A comparative study of different treadmill scores to diagnose Coronary Artery Disease among patients attending Bangabandhu Sheikh Mujib Medical University

NCT no: 02879032

Date of document: 16th November, 2016

1. Title of the study: **A comparative study of different treadmill scores to diagnose Coronary Artery Disease among patients attending Bangabandhu Sheikh Mujib Medical University.**

2.	Principle Investigator (PI)	:**Dr. Md. Mashiul Alam** MD (Cardiology), Phase –B Student, Department of Cardiology
3.	Name of the present course	: MD (Cardiology), Residency
4.	Joining date in Phase B	: September, 2015
5.	Name of the Institute	: Bangabandhu Sheikh Mujib Medical University
6.	Expected date of examination	: July, 2018
7.	Guide	: Dr. Md. MukhlesurRahman Associate Professor, Department of Cardioloy
8.	Co-Investigator/ Co- Guide	: Dr. TanjimaParvin Associate Professor, Department of Cardiology
9.	Place of Study	: Department of Cardiology, BSMMU, Shahbag, Dhaka
10.	Type of study	: Cross-sectional study
11.	Duration of study	: August 2016 to July 2017
12.	Total cost	: Tk-**42,500/=** (Forty two thousand five hundred taka only)
13.	Funding agency	: Department of Cardiology and Investigator

We agree to obtain approval of the Institutional Review Board of BSMMU for any changes involving the rights and welfare of subject or any changes of the methodology before making any such changes.

Principle Investigator	**Guide**
Dr. Md. Mashiul Alam	Dr. Md. MukhlesurRahman
MD(Cardiology), Phase B Student	Associate Professor
Department of Cardiology	Department of Cardiology
University Cardiac Center, BSMMU	University Cardiac Center,BSMMU

Date: 24/09/2016

To

The Chairman

Department of Cardiology

University Cardiac Center, BSMMU

Shahbag, Dhaka -1000

Sub: For permission of thesis work to be carried out in Department of Cardiology.

Sir,

With due respect and honor, I am a MD (phase-B) student in Cardiology, would like to seek your kind consideration about the thesis work to be carried out in the department of cardiology. My protocol was approved by our Departmental Academic and Thesis Committee and recommended for your kind consideration. My Supervisor has agreed to supervise and monitor my work regularly and communicate with you if needed.

Sincerely yours,

Dr. Md. Mashiul Alam

MD (Cardiology), Phase-B
Department of Cardiology
University Cardiac Center
BSMMU, Shahbag, Dhaka-1000

Date: 24/09/2016

To

The Pro-Vice Chancellor (Academic) and Chairman

Institutional Review Board of BSMMU

Shahbagh, Dhaka-1000

Sub: For permission of thesis work to be carried out in the Department of Cardiology, by

Dr. Md. Mashiul Alam, MD (Phase-B) student.

Sir,

With due respect and honor, I would like to seek your kind consideration about the thesis work to be carried out by Dr. Md. Mashiul Alam, MD (Phase-B) student. His protocol was approved by our Departmental Academic and Thesis Committee and recommended for your kind Consideration. Supervisor has agreed to supervise and monitor his work regularly and communicate with you if needed during the work.

Thanking you,

Professor (Dr.) Sajal Krishna Banerjee
Chairman & Professor
Department of Cardiology
University Cardiac Center
BSMMU, Shahbagh, Dhaka

Date: 24/09/2016

To

The Pro-Vice Chancellor (Academic) and Chairman

Institutional Review Board of BSMMU

Shahbagh, Dhaka-1000

Sub: For permission of thesis work to be carried out in Department of Cardiology by

Dr. Md. Mashiul Alam, MD (Phase-B) student.

Sir,

With due respect and honor, I would like to seek your kind consideration about the thesis work to be carried out by Dr. Md. Mashiul Alam, MD (Phase-B) student. His protocol was approved by our Departmental Academic and Thesis Committee and recommended for your kind consideration. I have agreed to supervise and monitor his work regularly and communicate with you if needed during the work.

With regards,

Guide

Dr. Md.MukhlesurRahman

Associate Professor
Department of Cardiology
University Cardiac Center
BSMMU, Shahbagh, Dhaka-1000

Date: 24/09/2016

To

The Pro-Vice Chancellor (Academic) and Chairman

Institutional Review Board of BSMMU

Shahbagh, Dhaka -1000

Sub: For permission of thesis work to be carried out in Department of Cardiology.

Sir,

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Sincerely yours,

Principle Investigator

Dr. Md. Mashiul Alam

MD (Cardiology), Phase-B
Department of Cardiology
University Cardiac Center
BSMMU, Shahbag, Dhaka-1000

Abstract for IRB

Background: Exercise treadmill test (ETT) is frequently done, inexpensive, relatively safe investigation for diagnosis of ischemic heart disease and prediction of exercise capacity. Ischemic heart disease is increasing by leaps and bounds all over the world even in the developing countries like Bangladesh. The incidence rate of coronary artery disease is not limited to male gender as previously seen. As a cause of industrialization and increased life expectancy, incidence of ischemic heart disease in females is escalating now in Bangladesh also. Though ETT is a well accepted investigation to diagnose Coronary Artery Disease (CAD), it has a high false positive and false negative result if ST segment response alone is calculated for interpretation of the test.

Rationale: Duke Treadmill Score (DTS) and Simple Treadmill Score (STS) are valid and well known scores which can predict coronary artery disease burden more efficiently than ST segment response alone. Computer generated Cleveland clinic score (CCS) is another valid treadmill score which has a complex algorithm but effective way to predict 3 year and 5 year survivability. These three scores are well tested on western population but to our best knowledge there is little or no information regarding their predictability of CAD. It's well known that ETT has a high false positive result in our population, so applying the scores may render ETT more efficient and abrogate unwanted risk of undergoing coronary angiography to diagnose CAD, especially in females.

Objective: To identify difference of predictability of DTS, STS and CCS to diagnose significant CAD by Coronary Angiography (CAG).

Method: A Cross-Sectional study will be carried out on patients attending University Cardiac Center in Bangabandhu Sheikh Mujib Medical University (BSMMU) for stable chest pain to find out the accuracy of commonly applied treadmill scores (DTS, STS) and ST segment response to diagnose CAD as well as accuracy of computer generated Cleveland Clinic Score will be tested. Total 102 people including male and female who have undergone ETT will be included according to inclusion and exclusion criteria and informed written consent will be taken. Treadmill scores will be calculated. The patients who have undergone exercise treadmill test for provocable ischemia and have their coronary angiogram done for confirmation and identification of coronary artery lesion according to the recommended guideline for CAG with-in 6 months will be selected. All available data will be analyzed using SPSS. The accuracy of different scores will be calculated and compared with each other. According to currently available data from studies in western population we predict the treadmill scores will have good predictability and will be efficient to control unwanted CAG procedure to diagnose CAD.

Declaration

We the undersigned solemnly declare and affirm that the research protocol entitled "**A comparative study of different treadmill scores to diagnose coronary artery disease in a tertiary care hospital**"has been developed by the under mentioned Principal Investigator (PI), Phase B student of MD Cardiology at the Department of Cardiology, University Cardiac Center, Bangabandhu Sheikh Mujib Medical University, Shahbag, Dhaka with the active guidance and supervision of his guide whose names are listed below. The concepts and methods underlying the research protocol are based on the original ideas developed by the PI who shall carry out the work and present the results as a thesis as an academic requirement for the degree being pursued by the student at the university.

The PI has developed this protocol following all ethical guidelines and principal for the protection of rights of human and children involved in biomedical research, including Helsinki Declaration, NIH GCP, and WHO. No part of the contents of this protocol has been published in any form nor submitted for publication in any media; it does not contain any printed and copyrighted material reproduced from available sources without permission of the copyright owner.

