Evaluating the performance of the GRACE and TIMI Risk scores in Acute Coronary Syndromes: A South African cohort.

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Format

This is a publication ready format manuscript. We are in the process of submitting it to the South Africa Medical Journal, SAMJ.

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List of abbreviations

ACE	Angiotensin Converting Enzyme
ACS	Acute Coronary Syndrome
ARB	Angiotensin Receptor Blocker
CABG	Coronary Artery Bypass Graft
CCRU	Cardiac Clinical Research Unit
CCS	Canadian Cardiovascular Society
CCU	Coronary Care Unit
COPD	Chronic Obstructive Pulmonary Disease
CRF	Case Report Form
CVD	Cardiovascular Diseases
ECG	Electrocardiogram
GRACE	Global Registry of Acute Coronary Events
GSH	Groote Schuur Hospital
GUSTO	Global Utilisation of Streptokinase and TPA for Occluded coronary arteries
HIV	Human Immunodeficiency Virus
IHD	Ischemic Heart Disease
LBBB	Left Bundle Branch Block
NSTEMI	Non-ST-Elevation Myocardial Infarction
PCI	Percutaneous Coronary Intervention
PPCI	Primary Percutaneous Coronary Intervention
PVD	Peripheral Vascular Disease
PURSUIT	Platelet glycoprotein IIb/IIIa in Unstable angina: Receptor Suppression Using Integrilin (eptifibatide) Therapy
RBBB	Right Bundle Branch Block
SA	South Africa
SRI	Simple Risk Index
SSA	Sub Saharan Africa
STEMI	ST-Elevation Myocardial Infarction
TIMI	Thrombolysis In Myocardial Infarction
TPA	Tissue Plasminogen Activator
UA	Unstable Angina

Chapter One: Literature Review

BACKGROUND

Ischaemic heart disease (IHD), stroke and hypertension are the top three causes of cardiovascular-related death in sub-Saharan Africa (SSA). Amongst the three, IHD is the leading cause of cardiovascular-related morbidity and mortality in SSA, with its prevalence on a steady upward trajectory.[1] Healthcare systems in SSA face an additional burden due to the elevated prevalences of communicable diseases, maternal death and trauma.[2] Individuals in SSA who present with acute coronary syndrome (ACS), either in the form of ST-elevation myocardial infarction (STEMI) or unstable angina(UA)/non ST-elevation myocardial infarction (NSTEMI), tend to be younger, have an increased burden of hypertension and higher rates of stress.[3,4] Despite advances in the diagnosis and management of ACS, patients experiencing ACS in our setting often have high morbidity and mortality due to limited pre-hospital care and scarcity of specialised medical services. Patients in SSA tend to present late to hospital, receive late reperfusion therapy, have limited access to invasive specialised treatment and often receive delayed revascularisation.[5]

To identify patients with ACS who may benefit from early invasive therapy and aggressive secondary prevention, various risk stratification tools have been developed to objectively identify those patients at highest risk of suffering in-hospital, thirty-day, and one-year major adverse cardiac events. These risk scores were developed to aid the treating physician in objectively risk stratifying patients and providing appropriate invasive care to patients at a greater chance of suffering major adverse cardiac events. In a prior study by *Yan et al*,[6] the prognostic significance of incorporating risk scores compared to global risk assessment conducted by physicians was examined. The study revealed that the combination of risk scores with the physician's global risk assessment resulted in a more substantial prognostic value.

Various risk scores, including Simple Risk Index (SRI), Platelet glycoprotein IIb/IIIa in Unstable angina: Receptor Suppression Using Integrilin (eptifibatide) Therapy (PURSUIT), Global Utilization of Streptokinase and TPA for Occluded coronary arteries (GUSTO) risk score, Global Registry of Acute Coronary Events (GRACE), Thrombolysis In Myocardial Infarction (TIMI) for STEMI and TIMI for UA/NSTEMI, amongst others, have been developed with a goal of objectively assisting physicians in assessing an individuals short-term and long-term risk. Relying solely on bedside clinical assessment for risk stratification can often yield inaccurate assessments and may potentially deny patients of life-saving interventions. This has prompted the development of these

scores. Validation of these risk scores[7-14,16,18] has been conducted in diverse cohorts of patients with ACS to ascertain whether their predictive accuracy can be consistently replicated across various patient populations.

The GUSTO score was one of the first scores developed from the GUSTO-I randomised controlled trial over two decades ago where patients with STEMI received combined regimens of streptokinase or alteplase with heparin.[7] This score is used to predict one-year outcomes after thirty-day survival. The SRI is yet another score that was derived from the Intravenous nPA for Treatment of Infracting Myocardium Early II Trial (InTIME II) trial.[8] This score identified three variables, age, heart rate and systolic blood pressure as main predictors of thirty-day mortality in patients with STEMI who received thrombolytic therapy. With only three variables in the score, its use has been encouraged in pre-hospital settings. The PURSUIT score, derived from the PURSUIT trial, randomised patients with unstable angina (UA) or NSTEMI to receive Eptifibatide versus placebo.[9] The endpoint was 30-day incidence of death and the composite of death or myocardial reinfarction.

The GRACE study was a prospective multi-national registry for patients presenting with ACS conducted over a decade in fourteen countries across North America, South America, Asia, Europe, Australia, and New Zealand.[10] The GRACE risk score was derived from this multi-national prospective registry, and various models of the score have since been formulated. The Granger model was the initial GRACE score and was designed to predict in-hospital mortality in patients with ACS.[11] The Eagle model predicted all-cause mortality 6 months post ACS discharge.[12] The Fox model, designed in 2006, had two primary endpoints, all-cause death or the composite measure of death or nonfatal myocardial infarction from hospital admission to 6 months.[13] Subsequently, the GRACE 2.0 score was developed, enabling the clinician to replace the Killip score and creatinine with diuretic use and renal failure, respectively, if the former were unavailable. The score exhibited good discriminatory capacity even when these substitutions were implemented.[14] It is worth noting that the weight of individual variables to form the composite score differed between models. The GRACE score further categorised patients into low-risk, intermediate-risk and high-risk, depending on the composite score. Patients with a score <109 were low-risk, 109-140 were intermediate-risk, and >140 were high-risk.[15]

The TIMI for STEMI risk score[16] was derived from a large randomised controlled trial, the InTIME II trial, conducted across eight hundred hospitals worldwide. In this trial, randomised patients with STEMI received lanoteplase or accelerated alteplase regimens.[17] The score[16] was validated in the TIMI 9 trials, and both derivation and validation sets demonstrated a good discriminatory accuracy of the TIMI score for STEMI. Interestingly, the presence of cardiogenic shock was one of the exclusion criteria for this trial, a variable that contributed strongly to the GRACE score. The TIMI for STEMI score predicted 30-day mortality for patients who received fibrinolytic therapy. Patients with a score of 0-3 were low-risk, 4-7 were intermediate-risk, and 8-14 were high-risk.

The TIMI for UA/NSTEMI[18] risk score was retrospectively derived from two randomised controlled clinical trials, Thrombolysis In Myocardial Infarction 11B (TIMI-11B) trial[19] and Efficacy and Safety of Subcutaneous Enoxaparin in Unstable Angina and Non-Q Wave (ESSENCE) trial.[20] These two trials randomised patients with UA/NSTEMI to receive either unfractionated heparin or enoxaparin. Patients who were planned to have revascularisation within twenty-four hours were excluded from the TIMI-11B trial while the presence of renal failure excluded patients from being enrolled into the ESSENCE trial. Based on this, the presence of renal dysfunction was not incorporated into the TIMI for UA/NSTEMI score. The score was used to predict a composite of all-cause mortality, new or recurrent myocardial infarction and severe recurrent ischemia within 14 days of presentation. Patients with a score of 0-2 were low-risk, 3-4 intermediate-risk and 5-7 were high-risk.

Despite the development and validation of multiple risk scores in patients with ACS, the two common risk scores universally accepted and commonly used are the GRACE and TIMI for UA/NSTEMI, respectively. Scoring systems with limited variables, such as the SRI, do not adequately address the clinical heterogeneity observed in patients with ACS and are consequently used less. With the increasing availability of primary percutaneous coronary intervention (PPCI), the preferred reperfusion strategy for STEMI, scores such as the SRI, GUSTO and TIMI for STEMI have fallen out of favour as they do not apply to patients who receive PPCI. The GRACE score accounts for a broad clinical presentation of patients across the spectrum of ACS and incorporates haemodynamic variables such as renal dysfunction and cardiac arrest on presentation. These variables have been shown to be powerful independent predictors of mortality.[11]

Most of these scores have been extensively validated in independent databases in developed countries.[21-23] One example is the MINAP database, a large prospective registry in 229 acute hospitals across England and Wales. Of the five scores that were compared (GUSTO-I, PURSUIT, SRI, EMMACE and GRACE), the GRACE had the best discriminatory capacity across the spectrum of ACS in predicting in-hospital and six-month mortality.[21] A study by *Yan et al*, done in North America, compared the performance of PURSUIT, TIMI and GRACE in predicting in-hospital and one-year mortality amongst patients with NSTEMI. The results identified the GRACE score as superior in predicting both in-hospital mortality (c-statistic= 0.80, 0.69, 0.81, respectively) and one-year mortality (c-statistics 0.77, 0.69, 0.79, respectively).[6] Another study in the United States of America (USA) compared GRACE to TIMI in predicting in-hospital and six-month mortality in patients with ACS. In patients with STEMI, both scores demonstrated effective prediction of in-hospital and six-month mortality. However, within the NSTEMI group, the GRACE score outperformed the TIMI score in predicting both in-hospital and six-month mortality.[22]

Similarly, smaller studies have been conducted in developing countries to evaluate the predictive accuracy of these scoring systems.[24-26]. A comparative study performed in Egypt, which assessed the GRACE and TIMI risk scores for predicting in-hospital MACE and 30-day all-cause mortality/recurrent myocardial infarction, indicated that the GRACE score performed better than TIMI in predicting in-hospital MACE for both STEMI and NSTEMI patients. Additionally, both scores demonstrated similar accuracy in predicting 30-day all-cause mortality/recurrent myocardial infarction.[24] In contrast, a study conducted in Brazil revealed comparable discriminative capacities of both scores in predicting in-hospital mortality amongst patients with STEMI; however, TIMI had better calibration than the GRACE score.[26] To our knowledge, no study has evaluated the performance of these scores in SSA.

Risk stratification is an integral part of managing patients with ACS. Current guidelines recommend the use of the GRACE score for early risk stratification.[27,28] The European Society of Cardiology (ESC) guidelines recommend that patients with an NSTEMI and a GRACE score >140 should receive early invasive treatment within 24 hours. The management of STEMI patients is not guided by risk scores as these patients should receive timely reperfusion irrespective of their risk. Studies conducted more than a decade ago in patients with NSTEMI indicated that invasive therapy resulted in better outcomes compared to conservative therapy, especially in high-risk patients.[29] However, optimal timing of invasive therapy remains controversial. Two large

randomised controlled trials, Timing of Intervention in Acute Coronary Syndrome (TIMACS) and Very Early Versus Deferred Invasive Evaluation Using Computerised Tomography (VERDICT) attempted to demonstrate whether early invasive therapy improved outcomes compared to delayed invasive therapy within 48-72 hours. The TIMACS trial randomised patients to early invasive (<24 hours) versus late invasive strategy (>36 hours). The primary outcome was a composite of death, myocardial infarction, or stroke at 6 months.[30] In the VERDICT trial, patients were randomised to a very early invasive (<12 hours) versus a delayed strategy (48-72 hours). The primary end point was a combination of all-cause death, nonfatal recurrent myocardial infarction, hospital admission for refractory myocardial ischemia, or hospital admission for heart failure.[31] Neither of these two studies demonstrated any disparity in outcomes between the two groups. However, subgroup analyses in both studies indicated that patients with a GRACE score >140 who underwent invasive therapy within 24 hours exhibited improved outcomes compared to high-risk patients who received invasive therapy after 24 hours.

