Intracoronary Urokinase for Intracoronary Thrombus Accumulation Complicating Percutaneous Transluminal Coronary Angioplasty in Acute Ischemic Syndromes*

Gregory Schieman, MD, Barry M. Cohen, MD, Joseph Kozina, MD, Joel S. Erickson, MD, Richard A. Podolin, MD, Kirk L. Peterson, MD, John Ross Jr., MD, and Maurice Buchbinder, MD

Intracoronary urokinase was used to treat flow-limiting intracoronary thrombus accumulation that complicated successful percutaneous transluminal coronary angioplasty (PTCA) during acute ischemic syndromes in 48 patients who were followed up through the acute phase of their illness. The study group comprised 10 patients with unstable angina pectoris, 18 patients with an evolving acute myocardial infarction, and 20 patients with postinfarction angina. The initial mean percent coronary diameter stenosis for the entire population was 95±7% and decreased with initial PTCA to 41±20% (p<0.001), with improved corresponding coronary flow by Thrombolysis in Myocardial Infarction trial (TIMI) grade. However, thrombus accumulation then resulted in a significant increase in percent diameter stenosis to 83±17% (p<0.001); a corresponding significant reduction in coronary flow also occurred by TIMI grade. After administration of intracoronary urokinase (mean dose, 141,000 units; range, 100,000–250,000 units during an average period of 34 minutes), with additional PTCA, mean percent diameter stenosis significantly decreased to 34±17% (p<0.001); a correspondingly significant improvement in mean coronary flow by TIMI grade occurred to 2.9±0.2. Overall, the angiographic success rate was 90%. There were no ischemic events requiring repeat PTCA and no procedure-related myocardial infarctions or deaths before hospital discharge. One patient was referred for urgent coronary artery bypass graft surgery after a successful PTCA. Plasma fibrinogen levels were obtained in 15 patients, and in no patient was the level below normal for our laboratory. Angiographic follow-up was obtained in 79% of patients (average time 30 days with 63% of all patients studied before discharge), and in no patient was there angiographic evidence of reocclusion, although two patients showed angiographic evidence of stenosis; improved vessel percent stenosis persisted, averaging 32±17%. In all patients studied, the coronary flow was TIMI grade 3 at follow-up. Thus, in patients with acute ischemic syndromes with flow-limiting intracoronary thrombus accumulation that complicated PTCA, intracoronary urokinase with repeated PTCA proved to be highly effective in restoring vessel patency and avoiding early complications. (Circulation 1990;82:2052–2060)

The acute ischemic syndromes of unstable angina pectoris, acute myocardial infarction, and postinfarction angina often share a common pathogenesis, with atherosclerotic plaque rupture leading to platelet aggregation, activation of the coagulation cascade, and formation of thrombus.1–6 Whether or not the thrombus becomes occlusive, the duration of the occlusion and the extent of collateral development determine whether or not myocardial infarction develops and to what extent. Interventions aimed at interrupting this sequence and salvaging myocardium include thrombolytic therapy, percutaneous transluminal coronary angioplasty (PTCA), and coronary artery bypass graft surgery (CABG).

Because the incidence of early acute myocardial infarction and sudden cardiac death is relatively high in patients with unstable angina pectoris,7–9 PTCA is
sometimes used in this setting for patients who have failed to stabilize on medical therapy. The primary success rate is similar to that after PTCA in patients with stable angina, but the major complication rate is higher in unstable patients, often because of the development of abrupt thrombotic occlusion resulting in acute myocardial infarction or emergency CABG. 10-12

Direct PTCA has been used to treat acute myocardial infarction and has had high initial success rates, but the incidence of abrupt thrombotic occlusion during the procedure, or shortly afterward, is higher than that for elective PTCA. 13,14 When PTCA has been used acutely to reduce the residual stenosis in patients who initially received systemic thrombolytic therapy, the complication rates of performing emergency CABG and of death also have been increased, and the incidence of reocclusion in successfully dilated arteries has been 11-12.5%. 15-17

Patients with early postinfarction ischemia are known to be at high risk for infarction and death, 18,19 and PTCA has been used in this setting with high early success rates. However, an increased incidence of major procedure-related complications including thrombotic coronary occlusion has been reported. 20-22

