Early invasive versus conservative treatment in patients with failed fibrinolysis—no late survival benefit: The final analysis of the Middlesbrough Early Revascularisation to Limit Infarction (MERLIN) randomized trial

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Background Early (30 days) and midterm (6 months) clinical outcomes in trials comparing rescue angioplasty (rescue percutaneous coronary intervention [rPCI]) with conservative treatment of failed fibrinolysis complicating ST-segment elevation myocardial infarction have shown variable results. Whether early rPCI confers late (up to 3 years) clinical benefits is not known.

Methods The MERLIN trial compared rPCI and a conservative strategy in patients with failed fibrinolysis complicating ST-segment elevation myocardial infarction. Three hundred seven patients with electrocardiographic evidence of failure to reperfuse at 60 minutes were included. Patients in cardiogenic shock were excluded. Thirty-day and 1-year results have been reported. Results of 3 years of follow-up are presented.

Results Three-year mortality in the conservative arm and rPCI, respectively, was 16.9% versus 17.6% ($P = .9$, relative difference [RD] −0.8, 95% CI [−9.3 to 7.8]). Death rates were similar (3.9% vs 3.2%) between 1- and 3-year follow-up, respectively. The incidence of the composite secondary end point of death, reinfarction, stroke, unplanned revascularization, or heart failure was significantly higher in the conservative arm (64.3% vs 49%, $P = .01$, RD 15.3, 95% CI [4.2-26]). There was no significant difference in the rate of reinfarction (0.7% vs 0.7%) or heart failure (1.3% vs 2.7%) between 1 and 3 years between the conservative and rPCI arms, respectively. The incidence of subsequent unplanned revascularization at 3 years was significantly higher in the conservative arm (33.8% vs 14.4%, $P < .01$, RD 19.4, 95% CI [10-28.7]), most of which occurred within 1 year; the rates between 1 and 3 years were 3.9% in the conservative arm versus 2% in the rPCI arm. There was a trend toward fewer strokes in the conservative arm at 3 years (conservative arm 2.6% vs rPCI 6.5%, $P = .1$, RD −3.9%, 95% CI [−9.4 to 0.8]), with similar stroke rates (1.3% vs 1.3%) between 1- and 3-year follow-up.

Conclusions Rescue angioplasty did not confer a late survival advantage at 3 years. The composite end point occurred less often in the rPCI arm mainly because of fewer unplanned revascularization procedures in the early phase of follow-up. The highest risk of clinical events in patients with failed reperfusion is in the first year, beyond which the rate of clinical events is low. (Am Heart J 2007;153:763-71.)

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Despite the recognized advantages of primary percutaneous coronary intervention (PCI) compared with hospital delivery of fibrinolysis for the treatment of acute ST-elevation myocardial infarction (STEMI), fibrinolytic treatment will remain a treatment option for STEMI for some years to come because of logistic limitations in delivering primary PCI to an entire population.[1] Inhospital fibrinolysis fails to restore full patency of the infarct-related arteries in up to 54% of patients.[2] Although higher patency rates might be achieved with prehospital delivery of treatment,[3] many patients will not benefit because of failure to restore normal (Thrombolysis in Myocardial Infarction [TIMI] 3) flow. Although the TIMI 3 flow rates at angiography performed 48 to 192 hours after the start of the study medication in the Clopidogrel as Adjunctive Reperfusion Therapy (CLARITY)–TIMI 28 study was 67.8% in the clopidogrel arm, the importance of adjunctive clopidogrel in improving very early patency rates is unknown.[4] The management of patients with failed fibrinolysis has been the subject of a number of recent studies. In both the Middlesbrough Early Revascularisation to Limit Infarction (MERLIN) and the REscue Angioplasty versus Conservative therapy or repeat Thrombolysis (REACT) trials, patients with failed fibrinolysis had fewer clinical end points at 30 days and 6 months with a strategy of early angiography with a view to performing rescue angioplasty (rescue PCI [rPCI]) than patients treated with the comparator strategies.[5,6] Although there are important differences in both the protocols and the results of these 2 studies, neither study was powered to demonstrate an early mortality benefit.

