Adjunctive treatment in patients treated with thrombolytic therapy

M A Brouwer, N Clappers and F W A Verheugt

Updated information and services can be found at:
http://heart.bmjjournals.com/cgi/content/full/90/5/581

These include:

Data supplement	*"Web-only References"* **http://heart.bmjjournals.com/cgi/content/full/90/5/581/DC1**
Rapid responses	You can respond to this article at: **http://heart.bmjjournals.com/cgi/eletter-submit/90/5/581**
Email alerting service	Receive free email alerts when new articles cite this article - sign up in the box at the top right corner of the article

Topic collections	Articles on similar topics can be found in the following collections Heart Education (189 articles) Drugs: cardiovascular system (631 articles) Coronary Disease (Education) (37 articles) Ischemic heart disease (1555 articles)

Notes

ADJUNCTIVE TREATMENT IN PATIENTS TREATED WITH THROMBOLYTIC THERAPY

581

M A Brouwer, N Clappers, F W A Verheugt

Thrombotic occlusion of an epicardial coronary artery has been implicated as a potential mechanism involved in acute myocardial infarction since as early as 1910,[w1] and became generally accepted after the landmark report by De Wood and colleagues in the early 1980s.[w2] In the search for pharmacological means to dissolve thrombi, the so called ''thrombolytics'' were developed. These agents target fibrin, the key element in clot formation, and are therefore more accurately referred to as ''fibrinolytics''. Large clinical trials confirmed the hypothesis that timely restoration of coronary patency had a notable impact on survival after ST elevation myocardial infarction: ~20–30 lives saved per 1000 patients treated.[w3] With improvements in techniques and experience, mechanical reperfusion therapy has been proven to be even more beneficial than in-hospital initiated fibrinolytic therapy.[w4] Yet, pharmacological reperfusion therapy is more widely available, more easily applicable, and less dependent of institutional experience.

Consequently, the majority of patients with ST elevation myocardial infarction receive fibrinolytic therapy. Given the profound impact of early reperfusion,[1] preferably within the first ''golden'' hour, the initiation of pre-hospital fibrinolysis programmes resulted in benefits in the same order as achieved by primary angioplasty, ~18 lives saved per 1000 patients, when compared to in-hospital fibrinolysis.[2] New pharmacological reperfusion strategies to achieve patency rates that could more favourably compare with those achieved by primary angioplasty constitute a second initiative. In addition to further optimisation of antithrombotic treatment in the acute phase, the experience with anti-ischaemic, plaque stabilising strategies applied in the (sub)acute phase and in the long term have evolved. The current review presents the latest pharmacological developments and their implications for daily clinical practice in patients with acute ST elevation myocardial infarction (fig 1).

STRATEGIES TO ENHANCE CORONARY PATENCY: THE ACUTE AND SUBACUTE PHASE

From the very first randomised trials with fibrinolytic agents, angiographic substudies demonstrated the concept of early restoration of coronary patency, better preservation of left ventricular function, and improved survival.[3] Secondly, the adverse consequences of reocclusion of the infarct artery were demonstrated in terms of impaired recovery of left ventricular function and higher rates of mortality and recurrent ischaemic events.[4]

In order to optimise the efficacy of reperfusion therapy, concomitant thrombin and platelet inhibition is required, which is aimed not only at enhancing early patency but also for reducing reocclusion and recurrent thrombotic events.

Pathophysiological rationale
Acute thrombotic occlusion of an epicardial artery is often initiated by plaque rupture or erosion, after which subendothelial matrix is exposed to the blood. Following vasoconstriction, the initial response to vessel injury, a cascade of events evolves. Platelets adhere to the damaged vessel wall and secrete chemoattractive substances, resulting in platelet recruitment and aggregation. Activation of tissue factor (factor VII) is one of the earliest involved responses, stimulating a prompt reaction of the extrinsic and intrinsic coagulation cascade. Thrombin constitutes one of the most important proteins. It has a potent effect on platelet aggregation, and promotes the formation of fibrin, the key element in the formation of a durable strong clot.[5] Fibrinolytics induce activation of plasminogen into plasmin, resulting in degradation of fibrin (fig 2).

REPERFUSION STRATEGIES
Despite many years of experience with fibrinolytic agents, some crucial aspects will be highlighted below. These concern relevant issues for the clinician's choice of adjunctive treatment, and aspects regarding the rationale for the development of new strategies.

See end of article for authors' affiliations
_____

Correspondence to:
Professor F W A Verheugt, University Medical Center St Radboud, Heartcenter, 540 Cardiology, PO Box 9101, Nijmegen, The Netherlands 6500 HB; f.verheugt@cardio. umcn.nl
_____

Figure 1 Schematic representation of the currently recommended pharmacological treatment strategy in acute myocardial infarction patients. ACE, angiotensin converting enzyme.

