A Randomized Trial of Rescue Angioplasty Versus a Conservative Approach for Failed Fibrinolysis in ST-Segment Elevation Myocardial Infarction

The Middlesbrough Early Revascularization to Limit INfarction (MERLIN) Trial

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OBJECTIVES

We sought to compare emergency coronary angiography with or without rescue percutaneous coronary intervention (PCI) with conservative treatment in patients with failed fibrinolysis complicating ST-segment elevation myocardial infarction (STEMI).

BACKGROUND

Most patients with STEMI receive fibrinolytic therapy and aspirin. The management of failed fibrinolysis is unclear.

METHODS

A total of 307 patients with STEMI and failed fibrinolysis were randomized to emergency coronary angiography with or without rescue PCI or conservative treatment.

RESULTS

Thirty-day all-cause mortality was similar in the rescue and conservative groups (9.8% vs. 11%, p = 0.7, risk difference [RD] 1.2%, 95% confidence interval [CI] −5.8 to 8.3). The composite secondary end point of death/re-infarction/stroke/subsequent revascularization/heart failure occurred less frequently in the rescue group (37.3% vs. 50%, p = 0.02, RD 12.7%, 95% CI 1.6 to 23.5), driven by less subsequent revascularization (6.5% vs. 20.1%, p < 0.01, RD 13.6%, 95% CI 6.2 to 21.4). Re-infarction and clinical heart failure were less common in the rescue group (7.2% vs. 10.4%, p = 0.3, RD 3.2%, 95% CI 3.3 to 9.9; and 24.2% vs. 29.2%, p = 0.3, RD 5.7%, 95% CI 4.3 to 15.6, respectively). Strokes and transfusions were more common in the rescue group (4.6% vs. 0.6%, p = 0.03, RD 3.9%, 95% CI 0.5 to 8.6; and 11.1% vs. 1.3%, p < 0.001, RD 9.8%, 95% CI 4.9 to 19.9, respectively).

CONCLUSIONS

Rescue angioplasty did not improve survival by 30 days, but improved event-free survival, almost completely due to a reduction in subsequent revascularization. Rescue angioplasty was associated with more strokes and more transfusions and did not result in preservation of left ventricular systolic function at 30 days.

The management of patients with acute ST-segment elevation myocardial infarction (STEMI) in whom fibrinolytic therapy is unsuccessful is not clear. This is partly due to the difficulty of making the diagnosis of failed thrombolysis without recourse to invasive techniques. As a result, many units have no structured policy for the management of failed thrombolysis (1,2). Many clinicians follow a conservative approach, allowing more time for fibrinolytic therapy to work. Others use repeat fibrinolytic therapy (3). Although rescue angioplasty is used in some centers, there are few randomized trials of this approach. A small trial by Belenkie et al. (4) had insufficient power to determine a clear advantage. A larger study by Ellis et al. (5) compared rescue angioplasty with continued conventional medical therapy in patients with a first anterior myocardial infarction (MI) and demonstrated a trend toward a reduction in the incidence of

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Manuscript received October 20, 2003; revised manuscript received December 5, 2003, accepted December 10, 2003.
Abbreviations and Acronyms
CABG = coronary artery bypass graft surgery  
LV = left ventricular  
MERLIN = Middlesbrough Early Revascularization to Limit INfarction trial  
PCI = percutaneous coronary intervention  
RD = risk difference  
RWMI = regional wall motion index  
STEMI = ST-segment elevation myocardial infarction  
TIMI = Thrombolysis In Myocardial Infarction

the non-prespecified end point of 30-day death or severe heart failure in the rescue arm (6% vs. 17%, p = 0.05). These studies investigated rescue angioplasty without the potential benefits of coronary stenting and pharmacologic adjuncts such as glycoprotein IIb/IIIa inhibitors. Their results have not provided clear guidance on whether cardiac units should actively seek the diagnosis of failed fibrinolysis with the aim of providing rescue angioplasty.

Transfer of selected patients receiving fibrinolytic therapy, with a view to rescue angioplasty, has been shown to be relatively safe and associated with a favorable outcome (6,7). The strategy of rescue angioplasty for failed fibrinolysis, including the transfer of patients from non-interventional centers, has not been re-assessed in prospective, randomized trials in the modern angioplasty era. The Middlesbrough Early Revascularization to Limit INfarction (MERLIN) trial was designed to compare a rescue angioplasty strategy with continued medical treatment for patients with acute STEMI and failed fibrinolysis.

METHODS

Participating hospitals. The trial center was The James Cook University Hospital, Middlesbrough, a Regional Cardiothoracic Unit, where all emergency coronary angiography and subsequent revascularization procedures were performed. Patients were enrolled from the Coronary Care Unit at The James Cook University Hospital and the Accident and Emergency Unit of the affiliated Middlesbrough General Hospital. Patients were also enrolled from the Coronary Care Units at the University Hospital of North Tees, Stockton-on-Tees, and Darlington Memorial Hospital, Darlington.

