Increased Risk of Myocardial Infarction in Depressed Patients With Type 2 Diabetes

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OBJECTIVE—To investigate major depressive disorder (MDD), which complicates the course of type 2 diabetes and is associated with an increased risk of cardiovascular disease and death. This risk may be due to a greater susceptibility for myocardial infarction (MI) in depressed patients with type 2 diabetes compared with nondepressed patients with type 2 diabetes.

RESEARCH DESIGN AND METHODS—Veterans Administration electronic medical records were analyzed to identify a cohort free of cardiovascular disease in fiscal years 1999 and 2000, aged 25 to 80 years. ICD-9-CM codes were used to create a four-level risk group indicating *1*) neither diabetes nor MDD (n = 214,749), *2*) MDD alone (n = 77,568), *3*) type 2 diabetes alone (n = 40,953), and *4*) comorbid MDD and type 2 diabetes (n = 12,679). Age-adjusted Cox proportional hazards models were computed before and after adjusting for baseline sociodemographic and time-dependent covariates.

RESULTS—After adjusting for covariates, patients with type 2 diabetes alone and patients with MDD alone were at ~30% increased risk for MI, and patients with type 2 diabetes and MDD were at 82% increased risk for MI (hazard ratio 1.82 [95% CI 1.69–1.97]) compared with patients without either condition.

CONCLUSIONS—Compared with patients with only diabetes or only MDD, individuals with type 2 diabetes and MDD are at increased risk for new-onset MI. Monitoring cardiovascular health in depressed patients with type 2 diabetes may reduce the risk of MI in this especially high-risk group.

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Type 2 diabetes and major depressive disorder (MDD) are independent contributors to cardiovascular disease and to an increased risk of myocardial infarction (MI). People with type 2 diabetes have at least a twofold increased risk of MI compared with those without type 2 diabetes (1,2), and people with MDD have a similarly increased risk of MI compared with people without MDD (3). Managing type 2 diabetes is a challenge in uncomplicated patients but is more difficult in those with comorbid MDD. MDD interferes with type 2 diabetes self-care and imposes an additional risk of hyperglycemia (4). Noncompliance with medication, poor health behaviors, inflammation, and other physiologic pathways may all contribute to poor cardiovascular outcomes in patients with MDD and type 2 diabetes (5–8).

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Katon et al. (9) reported that compared with nondepressed patients with type 2 diabetes, patients with type 2 diabetes and MDD were approximately twice as likely to have cardiovascular risk factors, including smoking, obesity, sedentary lifestyle, and glycosylated hemoglobin >8.0. These risk factors are associated with poor cardiovascular outcomes, and after adjustment for clinical characteristics and self-care, depressed patients with type 2 diabetes were at a 24% increased risk of macrovascular complications (7). In this same cohort, all-cause death and cardiovascular death were both significantly elevated in patients with MDD and type 2 diabetes than in patients without MDD. However, the risk of cardiovascular death was attenuated and no longer significant after adjustment for demographics, diabetes severity, comorbidity, health behaviors, and other clinical characteristics at baseline (6). These results from insurance enrollees in Washington state are supported by similar findings from the National Health and Nutrition Examination Survey, in which depression in type 2 diabetes was associated with greater all-cause mortality and with coronary heart disease (10).

Although evidence indicates that depression worsens cardiovascular outcomes in type 2 diabetes, extant studies have been limited to just two cohorts. In addition these studies have examined the effects of depression on composite cardiovascular outcomes but have not reported specific cardiovascular end points such as MI. To fill this gap in the literature, we analyzed data from the national Veterans Administration (VA) medical records system to determine if depressed patients with type 2 diabetes are at increased risk of MI compared with patients with neither MDD nor diabetes, with patients with diabetes alone, and with patients with MDD alone.

