Impact of Incident Diabetes and Incident Nonfatal Cardiovascular Disease on 18-Year Mortality

The Multiple Risk Factor Intervention Trial experience

LYNN E. EBERLY, PHD[1]
JEROME D. COHEN, MD[2]
RONALD PRINEAS, MD, PHD[3]
LINGFENG YANG, MS[1]
FOR THE MULTIPLE RISK FACTOR INTERVENTION TRIAL RESEARCH GROUP

OBJECTIVE — To report long-term risks for total, cardiovascular disease (CVD), and coronary heart disease (CHD) mortality associated with incident diabetes (using current diagnostic criteria) and with incident nonfatal CVD (NF-CVD).

RESEARCH DESIGN AND METHODS — A total of 11,645 participants without diabetes or CVD at baseline from the Multiple Risk Factor Intervention Trial who survived to the end of the trial were grouped by during-trial incident diabetes and/or NF-CVD events: neither diabetes nor NF-CVD, diabetes only, NF-CVD only, or both diabetes and NF-CVD. Incident diabetes was defined by use of hypoglycemic agents or fasting glucose ≥126 mg/dl at any time over the 6 trial years. Proportional hazards models tested group differences in mortality over 18 post-trial years.

RESULTS — Among 3,859 total deaths were 1,846 from CVD and 1,277 from CHD, with death rates per 10,000 person-years of 203, 97, and 67, respectively. Multivariate-adjusted hazard ratios (HRs) for total mortality were 2.75 ($P < 0.0001$) for those with NF-CVD and diabetes both, 1.92 ($P < 0.0001$) for those with NF-CVD only, and 1.49 ($P < 0.0001$) for those with diabetes only, relative to neither diabetes nor NF-CVD. NF-CVD was associated with a higher hazard of death than diabetes for total (HR 1.29, $P = 0.0004$), CVD (HR 1.76, $P < 0.0001$), and CHD (HR 1.88, $P < 0.0001$) mortality. Only the subgroup of participants on hypoglycemic agents showed an equivalent risk of total mortality relative to participants with NF-CVD (HR 0.93, $P = 0.54$).

CONCLUSIONS — Current diabetes diagnostic criteria conferred significantly increased total, CVD, and CHD mortality risks independent of the impact of NF-CVD. NF-CVD was more strongly predictive of mortality.

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From the [1]Division of Biostatistics, School of Public Health, University of Minnesota, Minneapolis, Minnesota; the [2]Saint Louis University School of Medicine, St. Louis, Missouri; and the [3]Department of Public Health Sciences, Wake Forest University School of Medicine, Winston-Salem, North Carolina. L.Y. is currently at the Department of Biostatistics and Epidemiology, School of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania.

Address correspondence and reprint requests to L.E. Eberly, Division of Biostatistics, School of Public Health, University of Minnesota, 420 Delaware St. SE, Mayo Mail Code 303, Minneapolis, MN 55455-0378. E-mail: lynn@biostat.umn.edu.

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Abbreviations: ADA, American Diabetes Association; CHD, coronary heart disease; CVD, cardiovascular disease; ECG, electrocardiogram; HGA, hypoglycemic agent; HR, hazard ratio; ICD-9, *International Classification of Diseases, Ninth Revision*; ICD-10, *International Classification of Diseases, Tenth Revision*; MI, myocardial infarction; MRFIT, Multiple Risk Factor Intervention Trial; NF-CVD, nonfatal CVD; OASIS, Organization to Assess Strategies for Ischemic Syndromes; SBP, systolic blood pressure; TG, triglyceride.