Inclusion criteria. Patients with STEMI and evidence of failure to respond to the administration of fibrinolytic therapy constituted the trial population. Presentation to the hospital within 10 h of the onset of major symptoms was required. Myocardial infarction was defined by the presence of ischemic chest pain lasting more than 30 min, unrelieved by sublingual nitrate and associated with typical ST-segment elevation on the 12-lead electrocardiogram (ECG; at least 2 mm of ST-segment elevation in 2 or more contiguous chest leads and at least 1 mm in 2 or more contiguous limb leads). Failure to respond to fibrinolytic therapy was defined by a second 12-lead ECG obtained 60 min after the onset of fibrinolytic therapy, showing failure of the ST-segment elevation in the worst lead (the lead with maximal ST-segment elevation) to have resolved by 50%, as compared with the pretreatment ECG (ST-segment measured 80 ms after the J point), as well as the absence of an accelerated idioventricular rhythm at the time of the 60-min ECG (8).

Exclusion criteria. These included cardiogenic shock (defined by systolic blood pressure ≤90 mm Hg, oliguria, and poor peripheral perfusion with or without clinical or radiologic evidence of pulmonary edema); confounding features on the pre-fibrinolytic ECG, preventing ST-segment reduction analysis; re-infarction in the same ECG territory within two months of an original infarction; absent femoral pulses; pregnancy; and the presence of significant co-existing pathology likely to affect the prognosis during the follow-up period.

Additional treatment. Patients fulfilling the inclusion criteria were treated initially with 300 mg aspirin and thereafter at least 75 mg/day aspirin. The administration of other pharmacologic agents, such as beta-blockers, calcium channel antagonists, nitrates, antithrombotic agents, and other antiplatelet agents (e.g., thienopyridines and glycoprotein IIb/IIIa inhibitors) in either arm was at the discretion of the attending physician or cardiologist.

Randomization. Randomization was by a telephone call to the Coronary Care Unit at The James Cook University Hospital. The patient was assigned to: 1) rescue angioplasty; or 2) conservative therapy by means of a sealed envelope system. The randomization sequence was created from standard random number charts and was a block randomization process (block size 4), ensuring equal numbers of patients in each arm of the trial after every four randomized patients and approximately equal numbers overall.

RESCUE ANGIOPLASTY. Patients randomized to the rescue angioplasty arm were transferred urgently to the cardiac catheterization laboratory at The James Cook University Hospital as soon as the 60-min ECG confirmed persistent ST-segment elevation and consent had been obtained. Coronary angiography was performed from any arterial access point, and percutaneous coronary intervention (PCI) was attempted if considered appropriate. Unfractionated heparin was administered to all patients undergoing PCI who had a target activated clotting time of 300 s at the time of intervention. The use of intracoronary stents, an intracoronary balloon pump, other mechanical devices, and adjunctive pharmacologic therapy was at the discretion of the attending cardiologist. After angioplasty, all patients continued to take regular aspirin, at least 75 mg/day, in the absence of a history of allergy. If one or more coronary stents were deployed, ticlopidine 250 mg twice daily following an initial immediate dose of 500 mg, or clopidogrel 75 mg/day following an initial dose of 300 mg, was administered. Electrocardiography was performed every 3 h after the initiation of fibrinolytic therapy for 24 h.
CONSERVATIVE ARM. Patients in the conservative arm received standard medical treatment after the administration of fibrinolytic therapy. The use of repeat fibrinolytic therapy was discouraged but allowed during the trial if this was standard local policy. The use of heparin and other treatments was at the discretion of the attending physician. Early crossover to the rescue angioplasty arm was not allowed, except for when cardiogenic shock developed. Electrocardiography was performed every 3 h after the initiation of fibrinolytic therapy for 24 h. Angiography and revascularization were permitted for re-infarction (defined subsequently) or for recurrent ischemia or a positive exercise test during the hospital admission.

Ethical considerations. The study received approval from the Local Research Ethics Committee for each of the participating hospitals. Informed, written consent from each patient was required for trial entry, taken in the presence of a relative if possible. A Data and Safety Monitoring Committee was established to review the results of the trial after enrolment of the first 100 and 200 patients and recommended trial continuation at each stage. Adverse events were monitored continuously. Initial follow-up was planned for a period of six months, but subsequently extended to three years with agreement of the Ethics Committees.

Exercise testing and echocardiograms. After the index event, the assessment of inducible ischemia and left ventricular (LV) systolic function was arranged in accordance with local guidelines. Formal assessment of LV function was performed at 30 days and six months by two experienced echocardiographers (Drs. Price and Graham), and all images were analyzed by a single observer (Dr. Graham), who was blinded to the treatment strategy. The 16-segment model for assessment of LV function, as recommended by the American Society of Echocardiography, was used, with the function of each segment scored as follows: 1 = normal; 2 = hypokineti c; 3 = akinetic; 4 = dyskinetic; and 5 = aneurysmal (9). The regional wall motion index (RWMI) was calculated.

