ACUTE MYOCARDIAL INFARCTION: REPERFUSION TREATMENT

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T he decision over whether to treat acute myocardial infarction (AMI) with a balloon or infusion of fibrinolytics remains controversial. During the past few years profound changes in both treatment modalities[1–3 w1 w2] have substantially changed the arguments surrounding this long-standing debate.[w3–5] The evidence shows that the alternative use of primary angioplasty or fibrinolysis is rarely an option, either because angioplasty is simply not available or because the patient is not eligible for fibrinolysis. This evidence reflects the difference in "applicability" of each treatment—that is, the proportion of patients in whom only one of the treatments would be suitable versus patients in whom either treatment would be appropriate. As a matter of fact, primary angioplasty is applicable to almost all victims of AMI (82–90% of patients randomised to primary angioplasty actually undergo the procedure), but it is not available to the majority of patients. Conversely, fibrinolysis is a widely available treatment but "applicable" to a variable percentage of patients which does not reach 50%. The large number of patients with AMI to whom fibrinolysis is not administered represents a big challenge for the future, and perhaps the most rational and undisputed argument in favour of the use of primary angioplasty.

The best reperfusion treatment is one that achieves the highest rate of early, complete and sustained infarct related artery patency in the largest number of patients, but with the lowest rate of undesirable effects. The results obtained with both treatments, in the way they were applied before the latest breakthroughs in the field, can be represented by a geometrically opposing relation between "applicability" and "efficacy" (fig 1).

UNCONTROVERSIAL EVIDENCE IN FAVOUR OF FIBRINOLYTIC TREATMENT

Clinical trials and experience have identified the following landmarks in the reperfusion treatment of ST segment elevation AMI.

▶ The daily administration of 162.5 mg of aspirin orally from the first day of AMI and continued for 30 days reduces the 30 day vascular mortality rate by 23% without risk of stroke.[w6]

▶ Intravenous infusion of streptokinase within six hours after AMI onset reduces 30 day total vascular mortality by 25%, but at the cost of 2–3 strokes per 100 patients treated and 3 severe bleedings requiring transfusion per 1000 patients treated. Combined treatment with aspirin has synergistic effects and will prevent 52 vascular deaths per 1000 patients treated and reduce significantly the risk of reinfarction.[w6]

▶ The initial benefit of streptokinase treatment on mortality is maintained at 10 year follow up.[4]

▶ The use of recombinant tissue plasminogen activator (rt-PA) using the "accelerated" dosing schedule plus heparin (instead of streptokinase) prevents another 10 deaths but causes two more strokes per 1000 patients treated.[5]

▶ Pre-hospital fibrinolysis can reduce one year mortality[w7] and should be considered when transport time exceeds 60 minutes.[w8]

▶ The combination of full dose of abciximab and half dose reteplase reduces non-fatal complications of AMI, but yields similar mortality rate compared with reteplase alone.[6]

EVIDENCE IN FAVOUR OF PRIMARY ANGIOPLASTY: CONSENSUS STATEMENTS

All the randomised clinical trials of primary angioplasty have shown a reduced incidence of stroke, recurrent ischaemia, and need for new target vessel revascularisation (TVR) compared to fibrinolysis, even in low risk patients.[7] In selected subsets, primary angioplasty preserves left ventricular ejection fraction[w4 w9] and benefits patients with anterior AMI treated up to 24 hours after symptom onset.[w10] The favourable effects on mortality and reinfarction appear to be more pronounced among high risk patients, in particular those with haemodynamic evidence of failure.[8] Benefits in this setting are also apparent from non-randomised data.[9] A quantitative overview by Weaver and colleagues[10] pooling 2606 patients showed that the mortality reduction obtained with primary angioplasty compared to fibrinolysis was approximately 32% (table 1). If this result can be reproduced everywhere, the magnitude of such treatment effect would be similar to that observed when fibrinolysis was used instead of placebo. However, these excellent results

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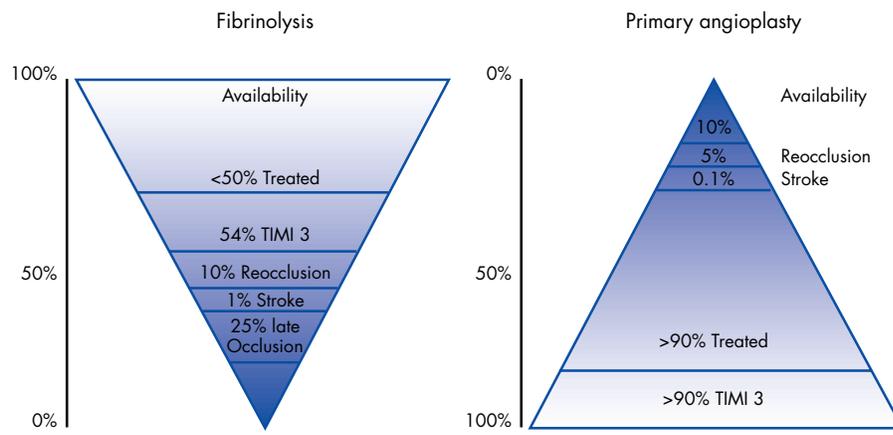william.wijns@olvz-aalst.be

