Predictors of Outcome in Patients With Acute Coronary Syndromes Without Persistent ST-Segment Elevation

Results From an International Trial of 9461 Patients

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Background—Appropriate treatment policies should include an accurate estimate of a patient's baseline risk. Risk modeling to date has been underutilized in patients with acute coronary syndromes without persistent ST-segment elevation.

Methods and Results—We analyzed the relation between baseline characteristics and the 30-day incidence of death and the composite of death or myocardial (re)infarction in 9461 patients with acute coronary syndromes without persistent ST-segment elevation enrolled in the PURSUIT trial [Platelet glycoprotein IIb/IIIa in Unstable angina: Receptor Suppression Using Integrilin (eptifibatide) Therapy]. Variables examined included demographics, history, hemodynamic condition, and symptom duration. Risk models were created with multivariable logistic regression and validated by bootstrapping techniques. There was a 3.6% mortality rate and 11.4% infarction rate by 30 days. More than 20 significant predictors for mortality and for the composite end point were identified. The most important baseline determinants of death were age (adjusted $\chi^2=95$), heart rate ($\chi^2=32$), systolic blood pressure ($\chi^2=20$), ST-segment depression ($\chi^2=20$), signs of heart failure ($\chi^2=18$), and cardiac enzymes ($\chi^2=15$). Determinants of mortality were generally also predictive of death or myocardial (re)infarction. Differences were observed, however, in the relative prognostic importance of predictive variables for mortality alone or the composite end point; for example, sex was a more important determinant of the composite end point ($\chi^2=21$) than of death alone ($\chi^2=10$). The accuracy of the prediction of the composite end point was less than that of mortality (C-index 0.67 versus 0.81).

Conclusions—The occurrence of adverse events after presentation with acute coronary syndromes is affected by multiple factors. These factors should be considered in the clinical decision-making process. **(*Circulation*. 2000;101:2557-2567.)**

Key Words: angina ■ myocardial infarction ■ coronary disease ■ prognosis ■ risk factors

Patients with acute coronary syndromes have a range of therapeutic alternatives. The decision of which therapy to use for individual patients depends on the clinical presentation and the estimated treatment benefits. Such benefits usually are proportional to the risk of adverse outcome in the absence of a specific therapy.[1,2] An appropriate treatment policy should include an estimate of this baseline risk, which can be achieved by application of a risk model that integrates important prognostic features. A number of such models have been developed for acute myocardial infarction (MI) with ST-segment elevation,[2–5] but few such tools exist for patients with unstable angina pectoris (UAP) or suspected MI without persistent ST-segment elevation.[6,7]

The Platelet glycoprotein IIb/IIIa in Unstable angina: Receptor Suppression Using Integrilin (eptifibatide) Therapy (PURSUIT) trial studied the effects of eptifibatide versus placebo in 9461 patients with acute coronary syndromes without persistent ST-segment elevation.[8] This population covers a variety of patients, hospital settings, and treatment policies and therefore is suitable for development of a clinical risk model. We assessed the relation between the baseline characteristics and the occurrence of death and of death or nonfatal (re)MI at 30 days.

Methods

Patient Population

The design and methods of the PURSUIT trial have been described in detail.[8] In summary, patients were eligible if they presented within 24 hours of an episode of ischemic chest pain (>10 minutes) and had

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TABLE 1. Baseline Characteristics

Demographics	
Age, y	64 (55, 71)
Male sex, %	65
White, %	89
Weight, kg	78 (69, 88)
Height, cm	170 (163, 176)
Region of enrollment, %	
Latin America	4
North America	40
Eastern Europe	16
Western Europe	39
History	
Hypertension, %	55
Diabetes mellitus, %	23
Smoking status, %	
Current	28
Former	33
Never	39
Hypercholesterolemia, %	42
Family history of CAD, %	36
MI, %	32
Worst CCS class past 6 weeks, %	
No angina	19
I	12
II	26
III	18
IV	25
CHF, %	11
Stroke, %	4
PVD, %	8
Bypass surgery, %	12
Angioplasty, %	13
Prior medication	
Aspirin, %	64
β-Blockers, %	43
Calcium antagonists, %	33
Nitrates, %	69
ACE inhibitors, %	24
Presenting characteristics	
Enrollment diagnosis, %	
MI	46
UAP	54
SBP, mm Hg	130 (116, 145)
DBP, mm Hg	75 (67, 83)
Heart rate, bpm	72 (63, 80)
Rales, %	
$<1/3$	8
$\geq 1/3$	1
ST depression, %	50
ST elevation, %	14
T-wave inversion, %	51
Time course	
Symptom onset to randomization, h	11.1 (5.7, 18.8)
PURSUIT study medication	
Eptifibatide, %	50

Data presented are median (25th, 75th percentiles) or percentages. CAD indicates coronary artery disease; CCS, Canadian Cardiovascular Society; CHF, congestive heart failure; PVD, peripheral vascular disease; SBP, systolic blood pressure; and DBP, diastolic blood pressure.

either transient ST-segment elevation (>0.5 mm), transient or persistent ST-segment depression (>0.5 mm), T-wave inversion (>1.0 mm), or elevation of the creatine kinase–MB fraction (CK-MB) above the upper limit of normal (ULN). Patients with persistent (>30 minutes) ST-segment elevation were excluded. There were no restrictions regarding age. Eligible patients were randomly assigned to treatment with eptifibatide or placebo. PURSUIT enrolled 9461 patients in 726 hospitals in 28 countries in western and eastern Europe and North and South America. There were 4308 patients (45.5%) with elevated CK-MB at admission; these were classified as having MI. The other 5129 patients (54.2%) were classified as having UAP. In 24 cases (0.3%), the qualifying ischemic episode was undefined.

