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Evidence-based Cardiology

Reperfusion strategies in acute myocardial infarction

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Introduction

The understanding that a myocardial infarction is usually caused by an acute thrombotic obstruction of a coronary artery has led to a major change in the approach of this disease[1]. Since the early 1980s, pharmacological and mechanical interventions have been introduced that aimed at rapid and sustained restoration of blood flow in the occluded artery. This approach has been successful, and considerable progress has been achieved since that time. In The Netherlands, in 1980, in-hospital mortality after myocardial infarction was approximately 15·6% (24·3%) in male (female) patients, whereas nowadays this figure is markedly reduced to about 11·3% (18·5%)[2].

The effects of various treatment strategies have been evaluated in a number of randomized trials. Special attention was paid to the properties of thrombolytic, antiplatelet and anticoagulant therapy, alone and in combination, and more recently direct angioplasty was studied. The present paper presents a survey of the most relevant results observed in these trials, and reviews whether and to what extent evidence for benefit can be claimed for different reperfusion strategies. An overview of other review articles is presented in Table 1.

Thrombolytic therapy

Treatment within 6 h of symptom onset

Restoration of blood flow to the jeopardised myocardium within 6 h of symptom onset preserves viable myocardial tissue, which protects left ventricular function, and consequently reduces mortality (we appreciate, that this reasoning simplifies complex biochemical processes, and disregards the paradoxical fact that early reperfusion might also cause some cellular injury, even though the overall effects are clearly beneficial)[3]. By intracoronary infusion of streptokinase recanalization can be achieved in approximately 80% of patients[4,5]. At the same time the enzymatic infarct size is reduced by 20% to 35% compared with control therapy, and left ventricular function is preserved[6,7]. Mortality after intracoronary-streptokinase was evaluated in a couple of relatively small randomized controlled clinical trials. Pooled analysis of the results of these trials (including approximately 1000 patients) indicate that use of intracoronary streptokinase results in a non-significant 15% relative reduction in 1 year mortality, from 14·7% to 12·5% (odds ratio (OR) 0·82 and 95% confidence interval (CI) 0·56 to 1·19; chi-square-test for 2×2 contingency table $P=0·32$)[8].

Intracoronary drug infusion requires angiography, which is laborious, expensive and causes further treatment delay. Therefore, subsequent investigations concentrated on intravenous infusion of streptokinase. The largest trials in this context, GISSI-1, ISAM and ISIS-2, comprised 30 600 patients, who were randomized to either intravenous-streptokinase or control therapy (Table 2)[9–11]. In the patients treated within 0–6 h of onset of symptoms (n=22 200), mortality at 1 month was significantly reduced by intravenous-streptokinase from 12·0% to 9·2% (23% reduction; OR 0·74 and 95% CI 0·68 to 0·81; $P<0·0001$; Fig. 1).

The most feared complication related to thrombolytic therapy is the occurrence of intracranial haemorrhage, which leads to death in half of the cases and to severe disability in another quarter[12]. Embolic stroke rates are reduced in patients receiving thrombolytic therapy. The occurrence of any cerebrovascular accident in the GISSI-1, ISAM and ISIS-2 trials was slightly, but not significantly, increased from 0·74% in the control group to 0·79% in the intravenous-streptokinase group (Fig. 1).

Other intravenous thrombolytic drugs have been developed that might produce more rapid thrombolysis than streptokinase, resulting in higher early coronary patency rates[13–15]. One such second-generation drug, anisoylated plasminogen streptokinase activator (APSAC), has the additional advantage of a relative long half-life, so that a single injection would be

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Table 1 Review articles which address mortality based on randomized trials on reperfusion therapy in acute myocardial infarction

Theme of the overview	Keywords	Author [Ref]	Year of publication
Mortality, reinfarction and adverse events after intracoronary and intravenous thrombolysis	thrombolytic therapy, intracoronary infusion, intravenous infusion	Yusuf *et al.*[8]	1985
Development of routine medical management	thrombolytic therapy, aspirin, heparin, beta-blockers, calcium blockers, nitrates	Yusuf *et al.*[58]	1990
All randomized trials between fibrinolytic and control therapy which include at least 1000 patients	thrombolytic therapy, overall evidence, subgroup analysis	Fibrinolytic Therapy Trialists' Collaborative Group[20]	1994
Prolonged antiplatelet therapy (in myocardial infarction patients among others)	antiplatelet therapy, vascular death, reinfarction, stroke	Antiplatelet Trialists' Collaboration[41]	1994
Effects of anticoagulant therapy in coherence with antiplatelet treatment	heparin, aspirin, reinfarction, stroke, pulmonary embolism	Collins *et al.*[39]	1996
Effects of thrombolytic treatment delay on mortality in randomised trials which include at least 100 patients	thrombolytic therapy, time to treatment	Boersma *et al.*[21]	1996
Randomised clinical trials of aspirin, heparin and fibrinolytic therapy	thrombolytic therapy, aspirin, heparin	Collins *et al.*[36]	1997
Comparison of thrombolytic therapy vs primary coronary angioplasty	thrombolytic therapy, angioplasty	Weaver *et al.*[50]	1997

