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Outcome after combined reperfusion therapy for acute myocardial infarction, combining pre-hospital thrombolysis with immediate percutaneous coronary intervention and stent

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Background Primary therapies in acute myocardial infarction (thrombolysis and angioplasty) have inherent limitations which may be overcome by combining them. So far, no trial has demonstrated a clinical benefit in combining mechanical and pharmacological treatment strategies.

Methods From January 1995 to December 1999, out of 1010 patients admitted to our institution for acute myocardial infarction, 148 had received pre-hospital full dose thrombolysis within 12 h of onset. One hundred and thirty-one patients were included and underwent immediate angioplasty and stenting when suitable, independent of the infarct-artery patency (TIMI grade flow 0–3). In-hospital outcome was assessed and clinical information was collected for a mean (± SD) of 2 ± 1 years.

Results Ninety-minute angiography revealed a patent (TIMI grade 3) infarct artery in 65 patients (49%). Immediate angioplasty was performed in 119 patients (91%) with stent implantation in 114 (96%). Angioplasty achieved TIMI 2, 3 flow in 98%, and complete patency (TIMI 3 flow) in 92%. Six other patients underwent deferred revascularization (surgery in one patient, angioplasty in five) and six received medical treatment. Stent thrombosis and reinfarction occurred in three patients (2·3%). In-hospital death occurred in six patients (4·6%), including four patients presenting with cardiogenic shock. Major bleeding was observed in 2·3% of cases. No patient had emergency surgery. Freedom from death and reinfarction at 2 years was 90% and freedom from death, reinfarction and target vessel revascularization was 83%.

Conclusion A strategy of combined reperfusion using full dose pre-hospital thrombolysis and immediate angioplasty with stent implantation in a non-selected acute myocardial infarction population is safe and achieves high and early patency rates. This preliminary experience suggests that a combined strategy in acute myocardial infarction may have a significant impact on both early and long-term outcomes.
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Key Words: Myocardial infarction, angioplasty, stents, thrombolysis.

See page 1067 for the Editorial comment on this article

Introduction

Complete (TIMI grade 3) patency of the infarct-related artery is a major predictor of survival and preserved left ventricular function following reperfusion therapy[1,2]. Thrombolysis has a major advantage over primary angioplasty in that it is widely available and allows a substantial reduction in the time to treatment

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implementation, particularly when delivered as pre-hospital reperfusion therapy[3–8]. There are, however, several limitations to thrombolysis the main one being the suboptimal restoration of TIMI grade 3 flow which is generally not reported in more than 55% to 65% of patients within 90 min of therapy[1,9]. Furthermore, recurrent ischaemic events have been documented in more than 20% of patients following thrombolysis[10]. Several studies have demonstrated that re-occlusion is frequent, occurring early after thrombolysis in 6% to 13% of patients, and in 30% at 3 months after successful thrombolysis[1,11,12]. Reocclusion constitutes an important event which is associated with severe outcomes such as deterioration in ejection fraction, higher frequency of pulmonary oedema, sustained hypotension, advanced atrioventricular block, and increased short- and long-term mortality[12–14].

We hypothesized that recent advances in interventional therapy could allow the systematic use of angiographic assessment followed by immediate angioplasty in non-selected, consecutive patients treated with pre-hospital thrombolysis. This strategy could provide both the advantages of primary angioplasty (early assessment of anatomy and artery patency, high reperfusion rate, low reocclusion rate with stent implantation) and those associated with thrombolysis (wide availability, reduced time to reperfusion therapy) and overcome the major disadvantages of each of the two reperfusion therapies taken as a stand-alone strategy: that is, namely, the negative impact of delayed primary angioplasty, and limited and transient reperfusion in the case of thrombolysis alone.

Randomized trials conducted more than 10 years ago failed to demonstrate the superiority of a routine strategy of immediate angiography and percutaneous coronary angioplasty (PTCA) after thrombolysis for the treatment of acute myocardial infarction[15–17]. The combined use of PTCA and thrombolytic therapy for acute myocardial infarction was found to maximize the risk of bleeding and adverse events compared to a strategy of delayed elective PTCA[18]. In addition, the re-occlusion and re-infarction rates following immediate post-thrombolytic angioplasty were as high as 18%[19].

