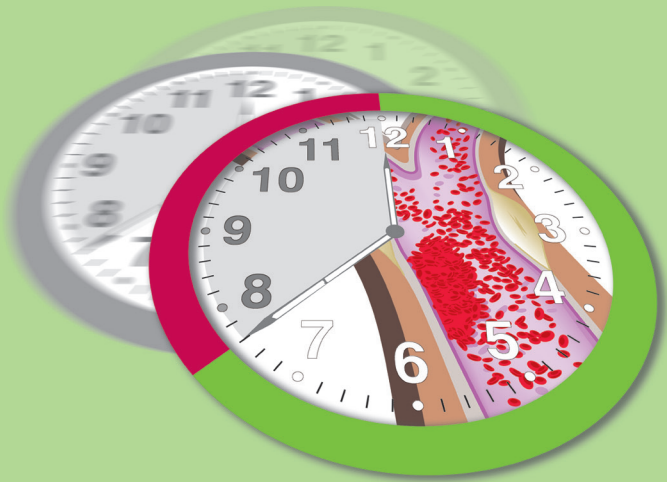


Arntz • Danchin • Goldstein • Huber

Contemporary management of acute ST elevation myocardial infarction

Thrombolysis and PCI as major treatment options



Edited by Raderschadt
Published by infill Kommunikation GmbH

CONTEMPORARY MANAGEMENT OF ACUTE ST-ELEVATION MYOCARDIAL INFARCTION

Thrombolysis and PCI as major treatment options

Hans-Richard Arntz
Nicolas Danchin
Patrick Goldstein
Kurt Huber

Edited by
Emma Raderschadt

Published by
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This eBook was edited by infill Kommunikation GmbH.

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This eBook was financially supported by Boehringer Ingelheim.

Boehringer Ingelheim has been in the forefront of research and development for the treatment of cardiovascular diseases for decades. This book has been made possible with financial support fromBoehringer Ingelheim.

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ISBN 978-3-00-028883-9

Introduction

Since the groundbreaking findings by DeWood et al. (1), showed that acute myocardial infarction is caused by vascular occlusion from a thrombus attached to a ruptured plaque (2,3), the treatment of this condition has definitely entered the era of reperfusion therapy. Today, thrombolysis is a cornerstone of acute treatment and aims at lysis of capillary thrombi and the reduction of blood viscosity.

In contrast to more systematic investigations in Göttingen and Berlin, early attempts by Chazov et al. using intracoronary lysis with streptokinase did not attract any attention (4,5). However, the existence of catheter laboratories at that time was small. Moreover, the time delay until execution was an inevitable drawback of intracoronary lysis, the more so as the rapid progression of myocardial necrosis was proven experimentally (6). Therefore, it was only logical to test the effects of lysis in uncomplicated and easy-to-conduct “systemic” applications. Even during the dose-finding studies, Schröder et al. suggested that in order to further optimise the time gain with i.v. lysis, treatment could be initiated pre-hospitally in the patient’s home by the emergency services (7).

The fundamental breakthrough of intravenous thrombolysis using streptokinase was achieved in the randomised, placebo-controlled GISSI study (8), comprising approximately 12,000 patients, where the time dependency of therapeutic success was impressively demonstrated. At the same time, this study also noted the high rate of re-infarctions, which is the Achilles heel of thrombolysis. In the ISIS-2 study, the combination of aspirin and streptokinase showed a mortality reduction of 47% (9). This additional gain was partly explained by the blockade of platelet aggregation, which is a possible source of re-occlusion. Even aspirin monotherapy led to a mortality reduction of approximately 24% (9). Since then aspirin has become standard in infarct therapy. In contrast, during the first major thrombolysis studies, heparin was rarely and not systematically investigated; instead, it was used both subcutaneously and intravenously for the prevention of re-occlusions.

The next major advance in reperfusion therapy for myocardial infarction was the recombinant technology production of the tissue plasminogen activator, t-PA. In angiography-controlled studies, where alternative thrombolytic agents

such as APSAC and urokinase were also tested, t-PA showed a significantly higher rate of reperfusion compared to streptokinase. The GUSTO-1 study compared streptokinase with t-PA in 41,000 patients and resulted in a clinically significant superiority of t-PA, albeit at the cost of a slightly elevated rate of intracranial haemorrhage, especially in elderly patients (10). The use of heparin with t-PA proved to be effective in preventing re-occlusions (11). Finally, t-PA became the gold standard of reperfusion therapy after Neuhaus et al. described an effective modified dosing scheme (12).

Although the time dependency of the effect of thrombolysis was the major driving force behind the introduction of intravenous lytic therapy, the option of the earliest possible pre-hospital lysis was widely postulated and discussed, but its potential was only investigated in a number of small and one larger study. The big EMIP-study (13) was also prematurely stopped due to lack of sponsorship. However, in general these studies proved the principal rationales of pre-hospital lysis were safe and showed a trend towards its use. Even so, this beneficial trend was first statistically proven in a meta-analysis (14). One possible reason for the lack of widespread interest in early pre-hospital thrombolysis could have been that cardiologists at that time were turning their focus to interventional catheterisation of an infarct, as an increasing number of hospitals were investing in cath labs. After a cautious start (15), rapid technological development took place, which enabled broad use of this method. From early on, balloon dilation was used in combination with thrombolysis (16-19), because angiography showed that lysis did not lead in all patients to an early, complete and sustained re-opening of infarcted vessels. However, these investigations had lots of complications and the results were discouraging.

The further development of coronary intervention was characterised by rapid technological progress (e.g. stents), the development of efficient adjuvant therapies (Gp IIb/IIIa receptor blockers, thienopyridines, alternative anti-thrombins) and extensive establishment of interventional centres. Comparative investigations of primary interventions with relatively late in-hospital thrombolysis appeared to prove the superiority of primary intervention in all circumstances (20). Only one study – the CAPTIM study, conducted in France – compared pre-hospital lysis (with the possibility of additional interventions following “liberal” criteria) with primary intervention (PPCI). This study showed that pre-hospital lysis (PHT) was equivalent to PPCI, and in patients treated within 120 minutes after symptom onset, PHT tended to show a lower 90-day mortality rate (21,22).

The development of injectable bolus thrombolytics with a longer half-life provided substantial additional potential for the future of lytic therapy. This easy-to-use method is especially valuable for pre-hospital use. Meanwhile, clopidogrel was also successfully applied in lytic therapy in addition to aspirin (23). Alternative antithrombins, such as enoxaparin, also contributed to significant improvements in the outcomes of lysis in ST-elevation myocardial infarction (STEMI) (24). Once again, the rationale of the combination of lysis and inter-

vention was considered in the course of technological advances. The concept of “facilitated PCI”, which is defined as immediate intervention after lytic therapy, did not turn out to be beneficial overall, although interestingly, it showed very good results after pre-hospital lysis (25,26). Conversely, the concept of a “pharmacoinvasive approach”, consisting of, above all, pre-hospital lysis with a time-delayed angiography and possible PCI, has turned out to be a promising strategy in some studies (27,28).

This book is intended to provide the rationale for the use of pre-hospital lysis, PPCI and combination strategies, taking into consideration the current guidelines, which were developed and refined using clinical and scientific experience collected over decades. Further chapters deal with practical considerations (e.g. adjunctive therapy), the procedures for specific patients groups, the organisation of networks of emergency medical services, hospitals with and without cath labs, and the comparison of various emergency systems with different levels of staff and equipment.

The aim of this book is to provide the interested reader with a current overview of the role of pre-hospital lysis as a primary reperfusion strategy within the scope of a general management of ST-elevation myocardial infarction. The authors hope to encourage the staff responsible within the emergency services to exploit the often unutilised potential of pre-hospital thrombolysis to benefit patients.

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Hans-Richard Arntz

The role of pre-hospital thrombolysis in ST-elevation myocardial infarction

Current Guidelines

Introduction

The basis for this chapter is derived from the guidelines for treatment of STEMI patients published at different time points. The oldest actual guidelines are the recommendations of the European Resuscitation Council published in October 2005 (1). A revision of these guidelines is under preparation and will be published in October 2010. The second guidelines are the report of the American Heart Association and the American College of Cardiology, which were developed in collaboration with the Canadian Cardiovascular Society and are endorsed by the American Academy of Family Physicians. This paper was published in January 2008 (2). The report is named a “Focused update” of the 2004 guidelines of the same societies (3). Finally, the European Society of Cardiology published the actual guidelines in November 2008 (4). Clearly many differences in the guidelines can easily be explained by the time point of publication. Beside this effect of timing there are, however, also remarkable differences in conception between the guidelines, which may be due to the specific background conditions, system differences and differences in infrastructure or legal conditions. National guidelines for different countries, for example France, incorporate some of these specific aspects.

Table 1: Classes of recommendation according to the ESC guidelines

Classes of Recommendations	Definition
Class I	Evidence and/or general agreement that a given treatment or procedure is beneficial, useful, effective.
Class II	Conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of the given treatment or procedure.
Class IIa	Weight of evidence/opinion is in favour of usefulness/efficacy.
Class IIb	Usefulness/efficacy is less well established by evidence/opinion.
Class III	Evidence or general agreement that the given treatment or procedure is not useful/effective, and in some cases may be harmful.

Level of Evidence A	Data derived from multiple randomised clinical trials or meta-analyses.
Level of Evidence B	Data derived from a single randomised clinical trial or large non-randomised studies.
Level of Evidence C	Consensus of opinion of the experts and/or small studies, retrospective studies, registries.

Van de Werf *et al.* Management of acute myocardial infarction in patients presenting with persistent ST-segment elevation, *European Heart Journal*. 2008; 29:2909-2945; 2912, by permission of Oxford University Press

The dynamic development in the field of acute coronary syndromes with nearly daily publications of new insights and results of clinical trials testing new hypotheses and therapeutic alternatives therefore needs continuous review on the background of actual developments. Consequently, the scientific “half life” of the guidelines is not very long. The guidelines generally try to follow the concept of evaluation of classes of true evidence, based on high quality clinical investigations (Table 1). Doubtlessly, sometimes a bias, influenced by the personal views of the authors and reviewers, cannot be denied.

Pathogenesis of STEMI and treatment

In all guidelines, there is a principal consensus on the atherothrombotic pathogenesis of STEMI (5). There is also uniform consensus on the outstanding importance of immediate targeted reaction on signs or symptoms suggesting an acute myocardial infarction in order to fight the enormous case fatality rate in the initial phase of STEMI (6, 7). Achieving reperfusion of the myocardium at risk as early as possible is the second target. Early reperfusion will reduce myocardial damage and reduce short term (e.g. cardiogenic shock) and long-term complications (e.g. risk of life-threatening arrhythmias or heart failure due to large myocardial damage).

Logistics of care

The overarching goals of care are to master any potential life-threatening complication e.g. ventricular fibrillation and to minimise the time to reperfusion. This conception underlines the increasing importance of care before hospital admission and the emerging role of the emergency medical services (EMS) not only with regard to first diagnostic steps. In advanced EMS organisations, e.g. physician-staffed systems, selection of the receiving hospital and initiation of symptomatic and causal treatment of STEMI also falls into the responsibility of the EMS.

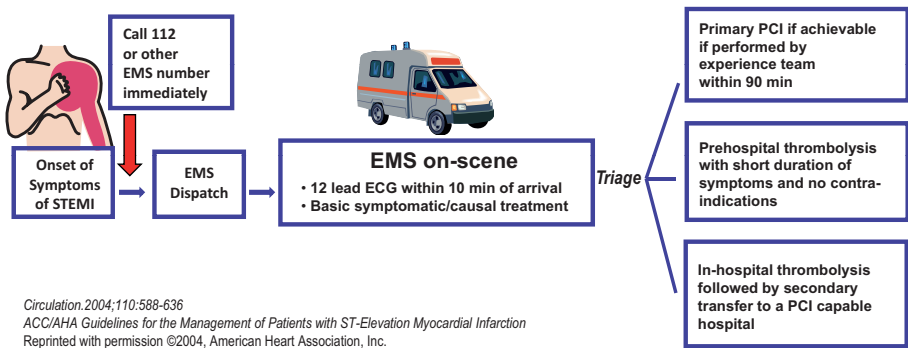


Figure 1: Idealised model for fast track treatment of a patient with an acute myocardial infarction: Principal target reperfusion initiated within 2 hrs, optimally within the “Golden hour” = the first 60 min.

The concept of accelerating the process until a safe and effective reperfusion is achieved is optimally realised in a network consisting of the EMS, non-PCI-capable hospitals, and PCI-capable hospitals. The latter definition should be restricted to institutions where experienced teams and supporting staff offer primary PCI in STEMI on a routine basis 24 hours a day, seven days a week and 365 days a year (4). A model of ideal initial out-of-hospital care and decision making for patients presenting with signs and symptoms of STEMI is outlined in *Fig 1*.

Role of the patients

A problem, which seems to be difficult to overcome, is the delayed reaction of patients to the symptoms of an evolving infarction. A large number of somatic, demographic, psychological and social factors influences the delay to seeking medical help (*Fig 2*; 8,9). Denial, which is also often found in patients who have already experienced an earlier event, seems to be one of the most problematic factors. It should be communicated to patients at risk, their relatives, and indeed the whole public, that the optimal response to medical emergencies in general and heart attacks as a typical life-threatening condition of outstanding urgency is to call the EMS. Travelling by private transport to the next hospital emergency department or even waiting for the next surgery hours of the pri-

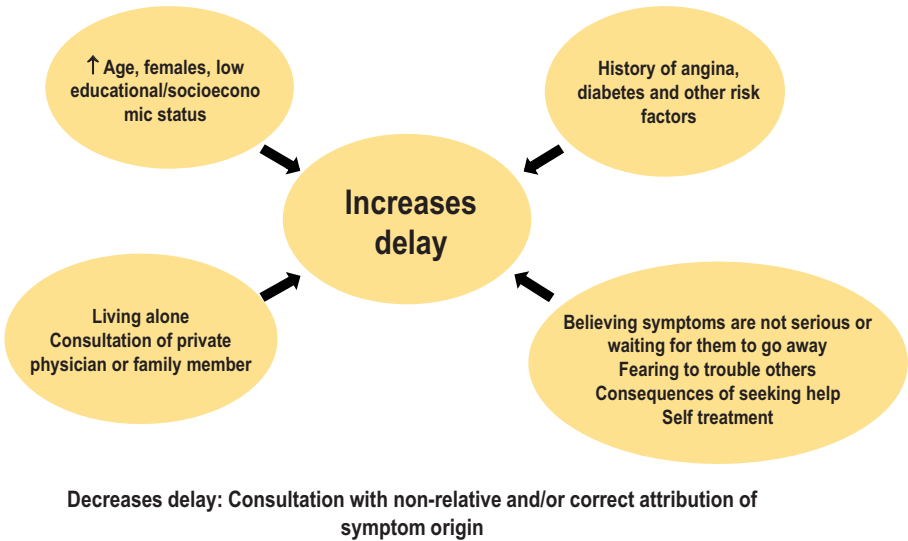


Figure 2: Factors affecting prehospital delay in patients with ACS

vate physician (perhaps the next day or after a weekend) can be deleterious if not fatal for a patient with an acute coronary syndrome, and therefore needs to be strictly discouraged. Instead, patients should be advised to call the EMS in case of a suspected heart attack, and informed about the risks of not doing so. It is the role of general practitioners and private physicians to advise their patients accordingly.

To shorten the time until definitive diagnosis and treatment, optimal organisation of the EMS is a precondition. A well-known and universally available emergency number (the recommended, but still not fully established emergency number for Europe is 112) is a principal necessity for realisation. Since the EMS has a critical role in initial management of STEMI patients (*Fig 1*), it should no longer be considered just as a transportation system but as an instrument of early diagnosis, triage, and initial symptomatic and causal treatment. Besides the skills needed to perform basic life support, even fundamentally trained EMS personnel should be able to recognise the typical symptoms of an acute coronary syndrome and may provide oxygen in ACS patients presenting with dyspnoea. These essential skills will enable them to travel - ideally after radio announcement - directly to a hospital capable of taking care of ACS patients. Other EMS services will send out ambulances or even helicopters staffed with crews with advanced training, e.g. in advanced life support. Advanced, two-tiered systems generally send out paramedics, nurses or even physicians and have the equipment to definitely establish the diagnosis of STEMI. In addition, these providers have a broad spectrum of therapeutic options and medications including prehospital thrombolysis at their disposal.

First medical contact

Irrespective of the route by which the patient seeks medical help (the EMS, the private physician or an emergency department of a hospital with or without PCI capabilities), the first medical contact should be the place for basic diagnostic measures and triage according to the guidelines (1-4). Depending on the resources and possibilities, the first medical contact should also be the place for initiation of symptomatic and causal treatment when the diagnosis of STEMI is confirmed by signs and symptoms on the one hand and the ECG finding on the other.

Clinical signs and symptoms

The working hypothesis “acute myocardial infarction” is primarily based on the patient history and presenting symptoms. Chest pain radiating to the arms, neck, shoulders, chin, or upper abdomen, often accompanied by vegetative signs such as sweating or nausea, shortness of breath, feeling oppressed and threatened to die, is typical for STEMI patients. However, in the elderly, in women, and in diabetics, symptoms are frequently hidden, atypical or oligo-

symptomatic. Dyspnoea, fatigue or general weakness may be the leading symptom as well as fainting or syncope. Thorough evaluation may reveal that these symptoms are being caused by an acute myocardial infarction. Registration of the blood pressure, the heart rate (arrhythmia?) and examination of the lungs (rales?) are necessary initial steps in clinical evaluation and triage.

While evaluating the patient, differential diagnoses (*Tab. 2*) should be kept in mind. This is of importance since treatment indicated for STEMI may be deleterious for misdiagnosed patients. Special attention should be drawn to patients who do not show any sign of ischaemia on the ECG and who are suffering from chest pain. Additional neurologic symptoms or missing peripheral pulses may lead to the diagnosis of aortic dissection. Chest pain aggravated by respiration may be a sign of any pleural or pulmonary disease. Dyspnoea of acute onset with tachycardia and reduced oxygen saturation with normal auscultation of the lung may be due to pulmonary embolism. ST-elevation in all leads of the ECG may be a sign of pericarditis. In addition, disease of the upper abdomen, e.g. acute pancreatitis, may mimic symptoms of an acute myocardial infarction.

Table 2: Differential diagnosis in patients presenting with chest pain

Cardiovascular diseases	<ul style="list-style-type: none"> ● Tachycardia arrhythmia ● Pericarditis ● Myocarditis ● Aortic dissection
Pulmonary diseases	<ul style="list-style-type: none"> ● Pulmonary embolism ● Pleuritis ● Pneumothorax
Skeletal diseases	<ul style="list-style-type: none"> ● Rib fractures/contusions ● Vertebral diseases ● Tietze's syndrome
Gastrointestinal diseases	<ul style="list-style-type: none"> ● Oesophagitis/rupture ● Ulcers ● Pancreatitis ● Gall bladder diseases
Further diseases	<ul style="list-style-type: none"> ● Herpes zoster ● Tumour diseases of the skeleton/thoracic wall

Role of the ECG

Persisting ST-elevation on a 12- or more lead ECG is by definition the mainstay of the diagnosis of STEMI. ST-elevation of ≥ 0.1 mV in two or more of the peripheral leads and/or ≥ 0.2 mV in ≥ 2 adjunct chest leads are the classical ECG signs of MI. In addition, ST depression in chest leads V1-V3 inversely representing ST elevation in V7-V9 is a sign of a posterior infarction. In patients with an inferior MI, ST-elevation registered in lead V4 R may be helpful to detect an infarction of the right ventricle. Also, a (presumably) new left bundle branch block together with typical (nitro refractory) chest pain is almost certainly a myocardial infarction and should be treated accordingly. A normal ECG finding does not exclude a threatening or evolving infarction with a sometimes “stuttering” character. If typical symptoms of an acute coronary syndrome are present, the patient has to stay under strict medical observation until this diagnosis has definitively been ruled out.