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

Diabetes is a strong independent risk factor for atherosclerotic diseases (1–11). This has led to the inclusion of diabetic individuals in the highest risk categories in both the sixth report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure and the Adult Treatment Panel III guidelines (12,13). Several studies (8–11) have examined the suggestion of Haffner et al. (7) that individuals with diabetes but no prior myocardial infarction (MI) are at roughly equivalent risk of coronary heart disease (CHD) death as those with a prior nonfatal MI but no diabetes. However, three of these studies relied on prevalent diabetes and/or prevalent MI cases based on self-report or patient registries (7–9); the proximity of the MI and of the diabetes diagnosis to the mortality ascertainment and the collection of risk factor data were variable and sometimes unreported. Two studies used both incident and prevalent cases of diabetes and MI but had limited information on cardiovascular disease (CVD) risk factors (10,11). None of these studies reported using measured fasting glucose or glucose challenge values to identify untreated diabetic individuals, and two included only treated diabetic individuals (7,8). In this article, we use the recent changes in the American Diabetes Association (ADA) criteria for the definition of diabetes (14,15) and examine total, CVD, and CHD mortality after incident diabetes and/or incident nonfatal CVD (NF-CVD) events in the large database of the Multiple Risk Factor Intervention Trial (MRFIT).

RESEARCH DESIGN AND METHODS

MRFIT study design

The design, methods, and results of MRFIT have been previously reported (16–18). Briefly, MRFIT was a randomized controlled trial of the primary pre-

vention of CHD mortality among men ages 35–57 years at baseline who were at increased risk but without definitive clinical evidence of CHD. Men were excluded at Screen 1 if their cigarette smoking, serum cholesterol, and blood pressure measurements did not place them in the upper 10–15% of a risk score distribution or if they had a history of hospitalization for heart attack, diabetes requiring medication, expected geographic mobility, serum cholesterol ≥350 mg/dl (1 mg/dl = 0.0259 mmol/l), or diastolic blood pressure ≥115 mmHg (18). Screen 2 excluded men for body weight >150% of standard, angina pectoris, history or electrocardiogram (ECG) evidence of MI, untreated symptomatic diabetes, diets incompatible with the MRFIT intervention, treatment with certain medications (e.g., hypoglycemic or lipid-lowering agents), illnesses or disabilities likely to restrict full trial participation, and diastolic blood pressure ≥120 mmHg (18). At Screen 3, 12,866 men were randomized to a usual care group (referred to their usual health care provider) or a special intervention group (dietary counseling to lower cholesterol, smoking cessation counseling, and medication for hypertension) (19–21). Through 28 February 1982, participants returned annually for a physician examination, collection of serum (fasting), and completion of a behavioral and medical history questionnaire. Follow-up was >90% at each of six annual visits (18).

Prospective study cohort

For inclusion in this prospective study cohort, men enrolled in MRFIT (n = 12,866) had to have survived to their sixth anniversary of randomization, which enabled us to use all six trial years of risk factor data. Of the remaining 12,436 men (n = 430 during-trial deaths excluded), those with no follow-up fasting glucose determinations (n = 184), who self-reported taking insulin at Screen 2 (n = 41), or who had a glucose level 1 h after a 75-g oral glucose load of >300 mg/dl at Screen 2 (n = 147, 1 mg/dl = 0.0555 mmol/l) were excluded. Also excluded were those men with a Screen 2 fasting glucose of ≥126 mg/dl, the ADA current criterion for diabetes diagnosis (15) (n = 293). Finally, an additional 126 men were excluded because of missing baseline covariate values. Thus, our study cohort had 11,645 men with no evidence of diabetes or CVD at baseline.

Data collection

At Screens 1, 2, and 3 and each annual visit, systolic blood pressure (SBP) and diastolic blood pressure were measured (21). The 12-h fasting serum samples were analyzed at a central laboratory for glucose, total serum cholesterol, triglycerides (TGs), and uric acid (22). In addition, HDL and LDL cholesterol were determined at Screen 2 and annual visits 2, 4, and 6. At Screen 3 and each annual visit, resting (in the supine position) ECGs were recorded electronically (23,24) and were coded (blinded) for Minnesota Code abnormalities (25), both visually and by computer. Cases with discordance for major Q-wave categories were adjudicated by two cardiologists who coded the ECGs separately.

