High Self-Reported Levels of Pain 1 Year After a Myocardial Infarction Are Related to Long-Term All-Cause Mortality: A SWEDEHEART Study Including 18,376 Patients

Linda Vixner, PT, PhD; Kristina Hambraeus, MD, PhD; Björn Ång, PT, PhD; Lars Berglund, PhD

BACKGROUND: Pain increases the risk for cardiovascular diseases, including myocardial infarction (MI). However, the impact of pain on mortality after MI has not yet been investigated in large studies with long-term follow-up periods. Thus, we aimed to examine various levels of pain severity 1 year after an MI as a potential risk for all-cause mortality.

METHODS AND RESULTS: We collected data from 18,376 patients, aged <75 years, who had a registered MI event during the period from 2004 to 2013 and with measurements of potential cardiovascular risk indicators at hospital discharge from the Swedish quality register SWEDEHEART (Swedish Web System for Enhancement and Development of Evidence-Based Care in Heart Disease Evaluated According to Recommended Therapies). Self-reported levels of experienced pain according to EuroQol-5 dimension instrument were recorded in secondary prevention clinics 1 year after hospital discharge. We collected all-cause mortality data up to 8.5 years (median, 3.4 years) after the 1-year visit. The Cox proportional hazard regression was used to estimate hazard ratio (HR) and 95% CI. Moderate pain and extreme pain were reported by 38.2% and 4.5%, respectively, of included patients. There were 1067 deaths. Adjusted HR was 1.35 (95% CI, 1.18–1.55) and 2.06 (95% CI, 1.63–2.60) for moderate and extreme pain, respectively. Pain was a stronger mortality predictor than smoking.

CONCLUSIONS: Pain 1 year after MI is highly prevalent, and its effect on mortality 1 year after MI was found to be more pronounced than smoking. Clinicians managing patients after MI should recognize the need to consider experienced pain when making prognosis or treatment decisions.

Key Words: mortality ■ myocardial infarction ■ pain ■ smoking

Myocardial infarction (MI) is one of the leading causes of mortality globally. However, the case-fatality rates following MI are declining, giving an increasing prevalence of long-term survivors.1-3 There remains a substantial risk for recurrent MI as well as other manifestations of cardiovascular disease or death in MI survivors, also in the long-term perspective.3,4 Musculoskeletal conditions, including pain, are well-known leading sources of human suffering and disability and are the cause of enormous global health problems.5,6 It has been found that people experiencing musculoskeletal pain have an increased risk of cardiovascular disease7,8 and all-cause mortality.8-11 It has also been shown that cardiovascular risk increases with pain duration and widespreadness.12 People with chronic pain and cardiovascular diseases share many common risk factors, such as smoking and obesity,8 low levels of physical activity,13 poor diet,14 as well as...
CLINICAL PERSPECTIVE

What Is New?
- Self-reported pain 1 year after myocardial infarction is highly prevalent.
- The effect of pain on mortality is more pronounced than the effect of smoking.
- The effect of pain on mortality is highest among those experiencing extreme pain.

What Are the Clinical Implications?
- The findings add new knowledge for healthcare personnel involved in cardiac rehabilitation programs, as they demonstrate pain as an important factor to explore and consider for each individual after myocardial infarction.
- Pain should be assessed at follow-up after myocardial infarction and acknowledged as an important risk factor.
- Extreme pain experiences should be highlighted as a potential rehabilitation barrier and as an obstacle for engaging in important cardioprotective activities.

Nonstandard Abbreviations and Acronyms

<table>
<thead>
<tr>
<th>Acronym</th>
<th>Description</th>
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<tr>
<td>CCS</td>
<td>Canadian Cardiovascular Society</td>
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<td>CR</td>
<td>cardiac rehabilitation</td>
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<tr>
<td>SWEDHEART</td>
<td>Swedish Web System for Enhancement and Development of Evidence-Based Care in Heart Disease Evaluated According to Recommended Therapies</td>
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<tr>
<td>SWEDHEART-CR</td>
<td>SWEDHEART Subregister for Cardiac Rehabilitation</td>
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Data, analytical methods, and study materials will not be made available to other researchers by the authors for the purpose of reproducing the results or replicating the procedure. The authors are not authorized to share data from Swedish quality registers. This prospective cohort study included patients aged <75 years who had been diagnosed with their first MI event (International Classification of Diseases, Tenth Revision [ICD-10], code I.21) between December 28, 2004, and October 25, 2013, recorded in the Swedish quality register, SWEDHEART (Swedish Web System for Enhancement and Development of Evidence-Based Care in Heart Disease Evaluated According to Recommended Therapies). The SWEDHEART registry is a nationwide quality registry that records patient characteristics, treatments, and outcomes of consecutive patients with MI admitted to coronary care units in Sweden. Data are also collected from SWEDHEART-CR (SWEDHEART Subregister for Cardiac Rehabilitation [CR]) registry, which collects data at outpatient visits to CR nurse or physician at 2 and 12 months after discharge. The registry data cover comorbidities, biochemistry, blood pressure, anthropometric variables, medication, psychosocial and lifestyle variables, readmissions, patient-reported outcome measures, including health-related quality of life, attendance in CR-related programs, and physical

