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Prehospital Thrombolysis: It's All About Time

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1. Introduction

Prehospital emergency care personnel can play a crucial role in the identification and management of patients presenting with ST Elevation Myocardial Infarction (STEMI). Specifically, prehospital thrombolysis by emergency medical personnel such as paramedics/nurses/prehospital doctors has been identified as being a successful and safe approach for the provision of accelerating reperfusion strategies for acute STEMI. Moreover, prehospital thrombolysis has no added specific risks (arguably, it is safer as delayed thrombolysis increases the risk of myocardial rupture) as compared to inhospital thrombolysis; nor is it an obstacle for later percutaneous coronary intervention (PCI). This chapter will focus on the general management of STEMI, the potential benefits related to prehospital thrombolysis and alternative, adjunctive therapies and provide some useful hints to drug administration.

Prehospital thrombolysis is an established emergency treatment and has been classified as a Class IIa recommendation therapy for acute STEMI by the leading international cardiology societies like European Society of Cardiology (2008). Prehospital thrombolysis research is ongoing with a large multi-center trial currently recruiting patients in 112 locations worldwide – STREAM – Strategic Reperfusion Early After Myocardial Infarction. STREAM aims to evaluate, in a proof of concept approach, the outcome of prehospital patients presenting with acute STEMI within 3 hours of symptom onset. Following randomization, a treatment strategy of early (prehospital) tenecteplase and additional antiplatelet and antithrombin therapy followed by catheterization within 6-24 hours with timely coronary intervention as appropriate (or by rescue coronary intervention if required) compared to primary angioplasty. This intention to treat study will therefore place patients into two groups; Group A will receive primary PCI performed according to local standards and Group B will receive prehospital thrombolysis supported by optimal supportive adjunctive therapy (http://clinical trials.gov.show/NCT00623623).

2. Development of prehospital thrombolysis

The first published study of prehospital thrombolysis involved the intravenous administration of 750,000 units of streptokinase by physicians was undertaken in 1985. This study demonstrated that patients treated less than 1.5 hours after the onset of pain had a significantly higher ejection fraction (56±15 vs. 47±14 %; $P<0.05$), improved infarct-related regional ejection fraction (51±19 vs. 34±20 %; $P<0.01$) and a lower QRS score (5.6±4.9 vs.

8.6±5.5; P<0.01) than patients receiving treatment between 1.5 and 4 hours from the onset of pain. Patients in the prehospital arm of the study also had better-preserved left ventricular function than patients treated in the hospital. The study concluded that thrombolytic therapy with streptokinase is most effective when administered within 1.5 hours from onset of symptoms of acute myocardial infarction. Although this study produced positive results it lacked statistical power (due to small sample size) but it served to highlight the importance of timely thrombolysis (Koren et al., 1985).

Arguably, the Grampian Region Early Anistreplase Trial (GREAT) was the most influential prehospital thrombolysis based study. The aim of GREAT was to determine the time saved by thrombolysis when initiated at home by trained general practitioners (GPs) / family physicians as compared to thrombolysis inhospital. The GPs randomly assigned thrombolytic therapy to 311 patients with suspected acute myocardial infarction into two groups; prehospital thrombolysis and thrombolysis after arrival at the hospital. GPs selected patients on the basis of a history of chest pain from 20 minutes to 4 hours with treatment initiated within 6 hours from onset of pain. Patients in the prehospital treatment group received thrombolysis up to 130 minutes earlier than patients at hospital (101 vs 240 minutes from the onset of symptoms) with a 50% reduction in mortality in the prehospital group; 17 (10.4%) vs 32 (21.6%). The greatest saving of time was seen in the rural environment as well as in areas where there were significant inhospital treatment delays (Rawles, 1994). Importantly, during the GREAT study, prehospital thrombolysis was undertaken using a single bolus thrombolytic agent.

Patients enrolled in the GREAT study were followed up at five years where investigators noted 25% of the prehospital treatment group had died compared to 36% in the inhospital treatment group (Rawles, 1997). The GREAT study reconfirmed the negative impact of time delays by demonstrating that delaying thrombolysis by one hour increased the hazard ratio of death by 20%, with the equivalent loss of 43 lives per 1000 patients treated at five years. In a subset analysis of GREAT patients who met current ECG criteria for thrombolysis undertaken after 10 years, a 16% difference in mortality was maintained between the two groups (Rawles, 2003). The benefits seen in GREAT were significantly higher than those seen in any other thrombolysis study. The long-term mortality patterns has not been replicated in other long-term (inhospital) follow up studies, like ISIS-2 (1988) or GUSTO-1 (1993).

Treatment delays and the potential time savings of prehospital thrombolysis are key factors in the decision-making process around reperfusion with a meta-analysis by Morrison et al. (2000) of six randomized controlled trials clearly demonstrating the impact of the time savings to be achieved with prehospital treatment over inhospital treatment. Morrison et al. reported on all-cause hospital mortality as well as symptom to treatment time and adverse events. Although individual trials failed to demonstrate a statistically significant difference in all cause inhospital mortality; the meta-analysis involving 6434 patients showed a pooled benefit with prehospital thrombolysis. Morrison et al. demonstrated that prehospital thrombolysis saved approximately 60 minutes ($p = 0.07$) per patient compared to inhospital thrombolysis (104 versus 162 minutes) thereby reducing all-cause hospital mortality by 17%. If we consider the data from the five year follow up of the GREAT study, such time-savings can be extrapolated into significant numbers of lives saved.

