A cross-sectional study of ECG patterns and outcomes of patients thrombolysed for ST-elevation myocardial infarction at a district, public Cape Town hospital

by

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Declaration

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Abbreviations

AMI: acute myocardial infarction

IHD: ischaemic heart diseases

ACS: acute coronary syndrome

USA: United States of America

ECG: electrocardiogram

STEMI: ST-elevation myocardial infarction

NSTE-ACS: non-ST-elevation acute coronary syndrome

NSTEMI: non-ST-elevation myocardial infarction

EC: emergency centre

AHA/ ACC: American Heart Association/ American College of Cardiology

PCI: percutaneous coronary intervention

SA: South Africa

TIMI: thrombolysis in myocardial Infarction

SD: standard deviation

WHO: World Health Organization

PART A: LITERATURE REVIEW

Background

Globally, ST-segment elevation myocardial infarction (STEMI) is a serious complication of coronary heart disease, with an estimated annual incidence affecting seven million people and a major cause of death worldwide.[1] In the United States of America (USA), approximately 500,000 episodes of acute myocardial infarction (including non-STEMI and STEMI) occur each year; approximately 600 men and 200 women in every 100,000 population suffer from a myocardial infarction every year.[1-3] Nonetheless, the overall mortality rate has been decreasing in the USA: the 30-day mortality rate among patients with myocardial infarction in 2010 ranged only from 2.5 to 10%. Elsewhere, the World Health Organization (WHO) estimates that 17.5 million people died from some form of coronary heart disease (including infarction) in 2012, which represented 31% of all deaths globally. [4] However, most of these data are collected from high-income countries and substantially less is known about coronary heart disease in low- to middle-income countries, specifically those in Africa.

Aim

It was the aim of this critical review to provide an overview of the existing literature surrounding the definition, diagnosis, management and outcomes of STEMI and to interpret this within a South African, middle-income context.

Objectives

- To describe the definition and diagnosis of STEMI
- To describe the management of STEMI in terms of percutaneous coronary intervention and thrombolysis
- To describe the reported outcomes following STEMI
- To contextualise the findings from the above objectives within a South African, middle-income setting.

Literature search strategy

The University of Cape Town Health Sciences Library website was used to perform searches to obtain the original articles reviewed in this study. PubMed and Google Scholar were primarily used to perform searches using the following MESH terms in various combinations: cardiovascular disease, coronary disease, coronary artery disease, myocardial ischaemia/ ischaemia, unstable angina, myocardial infarction, non-ST-elevation myocardial infarction, ST-elevation myocardial infarction, treatment, outcome, diagnosis, South Africa, acute, and emergency. A snowball strategy was then used whereby publications cited in the articles included from the initial search that directly addressed the review aim were also accessed and assessed for inclusion in the review.

Inclusion criteria:

- Publication date: January 2000 – March 2017
- Language: English, including studies translated and published

Exclusion criteria:

- Studies outside of the stipulated timeframe
- Studies where the full text was not accessible
- Studies that did not directly address the review objectives
- Language other than English

Quality criteria

Titles and abstracts were initially screened for relevance to the review aim. Those deemed to have low relevance or poor external validity were excluded. High-quality evidence, including systematic reviews, were sought to address the aim and objectives. Although critical reviews do not typically require a formal assessment of quality, included studies were appraised against a checklist from the Oxford Centre for Evidence-Based Medicine (http://www.cebm.net/critical-appraisal/) to provide at least some indication of the strength of each study's contribution. A representation in tabular form of appraised papers is not required for the MMed and was therefore omitted. Very little data were available that directly addressed some parts of the aim and objectives (particularly with regard to coronary heart disease and STEMI in low- and middle-income settings) and therefore criteria were applied less stringently here.

Terminology

Coronary artery disease (CAD): accounts for more than 30% of death in the West and presents acutely as acute coronary syndrome. Coronary artery disease is also known as coronary heart disease (CHD).[1-3,5,6]

Acute coronary syndrome (ACS): a spectrum of clinical presentation ranging from unstable angina to non-ST-segment elevation myocardial infarction and ST-segment myocardial infarction. Acute coronary syndrome refers to ischaemic symptoms resulting from acute coronary occlusion. [1-3,5,6]

Myocardial infarction: clinical evidence of acute myocardial ischaemia in the context of myocardial necrosis with rise and/or fall of cardiac troponins. Myocardial ischaemia is the initial step of the development of myocardial infarction and is due to oxygen supply and demand imbalance. The term 'myocardial infarction' should be used in the context of myocardial necrosis associated with the clinical presentation of myocardial ischaemia.[1-3,5,6]

ST-elevation myocardial infarction (STEMI): a presentation of clinical symptoms consistent with an ACS combined with ST-segment elevation on electrocardiogram (ECG).[1-3,5,6]

Non-ST-elevation myocardial infarction (NSTEMI): characterised by an elevation of serum troponin levels in the absence of ST-segment elevation. [1-3,5,6]

Non-ST-elevation acute coronary syndrome (NSTE-ACS): refers to any ACS that does not show ST-segment elevation. It includes NSTEMI and unstable angina and is characterised by ST-segment depression or transient ST-segment elevation which may become normal. [1-3,5,6]

Unstable angina: characterised by typical ischaemic symptoms, with or without ECG abnormalities and normal cardiac biomarkers and is due to underlying coronary artery disease. [1-3,5,6]

Literature review

Introduction

Although initially characterised by a low prevalence of non-communicable disease, sub-Saharan Africa has seen an increase of coronary heart disease over the last few decades.[4,7] The WHO has predicted that non-communicable diseases will exceed communicable or infectious diseases as the leading cause of death in Africa by 2030.[4] However, compared to other causes of heart disease, the burden of coronary heart disease remains low in African descendants.[7-14] Post-apartheid South Africa, with its emerging economy and urbanisation, has seen an increase in mortality and morbidity associated with coronary heart disease and its complications – such as myocardial infarction.[7-14] South African statistics indicate an annual mortality attributable to coronary heart disease in Indian and white populations as 207 and 163 deaths per 100,000 population, respectively.[14] However, in the African population the rate was only 13 deaths per 100,000 population.[14] The prevalence of acute myocardial infarction in Africa is estimated to be between 0.1 to 4%.[15] However, an accurate prevalence of acute myocardial infarction in sub-Saharan Africa has not been well established despite growing recognition of the increasing burden of cardiovascular disease in low- and middle-income countries.[15] There is insufficient population-based data describing the prevalence of acute myocardial ischaemia in sub-Saharan Africa using common diagnostic criteria. The lack of surveillance data and registries as well as the lack of diagnostic and interventional capacities has made the estimation of the magnitude of coronary heart diseases in Africa challenging.[16,17] The paucity of epidemiological data as well as the absence of specific tests for coronary heart disease has also contributed to the failure to accurately determine the true prevalence of STEMI in Africa.[16,17]

Most sources citing prevalence and incidence locally rely on estimated numbers. This is mainly due to a lack of consistent registry data.[16-19] As a result, the true burden of coronary heart disease is unknown. The ACCESS study conducted in 29 South African health facilities across all provinces from 2007-2008 was the first local study of its kind to establish registries and document the demographics and management strategies in patients admitted to hospital with a diagnosis of ACS.[20] Out of 642 patients enrolled in the study, 615 participants had a confirmed diagnosis of ACS: 41% had a diagnosis of STEMI at discharge versus 59% with NSTE-ACS (32% NSTEMI and 27% unstable angina). This study also revealed that the vast majority of South African patients with STEMI were managed at a facility without percutaneous coronary intervention (PCI) capabilities and by a non-cardiologist to boot – South Africa has only 62 cardiac catheterisation laboratories spread out between a few

tertiary public centres and selected private hospitals situated mainly in major urban centres. [21] What is interesting is that ACCESS was not a population representative sample. Study participants mostly had access to private health care, leaving the biggest cohort of South African patients with STEMI, namely, those from the public sector, largely excluded. [20] In a nutshell, this means that access to PCI capable facilities locally is likely more dreadful than what the study findings suggested.

Broad definition of STEMI

ACS is a broad term that refers to a cohort of clinical diseases resulting from acute myocardial ischaemia. [1-6] The term myocardial infarction refers to measurable evidence of myocardial necrosis (usually by means of a troponin rise), in the setting of a clinical presentation consistent with myocardial ischaemia.[1-6] It is an important concept to grasp when defining STEMI that not all ACS is associated with infarction and that not all infarction is associated with STEMI (Figure 1).

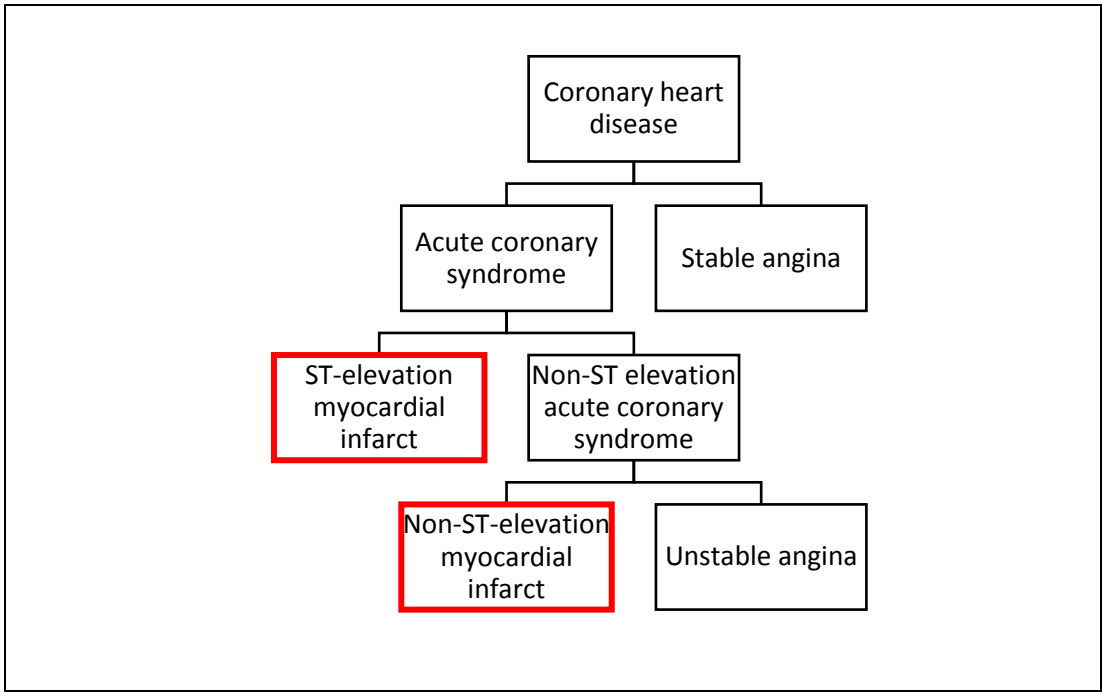

Figure 1. A simplified representation of the spectrum of coronary heart disease. Boxes in black indicate an association with ischaemia and boxes in red indicate ischaemia that has progressed to infarction

It is further important to note that not all myocardial infarction stems primarily from coronary heart disease. The cause of infarction may vary and currently acute myocardial infarction is classified into five different types (Box 1).[5,6,22,23] From an emergency centre (EC) perspective, we were mainly concerned with types 1 through 3, although the others may present at times.

