

Should Diabetes Be Considered a Coronary Heart Disease Risk Equivalent?

Results from 25 years of follow-up in the Renfrew and Paisley Survey

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OBJECTIVE — The purpose of our study was to confirm or refute the view that diabetes be regarded as a coronary heart disease (CHD) risk equivalent and to test for sex differences in mortality.

RESEARCH DESIGN AND METHODS — This was a prospective cohort study of 7,052 men and 8,354 women aged 45–64 years from Renfrew and Paisley, Scotland, who were first screened in 1972–1976 and followed for 25 years. All-cause mortality was calculated as death per 1,000 person-years. A Cox proportional hazards model was used to adjust survival for age, smoking habit, blood pressure, serum cholesterol, BMI, and social class.

RESULTS — There were 192 deaths in 228 subjects with diabetes and 2,016 deaths in 3,076 subjects with CHD. The highest mortality was in the group with both diabetes and CHD (100.2 deaths/1,000 person-years in men, 93.6 in women) and the lowest in the group with neither (29.2 deaths/1,000 person-years in men, 19.4 in women). Men and women with diabetes only and CHD only formed an intermediate risk group. The adjusted hazard ratio (HR) for CHD mortality in men with diabetes only compared with men with CHD only was 1.17 (95% CI 0.78–1.74; $P = 0.56$). Corresponding HR for women was 1.97 (1.27–3.08; $P = 0.003$).

CONCLUSIONS — Diabetes without previous CHD carries a lifetime risk of vascular death as high as that for CHD alone. Women may be at particular risk. Our data support the view that cardiovascular risk factors in diabetes should be treated as aggressively as in people with CHD.

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D iabetes is associated with an increased risk of cardiovascular morbidity and mortality (1,2), but the magnitude of that risk is disputed. In a Finnish study, Haffner et al. (3) showed that individuals with diabetes but without prior myocardial infarction have as high a risk for fatal cardiovascular events as people without diabetes who have survived a myocardial infarction. This was followed by a U.K. study showing that people with

type 2 diabetes were at lower risk of death from all causes and cardiovascular causes and of hospital admission for myocardial infarction than patients with established coronary heart disease (CHD) (4).

Two recent statin trials that included substantial numbers of patients with type 2 diabetes and cardiovascular risk factors showed significant reduction in a composite end point comprising fatal and nonfatal CHD and stroke (5,6), whereas

two trials did not show a reduction (7,8). The purpose of our study was to examine long-term CHD and other vascular mortality associated with having diabetes only, CHD only, both, or neither in a population survey of >15,000 middle-aged men and women who were followed for 25 years. Specifically, we wished to confirm or refute the view that diabetes be considered a CHD risk equivalent and to test for possible sex differences in outcome.

RESEARCH DESIGN AND METHODS

The Renfrew and Paisley Survey is a longitudinal study of 7,052 men and 8,354 women aged 45–64 years screened between 1972 and 1976. The survey was preceded by a census that identified all residents aged 45–64 years in Renfrew and Paisley, an industrial conurbation in the west of Scotland. In all, 79% of eligible subjects in Renfrew and 78% in Paisley accepted a postal invitation to take part in the study (9,10).

All participants in the Renfrew/Paisley Survey signed a confidentiality statement at initial screening agreeing that they would allow members of the research team to access their future medical records. After the establishment of the Argyll & Clyde Health Board local research ethics committee in the 1990s, an application was submitted and approved, ascertaining that this current practice was acceptable.

We divided our cohort into four groups based on their clinical status at the screening examination. These were diabetes with CHD ($n = 77$), diabetes only ($n = 151$), CHD only ($n = 3,015$), and neither diabetes nor CHD ($n = 10,796$). The diagnosis of diabetes was self-reported in 190 subjects. Random blood glucose measured in 4,702 subjects was ≥ 11.1 mmol/l in 38 additional patients, for a total of 228 people with diabetes (1.5%). We were unable to distinguish type 1 from type 2 diabetes or to determine the duration of diabetes before the screening examination; however, it is highly likely

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Abbreviations: CHD, coronary heart disease.

