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# Prognostic value of transient ischemic dilatation (TID) in patients with normal single photon emission computed tomography (SPECT) myocardial perfusion imaging (MPI)

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# PROGNOSTIC VALUE OF TRANSIENT ISCHEMIC DILATATION (TID) IN PATIENTS WITH NORMAL SINGLE PHOTON EMISSION COMPUTED TOMOGRAPHY (SPECT) MYOCARDIAL PERFUSION IMAGING (MPI).

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**A research report submitted to the Faculty of Health Sciences, University of the Witwatersrand.**

**In fulfilment of the requirements for the degree of**

**Master of Medicine**

**In the branch of Nuclear Medicine**

**April 2016**

**Candidate's declaration**

I, Isaac Olusola Fadiji declare that this research report is my work.

This research report is being submitted for the degree of Master of Medicine in the University of the Witwatersrand, Johannesburg.

It has not been submitted before for any degree or examination at this or any other University.

Dr. Fadiji Isaac Olusola

8th April, 2016

Master of Medicine in the branch of Nuclear Medicine

**Dedication**

**My family:** wife; Mobolaji and children; Toluwalope, Temiloluwa, Tifeoluwa. Thank you for your love, support, prayers and understanding. You are my pillars and source of joy.

**My parents**: Thank you for your support and prayers, it avails much.

**International Atomic Energy Agency (IAEA), Federal Government of Nigeria and University College Hospital Ibadan**: Thank you for the financial support without which it would have remained a mirage.

My profound appreciation goes to the almighty God for the gift of life, wisdom and good health. You are my shield and captain of my soul. To you be all the glory.

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**Prognostic value of transient ischemic dilatation (TID) in patients with normal single-photon emission computed tomography (SPECT) myocardial perfusion imaging (MPI)**

**Abstract**

**Objectives:** This study evaluated the clinical significance of an isolated transient ischemic dilatation (TID) in the otherwise normal or relatively normal single photon emission computed tomography (SPECT) myocardial perfusion imaging (MPI) in determining the risk of future cardiac events.

**Background**: the prognostic value of TID in patients with otherwise normal SPECT MPI has been a subject of controversy among clinicians. Therefore, there is no consensus on how best to manage this patient group of patients.

**Methods:** From a database of 4000 consecutive patients who underwent stress-rest MPI studies over a 13 year period (2000 -2013) at department of Nuclear Medicine, University of the Witwatersrand academic hospital, Johannesburg. 123 patients without known cardiac history of coronary artery disease and had normal or relatively normal SPECT MPI but TID > 1.21 were identified (study group 1). 41 patients, from the study group 1, with valid

telephone contacts and hospital records were interviewed to determine the prevalence of cardiac events. The images were retrieved, reviewed and re-processed by a 4th year Nuclear Medicine registrar to ensure they were rightly called. Both the telephone interviewer and the imaging analyst were blinded to the patients' clinical data.

**Results:** The prevalence of TID in a normal or relative normal SPECT MPI was 4%. There were 9 (21.9%) cases of angina, 2 (4.9%) cases of revascularization and 4 (9.8%) cases of myocardial infarction. Other independent predictor of cardiac events were; diabetes, summed stress score and summed rest score.

**Conclusion:** TID in the setting of normal or relatively normal SPECT MPI may signify a prognosis that is not good and may be a predictor of future cardiac events.

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**Nomenclature**

TID – Transient Ischemic Dilatation

SPECT – Single Photon Emission Computed Tomography

MPI – Myocardial Perfusion Imaging

CAD – Coronary Artery Disease

LV – Left Ventricle

LVCD – Left Ventricular Cavity Dilatation

LVEF – Left Ventricular Ejection Fraction

TI – Thallium

Tc-99m – Technetium 99 metastable

SSS – Summed Stress Score

SRS – Summed Rest Score

SDS – Summed differential Score

MI – Myocardial Infarction

EDV – End Diastolic Volume

ESV – End Systolic Volume

PCI – Percutaneous Coronary Intervention

## Introduction

Myocardial ischemia that results in ischemic heart disease is one of the leading causes of death all over the world. It is believed to account for 6.3 million deaths annually (1).

Over the past three decades, myocardial perfusion imaging (MPI) has evolved as a powerful imaging tool for the evaluation of coronary artery disease (CAD). The blood flow-dependent uptake of radiotracer allows for the assessment of regional myocardial perfusion and provides both diagnostic and prognostic information (2-4). Furthermore, other parameters including pulmonary Thalium-201 ($^{201}$Tl) chloride and left ventricular (LV) dilatation in post stress MPI images commonly known as transient ischemic dilation (TID) also have been shown to provide important diagnostic and prognostic information (5, 6).

Transient ischemic dilatation (TID) of the left ventricle post stress single photon emission computed tomography (SPECT) radionuclide MPI is considered to reflect myocardial ischemia that is sufficient enough and extensive to cause visually apparent left ventricular enlargement on post-stress relative to rest images (7-10).

There are thriving literature on the significance of TID as a marker of severity and extent of CAD in patients with concomitant MPI perfusion defects (11-13) and it has also shown to imply increased risk for cardiovascular events (14-16). However, the significance of TID as an isolated finding in a normal (with no perfusion defect) or relatively normal (with minimal perfusion defect) MPI is still a subject of controversy. Therefore, there is no consensus on how best to manage this group of patients.

The aim of this study is to assess whether TID as an isolated finding in normal or relatively normal MPI confers any prognostic value in determining future cardiac events; hard (cardiac death or myocardial infarction) or soft events; angina and revascularization.

## Study Objectives

### Primary objectives:

1. To determine the prevalence of TID in a normal or relatively normal MPI in our clinical setting.
2. To determine the prognostic value of an isolated TID in a normal or relatively normal MPI

### Secondary objectives:

1. To ascertain the type of intervention that was done to those patients that presented with cardiac events.
2. To determine if there is significant association between:
    a. Age and occurrence of cardiac event
    b. gender and occurrence of cardiac event
    c. race and occurrence of cardiac event
    d. cardiac risk factors and occurrence of cardiac event
    e. Degree of TID and occurrence of cardiac event
    f. Mode of stress and occurrence of cardiac event

g. Stress ischemic ECG changes and occurrence of cardiac event

h. LVEF and occurrence of cardiac event

## Literature review

Myocardial ischemia as a result of ischemic heart disease has been found to be one of the leading causes of all death all over the world. It is believed that about six million people die of it every year (1).

Myocardial perfusion imaging has evolved in the last thirty years as a powerful imaging tool for the evaluation of CAD. The blood flow and uptake pattern of radiotracer used in imaging allows for the assessment of regional myocardial perfusion and provides both diagnostic and prognostic information (2 -4). Also, other parameters including pulmonary $^{201}$Tl- chloride uptake and left ventricular cavity dilatation (LVCD) that is commonly referred to as TID also have been shown to provide important diagnostic and prognostic information (5, 6).

Transient ischemic dilation (TID), as detected by SPECT-MPI refers to the enlargement of LV lumen in post-stress scintigraphic images when compared to the resting images. It can also be referred to as LVCD (7).

