Electrocardiographic predictors of poor outcome in acute myocardial infarction

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PUBLICATION-READY MANUSCRIPT

Declaration

I, Samantha Robyn Shirley, herby declare, this thesis has been submitted and I confirm that my supervisors have seen my dissertation and any concerns revealed by such have been resolved with my supervisor. The dissertation is based on my own work in collaboration with my supervisors' approval.

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Abstract

Introduction

Myocardial infarction (MI) is a major cause of death worldwide. An ECG is indicated in all patients with suspected MI. The aim of this study was to evaluate electrocardiographic predictors of outcome in acute coronary syndrome (ACS).

Methods

We analyzed 12-lead ECGs of 301 consecutive patients admitted to the coronary care unit (CCU) at a tertiary centre during 2016 with a diagnosis of ACS. ECGs were done on admission, and after that daily throughout the hospitalisation. Poor outcome was defined as all-cause mortality within a three-year period after the index MI.

Results

This cohort of 301 patients (42.2% female) with a mean age of 57.4±11.9 years, presented with either ST-elevation myocardial infarction (STEMI, 57.5%) or non-ST elevation myocardial infarction (NSTEMI, 42.5%). Fifty-one (16.9%) patients died within three years after their index presentation. Multivariable regression analyses revealed that left atrial enlargement (LAE, odds ratio [OR] 3.91 [95% confidence interval [CI] 1.39-11.02], p=0.010) and ST depression (OR 3.64 [95% CI 1.33-9.93], p=0.012) were predictive of poor outcome, wheras sinus rhythm with normal rate was associated with a better prognosis (OR 0.33 [95% CI 0.12-0.91] p=0.032). Patients with two or more risk factors (i.e., LAE, ST depression, sinus tachycardia) experienced higher mortality rates (p<0.001).

Conclusion

Our study showed that the ECG has prognostic value in patients presenting with acute MI. ECG features that were independently associated with increased mortality within the first three years of MI (LAE, ST depression and/or sinus tachycardia) could assist with risk stratification of patients presenting with ACS.

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Title

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Introduction

Recent data from the Global Burden of Disease Study in 2017 highlighted that ischaemic heart disease (IHD) has an increasing incidence in sub-Saharan Africa (SSA). It is now believed to contribute to 39% of all cardiovascular (CVS) deaths, as compared to 48.8% in Western Europe and 58.9% in North America (1). The ECG has been studied as a risk predictor for patients with acute coronary syndromes from the Global North, but data from SSA is lacking (2).

Myocardial infarction (MI) causes metabolic and electrophysiological changes that can induce life-threatening arrhythmias (3). Occurrence of arrhythmias such as ventricular fibrillation (VF), ventricular tachycardia (VT), atrial fibrillation (AF) and atrioventricular (AV) blocks in acute coronary syndromes (ACS) is associated with a worse prognosis (4). Despite improvements in morbidity and mortality in ST-elevation myocardial infarction (STEMI) due to early reperfusion therapy, life-threatening arrhythmias still occur in up to 10% of patients (4). The European Society of Cardiology (ESC) guidelines for management of STEMI and non-ST elevation myocardial infarction (NSTEMI) advises rhythm monitoring for at least 24 to 48 hours after symptom onset or until revascularisation (5) (6).

The electrocardiogram (ECG) is a first-line diagnostic tool for the diagnosis of ACS (5) (6). The 12-lead ECG records arrhythmias and intervals of impulse conduction,and displays waveforms that inform the interpreter *inter alia* on chamber enlargement and ischaemia. ECG monitoring is non-invasive, cost efficient and widely available (7, 8). The identification of simple ECG measures has been shown to be useful for risk stratification and to predict the risk of arrhythmogenesis and mortality in ACS (9).

There is a lack of contemporary data regarding the incidence and prognostic implications of arrhythmias and ECG waveform abnormalities in patients with ACS within the South African and sub-Saharan African context. The aim of this study was therefore to determine the prevalence of arrhythmias and ECG waveform abnormalities in a South African cohort of ACS patients, and to establish electrocardiographic predictors of outcome.

Aim and Objectives

The aim of this study was to establish the prevalence of arrhythmias and waveform abnormalities on the 12-lead ECG of patients with myocardial infarction admitted to the CCU at Groote Schuur Hospital and to determine the outcomes of these electrocardiographic findings.

The objectives of this study are to:

1. Study the prevalence of arrhythmias in South African patients with ACS admitted to the CCU.

2. Determine whether there is a difference in prevalence of arrhythmias according to:
    a. Diagnosis (STEMI vs NSTEMI)

3. Determine the outcomes of patients:
    a. who had arrhythmias in the CCU
        i. Short term (during hospitalisation)
        ii. Long term (outpatient up to one year after index event, specifically referring to death or readmission for myocardial infarction.
    b. with arrhythmias vs those without

4. Study the prevalence in this population of PREDETERMINE risk factors (waveform abnormalities previously found to have a prognostic value in ACS):
    a. widened QRS (>120ms)
    b. fractionated QRS
    c. contiguous Q wave
    d. LVH
    e. prolonged QTc (>440ms in men, >460ms in women)

5.Determine whether there are other ECG features that have a prognostic value

Methods

Study design and patient recruitment

This single-centre, retrospective cohort study was conducted at Groote Schuur Hospital (GSH) Coronary Care Unit (CCU) in Cape Town, South Africa. All patients above the age of 18 years who were admitted to the CCU with a confirmed diagnosis of acute myocardial infarction (i.e., either ST-elevation myocardial infarction [STEMI] or non-ST elevation myocardial infarction [NSTEMI]) (10) between 1 January 2016 and 31 December 2016 were included in the study (11). Patients were referred to the CCU from health care centres within GSH's drainage area, which include primary, secondary, and tertiary health care centres in the public sector or private institutions within the Western Cape. Patients were excluded from this study if they were admitted with unstable angina (i.e., an acute coronary syndrome without infarction), a diagnosis other than AMI, or notes reflecting diagnostic uncertainty. Patients with Incomplete or missing records were also not included in the study.

The study was approved by the Human Research Ethics Committee (HREC) of the University of Cape Town (HREC ref no. 251/2021) and complies with the Declaration of Helsinki. No patient consent was required as this was a retrospective study. Patients' demographic profile, co-morbidities, clinical presentation, investigations, angiographic findings, management and outcome were recorded. The 12-lead ECG on day of admission, as well as the day of discharge or death were analysed. Daily ECGs during the CCU stay, in addition to telemetry ECG monitoring, were analysed for the occurrence of arrhythmias.

12-lead ECG

12-lead ECGs were obtained by trained ECG technologists using a MAC 5500 HD (GE Healthcare, Chicago, Illinois, USA) machine and recorded onto the MUSE™ Cardiology Information System ECG database. ECGs were done on admission, at least once daily thereafter throughout hospital stay, as well as on the day of discharge. All ECGs were retrospectively analysed by two reviewers (SRS and JH) in accordance with the Minnesota criteria (12). If discrepant values were reported, a third investigator (CV) acted as an adjudicator.

ECGs were analysed for rate, rhythm and waveform abnormalities. Sinus tachycardia was defined as a heart rate ≥100 beats per minute (bpm) with a normal p-wave axis, and PR interval < 200ms, with each P wave followed by a QRS complex (13-15), whereas sinus bradycardia was defined as a heart rate <60 bpm with a normal p-wave axis and normal PR interval preceding every QRS complex (14, 15). Sinus arrhythmia was defined as a normal sinus rhythm with >120ms variability of RR intervals (8). Atrial fibrillation was defined as

irregular RR intervals and fibrillatory waves (13, 16, 17). Premature ventricular complexes (PVC) or ventricular ectopics were defined as QRS complexes with different morphology than the intrinsic conduction, as impulses generated from an ectopic focus (18). Ventricular tachycardia (VT) was defined as a cardiac arrhythmia of ventricular origin characterised by three or more consecutive QRS complexes that are wide (i.e., ≥120ms) and that occur at a rate of ≥100 bpm (i.e., cycle length < 600ms) (18). Ventricular fibrillation was defined as rapid, grossly irregular electrical activity with marked variability in electrocardiographic waveform, ventricular rate usually ≥300bpm (19).

Atrioventricular (AV) block was classified into first, second and third degree (complete) AV block (20, 21). First degree AV block was defined as a PR prolongation ≥200ms, second degree AV block was defined as either Mobitz type I (PR interval increases in length until it fails to conduct an QRS) or Mobitz type II (PR interval remains the same and there is unpredictable loss of conduction of the QRS complex) (20, 21). Third degree AV block was defined as complete atrio-ventricular dissociation without evidence of atrioventricular conduction (20).

Left atrial enlargement (LAE) was defined as having a P wave duration of ≥120ms in leads I and II and negative portion ≥1mm in depth in lead V1 (22).

Complete left bundle branch block (LBBB) was defined as a QRS duration ≥120ms with an R wave peak time ≥60ms in leads V5 and V6 but normal in V1, V2, V3 with a small initial R wave in precordial leads (20, 23, 24). Complete right bundle branch block (RBBB) was defined as QRS duration >120ms, with an rSR pattern in V1 or V2 and an S wave duration ≥40ms in V6 (20, 23, 24). Whenever bundle branch block was identified on the ECG, these were classified as being incident (i.e., new) or prevalent (i.e., old), whenever it was known from previous ECG documentation. Fractionated QRS was considered if there was evidence of an RSR' pattern or notched S or R wave, or when a fragmented QRS occurs in two or more contiguous leads (8).