Fibrinolytic therapy: efficacy

With a varying survival benefit from ~20 per 1000 patients treated after 4–6 hours to ~50 per 1000 patients when starting treatment within 1–2 hours of symptom onset, agents that can easily be used in the pre-hospital setting have always been of interest (table 1).[1] After the initial success with streptokinase,[6] [w5] bolus treatment with anistreplase gained attention.[w6–8] A second initiative has been the search for a more potent agent, realising higher rates of early patency. A third goal constitutes the development of agents with less bleeding complications, which were thought to be related to the lack of fibrin specificity—that is, the action on both fibrin bound and circulating plasminogen, inducing systemic depletion of fibrinogen. "Second generation" agents like recombinant tissue plasminogen activator (rt-PA) were produced, but not until the introduction of an accelerated regimen was a breakthrough realised.[w9] This regimen resulted in an early and sustained survival benefit compared to streptokinase, and proved particularly effective in patients with anterior myocardial infarction.[7] [w10]

The strongest predictor of survival was identified as the realisation of early brisk, antegrade flow in the coronary artery—the so called 90 minute TIMI (thrombolysis in myocardial infarction) grade 3 flow—seen in 54% of patients on rt-PA versus 32% in those on streptokinase.[3] Based on these insights the "third generation" lytics were manufactured
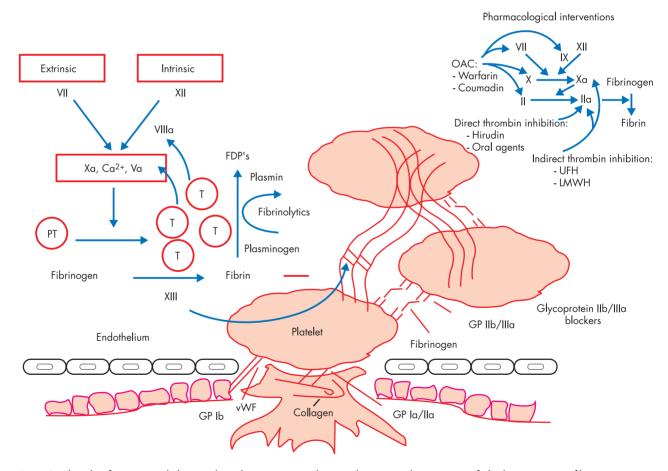

Figure 2 Thrombus formation and pharmacological interventions in the coagulation cascade. Interaction of platelet aggregation (fibrinogen, glycoprotein IIb/IIIa) and activation of the coagulation cascade results in the thrombin induced formation of a fibrin-rich clot. Fibrin cross-linking by factor XIII improves clot strength. Whereas oral anticoagulants interfere with the production of coagulation factors, other agents inhibit the action of activated clotting factors. Fibrinolytics target the degradation of fibrin, mediated through plasmin. FDP's, fibrin degeneration products; LMWH, low molecular weight heparin; OAC, oral anticoagulants; PT, prothrombin (II); T, thrombin (IIa); UFH, unfractionated heparin; vWF, von Willebrand factor. Modified from Brouwer and Verheugt,[5] with permission.

Table 1 Current fibrinolytic agents in the treatment of ST elevation myocardial infarction

	Streptokinase	Alteplase (rt-PA)	Reteplase (r-PA)	Tenecteplase (TNK-tPA)
T1/2 (mins)	15–25	4–8	11–14	17–20
Allergenic	Yes	No	No	No
Fibrin specific	−	+	+	++
PAI-1 resistant	−	−	−	+
Bolus	No	No	Double	Single
Dosing	1.5 MU over 30–60 mins	15 mg bolus, followed by 0.75 mg/kg (max 50 mg) over 30 mins, followed by 0.5 mg/kg (max 35 mg) over 1 hour	10 U bolus, twice, 30 mins apart	Weight adjusted: <60 kg: 30 mg 60–69 kg: 35 mg 70–79 kg: 40 mg 80–89 kg: 45 mg ≥90 kg: 50 mg

PAI-1, plasminogen activator inhibitor.

583

to further improve survival. Yet, despite promising patency data with the bolus agents reteplase and tenecteplase,[w11 w12] no additional improvement in clinical outcome was observed.[w13 w14]

Fibrinolytic therapy: safety

Clinically, the most threatening complication is the risk of intracranial haemorrhage (table 2), which varies between trials from 0.4–1.1%, depending on the agent and the proportion of high risk patients included.[7 8 w15–17] This constitutes a fatal complication in about half of patients, with another third being permanently disabled.[7 8 w15] Unexpectedly, fibrin specific agents increased this complication. Although patient factors are most important, the impact of the intensity of anticoagulation with unfractionated heparin cannot be stressed enough. Each 10 second increase of the 12 hour activated partial thromboplastin time (aPTT) over 70 seconds has been shown to increase the absolute chance of intracranial haemorrhage by 0.07%.[9] From past trials it has also been deduced that the dose of fibrinolytic therapy is of paramount importance.[w18] This deserves renewed interest with the introduction of weight adjusted bolus fibrinolytic therapy, given the potential impact of erroneous administration of a higher dose than indicated.