The protocol has been presented by the student in the department and categorically reviewed, revised, and approved by the assigned departmental supervisors and guides.We believe this protocol is likely to generate new information to fill in the existing knowledge gap leading to a productive and useful conclusion in the field of study.

We would highly appreciate if the protocol is reviewed and approved by the BSMMU IRB for immediate implementation.

| --- | --- | --- |
Principal investigator	Supervisor	Chairman and Dept.Head
Dr. Md. Mashiul Alam	**Dr. Md. MukhlesurRahman**	**Prof. (Dr.) Sajal Krishna Banerjee**
MD (Cardiology), Phase-B	Associate Professor	Chairman & Professor
Department of Cardiology	Department of Cardiology	Department of Cardiology
University Cardiac Center	University Cardiac Center	University Cardiac Center
BSMMU, Shahbagh, Dhaka	BSMMU, Shahbagh, Dhaka	BSMMU, Shahbagh, Dhaka
Mobile No-01786337788	Mobile No-01819238868	Mobile No-01711594017
Date:	**Date:**	**Date:**

IRB Check List for Study Population (List A)

(Please tick mark against your appropriate answers for all the statements below, write NA if not applicable)

1.Source of study population		**7. Does the study require:**	
a. Sick persons	✓Yes / No	a. Use of records (hospital, medical, death, birth, lab reports, or others).	Yes / ✓ No
b. Healthy persons	Yes / ✓No	b. Use of fetal tissue or abortus.	Yes / ✓No
c. Minors or persons under guardianship	Yes / ✓No	c. Use of organs or body fluids*(serum, blood, CSF, sputum, urine, stool, pus, tears, amniotic fluid etc).*	Yes / ✓ No
2. Age Groups of participants		**8. Are subjects clearly informed about**:	
a. 0-4 years	Yes / ✓ No	a. Nature and purpose of study.	✓Yes / No
b. 5-10 years	Yes / ✓ No	b. Procedures to be followed including alternatives used.	Yes / No
c. 11-17 years	Yes / ✓ No	c. Physical risks.	✓Yes / No
d. 18-64 years	✓Yes / No	d. Mental Risks.	Yes / ✓No
e. 65+ years	✓Yes / No	e. Private questions.	✓Yes / No
3 Gender Groups		f Benefits to be derived.	✓Yes / No
a. Male	✓Yes / No	g. Right to refuse to participate or to withdraw from the study.	✓Yes / No
b. Female	✓Yes / No	h. Confidential handling of data.	✓Yes / No
c. Transgender	✓Yes / No	i. Compensation (where there are risks or loss of working hours or privacy is involved in any particular procedure).	Yes / ✓No
4. Does the study involve special groups as listed below ?		**9. Signed informed consent form will be obtained from subjects before admission in to the study.**	
a. Pregnant women	Yes / ✓ No	a. From patients, if adults, >18 y	✓Yes / No
b. Fetus*in utero*	Yes / ✓ No	b. From parents or guardians if patients are minors, < 18 y.	Yes / No
c. Prisoners	Yes / ✓ No	**10. Will precaution be taken to protect anonymity of subjects ?**	✓Yes / No
d. Mentally impaired	Yes /✓ No	**11. Does the study involve:**	
e. Sex workers/ drug addicts	Yes /✓ No	a. Human exposure to radiation ?	✓Yes / No
f. Refugee/ tribal groups	Yes / ✓ No	b. Investigational new drug or device.	Yes / ✓ No
5. Physical Risks:		c. Human exposure to infectious,toxic, and other harmful agents.	✓Yes / No
a. Physical risks including venipuncture, x-ray, skin test	✓Yes / No	d. New treatment regimen.	Yes / ✓ No
d. Social risks	Yes / ✓ No	e. Observation of public behavior.	Yes / ✓No
e. Psychological risks	Yes / ✓ No	**12. Does the study population require the following groups ?**	
f. Discomfort to subject	✓Yes / No	a. Healthy volunteers.	Yes / ✓ No
g. Invasion of body	✓Yes / No	b. Healthy control groups	Yes / ✓ No
h. Invasion of privacy	✓Yes / No	c. Untreated or 'placebo' groups.	Yes / ✓ No
i. Disclosure of information damaging to subjects or others	✓Yes / No	d. Invasive tests on healthy subjects to assess "normal" values in population.	Yes / No
5. Project/ study site		**13. Describe what type of study**	
a. BSMMU Hospital	✓Yes / No	a. Cross-sectional study	✓Yes / No
b. Urban Community	Yes / No	b. Cohort, longitudinal study	Yes / ✓No
c. Rural Community	Yes / No	c. Controlled Clinical Trial	Yes / ✓No
d. Other hospitals	Yes / No		

IRB Check List B

1. Trial Registration

(a) Has the trial been registered with any registration authority? ✓**Yes** / **No**

(b) If yes, please provide full information including registration number, date of registration, and organization.

a. Organization name & address:

ClinicalTrials.gov PRS
Protocol Registration and Results System

b. Registration number: NCT02879032 C. Date of Registration: 24th August, 2016

2. Dissemination plan

Please describe the anticipated plan for disseminating the results of the study when completed.

Results will be presented as (check as many apply):

a. Thesis✓
b. Dissertation
c. Journal publication✓
d. Seminar at the university and international workshop/conference.✓
e. Internal report✓
f. CONSORT (Consolidated Standards for Reporting Trials) format has been included and will be followed in reporting the trial results when completed. This is required mostly for controlled clinical trials.

3. Conflicts of interests: Yes / ✓No

If yes, please describe any conflicts of interests involved or anticipated in the study.

4. Investigator's Certification: Has the PI successfully completed the NIH clinical investigator's qualifying exam online? ✓**Yes** / **No**

NIH Clinical Investigator Exam:

Completion date: 12th August, 2016

Certification obtained:NIH Office of Clinical Research Training and Medical Educationcomputer-based Clinical Research Training course.

5. **Expected Outcome:** What will be the expected outcome of the study if successfully completed.

The study will be expected to: (Check as many apply).

a. Generate new knowledge.✓
b. Confirm existing knowledge. ✓
c. Extend current knowledge to wider field of application. ✓
d. Reassess known effects of an intervention on BD population.
e. Provide basis for future, definitive studies. ✓
f. Change current diagnostic and therapeutic practice or procedures. ✓
g. Change current behavior among population.

Budget

Instrument or Material	Unit	Unit Cost	Total estimated budget (InTaka)
1. Cost of investigations	102	11400	(1,162,800/=) Patients Self expenditure for ETT and CAG
2.Internal work, literature search and purchase of article or reference paper	-	-	15,000/=
3.Stationeries, Paper files, staplers etc	-	-	5000/=
4.Printing and reproduction	-	-	10,000/=
5.Thesis writing, computer compose etc	-	-	10,000/=
6.Thesis binding	-	-	1500/=
7.Miscellaneous	-	-	1000/=
TOTAL42,500/=			

(In word:Forty two thousand five hundred)

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Signature of the Investigator Signature of the Supervisor

TITLE

A COMPARATIVE STUDY OF DIFFERENT TREADMILL SCORES TO DIAGNOSE CORONARY ARTERY DISEASE AMONG PATIENTS ATTENDING BANGABANDHU SHEIKH MUJIB MEDICAL UNIVERSITY

Principle Investigator

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Guide

Dr. Md. MukhlesurRahman

Associate Professor
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Co-guide

