Thrombolytic failure with streptokinase in acute myocardial infarction using electrocardiogram criteria

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ABSTRACT

Introduction: This study was primarily aimed to determine the failure rate of thrombolysis with streptokinase in acute myocardial infarction using electrocardiogram criteria and its association between various independent variables and outcome parameters.

Methods: A total of 192 subjects were recruited into this retrospective observational study. Thrombolysis failure with streptokinase was defined using electrocardiogram criteria of less than 50 percent reduction in ST elevation in the worst infarct lead. Multivariate analysis was used to test association with study outcome.

Results: A total of 109 patients (56.8 percent) failed thrombolysis using streptokinase. The failures were associated with five variables in multiple logistic regression analysis (backward stepwise method) including anterior location of myocardial infarct (odds-ratio [OR] 0.07, 95 percent confidence interval [CI] 0.03–0.16; p-value is less than 0.001), longer door-to-needle time (OR 1.01, 95 percent CI 1.00–1.02; p-value is 0.02), diabetes mellitus (OR 3.13, 95 percent CI 1.13–8.69; p-value is 0.03), hypertension (OR 2.06, 95 percent CI 0.92–4.60; p-value is 0.08) and high total white cell count (OR 1.12, 95 percent CI 1.01–1.24; p-value is 0.03). Thrombolysis failure with streptokinase was associated with recurrent acute coronary syndrome (crude OR 2.49, 95 percent CI 1.16–5.32; p-value is 0.02) and death after one year (crude OR 7.61, 95 percent CI 0.95–61.24; p-value is 0.04).

Conclusion: This study showed that streptokinase had a failure rate of 56.8 percent. History of diabetes mellitus, history of hypertension, anterior location of myocardial infarction, longer door-to-needle time and high total white cell count were highly predictive of thrombolysis failure using streptokinase. This group of patients may benefit from other early reperfusion strategy.

Keywords: electrocardiogram criteria, myocardial infarction, reperfusion failure, streptokinase, thrombolysis failure

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INTRODUCTION

Landmark studies, including GUSTO-1 and ISIS-2, have shown the convincing benefits of thrombolysis and provided the groundwork for current therapeutic practice. A review by fibrinolytic therapy trialists' (FTT) group has shown that thrombolysis prevents 20–30 deaths per 1,000 patients with 25% reduction in mortality.[1] However, 90 minutes arterial patency rate after streptokinase was only achieved in 50%–60%, and thrombolysis in myocardial infarct (TIMI) grade 3 flow from angiographical study was only achieved in 30% of the patients.[2] Coronary angiography was the gold standard to determine coronary artery patency after reperfusion therapy but it was expensive, invasive and not always available early. Therefore, bedside noninvasive markers were more attractive options. Among these, electrocardiogram (ECG) had good predictive value and sensitivity. It was also easily available and cheap. Sutton et al showed that less than 50% resolution of ST segment elevation in the worst infarct lead had a sensitivity of 81%, specificity of 88% and positive predictive value of 87% to predict less than TIMI-3 flow.[3] This study aims to determine the failure rate of thrombolysis with streptokinase in acute myocardial infarction (AMI) using ECG criteria and its association between various independent variables and outcome parameters.

METHODS

This retrospective cohort study involved patients who were admitted to the coronary care unit of Hospital Universiti Sains Malaysia with AMI (World Health Organisation criteria). Streptokinase infusion was given as per protocol at the standard dose of 1.5 MU over 60 min. Cohorts were selected from the computer registry of record department from the year 1996 to 2005. Data was extracted from the

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Table I. Summary of baseline characteristics.

