

# Patient-Specific Predictions of Outcomes in Myocardial Infarction for Real-Time Emergency Use: A Thrombolytic Predictive Instrument

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**Background:** Thrombolytic therapy can be life-saving in patients with acute myocardial infarction. However, if given too late or insufficiently selectively, it may provide little benefit but still cause serious complications and incur substantial costs.

**Objective:** To develop a thrombolytic predictive instrument for real-time use in emergency medical service settings that could 1) identify patients likely to benefit from thrombolysis and 2) facilitate the earliest possible use of this therapy.

**Design:** Creation and validation of logistic regression-based predictive instruments based on secondary analysis of clinical data.

**Patients:** 4911 patients who had acute myocardial infarction and ST-segment elevation on electrocardiogram; 3483 received thrombolytic therapy.

**Measurements:** Data were obtained from 13 major clinical trials and registries and directly from medical records, including electrocardiograms obtained at presentation. Input variables include presenting clinical and electrocardiographic features; predictive models generate probabilities for acute (30-day) mortality *if* and *if not* treated with thrombolysis, 1-year mortality rates *if* and *if not* treated with thrombolysis, cardiac arrest *if* and *if not* treated with thrombolysis, thrombolysis-related intracranial hemorrhage, and thrombolysis-related major bleeding episode requiring transfusion. Together, these models constitute the thrombolytic predictive instrument.

**Results:** The predictive models generated the following mean predictions for patients in the Thrombolytic Predictive Instrument Database: 30-day mortality rate, 7.1%; 1-year mortality rate, 10.9%; rate of cardiac arrest, 3.7%; rate of thrombolysis-related intracranial hemorrhage, 0.6%; and rate of other thrombolysis-related major bleeding episodes, 5.0%. They discriminated well between persons having and those not having the predicted outcome; areas under the receiver-operating characteristic (ROC) curve were between 0.77 and 0.84 for the five outcomes. Calibration between each instrument's predicted and observed rates was excellent. Validation of the predictive instruments for 30-day and 1-year mortality, done on a separate test dataset, yielded areas under the ROC curve of 0.76 for each.

**Conclusions:** After the basic features of a clinical presentation are entered into a computerized electrocardiograph, the predictions of the thrombolytic predictive instrument can be printed on the electrocardiogram report. This decision aid may facilitate earlier and more appropriate

use of thrombolytic therapy in patients with acute myocardial infarction.

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Thrombolytic therapy for acute myocardial infarction has great potential for reducing this most common cause of death in the United States. However, the benefits of this therapy depend on treating appropriate candidates as early as possible. Beyond the early hours and in patients with very small or low-risk infarctions, thrombolytic treatment offers little likelihood of benefit yet still incurs the risk for complications and costs. Many patients who would benefit from thrombolysis are not being treated because they are not recognized as suitable candidates and because of the fear of complications. To broadly maximize the benefit of thrombolytic therapy, a real-time method is needed in the emergency clinical setting that 1) identifies patients most likely to benefit from thrombolytic therapy and 2) facilitates the earliest possible administration of this therapy.

Predictive instruments for acute cardiac ischemia have been developed to assist emergency department physicians in making admission decisions for the hospital and coronary care unit (1-4). These logistic regression predictive models use a patient's clinical and electrocardiographic characteristics at presentation to compute the probability of acute ischemia. Incorporated into a computerized electrocardiograph, the probability can be printed automatically on the electrocardiogram (3-5). Clinical trials have shown that this decision aid speeds (6) and improves the accuracy of (7) emergency department triage of patients presenting with chest pain or other symptoms that suggest cardiac ischemia. Thus, printing the probabilities of predictive instruments

See editorial comment on pp 565-567.

on electrocardiograms may be an effective way to provide decision support to physicians.

An electrocardiograph-based instrument that could provide emergency clinicians with real-time predictions of outcomes of thrombolytic therapy for acute infarction might also improve care. Unfortunately, the currently available predictive instrument for death from acute infarction (8) does not take into account the use of thrombolytic therapy, nor does it predict outcomes other than acute mortality.

The major purpose of our study was to create a thrombolytic predictive instrument that would predict, for an individual patient, the effect of thrombolysis on the likelihood of key clinical outcomes: acute mortality, long-term mortality, cardiac arrest, and serious complications of thrombolytic therapy (hemorrhagic stroke and major bleeding). Incorporating this model into a computerized electrocardiograph so that its predictions are automatically printed on the electrocardiogram could help physicians 1) identify the patients most likely to benefit from thrombolytic therapy and 2) facilitate their earliest possible treatment. A secondary purpose was to produce a "time-insensitive" predictive instrument (4, 8–10) that could provide risk-adjusted outcome predictions for retrospectively judging quality of care.

## Methods

Creation of the thrombolytic predictive instrument required component predictive instruments that would predict the probabilities of five outcomes for a given patient with ST-segment elevation of at least 1 mm (0.1 mV) in two or more leads on the electrocardiogram. These were 1) acute (30-day) mortality from acute infarction *if given* and *if not given* thrombolytic therapy; 2) long-term (1-year) mortality *if given* and *if not given* thrombolytic therapy; 3) cardiac arrest within 48 hours after the first electrocardiogram *if given* and *if not given* thrombolytic therapy; 4) intracranial hemorrhage as a complication, *if given* thrombolytic therapy; and 5) bleeding that necessitates transfusion, *if given* thrombolytic therapy. These models were constructed and tested in three phases.

### Phase One: Creation of the Thrombolytic Predictive Instrument Database

The Thrombolytic Predictive Instrument Database and its derivative development and validation data sets included the original data on patients with myocardial infarction from 13 clinical trials and registries (1, 2, 11–22). Individual studies contributed between 57 and 1387 patients each; together, they included 107 hospitals of all types throughout the United States and 4911 patients treated between 1976 and 1989 (91% were treated after 1980).

Because the individual trials and registries used different inclusion and exclusion criteria, we created uniform criteria for inclusion in the Thrombolytic Predictive Instrument Database. All trials of thrombolytic therapy used similar enrollment criteria, but registries and the acute ischemia predictive instrument trials used broader criteria. The database was restricted to persons who would have been prospectively included in the thrombolytic trials: Persons who were 75 years of age or younger, had onset of chest pain or other ischemic symptoms of acute ischemia within 9 hours of presentation, had systolic blood pressure of 190 mm Hg or less, had ST-segment elevation of 1 mm (0.1 mV) or more in at least two contiguous leads on electrocardiogram, and had no known contraindications to thrombolytic therapy. The steps involved in generating specific data sets for each component predictive instrument are shown in the **Appendix Figure**.

For all patients in the database, we obtained electrocardiograms from the time of first presentation and follow-up and uniformly coded them lead-by-lead by using standardized measurement criteria (23). Important missing data were obtained from original study and hospital records. Missing data on 30-day and 1-year mortality were obtained from the National Death Index. Original hospital records were reviewed for the data needed to confirm the intracranial hemorrhage and cardiac arrest component predictive instruments (11). For the data needed to create the intracranial hemorrhage, detailed medical record reviews were done for all 59 thrombolysis-treated patients who were designated by their original studies as having had a stroke and for 216 control patients, matched by hospital, who are described elsewhere (24). For the data needed to construct the cardiac arrest, medical records were reviewed for 428 patients recorded as having had a cardiac arrest and for 428 control patients matched by hospital. Medical records were available for 85% of these patients; data obtained from the medical records included presenting electrolyte concentrations; electrocardiogram details, including corrected QT intervals (25); details of any invasive procedures; and details of the possible cardiac arrest.

Finally, data from the participating studies were compared for consistency of known major effects on outcomes (11). One subset, the Duke Coronary Care Unit Database from the prethrombolytic era, had substantially sicker patients who were much more likely to have previously had infarctions; thus, this subset was not included in the final model development or in test sets.

Before the mortality models were constructed, the database was randomly divided into a development data set, which consisted of two thirds of all patients ( $n = 3263$ ), and a test data set, which con-

sisted of the remaining one third ( $n = 1648$ ). Patients were randomly assigned to one data set or the other; stratification was done on study of origin to ensure that similar proportions of patients from the contributing studies were assigned to the development and test sets. For the cardiac arrest, intracranial hemorrhage, and major bleeding models, all patients were used for development.

### Phase Two: Construction of the Thrombolytic Predictive Instrument

A separate predictive instrument, each designed to be a component of the thrombolytic predictive instrument, was developed for each of the five outcomes by using logistic regression. For each component predictive instrument, we selected a subset of clinically important and statistically significant variables for inclusion in preliminary regression models. We then investigated alternative forms and combinations of these variables, reformulating models to optimize performance while keeping the models as parsimonious as possible.

In this process, we created two special electrocardiogram-based variables to reflect two key determinants of the effect of thrombolytic therapy on outcome: a measure of acute infarction size based on ST segments and an indicator of "earliness" in the course of the acute infarction, based on T-wave changes (Appendices A and B).

The logistic model for the 30-day mortality instrument was constructed on 1568 patients, 1224 of whom received thrombolytic therapy (**Appendix Figure, panel A**). The 1-year mortality instrument was based on the 1237 patients (894 of whom received thrombolytic therapy) for whom 1-year follow-up information was available (**Appendix Figure, panel B**). Patients who died during their index hospitalization were classified as dead at 30 days, even if their hospital stay was longer than 30 days.

The model for the cardiac arrest component predictive instrument was based on 296 patients, 61 of whom had confirmed primary cardiac arrests (defined as sudden loss of consciousness associated with ventricular tachycardia or fibrillation requiring cardioversion or cardiopulmonary resuscitation within 48 hours of admission) and 221 of whom received thrombolytic therapy (**Appendix Figure, panel C**). Patients originally considered to have possibly had a cardiac arrest were excluded if the cardiac arrest was thought to have occurred before admission, after coronary artery bypass surgery, after progressive hemodynamic deterioration of more than 1 hour or presentation while in cardiogenic shock (Killip class IV), or during catheter manipulations associated with cardiac catheterization or if the cardiac arrest was not confirmed upon record review. Control pa-

tients were excluded because of missing data or failure to satisfy inclusion criteria.

The thrombolysis-related intracranial hemorrhage component predictive instrument was based on 190 patients (18 with intracranial hemorrhage) (24) (**Appendix Figure, panel D**). Patients who had a history of stroke, seizure, or recent head trauma or had systolic blood pressure greater than 190 mm Hg were not used for modeling.

The thrombolysis-related major (transfusion-requiring) bleed component predictive instrument was based on 740 patients for whom sufficient detail of predictors and outcomes of bleeding was available (74% of these patients underwent coronary angiography), 55 of whom received a transfusion within 72 hours of arrival at the emergency department (**Appendix Figure, panel E**). Patients who underwent coronary artery bypass surgery or had intracranial bleeding episodes were excluded.

