A REVIEW OF THE DOOR TO NEEDLE TIME FOR

ADMINISTRATION OF FIBRINOLYTICS IN ACUTE MYOCARDIAL INFARCTION

IN

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BY

DR R C MAHARAJ

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Supervisor: DR HEIKE GEDULD

Division of Emergency Medicine

University of Cape Town

DECLARATION

I, Roshen Chathram Maharaj, hereby declare that this dissertation is my original work (except where acknowledgements indicate otherwise) and that neither the whole work nor any part of it has been, is being, or is to be submitted for another degree in this or any other university, and has not been published prior to registration for the abovementioned degree. I empower the university to reproduce for the purpose of research either the whole or any portion of the contents of this dissertation in any manner whatsoever.

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PRINCIPAL RESEARCHER: Dr R C MAHARAJ

CLINICAL SUPERVISORS: Dr H GEDULD

PROF. A WALLIS

Division of Emergency Medicine

University of Cape Town

DR R C MAHARAJ

University: University of Cape Town

Student number: MHRROS001

Email: roshenmaharaj@gmail.com

Telephone: 072 269 8840

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INTRODUCTION AND LITERATURE REVIEW

Cardiovascular disease is a major cause of morbidity and mortality worldwide, especially in industrialised societies. With South Africa undergoing rapid urbanisation in the post-apartheid era, adverse cardiovascular events, including acute myocardial infarction, are becoming more prevalent.(1,2)

While prevention of disease is the ideal, morbidity and mortality in individuals with acute myocardial infarction can be reduced with early administration of fibrinolytic therapy. The major benefit of early finbrinolysis lies in resolving the patency of the affected coronary artery. This reduces the infarct size of the myocardium. A delay in thrombolytic treatment by half an hour can reduce life expectancy by approximately one year in patients with acute myocardial infarction.(3,4)

The American Heart Association and American College of Cardiologists (AHA/ACC) guidelines recommend a door to needle time of 30 minutes for administration of fibrinolytics in patients with acute ST Segment Elevation Myocardial Infarction (STEMI).(5) This time period is considered as the gold standard for thrombolyisis and compliance with this is regarded as a marker of quality of care.(6)

The majority of patients with acute myocardial infarction in the Cape Metropole, are initially seen in the emergency centres (EC). Emergency centres are often overcrowded and understaffed, and despite good triage, delays in managing patients with myocardial infarction can occur.

Audits performed internationally; show that most hospitals fail to achieve a door to needle time in about half of their patients.(6,7)

Several factors have been identified as contributing to these delays. These include: delays in

obtaining or interpreting ECGs, obtaining a cardiology consult before initiating thrombolysis, thrombolysis being given in the ICU/CCU rather than the Emergency Centre, the time of day that patient presented to hospital and prehospital factors eg. inappropriate prehospital diagnosis and incorrect referral.(7,8,9)

AIM OF STUDY

The aim of this study is to determine the current door to needle time for administration of fibrinolytics in acute myocardial infarction in Emergency Centres in the Cape Metropole. This study will also aim to identify the factors contributing to the delay.

STUDY DESIGN

A RETROSPECTIVE audit will be conducted of all patients who received fibrinolytics for acute myocardial infarction in the emergency units of four hospitals in the Western Cape Metropole. Data will be collected from Groote Schuur Hospital, GF Jooste Hospital, New Somerset Hospital and Victoria Hospital. The clinical records of all patients who received fibrinolytic therapy for acute myocardial infarction in these emergency centres will be reviewed. These patients will be identified by the Emergency Centre Register.

Inclusion Criteria:

All patients with Acute ST Segment elevation or new onset LBBB on ECG meeting ACC/AHA criteria for fibrinolysis who received fibrinolytics in the emergency centre from 1 January 2008 to 31 July 2010.

Exclusion Criteria

- Patients who received prehospital fibrinolytics.

- Patients receiving fibrinolytics for conditions other than acute myocardial infarction.

From the case notes the following data will be collated and analysed:

- Time of presentation to hospital (taken from ambulance record/admission chart)
- Time taken to triage
- Time to ECG
- Time from ECG and to start of thrombolysis. This will include interpreting the ECG, obtaining consent for administration of fibrinolytics, obtaining IV access, and preparing the fibrinolytics for administration. Streptokinase is the fibrinolytic available in the public sector hospitals for treatment of ST elevation myocardial infarction. It needs to be reconstituted and given as an infusion.
- Total door-to-needle time will therefore be from presentation to lysis.
- Factors that may contribute to delay in receiving thrombolytics in our setting include:
    - private transport vs ambulance
    - patient demographics, language barrier
    - time of onset of pain
    - time of day that patient presents to Emergency Department
    - anatomical localization of infarct
    - level of experience of physician
    - atypical presentations

REFER TO ANNEXURE A

Estimated sample size is 600

All data will be collated on an EXCEL spread-sheet. Simple descriptive statistics will be used to describe the median time-to-triage, time-to -ECG and door-to-needle times for each Emergency

Centre.

Subgroup analyses will be performed for different sexes, age groups, anatomical localization of MI, transport types and physician experience.

ETHICS

Data will be collected from patient records by a single researcher. Permission will be obtained from the relevant hospitals to access these records. Patients will only be identified by hospital numbers. All data will be kept on a password protected database.

FUNDING

No funding required.

TIMELINE

This study will commence once Research Committee and Ethical Approval has been obtained. It is aimed to complete this dissertation for submission in August 2011.

ANNEXURE A

DATA COLLECTION SHEET

Patient Number: _____
DEMOGRAPHICS:
Age: _____ Sex: _____

AMBULANCE: Y / N
FORWARD ALERT BY PREHOSPITAL STAFF: Y/N PREHOSPITAL ECG: Y/N

LEVEL OF EXPERIENCE OF TREATING PHYSICIAN: INTERN, CSO, MO, REGISTRAR, CONSULTANT

CLINICAL:
Time of Onset of Pain: _____ Time of Day: W/H, A/H
Anatomical localization: _____
Typical Symptoms Y / N
If no describe: _____

	DURATION	COMMENT
TIME OF ARRIVAL		
TIME FROM ARRIVAL TO TRIAGE		
TIME FROM TRIAGE TO ECG		
TIME FROM ECG TO ACTUAL ADMINISTRATION OF FIBRINOLYTIC		
TOTAL DOOR TO NEEDLE TIME		

KEY: Y – YES
N – NO
CSO – COMMUNITY SERVICE OFFICER
MO – MEDICAL OFFICER
W/H – WORKING HOURS (08:00 – 17:00)
A/H – AFTER HOURS (17:01 – 07:59)

COMMENT: IDENTIFY DELAY IN DOOR TO NEEDLE TIME IF ANY

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PART B: LITERATURE REVIEW

LITERATURE REVIEW

AIM:

The aim of this literature review is to:

- Determine the global impact of Ischaemic Heart Disease (IHD).
- Review the epidemiology of IHD in the Western Cape.
- Review the current management of ST Elevation Myocardial Infarction (STEMI).
- Identify local research on door to needle time for the administration of thrombolytics for Acute Myocardial Infarction (AMI) in emergency centres.
- Identify factors affecting the door to needle time internationally.
- Identify quality improvement strategies to optimise the management of STEMI patients in Cape Town.

