Predictors of 30-Day Mortality in the Era of Reperfusion for Acute Myocardial Infarction

Results From an International Trial of 41 021 Patients

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Background Despite remarkable advances in the treatment of acute myocardial infarction, substantial early patient mortality remains. Appropriate choices among alternative therapies and the use of clinical resources depend on an estimate of the patient's risk. Individual patients reflect a combination of clinical features that influence prognosis, and these factors must be appropriately weighted to produce an accurate assessment of risk. Prior studies to define prognosis either were performed before widespread use of thrombolysis or were limited in sample size or spectrum of data. Using the large population of the GUSTO-I trial, we performed a comprehensive analysis of relations between baseline clinical data and 30-day mortality and developed a multivariable statistical model for risk assessment in candidates for thrombolytic therapy.

Methods and Results For the 41 021 patients enrolled in GUSTO-I, a randomized trial of four thrombolytic strategies, relations between clinical descriptors routinely collected at initial presentation, and death within 30 days (which occurred in 7% of the population) were examined with both univariable and multivariable analyses. Variables studied included demographics, history and risk factors, presenting characteristics, and treatment assignment. Risk modeling was performed with logistic multiple regression and validated with bootstrapping techniques. Multivariable analysis identified age as the most significant factor influencing 30-day mortality, with rates of 1.1% in the youngest decile (<45 years) and 20.5% in patients >75 (adjusted $\chi^2=717$, $P<.0001$). Other factors most significantly associated with increased mortality were lower systolic blood pressure ($\chi^2=550$, $P<.0001$), higher Killip class ($\chi^2=350$, $P<.0001$), elevated heart rate ($\chi^2=275$, $P<.0001$), and anterior infarction ($\chi^2=143$, $P<.0001$). Together, these five characteristics contained 90% of the prognostic information in the baseline clinical data. Other significant though less important factors included previous myocardial infarction, height, time to treatment, diabetes, weight, smoking status, type of thrombolytic, previous bypass surgery, hypertension, and prior cerebrovascular disease. Combining prognostic variables through logistic regression, we produced a validated model that stratified patient risk and accurately estimated the likelihood of death.

Conclusions The clinical determinants of mortality in patients treated with thrombolytic therapy within 6 hours of symptom onset are multifactorial and the relations complex. Although a few variables contain most of the prognostic information, many others contribute additional independent prognostic information. Through consideration of multiple characteristics, including age, medical history, physiological significance of the infarction, and medical treatment, the prognosis of an individual patient can be accurately estimated. (***Circulation*. 1995;91:1659-1668.**)

Key Words • myocardial infarction • prognosis • risk factors • thrombolysis

Substantial advances in the treatment of acute myocardial infarction (MI) have occurred over the past several years as a result of important observations in basic myocardial research and through the vital evaluative mechanism of randomized clinical trials.[1-10] Practitioners now have a variety of treatment strategies available, especially for patients with ST-segment elevation, to restore obstructed coronary blood flow and interrupt the evolving myocardial event. Despite therapeutic advances, recent large-scale randomized clinical trials report 6% to 9% early mortality rates (30 to 35 days), even for patients receiving thrombolytic therapy within 6 hours of symptom onset.[11-14] Often, choices among alternative therapies or decisions regarding the allocation of clinical resources are based on an assessment of patient risk. Careful attention to pivotal factors that increase the risk of early mortality might illuminate the role of second-tier interventions or adjunctive pharmacotherapeutics that would further lower the fatality rate of acute MI.

To be broadly useful, a risk-assessment algorithm should include all clinically relevant prognostic indicators and should be derived from a population that represents the types of patients seen in clinical practice so that stable estimates of true risk relations can be assessed. A useful model should appropriately weight

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clinically relevant predictors and be validated in a population with a broad spectrum of patients and hospital settings, in which risk profiles may soon be required. Though many studies have attempted to define the prognosis of patients with MI and/or provide risk algorithms,[15-23] they were performed before the widespread use of thrombolytic agents[15-19] or were limited in sample size, diversity of medical care systems, or spectrum of clinical data.

Using the large population of the international Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries (GUSTO-I) trial (41 021 patients admitted to 1081 hospitals in 15 countries),[14] we attempted to provide a comprehensive analysis of relations between baseline clinical factors and 30-day mortality after intravenous thrombolytic therapy. The goal was to develop a multivariable statistical model with patient data routinely collected at initial presentation that would be clinically useful in managing patients who are candidates for thrombolytic therapy.

Methods

Patient Population

The GUSTO-I trial enrolled 41 021 patients with acute MI presenting with ST-segment elevation (within 6 hours of symptom onset) between December 27, 1990, and February 22, 1993. The design and data collection methods of GUSTO-I were described previously.[14] Patients were randomized over the telephone, with selected baseline characteristics recorded to ensure eligibility. Exclusion criteria included a history of stroke, active or recent bleeding history or major coagulation abnormality, recent trauma or major surgery, noncompressible vascular punctures, and previous treatment with streptokinase or anistreplase (because of possible allergic reactions). There were no restrictions based on age, presentation in cardiogenic shock, or prior bypass surgery.

Treatments

Qualifying patients were randomly allocated to one of four treatment strategies: streptokinase 1.5 million U over 60 minutes with subcutaneous heparin 12 500 U twice daily, beginning 4 hours after the start of thrombolytic therapy; streptokinase 1.5 million U over 60 minutes with intravenous heparin bolus of 5000 U and then 1000 U/h, with dose adjustment to maintain an activated partial thromboplastin time of 60 to 85 seconds; accelerated tissue-plasminogen activator (TPA) bolus of 15 mg and then infusion of 0.75 mg/kg (up to 50 mg) over 30 minutes and 0.5 mg/kg (up to 35 mg) over the next 60 minutes, accompanied by the same intravenous heparin regimen; or a combination of intravenous TPA (1.0 mg/kg over 60 minutes, not to exceed 90 mg, with 10% given as a bolus) and streptokinase (1.0 million U over 60 minutes) given concurrently but through separate catheters, accompanied by the same intravenous heparin regimen.[14]

Baseline Clinical Information

Baseline clinical data were collected on all patients with a standard data collection form. Specific written instructions and definitions for each variable were provided to all sites for use in completing the forms. Definitions of the clinical variables in this trial were used in previous studies.[14,24] Extensive quality control checks have been used at the time of data entry, and missing or questionable answers were queried. A sample of 12% of the forms was audited by a comparison of the data on the form with hospital medical records.