All guidelines uniformly request that a 12- or more lead ECG should be registered in all chest pain patients as soon as possible. The ERC definition of “soon” is within 10 minutes of contact. This ECG will not only document ST-segment elevation in case of STEMI but in many patients it may also detect other signs of ischaemia and important arrhythmias. It has been shown repeatedly that on-scene ECG registration by the EMS shortens distinctly the time to reperfusion in the hospital, irrespective of whether reperfusion is achieved with thrombolysis or primary PCI (10,11). These ECG’s may be interpreted with high diagnostic reliability by EMS personnel, that is physicians, trained nurses or paramedics (11), with a precision comparable to in-hospital interpretation. Moreover, ECG readings can be supported by built-in computerised diagnostic algorithms in the ECG machine. Finally, many devices used for out-of-hospital ECG registration allow good quality radio or cellular phone transmission of the ECG to a remote hospital-based physician for interpretation and/or to speed up the preparation of procedures after admission of the patient (12).

Naturally, an ECG showing the typical features of an acute myocardial infarction is also a precondition for initiation of prehospital thrombolysis. Even though ECG registration by the EMS is an explicit postulation in the guidelines, many providers do not comply with that demand (2,3). Even advanced physician-staffed systems do not always have an ECG machine available or else do not use it even if at hand (13).

Biomarkers

Biomarkers of myocardial necrosis (troponins or CK-MB), even if quite specific, are principally helpful in the detection of an evolving infarction and also for the estimation of the extent of myocardial damage during the time course of the acute phase. Therefore, repeated blood sampling for these markers

is beneficial. For the initial diagnosis of STEMI, especially for patients with a short duration of symptoms, as typically seen in the prehospital setting of EMS care, these tests are less meaningful. Elevated levels of specific biomarkers are not found earlier than 2-3 hours after onset of symptoms (14). Therefore, use of bedside tests by the EMS, such as measuring biomarkers, is costly and not helpful (15). Moreover, in the presence of typical symptoms and ST elevation on the ECG, losing time waiting for the results of biomarkers before initiating reperfusion treatment must be avoided. In some cases, the use of echocardiography may be helpful in ruling out major myocardial ischaemia by normal wall motion or findings of other causes of chest pain. Portable ultrasound devices even for out-of-hospital use are now available and reliable results can be obtained with them.

Basic treatment of STEMI

Symptomatic therapy (Table 3)

Oxygen

Oxygen is recommended in all guidelines for patients with breathlessness and/or an oxygen saturation < 90 %. Even if it assumed that supplementary oxygen (2-8 l/min) may be reasonable for all patients with STEMI and may be helpful in patients with unrecognised hypoxia, it should be kept in mind that excess oxygenation may lead to systemic vasoconstriction (16) and may be harmful to some patients with severe obstructive pulmonary disease (16).

Nitroglycerin

In the ACC/AHA guidelines (IC recommendation) as well as in the ERC guidelines, nitroglycerin in repeated doses of 0.4 mg (maximum 1.2 mg) is recommended for all patients with ongoing ischaemic discomfort, provided that blood pressure is higher than 90 mmHg. Special caution should be given to patients with bradycardia. Nitroglycerin should not be given to patients with suspected right ventricular infarction. The role of nitroglycerin in the treatment of hypertension and pulmonary congestion is underlined in the ACC/AHA and ERC guidelines (1-3). In astonishing contrast, nitroglycerin is not mentioned in the ESC guidelines as a routine treatment for the acute phase. It is only briefly alluded to, and is recommended for the therapy of mild heart failure. In the chapter on routine prophylactic treatment after the acute phase, it is also mentioned but is classified as not of proven efficacy and therefore not recommended.

Table 3: Symptomatic treatment during the initial phase of STEMI

	ACC/AHA	ESC	ERC*
Oxygen	Class IB (with oxygen saturation <90%) Class IIaC (all patients within the first 6 hrs)	Class IC (with oxygen saturation <90%)	as ACC/AHA and ESC
Nitroglycerin	Class IC (max. 1.2 mg) Class III (not in patients with systolic RR <90 mmHg or RV infarction or heart rate <50/min)	Not mentioned	as ACC/AHA
Analgesia (Morphine)	Class IC	Class IC	as ACC/AHA and ESC

* ERC guidelines do not refer to classes of recommendation

Analgesia

Opiates, preferentially morphine, are recommended in all guidelines for pain relief and should be given in repeated doses until the patient is pain free. The recommendation for initial doses (3-8 mg) as well as repeated doses (2-8 mg) differs somewhat between the guidelines. Morphine also lessens anxiety and restlessness and reduces sympathetic activation, thus decreasing the workload and oxygen consumption of the heart. Nausea, observed in some patients after morphine injection, lasts only a few minutes and may be treated with metoclopramide.

Basic principles of causal treatment (Table 4, 5)

It has to be underlined that some of the data supporting early emergency department and out-of-hospital therapy, which is in the main scope of this chapter, is extrapolated from treatment experiences at a later time point after hospital admission. Insofar, this chapter contains here and there some uncertainty. In addition, specifically out-of-hospital treatment may contravene particular local regulations depending on capabilities, rules and even legislation.

Table 4: Basic causal treatment: Antiplatelets

	ACC/AHA	ESC	ERC ◊
Aspirin 162-325 mg	Class IA-C (dose depending)	Class IB	as ACC/AHA and ESC
Clopidogrel without reperfusion Tx 75 mg/day	Class IA	Class IA/B	---
Clopidogrel with planned fibrinolysis	Loading 300 mg if age <75 years 75 mg if age >75 years (Class IIaC)	Loading 300 mg if age <75 years 75 mg if age >75 years (Class IB)	Loading 300 mg
Clopidogrel with planned PCI	Not specifically mentioned as early treatment	Loading 300 mg preferably 600 mg (Class IB)	Loading 300 mg

◊ ERC guidelines do not refer to classes of recommendation

Table 5: Basic causal treatment: Anticoagulants

	ACC/AHA	ESC	ERC
Without reperfusion treatment	Low molecular weight heparin (Class IC) or fondaparinux	Fondaparinux or enoxaparin (enoxaparin without initial bolus in pts >75 years (Class IB)	---
With fibrinolysis	Heparin* (Class Ic) Enoxaparin* (Class IA) (without initial bolus if >75 years) Fondaparinux (Class IB)	Enoxaparin* (without initial bolus in pts >75 years), if fibrin specific lytic. If enoxaparin not available heparin* (Class IA) With streptokina- se fondaparinux or enoxaparin* (Class IIB) or heparin* (Class IIaC)	Heparin Enoxaparin for pts <75 years
With planned PCI	Heparin* (Class Ic) Enoxaparin* (Class IA) (without initial bolus if >75 years) Fondaparinux discouraged (Class III)	Heparin (Class Ic) Bivalirudin (Class IIaB) Fondaparinux discouraged (Class III)	Heparin

* switching between heparin and enoxaparin discouraged

Most cases of STEMI are caused by a thrombotic occlusion of a larger coronary artery (5). The underlying pathophysiological process is initiated by mural thrombus formation as a reaction of a rupture of an unstable atherosclerotic plaque or endothelial erosion (17). It is of interest that the majority of cases are not due to a higher degree of stenosis. Indeed, most infarctions develop at plaque sites that are haemodynamically irrelevant (18). The initial process of mural thrombus formation is adhesion and aggregation of platelets, followed by integration of fibrin via the glycoprotein IIb/IIIa (GP IIb/IIIa) receptor, which finally stabilises the clot. Following this concept, the initial causal treatment targets inhibition of both platelet activation and fibrin formation.

Antiplatelet treatment

Acetylsalicylic acid (ASA)

ASA is the mainstay of antiplatelet therapy, inhibiting the COX1 pathway of thromboxane formation (Fig 3). Thus ASA blocks one of the routes to the common final step of activation of the GP IIb/IIIa receptor, which is necessary for bridging platelets by fibrin and the final formation of a stable thrombus. ASA has been shown to reduce the case fatality rate by 1/4 in the ISIS II trial (19). Since then, ASA has become routine in the treatment of STEMI patients irre-

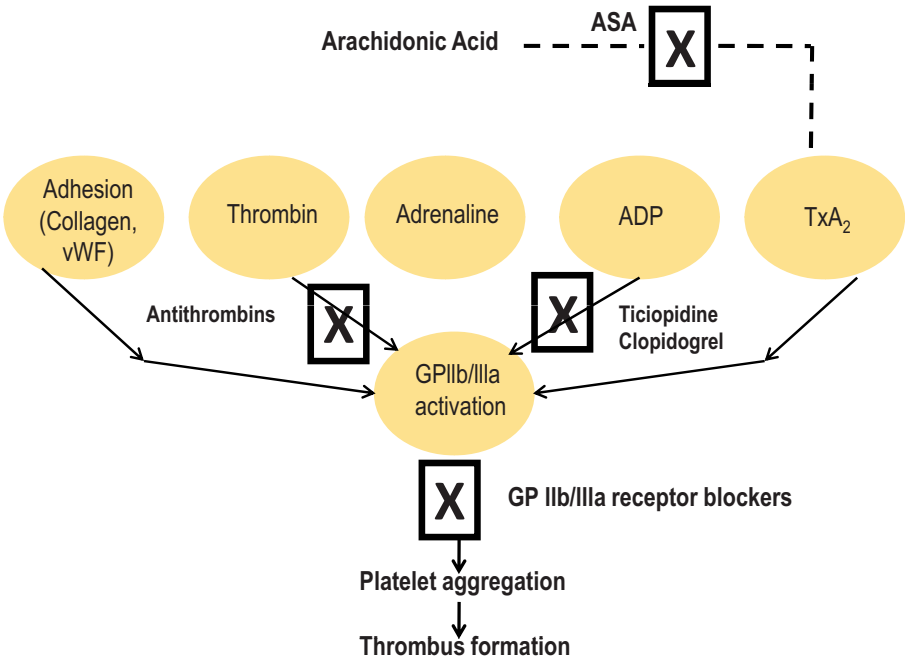


Figure 3: Mechanism of platelet activation

spective of whether primary PCI or thrombolysis is planned for reperfusion. In addition, ASA is standard for life-long secondary prevention after an ischaemic cardiac event (20). Even if there is no stringent data on time dependency of ASA treatment for STEMI, there is a general consensus in all guidelines that an initial loading dose of 160-325 mg as a chewable tablet or i.v. should be given as early as possible, provided that the patient does not suffer from a true allergy to ASA. This initial loading dose may also be given to patients who are already on ASA for reasons of primary or secondary prophylaxis.

Clopidogrel

Clopidogrel is a thienopyridine, which due to its superior efficacy and less side effects, has substituted ticlopidine. Thienopyridines block the P2Y₁₂ ADP receptor, another activator of the common GP IIb/IIIa activation endpoint (*Fig 3*). Clopidogrel has shown superiority in comparison to ASA in secondary prevention (21). Superiority with regard to major adverse cardiac events of long-term (1-year) treatment of the combination of clopidogrel plus ASA compared to ASA alone has been proven in patients with unstable angina and non-ST-elevation myocardial infarction with or without percutaneous coronary intervention (22, 23). Pre-treatment with clopidogrel prior to coronary intervention proved to be beneficial in patients with stable angina and those with non ST-elevation acute coronary syndromes (24-26). Finally, clopidogrel is a decisive part of long-term treatment of patients with intracoronary stents to avoid life-threatening stent thromboses (4, 27). The necessary duration of therapy depends on the stent type, e.g. for at least one year with drug eluting stents.

Clopidogrel (300 mg loading dose followed by 75 mg once daily) in addition to ASA and an antithrombin was given to patients with STEMI undergoing thrombolysis, including a group of patients with pre-hospital initiation of therapy (28, 29) in patients under 75 years of age and symptom duration > 6 hrs. The primary endpoint consisting of death, re-MI or TIMI flow grade 0 or 1 at angiography was reduced by 36 % with clopidogrel. There was no increased bleeding risk. In this study, the rate of re-infarction was reduced by nearly one half (30). In the Chinese COMMIT study (31), clopidogrel 75 mg/day without a loading dose was given in addition to ASA to patients without an upper age limit who presented within a symptom duration of ≤ 24 hrs. Clopidogrel was started after hospital admission. Further treatment was conservative or consisted of thrombolysis for reperfusion. With clopidogrel, the total in-hospital mortality, as well as the combination of death and stroke, was reduced significantly without increased bleeding risk. The most favourable effects were seen in patients with early treatment and those who received thrombolysis (31).

According to these results, the current guidelines recommend clopidogrel for all patients with STEMI. However, there are major differences in the individual recommendations, especially where dosing and time point of initiation of therapy are concerned. The ACC/AHA regulations (2) abide very strictly to the proven evidence. Without definition of time point (i.e. at first medical contact

or later after hospital admission) all patients with STEMI should receive 75 mg clopidogrel (Class IA) for at least 14 days (Class IIB). In patients < 75 years, who are treated with fibrinolysis, a loading dose of 300 mg clopidogrel is defined as reasonable (Class IIaC), followed by long-term treatment, for example 1 year (Class IIaC). The latter recommendation is also valid for patients without reperfusion treatment. In some contrast, the ERC guidelines recommend a 300 mg loading dose of clopidogrel at first medical contact for all patients with STEMI, irrespective of age and reperfusion strategy (4). The ESC guidelines (5) also recommend clopidogrel as early as possible for planned primary PCI. The preferred loading dose for the ESC is 600 mg. This proposal corresponds to the observation of a more rapid and stronger inhibition of platelet aggregation compared to the 300 mg loading dose recommended in the other guidelines (32). To date, however, data on pre-treatment (e.g. pre-hospital loading with planned PCI) in patients with STEMI is insufficient. A study to answer this question is underway (33). For fibrinolysis, the ESC follows the evidence recommending a 300 mg loading dose for patients < 75 years of age followed by 75 mg/day. Elderly patients should receive 75 mg clopidogrel initially, followed by 75 mg/day (5). Prasugrel, a new thienopyridine, has shown obvious advantages compared to standard dose (300 mg) clopidogrel given immediately before PCI in STEMI patients and non STEMI-ACS as shown in the TRITON-TIMI 38 study (34). Prasugrel, however, is still awaiting approval and therefore is not yet mentioned in the guidelines.

Glycoprotein IIb/IIIa inhibitors

Theoretically, blocking the GP IIb/IIIa receptor is the optimal strategy to inhibit platelet aggregation completely. Most of the studies have been performed with abciximab. Periprocedural use of GP IIb/IIIa receptor blockers – mainly abciximab - during PCI reduces mortality significantly (35). However, in contrast to pre-treatment with clopidogrel and possibly ASA, there is no proof that pre-treatment with a GP IIb/IIIa blocker before PCI is of benefit for the patient (36). Also, the combination of abciximab with a reduced dose of direct plasminogen-activating fibrinolytics did not improve outcome (37). Finally, it is unclear whether abciximab is of additional value for patients with clopidogrel pre-treatment prior to PCI. In a recent, out-of-hospital, placebo-controlled study utilising an initial high dose bolus of tirofiban before planned PCI in STEMI patients resulted in an improved ST-segment resolution but was without other clinical benefit (38).

Antithrombins/Anticoagulation (Table 5)

Due to the increasing number of studies published in the last years, investigating newer anticoagulants, the actual guidelines published between 2005-2008 are not completely compatible. In addition, the complexity of some studies is confusing. Reviparin, enoxaparin, fondaparinux and bivalirudin were studied utilising different reperfusion strategies, i.e. thrombolysis or primary PCI. Also, there are differences in the duration of treatment between the comparators and

mixed strategies for comparisons. For example unfractionated heparin (UFH) or placebo was compared with fondaparinux in the OASIS-6-trial with fibrinolysis (39), primary PCI, or no reperfusion treatment. Bivalirudin plus provisional use of a GP IIb/IIIa inhibitor was compared with UFH or enoxaparin plus routine addition of a GP IIb/IIIa receptor blocker in the Horizons AMI study (40).

In principle, anticoagulants are beneficial in patients with STEMI. Anticoagulants which inhibit more proximal steps in the coagulation cascade (i.e. have higher anti-Xa activity) seem to be superior to UFH due to an intensified reduction in thrombin generation. Prolonged treatment with the new anticoagulants exceeding the 48-h UFH standard seems to be beneficial, but may increase the bleeding risk. Finally, it has to be kept in mind that treatment with rivaroxan, fondaparinux, and enoxaparin requires dose reductions in patients with renal impairment. Because of increased intracranial bleeding risk (41), enoxaparin is also given in reduced doses in patients older than 75 years of age. Rivaroxan was tested in the CREATE trial (42), but is not discussed further in this chapter since it is not available in the EU and North American market.

Enoxaparin for 7 days was tested with fibrinolysis utilising streptokinase, alteplase, reteplase and tenecteplase, and was compared with UFH, which was given for only 48 hrs (43). In patients > 75 years of age, enoxaparin was injected in a reduced dose without an initial bolus. The rate of death and MI decreased significantly with enoxaparin (RR 0.83, 95 % CI 0.77-0.9) at the cost of more severe (but not lethal) bleedings (RR 1.53, 95 % CI, 1.23-1.89). More bleedings were seen preferentially in the younger age group (< 75 years) with full-dose enoxaparin. Rescue, urgent or elective PCI after thrombolysis was without problems and without additional bleeding risk with enoxaparin compared to UFH. It is of interest that in a non-randomised subgroup of the patients in the EXTRACT TIMI-25 study, who were treated with clopidogrel in addition to enoxaparin, the risk of major non-lethal bleedings was further increased compared to UFH, but the net clinical benefit when considering the incidence of death and MI was in favour of the enoxaparin/clopidogrel combination (44).

In the OASIS-6 trial (39) fondaparinux was compared with placebo or UFH in patients receiving fibrin, specific thrombolytics or non-specific thrombolytics, treated with primary PCI or no reperfusion treatment. With thrombolysis, fondaparinux was superior in comparison to the patients in the UFH or placebo groups (14 % risk reduction). Compared with UFH, fondaparinux led to significantly less bleedings with thrombolysis. With PCI, there were no significant differences between fondaparinux and UFH, neither with regard to bleedings nor to death or MI. With fondaparinux, there was however, the observation of clot formation on the catheters requiring additional UFH injections during PCI. In the subgroup of patients without reperfusion treatment, fondaparinux was superior to UFH with regard to death and MI (16 % risk reduction) but not to placebo. Also, there were no differences in bleeding rates between the groups without reperfusion treatment.

Bivalirudin is a short-acting direct thrombin inhibitor and was given as an adjunct to thrombolysis with streptokinase in the HERO-2 study (45). Re-infarction was reduced by 30 % with bivalirudin. Although bleeding rates were slightly higher, bivalirudin had no influence on mortality.

In the recent HORIZONS-AMI study, bivalirudin was tested with provisional addition of a GP IIb/IIIa inhibitor compared with UFH or enoxaparin in an obligatory combination with a GP IIb/IIIa receptor blocker (40). The primary endpoint of the 30-day incidence of major adverse cardiac events or major bleedings was significantly reduced by bivalirudin ($P < 0.001$) due to a 40 % reduction in major bleedings. The reduction in bleedings is considered to explain the 1 % lower total mortality ($P < 0.0047$) with bivalirudin, even if stent thromboses occurred more frequently.

According to these study results, in planned primary PCI, heparin (with ACT adjustment) is uniformly recommended in all guidelines (1-3). In addition, bivalirudin is recommended in the recent ESC guidelines (4). Both adjunct treatments should be stopped at the end of the procedures.

For fibrinolysis, enoxaparin at a dose adjusted for age and renal function is recommended in all guidelines and should be given for a maximum of 8 days. UFH should be given with fibrinolysis under aPTT control for a maximum of 48 hrs. Fondaparinux is recommended for a maximum of 8 days with fibrinolysis, provided that creatinine is < 3 mg/ml. Fondaparinux is not recommended in planned primary PCI (Class III).

Reperfusion treatment

All guidelines agree that reperfusion treatment is generally indicated in all patients with STEMI presenting within 12 hrs after symptom onset (1, 3, 4). In addition it may be indicated in patients with a longer duration of symptoms, e.g. in those with persisting or recurrent chest pain. Finally, in patients in cardiogenic shock, outcome will be improved by reperfusion treatment, which in this case is preferentially percutaneous intervention (46). The preferred reperfusion treatment strategy for an individual patient will depend on a number of different conditions and circumstances, which will be discussed in depth in later chapters. The increasing number of options regarding adjunct antiplatelets and anticoagulation has already been discussed above. Thus, only the basics of reperfusion therapeutic strategies, that is, fibrinolysis or primary PCI or the combined treatments remain to be outlined.

