Incidence and Predictors of Bleeding After Contemporary Thrombolytic Therapy for Myocardial Infarction

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Background Although the benefit of thrombolytic therapy in reducing mortality in acute myocardial infarction is well established, the types of bleeding and risk factors for bleeding are less well described in large trials.

Methods and Results We analyzed the baseline characteristics, outcomes, and incidence of bleeding by location, severity, and treatment assignment among 41 021 patients in the GUSTO-I trial of thrombolysis for acute myocardial infarction. Of the 40 903 patients for whom there were complete data, 1.2% suffered severe bleeding and 11.4% experienced moderate hemorrhage at a variety of sites. The most common sources of bleeding were procedure related. The thrombolytic regimen was strongly related to the incidence of bleeding; comparatively more bleeding was seen with the therapies of streptokinase plus intravenous heparin and the streptokinase and tissue plasminogen activator plus intravenous heparin combination. In multivariate analysis, the four most powerful independent predictors of hemorrhage were older age, lighter body weight, female sex, and African ancestry; they remained the most important predictors of bleeding when multivariate analysis was performed on patients who did not undergo invasive procedures. The presence of serious hemorrhage was associated with other undesirable outcomes (recurrent events, left ventricular dysfunction, arrhythmia, or stroke).

Conclusions Important predictors of bleeding in this population are increased age, lighter weight, female sex, African ancestry, and experiencing invasive procedures. Other nonhemorrhagic adverse clinical outcomes were associated with moderate and severe bleeding, which was in turn associated with increased length of hospital stay and mortality at 30 days. **(*Circulation*. 1997;95:2508-2516.)**

Key Words • thrombolysis • prognosis • myocardial infarction • streptokinase • plasminogen activators

Thrombolytic therapy reduces mortality[1] across the spectrum of patients with suspected acute myocardial infarction with ST-segment elevation or bundle-branch block, but some of the benefit of thrombolytic therapy is offset by the hazards of hemorrhagic stroke and noncerebral bleeding. Although both clinical characteristics and hemostatic variables have been studied in an attempt to define pertinent risk factors for hemorrhage,[2-6] few studies have focused on the detailed relation of clinical characteristics to hemorrhagic risk,[4,5] nor has a practically useful risk algorithm been developed. The Global Utilization of Streptokinase and t-PA for Occluded Coronary Arteries (GUSTO-I) trial[7] presented an opportunity to analyze the location and severity of hemorrhage and associated outcomes after treatment with thrombolytic therapy in a large patient population.

Methods

Patients and Treatment

Details of the study design, inclusion and exclusion criteria, trial medications, and guidelines for patient management have been described in detail elsewhere.[7] Briefly, patients presenting to the hospital within 6 hours of the onset of symptoms, with chest pain lasting ≥20 minutes and accompanied by ECG signs of ≥0.1 mV of ST-segment elevation in two or more leads, were eligible for enrollment. Exclusion criteria included active bleeding, recent trauma or major surgery, history of stroke, noncompressible vascular punctures, and previous treatment with streptokinase or anistreplase.

Patients were randomly allocated to one of four thrombolytic strategies: streptokinase 1.5 million U over 60 minutes plus subcutaneous heparin 12 500 IU twice daily beginning 4 hours after initiation of thrombolytic therapy; streptokinase 1.5 million U over 60 minutes plus intravenous heparin bolus of 5000 U followed by 1000 U/h, with dose adjustment to maintain an activated partial thromboplastin time (aPTT) of 60 to 85 seconds; accelerated tissue plasminogen activator (TPA) bolus of 15 mg immediately followed by infusion of 0.75 mg/kg (up to 50 mg) over 30 minutes and then 0.5 mg/kg (up to 35 mg) over the next 60 minutes, accompanied by the same intravenous heparin regimen; or the combination of intravenous TPA (1.0 mg/kg over 60

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*A complete list of GUSTO-I Investigators has been published previously and can be found in Reference 7.

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TABLE 1. Bleeding by Site

Bleeding Location	Moderate, n (%)	Severe,* n (%)	Moderate or Severe, n (%)
Any† (n=40 903)	4659 (11.4)	754 (1.8)	5388 (13.2)
CABG-related (n=40 580)	1339 (3.3)	102 (0.3)	1441 (3.6)
Groin (n=40 885)	744 (1.8)	97 (0.2)	841 (2.0)
Gastrointestinal (n=40 889)	610 (1.5)	132 (0.3)	742 (1.8)
Upper extremity (n=40 889)	431 (1.1)	29 (0.1)	460 (1.1)
Oropharyngeal (n=40 893)	294 (0.7)	19 (<0.1)	313 (0.8)
ICH (n=40 935)	...	268 (0.7)	268 (0.7)
Genitourinary (n=40 890)	266 (0.7)	15 (<0.1)	281 (0.7)
Retroperitoneal (n=40 888)	152 (0.4)	70 (0.2)	222 (0.5)
Optic (n=40 889)	26 (0.1)	0 (0)	26 (0.1)

CABG indicates coronary artery bypass graft; ICH, intracranial hemorrhage.

*Severe bleeds do not include ICH bleeding in the subsequent tables.