A normal QRS axis was defined as between -30 and +90°, and LVH was assessed using Sokolow-Lyon criteria (8, 25). Poor R wave progression was defined as an R wave amplitude < S wave amplitude in lead V4 (8). Pathological Q waves were defined as pathological if the Q wave ≥40ms (>1mm) wide and >2 mm deep or at least 25% of the QRS wave amplitude (8).

Heart rate adjusted QT interval was calculated using Bazett's formula. A QTc of ≥460ms was considered prolonged in women and ≥450ms in men (8, 26). QRS duration and QTc values, as measured by the two investigators, were correlated with computerised QTc measurements.

Outcome

Poor outcome was determined as all-cause mortality within a 3-year period from the day of index admission to the CCU. The date of death was recorded from folder reviews, and by verification on the provincial hospital information system, CliniCom. Readmission to hospital for myocardial infarction, heart failure or stroke, within the first three years of the index admission, was used as an additional marker of outcome. Similarly, the date of readmission was recorded from folder reviews, and by verification on the provincial hospital information system, CliniCom.

Statistical analysis

Data was collected onto a secure electronic database: Research Electronic Data Capture (REDCap version 9.5.36) hosted by the University of Cape Town (27). Anonymised data from REDCap was exported to Stata (Version 17, Stata Corp, College Station, TX, USA) for statistical analysis. Baseline patient and clinical characteristics, investigations, angiographic findings, management, and outcomes were reported using means ± standard deviation (SD) (for normally distributed continuous variables) or median with interquartile range (IQR) (for non-normally continuous variables), or frequencies and percentages for categorical data. Wilcoxon Rank Sum test was used to compare continuous variables between patients with or without good outcome, whereas categorical data were compared using Chi square tests or Fisher's exact test, where appropriate. For descriptive purposes, Kaplan-Meier curves were used to illustrate survival during the study period. Log-rank tests were used to compare the survival curves. A P value of <0.05 was considered statistically significant.

Results

Demographic and clinical characteristics

The 301 patients in this study had a mean age of 57.4±11.9 years, with a slight male preponderance (42.2% of patients were female). As shown in *Table 1*, the admission diagnosis was STEMI in 57.5% (anterior 47.1%, inferior 47.7%, lateral 2.9% and posterior 2.3%) and NSTEMI in 42.5% in this cohort. Fibrinolysis was administered in 70.3% of patients presenting with STEMI as part of a pharmaco-invasive strategy. Although overall, patients presented with a mean left ventricular ejection fraction (LVEF) of 48.1%±15%, almost a quarter of patients (23.3%) had clinical features of heart failure on admission. The mean systolic blood pressure (SBP) and diastolic blood pressure (DBP) were 122±23.5 mmHg and 71.2±13.7 mmHg, respectively. Inotropic support was required in 5.3% of patients. *Table 1* further elaborates on co-morbidities, clinical presentation and treatment initiated during the CCU stay.

Electrocardiographic characteristics

The mean heart rate on admission was 81±21 beats per minute (bpm) (*Table 1*). Sinus tachycardia was present in 55 (18.3%) patients at the time of admission to CCU. As shown in *Table 2A*, 79.4% of patients had normal sinus rhythm (*Table 2A*), 4.3% atrial fibrillation (AF), of which half was a new diagnosis. During the CCU admission, 4% of patients experienced sustained ventricular tachycardia (VT) or ventricular fibrillation (VF). All episodes of VT or VF occurred in patients with STEMI (Table 2B). Accelerated junctional or idioventricular rhythms occurred in 2.3% of patients, all of which were in the STEMI cohort (Table 2B). Second, and third degree atrioventricular (AV) blocks were uncommon (3.7% of patients) and occurred predominantly in those with inferior STEMI (72.73%). Pacing was required in 1.7% of the cohort.

Table 2B shows electrocardiographic features present on the admission ECG. Overall, 22.8% had left atrial enlargement (LAE). The mean average PR and QRS intervals were 160.3±26.0ms and 97.4±17ms respectively. Those with STEMI, more commonly presented with first degree AV block (Table 3B). A wide QRS complex (>100ms) was present in 37.5% of patients (9.9% had QRS complex of >120ms). Typical RBBB occurred in 3.3% of the cohort (of which 80% of which were presumed new RBBB) and typical LBBB in 4% of patients (of which 83.3% were presumed new LBBB). The mean QRS axis was 27.6±55.2°. Left axis deviation (19.1% vs 7.8%, p=0.006) and poor R wave progression (55% vs 32%, p<0.001) occurred more commonly in STEMI, whereas LVH was more common in patients with NSTEMI (7.8 vs 19.1, p=0.006). Pathological Q waves were present in 43.9% of patients (STEMI 60.7% vs 21.9%, p<0.001). Persistent ST depression was present in 56.6% of patients, in up to 8 leads and ranging from 1mm to 5mm in the lead with maximal ST depression. The mean QTc as measured by Bazett's (QTcB) was 454.4±42.0ms and 52.8% of patients had a prolonged QTcB.

Outcome

Fifty-one (16.9%) patients died within the first three years after their index presentation to the CCU (*Table 1*). The majority of these deaths occurred within the first year (54.9% of patients). There were fifteen in-hospital deaths accounting for 29% of all deaths. Supplementary table 1 describes readmissions within three years after the index admission.

Table 1 demonstrates significant differences in clinical and biochemical characteristics between those with good vs poor outcomes. Those with poor outcomes were older (age 64.2±10.7 vs 56.0±11.7, p<0.001), had more co-morbidities such as diabetes mellitus (56.9% vs 34.8%, p=0.003) or chronic kidney disease (21.6% vs 4%, p<0.001) and were more likely to present with clinical signs of heart failure at their initial presentation (51% vs 17.6%, p<0.001). Inotrope requirement was associated with a worse outcome (19.6% vs 2.4%), p<0.001), whereas beta-blockers were associated with better survival (88% vs 64.7%, p<0.001). Supplementary table 1 summarises the same data for readmission to hospital.

Electrocardiographic predictors of poor outcome

Table 2A shows that patients with arrhythmias such as sinus tachycardia (33.3% vs 15.2%, p=0.002), ventricular tachycardia (9.8% vs 2.8%, p=0.02) and accelerated junctional or idioventricular rhythms (7.8% vs 1.2%, p=0.004) during admission were more likely to have an adverse outcome whereas those with normal sinus rhythm and rate during admission were more likely to have a favourable outcome (81.6% vs 68.6%, p=0.037).

Table 3A illustrates that the presence of electrocardiographic waveform abnormalities such as LAE (33.3% vs 20%, p=0.03), wide QRS (i.e., >100ms in 51% vs 34.8%, p=0.030), LBBB (9.8% vs 2.8%, p=0.020), RBBB (70% vs 53.8%, p=0.036) and persistent ST depression (70% vs 53.8%, p=0.030) were all associated with adverse outcome. The degree of ST depression, as measured as the number of leads that demonstrated ST depression, or the depth of ST depression was not predictive of outcome.

The clinical and ECG features that were found to have a significant predictive value for mortality by univariable analyses, are summarised in *Table 4*. On multivariable regression analysis, we established that an age above mean (>57 years) of the cohort (odds ratio [OR] 3.31 [95% confidence interval [CI] 1.21-9.04] p=0.020), chronic kidney disease (OR 6.77 [95% CI 1.77-25.97] p=0.005) troponin above mean of the cohort (OR 2.78 [95% CI 1.00-7.71] p=0.050), LAE (OR 3.91 [95% CI 1.39-11.02] p=0.010), ST depression (OR 3.64 [95% CI 1.33-9.93] p=0.012) all remained significant predictors of 3-year mortality, whereas the presence of normal sinus rhythm (OR 0.33 [95% CI 0.12-0.91] p=0.032) was found to be protective.

Three-year survival, as stratified by the presence of sinus tachycardia, LAE and ST depression on admission ECG are depicted in Kaplan-Meier curves (*Figures 1A, B* and *C* respectively). *Figure 1D* shows that when patients were categorised by the number of risk factors (sinus tachycardia, LAE and ST depression) patients who had 2 or more risk factors had significantly worse 3-year survival/outcome.

Discussion

In this study of a South-African cohort of patients admitted to the CCU with ACS, we have shown that the 12-lead-ECG has prognostic value in predicting three-year mortality. The presence of ECG waveform abnormalities such LAE and ST depression were predictive of adverse outcome, whereas sinus rhythm with normal rate was shown to be associated with favourable outcome. Furthermore, when risk stratifying patients according to the number of these risk factors present (i.e., sinus tachycardia, LAE, ST depression), we could demonstrate that patients with two or more of these risk factors had significantly increased mortality at three years.