These findings indicate that when PTCA is performed in patients with unstable angina pectoris, early after acute myocardial infarction or during postinfarction ischemia, high complication rates may result from balloon-induced trauma to a highly thrombogenic site, leading to intractable occlusive thrombus. Because of these problems with the use of PTCA in acute ischemic syndromes, this study was designed to investigate the efficacy of intracoronary thrombolysis with urokinase in conjunction with repeated PTCA for the treatment of flow-limiting thrombus accumulation that complicates PTCA in these settings. Urokinase was selected because it has produced coronary reperfusion rates equivalent to those produced by streptokinase in patients with acute myocardial infarction when delivered by the intracoronary route and has resulted in significantly fewer bleeding complications and less systemic fibrinolysis. 23 Moreover, it has a longer half-life than recombinant tissue-type plasminogen activator, and some patients had already received that agent.

Methods

Study Patients

Between July 1986 and October 1988, PTCA was attempted in 248 consecutive patients with acute ischemic syndromes (Table 1). For the purposes of this study, acute ischemic syndromes included unstable angina pectoris, recurrent chest pain during the evolving phase of an acute myocardial infarction, and postinfarction angina. Of these 248 patients, 48 developed flow-limiting thrombus accumulation according to angiographic criteria (see below), and these 48 made up the study group.

Unstable angina pectoris was defined as the occurrence of ischemic pain at rest that lasted for at least 20 minutes and was associated with ST and T wave changes, without evidence of myocardial necrosis identified either by elevation of the total serum creatine kinase to twice the normal value with greater than 5% MB isoenzyme fraction or by the development of new pathological Q waves on the electrocardiogram. Angina pectoris during evolving acute myocardial infarction was defined as recurrent or persistent symptoms of chest pain occurring within 72 hours of Q wave myocardial infarction, and this definition applied to patients who had previously received systemic thrombolytic therapy. Postinfarction angina was defined as the occurrence of angina pectoris at rest with associated ST and T wave

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<th>TABLE 1. Patient Characteristics</th>
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<td>Total (n)</td>
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<td>With thrombus accumulation (n)</td>
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<td>Prior CABG/PTCA (%)</td>
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MI, myocardial infarction; CABG, coronary artery bypass graft surgery; PTCA, percutaneous transluminal coronary angioplasty.
changes occurring more than 72 hours after documented acute myocardial infarction but without evidence for additional myocardial necrosis (defined as a second peak in creatinine kinase levels during a documented decline, a lag or prolongation of the return of the creatinine kinase to baseline or as the development of new pathological Q waves).

Management Before PTCA

All patients were intensively treated initially with various combinations of β-blockers, calcium channel blockers, nitrates, aspirin, intravenous heparin, and systemic thrombolytic agents. Patients who failed to stabilize on an intensive medical regimen were referred for coronary angiography. Patients were selected for PTCA if the ischemia-related artery was suitable for dilation. The stenotic artery was considered to be ischemia related in patients with single-vessel disease; in patients with multivessel disease, the ischemia-related artery was defined by correlation with documented ST and T wave changes on the electrocardiogram at rest.

PTCA Procedure

All PTCA procedures were performed by one of three principal operators (M.B., K.L.P., or R.A.P.), predominantly using the femoral approach. The procedure was performed with preformed guiding catheters, steerable dilating balloon catheters (usually coaxial in design), and a pneumatic inflation device.

Ten thousand units of heparin were administered intravenously after arterial cannulation followed by an additional 1,000–1,500 units/hr in divided doses. This dosage was chosen empirically because activated clotting time measurements were not performed in the catheterization laboratory at the time the study was conducted. Preliminary angiography of the coronary artery was performed in at least two orthogonal projections. The balloon was positioned across the stenosis, and sequential dilations were then performed with balloons of increasing size, and a final balloon size was chosen that had an inflated diameter approximately equal to the apparently disease-free proximal lumen of the ischemia-related artery. As many inflations as necessary were performed to produce acceptable angiographic results. Only the ischemia-related artery was dilated. All treated lesions were observed by serial angiography in at least two projections for a minimum period of 10 minutes after the last dilation. Successful angioplasty was defined as a reduction in the initial percent diameter stenosis by at least 30%, with a final residual diameter narrowing of 50% or less at the time of the patient’s departure from the catheterization laboratory. Cardiotoracic surgery and anesthesiology teams were available during each dilation procedure.

