Prediction of One-Year Survival in High-Risk Patients with Acute Coronary Syndromes: Results from the SYNERGY Trial

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BACKGROUND: Despite advances in pharmacologic therapy and invasive management strategies for patients with non-ST-segment elevation acute coronary syndromes (NSTE ACS), these patients still suffer substantial morbidity and mortality.

OBJECTIVE: The objective of this study was to analyze independent predictors of 1-year mortality in patients with high-risk NSTE ACS.

DESIGN AND PARTICIPANTS: A total of 9,978 patients were assigned to receive enoxaparin or unfractionated heparin (UFH) in this prospective, randomized, open-label, international trial.

MEASUREMENTS: Vital status at 1 year was collected. Univariable and multivariable predictors of 1-year mortality were identified. Three different multivariable regression models were constructed to identify: (1) predictors of 30-day mortality; (2) predictors of 1-year mortality; (3) predictors of 1-year mortality in 30-day survivors. The last model is the focus of this paper.

RESULTS: Overall, 9,922 (99.4%) of patients had 1-year follow-up. Of the 56 patients (37 UFH-assigned and 19 enoxaparin-assigned) without 1-year data, 11 patients were excluded because of withdrawal of consent, and 45 could not be located. One-year mortality was 7.5% (7.7% enoxaparin-assigned patients; 7.3% UFH-assigned patients; P=0.4). In patients surviving 30 days after enrollment, independent predictors of 1-year mortality included factors known at baseline such as increased age, male sex, decreased weight, having ever smoked, decreased creatinine clearance, ST-segment depression, history of diabetes, history of angina, congestive heart failure, coronary artery bypass grafting, increased heart rate, rales, increased hematocrit, lowered hemoglobin, and higher platelet count. Factors predictive of mortality during the hospitalization and 30-day follow-up period were decreased weight at 30 days from baseline, atrial fibrillation, decreased nadir platelet, no use of beta-blockers and statins up to 30 days, and not receiving an intervention (c-index=0.82).

CONCLUSIONS: Easily determined baseline clinical characteristics can be used to predict 1-year mortality with reasonable discriminative power. These models corroborate prior work in a contemporary aggressively managed population. A model to predict 1-year mortality in patients surviving at least 30 days may be quite helpful to healthcare providers in setting expectations and goals with patients after ACS.

KEY WORDS: non-ST-segment elevation acute coronary syndrome; predictors; mortality; outcomes; low-molecular-weight heparin; unfractionated heparin.
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Despite remarkable advances in pharmacologic therapy and invasive management strategies for patients with non-ST-segment elevation acute coronary syndromes (NSTE ACS), these patients still suffer substantial morbidity and mortality. They also comprise a very heterogeneous spectrum of risk for adverse cardiac events. Several tools have been used to help calculate patient risk because identification of patients at the highest risk for worse outcomes is important in making judicious medical decisions.[1]

In the Superior Yield of the New Strategy of Enoxaparin, Revascularization, and GlYcoprotein IIb/IIIa Inhibitors (SYNERGY) trial, patients at high risk for death and myocardial infarction were randomly assigned to low-molecular-weight heparin (enoxaparin) or unfractionated heparin (UFH). These patients were treated with an early invasive management strategy. The 30-day, 6-month, and 1-year clinical outcomes have been previously reported, confirming that this was a high-risk cohort of patients with nearly 7.5% mortality at 1-year follow-up.[2,3]

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This large database provides an opportunity to develop clinically meaningful models using simple clinical and demographic information to predict long-term outcomes. It is hypothesized that several different models may be of some clinical value to physicians: (1) a model to predict 30-day mortality; (2) a model to predict 1-year mortality; and (3) a model to predict 1-year mortality in 30-day survivors. The latter model is the focus of this paper.