Early vessel patency after infarction has been shown to have late as well as short-term benefits.[7] Revascularization studies in other clinical subsets have often required longer-term follow-up to demonstrate late clinical benefits that more than offset any early hazard of intervention.[8,9] The purpose of this present study was to assess the long-term clinical outcomes of patients with acute MI who underwent early intervention for failed fibrinolysis compared with those treated conservatively. We also assessed the long-term clinical outcomes on patients who had ST resolution compared with those who had no ST resolution 6 hours after initiation of fibrinolytic therapy in both groups and patients who had stents implanted compared with those who had no stents implanted in the rPCI group.

Methods

The protocol of this prospective, randomized study, summarized here, has been previously published.[5,10]

Population

Between February 1999 and June 2002, 307 patients with STEMI and evidence of failure to respond to the administration of a fibrinolytic agent from 3 participating centers were randomized to either rPCI (n = 153) or conservative treatment (n = 154). Patients with electrocardiographic (ECG) evidence of failure to reperfuse as determined by failure of ST-segment elevation in the worst lead to fall by ≥50% and no idioventricular rhythm on a 12-lead ECG at 60 minutes from the start of fibrinolysis were included. Patients randomized to the rPCI arm were transferred urgently to the cardiac catheterization laboratory at The James Cook University Hospital. Coronary angiography was performed from femoral, radial, or brachial arterial access points; and rPCI was attempted if considered appropriate. Patients in the conservative arm received standard medical treatment after the administration of a fibrinolytic agent. Early crossover to the rPCI arm was not allowed except in the case of development of cardiogenic shock. Randomization occurred at 60 minutes after fibrinolysis to ensure that most patients underwent angiography as close to 2 hours as possible (including patients being transferred in from other centers).

Exclusion criteria included cardiogenic shock, confounding features on the prefibrinolysis ECG preventing analysis of ST-segment reduction, reinfarction in the same ECG territory within 2 months of an original infarction, absent femoral pulses, pregnancy, and presence of significant coexisting pathology likely to affect prognosis during the follow-up period. All patients gave written informed consent.

Three-year clinical follow-up

It was predetermined that the primary end point of all-cause mortality and the components of the secondary end point would be reassessed annually up to 3 years from randomization. The information was obtained by follow-up clinical visits, by telephone interview, via the referring physician, or from the patient's general practitioner. Follow-up data were complete for all participating patients.

Clinical end points

The primary end point was all-cause mortality at 30 days. The secondary end points included the composite end point of death, reinfarction, stroke, clinically driven unplanned revascularization, or heart failure at 30 days as well as the individual end points of the composite, at yearly intervals for 3 years. *Reinfarction* was defined as a further episode of ischemic chest pain after recovery from the initial event, associated with typical ST-segment re-elevation on the ECG and lasting >30 minutes despite treatment with opiate and nitrate therapy. In addition, we recorded patients admitted with *non-STEMI*, defined as clinical history of ischemic-type chest pain lasting for >20 minutes, changes in serial ECG tracings, and troponin T >0.1 ng/mL. *Stroke* was defined as any new neurological deficit lasting >24 hours; computed tomography was performed where possible. *Heart failure* was defined by the requirement for diuretic treatment in the presence of typical characteristics on chest radiography, or auscultatory crackles extending at least one third of the way up the lung fields without a history of chronic pulmonary disease, or a third heart sound with persistent tachycardia. Any catheter-based or surgical intervention in the conservative arm and any additional revascularization procedure in the rPCI arm that was not planned after the initial coronary angiogram were defined as *unplanned revascularization*.

Table I. Baseline characteristics of the MERLIN patients

Characteristics	Treatment arm		P
	Conservative (n = 154)	rPCI (n = 153)	
Age (y)	62.7 ± 10.9	63 ± 11.2	.71
Male sex (%)	114 (74)	108 (71)	.5
History of hypertension (%)	47 (31)	62 (41)	.07
History of diabetes (%)	23 (15)	18 (12)	.41
Insulin treatment (%)	7 (4.5)	4 (2.6)	.36
Known hypercholesterolemia (%)	24 (16)	29 (19)	.44
Total cholesterol on admission (mmol/L)	5.54 ± 1.17	5.82 ± 1.32	.05
Blood glucose on admission (mmol/L)	8.9 ± 3.0	9 ± 3.3	.88
Current smoker (%)	57 (37)	64 (42)	.39
Ex-smoker (%)	51 (33)	45 (29)	.48
Previous MI (%)	20 (13)	17 (11)	.61
Anterior MI (%)	62 (40)	74 (48)	.15
Pain to lysis (min)	170 ± 96	180 ± 120	.73
Lysis to laboratory time (min)	NA	146 ± 37	NA
Pain to laboratory time (min)	NA	327 ± 121	NA

Data are presented as the mean value ± SD or number (%) of patients. *NA*, Not applicable.