LITERATURE SEARCH STRATEGY:

The database of Medline, Pre-Medline and Embase on the OVID platform and Google Scholar were searched. Search words included, ST elevation myocardial infarction, thrombolytics, fibrinolysis, door to needle times, delay in door to needle time, quality analysis. 714 articles were identified from the above databases. In addition unpublished articles and web-sites (Biomed Central, Greynet) were sourced and 44 articles were identified, of these. A review of the references of these articles yielded a further 17 articles. A final total of 80 articles were selected on the basis of validity and relevance to this study.

LITERATURE APPRAISAL

Introduction:

Ischaemic heart disease (IHD) is a major cause of morbidity and mortality worldwide, with a high prevalence noted in industrialised societies.(1) In the United States approximately 732 000 of the annual 6 million patients with chest pain, seen in Emergency Centres (EC), are admitted with Acute Myocardial Infarction (AMI).(2) Mortality statistics show that South Africa is currently experiencing a quadruple burden of disease, namely infectious conditions such as tuberculosis; chronic diseases (diabetes, hypertension, cardiovascular diseases); HIV/AIDS; and mortality and morbidity from injuries resulting from interpersonal violence.(3)

With South Africa undergoing rapid urbanisation in the post-apartheid era, risk factors for IHD and adverse cardiovascular events, including AMI are becoming more prevalent.(4-6) In South Africa, data collected on disease profiles is based on findings from death notification forms received from the Department of Home Affairs.(7) This is the basis of mortality statistics from a particular disease. Although these are important and can be used to implement interventions, there are certain limitations to these statistics as recognised by Stats SA.(7) These include errors in filling out death notification forms, under registration of deaths and filling in the incorrect cause of death. In addition historical factors have influenced epidemiological studies in South Africa. Stats SA only began collecting data representative of all population groups from 1997 onwards.(7,8) Cause of death was classified by the ICD 10 coding system. Deaths from IHD consistently appeared amongst the top 10 causes of natural deaths in the country. Sub group analysis showed that acute myocardial infarctions accounted for more than 70 % of deaths in the IHD group (2003/2004 Statistics).(8)

A higher mortality from IHD was seen in males and a higher overall incidence was seen in the White and Indian population compared to the Black and Coloured population.(7,8) Recently released 2008 mortality statistics show that IHD was the number one cause of natural death in Whites, while it was the second and fourth leading cause of death in Asian/Indians and Coloureds respectively.(9) There is a paucity of data on the prevalence of AMI and number of AMIs admitted to our ECs. Data extrapolated from a recent audit of clinical presentations and procedures in ECs of three Western Cape hospitals, revealed that acute coronary syndromes and chest pain made up 1.2% and 2.9% of all clinical presentations respectively.(10) Electrocardiograms (ECGs) made up 9.2% , and thrombolysis accounted for 1.2% of procedures performed in the ECs collectively.(10)

The treatment of patients is usually initiated in the EC, thus making the functioning of an EC a critical component in the initiation of management of patients with AMI. The type, quality and timeliness of care AMI patients receive can have a significant impact on patient mortality and morbidity.(11-13)

Primary prevention of IHD, through early screening and detection of risk factors, lifestyle modification and aggressive treatment of hypertension, diabetes and hypercholesterolaemia is the ideal.(6, 14) For those already with established disease and presenting with AMI, mortality and morbidity can be significantly reduced with early reperfusion interventions.(15)

In South Africa two strategies may be employed to emergently manage patients presenting with acute ST Elevation Myocardial Infarction (STEMI) – fibrinolytic drug therapy, which can be initiated in the EC, or primary Percutaneous Coronary Intervention (PCI). Regardless of the strategy chosen, the adage that time is muscle should be adhered to for patients presenting with AMI.(15)

The Global Impact of Ischaemic Heart Disease:

The 2004 World Health Organisation (WHO) Global Burden of Disease survey, listed IHD as the leading cause of death globally.(16) Mortality from IHD was highest in the high income countries, but also featured high on the mortality list in the middle and low income countries.(16) In the United States coronary heart disease was the single leading cause of death.(17) IHD also accounted for a high incidence of hospital admissions in Europe.(18) The projected trends in global mortality by 2030, as determined by WHO, further predicted IHD as a leading cause of mortality in 2030.(16) The years of life lost due to premature mortality and disability could have a significant impact on the worlds economy.

The Burden of Ischaemic Heart Disease in the Western Cape:

In the Western Cape, cardiovascular disease was the leading cause of mortality in both males and females, accounting for 25% of all deaths in the year 2000.(3) Ischaemic heart disease was the single leading cause of mortality in this category and accounted for 12% of all deaths in 2000.(3) Data from Stats SA consistently places IHD in the top five natural causes of mortality in the Western Cape.(9) (see Table 1)

Table 1: Top 5 Natural Causes of Death, Western Cape (9)

CAUSE OF DEATH (BOTH SEXES)	%	CAUSE OF DEATH (MALE)	%	CAUSE OF DEATH (FEMALES)	%
Tuberculosis	9.7	Tuberculosis	10.5	Tuberculosis	8.7
Ischaemic Heart Disease	5.9	Ischaemic Heart Disease	6.2	Diabetes Mellitus	7.8

Diabetes Mellitus	5.8	Chronic Lung Disease	4.6	Cerebrovascular Disease	6.4
Cerebrovascular Disease	5.6	Diabetes Mellitus	4.2	Ischaemic Heart Disease	5.6
Human Immunodeficiency Virus (HIV)	4.3	Cerebrovascular Disease	4	Human Immunodeficiency Virus (HIV)	5.1

Mortality from IHD was found to be the highest in the City of Cape Town, Overberg, Eden and West Coast district municipalities of the Western Cape. (9) The hospitals chosen in this study service most of these drainage areas.

Men had a higher mortality from IHD than women in keeping with national statistics. (3, 9) Women however died more often from diseases that are risk factors or predictors for IHD (diabetes, hypertension, stroke).(3)

With age stratifying cause of mortality, IHD was the leading cause of mortality in males over 60 years (20.4%), while it was second only to tuberculosis in males aged 45-59. It accounted for 12.8% of deaths in this age group. In the female population similar trends were noted with stroke being the leading cause of death between ages 45-59 years. Notably IHD featured as the 6th leading cause of death in males less than 44 years (2.3%).(3)

Hence, IHD and its risk factors account for significant mortality in the Western Cape. Compared to the rest of the country, non communicable/chronic diseases such as diabetes, hypertension and cardiovascular diseases resulted in a higher number of deaths in the Western Cape (58% vs.

38%). This was attributed to the population of the Western Cape being older than the national population, hence the higher mortality from chronic diseases.(3) IHD and other non communicable diseases are traditionally more prevalent in western affluent societies. However studies done by the Medical Research Council (MRC) in collaboration with the School of Public Health (University of Western Cape), showed higher mortality rates from non communicable diseases in the poorer districts of Cape Town compared to the more affluent areas (19). The INTERHEART Africa Study with approximately 80% of participants from South Africa studied the impact of modifiable cardiovascular risk factors on myocardial infarction in Sub-Saharan Africa. In the Coloured-African group which was recruited from hospitals serving a low socioeconomic population, revealed that this ethnic group adopted "a hazardous, westernised lifestyle" with high rates of smoking and obesity.(20) Steyn et al in a community based cross sectional study in the Cape Peninsula, also reinforced the high prevalence of hypertension, smoking, and hyperlipidaemia in subjects.(21)

This highlights the fact that there is a high prevalence of risk factors for IHD especially myocardial infarction present across all socioeconomic groups in the Western Cape population.(21,22) No specific current data could be found for hospital presentations with acute STEMI in the Western Cape.

