BJPsych | The British Journal of Psychiatry (2012)
200, 137–142. doi: 10.1192/bjp.bp.111.096479

Treatment-resistant and insufficiently treated depression and all-cause mortality following myocardial infarction

Jeffrey F. Scherrer, Timothy Chrusciel, Lauren D. Garfield, Kenneth E. Freedland, Robert M. Carney, Paul J. Hauptman, Kathleen K. Bucholz, Richard Owen and Patrick J. Lustman

Background
Depression is a known risk factor for mortality after an acute myocardial infarction. Patients with treatment-responsive depression may have a better prognosis than those with treatment-resistant depression.

Aims
We sought to determine whether mortality following acute myocardial infarction was associated with treatment-resistant depression.

Method
Follow-up began after myocardial infarction and continued until death or censorship. Depression was counted as present if diagnosed any time during the study period. Treatment for depression was defined as receipt of 12 or more weeks of continuous antidepressant therapy at a therapeutic dose during follow-up. Treatment-resistant depression was defined as use of two or more antidepressants plus augmentation therapy, receipt of electroconvulsive therapy or use of monoamine oxidase inhibitors. Mean duration of follow-up was 39 months.

Results
During follow-up of 4037 patients with major depressive disorder who had had a myocardial infarction, 6.9% of those with insufficiently treated depression, 2.4% of those with treated depression and 5.0% of those with treatment-resistant depression died. A multivariable survival model that adjusted for sociodemographics, anxiety disorders, beta-blocker use, mortality risk factors and health service utilisation indicated that compared with treated patients, insufficiently treated patients were 3.04 (95% CI 2.12–4.35) times more likely and patients with treatment-resistant depression were 1.71 (95% CI 1.05–2.79) times more likely to die.

Conclusions
All-cause mortality following an acute myocardial infarction is greatest in patients with depression who are insufficiently treated and is a risk in patients with treatment-resistant depression. However, the risk of mortality associated with treatment-resistant depression is partly explained by comorbid disorders. Further studies are warranted to determine whether changes in depression independently predict all-cause mortality.

Declaration of interest
None.

It is well established that depression following a myocardial infarction increases risk for mortality. Those at greatest risk may be patients with treatment-resistant depression.[1,2] Treatment-resistant depression has been defined in many ways, including failure to respond to a single trial of an antidepressant at an adequate dose and duration,[3] evidence of simultaneous use of multiple antidepressants plus augmentation, or receipt of monoamine oxidase inhibitors and/or electroconvulsive therapy.[4] A graduated five-stage model ending in failure to respond to monoamine oxidase inhibitors and then electroconvulsive therapy has also been proposed.[4] Patients ($n = 361$) who continued to have depression following antidepressant treatment were 2.3 times more likely to die (i.e. all-cause mortality) following acute myocardial infarction in the Sertraline Antidepressant Heart Attack Randomized Trial (SADHART).[5] Similar findings in the Myocardial Infarction and Depression Intervention Trial (MIND-IT) indicate that patients who do not respond to therapy have over a fourfold risk of a new cardiovascular event.[6] The trial's authors concluded that treatment resistance is an independent risk factor for worse outcomes; however, the sample size in this trial was relatively small ($n = 168$). Because there have been few studies of treatment-resistant depression and mortality following myocardial infarction and because of the relatively small cohorts in the SADHART and MIND-IT analyses, we investigated whether there is an association between treatment resistance and mortality in a large, nationally distributed cohort of Veterans Administration (VA) patients.