Mortality ascertainment and end point definition

Mortality during the intervention phase (through 28 February 1982) was verified by clinical staff (18); causes of death were coded using *International Classification of Diseases, Ninth Revision* (ICD-9) (26). Post-trial mortality through 31 December 1990 was determined by matching identifying information provided by each participant with National Death Index records (27–29). Death certificates were then obtained; cause-specific mortality was coded independently by two nosologists using ICD-9, and a third nosologist adjudicated disagreements. Dates and causes of death for 1991 through 1998 (ICD-9) and for 1999 (*International Classification of Diseases, Tenth Revision* [ICD-10]) (30) were obtained using the National Death Index Plus service, which has been validated (31–35). Total mortality, CVD mortality (defined by ICD-9 350–459 and ICD-10 I00–I99), and CHD mortality (defined by ICD-9 410–414 and 429.2 and ICD-10 I20–I25) were analyzed here.

Definition of baseline and trial-averaged covariates

Cigarette use (number smoked per day), alcohol use (number of drinks consumed per week), and maternal and paternal histories of diabetes, heart attack, other heart disease, and stroke were determined by self-report at baseline. Proteinuria was recorded at baseline by dipstick as none, trace, 1+, 2+, 3+, or 4+ and dichotomized for this analysis into none/trace vs. 1+ to 4+. The heart rate–corrected QT interval was calculated as 0.179 × QT interval × (heart rate$^{0.42}$) from the baseline ECG.

Disrobed height and weight were recorded at all scheduled visits to calculate BMI in kilograms per meter squared. TGs, HDL cholesterol, LDL cholesterol, and uric acid were measured from the fasting serum samples, as described above. SBP at baseline was defined as the average of the two measurements at both Screens 2 and 3. Annual visit SBP measures were the average of two measurements made at that visit. Six variables (BMI, HDL cholesterol, LDL cholesterol, TGs, uric acid, and SBP) were averaged over the screening and annual visits to obtain a more accurate estimate of each participant's "usual" value (36). Incident thiazide drug use (or β-blocker use) was based on the reporting of a current prescription for any thiazide or thiazide-like diuretic (or β-blocker) at any of the first six annual visits.

Definition of incident diagnosis variables

Diabetes. Incident diabetes was coded if at one or more of the six annual visits a participant reported being on insulin or an oral hypoglycemic drug or if his fasting plasma glucose level was ≥126 mg/dl, as in the current ADA clinical guidelines (15). Use of a single fasting glucose determination to designate diabetic men is consistent with the ADA criteria for epidemiological studies. We use "hypoglycemic agent" (HGA) to refer to both insulin and oral drugs.

Nonfatal CVD event. Incident NF-CVD was defined by any of the following recorded at or before the sixth annual visit: *1*) coronary bypass surgery, *2*) nonfatal stroke, *3*) clinical (nonfatal) MI, or *4*) silent MI on ECG. History of coronary bypass surgery (*1* above) was recorded if at any of the six annual visits a participant self-reported surgery on the heart or arteries during the previous 12 months. Nonfatal stroke was recorded if observations of hemiplegia or hemiparesis were made at any annual visit by a MRFIT physician. MI events (*3*) and (*4*) were defined based on annual visit ECGs compared with each participant's baseline ECG (24,25). A clinical MI was recorded if a prespecified change from baseline in Q-waves was seen or by physician review of

Table 1—*Mortality and risk factor characteristics of study cohort at randomization and averaged across the 6 trial years by incident diabetes and incident NF-CVD groups (mortality follow-up through 1999)*