Fibrinolysis

(For contraindications dosing and recommended adjunct treatment see Tables 4-7)

The finding that most myocardial infarctions were caused by thrombotic occlusion of a coronary artery was of outstanding importance for the development of fibrinolysis (5). Fibrinolysis as a reperfusion treatment has been investigated as a stand-alone therapy, combined with additional earlier or immediate PCI as a so-called “facilitated PCI” strategy, or (under specific conditions) as “rescue PCI” (see paragraph on page 34). In addition, PCI has been investigated in patients with failed thrombolysis as defined by clinical signs e.g. persistent pain or incomplete resolution of ST-segment elevation as a specific time point after initiation of fibrinolysis. The combined strategies will be discussed within the PCI paragraph.

Table 6: Contraindications for fibrinolysis according to the ESC and ERC guidelines (1, 4)

Absolute contraindications

- Haemorrhagic stroke or stroke of unknown origin at any time
- Ischaemic stroke in preceding 6 months
- Central nervous system trauma or neoplasms
- Recent major trauma/surgery/head injury (within preceding 3 weeks)
- Gastrointestinal bleeding within the last month
- Known bleeding disorder
- Aortic dissection
- Non-compressible punctures (e.g. liver biopsy, lumbar puncture)

Relative contraindications

- Transient ischaemic attack in preceding 6 months
- Oral anticoagulant therapy
- Pregnancy or within 1 week post-partum
- Refractory hypertension (systolic blood pressure >180 mmHg and/or diastolic blood pressure >110 mmHg)
- Advanced liver disease
- Infective endocarditis
- Active peptic ulcer
- Refractory resuscitation

Table 7: Doses of fibrinolysis agents

	Initial treatment	Specific contraindications
Streptokinase (SK)	1.5 million units over 30–60 min i.v.	Prior streptokinase or anistreplase
Alteplase (t-PA)	15 mg i.v. bolus 0.75 mg/kg over 30 min then 0.5 mg/kg over 60 min i.v. Total dosage not to exceed 100 mg	
Retepase (r-PA)	10 U + 10 U i.v. bolus given 30 min apart	
Tenecteplase (TNK-tPA)	Single i.v. bolus 30 mg if <60 kg 35 mg if 60 to <70 kg 40 mg if 70 to <80 kg 45 mg if 80 to <90 kg 50 mg if ≥90 kg	

Van de Werf *et al.* Management of acute myocardial infarction in patients presenting with persistent ST-segment elevation, *European Heart Journal*. 2008; 29:2909-2945; 2919, by permission of Oxford University Press

The era of fibrinolysis started with investigations utilising intracoronary streptokinase (47, 48). With intracoronary streptokinase, the occluding thrombus could be dissolved and the coronary artery be reperfused in many patients. It was also shown that the extent of myocardial necrosis could be reduced (48, 49). The access to intracoronary thrombolysis, however, was principally limited by the complex method and availability of catheter labs. Consequently, the efficacy of i.v. streptokinase was tested. Angiographically controlled dose-finding studies resulted in a slightly lower reperfusion rate compared to intracoronary application of streptokinase but offered the chance for earlier treatment of more patients (50). For further time gain, i.v. treatment was shown not only to be efficacious but also to be safe. Therefore, it was proposed very early on to advance the start of treatment to prehospital care by the EMS (50).

The GISSI I trial was the first mega trial to test the standard dose of 1.5 Mill U streptokinase versus placebo in a randomised study (51) in STEMI patients with a symptom duration < 12 hrs. The 21-day mortality was reduced by 18 %, at the cost of a slightly increased number of haemorrhages and intracranial bleedings. In the ISIS-2 study (19), streptokinase and/or 325 mg aspirin were compared with placebo in STEMI patients with a symptom duration of less than 24 hrs. With combination treatment, the 30-day mortality was reduced by 47 %, with the effect appearing to be an additive of the effect with streptokinase alone and the effect with aspirin alone. The bleeding rate with combination treatment, which proved to be the standard approach, was 0.5 % versus 0.2 % for bleeding requiring major transfusion and 0.1 % versus 0.0 % for

intracranial haemorrhage. It is of interest that the initial benefit in GISSI I and ISIS-2 persisted for at least ten years with less other strokes (52, 53).

Already in GISSI I, the time dependency of the benefit achievable by thrombolysis was clearly proven. Patients treated within the first hour of symptom onset profited more than those treated later. Afterwards, time gained by speeding up the procedures until initiation of treatment, including out-of-hospital treatment, became of more interest. In several smaller studies as well as in the large European Myocardial Infarction Project trial, the out-of-hospital treatment concept was tested (54-60). Besides streptokinase, various thrombolytic agents, such as urokinase and APSAC (a bolus injectable streptokinase modification), were tested.

Only the GREAT study (58) showed superiority of pre-hospital compared to in-hospital initiation of treatment. In the other studies, only a trend favouring out-of-hospital thrombolysis was found. In the EMIP study (59), this may have been partially due to the ending of financial support, which led to early termination of the study. Meta-analyses of all randomised studies comparing pre-hospital initiation of thrombolysis with in-hospital start of treatment, however, revealed a 17 % reduction in 30-day mortality using the pre-hospital strategy (59, 61).

A further important step was the development of the more fibrin specific thrombolytic, alteplase (rt-PA), which showed superiority over streptokinase in the GUSTO I study in terms of reduced mortality at the cost of a slightly increased bleeding rate (62), particularly in the elderly. rt-PA in the optimised so-called "Neuhaus regimen" (63) became standard for thrombolysis in STEMI following GUSTO I. Further innovations in thrombolytics included the development of modifications of the rt-PA molecule with longer half lives now allowing single bolus (tenecteplase) or double bolus (reteplase) injections with a similar safety and efficacy profile to rt-PA (64, 65). Bolus injectable agents are of special interest for the out-of hospital setting because of the simplicity of the application. Mainly tenecteplase has been investigated with regard to this strategy (41, 66).

All guidelines state that fibrinolytic treatment is indicated in all patients without contraindications and with a symptom duration < 12 hrs (Class IA). A fibrin specific agent should be preferred (Class IB). With regard to the pronounced time dependency, initiation of pre-hospital fibrinolysis is uniformly recommended for systems capable of performing out of-hospital of treatment (Class IIa). In the ERC and ACC/AHA guidelines, fibrinolysis is the preferred strategy in the absence of contraindications and when the expected delay to PCI is > 90 min. In addition, the ERC recommends fibrinolysis for patients with a symptom duration < 3 hrs with an expected delay to PCI > 60 min.

Primary PCI

(adjunct treatment see Tables 4, 5)

Angiographically controlled trials have repeatedly shown that fibrinolysis has two major disadvantages besides (intracranial) bleeding risk. Firstly, a prognostically optimal TIMI flow grade III is only achieved in about 50 % of cases within 90 min after initiation of treatment (62). Secondly, a prognostically unfavourable reocclusion is observed in more than 10 % of patients in some studies (67). Both statements must, however, be considered with caution. The low rate of TIMI flow III grade success has been found in patients who generally received in-hospital fibrinolysis quite late.

The high reocclusion rates were observed in the pre-thienopyridine era. Nevertheless, both observations were of importance for the development of primary percutaneous interventions as an alternative strategy for reperfusion in STEMI. Basically, PCI was developed for the treatment of patients presenting with stable or unstable angina, and proved to be effective in more severely ill patients (68, 69). Early after having shown that primary PCI in STEMI is a reasonable option (70, 71) – even at the cost of some time delay compared to fibrinolysis – it was unclear whether the combined strategy of fibrinolysis should be the option of choice (72). Later, it was shown that this strategy together with streptokinase may lead to unfavourable or even deleterious results (73-75). On the other hand, the development of intracoronary stents (76), improvements of PCI technology, steerable guidewires, optimised antiplatelets (GP IIb/IIIa blockers, thienopyridines) and anticoagulation, etc., together with an increasing number of well-trained interventionalists offering their services on a 24-hr, 7-days-a-week basis in a rapidly growing number of catheter labs, resulted in a fast-growing proportion of STEMI patients treated with primary PCI (77, 78). The development of advanced techniques and new technologies cumulated in the application of drug eluting stents, which proved to be efficacious in overcoming the re-stenosis problem. This was, however, at the potential cost of a slightly elevated long-term risk of life-threatening stent thrombosis, which could occur even years after implantation. These new devices have lately also successfully been used for treatment of STEMI patients (79-81). According to the ESC guidelines, primary PCI is, therefore, generally the preferred reperfusion strategy if performed by an experienced team “as soon as possible” after first medical contact (Class IA). Tolerable delay to PCI is defined to be < 2 hrs in general and < 90 min in patients presenting early (symptom duration < 2 hrs) with large infarcts and low bleeding risk (Class IB). The ACC/AHA recommendation cuts the window for delay to PCI to 90 min as a principal system goal. This 90-min time window includes the delay necessary for transfer of a patient from a non-PCI-capable to a PCI-capable hospital (Class IA). In the ERC guidelines, delay to PCI is restricted generally to < 90 min and to 60 min for patients with a symptom duration of < 3 hrs.

Combined strategies

Combined strategies encompass the pharmacoinvasive strategy, facilitated PCI and rescue PCI.

Pharmacoinvasive strategy

This strategy is based on the idea of optimising the result of a primary fibrinolytic treatment by additional timely angiography and percutaneous intervention if suitable. Angiography and PCI with this procedure is optimised with regard to the time window for thrombolysis as well as the time point of angiography and eventually PCI. The pharmacoinvasive treatment strategy is supported by recent registry data (82-84) and study data (85).

Facilitated PCI

In contrast to pharmacoinvasive therapy, the strategy of facilitated PCI relies on the idea that early initiation of pharmacotherapy (GP IIb/IIIa receptor blockers and/or thrombolytics) may lead to a more or less complete reperfusion of the myocardial area at risk and may ease routine immediate PCI, e.g. by increasing already re-opened culprit coronary vessels. Reperfusion may then be accomplished and stabilised by additional routine percutaneous intervention as soon as possible. Thus, the advantage of early and ubiquitous initiation of reperfusion achievable by pharmacotherapy would be combined with the advantages of the complete and persistent reperfusion achievable by PCI. Some preliminary investigations have been promising (86). In several larger randomised studies, partially utilising additional GP IIb/IIIa receptor blockers failed to show any benefit. In fact, in one study the outcome was worse with facilitation (37, 87). Facilitated PCI as a concept, therefore, is discouraged in the ESC and (with some “possible” exemptions) in the ACC/AHA guidelines. However, an angiography performed not earlier than 3 hrs after initiation of fibrinolysis is a Class II A recommendation in the ESC guidelines and may even be performed immediately in case of uncertainty about success of fibrinolysis, i.e. a conception referred to as a “pharmacoinvasive strategy” in the former paragraph. The ACC/AHA guidelines refer primarily not to the indication for angiography but directly to PCI after fibrinolysis. Routine PCI after fibrinolysis in these guidelines is classified as a Class IIbB procedure; however, it is considered reasonable in selected high-risk patients and clearly indicated for patients with severe heart failure, cardiogenic shock and compromising ventricular arrhythmias. Thus, both guidelines discuss the pharmacoinvasive strategy at least as an option for specific situations.

Rescue PCI

Rescue PCI is defined in the ESC guidelines as PCI performed on a coronary artery that remains occluded despite fibrinolytic therapy. The usual surrogate for definition of failed thrombolysis is < 50 % ST-segment resolution

in the leads with the highest ST-segment elevation 60-90 min after the start of fibrinolysis, as used for example in the REACT trial (88). According to the ACC guidelines, rescue PCI should be performed within 12 hrs after onset of symptoms and has a Class IIa recommendation. In the ACC/AHA guidelines, rescue PCI is used in a somewhat broader definition for patients with cardiogenic shock after thrombolysis (Class I recommendation), haemodynamic or electrically instable patients after fibrinolysis or those with signs of failed thrombolysis (< 50 % ST-segment resolution) (Class IIa recommendation). In patients who do not fulfil the above criteria, "rescue PCI" is a Class IIbC recommendation without a well-established benefit risk relation.

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Data from registries and trials (part 1)

**Randomised controlled trials, meta-analyses,
NRMI, USIC, RIKS-HIA, FAST-MI**

Introduction

Data obtained from clinical trials, conducted on selected patients in optimised and standardised settings, often differ from data obtained from registries, which supposedly follow patients in “real-world” situations. From a methodological standpoint, clinical trials are limited by strict inclusion and exclusion criteria (and, more often still, operate de facto by excluding many patients, such as the elderly, who should have been included according to the predefined selection criteria). The population included in clinical trials, therefore, usually represents only a small minority of the patients with the condition for which the experimental treatment is intended, and extrapolation of the results of the trials to the whole population of patients with this condition, though usually done in clinical practice, is methodologically questionable. Conversely, registries are purely observational, and many biases are inherent to the fact that the treatment studied has been administered purposely and not at random. Although current statistical methods can take into account many potential confounders (for example, propensity score-matched cohorts of patients that received or did not receive the treatment studied present baseline characteristics that are strictly comparable), these only go to the extent of adjusting for the characteristics that have been recorded (in the above-mentioned example of propensity-score cohorts, only the baseline characteristics used to build the propensity score will be evenly distributed among the 2 groups, whereas characteristics not used to build the score will very likely differ between the 2 cohorts). Therefore, registry data can only be considered indicative of a correlation between a given treatment and clinical outcomes, and not of a causal relationship. Data from randomised clinical trials and registries thus appear truly complementary in the assessment of treatment effects.

The guidelines are therefore developed on the basis of evidence obtained from both randomised controlled trials (which are given the greatest weight, by far) and from registries. In the specific situation of STEMI, all guidelines agree that the most important factor in reperfusion is that of time. It would be too great a task to summarise all the trials that have ever been conducted on STEMI patients. Therefore, in this and the next chapter, we have selected what we thought were the most important and relevant trials and registries and especially those upon which the guidelines are based.

Randomised Controlled Trials

1) Trials comparing fibrinolysis and primary PCI: specific focus on PHT and transfer patients

CAPTIM

CAPTIM is the only randomised trial comparing pre-hospital fibrinolysis with primary PCI (PPCI). The trial compared PHT, followed by transfer to a centre with interventional facilities and rescue PCI if necessary, with PPCI in patients with STEMI (1). Beyond the primary endpoint of the trial (death, myocardial infarction or disabling stroke at day 30), CAPTIM also investigated the effect of time from symptom onset to treatment (<2 hours and ≥2 hours) on the outcomes in the different treatment groups. The time from symptom onset to treatment was notably shorter in the group receiving PHT (130 minutes) than in the PCI group (190 minutes). There was a non-significant trend favouring PPCI with regard to the primary endpoint (PHT: 8.2% vs. PPCI: 6.2%), but a reverse trend was observed for mortality (PHT: 3.8% vs. PPCI: 4.8%). Patients who were randomised earlier, tended to be younger, male, and with a lower baseline heart rate than those randomised later. In patients randomised within 2 hours of symptom onset, 30-day mortality was higher in the PPCI group compared to the PHT group (5.7% vs. 2.2%, 95% CI 0.95 to 7.24; P=0.058); but this trend was reversed in the patients randomised after 2 hours of symptom onset (3.7% vs. 5.9%, 95% CI 0.25 to 1.61; P=0.47; P=0.039 for heterogeneity between early and late randomisation) (2). In the 5-year analysis, the results were similar, with a lower mortality in the group treated within 2 hours of symptom onset with fibrinolysis compared to primary angioplasty (5.8% vs. 11.1%, 95% CI 0.25 to 0.97; P=0.04). This benefit was not seen in the cohort treated after 2 hours (14.5% vs. 14.4%, 95% CI 0.59-1.75; P=0.92) (3).

DANAMI-2 and PRAGUE-2

Several trials addressed the question of the best option for reperfusion therapy in patients presenting at non-PCI hospitals, comparing immediate fibrinolysis with immediate angioplasty requiring transfer at a tertiary centre.

DANAMI-2 randomised patients at referral hospitals (n=24) and intervention centres (n=5) to angioplasty or fibrinolysis. The primary endpoint was a composite of death, reinfarction or disabling stroke at 30 days. The baseline characteristics were similar between all patient groups. The combined endpoint was significantly less frequent in PCI patients (8.0% vs. 13.7%, P=0.001). It should be noted that out of the 782 patients who received fibrinolysis, 26 had repeated fibrinolysis and 15 underwent rescue angioplasty within 12 hours of randomisation. At 30 days, 148 patients in the fibrinolysis group had undergone mechanical revascularisation (angioplasty and/or coronary bypass surgery) compared to 72 patients in the primary angioplasty group (P<0.001). In the referral hospitals, 8.5% of patients who were randomised to angioplasty

(and therefore transferred to an interventional centre), and 14.2% of patients who received fibrinolysis, reached the primary endpoint ($P=0.002$). In the interventional centres, the primary endpoint was seen in 6.7% vs. 12.3% of patients, respectively ($P=0.05$). The benefit was mainly due to a reduction in reinfarction rates; the rates for mortality and stroke at 30 days were not significantly different (for the whole population: 6.6% vs. 7.8%, $P=0.35$; for transfer patients: 6.5% vs. 8.5%, $P=0.20$). Transfer from referral hospitals to interventional centres was shown to be safe, and could be carried out within 2 hours of randomisation in 96% of patients. The investigators concluded that transfer to a PCI centre is superior to fibrinolysis, providing that the transfer can be carried out in less than 2 hours (4).

The PRAGUE-2 trial enrolled 850 patients admitted to non-PCI centres. Mortality was not significantly different between patients who received fibrinolysis on site, compared with those transferred for PPCI, although there was a trend favouring PPCI (30-day mortality 6.8% vs. 10.0%, $P=0.12$). In patients randomised within 3 hours of symptom onset, mortality was comparable in the two groups (PPCI: 7.2%, fibrinolysis: 7.4%) (5).

PCAT-2

Subsequent to PRAGUE-2 and CAPTIM, a pooled analysis of randomised clinical trials looked at the effect of time to treatment on outcomes following PCI or in-hospital fibrinolysis. The primary endpoint was all-cause mortality. Male patients, younger patients and those who had a history of previous MI or PCI, tended to present earlier. Patients with diabetes mellitus generally presented later. An anterior infarction was associated with very early (0-1 h) or very late (>6 h) presentation. The median time from symptom onset to presentation was 142 minutes, and was similar for both the PPCI and fibrinolysis group. The time to fibrinolysis was significantly shorter than the time to PCI (19 vs. 76 minutes, respectively; $P<0.001$), with an overall delay to PCI of 55 minutes. Thirty-day mortality with fibrinolysis was 7.9% versus 5.3% with PPCI ($P<0.001$). Mortality increased significantly in the fibrinolysis group as the time to treatment increased from less than 1 hour to beyond 6 hours ($P<0.001$). In the PPCI group, there was a trend towards increased mortality with increasing time delay to treatment, but this was not significant. PPCI produced a 37% relative risk reduction on 30-day mortality, and this benefit was seen in all subgroups of patients (OR 0.63, 95% CI 0.42-0.84; $P<0.001$) (6). Of note, in virtually all of the trials, fibrinolysis was used as a “stand-alone” reperfusion treatment.

2) PCI after fibrinolytic treatment

In spite of the disappointing results achieved in the late 1980s with angioplasty immediately following intravenous fibrinolysis, new attempts were made in the 2000s, because considerable progress had been made in both angioplasty techniques and in adjunctive antithrombotic therapy, and in particular the combined use of aspirin, thienopyridine therapy and intravenous glycoprotein IIb/IIIa inhibitors. These attempts were made in two directions: improving the efficacy of primary PCI by administering fibrinolytic treatment or GP IIb/IIIa inhibitors upfront of the interventional procedure (so-called “facilitated” PCI); or improving the result of fibrinolysis by performing subsequent PCI in all or selected patients.