Transient ischemic dilatation of the left ventricle on single photon emission computed tomography myocardial perfusion imaging (MPI) is adjudged to reflect myocardial ischemia that is severe enough and extensive to cause visually apparent left ventricular enlargement on post-stress relative to rest images (7 - 10).

Initial clinical MPI studies were carried out with planar $^{201}$Tl-201 imaging. They showed that the number of reversible perfusion defects and the presence of abnormal lung $^{201}$TI-201 uptake were the most important variables in identifying high risk patients with multi-vessel disease who had an increased risk of cardiac death or non-fatal myocardial infarction (17 - 20). Those with normal findings on MPI had a combined subsequent death or non-fatal MI rate of less than 1% per year (21).

Early studies on MPI were done with planar imaging technique, but this has been overtaken by SPECT imaging technique with the use of technetium-99m ($^{99m}$Tc) labelled perfusion agents, which are $^{99m}$Tc sestamibi and tetrofosmin. The transformation to SPECT with these technetium based imaging agents

permitted gating of images and calculation of left ventricular ejection fraction (LVEF) as well as the end diastolic and systolic volumes, and the quantitation of

regional wall motion or thickening abnormalities. These functional variables provide additional prognostic information to perfusion variables (22).

Semi-quantitation of perfusion abnormalities using parameters such as summed stress score (SSS), which is an assessment of extent and severity of coronary artery disease (CAD), summed rest score (SRS), an assessment of infarction and ischemia and summed differential score (SDS), which indicate the burden of ischemia, have emerged as more objective tools in the determination of extent and severity of hypo perfusion or reversibility. These variables were derived from the well-accepted 17- segment model for SPECT (23)

The percentage of LV ischemia and the total ischemic perfusion deficit were other prognostic parameter. Those with >10% LV ischemia seemed to have a better outcome with revascularization than medical treatment (24).

Vasodilators pharmacological stressors for MPI in patients that are unable to adequately exercise also provide prognostic information similar to that with

exercise MPI (25). However, the cardiac events rate with either normal or abnormal findings on pharmacological stress SPECT MPI scans were higher than seen with post exercise stress. This was attributed to the fact that patients referred for pharmacological stress were a clinically higher risk population with co-morbidities (26).

The concept of transient ischemic dilatation was first described in a case report of planar $^{201}$TI imaging by Stolzenberg (27). The author described the phenomenon of transient stress-induced LV dilatation appearing on post-stress MPI compared with resting scans. He stated that 'The size differential can be used as an adjunct in the interpretation of borderline relative changes in perfusion seen in coronary artery disease or in elimination of some false-negatives secondary to balanced lesions'. This initial observation was based on visual assessment. However, the term transient ischemic dilatation, as well as its abbreviation of TID as used today was first mentioned by Weiss et al (2) in

their laboratory, in which TID was quantified as the stress-rest ratio of manually drawn regions of interest fitting the LV area of anterior-view, planar stress-redistribution $^{201}$TI myocardial perfusion images of 89 patients who also underwent coronary angiography.

Evaluation of TID may be purely visual, or based on calculation of TID ratio between stress and rest images. Manual or automatic definition of the

myocardial wall boundary is possible (epicardial or endocardial LV edges) in a non-gated images to calculate TID ratio (27, 28). There are few semi-automatic measures and automatic practical algorithms for the quantification of the TID ratio. Quantitative Perfusion SPECT (QPS) from Cedars Sinai Medical Centre and Emory Cardiac Toolbox (ECTb) are two current automatic methods which are use for the calculation of endocardial volumes of the LV from three dimensional images (1, 27, 29 - 31). Recently Heston et al (4) reported that by calculation of end systolic volumes (ESV) and end-diastolic volumes (EDV) using gated images, the relative contributions of each of the TID ratio may be estimated. Hence, they suggested that TID ratio could be estimated by the ratio of stress (ESV x 5 + EDV)/Rest (ESV x 5 + EDV).

Transient ischemic dilatation can be observed after exercise or pharmacological stress using stress/redistribution $^{201}$TI and single day or 2-day $^{99m}$Tc MPIs (27). However, the most important issue is to determine the cut-off value for an abnormal TID ratio. It has been well documented in the literature that the cut-off value for abnormal TID ratio varies widely. This is

said to vary with patient population, gender, stressing modality, radiopharmaceutical, time from injection to imaging after stress, injected dose of the radiopharmaceutical on the rest and stress studies and imaging protocol. Technical aspect of imaging such as the image matrix size, zoom and slice selection also may influence the calculation of TID (27).

The cut of value reported by various researchers range from 1.12 to 1.40 (3, 4, 27, 32 - 34). Most studies have reported that in male patients where normal LV

End diastolic volume (EDV) is >100mls in a dipyridamole pharmacological stressing two-day protocol that uses $^{99m}$Tc tracers, a TID ratio of > 1.19 is most likely abnormal (3, 4, 27, 34, 35)

Transient ischemic dilatation being considered as a consequence of ischemic heart disease has to be properly investigated as annual death arising from myocardial ischemia accounts for more than six million (5). Transient ischemic dilatation required an accurate investigation to assess if it has any prognostic value for the development of hard events (cardiac death or non-fatal myocardial infarction) or soft events (angina or revascularization) especially in the setting of normal or relative normal (SSS < 4) MPI (36).

Several pathophysiological mechanisms have being proposed to explain the presence of TID in a MPI, including 'actual stress induced transient cavity dilatation (2), a lack of subendocardial tracer uptake in the extensive subendocardial ischemia without true anatomic cavity enlargement' (3). Furthermore, a stress induced decrease in LV systolic function from stunning that appears as TID in SPECT images (1, 4). Regardless of the mechanism of the phenomenon, the presence of TID in patients with an abnormal MPI study has been shown to be a marker of severe and extensive CAD (11 -13) and in a few studies it confers increased risk for cardiovascular events (14 -16). However, the significance of TID in patients with an otherwise normal or relatively normal MPI study is not well understood. Several groups of authors have conflicting reports on this condition. Therefore, it remains unclear how best to manage these patients.

Aiden Abidov et al. 2003 (37) evaluated the prognostic value of TID of the left ventricle in patients with normal stress myocardial perfusion SPECT. They studied two groups of patients; the first group with 1560 patients with normal stress MPI and the second one with 2037 patients showing both normal and

minimal defects on MPIs. The patients were all followed-up for a period of two years for the presence of hard events (cardiac death or myocardial infarction),

soft event (revascularization) and total events; which is the combination of both the hard and soft events. They found that TID was a predictor of hard, soft and total events. They concluded that an entirely normal stress MPI study with a TID does not always imply an excellent prognosis and that patients with otherwise normal MPI, TID was an independent and incremental prognostic marker of total events even after significant clinical variables; age, typical angina and diabetes has been accounted for.