RESEARCH DESIGN AND METHODS

RESEARCH DESIGN AND METHODS—Data were obtained from inpatient and outpatient ICD-9-CM diagnoses, Current Procedural Terminology (CPT) codes (American Medical Association,

Chicago, IL), Pharmacy Benefits Management (PBM) records, and vital status files maintained by the Veterans Health Administration (VHA) beginning in fiscal year (FY) 1999, the first year that national outpatient data are available. These data are maintained by the VHA Office of Information at the Austin Information Technology Center (http://www.virec.research.va.gov/DataSourcesName/Medical-SAS-Datasets/SAS.htm).

Cohort eligibility

We used ICD-9-CM codes to identify a cohort free of diagnosed cardiovascular disease in FY1999 and FY2000. From among the 1,380,433 patients who used VA health care in 1999 and 2000, we excluded those with at least one primary or secondary diagnosis of hypertensive heart disease (ICD-9-CM 402–405), ischemic heart disease (410–414), disease of the pulmonary circulation (414–417), and other forms of heart disease (420–429), as well as patients with cerebrovascular disease (430–438). We then selected all patients with any ICD-9-CM code indicating a primary diagnosis for MDD (296.2, 296.3, or 311) and 300,000 randomly selected, non-MDD patients without cardiovascular disease. This resulted in a sample of 536,415 unique patients free of cardiovascular or cerebrovascular disease in FY1999 and FY2000. The 7-year follow-up period began 1 October 2000 and ended 30 September 2007.

Exclusion criteria

We excluded patients with psychotic disorders and bipolar disorder to reduce the risk of MDD misclassification. Patients must also have been aged between 25 and 80 years at the beginning of follow-up to allow for variability in risk of MI. To limit the sample to regular users of VA health care, patients who did not have at least one outpatient visit in both FY1999 and FY2000 were excluded. Patients were also excluded if an acute MI occurred within the first month of follow-up. The numbers of subjects excluded by these criteria have been previously reported (11). After applying these criteria, a final sample of 96,611 patients with MDD and 259,383 patients without MDD remained. From this cohort we excluded 4,548 who did not receive a minimum of 12 weeks of follow-up from baseline and 5,497 who had a diagnosis of dysthymia (ICD-9-CM 300.4) without MDD, resulting in 90,247 patients with MDD and 255,702 patients without MDD.

Type 2 diabetes cohort with and without MDD

Patients were considered to have type 2 diabetes at baseline if they had two or more ICD-9-CM codes for type 2 diabetes in 24 months from inpatient or outpatient visits on separate days or had a prescription for type 2 diabetes medication. ICD-9-CM codes for type 2 diabetes include 250, 357.2, 362.0, and 366.41 (12). As reported by Miller et al. (12), having two or more diagnoses has an 81% agreement with a prescription for type 2 diabetes medications such as insulin, sulfonylureas, biguanides, thiazolidinediones, and other hypoglycemic medications and glucose-monitoring supplies. A record of HbA_{1c} testing is available for 75% of those with two or more diagnostic codes for type 2 diabetes (12).

Diagnoses of MDD and diabetes were then used to create a four-level predictor variable: *1*) patients with neither diabetes nor MDD (n = 214,749), *2*) patients without diabetes and with MDD (n = 77,568), *3*) patients with diabetes and without MDD (n = 40,953), and *4*) patients with diabetes and MDD (n = 12,679).

Outcome variables

Incident MI. Incident MI during the period of 1 October 2000 to 30 September 2007 was identified by ICD-9-CM codes 410–411. The duration of follow-up was calculated as the time from 1 October 2000 to the diagnosis of MI. Conversely, if no MI codes were present, the follow-up duration was calculated as the time from 1 October 2000 to the last recorded visit (date of last inpatient or outpatient ICD-9-CM code). Follow-up time was calculated in months.

All-cause mortality. All deaths during the period of 1 October 2000 to 30 September 2007 were obtained from the VA Vital Status File, which tracks deaths by incorporating information from the Beneficiary Identification and Records Locator Subsystem (BIRLS) Death File created by the Veterans Benefits Administration, the Medical SAS Inpatient Datasets that track mortality and death dates that occur during a hospital stay, and the Social Security Administration Death Master File.