†ICHs were by definition severe bleeding events, and there were 268 such events (0.7%). If the ICHs were included in the analysis, the number of severe bleeding events at "Any" location would be 754 (1.8%); moderate or severe bleeding events would equal 5388 (13.2%). The description of the intracranial bleeding observed in GUSTO-I is reported.[8]

minutes, not to exceed 90 mg, with 10% given as a bolus) plus streptokinase (1.0 million U for 60 minutes) given concurrently but through separate catheters, followed by the same intravenous heparin regimen.

Definitions

Bleeding was defined as severe if it caused substantial hemodynamic compromise that required intervention or treatment and moderate if transfusion was required but did not lead to hemodynamic compromise requiring intervention. Intracranial hemorrhages were by definition severe bleeding events but were not included in this analysis. The description of the intracranial bleeding observed in GUSTO-I has been reported previously.[8]

Statistical Analysis

Baseline characteristics and clinical outcomes that are discrete factors are described in terms of frequencies and percentages of patients with the characteristic for categorical variables; continuous variables are described using the median and 25th and 75th percentiles. Odds ratios and 95% CIs were calculated by use of standard methods.

Logistic regression modeling techniques were used to evaluate the univariate relationship between baseline or procedural characteristics and the likelihood of having moderate or severe bleeding. Assumptions of linearity were tested by use of cubic spline functions as well as a variety of graphic techniques. These techniques were used to most appropriately describe any nonlinear relationships that existed, as previously described.[9]

Three multivariate models of moderate or severe bleeding versus mild or no bleeding were created. The first two models were developed in the entire GUSTO population. One model determined the relationship of the baseline clinical factors in the prediction of a bleeding complication. The other determined the relationship of both baseline clinical factors and subsequent predischarge procedures (pacemaker implantation, Swan-Ganz catheter placement, ventilator use, coronary bypass surgery, intra-aortic balloon pump insertion, cardioversion/defibrillation, angiography, or percutaneous coronary angioplasty) in the prediction of a bleeding complication. Recognizing that the incidence of bleeding was greatly influenced by the use of procedures, a third model was developed to determine the effect of the baseline clinical factors on bleeding without the procedural bias. This model was similar to the first but was applied only in the subset of patients who had no in-hospital procedures.

Logistic regression modeling techniques were used to develop each of the three multivariate models. A stepwise variable-reduction technique was used to find the combination of variables that contributed independent information. Once final models were developed, bootstrapping was used for internal validation. The quality of the final models based on the original as well as the bootstrapped samples is described with the use of the concordance index. The concordance index is a description of the discriminant power of the model to reliably predict an outcome.

On the basis of the coefficients of the clinical model of bleeding, a probability chart was developed (Table 9). Each variable in the model received a certain score based on the value of that variable. The total points were then easily transformed into predictive values.

Results

Bleeding complications occurred at a variety of sites (Table 1). The most common sources of moderate and severe bleeding were procedure related; almost 4% of the overall population experienced hemorrhage related to coronary artery bypass grafting, and 2.0% had hemorrhage at the groin site. The most common site of spontaneous bleeding was the gastrointestinal tract. More than 5% of patients had diminutions

TABLE 2. Bleeding According to Treatment Assignment*

		Bleeding, n (%)	
Treatment	Patients (N=40 903), n	Moderate or Severe	Severe
SK+SQ heparin	9809	1160 (11.8)†	117 (1.2)
SK+IV heparin	10 387	1451 (14.0)	151 (1.5)
TPA+IV heparin	10 366	1155 (11.1)‡	92 (0.9)
Combination	10 341	1388 (13.4)	135 (1.3)

SK indicates streptokinase; SQ, subcutaneous; IV, intravenous; and TPA, tissue plasminogen activator.

*These rates are higher than originally reported.[7] Cleanup of key variables performed since publication of the main manuscript led to corrections in rates of bleeding (see National Auxiliary Publication Service document #0512X).

†Less hemorrhage compared with SK+IV hep ($P<.0001$) and combination ($P<.0007$).

‡Less hemorrhage compared with SK+IV hep ($P<.0001$) and combination ($P<.0001$).

TABLE 3. Moderate or Severe Bleeding Observed by Baseline Characteristic

Characteristic	All GUSTO-I Patients (n=40 903)	Bleeding	
		Moderate or Severe (n=5154)	Severe (n=495)
Age, y*	62 (52, 70)	66 (58, 73)	68 (60, 75)
Female	10 292	1978 (19.2)	212 (2.1)
Male	30 600	3176 (10.4)	283 (0.9)
Weight, kg*	78 (70, 88)	74 (64, 84)	71 (63, 82)
Height, cm*	172 (165, 178)	170 (161, 175)	168 (160, 175)
White	36 302	4149 (11.4)	422 (1.2)
African ancestry	1155	197 (17.1)	12 (1.0)
Hispanic	677	93 (13.7)	7 (1.0)
Asian	615	60 (9.8)	8 (1.3)
US enrollment	23 041	3372 (14.6)	312 (1.4)
Non-US enrollment	17 862	1782 (10.0)	183 (1.0)
Hypertension	15 517	2321 (15.0)	230 (1.5)
Current smoker	17 481	1754 (10.0)	163 (0.9)
History of smoking	28 164	3022 (10.7)	278 (1.0)
Hypercholesterolemia	13 568	1842 (13.6)	176 (1.3)
Previous MI	6687	906 (13.5)	70 (1.0)
Killip class III	546	101 (18.5)	20 (3.7)
Killip class IV	309	77 (24.9)	18 (5.8)

MI indicates myocardial infarction.
*Median (25th percentile, 75th percentile); all other values are n (%).

in the hematocrit identified as representing moderate or severe bleeding, with no obvious source of bleeding reported.