Parameters	Thrombolysis with streptokinase	
	Failure, n (%)	Success, n (%)
Demographics		
Age* (years)	57.1 (11.2)	55.7 (56.5)
Race		
Malay	108 (59.0)	75 (41.0)
Chinese	1 (11.1)	8 (88.9)
Gender		
Male	93 (54.7)	77 (45.3)
Female	16 (72.7)	6 (27.3)
Presentation		
AMI location		
Anterior	87 (77.7)	25 (22.3)
Inferior	22 (27.5)	58 (72.5)
Symptom-to-needle time		
< 6 hours	54 (47.8)	59 (52.2)
6–12 hours	49 (70.0)	21 (30.0)
> 12 hours	6 (66.7)	3 (33.3)
Mean (SD) door-to-needle time (min)	114 (82.9)	93 (48.7)
Killip's Class		
Class I	57 (55.3)	46 (44.7)
Classes II–IV	52 (58.4)	37 (41.6)
Risk factors		
Smoking		
Current	66 (54.1)	56 (45.9)
Former	20 (58.8)	14 (41.2)
Prior diabetes mellitus	24 (64.9)	13 (35.1)
Prior hypertension	47 (66.2)	24 (33.8)
Vital Signs*		
Heart rate (bpm)	79.3 (18.3)	72.9 (17.1)
Systolic BP (mmHg)	136.7 (28.9)	127.3 (24.2)
Diastolic BP (mmHg)	83.8 (20.9)	75.9 (14.5)
Investigations*		
Total white cell count	12.8 (4.4)	12.3 (3.8)
Total cholesterol	6.2 (1.4)	6.2 (1.7)
Random blood sugar	9.7 (4.4)	9.1 (4.3)
Creatinine	123.4 (70.9)	115.5 (31.5)
Ejection fraction (%)	54.5 (13.5)	58.3 (12.5)
Stress test		
Positive test	12 (57.1)	9 (42.9)
Negative test	7 (36.8)	12 (63.2)
Medications		
Aspirin	106 (57.0)	80 (43.0)
Beta-blocker	65 (58.0)	47 (42.0)
ACE-inhibitor	86 (57.7)	63 (42.3)
Statin	88 (56.8)	67 (43.2)
Interventions		
PTCA	16 (61.5)	10 (38.5)
CABG	6 (60.0)	4 (40.0)
Outcome		
Recurrent ACS	30 (73.2)	11 (26.8)
Death after one year	10 (90.9)	1 (9.1)

* Data is expressed in mean (standard deviation)

patient records using a data extraction form. Exclusion criteria included bundle branch block AMI, non-ST elevation myocardial infarction (NSTEMI), patients who were not given streptokinase due to contraindications to the therapy, previous streptokinase use, streptokinase given in other hospitals, symptom-to-needle time of more than 24 hours and patients who had undergone primary angioplasty (PCI).

Streptokinase was administered according to the protocol. Two vials (750,000 IU per vial) of streptokinase were reconstituted with 5 ml of dextrose 5% and then added to 150 ml of dextrose 5%. This was infused through an intravenous line over 60 min using an infusion pump. Intravenous hydrocortisone 200 mg bolus was given

Table II. Univariate analysis model in predicting association between independent variables and outcome parameters with failure of thrombolysis using streptokinase in acute myocardial infarction.

