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Incidence and Follow-Up of Braunwald Subgroups in Unstable Angina Pectoris

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Objectives. **This study was performed to establish the prognosis of patients with unstable angina within the subgroups of the Braunwald classification.**

Background. **Among many classifications of unstable angina, the Braunwald classification is frequently used. However, the incidence and risk for each subgroup in clinical practice have not been established.**

Methods. **Prospective data for 417 consecutive patients admitted for suspected unstable angina were analyzed. Patients were classified according to Braunwald criteria and followed up for 6 months. Survival, infarct-free survival and infarct-free survival without intervention are reported for each class.**

Results. **After in-hospital observation the final diagnosis was acute myocardial infarction in 26 patients (6%), noncoronary chest pain in 109 (26%) and definite unstable angina in 282 (68%). Recurrence of chest pain was significantly different for the different severity classes (28%, 45% and 64% for classes I [accelerated angina], II [subacute angina at rest] and III [acute angina at rest], respectively) but not for clinical circumstances (49% and 53% for classes B [primary unstable angina] and C [postinfarction unstable angina], respectively). Six-month and infarct-free survival (96% and 88%, respectively) were not significantly different between severity classes but were significantly different ($p = 0.01$) between classes B (97% and 89%) and C (89% and 80%). Infarct-free survival without intervention was best for class II (72%), intermediate for class I (53%) and worst for class III (35%). In multivariate analysis, elderly age, male gender, hypertension, class C and maximal (intravenous) therapy were independent predictors for death; elderly age and class C for infarct-free survival; and male gender, class III, class C, electrocardiographic changes and maximal therapy were associated with infarct-free survival without intervention.**

Conclusions. **Braunwald classification is an appropriate instrument to predict outcome. Risk stratification by these criteria provides a tool for patient selection in clinical trials and for evaluation of treatment strategies.**

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The clinical syndrome unstable angina pectoris encompasses a variety of clinical presentations of transient episodes of myocardial ischemia. These episodes are caused by obstruction of coronary flow by different pathophysiologic mechanisms, including intracoronary atheromatous plaque rupture, platelet aggregation, thrombus formation and increased vasomotor tone (1,2). Other terms that have been used to describe the syndrome, such as impending myocardial infarction, preinfarction angina, acute coronary insufficiency or intermediate coronary syndrome (3), indicate concern for progression to myocardial infarction, which has been reported to occur in 7% to 16% of patients (4–6). The risk in a given patient depends on the actual pathophysiology and clinical presentation (6–13).

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To recognize groups of patients with different levels of risk, a classification of unstable angina was described by Braunwald (14). However, the precise risk of subgroups according to this classification has not been established. In fact, few data are available on the prognosis of a wide spectrum of patients with "unstable angina" because most reports address specific selected subgroups (8,12,15–18), which makes comparison between studies difficult.

To establish the incidence and prognosis of the various subgroups of unstable angina as defined in the Braunwald classification, we analyzed 417 consecutive patients who were admitted for chest pain of suspected ischemic origin, without signs of acute infarction or other diseases at the time of admission. The diagnostic and therapeutic procedures used in various subgroups were recorded as well as the incidence of events both in hospital and during 6 months of follow-up, including development of myocardial infarction, mortality and the need for revascularization procedures.

Methods

Patient selection and definitions. A prospective registry was maintained in two hospitals in Rotterdam, The Nether-

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lands, during a 7-month period in 1988 and 1989. All patients primarily admitted for suspected unstable angina, according to the attending physician, were included in the registry. The initial diagnosis, *suspected unstable angina*, was made immediately on admission on the basis of a history of chest pain at rest or at minimal exertion, probably of ischemic origin, without electrocardiographic (ECG) signs of acute infarction or signs of other causes of chest pain, such as dissecting aneurysm or arrhythmia. ST-T wave changes were not required for inclusion. Secondary referrals from other hospitals for further treatment were excluded.