The GRACE study demonstrated a risk-treatment paradox, where low-risk patients undergo more aggressive invasive therapy, and high-risk patients receive less aggressive treatment.[32] Revascularisation was performed more frequently in the lower-risk group (40% NSTEMI, 60% STEMI) than in the high-risk cohort (NSTEMI 25%, STEMI 41%). This same phenomenon has also been described in the MINAP study. This has the potential to expose low-risk patients to potential complications of invasive therapy, while high-risk patients may end up being treated conservatively, potentially resulting in unfavourable outcomes. Using the GRACE risk score, an Australian study aimed to determine the benefit of Objective Risk Assessment versus Standard Care for Acute Coronary Syndromes.[33] They attempted to measure the impact of the GRACE risk score in adhering to guideline-recommended treatments and whether the utilisation of GRACE improved clinical outcomes. The trial was prematurely stopped due to futility, and the authors concluded that the implementation of the GRACE score had minimal impact on adherence to guideline-based treatments and clinical outcomes. This trial involved multiple high-performance hospitals with established referral systems and high availability of cardiac catheterisation services. A significant proportion of the patients had STEMI, and it is well known that risk stratification does not alter or influence clinical management for STEMI. Hence, the findings of this study may not be directly applicable to our setting with limited resources, where specialised care is not easily accessible, patients experience delayed time to first medical contact, and a significant proportion of our patients undergo conservative treatment.

The rationale of this study

In our healthcare system, individuals with ACS often present to the hospital at a later stage of their disease, undergo thrombolytic therapy more than six hours after symptom onset, face limited access to specialised invasive treatment, and frequently receive delayed revascularisation. This is exacerbated by the substantial prevalence of infectious diseases, trauma, and violence, further straining an already overloaded health system. Risk stratification in our cohort of ACS patients may offer several advantages: objectively identifying high-risk patients in need of invasive therapy, minimising potential risks of invasive procedures in low-risk groups, selecting suitable candidates for robust secondary prevention and follow-up, and delivering cost-effective treatment benefits in our resource-limited environment.

Our objectives were to determine:

a) the demographic and risk factor profile of patients presenting with STEMI and NSTEMI;
b) the reperfusion strategies of patients with STEMI and NSTEMI;
c) in-hospital and 30-day case fatality rates;
d) the GRACE and TIMI risk scores for each patient;
e) the impact of using GRACE and TIMI risk stratification scores in relation to mortality.

Our study investigated the impact of the GRACE and TIMI risk predictive models in assessing in-hospital and 30-day mortality within our population.

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Publication Ready Manuscript

Evaluating the performance of the GRACE and TIMI risk scores in Acute Coronary Syndromes: A South African cohort.

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Introduction: The GRACE and TIMI scores are validated risk stratification tools that accurately predict risk of in-hospital, 30-day, and one-year major adverse cardiac events (MACE) in patients with Acute Coronary Syndromes (ACS). The performance of GRACE and TIMI scores in a setting where most ST-elevation myocardial infarction (STEMI) patients receive thrombolytic reperfusion therapy after 6 hours and a considerable proportion of non-ST elevation myocardial infarction (NTSEMI) patients receive delayed angiography and revascularisation after 48 hours, is unknown.

Objective: To evaluate the accuracy of GRACE and TIMI risk scores in predicting in-hospital and 30-day mortality in a population characterised by a significant prevalence of delayed ACS presentation, limited access to primary percutaneous coronary intervention (PPCI) and delayed revascularisation.

Methods: We conducted a retrospective review of all patients admitted to the coronary care unit (CCU) at Groote Schuur Hospital, Cape Town, with either STEMI or NSTEMI, between January 1st to December 31st, 2019. For each participant, both GRACE and TIMI risk scores were calculated and recorded electronically. Performance of each score was determined and compared using receiver operating characteristic curve (ROC) analysis.

Results: Of 329 participants with ACS, 58.6% presented with STEMI and 41.4% with NSTEMI. Mean age was 61.3 (SD±11.9) years, and 59.6% were male. Mean time from symptom onset to hospital admission was 18.3 (SD ± 37.4) hours, with only 4 participants (2.1%) receiving PPCI. STEMI in-hospital and 30-day mortality was 4.1% and 4.2%, respectively, whereas in-hospital mortality for NSTEMI was 1.5%. In the STEMI cohort, both GRACE and TIMI risk scores were comparable, showed excellent discrimination for in-hospital mortality (AUC=0.927, 95% CI: 0.83-1.00 versus AUC=0.923, 95% CI: 0.87-0.98; p 0.91), and demonstrated modest accuracy for predicting 30-day mortality (GRACE AUC=0.587, 95% CI: 0.29-0.88; TIMI AUC=0.530, 95% CI: 0.12-0.94; p 0.44).
In the NSTEMI cohort, GRACE performed significantly better than TIMI (AUC=0.905, 95% CI: 0.85-0.96 versus AUC=0.278, 95% CI: 0.00-0.68; p 0.001) for predicting in-hospital mortality.

Conclusion: Both GRACE and TIMI scores demonstrated high accuracy in predicting in-hospital mortality and their predictive accuracy was modest when predicting 30-day mortality for STEMI patients. In addition, GRACE outperformed the TIMI score in assessing NSTEMI in-hospital mortality. Further research in low-and middle-income countries in SSA is needed to evaluate the potential impact of these scores on treatment strategies and cardiovascular outcomes.

Introduction

Ischaemic heart disease is the commonest cause of cardiovascular death, and the second leading cause of overall mortality in sub-Saharan Africa (SSA).[1,2] Despite advances in the diagnosis and management of acute coronary syndromes (ACS), patients with ACS suffer high morbidity and mortality particularly in our environment where pre-hospital care is limited and the availability of specialised care is minimal.[3] To identify patients who may benefit from early invasive treatment and aggressive secondary prevention, several risk stratification scores have been developed to identify those patients at highest risk of in-hospital and 30-day major adverse cardiac events. The Global Registry of Acute Coronary Events (GRACE) risk score was derived from a multi-national registry of patients across fourteen countries, encompassing a spectrum of ACS presentations.[4] However, it is important to note that none of these countries were from SSA.[4] The Thrombolysis In Myocardial Infarction (TIMI) scores, used to risk stratify unstable angina (UA), non-ST elevation myocardial infarction (NSTEMI) and ST-elevation myocardial infarction (STEMI), are scores derived from clinical trials conducted in the global north.[5,6] Both the GRACE and TIMI scores have been validated across different populations worldwide, primarily focusing on high-income countries.[7-11] Risk stratification remains an integral part of managing patients with ACS, and current guidelines recommend using such scores.[12,13] Risk stratification further identifies high-risk patients who may benefit from aggressive and prompt invasive treatment options while minimising the potential harm of invasive treatments in low-risk groups. Individual risk assesement plays an essential role in our practice, particularly as a majority of patients present younger, exhibit a higher risk factor profile, present late to hospital, and have limited access to invasive therapies.[14,15] Whether the GRACE and TIMI risk scores accurately predict in-hospital and 30-day mortality in our population, where most patients with STEMI receive thrombolytic reperfusion therapy after six hours and a significant proportion of patients with NSTEMI receive delayed revascularisation, is unknown.

We aimed to determine the predictive accuracy of the GRACE and TIMI risk scores in predicting in-hospital and 30-day mortality in a population characterised by a significant prevalence of delayed presentation, limited access to primary percutaneous coronary intervention (PPCI) and delayed revascularisation.

Methods

Study design

We conducted a single-centre retrospective review of all patients admitted with ACS to the coronary care unit (CCU) at Groote Schuur Hospital (GSH), Cape Town, from January 1st to December 31st, 2019 (Figure 1). The Division of Cardiology at GSH is an academic and tertiary state referral centre in the Western Cape province, and forms the main teaching hospital for the University of Cape Town. The six-bed coronary care unit receives patients referred from healthcare facilities in the metropolitan area using the hub and spoke model to provide specialised definitive care for individuals with ACS.. Ethical approval was obtained from the Human Research Ethics Committee, University of Cape Town, South Africa: HREC 040/2022 and the study was conducted in accordance with the principles of good clinical practice and the Declaration of Helsinki. All patients over the age of 18 years with a confirmed diagnosis of ACS (either STEMI or NSTEMI according to the fourth universal definition of myocardial infarction[16]) admitted to the CCU at GSH were included. Participants with incomplete or missing medical records were excluded. Data was collected using electronic Case Report Forms (eCRFs), which included demographics, baseline clinical characteristics, electrocardiogram (ECG) features, laboratory results, in-hospital management, in-hospital mortality and 30-day mortality. Patients presenting with a STEMI received reperfusion therapy via thrombolysis only, a pharmaco-invasive strategy or PPCI. Thrombolysis involved administering a fibrinolytic agent (Streptokinase, Alteplase or Tenecteplase) with no PPCI. Pharmaco-invasive therapy was defined as a patient receiving thrombolysis followed by a coronary angiogram, with or without PCI, within twenty-four hours. PPCI involves conducting a coronary angiogram, with or without PCI, within the initial twelve hours of chest pain onset and without prior administration of a thrombolytic agent.

Data collection

Study data were collected and managed using Research Electronic Data Capture (REDCap) tools hosted at the University of Cape Town.[18,19] REDCap is a secure, web-based software platform designed to support data capture for research studies, providing an intuitive interface for validated data capture, audit trails for tracking data manipulation and export procedures, automated export procedures for seamless data downloads to standard statistical packages and procedures for data integration and interoperability with external sources. The electronic database was governed by strict password control access assigned to approved study members. The GRACE and TIMI scores were calculated for each participant (Table 1). In-hospital and 30-day outcomes were determined using clinical records.

Statistical analysis

Continuous data were expressed as means and standard deviations for normal distribution or as median and interquartile ranges for skewed distribution. Categorical data was expressed as percentages. Performance of each score was determined and compared using the receiver Operating Characteristics (ROC) curve analysis.

Results

Between January 1st, 2019, and December 31st, 2019, a total of 329 patients were admitted with ACS and followed up using an electronic health register for 30 days post-hospital discharge. Of these, 193 (58.6%) had a STEMI, and 136 participants (41.3%) suffered an NSTEMI. The mean age of the participants was 61.3 (SD ±11.9) years, with 196 participants (59.6%) being male. Hypertension (72.1%), cigarette smoking (72%), dyslipidemia (52%) and type 2 diabetes mellitus (43.5%) were the most prevalent cardiovascular risk factors (Table 2). Two patients (<1%) had Human Immunodeficiency Virus (HIV) infection.

