Sudden Cardiac Death After Myocardial Infarction

A. Seleuk Adabag, MD, MS
Terry M. Therneau, PhD
Bernard J. Gersh, MB, ChB, DPhil
Susan A. Weston, MS
Véronique L. Roger, MD, MPH

Sudden cardiac death is a devastating complication of myocardial infarction (MI).1 Long-term population studies outlining the incidence of sudden cardiac death after MI in the community are decades old.2-4 Since the publication of these reports, the in-hospital mortality after MI has decreased substantially because of evidence-based therapies, yielding a growing number of MI survivors potentially at risk for sudden cardiac death.7-11 Incidence and predictors of sudden cardiac death after MI recently have been examined in large clinical trials12-14 and among patients from tertiary care centers.15-18 However, these selected patients may not be representative of patients in the community.19 Thus, in an era when the long-term prognosis after MI has greatly improved, community-based data reflecting the contemporary risk of sudden cardiac death after MI are lacking.

Determining the risk of sudden cardiac death after MI remains challenging.20 Implantable cardioverter-defibrillators (ICDs) decrease mortality in patients with reduced ejection fraction. However, most patients receiving an ICD for primary prevention of sudden cardiac death do not use the devices to terminate cardiac tachyarrhythmias,21 at least not during the period of follow-up during most trials. Further, recent data from the Defibrillator in Acute Myocardial Infarction Trial (DINAMIT)22 and the second Multicenter Automatic Defibrillator Implantation Trial (MADIT-II)23 show that ICD placement less than 40 days after an MI does not reduce mortality, suggesting that sudden cardiac death risk after MI is dependent on time.24,25 One issue with current risk prediction approaches for sudden cardiac death is that predictions based solely on characteristics assessed at baseline, shortly after the MI, may be insufficient. This leads to our hypothesis, as yet untested, that intercurrent events such as recurrent ischemia and heart failure occurring after the index MI increase the risk of sudden cardiac death.

Context Sudden cardiac death after myocardial infarction (MI) has not been assessed recently in the community. Risk stratification for sudden cardiac death after MI commonly relies on baseline characteristics and little is known about the relationship between recurrent ischemia or heart failure and sudden cardiac death.

Objective To evaluate the risk of sudden cardiac death after MI and the impact of recurrent ischemia and heart failure on sudden cardiac death.

Design, Setting, and Participants Population-based surveillance study of 2997 residents (mean [SD] age, 67 [14] years; 59% were men) experiencing an MI in Olmsted County, Minnesota, between 1979 and 2005, and followed up through February 29, 2008.

Main Outcome Measures Sudden cardiac death defined as out-of-hospital death due to coronary disease; and observed survival free of sudden cardiac death compared with that expected in Olmsted County, Minnesota.

Results During a median follow-up of 4.7 years (25th-75th percentile, 1.6-7.1 years), 1160 deaths occurred, 282 from sudden cardiac death (24%). The 30-day cumulative incidence of sudden cardiac death was 1.2% (95% confidence interval [CI], 0.8%-1.6%). Thereafter, the rate of sudden cardiac death was constant at 1.2% per year yielding a 5-year cumulative incidence of 6.9% (95% CI, 5.9%-7.9%). The 30-day incidence of sudden cardiac death was 4-fold higher than expected (standardized mortality ratio, 4.2; 95% CI, 2.9-5.8). The risk of sudden cardiac death has declined significantly over time (hazard ratio [HR], 0.62 [95% CI, 0.44-0.88] for MIs that occurred between 1997 and 2005 compared with between 1979 and 1987; P=.03). The recurrent events of ischemia (n=842), heart failure (n=365), or both (n=873) occurred in 2080 patients. After adjustment for baseline characteristics, recurrent ischemia was not associated with sudden cardiac death (HR, 1.26 [95% CI, 0.96-1.65]; P=.09), while heart failure markedly increased the risk of sudden cardiac death (HR, 4.20 [95% CI, 3.10-5.69]; P<.001).