Statistical analysis

All end points were analyzed on an intention-to-treat basis. Groups were statistically compared by χ^2 analysis for the categorical variables with calculation of risk reduction and 95% CI. The Fisher exact test was used where expected values were <5. Survival and survival without occurrence of one (or more) of the individual end points were plotted on Kaplan-Meier curves. The statistical package used was StatsDirect Statistical Software (StatsDirect, Sale, UK).

Results

Table I shows the baseline characteristics of the MERLIN trial's randomized patients. The randomized groups were similar with respect to their demographic characteristics, except for a slightly higher mean admission cholesterol level in the rescue angioplasty group. Nearly 70% of all eligible patients at the revascularization center were enrolled in the trial, with most nonrandomization among eligible patients being due to failure to obtain informed consent. The mean time from the start of fibrinolysis to angiography was 146 ± 37 minutes.

Clinical results to 1 year have been published.[5,10] Rescue angioplasty did not confer a survival advantage, was associated with a lower event-free survival but more strokes and more transfusions, and did not result in preservation of left ventricular function at 30 days.

Three-year results

Follow-up on patients was 100% complete. Drug therapies at enrollment and follow-up at 3 years are shown in Table II. At 3 years, there were 26 and 27 deaths in the conservative arm and rPCI arm, respectively (16.9% vs 17.6%, $P = .9$, risk difference [RD] −0.8, 95% CI [−9.3 to 7.8]). The incidence of all-cause mortality was not significantly different between the groups. Of the 53 deaths, 32 (60%) occurred within 30 days of randomization and another 10 (19%) by 1 year. The 3-year all-cause mortality for those who actually underwent PCI (n = 101) was similar to those who had conservative management (conservative arm 16.9% vs PCI group 17.8%, $P = .9$). We have included the TIMI flow rates before and after PCI with outcomes in Table III.

Table II. Medications at discharge and 3 years

	Conservative arm (n = 154)	rPCI arm (n = 153)
	n (%)	n (%)
At discharge		
Aspirin	135/139 (98)	136/139 (98)
β-Blockers	114/139 (82)	110/139 (80)
Lipid-lowering medication	101/139 (73)	98/139 (71)
ACE inhibitor	97/139 (70)	109/139 (78)
3 years*		
Aspirin	115/118 (98)	119/119 (100)
β-Blockers†	94/108 (87)	89/108 (82)
Lipid-lowering medication	98/118 (83)	105/119 (88)
ACE inhibitor	91/118 (77)	103/119 (87)

*Alive and information available patients.
†Excluding patients with contraindication to β-blockers.

There was no significant difference in reinfarction (whether STEMI or non-STEMI) (Table IV) nor in clinical heart failure rates (conservative arm 32.5% vs rPCI arm 28.8%, $P = .5$, RD 3.7, 95% CI [−6.6 to 14]). Of 40 reinfarction events occurring within the 3 years of follow-up, 17.5% were fatal, although all the fatal events occurred within 6 days of the index infarction. There

Table III. TIMI flow grades with 3-year clinical outcomes in the rPCI group

	Total		Mortality		Combined end points	
	n	%	n	%	n	%
Before PCI						
TIMI 0	65	42	11	17	28	43
TIMI 1	8	5	3	38	5	63
TIMI 2	15	10	6	40	9	60
TIMI 3	61	40	6	10	30	49
Not assessable	4	3	1	25	3	75
Mortality						
TIMI 0/1 vs 2/3: 19% vs 16%, *P* = .59						
TIMI <2 vs 3: 23% vs 9.8%, *P* = .04*						
Combined end points						
TIMI 0/1 vs 2/3: 45% vs 51%, *P* = .46						
TIMI <2 vs 3: 48% vs 49%, *P* = .86						
After PCI						
TIMI 0	6	4	2	33	3	50
TIMI 1	3	2	2	67	2	67
TIMI 2	10	6.5	5	50	7	70
TIMI 3	130	85	17	13	60	46
Not assessable	4	2.6	1	25	3	75
Mortality						
TIMI 0/1 vs 2/3: 44% vs 8.6%, *P* = .06						
TIMI <2 vs 3: 47% vs 13%, *P* = .001*						
Combined end points						
TIMI 0/1 vs 2/3: 56% vs 48%, *P* = .67						
TIMI <2 vs 3: 63% vs 46%, *P* = .17						

*$P < .05$.

