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Coronary Angiographic Findings Do Not Predict Clinical Outcome in Patients With Unstable Angina

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Objectives. The presence of thrombus formation and type of coronary artery lesion were determined in patients with unstable angina and correlated with the angiographic findings and clinical outcome.

Background. Some previous studies have suggested that thrombus formation and lesions are predictive of the angiographic and clinical findings. This was evaluated in a retrospective analysis of 159 patients participating in the placebo-controlled Unstable Angina Study Using Eminase (UNASEM) trial on the effect of thrombolysis in unstable angina.

Methods. Patients without a previous myocardial infarction who presented with a typical history of unstable angina in the presence of abnormal findings on the electrocardiogram indicative of ischemia were included in the study. After baseline angiography, study medication (anistreplase or placebo) was given to 126 of 159 patients. Thirty-three patients did not receive medication because of significant main stem disease or normal coronary arteries or for other reasons. Angiography was repeated after 12 to 28 h.

Results. Quantitative angiography showed a significant decrease in diameter stenosis in the anistreplase-treated group compared with the placebo-treated group (decrease 11% vs. 3%, $p = 0.009$). No differences in clinical outcome were found when thrombolytic treatment was compared with placebo ($p = 0.98$). Neither the presence nor absence of thrombus formation ($p = 0.98$) nor the type of lesion ($p = 0.96$) was related to the changes in diameter stenosis or to clinical outcome ($p = 0.90$ and $p = 0.77$, respectively). The power of these analyses to detect a 20% difference varied between 56% and 74%.

Conclusions. In this selected group of patients with unstable angina, type of coronary artery lesion and the presence or absence of thrombus formation does not predict clinical outcome.

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As recently reviewed by Scrutinio et al. (1), the majority of studies, including the Unstable Angina Study Using Eminase (UNASEM) trial (2,3), showed that the clinical outcome in patients with unstable angina is not influenced by thrombolytic therapy. In the UNASEM trial, 159 patients with typical unstable angina and typical electrocardiographic (ECG) changes were included. After baseline coronary angiography, patients were randomly treated either with the thrombolytic agent anistreplase (eminase or anisoylated plasminogen streptokinase activator complex [APSAC]) or with placebo. The study showed that anistreplase produced a significant decrease in the severity of the culprit lesion compared with placebo. However, clinical outcome was independent of thrombolytic treatment.

This last finding is puzzling because it is well known that the incidence of coronary thrombus in unstable angina is high (4–6). Therefore, the question remains whether subgroups can be identified in whom thrombolytic treatment is beneficial. Some investigators (7–9) found a relation between the presence or absence of thrombus formation and the angiographic or clinical outcome after thrombolytic therapy. Others (8,10) reported that the type of lesion might influence clinical results. In the present study, we retrospectively investigated the possible role of coronary anatomy and presence of coronary clot formation on clinical outcome in patients from the UNASEM trial.

Methods

Patients. One hundred fifty-nine patients were enrolled in the UNASEM trial. The trial was double blind, placebo controlled and randomized. The full protocol has been published elsewhere (2). Patients had to fulfill the following inclusion criteria: 1) a typical history of unstable angina defined as a) angina at rest or on minimal exercise; b) angina of recent onset (<4 weeks); c) the last episode of chest pain within 12 h before admission; and 2) ECG abnormalities suggestive of ischemia a) in patients with chest pain before but not after admission, the presence of ST segment depression or the so-called high left anterior descending coronary artery

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pattern (11), showing terminal negative T waves in the precordial leads; or b) in patients with chest pain during hospital admission, temporary ST segment changes (elevation, depression or pseudonormalization).

The exclusion criteria were age <30 or >70 years; previous myocardial infarction or previous cardiac surgery or angioplasty; nonischemic ST segment changes (as in left ventricular hypertrophy); contraindications for thrombolytic therapy; or absence of informed consent.

After inclusion in the study, the patients were randomized to the trial medication (either anistreplase or placebo), but treatment was postponed until after the baseline angiogram.