In the STEMI group, the mean time from symptom onset to hospital admission was 18.3 (SD ± 37.4) hours, and the median time from admission to thrombolysis was 83 (IQR 45-140) minutes. 80 (41.5%) patients presented to hospital six hours from onset of chest pain. Half (50.7%) of the participants received pharmaco-invasive therapy, 16.1% received thrombolysis only, 31% were managed conservatively, and only 2.1% received PPCI. ECG features and laboratory results for STEMI participants are shown in Table 3.

In the NSTEMI group, 36.8% received PCI, 16.9% underwent a coronary artery bypass graft, and 46.3% were treated conservatively (Table 4).

The overall STEMI in-hospital mortality was 4.1%, and 30-day mortality was 4.2%. Comparatively, the NSTEMI in-hospital mortality was 1.5%, with no 30-day mortality (Table 5).

The discriminative performance of both GRACE (AUC=0.927, 95% CI: 0.83-1.00) and TIMI (AUC=0.923, 95% CI: 0.87-0.98) in predicting in-hospital mortality (Figure 2) in patients with STEMI were similar and accurate; however, the accuracy in predicting 30-day mortality (Figure 3) was modest for both GRACE (AUC=0.587, 95% CI: 0.29-0.88) and TIMI (AUC=0.530, 95% CI: 0.12-0.94), respectively. There was no statistical difference in discrimination for in-hospital (p 0.91) and 30-day mortality (p 0.44) between the GRACE and TIMI risk scores.

In the NSTEMI cohort, the GRACE score (AUC=0.905, 95% CI: 0.85-0.96) performed significantly better than the TIMI score (AUC=0.278, 95% CI: 0.00-0.68) for predicting in-hospital mortality (p 0.001) (Figure 4).

Table 1: Risk score variables and risk categories.		
GRACE Risk Score[17]	**TIMI-UA/NSTEMI**[5]	**TIMI-STEMI**[6]
Age	Age ≥ 65 years	Age ≥ 75 years
Killips class	≥3 risk factors for CAD	Age 65-74 years
Systolic blood pressure	Prior coronary stenosis ≥ 50%	Diabetes, hypertension, or angina
Prescence of ST segment deviation	ST segment deviation on ECG	Systolic blood pressure < 100mmHg
Cardiac arrest on presentation	At least 2 or more episodes of angina in past 24 hours	Anterior ST elevation or LBBB
Serum Creatinine	Elevated serum cardiac biomarkers	Heart rate > 100/minute
Elevated serum cardiac biomarkers	Aspirin use in past seven days	Killip class II-IV
Heart rate		Weight < 67kg
		Time to reperfusion > 4 hours
Low risk: <109	**Low risk:** 0-2	**Low risk:** 0-3
Intermediate risk: 109-140	**Intermediate risk:** 3-4	**Intermediate risk:** 4-8
High Risk: >140	**High risk:** 5-7	**High risk:** 9-14

Table 2. Baseline characteristics of ACS participants admitted to Groote Schuur Hospital in 2019				
	All n= 329 (%)	**STEMI n= 193 (%)**	**NSTEMI n=136 (%)**	**p***
Demographics				
Age [years; Mean (±SD)]	61.3 (±11.9)	59.8 (±11.3)	63.1 (±10.6)	**0.01**
Male, n (%)	196 (59.6)	116 (60.1)	80 (58.8)	**0.82**
Comorbid conditions				
Hypertension, n (%)	223 (72.1)	125 (64.8)	98 (72.1)	**0.16**
Type 2 Diabetes, n (%)	143 (43.5)	76 (39.3)	67 (49.2)	**0.08**
Previous Ischaemic stroke, n (%)	24 (7.3)	16 (8.3)	8 (5.9)	**0.41**
Chronic kidney disease, n (%)	26 (7.9)	12 (6.2)	14 (10.3)	**0.18**
HIV, n (%)	2 (0.6)	2 (1.0)	0 (0)	**0.51**
Previous Heart failure, n (%)	28 (8.5)	11 (5.7)	17 (12.5)	**0.30**
Dyslipidemia, n (%)	171 (52.0)	83 (43.0)	88 (64.7)	**0.00**
Peripheral arterial disease, n (%)	35 (10.6)	15 (7.8)	20 (14.7)	**0.45**
Chronic coronary syndrome, n (%)	65 (19.8)	28 (14.5)	37 (27.2)	**0.04**
Previous STEMI, n (%)	34 (10.3)	17 (8.8)	17 (12.5)	**0.28**
Previous NSTEMI, n (%)	29 (8.8)	13 (6.7)	16 (11.8)	**0.11**
Previous CABG, n (%)	9 (2.7)	4 (2.1)	5 (3.7)	**0.50**
COPD, n (%)	19 (5.8)	10 (5.2)	9 (6.6)	**0.58**
Cigarette Smoking, n (%)	237 (72.0)	144 (74.6)	93 (68.4)	**0.22**
Prior use of medical therapy				
Aspirin, n (%)	118 (35.9)	47 (24.4)	71 (52.2)	**0.00**
Statin, n (%)	138 (41.9)	60 (31.1)	78 (57.4)	**0.00**
Beta blocker, n (%)	79 (24.0)	32 (16.6)	47 (34.6)	**0.00**
ACE inhibitor, n (%)	130 (39.5)	59 (30.6)	71 (52.2)	**0.00**
Clinical features on presentation				
Typical chest pain, n (%)	256 (77.8)	149 (77.2)	107 (78.7)	**0.75**
NYHA class 1				**0.01**
1, n (%)	211 (64.1)	131 (67.9)	80 (58.8)	
2, n (%)	102 (31.0)	58 (30.1)	44 (32.4)	
3, n (%)	16 (4.9)	4 (2.1)	12 (3.8)	
Killip Class				**0.01**
1, n (%)	231 (70.2)	124 (64.2)	107 (78.7)	
2, n (%)	62 (18.8)	46 (23.8)	16 (11.8)	
3, n (%)	32 (9.7)	19 (9.8)	13 (9.6)	
4, n (%)	4 (1.2)	4 (2.1)	0	
Systolic blood pressure, mmHg, Mean (± SD)	131.2 (± 28.8)	128.1 (± 28.0)	135.5 (± 29.3)	**0.02**
Diastolic blood pressure, mmHg, Mean (± SD)	78.9 (± 16.8)	78.0 (± 16.8)	78.3 (± 6.8)	**0.86**
Heart rate, bpm, Mean (± SD)	78.6 (± 20.8)	78.9 (± 21.4)	78.2 (± 9.9)	**0.79**
Glucose, mmol/L, Mean (± SD)	8.9 (± 5.0)	9.2 (± 4.6)	8.5 (± 5.4)	**0.17**
Weight, Kg, Mean (± SD)	79.7 (± 14.7)	79.4 (±14.4)	80.1 (± 15.2)	**0.66**
Time from admission to first ECG, minutes, Median (IQR)	23 (12-44)	23 (12-46)	23.5 (14-43)	**0.13**

p* : t test for continuous variables and χ^2 for categorical variables.
ACE=angiotensin-converting enzyme. ACS=acute coronary syndrome. ARB=angiotensin receptor blocker. NSTEMI=non-ST elevation myocardial infarction. STEMI=ST elevation myocardial infarction.
Unless otherwise stated, numbers are n (%).

Table 3. In-hospital management of STEMI cohort (n= 193)	
Medical therapy initiated at presentation	**n (%)**
Aspirin, n (%)	**185 (95.9)**
Clopidogrel, n (%)	**168 (87.0)**
Heparin, n (%)	**119 (61.7)**
Statin, n (%)	**111 (57.5)**
Key investigations	
hs troponin T, ng/L, Mean (± SD)	**3763 (± 5505.8)**
Creatinine at admission, mmol/L, Mean (± SD)	**104.6 (± 70.2)**
ST elevation-occluded territory on ECG	
Anterior, n (%)	**50 (25.9)**
Anterolateral, n (%)	**31 (16.1)**
Inferior, n (%)	**73 (37.8)**
Infero-posterior, n (%)	**22 (11.4)**
Posterior, n (%)	**7 (3.6)**
aVR, n (%)	**1(0.5)**
Lateral, n (%)	**6 (3.1)**
LBBB, n (%)	**3 (1.5)**
Risk Score	
GRACE, Mean (± SD)	**114.4 (± 31.4)**
TIMI, Mean (± SD)	**3.91 (± 2.5)**
Key Timelines	
Symptom onset to hospital admission, hours, Mean (± SD)	**18.3 (± 37.4)**
Symptom onset to hospital admission < 6 hours, n (%)	**113 (58.5%)**
Symptom onset to hospital admission > 6 hours, n (%)	**80 (41.5%)**
Hospital admission to thrombolysis, minutes, Median (IQR)	**83 (45-140)**
Reperfusion strategy	
Thrombolysis only, n (%)	**31 (16.1)**
Pharmaco-invasive PCI, n (%)	**98 (50.7)**
PPCI, n (%)	**4 (2.1)**
Conservative, n (%)	**60 (31.1)**
Cardiac complications	
Cardiac arrest on presentation, n (%)	**7 (3.6)**
Cardiogenic shock, n (%)	**15 (7.8)**
Acute renal failure, n (%)	**32 (16.6)**
Ventricular arrhythmia, n (%)	**18 (9.3)**
Complete atrioventricular block, n (%)	**24 (12.4)**
Discharge medication	
Aspirin, n (%)	**179 (92.7)**
Clopidogrel, n (%)	**171 (88.6)**
Statin, n (%)	**177 (91.7)**
ACE inhibitor, n (%)	**146 (75.6)**
Beta blocker, n (%)	**162 (83.9)**
Spironolactone, n (%)	**6 (3.1)**
Duration of hospital stay (days), Mean (± SD)	**3.8 (± 3.3)**

ACE=angiotensin converting enzyme. GRACE= Global Registry of Acute Coronary Events. LBBB= left bundle branch block. PCI= percutaneous coronary intervention. PPCI= primary percutaneous coronary intervention. TIMI=Thrombolysis in Myocardial Infarction

Table 4. In-hospital management of NSTEMI cohort (n=136)	
Medical therapy initiated at presentation	**n (%)**
Aspirin, n (%)	**133 (97.8)**
Clopidogrel, n (%)	**122 (89.7)**
Heparin, n (%)	**122 (89.7)**
Statin, n (%)	**83 (61.0)**
ACE inhibitor/ARB, n (%)	**55 (40.4)**
Beta blocker, n (%)	**61 (44.9)**
Key investigations	
hs troponin T, ng/L, Mean (± SD)	**931 (± 1362.8)**
Creatinine on admission, mmol/L, Mean (± SD)	**94.38 (± 50.9)**
Risk Score	
GRACE, Mean (± SD)	**109.9 (± 29.5)**
TIMI, Mean (± SD)	**4.08 (± 1.4)**
Reperfusion strategy	
PCI, n (%)	**50 (36.8)**
CABG, n (%)	**23 (16.9)**
Conservative, n (%)	**63 (46.3)**
Cardiac complications	
Cardiac arrest on presentation, n (%)	**5 (3.7)**
Cardiogenic shock, n (%)	**1 (0.7)**
Acute renal failure, n (%)	**6 (4.4)**
Ventricular arrhythmia, n (%)	**5 (3.7)**
Complete atrioventricular block, n (%)	**1 (0.7)**
Discharge medication	
Aspirin, n (%)	**127 (93.4)**
Clopidogrel, n (%)	**112 (82.4)**
Statin, n (%)	**130 (95.6)**
ACE inhibitor, n (%)	**110 (80.9)**
Beta blocker, n (%)	**123 (90.4)**
Spironolactone, n (%)	**7 (5.1)**
Duration of hospital stay, days, Mean (± SD)	**5.4 (± 4.4)**
ACE=angiotensin converting enzyme. ARB=angiotensin II receptor blocker. CABG=coronary artery bypass graft. GRACE= Global Registry of Acute Coronary Events. PCI=percutaneous coronary intervention. TIMI=Thrombolysis in Myocardial Infarction	

