Association Between Myocardial Infarction and Fractures
An Emerging Phenomenon

Yariv Gerber, PhD; L. Joseph Melton III, MD, MPH; Susan A. Weston, MS; Véronique L. Roger, MD, MPH

Background—Data on the association between myocardial infarction (MI) and fractures are scarce. Recent changes in the epidemiology of MI justify exploring this relationship. We evaluated whether MI constitutes a risk factor for osteoporotic fracture and examined secular trends in this association.

Methods and Results—Consecutive Olmsted County, Minnesota, residents with incident MI diagnosed in 1979 to 2006 and community control subjects individually matched (1:1) to cases on age, sex, and year of onset (n=6642) were followed up through 2009. Outcome measures were time to osteoporotic fracture, overall and by anatomic site, and death. Fracture incidence rates were stable in controls but increased markedly over time among MI cases. Accordingly, although an overall excess of fracture risk after MI was observed (adjusted hazard ratio, 1.32; 95% confidence interval, 1.12 to 1.56), substantial temporal variations were noted (1979 to 1989: hazard ratio, 0.81; 95% confidence interval, 0.58 to 1.12; 1990 to 1999: hazard ratio, 1.47; 95% confidence interval, 1.10 to 1.96; 2000 to 2006: hazard ratio, 1.73; 95% confidence interval, 1.32 to 2.27; P for trend <0.001). Trends were similar regardless of age, sex or fracture site. Conversely, the overall hazard ratio for death in MI cases versus controls did not change materially despite a continuous decline in 30-day case fatality rate (12.5% in 1979 to 1989; 6.7% in 2000 to 2006). Observed changes in the baseline prevalence of cardiovascular risk factors, MI characteristics, and comorbidities did not fully account for the trends in fracture risk.

Conclusions—Over the past decades, the association between MI and osteoporotic fractures increased steadily. The trend is consistent with the displacement of post-MI outcomes toward noncardiovascular events, highlighting the need for comprehensive prevention strategies to accommodate the changing epidemiology of MI. (Circulation. 2011;124:00-00.)

Key Words: epidemiology • fractures, bone • myocardial infarction • prevention

Accumulating evidence links vascular factors to osteoporosis and fractures, yet much of it is conflicting. Although several studies included an assessment of fracture risk in patients with cardiovascular disease, the specific association between myocardial infarction (MI) and fractures has rarely been studied, and temporal trends have not previously been evaluated. Because the burden of MI has shifted in recent decades toward women and the elderly, in whom osteoporosis is also prevalent, the nature and strength of the association need further clarification, the urgency of which is anchored in the major clinical and public health impact of both MI and fractures in aging populations. Although we and others have recently demonstrated profound changes in the outcomes of MI, characterized by reduced short-term case fatality rates and a displacement of deaths toward noncardiovascular causes, the implications of these important observations on comorbid events among aging MI survivors have not been fully addressed. Because atherosclerotic disease and fractures likely share a common biological pathway, we used a population-based cohort study design to examine whether incident MI was associated with an excess risk of subsequent osteoporotic fracture, whether this association had changed over time, and whether risk factors for fracture among MI subjects could be identified to help design preventive strategies.

