Association of Coexisting Diabetes and Depression With Mortality After Myocardial Infarction

MARISKA BOT, MSC 1
FRANÇOIS POUWER, PHD 1
MARJ ZUIDERSMA, PHD 2
JOOST P. VAN MELLE, MD, PHD 3
PETER DE JONGE, PHD 1, 2

OBJECTIVE—Diabetes and depression are both linked to an increased mortality risk after myocardial infarction (MI). Population-based studies suggest that having both diabetes and depression results in an increased mortality risk, beyond that of having diabetes or depression alone. The purpose of this study was to examine the joint association of diabetes and depression with mortality in MI patients.

RESEARCH DESIGN AND METHODS—Data were derived from two multicenter cohort studies in the Netherlands, comprising 2,704 patients who were hospitalized for MI. Depression, defined as a Beck Depression Inventory score ≥ 10, and diabetes were assessed during hospitalization. Mortality data were retrieved for 2,525 patients (93%).

RESULTS—During an average follow-up of 6.2 years, 439 patients died. The mortality rate was 14% (226 of 1,673) in patients without diabetes and depression, 23% (49 of 210) in patients with diabetes only, 22% (118 of 544) in patients with depression only, and 47% (46 of 98) in patients with both diabetes and depression. After adjustment for age, sex, smoking, hypertension, left ventricular ejection fraction, prior MI, and Killip class, hazard ratios for all-cause mortality were 1.38 (95% CI 1.00–1.90) for diabetes only, 22% (118 of 544) in patients with depression only, and 47% (46 of 98) in patients with both diabetes and depression.

CONCLUSIONS—We observed an increased mortality risk in post-MI patients with both diabetes and depression, beyond the association with mortality of diabetes and depression alone.

Myocardial infarction (MI) is an important cause of morbidity and mortality worldwide (1). Major depression after MI is present in ~20% of all MI patients (2). A meta-analysis showed that depression is associated with an almost 2.5-fold increased risk for mortality in post-MI patients, independent from other established risk factors for mortality (3). Likewise, diabetes is common in MI patients and is independently associated with increased risk for cardiovascular morbidity (4) and mortality (5, 6).

Depression and diabetes are known to interact in the general population, and their combination results in poor health outcomes. The prevalence of depression is high in patients with diabetes, affecting ~18% of type 2 diabetic patients (7). Depression can impair diabetes management and diabetes outcomes through behavioral or biological pathways (8). For example, depression appeared to be associated with less optimal diabetes self-care behaviors and subsequent poor glycemic control (9). In addition, depression was related to hypothalamic-pituitary-adrenocortical hyperactivity, which subsequently can affect glucose metabolism (10). It has also been proposed that diabetes and depression may share a common underlying pathogenesis (8). Among diabetic patients, several studies show that depression is an independent risk factor for an increased risk of mortality (11–14). Moreover, studies in the general population suggest a synergistic, additive interaction between diabetes and depression on mortality (8,15–17) (e.g., that having both diabetes and depression results in an increased mortality risk, beyond that of having diabetes or depression alone).

The association of the coexistence of diabetes and depression with mortality has not been investigated in patients who had a recent MI, which are patients with a high mortality risk. Hence, the aim of this study is to investigate whether the coexistence of diabetes and depression is associated with increased risk of all-cause and cardiac mortality in patients who had an MI, beyond the risks associated with diabetes and depression alone.

RESEARCH DESIGN AND METHODS—Data were derived from the Depression and Myocardial Infarction Study (DepreMI) (18) and the Myocardial Infarction and Depression-Intervention Trial (MIND-IT) (19). In these multicenter studies, 528 and 2,176 MI patients, respectively, were screened for depression. Patients were recruited from 14 hospitals (including 4 university hospitals) located in different parts of the Netherlands. Patients were included from September 1997 through September 2000 in DepreMI and from October 1999 through November 2002 in MIND-IT if they met established criteria for MI (20). Exclusion criteria were cognitive dysfunction, not being able to speak or read Dutch, hospitalization for other reasons than MI, and not being able to speak or read Dutch. Patients were also excluded if they were already receiving psychiatric treatment for a current depressive episode (n = 104). Because the two studies were highly comparable in patient recruitment, inclusion and exclusion criteria, and depression assessment, data of both studies were combined for the present analyses. Both studies were approved by the local ethical committee of the participating hospitals, and all patients gave informed consent.
Measurements

Depression and diabetes. In patients who were hospitalized for index-MI, we assessed depression with the 21-item Beck Depression Inventory (BDI), using BDI scores $\geq 10$ to indicate depression. The BDI is a validated instrument for depression, and BDI scores $\geq 10$ are considered to signify at least mild depression (21). The presence of diabetes was based on either self-reported diagnosis at admission, which was verified by the medical chart, or a new diagnosis at discharge for which medication was necessary. This information was collected during hospitalization for index-MI.

