Impact of Diabetes and Previous Myocardial Infarction on Long-term Survival

25-Year Mortality Follow-up of Primary Screenees of the Multiple Risk Factor Intervention Trial

Olga Vaccaro, MD; Lynn E. Eberly, PhD; James D. Neaton, PhD; Lingfeng Yang, MS; Gabriele Riccardi, MD; Jeremiah Stamler, MD; for the Multiple Risk Factor Intervention Trial (MRFIT) Research Group

Background: The magnitude of coronary mortality risk associated with diabetes or prior myocardial infarction (MI) is debatable. Modulating effects of age, risk factors, and duration of follow-up may explain discrepancies in previous research. Associations with noncardiovascular mortality are little explored.

Objectives: To compare mortality patterns in men with a history of diabetes or MI and to assess modulating effects on mortality of age, cardiovascular risk factors, and follow-up duration.

Methods: We compared the 25-year mortality of 4809 men with diabetes only and 4625 men with MI only (all men aged 35-57 years).

Results: The adjusted hazard ratio (HR) for all-cause mortality for those with MI only vs those with diabetes only was 0.97 (95% confidence interval, 0.92-1.03; P = .32).

The pattern of deaths was different: higher coronary mortality (HR=1.37; P < .001) and lower mortality from noncardiovascular causes (HR=0.66; P < .001) in those with MI only compared with those with diabetes only. This finding prevailed across all ages and levels of cardiovascular risk factors. Hazard ratios for coronary mortality significantly declined over follow-up (2.7, 1.7, 1.2, 1.1, and 1.0 for ≤5, 6-10, 11-15, 16-20, and ≥20 years of follow-up, respectively), whereas HRs for noncardiovascular mortality remained relatively constant.

Conclusions: Overall, diabetes and MI were similarly strong predictors of total mortality. Higher mortality from noncardiovascular causes was observed in those with diabetes only, whereas prior MI was more strongly predictive of coronary mortality than diabetes at any age and level of cardiovascular risk factors. The difference in coronary mortality between the 2 groups was most evident in the first 10 years of follow-up.

Arch Intern Med. 2004;164:1438-1443

Diabetes mellitus is widely recognized as a strong independent risk factor for coronary heart disease (CHD). Several epidemiologic studies have confirmed that men with diabetes are 2 to 3 times more likely to die from CHD than those without diabetes and that the risk is even higher in women. Prior myocardial infarction (MI) is also a strong risk factor for coronary and cardiovascular disease (CVD) mortality. Expert groups have recommended that CHD-CVD prevention in all patients with diabetes include measures as vigorous as those for people with a prior MI, implying that the 2 conditions have a similar impact on risk. However, whether the excess cardiovascular risk conferred by diabetes rivals that of a previous MI has been explored only to a limited extent and with apparently inconsistent results. One investigation reported that diabetes and previous CHD were equally strong predictors of both CHD and all-cause mortality, but this conclusion has been challenged by results of later studies. The modulating roles of age, major cardiovascular risk factors, and duration of follow-up have been incompletely explored and may partly explain discrepancies. Furthermore, there is evidence that risk of noncardiovascular mortality is also increased in people with diabetes, but limited information exists on the comparative associations of MI and diabetes with noncardiovascular mortality. Clarifying these issues might provide evidence for enhanced risk stratification and preventive strategies.

The large sample size and long follow-up of men screened for the Multiple Risk Factor Intervention Trial (MRFIT) provide the opportunity to explore relations of diabetes and previous MI to cardiovascular and noncardiovascular mortality. Unlike previous studies, the present investigation has substantial power and has
collected sufficient information to permit detailed analyses of patterns of deaths in men with diabetes and/or previous MI and to study modulating effects thereon of major cardiovascular risk factors, age, and duration of follow-up.