Bjorklund et al. (2006) evaluated treatment delays and outcome in a large cohort of acute STEMI patients transported by ambulance who were either thrombolysed by paramedics in

the prehospital environment or thrombolysed inhospital. Importantly, Björklund et al. utilized data from the Swedish / Register of Cardiac Intensive Care drawing data from 75 hospitals. Although register based data lacks the scientific controls seen within clinical trials, it is arguably more reflective of 'real life' clinical care. Following this study, Bjorklund et al. were able to conclude that prehospital thrombolysis by paramedics in ambulances was associated with reduced time to thrombolysis by almost 1 hour and reduced adjusted 1-year mortality by 30%.

Minimizing treatment delays in the administration of thrombolysis is key to optimizing patient outcomes. Although the LATE study (Becker, 1995) demonstrated clinical benefits of thrombolysis up to 12 hours, the greatest benefits were seen within 6 hours with the highest mortality reduction seen in those patients treated within the first 3 hours from onset of symptoms. The most commonly perceived post thrombolysis risks of stroke or major haemorrhage remain static regardless of when within the 12 hour period thrombolytic therapy is administered. However, the typically lethal complication of myocardial rupture exponentially increases after six hours. As demonstrated in the GREAT, WEST (Armstrong, 2006) and CAPTIM (Bonnefoy et al., 2009) studies prehospital thrombolysis is more likely to recruit patients within the first 6 hours of symptom onset; typically within the first 3 hours were the clinical benefit of treatment is at its highest.

These trails and others help to confirm the feasibility and safety of prehospital thrombolysis in a wide variety of circumstances and settings ranging from traditional ambulance services through to use by ship-based medical teams (cruise ships) and deployed military medicine. However, the choice between reperfusion strategies to manage acute STEMI remains a topic of interest. While it is agreed that primary PCI is the best strategy for acute STEMI it is still time sensitive and therefore needs to be performed in a timely manner and by experienced centres. This is not always achievable in developing countries, in rural health care settings or in remote medical facilities such as cruise ships.

3. Prehospital thrombolysis supported by early intervention

A number of mixed strategies for reperfusion have been studied; to include prehospital thrombolysis (full dose thrombolytic therapy) supported by rescue PCI for failed thrombolytic reperfusion (a hybrid reperfusion strategy) plus pre-discharge or symptom/ischaemia driven PCI, reduced dose thrombolysis supported by immediate PCI (facilitated PCI) and primary PCI. The ASSENT-4 PCI (2006) study demonstrated that facilitated thrombolysis, that is, thrombolysis immediately followed by PCI has been proven to be an unsuccessful intervention and will not be discussed further.

A hybrid reperfusion service involves implementing the best combination of reperfusion options to meet the unique requirements of the patient and typically involves early prehospital thrombolysis for those patients with the greatest benefit e.g. anterior STEMI presenting within 2-3 hours supported by rescue PCI and pre-discharge angioplasty with a system of primary PCI for the remaining patients. It must be re-iterated that primary PCI does still offer a superior treatment option when it is available in a timely manner.

The WEST trial investigated the use of a number of different reperfusion strategies, immediate prehospital thrombolysis plus usual inhospital care (excluding routine PCI),

prehospital thrombolysis with compulsory rescue PCI for failed thrombolysis against primary PCI strategy. A key finding of the WEST study was a lower incidence of cardiogenic shock in patients who received thrombolysis early (within 3 hours) and the importance of prehospital triage/decisions for reperfusion with delays to definitive treatment being shorter when a decision was made in the prehospital setting. The WEST study also highlighted that thrombolysis used timeously remains an important treatment modality in the early management of acute STEMI.

The larger CAPTIM study used a similar design to the WEST study utilizing prehospital triage/decision to prehospital thrombolysis (this time supported by compulsory rescue PCI) with pre-discharge coronary intervention compared to primary PCI. The long term 5 year follow up of the CAPTIM study confirmed a significant reduction in mortality when thrombolysis was administered within 2 hours in the prehospital group when compared with primary angioplasty. The relationship between reperfusion strategy and the time from symptom onset on 1 year mortality was examined in a pooled analysis of patients from the CAPTIM and WEST studies. Mortality benefit was observed time (< 2 hours) (2.8% vs 6.9%, p = 0.021, hazard ratio 0.43, 95% CI 0.20-0.91) emphasizing that time from symptom onset was a key determinant when selecting the reperfusion strategy for acute STEMI (Westerhout et al., 2011). The optimal design of a hybrid reperfusion service is yet to be determined but the data from WEST and CAPTIM would support prehospital thrombolysis within the first 3 hours as along as all patients were delivered to a receiving hospital with interventional cardiology capability.

Prehospital thrombolysis can clearly be initiated earlier that inhospital thrombolysis or primary PCI and it can be performed with limited equipment. In fact, the same minimum equipment is required to perform prehospital thrombolysis as is required to identify prehospital patients requiring direct admission for primary PCI. Data from WEST (paramedic decision-makers), CAPTIM (doctor decision-makers) and projected findings from STREAM (paramedic/nurse/doctor decision-makers) are intended to inform the debate as to whether a hybrid reperfusion system is appropriate within developed countries. Regardless of the reperfusion strategy put into place, empowering the prehospital clinician is pivotal to success.

4. Education, training & equipment

The efficacy and safety of pre-hospital thrombolysis is dependent on several pre-requisites (Birkhead, 2004; Björklund et al., 2006; Mehta et al., 2002; Weaver, 1997; Welsh et al., 2006):

1. Prehospital personnel being trained to recognize symptoms and management of STEMI and its early complications (pain, ventricular fibrillation/ventricular tachycardia and bradycardic arrhythmias).
2. Diagnoses of STEMI using a 12 lead ECG with or without computer assistance for diagnosis and/or data transmission.
3. Intravenous access to be established and the administration of reperfusion therapy to be initiated within a treatment protocol / clinical guideline and supported by a thrombolysis checklist.