Definition of MI

The primary efficacy end point of PURSUIT was a composite of death or nonfatal (re)MI at 30 days. Within 18 hours of enrollment, MI was diagnosed on the basis of ischemic chest pain and new ST-segment elevation. After 18 hours, MI was diagnosed on the basis of new Q waves or new or repeated CK-MB elevations above the ULN. For patients undergoing percutaneous intervention or coronary bypass surgery, CK-MB elevation above 3 or 5 times the ULN was required. End points were adjudicated by a central Clinical Events Committee (CEC). A computerized algorithm was used to review the raw data. If a possible event was identified, additional documentation was collected and the case reviewed in detail. Local investigators also reported whether the patient had had an acute MI. Discrepancies that appeared between the CEC opinion and that of the investigator have been investigated and discussed in detail.[9] This analysis presents data based on the CEC judgment. Differences with analyses based on the investigators' opinions are discussed, but data will not be shown.

Statistical Analysis

Univariable and multivariable logistic regression analyses were applied to evaluate the relations between baseline characteristics and the 30-day occurrence of death alone and the composite of death or nonfatal (re)MI. All variables entered the multivariable stage, irrespective of the results of univariable analyses. The final multivariable model was constructed by backward deletion of the least significant characteristics, while the Akaike information criterion was applied (that is, the applied threshold of significance depended on the degrees of freedom [*df*] associated with the variable at hand; if $df=1$, then $P\approx 0.157$).[10]

The shape of the relation between continuous variables and outcome was examined by a model-fitting technique involving cubic spline functions.[11] A disadvantage of this approach is the complexity of the resulting regression function. Therefore, when the relation appeared to be nonlinear, the cubic polynomial was approximated by a limited number of high-order terms.

Furthermore, we evaluated whether the prognostic relation of any predictive characteristic differed for patients enrolling with UAP or MI: we tested for interactions between prognostic factors and the enrollment diagnosis. To prevent false-positive findings, we did not test for other interactions among prognostic variables. An unexpected finding in PURSUIT was the interaction between sex and study medication with respect to the composite end point.[8] We

TABLE 2. Univariable Relation Between Dichotomous Baseline Characteristics and 30-Day Outcome

	Death			Death or Nonfatal (Re)MI		
	Rate, %	χ^2 (*df*)	OR (95% CI)*	Rate, %	χ^2 (*df*)	OR (95% CI)*
Demographics						
Sex						
Female	3.8	<1 (1)	1.06 (0.85–1.33)	14.3	2 (1)	0.92 (0.81–1.03)
Male	3.5		1	15.4		1
Race						
Nonwhite	3.9	<1 (1)	1.09 (0.78–1.52)	12.8	5 (1)‡	0.82 (0.67–0.99)
White	3.6		1	15.3		1
Region of enrollment						
Latin America	7.6	20 (3)‖	2.42 (1.60–3.67)	15.9	42 (3)†	1.14 (0.85–1.51)
North America	3.2		0.97 (0.75–1.26)	13.4		0.93 (0.81–1.06)
Eastern Europe	4.5		1.39 (1.02–1.87)	20.4		1.54 (1.32–1.79)
Western Europe	3.3		1	14.3		1
History						
Hypertension						
Yes	4.3	16 (1)†	1.59 (1.26–1.99)	16.2	13 (1)‖	1.24 (1.10–1.39)
No	2.8		1	13.5		1
Diabetes mellitus						
Yes	5.6	30 (1)†	1.92 (1.53–2.41)	18.5	25 (1)†	UAP: 1.16 (0.96–1.42) MI: 1.60 (1.35–1.90)
No	3.0		1	14.0		1
Smoking status						
Current	2.2	23 (2)†	0.55 (0.41–0.75)	12.3	25 (2)†	0.77 (0.66–0.87)
Former	4.4		1.10 (0.86–1.39)	16.8		1.11 (0.97–1.26)
Never	4.0		1	15.4		1
Hypercholesterolemia						
Yes	3.2	4 (1)‡	0.80 (0.64–1.00)	15.0	<1 (1)	1.00 (0.89–1.12)
No	3.9		1	15.0		1
Family history of CAD						
Yes	3.1	4 (1)‡	0.79 (0.63–1.00)	14.2	3 (1)	0.90 (0.80–1.02)
No	3.9		1	15.5		1
MI						
Yes	5.1	28 (1)†	1.82 (1.46–2.26)	17.8	27 (1)†	1.37 (1.22–1.54)
No	2.9		1	13.6		1
Worst CCS class past 6 weeks						
III or IV	4.8	27 (1)†	1.78 (1.43–2.22)	17.9	48 (1)†	1.50 (1.33–1.68)
Other	2.7		1	12.7		1
CHF						
Yes	9.0	73 (1)†	3.25 (2.54–4.15)	21.6	37 (1)†	UAP: 1.22 (0.94–1.58) MI: 2.04 (1.66–2.52)
No	2.9		1	14.1		1
Stroke						
Yes	5.8	4 (1)‡	1.69 (1.06–2.69)	20.1	7 (1)¶	1.45 (1.11–1.90)
No	3.5		1	14.8		1
PVD						
Yes	6.1	13 (1)‖	1.86 (1.36–2.55)	21.7	28 (1)†	1.66 (1.38–1.98)
No	3.4		1	14.4		1