End points and definitions. The primary end point was all-cause mortality at 30 days. The secondary end points were: 1) a composite of death, re-infarction, stroke, heart failure, and clinically driven subsequent revascularization within 30 days; and 2) LV function at 30 days, as assessed by RWMI. The primary and secondary end points will be re-evaluated at six months and annually to three years.

Re-infarction was defined by a repeat episode of ischemic chest pain after recovery from the initial event, associated with typical ST-segment re-elevation on the ECG and lasting for >30 min despite opiate and nitrate therapy. Stroke was defined by any new neurologic deficit lasting >24 h; computed axial tomography was performed when possible. Heart failure was defined by the requirement for diuretic treatment in the presence of typical chest X-ray characteristics, or auscultatory crackles extending at least one-third of the way up the lung fields without a previous history of chronic pulmonary disease, or a third heart sound with persistent tachycardia. Subsequent revascularization was defined by any catheter-based or surgical intervention in the conservative group and any additional revascularization procedure in the rescue group that was not planned after the initial coronary angiogram.

Procedural success in the rescue angioplasty arm was defined by the presence of Thrombolysis In Myocardial Infarction (TIMI) flow grade 2 or 3 in the infarct-related vessel with <50% residual stenosis and no requirement for emergency coronary artery bypass graft surgery (CABG) as the result of a complication of PCI and the patient being transferred back to the coronary care unit.

Statistical methods. All end points were analyzed on an intention-to-treat basis. Statistical comparisons between the groups were made using chi-square analysis for the categorical variables, with calculation of the risk difference (RD) and 95% confidence interval (CI). The Fisher exact test was used where expected values were <5. The t test was used for continuous end points, and the difference in mean values with 95% CI was presented. Logistic regression was used to test for an association between specified variables and outcome. Survival and survival without occurrence of one (or more) of the individual end points were plotted on Kaplan-Meier curves.

The sample size was estimated on the basis of the following assumptions: from a review of the literature, the primary end point would occur in ~18% of those in the conservative arm (10,11) and in 6% of those in the rescue angioplasty arm (4,5,12–16), based on the available published data. Approximately 150 patients would be required in each arm to detect a mortality difference between 18% in the conservative group and 6% in the salvage group, with 90% power and a p value of 0.05.

RESULTS

Patients were enrolled into the study between February 1999 and June 2002. Enrollment in each center was as follows: The James Cook University Hospital, n = 176; The University Hospital of North Tees, n = 107 (from June 1999); and The Darlington Memorial Hospital, n = 24 (from July 2000). A total of 154 patients were randomized to the conservative arm and 153 to the rescue angioplasty arm. Streptokinase was administered to 149 patients in the conservative arm (10,11) and in 6% of those in the rescue angioplasty arm (4,5,12–16), based on the available published data. Approximately 150 patients would be required in each arm to detect a mortality difference between 18% in the conservative group and 6% in the salvage group, with 90% power and a p value of 0.05.

The MERLIN Trial

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JACC Vol. 44, No. 2, 2004
Four patients did not have a coronary angiogram: one patient with hematemesis on arrival in the catheterization laboratory and improvement of the ECG compared with the postfibrinolytic ECG; one patient in whom the coronary ostia could not be engaged from the right femoral artery due to extreme iliac artery tortuosity; one patient with a preexisting diagnosis of severe triple-vessel coronary disease unsuitable for PCI and who had ECG evidence of reperfusion on arrival; and one patient with ECG evidence of reperfusion who did not have coronary angiography due to misinterpretation of the trial protocol. All four were included on an intention-to-treat basis. The angiographic findings and subsequent management in the rescue angioplasty arm patients are shown in Figure 1. In 77 (94%) of the 82 patients undergoing intervention for TIMI flow grade <3, PCI was successful. A total of 130 patients in the rescue arm (85%) left the catheterization laboratory with TIMI flow grade 3 in the infarct-related vessel. The management, medications, and complications for all patients are shown in Table 2.

