Sudden Death and Recurrent Ischemic Events after Myocardial Infarction in the Community

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As myocardial infarction (MI) hospital fatalities decline, survivors are candidates for recurrent events. However, little is known about morbidity after MI and how it may have changed over time. The authors examined the incidence of sudden cardiac death and recurrent ischemic events post-MI to test the hypothesis that it has declined over time. MIs were validated by using standardized criteria. Sudden cardiac death and recurrent ischemic events (recurrent MI or unstable angina) were identified through Olmsted County, Minnesota, community medical records and their association with time examined after adjustment for age, sex, and comorbidity. Between 1979 and 1998, 2,277 MIs occurred (57% in men; mean age, 67 (standard deviation, 14) years). After 3 years, the event-free survival rate was 94% (95% confidence interval: 93, 95) for sudden cardiac death and 56% (95% confidence interval: 54, 58) for recurrent ischemic events. Both outcomes were more frequent with older age and greater comorbidity. The temporal decline in both events was of similar magnitude; for an MI occurring in 1998 versus 1979, risk of subsequent recurrent ischemic events or sudden cardiac death declined by 24% (relative risk = 0.76, 95% confidence interval: 0.63, 0.93). Thus, in the community, recurrent ischemic events are frequent post-MI, while sudden cardiac death is less common. Their incidence declined over time, supporting the notion that contemporary treatments effectively improve outcomes after MI.

deadth, sudden; myocardial infarction; outcome assessment (health care); time

Abbreviations: CI, confidence interval; ICD-9-CM, International Classification of Diseases, Ninth Revision, Clinical Modification; MI, myocardial infarction; RR, relative risk.

Over the past few decades, clinical trials established efficacious interventions to treat acute myocardial infarction (MI), leading to new practice recommendations (1, 2). In response to implementation of evidence-based therapies, MI severity (3) and case fatality rates decreased (4), thereby yielding a growing population of MI survivors. Although these survivors are conceptually at risk for future morbid events, the hypothesis that MI survivors contribute to the sustained burden of cardiovascular disease remains to be tested by studying their long-term outcome.

The importance of characterizing post-MI outcomes to understand the population implications of improved MI survival in the current era contrasts with the paucity of data on the subject. Indeed, clinical trials often report on earlier outcomes (5–10), focusing on total mortality, with more limited data on other outcomes. Moreover, the selection processes inherent to clinical trials (11) make it uncertain whether the event burden observed in clinical trials will reflect community outcomes.

Community surveillance studies provide the appropriate framework to address the important public health question of whether benefits observed in clinical trials translate into improved population outcomes and whether MI survivors contribute to cardiovascular morbidity. Previous surveillance studies that examined post-MI outcomes reported improvements, but most had an upper age limit of 74 years, thereby ignoring the older age groups in which the burden of MI is increasing (12). In addition, the reported data pertain primarily to in-hospital events and long-term overall survival, not fully characterizing post-MI morbidity (13–15).
Thus, there are persisting gaps in knowledge regarding the magnitude of the burden of recurrent ischemic events and sudden cardiac death after incident MI overall and whether their occurrence has changed over time. This issue is especially important given evidence of the increased focus on preventing sudden cardiac death post-MI (16). This study was undertaken to address these gaps in knowledge in the Olmsted County, Minnesota, community by characterizing the burden of recurrent ischemic events and sudden cardiac death post-MI and testing the hypothesis that it declined over time.

MATERIALS AND METHODS

Study setting

The study was conducted in Olmsted County, Minnesota. Although the diversity of the county population is increasing (refer to the following website: http://www.census.gov), its characteristics during the study period were similar to those of US Whites. Epidemiologic studies are possible in the county because it is relatively isolated from other urban centers and only a few providers— the Mayo Clinic, Olmsted Medical Center, and a few private practitioners—deliver nearly all health care to residents. Each provider uses a comprehensive record system in which all encounters are entered. Under the auspices of the Rochester Epidemiology Project, all records are indexed according to clinical and pathologic diagnoses and surgical procedures. This indexing system enables retrieval of medical data for use in epidemiologic studies and surgical procedures. This indexing system provides retrieval of medical data for use in epidemiologic studies and surgical procedures. This indexing system enables retrieval of medical data for use in epidemiologic studies and surgical procedures. This indexing system enables retrieval of medical data for use in epidemiologic studies and surgical procedures.