Covariates

Cardiovascular risk variables. Established risk factors for heart disease that are documented in the electronic medical record include hypertension, hyperlipidemia, and obesity. These conditions must have been present before the onset of MI or censoring to be counted as present. The ICD-9-CM codes used to identify these conditions were hypertension (401–401.9), hyperlipidemia (272, 272.0–272.4), and obesity (278.0–278.02; or BMI from height and weight data obtained from the Vital Signs data file and classified as obese vs. not obese according to Centers for Disease Control and Prevention guidelines). We also adjusted for posttraumatic stress disorder (PTSD), anxiety disorder unspecified, and panic disorder because previous research shows that anxiety disorders co-occur with MDD and are independent risk factors for incident MI in the VA patient population (13).

We considered alcohol abuse or dependence present if the patient had an ICD-9-CM code of 305.0 for abuse and/or 303, indicating dependence before the onset of MI or censorship. Nicotine dependence or smoking was defined by ICD-9-CM code 305.1 or V15.82, indicating personal history of tobacco use before the onset of MI or censorship.

Sociodemographic variables at baseline. Data were available on year of birth, sex, race, VA insurance status, and marital status. We adjusted for insurance status to control for potential bias in the detection of heart disease outcomes. Patients with private insurance may be more likely to use private sector care in addition to the VA health care resources, thus reducing the likelihood that all of their health care use will be detected. We adjusted for marital status because it is associated with social support and subsequent heart disease outcomes. Marital status was modeled as a three-level variable of married; divorced, widowed, or separated; and single or never married.

Cardiovascular screening and interventions

Differential rates of screening for heart disease and preventive interventions between patients with and without MDD and with and without type 2 diabetes could have confounded our results, so we constructed variables for both of these potential confounders using CPT codes and procedural ICD-9-CM codes. Our cardiac screening variable contained tests such as electrocardiogram (ECG), stress test, and echocardiography, which can be used to detect cardiovascular disease at an early stage. Cardiac procedures included interventions for MI such as stent placement and angioplasty. We also controlled for prescriptions of drugs used to decrease risk of MI, including those in the

lipid-lowering and in the vasodilator classes.

Antidepressant use

We have found a markedly reduced risk of MI among patients who are compliant with antidepressant use (13). Therefore, we adjusted for the receipt of 12 weeks of antidepressants prescribed at the minimum effective dose used to treat MDD. Patients were considered to have not been treated for MDD if they received less than 12 weeks of an antidepressant. All data on antidepressant use were based on the "days supply" variable from the PBM.

Analytic design

Bivariate analyses included *t* tests for continuous variables and χ^2 tests for categorical variables. We first investigated the relationship between covariates by diabetes and MDD status. Owing to a nonlinear relationship between age, MI, MDD, and pharmacotherapy, a linear and a quadratic age term were both included in all multivariate models. Survival models were computed to analyze time to MI. Hazard ratios for incident MI were estimated using Cox proportional hazards models with time-dependent covariates. Sociodemographic variables were modeled from their status at baseline, and the remaining variables were time-dependent covariates that must have occurred before the incident MI or the end of follow-up. Analyses were performed using SAS 9.1.3 software (SAS Institute, Cary, NC) with $\alpha = 0.05$. Two-tailed tests were used to allow for risk factors and protective effects. The PROC PHREG procedure was used to compute Cox proportional hazards models. Month was the unit of time for survival analyses.

This project was approved by the institutional review boards of the St. Louis VA and Washington University.