Table 5. In-hospital and 30-day mortality of study participants admitted with ACS at Groote Schuur Hospital in 2019.				
	TOTAL n= 329 (%)	**STEMI (n= 193)** n (%)	**NSTEMI (n=136)** n (%)	**p***
In-hospital mortality	10 (3.0)	8 (4.1)	2 (1.5)	0.21
30-day mortality	14 (4.2)	12 (4.2)	-	N/A
ACS=acute coronary syndrome. NSTEMI=non-ST elevation myocardial infarction. STEMI= ST-elevation myocardial infarction. p*: χ^2 test				

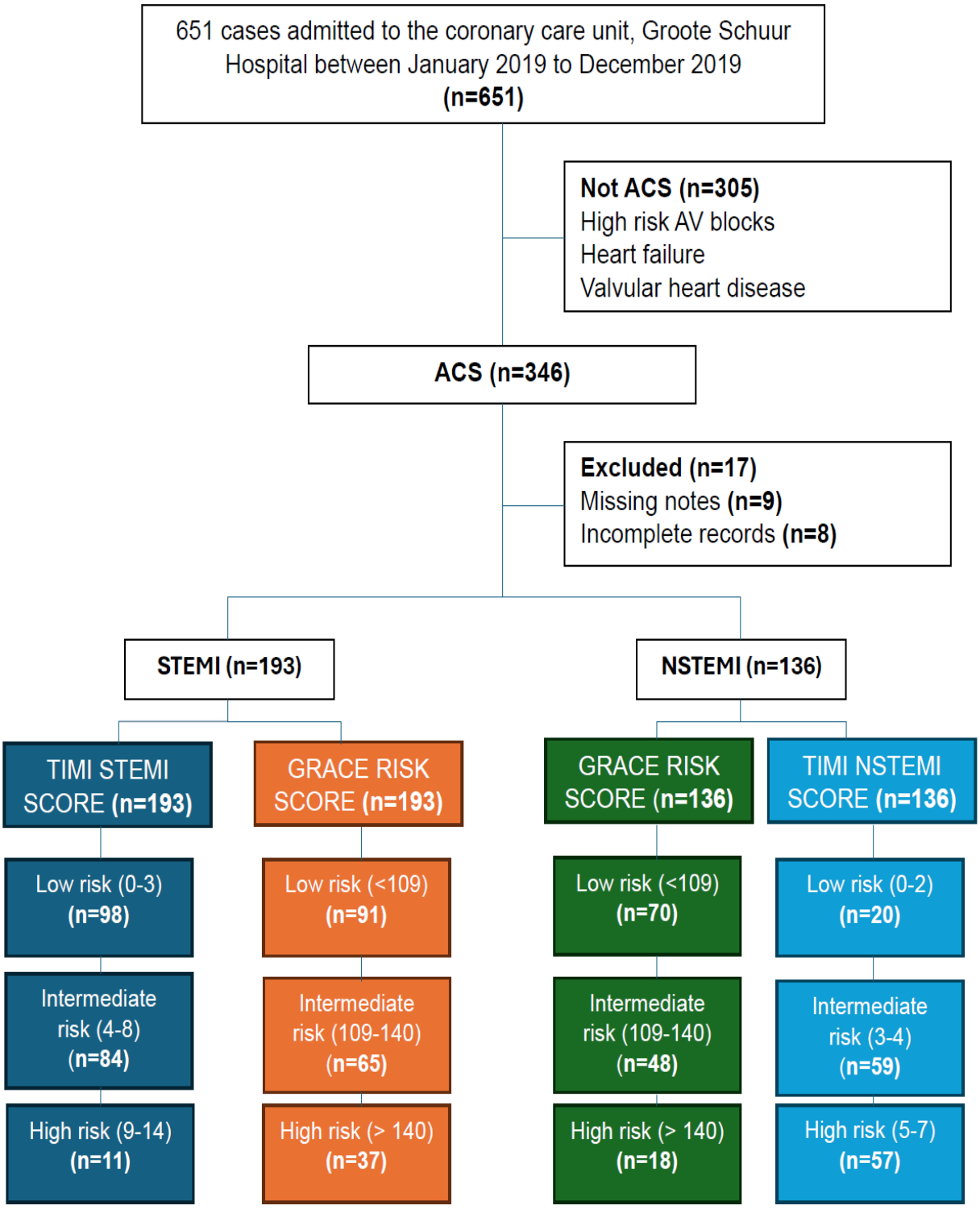

Figure 1: Consort Flow Diagram. AV: Atrioventricular. ACS: Acute Coronary Syndrome. STEMI: ST-elevation myocardial infarction. NSTEMI: non-ST-elevation myocardial infarction.

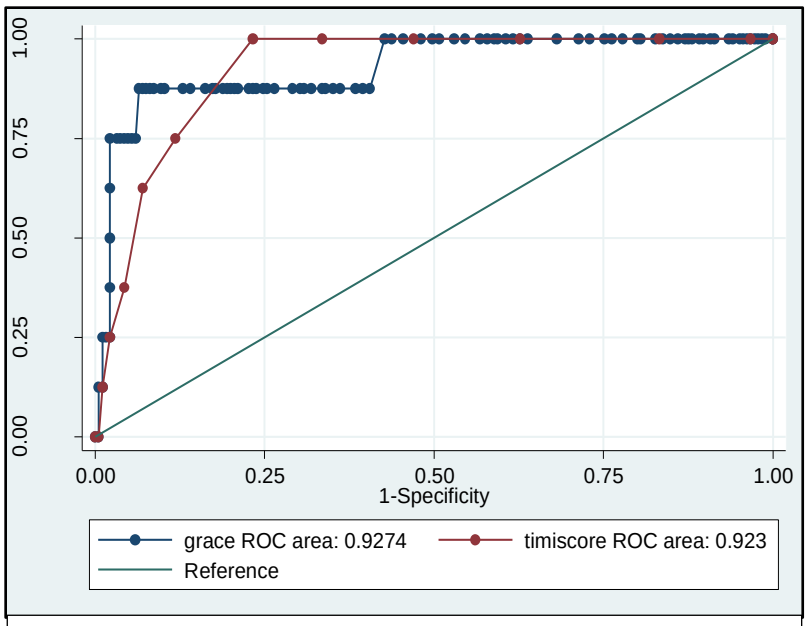

Figure 2: STEMI in-hospital mortality: comparison of GRACE vs TIMI risk scores

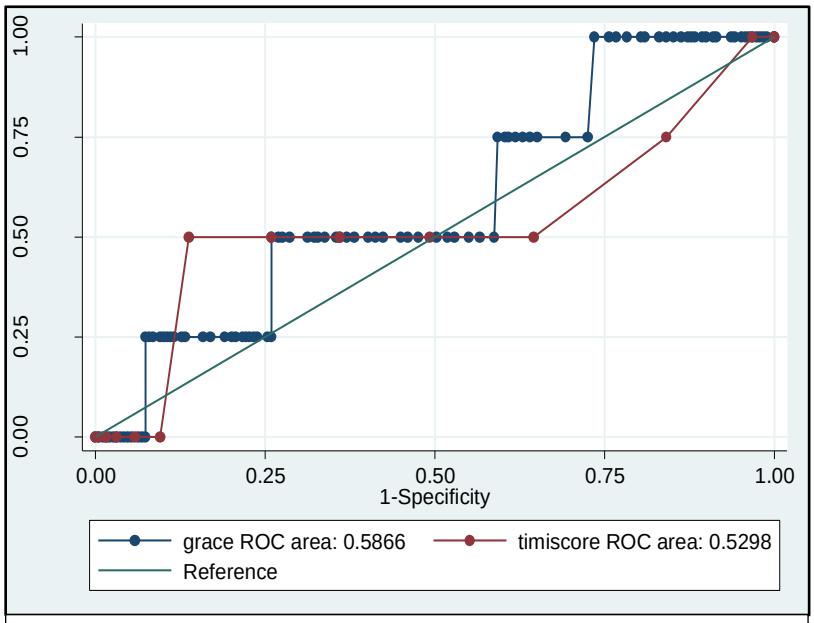

Figure 3: STEMI 30-day hospital mortality: comparison of GRACE vs TIMI risk scores

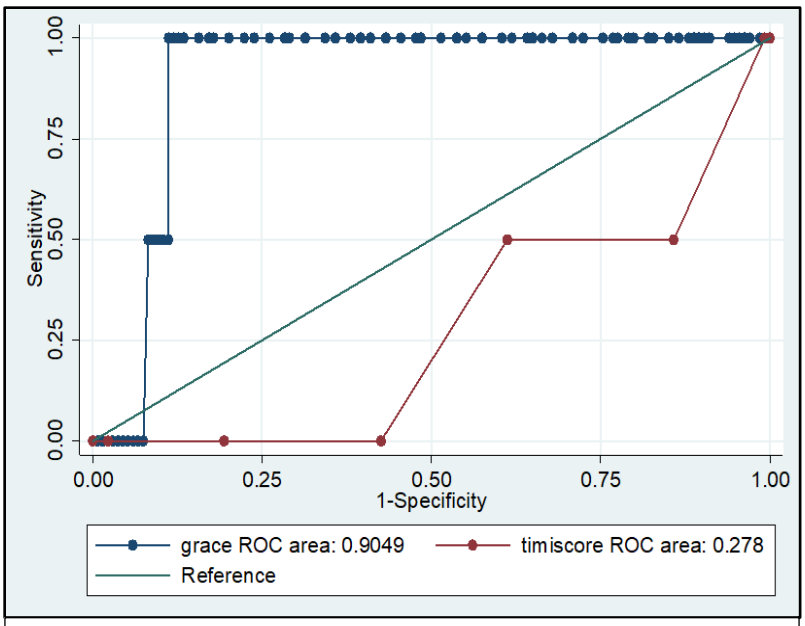

Figure 4: NSTEMI in-hospital mortality: comparison of GRACE vs TIMI risk scores

Discussion

We evaluated and compared the efficacy of two risk-predictive scores in predicting in-hospital and 30-day mortality within our centre where a significant portion of ACS patients present late, receive thrombolytic therapy more than 6 hours after presentation and have limited access to revascularisation. Our study demonstrated that the GRACE and TIMI STEMI risk scores exhibited equally excellent discrimination in predicting STEMI in-hospital mortality; however, GRACE outperformed TIMI in predicting in-hospital mortality for patients with NSTEMI.