Parameters	Failure	Success	Total n = 192	p- value	OR	95% CI
Categorical						
MI location, n (%)						
Anterior	87 (77.7)	25 (22.3)	112 (58.3)	< 0.001	0.11	0.06–0.21
Inferior	22 (27.5)	58 (72.5)	80 (41.7)			
Symptom-to-needle time, n (%)						
< 6 hours	54 (47.8)	59 (52.2)	113 (58.9)	0.01	2.07	1.22–3.52
6–12 hours	49 (70.0)	21 (30.0)	70 (36.5)			
> 12 hours	6 (66.7)	3 (33.3)	9 (4.7)			
Killip's class						
Class I	57 (55.3)	46 (44.7)	103 (53.6)	0.67	1.13	0.64–2.01
Classes II–IV	52 (58.4)	37 (41.6)	89 (46.4)			
Smoker, n (%)						
No	23 (63.9)	13 (36.1)	36 (18.8)	0.56	0.90	0.56–1.44
Current	66 (54.1)	56 (45.9)	122 (63.5)			
Former	20 (58.8)	14 (41.2)	34 (17.7)			
Diabetes mellitus, n (%)						
Yes	24 (64.9)	13 (35.1)	37 (19.3)	0.27	1.52	0.72–3.20
No	85 (54.8)	70 (45.2)	155 (80.7)			
Hypertension, n (%)						
Yes	47 (66.2)	24 (33.8)	71 (37.0)	0.04	1.86	1.02–3.42
No	62 (51.2)	59 (48.8)	121 (63.0)			
Numerical						
Age (years)						
Frequency	107	85	192	0.37	1.01	0.98–1.04
Mean	57.1	55.7	56.5			
SD	11.2	10.8	11.0			
Door-to-needle time (min)						
Frequency	109	83	192	0.03	1.01	1.00–1.01
Mean	114.0	93.0	104.9			
SD	82.9	48.7	70.8			
Total white cell ($10^3/mm^3$)						
Frequency	101	83	184	0.44	1.04	0.97–1.12
Mean	12.8	12.3	12.6			
SD	4.4	3.8	4.1			
Post-MI stratification stress test, n(%)						
No	16 (69.6)	7 (30.4)	23 (12)	0.21		
Positive test	12 (57.1)	9 (42.9)	21 (10.9)			
Negative test	7 (36.8)	12 (63.2)	19 (23.8)			
Equivocal	9 (52.9)	8 (47.1)	17 (21.3)			
Ejection fraction (%)						
Frequency	58	44	102	0.15		
Mean ± SD	54.5 ±13.5	58.3 ±12.5	56.2 ±13.1			
Interventions, n (%)						
PTCA	16 (61.5)	10 (38.5)	26 (49.1)	0.97		
CABG	6 (60.0)	4 (40.0)	10 (18.9)			
No/medical treatment	11 (64.7)	6 (35.3)	17 (32.1)			
Vessels, n (%)						
LAD/LCx	16 (72.7)	6 (27.3)	22 (11.5)	0.07		
RCA	4 (33.3)	8 (66.7)	12 (6.3)			
3VD/LMS	10 (66.7)	5 (33.3)	15 (7.8)			
Outcome						
Recurrent ACS, n (%)						
Yes	30 (73.2)	11 (26.8)	41 (21.4)	0.02		
No	79 (52.3)	72 (47.7)	151 (78.6)			
Survival after one year, n (%)						
Death	10 (90.9)	1 (9.1)	11 (5.7)			
Alive	71 (56.8)	54 (43.2)	125 (65.1)	0.04		
Censored	28 (50)	28 (50)	56 (29.2)			

prior to the administration of streptokinase. Infusion was stopped if there was a drop of blood pressure below systolic blood pressure of 90mmHg or if asthmatic attacks developed.

The first ECG was recorded prior to starting streptokinase, and the second ECG was then recorded after completion of streptokinase infusion. This was usually after 90 min, but a time window of 2–4 hours were

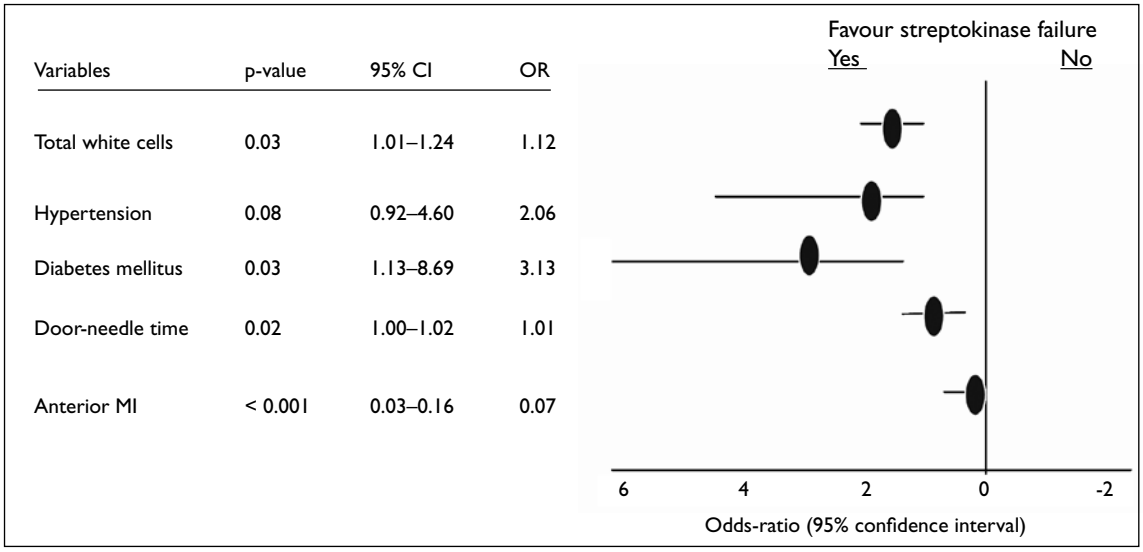

Fig. 1 Standard error chart shows odds-ratio, and confidence interval of independent variables in multiple logistic regression (backward stepwise: likelihood ratio) in predicting association with failure of thrombolysis using streptokinase in acute myocardial infarction.