Recent advances in interventional cardiology may overcome these limitations. It has been demonstrated that coronary stent implantation could be associated with a decreased need for additional target vessel revascularization and a significant reduction in reocclusion rates as compared with primary angioplasty[20–22]. In this era of effective antiplatelet agents, the use of smaller sheath sizes, routine 'mini-invasive' radial artery access and percutaneous suture devices may reduce bleeding associated with thrombolysis.

To address this issue, we decided to carry out a prospective, observational study evaluating a strategy of early angiographic assessment of infarct-related artery patency with immediate and systematic angioplasty and stenting after pre-hospital thrombolysis and whatever the TIMI flow.

Methods

Study population

Our centre is dedicated to primary angioplasty as the main and preferred treatment option for acute myocardial infarction. No patient receives in-hospital thrombolysis. However, in France, pre-hospital management of patients with suspected acute myocardial infarction is generally carried out in mobile emergency units staffed by one or two physicians trained in emergency cardiology. Now that the advantages of early, medically-assisted, pre-hospital administration of thrombolytic therapy are well demonstrated[3–8], thrombolysis is frequently initiated at home or in the ambulance when the expected transfer time exceeds 60 min. Intravenous heparin and aspirin (250 mg) are administered in combination with thrombolytic therapy.

From January 1995 to December 1999, Among 1010 patients admitted to our centre for acute myocardial infarction within 12 h of symptom onset (cardiogenic shock present in 13·4%, angioplasty with stent in 89·3%, final TIMI 3 flow in 90·5%, in-hospital death in 11·5%, 5·3% in non-shock patients) 148 had received pre-hospital thrombolysis (14·6%) and were screened for inclusion. No exclusion criteria were applied for age and patients who received thrombolysis after cardiac arrest were included, as were patients with cardiogenic shock or severe haemodynamic compromise. However, one patient with cardiogenic shock was excluded because of prolonged cardiac arrest prior to thrombolytic administration. Cardiogenic shock was defined as acute myocardial infarction with systemic arterial pressure less than 80 mmHg for more than 30 min despite medical treatment, with symptoms of low cardiac output. Patients who were transferred from other centres with no catheterization facilities, because of suspected reocclusion or recurrent ischaemic events after thrombolysis (namely rescue PTCA) were not included in this study (10 patients). Patients transferred from these centres for early (within 6 h) and systematic patency assessment only were included. Six patients admitted for late (exceeding 6 h) patency assessment were excluded. Therefore, the study population represented 131 consecutive patients.

In-hospital treatment

Study patients, as for all patients admitted to our institution for acute myocardial infarction within 12 h, were brought directly to the cardiac catheterization laboratory (bypassing emergency units) where two trained nurses, one anaesthetist and one experienced interventional cardiologist performing >300 PTCA procedures a year, were on 24-h duty. Immediate coronary and left ventricular angiography were performed with ionic contrast media, via the femoral or radial approach using a 6-French introducer. Angiographic patency of the infarct-related artery was immediately graded using

the TIMI score[23]. Immediate PTCA and stent implantation were performed in the case of TIMI 0–1 or 2 flow in the infarct related artery. PTCA and stenting were encouraged if anatomically appropriate in cases of TIMI 3 flow of the infarct related artery with severe residual post-thrombolytic lesions. Multivessel angioplasty was not performed except in cases of two-vessel occlusion with no clear indication of the culprit vessel. Stent implantation was performed in all suitable cases (vessel diameter $\geq 2{\cdot}5$ mm) using conventional pressure deployment without intra-coronary ultrasound guidance. Tubular stents were preferred to coil stents (only one coil stent was implanted). An additional bolus of heparin was administered to achieve an activated clotting time value >300 s. Patients received an intracoronary bolus of verapamil (200 μg) in the presence of no-reflow or in the absence of TIMI 3 flow. Procedural success was defined as TIMI 3 grade flow with no significant residual stenosis (<50%). Sheaths were systematically withdrawn immediately after PTCA using percutaneous suture (Techstar®, Perclose Inc.) when the femoral approach was selected. All patients received ticlopidine and aspirin post implantation; use of heparin after intervention was at the discretion of the individual physician. During the in-hospital phase, the outcomes assessed were death, reinfarction and urgent need for repeat target revascularization by PTCA or coronary artery bypass graft surgery. Major cardiac and cerebrovascular events were defined as death, reinfarction, urgent need for revascularization and stroke. Any clinically relevant bleeding was classified either as minor or major when fatal or necessitating transfusion and/or surgery. Emergency angiography was performed in any suspected reocclusion based on clinical recurrence or ECG abnormality. No systematic follow-up angiogram was performed during the in-hospital course.