Box 1. Classification of acute myocardial infarction[5,6,22,23]

Type 1 refers to spontaneous myocardial infarction. It is characterised by atherosclerotic plaque rupture, ulceration, erosion, or dissection with resulting intraluminal thrombus in one or more of the coronary arteries leading to decreased myocardial blood flow or distal platelet emboli with ensuing myocyte necrosis.

Type 2 refers to myocardial infarction due to ischaemic imbalance. It is caused by conditions other than coronary artery diseases and leads to imbalances between myocardial oxygen supply and/or demand e.g., coronary endothelial dysfunction, coronary artery spasm, coronary embolism, tachy-/ brady-arrhythmias, anaemia, respiratory failure, hypotension, and hypertension with or without left ventricular hypertrophy.

Type 3 is defined as myocardial infarction resulting in death before cardiac markers are available or collected. It is characterised by cardiac death with symptoms suggestive of myocardial ischaemia and presumed new ischaemic ECG changes or new left bundle branch block (LBBB), but death occurs before collection of blood samples, before rise of cardiac markers or cardiac markers were not obtained.

Type 4a refers to myocardial infarction related to percutaneous coronary interventions (complex specific criteria).

Type 4b is myocardial infarction related to stent thrombosis (complex specific criteria).

Type 5 is defined as myocardial infarction observed in patients with a coronary artery bypass graft (complex specific criteria).

A very specific acute myocardial infarction, STEMI, is characterised through clinical symptoms consistent with ACS in combination with specific ST-segment changes from baseline (bar a few exceptions) on the 12-lead ECG.[1-6,22,23] The reason STEMI has been identified separately from NSTEMI relates to the variation in treatment and outcomes between the two. ST-elevation myocardial infarction is most often caused by a total occlusion of a coronary artery that necessitates an earlier, more acute approach, compared to NSTEMI.[2-6,22,23] Outcomes

tend to be worse if not addressed in a timely fashion. The diagnosis of STEMI is rarely delayed for cardiac enzymes, but rather is made based on the 12-lead ECG findings. Interpretation of the ECG is an essential skill in the emergency centre for this very reason.

ST-elevation, cardiac anatomical regions and outcomes

ST-elevation myocardial infarction has been the subject of many studies. One area of our study has been to define the anatomical areas associated with different coronary vessels affected and its downstream complications and outcomes.

Inferior myocardial infarction accounts for more than half of all myocardial infarction presentations. It is characterised by ST-segment elevation in inferior leads (II, III and aVF) with reciprocal changes in leads I and aVL. It is caused by the occlusion of the right coronary artery distal to the right ventricle and has generally a more favourable prognosis than anterior myocardial infarction. Inferior myocardial infarction can be associated with concomitant right ventricular infarction and right precordial leads (V3R and V4R) are required to diagnose right ventricular infarction. Inferior myocardial infarction with right ventricular myocardial involvement is characterised by ST-segment elevation in inferior leads (II, III and aVF), in V1 and V4R. It is due to right coronary artery occlusion proximal to the right ventricle, represents 40% of all inferior myocardial infarction and is associated with a high mortality. [1-6,22-25]

Inferior STEMI can also be due to a posterior infarction. Acute myocardial infarction of the infero-basal portion of the heart is often caused by the occlusion of the right coronary artery as well as the left circumflex artery. The right coronary artery, through its posterior descending branches, perfuses the posterior wall of the heart. It is important to note that the left circumflex artery also supplies blood to the posterior wall. Acute posterior myocardial infarction occurs in 15-20% of STEMIs. It should be suspected in the presence of ST-depression in leads V1 through V3 particularly if the terminal T-wave is positive (ST-elevation equivalent) and can be confirmed by obtaining leads V7 through V9 which shows ST-elevation >0.1 mv (1mm) in these leads (V7-V9). Therefore, tall R waves, ST-segment depression and upright T waves are characteristics of posterior wall injury. This type of infarction leads to worse outcomes due to an increasing area of myocardium at risk. The combination of posterior myocardial infarction with ST-elevation in either the inferior or anterior regions has been shown to be associated with a more extensive infarct. A 15-lead ECG is paramount in

the diagnosis of posterior myocardial infarct and increases its diagnostic sensitivity to nearly 90%. [24-25]

Septal, anterior and lateral myocardial infarctions are due to an occlusion of the left anterior descending artery. The ECG diagnostic features of lateral myocardial infarction include ST-segment elevation in leads V5, V6, I and aVL, whilst septal myocardial infarction is characterised by ST-segment elevation in leads V1 and V2. [1-6,22-23] ST-elevation in leads V3 and V4 are features of an anterior myocardial infarction. Anterior myocardial infarction has been shown to carry the worst prognosis of all infarctions mainly due to the larger size of the infarct. Other presentations of anterior ischaemia include left mainstem coronary artery occlusion, De Winter and Wellens syndrome. [1-6,22-26]

ST-elevation in leads aVR and/ or V1 combined with ST-depression of more than 0.1 mv (1mm) in the inferior and lateral leads are suggestive of ischaemia caused by multi-vessel or left mainstem coronary artery obstruction. The ratio of ST-segment elevation (aVR/ V1) is an important clue in differentiating a left mainstem coronary artery occlusion from a left anterior descending artery occlusion. Although an acute left mainstem coronary artery occlusion is rare, it is a dangerous condition that needs urgent attention and management as the left mainstem coronary artery perfuses a large part of the anterior wall of the heart. Occlusion here may lead to life-threatening dysrhythmia and cardiogenic shock. However, the presence of collateral circulation may be the reason it is rarely observed. ST-elevation in the aVR lead is an excellent predictor of left mainstem coronary artery occlusion with nearly an 80% sensitivity and specificity. Patients with left mainstem coronary artery occlusion are characterised by a greater amplitude of ST-elevation in aVR than V1. Moreover, aVR abnormalities are associated with increased mortality and predict mortality with around a 75% specificity and sensitivity. [22-26]

The De Winter's wave is a very specific presentation of anterior myocardial infarction. It is also referred to as an anterior ST-elevation myocardial infarction equivalent. Its diagnostic features include ST-segment depression coupled with a peaked T, tall, symmetrical, narrow wave in the precordial leads. However, ST-elevation (0.5-1mm) in the aVR lead may also be observed. De Winter's wave presentation accounts for 2% of all left anterior descending artery occlusions and is sometimes considered as a subtype of the hyper-acute T-wave. It is suggestive of an acute high grade left mainstem coronary artery occlusion as opposed to the sub-acute occlusion of Wellens syndrome (see below) and characterises an unstable lesion that requires urgent reperfusion therapy prior to deterioration and progression to a STEMI. [27-29]

Wellens' syndrome is characterised by deeply inverted or biphasic T waves in V2-V3 and is suggestive of critical stenosis of the left anterior descending artery. It is diagnosed in the context of resolved angina-type chest pain associated with characteristic ECG changes and a normal to minimal leak of cardiac biomarkers. It carries a poor prognosis where treated medically and usually requires catheter-based intervention. Patients with a Wellens pattern are at an increased risk for left ventricular dysfunction. Performing a cardiac stress test when present is inappropriate due to a greater risk of STEMI. [27-30]

The diagnosis of acute myocardial infarction in the presence of left bundle branch block is difficult to establish but clinical algorithms have been designed to address the issue. New left bundle branch block alone is no longer an indicator for activating the cardiac catheterisation laboratory. However, percutaneous coronary intervention (PCI) for left bundle branch block should be considered in circumstances such as when an unstable patient presents with hypotension, pulmonary oedema or electrical instability, or the Sgarbossa and Smith-modified Sgarbossa criteria are satisfied. The original Sgarbossa criteria had a sensitivity of 52% for identifying STEMI in the presence of left bundle branch block. [31-33] Smith et al. replaced the third Sgarbossa criteria with the discordant (ST/ T-wave) ratio of more than 25%, which increased the sensitivity of the criteria to 91%.[34]

It is important to note that other conditions may present with ST-segment elevation and these need immediate recognition to avoid unnecessary treatment. These conditions are referred to as STEMI mimics and include left ventricular hypertrophy with secondary repolarisation pattern, Prinzmetal's angina, aneurysm, benign early repolarisation, acute pericarditis, pulmonary embolism and acute aortic dissection. Treating some of these conditions with thrombolytic therapy may result in serious complications and increase morbidity and mortality. [35]

Diagnosis of STEMI

Patient history, physical examination, 12-lead ECG and cardiac biomarkers are key components in the diagnosis and management of STEMI.

History and physical examination

The chief complaint of ACS is crushing central chest pain. Prolonged pain is documented in 80% of patients while new or crescendo angina is observed in 20% of patients. The typical

clinical presentation of ACS is retrosternal pressure or heaviness that radiates to the left arm, neck or jaw. [1-6,22,23]

However, atypical presentations are not uncommon and may include epigastric pain, indigestion, stabbing chest pain with some pleuritic features or increasing breathlessness. Atypical symptoms are more common in older patients (older than 75 years), in women and in patients with diabetes, chronic renal failure or dementia. [1-6,22,23]

Physical examination

The physical examination is chiefly aimed at ruling out non-cardiac causes of chest pain such as pulmonary embolism, aortic dissection, pericarditis, valvular heart disease and pulmonary diseases e.g., pneumothorax, pneumonia or pleural effusion.

The 12-lead ECG

Ideally, the 12-lead ECG should be performed and interpreted by an experienced provider within ten minutes from first medical contact. [1]

ST-segment elevation in acute myocardial infarction is measured at the J point (junction of the ST segment and QRS complex) in two contiguous leads. Measurements should be greater than 0.25 mv (2.5mm) in men younger than 40 years, greater than 0.2 mv (2mm) in men older than 40 years, greater than 0.15 mv (1.5mm) in women in leads V2-V3, and/ or greater than 0.1 mv (1mm) in other contiguous chest or limb leads (in the absence of left ventricular hypertrophy or left bundle branch block) to be diagnostic. [1-6,22,23]

The ECG is an important diagnostic tool for the initial triage of undifferentiated chest pain. It is very specific for STEMI but not very sensitive meaning that is very good to make the diagnosis of myocardial infarction but not so good at ruling it out. The sensitivity and specificity of a single ECG for acute myocardial infarction is estimated to be around 60% and 90%, respectively. [17] The predictive value of the ECG is very variable and depends on the pre-test probability of coronary disease in the patient. Moreover, the number and magnitude of ECG abnormalities also influence its specificity and sensitivity. [1-6,22,23] Therefore, non-diagnostic and even normal ECGs do not exclude the diagnosis of acute myocardial infarction. Roughly 20% of patients diagnosed with acute myocardial infarction had an initial non-diagnostic ECG. [1] Serial ECGs should be obtained in situations where the initial ECG is non-diagnostic but the clinical presentation is highly in favour of the diagnosis of ACS. It is also important to note that in the setting of on-going or recurrent chest pain, serial ECGs have

proven to decrease false negatives and false positives and therefore help to prevent unnecessary treatment or under-treatment. [1-6,22,23]

Although coronary angiography is the reference standard for the diagnosis of infarction, ECG remains the standard diagnostic tool that enables the identification of the presence, approximate location and extent of acute myocardial ischaemia and injury. Measurement of the absolute magnitude of ST-segment elevation or the width of QRS complexes is key in the ECG assessment of STEMI. [1-6,22,23]

As described earlier, different anatomical cardiac regions are associated with different outcomes and in some cases, slightly different treatment strategies. Table 1 describes the various STEMI regions and their ECG findings.

