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Time-based risk assessment after myocardial infarction. Implications for timing of discharge and applications to medical decision-making

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KEYWORDS
Early discharge;
acute myocardial infarction;
survival modelling

Aims We evaluated timing of adverse cardiac events after thrombolysis to guide length of stay after ST-segment elevation myocardial infarction.
Methods and Results Kaplan–Meier survival curves described timing of major post-infarction complications in 41 021 fibrinolytic-treated patients in GUSTO-I. Using model-fitting, these data were best explained by a mixed-exponential survival model: an acute curve describing most adverse events and a chronic curve describing a lower background rate. We replicated this strategy in 15 059 fibrinolytic-treated patients in GUSTO-III. From the relation between time and events described by the model's acute curve in GUSTO-III, we proposed times for hospital discharge. The acute curve explained 97% of deaths and 68%–96% of various event composites. Of complications within 10 days, 90% of deaths and 70% of acute curve death, stroke, shock, heart failure, or reinfarction occurred by 24 h. By 2.7 days, 95% of deaths, stroke, shock, heart failure, or reinfarction occurred. Most major ventricular arrhythmias occurred within 24 h, after which the hazard curve was flat.
Conclusions Mixed-exponential survival modelling describes timing of post-infarction complications and supports discharge 4 days after uncomplicated infarction. Such time-based risk assessment could guide decision-making in other settings in which randomized studies are impractical.

Introduction

Driven by better understanding of the disease process, advances in medical and interventional therapy, improved outpatient rehabilitation strategies, and (most recently) economic pressures, length of stay after acute myocardial infarction (MI) has decreased dramatically over the last three decades.

Previous studies in a variety of clinical circumstances have shown a low short-term risk of adverse outcomes in patients without major clinical complications by 3–5 days after MI,[1–5] and we have recently shown that for patients with uncomplicated courses through 72 h, prolonging

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hospitalization is not cost-effective.[6] Yet concern remains over how much hospitalization after MI should be shortened. Large databases now exist that report not only the occurrence but also the timing of major complications after MI. We postulated that with statistical techniques, this information could be used for time-based risk assessment to help establish the optimal timing of discharge after MI.

Thus, we evaluated the use of statistical modelling strategies to describe the timing of major adverse cardiac events after acute MI in the Global Utilization of Streptokinase and TPA (alteplase) for Occluded coronary arteries (GUSTO-I) population. We then replicated this work in the more contemporary Global Use of Strategies To Open occluded coronary arteries (GUSTO-III) cohort. We describe our modelling and findings, the implications for timing of discharge after acute MI, and the potential applications of our approach to other time-dependent management decisions for which randomized comparisons of different strategies would be impractical.

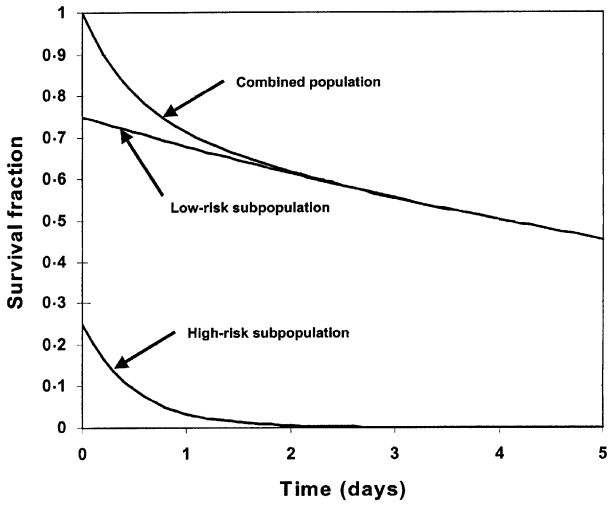

Figure 1 Hypothetical survival curves from two subpopulations (high-risk and low-risk) in a mixed-exponential survival model and the survival curve for the overall population (combined).

Methods

Study population

The 41 021 patients enrolled in GUSTO-I between 1990 and 1993 served as the population for development of our modelling strategy. Our modelling strategy was replicated in the study population of the more recent GUSTO-III trial (1995–1997), which is the focus of this report. The complete methods of both GUSTO-I and GUSTO-III have been described.[7,8] Briefly, GUSTO-I patients were randomized to one of four fibrinolytic strategies if they presented <6 h after symptom onset, met ECG inclusion criteria (≥0.1 mV ST-segment elevation in ≥2 limb leads or at ≥0.2 mV ST-segment elevation in ≥2 contiguous precordial leads), and had no contraindications to enrolment. In GUSTO-III, 15 059 patients meeting similar inclusion and exclusion criteria were randomly assigned in a 2:1 ratio to receive either reteplase or alteplase if they presented <6 h after symptom onset.