Facilitated PCI

A number of randomised trials have compared primary PCI with PCI “facilitated” by either fibrinolytic treatment, GP IIb/IIIa inhibitors, or both. A meta-analysis published in 2006 showed that, though more patients assigned to facilitated PCI had initial TIMI 3 flow, there was no clinical benefit, compared with primary PCI (7). Recently, facilitated PCI was evaluated in two large randomised trials. The ASSENT-4 PCI trial (8) compared primary PCI with PCI immediately preceded by tenecteplase and was stopped prematurely because an excess of events was observed in the facilitated arm, and this despite the fact that more patients had an open infarct-related artery before the angioplasty procedure. Two factors may have explained these findings: first, concomitant antithrombotic therapy may have been insufficient in the tenecteplase arm of the trial, with the use of a low dose of heparin and minimal use of GP IIb/IIIa inhibitors; second, PCI was performed soon after administration of fibrinolytic treatment (median time 104 minutes), at a time when platelet reactivity was still increased. Both factors may have played a role in the excess reinfarction rate observed in the facilitated arm. In the FINESSE trial, patients were randomised in a 1:1:1 fashion to primary PCI with in-lab abciximab, upfront abciximab-facilitated primary PCI, or half-dose reteplase/abciximab-facilitated PCI (9). The trial was stopped prematurely because of difficulties in recruiting patients. Median time from first bolus to balloon inflation was 90 minutes. Although ST-segment resolution was more frequently observed in the combination facilitated PCI, no difference was found in the primary outcome of the trial (death, late ventricular fibrillation, cardiogenic shock or congestive heart failure at 90 days).

Rescue PCI

Because intravenous fibrinolysis fails to restore arterial patency in a substantial proportion of patients, the potential benefit of early angioplasty in patients showing no signs of early reperfusion needed to be assessed. The REACT trial involved 427 patients treated with fibrinolysis in whom there was no sign of reperfusion (>50% resolution of ST segment elevation) at 90 minutes after

the administration of fibrinolytic treatment. The patients were randomised to conservative management, repeat fibrinolysis, or emergency PCI. The primary endpoint (death, re-MI, stroke, hospitalisation for heart failure) was observed in 29.8% of the conservative arm, 31.0% of the repeated thrombolysis arm, and 15.3% of the rescue PCI arm ($P<0.01$). Death occurred in 6.2% of the rescue PCI patients, compared with 12.8% of the conservative management patients ($P=0.12$) (10).

Routine PCI after lysis

Moving one step further, several trials have addressed the potential benefit of routine (systematic) coronary angiography, with PCI when needed, following intravenous fibrinolysis. GRACIA-1 included 500 patients, who were randomised to either “delayed” PCI (6-24 hours after fibrinolysis, mean 17 hours) or to an ischaemia-guided conservative approach (11). The systematic approach was associated with a reduction in mortality, re-infarction and revascularisation rates at one year (risk ratio 0.44; 95% confidence interval: 0.28-0.70), including favourable trends for mortality ($P=0.07$) and reinfarction. Similar results were achieved in the CAPITAL-AMI and SIAM-III trials (12,13).

The CARESS-in-AMI trial (14) included 600 patients and demonstrated that a strategy of immediate PCI was better than the standard of rescue-only angioplasty after fibrinolysis. In the non-systematic arm of the trial, 30% underwent rescue angioplasty, while 86% of the systematic arm received PCI. There was a significant and marked reduction in the primary endpoint of death, reinfarction, or refractory ischaemia at 30 days (10.7% vs. 4.4%, $P=0.005$). Favourable trends were observed for all individual endpoints. In this trial, the time delay from fibrinolysis to PCI was 135 minutes in the immediate angiography arm of the trial.

More recently, the Trial of Routine ANgioplasty and Stenting after Fibrinolysis to Enhance Reperfusion in Acute Myocardial Infarction (TRANSFER-AMI) trial enrolled 1,039 patients less than 12 hours after acute myocardial infarction who received fibrinolytic treatment and were randomly assigned to transfer for angioplasty within 6 hours or to a strategy limiting emergency angiography to rescue angioplasty, associated with elective angiography in those not needing rescue angioplasty. The results showed there was no difference in mortality between standard and pharmaco-invasive treatment (3.4% vs. 4.5%, 95% CI 0.71 to 2.36; $P=0.39$), but the composite primary endpoint of death, MI, or recurrent ischaemia, new or worsening congestive heart failure, or cardiogenic shock within 30 days, was strongly in favour of the pharmaco-invasive strategy (11.0% vs. 17.2%, 95% CI 0.47 to 0.87; $P=0.004$). At 6 months, there was no significant difference between the groups with regard to reinfarction and death or reinfarction (15).

The WEST study further strengthens the concept of a pharmaco-invasive approach, by suggesting that rapidly applied pharmacological reperfusion with

follow-up (rescue and routine) PCI within 24 hours produces results equivalent to PPCI (14). The WEST study compared contemporary pharmacological therapy with or without routine or rescue PCI with primary PCI. All patients (n=304) with STEMI were given ASA and subcutaneous enoxaparin on study entry and then randomised to: group A – tenecteplase with conventional care; group B – tenecteplase followed by routine or rescue PCI within 24 hours; or group C – primary PCI with a 300 mg loading dose of clopidogrel. Abciximab was also recommended for patients undergoing any kind of PCI, providing it was not given within 3 hours of fibrinolysis. The primary endpoint, a composite of 30-day mortality, re-infarction, refractory ischaemia, congestive heart failure, cardiogenic shock and major ventricular arrhythmia, was similar in all three groups (25% vs. 24% vs. 23%, all non-significant). However, the rate of death and recurrent MI was 13% in group A vs. 4% in group C (P=0.021), and 6.7% in group B (P=0.378 when compared with group C). Death rates were 1% in both the B and C arms, versus 4% in group A (P=NS). The time from symptom onset to treatment was also calculated for patients randomised before hospital admission and in hospital, and was approximately one hour less for group C patients randomised before admission, indicating that co-ordinated networks, with pre-hospital diagnosis result in faster randomisation and ultimately earlier treatment and reperfusion (16).

Overall, these trials show that rapid coronary angiography after fibrinolysis results in improved clinical outcomes compared with fibrinolysis in isolation. The REACT trial documented the benefit of rescue PCI in the absence of signs of reperfusion after fibrinolysis; the GRACIA-1, CAPITAL-AMI, SIAM-III, CARESS and TRANSFER-AMI trials showed that routine PCI was superior to rescue-only PCI, and the WEST trial showed that fibrinolysis followed by routine PCI within 24 hours yielded clinical results similar to those of PPCI (11-16).

Registries

A number of registries have focused on reperfusion therapy for STEMI patients. They have been run on either side of the Atlantic. All have documented that times to reperfusion were very often much longer than times recommended by guidelines. In addition, they have provided the opportunity to compare the outcomes of patients according to the type of reperfusion therapy used.

NRMI and NCDR registries (17-19)

The National Registry of Myocardial Infarction (NRMI) is an US observational database of patients presenting with AMI. In 2006, the data were taken over and merged with data from the CRUSADE registry to form the ongoing ACTION registry. Data on time to treatment were specifically studied during phases 3 and 4 of the registry.

In order to determine the effect of door-to-balloon time on mortality of STEMI patients after PPCI, a cohort study was conducted from 1 January 1999 to

31 December 2002. Out of 830,473 patients included in NRM1-3 and -4 during this time, 29,222 patients fulfilled the criteria for a cohort of STEMI patients who were treated with primary PCI within 6 hours of presentation at 395 participating hospitals. Patients were stratified according to door-to-balloon time (≤ 1 h, 1-2 h, > 1 h) and presence of risk factors (anterior/septal infarct, diabetes, SBP < 100 mmHg, HR > 100 bpm), as well as age, gender, medical history, etc. In transferred patients, door-to-balloon time was defined as time of arrival at the first hospital to time of PCI at the interventional hospital.

In-hospital mortality increased significantly with increasing door-to-balloon time, regardless of subgroup or the presence of risk factors. Overall, mortality increased from 3.0%, when door-to-balloon time was ≤ 90 minutes, to 7.4%, when door-to-balloon time was > 150 minutes. Interestingly, mortality increased with increasing door-to-balloon times, whatever the symptom-onset-to-door times. A more recent analysis confirmed these findings and showed that any increase in door-to-balloon times will result in increased mortality, although the relation is not linear: for instance, reducing door-to-balloon time from 90 to 60 minutes will result in 0.8% reduction in mortality, whereas a reduction in time from 60 to 30 minutes will result in a 0.5% reduction in mortality (20).

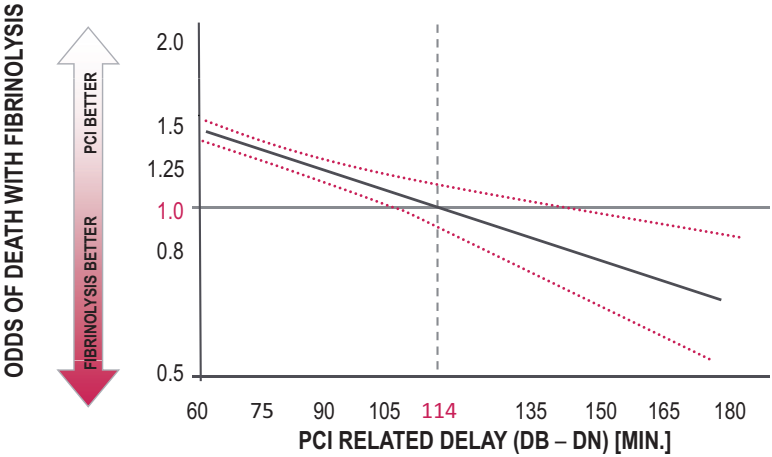
The influence of time to treatment was specifically assessed in 4,278 patients who were transferred for PPCI (18). Median total (first) door-to-balloon time was 180 minutes. Only 4.2% were treated within 90 minutes, and approximately 15% within 120 minutes.

Patients with longer door-to-balloon times were older, more often female, non-white and with more complex medical conditions. They also often presented much later after symptom onset or during weekends or off-hours. Finally, door-to-balloon times were longer when the annual case load of PPCI at the "receiving" hospital was less than 20.

Finally, a detailed analysis of the survival benefit associated with PPCI, compared with intravenous fibrinolysis was made in a population of 192,509 STEMI patients (19). The difference in time between use of fibrinolysis and PPCI was calculated by subtracting door-to-needle (DN) time from door-to-balloon (DB) time at a given hospital. Longer door-to-balloon minus door-to-needle times were associated with increased mortality (*Fig. 1*) and the time equipoise (i.e. the time beyond which the survival advantage of PPCI over fibrinolysis was lost) was calculated for the whole population and for different subgroups of patients (*Fig. 2*). Overall, the time equipoise was 114 minutes.

For every 30-minute increase in DB-DN time, in-hospital mortality increased by approximately 10% (OR 1.095; 95% CI 1.065 to 1.126, $P < 0.001$). Patients < 65 years lost the advantage of PPCI over fibrinolysis after just 71 minutes; ≥ 65 -year-olds had an advantage up to 155 minutes. PPCI had a survival advantage up to 94 minutes in those presenting within 120 minutes of symptom onset, but this increased to 190 minutes in patients presenting after 120 min-

utes of symptom onset. In contrast, infarct location had less influence (time equipoise for anterior MI: 112 minutes, non-anterior MI: 115 minutes), but the importance of infarct location was greater in patients over 65 years of age (19).



Pinto et al. Hospital Delays in Reperfusion for ST-Elevation Myocardial Infarction - Implications When Selecting a Reperfusion Strategy, *Circulation*. 2006;114:2019-2025

Figure 1: Multivariable analysis estimating the treatment effect of reperfusion therapy with PCI or fibrinolysis based on increasing PCI-related delay. After correction for patient and hospital-based factors, the time at which odds of death with PCI were equal to those for fibrinolysis occurred when the PCI-related delay (DB-DN time) was ≈114 minutes. Variables included in the model were treatment type (PPCI or fibrinolysis), age, gender, race, diabetes mellitus, hypertension, angina, Killip class 2/3, Killip class 4, previous infarction, current smoking, stroke, pulse, systolic blood pressure, payer, symptom duration, infarct location, and discharge year. Hospital covariates included STEMI volume, PPCI volume, transfer-in rate, rural location, and status as a teaching hospital.

Taking the two extremes from *Figure 2*, in a >65-year-old patient presenting with a non-anterior infarct later than 120 minutes after symptom onset, PPCI has an advantage over fibrinolysis in a DB-DN time of up to 179 minutes. However, a young patient, <65 years with an anterior MI, presenting early (within 120 minutes) loses the benefit of PPCI when the DB-DN time exceeds 40 minutes. So each patient has to be considered individually, and at least according to age, time of presentation, and location of infarct (19).

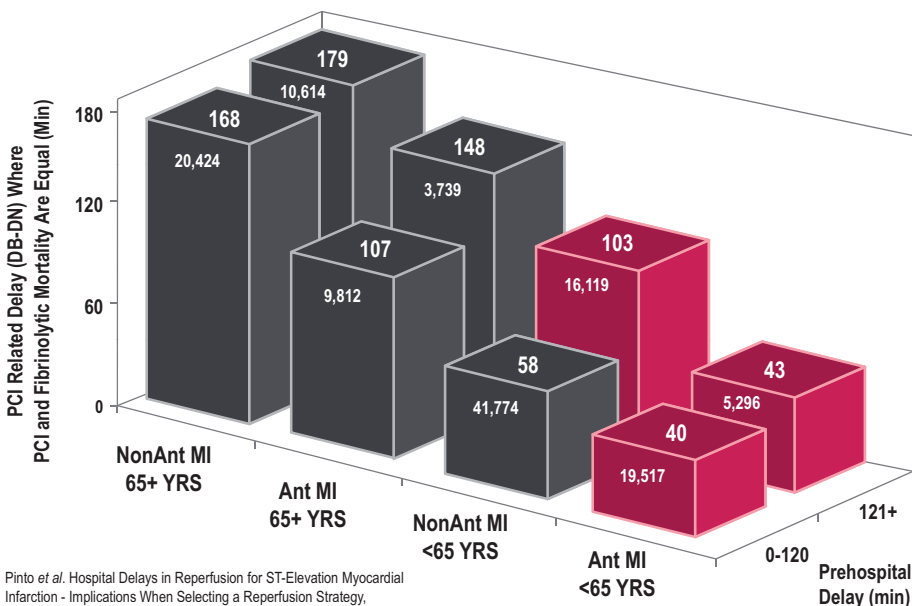


Figure 2: Adjusted analysis illustrating significant heterogeneity in the PCI-related delay (DB-DN time) for which the mortality rates with primary PCI and fibrinolysis were comparable after the study population was stratified by prehospital delay, location of infarct, and age. Ant indicates anterior; Non-Ant, nonanterior. To ensure a stable estimate of the mortality difference when primary PCI and fibrinolysis were compared in these subgroups, hospitals were excluded if fewer than 10 STEMI patients were treated with either PCI or fibrinolysis in either category. The DB-DN time at which the mortality benefit was lost was based on multivariate models. Variables included in the model were treatment type (PPCI or fibrinolysis), age, gender, race, diabetes mellitus, hypertension, angina, Killip class 2/3, Killip class 4, previous infarction, current smoking, stroke, pulse, systolic blood pressure, payer, symptom duration, infarct location, and discharge year. Hospital covariates included STEMI volume, PPCI volume, transfer-in rate, rural location, and status as a teaching hospital.

French registries. USIC and FAST-MI registries (21-24)

Three registries were carried out in France, each 5 years apart, from 1995 to 2005. All three were based upon the same principle: a consecutive collection of data on all AMI patients admitted to ICUs within 48 hours of symptom onset, over a one-month period. 60% to 75% of all French ICUs participated. In 1995, only 21% of STEMI patients getting reperfusion therapy were treated with primary PCI; 5-day mortality was 5.5% in the fibrinolysis group, versus 6.6% in the primary angioplasty group (21). Multivariate analyses showed that the type of reperfusion therapy was not correlated with early and one-year mortality. The percentage of patients treated with pre-hospital fibrinolysis was not known, and was probably low, because the use of pre-hospital lysis was not widespread in France at that time.

The USIC 2000 registry included 1,922 STEMI patients, of whom 49% received no reperfusion therapy. Of those with reperfusion therapy, 18% had pre-hospital fibrinolysis, 37% in-hospital fibrinolysis, and 44% primary PCI. Patients without reperfusion therapy were older, and had a higher prevalence of cardiovascular history and most risk factors. Median time from symptom onset to hospital admission was 3.6 hours for PHT, 3.5 hours for IHT, 3.2 hours for PPCI, and 12 hours for no reperfusion therapy. In-hospital mortality was 3.3% for PHT, 8.0% for IHT, 6.7% for PPCI and 12.2% for no reperfusion therapy. At one year, survival was 94% for PHT, 89% for IHT and PPCI, and 70% for no reperfusion therapy. In a multivariate analysis of all patients, the relative risk of death with PHT was 0.49 (95% CI 0.24-1.00; $P=0.05$). When the patients without reperfusion therapy were excluded from the analysis, the RR of death was 0.52 for PHT (95% CI 0.25-1.08; $P=0.08$), compared with other modes of reperfusion therapy (either IHT or primary PCI) (22).

Of note, a high proportion of patients who received PHT underwent subsequent coronary angiography and angioplasty: 37% within 1 day and 67% during the initial hospital stay. Overall, patients treated with pre-hospital fibrinolysis were those with the best clinical outcomes, particularly when they were admitted within 3.5 hours of symptom onset (22).

A further analysis of the USIC 2000 data, looking at the difference on outcomes for patients who bypassed the emergency room (ER) compared with those who were admitted via the ER to a cardiac unit (CCU), showed that bypassing the ER was associated with more frequent use of any type of reperfusion therapy (61.7% vs. 53.1%; $P=0.001$) and a shorter time from symptom onset to admission (244 vs. 292 minutes; $P<0.001$) (22). Five-day mortality rates were lower in patients who were admitted directly to a CCU (4.9% vs. 8.6%; $P=0.01$), regardless of the type of reperfusion therapy used. After adjustment on the TIMI risk score, admission via the ER was still an independent predictor for mortality (OR 1.67, 95% CI 1.01-2.75). Follow-up at one year also showed that mortality was less in the group who were originally admitted directly to the CCU (11.5% vs. 15.6%; $P<0.05$), although admission via the ER was not an

independent predictor of one-year mortality when adjusted for TIMI risk score (23). These findings emphasise the importance of choosing appropriate pathways in the management of STEMI patients.

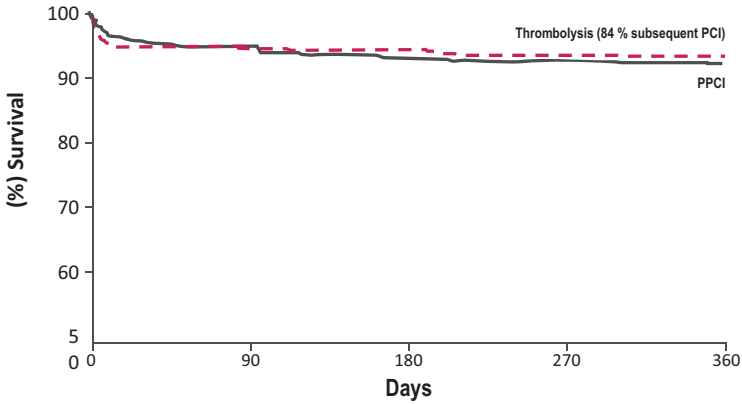
The French Registry on Acute ST-Elevation Myocardial Infarction (FAST-MI) compared the effects of PPCI with thrombolysis followed by routine angiography and PCI on outcomes (20). As with the previous ones, the survey was conducted over 1 month, at the end of 2005, and 223 centres in France included 1,714 STEMI patients. More than 60% of the patients received reperfusion treatment, with 33% getting PPCI, and 29% iv thrombolysis (18% PHT). Time from symptom onset to reperfusion treatment was significantly shorter in the group receiving iv thrombolysis (median time 130 minutes vs. 300 minutes in the PPCI group; 110 minutes for PHT, and 195 minutes for IHT). In patients who had directly called the emergency services (SAMU), the time from the first call to reperfusion therapy was 40 minutes for PHT vs. 130 minutes for PPCI and 85 minutes for IHT, $P<0.001$; hence, the PPCI-related time delay (onset-to-PPCI minus onset-to-prehospital fibrinolysis) was approximately 90 minutes over the time needed for administration of PHT. GP IIb/IIIa inhibitors were used more frequently within the first 48 hours of symptom onset in patients undergoing PPCI than in those receiving thrombolysis, and LMWH and clopidogrel also tended to be used less in thrombolysis patients. The use of statins, β -blockers and ACE inhibitors was similar in both groups. After thrombolysis, 96% of patients underwent coronary angiography, and 84% had subsequent PCI (58% within 24 hours), which represented a considerable increase, compared with what was observed in 2000. In-hospital mortality was 4.3% for thrombolysis (3.3% PHT; 6.1% IHT) and 5.0% for PPCI compared with 9.5% for those who received no reperfusion therapy. Thirty-day mortality was similar for PPCI and thrombolysis patients (4.5% vs. 4.4%, $P=0.92$) if therapy was initiated within 6 hours of symptom onset. After 6 hours, mortality increased with thrombolysis more than for PPCI (7.7% vs. 5.7%; $P=0.58$) (see *Table 1 (24)*).