Assembling the MI cohort

The inception cohort of persons with incident MI was assembled by using standardized surveillance methods described in detail elsewhere (18, 19). Briefly, we enumerated all patients discharged from Olmsted County hospitals between 1979 and 1998 with diagnoses compatible with an MI defined by the following target codes from the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM): 410 (acute MI), 411 (other acute and subacute forms of ischemic heart disease), 412 (old MI), 413 (angina pectoris), and 414 (other forms of ischemic heart disease). All events coded as 410 and samples of the other codes were reviewed by using sampling fractions comparable to those used in other studies (19). Trained abstractors ascertained incident status by completely reviewing the medical records. Events were ascertained during the whole follow-up period.

Recurrent ischemic events, including recurrent MI or unstable angina, were defined by using physicians’ diagnoses. Cases of possible recurrent MI in which the event relied solely on circumstantial evidence from the patient, without physician confirmation, were excluded. Unstable angina was defined as hospitalization because of cardiac pain with normal biomarker levels.

Death certificate data were used to ascertain date and underlying cause of death. Standardized algorithms were used to determine cause of death in the rare event that a Minnesota State nosologist assignment was not available. Underlying causes of death were classified according to ICD-9-CM codes into three groups: coronary heart disease death, codes 410–414; other cardiac death, codes 390–398, 401–405, or 420–429; and noncardiac causes of death including all other ICD-9-CM codes. As previously validated, sudden cardiac death was defined as out-of-hospital death by using ICD-9-CM codes 410–414 (22).

Statistical analyses

In this paper, the data are presented as frequency or as mean (standard deviation). Baseline characteristics were compared across time periods by using the Mantel-Haenszel chi-square test for categorical variables and the F test from analysis of variance for continuous variables. Survival was analyzed with the Kaplan-Meier method. The p value for comparison of the year tertiles was derived from the likelihood ratio test that assessed whether any of the year group coefficients was not equal to zero.

Proportional hazards regression was used to examine the association between recurrent ischemic events or sudden cardiac death and year of MI while controlling for age, sex, and ascertainment procedures during the study period. The study pertains to the cohort of validated incident cases; patients with prior MI were excluded.

Baseline characteristics, follow-up, endpoint definitions, and ascertainment

Clinical diagnoses were used to ascertain hyperlipidemia, smoking, hypertension, and diabetes mellitus at the time of the index MI. Smoking was categorized as past or current as documented in the medical record by a patient’s attending physician. History of familial coronary heart disease was defined as disease occurring in a first-degree relative at less than age 55 years for men and 65 years for women. Because of the change over time in normal values, peak creatine kinase ratio was used (ratio of maximum creatine kinase value to upper limit of normal). Comorbidities were ascertained by using physicians’ diagnoses as documented in the medical record by physicians’ clinical notes at the time of the index MI. They were summarized by using the Charlson comorbidity index (21).

Patients were followed until death or the date of the last follow-up as ascertained by reviewing the entire community (inpatient and outpatient) medical records. Events were ascertained during the whole follow-up period.

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and comorbidity. The relative risk comparing 1998 with 1979 data was estimated from exponentiation of the parameter estimate for year of MI multiplied by the number of years between 1979 and 1998, thereby making use of the entire duration of the study.

All analyses were weighted to account for the sampling strategy, in which the weights applied were the inverse of the sampling fractions for each code used to ascertain MI. Nonlinear effects of age and year of MI were examined by including quadratic terms in the models. Trends for both events were compared across ages and between sexes by including interaction terms between year and age and between year and sex. Competing risk analyses examined the effect of death on the occurrence of recurrent ischemic events and the effect of other causes of death on sudden cardiac death.