The Impact of Cardiovascular Disease on the Economy:

In determining the impact of disease on society and the economy, the 2000 Burden of Disease Study determined the years of life lost from death from a particular disease. The impact of the cardiovascular group on years of life lost was not considered as dramatic by the authors. (22) The reason being that the elderly (age > 60 yrs) were the most affected. However it should be

noted that the average working age of the South African population, including that in the Western Cape has increased. This could mean that more people of working age will be affected by cardiovascular disease, having a negative impact on the countries economy.(22)

Statistics from the Department of Health records of 2002 indicate that the direct health care costs of managing patients with cardiovascular diseases are much higher compared to other conditions. Costs per bed per day were six times higher than those of the average patients admitted in a tertiary facility, and almost ten times higher in a regional/district hospital.(22)

In response to the findings from the 2000 Burden of Disease survey, the Western Cape has initiated a task force to develop appropriate interventions to address the current pathology present.(22)

Optimal Management of STEMI:

Reperfusion therapy remains the main form of treatment for eligible STEMI patients. Various trials and meta-analysis has shown that early PCI has more advantages than fibrinolysis. PCI reduces mortality from re-infarction and the need for Coronary Artery Bypass Grafting (CABG) more than fibrinolysis.(23- 28) However access to PCI is often limited.

Access to PCI in the Western Cape public sector is limited to two tertiary hospitals, making fibrinolysis the most accessible reperfusion strategy available to most people.

The major benefit of early administration of fibrinolysis lies in resolving the patency of the affected coronary artery. This reduces the infarct size of the myocardium and improves left ventricular function. There is also conclusive evidence that fibrinolytics reduce mortality in patients with STEMI if given within 6-12hrs after onset of symptoms.(29 -34) Meta analysis of all randomised fibrinolytic trials, with more than 1000 patients, done by the Fibrinolytic Therapy

Trialist group showed that a shorter time from onset of symptoms to fibrinolysis resulted in a greater mortality benefit. The greatest mortality benefit was seen in patients fibrinolysed within 3 hours of presentation following STEMI, especially in the first hour.(35,36)

Statistical improvement in mortality was seen up to 12 hours post symptom onset. There was an absolute mortality benefit of 39 lives saved per 1000 patients if treated within one hour post onset of symptoms; 30 lives/1000 if treated within 2 -3 hours and 21/1000 if treated between 7-12 hours. There was an absolute benefit reduction of 1.6 lives/1000 for every hour of delay.(37,38) Early reperfusion also resulted in lower 30 day mortality. Data analysed retrospectively from The Myocardial Infarct Triage and Intervention (MITI) trial showed a 7 fold reduction of 30 day mortality in patients treated within 70 minutes of symptoms compared to those treated later (1.2% vs 7%).(37) The GREAT trial also confirmed that a delay in fibrinolytic treatment by half an hour can reduce life expectancy by approximately 1 year in patients with STEMI.(37, 39-42/32) Hence maximal benefit in re-establishing coronary vessel patency and reducing morbidity and mortality in STEMI patients is achieved if patients present early to a facility with reperfusion capability.

The Administration of Fibrinolytics :

The defined American Heart Association/American College of Cardiology (AHA/ACC) criteria for fibrinolysis are:

- chest pain duration of less than 12 hours
- ECG showing ST elevation of 2mm or more in chest leads and 1 mm or more in limb leads
- new onset Left Bundle Branch Block (LBBB)
- evidence of true posterior infarct.

Absolute contraindications to lysis include:

- risk of bleeding (recent trauma, major surgery or head injury within 6 weeks)
- gastrointestinal haemorrhage or proven peptic ulcer disease in the past 3 months
- bleeding diathesis or chronic liver disease complicated with portal hypertension
- cerebrovascular accident (residual disability) or transient ischemic attack in the past 6 months
- pregnancy
- allergy to fibrinolytic (streptokinase or anistreplase should not be repeated if given in the previous 5 days to 12 months).

Relative contraindications include:

- hypertension (Systolic Blood Pressure > 180 mmHg or Diastolic Blood Pressure > 110 mmHG) in which case urgent blood pressure lowering is required before administering fibrinolysis
- non compressible arterial puncture or dental extraction in the past 2 weeks
- prolonged Cardio Pulmonary Resuscitation (CPR)
- diabetic proliferative retinopathy and any other serious disease carrying a high risk of bleeding.(43,44)

Due to economic limitations, streptokinase is the fibrinolytic used in the public sector hospitals of Cape Town for treatment of STEMI's. It needs to be reconstituted and given as an infusion. Alteplase, available at Victoria and New Somerset Hospitals, is reserved for use in those patients who had previously received streptokinase.

The Door to Needle Time as a Quality of Care Marker:

The AHA/ACC guidelines recommend a door to needle time of 30 minutes or less for administration of fibrinolytics in patients with STEMI.(43,43) Compliance with this time period is internationally accepted as a marker of quality of care.(45) McNamara et al in their study of 62470 STEMI patients that were thrombolysed showed lower in-hospital mortality in patients with shortened door to needle times.(12)

Despite the proven advantages of early fibrinolysis, audits performed internationally show that most hospitals fail to achieve a door to needle time of 30 minutes or less in about half their patients.(40, 46-51) No South African data on the EC administration of fibrinolytics for STEMI were found.

There are various factors implicated in the delay in achieving optimal reperfusion times.

Identifiable factors include:

1. Pre-hospital Factors:
    - Patient delay in seeking medical attention and activation of EMS.
    - Pre-hospital transport delays.
2. In-hospital Factors
    - Prolonged door to needle times are due to delays in identifying patients with chest pain or those presenting with atypical symptoms, ineffective or lack of triage systems in ECs, delays in obtaining a 12 lead ECG and difficulty in ECG interpretation.
    - In cases identified with STEMI, delays in starting fibrinolytics timeously contributed to prolonged door to needle times.(38,50)

Pre-hospital Factors Delaying Thrombolysis:

Patient delays can be attributed to the lack of awareness or knowledge about fibrinolytic therapy and the need for early intervention in those with AMI; patient denial of having an AMI or inability to contact medical care due to their medical condition, or having no access to telecommunications.(52,53)

Pre-hospital transport delays can occur, secondary to limited resources such as availability of ambulances and staff. It is also influenced by the level of experience of the pre-hospital care giver and the availability of 12 lead ECG machines in the ambulances.

In-hospital Factors Delaying Thrombolysis:

The door to needle time is an important time sub-interval that can be influenced by in-hospital medical personnel and EC protocols. The door to needle time can be divided into the door to triage time, triage to ECG time and time from ECG acquisition to starting fibrinolytics. The sum of these times represents the door to needle time.

Jehanger et al, in their review of 201 patients receiving fibrinolysis for STEMI found that a door to needle time of less than 30 minutes was achieved in 54.7% of patients.(50) In the subgroup with a door to needle time of greater than 30 minutes (n 91), delays were attributed to the initial ECG showing subtle changes, requiring repeat ECG's. In twelve percent of the time, there was a delay in decision making and starting of the fibrinolysis. Patients complicated with ventricular fibrillation that required resuscitation accounted for seven percent of delays.(50) No reason could be found in one and a half percent of cases.