	Participants who did not develop diabetes or NF-CVD	Participants who developed diabetes but not NF-CVD	Participants who developed NF-CVD but not diabetes	Participants who developed both diabetes and NF-CVD	*P* for group differences
Number in study cohort	9,741	1,122	658	124	—
Number (rate*) of total deaths	2,930 (181)	499 (286)	342 (365)	88 (555)	<0.0001
Number (rate) of CVD deaths	1,320 (82)	245 (141)	228 (243)	53 (334)	<0.0001
Number (rate) of CHD deaths	883 (55)	171 (98)	177 (189)	46 (290)	<0.0001
Baseline characteristics					
Age (years)	46.1 ± 6.0	47.1 ± 5.6	47.3 ± 5.8	48.5 ± 5.6	<0.0001
Black (%)	7	9	4	8	0.0005
Heart rate (beats/min)	70.4 ± 11.0	72.8 ± 11.6	71.3 ± 10.9	71.5 ± 11.6	<0.0001
Heart rate–adjusted QT interval	408.7 ± 17.3	410.2 ± 16.8	411.1 ± 17.4	410.3 ± 17.0	0.0003
Fasting total cholesterol (mg/dl†)	239.7 ± 36.4	238.4 ± 37.4	249.2 ± 37.0	246.9 ± 36.8	<0.0001
Fasting glucose (mg/dl)	96.4 ± 9.9	106.1 ± 10.7	96.5 ± 9.7	104.7 ± 11.6	<0.0001
Proteinuria 1+ to 4+ (%)	3	4	4	2	0.33
Drinks per week	12.6 ± 12.1	12.8 ± 12.9	11.9 ± 12.7	10.7 ± 9.7	0.15
Smoker (%)	63	62	73	76	<0.0001
Cigarettes per day among smokers	34.0 ± 15.3	33.0 ± 15.5	34.8 ± 14.1	35.3 ± 17.9	0.0002
History of parental diabetes	17	26	19	32	<0.0001
History of parental heart disease	60	60	69	71	<0.0001
Trial-averaged characteristics					
HDL cholesterol (mg/dl)	43.1 ± 10.5	39.2 ± 10.2	40.2 ± 8.8	37.4 ± 9.0	<0.0001
LDL cholesterol (mg/dl)	155.3 ± 30.4	144.9 ± 34.1	161.5 ± 28.9	152.1 ± 34.5	<0.0001
Triglycerides (mg/dl)	177.8 ± 97.8	275.9 ± 214.7	190.3 ± 90.2	279.1 ± 181.4	<0.0001
Uric acid (mg/dl)	6.8 ± 1.1	7.1 ± 1.2	6.8 ± 1.1	7.4 ± 1.1	<0.0001
BMI (kg/m^2)	27.3 ± 3.4	29.2 ± 3.8	27.1 ± 3.3	28.5 ± 3.7	<0.0001
Systolic blood pressure (mmHg)	126.0 ± 11.0	129.3 ± 10.7	125.7 ± 11.1	127.9 ± 12.2	<0.0001
Other					
Smoker at sixth annual visit (%)	42	34	43	32	<0.0001
During-trial thiazide use (%)	53	72	59	74	<0.0001
During-trial β-blocker use (%)	17	29	41	52	<0.0001

Data are means ± SD unless otherwise indicated. *Rates are per 10,000 person-years; *P* values for mortality are from log-rank tests; †to convert to SI units: cholesterol, 1 mg/dl = 0.0259 mmol/l; glucose, 1 mg/dl = 0.0555 mmol/l; TG, 1 mg/dl = 0.0113 mmol/l; uric acid, 1 mg/dl = 59.48 μmol/l.

hospitalization records, serum enzyme levels, and ECGs (24).

Statistical analyses

Four "incident diagnosis" groups were created: with neither incident NF-CVD nor incident diabetes, with incident diabetes but no incident NF-CVD, with incident NF-CVD but no incident diabetes, and with both incident NF-CVD and incident diabetes. Participant characteristics were summarized within groups and tested for group differences with ANOVA *F* tests or logistic regression χ^2 tests, as appropriate. We analyzed post-trial mortality from the sixth anniversary of randomization. Death counts, death rates per 10,000 person-years, and Kaplan-Meier curves were computed for each of the four groups and for each mortality type (total, CVD, and CHD). Univariate and multivariate-adjusted proportional hazards models (37), stratified by clinical center, were carried out for each mortality type to test group differences. Adjusting variables were special intervention/usual care, age, race, baseline and sixth annual visit smoking status, alcoholic drinks per week, heart rate, heart rate–adjusted QT interval, height, parental diabetes, parental heart disease, proteinuria, and trial-averaged BMI, SBP, uric acid, TGs, HDL and LDL cholesterol, and thiazide use. Additional models subcategorized participants with incident diabetes into three groups: diabetic participants on HGAs (regardless of glucose level), diabetic participants with glucose ≥140 mg/dl (and no HGA use), and diabetic participants with glucose 126–139 mg/dl (and no HGA use). *P* values given are two-tailed; no adjustments for multiple comparisons were made.