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Introduction

At present several treadmill scores have been proposed as means for improving the diagnostic accuracy of the exercise treadmill test (ETT) and to predict future risk of cardiac events (Berman et al., 1978 & Do et al., 1997). Although a large number of noninvasive stress testing modalities are currently available, the exercise ECG is still used as a standard for comparison with other clinical and testing risk markers. It is also the least costly of all provocative noninvasive tests. The Duke Treadmill Score (DTS), traditionally a prognostic score, was recently tested as a diagnostic score and shown to predict CAD better than the ST response alone(Shaw et al., 1998). But questions remain regarding the diagnostic accuracy of treadmill scores when applied to a different patient population; furthermore, many treadmill scores have not been compared with one another in the same population(Fearon et al., 2002).To date, no composite stress-test score or noninvasive risk index has been shown to provide both accurate diagnostic and prognostic risk estimates. Despite that exercise treadmill test remains a useful test for diagnosing coronary artery disease (CAD) in patients with chest pain and at intermediate risk for CAD (Do et al., 1997).The sensitivity and specificity of ETT varies considerably. According to a meta-analysis conducted by Gianrossi et al there was a wide variability in sensitivity and specificity of ETT [sensitivity 68± 16% (range 23–100%); specificity 77±17% (range: 17–100%). Another Meta analysis showed sensitivity of 81± 12% (range: 40–100%) and specificity of 66± 16% (range: 17–100%) (Myers et al., 1994).Fearon WF et al showed sensitivity and specificity was higher when treadmill scores were applied in comparison to ST response alone. They used a consensus score consisting of the Morise, Dentrano and VA score and found predictive accuracy of the consensus score for stratifying patients to low and high likelihood for CAD was significantly higher than the predictive accuracy of DTS, 80(74-86)% versus 71(65-77)% ($p< 0.0001$). But Fearon WF et al conducted the study only on male population in USA and the consensus score was calculated by average of computer generated treadmill scores. In 2012 Mao L et al have shown 73 out of 104 male patients were detected CAD both by ETT and CAG, the accuracy rate was 70.2% which was much higher than that (50.0%) of the female patients ($p<0.05$) and they only used ST changes alone to demonstrate ETT positivity In this study, we will compare the diagnostic accuracy of well known prognostic scores namely, Duke Treadmill Score, Simple Treadmill Score and Cleveland Clinic Score to identify significant coronary artery lesion in Bangladeshi male and female patients.

Rationale

Though exercise treadmill test has high false positive and negative rates(Zang et al., 2007) , it is cheap, easily available, less time consuming to the interpret results and its accuracy can be increased by calculating ST/HR index, treadmill score, QT dispersion and so on (Kronander 2010 &Dentrano 1989). On the contrary the gold standard test coronary angiogram for detecting CAD is expensive, time consuming, potentially hazardous with many complications and often the CAG shows normal coronary arteries in female population.ST-segment depression and chest pain as the classic criteria for CAD diagnosis are well known and accepted. Besides If treadmill score were used the diagnostic accuracy of ETT would had been higher. The accuracy of different treadmill scores in Bangladeshi population especially the female population is largely unknown. Duke Treadmill Score and Simple Treadmill Score are well validated score in western population and are used for diagnostic & prognostic interpretation of ETT. The predictive accuracy of DTS to diagnose CAD is 71% (Fearon 2002). In 2001 Raxwal V et al. showed simple treadmill score has sensitivity of 88% and specificity of 96%. If we calculate the accuracy of simple treadmill score using the formula "Accuracy = (Sensitivity) x Prevalence + (Specificity) x (1- Prevalence)" it sums up nearly 93% according to prevalence of CAD in urban population. Cleveland Clinic Score is a prognostic score of ETT. It gives value from which we can predict the probability of 3 year or 5 year survival. It was shown that it has a very high negative predictive value approaching 97%. Besides to the best of our knowledge Cleveland Clinic Score was not tested as a diagnostic predictor of CAD and there are few studies regarding treadmill scores predictability in Bangladesh. In our study we will use all of these three scores and compare their accuracy to predict significant CAD. DTS, Simplified Treadmill Score, and Cleveland clinic score can be implemented effectively to identify patients with low probability of CAD and excluded from undergoing expensive and potentially hazardous CAG if the real scenario of the treadmill scores is known in our population.

Research question

Howdo different treadmill scores (Duke Treadmill Score, Simple Treadmill Score, Cleveland Clinic Score) vary to predictprobability of Coronary Artery Disease in Bangladeshi population in a tertiary care hospital?

General Objectives

To identify difference of predictability of DTS, Simple Treadmill Score and Cleveland Clinic Score to diagnose significant CAD by Coronary Angiography.

Specific Objectives

1. To estimate accuracy of ST segment response, DTS, Simple Treadmill Score and Cleveland Clinic Score to predict CAD.

2. To compare DTS, Simple treadmill score, Cleveland Clinic Score accuracy to predict coronary artery disease.

3. To identify the relation of different level of treadmill scores with severity of CAD.

Literature Review

According to Islam AKMM and Majumder AAS “Coronary artery disease in Bangladesh: A review published in 2013 the exact prevalence of CAD in Bangladesh is not known. Only a limited number of small-scale epidemiological studies are available. Probably the prevalence of IHD was first reported in 1976, which was 0.33%. More recent data indicates CAD prevalence between 1.85% and 3.4% in rural and 19.6% in an urban sample of working professionals. Despite marked disparity in values, there seems to be a rising prevalence of CAD in Bangladesh.

Gianrossi et al.investigated the diagnostic accuracy of ETT through a meta-analysis including 147 published reports involving 24,074 patients who underwent both coronary angiography and ETT.There was a wide variability in sensitivity and specificity of ETT [sensitivity 68± 16% (range 23–100%); specificity 77±17% (range: 17–100%)]. Another Meta analysisshowedsensitivity of 81± 12% (range: 40–100%) and specificity of 66± 16% (range: 17–100%).

2014 Taimur et al evaluated ETT (Treadmill) Positive Patients in a Tertiary Care Hospital of Bangladesh by doing angiogram subsequently. They found the overall positive predictive value of ETT is 77.9%, and for male patient PPV is 86.25% and for female patient it is 50%.

In 1987 Mark DB et al showed Duke Treadmill Score was useful for stratifying prognosis in patients with suspected coronary artery disease who were referred for catheterization, and may provide a useful adjunct to clinical decision making in the larger population of patients being evaluated for chest pain. They had evaluated 2842 patients with chest pain who had both treadmill testing and cardiac catheterization.

Shaw LJ et al in 1998 estimated DTS provides accurate diagnostic and prognostic information for the evaluation of symptomatic patients evaluated for clinically suspected ischemic heart disease.

In 2015 Gunaydin et al showed there was a strong negative correlation between DTS and Syntax Score ($r = -072$, $p < 0.001$). The area under the receiver-operating curve of DTS was 0.83 (0.77-0.88, $P < 0.001$) for predicting significant presence of CAD. The optimal cut-off value of DTS to predict the significant presence of CAD was -3.7 (sensitivity of

74% and a specificity of 73%).The area under the receiver-operating curve of DTS was 0.84 (0.78-0.90, P < 0.001) for predicting high SS. The optimal cut-off value of DTS to predict high SS was -11.2 (sensitivity of 81% and a specificity of 80%). They concluded DTS can predict the presence and severity of stable coronary artery disease before coronary angiography and may enable to estimate revascularization method that will be required after the procedure.

Raxwal V, Shetler K, Morise A et al, 2001 developed and validated a simple treadmill score for men using 1282 male patients which can be used and calculated without using a calculator and the score has a sensitivity of 88% and a specificity of 96%.

In 2002 a simple score was developed for use specifically in women by Morise AP et al. For the validation group, score ranges are shown with the prevalence of CAD: <20 = 0/5 or 0%, 20-29 = 3/26 or 11%, 30-39 = 20/56 or 36%, 40-49 = 33/81 or 41%, 50-59 = 24/49 or 49%, 60-69 = 22/32 or 69%, and >70 = 7/7 or 100%.