Cardiac catheterization. Baseline angiography, including coronary and left ventricular angiography, was performed within 3 h after inclusion in the study. Angiography was repeated after 12 to 28 h. To identify the location of the culprit lesion, the following criteria were used: 1) in case of single-vessel disease, the most severe lesion in that artery; 2) in case of multivessel disease, the location of coronary artery abnormality corresponding to the ECG abnormalities. For example, development of negative T waves in precordial leads was used as typical for left anterior descending coronary artery perfusion problems. If the ECG was inconclusive, the location of left ventricular wall motion abnormalities (if present) was used to identify the culprit artery. 3) If use of the first two criteria was inconclusive, the stenosis showing clear changes between the baseline and the posttreatment angiogram was taken to be the culprit lesion.

The criteria of Ambrose (7,12) were used to classify the type of lesion and the presence of coronary thrombus. Because of the limited number of patients in this study, we classified the lesions as only two types (Fig. 1): *type A (concentric lesion)* = symmetric narrowing with smooth or slightly irregular borders; and *type B or C (complex lesion)* = eccentric stenosis with asymmetric narrowing of the culprit lesion or multiple irregularities.

The culprit lesion was determined during the first angiography. If an occluded artery was present, the type of lesion could not be identified. If this vessel reopened, the type of lesion was determined in the second angiography.

If the artery at the baseline angiogram was open, an *intracoronary thrombus* was defined as a filling defect located proximal to, within or distal to a culprit stenosis surrounded by contrast medium on at least three sides and visible in multiple projections (Fig. 2). Not uncommonly, these filling defects moved up and down during the cardiac cycle. Occluded arteries during the first angiogram were presumed to contain thrombus material (Fig. 3).

Angiographic assessment and classification were performed in blinded manner by a committee with angiographic expertise. Van den Brand et al. (13) stated that quantitative analysis of coronary arteries in unstable angina is the most sensitive method of detecting changes in diameter stenosis or other characteristics of the lesion. Therefore, quantitative measurements were made using the Cardiovascular Angioplasty Analysis (CAAS) system (14). Analysis of the lesion was based on at least two projections. *Improvement* of a coronary lesion was defined as a decrease in diameter stenosis between the first and the second angiograms, measured by the CAAS system.

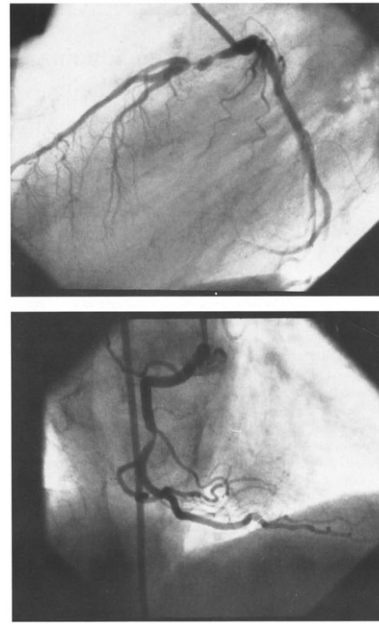

Figure 1. Top, Lateral view of the left anterior descending coronary artery showing a complex tandem (type B) lesion just before the origin of the first diagonal branch. **Bottom,** 30° right oblique projection of the right coronary artery shows a smooth, nearly symmetric (type A) lesion just beneath the right ventricular branch.

Trial medication and concomitant treatment. After angiography, trial medication was withheld in patients with main stem disease ≥70%, normal or nonsignificant coronary artery disease or development of myocardial infarction before the start of medication.

