A descriptive study of the use of Troponin I testing at a Cape Town district hospital

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Abbreviations:

ACS: Acute Coronary Syndrome

BNP: B-type natriuretic peptide

CK-MB: Creatine Kinase Muscle/Brain

EC: Emergency Centre

ECG: Electrocardiogram

GRACE: Global Registry of Acute Coronary Events

HEART: Score consists of the following factors: History, ECG changes, Age of the patient, Risk factors and the level of Troponin.

ICU: Intensive Care Unit

MACE: Major Adverse Cardiac Event

MI: Myocardial Infarction

NSTEMI: Non-ST Elevation myocardial infarction

STEMI: ST elevation myocardial infarction

TIMI: Thrombolysis in Myocardial Infarction

UA: Unstable Angina

Part A. Literature review

Introduction

Myocardial ischaemia occurs when there is interruption to the blood flow in a coronary vessel. This results in cardiac muscle cell (myocyte) injury due to the resulting inadequate oxygen supply. If ischaemia continues without restoration of blood flow, a myocardial infarction (MI) may result. An MI is marked by irreversible death of cardiac myocytes and subsequent impairment of cardiac function, and possibly death (1). Troponin testing has become the reference standard for defining an MI according to the third definition of MI: "The term Acute Myocardial Infarction (AMI) should be used when there is acute myocardial injury with clinical evidence of acute myocardial ischemia and with detection of a rise and / or fall of cardiac troponin values with at least one value above the 99th percentile upper reference limit and at least one of the following: symptoms of myocardial ischaemia, new ischaemic ECG changes, development of pathological Q waves, imaging evidence of new loss of viable myocardium… …or identification of a coronary thrombus by angiography or autopsy" (2).

Ischaemic heart disease, once fairly uncommon within Africa, has rapidly grown as a pathology throughout the continent alongside industrialisation and urbanisation (3). However, it is unclear whether the diagnostic ability to accurately identify MI grew alongside it (4). In resource limited settings (such as those found throughout Africa), the quality of a troponin assay may vary as much its availability (5). Therefore, as a scarce resource, it is important that troponin testing be used judiciously.

Aim

The aim of this review is to introduce and describe the indications for troponin testing, how troponin tests are used, and the interpretation of the findings (specifically where MI is not suspected) within the global and local African and South African context.

Objectives of the Literature Review

1. To provide a brief description of acute coronary syndrome (definition, presentation and diagnosis)

2. To describe the indications for the use of a troponin test
3. To describe the use of troponin in the hospital
4. To describe the interpretation of troponin results
5. To briefly describe the relevance of these objectives within the South African context

Literature search strategy, including inclusion and exclusion criteria

The Health Sciences Library was used to perform searches and to obtain the original articles reviewed in this study. PubMed and Google Scholar were used to perform additional searches using the terms “troponin”, “clinical decision rules”, “HEART score”, “emergency department/ centre/ unit”, “accuracy”, “rule out”, “acute cardiac syndrome”. The terms “risks”, “indications”, “low resource”, “Africa”, “South Africa” and “Western Cape” were added to the Boolean search terms to focus on specific areas of research. A snowball strategy was then used, whereby prominent articles cited in the papers obtained from the index search were also accessed and included in the review.

Inclusion criteria:

- Publication date: January 2008 - June 2018,
- Language: English, including studies translated and published,
- Relevance to topic of study

Exclusion criteria:

- Studies outside of the stipulated timeframe,
- Language other than English,
- Articles with restricted access

Quality criteria

Titles and abstracts were initially screened for relevance to the review and those deemed to have low relevance or poor external validity were excluded. High-quality evidence, including

systematic reviews, was sought to address the aim and objectives. Papers were informally appraised against a checklist from the Oxford Centre for Evidence-Based Medicine. A representation in tabular form of appraised papers is not required for a narrative review and therefore was omitted. Very little data were available that directly addressed some parts of the aim and objectives – particularly with regards to the current practice of troponin use in low- and middle-income settings and South Africa – and thus criteria were applied less stringently here.

Description of Acute Coronary Syndrome:

"Acute coronary syndrome is a term used to describe a range of conditions associated with sudden, reduced blood flow to the heart. One condition under the umbrella of acute coronary syndrome is myocardial infarction (heart attack) — when cell death results in damaged or destroyed heart tissue. Even when acute coronary syndrome causes no cell death, the reduced blood flow alters heart function and indicates a high risk of heart attack. Acute coronary syndrome often causes severe chest pain or discomfort. It is a medical emergency that requires prompt diagnosis and care. Treatment goals include improving blood flow, treating complications and preventing future problems." (6)

Presentation of Acute Coronary Syndrome

Acute Coronary Syndrome may often present with signs such as sweating, agitation, vomiting, tachypnoea, pale, cool skin, additional heart sounds or hypotension. Symptoms may include a sensation of shortness of breath, nausea, fatigue and pain or pressure in the thorax, specifically retrosternal, that can radiate to either side of the neck, jaw, arms, or shoulders. (7) Certain signs and symptoms may be grouped into what physicians may call 'typical' for acute coronary syndrome, including nausea, diaphoresis, retrosternal pressing chest pain, with radiation into the left side of the neck, jaw or arm. (8) In contrast, 'atypical' signs and symptoms may include fatigue only, dyspnoea only, delirium, right sided chest pain, with radiation into the right arm or side of the neck, stabbing chest pain, epigastric pain or positional or pleuritic chest pain. (9)

Diagnosis of Acute Coronary Syndrome:

Physicians typically describe their patient's history, presentation and physical examination uniformly, however, it has been shown by Body et al, in their prospective study, that *typical* signs and symptoms and *atypical* signs and symptoms do not persistently correlate with predicting the presence of ischaemia. For example, patients with left sided chest pain were less likely to have a proven infarct than patients with right sided chest pain. (10) Furthermore, their findings suggest that the utilisation of clinical signs and symptoms only, may miss an unacceptable number of patients with an MI, especially with regards to the timeous identification of Acute Coronary Syndrome (ACS) in the context of acute chest pain. This suggests that neither *typical* nor *atypical* clinical features are reliable as a sole indicator of the presence of cardiac ischaemia. Further investigations are thus required, in an effort to determine effective, but also affordable alternate methods of ACS identification.

Cervellin and Rastelli (2016), indicate that clinical gestalt does well to predict the presence of an ischemic event, in patients presenting with typical or atypical clinical signs. However, it does especially well when used in conjunction with a suggestive electrocardiogram (ECG), which is elaborated upon below. (11)

The electrocardiogram or ECG

Acute Coronary syndrome, as described earlier, encompasses a range of diagnoses – each with its own ECG features. These include ST elevation myocardial infarction (STEMI), Non-ST Elevation myocardial infarction (NSTEMI) and Unstable Angina (UA). STEMI is defined by the presence of an elevation of the ST segment of the ECG, corresponding to a region of the heart, with reciprocal ST depression in the opposite leads. NSTEMI presents with ST depression and UA may present with non-specific changes. In order to distinguish between these and in order to clarify the need for thrombolysis – specific biomarkers are used to diagnose the presence of infarcted myocardium. (12)

Cardiac Biomarkers

Since the first use of biomarkers in assisting with identification of myocardial ischaemia, there have been a number of different types used and studied. Over the years, these

included creatine kinase –muscle/brain (CK-MB), cardiac myoglobin, B-type natriuretic peptide (BNP), the troponins and other more obscure markers. The introduction and use of these cardiac biomarkers improved the correct identification of cardiac ischaemia. Cardiac biomarkers are typically enzymes which may be present in elevated levels in the patient's serum in the presence of cardiac myocyte injury, resulting, for example, in the leaking of enzyme from the myocyte. (13) CK-MB, cardiac myoglobin and BNP will be discussed briefly below. Troponin will be discussed separately.