different socioeconomic factors. Other important risk factors are deterioration in mental health and sleep disturbances. In addition, other comorbidities that are commonly associated with chronic pain, such as depression and anxiety, may also affect the risk of cardiovascular disease in patients with chronic pain. In the past decade, there has been a paradigmatic shift in the field of pain and pain rehabilitation for how it is viewed. Previously, pain was regarded as merely a symptom of disease rather than a disease itself, and it has been argued that this has contributed to the neglect of the condition. This calls for research aiming to explore the consequences of chronic pain connected to other health states; for example, patients diagnosed with severe chronic pain are twice as likely to have died of cardiovascular or pulmonary disease 10 years after diagnosis than pain-free patients or patients with mild pain. However, there remains more to be discovered about the effects of nontraditional cardiovascular risk factors, such as various aspects of pain conditions and their long-term impact on morbidity and mortality, both before MI events and after.

Although there is an increasing prevalence of long-term survivors of MI, the estimated population growth and aging suggest that sustained and high morbidity rates and the socioeconomic burden of cardiovascular disease will continue to have a major impact in the coming decades. Surprisingly, the impact of pain on mortality after MI has not yet been examined in large studies, including long-term follow-up periods.

The aim of this study was, therefore, to assess experienced pain 1 year after an MI as a potential risk factor for long-term all-cause mortality and putative interactions between pain and age, sex, and reported level of chest pain. In addition, we aimed to compare the effect of pain 1 year after MI on mortality with the effect of the well-established risk factor smoking. Furthermore, we aimed to describe how pain categories were associated with known risk factors of mortality after an MI.
fitness variables. When compared with the National Patient Registry, 60% of patients in Sweden who experience an acute MI are captured by the SWEDEHEART registry. During the period that this study was conducted, 67,823 MI survivors were registered in the SWEDEHEART registry, 58,286 were still alive 1 year after MI, and we included 18,376 patients with complete data on our independent variables, as described below.

The study was approved by the Ethical Review Board in Uppsala (diary number Swedish Ethical Review Board 2014/152). No informed consent was required.

The primary outcome in this study was all-cause mortality data collected from the Swedish National Population Registry. Mortality dates were extracted with end date October 7, 2014. Median (range) follow-up time (ie, between date for 12-month visit and date of death or end of study) was 3.37 (0.04–8.54) years. The Swedish National Population Registry entails all deaths in Sweden during the study period.

Data on patient characteristics at hospital discharge were collected from the SWEDEHEART registry, including year of hospital discharge (2004–2013), age, sex, body mass index, diabetes, hypertension, hyperlipidemia, creatinine levels, previous percutaneous coronary intervention (PCI), PCI during hospital stay, previous MI, previous stroke, and previous congestive heart failure. Type of MI was determined on the basis of a clinical assessment, and patients were classified as having a non–ST-segment–elevation MI or an ST-segment–elevation MI. In addition, data on coronary artery bypass grafting during hospital stay were included. Data on diabetes, hypertension, hyperlipidemia, previous MI, and previous stroke are entered into the registry based on patients reported history and confirmed if possible by audit of medical records. There remains a risk of these metrics not being correctly reported. However, to certify the correctness of the data entered in the registry, regular monitoring of registry data is performed and has consistently confirmed >95% agreement with data from medical records.

Data on patient characteristics at 12 months after hospital discharge were collected from the SWEDEHEART registry. The questionnaire entails the EuroQol-5 dimension instrument, including 5 self-reported dimensions of health (1 of them pain). The pain dimension entails 3 statements: “I have no pain or discomfort,” “I have moderate pain or discomfort,” or “I have extreme pain or discomfort.” In addition, data on pain from the follow-up visit 2 months after MI were also used to follow pain over time.