In another study that used the semi-quantitative method, Mario Petretta et al. (38) looked at 242 diabetic patients and found an abnormal TID in 6/58

patients with summed stress score (SSS) < 3, 8/56 patients with SSS between 3 and 7 and 18/128patients with SSS ≥ 8. They concluded that TID has prognostic value for predicting severe CAD over clinical data or clinical data and SSS score alone in diabetic patients.

Recent study by Rami Doukky et al. (39) followed 1236 patients with normal MPI for 2 years. They divided patients in their final analysis into two groups; group 1, consisted of 76 patients with normal MPI but with TID and group 2,

consisted of 1160 patients with normal MPI without TID. They found out that TID is a predictor of hard cardiac events. The annualized hard cardiac event

rates; MI was 5.1% vs 0.3% and cardiac death was 7.7% vs 0.7% in the TID+ group vs TID- group respectively. Furthermore, they observed that the presence of co-morbidity such as diabetes mellitus conferred a greater risk to development of cardiac events as compared with patients no diabetes mellitus. They concluded that among patients with TID in otherwise normal MPI, diabetes was associated with a significantly greater rate of cardiac death or MI when compared to the patients without diabetes (23.1% vs 0.7%).

Other studies however reported no increased in cardiac event rate associated

with TID in patients with normal or relatively normal MPI study (40 - 42)

In-fact Baddi et al. (40) analysed 1200 patients with normal MPI who were followed for a period of four years. 25 of these patients with TID had no report of death, no cardiac events or hospitalization and these patients were symptoms free.

In another study, Hakeem et al. (41) in their study of 1003 patients with normal MPI (SSS <4), 3.8% of these patients had TID. These patients were followed for a period of 2 years. There was no increase in all-cause mortality, although there was a trend towards increase cardiac events (21% Vs 10%).

More recently, a study by Valdiviezo et al. (42) reported that 28 patients with TID, but otherwise normal MPI, had a similar CAD burden to a cohort without TID. They inferred that TID noted on SPECT MPI scans without any concomitant perfusion defects does not predict multi-vessel CAD. These investigators also followed a cohort of 593 patients with TID, but otherwise normal MPI for an average of three and half years and did not find any difference in survival compared to patients without TID.

## Materials and Methods

### Study design and data

This is a retrospective study. The protocol (M130832) was approved by the ethics committee of the University of the Witwatersrand in Johannesburg.

We reviewed the database of 4000 consecutive patients that were referred for rest – stress MPI study from January 2000 to December 2013 in the Nuclear Medicine department at two hospitals - Charlotte Maxeke Johannesburg Academic Hospital and Chris Hanni Baragwanantha Hospital, Soweto.

The inclusion criteria was all patients without previously known coronary history (no myocardial infarction, no coronary revascularization, and no cardiomyopathy), who had normal or relatively normal perfusion images on initial clinically read and whom TID >1.21 has been entered into the data base. A TID of 1.21 was considered the upper limits of normal according to the published literature (3, 4, 32, 28, 34 - 35). We excluded all patients with cardiomyopathy, left bundle branch block or pacemaker perfusion patterns,

patients < 18 years of age at the time of initial scan and for those who had

numerous tests during the time interval, only the first test was used. A total of 123 patients were identified for analysis.

Of this group, we were able to contact 41 patients for telephonic interview and the other 82 patients could not be contacted telephonically and their case file could not not be retrieved from the referring clinics, hence were excluded from further analysis. We therefore analysed data of the above-mentioned 41 patients to determine the prevalence of cardiac events.

We recorded the time of occurrence of cardiac events from the time of scan, as occurrence of events within 1 year following scan or more than 1 year following scan. The recorded cardiac events were angina, myocardial infarction or revascularization.

Efforts were made to retrieve and reprocess the Images of these 41 patients to ensure that the images were truly normal in terms of perfusion (SSS < 4) (37). We retrieved from the archive images of 37 out of 41 patients for review, images of four patients could not be found. The images were reviewed and reprocessed by myself and a fourth year registrar who checked the same images for agreement.

Telephone interview were conducted with patients by a 3rd year Nuclear Medicine registrar blinded to the patients' clinical and scintigraphic results to avoid bias. However, I developed the questionnaire used for the purpose. Verbal consent was obtained from the patients prior to the telephonic interview (Appendix 1). Specific questions, based on a structured questionnaire (Appendix 2), were asked regarding incidence of hard or soft cardiac events within one year after being diagnosed with TID and for those who did not develop any cardiac event during the one year period whether they developed cardiac events subsequently.

**Cardiovascular risk factors**

Hypertension was defined by blood pressure of ≥ 140mm Hg systolic or ≥ 90 mm Hg diastolic or use of antihypertensive medication. Diabetes mellitus was defined as fasting glucose ≥ 6.9 mmol/l or use of antidiabetic treatment. Hyperlipidaemia was defined as a total cholesterol level of ≥ 5.2 mmol/l or use of lipid-lowering medication. Patients were considered smokers only if current tobacco use was stated. A positive family history was defined as a first-degree relative with a history of premature myocardial infarction or sudden coronary death regardless of age.

**Stress Protocol**

Wherever possible, beta blockers and calcium channel antagonists were terminated 48 to 72 hours before testing and nitrates at least 6 hours before testing. Patients were instructed not to consume coffee or other products containing caffeine for 24 hours before the test. After an overnight fast, the patients underwent either a physiological stress (Bruce protocol/Modifield Bruce protocol) or a pharmacological stress test (persantine, adenosine or dobutamine).

For dobutamine and physiological stress test, the end points were either achieving at least 85% of the target heart rate (220 – age in years), but not > 100% or patients developing severe chest pain clinically and with compactible ECG changes.

Near maximal physiological stress, between 740 MBq to 1,110 MBq of 99mTc-sestamibi were injected intravenously. Patients then continued the exercise protocol for an additional 1 -2 minutes, followed by a 1 minute cool-down period during which the patient walked at 1.6km/h on a level incline. Post stress images were started at approximately 1 hour after tracer injection.

For persantine and adenosine stressing, the end points were either complete intravenous infusion over 4 minutes for persantine and over 6 minutes for adenosine at infusion rate of 140 μg/kg/min or patients developing severe chest pain clinically with compactible ECG changes.

Approximately 740 MBq to 1100 MBq of 99mTc-sestmibi were injected intravenously at 7 minutes (3 minutes after completion of infusion for persantine) while 740 MBq to 1100 MBq of 99mTc-sestmibi were injected at 3 minutes following intravenous infusion of adenosine and adenosine infusion is continued for another 3 minutes. Post stress images were started at approximately 1 hour after tracer injection.

During both types of stresses, the heart rate, blood pressure and 12-lead Electrocardiogram (ECG) were recorded at baseline and every minute thereafter. The ECGs were monitored continuously for the development of arrhythmia or ischemic ST-segment deviation. Blood pressure was measured and recorded at rest, at the end of each stress stage and at peak stress.