In light of the above, the decision to choose fibrinolytic therapy, and the choice of agent, should be individually tailored, assessing the potential benefit and harm in the given situation. Because of the lack of better agents, some

Table 2 Risk factors for intracranial bleeding following fibrinolysis for ST elevation myocardial infarction

▶ Age >75 years
▶ Body weight <67 kg
▶ Female sex
▶ Hypertension
▶ Previous TIA/CVA
▶ Inappropriate anticoagulation*
▶ Dose and type of fibrinolytic agent†

*Unfractionated heparin is the recommended anticoagulant, in the following regimen: an intravenous bolus of 60 U/kg (max 4000 U), followed by a 48–72 hour infusion at 12 U/kg/hour (max 1000 U/kg/hour), aPTT monitoring at 3, 6, 12, and 24 hours after start of treatment (target aPTT 50–70 seconds).
†Fibrin specific agents like rt-PA and TNK-tPA increase the risk of intracranial haemorrhage by a factor 1.5 to 2 when compared to streptokinase. In the case of TNK-tPA, careful attention should be paid to the weight adjusted dose.
CVA, cerebrovascular accident; TIA, transient ischaemic attack.

institutions have primarily changed logistics by implementing pre-hospital fibrinolysis with a rather liberal rescue angioplasty policy, which resulted in comparable outcomes to primary angioplasty in the recent CAPTIM trial.[10] Although the available randomised data support rescue angioplasty,[11] a strategy of routine immediate angioplasty after non-fibrin specific agents seems less favourable, which may in part be explained by the increased bleeding risk.[w19] In individual cases with persisting pain, heart failure, or cardiogenic shock this type of strategy should always be considered. The use of glycoprotein IIb/IIIa receptor blockers after streptokinase should be avoided,[12] whereas the benefit of its periprocedural use following other fibrinolytics should be carefully weighed against the increased bleeding risk in each case individually.

Half dose lytic and glycoprotein IIb/IIIa receptor blockade: rationale

The lack of additional clinical benefit from angiographically more potent fibrinolytic regimens questioned the somewhat limited focus on the TIMI 3 flow concept, and broadened the search towards improved strategies. Some postulated increased reocclusion rates as a result of enhanced platelet activation after more fibrin specific therapy. A second suggestion was that improved epicardial patency per se may not translate into better outcome in the case where perfusion at tissue level is not (fully) restored.[w20 w21] Part of this lack of endocardial perfusion might be caused by peripheral embolisation of platelet-rich clot debris. Importantly, fibrinolytic therapy not only results in fibrin degradation and thrombus dissolution, but it also induces platelet aggregation by a thrombin and plasmin mediated pathway. In ISIS-2 the addition of 35 days of aspirin resulted in improved outcome after streptokinase.[6] Therefore, a combination of fibrinolytic therapy and stronger platelet inhibition was hypothesised to confer additional benefit—not only by the potential to enhance early TIMI 3 flow, but also by the above mentioned mechanisms.

Half dose lytic and glycoprotein IIb/IIIa receptor blockade: efficacy

The first results in angiographic pilot trials studying half dose rt-PA with full dose abciximab were impressive, with TIMI 3 flow rates at 60 minutes comparable to those at 90 minutes achieved with accelerated rt-PA alone (table 3).[12] This promising regimen has never been tested in a large clinical trial, probably because of the introduction of TNK-tPA. The clinical ASSENT-3 trial evaluated the impact of a combined regimen with TNK-tPA, which did not affect survival but

584

Table 3 Full dose lytic versus half dose lytic plus glycoprotein IIb/IIIa blocker: clinical and angiographic findings

	GUSTO V		ASSENT 3		TIMI 14		SPEED		Total*	
	r-PA	r-PA+Abc	TNK	TNK+Abc	rt-PA	rt-PA+Abc	r-PA	r-PA+Abc	ThX	ThX+Abc
n	8260	8328	4078	2016	163	173	108	187	12609	10704
Mortality % (n)	5.6 (488)	5.9 (468)	5.7 (231)	6.6 (133)	3.1 (5)	4.4 (5)	5.5 (6)	3.7 (7)	5.8 (730)	5.7 (613)
ICH % (n)	0.6 (49)	0.6 (52)	0.9 (37)	0.9 (19)	1.8 (3)	1.2 (2)	0.9 (1)	0.5 (1)	0.7 (90)	0.7 (74)
Major bleeding % (n)	2.3 (190)	4.6 (379)	2.6 (106)	4.3 (87)	4.3 (7)	3.5 (6)	3.7 (4)	8.0 (15)	2.4 (307)	4.5 (487)
Reinfarction	3.5 (291)	2.3 (190)	3.4 (140)	2.2 (44)	3.1 (5)	na	2.8 (3)	1.6 (3)	3.5 (439)	2.3 (237)
90 mins TIMI 3 %					62	74	47	57		

	Intro AMI		Integriti		Total†		Total‡	
	rt-PA	rt-PA+epti	TNK	TNK+epti	ThX+epti	ThX	ThX	ThX-GP
n	100	204	118	177	381	218	12827	11085
Mortality % (n)	7.0 (7)	4.4 (9)	5.1 (6)	3.6 (6)	3.9 (15)	6.0 (13)	5.8 (743)	5.7 (628)
ICH % (n)	2.0 (2)	2.0 (4)	1.7 (2)	0.6 (1)	1.3 (5)	1.8 (4)	0.7 (94)	0.7 (79)
Major bleeding % (n)	7.0 (7)	10.8 (22)	0.8 (1)	6.8 (12)	8.9 (34)	3.7 (8)	2.5 (315)	4.7 (521)
Reinfarction % (n)	3.0 (3)	4.9 (10)	0 (0)	4.0 (7)	4.5 (17)	1.4 (3)	3.4 (442)	2.3 (254)
90 mins TIMI 3 %	54	58	49§	62§				