Missing values did not exceed 5 percent for any of the variables used in the regression analyses. A \( p \) value of 0.05 was selected for the threshold of statistical significance, except when testing for interaction, when \( p \) values of up to 0.10 were considered. S-PLUS statistical software, version 6.0.4, was used (Insightful Corporation, Seattle, Washington).

This study was approved by the Mayo Foundation Institutional Review Board.

RESULTS

Baseline characteristics

Between 1979 and 1998, incident MIs were documented for 2,277 patients in Olmsted County. Their characteristics are presented in table 1. Fifty-seven percent were men, and persons 75 years of age or older accounted for a third of the subjects, a proportion tending to increase over time. The prevalence of hyperlipidemia, hypertension, and diabetes mellitus, as well as mean body mass index, increased over time. The prevalence of smoking decreased.

Burden of events

Recurrent ischemic events. During a mean follow-up of 6.3 (standard deviation, 5.3) years (range, 0–21 years), 1,029 unstable angina patients were admitted to the hospital, and 589 recurrent MIs occurred (table 1). At 3 years, the survival-free rate of unstable angina was 60 percent (95 percent confidence interval (CI): 58 percent, 63 percent), and the survival-free rate of recurrent MI was 82 percent (95 percent CI: 81 percent, 84 percent). When unstable angina and recurrent MI were analyzed as a combined endpoint, the 3-year survival-free rate of recurrent ischemic events was 56 percent (95 percent CI: 54 percent, 58 percent) (figure 1). Recurrent ischemic events occurred early after the index MI; during the first year post-MI, 57 percent of recurrent ischemic events had occurred. Three years after the index MI, the estimates for the proportions of men experiencing recurrent ischemic events were 0.40 (95 percent CI: 0.39, 0.42) for those less than age 75 years and 0.47 (95 percent CI: 0.43, 0.52) for those aged 75 years or more. The estimates for the proportions of women experiencing recurrent ischemic events were 0.45 (95 percent CI: 0.41, 0.48) for those less than age 75 years and 0.53 (95 percent CI: 0.49, 0.57) for those aged 75 years or more.

In a multivariable model, older age, female sex, and greater comorbidity were positively and independently associated with occurrence of recurrent ischemic events. For female sex, there was a 16 percent increase in the risk of

| TABLE 1. Characteristics of 2,277 patients experiencing incident myocardial infarction, Olmsted County, Minnesota, 1979–1998 |
|-------------------------------------------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| Mean age (years) (standard deviation)           | 67 (14)          | 66 (14)          | 68 (14)          | 68 (14)          | 0.078           |
| Age ≥75 years (%)                               | 36               | 32               | 37               | 37               | 0.047           |
| Female sex (%)                                  | 43               | 39               | 44               | 45               | 0.024           |
| Mean body mass index (kg/m²) (standard deviation) | 27 (6)          | 26 (5)          | 27 (5)          | 28 (7)          | <0.001          |
| Hyperlipidemia (%)                             | 32               | 21               | 29               | 43               | <0.001          |
| Hypertension (%)                               | 56               | 51               | 53               | 62               | <0.001          |
| Diabetes mellitus (%)                          | 20               | 18               | 16               | 24               | 0.006           |
| History of smoking (%)                         | 66               | 70               | 64               | 64               | 0.025           |
| History of familial coronary heart disease (%) | 21               | 19               | 22               | 23               | 0.053           |
| Mean peak creatine kinase ratio (standard deviation) | 5.4 (5.6)      | 6.1 (5.6)       | 5.8 (6.1)       | 4.3 (4.9)       | <0.001          |
| No. of comorbid conditions (%)                 |                 |                 |                 |                 |                 |
| 0                                              | 63               | 69               | 62               | 59               | <0.001          |
| 1 or 2                                         | 30               | 27               | 29               | 34               |                 |
| ≥3                                             | 7                | 3                | 9                | 8                |                 |
recurrent ischemic events (relative risk (RR) for women compared with men = 1.16, 95 percent CI: 1.03, 1.32; \( p = 0.018 \)) after adjustment for age and comorbidity. For age 75 years or older, there was a 24 percent increase in the risk of recurrent ischemic events post-MI (RR compared with their younger counterparts = 1.24, 95 percent CI: 1.08, 1.41; \( p = 0.002 \)) after adjustment for sex and comorbidity.