Table 1. Various STEMI regions, the main leads affected and their ECG findings

Location	**Leads affected**	**ST segment**
Anterior wall MI	V1 through V4 II, III, aVF	Elevation Depression
Lateral MI	I, aVL, V5 and V6	Elevation
Inferior wall MI	II, III and aVF I, aVL, V5 and V6	Elevation Depression
Right ventricular MI	V4R II, III, aVF	Elevation Elevation
Posterior wall MI	V8 and V9 V1 through V3	Elevation Depression

A good strategy after obtaining a 12-lead ECG is to rapidly classify patients into one of four categories as follows: those with evidence of ST-segment elevation on initial ECG; those without ST-segment elevation but who are at high risk based on ECG findings, haemodynamic instability, or history; those who have no objective evidence of ACS but have symptoms that warrant evaluation; and those who have an obvious non-cardiac cause for their symptoms. These categories allow the clinician to rapidly plan further management.

Cardiac biomarkers

High sensitivity troponins improve the rapid rule out of myocardial infarction and confirmation of NSTEMI. [1-6,22,23] The diagnosis of STEMI is made in the presence of specific clinical settings with appropriate ECG changes and is not based on troponins. However, cardiac biomarkers are required to differentiate NSTEMI from unstable angina in NSTE-ACS). [1-6,22-24] As such, a discussion of cardiac biomarkers falls beyond the scope of this review.

The acute management of STEMI

The optimal care of STEMI patients comprises provision of the fastest, safest and most effective method of reperfusion available within the boundaries of the resources available to a specific setting. The cornerstone of management of STEMI remains to be early reperfusion of the ischaemic myocytes. Treatment is aimed at establishing early patency of an infarcted area that is critical in determining short- and long-term outcomes. Two modalities for reperfusion therapy have been described and include percutaneous coronary intervention (mechanical revascularisation) and thrombolysis (pharmacological revascularisation). [1-6]

Percutaneous coronary interventions

Myocardial revascularisation is the mainstay for the management of STEMI and is indicated when the expected benefits such as survival or health outcomes (symptoms, functional status and/ or quality of life) outweigh the expected risks. Therefore, the main goal of coronary angiography with revascularisation includes relief of symptoms and improvement of short- and long-term outcomes. [1-6,22,23]

Primary PCI is defined as PCI provided to patients without previous or concomitant administration of thrombolytic therapy. Patients with isolated proximal left anterior descending artery disease, multi-vessel disease and left mainstem coronary artery occlusion usually require primary PCI as the management of choice. Primary PCI should ideally be offered to STEMI patients at a PCI-capable facility within 60 minutes of presentation to the EC.[1-6,22,23] However, where delays are anticipated to be more than 120 minutes from the time of presentation, thrombolysis should be administered.[1-6,22,23] Percutaneous coronary intervention and thrombolysis are equivalent in efficacy for patients presenting within three hours of onset of ischaemic symptoms.[5,6,22,23] Immediate transfer to a PCI-capable hospital for primary PCI is the recommended triage strategy for patients with STEMI who present at a non-PCI capable hospital with a first medical contact to device time goal of 120 minutes or

less.[1-6,22,23] The major benefits of reperfusion therapy as related to survival are time-dependent. That said, the loss of efficacy caused by a delay tends to be more pronounced with thrombolysis than with PCI. [1-6,22,23]

Delayed percutaneous coronary intervention

The persistence of STEMI despite thrombolysis (i.e., failed thrombolysis) and/ or persistent ischaemic chest pain post-thrombolytic administration, warrant a rapid transfer to a PCI centre for rescue PCI. The administration of a second dose of thrombolysis has not shown any benefit, but increases the risk of mortality and morbidity.[22-23] Other patients that may benefit from delayed PCI include those with successful reperfusion, or post-thrombolysis patients who are referred within 24 hours to a cardiac catheterisation laboratory for angiography and revascularisation.[22-23] It is important to note that similar benefits were observed in patients who presented between 12 and 24 hours from symptom onset and in some cases up to 60 hours from symptom onset.[22-23] There are no proven benefits of referring patients without on-going chest pain or inducible ischaemia who present beyond 72 hours for delayed PCI.[5,6,22,23]

Several randomised controlled trials and meta-analyses have shown benefit when transferring patients with STEMI from a non-PCI hospital to a PCI-capable facility for primary PCI. These benefits include effective restoration of vessel patency, reduced re-occlusion, improved left ventricular function, better clinical outcomes as well as reduced mortality. In the Danish Multicentre Randomised Study on thrombolytic therapy versus Acute coronary angioplasty in Acute Myocardial (DANAMI-2) study, timely transfer of patients with STEMI from non- PCI hospital to a PCI-capable facility for primary PCI resulted in the improvement of outcomes such as reduction in re-infarction rate. The average first door-to-device time was around 110 minutes. [36,37] The Acute Coronary Treatment and Interventions Registry Outcomes Network (ACTION) study looked at 14,821 patients and found that the median door-in/ door-out times were 68 minutes; only 11% of patients achieved a door-in/ door-out time of less than 30 minutes.[38]

On the flipside, prolonged transfer times to a PCI-capable centre were associated with worse prognosis. The National Registry of Myocardial Infarction (NRMI)-2, -3, -4, -5 showed that delays during transfer of patients with STEMI for primary PCI exceeding 120 minutes from first medical contact were associated with negation of the survival advantage of PCI over thrombolysis. In this study, delays beyond 120 minutes occurred in almost 50% of the patients with STEMI recruited in the analysis.[39] McNamara RL and colleagues looked at the

management of 29,222 patients with STEMI in the US National Registry of Myocardial Infarction databases 3 and 4 and concluded that prolonged door to balloon times resulted in higher mortality ranging from 3% mortality for times less than 90 minutes to 7.4% mortality for times more than 150 minutes.[40] The Australia registry data for STEMI revealed that only 36.5% of cases achieved a door to device time of less than 90 minutes. The median hospital door to angioplasty door and angioplasty door to angioplasty device time was 102 minutes. [41-42]

As described, even high-income countries such as the USA, Australia and those within the European Union failed to achieve the evidence-based goals set for PCI. The provision of primary PCI within an evidence-based timeframe is challenging and difficult to achieve and varies worldwide. Ideally, a rapid assessment of patients with STEMI at a non-PCI capable facility should include time from onset of symptoms, risk of complications related to STEMI, risk of bleeding with thrombolysis, the presence of shock or severe heart failure and time required for transportation of the STEMI patients to a PCI-capable facility.[22-23] Although PCI remains the treatment of choice for STEMI and should be offered to all patients with STEMI if it can be performed effectively with a door-to-balloon time of less than 90 minutes by a skilled provider at a skilled PCI centre, this is simply not achievable in much of sub-Saharan Africa.[16,21]

Thrombolytic therapy

The provision of thrombolytic therapy has been shown to improve survival in patients presenting with STEMI and is also more widely available compared to PCI. It is considered an appropriate alternative reperfusion therapy for patients presenting with STEMI to non-PCI capable facilities where delay to a PCI capable facility is anticipated to be more than 120 minutes, or if a PCI capable facility is simply not available. The decision to administer a thrombolytic agent to a patient with STEMI requires consideration of important factors such as location of the myocardial infarction, patient age, time of symptom onset to time of arrival at EC, time required to complete transfer to and performing of primary PCI (where available), and the capability of the primary PCI cardiologist and hospital.[1-6,22,23] Randomised controlled trials on thrombolytic therapy have demonstrated the benefits of early initiation of thrombolytic therapy after onset of STEMI. It has also been shown that myocardial infarction can be aborted completely and mortality significantly reduced if thrombolysis is provided within the first two hours, and particularly within the first hour. [1-6,22,23] Thrombolytic therapy has also shown benefit where PCI has been delayed for other, varied reasons.[1]

The maximum benefit of thrombolysis is seen when administered within 30 minutes of arrival at the EC (or first medical contact).[36,43-45] It is not appropriate in STEMI patients with contra-indications to the thrombolytic agent or for those who are in cardiogenic shock. In these circumstances, PCI is considered superior to thrombolytic therapy as it also improves survival rates and enhances other important outcomes. Unfortunately, as already stated, PCI is not widely available. [1-6,22,23]

In South Africa, a number of studies have considered the presentation of STEMI to public hospitals. Chetty et al. documented the incidence and management of patients with STEMI attending a public district hospital in KwaZulu-Natal, South Africa. [15] Out of 55 patients that presented with STEMI, 78% received thrombolysis, whilst 7% had contra-indications and 13% presented outside the effective thrombolysis window and did not receive thrombolysis. The investigators did not expand on how the non-thrombolysed cohort was subsequently managed. The study site achieved a mean door-to-needle time of 43 minutes. [15] Meel et al. considered similar objectives in their study conducted at a public tertiary hospital in Gauteng, South Africa. [46] Although the hospital did have a cardiology service, primary PCI was not available at the time. Out of 100 consecutive patients that presented with STEMI without a contra-indication to thrombolysis, only 37% received thrombolysis. Significant delays in presentation and transfer between healthcare facilities were mainly responsible for the poor results. Transfer from primary care and private facilities to the tertiary hospital took a median of eight hours. In-hospital delays contributed to a lesser extent, but it is worth mentioning as these are potentially modifiable variables. Delays here were mainly due to inappropriate triage, long queues to open folders, understaffed and overburdened ECs, and ECG machines that were not in working order. The study reported a median door-to-needle time of 63 minutes. [46] Maharaj et al. documented the course of 238 STEMI patients that presented to three public hospitals in Cape Town, South Africa.[38] Of these patients, 74% were thrombolysed whilst 5% had contra-indications and 21% presented outside the effective thrombolysis window and did not receive thrombolysis. Delays here were mainly due to junior doctors seeking confirmation from a senior doctor before commencing thrombolysis, interpretation of the ECG, atypical presentations, clinical issues requiring priority, patients presenting during staff hand-over, delays in investigations and absence of thrombolytic agents in the EC. The study reported a median door-to-needle time of 54 minutes. [38] What these studies tell us is that although thrombolysis can be considered an appropriate alternative to PCI, in settings where PCI is not available, systems do not support early and

appropriate thrombolysis either. This is likely due to the reasons provided in the Meel and Maharaj studies. [38,46]

