ASSESSMENT OF ASPIRIN RESISTANCE IN PATIENTS WITH RECURRENT THROMBOTIC EVENTS

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requirements for

M.D. DEGREE BRANCH I GENERAL MEDICINE

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CERTIFICATE

This is to certify that the dissertation titled **"ASSESSMENT OF ASPIRIN RESISTANCE IN PATIENTS WITH RECURRENT THROMBOTIC EVENTS"** is a bona fide work done by **Dr. J. S. THOMAS XAVIER PAULSINGH**, Post Graduate Student, Institute of Internal Medicine, Madras Medical College, Chennai – 600003, in partial fulfillment of the university rules and regulations for the award of MD DEGREE in GENERAL MEDICINE BRANCH-I, under our guidance and supervision, during the academic period from April 2010 to April 2013.

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DECLARATION

I solemnly declare that the dissertation titled **"ASSESSMENT OF ASPIRIN RESISTANCE IN PATIENTS WITH RECURRENT THROMBOTIC EVENTS"** was done by me at Madras Medical College, Chennai – 600003, during the period May 2012 to October 2012 under the guidance and supervision of **Prof. A. RADHAKRISHNAN, MD**, to be submitted to The Tamil Nadu Dr. M.G.R. Medical University towards the partial fulfillment of requirements for the award of MD DEGREE in GENERAL MEDICINE BRANCH-I.

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ABBREVIATIONS

CAD	Coronary artery disease
CVA	Cerebro vascular accident
SHT	Systemic hypertension
DM	Diabetes mellitus
PPI	Proton pump inhibitor
BMI	Body mass index
HDL	High density lipoprotein
LDL	Low density lipoprotein
TGL	Triglyceride
11dhTxB2	11-dehydro thromboxane B2
ESR	Erythrocyte sedimentation rate

TABLE OF CONTENTS

INTRODUCTION

Cardiovascular disease is a major cause of mortality and morbidity worldwide. Despite the development of newer antiplatelet drugs, aspirin is the most widely used antiplatelet drug to prevent first and recurrent myocardial infarcts and thrombotic cerebrovascular events including transient ischemic attacks.

Over the last few years several studies have shown that the response to aspirin is not uniform among the patients. Nowadays the term aspirin resistance has been employed to express the occurrence of cardiovascular events in spite of regular intake of aspirin at recommended doses.

Various studies have estimated the incidence of aspirin resistance to be 5 - 75%. It has been suggested that such patients have a three-fold higher risk of death, heart attack or stroke. Also 1 in 10 high risk patients suffer from the recurrence of a vascular event within the next 2 years despite regular daily aspirin therapy.

Urinary levels of the stable thromboxane metabolite, 11-dehydro thromboxane B2, reflect in vivo platelet activation and provide a surrogate marker of aspirin efficacy in patients on aspirin therapy.

It can be used to identify patients at increased risk of recurrent cardiovascular events, and in such patients therapy with higher doses of aspirin or additional antiplatelet may be necessary to prevent further cardiovascular events after compliance to aspirin therapy has been ascertained. This study aims to assess the influence of aspirin resistance in the secondary prophylaxis of patients with recurrent cardiovascular diseases.

AIMS AND OBJECTIVES

1. To assess the influence of aspirin resistance in the secondary prophylaxis of patients with recurrent thrombotic events
2. To quantify aspirin resistance as a risk factor in failure of secondary prophylaxis
3. To assess the prevalence of aspirin resistance in patients with recurrent thrombotic events

REVIEW OF LITERATURE

Cardiovascular diseases are one of the most common non communicable diseases in the world. It includes any disease that affects the cardiovascular system, principally cardiac diseases, vascular diseases of brain and kidney and peripheral artery disease. Cardiovascular diseases are the most common cause of death worldwide. Most common cause of death in developed countries is heart diseases. Second most common cause of death in developed countries is cerebrovascular accident. They are more common in developed countries. The mortality rate due to cardiovascular disease is improved in developed countries for the past two decades. But the incidence of cardiovascular disease is also increased in developing countries. Cardiovascular diseases are the most common cause of death in some developing countries also. They are more common in males compared to females. Postmenopausal females have same risk for cardiovascular diseases compared to males. Old age people are more prone to have cardiovascular diseases. Now young people are also affected by cardiovascular diseases. The incidence of cardiovascular diseases in India is also increasing now because of adaptation with western diet.

The major types of cardiovascular diseases are coronary artery disease, cerebrovascular accident, peripheral artery disease, cardiomyopathy, valvular heart disease, systemic hypertension, cardiac dysrhythmias, inflammatory heart disease and heart failure. Among these coronary artery disease, cerebrovascular accident and peripheral vascular disease usually occur due to thrombotic pathology. Aspirin is the most commonly used drug to prevent these thrombotic events.

CORONARY ARTERY DISEASE

Ischemic heart disease usually occurs due to imbalance between myocardial oxygen supply and demand. It usually occurs due to inadequate blood supply to heart. Heart rate, myocardial contractility and myocardial wall tension are the three important factors determining myocardial oxygen demand. It is increased in anemia and also in left ventricular hypertrophy due to aortic stenosis. Due to myocardial ischemia, regional wall motion abnormalities will occur. The myocardial pumping function will be affected. Coronary heart disease can occur in infants who have are origin of left anterior descending coronary artery from pulmonary artery.

CEREBROVASCULAR ACCIDENT

Cerebrovascular diseases include ischemic stroke, hemorrhagic stroke, intracranial aneurysm and AV malformation. Cerebrovascular accident is defined as acute onset of neurological deficit due to focal vascular cause. If cessation of blood flow lasts more than few seconds cerebral ischemia will occur. If cessation of blood flow lasts more than few minutes cerebral infarction will occur. Transient ischemic attack is defined as reversible focal neurological deficit without any radiological evidence of cerebral injury [1]. It must be reversible within twenty four hours. Symptoms in intracranial hemorrhage are due to mass affect and due to toxic effect of blood.

PERIPHERAL ARTERY DISEASE

Peripheral artery disease is a disease which is due to stenosis or occlusion of aorta or arteries of limbs.

- Atherosclerosis (commonest cause)
- Thrombosis
- Embolism
- Vasculitis

- Fibromuscular dysplasia
- Entrapment
- Cystic adventitial disease
- Trauma.

Diabetes mellitus, hypercholesterolemia, hypertension and hyperhomocysteinemia [2] are the risk factors for peripheral artery disease.

ATHEROSCLEROSIS

Atherosclerosis is the most common cause of cardiovascular diseases. Risk factors for atherosclerosis are:

- Age
- Gender
- Smoking
- Family history
- Obesity
- Lack of exercise
- Psychosocial factors

Arterial remodeling occurs in atherosclerosis. In early stage of atherosclerosis the plaque usually grows outward. In later stage only it grows inward and results in stenosis.

Atherosclerosis is usually a slow process. It usually begins in childhood and slowly progresses and manifests in old age. Precautions should be initiated in childhood to prevent atherosclerosis in old age. Causes of atherosclerosis in childhood are diabetes mellitus, nephrotic syndrome, chronic kidney disease, Kawasaki disease, childhood cancers, inflammatory bowel disease and certain types of congenital heart diseases.

Clinical features of atherosclerosis are due to the following consequences:

- Stenosis
- Aneurysm formation

Aorta is the most common site for development of aneurysm. Clinical feature due to atherosclerosis depends on the site of vessel involved.

- If it affects coronary arteries, myocardial infarction will occur.
- If it affects the arteries supplying central nervous system, cerebral thrombosis will occur.
- Atherosclerosis of peripheral arteries causes intermittent claudication and gangrene.
- Atherosclerosis of splanchnic circulation causes mesenteric ischemia.
- Atherosclerosis can affect kidney by causing stenosis of renal arteries.

Epicardial coronary arteries are the most common site for coronary atherosclerosis. The severity of symptoms depends on the degree of stenosis. If the blood vessel is narrowed >50%, patient will develop chest pain at exertion. If the stenosis is >80%, patient will develop pain at rest.

THROMBOSIS

Thrombosis is the most common pathology seen in many cardiovascular diseases. Thrombosis is the pathological form of hemostasis. Hemostasis is a tightly regulated process. It maintains the

fluidity of blood in normal blood vessels. In thrombosis clot formation occurs in uninjured blood vessel and vessel may be occluded after relatively minor injury. Both hemostasis and thrombosis involve the following three components:

- Vascular wall
- Platelets
- Coagulation cascade

ENDOTHELIAL CELLS

Normal endothelial cells maintain the fluidity of blood by inhibiting platelet adherence, preventing activation of coagulation factors and lysing blood clots. The sub endothelial extra cellular matrix is highly thrombogenic in nature. Normal endothelium inhibits exposure of platelets to the highly thrombogenic sub endothelial extra cellular matrix. Endothelial injury leads to exposure of underlying von Willebrand factor and basement membrane collagen to platelets.

PLATELETS

After endothelial injury platelets adhere to the extra cellular matrix and bind with von Willebrand factor through GpIb receptor and become activated. ADP, TXA2, P-Selectin and calcium are secreted by activated platelets. ADP promotes further platelet aggregation. TXA2 increases further platelets activation and causes vasoconstriction. Calcium is essential for activation of coagulation factors. von Willebrand factor is essential for stabilization of factor VIII. It prolongs the half-life of factor VIII. ADP activates GpIIb-IIIa receptors in platelets and stimulates the formation of primary haemostatic plugs.

COAGULATION CASCADE ACTIVATION

Coagulation cascade activation is essential for formation of secondary hemostatic plug. Endothelial injury leads to release of tissue factor which initiate coagulation cascade. At the end of coagulation, thrombin converts fibrinogen to insoluble fibrin which helps to form secondary hemostatic plug. Blood coagulation scheme is classified into extrinsic and intrinsic pathways that converge with activation of factor X. Prothrombin time is used to assess the proteins involved in extrinsic

pathway. APTT is used to assess the proteins involved in intrinsic pathway.

VIRCHOW'S TRIAD

Three factors are essential for thrombus formation. This is called Virchow's triad. They are:

- Endothelial injury
- Stasis or turbulence of blood flow
- Hypercoagulability of blood

The factors may act independently or in combination to promote thrombus formation.

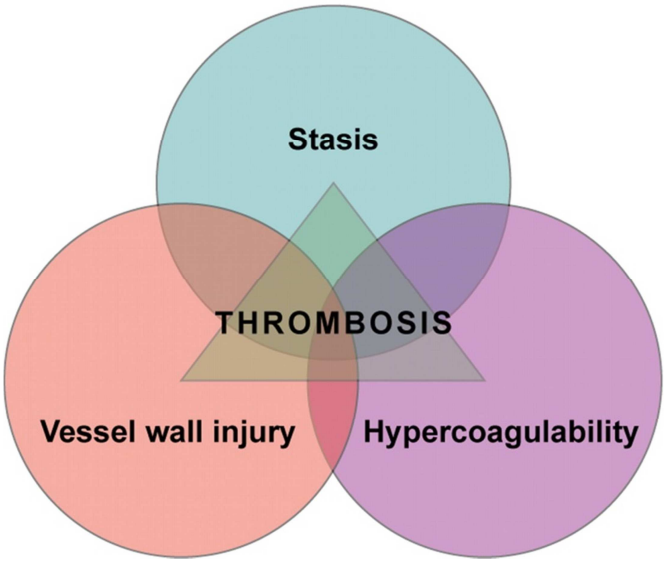


Figure **1**: Virchow's triad

ENDOTHELIAL INJURY

Endothelial injury may affect the normal blood flow and cause turbulent blood flow. It favors hypercoagulability of blood. Toxins, systemic hypertension, inflammation and metabolic products are responsible for endothelial injury.

TURBULENCE OF BLOOD FLOW

Abnormal blood flow may cause endothelial injury and initiate thrombus formation. Turbulence and stasis of blood contribute to thrombus formation.

- Atherosclerotic plaque causes turbulence of blood flow
- Aneurysm is responsible for stasis of blood
- Mitral stenosis leads to stasis of blood in left atrium
- Myocardial infarction leads to stasis of blood in left ventricle

All these situations predispose to thrombus formation at their respective sites.

HYPERCOAGULABILITY

Hypercoagulability generally contributes less frequently to thrombotic states but it nevertheless an important component for thrombus formation.

Primary causes for hypercoagulable state:

- Factor V Leiden mutation
- Methyltetrahydrofolate gene mutation
- Antithrombin III deficiency
- Protein C deficiency
- Protein S deficiency

Secondary causes for hypercoagulable state:

- Prolonged immobilization
- Myocardial infarction
- Atrial fibrillation
- Tissue damage by surgery
- Fracture
- Burns

- Cancer
- Prosthetic heart valve
- Disseminated intravascular coagulation
- Heparin induced thrombocytopenia
- Antiphospholipid antibody syndrome
- Nephrotic syndrome
- Sickle cell anemia
- Smoking
- Pregnancy

(*Heparin induced thrombocytopenia is a hypercoagulable state despite having thrombocytopenia. Antiphospholipid antibody syndrome is also a hypercoagulable state despite having prolonged prothrombin time.*)

TYPES OF THROMBUS

Thrombus may be formed anywhere in cardiovascular system – both arteries as well as veins.

ARTERIAL THROMBUS

Arterial thrombi are usually formed at the site of endothelial injury. Arterial thrombi are formed by platelets and coagulation cascade activation. Arterial thrombi are usually superimposed on an atherosclerotic plaque.

VENOUS THROMBUS

Venous thrombi are usually formed at the site of stasis. Platelets may play very minimal role in venous thrombus formation. Venous thrombi usually occur in superficial or deep veins of leg. Superficial venous thrombi can cause congestion, swelling and pain. Deep venous thrombi are more prone for embolization.

FATE OF THROMBUS

Thrombi may propagate, resolve or embolize.

- Propagation of thrombus leads to vessel obstruction
- Dislodge of fragment of thrombi distal to circulation is called embolization
- Thrombi may be resolved due to endogenous fibrinolytic system

ARACHIDONIC ACID

Platelets are small irregularly shaped cells derived from megakaryocytes. They circulate in blood and involved in hemostasis leading to thrombus formation. Arachidonic acid which is a 20 carbon polyunsaturated fatty acid present in its esterified form as a component of cell membrane phospholipid. Products derived from arachidonic acid may affect thrombosis. Arachidonic acid is released from membrane phospholipids by phospholipase enzyme which is stimulated by mechanical, chemical or physical stimulus. Cyclooxygenase enzyme acts on arachidonic acid and it is responsible for generation of prostaglandins. Lipooxygenase enzyme acts on arachidonic acid and it is responsible for production of leukotrienes and lipoxins.

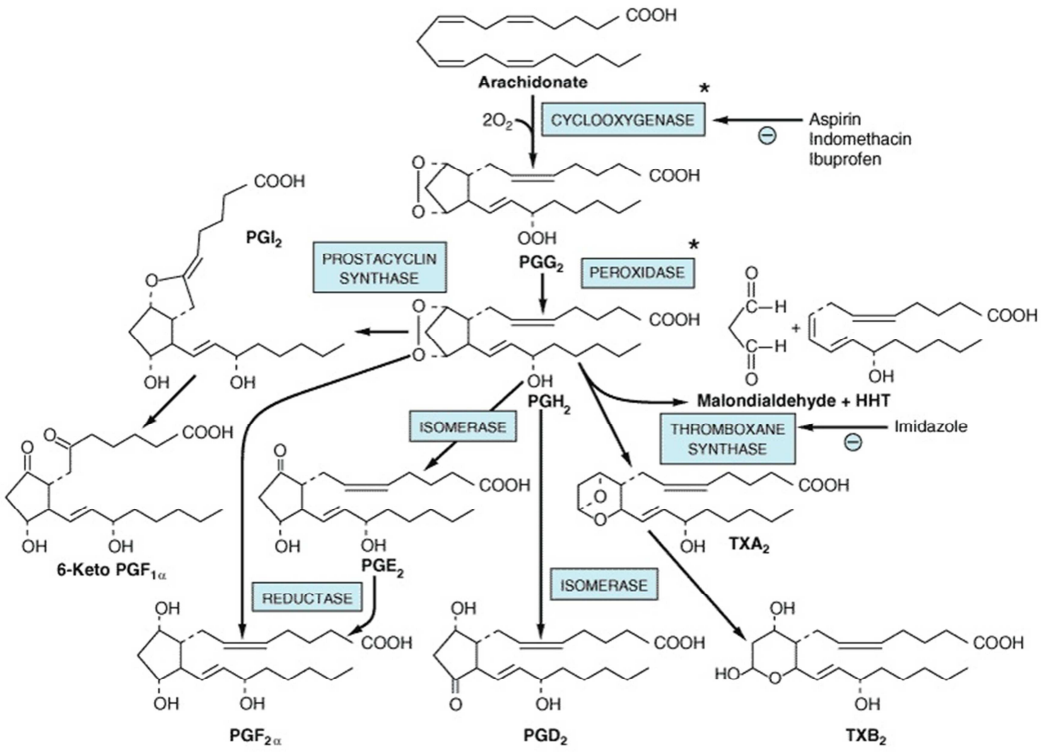


Figure **2**: Conversion of arachidonic acid to prostaglandins and thromboxanes of series 2

PROSTAGLANDINS

The type of prostaglandin generation usually depends on the cell in which it is formed:

Platelets contain thromboxane synthase enzyme. If platelets are activated they produce thromboxane A2 through activation of thromboxane synthase enzyme. TXA2 has potent platelet aggregatory and vasoconstriction properties.