These models may help physicians to easily identify patients at higher risk for worse outcomes at the time of hospital admission and during follow-up visits in the clinic after hospital discharge. The follow-up clinic visit, in particular, is a time during which the physician (who may not have been involved with patient care during the hospital admission) needs to provide patient and family education and establish expectations for long-term prognosis. A simple model may be a valuable tool to help guide these discussions.

METHOD

Study Population

The rationale and design as well as the primary results of SYNERGY have been previously reported.[2–4] Inclusion criteria were ischemic symptoms lasting for at least 10 minutes occurring within 24 hours of enrollment and at least 2 of the following features: age ≥60 years, troponin or creatinine kinase-MB elevation above the upper limit of normal for the local laboratory, or definitive ST-segment changes on 12-lead electrocardiograph.

Study Design

Patients were randomly assigned to enoxaparin or UFH and remained eligible if they had been already started on antithrombin therapy as long as they met all inclusion criteria. Study drug assignment was independent of pre-enrollment antithrombin use. The study drug was to be given immediately after randomization and continued through coronary angiography and percutaneous or surgical revascularization, if indicated, or until no further antithrombin was needed at the discretion of the treating physician. Specific dosing guidelines for UFH and enoxaparin have been reported.[2–4] Choice and use of all other medications during the baseline hospitalization, at the time of hospital discharge, and through long-term observation were at the discretion of the treating clinician with recommendation to follow the published practice guidelines.[5,6]

Patient Follow-Up

Detailed data were collected during the baseline hospitalization. Patients were contacted by telephone or seen in the clinic at 30 days after enrollment (minimum ≥27 days). Patients were subsequently contacted by telephone at 180 days (minimum ≥120 days) for ascertainment of cardiac events and by telephone at 1 year (minimum ≥10 months) to determine survival status. If patients were not able to be contacted by telephone, medical records were reviewed, national death indices were queried, or, if necessary, a private locator service was used (in the USA only).

Statistical Analyses

The protocol prespecified the incidence of death at 1 year as a key secondary end point. Overall, 10,027 patients were enrolled in the study, but 9,978 were included in the primary efficacy analyses because the first 49 patients enrolled in 1 country were not randomly assigned because of an error with the interactive voice-activated randomization system.

Categorical variables are presented as frequencies and percentages, and continuous variables are presented as medians and 25th and 75th percentiles. The Kaplan–Meier method was used to estimate the probability of death through 1 year, and efficacy comparisons were based on an intention-to-treat strategy using the log-rank test. Creatinine clearance was calculated using the Cockcroft–Gault formula.

A series of multivariable Cox proportional hazards models were constructed to identify independent predictors of 30-day mortality and 1-year mortality in the overall population and 1-year mortality in patients who survived through 30 days.[2] Potential baseline covariates for both models were randomized treatment, age, sex, weight, height, race, time from symptoms to randomization, region of the world, smoking status, creatinine clearance, Killip class, systolic and diastolic blood pressures, ST-segment elevation and depression, T-wave inversion, diabetes, hypertension, concomitant medications, prior coronary artery disease, recent angina, prior peripheral vascular disease, prior myocardial infarction, prior congestive heart failure, prior percutaneous coronary intervention (PCI), prior coronary artery bypass grafting (CABG), criteria for enrollment, heart rate, rales, hemoglobin, hematocrit, and platelet count. For the 30-day-to-1-year model, the following events up to 30 days were also considered. In-hospital factors were shock, congestive heart failure, atrial fibrillation, cardiac arrest, and nadir lab values. Factors at 30 days were weight, systolic and diastolic blood pressures, and concomitant medications. Factors from baseline through 30 days were myocardial infarction, stroke, recurrent ischemia, and PCI or CABG.