Figure 1 Nearly all patients with acute myocardial infarction (AMI) could potentially benefit from reperfusion treatment with fibrinolytics, but less than 50% will actually be treated; only 50–60% of those will achieve a TIMI 3 grade coronary flow, 10% will suffer from early reocclusion, 1% will have a stroke, and 20–30% will have late reocclusion. On the other hand, angioplasty can be offered to only 10% of patients with AMI, but more than 90% of these will actually be treated; 90% will achieve a TIMI 3 grade coronary flow, less than 5% will have reocclusion, and less than 0.1% will have a stroke.

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derive from the experience of selected centres working under the specific requirements of randomised investigation and may not be easily achieved in the community setting, as is suggested by the results of large national registries[9 w11 w12]

The GUSTO II-B trial[7] addressed this particular issue by testing the effect of angioplasty when performed mainly in low volume centres on a low risk population. In fact, GUSTO II-B showed a less favourable outcome of angioplasty than expected from other trials, which was caused by a higher event rate in the angioplasty arm rather than by a lower event rate in the fibrinolysis arm. Furthermore, 36% of patients allocated to fibrinolysis received an angioplasty before discharge, which may blunt the differences between the two strategies at six months. Crossover to angioplasty in patients initially randomised to pharmacological treatment is a common and important confounding factor when analysing differences in long term outcome.[w11] Long term benefit of angioplasty has been observed in the one year analysis of the SHOCK trial.[8]

The mortality reduction obtained with the emergency revascularisation strategy compared to the approach involving initial medical stabilisation was not significant at 30 days (46.7% v 56%, p = 0.11), but became so at six months (50.3% v 63.1%, p = 0.027) and increased further at one year (55% v 70%, p = 0.008). Albeit a negative study statistically, the number of lives saved per 1000 patients treated with the strategy of emergency revascularisation is the highest ever reported in a reperfusion trial (tables 1 and 2). The recent availability of long term results of primary angioplasty trials confirms the long lasting efficacy of the invasive approach also in patients without haemodynamic failure, despite some initial concern that early benefit may not be sustained[w13] (table 2).

NEW PERSPECTIVES IN REPERFUSION THERAPY

It is recognised that the success rate and durability of mechanical revascularisation procedures and the efficacy and safety of fibrinolytics have both improved. Primary angioplasty has been

Table 1 Event rate at short term follow up, number needed to treat, and events avoided per 1000 patients treated in randomised clinical trials comparing primary angioplasty and fibrinolysis.

30-day events	PTCA (%, n)	Lysis (%, n)	p Value	OR (95%CI)	ARR%	NNT	NEA × 1000
Mortality							
Weaver[10]	4.4%, 57/1290	6.5%, 86/1316	0.02	0.66 (0.46 to 0.94)	2.1	47	21/1000
GUSTO II-B[7]	5.7%, 32/565	7.0%, 40/573	0.37	0.80 (0.49 to 1.30)	1.3	77	13/1000
SHOCK[8]*	46.7%, 71/152	56%, 84/150	0.11	0.83 (0.67 to 1.04)	9.3	11	91/1000
C-PORT[w46]	5.3%, 12/225	6.2%, 14/226	0.7	Not available	0.9	111	9/1000
DANAMI-2†	6.6%, 52/790	7.6%, 59/782	0.35	Not available	1.0	100	10/1000
Mortality or non-fatal reinfarction							
Weaver	7.2%, 94/1290	11.9%, 156/1316	<0.001	0.58 (0.44 to 0.76)	4.7	21	48/1000
GUSTO-IIB	9.6%, 54/565	12.2%, 70/573	0.08	0.72 (0.49 to 1.05)	3.1	32	31/1000
C-PORT‡	9.8%, 22/225	16.8%, 38/226	0.03	0.52 (0.30 to 0.89)	7	14	71/1000
DANAMI-2†‡	8.0%, 63/790	13.7%, 107/782	0.0003	Not available	5.7	18	55/1000
Stroke							
Weaver	0.7%, 9/1290	2.0%, 26/1316	0.007	0.35 (0.14 to 0.77)	1.3	77	13/1000
PAMI[w27]	0	3.5%, 7/200	0.01	Not available	3.5	29	34/1000
Zijlstra[16]	0.7%, 1/152	2.0%, 3/149	0.6	0.32 (0.01 to 4.08)	1.3	77	13/1000
GUSTO II-B	1.1%, 6/565	1.9%, 11/573	0.34	0.54 (0.17 to 1.63)	0.8	125	8/1000
C-PORT	1.3%, 3/225	3.5%, 8/226	0.13	Not available	2.2	45	22/1000
DANAMI-2†	1.1%, 8/790	2.0%, 15/782	0.15	Not available	0.9	111	9/1000
Haemorrhagic stroke							
Weaver	0.1%, 1/1290	1.1%, 15/1316	<0.001	0.07 (0.0 to 0.43)	1	100	10/1000
PAMI	0	2.0%, 4/200	0.05	Not available	2	50	20/1000
Zijlstra	0.7%, 1/152	1.3%, 2/149	0.98	0.49 (0.01 to 9.47)	0.6	166	6/1000
GUSTO-IIB	0	1.4%, 8/573	0.007	Not available	1.4	71	14/1000