Life-threatening ventricular arrhythmias were uncommon during the entire CCU admission, but were not negligible. Ventricular tachycardia (VT) or ventricular fibrillation (VF) occurred in 4% of patients. A slightly lower incidence was reported by Orvin et al. who evaluated a cohort of 7669 patients with ACS and found the incidence of ventricular tachyarrhythmias (VTA) to be 3.8%.(28) In their study, VTA occurred more commonly in patients with STEMI, particularly anterior STEMI and in patients with reduced left ventricular ejection fraction (LVEF).(28) The overall incidence of VT and VF has been described to decline over recent years. (3, 6, 28) VT/VF in ACS is often believed to be the sequelae of ongoing myocardial ischaemia.(29) An explanation for the decline in VT/VF in recent years is likely due to timeous reperfusion and the use of beta-blockers, which contemporary guidelines recommend. (3, 6, 28)

Supraventricular arrhythmias such as atrial fibrillation (AF) and atrial flutter (AFL) occurred in 3.3% and 1% of patients in our study, respectively. A large systematic review by Schmitt et al. found the incidence of AF in AMI to vary between 6-21%.(30, 31) They found a higher incidence of AF in the fibrinolysis era with a decreasing incidence in more recent years due to percutaneous coronary intervention combined with the early use of beta-blockers and angiotensin-converting enzyme inhibitors.(30) Other patient factors that predispose to AF included older age (>64 years), previous MI, LAE, worsening LV dysfunction and the presence of heart failure. (30, 31) Pre-existing AF may account for up to 10% of patients presenting with AMI and may occur in as many as 20% of patients at the time of, or just after AMI.(31) It is well documented that patients with AMI and AF (even if paroxysmal) have poorer short-and-

long term outcome with an increased mortality rate due to higher rates of reinfarction, heart failure, cardiogenic shock and stroke.(30, 31) Our study did not find the presence of AF to be associated with increased 3-year mortality. This may be due to the smaller number of patients in our cohort and patients having a younger mean age (57.4±11.9 years).

Sinus tachycardia occurred in 18.3% of our patients during their admission to the CCU, which is in keeping with contemporary literature. (32, 33) An elevated heart rate in ACS is known to be associated with worsening myocardial ischaemia and heart failure. (3) We highlight that the presence of sinus tachycardia was associated with increased mortality within the first three years after the index MI, whereas sinus rhythm with normal rate was associated with more favourable outcome.

Sinus node dysfunction, high degree AV block and accelerated idioventricular rhythms were uncommon in this cohort. A study by Rosa et al. (34) found the incidence of complete heart block (CHB) in ACS to be decreasing in recent years, occurring in only 1.9% of a cohort of 4799 patients with ACS. As expected, they found CHB to be more prevalent in patients with inferior STEMI.(34) The incidence of CHB was reported to be higher in patients receiving fibrinolysis, as compared to those who underwent primary PCI (7.3% vs 2.5%). This difference was likely due to better reperfusion in patients undergoing PCI.(34) The higher incidence of high-degree AV blocks in our cohort may be due to differences related to infarct size, extent, location, delay in revascularisation and incomplete revascularisation. Patients with anterior STEMI and high-grade AV blocks have proximal left anterior descending artery (LAD) occlusion and more extensive myocardial necrosis with a mortality of up to 80%, whereas inferior STEMI (due to right or left circumflex coronary artery occlusion) were more commonly associated with transient AV blocks and a lower mortality risk (3, 34).

Accelerated idioventricular rhythms (AIVR) occurred in only 2.3% of patients in our cohort. Albeit uncommon, four of the seven patients with AIVR died within three years. A study by Terkelsen et al. evaluating patients admitted with STEMI who underwent primary PCI found that AIVR occurred in 42% of patients (32). The presence of AIVR is usually considered a marker of successful reperfusion in patients receiving fibrinolytic therapy. However, AIVRs are more commonly associated with larger infarcts and a delay in microvascular reperfusion.(32)

LAE occurred in 22.8% of patients in our cohort. We found the presence of LAE on ECG to be a risk factor for 3-year mortality. This finding is supported by literature from a systematic review and meta-analysis, which found that an increased left atrial volume index (LAVI) was an independent predictor of poor outcome in ACS.(35) LAVI as assessed by echocardiography serves as a surrogate marker of left atrial size.(35) It was found that increased LAVI (>32ml/m2) was associated with diastolic dysfunction, elevated left ventricular filling pressures, multi vessel coronary artery disease, heart failure, cardiogenic shock, an increase

in atrial fibrillation, and ischaemic stroke in patients presenting with ACS (35). Patients with ACS who had low/normal LAVI had lower short-and-long term risk of major adverse cardiovascular events (35). Secundo Junior et al. demonstrated similar findings in their cohort of patients from the Solar Registry (Acute Coronary Syndrome Registry of the Hospital Sao Lucas).(36) They highlighted that a LAVI>32ml/m2 was associated with a lower LVEF and that patients with ACS and an increased LAVI were more likely to have features of heart failure and had a significantly worse prognosis.(36) Another study by Ozyigit et al. showed a correlation between prolonging of P wave dispersion (PWD) on the ECG (≥40ms) and an increased LAVI as measured on echocardiography(37). Both PWD on ECG and increased LAVI were shown to be predictors of AF.(37)

In our study, LBBB and RBBB occurred in 4% and 3.3% of patients respectively. Although infrequent, LBBB was associated with increased three-year mortality on univariable regression analysis. Timoteo et al. reported a similar prevalence of LBBB (3.4%) and RBBB(4.3%) in their cohort of 3990 patients with ACS(38). They found patients with bundle branch blocks (BBB) to be older, have more co-morbidities, underlying cardiovascular disease, a history of previous MI and heart failure. (38, 39) These patients were less likely to receive fibrinolysis or coronary angiography.(38, 39) All-cause mortality was higher in patients with ACS and BBB (10% in-hospital vs 20% one-year mortality).(38) Similar findings were reported in a prospective study by Lewinter et al. who followed up 6676 patients admitted with AMI, both with and without BBB over a period of 15 years(39). RBBB and LBBB each had an incidence of 4%, both were associated with increased mortality.(39) Both studies found RBBB to be an independent predictor of mortality.(38, 39) Other studies have shown RBBB in anterior STEMI to be predictive of both in-hospital and long-term mortality.(40, 41) An explanation for this may be due to patients being older, having more co-morbidities in addition to the presence of BBB indicating both acute and pre-existing extensive damage to the ventricular myocardium in particular, resulting in conduction abnormalities(38, 39).

Furthermore, we found that 37.5% of our cohort had a wide QRS duration (≥100ms), which was associated with an increased 3-year mortality. This finding is in keeping with a previous study on a large cohort (12.456 patients with ACS), describing the association between baseline QRS prolongation and increased risk of 30-day mortality in patients with anterior STEMI (40). QRS prolongation represents abnormal electrical activation of the myocardium and can be as a result of intraventricular conduction delay and can precede the development of both LBBB and RBBB.(40)

ST segment deviation is an established surrogate marker of outcome, as it forms part of the TIMI and GRACE risk scores, which are used for risk stratification in NSTEMI (42, 43). In our study, ST segment depression was a common waveform abnormality on the admission ECG (present in 56.6% of patients) and was an independent predictor of 3-year mortality. This corresponds with findings from a study by Armstrong et al. which looked at quantitative ST-

segment depression on the ECG in ACS patients enrolled in the PLATO (Platelet inhibition and patient outcomes) study.(44) Patients with increased ST-segment depression (>1mm) at baseline and on discharge had worse 1-year outcome (myocardial infarction or death) when compared to patients with minimal (<0.5mm) or without ST-segment depression (44). Yan et al. studied 2590 patients presenting with NSTEMI and they found that patients with more extensive ST depression on ECG were older, had an increased prevalence of diabetes mellitus, heart failure, a higher Killip class, creatinine, and troponin(45). Mortality increased in patients who had more extensive ST depression (45).

In addition, we found older age, diabetes mellitus (DM) and chronic kidney disease (CKD) as further predictors of mortality. Leonardi et al. described that older patients were likely to have more co-morbidities, renal dysfunction and had a higher probability of having significant coronary artery disease (CAD), in addition to being at increased risk for complications such as bleeding and thrombosis.(46)

A study by Babes et al. highlighted that patients with DM had accelerated atherosclerosis, more extensive coronary artery disease and a higher risk of recurrence of ACS and death when compared to patients without DM.(47) CKD is a well-established poor predictive risk factor in ACS. Pilmore et al. demonstrated that patients with more advanced CKD had a higher incidence of NSTEMI, triple vessel coronary artery disease on angiography and lower rates of revascularisation by PCI or fibrinolysis.(48) CKD in ACS was associated with increased risk of stroke, recurrence of ACS and death when compared to patients with normal renal function.(48)

Chatterjee et al. developed an ECG score evaluating ECG parameters that were all independently associated with sudden arrhythmic death (SAD), these included: the presence of LVH, contiguous Q waves (both anatomic risk factors for SAD), QRS duration (depolarisation risk for SAD) and prolonged JTc interval (repolarisation risk for SAD) to risk stratify patients with coronary heart disease into those that were at high and low risk for SAD(9). In their cohort of 7363 patients those with a high-risk ECG score (≥3) had significantly increased mortality due to SAD when compared to those with a low risk ECG score (0-1), in both the derivation and validation cohort after multivariable adjustment for LVEF and clinical risk factors (24.9% vs 16.5%)(9). The Chatterjee ECG risk stratification score could not be validated for our cohort, this is likely to the small number of our cohort. We also did not routinely measure the JTc interval.

From our study we found the presence of sinus tachycardia, ST depression and LAE to all be independent risk factors for poor outcomes at 3-years. When combined, we were able to develop our own risk stratification score, patients with 2 or more of these risk factors present during their admission to the CCU with ACS had significantly increased mortality at 3-years. Risk stratification is important in clinical practice, so that treatment and

interventions can be individualised and effectively tailored to improve outcomes. Risk stratification allows for adequate resource allocation, ensuring that high-risk individuals receive adequate attention and monitoring (49).

