Coronary angioplasty in patients with unstable angina: clinical, electrocardiographic and angiographic predictors of in-hospital outcome

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Key words:
Coronary angioplasty; Culprit lesion; Refractory angina; Stents; Unstable angina.

Background. **In unstable angina early coronary arteriography is frequently performed, often followed by percutaneous revascularization with liberal use of stents. We intended to study the in-hospital outcome of patients receiving this treatment.**

Methods. **From April 1997 to April 1998, patients submitted to coronary arteriography due to unstable angina, and with no previous myocardial revascularization, were included in a multicenter registry.**

Results. **Out of 987 patients enrolled at 14 centers, 876 (89%) had percutaneous or surgical revascularization. Coronary angioplasty was performed in 571 patients (58%); 281 (49%) had Braunwald class IIIB or C angina. Refractory or prolonged chest pain, or both, were present in 133, 217 and 85 patients, respectively, and multivessel disease in 245 patients (43%). Stenting was performed in 486/571 cases (85%), abciximab was administered to 42 patients, and ticlopidine and/or aspirin to all. A procedural success was obtained in 96.9% of cases. In-hospital major adverse cardiac events occurred in 29/571 patients (5.1%). Pain-related ST segment depression (44% of cases) was not predictive of outcome after coronary angioplasty. In multivariate analysis prolonged plus refractory angina (p = 0.02), an ejection fraction < 0.4 (p = 0.04), multivessel disease (p = 0.01) and with the strongest predictive value *ad hoc* angioplasty (p = 0.007) and use of > 1 stent (p = 0.0008) were all independent predictors of in-hospital adverse outcome.**

Conclusions. **Coronary angioplasty with a liberal use of stents yields a high rate of procedural success, with few in-hospital major cardiac events also in high risk patients.**

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Introduction

The pathophysiology of the acute disease process is complex and variable in patients admitted with a diagnosis of unstable angina; this may be reflected by a variety of clinical and electrocardiographic (ECG) presentations which may be predictive of patients outcome. Previous reports indicate that an adverse in-hospital outcome is related to the severity of symptoms, and the prognostic importance of refractory angina with ECG changes is well recognized[1].

Coronary angioplasty (PTCA) is an accepted therapeutic option for revascularization of patients with unstable angina[2] and the use of stenting has been shown to reduce the incidence of restenosis[3]. Both ticlopidine[4] and inhibitors of platelet glycoprotein IIb/IIIa[5], in addition to aspirin, are effective in reducing subacute stent thrombosis. Moreover, the elective use of an inhibitor of the platelet glycoprotein IIb/IIIa receptor, even with a restricted use of stents[6-8], has been shown to reduce the rate of in-hospital major adverse cardiac events (MACE) in patients with acute unstable angina treated with PTCA.

In this study, the clinical and ECG characteristics at presentation in a large population of patients with unstable angina undergoing coronary angiography are described, and the correlation of clinical, ECG, angiographic and procedural variables with the in-hospital outcome in the patient cohort treated with PTCA is examined.

Methods

The study population consisted of consecutive patients submitted to coronary angiography for unstable angina in the 12-month period between April 1997 and April 1998 at 14 invasive cardiology centers in Northern Italy. Both the use of revascularization procedures and the in-hospital outcome of patients were prospectively monitored.

Inclusion criteria. Patients were included if they presented with new onset of angina (< 2 months), recent deterioration in stable angina with symptoms occurring during minimal effort, or early post-infarction angina. ECG changes were defined as transient or persistent ST segment depression, transient (< 30 min) ST segment elevation of > 1 mm 80 ms after the J point (both in at least two contiguous leads) or isolated changes in the T wave vector in the absence of ST segment changes. The different clinical subsets of unstable angina were classified as previously described[9].

Exclusion criteria. Exclusion criteria were: persistent (> 30 min) ST-T segment elevation or significant (> 2 times the basal level) elevation of plasma CK-MB, and previous PTCA or coronary bypass surgery.

Refractory angina was defined as recurrent ischemic chest pain at rest (with documented ECG changes compatible with myocardial ischemia) that occurred during treatment with at least two antianginal drugs one of which had to be intravenous nitrate plus aspirin and heparin, all drugs having been administered at least 2 hours previously.

Prolonged angina was defined as at least one episode of chest pain with a duration of > 20 min. All patients were treated with intravenous and oral medication[10] in order to stabilize the patient before coronary angiography, the latter defined as urgent in the case of prolonged and/or refractory angina.

