Clinical Impact of Subsequent Depression in Patients With a New Diagnosis of Stable Angina

A Population-Based Study

Natalie Szpakowski, MD; Maria C. Bennell, MSc, MPH; Feng Qiu, MSc; Dennis T. Ko, MD, MSc; Jack V. Tu, MD, PhD; Paul Kurdyak, MD, PhD; Harindra C. Wijeysundera, MD, PhD

Background—Depression is prevalent among patients with myocardial infarction and is associated with a worse prognosis. However, little is known about its importance in patients with chronic stable angina. We conducted a retrospective population-based cohort study to determine the occurrence and predictors of developing depression in patients with a new diagnosis of chronic stable angina. In addition, we sought to understand its impact on subsequent clinical outcomes.

Methods and Results—Our cohort included patients in Ontario, Canada, with stable angina based on obstructive coronary artery disease found on angiogram. Depression was ascertained by physician billing codes and hospital admissions diagnostic codes. We first developed multivariable Cox proportional hazards models to determine predictors of developing depression. Clinical outcomes of interest included all-cause mortality, admission for myocardial infarction, and subsequent revascularization. Using hierarchical multivariable Cox proportional hazards models with occurrence of depression as a time-varying variable to control for potential immortal time bias, we evaluated the impact of depression on clinical outcomes. Our cohort consisted of 22 917 patients. The occurrence of depression after diagnosis of stable chronic angina was 18.8% over a mean follow-up of 1084 days. Predictors of depression included remote history of depression, female sex, and more symptomatic angina based on Canadian Cardiovascular Society class. Patients who developed depression had a higher risk of death (hazard ratio 1.83, 95% confidence interval 1.62–2.07) and admission for myocardial infarction (hazard ratio 1.36, 95% confidence interval 1.10–1.67) compared with nondepressed patients.

Conclusions—Depression is common in patients with chronic stable angina and is associated with increased morbidity and mortality. **(*Circ Cardiovasc Qual Outcomes*. 2016;9:731-739. DOI: 10.1161/CIRCOUTCOMES.116.002904.)**

Key Words: angina ■ coronary disease ■ depression ■ myocardial infarction ■ prognosis

Depression is prevalent among patients with coronary artery disease and has significant consequences. After myocardial infarction (MI), the incidence of depression has been estimated to range between 10% and 40%,[1–3] and similar rates have been reported after coronary artery bypass graft (CABG).[4–6] Studies that have examined the impact of depression in patients who have experienced an MI have consistently found that it is associated with adverse outcomes. Patients with post-MI depression have a 1.6- to 2.7-fold increased risk of new cardiac events, cardiac mortality, and all-cause mortality within 24 months.[7] They also have an increased rate of subsequent heart failure,[8] hospital readmissions,[9] and overall increased healthcare resource utilization.[9]

There have been several biological mechanisms by which depression may be related to coronary artery disease. As compared with nondepressed patients, those with depression have increased catecholamine levels,[10] elevated resting heart rate,[11] and decreased heart rate variability,[12] all of which suggest increased sympathetic activity. Behavioral characteristics of patients with depression include poor medication adherence,[13] lower exercise tolerance,[14] physical inactivity,[15] poor dietary habits,[16] and tobacco use.[17]

Although depression and its impact have been well documented in post-MI patients, much less is known about its significance in patients with chronic stable angina.[18–20] Despite the fact that stable angina is the most common manifestation of coronary artery disease,[21,22] studies to date on the relationship between depression and chronic stable angina in the ambulatory setting have been small or restricted to a single center.[15,23–25] Further insight into the prognostic importance of

Received April 2, 2016; accepted August 23, 2016.

From the Schulich Heart Centre, Division of Cardiology, Department of Medicine, Sunnybrook Health Sciences Center (N.S., M.C.B., D.T.K., J.V.T., H.C.W.), Sunnybrook Research Institute (M.C.B., D.T.K., J.V.T., H.C.W.), Institute for Health Policy Management and Evaluation (D.T.K., J.V.T., P.K., H.C.W.), and Department of Psychiatry and Institute of Medical Science (P.K.), University of Toronto, Ontario, Canada; Institute for Clinical Evaluative Sciences, Toronto, Ontario, Canada (F.Q., D.T.K., J.V.T., P.K., H.C.W.); and Social and Epidemiological Research Department, Centre for Addiction and Mental Health, Toronto, Ontario, Canada (P.K.).

The Data Supplement is available at http://circoutcomes.ahajournals.org/lookup/suppl/doi:10.1161/CIRCOUTCOMES.116.002904/-/DC1.

Correspondence to Harindra C. Wijeysundera, MD, PhD, Sunnybrook Health Sciences Center, University of Toronto, 2075 Bayview Ave, Suite A202, Toronto, Ontario M4N3M5, Canada. E-mail harindra.wijeysundera@sunnybrook.ca

WHAT IS KNOWN

- Depression is common in patients after myocardial infarction and associated with poor outcomes, but its relationship with stable angina is less well established.

WHAT THE STUDY ADDS

- Occurrence of depression after a new diagnosis of stable angina is common and affects nearly 1 in 5 individuals.
- The strongest predictor of depression post angiography is a remote history of depression.
- Occurrence of depression is associated with poor outcomes, including death and myocardial infarction.

depression in stable angina is needed for developing appropriate diagnostic and management strategies in this large group of patients.

Accordingly, to address these gaps in knowledge, we sought to determine the occurrence of depression, time to first depressive episode post angiography, and predictors of depression in patients with a new diagnosis of stable angina. We also sought to elucidate the association between depression after angiogram and subsequent clinical outcomes, including MI and all-cause mortality. Finally, we examined the relationship between the timing of the occurrence of depression and subsequent outcomes.

Methods

This study was approved by the institutional review board at Sunnybrook Health Sciences Center, Toronto, Canada. Given the data sources used for the analyses as outlined below, the need for patient consent was waived under Ontario's Personal Health Information Protection Act.

Data Sources

This retrospective cohort study was conducted in the Canadian province of Ontario. Ontario is Canada's largest province with a population of ≈13.6 million, all of whom are provided universal medical coverage, which is publicly funded through a single third party payer, the Ministry of Health and Long Term Care. Data were obtained from the Cardiac Care Network of Ontario (CCN), which includes a network of 19 hospitals that offer invasive cardiac procedures, such as angiography, percutaneous coronary intervention, or cardiac surgery, including CABG.[26,27] CCN maintains a registry of all patients who have undergone these procedures and contains data on procedural details, including coronary anatomy. Patient demographics, comorbidities, including cardiac risk factors, cardiac testing, and Canadian Cardiovascular Society (CCS) angina class, were also obtained from the CCN. The validity of the CCN Cardiac Registry has been evaluated through selected chart audits and core-laboratory verification.[28]

Clinical data from CCN was linked to administrative databases using unique encoded identifiers and analyzed at the Institute for Clinical Evaluative Sciences (ICES) to protect patient confidentiality. These databases included the Ontario Health Insurance Plan (OHIP), Registered Persons Database, Canadian Institute for Health Information Discharge Abstract Database (CIHI-DAD), National Ambulatory Care Reporting System, ICES Physician Database, Ontario Mental Health Reporting System, and the Ontario Drug Benefit database. OHIP contains all claims made by physicians for insured inpatient and outpatient services. It captures information such as diagnostic codes and dates of service. Mortality was ascertained through the Registered Persons Database. CIHI-DAD contains data from hospital admissions and discharges, and the National Ambulatory Care Reporting System collects data from emergency department visits. Physician specialization was obtained from the ICES Physician Database. The Ontario Mental Health Reporting System reports on individuals admitted to adult mental health beds in Ontario. Hospitals disclose information to the Ontario Mental Health Reporting System, such as diagnostic codes, when a patient is admitted, discharged, or experiences a significant change in their mental health status. The Ontario Drug Benefit program provides full drug coverage for patients over the age of 65 and also contains accurate drug utilization information.

Patient Selection

Our cohort included residents over the age of 20 years with a valid health card number who had newly diagnosed stable angina, based on obstructive coronary artery disease found on an index coronary angiogram. Accrual began on October 1, 2008, and ended on September 30, 2013. The maximum follow-up date was September 30, 2014, for a minimum of 1-year follow-up on all patients. We included only the first angiogram in patients who underwent multiple angiograms within this time period. Obstructive disease was defined as >70% luminal stenosis in one or more major epicardial vessels or >50% luminal stenosis in the left main coronary artery. We excluded patients who presented with acute coronary syndrome and those with a previous history of coronary artery disease based on a previous MI, acute coronary syndrome, percutaneous coronary intervention, or CABG. We also excluded patients with a recent history of depression defined by documentation of depression in the 3-year look back window starting April 1, 2005, based on the same diagnostic codes as described later.