Limitations

This was a single-centre study observation study that produced a risk stratification in a relatively small cohort of patients. The findings from our study need to be validated in a larger, multi-centre study as our findings may not be reproducible in other settings within South Africa. ECGs were recorded on admission, daily throughout the period of hospitalization and on discharge from the CCU. We detected an overall low prevalence of arrhythmias on the ECG's that we interpreted. We may have underestimated the occurrence of arrhythmias as these may have been transient and not captured on ECG, and due to the absence of implanted loop recorders (ILR) or Holter-monitoring in our cohort.

We appreciate that a widened P wave could be due to LAE or delayed conduction. However, impaired interatrial or intra-atrial block is not described as an individual ECG pattern in most ECG books. LAE and interatrial or interatrial block are often associated (50) However, none of the patients in this study had EP studies, and it would therefore not be possible to know which had conduction delays. Nevertheless, the ECG feature coined as LAE was shown in this study to be associated with poor outcomes.

As the study would include all patients that fulfilled the eligibility criteria, no sample size calculation was done prior to the study. However, for post hoc power analysis with an alpha of 0.05,(51) we considered the three variables that predicted death in the three-year period after the index CCU admission: Sinus tachycardia had a power of 82.3% to predict three year mortality, but LAE and ST depression had a power of 52.7% and 57.1% respectively.

Unfortunately, we have a lack of data regarding patients who underwent revascularisation and the timing of revascularisation which may also affect our results found in our small cohort of patients.

Conclusion

Our study showed that the ECG has prognostic value in patients admitted to the CCU for ACS. Left atrial enlargement, ST depression and sinus tachycardia on the admission ECG were independently associated with increased three-year mortality, whereas sinus rhythm with normal rate was associated with more favourable outcome. In this regard, patients could be

risk stratified according to the number of risk factors (sinus tachycardia, LAE, ST depression) present on the ECG. Using this risk stratification tool should be evaluated to study whether its implementation would improve risk stratification of patients with ACS.

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Table 1: Clinical and biochemical characteristics as categorized by 3-year survival after the index presentation or not.

	Total	Survived	Died	P value
	N=301	N=250	N=51	
Age	57.4±11.9	56.0±11.7	64.2±10.7	<0.001
Gender				0.87
Male	174 (57.8)	144 (57.6)	30 (58.8)	
Female	127 (42.2)	106 (42.2)	21 (41.2)	
Smoker	221 (73.4)	184 (73.6)	37 (72.5)	0.88
Hypertension	200 (66.4)	160 (64)	40 (78.4)	0.047
Diabetes	116 (38.5)	87 (34.8)	29 (56.9)	0.003
Dyslipidaemia	141 (46.8)	115 (46.0)	26 (51.0)	0.52
BMI	28.1±5.5	28.2±5.7	27.3±4.5	0.54
Chronic Kidney Disease	21 (7.0)	10 (4.0)	11 (21.6)	<0.001
Clinical features of heart failure	70 (23.3)	44 (17.6)	26 (51.0)	<0.001
Killip Class				0.072
1	6 (8.6)	6 (13.6)	0 (0.0)	
2	24 (34.3)	17 (38.6)	7 (26.9)	
3	32 (45.7)	18 (40.9)	14 (53.8)	
4	8 (11.4)	3 (6.8)	5 (19.2)	
Systolic BP	122.0±23.5	122.0±22.7	121.9±27.9	0.97
Diastolic BP	71.2±13.7	71.6±14.0	69.1±12.4	0.28
Pulse rate	80.7±20.6	79.5±18.9	87.0±27.2	0.028
LVEF	48.1±15.0	51.0±14.4	40.0±13.7	<0.001
High-sensitivity Troponin T (ng/L)	3384.8±7260.5	2837.6±5936.9	6000.8±11432.8	0.011
Haemoglobin (g/dL)	14.6±11.9	15.0±13.0	12.4±2.5	0.15
Creatinine (µmol/L)	90.6±53.1	83.2±36.8	126.6±92.4	<0.001
Managing Diagnosis				0.30
STEMI	173 (57.5)	147 (58.8)	26 (51)	
NSTEMI	128 (42.5)	103 (41.2)	25 (49.0)	
Time to presentation to PCI centre				0.083
< 6 hours	75 (25.3)	67 (27.2)	8 (16.0)	
6 - 12 hours	41 (13.9)	30 (12.2)	11 (22.0)	
> 12 hours	180 (60.8)	149 (60.6)	31 (62.0)	
Fibrinolysis administered				0.056
No	51 (29.7)	45 (30.8)	6 (23.1)	
Referral hospital	84 (48.8)	66 (45.2)	18 (69.2)	
PCI centre	37 (21.5)	35 (24.0)	2 (7.7)	
Intra-aortic balloon pump	15 (5.0)	11 (4.4)	4 (7.8)	0.30
Medication:				
Statin	292 (97.0)	244 (97.6)	49 (96.1)	0.18
Aspirin	295 (98.0)	246 (98.4)	48 (94.1)	0.28
Clopidogrel	282 (93.7)	234 (93.6)	48 (94.1)	0.89
Warfarin	11 (3.7)	10 (4.0)	1 (2.0)	0.48
Beta-blocker	253 (84.1)	220 (88.0)	33 (64.7)	<0.001
ACE-Inhibitor	192 (63.8)	167 (66.8)	25 (49.0)	0.016
ARB	25 (9.3)	22 (8.8)	6 (11.8)	0.67
Calcium channel blocker	28 (9.3)	22 (8.8)	6 (11.8)	0.51
Loop diuretic	77 (25.6)	61 (24.4)	16 (31.4)	0.30
Thiazide	25 (8.3)	22 (8.8)	3 (5.9)	0.49
MRA	13 (4.3)	11 (4.4)	2 (3.9)	0.88
Inotropes	16 (5.3)	6 (2.4)	10 (19.6)	<0.001

Values are N (%), median (IQR) where appropriate.

Supplementary Table 1: Clinical and biochemical characteristics as categorized by readmission for acute myocardial infarction, heart failure or stroke or not, within 3-years after the index admission

	Total	No readmission	Readmitted	P value
	N=301	N=160	N=141	
Age	57.4±11.9	57.3±11.5	57.5±12.5	0.89
Gender				0.20
Male	174 (57.8)	98 (61.3)	76 (53.9)	
Female	127 (42.2)	62 (38.8)	65 (46.1)	
Smoker	221 (73.4)	110 (68.8)	111 (78.7)	0.051
Hypertension	200 (66.4)	101 (63.1)	99 (70.2)	0.19
Diabetes	116 (38.5)	64 (40.0)	52 (36.9)	0.58
Dyslipidemia	141 (46.8)	67 (41.9)	74 (52.5)	0.066
BMI	28.1±5.5	27.8±5.2	28.3±5.9	0.59
Chronic kidney disease	21 (7.0)	13 (8.1)	8 (5.7)	0.40
Clincial features of heart failure	70 (23.3)	29 (18.1)	41 (29.1)	0.025
Killip class				0.54
1	6 (8.6)	4 (13.8)	2 (4.9)	
2	24 (34.3)	9 (31.0)	15 (36.6)	
3	32 (45.7)	12 (41.4)	20 (48.8)	
4	8 (11.4)	4 (13.8)	4 (9.8)	
Systolic BP	122.0±23.5	122.9±22.3	121.0±24.9	0.51
Diastolic BP	71.2±13.7	71.2±13.0	71.3±14.6	0.95
Pulse rate	80.7±20.6	81.0±22.0	80.4±18.9	0.82
LVEF	48.1±15.0	49.1±14.6	47.2±15.4	0.53
Haemoglobin	14.6±11.9	14.5±11.7	14.6±12.2	0.92
Creatinine	90.6±53.1	94.7±62.2	85.9±40.2	0.15
Managing diagnosis				0.035
STEMI	173 (57.5)	101 (63.1)	72 (51.1)	
NSTEMI	128 (42.5)	59 (36.9)	69 (48.9)	
Fibrinolysis administered				0.19
No	51 (29.7)	26 (26.0)	25 (34.7)	
Referral hospital	84 (48.8)	48 (48.0)	36 (50.0)	
PCI centre	37 (21.5)	26 (26.0)	11 (15.3)	
Time to presentation to PCI centre				0.12
< 6 hours	75 (25.3)	47 (30.1)	28 (20.0)	
6 - 12 hours	41 (13.9)	19 (12.2)	22 (15.7)	
> 12 hours	180 (60.8)	90 (57.7)	90 (64.3)	
Intra-aortic balloon pump	15 (5.0)	7 (4.4)	8 (5.7)	0.61
Statin	292 (97.0)	154 (96.2)	138 (97.9)	0.41
Aspirin	295 (98.0)	154 (96.2)	141 (100.0)	0.020
Clopidogrel	282 (93.7)	151 (94.4)	131 (92.9)	0.60
Warfarin	11 (3.7)	3 (1.9)	8 (5.7)	0.080
Beta-blocker	253 (84.1)	132 (82.5)	121 (85.8)	0.43
ACE-inhibitor	192 (63.8)	102 (63.7)	90 (63.8)	0.99
ARB	25 (8.3)	10 (6.2)	15 (10.6)	0.17
Calcium channel blocker	28 (9.3)	11 (6.9)	17 (12.1)	0.12
Loop diuretic	77 (25.6)	30 (18.8)	47 (33.3)	0.004
Thiazide	25 (8.3)	14 (8.8)	11 (7.8)	0.77
MRA	13 (4.3)	4 (2.5)	9 (6.4)	0.098
Inotropes	16 (5.3)	12 (7.5)	4 (2.8)	0.072

Values are N (%), median (IQR) where appropriate.