Thrombolysis and routine transfer for angiography:

The practice of transfer of patients with STEMI for routine early coronary angiography after initial thrombolytic therapy is growing. This new approach referred to as 'early invasive strategy' is believed to have the advantage of being initiated at a non-PCI capable facility, providing additional time for the facility to arrange non-emergency PCI. [47] It supports early transfer after administration of thrombolytic therapy even in patients without high-risk features. Studies promoting this practice have demonstrated improvements and benefits in clinical outcomes such as lower two-year mortality rates and lower risks of re-infarction. [47-52]

The TRANSFER- AMI TRIAL (The Trial of Routine Angioplasty and STENTING after thrombolysis to Enhancing Reperfusion in Acute Myocardial) evaluated the transfer for coronary angiography and revascularisation among high risk patients (n=1059) and demonstrated a reduction in the combined primary endpoint of death, recurrent MI, recurrent ischaemia, new or worsening heart failure or shock at 30 days.[47] In the GRACIA study, early catheterisation within 6-24 hours after successful thrombolysis was associated with significant reduction in mortality, re-infarction or ischaemia-driven revascularisation at two years.[49] The CARESS- AMI trial, a randomised multicentre trial of 600 subjects, compared the outcomes of immediate transfer for PCI following thrombolytic therapy in high risk patients to standard care and rescue PCI and demonstrated a benefit of the former in all causes of death, re-infarction rate and refractory ischaemia.[50] And finally, the NORDISTEMI (Norwegian Study on District Treatment of ST-elevation Myocardial infarction) trial investigated the effect of immediate routine transfer for catheterisation versus ischaemia-guided management after thrombolysis of STEMI patients in areas with very long distances and showed a reduction in the incidence of death, recurrent MI or stroke in the immediate transfer group.[52]

As stated, although PCI remains the revascularisation treatment of choice for the management of STEMI in high-income countries it must be performed in less than 120 minutes from onset of chest pain or first medical contact by a skilled provider and at a skilled PCI centre to be effective. Early invasive strategy offers an evidence-based approach to achieving PCI that is unavoidably delayed, by starting with early thrombolysis. It is unclear,

however, what benefits this strategy holds for low- and middle-income countries where PCI is less available. [21]

Assessment of reperfusion therapy efficacy

In high-income countries, the assessment of thrombolytic therapy efficacy is based on various markers of perfusion. This includes the Thrombolysis in Myocardial Infarction trial (TIMI) flow grade classification, TIMI frame count (TMC), TIMI Myocardial Perfusion grade (TMP) and clinical variables such as relief of ischaemic symptoms, the presence of reperfusion arrhythmia and resolution of ST-segment elevation. [53,545] Several trials have demonstrated that complete or near complete ST-segment resolution at 90 minutes after thrombolysis is a marker of good prognosis. In contrast, the absence of improvement in ST- segment resolution is associated with worse prognosis. [53,54]

The Hirudin for Improvement of Thrombolysis (HIT)- 4 trial demonstrated the association between the resolution of ST-segment elevation in patients thrombolysed for STEMI and the detection of early infarction vessel patency.[55] Cooper et al. also established the association between ST-segment amplitude and patency of the infarcted vessel after administration of thrombolysis.[56] Purcell et al. went one step further and found that changes in ST-segment elevation 60 minutes after thrombolysis initiation could predict clinical outcomes as accurately as later ECG changes.[57] The International Joint Efficacy Comparison of Thrombolytic Trial (INJECT) then showed that the extent of early ST- segment elevation resolution was a strong predictor of outcomes in patients with STEMI and a sensitive measure for comparison between thrombolytic agents.[58]

The relatively sudden and complete relief of chest pain, combined with greater than 70% ST-segment elevation (in leads with the greatest elevation on presentation) is highly suggestive of restoration of normal blood flow and may be equivalent to TIMI 3 classification. The combination of 50% resolution of ST-segment elevation with the absence of reperfusion arrhythmia predicts TIMI flow <3 in the infarcted artery with a sensitivity of 81%, specificity 88%, positive predictive value 87% and negative predictive value of 83%. The lack of resolution of ST-segment elevation by at least 50% in the worst leads at 90 minutes prompts the need for an immediate coronary angiography and rescue PCI. [55] Therefore, successful reperfusion after thrombolysis is characterised by a significant improvement in ischaemic symptoms, resolution of ST-segment elevation on ECG as well as haemodynamic stability and the absence of heart failure.[55-61]

The evidence of unsuccessful reperfusion or failed primary reperfusion is clinically characterised by persistent or worsening chest pain associated with other symptoms such as dyspnoea and diaphoresis as well as persistent or worsening ST-segment elevation, and /or haemodynamic instability or heart failure. Failure of the primary reperfusion approach (thrombolysis) warrants emergency or immediate angiography with intention to perform rescue PCI. [56-58,62]

Prognosis and outcomes

Although thrombolytic therapy is easy to administer and widely available, it provides early reperfusion in only 80% of patients. [1] Sometimes, contra-indications of the thrombolytic agent hinder its administration to some patients presenting with STEMI. Myocardial revascularisation with PCI results in a higher reperfusion rate (approximately 90%) and has fewer contra-indications than thrombolysis. [63,64] Randomised controlled trials performed in high-volume academic centres comparing thrombolytic therapy with PCI for acute myocardial infarction demonstrated a 30% reduction in mortality and re-infarction rates, and a significant reduction in cerebrovascular accidents where PCI was employed. Although more forgiving than thrombolysis, primary PCI should be performed within 60-90 minutes of arrival to the hospital to achieve these figures. [63,64]

Anneke et al. looked at 22 randomised controlled trials that evaluated the efficacy and safety of primary PCI versus thrombolysis and found that 446 patients with STEMI (6.6%) died within 30 days after randomisation. [65] Patients randomised to primary PCI had lower mortality than those randomised to thrombolysis (5.3% versus 7.9%, adjusted odds ratio 0.63, 95% confidence interval 0.42-0.84, p=0.001). However, the absolute risk reduction was strongly related to estimated risk at baseline; the numbers needed to treat to prevent a death by primary PCI versus thrombolysis was 516 in the lowest quartile of estimated risk compared with only 17 in the highest quartile. Primary PCI was consistently associated with a strong relative reduction in 30-day mortality, irrespective of patient baseline risk. The investigators resultantly recommended that primary PCI should be considered as the first-choice reperfusion strategy whenever feasible. Where access to PCI is estimated to be more than two hours, the administration of thrombolysis remains a legitimate alternative option in low-risk patients where primary PCI would lead to only a small absolute risk reduction. [65]

Survivors of a first-time STEMI face an increased risk of further major cardiovascular events such as death, recurrent infarction, heart failure, arrhythmias, angina, and stroke.

Complications occurring after myocardial infarction are attributed to structural and electrical changes in the heart and depend on the extent of the myocardial damage. [63,65] There are early and late complications but only the former is considered in our study. Early complications include mortality, cardiogenic shock, severe heart failure, pericarditis, thromboembolic and bleeding complications, acute kidney injury, hyperglycaemia, recurrent ischaemia/ infarction, no-reflow phenomenon, right ventricular infarction, mechanical complications such as mitral regurgitation, ventricular septal rupture, left ventricle free-wall rupture, left ventricle aneurysm and electrical complications such as tachy-dysrhythmias or brady-dysrhythmias. [63,65]

Electrical

Dysrhythmias and conduction abnormalities occur in more than 90% of STEMI patients and can result in death within the first three days. Atrial fibrillation and atrial flutter have been found in about 10% of patients. Ventricular dysrhythmias such as ventricular fibrillation and ventricular tachycardia are also common. [63,65]

Structural complications

Structural complications post-myocardial infarction include papillary muscle rupture, ventricular aneurysm, ventricular septal rupture and ventricular free-wall rupture. Free-wall rupture is almost always fatal. [63,65]

Cardiogenic shock

Cardiogenic shock occurs in almost 7% of patients with STEMI and has a mortality rate of roughly 80-90% if not treated. Primary PCI or coronary artery bypass grafting are the treatments of choice for STEMI complicated by cardiogenic shock with early intervention having a significant effect on mortality. The 30-day mortality rate is nearly 50% when cardiogenic shock is treated with an early catheter-based mode of revascularisation. [1-6,22,23,63,65]

Summary of critical review

The selection of an appropriate method of myocardial revascularisation strategy requires consideration of information such as location of the myocardial infarction, patient age, the duration of STEMI from the onset of ischaemic symptoms, time required to complete transfer to a PCI facility and safely perform primary PCI, and the capability of the primary PCI cardiologist and health facility. Primary PCI is an effective treatment for STEMI if it is

performed within less than 90 minutes from onset of symptoms. It enhances early reperfusion in approximately 90% of patients who present with STEMI and has been associated with a 30% reduction in mortality and re-infarction rates as well as a significant reduction in recurrences. The main difficulty is that PCI is not widely available and requires special skills and a specialised facility. It is unfortunate to note that in low- and middle-income countries, many patients with STEMI will present to non-PCI capable facilities and therefore cannot be offered PCI. It has also been shown that many countries (including in high- and middle-income countries) struggle to meet the time-frames for effective PCI. Thrombolysis, despite being less effective than PCI, remains a treatment option for patients who present with STEMI where PCI is not available, or a delay in transfer to a PCI centre is expected. In the absence of PCI, the administration of thrombolytic agents is an effective alternative means of myocardial revascularisation and the treatment of choice in low- and middle-income countries as it is more readily available. Despite the risk of bleeding, reperfusion with thrombolysis results in an 80% success rate. However, lack of resources to provide PCI does not necessarily mean that resources exist to provide timely thrombolysis. Studies performed in South Africa have highlighted long delays in care and other challenges in providing thrombolysis for STEMI. [15,38,46] None of these studies specifically documented the contribution of rescue PCI.

Identification of gaps or needs for further research

There is a need for research within South Africa to consider the outcomes of patients with STEMI who were thrombolysed at a non-PCI capable facility in relation to the ECG changes associated with different coronary injury regions involved. A better understanding of the patients thrombolysed for STEMI that require transfer from a non-PCI capable facility may guide local decisions related to an early invasive strategy for some.

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PART B : ARTICLE MANUSCRIPT

As per Global Heart Journal instructions

Title page

Title:

A cross sectional study of ECG patterns and outcomes of patients thrombolysed for ST-elevation myocardial infarction at a district, public Cape Town hospital.

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Abstract

Introduction

There is insufficient data to describe ST-elevation myocardial infarction (STEMI) in sub-Saharan African settings using common diagnostic criteria. This study describes the outcomes at discharge (survival, death or transferred) of patients thrombolysed for STEMI at a public hospital without primary percutaneous coronary intervention capability as well as associated ECG changes.