*The total of all trials combining abciximab with thrombolysis; †the total of all trials combining epifibatide with thrombolysis; ‡the total of all trials combining glycoprotein IIb/IIIa blockers with thrombolysis; §TIMI grade 3 percentages at 60 minutes.
Abc, abciximab; epi, eptifibatide; GP, glycoprotein receptor blocker; ICH, intracranial haemorrhage; ThX, thrombolysis.

reduced recurrent ischaemia at the cost of higher bleeding rates.[13] Data from the angiographic pilot study, published half a year after the clinical trial, showed no improvement in TIMI 3 flow.[w22] The second large scale clinical trial on this subject, GUSTO-V, did not demonstrate a survival benefit either.[14] First, it should be realised that the regimen chosen was based on a subgroup analysis from the angiographic pilot trial SPEED. Whereas the randomised treatment arms showed no clear benefit on TIMI 3 flow, the subgroup of patients on standard dose heparin did.[w23] A second explanation results from the lessons learnt from GUSTO-1. To improve survival after pharmacological reperfusion by an absolute 1%, an absolute 20% improvement in TIMI-3 flow is necessary.[3 w24] Neither of the discussed regimens, nor the strategies performed with other glycoprotein blockers, met this criterion.[w24–26]

Half dose lytic and glycoprotein IIb/IIIa receptor blockade: safety

A combined regimen, using only half dose lytic, was expected to reduce the most serious bleeding complication of intracranial haemorrhage. Yet, findings from GUSTO-V seemed disappointing at first glance. More thorough analysis, however, showed that patients aged younger than 57 years had a reduced risk of intracranial haemorrhage, whereas in those over 57 this risk was increased.[w27] Older patients, especially those over 75 years, are a subgroup at particular high risk.[14] Similar observations were made in ASSENT-3, with reduced recurrent ischaemic events at the cost of higher bleeding, again specifically in the elderly.[13]

Despite these somewhat disappointing findings, the combined regimen remains an attractive alternative to full or half dose fibrinolysis as pre-treatment for facilitated angioplasty for acute myocardial infarction. As TIMI 3 flow before the procedure is a strong predictor of prognosis, the combined treatment strategy might confer benefit, with a door-to-balloon time often exceeding two hours.[w28] Moreover, the concomitant administration of abciximab could positively impact procedural success at the microcirculatory level. The pending FINESSE and ADVANCE-MI trials address this question in over 8500 patients with ST elevation myocardial infarction. Currently, the described combined regimen cannot be recommended for general implementation in daily clinical practice.

ADJUNCTIVE ANTITHROMBOTIC THERAPY

As stated before, the early and sustained success of fibrinolytic therapy is the result of the balance between forces stimulating lysis and those resulting in (re)occlusion. Adjunctive antithrombotic treatment should therefore be initiated as early as possible, and be continued indefinitely.

Antiplatelet therapy: efficacy and safety

Aspirin

Even in the absence of fibrinolytic treatment, the administration of aspirin has been shown to improve survival.[6] A simple 35 day intervention with aspirin improved survival with 25 per 1000 treated patients: 10.7% v 13.2%. This emphasises the need to start aspirin in any patient with an acute coronary syndrome. Interestingly, the efficacy of aspirin seems independent of the duration of symptoms,[6] in contrast to the benefits of fibrinolytic therapy.[1] To induce an immediate effect, the starting dose should be 160 mg or higher, whereas for long term administration 80–160 mg is

Table 4 Angiographic and clinical data on novel anticoagulant strategies as adjuncts to fibrinolytic therapy

		Fibrinolytic agent	New anticoagulant	Unfractionated heparin	New treatment
Angiographic trials				*90 minute TIMI 3 flow:*	
HART-2	(n = 400)	rt-PA	Enoxaparin	48%	53%
PENTALYSE	(n = 333)	rt-PA	Pentasaccharide	68%	64%
				5–7 day TIMI-3 flow:	
ASSENT-PLUS	(n = 439)	TNK-tPA	Dalteparin	63%	69%
AMI-SK	(n = 496)	Streptokinase	Enoxaparin	58%†	70%
Clinical trials, efficacy				*Death, reinfarction, refractory ischaemia:*	
HERO-2	(n = 17073)	Streptokinase	Hirulog	13.6%‡	12.6%
ASSENT-3	(n = 6095)	TNK-tPA	Enoxaparin	15.4%*	11.4%
ASSENT-3 PLUS	(n = 1639)	TNK-tPA	Enoxaparin	17.4%*	14.1%
Clinical trials, safety				*Intracranial haemorrhage:*	
ASSENT-3	(n = 6095)	TNK-tPA	Enoxaparin	0.93%	0.88%
ASSENT-3 PLUS	(n = 1639)	TNK-tPA	Enoxaparin	0.97%*	2.20%
HERO-2	(n = 17703)	Streptokinase	Hirulog	0.40%	0.60%

*Significant difference; †placebo control group, significant difference; ‡end point depicted: death and (adjudicated) reinfarction, p = 0.07.