Entry Criteria

The entry criteria for the study included an initially successful PTCA of the ischemia-related artery, followed by angiographic documentation of flow-limiting intracoronary thrombus accumulation. Flow-limiting intracoronary thrombus accumulation was defined as angiographic evidence of at least a twofold increase in the minimal percent diameter stenosis obtained after PTCA, obliteration of the coronary artery lumen at the site of a previously successful angioplasty, or progressive reduction of antegrade coronary flow to grade 0–1 as classified in the Thrombolysis in Myocardial Infarction (TIMI) study.24 Patients with evidence of coronary artery spasm or occlusive subintimal dissection were excluded (see definitions below).

Treatment of Intracoronary Thrombus Accumulation

Patients who met the inclusion criteria received a mean dose of 141,000 (range, 100,000–250,000) units of intracoronary urokinase (Abbokinase; Abbott Pharmaceuticals, North Chicago, Ill.) through the guiding catheter during a mean period of 34 minutes. Redilation was performed intermittently during the urokinase infusion in all patients as deemed necessary by the operator to maintain coronary flow at TIMI grade 2–3. Coronary angiograms of the involved vessel were repeated at 3–5-minute intervals to assess patency. Intracoronary nitroglycerin was administered in all patients to reduce the possibility of coronary spasm. A minimum of 20 minutes of angiographic observation in at least two projections was performed on each patient meeting the above inclusion criteria to ensure continued vessel patency before the patient’s departure from the catheterization laboratory.

Postprocedure Therapies

After successful recanalization, the femoral sheaths were secured in place for overnight monitoring in the coronary care unit. Full anticoagulation with heparin to achieve a partial thromboplastin time 2.5–3 times control was continued for 5 days after the procedure unless a contraindication was present. All patients received 80 mg aspirin twice daily during the heparin infusion, and 325 mg aspirin twice daily after discontinuation of heparin. Intravenous nitroglycerin was continued for 24 hours after the procedure and was discontinued after removal of the femoral sheaths. All patients were asked to submit to follow-up limited coronary angiography before hospital discharge, and patient refusal was the only reason for lack of follow-up angiography. Patients studied after discharge underwent follow-up angiography.

Complications

A procedure-related myocardial infarction was diagnosed either by elevation of the total serum creatine kinase to twice the normal value with greater than 5% MB isoenzyme fraction or by the development of new pathological Q waves on the electrocardiogram. Infarct extension was diagnosed when a second peak in the creatine kinase level occurred during a documented decline or when new pathological Q waves developed on the electrocar-
diagram. Ischemic events in the hospital requiring angiography and the number of patients requiring transfusion were tabulated.

**Definitions and Data Analysis**

The coronary angiograms of all patients who developed acute progressive vessel reclosure after a seemingly successful PTCA were reviewed in a blinded fashion by two observers who independently evaluated the stenosis site, its degree, and its morphology. Conclusions were reached by consensus. Assessments were made before and after the initial dilation, during reclosure, and after successful recalization with urokinase. The evaluation was confined solely to the lesion that developed progressive reclosure after PTCA and did not include lesions at other sites in the same or other vessels. When more than one lesion was present in an ischemia-related vessel, only the lesion that developed flow-limiting thrombus accumulation was assessed.

An intimal tear or dissection was considered to be present after PTCA when there was a curvilinear or linear intraluminal filling defect or vessel widening with extraluminal contrast staining at the site of dilation. Coronary artery spasm was defined as a transient decrease in vessel diameter that could be reversed by administration of intravenous, sublingual, or intracoronary nitroglycerin. The presence of intracoronary thrombus was defined as a clearly localized filling defect surrounded by contrast medium at the site of a high-grade stenosis or as luminal staining at the site of a high-grade stenosis or occlusion. Complete occlusion was defined as 100% coronary stenosis according to angiography with TIMI grade 0 or 1 flow. A peri-interventional myocardial infarction was diagnosed when new pathological Q waves developed or when an abnormal cardiac enzyme elevation was documented (see above definitions).

**Statistical Analyses**

Repeated measures analysis of variance was used to assess the significance of sequential changes in percent diameter stenosis and TIMI grade over time. After obtaining an overall significant time effect, multiple comparisons were made by Tukey's test. Follow-up data were not included in the analysis of variance because they were incomplete. Standard deviations or ranges are presented for the mean values in the tables and figures.