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

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Table 1—Baseline characteristics by presence or absence of diabetes and CHD

	Men				Women			
	Both diabetes and CHD	Diabetes only	CHD only	Neither	Both diabetes and CHD	Diabetes only	CHD only	Neither
n	38	74	1,402	4,938	39	77	1,613	5,858
Mean age (years)	57.5	55.4	55.7	56.6	57.1	55.8	55.4	54.0
Current smoker (%)	42	54	63	58	28	42	49	48
Systolic pressure (mmHg)	159	152	153	147	165	158	156	148
Diastolic pressure (mmHg)	90	86	88	85	93	87	88	88
Hypertensive* (%)	71	47	50	42	64	53	54	41
Serum cholesterol (mmol/l)	6.1	5.8	5.9	5.8	6.5	6.3	6.5	6.4
Cholesterol >6 mmol/l (%)	46	46	43	39	74	57	62	62
BMI (kg/m ²)	26.9	27.3	26.0	25.8	30.0	26.9	26.6	25.5
Social class III manual, IV, or V (%)	68	67	72	68	77	64	61	56

*Blood pressure \geq 160/90 mmHg.

given the age range of our subjects that most had type 2 diabetes (11). Subjects were considered to have CHD if they responded positively to the Rose Angina Questionnaire (12), had severe chest pain lasting >30 min, or one or more of the following Minnesota codes on a six-lead electrocardiogram: 1.1–1.3, 4.1–4.4, 5.1–5.3, or 7.1 (13). A total of 3,092 (20.1%) subjects fulfilled these criteria.

The following risk factors for cardiovascular disease were documented. Smoking habit was classified by mean number of cigarettes smoked per day using the following categories: never smoked, pipe or cigar smoker only, 1–14 per day, 15–24 per day, \geq 25 per day, and ex-smoker of \geq 5 years. We classified social class as I–V based on occupation at the time of screening (14). Participants were asked their usual occupation and, if retired, their last full-time occupation. Women were given their own occupation, except for housewives who received the code for their husband's or father's occupation. Clinical measurements included blood pressure and BMI, derived from height and weight measurements. Plasma cholesterol was measured in a nonfasting sample.

Records kept by the Registrar General in Edinburgh ensured notification of a subject's death (provided it occurred in the U.K.) together with the cause of death according to ICD-9. Less than 1% of patients were known to have emigrated during the course of the study. We considered three mutually exclusive groups of causes of death: CHD (ICD-9 codes 410–414), other vascular deaths comprising deaths from stroke (ICD-9

430–438) and other vascular causes (ICD-9 390–459), and all nonvascular deaths (all other ICD-9 codes). Mortality data were censored at 25 years of follow-up for each participant.

We had complete information on 6,452 men and 7,587 women; therefore, a total of 14,039 participants were included in our analyses. These were performed using SPSS for Windows, version 11 (Chicago, IL). Comparisons of the baseline characteristics for our cohort were by χ^2 test, Student's *t* test, and ANOVA. Mortality in our four groups of patients was calculated as deaths per 1,000 person-years of follow-up. Overall survival was compared using Kaplan-Meier plots. Comparison of CHD and all-cause mortality was undertaken using the Cox proportional hazards model after adjustments for age, smoking habit, blood pressure, serum cholesterol, BMI, and social class. Subjects with CHD only were the referent group. Tests for proportionality in the Cox model gave a nonsignificant result (men $P = 0.13$; women $P = 0.08$), indicating that the proportional assumption was met.

RESULTS— Baseline clinical characteristics for men and women in each of the four groups are shown in Table 1. In all, 112 men and 116 women had diabetes. The average age of men and women with diabetes only and CHD only was 55–56 years. Men with diabetes only were less likely to be current smokers ($P < 0.001$) than subjects with CHD only. The other differences in risk profiles in these two subgroups were small and not statistically significant.

In all, 4,267 (60%) of the men and 3,746 (45%) of the women died during the 25 years of follow-up. There were 192 (84%) deaths in 228 subjects with diabetes and 2,016 (65%) deaths in 3,092 subjects with CHD. The highest mortality was in the group with both diabetes and CHD (37 of 38 or 100.2 deaths/1,000 person-years in men; 37 of 39 or 93.6 deaths/1,000 person-years in women). The lowest mortality was in the group with neither diabetes nor CHD (29.2 deaths/1,000 person-years in men, 19.4 deaths/1,000 person-years in women).