RESULTS — Median post-trial follow-up through 31 December 1999 was 18.5 years with a total of 3,859 deaths, including 1,846 CVD deaths and 1,277 CHD deaths. Death rates per 10,000 person-years for total, CVD, and CHD mortality were 203, 97, and 67, respectively. A total of 1,246 cases of diabetes and 782 NF-CVD events were recorded. Participant characteristics are summarized in Table 1 by the four incident diagnosis groups. All characteristics except alcohol use and proteinuria were significantly different across groups. Of note, those participants who developed diabetes had higher BMI, fasting glucose, TGs, uric

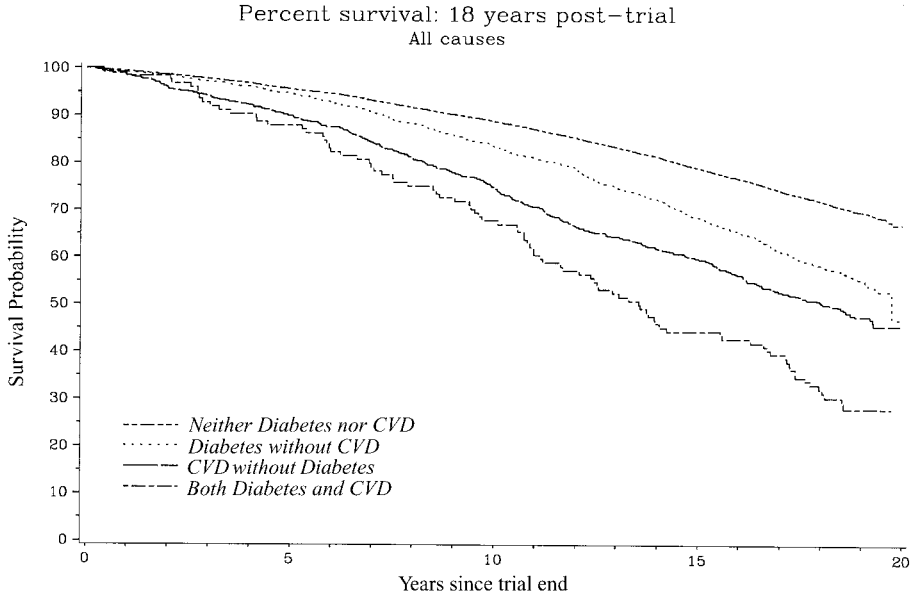

Figure 1—*Kaplan-Meier curves for post-trial total mortality through 1999 for four groups defined by incident diagnosis of diabetes and NF-CVD.*

acid, and blood pressure and lower HDL cholesterol levels.

Kaplan-Meier curves for each of the four groups for total mortality are shown in Fig. 1; curves for CVD and CHD mortality were similar. The separation in the curves begins after roughly the first 2 post-trial years and steadily increases thereafter. Death rates and log-rank tests indicated highly significant differences between the four groups for all three mortality types (Table 1; all *P* values <0.0001). There was a stepwise increase in rates across the four groups from patients with neither NF-CVD nor diabetes to patients with both NF-CVD and diabetes. Death rates for men with NF-CVD only were 30% (for total mortality) to 90% (for CHD mortality) higher than rates for men with diabetes only.

