Is early- and late-onset depression after acute myocardial infarction associated with long-term survival in older adults? A population-based study

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GL Grunau, PA Ratner, EM Goldner, S Sheps. Is early- and late-onset depression after acute myocardial infarction associated with long-term survival in older adults? A population-based study. *Can J Cardiol* 2006;22(6):473-478.

BACKGROUND: Early-onset depression after acute myocardial infarction (AMI) affects short-term survival in clinical samples of patients. There is no information on the impact of early-onset depression or late-onset depression on long-term survival.

OBJECTIVE: To investigate the impact of early- and late-onset depression on survival using administrative data.

METHODS: A historical inception cohort design was used, commencing in 1994 with up to eight years of follow-up. A province-wide administrative data set from British Columbia was used to select the cohort and construct the variables. Data regarding hospitalizations, physician visits and prescription drugs were available. All individuals 66 years of age and older who had an AMI in 1994 or 1995 were selected (n=4874). Individuals were categorized as depressed, possibly depressed or not depressed based on physician or hospital visits indicating depression as a diagnosis and/or prescriptions for antidepressants. Early-onset depression was assessed during the first six months post-AMI, and late-onset depression was assessed between six months and five years post-AMI. All-cause mortality up to eight years post-AMI was the outcome.

RESULTS: Both early- and late-onset depression were associated with long-term mortality. The hazard ratio was 1.34 (95% CI 1.04 to 1.73) for early-onset depression and 1.79 (95% CI 1.38 to 2.35) for late-onset depression.

CONCLUSIONS: Both early- and late-onset depression post-AMI were significantly associated with mortality up to eight years post-AMI. Depression is a strong independent predictor of post-AMI mortality in older adults.

Key Words: Myocardial infarction; Population health; Prognosis

Depression occurring shortly after acute myocardial infarction (AMI) has been shown to influence cardiac (1-7) and all-cause mortality (7). Indeed, in one study (8), even minimal symptoms of depression were shown to increase the risk for mortality at four months post-AMI. The mechanisms by which depression affects outcomes in cardiac disease are far from clear (9,10). One suggested biological mechanism linking depression with increased mortality is an abnormality in platelet reactivity (11,12), which is thought to play a central role in the development of atherosclerosis, thrombosis and acute

La dépression précoce ou tardive après un infarctus aigu du myocarde s'associe-t-elle à la survie à long terme chez les adultes âgés ? Une étude de population

HISTORIQUE : La dépression précoce après un infarctus aigu du myocarde (IAM) nuit à la survie à court terme au sein d'échantillons cliniques de patients. On ne possède pas d'information sur les répercussions de la dépression précoce sur la survie à long terme ou de la dépression tardive sur la survie.

OBJECTIF : Explorer les répercussions de la dépression précoce et de la dépression tardive sur la survie au moyen de données administratives.

MÉTHODOLOGIE : Une cohorte d'inception historique formée en 1994 a été utilisée. Le suivi a duré jusqu'à huit ans. Un ensemble de données administratives britanno-colombiennes a été utilisé pour sélectionner la cohorte et définir les variables. Les données relatives à l'hospitalisation, aux consultations chez le médecin et aux médicaments sur ordonnance étaient disponibles. Tous les patients de 66 ans qui avaient souffert d'un IAM en 1994 ou en 1995 ont été sélectionnés (n=4874). Ils ont été classés comme dépressifs, peut-être dépressifs, ou non dépressifs selon le diagnostic de consultations chez le médecin ou à l'hôpital ou selon la prescription d'antidépresseurs. La dépression précoce était évaluée pendant les six premiers mois suivant l'IAM, tandis que la dépression tardive l'était de six mois à cinq ans après l'IAM. L'issue était un décès toutes causes confondues jusqu'à 8 ans après l'IAM.

RÉSULTATS : La dépression précoce et la dépression tardive s'associaient toutes deux à une mortalité à long terme. Le risque relatif s'élevait à 1,34 (95 IC 1,04 à 1,73) en cas de dépression précoce et à 1,79 (95 IC 1,38 à 2,35) en cas de dépression tardive.