4. During transportation rhythm monitoring, availability of a defibrillator and advanced cardiac life support are mandatory
5. Pre-alerting receiving hospital of impending arrival of the patient supported by (if available) electronic transmission of the 12 lead ECG
6. Consultation for on-line support can support decision-making
7. On-going quality assurance

4.1 Education and training

The foundation for the practice of thrombolysis requires an understanding of anatomy and physiology of cardiovascular system and the pathophysiology of acute coronary syndromes. The complications of acute coronary syndromes / acute myocardial infarction must be covered as this will prepare the paramedic/nurse/prehospital doctor for complications that may arise during clinical practice. The ability to analyze a 12 lead ECG with a particular focus on recognition of AMI is required along with an understanding of thrombolytic therapy. An evidence based thrombolysis protocol which is subject to regular review is required taking into consideration the operational requirements for the practical implementation of the protocol. Classroom practice through the use of simulated clinical patient scenarios for stable angina, unstable angina, infarctions of the various territories including right ventricular infarction and scenarios where thrombolysis is contra-indicated will prepare and improve clinical practice. This theoretical and practical classroom education and training will need to be supported by clinical exposure within coronary care units and cardiac catheterization facilities.

4.2 Diagnosing acute STEMI

Van't Hof et al. (2006) demonstrated that prehospital diagnoses, triage and treatment in the ambulance is feasible in 95% of acute STEMI patients when undertaken by highly trained paramedics using a validated computerized ECG software. Prehospital decision-making can also be improved with the electronic transmission of an ECG although systems that support autonomous prehospital thrombolysis are well established and electronic data transmission can be problematic as they tend to rely on mobile telephone technology. The availability of prehospital 12 lead ECG capabilities serves to improve cardiac care in general and increased use of recording and subsequent interpretation of the 12 lead ECGs by prehospital clinicians improves overall confidence in using the prehospital ECG as a diagnostic tool. A particularly important aspect of the prehospital 12 lead ECG is that it is often obtained in the early phase of the patient's illness and becomes a useful ECG to compare against ECGs obtained later on in the patient's care.

The availability of diagnostic software and more importantly data transmission introduces an interesting concept for remote medical management of STEMI as the formal diagnosis of STEMI can be made by a distant clinician with the attending clinician acting primarily as a technician. This would involve the practical skills of cannulation, obtaining a 12 lead ECG and resuscitation skills (e.g. defibrillation) being undertaken by a junior clinician, but the decision to treat being made by a supervising clinician. This concept would expand the provision of prehospital thrombolysis whilst minimizing the education burden of the attending clinician and would be suitable for use in remote medical sites such as off shore

oil platforms or small remote communities (e.g. Scottish Islands). Such a system is not dissimilar to the early use of defibrillation by paramedics where external supervision was required before defibrillation was performed.

5. Protocols, checklists & consent

5.1 Protocols

The use of clinicians empowered to make individual thrombolysis decisions removes the requirement for fixed protocols, however at the very least an evidence-based clinical guidelines for thrombolysis will be required. The availability of a clinical guideline or protocol will depend on the level of training provided to the prehospital clinician as guidelines support lateral thinking, whereas protocols tend to be more prescriptive.

The development of the thrombolysis protocol / guidelines needs to incorporate adjunctive therapy such as anti-thrombotic agents (e.g. heparin) and anti-platelets agents. This is an important aspect of patient care as to date none of the completed prehospital or inhospital thrombolysis studies have incorporated optimal anti-platelet and anti-thrombotic therapy. However, STREAM is currently utilizing the most up-to-date thrombolysis strategy.

5.2 Checklist

A thrombolysis checklist (Table 1), as part of a protocol / guideline, can support rapid decision-making whilst acting as a prompt to steps in the patient's management. However, care must be taken to ensure that the checklist is not overly restrictive as this can lead to under treatment of appropriate patients and careful consideration of the checklist layout can rapidly identify those patients where prehospital thrombolysis is deemed inappropriate e.g. advanced age (Castle et al., 2007a).

All contra-indications to thrombolysis need to be carefully considered and weighted. Often the type and number of contra-indications selected will reflect the risk adverse nature of the service delivering prehospital thrombolysis and, therefore, the list of contra-indications may change as the prehospital service becomes more established. It is now agreed that previous contra-indications such as prior cardiac compressions (Castle et al., 2007b; Cross et al., 1991) are no longer barriers to thrombolysis (in fact post cardiac arrest survivors with STEMI require urgent reperfusion with either PCI or hrombolysis); nor is diabetic retinopathy. (Mahaffey et al., 1997). Furthermore, complete heart block (CHB) is an indicator for rapid reperfusion therapy with thrombolysis being an accepted form of treatment as prompt reperfusion of the AV node (inferior STEMI with CHB) or intra-ventricular septum/Bundle of His (anterior STEMI with CHB) will resolve the arrhythmia thereby removing the need for a temporary pacing wire (Castle et al., 2007b) - the very reason typically quoted for with-holding thrombolytic therapy. All contra-indications to thrombolysis, with the exception of myocardial rupture as shown by the LATE Study (1993), are static/not affected by time whereas the benefit of thrombolysis is time dependent. Therefore, denying prehospital thrombolysis in a patient with STEMI based on one contra-indication only for the patient to be transferred to hospital for thrombolytic therapy to be administered will be counter-productive.