Our study shares some similarities to the original GRACE study, with a comparable age distribution, a predominantly male population, and no significant differences in the prevalence and distribution of risk factors such as hypertension, diabetes, dyslipidemia, and smoking.[20] HIV infection is endemic in SSA, and infected individuals harbour an increased risk of developing ACS.[21] Patients who present with ACS are not routinely tested for HIV, and this may explain why our study only had two participants with HIV infection. These risk stratification scores[5,6,17] have not been validated in the HIV population and may serve as a potential area of future research.[22] In contrast to the GRACE study, majority of our participants presented with STEMI (58.6%) compared to 35.3% in GRACE. [20] The InTIMEII trial[23], which served as the derivation study for the TIMI STEMI score[6], enrolled patients with STEMI presenting within 6 hours of symptom onset. In contrast, the mean time from symptom onset to hospital admission in our STEMI cohort was 18.3 (SD ± 37.4) hours and 80 (41.5%) patients presented after six hours. Similar to previous ACS registries,[7,20] the morbidity and mortality in our NSTEMI cohort were less compared to the STEMI group. Notably, our STEMI subset had twice the number of high risk patients (GRACE risk score > 140) compared to the NSTEMI group (37 vs 18), this may also explain why individuals who suffered a STEMI developed greater rates of complications and mortality.

These risk assessment tools have undergone validation in diverse populations to assess their effectiveness in various heterogeneous groups of patients with ACS. The GRACE score has been shown to be superior compared to TIMI and other scores like PURSUIT.[7,8,24] In the (MINAP) database[7], the GRACE score accurately predicted in-hospital death across the spectrum of ACS. A comparative study in Egypt comparing GRACE and TIMI scores in predicting in-hospital MACE revealed that GRACE performed better than TIMI in predicting in-hospital MACE among patients with STEMI and NSTEMI. Both scores demonstrated similar accuracy in predicting 30-day all-cause mortality.[25] In contrast to our findings, a study in Brazil showed similar discrimination of both scores in predicting in-hospital mortality amongst patients with STEMI.[26] This study had a similar number of patients with STEMI compared to our study participants (152 vs 193), and both groups exhibited similar GRACE (116 ±36 vs 114 ±31) and TIMI (3.7 ± 2.3 vs 3.9 ± 2.5) risk scores. However, the in-hospital mortality rate in the Brazilian study was higher than that of ours (11% vs 4.1%).[26]

We investigated various factors contributing to the better predictive performance of GRACE over TIMI for in-hospital mortality in patients with NSTEMI. One key aspect is that the GRACE score was derived from a multi-national registry and included crucial hemodynamic variables and renal dysfunction, both recognised as potent independent predictors of mortality.[20] The TIMI score for UA/NSTEMI was derived from a specific group of participants enrolled in a clinical trial and did not incorporate these critical variables. In our study, individuals who experienced in-hospital mortality due to NSTEMI, either suffered a cardiac arrest on admission or presented with a higher Killip class, factors that are not considered in the TIMI for UA/NSTEMI scoring system. Although the initial risk score at presentation does not dictate acute treatment decisions in patients with STEMI, it can serve as a tool to identify high-risk individuals who may benefit from intensive secondary prevention measures and thorough follow-up.

It is worth noting that almost half (46.3%) of our participants with NSTEMI did not receive revascularisation. Potential reasons for this include lack of readily available, twenty-four hour operated cardiac catheterisation services and delayed presentation to hospital. Previous studies have demonstrated the benefit of a routine invasive versus conservative strategy, particularly in high-risk patients.[27] The optimal timing of intervention is further supported by two randomised controlled trials which showed a benefit when patients with a GRACE score >140 underwent an early invasive strategy within 24 hours.[28,29] On the contrary, this also helps avoid potential complications of invasive therapy in low-risk patients. Our study demonstrated the utility of applying risk scores in our resource-limited environment to objectively assist physicians in selecting suitable high-risk patients who may benefit from specialised care. A study by *Yan et al*[30] showed that using risk scores and physician assessment in risk-stratifying patients is superior to physician risk assessment alone in guiding treatment. Previous studies have defined a risk treatment paradox where low-risk patients receive more aggressive treatment in comparison to high-risk patients.[31] In our resource-limited setting, these risk scores prevent the previously well-defined risk-treatment paradox by selecting high-risk patients who will benefit from aggressive invasive strategies while providing a cost-treatment in our resource-limited environment.

Study Limitations

This study was retrospective by design and conducted in a single academic tertiary referral centre in South Africa with a limited sample size and fewer events in comparison to previous larger studies. As a result, it may not be representative of contemporary practices within our region.

Conclusion

Both GRACE and TIMI risk scores showed excellent discrimination for predicting in-hospital mortality and modest accuracy for 30-day mortality for the STEMI cohort. The GRACE score demonstrated high accuracy predicting in-hospital mortality in participants with NSTEMI compared to TIMI. In our resource-constrained environment, risk stratification is essential to assessing patients with ACS to determine appropriate treatment strategies and selecting high-risk patients for secondary prevention and follow-up. Additional studies in SSA are needed to identify the effect of risk stratification scores on treatment strategies and cardiovascular events.

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None

Competing Interests
The authors declare no competing interest that may have influenced the study and writing of this manuscript.

Author Contributions
MN conceptualised the study idea and undertook the final review and revision. KL reviewed the raw data, results, and performed critical reviews and revisions. MK collected the raw data, processed the data, and wrote the manuscript drafts. MB reviewed the results, tables, figures and did the statistical analysis.

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Data Availability
Raw data was generated at Groote Schuur Hospital. Data derived from the study is available from the corresponding author, Dr Mitesh Khiroya, on request.

Disclaimer
The views and opinions expressed in this article are those of the authors and do not necessarily reflect the official policy or position of any affiliated agenda of the authors.

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risk characteristics? The Global Registry of Acute Coronary Events (GRACE). Heart. 2007;93(2):177-82.

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

Room 45 E-52-E-Floor- Old Main Building
Groote Schuur Hospital
Observatory 7925
Telephone [021] 406 6492
Email: hrec-enquiries@uct.ac.za
Website: www.health.uct.ac.za/fhs/research/humanethics/forms

24 January 2022

HREC REF: 040/2022

Prof M Ntsekhe
Division of Cardiology
E-17 NGSH
Email: mpiko.ntsekhe@uct.ac.za
Student: khrmit001@myuct.ac.za

Dear Prof Ntsekhe

PROJECT TITLE : STEMI RELATED IN-HOSPITAL MORTALITY AND ITS PREDICTORS - A SOUTH AFRICAN TERTIARY CENTRE EXPERIENCE-MASTERS' CANDIDATE-DR MITESH KHIROYA -(SUB-STUDY LINKED TO R031/2017

Thank you for submitting your study to the Faculty of Health Sciences Human Research Ethics Committee (HREC) for review.

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

This approval is subject to strict adherence to the HREC recommendations regarding research involving human participants during COVID -19, dated 17 March 2020: 06 July 2020 & 01 July 2021.

Approval is granted for one year until the 30 January 2023.

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)

The HREC acknowledge that the student: Dr Mitesh Khiroya will also be involved in this study.

Please quote the HREC REF 040/2022 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.

Yours sincerely

PROFESSOR M BLOCKMAN
CHAIRPERSON, FACULTY OF HEALTH SCIENCES HUMAN RESEARCH ETHICS COMMITTEE
Federal Wide Assurance Number: FWA00001637. Institutional Review Board (IRB) number: IRB00001938 NHREC-registration number: REC-210208-007
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 Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use: Good Clinical Practice (ICH GCP), South African Good Clinical Practice Guidelines (DoH 2020), 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.

FHS016: Annual Progress Report / Renewal

HREC office use only (FWA00001637; IRB00001938)			
This serves as notification of annual approval, including any documentation described below.			
☑ Approved	Annual progress report	Approved until/next renewal date	30.01.2025
☐ Not approved	See attached comments		
Signature Chairperson of the HREC/ Designee		Date Signed	10/1/2024

Note: Please email this form and supporting documents (if applicable) in a combined pdf file to hrec-enquiries@uct.ac.za.
Please clarify your plan for research-related activities during COVID-19 lockdown.
Please use the latest form found on our website:
http://www.health.uct.ac.za/fhs/research/humanethics/forms

HUMAN RESEARCH ETHICS COMMITTEE
10 JAN 2024
HEALTH SCIENCES FACULTY
UNIVERSITY OF CAPE TOWN

Comments to PI from the HREC

Principal Investigator to complete the following:

1. Protocol information

Date (when submitting this form)	09/01/2024		
HREC REF Number	040/2022	Current Ethics Approval was granted until	30/01/2024
Protocol title	EVALUATING THE PERFORMANCE OF THE GRACE AND TIMI RISK SCORES IN ACUTE CORONARY SYNDROME: A SOUTH AFRICAN COHORT		
Protocol number (if applicable)	VERSION 1.0		
Are there any sub-studies linked to this study?		☐ Yes	✓ No
If yes, could you please provide the HREC Reference number for all sub-studies? Note: A separate FHS016 must be submitted for each sub-study.			

Principal Investigator	PROFESSOR MPIKO NTSEKHE
Department / Office Internal Mail Address	mpiko.ntsekhe@uct.ac.za

1.1 Does this protocol receive US Federal funding?	☐ Yes	✓ No
1.2 If the study receives US Federal Funding, does the annual report require full committee approval? **Note:** Any annual approvals for **Full Committee** review MUST be submitted on the monthly HREC submission dates. (Please send electronic copy for full committee review to hrec-submission@uct.ac.za)	☐ Yes	✓ No

If yes in 1.2 please complete section 1.3 below for invoicing purposes

1.3 Ethics Renewal Fee

Please **(tick ✓)**appropriate box for billing purposes:

Submission Type	***Description***	***New fee (Vat Incl.)***	***tick ✓***
Research funded solely from UCT departmental/ divisional/group budget	Annual evaluation of research progress report for re-certification	**R0,00**	✓
Non-sponsored student research for degree purposes at UCT/Other Universities & Colleges	Annual evaluation of research progress report for re-certification	**R0,00**	☐
Annual re-certification / Progress report (FHS016 Form)	Clinical Trial & International Grant Funded Research - Annual evaluation of research progress report for re-certification for Full Committee Approval	**R7000,00**	☐
Annual re-certification / Progress report (FHS016 Form)	Clinical Trial & International Grant Funded Research - Annual evaluation of research progress report for re-certification for Expedited review	**R3 710.00**	☐
Annual re-certification / Progress report (FHS016 Form)	National grant funded research - Annual evaluation of research progress report for re-certification for Full Committee Approval	**R6000.00**	☐
Annual re-certification / Progress report (FHS016 Form)	National Grant funded research for Annual evaluation of research progress report for re-certification for Expedited review	**R1 500,00**	☐

NB: Protocols funded by UCT (e.g. departmental funding / student research) and by certain grant funding organizations (e.g. MRC, NRF, CANSA,) are exempt from these charges.