Clinical Perspective on p

Methods
Setting, Design, and Participants
This research was conducted in Olmsted County, Minnesota, a location well suited for disease association studies because comprehensive medical records for the residents are available for review and are accessible through a centralized index of diagnoses made by all medical care providers serving the local population (with a few exceptions that are not relevant to this study). After approval was granted by the appropriate Institutional Review boards, a matched
cohort study was carried out using this unique record linkage system (the Rochester Epidemiology Project). Because almost all Olmsted County residents are represented in this system, this data source provides a virtually complete enumeration of the source population for many decades. Indeed, the Rochester Epidemiology Project Census enumeration has recently been compared with the US Census enumeration for Olmsted County and demonstrated to have excellent validity for every Census year since 1930. Exposed subjects (cases) were consecutive patients with an incident (ie, first ever) MI occurring between 1979 and 2006 (n=3321), identified with an algorithm previously described and validated according to standardized criteria. Unexposed subjects (controls) were randomly selected from the Olmsted County population and individually matched (1:1) to each case on age (≥3 years), sex, and incidence year. By matching on incidence year, we ensured that the controls had sought medical care the same year the case experienced the MI. Among all eligible controls who met the matching criteria, we selected the one with the medical record registration number closest to that of the corresponding case. Because information on exposures before the index date was obtained from community medical records, this matches for the duration of prior medical record documentation, ensures similar opportunities for ascertainment of comorbidities between the compared groups, and avoids biases inherent in many observational studies (eg, differential recall, nonresponse bias, and survivor bias). Potential controls with a prior MI were excluded. All participants were followed up through their complete (inpatient and outpatient) medical records in the community from index time to death or the most recent clinical contact (last follow-up, July 2009). Because virtually all local residents have at least 1 contact with the medical system in any 3-year period and the majority are seen annually, follow-up is quite complete.

Outcome Measures
Each subject’s medical record was searched electronically for the occurrence of any fracture through comprehensive diagnostic and surgical indexes that record all diagnoses made over time and hence are not limited to chief complaints. Consequently, fractures found incidentally on workups for other problems are included in this system, as are symptomatic fractures presenting for treatment. Because we have access to complete inpatient and outpatient medical records in the community, our data collection processes also identify fractures that occurred elsewhere through follow-up care, patient reports of interim medical history, or subsequent radiographs. This optimizes ascertainment of fractures, which should be nearly complete because the vast majority come to medical attention either directly or indirectly. Fractures were classified by anatomic site, with those of the proximal femur (hip), lumbar/thoracic vertebrae (spine), distal forearm (wrist), or humerus (shoulder) regarded as osteoporotic. However, all fractures were included in the analysis, and the date of first fracture event both before and after the index time, overall and by anatomic site, was used as the diagnosis date. Death was ascertained through multiple sources, including death certificates filed in Olmsted County, autopsy reports, obituary notices, and electronic death certificate files obtained from the Section of Vital Statistics, Minnesota Department of Health.

Additional Clinical Data
For the cases, the medical record was reviewed to ascertain cardiovascular risk factors and MI characteristics through the use of measurements recorded as of the index date or at the closest time before hospital admission. Cigarette use was classified into current versus noncurrent smoking. Body mass index was calculated from weight and height observed as of the index date or at the closest time. Clinical definitions were used to assess diabetes mellitus, hypertension, and hyperlipidemia. Myocardial infarction characteristics and severity indexes, including ST elevation, Q waves, infarct location, and Killip class, were recorded. For both MI cases and controls, all components of the Charlson index were retrieved electronically using medical diagnoses made before or during the index time. The Charlson index consists of 19 serious comorbid conditions weighted according to the degree to which they predict mortality (1, 2, 3, or 6 points for each).

Table 1. Baseline Characteristics Among Olmsted County, Minnesota, Residents With Incident Myocardial Infarction in 1979 to 2006 Compared With Community Control Subjects