	Primary assessment: Can you confirm the following?	**Yes**	**No**
1	The patient is conscious and coherent, and able to understand that clot dissolving drugs will be used?		
2	The patient has symptoms that are characteristic of a heart attack (severe, continuous pain in a typical distribution of 15 minutes duration or more without remission)?		
3	The symptoms started less than 12 hours ago? NOTE: Consider "stuttering start" MI – many infarcts start this way.		
4	The pain built up over seconds and minutes rather than starting totally abruptly?		
5	Breathing does not influence the severity of the pain?		
6	The systolic blood pressure is more than 80mmHg and less than 180mmHg and that the diastolic is below 110mmHg despite treatment? i.e. Analgesia & GTN for blood pressure and fluid challenge / atropine for hypotension).		
7	The electrocardiogram ECG shows abnormal ST elevation of 2mm or more in at least 2 standard leads or in at least 2 adjacent precordial leads, not including V1? NOTE: ST elevation can sometimes be normal in V1 and V2.		
8	The QRS width is 0.16 seconds (4 small squares) or less, and that left bundle branch block is absent from the tracing? NOTE: RBBB is permitted only with qualifying ST elevation. LBBB = QRS 140 ms or greater; small narrow R wave in V1 & V2 with big S wave; tall upright monophasic R in standard Lead 1 and V6.		
	Secondary assessment (contra-indications): Can you confirm the following?	**Yes**	**No**
9	The patient is **not** likely to be pregnant, nor has delivered within the last 2 weeks?		
10	The patient has **not** had an active peptic ulcer within the last 6 months?		
11	The patient has **not** had a stroke of any sort within the last 12 months and does not have any permanent disability from a previous stroke?		
12	The patient has **no** diagnosed bleeding tendency, has had no recent blood loss (except normal menstruation) and is not taking warfarin (anticoagulant) therapy?		
13	The patient has **not** had any surgical operation, tooth extractions, significant trauma, or head injury within the last 4 weeks?		
14	The patient has **not** been recently treated for any other serious head or brain condition?		
15	The patient is **not** being treated for liver failure, renal failure, or any other severe systemic illness?		

Table 1. An example of a thrombolysis checklist

5.3 Consent

It is standard practice to obtain consent from the patient for thrombolytic therapy. The complications from thrombolysis are well documented. The patient will need to be appraised of the risks in undergoing thrombolysis. A standard statement that is simple, clear and concise is used in most established prehospital settings. An example of such a statement is as follows (Table 2):

However, it remains arguable whether a patient in pain or post opiate administration is in a position to give informed consent. It, therefore, falls to the attending clinician to ensure that they are working in the patient's best interest.

Initial Consent

"It is likely that you are having a heart attack and the best treatment available to you is a clot dissolving drug called (***specify agent***). The quicker you receive this drug, the lower the risks of a heart attack-which is why Doctors recommend that the treatment is started as soon as possible. These drugs can cause serious side effects in a small minority of patients which I can explain to you in more detail if you so wish, but the risks attached to this treatment are very much less than the likely benefit. Would you like me to give you the injection or would you prefer to have more details?'

I hereby consent to the treatment:

_____	_____/_____	_____
Name of patient	Date / Time	Signature / Thumbprint

In the unlikely event that the patients do want more information they should be given the following information:

Further information

"Treatment at this stage saves the lives of about 1 in every 25 treated. But it can sometimes cause serious bleeding. The biggest risk is stroke which affects about 1 patient in every 200 treated. Some patients also have allergic and other effects that do not usually cause any major problems. Would you like me to give you the injection?"

Table 2. An example of consent

6. Drugs

6.1 Thrombolytic agents

There are a number of thrombolytic agents available, however Tenecteplase (TNK) is the only single-use bolus agent available making it the most suitable for prehospital use. Despite this, the ideal thrombolytic agent currently does not exist.

The characteristics of an "ideal thrombolytic agent" are as follows:

- Rapid reperfusion (15 - 30 minute)
- 100% efficacy at achieving 100% TIMI 3 in 30 minutes
- Administered as a single intravenous bolus
- Lower incidences of intracranial haemorrhage
- Lower incidences of systemic bleeding and other complications.
- Specific for recent thrombi
- Lower incidences for re-occlusion
- Long-term sustained patency
- No antigenicity
- No negative interaction with adjunctive therapy
- Affordable

The GUSTO trial (1993) demonstrated the superiority of the accelerated regimen of tissue plasminogen activator (tPA, Alteplase) over Streptokinase (STK), however, this came at a price of slightly greater risk of intracranial haemorrhage especially in female patients over the age of 75 years. However, stroke after thrombolysis is a known risk and in the GUSTO trial the stroke rate with STK was 1.19% compared to 1.55% with tPA (Gore et al., 1995). The issue of stroke is an important consideration as denying thrombolysis does not decrease the stroke rate as STEMI is an independent risk factor for stroke - unrelated to thrombolysis primarily due to the higher incidence of atrial fibrillation (AF) and poor left ventricular (LV) function caused by STEMI. Therefore, early treatment of STEMI with reperfusion that reduces the incidence of AF and LV dysfunction is an important aspect of stroke and morbidity reduction.

Single bolus TNK is now the most widely used thrombolytic agent in the developed world partly due to its improved efficacy but also because of ease of administration and variable dosing. TNK and Alteplase are equivalent in regard to 30 day mortality, but non-cerebral bleeding and blood transfusions are less with TNK.

The dose of TNK is weight adjusted and administered in a single bolus over 5 seconds as compared to 90 minutes of variable rate infusion with tPA or a 30 - 60 minute infusion of STK. Although a 30 minute regime for STK exists, it is associated with an increased risk of hypotension but by slowing the infusion rate of STK, the incidence of hypotension tends to decrease. Reteplase is a more fibrin specific agent administered as a 10 unit twin bolus given 30 minutes apart. However, the time sensitive nature of the twin bolus administration of Reteplase can be problematic. Reteplase is equivalent with reduction in mortality and hemorrhage rates achieved with Alteplase.

