The prognostic value of Discharge Versus Admission N-Terminal-Pro Brain Natriuretic Peptide in patients with Acute Coronary Syndrome in a South African Regional Hospital

By

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School of Clinical Medicine

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Declaration

I.....**Nomzi Nande Zibi**.....declare that

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Dedication

To my husband for his unwavering love and support and to my parents and siblings for their continued encouragement and support.

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Overview of the thesis

B-type natriuretic peptide (BNP) and its prohormone N-terminal proBNP (Nt-proBNP) are elevated following acute coronary syndrome (ACS), as BNP is secreted from both infarcted and non-infarcted myocytes. These neuroendocrine hormones are powerful prognostic indicators; however, no optimal time to test is established. B-type natriuretic peptides measured in patients with acute coronary syndrome at presentation, weeks, or several months post myocardial infarction shows correlation with mortality and new onset congestive cardiac failure. There are very few studies conducted in Africa regarding b-type natriuretic peptides and prognosis following ACS. In a study of 200 patients with ACS in South Africa, Nt-proBNP was found to be a better prognostic indicator compared to Troponin T, in patients with ST-segment elevation myocardial infarction (STEMI) and non-ST-segment elevation myocardial infarction NSTEMI. This effect was observed for both inpatient outcomes as well as up to 6 months follow up period.

As cardiovascular disease is a leading cause of non-communicable disease burden in sub-Saharan Africa with the incidence of ischaemic heart disease rising, it is important to find ways to risk stratify our patients in resource constraint environments in order to improve patient outcomes. Currently, more than 50% of global deaths from ischaemic heart disease occur in low-middle income countries, which are less developed and have lower levels of education. This further reiterates the need for us to develop risk stratification tools in order to choose the patients at highest risk of poor outcomes, to receive scarce treatment resources as a matter of priority.

This single-centre retrospective observational study analysed a database of all patients admitted to a South African Regional hospital's coronary care unit with a confirmed diagnosis of Acute Myocardial Infarction (AMI) between 2002 and 2016. A total of 1814 patients were eligible for inclusion with both an admission and a discharge Nt-proBNP measurement. The association of elevated Nt-proBNP levels to death or any of the preselected major adverse cardiovascular events was analyzed.

We concluded that Admission Nt-proBNP measurement is a more significant predictor of mortality and Major Adverse Cardiovascular Events (MACE) following myocardial infarction during hospital stay and up to 30-day follow-up.

Table of Contents

Declaration……..ii

Dedication……iii

Acknowledgements……..iv

Overview of the thesis……v

Table of Contents……vi

Part 1: The Review of Literature……1

Part 2: A submission ready manuscript……..7

Appendices……XVII

Appendix 1: The final Study Protocol (Include the final protocol which was given full approval by Brec and/or the postgrad office)……XVIII

Appendix 2: The Guidelines for Authorship for the Journal selected for submission of the manuscript …….. XXX

Appendix 3: Ethical approvals……XXXI

Part 1: The Review of Literature

Brain natriuretic peptide (BNP) was first isolated from the brains of pigs in 1988(1, 2). Human BNP was later isolated from the human atrium in 1990 and its 32-amino acid sequence determined (3). The human BNP gene, located on chromosome 1, encodes the 108 amino acid prohormone, pro-BNP. In circulation, the biologically active BNP is separated from the N-terminal portion of the prohormone, called N-terminal proBNP (Nt-proBNP) by the proteolytic enzyme Furin (1, 4). Radioimmunoassay testing specific for human BNP was developed in Kyoto, Japan (5) and allowed for plasma BNP measurement in 11 normal subjects as well as 41 patients with congestive heart failure. BNP was found to be markedly increased in patients with congestive heart failure, in proportion to the severity of disease (1, 3).

Localization of the secretion of BNP involved comparing the concentration of BNP and Atrial Natriuretic Peptide (ANP) from blood collected at different sites both centrally and peripherally in patients with, and patients without evidence of heart failure. Yasue et al(6) demonstrated that BNP and ANP levels are increased in patients with heart failure compared with normal cardiac function regardless of the site of blood sample collection. They also demonstrated that BNP is secreted mainly from the left ventricle, and that BNP is secreted increasingly from the left ventricle as left ventricular function deteriorates. Finally, their study demonstrated that plasma levels of BNP at peripheral veins reflected the amount of hormone secreted from the left ventricle, therefore plasma levels are able to be used as markers of left ventricular dysfunction (6).

The release of BNP is triggered by increased cardiac chamber wall stress, this trigger leads to upregulation of ventricular production of BNP. Intact cardiac myocytes, whether ischaemic or non-ischaemic, are the major source of BNP secreted into the circulation. Following myocardial infarction there is a biphasic release of BNP, an initial peak at up to 16 hours after presentation as well as a second peak in 5 days (4, 7, 8). Binding of BNP to the natriuretic peptide receptor type A, causes increased intracellular cyclic guanosine monophosphate (cGMP) production. This gives rise to the biological effects of BNP, which include diuresis, natriuresis, vasodilation, inhibition of Renin and Aldosterone production, as well as cardiac and vascular myocyte growth. The main clearance mechanism of (Nt-pro) BNP is via renal excretion, but it is also cleared from plasma by binding to natriuretic peptide receptors as well as by proteolysis by peptidases (8-10).

Several studies have shown the clinical utility of BNP and Nt-proBNP measurement in the diagnosis and management of heart failure (11-17), proving that natriuretic peptides provide for rapid ruling out of heart failure in different clinical environments. These two natriuretic peptides are comparable to each other, albeit with different laboratory cut-off values (17-19). Furthermore, both BNP and Nt-proBNP are of prognostic value in patients with chronic heart failure. Elevated blood concentration levels of these natriuretic peptides, whether tested on admission, at discharge or in follow up, are associated with increased risk of death or adverse cardiovascular events (13, 20-22).

BNP and Nt-proBNP are markedly increased following myocardial infarction (23-30) with the performance of BNP being comparable to that of Nt-proBNP (31,32). These biomarkers are able to identify patients at highest risk of subsequent death throughout the full spectrum of acute coronary syndromes (ACS) (33, 34) to the extent of predicting severity of coronary lesions (35, 36). Torbjorn Omland et al demonstrated Nt-proBNP concentration to differ according to final diagnosis, with highest concentrations in patients with ST-segment elevation Myocardial Infarction (STEMI) and lowest in patients with Unstable Angina (37).