Data collection

In both studies, information on postinfarction complications and their timing was collected by case-report form. The date and time of events were collected for in-hospital death, shock, reinfarction, stroke, congestive heart failure (Killip class ≥II), and recurrent ischaemia. In addition, the date of death after discharge was collected to 30 days in both studies.

Statistical methods

Continuous variables were described by medians with 25th and 75th percentiles, and discrete variables by percentages. We first assessed the timing of adverse events after MI in GUSTO-I by generating a series of Kaplan–Meier survival curves. Each event was added sequentially to generate composites, as follows: death, stroke, shock, congestive heart failure, reinfarction, and recurrent ischaemia. If patients had more than one event, they were considered to have had the composite event of interest when the first event occurred.

To further explain the data in the Kaplan–Meier survival curves, we applied a model-fitting program (DISFIT, written in Microsoft Basic PDS 7.0 for PC).[9] The type of model best fitted to these survival data differs slightly from most standard survival models. Based on the appearance of the Kaplan–Meier curves, we assumed that there was a small subpopulation at high early (acute) risk and a larger subpopulation at significantly lower, more constant (chronic) risk. An example of a Kaplan–Meier curve reflecting overall population risk (combined population) and the survival curves for these two subpopulations (high-risk subpopulation and low-risk subpopulation) that together compose it are shown in Fig. 1. In this artificial example, we assumed that the first subpopulation represented 25% of the overall cohort, and the second, 75% of the cohort. We further assumed that the hazard curves for

these two subpopulations were approximately constant over the relatively short period to which the curves were fitted. This kind of combined survival curve, known as a mixed-exponential survival curve, has been used for failure-time data.[10,11] Note that we do not assume that we know the relative fractions of the two subpopulations; nor do we assume that we know to which subpopulation any particular patient belongs.

For our analysis, all of the parameters (subpopulation fractions and hazard rates) were estimated from the observed data using maximum-likelihood techniques. To assess the period during which most postinfarction complications occurred and the question of discharge timing is most critical, we modelled events during the first 10 days after infarction.

We replicated the modelling using the same process in the 15 059 patients in the more contemporary, GUSTO-III acute MI database. To propose timing for changes in intensity of care and discharge, we examined the relation between the occurrence of events in the high-risk subpopulation described by the acute curve of the mixed-exponential hazards model and time after MI in this population. After identifying a proposed time for discharge based on this modelling, we further investigated the predictors of 'late' deaths after this time point using logistic regression modelling incorporating both baseline characteristics and occurrence of the in-hospital complications evaluated in our time to events modelling. This model was developed in GUSTO-I and validated in GUSTO-III. The c-index was used to describe the model's ability to discriminate risk.

Results

Kaplan–Meier survival curves for death and composite events in GUSTO-I are displayed in Fig. 2. Each curve comprises three phases, an early high-risk period over the first 24–48 h, followed by a less steep decline in survival over the next 3–5 days, and a relatively flat later portion of the curve. The pattern of event timing was similar in GUSTO III. Most complications were slightly more frequent in GUSTO-III than in GUSTO-I, but overall, the median time to the event was similar or slightly shorter in most cases (Table 1). In both studies, events most likely to require urgent cardiac care, such as ventricular arrhythmias and shock, occurred earlier and less often than congestive heart failure or recurrent ischaemia. Figure 3 displays the hazard-function curve for ventricular tachycardia or fibrillation in the GUSTO-III population from the time of symptom onset. Most of the risk for major ventricular arrhythmias occurred during the first 24 h, after which the hazard curve was flat.