Depression

We defined depression based on any combination of diagnostic codes obtained from physician claims codes (OHIP) and in-hospital/emergency department visits. The diagnostic codes in OHIP that were used to define depression included reactive depression (300) and depression (311). Depression was identified from CIHI-DAD and the National Ambulatory Care Reporting System using International Classification of Diseases, 10th Revision diagnostic codes for depression in any of the most responsible or comorbidities fields (see Table I in the Data Supplement). Although not formally validated by chart review, these codes have been used in other studies using administrative data to examine depression.[29–31] Codes associated with bipolar disorder in the CIHI-DAD, National Ambulatory Care Reporting System, or OHIP databases were excluded. In the Ontario Mental Health Reporting System, depression was defined using Diagnostic and Statistical Manual of Mental Disorders, 4th Edition codes as a single (296.20-0.26) or recurrent (296.30-0.36) episode of major depressive disorder as determined by a psychiatrist or attending physician during admission to an inpatient mental health bed. If a patient had any of these codes in the observation period from their first angiogram (October 1, 2008, to September 30, 2013) until the maximum follow-up date of September 30, 2014, they were classified as having depression. Among these patients, we determined time from index catheterization to the first episode of depression during the follow-up period and also the speciality of the physician (family physician versus psychiatrist) who diagnosed the depressive episode. In addition, we determined the proportion of patients over the age of 65 years on pharmacotherapy within 6 months of their first depressive episode (see Table II in the Data Supplement). Given the possible relationship between a remote diagnosis of depression and reoccurrence post angiography, we determined the proportion of patients with a diagnosis of depression 10 years before the index angiogram and included this as a predictor in our statistical models.

Outcomes

The primary outcome was all-cause mortality ascertained through the Registered Persons Database. Secondary outcomes included admission

for MI based on the CIHI-DAD using most responsible International Classification of Diseases, 10th Revision diagnostic codes based on a validated algorithm.[32] In addition, we determined subsequent revascularization (percutaneous coronary intervention or CABG) based on the CCN Cardiac registry, supplemented by data in the CIHI-DAD.

Statistical Analysis

To compare baseline characteristics of patients who developed depression to those who did not, *t* test was used for continuous variables, and χ^2 tests were used for categorical variables.

Objective 1

To determine patient-, physician-, and hospital- level predictors of receiving a diagnosis of depression, multivariable Cox proportional hazards regression models were developed. We used a robust sandwich variance estimator to account for any possible clustering of patients by hospital where index coronary angiogram was performed.

Objective 2

Kaplan–Meier curves were developed for unadjusted outcomes and compared using a log-rank test. Fully adjusted Cox proportional models were developed in our full cohort to examine the relationship between the occurrence of depression after angiogram and clinical outcomes. In these models, depression was treated as a time-varying variable. This type of analysis controls for potential immortal time bias.[33] Robust sandwich-type variance estimators accounted for potential homogeneity in outcomes for clusters of patients treated at the same hospital. These models were fully adjusted for patient-, physician-, and hospital-level variables. As a sensitivity analysis, we restricted the analysis to only patients who were diagnosed with an occurrence of depression post angiography. We then examined the impact of the timing of diagnosis of depression after angiogram on all-cause mortality, MI, and revascularization by comparing the outcomes for depression in patients who experienced an occurrence within 30 days of the angiogram to those who experienced an occurrence at later intervals.

All data analyses were performed using SAS version 9.3 (SAS Institute Inc, Cary, NC). Statistical significance was considered to be 2-sided *P* values of <0.05.

Results

Patients

Between October 1, 2008, and September 30, 2013, 272 250 angiograms were performed in patients who were referred for investigation of possible coronary artery disease. As seen in Figure, our final cohort consisted of 22 917 patients with stable angina based on obstructive coronary artery disease on an index angiogram. Approximately 12.7% of patients were excluded because of a recent diagnosis of depression; however, 31.1% in the final cohort had a remote diagnosis of depression within the previous 10 years. In our cohort, 4305 (18.8%) patients were found to have experienced their first occurrence of depression after angiogram over a mean follow-up of 1084 days (rate of 63.2/1000 patient years). Of the patients with depression, 84.9% were identified by family physicians, whereas 8.1% were identified by psychiatrists. With respect to timing of the depressive episode, 343 (8.0%) patients were recognized as depressed within 30 days, 445 (10.3%) at 30 to 90 days, 447 (10.4%) at 90 to 180 days, 726 (16.9%) at 180 to 365 days, with the remainder (54.4%) experiencing a depressive episode beyond 1 year after their index angiogram. Of the patients with depression over the age of 65 years, 36% were on antidepressant pharmacotherapy.

The baseline characteristics of the cohort are listed in Table 1. There were several differences between patients with and without depression, including a higher percentage of males and residents of rural areas among patients without depression. In addition, there were more smokers among the patients with depression, as well as a higher prevalence of peripheral vascular disease, and the traditional risk factors of diabetes mellitus, hypertension, and hyperlipidemia. In terms

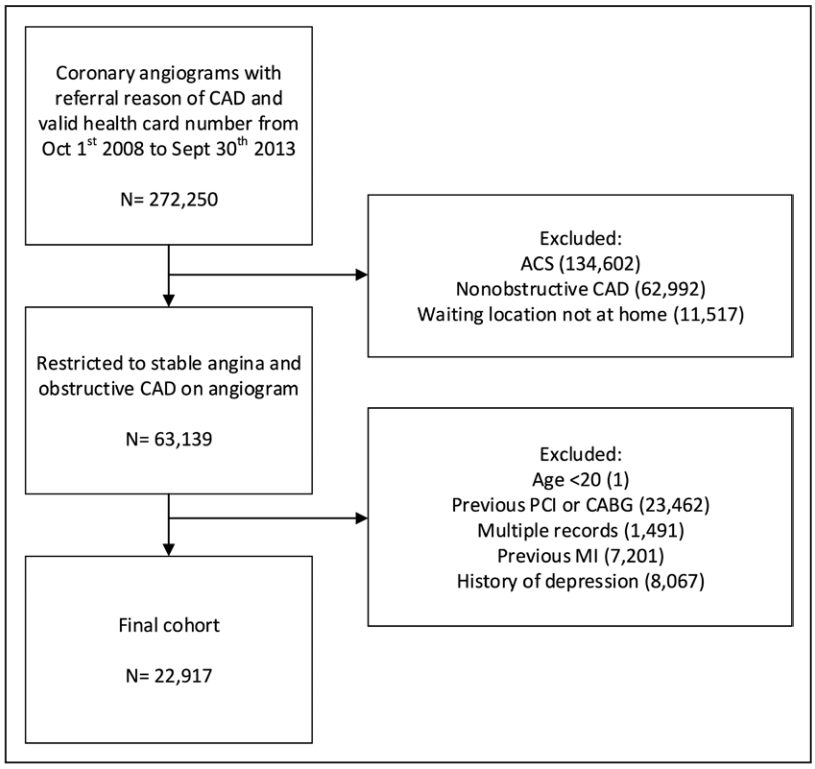

Figure. Cohort selection using Cardiac Care Network registry. ACS indicates acute coronary syndrome; CABG, coronary artery bypass grafting; CAD, coronary artery disease; MI, myocardial infarction; and PCI, percutaneous coronary intervention.

Table 1. Baseline Characteristics of the Cohort According to Diagnosis of Depression