Table IV. Total number of patients with major clinical events from randomization to 3 years

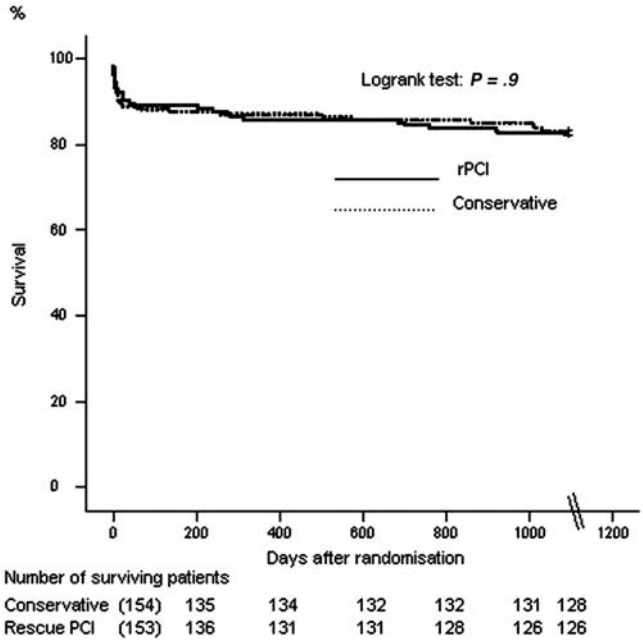
	Conservative (n = 154)		rPCI (n = 153)		RD	
Events	**n**	**%**	**n**	**%**	**(95% CI)**	***P***
Death	26	16.9	27	17.6	−0.8 (−9.3 to 7.8)	.9
Reinfarction*	23	15.0	17	11.1	3.8 (−3.8 to 11.6)	.3
Reinfarction†	24	16	22	14	1.2 (−7 to 9)	.8
Stroke	4	2.6	10	6.5	−3.9 (−9.4 to 0.8)	.1
Unplanned revascularization	52	33.8	22	14.4	19.4 (10 to 28.7)	<.01
Heart failure	50	32.5	44	28.8	3.7 (−6.6 to 14)	.5
Composite secondary end point‡	99	64.3	75	49.0	15.3 (4.2 to 26)	.01
Composite secondary end point§	99	64.3	78	51	13.3 (2.2 to 24.1)	.02
Composite secondary end point‖	75	48.7	72	47.1	1.6 (−9.5 to 13)	.77

Risk difference (conservative − rPCI).
*Includes only STEMI.
†Includes both STEMI and non-STEMI.
‡Death, reinfarction (only STEMI), stroke, unplanned revascularization, or heart failure.
§Death, reinfarction (both STEMI and non-STEMI), stroke, unplanned revascularization, or heart failure.
‖Death, reinfarction, stroke, or heart failure.

was a tendency toward fewer strokes in the conservative arm at 3 years (conservative arm 2.6% vs rPCI arm 6.5%, *P* = .1, RD −3.9, 95% CI [−9.4 to 0.8]); but this reflects a significant difference in stroke rates within the first 30 days, with equal numbers of strokes occurring in the 2 groups subsequently.