sufficient. This thrombolytic agent was evaluated in the placebo-controlled AIMS study (1000 patients randomized within 0–6 h; Table 2)[16], which reported a 6·4% mortality at 1 month in the APSAC group compared with 12·2% in the placebo (48% reduction; OR 0·48 and 95% CI 0·30 to 0·70; $P=0·001$). No excess cerebrovascular accidents occurred in the active group. The ASSET trial (Table 2) studied recombinant tissue-type plasminogen activator (rt-PA)[17], which has the advantage over streptokinase and APSAC of being non-antigenic. Approximately 5000 patients were randomized within 0–6 h, and mortality at 1 month was 26% reduced from 9·8% to 7·2% by rt-PA compared with placebo (OR 0·72 and 95% CI 0·58 to 0·88; $P=0·001$). Stroke rates were similar in both groups.

Very early treatment

Experimental data and measurements of myocardial enzymes in humans suggest that most of the irreversible damage to the myocardium occurs between 1 and 2 h after coronary occlusion[18,19]. Thus, appreciable additional benefit might be expected from very early thrombolytic therapy. However, in a pooled analysis of the large trials (n=58 600) by the Fibrinolytic Therapy Trialists (FTT analysis) there was no marked discontinuity in mortality reduction as a result of thrombolytic therapy with regard to time from symptom onset[20]. Recently, this analysis has been criticised, and it has been demonstrated that the beneficial effect of fibrinolytic therapy is indeed substantially higher in patients presenting within 2 h of symptom onset compared to those presenting later[21]. This 'golden hour' concept, however, is still controversial[6].

Treatment after 6h

Thrombolytic treatment after 6 h of continuous coronary occlusion is unlikely to prevent myocardial necrosis. Nevertheless, there are some reasons for a beneficial effect on post-infarct survival in patients presenting relatively late after onset of symptoms[6,22]. One argument is that many patients suffer from intermittent occlusions rather than one continuous occlusion — coronary thrombus formation and resolution is a dynamic process — so that partial salvage of ischaemic myocardium may still be achieved. Furthermore, existing collaterals may preserve some blood flow to the jeopardised area. Finally, even relatively late opening of the occluded artery will improve the healing process of the infarction and reduce left ventricular remodelling and dilatation.

The combined results of the GISSI-1, ISIS-2 and EMERAS trials indicate that treatment with intravenous-streptokinase within 6–12 h of onset of symptoms (n=8100) will reduce 1 month mortality by 11%, compared with control therapy from 13·9% to 11·9% (OR 0·87 and 95% CI 0·76 to 0·99; $P=0·04$)[10,11,23], which is half the reduction observed in the 0–6 h period. The LATE trial of rt-PA vs placebo (Table 2) reported a 26% mortality reduction (from 12·0% to 8·9%; OR 0·72 and 95% CI 0·53 to 0·96; $P=0·02$) in the relatively small 6–12 h cohort (n=2100)[24]. In patients randomized within 12–24 h of

Table 2 Characteristics of all randomized trials on short-term mortality after reperfusion therapy in acute myocardial that include at least 1000 patients