End-Point Assessment

The primary end point of the trial was death from any cause within 30 days of randomization. The study coordinator at each site recorded mortality information for patients who died in the hospital. Mortality data after discharge but within 30 days were obtained by a postcard returned by patients or their families. When no postcard was received, follow-up status was determined over the telephone.

Statistical Methods

Baseline characteristics of study patients were summarized in terms of frequencies and percentages for categorical variables and by the median and 25th and 75th percentiles for continuous variables. A logistic multiple regression model[25,26] was used to examine individual and joint relations between baseline clinical characteristics and the binary outcome of death within 30 days of randomization. For continuous clinical variables, we examined the shape and strength of the relation between individual variables and 30-day mortality by use of a flexible model-fitting approach involving cubic spline functions (cubic polynomials).[27-31] These functions were graphically and statistically examined to assess the assumption of this regression model that patient characteristics are linearly related to the log odds of the outcome event (30-day mortality). Where relations were nonlinear, their shape was characterized with spline functions. Determining how variables should be modeled was an important step in characterizing prognostic relations and identifying which variables were most strongly related to short-term mortality. We also examined whether the prognostic relation of any important variable differed for particular levels of other important descriptors (ie, we tested for interactions among the prognostic clinical variables).

Among the array of clinical characteristics considered potential predictor variables in the modeling analyses were occasional patients with missing values. Although a full set of analyses was performed in patients with complete data for all the important predictor variables (92% of the study patients), the subset of patients with one or more missing predictor variables had a higher mortality rate than the other patients, and excluding those patients could lead to biased estimates of risk. To circumvent this, a method for simultaneous imputation and transformation of predictor variables based on the concepts of maximum generalized variance and canonical variables was used to estimate missing predictor variables and allow analysis of all patients.[33,34] The iterative imputation technique conceptually involved estimating a given predictor variable on the basis of multiple regression on (possibly) transformed values of all the other predictor variables. End-point data were not explicitly used in the imputation process. The computations for these analyses were performed with S-PLUS statistical software (version 3.2 for UNIX[32]), using a modification of an existing algorithm.[33,34] The imputation software is available electronically in the public domain.[33]

The full study population was used in the model development process, and the predictive performance of the model was internally validated through cross validation and bootstrapping.[35-39] First, 10-fold cross validation was performed: the model was fitted on a randomly selected subset of 90% of the study patients, and the resulting fit was tested on the remaining 10%. This process was repeated 10 times to estimate the extent to which the predictive accuracy of the model (based on the entire sample) was overoptimistic. Second, for each of 100 bootstrap samples (samples of the same size as the original population but with patients drawn randomly, with replacement, from the full study population), the model was refitted and then tested on the original sample, again to estimate the degree to which the predictive accuracy of the model would be expected to deteriorate when applied to an independent sample of patients.[39] The software used for model validation is also available electronically in the public domain.[40]

TABLE 1. Baseline Characteristics of Patients in the GUSTO-I Mortality Analysis

	Overall Population (n=40 830)	Deaths (n=28 151)
Demographics		
Age, y	62 (52, 70)	72 (64, 78)
Male	75	59
White	92	92
Weight, kg	78 (70, 88)	73 (64, 82)
Height, cm	172 (165, 178)	168 (160, 175)
Enrolled in United States	56	55
Risk factors		
Hypertension	38	47
Diabetes	15	23
Smoking status		
Current	43	26
Ex-smoker	27	28
Never smoked	30	46
Hypercholesterolemia	34	27
Family history	42	32
Other history		
Previous MI	16	28
Previous angina	37	45
Cerebrovascular disease	2	5
Prior bypass surgery	4	7
Prior angioplasty	4	3
Presenting characteristics		
Systolic BP, mm Hg	130 (112, 144)	120 (100, 140)
Diastolic BP, mm Hg	80 (70, 90)	74 (61, 85)
Heart rate, bpm	74 (62, 86)	80 (67, 96)
Infarct location		
Anterior	39	56
Inferior	58	41
Other	3	4
Killip class		
I	85	63
II	13	25
III	1	6
IV	1	6
Time course		
Symptom onset to randomization, min	120 (80, 180)	135 (90, 210)
Symptom onset to treatment, min	165 (120, 235)	185 (130, 260)

MI indicates myocardial infarction; BP, blood pressure. Values are the median (25th, 75th percentiles) for continuous variables or the percentage of patients in each category.

The measure of predictive discrimination used to characterize model performance, in both the original sample and the validation samples, was the area under the receiver operating characteristic curve.[41] This index measures the concordance of predictions with actual outcomes (how well the predictions rank order patients with respect to their outcomes) and is a simple transformation of Somer's D_{xy} rank correlation between the model predictions and actual outcomes.[42] Calibration of the model predictions was assessed by comparison of the average model prediction to the observed mortality rate across deciles of risk and among specific subgroups of patients with different risk levels.[43]

Results

Thirty-day mortality status was known in 40 830 patients (99.5%). Table 1 summarizes the baseline clinical characteristics of this population. The demographics and clinical characteristics of these patients encompass the spectrum of acute MI patients who present with ST-segment elevation and are considered eligible for thrombolytic therapy based on GUSTO-I entry criteria. As previously reported,[14] there were no differences in baseline characteristics among the four treatment groups in the trial. A total of 2851 patients (7.0%) died within 30 days of study enrollment. Thirty-nine percent of the deaths (1125) occurred within 24 hours; more than half (55%) occurred within 48 hours of randomization.

In Table 2, 30-day mortality rates are reported for each categorical baseline characteristic, accompanied by univariable χ^2 statistics and unadjusted odd ratios (ORs), reflecting the degree of risk stratification associated with each characteristic when considered alone. The most significant factor among these variables was Killip class at enrollment. Although relatively few patients presented in Killip class III or IV (2%), their mortality rate was very high. The other more significant univariable predictors of higher mortality were female sex, anterior wall MI, history of previous MI, and history of diabetes. Smoking status was a highly significant univariable predictor, with current or prior smoking associated with lower mortality.