Table 2A: Rhythms documented during CCU stay as categorized by 3-year survival after the index presentation.

	Total	Survived	Died	P value
	N=301	N=250	N=51	
Normal sinus rhythm	239 (79.4)	204 (81.6)	35 (68.6)	0.037
Sinus arrhythmia	8 (2.7)	8 (3.2)	0 (0.0)	0.20
Sinus tachycardia	55 (18.3)	38 (15.2)	17 (33.3)	0.002
Atrial fibrillation	10 (3.3)	8 (3.2)	2 (3.9)	0.79
Atrial flutter	3 (1.0)	3 (1.2)	0 (0.0)	0.43
Ventricular tachycardia or fibrillation	12 (4.0)	7 (2.8)	5 (9.8)	0.02
Sinus bradycardia	83 (27.6)	74 (29.6)	9 (17.6)	0.082
Sinus node dysfunction	3 (1.0)	3 (1.2)	0 (0.0)	0.43
Second or third-degree AV block	11 (3.7)	8 (3.2)	3 (5.9)	0.35
Accelerated junctional or idioventricular rhythm	7 (2.3)	3 (1.2)	4 (7.8)	0.004
Paced rhythm	5 (1.7)	4 (1.6)	1 (2.0)	0.85

Values are N (%)

Table 2B: Rhythms documented during CCU stay as categorized by having STEMI or NSTEMI.

	Total	STEMI	NSTEMI	P value
	N=301	N=173	N=128	
Normal sinus rhythm	239 (79.4)	139 (80.3)	100 (78.1)	0.64
Sinus arrhythmia	8 (2.7)	5 (2.9)	3 (2.3)	0.77
Sinus tachycardia	55 (18.3)	36 (20.8)	19 (14.8)	0.19
Atrial fibrillation	10 (3.3)	8 (4.6)	2 (1.6)	0.14
Atrial flutter	3 (1.0)	2 (1.2)	1 (0.8)	0.75
Ventricular tachycardia or fibrillation	12 (4.0)	9 (5.2)	3 (2.3)	0.21
Sinus bradycardia	12 (4.0)	12 (6.9)	0 (0.0)	0.002
Sinus node dysfunction	83 (27.6)	33 (19.1)	50 (39.1)	<0.001
Second or third-degree AV block	3 (1.0)	2 (1.2)	1 (0.8)	0.75
Accelerated junctional or idioventricular rhythm	11 (3.7)	9 (5.2)	2 (1.6)	0.096
Paced rhythm	7 (2.3)	7 (4.0)	0 (0.0)	0.021
Normal sinus rhythm	5 (1.7)	4 (2.3)	1 (0.8)	0.30

Values are N (%)

Table 2C: Rhythms documented on the admission ECG and subsequently during CCU stay.

	Admission	After admission	P value
	N=250	N=51	
Normal sinus rhythm	192 (63.79)	239 (79.40)	< 0.001
Sinus arrhythmia	3 (1.00)	8 (2.66)	0.1317
Sinus tachycardia	36 (11.96)	55 (18.27)	< 0.001
Atrial fibrillation	0	10 (3.32)	0.002
Atrial flutter	1 (0.33)	3 (1.00)	0.1573
Ventricular tachycardia or fibrillation	0	12 (3.99)	< 0.001
Sinus bradycardia	47 (15.61)	83 (27.57)	< 0.001
Sinus node dysfunction	0	3 (1)	0.0833
Second or third-degree AV block	7 (2.33)	11 (3.65)	0.0455
Accelerated junctional or idioventricular rhythm	4 (1.33)	7 (2.33)	0.0833
Paced rhythm	1 (0.33)	5 (1.66)	0.0455

Values are N (%)

Supplementary Table 2: Rhythms documented during CCU stay as categorized by readmission for acute myocardial infarction, heart failure or stroke or not, within 3-years after the index admission

	Total	No readmission	Readmission	P value
	N=301	N=160	N=141	
QRS rate	77.3±20.2	77.6±20.8	77.0±19.6	0.81
Normal sinus rhythm during admission	239 (79.4)	127 (79.4)	112 (79.4)	0.99
Sinus arrhythmia during admission	8 (2.7)	3 (1.9)	5 (3.5)	0.37
Sinus tachycardia during admission	55 (18.3)	28 (17.5)	27 (19.1)	0.71
Atrial fibrillation during admission	10 (3.3)	6 (3.8)	4 (2.8)	0.66
Atrial flutter during admission	3 (1.0)	1 (0.6)	2 (1.4)	0.49
Atrial fibrillation or flutter during admission	12 (4.0)	6 (3.8)	6 (4.3)	0.82
VT or VF arrest	12 (4.0)	10 (6.2)	2 (1.4)	0.033
Sinus bradycardia during admission	83 (27.6)	46 (28.7)	37 (26.2)	0.63
Sinus node dysfunction during admission	3 (1.0)	2 (1.2)	1 (0.7)	0.64
Mobitz I during admission	2 (0.7)	1 (0.6)	1 (0.7)	0.93
Mobitz II during admission	2 (0.7)	1 (0.6)	1 (0.7)	0.93
2:1 AV block during admission	0 (0.0)	0 (0.0)	0 (0.0)	
High degree AV block during admission	1 (0.3)	0 (0.0)	1 (0.7)	0.29
Third degree AV block during admission	8 (2.7)	6 (3.8)	2 (1.4)	0.21
Second or third degree AV block	11 (3.7)	6 (3.8)	5 (3.5)	0.93
Accelerated junctional rhythm during admission	5 (1.7)	3 (1.9)	2 (1.4)	0.76
Accelerated idioventricular rhythm during admission	2 (0.7)	2 (1.2)	0 (0.0)	0.18
Accelerated junctional or idioventricular rhythm	7 (2.3)	5 (3.1)	2 (1.4)	0.33
Paced rhythm during admission	5 (1.7)	2 (1.2)	3 (2.1)	0.55
Heart rate variability	7 (2.4)	4 (2.5)	3 (2.2)	0.86

Values are N (%), median (IQR) where appropriate.

Table 3A: ECG features present on admission ECG as categorized by 3-year survival after the index presentation or not.

	Total	Survived	Died	p-value
	N=301	N=250	N=51	
QRS rate	77.3±20.2	76.0±19.1	83.9±24.0	0.012
Heart rate variability	7 (2.4)	6 (2.4)	1 (2.0)	0.86
Premature Ventricular Complex	25 (8.4)	19 (7.7)	6 (12.0)	0.31
Left atrial enlargement	67/294 (22.8)	50/245 (20.4)	17/49 (34.7)	0.030
PR interval	160.3±26.0	159.2±25.4	165.9±28.3	0.12
Prolonged PR interval	44 (14.6)	32 (12.8)	12 (23.5)	0.048
QRS duration	97.4±17.0	96.2±15.8	103.0±21.6	0.010
Wide QRS (QRS > 100ms)	113 (37.5)	87 (34.8)	26 (51.0)	0.030
QRS morphology				0.014
Normal	263 (88.3)	225 (90.7)	38 (76.0)	
LBBB	12 (4.0)	7 (2.8)	5 (10.0)	
RBBB	10 (3.4)	6 (2.4)	4 (8.0)	
NSIVCD	13 (4.4)	10 (4.0)	3 (6.0)	
QRS axis	27.6±55.2	26.4±53.5	33.9±63.1	0.38
Left axis deviation	43 (14.3)	35 (14.0)	8 (15.7)	0.75
Right axis deviation	36 (12.0)	29 (11.6)	7 (13.7)	0.67
LVH	16 (5.4)	12 (4.9)	4 (8.0)	0.37
Poor R wave progression	134 (45.1)	111 (44.9)	23 (46.0)	0.89
Fractionated QRS	60 (20.4)	47 (19.2)	13 (26.5)	0.24
Pathological Q waves	130 (43.9)	105 (42.7)	25 (50.0)	0.34
ST segment elevation	222 (74.7)	184 (74.5)	38 (76.0)	0.82
ST segment elevation in V1	102 (35.4)	87 (36.2)	15 (31.2)	0.51
ST segment elevation in aVR	48 (16.3)	40 (16.4)	8 (16.0)	0.95
ST segment depression	168 (56.6)	133 (53.8)	35 (70.0)	0.036
T wave inversion	235 (79.4)	193 (78.5)	42 (84.0)	0.38
QTc by Bazett	454.4±42.0	452.3±40.3	464.6±48.7	0.060
Prolonged QTcB	159 (52.8)	126 (50.4)	33 (64.7)	0.062

Values are N (%), median (IQR) where appropriate.

Table 3B: ECG features present on admission ECG as categorized by having STEMI or NSTEMI.