Materials and methods

A retrospective, cross- sectional study was conducted at an urban, public emergency centre in Cape Town, South Africa that did not have direct access to percutaneous coronary intervention for STEMI. Descriptive statistics for age, length of stay and the various timings surrounding thrombolysis were presented using proportions, mean and standard deviation. Assumptions were tested using the X^2-test or Fishers Exact test. A p-value less than 0.05 was considered significant.

Results

The study enrolled 104 patients of which 25 were excluded for insufficient data and two for thrombolysis of an incorrect STEMI diagnosis. Of the remaining patients, 56 (64%) survived to discharge, 26 (30%) required transfer and five (6%) died. There was no difference between regions affected and patient outcome (p=0.31). Resolution of ST-segments was seen in 48 (86%) survivors. It was not seen in 21 (81%) who were transferred and in none that died. The difference between resolution of ST-segments between survivors versus those transferred or dead was highly significant (p<0.001).

Conclusion

This study described a higher than expected thrombolysis failure rate as well as a higher than expected association of poor outcome with inferior STEMI. It highlights the need for improved health care records to improve health research in low-resourced settings. The creation of a STEMI registry could contribute to research but will need funding. The use of clinical messaging apps to gain senior ECG interpretation may provide an additional layer toward quality care.

Keywords

Myocardial infarct; Africa; electrocardiogram; outcome; thrombolysis

Manuscript

Introduction

Sub-Saharan Africa has been characterised by an increase in coronary heart disease over the last few decades. [1-2] The World Health Organization has predicted that non-communicable diseases will exceed communicable or infectious diseases as the leading cause of death in Africa by 2030.[1] Compared to other causes of heart disease, the burden of coronary heart disease remains low in African descendants compared to Caucasian descendants.[2-9]

The prevalence of acute myocardial infarction in Africa is currently estimated to be between 0.1 to 4%.[10] But an accurate prevalence of acute myocardial infarction in sub-Saharan Africa has not been well established despite growing recognition of an increasing burden of cardiovascular disease in low- and middle-income countries.[11-13] There is insufficient population-based data that describes the prevalence of acute myocardial ischaemia in sub-Saharan Africa using common diagnostic criteria. The lack of surveillance data and registries as well as the lack of diagnostic and interventional capacities has made the estimation of the magnitude of coronary heart diseases in Africa challenging. The paucity of epidemiological data as well as the absence of specific tests for coronary heart disease has also contributed to the failure to accurately determine the true prevalence of ST-elevation myocardial infarction (STEMI) in Africa. [11-13]

There has been an increase in mortality and morbidity rates associated with coronary heart disease and its complications – such as myocardial infarction – in post-apartheid South Africa with its emerging economy and increased urbanisation.[2-9] The ACCESS study conducted in 29 South African health facilities across all provinces from 2007-2008 was the first local study to establish registries and document the demographics and management strategies in patients admitted to hospital with a diagnosis of acute coronary syndrome (ACS).[14] Out of 642 patients enrolled in the study, 615 participants had a confirmed diagnosis of ACS: 41% had a diagnosis of STEMI at discharge versus 59% with non-ST-elevation ACS (NSTE-ACS) (32% non-ST-elevation MI and 27% unstable angina). This study also revealed that most South Africans presenting with STEMI were managed at a facility without percutaneous coronary intervention (PCI) capabilities and by a non-cardiologist – South Africa has only 55 cardiac catheterisation laboratories for a population of 56 million, spread out between a few tertiary public centres and selected private hospitals, mostly situated in major urban centres. [9,14] What is important to note is that ACCESS was not a population representative sample. Study participants mostly had access to private health care, leaving the biggest cohort of South

African patients with STEMI, namely, the 68% without access to private health care from the public sector, largely excluded.[15] In a nutshell, this means that access to PCI capable facilities is likely to be worse than what the ACCESS study findings suggested.

It was the aim of this research to describe the outcomes at discharge from hospital, of patients thrombolysed for STEMI; and the ECG changes (e.g. STEMI regions and STEMI resolution) associated with this outcome, at a public hospital without PCI capability in Cape Town.

Materials and methods

This cross-sectional, retrospective study was conducted at Victoria Hospital, Cape Town. Victoria Hospital is a large, secondary-level hospital that provides medical and surgical services but has no PCI suite or cardiologist on site. The emergency centre (EC) has two resuscitation beds, eight beds for other EC patients (including three monitored beds) with a further 16 observation beds in an adjacent ward. Daily, the EC manages approximately 132 patients of which around 15 present with chest pain. On average, five patients are admitted to medicine daily with a diagnosis of ACS and approximately two to five STEMIs are thrombolysed per week in the EC. Streptokinase is the preferred agent for all patients without contra-indications to the drug. Alteplase is only used in instances where Streptokinase is contra-indicated. Victoria Hospital is approximately ten kilometres away from the nearest PCI capable centre at Groote Schuur Hospital, a 20 to 40-minute trip depending on traffic.[16]

We included all patients aged 18 years or older who presented with STEMI as defined by the clinical and ECG criteria described by the American College of Cardiology/ American Heart Association and were received in the EC between July 2014 and June 2015.[17-19] We excluded patients younger than 18 years; patients who did not receive thrombolytic therapy; patients with stable and unstable angina, or NSTE-ACS; those who did not receive pre-hospital fibrinolysis; patients with conditions other than STEMI (e.g. stroke, pulmonary embolism); and referrals post-thrombolysis from other medical facilities to Victoria EC. Patients that lacked outcome information at discharge (e.g. survival, death or transferred) or a diagnostic ECG were also excluded from further analysis.

Given that between two and five patients are thrombolysed per week, and the limitations with respect to local paper record keeping, we estimated that a sample size of between 100 and 150 cases would be required. As the rate of thrombolysis was based on an estimation,

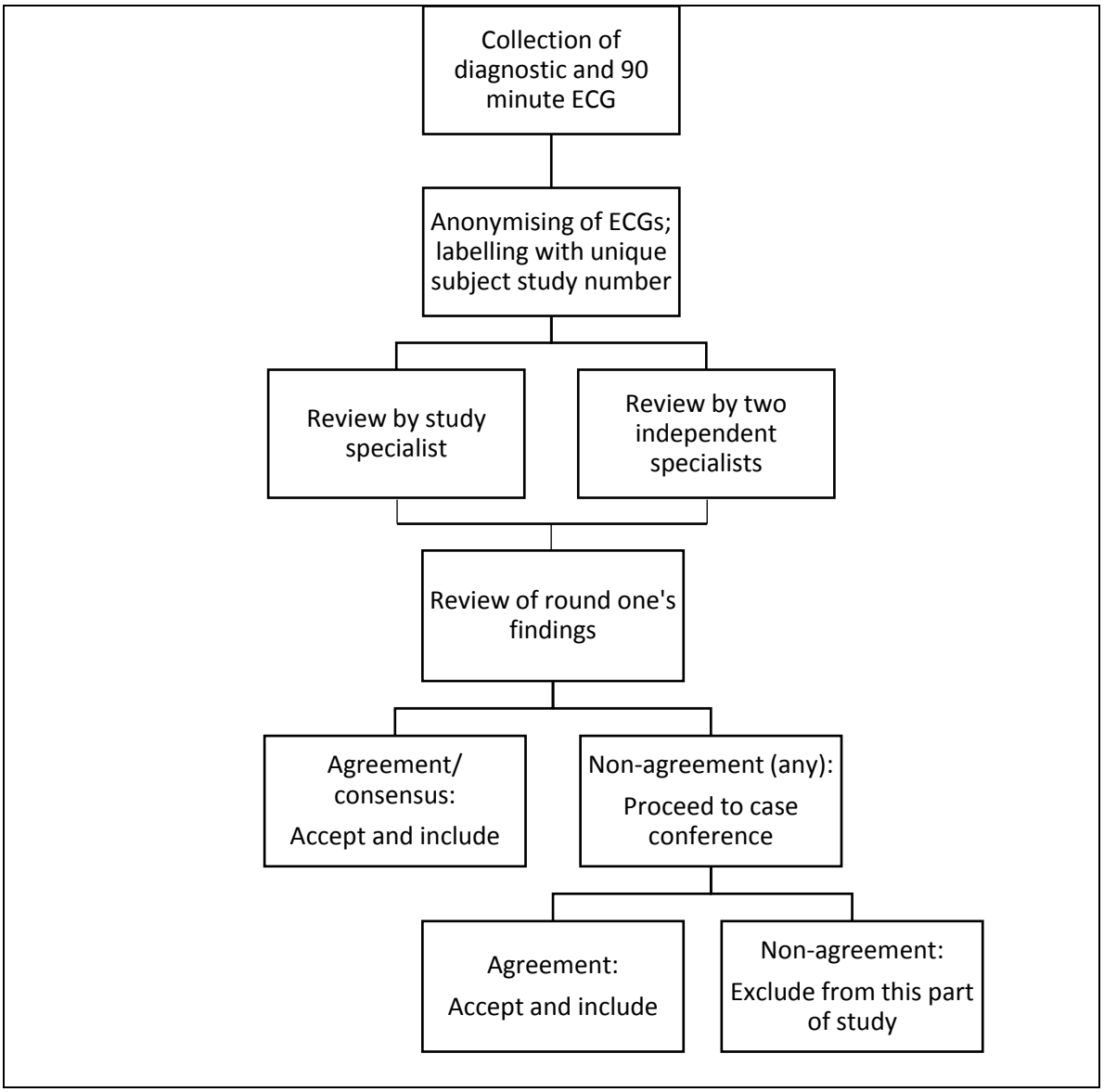
we decided to settle for a convenience sample without specifically powering the sample. As we did not plan inferential statistics that would be dependent on a specific sample size, we felt this would be appropriate.

Initially, study participants were identified using Victoria EC's resuscitation register. Specific data variables were then extracted from clinical records. The initial diagnostic ECGs and 90-minute post-thrombolysis ECGs were copied, anonymised and sent for interpretation. Three emergency medicine specialists, all with an enhanced emergency cardiology skillset, were involved as topic experts in the interpretation of the study ECGs. The ECGs were first analysed by Dr. Malan, one of the authors, followed by independent verification by another two specialist emergency medicine physicians who were not part of the research team. In instances of non-agreement on any of the ECG interpretations from any of the assessors, a final decision was made at a case conference involving all three assessors. Where assessors could still not agree on interpretation, the concerned ECG and corresponding case were excluded from the study. The interpretation and verification process is described in Figure 1.

Other variables collected included age, gender, time of arrival/ triage, time of diagnostic ECG, time of thrombolysis, disposition from Victoria Hospital (i.e. discharge/ transfer) as well as outcome (i.e. survival or death). The latter relates to survival or death at Victoria Hospital following thrombolysis. We did not include disposition or outcome variables for patients that were transferred for PCI as the study protocol did not allow for data collection beyond Victoria Hospital.