Morita et al demonstrated a biphasic pattern in BNP secretion following myocardial infarction. Patients with a biphasic pattern tended to have more incidence of anterior infarction, congestive heart failure, higher level of maximal creatine kinase-MB isoenzyme, as well as lower left ventricular ejection fraction compared to the monophasic group(24). All patients in this study were able to be classified as either monophasic or biphasic BNP response. Talwar et al sought to determine the optimal timing of Nt-proBNP measurement by performing serial Nt-proBNP testing in patients with acute MI. This study demonstrated the biphasic pattern of NT=-proBNP secretion in patients with anterior MI only (38).

BNP is not only an excellent marker for predicting mortality following myocardial ischaemia, but also correlates well with LV dysfunction, with low BNP levels after MI predicting LVEF greater than 40% and higher BNP levels predicting higher likelihood of LVEF <40% (25, 31).

There is no consensus as to the optimal time to measure BNP or Nt-proBNP following acute coronary syndromes. B-type natriuretic peptides measured in patients with acute coronary syndrome at presentation, weeks, or several months post myocardial infarction shows correlation with mortality and new onset congestive cardiac failure (24, 39-41).

There are very few studies conducted in Africa regarding b-type natriuretic peptides and prognosis following ACS. In a study of 200 patients with ACS in South Africa, Nt-proBNP was found to be a better prognostic indicator compared to Troponin T, in patients with STEMI and NSTEMI. This effect was observed for both inpatient outcomes as well as up to 6 months follow up period (42).

As cardiovascular disease is a leading cause of non-communicable disease burden in sub-Saharan Africa with incidence of ischaemic heart disease rising, it is important to find

ways to risk stratify our patients in resource constraint environments in order to improve patient outcomes (43). Currently, more than 50% of global deaths from ischaemic heart disease occur in low-middle income countries, which are less developed and have lower levels of education (44, 45).

This further reiterates the need for us to develop risk stratification tools in order to choose the patients at highest risk of poor outcomes, to receive scarce treatment resources as a matter of priority.

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Part 2: A submission ready manuscript.

The Prognostic Value of Discharge Versus Admission Nt-proBNP in Patients with Acute Coronary Syndrome in a South African Regional Hospital

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ABSTRACT

Objective: B-type natriuretic peptide (BNP) and its prohormone N-terminal proBNP (Nt-proBNP) are elevated following myocardial infarction, as BNP is secreted from both infarcted and non-infarcted myocytes. These neuroendocrine hormones are powerful prognostic indicators, however, no optimal time to test is established. This study investigated the prognostic significance of admission compared to discharge Nt-proBNP for predicting major adverse cardiovascular events (MACE) or mortality within a 30-day period following acute myocardial infarction (AMI).

Methods: This single-centre study analysed a database of all patients admitted to a South African Regional hospital's coronary care unit with a confirmed diagnosis of Acute Myocardial Infarction (AMI) between 2002 and 2016. A total of 1814 patients were eligible for inclusion with both an admission and a discharge Nt-proBNP measurement. The association of elevated Nt-proBNP levels to death or any of the preselected MACE was analyzed.

Results: The study population comprised 1814 patients with a mean age of 57.4 (±11.1) years, the majority of whom were males (66.4%). The predominant diagnosis in the study population was ST segment Elevation Myocardial Infarction (77.2%) and most common site of infarction, the anterior territory (67.4%). One or more MACE occurred in 516 patients (28.4%) while 143 patients (7.9%) died during the study period. Admission Nt-proBNP had a statistically significant association with both mortality and MACE (both $p \leq 0.001$). Discharge Nt-proBNP did not predict mortality (p=0.514) but had a significant association with MACE (p=0.037).

Conclusion: Admission Nt-proBNP measurement is a more significant predictor of mortality and MACE following myocardial infarction during hospital stay and up to 30-day follow-up.

INTRODUCTION:

Brain natriuretic peptide (BNP) is a neuro-endocrine hormone released by cardiac myocytes in response to increased myocardial wall stress. In the circulation, the biologically active 32-amino acid BNP, is separated from the N-terminal portion of its prohormone called N-terminal pro-brain natriuretic peptide (Nt-proBNP). Following myocardial infarction, there is increased secretion of BNP from both infarcted as well as non-infarcted cardiac myocytes. The physiological effects of BNP include diuresis, vasodilation, inhibition of renin and aldosterone production, as well as stimulation of cardiac and vascular myocyte growth. The half-life of Nt-proBNP is 70-120minutes, which is much longer than that of BNP, which is 20 minutes. Renal excretion is the main clearance mechanism of these natriuretic peptides, though circulating endopeptidases degrade them as well (1-4).

B-type natriuretic peptide testing has been extensively investigated in the setting of heart failure. BNP levels are elevated in patients with congestive heart failure (CHF), with a positive correlation between symptom severity and natriuretic hormone level (5-7) . BNP is not only useful in identifying the presence of systolic and diastolic heart failure (8-11), but also serves as a prognostic indicator for readmission and mortality (12-15).

Several studies have demonstrated that BNP levels are elevated following acute coronary syndromes (16-21). BNP levels peak between 7-40 hours but some patients have demonstrated a

biphasic release with a second peak at 73-100 hours after an acute ischaemic event. This is thought to represent the long-term adverse effect of left ventricular remodeling. This biphasic secretion of BNP has been shown to be associated with a poorer prognosis when compared to the monophasic response (2, 19).

Some authors have sought to find the optimal time to test natriuretic peptides following acute coronary syndromes, with blood samples taken in the immediate hospital stay, up to a twelve month follow up period (18, 22-24). In patients presenting with chest pain, the failure of Nt-proBNP to decline rapidly by 72hrs after symptom onset, was associated with a higher risk of death within 30days(23) . The occurrence of persistently elevated B-type natriuretic peptide levels weeks, and even months after an acute myocardial infarction, is associated with a higher risk of death or new CHF both in the short term as well as the very long term following Acute Coronary Syndrome (ACS) (22, 24, 25). BNP and its prohormone Nt-proBNP, are powerful independent predictors of mortality and perform in a comparable manner to each other (26-28).