allowed. Vertical height of ST segment elevation in the lead with the maximum ST segment elevation (worst infarct lead), before and after streptokinase, was measured using a standard ruler in mm. The ST segment was measured 80 ms from J point, which corresponded to the peak of ST elevation. J point was defined as the first turning point in the ST segment on ECG. Failure of thrombolysis with streptokinase was defined as less than 50% reduction in ST segment elevation after 90 min (time window 2–4 hours) in the worst infarct lead with no idioventricular rhythm.

Data analysis was conducted using the Statistical Package for Social Sciences version 12.0.1 (SPSS Inc, Chicago, IL, USA). Numerical data was recorded as mean and standard deviation, and categorical data as frequency and percentages. The numerical and categorical variables used in this study were chosen based on previous clinical studies.[4] A p-value of less than 0.05 was considered significant association with thrombolysis failure using streptokinase. Univariate analysis using chi-square test for categorical data and Student's *t*-test for numerical data were used to compare the association of variables. The results of univariate analysis were recorded as p-value, crude odds-ratio (OR) and 95% confidence interval (CI). Multiple logistic regression analysis was employed to assess the association of multiple variables after adjustment of confounding variables. Results of the multiple logistic regression analysis were recorded as p-value, adjusted odds-ratio (AOR) and 95% CI.

RESULTS

A total of 192 patients with AMI and received streptokinase infusion were recruited between 1996 and 2005. There were a total of 109 patients (56.8%) who had failed thrombolysis with streptokinase compared to 83 patients (43.2%) who had a successful thrombolysis (Table I). A total of 12 independent variables were included in the univariate analysis (Table II) and five variables in the multiple logistic regression analysis (Fig. 1). This study was conducted in the Kelantan state, which is a predominantly Malay society. There were 183 (95.3%) Malay patients and only 9 (4.7%) Chinese patients. The study consisted of 170 males (88.5%) and 22 females (11.5%). The mean age was 56.5 (SD 11.0) years.

There were more patients with anterior location of infarct (87; 77.7%) and who had a significant association with failure of thrombolysis using streptokinase (AOR 0.07, 95% CI 0.03–0.16; $p < 0.001$). The mean door-to-needle time was 104.9 minutes. A longer door-to-needle time was significantly associated with failure of thrombolysis using streptokinase (AOR 1.01, 95% CI 1.00–1.02; $p = 0.02$). Patients with a history of diabetes mellitus (24; 64.9%) and AMI had thrice the risk for thrombolysis failure using streptokinase, and this association was significant (AOR 3.13, 95% CI 1.13–8.69; $p = 0.03$). A total of 71 (37%) of the AMI patients who received streptokinase had prior history of hypertension. The past history of hypertension had twice the risk of failure of thrombolysis with streptokinase (47; 66.2%) and a trend towards significance on multiple logistic regression analysis ($p = 0.08$). The mean total white cell count was 12,600 cells/mm^3. Thrombolysis failure with streptokinase was significantly associated with a higher mean white cell count (mean difference 0.47, standard error of the mean 0.62; AOR 1.12, 95% CI 1.01–1.24; $p = 0.03$).

There were more patients with Killip's Classes II to

IV (52; 58.4%) in the group which had failed thrombolysis with streptokinase, but this association was not significant (p = 0.67). There were more current smokers (122; 63.5%), but no association was noted between the current smoking status and failure of thrombolysis with streptokinase (p = 0.56). A longer symptom-to-needle time predicted failure of thrombolysis with streptokinase with a crude OR 2.07 (p = 0.01).

Most of the patients had undergone a treadmill stress test (80; 41.7%) and echocardiogram (102; 53.1%) after AMI. The mean ejection fraction was 56.2%. A total of 53 (27.6%) patients had undergone an angiographic study. 26 (49.1%) patients who had the angiogram had angioplasty, and ten (18.9%) of the patients had their bypass surgery. Left descending artery, left circumflex artery, left main stem and three vessels disease were more often involved when patients had failed thrombolysis with streptokinase, but the association was not significant (p = 0.07).