Men and women with diabetes only and with CHD only formed an intermediate risk group. Men with diabetes only had marginally higher mortality than men with CHD only (54.0 vs. 50.5 deaths per 1,000 person-years), whereas women with diabetes only appeared to have a considerably higher risk of vascular death than women with CHD only (46.7 vs. 29.2 deaths per 1,000 person-years) (Fig. 1). Similar trends were observed for each group of causes of death. Specifically, men with diabetes only had marginally higher CHD and other vascular mortality than men with CHD only, whereas women with diabetes only had higher CHD and other vascular mortality than women with CHD only (Fig. 1).

Overall survival over the course of 25 years is shown in Fig. 2. This confirms the similarity in outcome between men with diabetes only and men with CHD only (log-rank $\chi^2 = 0.19$, $P = 0.664$) as well as the difference in outcome between women with diabetes only and women with CHD only (log-rank $\chi^2 = 8.54$, $P = 0.004$). Survival was least in men and

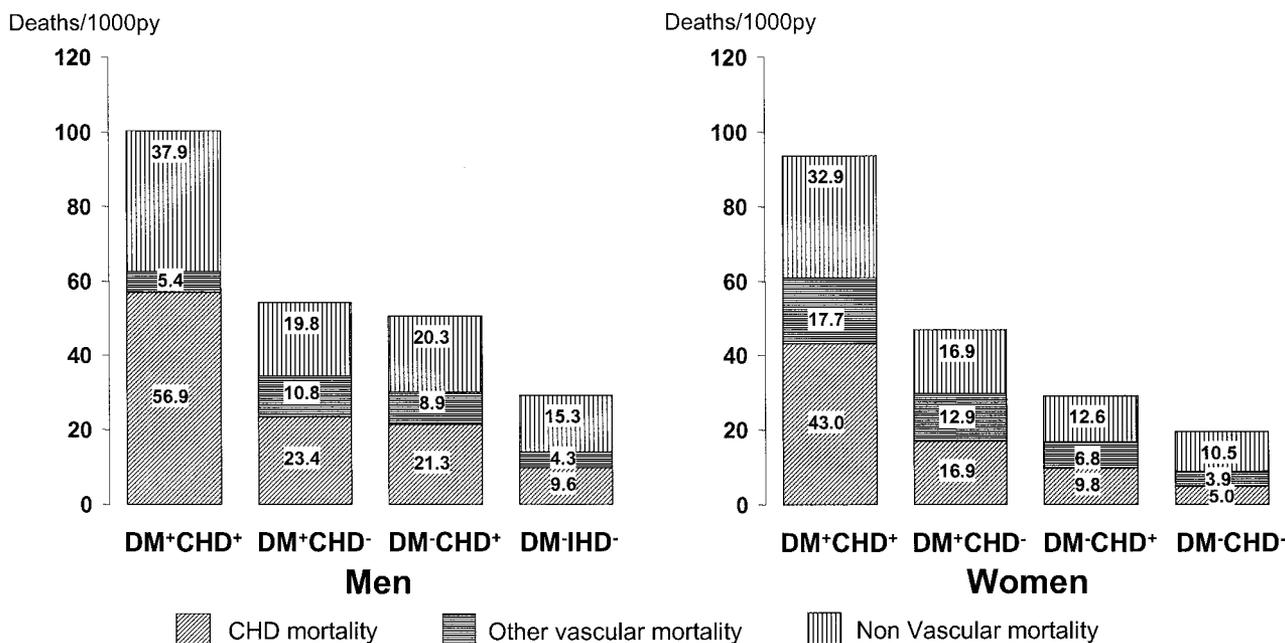


Figure 1—CHD, other vascular, nonvascular, and all-cause mortality in deaths per 1,000 patient-years for men and women with both diabetes and CHD, diabetes only, CHD only, and neither.

women with both diabetes and CHD and greatest in those with neither (Fig. 2).