Comparison	Study [Ref]	No of pts	Antiplatelet therapy	Anticoagulant therapy	Time to therapy	Follow-up	Year of publication
intravenous-streptokinase vs standard therapy	GISSI-1[10]	11 806	no	no	0–12 h	21 days	1986
intravenous-streptokinase vs placebo and aspirin vs placebo	ISIS-2[11]	17 187	aspirin (50%)	no	0–24 h	35 days	1988
intravenous-streptokinase vs placebo	ISAM[9]	1741	aspirin	intravenous-heparin[1]	0–6 h	21 days	1986
	EMERAS[23]	4534	aspirin	no	>6–24 h	in hospital	1993
APSAC vs placebo	AIMS[16][2]	1254	no	intravenous-heparin	0–6 h	30 days	1988
rt-PA vs placebo	ASSET[17]	5012	no	intravenous-heparin	0–6 h	1 month	1988
	LATE[24]	5711	aspirin	intravenous-heparin (64%)[3]	>6–24 h	35 days	1993
intravenous urokinase vs standard therapy	USIM[59]	2201	no	intravenous heparin[4]	0–6 h	in hospital	1991
intravenous-streptokinase vs rt-PA (ISIS-3: vs APSAC) and heparin vs non-heparin	GISSI-2[28,29]	20 749	aspirin	subcutaneous-heparin (50%)	0–6 h	in hospital	1990
	ISIS-3[30][5]	41 299	aspirin	subcutaneous-heparin (50%)	0–24 h	35 days	1992
intravenous-streptokinase vs rt-PA vs combination	GUSTO-1[33][6]	41 021	aspirin	heparin (subcutaneous 25% and intravenous 75%)	0–6 h	30 days	1993
intravenous-streptokinase vs reteplase	INJECT[37]	6010	aspirin	intravenous-heparin	0–12 h	35 days	1995
rt-PA vs immediate angioplasty	GUSTO-2b[49][7]	1138	aspirin	intravenous-heparin (50%) hirudin (50%)	0–12 h	30 days	1996
rt-PA vs reteplase	GUSTO-3[38][8]	15 100	aspirin	intravenous-heparin	0–6 h	30 days	1996

If no comments are made, treatment schedules were as follows: streptokinase: 1·5 MU over 1 h; standard *urokinase* regimen: 1 MU bolus, repeated after 1 h; alteplase (rt-PA): 10 mg bolus + 50 mg over 1 h + 20 mg over next 2 h; plasminogen streptokinase activator (APSAC): 30 U over 3 to 5 min; reteplase: two boluses of 10 U given 30 min apart; aspirin: 160 to 325 mg . day^{-1}; subcutaneous heparin: 12 500 U twice daily; intravenous heparin: 5000 U bolus + 800 to 1200 U/h.

[1]additional oral anticoagulant therapy; [2]AIMS planned to include 2000 patients, but terminated prematurely because of an extreme mortality reduction by APSAC observed in an interim analysis half way through the trial; no heparin bolus was given, but instead 1000 to 1500 U . h^{-1}; additional oral anticoagulant therapy; [3]after protocol amendment, some patients received two boluses of 5000 U; [4]10 000 U bolus; [5]rt-PA regimen: 0·04 MU.kg^{-1} bolus + 0·36 MU.kg^{-1} over 1 h + 0·067 MU.kg^{-1} over next 3 h; [6]comparison of four groups: intravenous-streptokinase, subcutaneous-heparin vs intravenous-streptokinase, intravenous-heparin vs rt-PA (15 mg bolus + 0·75 mg.kg^{-1} over 30 min + 0·5 mg . kg^{-1} over next h), intravenous-heparin vs rt-PA (0·1 mg . kg^{-1} bolus + 0·9 mg . kg^{-1} over 1 h), intravenous-streptokinase (1·0 MU over 1 h), intravenous-heparin; [7]primary study end-point was a composite of death, non-fatal reinfarction and non-fatal disabling stroke; the rt-PA regimen is equal to GUSTO-1; patients were randomized to intravenous heparin or hirudin (0·1 mg . kg^{-1} bolus + 0·1 mg . kg^{-1} . h^{-1}); [8]the rt-PA regimen is equal to GUSTO-1.