The 30-day end points are shown in Table 3. The primary end point of all-cause mortality occurred in 15 patients in the rescue angioplasty arm and 17 patients in the conservative arm (9.8% vs. 11%, p = 0.7, RD 1.2%, 95% CI 5.8 to 8.3; chi-square test). Two patients in the rescue angioplasty arm died of noncoronary causes before 30 days (1 killed on day 24 in a road traffic accident and 1 with a normal coronary arteriogram who died on day 2 with a postmortem diagnosis of acute myocarditis). Thirty-day mortality attributable to coronary artery disease was 8.5% in

### Table 1. Demographic Details

<table>
<thead>
<tr>
<th></th>
<th>Conservative Arm (n = 154)</th>
<th>Rescue Angioplasty Arm (n = 153)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male (%)</td>
<td>114 (74)</td>
<td>108 (71)</td>
</tr>
<tr>
<td>Age (yrs)</td>
<td>62.7 ± 10.9</td>
<td>63.0 ± 11.2</td>
</tr>
<tr>
<td>History of hypertension (%)</td>
<td>47 (30.5)</td>
<td>62 (40.5)</td>
</tr>
<tr>
<td>History of diabetes (%)</td>
<td>23 (14.9)</td>
<td>18 (11.8)</td>
</tr>
<tr>
<td>Insulin therapy (%)</td>
<td>7 (4.5)</td>
<td>4 (2.6)</td>
</tr>
<tr>
<td>Known hyperlipidemia (%)</td>
<td>24 (15.6)</td>
<td>29 (19.0)</td>
</tr>
<tr>
<td>Total cholesterol on admission (mmol/l)</td>
<td>5.54 ± 1.17</td>
<td>5.82 ± 1.32*</td>
</tr>
<tr>
<td>Blood glucose on admission (mmol/l)</td>
<td>8.9 ± 3.0</td>
<td>9.0 ± 3.3</td>
</tr>
<tr>
<td>Current smoker (%)</td>
<td>57 (37.0)</td>
<td>64 (41.8)</td>
</tr>
<tr>
<td>Ex-smoker (%)</td>
<td>51 (33.1)</td>
<td>45 (29.4)</td>
</tr>
<tr>
<td>Previous MI (%)</td>
<td>20 (13.0)</td>
<td>17 (11.1)</td>
</tr>
<tr>
<td>Anterior MI (%)</td>
<td>62 (40.3)</td>
<td>74 (48.4)</td>
</tr>
<tr>
<td>Pain to lysis time (min)</td>
<td>170 ± 96</td>
<td>180 ± 120</td>
</tr>
<tr>
<td>Lysis to laboratory time (min)</td>
<td>—</td>
<td>146 ± 37</td>
</tr>
<tr>
<td>Pain to laboratory time (min)</td>
<td>—</td>
<td>327 ± 121</td>
</tr>
</tbody>
</table>

*p = 0.05. Data are presented as the mean value ± SD or number (%) of patients.

MI = myocardial infarction.

### Table 2. In-Hospital Treatment

<table>
<thead>
<tr>
<th></th>
<th>Conservative Arm (n = 154)</th>
<th>Rescue Angioplasty Arm (n = 153)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immediate coronary angiography (%)</td>
<td>0</td>
<td>149 (97.4)</td>
</tr>
<tr>
<td>Immediate coronary angioplasty (%)</td>
<td>0</td>
<td>100 (65.4)</td>
</tr>
<tr>
<td>Stent(s) deployment (%)</td>
<td>0</td>
<td>77 (50.3)</td>
</tr>
<tr>
<td>Glycoprotein IIb/IIIa inhibitor (%)</td>
<td>0</td>
<td>5 (3.3)</td>
</tr>
<tr>
<td>IABP (%)</td>
<td>0</td>
<td>19 (12.4)</td>
</tr>
<tr>
<td>Transfusion (%)</td>
<td>2 (1.3)</td>
<td>17 (11.1)</td>
</tr>
<tr>
<td>Discharge medication*</td>
<td>135 (97.1)</td>
<td>136 (97.8)</td>
</tr>
<tr>
<td>Aspirin (%)</td>
<td>21 (15.1)</td>
<td>84 (60.4)</td>
</tr>
<tr>
<td>Thienopyridine (%)</td>
<td>4 (2.9)</td>
<td>6 (4.3)</td>
</tr>
<tr>
<td>Warfarin (%)</td>
<td>114 (82.0)</td>
<td>110 (79.1)</td>
</tr>
<tr>
<td>Beta-blocker (%)</td>
<td>101 (72.7)</td>
<td>98 (70.5)</td>
</tr>
<tr>
<td>Lipid-lowering medication (%)</td>
<td>97 (69.8)</td>
<td>109 (78.4)</td>
</tr>
<tr>
<td>ACE inhibitor (%)</td>
<td>—</td>
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*In each arm, 139 patients were discharged from the hospital.

ACE = angiotensin-converting enzyme; IABP = intra-aortic balloon pump.

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**Figure 1.** Rescue angioplasty patients, showing catheterization laboratory findings and outcomes. “Success” was defined by patent infarct-related vessel (Thrombolysis In Myocardial Infarction [TIMI] flow grade 2 or 3), no emergency coronary artery bypass graft, and survival during the procedure. Unsched revasc = subsequent revascularization; CCF = congestive cardiac failure; IRV = infarct-related vessel; PCI = percutaneous coronary intervention.
the rescue arm and 11.0% in the conservative arm (p = 0.4, RD 2.5%, 95% CI –4.3 to 9.5; chi-square test). Causes of death in the 32 patients who died were: progressive cardiac shock (n = 21), cardiac arrest with failed resuscitation (n = 4), myocarditis (n = 1), re-infarction (n = 1), probable intracerebral hemorrhage (n = 1), presumed cardiac dysrhythmia (n = 3), and a road traffic accident (n = 1).