The linearity assumption for all continuous measures was evaluated in the Cox proportional hazards model using restricted cubic spline transformations. Appropriate transfor-

Table 1. Association Between Inclusion Criteria and 30-Day, 6-Month, and 1-Year Mortality Outcomes

	Overall*	Death from 0–30 Days	Death from Day 0–6 Months	Death from Day 0–1 Year
Age ≥60 and elevated cardiac biomarkers	1,948/ 9,658 (20.2%)	48 (2.5%)	93 (4.8%)	129 (6.7%)
Age ≥60 and ECG changes	1,535/ 9,658 (15.9%)	45 (2.9%)	75 (4.9%)	113 (7.4%)
Age ≥60, elevated cardiac biomarkers, and ECG changes	4,314/ 9,658 (44.7%)	201 (4.7%)	329 (7.7%)	437 (10.2%)
Elevated cardiac biomarkers and ECG changes	1,861/ 9,658 (19.3%)	15 (0.8%)	35 (1.9%)	50 (2.7%)

ECG Electrocardiograph
**Observed frequency (%)*

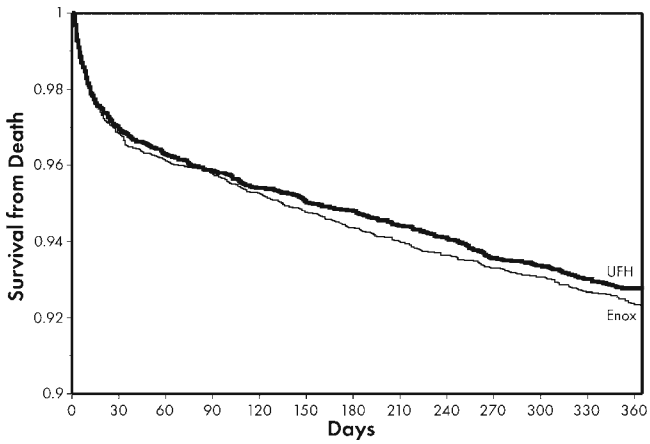


Figure 1. Kaplan–Meier curves for survival from death through 1-year follow-up by treatment.

mations were made to the variables when needed. The proportional hazards assumption was evaluated for each of the factors. If a factor was found to violate this assumption, it was stratified for modeling. Both backwards and stepwise regression variable selection techniques were used. The results of these 2 techniques were compared, and the final model was based on clinical relevance.

For the model to predict mortality at 1 year in 30-day survivors, a subsequent model of baseline factors and events during baseline hospitalization and at 30 days was developed, and the most significant factors were used in a nomogram.[7] The nomogram allows one to calculate the predicted probabil-

Table 2. Baseline Clinical Demographics and Index Hospitalization Procedures in Patients Who Died by 30 Days, between 30 Days and 1 Year, and Who Survived to 1 Year

	Died ≤30 Days, *n*=314	Died between 30 Days and 1 Year, *n*=425	Survived to 1 Year, *n* =9,183
Age (years), mean (25th, 75th percentile)	74.0 (68.0, 80.0)	72.1 (67.0, 79.0)	66.5 (60.0, 74.0)
Male sex	64.0%	68.5%	66.0%
Systolic BP (mmHg), mean (25th, 75th percentile)	129 (110, 143)	134 (118, 150)	133 (117, 147)
Heart rate (bpm), mean (25th, 75th percentile)	81 (69, 90)	78 (66, 88)	72 (62, 80)
Killip class			
I	70.2%	69.8%	88.8%
II	22.5%	21.7%	9.1%
III	6.0%	7.2%	1.7%
IV	1.3%	1.2%	0.4%
ST-segment elevation	11.5%	9.4%	13.1%
ST-segment depression	67.5%	62.3%	54.0%
Family history of CAD	41.6%	41.7%	46.1%
Medical history			
Hypertension	73.6%	76.7%	67.5%
Diabetes	38.2%	43.5%	28.4%
Myocardial infarction	39.2%	39.5%	27.2%
CHF	24.2%	26.4%	8.0%
CABG	20.4%	27.3%	16.0%
PCI	19.4%	27.1%	19.9%
Current smoker	20.2%	21.4%	24.3%
In-hospital procedures			
PCI	26.8%	31.1%	48.5%
CABG	26.8%	17.2%	18.5%
Catheterization	75.5%	81.4%	93.2%