The thrombolytic regimen was strongly related to the incidence of bleeding (Table 2). Less moderate or severe hemorrhage was seen with streptokinase plus subcutaneous heparin treatment compared with streptokinase plus intravenous heparin ($P<.0001$) and the combination therapies ($P<.0007$). Less moderate or severe hemorrhage was seen with TPA plus intravenous heparin compared with either streptokinase plus intravenous heparin ($P<.0001$) or the combination therapies ($P<.0001$). The bleeding incidences were comparable for streptokinase plus subcutaneous heparin and TPA plus intravenous heparin, and for streptokinase plus intravenous heparin and the combination therapies.

Table 3 illustrates the distribution of the key baseline characteristics for patients who had serious hemorrhage. Bleeding occurred more commonly in patients of older age, female sex, lighter body weight, shorter stature, and African ancestry and in patients in the United States. Less bleeding was seen in current smokers and in patients with a history of smoking.

Regardless of thrombolytic assignment, higher bleeding rates were associated with higher aPTTs (Fig 1, top and bottom). The relationship of aPTT with bleeding risk, however, was different for different thrombolytic agents. That is, for a given aPTT, the risk of bleeding was higher for streptokinase-assigned patients than for TPA-assigned patients.

In multivariate analysis, the three most powerful independent predictors of hemorrhage were older age, lighter body weight, and female sex (Table 4; Fig 2). Several variables added significantly to the model but exhibited a different effect in US versus non-US patients. Worsening in Killip class was related to a significant increase in the incidence of bleeding complications for US but not for non-US patients. For patients randomized to streptokinase plus subcutaneous heparin who were in Killip class I, there was a 76% higher likelihood of having a serious hemorrhage for US than for non-US patients. With the streptokinase plus subcutaneous heparin as the comparative group in the non-US patients, those who received streptokinase plus intravenous heparin or the combination (streptokinase plus TPA plus heparin) treatments were associated with 63% and 66% more bleeding, respectively. Hemorrhage in US patients was much less with streptokinase plus intravenous heparin and not significantly different for combination therapy. US patients assigned to TPA had significantly less bleeding than US patients given streptokinase plus subcutaneous heparin; non-US patients assigned to TPA had more bleeding.