Mortality. The primary outcome was all-cause mortality. Mortality records up until 31 December 2007 were provided by Statistics Netherlands through linkage to the Municipal Personal Records Database. We calculated time to mortality from the index-MI to date of death. Survivors were censored at 31 December 2007. Secondary outcome was death from cardiac disease as primary cause of death (cardiac mortality), based on ICD-10 (codes I11, I21, and I22). Mortality records. For this outcome, survivors were censored at 31 December 2007. Patients who died for noncardiac reasons were censored at the date of death.

Covariates. Demographic, lifestyle, and cardiovascular data were collected during hospitalization for index-MI and included age, sex, smoking status, hypertension, left ventricular ejection fraction (LVEF), prior MI, and Killip class. Smoking was defined as current smoking or cessation of smoking <3 months ago. Information about hypertension was derived from the medical chart. LVEF was assessed by either echocardiography or radionuclide ventriculography. Killip class was determined at hospital admission, with a standardized 4-point clinical assessment of the degree of heart failure, based on pulmonary rales and X-ray. Killip class was divided in two categories (class 1 and class 2, 3, or 4).

Statistical analysis

We classified the patients according to their diabetes and depression status into the following four categories: 1) no diabetes, no depression; 2) diabetes, no depression; 3) no diabetes, depression; and 4) diabetes, depression. First, we evaluated with multinomial regression whether baseline characteristics for groups 2 to 4 differed significantly from group 1 (no diabetes, no depression). Next, we assessed time to all-cause and cardiac mortality using Cox regression models, in a crude model, and after adjusting for a priori defined covariates, in a stepwise approach: 1) age and sex; 2) age, sex, hypertension, and smoking; and 3) age, sex, hypertension, smoking, LVEF, prior MI, and Killip class. The group without diabetes and depression served as reference group. To illustrate the relationships between depression and diabetes with mortality, we plotted Kaplan-Meier curves for each diabetes and depression category. Furthermore, we tested whether biological interaction had occurred. Biological interaction refers to a deviation from additivity of two or more causes of disease that together influence the disease outcome (22).

In Cox regression analysis, biological interaction differs from statistical interaction because in Cox regression models, statistical interaction is implicitly exponential and therefore multiplicative. We tested whether biological interaction had occurred using the Relative Excess Risk due to Interaction (RERI) (22) by using the method outlined by Andersson et al. (23). RERI represents the risk that is in excess of what would be expected if the combination of two risk factors would be purely additive (e.g., no synergism). An RERI $>$ 0 indicates a synergistic, additive interaction. We adjusted for the same sets of covariates as described for the Cox regression models.

Missing values for the variables used in the statistical analyses were assumed to be missing at random and were multiply imputed using imputation by chained equations. Ten imputed datasets were created. Variables used to impute datasets were diabetes, log-transformed BDI score at baseline, log-transformed BDI score at 3 months, factor scores for somatic/affective depressive symptoms and cognitive/affective depressive symptoms, mortality, log-transformed time to mortality, age, sex, hypertension, smoking, LVEF, prior MI, Killip class, BMI, study, location of MI, hypercholesterolemia, family history of coronary artery disease, rehospitalization, and log-transformed time to rehospitalization. The numbers and hazard ratios (HRs) reported in this study were based on the multiply imputed datasets. HRs from the imputed datasets were combined using Rubin’s rules (24). The numbers were averaged over the 10 imputed datasets. Although mortality data were used to create the imputed datasets, cases with imputed mortality data were excluded from the Cox regression analysis as recommended by von Hippel (25). We also did an available-case analysis in which we repeated the Cox regression analysis with the existing data. We tested statistical interaction between depression and diabetes for mortality by testing the significance of the interaction term depression-diabetes as a supplementary analysis. Analyses were performed in STATA 10.1 (StataCorp., College Station, TX). A two-sided $\alpha$ of 0.05 was used to indicate statistical significance.