Creatine Kinase Muscle/Brain (CKMB)

CKMB is an enzyme that is released by muscle cells in the body when they undergo cell death. It is useful, because acute cardiac cell death will cause a predictable rise in the level of CKMB, and correlates well with the extent of the infarct. The problem with CKMB is that other causes of non-cardiac muscle death, such as trauma, may also cause a rise above the normal limit, causing a false positive test. To help clarify the source of the CKMB rise, clinicians may repeat the test and observe a significant rise in levels over time, but this is both time-consuming and resource intensive. (14)

Cardiac Myoglobin

Myoglobin is a haem protein present in skeletal and cardiac muscle and was initially of interest due to its rapid rise (2-4 hours, compared to 4-6 for CKMB), a result of its low molecular weight. Similar problems exist, however – the protein may rise in the presence of other causes of skeletal muscle damage, obfuscating the clinical picture. (15)

B-type natriuretic Peptide

BNP is a hormone released by cardiac myocytes in the presence of left ventricular dysfunction and has been shown to increase predictably in the presence of infarction. The hormone is not specific, however, and may also be elevated in the presence of long-standing heart failure and renal impairment. (16)

Troponin

Troponins are regulatory proteins that are involved in the calcium mediated interaction between actin and myosin in cardiac myocytes. Troponin I and T have been found to be superior to other biomarkers in terms of sensitivity, though Troponin T may appear in very small amounts in skeletal muscle cells. Troponins are commonly used in conjunction with clinical history and examination and ECG findings in order to make definitive treatment decisions. (17) Unfortunately, Troponin's specificity may be compromised by the fact that various other causes of cardiac myocyte ischaemia can cause elevated levels.

Indications for the use of Troponin Testing

Troponin is a protein present in cardiac and skeletal muscle that plays a role in muscle contraction. (18) Troponin I, a subunit of Troponin, is present only in myocardium. (13) During damage to myocytes, such as myocardial infarction, Troponin I is released into the blood – and can be used as a marker of cardiac cell death. (19) This distinction allows the clinician to distinguish between infarction and angina, in a patient with chest pain, which has led to its implementation in the diagnosis of MI. (20)

In general, the sensitivity of Troponin I is estimated at >99% if taken between 3-6 hours from onset of injury, while the specificity is estimated at 80-85%. (21, 22) This means that the test has a high likelihood of detecting cardiac myocyte damage, but that other conditions may cause the result to be elevated. (22) Its high sensitivity also allows myocardial damage to be excluded with confidence if negative. (23)

The release of Troponin takes place during any form of myocyte damage – this means that the protein will be present in patients who have sustained cardiac muscle damage by other means. (24) This includes chronic cardiac causes of myocyte damage, such as in heart failure, arrhythmias, and inflammatory conditions such as myocarditis or pericarditis, cardiomyopathies or traumatic cardiac injury, such as contusion. (25) Non-cardiac conditions, which cause cardiac myocyte damage by indirect means, can also cause raised Troponin I levels – such as sepsis, kidney disease, aortic aneurysm, COPD or central nervous system disorders such as subarachnoid haemorrhage. (20, 26, 27) Certain drugs and toxins may have the same effect. As such, there are a multitude of reasons why Troponin I results need to be interpreted in the context of clinical history, physical examination and the electrocardiogram

(ECG). (28) Serial testing which reveals a significant increase in Troponin I levels over time is the best indicator of the presence of infarction. (29)

History of Troponin use in Hospitals

In 1997, Mair suggested that other biomarkers should no longer be used and that attention of clinicians should be focused on the Troponin markers, which seemed superior in both sensitivity and specificity. (13) This was supported by Thygesen et al (2012), whose report indicated high sensitivity with the use of Troponins, specifically in the acute care setting, while Wu et al, stated that: "…use of a highly sensitive assay produces a higher clinical sensitivity for AMI patients compared to an assay with conventional analytical sensitivity." (19, 30)

The use of Troponin I as point of care tests underwent critical review by Bingisser et al. in 2012 and Keller et al (2011) showed that using specifically Troponin I as an early marker of myocardial ischaemia improved diagnostic yield. (22, 31) This is supported by further studies by Kaess et al (2017), Lewandrowski et al (2014) and also in a systematic review by Westwood et al (2015). (27, 32, 33) Conversely, Troponin I is also able to rule out the presence of an ischemic event by way of its absence when used in the appropriate time frame. (22)

Bingisser et al. (2012), further described the use of cardiac troponin I to identify the presence of cardiac ischaemia within the specific context of the emergency department. Their study described the high sensitivity and specificity in this context and went on to discuss the relationship between clinical signs, ECG and the use of biomarkers. (31) Kemper et al (2017), further find support for the use of Troponin I in the emergency setting. (34) Thygesen et al and Amsterdam et al identify Troponin I as the preferred biomarker in diagnosing AMI. (5, 35)

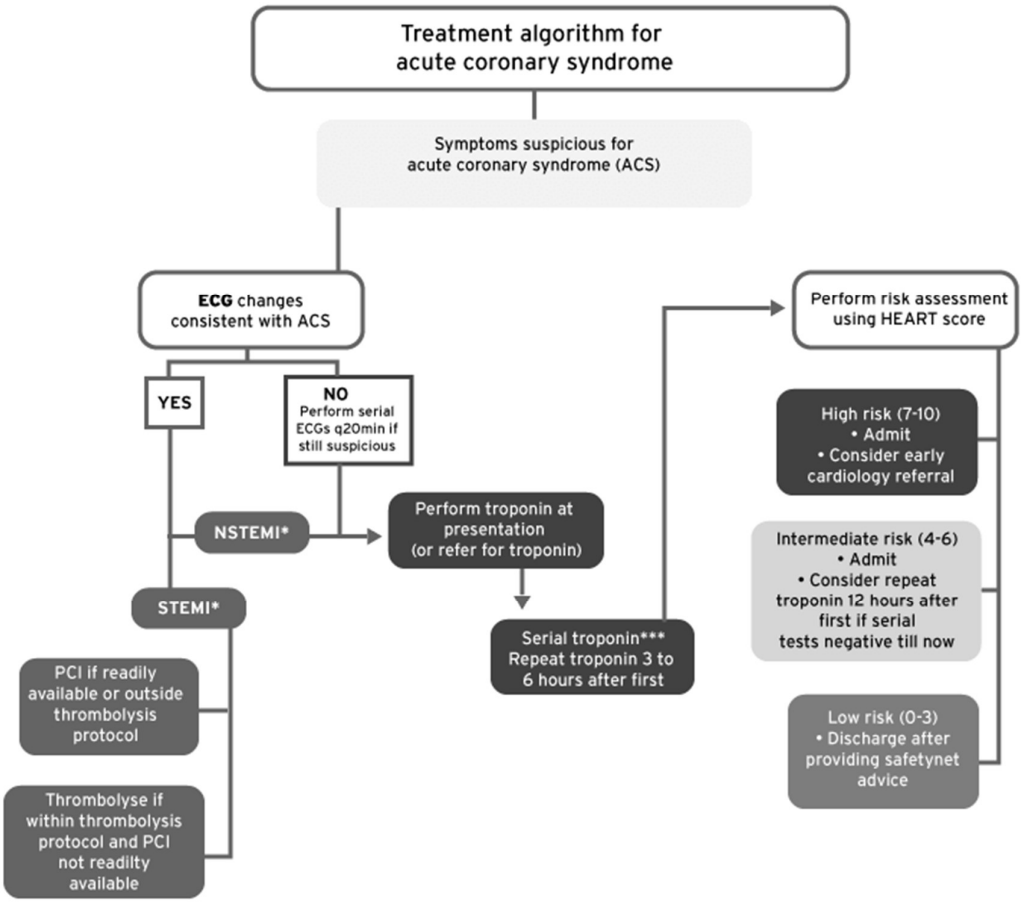
In order to remain cost-effective, Troponin testing should not be delayed beyond a certain time frame, allowing appropriate, timeous therapeutic intervention and avoiding delay to reperfusion of cardiac myocytes and prolonged stay in ICU. (36) When Troponin I testing is used, it should be done early enough to allow for appropriately timed intervention.