BP Blood pressure, bpm beats per minute, CABG coronary artery bypass grafting, CAD coronary artery disease, CHF congestive heart failure, PCI percutaneous coronary intervention

Table 3. Independent Predictors of 30-Day Mortality

Variable	Chi-square	Odds Ratio (95% Confidence Limits)	*P* Value
Increased heart rate (bpm)†	56.6	1.31 (1.22, 1.40)	<0.0001
Current smoker vs others‡	15.4		0.0004
Enoxaparin users		1.00 (0.62, 1.63)	
UFH users		2.29 (1.51, 3.27)	
Prior CHF	8.1	1.58 (1.15, 2.17)	0.004
Increased age (years)†	22.7	1.54 (1.29, 1.84)	<0.001
Baseline rales	12.8	1.71 (1.28, 2.30)	0.0003
Increased weight (kg)*†	10.3		0.006
≤60 kg		0.77 (0.52, 1.14)	
>60 kg		1.17 (1.06, 1.29)	
Increased CrCl (ml/min)*†	41.0		<0.0001
CrCl ≤110 ml/min		0.77 (0.71, 0.84)	
CrCl >110 ml/min		0.90 (0.70, 1.17)	
T-wave inversion on baseline ECG	15.7	0.50 (0.35, 0.70)	<0.0001
Increased systolic BP (mm Hg)*†	15.3		0.0005
Increased systolic BP ≤145 mmHg		0.85 (0.78, 0.92)	
Increased systolic BP >145 mmHg		1.14 (1.00, 1.30)	
Meets 2 inclusion criteria§	12.1	0.55 (0.39, 0.77)	0.0005
Prior MI	10.6	1.56 (1.19, 2.04)	0.001
Enrollment at a Latin American site	8.1	1.95 (1.23, 3.09)	0.004
Enoxaparin vs UFH§	7.0		0.031
Previous or never smokers		1.21 (0.93, 1.59)	
Current smokers		0.53 (0.30, 0.92)	
Randomized treatment by current smoker interaction	6.9		0.009
Increased diastolic BP >85 (mm Hg)†	5.1	0.63 (0.42, 0.94)	0.024
Prior PCI	4.2	0.71 (0.51, 0.98)	0.04

C-index=0.80

BP Blood pressure, CHF congestive heart failure, CrCl creatinine clearance, ECG electrocardiograph, MI myocardial infarction, PCI percutaneous coronary intervention, UFH unfractionated heparin

**2 degrees of freedom (df); all others have 1. Linear spline transformations have been applied to these factors.*

†Odds ratios are in units of 10. For example, the OR of 1.54 for age indicates increased odds of dying by 30 days for a 50-year-old vs a 40-year-old as well as for a 65-year-old vs a 75-year-old.

‡The odds ratio for current smoker vs others is by randomized treatment arm because there is a statistically significant interaction term between the two factors, thus, the interpretation of one must be with regard to the other. Similarly, the odds ratio for enoxaparin vs UFH is by smoking group.

§Age ≥60, ST-segment changes, and negative cardiac biomarkers.