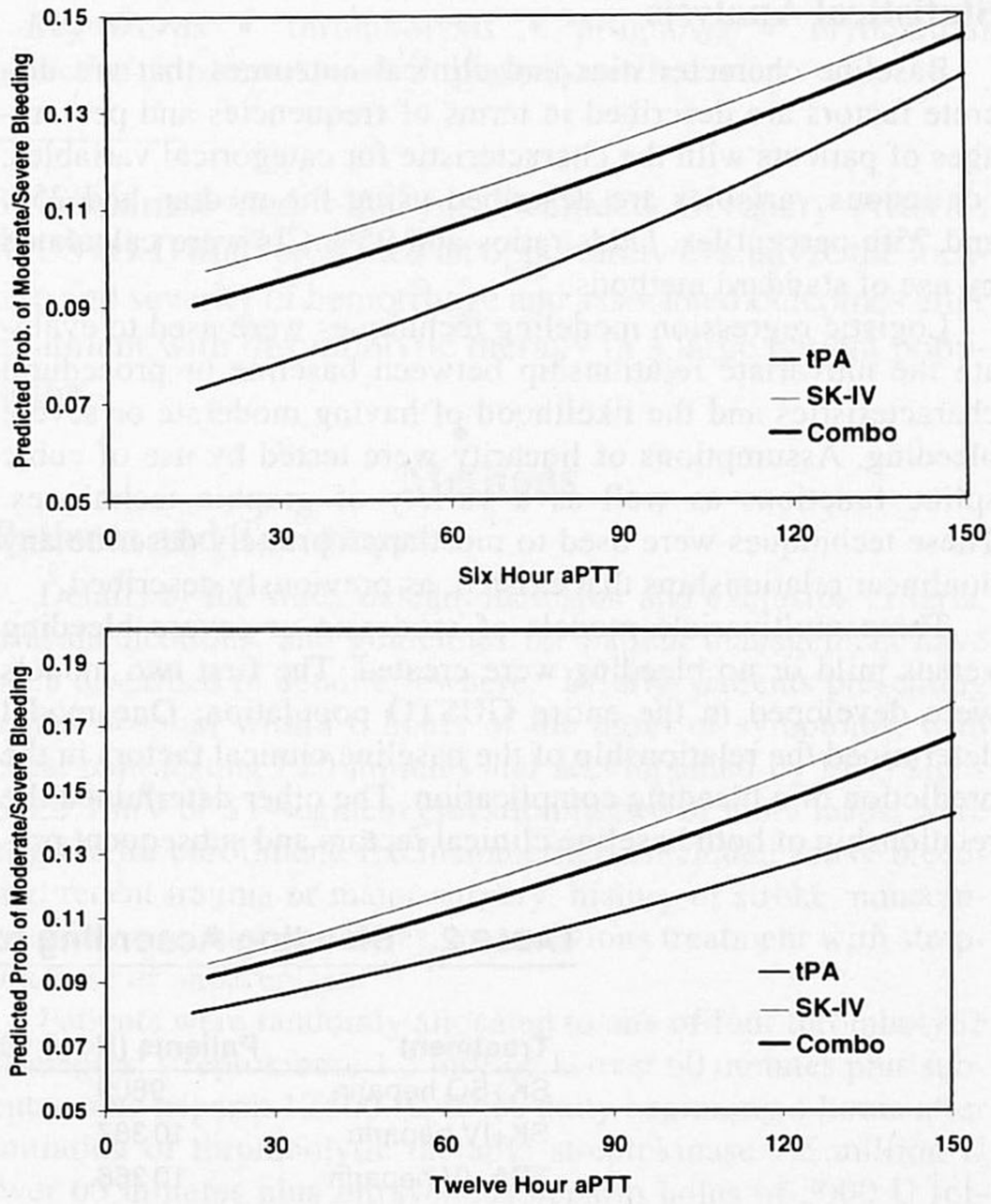

FIG 1. Predicted probability (prob.) of moderate or severe bleeding versus 6-hour (top) and 12-hour (bottom) activated partial thromboplastin time (aPTT) (in seconds) according to thrombolytic assignment for accelerated tissue plasminogen activator (TPA), streptokinase plus intravenous heparin (SK-IV), and combination TPA and streptokinase (Combo).

TABLE 4. Multivariate Model to Predict Hemorrhage

Variable	Odds Ratio*	95% CI	χ^2†
Patients treated in US	1.76	1.08, 2.85	520.78
Age (60 vs 50 y)	1.30	1.26, 1.35	222.05
Weight			163.88
100 vs 90 kg	0.83	0.73, 0.95	
85 vs 75 kg	0.81	0.78, 0.85	
Female	1.42	1.31, 1.53	72.84
SK+IV heparin vs SK+SQ heparin			32.82
US patients	1.13	1.01, 1.26	
Non-US patients	1.63	1.36, 1.95	
Combo vs SK+SQ heparin			31.15
US patients	1.02	0.92, 1.14	
Non-US patients	1.66	1.39, 1.99	
BP 90 vs 80 mm Hg diastolic	0.94	0.92, 0.96	28.51
African ancestry	1.33	1.12, 1.57	10.17
TPA vs SK+SQ heparin			9.20
US patients	0.85	0.76, 0.96	
Non-US patients	1.14	0.94, 1.38	

SK indicates streptokinase; IV, intravenous; SQ, subcutaneous; Combo, combination thrombolytic therapy; BP, blood pressure; and TPA, tissue plasminogen activator.

Values are listed in order of strength of relationship.

*Odds of US versus Non-US for patients with SK+SQ hep treatment and Killip class I at baseline.

†Concordance index=0.725; validated model=0.720.

A higher incidence of bleeding events was strongly related to invasive procedures (Table 5). Fifty-eight percent of patients (73% US, 27% non-US) had at least one procedure (Swan-Ganz catheter placement, insertion of pacemaker or balloon pump, angiography, angioplasty, or bypass surgery). Moderate or severe bleeding occurred in 50% of patients having coronary artery bypass grafting or intra-aortic balloon pump insertion, five times the rate in patients without these procedures. The only procedure not associated with more bleeding was coronary angioplasty. Moderate or severe bleeding was found in only 6% of patients who did not undergo any of these procedures.

Table 6 summarizes a second multivariate model to predict bleeding, which adjusts for the baseline characteristics of the patients and highlights the effect of the procedures on bleeding according to country of origin and treatment assignment. The prognostically important baseline characteristics remained fairly consistent with those seen in the first model, except that previous angina and infarct location were no longer important contributors, but previous bypass surgery was. Bypass surgery was the procedure most strongly associated with bleeding risk, but this risk was greater for US patients than for non-US patients, whereas the opposite was true for angiography and Swan-Ganz catheter placement. There was a significantly increased risk of bleeding in the use of an intra-aortic balloon pump with drug regimens other than combination therapy. The implantation of a pacemaker was related to an increased risk of bleeding regardless of which thrombolytic therapy was given or country of origin. Angioplasty was significantly related to an increased risk of bleeding for patients not randomized to TPA.

Table 7 summarizes the effect of the baseline characteristics in the 42% of patients who received no procedure during their hospitalization. Age, weight, and sex remained the most important predictors of bleeding. Treatment assignment was the next most important predictor. Race, pulse, and Killip class remained important but had strong differential effects according to treatments received. Of the other baseline characteristics, the risk factors of hypertension and current smoking, the presentation variables of diastolic blood pressure and infarct location, and a history of previous angina were no longer significant independent predictors. Of most interest is the absence of an effect from US versus non-US status. Once differences in the use of procedures were accounted for, patients in the US were no longer at significantly increased