Similar delays were identified in a small study done by Masurker et al in Mumbai (40). There are certain patient factors such as cardiac arrest and hypertension (blood pressure beyond

recommended guidelines) that require correction first, before commencing thrombolytics, hence causing an unavoidable prolongation in door to needle times.

Magid et al investigated the effect the time of day, day of week and time to reperfusion had on door to needle times and correlated it with mortality. In the door to drug segment of the study 67.9% (n -68439) patients received fibrinolytic therapy after hours. Door to needle times were statistically slightly longer during after hours (34.3 min) than regular working hours (33.2 min) {95% CI 0.7 –1.4, P< .001}.

The absolute difference was 1 minute. They concluded that patient arrival time did not influence the fibrinolytic treatment time subintervals appreciably.(54)

In determining mortality after adjusting for all patient co-variants, patients presenting after hours had higher in hospital mortality, but the difference was considered not statistically significant [OR 1.06; 95%CI, 0.98-1.15 P=0.13].(54)

The AMI- Quebec study also retrospectively investigated the delays in reperfusion therapy for STEMI's in 17 hospitals in Quebec, Canada. Forty nine percent of patients were thrombolysed within 30 minutes of arrival. Patients presenting outside working hours had longer door to needle times. Median door to ECG times were twelve minutes for patients presenting during normal working hours and thirteen minutes for those presenting after hours. Fewer staff being present after hours was identified as a probable cause of this delay.(48)

The time of presentation to hospital however did not seem to significantly affect the door to needle time when statistical analysis was undertaken.

The AHA/ACC guidelines recommend a door to ECG time of ten minutes in all patients with chest pain/discomfort or symptoms suspicious of acute coronary syndromes(ACS). This also

included interpretation of the ECG.(44,55-57) Despite set recommendations, studies done internationally show that approximately a third of patients with ACS received ECGS within ten minutes.(58,59)

Prolonged door to ECG times led to an increase risk of adverse clinical outcomes at 30 days in STEMI patients [OR 3.95 95%CI, 1.06 – 14.72, P =0.04].(56) Adverse outcomes were secondary to prolongation of the reperfusion time. The door to ECG time is a sub interval in the calculation of the door to reperfusion time.

Various studies also investigated the influence that patient demographics had on door to needle times.(48,60-63) An increased age was associated with decreased odds of timely administration of fibrinolysis. Possible factors identified were atypical symptoms being more prevalent in the elderly. The elderly were also thought to be at increased risk of intracranial haemorrhage, which may have deterred doctors from administrating fibrinolysis initially. The average age of patients receiving fibrinolysis was 60.2 years with a male predominance.(48,60-63) There therefore needs to be a high index of suspicion for STEMI in elderly patients (greater than 60 years) presenting to ECs.

Quality Improvement Strategies:

Most studies and audits reviewed suggest an efficient, organised team based approach to reduce door to needle times.(38,46,48,54,64-67) Development of institutional or provincial care pathways should be emphasised. This requires pre-hospital care providers, hospital administration, emergency centre staff and pharmacists to be part of an integrated team response.

Prehospital Quality Improvement Strategies:

Patient factors described above need to be addressed by extensive public education and improvement of infrastructure.(15,50)

The role of paramedics in the management of patients with possible ACS, is to take a goal directed history; obtain a 12 lead ECG, complete a reperfusion checklist en-route to hospital, and prioritise all of the above information during patient handover at the receiving hospital.

In a US study, pre-hospital ECG acquisition led to a 36.1 minutes mean savings in the door to needle time.(68) This could correlate into improved mortality and morbidity in STEMI patients.

In the Western Cape, not all paramedics in the public sector are equipped with 12 lead ECG machines.

Many pre-hospital staff attending to ACS's has variable levels of training (Basic Life Support to Advanced Life Support), making paramedic initiated ECG acquisition difficult.

Current handover practice in Western Cape Emergency Centres between pre-hospital staff and hospital staff is mainly by verbal communication and an ambulance record sheet.

A DeMIST system introduced by METRO Emergency Medical Services recently aimed at more efficient handover practices.(69) The DeMIST emphasises important patient demographics, mechanism of injury or type of illness, vital signs and treatment given.(69,70) The DeMIST system can be adapted to use during handover of STEMI patients but requires training of pre-hospital and in hospital staff.(70)

Advance notification by pre-hospital staff to the receiving hospital is also important in aiding the EC staff in preparing for the STEMI patient.

Initiation of pre-hospital fibrinolysis should also be considered, although no protocol has been

set up in the Western Cape. Pre-hospital fibrinolysis can decrease call to needle times and has the potential to decrease morbidity and mortality in STEMI patients.(71,72)

In-hospital quality improvement strategies:

Recommendations for improving in-hospital care of patients arriving with ACS include the establishment of efficient patient flow and triaging systems, so that patients with chest pain could be fast tracked.(64)

The South African Triage Scale (SATS) is used in the Western Cape. It consists of triage early warning indicators (vital signs) and a discriminator list. The discriminator list is the final factor used to determine the triage colour and severity of the patient. Chest pain is incorporated as a discriminatory factor, enabling the triage officer to 'uptriage' a patient even if their vital signs are normal. This helps identify and prioritise patients with chest pain.(73,74) Efficient triaging can thus lead to shorter door to needle times.

Organisational and administrational support also plays an important role in rapidly investigating chest pain patients. Obtaining a door to ECG time of ten minutes should be aimed for.(54) This rapidly identifies patients with STEMI's enabling the clinician to timeously work up the patient for a reperfusion strategy.

Good senior physician leadership, knowledge and managerial experience in the EC can help expedite fibrinolysis in eligible patients. It has been shown that ECG interpretation and decision to thrombolyse were more reliable in the more experienced doctors compared to junior doctors.(75) Furthermore, computer generated ECG reports did not seem to reduce errors in ECG interpretation.(76) It is therefore important for a senior Emergency Physician to oversee junior staff and provide advice on difficult management decisions and

disposition of patients. A good professional relationship between EC doctors, cardiologists, nursing staff and support personnel also aids in providing fibrinolysis timeously.

Establishing a specific chest pain team to co-ordinate fibrinolysis may be ideal.

There should be local standard protocols developed for EC doctors and nurses to follow for a patient arriving with a STEMI. The AHA/ACC has developed an acute coronary syndrome algorithm to aid in managing patients with ACS.(44) The algorithm could be incorporated into local protocols.

Emphasis should also be placed on efficient management of STEMI patients arriving after hours.(38)

The type of service an EC of a hospital provides can be determined by analysing its quality of care markers. Efficient management of patients with AMI forms a critical segment of EC care and early fibrinolytic therapy does influence patient morbidity and mortality.(35) Quality of care markers such as timeliness of obtaining an ECG, early administration of drugs such as aspirin, timely fibrinolytic therapy and efficient disposition of STEMI patients can be used to determine emergency centre performance in the management of patients with AMI.(46,77,78) The American College of Cardiology, Door to Balloon Alliance and the American Heart Association's Mission: Lifeline programs initiated in the US aims at improving health care systems for STEMI patients requiring reperfusion.(79) Achieving the target door to needle time of 30 minutes or less is an acceptable and appropriate benchmark for providing quality care for STEMI patients in Western Cape hospitals.