	Total	STEMI	NSTEMI	p-value
	N=301	N=173	N=128	
QRS rate	77.3±20.2	80.3±19.5	73.2±20.5	0.003
Heart rate variability	7 (2.4)	0 (0.0)	7 (5.6)	0.002
Premature ventricular complex	25 (8.4)	15 (8.8)	10 (7.8)	0.76
Left atrial enlargement	67/294 (22.8)	34/168 (20.2)	33/126 (26.2)	0.23
PR interval	160.3±26.0	160.4±25.8	160.2±26.3	0.95
Prolonged PR interval	44 (14.6)	32 (18.5)	12 (9.4)	0.027
QRS duration	97.4±17.0	97.8±18.3	96.8±15.2	0.65
Wide QRS (QRS > 100ms)	113 (37.5)	61 (35.3)	52 (40.6)	0.34
LBBB	12 (4.0)	8 (4.6)	4 (3.1)	0.51
RBBB	10 (3.3)	5 (2.9)	5 (3.9)	0.63
QRS morphology				0.41
Normal	263 (88.3)	147 (86.5)	116 (90.6)	
LBBB	12 (4.0)	8 (4.7)	4 (3.1)	
RBBB	10 (3.4)	5 (2.9)	5 (3.9)	
NSIVCD	13 (4.4)	10 (5.9)	3 (2.3)	
QRS axis	27.6±55.2	25.2±61.4	30.9±45.6	0.38
Left axis deviation	43 (14.3)	33 (19.1)	10 (7.8)	0.006
Right axis deviation	36 (12.0)	24 (13.9)	12 (9.4)	0.23
LVH	17 (5.7)	4 (2.4)	13 (10.2)	0.004
Poor R wave progression	134 (45.1)	93 (55.0)	41 (32.0)	<0.001
Fractionated QRS	60 (20.4)	40 (24.0)	20 (15.7)	0.084
Pathological Q waves	130 (43.9)	102 (60.7)	28 (21.9)	<0.001
ST segment elevation	222 (74.7)	140 (82.8)	82 (64.1)	<0.001
ST segment elevation in V1	102 (35.4)	61 (37.0)	41 (33.3)	0.52
ST segment elevation in aVR	48 (16.3)	13 (7.8)	35 (27.6)	<0.001
ST segment depression	167 (56.2)	91 (53.8)	76 (59.4)	0.34
T wave inversion	235 (79.4)	129 (76.3)	106 (83.5)	0.13
QTc by Bazett	454.4±42.0	456.6±46.6	451.4±35.0	0.29
Prolonged QTcB	159 (52.8)	94 (54.3)	65 (50.8)	0.54

Values are N (%), median (IQR) where appropriate.

Supplementary Table 3: ECG features present on admission ECG as categorized by readmission for acute myocardial infarction, heart failure or stroke or not, within 3-years after the index admission

	Total	No readmission	Readmission	p-value
	N=301	N=160	N=141	
Heart rate variability	7 (2.4)	4 (2.5)	3 (2.2)	0.86
Premature ventricular complex	25 (8.4)	14 (8.8)	11 (8)	0.81
Left atrial enlargement	67 (22.8)	31 (19.6)	36 (26.5)	0.16
PR interval	160.3±26.0	159.8.4±25.4	160.9±26.6	0.72
Prolonged PR interval	44 (14.6)	22 (13.8)	22 (15.6)	0.65
QRS duration	97.4±17.0	96.8±17.4	98.0±16.6	0.53
Wide QRS (QRS > 100ms)	113 (37.5)	50 (31.2)	63 (44.7)	0.01
LBBB	12 (4.0)	8 (5)	4 (2.8)	0.51
RBBB	10 (3.3)	5 (2.9)	5 (3.9)	0.63
QRS morphology				0.42
Normal	263 (88.3)	143 (89.4)	120 (87)	
LBBB	12 (4.0)	8 (5.0)	4 (2.9)	
RBBB	10 (3.4)	4 (2.5)	6 (4.3)	
NSIVCD	13 (4.4)	5 (3.1))	3 (5.8)	
QRS axis	27.6±55.2	26.2±58.6	29.3±51.1	0.62
Left axis deviation	43 (14.3)	26 (16.2)	17 (12.1)	0.30
Right axis deviation	36 (12.0)	24 (13.9)	12 (9.4)	0.45
LVH	17 (5.7)	5 (3.1)	12 (8.7))	0.040
Poor R wave progression	134 (45.1)	71 (44.7)	63 (45.70)	0.86
Fractionated QRS	60 (20.4)	33 (21.0)	27 (19.7)	0.78
Pathological Q waves	130 (43.9)	76 (48.1)	54 (39.1)	0.12
Number of leads with Q waves	1.4±1.7	1.5±1.7	1.3±1.8	0.26
ST segment elevation	222 (74.7)	117 (73.6)	105 (76.1)	0.62
ST segment elevation in V1	102 (35.4)	52 (33.5)	50 (37.6)	0.47
ST segment elevation in aVR	48 (16.3)	21 (13.3)	27 (19.9)	0.13
Maximum ST elevation (mm)	2.00 (0.00-2.0)	2.00 (0.00-2.0)	2.00 (0.00-2.0)	0.39
ST segment depression	167 (56.2)	82 (51.6)	85 (61.6)	0.083
T wave inversion	235 (79.4)	123 (77.8)	112 (81.2)	0.48
No.leads with T wave inversion	3.0 (1.0-6.0)	3.0 (1.0-6.0)	3.5 (1.00-7.00)	0.25
Actual QT interval	409.5±59.4	409.5±61.5		1.00
QTc by Bazett	454.4±42.0	454.6±41.6	454.4±42.7	0.92
Prolonged QTcB	159 (52.8)	82 (51.2)	77 (54.6)	0.56
QTc by Fridericia	438.1±41.2	438.2±42	438.0±40.4	0.96
Prolonged QTcF	104 (34.6)	55 (34.4)	49 (34.8)	0.95

Values are N (%), median (IQR) where appropriate.

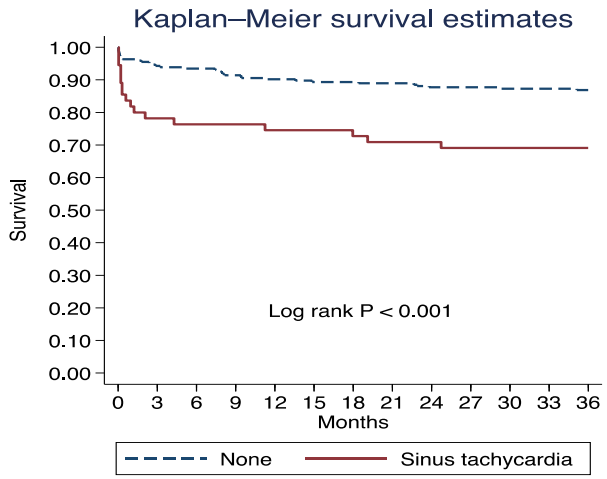
Table 4: Predictors of increased three-year mortality, as determined by univariable and multivariable regression analyses.

	Univariable regression analysis			Multivariable regression analysis		
	Unadjusted OR	95% CI	p-value	Adjusted OR	95% CI	p-value
Clinical and biochemical characteristics						
Age above mean *	3.20	1.60-6.40	0.001	3.31	1.21-9.04	0.020
Diabetes	2.47	1.34-4.56	0.004	1.58	0.64-3.90	0.320
Chronic kidney disease	6.60	2.63-16.55	0.000	6.77	1.77-25.97	0.005
Clinical features of heart failure	4.87	2.57-9.22	0.000	2.10	0.79-5.61	0.140
High sensitivity Troponin T above mean **	2.30	1.10-4.83	0.030	2.78	1.00-7.71	0.050
Creatinine above mean ***	3.20	1.72-5.95	0.000	0.92	0.35-2.41	0.863
ECG characteristics						
Sinus rhythm with normal rate	0.50	0.25-0.97	0.040	0.33	0.12-0.91	0.032
Sinus tachycardia	2.79	1.42-5.49	0.003	2.11	0.72-6.19	0.173
Ventricular tachycardia or fibrillation	3.77	1.15-12.40	0.030	6.11	0.82-45.59	0.080
Accelerated junctional or idio-ventricular rhythm	7.01	1.52-32.33	0.013	5.52	0.32-95.77	0.240
Left atrial enlargement	2.07	1.06-4.03	0.032	3.91	1.39-11.02	0.010
Wide QRS complex	1.95	1.06-3.58	0.031	2.03	0.81—5.06	0.130
Left bundle branch block	3.77	1.15-12.40	0.030	1.98	0.273-14.33	0.500
ST-depression	2.00	1.04-3.85	0.040	3.64	1.33-9.93	0.012

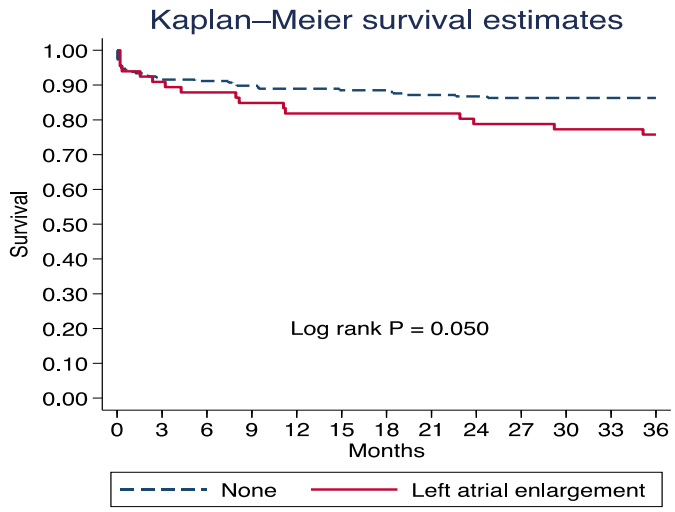
* age > 57 years, ** troponin > 3385 ng/L,

Figure 1. Patients with sinus tachycardia (A), left atrial enlargement (B) and ST depression (C) were found to have increased three-year mortality. Patients with two or more of these risk factors had worse survival within the first three years of the index MI (D).