In the rescue angioplasty arm, seven patients underwent emergency subsequent revascularization for re-infarction: five by PCI and two by CABG. Three patients with re-infarction were managed conservatively: one patient with re-occlusion of a saphenous vein graft; one patient who had sustained a stroke seven days after the initial PCI and who sustained a re-infarction on day 30; and one patient with severe aortic arch dilation, who subsequently required unplanned urgent CABG after re-admission with unstable angina. One other patient had a re-infarction and died before further intervention could be performed. Two patients with TIMI flow grade 3 in the infarct-related vessel at initial angiography and who did not undergo rescue PCI underwent unplanned PCI for postinfarction angina (n = 1) or a significantly positive exercise treadmill test (n = 1). Thus, re-infarction occurred in 11 patients and subsequent revascularization in 10 patients in the rescue arm.

In the conservative arm, unscheduled emergency PCI was performed in 11 patients for re-infarction, in two patients who developed cardiogenic shock as a complication of the original STEMI, and in two patients with postinfarction unstable angina (both of whom had also sustained a re-infarction treated with second doses of fibrinolytic therapy). Emergency CABG and path repair were performed in one patient who developed a postinfarction ventricular septal defect, and urgent CABG was performed in one patient with postinfarction angina and severe triple-vessel coronary disease. Another 14 patients in the conservative arm required unscheduled PCI for postinfarction angina with ECG changes (n = 8) or a positive inpatient exercise treadmill test (n = 6). Another three patients in the conservative arm sustained a re-infarction but did not undergo revascularization: one patient treated with further fibrinolytic therapy; one who declined coronary angiography and was managed conservatively; and one who developed a ventricular septal defect after a re-infarction and who died without attempted revascularization. Thus, re-infarction occurred in 16 patients and subsequent revascularization in 31 patients in the conservative arm.

There was no significant difference in the incidence of re-infarction in the rescue angioplasty arm compared with the conservative arm (7.2% vs. 10.4%, p = 0.3, RD 3.2%, 95% CI –3.3 to 9.9; chi-square test), but there was a highly significant reduction in the incidence of subsequent revascularization (6.5% vs. 20.1%, p < 0.01, RD 13.6%, 95% CI 6.2 to 21.4; chi-square test).

The incidence of clinical heart failure requiring hospital treatment in the first 30 days was 24.2% in the rescue arm and 29.2% in the conservative arm (p = 0.3, RD 5.7%, 95% CI –4.3 to 15.6; chi-square test).

Stroke occurred in seven patients in the rescue angioplasty arm and one patient in the conservative arm (4.6% vs. 0.6%, p = 0.03, RD 3.9%, 95% CI 0.5 to 8.6; Fisher exact test). In the rescue arm, one stroke was fatal (a computed tomographic scan could not be performed, but the clinical presentation suggested intracranial hemorrhage). There were six thromboembolic strokes, as confirmed by computed tomography (n = 5) or magnetic resonance imaging (n = 1), two of which resulted in long term disability. One of the thromboembolic strokes occurred in a patient who did not undergo coronary angiography or attempted rescue PCI because of hematemesis, and one occurred in a patient with documented LV thrombus. Three strokes in the rescue arm occurred within the first 24 h and were more readily attributable to the procedure. For patients with anterior STEMI in the rescue arm, the incidence of stroke was 6.8%. The single stroke in the conservative arm was thromboembolic in nature, as judged by clinical presentation, but was not disabling. Eighteen patients in the conservative arm (11.7%) received additional fibrinolytic therapy as part of the management of initial failed fibrinolysis, but there were no episodes of intracranial hemorrhage in this small group.

The composite secondary end point occurred in 57 patients in the rescue angioplasty arm and 77 patients in the conservative arm (37.3% vs. 50.0%, p = 0.02, RD 12.7%, 95% CI 1.6 to 23.5; chi-square test).

Although not a prespecified analysis, the end points for patients with an anterior MI are shown in Table 4.

Survival and event-free survival are shown in Figures 2 and 3. At 30 days, the RWMI was 1.52 in the rescue arm and 1.35 in the rescue angioplasty arm (p = 0.06, RD 5.3%, 95% CI 0.1 to 6.8; chi-square test).
group and 1.58 in the conservative group, a difference of 
\(-0.06\) (95% CI \(-0.15\) to 0.03) (Table 5).