Method

Data were obtained from in-patient and out-patient ICD-9-CM diagnoses,[7] Current Procedural Terminology codes, Pharmacy Benefits Management records, and Vital Status files maintained by the Veterans Health Administration (VHA) beginning in fiscal year (FY) 1999. Data are maintained by the VHA Office of Information at the Austin Information Technology Center (www.virec.research.va.gov/datasourcesname/medical-sas-datasets/SAS.htm). The sample and detailed method of deriving the cohort have been described previously.[8,9]

Cohort eligibility

Using ICD-9-CM codes, we identified a patient cohort free of diagnosed cardiovascular disease in the fiscal years FY1999 and FY2000. From 1 380 433 patients using VA healthcare in 1999 and 2000 we excluded those with at least one primary or secondary diagnosis of hypertensive heart disease (ICD-9-CM 402–405), ischaemic heart disease (ICD-9-CM 410–414), disease of the pulmonary circulation (ICD-9-CM 414–417) and other forms of heart disease (ICD-9-CM 420–429) as well as patients

with cerebrovascular disease (ICD-9-CM 430–438). We then selected all patients with a primary diagnosis of major depressive disorder (ICD-9-CM 296.2, 296.3 or 311) and a set of 300 000 randomly selected, cardiovascular disease-free patients without depression. This resulted in a sample of 536 415 unique patients free of cardiovascular and cerebrovascular disease in both 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 and bipolar disorders to reduce the risk of misclassifying major depressive disorder. Patients also had to be between the ages of 25 and 80 at the beginning of follow-up to allow for variability in risk for myocardial infarction and mortality. In order to limit the sample to regular users of VA healthcare, patients who did not have at least one out-patient visit in both FY1999 and FY2000 were excluded. Patients were also excluded if an acute myocardial infarction occurred within the first month of follow-up. After applying these criteria, a final sample of 96 612 patients with major depressive disorder and 259 387 patients without major depressive disorder remained. From this cohort of 355 999 veterans, we identified 12 304 patients with an incident myocardial infarction during the follow-up period. Of these patients, 4242 patients with depression were eligible for analysis. We excluded 126 patients who did not have 12 weeks of follow-up time after myocardial infarction because this was the minimum follow-up time necessary to define the primary independent variable (i.e. guideline-concordant antidepressant use). Also, 79 patients of unknown ethnicity or marital status were excluded. This resulted in a sample of 4037 patients available for analysis.

Predictor variables

Treatment

We have previously found a markedly reduced risk of myocardial infarction among patients who receive 12 weeks of continuous antidepressants at therapeutic doses (i.e., guideline-concordant acute phase treatment).[9] Therefore, we considered patients to have been treated for depression if they received 12 or more weeks of a selective serotonin reuptake inhibitor (citalopram, fluoxetine, paroxetine, sertraline), serotonin–noradrenaline reuptake inhibitor (venlafaxine, mirtazapine), tricylic (amitriptyline, doxepin, nortriptyline) or other antidepressant (bupropion, nefazodone, trazodone) during follow-up. Patients were considered to have been insufficiently treated if they did not receive guideline-concordant acute phase treatment for depression. All antidepressant use data were based on the days supply variable from the Pharmacy Benefits Management records.

Post-myocardial infarction depression

This was defined as a new onset of major depression following a myocardial infarction. We chose to model new-onset depression and not lifetime depression because Parker *et al*[10] have reported strong evidence that incident depression, but not lifetime depression, following acute coronary syndrome was associated with poorer cardiovascular outcomes.

Treatment-resistant depression

Using an adaptation of Corey-Lisle *et al*'s[11] method for identifying treatment-resistant depression in administrative data, we considered patients to be treatment-resistant if they received: (a) electroconvulsive therapy; (b) a monoamine oxidase inhibitor; or (c) two or more antidepressants at the same time plus augmentation therapy. Combination antidepressant therapy was defined as the use of two or more antidepressants overlapping at least 31 days. Augmentation therapy was defined as receipt of a mood-stabilising or atypical antipsychotic.