**Results**

Of the 248 patients undergoing PTCA for acute ischemic syndromes during the period of study, 126 (51%) had unstable angina, 35 (14%) were being treated for evolving myocardial infarction, and 86 (35%) had recurrent angina more than 72 hours after acute myocardial infarction (Table 1).

Forty-eight of the 248 patients (19%) with ischemic syndromes underwent an initially successful PTCA but developed flow-limiting intracoronary thrombus accumulation in the dilated vessel and are the subject of this report. Of the 48 patients, 10 (21%) were in the unstable angina group, 18 (37%) were being treated for evolving myocardial infarction, and 20 (43%) were in the postinfarction angina group (Table 1). There was a significantly higher incidence of flow-limiting thrombus accumulation in the evolving myocardial infarction group than in either the unstable angina or postinfarction angina groups ($p<0.001$ and $p<0.005$, respectively, by $\chi^2$ analysis). In the total group, 13 (27%) had complete coronary occlusion.

In the entire group, the mean age of the patients was 53 years (range, 38–76 years) (Table 1). Seventy-seven percent of the patients were men, 13% had a history of previous myocardial infarction, and 44% were smokers at the time of hospital admission. Among the patients in the evolving myocardial infarction group, 78% had received prior fibrinolytic therapy with either recombinant tissue-type plasminogen activator or streptokinase (Table 1). Table 1 also shows these data for the treated patients with each of the three types of ischemic syndromes.

**Baseline Angiographic Data**

The baseline angiographic characteristics for all study patients showed a preponderance of right coronary artery (42%) and left anterior descending artery lesions (48%). Eight percent had a circumflex artery graft lesion, and one patient had dilation of a saphenous vein graft to the distal right coronary artery. The average percent stenosis before intervention was $95\pm7\%$ (SD), and coronary flow by average TIMI grade was $2.0\pm1.1$. Sixty-three percent of the patients had angiographic evidence of intracoronary thrombus at baseline.

**Angiographic Data During and After Initial Intervention**

The interventional angiographic data on percent stenosis in the entire group are summarized in Figure 1. The percent coronary stenosis after initial PTCA was $41\pm20\%$ and was significantly reduced compared with baseline. Coronary flow by TIMI grade was also significantly improved from $2.0\pm1.1$ to $2.8\pm0.6$ ($p<0.01$).

After PTCA and before the administration of urokinase, there was a significant increment in the severity of the percent diameter stenosis due to thrombus accumulation, and the average percent diameter stenosis of the ischemia-related artery increased to $83\pm17\%$ (Figure 1). The corresponding TIMI grade for coronary flow decreased to $2.1\pm1.1$ ($p<0.01$).

**Angiographic Data After Urokinase Administration and Repeated PTCA**

The mean urokinase dose was 141,000 units (range, 100,000–250,000 units), and the mean infusion period was 34 minutes (range, 20–65 minutes). The final angiographic results obtained after the
administration of urokinase with repeated PTCA before departure from the catheterization laboratory showed significant improvement in the percent diameter stenosis, from 83±17% to 34±17%, with an angiographic success rate of 90% for the entire group (Figure 1). On departure from the catheterization laboratory, the TIMI grade was 2.9±0.2 for coronary flow, and 94% of patients had TIMI grade 3 flow.

Angiographic Data From Follow-up Studies

Follow-up angiograms were obtained in 79% of the total group, with 63% of the patients being studied before hospital discharge. The mean time to angiographic follow-up was 30 days (range, 4 days to 13 months). Reocclusion did not occur, although one patient who was not studied before hospital discharge had an 80% stenosis when studied at 4 months, and another patient exhibited an 80% stenosis 10 days after treatment with persistent angiographic evidence of intraluminal thrombus. This latter patient was discharged on a Coumadin regimen and had a negative thallium treadmill test 3 weeks after hospital discharge. The mean percent diameter stenosis was 32±17% for all patients with follow-up studies and was similar to that obtained before departure from the cardiac catheterization labora-
In all of these patients, the coronary flow was TIMI grade 3.0 at follow-up.