RESULTS—From the 2,704 patients in the dataset, 2,111 (78%) were men. The mean age at baseline was 61 years (SD 12). Missing data of depression and diabetes were multiply imputed for 236 patients (9%) and 15 patients (<1%), respectively. At baseline, 1,789 patients (66%) had no diabetes and no depression, 224 patients (8%) had diabetes but no depression, 585 patients (22%) had depression but no diabetes, and 106 patients (4%) had both diabetes and depression. Table 1 presents the baseline characteristics across these four categories. Those with both diabetes and depression were on average less healthy and had a worse cardiovascular risk profile but were less often current smokers than patients without diabetes and depression. Table 1 also shows the percentage of missing values that were imputed per baseline variable, which varied between 0 and 9%.

For 179 patients (7%), data on mortality could not be retrieved. These patients were therefore excluded from the Cox regression analyses. Additional analyses showed that these patients did not differ from those with mortality data regarding presence of depression, diabetes, and the other covariates, except for prior MI. There was a higher prevalence of prior MI in patients whose mortality data could not be retrieved (21 vs. 14%, $P = 0.005$). Of the remaining 2,525 patients with data on mortality, a total of 439 participants (17%) died during follow-up, of which 175 (7%) were classified as cardiac death. The all-cause mortality rate was 14% (226 of 1,673) for patients without depression and without diabetes, 23% (49 of 210) for patients with diabetes only, 22% (118 of 544) for patients with depression only, and 47% (46 of 98) for patients with both depression and diabetes. The mean follow-up time for the participants was 6.2 years (SD 2.0).

Figures 1 and 2 show the Kaplan-Meier curves for all-cause and cardiac mortality for each strata of diabetes and depression. Table 2 shows the number
of deaths and the HRs for all-cause and cardiac mortality across the four categories of diabetes and depression. Patients who had both diabetes and depression had a considerably higher HR for mortality. For all-cause mortality, the HR was 4.58 (95% CI 3.29–6.37) for the patients with both diabetes and depression in the unadjusted analyses compared with the reference group (patients without diabetes and without depression). The strength of the relationship with mortality decreased to some extent after adjustment for the potential confounders (age, sex, smoking, hypertension, LVEF, previous MI, and Killip class) but remained significant. Furthermore, post hoc comparisons showed that the HR in those with both diabetes and depression was higher compared with patients with diabetes only (full model: 2.10 [1.38–3.21]) and depression only (full model: 2.08 [1.46–2.98]). The association between diabetes, depression, and mortality did not differ by sex; the interaction terms of the diabetes depression categories with sex were not statistically significant. The HR for cardiac mortality in the diabetes and depression group was 5.77 (3.53–9.43) in the unadjusted model and 3.27 (1.97–5.41) in the fully adjusted model. Post hoc comparisons showed that the HR in patients with both diabetes and depression was higher compared with patients with diabetes only (full model: 2.54 [1.32–4.89]) and depression only (full model: 2.10 [1.25–3.54]).

When we repeated the Cox regression analysis as an available-case analysis in the nonimputed dataset, approximately similar results were found (data not shown). For example, the HR for all-cause mortality in the fully adjusted model was 1.37 (95% CI 0.95–1.98) for those with diabetes only, 1.32 (1.02–1.71) for those with depression only, and 3.23 (2.25–4.64) for those with both diabetes and depression compared with those without diabetes and depression in the available-case analysis.

### Biological interaction

For all-cause mortality, the RERI was 1.94 (95% CI 0.37–3.51) in the unadjusted analyses and 1.13 (0.12–2.14) in the fully adjusted analyses. This exceeds the value 0 and, thus, suggests a positive interaction.
between diabetes and depression as departure from additivity. This means that the joint effect of diabetes and depression is significantly larger than the sum of the individual effects of diabetes and depression, even after controlling for confounders. For cardiac mortality, there was a trend for a positive additive interaction between diabetes and depression, but this was not statistically significant (unadjusted analysis: 2.90 [−0.02 to 5.82]; fully adjusted analysis: 1.42 [−0.21 to 3.06]).

Supplemental analyses
We tested formal statistical (multiplicative) interaction between depression and diabetes for mortality. Although the direction of the multiplicative interaction was positive, this interaction was not significant for all-cause mortality (range P = 0.10–0.20 across the models) and cardiac mortality (range P = 0.21–0.30 across the models).