**METHODS**

**STUDY COHORT AND BASELINE MEASUREMENTS**

The MRFIT was a randomized controlled trial on the primary prevention of CHD in men at high CHD risk. During 1973-1975, 361662 men aged 35 to 57 years were screened for trial participation at 22 centers in 18 US cities; details have been reported. Logistical and cost constraints related to the need to screen hundreds of thousands of men to recruit almost 13,000 eligible subjects for the trial limited initial data collection to established major CHD risk factors only: cigarettes currently smoked per day, serum cholesterol level, and systolic and diastolic blood pressure. Additional information was collected to apply simple exclusion criteria: age, self-reported current use of medication for diabetes, and self-reported previous hospitalization for heart attack. Participants were asked to identify themselves as American Indian, Asian, black, Hispanic, white, or other ethnicity. Income data were later estimated by matching ZIP code of residence with data (median family income by ZIP code) from the 1980 US population census. In the present study, we use race-specific median family income (black and nonblack). Our report focuses on the comparison of 4809 men who reported using medication for diabetes and not being previously hospitalized for a heart attack (diabetes only) and 4625 men who reported prior hospitalization for a heart attack and not taking medication for diabetes (MI only).

Blood pressure of seated participants was measured according to a uniform protocol: first and fifth Korotkoff sounds identified systolic and diastolic blood pressure. Three readings were taken; the mean of the last 2 was used in analyses. Serum cholesterol level (nonfasting) was determined in 1 of 14 laboratories under supervision of the MRFIT central laboratory in San Francisco, Calif, and the Lipid Standardization Laboratory, Centers for Disease Control and Prevention, Atlanta, Ga.

**MORTALITY ASCERTAINMENT**

Prior to 1979, a data file of known deaths provided by the US Social Security Administration was used to ascertain vital status. For 1979 through 1990, the US National Death Index was used. Details on death ascertainment procedures and their validation have been published. Death certificates were coded centrally for underlying cause of death according to the ICD-9-NACM through 1990. Dates and causes of deaths from 1990 through 1999 were obtained through the National Death Index-Plus service. Total CVD deaths (ICD-9-NACM codes 390-459) were further subdivided into deaths from myocardial infarction (code 410), other CHD (codes 411-414, 429.2), stroke (codes 430-438), and other CVD. Among noncardiovascular causes, deaths from diabetes (code 250), end-stage renal disease (codes 250.4, 274.1, 275.4, 580-591, 593.3-593.5, 593.7, 593.9, 596.0, 600, 753.1), and cancer (codes 140-208) were analyzed. During follow-up, only mortality data were collected. Thus, information on nonfatal outcomes, revascularization procedures, and drug treatments are not available.

**STATISTICAL ANALYSES**

Baseline characteristics were summarized as means and standard deviations or percentages within each group. Group differences were tested by stratified (by center) analysis of variance and Mantel-Haenszel $\chi^2$ statistics, as appropriate.

Mortality was computed as age-adjusted rate per 10,000 person-years; age adjustment was by the direct method based on age distribution of all men screened. Multivariate Cox proportional hazards models were used to compute hazard ratios (HRs) for those with MI only vs diabetes only using post-screening time to death for all-cause and cause-specific mortality including CHD and non-CVD with stratification by screening center. Except as noted, HRs were adjusted for age at screening, race (white/nonwhite), income, serum cholesterol level, systolic blood pressure, and cigarette smoking status (smoker/nonsmoker).

To explore the impact of age at screening, CHD and non-CVD mortality were analyzed in relation to diabetes and/or previous MI with participants stratified into 5 age groups (35-39, 40-44, 45-49, 50-54, and 55-57 years). Similarly, to assess the modulating role of major cardiovascular risk factors, the cohort was stratified according to risk factor status (systolic blood pressure, $<130$ or $130$ mm Hg; serum cholesterol level $<200$ or $\geq 200$ mg/dL; $<3.58$ or $\geq 3.58$ mmol/L; or current smoker, yes or no). Four categories were created based on number of risk factors: no risk factors; any 1 risk factor only; any 2 risk factors only; and all 3 risk factors. Mortality rates for those with MI vs diabetes only were compared within risk factor strata.