Sequential angiograms of the left anterior descending coronary artery in the right anterior oblique projection from a representative patient are depicted in Figure 2. The angiographic result after initial PTCA was excellent (Figure 2B), but intracoronary thrombus accumulation resulted in worsened stenosis and diminished antegrade flow (Figure 2C). After the urokinase infusion and repeated PTCA, there were luminal filling defects and haze indicative of residual thrombus, but the stenosis severity was decreased and coronary flow was TIMI grade 3 (Figure 2D). These abnormalities do not appear on the follow-up angiogram (Figure 2E).

Complications

Only one patient was referred for urgent CABG. This patient had an evolving acute myocardial infarction, and after successful restoration of flow in the infarct-related artery (RCA), symptoms recurred because of a high-grade proximal stenosis in the left anterior descending coronary artery.

In the entire group, there was no in-hospital mortality and no procedure-related myocardial infarction or extension occurred. Also, no recurrent ischemic events requiring repeated angiography or PTCA occurred before hospital discharge in any patient. The incidence of transfusion was 10%; one of these patients bled after CABG surgery.

Plasma fibrinogen levels were determined in 15 patients, and in no patient was the measured level below the normal range for our laboratory (200–400 mg/dl).

Discussion

PTCA has been used with high initial success rates in the treatment of unstable angina pectoris, evolving acute myocardial infarction, and postinfarction angina, but the rates of coronary reocclusion, emergency CABG, and death have been increased compared with elective PTCA.
In patients with unstable angina, a major complication rate (myocardial infarction, CABG, or death) of 10.5% was reported by de Feyter et al\textsuperscript{25} in a series of 200 consecutive patients treated with PTCA. These data are representative of a large experience in patients with unstable angina approached with steerable angioplasty systems.\textsuperscript{26–28} Angiographic evidence of intracoronary thrombus in patients with unstable angina ranges from 1% to 53%, depending on the criteria used for defining the presence of thrombus and the time elapsed between the onset of symptoms and angiography.\textsuperscript{29–34} In a preliminary report, Suryapranata et al\textsuperscript{29} used intracoronary streptokinase to treat acute thrombotic closure that complicated PTCA for unstable angina in 200 consecutive patients; the initial success rate was 94%, but 21 patients developed acute vessel closure. Intracoronary streptokinase was administered in 12 of these patients, and repeated PTCA was successful in restoring vessel patency in nine patients. In that study, the patients were not restudied before discharge. In the experience reported here with intracoronary urokinase in 10 patients with unstable angina, we also found a high incidence of angiographic evidence for intracoronary thrombus in patients who developed flow-limiting thrombus accumulation. Angiographic success was obtained in nine of 10 patients, and all patients had normal antegrade flow restored. Of importance, our initial success was maintained throughout the hospitalization with no mortality or episodes of recurrent ischemia requiring repeated PTCA, and 100% patency was present in those patients who underwent angiography before discharge or as late as 13 months after discharge.

The experience with PTCA for the treatment of acute myocardial infarction has been less encouraging. When direct angioplasty without prior systemic thrombolytic therapy has been used, angiographic success rates in selected patients have been high, but reocclusion rates were 9–15%.\textsuperscript{35–41} When the strategy of PTCA after thrombolytic therapy has been compared with thrombolysis alone, acute complication rates have been higher in the PTCA groups, and infarct-related artery reocclusion rates were high and not significantly different.\textsuperscript{15–17} Our experience in the small number of such patients in the present pilot study who were treated with PTCA during acute myocardial infarction shows a significantly higher incidence of intracoronary thrombus reaccumulation but suggests that adjunctive intracoronary urokinase, with repeated PTCA if needed, can successfully treat acute thrombotic closure in this setting, thereby avoiding the need for emergency CABG. Of the 35 patients treated with PTCA for evolving myocardial infarction in the present study, the majority of whom had received prior thrombolytic therapy, 18 were treated with intracoronary urokinase for progressive thrombus accumulation. Only one patient in this group was referred for urgent CABG after successful PTCA of the right coronary artery, but this was because of a high-grade lesion in the proximal left anterior descending coronary artery. As with our experience in the unstable angina group, there were no recurrent ischemic episodes, and the angiographic infarct-related artery patency was 100% at follow-up angiography in those patients studied. The very high infarct-related artery patency rate suggests a role for adjunctive intracoronary urokinase when PTCA is complicated by flow-limiting thrombus accumulation during acute myocardial infarction.