585

sufficient. With regard to safety, quantitative review showed that the irreversible inhibition of cyclo-oxygenase-1 does not result in significant gastrointestinal bleeding, nor in an increase in intracranial haemorrhage.[15]

Other antiplatelet agents

In those patients allergic or intolerant to aspirin, the ADP receptor antagonist clopidogrel may be considered, although it has only been tested in the setting of non-ST elevation acute coronary syndromes.[w29] The impact of the routine administration of clopidogrel on top of aspirin in patients treated with fibrinolytic therapy is evaluated in the currently running CLARITY/TIMI-28-trial.

Anticoagulant therapy: efficacy

Table 4 summarises the angiographic and clinical data on anticoagulant strategies as adjuncts to fibrinolytic therapy.

Unfractionated heparin

This agent exerts its effect through potentiation of anti-thrombin III—so called "indirect thrombin inhibition". In the pre-fibrinolytic era, its use has been proven to notably improve prognosis.[16] Yet, since the standardised combined use of aspirin and fibrinolysis few trials re-evaluated its magnitude of benefit.[w30]

Based on pharmacological principles, the use of a bolus of heparin before, or concomitant with, fibrinolytic therapy would counteract the liberated, initially clot entrapped thrombin, and facilitate early reperfusion. From the randomised trials on subcutaneous administration of unfractionated heparin, it was found that in-hospital outcome was modestly improved, a benefit that dissipated within three weeks after discontinuation of treatment.[w7] For agents such as streptokinase, which result in prolonged fibrin depletion, 48–72 hours of unfractionated heparin is not believed to be of benefit, but placebo controlled evidence is lacking. The recent findings in the AMI-SK trial suggest that adjunctive anticoagulation is required.[w31] As the most successful reperfusion regimen to date,[7] the fibrin specific accelerated rt-PA, has never been tested without heparin, the regimen of newer fibrinolytics has always included heparin. This is also based on the observation of a clustering of reinfarctions within the first 10 hours of discontinuation of intravenous heparin.[9] This suggests an effect on rethrombosis and recurrent ischaemic events after fibrinolysis, and forms the rationale of the 48–72 hour infusion. Intravenous heparinisation constitutes several drawbacks, varying from the use of an infusion pump, hampering mobilisation, to the need for regular monitoring as a result of its rather unpredictable and varying plasma values.

Low molecular weight heparin

The introduction of agents like enoxaparin and dalteparin has overcome these problems. They have a better bioavailability, plasma concentrations are more stable, and monitoring is not necessary. Their impact is believed to be mostly achieved through inhibition of factor Xa and less by inhibition of thrombin activity, and results in similar early patency as unfractionated heparin.[w32] The ease of subcutaneous administration also promotes prolonged treatment as performed in the old trials with subcutaneous unfractionated heparin. This reduced in-hospital reinfarction rates during treatment, with a catch up phenomenon after discontinuation resulting in comparable outcome at 30 days[w33] to one year.[w34] This supports the impact of continued anticoagulation therapy after fibrinolysis. Interestingly, the AMI-SK trial was the first to properly address the impact of an immediate, prolonged anticoagulation regimen in patients treated with streptokinase. In this placebo controlled trial, early ST resolution was significantly better in patients on enoxaparin, as was 5–7 day patency.[w31]

Direct thrombin inhibitors

In contrast to heparins, this group of anticoagulants also affects thrombin bound to fibrin and fibrin degeneration products. The impact of hirulog was compared with unfractionated heparin in over 17 000 patients in the HERO-2 trial, addressing ST elevation myocardial infarction treated with streptokinase. Survival was not affected. In-hospital reinfarction, adjudicated in a blinded fashion, was significantly reduced from 3.6% to 2.8%.[w35]

Pentasaccharides

A pentasaccharide is a compound of unfractionated heparin, with the ability to activate the anti-Xa activity of antithrombin-III, affecting the generation of thrombin without any direct effect on thrombin itself.[w36] This new agent resulted in

586

similar 90 minute patency after fibrinolysis as unfractionated heparin. In a secondary analysis, reocclusion was assessed in the subset of patients who did not undergo an intervention. A 5–7 day regimen of this new agent resulted in lower reocclusion rates, as compared to a 48–72 hour treatment with unfractionated heparin: 0.9% v 7.0%, respectively (p = 0.065).

In summary, low molecular weight heparins are certainly more easy to administer and seem more effective than unfractionated heparin, which may in part be related to their prolonged administration. Whether these or other new agents should be implemented in daily clinical practice also depends on safety aspects.

Anticoagulation: safety
Unfractionated heparin
Given the association between the level of anticoagulation and the risk of intracranial haemorrhage after fibrinolysis,[9] downward dose adjustments and more frequent assessment of the aPTT have been introduced.[17] This has resulted in reduced rates of intracranial bleeding, without loss of efficacy.[w37] The advantage unfractionated heparin has over the newer anticoagulants is the long term experience of using this agent in hundreds of thousands of patients. Given the modest impact on survival and reinfarction, safety is an important aspect.