There are very few studies conducted in Africa regarding b-type natriuretic peptides and prognosis following ACS. In a study of 200 patients with ACS in South Africa, Nt-proBNP was a better prognostic indicator compared to Troponin T, in patients with ST-segment elevation myocardial infarction (STEMI) and non-ST-segment elevation myocardial infarction (NSTEMI). This effect was observed for both inpatient outcomes as well as up to 6 months follow up period (21).
As cardiovascular disease is a leading cause of non-communicable disease burden in sub-Saharan Africa with incidence of ischaemic heart disease rising, it is important to find ways to risk stratify our patients in resource constrained environments in order to improve patient outcomes (29). Currently, more than 50% of global deaths from ischaemic heart disease occur in low-middle income countries, which are less developed and have lower levels of education (30, 31).

Therefore, in our resource-limited environment, it would be useful to identify the superiority of a single natriuretic peptide measurement to provide the most significant prognostic information with regards to mortality and cardiovascular morbidity in patients presenting with acute coronary syndromes. Such information can assist in prioritizing limited services to the most urgent cases.

The purpose of our retrospective observational study was to evaluate the prognostic value of N-terminal-proBNP levels obtained at the time of hospital discharge, compared to an admission Nt-proBNP measured at the time of admisssion to a coronary care unit with a diagnosis of an acute myocardial infarction. We compared this to Nt-proBNP measurements taken at the time of admission in order to evaluate which measurement provided the most useful information on 30-day survival and major adverse cardiovascular events.

METHODS:

This single-centre retrospective observational study used a computerized database of all patients admitted to the coronary care unit of a South African Regional hospital (RK Khan Hospital). This database comprised data collected between 2002 and 2016. According to the study protocol, only patients with a confirmed diagnosis of acute coronary syndrome based on standard criteria were included. Patients with unstable angina were excluded. Patients with only a single Nt-proBNP measurement were also excluded as both admission and discharge values were necessary for further analysis. This data was organized according to various clinical and laboratory variables, together with patient outcomes where it was known. Patient anonymity was maintained by using computer generated identity numbers for all patients in the database.

Clinical Variables

All patients had clinical assessments, which included measurements for blood pressure, pulse rate, waist circumference and body mass index. Patient risk factor profiles included were Hypertension, Diabetes Mellitus (DM), Smoking history as well as Hypercholesterolaemia. Family history of vascular disorder was recorded, which included the presence of Premature Coronary Artery Disease, Hypertension, DM or Cerebrovascular accident present in a parent, sibling or other 1st degree relative younger than 55 years of age at onset. The type of myocardial infarction as well as site of infarction were noted. Post-infarct complications were recorded during the initial hospital stay as well as at an outpatient assessment a month after hospital admission. These preselected adverse cardiovascular events were Recurrent Myocardial Infarction, recurrence of Angina, the presence of Heart Failure, occurrence of Atrial Fibrillation, Ventricular Tachycardia, Ventricular Fibrillation, Cardiogenic Shock and Death.

Laboratory Samples

Blood samples for Nt-proBNP were taken within 6 hours of hospital admission and discharge blood samples taken at approximately day 5 of hospital admission. All samples were analyzed by the National Health Laboratory Service (NHLS) which issues results measured as Nano grams per litre. There was no special sampling technique used and blood collection was by routine methods.

Ethics

This study received ethical approval from the University of KwaZulu-Natal Biomedical Ethics Committee (BREC). BREC reference number: BE419/16

Statistical Analysis

Data was analysed using IBM SPSS version 23. Continuous variables (e.g. admission and discharge BNP were summarized medians and interquartile ranges since they were highly skewed. Categorical data were presented using frequency tables. Association between categorical variables were assessed using the Pearson's chi-square ($\chi 2$) test. Paired binary proportions were compared using McNemar's chi square tests within specific subgroups. The non-parametric Mann Whitney test was used to compare the mean of continuous explanatory variables (such as Nt-proBNP) by

dichotomous outcome classification. Admission and discharge Nt-proBNP were tested for association with mortality and MACE using bivariate and multivariable logistic regressions to account for other risk factors and/or confounding variables. Coefficients were exponentiated to represent odds ratios [ORs] and 95% confidence intervals. Model fit (adequacy) was assessed using goodness of fit tests, variance inflation factors [VIFs] and predictive performance. An adjusted p-value of <0.05 was considered statistically significant.

The primary endpoints were in-hospital and 30-day mortality and major adverse cardiovascular events (MACE) that included recurrent myocardial infarction, recurrence of angina, the development of heart failure, atrial fibrillation, ventricular dysrhythmia, cardiogenic shock.

RESULTS:

Study Population

Of the 3886 patients in our database, 1961 (50.5%) had both admission and discharge Nt-proBNP values. After excluding all patients with Unstable Angina, we had a study population of 1814 patients. Of these 1814 patients, three (3) had missing information for Major Adverse Cardiovascular Events (MACE) outcome. Demographic and clinical characteristics of the study population are depicted in Table I. The mean age of the study population was 57.4years (SD 11.2). The majority of patients were male (64%) with nearly a quarter being obese (23.4%). The most prevalent risk factors for acute coronary syndrome were Diabetes Mellitus (n=1073; 59.2%) as well as a family history of coronary artery disease (n=1076; 59.3%). Other clinically significant risk factors present in our population were the presence of hypertension as well as smoking history. The majority of our patient presented with ST segment elevation myocardial infarcts (STEMI) (n=1400; 77.2%) with the most frequent sites of infarction being Anterior (67.4%) and Inferior (50.1%) territories.
Nt-proBNP values obtained ranged between 5-35000pg/ml. We further categorized NT-pro BNP levels into normal (≤124 pg/ml) and abnormal (≥ or equal to 125 pg/ml). At admission, 1474 (81%) patients had abnormal Nt-proBNP levels, whilst 1658 (91%) had abnormal Nt-proBNP levels at the time of hospital discharge. Table II contains the breakdown of all major adverse cardiovascular events, including death.

Major Adverse Cardiovascular Events (MACE)

Five-hundred and sixteen patients (28.4% of study cohort) developed major adverse cardiovascular events (MACE) during the study period. Of these patients, 455 (88%) had abnormal admission Nt-proBNP levels and 474 (92%), had abnormal discharge Nt-proBNP levels. Sixty-one patients with MACE had normal Nt-proBNP blood levels on admission, 53 patients (87%) of these went on to become abnormal at the time of discharge. Admission Nt-proBNP had a highly significant correlation with MACE (p<0.001) while discharge Nt-proBNP also had a significant correlation with MACE (p=0.037). There was a borderline non-significant difference when comparing admission and discharge Nt-proBNP measurements for predicting MACE (p=0.053).