### Phase Three: Validation of Mortality Predictive Instruments on the Test Data Set

After they were developed, the 30-day and the 1-year mortality component predictive instruments were tested on the subset of the database set aside for this purpose before model construction.

### Statistical Analysis

Logistic regression models were constructed by using SAS software (26); nonlinear terms and interactions were investigated by generalized additive spline models in S-PLUS (27, 28). The significance of individual variables in the final logistic regression model was based on the Wald statistic (two-sided).

The performance of component predictive instruments was evaluated by the area under the receiver-operating characteristic (ROC) curve (29) (a measure of a prediction's diagnostic performance over its entire 0% to 100% range) and calibration (the match of predicted and observed outcomes calculated across groups with different likelihoods of the outcomes, using deciles [mortality and bleed models] or quartiles [intracranial hemorrhage and cardiac arrest] of predicted risk).

Because some persons who received thrombolytic therapy had their cardiac arrest before they received the treatment, standard logistic regression (which does not account for time-related changes in risk during the prediction period) was not appropriate for the cardiac arrest component predictive instrument. We therefore used pooled logistic regression (30) instead, dividing the 48-hour time-at-risk into nine intervals and then computing for each patient the total risk based on the nine interval-specific probabilities for cardiac arrest generated by logistic regression (31). The effect of thrombolytic therapy was thereby assigned only to intervals during or after



**Table 1. Characteristics of Patients in the Thrombolytic Predictive Instrument Database\***

	All Patients in TPI Database (n = 4911)	Patients in TPI Database without Pre-1985 Duke Database (n = 4232)	Patients Used in Model Construction† (n = 2525)
Median patient age, y	58	58	58
Patients > 75 years of age, %	3.3	2.2	0.0
Patients with a history of myocardial infarction, %	20.3	18.8	17.0
Patients with a history of hypertension, %	43.3	41.6	40.6
Patients with a history of diabetes, %	16.1	15.6	14.7
Median time from onset of chest pain to treatment, h	2.9	2.9	2.9
Median systolic blood pressure, mm Hg	130	130	130
Patients with systolic blood pressure > 190 mm Hg, %	2.3	2.0	0.0
Patients with systolic blood pressure < 100 mm Hg, %	8.5	8.5	7.3
Median leads with contiguous ST-segment elevation, n	3	3	4
Patients with no significant ST-segment elevation, %	7.5	7.2	<0.1
Patients with significant anterior ST-segment elevation, %‡	43.7	40.3	42.7
Patients with significant inferior ST-segment elevation, %‡	51.6	54.4	59.2

\* TPI = thrombolytic predictive instrument.

† Includes patients used in the construction of any component predictive instrument.

‡ Because patients may have had both anterior and inferior leads with ST-segment elevation, percentages may add up to more than 100.

treatment was given. Like a Cox proportional hazards model with a time-dependent covariate, the cumulative probability of cardiac arrest was computed by combining the interval-specific probabilities. For this model, area under the ROC curve and calibration were based on the interval-specific probabilities.

Because the component predictive instruments for cardiac arrest, intracranial hemorrhage, and bleeding complications were created on special subsets of the Thrombolytic Predictive Instrument Database, their regression constants (intercepts) were adjusted so that the average of the corrected predicted probabilities equaled the incidences of these events among all patients in the full database: 0.6% for intracranial hemorrhage, 5.0% for major bleeding complication, and 4.5% for cardiac arrest among control patients. We made the standard assumption that the model was otherwise unchanged by the case-control sampling. For calibration of these models, however, we compared the observed incidence rates in the case-control sample to the unadjusted predicted probabilities.

## Results

The overall Thrombolytic Predictive Instrument Database had 4911 patients, of whom 3483 (71%) received thrombolytic therapy. The characteristics of these patients at presentation are shown in **Table 1**. Of the 2525 patients used in model development, the median age was 58 years, 17% had previously had an infarction, 42.7% presented with acute anterior or anterolateral infarction (ST-segment elevation in at least two contiguous leads among V1 through V6), and 59.2% presented with inferior infarction (ST-segment elevation in at least two contiguous nonanterior leads).

The formulas and variable definitions for each thrombolytic predictive instrument component pre-

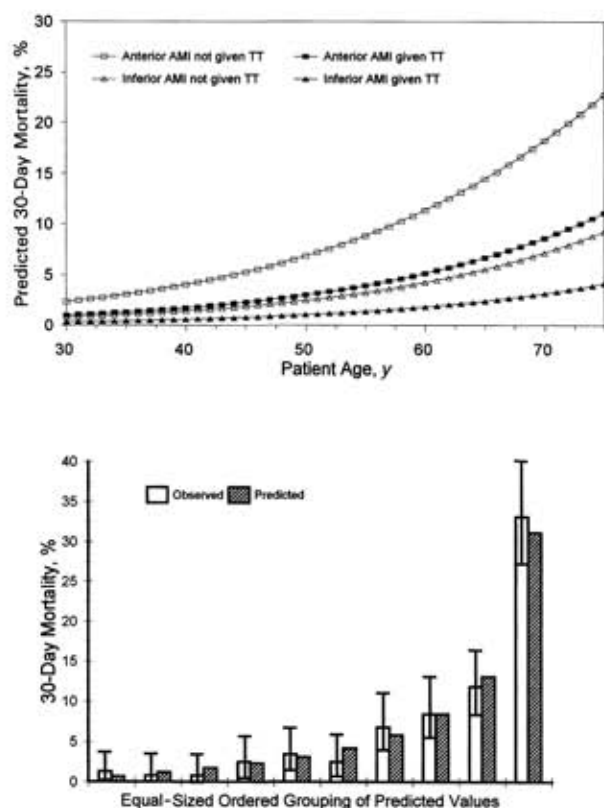
dictive instrument are shown in Appendices A and B; their clinical variables are described below.

## Description and Performance of Component Predictive Instruments

### Acute 30-Day Mortality Component Predictive Instrument

The acute (30-day) mortality component predictive instrument was based on 10 presenting variables: 1) age; 2) history of diabetes; 3) systolic blood pressure conditioned on the infarction location; 4) heart rate; 5) location of the acute infarction; 6) size of the acute infarction on electrocardiogram, measured by number of leads and degree of ST-segment elevation (Appendices A and B); 7) the number of contiguous leads with abnormal Q waves (in patients with nonanterior infarction) (32) without significant ST-segment elevation; 8) right bundle-branch block; 9) systolic blood pressure; and 10) the use of thrombolytic therapy conditioned on an electrocardiogram-based infarction Earliness Index (Appendices A and B) combined with time since onset of ischemic symptoms.

The probability of dying calculated by the acute mortality component predictive instrument varied depending on the patient's characteristics. The top panel of **Figure 1** shows that anterior infarction, increasing age, and not using thrombolytic therapy were all associated with increased risk for death within 30 days. Among Thrombolytic Predictive Instrument Database patients, predicted probabilities of dying within 30 days ranged from 0.2% to 80.4%. The mean  $\pm$  SD was  $7.1\% \pm 9.7\%$ . For patients who were given thrombolytic therapy, the mean probability was  $6.2\% \pm 8.6\%$ ; for those who were not given thrombolytic therapy, the probability was  $10.6\% \pm 12.1\%$ . The area under the ROC curve was 0.84 on the development set and 0.76 on the test data set. The lower value on the test data set



**Figure 1. Acute (30-day) mortality.** **Top.** The thrombolytic predictive instrument's predicted probability of 30-day mortality by patient age. The example is for a man with an initial systolic blood pressure of 130 mm Hg, a heart rate of 70 beats/min, no history of diabetes, one lead with abnormal Q waves, 60% of leads with early changes, and an infarction size of 20 for an anterior acute myocardial infarction (AMI) and 5 for an inferior AMI. TT = thrombolytic therapy. **Bottom.** Predicted and actual 30-day mortality rates. Mortality rates as predicted by the 30-day mortality component predictive instrument and the actual mortality rates, in deciles of ascending severity of illness (risk for dying), are depicted on the combined development and test data sets ( $n = 2369$ ).

seemed to result from the presence of lower risk among patients with increasing age and lower initial systolic blood pressure. Final model coefficients (Appendices A and B) were derived on the combined development and test data sets ( $n = 2369$ ). The calibration curve in the bottom panel of Figure 1 shows the match between predicted and actual 30-day mortality rates across the entire range of infarction severity. On the combined dataset, the area under the ROC curve for this model was 0.82 (95% CI, 0.78 to 0.86).

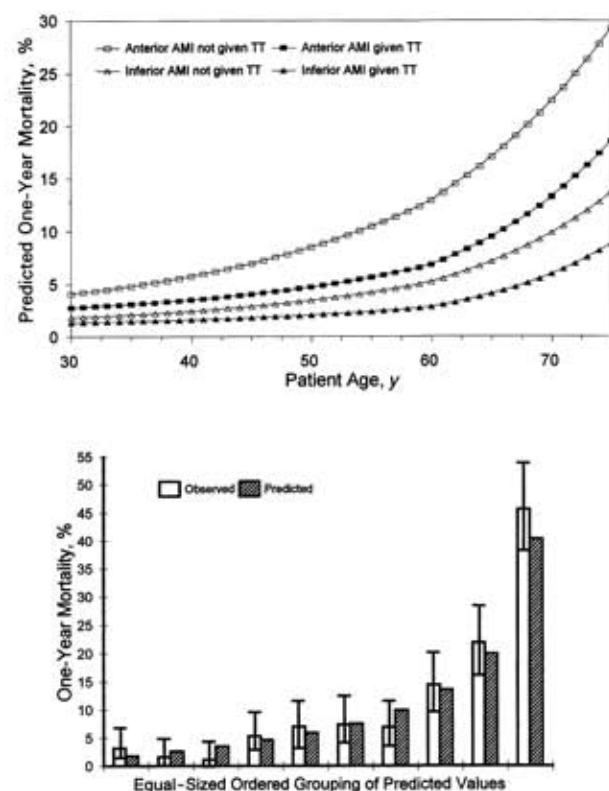
#### One-Year Mortality Component Predictive Instrument

The predictions of the 1-year mortality component predictive instrument are based on combining the predictions of the 30-day mortality model for month 1 of the year with the predictions of a "post-30-day" model that reflects mortality in months 2 through 12. The post-30-day model is based on five presenting clinical variables: age, heart rate, anterior location of the acute infarction, number of electrocardiogram leads with abnormal Q waves, and right bundle-branch block.