Covariates	Total (n=22 917)	No Depression After Cath (n=18 612)	Depression After Cath (n=4305)	*P* Value
Patient-level factors				
Demographics				
Age, y (mean±SD)	65.6±10.2	65.7±10.1	65.3±10.7	0.02
Female	5280 (23.0%)	4085 (21.9%)	1195 (27.8%)	<0.001
Rural	3363 (14.7%)	2830 (15.2%)	533 (12.4%)	<0.001
Income*				
1	3919 (17.1%)	3124 (16.8%)	795 (18.5%)	
2	4595 (20.1%)	3721 (20.0%)	874 (20.3%)	
3	4779 (20.9%)	3903 (21.0%)	876 (20.3%)	0.06
4	4812 (21.0%)	3908 (21.0%)	904 (21.0%)	
5	4698 (20.5%)	3858 (20.7%)	840 (19.5%)	
Medical comorbidities				
Renal function	480 (2.1%)	378 (2.0%)	102 (2.4%)	0.16
PVD	1526 (6.7%)	1201 (6.5%)	325 (7.5%)	0.009
COPD	1194 (5.2%)	960 (5.2%)	234 (5.4%)	0.46
Previous stroke	241 (1.1%)	189 (1.0%)	52 (1.2%)	0.27
Malignancy	587 (2.6%)	478 (2.6%)	109 (2.5%)	0.89
Charlson score (mean±SD)	0.34±0.91	0.33±0.90	0.39±0.96	<0.001
Charlson score >0	3913 (17.1%)	3081 (16.6%)	832 (19.3%)	<0.001
Cardiac risk factors				
Diabetes mellitus	9426 (41.1%)	7566 (40.7%)	1860 (43.2%)	0.002
Hypertension	19 070 (83.2%)	15 436 (82.9%)	3634 (84.4%)	0.02
Hyperlipidemia	17 157 (74.9%)	13 867 (74.5%)	3290 (76.4%)	0.009
Smoking				
Former smoker	6501 (28.4%)	5296 (28.5%)	1205 (28.0%)	0.54
Current smoker	4829 (21.1%)	3845 (20.7%)	984 (22.8%)	0.002
CCS angina class				
0	4228 (18.4%)	3480 (18.7%)	748 (17.4%)	
1	3768 (16.4%)	3057 (16.4%)	711 (16.5%)	
2	9382 (40.9%)	7660 (41.2%)	1722 (40.0%)	<0.001
3	5238 (22.9%)	4191 (22.5%)	1047 (24.3%)	
4	301 (1.3%)	224 (1.2%)	77 (1.8%)	
Cardiac status/testing				
LV function				
≥50%	12 769 (55.7%)	10 246 (55.1%)	2523 (58.6%)	
35%–49%	1688 (7.4%)	1388 (7.5%)	300 (7.0%)	
20%–34%	534 (2.3%)	433 (2.3%)	101 (2.3%)	<0.001
>20%	144 (0.6%)	121 (0.7%)	23 (0.5%)	
NA	7782 (34.0%)	6424 (34.5%)	1358 (31.5%)	
Exercise ECG risk				
Low risk	5821 (25.4%)	4740 (25.5%)	1081 (25.1%)	
High risk	7478 (32.6%)	6149 (33.0%)	1329 (30.9%)	0.01

(*Continued*)

Table 1. Continued

Covariates	Total (n=22 917)	No Depression After Cath (n=18 612)	Depression After Cath (n=4305)	*P* Value
Uninterpretable	1141 (5.0%)	911 (4.9%)	230 (5.3%)	
NA	8477 (37.0%)	6812 (36.6%)	1665 (38.7%)	
Functional imaging risk				
Low risk	5745 (25.1%)	4569 (24.5%)	1176 (27.3%)	
High risk	7850 (34.3%)	6427 (34.5%)	1423 (33.1%)	<0.001
Unknown	9322 (40.7%)	7616 (40.9%)	1706 (39.6%)	
Native stenosis†				
LM	2707 (11.8%)	2196 (11.8%)	511 (11.9%)	0.90
Proximal LAD	6958 (30.4%)	5667 (30.4%)	1291 (30.0%)	0.55
Mid/distal LAD	11 803 (51.5%)	9591 (51.5%)	2212 (51.4%)	0.86
Circumflex	11 123 (48.5%)	9056 (48.7%)	2067 (48.0%)	0.45
RCA	13 063 (57.0%)	10 594 (56.9%)	2469 (57.4%)	0.61
Treatment within 90 days				
CABG	6374 (27.8%)	5119 (27.5%)	1255 (29.2%)	
MED	7202 (31.4%)	5840 (31.4%)	1362 (31.6%)	0.04
PCI	9341 (40.8%)	7653 (41.1%)	1688 (39.2%)	
Hospital-level factors				
Availability				
Cath, PCI, and CABG	16 908 (73.8%)	13 706 (73.6%)	3202 (74.4%)	
Cath only	3467 (15.1%)	2857 (15.4%)	610 (14.2%)	0.13
Cath and PCI only	2542 (11.1%)	2049 (11.0%)	493 (11.5%)	
Physician-level factors				
Referring physician				
Cardiology	12 849 (56.1%)	10 440 (56.1%)	2409 (56.0%)	
GP/FP	5611 (24.5%)	4490 (24.1%)	1121 (26.0%)	0.004
Other	4457 (19.4%)	3682 (19.8%)	775 (18.0%)	
Physician performing cath				
PCI physician	10 965 (47.8%)	8947 (48.1%)	2018 (46.9%)	0.16

CABG indicates coronary artery bypass grafting; cath, catheterization; CCS, Canadian Cardiovascular Society; COPD, chronic obstructive pulmonary disease; ECG, electrocardiogram; GP/FP, General practitioner/Family physician; LAD, left anterior descending; LM, left main; LV, left ventricular; MED, medical therapy; MI, myocardial infarction; NA, not done or missing; PCI, percutaneous coronary intervention; PVD, peripheral vascular disease; and RCA, right coronary artery.

*Income quintile: 1, lowest; 5, highest.

†Significant stenosis ≥70%, except ≥50% stenosis significant for LM.

of initial treatment strategy, more patients who underwent CABG subsequently experienced depression; however, these differences were modest (Table 1).

Predictors of Depression

Independent predictors of developing depression are found in Table 2. The strongest predictor was a remote episode of depression within the past 10 years (hazard ratio [HR] 1.88, 95% confidence interval [CI] 1.75–2.02). Other factors that were associated with an increased risk of depression were female sex (HR 1.21, 95% CI 1.13–1.29; *P*<0.001), a higher Charlson score (HR 1.06, 95% CI 1.03–1.11; *P*=0.001), being a current smoker (HR 1.10, 95% CI 1.04–1.17; *P*=0.001), and increasing CCS angina class (HR 1.38, 95% CI 1.13–1.68; *P*=0.002 for CCS 4 versus no symptoms). Rurality (HR 0.81, 95% CI 0.73–0.90; *P*<0.001) and increasing age were associated with a lower likelihood of having depression (Table 2). Patients who had high-risk functional imaging before their angiogram were less likely to subsequently experience depression (HR 0.89, 95% CI 0.82–0.96; *P*=0.002). There was no statistically significant relationship between the initial treatment strategy and subsequent depression, nor were any hospital factors statistically significant predictors. Of the physician factors, if the referring

Table 2. Adjusted Predictors of Depression in Patients With Chronic Stable Angina

Covariates	HR (95% CI)	*P* Value
Patient-level factors		
Depression within 10 y	1.88 (1.75–2.02)	<0.001
Demographics		
Female	1.21 (1.13–1.29)	<0.001
Age <50 y	Referent	
Age 50–64 y	0.75 (0.66–0.84)	<0.001
Age 65–80 y	0.70 (0.64–0.77)	<0.001
Age >80 y	0.93 (0.82–1.04)	0.21
Rural	0.81 (0.73–0.90)	<0.001
Income*		
1	Referent	
2	0.96 (0.85–1.09)	0.55
3	0.93 (0.86–1.06)	0.09
4	0.95 (0.86–1.06)	0.35
5	0.92 (0.83–1.02)	0.11
Medical comorbidities		
Renal function	0.99 (0.80–1.23)	0.91
PVD	1.10 (0.99–1.23)	0.09
COPD	1.02 (0.89–1.16)	0.76
Previous stroke	1.05 (0.85–1.31)	0.65
Malignancy	0.94 (0.72–1.23)	0.64
Comorbidities: Charlson score	1.06 (1.03–1.11)	0.001
Cardiac risk factors		
Diabetes mellitus	1.06 (1.00–1.11)	0.06
Hypertension	1.05 (0.98–1.12)	0.20
Hyperlipidemia	1.02 (0.92–1.14)	0.71
Smoking		
Non smoker	Referent	
Former smoker	1.07 (0.99–1.15)	0.09
Current smoker	1.10 (1.04–1.17)	0.001
CCS class		
0	Referent	
1	1.09 (0.99–1.21)	0.09
2	1.03 (0.95–1.11)	0.51
3	1.05 (0.97–1.14)	0.20
4	1.38 (1.13–1.68)	0.002
Cardiac status/testing		
LV function		
≥50%	Referent	
35%–49%	0.89 (0.81–0.98)	0.02
20%–34%	0.96 (0.79–1.15)	0.63
>20%	0.84 (0.64–1.09)	0.19
NA	0.85 (0.79–0.91)	<0.001
Exercise ECG risk		
Low risk	Referent	
High risk	1.03 (0.92–1.16)	0.56
Uninterpretable	1.15 (1.00–1.33)	0.05
NA	1.11 (0.99–1.23)	0.07
Functional imaging risk		
Low risk	Referent	
High risk	0.89 (0.82–0.96)	0.002
Unknown	0.94 (0.87–1.02)	0.11
Native stenosis†		
LM	1.04 (0.91–1.19)	0.59
Prox LAD	1.01 (0.94–1.08)	0.87
Mid/distal LAD	1.03 (0.95–1.12)	0.48
Circumflex	1.00 (0.92–1.08)	0.94
RCA	1.02 (0.96–1.09)	0.50
Treatment within 90 days		
MED	Referent	
CABG	1.04 (0.93–1.16)	0.50
PCI	0.93 (0.85–1.02)	0.11
Hospital-level factors		
Availability		
Cath only	Referent	
Cath and PCI only	1.08 (0.89–1.30)	0.44
Cath, PCI, and CABG	1.03 (0.95–1.11)	0.52
Physician-level factors		
Referring physician		
GP/FP	Referent	
Cardiology	0.93 (0.87–0.99)	0.03
Other	0.93 (0.87–1.00)	0.05
Physician performing cath		
PCI physician	0.99 (0.93–1.06)	0.83

CABG indicates coronary artery bypass grafting; cath, catheterization; CCS, Canadian Cardiovascular Society; CI, confidence interval; COPD, chronic obstructive pulmonary disease; ECG, electrocardiogram; GP/FP, general practitioner/family physician; HR, hazard ratio; LAD, left anterior descending; LM, left main; LV, left ventricular; MED, medical therapy; MI, myocardial infarction; NA, not done or missing; PCI, percutaneous coronary intervention; PVD, peripheral vascular disease; and RCA, right coronary artery.