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PART C: ARTICLE FOR SUBMISSION

A REVIEW OF THE DOOR TO NEEDLE TIME FOR ADMINISTRATION OF FIBRINOLYTICS IN ACUTE MYOCARDIAL INFARCTION IN CAPE TOWN

Roshen C Maharaj, Heike Geduld, Lee A Wallis

Division of Emergency Medicine
University of Cape Town
Cape Town
South Africa

Corresponding Author: Dr Roshen C Maharaj

Postnet Suite 318, Private Bag X18, Rondebosch, 7700
roshenmaharaj@gmail.com
+27(0)722698840
Fax: +27(0)86539644

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Abstract

Objectives:

To determine the current door to needle time for the administration of fibrinolytics for Acute Myocardial Infarction (AMI) in Emergency Centres (EC) at three hospitals in Cape Town, and to compare it to the current American Heart Association/American College of Cardiology (AHA/ACC) recommendation of 30 minutes.

Methods:

A retrospective audit of all patients receiving thrombolytics for AMI in the ECs of three Cape Town hospitals was performed. Case notes from January 2008 to July 2010 were reviewed. The total door to needle time was calculated. In addition, patient demographics and presentation, physician qualification, clinical symptomology, infarct location and reasons for delays in thromobolytic administration were also analysed.

Results:

A total of 372 patients with acute ST elevation myocardial infarction (STEMI) were identified. One hundred and sixty one patients were eligible for this study. The median door to needle time achieved was 54 minutes (Range 13 -553 min). A door to needle time of 30 minutes or less was achieved in 33 patients (20.5%). More than half of the patients (51.3%) arrived by ambulance. Thirty four percent of patients had a pre-hospital 12 lead ECG. The majority (88.8%) had typical symptoms of myocardial infarction. Medical Officers administered thrombolytics to 44.7% of the cases thrombolysed. The predominant infarct location on ECG was inferior (55.9%).

Conclusion:

A significant number of patients were not thrombolysed within 30 minutes of presentation. The lack of senior doctors, difficulty interpreting ECGs, atypical presentations and EC system delays prolonged the door to needle time in this study.

INTRODUCTION

Ischaemic Heart Disease (IHD) is a major cause of mortality and morbidity worldwide, especially in industrialised countries.[1] In the Western Cape, IHD has been reported as the leading cause of mortality in the cardiovascular category in the year 2000 and has consistently appeared in the top five causes of mortality since.[2] In keeping with international studies mortality from IHD was higher in males than females.[3]

While primary prevention of IHD is considered the ideal, mortality and morbidity in patients presenting with Acute Myocardial Infarction (AMI) can be reduced with early interventions such as fibrinolysis or percutaneous coronary intervention (PCI).[4] Multiple studies have shown that early PCI is more advantageous in reducing mortality from re-infarction and the need for a coronary artery bypass graft (CABG) than fibrinolytic drug therapy.[5-7] In the Western Cape PCI is limited to two tertiary hospitals, making fibrinolytic drug therapy the more accessible form of treatment for ST elevation myocardial infarction (STEMI) patients.

Early administration of fibrinolytic therapy has shown to improve patient outcomes in terms of limiting infarct size, thus preserving left ventricular function.[8,9] This is achieved by re-establishing the patency of the occluded coronary vessel.[8-10] Maximal benefit from fibrinolysis is seen when the fibrinolytic is given within the first hour of symptom onset.[11,12] Delaying fibrinolytic therapy by one hour increases the hazard ratio of death by 20%, (95% CI 7 – 88), and a delay of 30 minutes or more can reduce the average life expectancy by one year.[13]

Minimising the time delay between onset of symptoms to definitive treatment is integral in improving mortality and morbidity.

The period between the onset of symptoms to administration of fibrinolytic therapy can be

divided into the following components:

- Interval between onset of symptoms to seeking medical attention
- Period taken to transport patient to definitive care
- Interval between arrival at hospital to initiation of fibrinolytics (door to needle time)

The first two components can be improved by public education and developing efficient pre-hospital systems. The door to needle time is the one in-hospital factor that can be addressed by medical practitioners.

The American Heart Association /American College of Cardiology (AHA/ACC) guidelines recommend a door to needle time of 30 minutes or less for administration of fibrinolytics for STEMI patients.[14] Compliance with this time period is considered a marker of quality of care.[15]

No current data could be found on the door to needle time in the Emergency Centres (EC) of public hospitals in Cape Town . The aim of this study is to determine the current door to needle time for fibrinolytic administration in patients with STEMI's, determine patient demographics and assess factors that could influence the door to needle time.

METHODS

A retrospective audit was conducted of all patients who received thrombolytics for AMI in the ECs of 3 hospitals in Cape Town from January 2008 to July 2010.

Inclusion criteria:

- All adult patients with acute ST segment elevation, new onset Left Bundle Branch Block (LBBB), or posterior infarct on electrocardiogram (ECG) meeting AHA/ACC criteria for thrombolysis, who received thrombolytics in the above ECs.

The following patients were excluded:

- patients who received pre-hospital thrombolysis or those thrombolysed at other centres before referral.
- Patients receiving thrombolysis for conditions other than myocardial infarction.
- Cases where patient files were missing from central records and cases with incomplete data such that door to needle time could not be calculated.

Data Collection

Patients with a diagnosis of acute coronary syndrome, acute myocardial infarction and ST elevation myocardial infarction were identified from the EC registry. Case notes were reviewed by a single observer. The required data were extracted onto a standardised data collection form. The quality of data collected was dependent on the availability and accuracy of the case notes. Incomplete documentation, illegible and ambiguous notes were identified.

The following data were collated and analysed:

- Patient demographics
- Transport mode to hospital
- Pre-hospital ECG acquisition , either by Emergency Medical Services (EMS) or the primary care facility staff.
- Time of day (working hours vs. after hours) patient arrived. Working hours was defined as 08.00 to 17.00 and after hours between 17.00 and 08.00 the next day. No distinction was made between weekdays or weekends as the EC's had similar staffing and dynamics on both weekdays and weekends.

The following time intervals were calculated:

- Earliest time of presentation to hospital (taken from EMS records or admission chart) to time of triage.
- Time from triage to ECG acquisition.
- Time from ECG acquisition to actually commencing thrombolytics.

This time interval included interpretation of ECG, obtaining consent for administration of thrombolytic, determining if any contraindications existed to the thrombolytic agent, obtaining intravenous access and preparing the thrombolytic for administration.

The sum of the above time intervals constitutes the total door to needle time.

All data were collected and transferred onto an Excel spreadsheet. Simple descriptive statistics were used to describe the median time to triage, triage to ECG, ECG to fibrinolytic and total door to needle times.

Subgroup analysis was performed for determining prevalence of STEMI's fibrinolysed based on gender and age group; anatomical localization of myocardial infarction; transport times and level of experience of treating physician.

The symptomology on presentation was also assessed. Typical symptoms were defined as an acute onset of chest pain with radiation to the left arm, neck or jaw with associated autonomic symptoms (sweating, nausea or vomiting).

Statistical analysis was undertaken using Microsoft Excel (Microsoft, Richmond, Va), EpiCalc 2000 (Brixton Books, London, UK) and STATA (Stata Corp, College St, Tx).

RESULTS

From the EC registries of the 3 hospitals under study a total of 372 patients with STEMI were identified. The final number included in the study was 161.

The consort diagram is shown as Figure 1.

Table 1 lists the demographic variables.