*The SHOCK trial did not compare PTCA with lysis, but a strategy of emergency revascularisation versus initial medical stabilisation.
†Data not published. Presented at the scientific sessions of the American College of Cardiology, March 2002.
‡Includes disabling stroke.
ARR, absolute risk reduction; NEA × 1000, number of events avoided per 1000 patients treated; NNT, number needed to treat.

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Table 2 Event rate at long term follow up, number needed to treat, and events avoided per 1000 patients treated in randomised clinical trials comparing primary angioplasty and fibrinolysis

Long term events	PTCA (%)	Lysis (%)	p Value	Odds ratio (95% CI)	ARR	NNT	NEA × 1000
Mortality							
Weaver 6 months*	6.1	8.1	0.055	0.73 (0.52 to 0.98)	2	50	20/1000
PAMI 2 years[w29]	6.2	9.5	0.21	Not available	3.3	30	33/1000
Zijlstra 5±2 years[16]	13.4	23.9	0.01	0.54 (0.36 to 0.87)	10.5	10	100/1000
SHOCK 6 months[8]†	50.3	63.1	0.027	0.80 (0.65 to 0.95)	12.8	8	125/1000
SHOCK 1 year†	55	70	0.008	Not available	15	7	143/1000
C-PORT 6 months[w46]	6.2	7.1	0.72	Not available	0.9	111	9/1000
Reinfarction							
Weaver 6 months	4.4	9.7	0.0001	0.43 (0.3 to 0.6)	5.3	19	53/1000
PAMI 2 years	10.8	16.0	0.01	Not available	5.2	19	53/1000
Zijlstra 5±2 years	6	22	0.0001	0.27 (0.15 to 0.52)	6	6	167/1000
C-PORT 6 months	5.3	10.6	0.04	Not available	5.3	19	53/1000
Mortality or non-fatal reinfarction							
Weaver 6 months	6.8	13.4	0.0001	0.47 (0.43 to 0.7)	6.6	15	67/1000
PAMI 2 years	14.9	23	0.034	Not available	8.1	12	83/1000
Zijlstra 5±2 years	22	46	0.0001	0.13 (0.43 to 0.91)	24	4	250/1000
C-PORT 6 months‡	12.4	19.9	0.03	0.57 (0.34 to 0.95)	7.5	13	77/1000
New revascularisation							
PAMI 2 years	32.8	54	0.001	Not available	21.2	5	200/1000
Zijlstra 5±2 years	46.4	71.1	<0.001	Not available	24.7	4	300/1000
Recurrence of ischaemia							
PAMI 2 years	36.4	48	0.026	Not available	11.6	9	111/1000
Zijlstra 5±2 years	52	89.5	<0.001	Not available	37.5	3	333/1000

*Data on 2635 patients. Presented at the American Heart Association meeting in Atlanta, October 1999.
†The SHOCK trial did not compare PTCA with lysis, but a strategy of emergency revascularisation versus initial medical stabilisation.
‡Includes disabling stroke.
For explanation of abbreviations see table 1.

enhanced by the use of coronary stents[w14] and the availability of glycoprotein IIb/IIIa inhibitors,[2] or the combined use of both,[11 12 w15] while new fibrinolytic regimens offer better results than those obtained with streptokinase or even with front loaded rt-PA.[1 w1 w16]

New infusive schemes
New fibrinolytic drugs are being developed and evaluated with the aim of improving pharmacological reperfusion.[1 13 w1 w16] Initial studies suggested that lytic therapy may be as effective as primary angioplasty.[w17]

Efficacy
The combined use of fibrinolytics with glycoprotein IIb/IIIa inhibitors appears encouraging at first glance. In the TIMI 14 trial[1] a high rate of TIMI 3 flow grade was observed at 90 minutes after the infusion of 50 mg of alteplase and a full dose of abciximab plus low dose heparin. This promising finding relates to only 87 patients included in the dose finding and dose confirmation phases of the study, which included angiography at 90 minutes. Out of the 34 patients studied in the dose finding phase, a TIMI 3 flow was observed in 22 patients (76%), 3% of patients died, 3% suffered major bleeding, and 27% needed an urgent revascularisation procedure. Moreover, 59% of these patients underwent angioplasty before discharge, 18% as an emergency rescue procedure.