To investigate whether differences in risk for those with MI only vs diabetes only varied over follow-up, proportional hazards models were computed for 5-year intervals of follow-up (for the first 5 years only, years 6-10, years 11-15, years 16-20, and $\geq 20$ years). To test for proportional hazards (constant MI vs diabetes HR over time), an interaction between disease group and failure time was tested.

**RESULTS**

**BASELINE CHARACTERISTICS**

Among the 361662 men screened, 332547 had complete screening data including census data income estimates. Of these, 322775 men reported neither a history of hospitalization for heart attack nor taking medication for diabetes, and 338 reported both. These groups are not the focus of the present report; however, 25-year mortality rates for these groups are included for reference in Table 1.

Table 2 gives baseline data for participants in the 2 disease history groups that are the focus of the present report. Men with diabetes only had higher blood pressure and smoked more cigarettes than men with MI only; they also had lower income and were also more likely to be nonwhite. Men with MI were older and had higher serum cholesterol levels.

**TOTAL AND CAUSE-SPECIFIC MORTALITY**

With median follow-up 25 years, 5570 deaths were recorded, 2715 among the 4625 men with MI only and 2855 among the 4809 men with diabetes only (HR = 0.97; 95% confidence interval, 0.92-1.03; $P = .32$) (Table 1 and Table 3). The pattern of mortality was different for the 2 groups. Cardiovascular disease mortality was greater for men with MI only (HR = 1.25; $P < .001$) owing to an excess of CHD deaths (HR = 1.37; $P < .001$). In contrast, non-CVD mortality was lower among men with MI only than among men with diabetes only (HR = 0.66; $P < .001$).
For all causes of death, rates for men with a prior MI or with diabetes were greater than for men with neither disease history. All-cause mortality was 2.5-fold greater for those with either condition than those with neither condition (Table 1).

For non-CVD mortality, greater mortality among those with diabetes only was primarily due to deaths from diabetes (35 deaths for those with MI only vs 445 deaths for those with diabetes only, 3.2 vs 46.3 per 10,000 person-years) and renal causes (2.0 vs 5.8 per 10,000 person-years for those with MI only vs diabetes only) but not cancer (45.5 vs 40.2 per 10,000 person-years for those with MI only vs diabetes only). Other non-CVD causes, primarily infections (pneumonia and influenza) and digestive diseases (specifically, liver cirrhosis) were also responsible for a higher non-CVD mortality among men with diabetes only (30.9 vs 39.2 per 10,000 person-years for men with MI only vs men with diabetes only).

**BASELINE AGE AND MORTALITY**

Coronary heart disease and non-CVD mortality progressively and significantly increased with age in both groups (Table 4). For each age stratum, CHD mortality rates were significantly higher for men with MI only than for men with diabetes only. However, risk factor–adjusted CHD HRs comparing MI only to diabetes only declined significantly with increasing age: 1.9, 1.9, 1.6, 1.2, and 1.2 (P < .001 for age by disease group interaction). For non-CVD mortality, HRs were significantly lower for those with MI only than for those with diabetes only in each age group; there was no apparent trend in these HRs across age groups.

**BASELINE CARDIOVASCULAR RISK FACTORS AND MORTALITY**

Coronary heart disease mortality increased with number of cardiovascular risk factors for both groups (Table 4). At every level of cardiovascular risk, age-, race-, and income-adjusted HRs were significantly higher for men with MI only than for men with diabetes only (range of HRs, 1.32-1.49). Non-CVD mortality also increased for both groups as the number of risk factors increased. In each stratum, except for the group with no risk factors, age-, race-, and income-adjusted HRs for non-CVD were significantly lower for men with MI only than for men with diabetes only (range of HRs, 0.57-0.69).