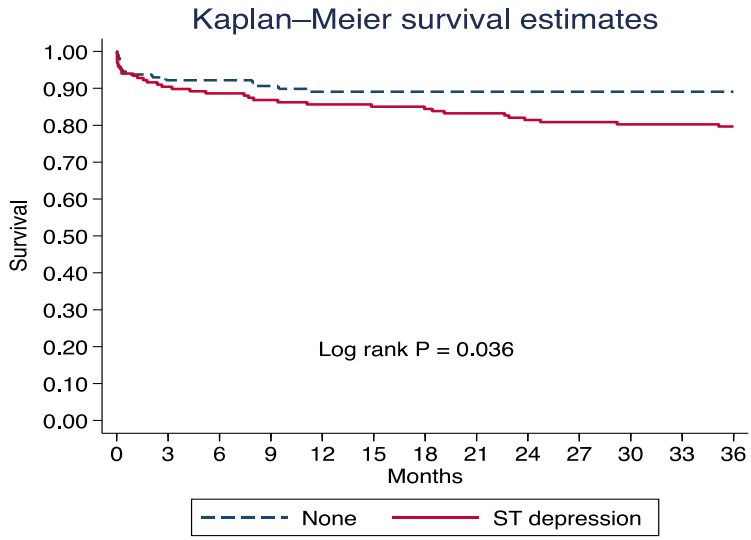
A



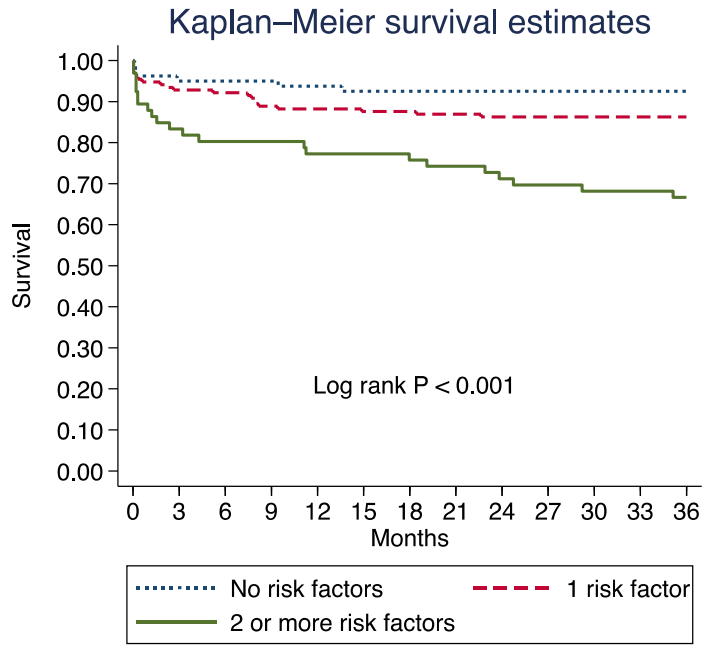
B



C


Kaplan–Meier survival estimates
1.00
0.90
0.80
0.70
0.60
0.50
0.40
0.30
0.20
0.10
0.00
Survival
Log rank P = 0.036
0 3 6 9 12 15 18 21 24 27 30 33 36
Months
None
ST depression

D


Kaplan–Meier survival estimates
1.00
0.90
0.80
0.70
0.60
0.50
0.40
0.30
0.20
0.10
0.00
Survival
Log rank P < 0.001
0 3 6 9 12 15 18 21 24 27 30 33 36
Months
No risk factors
1 risk factor
2 or more risk factors

Appendices and supplementary material

Appendix 1: Research Protocol

Electrocardiographic predictors of outcome in acute myocardial infarction

Protocol version 1.1

A sub study of the
PERFUSION registry
(HREC ref no: R031/2017)

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2. Introduction

2.1. Background

Historically, it was believed that there was a low prevalence of ischaemic heart disease (IHD) in sub-Saharan Africa. However, recent data from the Global Burden of Disease Study in 2017 shows that IHD is increasing in incidence in sub-Saharan Africa, and contributes to 39% of all cardiovascular (CVS) deaths compared to 48.8% in Western Europe and 58.9% North America (1).

Acute coronary syndromes (ACS) encompass ST-elevation myocardial infarction (STEMI), non-ST-elevation myocardial infarction (NSTEMI) and unstable angina (UA). Myocardial infarction (MI) causes metabolic and electrophysiological changes that can induce life-threatening arrhythmias (3). Electrolyte disturbances and electrical changes in the border zone of an acute MI due to either myocardial ischaemia or reperfusion can trigger arrhythmogenesis early in the course of ACS (3). Arrhythmias in ACS are associated with a worse prognosis (52).

ACS is associated with both atrial and ventricular tachyarrhythmias, as well as bradyarrhythmias, which may cause haemodynamic instability, circulatory collapse and require prompt emergency treatment (3). Prior to the use of early reperfusion therapies such as fibrinolytics or percutaneous coronary intervention (PCI) the mainstay of management for ACS included: monitoring for arrhythmias (53), electrical cardioversion/defibrillation in case of haemodynamic instability and initiation of heart failure therapy (3). Early revascularisation therapy in combination with secondary prevention therapies such as antithrombotic therapy, beta-blockers, statins, angiotensin converting enzyme inhibitors (ACE-I) angiotensin-receptor blockers (ARB) and mineralocorticoid receptor antagonists (MRA's) have markedly reduced mortality and the incidence of life-threatening arrhythmias to <3% (3, 54).

Arrhythmias that occur before or during PCI indicates ongoing myocardial ischaemia or reperfusion injury (3). These arrhythmias include (in order of occurrence): accelerated idioventricular rhythm 15 to 42%, sinus bradycardia 28%, non-sustained ventricular tachycardia (NSVT) 26%, sinus tachycardia 22%, atrial fibrillation (AF) 9%, high-degree AV block 5 to 10%, sustained ventricular tachycardia (VT) 2 to 4% and ventricular fibrillation (VF) 2 to 5% (3). Following PCI, the incidence of arrhythmias ranges from 6 to 28% for new-onset AF, 5 to 10% for NSVT, 5 to 10% for high grade AV block, 7 to 16% for sinus bradycardia, 5% for sinus arrest, 3-6% for sustained VT and 3 to 6% for VF (3). Supraventricular tachycardias (SVT) are relatively uncommon and are usually self-limiting (3).

Despite improvements in morbidity and mortality in STEMI due to emergency thrombolysis and advances in primary PCI, life threatening ventricular arrhythmias still occur in up to 10% of patients (4). In hospital mortality rates have been reported as being 3-fold higher for patients presenting with ventricular tachyarrhythmias (VTA) (28). VTA occurrence increases with increasing duration of ischaemia (3). Patients at increased risk for VTA are those with higher TIMI/GRACE scores, larger infarcts and patients with persistent symptoms after initiation of therapy or patients with incomplete revascularisation (3). Patients may also have an underlying arrhythmogenic substrate prior to presenting with ACS leading to increased risk of sustained VTA such as previous myocardial infarction, myocardial scar, underlying cardiomyopathies, genetic predisposition to ventricular arrhythmias, and pre-existing reduced LV function (3).

VTAs are more commonly seen in anterior STEMI with a slight increase in LAD culprit disease (28). NSVT is a risk factor for VT/VF and is associated with increased cardiovascular and arrhythmic death most marked during the convalescent phase (2 months post ACS) (7). Ventricular ectopy recorded on Holter-ECG, combined with low left ventricular ejection fraction (LVEF) predicts a higher risk of mortality post MI (7). Indeed, premature ventricular complexes (PVC's), which in healthy individuals are believed to be benign, have consistently been shown to be associated with adverse outcomes after myocardial infarction (MI) (18).

Early VTA develops within the first 48 hours of ACS and are the most frequent cause of pre-hospital and in-patient ACS related death (28). Findings from the ACSIS (Acute Coronary Syndrome Israel Survey) registry showed that patients with late VTA (occurring 48 hours following acute MI) had larger infarcts, severe impairment of LV function and an 8-fold increase of in-patient mortality, a 5-fold increase of 30-day mortality and increased 1 year mortality (28).

Acute myocardial infarction (AMI) is an established risk factor for atrial fibrillation (AF) and occurs in 6 to 21% of patients with AMI (31). AF is associated with poor short- and long-term prognosis with an increase in overall mortality (31). ACS patients with new onset AF are twice as likely to have heart failure and acute stroke and 3 times more likely to develop cariogenic shock during admission (31). There is an additional 2-fold increase in death at 30 days after AMI in patients who developed AF (31). One study showed that patients with AF and MI had a higher number of diseased vessels at angiography (31). AF is associated with worsening haemodynamics due to rapid ventricular rates, irregular ventricular filling and loss of atrial kick (3). Risk factors for AF in ACS patients include older age, pre-existing AF, left ventricular hypertrophy/dysfunction and the presence of heart failure symptoms (3).

Bradyarrhythmias may be induced by autonomic imbalance with vagal hyperactivity or may be due ischaemia or infarction of the conduction system (3). Second- or third-degree atrioventricular block (AV) block in patients with an acute inferior MI is located above the

bundle of HIS in 90% of cases which most often results in a moderate bradycardia with a narrow junctional escape which is frequently transient and associated with a low mortality risk (3). In contrast to patients with anterior MI where the AV block is located below the AV node and typically occurs within the first 24hrs of an MI and is associated with extensive myocardial necrosis of the septum and anterior wall in the presence of severe multi vessel disease involving the LAD and RCA or left circumflex artery leading to haemodynamic instability and death due to cardiogenic shock/cardiac arrest (3). A higher incidence of third degree AV block is associated with inferior STEMI but can be seen in patients presenting with anterior STEMI's where the in-patient mortality rate is substantially higher (18.1% vs 50% respectively) (34).