**Imaging protocol and interpretation**

All patients underwent 2-day stress-rest 99mTc-sestamibi protocol. Patients were stressed on day one and a rest study was done on day two. Approximately 1 hour following intravenous injection of the tracer for both stress and rest phases, images were acquired with a rotating dual head gamma camera (Infinia Hawkeye, GE Medical Systems). The two heads were place in an L-shaped configuration. Images were acquired with a low energy high resolution collimator, using 180-degree semi-circular orbit from 45-degree right anterior oblique (RAO) to 45-degree left posterior oblique in a step and shoot mode (32 projections, 25 seconds per projection), 20 % symmetric energy window centred at 140 KeV and gating at 8 frames/cardiac cycle. Images were stored in 64 x 64 matrices in the computer. All patients were placed in supine position with arms over their heads for rest and stress phases. Additional prone images were acquired during stress phase. Images were reconstructed with a filtered backprojection using a Butterworth filter. Paired images of stress and rest short axis, vertical long axis and horizontal long axis slices were generated for visual analysis.

These images were semi quantitatively interpreted by myself and a fourth year

registrar who was blinded to patients' clinical and outcome data. On a 17 segment model, the segmental radiotracer activity in both the stress and rest scans were scored according to the 5 point scale (0: normal; 1: mild; 2: moderate; 3: severe; 4: absent) (43). The segmental scores were summed to generate summed rest score (SRS) and summed stress scored (SSS). The normal myocardial perfusion was defined as SSS ≤4.

**TID measurement**

TID ratio was manually determined by measuring the greatest diameter across the endocardial boundaries of the left ventricles on the corresponding rest and stress well aligned images as displaced in the short axis. This was done by drawing a horizontal line across the largest diameter of the left ventricles on the corresponding rest and stress images. The values got were used to calculate the TID ratio.

**Outcome determination**

Two methods for ascertaining outcome of events were uniformly applied: firstly, review of patients' hospital records at the referring physician clinics and secondly, telephone interviews were conducted with patients. The cardiac

events assessed were: cardiac death, myocardial infarction, angina or coronary revascularization.

**Variable definition/Data Analysis**

Categorical variables were created for: gender (0 = male; 1 = female); race (0 = Black; 1 = White; 2 = Indian; 3 = Coloured); presence of cardiac risk factors (0 = no; 1= yes); stress protocol (0= physical; 1 = pharmacological); stress ECG findings (0 = negative; 1 = positive; 2 = equivocal; 3 = not known); indication for MPI (0 =diagnosis; 1 = chest pain; 2 = extent and severity of CAD; 3 = no indication); SRS (0 = perfectly normal perfusion; 1 – 3 = mild perfusion defect); SSS (0 = perfectly normal perfusion; 1 – 3 = mild perfusion defect); types of events (0 = no event; 1 = angina; 2 = MI; 3 = revascularisation; 4 = not known);

time to events (0 = < 6 months; 1 = 6 - 12 months; 2 = > 12 months); intervention (0= medical treatment; 1 = PCI; 2 = CABG); and degree of TID (0 = 1.22 – 1.25; 1 = 1.26 – 1.50; 2 = 1.51 – 1.75; 3 = not known). Age, LVEF rest and LVEF stress were measured as continuous variables. In the further analysis, the variable – type of event – was dichotomized as 0 = no event, 1 = event. We treated this variable - type of event – as an outcome/dependent variable in all the analyses.

**Statistical analysis**

The statistical analysis employed STATA v.12 statistical software.

Descriptive results were presented as averages and interquartile range for continuous variables. We checked for normality of continuous variables using Shapiro-Wilk test. Categorical variables were summarized as frequencies and percentages. To assess the differences between continuous variables (age, LVEF, stress and LVEF, rest), not normally distributed, and independent variables, Kruskal-Wallis test (where the independent variables were three or more or Mann-Whitney where the independent variables were two) was used. To compare frequencies of different categorical variables with independent variables, Chi – square test or Fisher's exact test (where some of the cell counts of a cross-tabulation are less than five) was used where appropriate. In all the statistical analyses, difference of between-groups was considered to be significant at a p-value of less than 0.05.

**Results**

Out of the 123 patients that we identified from the database of 4000 patients who were referred for MPI from January 2000 to December 2013, prevalence of TID in a normal or relatively normal SPECT MPI is found to be 3.1%. The basic clinical and imaging characteristics of the patients are summarized in Table 1. Notably, the median age is 61 years (interquartile range = 50 - 71 years) and 56 (45.5%) are men. Regarding race, the table shows that Whites constitutes the largest, 42.3%, of the entire study sample. All patients have one or more cardiac risk factors, with hypertension, 70.7%, being the commonest among the study sample. Majority of the patients, 82.1%, show no abnormal stress ECG findings. The mean LVEF on rest and stress is 62.0 ± 10.2 and 58.0 ± 9.3 respectively. Most of the patients, 74.0%, were referred for the diagnosis of CAD. 85.4% had perfectly normal rest SPECT MPI while on post stress images, approximately half of the patients, 55.3%, have some degree of perfusion defects with SSS of 1-3.

Table 2 shows results of study group 2 (41 patients). The basic clinical and imaging characteristics of these patients are depicted in this table. The median age of the group is 64 years (Interquartile range is 55 -72 years) and 43.9% are men. Whites constitute the largest, 31.7%, of the entire study group. All patients have one or more cardiac risk factors, with hypertension, 80.5%, being the commonest among the study group. About half of the patients, 46.3%, were stressed by physical exercise. Majority of the patients, 87.8%, show no abnormal stress ECG findings. The mean LVEF on rest and stress is 62.5 ± 9.8 and 58.1 ± 9.8 respectively. Most of the patients, 78.1%, were referred for the diagnosis of CAD. 85.4% had perfectly normal rest SPECT MPI while on post stress images, 43.9%, had some degree of perfusion defects with SSS of 1-3. TID ratio of 1.26 – 1.50 is commonest (39.0%) among the study group.

Of the 41 patients that were contacted, 15 (36.6%) had cardiac events, of which 11 (73.3%) were soft events; angina and revascularization, while 4 (26.7%) were hard event; myocardial infarction.

Figure 1 and Figure 2 show the distributions of prevalence of cardiac event over 12 and 41.6 ± 28 months respectively, following diagnosis of TID. Most of these cardiac events (60%) occurred within 12 months following diagnosis of TID. In Figure 1, the annualized event rate of angina, revascularization, and myocardial infarction is 9.8%, 4.9% and 7.3% respectively.

Table 3 shows the results of associations between independent variables and type of events (no event; angina; MI; revascularization). While Table 4 shows the results of associations between independent variables and type of event as a dichotomous outcome variable (having event vs no event).

Notably, Table 3 shows that there is no statistically significant association between diabetes (p=0.131), hypertension (p=0.901), dyslipidaemia (p=1.000), smoking (p=0.204), and family history of CAD (p=1.000) and types of events. However, there is an increasing trend towards the prevalence of cardiac events among patients with cardiac risk factors as compared with those without cardiac risk factors (DM; 52.6% Vs 22.7%; hypertension; 39.4% Vs 25.0%; dyslipidaemia; 39.1% Vs 33.3%; smoking; 62.5% Vs 20.3%). Family history of CAD, however shows a decreasing trend (37.8% Vs 25.0%). In Table 4, the results show statistically significant association between DM and occurrence of an event (p =0.047).