Covariates

Covariates were selected because of their known association with mortality and high co-occurrence with depression. Nicotine dependence was defined by ICD-9-CM code 305.1 or V15.82 indicating personal history of tobacco use prior to mortality or censorship. Alcohol misuse/dependence was defined by ICD-9-CM code 305.0 for misuse and/or 303 indicating dependence. We adjusted for the following anxiety disorders: generalised anxiety disorder (ICD-9-CM 300.02), panic disorder (ICD-9-CM 300.1), anxiety disorder not otherwise specified (ICD-9-CM 300.0), obsessive–compulsive disorder (ICD-9-CM 300.3), social phobia (ICD-9-CM 300.23) and post-traumatic stress disorder (ICD-9-CM 309.81). Because beta-blocker use may be associated with symptoms of depression we adjusted for the medication possession ratio for atenolol, bisoprolol, carvedilol, labetalol, metoprolol, propranolol, sotalol, nadolol and pindolol. Obesity was defined as ICD-9-CM codes 278.0–278.02 or as a body mass index of >30 from height and weight data obtained from the Vital Signs data file and classified as obese *v.* not obese according to the Centers for Disease Control and Prevention guidelines.[12] The Romano adaptation of the Charlson Comorbidity Index,[13,14] a list of 17 health conditions associated with morbidity and mortality, was included to adjust for underlying risk for all-cause mortality. We have found that health service utilisation is inversely associated with mortality, therefore we adjusted for clinic stops per month.

Sociodemographics at baseline

Data were available on year of birth, gender, ethnicity and marital status. We adjusted for marital status because it is associated with social support and subsequent mortality. Marital status was modelled as a three-level variable (married, divorced/widowed/separated and single/never married).

Outcome variable: all-cause mortality

All deaths during the period 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 (VBA), the Medical SAS Inpatient Datasets that track mortality and death dates that occur during a hospital stay, and the Social Security Administration (SSA) Death Master File.

Analytic design

Bivariate analyses included *t*-tests for continuous variables and chi-squared tests for categorical variables. We first characterised the association between covariates and mortality. Then we investigated the relationship between covariates and major depressive disorder treatment status. Survival models were then computed to analyse time to mortality. Hazard ratios (HRs) for mortality were estimated using Cox proportional hazards models with time-dependent covariates. Owing to a nonlinear relationship between age, mortality and major depressive disorder treatment status, both a linear and a quadratic age term were included in all multivariable survival models. Sociodemographics were modelled from their status at baseline, clinic stops were modelled continuously as number of clinic stops per month,

https://doi.org/10.1192/bjp.bp.111.096479 Published online by Cambridge University Press

and the remaining adjustments were based on time-dependent covariates that could occur any time before the end of follow-up. Analyses were performed using SAS version 9.1.3 for Windows, with α set at 0.05. Two-tailed tests were used to allow for both 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 and the index myocardial infarction date was the beginning of follow-up.

This project was approved by the institutional review boards of the St Louis Veterans Affairs Medical Center and Washington University.

Results

Among the 4037 patients with depression after incident myocardial infarction, 25.6% were insufficiently treated, 62.4% were successfully treated and 12.1% had treatment-resistant depression. As shown in Table 1, insufficiently treated patients were more likely to be older (mean age 60.4 years, s.d. = 11.3) and treatment-resistant patients more likely to be younger (mean age 56.2 years, s.d. = 9.5) than treated patients (mean age 58.1 years, s.d. = 10.0). Treated patients were more likely to be White ($P<0.0001$) and married ($P<0.05$). Alcohol misuse/dependence was more common in treatment-resistant depression ($P=0.0025$) as was having any anxiety disorder ($P<0.0001$). Obesity was more common in patients with treatment-resistant depression ($P<0.0001$). Beta-blocker use was more common among patients who were treated or had treatment-resistant depression ($P<0.0001$). The mean comorbidity index was highest ($P<0.0001$) among treatment-resistant patients. Last, mean clinic stops per month was greatest in the treatment-resistant group ($P<0.0001$).