Please provide details for Invoicing, either complete section 1 or 2 :

1. Invoice billing – Directly to Sponsor

Sponsor's name	

(Note: Please complete the Closure form (FHS010) if the study is completed within the approval period)

Billing Address of Sponsor:	
Vat Number:	
Contact person	
Telephone number	
Email Address	
2. **Internal Journal Billing:**	
Fund Number:	
Cost Centre Number:	
Account Holder Name:	
Division of Account Holder:	

2. List of documentation for approval

NONE

3. Protocol status (tick ✓)

☐	Open Enrolment
✓	Closed to enrolment (tick ✓)
☐	Research-related activities are ongoing
☐	Research-related activities are complete, long-term follow-up only
✓	Research-related activities are complete, data analysis only
☐	Main study is complete but sub-study research-related activities are ongoing
☐	Study is closed → Please submit a Study Closure Form (FHS010)

4. Enrolment

Number of participants enrolled to date	329
Number of participants enrolled, since last HREC Progress report (continuing review)	0
Additional number of participants still required	0

5. Refusals

Total number of refusals (participants invited to join the study, but refused to take part)	0

6. Cumulative summary of participants

Total number of participants who provided consent	0
Number of participants determined to be ineligible (i.e. after screening)	17
Number of participants currently active on the study	0
Number of participants completed study (without events leading to withdrawal)	329
Number of participants withdrawn at participants' request (i.e. changed their mind)	0
Number of participants withdrawn by PI due to toxicity or adverse events	0
Number of participants withdrawn by PI for other reasons (e.g. pregnancy, poor compliance)	0
Number of participants lost to follow-up. Please comment below on reasons for loss of follow-up.	0
Number of participants no longer taking part for reasons not listed above. Please provide reasons below:	0

7. Progress of study

Please provide a brief summary of the research to date including the overall progress and the progress since the last annual report as well as any relevant comments/issues you would like to report to the HREC:
This is a retrospective folder review study for purposes of a MMED which started in January 2022. A total of 346 folders were reviewed and data collection is complete. Data analysis is complete however MMED is yet to be marked.

8. Protocol violations and exceptions (tick ✓ all that apply)

✓	No prior violations or exceptions have occurred since the original approval
☐	Prior violations or exceptions have been reported since the last review and have already been acknowledged or approved
☐	Unreported minor violations that have occurred since the last review, as well as significant deviations not yet reported, are attached for review

(Note: Please complete the Closure form (FHS010) if the study is completed within the approval period)

9. Amendments (tick ✓ all that apply)

☐	No Prior amendments have been made since the original approval
✓	Prior amendments have been reported since the last review and have already been approved
☐	New protocol changes/ amendments are requested as part of this continuing review (See note below)

Note: If new protocol changes are being requested in this review, please complete an amendment form (FHS006).
Specific changes in the amended protocol and consent/assent forms must be **bolded**, *italicised* or tracked and all changes must include a rationale.

10. Adverse events

10.1 Please provide below or attach a narrative summary of serious adverse events and/ or unanticipated problems since the last progress report. Please indicate changes made to the protocol and informed consent document(s) as a result (if not already reported to the HREC). Please comment on whether causality to any study procedure or intervention could be established.
NONE

10.2 Have participants received appropriate treatment/ follow-up/ referral when indicated (e.g. in the case of abnormal or incidental clinical findings, distress or anxiety)?		
☐ Yes	☐ No	✓ Not applicable
If yes, please describe:		

11. Summary of Monitoring and Audit Activities (tick ✓)

11.1 Was this study monitored or audited by an external agency (e.g. SAHPRA, FDA)?		
☐ Yes	☐ No	✓ Not applicable

11.2 Did a Data and Safety Monitoring Board publish a report?		
☐ Yes	☐ No	✓ Not applicable

11.3 If yes, please identify the agency and attach a summary of the findings.					
Agency Name		Report attached	☐ Yes	☐ No	☐ Not applicable
		DSMB report attached	☐ Yes	☐ No	☐ Not applicable

11.4 Has there been any agency, institutional or other inquiry into non-compliance in this study, or any finding of non-compliance concerning a member of the research team?	
☐ Yes	✓ No
If yes, please explain:	

12. Level of risk (tick ✓)

12.1 In light of your experience of this research, please indicate whether the level of risk to participants has:	
☐	Increased
☐	Decreased
✓	Shown no change
If there has been a change, please explain:	

12.2 Please provide a narrative summary of recent relevant literature that may have a bearing on the level of risk.
This is a retrospective folder review with no additional risks to participants recruited.

13. Insurance

Please confirm that valid no fault insurance is still in place? **(tick ✓)**			
☐ Yes	☐ No		✓Not Applicable – N/A
If yes, please complete the following:			
Insurer's name:			
Policy no.		*Coverage Period:	
For UCT sponsored studies please liaise the Insurance office via fhs.sponsorship@uct.ac.za regarding the required documentation and information required obtain a renewed UCT No-fault Insurance Certificate.			

14. Statement of conflict of interest

Has there been any change in the conflict of interest status of this protocol since the original approval? (tick ✓)	
☐ Yes	✓ No

If yes, please explain and if necessary, attach a revised conflict of interest statement (Section #7 in the New Protocol Application Form FHS013):

15. Signature

My signature certifies that the above is complete and correct.			
Signature of PI	Mpiko Ntsekhe	Date	09/01/2024

HUMAN RESEARCH ETHICS COMMITTEE
09 JAN 2023
HEALTH SCIENCES FACULTY
UNIVERSITY OF CAPE TOWN

UNIVERSITY OF CAPE TOWN

FACULTY OF HEALTH SCIENCES
Human Research Ethics Committee

FHS016: Annual Progress Report / Renewal

HREC office use only (FWA00001637; IRB00001938) This serves as notification of annual approval, including any documentation described below.			
☑ Approved	Annual progress report	Approved until/next renewal date	30.01.2024
☐ Not approved	See attached comments		
Signature Chairperson of the HREC/ Designee		Date Signed	14/1/2023

Note: Please email this form and supporting documents (if applicable) in a combined pdf-file to hrec-enquiries@uct.ac.za.
Please clarify your plan for research-related activities during COVID-19 lockdown.
Please use the latest form found on our website:
http://www.health.uct.ac.za/fhs/research/humanethics/forms

Comments to PI from the HREC

Principal Investigator to complete the following:

1. Protocol information

Date (when submitting this form)	09th January 2023		
HREC REF Number	040/2022	Current Ethics Approval was granted until	30th January 2023
Protocol title	STEMI RELATED IN-HOSPITAL MORTALITY AND ITS PREDICTORS - A SOUTH AFRICAN TERTIARY CENTRE EXPERIENCE		
Protocol number (if applicable)	Version 1.0		
Are there any sub-studies linked to this study?		☐ Yes	✓No
If yes, could you please provide the HREC Reference number for all sub-studies? Note: A separate FHS016 must be submitted for each sub-study.			
Principal Investigator	Professor Mpiko Ntsekhe		
Department / Office Internal Mail Address	Mpiko.ntsekhe@uct.ac.za		

(Note: Please complete the Closure form (FHS010) if the study is completed within the approval period)

1.1 Does this protocol receive US Federal funding?	☐ Yes	✓ No
1.2 If the study receives US Federal Funding, does the annual report require full committee approval? **Note:** Any annual approvals for **Full Committee** review MUST be submitted on the monthly HREC submission dates. (Please send electronic copy for full committee review to hrec-submission@uct.ac.za)	☐ Yes	☐ No

If yes in 1.2 please complete section 1.3 below for invoicing purposes

1.3 Ethics Renewal Fee

Please **(tick ✓)** appropriate box for billing purposes:

Submission Type	***Description***	***New fee (Vat Incl.)***	***tick ✓***
Research funded solely from UCT departmental/ divisional/group budget	Annual evaluation of research progress report for re-certification	**R0,00**	✓
Non-sponsored student research for degree purposes at UCT/Other Universities & Colleges	Annual evaluation of research progress report for re-certification	**R0,00**	☐
Annual re-certification / Progress report (FHS016 Form)	Clinical Trial & International Grant Funded Research - Annual evaluation of research progress report for re-certification for Full Committee Approval	**R7000,00**	☐
Annual re-certification / Progress report (FHS016 Form)	Clinical Trial & International Grant Funded Research - Annual evaluation of research progress report for re-certification for Expedited review	**R3 710.00**	☐
Annual re-certification / Progress report (FHS016 Form)	National grant funded research - Annual evaluation of research progress report for re-certification for Full Committee Approval	**R6000.00**	☐
Annual re-certification / Progress report (FHS016 Form)	National Grant funded research for Annual evaluation of research progress report for re-certification for Expedited review	**R1 500,00**	☐

NB: Protocols funded by UCT (e.g. departmental funding / student research) and by certain grant funding organizations (e.g. MRC, NRF, CANSA,) are exempt from these charges.

Please provide details for Invoicing, either complete section 1 or 2 :

1. Invoice billing – Directly to Sponsor

Sponsor's name	
Billing Address of Sponsor:	
Vat Number:	
Contact person	
Telephone number	

Email Address	
2. **Internal Journal Billing:**	
Fund Number:	
Cost Centre Number:	
Account Holder Name:	
Division of Account Holder:	

2. List of documentation for approval

None

3. Protocol status (tick ✓)

☐	Open Enrolment
✓	Closed to enrolment (tick ✓)
✓	Research-related activities are ongoing
☐	Research-related activities are complete, long-term follow-up only
☐	Research-related activities are complete, data analysis only
☐	Main study is complete but sub-study research-related activities are ongoing
☐	Study is closed → Please submit a Study Closure Form (FHS010)

4. Enrolment

Number of participants enrolled to date	329
Number of participants enrolled, since last HREC Progress report (continuing review)	329
Additional number of participants still required	0

5. Refusals

Total number of refusals (participants invited to join the study, but refused to take part)	0

6. Cumulative summary of participants

Total number of participants who provided consent	0

Number of participants determined to be ineligible (i.e. after screening)	17
Number of participants currently active on the study	0
Number of participants completed study (without events leading to withdrawal)	329
Number of participants withdrawn at participants' request (i.e. changed their mind)	0
Number of participants withdrawn by PI due to toxicity or adverse events	0
Number of participants withdrawn by PI for other reasons (e.g. pregnancy, poor compliance)	0
Number of participants lost to follow-up. Please comment below on reasons for loss of follow-up.	0
Number of participants no longer taking part for reasons not listed above. Please provide reasons below:	0

7. Progress of study

Please provide a brief summary of the research to date including the overall progress and the progress since the last annual report as well as any relevant comments/issues you would like to report to the HREC:
This is a retrospective folder review study for a masters degree which started in January 2022. 346 Folders have been reviewed. Data entry has been completed. Data is currently being analysed by our statistician and will be reported in the current year.

8. Protocol violations and exceptions (tick ✓ all that apply)

✓	No prior violations or exceptions have occurred since the original approval
☐	Prior violations or exceptions have been reported since the last review and have already been acknowledged or approved
☐	Unreported minor violations that have occurred since the last review, as well as significant deviations not yet reported, are attached for review

9. Amendments (tick ✓ all that apply)

✓	No Prior amendments have been made since the original approval
☐	Prior amendments have been reported since the last review and have already been approved
☐	New protocol changes/ amendments are requested as part of this continuing review (See note below)

(Note: Please complete the Closure form (FHS010) if the study is completed within the approval period)

Note: If new protocol changes are being requested in this review, please complete an amendment form (FHS006).
Specific changes in the amended protocol and consent/assent forms must be **bolded**, *italicised* or tracked and all changes must include a rationale.