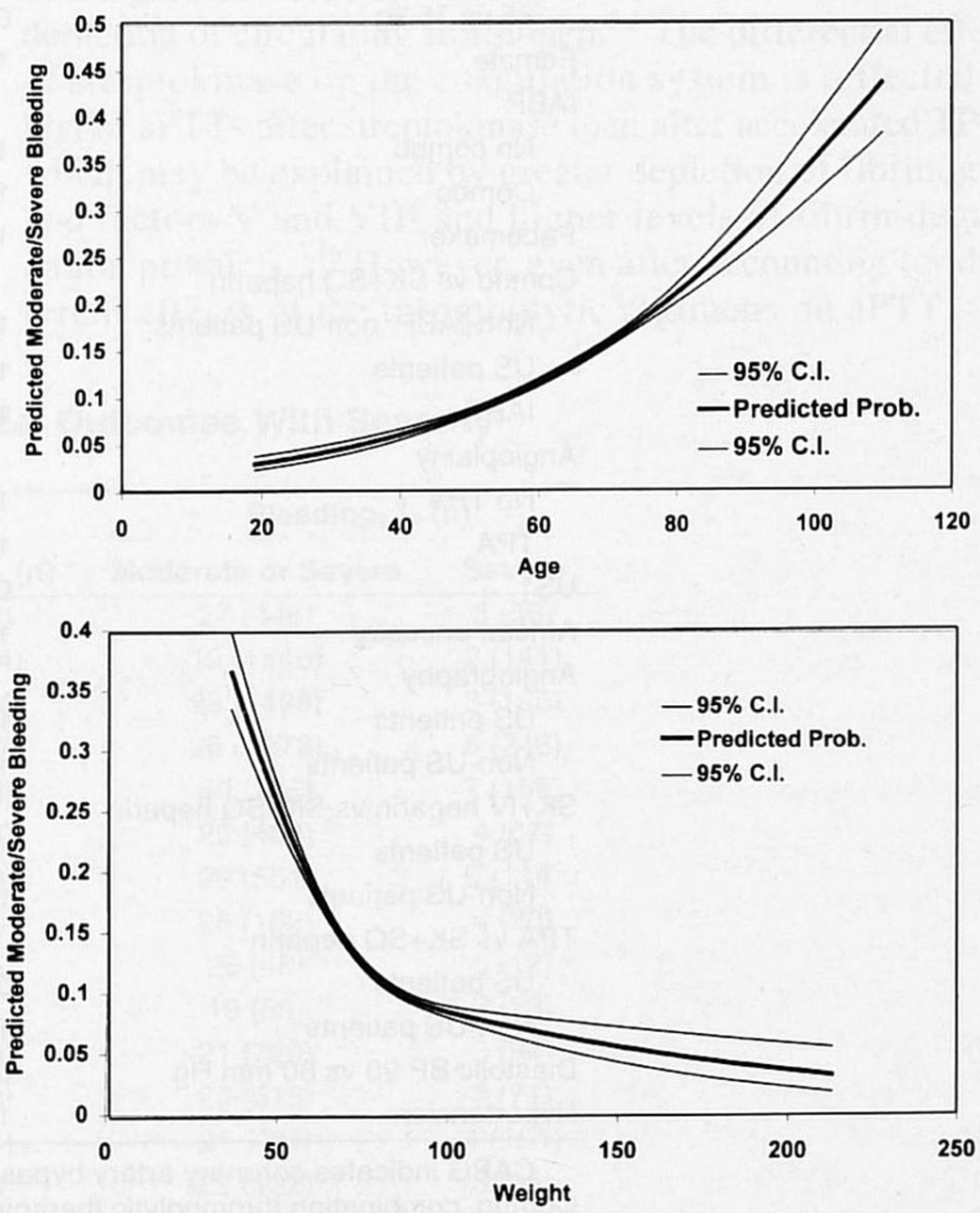

FIG 2. Relationship between age (in years) (top) and weight (in kilograms) (bottom) as continuous variables versus the predicted probability (Prob.) of moderate or severe bleeding.

TABLE 5. Procedures Associated With Bleeding

Procedures		Bleeding Events, % (n)	
Type	% (n)	Moderate or Severe	Severe
Angiography	55 (22 671)	17 (3801)	1 (340)
No angiography	44 (18 161)	7 (1345)	<1 (151)
PTCA	22 (8919)	15 (1303)	1 (129)
No PTCA	78 (31 913)	12 (3843)	1 (362)
CABG	9 (3517)	50 (1754)	4 (141)
No CABG	91 (37 293)	9 (3385)	<1 (349)
Swan-Ganz catheter	12 (5049)	43 (2158)	5 (248)
No Swan-Ganz catheter	87 (35 759)	8 (2979)	<1 (243)
Pacemaker	7 (2867)	37 (1065)	4 (121)
No pacemaker	93 (37 955)	11 (4070)	1 (370)
IABP	4 (1482)	50 (735)	9 (130)
No IABP	96 (39 335)	11 (4404)	<1 (361)
None of the above	41 (16 923)	6 (1066)	<1 (105)

PTCA indicates percutaneous transluminal coronary angioplasty; CABG, coronary artery bypass grafting; and IABP, intra-aortic balloon pump insertion.

risk of bleeding compared with other patients. There was no evidence of a lower threshold for transfusion (and therefore for identification of hemorrhage as moderate) in US patients: the median nadir hematocrit among patients transfused was 25.0% in US versus 26.9% in non-US patients.