The only univariate predictor of all-cause mortality by 30
days was anterior MI (odds ratio [OR] 4.37, 95% CI 1.89 to
10.10). Anterior MI was also a univariate predictor of the
composite secondary end point (OR 2.33, 95% CI 1.47 to
3.71). Predictors of the composite secondary end point by
multivariate logistic regression analysis are shown in Table
6. Anterior MI, female gender, and conservative treatment
were predictors of reaching the composite secondary end
point. Multivariate predictors of major adverse cardiac
events (death, re-infarction, or subsequent revascularization)
were anterior MI and conservative treatment, although
this was not a prespecified analysis. Further analysis of the
rescue group demonstrated that implantation of one or more
coronary stents was not a predictor of freedom from the
composite secondary end point or from major adverse
cardiac events.

Analysis by actual treatment received, as opposed to the
intention-to-treat principle, showed results similar to those
in Table 3, with the exception of a statistically significant
reduction in the incidence of clinical heart failure in the
rescue group (19.8% vs. 30.6%, \(p = 0.046\), RD 10.8%, 95%
CI 0.2 to 20.3).

In both groups, the incidence of the primary and second-
ary composite end points was higher in patients with
persistent ST-segment elevation 6 h after initiation of
fibrinolytic therapy than in those with ST-segment resolu-
tion by \(\geq 50\%\) in the worst lead. There was a borderline
statistically significant difference between the proportion
of patients in the rescue arm and those in the conservative
arm developing ST-segment resolution by 6 h (61.4% vs. 50.5%,
\(p = 0.05\)). In the rescue arm, there was a highly statistically
significant difference in the 30-day mortality for patients
with persistent ST-segment elevation at 6 h, as compared
with those with ST-segment resolution (20.3% vs. 3.2%,
\(p = 0.001\)), and a similar reduction in the incidence of the
composite secondary end point (47.5% vs. to 30.9%, \(p =
0.04\)). These differences were less marked in the conserva-
tive group (Fig. 4).

Transfusion was required in 17 patients in the rescue
angioplasty arm, compared with two in the conservative arm
(11.1% vs. 1.3%, \(p < 0.001\), RD 9.8%, 95% CI 4.9 to 19.9).
Transfusion was reserved for those with a fall in hemoglobin
of \(\geq 2\) g/dl, and only if this took the total hemoglobin to
<10 g/dl. The majority of the patients in the trial receiving
transfusion did so for a hemoglobin fall much greater than
2 g/dl. In the rescue arm, transfusion was required for the

### Table 4. Thirty-Day End Points for Anterior Myocardial Infarction

<table>
<thead>
<tr>
<th></th>
<th>Conservative Arm (n = 62)</th>
<th>Rescue Angioplasty Arm (n = 74)</th>
<th>(p) Value</th>
<th>RD* (%) (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death (%)</td>
<td>12 (19.3)</td>
<td>12 (16.2)</td>
<td>0.6</td>
<td>3.1 (9.8 to 16.7)</td>
</tr>
<tr>
<td>Subsequent revascularization (%)</td>
<td>14 (22.6)</td>
<td>4 (5.4)</td>
<td>0.003</td>
<td>17.2 (6.0 to 29.8)</td>
</tr>
<tr>
<td>Stroke (%)</td>
<td>1 (1.6)</td>
<td>5 (6.8)</td>
<td>0.2</td>
<td>-5.1 (13.5 to 2.6)</td>
</tr>
<tr>
<td>Re-infarction (%)</td>
<td>8 (12.9)</td>
<td>4 (5.4)</td>
<td>0.1</td>
<td>7.5 (2.3 to 18.8)</td>
</tr>
<tr>
<td>Heart failure (%)</td>
<td>24 (38.7)</td>
<td>22 (29.7)</td>
<td>0.3</td>
<td>9.0 (7.0 to 24.8)</td>
</tr>
<tr>
<td>Composite secondary end point (%)</td>
<td>39 (62.9)</td>
<td>36 (48.6)</td>
<td>0.09</td>
<td>14.3 (2.6 to 30.2)</td>
</tr>
</tbody>
</table>

*Conservative–rescue angioplasty difference.
Abbreviations as in Table 3.

Figure 2. Thirty-day Kaplan-Meier survival curve. Dotted line = conservative arm; solid line = rescue angioplasty arm.
following: 12 patients for significant groin hematoma (3 of whom also had upper gastrointestinal bleeding); three patients for significant gastrointestinal hemorrhage (1 after CABG); one patient who required blood after urgent CABG; and one patient with a fall in hemoglobin from 15 to 8 g/dl, with no clear bleeding source. The mean hemoglobin value at which transfusion was initiated in the rescue arm was 8.6 g/dl (95% CI 8.0 to 9.1). None of the 12 patients with groin complications requiring transfusion had required intra-aortic balloon pump support. Gastrointestinal bleeding, ranging from a small hematemesis requiring no specific treatment to a duodenal ulcer requiring injection and transfusion, occurred in 11 patients in the rescue angioplasty arm, six of whom required transfusion, and nine patients in the conservative arm, two of whom required transfusion (7.2% vs. 5.8%, p = 0.6, RD 1.3%, 95% CI −4.5 to 7.3).