---

**Table 1. All-Cause and Cause-Specific Mortality According to History of MI and Diabetes at Initial Screening for the MRFIT**

<table>
<thead>
<tr>
<th>Cause of Death</th>
<th>Neither MI Nor Diabetes</th>
<th>MI Only</th>
<th>Diabetes Only</th>
<th>Both Diabetes and MI</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of Deaths*</td>
<td>Age-Adjusted Rate†</td>
<td>No. of Deaths*</td>
<td>Age-Adjusted Rate†</td>
<td>No. of Deaths*</td>
</tr>
<tr>
<td>All causes</td>
<td>76,419</td>
<td>2715</td>
<td>2855</td>
<td>250</td>
</tr>
<tr>
<td>CVD</td>
<td>30,620</td>
<td>1852</td>
<td>1502</td>
<td>159</td>
</tr>
<tr>
<td>CHD</td>
<td>20,795</td>
<td>1498</td>
<td>1057</td>
<td>126</td>
</tr>
<tr>
<td>Stroke</td>
<td>3168</td>
<td>90</td>
<td>154</td>
<td>10</td>
</tr>
<tr>
<td>Other CVD</td>
<td>6657</td>
<td>264</td>
<td>261</td>
<td>23</td>
</tr>
<tr>
<td>Non-CVD</td>
<td>45,153</td>
<td>841</td>
<td>1334</td>
<td>90</td>
</tr>
<tr>
<td>Cancer</td>
<td>28,244</td>
<td>470</td>
<td>431</td>
<td>32</td>
</tr>
<tr>
<td>Renal disease</td>
<td>665</td>
<td>24</td>
<td>55</td>
<td>3</td>
</tr>
<tr>
<td>Diabetes</td>
<td>1101</td>
<td>35</td>
<td>445</td>
<td>31</td>
</tr>
<tr>
<td>Other</td>
<td>15,143</td>
<td>312</td>
<td>403</td>
<td>24</td>
</tr>
</tbody>
</table>

Abbreviations: CHD, coronary heart disease; CVD, cardiovascular disease; MI, myocardial infarction; MRFIT, Multiple Risk Factor Intervention Trial.

* A total of 688 deaths (646, 22, 19, and 1 in the Neither MI nor Diabetes, MI Only, Diabetes Only, and Both Diabetes and MI groups, respectively) had unknown causes.

† Rates are given as age-adjusted deaths per 10,000 person-years.

**Table 2. Baseline Characteristics for Men Defined According to History of MI and Diabetes at Initial Screening for the MRFIT**

<table>
<thead>
<tr>
<th>Baseline Characteristic</th>
<th>MI Only</th>
<th>Diabetes Only</th>
<th>P Value for Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>50.3 (5.1)</td>
<td>49.1 (5.7)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>DBP, mm Hg</td>
<td>131.9 (17.1)</td>
<td>137.8 (19.2)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>SBP, mm Hg</td>
<td>85.0 (10.9)</td>
<td>86.0 (11.6)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Patients with SBP &lt;130 mm Hg and DBP &lt;85 mm Hg, %</td>
<td>37.5</td>
<td>28.4</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Serum cholesterol, mg/dL [mmol/L]</td>
<td>228.8 (44.2) [5.93 (1.14)]</td>
<td>213.8 (48.0) [5.54 (1.24)]</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Current smoker, %</td>
<td>37.4</td>
<td>36.0</td>
<td>.09</td>
</tr>
<tr>
<td>No. of cigarettes/d for current smokers</td>
<td>23.7 (12.8)</td>
<td>25.8 (14.7)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Nonwhite, %</td>
<td>7.5</td>
<td>16.9</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Income × 1000, $</td>
<td>23.8 (5.8)</td>
<td>22.8 (6.4)</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

Abbreviations: DBP, diastolic blood pressure; MI, myocardial infarction; MRFIT, Multiple Risk Factor Intervention Trial; SBP, systolic blood pressure.