Fig 1 shows the univariable prognostic relations for continuous baseline characteristics. The most significant prognostic factor among this group of variables was age, where beyond 60 years there was a dramatic effect of increasing age on mortality. A strong prognostic relation was also present for systolic blood pressure, notably in the range below 120 mm Hg. A similar but less significant pattern existed for diastolic blood pressure. Heart rate at entry displayed a significant U-shaped relation, with elevated mortality at very low and at high heart rates. Weaker prognostic relations were demonstrated for both weight and height, with lighter and shorter patients exhibiting slightly higher risk. In patients who were treated more than 2 hours from symptom onset, the risk of mortality gradually increased with longer time to treatment. Compared with the other clinical factors in Fig 1, the relation between time to treatment and mortality was less significant.

In the multivariable analysis, many characteristics significantly associated with mortality in univariable analysis remained important (Table 3). Variables that were not significant, however, included prior angina, prior angioplasty, diastolic blood pressure, and family history of coronary heart disease. Female sex (P=.043) and enrollment in the United States (P=.047) had borderline relations with outcome after adjustment for the other prognostic variables and thus were not included in the final multivariable model. The variable demonstrating the strongest independent relation with 30-day mortality was age. Even after adjustment for the other important clinical factors, patients at the upper quartile of the age distribution in this population (70 years) were nearly four times more likely to die within 30 days than patients at the lowest quartile (52 years; adjusted OR, 3.88; 95% CI, 3.52 to 4.28). The other more significant independent predictors of mortality were systolic blood pressure, Killip class, heart rate, and MI location.

Only one interaction among these factors was significant to the degree that it was appropriate to include in the model—the interaction between age and Killip class. The prognostic effect of age was reduced somewhat among patients with a more severe Killip class at entry,

TABLE 2. Unadjusted Mortality Rates and ORs for Categorical Baseline Characteristics

Variable	Category	Mortality Rate, %	χ^2	OR	95% CI
Sex	Female	11.3	391	2.17	(2.01, 2.35)
	Male	5.5			
Race	Caucasian	7.0	0.15	0.97	(0.85, 1.12)
	Other	7.1			
Country	United States	6.8	2.9	0.94	(0.87, 1.01)
	Non–United States	7.2			
Hypertension	Yes	8.5	103	1.49	(1.38, 1.61)
	No	5.9			
Diabetes	Yes	10.6	155	1.79	(1.64, 1.97)
	No	6.2			
Smoking	Never	10.3	445	2.74	(2.50, 3.01)
	Past	6.7		1.58	(1.44, 1.75)
	Current	4.0			
Hypercholesterolemia	Yes	5.1	61	0.70	(0.64, 0.77)
	No	7.2			
Family history	Yes	4.8	108	0.63	(0.58, 0.69)
	No	7.4			
Previous MI	Yes	11.7	293	2.11	(1.93, 2.29)
	No	5.9			
Previous angina	Yes	8.3	81	1.43	(1.32, 1.54)
	No	6.0			
Cerebrovascular disease	Yes	15.5	99	2.56	(2.13, 3.08)
	No	6.7			
Prior bypass surgery	Yes	10.7	41	1.66	(1.42, 1.93)
	No	6.7			
Prior angioplasty	Yes	5.6	4.4	0.80	(0.64, 0.98)
	No	7.0			
Infarct location	Anterior	9.9	361	2.11	(1.96, 2.28)
	Inferior	5.0			
	Other	7.2		1.48	(1.20, 1.82)
Killip class	I	5.1	2343		
	II	13.6		2.95	(2.70, 3.23)
	III	32.2		8.91	(7.63, 10.40)
	IV	57.8		25.68	(21.96, 30.03)

MI indicates myocardial infarction; OR, odds ratio; and CI, confidence interval.

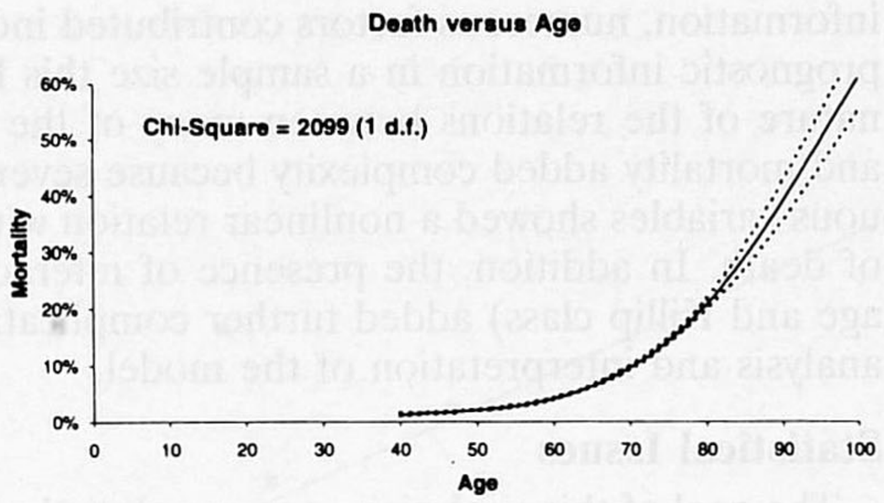
and conversely, risk differences among Killip classes were less in older patients.

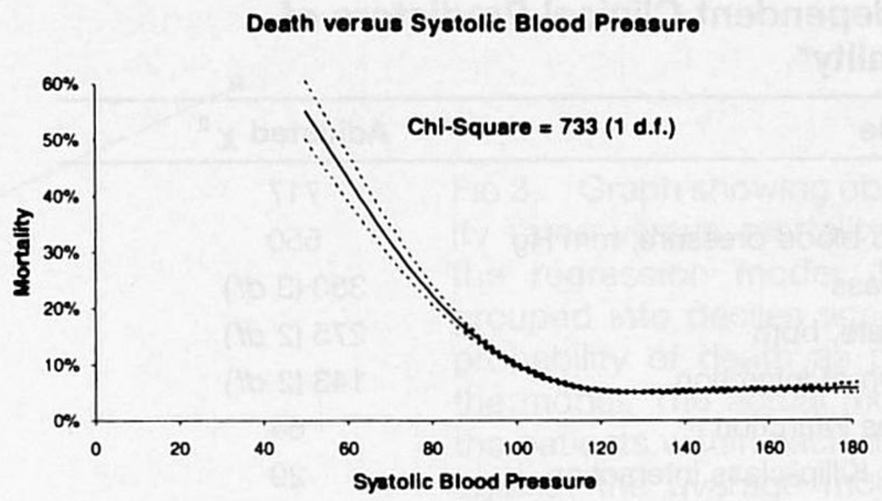
Fig 2 shows adjusted ORs for mortality for each of the variables in the final multivariable model. The ORs were most dramatic for factors such as age and Killip class, each exhibiting a highly significant relation with mortality in the multivariable regression analysis. After adjustment for all other factors, the OR associated with Killip class III versus I for an average-age patient was 4.37 (95% CI, 3.34 to 5.71), whereas the OR for Killip class IV versus I was 7.86 (95% CI, 5.88 to 10.49).