Conclusions The risk of sudden cardiac death following MI in community practice has declined significantly over the past 30 years. Sudden cardiac death is independently associated with heart failure but not with recurrent ischemia.
The objectives of our investigation were to address the aforementioned gaps in knowledge within a population-based surveillance study of all patients who had an MI in Olmsted County, Minnesota, between 1979 and 2005. Specifically, we set out to define the burden of sudden cardiac death after MI in the community, to examine if it changed over time, and to assess its relationship with intercurrent ischemia and heart failure after MI.

METHODS
Study Setting
Epidemiological research is possible in Olmsted County, Minnesota, because the county is relatively isolated from other urban centers and nearly all medical care is delivered to local residents by a small number of health care providers. Except for the fact that a higher proportion of the working population is employed in the health care industry, the characteristics of the population of Olmsted County, Minnesota, are similar to those of white persons in the United States (http://www.census.gov). All medical care providers, including the Mayo Medical Center, the Olmsted Medical Group, and its affiliated Olmsted Community Hospital, use a unit medical record system. Thus, detailed information on all inpatient, outpatient, and emergency department visits, and all laboratory results, pathology reports, correspondence, and records of physician visits to nursing homes or private homes are kept in one place. Since the early 1960s, extensive indices based on clinical or histological diagnosis, surgical procedures, and billing data also have been kept for all providers of health care under the auspices of the Rochester Epidemiology Project.26 This allows linkage of information from essentially all sources of health care available to and used by the residents of Olmsted County, Minnesota, and provides a unique infrastructure for analyzing disease determinants and outcomes.

Assembling the MI Cohort
Methods used in the identification of patients with incident MI have been published before.26 Briefly, lists of patients discharged from Olmsted County, Minnesota, hospitals between 1979 and 2005 with a diagnosis compatible with MI were obtained from the Rochester Epidemiology Project index of diagnoses. The target International Classification of Diseases, Ninth Revision codes were 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, a 50% random sample of codes 411, and a 10% random sample of codes 412, 413, and 414 were reviewed. The sampling fractions were similar to those used in other studies.27 Minnesota law requires obtaining general research authorization from every patient before the release of any information from medical records for research purposes. Because this study did not include patient contact, no specific consent was necessary. The Mayo Clinic and Olmsted Medical Center institutional review boards reviewed and approved all aspects of the study.

To ascertain the incident MI status, medical records were reviewed by abstractors and data on cardiac pain, cardiac biomarkers, and electrocardiogram results were obtained. All electrocardiograms were interpreted according to the Minnesota code.28 Standard criteria were applied to assign an MI diagnosis based on these data. Information on the reliability of these criteria has been published before.11

Clinical Data and Intercurrent Cardiac Events
Baseline demographic and clinical characteristics, including hypertension, hyperlipidemia, smoking status, diabetes mellitus, obesity, family history of coronary heart disease, Killip class, and other comorbidities at the time of index MI, were recorded from physicians’ clinical notes. Total comorbidity burden was summarized by the Charlson comorbidity index.29

The first episodes of intercurrent cardiac events that occurred after the incident MI were recorded. Heart failure was diagnosed using the Framingham Heart Study criteria requiring the simultaneous presence of at least 2 major criteria (ie, paroxysmal nocturnal dyspnea or orthopnea, neck vein distension, rales, cardiomegaly, acute pulmonary edema, S3 gallop, venous pressure >16 cm H2O, hepatojugular reflux) or 1 major criterion with 2 minor criteria (ie, ankle edema, night cough, dyspnea upon exertion, hepatomegaly, pleural effusion, vital capacity decreased by one-third from maximum, heart rate >120/min).30 Recurrent ischemia was defined as hospitalization for recurrent MI or unstable angina using the physicians’ diagnosis.31,32