**Sudden cardiac death.** During follow-up, 253 sudden cardiac deaths occurred. Overall, the 3-year survival-free rate of sudden cardiac death was 94 percent (95 percent CI: 93 percent, 95 percent) (figure 1). Sudden cardiac death occurred throughout the follow-up period after the index MI; during the first year post-MI, 25 percent of sudden cardiac deaths had occurred.

In a multivariable model that included year, age, sex, comorbidity, and recurrent MI, the occurrence of sudden cardiac death was positively associated with older age, greater comorbidity, and occurrence of a recurrent MI. For persons aged 75 years or older compared with their younger counterparts, the relative risk of sudden cardiac death after incident MI was 3.36 (95 percent CI: 2.54, 4.45; \( p < 0.001 \)). Recurrent MI was independently associated with a 44 percent increase in the risk of sudden cardiac death (RR = 1.44, 95 percent CI: 1.12, 1.86; \( p = 0.005 \)).

**Secular trends**

**Recurrent ischemic events.** Over time, the occurrence of recurrent ischemic events declined, and the magnitude of the decline did not differ according to age, sex, or comorbidity. Table 2 presents the crude and adjusted relative risks for unstable angina and recurrent MI using 1979 as the reference level. After adjustment for age, sex, and comorbidity, the risk of unstable angina after an incident MI occurring in 1998 versus 1979 was 19 percent lower (RR = 0.81, 95 percent CI: 0.66, 1.00; \( p = 0.052 \)). The adjusted risk of recurrent MI after an incident MI occurring in 1998 compared with 1979 was 32 percent lower (RR = 0.68, 95 percent CI: 0.51, 0.92; \( p = 0.012 \)), equating to a decline of 2 percent a year. When unstable angina and recurrent MI were analyzed as a combined endpoint, and after adjustment for age, sex, and comorbidity, the risk of a recurrent ischemic event after an incident MI occurring in 1998 versus 1979 was 24 percent lower (RR = 0.76, 95 percent CI: 0.62, 0.92; \( p = 0.007 \)).

**Sudden cardiac death.** Overall, no change over time in the survival-free rate of sudden cardiac death was detected (figure 1), and the secular trend did not differ according to age, sex, comorbidity, or recurrent MI. After adjustment for age, sex, and comorbidity, the magnitude of the decline in sudden cardiac death over the 20-year period was similar to that for recurrent ischemic events, albeit not reaching statistical significance (RR for sudden cardiac death post-MI occurring in 1998 compared with MI occurring in 1979 = 0.76, 95 percent CI: 0.47, 1.23; \( p = 0.26 \)) (table 2). After further adjustment for recurrent MI, the relative risk of subsequent sudden cardiac death post-MI occurring in 1998 compared with MI occurring in 1979 was 0.80 (95 percent CI: 0.49, 1.30; \( p = 0.36 \)).

**Recurrent ischemic events and sudden cardiac death combined.** We combined recurrent ischemic events and sudden cardiac death in the analyses and adjusted for age, sex, and comorbidity. We found that the risk of recurrent ischemic events or sudden cardiac death declined by 24 percent over the 20-year period (RR for subsequent recurrent ischemic events or sudden cardiac death occurring in 1998 compared with MI occurring in 1979 = 0.76, 95 percent CI: 0.63, 0.93; \( p = 0.006 \)).
Death as a competing risk