Clinical follow-up

Patients were called 30 days after discharge for evaluation of their clinical status and potential adverse events. No specific follow-up angiography was planned for screening infarct artery reocclusion or restenosis. Long-term follow-up information was obtained in December 1999–January 2000. All patients and/or their general practitioners were contacted by telephone. All subsequent hospital admissions for cardiac reasons (death, angina, recurrent infarction, heart failure, additional intervention) were recorded. Patients were asked about their symptoms and any additional interventions were reported with special attention to target vessel revascularization and documented infarct artery restenosis.

Results

Characteristics of patients

One hundred and thirty-one patients, meeting inclusion criteria, were admitted following full dose pre-hospital thrombolysis. Different regimens of thrombolytic therapy were used, depending on the protocol of the mobile unit physician on call but the recombinant tissue-type plasminogen activator (rt-PA) represented the main option given in the accelerated full dose (alteplase: 92%, reteplase: 5%, streptokinase: 4%). Thrombolysis was initiated at a median time interval of 2 h after the onset of chest pain. Clinical and pre-admission data for the 131 study patients are shown in Table 1. Anterior acute myocardial infarction was documented in 49% of the study group. Patients with cardiogenic shock accounted for a noticeable proportion of the study population (7%).

Table 1 Clinical and pre-admission characteristics

Median age, years*	57 (32–82)
Male, n (%)	104 (79)
Previous myocardial infarction, n (%)	12 (9)
Previous revascularization (PTCA or CABG), n (%)	6 (5)
Risk factors, n (%)	
History of smoking	89 (68)
Hypertension	42 (32)
Dyslipidaemia	59 (45)
Diabetes mellitus	23 (18)
Family history of CAD	21 (16)
Shock upon admission, n (%)	9 (7)
Chest pain upon admission, n (%)	55 (42)
Anterior MI location, n (%)	64 (49)
Median interval between pain to admission, min*	240 (180–960)
Median time from onset to drug, h*	2 (1–12)
Median time from drug to needle, min*	95 (70–450)
Pre-hospital thrombolytic treatment, n (%)	
Alteplase	120 (92)
Reteplase	6 (5)
Streptokinase	5 (4)

Because of rounding, not all percentages total 100.
PTCA=percutaneous transluminal coronary angioplasty; CABG=coronary artery bypass grafting; CAD=coronary artery disease; MI=myocardial infarction.
*Median (IQR).

Percutaneous coronary intervention

Angiography was performed at a median interval of 95 min from initiation of thrombolytic therapy (range 70–450). The radial approach was used in 42 patients (32%). Angiographic data are summarized in Table 2. At 90 min post thrombolysis infusion, angiography revealed patent (TIMI 3 flow) arteries in 64 cases (49%). All patients with TIMI 0–2 grade flow underwent immediate PTCA except for two patients with TIMI 2 grade flow and unsuitable anatomy for any form of revascularization. Among the 64 patients in whom complete reperfusion was achieved (TIMI grade 3 flow) post thrombolysis, 54 (84%) underwent immediate PTCA. The remaining 10 patients with patent arteries were treated as follows: four received conservative treatment because of non-significant lesions, one underwent elective coronary artery bypass graft (CABG)

Table 2 Angiographic and procedural data

Clinically significant coronary artery disease, no. (%)	
Single-vessel disease	68 (52)
Two-vessel disease	41 (31)
Three-vessel disease	22 (17)
Mean left ventricular ejection fraction, %	51 ± 13
Infarct-related artery location, n (%)	
Left anterior descending artery	65 (50)
Circumflex artery	16 (12)
Right coronary artery	49 (37)
Left main	1 (1)
Infarct-related artery patency, n (%)	
TIMI 0–1 flow	39 (30)
TIMI 2 flow	28 (21)
TIMI 3 flow	64 (49)
Mean post thrombolysis stenosis, %	87 ± 16
Clinically non-significant (<50% stenosis) lesion, n (%)	8 (6)
Immediate angioplasty, n (%)	119 (91)
Intracoronary stenting, n (%)	114 (96)
Final TIMI grade flow, n (%)	
TIMI 0–1 flow	2 (1)
TIMI 2 flow	9 (7)
TIMI 3 flow	120 (92)

TIMI = thrombolysis in myocardial infarction.