Low molecular weight heparin
Whereas enoxaparin seemed an attractive alternative to unfractionated heparin, recent findings call for a more thorough evaluation of the safety of this agent as an adjunctive treatment to fibrinolysis. In the setting of non-ST elevation myocardial infarction, enoxaparin proved safe, and seemed to reduce recurrent ischaemic events with administration until discharge, as compared to 48–72 hours of unfractionated heparin.[w38] The first trial using this enoxaparin regimen with in-hospital fibrinolysis showed increased overall bleeding rates, but was too small to be conclusive in regard to the risk of intracranial haemorrhage.[13] The pre-hospital moderately sized ASSENT-3 PLUS trial, however, reported a significant increase in the incidence of intracranial haemorrhage in patients on enoxaparin: 2.0% v 0.9% with unfractionated heparin.[w39] This finding arose because the trial included a higher proportion of older, female patients with a low body weight. Other important aspects are the lack of a weight adjusted bolus and the almost doubled half-life of the subcutaneous doses in elderly patients. The TIMI-25 EXTRACT trial will address the safety of subcutaneous enoxaparin with or without bolus, and in a weight adjusted dose over the age of 75. In the pending CREATE trial, reviparin, a new low molecular weight heparin, will be tested.

Other anticoagulants
Given the limited experience with anti-Xa agents, and the higher bleeding rates with the rather expensive direct thrombin inhibitors, these agents are not to be recommended for general implementation. For patients with a heparin induced thrombo-cytopenia hirudin could serve as an alternative.

PREVENTION OF RECURRENT ISCHAEMIC EVENTS: THE (SUB)ACUTE AND CHRONIC PHASE
Irrespective of the initiation of reperfusion therapy, it is of the utmost importance to initiate interventions aimed at early haemodynamic stabilisation, and prevention of recurrent ischaemia and malignant arrhythmias. Moreover, the unstable "hot" plaque should be "cooled off", with agents affecting endothelial function and inflammation as additional treatment to antithrombotic agents (fig 1).

Nitrates
Due to their vasodilatating properties these agents are recommended for the first 24–48 hours in patients with persistent ischaemia, hypertension, heart failure, and large anterior infarction.[w40 w41]

β Blockers
Given the unfavourable prognostic impact of recurrent ischaemia,[w42] β blockers are a key intervention in the setting of myocardial infarction. In addition, their antihypertensive and, in particular, antiarrhythmic properties are thought to make a major contribution to their beneficial effects on survival, as well as their beneficial effect on the incidence of cardiac rupture. Although the majority of evidence stems from the pre-fibrinolytic era,[18 w43] this does not limit their applicability in the current era of reperfusion therapy. Specifically in patients with restored patency the salvaged myocardium remains at renewed risk of ischaemia, especially in the early phase, which was underscored in the TIMI-IIb trial. Early initiation—that is, within two hours—significantly reduced the combined (secondary) end point of reinfarction and recurrent ischaemia in the first week as compared to patients in whom β blockers were initiated after this first week.[w44] With respect to the choice of agent, cardioselective β blockers such as atenolol and metoprolol are to be preferred over agents like propranolol, in order to avoid or reduce β2 related side effects. Importantly, randomised data on the use of cardioselective agents in patients with reactive airway disease only resulted in a limited decrease in forced expiratory volume in one second (FEV_1) which was not associated with adverse respiratory effects.[w45] Moreover, observational data in over 200 000 patients suggest that patients believed to have a relative contraindication, such as diabetes or asthma, benefit from β blockers without clinically important side effects.[w46] Thus, β blockers should be initiated as early as possible and deserve a central role in the (sub)acute phase and follow up treatment of all patients with acute myocardial infarction, including those with left ventricular dysfunction, in the era of reperfusion therapy.[w47] Importantly, intolerable side effects can be directly antagonised, in contrast to those of calcium channel blockers.

Calcium channel blockers
Short acting agents from the dihydropyridine class such as nifedipine are contraindicated in the setting of myocardial infarction, given their negative effects as a result of reflex sympathetic stimulation, tachycardia, and hypotension.[19 w48] Long acting agents, and other calcium antagonists such as diltiazem and verapamil, have failed to improve survival.[w49–53] For the latter agents, reduction of recurrent ischaemic events has been demonstrated in a selected patient population, without left ventricular dysfunction.[w49 w50] Therefore, their use should primarily be restricted to co-administration with a β blocker in the case of recurrent ischaemia.