During follow-up, 1,152 deaths occurred, including 700 from cardiac-related causes (61 percent of the total deaths); 253 were attributed to sudden cardiac death (22 percent of the total deaths, 36 percent of the cardiac deaths) and 428 to noncardiac death (37 percent of the total deaths). The 3-year survival rate was 74 percent (95 percent CI: 72 percent, 75 percent). When death was analyzed as a competing risk regarding survival of recurrent ischemic events, the 3-year estimate of survival free of recurrent ischemic events was 62 percent, representing an absolute increase of 6 percent in the conventional survival analysis estimate of 56 percent. Similarly, when nonsudden cardiac death was analyzed as a competing risk regarding the survival of sudden cardiac death, the 3-year estimate of survival of sudden cardiac death was 95 percent, representing an absolute increase of 1 percent in the conventional survival analysis estimate of 94 percent.

DISCUSSION

Recurrent ischemic events are frequent post-MI, while sudden cardiac death is less frequent. Both events occur more often with older age and greater comorbidity. We found that, over the last two decades, the incidence of both events declined by 24 percent among persons experiencing an MI, thereby indicating that morbidity after MI decreased over time.

Post-MI outcomes in the population: the need for observational studies

Several treatments improve survival post-MI, as shown by clinical trials, the "gold standard" used to determine efficacy. However, the selection bias inherent to trials can limit generalizability of the outcomes observed in clinical trials to the population (11). Thus, surveillance studies complement clinical trials by monitoring disease outcomes in the population and assessing whether disease outcomes change in response to incorporation of new therapies in practice. To this end, surveillance studies have documented an improvement in MI case fatality rates in the community (4, 13, 14, 23, 24), but little is known about recurrent ischemic events and sudden cardiac death post-MI.

Recurrent ischemic events after incident MI

Recurrent ischemic events are important indicators of post-MI outcomes. Indeed, one could speculate that, as MI severity decreases over time (3) and use of reperfusion therapy increases, MI survivors retain more viable myocardium, thereby increasing their risk of recurrent ischemic events. The Framingham Heart Study reported no change in recurrent Q-wave and non-Q-wave MIs after an index Q-wave MI occurring between 1950 and 1989 (13). Because only a relatively small number of Q-wave MIs (n = 363) were considered, it is unclear whether these findings are generalizable to all MIs, larger populations, and more contemporary time periods. The Minnesota Heart Survey and the Atherosclerosis Risk in Communities (ARIC) study reported a decline in recurrent MI during the late 1980s and early 1990s (4, 24). Both studies have an upper age limit of 74 years, so these encouraging findings need to be corroborated in populations including all age groups.

The results presented herein extend the aforementioned results by indicating that, over the last two decades, the occurrence of recurrent MIs declined by 32 percent among all subjects experiencing a first MI. Because the yearly decline in recurrent MI is similar to the 1.9 percent per year decline reported in the Atherosclerosis Risk in Communities study (24), this finding supports the fact that recurrent MI is indeed declining over time.

Little is known about angina post-MI in the community. While the Framingham Heart Study reported in 1979 that, within 5 years post-MI, 50 percent of patients experienced angina defined by self-report (23), there are, to the best of our knowledge, no recent published data from population studies on the occurrence of unstable angina post-MI. Our results indicate that, in a geographically defined MI cohort, unstable angina occurs frequently but is declining over time.
Unstable angina and recurrent MI are part of a spectrum of ischemic events thought to have similar mechanistic underpinnings. When combined as a composite indicator of the burden of recurrent ischemic events, our results document two important points. First, the burden of recurrent ischemic events post-MI is high; approximately half of all MI subjects experience events within 3 years post-MI, and older age, female sex, and increased comorbidity confer a greater risk. Second, the occurrence of recurrent ischemic events post-MI is declining noticeably over time; the decline over the last 20 years exceeded 20 percent. These trends are evident within the context of increasing use of evidence-based therapies after MI at discharge, as reported in this cohort (25), while, conversely, use of cardiac rehabilitation has remained stable (26).