The major benefit of the bolus agents lies in the ease of administration and in the simplified dosing regimen that reduces the risk of dosing errors. However, the cost of TNK and its manufacturer's recommendation for use up to 6 hours makes the cheaper STK a more practical drug of choice for use in the developing world as for each patient treated with TNK five patients could be treated with STK (Table 3) (BNF, 2011). Its use as a prehospital thrombolytic is worth consideration, particularly in static remote health care settings, although its requirement for an infusion plus the incidence of hypotension makes it more labour intensive.

	Streptokinase (STK)	Alteplase (tPA)	Reteplase (rtPA)	Tenecteplase (TNK)
Fibrin selective	No	Yes	Yes	Yes
Plasminogen binding	Indirect	Direct	Direct	Direct
Duration of infusion (minutes)	60	90	10 + 10	5-10 seconds
Half life (minutes)	23	<5	13-16	20
Fibrinogen breakdown	4+	1-2+	Not known	>tPA
Early heparin	Yes	Yes	Yes	Yes
Hypotension	Yes	No	No	No
Allergic reactions	Yes	No	No	No
Approximate cost/dose	£83.44/1.5 MU	£600/100 mg	£627.27/20 unit kit	£502.25/50 mg
TIMI reflow grade 3 at 90 min	32	45-54	60	>tPA
Recommended use	Up to 12 hours	Up to 12 hours	Up to 12 hours	Up to 6 hours (typically used up to 12 hours)

Table 3. Characteristics of commonly used thrombolytic agents. Adapted from Opie (2009).

There are two key considerations for the use of STK in the prehospital environment. The first is duration of infusion and second the requirement for an expensive infusion pump. Although an infusion pump offers better control of drug delivery, this is less of an issue with STK as the delivery of STK is less time sensitive when compared to tPA. In static medical care environments (e.g. remote medical center) the infusion can be completed before hospital transfer as STK can be safely delivered without an infusion pump using either a small intravenous bag (100/250ml 0.9% saline) or a pediatric burette supported by close clinician supervision. The use of a pediatric burette or a 100/250ml bag of saline is not an option for administration during ambulance transfer as the low ceilings in ambulances lack the height to ensure fluid flow and this is further aggravated by ambulance movement. Novel techniques involving the use of low cost drip counters (that restrict flow through an administration set) supported by a pressure infusion bag to maintain a constant pressure through the drip counter is feasible but as yet, is unproven.

The second consideration is the much higher incidence of hypotension and bradycardia. This is due to the release of bradykinin and not as commonly thought as an allergic reaction (although anaphylaxis is more common with STK, it remains rare). Therefore, the treatment of hypotension consists of slowing or stopping the infusion and the administration of a 250-500ml crystalloid bolus. The routine use of intravenous steroids and anti-histamines offers no clinical benefit and in the case of intravenous steroids, it may adversely affect patient outcome by affecting myocardial scar tissue formation, thereby potentially increasing the risk of myocardial rupture.

Streptokinase	Tenecteplase
1.5 mega units over 30-60 minutes (requires an infusion pump)	Single weight adjusted bolus
Aspirin 300mg	Aspirin 300mg
Clopidogrel age adjusted (75-300mg)	Clopidogrel age adjusted (75-300mg)
No heparin (local policy my vary)	Weight adjusted heparin bolus followed by infusion or weight adjusted subcutaneous injection of heparin: 4000 unfractionated heparin bolus followed by infusion (an infusion pump is mandatory) Age adjusted enoxaparin.
Bradycardia (common) reversed by atropine	Bradycardia (less common than STK) reversed by atropine
High risk of drug induced hypotension responsive to fluid challenge stopping/slowing infusion	No specific drug induced hypotension
Labour intensive	Not labour intensive
Affordable (if no infusion pump used)	Expensive

Table 4. Comparison of a STK and TNK treatment regime

6.2 Adjunctive drug treatment

6.2.1 Oxygen

Oxygen is commonly administered during the management of patients during thrombolysis. Its routine use in patient with pulse oximetry above 95% has been questioned primarily due to the possibility of vasoconstriction and limited evidence of benefit (O'Driscoll, 2008). Oxygen remains an important adjunctive therapy in the presence of left ventricular failure although it is better provided as part of continuous positive airway pressure. Oxygen should routinely be administered in the presence of arrhythmias (e.g. ventricular tachycardia) (Neumar, 2010), hypotension/hypo-perfusion and any post cardiac arrest.

6.2.2 Analgesia

Analgesia is a priority therapy in the management of STEMI and intravenous opiates (morphine, diamorphine or fentanyl) offer the most effective analgesia although the legal framework for administration of these drugs can be problematic resulting in drugs such as Tramadol or Nubain being used if legal barriers to opiates do exist. The use of inhaled nitrous oxide (Entonox™) remains a useful supplementary analgesic (or primary analgesic if prehospital opiates are not available) providing both supplementary oxygen and analgesia and the use of Pentrane (common in Australia) is also a useful inhaled analgesic allowing higher percentage of inhaled oxygen if required. Thrombolysis also represents effective analgesia as the restoration of myocardial blood flow results in pain relief reflecting successful reperfusion.

Non-pharmacological interventions (re-assurance, calm professional mannerism of the care provider) are important aspects of pain relief. The use of rapid road transfer with lights and sirens may induce greater patient anxiety (as well as the risk of road traffic collision). If prehospital thrombolysis has been administered (with appropriate adjunctive therapy) there is little to be gain from rapid transfer to hospital.

6.2.3 Nitrates

Although there is no survival benefit to be gained from nitroglycerin it remains a common early therapy primarily providing analgesia. Nitroglycerin (0.4mg) is typically administered sublingually although intravenous nitrates are also used to manage on-going ischaemic chest discomfort, control of hypertension and for the management of pulmonary oedema (nitrates are a Class I recommendation for left ventricular failure). Nitrates should not be administered to patients who have received phosphodiesterase inhibitor within 24 to 48 hours and should be administered with care in patients with suspected right ventricular infarction as they may induce marked hypotension. Despite this, nitrates are very safe drugs for use by prehospital clinicians and it must be remembered that known cardiac patients may have already treated themselves with varying doses of nitrates prior to the arrival of the prehospital clinician.