Troponin Testing in the South African Context

South African clinicians have, until recently, still been using a combination of older cardiac enzymes, according to Bellhudder (2012), which reduces cost-effectiveness and potentially contributes to misdiagnosis. (37) Following a South African review in the same year, Troponin I has become accepted as standard of care. (38, 39) A study by Beukes et al (2018), indicates that initial and serial cardiac troponins are less readily accessible in Lower Middle Income Countries compared to High Income Countries. (40)

The HEART guidelines have become integral to the South African acute cardiac ischaemia decision matrix. South Africa's local clinical guidance resource, the Essential Medical Guidance, has incorporated the HEART score in its protocols since 2017, as illustrated below. (41)

Figure 1: The Clinical Decision Pathway (41)



Note: Reprinted from Acute Coronary Syndromes, by EMCT (2017), *retrieved from https://emguidance.com/guidelines by* EMGuidance

Troponin I is a quick, useful, easy to perform, but expensive resource. As an observational study our study describe how Troponin I tests are used at a typical public setting; describing inconsistencies in the application of clinical resources and judgement. It should also highlight associations between the result and other quality and application measures, i.e. time to testing and symptoms prompting testing. This would provide information regarding local testing thresholds and perceived risk that could be addressed from an educational and cost-savings potential.

Risk assessment in acute coronary syndrome: Clinical Decision Rules

By integrating history and clinical signs and symptoms, with characteristic ECG changes and the elevation of Troponin I, clinicians can further enhance the correct identification of cardiac ischaemia. This strategy requires that the using clinician follow a set standard of steps in order to risk stratify each patient's likelihood of having had an ischaemic event. Clinical Decision Rules are tools that doctors may use in order to facilitate bedside clinical decisions and therapeutic interventions.

Clinical Decision Rules may consist of a collection of signs and symptoms, patient-related demographic factors, bedside or laboratory tests or imaging and history. These collections of data need to be validated and show consistency in clinical practise, and require ease of use. Chang et al (2017) support the use of Clinical Decision Rules in addition to Troponin. Other studies which looked specifically at Clinical Decision Rules include Long et al (2017), which describes the HEART Score and pathway. (41, 42) Of the Clinical Decision Rules developed and tested, The HEART Score consistently performs the best. Similar tools such as the Thrombolysis in Myocardial Infarction (TIMI) and modified TIMI were found to be unable to classify patients into discrete groups, while the Global Registry of Acute Coronary Events (GRACE) Score was not designed to assess undifferentiated chest pain. (43, 44, 45)

The HEART score consists of the following factors: History, ECG changes, Age of the patient, Risk factors and the level of Troponin. Points are allocated based on the nature of each factor: History, for example, would need to differentiate between non-specific, specific and highly suspicious for a myocardial infarction. Troponin results are allocated points based on whether they are negative, equivocal, or positive. These factors allow patients to be stratified according to their risk in the context of undifferentiated chest pain, and patients at a higher risk of a major adverse cardiac event (MACE) within the next 6 weeks to be identified. MACE events may include cardiovascular death, myocardial infarction, stroke, or non-coronary artery bypass graft-related major bleeding.

Interpretation of Troponin Testing

In the setting of a suspected AMI, ECG changes may suggest a STEMI or show features of NSTEMI. In the case of NSTEMI, Serial Troponins can be performed, with a repeat at 3-6 hours. If the Troponin continues to be negative, the treating doctor may then use the HEART Score to risk stratify the patient into High, Intermediate, or Low Risk. Each risk level requires

a different action. High Risk patients are admitted, and cardiology referral is considered. Intermediate Risk patients May be admitted with a repeat Troponin done at 12 hours. Low Risk patients may be discharged.

Risks of Over Testing

We have explained how Troponin tests may be raised in conditions other than AMI, which has the potential to complicate the final treatment pathway. Unnecessary use of the Troponin test can be harmful and may lead to incorrect clinical diagnosis as well as costly and invasive investigations, such as angiography, which carries its own inherent risks. Further problems include prolonged hospital stay and waste of financial resources – especially of concern in this resource context. (46, 47, 48)

Conclusion

Diagnostic tests are required to aid the clinician in identifying patients at risk of MI, make a timeous diagnosis which allows for appropriate intervention and avoid missing patients who present atypically, but are at risk of cardiac ischaemia. We discussed the Troponin I test and its use as the primary cardiac enzyme, rather than other less sensitive or specific markers, appears to be well justified. We also discussed the role of the clinical decision-making guidelines and motivation is made for the use of the HEART guideline both internationally and locally.

There appears to be a paucity of data describing how Troponin I tests are used in the broader South African context and in the Western Cape and Cape Town. It is possible that the tests can be more judiciously applied, providing a cost-wise solution, without affecting safety and quality. This links in with the aim of our study in the next chapter which is to describe the use of the relatively expensive Troponin I test within a local secondary level hospital. Understanding how this test is used in this clinical setting may provide guidance on its rational use in the Western Cape.

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Part B. Manuscript in article format

Title Page

A descriptive study of the use of Troponin I testing at a Cape Town district hospital

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Abstract

Introduction

Troponin I tests have been shown to be accurate and are relied upon to assist in making critical decisions regarding patient care in patients presenting with chest pain. The tests are expensive, however, and so their rational use becomes extremely important in a budget-constrained public health sector. The aim of this study was to describe how Troponin I tests are used throughout Victoria Hospital, by a range of requesting clinicians, working in different specialties.

Methods

A cross-sectional, prospective design was employed, using multiple data sources. We collected a consecutive sample over a three-month period from Victoria hospital's Emergency Centre using a dedicated data collection tool connected to use of the point-of-care troponin I test. We supplemented this prospective sample with outcome data, using the hospital's electronic admission record.

Results

Three hundred and sixteen patient entries were included in the final results. The majority of Troponin tests were negative (70%). Discharge directly from Emergency Centre was 10% in Troponin I positive patients, 37,5% in Equivocal Troponin patients, and 65% in Troponin negative patients. Furthermore, patients were twice as likely to be transferred to a tertiary facility if their Troponin was positive (24%), compared to equivocal (10.4%) or negative (12%).

Discussion

Chest pain was the most common presenting complaint, with Acute Coronary Syndrome being the most common working diagnosis. The clinical management of patients varied considerably when comparing their Troponin I result. Troponin I appears to be used as an effective rule-out tool in the decision-making pathway.

Introduction

The sensitivity of Troponin I is estimated at >99% if taken between 3-6 hours from onset of injury, while the specificity is estimated at 80-85%.(1,2) This means that the test has a high likelihood of detecting cardiac myocyte damage, but that other conditions may cause the result to be elevated, resulting in a fairly high number of false positives.(2) Its high sensitivity also allows myocardial damage to be excluded with confidence if negative.(3)

The cost of each Troponin I test ranges between ZAR 95.00 to ZAR 115.00, which is expensive for a single use test in a low- to middle-income setting. The machines used to interpret the test, the routine maintenance, and the requirement for Troponin I to be stored in a refrigerator all add to this cost.(4) Although its sensitivity is useful from an acute care perspective the relatively high cost compared to other commonly used tests is important from a local health economics context.(5) Inappropriate use of Troponin and the misinterpretation of a false positive result can lead to further unnecessary testing later, including stress echocardiography, cardiac catheterisation and percutaneous intervention.(6)

The aim of this study was to describe how Troponin I tests are used throughout Victoria Hospital, by a variety of requesting clinicians, across various levels of seniority and training and working in a range of specialties and areas within the hospital, in terms of indication, test finding (positive or negative), working diagnosis and outcome.

Materials and Methods

Study Design:

A prospective, cross-sectional design was used, including multiple data sources.