*Income quintile: 1, lowest; 5, highest.

†Significant stenosis ≥70%, except ≥50% stenosis significant for LM.

physician for the angiogram was a cardiologist, there was a lower likelihood of identifying a depressive episode, compared with if the referring physician was a family physician (HR 0.93, 95% CI 0.87–0.99; *P*=0.03).

Table 3. Fully Adjusted Cox Proportional Hazards Regression Model Predicting Clinical Outcomes of Patients With Depression*

	All-Cause Mortality		Admission for MI		Revascularization	
	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
Depression	1.83 (1.62–2.07)	<0.001	1.36 (1.10–1.67)	0.005	1.13 (0.99–1.28)	0.07

CI indicates confidence interval; HR, hazard ratio; and MI, myocardial infarction.
*Refer to Table III in the Data Supplement for full model with all adjusted covariates.

Clinical Outcomes

Unadjusted all-cause mortality was higher in patients with depression than in those without depression (7.6% and 6.4%, respectively; *P*=0.005). Similar findings were found for other unadjusted clinical outcomes, including admission for MI (4.7% and 2.8%, respectively; *P*<0.001) and subsequent revascularization (14.0% and 10.7% respectively; *P*<0.001).

As seen in Table 3, in the fully adjusted model, depression was associated with an 83% increased hazard of death (HR 1.83, 95% CI 1.62–2.07; *P*<0.001). Depression was also significantly associated with admission for MI (HR 1.36, 95% CI 1.10–1.67; *P*=0.005). There was no significant effect of depression on the need for subsequent revascularization (HR 1.13, 95% CI 0.99–1.28; *P*=0.07; see Table III in the Data Supplement for full multivariable Cox models). In the sensitivity analysis restricted to patients with depression, time to first episode of depression was not an important predictor of clinical outcomes (Table IV in the Data Supplement). When compared with patients who experienced depression within 30 days of their angiogram, those who had an occurrence in later periods did not have statistically significant differences in subsequent outcomes.

Discussion

In this retrospective population-based cohort study, the occurrence of depression after diagnosis of chronic stable angina was 18.8% or roughly 1 in 5 patients. We found that patients with chronic stable angina who experienced a depressive episode had a worse prognosis, with a significantly higher likelihood of all-cause mortality and admission for MI.

Our findings complement the current literature on depression and cardiovascular disease, which has thus far focused on more acute manifestations of coronary artery disease, in contrast to stable angina. Similar to the post-MI population, however, we found that patients with chronic stable angina are at a high risk of experiencing depression. Our study is unique in that it evaluated angina patients at a population level using a contemporary province-wide registry. As such, it adds to the literature by providing useful insights into the occurrence of depression in the outpatient and ambulatory care setting and indicates patients with coronary artery disease are susceptible to depression irrespective of whether they have experienced a major cardiac event requiring hospitalization.

In this study, predictors of depression in the setting of chronic stable angina were consistent with the current literature on depression. In particular, it is important to recognize the importance of a previous, remote history of depression, which was the strongest predictor of a subsequent occurrence, reinforcing the remitting and relapsing nature of depression. In general, women are more likely to suffer depression than men,[3] and we found this to be true for patients with stable chronic angina. Various plausible biological and environmental mechanisms have been studied, including the role of sex hormones and women's social roles, to explain this sex disparity, but to date none have been conclusive.[34] Our results also showed that a higher Charlson score and smoking were associated with depression. These findings are in keeping with previous work that has shown individuals with multiple comorbid medical illnesses are vulnerable to mood disorders.[17] CCS class 4 angina symptoms were also an important predictor of depression in our cohort, potentially because of increased symptom burden, leading to physical limitations, decreased quality of life, and, hence, depression.[35] There was no significant relationship between initial treatment strategy and depression, which suggests that revascularization does not mitigate future risk of a depressive episode.

We found that depression was an important predictor for adverse outcomes in stable angina, and this has been similarly observed in post-MI and CABG patients. A recent meta-analysis by Meijer et al[7] reported an increased likelihood of all-cause mortality and cardiac events among post-MI patients who developed depression. Connerney et al[4] found that patients who underwent CABG and met Diagnostic and Statistical Manual of Mental Disorders, 4th Edition criteria for major depression had a 2-fold increased risk of death or readmission for cardiac causes within 12 months. Similar to post-MI and CABG patients, the higher likelihood of death and readmission for MI associated with depression in patients with chronic stable angina is likely multifactorial in pathogenesis, involving both biological mechanisms and health behaviors, such as medication noncompliance. In our cohort, this may have been reflected in the fact that patients who developed depression had a slightly more unfavorable cardiovascular risk factor profile.

Our findings indicate that patients may experience their first depressive episode at any given time after diagnosis of chronic stable angina; it may occur shortly after an individual is found to have obstructive coronary artery disease or several years after this diagnosis. Unfortunately, depression is often recurrent in patients with coronary artery disease[24] and, without treatment, is likely to persist. Studies have shown that cognitive behavioral therapy may reduce depressive symptoms,[36] and antidepressants may improve cardiac outcomes, as suggested by a post hoc analysis of the Enhancing Recovery in Coronary Heart Disease Patients trial.[37] The possible benefits of treating depression provide an opportunity to reduce adverse cardiovascular outcomes and their associated costs in this population.

Limitations

Our results should be interpreted in the context of the following limitations that merit discussion. The majority of previous work done in the area of depression and coronary artery disease defined depression based on structured psychiatric interviews or screening instruments, such as the Patient Health Questionnaire. We defined depression more broadly with International Classification of Diseases, 10th Revision diagnostic codes validated for depressive disorders, as well as with OHIP diagnostic codes used by primary care providers for presentations related to mood disturbances. As a result, patients with depression outside the formal Diagnostic and Statistical Manual of Mental Disorders, 4th Edition criteria for major depressive disorder were included in the cohort, and this likely included some patients with general psychosocial distress. The fact that only one third of patients were on pharmacotherapy reinforces this point. This may have resulted in a misclassification bias and, consequently, in an inflation of the occurrence of depression as well as a dilution of the association with outcomes. However, with this inclusive definition, the presence of depression as we defined it was, nonetheless, significantly predictive of all-cause mortality and admission for MI. This is important to emphasize because it suggests that a formal diagnosis of major depressive disorder is not required for an impact on outcomes and that patients with true major depressive disorder based on Diagnostic and Statistical Manual of Mental Disorders, 4th Edition criteria may have an even worse prognosis than estimated by our results. Second, to control for immortal time bias, depression was treated as a time-varying covariate in Cox proportional hazards models. Residual survivorship would tend to bias to the null, in that patients who died early would be classified in the no depression category. As such, we may be underestimating the impact of depression on clinical outcomes. It is important to acknowledge that directionality of the relationship between angina and depression cannot be confirmed from our analysis. It is possible that patients with escalating angina symptoms have greater clinical follow-up and, therefore, more opportunity for a diagnosis of depression as opposed to vice versa. In addition, we were only able to evaluate all-cause mortality, as cause-specific mortality was not available in the administrative databases used in our study. Furthermore, we only included patients with a diagnosis of stable angina based on an angiogram; this represents a more restrictive subset of patients with stable angina, many of whom would be diagnosed based on noninvasive testing. Caution should be applied in generalizing our results to this broader population.