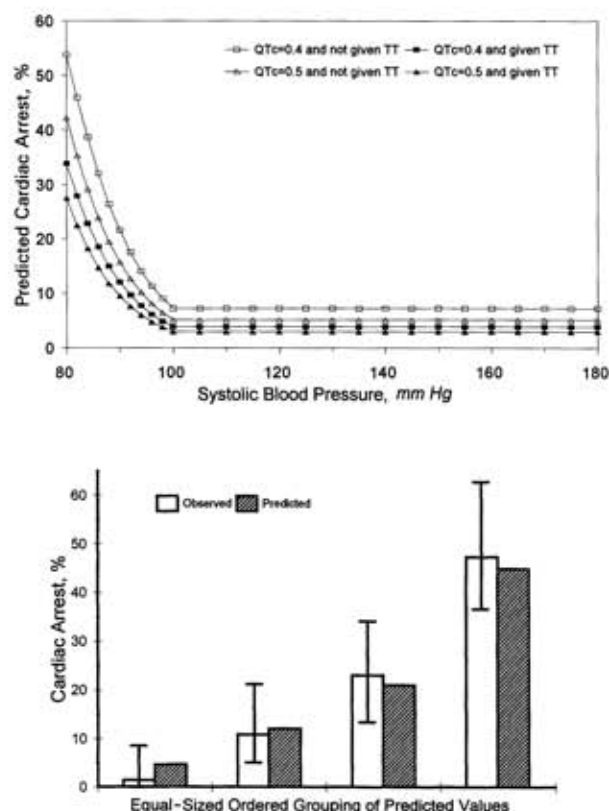
The top panel of Figure 2 shows the predicted risk for death within 1 year, related to patient age, infarction location, and use of thrombolytic therapy. Predicted 1-year mortality for the Thrombolytic Predictive Instrument Database patients ranged from 1.2% to 86.9%. The mean predicted 1-year mortality rate was  $10.9\% \pm 12\%$ ; for patients who were given thrombolytic therapy, the rate was  $9.5\% \pm 10.5\%$ ; and for patients who were not given thrombolytic therapy, the rate was  $14.7\% \pm 14.6\%$ . Calibration is shown in the bottom panel of Figure 2. The area under the ROC curve was 0.82 on the development set, 0.76 on the test data set, and 0.80 (CI, 0.76 to 0.83) on the combined data sets.

#### Cardiac Arrest Component Predictive Instrument

The cardiac arrest component predictive instrument was based on 1) variables representing nine distinct time intervals since the onset of chest pain, 2) age, 3) systolic blood pressure, 4) electrocardiogram-based size of infarction (slightly different from that in the mortality models), 5) sum of ST-segment elevation, 6) corrected QT interval, and 7) use of



**Figure 2. Long-term (1-year) mortality.** **Top.** The thrombolytic predictive instrument's predicted probability of 1-year mortality by patient age. The example is for a man with an initial systolic blood pressure of 130 mm Hg, a heart rate of 70 beats/min, no history of diabetes, one lead with abnormal Q waves, 60% of leads with early changes, and an infarction size of 20 for an anterior acute myocardial infarction (AMI) and 5 for an inferior AMI. TT = thrombolytic therapy. **Bottom.** Predicted and actual 1-year mortality rates. Mortality rates as predicted by the 1-year mortality component predictive instrument and the actual mortality rates, in deciles of ascending severity of illness (risk for dying), are depicted on the combined development and test data sets ( $n = 1878$ ).



**Figure 3. Cardiac arrest.** **Top.** The thrombolytic predictive instrument's predicted probability of cardiac arrest by systolic blood pressure. The example is for a baseline set of characteristics for a 65-year-old patient with 1 hour of chest pain, 8 mm of ST-segment elevation, and an infarction size of 10. TT = thrombolytic therapy. **Bottom.** Predicted and actual cardiac arrest rates. Cardiac arrest rates as predicted by the cardiac arrest component predictive instrument and the actual cardiac arrest rates, in quartiles of ascending severity of illness, are depicted. These rates are not the prevalence-adjusted rates but are on a scale of prevalence observed among the patients in the model construction data set (61 patients with a cardiac arrest among 296 total patients [20.6%]).

thrombolytic therapy. The effects of corrected QT interval and ST-segment elevation varied in time from symptom onset.

The top panel of **Figure 3** shows the predicted impact of thrombolytic therapy on cardiac arrest during the first 48 hours after presentation. The predicted probabilities for cardiac arrest in Thrombolytic Predictive Instrument Database patients ranged from 0% to 53%. The mean probabilities were  $3.7\% \pm 4.8\%$  overall,  $2.9\% \pm 2.9\%$  for patients receiving thrombolytic therapy,  $5.4\% \pm 7.2\%$  for patients who did not receive thrombolytic therapy (including intended recipients of thrombolytic therapy who had cardiac arrest before it was given), and  $4.5\% \pm 7.1\%$  for patients for whom thrombolytic therapy was never intended. Calibration is shown in the bottom panel of **Figure 3**. The area under the ROC curve on the development set was 0.77 (CI, 0.69 to 0.85).

#### Thrombolysis-Related Intracranial Hemorrhage Component Predictive Instrument

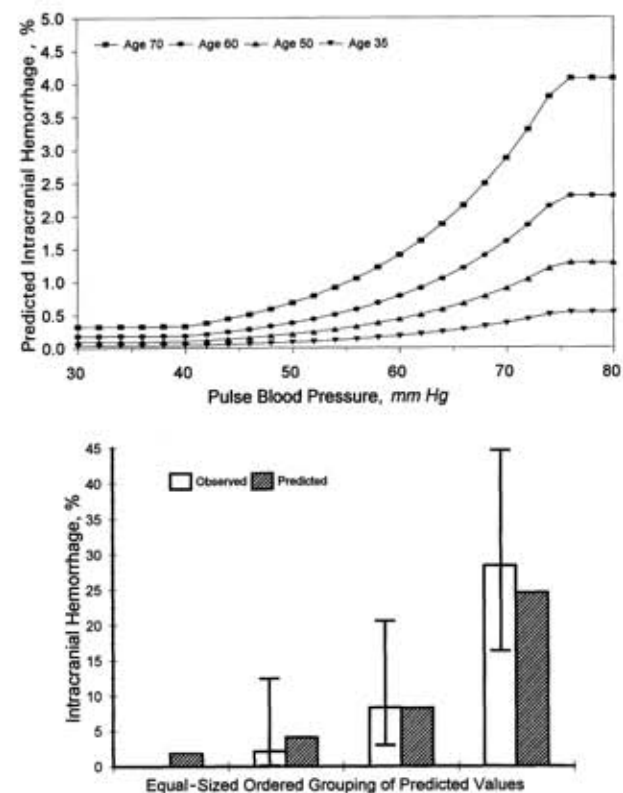
The thrombolysis-related intracranial hemorrhage

component predictive instrument was developed by using age and excess pulse pressure (defined as the amount by which the pulse pressure [systolic pressure minus diastolic pressure] exceeds 40 mm Hg for patients with systolic blood pressures greater than 120 mm Hg) (24). Because data were sparse for patients with very high blood pressures, excess pulse pressure was truncated at 35 in the model.

Shown in the top panel of **Figure 4**, this instrument predicts increasing risk for thrombolysis-related intracranial hemorrhage for patients with pulse pressures greater than 40 mm Hg, especially those with advancing age. Predicted risk for thrombolysis-related intracranial hemorrhage among treated Thrombolytic Predictive Instrument Database patients ranged from 0% to 4.4% (mean,  $0.6\% \pm 0.8\%$ ). Calibration is shown in the bottom panel of **Figure 4**; the area under the ROC curve on the development set was 0.82 (CI, 0.68 to 0.96).

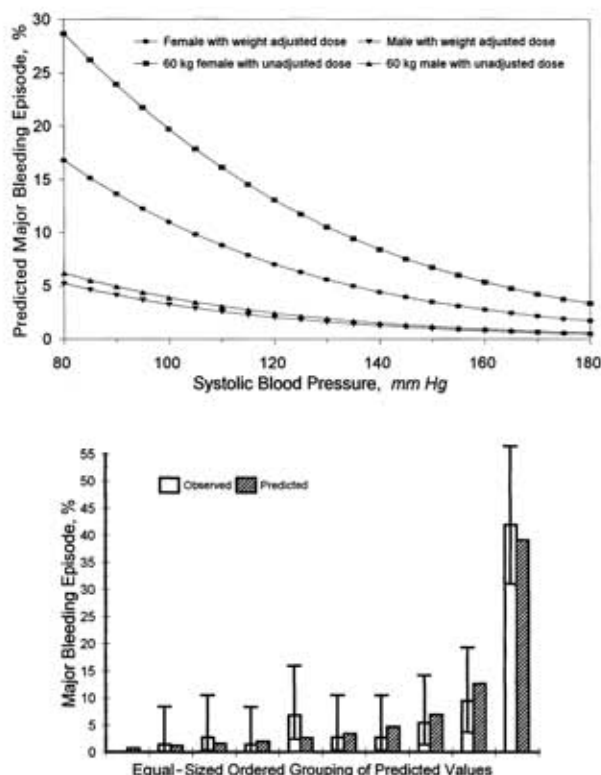
#### Thrombolysis-Related Major Bleed Component Predictive Instrument

The thrombolysis-related major (transfusion-requiring) bleed component predictive instrument



**Figure 4. Intracranial hemorrhage.** **Top.** The thrombolytic predictive instrument's predicted probability of intracranial hemorrhage by pulse pressure. The example is for patients with a systolic blood pressure of 140 mm Hg or more. **Bottom.** Predicted and actual intracranial hemorrhage rates. Intracranial hemorrhage rates as predicted by the intracranial hemorrhage component predictive instrument and the actual intracranial hemorrhage rates, in quartiles of ascending severity of illness, are depicted. These rates are not the prevalence-adjusted rates but are on a scale of prevalence observed among the patients in the model construction data set (18 patients with an intracranial hemorrhage among 190 patients [9.5%]).





**Figure 5. Major bleeding.** **Top.** The thrombolytic predictive instrument's predicted probability of major bleeding by systolic blood pressure. The predicted probabilities for a major nonintracranial bleeding episode requiring a transfusion are for a 50-year-old patient with a heart rate of 90 beats/min and no history of hypertension. **Bottom.** Predicted and actual rates of major bleeding. Rates of bleeding that require transfusion, as predicted by the major bleed component predictive instrument, and the actual rate of bleeding requiring transfusion, in deciles of ascending severity of illness, are depicted. These rates are not the prevalence-adjusted rates but are on a scale of prevalence observed among the patients in the model construction data set (55 patients with a major systemic bleeding episode among 740 patients [7.4%]).

was developed by using age, sex, history of hypertension, dose of thrombolytic therapy adjusted by weight, systolic blood pressure, an interaction of sex with adjusted dose of thrombolytic therapy, and an interaction of low heart rate with low systolic blood pressure.