6.2.4 Antiplatelet agents

Antiplatelets are vital in the management of all acute coronary syndromes (unstable angina, non-STEMI and STEMI). Within the context of STEMI management anti-platelet therapy is as important as thrombolytic therapy. This is because the intra-coronary thrombus responsible for re-infarction tends to be platelet rich and thrombolysis may raise the possibility of thrombolytic-induced platelet aggregation (Keeley et al., 2006).

6.2.4.1 Aspirin

All patients with suspected acute coronary syndrome (unstable angina, non-STEMI and acute STEMI), should be considered for prehospital aspirin treatment as there are relatively few contra-indications to a single dose of aspirin (Class I recommendation). Despite this, aspirin is often withheld either due to concerns over allergy, adverse drug interactions (e.g. Warfarin), confusion due to chronic ongoing use of aspirin or uncertainty of diagnosis. Typically unless a patient has a known documented allergic reaction (not just gastric irritation) to aspirin or is actively bleeding from a gastrointestinal tract ulcer, aspirin at the 300mg dose should be given. The choice of 300mg is typically the dose of a single aspirin with the administration being initiated as early as possible with consideration being given to emergency call takers being empowered to recommend aspirin before the arrival of emergency personnel (Class IIb recommendation).

The benefit of aspirin was established in the ISIS 2 trial (1988) where 162.5 mg aspirin resulted in 25 lives saved per 1000 patients primarily by reducing the incidence of re-infarctions (10 non-fatal re-infarctions per 1000) as well as preventing 3 non-fatal strokes per 1000 patients. The results from ISIS 2 highlighted that the effectiveness of aspirin alone was nearly as effective as STK without aspirin (23% v 25% odds reduction of death) and that by

combining aspirin with STK, the magnitude of benefit was highly significant (42% odds reduction of death). It is noteworthy that aspirin administration during the ISIS 2 trial was anytime within the first 24 hours but a meta-analysis by Freimark et al. (2002) demonstrated that early aspirin administration (before thrombolysis) was an independent factor in patient survival at 1 year (5% vs 11% survived with early aspirin; odds ratio 0.41; 95% CI 0.21-0.74).

The benefits of aspirin for acute STEMI are attributed to its inhibition cyclo-oxygenase dependent platelet activation. The administration of an initial dose of 160-300mg aspirin ideally non-enteric coated formulation chewed is a Class I recommendation for acute STEMI. Intravenous or rectal aspirin are also acceptable routes of administration.

Although over-treatment of patients or the administration of an unnecessary treatment cannot be endorsed, the benefits of early use of aspirin in any patient with symptoms suspected of a STEMI (or other acute coronary syndrome) is such that the potential of over-treatment of patients is arguably worth the risk, especially when comparing the maximum acute anti-platelet dose of aspirin (300mg) to the analgesic dose of aspirin of 600-900mg.

6.2.4.2 Clopidogrel

Clopidogrel is a potent platelet inhibitor and the anti-platelet benefits of clopidogrel in combination with aspirin is to reduce ischaemic events in non ST-elevation acute coronary syndromes (Yusuf et al., 2001) and in patients undergoing percutaneous coronary intervention - PCI CLARITY (2005). The COMMIT-CCS 2 (2005) trial involving more than 45 000 patients (many post thrombolysis) demonstrated that administration of Clopidogrel (75mg daily) with aspirin and standard treatment safely reduced mortality and major vascular events. In the CLARITY-TIMI 28 Trial (2006), patients 75 years and younger with acute STEMI received thrombolysis supported by a loading dose of 00mg Clopidogrel followed by 75mg once daily and either low molecular weight heparin (LMWH) or unfractionated heparin (UFH). The combination of dual anti-platelet therapy (aspirin/clopidogrel) with thrombolytic treatment demonstrated more favorable angiographic patency of the infarct related artery and a reduction in mortality. A major contributor to mortality reduction was the reduction in the re-infarction rate in those patients receiving dual anti-platelet therapy. This was without an associated increase in the rate of bleeding.

The importance of improved patency and lower incidence of re-infarction was confirmed in the ECG CLARITY-TIMI 28 Study (2006) where the use of clopidogrel was shown to improve late coronary patency and clinical outcomes in those patients who achieve ST-segment resolution by preventing re-occlusion of open arteries rather than by facilitating early reperfusion. The administration of 300mg loading dose of clopidogrel in association with thrombolysis to patients less than 75 years of age is a Class IIa recommendation and it is common practice to adjust the dose in the over 75 year old patients to 75mg based on the COMMIT data.

Newer oral antiplatelets such Prasugrel and Ticagrelor are now available with potentially improved antiplatelet as Ticagrelor produces a more profound and consistent antiplatelet effect than clopidogrel (Wallentin et al., 2003), but as yet to be studied in conjunction with thrombolytic therapy.

6.2.5 Anticoagulants

Heparin is considered to be effective and is routinely given as an adjunct for PCI and thrombolytic therapy although it is commonly withheld in the first 24 hours in those patients receiving STK. The role of heparin is primarily to reduce re-infarction but the combination of dual anti-platelet therapy, thrombolysis and heparin may increase the risk of bleeding. The American Heart Association guidelines call for careful weight based dosing of heparin with thrombolytic therapy in STEMI (Antman et al., 2008).