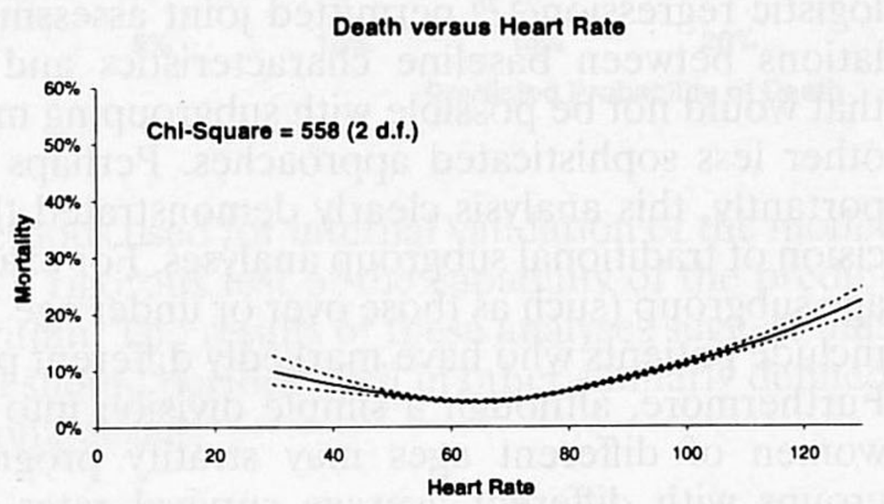
The model formulation that includes all factors in Table 3 is given in the "Appendix." With the coefficients in this model and the ORs in Fig 2, relative effects of various clinical factors can be quantified. For example, each additional year of age in Killip class I patients imparts a risk equal to a 2 mm Hg reduction in systolic blood pressure (for patients presenting with systolic blood pressures below 120 mm Hg) or to treating patients 45 minutes later. An additional 7 years of age confers a risk similar to the difference between an inferior and anterior MI, and the risk reduction associated with use of accelerated TPA is equivalent to a reduction in age of about 3 years.

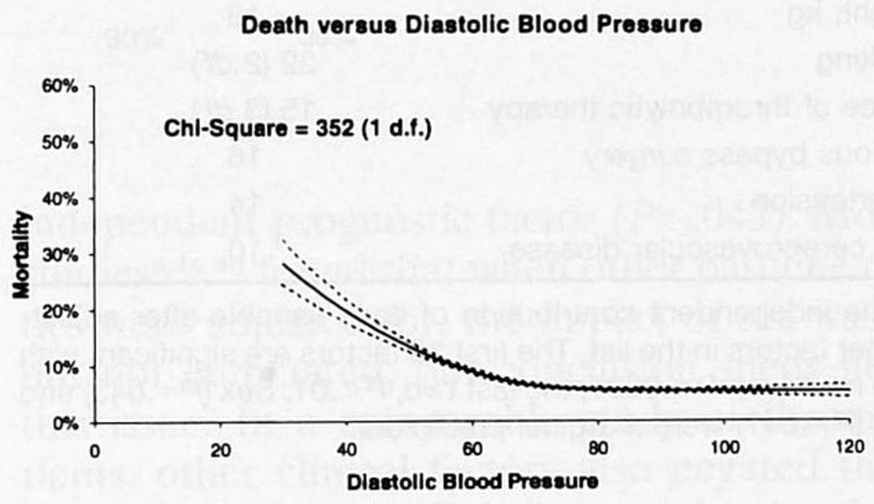
The index of predictive discrimination for this model, namely the area under the receiver operating characteristic curve, was 0.836, reflecting excellent ability of the model to discriminate between patients who do and do not have a fatal event within 30 days.

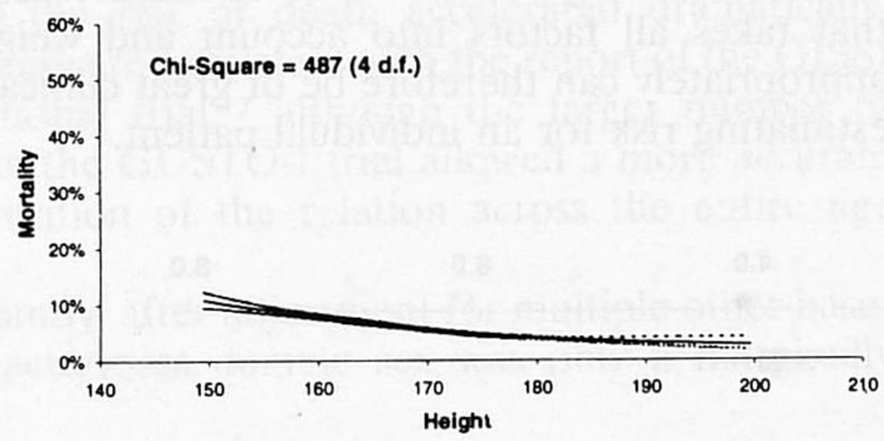
Fig 3 shows the calibration (reliability) of the model predictions. Patients were divided into deciles of risk according to their model predictions, and the observed mortality rate among the patients in each decile was calculated and plotted against the average predicted probability. The points all fell very close to the 45° line (perfect calibration), demonstrating excellent calibration of the predictions from this model. Table 4 illustrates the same concept for several arbitrarily chosen subgroups defined by specific clinical characteristics, namely sex, age, infarct location, and Killip class. The average predicted mortality for patients in each of these subgroups (even subgroups defined by a factor not included in the multivariable model, such as male and female patients) coincided very closely with the observed mortality, again reflecting excellent calibration of the model predictions. Results of the internal validation revealed very little overoptimism in the predictive discrimination of the model. The correction to the receiver operating characteristic area determined by cross validation was only 0.002 (reducing the value from 0.836 to 0.834). The bootstrapping technique produced exactly the same correction. As a result, the calibration curve in Fig 3 did not need an optimism correction.