10. Adverse events

10.1 Please provide below or attach a narrative summary of serious adverse events and/ or unanticipated problems since the last progress report. Please indicate changes made to the protocol and informed consent document(s) as a result (if not already reported to the HREC). Please comment on whether causality to any study procedure or intervention could be established.
None

10.2 Have participants received appropriate treatment/ follow-up/ referral when indicated (e.g. in the case of abnormal or incidental clinical findings, distress or anxiety)?		
☐ Yes	☐ No	✓ Not applicable
If yes, please describe:		

11. Summary of Monitoring and Audit Activities (tick ✓)

11.1 Was this study monitored or audited by an external agency (e.g. SAHPRA, FDA)?		
☐ Yes	☐ No	✓ Not applicable

11.2 Did a Data and Safety Monitoring Board publish a report?		
☐ Yes	☐ No	✓ Not applicable

11.3 If yes, please identify the agency and attach a summary of the findings.					
Agency Name		Report attached	☐ Yes	☐ No	☐ Not applicable
		DSMB report attached	☐ Yes	☐ No	☐ Not applicable

11.4 Has there been any agency, institutional or other inquiry into non-compliance in this study, or any finding of non-compliance concerning a member of the research team?	
☐ Yes	✓ No
If yes, please explain:	

12. Level of risk (tick ✓)

12.1 In light of your experience of this research, please indicate whether the level of risk to participants has:	
☐	Increased
☐	Decreased
✓	Shown no change
If there has been a change, please explain:	

12.2 Please provide a narrative summary of recent relevant literature that may have a bearing on the level of risk.
This is a retrospective folder review with no additional risk to participants recruited.

13. Insurance

Please confirm that valid no fault insurance is still in place? **(tick ✓)**			
☐ Yes		✓ No	
If yes, please complete the following:			
Insurer's name:			
Policy no.		*Coverage Period:	
For UCT sponsored studies please liaise the Insurance office via fhs.sponsorship@uct.ac.za regarding the required documentation and information required obtain a renewed UCT No-fault Insurance Certificate.			

14. Statement of conflict of interest

Has there been any change in the conflict of interest status of this protocol since the original approval? (tick ✓)	
☐ Yes	✓ No
If yes, please explain and if necessary, attach a revised conflict of interest statement (Section #7 in the New Protocol Application Form FHS013):	

15. Signature

My signature certifies that the above is complete and correct.			
Signature of PI	Mpiko Ntsekhe	Date	2023/01/09

(Note: Please complete the Closure form (FHS010) if the study is completed within the approval period)

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

Room 45 E-52-E-Floor- Old Main Building
Groote Schuur Hospital
Observatory 7925
Email: hrec-enquiries@uct.ac.za
Website: www.health.uct.ac.za/fhs/research/humanethics/forms

18th December 2023

HREC REF: 040/2022

Prof M Ntsekhe
Division of Cardiology
E-17 New Groote Schuur Hospital
Email: mpiko.ntsekhe@uct.ac.za
Student: khrmit001@myuct.ac.za

Dear Prof Ntsekhe

PROJECT TITLE: EVALUATING THE PERFORMANCE OF THE GRACE AND TIMI RISK SCORES IN ACUTE CORONARY SYNDROMES: A SOUTH AFRICAN COHORT'. -MASTERS' CANDIDATE- DR MITESH KHIROYA -(SUB-STUDY LINKED TO R031/2017)

Thank you for submitting your FHS006 – Protocol Amendment dated 5th December 2023 to the Faculty of Health Sciences Human Research Ethics Committee (HREC) for review.

Approval is granted for one year until the 30 January 2024.

The HREC acknowledge that the student: Dr Mitesh Khiroya will also be involved in this study.

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

Please quote the HREC REF 040/2022 in all your correspondence.

Yours sincerely

PROFESSOR MARC BLOCKMAN
CHAIRPERSON, FACULTY OF HEALTH SCIENCES HUMAN RESEARCH ETHICS COMMITTEE

Form FHS006: Protocol Amendment

HREC office use only (FWA00001637; IRB00001938)			
☑ Approved	☐ Type of review: Expedited	☐ Full committee	
This serves as notification that all changes and documentation described below are approved.			
Signature HREC Chairperson / Designee		Date	11/12/2023

Note: All **Major** amendments must include a **Cover Letter** and a local **PI Synopsis** justifying the changes for the amendment. Please note that incomplete amendment submissions will not be reviewed.

Please email this form and supporting documents (if applicable) in a combined pdf-file to hrec-enquiries@uct.ac.za with subject line: FHS006 + (HREC Reference number).

The latest forms are found on our website.

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

Please also clarify your plan for research-related activities during COVID-19 lockdown.

HUMAN RESEARCH ETHICS COMMITTEE
- 7 DEC 2023
HEALTH SCIENCES FACULTY
UNIVERSITY OF CAPE TOWN

Comments from the HREC to the Principal Investigator:
Note: The approval of this protocol amendment does not grant annual approval. Please complete the FHS016 / FHS017 form for annual approval at least one month before study expiration.

Principal Investigator to complete the following:

1. Protocol information

Date (when submitting this form)	06 December 2023
HREC REF Number	040/2022
Protocol Title	STEMI RELATED IN-HOSPITAL MORTALITY AND IT'S PREDICTORS-A SOUTH AFRICAN TERTIARY CENTRE EXPERIENCE"
Protocol Number (if applicable)	Version 1.0
Principal Investigator	PROFESSOR MPIKO NTSEKHE
Department / Office Internal Mail Address	mpiko.ntsekhe@uct.ac.za

1.1 Is this a major or a minor amendment? (see FHS006hlp) Major (tick box) Minor (tick box)	☐ Major	✓ Minor
1.2 Does this protocol receive US Federal funding?	☐ Yes	✓ No
1.3 If the amendment is a major amendment and receives US Federal Funding, does the amendment require full committee approval? **Note:** Any protocol amendments for **Full Committee Review** MUST be submitted on the monthly HREC submission dates. (Please email an electronic copy to hrec-enquiries@uct.ac.za)	☐ Yes	✓ No
1.4 Did the initial study require UCT No-Fault Insurance	☐ Yes	✓ No

2. List of Proposed Amendments with Revised Version Numbers and Dates

Please itemise on the page below, all amendments with revised version numbers and dates, which need approval.
This page will be detached, signed and returned to the PI as notification of approval. Please add extra pages if necessary.

1. **Change of Title**

Proposed changes: On page 1 of protocol. Change of title to new title: 'EVALUATING THE PERFORMANCE OF THE GRACE AND TIMI RISK SCORES IN ACUTE CORONARY SYNDROMES: A SOUTH AFRICAN COHORT'.
The change of the study title is to apply a more suitable title for submitting the MMED Thesis for marking.
The change in study title does not affect the study aims/objectives, data or results.

3. Protocol status (tick ✓)

☐	Open to enrolment
☐	No participants have been enrolled
	Closed to enrolment (tick ✓)
☐	Research-related activities are ongoing
☐	Research-related activities are complete, long-term follow-up only
✓	Research-related activities are complete, data analysis only

4. Proposed changes will affect: (tick ✓ all the categories that apply)

Protocol	
☐	Study objectives, design (including investigator's brochure, clinical activities, study length)
☐	Study instruments, questionnaires, interview schedules
☐	Sample size
☐	Recruitment methods

☐	Eligibility criteria (inclusion and exclusion criteria)
☐	Drug/device (composition, amount, schedule, route of administration, combination with other drugs/devices, safety information)
☐	Data collection/ analysis
☐	Principal Investigator. (Please attach revised conflict of interest and PI declaration statements. Refer: sections 7 and 8.4 in the New Protocol Application Form FHS013)
☐	Consent form and information sheet
☐	Recruitment materials (e.g. advertisements)
☐	Administrative (e.g. change in sponsor's name, change in contact information)
✓	Other. Please specify: Title of study

**Note: Amendment changes involving study length, sample size, additional sites and eligibility criteria (i.e. inclusion of minors and /or pregnant woman) need to be declared to the Insurance office. Please liaise via fhs.sponsorship@uct.ac.za regarding the required documentation and information to be submitted to obtain an updated UCT No-fault Insurance Certificate- it should be included herewith*

4.1 In your opinion, will there be any **increase** in risk, discomfort or inconvenience to participants?	☐ Yes	✓ No
If yes, please provide a detailed justification/explanation:		
N/A		

4.2 What follow-up action do you propose for participants who are already enrolled in the study?	
☐	Inform current participants as soon as possible
☐	Re-consent current participants with revised consent/assent forms (append)
✓	No action required
☐	Other. Please describe:

5. Detailed description of the change(s)

Please attach, for each amendment, a summary of all changes which clearly indicates:

i. Old wording (e.g. ~~strikethrough~~ text, CHANGED FROM and CHANGED TO)

ii. New wording (e.g. *italicized*, **bold**, tracked)

iii. Detailed rationale/ justification/ explanation for each change

6. Ethics Review for Amendment Levy – cost including vat

Amendment Review Costs including VAT

Please tick amount to be billed:

Submission Type	*Description*	*New fee (Vat Incl.)*	*tick* ✓
Research funded solely from UCT departmental/ divisional/group budget	Major/ Minor Amendments	**R0,00**	✓
Non-sponsored student research for degree purposes at UCT/Other Universities & Colleges	Major/ Minor Amendments	**R0,00**	☐
Protocol amendment - Major (FHS006 Form)	Clinical Trial & International Grant Funded Research - Any changes to the protocol that requires Full Committee review	**R8 000.00**	☐
Protocol amendment - Major (FHS006 Form)	Clinical Trial & International Grant Funded Research - Any change to the protocol that requires Expedited review that does not require Full Committee Review	**R5 000,00**	☐
Protocol amendment - Minor (FHS006 Form)	Clinical Trial & International Grant Funded Research - Minor amendments, administrative changes that do not affect study design e.g. changes to informed consent form, changes in study staff, etc.	**R2 250,00**	☐
Protocol amendment - Major (FHS006 Form)	National grant funded research - Any change to the protocol that requires Full Committee review	**R7 000,00**	☐
Protocol amendment - Major (FHS006 Form)	National grant funded research - Any change to the protocol that requires Expedited review that does not require Full Committee review	**R2 500,00**	☐
Protocol amendment - Minor (FHS006 Form)	National grant funded research - Minor amendments, administrative changes that do not affect study design e.g. changes to informed consent form, changes in study staff, etc.	**R1 000,00**	☐

NB: Protocols funded by UCT (e.g. departmental funding / student research) and by certain grant funding organizations (e.g. MRC, NRF, CANSA,) are exempt from these charges.

Please provide details for Invoicing, either complete section 1 or 2 :

1. Invoice billing – Directly to Sponsor

Sponsor's name	
Billing Address of Sponsor:	
Vat Number:	
Contact person:	
Telephone number:	
Email Address:	

2. Internal Journal Billing:

Fund Number:	
Cost Centre Number:	
Account Holder Name:	
Division of Account Holder:	

7. Amendment Submission checklist (tick ✓)

7.1 Please tick that all the documents are attached before submitting to the HREC. NB: Incomplete submissions will not be processed	
✓	Latest FHS006 form completed with all sections completed as per our website
✓	Cover Letter
✓	PI Justification/ Summary for the reasons for the amendment
✓	Protocol - Track changes & Clean Copy (where necessary)
☐	Informed Consent Forms (ICF), if applicable (Any changes made to ICF tracked & clean copy)
☐	Any other additional documentation in support of amendment
☐	Updated no fault insurance certificate (if applicable)

Please email this form and supporting documents (if applicable) in a combined pdf-file to hrec-enquiries@uct.ac.za with subject line: FHS006 + (HREC Reference number). The latest forms are found on our website.