Table 1—*Comparision of patients who were free of heart disease at baseline (1999–2000) with and without MI

Variable	Total *n* = 345,949	MI *n* = 11,659	No MI *n* = 334,290	*P*
No diabetes plus no depression	62.1	48.3	62.6	<0.0001
No diabetes plus depression	22.4	23.0	22.4	
Diabetes plus no depression	11.8	20.7	11.5	
Diabetes plus depression	3.7	8.0	3.5	
Age (years)	55.6 ± 13.17	59.26 ± 11.06	55.52 ± 13.22	<0.0001
Female	11.7	4.7	12.0	<0.0001
Race				
White	71.1	78.2	70.9	<0.0001
Nonwhite	20.9	20.7	20.9	
Unknown	8	1.1	8.3	
Marital status				<0.0001
Married	49.4	49.2	49.5	
Not married†	44.9	49.1	44.7	
Unknown	5.7	1.7	5.8	
Health care coverage				0.0571
VA only	62.4	63.3	62.4	
Other	37.6	36.7	37.6	
PTSD	14.6	16.8	14.5	<0.0001
Anxiety disorder unspecified	9.8	11.3	9.8	<0.0001
Panic disorder	2.1	2.5	2.1	0.0091
Hypertension	64.0	78.1	63.5	<0.0001
Hyperlipidemia	55.0	60.5	54.8	<0.0001
Nicotine dependence	34.4	38.9	34.3	<0.0001
Alcohol/drug dependence	23.8	24.2	23.8	0.3399
Obesity	49.9	55.0	49.7	<0.0001
Cardiac screen	57.7	59.0	57.6	0.0031
Cardiac procedure	2.1	4.5	2.0	<0.0001
Vasodilator Rx	9.1	19.6	8.7	<0.0001
Lipid-lowering Rx	44.2	48.3	44.1	<0.0001
Health care utilization‡				<0.0001
Lowest 25%	46.4	20.8	47.3	
25th–50th percentile	24.0	26.5	23.9	
50th–75th percentile	17.2	27.9	16.8	
Highest 25%	12.4	24.8	11.9	
12 Weeks of any antidepressant	32.4	33.6	32.4	0.0049

Data are presented as mean ± SD or percentage. Rx, prescription medication. *MI during follow-up from 1 October 2001 to 30 September 2007. †Includes divorced, widowed, separated, and never married. ‡Clinic stops per month, categorized by quartile values in the entire sample.

RESULTS—The incidence of MI increased in a stepwise fashion from unaffected patients (2.6% incidence of MI) to patients with depression only (3.5%) to patients with diabetes only (5.9%) to patients with both conditions (7.4%). The incidence of all-cause mortality was 2.1% for unaffected, 2.0% for depression only, 3.7% for diabetes only, and 3.9% for combined depression and diabetes.

As presented in Table 1, 62.1% of the cohort was free of type 2 diabetes and MDD, 22.4% had only depression, 11.8% had only diabetes, and 3.7% had both conditions. The prevalence of comorbid diabetes and depression was significantly higher in patients who had an MI compared with those who did not have an MI (8.0 vs. 3.5%; $P < 0.0001$).

A comparison of patients with and without an incident MI during follow-up (Table 1) showed those who had an MI were older ($P < 0.0001$), less likely to be women ($P < 0.0001$), were significantly more often white ($P < 0.0001$), and were less likely to be married ($P = 0.0001$).

Patients with PTSD ($P < 0.0001$), anxiety disorder unspecified ($P < 0.0001$), and panic disorder ($P = 0.0091$) were more likely to have an MI ($P = 0.0001$). Patients who were nicotine-dependent or smokers ($P < 0.0001$) and those with hypertension ($P = 0.0001$), hyperlipidemia ($P < 0.0001$), and obesity ($P < 0.0001$) were more likely to have an MI.

Cardiovascular screening ($P = 0.0031$), cardiac procedures ($P < 0.0001$), and receipt of vasodilators ($P < 0.0001$) and lipid-lowering drugs ($P < 0.0001$) were all more prevalent among patients who had an MI compared with those who did not. Higher health care utilization was associated with incident MI ($P < 0.0001$), whereas receipt of 12 weeks of an antidepressant was associated with a lower incidence of MI ($P < 0.0001$).