Table 1 Association between covariates and treatment status in 4037 patients

	Total	Insufficiently treated (*n* = 1032)	Treated (*n* = 2517)	Treatment-resistant (*n* = 488)	*P*
Age, years: mean (s.d.)	58.5 (10.4)	60.4 (11.3)	58.1 (10.0)	56.2 (9.5)	<0.0001
Ethnicity, *n* (%)					
White	3282 (81.3)	782 (75.8)	2117 (84.1)	383 (78.5)	<0.0001
Black and minority ethnic	755 (18.7)	250 (25.2)	400 (15.9)	105 (21.5)	
Female, *n* (%)	266 (6.6)	64 (6.2)	160 (6.4)	42 (8.6)	0.1573
Marital status, *n* (%)					
Married	1868 (46.3)	441 (42.7)	1202 (47.8)	225 (46.1)	0.0243
Not married	2169 (53.7)	591 (57.3)	1315 (52.2)	263 (53.9)	
Nicotine dependence/tobacco use, *n* (%)	2430 (60.2)	621 (60.2)	1503 (59.7)	306 (62.7)	0.4662
Alcohol misuse/dependence, *n* (%)	1531 (37.9)	367 (35.6)	946 (37.6)	218 (44.7)	0.0025
Any anxiety disorder,[a] *n* (%)	2394 (59.3)	475 (46.0)	1578 (62.7)	341 (69.9)	<0.0001
Obesity, *n* (%)	2824 (70)	651 (63.1)	1807 (71.8)	366 (75)	<0.0001
Beta-blocker,[b] *n* (%)	0.57 (0.38)	0.51 (0.39)	0.59 (0.38)	0.61 (0.36)	<0.0001
Comorbidity Index, mean (s.d.)	6.0 (3.8)	6.1 (4.0)	5.80 (3.7)	6.9 (4.0)	<0.0001
Clinic stops per month, mean (s.d.)	3.6 (3.7)	2.9 (4.2)	3.6 (4.2)	4.9 (4.1)	<0.0001

a. Generalised anxiety disorder, panic disorder, anxiety disorder not otherwise specified, obsessive–compulsive disorder, social phobia and post-traumatic stress disorder.
b. Medication possession ratio (% of follow-up time on beta-blocker).

Table 2 Association between covariates, treatment-resistant depression and mortality

	Deceased (*n* = 155)	Alive (*n* = 3882)	*P*
Age, years: mean (s.d.)	65.0 (12.50)	58.21 (10.18)	<0.0001
Ethnicity, *n* (%)			
White	125 (80.6)	3157 (81.3)	0.8317
Black and minority ethnic	30 (19.4)	725 (18.7)	
Female, *n* (%)	3 (1.9)	263 (6.8)	0.0172
Marital status, *n* (%)			
Married	57 (36.8)	1811 (46.7)	0.0156
Not married	98 (63.2)	2071 (53.3)	
Nicotine dependence/tobacco use, *n* (%)	89 (57.4)	2341 (60.3)	0.4719
Alcohol misuse/dependence, *n* (%)	57 (36.8)	1474 (38.0)	0.7635
Any anxiety disorder,[a] *n* (%)	70 (45.2)	2324 (59.9)	0.0003
Obesity, *n* (%)	93 (60)	2731 (70.4)	0.0058
Beta blocker,[b] *n* (%)	0.54 (0.38)	0.57 (0.38)	0.3210
Comorbidity Index, mean (s.d.)	11.0 (4.2)	5.8 (3.6)	<0.0001
Clinic stops per month, mean (s.d.)	3.3 (4.2)	3.6 (3.7)	<0.0001
Treatment category, *n* (%)			
Treated	60 (38.7)	2457 (63.3)	<0.0001
Insufficiently treated	71 (45.8)	961 (24.8)	
Treatment-resistant	24 (15.5)	464 (12)	

a. Generalised anxiety disorder, panic disorder, anxiety disorder not otherwise specified, obsessive–compulsive disorder, social phobia and post-traumatic stress disorder.
b. Medication possession ratio (% of follow-up time on beta-blocker).

https://doi.org/10.1192/bjp.bp.111.096479 Published online by Cambridge University Press

The distribution of covariates and treatment status by mortality status is shown in Table 2. As expected, older age ($P<0.0001$) and higher comorbidity index scores ($P<0.0001$) were associated with higher risks of mortality, and female ($P<0.05$) and married ($P<0.05$) patients and those with any anxiety disorder ($P<0.001$) had a lower likelihood of mortality. Obesity ($P=0.0058$) was associated with a lower risk of mortality. More clinic stops per month was associated with lower mortality ($P<0.0001$). Insufficient treatment was associated with higher mortality ($P<0.001$).