The similarity in men and the difference in women persisted after adjustments for age, smoking, hypertension, serum cholesterol, BMI, and social class (Table 2). Adjusted hazard ratios (HRs) for CHD and all-cause mortality in men with diabetes only compared with men

with CHD only were 1.17 (95% CI 0.78–1.74; $P = 0.450$) and 1.20 (0.92–1.56; $P = 0.172$), respectively. Corresponding HRs for women were 1.97 (1.27–3.08; $P = 0.003$) for CHD mortality and 1.80 (1.37–2.35; $P < 0.001$) for all-cause mortality. Table 2 also shows HRs for the other covariates in the Cox model. Increasing age, cigarette smoking, hyper-

tension, and hyperlipidemia were all associated with CHD mortality. There were trends toward increased CHD mortality with increasing BMI, but these did not achieve statistical significance. Low social class predicted CHD mortality in women but not men. Increasing age, cigarette smoking, hypertension, and low social class were each associated with all-

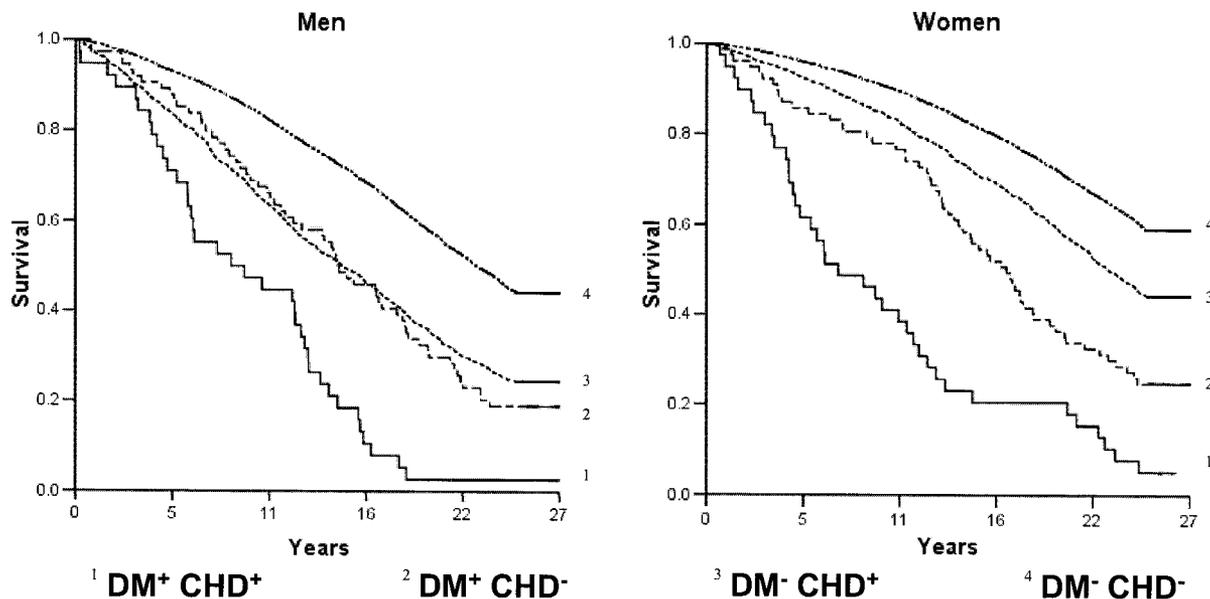


Figure 2—Kaplan-Meier plot showing 25-year survival in men and women with both diabetes and CHD, diabetes only, CHD only, and neither. For comparison between all four groups, $\chi^2 = 316.8$ with $P < 0.001$ in men and $\chi^2 = 253.73$ with $P < 0.001$ in women. For comparison between CHD only and diabetes only, $\chi^2 = 0.19$ with $P = 0.664$ in men and $\chi^2 = 8.54$ with $P = 0.004$ in women.

