Pre-existent depression in the 2 weeks before an acute coronary syndrome can be associated with delayed presentation of the heart attack

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Received 19 September 2007 and in revised form 11 December 2007

Summary

Background: Depression is common among patients with acute coronary syndrome (ACS).

Aim: To examine how depression may alter outcome of ACS.

Design: Observational study on how ongoing depression influences the time delay to seeking help and its effects on subsequent treatment compliance after discharge.

Methods: Depression was measured by Beck Depression Inventory (BDI) 2 weeks prior to presentation on consecutive patients with ACS.

Results: Of the 276 patients, 81 had BDI ≥10 and 195 had BDI score <10. The time from onset of the predominant symptom to seeking help tended to be longer in those with BDI ≥10 than in those with BDI <10 [180 (IQR 37.5–1042.5) min vs. 120 (IQR 30–735) min, P=0.099]. Results were similar for the 68 with ST elevation myocardial infarction (MI) [238 (IQR 49–709) min vs. 60 (IQR 20–352) min, P=0.071]. Each point increase of BDI predicted an ~4.2% [95% confidence interval (CI) 0.4–8.0%] increase in the time duration, P=0.029. On multivariable analysis, the effect of BDI persisted (6.0% increase in duration per each point increase in BDI, 95% CI 2.4–9.7%, P=0.001). Among the 68 patients who had ST elevation MI, results were similar with an 8.0% (95%CI 1.7–14.7%, P=0.013) increase in time duration for each unit increase in BDI. Results were also similar when BDI was evaluated as a dichotomous variable. Small differences were observed for subsequent treatment compliance.

Conclusion: Ongoing depression delays the presentation of ACS.

Introduction

Depression is estimated to be present in 1 of 5 outpatients with coronary artery disease,¹,² and perhaps higher among the in-patients (up to 27%).³ Three recent trials tested the effects of antidepressants or cognitive behavioural therapy among depressed patients with coronary disease.⁴–⁶ A rationale for the trials is that while associations between depression and adverse cardiovascular outcomes are strong from observational studies⁷–¹¹ and the detrimental cardiac effects of depression are biologically plausible from neuro-endocrine and other mechanisms,¹ an improved cardiovascular outcome with anti-depressive therapy will support causality. However, results were neutral in this regard.⁴–⁶,¹²

The timing of depression has received recent attention. Incident depressive episodes (i.e. episodes...
of depression clearly related to the coronary event) but not a history of depression prior to the event were found to confer an adverse cardiovascular prognosis. In the interventional trials, the response rates to therapies with SSRIs were actually higher in those with pre-existent depression in both the Sertraline antidepressant heart attack randomised trial (SADHART) and the Canadian cardiac randomised evaluation of antidepressant and psychotherapy efficacy (CREATE) studies; while little evidence of benefit was seen in those with a first depression related to the coronary event.

Amid this perplexing data, there was little information on how depression may affect the timing of presentation of heart attacks, the best known modifiable variable that potentially alters outcome. If ongoing depression delays the presentation of heart attacks, it can be disastrous. The current study evaluated this and whether there was also an association between depression and lowered compliance with therapies after hospital discharge, another known adverse prognostic factor.

**Methods**

All patients admitted to the Cardiology unit of Dunedin hospital in the period of January to December 2005 were prospectively screened. Patients with a diagnosis of acute coronary syndrome (ACS) were invited to participate in the study once they were clinically stable. The protocol was approved by the Otago Ethics Committee (OTA/04/10/080). Patients who agreed to participate signed an informed consent. Participants were asked to complete a Beck Depression Inventory (BDI) and to be interviewed by a single researcher (E.W.T.).

**Depression assessment**

It was specifically explained to the participant both verbally by the researcher (E.W.T.) and written on the questionnaire that he/she had to recollect his/her state of mind in the 2 weeks prior to presenting with the current episode of chest pain when completing the BDI. On the first page before the BDI questionnaire, two screening questions were asked and the participant had to circle either yes or no.

I. Have you been consistently depressed or down, most of the day, nearly every day, for the 2 weeks before the symptom onset, prior to the current admission?

II. In the 2 weeks prior to symptom onset, have you been less interested in most things or less able to enjoy things you used to enjoy most of the time?

Participants were also asked to write down their education level as primary, secondary or tertiary level on the first page with the screening questions. The participant completed the questionnaire (including the BDI) alone in a quiet place after the researcher left.