Table 3, show no statistical significant association between gender and type of events ($p = 0.440$), although there is an increasing trend towards events occurring in males as compared to females (45.4% Vs 29.4%). Similarly in Table 4, gender is not associated with the occurrence of an event ($p = 0.355$).

There is no statistical significant association between race and occurrence of an event in both Table 3 ($p = 0.718$) and Table 4($p = 1.000$). Further, there is no increasing trends towards occurrence of an event among these racial groups. The coloured however, show a marginal decrease in event rate (3 out of 10 Vs

4 of 10) in table 3 and table 4. Table 3 shows that the mean age of patients with events is slightly higher than those without events. Hard cardiac event (MI), is more prevalent in the elderly, mean age 71.3 ± 8.2. Soft cardiac events is more prevalent in the younger patients, mean age 62.8 ± 10.6.

Table 4 shows marginal statistical significant association between age and occurrence of an event at $p \leq 0.05$ ($p = 0.062$). Table 3 shows that patients with low EF have more events than those with higher EF. In Table 4, the results show a marginally statistically significant association between lower EF (stress) and occurrence of an event at $p \leq 0.05$($p = 0.058$).

There is no statistical significant association between ECG findings and occurrence of an event in Table 3 (p = 0. 892) and in Table 4 (p = 0.255). Similarly, there is no statistical significant association between mode of stress and occurrence of an event in Table 3 (p = 0. 940) and Table 4 (p = 0.495).

There is no statistical significant association between the degree of TID groups and occurrence of an event in Table 3 (p = 0.890) and in Table 4 (p =0.722), although there is an increasing trend towards occurrence of an event as the degree of TID increases (28.6% Vs 31.3% Vs 50.0%). There is no statistical significant association between SSS and types of events (p = 0.130) in Table 3, but in Table 4, there is statistical significant association between SSS and occurrence of an event (0.040), implying that those with relatively normal heart are more likely to have an event. Majority of the patients with events were treated medically (73.3%).

**Table 1: Basic characteristics of all the patients (N = 123)**

| Variables | N (%) Or Median (Interquartile Range) |
|---|---|
| **Age (years)** | 61 (50 – 71) |
| **Male gender** | 56 (45.5) |
| **Race** | |
| Black | 31 (25.2) |
| White | 52 (42.3) |
| Asian | 29 (23.6) |
| Coloured | 11 (8.9) |
| **Cardiac risk factors** | |
| Hypertension | 87 (70.7) |
| Diabetes mellitus | 32 (26.0) |
| Dyslipidaemia | 43 (35.0) |
| Smoking | 29 (23.6) |
| Family history of CAD | 12 (9.8) |
| **Stress protocol** | |
| Physical | 60 (48.8) |
| **ECG results** | |
| Negative | 101 (82.1) |
| Positive | 10 (8.1) |
| Equivocal | 2 (1.6) |
| Not known | 10 (8.1) |
| **LVEF (rest)** | 62. 0 ± 10.2 |
| **LVEF (stress)** | 58.0 ± 9.3 |
| **Indication** | |

| | |
|---|---|
| Diagnosis | 91 (74.0) |
| Chest pain | 3 (2.4) |
| Extent and severity | 25 (20.3) |
| Not known | 4 (3.3) |
| **SRS** | |
| 0 | 105 (85.4) |
| 1 -3 | 18 (14.6) |
| **SSS** | |
| 0 | 55 (44.7) |
| 1 – 3 | 68 (55.3) |
| **Types of events** | |
| No event | 26 (21.1) |
| Angina | 9 (7.3) |
| MI | 4 (3.3) |
| Revascularization | 2 (1.6) |
| Unknown | 82 (66.7) |
| **Time to event*** | |
| < 6 months | 5 (33.3) |
| 6 – 12 months | 4 (26.7) |
| > 12 months | 6 (40.0) |
| **Intervention*** | |
| Medical Rx | 11 (73.3) |
| Surgical Rx (PCI & CABG) | 4 (26.7) |
| **Degree of TID** | |
| 1.22 – 1.25 | 14 (11.4) |
| 1.26 – 1.50 | 16 (13.0) |
| 1.51 – 1.75 | 6(4.9) |

| | |
|---|---|
| Unknown | 87 (70.7) |

*Only on patients with events (N=15)

**Table 2: Basic characteristics of patients that were interviewed telephonically to determine the prevalence of cardiac events (N = 41)**

| Characteristics | N (%) or Median(Interquartile Range) |
|---|---|
| **Age (years)** | 64 (55 – 72) |
| **Male gender** | 18 (43.9) |
| **Race** | |
| Black | 10 (24.4) |
| White | 13 (31.7) |
| Asian | 11 (26.8) |
| Coloured | 7 (17.1) |
| **Cardiac risk factors** | |
| Hypertension | 33 (80.5) |
| Diabetes mellitus | 19 (46.3) |
| Dyslipidaemia | 17 (41.5) |
| Smoking | 8 (19.5) |
| Family history of CAD | 4 (9.8) |
| **Stress protocol** | |
| Physical | 19 (46.3) |
| **ECG results** | |
| Negative | 36 (87.8) |
| Positive | 2 (4.9) |
| Not known | 3 (7.3) |
| **LVEF (rest)** | 62.5 ± 9.8 |
| **LVEF (stress)** | 58.1 ± 8.9 |
| **Indication** | |

| | |
|---|---|
| Diagnosis | 32 (78.1) |
| Chest pain | 2 (4.9) |
| Extent and severity | 7 (17.1) |
| **SRS** | |
| 0 | 35(85.4) |
| 1 -3 | 6 (14.6) |
| **SSS** | |
| 0 | 23 (56.1) |
| 1 – 3 | 18 (43.9) |
| **Types of events** | |
| No event | 26 (63.4) |
| Angina | 9 (21.9) |
| MI | 4 (9.8) |
| Revascularization | 2 (4.9) |
| **Time to event*** | |
| < 6 months | 5 (33.3) |
| 6 – 12 months | 4 (26.7) |
| > 12 months | 6 (40.0) |
| **Intervention*** | |
| Medical Rx | 11 (73.3) |
| Surgical Rx (PCI, CABG) | 4 (26.7) |
| **Degree of TID** | |
| 1.22 – 1.25 | 14 (34.2) |
| 1.26 – 1.50 | 16 (39.0) |
| 1.51 – 1.75 | 6 (14.6) |
| Unknown | 5 (12.2) |

*Only on patients with events (N=15)