TABLE 2. Continued

	Death			Death or Nonfatal (Re)MI		
	Rate, %	χ^2 (*df*)	OR (95% CI)*	Rate, %	χ^2 (*df*)	OR (95% CI)*
Bypass surgery						
Yes	5.2	8 (1)§	1.56 (1.17–2.08)	15.9	<1 (1)	1.08 (0.91–1.28)
No	3.4		1	14.9		1
Angioplasty						
Yes	2.0	12 (1)‖	0.50 (0.33–0.77)	13.4	3 (1)	0.86 (0.72–1.03)
No	3.9		1	15.2		1
Prior medication						
Aspirin						
Yes	4.0	9 (1)§	1.43 (1.13–1.81)	16.1	17 (1)†	1.29 (1.14–1.45)
No	2.9		1	13.0		1
β-Blocker						
Yes	4.1	5 (1)‡	1.27 (1.02–1.58)	16.8	18 (1)†	1.28 (1.14–1.43)
No	3.3		1	13.7		1
Calcium antagonists						
Yes	5.1	26 (1)†	1.78 (1.43–2.21)	17.8	28 (1)†	1.37 (1.22–1.54)
No	2.9		1	13.6		1
Nitrates						
Yes	4.2	25 (1)†	1.92 (1.46–2.51)	16.4	32 (1)†	1.44 (1.27–1.64)
No	2.3		1	12.0		1
ACE inhibitors						
Yes	4.6	8 (1)§	1.42 (1.12–1.79)	17.0	9 (1)§	1.22 (1.08–1.39)
No	3.3		1	14.3		1
Presenting characteristics						
Enrollment diagnosis						
MI	4.7	26 (1)†	1.77 (1.42–2.21)	18.4	73 (1)†	1.64 (1.46–1.84)
UAP	2.7		1	12.1		1
Rales						
≥1/3	10.5	109 (2)†	5.85 (3.32–10.3)	23.2	63 (2)†	2.77 (1.81–4.26)
<1/3	15.1		UAP: 2.34 (1.40–3.89)	31.1		UAP: 1.21 (0.88–1.68)
			MI: 4.93 (3.58–6.78)			MI: 2.19 (1.76–2.73)
None	2.8		1	13.9		1
ST depression						
Yes	5.1	65 (1)†	2.54 (2.00–3.21)	17.9	63 (1)†	1.59 (1.42–1.78)
No	2.1		1	12.1		1
ST elevation						
Yes	2.9	2 (1)	0.78 (0.55–1.09)	13.0	5 (1)‡	0.83 (0.70–0.99)
No	3.7		1	15.3		1
T-wave inversion						
Yes	2.9	16 (1)†	0.65 (0.52–0.80)	14.1	5 (1)‡	UAP: 0.83 (0.70–0.98)
						MI: 1.07 (0.92–1.25)
No	4.4		1	15.8		1
PURSUIT study medication						
Eptifibatide	3.5	<1 (1)	UAP: 1.25 (0.89–1.76)	14.2	4 (1)‡	0.89 (0.79–0.99)
			MI: 0.74 (0.56–0.99)			
Placebo	3.7		1	15.7		1

χ^2 indicates −2 log likelihood of the univariable model without interaction terms.

*If a significant interaction was observed between the variable and enrollment diagnoses (MI or UAP), 2 separate ORs are presented.

†$P<0.0001$; ‡$P<0.05$; §$P<0.005$; ‖$P<0.001$; ¶$P<0.01$.

Abbreviations as in Table 1.