Trial medication consisted of 30 U of intravenous anistreplase or placebo and was given over 5 min after the pretreatment angiogram had been made. An intravenous drip of nitroglycerin was started before the pretreatment angiography; 5,000 U of intravenous heparin was injected during baseline angiography and continued with a starting dose of 1,000 U/h. Further titration was done depending on the activated partial thromboplastin time. Aspirin in a dose of 300 mg once daily was started after the posttreatment angio-

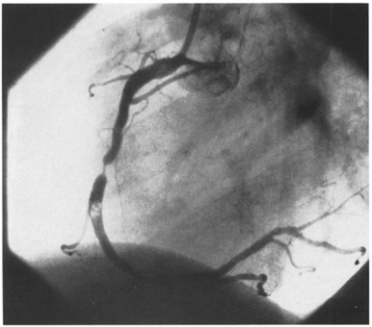

Figure 2. Right coronary artery in the 60° left oblique projection. Just after the right ventricular branch, a large thrombus is visible after a severe, symmetric (type A) stenosis. It is surrounded by dye on three sides, showing its somewhat round shape. This thrombus was moving slightly up and down during the cardiac cycle. Because of the force of the contrast injection, the thrombus mobilized and fragmented into two large pieces. These two parts embolized into the posterior descending branch, resulting in a distal occlusion of that vessel.

gram. Additional antianginal medication was given according to usual local protocols.

Statistics. When applicable, a Fisher exact test, Student *t* test or chi-square test (without Yates correction) was performed. Two-tailed p values are reported. Significance was defined as $p < 0.05$.

Results

In total, 159 patients were included in the study (Table 1). Thirty-three of 159 patients did not receive study medication because of exclusion criteria or other reasons (severe left main stem stenosis [7 patients], normal coronary arteries [17 patients], myocardial infarction occurring before the start of study medication [4 patients], severe groin bleeding [2 patients], technical problems preventing catheterization [2 patients], cardiogenic shock [1 patient]). Of the remaining 126 patients, 65 were randomized to receive anistreplase and 61 placebo. We were unable to determine the presence or absence of thrombus formation in five patients, and an additional two patients did not have two angiograms. This resulted in a total of 119 of 126 treated patients in whom thrombus formation could be analyzed. The type of lesion could not be determined in 20 patients (normal artery [1 patient], occluded artery [16 patients], not identified [3 patients]), and one other patient had only one angiogram. This resulted in 105 of the 126 treated patients in whom the type of lesion could be analyzed. Table 2 shows the number of patients available for each analysis.

Decrease in coronary artery stenosis. As previously reported (2), a significant decrease in stenosis severity ($p = 0.002$) was found in the anistreplase-treated group compared with the placebo-treated group by qualitative assessment. Quantitative CAAS analysis showed identical results: Diameter stenosis decreased 11% in patients treated with anistreplase versus 3% in patients receiving placebo ($p = 0.008$). Seventeen of 65 anistreplase-treated patients and 11 of 61 placebo-treated patients had an occluded artery at baseline angiography; in all of these patients, collateral vessels provided blood supply to the ischemic area. The difference in degree of stenosis before and after study medication was the result of the reopening of 12 of 17 occluded arteries in the anistreplase-treated patients, whereas none of the coronary arteries reopened in the 11 placebo-treated patients. The decrease in diameter stenosis of open arteries between the first and second angiography was 5% in the anistreplase-treated group compared with 3% in the placebo-treated group (p = NS) (2).

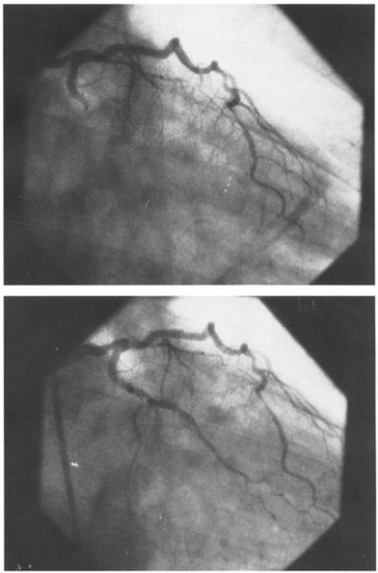

Figure 3. Top, Left circumflex coronary artery in the 30° right oblique projection, occluded proximally, with some minor collateral vessels visible. **Bottom,** After thrombolytic therapy, the circumflex artery reperfused. In this projection, the culprit lesion is hardly visible. In other views, the residual stenosis was only 50%.