Table 4. Independent Predictors of 1-Year Mortality

Variable	Chi-square	Hazard Ratio (95% Confidence Limits)	*P* Value
Male sex	17.0	1.45 (1.21, 1.74)	<0.0001
Increased creatinine clearance (ml/min)*	64.0		<0.0001
CrCl≤110		0.83 (0.79, 0.87)	
CrCl>110		0.92 (0.80, 1.07)	
Increased heart rate (bpm)*	62.0	1.19 (1.14, 1.24)	<0.0001
Smoking status	27.0		<0.0001
Current smoker		1.77 (1.42, 2.21)	
Former smoker		1.34 (1.12, 1.59)	
History of CHF	32.0	1.73 (1.43, 2.09)	<0.0001
Increased age (years)*	49.0	1.47 (1.32, 1.64)	<0.0001
History of diabetes	21.0	1.45 (1.23, 1.70)	<0.0001
Baseline rales	23.0	1.59 (1.31, 1.93)	<0.0001
ST depression on baseline ECG	21.0	1.46 (1.24, 1.73)	<0.0001
Increased weight (kg)*	16.0		0.0003
Weight ≤60 kg		0.61 (0.48, 0.78)	
Weight >60 kg		1.05 (0.99, 1.12)	
History of PVD	15.0	1.45 (1.20, 1.76)	0.0001
Killip class 3 or 4	6.7	1.49 (1.10, 2.01)	0.001
No positive biomarkers at randomization	6.7	0.75 (0.61, 0.93)	0.001
T-wave inversion on baseline ECG	5.7	0.78 (0.64, 0.96)	0.017
Enoxaparin vs UFH	0.3	1.04 (0.90, 1.21)	0.59

C-index=0.79

CHF Congestive heart failure, CrCl creatinine clearance, ECG electrocardiograph, PVD peripheral vascular disease, UFH unfractionated heparin

**Hazard ratios are in units of 10. For example, the HR of 1.54 for age indicates increased hazard of dying by 30 days for a 50-year-old vs a 40-year-old as well as for a 65-year-old vs a 75-year-old.*

ity of death during this time period using a simple algorithm at the time at which a patient enters the hospital. The reduced model was validated using 200 bootstrapped samples. The *c*-index for the reduced model was recalibrated to account for the optimism from having generated the model on the same data on which it was tested.

SAS® version 8.2 was used for all analyses (Cary, NC, USA). A *P* value of 0.05 was considered statistically significant, bearing in mind the secondary nature of these analyses.

RESULTS

Complete follow-up through 1 year was available for a total of 9,922/9,978 (99.4%) patients: 4,974 (99.6%) of patients assigned enoxaparin and 4948 (99.6%) of patients assigned UFH. Missing follow-up data because of withdrawal of consent (4 enoxaparin and 7 UFH patients) or lack of patient contact (lost to follow-up; 15 enoxaparin and 30 UFH patients) occurred in only 0.6% of all patients.

Overall, 314 patients died by 30-day follow-up, 227 patients died from 30 days through 180 days, and 198 died from 180 days through 1 year after enrollment, making for a total of 739 patients who died by 1 year. Table 1 shows the proportion of patients who died by 1-year follow-up by inclusion criteria. Patients who met all 3 key inclusion criteria have a 1 in 10 chance of dying by 1 year.

Table 5. Independent Predictors of 1-Year Mortality in Patients Surviving through 30 Days

Variable	Chi-square	Hazard Ratio (95% Confidence Limits)	*P* Value
Increased Hgb, truncated above 15	32.4647	0.805 (0.748, 0.868)	<0.0001
Atrial fibrillation/ flutter	25.2975	2.307 (1.666, 3.195)	<0.0001
Post-randomization CABG within 30 days of enrollment	25.0791	0.363 (0.244, 0.540)	<0.0001
Male sex	22.1412	1.991 (1.495, 2.652)	<0.0001
Baseline platelet beyond 200*	21.2266	1.037 (1.021, 1.053)	<0.0001
Use of statin at day 30	16.5374	0.607 (0.477, 0.772)	<0.0001
Increased nadir platelet up to 200*	16.2486	0.932 (0.901, 0.965)	<0.0001
Increased creatinine clearance up to 110 ml/min*	13.8349	0.870 (0.808, 0.936)	0.0002
Increased heart rate*	11.9178	1.130 (1.054, 1.211)	0.0006
Current smoker	11.3018	1.767 (1.268, 2.462)	0.0008
History of CHF	10.2144	1.623 (1.206, 2.185)	0.0014
Post-randomization PCI within 30 days of enrollment	9.0854	0.666 (0.512, 0.868)	0.0026
Increased age (years)*	8.4296	1.262 (1.078, 1.476)	0.0037
Prior CABG	6.8831	1.439 (1.096, 1.888)	0.0087
Former smoker	6.7675	1.408 (1.088, 1.822)	0.0093
History of diabetes	6.6485	1.383 (1.081, 1.770)	0.0099
Use of beta-blockers at day 30	6.4919	0.716 (0.553, 0.926)	0.0108
Baseline rales	6.2843	1.446 (1.084, 1.930)	0.0122
ST depression on baseline ECG	6.2579	1.355 (1.068, 1.719)	0.0124
In-hospital post-randomization diagnostic catheterization	5.9511	0.674 (0.491, 0.925)	0.0147
Increased weight at day 30 (kg; baseline—30-day)	5.4519	0.855 (0.750, 0.975)	0.0195
Increased weight at baseline (kg)	4.9521		0.0841
Weight≤60		0.652 (0.446, 0.953)	
Weight>60		1.004 (0.916, 1.100)	
History of angina	4.9443	1.315 (1.033, 1.673)	0.0262