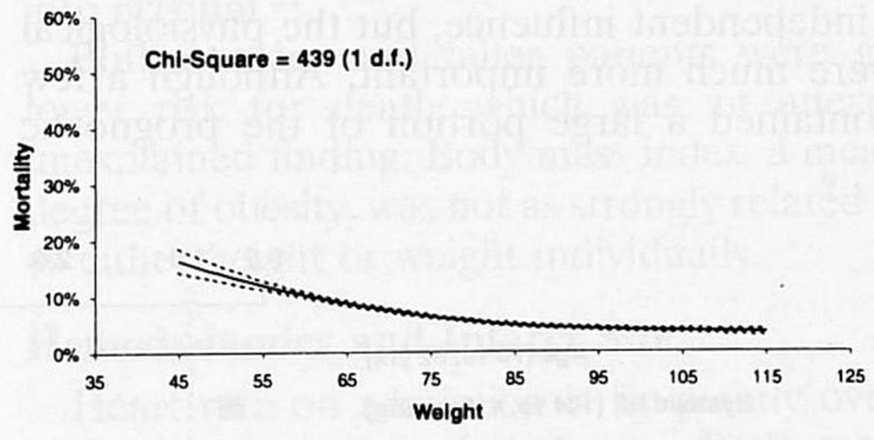
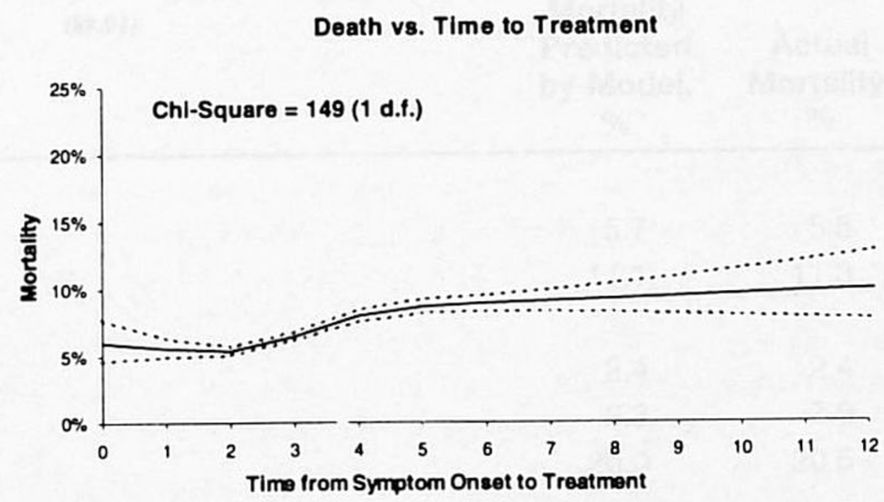


FIG 1. Plots showing unadjusted (univariate) relations between continuous baseline variables and 30-day mortality based on logistic regression. Each panel depicts the probability of death (solid curve) with 95% CIs (dotted curves) as a function of the baseline variable. The degrees of freedom (*df*) associated with the χ^2 statistic in each case depend on the complexity of the relation between the variable and the log odds of mortality. Where *df*=3, the relation was nonlinear and characterized with cubic spline functions. Where *df*=1, the relation was linear even though the plot shown here, which reflects mortality (rather than the log odds), exhibits a nonlinear relation. For heart rate (2 *df*), two linear splines were used to model the relation. Age was measured in years, blood pressure in millimeters of mercury, heart rate in beats per minute, height in centimeters, weight in kilograms, and time to treatment in hours.



A perspective on the overall contribution of various components of the baseline clinical data to the prediction of mortality can be obtained by use of the global χ^2 statistic from the logistic model as an index of prognostic information and a comparison of this index from the full model containing all the variables listed in Table 3 with reduced models containing a smaller number of variables. The likelihood ratio χ^2 statistic for a model containing all of the prognostic factors in Table 3 was 4379. In contrast, this statistic for a model containing age alone was 2099, meaning that age provides nearly half the prognostic information. Adding other variables provides an increased proportion of information; combining age, systolic blood pressure, Killip class, heart rate, infarct location, and age-by-Killip-class interaction provides approximately 90% of the total prognostic information contained in this array of baseline clinical characteristics.

Discussion

The clinical determinants of mortality in patients treated with thrombolytic therapy for ST-segment elevation within 6 hours of symptom onset are complex and multidimensional. Much of the important prognostic information was contained in the patient's age, location of the infarction, and physiological characteristics rep-

TABLE 3. Independent Clinical Predictors of 30-Day Mortality*

Variable	Adjusted χ^2
Age, y	717
Systolic blood pressure, mm Hg	550
Killip class	350 (3 *df*)
Heart rate, bpm	275 (2 *df*)
Location of infarction	143 (2 *df*)
Previous infarction	64
Age-by-Killip-class interaction	29
Height, cm	31 (4 *df*)
Time to treatment, h	23
Diabetes	21
Weight, kg	16
Smoking	22 (2 *df*)
Choice of thrombolytic therapy	15 (3 *df*)
Previous bypass surgery	16
Hypertension	14
Prior cerebrovascular disease	10

*Indicates the independent contribution of each variable after adjustment for all other factors in the list. The first 10 factors are significant with $P<.00001$; the next four, $P<.0001$; the last two, $P<.01$. Sex ($P=.043$) and US enrollment ($P=.047$) were marginal predictors.

resenting the severity of the derangement in myocardial function. Another tier of variables reflecting the circumstances under which the infarction was treated (eg, time to treatment and type of thrombolytic therapy) also exerted an independent influence, but the physiological variables were much more important. Although a few variables contained a large portion of the prognostic information, numerous factors contributed independent prognostic information in a sample size this large. The nature of the relations between many of the attributes and mortality added complexity because several continuous variables showed a nonlinear relation with the risk of death. In addition, the presence of interactions (eg, age and Killip class) added further complication to the analysis and interpretation of the model.