If endothelial cells are stimulated they produce prostacyclins through activation of cyclooxygenase enzyme. Prostacyclins, PGE1, PGE2 and PGD2 have vasodilatory property. TXA2, leukotriene C4, D4 and E4 have vasoconstricting property. PAF is derived from membrane phospholipids by phospholipase A2. PAF causes vasoconstriction and bronchoconstriction. It also stimulates the synthesis of prostaglandins.

Glucocorticoids act by inhibiting phospholipase A2 enzyme and preventing the release of arachidonic acid. This property is responsible for anti-inflammatory action of steroids.

There are three isoforms in COX enzyme:

- COX 1 is a constitutive enzyme. It acts mainly in hemostasis and thrombus formation
- COX 2 is an inducible enzyme. It is mainly involved in inflammation
- COX 3 is a variant of COX 1

ASPIRIN

Aspirin is the most commonly used drug for secondary prevention of cardiovascular diseases. It is one of the cheapest drugs used in day today practice. Aspirin belongs to the group of non-steroidal anti-inflammatory drugs. But aspirin differs from all other drugs by irreversibly inhibiting COX enzyme. Aspirin has antiplatelet, anti-pyretic and anti-inflammatory action. Antiplatelet action is due to inhibition of cyclooxygenase enzyme [3]. In addition to antiplatelet action, aspirin is responsible for increased formation of NO [4]. This property usually augments the anti-platelet property of aspirin to prevent cardiovascular diseases.

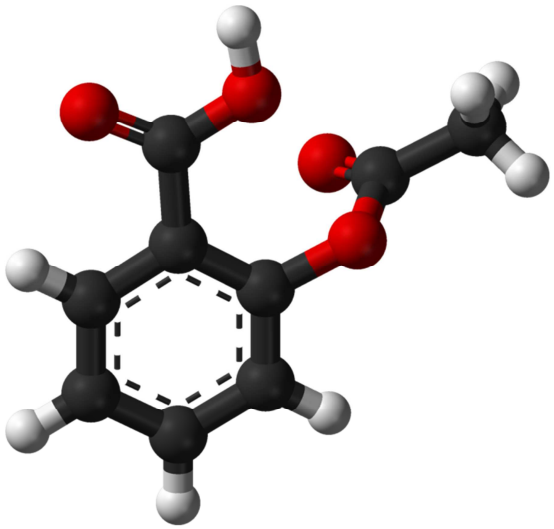


Figure **3**: Ball-and-stick model of the aspirin molecule

EFFECTS OF ASPIRIN

Effects of aspirin depend on the dose in which it is used:

- *Low dose aspirin*: 75-81 mg per day irreversibly inhibits platelet COX 1 enzyme. TXA2 synthesis alone impaired and responsible for antiplatelet effect. Platelets have life span of 7 days. Antiplatelet action of aspirin lasts for 7 days. In other tissues synthesis of new COX enzyme replaces the inactivated enzymes so that ordinary doses have duration of 6 - 12 hours. Platelet prostaglandin synthesis is inhibited completely by single dose of 100 mg aspirin or by 30 mg aspirin daily for 7 - 10 days.

- *Intermediate dose*: 650 mg - 4 g per day inhibits COX 1 and COX 2 enzymes and inhibits the synthesis of all prostaglandins. Intermediate dose has anti-pyretic and analgesic property.
- *High dose*: 4 - 8 g per day has anti-inflammatory effect due to prostaglandin dependent (particularly COX 2 dependent PGE2) and independent effects. High dose aspirin is mainly used in rheumatic diseases. However the usefulness of high dose aspirin is limited by toxicity such as tinnitus, hearing loss and gastric upset.

For antiplatelet action aspirin is usually used as once daily dose. For anti-inflammatory action in rheumatic diseases it is usually used as thrice daily dose.

Low dose aspirin is enough to produce antiplatelet activity. Medium dose aspirin has no advantage over low dose aspirin to produce anti platelet action [5]. Low dose aspirin has more antiplatelet action than medium dose aspirin because low dose aspirin will not inhibit prostacyclin synthesis. Long term use of low dose aspirin for more than

five years is associated with lower incidence of colon cancer. The mechanism for this protective effect is not known.

ASPIRIN INTOLERANCE

Some people may develop hypersensitivity reaction to aspirin in the form of rhinitis, asthma and angioedema. Aspirin induced exacerbation of asthma is due to increased production of leukotrienes from arachidonic acid because of inhibition of cyclooxygenase pathway. Aspirin desensitization should be tried in these patients. The incidence of rhinitis and asthma due to aspirin intolerance is 10% and the incidence of angioedema is 0.07 - 2% [6-8]. If anti platelet activity is immediately needed in these patients, other antiplatelet drugs like clopidogrel can be tried.

ADVERSE EFFECTS

The adverse effects are generally similar for all NSAIDS:

- Headache
- Tinnitus
- Dizziness
- Proteinuria

- Thrombocytopenia
- Abnormal liver function

The adverse effects specific to aspirin in cardiovascular disease patients are gastric upset with bleed, worsening of heart failure and acute kidney injury.

Gastro intestinal bleed

Aspirin increases the risk of gastrointestinal bleed and rarely intra cranial bleed. Low dose aspirin has same risk to produce gastro intestinal bleed compared to higher dose [9-11]. If any antiplatelet drug or anticoagulant drug is added to aspirin the bleeding risk is increased. Males are more prone for gastro intestinal bleed compared to females. Patients who are having gastro intestinal ulcer are more prone to develop gastro intestinal bleed than others.

The risk of gastro intestinal bleed is reduced with concomitant use of proton pump inhibitors. Proton pump inhibitors will not prevent lower gastro intestinal bleed [12]. The optimal regimen for patients who developed gastro intestinal bleed with low dose aspirin is to add a proton pump inhibitor rather than switching over to clopidogrel.

Congestive cardiac failure

Intermediate dose of aspirin may precipitate congestive cardiac failure. It is due to inhibition of synthesis of vasodilatory prostaglandins which may increase blood pressure. Studies have shown that aspirin may attenuate the effect of ACE inhibitors.

Acute kidney injury

Prostaglandins improve the autoregulation of blood flow in kidneys. Aspirin inhibits the auto regulation and leads to renal vasoconstriction and acute interstitial nephritis. Aspirin may precipitate acute kidney injury. If aspirin is used with paracetamol the risk of chronic kidney disease is increased. Aspirin alone will not cause chronic kidney disease.

CONTRAINDICATIONS

Aspirin is contraindicated in hemophilia because of antiplatelet action. It is also contraindicated in children with viral fever due to the risk of Reye's syndrome. Dose reduction should be done in both liver and renal failure.

Aspirin may prolong bleeding slightly not more than 1.2 - 2 times of pre-aspirin bleeding time. After discontinuation the bleeding time will become normal on fourth day and platelet aggregatory tests will become normal on eighth day. Aspirin must be stopped at least 1 week before surgery in surgical patients. Aspirin is rapidly converted into salicylic acid in the body.

The ideal therapeutic serum salicylate concentration is 10 - 30 mg/dl. Values greater than 40 mg/dl are associated with toxicity.

OTHER ANTIPLATELET DRUGS

Another antiplatelet drug clopidogrel which is a P2Y12 receptor blocker has some advantage over aspirin. It has less risk of gastro intestinal bleed and upset. Some studies have shown that it has more efficacy than aspirin. But compared to aspirin it is more expensive. Patients for whom cost is not an issue clopidogrel is probably better than aspirin for secondary prevention of cardiovascular diseases because of slightly greater efficacy and lesser side effects.

Dual antiplatelet therapy improves survival in acute coronary syndrome but it is not advised for cerebral thrombosis because of increased risk of intra cranial bleed.

ASPIRIN FORMULATIONS

There different types of aspirin formulations are available:

- Regular
- Buffered
- Enteric coated

Enteric coated aspirin will not disintegrate in stomach. So the risk of gastric upset is low with enteric coated aspirin [13]. Enteric coated aspirin has low bioavailability than regular aspirin because of reduced absorption in small intestine because of high pH. Low dose enteric coated aspirin has less anti platelet action compared to low dose regular aspirin [14-16]. Enteric coated aspirin should not be used as loading dose drug in acute myocardial infarction because of poor bio availability.

PREVENTION OF CARDIOVASCULAR DISEASES

- Weight reduction
- Smoking cessation
- Mild alcohol intake
- Hypertension control
- Control of dyslipidemia and blood sugar
- Good compliance with drugs like anti platelet drugs and anti-hypertensive drugs

ASPIRIN RESISTANCE

Clinical aspirin resistance is failure of aspirin to prevent recurrent thrombotic events despite regular intake of aspirin at regular interval [17-22].

The term "laboratory aspirin resistance" is used to describe persistent platelet activation despite taking regular aspirin at regular interval [23-27].

The incidence of laboratory aspirin resistance is highly variable depending upon the type of the test done and for whom the test is done. The incidence of aspirin resistance is 5 - 45% worldwide.

GENETIC VARIABILITY

Poor compliance with aspirin is the most common cause of aspirin resistance. Single nucleotide polymorphism is responsible for variable response to aspirin in aspirin taking patients.

PROTON PUMP INHIBITORS

Proton pump inhibitors may decrease the efficacy of aspirin. It may be due to decreased aspirin absorption in stomach due to elevated pH. Low pH is essential for absorption of aspirin. Würtz et al studied about the relationship between proton pump inhibitor and aspirin. They found that proton pump inhibitor may inhibit aspirin effect [28-30].

ATHEROSCLEROSIS

Advanced atherosclerotic patients may have resistance to aspirin. In advanced atherosclerosis stimulation of COX 2 enzyme occurs from activated macrophages. TXA2 synthesis occurs through activation of COX 2 enzyme. This enzyme will not be inhibited by low dose aspirin.

CONCOMITANT INTAKE OF OTHER NSAIDS

Concomitant intake with other NSAIDs may decrease the efficacy of aspirin. It is due to competitive inhibition in pharmacokinetics and pharmacodynamics of aspirin. Case control study from Physicians' Health Study showed that concomitant use of NSAIDs for more than 60 days per year may decrease the beneficial effects of aspirin.

INCREASED PLATELET TURNOVER

Increased platelet turnover is also a risk factor for aspirin resistance. In essential thrombocytosis once daily dose is not enough to inhibit the platelets. Twice daily dose may be advised in these patients.

EARLY POST CABG PERIOD

Aspirin resistance usually occurs in early post CABG period. It is due to the release of increased number of platelets from bone marrow in early post-operative period due to stress.

DIABETES MELLITUS

Diabetes mellitus is also a risk factor for aspirin resistance. Russo et al proposed that hyperglycemia interferes with aspirin induced NO

activation. This property is responsible for aspirin resistance in diabetes mellitus. Hyperglycemia will not interfere with thromboxane synthesis.

Dillinger et al compared the efficacy of same dose of aspirin either once or twice daily in diabetes mellitus. They compared the efficacy of aspirin between 150 mg once daily taking patients and 75 mg twice daily taking patients. They found that twice daily dose was more effective than once daily dose.

RENAL FAILURE

Blann et al studied the relationship between aspirin resistance and renal function. Their study showed that patient having advanced renal dysfunction had more aspirin resistance than others. Aspirin may worsen renal failure.

SMOKING

Smoking is also a risk factor for aspirin resistance. Isoprostenes are prostaglandin F2 like components. They are produced from arachidonic acid which is COX independent. They induce vasoconstriction and have prothrombotic effects. Production of isoprostenes is directly proportional

to the number of cigarettes smoked. Smokers are more prone to develop aspirin resistance due to production of isoprostenes.

OBESITY

Obesity affects pharmacokinetics and pharmacodynamics of many drugs by changing body composition, regional blood flow, distribution of volume and clearance in kidney and liver. Rocca et al studied about the variable risk factors affecting the pharmacokinetics of aspirin. Their study showed that obesity was associated with decreased absorption of aspirin.

Other risk factors for aspirin resistance are systemic hypertension and hypercholesterolemia.

Al azzam et al performed study to find out the prevalence and risk factors for aspirin resistance. Their study showed that female gender and diabetes mellitus were risk factors for aspirin resistance. Their study also showed that statin therapy improved aspirin resistance. As per their study age, obesity, smoking, family history, dose and duration of aspirin intake were not related with aspirin resistance.

LABORATORY ASPIRIN RESISTANCE

Laboratory aspirin resistance mostly correlates with clinical aspirin resistance. Grundman et al reported that 35% of clinically resistant patients had laboratory aspirin resistance and no clinically responsive patient had laboratory resistance. Anderson et al reported that 4.4% of biochemically sensitive patients had clinical resistance but 40% of biochemically resistant patients had clinical resistance.

METHODS

Several methods are available to estimate biochemical aspirin resistance. They will be discussed subsequently.

URINARY TXB2 LEVEL ESTIMATION

Measurement of TXA2 is not possible because of short half-life of TXA2. TXA2 is rapidly converted into TXB2. TXB2 excreted in the form of 11-dehydro thromboxane B2. High levels of urinary 11-dehydro thromboxane B2 are associated with aspirin resistance. Urinary TXB2 level estimation is a simple method. It is well correlated with clinical events.

HOPE study showed that patients in upper quartile of 11-dehydro TXB2 excretion had more risk for occlusive thrombotic events.

CHARISMA study also showed that patients who had high 11-dehydro thromboxane B2 excretion had more risk for occlusive thrombotic events.

P SELECTIN LEVEL ESTIMATION

P Selectin is a protein stored in alpha granules in platelets which are not activated. If platelets are activated P Selectin is expressed in platelet surface after degranulation. Then P Selectin moves to plasma. Estimation of P Selectin indicates platelet activation. Patients who are having high serum P Selectin are more prone for occlusive thrombotic events. Two methods are available to estimate P Selectin level. P Selectin flow cytometry is more expensive than soluble P Selectin estimation, whereas soluble P Selectin estimation is simpler than P Selectin flow cytometry.

PLATELET AGGREGATORY METHODS

Platelet aggregation is induced in by adding adenosine diphosphate. Platelet function analyser 100 is clinically more relevant

than optical platelet aggregation tests because PFA 100 is performed in the presence of red blood cells and optical platelet aggregation test must be done in the absence of red cells. PFA 100 is a simple and rapid method compared to others. PFA 100 test is more expensive than others. It should be done within four hours after blood collection. It is less suitable for epidemiologic studies. Optical platelet aggregatory method is widely available but it is operator dependent.

Aspirin resistant patients may be benefited from:

- Rectifying the risk factors which are aggravating resistance
- Increasing the dose of aspirin
- Adding another anti platelet drug or omega 3 fatty acid

MATERIALS AND METHODS

STUDY CENTER

Institute of Internal Medicine, Madras Medical College and Rajiv Gandhi Government General Hospital, Chennai – 3.

STUDY DESIGN

Cross sectional study.

PERIOD OF STUDY

Study was conducted from June 2012 to November 2012

SAMPLE SIZE

- Cases: 40
- Controls: 40

INCLUSION CRITERIA

- Age 18 to 65 years
- On aspirin for more than 7 days

EXCLUSION CRITERIA

- Age <18 years and >65 years
- Concomitant therapy with NSAIDs or anticoagulants

- History of active peptic ulcer
- History of acute coronary syndrome during the previous seven days
- Poor drug compliance
- Thrombocytopenia
- Thrombocytosis

METHODOLOGY

Forty patients with recurrent thrombotic events despite on aspirin therapy were selected as cases. Forty patients who were on aspirin following a cardiovascular event without any recurrence were selected as controls.