More patients (30; 73.2%) had recurrent admissions for acute coronary syndrome in the group which had failed thrombolysis with streptokinase (crude OR 2.49, 95% CI 1.16–5.32; p = 0.02). There were a total of 11 deaths after one year. Cardiovascular death accounted for ten patients (90.9%) and all of the patients were from the failure of thrombolysis with streptokinase group (crude OR 7.61, 95% CI 0.95–61.24; p = 0.04). The only patient from the non-cardiovascular group had died of lung malignancy.

DISCUSSION

The failure rate for thrombolysis with streptokinase was 56.8% (105 cohorts) in AMI, when using the ECG criteria. The results were in concordance with the multicentre GUSTO-I trial which compared different thrombolytic strategies, where streptokinase was shown to have 54% arterial patency rate after 90 min.[2] Patients with anterior location of infarct had a worse clinical outcome, compared to inferior infarct. This was related to a larger final infarct size and a lower subsequent left ventricular ejection fraction.[5] Large clinical trials, including GUSTO-I, showed that streptokinase in patients with anterior infarct was associated with lower mortality and morbidity.[2] However, subsequent studies including INJECT also showed that patients with anterior infarct achieved less reperfusion success compared to inferior infarct when given thrombolytic agent.[6] Our study has shown that anterior infarct was associated with higher thrombolysis failure with streptokinase, which was compatible with other studies.

The mean door-to-needle time of 104.9 min in our study had already exceeded the recommended time of 30 min, as suggested by the AHA/ACC 2004 task force.[7] Myocardium loss was the greatest within the first one hour from onset of symptoms, and the optimal time of thrombolysis was recommended at 70 min. In this study, 36.5% of cohorts presented to the emergency department after six hours of symptoms. Of these, 70% had failed thrombolysis with streptokinase. This would mean that for every one minute increase in door-to-needle time, there would be an increase in risk of failure of thrombolysis with streptokinase by an additional 10%. This study was not intended to look into the causes of longer door-to-needle time, but a search through the records had identified possible reasons which included inappropriate initial triage, delay in transport, missed initial diagnosis and delay in starting treatment.

Being a "myocardial infarction equivalent", history of diabetes mellitus had strongly predicted subsequent episode of cardiac event as well as mortality. As shown by Mak et al, diabetic cohorts in a GUSTO-I trial (n = 5,944) had a higher mortality rate at 30 days with OR 1.77 and this risk was maintained after one year.[8] Although only 19.3% of the study cohorts were diabetic patients, 64.9% of the diabetic patients did not achieve successful thrombolysis using streptokinase with thrice the risk of failure. The reasons for the higher risk of failure were the diffuse and multiple small vessel diseases in diabetic patients, which did not respond well to streptokinase. Diabetic patients usually present to the hospital later, due to their impaired sensation in myocardial ischaemic pain. In addition, diabetic patients had a lower ejection fraction and were more common among females.

Hypertension is a known risk factor for higher mortality in patients who had AMI, and it is additive to other known risk factors, as shown in the Framingham study.[9] Large international trials had showed that hypertension remained as an important predictor of mortality in the thrombolysis era, including GUSTO-I[2] and GISSI-2.[10] A total of 37% cohorts were hypertensive in this study. Most of the hypertensive cohorts (66.2%) did not achieve thrombolysis with streptokinase and the risk was twofold. Possible reasons for the higher failure rate were poorly-controlled hypertension, high-risk nature of hypertension, and possible accelerated atherosclerosis associated with endothelial dysfunction. Further studies are required to determine the prognostic value of hypertension.