A survival model that adjusted only for age indicated that patients with insufficiently treated depression were 2.98 (95% CI 2.10–4.22) times more likely to die during follow-up and treatment-resistant patients were 1.96 (95% CI 1.22–3.15) times more likely to die as compared with treated patients.

A full model indicated that compared with treated patients, insufficiently treated patients were 2.93 (95% CI 2.03–4.21) times more likely to die during follow-up (Table 3). Treatment-resistant patients were significantly more likely to die during follow-up after multiple covariate adjustment (HR = 1.71; 95% CI 1.05–2.79). As expected, a higher comorbidity index was associated with a greater likelihood of death (HR = 1.35; 95% CI 1.31–1.40). Lastly, more clinic stops per month was associated with lower likelihood of death (HR = 0.95; 95% CI 0.90–0.99).

After adjusting for each covariate in separate models (Table 4), we found that the comorbidity index partially accounted for the association between treatment-resistant depression and mortality but did not account for the association between insufficiently treated depression and mortality.

Table 3 Hazard of all cause mortality in 4037 veterans as a function of treatment status[a]

	Hazard ratio (95% CI)
Insufficiently treated *v.* treated	2.93 (2.03–4.21)
Treatment-resistant *v.* treated	1.71 (1.05–2.79)
Comorbidity Index	1.35 (1.31–1.40)
Obesity	0.96 (0.68–1.34)
Nicotine dependence/tobacco use	1.28 (0.89–1.83)
Alcohol misuse/dependence	1.13 (0.77–1.65)
Any anxiety disorder[b]	0.78 (0.56–1.10)
Beta-blocker[c]	0.85 (0.55–1.32)
Clinic stops per month	0.95 (0.90–0.99)

a. Adjusted for age, gender, ethnicity and marital status.
b. Generalised anxiety disorder, panic disorder, anxiety disorder not otherwise specified, obsessive–compulsive disorder, social phobia and post-traumatic stress disorder.
c. Medication possession ratio (% of follow-up time on beta-blocker).

Discussion

After adjustment in a multivariate model, treatment-resistant depression was significantly associated with mortality and this association was partly explained by comorbid conditions. In addition, patients were less likely to die if they had any treatment whether in the context of the treatment-resistant depression paradigm or as part of sufficient treatments compared with insufficiently treated depression.

Our data are consistent with previous SADHART results that show patients who do not respond to antidepressant treatment to be over twice as likely to die following acute myocardial infarction (SADHART).[5] The present study supports the conclusion that treatment-resistant depression results in worse outcomes as compared with successful acute phase treatment, which is consistent with the conclusion that treatment resistance is a risk factor for poor prognosis following myocardial infarction.[1,6,15] In addition, individual covariate adjustment suggests that physical comorbidities may partly account for the association between treatment-resistant depression and mortality.

We are unable to determine whether patients eventually responded to one of the types of treatment in our treatment-resistant algorithm. For instance, it is possible that patients responded to augmentation therapy or electroconvulsive therapy. This would be consistent with the finding that patients with treatment-resistant depression were at lower risk for mortality (HR = 1.71) compared with insufficiently treated patients (HR = 2.93) if responding to a second- or third-line therapy reduced depression and thereby decreased depression-related mortality. Indeed, results from STAR-D provide evidence that some patients respond to second- or third-line treatments after failing initial pharmacotherapy.[16]

Non-adherence to medical care may help to explain the greater risk of mortality in insufficiently treated patients with depression. Insufficiently treated patients received less than 12 weeks of continuous antidepressant therapy, possibly because of poor adherence to antidepressant medication. Antidepressant non-adherence could be a marker for poor adherence to other medical regimens. In fact, *post-hoc* analyses of beta-blocker use following myocardial infarction indicated that treated patients and patients with treatment-resistant depression were taking beta-blockers for a significantly longer time compared with insufficiently treated patients. Thus adherence with pharmacotherapy may partly explain our findings. In addition, patients who are non-adherent to pharmacotherapy may be non-adherent to other aspects of cardiac aftercare. This is consistent with our finding that greater clinic utilisation, and the additional screening and prevention