CONCLUSIONS : Tant la dépression précoce que la dépression tardive après un IAM étaient associées de manière significative à une mortalité jusqu'à sept ans après l'IAM. La dépression est un solide prédicteur indépendant de mortalité après un IAM chez les adultes âgés.

coronary syndromes (11,12). Compared with normal controls, individuals with depression have been found to have enhanced baseline platelet activation and responsiveness (11,12). The mechanisms responsible remain unknown; however, this heightened susceptibility to platelet activation may contribute to the increased vulnerability of depressed patients to mortality post-AMI (11,12). Depression may be associated with mortality through the association found between depression and insulin resistance, as previously shown in a review article focusing on this topic (13). Also, one study (14) found that major depressive

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Received for publication July 26, 2005. Accepted December 7, 2005

disorder increases the risk for onset of type II diabetes; however, it was difficult to determine the temporal order of the two conditions. Behavioural mechanisms have also been suggested because individuals with depression have been found to have greater dropout rates from cardiac rehabilitation programs and higher rates of noncompliance with medication regimens (15).

There are several important limitations regarding studies investigating the impact of depression on survival. First, follow-up in most of these studies was short (ie, no longer than 18 months) (4). Thus, it is unclear whether depression post-AMI has an impact on longer term mortality. Second, most of the studies to date assessed depressive symptomatology shortly after admission for the cardiac event (1,3,4,8,16-18), which may not be an optimal or relevant measure of major depression because it may capture only transient states occurring after a traumatic cardiac event rather than actual episodes of major depression. Moreover, because no data were available on depression in these studies in the period before admission, it is impossible to distinguish between prevalent and incident depression. Individuals with chronic depression may be different than those who become depressed as a consequence of the life changes associated with AMI. Some have proposed that individuals with depression first occurring after 60 years of age comprise a separate group of patients suffering from a mood disorder secondary to vascular disease, including ischemic disease of the neuronal circuits that are involved in the mood regulation (19). Finally, most of the studies did not investigate the impact of depression occurring later in the course of recovery from AMI, even though a significant number of individuals become depressed throughout the first year post-AMI, with estimates ranging between 6% and 20% (2,20,21). While some researchers have measured depression at one year following AMI (2,7,20), only one study (7) investigated the impact of one-year depression on mortality.

The present study investigated the impact of early- and late-onset depression post-AMI on short- and long-term survival using administrative data, a data source that has not been previously used to investigate this question. Administrative data, gathered at a population level (22), can expand current knowledge because they provide information about an entire population rather than a clinical sample, increasing the generalizability of the findings and reducing the likelihood of selection bias. These types of data also allow for the explicit identification of incident depression and the explicit exclusion of individuals with prevalent depression.

METHODS

Data sources

The present study used the British Columbia Linked Health Database (BCLHD) (23) to identify the study population and construct the variables. The BCLHD is a population-based data resource developed and maintained by the Centre for Health Services and Policy Research (CHSPR). CHSPR acts as the custodian of and access point for the various data holdings of the BCLHD, which remain under the stewardship of the agencies that originally collected them (eg, within the British Columbia [BC] government). The BCLHD is one of only a small number of data resources in the world where longitudinal research on an entire population can be carried out because the database covers the entire population of BC, a population of approximately 3,900,000 people. The responsibility for the use and interpretation of the data was entirely that of the authors.

The databases that were linked in the present study were the medical services plan payment information masterfile (MSP), the hospital separation file, BC PharmaCare, the registry file and the vital statistics deaths file. MSP insures medically required services provided by physicians and other health care practitioners, laboratory services and diagnostic procedures. The hospital separation files include records of admissions, discharges, transfers, and deaths of inpatients and day surgery patients from acute care hospitals in BC. PharmaCare subsidizes eligible prescription drugs and designated medical supplies; the files include records of prescriptions paid by the plan. All seniors 65 years of age and older are covered by PharmaCare. The registry file reflects the work CHSPR has done to clean up and consolidate the information on the MSP registration and premium billing file, which contains demographic information on the individuals, including age, sex and socioeconomic status (SES). The vital statistics deaths file includes all deaths that occurred in BC or in a hospital elsewhere in Canada.

All aspects of the study design and data use were reviewed by the University of British Columbia's Research Ethics Board and the BC Ministry of Health's Data Access Committee. A person-level analytical file was constructed to link all data relevant to the patient. Patient identifiers were removed from the data file to maintain patient and provider anonymity.

Study design and selection of the cohort

The present study employed a historical inception cohort design. Cohort members were selected from the entire BC population if they had a diagnosis of AMI (not necessarily their first AMI) in 1994 or 1995. A diagnosis of AMI included any record with a principal diagnosis *International Classification of Diseases, 9th revision* (ICD-9) code of 410 and its derivatives (410.0, 410.00, 410.1, etc) (24). Patients discharged with a total length of stay of less than three days, including days at a receiving hospital if they were transferred, were excluded under the assumption that these patients had AMIs 'ruled out' rather than confirmed AMIs (25). Only individuals who were 66 years of age or older at the time of their AMI were included because data on prescription drugs, a criterion necessary to determine evidence of prevalent depression, were available only from the age of 65 years. A cohort of 5559 individuals met these criteria.