Coronary arteriography and angioplasty. Selective coronary arteriography and a left ventricular angiogram were performed in all patients. Significant coronary lesion was defined as diameter narrowing > 50% in at least one coronary artery or its major branch. Patients were classified as having one-, two- or three-vessel disease, and ejection fraction was calculated from the ventriculogram performed in 30 left anterior oblique projection.

The culprit coronary lesion was indicated when possible on the basis of ECG changes (site and extension), angiographic complexity of the lesion, and regional abnormalities of left ventricular kinesis. The culprit lesion, when recognized, was described as type A, B1, B2, C according to the American College of Cardiology/ American Heart Association classification[11]. The presence of intralesion thrombus was also annotated.

PTCA was defined as *ad hoc* whenever it was performed immediately after coronary angiography, due to either clinical emergency, or the operator s or patient s preference, or to logistic reasons. Elective PTCA was performed within a few days from the diagnostic procedure and possibly before discharge; in these patients ticlopidine 250 mg bid was started at least 2 days before angioplasty.

An intraprocedural value of activated clotting time (HemoTec Inc., Englewood, CO, USA) > 300 s (optimal heparin activity) was recommended, while the use of stents and elective infusion of abciximab were left to the decision of the interventional cardiologist performing the procedure. Procedural success was defined as the achievement of a final diameter stenosis < 30% with a TIMI grade 3 flow.

Bail-out use of abciximab was defined as infusion of the drug during the procedure for abrupt occlusion (TIMI flow < 3) of the vessel due to thrombus or extensive dissection.

Outcome measures. The following in-hospital outcome measures were considered as MACE: cardiac death, non-fatal myocardial infarction (at least two of the following: prolonged chest pain, more than a 2-fold rise in serum CK and CK-MB activity above the local upper normal limit, the appearance of new Q waves on serial ECG tracings), need for new emergent revascularization with PTCA or coronary bypass surgery. In patients with multiple adverse events only the most severe was considered.

Statistical analysis. All data analysis was performed using the Statistical Package for Social Science (SPSS Rel 7.0, Cary, NC, USA) software. Continuous variables are expressed as the mean and standard deviation. Comparison of categorical variables was evaluated by χ^2 analysis and Fisher s exact test when appropriate.

A stepwise multivariate logistic regression analysis was performed for all the variables of potential significance from the univariate analysis.

Because of the large number of statistical comparisons performed in this study, values of $p < 0.1$ were assumed to provide some evidence of association, and values of $p < 0.001$ a strong evidence of association. A p value < 0.05 was considered statistically significant.

Results

Baseline clinical and angiographic characteristics of the whole population. The registry included 987 patients with unstable angina and submitted to coronary angiography. Selected baseline clinical features in the whole patient population are shown in table I, together with the admission ECG characteristics.

More than 90% of patients were treated with oral aspirin and intravenous nitrates, and more than half with beta-blockers; calcium-antagonists and intravenous he-

Table I. Baseline clinical and electrocardiographic features of the whole population.

Characteristics	No. patients	%
Clinical		
Mean age (years)	63 – 11 (range 31-91)	
Sex (M/F)	749/238	75/25
Family history	346	35
Smoking history	461	48
Hypercholesterolemia	460	48
Hypertension	522	53
IDDM	11	1
NIDDM	134	14
Previous AMI	217	22
Recent (< 15 days) AMI	140	18
Braunwald class		
IB	140	15
IIB	356	36
IIIB	351	35
IIC	47	4
IIIC	93	10
Electrocardiographic		
ST elevation	343	35
ST depression	450	46
T wave changes	99	10
Absence of ECG changes	95	9

AMI = acute myocardial infarction; IDDM = insulin-dependent diabetes mellitus; NIDDM = non-insulin-dependent diabetes mellitus.

parin were given to 59% of patients. The combination of oral aspirin with heparin and intravenous nitrates was administered to 576 patients (58.4%).

Despite maximal antianginal therapy 284 patients (28.8%) had refractory angina; 397 (40.2) patients experienced at least one episode of prolonged angina, and 149 of them were refractory to maximal medical treatment.

Coronary angiography revealed a single-vessel, a multivessel and a non-significant disease respectively in 379 (38.5%), 583 (59%), and 25 (2.5%) patients. Mean angiographic left ventricular ejection fraction of the whole population was 57 – 11%.

The culprit lesion was identified in 675/987 (68%) patients, in 525/571 (92%) of those treated with PTCA, in 102/305 (33%) cases following surgical revascularization, and in 48/108 (44%) cases treated with medical therapy.