DEMOGRAPHIC VARIABLE	MEDIAN (RANGE)	N(%)/ 95% CI
Median age(yrs)	54 (31-84)	
Sex		
Male		66.5 (58.5, 73.6)
Female		33.5 (26.4, 41.4)
Mode of arrival		
Ambulance		51.2 (43.2, 59.2)
Walk –in		48.8 (40.8, 56.7)
Time of arrival		
Working hours		52.2 (39.9, 55.8)
After hours		47.8 (44.2, 60.1)
Prehospital ECG		33.9 (26.8, 41.9)
Median pain to arrival time(min)	192.5 (10-765)	
Symptomology		
Typical		88.8 (82.7, 93.1)
Atypical		11.2 (6.9, 17.3)

TABLE 1: DEMOGRAPHIC VARIABLES

The majority of patients, 39.8% (95% CI 32.1, 47.4), thrombolysed were in 45 to 54 year age group, with the next highest in 55 to 64 year age group.

A door to needle time of 30 minutes or less was achieved in 33 (20.5%) patients. Table 2 shows the door to needle time of the entire study.

DOOR TO NEEDLE TIME (MINUTES)	%/ N -161
WITHIN 30 MIN	20.5 (33)
31 -60 MIN	37.9 (61)
61 -90 MIN	26.7 (43)
> 90 MIN	14.9 (24)

TABLE 2: DOOR TO NEEDLE TIME IN MINUTES

The median door to needle time was 54 minutes (Range 13 - 553). Table 3 depicts the median

time achieved for each of the intervals studied.

TIME INTERVAL	MEDIAN TIME (RANGE) MINUTES
DOOR TO TRIAGE	6 (0 -157)
TRIAGE TO ECG	2 (0 -245)
DOOR TO ECG	13 (1-402)
ECG TO FIBRINOLYTIC	38 (4 -262)
DOOR TO NEEDLE	**54 (13 -553)**

TABLE 3: MEDIAN TIME ACHIEVED FOR EACH INTERVAL IN MINUTES

Most of the patients, (44.7% {36.9, 52.7}), were seen and given fibrinolysis by medical officers, with 34.8 % (27.5, 42.7) treated by emergency medicine registrars. The rest of the patients were seen and treated by interns (4.4% {1.9, 9.1}), junior community service doctors (14.9% {9.8, 21.6}), and emergency physicians (1.2% {6.2, 14.9}).

The predominant infarct location on ECG was inferior (55.9% {47.9, 63.6}) followed by anterior (38.5% {31.0, 46.5}). A door to ECG time of less than ten minutes was achieved in 41.2% of patients.

The influence of mode of arrival, time of arrival, symptomology, pre-hospital ECG and level of experience of treating doctor on the door to needle time was assessed and are listed in Table 4.

VARIABLE	MEDIAN DOOR TO NEEDLE TIME (RANGE) MINUTES
MODE OF ARRIVAL:	
AMBULANCE	53 (10-553)
WALK IN	50 (10-270)
TIME OF ARRIVAL:	
WORKING HOURS	53 (15-553)
AFTER HOURS	54.5 (13-457)
SYMPTOMOLOGY:	
TYPICAL	53 (13-245)
ATYPICAL	65 (17-553)
PREHOSPITAL ECG:	
YES	50 (15-553)
NO	55 (13-270)
LEVEL OF EXPERIENCE OF DOCTOR:	

MEDICAL OFFICER	50 (17-553)
EMERGENCY MEDICINE REGISTRAR	55 (15-195)

TABLE 4: COMPARISON OF MEDIAN DOOR TO NEEDLE TIMES

The reasons for delays in fibrinolytic therapy were documented by the attending doctor in 70 of the 161 cases (43.5%).

Delays in initiating fibrinolytic therapy were due to:

- The attending doctor seeking advice from the senior doctor in the EC or the Internal Medicine registrar before commencing fibrinolysis. The reason for consulting the senior was not documented.(28.6%)
- Difficulty in interpreting the ECG.(18.6%)
- Patients presenting with atypical symptoms, hence delaying the diagnosis of AMl.(12.9%)
- Patients going into cardiac arrest and requiring cardiopulmonary resuscitation (CPR) before thrombolytic therapy could be commenced.(11.4%)
- Patients presenting with hypertension (systolic blood pressure greater than 180 mmHg) which is a relative contraindication to fibrinolysis. Blood pressure control was needed before administration of fibrinolytics.(7.1%)
- Patients presenting during change of shifts for nurses or doctors were not attended to timeously.(7.1%)
- Delays in obtaining a chest X Ray.(4.3%)
- Fibrinolytic agent not available in the EC. The nurse had to fetch it from the pharmacy.(4.3%)
- Waiting for results of cardiac enzymes, non availability of intensive care beds and equipment (infusion pump) failure accounted for the remainder of the delays.(5.7%)

DISCUSSION

Minimising the time between the onset of an AMI to initiation of a reperfusion strategy is important for improving prognosis and survival.[11,12] In this study less than a third of patients with STEMI received thrombolytics within the prescribed time interval of 30 minutes. The median door to needle time of 54 minutes was higher than that of North American and European hospitals which recorded median door to needle times of less than 45 minutes.[16-19] It was comparable to studies done in the Middle East, Pakistan and India, and one study done by Zed et al in Vancouver.[20-23] However it should be noted that in some of the above studies thrombolysis was given in the intensive care unit (ICU) and not in the EC thereby prolonging door to needle times.

The number of patients thrombolysed within 30 minutes was lower than other contemporary studies, although some of these studies had smaller sample sizes.[16,17,20-23]

The key modifiable factors in this study contributing to prolonged door to needle times were the need for senior review or advice on ECG interpretation. This contributed to almost half of the documented delays in thrombolysis. This delay in diagnosis or ECG interpretation has been identified in other studies as a contributory factor to prolonged door to needle times.[20,21]

In our setting physician experience may also be a contributory factor. Medical Officers working in Cape Town public sector hospitals have variable levels of experience and training. Emergency Medicine is also a relatively new speciality in South Africa, with emergency medicine registrars at different points in their training. Although Medical Officers had shorter median door to needle times than Emergency Medicine (EM) registrars, they had a wider range compared to EM registrars. It has been shown that ECG interpretation and the decision to thrombolyse were

more reliable in more experienced doctors compared to junior doctors.(24) Other reasons for seeking senior advice could not be reliably identified from the case notes.

Patients presenting with atypical symptoms or with undifferentiated chest pain require an ECG to diagnose a STEMI. A door to ECG time of less than 10 minutes has been recommended by the AHA/ACC for all patients with chest pain or symptoms suggestive of ACS.[14] It has been shown that a prolonged door to ECG time leads to an increased risk of adverse clinical outcomes in patients with a STEMI.[25] Our study gave a median door to ECG time of 13 minutes (Range 1 -402 min), with less than 50% of patients having an ECG within 10 minutes.

The three hospitals studied have busy EC's often burdened with overcrowding. Overcrowding can prolong the door to triage sub interval of the door to needle time. The Western Cape employs the South African Triage Scale which has been validated in community health centres and hospitals.[26] It consists of 2 parts. A triage early warning score which involves taking the patients vitals, assessing the patients level of consciousness, mobility and evidence of trauma. The second component is a discriminator list which allows the "triager" to upgrade a patient to a higher colour category. Chest pain is part of this discriminator list and upgrades all chest pain patients to at least an orange category. All orange/red patients should be attended to immediately or within 10 minutes of presentation.[26] The median door to triage time was 6 minutes. The time from triage to first physician contact was not measured in this study due to the poor record keeping of this time in the patient records.