Individuals with evidence of depression in the year before their AMI were excluded, allowing assessment of incident rather than prevalent depression post-AMI. Individuals who had any prescriptions for antidepressants in the year before their AMI were excluded (n=471), leaving a cohort of 5088. Individuals were also excluded if they had a diagnosis of depression in the year before their index AMI based on physician and hospital visits coded for depression. Individuals were excluded if they had two or more diagnoses (not necessarily the principal diagnosis) of ICD-9 300 (neurotic disorders, including neurotic depression), 296 (affective psychoses), 311 (depressive disorder, not elsewhere classified) or 50B (anxiety/depression in MSP files) (n=199), leaving a cohort of 4889. Two diagnostic entries were required to minimize the exclusion of individuals who had depression coded as an error or misdiagnosis.

Fifteen additional cohort members were excluded because they did not appear in the registry file (n=8) or because they were no longer residents of BC (although they had had their AMI in BC and therefore were initially selected) (n=7). This left a cohort of 4874 individuals.

From this cohort, two cohorts were selected for the analysis. Cohort 1 consisted of 3945 individuals who survived at least six

months after the index AMI. This cohort was used to assess the impact of early-onset depression (within the first six months post-AMI) on survival. Cohort 2 consisted of 2311 individuals who survived at least five years after the index AMI, and were not categorized as depressed or possibly depressed within the first six months post-AMI. This cohort was used to assess the impact of late-onset depression (depression between six months and five years post-AMI) on survival. It was important to create cohorts where individuals had equal 'opportunity' (survival time post-AMI) to develop depression (Figure 1).

Study variables

Age, sex and SES: Age, sex and SES were obtained from the registry file. The SES variable was determined using SES quintiles, which were constructed based on a household size-adjusted measure of household income derived from the 1996 Canadian Census (Statistics Canada) (26).

Definition of depression: To be categorized as 'depressed', an individual had to meet at least one of two criteria:

- At least four visits to a physician or hospital that included one of the following ICD-9 codes: 300 (neurotic disorders, including neurotic depression), 296 (affective psychoses), 311 (depressive disorder, not elsewhere classified) or 50B (anxiety/depression in MSP only); or
- At least two unique prescription days for antidepressants. Unique prescription days was defined as the number of unique dates in which an individual filled a prescription for antidepressants as shown in the PharmaCare files. The reason that the number of unique prescriptions days was used, rather than the total number of prescriptions, was that an individual could have more than one prescription filled on a given date. Use of prescription days rather than number of prescriptions established the stability of antidepressant use over time.

Individuals with no prescriptions days and no visits for depression were categorized as 'not depressed'. Individuals with one prescription day or one to three visits for depression were categorized as 'possibly depressed'. For cohort 1, the criteria for depression had to be met within the first six months after the index AMI. For cohort 2, the criteria for depression had to be met after six months post-AMI and before five years post-AMI.

Previous AMI and cardiac-related procedures at the time of the index AMI: A binary variable for previous AMI was positive for individuals who had any number of AMIs in the three years before the index AMI and negative for no AMIs in the three years before the index AMI. Data on cardiac-related procedures completed during the hospitalization for the index AMI were available and categorized into two classes: 'operations on vessels of the heart' and 'other operations on the heart and pericardium'. This division was based on the Canadian Classification of Diagnostic, Therapeutic and Surgical Procedures (27). These variables were also categorized as positive or negative.

Comorbidities: To determine the independent effect of depression on survival, it was important to control for comorbidities. The method used in the present study was based on the work of Tu et al (28), who developed a model to predict mortality post-AMI. The

Figure 1) Selection of cohort. AMI Acute myocardial infarction; BC British Columbia

comorbidities found in their model include shock, diabetes, congestive heart failure, cancer, cerebrovascular disease, pulmonary edema, acute renal failure, chronic renal failure and cardiac dysrhythmia. In cohort 1, these comorbidities were measured for each individual over the first six months post-AMI, and in cohort 2, they were measured over the first five years post-AMI (which was the common survival period of all individuals in the cohorts). To validate these findings, comorbidities were also measured using D'Hoore et al's adaptation of the Charlson Index (29). The results were essentially identical to those obtained using Tu et al (28) comorbidities, and thus are not reported here.