The timing of heparin therapy when using fibrin specific thrombolytic agents (tPA, reteplase and TNK) is an important aspect of patient management. In an observational study of the United Kingdom (UK) national registry the frequency of re-infarction during hospital admission after thrombolytic treatment of 35, 356 STEMI patients during 2005–2006 was analyzed. Re-infarction rates with inhospital treatment were similar for reteplase (6.5%) and TNK (6.4%) but were higher for those patients treated by paramedics in the community. When the interval from prehospital treatment to hospital arrival was greater than 30 minutes re-infarction rates were 12.5% for reteplase, and 11.4% for TNK. For intervals shorter than 30 minutes the re-infarction rates were significantly greater for TNK (9.3% than reteplase (4.2%). Overall, re-infarction rates were higher after prehospital treatment with TNK than reteplase (9.6% vs 6.6%, p=0.005).

The differences in re-infarction rates were considered to be primarily due to the different uses of adjunctive anti-thrombotic therapy as UK paramedic thrombolysis protocols only allowed a single bolus dose of heparin prior to thrombolysis but did not allow for ongoing heparinization until arrival inhospital as compared to inhospital practice which resulted in either an infusion of UFH (800-1000 IU per hour adjusted to aPTT) or weight adjusted LMWH. It was also noted that on arrival at hospital there was often a delay in the commencement of heparin therapy, either due to confusion about the prehospital protocol or other time related pressures. In addition, clopidogrel was commonly administered early in association with inhospital thrombolysis but only after arrival at hospital for those patients receiving prehospital thrombolysis (Horne et al., 2009). This may also have been a confounding factor as Keeley (2006) noted that thrombolysis induced platelet aggregation was a possible cause of re-infarction following thrombolysis.

UFH has long been regarded as the anti-thrombotic agent of choice in the adjunctive treatment of patients with STEMI until the introduction of enoxaparin. The ASSENT-3 PLUS Trial (2003) evaluated the feasibility, efficacy and safety of prehospital enoxaparin or UFH with tenecteplase. There was a reduction in the composite of 30 day mortality, inhospital re-infarction or inhospital refractory ischemia in the enoxaparin group (14.2% vs 17.4%., p = 0.08). However, there was a tendency towards higher rates of intracranial haemorrhage (ICH) and major bleeding in the enoxaparin group. The risk for ICH and major bleeding was mainly confined to patients > patients over 75 years. It must be noted that in ASSENT-3 PLUS, the dose of enoxaparin was not weight adjusted. The safety concern of enoxaparin among elderly patients was addressed by the ExTRACT-TIMI-25 Trial (2005) that randomized more than 20 000 thrombolysed patients to receive either enoxaparin or UFH. The ExTRACT-TIMI 25 study was significantly changed from the ASSENT 3 study with patients > to greater than 75 years of age not receiving the IV bolus of enoxaparin as well as receiving a reduced dose of subcutaneous enoxaparin (75%) with a maximum ceiling dose

of subcutaneous enoxaparin for the patients under 75 being set at 100mg and 75mg for the over 75 age group. The primary endpoint of this study was all cause mortality or non-fatal reinfarction at 30 days. Treatment with enoxaparin was found to be superior to UFH but was associated with an increase with major bleeding episodes. A telephone follow up at 1 year showed a sustained reduction in mortality or re-infarction when using the enoxaparin strategy (Morrow et al., 2010). Data from a meta-analysis from 12 earlier trials involving more than 49 000 patients support these results (Murphy et al., 2007). Enoxaparin is administered as an initial dose of 30mg intravenous bolus, followed by 1mg/kg subcutaneously within 15 minutes and is a Class I recommendation.

The likely reason for both the reduction in re-infarctions but also the increased risk of bleeding associated with enoxaparin is that enoxaparin (in fact all LMWHs) provide more predictable anticoagulation. Whereas UFH is both dose and person sensitive typically requiring frequent dose changes as dictated by aPTT and commonly results in either under or over anti-coagulation.

Enoxaparin offers a number of operational benefits for use with prehospital thrombolysis; primarily the absence of an infusion pump that is required when administering an infusion of UFH. Two single 100mg dose syringes of enoxaparin is adequate to support prehospital thrombolysis with one syringe being used for the 30mg IV dose followed by subsequent subcutaneous dose (the maximum subcutaneous dose of enoxaparin remains 100mg). The intravenous dose of enoxaparin can be simply administered by decanting all of a 100mg dose of enoxaparin into a 10ml syringe and then diluting with water for injection to a total volume of 10mls thereby providing 10mg enoxaparin per ml. A multiple use vial of enoxaparin for IV administration is also available.

6.2.6 Steroids and antihistamines

The routine administration of steroids and antihistamines to prevent hypotension/bradycardia especially in association with Streptokinase complicates the administration process and is unlikely to prevent hypotension as the cause of Streptokinase induced hypotension is primarily due to speed of administration (Lew et al., 1985; Tatu-Chițoiu et al., 2004) and the action of bradykinin activated by Streptokinase (Hoffmeister et al., 1998).

Tatu-Chițoiu et al (2004) noted that the incidences of hypotension occurred in nearly half of all patients treated with Streptokinase but it did not adversely affect patient outcome whereas the prophylactic use if steroids is linked with an increased risk of myocardial rupture (Mannisi et al., 1987) and is not recommended by the leading international cardiology societies (Van de Werf et al., 2008).

7. Support systems

Studies have clearly demonstrated that thrombolytic therapy can be safely administered in the prehospital environment by doctors, paramedics and nurses. The most effective system will depend on population demographics, geographical factors, the structure and financial resources of the emergency medical services. Regardless of who undertakes thrombolysis, the personnel need to be capable of rapid diagnosis, early risk stratification, minimal

treatment delay and rapid administration of a thrombolytic agent. EMS systems vary throughout the world. In 75% of Europe thrombolysis is undertaken by emergency physicians while in many other settings like United Kingdom, Australia and United States of America, it is undertaken by paramedics. In most countries, the use of non-doctors in the prehospital environment seems to be the most practical and cost effective option.