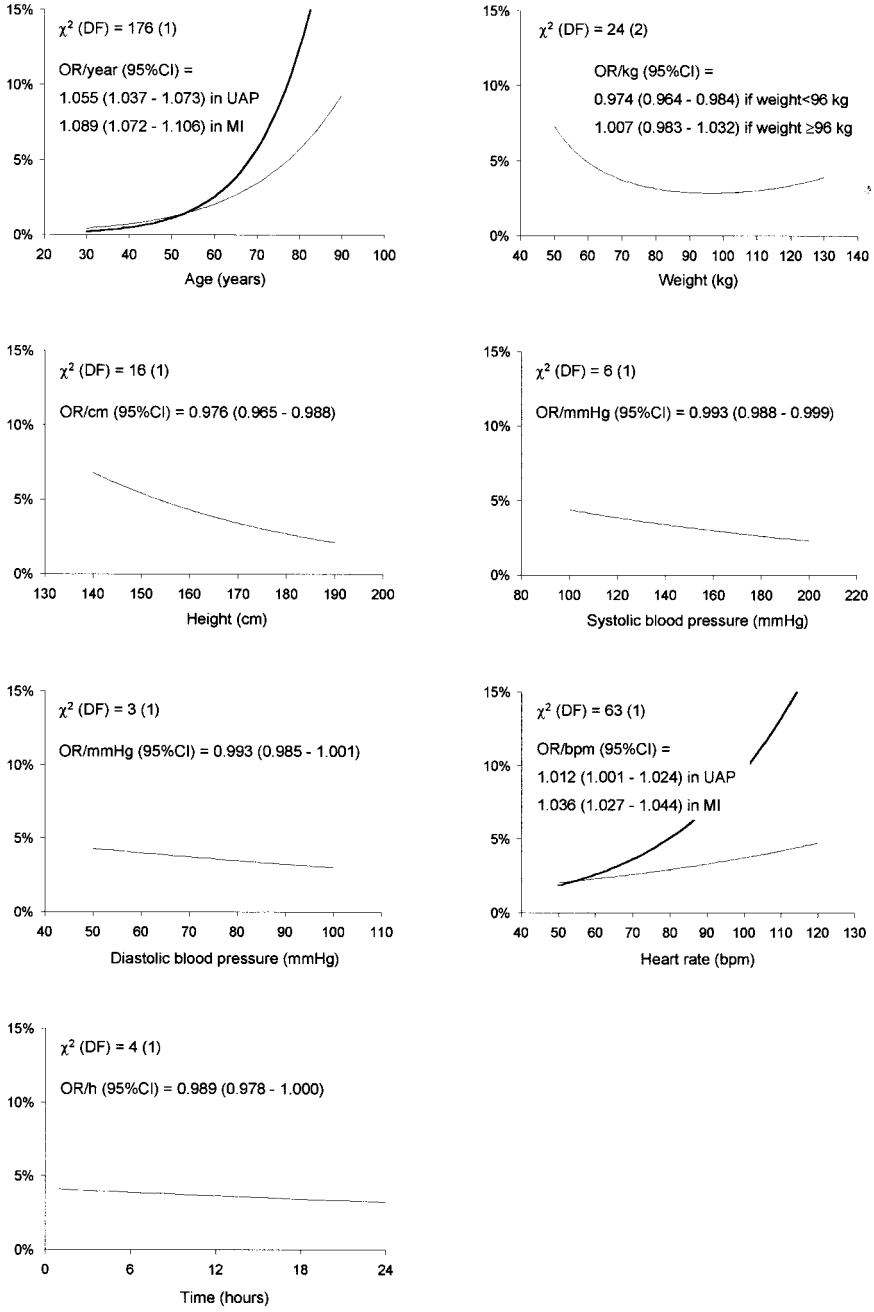

Figure 1. Univariable relations between continuous baseline characteristics and 30-day mortality. If 2 curves are presented, bold curve indicates MI patients and light curve indicates UAP patients. χ^2 indicates −2 log-likelihood of the univariable model without interaction terms; OR, unadjusted odds ratio; CI, confidence interval; bpm, beats per minute.

evaluated the extent to which the model performance would have changed had this interaction been incorporated.

Clinical variables were missing for 8% of the patients. This subset had a higher 30-day mortality rate than patients with complete data (4.7% versus 3.5%; $P=0.08$). The exclusion of patients with missing data, therefore, could lead to biased risk estimates.[12] To partly correct for this, all multivariable analyses were performed on a data set that included imputed predictive variables. The applied iterative imputation technique estimated the missing value of a given predictor on the basis of multivariable regression on all other predictors.[12,13] End-point data were not used in this process. Computations were performed with S-PLUS statistical software (version 3.3).[14]

The predictive accuracy of multivariable models was evaluated by the C-index.[15] The models developed in the full study population were further evaluated by bootstrapping techniques: 100 bootstrap samples were drawn, with replacement, to estimate the extent to which the predictive accuracy of the models based on the entire population was overoptimistic.[16]

Results

Baseline characteristics of the population are described in Table 1. Data for the 30-day occurrence of death or nonfatal (re)MI were complete. A total of 342 patients (3.6%) died, and another 1075 (11.4%) had a nonfatal (re)MI.

Univariable Analyses

Table 2 presents the univariable relations between dichotomous baseline characteristics and 30-day outcome. The relations between continuous variables and outcome are described in Figures 1 and 2. Age was strongly related with death, as were measures of left ventricular function (rales and history of heart failure), ST-segment depression on the presenting ECG, and admission heart rate. Other important risk factors were diabetes mellitus, prior MI, previous anginal

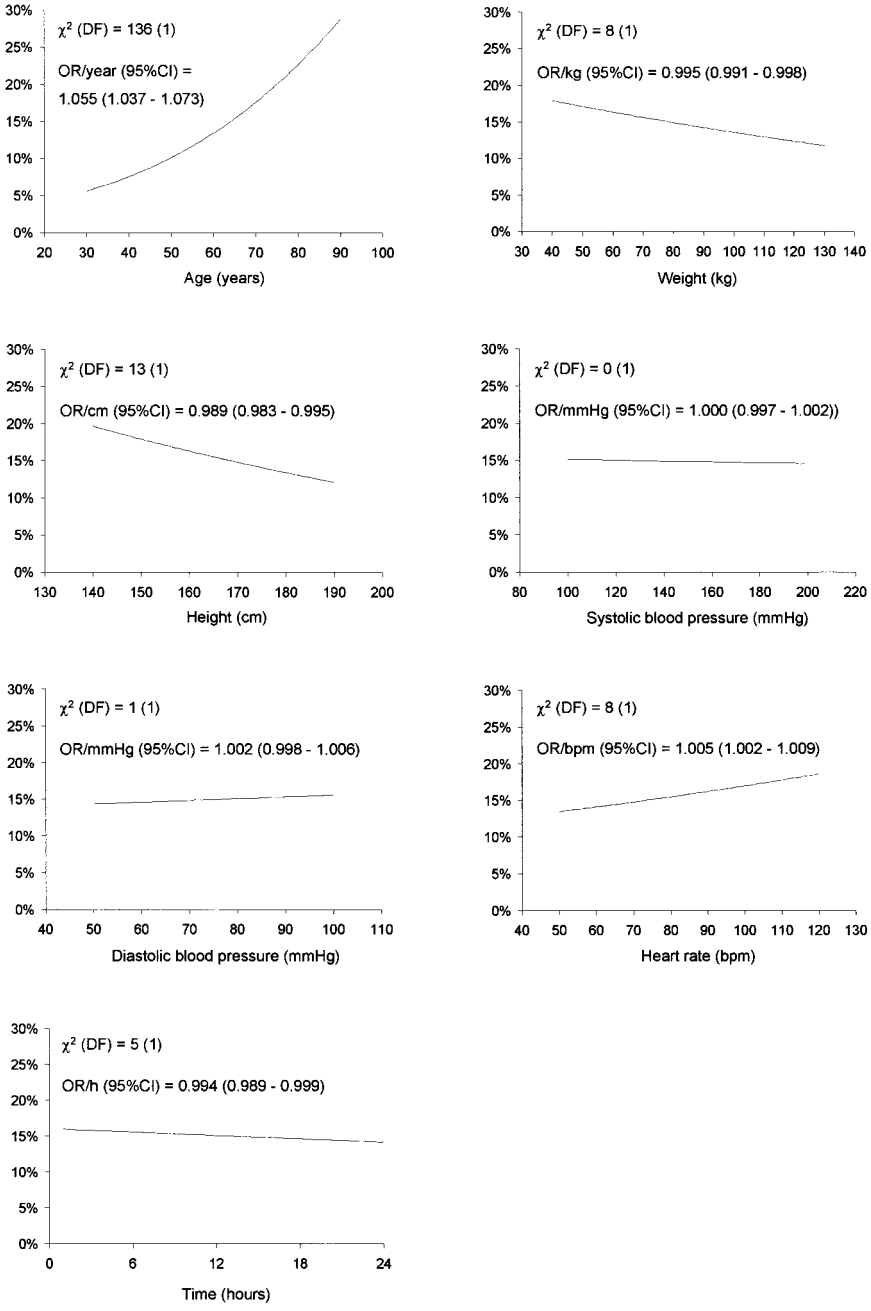

Figure 2. Univariable relation between continuous baseline characteristics and 30-day rate of death or nonfatal MI. Abbreviations as in Figure 1.