Table 1: Thirty-Day Mortality Rates in Patients With Intravenous Thrombolysis Versus PPCI According to Time From Symptom Onset to Reperfusion

	≤120 min (n=263)	121 to 180 min (n=183)	181 to 360 min (n=300)	>360 min (n=282)
Thrombolysis (n=465)	4.2% (9/216)	4.6% (5/108)	4.5% (4/89)	7.7% (4/52)
PPCI (n=563)	4.3% (2/47)	4.0% (3/75)	4.7% (10/211)	5.7% (13/230)

Danchin et al. Comparison of Thrombolysis Followed by Broad Use of Percutaneous Coronary Intervention With Primary Percutaneous Coronary Intervention for ST-Segment–Elevation Acute Myocardial Infarction – Data From the French Registry on Acute ST-Elevation Myocardial Infarction (FAST-MI), *Circulation*. 2008;118:268-276

One-year survival was 94% for thrombolysis (92% for IHT; 95% for PHT) and 92% for PPCI (P=0.31); after propensity score matching, one-year survival was 94% for thrombolysis and 93% for PPCI.



Danchin *et al.* Comparison of Thrombolysis Followed by Broad Use of Percutaneous Coronary Intervention With Primary Percutaneous Coronary Intervention for ST-Segment–Elevation Acute Myocardial Infarction – Data From the French Registry on Acute ST-Elevation Myocardial Infarction (FAST-MI), *Circulation*. 2008;118:268-276

Figure 3: One-year survival in thrombolysis and PPCI patients matched on a propensity score of undergoing thrombolysis or PPCI. Of note, 96% of patients with thrombolysis underwent subsequent coronary angiography.

Overall, the results (in terms of early and one-year survival) of a pharmacoinvasive strategy, using intravenous fibrinolysis, followed by early coronary angiography and PCI compare favourably with those of primary PCI. The results of the FAST-MI registry also underline the importance of time in the selection of procedures (70% of the patients treated with fibrinolysis had treatment initiated within 3 hours of symptom onset) and suggest a benefit for back-up angiography and PCI in STEMI patients who receive thrombolysis.

The Swedish RIKS-HIA registry (25,26)

The Swedish National Registry offers the advantage of a continuous recording of data for virtually all (> 95 %) patients admitted for AMI <15 hours from symptom onset in Sweden. It is linked with the National Health and National Cause of death Registries, which collect mortality, reinfarction and re-admissions. Two analyses of the database were published in 2006: the first compared patients with pre-hospital fibrinolysis administered in the ambulance, versus in-hospital fibrinolysis; and the second compared outcomes of patients treated with primary PCI, or intravenous fibrinolysis.

Of the 26,205 patients included in the main database, 7,084 (18.2%) received PPCI, 3,078 (8.3%) PHT and 16,043 (41.3%) IHT. The rates changed over the years with improvement in standards of therapy, so that in 1999 only 8.3% of STEMI patients received PPCI, whereas in 2004, the percentage increased to 37.2%. Nearly half the PHT group and one third of the IHT group underwent subsequent angiography and PCI within 2 weeks of admission. Patients who received PHT were younger, more often male, smokers and with a lower rate of previous heart disease than those receiving IHT. Patients who underwent PPCI were the youngest, with a higher rate of previous coronary interventions, and they were more often on medications such as ASA, β -blockers and statins on admission. After adjustment for age and comorbidity, 30-day mortality was lower with PPCI than IHT (4.9% vs. 11.4%; HR 0.61; 95% CI 0.53-0.71) or PHT (7.6%; HR 0.70; 95% CI 0.58-0.85). At one year, PPCI still had lower mortality than PHT (7.6% vs. 10.3%; HR 0.81; 95% CI 0.69-0.94) and PHT was lower than IHT (HR 0.84; 95% CI 0.74-0.95). Of note, little change in mortality was observed with PPCI, whether initiated within or after 2 hours of symptom onset. In contrast, mortality was higher in the PHT group when fibrinolytic treatment was administered beyond two hours of symptom onset.

In the population of ambulance-transported patients, however, those who received PHT had 30-day and 1-year mortality rates which were similar to that observed with PPCI (see *Table 2*) (27). Interestingly, the ages of the patients (a major determinant of outcomes in AMI patients) were similar in ambulance-transported PHT and in PPCI patients, whereas the age of the whole group of PHT patients was notably older.

Table 2: Differences in 30 day and 1 year mortality between all pre-hospital thrombolysis, ambulance-transported pre-hospital thrombolysis, primary percutaneous coronary intervention, and in-hospital thrombolysis for ST-elevation myocardial infarction patients in the RIKS-HIA registry

	Ambulance-transported PHT, 2001-2004	All PHTs, 1999-2004	PPCI, 1999-2004	IHT, 1999-2004
Mean age (years)	64	66.3	64.2	68.6
30 day mortality (%)	5.4	7.6	4.9	11.4
1 year mortality (%)	7.2	10.3	7.6	15.9
Data from Björklund et al. ²⁵ Stenestrand et al. ²⁶				

N. Danchin et al. Pre-hospital thrombolysis in perspective, *European Heart Journal*. 2008 29, 2835–2842 by Oxford University Press

Summary

Primary PCI is the reference treatment in patients with STEMI. Overall, however, data from randomised clinical trials and registries suggest that both time delays and patient-related factors are determinant in selecting the best option for reperfusion therapy. Intravenous fibrinolysis, particularly in the pre-hospital setting, offers the advantage of an easier (and therefore quicker) administration, but the disadvantage of a lower rate of reopening of the culprit artery with a higher risk of subsequent reocclusion. Current evidence mandates rescue angioplasty when there are no signs of reperfusion after fibrinolysis, and strongly suggests a beneficial effect of routine angiography, early after administration of fibrinolytic treatment. Thus, the practical choice should be between primary angioplasty and a pharmaco-invasive strategy (intravenous fibrinolysis followed by angiography and PCI), depending on individual situations. Recent data from registries around the world have documented the excellent outcomes associated with organisations based upon the use of both reperfusion strategies. Notwithstanding these results, continued efforts should be made to shorten time delays, whatever the reperfusion option chosen, and ways to shorten the initial onset-of-pain-to-first-call time should also be sought.

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Kurt Huber

Data from registries and trials (part 2)

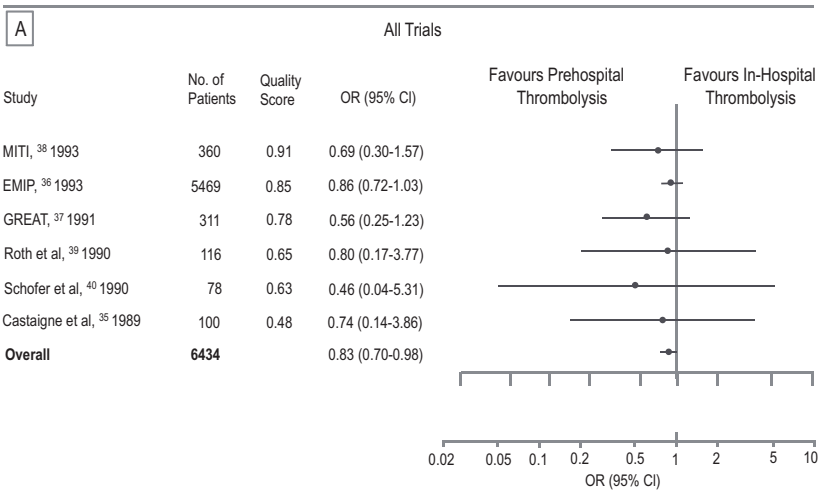
Meta-analyses, Vienna Registry, GRACE Registry

Introduction

In order to try to make sense of all the data, meta-analyses of randomised trials have been performed. These attempt to compare one reperfusion method with another. However, due to the variation in trial data, inclusion criteria, concomitant treatment received and most importantly treatment times, it is hard to draw any firm conclusions from these. Registries such as GRACE and the Vienna Registry have the advantage of being able to analyse “real-life” data from a much larger study group. This chapter summarises the data from these registries and two of the most important meta-analyses comparing PPCI and thrombolysis.

Meta-analyses

A meta-analysis of 6 randomised controlled trials and 3 follow-up studies of pre-hospital thrombolysis (PHT) versus in-hospital thrombolysis (IHT) in patients with acute myocardial infarction (AMI) favoured PHT in the time to treatment and in all-cause in-hospital mortality. One-year mortality in the GREAT trial showed a statistically significant benefit with PHT (OR 0.42; 95% CI, 0.21-0.83; P=0.007) compared to IHT. In the MITI trial, the one-year survival benefit with PHT was not significant (OR 1.14; 95% CI, 0.51-2.53; P=0.73). The GREAT trial was the only trial in this analysis to record 5-year mortality, and showed a persistent survival benefit with PHT over IHT (P<0.03). Overall, the pooled OR indicated a relative risk reduction of 17% with PHT for all-cause mortality (1).



Panel A, z score= -2.14; P= .03. Panel B, z score=-2.06; P= .04. Panel C, z score= -1.73; P= .08. OR indicates odds ratio; CI, confidence interval; EMIP, The European Myocardial Infarction Project; and GREAT, Grampian Region Early Anistreplase Trial.

JAMA. May 24/31, 2000; 283 (20): 2691
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Figure 1: Results of Randomised Trials of Prehospital Thrombolysis on Hospital Mortality

The time to thrombolysis was also less for PHT than for IHT, with an overall difference of approximately 60 min ($P=0.007$). This included the GREAT trial, which was conducted in the Scottish highlands, with long transfer times. When GREAT was removed from the analysis, the average difference in the time to thrombolysis was approximately 45 min ($P=0.01$) (1).

Data from another meta-analysis of 23 randomised trials comparing PPCI with fibrinolysis in STEMI patients revealed that PPCI was superior to fibrinolysis with regard to short-term death (7% vs. 9%; $P=0.0002$), non-fatal reinfarction (3% vs. 7%; $P=0.0003$), stroke (1% vs. 2%; $P=0.0004$) and the combined endpoint of all three (8% vs. 14%; $P<0.0001$). In the long-term, the benefit of PPCI persisted over fibrinolysis, and was independent of the type of fibrinolytic used or whether the patient was transferred for PPCI or not (2).

GRACE Registry

The Global Registry of Acute Coronary Events (GRACE) was conducted from July 1999 until December 2006 and included over 16,000 STEMI patients. The registry set out to determine whether changing hospital management strategies through the implementation of evidence-based medicine would affect the outcomes of patients with acute coronary events (3).

Among the STEMI patients, use of aspirin was high (>94%) throughout the study period. Use of other medications varied more dramatically (see *Table 1*): beta-blockers increased by 11%, statins by 48%, ACE inhibitors or ARBs by 22%, and LMWH by 20%. The use of UFH decreased, however, by 19%. In addition, thienopyridines increased by 49% overall and by 56% in patients who did not undergo PPCI, and GP IIb/IIIa inhibitors increased by 24% (3).

In-hospital mortality and incidence of cardiogenic shock following STEMI decreased by 3.9% (95% CI -5.3 to -1.9; $P<0.001$) and 2.4% (-4.3 to -0.5; $P=0.02$) respectively; but the risk of stroke did not change (see *Table 2*) (3).

The data for STEMI patients, taken from the GRACE Registry show that the use of evidence based medicine and contemporary management strategies can improve the outcomes.

A further analysis from the GRACE Registry looked at the trends in the number of patients receiving reperfusion therapy after STEMI. 10,954 STEMI patients were entered into the registry between April 1999 and June 2006 with STEMI or LBBB, presenting within 12 hours of onset of symptoms. Throughout the study period, the use of PPCI increased from 15% to 44% ($P<0.001$), whereas the use of thrombolysis decreased from 41% to 16% ($P<0.01$). Although there was no significant difference in the time to PPCI, the time to thrombolysis decreased from 40 min to 34 min ($P<0.001$). In-hospital mortality decreased from 6.9 to 5.4% ($P<0.01$). However, 33% of all STEMI patients still received

Table 1: Changes in Therapy of 44,372 Patients Treated for STEMI and NSTEMI ACS, 1999 and 2005

	No./Total (%) of Patients		% Difference in Rates (95% Confidence Interval)	P Value for Linear Trends*
	July to December 1999	July to December 2005		
ST-segment MI Aspirin	1064/1118 (95.1)	815/842 (96.7)	1.6 (-0.1 to 3.4)	<0.01
β-Blocker	718/858 (83.6)	603/639 (94.3)	11 (7.6 to 14)	<0.001
Statin	486/1302 (37.3)	816/955 (85.4)	48 (45 to 52)	<0.001
ACE inhibitor/ ARB	760/1181 (64.3)	714/832 (85.8)	22 (18 to 25)	<0.001
Low-molecular-weight heparin	493/1151 (42.8)	547/869 (62.9)	20 (16 to 24)	<0.001
Unfractionated heparin	720/1146 (62.8)	367/864 (42.4)	-19 (-0.24 to -15)	<0.001
Thienopyridine Any	329/1112 (29.5)	664/849 (78.2)	49 (45 to 53)	<0.001
No PCI	39/759 (5.1)	181/298 (60.7)	56 (50 to 61)	<0.001
Glycoprotein IIb/IIIa antagonist	184/1177 (15.6)	343/875 (39.2)	24 (20 to 27)	<0.001
Glycoprotein IIb/IIIa antagonist without PCI	19/810 (2.3)	28/310 (9.0)	6.7 (3.3 to 10)	<0.001
Nonstatin lipid-lowering drug	32/1287 (2.5)	31/937 (3.3)	0.8 (-0.6 to 2.2)	0.49
Calcium channel blocker	255/1209 (21.1)	102/915 (11.1)	-9.9 (-13 to -6.9)	<0.001
Fibrinolytic	387/781 (49.5)	144/517 (27.8)	-22 (-27 to -17)	<0.001
Cardiac catheterisation	602/1224 (49.1)	738/925 (79.7)	31 (27 to 34)	<0.001
Primary PCI	177/1099 (16.1)	406/769 (52.7)	37 (33 to 41)	<0.001
PCI	396/1219 (32.4)	591/927 (63.5)	31 (27 to 35)	<0.001
CABG	39/1217 (3.2)	25/920 (2.7)	-0.5 (-1.9 to 1.0)	0.54
No reperfusion	365/1069 (34.1)	216/754 (28.6)	-5.5 (-9.8 to -1.2)	0.90

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Table 2: Changes in Clinical Outcomes in 44,372 Patients Treated for STEMI or NSTEMI ACS, 1999 and 2005

	No./Total (%) of Patients		% Difference in Rates (95% Confidence Interval)	P Value for Linear Trends*
	July to December 1999	July to December 2005		
ST-segment MI In-hospital Death	112/1335 (8.4)	45/992 (4.6)	-3.9 (-5.3 to -1.9)	<0.001
CHF or pulmonary edema	265/1351 (19.5)	106/993 (11)	-9.0 (-12 to -6)	<0.001
MI >24 h after presentation or recurrent MI	14/390 (3.6)	20/994 (2.0)	-1.6 (-3.6 to 0.5)	<0.01
Cardiogenic shock	96/1354 (7.1)	47/993 (4.7)	-2.4 (-4.3 to -0.5)	0.02
Stroke	15/1356 (1.1)	7/997 (0.7)	-0.4 (-1.2 to 0.4)	0.08
6-mo Outcomes Death	54/1099 (4.9)	28/620 (4.5)	-0.4 (-2.5 to 1.7)	0.64
Stroke	14/1084 (1.3)	3/601 (0.5)	-0.8 (-1.7 to 0.1)	0.04
MI	7/147 (4.8)	12/601 (2.0)	-2.8 (-6.4 to 0.9)	0.01

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no reperfusion therapy and of those that did, the door-to-needle time for thrombolysis was more than 30 min in 52% of cases, and the door-to-balloon time for PPCI was greater than the recommended time window of 90 min in more than 42% of cases (4).

Thus, it was clear that improving treatment strategies can help to improve outcome and mortality, but something more was necessary to ensure that more patients received reperfusion therapy in the first instance.

Vienna Registry

Despite the magnitude of evidence in favour of rapid reperfusion following ST-segment myocardial infarction, 25-40% of all patients were not receiving any form of reperfusion prior to the start of the Vienna Registry. Guidelines were very clear: PPCI should be given to all STEMI patients if the estimated time from FMC to balloon or door-to-balloon time was <90 min. In addition, PPCI could be given if the PCI-related delay in comparison to thrombolysis was less than 1 hour. However, PPCI had to be performed by an experienced interventionalist (>75 PPCI/year) and in a high volume (>36 PPCI/year). It could also be given to patients who had contra-indications to thrombolysis, or else angiography could be performed with a view to PPCI if the diagnosis was unsure, or if the patient had high risk factors (Killip class 3; cardiogenic shock). But, the logistics of providing PPCI according to these conditions was limiting its use.

In terms of in-hospital and 30-day mortality, PPCI and thrombolysis have been shown to be comparable up to 2-3 hours. After this, the benefit of thrombolysis decreases dramatically, although it is still effective to some degree up to 12 hours after the onset of symptoms (6,7).

The Vienna STEMI Registry Group initiated a central triage for STEMI patients, which was carried out by the Viennese Ambulance Service (VAS). Patients were diagnosed on site with the aid of an ECG and then allocated to thrombolysis or PPCI according to the guidelines. Concomitant therapy with aspirin, UFH, clopidogrel, and a GP IIb/IIIa inhibitor was also generally administered in patients undergoing PPCI. For those who received thrombolysis, UFH was offered (preferably to patients with an anterior wall infarct or infarct of <2 hours duration). Patients were transferred directly to a catheterisation laboratory after receiving PHT and would either undergo rescue PCI if thrombolysis failed, facilitated PCI (routine PCI after thrombolysis), or routine angiography within 1-5 days with a view to PCI if necessary (5).

In 2002, 34% of STEMI patients in Vienna received no form of reperfusion at all. 66% were reperfused: 16% with PPCI and 50% with IHT. (PHT was only introduced in March 2004, because of a prior lack of faith in its benefits by many cardiologists). The reasons why so many patients did not receive reperfusion are multiple, and include long time delays to diagnosis; lack of available facilities, especially “out-of-hours” in the evenings and at weekends; or transfer of patients to the nearest cardiology unit regardless of the interventional facilities available (5).

After restructuring and forming an efficient STEMI network, the number of patients that received no reperfusion fell dramatically to 13.4% (mainly due to age, complications or contra-indications). Of the 86.6% of patients that received reperfusion therapy, approximately 60% received PPCI and 26.7% thrombolysis. 91% of thrombolysis patients underwent angiography during the

initial hospital stay (50% within one day). In-hospital mortality decreased overall from 16% in 2002 to 9.5%. There was no difference in mortality rates for PPCI and thrombolysis if performed within 2 hours of symptom onset. However, after 3 hours of symptom onset, (as was also observed in the CAPTIM trial (6)) PPCI was significantly better than thrombolysis (5).

The Vienna STEMI registry demonstrates that implementing the guidelines by forming an efficient network and implementing reperfusion therapy as quickly as possible after the onset of symptoms is beneficial in terms of reducing mortality and increasing the number of patients that receive reperfusion therapy (5).

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Hans-Richard Arntz

Thrombolysis vs PCI

The point of view of an emergency physician:

According to the results of several randomised studies and a meta-analysis of these studies (1) there is general consensus that primary PCI (PPCI) is the optimal reperfusion strategy when compared to thrombolysis. There are, however, several caveats to be considered before this statement can be generally accepted (2):

- 1) All patient-related factors as well as timelines have to be equal.
- 2) Adjunct treatment, e.g. secondary prevention measures after primary care have to be equally effective. This is of outstanding importance for long-term outcome.
- 3) Also, outcomes may depend on the experience of the institution/operator. Even the time of day and day of the week may influence results. Indeed, the meta-analysis by Keeley (1), which forms the main basis for the preference of PPCI over thrombolysis, has not only to be seen under these major caveats but also under several further aspects, the major consequences of which will be discussed in the following paragraphs.