There was no difference in the length of hospital stay between the two arms. In the rescue arm, the median stay was seven days (range 2 to 46), and in the conservative arm, the median stay was seven days (range 2 to 23; p = 0.95).

**DISCUSSION**

Patients failing to respond to fibrinolytic therapy can be identified by persistent ST-segment elevation on the 12-lead ECG. Persistent ST-segment elevation as soon as 60 min after initiation of fibrinolytic therapy has been shown to be just as good at identifying high-risk patients as a later ECG (10,11). Repeat fibrinolysis and rescue angioplasty are probably the most commonly used strategies for failed reperfusion. In the limited number of patients in whom second fibrinolysis has been studied, a benefit has been confined to those who had failed to reach a systemic lytic state (3).

Most data on rescue angioplasty are from nonrandomized, observational studies. The range of 30-day or hospital mortality is large, from 2% to 12% (4,5,12–19). In the only previous reasonably sized, randomized study of rescue angioplasty versus conservative therapy for failed fibrinolysis, Ellis et al. (5) demonstrated a borderline statistically significant reduction in the incidence of death or severe heart failure among patients undergoing rescue angioplasty for angiographically demonstrated occlusion of the left anterior descending coronary artery after fibrinolytic therapy for a first anterior MI, as compared with those managed conservatively (6.4% vs. 16.6%, p = 0.05), although this was not a prespecified end point. A low 30-day mortality rate of 5.1% in the rescue arm was achieved, even without the widespread use of stents, glycoprotein IIb/IIIa inhibitors, and intra-aortic balloon pumps, the latter being beneficial in some patients during rescue angioplasty (20,21).

It is probable that Ellis enrolled lower risk patients than did MERLIN, on the basis of younger age (mean ± SD: 59 ± 11 years), shorter chest pain to presentation times (<6 h

**Table 5.** Regional Wall Motion Score at 30 Days

<table>
<thead>
<tr>
<th></th>
<th>Rescue Angioplasty Arm (n = 123)</th>
<th>Conservative Arm (n = 125)</th>
<th>Difference in Mean Values* (95% CI)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean RWMI</td>
<td>1.52</td>
<td>1.58</td>
<td>−0.06 (−0.15 to 0.03)</td>
<td>NS</td>
</tr>
</tbody>
</table>

*Rescue angioplasty–conservative difference. Regional wall motion score analysis at 30 days was not performed in 27 patients (12 in the conservative arm and 15 in the rescue arm) because either the patient declined to attend for the study or the endocardial definition was inadequate.

CI = confidence interval; NS = not significant; RWMI = regional wall motion index.
required for trial entry with discretion to extend to 8 h), shorter presentation to angioplasty times (mean 4.5 ± 1.9 h), exclusion of patients with previous MI or left main stem disease, and overall lower early rates of death (7.3% vs. 17.6%) and heart failure (4% vs. 34%), compared with the MERLIN trial’s anterior MI subgroup. In addition, the recruitment rate of less than three patients per center per year suggests a highly selective approach to patient enrolment. Nonetheless, demonstration of a benefit from a rescue angioplasty strategy in a low-risk group might be expected to translate into more benefit in a higher risk group. It is possible that higher risk patients might have been enrolled into MERLIN by only considering those patients with persistent chest pain. However, we do not believe the presence or absence of chest pain is particularly helpful in making the diagnosis of failed fibrinolysis, and the MERLIN results support this. At the time of coronary angiography, TIMI flow in the infarct-related vessel was grade <3 in 53% of those without chest pain and grade 3 in 38% of those still in pain.

We have demonstrated that rescue angioplasty has a high success rate in terms of restoring normal anterograde flow in an occluded or partially occluded vessel. Successful catheter laboratory outcomes are also achieved in patients with TIMI flow grade 3 at initial angiography, but who have a critical coronary artery stenosis. Patients offered urgent rescue angioplasty have a significant reduction in the 30-day incidence of the combined end point of death, re-infarction, stroke, subsequent revascularization, or heart failure, but this advantage is driven almost exclusively by a highly significant reduction in the requirement for subsequent revascularization. At least part of the explanation for the lower rate of subsequent revascularization in the rescue angioplasty arm is simply that revascularization occurs at an earlier point in the patient’s hospital course.