The IMPACT-AMI trial[w18] failed to detect a dose–response relation using a combination of eptifibatide (Integrilin) and 100 mg of alteplase. On the contrary, the group treated with eptifibatide had a tendency towards increased incidence of in-hospital adverse events (51% v 39%) and mortality (11% v 0%), despite a significantly higher rate of TIMI 3 flow grade at 90 minutes (66% v 39%). Despite the discrepancy between the excellent angiographic results and the less impressive clinical outcome in these small sized studies, these preliminary results primed a new large scale trial which was recently published.[6]

GUSTO V was powered to detect a 15% reduction in mortality and randomised 16 588 patients to either standard lytic treatment with reteplase or a combination of half dose reteplase with full dose abciximab. The results obtained with the combination therapy did not lower the mortality rate (5.6%) compared to standard fibrinolysis (5.9%). Non-fatal complications of AMI were significantly reduced, at the cost of higher rates of non-intracranial bleeding. Thus, the relation between patency and survival is not as straightforward as initially anticipated; furthermore, the failure to reduce mortality in the megatrials performed in this new era of reperfusion has diverted attention to the reduction in non-fatal clinical events.

Drug delivery
Ease and speed of delivery of fibrinolytic drugs have been improved with the use of a single bolus of mutant forms of rt-PA. Recently, the results of two megatrials (ASSENT-2 and InTime-II) have been presented.[w19] Both studies confirmed that the bolus injection of TNK-tPA and lanoteplase was as effective as the long lasting infusion of rt-PA. However, lanoteplase caused a significantly higher rate of intracranial bleeding compared to rt-PA in InTime-II (1.13% v 0.62%, p = 0.003); that was not the case for TNK-tPA (0.93%) when compared to rt-PA (0.94%) in ASSENT-2.

Safety
Clinical studies aimed at assessing the efficacy and safety of combinations of potent thrombolytic treatments have caused thousands of intracranial bleeds.[w20] Furthermore, the inappropriate administration of a fibrinolytic agent may not be without complications.[w21] Indeed, nearly 4.1% of patients who receive fibrinolysis have non-coronary syndromes and the 30 day mortality of these patients was 9.5% versus 1.2% of those allocated to placebo in the ASSET trial (p < 0.01).[w22] The underutilisation of fibrinolytics in the real world as shown in NRMI-2[w2] may reflect a certain "fear to treat", particularly in

Trial acronyms

ASSENT: Assessment of the Safety and Efficacy of a New Thrombolytic regimen
CADILLAC: Controlled Abciximab and Device Investigation to Lower Late Angioplasty Complications
DANAMI: Denish trial in Acute Myocardial Infarction
GUSTO: Global Use of Strategies to Open Occluded Coronary Arteries in Acute Coronary Syndromes
IMPACT: Integrilin to Manage Platelet Aggregation in Combatting Thrombosis
NRMI: National Registry of Myocardial Infarction
PACT: Plasminogen-activator Angioplasty Compatibility Trial
RAPPORT: Reopro and Primary PTCA Organization and Randomized Trial
SHOCK: Should we emergently revascularize Occluded coronary arteries for Cardiogenic shock?
STENT-PAMI: STENT Primary Angioplasty in Myocardial Infarction
TIMI: Thrombolysis In Myocardial Infarction

high risk patients. This concern will lead physicians to accept the natural history of the disease rather than to prescribe the reperfusion treatment that is available to most cardiologists, which can be lifesaving, but will potentially induce a severe complication. From a safety standpoint, lytic treatment may therefore be perceived as being more hazardous than the invasive approach.

Primary stented angioplasty and new antiplatelet agents

The systematic use of coronary stents during primary angioplasty was shown to reduce the incidence of reocclusion and the need for new TVR compared to balloon dilatation. The rate of TIMI 3 flow grade did not improve nor did systematic stent implantation reduce the incidence of reinfarction and mortality in the large STENT-PAMI and CADILLAC trials.[w14 w15] Similarly, initial experience with the use of IIb/IIIa receptor inhibitors in association with primary angioplasty has yielded contradictory results between some small studies[11 12] and the larger RAPPORT[2] and CADILLAC trials.[w15] In RAPPORT, the use of abciximab or placebo with primary angioplasty did not affect the incidence of death, reinfarction or TVR at six months; similarly, the CADILLAC trial yielded identical incidence of the primary end point (mortality, reinfarction, ischaemic TVR, and stroke) at six months in patients undergoing stented angioplasty with or without administration of abciximab (11.5% and 10.2%, respectively). In both studies, stent implantation offered better results than balloon dilatation independently of the use of abciximab.