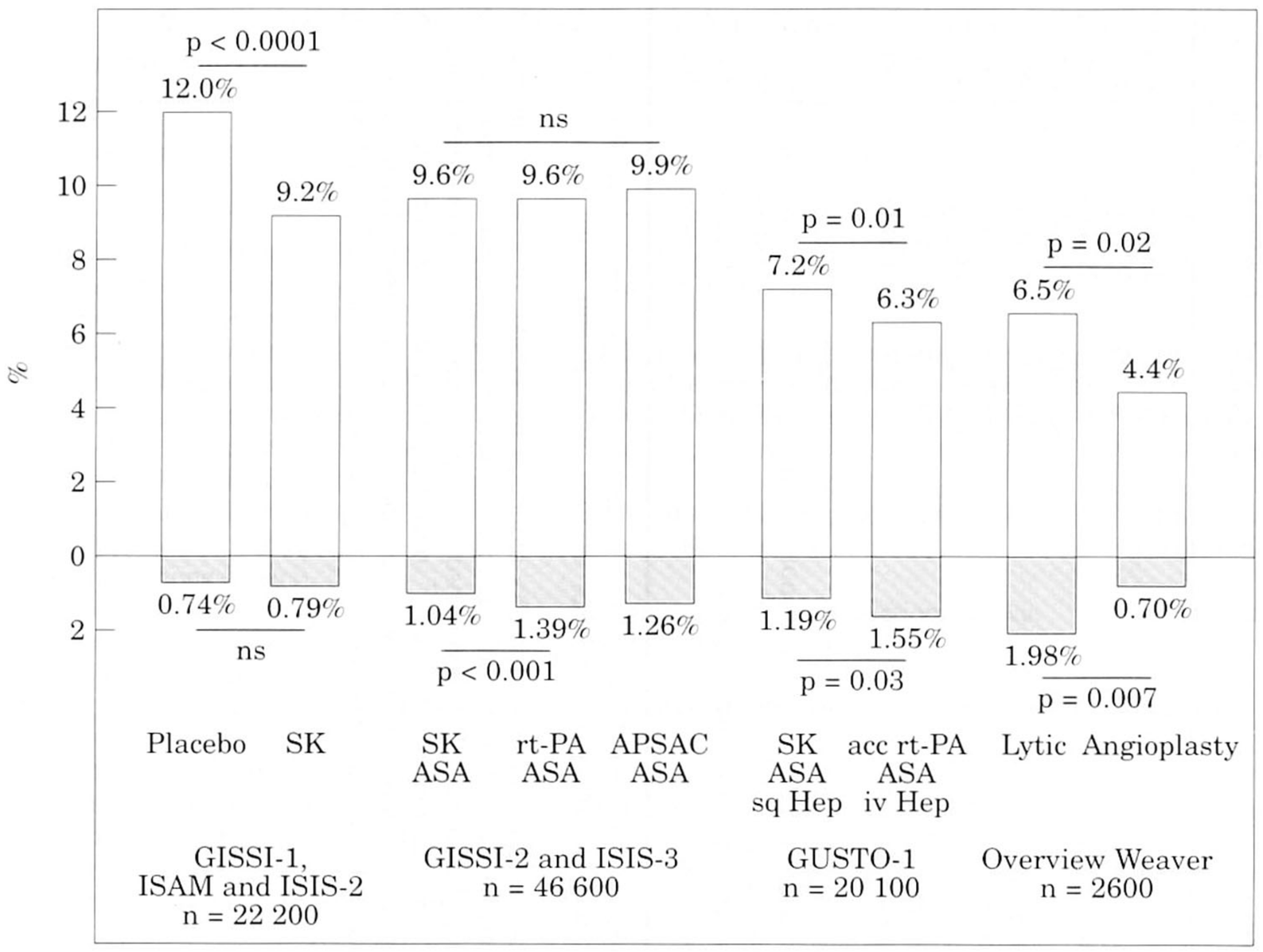

Figure 1 **One month mortality and stroke rates after thrombolytic therapy or immediate angioplasty in patients with suspected myocardial infarction treated within 0–6 h of onset of symptoms. Open bars represent mortality in the 0–6 h patients. Solid bars represent stroke rates (haemorrhagic or embolic) in all patients. Mortality data from the overview of Weaver *et al.* is also not restricted to the 0–6 h cohort. SK = streptokinase; ASA = aspirin; rt-PA = recombinant tissue type plasminogen activator; APSAC = anisoylated plasminogen streptokinase activator; Hep = heparin.**

symptom onset (n = 9000 in the FTT analysis) no significant reduction in 1 month mortality was observed following thrombolytic therapy[20].

Overall clinical benefit of thrombolytic therapy

From 1980 over 61 000 patients with suspected myocardial infarction participated in trials that randomized between thrombolytic therapy and control, within 24 h of onset of symptoms. The FTT analysis, which covers about 95% of the data, indicates a highly significant 17% 1 month mortality reduction by thrombolysis from 11·5% to 9·6% (OR 0·82 and 95% CI 0·78 to 0·87; $P<0·0001$), which corresponds to an avoidance of 18 (SD 3) deaths per 1000 patients treated[6,20]. Thrombolytic therapy increases the occurrence of cerebrovascular accidents from 0·76% to 1·16% (OR 1·52 and 95% CI 1·28 to 1·81; $P<0·0001$), reflecting a small excess of about four (SD 1) strokes (mainly intracranial bleedings) per 1000 treated. It should be realised that half of this excess is already accounted for in the mortality data. Follow-up studies show that the mortality reduction produced by thrombolytic therapy is sustained throughout at least 4 to 10 years[25–27].