Data were summarised in a Microsoft Excel spread sheet (Microsoft Office, Redmond, USA). Descriptive statistics are provided using the mean and standard deviation (SD) and proportions are given throughout. We used the X^2 and Fisher's Exact test depending on sample size involved to test associations between the STEMI region affected and outcome (e.g. discharge from hospital, transfer or death). We also tested associations between the ECG resolution of STEMI at 90 minutes and outcome. A p-value of less than 0.05 was used to indicate significance.

The study was approved by the Human Research Ethics Committee of the University of Cape Town (HREC 087/2016) and approval was given by Victoria Hospital to conduct the study.



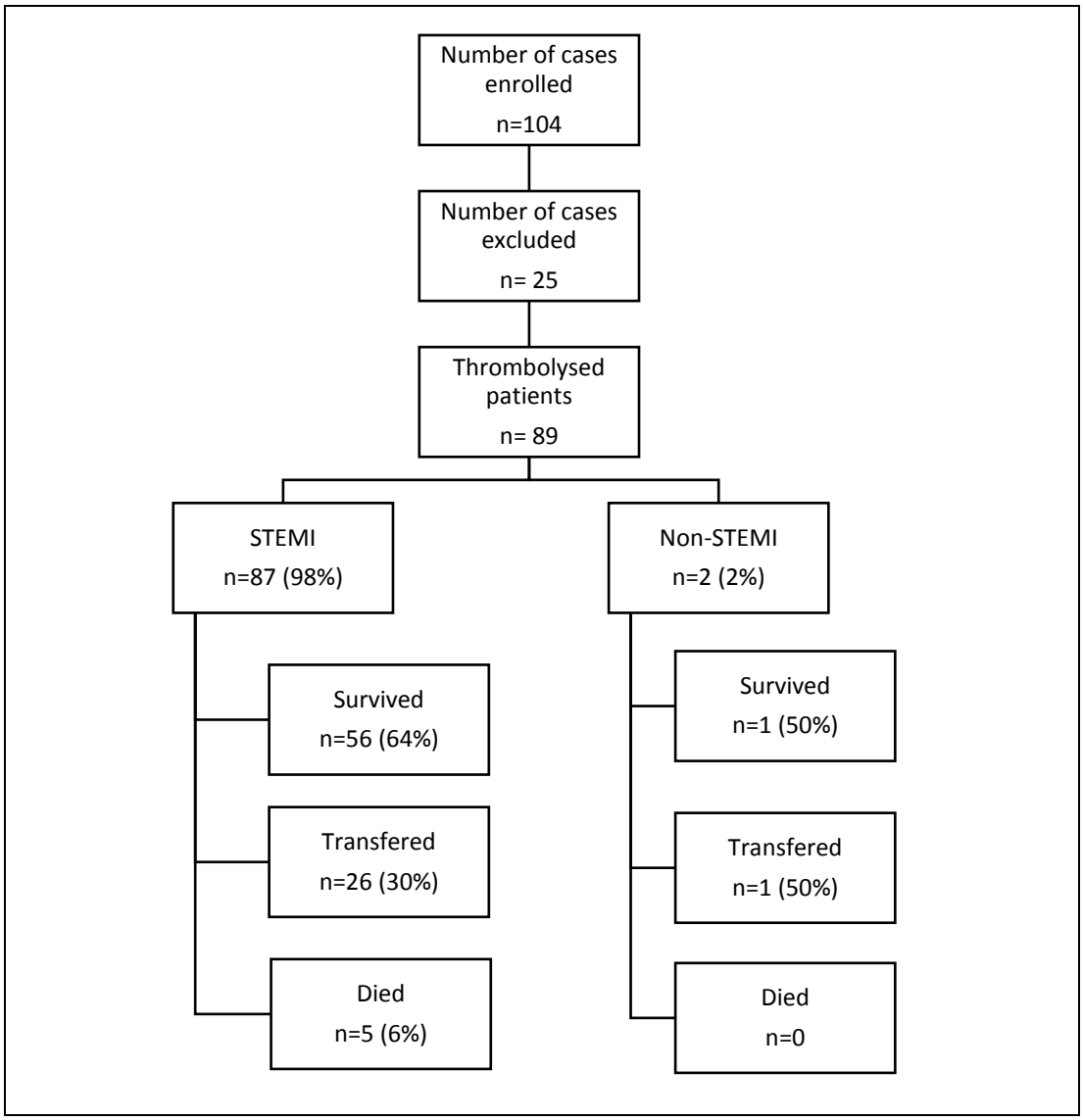
ECG, electrocardiogram

Figure 1. Flowchart depicting evaluation of ECGs by topic experts

Results

Figure 2 describes the study subjects at each stage of the analysis. The ECG reviewers reached consensus in the first round of ECG interpretation for 83 of the cases and full consensus on the second round for the remainder of cases. Exclusions were mainly due to poor record keeping as well as records lacking the pre- and/or post thrombolysis ECG. Two patients with STEMI were excluded as thrombolysis was administered prior to attending Victoria hospital, and a further two patients were excluded due to an incorrect diagnosis of STEMI with subsequent thrombolysis. The latter two patients were both male patients aged 46 and 50 years, respectively. Their ECGs revealed a Brugada configuration, a known pitfall in the

interpretation of ECGs for STEMI. For both patients, the error was later recognised and treatment was amended accordingly. Both patients survived although one required acute transfer to a tertiary centre for management.



STEMI, ST-elevation myocardial infarct

Figure 2. Participants to study at each stage of the analysis

Table 1 describes the gender, age and main outcomes of the study. Patients who died were older than those that survived but not significantly so (X^2=0.3; p=0.87).

Table 1. Gender, age and main outcomes of the study

Variables	STEMI n (%)	Male n (%)	Age (year) Mean ± SD	Inpatient stay (days) Mean ± SD	Time from arrival to ECG (min) Mean ± SD	Time from arrival to thrombolysis (min) Mean ± SD
Total	87	64 (72)	56 ± 12	3 ± 2	30 ± 30	96 ±81
Survive	56 (64)	40 (70)	56 ± 13	4 ± 1	27 ± 26	88 ± 64
Transfer	26 (30)	22 (81)	55 ± 12	1 ± 0	34 ± 35	88 ± 58
Died	5 (6)	2 (40)	61 ± 9	1 ± 0	10 ± 0	105 ± 106

SD, standard deviation; STEMI, ST-elevation myocardial infarct; MI, myocardial infarct; ECG, electrocardiogram; min, minute; Survive, refers to patients discharged from Victoria Hospital following thrombolysis; Transfer, refers to patients transferred from Victoria Hospital following thrombolysis; Died, refers to patients that died at Victoria Hospital following thrombolysis

Table 2 describes the suspected coronary regions affected (as per ECG interpretation), and the outcome matched to each of the affected areas. There was no difference between regions affected and patient outcome (p=0.31). Deaths were from just four of the 11 territories, with the left anterior descending and right coronary artery territories mainly implicated.

Table 2. Suspected coronary regions affected by the STEMI (as per ECG) and the outcome matched to each affected area

Suspected region affected	**n (%)**	**Survived**	**Transfer**	**Died**
Any region	87	56 (64)	26 (30)	5 (6)
Left Anterior Descending territory	31 (37)	18	10	3
• Anterior Septal	10 (12)	7 (70)	2 (20)	1 (10)
• Anterior lateral	1 (1.2)	1 (100)	0	0
• Septal	1 (1.2)	1 (100)	0	0
• Anterior	19 (23)	9 (47)	8 (42)	2 (11)
Right Coronary Artery territory	43 (52)	31	10	2
• Inferior	30 (36.1)	25 (83.3)	4 (13.3)	1 (3.3)
• Inferior- Posterior	7 (8.4)	3 (43)	3 (43)	1 (14)
• Inferior Right Ventricle	6 (7.2)	3 (50)	3 (50)	0
Left Circumflex Artery territory	5 (6)	2	3	0
• Inferior lateral	2 (2.4)	1 (50)	1 (50)	0
• Lateral	2 (2.4)	0	2 (100)	0
• High lateral	1 (1.2)	1 (100)	0	0
Left main stem stenosis	4 (4.8)	2 (50)	2 (50)	0

STEMI, ST-elevation myocardial infarct; ECG, electrocardiogram

Of patients that survived, 84% (48/57) had resolution of their ST-segments. Of patients that were transferred, 88% (21/24) showed no resolution of their ST-segments. Resolution of ST-segments was not seen for any patient that died. The difference between resolution of ST-segments and survival, transfer/ death was highly significant (X^2=44.6; p<0.001).

Discussion

A notable finding of this study was that almost two-thirds of STEMI patients who presented to Victoria Hospital's EC and received thrombolysis had subsequent resolution of ST-segments and survived to discharge – none of which required rescue PCI. In contrast, just over a third of the thrombolysed patients had non-resolution of the ST-segment and either required transfer to a tertiary institution for rescue PCI or died at Victoria Hospital. Despite the limitations, this finding is significant. We already know from the literature that thrombolytic therapy is associated with an 80% resolution rate (compared to 90% for PCI).[17,18,20-25] However, our study findings suggest that the rate is substantially lower within our cohort. The study did not go into any detail regarding the various variables that may account for this. It does however suggest a greater reliance on rescue PCI than what would be expected judging from the existing literature. This is an important finding within a resource-limited environment if similar findings are made in replication of this study, as it may affect the way the local system is designed to respond to patients presenting with STEMI to centres without PCI capability (or even perhaps before patients reach these centres). The challenge is predicting the cohort that will show poor resolution.

With regards to the STEMI region involved, the inferior region was most commonly affected, followed by the anterior region. This is a similar finding as to what Maharaj described back in 2012, also within a Cape Town setting.[26] These two regions represented more than half of all STEMI patients included in our study. Moreover, anterior and inferior STEMI were disproportionately associated with a higher risk of transfer for rescue PCI and mortality. Naturally, the latter finding may simply be due to over-representation of the STEMIs found to affect these areas. What is interesting though is that mortality differed slightly from what has been described in the literature. Inferior STEMI tends to be associated with a better outcome and low in-hospital mortality (2%) which was not the case in our study.[17,18,20-24] Given the small mortality numbers, one should be careful to interpret this as significant. A larger sample is needed to review these findings as it may present a key to identifying potential patients that would benefit from earlier PCI within our resource-limited setting. There was little difference with existing literature in terms of the proportions of the various regions affected by STEMI.[17,18,20-24] It is worth noting that the longer delay in providing thrombolysis to patients that died, despite an earlier ECG diagnosis, was due to resuscitation requirements that were prioritised above thrombolysis in these patients.