The concept of facilitated angioplasty or combined "pharmaco-mechanical reperfusion" was evaluated by the PACT investigators[3]; a bolus of 50 mg rt-PA or placebo was given on admission, followed by immediate angiography and angioplasty unless TIMI 3 flow was observed. This use of fibrinolytic agents differs from the concept of "rescue angioplasty" for failed lysis and, unlike rescue procedures, offers better preservation of the left ventricular function without complications secondary to the lytic bolus. Although some benefit can be expected from the combined form of reperfusion on "soft" end points, such as preservation of left ventricular ejection fraction and a reduced need for urgent TVR, there is no evidence so far that this form of combined pharmaco-mechanical strategy will reduce mortality or widen the window of opportunity for reperfusion.

CONTEMPORARY ANGIOPLASTY AND FIBRINOLYSIS: ARE THEY TRULY EQUIVALENT?

Whenever primary angioplasty and fibrinolysis are to be evaluated as potentially equivalent,[w18] the following issues should be considered.

Time delay

Setting up for and performing primary angioplasty requires more time than starting an intravenous infusion. In randomised clinical trials, the in-hospital delay in starting fibrinolysis was on average 45–50 minutes shorter than the time needed to start angioplasty.[10] The in-hospital procedure related delay for primary angioplasty must be no longer than 90 minutes according to the American Heart Association/American College of Cardiology recommendations.[w8] In nearly 90% of cases, the invasive strategy results in immediate TIMI 3 flow grade of the infarct related artery, while with lytic agents there is an additional delay before their effect starts. In the TIMI-14 study[1] the administration of a bolus of alteplase alone or a bolus followed by a 30 minute infusion of rt-PA and abciximab was far less effective (TIMI 3 flow grade at 90 minutes: 48% and 62%, respectively) than the same bolus followed by a 60 minute infusion (TIMI 3 flow grade 74%, p < 0.02). Even with the addition of abciximab, this indicates that the concentration of the lytic agent must be maintained for at least 60 minutes. Therefore, the time delay needed for the optimal lytic regimen to be effective may be not much shorter than that for primary angioplasty.

Following primary angioplasty, a longer time delay could result in a larger infarct size and a lower left ventricular ejection fraction,[w23 w24] but apparently this does not adversely affect the patency rate of the infarct related artery or the six month clinical outcome.[w23] Hospital mortality rates remain low and predictable in patients treated within 12 hours of symptom onset unless they present with cardiogenic shock.[14 w25 w26] On the contrary, with lytic treatment, reperfusion rates decrease and the mortality rates increase with increasing time, in particular beyond the third to fourth hour after symptom onset.[5 14 w27] Short term mortality strongly depends on the quality and time frame of reperfusion.[15] Angioplasty yields a higher degree of TIMI 3 flow grade than fibrinolysis and this translates in a better short term outcome. Long term survival largely depends on left ventricular function[5 16]; this in turn depends on the extent of myocardial damage, which increases as reperfusion is delayed. Thus angioplasty may be better for patients admitted late—that is, more than four hours after onset of symptoms[14]—in whom 30 day mortality with angioplasty remains under 5% but rises to over 12% with lysis.[w26 w28] The transportation of high risk patients to hospitals offering invasive facilities should be considered since the additional treatment delay does not seem to jeopardise the result of mechanical reperfusion.[w23 w25 w26]

Patients subgroups

Primary angioplasty applied to selected candidates may prove more beneficial than its indiscriminate use, particularly in patients with small low risk AMI. Available data support the use of primary angioplasty over fibrinolysis in high risk patients and in patients with haemodynamic impairment (class I indication[w8]). Indirect data suggest that the mechanical approach is a better alternative than fibrinolysis in clinical subsets such as the elderly, patients with right ventricular involvement, patients with AMI caused by the occlusion of vein grafts, late presenters, or subjects who are ineligible for

fibrinolysis. However, subgroup analysis should be considered with caution since data fragmentation reduces the statistical power and may cause type II errors. Proper randomised trials are needed if these indications are to be fully legitimised.

Number needed to treat and number needed to harm

The demonstration of a significant reduction in mortality of about 25% with fibrinolytic agents has required the randomisation of more than 10 000 patients in each of the initial studies. Later on, the GUSTO-I study[5] enrolled 41 021 patients to obtain a further 14.6% risk reduction in mortality with rt-PA versus streptokinase (95% confidence interval (CI) 5.9% to 21.3%, p = 0.001). Equivalence trials have randomised more than 31 000 patients to show that new fibrinolytic agents "do not cause a clinically significant excess in events".[w19] Assuming a 30 day mortality rate of 7% in patients treated with fibrinolysis, about 12 000 patients would need to be randomised to show a worthwhile 20% relative risk reduction with any alternative treatment. Primary angioplasty has been shown to have favourable effects on end points such as mortality and reinfarction, even in smaller sized studies. These considerations would support the contention that megatrials on direct angioplasty are no longer necessary, but this position has not gained universal acceptance.