In 1998 Alexander KP et al determined the ability of a treadmill score to provide accurate diagnostic and prognostic risk estimates in women. They estimated the diagnostic and prognostic value of the DTS in 976 women and 2,249 men who underwent both treadmill testing and cardiac catheterization in a single institution from 1984 to 1994.Results. Women and men differed significantly in DTS (1.6 vs. −0.3, p < 0.0001), disease prevalence (32% vs. 72% significant coronary artery disease [CAD], p < 0.001), and 2-year mortality (1.9% vs. 4.9%, p < 0.0001). Although overall women had better survival, the DTS performed equally well in stratifying both genders into prognostic categories. The DTS actually performed better in women than in men for excluding disease.

Materials and Methods

Study design

Type of study: Cross sectional study

As we want to correlate the different treadmills scores and identify which one is better to predict coronary artery disease in male and female population, cross sectional study is good one. By this study design we can find the different treadmill scores and angiographic data within a short time, easily and with less cost.

Study Area

University Cardiac Center, Bangabandhu Sheikh Mujib Medical University (BSMMU).

BSMMU is a renowned institute in Bangladesh with good indoor and outdoor facility. It also has good inpatient and outpatient services for local and other patients coming from distant places. There is a good mix of male and female patients also which is needed to test the study hypothesis. Overall, the patients coming in outdoor facility to get treatment represent the Bangladeshi population very well and uniformly.

Period of study: November 2016 to November 2017 (One year).

Study population: All stable patients visited University Cardiac Center, Bangabandhu Sheikh Mujib Medical University (BSMMU) for evaluation of stable chest pain.

Sampling Procedures

Patient presented with stable chest pain, who have undergone ETT according to Bruce protocol and admitted for CAG, will be selected as case considering inclusion and exclusion criteria. Detailed and thorough clinical assessment will be done and recorded. All available previous medical documents will be checked meticulously. Patients with previous revascularization, left bundle-branch block, paced rhythms or Wolff-Parkinson-White syndrome (WPW) on resting electrocardiogram (ECG), or valvular heart disease, congenital heart disease will be excluded from the study. To avoid falsely increasing the accuracy of the exercise treadmill test, patients with a previous myocardial infarction by history or by diagnostic Q wave will be excluded.

With history, clinical findings and investigations cases other than stable chest pain will be excluded. Informed written consent will be taken from the patient. CAG report will be collected from the Cath lab after the procedure.

Inclusion criteria:

1. Male and female patients undergone CAG and ETT within 6 months interval for stable angina.
2. Age between 30-69 years (Gibbons et al., 2002).

Exclusion criteria:

1. Previous myocardial infarction by history or ECG
2. Previous revascularization or valvular heart disease
3. Baseline abnormalities that may obscure electrocardiographic changes during exercise
    - Left bundle branch block or Right bundle branch block
    - Left ventricular hypertrophy with repolarization abnormality
    - Digitalis therapy
    - Vantricular paced rhythm
    - Wolf-Perkinson-White syndrome
    - ST abnormality associated with supraventricular tachycardia or atrial fibrillation

Procedures during study

Exercise Treadmill Testing

Patients will be undergoing treadmill testing using Bruce treadmill protocol. Before treadmill testing, the patients will be given a questionnaire. This questionnaire will estimate the patient's exercise capacity before the test and thus will allow most patients to reach maximal exercise capacity (Myers 1994). Visual ST-segment deviation will be measured at the J junction and will be corrected for pre-exercise ST-segment depression while standing; ST slope will be measured over the following 80 ms and will be classified as up sloping, horizontal, or down sloping. Slope will be coded as 1 horizontal, down sloping, or upslopingST depression and 0 for normal slope (up sloping<2 mm or ST-segment depression of <0.5 mm). The ST response will be considered which has the most horizontal, downsloping or up sloping ST-segment depression in any lead, except aVR, during exercise or recovery. An abnormal response will be defined as ≥ 1 mm of horizontal or downsloping or ≥2 mm upsloping ST-segment depression (Griffin 2013). The exercise tests will be analyzed, and reported per standard protocol and manual calculation. Decision for cardiac catheterization will be consistent with clinical practice. Analyses will be performed with the investigators blinded to clinical and angiographic results.

Coronary Angiography

Coronary artery narrowing will be visually estimated and expressed as percent lumen diameter stenosis. Patients with a 70% narrowing in one or more of the following is considered to have significant angiographic coronary artery disease: the left anterior descending, left circumflex, right coronary arteries or their major branches, or a 50% narrowing in the left main coronary artery (Kern 2013).

Treadmill Scores

Treadmill scores and their calculation are shown in Appendix A.

Data collection:

Data will be recorded in pre-designed questionnaires by history, clinical examination and investigation with the patient of University Cardiac Center, BSMMU.

Quality assurance strategy:

A set of questionnaire will be formulated & checked. To make the study credible, reliable & dependable data will be collected by principal investigator by using those questions over a month of period. Again the questions will be edited accordingly & necessarily after discussion with the guide and co-guide of this study.

Ethical Issues

At first ethical clearance will be taken from the ethical review committee of Bangabandhu Sheikh Mujib Medical University (BSMMU). The study will be carried out according to 1964 Helsinki Declaration for Medical Research involving Human subjects and amended by the 64th World Medical Association General Assembly, October 2013. No drugs or placebo will be used for this study. Each participant will enjoy every right to participate or refuse participation. They will be free to withdraw their participation at any stage of the study. Data taken from the participants will be regarded as confidential. Data will be used only for this scientific study. Participants will be informed in detail about the nature and purpose of the study, and informed written consent will be taken from each participant.

Sample size calculation

Sample size is calculated by using the following equation (One sample comparison of proportion):

$$n=\frac{\left[Z\beta\sqrt{p(1-p)}+Z\alpha\sqrt{p1(1-P1)}\right]^2}{(p-p1)^2}$$

n = required sample size

p = Proportion under alternative hypothesis that is proposed to be detected or worst possible outcome

p1= Proportion under null hypothesis or proportion in the population

$Z\alpha$ = 1.96 (5% level of significance)

Zβ = 1.28 when power is 0.9

According to Fearon WF et al (2002) the predictive accuracy of DTS is 71% (0.71).

If we assume: p1= 0.71

P = 0.55, Power = 0.8, α = 0.05

Sample size n =

$$\frac{\left[1.28\sqrt{.55(1-.55)}+1.96\sqrt{.71(1-.71)}\right]^2}{(.55-.71)^2}$$

= 91

Correction for non-response:

$N_f = 100/100 - N_r$

If Nr= Percentage of expected non-response is 10%

Nf= 100/100- 10 = 1.11

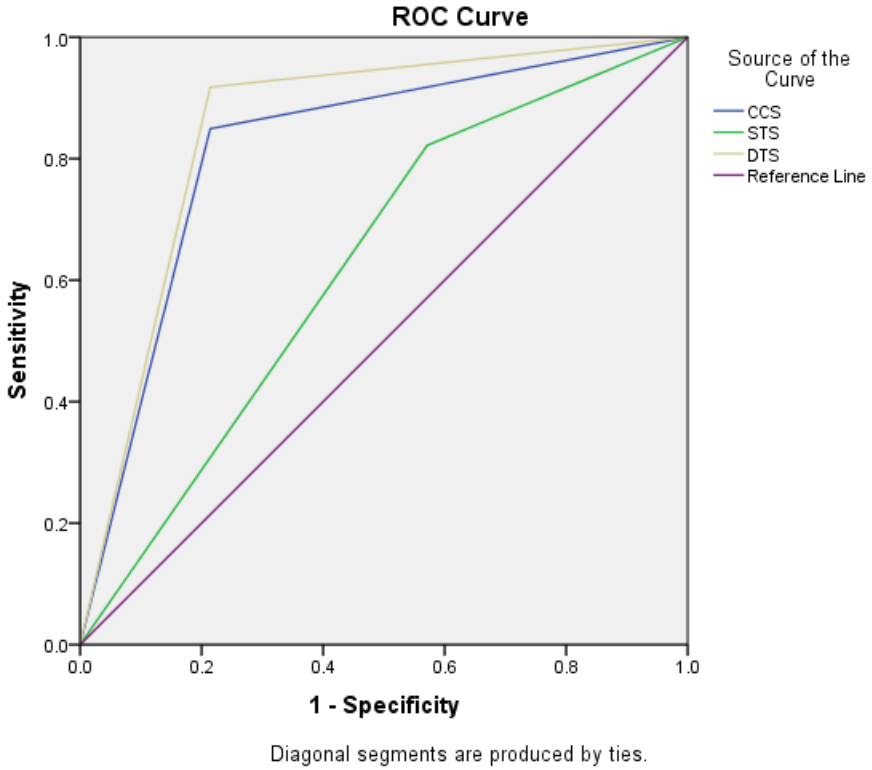
Final sample size will be estimated sample size (n) x Nf

= 91 x 1.11 = 102. So our required sample size is at least 102.

StatisticalMethods

Using angiographic evidence of CAD as the reference, area under the curve (AUC) of receive operator characteristic (ROC) plots will be determined for the ST response alone and for each treadmill score. The AUC for each treadmill score will be compared with the AUC of the ST response alone and the AUCs of the other treadmill scores. A significant difference is defined as a z-score >1.96, with z-score = $(AUC_1 - AUC_2) / (SE_1^2 + SE_2^2)$-2. The predictive accuracies of the DTS, the Simple Treadmill Score and Cleveland Clinic Score to stratify patients into high or low likelihood for CAD will be calculated and compare. Test of agreement will be calculated using Kappa statistics. Statistically significant difference between predictive accuracies is defined as a p value <0.05 using the two-tailed Fischer's exact test. Statistical analysis will be performed with the SPSS.

Dummy Tables/Graphs



Area Under the Curve

Test Result Variable(s)	Area	Std. Error[a]	Asymptotic Sig.[b]	Asymptotic 95% Confidence Interval	
				Lower Bound	Upper Bound
CCS					
STS					
DTS					

The test result variable(s): CCS, STS, DTS has at least one tie between the positive actual state group and the negative actual state group. Statistics may be biased.

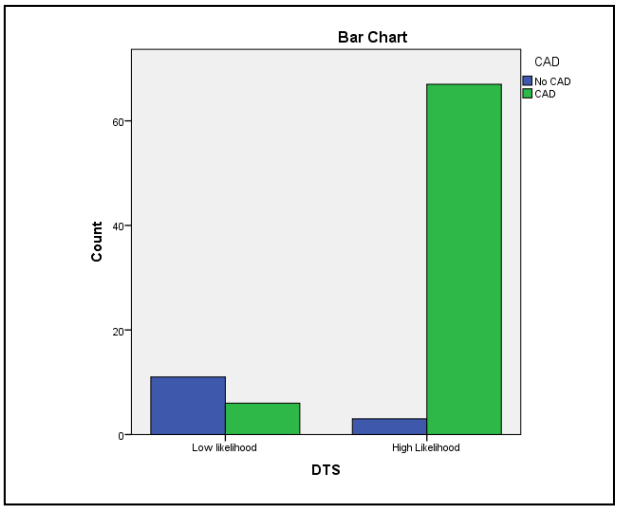
a. Under the nonparametric assumption

b. Null hypothesis: true area = 0.5

DTS * CAD

Crosstab
Count

	CAD		Total
	No CAD	NCAD	
Low likelihood			
High Likelihood			
Total			



Chi-Square Tests

	Value	Df	Asymp. Sig. (2-sided)	ExactSig. (2-sided)	Exact Sig. (1-sided)
Pearson Chi-Square					
Continuity Correction[b]					
Likelihood Ratio					
Fisher's Exact Test					
Linear-by-Linear Association					
N of Valid Cases					

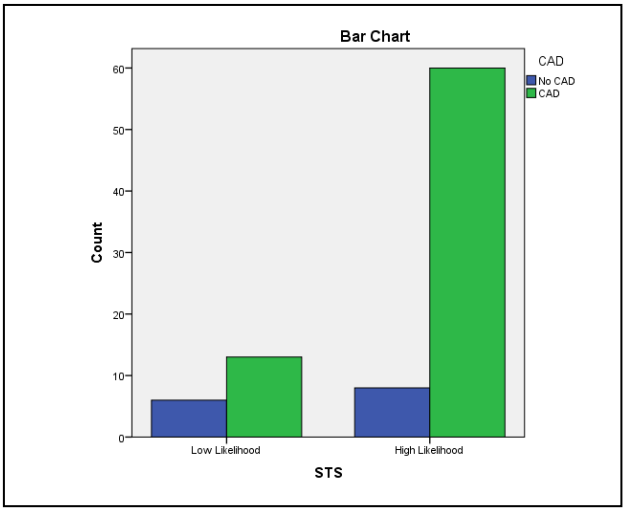
a. 1 cells (25.0%) have expected count less than 5. The minimum expected count is 2.74.
b. Computed only for a 2x2 table

Symmetric Measures

		value	Asymp. Std. Error[a]	Approx. T[b]	Approx. Sig.
Measure of Agreement	Kappa				
N of Valid Cases					

a. Not assuming the null hypothesis.
b. Using the asymptotic standard error assuming the null hypothesis.

STS * CAD



Crosstab
Count

	CAD		Total
	No CAD	CAD	
Low likelihood			
High likelihood			

Chi-Square Tests

	Value	Df	Asymp. Sig. (2-sided)	Exact Sig. (2-sided)	Exact Sig. (1-sided)
Pearson Chi-Square					
Continuity Correction[b]					
Likelihood Ratio					
Fisher's Exact Test					
Linear-by-Linear Association					
N of Valid Cases					

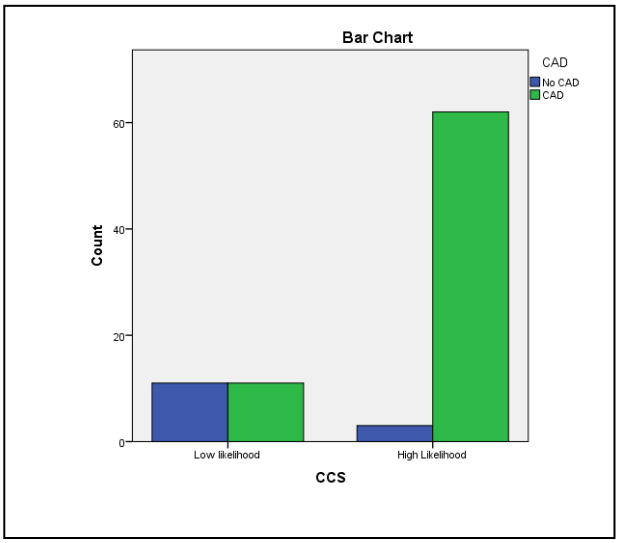
a. 1 cells (25.0%) have expected count less than 5. The minimum expected count is 3.06.
b. Computed only for a 2x2 table

Symmetric Measures

		Value	Asymp. Std. Error[a]	Approx. T[b]	Approx. Sig.
Measure of Agreement	Kappa				
N of Valid Cases					

a. Not assuming the null hypothesis.
b. Using the asymptotic standard error assuming the null hypothesis.