A *final* diagnosis was established using subsequent information acquired during admission, including the occurrence or absence of new episodes of chest pain, ECG changes or elevated serum enzyme levels. The major diagnostic groups were acute myocardial infarction, definite unstable angina and extracoronary or nonspecific disease (other) (1,19). The final diagnosis, *definite unstable angina*, was based on the evaluation of symptoms and on the documentation of ECG changes (see Data collection) during in-hospital observation or exercise testing. *Myocardial infarction* was defined as the occurrence of serum creatine kinase levels above twice the local upper limit of normal. The time of onset of infarction was determined from analysis of history and ECG and enzyme changes. Patients who developed recurrent anginal pain ≥24 h after myocardial infarction were classified as having postinfarction angina.

All patients were classified at admission, and for patients with definite unstable angina, a final classification was applied at the time when the decision for definite therapy was made (coronary intervention or continuation on medical therapy), according to the clinical aspects as defined by Braunwald for classification of unstable angina (14):

Severity. New onset of severe or accelerated angina without pain at rest (*class I* = accelerated angina) angina at rest but not within the preceeding 48 h (*class II* = subacute angina at rest) or angina at rest within 48 h (*class III* = acute angina at rest).

Clinical circumstances. Unstable angina secondary to an extracardiac condition (*class A* = secondary unstable angina), angina developed in the absence of extracardiac condition (*class B* = primary unstable angina) or developed shortly after acute myocardial infarction (*class C* = postinfarction unstable angina). Patients with class A unstable angina were excluded at admission.

Electrocardiographic changes. Electrocardiographic changes were scored as present or absent.

Medical treatment intensity. None or one of the major antianginal drugs, nitrates, beta-adrenergic and calcium channel blocking agents (minimal therapy); more than one of these drugs (extensive oral therapy); or use of antianginal therapy, including intravenous nitrates (maximal therapy).

Data collection. The data were prospectively collected with particular attention to various decision moments during a patient's hospital stay. Demographic data, history and characteristics of presentation were recorded at admission. A log was kept of new pain episodes, new infarctions or death and of diagnostic and therapeutic measures, such as ECGs, exercise tests, medication and interventions. The ECGs were coded with respect to the presence or absence of Q waves, signs of left ventricular hypertrophy or intraventricular conduction disturbances (20). The ST segment was scored as ST elevation or depression ≥0.1 mV or T wave inversion, or both. The ECG changes were defined as additional ST elevation/depression ≥0.1 mV or T wave deviation ≥0.1 mV versus that on the baseline ECG, without pain.

Follow-up data. Follow-up data after discharge were acquired by review of the clinical records or through a simple questionnaire sent to the general practitioner. Follow-up data could be obtained for 407 patients (97%). The occurrence of new pain episodes, myocardial infarction, death or any coronary intervention (coronary angioplasty or bypass) was recorded until 6 months after admission. Combined end points are presented in terms of "survival without myocardial infarction" and "survival without infarction or revascularization."

Statistical analysis. Patient groups were compared with a Student *t* test for continuous variables and a chi-square test for discrete variables. The probability of survival, survival without infarction and survival without infarction or revascularization was estimated using the Kaplan-Meier method. Differences between curves were analyzed with log-rank tests. A stepwise proportional hazards model was used to select predictors of (event-free) survival, specifically to relate the various Braunwald classes to prognosis. The following variables were considered: age, gender, history of myocardial infarction, hypertension, Braunwald classes I to III (severity) and B and C (clinical circumstances), ECG changes and intensity of medical treatment. Two-level variables were coded as indicator variables, assuming 1 if the property at issue was present and 0 otherwise. Three-level variables were coded with two separate indicator variables.

Results

Baseline characteristics. A total of 417 patients were admitted for observation for suspected unstable angina. This initial diagnosis was supported by an abnormal repolarization pattern on admission or by dynamic ECG changes during or shortly after pain in 214 patients. In 203 patients the diagnosis of suspected unstable angina was based on history alone. Demographics, historic data and the classification of unstable angina at admission are presented in Table 1. There was no difference in age between patients with a final diagnosis of unstable angina, myocardial infarction or chest pain of other causes. Patients with unstable angina more often had a history of documented coronary artery disease. Acute angina at rest (class III) was present in the majority of patients (n = 309) (74%). In contrast, only four patients were admitted without pain in the last 48 h before admission (class II). Patients with a final diagnosis of chest pain of other causes had fewer ECG changes and less intensive medical treatment before admission.