Cardiac Failure

The most common adverse event was cardiac failure. Cardiac failure developed in 266 patients (14.7% of study cohort), this represented 50.8% of all major adverse events. The majority of patients with heart failure (95%) had abnormal Nt-proBNP on admission, whilst 92% had abnormal Nt-proBNP at discharge. In this group of patients who developed heart failure, 65 patients died (24%). Of these patients, 62 (95%) had abnormal Nt-proBNP levels at both admission and discharge. In this cardiac failure subgroup of 266 patients, median admission Nt-proBNP was 3705pg/ml (IQR 1459-9410pg/ml) while the median discharge level was 1187pg/ml (IQR 424-3181pg/ml). Nt-proBNP at admission within this subgroup of patients did not predict death (p=0.963) and neither did discharge Nt-proBNP (p=0.549). Discharge Nt-proBNP when arranged into quartiles did not yield any statistical significance in predicting mortality (p=0.608). The relationship of discharge Nt-proBNP quartiles to mortality was non-linear with the lowest and highest quartiles with similar risk of mortality and the third quartile with the highest risk of mortality.

Mortality

The total number of patients who died during the study period was 143 (7.9% of study cohort). Of these patients, 138 had abnormal admission Nt-proBNP with 133 being abnormal at discharge. Only five patients who died had normal Nt-proBNP on admission, however all five went on to develop abnormal levels of Nt-proBNP at discharge. Admission Nt-proBNP had a highly significant association (P<0.001) with death but discharge Nt-proBNP did not (p=0.514). There was no significant difference when comparing admission and discharge Nt-proBNP for predicting death (p=0.302). For a combined outcome of MACE or death, admission Nt-proBNP had a highly significant association (p<0.001) while discharge Nt-proBNP demonstrated no association (p=0.562). When arranged into quartiles discharge Nt-proBNP showed a significant association to the combined outcome of MACE or death (p=0.015). Admission Nt-proBNP in quartiles remained highly significant for the outcome of MACE or death (p<0.001).

Quartiles of Nt-proBNP

We proceeded to analyze our data by arranging admission and discharge Nt-proBNP into quartiles. Quartiles of admission Nt-proBNP are linear, and were highly significant for both death (p<0.001) and MACE (p<0.001). Quartiles of discharge Nt-proBNP were not linear and had no significant association to the outcome of death (p=0.514). Quartiles of discharge Nt-proBNP, though non-linear, did have a significant association with the outcome of MACE (p=0.037). Although this relationship was non-linear, the risk of MACE was highest in the highest quartile (33.1%) compared to the lowest quartile (29.1%). The medians and interquartile ranges of the admission and discharge quartiles are shown on Table III.

DISCUSSION:

This study set out to compare the prognostic value of discharge Nt-proBNP as compared to admission Nt-proBNP following acute myocardial infarction (MI). We assessed the occurrence of major adverse cardiovascular events in a database of patients admitted to a Coronary Care Unit in a public hospital in South Africa. The majority of patients presented with an ST-segment elevation MI (77.2%). The most common site of infarction was the anterior territory (67.4%) followed by inferior territory (50.1%). The three most prevalent cardiovascular risk factors were Diabetes Mellitus (59.2%), Hypertension (54%) and current smoking (49.2%). These findings are consistent with the risk factor profile previously demonstrated in a smaller study of 94 patients in the same hospital(32).

Cardiac failure was the most common complication of Myocardial Infarction in our study cohort accounting for 50.4% of all adverse events. Natriuretic peptides are a useful diagnostic tool in heart failure (6, 11) and also a prognostic marker in patients with heart failure as well as acute coronary syndromes (12-14). We assessed the prognostic function of Nt-proBNP in this subgroup of patients. Admission Nt-proBNP (p=0.963) and discharge Nt-proBNP (p=0.549) did not have a significant association with mortality in the group of patients with cardiac failure. Patients with cardiac failure however, accounted for 45% of all mortality cases in our study cohort and all but three (3) had elevated natriuretic peptide levels at both admission and discharge. The development of heart failure after myocardial infarction is an indication for angiography(33). The presence of cardiac failure itself, following myocardial infarction is a poor prognostic indicator (34-36). While B-type natriuretic peptides are powerful prognostic indicators in cardiovascular disease, the presence of raised natriuretic peptides is also associated with non-cardiac causes as well (37). In a study by Talwar et al(19), serial measurements of Nt-proBNP following myocardial infarction, Nt-proBNP levels did not differ between patients with clinical or radiological features of cardiac failure and those who did not. That study however, like Morita et al(16), demonstrated a biphasic pattern of Nt-proBNP secretion following myocardial infarction. The most common site of myocardial infarction in this present study was anterior infarction which was consistent with that of Morita et al. Morita et al however, demonstrated that the second peak of Nt-proBNP at around day 5, found predominantly in patients with anterior infarction, was associated with higher mortality. This significance of a later Nt-proBNP measurement was not demonstrated in the present study.

Our results demonstrate that elevated levels of Nt-proBNP measured at the time of hospital admission are a highly sensitive indicator of adverse cardiovascular events and death (p<0.001). This is in keeping with literature. However, there is no consensus as to the optimal time to measure natriuretic peptides in coronary artery disease. Elevated levels of these hormone are able to predict mortality whether they are measured early within 6 hours of symptom onset (38) but also remain sensitive if elevated many months following myocardial infarction (22).

In our study population, abnormal Nt-proBNP levels measured around day 5 were better at predicting adverse cardiovascular events (p=0.037) than death (p=0.514). This is in spite day 5 corresponding to the expected time of a second peak of Nt-proBNP secretion as well as the predominant anterior territory involvement within our study cohort. If we look closer at the patients with adverse cardiovascular events, 53 patients had normal admission Nt-proBNP but abnormal levels at the time of discharge. We can compare this to only five patients who died, who had normal Nt-proBNP levels on admission, though all five became elevated at the time of hospital discharge. Rising BNP levels and a failure of decline in BNP levels is a poor prognostic indicator (18, 19). More patients had abnormal Nt-proBNP at discharge (474) compared to admission (455) in the group of patients with adverse cardiovascular events, for which Nt-proBNP had a statistically significant association with this outcome.