Shown in the top panel of **Figure 5**, this component predictive instrument computed risks for major bleeding that were higher for women than men and (for those who weighed < 70 kg) were higher with a standard dose of the thrombolytic agent than with a weight-adjusted dose. Predicted probabilities for major bleeding among treated Thrombolytic Predictive Instrument Database patients ranged from 0.1% to 87.8% (mean,  $5.0\% \pm 9.4\%$ ). Calibration is shown in the bottom panel of **Figure 5**. The area under the ROC curve on the development set was 0.83 (CI, 0.75 to 0.91).

#### Application of the Thrombolytic Predictive Instrument: Case Examples

The combined presentation of the component predictive instruments, as intended for clinical use on electrocardiograms, is shown in **Figure 6**.

The electrocardiogram in the top panel of **Figure 6** shows predictions for a 57-year-old man who presented to the emergency department 2 hours after the onset of chest pain with a blood pressure of 156/88 mm Hg, a history of diabetes and hypertension, and ST-segment elevation. The specific values of these and other thrombolytic predictive instrument variables, and the resulting predictions, are printed on the electrocardiogram header. The model predicts that thrombolysis will reduce the probabilities of acute mortality (from 9.3% to 4.5%, largely because the infarction is anterior and was caught relatively early in its course), 1-year mortality, and cardiac arrest. Despite the higher-than-average probability of thrombolysis-related stroke (1.2%, related to the hypertension and high pulse pressure), the greater projected benefits might encourage the clinician, in the absence of other countervailing factors, to promptly use thrombolytic therapy. In addition, these predictions could be used to help inform the patient of the potential benefits and risks of treatment.

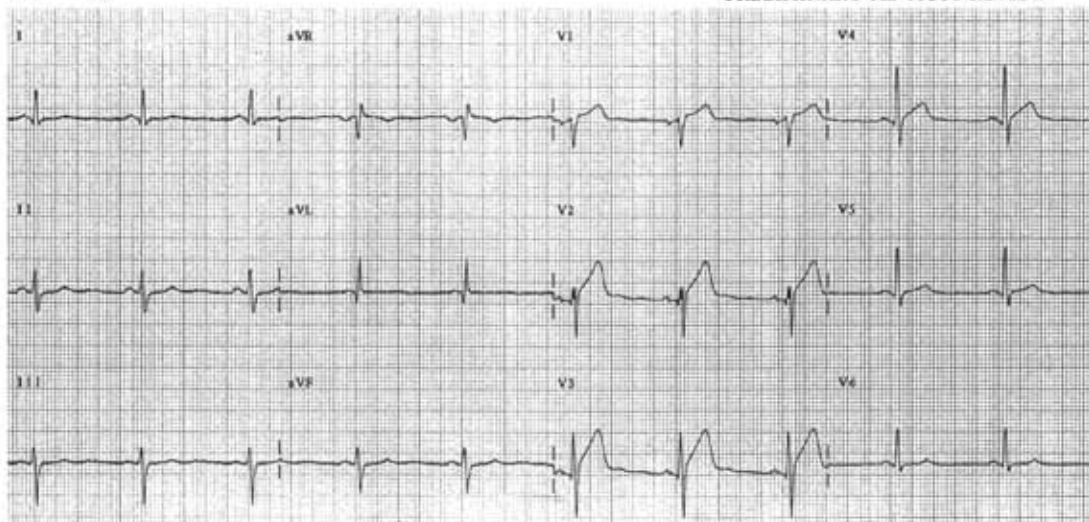
The bottom panel of **Figure 6** shows the electrocardiogram of a woman with a smaller infarction who presented later in the course of that infarction. The predicted probabilities of death and cardiac arrest are not greatly improved by thrombolytic therapy compared with the increased probabilities of serious bleeding complications. Thus, in the absence of other compelling factors, the output of the thrombolytic predictive instrument might influence the clinician to not treat the patient with thrombolysis. Again, information given to the patient about treatment options might be enhanced by the availability of these predictions.

#### Discussion

The thrombolytic predictive instrument provides specific predictions of the benefit that a presenting patient will receive from thrombolysis; these predictions are based on reductions in risks for acute (30-day) mortality, long-term (1-year) mortality, and cardiac arrest. It simultaneously provides predictions of risks for complicating intracranial hemorrhage and other major bleeding in treated patients. Intended for incorporation into a conventional computerized electrocardiograph when the electrocardiograph detects significant ST-segment elevation, the predictions are computed and printed on the electrocardiogram header (**Figure 6**). The thrombolytic predictive instrument could be used not only in the emergency department but also in prehospital emergency medical service settings through the transmission of full electrocardiograms (including text headers) by cellular and regular telephones. Like earlier predictive instruments (2, 4, 8, 9), it

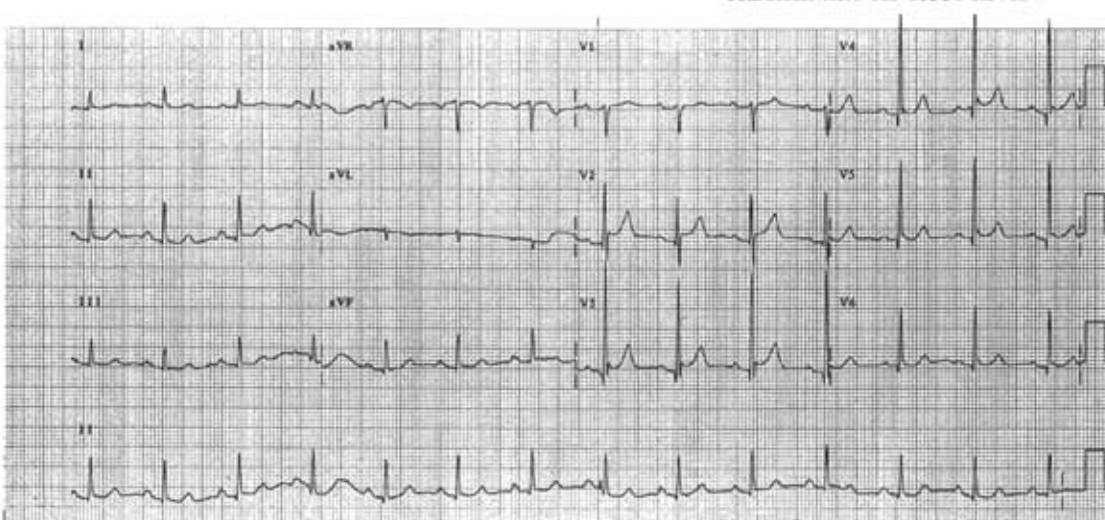
1223246      11/15/1995      01:39:47      JOHN DOE      76 kg      BP:156/88  
 57 years      Male      Time since acute ischemic symptom: 2 Hrs (120 Min)  
 Hx: Diabetes, Hypertension

Rate 60      Acute Anterior MI; ST  $\geq$  0.1mV in 4 of V1-4; Abnormal Qs in 4 Lead(s)  
 PR 130      >> MD NOTE: Use predictions ONLY if MD-diagnosed acute MI with 0.1mV ST elev <<  
 QRSD 94      THROMBOLYTIC PREDICTIVE INSTRUMENT (TPI)  
 QT 351      TPI PREDICTED OUTCOMES:      WITHOUT / WITH THROMBOLYSIS  
 Qtc 351      30-Day Mortality      9.5% / 4.3%  
 One-Year Mortality      11.7% / 6.5%  
 Cardiac Arrest Probability Within 48 Hrs      5.1% / 3.3%  
 Thrombolysis-Related Intracranial Hemorrhage      1.2%  
 Thrombolysis-Related Other Major Bleed      1.3% (with std dose)  
 --AXIS--  
 P 51      MD NOTE: Consider above in context of patient contraindications to thrombolysis.  
 QRS -36      PRELIMINARY-MD MUST REVIEW  
 T 57



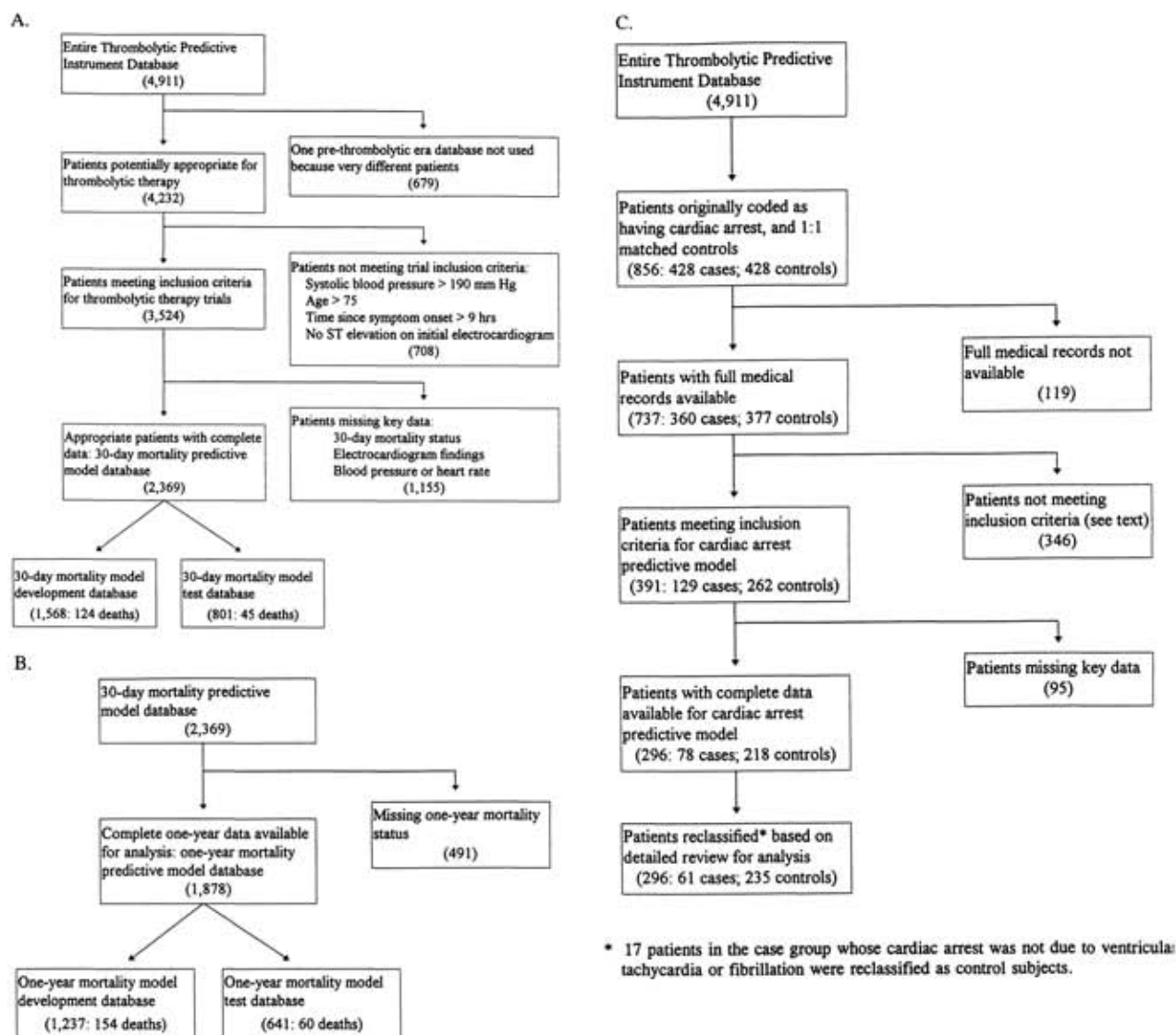
23440      05/31/1996      19:37:08      JANE DOE      66 kg      BP:160/95  
 73 years      Female      Time since acute ischemic symptom: 4 Hrs (240 Min)  
 Hx: Hypertension