There have been a number of reports on the treatment of early postinfarction angina with PTCA in which initial recanalization rates were high (81–91%), but the rates of major procedure-related complications of myocardial infarction (1.5–8%) and emergency CABG (1.5–12%) were increased compared with elective PTCA.\textsuperscript{20,21,42–45} To our knowledge, the efficacy of adjunctive intracoronary urokinase in patients with postinfarction angina who developed thrombotic reclosure after a successful PTCA has not been reported. In the present series, the primary success rate with PTCA was high; intracoronary urokinase with repeated PTCA was successful in restoring normal antegrade flow in all patients; no recurrent ischemic events requiring repeated PTCA occurred before hospital discharge, and there was no evidence for restenosis in the 65% of patients undergoing predischarge angiography.

The results obtained by using adjunctive intracoronary urokinase with repeated PTCA for flow-limiting thrombus accumulation in the present study were consistent: high angiographic success rates that were maintained throughout the acute phase of their illness without reocclusion. Thus, in addition to the immediate benefit of restoration of coronary flow, the use of adjunctive intracoronary urokinase may result in maintained vessel patency in patients undergoing PTCA for acute ischemic syndromes. The benefit of establishing and maintaining vessel patency has been demonstrated in three separate trials in which a significant correlation between survival 1 year after acute myocardial infarction and patency of the infarct-related artery was reported.\textsuperscript{46–48} Less late left ventricular dilation after infarction has been described in patients with patent infarct-related arteries before discharge,\textsuperscript{49} and it has been proposed that maintenance of successful reperfusion, even when it occurs late, may lead to more favorable left ventricular remodeling.\textsuperscript{50} Long-term follow-up of the patients in the present study, and in additional patients subsequently treated with intracoronary urokinase, is currently underway to determine whether the favorable initial results on vessel patency are maintained.

Limitations of the Study

This pilot study is limited by the lack of randomized design and the relatively small number of patients in each group. Nonetheless, this represents the largest experience reported on the efficacy of intracoronary urokinase in the treatment of acute ischemic syndromes. Although the angiographic follow-up is incomplete, 79% of patients underwent...
follow-up coronary angiography, and the lack of recurrent ischemic events in the other patients suggests that a high patency rate was maintained throughout the hospitalization. Quantitative angiography was not used, but the changes in percent diameter stenosis were large and corresponded to observed changes in TIMI grades of coronary flow.

Fibrinogen levels were measured in too few patients to state definitively that a systemic lytic state was avoided with this approach. We have continued to measure fibrinogen levels in all subsequent patients treated with intracoronary urokinase for thrombotic closure complicating PTCA in acute ischemic syndromes (40 patients), and in none has the fibrinogen level been abnormal. We believe this to be an important advantage of this approach, and our findings are consistent with the data from the only randomized trial comparing intracoronary urokinase with streptokinase in patients with acute myocardial infarction. In that study, reperfusion rates were equivalent for the two lytic agents, but fibrinogen levels less than 100 g/dl were significantly more frequent with streptokinase (66%) than with urokinase. Bleeding complications were also significantly increased in the streptokinase group.

Implications

The exact role of PTCA in the treatment of acute ischemic syndromes remains to be defined. In the randomized trials on patients with acute myocardial infarction treated with recombinant tissue-type plasminogen activator with or without immediate PTCA, it can only be speculated whether or not the concomitant use of intracoronary urokinase could have diminished the rate of major complications in the patient groups receiving immediate PTCA. Patients with postinfarction ischemia, whether or not they have received antecedent systemic thrombolytic therapy, often require emergency PTCA in the setting of an acute ischemic syndrome, and our data suggest that intracoronary urokinase may be helpful when thrombus accumulation limits flow. Primary PTCA has potential application in many patients in whom thrombolytic therapy is contraindicated, and its usefulness may be enhanced with development of an effective approach for treating flow-limiting intracoronary thrombus accumulation.

The conventional approach to patients with acute ischemic syndromes involves medical therapy with antianginal agents, systemic anticoagulants, and antiplatelet agents. If patients fail to stabilize early, coronary angiography is indicated, and if suitable coronary anatomy is present, PTCA may be attempted. If flow-limiting thrombus accumulation occurs in this setting, our data suggest that it can be successfully managed with intracoronary urokinase and repeated PTCA in most patients. However, the high success rates in this pilot study will need to be confirmed in randomized trials, and the late results of this approach will also require assessment in such trials and in ongoing follow-up studies.

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