Table 4 Effect of individual covariate adjustment on hazard of all-cause mortality in insufficiently treated *v.* treated and insufficiently treated *v.* treatment-resistant depression in 4037 veterans

	Insufficiently treated *v.* treated, HR (95% CI)	Treatment-resistant *v.* treated, HR (95% CI)
Model 1: adjusted only for age	2.98 (2.10–4.22)	1.96 (1.22–3.15)
Model 2: adjusted for age and ethnicity	2.94 (2.07–4.17)	1.93 (1.20–3.11)
Model 3: adjusted for age and gender	3.03 (2.14–4.30)	1.97 (1.22–3.17)
Model 4: adjusted for age and marital status	2.84 (2.00–4.02)	1.96 (1.22–3.16)
Model 5: adjusted for age and comorbidity index	3.34 (2.36–4.73)	1.42 (0.88–2.31)
Model 6: adjusted for age and obesity	2.97 (2.09–4.21)	1.96 (1.22–3.16)
Model 7: adjusted for age and nicotine dependence/tobacco use	2.92 (2.06–4.14)	1.99 (1.23–3.20)
Model 8: adjusted for age and alcohol misuse/dependence	2.97 (2.09–4.20)	1.96 (1.22–3.15)
Model 9: adjusted for age and anxiety disorder	2.88 (2.03–4.10)	1.99 (1.24–3.21)
Model 10: adjusted for age and beta-blocker	2.96 (2.09–4.36)	1.97 (1.22–3.17)
Model 11: adjusted for age and clinic stops per month	3.01 (2.12–4.27)	1.91 (1.18–3.09)

https://doi.org/10.1192/bjp.bp.111.096479 Published online by Cambridge University Press

associated with more healthcare use, is associated with a lower risk of mortality. However, it does not appear that unhealthy behaviours in insufficiently treated patients with depression could explain our findings because they were the least likely to be obese and did not differ in terms of nicotine dependence/tobacco use compared with the treated and treatment-resistant groups. Alternatively, if more aggressive treatment for treatment-resistant depression involves the addition of augmentation therapy with atypical antipsychotics, then it is possible that the poor metabolic consequences associated with these drugs may increase risk for greater cardiac morbidity and mortality. However, in *post-hoc* analysis, patients with treatment-resistant depression on antipsychotics did not significantly differ in risk of mortality from patients with treatment-resistant depression not on these medications (HR = 0.54; 95% CI 0.20–1.51). Exposure to antipsychotics does not account for the association between treatment-resistant depression and mortality in our analysis.

Our results may not generalise beyond mortality to other unfavourable outcomes following myocardial infarction. In *post-hoc* analysis we observed that risk of new-onset stroke was not significantly associated with insufficiently treated depression (HR = 1.24; 95% CI 0.91–1.70) and treatment-resistant depression (HR = 0.88; 95% CI 0.58–1.33). But the risk of new-onset heart failure was significantly associated with insufficiently treated (HR = 1.67; 95% CI 1.27–2.20) but not treatment-resistant depression (HR = 0.92; 95% CI 0.61–1.39). The lower magnitude of association between post-myocardial infarction depression status and these cardiac events is consistent with recent meta-analysis demonstrating that post-myocardial infarction depression is more strongly associated with cardiac mortality than with cardiac events.[17]

Strengths

The large sample size permitted adjustment for many pertinent covariates. The long period of observation allowed us to model rare outcomes and the effects of covariates over time. Our study overcomes a limitation of projects that have utilised only pharmacy data because we can establish the effect of antidepressants in a cohort diagnosed with depression rather than relying on the use of antidepressants as an indicator of depression status.