Rate 81      POSSIBLE Acute Anterior MI; ST elevation in 3 of V1-4  
 PR 194      >> MD NOTE: Use predictions ONLY if MD-diagnosed acute MI with 0.1mV ST elev <<  
 QRSD 86      THROMBOLYTIC PREDICTIVE INSTRUMENT (TPI)  
 QT 337      TPI PREDICTED OUTCOMES:      WITHOUT / WITH THROMBOLYSIS  
 Qtc 391      30-Day Mortality      6.8% / 5.2%  
 One-Year Mortality      18.9% / 17.5%  
 Cardiac Arrest Probability Within 48 Hrs      5.1% / 1.0%  
 Thrombolysis-Related Intracranial Hemorrhage      2.4%  
 Thrombolysis-Related Other Major Bleed      9.9% (with std dose)  
 --AXIS--  
 P 54      MD NOTE: Consider above in context of patient contraindications to thrombolysis.  
 QRS 64      PRELIMINARY-MD MUST REVIEW  
 T 60



**Figure 6. Thrombolytic predictive instrument electrocardiograms.** Top. Example of a thrombolytic predictive instrument electrocardiogram for a patient likely to benefit from thrombolytic therapy. Bottom. Example of a thrombolytic predictive instrument electrocardiogram for a patient less clearly likely to benefit from thrombolytic therapy. MI = myocardial infarction.



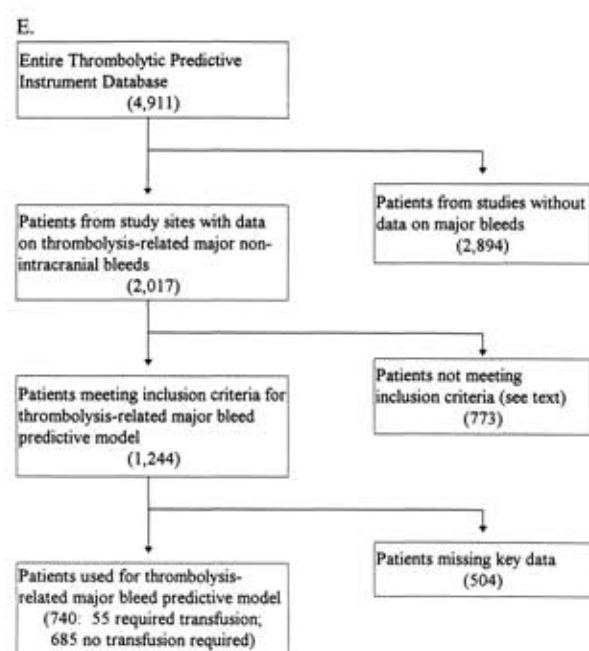
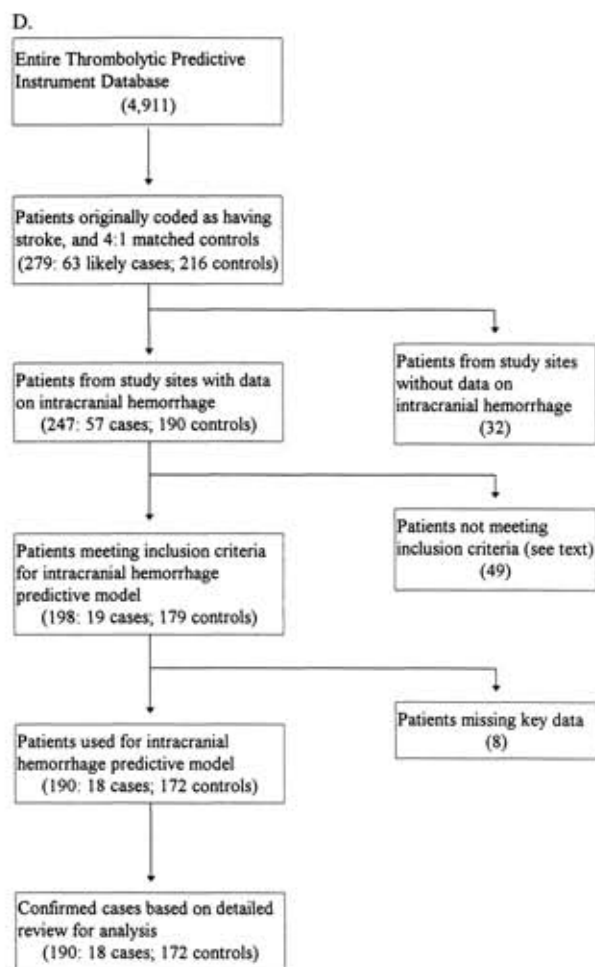


**Appendix Figure. Generation of the database used for constructing and testing predictive instruments. A.** Component predictive instrument for 30-day mortality. **B.** Component predictive instrument for 1-year mortality. **C.** Component predictive instrument for cardiac arrest. **D.** Component predictive instrument for thrombolysis-related intracranial hemorrhage. **E.** Component predictive instrument for thrombolysis-related major bleed.

should be used as an aid to, not a replacement for, the judgment of emergency clinicians.

The five component predictive instruments of the thrombolytic predictive instrument each generate results consistent with known clinical influences on acute mortality, long-term mortality, cardiac arrest, thrombolysis-related hemorrhagic stroke, and bleeding that requires transfusion (Figures 1–5). However, unlike conventional reports of these effects, the thrombolytic predictive instrument can provide quantitative results specifically based on an individual patient's characteristics (Figure 6). Thus, it can assist in decision making about treatment in light of the three major determinants of outcome from thrombolytic therapy: time from onset of acute infarction until treatment, size and location of the infarction, and likelihood of serious thrombolysis-related bleeding complications.

It is well known that the time elapsed from the onset of chest pain until treatment is a critical determinant of the efficacy of thrombolytic therapy (33–35), but treatment is often delayed. The MITI (Myocardial Infarction Triage and Intervention) Trial, which studied the very early use of thrombolytic therapy, showed that compared with patients treated 70 to 360 minutes after symptom onset (who had a mortality rate of 8.7%), patients treated within 70 minutes of symptom onset had 50% smaller infarctions and a mortality rate of 1.2% (36). In that trial, prehospital cellular telephone-transmitted 12-lead electrocardiograms not only allowed thrombolytic therapy to be used before arrival at the emergency department but also, for patients treated at the hospital, shortened the time from arrival to treatment from 60 to 20 minutes. The thrombolytic predictive instrument electrocar-



**Appendix Figure continued**

diagram is intended to build on this approach and to inform caregivers in both the prehospital and hospital settings, thus facilitating the earliest possible treatment.

It is also well known that the accrued benefits from thrombolytic therapy are greatest for patients with larger, high-risk anterior infarctions; moderate for patients with large inferior infarctions; and relatively small for patients with smaller, inferior infarctions (20, 21, 37–39). However, categories of infarction location and size in the literature often do not fit the particular patient for whom a treatment decision must be made. Similarly, reported results do not adjust in detail for a variety of important clinical factors at presentation, such as age, vital signs, and history of diabetes or hypertension. The thrombolytic predictive instrument, by using multiple independent measures of infarction location and size together with other key clinical factors, can immediately provide outcome predictions tailored to the attributes of a given patient. Moreover, because it integrates information from many independent sources in their most predictive forms (for example, detailed waveform electrocardiogram measurements rather than general electrocardiogram-based categories), the thrombolytic predictive instrument makes maximum use of the information available for each individual patient. Therefore, it is likely to identify candidates for thrombolytic therapy who would not be identified in current practice (that is, it increases sensitivity) and should expand the pool of patients benefiting from thrombolysis.

The thrombolytic predictive instrument should also better identify patients who are likely to have bleeding complications as a result of thrombolytic therapy and are therefore less likely to accrue net benefit but who would have met conventional treatment criteria (that is, it increases specificity). This should reduce adverse effects (and costs) resulting from untoward use. Conversely, fear of bleeding complications, especially intracranial hemorrhage, remains a major barrier to the appropriate use of thrombolytic therapy (40). By providing patient-specific predicted probabilities of thrombolysis-related intracranial hemorrhage and serious bleeding, simultaneously with the patient's probable benefit in terms of the probabilities of mortality and cardiac arrest, the thrombolytic predictive instrument may assist clinicians in dealing with this difficult clinical trade-off as accurately and expeditiously as possible.

Incorporation of the thrombolytic predictive instrument into a computerized electrocardiograph not only may assist real-time care but will also allow the storing of the predicted outcomes in databases for retrospective assessment of care. By providing accurate risk-adjusted predictions of expected outcomes of acute myocardial infarction and its therapy, the component predictive instruments should be usable for retrospectively comparing outcomes of care by different providers and institutions, inasmuch as they are based on variable types previously

shown to be "time-insensitive" (4, 8) and thus valid for both real-time and retrospective use. Of note, because the predictive models are clinically based and use only data available to the clinician in real-time care, their use for evaluating care should facilitate communication among clinicians, administrators, payers, and agencies (10). Combining primary data from multiple clinical trials and registries to create a single database with which to develop outcome predictive instruments has potential advantages (11). It allows more patients to be studied than would be possible in a single study, without the enormous costs and substantial time that would otherwise be needed to collect such data (if, indeed, such data could still be obtained). Moreover, the resulting data set may be less biased than the data sets of individual clinical trials (for example, individual trials may have excluded women) (41). Thus, useful models of clinical outcomes can be developed that otherwise might not be available because of practical or ethical barriers to their creation.

This approach has potential pitfalls (11). The data come from studies and trials that were done over a wide span of years and had a variety of designs. The need to apply uniform inclusion criteria to all contributing data sets resulted in a reduction in the number of patients available for study. In addition, because the clinical trials had used somewhat restrictive inclusion criteria, we did not have sufficient data with which to make projections beyond their criteria (for example, for patients older than 75 years of age or patients with systolic blood pressures > 190 mm Hg). Thus, the use of this instrument was prevented in some patients. Nonetheless, we believe that these methods deserve further investigation as a way to make optimal use of clinical trial and registry data. This approach could also be used for ongoing updating of databases and their derived predictive instruments.