When arranged into quartiles, admission Nt-proBNP remained highly sensitive for both death and adverse events (p<0.001). Quartiles of discharge Nt-proBNP, had a significant association with major adverse cardiovascular events (p=0.037), but not death (p=0.514). The relationship between discharge Nt-proBNP and MACE was non-linear, however, the highest quartile of discharge Nt-proBNP carried the highest risk of the development of adverse cardiovascular events. This group had a median Nt-proBNP value of 4965pg/ml (see Table III).

Perhaps further studies could assess a cutoff value within the fourth quartile of discharge Nt-proBNP, above which adverse cardiovascular events or mortality can be predicted. Higher Nt-proBNP levels are associated with higher mortality, lower left ventricular ejection fraction as well as extent of coronary artery involvement (18, 21, 23).

In the present study, discharge Nt-proBNP is not superior to an admission measurement of Nt-proBNP in predicting the occurrence of major adverse cardiovascular events or mortality. Quartiles of discharge Nt-proBNP have demonstrated a role in predicting adverse cardiovascular events. As cardiovascular disease is a leading cause of non-communicable disease burden in sub-Saharan Africa with incidence of ischaemic heart disease rising, it is important to find ways to risk stratify our patients in resource constrained environments in order to improve patient outcomes (29). Currently, more than 50% of global deaths from ischaemic heart disease occur in low-middle income countries, which are less developed and have lower levels of education (30, 31).
This further reiterates the need for us to develop risk stratification tools in order to choose the patients at highest risk of poor outcomes, to receive scarce treatment resources as a matter of priority.

Conclusion

Abnormal admission Nt-proBNP, ≥125 pg/ml, is superior to discharge Nt-proBNP in predicting mortality and major adverse cardiovascular events. Quartiles of discharge Nt-proBNP are able to predict major adverse cardiovascular events but not death following acute myocardial infarction. Further studies are needed

to establish a cutoff point of Nt-proBNP for prognosis in our clinical environment.

TABLES & FIGURES:

Table I: Study Population		
Total Patient Number		1814
Mean Age in years (±SD)		57.4 [±SD 11.1]
Gender		**n [%]**
	Male	1205 [66.4 %]
	Female	609 [33.6 %]
Body Mass Index(BMI) (kg/m^2) [a]		
	Normal [<25]	608 [33.5 %]
	Pre-Obese [26-29]	210 [11.6 %]
	Obese [≥30]	425 [23.4 %]
RISK FACTORS		
Diabetes Mellitus		1073 [59.2 %]
Hypertension		980 [54 %]
Smoking	Current	892 [49.2 %]
	Non-smoker	665 [36.7 %]
	Ex-smoker	257 [14.1%]
Previous Myocardial infarction		187 [10.3 %]
Previous Angina		199 [11 %]
Family History		
	Coronary Artery Disease	1076 [59.3 %]
	Diabetes Mellitus	862 [47.5 %]
	Hypertension	802 [44.2 %]
	Cerebrovascular disease	344 [19 %]
CLINICAL VARIABLES		**Median [IQR]**
	Systolic Blood Pressure [mmHg]	129 [111-149]
	Diastolic Blood Pressure [mmHg]	80 [70-91]
	Admission Troponin T [ng/ml]	0.62 [0.16-3.61]
	Troponin T 24Hours [ng/ml]	2.56 [1.58-3.55]
	Haemoglobin [g/dL]	14.8 [11.5-17.0]
	Creatinine [umol/L]	90 [70-110]
	Total Cholesterol [mmol/L]	5.20 [4.39-6.02]
	Triglycerides [mmol/L]	1.68 [1.18-2.48]
	LDL Cholesterol [mmol/L]	3.26 [2.57-3.97]
Type of Infarct		**n [%]**
	ST-segment Elevation Myocardial Infarction (STEMI)	1400 [77.2 %]
	Non-ST-segment Elevation Myocardial Infarction (NSTEMI)	414 [22.8 %]
Site of Infarction [b]		**n [%]**
	Anterior	1223 [67.4%]
	Inferior	908 [50.1 %]
	Posterior	165 [9.1 %]
	High Lateral	82 [4.5 %]
Coronary Angiogram Findings [c]		**n=844 [% of those with Angiogram]**
	Triple vessel disease	385 [45.6%]
	Double vessel disease	219 [25.9 %]
	Single vessel disease	204 [24.2 %]
	Normal	36 [4.3 %]
Management Strategies [d]		
	PTCA +- Stent	176 [10 %]
	CABG	418 [23 %]
	Medical Management	274 [15 %]

a) Missing BMI variable in 571 participants
b) Some patients with combination of territories
c) 969 patients did not have coronary angiogram (54%)
d) 946 patients with missing variables for management strategies (52%)

Table II: Major Adverse Cardiovascular Events (MACE) or Death	
Patients with occurrence of MACE or Death	**n=524 [28.9%]**
Cardiac Failure	266 [14.7%]
Death	143 [7.9 %]
Cardiogenic Shock	70 [3.8%]
Atrial Arrhythmia	54 [3.0%]
Ventricular Arrhythmia	69 [3.8%]
Heart Block	38 [2.1%]
Cerebrovascular Accident	37 [2.0%]

Table III: Quartiles of Nt-proBNP	
Admission Nt-ProBNP	**Median [Interquartile Range]***
Quartile 1	75 [39-125]
Quartile 2	374 [263-546]
Quartile 3	1345 [964-1837]
Quartile 4	5993 [3578-10307]
Discharge Nt-ProBNP	**Median [Interquartile Range]***
Quartile 1	180 [92-270]
Quartile 2	668 [536-835]
Quartile 3	1671 [1334-2104]
Quartile 4	4965 [3354-9040]
*All measurements in pg/ml	

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Appendices

Appendix 1: The final Study Protocol (Include the final protocol which was given full approval by Brec and/or the postgrad office)…….. Page XVIII

Appendix 2: The Guidelines for Authorship for the Journal selected for submission of the manuscript …….page XXX

Appendix 3: Ethical approvals……..page XXXI

Appendix 1: The final Study Protocol (Include the final protocol which was given full approval by Brec and/or the postgrad office)

University of KwaZulu-Natal
College of Health Sciences
School of Clinical Medicine

Title: The prognostic value of Discharge Versus Admission N-Terminal-Pro Brain Natriuretic Peptide in patients with Acute Coronary Syndrome in a South African Regional Hospital

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JUNE 2016

EXECUTIVE SUMMARY:

The purpose of this retrospective observational study is to evaluate the prognostic significance of brain natriuretic peptide (BNP) levels obtained at the time of discharge in patients admitted to a coronary care unit with a diagnosis of an acute coronary syndrome. We will compare this to BNP measurements taken at the time of admission in order to evaluate which measurement provides the most useful information on 30-day survival.