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Cases (n)</th>
<th>Controls (n)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD), y</td>
<td>67.4 (14.2)</td>
<td>67.4 (14.2)</td>
<td>0.95</td>
</tr>
<tr>
<td>Female, n (%)</td>
<td>1425 (43)</td>
<td>1425 (43)</td>
<td>1.00</td>
</tr>
<tr>
<td>Prior osteoporotic fracture, n (%)</td>
<td>476 (14)</td>
<td>468 (14)</td>
<td>0.78</td>
</tr>
<tr>
<td>Charlson Comorbidity Index, median (quartiles 1, 3)</td>
<td>1 (0, 3)</td>
<td>1 (0, 2)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Results
The study included 6642 subjects: 3321 incident MI cases (mean age at baseline, 67.4 years; SD, 14.2 years; 43% women) and 3321 age- and sex-matched controls. On average, MI cases had greater comorbidities than controls, whereas the distribution of prior osteoporotic fractures was similar (Table 1).
During a mean follow-up of 4.0 years (SD, 1.7 years), 561 participants developed an incident osteoporotic fracture; 1650 subjects died. The overall rates per 1000 person-years in MI cases versus controls were 24.1 versus 20.9 for fracture and 90.3 versus 39.8 for death, respectively. However, although fracture rates were stable in the control group (22.2 in 1979 to 1989, 19.1 in 1990 to 1999, and 21.7 in 2000 to 2006; \( P \) for trend=0.88), a steady increase was noted among MI patients (16.3, 22.5, and 34.0, respectively; \( P \) for trend<0.001). This secular trend persisted after adjustment for age, sex, and prior osteoporotic fracture (Figure 1). On a relative scale, although the overall HR for fracture in MI versus controls was moderate (1.32; 95% CI, 1.12 to 1.56), substantial temporal variations were evident (in 1979 to 1989: HR, 0.81; 95% CI, 0.58 to 1.12; in 1990 to 1999: HR, 1.47; 95% CI, 1.10 to 1.96; and in 2000 to 2006: HR, 1.73; 95% CI, 1.32 to 2.27; \( P \) for trend<0.001; Table 2). Repeating this analysis with shorter time-period categories supported a steady, monotonic in-

![Osteoporotic fracture-free survival curves by time period adjusted for age, sex, and prior fracture among Olmsted County, Minnesota, residents with incident myocardial infarction in 1979–1989 (A), 1990–1999 (B), and 2000–2006 (C) vs community control subjects.](image)

### Table 2. Temporal Trends in the Associations Between Incident Myocardial Infarction and 5-Year Risk of Osteoporotic Fracture, Overall and in Specific Subgroups, Nonosteoporotic Fracture, and Death Among Olmsted County, Minnesota, Residents in 1979 to 2006