Patients' compliance with aspirin was checked. A complete history was taken either from the patient or his or her attender including past history of diabetes, hypertension, coronary artery disease and cerebrovascular accident. His or her personal habits were enquired.

A complete physical examination was done with monitoring of vitals and anthropometry. A battery of blood investigations were done including renal function test, liver function test, complete blood count,

fasting lipid profile, fasting blood sugar, post prandial blood sugar, and thyroid function test. Other investigations included were ECG, echocardiogram and CT brain.

Urine was collected from all the patients enrolled in the study and urinary levels of 11-dehydro thromboxane B2 were measured by Immunometric Assay using clinical chemistry analyzers.

STATISTICAL ANALYSIS

Data collected from the patients were analyzed using SPSS software version 21. The following tests were used to look for significance of the obtained results:

- Chi-square test
- Paired student t-test
- ANOVA

P value of <0.05 was considered as statistically significant at 95% confidence interval.

CONSENT

Written informed consent was obtained from all the participants of the study

ETHICAL COMMITTEE APPROVAL

Institutional Ethics Committee of Madras Medical College approved the study

CONFLICTS OF INTEREST

Nil

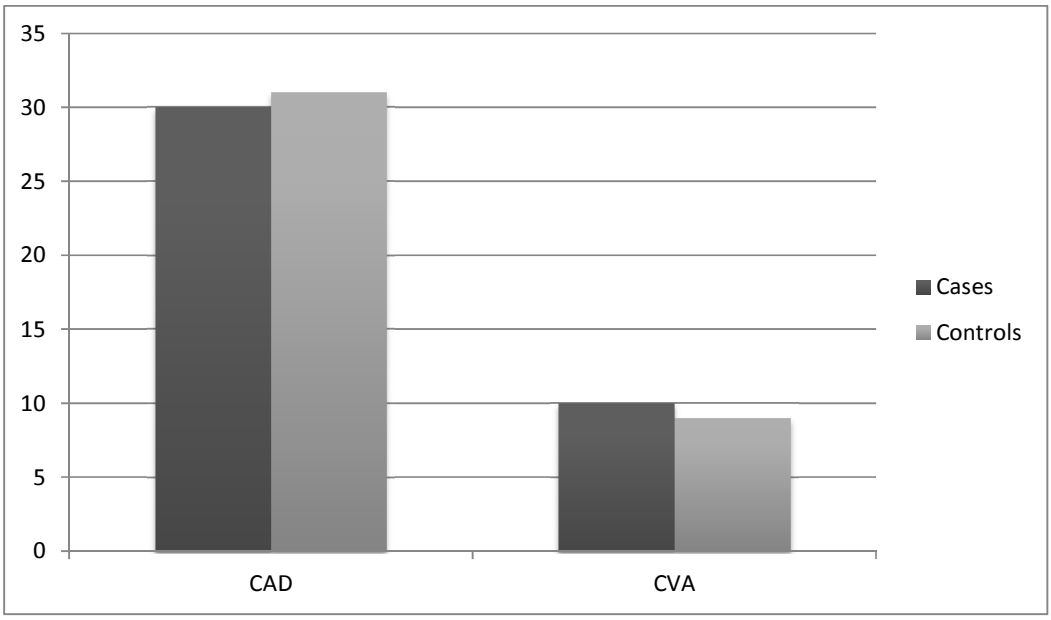
OBSERVATIONS AND RESULTS

CHARACTERISTICS OF THE STUDY POPULATION

	Group	Mean	SD
Age	Cases	49.85	4.933
	Control	49.28	5.472
Ht (cm)	Cases	167.65	5.972
	Control	167.00	6.329
Wt (kg)	Cases	62.43	5.970
	Control	61.58	5.593
BMI	Cases	22.1935	1.56716
	Control	22.0547	1.27683
FBS	Cases	97.05	15.727
	Control	96.30	13.373
PPBS	Cases	141.30	30.512
	Control	139.65	26.639
Cholesterol	Cases	174.18	10.964
	Control	173.13	9.455
HDL	Cases	50.25	6.448
	Control	50.65	6.967
TGL	Cases	144.95	12.157
	Control	142.38	11.790
LDL	Cases	94.935	13.5338
	Control	94.000	12.5560
Creatinine (mmol/l)	Cases	80.8860	14.37306
	Control	83.7590	18.12628
Duration of aspirin therapy	Cases	3.30	0.966
	Control	3.05	0.904

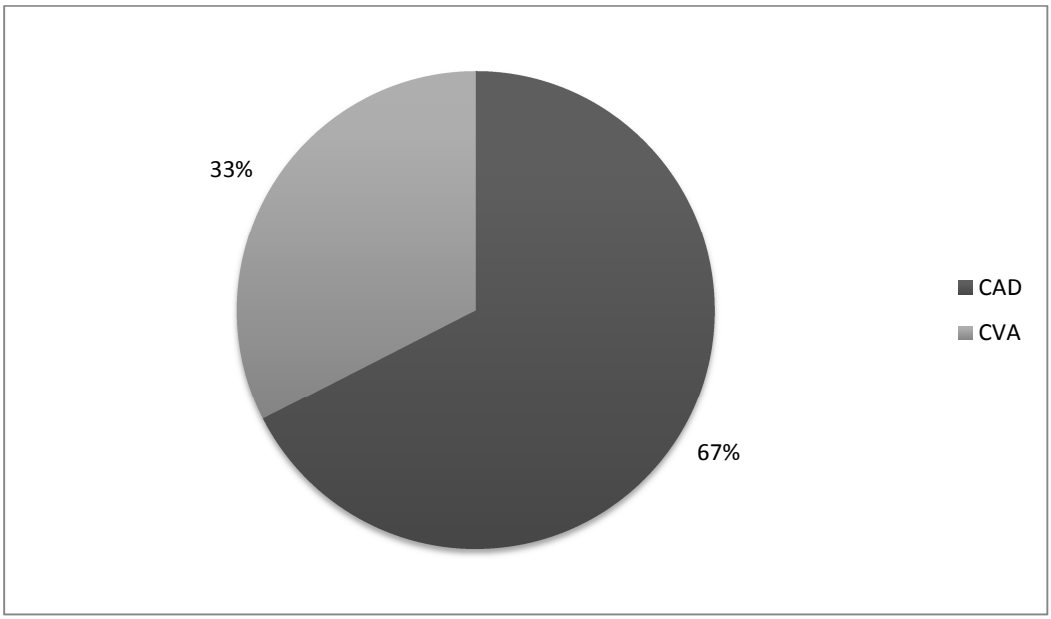
PRIMARY EVENT

Primary event	Cases	Controls	Total
CAD	30	31	61
CVA	10	9	19
Total	40	40	80



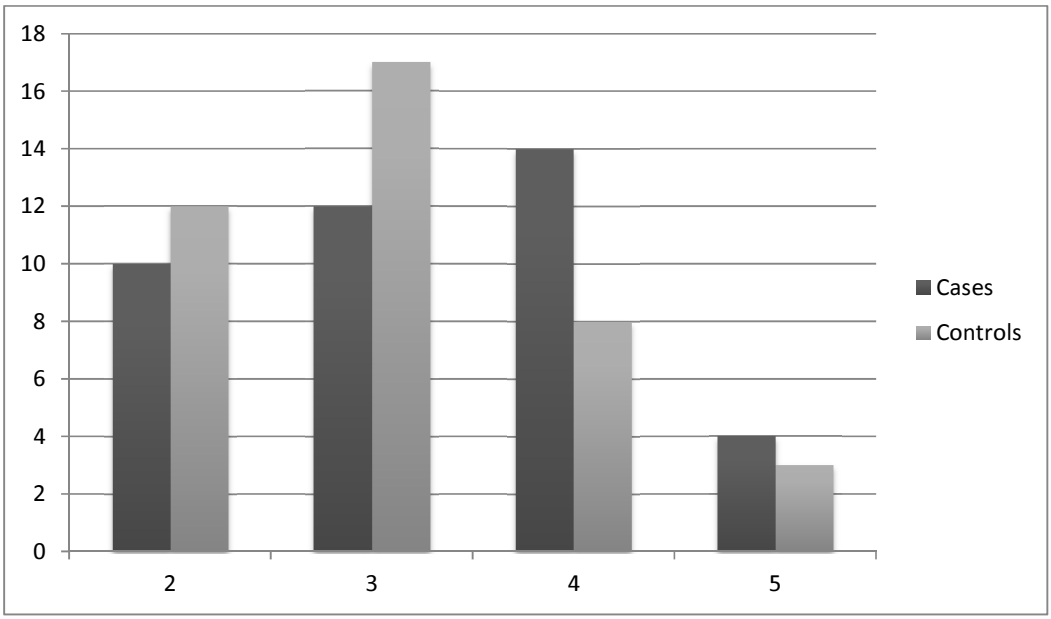
SECONDARY EVENT

CAD	27
CVA	13



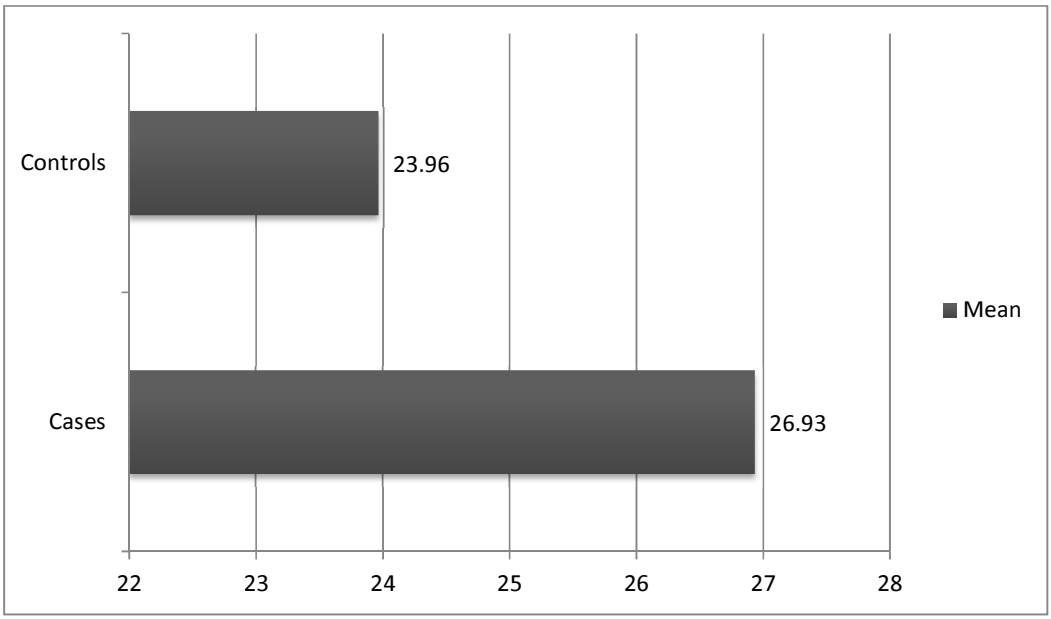
DURATION OF ASPIRIN THERAPY

Duration of aspirin therapy [years]	Cases	Controls	Total
2	10	12	22
3	12	17	29
4	14	8	22
5	4	3	7
Total	40	40	80



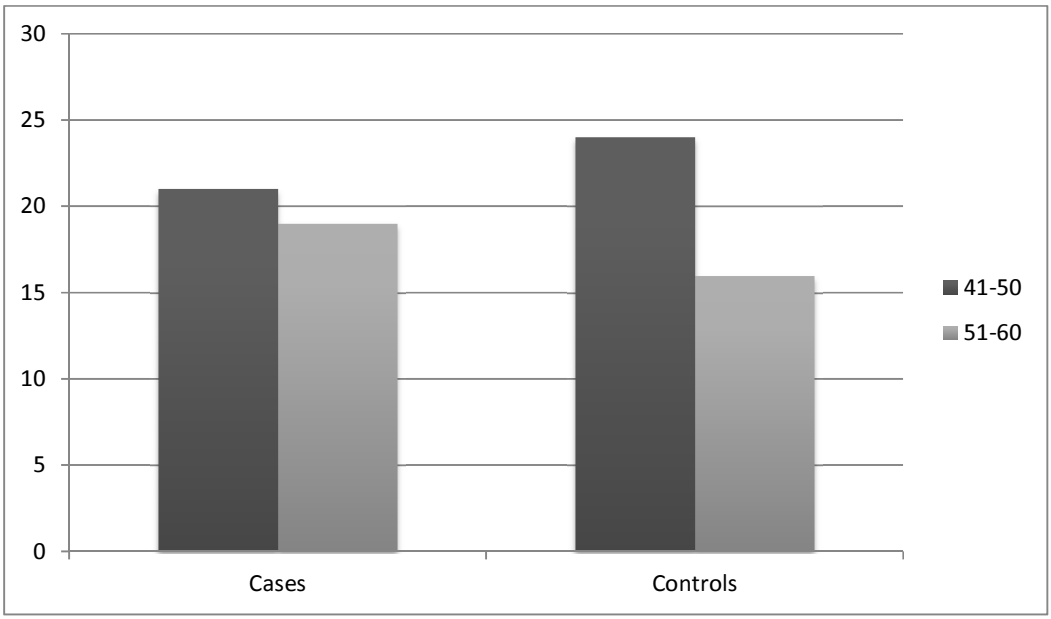
URINARY 11-DH TXB2 LEVELS AMONG CASES AND CONTROLS