Characteristics of the Study Population:

Victoria Hospital is a district level hospital, in Wynberg, Cape Town. It has 181 ward beds, 3 day ward beds and an overnight ward. The available specialties include Surgery and Medicine, Emergency Medicine, Paediatrics, Psychiatry, Orthopaedics, Palliative Care and Auxiliary services. The hospital has a High Care Unit. Victoria hospital operates in the South Peninsula Health District of the Metro Region. The Emergency Centre (EC) sees 47,000 patients annually, while Victoria Hospital sees 83,950 annually.

We tracked the use of the Alere Triage Troponin I for this study as supplied by the local laboratory. This assay is situated in the EC of Victoria hospital and has to be used here. The user protocol requires that all hospital areas should have access to the assay via the EC. Presently, only clinicians have access to use of the assay, and testing is controlled through the EC. Given the cost of the test, quality control and record keeping, clinicians have to complete a register when making use of the test. The register includes patient location, indication for testing, working diagnosis and the result of the test. Further formal Troponin testing requires samples to be sent off-site to a tertiary hospital laboratory, 11km away.

We estimated that the EC assay is used for approximately 50 patients over a 30-day period. As it was unclear exactly how the data would present following analysis, and due to the lack of local research on user workflow in troponin testing, we did not attempt a power calculation. Instead we decided to collect a convenience sample over a three-month period.

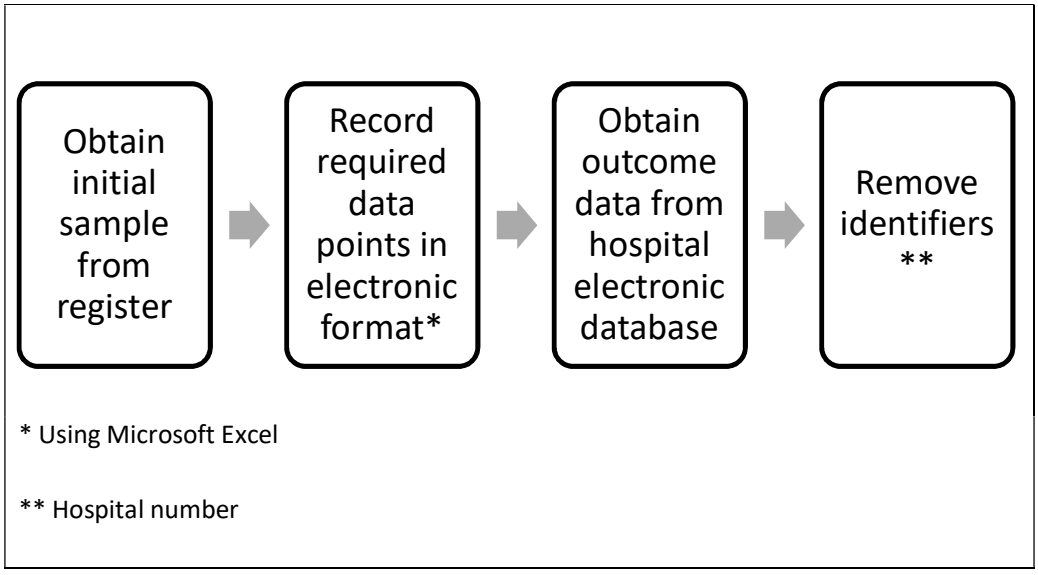
Recruitment and Enrolment:

Data were collected from multiple sources. We prospectively collected a consecutive sample of troponin testing over the study period using a dedicated data collection tool. Essentially this data collection tool replaced the troponin I test register over the study period. It captured all the information previously included with a few additional variables added for study purposes. To reduce confusion, a hard copy register similar to the register used outside of the study was used. A sample page from the register is provided in Appendix A. We supplemented this sample with outcome data (discharge from Victoria EC, discharge from Victoria Hospital, transfer to tertiary centre, or death at Victoria Hospital or EC) using the hospital's electronic admission record by matching the patient identifier (hospital number) from the register to the admission records. Missing data fields (outcome, patient age, patient gender and hospital area) in the hospital's electronic admission record prompted a review of the clinical record of the relevant patient for the missing data points. The variables collected from the register are listed in Table 1 (second column). We excluded patients in which a full data set could not be obtained. We accepted the following missing variables: patient age, gender and hospital area where the patient was situated. Any other missing variables resulted in an unusable entry with exclusion of the patient. Figure 1 describes the data collection strategy.

Table 1. Variables collected for the sample

Variables from register	Variables from hospital electronic admission record and clinical record
1. Hospital number 2. Patient age 3. Patient gender 4. Hospital area where patient situated 5. Clinician rank: consultant, medical officer, specialist trainee, community service medical officer, intern 6. Primary indication for performing the test from the following: • chest pain, • other pain suggestive of ACS (arm(s), neck, back, abdomen), • shortness of breath, • observed ECG abnormalities associated with ACS 7. Other indication (optional/ specified) 8. Time of onset of symptoms 9. Working diagnosis (specified) 10. Troponin I result	1. Outcome: discharge from Victoria EC, discharge from Victoria Hospital, transfer to tertiary centre, or death at Victoria Hospital/ EC 2. Outcome: date outcome was achieved 3. (Patient age) 4. (Patient gender) 5. (Hospital area where patient was situated during admission)
EC, emergency centre; ACS, acute coronary syndrome; ECG, electrocardiogram; Variables in parenthesis indicate that variable will be supplemented only if not collected in the prospective register	

Figure 2. Data collection strategy



Data Analysis:

Data was captured in an Excel spreadsheet (Microsoft Office, Redmond, USA) which was also used to conduct the analysis. Descriptive statistics were applied to the sample as follow: categorical variables, such as outcome, were described using proportions. Where applicable, data were described using histograms and charts. We specifically looked for associations between troponin test results, indications for testing, onset of symptoms, working diagnosis and outcome. For outcome, we also described the proportion of patients who reached an outcome within 48 hours of troponin testing.

The study was approved by the Human Research Ethics Committee of the University of Cape Town, Reference Number: 737/2017.

Results

A total of 356 samples were collected, of which 40 were excluded due to incomplete entries, illegible entries and missing variables.

Table 2. Patient Demographics and Baseline Characteristics

Patient:	Troponin Positive (49/16%)	Troponin Equivocal (48/15%)	Troponin Negative (219/69%)	Total (316/100%)
Sex				
Men	21/43%	22/46%	102/47%	145/46%
Sex				
Women	28/57%	26/54%	117/53%	171/54%
Age				
Median	70	59	54	60
Range	27-83	40-83	25-94	25-94
Hospital Area				
EC	48/15.3%	48/15.3%	217/69.3%	313/99%
Other	1/2%	0/0%	2/0.8%	3/0.9%
Outcome				
Transfer to Tertiary	12/25%	18/38%	29/13%	59/19%
Discharge from EC	5/10%	5/10%	129/59%	139/44%
Discharge from Hospital	32/65%	23/48%	59/27%	114/36%
Death	0/0%	2/4%	2/1%	4/1%

Clinicians requesting the troponin test consisted of 252/80% medical officers, 38/12% specialist trainees and 25/8% consultants.