Results of our multivariate-adjusted survival model predicting time to MI are reported in Table 2. After adjusting for sociodemographic variables, we found patients with type 2 diabetes and depression were significantly more likely to have an MI than patients without MDD and type 2 diabetes (hazard ratio [HR] 1.82 [95% CI 1.69–1.97]). Patients who had only depression or had only diabetes had approximately the same elevated risk of MI as patients without either condition (1.29 [1.22–1.37] and 1.33 [1.27–1.40], respectively).

Each of the anxiety disorders was significantly associated with greater risk of MI (HR range 1.08–1.16). As expected, other cardiac risk factors, hypertension, hyperlipidemia, nicotine dependence, and obesity were all significantly associated with the risk of MI (HR range 1.07–1.55).

Cardiac screening tests, cardiac procedures, and receipt of vasodilators were all significantly associated with the risk of incident MI (HR range 1.35–2.37). Compared with high users of health care, lower users were less likely to have had an incident MI (0.34 [0.32–0.36]). Lastly, as we have previously reported (13), receipt of 12 weeks of antidepressants was significantly associated with a reduced risk of incident MI (0.52 [0.49–0.54]).

Table 2—*HR of incident MI among 345,949 VA patients with type 2 diabetes and free of heart disease at baseline (1999–2000)**

Variable		HR (95% CI)
No diabetes plus	No depression	1.0
	Depression	1.29 (1.22–1.37)
Diabetes plus	No depression	1.33 (1.27–1.40)
	Depression	1.82 (1.69–1.97)
PTSD	No	1.0
	Yes	1.08 (1.02–1.14)
Anxiety disorder unspecified	No	1.0
	Yes	1.11 (1.04–1.18)
Panic disorder	No	1.0
	Yes	1.16 (1.02–1.14)
Hypertension	No	1.0
	Yes	1.55 (1.47–1.62)
Hyperlipidemia	No	1.0
	Yes	1.09 (1.04–1.15)
Nicotine dependence	No	1.0
	Yes	1.40 (1.34–1.45)
Alcohol/drug dependence	No	1.0
	Yes	1.0 (0.95–1.05)
Obesity	No	1.0
	Yes	1.07 (1.03–1.11)
Cardiac screen	No	1.0
	Yes	1.35 (1.29–1.41)
Cardiac procedure	No	1.0
	Yes	1.37 (1.25–1.51)
Vasodilator Rx	No	1.0
	Yes	2.37 (2.25–2.49)
Lipid-lowering Rx	No	1.0
	Yes	1.03 (0.98–1.09)
Health care utilization†	Lowest 25%	0.34 (0.32–0.36)
	25th–50th percentile	0.56 (0.53–0.59)
	50th–75th percentile	0.77 (0.73–0.81)
	Highest 25%	1.0
12 Weeks of any antidepressant	No	1.0
	Yes	0.52 (0.49–0.54)

*Adjusted for age, sex, race, marital status, and insurance type. †Clinic stops per month, categorized by quartile values in the entire sample.

CONCLUSIONS—In a cohort of 345,949 patients free of cardiovascular disease at baseline, we observed that patients with comorbid MDD and type 2 diabetes were 82% more likely to experience an incident MI than those without MDD and type 2 diabetes. Although most studies have demonstrated that a history of depression increases the likelihood of incident heart disease, including MI, by approximately twofold (14–18), we found patients with depression were 29% more likely to have an MI. The 29% increased risk of MI associated with MDD alone was similar to that of the 33% increased risk of MI among patients with type 2 diabetes alone. We can conclude that patients with MDD are at the same risk of incident MI as patients with diabetes. In addition, having both conditions is worse than having either alone. Effects remained significant even after adjusting for other psychiatric disorders, cardiovascular risk factors, cardiovascular care, and health service utilization.