Few studies have evaluated the most useful time to measure BNP in resource poor settings where serial measurements may not be feasible.

We will conduct a retrospective chart analysis of a cohort of patients admitted to a coronary care unit in a government hospital in the Province of KwaZulu-Natal, South Africa. Data will be obtained using inpatient notes as well as outpatient records to evaluate survival status at 30days after the index event.

We hope to impact the risk stratification of patients presenting with acute coronary syndrome.

THE PROTOCOL

TABLE OF CONTENTS

1. INTRODUCTION ……4

2. BACKGROUND AND LITERATURE REVIEW ……..5
2.1 Clinical problem ……5
2.2 Literature Review ……..5
2.3 Research question ……6

3. AIMS AND OBJECTIVES ……6

4. METHODS……7
4.1 Study Design ……7
4.2 Setting ……7
4.3 Participant Selection and Sampling Strategy ……...7
4.4 Data Collection and Statistical Analysis ……7

5. ETHICAL CONSIDERATIONS ……..8

6. REFERENCES……9

7. APPENDICES ……10

INTRODUCTION:

Brain natriuretic peptide (BNP) is a neuro-endocrine hormone released by cardiac myocytes in response to increased cardiac wall stress. In the circulation the biologically active 32 amino-acid BNP is separate from the n-terminal portion of the prohormone termed NT-proBNP. Physiological effects of BNP include diuresis, vasodilation, inhibition of renin and aldosterone production and of cardiac and vascular myocyte growth. BNP is cleared from plasma mainly through renal excretion. The half-life of NT-proBNP (70-120min) is considerably longer than that of BNP (20min).

Following acute myocardial infarction, there is increased synthesis of natriuretic peptides in both the infarcted and non-infarcted myocardial tissue. It has been shown that measurement of serum NT-proBNP as well as BNP provides powerful prognostic information for patients with acute coronary syndrome across all spectrums of disease. Prognostic utility of B-type natriuretic peptides applies to short term as well as long term outcomes.

Few studies have looked at the prognostic value of serial BNP measurements in acute coronary syndromes. In our environment with limited resources, it would be useful to identify the superiority of a single BNP measurement in providing the most significant prognostic information with regards to mortality in patients presenting with acute coronary syndromes.

1. BACKGROUND AND LITERATURE REVIEW

1.1 The Clinical Problem

Elevated levels of B-type natriuretic peptide (BNP) and the N-terminal fragment of its prohormone, N-terminal-pro-BNP (NT-proBNP) has been shown to be independent predictors of poor outcomes in patients with Acute Coronary Syndrome. There have been limited studies assessing the optimal time of measuring NT-proBNP levels as well as comparing admission to discharge NT-proBNP levels.

1.2 The Literature Review

A study of 60 patients admitted to a coronary care unit with Q wave acute myocardial infarction (AMI) measured serial blood samples for NT-proBNP at four intervals during hospital admission up to day 8 as well as a single measurement as an outpatient[(1)]. Although this study had a small sample size it demonstrated that BNP is elevated at all time points following AMI including outpatient follow up. BNP profile particularly following anterior AMI shows a biphasic response with a late rise in BNP around day 4. It has been demonstrated that BNP measured late during the admission was a strong predictor of poor outcomes.

Larger studies with single baseline measurements of BNP[(2)] have confirmed that mortality rates increase in a step wise fashion across increasing levels of BNP at presentation. It has been suggested that a threshold of 80pg/mL[(2, 3)] is also appropriate in patients with Acute coronary syndromes (ACS) as it is in patients with heart failure, as an indication of neurohormonal activation. Large studies with serial inpatient measurement of BNP have supported that a second later sample provides information about the further clinical course. Failure to decrease BNP levels at 72hrs after symptom onset or a further/new elevation in BNP is associated with worst outcomes[(4)]. Rapid decline in BNP may indicate responsiveness to therapeutic interventions[(4)]. Serial BNP measurements during long term follow up have yielded similar prognostic utility with persistently elevated BNP carrying the highest risk of death or new onset congestive heart failure (CHF)[(2, 3)].

There has been recent attempts at estimating optimum inpatient timing of BNP for prognostication but elevated BNP levels at all time points have proven to be statistically significant matched to patients with non-fatal outcomes[(5)].

Whilst there is no doubt from current literature as to the utility of BNP as a prognostic indicator for death or new CHF in both short and long-term follow up it is yet unclear which single measurement would derive the most utility in resource poor environments where serial measurement of BNP may not be possible.

1.3 The Research Question

Can discharge NT-proBNP be used as a single measure to risk stratify patients treated with Acute Coronary Syndrome, as opposed to admission NT-proBNP.

2. AIMSAND OBJECTIVES

The aim of this study is to establish if discharge N-Terminal proBrain Natriuretic Peptide (NT-proBNP) is superior to admission NT-proBNP in predicting 30day mortality in patients with acute coronary syndrome admitted to a resource poor environment

The objectives are

- To compare the prognostic significance of admission versus discharge NT-proBNP in predicting adverse outcomes in patients with acute coronary syndrome.
- To classify which patients are at greatest risk of poor outcomes based on admission versus discharge NT-pro BNP.
- To assess whether a single BNP level obtained at the time of discharge can be used to guide clinical course and outcomes

3. METHODS

3.1 Study Design

This is a Quantitative Retrospective Observational study

3.2 Setting

Our study is based at RK Khan Hospital; A regional hospital in KwaZulu-Natal Province of South Africa. Information will be derived from a computerized database comprising patients admitted to the coronary care unit.