The organisational ability and patient flow characteristics of a hospital also influences door to needle times. Multiple factors that hindered patient flow were identified in this review. Delays in obtaining x rays, patients arriving during nurse and doctor handovers not being attended to timeously, and prolonged door to ECG times all suggest shortcomings in patient flow pathways.

The ECG to commencement of fibrinolytic time interval constituted the longest delay in the door to needle time. Delays identified in this interval are attributed to patient factors and physician factors. A proportion of patients went into cardiac arrest and required cardiopulmonary resuscitation. Others presented with hypertension, which required blood pressure lowering before commencing lysis.

Pre-hospital factors prolonging door to needle times included patient demographics, pre-hospital transport delays and time of presentation to hospital.

The AMI QUEBEC STUDY investigated some of these factors. The study found that older patients had a decreased likelihood of getting timeous reperfusion therapy.[16] Possible reasons for this were that elderly patients had more atypical symptoms and also had increased risk of complications from fibrinolysis.[27,28] Patients presenting after hours had longer door to needle times, probably due to fewer staff being available after hours.[16] In another study the time to fibrinolyisis did not differ much by patient arrival time.[29]

Patient factors such as denial of symptoms and delays in activating EMS also contribute to delayed fibrinolysis.[30]

Pre-hospital transport delays secondary to resource limitations, the distance to hospital with reperfusion capability and traffic delays are other contributory factors to prolonged times to fibrinolysis.[30,31]

Although this study suggested that shorter median door to needle times were achieved in patients who arrived with their own transport, presented during working hours, had typical symptoms of AMI and in those that had a pre-hospital ECG, the sample size was small and it did not have the power to draw definite conclusions.

Most of the quality improvement studies suggest a team based approach to improving the time to reperfusion therapy for MI patients.[16,17,31]

In our setting quality improvement audits need to focus on in-hospital and pre-hospital factors.

Most of the in-hospital reasons for delays in door to needle times identified in our study, could be improved through efficient triaging, early ECG acquisition for at risk patients, EC physician training , the presence of a senior doctor/physician on the floor or being readily available telephonically, knowing your population profile and having a low threshold for investigating those with atypical symptoms.

Other in hospital organisational strategies include close co-operation between hospital administration, emergency centre staff and auxiliary services to enhance patient flow, interpretation of the ECG by the most competent physician in the EC.

The ready availability of fibrinolytic stock in the EC, and rapid nurse driven administration of fibrinolytics once diagnosis has been made should be encouraged.

Keeping a provincial registry of all AMI presentations will aid in data analysis and protocol development.

Pre-hospital quality improvement in our setting should include education of the public to recognise signs and symptoms of AMI, early activation of emergency services or accessing the nearest health facility.

An integrated local EMS chest pain protocol supporting rapid diagnosis and pre-hospital ECG acquisition should be developed.

As earlier quality improvement audits done internationally have shown significant decreases in door to needle times, similar audits need to be done in Cape Town hospitals to improve door to needle time and hence reduce mortality and morbidity from STEMI.[17] Development of a

standardised protocol and checklist for thrombolysis would be beneficial in this regard.

LIMITATIONS:

This was a retrospective chart review and hence relied on the accuracy of data recorded.

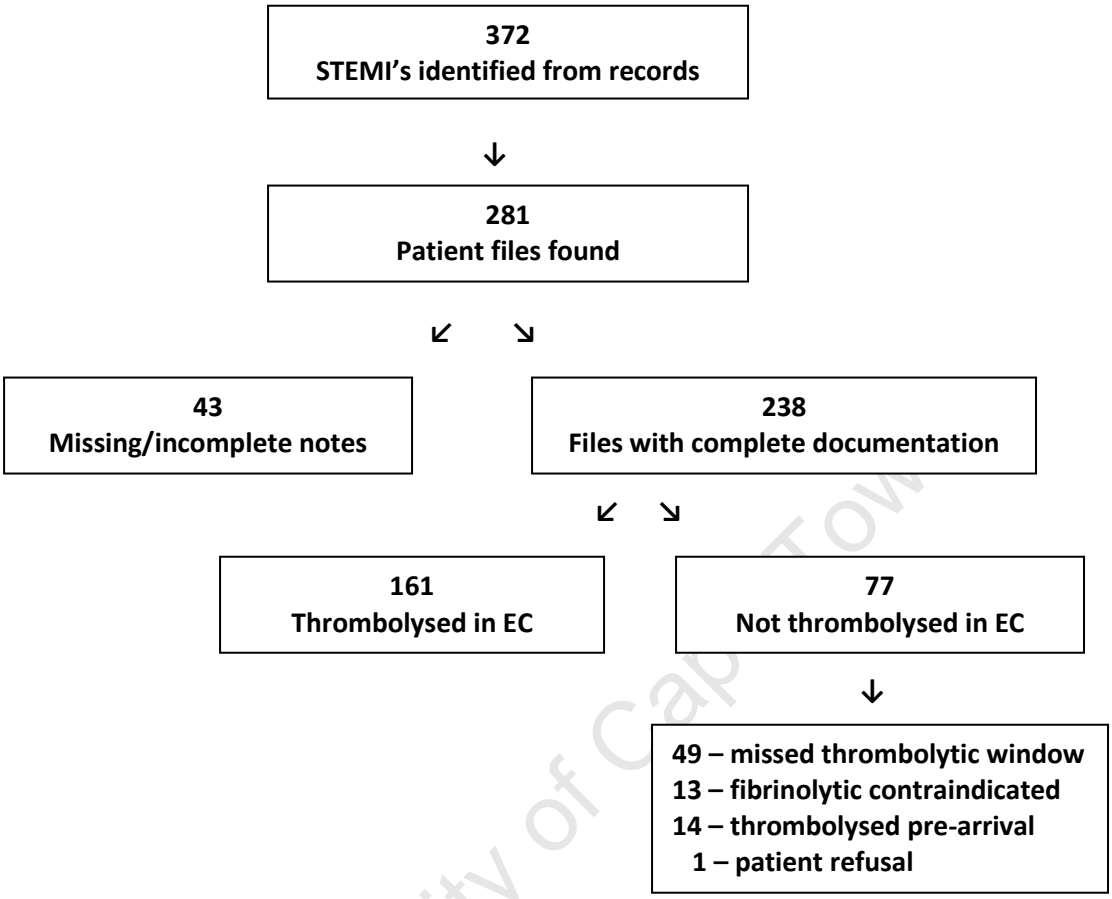
A significant proportion of patient files (24.5%) could not be located from the central records of the hospitals under study. Furthermore 15% of the files located had incomplete documentation or missing notes and could not be included in this study. Times recorded are dependent on the attending doctor or nurse. Fewer than 50% of the files had a reason for delay noted. These could have influenced the accuracy of our findings.

CONCLUSION

Only 20.5% (95% CI 14.71, 27.72) of patients with STEMI met the AHA/ACC guideline of receiving fibrinolytics within a 30 minute door to needle time. This is below international standards of greater than 40%.[22,23]

There are multiple factors contributing to a prolonged door to needle time and need to be addressed by creating an efficient, team based approach to managing these patients. A repeat audit is needed once hospital systems are changed to determine if there is an improvement in the door to needle time.