An emergency physician, while taking care of an individual patient with ST-elevation myocardial infarction (STEMI) in an out-of-hospital setting or in the emergency department of a non-PCI capable hospital, has to take a wide variety of different aspects into account to decide on the optimal reperfusion strategy. This strategy could be transfer for PPCI, immediate start of thrombolysis as a lone standing concept, thrombolysis with secondary transfer to a PCI centre for rescue PCI in case of failing thrombolysis, or “facilitated PCI”, i.e. routine PCI as early as possible after thrombolysis. A further alternative is termed the “pharmacoinvasive approach”. This involves coronary angiography and PCI, if necessary, after a delay of several hours from initiation of thrombolysis in order to avoid intervention during the early phase after thrombolysis, which is characterised by platelet activation and barely controllable alterations in coagulation.

Basic concepts of evaluation of the patient, including ECG findings, categorising a patient’s risk according to history and concomitant diseases such as diabetes, age-dependent bleeding risk, and contraindications for thrombolysis are discussed in other chapters of this book. When choosing the optimal reperfusion strategy, these factors have to be put into context in relation to various clinical signs, e.g. Killip class, infarct localisation and time-dependent conditions so that the risk-benefit ratio for a given patient can be calculated.

Role of timing

Timing includes time from symptom onset to definitive diagnosis, and to the start of thrombolysis. Alternatively, it includes the diagnosis-to-balloon interval in a PCI-capable hospital or transfer time, which may also include time to organise transfer for walk-in patients in a non-PCI-capable hospital, and door-to-balloon interval after arrival at the PCI centre. When transferring a patient, not only the capacities of the catheter laboratory and the intensive care unit in the target hospital have to be considered, but also the capacity of the EMS, especially in rural areas. Last but not least, additional costs partially depending on the mode of transfer, i.e. ground-bound or by helicopter, have to be taken into account.

The most important time factor when choosing optimal reperfusion treatment for an individual patient is the time delay between symptom onset and reperfusion of the myocardium at risk (*Fig 1*) (3). The meta-analysis by Keeley (1) has to be criticised with regard to these timelines, since the majority of the evaluated studies included patients with a symptom duration up to 12 hrs (the SHOCK trial (4) even up to 36 hrs). Thrombolysis performed up to 12 hrs after symptom onset has proven to be effective (5) but is generally accepted only as a provisional therapeutic strategy later than 6 hrs after symptom onset. In other words, with regard to the late 6-12-hr time window, the results of the meta-analysis by Keeley (1) are in part a self-fulfilling prophecy.

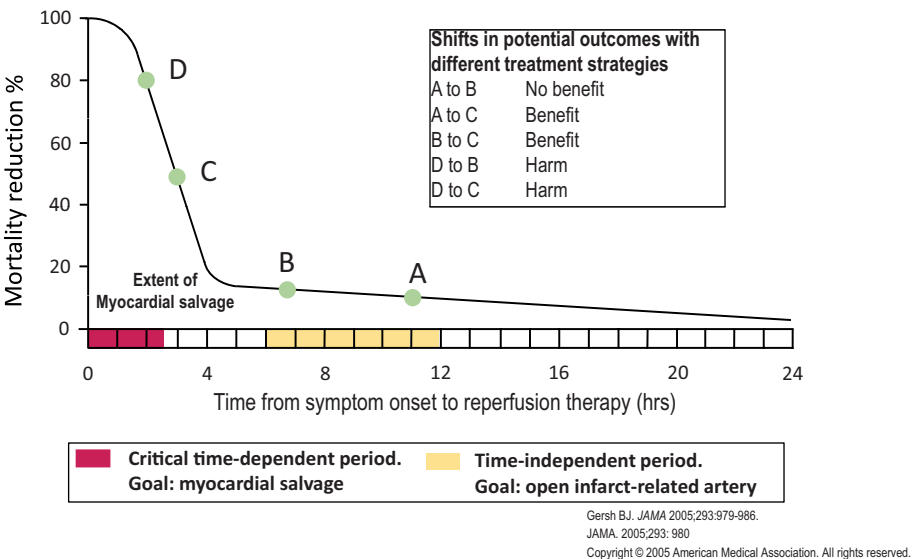


Figure 1: The relationship among the duration of symptoms of STEMI before reperfusion therapy, mortality reduction and extent of myocardial salvage (reproduced from Gersh et al (6) with permission)

Specifically for the EMS, timelines play a paramount role. Patients with STEMI (and other forms of ACS), who alert the EMS, are typically those with the shortest delay from symptom onset to call for help and subsequent “first medical contact”. Those who travel to an emergency department by private transport and even more patients who visit their private physician first, often come with a delay beyond the time window for myocardial salvage (*Fig 1*) (6). In fact, about 2/3 of the patients who call the EMS have treatment started within the optimal time window (*Table 1*). Indeed, the average time gain of about 60 min achievable by prehospital thrombolysis compared to in-hospital initiation results in a 17 % relative reduction in mortality, even in patients with a symptom duration up to six hours (7).

The unique opportunity of earliest out-of-hospital initiation of thrombolysis,

Table 1: Percentage (cumulative) of patients with initiation of out-of-hospital thrombolysis within two hours after symptom onset

	1st hr	2nd hr
EMIP	10 %	43 %
GREAT	12 %	61 %
MITI	30 %	80 %
ASSENT 3+	---	53 %
CAPTIM	---	57 %
Leipzig	19 %	64 %
BERLIN 2000/1	50 %	66 %
DANAMI II: Start of (in-hospital) thrombolysis in 50 % of pts > 3h 20min		

however, also has to be seen under the general limitations of thrombolysis, e.g. contraindications and the restriction that reperfusion of myocardium is not identical with start of the infusion/injection of the thrombolytic agent and/or adjunct antiplatelet and antithrombin treatment. Reperfusion will only be achieved with some delay. Angiographically controlled trials, starting with in-hospital, i.e. relatively late initiated thrombolysis, resulted in TIMI grade 3 flow in only about 60-70 % of patients at 90 min and an even lower percentage of complete reperfusion as measured by a >70 % resolution of the initial ST segment elevation (8). The fact, however, that patients who turn to the EMS have a shorter duration of symptoms than those seen with a delay of 1-2 hrs or more in the hospital and a delayed initiation of thrombolysis brings the angiographic findings cited above into question. Results from clinical studies and registries shed a distinct light on the critical early time window, also referred to as the “golden hour of reperfusion” (9), underlining the critique on the 12-hr time window for thrombolysis in Keeley’s meta-analysis (1, 2, 10-15). For example,

data from patients with out-of-hospital thrombolysis started within the first 70 min after symptom onset in the MITI trial (13) developed much less myocardial necrosis or even experienced “abortion” of myocardial infarction by this early initiation of therapy. Early treatment also led to higher long-term survival rates compared to patients treated later and up to 6 hrs after symptom onset (13). The increased susceptibility of a fresh clot to the lytic agent is thought to be the mechanism underlying this observation (16) and may also explain the finding that the efficacy of thrombolysis compared to PPCI is clearly related to the delay from symptom onset to start of reperfusion treatment (9, 17).

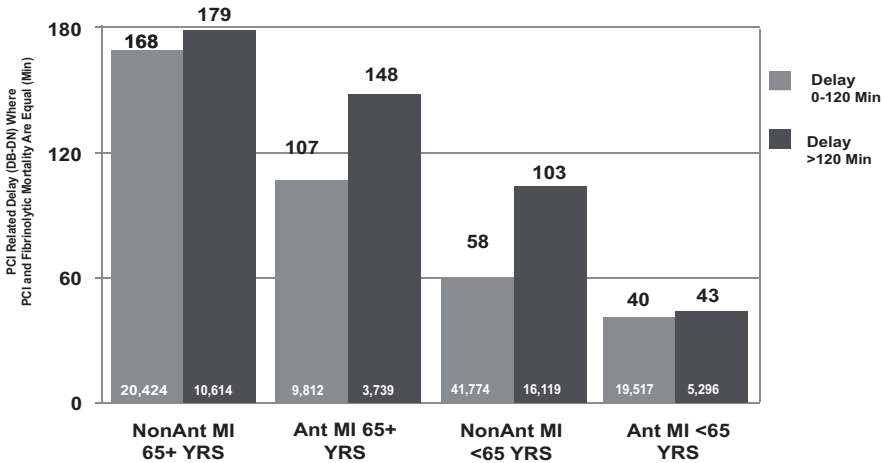
It has to be kept in mind that the thrombolytic agent given is also of importance when evaluating the efficacy of treatment. In the Keeley meta-analysis (1) results are still in favour of PPCI when fibrin specific agents and streptokinase are compared. There is, however, a strong trend favouring fibrin specific thrombolytics over streptokinase in all endpoints except stroke. Thus, in the Keeley meta-analysis (1), less effective regimens for thrombolysis are mixed up with more modern fibrinolytic treatments. But even with streptokinase, which was used in the PRAGUE II study (14), mortality with thrombolysis was equal compared with transfer for PPCI when treatment was initiated within the first 3 hours after symptom onset.

Efficacy of PPCI may be less time dependent since an older more stable and thrombolysis resistant clot can be overcome mechanically. In consequence, even if the principal deleterious role of delay to reperfusion also exists for PPCI, it can be derived from the results of the CAPTIM study (10) and also from PRAGUE II and the registries (12, 14, 16-19) that the superiority of PPCI as a strategy may be preferentially observed at a later time window after symptom onset, e.g. beyond later than 2-3 hrs. Thrombolysis initiated within the first 2-3 hrs after symptom onset may be at least equal or even superior to PPCI (11, 12, 16-18).

Some investigators intending to find an equipoise of efficacy of thrombolysis or PPCI, calculated outcomes in relation to time delays to the start of thrombolysis or PPCI. From the data incorporated into the meta-analysis by Keeley et al (1), Nallamothu and co-workers (20) calculated an acceptable time delay to PPCI of up to 110 min for superiority of PPCI over thrombolysis with regard to the triple endpoint of death, stroke or re-infarction. A maximum delay of 90 min was calculated for mortality. With longer delays, thrombolysis would be superior to PPCI. This analysis has been methodically criticised (21). A further analysis of the same data using another calculation strategy came to a longer acceptable delay. Even a delay of 110 min resulted in the same mortality rate for PPCI and fibrinolysis (22). Some investigators came to other conclusions. A meta-analysis by Boersma et al on the role of time delays in 25 studies comparing thrombolysis with PPCI results in superiority of PPCI irrespective of delays (23). The results in this study, however, are based on the delays from randomisation and not the total time from symptom onset.

In the DANAMI II study (24) the largest study included in the meta-analysis by Keeley (1), the median time delay from (in-hospital!) initiation of thrombolysis was 200 min, i.e. 50 % of the patients were treated later. Thus, a majority of patients was treated at a time point when the “golden hour” for myocardial salvage was clearly gone. This may explain the superiority of PPCI in DANAMI II (24). Moreover, the overall result of this study favouring PPCI, is based nearly exclusively on the exceptionally high re-infarction rate but not on short-term or long-term mortality and even not when the combination of mortality and stroke is taken into account.

A more sophisticated analysis with regard to superiority or inferiority of PPCI compared with thrombolysis will result when time delays are set in relation to further factors of major prognostic importance (16), specifically the age of the patient and localisation of the infarction. The NRM registry with more than 190,000 patients is large enough to perform such a complex analysis (25). An overall calculation of the acceptable time delay between thrombolysis to PPCI gave similar results to those found by Nallamothu and Betriu and co-workers (20, 22). A more in-depth calculation, however, including the patient’s age and localisation of infarction as well as duration of symptoms, results in timelines requiring a more individualised approach in selection of the optimal reperfusion strategy (Fig 2). Even if this analysis does not evaluate early pre-hospital thrombolysis, it should have practical consequences from the emergency physicians point of view. Thrombolysis seems to be the better choice in younger patients (< 65 years of age) suffering from an anterior wall infarction if the expected time difference between start of thrombolysis and first bal-



Pinto et al. Hospital Delays in Reperfusion for ST-Elevation Myocardial Infarction - Implications When Selecting a Reperfusion Strategy, *Circulation* 2006;114:2019-2025

Figure 2: Acceptable PPCI-related delay (calculated as the difference of door-to-balloon minus door-to-needle intervals) in relation to age of the patient, infarct localisation and symptom duration in the NRM registry (25). Longer delays in the individual groups will result in a better outcome with fibrinolysis compared to PPCI

loon inflation is more than just 40 min. This very short, acceptable timeline for younger patients with anterior infarction is independent of a symptom duration of more or less than 2 hrs. The other extreme is patients over 65 years of age with non-anterior infarctions and a symptom duration of more than 2 hrs where thrombolysis should be considered an exception only. PPCI in this patient group is superior even with a delay up to 3 hrs to first balloon inflation in comparison to start of thrombolysis (25). From an emergency physician's point of view, these data are of outstanding importance, since it seems to be nearly impossible to transfer a younger patient with an anterior infarction from a non-PCI-capable hospital to a PCI centre and achieve first balloon inflation within 40 min, as required. Even from the out-of-hospital viewpoint, the time needed for basic care of the patient and direct transportation to a PCI hospital usually causes a time delay to PCI that is far outside the required time limit of 40 min. On the other hand, it should generally be possible to stay within the 3-hr time limit from FMC when transferring elderly patients with non-anterior infarctions and a longer duration of symptoms.

Role of adjunct treatment

DANAMI II (24) is a typical example of the important considerations to be mentioned when evaluating the results of the meta-analysis by Keeley et al (1) and individual studies comparing PPCI and thrombolysis. Selection of patients in DANAMI II was criticised in letters to the editor when the study was first published in the *New England Journal of Medicine* (24). In DANAMI II, several patients with a stroke history were randomised to receive thrombolysis i.e. these patients were put at an increased risk for intracranial bleeding, since they had a contraindication for this therapy. Also, the vast majority of patients randomised to PPCI, but not the patients randomised to thrombolysis, received clopidogrel as a periprocedural and follow-up treatment. This difference clearly discriminates patients treated by thrombolysis, as we know from the CLARITY-TIMI 28 and the COMMIT studies (26, 27). The observation of discriminating differences in intensity of treatment can also be observed and may explain the results of a Swedish registry (19). In this registry, the tendency favouring the PPCI group because of better and more intense secondary prevention therapy was not restricted to clopidogrel alone, but also extended to statins and β -blockers.

There are other questionable points regarding DANAMI II (24), the main study of influence in the Keeley meta-analysis (1). Periprocedural myocardial infarctions were not evaluated in the PPCI group. Re-infarctions following thrombolysis were treated with re-thrombolysis, an ineffective procedure, which has generally been abandoned for years, and has recently been shown once again to lack efficacy by the REACT trial (28). Accordingly, the rate of rescue-PCI procedures was lowest in DANAMI II if compared with larger recent studies investigating thrombolysis. Moreover, the re-infarction rate was extensively high in this study (*Fig 3*) (29).

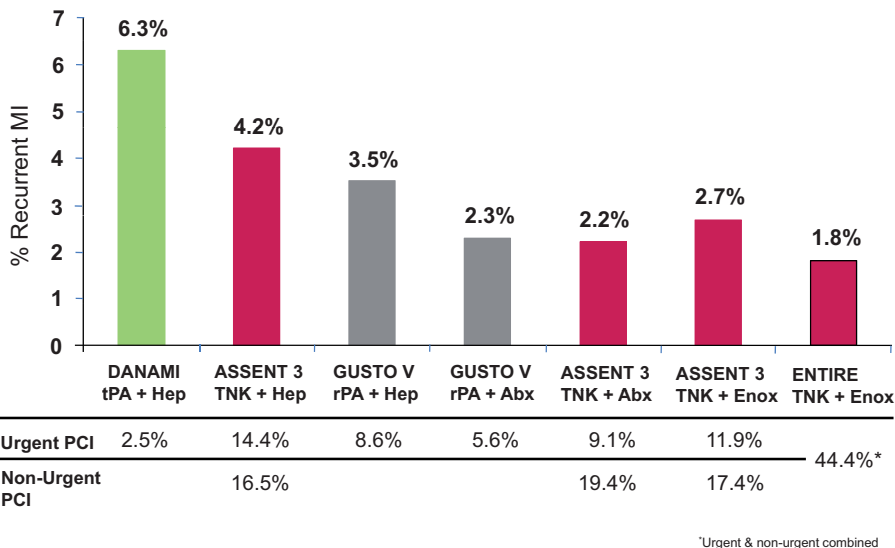


Figure 3: Re-infarction rate in studies with thrombolysis in relation to frequency of rescue or delayed PCI (29)

Finally, when thrombolysis is evaluated against PPCI for reperfusion in STEMI, it must not be forgotten that progress in adjunct medication has been made, with a major influence on outcome (26, 27, 30-33). This progress has improved outcomes with PPCI as well as outcomes with thrombolysis and encompasses antiplatelet and antithrombotic therapy. In addition, new techniques and devices, such as the use of drug eluting stents, may improve short-term outcome but may also lead to new and unexpected problems (34).

Special situations and open questions

Severe pump failure (Killip class IV and possibly class III) and shock, as complications of an acute myocardial infarction, are associated with a poor short- and long-term prognosis (16). Successful treatment of this life-threatening condition requires specific care by an experienced team of physicians and nurses. Whenever possible, these patients should therefore be primarily transported – or immediately transferred if first seen in a primary care hospital - to a tertiary care centre with a 24/7 PCI capability. Severe pump failure or cardiogenic shock is not a contraindication for thrombolysis, especially not when initiated with a short duration of symptoms. It has, however, convincingly been shown in the SHOCK trial (4), that at least for patients < 75 years of age, PCI offers one of the few available chances for improved outcome and is therefore part of the treatment of choice. On the other hand, it has to be kept in mind that thrombolysis per se, especially if initiated early after symptom onset,

is the best strategy to avoid development of cardiogenic shock, as shown by the Fibrinolytic Therapy Trialists (FTT) Group and the CAPTIM investigators (5, 10, 11).

Last but not least, there are still many important unanswered questions when discussing PPCI and thrombolysis in STEMI, particularly if strategies combining fibrinolysis with PCI are considered. For example, an appropriate and fitting definition of the role of timing is needed as well as the optimal criteria for rescue PCI in patients with suspected failure of thrombolysis. Even if the results of several studies (35-39) indicate that timely angiography and eventual PCI after fibrinolysis improves prognosis (and therefore is recommended in the guidelines), neither the optimal time window for angiography nor the criteria for eventual PCI in this situation is known. The strategy of targeted intervention, recently termed a “pharmacoinvasive” strategy, is being investigated in the ongoing STREAM (Strategic Reperfusion Early After Myocardial Infarction) trial and is one of the hot topics of the actual discussion. Results are urgently needed, since the combination strategy of primary thrombolysis and targeted secondary angiography and eventual PCI may be a problem solution for many patients without timely access to an experienced PCI centre.

Further specific questions in special situations await definitive answers. For example, the optimal reperfusion treatment in patients resuscitated from a cardiac arrest due to a STEMI has not yet been investigated in an adequate study. Thrombolysis initiated in patients with refractory arrest (so called “ultima ratio” strategy) proved not to be effective in the placebo controlled randomised TROICA study (29). Observational series in STEMI, particularly in those who are primarily successfully resuscitated, however, seem to profit from thrombolysis (41, 42). There are also encouraging reports on patients of this group treated by PPCI (43, 44). Thus, resuscitated cardiac arrest in STEMI patients may be another important field for future research comparing primary PCI and thrombolysis.

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Kurt Huber

Application in daily clinical practice

Introduction

Acute ST-elevation myocardial infarction (STEMI) is a condition strongly related to cardiac arrest, with estimates of up to 90% of cardiac arrests being preceded by STEMI (1). The overall survival rate of out-of-hospital cardiac arrest is approximately 5-10% (1); therefore, the main objective in the management of STEMI has been to treat the greatest number of patients possible with early reperfusion therapy, indiscriminate of treatment option (2). The use of the fastest available reperfusion therapy within 3 hours after symptom onset has been proven to decrease in-hospital mortality (3). Despite international guideline recommendations, the overall proportion of eligible patients that receive any form of treatment still tends to remain low (2). Previous studies have found that up to one third of eligible patients with STEMI or left bundle branch block (LBBB) remain untreated, findings that resemble those reported in the 2nd Euro Heart Survey, where over 30% of the patients with STEMI underwent no reperfusion therapy (2). Time delays in treatment delivery have also remained largely unchanged, with a median of 2.5 to 3 hours for primary PCI (4). Accordingly, pharmacologic reperfusion (thrombolytic therapy) might be an option especially for patients with a short delay (2-3 hours) from onset of symptoms until first medical contact if primary PCI cannot be offered within 90-120 minutes and if no contraindications are present (5, 6).