Urinary 11-dh TxB2 levels	n	Mean	SD
Cases	40	26.93	0.840
Controls	40	23.96	0.771

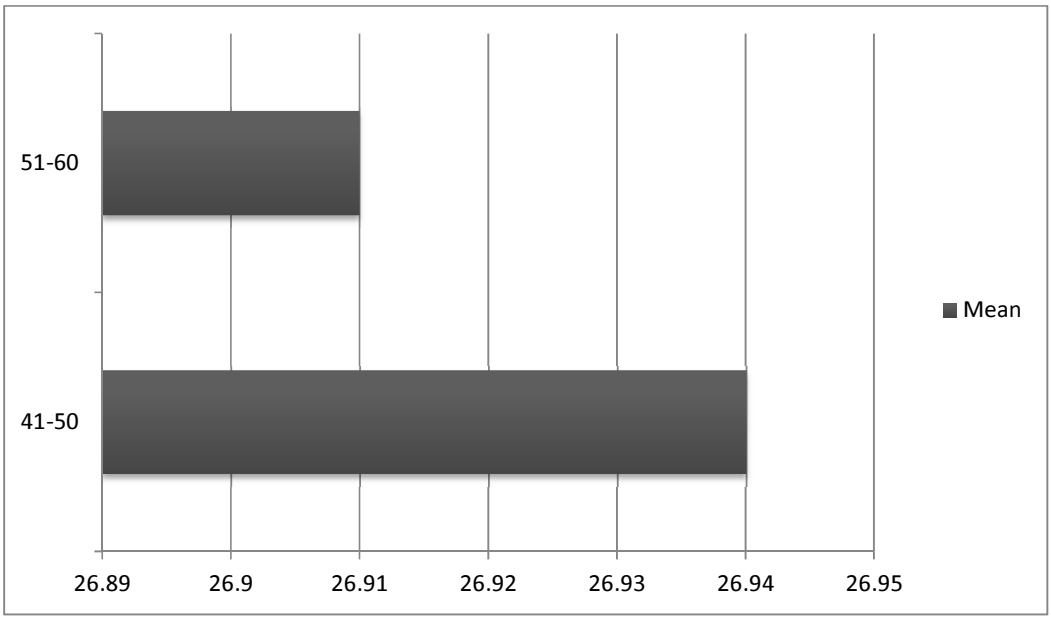


Age group

Age group	41-50	51-60	Total
Cases	21	19	40
Controls	24	16	40
Total	45	35	80



Urinary 11-dhTxB2 levels	n	Mean	SD
41-50	21	26.94	0.820
51-60	19	26.91	0.882

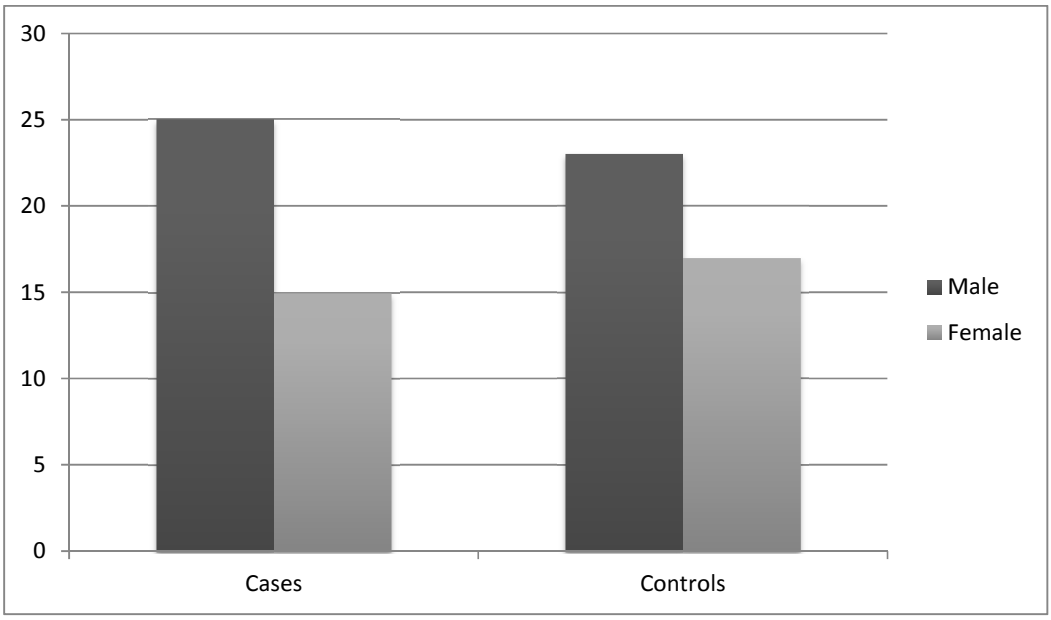


41-50 years	n	Mean	SD
Cases	21	26.94	0.820
Controls	24	24.03	0.761

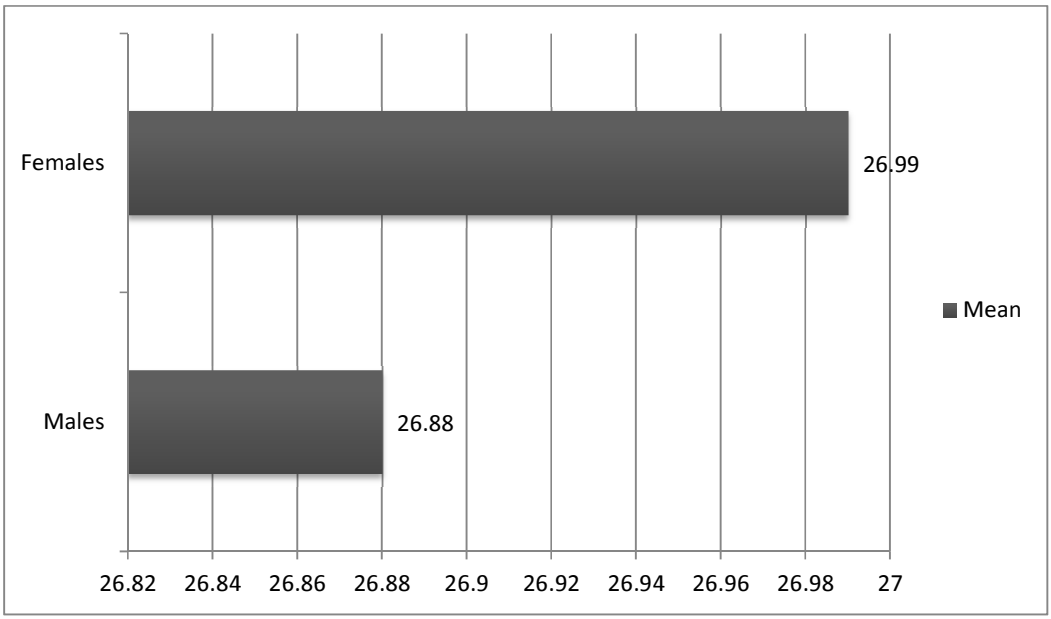
51-60 years	n	Mean	SD
Cases	19	26.91	0.882
Controls	16	23.85	0.797

SEX

Sex	Male	Female	Total
Cases	25	15	40
Controls	23	17	40
Total	48	32	80



Urinary 11-dhTxB2 levels	n	Mean	SD
Males	25	26.88	0.898
Females	15	26.99	0.756

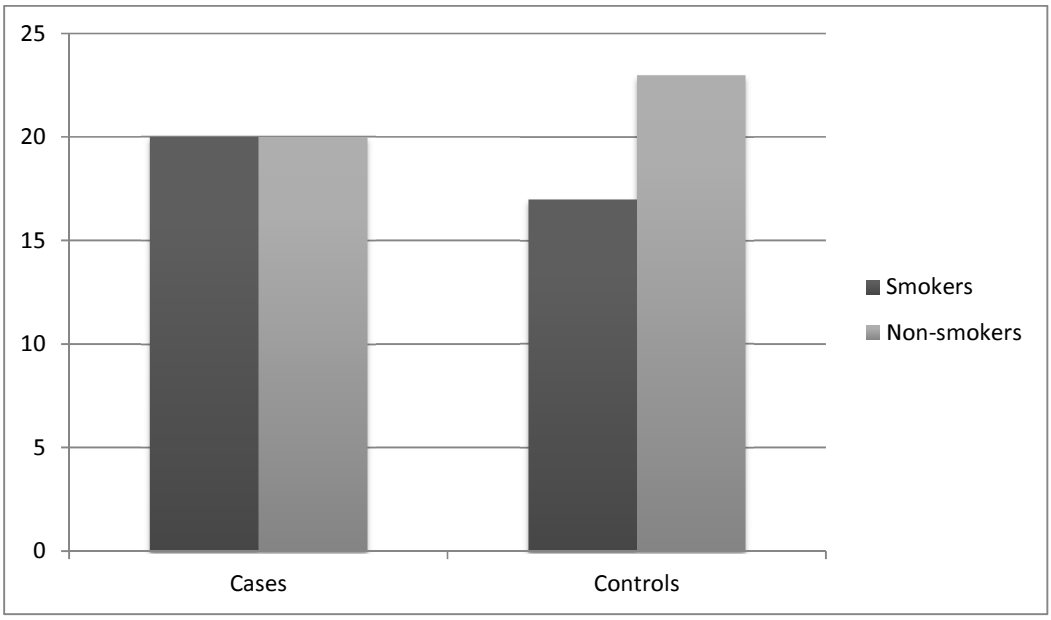


Male	n	Mean	SD
Cases	25	26.88	0.898
Controls	23	23.99	0.728

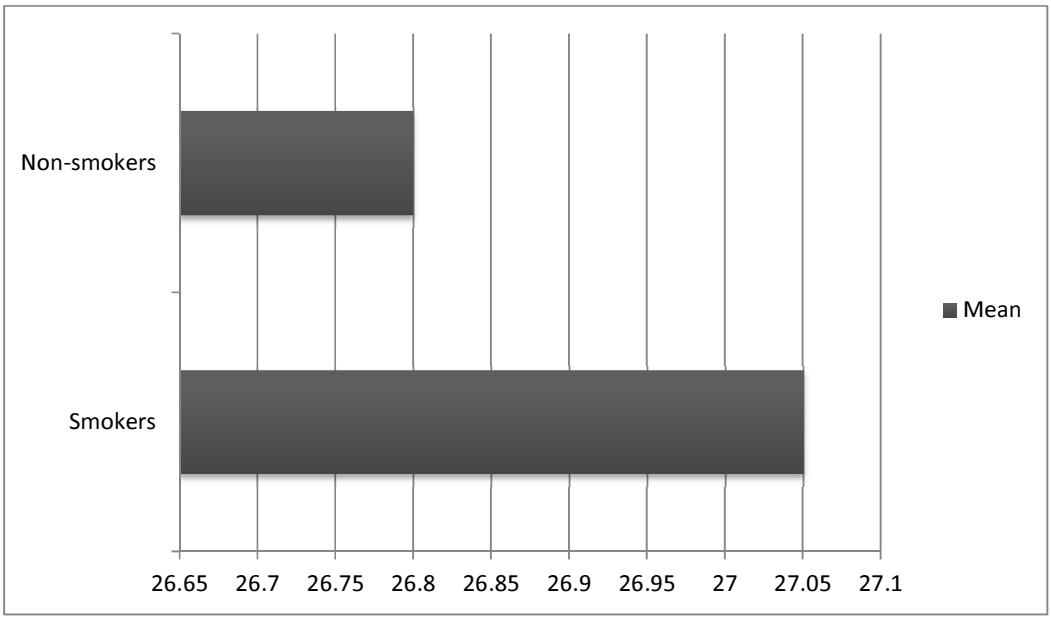
Female	n	Mean	SD
Cases	15	26.99	0.756
Controls	17	23.90	0.844

SMOKING

Smoking	Smokers	Non-smokers	Total
Cases	20	20	40
Controls	17	23	40
Total	37	43	80



Urinary 11-dhTxB2 levels	n	Mean	SD
Smokers	20	27.05	0.879
Non-smokers	20	26.80	0.800

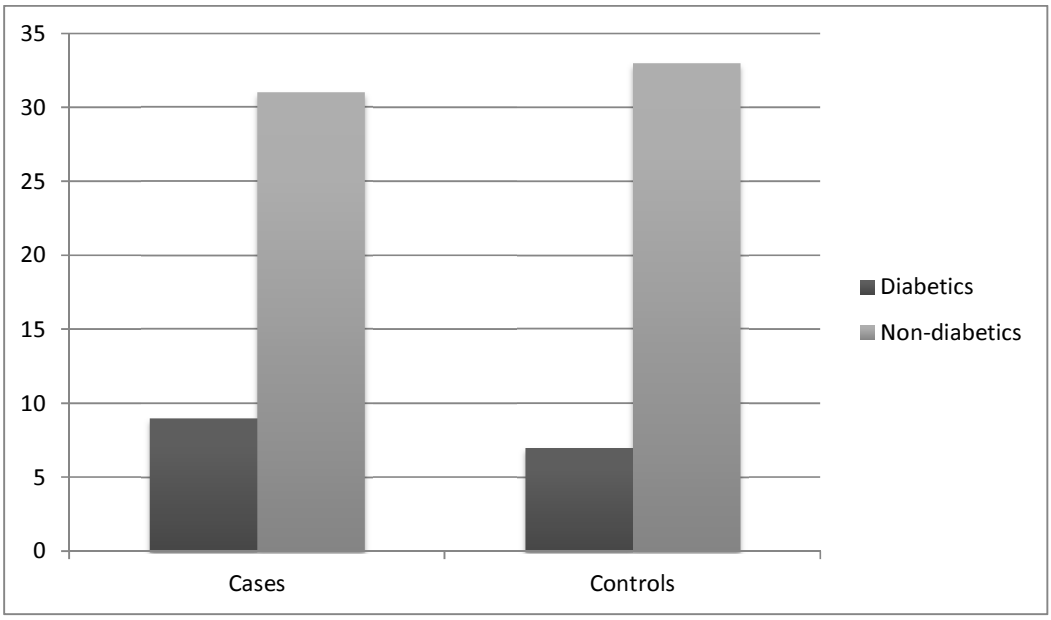


Smokers	n	Mean	SD
Cases	20	27.05	0.879
Controls	17	23.99	0.794

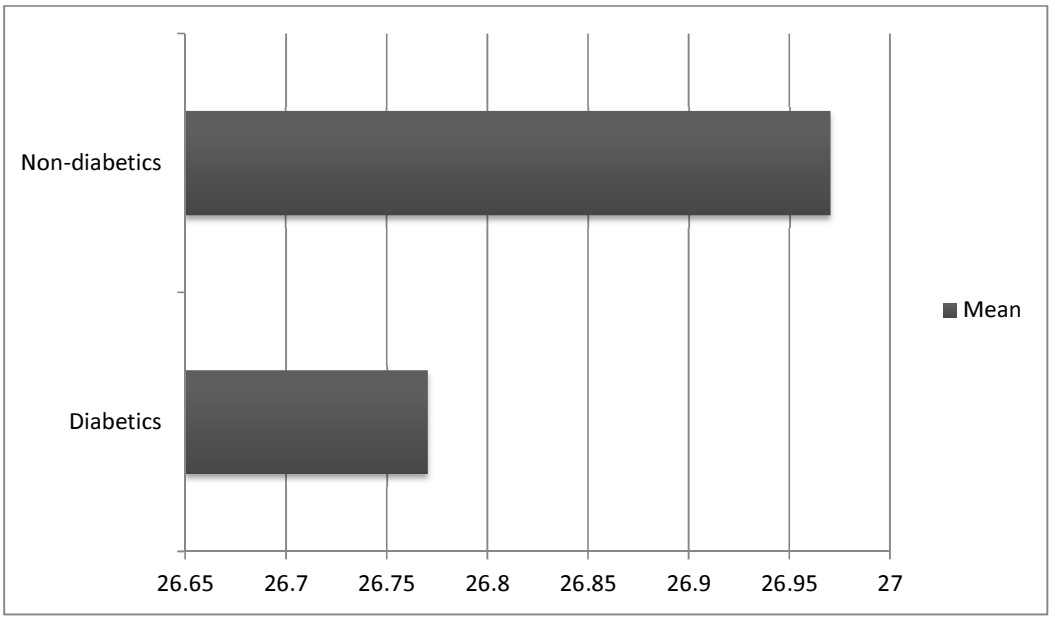
Non-smokers	n	Mean	SD
Cases	20	26.80	0.800
Controls	23	23.93	0.770

DIABETES

Diabetes	Diabetics	Non-diabetics	Total
Cases	9	31	40
Controls	7	33	40
Total	16	64	80



Urinary 11-dhTxB2 levels	n	Mean	SD
Diabetics	9	26.77	1.074
Non-diabetics	31	26.97	0.774

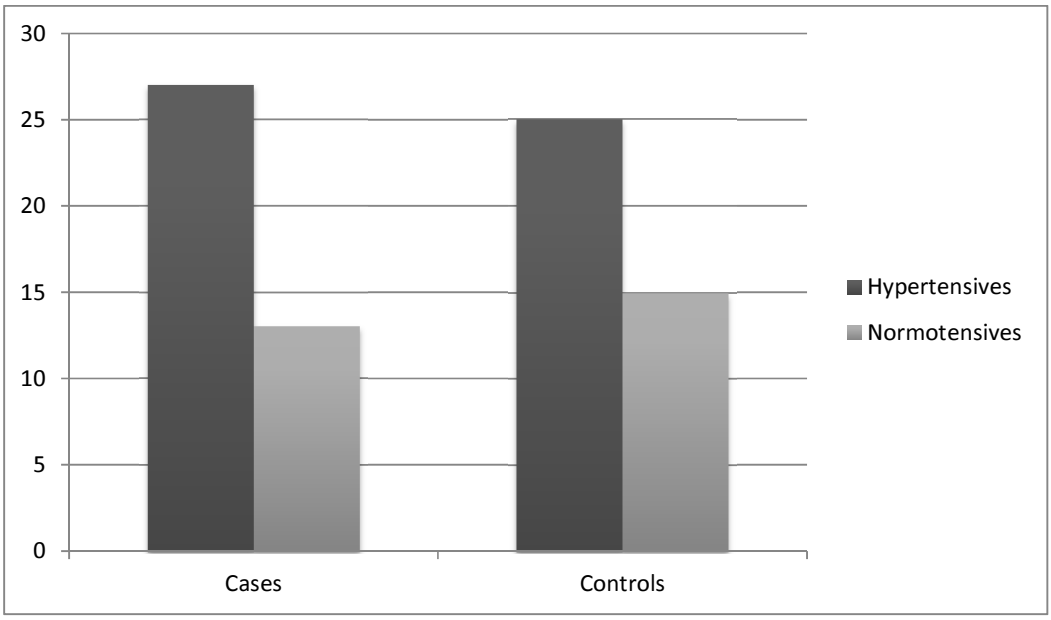


Diabetics	n	Mean	SD
Cases	9	26.77	1.074
Controls	7	24.12	1.015

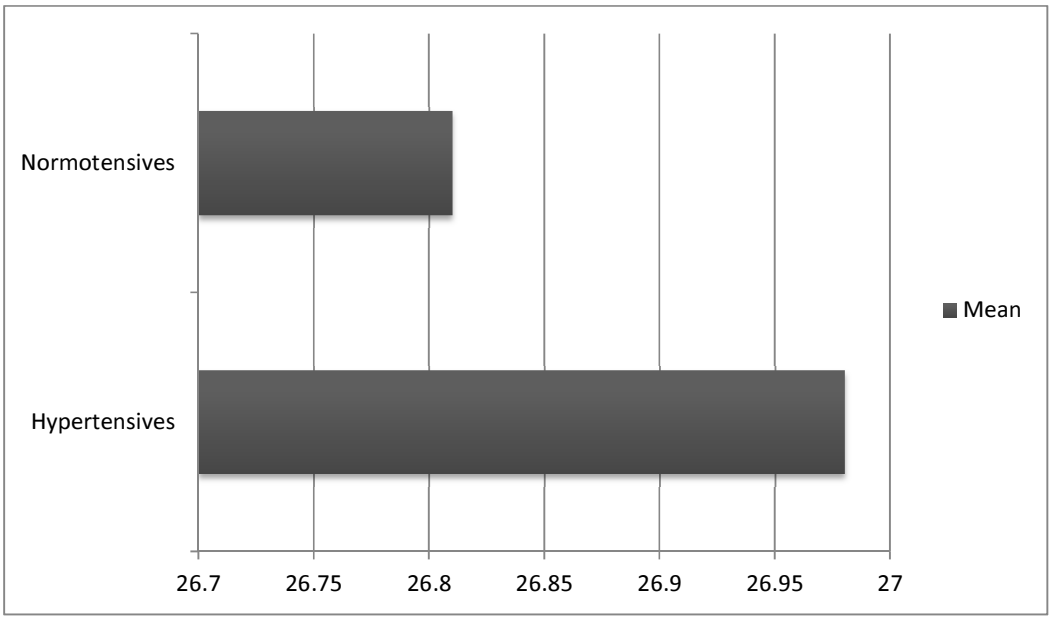
Non-diabetics	n	Mean	SD
Cases	31	26.97	0.774
Controls	33	23.92	0.724