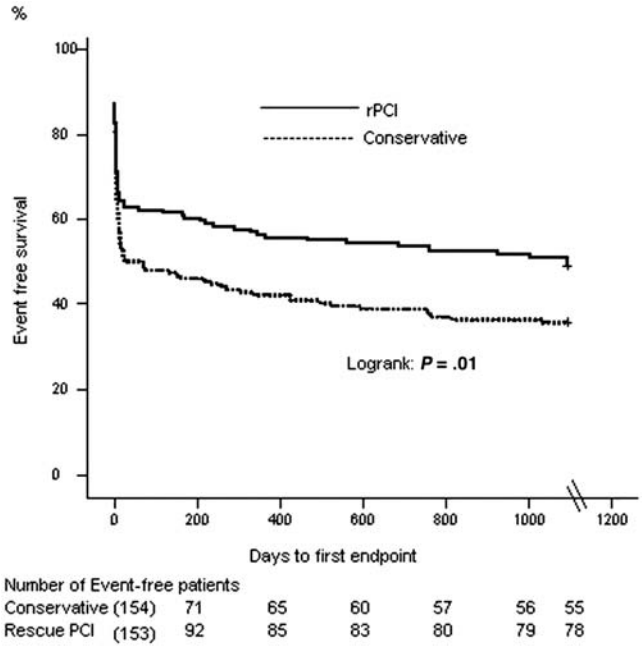
The incidence of the composite secondary end point was significantly higher in the conservative arm (conservative arm 64.3% vs rPCI arm 49%, *P* = .01, RD 15.3, 95% CI [4.2-26]). This was driven almost exclusively by a significantly higher incidence of subsequent unplanned revascularization in the conservative arm (conservative

Figure 1



Three-year Kaplan-Meier survival curve.

Figure 2



Three-year event-free Kaplan-Meier survival curve.

arm 33.8% vs rPCI arm 14.4%, $P < .01$, RD 19.4, 95% CI [10-28.7]). Figure 1 shows survival and Figure 2 shows event-free survival at 3 years. Most unplanned revascularization procedures in the conservative arm were carried out in the first 30 days after initial presentation (n = 31, 60%), with a further 15 patients in the conservative arm (10.9% of those alive at 30 days) and 9 in the rPCI arm (6.5% of those alive at 30 days) undergoing unplanned revascularization between 30 days and 1 year (mostly in the setting of an acute coronary syndrome) (Table V). Between 1 and 3 years, a further 6 patients in the conservative arm underwent unplanned revascularization, mostly for recurrent angina (n = 6; 4 patients had PCI and 2 patients had coronary artery bypass graft). In the rPCI arm, 3 patients had unplanned revascularization between 1 and 3 years by PCI. Two of these patients underwent unplanned revascularization after emergency readmission with an acute coronary syndrome and the third one had PCI for ongoing angina. Only one patient in the rPCI had a planned staged procedure after the initial treatment.

In both groups, the incidence of the primary and secondary composite end points was higher in patients with persistent ST-segment elevation 6 hours after initiation of fibrinolytic therapy than in those with ST-segment resolution by ≥50% in the worst lead (Figure 3). 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 hours (61.4% vs 50.5%, $P = .05$). In the rescue arm, there was a highly statistically significant difference in the 30-day (20.3% vs 3.2%, $P = .001$) and 3-year mortality (30.5% vs 9.6%, $P < .01$) for patients with persistent ST-segment elevation at 6 hours, as compared with those with no or <50% ST-segment resolution. A similar reduction in the incidence of the composite secondary end point (47.5% vs 30.9%, $P = .04$) was seen at 30 days, but it was not significant at 3 years. There were no statistically significant differences in the conservative group (Figure 3).

Early differences in heart failure at 30 days did not translate into mortality benefit at 3 years. At 3 years, there was no difference in the all-cause mortality between the conservative arm and rPCI arm in those patients with heart failure (conservative arm 32% vs rPCI arm 34.1%, $P = .83$) and in those with no heart failure (conservative arm 11.5% vs rPCI arm 9.2%, $P = .57$). There was however a significantly increased incidence of all-cause mortality in patients who had heart failure (33%) compared with those did not have heart failure (10.3%) ($P < .0001$) despite the appropriate treatment with angiotensin-converting enzyme (ACE)–inhibitors and β-blockers (Table II).