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Time Period</th>
<th>Overall 1979–1989</th>
<th>1990–1999</th>
<th>2000–2006</th>
<th>( P_{\text{trend}} )</th>
<th>( P_{\text{interaction}} )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Osteoporotic fracture</td>
<td>Cases HR (95% CI)*</td>
<td>561 1.32 (1.12–1.56)</td>
<td>155 0.81 (0.58–1.12)</td>
<td>191 1.47 (1.10–1.96)</td>
<td>215 1.73 (1.32–2.27)</td>
<td>&lt;0.001...</td>
</tr>
<tr>
<td>Stratified by baseline age groups</td>
<td></td>
<td>½75 y 190 1.40 (1.05–1.86)</td>
<td>58 0.99 (0.59–1.66)</td>
<td>62 1.63 (0.99–2.71)</td>
<td>70 1.67 (1.04–2.70)</td>
<td>0.02 0.68</td>
</tr>
<tr>
<td></td>
<td>&gt;75 y 371 1.29 (1.05–1.58)</td>
<td>97 0.72 (0.47–1.09)</td>
<td>129 1.41 (0.99–2.00)</td>
<td>145 1.79 (1.29–2.49)</td>
<td>0.001...</td>
<td></td>
</tr>
<tr>
<td>Stratified by sex</td>
<td></td>
<td>Women 393 1.35 (1.11–1.65)</td>
<td>115 0.71 (0.48–1.04)</td>
<td>148 1.72 (1.24–2.39)</td>
<td>130 1.81 (1.27–2.56)</td>
<td>&lt;0.001 0.62</td>
</tr>
<tr>
<td></td>
<td>Men 168 1.25 (0.92–1.69)</td>
<td>40 1.20 (0.64–2.23)</td>
<td>43 0.79 (0.43–1.46)</td>
<td>85 1.62 (1.06–2.49)</td>
<td>0.25...</td>
<td></td>
</tr>
<tr>
<td>Stratified by prior fracture status</td>
<td></td>
<td>No 347 1.45 (1.17–1.79)</td>
<td>90 1.03 (0.68–1.57)</td>
<td>119 1.32 (0.92–1.89)</td>
<td>138 1.98 (1.41–2.79)</td>
<td>0.008 0.98</td>
</tr>
<tr>
<td></td>
<td>Yes 214 1.13 (0.86–1.48)</td>
<td>65 0.58 (0.35–0.99)</td>
<td>72 1.68 (1.04–2.69)</td>
<td>77 1.36 (0.86–2.13)</td>
<td>0.002...</td>
<td></td>
</tr>
<tr>
<td>Restricted to specific anatomic sites</td>
<td></td>
<td>Spine 183 1.22 (0.91–1.63)</td>
<td>56 0.60 (0.34–1.06)</td>
<td>54 1.94 (1.12–3.34)</td>
<td>73 1.42 (0.89–2.25)</td>
<td>0.004...</td>
</tr>
<tr>
<td></td>
<td>Nonspine 415 1.45 (1.20–1.76)</td>
<td>109 1.01 (0.69–1.47)</td>
<td>147 1.43 (1.03–1.99)</td>
<td>159 1.94 (1.41–2.66)</td>
<td>0.003...</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hip 269 1.42 (1.12–1.81)</td>
<td>74 0.92 (0.58–1.47)</td>
<td>104 1.75 (1.18–2.58)</td>
<td>91 1.66 (1.09–2.51)</td>
<td>0.01...</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Forearm 114 1.47 (1.01–2.12)</td>
<td>27 0.91 (0.42–1.96)</td>
<td>35 1.32 (0.68–2.57)</td>
<td>52 2.00 (1.14–3.50)</td>
<td>0.11...</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Humerus 56 1.69 (1.00–2.87)</td>
<td>16 1.39 (0.52–3.72)</td>
<td>14 0.62 (0.19–2.01)</td>
<td>26 3.57 (1.50–8.51)</td>
<td>0.18...</td>
<td></td>
</tr>
<tr>
<td>Nonosteoporotic fracture</td>
<td></td>
<td>781 1.20 (1.04–1.38)</td>
<td>187 1.06 (0.80–1.42)</td>
<td>315 1.26 (1.01–1.57)</td>
<td>279 1.21 (0.96–1.53)</td>
<td>0.19...</td>
</tr>
<tr>
<td>Death</td>
<td>1,650 2.47 (2.24–2.74)</td>
<td>574 2.47 (2.08–2.93)</td>
<td>569 2.30 (1.93–2.73)</td>
<td>507 2.77 (2.30–3.34)</td>
<td>0.55...</td>
<td></td>
</tr>
</tbody>
</table>

HR indicates hazard ratio; CI, confidence interval.

*HRs are adjusted for age, sex, and prior osteoporotic fracture.
create in fracture risk associated with MI (Figure 2). This increasing trend applied to both vertebral and nonvertebral fractures and did not differ significantly by age, sex, or prior fracture status, whereas little association was found with nonosteoerotic fractures, indicating the specificity of the association between MI and osteoporotic fractures (Table 2).

We further evaluated temporal trends in the prevalence of traditional cardiovascular risk factors and MI characteristics among the cases and their relationship to subsequent fracture risk. These 2 complementary analyses are summarized in Table 3. Variables associated with an excess fracture risk that increased in prevalence over time were hypertension and non–ST-segment–elevation MI. Obesity, on the other hand, which was inversely associated with fracture, more than doubled in rate during the study period.