Type of culprit lesion or presence of thrombus and angiographic outcome. The type of culprit lesion could be classified in 105 patients. In 75 patients (71%) the lesion was judged to

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Table 1. Baseline Clinical Characteristics of 159 Study Patients

	Anistreplase Treatment (n = 80)	Placebo Treatment (n = 79)
Mean (±SD) age (yr)	59 ± 8	57 ± 9
Men	57	63
Chest pain		
In-hospital	58	54
Only before admission	22	25
At rest	58	63
With minimal exercise	22	14
Median duration of last attack (min)	20	15
Median duration of unstable angina (days)	6.5	5.8
Single-vessel disease	33	24
Multivessel disease	37	44
Normal coronary arteries	10	9*
No angiography	0	2
Culprit vessel		
LMCA	0	7
LAD	40	32
LCx	16	12
RCA	13	17
ND	1	0

*Two patients received placebo as study medication, but the conclusion of the central angiographic analysis was nonsignificant coronary artery disease. Data presented are number of patients, unless otherwise indicated. LAD = left anterior descending coronary artery; LCx = left circumflex coronary artery; LMCA = left main coronary artery; ND = not determined; RCA = right coronary artery.

be concentric, and in 30 (29%) eccentric or complex. In 119 patients the presence or absence of thrombus could be analyzed. A clear thrombus was visible in 39 of them (33%). In the remaining 80 patients (67%), the presence of thrombus could not be determined by the criteria mentioned previously in the Methods section. Neither the type of lesion (concentric or complex) nor the presence or absence of thrombus influenced the angiographic outcome of the second catheterization ($p = 0.96$ and $p = 0.98$). The power of the test to detect a 20% higher or lower incidence of improved coronary anatomy in concentric versus eccentric lesions was 57% and 56%, respectively. The power to detect these differences in cases where the thrombus was visible versus cases where the thrombus was not visible was 66% in both situations. These results were independent of type of study medication (Table 3).

Type of lesion or presence of thrombus and clinical outcome. During hospital admission, cardiac events (defined as mortality, myocardial infarction, recurrence of angina, need for bypass graft or angioplasty) were common. Sixty-three percent of patients had at least one of these events. We previously reported (2) that in the total group of patients angiographic outcome was independent of clinical outcome. The anatomic characteristics (type of lesion or presence of thrombus) were not related to the occurrence of any cardiac event or the type of event (death, myocardial infarction, coronary artery bypass surgery, angioplasty or angina) ($p = 0.77$ and $p = 0.90$). The power of the test to detect a 20% higher or lower incidence of cardiac events in concentric versus eccentric lesions was 70% and 65%, respectively. These figures for visible versus nonvisible thrombus were 72% and 74%, respectively. These results were again independent of study medication (Table 4).

Table 2. Patients Available for Analysis

	No.
Total study patients	159
Patients receiving study medication	126
Patients with two angiograms	123
Identifiable type of lesion	105
Identifiable presence of thrombus	119

Table 3. Type of Lesion and Presence or Absence of Thrombus Related to Changes in Coronary Anatomy: Anistreplase (APSAC) Versus Placebo Treatment

Lesion Type/Study Medication	No. of Pts (%)	Improved Coronary Anatomy, No. of Pts (%)	p Value
Concentric	75		
APSAC	37 (49)	24 (65)	0.13
Placebo	38 (51)	18 (47)	
Eccentric	30		
APSAC	19 (63)	10 (53)	0.92
Placebo	11 (37)	6 (55)	
Thrombus			
Visible	39		
APSAC	19 (49)	11 (58)	0.43
Placebo	20 (51)	9 (45)	
Not visible	80		
APSAC	42 (53)	24 (57)	0.12
Placebo	38 (47)	15 (40)	

APSAC = anisoylated plasminogen streptokinase activator complex; Pts = patients.