symptoms, and CK-MB level at enrollment (enrollment MI versus UAP). The region of enrollment appeared to be prognostic, with higher mortality rates in Latin America and eastern Europe relative to western Europe and North America. Systolic and diastolic blood pressures were only weak predictors. There was a significant nonlinear relation between weight and mortality. Patients taking cardiac medications had a worse prognosis than patients not taking such medication before enrollment.

Clinical characteristics that predicted 30-day mortality generally also predicted the occurrence of either death or nonfatal (re)MI. The ranking order according to prognostic importance, however, was somewhat different, with enrollment diagnosis among the most important risk factors for the composite end point, whereas heart rate was of only modest predictive value. Unlike death alone, the composite event rate in Latin America was rather close to that of western Europe and North America.

With respect to 30-day mortality, there were interactions between enrollment diagnosis and the variables age, heart rate, rales, and PURSUIT study medication. As far as the composite end point was concerned, interactions were observed between enrollment diagnosis and the variables diabetes, history of heart failure, rales, and T-wave inversion.

Multivariable Models

Many of the univariably significant mortality predictors remained important in the multivariable models (Table 3; the mortality model is described in detail in the Appendix). After correction for other determinants, age showed the strongest

TABLE 3. Multivariably Adjusted Effects of Baseline Characteristics on 30-Day Outcome

	Death		Death or Nonfatal (Re)MI	
	χ^2 (*df*)	OR (95% CI)*	χ^2 (*df*)	OR (95% CI)*
Demographics				
Age, y†				
55	95 (1)‡	UAP: 0.63 (0.53–0.74) MI: 0.47 (0.40–0.55)	75 (1)‡	0.77 (0.73–0.82)
64		1		1
71		UAP: 1.44 (1.26–1.65) MI: 1.81 (1.59–2.05)		1.23 (1.17–1.28)
Sex				
Female	9 (1)§	0.61 (0.44–0.84)	21 (1)‡	0.56 (0.45–0.69)
Male		1		1
Weight, kg†				
69	14 (2)‖	1.04 (0.95–1.15)	7 (2)¶	1.02 (0.97–1.07)
78		1		1
88		1.05 (0.96–1.14)		1.01 (0.97–1.06)
Height, cm†				
163	6 (1)¶	1.18 (1.04–1.33)	12 (1)‖	1.12 (1.05–1.20)
170		1		1
176		0.87 (0.78–0.97)		0.91 (0.86–0.96)
Region of enrollment				
Latin America	23 (3)‡	3.04 (1.93–4.78)	22 (3)‡	1.31 (0.98–1.77)
North America		0.90 (0.68–1.21)		0.95 (0.82–1.10)
Eastern Europe		1.03 (0.74–1.43)		1.40 (1.19–1.65)
Western Europe		1		1
History				
Hypertension				
Yes	3 (1)	1.25 (0.97–1.62)	...	
No		1		
Diabetes mellitus				
Yes	6 (1)¶	1.38 (1.07–1.76)	6 (1)¶	1.18 (1.03–1.36)
No		1		1
Smoking status				
Current	3 (1)	1.29 (0.91–1.83)	3 (1)	1.09 (0.92–1.29)
Former		1.27 (0.97–1.66)		1.14 (0.99–1.32)
Never		1		1
Worst CCS class past 6 weeks				
III or IV	14 (1)‡	1.56 (1.23–1.97)	26 (1)‡	1.36 (1.20–1.53)
Other		1		1
CHF				
Yes	5 (1)¶	1.73 (1.31–2.28)	...	
No		1		
PVD				
Yes	...		7 (1)#	1.29 (1.06–1.56)
No				1
Bypass surgery				
Yes	5 (1)¶	1.44 (1.04–2.00)	...	
No		1		
Angioplasty				
Yes	9 (1)§	0.51 (0.33–0.80)	...	
No		1		

TABLE 3. Continued

	Death		Death or Nonfatal (Re)MI	
	χ^2 (*df*)	OR (95% CI)*	χ^2 (*df*)	OR (95% CI)*
Prior medication				
β-Blockers				
Yes	8 (1)§	1.40 (1.10–1.79)	14 (1)‡	1.26 (1.11–1.43)
No		1		1
Calcium antagonists				
Yes	6 (1)¶	1.35 (1.06–1.70)	8 (1)§	1.20 (1.06–1.36)
No		1		1
Nitrates				
Yes	3 (1)	1.34 (0.99–1.81)	4 (1)¶	1.16 (1.01–1.34)
No		1		1
Presenting characteristics				
Diagnosis				
MI	15 (1)‡	**	68 (1)‡	**
UAP				
SBP, mm Hg†				
116	20 (1)‡	1.21 (1.12–1.31)	7 (1)#	1.08 (1.02–1.13)
130				1
145		0.82 (0.75–0.89)		0.92 (0.87–0.97)
DBP, mm Hg†				
67	...		4 (1)¶	0.95 (0.91–1.00)
75				1
83				1.05 (1.00–1.10)
Heart rate, bpm†				
62	32 (1)‡	UAP: 0.90 (0.80–1.01)	...	
		MI: 0.73 (0.67–0.80)		
72		1		
80		UAP: 1.09 (0.99–1.19)		
		MI: 1.28 (1.19–1.37)		
Rales				
≥1/3	18 (2)‡	1.85 (1.36–2.51)	17 (2)‡	2.00 (1.27–3.13)
<1/3		2.05 (1.08–3.88)		UAP: 0.96 (0.69–1.34)
				MI: 1.59 (1.26–2.01)
None		1		1
ST depression				
Yes	20 (1)‡	1.80 (1.40–2.33)	14 (1)‡	1.27 (1.12–1.44)
No		1		1
Time course				
Symptom onset to randomization, h†				
5.7	3 (1)	1.05 (0.99–1.12)	2 (1)	1.02 (0.99–1.06)
11.2		1		1
18.8		0.93 (0.85–1.02)		0.97 (0.93–1.01)
PURSUIT study medication				
Eptifibatide	<1 (1)	UAP: 1.28 (0.91–1.81)	3 (1)	0.90 (0.80–1.01)
		MI: 0.79 (0.58–1.07)		
Placebo		1		1