Limitations

Our treatment-resistant depression algorithm is based on administrative medical record data in which the cause of death is unknown. However, the accuracy of psychiatric diagnosis in administrative data is excellent if the correct algorithm is applied as was done in the present study. Comparison of chart review with an algorithm requiring two or more visits with an ICD-9 code for depression has been shown to have 99% positive predictive value for depression diagnoses in administrative claims data.[18] ICD-9-CM codes for myocardial infarction have very high agreement (>99%) with written medical records in the VA.[19] Although it is unlikely, it is possible that in some cases, the cardiac event that we classified as the incident myocardial infarction may instead have been 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. in managed care health plans); however, the automated and systematic method of maintaining electronic records in the VA improves diagnostic accuracy. Lastly, it is possible that patients with treatment-resistant depression improved more than insufficiently treated patients; however, it is not possible to determine the symptom status of patients using only administrative data. If active depression is associated with increased risk of death, it is possible that continued depression in treatment-resistant patients could account for the relationship between treatment-resistant depression and mortality. In further analyses, we observed that compared with patients without depression, patients with depression that received 12 or more weeks of treatment with antidepressants were significantly less likely to die during follow-up (HR = 0.54; 95% CI 0.41–0.71). In contrast, patients with depression who were not treated were significantly more likely to die during follow-up (HR = 1.61; 95% CI 1.24–2.08) and there was a non-significant trend for treatment-resistant patients (HR = 1.33; 95% CI 0.93–1.96) to be at increased risk for death, providing some evidence that active depression is associated with mortality.

Implications

The present analysis adds to the nascent literature suggesting that treatment-resistant depression contributes to the poor outcomes of patients with depression following myocardial infarction. This may be partly due to comorbid conditions in patients with treatment-resistant depression. Compared with insufficient treatment, these data suggest that any guideline-concordant treatment reduces risk of mortality after myocardial infarction. Future studies should consider whether worsening of depression is the mechanism underlying the association between untreated depression, treatment-resistant depression and increased risk of mortality after myocardial infarction. Large prospective cohort studies with sensitive repeated measures of depression status are warranted.

Funding

This study was supported by Veteran Administration Health Services Research and Development, Career Development Award-2 to Jeffrey F. Scherrer.

Jeffrey F. Scherrer, PhD, Research Service, Clinical Research and Epidemiology Workgroup, St. Louis Veterans Affairs Medical Center, and Department of Psychiatry, Washington University School of Medicine, St Louis, Missouri; **Timothy Chrusciel**, MPH, Department of Internal Medicine, Washington University School of Medicine, St Louis, Missouri; **Lauren D. Garfield**, MPH, Department of Psychiatry, Washington University School of Medicine, and Saint Louis University School of Medicine, St Louis, Missouri; **Kenneth E. Freedland**, PhD, **Robert M. Carney**, PhD, Department of Psychiatry, Washington University School of Medicine, St Louis, Missouri; **Paul J. Hauptman**, MD, Saint Louis University School of Medicine, St Louis, Missouri; **Kathleen K. Bucholz**, PhD, Department of Psychiatry, Washington University School of Medicine, St Louis, Missouri; **Richard Owen**, MD, HSR&D Center for Mental Healthcare & Outcomes Research, Central Arkansas Veterans Healthcare System, and Departments of Epidemiology and Psychiatry, College of Public Health, University of Arkansas for Medical Sciences, Little Rock, Arkansas; **Patrick J. Lustman**, PhD, Research Service, Clinical Research and Epidemiology Workgroup, St. Louis Veterans Affairs Medical Center, and Department of Psychiatry, Washington University School of Medicine, St Louis, Missouri, USA

Correspondence: Jeffrey F. Scherrer, PhD, St. Louis Veterans Affairs Medical Center, Research Service (151–JC), 501 North Grand Boulevard, St Louis, MO 63103, USA. Email: scherrej@psychiatry.wustl.edu

First received 12 May 2011, final revision 13 Sep 2011, accepted 26 Oct 2011

References

1 Carney RM, Freedland KE. Treatment-resistant depression and mortality after acute coronary syndrome. *Am J Psychiatry* 2009; **166**: 410–7.

2 Culpepper L. Why do you need to move beyond first-line therapy for major depression? *J Clin Psychiatry* 2010; **71** (suppl 1): 4–9.