The presence of serious hemorrhage was associated with other undesirable outcomes (recurrent events, left

TABLE 6. Multivariate Model of Clinical Plus Procedural Information to Predict Moderate or Severe Bleeding

Variable	Odds Ratio	95% CI	χ^{2*}
CABG			774.63
US patients	7.15	6.232, 8.213	
Non-US patients	3.78	2.909, 4.916	
Swan-Ganz catheter			418.82
US patients	2.38	2.102, 2.692	
Non-US patients	4.13	3.274, 5.200	
60 vs 50 years of age	1.37	1.315, 1.425	267.15
Weight			217.62
100 vs 90 kg	0.79	0.678, 0.914	
85 vs 75 kg	0.77	0.735, 0.803	
Female	1.73	1.583, 1.889	136.40
IABP			106.65
No combo	1.92	1.617, 2.272	
Combo	1.21	0.905, 1.610	
Pacemaker	1.51	1.346, 1.694	59.09
Combo vs SK+SQ heparin			49.37
Non-IABP, non-US patients	1.86	1.538, 2.237	
US patients	1.07	0.938, 1.225	
IABP	1.17	0.808, 1.689	
Angioplasty			48.20
No TPA	1.53	1.361, 1.711	
TPA	1.18	0.974, 1.440	
US†	0.47	0.348, 0.642	47.45
African ancestry	1.91	1.572, 2.322	41.67
Angiography			41.63
US patients	1.23	1.072, 1.403	
Non-US patients	1.56	1.355, 1.807	
SK+IV heparin vs SK+SQ heparin			41.59
US patients	1.21	1.061, 1.370	
Non-US patients	1.75	1.450, 2.114	
TPA vs SK+SQ heparin			14.74
US patients	0.91	0.783, 1.050	
Non-US patients	1.21	0.989, 1.480	
Diastolic BP 90 vs 80 mm Hg	0.96	0.934, 0.984	12.54
Hypertension	1.12	1.039, 1.213	10.63

CABG indicates coronary artery bypass graft; IABP, intra-aortic balloon pump insertion; Combo, combination thrombolytic therapy; SK, streptokinase; SQ, subcutaneous; TPA, tissue plasminogen activator; IV, intravenous; and BP, blood pressure.

Variables are listed in order of strength of relationship.

*Concordance index=0.825; validated model=0.823.

†Odds of US versus Non-US for patients with SK+SQ heparin treatment and Killip class I at baseline.

ventricular dysfunction, arrhythmia, or stroke) (Table 8). Twenty percent to 30% of patients with any one of these adverse events had moderate or severe bleeding. Length of hospitalization for patients with bleeding complications was longer (P=.0001). The predicted value for the likelihood of experiencing a moderate or severe bleeding complication in this patient population can be obtained from the probability chart we developed (Table 9). Because the decision to use invasive therapy was made after treatment assignment, a separate probability chart based on the model in patients treated without catheterization was developed to calculate the predicted value for their likelihood of experiencing a moderate or severe bleeding complication (Table 10).

Discussion

As expected from prior studies, older age,[4,10] lower body weight,[10] and female sex[10-13] were the three most powerful independent predictors of hemorrhage that could be determined at the time of presentation with acute myocardial infarction. Coronary artery bypass surgery and invasive procedures were strongly related to bleeding. Regardless of whether use of procedures was included in the multivariate analyses, age, weight, and sex (in order of importance) remained the most powerful baseline predictors of bleeding. An additional finding that has not been well established from prior studies is the higher likelihood of bleeding in patients of African descent, especially when treated with TPA.

Bleeding After Thrombolysis in Prior Trials

The Fibrinolytic Therapy Trialists' (FTT) Collaborative Group evaluated nine trials including 58 600 patients randomized to thrombolytic therapy versus control therapies in suspected acute myocardial infarction.[1] An excess of 0.7% in major noncerebral bleeding (life-threatening or requiring blood transfusion) was detected, with a rate of 1.1% in those assigned to thrombolytic therapy versus 0.4% in control subjects (P<.0001). The combined data from GISSI-2[14] and ISIS-3[15] included 48 294 patients randomized to standard-dose TPA or streptokinase and 62 067 patients randomized to aspirin plus subcutaneous heparin or aspirin. Major bleeding rates were higher for streptokinase than for TPA (0.9% versus 0.7%; P<.05) and for subcutaneous heparin than for no heparin (1.0% versus 0.7%; P<.00001).

TABLE 7. Baseline Clinical Model for Patients With No In-Hospital Procedures

Variable	Odds Ratio	95% CI	χ^{2*}
60 vs 50 years of age	1.53	1.434, 1.641	147.12
100 vs 90 kg weight	0.76	0.712, 0.815	71.94
Combo†			32.79
Killip class III or IV	1.50	1.217, 1.855	
Killip class II	2.22	1.602, 3.072	
Female	1.49	1.276, 1.738	29.82
SK+IV heparin*	1.53	1.260, 1.864	20.18
African ancestry			19.62
Non-TPA therapy	1.73	1.030, 2.898	
TPA therapy	4.77	2.387, 9.533	
80- vs 70-bpm pulse	1.15	1.053, 1.246	12.33
Killip class I vs >I			7.76
No combo therapy	0.95	0.781, 1.165	
Combo therapy	1.41	1.059, 1.872	
TPA†			5.39
Non-African ancestry	1.08	0.872, 1.331	
African ancestry	2.97	1.262, 7.007	

Combo indicates combination thrombolytic therapy; SK, streptokinase; IV, intravenous; and TPA, tissue plasminogen activator.