Among the 109 other patients (26%) with a final diagnosis of chest pain of other causes, in 25 patients an extracoronary

Table 1. Characteristics of 417 Study Patients in Relation to Final Diagnosis

	Initial Diagnosis of Suspected UAP (n = 417)	Final Diagnosis		
		AMI (n = 26)	UAP (n = 282)	Other (n = 109)
Demographics				
Age (yr)	62 ± 13	62 ± 13	62 ± 12	61 ± 14
Male gender	276 (64)	20 (77)	181 (64)	66 (61)
History				
Hypertension	152 (36)	10 (38)	102 (36)	40 (37)
Diabetes mellitus	49 12)	2 (8)	37 (13)	10 (9)
Hypercholesterolemia	59 (14)	4 (15)	47 (17)	8 (7)
Current smoking	142 (34)	8 (31)	100 (35)	34 (31)
Family history of CAD	151 (36)	4 (15)	113 (40)	34 (31)*
Myocardial infarction	193 (46)	10 (38)	142 (50)	41 (38)
PTCA	51 (12)	1 (4)	45 (16)	5 (5)*
CABG	63 (15)	2 (8)	51 (18)	10 (9)*
Severity				
Class I	104 (25)	3 (12)	78 (28)	23 (21)
Class II	4 (1)	—	4 (1)	—
Class III	309 (74)	23 (88)	200 (71)	86 (79)
Clinical circumstances				
Class A	—	—	—	—
Class B	382 (92)	26 (100)	248 (88)	108 (99)
Class C	35 (8)	—	34 (12)	1 (1)*
ECG abnormalities				
No	203 (49)	7 (27)	110 (39)	86 (79)
Yes	214 (51)	19 (73)	172 (61)	23 (21)*
Intensity of treatment before admission				
Minimal	303 (73)	18 (69)	189 (67)	96 (88)
Extensive oral	114 (27)	8 (31)	93 (33)	13 (12)*

*$p < 0.05$ for comparison among the three patient groups. Data presented are mean ± SD or number (%) of patients. AMI = acute myocardial infarction; CABG = coronary artery bypass grafting; Class A = secondary unstable angina; Class B = primary unstable angina; Class C = postinfarction angina; Class I = accelerated angina; Class II = subacute angina at rest; Class III = acute angina at rest; ECG = electrocardiographic; Extensive oral = more than one antianginal drug (see Methods for details); Family history of CAD = cardiac death by infarction at >60 years old in first- or second-degree relative [CAD = coronary artery disease]; Hypercholesterolemia = serum cholesterol >6.5 mmol/liter or current treatment; Hypertension = blood pressure >160/90 mm Hg or current treatment; Minimal = none or one of the major antianginal drugs, nitrates, beta-blockers and calcium channel blockers; PTCA = percutaneous transluminal coronary angioplasty; UAP = unstable angina pectoris.

cause was found: gallbladder and liver disease (in 2), gastrointestinal problems (in 4), musculoskeletal pain (in 2), hypertension (in 4), heart failure (in 6), valvular disease (in 2), arrhythmias (in 3), cardiomyopathy (in 1) and pericarditis (in 1).

Clinical course during hospital stay. *Patients with "definite" unstable angina.* In 282 patients (68%), 210 of whom (74%) showed new ECG changes, a definite diagnosis of unstable angina was made between admission and the decision between coronary intervention and continuation of medical therapy. In-hospital medical treatment was started with intravenous nitrates in 164 patients (58%), with extensive oral therapy (more than one antianginal drug) in 73 patients (26%) and minimal therapy (none or one antianginal drug) in 45 patients (16%). The initial and final classifications of these patients are presented in Table 2. Although a few patients in class IB at admission progressed to class IIIB during the hospital period, half of the patients (n = 88) with acute unstable angina at admission (classes IIIB and IIIC) stabilized and became "subacute" unstable angina (classes IIB and IIC).