Table 4. Type of Lesion and Presence or Absence of Thrombus Related to Cardiac Events In-Hospital: Anistreplase (APSAC) Versus Placebo Treatment

Lesion Type/Study Medication	No. of Pts (%)	Cardiac Events, No. of Pts (%)	p Value
Concentric	75		
APSAC	37 (49)	28 (76)	0.49
Placebo	38 (51)	26 (68)	
Eccentric	30		
APSAC	19 (63)	15 (79)	0.41
Placebo	11 (37)	10 (91)	
Thrombus			
Visible	39		
APSAC	19 (49)	11 (58)	0.27
Placebo	20 (51)	15 (75)	
Not visible	80		
APSAC	42 (53)	34 (81)	0.08
Placebo	38 (47)	24 (63)	

Abbreviations as in Table 3.

Table 5. Clinical Outcome During Hospital Admission

	Anistreplase	Placebo	p Value
No. of Pts	80 (15)	79 (18)	
Mortality	3 (1)	1 (0)	
MI	29 (3)	21 (3)	
CABG	6 (0)	16 (6)	0.02
PTCA	30 (3)	26 (0)	
Recurrent angina	27 (5)	12 (0)	0.06
≥1 cardiac event	55 (6)	51 (9)	
Bleeding	21 (1)	7 (2)	0.001

Numbers in parentheses indicate patients who did not receive study medication. CABG = coronary artery bypass graft surgery; MI = myocardial infarction; PTCA = percutaneous transluminal coronary angioplasty; Pts = patients.

Discussion

Type of lesion. Ambrose et al. (12) defined a number of typical anatomic variations in the coronary arteries in patients with unstable angina. Recently, they simplified these criteria (7). In the present study, this last set of criteria was used. Freeman et al. (8) used the first-mentioned Ambrose et al. criteria when they prospectively studied the coronary anatomy in 80 patients with unstable angina. In that study, complex morphology of the culprit lesion was seen in ~40% of the patients. They concluded that the presence of a complex lesion predicted a worse clinical outcome. They stated that in most of these lesions thrombus formation was likely to be present. Ellis et al. (10), using multivariate analysis, also indicated that roughness and length of the culprit lesion strongly predicted risk of myocardial infarction. The findings of these two studies disagree with our observations, where the type of culprit lesion had no predictive value as to clinical outcome. In addition, plaque morphology did not discriminate for angiographic improvement in our study. The recently published Thrombolysis in Myocardial Infarction (TIMI) IIIA study (9), performed in a sizable number of patients, also indicated that no significant relation was found between the type of the culprit lesion and angiographic outcome.

Thrombosis. Coronary thrombosis plays an important role in unstable angina. This has been shown by angiography, angioscopy, autopsy and indirectly by biochemical examinations and effect of treatment (9,15–39). In those studies, the frequency of thrombus formation varied between 1% and 85%. This wide variation can be explained by the timing and type of the investigation and the criteria used (3). For example, it has been reported (4–6) that the presence of thrombus is dependent on the delay between onset of complaints and cardiac catheterization: The incidence of observing thrombi is inversely related to the time from appearance of symptoms until angiography. In our trial, patients were studied in the acute phase of unstable angina. However, even after patients with occluded arteries had been included, only 33% of the patients had definite evidence of thrombi in the pretreatment angiogram. Van den Brand et al. (13) reported a visible thrombus in 4 of 36 patients with unstable angina; an additional 3 patients had an occluded artery that was suggestive of thrombosis. Our findings correspond with the TIMI IIIA results. In that study (10), apparent thrombus was observed in 35% of all culprit lesions, including 9% of patients who had an occluded artery. That study had inclusion criteria and time delays similar to UNASEM. Freeman et al. (8) found a 43% incidence of thrombus formation in angiograms made within 24 h after admission. The incidence decreased to 21% in angiograms made later that week; however, patients with ongoing chest pain showed thrombus formation in 75% of cases. Thus, percent of thrombosis is most certainly influenced by the criteria defining thrombus formation, type of patients and timing of the angiogram. These criteria vary from study to study, resulting in marked differences in the incidence of thrombus formation.