CONCLUSIONS—This is the first study that aimed to investigate the association of coexisting diabetes and depression with mortality after MI. We observed an increased mortality risk in patients with both diabetes and depression who were hospitalized for MI, beyond the association with mortality for diabetes and depression alone. This association weakened somewhat but remained statistically significant after adjustment for demographic and established prognostic cardiac factors. Most striking, there was a synergistic additive interaction between diabetes and depression for mortality, which weakened but remained statistically significant after adjusting for cardiac disease severity. Our results are similar to population-based, epidemiological studies that suggest a possible synergistic interaction between diabetes and depression or psychological distress for mortality (8,15–17,26). Although the absolute mortality rate in this high-risk group for mortality was considerably higher, the strength of the association of diabetes and depression with mortality is within the range of associations observed in the population-based studies.

Several explanations might be suggested for our results. First, depression might aggravate the course of diabetes in MI patients. It is known that diabetic patients with depression have more diabetes-related complications (such as diabetic retinopathy, nephropathy, and neuropathy) (27) and are more often in poor glycemic control, as denoted by elevated levels of glycated hemoglobin (HbA1c) (28), than diabetic patients without depression. In a population study of people with psychological distress and diabetes, elevated HbA1c levels did not explain the increased mortality risk (26). On the other hand, HbA1c levels appeared to be related to mortality in a study with MI patients, both in nondiabetic patients and in diabetic patients (29). Depression is known to be related to a reduced adherence to self-care behaviors (i.e., diet, exercise, and smoking cessation) and to reduced medication adherence in diabetic as well as MI patients (30,31). Not only major depression but also subthreshold depression is associated with

Figure 1—Kaplan-Meier curves for all-cause mortality for each diabetes and depression category (unadjusted analysis).

Figure 2—Kaplan-Meier curves for cardiac mortality for each diabetes and depression category (unadjusted analysis).
nonadherence to different aspects of diabetes self-care (32). For MI patients with diabetes, poorer self-care might be more deleterious compared with MI patients without diabetes because of the many and often complex self-care activities involved in diabetes management. Furthermore, depression is related to several biological changes, such as increased inflammation and dysfunction of the autonomic nervous system, which in turn are related to increased cardiovascular mortality (33).

Second, we found that part of the excess risk associated with the coexistence of diabetes and depression was explained by the baseline cardiac disease severity parameters. Specifically, patients with both diabetes and depression had worse physical health to start with, such as more peripheral vascular disease and cerebrovascular disease. It is unclear whether this represents confounding (i.e., that depression and diabetes may serve as a risk indicator for MI patients with a poor clinical profile) or whether this is already a consequence of the diabetes-depression interaction. A possible explanation for these findings rests on the premise that depression may have a different etiology in diabetic patients compared with patients without diabetes. Diabetes and depression share several metabolic alterations in proinflammatory cytokines, glucocorticoid signaling, and cellular respiration (34). The combination of diabetes and depression in MI patients might be an expression of such metabolic alterations and may therefore be associated with a poorer cardiac prognosis. This is in line with the many reports on the association of proinflammatory cytokines with the development and progression of a cardiac disease, including increased mortality risk (35,36).

What are the clinical implications of our findings? In the next decades, an immense increase in the prevalence of type 2 diabetes is expected to occur. Because the prevalence of depression in patients with type 2 diabetes is almost twice that of nondiabetic people (7), both diabetes and depression will become highly prevalent health problems in MI patients. Physicians should be aware that MI patients with diabetes and depression have an increased mortality risk. Therefore, it may be relevant to identify patients at risk with screening. However, there is an ongoing debate whether screening for depression will benefit the patients’ prognosis. Although identification can be useful, there are no studies showing that screening alone improves depressive symptoms and cardiac outcomes (37) or diabetes outcomes (38) in patients with cardiovascular disease or diabetes, respectively. Recently, a nurse-led collaborative care management for primary care patients with poorly controlled diabetes and/or coronary artery disease and depression was evaluated (39). The intervention group had improved with respect to blood pressure, HbA1c, and depression after 12 months, which are factors that are known to be related to increased mortality (39). It may be worthwhile to monitor MI patients with both diabetes and depression closely to evaluate their mood, adherence to treatment regimens, and compliance with lifestyle recommendations, such as enhancing physical activity. Likewise, prevention of the onset of diabetes and depression might be important. Furthermore, in our study, we had a relatively low prevalence of diabetes. It might be relevant to investigate whether our results can be replicated in countries with a higher prevalence of diabetes in MI patients.