Although the clinical concepts embedded in the component statistical models of the thrombolytic predictive instrument are similar to those in the literature, the outcome predictions from these models should be studied further. For example, the thrombolytic predictive instrument's estimate of the mortality benefit, especially for patients who are treated early, is larger than that reported by the Fibrinolytic Therapy Trialists (FTT) Collaborative Group (33), which combined basic data from large controlled trials of thrombolytic therapy. This difference could result from the inclusion of multiple thrombolytic regimens and many late-treated patients in the FTT overview, either because late-treated patients receive less benefit or because the FTT's summary linear regression underrepresented the impact of time to treatment on mortality in the first hours, or both (33). Alternatively, the estimates

of mortality in clinical trials included in the thrombolytic predictive instrument could underestimate mortality of thrombolysis-treated patients because of the restrictive inclusion criteria while overestimating the mortality of patients not treated with thrombolysis, as a result of the wide entry criteria of its database. However, the very close comparability of the database's treatment and control groups makes this unlikely. Indeed, although the difference was not statistically significant, treated patients had slightly larger infarctions (electrocardiogram size score, 14.8 compared with 13.1) and slightly lower mean systolic blood pressures (130 compared with 140 mm Hg), which would bias against an exaggerated effect of thrombolysis. A separate concern is that the thrombolysis-related intracranial hemorrhage component predictive instrument is based on a relatively small number of strokes; it might be improved by the use of more data. In addition, this model implicitly assumes that the rate of nonhemorrhagic stroke would be equivalent in treated and untreated patients, even though recent evidence suggests a modest decrease in nonhemorrhagic strokes in treated patients (33).

Finally, the thrombolytic predictive instrument's major systemic bleed component predictive instrument is probably biased by the high rates of invasive procedures in the thrombolytic trials included in the Thrombolytic Predictive Instrument Database. Thus, it may overestimate the likelihood of bleeding.

All of these issues point to the need for continued data collection to improve predictions of patient outcomes. Unfortunately, this may not be possible to do in patients who do not receive thrombolytic therapy, because reperfusion therapy is now the standard of care. Nonetheless, although the thrombolytic predictive instrument offers promise as a real-time clinical decision aid and as a tool for retrospective review of care, it must still be viewed as experimental. Further testing of its performance on other data sets, investigation of the optimal form for presentation to physicians (42), and prospective controlled clinical trials of its impact on clinicians' use of thrombolytic therapy will be required before it is ready for routine, widespread use (43–45).

## Appendix A

All of the component predictive instruments of the thrombolytic predictive instrument use the logistic regression equation, which predicts the 1% to 100% probability of the given outcome. The definitions and coefficients for variables included in the component predictive instruments are shown here. The component predictive instruments are for 30-day mortality, 1-year mortality, cardiac arrest (within 48 hours), intracranial hemorrhage related to thrombolytic therapy, and bleeding related to thrombolytic therapy.



# Thrombolytic Predictive Instrument: 30-Day Mortality Component Predictive Instrument

## Variable Coefficients

Variable	Coefficient	P Value
Patient age	0.0557	<0.001
Systolic blood pressure		
Patients with anterior or posterior acute myocardial infarction	-0.0277	<0.001
Patients without anterior or posterior acute myocardial infarction	-0.0080	
History of diabetes	0.9215	<0.001
Heart rate	0.0271	<0.001
ST-segment elevation (echocardiogram size of acute myocardial infarction)	0.0424	0.0020
Q waves without ST-segment elevation in inferior acute myocardial infarction	0.3184	0.0383
Acute myocardial infarction location (anterior or posterior acute myocardial infarction)	3.6240	<0.001
Right bundle-branch block	0.5763	0.0805
Time from symptom onset to emergency department electrocardiogram	-0.1407	0.0448
Impact of use of thrombolytic therapy	-1.2097	0.0097
Intercept	-5.6340	

## Variable Definitions

### User input variables

Patient age	
= 40	If age <40 years
= age	If age ≥40 years and <75 years
= 75	If age ≥75 years
Systolic blood pressure	
= 60	If systolic blood pressure < 60 mm Hg
= systolic blood pressure	If systolic blood pressure ≥60 and <190 mm Hg
= 190	If systolic blood pressure ≥190 mm Hg
History of diabetes	
= 1	If history of diabetes is present
= 0	If history of diabetes is not present

### Electrocardiogram-based variables

All location-specific variables are based on having two contiguous leads in a region, with one lead having 1 mm or more and one having 0.5 mm or more ST-segment elevation

Heart rate	
= 0	If heart rate <70 beats/min
= heart rate - 70	If heart rate ≥70 beats/min and <120 beats/min
= 50	If heart rate ≥120 beats/min
ST-segment elevation (electrocardiogram size of acute myocardial infarction)*	
If 2 or more contiguous leads of ST-segment elevation in V1, V2, V3, V4 then	
= (number of contiguous leads V1-V6 with ST-segment elevation) + (sum of ST-segment elevation in contiguous leads)	
If no posterior acute myocardial infarction and less than two contiguous leads of ST-segment elevation in V1, V2, V3, V4 then	
= (number of contiguous leads V5, V6, I, aVL, II, III aVF with ST-segment elevation) + (sum of ST-segment elevation in V5, V6, I, aVL, II, III aVF)	
If posterior acute myocardial infarction and less than two contiguous leads of ST-segment elevation in V1, V2, V3, V4 then	
= (number of contiguous leads V5, V6, I, aVL, II, III aVF with ST-segment elevation) + (sum of contiguous leads with ST-segment elevation in V5, V6, I, aVL, II, III aVF) + (number of leads V1, V2, V3 with ST-segment depression of 0.5 mm or more) + (absolute sum of ST-segment depression 0.5 mm or more in V1, V2, V3)	
Q waves without ST-segment elevation in inferior acute myocardial infarction†	
= 0	If less than two contiguous leads of ST-segment elevation in inferior region
= number of contiguous leads with abnormal Q waves and no ST-segment elevation for inferior acute myocardial infarction	
Location of acute myocardial infarction	
= 1	If two or more contiguous leads of ST-segment elevation in V1, V2, V3, V4
= 1	If posterior acute myocardial infarction with two or more contiguous leads of ST-segment elevation in both inferior (II, III, aVF) and lateral (V5, V6, I, aVL) regions
= 1	If posterior acute myocardial infarction without two or more contiguous leads of ST-segment elevation
= 0	For all others
Right bundle-branch block	
= 1	If right bundle-branch block is present
= 0	If right bundle-branch block is not present

### Impact of the use of thrombolytic therapy

Time from symptom onset‡	
If patient received thrombolytic therapy, then	
= 6.25	
If patient did not receive thrombolytic therapy, then	
= 1.00 × time from symptom onset to electrocardiogram	If time from symptom onset to electrocardiogram ≥0 and <1
= 2.00 × time from symptom onset to electrocardiogram - 1.00	If time from symptom onset to electrocardiogram ≥1 and <2
= 1.50 × time from symptom onset to electrocardiogram	If time from symptom onset to electrocardiogram ≥2 and <3
= 0.75 × time from symptom onset to electrocardiogram + 2.25	If time from symptom onset to electrocardiogram <4
= 0.25 × time from symptom onset to electrocardiogram + 4.25	If time from symptom onset to electrocardiogram ≥4

Early acute myocardial infarction on electrocardiogram with use of thrombolytic therapy§	
= (1 - hours from onset to treatment of thrombolytic therapy/9) × electrocardiogram earliness	
= 0	If patient did not receive thrombolytic therapy

\* Values greater than 25 are set to 25.

† Values greater than 4 are set to 4.

‡ If time from symptom onset to electrocardiogram is greater than 8 hours, this value is set to 8.

§ Values for hours from onset to treatment greater than 8 are set to 8.

|| Values for leads with early electrocardiogram characteristics less than 0.25 are set to 0.25.

Percentage of leads with early electrocardiogram characteristics = (number of contiguous leads with ST-segment elevation and tall T-waves) + (0.5 × number of contiguous leads with ST-segment elevation without abnormal Q waves or tall T waves)/(number of contiguous leads with ST-segment elevation). Each lead was scored as having a tall T-wave when the maximal T-amplitude from the PR interval baseline was above a specified value as given: (lead: threshold - V1:3.5; V2:10.0; V3:10.0; V4:10.0; V5:6.0; V6:4.0; I:2.5; aVL:2.5; II:5.0; aVF:5.0; III:5.0). For example, a measurement of 8.0 mm for the T amplitude in lead V2 would not be classified as a tall T wave, but an amplitude of 8.0 mm in lead V5 would be classified as a tall T wave.

## Thrombolytic Predictive Instrument: 1-Year Mortality Component Predictive Instrument

The predictions for 1-year mortality are given by:

$$\text{Prob}_{1 \text{ year}} = \text{Prob}_{30 \text{ day}} + (1 - \text{Prob}_{30 \text{ day}}) \times \text{Prob}_{\text{post } 30 \text{ day}}$$

where  $\text{Prob}_{30 \text{ day}}$  is the probability given by the 30-day mortality thrombolytic predictive instrument component model and  $\text{Prob}_{\text{post } 30 \text{ day}}$  is the additional probability of mortality from 30 days to 1 year given by the logistic regression model below.

### Variable Coefficients

Variable	Coefficient	P Value
Patient age	0.1085	<0.001
Heart rate	0.0371	<0.001
Number of leads with contiguous Q waves	0.1464	0.1293
Anterior acute myocardial infarction	0.5855	0.0412
Right bundle-branch block	1.2458	0.0148
Intercept	-11.1084	

### Variable Definitions

#### User input variables

Patient age	
= 60	If age <60 years
= 75	If age ≥60 years and <75 years
= age	If age ≥75 years

#### Electrocardiogram-based variables

All location-specific variables are based on having two contiguous leads in a region with one lead having 1 mm or more and one having 0.5 mm or more ST-segment elevation

Heart rate	
= 0	If heart rate <70
= heart rate - 70	If heart rate ≥70 beats/min and <120 beats/min
= 50	If heart rate ≤120 beats/min
Anterior acute myocardial infarction	
= 1	If two or more contiguous leads with ST-segment elevation in leads V1, V2, V3, V4
= 0	If less than two contiguous leads with ST-segment elevation in leads V1, V2, V3, V4
Number of contiguous Q waves*	
= 0	If number of contiguous leads with abnormal Q waves <2
= number of contiguous leads with abnormal Q waves - 1	If number of contiguous leads with abnormal Q waves ≥2 and ≤4
Right bundle-branch block	
= 1	If right bundle-branch block is present
= 0	If right bundle-branch block is not present

\* Values greater than 4 are set to 4.