Follow-up and Ascertainment of Sudden Death
All patients were followed up until death or the date of the last follow-up as ascertained by reviewing the entire community medical records. The final date of follow-up was February 29, 2008. All death certificate data obtained from the Minnesota Department of Health were searched to identify individuals older than 25 years who were listed as residents of Olmsted County, Minnesota, at the time of death. Information on age and sex of the decedent and the date, site, and underlying cause of death, as determined by the state nosologist, was collected. Since 1968, all death certificates issued in Minnesota have described the site of death. Out-of-hospital deaths were defined as those occurring outside of acute care or long-term care hospitals, including deaths occurring in emergency departments, private homes, public places, nursing or boarding care homes, and infirmaries, as well as deaths among persons declared dead on arrival at a hospital. Sudden cardiac death was defined as out-of-hospital deaths whose primary cause of death was classified as coronary heart disease on the death certificate (International Classification of Diseases, Ninth Revision codes 410-414). This definition, previously validated in the Olmsted County, Minnesota, popula-
Predictors of sudden cardiac death were assessed by Cox proportional hazards regression, with recurrent ischemic events and heart failure treated as time-dependent covariates. Heart failure that occurred after hospitalization for MI but before dismissal from the hospital was included as an intercurrent event. In the model, patients were treated as being at risk for sudden cardiac death after hospital dismissal. Interactions between year of MI and all predictor variables were tested. Only the year $\times$ age interaction was found to be significant. The proportional hazards assumption was assessed using the Schoenfeld residuals and found to be valid. Additional hazard models were used to assess the absolute increment in sudden cardiac death risk associated with intercurrent events. Differences in the baseline hazard were observed before and after 30 days after hospital dismissal, so time epochs were created for the first 30 days after MI and yearly thereafter. The additive model was fit in terms of event rate per epoch. A $P$ value of less than .05 was considered statistically significant. Analyses were performed using SAS version 8.2 (SAS Institute Inc, Cary, North Carolina) and S-PLUS version 8.0.1 (TIBCO Software, Palo Alto, California).

RESULTS

MI Incidence Cohort

Between 1979 and 2005, a total of 3296 incident MIs occurred in Olmsted County, Minnesota; 299 died in the hospital, leaving 2997 hospital survivors as the study population. At the time of index MI, these patients had a mean (SD) age of 67 (14) years and 59% were men. Cardiovascular risk factors were prevalent and 59% of the patients had at least 1 comorbid condition. Most cases in this community cohort presented electrocardiographically as non–ST-segment elevation MIs (TABLE 1). Approximately half were treated with reperfusion or revascularization: 1156 underwent percutaneous coronary intervention (39%), 282 underwent coronary artery bypass grafting (9%), and 318 were treated with thrombolytics (11%).

Incidence of Sudden Death After MI

Over a median follow-up of 4.7 years (25th–75th percentile, 1.6–7.1 years), 1160 deaths occurred, 282 of which were
classified as sudden cardiac death (24%). During the first 30 days after hospital dismissal, 35 sudden cardiac deaths occurred for a cumulative incidence of 1.2% (95% confidence interval [CI], 0.8%-1.6%) in the first month. Thereafter, the rate of sudden cardiac death was constant at 1.2% per year.

**Intercurrent Events and Sudden Death**

Intercurrent cardiac events occurred frequently after MI (2080 of the 2997 patients, 69%). A total of 842 patients had recurrent ischemia alone, 365 had heart failure alone, and 873 had both events. Among the patients who experienced both events, the events occurred within 30 days of each other in 378 patients (43%). For recurrent ischemia, the 30-day cumulative incidence was 28% (95% CI, 26%-29%) and the 1-year cumulative incidence was 42% (95% CI, 41%-44%) (Figure 2). Beyond the first year after the MI, the cumulative incidence of recurrent ischemia exhibited a constant increase with a 5-year cumulative incidence of 56% (95% CI, 55%-58%). This equates to a yearly rate of recurrent ischemia of 3.5% beyond the first year after MI. Recurrent ischemia during follow-up was associated with an increased risk of sudden cardiac death (HR, 1.31 [95% CI, 1.01-1.71]; P = .04). After adjusting for baseline clinical characteristics (age, sex, year of MI, hypertension, diabetes mellitus,

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**Table 2. Observed Number of Sudden Cardiac Deaths After Myocardial Infarction (MI) Compared With the Numbers Expected in the General Population of Olmsted County, Minnesota**