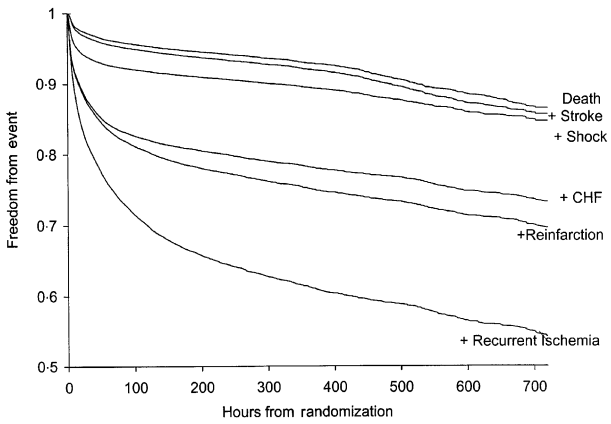

Figure 2 Kaplan–Meier survival curves for adverse events after acute MI in GUSTO-I. Each curve represents the composite of the listed event and the events listed above it.

Mixed-exponential hazards modelling

Mixed-exponential survival models were fit to the data describing the first 10 days of each Kaplan–Meier survival curve for GUSTO I. Figure 4(a) is representative and displays the results of fitting a mixed-exponential survival model to the data for the composite of all events in GUSTO-I. Similar results were obtained when mixed-exponential survival models were fit to the data in GUSTO-III. Figure 4(b) displays the results of fitting the mixed exponential survival curve to the data for the composite of all events. The 'chronic' curve of the model reflects the low, background event rate in most of the population (relatively flat curve and high survival), while the 'acute' curve describes the smaller subpopulation with a high early event rate (steep curve describing most early adverse events). As time from MI increased, the rate of events in the subpopulation described by the acute curve approached that of the chronic curve. The overall population risk (the 'combined' curve), which is a summation of the acute (early, high-risk) and chronic (low, background risk) event curves, is also shown.

The modelling strategy performed similarly in separating the events in GUSTO-I and GUSTO-III into acute and chronic components. Ninety-seven percent of deaths and most (74%–96%) of the other adverse-event composites in GUSTO-I were explained by the acute curve of the model compared with 97% of deaths and 68%–96% of other adverse-event composites in the GUSTO-III

Table 1 Incidence and timing of adverse events in GUSTO-I and GUSTO-III

	Event rate (%)		Time to event (h)	
	GUSTO-I	GUSTO-III	GUSTO-I	GUSTO-III
Death*	7.0	7.4	42 (9, 137)	37 (5, 139)
Stroke	1.4	1.7	27 (12, 92)	37 (5, 139)
Shock	6.0	4.6	8 (3, 33)	8 (4, 40)
Congestive heart failure	16.2	17.3	24 (5, 59)	29 (11, 68)
Reinfarction	4.0	4.2	89 (49, 146)	84 (38, 134)
Recurrent ischaemia	19.8	28.8	49 (15, 107)	24 (10, 73)
Ventricular tachycardia/fibrillation†	7.0	7.5	0 (0, 1)	0.21 (0.13, 1)

*Rate for death reflects 30-day follow-up; all other events were measured while in hospital. Times to adverse event are shown as medians (25th, 75th percentiles).
†Cardioversion or defibrillation used as a marker of major ventricular arrhythmia in GUSTO-I, median time in days.

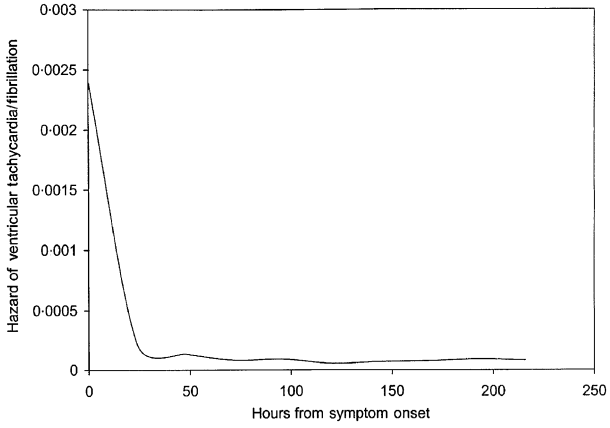

Figure 3 Hazard-function curve for ventricular tachycardia or fibrillation in 15 059 patients in GUSTO-III undergoing thrombolysis for acute MI.