Comparison of thrombolytic regimens

Superficial comparison of the results described above suggests that APSAC (single injection of 30 U) and, to a lesser extent, rt-PA (100 mg infusion over 3 h) might be more effective than streptokinase (infusion of 1·5 MU over 1 h). However, direct comparisons in patients randomized within 0–6 h in the GISSI-2 (streptokinase vs rt-PA, n = 20 800) and ISIS-3 (streptokinase vs rt-PA vs APSAC, n = 25 800; Table 2) trials[28–30], showed no significant difference in 1 month mortality between streptokinase and non-streptokinase regimens (Fig. 1). On the other hand, cerebrovascular accidents were slightly, but significantly, more frequent in the non-streptokinase groups (stroke rate 1·39% in rt-PA vs 1·04 in streptokinase; OR 1·37 and 95% CI 1·15 to 1·62; $P<0·001$). Thus, the chosen rt-PA and APSAC regimens in GISSI-2 and ISIS-3 appeared not to be superior to streptokinase. There were some indications, however, that a so-called 'accelerated' rt-PA infusion, i.e. over 1·5 h, with two thirds of the dose given in the first 30 min, will lead to greater infarct artery patency, which can be sustained with intravenous heparin infusion[31,32]. The accelerated rt-PA regimen has been evaluated in the GUSTO-1 trial, which randomly assigned 41 000 patients (within 0–6 h of symptom onset) to four different thrombolytic strategies (Table 2). Treatment with