**Table 3: Bivariate analysis of type of events and independent variables.**

| Independent variables | Types of events | | | | |
|---|---|---|---|---|---|
| | No events N (%) | Angina N (%) | MI N (%) | Revascul-arization N (%) | P-value |
| **Mode of stress** | | | | | 0.940 |
| Physical | 11 (42.3) | 5 (55.6) | 2(50.0) | 1(50.0) | |
| Pharmacological | 15 (57.7) | 4 (44.4) | 2(50.0) | 1(50.0) | |
| **Diabetes Mellitus** | | | | | 0.131 |
| No | 17 (65.4) | 2(22.2) | 2(50.0) | 1(50.0) | |
| Yes | 9 (34.6) | 7 (77.8) | 2(50.0) | 1(50.0) | |
| **Hypertension** | | | | | 0.901 |
| No | 6 (23.1) | 1 (11.1) | 1(25.0) | 0(0.0) | |
| Yes | 20 (76.9) | 8 (88.9) | 3 (75.0) | 2(100.0) | |
| **Dyslipidaemia** | | | | | 1.000 |
| No | 16 (61.5) | 5 (55.6) | 2(50.0) | 1(50.0) | |
| Yes | 10 (38.5) | 4(44.4) | 2(50.0) | 1(50.0) | |
| **Smoking** | | | | | 0.204 |
| No | 23 (88.5) | 6(66.7) | 3 (75.0) | 1(50.0) | |
| Yes | 3 (11.5) | 3(33.3) | 1(25.0) | 1(50.0) | |
| **Family history of CAD** | | | | | 1.000 |
| No | 23 (88.5) | 8(88.9) | 4(100.0) | 2(100.0) | |
| Yes | 3 (11.5) | 1 (11.1) | 0(0.0) | 0(0.0) | |
| **Race** | | | | | 0.718 |

| | | | | | |
|---|---|---|---|---|---|
| Black | 6 (23.1) | 4(44.5) | 0(0.0) | 0(0.0) | |
| White | 8 (30.8) | 2(22.2) | 1(25.0) | 2(100.0) | |
| Asian | 7 (26.9) | 2(22.2) | 2(50.0) | 0(0.0) | |
| Coloured | 5 (19.2) | 1 (11.1) | 1(25.0) | 0(0.0) | |
| **Gender** | | | | | 0.440 |
| Male | 10 (38.5) | 6(66.7) | 1(25.0) | 1(50.0) | |
| Female | 16 (61.5) | 3(33.3) | 3(75.0) | 1(50.0) | |
| **SRS** | | | | | 0.022 |
| 0 | 24 (92.3) | 7(77.8) | 4(100.0) | 0(0.0) | |
| 1 -3 | 2 (7.7) | 2(22.2) | 0(0.0) | 2(100.0) | |
| **SSS** | | | | | 0.130 |
| 0 | 17 (65.4) | 3(33.3) | 3(75.0) | 0(0.0) | |
| 1 -3 | 9 (34.6) | 6(66.7) | 1(25.0) | 2(100.0) | |
| **Intervention**** | | | | | 0.005 |
| Medical Rx | | 9(100.0) | 2(50.0) | 0(0.0) | |
| Surgical Rx (PCI & CABG) | | 0(0.0) | 2(50.0) | 2(100.0) | |
| **ECG** | | | | | 0.892 |
| Negative | 21(80.8) | 9(100.0) | 4(100.0) | 2(100.0) | |
| Positive | 2(7.7) | 0(0.0) | 0(0.0) | 0(0.0) | |
| Not known | 3(11.5) | 0(0.0) | 0(0.0) | 0(0.0) | |
| **Degree of TID*** | | | | | |
| 1.22 – 1.25 | 10 (41.7) | 3 (37.5) | 1(25.0) | | |
| 1.26 – 1.50 | 11 (45.8) | 3 (37.5) | 2(50.0) | | |
| 1.51 – 1.75 | 3 (12.5) | 2(25.0) | 1(25.0) | | |
| **Age** | 60.7 ± 9.9 | 62.8±10.6 | 71.3 ± 8.2 | 73.5 ± 0.7 | 0.890 |

| | | | | | |
|---|---|---|---|---|---|
| **LVEF (stress)** | 64.3 ± 9.9 | 58.3 ± 9.0 | 61.3±13.1 | 60.5 ± 4.9 | |
| **LVEF (rest)** | 60.0 ± 8.7 | 54.6 ± 8.0 | 56.5±11.9 | 52.0±2.8 | |

*Five unknown cases of the degree of TID were excluded.

** Analysis only on those that had event (N =15)

**Table 4: Bivariate analysis of type of events and independent variables.**

| **Independent variables** | **Types of events** | | |
|---|---|---|---|
| | **No events N (%)** | **Events N (%)** | **P-value** |
| **Mode of stress** | | | 0.495 |
| Physical | 11 (42.3) | 8 (53.3) | |
| Pharmacological | 15 (57.7) | 7 (46.7) | |
| **DM** | | | 0.047 |
| No | 17 (65.4) | 5 (33.3) | |
| Yes | 9 (34.6) | 10 (66.7) | |
| **Hypertension** | | | 0.687 |
| No | 6 (23.1) | 2 (13.3) | |
| Yes | 20 (76.9) | 13 (86.7) | |
| **Dyslipidaemia** | | | 0.607 |
| No | 16 (61.5) | 8 (53.3) | |
| Yes | 10 (38.5) | 7 (46.7) | |
| **Smoking** | | | 0.117 |
| No | 23 (88.5) | 14 (66.7) | |
| Yes | 3 (11.5) | 1 (33.3) | |
| **Family history of** | | | 1.000 |

| | | | |
|---|---|---|---|
| **CAD** | | | |
| No | 23 (88.5) | 14 (93.3) | |
| Yes | 3 (11.5) | 1 (6.7) | |
| **Race** | | | 1.000 |
| Black | 6 (23.1) | 4 (26.7) | |
| White | 8 (30.8) | 5 (33.3) | |
| Asian | 7 (26.9) | 4 (26.8) | |
| Coloured | 5 (19.2) | 2 (13.3) | |
| **Gender** | | | 0.355 |
| Male | 10 (38.5) | 8 (53.3) | |
| Female | 16 (61.5) | 7 (46.7) | |
| **SRS** | | | 0.101 |
| 0 | 24 (92.3) | 11 (73.3) | |
| 1 -3 | 2 (7.7) | 4 (26.7) | |
| **SSS** | | | 0.040 |
| 0 | 17 (65.4) | 6 (40.0) | |
| 1 -3 | 9 (34.6) | 9 (60.0) | |
| **Intervention*** | | | |
| Medical Rx | 26(100.0) | 11(73.3) | |
| Surgical Rx | 0(0.0) | 4(26.7) | |
| **ECG** | | | 0.255 |
| Negative | 21(80.8) | 15(100.0) | |
| Positive | 2(7.7) | 0(0.0) | |
| Not known | 3(11.5) | 0(0.0) | |
| **Degree of TID**** | | | 0.722 |
| 1.22 – 1.25 | 10 (41.7) | 4 (33.3) | |

| | | | |
|---|---|---|---|
| 1.26 – 1.50 | 11 (45.8) | 5 (41.7) | |
| 1.51 – 1.75 | 3 (12.5) | 3 (25.0) | |
| **Age** | 60.7 ± 9.94 | 66.5 ± 10.02 | 0.062 |
| **LVEF (stress)** | 60.0 ± 8.72 | 54.7 ± 8.32 | 0.058 |
| **LVEF (rest)** | 64.3 ± 9.86 | 59.4± 9.30 | 0.155 |