Guideline Recommendations

The American College of Cardiologists, in association with the American Heart Association (ACC/AHA) (5) and the European Society of Cardiology (ESC) (6) recommend reperfusion therapy in patients with STEMI by use of primary percutaneous intervention (PPCI) within 90 to 120 minutes after first medical contact (FMC), i.e. diagnosis of STEMI by use of 12-lead ECG and symptoms by a physician or well-trained paramedic. Favourable outcome can be expected when treatment starts within 2-3 hours of symptom onset (7). Thrombolytic therapy (TT) is preferred for patients when PPCI cannot be delivered within 90 to 120 minutes of FMC by an experienced team if no contraindications for pharmacologic reperfusion are present (5, 6). TT should be initiated within 30 minutes of FMC. Best outcome with TT can be expected in patients treated within 3-4 hours of symptom onset, in big infarctions, and in patients with low bleeding risk (usually the younger below 75 years of age); but from a clinical data point of view, it is efficacious (versus no reperfusion) up to 12 hours of symptom onset and also in the elderly (8, 9).

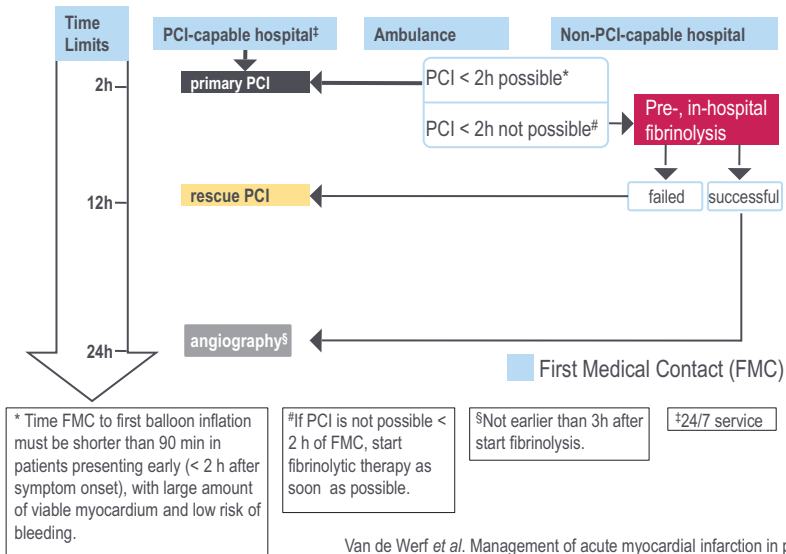


Figure 1: ESC Guidelines Recommendations for Reperfusion Strategies (6)

Concomitant Medications

In the management of AMI, guidelines have always recommended use of concomitant medications to help achieve and maintain therapeutic effects and offer greater benefits in terms of long-term mortality.

Antiplatelet therapy

After plaque rupture, thrombus formation involves activation of the coagulation cascade, formation of fibrin strands and platelet activation (10). When a fibrinolytic agent is used for thrombus dissolution, local production of thrombin is paradoxically increased, causing a pro-thrombotic phase in which the risk of thrombus formation and re-occlusion of the infarct artery is high (10).

An initial dose of chewable aspirin (150-325 mg) is recommended for all patients with STEMI providing they are not allergic to aspirin. Thereafter, aspirin should be continued at a dose of 75-100 mg daily (5, 6).

In order to reduce the risk of thrombus formation, guidelines recommend the addition of clopidogrel in the acute phase: when PPCI is planned, a (300-)600 mg loading dose followed by 75 mg daily maintenance dose for up to 12 months is recommended. In patients with STEMI and pharma-

cologic reperfusion, a loading dose of 300 mg for patients under 75 years is recommended, while older patients should only receive 75 mg/day from the beginning. Long-term maintenance of dual antiplatelet therapy (aspirin+clopidogrel) is recommended for all STEMI patients up to 12 months. However, if CABG or other major surgery is planned, clopidogrel should be withheld for 5-7 days prior to the procedure, while aspirin should be maintained if possible (5, 6).

Gastric protection with proton pump inhibitors

Recently, there has been discussion whether the concomitant use of proton pump inhibitors (PPI) in patients on dual antiplatelet therapy, as recommended by international experts (11), might negatively influence clinical outcome (12). One explanation for a reduced action of clopidogrel under concomitant PPI use is that drug absorption is enhanced in an acidic environment, and therefore the use of a PPI or other antacids may potentially diminish or slow drug absorption. Another hypothesis is that PPIs might inhibit the hepatic isoenzyme CYP2C19 and consecutively prevent the metabolism of the pro-drug clopidogrel to its active metabolites through competition for the same substrate (13). A recent trial (14) and a recent meta-analysis (15), however, have proven that the use of PPIs is safe and that co-morbidities and a higher risk profile seem to be responsible for a worse clinical outcome in patients under PPIs.

Platelet glycoprotein (GP) IIb/IIIa inhibitors

GP IIb/IIIa inhibitors are recommended for use in STEMI patients who are referred for PPCI (5, 6). Abciximab is preferred over small molecules (eptifibatide, tirofiban) based on a higher efficacy and more clinical data (5, 6). In the recent ESC guidelines, the early use (in the organisation phase for PPCI) is, however, not recommended based on the only prospective randomised trial (FINESSE), which was negative (6). However, there is meanwhile evidence for the benefit of early use of abciximab based on meta-analyses (16, 17), the EUROTRANSFER registry (18) and post-hoc investigations of a huge prospective trial (19). These data were not fully known when the recent ESC guidelines were published and it is expected that future updated guidelines will reflect this new information.

The use of GP IIb/IIIa blockers adjuvant to TT was beneficial in pilot trials, when used early before the catheter laboratory by demonstrating a higher TIMI-3 flow rate in the infarct-related artery in the first diagnostic angiogram (20, 21). After FINESSE, however, this strategy has been abandoned because it was not effective but led to higher bleeding complications (22).

Anticoagulant therapy

In patients with STEMI and a conservative strategy, the guidelines prefer the use of fondaparinux or the low molecular weight heparin enoxaparin during the period of hospitalisation (5, 6).

Administration of unfractionated heparin (UFH) is now standard practice with PPCI. UFH is usually given as an i.v. bolus (70-100 mg/kg body weight or 40-60 mg/kg if given together with a GP IIb/IIIa inhibitor). While fondaparinux is not recommended in patients referred for PPCI (6, 23), bivalirudin has recently been shown to be effective and safe (HORIZONS trial) (24) and will enter future guidelines. The role of enoxaparin as adjuvant antithrombin during PPCI is currently under investigation (ATOLL trial).

In STEMI patients treated with TT, enoxaparin, unfractionated heparin as well as fondaparinux are potential options for adjuvant anticoagulation (5, 6). The ExTRACT trial with 20,506 patients used a reduced dose of enoxaparin in the elderly (> 75 years) and those with renal impairment, with the result that although there was a significant increase in non-cerebral bleeding, the overall net benefit with regard to mortality, ICH, or non-fatal infarction was in favour of enoxaparin (25).

In the OASIS-6 trial, the factor Xa inhibitor, fondaparinux, was compared to heparin or placebo (if heparin was contra-indicated) in STEMI patients. The trial concluded that fondaparinux was associated with a 17% relative risk reduction in mortality and reinfarction in patients that underwent thrombolysis (23). Thus, fondaparinux (2.5 mg i.v. bolus followed by 2.5 mg daily s.c for up to 8 days) can be given as an adjunctive therapy in patients with STEMI as long as PPCI is not the treatment of choice (5). Direct thrombin inhibitors, such as bivalirudin, are at present not recommended in patients undergoing fibrinolysis (5).

Practical Considerations

Current trial results and international guideline recommendations emphasise treatment strategies to reduce total ischaemic time (defined as the time from onset of symptoms to reperfusion of the infarct-related artery) with the fastest available, safest, and most efficacious reperfusion strategy (5, 6). Early reperfusion of an occluded infarct-related artery has been associated with increased myocardial blood flow restoration, decreased risk of myocardial necrosis, improved myocardial salvage, and improved clinical outcomes, irrespective of the therapy applied (26). Early treatment strategies include development of mobile coronary care units, with trained staff in the diagnosis and management of STEMI, to reduce transport and hospital time delays (27), and usually only can be offered in well organised systems of care (networks). More information about STEMI networks is provided in chapter 7.

Baseline characteristics of patients with different reperfusion strategies

Younger subjects with fresh infarctions are more frequently submitted to TT (preferably pre-hospital lysis, PHT) than the elderly (8). Elderly patients tend to have co-morbidities (hypertension, diabetes) and a higher risk of poor outcomes according to Killip class, TIMI risk scores and TIMI risk index (25). Regardless of the chosen reperfusion therapy, variables such as age, haemodynamic indicators on admission, high heart rate, heart failure, and site of first treatment have been reported as independent variables for adverse in-hospital mortality (27). In patients receiving TT, higher age, haemodynamic indicators on admission, increased heart rate, heart failure, time delay until administration of TT, and non-optimal in-hospital management have been significantly associated with greater in-hospital mortality (27). Older age and presence of co-morbidities (history of peripheral vascular disease, anterior location of infarction, presence of diabetes mellitus, history of congestive heart failure, and history of renal failure) have also been reported as independent predictors of increased 1-year mortality (8) in patients with STEMI independent of the kind of reperfusion strategy. Women also present with higher mortality rates, and gender seems to be related to presence of a higher risk profile (age, incidence of shock, and time to treatment) (3).

Table 1: Multivariable Analysis of Predictors of Mortality

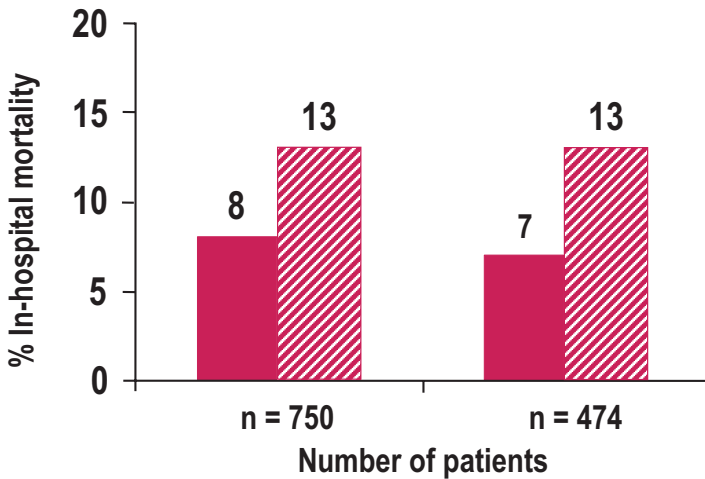
Variables	P	OR
Shock	<0.001	54.21
Age	<0.001	11.05
Pain to reperfusion time	0.05	1.23
Infarct location	0.036	0.474
Gender	0.855	0.932

Kalla et al, Vienna STEMI Registry Group. Implementation of guidelines improves the standard of care. The Viennese Registry on Reperfusion Strategies in ST-Elevation Myocardial Infarction (Vienna STEMI Registry). *Circulation* 2006;113:2398-2405.

In addition, patients without reperfusion therapy have a typical profile of clinical characteristics, which is different from that of patients with either type of reperfusion treatment (28): they are usually older with a higher risk profile, as documented by a higher GRACE risk score, while patients treated with TT or PPCI have a comparable GRACE score (28).

Despite age group variances, lower in-hospital mortality is obtained in patients who receive pre-hospital thrombolysis (PHT). Mathew et al. reported significantly lower in-hospital mortality for the PHT group compared to the

in-hospital thrombolysis (IHT) group (Fig 2) (27/326: 8% vs. 55/424: 13%, P=0.04) in their STEMI cohort (27). Trials have shown that both in-hospital mortality and 1-year mortality are dependent on time delays (3, 8).



In-hospital mortality according to source of admission in all patients (n=750) and those who received fibrinolytic therapy (n=474).
 ■ pre-hospital; ▨ in-hospital.

Mathew et al. Impact of pre-hospital care in patients with acute myocardial infarction compared with those first managed in-hospital. *Eur Heart J* 2003;24:161-171.

Figure 2: Impact of pre-hospital care in patients with acute myocardial infarction compared with those first managed in-hospital (27)

Special Groups

Recent trials have shown that survival benefits with PPCI over fibrinolysis seem to be lost after determination of door-to-balloon minus door-to-needle (DB-DN) times (29). Excellent outcomes with TT have been reported when used in properly selected subgroups of patients (28), making consideration of patient characteristics, as well as system delays, as well as benefits and limitations of the reperfusion therapy an important part of the selection procedure (29). Therefore, the international guidelines recommend selection of optimal reperfusion strategy, based not only on anticipated door-to-balloon – door-to-needle (DB-DN) time, but also on patient characteristics (6, 30). Baseline characteristics for STEMI patients referred for any reperfusion strategy tend to be similar in most trials. Subjects seem to be more often males, between 55 and 75 years of age, hypertensive, diabetic, and with a previous history of MI (31). Higher age and female gender seem to be independent variables adding up to higher mortality rates in patients with STEMI.

STEMI is a condition frequently seen in older patients (≥ 75 yrs); in general, STEMI is more frequent in patients between 40 and 70 years of age, but with growing populations and longer life spans, the incidence is increasing in the seventh and eight decades, making the elderly the fastest growing segment of the STEMI patient population (25). Trials have reported that more than one half of the mortality rates can be attributed to this group of patients, due to the high frequency of complications, such as heart failure, stroke, and re-infarction (25). Elderly patients are also associated with a higher risk of adverse events related to treatment (i.e. bleeding) (25). Fox et al. reported that after STEMI, higher rates of reinfarction and stroke are present, especially in the early phase (within the first 4 days following STEMI), with an increased mortality risk during the first 2 weeks (31). For patients receiving TT, significant univariate predictors of in-hospital mortality have been identified in several trials, including older age (≥ 75 years), female gender, non-smoking status, non-ST-elevation myocardial infarction, haemodynamic indicators (admission heart rate, Killip class II & III and hypotension), initial hospital admission and longer delay time (call to fibrinolytic therapy) (27). In contrast, younger patients (< 60 yrs) have reported lower in-hospital mortality when compared to other age groups (3).

With respect to PPCI, time delays with longer DB-DN times as recommended have also been independently associated with mortality in patients with STEMI: Pinto et al described how the survival advantage of PPCI over TT decreases 0.15% as DB-DN times increase in patients with STEMI, for every 10-minute delay in the overall study population (29). But this rate of loss of survival advantage varied depending on patient characteristics. According to survival advantage related to time delays and age, patients younger than 65 years tended to lose the survival advantage with PPCI after 71 minutes of delay (vs. 155 minutes in those ≥ 65 years) (*Table 2*) (29). These authors were also able to show how mortality advantage with PPCI was greater in younger patients, who presented with anterior MI treated within 2 hours of symptom onset, but only when performed within 40 minutes (29). In older subjects, not only was the survival advantage with PPCI present after greater delay (115 minutes) but it also showed equal advantage to fibrinolysis therapy, mainly because of the higher risk of ICH in this specific population treated with TT (29).

Table 2: Relationship of Prehospital Delay, Age, and Infarct Location to the Loss of PCI-Related Mortality Benefit

	Symptom Duration ≤120 min	Symptom Duration >120 min	Age <65 y	Age ≥65 y	Anterior Infarction	Non- anterior Infarction
Time, min (No. of patients)*	94 (n=125,737)	190 (n=66,772)	71 (n=115,293)	155 (n=77,141)	115 (n=69,331)	112 (n=123,178)
<i>P</i> †	<0.001	0.01	0.001	<0.001	0.001	0.002
<p>* Times represent PCI-related delay (DB-DN time) at which mortality with PCI and fibrinolysis were equal, stratified by symptom duration, age, or location of infarct. To ensure a stable estimate of the mortality difference when primary PCI and fibrinolysis were compared in these subgroups, hospitals were excluded if fewer than 10 STEMI patients were treated with either PCI or fibrinolysis in each category.</p> <p>† <i>P</i> values for the interaction of treatment with fibrinolysis and DB-DN time.</p>						

Pinto et al, Hospital Delays in Reperfusion for ST-Elevation Myocardial Infarction Implications When Selecting a Reperfusion Strategy. *Circulation* 2006;114:2019-2025

Female gender has been described in several trials as an independent risk factor for STEMI and higher mortality in STEMI patients. Gender and increasing age have been reported as independent predictors (univariate analysis) of higher in-hospital mortality rates in both reperfusion groups (3). Results from the Vienna STEMI registry reported a non-significant almost doubled mortality rate in the female cohort compared to males in the group submitted to PPCI ($P=0.18$) (3). Likewise with TT, mortality rates were almost 3 times higher in women than in men ($P<0.005$) (3).

The importance of timing

The benefits of reperfusion on morbidity and mortality in patients with STEMI are more dependent on the time to reperfusion than on the type of reperfusion. The French Registry on Acute ST-Elevation Myocardial Infarction (FAST-MI) demonstrated that over the last 10 years, with the development and optimisation of STEMI treatment networks and treatment, mortality significantly declined in France. TT was administered early and was followed in 96% of cases by coronary angiography with 84% receiving subsequent coronary intervention (28), data, which were similar to that of the VIENNA STEMI network (%). The outcomes in-hospital mortality, 30-day mortality, and 1-year mortality, were comparable in patients receiving TT (with consecutive angiogram and revascularisation) or PPCI, although some difference was seen in 30-day mortality when reperfusion treatment was initiated more than 6 hours after symptom onset: within 6 hours of symptom onset, 30-day mortality was 4.4% with TT and 4.5% with PPCI ($P=0.92$); in those treated later than 6 hours, 30-day mortality was 7.7% versus 5.7% respectively ($P=0.58$) (28).

In both the CAPTIM trial (32, 33) and the Vienna STEMI Registry (3), PHT was associated with a lower incidence of mortality compared to PPCI in STEMI patients treated within 2 hours of symptom onset. Interestingly, patients referred for PHT displayed signs of cardiogenic shock less often when they reached the hospital than non-pretreated patients (3). After 2 hours, PPCI was more beneficial with regard to mortality (3, 32, 33).

In real-life terms, this means that patients with infarctions in the very early phase (within 2 hours of symptom onset) need to receive reperfusion therapy as soon as possible after the onset of symptoms. Ideally, this is performed at the first point of contact, which again re-emphasises the importance of implementing optimal STEMI management networks to ensure rapid recognition and initiation of treatment. PHT followed by coronary angiography and PCI if necessary seems to be a practical, logical, and successful solution in a well-organised system of care, if PPCI cannot be offered within the given time frame.

Practicalities and difficulties (see also chapter on Networks)

Pre-hospital care offers potential benefit to patients with STEMI, especially when it is readily available and can be delivered by trained healthcare professionals (26). Rapid and accurate recognition and management of STEMI not only improves outcomes, but also reduces transportation and hospital delay times, which also improves mortality rates for STEMI patients (27).

PHT has been shown to reduce the time to treatment by 0.5-1 hour in comparison to IHT (4), while in patients without any type of reperfusion therapy, time to treatment delays remain rather high (8). Comparing reperfusion strategies, TT usually offers shorter mean time delays than PPCI. Time to first call was significantly longer in patients with PPCI (median 75 vs. 60 minutes, $P=0.001$), as well as time to initiation of reperfusion therapy, as reported in the FAST-MI results (28). Other trials have shown that about half of the patients (50.5%) treated with TT receive therapy within 2 hours after symptom onset, while only 14.6% of the patients receiving PPCI can be treated within 2 hours of symptom onset (3).

Reduced overall mortality

Mortality rates are significantly reduced with early treatment strategies, especially for those receiving pre-hospital management. Mathew et al reported an absolute risk reduction of 14% in mortality for patients first seen and managed by the MCCU in comparison to those first managed in-hospital (OR for PH 0.497, 95% CI 0.2-1.01, $P=0.051$) (27). Greater 1-year survival rates are also higher in patients treated with PHT (94.7% vs. 91.8%) than for those undergoing PPCI (1). PHT is also associated with lower 1-year (RR, 0.49; 95% CI, 0.24 to 1.00; $P=0.05$) and in-hospital mortalities (3.3%) (8). Overall

causes of death tend to be similar for patients with thrombolysis and PPCI, and no greater differences in in-hospital complications have been seen between those treated with thrombolysis and those undergoing PPCI (28). In-hospital mortality was the highest in patients without reperfusion therapy (9.5%) (28).