## Thrombolytic Predictive Instrument: Cardiac Arrest Component Predictive Instrument

### Variable Coefficients

Variable	Coefficient	P Value
Patient age	-0.00336	0.0240
Systolic blood pressure	-0.1185	0.0036
Electrocardiogram size of acute myocardial infarction	-0.00505	0.0076
Sum of ST-segment elevation by chest pain onset	0.1026	<0.001
Corrected QT interval by chest pain onset	11.8936	0.0185
Use of thrombolytic therapy	-0.5461	0.0711
Time interval 1	8.3110	
Time interval 2	8.3865	
Time interval 3	8.5451	
Time interval 4	8.6451	
Time interval 5	8.7791	
Time interval 6	8.9471	
Time interval 7	9.1565	
Time interval 8	8.9045	
Time interval 9	8.7714	
Intercept	-2.0005	

## Variable Definitions

### User input variables

Patient age

$$= (35 - 53.6)^2$$

$$= (\text{age} - 53.6)^2$$

$$= (70 - 53.6)^2$$

If age < 35 years

If age ≥ 35 years and ≤ 70 years

If age > 70 years

Systolic blood pressure

$$= 80$$

$$= \text{systolic blood pressure}$$

$$= 100$$

If systolic blood pressure < 80 mm Hg

If systolic blood pressure ≥ 80 mm Hg and ≤ 100 mm Hg

If systolic blood pressure > 100 mm Hg

### Electrocardiogram-based variables

All location-specific variables are based on having the contiguous leads in a region with one lead having 1 mm or more and one having 0.5 mm or more ST-segment elevation

Electrocardiogram size of acute myocardial infarction\*

If anterior acute myocardial infarction, then

$$= [2 \times (\text{number of leads in V1-V6 with ST-segment elevation}) + (\text{amount of ST-segment elevation in these leads over 1 mm}) - 13.5]^2$$

If no anterior ST-segment elevation, then

$$= [0.67 \times (\text{sum of ST-segment elevation in leads II, aVF, III, I, aVL}) - 13.5]^2$$

Sum of ST-segment elevation in all leads adjusted for chest pain onset to time of electrocardiogram

= sum of ST-segment elevation

If chest pain to electrocardiogram ≤ 0.25 and sum of ST-segment elevation ≤ 22 or

If chest pain to electrocardiogram > 0.25 and ≤ 0.75 and sum of ST-segment

elevation ≤ 27 - 20 × chest pain to electrocardiogram or

If chest pain to electrocardiogram > 0.75 and ≤ 1.25 and sum of ST-segment

elevation ≤ 15 - 4 × chest pain to electrocardiogram or

If chest pain to electrocardiogram > 1.25 and ≤ 2.0 and sum ≤ (80 - 40 × chest

pain to electrocardiogram)/3

If chest pain to electrocardiogram ≤ 0.25 and sum of ST-segment elevation > 22

If chest pain to electrocardiogram > 0.25 and ≤ 0.75 and sum of ST-segment

elevation > 27 - 20 × chest pain to electrocardiogram

If chest pain to electrocardiogram > 0.75 and ≤ 1.25 and sum of ST-segment

elevation > 15 - 4 × chest pain to electrocardiogram

If chest pain to electrocardiogram > 1.25 and ≤ 2.0 and sum of ST-segment

elevation > (80 - 40 × chest pain to electrocardiogram)/3

If chest pain to electrocardiogram ≥ 2

$$= 22$$

$$= 27 - 20 \times \text{chest pain to electrocardiogram}$$

$$= 15 - 4 \times \text{chest pain to electrocardiogram}$$

$$= (80 - 40 \times \text{chest pain to electrocardiogram})/3$$

$$= 0$$

Corrected QT interval adjusted to time from onset of chest pain to electrocardiogram†

$$= 0$$

$$= (QT_c - 0.44)$$

$$= (QT_c - 0.44) \times (5.5 - 6 \times \text{chest pain to electrocardiogram})$$

$$= (QT_c - 0.44) \times (-2)$$

If  $QT_c < 0.44$

If  $QT_c \geq 0.44$  and onset of chest pain to electrocardiogram ≤ 0.75 hours

If  $QT_c \geq 0.44$  and onset of chest pain to electrocardiogram > 0.75 and < 1.25 hours

If  $QT_c \geq 0.44$  and onset of chest pain to electrocardiogram ≥ 1.25 hours

### Impact of the use of thrombolytic therapy

Use of thrombolytic therapy

$$= 1$$

$$= 0$$

If thrombolytic therapy given in or before time interval

If thrombolytic therapy not given in or before time interval

Time interval variables‡

Time interval 1

$$= 1$$

$$= 0$$

If hours from electrocardiogram > 0 and ≤ 0.5

If hours from electrocardiogram > 0.5

Time interval 2

$$= 1$$

$$= 0$$

If hours from electrocardiogram > 0.5 and ≤ 0.75

If hours from electrocardiogram ≤ 0.5 or > 0.75

Time interval 3

$$= 1$$

$$= 0$$

If hours from electrocardiogram > 0.75 and ≤ 1.25

If hours from electrocardiogram ≤ 0.75 or > 1.25

Time interval 4

$$= 1$$

$$= 0$$

If hours from electrocardiogram > 1.25 and ≤ 1.75

If hours from electrocardiogram ≤ 1.25 or > 1.75

Time interval 5

$$= 1$$

$$= 0$$

If hours from electrocardiogram > 1.75 and ≤ 2.5

If hours from electrocardiogram ≤ 1.75 or > 2.5

Time interval 6

$$= 1$$

$$= 0$$

If hours from electrocardiogram > 2.5 and ≤ 4

If hours from electrocardiogram ≤ 2.5 or > 4

Time interval 7

$$= 1$$

$$= 0$$

If hours from electrocardiogram > 4 and ≤ 8

If hours from electrocardiogram ≤ 4 or > 8

Time interval 8

$$= 1$$

$$= 0$$

If hours from electrocardiogram > 8 and ≤ 24

If hours from electrocardiogram ≤ 8 or > 24

Time interval 9

$$= 1$$

$$= 0$$

If hours from electrocardiogram > 24 and ≤ 48

If hours from electrocardiogram ≤ 24 or > 48

\* If size of infarction is greater than 462.5 (equals  $[35 - 13.5]^2$ ).

† Corrected QT interval is the QT interval divided by the square root of the RR interval.

‡ The time interval is the number of hours from the electrocardiogram to cardiac arrest.



## Thrombolytic Predictive Instrument: Thrombolysis-Related Intracranial Hemorrhage Component Predictive Instrument

### Variable Coefficients

Variable	Coefficient	P Value
Patient age	0.0591	0.0397
Excess pulse blood pressure	0.0729	0.0010
Intercept	-7.7784	

### Variable Definitions

#### User input variables

Patient age	
= age - 35	If age $\geq 35$ and $\leq 75$ years
= 0	If age $< 35$ years
= 40	If age $> 75$ years
Excess pulse blood pressure*†	
= 0	If (systolic blood pressure $\leq 120$ ) or (systolic blood pressure - diastolic blood pressure) $\leq 40$
= (systolic blood pressure - diastolic blood pressure - 40) $\times$ (systolic blood pressure - 120)/5	If (systolic blood pressure $> 120$ and $< 125$ ) and (systolic blood pressure - diastolic blood pressure) $> 40$
= systolic blood pressure - diastolic blood pressure - 40	If (systolic blood pressure $\geq 125$ ) and (systolic blood pressure - diastolic blood pressure) $> 40$ and $\leq 75$
= 35	If systolic blood pressure $\geq 125$ and (systolic blood pressure - diastolic blood pressure) $> 75$
= 35	If (systolic blood pressure $> 120$ and $< 125$ ) and [(systolic blood pressure - diastolic blood pressure - 40) $\times$ (systolic blood pressure - 120)/5] $> 35$

\* If the diastolic blood pressure is less than 65 mm Hg, then the diastolic blood pressure is set to 65. Otherwise, the actual value is used.

† Excess pulse blood pressure = systolic blood pressure - diastolic blood pressure.

## Thrombolytic Predictive Instrument: Thrombolysis-Related Major Bleed Component Predictive Instrument

### Variable Coefficients

Variable	Coefficient	P Value
Patient age	0.0378	0.0332
Sex	-0.3919	0.5763
History of hypertension	0.8017	0.0143
Systolic blood pressure	-0.0246	$< 0.001$
Heart rate with systolic blood pressure	0.2181	0.0024
Standard dose of thrombolytic agents by weight	4.1339	$< 0.001$
Sex with dose of thrombolytic agents	-3.0338	0.0719
Intercept	-3.3296	

### Variable Definitions

#### User input variables

Patient age	
= 30	If age $< 30$ years
= age	If age $\geq 30$ years and $\leq 75$ years
= 75	If age $> 75$ years
Sex	
= 0	If patient is female
= 1	If patient is male
History of hypertension	
= 0	If history of hypertension is not present
= 1	If history of hypertension is present
Systolic blood pressure	
= 60	If systolic blood pressure $< 60$ mm Hg
= systolic blood pressure	If systolic blood pressure $\geq 60$ mm Hg and $\leq 190$ mm Hg
= 190	If systolic blood pressure $> 190$ mm Hg
Heart rate with systolic blood pressure	
= 15	If systolic blood pressure $< 100$ mm Hg and heart rate $< 40$ beats/min
= (55 - heart rate)	If systolic blood pressure $< 100$ mm Hg and heart rate $\geq 40$ beats/min and $\leq 55$ beats/min
= $15 \times (120 - \text{systolic blood pressure})/20$	If systolic blood pressure $\geq 100$ mm Hg and $\leq 120$ mm Hg and heart rate $< 40$ beats/min
= $(55 - \text{heart rate}) \times (120 - \text{systolic blood pressure})/20$	If systolic blood pressure $\geq 100$ mm Hg and $\leq 120$ mm Hg and heart rate $\geq 40$ beats/min or $\leq 55$ beats/min
= 0	If systolic blood pressure $> 120$ mm Hg or heart rate $> 55$ beats/min
Sex with standard dose of thrombolytic agents adjusted to weight	
= dose adjusted to weight	If patient is male
= 0	If patient is female
Standard dose of thrombolytic agents adjusted by weight*	
= 0	If $70 \times \text{standard dose/weight} < 0.7$
= $(70 \times \text{standard dose/weight}) - 0.7$	If $70 \times \text{standard dose/weight} \geq 0.7$ and $\leq 1.4$
= 0.7	If $70 \times \text{standard dose/weight} > 1.4$

Standard dose = number of units/100 if tissue plasminogen activator is used; number of units/1.5 million if streptokinase is used; and number of units/1.0 million if urokinase is used.