Most potentially effective lytic drugs have been tested in large clinical trials which were funded by companies with a vested interest in orienting medical care at large. Regrettably, there has not been enough interest to support prospective randomised clinical trials comparing angioplasty and fibrinolysis that are large enough to provide unequivocal results. The largest randomised study of this kind, GUSTO II-b, included only 1138 patients and showed a non-significant mortality reduction of 18.6%, resulting in 13 lives saved per 1000 patients.[7]

A useful tool for the interpretation and comparison of outcomes is the "number needed to treat" (NNT). NNT is calculated as the reciprocal of the absolute outcome difference between two treatment groups and offers an ingenious measurement of the "therapeutic effort to clinical yield" ratio. The NNT to prevent one death, reinfarction, stroke or a combined end point in the short term, according to the most relevant trials comparing angioplasty and fibrinolysis, is shown in table 1. Similar calculations in regard to long term results are given in table 2.

When using angioplasty instead of fibrinolysis in 1000 patients, 21 more lives would be saved and 13 stokes avoided within the first month after AMI.[10] Even though the debated 32% mortality reduction obtained in the combined analysis of these trials may not be representative of current practice, the magnitude of the benefit obtained with angioplasty in the real world seems at least as important as the benefit obtained with front loaded rt-PA compared to streptokinase.[5 7] In GUSTO V the absolute risk reduction in mortality was 0.3, resulting in 3 lives saved per 1000 patients treated with combined therapy instead of reteplase only (NNT = 333). Long term analysis shows that angioplasty would save 20 more lives than fibrinolysis per 1000 patients at six months, 33 at two years,[w29] and 100 at five years.[16] Furthermore, 200 new TVRs would be prevented at two years and 300 at five years after the index AMI.

A similar analysis can be applied to determine the adverse effects of medical interventions ("number needed to harm"). Out of 1000 patients treated with fibrinolysis, 8 would have suffered from stroke in GUSTO II-B and 34 in PAMI (table 1). Such an event is fatal in 40% of patients and causes severe morbidity in the remainder,[5] reducing the net clinical benefit of fibrinolysis.

Applicability: the true frontier of reperfusion treatment in the "real world"

Because the limitations to the applicability of each form of reperfusion treatment are different, we believe that they rarely present as an equivalent alternative.

The major limitation of primary angioplasty is the difficulty in setting up the programme, performing the procedures in a timely fashion, and reproducing the results of clinical trials. However, a similar frontier exists for fibrinolytic treatment. In the NRMI-2[w2] only 31% of the 272 651 patients analysed were eligible for reperfusion, 3% had formal contraindications, 41% presented after six hours, and 25% had non-diagnostic ECG; furthermore, 24% of eligible patients were not given reperfusion treatment. Not surprisingly, unadjusted mortality in patients not receiving reperfusion treatment was nearly three times higher than in treated patients. Had angioplasty been available, these patients could have benefited from reperfusion treatment.

Results from the NRMI-2 study can be considered to be representative of cardiology practice in the USA. Despite differences between countries in eligibility criteria, time delay, lytic agents, and treatment strategies, the major findings in NRMI-2 are largely reproduced in Western Europe and Canada, confirming the under utilisation of reperfusion treatment. Overall fibrinolysis is given to only 66% of eligible patients, and the use of invasive procedures ranges from 2.5–11% of AMI patients between community and academic institutions.[17] Among European countries, the UK has reported the largest use of fibrinolytic agents: 71.6% of patients with suspected AMI, ranging from 49–85% in different hospitals,[w30] in the context of limited availability of invasive facilities.[w31] Other countries use lytic agents less often, perhaps in part because angioplasty is more readily available. In Germany fibrinolysis is given in 36–42% of patients while angioplasty is used in 10–25% of cases.[w32 w33] In France 37% of AMI patients receive reperfusion treatment,[w34] either by means of systemic lysis (32–45%) or angioplasty (13–43%).[w35 w36] Other reports from Israel, Italy, Scandinavia or Spain indicate that fibrinolysis is given to 35–45% of patients.[17 w37–41] Data from Australia and New Zealand state an eligibility rate of 53%, lytics being actually given in 43%, with a predominant use of streptokinase (78%) over rt-PA (15.7%), and a growth in surgery or angioplasty from 8.7% in 1986 to 17.4% in 1994.[w42 w43] Despite these differences in management of AMI among western countries, there are no significant differences in short term outcome,[w44] perhaps because the proportion of reperfused patients is similar. Thus in daily practice, half of the patients with AMI do not receive reperfusion treatment. Reperfusion is rarely denied because of formal contraindications but usually because of late arrival, non-diagnostic ECG changes, advanced age or other various reasons that raise a "fear to treat" in about 25–35% of potentially eligible cases.[17 w2 w44] Under all these circumstances, angioplasty, when available, is not an "alternative" to lysis but the sole opportunity for reperfusion. Paradoxically, the results of angioplasty in this large patient subgroup, which represent an ideal and undisputed setting for its use, are mostly unknown.[w45]