Table 2—HRs for CHD and all-cause mortality in men and women

	All-cause mortality		CHD mortality	
	Men	Women	Men	Women
<i>n</i>	3,867	3,365	966	1,391
Diabetes and CHD status				
CHD only	1	1	1	1
Diabetes only	1.20 (0.92–1.56)	1.80 (1.37–2.35)*	1.17 (0.78–1.74)	1.97 (1.27–3.08)†
Both	2.34 (1.67–3.26)*	4.33 (3.10–6.04)*	2.84 (1.82–4.42)*	5.86 (3.56–9.67)*
Neither	0.65 (0.60–0.70)*	0.74 (0.68–0.80)*	0.52 (0.46–0.59)*	0.60 (0.53–0.70)*
Other covariates				
Age	1.09 (1.08–1.10)*	1.10 (1.09–1.11)*	1.07 (1.06–1.08)*	1.09 (1.08–1.11)*
Cholesterol <6 mmol/l	1	1	1	1
Cholesterol ≥6 mmol/l	1.01 (0.95–1.08)	0.99 (0.92–1.06)	1.23 (1.11–1.37)*	1.35 (1.17–1.56)*
BMI 20.0–24.9 kg/m ²	1	1	1	1
BMI <20.0 kg/m ²	1.28 (1.14–1.45)*	1.43 (1.28–1.60)*	1.08 (0.86–1.35)	1.33 (1.07–1.65)†
BMI 25.0–29.9 kg/m ²	0.99 (0.92–1.06)	1.03 (0.95–1.12)	1.05 (0.93–1.18)	1.04 (0.89–1.22)
BMI 30.0–34.9 kg/m ²	1.04 (0.90–1.19)	1.16 (1.02–1.31)‡	1.23 (0.99–1.51)	1.22 (0.96–1.49)
BMI ≥35.0 kg/m ²	1.55 (1.05–2.29)‡	1.26 (1.03–1.53)‡	1.64 (0.92–2.98)	1.35 (0.96–1.86)
Never smoked	1	1	1	1
Current smoker	2.04 (1.85–2.26)*	1.68 (1.56–1.81)*	1.94 (1.64–2.29)*	1.81 (1.57–2.09)*
Ex-smoker	1.26 (1.12–1.41)*	1.20 (1.04–1.38)†	1.40 (1.16–1.68)*	1.18 (0.90–1.54)
Normotensive	1	1	1	1
Hypertensive	1.38 (1.29–1.47)*	1.31 (1.21–1.41)*	1.68 (1.50–1.87)*	1.57 (1.37–1.78)*
Social class I, II, III nonmanual	1	1	1	1
Social class III manual, IV, V	1.17 (1.09–1.26)*	1.21 (1.13–1.31)*	1.05 (0.94–1.18)	1.38 (1.20–1.59)*

Data are HR (95% CI). **P* < 0.001; †*P* < 0.01; ‡*P* < 0.05.

cause mortality in both sexes. Hyperlipidemia did not predict all-cause mortality in men or women, whereas BMI ≥35.0 kg/m² did (Table 2).

CONCLUSIONS— The main finding of our study is that, after adjusting for known cardiovascular risk factors, middle-aged men and women with diabetes but no clinical evidence of CHD experience a lifetime vascular risk that is at least as high as (and for women, possibly higher than) that for subjects of similar age who have CHD but no diabetes. In this respect our data reinforce those of Haffner et al. (3) in their study of Finnish men and women. These authors compared the risk of fatal CHD in 890 subjects with type 2 diabetes without prior myocardial infarction and 69 with prior myocardial infarction but no diabetes and found an HR of 1.2 (95% CI 0.6–2.4). When comparing the two studies, however, one should note that Haffner et al. (3) followed their subjects for 7 years rather than 25 years, had only eight deaths in their patients with CHD but no diabetes, and were therefore unable to examine outcome in men and women separately.

Not all authors have reached the same conclusions. Although all recognize that type 2 diabetes is associated with high vascular and all-cause mortality, the belief that diabetes is a CHD risk equivalent is not supported as strongly as we expected, given the views and recommendations of the guideline writers. The Haffner study (3) and an analysis of registry data of patients hospitalized for unstable angina and non-Q-wave myocardial infarction in six different countries (15) both showed that people with diabetes but no previous cardiovascular disease had the same event rates as people with previous cardiovascular disease only. By contrast, the cross-sectional and cohort studies from Tayside (4), the U.S. Physicians Health Study (16), the U.S. Nurses' Health Study (17), and an analysis of data from the Multiple Risk Factor Intervention Trial (MRFIT) (18) all concluded that patients with diabetes only carry lower vascular risks than those with CHD only. So why are there discrepancies in the results?