Table 3 In-hospital outcome in the 131 study patients

Median CPK Peak (IU)*	2109 (1124–11800)
Median hospital stay duration, days*	7 (4–30)
Re-infarction, n (%)	3 (2·3)
Emergency revascularization, n (%)	4 (3)
Repeat PTCA, n (%)	4 (3)
CABG, n (%)	0
Death, n (%)	6 (4·6)
MACCE, n (%)	10 (7·6)
Major bleeding, n (%)	3 (2·3)
Minor bleeding, n (%)	6 (4·5)
Intra-cranial haemorrhage, n (%)	1 (0·7)

CPK = creatine phosphokinase; PTCA = percutaneous transluminal coronary angioplasty; CABG = coronary artery bypass grafting; MACCE = major cardiac and cerebrovascular events.
*Median (IQR).

for three-vessel disease, and five had deferred PTCA because of complex lesion anatomy. Intra-aortic balloon pumping was used in seven patients with cardiogenic shock. Consequently, following angiographic assessment, a total of 119 patients underwent immediate angioplasty (91%). Stent implantation was performed in 114 cases (96%). The reasons for not implanting a stent were as follows: thrombotic in-stent restenosis in one case, presence of a large thrombus in one case, small vessel diameter in two cases and angioplasty failure in one case. A total of 132 stents were implanted in 114 patients (1·2 stent per patient) at a median time from admission of 35 min (range 20–240). The median heparin in-lab dose was 8000 IU (range 5000–10000). During angioplasty 12 patients exhibited a transient, reversible no-reflow phenomenon. Two patients had in-lab acute closure following two-vessel stenting performed in the same session and were successfully treated with immediate repeat PTCA and abciximab (Reopro®, Lilly Inc). Angiographic success as defined by TIMI 3 flow was achieved in 110 patients (92%). Upon completion of the angiographic procedures, the combined reperfusion strategy resulted in artery patency, as documented by final TIMI 3 flow rate, in 92% of patients (120/131). Nine patients had a final TIMI 2 flow grade and only 2 had TIMI 0–1 flow grade. No patient required emergency surgery.

In-hospital outcome

In-hospital outcome for the entire study population is summarized in Table 3. Recurrent ischaemia occurred in four patients including reinfarction, secondary to subacute stent thrombosis, in three patients (2·3%). All underwent emergency repeat PTCA. In one case, subacute thrombosis and reinfarction were secondary to a bleeding event necessitating the discontinuation of ticlopidine and the patient was successfully treated by repeat PTCA. In one case repeat PTCA was not successful. None of these patients required urgent or emergency CABG. Seventeen patients underwent deferred PTCA in the non-culprit artery.

Six patients had a minor haematoma at the femoral access site and one had non-significant haematuria; only three patients suffered major bleeding (2·3%). The cause of major bleeding was gastrointestinal in two cases (one following PTCA and stenting with subsequent subacute stent thrombosis, one fatal in a medically treated patient) and catheter-related in only one case. No cases of stroke occurred (one patient had a transient ischaemic attack). One patient had a pauci-symptomatic intracranial haemorrhage and recovered without clinical consequences.

In-hospital death occurred in six patients (4·6%). In haemodynamically stable patients the death rate was 1·6%. Four patients died as a consequence of cardiogenic shock and one medically treated patient died following severe gastro-intestinal bleeding. One patient with late infarct recognition died from cardiac rupture despite successful reperfusion.

Long-term clinical follow-up

Follow-up was obtained at a mean time of 2 ± 1 years (only one patient was lost to follow-up). Only two patients died after hospital discharge; one patient with poor left ventricular function, prior myocardial infarction and prior bypass surgery with several angioplasties died suddenly at 2 months, the other patient died at 6 months from a non-cardiac cause (severe neurodegenerative disease). The mortality rate at 2-year follow-up was 6% (eight patients). Non fatal reinfarctions occurred in two patients: after 1 year in one patient, and after 2 months in a severely diabetic patient with restenosis who

initially presented with cardiogenic shock and cardiac arrest. This patient underwent repeat PTCA but refused elective CABG. Therefore, the 2-year cumulative survival and freedom from reinfarction rate was 90%. A total of 94 patients (70%) were symptom-free, and did not require re-hospitalization or further revascularization. Additional revascularization procedures were documented in 17 patients, including the ones on the infarct related artery in eight patients. One patient had CABG for restenosis. Target vessel revascularization was performed in 9 patients (7%).