As a specific, rather than sensitive diagnostic tool, ECG interpretation can be a high-stakes decision depending on who interprets it. Two patients were wrongly diagnosed with STEMI

and subsequently thrombolysed. Although both cases were excluded, the inappropriate administration of thrombolysis (and the serious potential risks involved) highlights the importance of a skilled frontline workforce. As a new specialty, emergency physicians are not present locally in the same concentrations seen in more developed settings. [27] During the time of the study, there were only two emergency physicians employed by Victoria Hospital, which would suggest that there was no on-site specialist cover for most of the day. The Royal College of Emergency Medicine in the United Kingdom has specifically identified specialist sign off on all ECGs as a quality marker due to the recognition of the risks involved with error.[28] South Africa, and by extension the rest of Africa, have a long way to go to provide the same level of quality assurance within our ECs. The use of telemedicine, including various smartphone medical messaging applications, is seen as a potential bridge to the absence of on-site specialist cover. Specialist interpretation of ECGs would be an easy inclusion for such developments, however it needs to be built into a system that supports the findings. Seeing that the outcome appears to be worse within our setting, in terms of rescue PCI requirement and death, this could potentially hold much benefit for local patients.

This study had a few limitations. As a retrospective, descriptive study it relied mostly on information recorded from the patient record. A large proportion of the sample had to be excluded due to poor record keeping, which, if available, may have affected the findings of this study. The numbers were therefore smaller than what was anticipated. We were unable to describe the time from onset of chest pain to presentation (or thrombolysis for that matter) as a direct result of poor record keeping. As such, we are unable to comment on whether any of the patients that suffered poor outcomes were due to a delay in presentation. A prospective study design will be required to improve the robustness of the dataset in future studies. The outcome (i.e. survival or death) of patients that were transferred was not described. This may not only have affected results, but also provided information about outcomes of patients sent for rescue PCI. Given the relatively large number of patients that required rescue PCI, this may warrant further study. The study did not record the specific agent used for thrombolysis. Although Streptokinase tends to be used for the majority of cases, Alteplase is used should contra-indications apply to Streptokinase. The difference in 90-minute patency rates between the two agents (Streptokinase 60-68% versus Alteplase 73-84%) may have affected resolution of the ST-segment post-thrombolysis. [17] This should be an important consideration for future study as better agents may hold a cost-benefit in the absence of access to PCI that may also benefit outcome. Caution should therefore be taken when comparing the findings of this study with studies where different agents, such as

Tenecteplase or Reteplase, were used. Given the study's descriptive nature, none of the findings can assume direct relationships, but rather associations. Missing information is a huge challenge for any study conducted in a low- or middle-income setting. The improvement of quality care for patients with STEMI who present to the Victoria Hospital EC as well as the quality of the record keeping at the hospital constitute some of the opportunities highlighted by this study.

Conclusions

ST-elevation myocardial infarction is a serious complication of ischaemic heart disease. Up until recently, this has been less of a concern in sub-Saharan Africa but urbanisation and Westernised lifestyle changes have led to an increase in disease over the last few decades. Very little is known about the acute EC management of STEMI within this population, even in South Africa. This study described a higher than expected thrombolysis failure rate as well as a higher than expected association with inferior region STEMI for patients that attended an urban, South African, public hospital without PCI capability. The study produced a number of findings that will need unpacking in future research projects that may hold promise for service improvement. Replication of the study methods using prospective sampling, including outcome variables for patients referred for rescue PCI, thrombolysis agent and onset of symptoms, may provide insight into local STEMI pathways. The addition of variables related to the grade and experience of the ECG interpreter may also be of value. Finally, as with the Maharaj study, this study highlighted the need for improved health care records. It is ironic that the settings with the most to gain from clinical retrospective research are also the settings that are the least likely to consistently keep an adequate record to do so. The creation of a STEMI registry may address this, however, this will require funding that we currently do not have access to.

Vitae

Dr Crispin N. Kibamba is a registrar in the Division of Emergency Medicine at the University of Cape Town. He is keen to develop emergency medicine as a discipline and improve the care of acutely ill and injured patients in the Democratic Republic of the Congo upon completion of his training in South Africa.

Dr Jacques Malan is an emergency medicine specialist in Victoria Hospital's emergency centre and honorary lecturer in the Division of Emergency Medicine at the University of Cape Town. He has a specific interest in emergency cardiology and co-directs a two-day ECG workshop that is underwritten by the University of Cape Town.

Dr Stevan R Bruijns is an emergency medicine specialist and senior lecturer in the Division of Emergency Medicine at the University of Cape Town. He is the immediate past chair of the Emergency Medicine Divisional Research Committee and Editor-in-Chief of the African Journal of Emergency medicine.

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PART C: ADDENDA

Relevant journal Instructions to Authors

Global heart journal instructions for authors are published at the following URL: https://www.elsevier.com/journals/global-heart/2211-8160/guide-for-authors

Acknowledgements

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This project would not have been completed without the help of administration staff at Victoria Hospital for their invaluable contributions in availing patients' medical records during the process of data collection.

Lastly, I am also thankful to my wonderful and amazing wife, Liliane, and children, Godwin, Beinish, Gaddiel and Obbie, for the unconditional support and understanding that kept me going when confronted with challenges and discouragements.

Research protocol

A Retrospective, Descriptive Study of ECG Patterns and Survival to Discharge of Patients Thrombolysed for ST- Elevation Myocardial Infarction at a Provincial Level-Public Hospital in Cape Town.

By

Dr Crispin Ngoy KIBAMBA

University of Cape Town (student no KBMCRI001)

Supervisors:

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2. Dr Jacques Malan, Specialist Emergency Physician, Emergency Centre, Victoria Hospital, Cape Town

PURPOSE OF THE STUDY

The purpose of this study is to describe ECG patterns and outcomes at discharge of thrombolysed ST-Elevation Myocardial Infarction (STEMI) patients at Victoria hospital (a facility without Primary Coronary Intervention capability) in Cape Town. This study is being used to explore the creation of a larger registry to track short to medium term outcomes of thrombolysed STEMI patients who did not receive Primary Coronary Intervention within a low-to-middle-income setting.

INTRODUCTION:

STEMI is a serious complication of ischemic heart disease (IHD) and a major cause of death worldwide with an estimated annual incidence of seven million people. [1-2)] In the United States of America (USA), approximately 500,000 episodes of Acute Myocardial Infarction (AMI) occur each year. Approximately 600 in every 100,000 men and 200 in every 100,000 women have an AMI every year. The World Health Organization (WHO) estimates that 17.1 million people died from ischemic heart disease (IHD) in 2004, representing 29% of all deaths globally. In the U.S., the overall mortality rates have been decreasing. The 30-day mortality rate among patients with AMI in 2010 ranged from 2.5% to 10%. Most of the studies were conducted in western countries and little is known about Africa. [(1-2)]

Africa, and particularly sub-Saharan Africa, although initially characterized by a low prevalence of non- communicable disease, has seen in the last decades an increase in number of cardio-vascular events particularly coronary heart disease .The World Health Organization has predicted that Non- communicable diseases will exceed communicable diseases as the leading cause of death in Africa in 2030.[3]However, compared to other causes of heart disease, the burden of ischemic heart disease remains low in African descendants. The lack of surveillance data and registries as well as diagnostic and interventional capacities has made difficult the estimation of the magnitude of ischemic heart diseases in Africa.

Post- apartheid South Africa with its emerging economy and urbanisation has seen an increase in mortality and morbidity associated with coronary heart disease and its complications such as AMI. [(12-16)] However, the true incidence of IHD is unknown due to lack of registry and epidemiologic data. The ACCESS study- South Africa conducted in 29 South African health facilities (in all provinces) from 2007-2008 was the 1st of its kind in the country to have established registries and documented the demographics and management strategies in patients admitted to hospital with a diagnosis of ACS. [(12-16)]

Acute Coronary Syndrome (ACS) is a huge problem worldwide and the standard of care is early diagnosis by ECG followed by treatment with Primary Coronary Intervention if STEMI is diagnosed.[17]ACS is also considered a problem locally. Although we have no good data to describe its incidence, anecdotal evidence suggests that hardly anyone presenting to a public hospital is likely to be treated with primary coronary intervention. The local standard of care is thrombolysis with ECG used to diagnose STEMI. [(18)]

ECG as a test for STEMI is very specific but not very sensitive meaning that is very good to make the diagnosis of myocardial infarction but not so good at ruling it out (98% specificity but only 20% sensitivity). [(22)] Therefore , some patients with STEMI could potentially be missed and some patients without STEMI could be diagnosed as such (referred to as a STEMI mimic).[(22)] Treating a STEMI mimic with PCI has a relatively low risk of harm; in contrast, a STEMI mimic treated with thrombolysis – and its risk of causing haemorrhage – could potentially be fatal.[(23-24)] In addition, different STEMI regions carry different outcomes and responses to thrombolysis, suggesting that at least some patients will be better off with primary coronary intervention versus thrombolysis.[(25)] The different STEMI regions and their ECG findings are summarized in Table 1.

Table 1. STEMI regions, ECG findings and ST segment changes

Location	**Leads**	**ST segment**
Anterior wall MI	V1 through V4	Elevation
Lateral MI	I, aVL, V5 and V6	Elevation
Inferior Wall MI	II, III and aVF	Elevation
Right Ventricular MI	V4R	Elevation
Posterior wall MI	V8 and V9 V1 through V3	Elevation Depression

AIM

The aim of this study is to describe the outcomes at discharge from hospital of thrombolysed patients for STEMI and ECG changes associated with different coronary anatomical injury regions at a public hospital without Primary Coronary Intervention capability in Cape Town.

OBJECTIVES

- To describe outcome at discharge from hospital (survival, death or transferred) of patients thrombolysed for STEMI, and.
- To describe the ECG findings associated with the different coronary injury regions represented in each STEMI case.
- Sub-objectives
  - To describe outcome at discharge from hospital (survival, death or transferred) as per standard ECG coronary anatomical injury regions.
  - To describe timings (onset of chest pain, time of presentation and presentation time to thrombolysis time) surrounding thrombolysis in the Emergency Centre.
  - To evaluate ECG difference at 90 minutes following thrombolysis of each case.

METHODOLOGY

Study design

It is a descriptive, retrospective study.

Characteristics of the study population

The study will be conducted at Victoria hospital, Cape Town. Victoria hospital is a larger district hospital which provides medical and surgical services but has no percutaneous coronary intervention suite or cardiologist on site.

Victoria hospital EC has 2 resuscitation beds, 8 cubicles in major (3 monitored beds) with a further 16 trolleys in the unit. The unit sees 132 patients per day with an average of 15 chest pain patients per day. On average five patients are admitted daily to medicine as ACS and approximately four to five STEMIs are thrombolysed per week in the EC.

Inclusion criteria

All patients aged 18 years or older who presented with presumed STEMI (ECG) meeting AHA/ACC criteria for thrombolysis and who received thrombolysis in the EC at Victoria hospital during the study period: July 2014 to July 2015.