ACE inhibitors

Patients who particularly benefit from treatment with angiotensin converting enzyme (ACE) inhibitors are those with large infarcts—not only those with clinical signs of heart failure[w54 w55] but also asymptomatic patients with reduced left ventricular function.[w55 w56] As much of the survival advantage is realised in the first 48 hours, early initiation of oral treatment is indicated.[20 w40 w41 w57 w58] With the emerging evidence that various subgroups of patients benefit from treatment, a six week treatment period for all patients after infarction can certainly be considered.[20] In the case of heart failure and reduced left ventricular function, angiotensin blockers can be used as an alternative, but they can also be used in addition to ACE inhibitors to reduce cardiovascular, though not all cause, mortality.[w59]

Statins

The need for long term use of statins is undisputed.[w60–62] With respect to the additional impact of early initiation, no trial data on ST elevation myocardial infarction are available. Data from the MIRACL study suggest a reduced incidence of recurrent ischaemic events with early treatment after a non-ST elevation acute coronary syndrome.[w63]

Additional antithrombotic treatment

Although a prolonged combined antithrombotic regimen of aspirin and (oral) anticoagulation has additional benefit,[5] the need for a good infrastructure of oral anticoagulation control has hampered implementation in daily care. With the successful initial data on the use of the oral direct thrombin inhibitor ximelagatran in addition to aspirin, this problem may be solved, which facilitates future comparisons with dual antiplatelet regimens.[w64] The beneficial impact of the standard addition of clopidogrel has been proven in non-ST elevation acute coronary syndromes, and is currently under investigation in the large ST elevation CCS2 trial. Therefore, the majority of patients after ST elevation myocardial infarction only receive treatment with aspirin at discharge, which should be used indefinitely.

RECOMMENDATIONS

In the majority of patients with an ST elevation myocardial infarction for whom treatment by primary angioplasty is not possible, optimal pharmacological treatment is warranted. Importantly, time to initiation of treatment is a crucial element, a factor that can be positively influenced by early, preferably pre-hospital, initiation of pharmacological reperfusion therapy. When primarily adopting a pharmacological approach to reperfusion therapy in ST elevation myocardial infarction, an individually tailored approach with respect to the choice of a fibrin specific or non-fibrin specific agent is a prerequisite, balancing the respective risks and benefits, which also holds true for the decision over rescue angioplasty. Aspirin, anticoagulation, and early initiation of β blockade provide the basis for adjunctive treatment in the acute phase. The use of calcium channel blockers should be reserved for co-treatment with a β blocker; only agents from the non-dihydropyridine class, such as diltiazem, can be considered as an alternative to β blocker treatment in the case of clinically proven intolerance. In the subgroups of patients with a reduced left ventricular function, or clinical signs of heart failure, ACE inhibitors are indicated, and a six week treatment period can be considered in all patients with an acute coronary syndrome. Finally, in order to prevent recurrent ischaemic events and malignant arrhythmias and to stabilise the "hot" plaque, the continued use of aspirin and β blockers is recommended, complemented by long term statin treatment.

. . . .

Authors' affiliations
M A Brouwer, N Clappers, F W A Verheugt, Department of Cardiology, Heartcenter, University Medical Center Nijmegen, The Netherlands

587

REFERENCES

1 **Boersma E**, Maas ACP, Deckers JW, et al. Early thrombolytic treatment in acute myocardial infarction: reappraisal of the golden hour. Lancet 1996;**348**:771–5.

2 **Morrison LJ**, Verbeek PR, McDonald AC, et al. Mortality and prehospital thrombolysis for acute myocardial infarction: a meta-analysis. JAMA 2000;**283**:2686–92.

▶ **Meta-analysis of randomised trials comparing pre-hospital thrombolysis with in-hospital thrombolysis. Pre-hospital thrombolysis reduced time to treatment by almost one hour, resulting in a 17% relative reduction in mortality, representing about 18 deaths per 1000 patients treated.**

3 **GUSTO Angiographic Investigators**. The effects of tissue plasminogen activator, streptokinase, or both on coronary-artery patency, ventricular function, and survival after acute myocardial infarction. N Engl J Med 1993;**322**:33–42.

▶ **Landmark trial comparing streptokinase with the accelerated alteplase regimen, showing a reduction of mortality from 7.3% to 6.3% in favour of the new regimen. This 1% absolute reduction in mortality was attributed to an absolute increase in 90 minute TIMI grade 3 flow by 20%, which was found in the angiographic substudy. After this trial "accelerated rt-PA" became the gold standard of pharmacological reperfusion therapy.**

4 **Verheugt FWA**, Meijer A, Lagrand WK, et al. Reocclusion, the flip side of coronary thrombolysis. J Am Coll Cardiol 1996;**27**:766–73.

▶ **Review on the adverse effects of reocclusion of the infarct artery, which occurs in about 30% of patients within a year after successful thrombolysis. Reocclusion increases the risk of mortality and recurrent ischaemic events, so called symptomatic reocclusion. Importantly, even in the absence of clinical reinfarction, reocclusion is associated with impaired left ventricular recovery.**

5 **Brouwer MA**, Verheugt FWA. Oral anticoagulants in acute coronary syndromes. Circulation 2002;**105**:1270–4.

6 **ISIS-2 Collaborative Group**. Randomised trial of intravenous streptokinase, oral aspirin, both, or neither among 17,187 cases of suspected acute myocardial infarction: ISIS-2. Lancet 1988;**ii**:349–60.

7 **GUSTO Investigators**. An international randomised trial comparing four thrombolytic strategies for acute myocardial infarction. N Engl J Med 1993;**329**:673–82.