HYPERTENSION

Hypertension	Hypertensives	Normotensives	Total
Cases	27	13	40
Controls	25	15	40
Total	52	28	80



Urinary 11-dhTxB2 levels	n	Mean	SD
Hypertensives	27	26.98	0.883
Normotensives	13	26.81	0.764

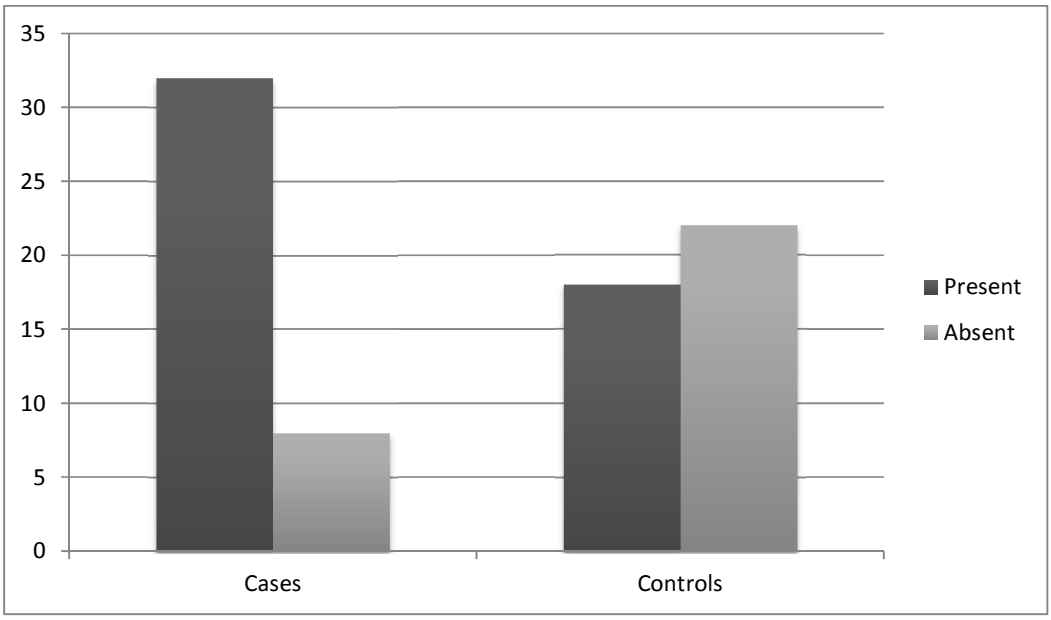


Hypertensives	n	Mean	SD
Cases	27	26.97	0.883
Controls	25	23.84	0.827

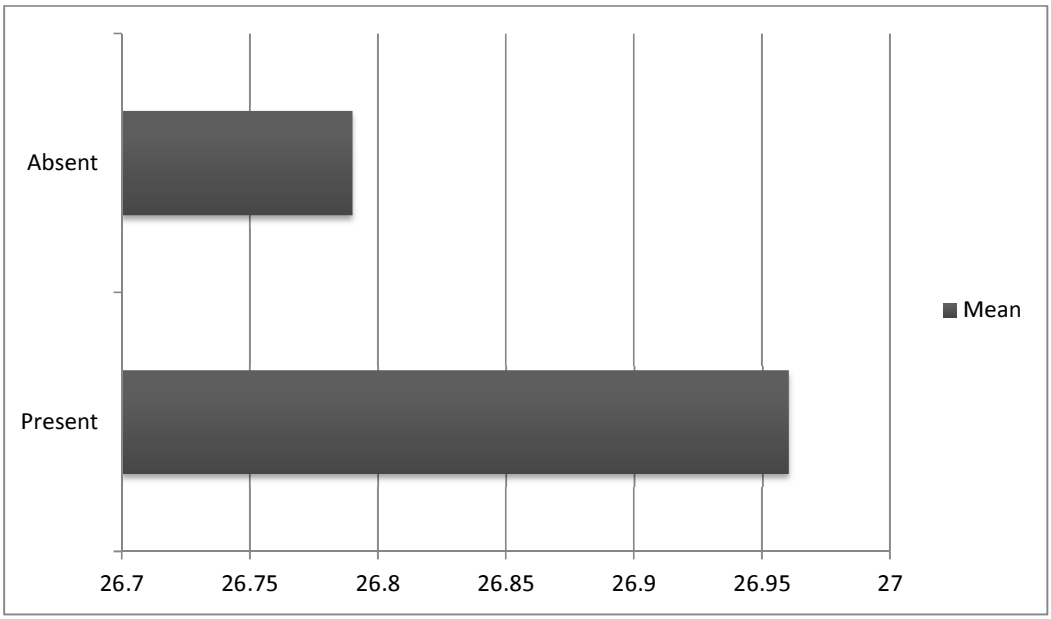
Normotensives	n	Mean	SD
Cases	13	26.82	0.764
Controls	15	24.15	0.646

PROTON PUMP INHIBITOR THERAPY

PPI intake	Present	Absent	Total
Cases	32	8	40
Controls	18	22	40
Total	50	30	80



Urinary 11-dhTxB2 levels	n	Mean	SD
Present	32	26.96	0.852
Absent	8	26.79	0.827

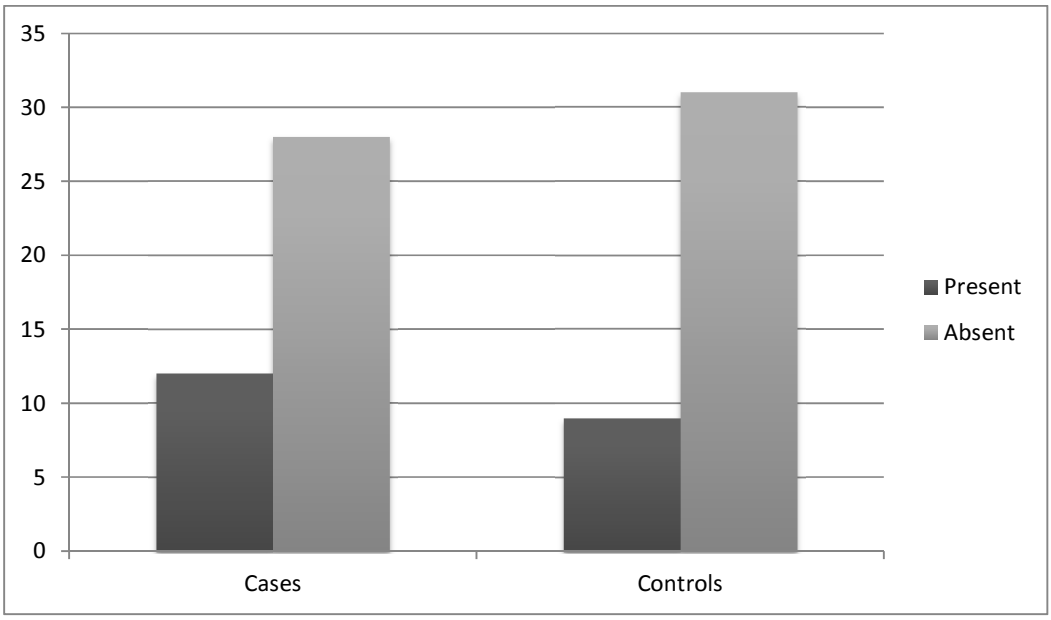


Patients on PPI	n	Mean	SD
Cases	32	26.97	0.852
Controls	18	23.97	0.757

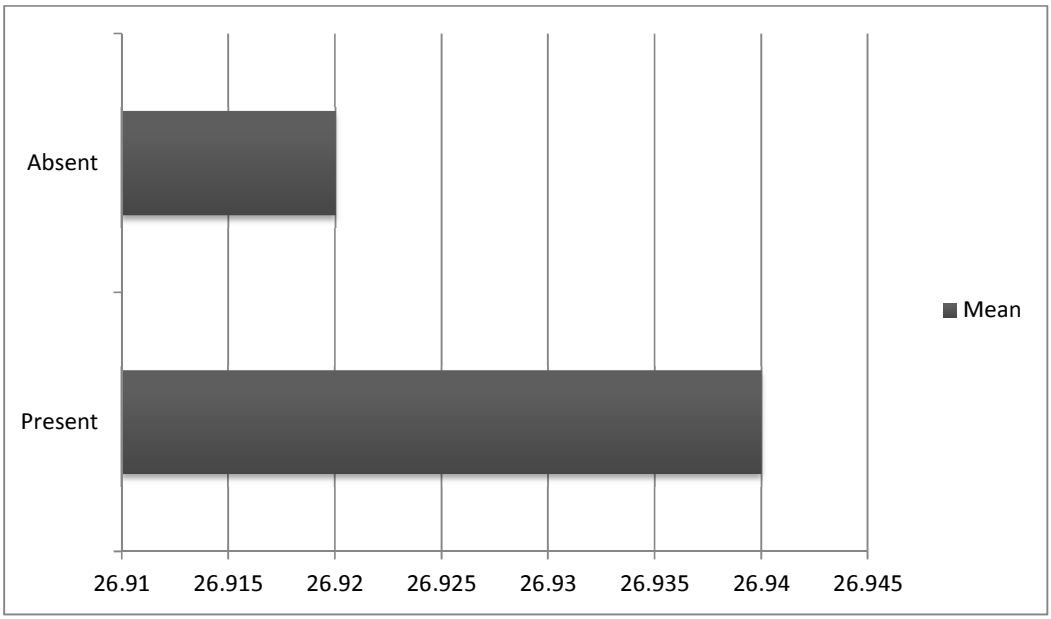
Patients of PPI	n	Mean	SD
Cases	8	26.79	0.827
Controls	22	23.95	0.800

FAMILY HISTORY OF CARDIOVASCULAR DISEASE

Family history	Present	Absent	Total
Cases	12	28	40
Controls	9	31	40
Total	21	59	80



Urinary 11-dhTxB2 levels	n	Mean	SD
Present	12	26.94	0.823
Absent	28	26.92	0.861

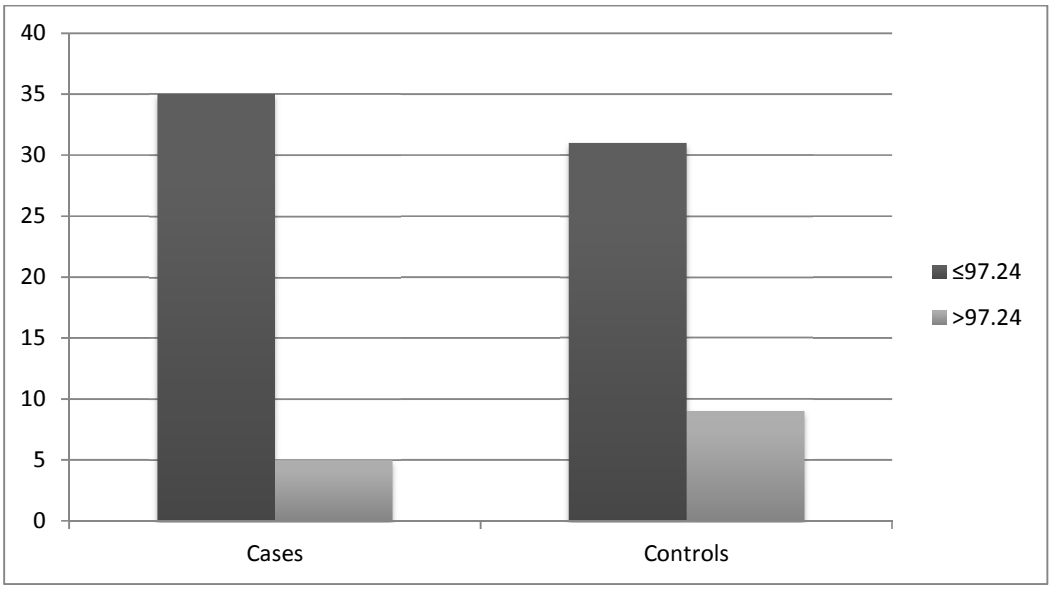


Positive	n	Mean	SD
Cases	12	26.94	0.823
Controls	9	24.04	1.070

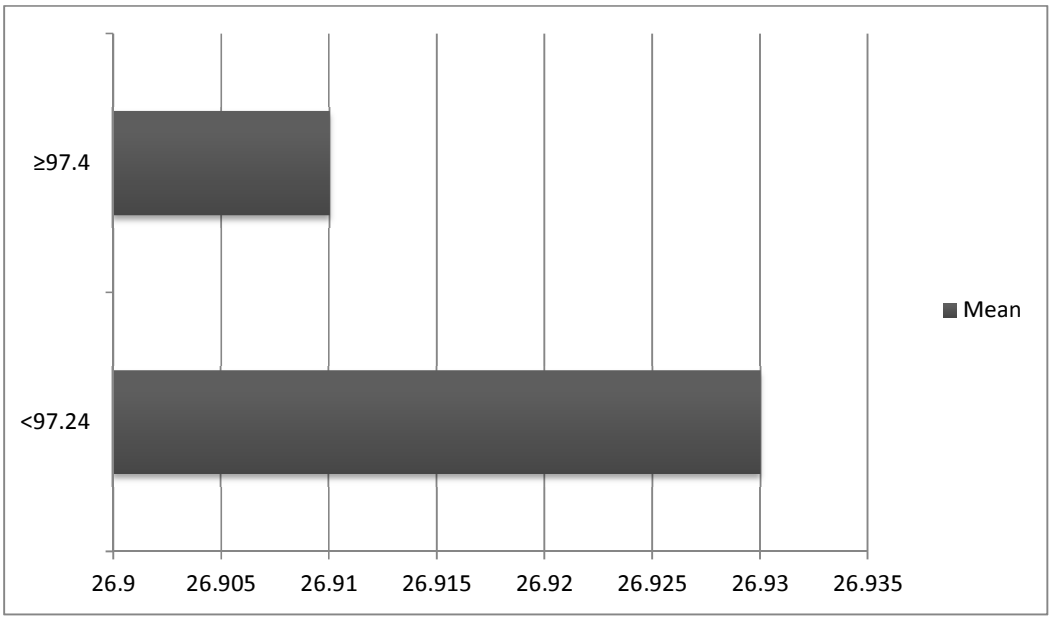
Negative	n	Mean	SD
Cases	28	26.92	0.861
Controls	31	23.93	0.681