**Clinical information collected in the interview**

I. History of coronary artery disease, myocardial infarction (MI), hospitalisations and cardiac interventions

II. History of depression and anti-depressive therapy

III. History of diabetes, smoking, hypertension, stroke/transient ischaemic attack, chronic obstructive pulmonary disease and mobility problems

IV. Time of symptom onset

V. Predominant symptom (chest pain, shortness of breath, dizziness, sweatiness, weakness, tiredness, arm pain, epigastric pain, neck pain)

VI. Severity of the predominant symptom on a 1 (mild)–10 (severe) scale

VII. Time from onset of the predominant symptom to seeking help

VIII. The person who sought help (patient, partner/spouse, family/fatmate, friend)

IX. From whom help is being sought (ambulance, general practitioner, after-hour general practitioner, hospital emergency department)

X. Time from symptom onset to the time when medical help became available (ambulance, general practitioner or hospital emergency department)

XI. Time from symptom onset to hospitalisation

XII. People living with the participant (none, partner/spouse, flatmate/family, friend)

Age, gender, evidence for heart failure when first assessed in the hospital, and investigations results including stress tests or coronary angiography were collected from the hospital record. The diagnosis was categorised as ST elevation MI, non-ST elevation MI, unstable angina with resting ST or T changes and unstable angina without resting ST or T changes.

**Assessment for treatment compliance**

Participants who were also undergoing a cardiac rehabilitation programme were invited to have a follow-up telephone interview for compliance with therapy. This was performed by a separate researcher (L.B.) at around 6 months after discharge. L.B. was blinded to both the patient’s self reported BDI during hospital admission and their time to presentation. Compliance to medications prescribed (including aspirin, beta-blockers, ACE-inhibitors or Angiotensin II antagonists, statins) and to life-style modifications (smoking cessation, low fat diet, regular exercise) were assessed using a 1–6 analogue scale to give a score for compliance: 1 – none
of the time, 2 – a little of the time, 3 – some of the time, 4 – a good bit of the time, 5 – most of the time and 6 – all of the time.

After the telephone interview, participants were invited to do a second BDI questionnaire reflecting their state of mind in the preceding 2 weeks and return it by mail.

Statistics

Of the three time intervals collected, the time from onset of the predominant symptom to seeking help was the primary endpoint variable for analysis. Log transformation of time duration measurements was used where appropriate because of their skewed distribution. BDI was analysed both as a continuous variable and as a dichotomous variable using a cut-off of $\geq 10$, a commonly adopted cut-point in studies on patients with ACS because of its association with higher mortality risks.\(^{19,20}\) Data for time durations are presented as median and interquartile range [IQR].

Potential predictor variables (BDI, sex, age, education level, type of ACS, history of heart disease, prior MI, prior cardiac intervention, previous angioplasty, previous CABG, history of anti-depressant use, current use of anti-depressants, smoking status, severity of the predominant symptom, heart failure at presentation, who the patient lived with, who sought help and from whom help was sought) were screened by entering them into a univariable linear regression on the log of the delay time from onset of the predominant symptom to seeking help. Variables significant at $P<0.1$ were then entered in a multivariable linear regression and the least significant variable removed until only significant ones remained.

Based on our previous studies on patients from the same geographic region,\(^{21–22}\) we assumed that the delay from symptom onset to seeking help would have a median of 180 mins with an IQR of 90–280 min. With 300 patients and assuming 25% had depression, there would be 80% power to detect a 100 min difference in delay for seeking help between those depressed and those not depressed with $\alpha = 0.05$.

Results

Of 311 patients with ACS who were invited to participate, 276 agreed to the study and were interviewed at 3.0 (IQR 1.9–4.9) days after initial hospitalisation. Among them, 68 had ST elevation MI, 107 had non-ST elevation MI, 101 had unstable angina including 36 with and 65 without resting ECG changes. The time from onset of the predominant symptom to seeking help (i.e. the primary variable for analysis) correlated well both with the time duration from symptom onset to the time when medical help became available ($r=0.85$) and with the time from symptom onset to hospitalisation ($r=0.85$).

Of the 276 patients, the median BDI score in the 2 weeks prior to seeking help was 7 (IQR 4–10) and mean (±standard deviation) BDI score was $8.1 \pm 6.9$. For the screening questions for depression, 29 answered yes to question one and 94 answered yes to question two. The BDI score was higher for those answering positively to the screening questions: $17.1 \pm 10.9$ vs. $7.0 \pm 5.4$, $P<0.001$ for question 1 and $12.7 \pm 8.1$ vs. $5.7 \pm 4.7$, $P<0.001$ for question 2, with no interactions observed between the two screening questions in predicting BDI.

Table 1 compared the baseline characteristics of the 195 (70.7%) who had BDI <10 and the 81 (30.3%) who had BDI $\geq 10$. The 81 patients with BDI $\geq 10$ more frequently had a history of depression (39.5 vs. 8.7%, $P<0.001$), used anti-depressants both in the past (33.3 vs. 5.6%, $P<0.001$) and prior to presentation (12.4 vs. 0.5%, $P<0.001$) and had history of past medical illnesses.