MDD has long been known to cooccur with type 2 diabetes and have a negative effect on the course of type 2 diabetes (10,19,20). Katon et al. (9,20) used patient administrative data from non-VA resources to demonstrate MDD increases the risk for all-cause mortality among patients with diabetes. Compared with nondepressed patients with diabetes, those with depression were 2.3-times more likely to die during a 3-year follow-up. The Katon et al. review concluded that four of five studies found increased risk of death in depressed patients with diabetes. We are not aware of any previous research that specifically examines the risk of MI in depressed patients with type 2 diabetes; however, our findings are consistent with the growing evidence that MDD in type 2 diabetes not only complicates the course of type 2 diabetes but is also an independent contributor to cardiovascular disease.

There are several potential mechanisms by which MDD may interact with type 2 diabetes to worsen the prognosis of cardiovascular disease. MDD may impair type 2 diabetes self-care and increase physical inactivity and other behavioral risk factors such as smoking and obesity. MDD may also impose physiologic changes that add to cardiovascular disease risk. Abnormally elevated blood glucose levels and insulin responses to glucose tolerance testing have been demonstrated in depressed subjects with and without diabetes. MDD has also been associated with increased deposition of intrahepatic fat and increases in coagulation and fibrinolysis. Conversely, type 2 diabetes–associated insulin resistance may interfere with MDD

treatment, thus worsening the MDD prognosis and increasing the time spent in MDD.

Strengths

By excluding all patients with a history of cardiovascular disease at baseline, we established strong evidence for the temporal relationship between MDD and type 2 diabetes in MI. The large sample size and large number of cardiac end points yielded very precise point estimates that increase the likelihood that the current study reflects the real-world relationship between MDD, type 2 diabetes, and incident MI.

Limitations

Misclassification of covariates could have confounded our results if comorbidities were systematically under- or overdiagnosed by MDD or MI status. It is possible that patients with depression, especially less severe depression, may be less likely to receive a diagnosis (21). Thus, our estimates would be conservative to the degree that patients were misclassified as unaffected. However, the quality of psychiatric diagnoses is excellent if the correct algorithm is applied, as was done in the current study. For instance, a comparison of the medical record review with an algorithm requiring two or more visits has been shown to have a 99% positive-predictive value for depression diagnoses in administrative claims data (22). ICD-9-CM codes for MI have very high agreement (>99%) with written medical records in the VA (23). Although unlikely, we acknowledge that the classification of incident MI may be a recurrence or exacerbation of a pre-existing cardiovascular condition that was first recorded in non-VA records. It is possible that the accuracy of ICD-9-CM diagnoses may differ outside the VA system (e.g., managed care health plans); however, we expect the automated and systematic method of maintaining electronic records in the VA improves diagnostic accuracy.

Patients in the VA generally have more comorbidities that would increase the risk for MI in the patients with depression and diabetes as well as in those without either condition. If any effect is observed, we expect that comorbidity in the unaffected patients would act to reduce differences between groups and our estimates are therefore conservative.

It is possible that patients who have had depression and/or diabetes for longer periods of time, especially longer than our observation period, may be at an even greater increased risk of incident MI than patients with shorter duration of disease. However, we are not able to account for total time spent with these conditions beyond the time frame of our study. Increased chronicity of MDD seen in patients with type 2 diabetes likely contributes to a worsened type 2 diabetes prognosis by providing the opportunity for MDD and type 2 diabetes to interact in pathogenic ways. It is possible that the results could be explained by a longer duration of type 2 diabetes and/or MDD being more common in patients with both conditions. In this case, exposure to either condition for a longer period of time may increase the likelihood of developing comorbidity as well as increase the likelihood of developing an MI.

The current study confirms that MDD is associated with a greater hazard of incident MI in patients with type 2 diabetes. Patients may benefit from first receiving cognitive behavior therapy or other nonpharmacologic treatment if antidepressants increase the risk for further cardiovascular disease such as heart failure. Collaborative care models that incorporate cardiology, mental health, and primary care may improve outcomes in this complex patient population, as is now being undertaken in the evidence-based depression, type 2 diabetes, and coronary heart disease TEAMcare model developed by Katon et al. (24) that has recently proven effective in treating patients with mental and physical comorbidity (25).

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