Third degree AV block (also referred to as 'complete heart block') has a much lower incidence in patients who have undergone prompt complete revascularisation and is usually transient (3). However, the mortality rate of symptomatic high-grade AV blocks is approximately 80% in patients with larger infarcts or who have undergone incomplete revascularisation with persistent symptomatic high-grade AV block due to loss of functioning myocardium (3). The presence of complete third-degree AV block has been associated with worse short-term prognosis as there is an increase in the incidence of heart failure, cardiogenic shock, ventricular arrhythmias, need for invasive mechanical ventilation, acute kidney injury and death in these patients (34). Lower rates of complete AV block have been reported in patients who receive primary PCI 2.5% as opposed to fibrinolysis 7.3% (34).

In ACS, potassium imbalance has been associated with increased risk of in-hospital arrhythmias such as ventricular arrhythmias, cardiac arrest and death. Hyperkalaemia is associated with increased mortality and potassium levels of < 3 are associated with new-onset atrial fibrillation (55). Normokalaemia is associated with the lowest incidence of adverse events (55).

The European Society of Cardiology (ESC) guidelines for management of STEMI and NSTEMI advises rhythm monitoring for at least 24 hours after symptom onset or until revascularisation in low-risk patients for cardiac arrhythmias (6, 54). Longer monitoring should be considered in patients with intermediate to high risk for cardiac arrhythmias, with one or more of the following criteria: haemodynamically unstable, major arrhythmias, LVEF <40% and failed reperfusion (6, 54).

The electrocardiogram (ECG) is the gold standard and first-line diagnostic tool for the diagnosis of ACS and assessing patients at risk of developing cardiac arrhythmias (7). ECG monitoring is non-invasive, cost efficient and widely available (7, 8). Simple ECG measures can be used to predict greater arrhythmogenesis and sudden arrhythmic death (SAD) risk in ACS (56). Predictors of SAD are contiguous Q waves, left ventricular hypertrophy, QRS duration and JTc prolongation (56).

The PRE-DETERMINE registry is a prospective cohort study comprised of 5764 patients with coronary disease on angiography or with a documented history of myocardial infarction and mild to moderate left ventricular dysfunction who did not fulfil criteria for ICD implantation (57). The ARTEMIS registry recruited patients who had undergone angiography with documented CAD on angiography with or without diabetes mellitus (57). Chatterjee et al. looked at electrocardiographic markers associated with arrhythmic risks in both subsets of patients from the derivation cohort (PREDETERMINE registry) and the validation cohort (ARTEMIS registry). Chatterjee et al. organised electrocardiographic markers into risk domains which included: anatomic risk (contiguous Q waves, left ventricular hypertrophy (LVH), left atrial enlargement (LAE), autonomic function (resting heart rate, PR interval), depolarisation (QRS duration and fragmentation) and repolarisation (JTc prolongation, early depolarisation, contiguous T wave inversion) (57). These risk domains were associated with arrhythmic mortality/SAD (57). Chatterjee et al. developed a risk-based ECG score. The score was comprised of four ECG markers that were independently associated with arrhythmic death including: LVH (1 point), contiguous Q waves (1 point), QRS duration (80-110ms 1point, >110ms 2 points) and prolonged JTc interval (1 point). The ECG score was divided into low risk (0-1 points), moderate risk (1-2 points) and high risk (>3 points) (57). The 5-year risk of sudden arrhythmic death (SAD) for low- and high-risk group was 1.5% and 6.2% respectively in the PREDETERMINE derivation cohort and 0.9% and 5.2% in the ARTEMIS validation cohort for low- and high-risk groups respectively(57). An increasing ECG score (>3) was associated with an increase in the incidence of SAD and the risk was further enhanced in patients with moderately depressed LV function where the five-year incidence of SAD was 7.4% in patients with a high-risk vs. 2.4% with low-risk ECG score (57).

There is a lack of data regarding the incidence and prognostic implications of arrhythmias in patients admitted to coronary care units (CCU) with ACS especially in the South African and sub-Saharan Africa context. We also intend to validate the ECG scoring system developed by Chatterjee et al. within a South African cohort of ACS patients to determine its prognostic implication and to improve long-term patient outcomes.

2.2. Definitions

Myocardial infarction (MI)

Myocardial infarction refers to acute myocardial injury with clinical evidence of acute myocardial ischaemia, 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 in keeping with myocardial ischaemia;
- New ischaemic ECG changes;
- Development of pathological Q waves;
- Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality in a pattern consistent with an ischaemic aetiology;
- Identification of a coronary thrombus by angiography or autopsy (11).

ST elevation myocardial infraction (STEMI)

Patients with acute ischaemic chest pain and persistent ST-segment elevation for > 20min (6, 58). ECG criteria include (6, 58):

- New ST- elevation at the J point in at least 2 contiguous leads ≥ 0.1mV in all leads other than V2-V3; where men ≥ 40 years V2-V3 ≥ 0.2mV; men < 40 years V2-V3 ≥ 0.25mV; and women V2-V3 ≥ 0.15mV.
- Presumed new left bundle branch block: Defined as QRS duration ≥ 120ms with small initial deflection followed by deep S wave with nadir within 70ms of onset of QRS complex in V1 or V2
- Broad, notched, or slurred R waves in leads I, aVL, V5, and V6;
- Absent q waves in leads I, V5, and V6
- Additional STEMI equivalents will also be considered, such as classical De Winters ECG.

Non-ST elevation myocardial infarction (NSTEMI)

Patients with acute ischaemic chest pain without persistent ST elevation on ECG, but with myocyte necrosis present as proved by elevated cardiac biomarker (e.g. Troponin T, Troponin I, CK-MB) (54) ECG criteria may have the following:

- Transient ST-segment elevation (< 20 minutes)
- Transient or persistent ST-segment depression
- T-wave inversion
- Flat T waves or pseudo-normalization of T waves

- Normal ECG (54)

Unstable angina (UA)

Unstable angina is defined as myocardial ischaemia at rest or minimal exertion in the absence of myocyte necrosis with a negative cardiac biomarker result (6, 58)

2.3. ECG diagnostic criteria

Sinus tachycardia

Sinus tachycardia is defined as a heart rate >100 beats per minute (bpm), with atrial activation that occurs via the sinus node. In sinus tachycardia there is a normal, upright P wave that precedes every QRS complex with normal a P wave axis where the P wave is positive in lead II and negative in AVR (13).

Sinus bradycardia

Sinus bradycardia is defined as a heart rate <60 bpm, with atrial activation that occurs via the sinus node (8). In sinus bradycardia there is a normal, upright P wave that precedes every QRS complex, with a normal P wave axis (where the P wave is positive in lead II and negative in AVR).

Sinus arrhythmia

Sinus arrhythmia is defined as an irregularity in the rate of normal sinus rhythm (8). Sinus arrhythmia is considered to be present when there appears to be a variation in the P-P interval by 120 milliseconds or more, but normal atrial activation occurs via the sinus node.

Atrial fibrillation (AF)

Atrial fibrillation is a pathological supraventricular tachycardia. It is caused by multiple electrical wavelets appearing in the atria simultaneously, lasting at least 30sec (16). The ventricular response is irregular and the ventricular rate ranges from 60 to 220 beats per minute (13). The typical pattern of AF consists of absolutely irregular RR intervals and fibrillatory waves (17).

Premature Ventricular Complex

Premature ventricular complexes (PVC) or ventricular ectopics are synonyms for the impulse that originates in an ectopic focus in the ventricular myocardium or conduction tissue, independent of sinus impulse generation in the sinus node (18).

Ventricular Tachycardia (VT)

Ventricular tachycardia is a cardiac arrhythmia of ventricular origin characterised by three or more consecutive QRS complexes that are wide (i.e >120ms) and occur at rate of greater than 100 bpm with the cycle length being less than 600ms. Ventricular tachycardias are further divided by whether they are sustained or non-sustained and by the QRS morphology (59).

- **Non sustained VT** – Three or more beats in duration, terminating spontaneously in less than 30s.
- **Sustained** VT – greater than 30s in duration and/or requiring termination due to hemodynamic compromise in less than 30s.
- **Monomorphic VT** – VT with a single QRS morphology.
- **Polymorphic VT** – VT with a changing QRS morphology at cycle length between 600 and 180ms (59).

Ventricular fibrillation

Rapid, grossly irregular electrical activity with marked variability in electrocardiographic waveform, ventricular rate usually >300bpm (19).

Atrioventricular block

Atrioventricular block can be classified into first, second and third degree (complete) AV block.

In first degree P waves are associated with 1:1 AV conduction and the PR interval is prolonged and is greater than >200ms (20).

In second-degree AV block, the atrial depolarisation intermittently fails to conduct to the ventricles. On the 12-lead ECG there are more P waves than QRS complexes:

- Mobitz type I second-degree AV block The PR interval increases in length until the

pause where it is not followed by a QRS complex as the atria fails to conduct to the ventricles. The PR interval after the pause is shorter than the PR interval before the pause.

Mobitz type II second-degree AV block has constant PR intervals. There is unpredictable loss of conduction of P waves not followed by QRS complexes (21)