Difficulties related to pre-hospital thrombolysis

Trials have reported frequent use of rescue PCI performed within 1 day of admission in a higher proportion of patients treated with PHT (37%) compared with those who received in-hospital thrombolysis (18%), primary PCI (0.7%), or no reperfusion therapy (12%) (8). In addition, the risk of intracranial haemorrhage (ICH) with TT, especially in elderly patients, is higher which limits its use in this population (34). This risk of ICH, at least in part, can be associated with the adjuvant antithrombotic therapy and has been reported not only for UFH but also for direct thrombin inhibitors and LMWH (34).

Conclusion

In the management of STEMI patients, early access to reperfusion strategies has been consistently shown to significantly decrease morbidity and mortality rates in the overall population (3). This requires that STEMI be rapidly recognised and treated. Time delays and patient characteristics should be taken into consideration when choosing reperfusion strategies as well as concomitant therapies. In particular, prehospital thrombolysis has been associated with reduced time delays in STEMI management (27).

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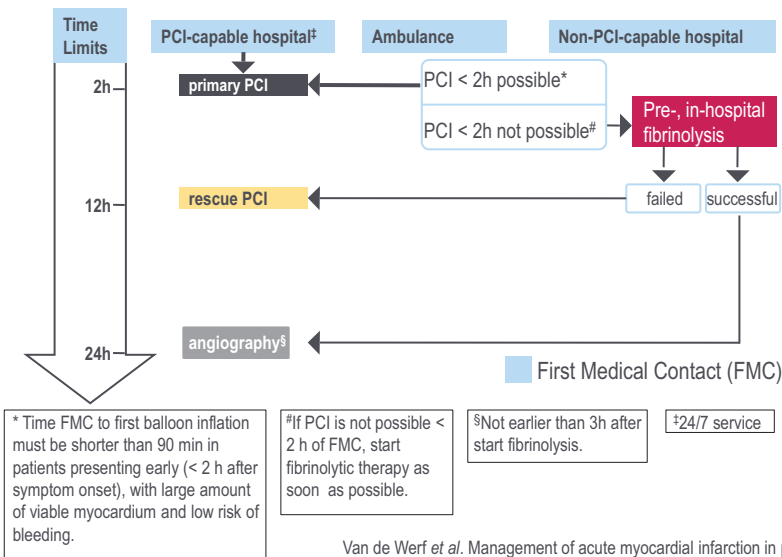
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Networks

Organisation of networks and emergency medical services

Comparison of different systems, type of personnel staffing the ambulances, etc

Rapid implementation of reperfusion therapy can reduce the overall mortality in patients after myocardial infarction. In patients presenting within 12 hours of symptom onset, and with persistent ST-segment elevation or new or presumed left bundle branch block, guidelines recommend the use of early primary percutaneous coronary intervention (PPCI) or pharmacological reperfusion (thrombolysis), according to the period of time after onset of symptoms to first medical contact (FMC) with a physician or healthcare provider (2). PPCI is recommended as a first-line treatment option when the FMC-to-balloon or door-to-balloon time is <120 mins after the onset of symptoms (<90 mins in infarctions of <2 hours duration, in patients with anterior wall infarctions and low bleeding risk (see Fig. 1), when an experienced team is available or when patients are treated in high volume centres (1). If PPCI cannot be offered within 90 mins, fibrinolytic therapy, preferably with a fibrin-specific agent, should be



Van de Werf et al. Management of acute myocardial infarction in patients presenting with persistent ST-segment elevation, *European Heart Journal*. 2008; 29:2909-2945; 2915, by permission of Oxford University Press

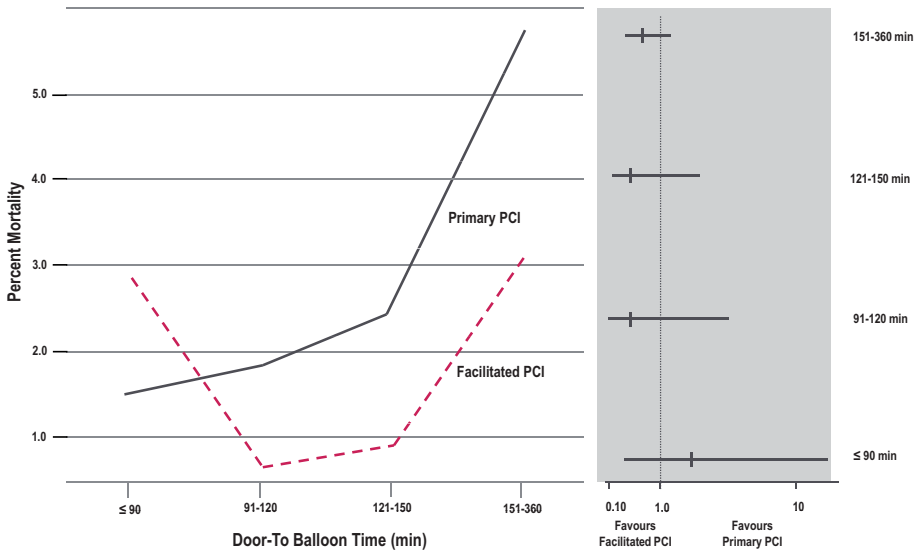
Figure 1: Reperfusion strategies for STEMI (taken from the ESC Guidelines, Van der Werf et al, 2008) (The thick arrows indicated the preferred strategies)

administered within 30 minutes of presentation of the patient. This means within 30 mins of arrival of the ambulance, or a door-to-needle time of 30 mins for those patients arriving at the hospital (1,2). The overall goal of all strategies is to provide rapid and effective reperfusion of the ischaemic area of myocardium (4).

However, the reality is far from ideal at the moment. Only 20-25% of US hospitals provide 24-hour/7-day PCI and the median FMC-to-needle time is 180 mins (3,4). The GRACE registry demonstrated that approximately one third of STEMI patients who are eligible for reperfusion do not receive it (5). Furthermore, the patient-dependent delay is also long and adds significantly to the total ischaemic time (6). There are multiple reasons and explanations for why this is so: lack of public awareness about the symptoms of acute myocardial infarction and how to react (react immediately, call the emergency services via a specific unique number, etc); co-ordination of emergency services and transfer times, especially between non-PCI and PCI-capable hospitals; early STEMI diagnosis (trained paramedics and equipped ambulances); availability of PCI 24/7; and reluctance to use pre-hospital thrombolysis (worries about complications, lawsuits, lack of confidence in diagnosis, etc) (3,6,7).

Delays to treatment have a great impact on outcome and mortality. The benefits of therapy decrease exponentially with delays in treatment (1,2). Greater intervals are seen in patients submitted for PPCI than in those receiving pre-hospital thrombolysis (PHT). The use of the fastest available reperfusion therapy decreases in-hospital mortality when given in less than 3 hours after symptom onset (8). Some trials have reported a 60% thrombolytic therapy coverage within 3 hours after onset of symptoms in patients managed in mobile coronary care units (MCCU) (9). The analysis of those patients admitted by MCCUs shows an 8% lower mortality risk compared to a 13% risk in those who were admitted by other means to high volume centres ($P < 0.04$) (10). Danchin et al reported that those managed in-hospital had worse outcomes than those who received PHT. They found a 5% risk of in-hospital mortality for patients who did not receive PHT (compared to a 4.3% risk in those who did) (11). They also outlined that 96% of patients who received PHT were submitted to coronary angiography once admitted to a coronary unit; 84% received subsequent PCI (11). In both the Vienna registry and the Mayo Clinic experience, coronary angiography and, if necessary, PCI was performed in a high percentage of patients, thus indicating that a pharmaco-invasive strategy is important to optimise treatment results (8,12). This interventional procedure post lysis offered even lower mortality rates and increased 1-year survival when compared to PPCI.

Despite discouraging results from previous trials on facilitated PCI (13,14), a recent retrospective study looked at 1,553 consecutive STEMI patients, who received PCI without prior administration of a thrombolytic or glycoprotein IIb/IIIa inhibitor ($n=767$) or “facilitated” PCI ($n=786$) with one or both treatments prior to PCI. The results showed that facilitated PCI was safe and effective when used in STEMI patients with door-to-balloon time >90 mins and ≤ 150 mins. Facilitated reperfusion was also associated with a lower incidence of adverse events (mortality, myocardial infarction, repeat PCI, ischaemic and haemorrhagic stroke, and non-intracranial TIMI major bleeding) compared to PCI in patients with door-to-balloon times of >90 mins and ≤ 150 mins (see *Fig. 2*). Thus, facilitated reperfusion may be useful to increase the therapeutic window



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Figure 2: Relation between door-to-balloon time and in-hospital mortality for the primary and facilitated PCI groups (from McKay et al, 2009)

for PCI, especially when patients have to be transferred from non-PCI- to PCI-capable hospitals, with the inherent time delay that is involved in doing so (15).

Implementation of organised networks can optimise early diagnosis and treatment, and promote the adequate use of guidelines (8). In addition, a prolonged total ischaemic time followed by long-term complications (congestive heart failure, need for an internal cardiac defibrillator, etc) can also be prevented by the development and installation of an integrated framework of reperfusion strategies (3,6,7).

Strategies seeking reductions in time delays, if delivered, have immediately led to satisfactory results. Networks consisting of mobile intensive care units managed by a team of experienced healthcare providers pursue decreasing pain-to-treatment times, and are the basis of success. Pinto et al demonstrated that the benefit on mortality achieved with PCI in comparison to thrombolysis decreases as door-to-balloon times increase, and that this is dependent on patient characteristics, such as age and infarct location (see Chapter 6) (16).

- The French Registry on Acute ST-Elevation MI (FAST-MI) provided an accurate example with the SAMU (mobile intensive care units) network, which increased the rapid delivery of thrombolytic therapy by 73% in patients with MI ($P < 0.001$). Around 60% of patients received PHT, with increased time delays in those who underwent PPCI. Both times to admission and to reperfusion treatment were reduced in patients with PHT (170 vs. 180 min and 130 vs. 300 min respectively), and in those patients who called SAMU, a 90-minute difference was seen in management for those who were taken to PPCI (40 vs. 130 min $P < 0.001$) (11).
- In the Vienna registry, the central triage network via Viennese Ambulance Systems (VAS) produced an increase from 66% (in 2002) to 86.6% (in 2004) of patients treated with reperfusion therapy within the recommended time period. Subsequently, in-hospital mortality after STEMI fell from 16% to 9.5% (6,8).

Other models of emergency networks exist and are implemented in different countries, showing results that resemble the results obtained by the European networks (4/12).

In the patients included in the NRMI 3 and NRMI 4 studies, who were transferred for PCI, a door-to-balloon time of up to 90 mins was only achieved in 4.2%; and up to 120 mins in 16.2% (3). Two recent studies in the US set out to show that co-ordinated systems of care and transfer to PCI centres is safe and feasible over long distances. The first one took place between March 2003 and November 2006 and involved 30 hospitals located up to 210 miles from a PCI centre. 1,345 patients with STEMI were included and 1,045 of these were transferred from non-PCI capable hospitals. The median door-to-balloon time was 95 mins for patients within 60 miles of a PCI centre, and 120 mins for those 60-120 miles from a PCI centre. The in-hospital mortality was 4.2% with an average stay of 3 days (4).

The second study involved one PCI centre and 28 regional hospitals, located up to 150 miles away and across 3 states. 597 STEMI patients were included: 258 received PPCI at the central hospital; 105 were transferred after 3 hours for PPCI; and 131 received fibrinolytic therapy within 3 hours at the regional hospital. The median door-to-needle time for the first group was 71 mins (75% received treatment within 90 mins); for the second group, it was 116 mins

(although only 12% received treatment within 90 mins); and for the third group, it was 25 mins, with 70% of patients in this group receiving treatment within 30 mins (12).

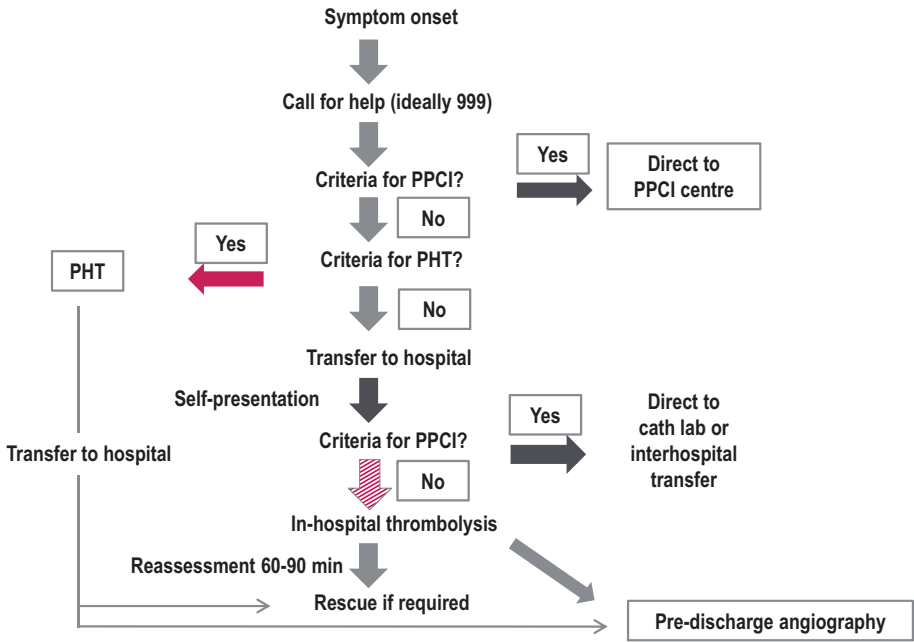
Both studies show that it is feasible to implement reperfusion in a timely manner, even with long transfer distances.

In 88% of hospitals in the UK, 75% of patients receive in-hospital thrombolysis within 30 mins of arrival. But more needs to be done to improve the use of pre-hospital thrombolysis, which has been shown to have a 17% benefit in survival over in-hospital thrombolysis. This is especially important in countries and regions where availability of PCI is limited or transfer times are very long (17).

Developing the optimal network for STEMI management

The ideal network and organisation of emergency medical services (EMS) will, of course, depend on the region and availability of treatment options. It is the responsibility of the cardiologist to ensure that the optimal system of care is in place to suit the regional situation. The hurdles he may have to overcome include:

- Patient and public awareness of symptoms and how to react when they occur
- Communication of emergency medical numbers and, in particular, one specialised number to call in the case of chest pain
- Organisation and co-ordination of EMS
- Staffing and training of EMS personnel (doctors, paramedics) and equipment of the ambulances (12-lead ECG, possibly also telemedicine devices, to transfer the ECG to a cardiologist for a diagnosis and decision to treat)
- Enhancement of PPCI facilities
- Promotion of use of pre-hospital thrombolysis
- Direct transfer to ICUs/CCUs with PCI facilities (bypassing regional hospitals with CCU/ICU option only)
- Availability of PCI facilities (24/7, staffing)
- Re-imburement policies, funding and insurance policies
- Regional legislation (inter-state transfer, etc)
- Physician and hospital capacity issues



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Figure 3: Stage 4 in the evolution of an emergency ST elevation myocardial infarction protocol. The optimum reperfusion pathway. Robust prehospital thrombolysis (PHT), primary percutaneous coronary intervention (PPCI), rescue percutaneous coronary intervention (PCI).

Conclusion

Current guidelines for the management and treatment of patients with acute ST-elevation myocardial infarction recommend early treatment strategies, but time delays continue balancing towards negative outcomes the benefits and efficacy of early reperfusion treatments. Numerous trials and observational studies have presented their results offering positive numbers in terms of reduced mortality favouring pre-hospital thrombolysis. Networks of emergency care units are being developed and offered as mechanisms to reduce pain-to-treatment times, improve outcomes, and decrease mortality. More needs to be done to encourage the development and implementation of these networks throughout Europe and the rest of the World.

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Conclusion

All data that we currently have access to favour initiation of reperfusion therapy in ST-elevated myocardial infarction as early as possible. This applies to PPCI as well as to thrombolysis. Pre-hospital thrombolysis provides the earliest causal therapeutic option, a fact that was already realised in the early stages of systemic short-term lysis. Pre-hospital thrombolysis is independent of location, time, and even almost independent of the practitioner's experience. With the convincing potential of modern, highly effective thrombolytics and improved adjunct therapies, we see a challenge, which has not yet been sufficiently accepted. This book is intended to encourage the reader to successfully face this challenge.

In order to effectively and reasonably establish pre-hospital thrombolysis in acute ST-elevation myocardial infarction, a number of important prerequisites should be implemented. Some of them form the general basis of an appropriate and guideline-orientated care for patients with an acute coronary syndrome.

First of all, organisational requirements have to be considered. One aspect is to provide more intensive education of the population in order to improve the awareness about the impact and danger of an acute myocardial infarction. An essential point of public education is to make clear, that in case of acute chest pain, the only adequate contact is the emergency medical services (EMS) and not private transport to a hospital or a delayed visit from the general practitioner.

At the emergency services dispatching centre, suspected acute coronary syndrome must be given the highest priority. Accordingly, the centre has to alert a qualified emergency team, equipped with at least a defibrillator and a 12-lead ECG, and trained in advanced life support and cardiopulmonary resuscitation. Specific training and/or the use of specific questionnaires for the staff in the emergency services dispatching centre or the presence of a physician at the centre ensures the recognition of an acute coronary syndrome during an emergency call.

In addition to a defibrillator and a 12-lead ECG, another fundamental requirement for appropriate care of ST-elevation myocardial infarction is the ability to correctly interpret the ECG. This can be achieved in various ways – either the EMS staff are trained to interpret the ECG, or the ECG data are directly transmitted to the hospital by telemedicine, including additional information, for example, about potential contraindications for thrombolysis. In the hospital, a physician can decide about the indication for thrombolysis. Likewise, computerised ECG interpretation programmes are also suited for assisting emergency staff with a pre-hospital diagnosis. 12-lead ECG registration is not only important for the indication for pre-hospital thrombolysis, but also provides essential basic information to prepare the catheter lab and alert the intervention team in case of primary PCI.

Pre-hospital thrombolysis is an essential component of reperfusion therapy. It should be embedded in a network structure consisting of EMS and hospitals with and without PCI-facilities. Saving time and restoring blood flow as quickly as possible is the most relevant advantage of pre-hospital thrombolysis. The resulting benefit increases exponentially with a shorter time from symptom onset. If pre-hospital lysis, and of course early lysis in peripheral hospital is being used appropriately, the time advantage has to be calculated. This time factor consists of the time for the transfer to hospital and the anticipated in-hospital time delay in the PCI clinic. Likewise, the time of treatment at the emergency scene has to be calculated. Moreover, the EMS needs information about the treatment capacities of the hospitals within the network. It also cannot be ignored that the decision for PPCI specifically in case of a weak infrastructure may lead to a lack of availability of emergency services due to long transportation times to distant hospitals (including the return journey). Finally, it has to be considered, which adjuvant medication should be applied either in conjunction with thrombolysis or in preparation for a planned PPCI. Consultations between network participants should take these issues into account and lead to optimal decisions.

The crucial step in making the decision for reperfusion therapy – if necessary, together with a hospital-based physician via telephone or pager - is to choose the treatment method which will provide the patient with the most benefit, taking into account the risk-benefit ratio. The typical pre-hospital thrombolysis patients are < 65 years, with an anterior infarction or a posterior infarction involving the right ventricle, and a symptom duration < 120-180 minutes. Since, from the EMS perspective, the expected time between first patient contact and performance of PCI regularly exceeds 60 minutes (even in urban areas with good PCI infrastructures), this patient group is ideally suited to receive pre-hospital thrombolysis, with maximum benefit and minimum risk.

The success of lysis can be easily measured by the grade of resolution of the initial ST-elevation on the ECG printed approximately 90 minutes after initiation of thrombolysis. Rescue PCI is indicated if ST-resolution is not sufficient. If the initial therapy is successful, delayed angiography and possibly additional interventions (which are used with early and above all pre-hospital thrombolysis) can and should be incorporated into the broader concept of a pharmaco-invasive strategy.