Half of the patients (n = 137) had recurrent pain during in-hospital observation, usually (80%) within 48 h after admission. Recurrent ischemia after admission was more frequent in patients with acute angina at rest (class III) compared with those in class I or II (p = 0.0001) (Fig. 1). There was no significant difference in recurrent ischemia between patients with primary (class B) and postinfarction angina (class C). In fact, the strongest predictor of recurrent ischemia was the time interval since the previous episode. The probability of development of recurrent chest pain rapidly decreased during the first days after a previous episode (Fig. 2). After a pain-free period of 48 h, the probability of developing new chest pain decreased to <20% and to <10% after 3 days. It was striking that the decline of probability of developing recurrent pain was similar after the first and subsequent episodes.

The frequencies of events and interventions are summarized in Table 3. Progression to infarction or death during the in-hospital period was most frequently observed in patients with acute angina at rest (class III) and with postinfarction angina (class C). In-hospital decisions for coronary angiogra-

Table 2. Classification at Admission and After In-Hospital Observation for 282 Patients With Definite Unstable Angina

	Postobservation						
Admission	IB	IC	IIB	IIC	IIIB	IIIC	Total (%)
IB	50	1	7	0	13	2	73 (26)
IC	0	4	0	1	0	0	5 (2)
IIB	0	0	4	0	0	0	4 (1)
IIC	0	0	0	0	0	0	0 (0)
IIIB	0	0	73	3	89	6	171 (61)
IIIC	0	0	0	12	0	17	29 (10)
Total	50 (18)	5 (2)	84 (30)	16 (6)	102 (36)	25 (9)	282 (100)

Data presented are number (%) of patients. Classification of severity (classes I to III) and clinical circumstances (classes B and C) at admission and at the time that the decision for final treatment is made (Postobservation). Definitions of classification categories as in Table 1.

phy and angioplasty or bypass were made most frequently in patients with recurrent chest pain at rest (class III) and only in 10% to 15% of patients with class II angina. Patients with accelerated angina (class I) were scheduled for interventions twice as often as class II patients. The frequency of in-hospital decisions for interventions was significantly higher for postinfarction angina (class C).

Six-month follow-up. Survival, survival without infarction, and infarct-free survival without intervention are shown as Kaplan-Meier curves for the 6-month follow-up period for the different subgroups of severity and clinical circumstances (Fig. 3). Survival and infarct-free survival were both higher in patients with primary unstable angina (class B) compared with that in postinfarction patients (class C, $p = 0.01$ and $p = 0.1$, respectively). These end points were not significantly different for the three severity subgroups. For both Braunwald classes I to III and B and C, there was a distinct difference when the outcome of infarct-free survival without intervention was considered ($p = 0.0001$ and $p = 0.01$, respectively).

For all three outcomes, the adjusted risk ratio for the different classes was estimated, using proportional hazards multivariate analysis (Table 4). For both mortality and infarction, the risk difference between classes B and C was confirmed after correction for other covariates. Elderly age, male gender, hypertension, postinfarct angina (class C) and maximal antianginal therapy were independent predictors of mortality. Survival without infarction was impaired for elderly patients and patients with postinfarct angina (class C). All four categories described in the Braunwald classification were indicators for a higher risk of mortality, infarction or revascularization: acute angina at rest (class III), postinfarction angina (class C), presence of ECG changes and use of maximal antianginal therapy (two or more antianginal drugs) in addition to the risk factor of male gender.

Eight of 109 patients with a final diagnosis of chest pain of other causes developed myocardial infarction (two), died (four) or underwent coronary angioplasty (one) or bypass surgery (two) within 6 months after admission. Four of these eight patients were discharged with atypical chest pain, and four had a history of heart failure (two), arrhythmia (one) or myocardial infarction (one).