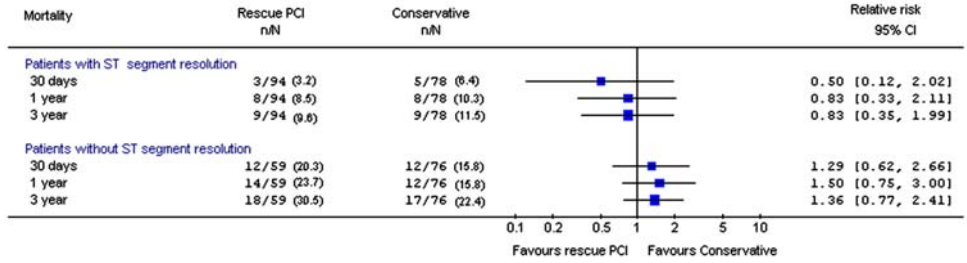
In the patients who had anterior MI, there was no significant difference in the primary (rPCI 28% vs conservative 27%, $P = .9$) and secondary end points

Table V. Events at 30 days, 1 year, and 3 years

	30 d		30 d to 1 y		1-3 y	
	CM	rPCI	CM	rPCI	CM	rPCI
Events	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Death	17 (11.0%)	15 (9.8%)	3 (2.2%)	7 (5%)	6 (3.9%)	5 (3.2%)
Reinfarction	16 (10.4%)	11 (7.2%)	6 (4.4%)	5 (3.6%)	1 (0.7%)	1 (0.7%)
Stroke	1 (0.6%)	7 (4.6%)	1 (0.7%)	1 (0.7%)	2 (1.3%)	2 (1.3%)
Revascularization*	31 (20%)	10 (6.5%)	15 (11%)	9 (6.5%)	6 (3.9%)	3 (2%)
Heart failure	46 (29.9%)	37 (24%)	2 (1.5%)	3 (2.2%)	2 (1.3%)	4 (2.7%)

CM, Conservative management.
*Unplanned revascularization.

Figure 3



Relative risks (95% CI) for primary end point (mortality) at 3 different periods (30 days, 1 year, and 3 years) according to ST-segment resolution (≥50%) 6 hours after initiation of fibrinolytic therapy.

(rPCI 59% vs conservative 71%, $P = .2$) at 3 years between both groups and no difference in event rates occurring between 30 days and 3 years. For this subgroup, subsequent unplanned revascularization occurred less frequently in the rPCI group compared with the conservatively treated patients with anterior MI group (rPCI 11% vs conservative 35%, $P < .01$).

Discussion

This is the first report on 3-year outcomes of patients with failed fibrinolysis complicating STEMI randomized to treatment by urgent revascularization or an initial conservative strategy. Previously, most information concerning outcomes after rescue angioplasty has come from nonrandomized, observational studies that provided only short- or medium-term data. Up until now, the few randomized studies have, variously, provided outcomes to 6 months or a year after randomization.

In this analysis of the 3-year follow-up of the MERLIN trial patients, 2 major points emerge. First, events rates in survivors beyond 1 year of follow-up are low (we have previously described the events occurring within the first year). Secondly, we have failed to show any late benefit in the cohort of patients randomized to a strategy of angiography with a view to immediate rPCI.

In the Randomised Evaluation of Salvage angioplasty with Combined Utilization of End points (RESCUE I) trial, Ellis et al reported a nonsignificant trend toward reduction in the combined incidence of death and congestive heart failure (6.4 vs 16.6%, $P = .055$) with rescue angioplasty compared with conventional medical treatment in patients with an anterior MI treated within 8 hours of symptom onset, although this was not a prespecified end point.[11] The pooled data on 1-year follow-up for patients randomly assigned in the RESCUE I and the smaller Canadian study by Belenkie et al suggested a survival advantage with rPCI.[12,13] However, these studies included a small number of patients and excluded high-risk patients (not only cardiogenic shock but also those with a previous MI); and in RESCUE I, patients were only randomized after angiography revealed the presence of an occluded infarct-related artery. RESCUE II was a small study conducted between 1995 and 1998. It showed that the 14 rPCI patients seemed to have a worse 30-day outcome compared with