CCS * CAD



Crosstab
Count

		CAD		Total
		No CAD	CAD	
CCS	Low likelihood			
	High Likelihood			
Total				

Chi-Square Tests

	Value	df	Asymp. Sig. (2-sided)	Exact Sig. (2-sided)	Exact Sig. (1-sided)
Pearson Chi-Square					
Continuity Correction[b]					
Likelihood Ratio					
Fisher's Exact Test					
Linear-by-Linear Association					
N of Valid Cases					

a. 1 cells (25.0%) have expected count less than 5. The minimum expected count is 3.54.
b. Computed only for a 2x2 table

Symmetric Measures

		Value	Asymp. Std. Error[a]	Approx. T[b]	Approx. Sig.
Measure of Agreement	Kappa				
N of Valid Cases					

a. Not assuming the null hypothesis.
b. Using the asymptotic standard error assuming the null hypothesis.

Operational Definitions

Stable IHD

Stable IHD is defined as stable angina if there is no substantial change in symptoms over several weeks. It is usually characterized by episodes of reversible myocardial supply-demand mismatch, related to ischemia or hypoxia, which may be inducible by exercise, emotion or other stress and reproducible—but, which may also be occurring spontaneously. Stable angina has duration less than 20 mins and relieved by taking rest or sublingual nitroglycerine. (Partick et al., 1999)

Chest pain is defined as "typical angina" if it consists of characteristic (1) substernal discomfort, (2) is provoked by stress, and (3) is relieved by rest or nitroglycerin. It is considered "atypical" if it involves two or less of the previously mentioned criteria. It is labeled as non-cardiac chest pain if only one or none of the above three characters is present. (Griffin 2013)

STEMI

New ST elevation at the J point in at least 2 contiguous leads of ≥2 mm (0.2 mV) in men or ≥1.5 mm (0.15 mV) in women in leads V_2–V_3 and/or of ≥1 mm (0.1 mV) in other contiguous chest leads or the limb leads (Thygesen et al., 2012).

The majority of patients will evolve ECG evidence of Q-wave infarction. New or presumably new LBBB has been considered a STEMI equivalent. Most cases of LBBB at time of presentation, however, are "not known to be old" because of prior electrocardiogram (ECG) is not available for comparison. New or presumably new LBBB at presentation occurs infrequently, may interfere with ST-elevation analysis, and should not be considered diagnostic of acute myocardial infarction (MI) in isolation .Criteria for ECG diagnosis of acute STEMI in the setting of LBBB have been proposed . Baseline ECG abnormalities other than LBBB (e.g., paced rhythm, LV hypertrophy, Brugada syndrome) may obscure interpretation. In addition, ST depression in ≥2 precordial leads (V_1–V_4) may indicate transmural posterior injury; multilead ST depression with coexistent ST elevation in lead aVR has been described in patients with left main or proximal left anterior descending artery occlusion . Rarely, hyperacute T-wave changes

may be observed in the very early phase of STEMI, before the development of ST elevation (Patrick et al., 2013).

Acute MI

The classic world health organization (WHO) criteria for an acute MI require that two of the following three elements be present (Thygesen et al., 2012).

i. A history suggestive of coronary ischemia for a prolonged period of time (> 30 minutes)

ii. Evolutionary changes on serial ECGs suggestive of MI and

iii. A rise and fall in serum cardiac markers consistent with myonecrosis

UNSTABLE ANGINA/NSTEMI

Unstable angina (UA) and non–ST-segment elevation myocardial infarction (NSTEMI) remain leading causes of morbidity and mortality in the United States. These conditions are part of a continuum of acute coronary syndromes (ACSs) that range from UA and NSTEMI to ST-segment elevation myocardial infarction (STEMI). The clinical presentation of non–ST-elevation acute coronary syndrome (NSTE-ACS) can be variable, ranging from progressive exertional angina to postinfarction angina.

Braunwald classification of unstable angina (Griffin 2013)

Class	Clinical Characteristics
I	**Exertional angina** New onset, severe, or accelerated, Angina of < 2 moduration,More frequent angina,Angina precipitated by less exertion, No rest angina in the last 2 mo
II	**Rest angina, subacute** Rest angina within the last month but none within 48 h of presentation
III	**Rest angina, acute** Rest angina within 48 h of presentation

	Clinical Circumstances
A	**Secondary unstable angina** Caused by a noncardiac condition, such as anemia, infection, thyrotoxicosis, or hypoxemia
B	**Primary unstable angina**
C	**Postinfarction unstable angina** Within 2 wk of documented myocardial infarction

Because NSTEMI is distinguished from UA by the presence of elevated serum levels of cardiac biomarkers, serial measurements in patients presenting with ACS should be performed. With improvements in the diagnosis and risk stratification of patients with UA and NSTEMI, therapeutic approaches to NSTE-ACS have continued to evolve (Griffin 2013).

DIABETES MELLITUS(ADA Guideline, Jan 2016)

Diabetes is a group of metabolic diseases characterized by hyperglycemia resulting from defects in insulin secretion, insulin action, or both. Diabetes mellitus is defined by HbA1C $\geq$ 6.5% or fasting plasma glucose of 7.0 mmol/L or above, or post- prandial plasma glucose of 11.1 mmol/L or above with symptoms of hyperglycemia. An abnormal oral glucose tolerance test done recently or previously diagnosed as DM by a physician with or without on antidiabetic medication are also considered as diabetic patient.

SMOKING(Cannon, et al., 2001)

History of confirmed cigarette smoking in the past or in recent days is classified as following categories-

1. Current: Smoking cigarettes within 1 month of this admission.
2. Recent: Stopped smoking cigarettes between 1 month and 1 year before this admission.
3. Former: Stopped smoking cigarettes more than 1 year before this admission.
4. Never: Never smoked cigarettes.

HYPERTENSION (Whelton et al., 2017)

Sustained elevation of systolic and/or diastolic blood pressure which is measured over few weeks or history of taking medication for elevated blood pressure has considered as hypertension. The following categories are considered while labeling hypertension.

Categories of blood pressure	Sytolic Blood Pressure (mmHg)		Diastolic Blood Pressure (mmHg)
Normal	<120	and	<80
Elevated BP	120-129	and	<80
Stage 1 Hypertension	130-139		80-89
Stage 2 Hypertension	≥ 140		≥ 90

DYSLIPIDEMIA(Adult Treatment Panel III, 2001)

Patient has history of abnormal blood lipid profile or on treatment due to high blood lipid by a physician or current blood reports showing any of the following -
LDL Cholesterol……≥ 100 mg/dl
Total Cholesterol……..≥200 mg/dl
HDL Cholesterol…… ≤40 mg/dl.
Serum Triglycerides……..≥150 mg/dl

OBESITY AND OVERWEIGHT

Overweight and obesity are defined as abnormal or excessive fat accumulation that may impair health.

Body mass index (BMI) is a simple index of weight-for-height that is commonly used to classify overweight and obesity in adults. It is defined as a person's weight in kilograms divided by the square of his height in meters (kg/m2).

According to the WHO definition for Asian population (Who expert consultation, 2004):

- BMI greater than or equal to 23 is overweight
- BMI greater than or equal to 25 is obesity.

FAMILY HISTORY OF CAD

Any first degree relatives (parents, siblings or offspring) who have had any of the following at age less than 55 years in case of male and less than 65 years in case of female-

1. Typical Angina or
2. Myocardial Infarction
3. Sudden cardiac death without obvious cause.

CORONARY ARTERY DISEASE

Patients with a 70% narrowing in one or more of the following is considered to have significant angiographic coronary artery disease: the left anterior descending, left circumflex, right coronary arteries or their major branches, or a 50% narrowing in the left main coronary artery. Ischemic heart disease and coronary artery disease terms are used interchangeably (Kern M.J. 2013).