SERUM CREATININE

Serum creatinine [mmol/l]	≤97.24	>97.24	Total
Cases	35	5	40
Controls	31	9	40
Total	66	14	80



Urinary 11-dhTxB2 levels	n	Mean	SD
<97.24	35	26.93	0.852
≥97.4	5	26.91	0.840

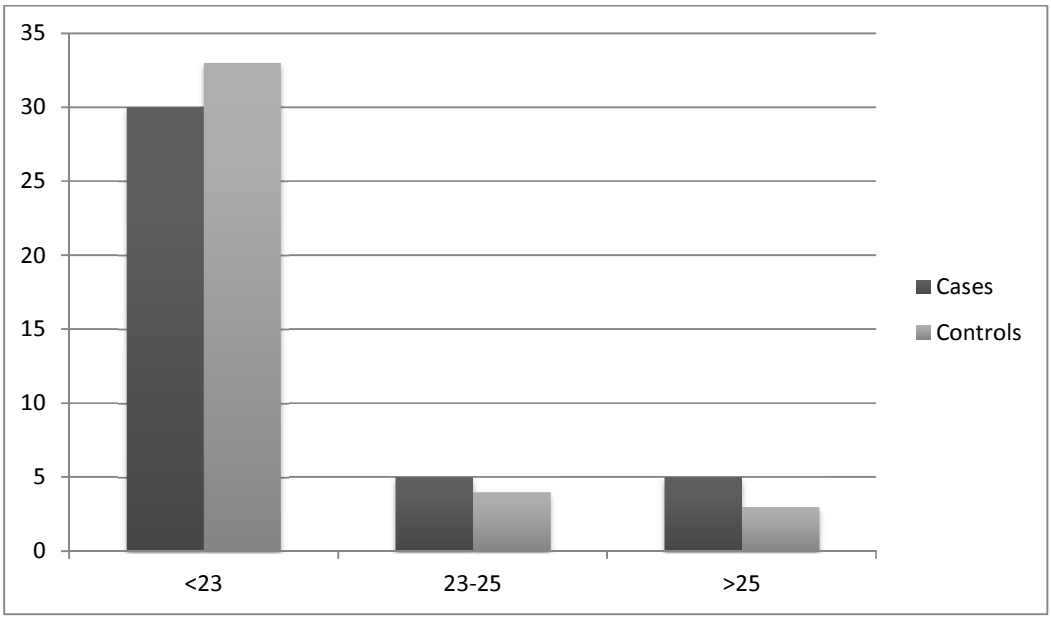


<97.24 mmol/l	n	Mean	SD
Cases	35	26.93	0.852
Controls	31	23.89	0.766

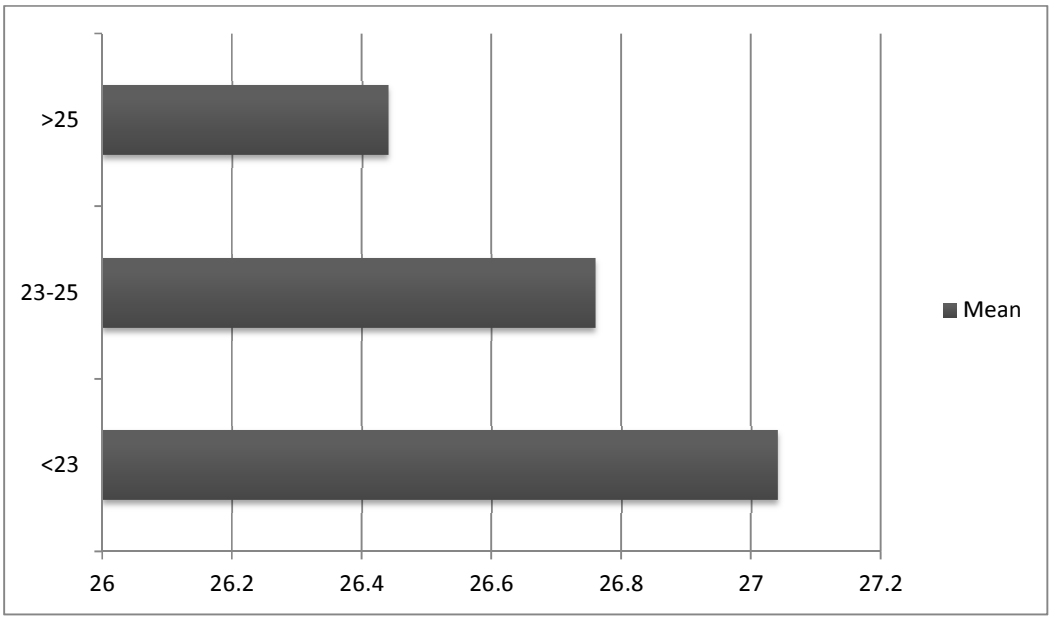
≥97.24 mmol/l	n	Mean	SD
Cases	5	26.91	0.840
Controls	9	24.16	0.797

BMI

BMI [kg/m^2]	Cases	Controls	Total
<23	30	33	63
23-25	5	4	9
>25	5	3	8
Total	40	40	80



Urinary 11-dhTxB2 levels	n	Mean	SD
<23	30	27.04	0.770
23-25	5	26.76	0.857
>25	5	26.44	1.189



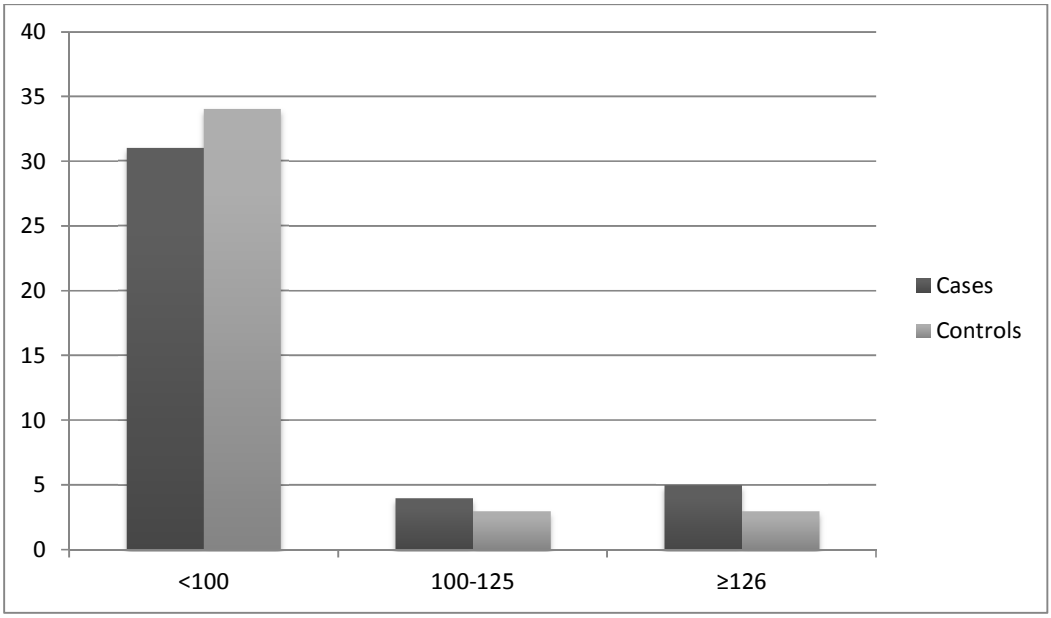
<23	n	Mean	SD
Cases	30	27.04	0.770
Controls	33	23.97	0.718

23-25	n	Mean	SD
Cases	5	26.76	0.857
Controls	4	23.25	0.923

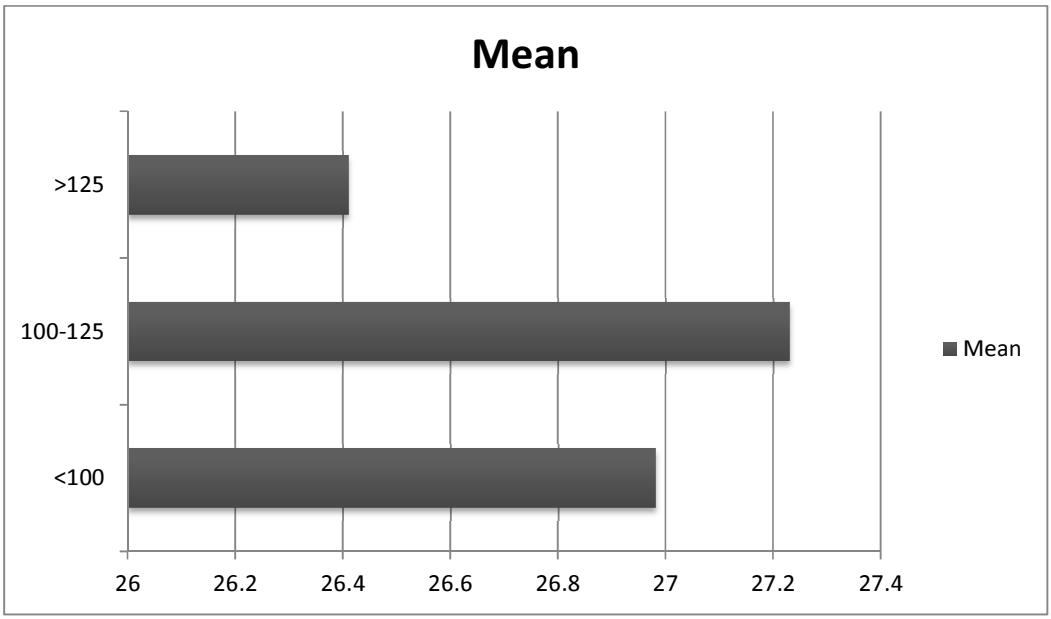
>25	n	Mean	SD
Cases	5	26.44	1.189
Controls	3	24.74	0.365

FASTING BLOOD SUGAR

FBS [mg/dL]	Cases	Controls	Total
<100	31	34	65
100-125	4	3	7
≥126	5	3	8
Total	40	40	80



Urinary 11-dhTxB2 levels	n	Mean	SD
<100	31	26.98	0.774
100-125	4	27.23	1.267
>125	5	26.41	0.858



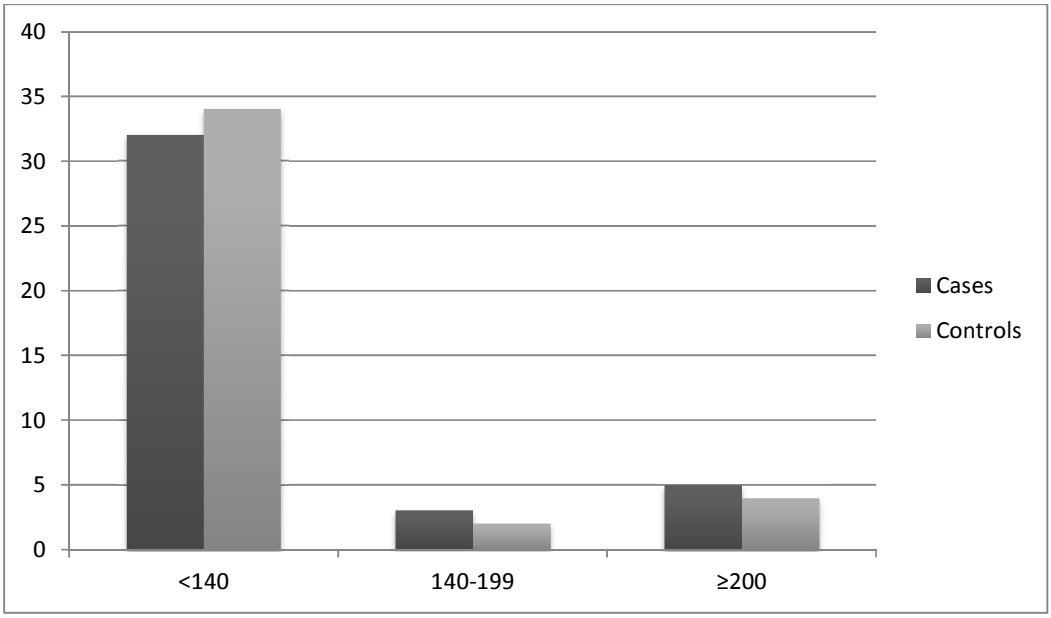
<100	n	Mean	SD
Cases	31	26.97	0.774
Controls	34	23.89	0.739

100-125	n	Mean	SD
Cases	4	27.23	1.267
Controls	3	24.80	0.293

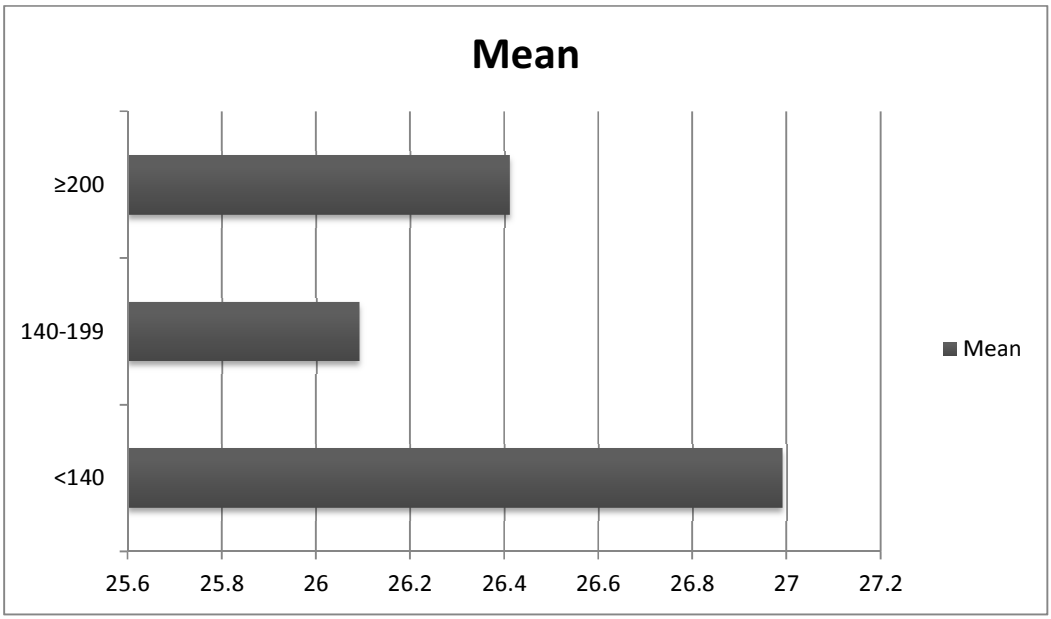
≥126	n	Mean	SD
Cases	5	26.41	0.858
Controls	3	23.88	1.155

POST PRANDIAL BLOOD SUGAR

PPBS [mg/dL]	Cases	Controls	Total
<140	32	34	66
140-199	3	2	5
≥200	5	4	9
Total	40	40	80



Urinary 11-dhTxB2 levels	n	Mean	SD
<140	32	26.99	0.771
140-199	3	26.09	1.512
≥200	5	26.41	0.858



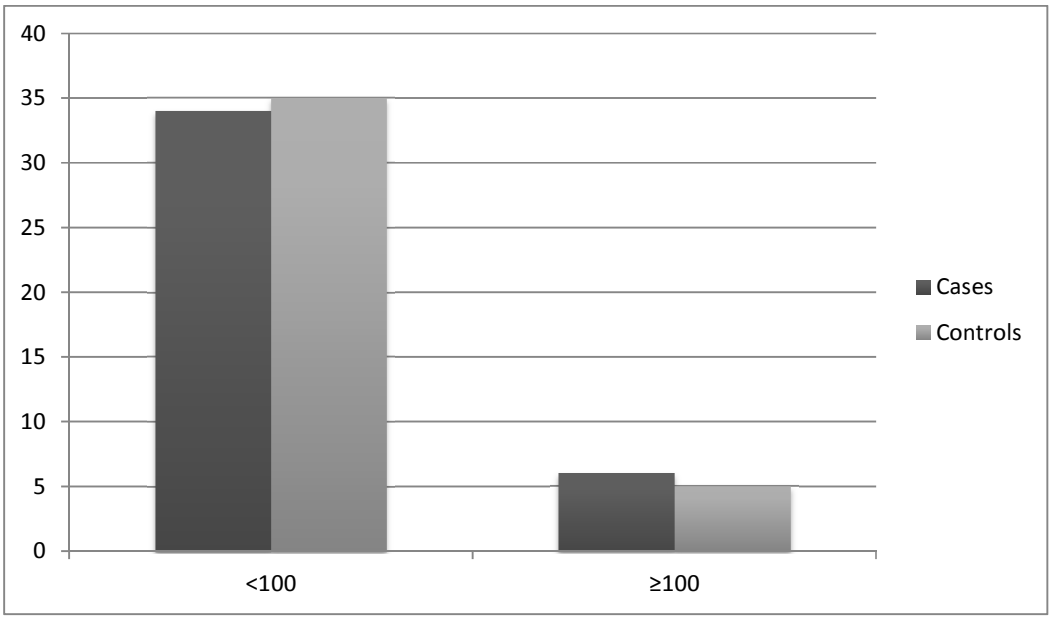
<140	n	Mean	SD
Cases	32	26.99	0.771
Controls	34	23.89	0.739