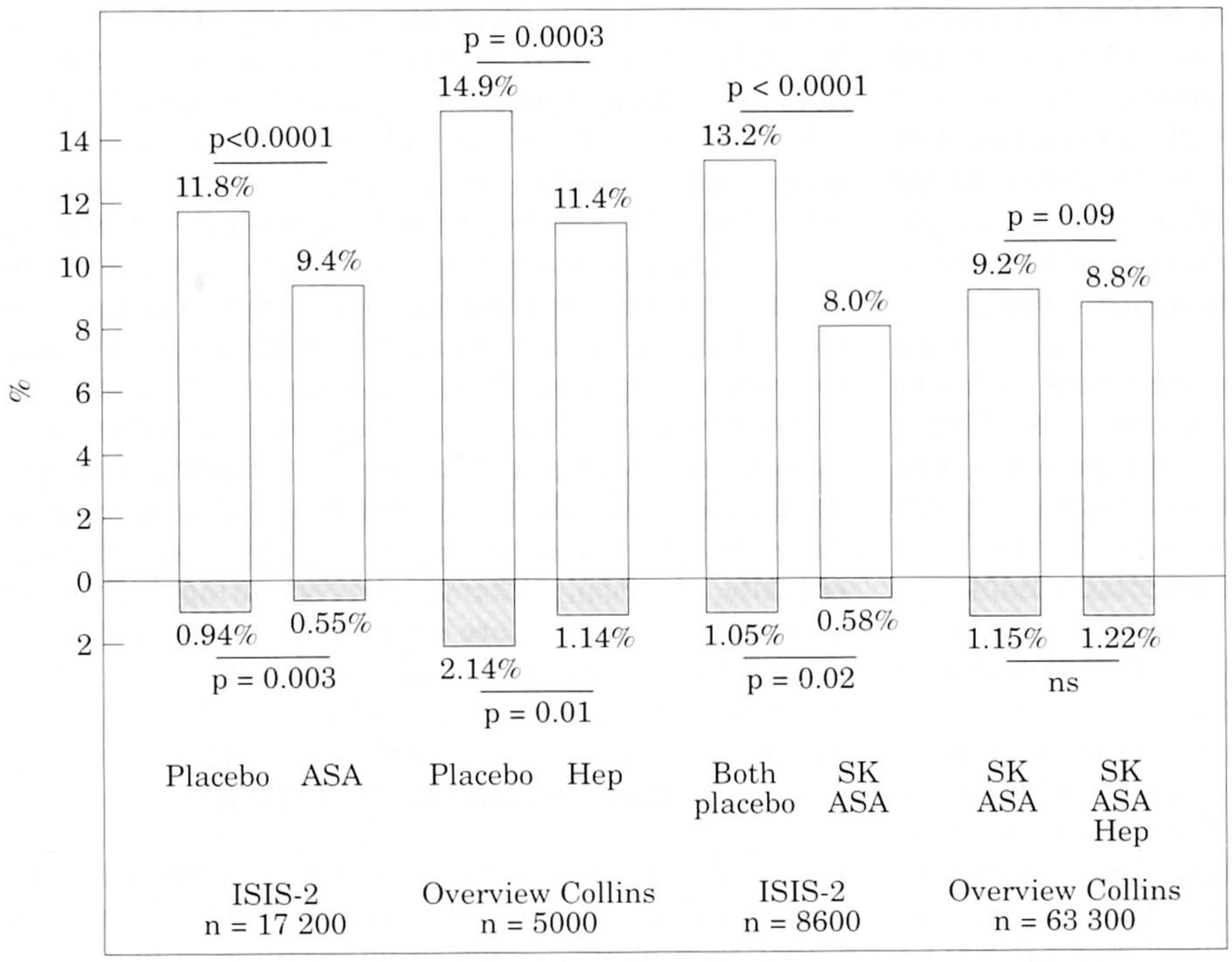

Figure 2 **One month mortality and stroke rates after antiplatelet or anticoagulant therapy in patients with suspected myocardial infarction. Open bars represent mortality and solid bars represent stroke rates (haemorrhagic or embolic). For abbreviations, see legend to Table 1.**

accelerated rt-PA and intravenous heparin significantly reduced 1 month mortality compared with streptokinase and subcutaneous heparin, the 'standard' streptokinase regimen from 7·2% to 6·3% (13% reduction; OR 0·87 and 95% CI 0·78 to 0·97; $P=0·01$; Fig. 1)[33]. This mortality reduction was sustained for at least 1 year[34]. Left ventricular function was also better in patients randomized to accelerated rt-PA[35]. Conversely, the incidence of cerebrovascular accidents was increased from 1·19% to 1·55% (OR 1·31 and 95% CI 1·02 to 1·67; $P=0·03$)[12]. Thus, the accelerated rt-PA regimen produces a clear, albeit modest, overall clinical benefit compared with standard streptokinase. This conclusion, however, is not shared by all investigators in the field.[6,36].

Nowadays, to prove that new thrombolytic agents significantly reduce mortality compared with established strategies, trials require inclusion of tens of thousands of patients. To demonstrate, however, that the properties of new drugs are similar to established therapies, considerably fewer patients are needed. One such 'equivalence' trial is INJECT (n=6000; Table 2). This trial demonstrated that the two boluses of 10 MU reteplase regimen is at least equivalent to standard streptokinase: mortality at 1 month was 9·0% and 9·5%, respectively, whereas stroke rates were 1·23% and 1·00%[37]. The recent GUSTO-3 trial (n=15 000; Table 2) compared reteplase with the GUSTO-1 accelerated rt-PA regimen, and observed no statistically significant differences in 30-day mortality (7·2% after accelerated rt-PA and 7·4% after reteplase) or cerebral complications (stroke rates were 1·83% and 1·67%, respectively)[38]. Thus, the clinical effects of reteplase seem to be in between standard streptokinase and accelerated rt-PA.

Antiplatelet and anticoagulant therapy

Immediate and temporary use

ISIS-2 (n=17 200) assessed the value of antiplatelet therapy in acute myocardial infarction[11]. Patients were randomized not only to intravenous streptokinase or placebo, but also to oral aspirin (162·5 mg daily for 1 month) or placebo (Table 2). Aspirin significantly reduced 1 month mortality from 11·8% to 9·4% (20% reduction; OR 0·77 and 95% CI 0·70 to 0·85; $P<0·0001$; Fig. 2). The occurrence of cerebrovascular accidents was also significantly reduced, from 0·94% to 0·55% (41% reduction; OR 0·58 and 95% CI 0·40 to 0·84; $P=0·003$; intracranial haemorrhage rates were similar). In patients allocated both intravenous streptokinase and aspirin, 1 month mortality was 8·0% compared with 13·2% in those allocated both placebo (39% reduction; OR 0·56 and 95% CI 0·48 to 0·66; $P<0·0001$; Fig. 2). Thus, streptokinase and aspirin show additive effects.