**Sudden cardiac death post-MI**

Although sudden cardiac death is a major public health problem, little is known about its occurrence post-MI, and integration of currently published data is challenging because there is no uniformly accepted definition of sudden cardiac death (27, 28). In 1979, the Framingham Heart Study (23) reported that sudden cardiac death, defined as death within 1 hour of the onset of symptoms, accounted for 38 percent of cardiac deaths among 219 patients post-MI. The Atherosclerosis Risk in Communities study (24) defined sudden cardiac death as out-of-hospital deaths that have the following ICD-9-CM codes: 250 (diabetes mellitus), 401–402 (hypertension and hypertensive heart disease), 410–414 and 427 (cardiac dysrhythmias), 428 (heart failure), 429 (ill-defined descriptions and complications of heart disease), 440 (atherosclerosis), 518.4 (acute lung edema), 798 (sudden death, cause unknown), and 799 (ill-defined cause of death). In the Atherosclerosis Risk in Communities study, sudden cardiac death accounted for 70–80 percent of cardiovascular deaths within the first 28 days post-MI. However, to the best of our knowledge, no reported data are available on long-term secular trends in post-MI sudden cardiac death in the population. Thus, the present study, using a definition validated in the population of Olmsted County, found that sudden cardiac death accounted for 22 percent of all deaths and for 36 percent of all cardiac deaths post-MI (22). The risk of sudden cardiac death is greater among older persons, among persons with greater comorbidity, and after a recurrent MI. Importantly, over the last two decades, the risk of sudden cardiac death post-MI declined by a magnitude similar to that for recurrent ischemic events, albeit not reaching statistical significance because of its rare occurrence.

**Implications**

Our findings underscore that the outcome of acute MI is currently characterized by not only early survival gains but also a long-term reduction in adverse outcomes as measured by recurrent ischemic events and sudden cardiac death. Combined with data reported in the same population and others indicating that heart failure post-MI is declining over time (29), these findings point to the effectiveness of current treatments (4, 30) in improving population outcomes. Because this change is occurring while the frequency of risk factors is seemingly increasing among patients with MI, one could infer that more aggressive risk factor management among these patients might result in further improvement. Indeed, the high residual frequency of recurrent ischemic events post-MI should lead to intensified secondary prevention.

With regard to sudden cardiac death, while its occurrence is less frequent, its declining trend parallels that of recurrent ischemic events, supporting the effectiveness of current strategies to prevent sudden cardiac death. Our results do not reflect use of implantable defibrillators recently reported as efficacious in preventing sudden cardiac death among high-risk MI survivors (16). As use of these approaches, currently perceived as submaximal (31), increases, continued monitoring of the risk of sudden cardiac death post-MI will be important.

While the trends reported herein are unequivocally favorable, the increased risk of adverse events conferred by age and comorbidity is important to underscore. Indeed, the increasing number of MI cases in an aging population (12) may augment the absolute numbers of recurrent ischemic events and sudden cardiac death, thereby leading to an increased burden on the health care system even within the context of favorable secular trends in outcome.

Although these results provide important insights into long-term outcomes post-MI, potential limitations should be kept in mind. The racial composition of Olmsted County limits generalization of these data to underrepresented groups, and its medical care system may differ from that of other populations. Thus, this study should be replicated in other settings. However, no population is representative of the United States, and the unique strengths of Olmsted County data are their ability to enable characterization of diseases in a single population in which outcomes can be optimally ascertained with longitudinal data. Although detection of MIs conceivably improved over time, troponin was not used in Olmsted County during the study period and does not impact the present results. However, we cannot exclude the possibility that other factors contributed to enhanced detection of MI over time. The reliability of death certificate data is dependent on local practices, but the methods used in the present study to ascertain sudden cardiac death have been fully validated in the Olmsted County population (22).

**Conclusion**

In the community, recurrent ischemic events are frequent post-MI, while sudden cardiac death is less common. Older age and greater comorbidity increase the risk of both post-MI outcomes.

In the present study, the incidence of recurrent ischemic events and sudden cardiac death declined over time. This finding supports the notion that contemporary therapeutic measures are effective in improving long-term outcomes post-MI.
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