The extent and severity of CAD is defined as 1-vessel, 2-vessel, 3-vessel, or left main disease, with a significant stenosis ≥70% diameter reduction. (Neglia, et al., 2015)

CORONARY ANGIOGRAM/ CARDIAC CATHETERIZATION

Left heart catheterization or coronary arteriography remains the clinical gold standard for determining the presence of significant coronary artery disease (CAD).

Cardiac catheterization is the insertion and passage of small plastictubes (catheters) into the heart to obtain x-raypictures (angiography) of coronary arteries. The cardiac catheterization laboratory performs angiography to obtain images to diagnose coronary artery disease as well as other disease condition (Kern M.J. 2013).

Stable IHD

Anginal symptoms are defined as stable if there is no substantial change in symptoms over several weeks. Symptoms of stable angina can fluctuate from time to time, depending on myocardial oxygen consumption, emotional stress, or change in ambient temperature. In general, the clinical definition of stable angina pectoris closely correlates with the stability or quiescence of an atherosclerotic plaque and decreased clinical risk.

Chest pain is defined as “typical angina” if it consists of characteristic (1) substernal discomfort, (2) is provoked by stress, and (3) is relieved by rest or nitroglycerin. It is considered “atypical” if it involves two or less of the previously mentioned criteria. (Griffin 2013)

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Appendix A

Treadmill Scores and their calculation

The DTS will be calculated as DTS = exercise time - (5 x ST deviation) - (4 x exercise angina), with 0 = none, 1 = non-limiting, and 2 = exercise-limiting angina. The METs will be calculated by modified Bruce protocol and be inputted into the DTS equation (Fletcher et al., 1995). Based on the study by Shaw *et al. (1998)*, a DTS < + 5 is considered abnormal. High risk when DTS is < -10 and low risk when DTS is > +5.

The simple Treadmill Score for men will calculated as follows:

(6 x maximal heart rate code) + (5 x ST-segment depression code) + (4 x age code) + angina pectoris code + hypercholesterolemia code + diabetes code + treadmill angina index code.

The simplified score had a range from 6 to 95, with < 40 designated as low probability, between 40 and 60 was intermediate probability, and > 60 was high probability for CAD.

For male patient

Variable	Choose Response	Sum
Maximal HR	<100 bpm = 30	
	100-129 bpm = 24	
	130-159 bpm = 18	
	160-189 bpm = 12	
	190-220 bpm = 6	
Exercise ST depression	1 – 2 mm = 15	
	>2 mm = 25	
Age	>55 yr = 20	
	40-55 yr = 12	
Angina history	Definite/typical = 5	
	Probable/atypical = 3	

	Non-cardiac pain = 1	
Hypercholesterolemia	Yes = 5	
Diabetes	Yes = 5	
Exercise test: induced angina	Occurred = 3	
	Reason for stopping = 5	
	Total score:	

For Female patients

Variable	Choose Response	Sum
Maximal HR	<100 bpm = 20	
	100-129 bpm = 16	
	130-159 bpm = 12	
	160-189 bpm = 8	
	190-220 bpm = 4	
Exercise ST depression	1 – 2 mm = 6	
	>2 mm =10	
Age	>65yr = 25	
	50-65 yr = 15	
Angina History	Definite/typical = 10	
	Probable/atypical = 6	
	Non-cardiac pain = 2	
Smoking	Yes = 10	
Diabetes	Yes = 10	
Exercise test: Induced angina	Occurred = 9	
	Reason for stopping = 15	
Estrogen status	+ve = -5, -Ve = 5	
	Total =	

Cleveland Clinic Score:(Lauer et al., 2007)

Arbitrarily, we assume CCS will predict significant CAD with high probability if the value is > 140 and low probability it is <100.

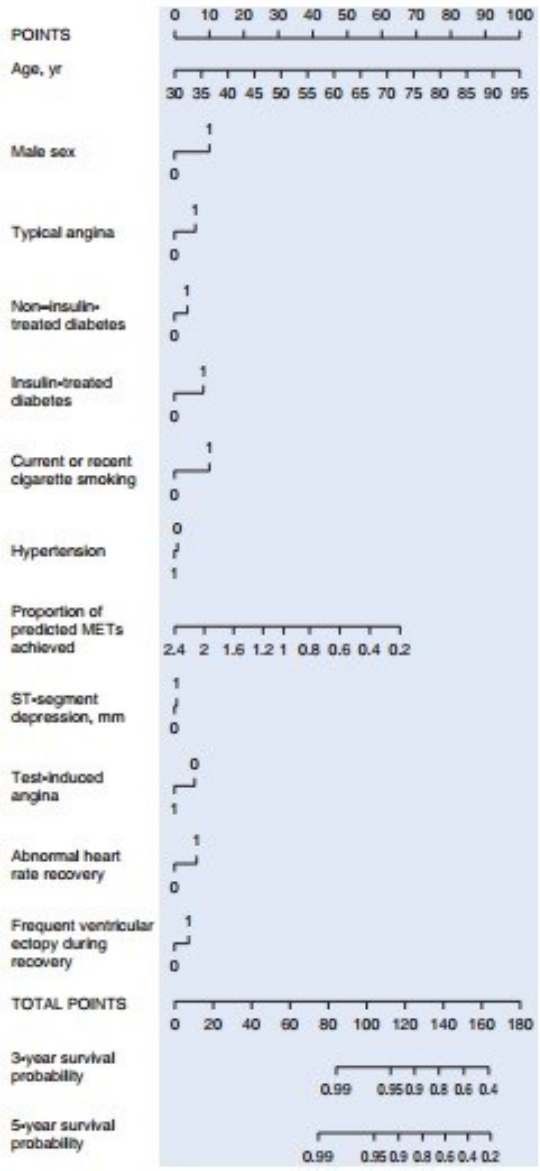
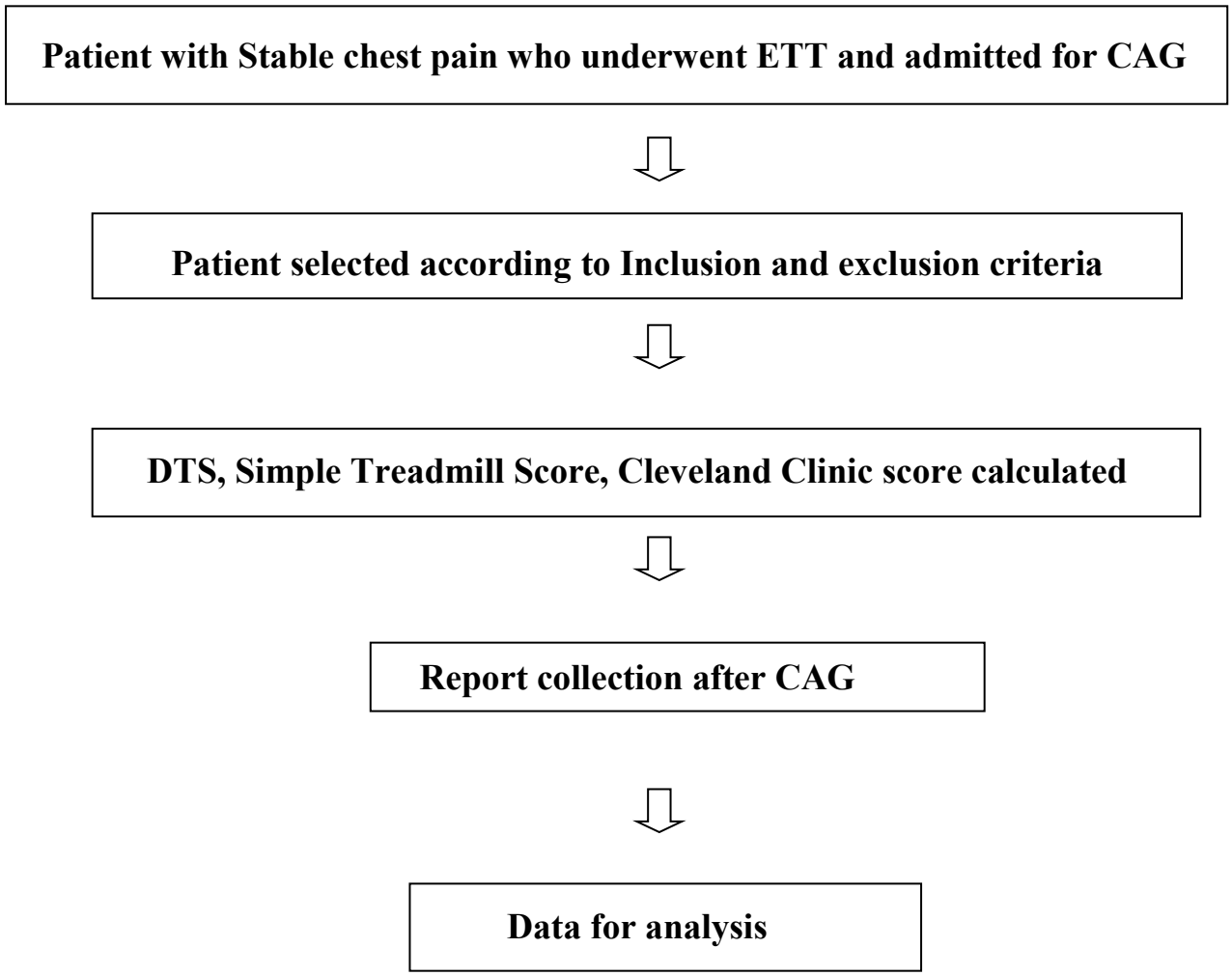