The properties of anticoagulant therapy in the absence of antiplatelet therapy are evaluated in a couple of randomized trials, covering about 5000 patients (all of them received heparin, but doses and modes of administration varied)[39]. Heparin decreased short-term

mortality to 11·4%, compared with 14·9% after control treatment (23% reduction; OR 0·74 and 95% CI 0·62 to 0·87; $P=0·0003$; Fig. 2), and cerebral complications were reduced from 2·14% to 1·14% (47% reduction; OR 0·53 and 95% CI 0·31 to 0·90; $P=0·01$). These results are comparable with aspirin in the absence of anticoagulant therapy. There are very few data about the combination of thrombolytic and anticoagulant therapy in non-aspirin patients[39].

The value of anticoagulant treatment added to the combination of thrombolytic and antiplatelet therapy was evaluated in about 63 300 patients, who were randomized to subcutaneous heparin (the GISSI-2 and ISIS-3 regimen, Table 2) or control therapy[39]. A small non-significant 4% short-term mortality reduction was observed in the heparin group (mortality 8·8% in the heparin group and 9·2% in controls; OR 0·95 and 95% CI 0·90 to 1·01; $P=0·09$; Fig. 2). Stroke rates were 1·22% and 1·15% in heparin vs non-heparin patients, respectively (OR 1·07 and 95% CI 0·92 to 1·24; $P=0·37$). In the GUSTO-1 study, no significant difference was observed between subcutaneous and intravenous heparin in patients treated with streptokinase. Thus, it may be concluded from the GISSI-2, ISIS-3 and GUSTO-1 studies that neither subcutaneous nor intravenous heparin adds much to the outcome in streptokinase patients. Therefore, recent guidelines do not recommend heparin as adjunctive therapy in myocardial infarction patients treated with streptokinase and aspirin[40].

Angiographic studies indicate that coronary patency is improved by adding intravenous heparin to rt-PA[31,32]. As described above, the GUSTO-1 accelerated rt-PA regimen, which included intravenous heparin, was significantly better than standard streptokinase. Thus, although there are no large randomized trials that assess the clinical benefit of adding heparin to rt-PA, the available data support the use of intravenous heparin for 2 or 3 days in patients receiving rt-PA.

Secondary prevention

Approximately 19 800 patients with recent myocardial infarction participated in trials that randomized between prolonged use, i.e. for at least 1 month, of aspirin or other antiplatelet agents (such as dipyridamole and sulfinpyrazone) and control therapy[41]. Antiplatelet therapy significantly reduced long-term mortality by 12% (from 10·4% to 9·2%; OR 0·88 and 95% CI 0·80 to 0·96; $P=0·006$), non-fatal myocardial reinfarction by 28% (from 6·5% to 4·7%; OR 0·70 and 95% CI 0·62 to 0·80; $P<0·0001$) and non-fatal stroke by 33% (from 1·5% to 1·0%; OR 0·63 and 95% CI 0·47 to 0·84; $P<0·001$).

Two recent randomized trials evaluated the value of long-term oral anticoagulant treatment (warfarin or coumadin vs placebo) in about 4600 survivors of myocardial infarction[42,43]. Mortality at 3 years was 11·4% in the anticoagulant group and 13·5% in the placebo group, with implies a reduction of 15% (OR 0·83 and 95% CI 0·69 to 0·99; $P=0·03$). Recurrence of myocardial infarction was reduced by 46% (from 15·8% to 8·5%; OR 0·49 and 95% CI 0·41 to 0·60; $P<0·0001$), as was the occurrence of cerebrovascular accidents (from 4·6% to 2·5%; OR 0·53 and 95% CI 0·37 to 0·74; $P=0·0001$).

Thus, prolonged use of aspirin or coumadin prevents reinfarction, stroke and mortality after myocardial infarction. The salutary effects of coumadin seem somewhat larger, but direct comparisons of antiplatelet and anticoagulant therapy are lacking. One trial recently reported that aspirin and low-dose coumadin resulted in similar effects[44]. However, that trial was stopped prematurely because outcomes in the two groups were virtually identical. Other trials comparing high dose coumadin and aspirin are ongoing.