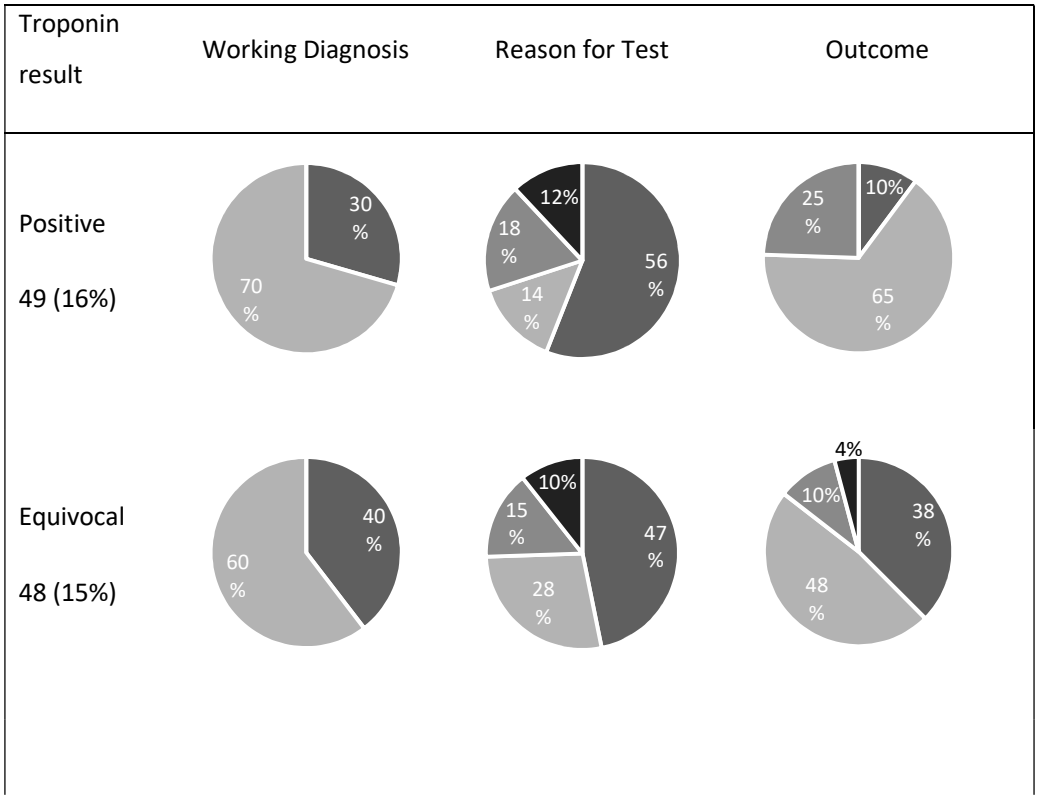
The test was performed by 167/53% medical officers, 111/35% interns, 25/8% specialist trainees and 13/4% consultants.

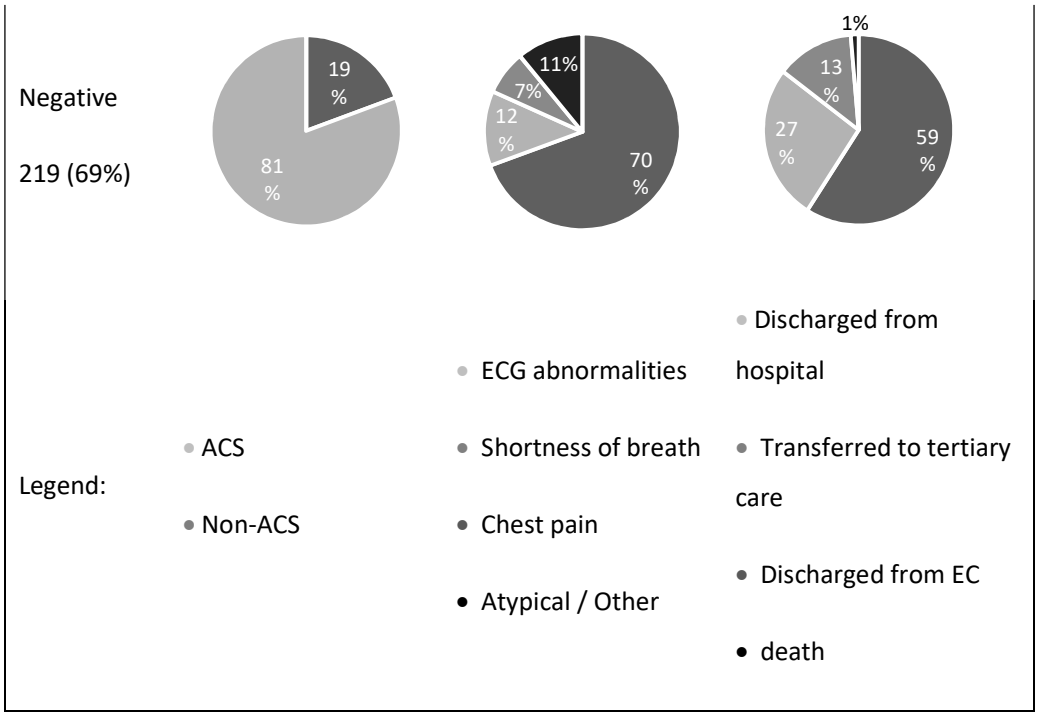
Chest pain was the most common primary indication for performing the test 218/69%, followed by ECG abnormalities associated with ACS 94/30%, shortness of breath 84/27%, other clinical features of ACS 42/13%, and other types of pain (described by pain radiating to the arm, neck or back, or abdominal pain) 37/12%. Many clinicians included more than one type of indication on the data sheet – this is described in limitations.

The amount of time passed between the first onset of symptoms and the test being performed was described by the area in which the testing took place. The time in hours for Troponin testing in all areas was 9.37(±5.96), time for testing done in the EC was 9.03(±5.2) and time for Troponin testing done outside of the EC was 35(±4.5).

Of patients with positive Troponin I tests, 65% were finally discharged from hospital, meaning that they were admitted under another specialty, such as Internal Medicine, and discharged once their treatment had been completed there. Further testing and interventions would then be carried out, including confirmation of a final diagnosis, but this did not form part of the study and is not commented on.

Figure 3. Troponin test results with indications and outcomes





Discussion

The primary indication or clinical presenting complaint spurring the use of Troponin I testing was chest pain. Shortness of breath, ECG Changes and other ACS symptoms made up the bulk of the rest of the tests, as may be expected in the multimodal pathway used to diagnose ischemia. (7) In the presence of chest pain, and following the Clinical Decision Pathway in use in the Western Cape Troponin is extremely useful in ruling out the presence of ischemia when used appropriately. (8) Limitations on indications are discussed in the Limitations section.

Most of the Troponin tests performed were used for appropriate indications. There were, however, a large number (50) of working diagnoses for which Troponin testing would not have been indicated. These included diagnoses such as schizophrenia, diabetes, asthma exacerbation or similar. Inappropriate use of Troponin I tests are a potential source of wasted resources and can lead to further unnecessary testing later, including stress ECG, cardiac catheterisation and percutaneous intervention. (6)

Where Troponin test results were positive, however, the majority of working diagnoses were appropriate. There were three tests done with positive results but no indication: two for gastritis, and one for pneumonia. Serial testing was done in a small amount of cases, which can be appropriate in excluding ischemia by comparing levels over time, or when levels are equivocal.

Troponin I is able to rule out the presence of an ischemic event by way of its absence when used in the appropriate time frame and this study looked at the duration of time passed between symptom onset and Troponin testing. The time taken between the onset of symptoms and performing the troponin tests appeared to be quite long, with a mean time of 11 hours in EC. Although this could be beneficial in the context of ensuring a positive Troponin result, in the presence of ischaemia, it is detrimental in terms of patient treatment and addressing the presence of ischemia. Delayed diagnosis and intervention has been shown to result in prolonged stays in ICU. (9,10)

There may be various factors responsible for this, presumably partly related to accessing health care facilities and partly to waiting times upon arrival in the EC. Access issues may include lack of means to contact an ambulance, lack of transport to get to hospital, long waiting times when waiting for an ambulance, long waiting times to be seen in the EC due to high volume of patients, despite the triage system being used effectively.

Time taken to testing outside of EC was higher with a mean time of 35 hours. It is not clear what the reason for this delay was, but may include new symptoms, delay to clinical suspicion, or clinical error. These were initial tests, belonging to patients who had not had a Troponin I before admission to their ward, either form EC or via transfer. The register was able to track repeat Troponins done via EC, but not those done through the National Health Laboratory Service.