We also examined the relationship of comorbidities with osteoporotic fracture and found positive associations with heart failure, peripheral vascular disease, stroke, chronic obstructive pulmonary disease, renal disease, rheumatologic disease, and cancer. However, no diverging trends in the prevalence of these comorbidities between MI patients and controls were detected over time, with the exception of heart failure, which was stable in controls but declined among MI cases. The overall comorbidity burden, as assessed by the Charlson index, increased over time (P<0.001) in both cases (median, 2 [quartiles 1 and 3] in 1979 to 1989; 2 [quartiles 1 and 3] in 1990 to 1999; 2 [quartiles 1 and 3] in 2000 to 2006) and controls (0 [quartiles 1 and 3] in 1979 to 1989; 1 [quartiles 1 and 3] in 2000 to 2006). In multivariable Cox models adjusted for age, sex, prior fracture, and overall comorbidity, the HRs for fracture in MI patients versus controls were 0.72 (95% CI, 0.51 to 1.02) in 1979 to 1989, 1.38 (95% CI, 1.03 to 1.85) in 1990 to 1999, and 1.50 (95% CI, 1.13 to 1.98) in 2000 to 2006 (P for trend <0.001).

## Discussion

The present population-based study provides strong evidence for an emerging association between MI and the risk of osteoporotic fracture in the community. Using data spanning 30 years (1979 to 2009), originating from carefully characterized cohorts with complete ascertainment of outcomes, we detected a steady increase in fracture risk after MI, a novel finding not observed in the general population. This alarming temporal trend was robust across patient groups and fracture sites. Long-term mortality risk, on the other hand, remained largely unchanged in MI cases compared with controls, despite a substantial decline in 30-day case fatality rate. Although several characteristics were associated with an...
and ascertainment is deemed to be complete and constant over time in this study setting.18 Nonvertebral fractures are almost invariably symptomatic, fractures were at least as strong as for vertebral fractures.19,20 Polypharmacy and escape clinical diagnosis.10 However, this concern can be substantially proportion of these fractures are asymptomatic and escape clinical diagnosis.10 However, this concern can be largely ruled out because the trends seen for nonvertebral fractures were at least as strong as for vertebral fractures. Nonvertebral fractures are almost invariably symptomatic, and ascertainment is deemed to be complete and constant over time in this study setting.18

Increased Risk of Fracture Among the Subjects With MI, None of These Clinical Factors Exhibited Secular Trends That Could Explain the Temporal Increase in Fracture Risk.

Excess Risk of Fractures After Myocardial Infarction

To the best of our knowledge, the present study provides the first specific longitudinal examination of the relationship between MI and fractures. Previous studies of this association were conducted in different populations and have used heterogeneous cardiovascular events rather than MI.6,7 Several explanations may be considered for our findings. Ascertainment bias is theoretically possible for vertebral fractures because there is no universally accepted definition, and a substantial proportion of these fractures are asymptomatic and escape clinical diagnosis.10 However, this concern can be largely ruled out because the trends seen for nonvertebral fractures were at least as strong as for vertebral fractures. Nonvertebral fractures are almost invariably symptomatic, and ascertainment is deemed to be complete and constant over time in this study setting.18

A role for pharmacological agents could be suggested because more recent MI patients have an increasing number of diagnosed comorbidities9,21,22 and are therefore treated more intensively with drugs than before.9,13,22 Polypharmacy has been previously linked to an elevated risk of adverse events.23 Furthermore, attention has recently been drawn to drug-induced osteoporosis, including medications taken for cardiovascular disease such as heparins, oral anticoagulants, and loop diuretics.24 Adverse effects of vitamin D and calcium supplementation on falls and fractures have also been suggested,25,26 with a possible relation to MI risk.27 Although it is challenging to fully account for medication use, including over-the-counter drugs, we have tried to rule out its possible confounding effect indirectly by showing that the association between MI and subsequent fractures has increased steadily not only for non-ST-segment elevation MI, which occurs in older subjects who are more frail, have a greater number of comorbidities, and are therefore more likely to be subject to polypharmacy, but also for ST-segment elevation MI; thus, trends apparently were not influenced by case-mix changes. In addition, the observed trends were not substantially affected by adjustment for the Charlson index, a comprehensive comorbidity index that captures an extensive array of comorbidities that has previously been demonstrated to predict various health outcomes effectively.28 These analyses provide an indirect argument against the comorbidities/medications hypothesis as a primary explanation for our findings.