Results are based on the imputed data set (see Methods). χ^2 indicates difference between −2 log likelihood of the full model and the model with the variable at hand removed, both without interaction terms.

*If a significant interaction was seen between the variable and enrollment diagnoses (MI or UAP), 2 separate ORs are presented.

†For continuous variables, ORs are presented for the first and third quartiles vs the median.

‡$P<0.0001$; §$P<0.005$; ‖$P<0.05$; #$P<0.01$.

**The contribution of enrollment diagnosis should be interpreted in combination with all interaction terms. Therefore, the OR for diagnosis separately is not presented. Abbreviations as in Table 1.

relationship with 30-day mortality; baseline heart rate was the next-strongest predictor. The interactions between enrollment diagnosis and both age and heart rate were maintained. The adjusted 30-day mortality rate for eastern Europe was similar to western Europe and North America, but patients treated in Latin America still had a higher risk of death. Other important risk factors were (lower) systolic blood pressure, ST-segment depression, and signs of heart failure (rales). Sex also appeared to be an important determinant of 30-day mortality in the multivariate analysis: women were at lower risk than men. This observation was not made in the univariable analysis: the crude 30-day mortality rates of men and women were similar (Table 2). The prognostic importance of systolic blood pressure was more pronounced in multivariable than in univariable analyses.

In combination with other baseline information, age was again the strongest predictor of the composite of 30-day death or nonfatal (re)MI, but the relative contribution of age in the composite end-point model was smaller than in the mortality model. In contrast, the relative contribution of enrollment diagnosis was greater in the composite end-point model. Again, there was a difference between univariable and multivariable analyses with respect to the sex-outcome relation: after correction for differences in baseline characteristics, women appeared to be at lower risk for the composite end point than men.

Predictive Accuracy

The C-index for the mortality model was 0.814, reflecting good ability to discriminate between patients who did and did not have a fatal outcome. The correction factor determined by bootstrapping was 0.01 (reducing the C-index to 0.804), implying that there was little overoptimism in the estimated predictive accuracy of the model. The composite end-point model had a weaker discriminative power, with a C-index of 0.669 (correction factor also 0.01). The performance of the latter model showed only minimal improvement after incorporation of the interaction between sex and eptifibatide (C-index 0.670). If events were ignored that occurred within 48 hours of an invasive procedure, the C-indices of both the mortality and the composite end-point model increased to 0.844 and 0.736, respectively.

Discussion

The prognosis of patients with acute coronary syndromes generally depends on the occurrence and extent of myocardial damage. Patients presenting without persistent ST-segment elevation or a typical enzyme rise have the lowest incidence of mortality and morbidity.[7] Intermediate complication rates are seen in those presenting without ST-segment elevation but with a rise in cardiac enzymes,[7] whereas prognosis is worst in patients with ST-segment elevation and substantial myocardial damage.[1,3] Apart from this simple classification, analyses of the GUSTO-1 (Global Utilization of Streptokinase and Tissue plasminogen activator for Occluded coronary arteries) population have demonstrated that age, heart rate, blood pressure, and signs of heart failure (Killip class) are the key factors in predicting outcome in patients with ST-segment–elevation MI.[3] The present analysis in non–ST-segment–elevation acute coronary syndromes showed a remarkable homology with ST-segment–elevation patients, as basically the same prognostic factors were determined.

Demographics

Age was the most important determinant of outcome in this non ST-segment–elevation population, as was the case in a population with ST-segment elevation.[3] The contribution of age to mortality was more pronounced in patients with MI rather than in those with UAP. This suggests that the relation between age and outcome depends on the presence and extent of myocardial necrosis at admission.

The results with respect to sex (and blood pressure) emphasize that possible prognostic factors should be considered in association with other outcome predictors. In univariable analysis, no relation was observed between sex and mortality, whereas multivariable analysis revealed women to be at lower risk than men.

The difference in outcome between regions of enrollment could not be explained fully on the basis of other baseline differences. Univariable analysis showed an increased risk for adverse events in eastern Europe compared with western Europe and North America. After correction for differences in baseline characteristics, mortality rates in these regions were similar, but the difference in the combined end point remained. The definition of MI should be considered in this respect. Particularly in eastern Europe, the number of MIs differed according to the definition of the CEC versus the local investigator.[9] Eastern European origin was not a risk factor for the combined outcome of death or nonfatal (re)MI when MI was classified by local investigators. Furthermore, there were interregional differences in applied treatment strategies.[17] Percutaneous interventions were much more common in North America than in eastern Europe. These variations in treatment may have caused differences in outcome. The high mortality rate in Latin America is still an unexplained finding.

Presenting Features

The contribution of heart rate to the mortality model was of similar importance as patients with persistent ST-segment elevation.[3] In contrast to observations in ST-segment elevation,[3] however, no U-shaped relation between heart rate and mortality was observed, although the numbers of patients with very low or very high values were too small to draw strong conclusions.