The failed thrombolysis with streptokinase group had a higher mean total white cell count of 12,800 cells/mm^3 and the association was significant (p = 0.03). The TIMI 10A and 10B studies showed that a higher initial total white cell count was associated with a higher mortality, more resistance to thrombolysis, heart failure and shock.[11] After successful epicardial reperfusion, neutrophils can worsen microvascular reperfusion by adhering to the endothelium with platelets. Neutrophils can also release cytokines and other factors which reduce microvascular flow. A total of

53 (27.6%) of the patients had a coronary angiogram. This figure is low because this centre was only established in 2002. Among the patients who had undergone angioplasty, the left anterior descending artery (LAD) and left circumflex artery (LCx) were more often involved in those who had failed thrombolysis with streptokinase. The LAD and LCx arteries involvement corresponded to the anterior location of infarct. In a substudy of the GUSTO-I trial which looked into the clinical predictors of early infarct-related artery patency following thrombolysis, involvement of LAD was predictive of thrombolysis failure ($p < 0.001$).[4]

Many patients (30; 73.2%) in the failed thrombolysis with streptokinase group experienced recurrent episodes of acute coronary syndrome requiring multiple hospital admissions ($p = 0.02$). Recurrent ischaemia is a frequent occurrence as shown in the GUSTO-I trial, where close to a third of the patients had recurrent ischaemic episodes.[2] They had more post-infarct complications but eventual mortality was not different. Predictors of recurrent ischaemia include previous history of angina, short symptom-to-needle time, female gender and nonsmoker.[12]

Total mortality (cardiovascular and non-cardiovascular deaths) was low, with 11 (5.7%) patients, but 10 (90.9%) of the patients died after failure of thrombolysis with streptokinase (crude OR 7.61, 95% CI 0.94–61.24; $p = 0.04$). Large trials had shown improvement in mortality with thrombolysis using streptokinase. For example, in ISIS-2 involving 17,817 patients, both streptokinase and aspirin were associated with 8% mortality rate, compared to 13.2% when patients did not receive either drug.[13] Similarly, the GISSI trial also showed that streptokinase recipients were associated with 10.7% of mortality, compared to 13% of non-recipients.[10] Current smokers have an increased risk of thrombolysis failure with streptokinase, as shown in other studies[5], but this did not reach significance in this study. The possible explanation was the "smoker's paradox" theory, where current smokers were shown to have earlier presentation to the hospital and therefore achieved a better outcome of thrombolysis compared to the nonsmokers.

Streptokinase was the first generation thrombolytic agent. It acted by complexing with plasminogen and it is not fibrin specific. Eventually there will be depletion of plasminogen, known as "plasminogen steal", which will limit the fibrinolytic action accounting partly for the thrombolysis failure.[14] In addition, streptokinase was shown to have the highest paradoxical thrombin activation (or "thrombolytic paradox"), when compared to other thrombolytic agents.[15] Thrombolytic paradox was due to the pro-coagulant effect of thrombolytic agent despite its action of lysing the clots. The main hypothesis for the pro-coagulant effect was due to plasmin-mediated activation of the contact system of the coagulation pathway (Kallikrein/factor XII), as coined by Ewald and Eisenberg in 1995.[16]

Even with the same thrombolytic agent, different doses, different administration regimens and concomitant use of adjunctive agents can cause variations to the patency rates significantly.[14] There are different preparations of streptokinase in the market and it is possible that each of them may have different effects to arterial patency rates. In addition, the fixed dose of 1.5 MU used across major streptokinase trials, including GISSI-I and GUSTO-I, may have different responses among different races, gender and age groups.

There were a few limitations in this study which should be highlighted. This study was conducted in the Kelantan state with a predominantly Malay society. The retrospective design had obvious limitations. The criteria for thrombolysis failure with streptokinase was based solely on ECG, and achievement of TIMI grade 3 flow was not confirmed with coronary angiography, which is the gold standard. ECG recording should ideally be carried out at baseline and 90 min after streptokinase infusion. However, a time window of 2–4 hours was allowable for ECG recording after streptokinase. This time window would not have changed the results of the analysis.[6]

Since streptokinase had a high failure rate of thrombolysis among AMI patients, other reperfusion strategies should be considered, especially in the high-risk patients. Newer generation thrombolytic agents include the tissue plasminogen activators (tPA) (e.g. alteplase and reteplase). These are associated with a better thrombolysis outcome compared to streptokinase. However, these agents are expensive and not always available in resource-poor areas. Another strategy is PCI, which in many prospective trials, have shown better mortality outcome compared to thrombolytic agents.[17] A recently published study has proven that PCI was associated with better reperfusion and mortality outcome compared to streptokinase in patients with anterior AMI (relative risk 1.6, $p = 0.03$).[18] Another option would be rescue angioplasty. There are three randomised trials that suggested rescue angioplasty offered benefit, although the data is not compelling as yet.[19]

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