaries (39–41), but these have not been considered in the recent enthusiasm surrounding aggressive lipid lowering. The results of this study, supported by other available data, indicate that wide variation occurs in rates of CVD in diabetic individuals, depending on both the population and the profile of concomitant cardiovascular risk factors. Studies are currently under way to evaluate lower LDL cholesterol targets in diabetic individuals. Until data from these studies are available, it may be prudent to consider targets based on the entire risk factor profile of diabetic individuals. In recent trials of diabetic patients reaching lower targets, the individuals who entered had high levels of associated risk factors, such as hypertension and smoking. It also remains to be determined whether, if all of these risk factors were controlled through maintaining blood pressure at target levels and achieving smoking cessation, the effect of lowering LDL cholesterol would be as significant. Answers to these questions about appropriate targets should be aggressively pursued because they will have major economic as well as public health implications.

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