Table VI. Events at 30 days to 6 months in the MERLIN and REACT trials

	MERLIN		REACT	
	CM (n = 154)	rPCI (n =153)	CM (n =141)	rPCI (n =144)
Events	n (%)	n (%)	n (%)	n (%)
Death				
0 to 30 d	17 (11)	15 (9.8)	15 (11)	7 (4.9)
30 d to 6 m	2 (1.3)	2 (1.3)	3 (2)	2 (1.4)
Reinfarction				
0 to 30 d	16 (10)	11 (7.2)	9 (6.4)	1 (0.7)
30 d to 6 m	4 (2.6)	1 (0.7)	3 (2)	2 (1.4)
Stroke				
0 to 30 d	1 (0.6)	7 (4.6)	1 (0.7)	2 (1.4)
30 d to 6 m	1 (0.7)	0	0	1 (0.7)
Unplanned revascularization*				
0 to 30 d	31 (20)	15 (9.8)	NA	NA
30 d to 6 m	9 (5.8)	4 (2.6)	NA	NA
Heart failure*				
0 to 30 d	46 (30)	37 (24)	10 (7.1)	6 (4.2)
30 d to 6 m	2 (1.3)	2 (1.3)	1 (0.7)	1 (0.7)

CM, Conservative management.
*Different definitions of heart failure were used in both trials (*heart failure* was defined as severe heart failure [New York Heart Association functional class III or IV] in the REACT trial; and in the MERLIN trial, it was requirement of diuretics by clinical and x-ray features of heart failure).

those 15 patients treated conservatively (death 7.1 vs 0%). One-year outcome was no different (7.1% vs 6.7%, respectively), although reintervention was less in the rPCI group (21.4% vs 46.7%, respectively).[12] Neither of these studies gave an answer to the clinical dilemma of whether patients with failed fibrinolysis (defined electrocardiographically) should be transferred for coronary angiography and revascularization as necessary.

In the MERLIN trial, a strategy of angiography and early rPCI was not associated with a survival advantage at 3 years when compared with the conservatively managed patients, consistent with the 30-day results. These patients did well on follow-up between 30 days and 3 years. We have proposed a number of reasons for a lower than anticipated mortality in the conservative arm. Firstly, using a protocol based on a 60-minute ECG after the start of fibrinolysis, relatively low-risk patients who would have reperfused in the next 30 to 60 minutes would have been included.[14] Secondly, although this was dependent on the responsible physician, patients in the conservative arm underwent relatively rigorous postinfarction risk stratification, contributing to the 20% rate of unplanned revascularization within 30 days. Thirdly, the inclusion of lower-risk inferior MIs could have also lowered the anticipated mortality rate in the conservative arm. It is of note that mortality after 30 days in both arms was low, of the order of 2% to 3% per annum; reinfarction rates were low. This possibly reflects optimal secondary preventive measures. There was no difference in the incidence of strokes between 1 and 3 years in both groups. The reason for the high incidence of strokes at 30 days in the rPCI arm is uncertain, but was not clearly related to hemorrhagic strokes.

The MERLIN trial did not mandate PCI for all patients in the rPCI arm, but rather it was a trial of angiographically driven treatment. In a previous study, we had demonstrated that the early clinical event rates for those with a residual stenosis of <75% on an angiogram 2 hours after the onset of fibrinolysis were very low.[15] In the MERLIN trial, we have shown that rPCI has a high success rate in terms of restoring normal flow in occluded or partially occluded arteries and also in treating patients with TIMI 3 flow with a critical stenosis. The results of our previous study might not be applicable when performing angiography at times other than 2 hours after the start of fibrinolysis; and the default perhaps should be to perform stenting where possible, even if there is only a moderate residual stenosis, to help "stabilize" the plaque. It should be noted that early studies of immediate PCI after fibrinolysis showed that PCI could be potentially hazardous in patients whose vessels were patent. Although PCI is now performed with powerful antiplatelet strategies and stenting, there may be bleeding hazards and other downsides.[16] The benefits of intervening therefore may still be more beneficial in patients with persistently occluded vessels than in those with patent vessels at the time of angiography. This has been the approach of Steg et al, who routinely perform angiography 90 minutes after fibrinolysis and perform rescue angioplasty for those with TIMI 0/1 flow but treat those with TIMI 3 flow conservatively.[17] To answer these points, it would be necessary to randomize all patients to

either intervention or conservative management after angiography, not just those with occluded vessels (as in RESCUE I). It is unlikely that such a trial will be performed.