**Five unknown cases of the degree of TID were excluded.

* Analysis only on those that had event (N =15)

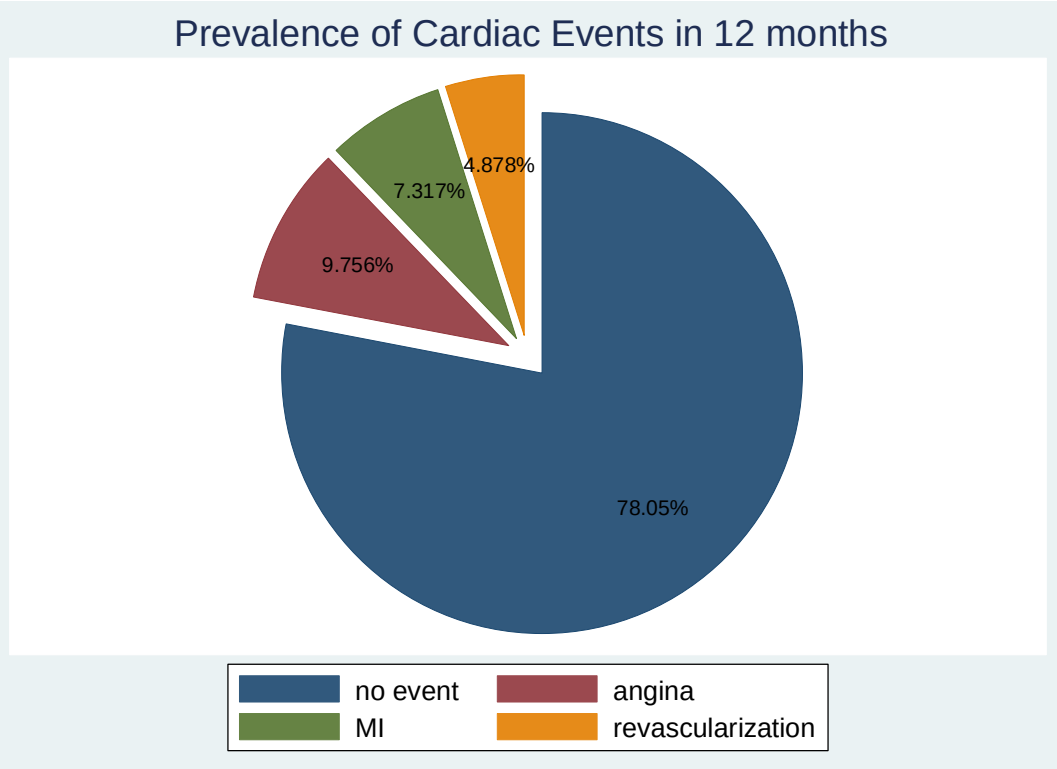



Figure 1: prevalence of cardiac events over 12 months following diagnosis of TID.

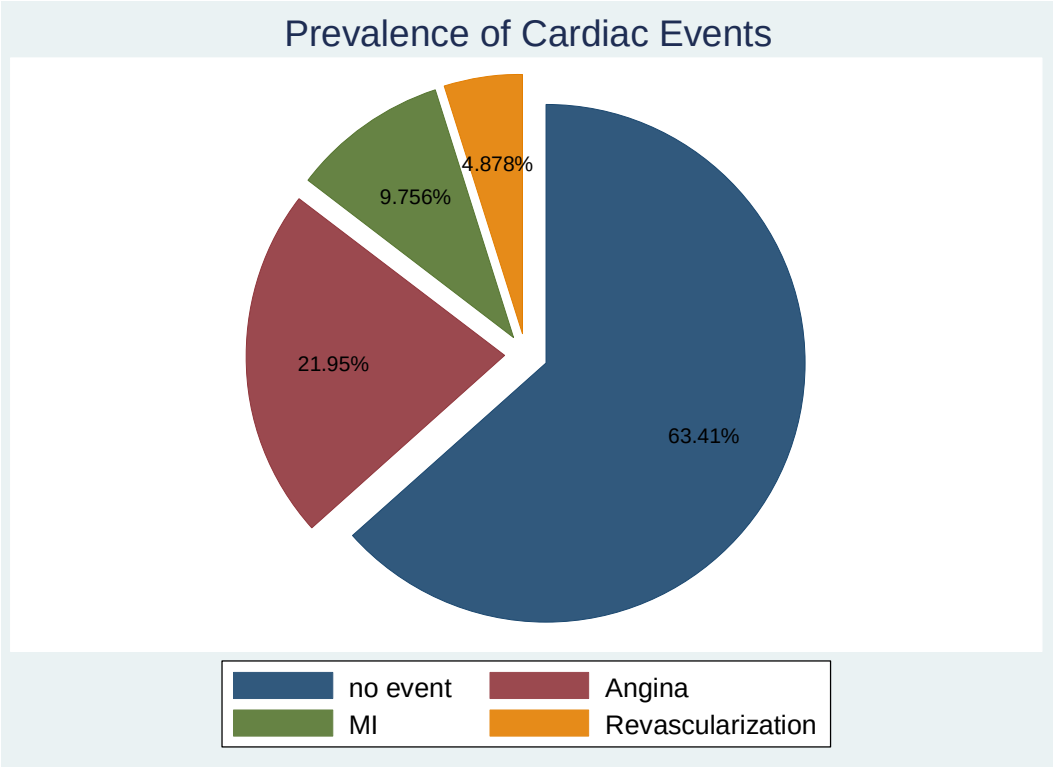



Figure 2: prevalence of cardiac event over 41.6 ± 28 months following diagnosis of TID.

**Discussion:**

Our study shows the followings: that the prevalence of TID in a normal or relative normal SPECT MPI is 3.1%; that presence of TID in an entirely or relatively normal SPECT MPI does not always signify an excellent prognosis. In addition, majority of patients with events in this study were treated medically. Moreover, our results show that patients with diabetes or mild perfusion (SSS=0 vs SSS =1-3) defects were more likely to have cardiac events. However, our results show marginal statistically significant association between age, LVEF (stress) and occurrence of cardiac events. The other factors such as race, gender, mode of stress, ischemic ECG changes, and degree of TIDs were not significantly associated with the occurrence of events. There is also no significant association between cardiac risk factors (apart from DM) and occurrence of cardiac events.

However, the exclusion of 82 patients (two-third of our study population) posed a major limitation to our study. If majority of the 82 patients were to fall into any of the sub-groups of the cardiac events, it would have skewed our

results. Therefore, inferences that are drawn from our study should be taking cautiously. Consequently, we recommend a similar study with a larger sample size to verify our results.