Ad hoc or elective PTCA was attempted in 571 out of 987 patients (58%), while 305 patients (31%) were referred for coronary bypass surgery; only a minority of cases were treated with medical therapy alone.

The coronary angioplasty cohort and procedural outcome. In the cohort of patients treated with percutaneous revascularization (571 patients), mean age was 62 – 12 years with a range included between 31 and 91 years, and there were 126 women (22%). Braunwald class III angina was present in about half of the patients (279 out of 571 cases), while refractory or prolonged angina was present respectively in 173 (30%) and 217 (38%) of patients, both types of symptoms being present in 85 (15%) of them; a history of a recent or previous myocardial infarction was found in 54% of cases. Single-vessel and multivessel coronary disease was present in 57 and 43% of patients respectively, and mean left ventricular ejection fraction was 55 – 10%; the latter was not different from that of patients treated with surgical revascularization (55 – 11%). *Ad hoc* PTCA was performed in 385 patients, the remaining elective procedures being performed after an average delay of 6 days. *Ad hoc* PTCA was performed in 245/385 (64%) cases due to the patient s clinical instability (class IIIB or C unstable angina), of which 107 suffered from an episode of prolonged angina, 127 had refractory chest pain and 61 experienced both refractory and prolonged angina. The remaining 140 cases had an *ad hoc* PTCA according to the operator s or patient s preference or for logistic reasons. The mean time elapsed from the last chest pain to *ad hoc* PTCA was 1.8 – 1.7 days.

Ticlopidine and/or aspirin were given to all patients, while abciximab was administered to only a minority of them (42 patients - 7.3% -, in half of cases in a bail-out procedural setting), probably because the use of the drug at the time of the registry was limited compared to a widespread use of elective stents, although PTCA was performed in 279 patients (49%) with class III (B or C) unstable angina. Since the drug was utilized in a bail-out situation in 50% of cases, in-hospital MACE were more frequent in the abciximab group (7/42 patients) than in the group in which abciximab was not used (22/529 cases) ($p = 0.003$).

PTCA was attempted on 691 coronary arteries in 571 patients. Treated vessels were the left main coronary artery in 3 cases, the left anterior descending coronary artery in 357 cases (52%), the left circumflex artery in 150 cases (21%), and the right coronary artery in 181 cases (26%). Stents were implanted in 486 out of 571 patients (85%), electively in 338 (69% of the cases); a poor result and a dissection with threatened coronary occlusion after balloon angioplasty were the indication for a non-elective stent respectively in 24 and 7% of cases. Multiple stenting was utilized in 77/486 of stented patients (16%), for a poor post-balloon result or threatened coronary occlusion in 17 (22%) and 11 (14%) cases respectively. Directional or rotational atherectomy preceding balloon angioplasty was used in only 24 cases.

Procedural success was achieved in 553 patients (96.9%). Nine out of the 18 patients without procedural success had in-hospital MACE (2 patients died, 4 had non-fatal myocardial infarction, and 3 underwent emergent surgical revascularization). In addition, 20 patients with initial procedural success suffered from MACE before discharge. Therefore, the overall incidence of in-hospital MACE was 29/571 patients (5.1%): 8 patients (1.4%) died due to cardiac death, 16 (2.7%) had a non-fatal acute myocardial infarction (after a new emergent PTCA in 4), and 5 patients had a new, uncomplicated, emergent revascularization procedure (PTCA in 3 patients and coronary bypass surgery in 2).

Table II summarizes the correlation between the baseline clinical, ECG and angiographic characteristics and the occurrence of in-hospital MACE. According to univariate analysis, among clinical variables a history of prolonged angina alone (p = 0.04), particularly if associated with refractory chest pain (p = 0.006) was predictive of a worse in-hospital outcome, while refractory angina alone was not. Braunwald class III unstable angina, post-infarction angina (Braunwald class IIC-IIIC) and a history of myocardial infarction were all related to in-hospital events (p = 0.02, p = 0.03, and p = 0.04 respectively).

Patients presenting with pain-related ST segment depression had similar in-hospital outcome as compared to those with ST segment elevation (4.8 vs 6.3% of MACE, respectively); moreover, ST segment depression was not predictive of a worse in-hospital outcome, although it was associated with a higher incidence of multivessel disease (67 vs 51% of patients with ST segment elevation), with a p value of 0.4.

Ad hoc PTCA was performed in 385 patients with a higher incidence of MACE (7.1%) as compared to 186 patients with elective PTCA (1.4%, p = 0.003).