Discussion

The classification of unstable angina as defined by Braunwald (14) was applied to a group of 417 patients admitted for chest pain suspected of being unstable angina pectoris. The selection of patients immediately at admission ensured that the whole spectrum of unstable angina was included in this registry. This is in contrast with most other studies on unstable angina, where only selected patients were included, restricted by age (12,21), absence of recent myocardial infarction or bypass surgery (7,9,12,22), duration of pain episodes (9,22,23) or by presence of ischemic signs on the ECG (7,23,24). In most studies, patients were selected 24 to 48 h after admission, when myocardial infarction had been ruled out by serial enzyme analysis, which also excludes most patients with a final diagnosis of chest pain of other causes. In contrast, the only

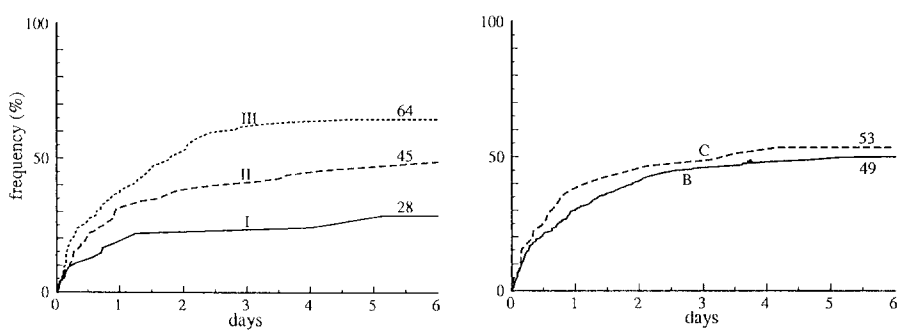

Figure 1. Frequency of recurrent ischemia for the various subgroups. **Left,** Severity classes: accelerated angina (I), subacute angina at rest (II) and acute angina at rest (III). **Right,** Primary unstable (B) and postinfarction (C) angina.

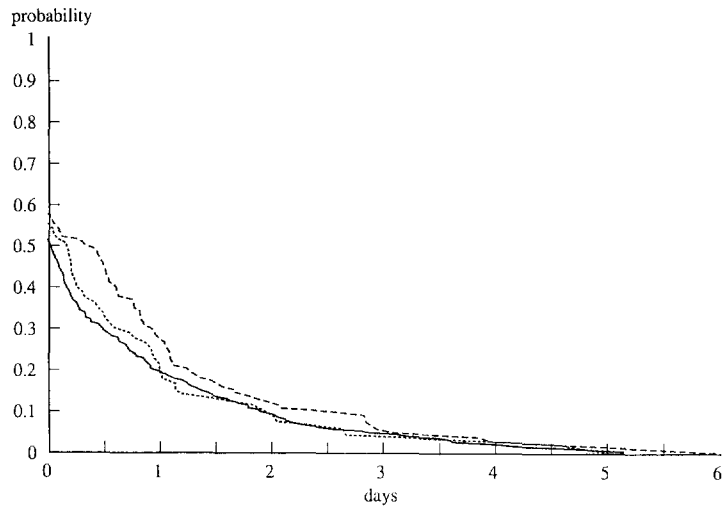

Figure 2. Probability of development of recurrent pain after admission (**solid line**), development of a second pain episode after a first recurrence (**long-dashed line**) and development of a third episode after a second episode (**short-dashed line**).

exclusion criterion in the present study was evidence of other disease assumed to be causing the chest pain, such as aneurysm dissecans, and referral from other hospitals for further treatment of patients in whom a complete diagnostic workup had already been performed.

For practical reasons, the tentative diagnosis of unstable angina should be made at the time of hospital admission. A patient with chest pain severe enough to warrant hospital admission will be classified at admission as having suspected unstable angina when symptoms and signs are such that transient myocardial ischemia is believed to be the underlying cause. The patient will be monitored to detect possible life-threatening arrhythmias from recurrent ischemia or evolving myocardial infarction. Often treatment will be started with beta-blockers, nitrates, aspirin or heparin. Subsequent information acquired during admission, such as the occurrence or absence of new episodes of chest pain, ECG changes or elevated serum enzyme levels, will contribute to a *final* diagnosis that can be either acute myocardial infarction, unstable angina, noncardiac disease or nonspecific chest pain (1,19).