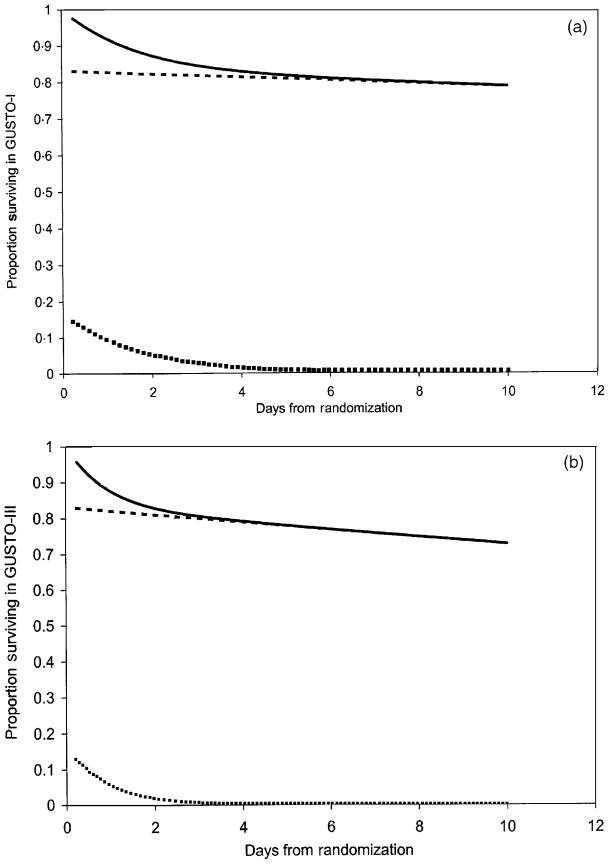

Figure 4 Mixed-exponential survival model for the composite of all events considered in the Kaplan–Meier analysis. Overall (combined) population (solid line) and for the acute (dotted line) and chronic models (broken line) for GUSTO-I (a) and GUSTO-III (b).

population. Recurrent ischaemia followed by heart failure contributed most significantly to the events explained by the chronic curve of the mixed-exponential models.

As previously reported, patients in GUSTO-III were slightly older (median 63 (53, 71) years vs 62 (52, 72) years), more often aged >75 years (13.6% vs 10.5%), more often female (27.4% vs 25.2%), and more likely to have anterior MI (47.5% vs 39.1%) compared with GUSTO-I patients.[8] Median length of stay in GUSTO-I was 9 (7, 13) days compared with 7 (5, 12) days in GUSTO-III.

Timing of events in the high-risk subpopulation (acute curve)

The timing of complications accounted for by the acute curve of the model only is shown for GUSTO-III in Table 2. By 24 h, 90% of deaths and 70% of death, stroke, shock, heart failure, or reinfarction described by the acute curve had occurred. Ninety-five percent of deaths had occurred by 1.4 days, and 95% of the composite of death, stroke, shock, heart failure, or reinfarction had occurred by 2.7 days. Reflecting the earlier occurrence of recurrent ischaemia in GUSTO-III, if recurrent ischaemia was

Table 2 Timing of adverse events explained by the acute curve of the GUSTO-III mixed-exponential survival model

Event(s)	% Acute curve*	Days until percentage of events had occurred									
		95%	90%	85%	80%	75%	70%	65%	60%	55%	50%
Death	97%	1.4	1.1	0.88	0.74	0.64	0.55	0.49	0.42	0.37	0.32
Death or stroke	96%	1.4	1.0	0.86	0.73	0.63	0.54	0.47	0.41	0.36	0.31
Death, stroke, or shock	95%	1.0	0.81	0.67	0.56	0.49	0.42	0.36	0.32	0.28	0.24
Death, stroke, shock, or CHF	84%	2.6	2.0	1.7	1.4	1.2	1.1	0.92	0.81	0.71	0.61
Death, stroke, shock, CHF, or reMI	83%	2.7	2.1	1.7	1.5	1.3	1.1	0.94	0.83	0.72	0.62
Death, stroke, shock, CHF, reMI, or ischaemia	68%	2.3	1.8	1.4	1.2	1.1	0.91	0.80	0.70	0.61	0.53

CHF = congestive heart failure; reMI = reinfarction.

*Percentage of events or event composites that are explained by the acute curve of the survival model.