The outcomes and disposition vary significantly for each of the Troponin result categories. Possible outcomes listed in the data collection tool included: discharge from Victoria EC, discharge from Victoria Hospital, transfer to tertiary centre, or death at Victoria Hospital/ EC. Where the test was positive, patients were more likely to be admitted to hospital and discharged later, or be transferred to a tertiary facility. There is a significant proportion of patients with positive Troponins who were entered as discharged from Victoria EC – it is unclear whether this is a problem related to the options provided by the form itself, which may have led to misinterpretation by the using clinician or whether the limited disposition outcomes listed on the Clinicom are a contributing factor. Patients with negative results were far more likely to be discharged directly from the EC. It is interesting to note that of the deaths recorded in this study, none had positive Troponins.

Most Troponin tests were requested and performed by Emergency Medicine, with Internal Medicine requesting ten tests. Patients for whom the tests were performed were almost exclusively located in the Emergency Centre. High Care, Medical and Overnight wards each had one patient for whom a test was ordered. It is possible that a higher number of other specialties may request troponin I tests, but that the patients are still located in the EC, due to long waiting times to access ward beds. It should be noted that Internal Medicine sends an additional non-urgent Troponin specimen for laboratory testing, which may influence their use of the test.

The majority of Troponin I tests were both requested and performed by medical officers, which make up the bulk of the employees in the Emergency Centre at Victoria Hospital. In cases where Consultants requested the Troponin tests, medical officers were also the most likely to perform them. These findings are not unexpected. It is possible that consultants should perhaps be more involved in the decision to perform tests, as a cost-saving measure.

Limitations:

The indications provided as options on the data collection tool, distributed by the researcher, allowed for the options of chest pain, other pain which may be associated with ACS such as arm, neck, back or abdominal pain, shortness of breath and ECG abnormalities associated with ACS. The user was able to decide between these options. Many users entered more than one indication on their data sheet – which makes identifying the primary indication impossible.

There are further problems that arise with the data collection tool. Although it is assumed that the user has a knowledge of nuances in the complain of pain in ACS, the sheet does not provide any further explanation. It relies on the user's discretion. If there were other subtler clinical signs present, which prompted the decision to perform a Troponin test, that did not clearly fit into any of the four options listed, the user would be forced to make a choice which may not entirely be explained by one of the four options listed.

The data collection tool was not validated – it was not trialled before use to check appropriateness and understanding. Furthermore, it does not clarify what is meant by ECG abnormalities associated with ACS. It is not clear if there may have been a problem with the design of the form, as the working diagnosis was stated.

It is possible that a higher number of other specialties may request troponin I tests, but that the patients are still located in the EC, due to long waiting times to access ward beds. The register did not specify that patients should clearly be under another specialty's care – so it is not possible to clarify this.

Medical records do not indicate whether clinical support tools such as HEART score were used to guide care, though this is a guideline in place at present. ECG findings were not documented, which could have been useful to report on, as the HEART score uses normal/nonspecific repolarization abnormalities/significant ST deviation.

Conclusion:

The aim of this study was to describe the use of the relatively expensive, but essential, Troponin I test within Victoria Hospital. Understanding how these tests are used in the clinical setting can provide guidance on their rational use in the Western Cape, a relatively resource-limited setting. This study described the use of Troponins by user seniority and training, department, indications for use, as well as final disposition.

We noted that inappropriate use of the Troponin test decreased as the using clinician's training and seniority increased. We showed increased waiting times for Troponin testing and suggested reasons for this, including possible causes of reduced access. We noted the inappropriate use of Troponin I based on presenting complaints and differential diagnosis – allowing for recommendations to be made.

Major limitations include the use of the data collection tool, which was not validated before use. This may have contributed to user error.

Suggestions for further research:

Further research should be directed towards attempting to clarify treatment outcomes, and perhaps could further explore the reasons for users' knowledge or interpretations of testing indications. The findings could also be compared to other similar hospitals in the region, which would enhance the strength of any recommendation.

Important limitations include a lack of data about clinicians' use of a clinical decision tool, their interpretation of Troponin I results and how those influenced their care including further testing and interventions. Further limitations include a lack of data on the final diagnosis of MI, how transfer and referral decisions were made and outcomes of transferred patients.

A mixed methods evaluation that integrates provider insights about how they decide to order troponins, whether cost factors into ordering decisions, and how they incorporate results into their management would be another informative follow-up study.

Acknowledgements, competing interests and funding

I would like to thank the remarkable team at Victoria Hospital for their contribution to this thesis, and for their ongoing commitment to delivering excellent emergency care under challenging conditions.

I would like to thank Dr. Jacques Malan for guiding and driving the data collection process on the ground, as well as his indefatigable support over the years.

Thank you to Prof. Stevan Bruijns, for his careful and consistent advice throughout the entire process. His skilled editing and academic insight are unmatched.

I have no competing interests to declare.

This entire thesis is self-funded.

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Part C. Addenda

A. Relevant journal Instructions to Authors

The relevant journal instructions for authors can be found at the following URL:

http://www.journals.ac.za/index.php/SAHJ/article/view/1878

B. Data collection tool

Patient sticker (if no sticker, please provide the following) Name: Hospital number:	 Surname: Date of birth
Date now:	**Time now:**
Patient Location (e.g. EC, medical ward (specify which), theatre, etc.)	
Requesting clinician rank ☐ Consultant ☐ medical officer ☐ Specialist trainee ☐ Intern ☐ Community service medical officer	**Working diagnosis?**
Person performing test ☐ I am the requesting clinician (if not, please indicate below) ☐ Consultant ☐ medical officer ☐ Specialist trainee ☐ Intern ☐ Community service medical officer	**Reason for Test (Mark ALL that apply)** ☐ Chest pain, ☐ Other pain suggestive of ACS (arm(s), neck, back, abdomen) ☐ Shortness of breath, ☐ ECG abnormalities associated with ACS ☐ Other (specify in box below)
Specialty ☐ Emergency medicine	**Time of onset of symptoms?**

☐ Internal medicine ☐ Critical care ☐ Anaesthesia ☐ Surgery	**Date:** **Time:**

C. Acknowledgements

I would like to thank the remarkable team at Victoria Hospital for their contribution to this thesis, and for their ongoing commitment to delivering excellent emergency care under challenging conditions.

I would like to thank Dr. Jacques Malan for guiding and driving the data collection process on the ground, as well as his indefatigable support over the years.

Thank you to Prof. Stevan Bruijns, for his careful and consistent advice throughout the entire process. His skilled editing and academic insight are unmatched.

Part D. Proposal for Research:

A descriptive study of the use of Troponin I testing at a Cape Town district hospital

- Lead Investigator: Joshua Gibson, GBSJOS001 (University of Cape Town)
- Supervisor (principal): Stevan R Bruijns (University of Cape Town)
- Supervisor: Jacques Malan (Victoria Hospital)

Abstract

Introduction

Troponin I tests have been shown to be accurate and are relied upon to assist in making critical decisions regarding patient care in patients presenting with chest pain. The tests are expensive, however, and so their rational use becomes extremely important in a budget-constrained public health sector. With the recent imperative to limit costs wherever possible, it becomes very important to ensure both quality control and judicious use of an expensive resource.

The aim of this study is to describe how Troponin I tests are used throughout Victoria Hospital, by a range of requesting clinicians, across various levels of seniority and training (consultant, medical officer, specialist trainee, community service medical officer, or intern), and working in a range of specialties including surgery, critical care, anaesthetics, internal medicine and emergency care in terms of indication, finding (positive or negative), working diagnosis and outcome.

Methods

A cross-sectional (across a data range), prospective (pre-determined) design will be used, using multiple data sources. The troponin I assay is situated in the EC of the hospital. All hospital departments must use the assay in the EC to perform a troponin test as a troponin test is not offered by the local laboratory. We will prospectively collect a consecutive sample over a three-month period from Victoria hospital's EC using a dedicated data collection tool that will be connected to use of the point-of-care troponin I test. During the study period

this data collection tool will replace the existing troponin I test results register and will capture all the data points previously captured with an additional few specifically for study purposes. Variables will include patient demographics, indications for test, working diagnosis and test result. We will then supplement this prospective sample with outcome data, using the hospital's electronic admission record (Clinicom). It is estimated that EC Troponin test are used for approximately fifty patients per 30-day period. A three-month data collection should yield approximately 150 entries.