We have not demonstrated a mortality benefit by 30 days with rescue angioplasty compared with medical treatment. The mortality in the rescue angioplasty arm was higher than anticipated, particularly in patients who achieved normal anterograde flow after rescue angioplasty. In our previous experience, patients with TIMI flow grade 3 upon leaving the catheterization laboratory, irrespective of whether angioplasty had been performed, had a 30-day mortality rate of 6.9% (22). In MERLIN, the equivalent figure was 9.2%. The higher than anticipated mortality in MERLIN may partly be related to failure to achieve reperfusion at the microvascular level, despite restoration of normal anterograde flow in the epicardial vessel. Although 85% of patients left the catheterization laboratory with normal flow in the infarct-related vessel, only 61% had ≥50% ST-segment resolution within 6 h of the initiation of fibrinolytic therapy. The use of adjuncts such as distal protection devices during rescue angioplasty might result in more patients achieving optimal myocardial perfusion. It is noteworthy that the

<table>
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<tr>
<th>Predictor</th>
<th>OR</th>
<th>95% CI</th>
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<tbody>
<tr>
<td>Group</td>
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<tr>
<td>Conservative</td>
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<tr>
<td>Angioplasty</td>
<td>0.51</td>
<td>0.32 to 0.83</td>
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<tr>
<td>Gender</td>
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<tr>
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<tr>
<td>Yes</td>
<td>2.80</td>
<td>1.71 to 4.57</td>
</tr>
</tbody>
</table>

CI = confidence interval; MI = myocardial infarction; OR = odds ratio.

Figure 4. Thirty-day mortality according to ST-segment reduction 6 h after initiation of fibrinolytic therapy. PCI = percutaneous coronary intervention.
mortality of those with persistent ST-segment elevation after rescue PCI (20.3%) was higher than the mortality of those with persistent ST-segment elevation in the conservative arm (15.8%), suggesting the possibility that a failed rescue angioplasty may actually be harmful to patients.

The bleeding rate in the rescue angioplasty arm was high, with a requirement for transfusion in 11%. In our view, all the transfusions administered were clinically indicated, with no bias toward either group. The incidence of gastrointestinal bleeding was similar in the two groups, but unsurprisingly, the rate of access complications was higher in the rescue group. The 11% rate is comparable to the major bleeding rate of 9.8% observed by Scheller et al. (23) in patients undergoing PCI at a mean time of 3.5 h after receiving fibrinolytic treatment with the fibrin-specific agent reteteplase for STEMI, the transfusion rate of 9% observed in the Strategies for Patency Enhancement in the Emergency Department (SPEED, or Global Use of Strategies To Open Occluded coronary arteries [GUSTO-4 Pilot]) trial for patients with STEMI undergoing PCI at a mean time of 63 min after reperfusion therapy began (24), and the transfusion rate of 8.5% observed in the Plasminogen activator Angioplasty Compatibility Trial (PACT) rt-PA arm (25). We do not believe that transfusion itself results in an adverse outcome, and rates of this magnitude have recently been described as “low” (26). However, in contrast to these three trials, in which the use of PCI soon after reperfusion therapy did not result in transfusion rates significantly different from those seen in the comparator arms, the transfusion rate in the rescue arm of MERLIN was significantly higher than that in the conservative arm. One explanation for this is the long half-life of streptokinase, compared with the fibrin-specific lytic agents. However, the transfusion rate was much lower than that observed in historical trials of PCI after streptokinase (27).

The explanation for the number of strokes in the rescue arm is uncertain. To our knowledge, this has not been previously observed. However, the 95% CI around the absolute RD is large (and includes a 0.5% absolute RD). It is therefore possible that the observed difference is partly due to chance. In addition, one stroke in the rescue arm occurred in a patient who did not undergo coronary angiography or rescue PCI but is included in the analysis on an intention-to-treat basis. We have speculated that the combination of antiplatelet agents administered so soon after fibrinolysis may be responsible for thromboembolic events from LV thrombus (1 stroke occurred in a patient with documented LV thrombus), but we have no proof for this theory. We cannot exclude cerebral hemorrhage as a cause for events in those patients who did not undergo computed tomographic scanning, but there is no evidence to suggest that these events were due to this mechanism.

The benefits of rescue angioplasty observed in this trial are small, the principle effect being a reduced requirement for subsequent revascularization. Although some of these subsequent revascularizations are “expected” (for example, after a positive exercise test), the vast majority of subsequent revascularizations were performed for re-infarction or ongoing unstable ischemia. This benefit of rescue angioplasty is achieved at the expense of more strokes and more transfusions and with no early preservation of LV systolic function. Pending results of other ongoing trials of rescue angioplasty, with particular reference to the pharmacologic treatment and technical aspects of the rescue angioplasty procedure, it is currently reasonable to pursue a policy of watchful waiting in patients with failed fibrinolysis. However, our results are perhaps less applicable to those receiving initial therapy with fibrin-specific lytic agents and do not preclude the selective use of rescue angioplasty for those with ongoing chest pain or extensive ST-segment changes, nor are they relevant in the context of immediate or facilitated angioplasty. Rescue angioplasty might also be more appropriate offered later after fibrinolysis, but this requires further study.

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APPENDIX

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