Data on body mass index were based on measured weight and height, with the subject standing, to the nearest 0.1 kg and 1 cm, respectively. If it was not possible to perform measurements, self-reported data were registered if the patient was able to provide them. If not, data were registered as missing. Waist circumference was measured to the nearest centimeter with the patient standing, at the level midway between the lower rib margin and the iliac crest. In the SWEDEHEART-CR registry, chest pain is classified as no pain/Canadian Cardiovascular Society (CCS) class I/CCS class II/CCS class III/CCS class IV/nonischemic chest pain, according to the Canadian Cardiovascular Society Angina Grade CCS. Smoking is classified as never/previous (stopped smoking >1 month ago) or current smoker. Self-reported physical activity is registered in the SWEDEHEART-CR registry as self-reported number of sessions, lasting ≥30 minutes, and being of at least moderate intensity, during the past 7 days. We classified patients as “inactive” if they reported 0 to 1 session of physical activity per week, and we classified patients reporting ≥2 sessions per week as “active.”

Of the 58,286 patients who were still alive 1 year after MI, 17,323 had missing pain measurements at the 12-month visit, and an additional 18,074 patients had missing data for at least 1 of the other covariates at the 12-month visit. Furthermore, an additional 4513 patients had missing data for at least 1 of the covariates measured at hospital discharge. Thus, we included 18,376 patients with complete covariate data into this study.

**Statistical Analysis**

Continuous variables were described as means and SDs, and categorical variables were described as numbers and percentages. Comparisons of pain groups were made using the Kruskal-Wallis test for continuous variables and a χ² test for categorical variables.

In our analyses, the Cox proportional hazards regression model was used to examine how all-cause mortality was associated with pain 12 months after hospital stay. In a basic model, the association was adjusted for age and sex, and in the extended model, adjustments were made for the following: year of hospital stay, age, sex, smoking status (12 months after hospital stay), diabetes, hypertension, hyperlipidemia, creatinine level, previous PCI, PCI during hospital stay, previous MI, previous stroke, previous congestive heart failure, diagnosis at discharge (non–ST-segment–elevation MI or ST-segment–elevation MI), coronary artery bypass grafting, body mass index (12 months after hospital stay), waist circumference (12 months after hospital stay), chest pain (12 months after hospital stay), and level of physical activity (12 months after hospital stay).

Estimated models were presented with hazard ratios (HRs) with 95% CIs and P values for moderate and
extreme pain, where no pain was the reference category. Interactions between pain 12 months after hospital stay and age, sex, and chest pain 12 months after hospital stay were tested in Cox proportional hazards regression models including the above-mentioned covariates. In another model, chest pain was dichotomized into “no chest pain” and “any chest pain,” and its interaction with pain 12 months after hospital stay was tested as above. We examined the proportional hazards assumptions of the Cox models with plots of log[−log(survival)] versus log of survival time. To explore the putative effects of reverse causation, we conducted sensitivity analyses where patients with a shorter follow-up time than 2 years after the 12-month visit were excluded. In an additional sensitivity analysis, we examined if the analysis sample would indicate biased estimates. A Cox regression model with pain 12 months after hospital stay, age, and sex using all available pain data (n=40963) was estimated and compared with results from the same model in the analysis sample (n=18376).

In Kaplan-Meier curves, survival was displayed for no pain, moderate pain, and extreme pain. For comparison, Kaplan-Meier survival curves were displayed for smoking categories. Comparisons of Kaplan-Meier survival curves were made with the log-rank test.

We made a comparison of the predictive ability of all-cause mortality for pain 12 months after hospital stay and for smoking 12 months after hospital stay when each variable was used as a single predictor in a Cox proportional hazard model. The Harrell concordance-statistic (c-statistic) was used as a predictive measure, and the comparison was made with the percentile bootstrap method with a 95% CI for the difference between the 2 c-statistics.

All statistical tests and CIs were 2 sided. Results with P<0.05 were considered statistically significant without adjustments for multiplicity. The statistical analyses were performed with the statistical program package SAS version 9.4 (SAS Institute Inc, Cary, NC).

RESULTS

One year after MI, 58286 patients were still alive (86%), and we included 18376 patients with complete data on our dependent and independent outcome measures. Included and nonincluded patients were comparable for age (mean age, 62.0 and 61.9 years, respectively), sex (24.5% and 26.5% women, respectively), and year of MI event (mean year, 2009 in both groups) but differed for mortality (5.8% and 9.6%, respectively).