## Appendix B

The predicted probability for each of the component predictive instruments is generated by assigning information about a specific patient, such as age or systolic blood pressure, to a variable in the logistic regression equation. The predicted probability is then calculated as

$$\text{Probability of an outcome} = \frac{1}{1 + \exp(-\sum \beta x)}$$

where  $\exp(e) = e^x$ ,  $\beta$  is the model coefficient,  $x$  is the variable value for the patient, and the sum is across all variables in the model. The calculations for each of the component predictive instruments are provided for the patient with the electrocardiogram shown in the top panel of **Figure 6**. For each variable in a model, the actual clinical data, the derived form needed for the calculations (given as  $x$  in column 1), the variable coefficient (given as  $\beta$  in column 2), and the weighted product (given as  $\beta x$  in column 3) are provided. Additional details on variable definitions can be found in Appendix A.

### Calculation for Sample Patient Using the Thrombolytic Predictive Instrument 30-Day Mortality Component Predictive Instrument

Patient Information Required for Model	Value for Patient	Variable Definition	Derived Value (x)	Regression Coefficient ( $\beta$ )	Product ( $\beta \cdot x$ )
Patient age	57 years	If age >40 years and <60 years, then $x =$ age	57	0.0557	3.1749
Initial systolic blood pressure	156 mm Hg	If anterior ST-segment elevation and systolic blood pressure >60, then $x =$ systolic blood pressure	156	-0.0277	-4.3212
History of diabetes	Yes	If history of diabetes present, then $x = 1$	1	0.9215	0.9215
Heart rate	60 beats/min	If heart rate $\geq 0$ beats/min and <70 beats/min, then $x = 0$	0	0.0271	0.0000
Amount of ST-segment elevation	5.6	$x =$ number of leads with ST-segment elevation + sum of ST-segment elevation in these leads	9.6	0.0424	0.4070
Leads with abnormal Q waves and no ST-segment elevation	1	If anterior ST-segment elevation, then $x = 0$	0	0.3184	0.0000
Anterior infarction or posterior acute myocardial infarction	Yes	If anterior ST-segment elevation, then $x = 1$	1	3.6240	3.6240
Presence of right bundle-branch block	None	If no right bundle-branch block is present, then $x = 0$	0	0.5763	0.0000
Time from symptom onset to electrocardiogram (TONSET)	2 hours	If not given thrombolytic therapy	3	-0.1407	-0.4221*
		If TONSET >2 hours and $\leq 3$ hours, then $x = 1.50 \times \text{TONSET}$			
Leads with ST-segment elevation	4	If given thrombolytic therapy, then $x = 6.25$	6.25	-0.1407	-0.8794†
		Earliness index = (number of leads with tall T waves + $0.5 \times$ leads with ST-segment elevation without abnormal Q waves)/number of leads with ST-segment elevation	0.50	-	-
With tall T waves	0				
No abnormal Q waves	4				
Impact of use of thrombolytic therapy					
Time to treatment	3 hours	$x = (1 - \text{time to treatment}/9) \times \text{Earliness Index}$	0.33	-1.2097	-0.4032†
Model intercept			1	-5.6340	-5.6340
Sum of weighted patient-specific values without thrombolytic therapy = $\sum \beta x =$					-2.2499
Sum of weighted patient-specific values with thrombolytic therapy = $\sum \beta x =$					-3.1104

\* Include only in sum for probability without thrombolytic therapy.

† Include only in sum for probability with thrombolytic therapy.

$$\text{Probability of 30-day mortality without thrombolytic therapy} = \frac{1}{1 + \exp(-\sum \beta x)} = \frac{1}{1 + \exp(2.2499)} = 0.095$$

$$\text{Probability of 30-day mortality with thrombolytic therapy} = \frac{1}{1 + \exp(-\sum \beta x)} = \frac{1}{1 + \exp(3.1104)} = 0.043$$

### Calculation for Sample Patient Using the Thrombolytic Predictive Instrument 1-Year Mortality Component Predictive Instrument

Patient Information Required for Model	Value for Patient	Variable Definition	Derived Value (x)	Regression Coefficient (β)	Product (β · x)
Patient age	57 years	If 60 years ≤ age, then x = age	60	0.1085	6.5100
Heart rate	60 beats/min	If heart rate ≥ 0 beats/min and < 70 beats/min, then x = 0	0	0.0371	0.0000
Leads with abnormal Q-waves and no ST-segment elevation (NQWAVE)	3	If number of leads with abnormal Q-waves ≥ 1 and ≤ 5, then x = NQWAVE - 1	2	0.1464	0.2928
Anterior infarction	Yes	If anterior ST-segment elevation present, then x = 1	1	0.5855	0.5855
Presence of right bundle-branch block	None	If no right bundle-branch block present, then x = 0	0	1.2458	0.0000
Model intercept			1	-11.1084	-11.1084
Sum of weighted patient-specific values = Σ βx =					-3.7201

$$\text{Probability of post-30-day mortality} = \frac{1}{1 + \exp(-\Sigma \beta x)} = \frac{1}{1 + \exp(3.7201)} = 0.0237$$

Probability of 1-year mortality = (probability of death within 30 days) + (probability of being alive at 30 days) × (probability of death after 30 days)

If patient is not given thrombolysis: probability of 1-year mortality = (0.095) + (0.905)(0.0237) = 0.117

If patient is given thrombolysis: probability of 1-year mortality = (0.043) + (0.957)(0.0237) = 0.065

### Calculation for Sample Patient Using the Thrombolytic Predictive Instrument Cardiac Arrest Component Predictive Instrument

Patient Information Required for Model	Value for Patient	Variable Definition	Derived Value (x)	Regression Coefficient (β)	Product (β · x)
Patient age	57 years	If age ≥ 35 years or ≤ 70 years, then x = (age - 53.6) <sup>2</sup>	11.56	-0.0034	-0.0393
Systolic blood pressure	156 mm Hg	If systolic blood pressure > 100 mm Hg, then x = 100	100	-0.1185	-11.8500
Leads with ST-segment elevation	4	If anterior infarction, then electrocardiogram size of infarction = 2 × (number of leads V1-V4 with ST-segment elevation) + amount of ST-segment elevation	11.90	-	-
Sum of ST-segment elevation	3.9				
Electrocardiogram size of infarction	11.90	x = (electrocardiogram size of infarction - 13.5) <sup>2</sup>	2.56	-0.0051	-0.0131
Time from symptom onset to electrocardiogram	2 hours	If time from symptom onset to electrocardiogram ≥ 2 hours, then x = 0	0	0.1026	0
Corrected QT interval (QT <sub>c</sub> )	0.351	If QT <sub>c</sub> < 0.44, then x = 0	0	11.8936	0
Model intercept	-		1	-2.0005	-2.0005
Sum of weighted patient-specific values = Σ βx =					-13.9029

Interval	Not Treated			Treated		
	Intercept (1)	Survival (2)	Cumulative Survival (3)	Intercept (1)	Survival (2)	Cumulative Survival (3)
1	8.3110	0.996	0.996	8.3110	0.996	0.996
2	8.3865	0.996	0.992	8.3865	0.996	0.992
3	8.5451	0.995	0.988	7.9990	0.997	0.990
4	8.6451	0.995	0.983	8.0990	0.997	0.987
5	8.7791	0.994	0.977	8.2330	0.997	0.983
6	8.9471	0.993	0.970	8.4010	0.996	0.979
7	9.1565	0.991	0.962	8.6104	0.995	0.974
8	8.9045	0.993	0.955	8.3584	0.996	0.971
9	8.7714	0.994	0.949	8.2253	0.997	0.967

Each entry in column 1 is the interval-specific intercept from the pooled logistic regression, adjusted for the impact of the use of thrombolytic therapy.

Each entry in column 2 is calculated from the following formula:

$$\text{column 2} = \frac{1}{1 + \exp(\text{column 1} - 13.9029)}$$

Each entry in column 3 is a cumulative probability calculated by multiplying all the probabilities in column 2 that occur before and in interval (for example, for interval 4, 0.983 = 0.996 × 0.996 × 0.995 × 0.995).

Probability of cardiac arrest without thrombolytic therapy = 1 - 0.949 = 0.051.

Probability of cardiac arrest with thrombolytic therapy = 1 - 0.967 = 0.033.



## Calculation for Sample Patient Using the Thrombolytic Predictive Instrument Intracranial Hemorrhage Component Predictive Instrument

Patient Information Required for Model	Value for Patient	Variable Definition	Derived Value (x)	Regression Coefficient (β)	Product (β · x)
Patient age	57 years	If age ≥35 years or ≤75 years, then x = age - 35	22	0.0591	1.3002
Systolic blood pressure (SBP)	156 mm Hg	If SBP ≥125 mm Hg and (SBP - DBP) >40 and ≤75, then x = SBP - DBP - 40	28	0.0729	2.0412
Diastolic blood pressure (DBP)	88 mm Hg				
Model intercept			1	-7.7784	-7.7784
Sum of weighted patient-specific values (column 3) = Σ βx =					-4.4370

$$\text{Probability of intracranial hemorrhage} = \frac{1}{1 + \exp(-\Sigma \beta \cdot x)} = \frac{1}{1 + \exp(4.4370)} = 0.012$$

## Calculation for Sample Patient Using the Thrombolytic Predictive Instrument Major Bleed Component Predictive Instrument

Patient Information Required for Model	Value for Patient	Variable Definition	Derived Value (x)	Regression Coefficient (β)	Product (β · x)
Patient age	57 years	If age ≥30 years and ≤75 years, then x = age	57	0.0378	2.1546
Sex	Male	If patient is male, then x = 1	1	-0.3919	-0.3919
History of hypertension	Yes	If history of hypertension is present, then x = 1	1	0.8017	0.8017
Initial systolic blood pressure	156 mm Hg	If systolic blood pressure ≥60 mm Hg and ≤190 mm Hg, then x = systolic blood pressure	156	-0.0246	-3.8376
Heart rate	60 beats/min	If systolic blood pressure >120 mm Hg or heart rate >55 beats/min, then x = 0	0	0.2181	0
Standard dose	1	If 70 × standard dose/weight ≥0.7 and ≤1.4, then adjusted dose = (70 × standard dose/weight) - 0.7	0.22	4.1339	0.9095
Weight	75.9 kg				
Sex with adjusted standard dose	0.22	If patient is male, then x = adjusted dose	0.22	-3.0338	-0.6674
Model intercept			1	-3.3296	-3.3296
Sum of weighted patient-specific values (column 3) = Σ βx =					-4.3607

$$\text{Probability of major bleeding} = \frac{1}{1 + \exp(-\Sigma \beta \cdot x)} = \frac{1}{1 + \exp(4.3607)} = 0.013$$

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