ECG criteria for acute STEMI in the absence of LVH and left bundle branch block (LBBB) have been defined by The European Society of Cardiology/ACCF/AHA/ World Federation task force and include the following [17-18]

- ST elevation at J point of greater or equal to 2 mm (0.2 mv) in at least 2 contiguous leads in men or 1.5 mm (0.15 mv) in women in leads V2-V3
- And/or greater or equal 1 mm (0.1 mv) in the other contiguous chest or limb leads.
- Sgarbossa criteria are applied to a new or presumed new LBBB and a score of equal or more than 3 patients is considered for thrombolysis. [26]

Exclusion criteria

The following patients are excluded: patients younger than 18 years, patients who did not receive lytics, stable and unstable angina, Non-ST-Elevation Acute Coronary Syndromes (NSTE-ACS) [27] pre-hospital thrombolysis, thrombolysis for conditions other than MI (stroke, pulmonary embolism), thrombolysis from other medical facilities before referral to Victoria EC.

Patients that lack outcome at discharge information (survival, death or transferred) or a diagnostic ECG will also be excluded from further analysis. Patients with missing variables surrounding sub-objectives will not be excluded from analysis. In these instances, calculations will be adapted to accommodate the missing values.

Recruitment and Enrolment

This study aims at collecting 100 eligible participants. The data collection will start using the period covering 1 July 2014 to 1 July 2015 and be extended if necessary. Participants will be recruited by perusing Victoria hospital EC resuscitation register and additional relevant information will be extracted from patients' clinical records (hospital folders). Entry criteria will be patients that have received thrombolysis in the emergency centre. Inclusion and exclusion criteria will be applied from there. Anonymised copies of ECG scripts will be forwarded (see below under research procedures) to an independent panel for evaluation and agreement of STEMI anatomical classification.

Research procedures and data collection methods

Initially, study participants will be identified using Victoria Emergency Centre resuscitation register which is kept in the resuscitation bay of the Emergency Centre. A Microsoft Excel spread sheet will be used to capture relevant information from the resuscitation register and

clinical records of participants. Specific data variables will then be extracted from the records of identified patients as summarized below in Table 2. The initial diagnostic ECG and 90 - minute post- thrombolysis ECG will be copied from the folder for further analysis. Once all the data has been collected, folder numbers will be replaced with an individual study number. The ECGs will be anonymised similarly and labelled with the corresponding study number.

The initial diagnostic ECG and 90-minute post- thrombolysis ECG will be copied from the folder for further analysis. Once all the data has been collected, folder numbers will be replaced with an individual study number. ECG will be anonymised similarly and labelled with the corresponding study number.

Table 2 Variables to be collected

Patient folder number
Age
Gender
Time of arrival/ triage
Time of diagnostic ECG
Time of thrombolysis
Disposal from hospital (discharge/ transfer)
Hospital survival

Three emergency medicine specialists, all with a particular interest in ECG interpretation, will be involved in the assessment of the study ECGs. Drs. Malan, Vallabh and Lahri are registered with the HPCSA and College of Emergency Physicians as specialist emergency physicians and jointly direct a two-day ECG workshop that is underwritten by the University of Cape Town [(28).] The ECG will firstly be analysed by Dr Malan, who is also study investigator and then independently verified by two specialists (emergency physicians) who are not part of the research team, Drs. Vallabh and Lahri. In instances of non-agreement (from one or more of the three assessors) then the ECG will be discussed in a meeting by all three assessors and a final result will be agreed upon. In case of non-agreement at the meeting, concerned ECG

and corresponding case will be excluded from this part of the study. The outcome data for the partially excluded case will still be included. This is graphically described in Figure 1 below.

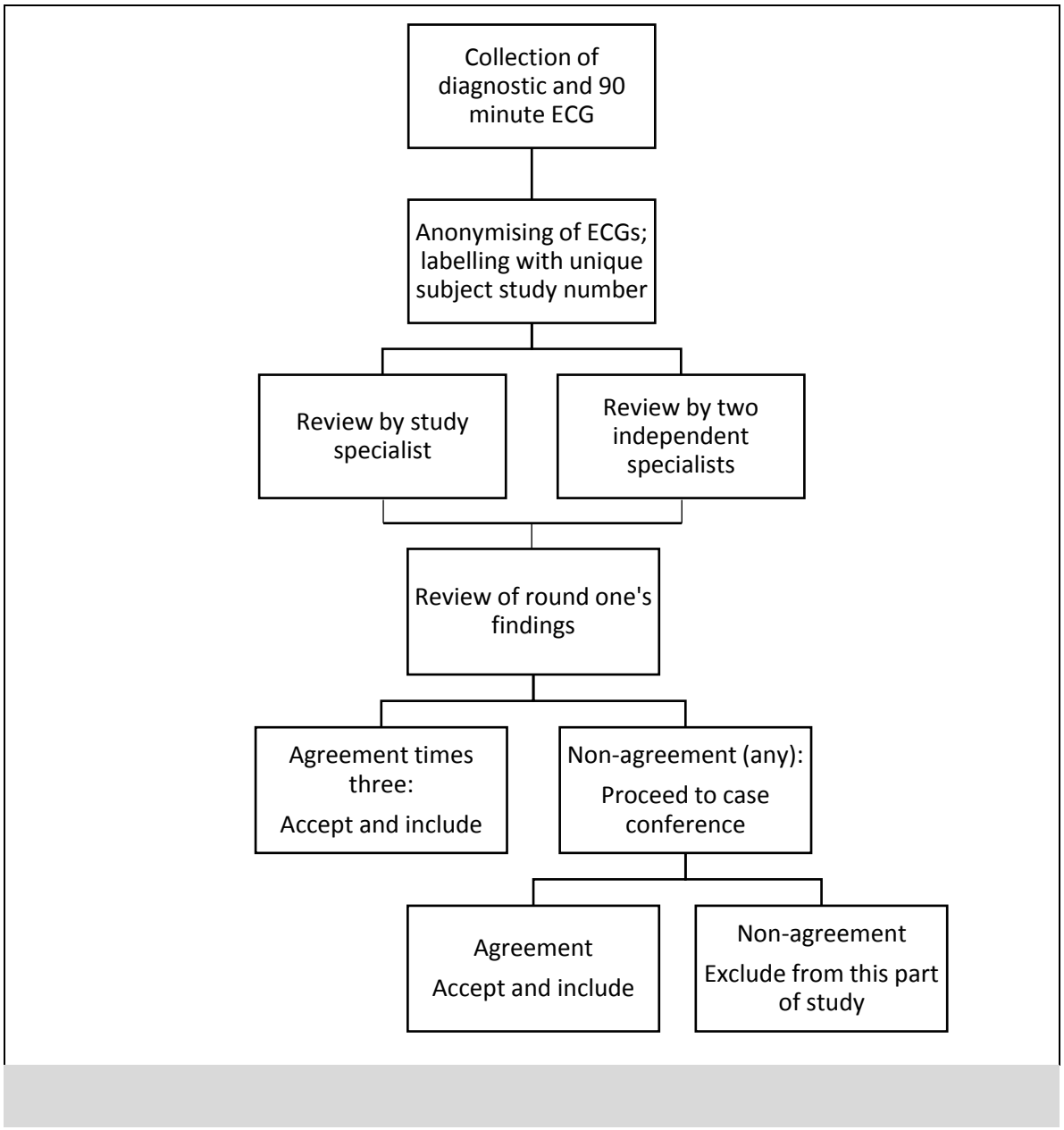

Figure 1 Flowchart depicting evaluation of ECGs by specialists

Data safety and Monitoring

The EC resuscitation register is kept in the resuscitation bay of the EC while clinical records are stored at the central admission department. The electronic record is available to senior clinical persal staff. The patients' folder number will initially be used to link the register entries, the

clinical and electronic record. Other identifiable information (name, addresses, etc.) will not be collected. Participants will be allocated a unique study number after data collection has been completed. This will occur prior to analysis. Anonymised ECGs will be hand delivered by Dr Kibamba to each of the study specialists and he will collect the ECGs once again after assessments are completed. All hardcopy copies of ECGs included in the study will be safely stored in a lockable cupboard in an access controlled office at Victoria Hospital. Data captured electronically will be stored in a password protected folder on a work computer situated in the same access controlled office described above.

Data analysis

A statistician was consulted for the data analysis plan. Descriptive statistics will be provided, using mean or median as a measure of central tendency and standard deviation or interquartile range as a measure of spread. Proportions will be given throughout. It is unlikely that the sample will provide a large enough power to perform detailed statistics on the intended subgroups and this will not be included. This will be considered once the data proves useful and a larger registry is set up, once again in consultation with the statistician. Confidence intervals will be quoted as a measure of precision. Once data collection has been completed the statistician will again be consulted to reassess the data analysis plan and amendments will be made accordingly.

ETHICAL CONSIDERATIONS

Risks and benefits.

Study investigators will not have direct contact with patients and only the clinical records and EC resuscitation register will be utilized. This study is being used to explore the creation of a larger registry to track short to medium term outcomes of thrombolysed STEMI patients. Understanding the nuances surrounding outcome in a thrombolysed STEMI community within the local setting will be useful to guide policy and guidance both at the facilities providing thrombolysis and the tertiary referral centres with Primary Coronary Intervention capability in terms of referral protocols. The main risks are exposing personal information. However, safeguard measures are in place to avoid that (see data safety above)

Informed consent process

Relevant study information will be obtained from EC registers and clinical records. Following collection, data sets will be anonymised prior to analysis starting and a waiver of consent will be requested.

Privacy and confidentiality

Efforts will be made to preserve privacy and confidentiality of participants through early anonymization. Unique study numbers will be allocated to each participant prior to analysis starting.

DISSEMINATION OF FINDINGS PLAN

This project will serve as a pilot study for further investigations and establishment of larger registry to track short to medium term outcomes. The findings of this study not only will be published in a form of original article or short report in an open access journal but also will be shared with Victoria hospital emergency centre management, the University of Cape Town as well as the Western Cape provincial government (DOH).

PROJECT TIME LINE

December 2015: EMDRC proposal submission

January 2016 – February 2016: UCT HREC Application

February 2016 – April 2016: WCG Health Application

April – May 2016: Data collection

May – June 2016: Data Analysis

June – Sep 2016: Write up and submission for publication

RESOURCES UTILISATION

The study investigators will not conduct the study either data collection or analysis while on duty at the hospital. However, the hospital data or admin clerk will be utilized for the retrieval of study participants' clinical records (patients' folders). Writing- up, printing, and binding of copies of the project will be done without hospital resources.

BUDGET

It is important to note that there will not be external funding and the cost of this study will be borne by the investigator.

Item	**Cost**
Personnel Compensation	**R 00.00**
Consulting services	**R 0.00**
Statistical services	
Travel	**R 00.00**

Transport and travel cost	
Equipment and furniture	**R 0.00**
Computer	
Other	**R 2000.00**
Telephone, cell phone, fax	R 250.00
Printing, copying & binding	R 1500.00
Internet & email	R 250.00
Ethics committee fee	**R 0.00**
Total cost	**R 2000.00**

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