Final diagnosis. The diagnosis of unstable angina was confirmed in 68% of patients, whereas in 26% the complaints were attributed to causes other than coronary insufficiency after observation. This proportion is low compared with Duncan et al. (25), who reported that 60% did not satisfy the criteria for unstable angina in an outpatient study of 616 men who were referred for chest pain by general practitioners. This difference suggests that a considerable proportion of patients with chest pain from other causes may be filtered before admission. At the other end of the spectrum, myocardial infarction had already occurred in 9% of all admitted patients, which became apparent from subsequent serum enzyme assays. Similarly, in the HINT study (23), myocardial infarction had occurred at the time of randomization in 8% of patients with prolonged chest pain and concomitant ECG changes.

Clinical course and underlying pathophysiology. During the hospital stay, patients moved from one class to another. For example, 12 patients appeared to have, in addition to the 34 patients who actually had, postinfarction angina (class C) recognized as such on admission. By contrast, 88 patients who presented with class III symptoms were in class II after observation, indicating that the unstable period had stabilized. This illustrates the dynamic aspects of unstable angina as an intermediate condition between chronic stable angina and acute myocardial infarction (5,26) and corresponds to the dynamic changes within the coronary arteries described in relation to unstable coronary disease (1,19,27). The similarity of occurrence of subsequent pain episodes over time may

Table 3. Events and Interventions During the Hospital Period by Class

Class	Total	AMI/Death	Angiography*	PTCA/CABG*
Severity				
I	55	2 (4)	22 (40)	19 (35)
II	100	4 (4)	15 (15)	10 (10)
III	127	14 (11)†	100 (79)*‡	71 (56)‡
Clinical circumstances				
B	236	13 (6)	104 (44)	77 (33)
C	46	7 (46)†	33 (72)*‡	23 (50)†
Total	282	20	137	100

*Including both emergency and elective procedures. †$p < 0.05$, ‡$p < 0.01$, for comparison of subgroups. Data presented are number (%) of patients. Definition of classification categories and abbreviations as in Table 1.