<table>
<thead>
<tr>
<th>Time After MIa</th>
<th>Observed Sudden Deaths After MI, No.</th>
<th>Rate per Person-Year, %</th>
<th>Expected Sudden Deathsb</th>
<th>SMR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-30 d</td>
<td>35</td>
<td>14.8</td>
<td>8.4</td>
<td>4.18 (2.91-5.81)</td>
</tr>
<tr>
<td>1 y</td>
<td>59</td>
<td>2.2</td>
<td>89.4</td>
<td>0.66 (0.50-0.86)</td>
</tr>
<tr>
<td>2 y</td>
<td>30</td>
<td>1.3</td>
<td>73.5</td>
<td>0.41 (0.28-0.58)</td>
</tr>
<tr>
<td>3 y</td>
<td>29</td>
<td>1.5</td>
<td>65.9</td>
<td>0.44 (0.30-0.63)</td>
</tr>
<tr>
<td>4 y</td>
<td>21</td>
<td>1.2</td>
<td>59.6</td>
<td>0.35 (0.22-0.54)</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; SMR, standardized mortality ratio.

a Year intervals are every 365 days after the first 30 days.
b Age- and sex-matched population from Olmsted County. 

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**Figure 1. Cumulative Incidence of Sudden Cardiac Death and All-Cause Mortality After Myocardial Infarction Among Residents of Olmsted County, Minnesota**

The blue area on the plot represents the cumulative incidence of sudden death during the first 120 days after the index myocardial infarction.

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comorbidity, Killip class, reperfusion or revascularization, and heart failure after MI), the association between sudden cardiac death and recurrent ischemia was attenuated and became nonsignificant (HR, 1.26 [95% CI, 0.96-1.65]; P = .09) (Table 3).

For heart failure, the 30-day cumulative incidence was 26% (95% CI, 24%-27%) and at 5 years it was 38% (95% CI, 37%-40%) (Figure 2). This equates to a yearly heart failure rate of 2.4% beyond the first 30 days after MI. Heart failure exhibited a strong adverse association with sudden cardiac death (HR, 8.1 [95% CI, 6.2-10.6]; P < .001), which remained strong after adjustment for baseline clinical characteristics (age, sex, year of MI, hypertension, diabetes mellitus, comorbidity, Killip class, reperfusion or revascularization, and recurrent ischemia after MI) (HR, 4.20 [95% CI, 3.10-5.69]; P < .001) (Table 3). Expressed in terms of absolute risk and compared with patients who did not experience heart failure during follow-up, the absolute risk of sudden cardiac death for patients with heart failure was on average 2.5% (95% CI, 1.9%-3.1%; P < .001) higher in the first 30 days after MI, and in each year thereafter.

Given the aforementioned temporal decline in the risk of sudden cardiac death, we then examined the absolute risks of sudden cardiac death according to the presence or absence of heart failure by time. Considering 75-year-old patients experiencing an MI between 1979 and 1987 as an example, the absolute risk of sudden cardiac death for those with heart failure was 4.3% (95% CI, 3.6%-5.1%) within the first 30 days after MI and in each year thereafter compared with an absolute risk of sudden cardiac death of 1.9% (95% CI, 1.3%-2.4%) among those who did not experience heart failure. For 75-year-old patients experiencing an MI between 1988 and 1996, the absolute risk of sudden cardiac death was 3.7% (95% CI, 3.0%-4.4%) and 1.2% (95% CI, 0.7%-1.6%) for those experiencing and not experiencing heart failure, respectively. Finally, for 75-year-old patients experiencing an MI during the most recent period (1997-2005), the absolute risk of sudden cardiac death was 2.4% (95% CI, 1.7%-3.2%) and 0% (95% CI, 0.7%-0.6%) depending on the occurrence or nonoccurrence of heart failure, respectively.

Ancillary Analyses

For the 1204 MIs occurring between 1988 and 1998, left ventricular systolic function was assessed among 693 patients (58%) within 30 days after index MI. Of these, 337 patients (49%)
had left ventricular ejection fraction below 50%. When left ventricular ejection fraction was included in the multivariate analysis, there was no change in the association between sudden cardiac death and intercurrent cardiac events (recurrent ischemia HR, 1.60 [95% CI, 0.90-2.82]; P = .11 and heart failure HR, 3.64 [95% CI, 1.71-7.75]; P < .001). In particular, the strength of the association between heart failure and sudden cardiac death remained strong. Fifty patients had defibrillators implanted before their last follow-up date. All analyses were repeated while excluding these patients and yielded similar results.