Table 3 Predictors of 'late' (day 4 through day 30) mortality among survivors through day 3

	Degrees of freedom	Wald chi-square	*P*-value
Baseline characteristics			
Age			
Main effects	1	57.8	<0.0001
Main effects plus higher order terms	2	426.4	<0.0001
Killip class			
Main effects	1	17.4	<0.0001
Main effects plus higher order terms	2	46.4	<0.0001
Killip class×age	1	10.4	0.0012
Systolic blood pressure	2	9.9	0.007
Heart rate	2	52.2	<0.0001
Myocardial infarction location	2	35.2	<0.0001
Previous myocardial infarction	1	46.0	<0.0001
Previous bypass surgery	1	13.3	0.0003
Weight	2	6.6	0.0374
Hypertension	1	5.5	0.0187
Diabetes	1	22.5	<0.0001
In-hospital events			
Shock	1	315.4	<0.0001
Stroke	1	240.0	<0.0001
Congestive heart failure	1	55.1	<0.0001
Reinfarction	1	23.8	<0.0001
Recurrent ischaemia	1	5.5	0.019

considered a major post-infarction complication, patients were identified as complicated even sooner; 95% of the composite of all acute curve events including recurrent ischaemia had occurred by 2.3 days. The time to account for 95% of acute-curve deaths was shorter in GUSTO-III than in GUSTO-I (1.4 vs 2.5 days). A similar pattern was observed for other event composites.

Predictors of 'late' mortality

Using logistic regression modelling we determined the predictors of 'late' deaths (from 4 through 30 days) among patients surviving through 3 days. The variables associated with 'late' mortality in this cohort and their strengths of association are shown in Table 3. There was an interaction of age with Killip class, and considering the effect of age alone along with the effect of age in the interaction term, it was the strongest predictor of mortality from day 4 through day 30. The occurrence of all in-hospital complications that were considered in the time to events modelling that is presented above contributed significantly to the risk of 'late' deaths, although the effect of recurrent ischaemia was small compared with shock, stroke, congestive heart failure and reinfarction. Even after accounting for these factors, baseline characteristics such as infarct location and prior history of MI were strong predictors of 'late' mortality. The model c-index was 0.846 in the GUSTO-I development cohort and 0.839 in GUSTO III.

Discussion

Using statistical modelling techniques, we studied the relation between time after acute MI and the occurrence of major postinfarction complications. The mixed-exponential survival model separated acute events from those occurring at a constant background rate and best described the timing of major complications after MI. The modelling strategy described the survival data similarly in both the GUSTO-I and GUSTO-III populations, with the acute curve accounting for 97% of all deaths. The information arising from the application of the time-to-event modelling strategy in GUSTO-III supports observations suggesting that hospital stays of 3–4 days are sufficient to capture most patients at risk for major acute postinfarction complications. At a fairly constant rate over the 10 days that we modelled, a modest proportion of all adverse events (predominantly recurrent ischaemia or heart failure, but only 3% of deaths), were described by the chronic curve of our model. Since all of these events occurred in the hospital over 10 days, it suggests that some events may not

be preventable simply by extending hospital stays beyond 3 or 4 days in patients who are free of complications to that point.

Although a successful pilot has been performed,[1] an adequately powered, randomized trial of early discharge, which would provide the most stringent information about the safety of this practice from the standpoint of its impact on mortality, would be logistically complex due to large sample sizes required and other issues including method of randomization. Short of a randomized trial to assess the safety of early discharge strategies, our statistical approach provides a method to gain additional insight into the timing of major acute postinfarction complications from which to make such an assessment, and it supports and extends previous work.

In the 15 059 GUSTO-III patients, the incidence of life-threatening events in the high-risk subpopulation (accounting for 97% of all study deaths) fell rapidly over the first 24 h after MI, with a less-steep decline over the next 48 h. By day 3, 99% of all deaths in this group had occurred and over 95% of patients with a course complicated by any one event in a composite of major complications were identified. One would expect that at this point, prolonging hospitalization in uncomplicated patients would be unlikely to prevent major complications. Importantly, of the events explained by the chronic curve of the model (the lower-risk subpopulation) the majority were recurrent ischaemia and heart failure. Because the events (including death) in this population occur at a relatively constant rate over time in previously uncomplicated patients, it is unlikely that simply altering the timing of discharge would impact the occurrence of such events. Our assessment of predictors of 'late' (day 4 through day 30) deaths suggests that much of the risk for 'late' mortality is accounted for by early clinical complications. After accounting for the effects of these early complications, it appears that baseline characteristics such as age, history of prior infarction, and infarct location may help to further risk stratify for 'late' mortality among survivors of acute MI who are uncomplicated through 3 days.