Proportional hazards regression models for mortality showed highly significant differences among the four groups for each cause of death (Table 2). All hazard ratios (HRs) were reduced after adjusting for the potential confounders. Both incident NF-CVD and incident diabetes showed excess mortality risk. The adjusted HR for total mortality, relative to neither NF-CVD nor diabetes, was 1.49 ($P < 0.0001$) for diabetes only, 1.92 ($P < 0.0001$) for NF-CVD only, and 2.75 ($P < 0.0001$) for both NF-CVD and diabetes. Participants with NF-CVD alone were at greater risk than those with diabetes alone (HR 1.29, $P = 0.0004$). Additional adjustment for during-trial β-blocker use gave similar results. Thus, although not posing as great a risk as incident NF-CVD, incident diabetes was a highly significant risk factor for total mortality, independent of incident NF-CVD; furthermore, incident diabetes greatly increased the risk when occurring together with NF-CVD.

Similar results were found for CVD and CHD mortality (Table 2). NF-CVD only is associated with an almost 80% higher risk of CVD death than diabetes only (HR = 1.76, $P < 0.0001$) and an almost 90% higher risk of CHD death than diabetes only (HR = 1.88, $P < 0.0001$).

To examine the impact of the most recent change in ADA diagnostic criteria, participants with incident diabetes diagnoses (n = 1,246) were subcategorized

Table 2—*HRs and 95% CIs for the incident diabetes and incident NF-CVD groups for total, CVD, and CHD mortality (mortality follow-up through 1999)*

	Unadjusted		Multivariate adjusted*	
	HR (95% CI)	*P*	HR (95% CI)	*P*
Total mortality				
With diabetes vs. neither diabetes nor NF-CVD	1.62 (1.47–1.78)	<0.0001	1.49 (1.34–1.64)	<0.0001
With NF-CVD vs. neither diabetes nor NF-CVD	2.12 (1.90–2.37)	<0.0001	1.92 (1.71–2.15)	<0.0001
With diabetes and NF-CVD vs. neither diabetes nor NF-CVD	3.34 (2.70–4.13)	<0.0001	2.75 (2.22–3.42)	<0.0001
With NF-CVD vs. with diabetes	1.31 (1.14–1.51)	0.0001	1.29 (1.12–1.49)	0.0004
CVD mortality				
With diabetes vs. neither diabetes nor NF-CVD	1.77 (1.54–2.03)	<0.0001	1.51 (1.31–1.75)	<0.0001
With NF-CVD vs. neither diabetes nor NF-CVD	3.13 (2.72–3.60)	<0.0001	2.66 (2.30–3.07)	<0.0001
With diabetes and NF-CVD vs. neither diabetes nor NF-CVD	4.50 (3.41–5.93)	<0.0001	3.45 (2.60–4.58)	<0.0001
With NF-CVD vs. with diabetes	1.77 (1.48–2.12)	<0.0001	1.76 (1.45–2.12)	<0.0001
CHD mortality				
With diabetes vs. neither diabetes nor NF-CVD	1.85 (1.57–2.18)	<0.0001	1.62 (1.36–1.93)	<0.0001
With NF-CVD vs. neither diabetes nor NF-CVD	3.63 (3.09–4.27)	<0.0001	3.05 (2.58–3.60)	<0.0001
With diabetes and NF-CVD vs. neither diabetes nor NF-CVD	5.81 (4.31–7.83)	<0.0001	4.56 (3.35–6.20)	<0.0001
With NF-CVD vs. with diabetes	1.96 (1.59–2.42)	<0.0001	1.88 (1.51–2.34)	<0.0001

*Adjusted for special intervention/usual care, age, race, baseline and sixth annual visit smoking status, drinks per week, heart rate, heart rate–adjusted QT interval, height, parental diabetes, parental heart disease, proteinuria, BMI, SBP, uric acid, TGs, LDL cholesterol, HDL cholesterol, and thiazide use.