Variables are listed in order of strength of relationship.

*Concordance index=0.706; validated model=0.704.

†Odds compared with streptokinase plus subcutaneous heparin treatment and Killip class I at baseline.

Relationship of Thrombolytic and Heparin Regimens to Bleeding in GUSTO-I

As in previous large trials comparing streptokinase and TPA, the risk of noncerebral bleeding was greater after streptokinase than after accelerated TPA. This may be due in part to the greater fibrin specificity of TPA, with less resultant depletion of circulating fibrinogen.[3,5] The differential effect of streptokinase on the coagulation system is reflected in higher aPTTs after streptokinase than after accelerated TPA, which may be explained by greater depletion of fibrinogen and factors V and VIII and higher levels of fibrin-degradation products.[3,16] However, even after accounting for different effects of the thrombolytic regimens on aPTT, the

TABLE 8. Association of Other Clinical Outcomes With Severity of Bleeding

Outcomes	Events, % (n)	Bleeding, % (n)	
		Moderate or Severe	Severe
Reinfarction	4 (1627)	27 (446)	3 (56)
Recurrent ischemia	20 (8124)	19 (1545)	2 (141)
CHF or pulmonary edema	16 (6624)	23 (1498)	3 (195)
Sustained hypotension	12 (4867)	26 (1273)	5 (248)
Cardiogenic shock	6 (2433)	30 (735)	7 (159)
Killip class III	4 (1808)	25 (460)	4 (67)
Killip class IV	5 (1880)	29 (551)	6 (114)
Acute mitral regurgitation	1 (571)	28 (162)	4 (20)
Acute ventricular septal defect	<1 (195)	25 (48)	6 (12)
Tamponade	<1 (311)	19 (59)	7 (23)
Atrioventricular block	8 (3379)	21 (720)	3 (94)
Sustained ventricular tachycardia	6 (2519)	20 (515)	3 (71)
Asystole	6 (2334)	21 (481)	4 (104)
Stroke	1 (599)	22 (132)	3 (18)
Death within 30 days	7 (2823)	20 (554)	5 (148)
Length of hospital stay, d*	9 (7, 13)	14 (10, 18)	15 (11, 21)

CHF indicates congestive heart failure.

*Median (25th percentile, 75th percentile).

TABLE 9. Prediction of Moderate or Severe Bleeding Event

1. Find points for each predictive factor:

Age		Weight		DBP		Pulse		Misc RF		Killip Class/Treatment Interaction				
										Killip	Treatment, Pts			
y	Pts	kg	Pts	mm Hg	Pts	bpm	Pts	Factor	Pts	Class	SK+SQ	TPA	SK+IV	Combo
30	18	140	35	200	0	0	0	Female sex	12	I	38	32	43	39
40	27	120	43	180	4	40	4	African ancestry	10	II	46	39	50	42
50	36	100	52	160	8	80	8	Current smoker	8	III	53	48	57	54
60	45	80	61	140	13	120	12	Hypertension	7	IV	60	55	65	60
70	54	60	74	120	17	160	16	Previous angina	3					
80	63	40	87	100	21	200	19	Previous MI	2					
90	72			80	25	240	23							
				60	30									

2. Sum points for all predictive factors:

____ Age + ____ Weight + ____ DBP + ____ Pulse + ____ Misc RF + ____ Interaction = ____ Total points

3. Look up risk corresponding to total points:

Pts	Predictive Value
182	10%
210	20%
228	30%
243	40%
257	50%
271	60%
286	70%

Pts indicates points; DBP, diastolic blood pressure; Misc RF, miscellaneous risk factors; MI, myocardial infarction; SK+SQ, streptokinase plus subcutaneous heparin treatment; TPA, tissue plasminogen activator; SK+IV, streptokinase plus intravenous heparin treatment; and Combo, combination thrombolytic therapy.

In step 1, find the value most closely matching the patient's risk factors and circle the points. In step 2, sum the points for all predictive factors. In step 3, determine the risk corresponding to the total number of points. For example, a 71-year-old, 124-lb female nonsmoker of African ancestry with a history of hypertension who presents with a DBP of 62 mm Hg and pulse of 121 bpm in Killip class IV heart failure and who was then treated with SK+IV would have a total score of [54+44+30+12+(12+10+0+7+0+0)+65]=234. This score corresponds to an estimated risk of bleeding of 38%.

risk of bleeding was greater after streptokinase than after accelerated TPA. The effect of thrombolytic therapy on hemostasis is complex, and other possible contributors to bleeding risk include cleavage of large-molecular-weight von Willibrand factor multimers[17,18] and of glycoprotein Ib and IIb/IIIa platelet receptors.[17,19]

In contrast to the greater risk of noncerebral bleeding with streptokinase, the risk of intracranial hemorrhage was greater after accelerated TPA both in the GUSTO-I study[8] and in previous studies.[20] The reason for the differential effect on the risk of cerebral versus noncerebral bleeding is unclear. To the extent that noncerebral bleeding is more related to vascular injury after administration of thrombolytic therapy (ie, vascular puncture for cardiac catheterization or development of new gastric ulcer) and therefore to an intact ability to form a new fibrin clot, compared with cerebral bleeding as a result of preexisting vascular injury, one would expect the differential effect seen.