Third, major changes have taken place in recent years in the epidemiology of MI pertaining to its definition,29,30 case mix,9,13,22 and management.9,22,31 In the present study, temporal trends in cardiovascular risk factors, MI characteristics, and comorbidities as measured at study entry were examined as potential mediators of the relationship between fracture risk after MI and time; however, no such mechanism was evident. Furthermore, heart failure, which was recently found to be a strong risk factor for osteoporotic fracture in large-scale epidemiological studies,6,7 has been shown previously to decline in occurrence after MI in this cohort.8,9 Stroke after MI, on the other hand, had increased somewhat from 1979 to 1988, with no further rise observed afterward.33 Thus, secular changes in the rates of heart failure and stroke after MI are probably not responsible for the observed trends in fracture risk.

Over the past 2 decades, medical breakthroughs related to technological developments, invasive procedures, and advanced drugs have led to a steady reduction in cardiovascular mortality.17 Consequently, the population of MI survivors has increased, often at the expense of increased disability,34 and there is increased awareness of the burden of frailty in these patients.35 Indeed, our data reveal that the dramatic decline in 30-day case fatality rate in Olmsted County was driven primarily by improved short-term survival of women and elderly patients. Hence, the trend of increasing fracture risk, an expected outcome of frailty-related impairments,34,36 in the aftermath of MI may be a result. Furthermore, although long-term survival remained largely unchanged among 30-day survivors in this population13 and others,14 the deaths shifted from cardiovascular to noncardiovascular causes.13,14 This shift may be partially attributable to the trend of increased fracture risk after MI identified here because fracture confers a high mortality risk, especially in men.10,37

Limitations, Strengths, and Clinical Implications

These data emanate from a single Midwestern community that is predominantly white.15 Yet, the incidence of fractures in this community is quite comparable to national figures for US whites.38 Although no population can be representative of the nation as a whole, these findings should be reexamined in different racial and ethnic groups. Measurements of bone mineral density or biochemical markers of bone turnover...
were not routinely performed, so the role of bone loss in fracture risk could not be assessed directly. In addition, data on pharmacological treatments possibly related to fractures were not available, nor were data on healthcare encounters (eg, number of visits in a healthcare episode). Finally, temporal changes in definition and ascertainment of MI have occurred over the very long time period studied, as was the case with several covariates evaluated, including hypertension, diabetes mellitus, hyperlipidemia, chronic obstructive pulmonary disease, and renal disease. As in any other secular trend analysis, caution should be taken in the interpretation of these results.

Our study, conducted in a geographically defined population, has several important strengths. Addressing the crucial and challenging issue of chronic disease burden requires the ability to study cohorts relevant to real-world clinical practice such as the present ones. Detecting unfavorable trends that call for intervention requires longitudinal data as can be obtained under the auspices of the Rochester Epidemiology Project.

Our findings, demonstrating a substantial increase in fracture risk among contemporary survivors of an MI, have important clinical and public health implications. Fracture prevention initiatives after MI are likely warranted, particularly among high-risk patient groups such as the elderly, women, and those with prior fracture and/or coexisting illnesses. Furthermore, deficits such as sensory impairments, locomotor disturbances, and cognitive disorders, which are frequently overlooked in the traditional disease-specific model of cardiac care applied to MI patients, should be assessed and treated. Participation in secondary prevention programs, found to be consistently beneficial in this population as in others, should be aggressively pursued given the beneficial role of physical activity for the prevention of bone loss and falls, crucial elements in fracture prevention.

Conclusions

In this geographically defined population, we found a large excess risk of osteoporotic fracture after MI, which increased markedly over the past 3 decades. The trend applied to all segments of the population and all fracture sites. Given the deleterious impact of fracture on outcomes, fracture prevention is required in the aftermath of MI, with a particular focus on the elderly, women, and patients with coexisting illnesses.

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Disclosures

None.

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