into three groups: those on HGAs (regardless of glucose level, $n = 218$), those with glucose ≥140 mg/dl (and no HGA use, $n = 495$), and those with glucose between 126 and 139 mg/dl (and no HGA use, $n = 533$). Participants with glucose between 126 and 139 mg/dl contributed 43% of the diabetes cases and increased the incidence of diabetes by 75%. Across these three subgroups of participants with diabetes only, a strong gradient was observed in the associations with total mortality: relative to men with neither diabetes nor NF-CVD, HR = 2.07 ($P < 0.0001$) for men with HGA use, 1.65 ($P < 0.0001$) for those with fasting glucose ≥140 mg/dl and no HGA use, and 1.19 ($P = 0.03$) for those with fasting glucose between 126 and 139 mg/dl and no HGA use. Relative to men with incident NF-CVD only, we again saw a gradient of risk: HR = 0.93 ($P = 0.54$) for men with HGA use, 1.18 ($P = 0.09$) for those with glucose ≥140 mg/dl but no HGA use, and 1.61 ($P < 0.0001$) for those with glucose between 126 and 139 mg/dl but no HGA use. Results were similar for CVD and CHD mortality. Thus, incident NF-CVD was equally predictive of mortality compared with incident HGA-treated diabetes but showed a greater risk for mortality compared with incident diabetes diagnoses defined only by a modestly elevated fasting glucose.

CONCLUSIONS — The major impact of diabetes as a risk factor for CVD has been emphasized in the guidelines from the sixth report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure and the Adult Treatment Panel III (12,13), both of which place diabetic individuals in the highest risk status category. The magnitudes of prior risk estimates were based on diagnostic criteria for diabetes that have recently been changed by the ADA (14,15). From current ADA criteria, our data confirm some findings from previous studies (1–11) and extend them to incident diabetes and CVD cases. Among the cohort of MRFIT survivors, men without diabetes who had a during-trial NF-CVD event had higher mortality compared with those with during-trial incident diabetes but without NF-CVD. However, both groups had higher mortality than those who had neither incident NF-CVD nor diabetes. The excess risk attributable to diabetes was also evident for CVD and CHD mortality. The excess mortality risk attributable to NF-CVD was stronger for CVD and CHD mortality than for total mortality. Further, men with only NF-CVD had the equivalent risk for total mortality as men with only diabetes and on HGAs. Use of incident cases and concurrently measured risk factor variables avoids the confounding of results that could come from two sources: differences due to each disease's impact on mortality and differences due to the relative proximity of each disease's occurrence to the study period. Use of incident cases makes the latter issue moot, except for in those with both diabetes and NF-CVD. For the 124 men with both, we could not determine which disease occurred first.

Prior studies on the association of diabetes and NF-CVD with mortality have not used incident diabetes cases based on both treatment and measured glucose levels according to the current ADA criteria, and most have not had such long-term mortality follow-up and extensive CVD risk factor data. In a study of a Finnish population group totaling 2,432 men and women Haffner et al. (7) reported a high risk of CHD mortality for prevalent treated diabetes cases without prior MI. These investigators found that the group with prevalent diabetes but without MI had a multivariate-adjusted HR of 1.2 (95% CI 0.6–2.4) for CHD mortality compared with the group with prevalent MI but without diabetes over a 7-year follow-up. This excess risk was not statistically significant; there were only 69 individuals in the nondiabetic subgroup with prior MI. Mean duration of diabetes was roughly 8 years; mean time since MI was not reported. Malmberg et al. (8) followed 8,013 individuals admitted to a hospital for unstable angina or MI in the Organization to Assess Strategies for Ischemic Syndromes (OASIS) study and categorized each as with or without diabetes according to self-report on dietary or HGA treatment for diabetes. After a 2-year follow-up, the multivariate-adjusted HR for diabetes was 1.6 (95% CI 1.4–1.8) for total mortality and 1.5 (1.3–1.7) for CVD mortality; CHD mortality was not reported. Mean duration of diabetes was also not reported. The differences between our study results and these two studies are likely due to a number of factors, including the larger sample size and longer follow-up in MRFIT, the different diagnostic criteria used for defining diabetes, the younger mean age and use of incident rather than prevalent cases in MRFIT, the proportion of women (50% in the Finnish study, 39% in the OASIS study), and the selection of men at high risk for CHD in MRFIT.