The time from onset of the predominant symptom to seeking help had a skewed distribution and tended to be longer in those with BDI $\geq 10$ (180 (IQR 37.5–1042.5) min vs. 120 (IQR 30–735) min, $P=0.099$). This was also true in the 68 patients with ST elevation MI (238 (IQR 49–709) min for the 12 with a BDI of $\geq 10$ vs. 60 (IQR 20–352) min for the 56 with a BDI of <10; $P=0.071$).

Of those who participated in the telephone follow-up study, 149 patients returned the second questionnaire. The BDI score in the first test was similar to the second test (8.2 $\pm$ 7.1 vs. 7.6 $\pm$ 5.9 $P=0.266$) and the two BDI scores had good correlation ($r=0.55$).

Relationship between BDI evaluated as a continuous variable and the time duration from onset of the predominant symptom to seeking help

After log transformation, the time from onset of the predominant symptom to seeking help was having a more normal distribution for linear regression analyses. Table 2 shows the results. After applying anti-log function, each point increase of BDI predicted an $\sim 4.2\%$ (95% CI 0.4–8.0%) increase of the time duration, $P=0.029$. Figure 1 showed this relationship.

On multivariable analysis, the effect of BDI, after applying anti-log function, was slightly larger
(6.0% increase in duration per each point increase in BDI, 95% CI 2.4–9.7%, $P=0.001$). Other independent predictors were severity of the symptoms and from whom help is being sought (Table 2). None of the other parameters in Table 1 including age, gender, history of depression or taking anti-depressants and history of medical illnesses were predictors of time from symptom onset to seeking help.

The relationship between BDI and the log transformed time duration from symptom onset to seeking help among the 68 patients who had ST elevation MI was shown in Figure 2 and Table 2. Results were similar with an 8.0% (95%CI 1.7–14.7%, $P=0.013$) increase in time duration for each unit increase in BDI.

**Relationship between BDI evaluated as a dichotomous variable and the time duration from onset of the predominant symptom to seeking help**

As in the previous analysis, the time from onset of the predominant symptom to seeking help was
log transformed in the regression analysis (Table 3), with anti-log function applied at the final stage to discern its effect. Depressed patients (BDI $\geq 10$) had a 62.8% (95% CI 7.0–185%) longer time duration from onset of the predominant symptom to seeking help compared with non-depressed patients (BDI $< 10$), $P = 0.09$. After adjustment for the other predictors this became 96.5% longer (95%CI 16.5–231%, $P = 0.012$). The other multivariable predictors were severity of the symptoms and from whom help was being sought (Table 3). None of the other parameters in Table 1 including age, gender, history of depression or taking anti-depressants and history of medical illnesses were predictors.

Among the 68 patients who had ST elevation MI, the results were similar but the CI were wider, and seeking help from the GP was the only other predictor that remained statistically significant.

**Relationship between BDI and time duration from onset of predominant symptom to having medical help**

Results were similar to data presented above on the primary endpoint of the time duration between the onset of the predominant symptom and seeking help. In the 276 patients, BDI ($P = 0.016$), symptoms severity ($P = 0.010$) and seeking help from GP ($P < 0.001$) continued to be the significant multivariable predictors.

**Treatment compliance**

Of the patients who had telephone follow-up, useful data on compliance were available from 240. Compared with the 168 patients with initial BDI $< 10$, the 72 patients with initial BDI $\geq 10$ had lower compliance with taking aspirin and with performing regular exercise. There was no difference in compliance with other medications or other aspects of life style modification (Table 4).
Discussion

The current study showed that depression in the 2 weeks prior to presentation of ACS delayed the heart attack presentation, regardless of whether BDI was assessed as a continuous or a dichotomous variable. Importantly, among those diagnosed with an ongoing ST elevation acute MI this relationship was also observed. Delay in the presentation or treatment of an ST elevation MI is one of the best-known factors for poor outcomes in the current reperfusion era.16

Some7–11 but not all23 observational studies showed associations between depression and adverse cardiovascular outcomes. In the INTERHEART study including 11 119 cases of acute MI and 13 648 controls, psychological risk factors including depression, as assessed in the 12 months prior to the event, were more common among the cases and actually explained 32.5% of the population attributable risk for MI.24 However, a recent study examining the relationship between psychosocial factors (including depression) and sub-clinical coronary atherosclerosis as measured by CT scanning for coronary calcium in 6789 subjects found no associations at all.25 A possible explanation is that ongoing depression and its associated behavioural changes could trigger or alter the course of acute MI in the short term, while the progression of sub-clinical atherosclerosis takes decades.

The current study addressed possible direct mechanistic links between depression and adverse cardiovascular outcomes. More depression as measured by higher BDI in the 2 weeks prior to the presentation was independently associated with longer time from symptom onset to seeking help, after controlling for potential confounders. While symptom severity was an independent predictor in the whole cohort, with more symptomatic patients presenting earlier, this was not the case when only patients with ST elevation MI were analysed. However, the effect of depression in delaying presentation was similar in this important subgroup. Only few studies have investigated the relationship between psychological factors and delay in seeking help. A study on 103 patients with acute MI admitted to a Detroit metropolitan hospital found that the only factor predictive of a delayed presentation was the lack of somatic and emotional awareness. Patients who were more capable of identifying inner experiences of emotions and/or body sensations sought treatment significantly earlier than patients with low emotional or somatic awareness.26 In another study of 433 patients post-MI,27 five reasons were found to explain a delay in seeking treatment (i) symptoms being considered non-cardiac in origin, (ii) mild symptoms, (iii) gastrointestinal distress, (iv) absence of sweating and (v) a self report of being depressed.

The time from symptom onset to seeking help spanned a very broad range (Figure 1) even among those with ST elevation MI (Figure 2), perhaps reflecting that seeking help is one kind of human behaviour that is influenced by many factors. Some patients might have genuine late presentations of their ST elevation MI, others might actually experience prodromal angina lasting up to days prior to their presentation.28 While the system of health care, geographic location, culture and public health education are all relevant factors potentially altering the behaviour in seeking help, our important finding is the relationship between this time delay to seeking help and ongoing depression as measured by BDI.

<table>
<thead>
<tr>
<th>Compliance score with medications</th>
<th>BDI &lt;10 (n = 168)</th>
<th>BDI ≥10 (n = 72)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>aspirin</td>
<td>5.78 ± 1.01</td>
<td>5.48 ± 1.41</td>
<td>0.015</td>
</tr>
<tr>
<td>beta-blockers</td>
<td>5.10 ± 1.91</td>
<td>5.19 ± 1.81</td>
<td>0.925</td>
</tr>
<tr>
<td>ACE-inhibitors/A-II antagonist</td>
<td>4.80 ± 2.13</td>
<td>4.76 ± 2.12</td>
<td>0.608</td>
</tr>
<tr>
<td>statins</td>
<td>5.48 ± 1.50</td>
<td>5.38 ± 1.57</td>
<td>0.533</td>
</tr>
<tr>
<td>with smoking cessation(only</td>
<td>4.89 ± 1.68</td>
<td>3.8 ± 2.04</td>
<td>0.180</td>
</tr>
<tr>
<td>for smokers at the time of</td>
<td></td>
<td></td>
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<td>presentation, n = 45)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>with low fat diet</td>
<td>4.82 ± 1.06</td>
<td>4.82 ± 0.94</td>
<td>0.742</td>
</tr>
<tr>
<td>with regular exercise</td>
<td>4.58 ± 1.38</td>
<td>4.15 ± 1.51</td>
<td>0.037</td>
</tr>
</tbody>
</table>

Compliance was assessed using a 1–6 analogue scale to give a score for compliance: 1-none of the time, 2-a little of the time, 3-some of the time, 4-a good bit of the time, 5-most of the time and 6-all of the time. A-II antagonist: angiotensin II antagonists.
Seeking help from general practitioners is another consistent predictor for a longer delay. Patients may choose to seek help from their general practitioners, rather than calling the ambulance, when they do not perceive their symptoms as serious. Alternatively, having an appointment to see their family doctors may have given them a false reassurance.

Previous studies have demonstrated relationship between depression after ACS and treatment compliance.\textsuperscript{29–31} The current study adds by investigating persons who had depression (BDI ≥ 10) in the 2 weeks prior to presentation, and found a small difference between those who had BDI < 10 and BDI ≥ 10. However, many factors might have contributed to compliance, including the rehabilitation programme itself.

Limitations

Participants were interviewed after the ACS had stabilised and they had to recollect their state of mind in the 2 weeks prior to presentation of ACS in completing the BDI questionnaire. A prospective study with fortnightly measured BDI questionnaires in a cohort at risk for heart attacks will circumvent the limitation of assessing depression retrospectively, but this approach faces practical difficulties given the relatively low occurrence rate of heart attacks. However, the current findings should set the stage for future large-scale prospective studies on this important question.

Conclusion

There is an association between ongoing depression and delayed presentations of heart attacks. The result provides one credible mechanistic link between depression and adverse outcomes among patients at risk for heart attacks.

Acknowledgement

E.W.T. was a senior research fellow supported by The Cardiac Society of Australia and New Zealand/MSD Fellowship in the year 2005.

Conflict of interest: None declared.

References


Figure 2. Plot of the time to seeking help (log scale) vs. the BDI score in the 2 weeks prior to presentation in the 68 patients with ST elevation myocardial infarction.