Subject characteristics for the 18376 included patients with MI are presented in Tables 1 and 2. Mean age was 62.0 years. A total of 75% were men. All the examined variables differed across pain categories.
12 months after hospital discharge (P<0.0001), except for coronary artery bypass grafting, where no difference was found. Some differences were small, although statistically significant (age, hypertension, hyperlipidemia, creatinine, year of hospital discharge, and PCI). In addition to the overrepresentation of women in the extreme pain category (women, 7.5%; men, 3.6%), current smokers, patients with diabetes, previous MI, previous stroke, previous PCI, non–ST-segment–elevation MI, and any kind of chest pain 12 months after hospital discharge, and patients classified as physically inactive 12 months after hospital discharge, and patients classified as physically inactive 12 months after hospital discharge were overrepresented in this category. Furthermore, patients with extreme pain had higher body mass index and waist circumferences 12 months after hospital discharge. Most (73%) of the 7889 patients who stated they had no pain at the 2-month follow-up after MI were also pain free at the 12-month follow-up, and 65% of those experiencing pain at the 2-month follow-up were also experiencing pain at the 12-month follow-up.

Our main findings were that pain 1 year after MI is highly prevalent, and the mortality among patients with moderate and extreme experienced pain 1 year after MI was higher over an 8.5-year follow-up period than it was among patients without pain. Of the 1067 deaths (5.8% of the 18376 included patients) up to 8.5 years after the SWEDHEART-CR registry visit (12 months after hospital discharge), patients with extreme pain were overrepresented (no pain, 420 deaths [4.0% of n=10517]; moderate pain, 543 deaths [7.7% of n=7025]; and extreme pain, 104 deaths [12.5% of n=834]). Proportional hazards assumptions for the Cox regression models were confirmed with the log[−log(survival)] versus log of survival time plot. In addition, in the fully adjusted model, HRs were 1.35 (95% CI, 1.18–1.55) and 2.06 (95% CI, 1.63–2.60) for moderate and extreme pain categories, respectively (Table 3). No interactions were found for all-cause mortality between pain 12 months after hospital stay and age (P=0.93), sex (P=0.50), or chest pain 12 months after hospital stay (P=0.99). When chest pain was dichotomized into “no chest pain” and “any chest pain,” no interaction was found between chest pain and pain 12 months after hospital stay (P=0.77) for all-cause mortality. In sensitivity analyses, where patients with a shorter follow-up time than 2 years after the 12-month visit were excluded, results were similar (Table 4). In the additional sensitivity analysis with all available pain data (n=40963), the HR for moderate pain (adjusted for sex and age) was similar to corresponding HR in the analysis sample (1.71 and 1.77, respectively), whereas the HR for extreme pain was somewhat lower (3.04) in the larger sample than in the analysis sample (3.77). C-statistics for pain and for smoking were 0.60 and 0.55, respectively (95% CI for the difference, 0.03–0.07). Survival by pain categories is presented in Kaplan-Meier curves (Figure). For comparison, similar curves are shown for smoking categories: never, stopped smoking >1 month ago, and current smokers.
DISCUSSION

Our study, which included 18,376 patients recruited from a national registry of unselected patients with MI, found that mortality among patients who reported moderate and extreme experienced pain at 1-year outpatient follow-up after MI was higher over an 8.5-year follow-up period than it was among patients without pain. Furthermore, the predictive ability of pain 1 year after MI on mortality was found to be more pronounced than that of smoking in univariate models. However, our follow-up time was 4 times longer, and, in addition, in our study, pain was categorized by severity. Pain severity seems to be an important factor, because mortality among patients with chronic pain is higher than in the general population,26,27 especially when chronic pain is severe.26 In addition, we found that patients with extreme pain were less physically active, which has also been found elsewhere,13 or to address the other side of the coin, an increased level of physical activity has been found to reduce mortality.29

Pain and cardiovascular diseases share many lifestyle-related risk factors5,12,13 and risk factors related to socioeconomic status,15 which could be one explanation as to why mortality among patients with 1 year after MI was significantly higher than mortality in patients without pain. Pharmaceuticals commonly used in pain treatment (both opioids and nonsteroidal anti-inflammatory agents) are associated with increased cardiovascular risk,30–32 which could also be a part of the explanation. In line with other studies, we also found that women are overrepresented in both pain categories, which supports the finding that chronic pain is more common in women.5,32–35

The large sample is a strength of the study as well as the sample being representative of Swedish MI cases over a 10-year period. The large sample made it possible to examine possible interactions between age, sex, chest pain, and pain on mortality. A further strength of