Immediate angioplasty

The most important conceptual deficit of thrombolytic therapy in patients with evolving myocardial infarction is that such pharmacological intervention only aims to dissolve the acute coronary thrombus. On the other hand, mechanical intervention by means of immediate coronary angioplasty also treats the underlying atherosclerotic plaque. Thus, recurrence of ischaemia and reocclusion are less likely after angioplasty than after thrombolysis. Additionally, less serious (cerebral) bleeding complications are to be expected. Whereas routine angioplasty after thrombolytic therapy appeared not be successful[45,46], clinical trials that randomized between direct angioplasty and thrombolytic therapy initially reported excellent (extreme) results in support of the invasive strategy[47,48]. However, results of the recent larger GUSTO-2b angioplasty substudy (n=1100; Table 2), which applied the GUSTO-1 accelerated rt-PA regimen, were less favourable[49]. Overall, among the 2600 patients randomized in all of the angioplasty trials, short-term mortality was significantly reduced from 6·5% after thrombolytic treatment to 4·4% after primary angioplasty (33% reduction; OR 0·66 and 95% CI 0·46 to 0·95; $P=0·02$; Fig. 1)[50]. The risk of stroke was reduced from 1·98% to 0·70% (65% reduction; OR 0·35 and 95% CI 0·14 to 0·77; $P=0·007$). The wide confidence intervals reflect the relatively small number of patients randomized, which necessitates a careful interpretation of the estimates of benefit. Furthermore, it should be realised that these results are obtained by high volume PTCA operators and experienced teams. Nevertheless, direct angioplasty might be considered the treatment of choice, particularly in patients at high risk of death or cerebral haemorrhage.

Current trials address the issue whether implantation of coronary stents is associated with additional benefits[51]. Trials are also ongoing to establish the value of special catheter devices designed to remove thrombotic material by section or ultrasound in selected patients with a high clot burden.

Future directions

Direct thrombin inhibitors

Heparin is an indirect thrombin inhibitor, requiring the presence of anti-thrombin III. Direct thrombin inhibitors, like hirudin and hirulog, do not require this enzyme and might therefore be expected to be more effective. Direct thrombin inhibitors also act on platelet bound thrombin. However, two large randomized studies in patients with evolving myocardial infarction (TIMI-9 and GUSTO-2) did not show a significant advantage of hirudin over heparin in combination with thrombolysis[52,53]. The high dose of hirudin initially used in these trials resulted in an unacceptably high rate of intracranial haemorrhage, which was also observed in the HIT trial[54]. The subsequent low doses used largely avoided these complications, but had little (GUSTO-2b) or no (TIMI-9b) effect on survival[55,56]. Studies with other thrombin inhibitors in combination with thrombolytic therapy are ongoing.

Platelet glycoprotein IIb-IIIa receptor blockers

Aspirin is a weak inhibitor of platelet aggregation. More extensive, or even full inhibition of platelet aggregation can be achieved with the new platelet glycoprotein IIb-IIIa receptor blockers. The first such agent, abciximab, has been shown to be very effective in patients undergoing coronary angioplasty, including angioplasty for myocardial infarction. Pre-treatment with abciximab while preparing for direct angioplasty may resolve the occlusive clot in some patients[57]. In animal experiments, combined treatment with glycoprotein IIb-IIIa receptor blockers and thrombolytics has been shown to facilitate clot lysis. Studies assessing the clinical value of such treatment in patients with evolving myocardial infarction are ongoing. Again, it is possible that such combination treatment will improve reperfusion and reduce reocclusion rates, but it might also increase the bleeding risk.

Conclusions

(1) Thrombolytic treatment of suspected myocardial infarction within 0–6 h of onset of symptoms will avoid approximately 25 deaths per 1000 patients, while four cerebrovascular complications will be caused.
(2) The beneficial effect of thrombolytic therapy very much depends on time from symptom onset. However, thrombolytic therapy is generally beneficial up to 12 h after the onset of symptoms, and in some patients (those with ongoing ischaemia) even up to 24 h.
(3) Administration of antiplatelet or anticoagulant therapy will avoid about 20 deaths and five cerebrovascular accidents per 1000 patients. The beneficial effects of thrombolytic therapy and aspirin are largely independent. Subcutaneous heparin adds little to combination therapy with a thrombolytic agent and aspirin, while intravenous heparin is recommended in patients treated with (accelerated) alteplase.
(4) There are moderate, but significant differences in outcome between several reperfusion strategies: direct angioplasty being most effective, and accelerated alteplase (with intravenous heparin) being slightly superior to streptokinase. However, most emphasis should be on rapid installation of some effective therapy without worrying overmuch about which strategy to choose.
(5) Secondary prevention with either antiplatelet or anticoagulant therapy has a modest effect on mortality, but substantially reduces the risk of recurrent myocardial infarction.

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