8. Signature

My signature certifies that I will maintain the anonymity and/ or confidentiality of information collected in this research. If at any time I want to share or re-use the information for purposes other than those disclosed in the original approval, I will seek further approval from the HREC.			
Signature of PI	Mpiko Ntsekhe	Date	2023/12/06

South African Medical Journal-SAMJ: Author Guidelines

Author Guidelines

The SAMJ has launched a new submission and tracking system. Authors will be required to register a profile on the in order to submit a manuscript.

To submit a manuscript, please proceed to: https://samajournals.co.za/index.php/samj

General article format/layout

Accepted manuscripts that are not in the correct format specified in these guidelines will be returned to the author(s) for correction, which will delay publication.

General:

- Manuscripts must be written in UK English.
- The manuscript must be in Microsoft Word format. Text must be single-spaced, in 12-point Times New Roman font, and contain no unnecessary formatting (such as text in boxes).
- Please make your article concise, even if it is below the word limit.
- Qualifications, full affiliation (department, school/faculty, institution, city, country) and contact details of ALL authors must be provided in the manuscript and in the online submission process.
- Abbreviations should be spelt out when first used and thereafter used consistently, e.g.' intravenous (IV)' or 'Department of Health (DoH)'.
- Include sections on Acknowledgements, Conflict of Interest, Author Contributions and Funding sources. If none is applicable, please state 'none'.
- Scientific measurements must be expressed in SI units except: blood pressure (mmHg) and haemoglobin (g/dL).
- Litres is denoted with an uppercase L e.g.' mL' for millilitres).
- Units should be preceded by a space (except for % and ºC), e.g. '40 kg' and '20 cm' but '50%' and ''19ºC'.
- Please be sure to insert proper symbols e.g. µ not u for micro, a not a for alpha, b not B for beta, etc.
- Numbers should be written as grouped per thousand-units, i.e. 4 000, 22 160.
- Quotes should be placed in single quotation marks: i.e. The respondent stated: '...'
- Round brackets (parentheses) should be used, as opposed to square brackets, which are reserved for denoting concentrations or insertions in direct quotes.
- If you wish material to be in a box, simply indicate this in the text. You may use the table format –this is the only exception. Please DO NOT use fill, format lines and so on.

SAMJ is a generalist medical journal, therefore for articles covering genetics, it is the responsibility of authors to apply the following:
- Please ensure that all genes are in italics, and proteins/enzymes/hormones are not.

- Ensure that all genes are presented in the correct case e.g. TP53 not Tp53.

**NB: Copyeditors cannot be expected to pick up and correct errors wrt the above, although they will raise queries where concerned.

- Define all genes, proteins and related shorthand terms at first mention, e.g. '188del11' can be glossed as 'an 11 bp deletion at nucleotide 188.'

- Use the latest approved gene or protein symbol as appropriate:
- Human Gene Mapping Workshop (HGMW): genetic notations and symbols
- HUGO Gene Nomenclature Committee: approved gene symbols and nomenclature
- OMIM: Online Mendelian Inheritance in Man (MIM) nomenclature and instructions
- Bennet et al. sStandardised human pedigree nomenclature: Update and assessment of the recommendations of the National Society of Genetic Counselors. J Genet Counsel 2008;17:424-433: standard human pedigree nomenclature.

Research

Guideline word limit: 4 000 words

Research articles describe the background, methods, results and conclusions of an original research study. The article should contain the following sections: introduction, methods, results, discussion and conclusion, and should include a structured abstract (see below). The introduction should be concise – no more than three paragraphs – on the background to the research question, and must include references to other relevant published studies that clearly lay out the rationale for conducting the study. Some common reasons for conducting a study are: to fill a gap in the literature, a logical extension of previous work, or to answer an important clinical question. If other papers related to the same study have been published previously, please make sure to refer to them specifically. Describe the study methods in as much detail as possible so that others would be able to replicate the study should they need to. Results should describe the study sample as well as the findings from the study itself, but all interpretation of findings must be kept in the discussion section, which should consider primary outcomes first before any secondary or tertiary findings or post-hoc analyses. The conclusion should briefly summarise the main message of the paper and provide recommendations for further study.

Select figures and tables for your paper carefully and sparingly. Use only those figures that provided added value to the paper, over and above what is written in the text.

Do not replicate data in tables and in text .

Structured abstract
This should be 250-400 words, with the following recommended headings:
o **Background:** why the study is being done and how it relates to other published work.

o **Objectives:** what the study intends to find out

o **Methods:** must include study design, number of participants, description of the intervention, primary and secondary outcomes, any specific analyses that were done on the data.

o **Results:** first sentence must be brief population and sample description; outline the results according to the methods described. Primary outcomes must be described first, even if they are not the most significant findings of the study.

o **Conclusion:** must be supported by the data, include recommendations for further study/actions.

- Please ensure that the structured abstract is complete, accurate and clear and has been approved by all authors.
- Do not include any references in the abstracts.

Here is an example of a good abstract.

Main article
All articles are to include the following main sections: Introduction/Background, Methods, Results, Discussion, Conclusions.

The following are additional heading or section options that may appear within these:

- Objectives (within Introduction/Background): a clear statement of the main aim of the study and the major hypothesis tested or research question posed
- Design (within Methods): including factors such as prospective, randomisation, blinding, placebo control, case control, crossover, criterion standards for diagnostic tests, etc.
- Setting (within Methods): level of care, e.g. primary, secondary, number of participating centres.
- Participants (instead of patients or subjects; within Methods): numbers entering and completing the study, sex, age and any other biological, behavioural, social or cultural factors (e.g. smoking status, socioeconomic group, educational attainment,

co-existing disease indicators, etc)that may have an impact on the study results. Clearly define how participants were enrolled, and describe selection and exclusion criteria.
- Interventions (within Methods): what, how, when and for how long. Typically for randomised controlled trials, crossover trials, and before and after studies.
- Main outcome measures (within Methods): those as planned in the protocol, and those ultimately measured. Explain differences, if any.

Results
- Start with description of the population and sample. Include key characteristics of comparison groups.
- Main results with (for quantitative studies) 95% confidence intervals and, where appropriate, the exact level of statistical significance and the number need to treat/harm. Whenever possible, state absolute rather than relative risks.
- Do not replicate data in tables and in text.
- If presenting mean and standard deviations, specify this clearly. Our house style is to present this as follows:
- E.g.: The mean (SD) birth weight was 2 500 (1 210) g. Do not use the ± symbol for mean (SD).
- Leave interpretation to the Discussion section. The Results section should just report the findings as per the Methods section.

Discussion
Please ensure that the discussion is concise and follows this overall structure – sub-headings are not needed:
- Statement of principal findings
- Strengths and weaknesses of the study
- Contribution to the body of knowledge
- Strengths and weaknesses in relation to other studies
- The meaning of the study – e.g. what this study means to clinicians and policymakers
- Unanswered questions and recommendations for future research

Conclusions
This may be the only section readers look at, therefore write it carefully. Include primary conclusions and their implications, suggesting areas for further research if appropriate. Do not go beyond the data in the article.

Illustrations/photos/scans

- If illustrations submitted have been published elsewhere, the author(s) should provide consent to republication obtained from the copyright holder.
- Figures must be numbered in Arabic numerals and referred to in the text e.g. '(Fig. 1)'.
- Each figure must have a caption/legend: Fig. 1. Description (any abbreviations in full).
- All images must be of high enough resolution/quality for print.
- All illustrations (graphs, diagrams, charts, etc.) must be in PDF or jpeg form.
- Ensure all graph axes are labelled appropriately, with a heading/description and units (as necessary) indicated. Do not include decimal places if not necessary e.g. 0; 1.0; 2.0; 3.0; 4.0 etc.
- Scans/photos showing a specific feature e.g. Intermediate magnification micrograph of a low malignant potential (LMP) mucinous ovarian tumour. (H&E stain). –include an arrow to show the tumour.
- Each image must be attached individually as a 'supplementary file' upon submission (not solely embedded in the accompanying manuscript) and named Fig. 1, Fig. 2, etc.

Tables

- Tables should be constructed carefully and simply for intelligible data representation. Unnecessarily complicated tables are strongly discouraged.
- Large tables will generally not be accepted for publication in their entirety. Please consider shortening and using the text to highlight specific important sections, or offer a large table as an addendum to the publication, but available in full on request from the author
- Embed/include each table in the manuscript Word file - do not provide separately as supplementary files.
- Number each table in Arabic numerals (Table 1, Table 2, etc.) and refer to consecutively in the text.
- Tables must be cell-based (i.e. not constructed with text boxes or tabs) and editable.
- Ensure each table has a concise title and column headings, and include units where necessary.
- Footnotes must be indicated with consecutive use of the following symbols: * † ‡ § ¶ || then ** †† ‡‡ etc.

Do not: Use [Enter] within a row to make 'new rows':
Rather:
Each row of data must have its own proper row:

Do not: use separate columns for n and %:

Rather:
Combine into one column, n (%):

Do not: have overlapping categories, e.g.:

Rather:
Use <> symbols or numbers that don't overlap:

References
NB: Only complete, correctly formatted reference lists in Vancouver style will be accepted. Reference lists must be generated manually and not with the use of reference manager software. Endnotes must not be used.

- Authors must verify references from original sources.
- Citations should be inserted in the text as superscript numbers between square brackets, e.g. These regulations are endorsed by the World Health Organization,[2] and others.[3,4-6]
- All references should be listed at the end of the article in numerical order of appearance in the Vancouver style (not alphabetical order).
- Approved abbreviations of journal titles must be used; see the List of Journals in Index Medicus.
- Names and initials of all authors should be given; if there are more than six authors, the first three names should be given followed by et al.
- Volume and issue numbers should be given.
- First and last page, in full, should be given e.g.: 1215-1217 not 1215-17.
- Wherever possible, references must be accompanied by a digital object identifier (DOI) link). Authors are encouraged to use the DOI lookup service offered by CrossRef:

o On the Crossref homepage, paste the article title into the 'Metadata search' box.

o Look for the correct, matching article in the list of results.

o Click Actions > Cite

o Alongside 'url =' copy the URL between { }.

o Provide as follows, e.g.: https://doi.org/10.7196/07294.937.98x

Some examples:

- Journal references: Price NC, Jacobs NN, Roberts DA, et al. Importance of asking about glaucoma. Stat Med 1998;289(1):350-355. http://dx.doi.org/10.1000/hgjr.182
- Book references: Jeffcoate N. Principles of Gynaecology. 4th ed. London: Butterworth, 1975:96-101.
- Chapter/section in a book: Weinstein L, Swartz MN. Pathogenic Properties of Invading Microorganisms. In: Sodeman WA, Sodeman WA, eds. Pathologic Physiology: Mechanisms of Disease. Philadelphia: WB Saunders, 1974:457-472.
- Internet references: World Health Organization. The World Health Report 2002 - Reducing Risks, Promoting Healthy Life. Geneva: WHO, 2002. http://www.who.int/whr/2002 (accessed 16 January 2010).
- Legal references

Publication
Online v. print

The SAMJ is an online journal. The online version of the journal is the one that has the widest circulation, is indexed by bibliographic databases including PubMed and SciELO, and is accessible in academic libraries. A printed edition , containing material selected by the Editor is also published each month and distributed to the membership of the South African Medical Association.

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You may want to make use of the advantages of online publication e.g. specify web links to other sources, images, data or even a short video.

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Not all articles will be selected for print.
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