Statistical Issues

The goal of this analysis was to use statistical methods to model the medical issues as closely as possible. The use of cubic spline functions[27-31] in conjunction with logistic regression[25,26] permitted joint assessment of relations between baseline characteristics and outcome that would not be possible with subgrouping methods or other less sophisticated approaches. Perhaps most importantly, this analysis clearly demonstrated the imprecision of traditional subgroup analyses. For example, any age subgroup (such as those over or under age 75) would include patients who have markedly different prognoses. Furthermore, although a simple division into men and women of different ages may stratify prognosis into groups with different average survival rates (eg, men <70 years versus women >70 years), the presence or absence of multiple other characteristics could place an individual patient within this broadly defined subgroup at a dramatically different risk. A multivariable model that takes all factors into account and weights them appropriately can therefore be of great clinical value in estimating risk for an individual patient.

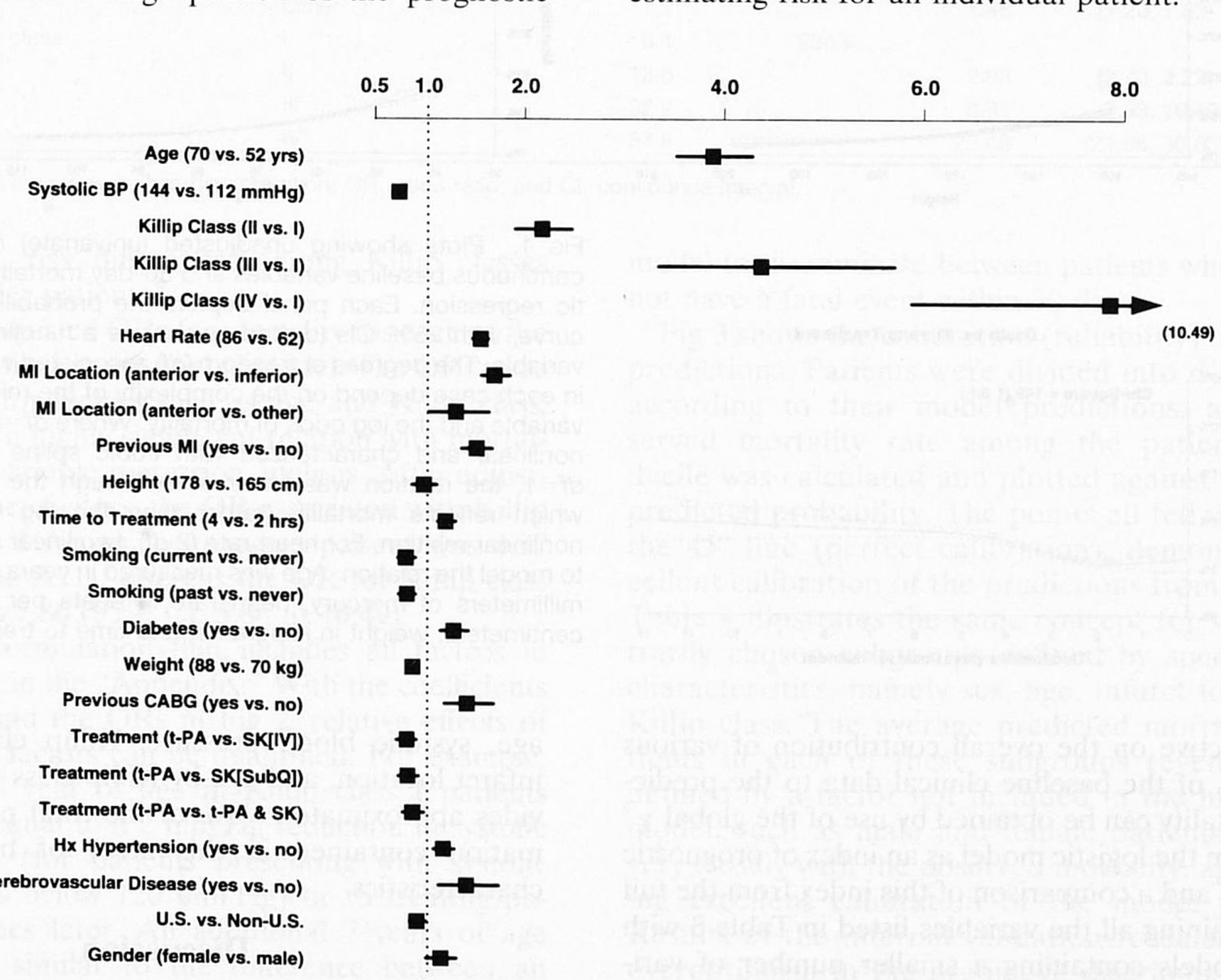


FIG 2. Graph showing ORs and 95% CIs for variables in the final multivariable mortality risk model (Table 3). Calculated from the model containing all the factors listed in Table 3, each OR is adjusted to account for the other variables in the model. Also shown are adjusted ORs for the two marginally significant variables, sex and enrollment in the United States. For continuous variables, the value depicted reflects the odds of death for patients at the 75th percentile of the distribution of the variable versus patients at the 25th percentile. An OR of 1.0 represents no prognostic stratification; a value >1 reflects increased risk of death; a value <1 reflects reduced risk of death. BP indicates blood pressure; MI, myocardial infarction; CABG, coronary artery bypass surgery; TPA (t-PA), accelerated tissue-plasminogen activator; SK, streptokinase; SubQ, subcutaneous; and Hx, history.