Predictors of Bleeding

Older age has been found to be a risk factor for bleeding after thrombolysis in some[4,10] but not all[1] previous studies. The largest previous experience, reported by the FTT Collaborative Group, did not find a relationship between older age and higher incidence of noncerebral bleeding. In GUSTO-I, however, age was the strongest predictor of moderate or severe bleeding. Even among patients who did not undergo interventional procedures or bypass surgery in GUSTO-I, age was the most important baseline characteristic in predicting hemorrhage.

Patients with lighter weight had a higher incidence of bleeding in prior studies of thrombolytic therapy for acute myocardial infarction. We have confirmed that more bleeding occurred in lighter-weight patients (Table 3), whether or not an invasive management strategy was used.

Female sex, even after adjustment for the presence of other factors, was a potent predictor of bleeding both in prior trials[10-12] and in GUSTO I. Weaver et al[21] reported on the characteristics and treatment outcome of women in the GUSTO-I trial.

The finding of increased bleeding in patients of African ancestry is intriguing. In the Thrombolysis and Angioplasty in Myocardial Infarction (Phase I) study of 324 white patients and 24 patients of African ancestry, Sane et al[6] noted an enhanced sensitivity among African Americans to TPA, which produced increased thrombolytic efficacy and more pronounced systemic fibrinogenolysis and resulted in an increase in bleeding that required transfusions. Lower fibrinogen levels and elevated fibrin(ogen)-degradation products in the circulation after treatment with TPA in this population is postulated to cause excessive bleeding due to poor clot formation and the antithrombotic properties of the fibrin(ogen)-degradation–product fragments.

Previous publications have noted an increase in bleeding complications with invasive management strategies,[5] including balloon pumping[22] and coronary angioplasty and bypass surgery.[10] A second multivariate model was developed to evaluate the importance of the occurrence of hemorrhage with invasive procedures after adjusting for baseline characteristics and treatment assignment; this model showed that performance of an invasive procedure was independently associated with bleeding (Table 6). The finding of more moderate and severe bleeding in US patients appears to be explained by the higher use of invasive management

TABLE 10. Prediction of Moderate or Severe Bleeding Events for Noncatheterized Patients

1. Find points for each predictive factor:

Age		Weight		Pulse		Misc RF	
y	Pts	kg	Pts	bpm	Pts	Factor	Pts
40	0	120	0	40	91	Female sex	12
50	6	100	0	60	91	SK+IV	13
60	18	80	4	80	96		
70	29	60	20	100	100		
80	41	40	37	120	98		
90	53			140	91		
100	64			160	77		
110	76			180	57		
				200	32		

Risk Factor/Treatment Interaction	Treatment, pts			
	TPA	No TPA	Combo	No Combo
I. African ancestry				
No	0	0	...	...
Yes	43	15	...	...
II. Killip Class				
I	...	...	15	3
II	...	...	25	0
III/IV	...	...	11	7

2. Sum points for all predictive factors:

_____ Age + _____ Weight + _____ Pulse + _____ Misc RF + _____ Interaction I + _____ Interaction II = _____ Total points

3. Look up risk corresponding to total points:

Pts	Predictive Value
142	5%
162	10%
175	15%
185	20%
192	25%
199	30%
206	35%
211	40%
217	45%
223	50%

Pts indicates points; Misc RF, miscellaneous risk factors; TPA, tissue plasminogen activator; SK+IV, streptokinase plus intravenous heparin treatment; and Combo, combination thrombolytic therapy.

In step 1, find the value most closely matching the patient's risk factors and circle the points. In step 2, sum the points for all predictive factors. In step 3, determine the risk corresponding to the total number of points.

strategies in the United States. Because invasive procedures occurred after randomization, we cannot conclude whether the increased risk of bleeding was related to greater general severity of illness of the patient, the particular invasive procedure, or other instrumentation deemed necessary for patient care (eg, urinary catheter placement or nasogastric tube), data that were not collected.

When the effect of baseline characteristics and treatment of patients who did not have a procedure during their hospitalization was analyzed, age, weight, female sex, thrombolytic treatment assignment, and African ancestry, in order of importance, remained significant predictors for bleeding (Table 7).

Conclusions

Patients treated with thrombolytic therapy for acute myocardial infarction are more likely to have bleeding complications if they are of increased age, lighter weight, female sex, or African ancestry or if they undergo invasive procedures. Less bleeding was associated with current smoking and with treatment with streptokinase plus subcutaneous heparin than with the other three thrombolytic regimens. Age, weight, treatment regimen, female sex, and African ancestry remained important predictors of bleeding when patients who had invasive procedures were excluded. Bleeding was associated with other adverse outcomes and with increased length of hospital stay and mortality at 30 days. Defining those patients at high risk for hemorrhagic complications should help practicing clinicians to balance the hazards of aggressive systemic thrombolytic therapies in the treatment of patients presenting with acute myocardial infarction.

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