COMMENT

The present data, which represent the experience of a large, community-based incidence cohort, indicate that the risk of sudden cardiac death after MI is the highest during the first month, when it markedly exceeds that noted in the general population. Thereafter, however, among 30-day survivors, the risk of sudden cardiac death declines markedly to 1.2% per year, lower than that expected in the general population. Furthermore, the risk of sudden cardiac death after MI has declined by more than 40% over the past quarter of a century, a decline that predates the widespread use of defibrillators but parallels drastic changes in medical therapy for acute MI, including reperfusion and secondary prevention. While the risk of sudden cardiac death beyond the first 30 days is low, it is markedly increased by the occurrence of heart failure during follow-up, which undercuts the importance of continued surveillance of patients after MI and the dynamic nature of risk stratification.

Sudden Death After MI

The rather sparse community data on the incidence of sudden cardiac death after MI largely predate the widespread use of evidence-based treatment for MI. In the Framingham Heart Study, the 5-year cumulative incidence of sudden cardiac death was approximately 7%, using a conservative definition of sudden cardiac death whereby only deaths within 1 hour of symptom onset were included. In the Multicenter Post Infarction Program, conducted in the 1980s, sudden cardiac deaths were more frequent (3.6% per year). More recently, in a cohort study of MI patients discharged from several Canadian medical centers, sudden cardiac death occurred at a rate of 1.9% per year, a figure consistent with the present data. On the other hand, sudden cardiac death after MI was less common (<1% per year) among patients discharged after optimal treatment, including revascularization and medical therapy, in single-center European studies. These differences across studies likely reflect multiple factors, including differences in definitions, differences in periods when studies were conducted, and differences between community experiences and single-center studies. Methodological issues notwithstanding, taken collectively, these reports indicate that beyond the first month after MI, sudden cardiac death is a rather infrequent albeit devastating complication. The present data augment previous reports by indicating that the risk of sudden cardiac death after MI has markedly declined over time and by providing a reference framework on the occurrence of sudden cardiac death among age- and sex-matched individuals from the same source population.

After the initial month after the MI event, the rate of sudden cardiac death becomes less than expected in the general population, most likely reflecting the well-known survivor bias effect, which is amplified as the duration of follow-up increases. With regard to the temporal decline in sudden cardiac death after MI, there was prior indirect evidence that this might be occurring. Indeed, whereas approximately 40% to 50% of all deaths after MI were due to sudden cardiac death in studies prior to the 1980s, this proportion has decreased to 20% to 30% in more contemporary cohorts including the present one. However, historical comparisons across cohorts are fraught with challenges because source populations often differ markedly, which can in turn explain differences in outcomes.

The present study, using the same population and robust, standardized methods of MI ascertainment, which have remained constant during the study period, directly demonstrates a profound reduction in the occurrence of sudden cardiac death after MI in a single population under rigorous surveillance. Importantly, the practice of implanting defibrillators is unlikely to have affected the present findings because their use was minimal in this cohort.

The risk of sudden cardiac death after MI is the highest during the first 30 days, as was underscored by data from theValsartan in Acute Myocardial Infarction Trial (VALIANT) and the Home Automated External Defibrillator Trial (HAT). Both of these trials focused on high-risk groups and indicated that the occurrence of sudden cardiac death among 30-day MI survivors was approximately 1% per year. The present community data extend these findings by indicating that in a community-based cohort, the risk of sudden cardiac death among all patients with MI is analogous to that of the highest risk groups in these trials, is highest early after the MI, and declines markedly thereafter. While these data may come across as seemingly at odds with the efficacy of ICD as reported in most randomized trials, interpreting the results of these trials is challenging as recently underscored.