Ethics

There are a number of benefits to describing the use of an expensive resource from a quality control perspective, but also from a cost reduction perspective (identifying waste, improving understanding of test indications, etc.). The study will not affect work flow and should not inconvenience the clinical pathway any more than the existing register does. Patient identity will be protected through judicious record keeping. Although data will be collected prospectively performing consent would simply not be feasible, nor would it allow us to collect a reasonable sample with the resources available to the study team.

Introduction

Troponin is a protein present in cardiac and skeletal muscle that plays a role in muscle contraction.(1) Troponin I, a subunit of Troponin, is present only in myocardium.(2) During damage to myocytes, such as myocardial infarction, Troponin I is released into the blood – and can be used as a marker of cardiac cell death.(3) This distinction allows the clinician to distinguish between infarction and angina, in a patient with chest pain.(4)

The sensitivity of Troponin I is estimated at >99% if taken between 3-6 hours from onset of injury, while the specificity is estimated at 80-85%.(5,6) This means that the test has a high likelihood of detecting cardiac myocyte damage, but that other conditions may cause the result to be elevated.(6) Its high sensitivity also allows myocardial damage to be excluded with confidence if negative.(7)

The release of Troponin takes place during any form of myocyte damage – this means that the protein will present in patients who have sustained cardiac muscle damage by other means.(8) This includes chronic cardiac causes of myocyte damage, such as in heart failure, arrhythmias, and inflammatory conditions such as myocarditis or pericarditis,

cardiomyopathies or traumatic cardiac injury, such as contusion (9) Non-cardiac conditions, which cause cardiac myocyte damage by indirect means, can also cause raised Troponin I levels – such as sepsis, kidney disease, aortic aneurysm, COPD or central nervous system disorders such as subarachnoid haemorrhage.(4,10,11) Certain drugs and toxins may have the same effect. This is why Troponin I results need to be interpreted in the context of clinical history, physical examination and the electrocardiogram (ECG).(12) Serial testing which reveals a significant increase in Troponin I levels over time is the best indicator of the presence of infarction.(13)

Troponin I tests are expensive. The cost of each Troponin I test ranges between R95 – R115. The machines used to interpret the test, the routine maintenance and the requirement for Troponin I to be stored in a refrigerator, add to the cost.(14) Although its sensitivity is useful from an acute care perspective the relatively high cost compared to other commonly used tests is important from a local health economics context.(15) Inappropriate use of Troponin and the misinterpretation of a false positive result can lead to further unnecessary testing later, including stress echocardiography, cardiac catheterisation and percutaneous intervention.(16)

Aim

The aim of this study is to describe how Troponin I tests are used throughout Victoria Hospital, by a range of requesting clinicians, across various levels of seniority and training (consultant, medical officer, specialist trainee, community service medical officer, or intern), and working in a range of specialties including surgery, critical care, anaesthetics, internal medicine and emergency care in terms of indication, finding (positive or negative), working diagnosis and outcome. It should be noted that Internal Medicine sends an additional non-urgent Troponin specimen for laboratory testing, which may influence their use of the test.

Troponin I is a quick, easy to perform, useful but expensive resource. As an observational study this study should describe how Troponin I tests are used throughout Victoria Hospital; describing inconsistencies in the application of clinical resources and judgement. It should also highlight associations between the result and other quality and application measures, i.e. time to testing and symptoms prompting testing. This would provide suggestions regarding local testing thresholds and perceived risk that could be addressed from an educational and cost-savings potential.

Objectives:

Description of Troponin I test utilization throughout Victoria Hospital, by requesting clinicians in terms of:

1. The hospital area where the patient requiring the test is situated (e.g. EC, specific ward, theatre, etc.)
2. The primary indication for performing the test using any of the following pre-specified symptoms or signs: chest pain, other pain suggestive of ACS (arm(s), neck, back, abdomen), shortness of breath, observed ECG abnormalities associated with ACS as well as the time of onset of symptoms
3. The troponin I result (positive or negative)
4. The recorded working diagnosis
5. The outcome following test in terms of discharge from EC, discharge from hospital, transfer to tertiary centre, or death

Methodology

Study Design:

A cross-sectional (across a data range), prospective (pre-determined) design will be used, using multiple data sources.

Characteristics of the Study Population:

Victoria Hospital is a district level hospital, in Wynberg, Cape Town. It has 181 ward beds, 3 day ward beds and an overnight ward. The available specialties include Surgery and Medicine, Emergency Medicine, Paediatrics, Psychiatry, Orthopaedics, Palliative Care and Auxiliary services. The hospital has a High Care Unit. Victoria hospital operates in the South Peninsula Health District of the Metro Region. The EC sees 47,000 patients annually, while Victoria Hospital sees 83,950 annually.

The troponin I assay is situated in the EC of the hospital. All hospital departments must use the assay in the EC to perform a troponin test as a troponin test is not offered by the local laboratory. Only clinicians have access to the assay and testing is directed through the EC staff. Clinicians are not denied use of the assay, but given the cost of the test, quality control and to ensure a clinical record of use, users have to complete a register with patient details that includes patient location, indication for testing and working diagnosis, prior to using the test. Users also have to record the result after completing the test. It is estimated that EC Troponin test are used for approximately fifty patients per 30 day period. A three month data collection should yield approximately 150 entries.

Recruitment and Enrolment:

Data will be collected from multiple data sources. We will prospectively collect a consecutive sample for objectives one through four over a three month period from Victoria hospital's EC using a dedicated data collection tool that will be connected to use of the point-of-care troponin I test. During the study period this data collection tool will serve as the troponin I test results register and will capture all the data points previously captured with an additional few specifically for study purposes. For this purpose, a dedicated hard copy register with additional variable fields included would be used. The variables to be collected from the register are listed in Table 1 (first column) and a sample of the form is provided in Appendix A. Acceptable missing variables may include patient age, patient gender and hospital area where the patient is situated. These will not result in exclusion of the data point. Any further missing variables will result in an unusable entry.

We will then supplement this prospective sample with outcome data, using the hospital's electronic admission record (Clinicom) by matching the patient identifier (hospital number) from the register to the admission records. Missing data fields (outcome, patient age, patient gender and hospital area) in the hospital's electronic admission record may also prompt reviewing the physical clinical record of the relevant patient for the missing data points. The variables to be collected from the register are listed in Table 1 (second column). We will exclude patients in which a full data set cannot be obtained.

Table 1. Variables to be collected for the sample

Variables from register	Variables from hospital electronic admission record and clinical record
11. Hospital number 12. Patient age 13. Patient gender 14. Hospital area where patient situated 15. Clinician rank: consultant, medical officer, specialist trainee, community service medical officer, intern 16. Primary indication for performing the test from the following: • chest pain, • other pain suggestive of ACS (arm(s), neck, back, abdomen), • shortness of breath, • observed ECG abnormalities associated with ACS 17. Other indication (optional/ specified) 18. Time of onset of symptoms 19. Working diagnosis (specified) 20. Troponin I result	6. Outcome: discharge from Victoria EC, discharge from Victoria Hospital, transfer to tertiary centre, or death at Victoria Hospital/ EC 7. Outcome: date outcome was achieved 8. (Patient age) 9. (Patient gender) 10. (Hospital area where patient were situated during admission)