Fig: Cleveland Clinic Score Nomogram.

Appendix B

Study design flow chart:



Appendix C

Questionnaire/ Data Collection Form

Title: A comparative study of different treadmill scores to diagnose Coronary Artery Disease in among patients attending Bangabandhu Sheikh Mujib Medical University.

SL No…… **Date: ……**

Name: ……..

Address: ……

Hospital Reg. No. ……....

Date of ETT: …… Date of CAG: ……. CD No……

Demographic and anthropometric variables:

1.	**Age: ……Yrs**	
2.	**Gender: 1= Male 2= Female**	
3.	**Weight: …… Kg**	
4.	**Height: …… cms**	
5.	**Marital status: 0= No 1= yes**	

Baseline variables:

6.	**Anginal pain: 0= Non cardiac 1=Typical 2= Atypical**	
7.	**Past Smoker: 0= No 1= Yes**	
8.	**Current smoker: 0= No 1= Yes**	
9.	**Hypertension: 0= No 1= Yes**	
10.	**NIDDM: 0= No 1= Yes**	
11.	**IDDM: 0= No 1= Yes**	
12.	**Oestrogen status: 0= Negative 1= Positive**	
13.	**Family history of CAD: 0= No 1= Yes**	

14. Sudden death of 1st degree relatives: 0= No 1= Yes

Biochemical Investigations:

15. Lipid profile: TC….. mg/dl; LDL…… mg/dl; HDL….. mg/dl; TG…... mg/dl

16. RBS: ….……mg/dl

17. Serum creatinine: ……..mg/dl

Exercise test variables:

18. Duration of exercise: ……..min

19. METs …….

20. Maximum Heart Rate: ……bpm

21. Peak Systolic BP: ……mmHg

22. Maximum ST segment depression: ……mm

23. Exercise induced angina: 0= No angina 1= Non-test limiting

2= Test limiting angina

24. Abnormal heart rate recovery: 0= No 1= Yes

25. Frequent VE during recovery: 0= No 1= Yes

26. Duke Treadmill Score: ……. 0= Low risk

1= High risk

27. Simple Treadmill Score: …….. 0=Low probability

1=High probability

28. Cleveland Clinic Score: …….. 0=Low probability

1= High probability

Coronary angiogram:

29. Extent of disease: 0= Normal, 1=SVD, 2= DVD, 3= TVD, 4=LM

Appendix D

Informed written consent

The objective of this consent from is to inform you all necessary information to help you decide whether you want to participate in this study or not.

Objectives & Procedures:

This study will be conducted on the patients visiting Bangabandhu Sheikh Mujib Medical University (BSMMU) with the complaints of chest pain or shortness of breath or palpitation. At first ECG, ETTfindings of these patients will be recorded. Subsequently who are eligible for coronary angiogram (CAG), will be undergone this procedure. Thought this study high risk patients can be identified only by ETT and by providing timely medical treatment incidence of mortality and morbidity can be reduced. Provided you are eager to participate in this study, the physician involved in this research will ask you few questions regarding your health and life style. Numerous patients may get up to date treatment with the help of this study outcome.

Risks:

Participants of this study will get all necessary treatment according to current standard medical guideline. ECG, Echo, ETT are non-invasive tests having no risk of death or physical injury. CAG is an invasive test and is a common procedure here in the department of cardiology, BSMMU to diagnose and confirm Coronary Artery Disease. Chance of major complication during and after the procedure is in minimal.

Benefits:

If you participate in this study you will be benefited in the long run. By this study we will be able to detect high risk patients with the help of ETT alone, which is easy, less costly and has negligible risk. And overall mortality related to cardiac disease can be restricted.

Alternatives:

You can independently decide to participate or not to participate. And after participation you can withdraw yourself from this study anytime.

Cost:

You do not need to spend for you participation in this research activities. At the same time no allowance will be assigned to you for your participation.

Privacy:

During and after the research activity your privacy will be maintained confidentially. An I.D. will be assigned for future follow up and references. All your documents will be labeled with your name and address, and will be under lock and key.

Voluntary participation:

Your participation in this study is all voluntary. You can disagree to participate or can withdraw yourself from this study anytime. Despite that your current treatment will not be hampered and your legal rights will be abrogated while you are a participant.

Queries:

If you have any query, please do ask us. We will be happy to answer your questions. Also if any question arises in future while you are in the study, please communicate with the physician.

Consent Agreement:

I theundersigned satisfied after talking with the investigator of this study. I understand this participation is voluntary and I can with draw anytime without any bindings. I have read the aforementioned conditions and I agree to participate in this study.

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Interviewer's Signature	Participant's Signature	First Witness: ----------
Date:	Date:	Second Witness: ----------

Appendix E

Abbreviations

ACC……..American College of Cardiology

AHA…….American Heart Association

BMI……..Body Mass Index

BP…….Blood Pressure

BSMMU…….. ...Bangabandhu Sheikh Mujib Medical University

CAD……Coronary Artery Disease

DVD ……....Double Vessel Disease

DTS……Duke Treadmill Test

CAG……....Coronary angiogram

ETT…….Exercise Tolerance Test/ Exercise Treadmill Test

ECG……....Electrocardiogram

HDL…….High Density Lipoprotein

HR…….. …Heart Rate

IDDM……...Insulin dependent diabetes mellitus

IHD……..Ischemic Heart Disease

HTN…….Hypertension

LBBB……...Left Bundle Branch Block

LVH……..…Left Ventricular Hypertrophy

LDL……..…Low density lipoprotein

MET…….Metabolic Equivalent

MI……Myocardial Infarction

NIDDM……Non insulin dependent diabetes mellitus

SD…….....Standard Deviation

SPSS…….....Statistical Program for Social Science

SVD……..…Single Vessel Disease

TVD…….Triple Vessel Disease

VE……Ventricular Ectopic

WPW……. Wolf-Perkison-White syndrome