C-index=0.82

CABG Coronary artery bypass grafting surgery, CHF congestive heart failure, ECG electrocardiograph, Hgb hemoglobin, PCI percutaneous coronary intervention

**Hazard ratios are in units of 10. For example, the HR of 1.54 for age indicates increased hazard of dying by 30 days for a 50-year-old vs a 40-year-old as well as for a 65-year-old vs a 75-year-old.*

Figure 1 shows the Kaplan–Meier curves for survival from death by treatment. While most deaths occurred early after presentation, there is still accrual of deaths during 1-year follow-up, with nearly 8% overall mortality by 1 year.

Table 2 shows baseline clinical demographics and index hospitalization procedures in patients who died before 30 days, died between 30 days and 1-year follow-up, and survived to 1 year. As expected, patients who died early were older, had more comorbidities, and had fewer cardiac procedures during the index hospitalization because they either died or were too sick to have procedures.

Age	Score	Baseline Creatinine Clearance (ml/min)	Score	Weight (kg)	Score	Baseline Hgb	Score	Baseline Platelet	Score	Nadir Platelet	Score
35	0	**0**	56	**20**	43	**5**	74	**200**	0	**0**	48
45	4	**10**	51	**40**	22	**6**	67	**300**	13	**20**	43
55	7	**20**	46	**60**	0	**7**	59	**400**	25	**40**	38
65	11	**30**	41	**80**	5	**8**	52	**500**	37	**60**	33
75	15	**40**	35	**100**	11	**9**	45	**600**	50	**80**	29
85	18	**50**	30	**120**	16	**10**	37	**700**	62	**100**	24
90	20	**60**	25	**140**	22	**11**	30	**800**	75	**120**	19
		70	20	**160**	27	**12**	22	**900**	87	**140**	14
		80	15			**13**	15	**1000**	100	**160**	10
		90	10			**14**	7			**180**	5
		100	5			**15**	0			**200**	0
		110	0								
	____	+	____	+	___	+	___	+	___		
Atrial fibrillation / flutter			23			*SUM of Age – Nadir Platelet=*			____		
No statin use during the first 30 days since initial hospitalization			17								
No CABG during the first 30 days after the initial hospitalization			20			*SUM of additional risk factors (to the left)=*			____		
Male sex			20			**TOTAL SCORE**			____		

Figure 2. Nomogram for 30-day to 1-year mortality (reduced model). *CABG* Coronary artery bypass grafting, *Hgb* hemoglobin. In Figure 2, find the value most closely matching the patient's risk factors and circle the corresponding point assignment. Sum the points for all predictive factors. Then use Figure 3 to determine probability of death from 30 days to 1 year after randomization. Example: A 70-year-old male with baseline creatinine clearance of 80, weight of 80 kg, a baseline hemoglobin of 12, a baseline platelet count of 300, and a nadir platelet count of 200, who had a PCI on day 2 of his hospitalization and was discharged from the hospital without a statin would have a total score of (13 (age)+20(male sex)+15(CrCl)+5(wt)+22(Hgb)+13(baseline platelet)+0(nadir platelet)+0(afib)+17(statin)+20(CABG))=125. This score corresponds to a predicted probability of death at 1-year follow-up of ~10% in patients who survived to 30 days.