8 **Gurwitz JH**, Gore JM, Goldberg RJ, et al. Risk for intracranial hemorrhage after tissue plasminogen activator treatment for acute myocardial infarction. Participants in the national registry of myocardial infarction 2. Ann Intern Med 1998;**129**:597–604.

9 **Granger CB**, Hirsch J, Califf RM, et al. Activated partial thromboplastin time and outcome after thrombolytic therapy for acute myocardial infarction: results from the GUSTO trial. Circulation 1996;**93**:870–88.

10 **Bonnefoy E**, Lapostolle F, Leizorovicz A, on behalf of the Comparison of Angioplasty and Prehospital Thrombolysis in Acute Myocardial Infarction (CAPTIM) study group, et al. Primary versus prehospital fibrinolysis in acute myocardial infarction: a randomised study. Lancet 2002;**360**:825–9.

11 **Ellis SG**, Da Silva ER, Spaulding CM, et al. Review of immediate angioplasty after fibrinolytic therapy for acute myocardial infarction: insights from the RESCUE I, RESCUE II, and other contemporary clinical experiences. Am Heart J 2000;**139**:1046–53.

▶ **Meta-analysis on the few randomised evaluations addressing the impact of rescue angioplasty. In a setting of a primarily pharmacological approach for ST elevation myocardial infarction, this report shows that rescue angioplasty after failed thrombolysis deserves to be considered as adjunctive therapy. In clinical practice, this may not become routine due to logistics and infrastructure problems, but its use should at least be considered in individual cases.**

12 **Antman EM**, Giugliano RP, Gibson CM, et al. Abciximab facilitates the rate and extent of thrombolysis. Results of the thrombolysis in myocardial infarction (TIMI) 14 trial. Circulation 1999;**99**:2720–32.

13 **ASSENT-3 Investigators**. Efficacy and safety of tenecteplase in combination with enoxaparin, abciximab, or unfractionated heparin: the ASSENT-3 randomised trial in acute myocardial infarction. Lancet 2001;**358**:605–613.

▶ **Clinical trial randomising 6095 patients to (1) full dose tenecteplase, (2) half dose tenecteplase plus abciximab, or (3) full dose tenecteplase and enoxaparin. No reduction in mortality was shown, and intracranial haemorrhage rates were similar. Nevertheless, in-hospital reinfarction rates were reduced on the new antithrombotic regimens, but this was at the cost of an increase in extracranial haemorrhage.**

14 **GUSTO V Investigators**. Reperfusion therapy for acute myocardial infarction with fibrinolytic therapy or combination reduced fibrinolytic therapy and platelet glycoprotein IIb/IIIa inhibition: the GUSTO V randomised trial. Lancet 2001;**357**:1905–14.

▶ Randomised trial comparing full dose reteplase with half dose reteplase plus abciximab. Based on favourable angiographic results of combination therapy, better results on clinical end points were expected. Results from 16 588 patients showed reduced reinfarction rates, but also increased rates of major non-cerebral bleeds and no mortality benefit.

15 **Antithrombotic Trialists' Collaboration**. Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients. *BMJ* 2002;**324**:71–86.

▶ Meta-analysis of randomised trials comparing antiplatelet agents with placebo for several indications, such as previous or acute myocardial infarction and previous and acute stroke. A relative reduction of serious vascular events of about 25% was reported.

16 **Collins R**, Peto R, Baigent C, *et al.* Aspirin, heparin, and fibrinolytic therapy in acute myocardial infarction. *N Engl J Med* 1997;**336**:847–60.

▶ Important review concerning fibrinolytic treatment and the available antithrombotic adjuvant therapies at that time.

17 **Van de Werf F**, Ardissino D, Betriu A, *et al.* Task force on the management of acute myocardial infarction of the European Society of Cardiology. Management of acute myocardial infarction in patients presenting with ST-segment elevation. *Eur Heart J* 2003;**24**:28–66.

18 **Yusuf S**, Peto R, Lewis J, *et al.* Beta blockade during and after myocardial infarction: an overview of the randomised trials. *Prog Cardiovasc Dis* 1985;**27**:335–371.

▶ Large overview of all randomised, placebo controlled trials comparing β blockers with placebo. It showed that mortality can be reduced by 25% for many patients after myocardial infarction, with little risk of clinically important side effects. Treatment is to be started early and continued in the long term. Early intravenous β blockade reduced infarct size, but effect on mortality remained unclear.

19 **Furberg CD**, Psaty BM, Meyer JV. Nifedipine. Dose-related increase in mortality in patients with coronary heart disease. *Circulation* 1995;**92**:1326–31.

20 **ACE Inhibitor Myocardial Infarction Collaborative Group**. Indications for ACE inhibitors early treatment of acute myocardial infarction. Systematic overview of individual data from 100 000 patients in randomized trials. *Circulation* 1998;**97**:2202–12.

▶ Pooled analysis of randomised placebo controlled trials larger than 1000 patients for ACE inhibitors. It showed lower 30 day mortality rates for ACE inhibitor treated patients, largely due to the effect of therapy in the first week of treatment. The effect was more pronounced in patients with anterior infarction, heart failure, or tachycardia.

Additional references appear on the *Heart* website—
http://www.heartjnl.com/supplemental