This cohort study showed that patients with chronic stable angina diagnosed at the time of angiography are at a high risk for experiencing depression. Similar to post-MI patients, the presence of depression portends a worse prognosis independent of traditional cardiac risk factors. Our findings suggest depression may relapse or develop at any point in time after a diagnosis of stable angina. Co-morbid depression and chronic stable angina have significant clinical implications, and further attention to finding efficacious treatments is warranted.

Sources of Funding

This study is funded through an operating grant from the Canadian Institute of Health Research (CIHR) and in part by research funding from the Schulich Heart Center at Sunnybrook Health Sciences Center and the Sunnybrook Research Institute. The authors acknowledge that the clinical registry data used in this publication are from Cardiac Care Network of Ontario (CCN) and its participating hospitals. CCN serves as an advisory body to the Ministry of Health and Long Term Care (MOHLTC) and is dedicated to improving the quality, efficiency, access, and equity of adult cardiovascular services in Ontario, Canada. CCN is funded by the MOHLTC. This study was supported by the Institute for Clinical Evaluative Sciences (ICES), which is funded by an annual grant from the MOHLTC. The opinions, results, and conclusions reported in this article are those of the authors and are independent from the funding sources. No endorsement by ICES or the Ontario MOHLTC is intended or should be inferred. Parts of this material are based on data and information compiled and provided by Canadian Institute for Health Information (CIHI). However, the analyses, conclusions, opinions, and statements expressed herein are those of the authors and not necessarily those of CIHI. Dr Wijeysundera is supported by a Distinguished Clinical Scientist Award from the Heart and Stroke Foundation of Canada. Dr Tu is supported by an Eaton Scholar award and is a Canada Research Chair in Health Services Research. Dr Ko is supported by a Clinician Scientist Phase II personnel award from the Heart and Stroke Foundation, Ontario Provincial Office.

Disclosures

None.

References

1. Thombs BD, Bass EB, Ford DE, Stewart KJ, Tsilidis KK, Patel U, Fauerbach JA, Bush DE, Ziegelstein RC. Prevalence of depression in survivors of acute myocardial infarction. *J Gen Intern Med*. 2006;21:30–38. doi: 10.1111/j.1525-1497.2005.00269.x.
2. Kaptein KI, de Jonge P, van den Brink RH, Korf J. Course of depressive symptoms after myocardial infarction and cardiac prognosis: a latent class analysis. *Psychosom Med*. 2006;68:662–668. doi: 10.1097/01.psy.0000233237.79085.57.
3. Mallik S, Spertus JA, Reid KJ, Krumholz HM, Rumsfeld JS, Weintraub WS, Agarwal P, Santra M, Bidyasar S, Lichtman JH, Wenger NK, Vaccarino V; PREMIER Registry Investigators. Depressive symptoms after acute myocardial infarction: evidence for highest rates in younger women. *Arch Intern Med*. 2006;166:876–883. doi: 10.1001/archinte.166.8.876.
4. Connerney I, Shapiro PA, McLaughlin JS, Bagiella E, Sloan RP. Relation between depression after coronary artery bypass surgery and 12-month outcome: a prospective study. *Lancet*. 2001;358:1766–1771. doi: 10.1016/S0140-6736(01)06803-9.
5. Ravven S, Bader C, Azar A, Rudolph JL. Depressive symptoms after CABG surgery: a meta-analysis. *Harv Rev Psychiatry*. 2013;21:59–69. doi: 10.1097/HRP.0b013e31828a3612.
6. Gallagher R, McKinley S. Anxiety, depression and perceived control in patients having coronary artery bypass grafts. *J Adv Nurs*. 2009;65:2386–2396. doi: 10.1111/j.1365-2648.2009.05101.x.
7. 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;33:203–216. doi: 10.1016/j.genhosppsych.2011.02.007.
8. May HT, Horne BD, Carlquist JF, Sheng X, Joy E, Catinella AP. Depression after coronary artery disease is associated with heart failure. *J Am Coll Cardiol*. 2009;53:1440–1447. doi: 10.1016/j.jacc.2009.01.036.
9. Kurdyak PA, Gnam WH, Goering P, Chong A, Alter DA. The relationship between depressive symptoms, health service consumption, and prognosis after acute myocardial infarction: a prospective cohort study. *BMC Health Serv Res*. 2008;8:200. doi: 10.1186/1472-6963-8-200.
10. Veith RC, Lewis N, Linares OA, Barnes RF, Raskind MA, Villacres EC, Murburg MM, Ashleigh EA, Castillo S, Peskind ER. Sympathetic nervous system activity in major depression. Basal and desipramine-induced alterations in plasma norepinephrine kinetics. *Arch Gen Psychiatry*. 1994;51:411–422.
11. Carney RM, Rich MW, teVelde A, Saini J, Clark K, Freedland KE. The relationship between heart rate, heart rate variability and depression in patients with coronary artery disease. *J Psychosom Res*. 1988;32:159–164.