The enrollment diagnosis was the second most important predictor of the composite end point. Patients presenting with MI had an almost 50% increase in the 30-day (re)infarction rate compared with UAP. According to local investigator reports, the prognostic importance of enrollment diagnosis was less pronounced. Patients classified as having MI by the CEC who were not labeled as such by the investigators represent a subgroup with minor CK-MB elevations. These patients are probably similar to patients with elevated cardiac troponin levels, who are at increased risk for repeat thrombotic events.[18]

		Score	
		Mortality only	Mortality or infarction
Age (year)	50	0	8 (11)
	60	2 (3)	9 (12)
	70	4 (6)	11 (13)
	80	6 (9)	12 (14)
Gender	Female	0	0
	Male	1	1
Worst CCS-class in previous 6 weeks	No angina; I or II	0	0
	III or IV	2	2
Heart rate (bpm)	80	0	0
	100	1 (2)	0
	120	2 (5)	0
Systolic blood pressure (mmHg)	120	0	0
	100	1	0
	80	2	0
Signs of heart failure (rales)	No	0	0
	Yes	3	2
ST-depression on presenting ECG	No	0	0
	Yes	3	1

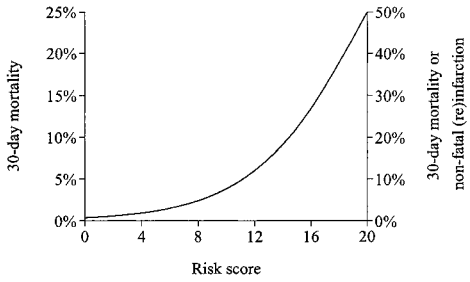

Figure 3. Simple scheme to estimate risk of 30-day complications in individual patients. Points are given for each predictive factor. With respect to age and heart rate, there are separate points for enrollment diagnosis of UAP and MI (between parentheses). Summed points will provide a risk score, which can be converted into a probability with help of the graph. CCS indicates Canadian Cardiovascular Society.

History

Among the history variables, the prognostic contribution of prior revascularization was most interesting. Patients who had undergone angioplasty generally had a better survival rate than those who had not, but previous bypass surgery was associated with worse prognosis. Most likely, the type of prior revascularization procedure is a marker of coronary disease severity, which is less severe in the angioplasty group (single-vessel disease) and more severe in the bypass group (multivessel disease and impaired left ventricular function).

Treatment, In-Hospital Course, and Modeling Aspects

The treatment of acute coronary syndrome patients is an interactive process that is guided by the physician's perceptions of patient risk and risk reduction by available therapies and by the response to such therapy. Because we concentrated on risk estimation at hospital admission, response to treatment was not part of the model, nor were markers of changes during hospitalization, such as recurrent ischemia. An exception was assignment to eptifibatide, which occurred at random in PURSUIT.

The predictive power of the mortality model was substantial and was similar to an established model for patients with ST-segment elevation.[3] Prediction of (re)MI was less accurate, which reflects the fact that disruption of atherosclerotic plaque, which ultimately leads to MI, often occurs at multiple locations in the coronary system, independently of prior ischemic events.[19] MIs caused by percutaneous interventions are even more difficult to predict from information known at hospital admission. Indeed, if these events are ignored, the predictive power of both the mortality and the composite end-point models improved significantly.

Clinical Implications

Although the developed risk models can be helpful for evaluating a patient's prognosis at hospital admission, these may be too complex to be integrated in clinical practice. We therefore present in Figure 3 a simple risk-evaluation scheme based on the most important prognostic factors. The observed 30-day mortality rates in the first quartile of predicted mortality according to this scheme ($\leq$1%), the interquartile range ($>$1% and $\leq$4%), and the highest quartile ($>$4%) were 0.6%, 2.2%, and 8.9%, respectively. The observed event rates in the first quartile of the predicted composite end point ($\leq$10%), the interquartile range ($>$10% and $\leq$19%), and the highest quartile ($>$19%) were 8.2%, 16.5%, and 24.1%.

It is beyond the scope of the data presented in this article to make firm statements about the appropriate treatment of patients in the several risk categories. Still, we may indicate how knowledge of the risk profile may affect the clinical decision-making process. For patients at low risk for recurrent events, early discharge seems warranted. The intermediate-risk group may benefit from a strategy of "watchful waiting": close observation in intensive or medium-care units with ischemia monitoring and serial determination of markers of myocardial damage. Some of these patients will be candidates for additional, invasive therapy; others may be treated medically. Antiplatelet therapy should be considered for high-risk patients, especially in case of elevated levels of cardiac troponins. Platelet glycoprotein IIb/IIIa inhibitors can reduce the probability of MI beyond that achieved by aspirin and heparin.[8,20,21] Percutaneous revascularization may be of particular benefit in this group.[22] Again, platelet glycoprotein IIb/IIIa receptor blockers should be given to reduce the risk of procedure-related thrombotic complications.[23] Bypass surgery should be considered in

patients with impaired left ventricular function and multivessel disease.

Conclusions

By systematic analysis of the PURSUIT database, several pivotal factors were identified that have a profound impact on clinical outcome. Knowledge of these factors may facilitate the clinical decision-making process.