When angiographic features were analyzed, both multivessel coronary disease and left ventricular ejection fraction < 0.4 were significantly correlated with in-hospital events (p = 0.002 and p = 0.03 respectively). An angiographic intralesion thrombus was detected in 101 (18%) patients treated with PTCA and abciximab was administered before or during the procedure in 22 cases; MACE were more frequent (7.9%) than in PTCA performed in non-thrombotic lesions (4.5%) but this difference was not statistically significant (p = 0.152). Similarly, the presence of an American College of Cardiology/American Heart Association type B2 or C culprit lesion was not associated with a worse outcome after angioplasty. Finally, the use of > 1 stent was also associated with a higher incidence of MACE (10/77 patients, p = 0.001): in half of these 10 MACE occurred in patients with coronary type A or B1 lesions, the remaining in patients with B2 or C lesions; 29 out of 77 patients (38%) who received > 1 stent had a type A or B1 lesion.

Independent predictors of outcome. In the multivariate model shown in table III, a history of prolonged plus refractory angina (p = 0.02), multivessel disease (p = 0.01), ejection fraction < 0.4 (p = 0.04), *ad hoc* PTCA (p = 0.007) and use of > 1 stent (p = 0.0008) retained an independent predictive value for in-hospital MACE, with a 94.9% overall accuracy in the stepwise logistic regression model used.

Table III. Independent predictors of in-hospital adverse outcome.

Characteristics	Odds ratio (95% CI)	p
Prolonged + refractory angina (n=85)	1.65 (1.07-2.53)	0.02
Ad hoc PTCA (n=364)	2.34 (1.26-4.35)	0.007
Multivessel disease (n=245)	1.68 (1.11-2.53)	0.01
LVEF < 0.4 (n=38)	1.77 (1.02-3.08)	0.04
Use of > 1 stent (n=77)	2.08 (1.35-3.20)	0.0008

CI = confidence interval. Other abbreviations as in table II.

Table II. Univariate analysis of clinical, electrocardiographic and angiographic predictors of adverse outcome in 571 patients treated with coronary angioplasty.

Characteristics	Yes	MACE	No	MACE	κ^2	p
Demographic						
Age > 70 years	126	8 (6.6%)	445	21 (4.8%)	1.6	0.142
Clinical						
Refractory angina	173	12 (6.9%)	398	17 (4.2%)	1.7	0.131
Prolonged angina	217	16 (7.4%)	354	13 (3.7%)	3.8	0.041
Refractory + prolonged angina	85	10 (11.8%)	486	19 (3.9%)	9.2	0.006
Class IIIB + IIIC	279	20 (7.2%)	292	9 (3.1%)	4.9	0.020
Class IIC + IIIC	108	10 (9.3%)	463	19 (4.0%)	4.8	0.031
Previous AMI	200	15 (7.5%)	371	14 (3.8%)	3.7	0.044
Electrocardiographic (n=558)						
ST elevation	253	16 (6.3%)	305	13 (4.3%)	1.2	0.184
ST depression	252	12 (4.8%)	306	17 (5.6%)	0.1	0.412
Angiographic						
Ad hoc PTCA	385	26 (7.1%)	186	3 (1.4%)	11.5	0.003
Multivessel disease	245	19 (7.7%)	326	10 (3.1%)	6.4	0.002
LVEF < 40%	38	5 (13.2%)	533	24 (4.5%)	5.5	0.036
Complex lesion (B2+C)	302	18 (6.0%)	269	11 (4.1%)	1.0	0.344
Intralesion thrombus	101	8 (7.9%)	470	21 (4.5%)	2.1	0.152
Use of > 1 stent	77	10 (13%)	494	19 (3.8%)	8.9	0.001

Yes and No indicate the number of patients with and without the characteristics listed on the left side. AMI = acute myocardial infarction; LVEF = left ventricular ejection fraction; MACE = major adverse cardiac events; PTCA = coronary angioplasty.

Discussion

Unstable angina is most often caused by plaque fissuring or rupture; this phenomenon leads to increased platelet adhesion, aggregation and intracoronary thrombosis, and therefore antithrombotic therapy with aspirin and heparin dramatically improves the clinical course of these patients[12].

Controversy still exists on the optimal management strategy for patients with this syndrome. So far there has been no general agreement about a conservative or invasive (i.e. immediate coronary revascularization) strategy[13,14], since most previous trials were performed before the widespread use of intracoronary stents and the advent of glycoprotein IIb/IIIa inhibitors, both of which have been shown to improve the clinical outcome of PTCA[3,6-8,15]; nevertheless, the risk of complications during revascularization procedures is increased in patients with unstable angina[16].