**Strengths and limitations**

Several strengths and weaknesses of this study should be acknowledged in interpreting our findings. First, our large cohort of MI patients and long follow-up period made it possible to study the effect of the coexistence of diabetes and depression on mortality. Second, both demographic and cardiac risk factors were included as confounders. Finally, by merging our data with the national mortality records, reliable and high-quality data of the primary cause of death could be retrieved. A limitation of our study was the use of depression questionnaires instead of diagnostic interviews. However, the BDI has been validated in MI patients against a structural clinical interview for depression (40). In MIND-IT, patients with psychiatric treatment for depression during screening were excluded. This reduced the number of depressed patients in our study. Furthermore, depression was measured during hospitalization, and we did not have data on lifetime depression for the majority of our patients. The presence of diabetes was not systematically tested according to a prespecified laboratory protocol. Therefore, some patients with MI might have had undetected diabetes. Others might have been incorrectly designated as a diabetic patient. This might have influenced our associations with mortality. Furthermore, for 7% of the sample, data on mortality were not available. In addition, the ratio of cardiac deaths per covariate is small. This increases the risk of overfitting. We therefore showed several models where we adjusted for covariates in a stepwise approach. Finally, we did not assess other relevant diabetes-related aspects (HbA1c and diabetes complications) or self-care behaviors (physical activity and medication adherence) that might help to explain our findings.

To conclude, we found that the coexistence of diabetes and depression after MI is related to increased mortality, be-

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**Table 2—Number of deaths and HRs for all-cause and cardiac mortality for the four diabetes and depression categories**

<table>
<thead>
<tr>
<th></th>
<th>No depression, no diabetes</th>
<th>Diabetes, no depression</th>
<th>Depression, no diabetes</th>
<th>Diabetes, depression</th>
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<td><strong>All-cause mortality</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of deaths*</td>
<td>226 of 1,673</td>
<td>49 of 210</td>
<td>118 of 544</td>
<td>46 of 98</td>
</tr>
<tr>
<td>Unadjusted</td>
<td>1.00</td>
<td>1.89 (1.38–2.60)</td>
<td>1.75 (1.39–2.20)</td>
<td>4.58 (3.29–6.37)</td>
</tr>
<tr>
<td>Model 1</td>
<td>1.00</td>
<td>1.56 (1.13–2.15)</td>
<td>1.63 (1.29–2.06)</td>
<td>3.78 (2.71–5.28)</td>
</tr>
<tr>
<td>Model 2</td>
<td>1.00</td>
<td>1.38 (1.15–2.17)</td>
<td>1.61 (1.27–2.03)</td>
<td>3.79 (2.71–5.29)</td>
</tr>
<tr>
<td>Model 3</td>
<td>1.00</td>
<td>1.38 (1.00–1.90)</td>
<td>1.39 (1.10–1.76)</td>
<td>2.90 (2.07–4.07)</td>
</tr>
<tr>
<td><strong>Cardiac mortality</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of deaths*</td>
<td>84 of 1,673</td>
<td>18 of 210</td>
<td>51 of 544</td>
<td>22 of 98</td>
</tr>
<tr>
<td>Unadjusted</td>
<td>1.00</td>
<td>1.86 (1.07–3.24)</td>
<td>2.01 (1.39–2.92)</td>
<td>5.77 (3.53–9.43)</td>
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<tr>
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<td>1.58 (0.91–2.76)</td>
<td>1.92 (1.32–2.80)</td>
<td>4.97 (3.02–8.18)</td>
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<td>1.90 (1.30–2.76)</td>
<td>4.91 (2.98–8.09)</td>
</tr>
<tr>
<td>Model 3</td>
<td>1.00</td>
<td>1.29 (0.75–2.22)</td>
<td>1.56 (1.07–2.26)</td>
<td>3.27 (1.97–5.41)</td>
</tr>
</tbody>
</table>

Data are HR (95% CI) unless noted otherwise. Model 1: adjusted for age and sex. Model 2: adjusted for age, sex, smoking, and hypertension. Model 3: adjusted for age, sex, smoking, hypertension, previous MI, Killip class, and LVEF. *Using multiple imputation for missing values. Missing data for mortality are not multiply imputed.
yond the effect on mortality of diabetes and depression alone in MI patients.

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M.B. researched data and wrote the manuscript. F.P. contributed to discussion and reviewed and edited the manuscript.

M.Z. researched data, contributed to discussion, and reviewed and edited the manuscript. J.P.V.M. and P.D.J. acquired data, contributed to discussion, and reviewed and edited the manuscript. M.B. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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