12. Carney RM, Blumenthal JA, Freedland KE, Stein PK, Howells WB, Berkman LF, Watkins LL, Czajkowski SM, Hayano J, Domitrovich PP, Jaffe AS. Low heart rate variability and the effect of depression on post-myocardial infarction mortality. *Arch Intern Med*. 2005;165:1486–1491. doi: 10.1001/archinte.165.13.1486.
13. Gehi A, Haas D, Pipkin S, Whooley MA. Depression and medication adherence in outpatients with coronary heart disease: findings from the Heart and Soul Study. *Arch Intern Med*. 2005;165:2508–2513. doi: 10.1001/archinte.165.21.2508.
14. Ruo B, Rumsfeld JS, Pipkin S, Whooley MA. Relation between depressive symptoms and treadmill exercise capacity in the Heart and Soul Study. *Am J Cardiol*. 2004;94:96–99. doi: 10.1016/j.amjcard.2004.03.035.
15. Whooley MA, de Jonge P, Vittinghoff E, Otte C, Moos R, Carney RM, Ali S, Dowray S, Na B, Feldman MD, Schiller NB, Browner WS. Depressive symptoms, health behaviors, and risk of cardiovascular events in patients with coronary heart disease. *JAMA*. 2008;300:2379–2388. doi: 10.1001/jama.2008.711.
16. Rutledge T, Kenkre TS, Thompson DV, Bittner VA, Whittaker K, Eastwood JA, Eteiba W, Cornell CE, Krantz DS, Pepine CJ, Johnson BD, Handberg EM, Bairey Merz CN. Depression, dietary habits, and cardiovascular events among women with suspected myocardial ischemia. *Am J Med*. 2014;127:840–847. doi: 10.1016/j.amjmed.2014.04.011.
17. Carney RM, Freedland KE, Miller GE, Jaffe AS. Depression as a risk factor for cardiac mortality and morbidity: a review of potential mechanisms. *J Psychosom Res*. 2002;53:897–902.
18. Lichtman JH, Froelicher ES, Blumenthal JA, Carney RM, Doering LV, Frasure-Smith N, Freedland KE, Jaffe AS, Leifheit-Limson EC, Sheps DS, Vaccarino V, Wulsin L; American Heart Association Statistics Committee of the Council on Epidemiology and Prevention and the Council on Cardiovascular and Stroke Nursing. Depression as a risk factor for poor prognosis among patients with acute coronary syndrome: systematic review and recommendations: a scientific statement from the American Heart Association. *Circulation*. 2014;129:1350–1369. doi: 10.1161/CIR.0000000000000019.
19. Huffman JC, Celano CM, Beach SR, Motiwala SR, Januzzi JL. Depression and cardiac disease: epidemiology, mechanisms, and diagnosis. *Cardiovasc Psychiatry Neurol*. 2013;2013:695925. doi: 10.1155/2013/695925.
20. Leung YW, Flora DB, Gravely S, Irvine J, Carney RM, Grace SL. The impact of premorbid and postmorbid depression onset on mortality and cardiac morbidity among patients with coronary heart disease: meta-analysis. *Psychosom Med*. 2012;74:786–801. doi: 10.1097/PSY.0b013e31826ddbed.
21. Wijeysundera HC, Machado M, Farahati F, Wang X, Witteman W, van der Velde G, Tu JV, Lee DS, Goodman SG, Petrella R, O'Flaherty M, Krahn M, Capewell S. Association of temporal trends in risk factors and treatment uptake with coronary heart disease mortality, 1994-2005. *JAMA*. 2010;303:1841–1847. doi: 10.1001/jama.2010.580.
22. Go AS, Mozaffarian D, Roger VL, Benjamin EJ, Berry JD, Blaha MJ, Dai S, Ford ES, Fox CS, Franco S, Fullerton HJ, Gillespie C, Hailpern SM, Heit JA, Howard VJ, Huffman MD, Judd SE, Kissela BM, Kittner SJ, Lackland DT, Lichtman JH, Lisabeth LD, Mackey RH, Magid DJ, Marcus GM, Marelli A, Matchar DB, McGuire DK, Mohler ER 3rd, Moy CS, Mussolino ME, Neumar RW, Nichol G, Pandey DK, Paynter NP, Reeves MJ, Sorlie PD, Stein J, Towfighi A, Turan TN, Virani SS, Wong ND, Woo D, Turner MB; American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Heart disease and stroke statistics–2014 update: a report from the American Heart Association. *Circulation*. 2014;129:e28–e292. doi: 10.1161/01.cir.0000441139.02102.80.
23. Frasure-Smith N, Lespérance F. Depression and anxiety as predictors of 2-year cardiac events in patients with stable coronary artery disease. *Arch Gen Psychiatry*. 2008;65:62–71. doi: 10.1001/archgenpsychiatry.2007.4.
24. Hance M, Carney RM, Freedland KE, Skala J. Depression in patients with coronary heart disease. A 12-month follow-up. *Gen Hosp Psychiatry*. 1996;18:61–65.
25. Barefoot JC, Helms MJ, Mark DB, Blumenthal JA, Califf RM, Haney TL, O'Connor CM, Siegler IC, Williams RB. Depression and long-term mortality risk in patients with coronary artery disease. *Am J Cardiol*. 1996;78:613–617.
26. About the Cardiac Care Network of Ontario. http://www.ccn.on.ca/ccn_public/FormsAboutCCN/about.aspx. Accessed January 8, 2016.
27. Annual Report 2014–2015. http://www.ccn.on.ca/ccn_public/uploadfiles/files/CCN_Annual_Report_2014_15.pdf. Accessed January 8, 2016.
28. Gurevich Y, McFarlane A, Morris K, Jokovic A, Peterson GM, Webster GK. Estimating the number of coronary artery bypass graft and percutaneous coronary intervention procedures in Canada: a comparison of cardiac registry and Canadian Institute for Health Information data sources. *Can J Cardiol*. 2010;26:e249–e253.
29. Fiest KM, Jette N, Quan H, St Germaine-Smith C, Metcalfe A, Patten SB, Beck CA. Systematic review and assessment of validated case definitions for depression in administrative data. *BMC Psychiatry*. 2014;14:289. doi: 10.1186/s12888-014-0289-5.
30. Hiller W, Dichtl G, Hecht H, Hundt W, Mombour W, von Zerssen D. Evaluating the new ICD-10 categories of depressive episode and recurrent depressive disorder. *J Affect Disord*. 1994;31:49–60.
31. Kessing L. A comparison of ICD-8 and ICD-10 diagnoses of affective disorder -a case register study from Denmark. *Eur Psychiatry*. 1998;13:342–345. doi: 10.1016/S0924-9338(99)80700-7.
32. Wijeysundera HC, Bennell MC, Qiu F, Ko DT, Tu JV, Wijeysundera DN, Austin PC. Comparative-effectiveness of revascularization versus routine medical therapy for stable ischemic heart disease: a population-based study. *J Gen Intern Med*. 2014;29:1031–1039. doi: 10.1007/s11606-014-2813-1.
33. Mantel N, Byar DP. Evaluation of response-time data involving transient states: An illustration using heart-transplant data. *J Am Stat Assoc*. 1974;69:81–86.
34. Kessler RC. Epidemiology of women and depression. *J Affect Disord*. 2003;74:5–13.
35. Rumsfeld JS, Magid DJ, Plomondon ME, Sales AE, Grunwald GK, Every NR, Spertus JA. History of depression, angina, and quality of life after acute coronary syndromes. *Am Heart J*. 2003;145:493–499. doi: 10.1067/mhj.2003.177.
36. Berkman LF, Blumenthal J, Burg M, Carney RM, Catellier D, Cowan MJ, Czajkowski SM, DeBusk R, Hosking J, Jaffe A, Kaufmann PG, Mitchell P, Norman J, Powell LH, Raczynski JM, Schneiderman N; Enhancing Recovery in Coronary Heart Disease Patients Investigators (ENRICHD). Effects of treating depression and low perceived social support on clinical events after myocardial infarction: the Enhancing Recovery in Coronary Heart Disease Patients (ENRICHD) Randomized Trial. *JAMA*. 2003;289:3106–3116. doi: 10.1001/jama.289.23.3106.
37. Taylor CB, Youngblood ME, Catellier D, Veith RC, Carney RM, Burg MM, Kaufmann PG, Shuster J, Mellman T, Blumenthal JA, Krishnan R, Jaffe AS; ENRICHD Investigators. Effects of antidepressant medication on morbidity and mortality in depressed patients after myocardial infarction. *Arch Gen Psychiatry*. 2005;62:792–798. doi: 10.1001/archpsyc.62.7.792.

Circulation
Cardiovascular Quality and Outcomes

Clinical Impact of Subsequent Depression in Patients With a New Diagnosis of Stable Angina: A Population-Based Study

Natalie Szpakowski, Maria C. Bennell, Feng Qiu, Dennis T. Ko, Jack V. Tu, Paul Kurdyak and Harindra C. Wijeysundera

Circ Cardiovasc Qual Outcomes. 2016;9:731-739; originally published online October 4, 2016;
doi: 10.1161/CIRCOUTCOMES.116.002904
Circulation: Cardiovascular Quality and Outcomes is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

Print ISSN: 1941-7705. Online ISSN: 1941-7713

Supplemental Material

Supplemental Table 1. ICD-10 codes for depression

ICD-10 Code	Description
F32	Major depressive disorder, single episode
F32.0	Major depressive disorder, single episode, mild
F32.1	Major depressive disorder, single episode, moderate
F32.2	Major depressive disorder, single episode, severe without psychotic symptoms
F32.3	Major depressive disorder, single episode, severe with psychotic symptoms
F32.4	Major depressive disorder, single episode, in partial remission
F32.5	Major depressive disorder, single episode, in full remission
F32.8	Other depressive episodes
F32.9	Major depressive disorder, single episode, unspecified
F33	Major depressive disorder, recurrent
F33.0	Recurrent depressive disorder, current episode mild
F33.1	Recurrent depressive disorder, current episode moderate
F33.2	Recurrent depressive disorder, current episode severe without psychotic symptoms
F33.3	Recurrent depressive disorder, current episode severe with psychotic symptoms
F33.41	Recurrent depressive disorder, currently in partial remission
F33.42	Recurrent depressive disorder, currently in full remission
F33.8	Recurrent depressive disorder, other
F33.9	Recurrent depressive disorder, unspecified
F34.1	Dysthymia
F34.8	Other persistent mood disorders
F34.9	Persistent mood disorder, unspecified
F38.0	Other single mood disorders
F38.1	Other recurrent mood disorders
F38.8	Other specified mood disorders
F39	Unspecified mood disorder
F41.2	Mixed anxiety and depressive disorder

Supplemental Table 2. Antidepressants

Selective serotonin reuptake inhibitors

- Sertraline
- Fluoxetine
- Citalopram
- Escitalopram
- Paroxetine
- Fluvoxamine
- Trazadone

Serotonin and norepinephrine reuptake inhibitors

- Desvenlafaxine
- Duloxetine
- Venlafaxine
- Milnacipran

Norepinephrine reuptake inhibitors

- Reboxetine

Tricyclic antidepressants

- Amitriptyline
- Amoxapine
- Clomipramine
- Desipramine
- Doxepin
- Imipramine
- Nortriptyline
- Protriptyline
- Maprotiline

Norepinephrine and dopamine reuptake inhibitors

- Bupropion

Monoamine oxidase inhibitors

- Moclobemide
- Phenelzine
- Selegiline
- Tranylcypromine

Noradrenergic and specific serotonergic antidepressants

- Mirtazapine

Supplemental Table 3. Factors associated with all-cause mortality, admission for MI and revascularization in full cohort