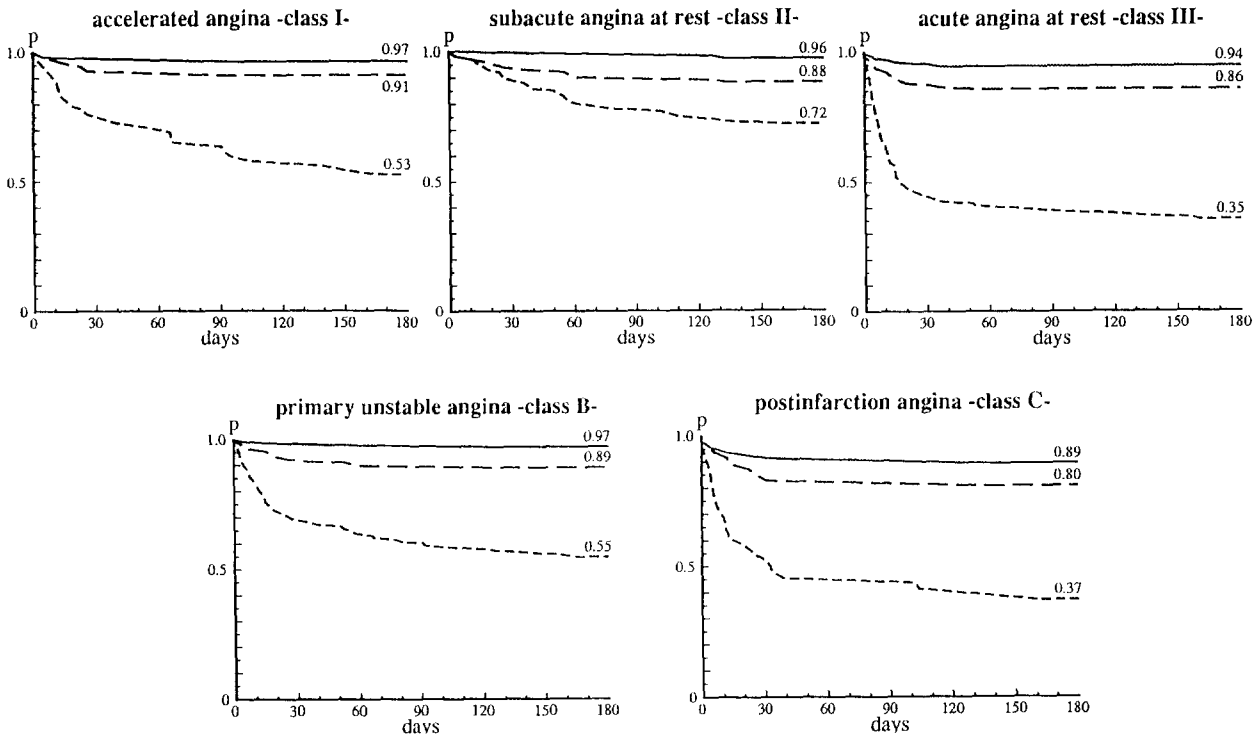

Figure 3. Six-month follow-up outcomes: survival (**solid lines**), infarct-free survival (**long-dashed lines**) and infarct-free survival without intervention (**short-dashed lines**) for the various subgroups. p = probability.

correspond to repeated formation and recovery of an unstable plaque, resulting in a layered thrombus (28). Furthermore, the clinical decrease of frequency of symptoms over time corresponds to the decrease of angiographic presence of intracoronary thrombus over time (29).

Events and interventions. For patients with definite unstable angina, the rate of death or infarction was 4.3% during the in-hospital period and 9.6% at 6-month follow-up. This relatively good prognosis compares favorably with other reports (12,13,23,30,31) and may be related to the intensive medical therapy and high intervention rate. After hospital admission, 78% of all patients received either oral or intravenous nitrates, 58% received beta-blockers, 33% received calcium antagonists, and 78% of the patients were initially treated with either aspirin or heparin. In addition to medical therapy, 35% of patients with a final diagnosis of angina pectoris underwent revascularization, most of them during the hospital period. Similar revascularization rates after extensive medical treatment were reported by Theroux et al. (30) and Cairns et al. (32), whereas others reported lower numbers of 4% and 18% within the first 3 to 8 months (11,33).

Table 4. Multivariate Analysis: Independent Predictors of Long-Term Outcome (6 months) in 282 Patients With Unstable Angina Pectoris

	Rate Ratio	95% CI
Mortality		
Age >70 yr	14.5	3.5–61
Male gender	3.7	0.9–14.8
Hypertension	3.5	1.0–12
Class C	8.0	2.2–28
Maximal antianginal therapy	3.2	1.0–10.4
Death or infarction		
Age >70 yr	2.1	1.1–4.1
Class C	2.1	1.0–4.6
Death, infarction or intervention		
Male gender	2.7	1.8–4.1
Class III	3.0	2.1–4.3
Class C	1.6	1.0–2.4
ECG changes present	1.8	1.2–2.8
Maximal (IV) antianginal therapy	2.1	1.5–3.1

CI = confidence interval; ECG = electrocardiographic; IV = intravenous. Definitions of classification categories as in Table 1.

Classification system. The classification system proposed by Braunwald appeared to be appropriate for risk stratification in clinical practice. The subgroups of the four categories—severity, clinical circumstances, ECG changes and intensity of treatment—were all related to different prognoses. However, for the severity category, prognosis was best for class II, intermediate for class I and worst for class III (Fig. 3). Apparently, absence of pain for >48 h is a better indicator for outcome than the occurrence of pain at exertion or at rest. If a patient is pain free for >48 h, the probability of new episodes is <20%. The relation between recurrent pain and prognosis has been described in earlier reports (8–10,22). The good

prognosis of patients without pain over the previous 48 h may be reflected in the low number of class II patients at admission.

Conclusions. The classification proposed by Braunwald can be used easily in clinical practice and is a helpful tool to predict outcome. For classification of severity, the pain-free period is a better risk indicator than the distinction between accelerated angina and angina at rest. In general, unstable angina has a relatively good prognosis under the current management strategy.

Survival without infarction varies between 80% and 91% among the various classes, with the best prognosis in classes I, II and B and the worst prognosis in classes III and C. Between 35% and 72% of the patients have an uncomplicated course with medical therapy alone, with the best outcome for class II and the worst for classes III and C. The different outcome rates for the individual classes are confirmed by multivariate analysis and provide a useful tool for risk stratification in patients selected for clinical trials and evaluation of treatment strategies.

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