* Unless otherwise indicated, data are mean (SD) or percentage.
DURATION OF FOLLOW-UP AND MORTALITY

Hazard ratios for CHD comparing those with MI only vs those with diabetes only were not constant over follow-up (Table 4). The risk factor–adjusted HR for CHD mortality was greatest for the first 5 years after screening and declined significantly afterwards: 2.7, 1.7, 1.2, 1.1, and 1.0 (P<.001 for follow-up time by disease group interaction). There was no such trend over follow-up for non-CVD mortality. Thus, the trend for all-cause mortality (not shown) was similar to that for CHD mortality (ie, HRs for the 5 follow-up periods were 1.7, 1.2, 0.87, 0.84, and 0.80, respectively).

Findings from long-term follow-up of this large cohort indicate that both diabetes and prior MI were strong independent predictors of all-cause and CHD mortality. Higher proportionate mortality from noncardiovascular causes was observed in those with diabetes only, whereas prior MI was a significantly more powerful predictor of CHD mortality than diabetes. These findings held across all ages and levels of cardiovascular risk factors. The MI–diabetes difference for CHD mortality was not constant over follow-up; it was greatest during the first 5 years and then declined.

Results from previous studies on magnitude of CHD risk associated with diabetes or prior CHD appear inconsistent. In a 7-year follow-up of 2432 Finnish men and women (aged 40–65 years), CHD mortality was as high among diabetic individuals without prior MI as among nondiabetic persons with prior MI.10 Lotufo et al,12 in a 5-year follow-up of 91 285 US male physicians (aged 40–80 years), found that diabetes and prior MI were quantitatively similarly strong risk factors for all-cause mortality, whereas for CHD mortality prior MI was a stronger predictor than diabetes. In the Nurses Health Study of 121 046 women (aged 30–55 years) observed for 20 years, excess risk of fatal CHD for women with clinical diabetes for more than 15 years was similar to that conferred by prior CHD but less for women with diabetes of shorter duration. A report based on analyses of routinely collected data (diabetes registers and hospital admissions) in Scotland showed that patients with type 2 diabetes mellitus were at lower risk of cardiovascular outcomes than patients with established CHD.14 The MRFIT findings differ from the Finnish data but are similar to results for the US physicians, a study with similar design (ie, large sample size and men only) but shorter follow-up. Our results are also in keeping with the data collected in Scotland, although differences in study end points do not allow detailed comparison.

Discrepancies in findings across studies may be due largely to differences in participant age-sex composition, cardiovascular risk factor distributions, proximity of the prior MI to screening, and duration of diabetes. The present study expands current knowledge and clarifies apparent inconsistencies by exploring modulating effects of age, cardiovascular risk factors, and duration of mortality follow-up. In particular, the interaction with follow-up time shown in the present article indicates that the magnitude of the difference in risk of CHD associated with diabetes and MI depends on diabetes duration and on how proximal in time the prior MI is. Although neither date of diabetes diagnosis nor date of prior MI were known, CHD deaths during the first 10 years of follow-up occurred closer in time to diabetes onset and prior MI than deaths occurring after 10 years. Once an individual survived an MI for several years, the hazard of excess CHD death associated with the event declined; that was not the case for diabetes: CHD risk increased with diabetes duration. The interaction with age may partly reflect the same phenomenon. Nonrecognition of this point, among others, may explain differences in results among past studies.

Excess of CHD deaths in MI survivors compared with people with diabetes only was at most only marginally higher owing to higher prevalence of CHD risk factors in the MI only group. Coronary heart disease mortality was in fact consistently higher across all levels of risk factors in participants with a previous MI than in those with diabetes only.