Gotoh et al. (17) found angiographic improvement after thrombolytic treatment in 20 of 21 patients with thrombus. The UNASEM trial confirmed that coronary anatomy improves after thrombolytic therapy (2). However, angiographic improvement was seen only in patients with occluded arteries, in whom thrombosis is likely to be present. This is in line with the TIMI IIIA findings (9), where the angiographic characteristics favoring measurable improvement included a recent coronary occlusion. Patients with open arteries did not have a better angiographic outcome after thrombolytic treatment in our study as in TIMI IIIA. This finding was independent of the presence or absence of intraluminary thrombi. Scrutinio et al. (1) reviewed data on the clinical outcome from seven studies and found that Vetrovec et al. (5) were the only investigators to report a beneficial clinical outcome after thrombolytic therapy. Small pilot studies suggest that thrombolysis might be more effective if a longer infusion duration is used (40,41).

The UNASEM trial confirms that thrombolytic therapy is clinically ineffective in the total group of patients. Also, in patients with coronary thrombosis, no significant difference in clinical outcome was found.

It is tempting to speculate on possible explanations for the lack of improvement after thrombolytic therapy in patients with unstable angina. They include the following:

1. Platelet aggregation is not affected in vessels containing thrombus. Thrombolytic agents do lyse clots but do not inhibit platelet aggregation. The angioscopic appearance of the thrombus in patients with unstable angina is different from that in patients with acute myocardial infarction (6,18). In myocardial infarction, a red thrombus is commonly found. In unstable angina, most patients show a gray thrombus, which suggests that the thrombus is already older and covered by platelet deposits. Such older thrombi might therefore dissolve less after thrombolytic therapy.

2. Some thrombolytic agents may ultimately cause platelet activation and thrombus formation in vivo, possibly through plasmin (19). Plasmin can activate platelet aggregation and Factor V directly. This may limit thrombolysis in unstable angina. Platelets increase the resistance of thrombi to lysis by inducing clot retraction and cross-linking and by releasing inhibitors (20).

3. A small decrease in stenosis of an open artery is more difficult to detect than reopening of an occluded artery: Reopening, even to a minor degree, leads to a clearly visible angiographic difference.

4. In contrast to myocardial infarction, pathogenesis of unstable angina is more complex (42). It most certainly cannot be explained by thrombus formation on a ruptured plaque alone. A gradual increase in a stable atherosclerotic plaque can lead to unstable angina. A recent study from Flugelman et al. (43) is indeed suggestive of this. They performed (immuno) histopathologic investigations of 32 patients atherectomy specimens from patients with unstable angina. In 56% of these patients, smooth muscle cell proliferation had led to plaque expansion and thereby to lumen narrowing and unstable angina. Also, a spastic component in the coronary artery could play a role in the instability of some cases (30,37,38).

5. Thrombosis is a dynamic process in which a delicate interplay between thrombosis and thrombolysis, migration with or without disintegration of thrombus and platelet aggregation and inhibition play a role. In addition, local intimal dissections, gradual intimal growth and spasm further complicate the local process.

6. Recent data suggest that only half of the lesions assessed have concordant morphologic, angiographic and ultrasound findings (44). Angioscopic results indicate that angiography might also be misleading in the diagnosis of an intimal flap or thrombus (45,46). Thus, these new techniques show that angiography has severe limitations and probably should no longer be used as the reference standard.

Study limitations. The complex pathophysiology of unstable angina seems to be responsible for the disappointing results of thrombolytic therapy. Some limitations of the study were discussed earlier. Most important, angiographic proof of thrombus is still difficult. In addition, this was a retrospective analysis, and the UNASEM protocol was not specifically designed to address the items 1 to 6. Finally, although larger than in most of the other studies, the number of patients included in this trial was limited, making it impossible to analyze all aspects with sufficiently large numbers of patients.

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