Covariates	All-Cause Mortality		Admission for MI		Revascularization	
	HR (95% CI)	**p-value**	**HR (95% CI)**	**p-value**	**HR (95% CI)**	**p-value**
Depression	1.83 (1.62-2.07)	<.001	1.36 (1.10-1.67)	0.005	1.13 (0.99-1.28)	0.07
Patient-level Factors						
Demographics						
Female	0.88 (0.78-1.0)	0.04	0.99 (0.81-1.23)	0.95	1.04 (0.96-1.13)	0.33
Age <50	Referent		Referent		Referent	
Age 50-64	1.43 (1.04-1.98)	0.03	0.89 (0.67-1.18)	0.42	0.84 (0.72-0.96)	0.01
Age 65-80	3.01 (2.12-4.26)	<.001	1.03 (0.76-1.32)	0.98	0.78 (0.70-0.87)	<.001
Age >80	7.12 (4.92-10.30)	<.001	1.75 (1.31-2.34)	<.001	0.50 (0.39-0.62)	<.001
Rural	1.03 (0.94-1.13)	0.49	0.99 (0.83-1.18)	0.93	0.91 (0.81-1.03)	0.14
Income*						
1	Referent		Referent		Referent	
2	0.99 (0.83-1.17)	0.87	1.02 (0.90-1.15)	0.82	0.93 (0.81-1.06)	0.26
3	0.86 (0.74-0.99)	0.04	0.76 (0.6-0.97)	0.03	1.03 (0.89-1.20)	0.67
4	0.96 (0.84-1.09)	0.50	0.85 (0.68-1.06)	0.16	0.97 (0.87-1.09)	0.57
5	0.83 (0.75-0.93)	<.001	0.83 (0.67-1.04)	0.11	0.98 (0.87-1.09)	0.67
Medical Comorbidities						
Renal function	1.98 (1.52-2.57)	<.001	2.17 (1.45-3.26)	<.001	1.31 (0.91-1.90)	0.15
PVD	1.55 (1.35-1.78)	<.001	1.42 (1.12-1.80)	0.004	1.12 (1.02-1.25)	0.05
COPD	1.72 (1.54-1.93)	<.001	1.08 (0.79-1.49)	0.62	1.00 (0.83-1.21)	0.99
Previous stroke	1.06 (0.80-1.41)	0.67	1.17 (0.58-2.37)	0.66	0.90 (0.59-1.36)	0.61
Malignancy	1.71 (1.25-2.33)	0.001	1.05 (0.60-1.83)	0.86	1.25 (0.99-1.59)	0.07
Comorbidites: Charlson score	1.17 (1.10-1.24)	<.001	1.08 (0.98-1.19)	0.15	1.01 (0.95-1.06)	0.78
Cardiac Risk Factors						
Diabetes	1.34 (1.21-1.47)	<.001	1.48 (1.27-1.73)	<.001	1.24 (1.17-1.31)	<.001
Hypertension	1.23 (1.05-1.42)	0.008	1.00 (0.86-1.16)	0.97	0.94 (0.83-1.06)	0.29

Supplemental Table 3. Factors associated with all-cause mortality, admission for MI and revascularization in full cohort (continued)

Hyperlipidemia	0.78 (0.68-0.89)	<.001	0.86 (0.73-1.02)	0.09	1.02 (0.93-1.12)	0.66
Smoking						
Non smoker	Referent		Referent		Referent	
Former smoker	1.31 (1.19-1.45)	<.001	1.13 (0.99-1.28)	0.06	0.97 (0.89-1.06)	0.52
Current smoker	1.38 (1.12-1.70)	0.002	0.94 (0.79-1.12)	0.48	1.03 (0.96-1.10)	0.46
CCS Angina Class						
0	Referent		Referent		Referent	
1	0.92 (0.79-1.07)	0.28	1.08 (0.83-1.40)	0.57	1.18 (0.99-1.41)	0.07
2	0.86 (0.76-0.97)	0.02	1.23 (0.91-1.65)	0.18	1.31 (1.14-1.50)	<.001
3	0.96 (0.84-1.10)	0.59	1.29 (0.99-1.68)	0.59	1.50 (1.31-1.70)	<.001
4	0.81 (0.48-1.36)	0.42	1.57 (1.05-2.33)	0.03	1.74 (1.46-2.08)	<.001
Cardiac Status/Testing						
LV Function						
>=50%	Referent		Referent		Referent	
35-49%	1.43 (1.15-1.78)	0.001	1.09 (0.88-1.36)	0.43	0.86 (0.78-0.95)	0.002
20%-34%	1.60 (1.30-1.97)	<.001	1.00 (0.67-1.47)	0.99	0.96 (0.75-1.24)	0.77
>20%	1.96 (1.27-3.03)	0.002	1.06 (0.52-2.19)	0.87	0.98 (0.72-1.34)	0.91
NA	0.90 (0.77-1.06)	0.22	0.87 (0.74-1.04)	0.13	0.95 (0.87-1.03)	0.18
Exercise ECG Risk						
Low risk	Referent		Referent		Referent	
High risk	1.09 (0.90-1.30)	0.38	0.94 (0.77-1.15)	0.53	1.01 (0.92-1.10)	0.89
Uninterpretable	1.45 (1.1-1.92)	0.008	0.99 (0.72-1.37)	0.96	0.83 (0.69-1.00)	0.05
NA	1.80 (1.55-2.09)	<.001	1.25 (1.09-1.42)	0.001	0.96 (0.87-1.07)	0.47
Functional Imaging Risk						
Low risk	Referent		Referent		Referent	
High risk	0.92 (0.81-1.05)	0.20	1.04 (0.89-1.20)	0.64	1.00 (0.91-1.09)	0.95
Unknown	1.11 (0.95-1.30)	0.19	1.17 (0.96-1.43)	0.11	0.99 (0.89-1.09)	0.79
Native Stenosis[†]						
LM	1.51 (1.27-1.80)	<.001	1.28 (0.94-1.75)	0.11	1.44 (1.24-1.68)	<.001

Supplemental Table 3. Factors associated with all-cause mortality, admission for MI and revascularization in full cohort (continued)

Prox LAD	1.26 (1.12-1.42)	<.001	1.24 (1.09-1.40)	0.001	1.53 (1.39-1.69)	<.001
Mid/distal LAD	1.06 (0.96-1.17)	0.24	1.18 (0.97-1.44)	0.09	1.47 (1.36-1.60)	<.001
Circumflex	1.19 (1.06-1.33)	0.003	1.27 (1.09-1.49)	0.003	1.49 (1.36-1.63)	<.001
RCA	1.31 (1.16-1.48)	<.001	1.16 (1.00-1.35)	0.05	1.55 (1.45-1.65)	<.001
Treatment within 90 days						
MED	Referent		Referent		Referent	
CABG	0.51 (0.44-0.61)	<.001	0.32 (0.25-0.42)	<.001	0.10 (0.08-0.13)	<.001
PCI	0.68 (0.59-0.80)	<.001	0.71 (0.56-0.89)	0.003	0.56 (0.47-0.67)	<.001
Hospital-level Factors						
Availability						
Cath only	Referent		Referent		Referent	
Cath and PCI only	0.94 (0.76-1.17)	0.59	1.07 (0.74-1.55)	0.70	1.14 (0.97-1.35)	0.11
Cath, PCI and CABG	0.93 (0.84-1.03)	0.19	0.94 (0.80-1.09)	0.39	0.97 (0.87-1.09)	0.66
Physician-level Factors						
Referring Physician						
GP/FP	Referent		Referent		Referent	
Cardiology	1.16 (1.06-1.27)	0.002	0.93 (0.79-1.11)	0.42	0.98 (0.88-1.09)	0.74
Other	1.15 (1.02-1.29)	0.02	1.08 (0.86-1.35)	0.52	0.98 (0.90-1.06)	0.59
Physician performing Cath						
PCI physician	1.05 (0.91-1.21)	0.51	1.00 (0.90-1.11)	0.97	0.99 (0.90-1.09)	0.91

Cath = catheterization, CCS = Canadian Cardiovascular Society, CI = confidence interval, CABG = coronary artery bypass grafting, COPD = chronic obstructive pulmonary disease, ECG = electrocardiogram, GP/FP = General practitioner/Family physician, HR = hazard ratio, LAD = left anterior descending, LM = left main, LV = left ventricular, MED = medical therapy, MI = myocardial infarction, PCI = percutaneous coronary intervention, PVD = peripheral vascular disease, NA= not done or missing, RCA = right coronary artery,
* Income quintile: 1=lowest, 5 = highest, † Significant stenosis ≥70%, except ≥50% stenosis significant for LM

Supplemental Table 4. Factors associated with all-cause mortality, admission for MI, and revascularization among patients with depression