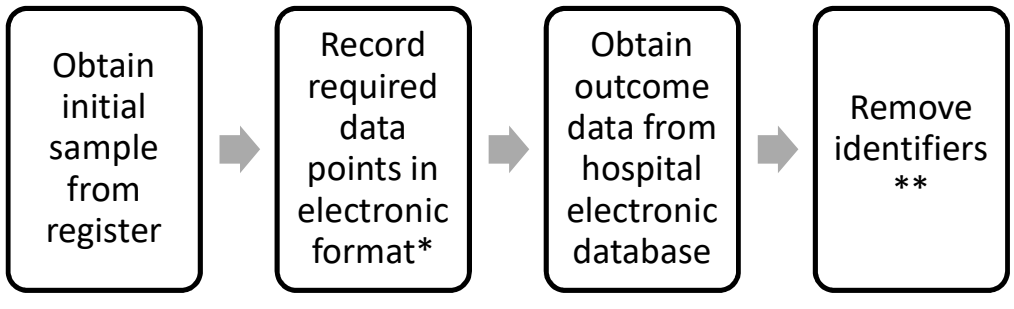
EC, emergency centre; ACS, acute coronary syndrome; ECG, electrocardiogram; Variables in parenthesis indicate that variable will be supplemented only if not collected in the prospective register

Research Procedures and Data collection methods:

Figure 1 describes the data collection strategy. Initial data obtained from the register will include a hospital number, but no other patient identifiers (i.e. names, date of birth, addresses, phone numbers, etc.). The hospital number will be required to link the datasets from the register with the outcome as recorded in the hospital's electronic admission record.

Data Analysis:

Data will be captured in an Excel spreadsheet (Microsoft Office, Redmond, USA) which will also be used to conduct the analysis. Descriptive statistics would be applied to the sample. Continuous data such as age will be described using the mean and standard deviation. Categorical variables such as outcome will be described using proportions. Where applicable data will be described using histograms and charts. Where appropriate, statistical tests will be performed between categorical variables to show the strength of associations. However, the study's main strength is felt to be in the descriptive findings. We will specifically look for associations between troponin test results, indications for testing, onset of symptoms, working diagnosis and outcome. For outcome, we will also describe the proportion of patients who reached an outcome within 48 hours of troponin testing. Additional testing is not planned but may be included depending on the findings.



* Using Microsoft Excel

** Hospital number

Figure 1. Data collection strategy

Data Safety and Monitoring:

Although the folder number will be captured initially to match data sets, it will be removed from the data sample **prior** to analysis starting. Data will be collected onto a password protected Excel document and stored on an access controlled computer in an access controlled office. No hard copy data are to be collected and copies of the register will not be made. Transfer of data between study team will be made using encrypted institution email only.

Ethical Considerations:

Guidance on rational use of an expensive test is one of the beneficial outcomes expected. However, better use of the troponin test may have patient level benefits as well (in terms of interpretation and correctly guiding care). The study won't affect the care pathway, but cannot reasonably be carried out if consent is required given the nature of the subject.

Potential risks include:

- Patient confidentiality is always important to maintain and in this study it will not be threatened. Upon completion of data collection, and before data analysis, all personal identifying information will be removed from the data, ensuring that the information collected cannot be traced back to individual patients.
- Staff resources of the studied institution should not be burdened, as the lead investigator is not employed at Victoria Hospital and all activities related to the study will be performed out of normal work hours. Study will not affect work flow and should not inconvenience clinicians in any way.

Potential Benefits:

- By understanding how the Troponin I test is used in Victoria Hospital, this study could act to assist in improving the rational use of Troponins within not only the EC but the whole hospital.
- This could lead to cost-saving in a financially strained setting.
- This could also assist in developing education around the use of Troponin I within the hospital.

Informed consent process

We request a waiver of consent. As described below the data is de-identified. Although data will be collected prospectively performing consent would simply not be feasible, nor would it allow us to collect a reasonable sample with the resources available to the study team, to achieve the desired objectives of the study. We feel that we have made reasonable arrangements for data management.

Privacy and confidentiality

Individual patients or participants' identities will be protected by de-identifying the data prior to analysis. Although the patients' folder numbers will be collected initially this will only be in order to link records to obtain outcome data. However, we would not include any of these in the final sample to be analysed. As described, the only identifier collected (hospital number) will be removed after data collection and prior to analysis.

Reimbursement for participation

There is no reimbursement for participation

Emergency care and insurance for research-related injuries

There is no risk for research related injury

Dissemination of Findings:

It is expected that the findings could be published as a short report or full paper in an open access journal. We would also like to disseminate its findings by presenting it at a conference.

All stakeholders will have access to the findings and data of the study. This includes the Western Cape Government and Victoria Hospital and Emergency Centre Management.

Project Timeline:

EMDRC (full): 2 months

Ethics (HREC): 2 months

WCG Health application: 2 months

Data collection: 3 months

Data Analysis: 3-4 months

Write-up: 2 months

Budget:

The costs of this study will be borne by the lead investigator. An estimated breakdown:

Personnel Compensation		**R0**
Principal Investigator	R0	
Consulting Services		**R0**
Statistical Services	R0	
Travel		**R500**
Transport and Travel	R500	
Equipment and Furniture		**R0**
Computer	R0	
Other		**R1400**
Telephone	R200	

Internet	R200	
Ethics Committee fee	R0	
Stationery	R500	
Printing	R500	
Total costs:		**R1900**

Travel to and from Victoria Hospital, in order to collect data recorded in register. Telephone use will be limited to single cell phone use and internet data or home internet use. UCT MMed students are able to access one hour free statistics service. Stationery and printing will be required on an ongoing basis.

Conclusion:

The aim of this study is to describe the use of the relatively expensive Troponin I test within Victoria Hospital by determining which symptoms prompt testing, which departments utilise the tests, and correlating this with outcome and working diagnosis. Understanding how these tests are used in the clinical setting can provide guidance on their rational use in the Western Cape.

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E. HREC approval letter

UNIVERSITY OF CAPE TOWN
Faculty of Health Sciences
Human Research Ethics Committee

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Website: www.health.uct.ac.za/fhs/research/humanethics/forms

15 November 2017

HREC REF: 737/2017

Dr SR Bruijns
Emergency Medicine
F51, OMB

Dear Dr Bruijns

PROJECT TITLE: A DESCRIPTIVE STUDY OF THE USE OF TROPONIN 1 TESTING AT A CAPE TOWN DISTRICT HOSPITAL-(MMed-candidate-Dr J Gibson)

Thank you for submitting your response to the Faculty of Health Sciences Human Research Ethics Committee darted 13 November 2017.

It is a pleasure to inform you that the HREC has **formally approved** the above-mentioned study subject to approval from Victoria Hospital as well as the use of the notice.

Approval is granted for one year until the 30 November 2018.

Please submit a progress form, using the standardised Annual Report Form if the study continues beyond the approval period. Please submit a Standard Closure form if the study is completed within the approval period.
(Forms can be found on our website: www.health.uct.ac.za/fhs/research/humanethics/forms)

Please quote the HREC REF in all your correspondence.

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

Please note that for all studies approved by the HREC, the principal investigator **must** obtain appropriate institutional approval, where necessary, before the research may occur.

The HREC acknowledge that the student, Dr Joshua Gibson will also be involved in this study.

Yours sincerely

Signature Removed

PROFESSOR M BLOCKMAN
CHAIRPERSON, FHS HUMAN RESEARCH ETHICS COMMITTEE
Federal Wide Assurance Number: FWA00001637.
Institutional Review Board (IRB) number: IRB00001938
This serves to confirm that the University of Cape Town Human Research Ethics Committee complies to the Ethics Standards for Clinical Research with a new drug in patients, based on the Medical

Research Council (MRC-SA), Food and Drug Administration (FDA-USA), International Convention on Harmonisation Good Clinical Practice (ICH GCP), South African Good Clinical Practice Guidelines (DoH 2006), based on the Association of the British Pharmaceutical Industry Guidelines (ABPI),and Declaration of Helsinki (2013) guidelines.
The Human Research Ethics Committee granting this approval is in compliance with the ICH Harmonised Tripartite Guidelines E6: Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95) and FDA Code Federal Regulation Part 50, 56 and 312.

HREC 737/2017