140-199	n	Mean	SD
Cases	3	27.09	1.512
Controls	2	24.87	0.381

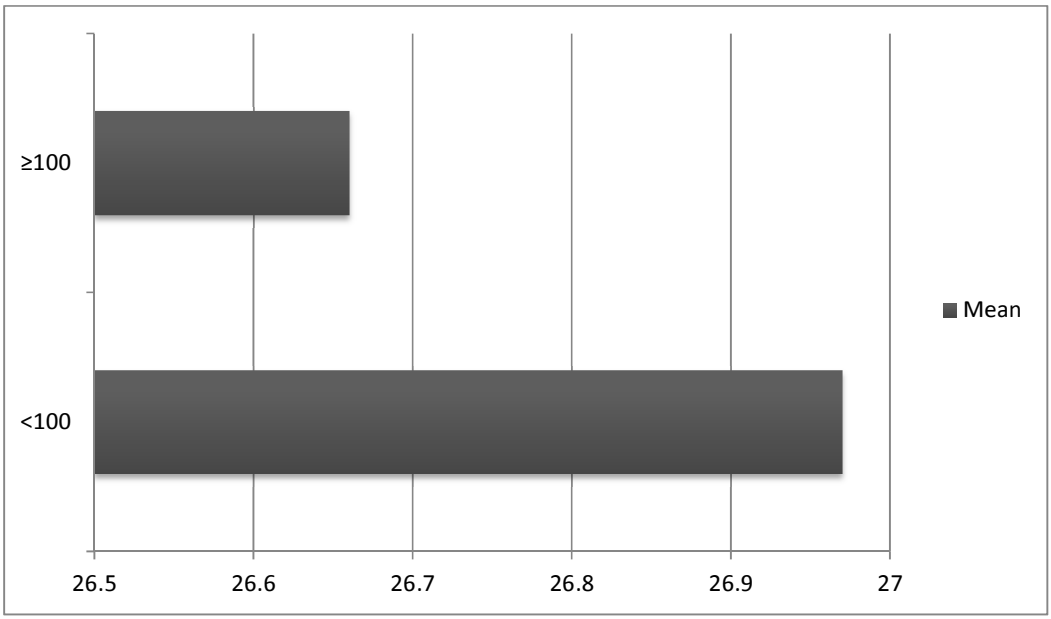
≥200	n	Mean	SD
Cases	5	26.41	0.858
Controls	4	24.08	1.023

LDL LEVEL

LDL [mg/dL]	Cases	Controls	Total
<100	34	35	69
≥100	6	5	11
Total	40	40	80



Urinary 11-dhTxB2 levels	n	Mean	SD
<100	34	26.97	0.777
≥100	6	26.66	1.188



<100 mg/dl	n	Mean	SD
Cases	34	26.97	0.777
Controls	35	23.96	0.722

≥100 mg/dl	n	Mean	SD
Cases	6	26.66	1.188
Controls	5	23.91	1.167

DISCUSSION

Eighty patients were enrolled as our study population. Among them 40 patients were cases with recurrent cardiovascular events and the remaining 40 patients were controls with only one thrombotic event.

CAD was the initial event in 30 cases (75%) and 31 controls (77.5%). CVA was the initial event in 10 cases (25%) and 9 (22.5%) controls.

Among the cases, CAD was the recurrent event in 27 cases (67.5%) whereas CVA was the recurrent event in 13 cases (32.5%).

Patients on longer duration of aspirin therapy showed more incidence of aspirin resistance. 22 cases and 29 controls were taking aspirin for ≤3 years whereas 18 cases and 11 controls were taking aspirin for >3 years.

Mean urinary 11-dehydro thromboxane B2 level was 26.93 (SD = 0.840) among cases and 23.96 (0.771) among controls ($p < 0.001$) which was statistically significant.

AGE

21 cases and 24 controls were in the age group of 41 – 50 years. 19 cases and 16 controls were in the age group of 51 – 60 years. Age did not show any association with aspirin resistance (p = 0.88). Subgroup analysis also was not significant between cases and controls.

SEX

25 males and 15 females were in 'case' group and 23 males and 17 females were in 'control' group. Sex was not associated with any significant difference in urinary levels of 11-dhTxB2 (p = 0.683). Subgroup analysis also showed no significant difference based on sex.

SMOKING

20 patients among cases and 17 patients among controls were smokers. Smoking was did not have any correlation with aspirin resistance (p = 0.350).

DIABETES

Among 16 diabetics in the study population, 9 patients were cases and 7 were controls. Presence of diabetes was not associated with any significant difference among cases (p = 0.547). Both diabetics as well as

non-diabetics showed significant difference between cases and controls whereas the difference between their means was not significant.

HYPERTENSION

27 cases and 25 controls were hypertensive. 13 cases and 15 controls were normotensive. No significant difference was noted between these two groups ($p = 0.576$).

PPI THERAPY

32 cases and 18 controls were on proton pump inhibitor therapy. The mean difference between cases on PPI therapy and who were not on PPI therapy was not significant ($p = 0.613$). The mean difference was not significant between cases and controls also.

FAMILY HISTORY

In our study population, 21 patients had family history of cardiovascular disease (12 cases, 9 controls). Family history did not show any significant association with aspirin resistance among cases ($p = 0.962$).

SERUM CREATININE

Serum creatinine level was elevated more than 97.24 mmol/l in 5 cases and 9 controls. Renal failure did not reveal any significant association with urinary levels of 11-dh TxB2 ($p = 0.963$). Subgroup analysis also revealed no significant difference between cases and controls.

BMI

30 cases (75%) and 33 controls (82.5%) had BMI less than 23. 5 cases (12.5%) and 4 controls (10%) had BMI between 23 and 25. 5 cases (12.5%) and 3 controls (7.5%) had BMI above 25. Obesity was not associated with statistically significant difference among cases ($p = 0.316$) and between cases and controls.

FASTING BLOOD SUGAR

Fasting blood sugar was less than 100 mg/dl in 31 cases (77.5%) and 34 controls (85%). It was between 100 and 125 mg/dl in 4 cases (10%) and 3 controls (7.5%). Fasting hyperglycemia was seen in 5 cases (12.5%) and 3 control (7.5%). Fasting blood sugar level did not show any correlation with aspirin resistance.

POSTPRANDIAL BLOOD SUGAR

Postprandial blood sugar was less than 140 mg/dl in 32 cases (80%) and 34 controls (85%); between 140 and 199 mg/dl in 3 cases (7.5%) and 2 controls (5%); and ≥200 mg/dl in 5 cases (12.5%) and 4 controls (10%). Postprandial blood sugar was not associated with elevated urinary levels of 11-dh TxB2.

LDL

LDL level was less than 100 mg/dl in 34 cases (85%) and 35 controls (87.5%) and it was ≥100 mg/dl in 6 cases (15%) and 5 controls (12.5%). No significant mean difference was noted among cases ($p = 0.403$) as well as between cases and controls in terms of hyperlipidemia and aspirin resistance.

LIMITATIONS OF STUDY

1. Coronary angiography was not done in all ischemic heart disease patients
2. Patients were not classified based on whether they received thrombolysis or not
3. Patients were not limited to same batch of aspirin on manufacturing basis
4. Drug compliance was not assessed by estimating serum salicylate levels
5. Test was not correlated with other platelet function assays

CONCLUSION

1. Urinary 11-dehydro thromboxane B2 level estimation is a simple method
2. Urinary 11-dehydro thromboxane B2 has been found to be significantly elevated in patients with recurrent thrombotic events
3. Urinary 11-dehydro thromboxane level estimation should be considered in patients with recurrent thrombotic events to find out aspirin resistance

BIBLIOGRAPHY

1. Easton JD, Saver JL, Albers GW, et al. Definition and evaluation of transient ischemic attack: a scientific statement for healthcare professionals from the American Heart Association/American Stroke Association Stroke Council; Council on Cardiovascular Surgery and Anesthesia; Council on Cardiovascular Radiology and Intervention; Council on Cardiovascular Nursing; and the Interdisciplinary Council on Peripheral Vascular Disease. The American Academy of Neurology affirms the value of this statement as an educational tool for neurologists. Stroke 2009; 40:2276.
2. Asfar S, Safar HA. Homocysteine levels and peripheral arterial occlusive disease: a prospective cohort study and review of the literature. J Cardiovasc Surg (Torino) 2007; 48:601.
3. Fuster V, Badimon L, Badimon JJ, Chesebro JH. The pathogenesis of coronary artery disease and the acute coronary syndromes (1). N Engl J Med 1992; 326:242.
4. Hennekens CH, Schneider WR, Pokov A, et al. A randomized trial of aspirin at clinically relevant doses and nitric oxide formation in humans. J Cardiovasc Pharmacol Ther 2010; 15:344
5. Antithrombotic Trialists' Collaboration. Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients. BMJ 2002; 324:71.
6. Stevenson DD. Aspirin and NSAID sensitivity. Immunol Allergy Clin North Am 2004; 24:491.

7. Jenkins C, Costello J, Hodge L. Systematic review of prevalence of aspirin induced asthma and its implications for clinical practice. BMJ 2004; 328:434.
8. Grattan CE. Aspirin sensitivity and urticaria. Clin Exp Dermatol 2003; 28:123.
9. Antithrombotic Trialists' Collaboration. Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients. BMJ 2002; 324:71
10. Peters RJ, Mehta SR, Fox KA, et al. Effects of aspirin dose when used alone or in combination with clopidogrel in patients with acute coronary syndromes: observations from the Clopidogrel in Unstable angina to prevent Recurrent Events (CURE) study. Circulation 2003; 108:1682.
11. Topol EJ, Easton D, Harrington RA, et al. Randomized, double-blind, placebo-controlled, international trial of the oral IIb/IIIa antagonist lotrafiban in coronary and cerebrovascular disease. Circulation 2003; 108:399.
12. Chan FK, Ching JY, Hung LC, et al. Clopidogrel versus aspirin and esomeprazole to prevent recurrent ulcer bleeding. N Engl J Med 2005; 352:238
13. Kelly JP, Kaufman DW, Jurgelon JM, et al. Risk of aspirin-associated major upper-gastrointestinal bleeding with enteric-coated or buffered product. Lancet 1996; 348:1413.

14. Cox D, Maree AO, Dooley M, et al. Effect of enteric coating on antiplatelet activity of low-dose aspirin in healthy volunteers. Stroke 2006; 37:2153.
15. Maree AO, Curtin RJ, Dooley M, et al. Platelet response to low-dose enteric-coated aspirin in patients with stable cardiovascular disease. J Am Coll Cardiol 2005; 46:1258.
16. Karha J, Rajagopal V, Kottke-Marchant K, Bhatt DL. Lack of effect of enteric coating on aspirin-induced inhibition of platelet aggregation in healthy volunteers. Am Heart J 2006; 151:976.e7
17. Michelson AD, Cattaneo M, Eikelboom JW, et al. Aspirin resistance: position paper of the Working Group on Aspirin Resistance. J Thromb Haemost 2005; 3:1309.
18. Hankey GJ, Eikelboom JW. Aspirin resistance. Lancet 2006; 367:606.
19. Wang TH, Bhatt DL, Topol EJ. Aspirin and clopidogrel resistance: an emerging clinical entity. Eur Heart J 2006; 27:647.
20. Michos ED, Ardehali R, Blumenthal RS, et al. Aspirin and clopidogrel resistance. Mayo Clin Proc 2006; 81:518.
21. Angiolillo DJ. Variability in responsiveness to oral antiplatelet therapy. Am J Cardiol 2009; 103:27A.
22. Sweeny JM, Gorog DA, Fuster V. Antiplatelet drug 'resistance'. Part 1: mechanisms and clinical measurements. Nat Rev Cardiol 2009; 6:273.

23. Hjemdahl P. Should we monitor platelet function during antiplatelet therapy? Heart 2008; 94:685.
24. Jennings LK. Variability in platelet response to the antiplatelet agents aspirin and clopidogrel: mechanisms, measurement, and clinical relevance. Crit Pathw Cardiol 2009; 8:20.
25. Beigel R, Hod H, Fefer P, et al. Relation of aspirin failure to clinical outcome and to platelet response to aspirin in patients with acute myocardial infarction. Am J Cardiol 2011; 107:339.
26. Ben-Dor I, Kleiman NS, Lev E. Assessment, mechanisms, and clinical implication of variability in platelet response to aspirin and clopidogrel therapy. Am J Cardiol 2009; 104:227.
27. Hennekens CH, Schror K, Weisman S, FitzGerald GA. Terms and conditions: semantic complexity and aspirin resistance. Circulation 2004; 110:1706.
28. Würtz M, Grove EL, Kristensen SD, Hvas AM. The antiplatelet effect of aspirin is reduced by proton pump inhibitors in patients with coronary artery disease. Heart 2010; 96:368.
29. Charlot M, Grove EL, Hansen PR, et al. Proton pump inhibitor use and risk of adverse cardiovascular events in aspirin treated patients with first time myocardial infarction: nationwide propensity score matched study. BMJ 2011; 342:d2690.
30. Hennekens CH, DeMets D. Statistical association and causation: contributions of different types of evidence. JAMA 2011; 305:1134

URINE 11-DEHYDRO THROMBOXANE B2 LEVELS AND ITS CORRELATION WITH ASPIRIN RESISTANCE IN PATIENTS WITH RECURRENT CARDIOVASCULAR EVENTS

Name: Age/Sex:

Address: Occupation:

Symptoms:

☐ Chest pain ☐ Syncope

☐ Dyspnea ☐ Giddiness

☐ Weakness of limbs ☐ Any other drug intake

Past history:

☐ DM ☐ Acid peptic disease

☐ SHT ☐ Renal failure

☐ CAD

Personal history:

☐ Smoking

☐ Alcoholism

PHYSICAL EXAMINATION:

General examination:

Pulse:

Blood pressure:

Systemic examination:

CVS:

RS:

ABDOMEN:

CNS:

INVESTIGATIONS:

Hemogram			**RFT**		
TC		cells/mm^3	Glucose (F)		mg/dl
DC			Glucose (PP)		mg/dl
ESR		mm/hr	Urea		mg/dl
Hb		g/dl	Creatinine		mg/dl
PCV		%	Na+		mEq/l
Platelets		lakhs/mm^3	K+		mEq/l
RBCs		million/mm^3			
Lipid profile			TSH		
Total cholesterol		mg/dl	Free T3		
LDL		mg/dl	Free T4		
HDL		mg/dl	**Urine 11-dehydrothromboxane B2**		
Triglycerides		mg/dl			

ECG:

ECHO CARDIOGRAM:

<u>ஆராய்ச்சி தகவல் தாள்</u>

சென்னை இராஜிவ் காந்தி அரசு பொது மருத்துவமனையில் இரத்தக் குழாய் அடைப்பினால் ஏற்படும் பாதிப்புகளால் அனுமதிக்கப்படும் நோயாளிகளைப் பற்றிய ஒரு ஆராய்ச்சி நடைபெற்று வருகிறது.

இரத்தக் குழாய் அடைப்பினால் பாதிப்பு ஏற்பட்டு ஆஸ்பிரின் மாத்திரை உட்கொண்டு வரும் பொழுதும் மீண்டும் இரத்தக் குழாய் அடைப்பினால் பாதிப்பு ஏற்படுபவர்களிடம் ஆஸ்பிரின் மாத்திரையின் செயலற்ற தன்மையினை அறிந்து கொள்வதே இந்த ஆராய்ச்சியின் நோக்கமாகும்.