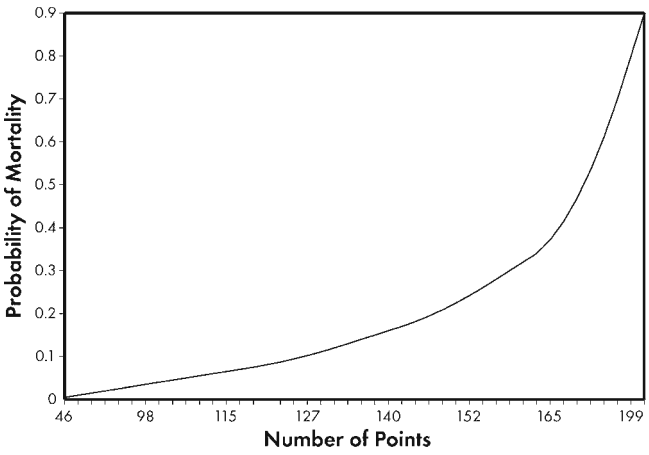
Tables 3, 4, and 5 show the results of the multivariable regression modeling for mortality at 30 days, 1 year, and 1 year in 30-day survivors. Independent baseline predictors of mortality from hospital arrival through 1 year included increased age, male sex, decreased weight, ever having smoked, decreased creatinine clearance, Killip class 3 or 4, ST-segment depression, history of diabetes, peripheral vascular disease or congestive heart failure, having biomarkers as part of the inclusion criteria, increased heart rate, rales, and an absence of T-wave inversion (*c*-index=0.789, bootstrapped=0.785). In patients surviving 30 days after enrollment, independent predictors of 1-year mortality included factors known at baseline such as increased age, male sex, decreased weight, having ever smoked, decreased creatinine clearance, ST-segment depression, history of diabetes, history of angina, congestive heart failure, CABG, increased heart rate, rales, increased hematocrit, lowered hemoglobin, and higher platelet count. Factors during the hospitalization and 30-day follow-up period that were also important in the 30-day-to-1-year model were decreased weight at 30 days from baseline, atrial fibrillation, decreased nadir platelet, no use up to 30 days of beta-blockers and statins, and not receiving an intervention (*c*=0.822, bootstrapped=0.816).

Although the 3 models vary with regard to the candidate variables—baseline factors are only included in Tables 3 and 4—important comparisons can be made about the clinical characteristics predictive of mortality in the 3 models. Increased age, increased weight, diabetes, smoking, male sex, renal dysfunction, and prior cardiac events such as congestive heart failure remain, as expected, key predictors of long-term mortality, but the relative contribution of each factor may change.

A nomogram was generated using the most significant subset of patient-specific factors from the final 30-day-to-1-year model (Fig. 2). This procedure applies a Cox proportional hazards model to this subset and uses the coefficients from this model to develop scores for each factor in the model. The scores are associated with probabilities of survival at day 365 (assuming baseline is at day 30) and can thus be used to estimate a subsequent event (Fig. 3). The reduced model had a *c*-index of 0.734. When validated, the bootstrapped *c*-index was 0.728.

DISCUSSION

The 1-year follow-up data from the SYNERGY trial patients show that this cohort of ACS patients remains at high risk for mortality through 1-year follow-up. Overall, 7.5% of patients died, with 42.5% of the deaths occurring within 30 days of randomization, but patients in this population continue to die during long-term follow-up. No difference was found in mortality rates between enoxaparin and UFH.