Outcomes and follow-up: The outcome was all-cause mortality. Individuals were followed until 2001 (a maximum of eight years).

Analysis

For cohort 1, RRs and their 95% CIs were calculated for death by the first, second, third, fourth, fifth and sixth year following the index AMI. For cohort 2, an RR and 95% CI was calculated for death by the sixth year.

Kaplan-Meier (KM) (30) survival curves were used to compare the survival of the depressed, possibly depressed and not depressed groups. The log-rank test was used to determine whether the survival curves were significantly different.

Cox regression analysis (31) was used to determine whether depression had an independent association with mortality after controlling for confounding factors (including age, sex, SES, previous AMI, operations at time of index AMI and comorbidities). The proportional hazards assumption was tested using log-minus-log graphs. A significance level of 0.05 was used.

TABLE 1
Mortality by depression status

Cohort (outcome)	Depressed	Possibly depressed	Not depressed
Cohort 1 (n)	108	352	3485
Died by end of year 1, %	12.0	8.2	5.6
Died by end of year 2, %	22.2	19.9	13.0
Died by end of year 3, %	32.4	27.3	20.6
Died by end of year 4, %	38.9	34.4	27.2
Died by end of year 5, %	44.4	38.6	33.7
Died by end of year 6, %	49.1	42.3	39.2
Cohort 2 (n)	274	522	1515
Died by end of year 6, %	13.9	10.3	6.7

TABLE 2
Relative risks for the depressed group versus the nondepressed group

Cohort, outcome	RR (95% CI)
Cohort 1	
Died by the first year	2.15 (1.26 to 3.56)
Died by the second year	1.71 (1.17 to 2.40)
Died by the third year	1.57 (1.17 to 2.04)
Died by the fourth year	1.43 (1.11 to 1.79)
Died by the fifth year	1.32 (1.05 to 1.61)
Died by the sixth year	1.25 (1.03 to 1.52)
Cohort 2	
Died by the sixth year	2.06 (1.45 to 2.92)

Role of the funding source

The funding sources – the Canadian Health Services Research Foundation, Alberta Heritage Foundation for Medical Research and the Canadian Institutes of Health Services and Policy Research – had no involvement in the study design, data collection, analysis, data interpretation, writing or submission of the paper for publication.

RESULTS

In cohort 1, 108 (2.7%) individuals were depressed, 352 (8.9%) were possibly depressed and 3485 (88.3%) were not depressed. In cohort 2, 274 (11.9%) were depressed, 522 (22.6%) were possibly depressed and 1515 (65.6%) were not depressed. The distribution of mortality by depression status is shown in Table 1.

The RRs of annual mortality after index AMI for the depressed group versus the nondepressed group and their 95% CIs are shown in Table 2. Early-onset depression occurring within the first six months post-AMI (cohort 1) was associated with short- and long-term all-cause mortality. Early-onset depression had the strongest effect on short-term mortality; however, the effect, even though decreased, was still significant up to six years post-AMI. Late-onset depression occurring after the first six months post-AMI (cohort 2) was also significantly associated with long-term mortality.

The proportional hazards assumption was valid for all models. The KM curves for each cohort comparing all three depression categories were significantly different. The depressed group and not depressed group were significantly different, as were the depressed and possibly depressed groups. However, there was no difference between the possibly depressed and nondepressed group. Figures 2 and 3 show the KM curves for cohorts 1 and 2, respectively.

Figure 2) Kaplan-Meier curve for cohort 1 for depressed versus non-depressed groups

Figure 3) Kaplan-Meier curve for cohort 2 for depressed versus non-depressed groups

Both early-onset depression (cohort 1) and late-onset depression (cohort 2) were strong predictors of mortality after controlling for potential confounders using Cox regression. The hazard ratio for the depressed group compared with the not depressed group was 1.34 (95% CI 1.04 to 1.73) in cohort 1 (early-onset depression) and 1.79 (95% CI 1.38 to 2.35) in cohort 2 (late-onset depression). Although depressed individuals were at significantly higher risk for mortality, the possibly depressed (whether early- or late-onset) were not different than the nondepressed. Age, sex and previous AMI were significant predictors, but SES was not. Most of the comorbidities were found to be significant predictors of mortality. The interactions between age and depression, and sex and depression were tested and were not significant. No other interactions were tested. Table 3 shows the Cox regression analysis results for cohort 1.