Nonetheless, some of our findings are similar to the existing studies. For example, our finding on the prevalence of TID in a normal or relatively normal SPECT MPI is similar to the study of Mohamed and colleagues (32) which showed the prevalence of 4% and that of Abidov et al (37) which showed prevalence of 2.5%. Secondly, our findings on annual hard cardiac event rate (MI) of 7.3% is similar to the findings of Rami Doukky et al. (39). In their study of 76 patients with normal MPI but with TID, they found annual hard cardiac event rate (MI) of 5.9%. Thirdly, our finding that patients with diabetes are more likely to have cardiac events is in agreement with other studies published in the literature (37 – 39, 44). Furthermore, our study did not show statistical significance association between hypertension, dyslipidaemia, ischaemic stress ECG changes and occurrence of an event. These findings are similar to the findings of Abidov A et. al (37).

Some of our findings showed disparity with what is published in the literature. For example, our results did not find any statistically significant association between mode of stress and occurrence of events. This is at variance with study of Navare SM et al. (25) whom in their study showed higher cardiac events rate in patient who underwent pharmacological stressing. Similarly, in the study of Rami Doukky et al. (39), they showed that cardiac event rate were higher in patients who underwent pharmacological stress testing than that of patients who had physical stress (3.1% vs 0.4%). This disparity could be explained by the fact that there is no strict protocol in our department as to who undergo physical or pharmacological stressing.

Our study showed soft cardiac event rate, revascularization, of 4.9%, which is on the higher side compared to findings of Abidov et al. (37) who followed two groups of patients for 2.30 ± 0.67 years and 2.26 ± 0.69 years. The soft cardiac event rate in their study, revascularization, was 2.3% and 2.6% respectively. Also, the study of Doukky et al. (39) found an annual rate of revascularization to be 3.8% in their patients that were follow-up for 27 ± 9 months. The difference could be attributed to small sample size of our study. We suggest another study with larger sample size to confirm our findings.

Contrary to published literature (37, 39, 45) which showed significant association between age, LVEF stress and occurrence of an event, our study showed no statistical significance on the same factors. Furthermore, our results of significance association between SSS =0 vs. SSS =1-3, SRS =0 vs. SRS =1 -3 and occurrence of an event differs from that of Abidov et.al (37) who found no statistical significant association between these variables. This disparity could be as a result of difference in patients' selection criteria. In their study, majority of their patients had a TID ratio of less than 1.21 compared to our study which had a minimum TID cut-off of 1.22. Similar reason could be alluded to no significance association between degree of TIDs and occurrence of cardiac events in our study, although there is an increasing trend towards cardiac events in a higher degree of TID. This differs from that of Abidov et al (37) that showed higher likelihood of events occurring in those patient with highest quartile of TID. To the best of our knowledge, this is the first time racial groups, as we have in South Africa, is being compared to the prevalence of cardiac events in TID patients. We found no statistical significant association between racial groups and occurrence of cardiac events. However, because of our small sample size, we recommend a similar study with larger sample size to confirm our findings.

**Limitation of the study.**

A large proportion of our patients could not be contacted due to wrong/invalid telephone numbers in their hospital records, this limit our study sample size.

Similarly, as a result of the above reason, cardiac death as an independent outcome could not be assessed. Therefore, one would not be able to know which direction the outcomes of this study would take if these patients were available for interview and their data included in our analysis. However, some of our findings were significant and consistent with previous reports in the literatures (37 - 39).

**Conclusion:**

Transient ischemic dilation in the setting of normal or relatively normal SPECT MPI may signify a prognosis that is not good and may be a predictor of future cardiac events especially in patients with diabetes or who are elderly as well as in those with lower ejection fraction in the post stress MPIs. It is not clear how the inclusion of the missing data would impact on this study' outcomes. Further and preferably a prospective larger study in our environment may elucidate the outcomes of such patients with more accuracy.

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Appendix 1

**CARDIAC IMAGING IN PATIENTS WITH CORONARY ARTERY DISEASE**

Good day

My name is Dr. Fadiji from the Nuclear Medicine department. We are conducting a study on the role of scans in patients with heart disease. In this study, we want to learn if the heart chamber that get bigger after exercise can predict future heart problems like heart attack.

You were chosen to take part in this study because your heart scan that was done in Nuclear Medicine showed findings that are similar to the ones that are being reviewed.

I am inviting you to participate in this study.

**What is involved in the study?**

We will look at your previous heart scan that was done in our department and then would like you to answer a few questions, if it is okay by you.

**Benefit of being in the study:**

Your participation will help us to decide on future management of patients with similar scan findings.

**Your participation is voluntary.**

Should you choose not to participate, this will not influence the way you are treated in this hospital.

**Confidentiality.**

Your identity will not be disclosed to anybody.

Are you happy to participate by answering few questions?

Appendix 2

**University of the Witwatersrand**
**Department of Nuclear Medicine**

**Structured questionnaire**

**Title of the Study: Prognostic value of transient Ischemic dilatation (TID) in patients with normal single-photon emission tomography (SPECT) myocardial perfusion imaging (MPI).**

Questions:

1. Since your last visit to have image of the heart scan at Nuclear Medicine Department at Charlotte Maxeke Johannesburg Hospital;

    - Were you admitted to any hospital?

| | Date of admission | Date of discharge | Hospital of admission | Physician that treated you: Name/contact |
|---|---|---|---|---|
| YES | | | | |
| NO | | | | |

A. If yes;
    a. What was the reason for the admission
    b. If the answer was heart trouble, what was done at the hospital?
B. If no;
    a. Did you expirience any chest discomfort since then?
        i. If yes;
            1. Did you see any General practitioner?
            2. What was done?

C. If patient is dead, effort will be made to get the copy of the death certificate in the event that it did happen in the hospital.

R14/49 Dr Isaac Olusola Fadiji

## HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

## CLEARANCE CERTIFICATE NO. M130832

| | |
|---|---|
| **NAME: (Principal Investigator)** | Dr Isaac Olusola Fadiji |
| **DEPARTMENT:** | Nuclear Medicine<br>Charlotte Maxeke Johannesburg Academic Hospital |
| **PROJECT TITLE:** | Prognostic Value of Transient Ischemic Dilatation (TID) in Patients with Normal Single-Photon Emission Computed Tomography (SPECT) Myocardial Perfusion Imaging (MPI) |
| **DATE CONSIDERED:** | 30/08/2013 |
| **DECISION:** | Approved unconditionally |
| **CONDITIONS:** | |
| **SUPERVISOR:** | Prof MDTHW Vangu |
| **APPROVED BY:** | Professor PE Cleaton-Jones, Chairperson, HREC (Medical) |
| **DATE OF APPROVAL:** | 05/03/2014 |

**This clearance certificate is valid for 5 years from date of approval. Extension may be applied for.**

**DECLARATION OF INVESTIGATORS**

To be completed in duplicate and **ONE COPY** returned to the Secretary in Room 10004, 10th floor, Senate House, University.
I/we fully understand the conditions under which I am/we are authorized to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated, from the research protocol as approved, I/we undertake to resubmit the application to the Committee. **I agree to submit a yearly progress report**.

Principal Investigator Signature Date

**PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES**