Epidemiology and Prevention

Risk of Acute Myocardial Infarction After the Death of a Significant Person in One’s Life

The Determinants of Myocardial Infarction Onset Study

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Background—Acute psychological stress is associated with an abrupt increase in the risk of cardiovascular events. Intense grief in the days after the death of a significant person may trigger the onset of acute myocardial infarction (MI), but this relationship has not been systematically studied.

Methods and Results—We conducted a case-crossover analysis of 1985 participants from the multicenter Determinants of Myocardial Infarction Onset Study interviewed during index hospitalization for an acute MI between 1989 and 1994. We compared the observed number of deaths in the days preceding MI symptom onset with its expected frequency based on each patient’s control information, defined as the occurrence of deaths in the period from 1 to 6 months before infarction. Among the 1985 subjects, 270 (13.6%) experienced the loss of a significant person in the prior 6 months, including 19 within 1 day of their MI. The incidence rate of acute MI onset was elevated 21.1-fold (95% confidence interval, 13.1–34.1) within 24 hours of the death of a significant person and declined steadily on each subsequent day. The absolute risk of MI within 1 week of the death of a significant person is 1 excess MI per 1394 exposed individuals at low (5%) 10-year MI risk and 1 per 320 among individuals at high (20%) 10-year risk.

Conclusions—Grief over the death of a significant person was associated with an acutely increased risk of MI in the subsequent days. The impact may be greatest among individuals at high cardiovascular risk.

Key Words: bereavement ■ crossover studies ■ epidemiology ■ myocardial infarction

Grief over the death of a significant person is associated with symptoms of depression, anxiety, and anger. Although the death of a significant person in one’s life is rare at any given moment, bereavement is a part of almost everyone’s life. Among people ≥65 years of age, ≈45% of women and 15% of men become widowed.1 Most people adjust to the loss of a significant person, but there is a heightened risk of mortality in the early weeks and months after loss,2,3 with cardiovascular disease accounting for 20% to 53% of the excess deaths during spousal bereavement.4,5 For instance, in a prospective study of 4395 married couples in Scotland, Hart and colleagues7 found that bereaved individuals had higher rates of mortality than nonbereaved individuals. Even after adjustment for cardiovascular risk factors, death of a spouse is associated with an increased rate of mortality from cardiovascular disease (incidence rate ratio [IRR]=1.18; 95% confidence interval [CI]=1.08–1.29) and coronary heart disease (IRR=1.22; 95% CI=1.08–1.37).

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Despite vast literature on the association between spousal bereavement and increased risk of mortality in the subsequent weeks and months, whether bereavement for a significant person in one’s life is associated with an acutely increased risk of cardiovascular events has not been systematically studied. Therefore, we evaluated whether there is an increased risk of myocardial infarction (MI) in the days after the death of a significant person in one’s life among participants enrolled in the Determinants of Myocardial Infarction Onset (MIOS) Study.

Methods

Study Design

The MIOS Study used a case-crossover design, a variation of a case-control design that is appropriate when a transient exposure (death of a significant person in the patient’s life) is associated with an acute change in the risk of an acute outcome (nonfatal MI).6,7 We
compared a subject’s report of the loss of a significant person in the days before the onset of the MI (the case period) with the same subject’s report of bereavement for a significant person in his or her life in the prior 6 months (the control period). Because control information for each subject is based on his or her own past exposure experience, self-matching eliminates confounding by risk factors that are constant within individuals over the sampling period but often differ between study subjects.

Study Population
Between 1989 and 1994, 1985 people (1378 men and 607 women; mean age, 61.6 years) were interviewed at 22 community hospitals and 23 tertiary care centers a median of 4 days after admission for MI. The cohort was followed up prospectively for all-cause mortality through December 31, 2007. This report is based on the data collected at the time of enrollment. Interviewers identified eligible cases by reviewing coronary care unit admission logs and patient charts. For inclusion in the study, patients were required to meet all of the following criteria: at least 1 creatine kinase level above the upper limit of normal for the clinical laboratory performing the test, positive MB isoenzymes, an identifiable onset of pain or other symptoms typical of infarction, and the ability to complete a structured interview. The protocol was approved by the institutional review board at each participating center, and informed consent was obtained from each patient.

As previously described, detailed chart reviews and patient interviews were conducted by trained research personnel. Data were collected on standard demographic variables and risk factors for coronary artery disease. The interview identified the time, place, and quality of MI pain and other symptoms, as well as the timing and estimated usual frequency of exposure to potential triggers of MI onset during the prior year. In addition, patients were asked, “During the past year, did you hear news of the death of a friend, relative, or someone who was very significant in your life?” If patients answered affirmatively, they were asked to identify the time of occurrence of the loss of a significant person that would result in 1 day and 1

Statistical Analysis
Each subject in a case–crossover study forms his or her own stratum and thus is his or her own control. We evaluated the incidence rate of MI within 1, 2 to 3, 3 to 7, and 7 to 30 days (case periods) after the death of a significant person. A priori, we selected a control period of 1 to 6 months (150 days, ie, 31–180 days before infarction) because it is recent enough that patients are likely to correctly report the loss of a significant person in one’s life and health characteristics remain fairly stable over a span of only 6 months. The number of exposed control days was equal to the number of reported deaths of a significant person in one’s life and health characteristics remain fairly stable over a span of only 6 months. The number of exposed control days was equal to the number of reported deaths of a significant person in one’s life during that time period, and the remaining days were considered nonexposed. We compared the observed number of deaths that occurred during each of these periods with the number expected on the basis of each patient’s control information using the Mantel-Haenszel estimator of the IRR. In this analysis, the proportion of exposed days in the control period represents the expected frequency of exposure in the case period.

For ease of interpretation, we estimated the absolute risk of MI associated with the death of a significant person within 1 day and 1 week for populations with baseline 10-year MI risk of 5%, 10%, and 20% based on the Framingham Risk Score. To estimate the absolute risk of MI in the days after the death of a significant person, we calculated the baseline risk of MI per day for individuals with 10-year risk of 5%, 10%, and 20% using the following formula:

\[
\text{Risk}_{x} = 1 - \exp \left( \left( \frac{-\ln(1 - \text{Risk}\text{baseline})}{0.25} \right) \times x \right)
\]

where Risk\text{baseline} is the baseline risk of MI for x days (in this case, 1 or 7 days) for an individual with a 10-year (3652.5-day) risk of Risk\text{baseline} (5%, 10%, or 20%). We calculated the risk among the exposed as the baseline risk multiplied by the IRR. As an estimate of absolute risk, we computed the risk difference by subtracting the baseline risk from the risk among the exposed; the reciprocal of this value represents the number needed to harm, ie, the number of individuals who recently experienced the loss of a significant person that would result in 1 excess case of MI.

We stratified by sex, age (<65 versus ≥65 years), smoking status (former versus current), frequency of habitual physical activity (≥3 versus <3 times per week), and history of coronary artery disease (prior MI or angina versus neither) and compared the IRRs by means of a test for homogeneity. We conducted several sensitivity analyses; in the first sensitivity analysis, we estimated the association between MI onset and death of a significant person in the past week. We also conducted an analysis using days 3 to 7 as the control period, an analysis excluding subjects reporting a history of MI, and an analysis restricted to subjects reporting that the recent death was moderately or extremely meaningful. All reported P values are 2 sided.

Results
The characteristics of the population interviewed are summarized in Table 1. Among the 1985 MIOS participants, 270
reported the death of at least 1 significant person in the 6 months preceding MI onset. Of the 270 subjects reporting a death in the prior 6 months, 193 provided details about the decedent: 12 lost a parent, 2 lost a child, 20 lost a sibling, 6 lost a spouse, and 153 lost a more distant relative or friend. Nineteen patients reported the death of a significant person within 24 hours of the onset of their MI symptoms. For the days leading up to the infarction, 7 patients reported a death 24 to 48 hours before their symptoms, 5 patients reported a death 48 to 72 hours before their symptoms, and 21 patients reported deaths from 4 to 7 days before the onset of MI. Among the 19 patients reporting the death a significant person within 24 hours of the onset of their infarction symptoms, 12 (63%) found it moderately or extremely meaningful.

The rate of acute MI onset was elevated 21.1-fold (95% CI=13.1–34.1) within 24 hours of learning of the death of a significant person. The Figure shows that the IRR declined each day after the death but remained significantly elevated for at least 1 month after the death of a significant person.

To put this finding into context, we estimated the absolute risk on the day after the death of a significant person among individuals at different levels of 10-year MI risk. Among individuals at relatively low risk (5%), there would be 1 excess MI per 3543 exposed individuals; for intermediate risk (10%), 1 excess MI per 1725 exposed individuals; and for high risk (20%), 1 excess MI per 815 exposed individuals. Furthermore, our data suggest that within 1 week of the death of a significant person, there would be 1 excess MI per 1394, 678, and 320 exposed individuals at 5%, 10%, and 20% 10-year MI risk, respectively.

There were no statistically significant differences defined by age, sex, frequency of physical activity, or history of coronary artery disease. The estimated IRR was greater for men than for women, for those <65 years of age than for people ≥65 years of age, for those reporting engaging in physical activity ≥3 times per week than for those reporting less frequent physical activity, and for those with no history of coronary artery disease (Table 2).

In a sensitivity analysis, the IRR remained elevated when the hazard period was defined as the entire week before MI onset (IRR=8.3; 95% CI=6.0–11.4), when we defined the

![Figure. Time of onset of acute myocardial infarction (MI) after the loss of a significant person in one's life. Each of the hazard periods before MI onset was assessed as an independent hazard period, and each window was compared with exposure during the control period of 1 to 6 months. Error bars indicate the 95% confidence limits; dashed line indicates baseline risk.](http://circ.ahajournals.org/)

Table 2. Incidence Rate Ratio for Myocardial Infarction Within 1 Day of the Death of a Significant Person in One’s Life Among 1985 Patients Hospitalized for Myocardial Infarction According to Patient Characteristics: Determinants of Myocardial Infarction Onset Study, 1989–1994

<table>
<thead>
<tr>
<th></th>
<th>Exposed in Past 1–6 mo, n</th>
<th>Exposed in Past Day, n</th>
<th>IRR</th>
<th>95% CI</th>
<th>P</th>
<th>P for Homogeneity†</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
<td>135</td>
<td>19</td>
<td>21.1</td>
<td>13.1–34.1</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>74</td>
<td>15</td>
<td>29.2</td>
<td>16.8–50.8</td>
<td>&lt;0.001</td>
<td></td>
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<tr>
<td>Female</td>
<td>56</td>
<td>4</td>
<td>10.3</td>
<td>3.8–28.5</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Age, y</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;65</td>
<td>72</td>
<td>13</td>
<td>27.1</td>
<td>15.0–48.9</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>≥65</td>
<td>63</td>
<td>6</td>
<td>14.3</td>
<td>6.2–33.0</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Smoking status</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Current</td>
<td>49</td>
<td>7</td>
<td>21.4</td>
<td>9.7–47.3</td>
<td>&lt;0.001</td>
<td></td>
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<tr>
<td>Former</td>
<td>53</td>
<td>8</td>
<td>22.6</td>
<td>10.8–47.6</td>
<td>&lt;0.001</td>
<td></td>
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<tr>
<td>Physical activity, times/wk</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>&lt;3</td>
<td>119</td>
<td>16</td>
<td>20.2</td>
<td>12.0–34.0</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>≥3</td>
<td>11</td>
<td>2</td>
<td>27.3</td>
<td>6.0–123.0</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>History of myocardial infarction</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>41</td>
<td>3</td>
<td>11.0</td>
<td>3.4–35.4</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>87</td>
<td>15</td>
<td>25.9</td>
<td>15.0–44.7</td>
<td>&lt;0.001</td>
<td></td>
</tr>
</tbody>
</table>

IRR indicates Mantel-Haenszel incidence rate ratio; CI, confidence interval.

*P for the stratum-specific IRR.

†P for the χ² test for homogeneity.
control period as days 3 to 7 (IRR = 3.6; 95% CI = 2.0–6.7), and when the analysis was restricted to patients with no history of MI (IRR = 25.9; 95% CI = 15.0–44.7). Compared with the overall estimate of 21.1, the IRR was higher among patients reporting that the recent death was moderately or extremely meaningful (IRR = 27.7; 95% CI = 15.0–51.3).

Discussion

In MIOS, the risk of MI onset was greatly elevated in the days after the death of a significant person. The IRR was greatest in the first 24 hours (IRR = 21.1; 95% CI = 13.1–34.1) and progressively declined over time to 5.8 (95% CI = 3.7–9.2) by the end of the first week. Although the death of a significant person is a rare event for an individual, the risk of MI within the first week may be substantial, ranging from 1 excess MI per 320 exposed individuals to 1 per 1394 for individuals at high and low baseline MI risk, respectively. These results require confirmation in prospective studies.

Almost all of the prior studies on cardiovascular risk associated with bereavement have focused on the death of a spouse, comparing bereaved with nonbereaved individuals.\(^2,3\) Initial studies ignored the fact that the elevated risk may be due to the emotional stress of grief, but it may also be due to the fact that couples may share similar lifestyle and risk factors. Therefore, people who lose a spouse may be the same people who are already at increased risk of cardiovascular disease or all-cause mortality. Subsequent studies (eg, the work by Hart et al\(^7\) and Elwert and Christakis\(^13\)) addressed this potential confounding by adjusting for cardiovascular risk factors in their statistical model. In our study, we used the case-crossover design, which compares each person with himself or herself. Thus, there is no variability in traditional cardiovascular risk factors within each stratum, so there is no confounding by these chronic risk factors.

Although there have been no prospective studies showing the acute impact of bereavement on MI risk, Fang and colleagues\(^14\) have used population-based registry data to examine whether cancer diagnosis is associated with an acutely increased risk of suicide and cardiovascular death. Future research using registry data to examine the association between bereavement and cardiovascular risk would provide an opportunity to examine this question using data on the timing of death and MI that are collected prospectively and not vulnerable to miscategorization inherent in self-report.

In our study, 6 participants reported the loss of a spouse within 6 months of MI onset, but none were within the prior day. Although our study examines the MI risk associated with the loss of any significant person, our findings are consistent with prior studies showing that men are more vulnerable to the health consequences from bereavement than women\(^1\) and that younger bereaved people are more vulnerable than older bereaved people.\(^2\)

Our study is the first to examine whether the death of a significant person triggers MI. Previous research has shown that related emotional stressors such as anger,\(^16,17\) anxiety,\(^16\) and depression\(^18\) may trigger cardiovascular events in the following hour(s).\(^9,20\) For instance, in our study population, 39 of the 1623 patients (2.4%) recruited by 1995 reported an episode of anger in the 2 hours before MI onset, resulting in a 2.3-fold (95% CI = 1.7–3.2) increased risk of MI; there was a 1.6-fold (95% CI = 1.1–2.2) elevated risk of MI in the 2 hours after episodes of marked anxiety. In a study of 295 patients interviewed immediately after an acute coronary event,\(^18\) 46 (18.2%) reported a time-limited episode of depression in the 2 hours before symptom onset. The odds of acute coronary syndrome were 4.33-fold (95% CI = 3.39–6.11) greater in the 2 hours after an acute episode of depression compared with other times.

A number of pathways may explain the link between emotional triggers and the onset of acute cardiac events.\(^21,22\)

Acute bereavement is associated with psychological, behavioral, and physiological sequelae.\(^20–22\) In particular, bereavement is associated with higher levels of negative affect, including symptoms of depression, anxiety, and anger.\(^20\)

Acute bereavement is also associated with reduced sleep time, reduced appetite, lower total cholesterol and low-density lipoprotein levels, and higher cortisol levels. These changes may contribute to the increased cardiovascular risk.\(^20\)

The emotional stress of bereavement stimulates heightened sympathetic activation. The hemodynamic changes that result such as increased vascular resistance may cause transient myocardial ischemia and/or disruption of a vulnerable coronary plaque, especially among susceptible patients. Furthermore, it may stimulate an inflammatory and prothrombotic response.\(^23\) These physiological changes may lead to occlusive coronary arterial thrombosis by increasing thrombogenicity and vasoconstriction.

Emotional and physical stress can lead to symptoms similar to those seen in acute MI, including chest pain, ST-segment elevation, and increased creatine kinase and troponin levels.\(^24,25\) This stress cardiomyopathy (also known as takotsubo cardiomyopathy or broken heart syndrome) is associated with severe but transient left ventricular dysfunction that is usually resolved within days or weeks. Because angiographic data are not available, we cannot rule out the possibility that some of the cases included in our sample had Takotsubo cardiomyopathy rather than an acute coronary syndrome.

It is possible that bereavement results in poor medication compliance, which thereby increases cardiovascular risk.\(^20\) However, in our study, the magnitude of the association between bereavement and MI was strongest in the day after the loss of a significant person, suggesting that our findings are not due to acute washout of a missed dose of a drug. Among the 19 patients reporting the death a significant person within 24 hours of the onset of their infarction symptoms, 1 patient missed a dose of an oral hypoglycemic agent on the day before symptom onset. Among the 52 patients reporting the death a significant person within 7 days of symptom onset, 1 patient missed a dose of a short-acting angiotensin-converting enzyme inhibitor 14 hours before symptoms of infarction. Importantly, no patients reported skipped doses of ß-blockers, which could have caused a rebound in hypertension and subsequent onset of infarction symptoms. Because behavioral changes represent factors occurring after the loss of a significant person, we do not account for these factors in our analysis; they mediate rather than confound the relationship of interest.
There are some limitations that warrant discussion. Only 19 people were exposed to the death of a significant person in the 24 hours before MI onset, so we did not have sufficient data to evaluate whether the association varies by the relationship between the deceased and the bereaved or by the reason for the significant person’s death. Future research is needed to examine whether these factors are associated with a higher risk. However, we found that the risk of MI after the death of a significant person was particularly high among those reporting that the loss was moderately or extremely meaningful. In a case-crossover study, each individual provides information about exposure during both the hazard and control periods. Patients may attempt to explain their cardiac event by emphasizing emotional stressors immediately before symptom onset and inadvertently underestimate exposure during the control period, which may lack the salience of the hours preceding symptom onset. This can result in an overestimation of IRR. To reduce recall bias, we restricted our analysis to include only deaths reported during the 6 months before MI onset. Furthermore, in a sensitivity analysis using days 3 to 7 as the control period, the association remained statistically significant. A second concern is that some people may have incorrectly reported the timing of the death of the significant person, resulting in misclassification of the time between the death and symptom onset. However, the death of a significant person is a major life event, so it is probable that the timing is correctly reported. Even if some patients reported the timing of the death incorrectly by a day or 2, the association remained elevated when the hazard period was defined as the entire week before MI onset. Because the case-crossover design uses subjects as their own controls, there can be no confounding by risk factors that are stable over time, but confounding by factors that change over time within individuals can occur if other transient risk factors occur during the case period. However, it is unlikely that patients experienced other rare potential triggers at the same time as the death of a significant person. It is possible that compared with other MI cases, patients who experienced the death of a significant person are more likely to survive and to participate in our study, resulting in an overestimate of the IRR and the frequency of MI associated with bereavement. Alternatively, patients experiencing bereavement may be less likely to survive, resulting in an underestimate of the IRR and the frequency with which this occurs. However, it seems unlikely that MI survival is different for cases triggered by different mechanisms.

Although it cannot be tested easily in a randomized clinical trial, it seems plausible that providing social support at the time of bereavement may help mitigate the heightened risk. Another approach is to consider the use of preventive agents to address hemodynamic and thrombosis-related changes. The data were collected before common use of statins. Future research could examine whether the risk is mitigated with aspirin and/or regular statin use. One author (G.H.T.) is currently conducting a randomized clinical trial to evaluate whether low-dose aspirin and/or β-blockers may prevent the hemodynamic and thrombotic changes associated with early bereavement.

Compared with other cardiovascular triggers such as physical activity or episodes of anger, bereavement is obviously rarer, so the absolute lifetime risk of a bereavement-induced MI may be extremely low. However, as our results indicate, the absolute risk in the week after this life event can be large and warrants attention by the clinical community.

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Disclosures

None.

References

Grief over the death of a significant person is associated with symptoms of depression, anxiety, and anger. Several studies have shown that spousal bereavement is associated with an increased risk of mortality in the subsequent weeks and months after the death, but whether bereavement for a significant person in one’s life is associated with an acutely increased risk of cardiovascular events has not been systematically studied. Therefore, we evaluated whether there is an increased risk of myocardial infarction in the days after the death of a significant person among participants enrolled in the Determinants of Myocardial Infarction Onset (MIOS) Study. Among the 1985 MIOS participants, 270 reported the death of a significant person in the 6 months preceding myocardial infarction onset, and 19 patients reported a death within 24 hours of symptom onset. The rate of myocardial infarction was elevated 21.1-fold within 24 hours of learning about the death of a significant person. In terms of absolute risk, our results suggest that within 1 week of the death of a significant person, there would be 1 excess myocardial infarction per 1394, 678, and 320 exposed individuals at 5%, 10%, and 20% 10-year myocardial infarction risk, respectively. Although experiencing the loss of a significant person in one’s life is a rare cardiovascular trigger, the absolute risk in the following week deserves attention. It seems plausible that providing social support and ensuring compliance with primary and secondary prevention measures may help mitigate the heightened cardiovascular risk among individuals who recently experienced the loss of a significant person.
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