3.3 Participant Selection and Sampling Strategy

Inclusion Criteria

- All patients admitted with a confirmed diagnosis of Acute Myocardial Infarction based on standard criteria
- Only patients who have both admission and discharge NT-proBNP measurements will be included in the study.

Exclusion Criteria

- Patients with unstable angina will not be included
- Patients with missing laboratory variables for NT-proBNP will not be included

3.4 Data Collection and Statistical Analysis

Please refer to the attached appendix for a detailed description of all variables that will be assessed in all participants.

- Patient anonymity will be maintained by using computer numbers for all patients included in the study

Professor Ben Sartorius will be performing all statistical analyses.

Sample size and power:

- The anticipated sample size will be >2000 patients after application of the eligibility criteria.
- A minimum sample size of 2000 achieves 80% power to detect a very small effect size (W) < 0.10 using a 1 degree of freedom Chi-Square Test with a significance level (alpha) of 0.05 or 5%.
- Similarly a sample size of 1000 achieves 80% power to detect a very small effect size (Cohen's d) (Cohen, 1988) of <0.15 based on a standard t-test approach i.e. comparisons of differences of means of a continuous variables such as NT-proBNP by dichotomous outcome i.e. mortality and/or Major Adverse

Cardiovascular Events (MACE). This assumes a significance level (alpha) of 0.05 or 5%.
***Cohen, Jacob. 1988. Statistical Power Analysis for the Behavioral Sciences, Lawrence Erlbaum Associates, Hillsdale, New Jersey.

- These sample size calculations were performed using PASS 12 software (Hintze, J. (2013). PASS 12. NCSS, LLC. Kaysville, Utah, USA. www.ncss.com).

Data analysis plan:
Data will be analysed using Stata 13.1 SE. Continuous variables (e.g. admission and discharge BNP were summarized using mean and standard deviation (SD). If these data were skewed then medians and interquartile ranges will be presented instead. Categorical data will be presented using frequency tables. Association between categorical variables will be assessed using the standard Pearson's chi-square ($\chi 2$) test. If expected cell count in the cross tabulation contains fewer than 5 observations (sparse numbers) then the Fishers exact test will be employed. The standard t-test was used to compare the mean of continuous explanatory variables (such as NT-proBNP) by dichotomous outcome classification. If the normality assumption is not upheld, then the non-parametric equivalent Wilcoxon rank-sum test will be used instead. Admission and discharge NT-proBNP will be tested for associated with mortality and MACE using bivariate and multivariable logistic regressions to account for other risk factors and/or confounding variables. Coefficients will be exponentiated to represent odds ratios [ORs] and 95% confidence intervals. Model fit (adequacy) will be assessed using goodness of fit tests, variance inflation factors [VIFs] and predictive performance. An adjusted p-value of <0.05 will be considered statistically significant.

4. ETHICAL CONSIDERATIONS

We will be using data extrapolated from a computerized data bank.
Patient confidentiality will be maintained at all times by assigning computer-generated numbers to all study participants.

REFERENCES:

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2. de Lemos JA, Morrow DA, Bentley JH, Omland T, Sabatine MS, McCabe CH, et al. The prognostic value of B-type natriuretic peptide in patients with acute coronary syndromes. New England Journal of Medicine. 2001;345(14):1014-21.
3. Morrow DA, de Lemos JA, Blazing MA, Sabatine MS, Murphy SA, Jarolim P, et al. Prognostic value of serial B-type natriuretic peptide testing during follow-up of patients with unstable coronary artery disease. Jama. 2005;294(22):2866-71.
4. Heeschen C, Hamm C, Mitrovic V. N-terminal pro-B-type natriuretic peptide levels for dynamic risk stratification of patients with acute coronary syndromes. ACC Current Journal Review. 2005;14(3):16-7.
5. Nørgaard BL, Terkelsen CJ, Riiskjær M, Holmvang L, Grip L, Heickendorff L, et al. Risk prediction in acute coronary syndrome from serial in-hospital measurements of N-terminal pro-B-type natriuretic peptide. Acute cardiac care. 2008;10(3):159-66.

STUDY DATA SHEET

PATIENT NUMBER:	

DEMOGRAPHIC CHARACTERISTICS

AGE (years):				
Gender:	MALE	☐	FEMALE	☐

CLINICAL VARIABLES

Waist Circumference (cm):				
Blood Pressure:	Systolic	☐	Diastolic	☐
Heart rate:				
Type of Infarct:	STEMI	☐	NSTEMI	☐
Site of Infarct:	Anterior	☐		
	Anterolateral	☐		
	Anteroseptal	☐		
	High Lateral	☐		
	Posterior	☐		
	Inferior	☐		
Heart Failure	yes	☐	no	☐
	Killip Classification:	Killip I	☐	
		Killip II	☐	
		Killip III	☐	
		Killip IV	☐	

ECHO FINDINGS:					
RISK PROFILE:					
	Hypertension				
	Diabetes				
	Smoking				
	Hypercholesterol aemia				
	Family history of Vascular Disorder				
	1. Premature CAD				
	2. Hypertension				
	3. Diabetes				
	4. CVA				
LABORATORY VARIABLES:					
NT-proNT-PROBNP:	Admission				
	Discharge (+- Day5)				
Troponin T	Admission:				
	24 Hours:				

	Discharge (+- Day5)	
Urea (mmol/L)		
Creatinine (µmol/L)		
Lipid Profile	Total cholesterol	
	Triglycerides	
	HDL	
	LDL	

IN-HOSPITAL & 30-DAY COMPLICATIONS				
Recurrent MI	Yes		No	
Recurrence of Angina	Yes		No	
Heart Failure	Yes		No	
Atrial Fibrillation	Yes		No	
Ventricular Dysrhythmia	Yes		No	
Cardiogenic Shock	Yes		No	
Death	Yes		No	

CORONARY ANGIOGRAM	
Single Vessel Disease	
Double Vessel Disease	
Triple Vessel Disease	
CARDIAC REVASCULARIZATION	
PCI + Stent	
CABG	
Medical Management	

Appendix 2: The Guidelines for Authorship for the Journal selected for submission of the manuscript

SA HEART® IS AN OFFICIAL JOURNAL OF THE SOUTH AFRICAN HEART ASSOCIATION AND APPEARS ON A QUARTERLY BASIS

2021 Volume 18 Number 3

sa heart

Instructions for authors

SA Heart® publishes peer reviewed articles dealing with cardiovascular disease, including original research, topical reviews, state-of-the-art papers and viewpoints. Regular features include an ECG quiz, image in cardiology and local guidelines. Case reports are considered for publication only if the case or cases are truly unique, incorporates a relevant review of the literature and makes a contribution to improved future patient management.