Total points	Predicted value
64	1%
107	5%
127	10%
138	15%
147	20%
159	30%
169	40%
177	50%
184	60%
191	70%
199	80%
209	90%

Figure 3. Plot of mortality rates associated with scores calculated from the nomogram in Figure 2. Table shows the predicted values for common point tallies.

Treatment Effect on Mortality

Despite the significant morbidity associated with NSTE ACS, no therapeutic intervention evaluated in the last 10 years has been shown to improve mortality in this patient population. While there have been tremendous advances in the understanding of the pathophysiology of ACS and the importance of a variety of pharmacologic interventions, as well as a greater appreciation of the need for invasive management approaches and improvements in revascularization techniques and devices, the primary impact of these advances has been the reduction in ischemic complications. Therefore, it is expected that the randomly allocated study medication, given for a few days, would not affect mortality.

Need for Models that Predict Clinical Outcomes

There is a growing need for clinical prediction tools. Many important contributions have been made with such tools, although the relative merits of various tools have been debated.[1,8–10] The models presented in the current study are developed from a large cohort of patients with higher risk for worse outcomes than have been previously studied. Also, a model that can be used to reassess long-term risk in those patients who survive the acute event provides a unique tool for clinicians to use during outpatient follow-up when reevaluation and review of risk and expectations with patients and family members is critical.

While our ability to predict outcomes based on simple, readily available markers is improving, reliance on individual markers or clinical characteristics is unlikely to advance our understanding of the important relationships between multiple clinical features of a particular patient.

Continuing to advance our approach to identifying patients at higher risk for worse outcomes is important because the most aggressive therapy can be tailored to those patients at highest risk and therefore most likely to derive enhanced benefit. The evolution of cardiac troponins as markers of both increased risk and of enhanced benefit with glycoprotein IIb/IIIa inhibitors and enoxaparin is a classic paradigm, although the combination of therapies and procedures is made increasingly complex when considered in various patient populations defined by risk.

In practice settings where individual patient decisions are influenced directly by cost constraints and limited resources, models that easily and quickly identify higher risk patients will be valuable in the rationing of health care resources. While difficult to accept, this reality may become more widespread as our population ages and cardiovascular disease becomes more prevalent.

Patients are becoming increasingly savvy about their health care issues. Access to Internet information and direct-to-consumer marketing has increased patients' awareness of diseases and treatments. This trend is expected to continue. Many physicians struggle with how to discuss technical and challenging topics with patients, particularly when the time spent with each patient continues to dwindle based on pressures to see more patients. Providing clear succinct information based on long-term outcomes data would be a valuable tool to assist clinicians in discussing goals and expectations with patients and their families after presentation with ACS.

Limitations

These analyses have several limitations. First, the open-label trial design could potentially bias the reporting of events over time because of knowledge of the treatment assignment, although this is less likely to affect reports of death, and the completeness of the follow-up was more than 99%. Second, the models created from the SYNERGY data set are robust but only include variables that were collected on the standard case report form (CRF) tool. Therefore, there may be important predictors that were not included on the CRF including genetic factors, angiographic findings, and metabolic and inflammatory markers. Third, these results are only applicable to high-risk patients similar to those enrolled in the SYNERGY trial, and while the models enable the prediction of mortality, these data do not address whether changes in treatment or follow-up will change long-term outcomes.

CONCLUSIONS

The SYNERGY trial studied a high-risk cohort of NSTE ACS patients. The 1-year data show that this cohort of patients

remains at high risk for morbidity and mortality through 1-year follow-up. The models presented are consistent with prior work by others, but in a contemporary and aggressively managed population with high use of evidenced-based therapies. A unique model is presented with a simple nomogram that has good discriminative power to predict 1-year mortality in patients surviving at least 30 days after an ACS event. This clinical tool may be quite useful to healthcare providers to predict long-term outcome during follow-up clinic visits and to set expectations and goals with patients and families after an ACS event. The impact of risk assessment on patient management requires further study.

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