Therefore, increasing the availability of primary angioplasty, or shaping the triangle of fig 1 into a rectangle, would be a worthwhile effort. As mentioned earlier, patient transportation to high workload tertiary centres is a safe and valuable therapeutic approach and, at least in theory, it may prove a more rational and cost effective option than the emergence of a widespread network of low volume centres in which

optimal results may not be achieved. Such a strategy has been investigated in a large randomised study in Europe (DANAMI-2). The study randomly assigned AMI patients to front loaded rt-PA or angioplasty in interventional centres, or to rt-PA versus transportation for angioplasty elsewhere in non-invasive centres, and was prematurely stopped on 1 October 2001 after a planned interim analysis because of the benefit observed in the invasive strategy of the study (table 1). In the USA, a recent small randomised trial has shown that the better outcome of angioplasty over fibrinolysis can also be obtained in community hospitals without on-site cardiac surgery.[w46]

Which yardstick for measuring treatment effect?

If reperfusion strategies are considered as nearly equivalent, then the accuracy of the measurement of their respective effects becomes of major relevance. Randomisation is the best tool for testing two treatment strategies; however, in this particular case, the method may have some pitfalls that must be acknowledged. On the one hand, randomisation precludes enrolment of patients who are ineligible for fibrinolysis. This represents a group of patients at particularly high risk in whom angioplasty is likely (but was not proven) to be beneficial. On the other hand, double blinded analysis and outcome adjudication is problematic. In patients assigned to angioplasty, information on coronary anatomy and ventricular function is immediately available and complications may be diagnosed and managed readily, leading to a more proactive management of patients treated invasively.

ANCILLARY BENEFIT OF THE INVASIVE APPROACH

While the primary goal of any kind of reperfusion therapy is to save lives by re-establishing effective myocardial perfusion, some potential additional benefits are granted *only* with the invasive approach. Admittedly, these ancillary benefits only pertain to the few patients who have prompt access to the invasive treatment.

The invasive approach enables the use of a variety of tools such as stents, ultrasound imaging, thrombectomy or aspiration devices, and provides the possibility of intracoronary or local drug delivery, all of which may in the future prove to be useful adjunctive agents to optimise reperfusion. Invasive diagnostic tools may also help to gain additional insights into the "mysteries" of reperfusion at the tissue level[18]—that is, why one out of four patients who achieve a brisk epicardial TIMI 3 coronary flow does not have tissue reperfusion.[w47]

The immediate knowledge of the coronary anatomy and left ventricular function facilitates accurate risk stratification and allows the most appropriate individual treatment strategy to be selected and implemented. New standards of care after AMI have ensued and reduced the length of hospital stay and the need for further diagnostic testing.[w48 w49]

Primary angioplasty is cost saving compared to fibrinolysis.[19 w48 w49] This is mainly because of the lower incidence of in-hospital reinfarction, recurrent ischaemia, stroke, and shorter hospital stay.[w49]

Late reocclusion of the infarct related artery with or without reinfarction occurs in nearly 30% of patients after fibrinolysis and bears a negative prognosis and a high mortality rate.[5 w50] This likely explains the lack of survival benefit between fibrinolysed and control patients 10 years after discharge in the GISSI study.[4 w20] Conversely, with contemporary primary angioplasty and stenting, reocclusion and reinfarction rates are as low as 1–5%.[w14 w15]

> ### Reperfusion treatment for acute myocardial infarction: key points
>
> ▶ Reperfusion treatment for acute myocardial infarction remains largely underused
> ▶ Applicability of thrombolytic therapy and primary angioplasty is the major limitation to the use of reperfusion treatment
> ▶ Most recent efforts have aimed at "doing more for few patients". The real challenge is to "do more for more patients"
> ▶ Pre-hospital fibrinolysis shortens the duration of ischaemia and increases myocardial salvage
> ▶ Transportation of patients with acute myocardial infarction to a catheterisation laboratory must be considered after failed thrombolysis in high risk patients
> ▶ Advantages of primary angioplasty are sustained in the long term
> ▶ Combined treatment with lytics and glycoprotein IIb/IIIa inhibitors reduces complications, but not mortality
> ▶ Combined use of pharmacological and mechanical reperfusion improves secondary clinical end points, but not survival
> ▶ Clinical trials in specific patient subsets are needed to establish the advantages of primary angioplasty
> ▶ A tailored reperfusion strategy based on the risk profile at presentation may prove more rational than their indiscriminate use in the few patients who have access to all resources