FIGURE 1: Patient Profile



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PART D: APPENDICES

APPENDIX A: DATA COLLECTION SHEET

APPENDIX B: EMERGENCY MEDICINE JOURNAL INSTRUCTIONS TO AUTHORS

APPENDIX C: ETHICS APPROVAL LETTER

APPENDIX A

DATA COLLECTION SHEET

Patient Number: _____
DEMOGRAPHICS:
Age: _____ Sex: _____

AMBULANCE: Y / N
FORWARD ALERT BY PREHOSPITAL STAFF: Y/N PREHOSPITAL ECG: Y/N

LEVEL OF EXPERIENCE OF TREATING PHYSICIAN: INTERN, CSO, MO, REGISTRAR, CONSULTANT

CLINICAL:
Time of Onset of Pain: _____ Time of Day: W/H, A/H
Anatomical localization: _____
Typical Symptoms Y / N
If no describe: _____

	DURATION	COMMENT
TIME OF ARRIVAL		
TIME FROM ARRIVAL TO TRIAGE		
TIME FROM TRIAGE TO ECG		
TIME FROM ECG TO ACTUAL ADMINISTRATION OF FIBRINOLYTIC		
TOTAL DOOR TO NEEDLE TIME		

KEY: Y – YES
N – NO
CSO – COMMUNITY SERVICE OFFICER
MO – MEDICAL OFFICER
W/H – WORKING HOURS (08:00 – 17:00)
A/H – AFTER HOURS (17:01 – 07:59)
COMMENT: IDENTIFY DELAY IN DOOR TO NEEDLE TIME IF ANY

APPENDIX B

EMERGENCY MEDICINE JOURNAL INSTRUCTION TO AUTHORS

Original articles

For full length accounts of original research, often shorter articles are better. Additional information may be placed on the web site as a data supplement.

Word count: up to 3000 words.

Illustrations and tables: up to 6.

References:25.

Peer review: all papers are reviewed by at least one reviewer.

If there is uncertainty about acceptance after review, papers are reviewed by the editors.

All material submitted is assumed to be submitted exclusively to the journal unless the contrary is stated. Submissions may be returned to the author for amendment if presented in the incorrect format.

The title page **must** contain the following information:

1. The title.

2. The name, postal address, e--mail, telephone and fax numbers of the corresponding author.

3. The full names, institutions, city and country of all co---authors.

4. Up to five keywords or phrases suitable for use in an index (it is recommended to use MeSH terms).

5. Word count --- excluding title page, abstract, references, figures and tables.

The manuscript format must be presented in the following order:

1. Title page

2. Abstract (or summary for case reports)

3. Main text (tables should be in the same format as your article and embedded into the document where the table should be cited; images must be uploaded as separate files)

4. Acknowledgments, Competing interests, Funding

5. Copyright licence statement

6. References

7. Appendices

Do not use the automatic formatting features of your word processor such as endnotes, footnotes, headers, footers, boxes etc.

Provide appropriate headings and subheadings as in the journal.

We use the following hierarchy: **BOLD CAPS, bold lower case**, Plain Text, Italics. Cite illustrations in numerical order (fig 1, fig 2 etc) as they are first mentioned in the text. Tables should be in the same format as your article and embedded into the document where the table should be cited.

Images **must not** be embedded in the text file but submitted as individual files.

Statistics: Statistical analyses must explain the methods used.

Style: Abbreviations and symbols must be standard and SI units used throughout except for blood pressure values which are reported in mm Hg. Acronyms should be used sparingly and fully explained when first used.

Figures/illustrations: Black and white images should be saved and supplied as GIF, TIFF, EPS or JPEG files, at a minimum resolution of 300 dpi and an image size of 9 cm across for single column format and 18.5 cm for double column format. Colour images should be saved and supplied as GIF, TIFF, EPS or JPEG files, to a minimum resolution of 600 dpi at an image size of 9 cm across for single column format and 18.5 cm for double column format. Images should be

mentioned in the text and figure legends should be listed at the end of the manuscript. During submission, when you upload the figure files please label them as Figure 1, Figure 2, etc.
The file label will not appear in the pdf but the order in which the figures uploaded should be sufficient to link them to the correct figure legend for identification.
Histograms should be presented in a simple, two---dimensional format, with no background grid.
Tables: Tables should be submitted in the same format as your article and embedded into the document where the table should be cited. Tables should be self---explanatory and the data they contain must not be duplicated in the text or figures.

References: Authors are responsible for the accuracy of references cited: these should be checked against the original documents before the paper is submitted. It is vital that the references are styled correctly so that they may be hyperlinked.
In the text: References must be numbered sequentially as they appear in the text. References cited in figures or tables (or in their legends and footnotes) should be numbered according to the place in the text where that table or figure is first cited.
Reference numbers in the text must be given in square brackets immediately after punctuation (with no word spacing) --- for example, [6] not [6]. Where more than one reference is cited, separate by a comma --- for example, [1, 4, 39]. For sequences of consecutive numbers, give the first and last number of the sequence separated by a hyphen --- for example, [22---25].
References provided in this format are translated during the production process to superscript type, which act as hyperlinks from the text to the quoted references in electronic forms of the article. In the reference list: References must be double spaced (numbered consecutively in the order in which they are mentioned in the text) in the [slightly modified] Vancouver style.

Only papers published or in press should be included in the reference list. (Personal communications or unpublished data must be cited in parentheses in the text with the name(s) of the source(s) and the year. Authors should get permission from the source to cite unpublished data.) Punctuation of references must follow the [slightly modified] Vancouver style: 12 Surname AB, Surname CD. Article title. Journal abbreviation. Year;Vol:Start page---End page. Use one space only between words up to the year and then no spaces. The journal title should be in italic and abbreviated according to the style of Medline. If the journal is not listed in Medline then it should be written out in full.

APPENDIX C
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UNIVERSITY OF CAPE TOWN

Health Sciences Faculty
Research Ethics Committee
Room E52-24 Groote Schuur Hospital Old Main Building
Observatory 7925
Telephone [021] 406 6338 • **Facsimile** [021] 406 6411
e-mail: sumayah.ariefdien@uct.ac.za

22 December 2009

REC REF: 535/2009

Dr R Maharaj
Emergency Medicine

Dear Dr Maharaj

PROJECT TITLE: A MULTI CENTRE REVIEW OF DOOR TO NEEDLE TIME FOR ADMINISTRATION OF FIBRINOLYTICS IN ACUTE MYOCARDIAL INFARCTION IN EMERGENCY CENTRES IN THE WESTERN CAPE METROPOLE

Thank you for submitting your study to the Research Ethics Committee for review

It is a pleasure to inform you that the Ethics Committee has **formally approved** the above-mentioned study.

Approval is granted for one year till the 30th December 2010.

Please submit an annual progress report if the research continues beyond the expiry date. Please submit a brief summary of findings if you complete the study within the approval period so that we can close our file.

Please note that the ongoing ethical conduct of the study remains the responsibility of the principal investigator.

Please quote the REC. REF in all your correspondence.

Yours sincerely

pp **PROFESSOR M BLOCKMAN**
CHAIRPERSON, HSF HUMAN ETHICS

Federal Wide Assurance Number: FWA00001637.
Institutional Review Board (IRB) number: IRB00001938

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