Publication policy

Articles must be the original, unpublished work of the stated authors. Written permission from the author or copyright holder must be submitted with previously published material including text, figures or tables. Articles under consideration elsewhere or previously published (except as abstracts not exceeding 400 words) may not be submitted for publication in SA Heart®. On acceptance transfer of copyright to the South African Heart Association will be required. No material published in SA Heart® may be reproduced without written permission. Permission may be sought from the Editor (Email: ntobeko.ntusi@uct.ac.za).

Disclosures

Authors must declare all financial disclosures and conflicts of interest in the cover letter and on the title page of the manuscript.

Ethics

All studies must be in compliance with institutional and international regulations for human and animal studies such as the Helsinki declaration (2008) (https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects) and the South African MRC ethics guidelines (https://www.samrc.ac.za/research/ethics/guideline-documents). Human studies require ethics committee approval and informed consent which must be documented in your manuscript. Animal studies require ethics committee approval and must conform to international guidelines for animal research. Compliance with these requirements must be documented in your manuscript.

Content

1. Title page: It should contain the title of the manuscript, the names of all authors in the correct sequence, their academic status and affiliations. If there are more than 4 authors, the contribution of each must be substantiated in the cover sheet. The main author should include his/her name, address, phone, fax and email address.
2. Authors are solely responsible for the factual accuracy of their work.
3. Articles should be between 3 000 and 5 000 words in length.
4. A 200-word abstract should state the main conclusions and clinical relevance of the article.
5. All articles are to be in English.
6. Abbreviations and acronyms should be defined on first use and kept to a minimum.
7. Tables should carry Roman numeral, I, II etc., and figures Arabic numbers 1, 2 etc.
8. References should be numbered consecutively in the order that they are first mentioned in the text and listed at the end in numerical order of appearance. Identify references in the text by Arabic numerals in superscript after punctuation, e.g. …trial.[13]

The following format should be used for references:

Articles
Kaplan FS, August CS, Dalinka MK. Bone densitometry observation of osteoporosis in response to bone marrow transplantation. Clin Orthop 1993;294:73-8. (If there are more than six authors, list only the first three followed by et al.).

Chapter in a book
Young W. Neurophysiology of spinal cord injury. In: Errico TJ, Bauer RD, Waugh T (eds). Spinal Trauma. Philadelphia: JB Lippincott; 1991:377-94.

Online media
Perreault, L. (2019). Obesity in adults: Role of physical activity and exercise. UpToDate. Retrieved January 12, 2020, from https://www.uptodate.com/contents/obesity-in-adults-role-of-physical-activity-and-exercise

9. Articles are to be submitted on the online SA Heart® platform https://tinyurl.com/y9prlopt. The text should be in MS Word. Pages should be numbered consecutively in the following order wherever possible: Title page, abstract, introduction, materials and methods, results, discussion, acknowledgements, tables and illustrations, references.
10. Where possible all figures, tables and photographs must also be submitted electronically. The illustrations, tables and graphs should not be imbedded in the text file, but should be provided as separate individual graphic files, and clearly identified. The figures should be saved as a 300 dpi jpeg file. Tables should be saved in a MS Word or PowerPoint document. If photographs are submitted, two sets of unmounted high quality black and white glossy prints should accompany the paper. Figures and photographs should be of high quality with all symbols, letters or numbers clear enough and large enough to remain legible after reduction to fit in a text column. Each figure and table must have a separate self-explanatory legend.
11. Remove all markings such as patient identification from images and radiographs before photographing.
12. Include 3 challenging questions on the content of the manuscript relating to the key messages. The questions will be included in a questionnaire for CPD accreditation purposes. Please supply each question with a choice of 4 - 5 possible answers of which only one is correct (multiple correct answers not allowed) and highlight the correct answer. Please do not supply questions with a simple yes/no option.

Submission of manuscripts

The manuscript should be submitted online on the SA Heart® Journal open access platform https://tinyurl.com/y9prlopt. Follow further instructions on this website.

Appendix 3: Ethical approvals

UNIVERSITY OF KWAZULU-NATAL
INYUVESI YAKWAZULU-NATALI

19 August 2016

Dr NN Zibi (202511184)
Department of Medicine
School of Clinical Medicine
NRMSM
zibitjie@yahoo.com

Title: The prognostic value of discharge versus admission N-Terminal-proBrain natriuretic peptide in patients with acute coronary syndrome in a South African regional hospital.
Degree: MMEd
BREC Ref No: BE419/16

EXPEDITED APPLICATION

A sub-committee of the Biomedical Research Ethics Committee has considered and noted your application received on 12 July 2016.

The conditions have been met and the study is given full ethics approval and may begin as from 19 August 2016.

This approval is valid for one year from **19 August 2016.** To ensure uninterrupted approval of this study beyond the approval expiry date, an application for recertification must be submitted to BREC on the appropriate BREC form 2-3 months before the expiry date.

Any amendments to this study, unless urgently required to ensure safety of participants, must be approved by BREC prior to implementation.

Your acceptance of this approval denotes your compliance with South African National Research Ethics Guidelines (2004), South African National Good Clinical Practice Guidelines (2006) (if applicable) and with UKZN BREC ethics requirements as contained in the UKZN BREC Terms of Reference and Standard Operating Procedures, all available at http://research.ukzn.ac.za/Research-Ethics/Biomedical-Research-Ethics.aspx.

BREC is registered with the South African National Health Research Ethics Council (REC-290408-009). BREC has US Office for Human Research Protections (OHRP) Federal-wide Assurance (FWA 678).

The sub-committee's decision will be **RATIFIED** by a full Committee at its next meeting taking place on **13 September 2016.**

We wish you well with this study. We would appreciate receiving copies of all publications arising out of this study.

Yours sincerely

[redacted]

Professor J Tsoka-Gwegweni
Chair: Biomedical Research Ethics Committee

cc supervisor: ranjith@lantic.co.za
cc postgraduate administrator: konar@ukzn.ac.za