DISCUSSION

There were several new findings in the present study. We found that early-onset incident depression (occurring within six months post-AMI) is a strong predictor of short- and long-term survival post-AMI. Long-term survival of early-onset incident depression has rarely been studied because the follow-up periods in the relevant studies were short and most researchers

TABLE 3
Cox regression analysis for cohort 1

Variable	B	SE	Wald	Sig	Exp (B)	95.0% CI for Exp (B)	
						Lower	Upper
Female sex	-0.210	0.051	17.205	0.000	0.811	0.734	0.895
Unknown sex	-0.919	0.319	8.300	0.004	0.399	0.214	0.746
Age	0.077	0.004	395.822	0.000	1.080	1.072	1.089
SES quintile 2	-0.042	0.072	0.347	0.556	0.959	0.833	1.103
SES quintile 3	-0.107	0.075	2.028	0.154	0.899	0.775	1.041
SES quintile 4	-0.045	0.075	0.368	0.544	0.956	0.825	1.106
SES quintile 5	-0.001	0.081	0.000	0.991	0.999	0.853	1.170
SES quintile unknown	0.003	0.095	0.001	0.978	1.003	0.832	1.208
Previous acute myocardial infarction	0.385	0.099	15.077	0.000	1.469	1.210	1.784
Heart operation	-0.503	0.132	14.565	0.000	0.605	0.467	0.783
Other heart operation	-0.027	0.119	0.053	0.818	0.973	0.771	1.228
Diabetes	0.404	0.056	51.771	0.000	1.497	1.341	1.671
Heart failure	0.645	0.051	162.085	0.000	1.906	1.726	2.105
Cancer	0.430	0.082	27.305	0.000	1.537	1.308	1.806
Pulmonary edema	0.381	0.101	14.158	0.000	1.463	1.200	1.784
Acute renal failure	0.079	0.082	0.945	0.331	1.083	0.923	1.270
Cardiac dysrhythmia	0.212	0.049	18.488	0.000	1.236	1.122	1.362
Chronic renal failure	0.589	0.099	35.008	0.000	1.801	1.482	2.189
Shock	0.347	0.171	4.117	0.042	1.415	1.012	1.979
Cerebrovascular disease	0.543	0.072	57.240	0.000	1.721	1.495	1.981
Possibly depressed	0.155	0.083	3.526	0.060	1.168	0.993	1.374
Depressed	0.295	0.130	5.138	0.023	1.343	1.041	1.733

B Beta; Exp (B) Hazard ratio; SES Socioeconomic status; Sig Significance level; Wald Wald statistic

measured prevalent depression rather than incident depression. We also found that late-onset depression (depression occurring after the first six months post-AMI and up to five years post-AMI) had an impact on long-term survival. The impact of late-onset depression, up to five years post-AMI, has not been studied previously, making this a new and important finding.

The group that was categorized as 'possibly depressed' was not found to be different than the 'not depressed' group with regard to survival. It was likely that these individuals did not have major depression, but rather transient depressive states. Such a null association between subsyndromal depression and death has been found by other investigators (32).

An advantage of the present study was that we controlled for a larger spectrum of comorbid diseases and prior AMI, rather than AMI severity as controlled in previous studies (3,4). This may be a more appropriate method to control for overall severity of illness when investigating long-term mortality (33).

Another main advantage of the present study was that it used a population-based framework. No sampling was used and, thus, it was much easier to generalize the results to the older adult population. However, it would be interesting to determine whether similar results would be found in younger individuals.

A limitation of the data available for the present study was that it only captured deaths that occurred in BC or deaths that occurred in hospitals elsewhere in Canada. However, because only 32 individuals died in a hospital outside of BC, we are fairly confident that the number of individuals who may have died outside of Canada, or outside of BC and not in a hospital, was very small.

Another limitation of the study was that some individuals may have been erroneously categorized as not depressed

because their incident depression post-AMI was not recognized by their physician. This potential misclassification would have led the results closer to the null hypothesis; thus, any results found in the present study are valid and likely, if anything, to underestimate the relationship between early- and late-onset depression and survival in this population.

SUMMARY

The present study has demonstrated that early- and late-onset incident depression has a significant impact on short- and long-term survival. It also showed that administrative data are a useful data source for investigations of this sort, and are thus likely to be of value in assessing factors affecting long-term mortality in many other clinical conditions.

FINANCIAL SUPPORT: Dr Gilat L Grunau acknowledges a Western Regional Training Centre studentship funded by the Canadian Health Services Research Foundation, Alberta Heritage Foundation for Medical Research, Canadian Institutes of Health Research and the Canadian Institute of Health Services and Policy Research for financial support. Dr Pamela Ratner is supported by the Canadian Institutes of Health Research.

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