Appendix

The probability of 30-day mortality is $[1+\exp(+8.9294-S)]^{-1}$, where S is the sum of:

$0.0483\times$[age (years)]$+0.0317\times$[age (years)]$\times$[enrollment MI]
$-0.4787\times$[female sex]
$0.1608\times$[weight (kg)]$-2.8481\times\sqrt{}$[weight (kg)]
$-0.0216\times$[height (cm)]
$-0.1048\times$[North America]$+1.0978\times$[Latin America]$+$
$0.0336\times$[eastern Europe]
$0.2247\times$[history of hypertension]
$0.3197\times$[diabetes mellitus]
$0.2508\times$[current smoker]$+0.2185\times$[former smoker]
$0.4418\times$[worst Canadian Cardiovascular Society class in previous 6 weeks=III or IV]
$0.3517\times$[history of heart failure]
$0.3771\times$[history of angioplasty]
$-0.6552\times$[history of bypass surgery]
$0.3510\times$[β-blocker use]
$0.2977\times$[calcium antagonist use]
$0.2744\times$[nitrate use]
$-3.0787\times$[enrollment infarction]
$-0.0127\times$[systolic blood pressure (mm Hg)]
$0.0088\times$[heart rate (bpm)]$+0.0204\times$[heart rate (bpm)]$\times$[enrollment MI]
$0.6150\times$[rales $<1/3$]$+0.7174\times$[rales $\geq 1/3$]
$0.5906\times$[ST-segment depression]
$-0.0098\times$[time from onset of symptoms]
$0.2635\times$[eptifibatide]$-0.4760\times$[eptifibatide]$\times$[enrollment MI]

Age, weight, height, systolic blood pressure, heart rate, and time from onset are continuous variables; all other determinants are 0/1 variables, with 0=no and 1=yes.

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References

1. The Reperfusion Therapy Consensus Group. Selection of reperfusion therapy for individual patients with evolving myocardial infarction. *Eur Heart J*. 1997;18:1371–1381.
2. Boersma E, Steyerberg EW, Van der Vlugt MJ, et al. Reperfusion therapy for acute myocardial infarction: which strategy for which patient? *Drugs*. 1998;56:31–48.
3. Lee KL, Woodlief LH, Topol EJ, et al, for the GUSTO-I Investigators. Predictors of 30-day mortality in the era of reperfusion for acute myocardial infarction: results from an international trial of 41,021 patients. *Circulation*. 1995;91:1659–1668.
4. Simoons ML, Arnold AER. Tailored thrombolytic therapy: a perspective. *Circulation*. 1993;88:2556–2564.
5. Boersma E, Vlugt van der M, Arnold AER, et al. Estimated gain in life expectancy: a simple tool to select optimal reperfusion treatment in individual patients with evolving myocardial infarction. *Eur Heart J*. 1996;17:64–75.
6. Maseri A, Rebuzzi AG, Cianflone D. Need for a composite risk stratification of patients with unstable coronary syndromes tailored to clinical practice. *Circulation*. 1997;96:4141–4142.
7. Armstrong PW, Fu Y, Chang WC, et al. Acute coronary syndromes in the GUSTO-IIb trial: prognostic insights and impact of recurrent ischemia. *Circulation*. 1998;98:1860–1868.
8. The PURSUIT Trial Investigators. Inhibition of platelet glycoprotein IIb/IIIa with eptifibatide in patients with acute coronary syndromes. *N Engl J Med*. 1998;339:436–443.
9. Harrington RA. Clinical trials in acute coronary syndromes: lessons from PURSUIT. *Eur Heart J*. 1999;1(suppl R):R28–R34.
10. Akaike H. Information theory as an extension of the maximum likelihood principle. In: Petrov BN, Csaki F, eds. *Second International Symposium on Information Theory*. Budapest, Hungary: Akademia Kiado; 1973: 267–281.
11. Smith PL. Splines as a useful and convenient statistical tool. *Am Statistician*. 1979;33:57–62.
12. Harrell FE Jr, Lee KL, Mark DB. Multivariable prognostic models: issues in developing models, evaluating assumptions and adequacy, and measuring and reducing errors. *Stat Med*. 1996;15:361–387.
13. Little RJ. Regression with missing X's: a review. *J Am Stat Assoc*. 1992;87:1227–1237.
14. *S-Plus Guide to Statistical and Mathematical Analysis, Version 3.3*. Seattle, Wash: Statistical Sciences; 1996.
15. Kendal DG. *Rank Correlation Methods*. 3rd ed. London, UK: Charles Griffin; 1962.
16. Gong G. Cross-validation, the jackknife, and the bootstrap: excess error estimation in forward logistic regression. *J Am Stat Assoc*. 1986;81: 108–113.
17. Kleiman NS, Lincoff AM, Flaker GC, et al. Early percutaneous coronary intervention, platelet inhibition with eptifibatide, and clinical outcomes in patients with acute coronary syndromes. *Circulation*. 2000;101:751–757.
18. Lindahl B, Venge P, Wallentin L, for the FRISC Study Group. Relation between troponin-T and the risk of subsequent cardiac events in unstable coronary artery disease. *Circulation*. 1996;93:1651–1657.
19. Falk E, Shah PK, Fuster V. Coronary plaque disruption. *Circulation*. 1995;92:657–671.
20. Kong DF, Califf RM, Miller DP, et al. Clinical outcomes of therapeutic agents that block the platelet glycoprotein IIb/IIIa integrin in ischemic heart disease. *Circulation*. 1998;98:2829–2835.
21. Hamm CW, Heeschen C, Goldmann B, et al. Benefit of abciximab in patients with refractory unstable angina in relation to serum troponin T levels: c7E3 Fab Antiplatelet Therapy in Unstable Refractory Angina (CAPTURE) Study Investigators. *N Engl J Med*. 1999;340:1623–1629.
22. Madsen JK, Grande P, Saunamaki K, et al. Danish multicenter randomized study of invasive versus conservative treatment in patients with inducible ischemia after thrombolysis in acute myocardial infarction (DANAMI): DANish trial in Acute Myocardial Infarction. *Circulation*. 1997;96:748–755.
23. Boersma E, Akkerhuis KM, Theroux P, et al. Platelet glycoprotein IIb/IIIa receptor inhibition in non–ST-elevation acute coronary syndromes: early benefit during medical treatment only, with additional protection during percutaneous coronary intervention. *Circulation*. 1999; 100:2045–2048.