Although overall complication rates were similar, and the acute curve of the mixed-exponential hazards model explained similar proportions of these events in the two populations, the time to postinfarction complications accounted for by the acute curve was generally about 1 day shorter in GUSTO-III than in GUSTO-I. The explanation for this observation is unclear from these databases but could relate to changes in practice that may lower the occurrence of later in-hospital events in those who do not succumb to early complications.

Another application of our modelling results to postinfarction care may be to guide timing of changes in the level or intensity of inpatient care. Most patients with acute MI are admitted to cardiac-care units (CCUs), which were created in 1962 with the recognition that early treatment of infarct-related dysrhythmias (particularly ventricular fibrillation) could improve survival.[12] Technological advances also have allowed the treatment of many other life-threatening early complications of acute MI (for example, shock) in CCUs. To maximize clinical and economic efficiency, however, patients could be transferred to less-intense care when the risk of major complications best managed in CCUs has fallen to an acceptable level.

In our analysis of GUSTO-III, 95% of patients with postinfarction courses complicated by death, stroke, or shock and 75% of those identified by a composite of postinfarction death, stroke, shock, heart failure, reinfarction, or recurrent ischaemia were accounted for by 24 h. Further, the hazard curve for major ventricular arrhythmias was flat within 24 h after MI. Although few would disagree that acute MI complicated by shock, stroke, or early reinfarction or recurrent ischaemia justifies CCU-level care, it is difficult to argue from these data that continuing such care beyond 24 h, if there have been no complications since presentation, would prevent these events. Thus, we propose that after uncomplicated MI, transfer from CCUs to lower-level care at 24 h is clinically reasonable for continued rhythm monitoring, observation for complications such as recurrent ischaemia, and for pre-discharge teaching and rehabilitation. Depending on capabilities and needs of the individual institution, this change in level of care may be virtual (such as a reduction in nurse to patient ratio) or involve physical transfer to a 'stepdown' unit or monitored ward setting.

A potential limitation of our study is that we had information on non-fatal complications only until the time of discharge. However, recent work by van der Vlugt and colleagues in an unselected MI population suggested that in uncomplicated patients who are actually discharged early, post-discharge complication rates are extremely low over the subsequent 7 days.[13] Given this finding, it is unlikely that prolonging stay would prevent such complications or that early discharge itself results in a substantial increase in events. In previous work, we have also shown that even if recurrent ischaemia (the most common post-infarction complication) were 30% more frequent because of

early discharge, only if the life-expectancy benefit from extending hospitalization another day increased by 2.1 times would keeping uncomplicated patients in the hospital to prevent such complications be cost-effective.[6]

Reasons other than patient safety and cost may also exist for prolonging hospital stay after uncomplicated myocardial infarction, not the least of which may include organizational issues at a given hospital. Facilities and services would have to be available to accomplish necessary care, teaching and risk stratification during shorter stays or to provide them as an outpatient. Further, patient and family satisfaction and comfort is clearly of concern to both physicians and patients. However, when Topol and colleagues explored the psychosocial ramifications of early discharge on patients and their families, they found no differences on pre-and post-discharge measures of psychosocial functioning (on day 3 pre-discharge and at 1 month) between the early (day 3) and conventional (day 7–10) discharge groups.[1] They also found that patients discharged early tended to return to work earlier.[1]

We evaluated the timing of events after ST-segment elevation MI in groups of patients randomized in clinical trials who underwent thrombolysis within 6 h after symptom onset. Our event timing results might not apply to patients treated by other means such as primary angioplasty or thrombolysis outside of clinical trials, or not treated with reperfusion therapy. However, previous studies across a spectrum of populations have found similar results with early discharge.[1–5,13] Further, the modelling technique we have described could be applied to acute MI cohorts from other trials, clinical practice registries, or administrative databases, to confirm that our findings are broadly applicable or, if not, to establish other criteria for discharge based on timing of complications specific to these populations.

In conclusion, although first developed to describe failure-time data for vacuum tubes,[10] we have shown that mixed-exponential hazards modelling can describe the timing of adverse cardiac events after acute MI. There appears to be a low background rate of complications that is unlikely to be affected by length of stay. By about 2 days, acute mortality approaches the background rate, and by day 3, most patients with any major acute complication are accounted for. These data further support a clinical rationale for hospital discharge by day 4 after acute MI, if patients have had no interim events. Application of such a continuous event-modelling strategy also could be informative in guiding or changing clinical practice in other areas as well.

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