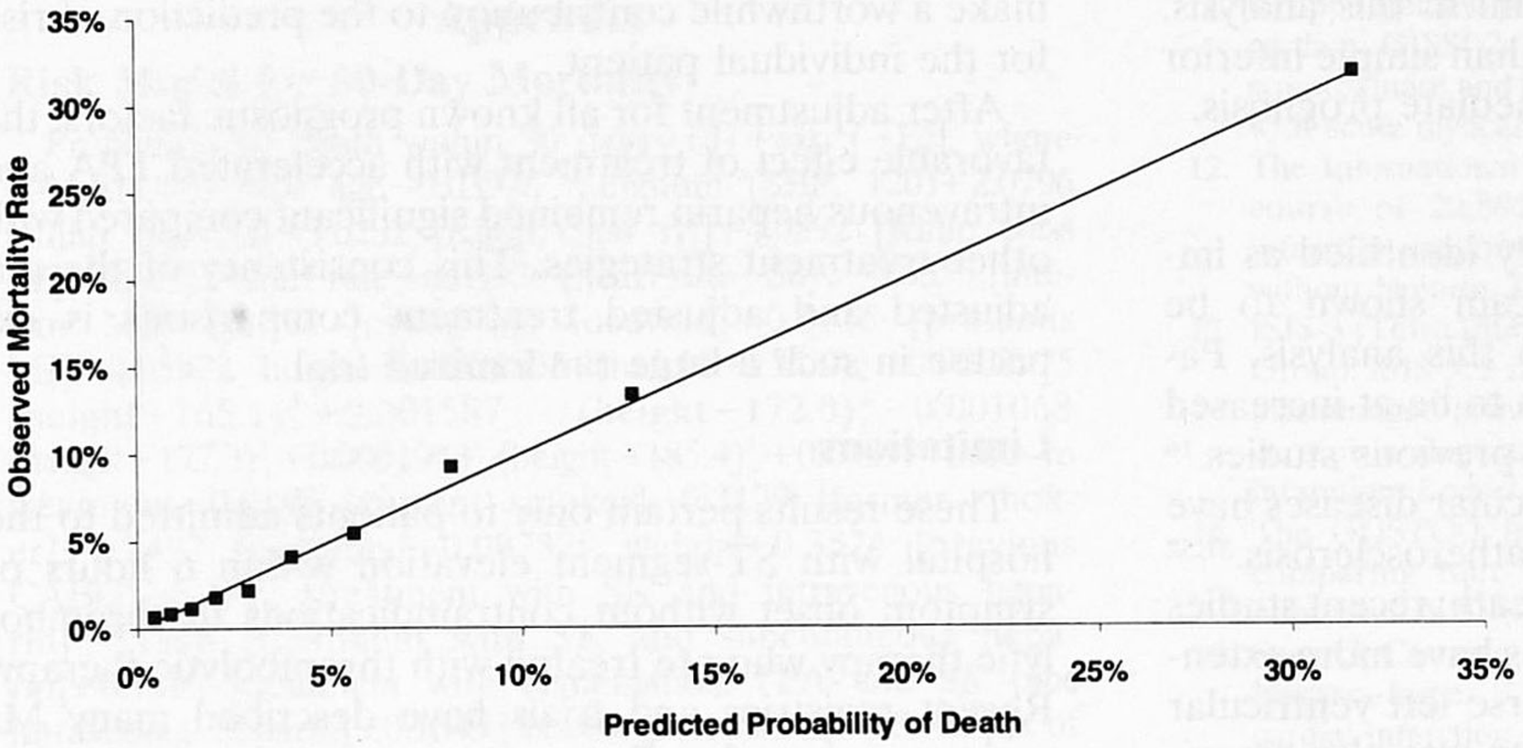


FIG 3. Graph showing observed mortality rates versus mortality predicted by the regression model. Patients were grouped into deciles according to their probability of death as predicted from the model. The actual mortality rate for the patients within each decile is plotted against the average model prediction. The solid diagonal line reflects perfect calibration of the model predictions.

The methods used for internal validation of the model represent a rigorous test of the capability of the prediction algorithm. The results of these analyses suggest that the model should perform well in other similarly defined patient populations.

Demographics

Age has been increasingly recognized as a critical determinant of outcome in patients with acute ischemic heart disease. The relation was relatively flat until age 60, when the risk of death accelerated dramatically. These results are consistent with the report of the GISSI 2/International trial,[12] although the larger number of patients in the GUSTO-I trial allowed a more accurate characterization of the relation across the entire age range.

Importantly, after adjustment for multiple other baseline characteristics, female sex was only a marginally independent prognostic factor (P=.043). Most previous studies[8,44-46] found that when other baseline characteristics were adjusted for, the impact of sex was weakened but not eliminated; our conclusion sheds new light on this issue. In a comparable study of thrombolytic patients, other clinical factors also negated the independent effect of sex, although that study involved a much smaller number of patients and the OR for mortality in women was 1.31, even after the degree of obstructive coronary disease and left ventricular function were taken into account.[44]

Both heavier and taller patients were generally at lower risk for death, which was an unexpected and unexplained finding. Body mass index, a measure of the degree of obesity, was not as strongly related to outcome as either height or weight individually.

TABLE 4. Comparison of Predicted and Actual 30-Day Mortality in Selected Patient Subgroups

Subgroup	Mortality Predicted by Model, %	Actual Mortality, %
Sex		
Male	5.7	5.5
Female	11.1	11.3
Age, y		
<60	2.4	2.4
60-75	8.3	7.9
>75	20.0	20.5
Infarct location		
Anterior	10.0	9.9
Inferior	5.0	5.0
Killip class		
I	5.1	5.1
II	13.9	13.6
III	32.7	32.2
IV	57.8	57.8
Factor combinations		
Female, age >75	22.6	22.9
Female, age >75, inferior MI	17.3	16.6
Female, age >75, inferior MI, Killip class I	14.7	14.1
Male, age <60	2.2	2.2
Male, age <60, anterior MI	3.1	3.5
Male, age <60, anterior MI, Killip class I	2.0	2.3

MI indicates myocardial infarction.

Hemodynamics and Infarct Site

Heart rate on admission is frequently overlooked as an important prognostic indicator. Patients with significant sinus tachycardia or bradycardia on hospital admission had an increased risk of death. Previous studies have identified sinus tachycardia as an independent prognostic factor,[47] presumably because it represents activation of the sympathetic nervous system as a consequence of infarction size. The physiological significance of bradycardia may represent a variety of underlying pathophysiological problems, ranging from conduction system disturbances to agonal rhythms.

Systolic blood pressure is a critical factor. It is no surprise that hypotension was associated with a decrease in survival, but the level at which prognosis began to decline (120 mm Hg) is somewhat higher than expected. We could not find an effect of elevated blood pressure on survival. Many patients with extreme elevations of systolic blood pressure were excluded from GUSTO-I because of concern about the risk of intracranial hemorrhage, but 602 patients with a systolic blood pressure exceeding 180 mm Hg were included.

The relation between outcome and location of infarction is complicated. Multiple previous studies have reported that patients with anterior infarction have the highest risk of death,[47-49] and isolated inferior infarction has been associated with the lowest risk. A detailed analysis from the GISSI I trial showed that the number of leads with ST-segment elevation was more important than infarction location,[50] but ECG information from

GUSTO-I is not yet available to confirm this analysis. We found that infarct location other than simple inferior or anterior infarctions had an intermediate prognosis.