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<th>EQ-5D pain category 12 mo after hospital discharge</th>
<th>Whole sample (n=18,376, 1076 deaths, 65,481 person-years)</th>
<th>Adjusted for age and sex</th>
<th>Fully adjusted*</th>
</tr>
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<tbody>
<tr>
<td>No pain (n=10,517, 420 deaths)</td>
<td>1 (Reference)</td>
<td>1 (Reference)</td>
<td></td>
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<tr>
<td>Moderate pain (n=7,025, 543 deaths)</td>
<td>1.77 (1.56–2.01)</td>
<td>&lt;0.0001</td>
<td>1.35 (1.18–1.54)</td>
</tr>
<tr>
<td>Extreme pain (n=834, 104 deaths)</td>
<td>3.71 (2.98–4.61)</td>
<td>&lt;0.0001</td>
<td>2.05 (1.62–2.59)</td>
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EQ-5D indicates EuroQol-5 dimension instrument; HR, hazard ratio; and MI, myocardial infarction.

**Table 3.** HRs With 95% CIs for EQ-5D Pain Categories for Mortality Up to 8.5 Years Subsequent to the Visit 1 Year After MI

**Table 4.** HRs With 95% CIs for EQ-5D Pain Categories for Mortality Up to 8.5 Years Subsequent to the Visit 1 Year After MI
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This study is that pain was measured 1 year after MI, indicating low contamination from acute chest pain after MI. Also, we were able to study long-term mortality because the follow-up time was up to 8.5 years after the visit 12 months after MI. However, results may partly be affected by reverse causation. Thus, we made sensitivity analyses where patients with a shorter follow-up time than 2 years after the 12-month visit were excluded. Results were essentially unaltered, indicating that the effect of reverse causation was limited. In an additional sensitivity analysis where we examined association between pain adjusted for sex and age, using all available pain data, we noted similar results as in the analysis sample, indicating that no large selection bias was likely attributable to missing values on other covariates than pain.

A limitation of the study was that we could not analyze cause-specific mortality. Residual confounding may have been present. We were able to adjust for important variables, both lifestyle related and others. However, we could not adjust for socioeconomic variables or the use of pain pharmaceuticals. Furthermore, CRP (C-reactive protein), which is associated with pain sensitivity, and thus could be a potential confounder, was not measured in our study.

We have not considered mortality during the first year after hospital discharge because of the study design. Also, patients in the analysis sample must have visited a secondary prevention clinic 12 months after hospital discharge. However, these restrictions imply a healthier sample than the general population with MI, meaning that our risk estimates are most likely underestimations. The age limit of 75 years in the registry does not allow for conclusions to be made for patients older than this at the time of their MI. Because comorbidities that potentially affect pain may be more prevalent among the elderly patients, more detailed information on existing and added comorbidities will be needed to study this group of patients. Another limitation in this study is that it is solely based on a Swedish population, which might hinder the interethnic extrapolation of our findings.

Figure. Kaplan-Meier estimates of all-cause mortality from 1 year after a myocardial infarction (MI) and number of subjects at risk by pain categories 1 year after MI (left) and by smoking categories 1 year after MI (right).

EQ-5D indicates EuroQol-5 dimension instrument.
CONCLUSIONS

Pain 1 year after MI is highly prevalent, and its effect on mortality 1 year after MI was found to be more pronounced than the effect of the more well-known risk factor, smoking. Mortality among patients with moderate and extreme experienced pain 1 year after MI was higher, over an 8.5-year follow-up period, than that of patients without pain. This association was driven mainly by the extreme pain category. Clinicians managing patients after MI should recognize the need to consider experienced pain as a prognostic factor comparable to persistent smoking, and to address this when designing individually adjusted CR and secondary prevention treatments.

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Affiliations

School of Health and Welfare, Dalarna University, Falun, Sweden (L.V., B.Ä., L.B.); Center for Clinical Research Dalarna, Uppsala University, Uppsala, Sweden (K.H., B.Ä.); Regional Board Administration (B.Ä.), and Department of Cardiology Falun, Health Care Dalarna (K.H.), Region Dalarna, Falun, Sweden; Division of Physiotherapy, Department of Neurobiology, Care Sciences and Society, Karolinska Institutet, Huddinge, Sweden (B.Ä.); and Department of Public Health and Caring Sciences, Geriatrics (L.B.), Uppsala University, Uppsala, Sweden.

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Disclosures

None.