In the setting of primary angioplasty, stenting provides benefit by reducing reocclusion and restenosis, whereas the use of glycoprotein IIb/IIIa inhibitors is thought to reduce thrombotic complications and improve distal tissue perfusion.[18] It is possible that a higher rate of stenting and glycoprotein IIb/IIIa inhibitor use in our rPCI arm might have improved the results[19,20]; but any potential benefit of the latter has to be weighed against the risks of hemorrhage, especially when streptokinase is used as the fibrinolytic agent.[21] In the recent ASSENT-4 trial, in addition to the higher 30-day mortality, the inhospital total stroke rates (1.8% [15 of 829] vs 0, $P < .0001$) and bleeding complications were higher in the tenecteplase and PCI arm compared with those in the PCI-alone arm.[16] Thus, even when using a fibrin-specific lytic agent such as tenecteplase, PCI in combination with a lytic therapy is associated with an increased incidence of stroke and bleeding.

Although a higher rate of intervention in the rescue angioplasty arm might have had a small impact on the early mortality figures (and would almost certainly have had an even greater impact on the composite end point than was seen), we do not believe that this would have had a major impact on the incidence of late outcomes, given that these were so low in both groups. We cannot exclude the possibility of late benefit, however, given that a higher rate of early intervention might have reduced the incidence of reinfarction and that the prevention of reinfarction has been shown to reduce mortality.[22,23] In the rPCI arm, reinfarction rates were higher in the MERLIN trial compared with those seen in the recent REACT trial (7.8% vs 2.1%), possibly because of the lower rate of stenting (50.3% vs 68.5%) and less use of glycoprotein IIb/IIIa inhibitors (3.3% vs 43.4%). Even in the REACT trial though, there was clearly some reluctance in using these agents as a default strategy in rPCI. Stenting during primary angioplasty has been shown to have more of an impact on restenosis and reinfarction than on reducing mortality, and it is unlikely that the difference in mortality rates in the rPCI arms of these 2 trials (which were not statistically significant from those in the conservative arms in either study) would have been fully explained by differences in stenting and glycoprotein IIb/IIIa inhibitor use. Although the methodologies of the MERLIN and REACT trials differ significantly, there were few clinical events after 30 days in both trials (Table VI).[6,24]

The combined available data from randomized trials on rPCI shows a reduction in 30-day mortality from 11% in the conservative group (n = 395) to 7% in the rPCI group (n = 405).[25] To demonstrate a 4% mortality difference in a definitive trial (power of 80%), 803 patients would be required in each arm with a 2-sided α value of .05 (1074 in each arm for 90% power). A multicenter trial of this size would be feasible, albeit difficult, and perhaps easier to recruit to than was the case with the REACT trial, which incorporated a third arm (of repeat fibrinolysis). This relates to randomization between an invasive as opposed to a conservative approach based on ECG criteria.

Limitations

The limitations of the early phase of the MERLIN trial have been fully discussed in the original publications and ensuing correspondence.[26,27] This follow-up to 3 years was prespecified in the protocol to determine whether any benefits of rescue angioplasty occurred late. Although our original power calculation was in hindsight optimistic, the results in both MERLIN and REACT are in favor of rPCI in terms of the composite end points. There has been criticism in the use of unplanned revascularization in our composite end point; but we would argue that unplanned revascularization is most often used for patients with unstable symptoms, reinfarction, or strongly positive perfusion tests, and as such is likely to have an impact on overall outcome. Using a composite including mortality, reinfarction, heart failure, and stroke (albeit using a different definition of heart failure than that used in REACT), we have shown no statistically significant benefit with rPCI compared with conservative management both at 30 days (conservative arm 40.9% vs rPCI arm 36.6%, $P = .44$; or vs those actually undergoing rPCI [n = 101] 32.7%, $P = .18$) and at 3 years (conservative arm 48.7% vs rPCI arm 47.1%, $P = .77$; or vs those actually undergoing rPCI 43.6%, $P = .42$). We did not perform 3-year echocardiography on the survivors.

Conclusions

In conclusion, we have not shown a late survival advantage at 3 years with a strategy of angiography and early rPCI compared with those managed more conservatively. The composite end point occurred less often in the rPCI arm mainly because of fewer unplanned revascularization procedures in the early phase of follow-up. The highest risk of clinical events in patients with failed reperfusion is in the first year; beyond this, the rate of clinical events is low. The continuing debate about the magnitude of early benefit to be achieved with rescue angioplasty may become historic as efforts to provide a universal primary angioplasty service continue.

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