The MRFIT data used herein also included information on noncardiovascular mortality, thus permitting assessment of the whole mortality pattern in people with diabetes or MI. This is particularly relevant since the contribution of noncardiovascular mortality to excess all-cause mortality associated with diabetes has not received as much attention as CVD risk.15–17,26–28 In the present study, although total mortality was quantitatively similar for men with diabetes or previous MI, the relative contribution of causes of death in the 2 groups was different, with substantial excess of deaths from CVD, and in particular recurrent MI, in men with a prior MI and excess mortality from diabetes, renal disease, stroke, and other medical conditions—including infections and digestive diseases—in men with diabetes only. It is unlikely that men with a history of an MI but not diabetes are less susceptible to non-CVD causes other than death from diabetes. A more likely explanation is that there is a competing risk effect between non-CVD mortality and CVD mortality for men with a history of MI. Nevertheless, this information is relevant for diabetes care in the...
clinical setting and in public health because strategies for reducing CVD risk may only partly overlap with measures aimed at reducing noncardiovascular mortality. A comprehensive approach taking into account the multiple modifiable risk factors for late complications in patients with type 2 diabetes mellitus has the greatest potential for prevention, as shown by a recent study in which incidence of both macrovascular and microvascular events was markedly and significantly reduced (about 50%) by a target-driven intensified intervention on multiple risk factors.20

The strengths of the MRFIT data are as follows: extraordinarily large sample size and sufficient power for stratified analyses; long follow-up; and careful baseline measurement of 3 major cardiovascular risk factors. Limitations include lack of data on women and lack of information on type of diabetes, duration of diabetes, and dates of diagnosis and hospitalization for MI. From surveys of representative US population strata, we may assume that over 90% of persons with diabetes aged 35 years or older are likely to have type 2 diabetes mellitus.30 Also, diagnosis of diabetes was based on self-reported use of drugs for this disease; therefore, the MRFIT data may not be fully comparable to results for other diabetic cohorts. Patients taking medication to treat diabetes mellitus are likely to have longer duration of the disease, more severe metabolic abnormalities, and higher prevalence of microvascular complications than people identified with diabetes through population screening. All of these cited conditions are known to increase CVD risk and therefore would have intensified cardiovascular risk in this diabetic cohort. Nevertheless, in the present study, MI was a stronger predictor of CHD mortality than diabetes. In this respect it is relevant to mention that a study conducted on incident cases of diabetes identified through serum fasting glucose among approximately 12000 men randomized into the MRFIT yielded a similar finding.31

In conclusion, results of this study have several implications for clinical practice: First, they support the need for intensive measures for primary and secondary prevention of CHD in diabetic people by correction of coexisting cardiovascular risk factors. Furthermore, since they clearly show that non-CVD mortality is also high in people with diabetes, they support the judgment that survival in patients with diabetes may be considerably improved by a comprehensive approach to the disease, including optimal blood glucose control, screening for and prevention of microvascular complications, careful surveillance for and treatment of infection, and control of major CVD risk factors.

Accepted for publication October 17, 2003.

From the Department of Clinical and Experimental Medicine, Federico II University of Naples (Dr Vaccaro and Ms Riccardi); Division of Biostatistics, School of Public Health, University of Minnesota, Minneapolis (Drs Eberly and Neaton and Mr Yang); Department of Preventive Medicine, Feinberg School of Medicine, Northwestern University, Chicago, Ill (Drs Vaccaro and Stamler). Mr Yang is currently with the Department of Biostatistics and Epidemiology, School of Medicine, University of Pennsylvania, Philadelphia. A list of the principal investigators and senior staff members of the MRFIT clinical, coordinating, and support centers and the National Heart, Lung and Blood In-
stitute (NHLBI) project office were published previously in JAMA. 1982;248:1476-1477.

This work was supported by NHLBI grants R01-HL-43232 and R01-HL-68140. The MRFIT was conducted under contract with the NHLBI, Bethesda, Md.

This article was presented at the American Diabetes Association Meeting; June 18-22, 2002; San Francisco, Calif. We thank the many colleagues who contributed to the accomplishment of the MRFIT.

Correspondence: James D. Neaton, PhD, Division of Biostatistics, 2221 University Ave SE, Suite 200, Minneapolis, MN 55414-3080 (jim@ccbr.umn.edu).

REFERENCES