3 Fava M, Davidson KG. Definition and epidemiology of treatment-resistant depression. *Psychiatr Clin North Am* 1996; **19**: 180–200.

4 Thase ME, Rush JA. When at first you don't succeed: sequential strategies for antidepressant nonresponders. *J Clin Psychiatry* 1997; **58** (suppl 13): 23–9.

https://doi.org/10.1192/bjp.bp.111.096479 Published online by Cambridge University Press

5 Glassman AH, Bigger Jr T, Gaffney M. Psychiatric characteristics associated with long-term mortality among 361 patients having an acute coronary syndrome and major depression. Seven-year follow-up of SADHART participants. *Arch Gen Psychiatry* 2009; **66**: 1022–9.

6 Zuidersma M, de Jonge P. The effects of treatment-resistant depression and first-ever depression on mortality following acute coronary syndrome: interactive or independent? *Am J Psychiatry* 2009; **166**: 828–9.

7 World Health Organization. *International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM)*. WHO, 2009.

8 Scherrer JF, Chrusciel T, Zeringue A, Garfield LD, Hauptman PJ, Lustman PJ, et al. Anxiety disorders increase risk for incident myocardial infarction in depressed and nondepressed Veterans Administration patients. *Am Heart J* 2010; **159**: 772–9.

9 Scherrer JF, Garfield JD, Lustman PJ, Hauptman PJ, Chrusciel T, Zeringue A, et al. Antidepressant drug compliance is associated with reduced risk of incident myocardial infarction and mortality in depressed patients. *Am J Med* 2011; **124**: 318–24.

10 Parker GB, Hilton TM, Walsh WF, Owen CA, Heruc GA, Olley A, et al. Timing is everything: the onset of depression and acute coronary syndrome outcome. *Biol Psychiatry* 2008; **64**: 660–6.

11 Corey-Lisle PK, Brinbaum HG, Greenberg PE, Marynchenko MB, Claxton AJ. Identification of a claims data ''signature'' and economic consequences for treatment-resistant depression. *J Clin Psychiatry* 2002; **63**: 717–26.

12 Centers for Disease Control and Prevention. Defining overweight and obesity. CDC, 2010 (http://www.cdc.gov/obesity/defining.html).

13 Romano PS, Roost LL, Jollis JG. Presentation adapting a clinical comorbidity index for use with ICD-9-CM administrative data: differing perspectives. *J Clin Epidemiol* 1993; **46**: 1075–9.

14 Schneeweiss S, Wang PS, Avorn J, Glynn RJ. Improved comorbidity adjustment for predicting mortality in Medicare populations. *Health Serv Res* 2003; **38**: 1103–20.

15 Carney RM, Blumenthal JA, Freedland KE, Youngblood M, Veith RC, Burg MM, et al. Depression and late mortality after myocardial infarction in the Enhancing Recovery in Coronary Heart Disease (ENRICHD) study. *Psychosom Med* 2004; **66**: 466–74.

16 Rush AJ, Trivedi MH, Wisniewski SR, Stewart JW, Nierenberg AA, Thase ME, et al. Bupropion-SR, sertraline or venlafaxine-XR after failure of SSRIs for depression. *New Engl J Med* 2006; **354**: 1231–42.

17 Meijer A, Conradi HJ, Bos EH, Thombs BD, van Melle JP, de Jonge P. Prognostic association of depression following myocardial infarction with mortality and cardiovascular events: a meta-analysis of 25 years of research. *Gen Hosp Psychiatry* 2011; **33**: 203–16.

18 Solberg LI, Engebretson KI, Sperl-Hillen JM, Hroscikoski, MC, O'Connor PJ. Are claims accurate enough to identify patients for performance measures or quality improvement? The case of diabetes, heart disease and depression. *Am J Med Qual* 2006; **21**: 238–45.

19 Kashner TM. Agreement between administrative files and written medical records: a case of the Department of Veterans Affairs. *Med Care* 1998; **36**: 1324–36.

https://doi.org/10.1192/bjp.bp.111.096479 Published online by Cambridge University Press