In the U.S. Physicians' Health Study, 91,285 male physicians self-reported diabetes status, prior CHD status (MI or angina pectoris), and various risk factor levels at baseline (9). After 5 years of follow-up, the age-adjusted HR for CHD versus diabetes was 0.96 ($P > 0.05$) for total mortality, whereas it was 1.7 ($P < 0.05$) for CHD mortality; multivariate adjustment did not materially alter the results. Mean duration of diabetes or time since CHD was not reported. These HRs are slightly lower than ours; however, they were computed over a much shorter follow-up using self-reported diabetes and self-reported nonfatal CHD events rather than NF-CVD events. Similar analyses were done for 121,046 female participants in the U.S. Nurses' Health Study (10) but incorporated both prevalent (at baseline) and incident (over ten consecutive periods of 2-year follow-up) self-reported cases of diabetes and MI. The multivariate-adjusted relative risks comparing patients with MI to patients with diabetes were 1.1 ($P > 0.05$) for total mortality and 1.9 ($P < 0.05$) for CHD mortality. Despite our exclusion of during-trial deaths (which likely resulted in lower HRs), our inclusion of only men at slightly higher risk of CVD death may have led to our greater HRs for total mortality.

This study used both measured fasting glucose values and treatment information to determine diabetes status. There was an increase in risk across the groups defined by incident fasting blood glucose level of 126–139 mg/dl with no HGA use, incident fasting blood glucose level ≥140 mg/dl with no HGA use, and incident HGA use regardless of glucose level. In addition, the highest diabetes risk group (patients with HGA use) had risks for mortality similar to men who had incident NF-CVD and no incident diabetes. Previous studies also have shown a risk gradient with glucose (38) or HbA_{1c} levels (39) (not available in MRFIT). The Cardiovascular Health Study focused on older adults and found the prevalence of both clinical and subclinical CVD, as well as the proportion of clinical disease rela-

tive to subclinical disease, to be higher in patients with glucose disorders than in subjects with normoglycemia (40). The authors concluded that factors associated with glucose disorders promote atherosclerosis and its progression to clinical disease. Consistent with these findings are those of the present study, which show that factors associated with the metabolic syndrome (13) are characteristic of the participants who develop diabetes, and patients with diabetes have a higher risk of CVD mortality than those without. Thus, the metabolic syndrome may predate the onset of clinical diabetes.

One limitation of our study is that it included only relatively high-risk middle-aged men. In addition, whereas we incorporated 6 years of risk factor data in all analyses, these 6-year summary measures are not necessarily representative of the participant's risk factor profile over the subsequent 18-year mortality follow-up. We also have no information on any nonfatal events during that follow-up period. Whereas ADA guidelines (15) for epidemiologic studies require only one fasting glucose determination, this does potentially misclassify men who had an isolated high reading. Requiring two consecutive high readings (in our case, a full year apart) would have restricted the study cohort diabetes groups to individuals at even higher risk and moved individuals with a single high reading to the "no diabetes" groups. Thus, both groups would see increased risk, resulting in similar group differences to those shown here.

In summary, using the current diagnostic criteria for diabetes, this study confirms and extends previous observations of the importance of the increased risk associated with incident diabetes on total, CVD, and CHD mortality independent of incident NF-CVD, even for patients with glucose between 126 and 139 mg/dl. The magnitude of this significant effect of diabetes increased with the severity of the disorder, as assessed by fasting glucose level and use of HGAs. These findings confirm the wisdom of the inclusion of diabetic individuals in the highest risk categories for aggressive management of frequently coexisting CVD risk factors, especially hypertension and/or dyslipidemia, and of changing the diabetes diagnostic criteria so that more individuals at higher risk for CVD mortality are now recognized.

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