Our registry selected a particular population among unstable angina patients, that is patients observed in tertiary referral centers, in whom a coronary angiogram was indicated on the basis of clinical or ECG characteristics.

Among patients who entered the registry, 89% were referred for surgical (31%) or percutaneous (58%) revascularization. This rate of revascularization was higher than previously described in the aggressive treatment arms of the TIMI IIIB and VANQWISH trials, in which 61 and 44% of cases, respectively, were revascularized[17,18], and it was similar to that reported in a recent observational study[19], and in the aggressive arm of the randomized FRISC II trial[20].

Risk stratification with biochemical markers[21] was not routinely performed in our patients; most of them had been referred for coronary arteriography from secondary centers, at a variable time interval from the acute episode.

Although our patients in the cohort treated with PTCA can be considered at high risk according to their clinical characteristics, the procedural success was high (96.9%), and in-hospital death and myocardial infarction were infrequent (1.4 and 2.7% respectively). Similar results were previously described in patients treated with PTCA and a restricted use of stents in the TIMI IIIB trial[22] and in the more recent EPISTENT trial[5]; more than one half of all procedures in those studies, however, were elective.

Among the clinical variables predictive of in-hospital MACE, refractory plus prolonged angina retained an independent value in our experience ($p = 0.02$), as indicated in previous trials[16,23]. Furthermore, the performance of the PTCA procedure, for whatever reason, immediately after coronary angiography (*ad hoc* PTCA) was a strong independent predictor of MACE, as shown in a large registry of PTCA in unselected patients, with limited use of stents[22]. In the CAPTURE trial, the use of abciximab to stabilize patients with refractory unstable angina was associated with a reduction of recurrent ischemia and of total ischemic burden resulting in a significantly lower incidence of death and myocardial infarction both before and during PTCA[7]. Thus, it seems probable that, in patients who are stabilized by a combination of antianginal and intense antithrombotic medical therapy, the PTCA procedure should be deferred; this would allow further passivation of the unstable plaque resulting in an improved procedural outcome. This approach was used in patients assigned to the early invasive arm in the FRISC II trial[20], and it may partly explain the superior outcome of these patients as compared to those assigned to the conservative treatment in that study. On the contrary, a strategy of immediate aggressive revascularization in patients with unstable angina or non-Q wave myocardial infarction was adopted in the invasive arm of two previous large randomized trials[13,18], and was monitored in the OASIS Registry[14]; these studies showed that a generalized approach of very early revascularization may be less beneficial than a conservative one, especially in patients with Braunwald class III angina. Likewise, emergent PTCA was the most powerful predictor of experiencing an untoward event in patients enrolled in the TIMI IIIB trial and treated with PTCA[22].

According to univariate analysis, neither the presence of intracoronary thrombus, nor type B2 and C culprit lesions was predictive of MACE after PTCA in our patients. Similarly, neither the angiographic outcome of PTCA, nor the incidence of MACE were influenced by age, sex or location of the culprit lesion, while both the presence of multivessel disease, and an ejection fraction < 0.4 retained a significant predictive value ($p = 0.01$ and $p = 0.04$, respectively). Although a complex culprit lesion was not predictive of MACE in our registry, the use of > 1 stent was strongly associated with adverse events (13 vs 3.8% in the case of implantation of a single or no stent, $p = 0.001$). In fact 29 out of 77 patients with > 1 stent had a type A or B1 lesion, and half (5/10) of the cases with MACE in multiple stenting occurred among those 29 patients with a non-complex lesion; therefore multiple stenting represented a strong factor of adverse outcome independent of the complexity of the treated lesion.

Previous studies have documented a significant association between ST segment depression on the admission electrocardiogram and an increased risk of death or myocardial infarction at both in-hospital and long-term follow-up[24-26]. In the present study, ST segment depression was frequently associated with multivessel disease (67% of cases), in keeping with the TIMI IIIB registry findings[24], but as recently described[19] it was not predictive of outcome after PTCA.

In conclusion, our data show that PTCA with extensive use of stents in high risk unstable angina is characterized by a favorable in-hospital outcome and a low mortality rate. Prolonged plus refractory angina, an ejection fraction < 0.4 and multivessel disease still represent significant predictors of an unfavorable in-hospital

outcome. The strongest predictors of in-hospital MACE were *ad hoc* PTCA and the use of > 1 stent during the procedure. Efforts to stabilize such patients with a strong antithrombotic therapy and to delay PTCA may improve their in-hospital outcome and seem, therefore, to be advisable.

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Appendix

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