Discussion

Percutaneous coronary intervention and thrombolysis compatibility

In this non-selected series of acute myocardial infarction patients treated with pre-hospital thrombolysis, the first important finding is the absence of adverse effects in combining percutaneous coronary intervention using stents with full dose thrombolytic drugs. Immediate angiography followed by PTCA and stenting does indeed appear to be a safe strategy. Our study demonstrates the compatibility of a combined, full dose lytic therapy with an early interventional procedure. No patient underwent emergency surgery; major bleeding was observed in only 2·3% of patients and was rarely catheter-related. These results compare very favourably with those of previous obsolete studies in which emergency surgery was reported in 2% to 10% and bleeding in approximately 40%, necessitating transfusion in 10% to 39% of the study patients, most of the bleeding occurring at the puncture sites in the invasive group[15–19]. The reason for this major difference lies in the improved revascularization techniques and the management of patients. The increased use of stents has definitively modified the need for surgery which accounts for less than 0·5% of the current procedures in France[24]. Smaller sheath sizes together with the discontinuation of anticoagulation regimens following angioplasty and stenting have been shown to dramatically reduce complications at the access sites[25]. Contrary to the classical management of the femoral puncture site, sheaths were no longer left in place but were immediately withdrawn, with instantaneous haemostasis being achieved by percutaneous suture. The use of the radial approach in our study may also have contributed to the low access site complication rate as demonstrated in two recent randomized clinical trials[26,27].

Clinical impact of the combined strategy

The second relevant finding of our study is the dramatic efficacy of the strategy described here in achieving a very low rate of adverse events including in-hospital and long-term mortality. Major recent clinical trials[10,28,29] evaluating thrombolytic agents still report a 30-day mortality rate remaining constant at 6 to 7·5%, and markedly higher than the 4·6% in-hospital mortality rate reported here despite several severe clinical characteristics with a higher proportion of cardiogenic shock. The impact of the combined strategy is even more obvious in view of the long-term outcome and compares favourably with the results of each treatment strategy. The Netherlands trials reported a mean mortality of 13% at 3 years after thrombolysis by streptokinase, and the GISSI trial reported a 45% mortality rate at 10 years[30,31]. Recently, a 24% mortality rate was reported at 5 years after thrombolysis by streptokinase, compared to 13% after primary angioplasty[32]. The 6% late mortality rate we observed in a non-selected population in which patients with cardiogenic shock were included supports the idea of a synergistic combination of these two distinct reperfusion therapies. A 10% combined incidence of death and reinfarction at 2 years compares favourably with the most recent and significant long-term analyses of primary angioplasty outcomes: a 5-year mortality rate of 13% in the Netherlands trial, and a 15% combined incidence of death and reinfarction 2 years after primary angioplasty in the PAMI-1 trial[32,33].

Potential benefits of combination treatments

This is the first study suggesting that a definite survival benefit might be achieved through the combination of two traditionally opposed reperfusion modalities: PTCA and thrombolysis. Early and sustained patency may account for many of the results we obtained after combining the two reperfusion approaches at an early stage. It has recently been demonstrated that the outcome of patients treated by primary angioplasty is significantly better when reperfusion occurs before intervention[34]. A recent report from the PACT trial supports part of our findings by demonstrating improved patency rates after combining PTCA with low-dose thrombolytic drugs[35]. In particular, the study demonstrated the compatibility of the combined and adjunctive reperfusion therapies. However, the PACT study failed to demonstrate the impact of the adjunct of thrombolytic drugs on the clinical outcome of primary angioplasty. The absence of a significant effect may have been related to the non-optimal thrombolytic dose used, leading to a limited TIMI 3 grade reperfusion rate prior to intervention (33%), and because of short, in-hospital, delays in between the two therapies. The PACT study also differed from our study with its conservative attitude (no intervention) to patients with post thrombolytic TIMI 3 coronary blood flow. Our study gives further insight into these combined reperfusion therapies: using full-dose and pre-hospital delivery of thrombolytic drugs allows the achievement of a high patency rate before angioplasty (TIMI 3 grade flow in almost half of the patients), leading to an immediate survival advantage. This approach could overcome the negative impact of inherent delays necessary to achieve reperfusion with