The practice of paramedic thrombolysis may be undertaken independently or under direct supervision depending on the local emergency medical system. A system of consultation and 12-lead ECG transmission with CCU nurses/a senior paramedic/specialist clinician experienced in STEMI management is highly recommended at the initial implementation of thrombolysis and for on-going clinical support in difficult cases (Liem et al., 2007; McLean et al., 2008). Furthermore, paramedics can also fast track acute STEMI patients to CCU by by-passing the emergency department as well as by-passing local hospitals to deliver the patient to a hospital with an on-site catheter laboratory for either rescue angioplasty or pre-discharge angioplasty. These strategies have demonstrated reductions in door-to-balloon time and mortality (Afolabi et al., 2007; Bång et al., 2008; Le May et al., 2006).

The transmission of 12-lead ECG may be challenging and is dependent of the use of cellular technology which may result in the inability to transmit the ECG due to poor coverage or drop zones. The transmission of the ECG may involve the pairing of cellular phones and ECG machines therefore will need to be tested and practiced to prevent user error.

8. Quality assurance

An on-going continuous professional development programme which incorporates quality improvement measures obtained by on-going monitoring of prehospital thrombolysis via clinical audit and feedback should be mandatory for continued safe prehospital thrombolysis and staff development. A clinical review team incorporating all role players would need to meet regularly to appraise all cases of prehospital thrombolysis. In settings where the frequency of the performance of thrombolysis is low, an on-going programme of refresher training is essential to maintain skill competence. External surveillance registries like MINAP and the Swiss registries provide valuable information on trends in management of acute STEMI and should be used to guide treatment timeframes and clinical outcomes.

9. Other uses for prehospital thrombolysis

Prehospital thrombolysis is primarily aimed at the treatment of patients with symptoms and ECG diagnosis of STEMI. Although this will remain the mainstay of the use of thrombolytic therapy, thrombolysis is also used in the treatment of other clinical emergencies.

9.1 Stroke

Although stroke thrombolysis is not suitable for initiation in the community due to the need for a CT scan and in a small subset of patients an MRI, the early identification of patients with a possible stroke is vital. This has required a change in emphasis within emergency departments and ambulance services where an acute stroke has now been identified as a time-sensitive clinical emergency. The UK has just completed a mass TV awareness campaign for the recognition of stroke, building on the brain attack model developed in

America. Prehospital clinicians are, therefore, pivotal in the early identification of suspected stroke patients typically using the **F**ast, **A**rm, **S**peech, **T**est (FAST) supported by pre-arrival alerts to hospitals equipped to deliver stroke thrombolysis (with 3-4 hours of onset of symptoms).

9.2 Cardiopulmonary resuscitation (CPR)

The use of thrombolysis during resuscitation is also a potential treatment option but the routine administration of thrombolysis during cardiac arrest management is not endorsed (Class III recommendation). However, its use to treat a confirmed or suspected massive pulmonary embolism or STEMI should be considered on a case-per-case bases (Class IIa recommendation) (Neumar, 2010). Confirmation of diagnosis remains challenging but is primarily based on clinical history supported by clinical suspicion although the use of bedside ECHO for the diagnosis of massive pulmonary embolism is worth consideration (typically to look at the right ventricle) but the expertise for this is limited in the prehospital environment.

Following the administration of thrombolytic therapy, during CPR, the period of resuscitation should be extended to a minimum of 60 minutes (Neumar, 2010) and this protracted period of resuscitation is an important consideration when initiating thrombolytic therapy. The administration of thrombolysis during resuscitation does not replace the need for effective compressions and supportive ventilation but represents a targeted treatment for a small subset of patients.

10. Conclusion

Prehospital thrombolysis offers two unique clinical pathways for the patient presenting with STEMI. Prehospital thrombolysis can be the preferred reperfusion strategy in developing countries or countries without rapid access to primary angioplasty facilities or can provide ultra-early reperfusion as part of a hybrid reperfusion service. Key to the success of any prehospital service is the recruitment and training of appropriately qualified personnel although in remote areas the use of telemedicine and electronic data transmission can support the administration of thrombolysis by junior clinicians. Although thrombolysis offers significant patient benefits, it needs to be appropriately delivered and supported by adjunctive therapy which should include dual anti-platelet therapy for all patients supported by heparin (ideally LMWH) as appropriate.

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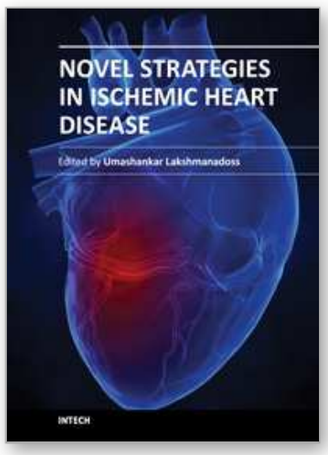

Novel Strategies in Ischemic Heart Disease

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The first edition of this book will provide a comprehensive overview of ischemic heart disease, including epidemiology, risk factors, pathogenesis, clinical presentation, diagnostic tests, differential diagnosis, treatment, complications and prognosis. Also discussed are current treatment options, protocols and diagnostic procedures, as well as the latest advances in the field. The book will serve as a cutting-edge point of reference for the basic or clinical researcher, and any clinician involved in the diagnosis and management of ischemic heart disease. This book is essentially designed to fill the vital gap existing between these practices, to provide a textbook that is substantial and readable, compact and reasonably comprehensive, and to provide an excellent blend of "basics to bedside and beyond" in the field of ischemic heart disease. The book also covers the future novel treatment strategies, focusing on the basic scientific and clinical aspects of the diagnosis and management of ischemic heart disease.

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