As has been determined from postmortem examination[w51] and has been recently confirmed in vivo,[w52] AMI may not always be the consequence of a thrombotic coronary occlusion. Acute events such as plaque rupture, spontaneous dissections or intramural plaque haemorrhage associated with spasm are the cause of AMI in nearly 30% of cases, a figure which is close to the percentage of cases in which optimal lytic therapy is ineffective.[1 w17] Under those pathophysiological circumstances, fibrinolysis and antiplatelet agents, even when given at doses that go beyond their "safety ceiling", will never work, because the substratum on which these drugs act is non-existent.[20]

CONCLUSIONS AND FUTURE DIRECTIONS

Currently available evidence does not fully support the contention that either the immediately invasive approach or combined antithrombotic or pharmaco-mechanical strategies are clearly superior to fibrinolysis in reducing mortality. We need to learn from appropriately powered randomised clinical trials whether or not primary angioplasty is beneficial when applied to subgroups of patients who otherwise do not receive reperfusion treatment. When appropriate, current guidelines should be revised to incorporate specific recommendations for these specific patient subsets.

In the meanwhile, primary angioplasty cannot be advocated as the first therapeutic approach where it is not performed on a regular basis by experienced operators. Reperfusion by lytic treatment remains the therapy of choice for AMI in most cases, although its efficacy and applicability in the real world remain far from optimal.

Rather than taking a dogmatic approach to either form of reperfusion treatment, percutaneous coronary intervention and/or drugs should be used as needed to increase the overall impact of reperfusion treatment in the community, taking advantage of the best, locally available potential of each approach.[13] The real challenge is to increase the proportion of
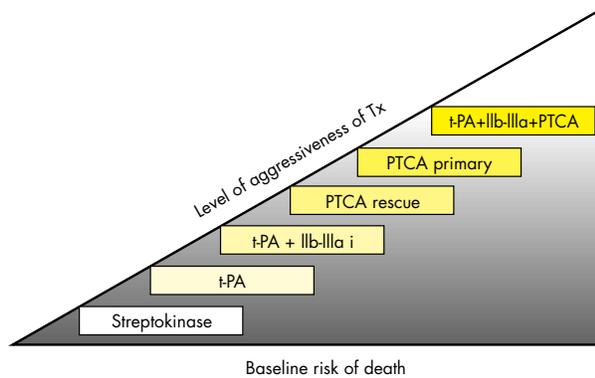
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Figure 2 Streptokinase can still be used as a first choice treatment in low risk patients (as currently done in many patients treated in South America, UK, Australia, New Zealand, and the Netherlands), while patients presenting with higher clinical risk would benefit from the use of the more expensive recombinant tissue plasminogen activator (t-PA). The combination of recombinant t-PA and a glycoprotein IIb/IIIa inhibitor (abciximab) will reduce the clinical complications of acute myocardial infarction, but will not reduce mortality. Rescue angioplasty (PTCA) can be reserved for high risk patients who did not achieve reperfusion or have a poor clinical course. Primary angioplasty should be preferred for patients presenting with haemodynamic failure, advanced age (> 75 years) or presenting late (more than 4–5 hours after symptom onset). The previous administration of half doses of lytic treatment is desirable when it can be given out of hospital by first aid providers, or in the emergency department when access to the catheterisation laboratory is delayed. The use of stents and glycoprotein IIb/IIIa inhibitors during angioplasty does not reduce mortality. Instead of being used indiscriminately, these tools should be considered in unfavourable patient or lesion subsets, such as in the presence of a large thrombotic burden after wire crossing or suboptimal flow after angioplasty.

patients with AMI receiving reperfusion treatment and to "do more for more patients" rather than "do more for fewer patients". Pre-hospital diagnosis and treatment of AMI are important. At a time when mortality from AMI has decreased to lower levels, pre-hospital treatment will likely be the only way to reduce mortality any further. Immediate treatment with lytic and/or antiplatelet drugs and transportation for angioplasty seem to be the most rational approach. Prompt restoration of coronary flow and subsequent intervention should optimise tissue reperfusion and avoid coronary reocclusion.[3 w53] Transfer of selected patients to a centralised, high volume invasive service while reperfusion is continuing would render angioplasty applicable to a much larger patient population, shorten the duration of ischaemia, and increase the potential for myocardial salvage. Such an approach will occur when both the availability of percutaneous coronary intervention services is increased and these resources are used to treat high risk patients. To treat all AMI patients with half doses of expensive lytic agents, full doses of very expensive glycoprotein IIb/IIIa inhibitors, stents, aspiration and protection devices, followed by conventional drug treatment, would not be sensible. The available reperfusion tools should be applied selectively, tailored to the patient's risk profile and temporal presentation, as shown in fig 2.

There is at present little scientific evidence supporting this "common sense" line of action for the future. Widespread use of glycoprotein IIb/IIIa inhibitors in combination with lytics and an increase in the availability of invasive facilities will have a major impact on treatment costs that need to be weighed against the expected incremental reduction in mortality and postinfarction heart failure.

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