Intercurrent Cardiac Events

Intercurrent cardiac events are common after MI and remain common even in contemporary cohorts. The frequent occurrence of heart failure is of particular concern given its adverse impact on the occurrence of sudden cardiac death, which is far greater than and independent of risk factors that can be measured at the time of the index MI. In a recent report from MADIT-II, participants randomized to ICD were studied to assess the effects of intercurrent cardiac events on appropriate ICD discharges for ventricular tachycardia or
fibrillation. After adjustment for numerous factors including left ventricular ejection fraction, New York Heart Association functional class, medications, and laboratory results, heart failure and recurrent ischemia were associated with a 2.5 and 1.5 times higher risk of device therapy, respectively. The findings presented herein support and amplify such previous reports by indicating that, in a community-based cohort, cardiac events during follow-up are associated with a marked increase in the risk of sudden cardiac death, particularly for heart failure, which increases the risk of sudden cardiac death by a factor of 4-fold. This increase in the risk related to the occurrence of heart failure cannot be fully interpreted without its integration within the appraisal of the absolute risk of sudden cardiac death, which is particularly high during the first month after MI. Indeed, understanding the excess risk conferred by heart failure requires integrating its relative risk with the absolute risk of the sudden cardiac death at a given point in time during follow-up. Thus, clinicians should be particularly concerned about the adverse impact of heart failure on sudden cardiac death when heart failure occurs early during follow-up.

Strengths and Limitations

The racial and ethnic composition of Olmsted County, Minnesota, may limit the generalization of these data to groups underrepresented in the population. While no single community can completely represent the nation as a whole, studies of chronic diseases in Olmsted County, Minnesota, indicate that results from the county can be extrapolated to a large part of the population. Left ventricular function was not uniformly assessed in all patients, consistent with current practice. However, an ancillary analysis restricted to persons with measurement of left ventricular function showed similar results.

Herein, we defined sudden cardiac death as out-of-hospital deaths whose primary cause of death was coronary heart disease. The validity of this method is quite robust for sudden cardiac death due to coronary disease occurring within 24 hours of symptom onset and this definition is analogous to that used by others. In our experience, using 1 hour as the time frame to determine the sudden nature of death could not be implemented with an acceptable level of accuracy. To the extent that individuals would have sought care prior to death, the presence of clinical, nonfatal conditions would have been taken into account in the analysis. It is conceivable that out-of-hospital deaths occurring after MI may be more likely to be coded as cardiac in origin. This limitation is shared by all studies addressing this subject. Importantly, the temporal trends in sudden cardiac death after MI are not affected by definitional issues because the definition of sudden cardiac death remained constant during the study period.

Our study also has a number of important strengths. The internal validity of the present data are quite robust because our ascertainment identified all consecutive incident MIs in the community evaluated according to rigorous validation criteria, which remained constant over time. Indeed, the present data represent the comprehensive experience of a community for more than 2 decades during a period that is minimally affected by the trials of defibrillator implant after MI, such that the present results are not influenced by this evolving practice. The availability of rich clinical follow-up for nonfatal clinical events that occur after the initial hospitalization is a distinct feature of the present community study because most other MI registries and surveillance studies seldom include clinical follow-up after hospitalization. This unique strength enabled us to integrate intermittent clinical events after MI in the prediction of sudden cardiac death, which has important direct clinical implications for risk stratification. Indeed, these data underscore the dynamic nature of risk stratification and the crucial importance of clinicians reassessing patients’ risks after MI if they develop heart failure. Finally, the innovative statistical methods applied herein, which build on extensive experience with survival analysis, allowed us to report on the absolute risk after MI, an important yet seldom reported element of risk stratification.

To this end, the present data document that in contemporary times, the risk of sudden cardiac death after MI in the absence of intercurrent heart failure is quite low, which can help in decision making for primary prevention of sudden cardiac death among patients after MI.

CONCLUSION

In the community, the risk of sudden cardiac death is the highest during the first month after MI when it markedly exceeds the rate in the general population. Among 30-day survivors, the risk of sudden cardiac death declines rapidly but it is markedly increased by the occurrence of heart failure during follow-up. This underscores the importance of continued surveillance of patients after MI and the dynamic nature of risk stratification. Moreover, the risk of sudden cardiac death after MI has declined substantially over the past quarter of a century before the widespread use of defibrillators, which underscores the importance of evidence-based therapy for acute MI including reperfusion and secondary prevention.

Author Contributions: Dr Roger had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Adabag, Roger.

Acquisition of data: Roger.

Analysis and interpretation of data: Adabag, Therneau, Gersh, Weston, Roger.

Drafting of the manuscript: Adabag, Roger.

Critical revision of the manuscript for important intellectual content: Adabag, Therneau, Gersh, Weston, Roger.

Statistical analysis: Therneau, Weston.

Obtained funding: Roger.

Study supervision: Adabag, Roger.

Financial Disclosures: None reported.

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