primary angioplasty. Data from The National Registry for Myocardial Infarction-2 demonstrated the major impact of in-hospital delays in the clinical outcome after primary angioplasty[36]. In the GUSTO IIb trial, time to treatment with direct PTCA was found to be a critical, independent determinant of early mortality[37]. The 30-day mortality of patients who underwent balloon inflation within 60 min was 1% compared to 6·4% when exceeding 91 min ($P=0·001$). Our results suggest that primary angioplasty should benefit from pre-hospital pharmacological therapy, focusing on rapidly reopening arteries in as many patients as possible. An additional and important lesson to be learned from our study is the applicability of such a combined strategy in a 'real-world' situation and in consecutive patients generally ineligible for inclusion in major primary angioplasty trials.

Role of percutaneous coronary intervention with stents

In contrast to recent and previous trials, our study demonstrates the safety and efficacy of the strategy of immediate and systematic angioplasty, rather than evaluating elective or rescue angioplasty[35,38–40]. The role of the combined strategy is to achieve early reperfusion but also to prevent reocclusion rather than to treat it. A strategy of systematic angioplasty in patent, TIMI 3 grade flow arteries, is intended to maintain patency and avoid reocclusion and recurrent events. Consistent with the results of the Primary Angioplasty in Myocardial Infarction stenting trial, the rate of target-vessel revascularization at follow-up proved to be very close to the reported 7·7% rate at 6 months[22]. Intra-coronary stenting may have contributed to the low recurrent event and low reintervention rates observed in our study. Stents have been demonstrated to reduce restenosis, reocclusion and target vessel revascularization in several acute myocardial infarction trials[21,22,41]. At 6-month follow-up after coronary stenting in recent non-randomized myocardial infarction, Bauters *et al.*[42] observed a 1% total occlusion rate compared to 14% after balloon angioplasty ($P<0·005$). The negative impact of late reocclusion on long-term survival after myocardial infarction has been analysed and reported by several authors[12–14]. Therefore, we can speculate that the systematic use of stenting as part of our combined strategy may have contributed to the sustained benefit and low late mortality rates that we observed.

Study limitations

Certain limitations of our study should be noted. The first limitation is inherent in an observational trial. Definite confirmation of the superiority of a combined reperfusion therapy can only be obtained through a randomized comparison of this strategy with routinely implemented treatments. Furthermore, in contrast to major primary angioplasty and thrombolytic trials involving thousands of patients, the present study, initiated as early as 1995, included only 131 patients. Consequently, additional evaluation through large clinical trials is warranted and should include recent preliminary data suggesting a role for other pharmacological agents such as GP IIb/IIIa inhibitors. However, this observational study provides a unique opportunity to address an original preliminary approach to acute myocardial infarction therapy with provocative early and long-term results despite a non-selected population of consecutive patients eligible for thrombolysis.

Clinical implications

These results have several potential implications. First, they stress that the reperfusion therapies currently recommended may have limitations and show that improvements in the strategies applied may achieve a clear survival advantage. Current approaches to patients who received thrombolysis for acute myocardial infarction should at least be revisited. Conversely, primary angioplasty may benefit from additional therapies, particularly when significant delays to treatment are anticipated. These observations should encourage prospective studies to evaluate combined mechanical and/or pharmacological therapies. Recent preliminary studies suggest a role for platelet glycoprotein IIb/IIIa receptor inhibitors associated with primary PTCA or combined with low-dose thrombolytics as new reperfusion modalities for acute myocardial infarction[43–46]. The addition of antiplatelet agents to a pre-hospital reperfusion 'cocktail' may have a considerable clinical effect on the outcome of combined mechanical and pharmacological reperfusion strategies for acute myocardial infarction. Finally, our results support the key role of intracoronary stenting in maintaining patency with favourable long-term outcome. In our opinion, studies currently underway assessing the survival benefit associated with stenting in acute myocardial infarction should probably focus on the long-term outcome.

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