Covariates	All-Cause Mortality		Admission for MI		Revascularization	
	HR (95% CI)	**p-value**	**HR (95% CI)**	**p-value**	**HR (95% CI)**	**p-value**
Patient-level Factors						
Time to Diagnosis of Depression*						
1: 0-30 days	Referent		Referent		Referent	
2:30-90 days	1.36 (0.75-2.47)	0.31	1.28 (0.62-2.65)	0.51	0.90 (0.52-1.55)	0.70
3:90-180 days	1.80 (0.78-4.15)	0.17	1.84 (0.65-5.17)	0.25	1.06 (0.66-1.70)	0.81
4:180-365 days	1.65 (0.75-3.66)	0.22	1.53 (0.65-3.60)	0.34	1.07 (0.71-1.62)	0.75
5: 1-3 years	1.03 (0.59-1.79)	0.93	1.24 (0.53-2.91)	0.62	1.03 (0.68-1.56)	0.88
6: >3 years	0.56 (0.29-1.08)	0.08	1.65 (0.65-4.15)	0.29	1.10 (0.73-1.67)	0.65
Demographics						
Female	0.73 (0.60-0.90)	0.003	1.08 (0.80-1.46)	0.63	1.02 (0.87-1.20)	0.80
Age <50	Referent		Referent		Referent	
Age 50-64	2.06 (0.93-4.57)	0.07	0.85 (0.45-1.58)	0.60	0.77 (0.61-0.96)	0.02
Age 65-80	4.27 (1.99-9.16)	<.001	1.14 (0.64-2.03)	0.66	0.72 (0.58-0.89)	0.003
Age >80	13.55 (6.23-29.49)	<.001	1.72 (0.87-3.38)	0.12	0.29 (0.18-0.46)	<.001
Rural	1.00 (0.64-1.57)	0.99	1.11 (0.75-1.65)	0.59	0.89 (0.75-1.06)	0.18
Income†						
1	Referent		Referent		Referent	
2	0.99 (0.70-1.41)	0.97	1.12 (0.77-163)	0.56	0.79 (0.61-1.02)	0.07
3	0.62 (0.48-0.79)	<.001	0.63 (0.38-1.05)	0.07	0.89 (0.67-1.18)	0.42
4	0.92 (0.67-1.26)	0.59	0.73 (0.52-1.03)	0.07	0.79 (0.59-1.05)	0.10
5	0.73 (0.46-1.14)	0.17	0.65 (0.43-0.99)	0.04	0.90 (0.66-1.23)	0.51
Medical Comorbidities						
Renal function	3.29 (2.37-4.56)	<.001	1.99 (0.88-4.48)	0.10	1.02 (0.54-1.93)	0.95
PVD	1.80 (1.23-2.64)	0.003	1.51 (0.85-2.68)	0.16	1.20 (1.01-1.44)	0.04
COPD	1.69 (1.25-2.29)	0.001	1.30 (0.79-2.14)	0.31	1.20 (0.95-1.53)	0.13

Supplemental Table 4. Factors associated with all-cause mortality, admission for MI, and revascularization among patients with depression (continued)

Previous stroke	1.99 (1.13-3.52)	0.02	0.75 (0.17-3.32)	0.71	1.08 (0.61-1.93)	0.79
Malignancy	2.58 (1.35-4.94)	0.004	0.60 (0.13-2.71)	0.51	1.42 (0.74-2.71)	0.29
Comorbidites: Charlson score	1.03 (0.91-1.16)	0.69	0.96 (0.78-1.18)	0.70	1.07 (0.96-1.18)	0.22
Cardiac Risk Factors						
Diabetes	1.25 (1.03-1.51)	0.02	1.79 (1.27-2.53)	0.001	1.11 (0.96-1.28)	0.17
Hypertension	1.08 (0.66-1.77)	0.75	0.89 (0.61-1.29)	0.54	0.87 (0.73-1.04)	0.12
Hyperlipidemia	0.90 (0.67-1.21)	0.47	0.77 (0.61-0.97)	0.03	0.91 (0.76-1.09)	0.31
Smoking						
Non smoker	Referent		Referent		Referent	
Former smoker	1.57 (1.24-2.00)	<.001	1.17 (0.86-1.59)	0.31	0.98 (0.84-1.14)	0.79
Current smoker	1.49 (1.13-1.95)	0.005	0.84 (0.62-1.14)	0.26	0.96 (0.84-1.11)	0.58
CCS Angina Class						
0	Referent		Referent		Referent	
1	0.78 (0.56-1.10)	0.15	1.04 (0.55-1.94)	0.91	1.14 (0.79-1.65)	0.49
2	1.09 (0.87-1.37)	0.45	1.04 (0.60-1.80)	0.88	1.23 (0.97-1.53)	0.09
3	0.95 (0.65-1.38)	0.78	1.04 (0.59-1.85)	0.89	1.29 (1.05-1.58)	0.02
4	0.85 (0.25-2.95)	0.80	2.11 (1.28-3.51)	0.004	0.95 (0.51-1.77)	0.86
Cardiac Status/Testing						
LV Function						
>=50%	Referent		Referent		Referent	
35-49%	1.75 (1.24-2.45)	0.001	0.83 (0.47-1.47)	0.53	1.02 (0.77-1.36)	0.87
20%-34%	1.56 (0.77-3.17)	0.22	0.63 (0.29-1.35)	0.23	0.85 (0.59-1.23)	0.40
>20%	4.00 (1.74-9.19)	0.001	1.18 (0.35-3.98)	0.79	1.13 (0.51-2.52)	0.76
NA	0.84 (0.61-1.17)	0.30	0.84 (0.61-1.17)	0.30	0.91 (0.77-1.07)	0.26
Exercise ECG Risk						
Low risk	Referent		Referent		Referent	
High risk	1.16 (0.72-1.86)	0.55	0.85 (0.61-1.19)	0.35	0.87 (0.73-1.01)	0.06
Uninterpretable	1.25 (0.76-2.03)	0.38	1.36 (0.80-2.31)	0.26	0.84 (0.56-1.25)	0.38

Supplemental Table 4. Factors associated with all-cause mortality, admission for MI, and revascularization among patients with depression (continued)

NA	1.70 (1.21-2.39)	0.002	1.27 (0.95-1.69)	0.11	0.92 (0.74-1.15)	0.46
Functional Imaging Risk						
Low risk	Referent		Referent		Referent	
High risk	0.88 (0.61-1.26)	0.47	1.12 (0.84-1.50)	0.44	0.95 (0.79-1.14)	0.56
Unknown	1.01 (0.73-1.40)	0.96	1.21 (0.86-1.70)	0.28	0.99 (0.82-1.21)	0.95
Native Stenosis‡						
LM	1.30 (0.85-2.00)	0.23	1.05 (0.51-2.16)	0.90	1.38 (0.93-2.05)	0.11
Prox LAD	1.34 (1.02-1.76)	0.04	1.38 (1.03-1.86)	0.03	1.40 (1.20-1.64)	<.001
Mid/distal LAD	1.19 (0.95-1.49)	0.13	1.27 (0.96-1.67)	0.09	1.49 (1.29-1.73)	<.001
Circumflex	1.04 (0.82-1.32)	0.75	0.97 (0.77-1.23)	0.81	1.44 (1.25-1.66)	<.001
RCA	1.10 (0.85-1.43)	0.46	1.02 (0.76-1.37)	0.89	1.47 (1.25-1.72)	<.001
Treatment within 90 days						
MED	Referent		Referent		Referent	
CABG	0.63 (0.48-0.83)	0.001	0.33 (0.22-0.51)	<.001	0.14 (0.10-0.18)	<.001
PCI	0.86 (0.66-1.11)	0.24	0.68 (0.49-0.93)	0.02	0.58 (0.49-0.69)	<.001
Hospital-level Factors						
Availability						
Cath only	Referent		Referent		Referent	
Cath and PCI only	1.25 (0.83-1.90)	0.29	1.19 (0.62-2.28)	0.60	1.22 (1.03-1.45)	0.02
Cath, PCI and CABG	1.10 (0.85-1.43)	0.48	0.84 (0.55-1.28)	0.41	0.84 (0.71-0.99)	0.04
Physician-level Factors						
Referring Physician						
GP/FP	Referent		Referent		Referent	
Cardiology	0.98 (0.75-1.29)	0.91	1.04 (0.72-1.49)	0.85	1.06 (0.88-1.28)	0.52
Other	1.12 (0.84-1.50)	0.45	1.14 (0.74-1.76)	0.55	0.96 (0.72-1.27)	0.76

Supplemental Table 4. Factors associated with all-cause mortality, admission for MI, and revascularization among patients with depression (continued)

Physician performing Cath						
PCI physician	1.12 (0.89-1.62)	0.24	1.29 (0.96-1.73)	0.10	1.08 (0.97-1.21)	0.16

Cath = catheterization, CCS = Canadian Cardiovascular Society, CI = confidence interval, CABG= coronary artery bypass grafting, COPD = chronic obstructive pulmonary disease, ECG = electrocardiogram, GP/FP = General practioner/Family physician, HR = hazard ratio, LAD = left anterior descending, LM = left main, LV = left ventricular, MED = medical therapy, MI = myocardial infarction, PCI = percutaneous coronary intervention, PVD = peripheral vascular disease, NA= not done or missing, RCA = right coronary artery,
* time after diagnosis of stable angina † Income quintile: 1=lowest, 5 = highest, ‡ Significant stenosis ≥70%, except ≥50% stenosis significant for LM