The studies differ in several respects including age range, sex, criteria for diagnosis of diabetes and CHD, and duration of diabetes. None of these seems likely to account for the discrepancies in results in

our view, except for the duration of diabetes, which varied substantially. Studies comparing incident and prevalent cases of diabetes showed higher mortality risks for prevalent diabetes, presumably by virtue of their longer duration of follow-up (3,17). Hu et al. (17) explored this possibility further and were able to show a linear relationship between duration of diabetes and risk. Diabetes duration of <5 years carried a lesser risk of fatal CHD than previous myocardial infarction. Risks were equivalent after 10 years of diabetes and began to exceed those of previous myocardial infarction after 15 years of diabetes. Although we do not know when subjects in the Renfrew and Paisley Survey first developed their diabetes, the 25-year follow-up guaranteed a long duration of diabetes and may therefore be the main reason why our results support the view that diabetes is a CHD risk equivalent.

Studies such as ours have strengths and limitations. We do not know if there were differences between respondents and nonrespondents because we did not have permission to track the nonrespondents, although we believe that a 79% response rate means that subjects in the

Renfrew and Paisley Survey were likely to have been representative of the general population from which they were drawn. The inclusion of both sexes, the long duration of follow-up, and the large number of deaths are also strengths, as is the adjustment for the effects on outcome of six possible confounding variables including age, smoking habit, blood pressure, cholesterol, BMI, and social class.

Set against these strengths are a number of limitations. The diagnosis of diabetes was for the most part based on the response to the question, "Do you have or have you ever had diabetes?" Self-reporting of medical conditions such as diabetes is considered to be reliable (19), and other studies we reviewed also based their analyses on self-reported illness (16,17). We did not include any new cases of diabetes or CHD after screening. This is not so much a limitation as an acknowledgment that our findings reflect the risks associated with prevalent rather than incident diabetes. We were unable to distinguish type 1 from type 2 diabetes but suspect, given the age range of our cohort, that the majority had type 2 diabetes.

Of greater potential concern is that we may have overestimated the risk of diabetes and underestimated the risk of CHD. Self-reporting might exaggerate the risks of diabetes by excluding milder cases. However, the prevalence of diabetes at recruitment (1972–1976) in the subgroup of subjects who had a random glucose measurement (74 of 4,702 or 1.5%) was not dissimilar from the self-reported prevalence of diabetes (190 of 14,039 or 1.3%). At the time of data collection, the random glucose cutoff for diagnosis of diabetes was generally accepted to be 14 mmol/l. A single random glucose of >11.1 mmol/l (the cutoff point used to extend the diabetes population in our analysis) does not on its own fully validate a diagnosis of diabetes but may be associated with a higher CHD risk than abnormal fasting glucose levels (20). The prevalence of type 2 diabetes has since increased to ~3% (21) as a result of increasing levels of obesity; however, this should not alter the ability of a diagnosis of diabetes made 25 years prior to predict outcome.

We may in addition also have underestimated the risk of CHD, particularly in women, by relying on the Rose Angina Questionnaire. It is well known that a

higher proportion of women with a typical history of angina do not have CHD (22). Even if we did underestimate CHD risk, however, it is unlikely that we did so to the extent that the CHD death rate in women with CHD only (9.8/1,000 person-years) would then have exceeded that in women with diabetes only (16.9/1,000 person-years).

In conclusion, although there remain some differences in the detail, U.S. (23,24), European (25), and U.K. (26,27) guidelines now all recommend that type 2 diabetes be considered a CHD risk equivalent and that people with diabetes should be treated as if they already have vascular disease. The move to more aggressive therapies is supported by the results of the Heart Protection Study (5) and the Collaborative Atorvastatin Diabetes Study (6), which provide clear evidence of benefit from cholesterol lowering drug therapy in patients with diabetes only and no evidence of vascular disease. Two other statin trials containing subgroups of patients with type 2 diabetes failed to show benefit, although the Anglo Scandinavian Cardiac Outcomes Trial simply was not powered to do so (8) and the difference in serum cholesterol between treated and usual care groups in the Antihypertensive and Lipid Lowering Treatment to Prevent Heart Attack Trial was likely to have been insufficient for a difference in outcome to emerge (7). Our study shows that middle-aged men and women with diabetes but no clinical evidence of CHD experience a lifetime vascular risk that is at least as high as (and for women, possibly higher than) that for subjects of similar age who have CHD but no diabetes. These data support the view that patients with type 2 diabetes who have not yet had a myocardial infarction or developed angina should be given the same advice and treatment as is currently recommended for patients with overt vascular disease to prevent vascular events.

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