Medical History

Several baseline features previously identified as important prognostic factors were again shown to be important predictors of mortality in this analysis. Patients with prior MI have been shown to be at increased risk of subsequent death in multiple previous studies.[16] Similarly, peripheral and cerebral vascular diseases have been associated with more extensive atherosclerosis.[51,52] Diabetes was a major risk factor for death; recent studies have shown that patients with diabetes have more extensive coronary atherosclerosis and worse left ventricular function.[53,54] A history of hypertension was also associated with increased risk, although the strength of the relation was much less than that of diabetes. At least a portion of the increased risk may be due to heightened risk of stroke.

The influences of smoking, family history, and elevated cholesterol were paradoxical: they were associated with lower mortality despite being traditional risk factors for coronary artery disease. Several other studies also reported lower mortality in patients with a history of smoking.[21,55,56] We presume that these relations are mediated by the association of these risk factors with premature atherosclerosis and thrombotic occlusion: the acute event occurs in a younger patient with less overall atherosclerosis and other comorbidity or is precipitated by a lesser stimulus, which may respond better to thrombolytic therapy. Despite this construct, we were unable to demonstrate that adjustment for other noninvasive measures of severity of illness completely explained the more benign prognosis of patients who were current or past smokers. Detailed assessment of coronary angiographic findings will be required to understand these relations more clearly.

The influences of prior percutaneous coronary angioplasty and coronary bypass grafting are complicated. Because most patients undergoing initial angioplasty have single-vessel disease, it is not surprising that they have a better prognosis than those who have an array of single-, double-, and triple-vessel disease. No previous studies included enough patients with prior angioplasty to allow comparison. The negative prognostic implications of prior coronary artery bypass grafting probably reflect the presence of more left ventricular dysfunction and multivessel coronary disease, leaving patients at increased risk of adverse outcomes in the setting of an acute event.

Modifiable Factors

Of the predictors of adverse outcome that can be modified, time from symptom onset to hospital arrival or treatment is the most important. After adjustment for other factors in the model, each additional hour was associated with a measurable increase in the risk of death. This relation, however, was not linear for reasons that are unclear.

After adjustment for other baseline characteristics, treatment in the United States (compared with other countries) was marginally associated with a better prognosis. The small difference ($P=.047$) was not enough to make a worthwhile contribution to the prediction of risk for the individual patient.

After adjustment for all known prognostic factors, the favorable effect of treatment with accelerated TPA and intravenous heparin remained significant compared with other treatment strategies. This consistency of the unadjusted and adjusted treatment comparisons is expected in such a large randomized trial.

Limitations

These results pertain only to patients admitted to the hospital with ST-segment elevation within 6 hours of symptom onset without contraindications to thrombolytic therapy who are treated with thrombolytic therapy. Recent registries and trials have described many MI patient groups that have a higher risk of death than those in this analysis. Patients with contraindications to thrombolytic therapy have the highest mortality,[57] and those with an acute MI without ST-segment elevation have an intermediate risk.[58] Though many of the same factors identified in this analysis would be expected to relate to mortality, the quantitative relations described here may not apply.

Additional clinical measurements not included in these analyses would also be expected to add to the prognostic model, especially additional ECG and angiographic information. Recent studies show that detailed measures of ST-segment elevation and T-wave height may provide substantial information about prognosis,[50,59] independent of infarction location or other physiological factors. Also, coronary anatomy,[60] left ventricular function,[61] and patency and degree of mitral regurgitation[62] would be expected to play major roles in determination of prognosis. Because most patients with acute ischemic disease do not undergo acute cardiac catheterization, using this information for risk assessment would not be meaningful in most patients. However, the information available from the GUSTO-I angiographic substudy[63] provides insight into the pathophysiological basis for the risks associated with various baseline characteristics.

Conclusions

Careful modeling of 30-day mortality, using the large population of GUSTO-I patients and data routinely collected at initial presentation, has yielded a method to accurately predict short-term risk in individual patients. This risk-assessment algorithm should be useful clinically in managing patients who are candidates for thrombolytic therapy. Many prognostic factors identified in this analysis cannot be modified, but the importance of early detection and treatment of MI remained evident: even after adjustment for physiological measures of hemodynamic deterioration, time to treatment and type of thrombolytic therapy remained independent prognostic factors. Only by considering the effect of multiple characteristics, including age, medical history, physiological significance of the current event, and medical treatment, can the prognosis of an individual patient be estimated with confidence.

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Appendix

Risk Model for 30-Day Mortality

Probability of death within 30 days=1/[1+exp (−L)], where L=3.812+0.07624 age−0.03976 minimum (SBP, 120)+2.0796 [Killip class II]+3.6232 [Killip class III]+4.0392 [Killip class IV]−0.02113 heart rate+0.03936 (heart rate−50)$_+$−0.5355 [inferior MI]−0.2598 [other MI location]+0.4115 [previous MI]−0.03972 height+0.0001835 (height−154.9)$^3_+$−0.0008975 (height−165.1)$^3_+$+0.001587 (height−172.0)$^3_+$−0.001068 (height−177.3)$^3_+$+0.0001943 (height−185.4)$^3_+$+0.09299 time to treatment−0.2190 [current smoker]−0.2129 [former smoker]+0.2497 [diabetes]−0.007379 weight+0.3524 [previous CABG]+0.2142 [treatment with SK and intravenous heparin]+0.1968 [treatment with SK and subcutaneous heparin]+0.1399 [treatment with combination TPA and SK plus intravenous heparin]+0.1645 [hx of hypertension]+0.3412 [hx of cerebrovascular disease]−0.02124 age · [Killip class II]−0.03494 age · [Killip class III]−0.03216 age · [Killip class IV].

Explanatory notes.

1. Brackets are interpreted as [c]=1 if the patient falls into category c, [c]=0 otherwise.
2. $(x)_+=x$ if $x>0$, $(x)_+=0$ otherwise.
3. For systolic blood pressure (SBP), values >120 mm Hg are truncated at 120.
4. For time to treatment, values <2 hours are truncated at 2.
5. The measurement units for age are years; for blood pressure, millimeters of mercury; for heart rate, beats per minute; for height, centimeters; for time to treatment, hours; and for weight, kilograms.
6. "Other" MI location refers to posterior, lateral, or apical but not anterior or inferior.
7. CABG indicates coronary artery bypass grafting; SK, streptokinase; and hx, history.

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