நீங்களும் இந்த ஆராய்ச்சியில் பங்கேற்க நாங்கள் விரும்புகிறோம். முடிவுகளை அல்லது கருத்துக்களை வெளியிடும் போதோ அல்லது ஆராய்ச்சியின் போதோ தங்களது பெயரையோ அல்லது அடையாளங்களையோ வெளியிடமாட்டோம் என்பதையும் தெரிவித்துக் கொள்கிறோம்.

இந்த ஆராய்ச்சியில் பங்கேற்பது தங்களுடைய விருப்பத்தின் பேரில் தான் இருக்கிறது. மேலும் நீங்கள் எந்நேரமும் இந்த ஆராய்ச்சியிலிருத்து பின்வாங்கலாம் என்பதையும் தெரிவித்துக் கொள்கிறோம்.

இந்த சிறப்புப் பரிசோதனைகளின் முடிவுகளை ஆராய்ச்சியின் போது அல்லது ஆராய்ச்சியின் முடிவில் தங்களுக்கு அறிவிப்போம் என்பதையும் தெரிவித்துக் கொள்கிறோம்.

ஆராய்ச்சியாளர் கையொப்பம் பங்கேற்பாளர் கையொப்பம்

தேதி:

<u>ஆராய்ச்சி ஒப்புதல் கடிதம்</u>

ஆராய்ச்சி தலைப்பு:

இரத்தக் குழாய் அடைப்பினால் பாதிப்பு ஏற்பட்டு ஆஸ்பிரின் மாத்திரை உட்கொண்டு வரும் பொழுதும் மீண்டும் இரத்தக் குழாய் அடைப்பினால் பாதிப்பு ஏற்படுபவர்களிடம் ஆஸ்பிரின் மாத்திரையின் செயலற்ற தன்மையினை குறித்த ஆராய்ச்சி.

பெயர்: தேதி:

வயது: உள்நோயாளி எண்:

பால்: ஆராய்ச்சி சேர்க்கை எண்:

இந்த ஆராய்ச்சியின் விவரங்களும் அதன் நோக்கங்களும் முழுமையாக எனக்கு தெளிவாக விளக்கப்பட்டது. எனக்கு விளக்கப்பட்ட விஷயங்களை நான் புரிந்து கொண்டு நான் எனது சம்மதத்தை தெரிவிக்கிறேன்.

இரத்தக் குழாய் அடைப்பு பற்றியும், அதனைத் தடுக்கப் பயன்படுத்தப்படும் ஆஸ்பிரின் மாத்திரை மற்றும் அதன் செயலற்ற தன்மையைக் கண்டறியக்கூடிய இரத்தப் பரிசோதனைகள் குறித்தும் ஆராய்ச்சியாளர் கூற முழுவதும் விளங்கப்பெற்றேன்.

மேற்கொண்ட பரிசோதனையின் போது ஏற்படக்கூடிய பின்விளைவுகளையும் முழுவதும் உணர்ந்து இந்த பரிசோதனைக்கு மனமார சம்மதிக்கிறேன்.

கையொப்பம்

INSTITUTIONAL ETHICS COMMITTEE
MADRAS MEDICAL COLLEGE, CHENNAI -3

Telephone No : 044 25305301
Fax : 044 25363970

CERTIFICATE OF APPROVAL

To
Dr. J.S. Thomas Xavier Paulsingh
PG in MD General Medicine
Madras Medical College, Chennai -3

Dear Dr. J.S. Thomas Xavier Paulsingh

The Institutional Ethics committee of Madras Medical College, reviewed and discussed your application for approval of the proposal entitled " Urine 11 – Dehydro Thromboxane B2 levels and its correlation with aspirin resistance in patients with recurrent cardiovascular events " No.28062012.

The following members of Ethics Committee were present in the meeting held on 19.06.2012 conducted at Madras Medical College, Chennai -3.

1. Dr. S.K. Rajan. M.D.,FRCP.,DSc -- Chairperson
2. Prof. K. Ramadevi MD -- Member
   Prof of Biochemistry, MMC, Ch-3
3. Prof. R. Nandhini MD -- Member
   Director, Inst. of Pharmacology ,MMC, Ch-3
4. Prof. C. Rajendiran, MD -- Member
   Director , Inst. of Internal Medicine, MMC, Ch-3
5. Prof. S. Deivanayagam MS -- Member
   Prof of Surgery, MMC, Ch-3
6. Prof. A. Radhakrishnan MD -- Member
   Prof of Internal Medicine, MMC, Ch-3

We approve the proposal to be conducted in its presented form.

Sd/ Chairman & Other Members

The Institutional Ethics Committee expects to be informed about the progress of the study, and SAE occurring in the course of the study, any changes in the protocol and patients information / informed consent and asks to be provided a copy of the final report.

Member Secretary, Ethics Committee

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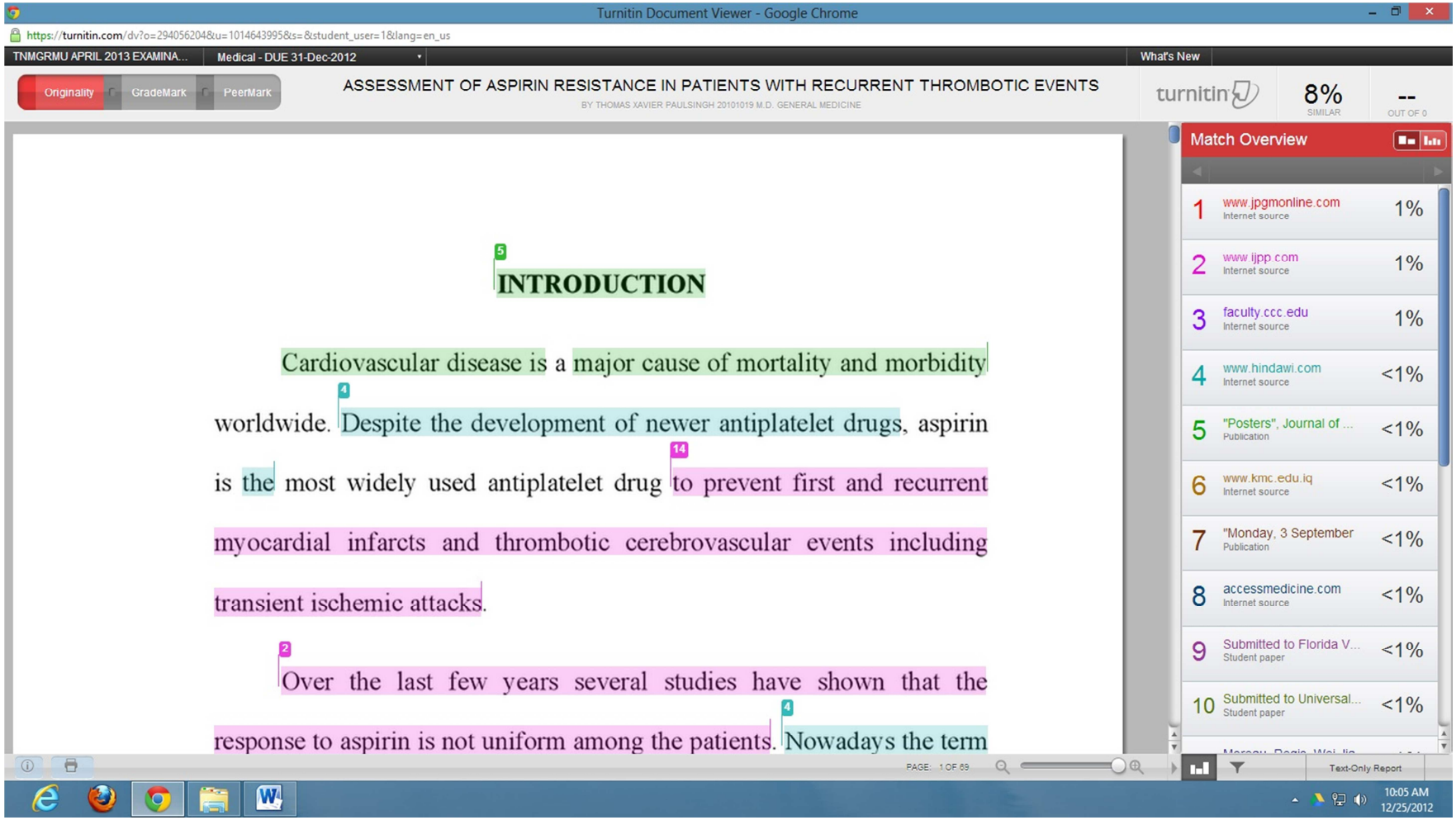
INTRODUCTION Cardiovascular disease is a major cause of mortality and morbidity worldwide. Despite the development of newer antiplatelet drugs, aspirin is the most widely used antiplatelet drug to prevent first and recurrent myocardial infarcts and thrombotic cerebrovascular events including transient ischemic attacks. Over the last few years several studies have shown that the response to aspirin is not uniform among the patients. Nowadays the term aspirin resistance has been employed to express the occurrence of cardiovascular events in spite of regular intake of aspirin at recommended doses. Various studies have estimated the incidence of aspirin resistance to be 5 - 75%. It has been...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INTRODUCTION
Cardiovascular disease is a major cause of mortality and morbidity worldwide. Despite the development of newer antiplatelet drugs, aspirin is the most widely used antiplatelet drug to prevent first and recurrent myocardial infarcts and thrombotic cerebrovascular events including transient ischemic attacks.
Over the last few years several studies have shown that the response to aspirin is not uniform among the patients. Nowadays the term
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ID	Age [years]	Sex	Smoking	DM	SHT	PPI therapy	Family history	Ht[cm]	Wt[kg]	BMI [kg/m^2]	FBS [mg/dl]	PPBS [mg/dl]	Cholesterol [mg/dl]	HDL [mg/dl]	TGL [mg/dl]	LDL [mg/dl]	Creatinine [mmol/l]	Duration of aspirin [years]	Primary event	Secondary event	Urinary 11 dhTxB2 [ng/mmol]
1	42	M	Y	N	Y	Y	Y	174	62	20.48	89	123	172	48	139	96.2	79.56	2	CAD	CAD	26.14
2	56	M	Y	N	N	Y	N	169	65	22.76	94	131	168	47	136	93.8	88.4	4	CAD	CVA	27.86
3	46	F	N	N	Y	Y	N	159	52	20.57	88	119	174	53	138	93.4	70.72	4	CAD	CVA	27.96
4	47	M	Y	N	N	Y	N	167	61	21.87	91	139	165	43	142	93.6	70.72	4	CVA	CAD	26.29
5	49	M	N	Y	N	N	N	173	77	25.73	119	165	189	33	169	122.2	88.4	5	CAD	CAD	25.41
6	56	M	Y	Y	N	N	Y	172	69	23.32	131	215	169	52	137	89.6	79.56	5	CVA	CVA	25.88
7	53	F	N	Y	Y	Y	N	160	65	25.39	134	217	197	43	175	119.0	70.72	2	CAD	CAD	26.63
8	51	F	N	N	Y	Y	Y	163	55	20.70	95	128	171	57	147	84.6	88.4	4	CAD	CVA	26.95

9	43	M	Y	N	Y	Y	N	173	68	22.72	96	134	170	48	142	93.6	79.56	2	CAD	CVA	26.63
10	48	F	N	N	N	Y	N	162	53	20.20	88	126	171	51	149	90.2	79.56	4	CVA	CAD	27.22
11	57	F	N	N	N	N	N	159	55	21.76	83	128	167	53	137	86.6	88.4	4	CAD	CAD	27.48
12	51	M	Y	Y	Y	Y	N	170	74	25.61	123	180	191	35	171	121.8	88.4	3	CAD	CAD	28.35
13	45	M	Y	N	Y	Y	N	169	61	21.36	84	123	166	43	134	96.2	70.72	4	CAD	CAD	26.03
14	56	M	N	N	N	Y	N	168	60	21.26	88	116	166	57	138	81.4	70.72	4	CVA	CAD	26
15	51	M	Y	N	Y	Y	Y	173	66	22.05	90	137	175	55	132	93.6	61.88	2	CAD	CAD	27.94
16	44	M	Y	N	N	N	N	170	63	21.80	87	118	174	58	146	86.80	79.56	3	CAD	CVA	27.46
17	48	F	N	N	Y	Y	N	160	57	22.27	93	135	165	52	132	86.6	88.4	3	CVA	CAD	27.74
18	52	M	Y	N	Y	Y	N	175	69	22.53	96	127	164	52	138	84.4	79.56	3	CAD	CAD	26.46
19	49	M	N	N	N	Y	N	173	65	21.72	91	129	174	49	148	95.4	79.56	4	CAD	CVA	26.94
20	55	F	N	Y	Y	Y	Y	161	58	22.38	128	212	198	47	167	117.6	61.88	3	CAD	CAD	27.74
21	51	M	N	N	Y	Y	N	171	63	21.55	84	118	168	59	143	80.4	70.72	2	CVA	CVA	25.81
22	42	F	N	N	Y	Y	N	164	58	21.56	82	124	165	56	146	79.8	88.4	2	CAD	CAD	25.44
23	49	M	Y	N	Y	Y	N	169	60	21.01	85	128	169	57	140	84.0	88.4	4	CAD	CAD	28
24	59	M	Y	Y	N	N	Y	173	70	23.39	105	139	173	51	137	94.6	70.72	5	CVA	CAD	27.65
25	43	M	Y	N	Y	Y	Y	167	59	21.16	92	130	168	54	134	87.2	61.88	2	CAD	CVA	27.47
26	47	M	Y	N	Y	Y	Y	176	62	20.02	81	121	172	56	141	87.8	97.24	3	CVA	CAD	26.93
27	45	F	N	N	Y	Y	N	158	55	22.03	95	132	178	58	139	92.2	70.72	4	CAD	CAD	26.2
28	56	M	Y	N	Y	Y	N	175	63	20.57	92	136	173	47	147	96.6	79.56	3	CAD	CAD	27.7

29	53	F	N	N	Y	Y	N	164	57	21.19	92	126	171	52	134	92.2	79.56	4	CAD	CVA	27.09
30	56	M	Y	Y	Y	Y	Y	170	75	25.95	133	216	205	38	177	131.6	61.88	2	CAD	CAD	25.49
31	51	M	Y	N	Y	Y	N	173	69	23.05	85	125	172	43	148	99.4	97.24	3	CAD	CAD	25.86
32	43	F	N	Y	N	N	Y	157	62	25.15	129	214	207	41	169	132.2	97.24	3	CAD	CVA	26.33
33	59	F	N	N	Y	Y	N	164	58	21.56	82	116	167	55	141	83.8	88.4	5	CAD	CAD	25.95
34	51	F	N	Y	Y	Y	N	159	59	23.34	110	141	163	52	145	82.0	141.44	3	CVA	CAD	27.5
35	47	M	Y	N	N	N	N	178	69	21.78	84	119	168	49	142	90.6	79.56	2	CAD	CAD	27.2
36	53	M	N	N	Y	Y	Y	168	65	23.03	92	129	170	47	136	95.8	79.56	3	CAD	CAD	26.89
37	50	M	Y	N	Y	Y	N	169	59	20.66	94	137	169	55	137	86.6	61.88	4	CAD	CVA	27.78
38	41	F	N	N	N	N	N	161	58	22.38	95	132	172	54	138	90.4	88.4	2	CVA	CVA	26.91
39	49	F	N	N	Y	Y	Y	163	57	21.45	92	136	173	58	142	86.6	70.72	3	CAD	CAD	27.83
40	50	M	Y	N	Y	Y	N	177	64	20.43	90	131	178	52	145	97.0	97.24	4	CAD	CAD	27.93
41	46	F	N	N	Y	Y	N	156	52	21.37	88	120	172	57	147	85.6	70.72	3	CAD	Nil	23.42
42	49	M	Y	N	Y	Y	N	173	65	21.72	94	139	170	59	134	84.2	79.56	4	CAD	Nil	23.31
43	56	M	Y	Y	Y	Y	Y	168	72	25.51	130	216	190	34	172	121.6	79.56	3	CAD	Nil	24.42
44	51	M	Y	Y	N	N	N	171	70	23.94	123	170	169	53	140	88.0	97.24	2	CVA	Nil	24.6
45	59	F	N	N	Y	Y	N	162	56	21.34	96	128	168	55	138	85.4	79.56	3	CAD	Nil	22.9
46	41	M	Y	N	Y	Y	N	175	64	20.90	87	123	172	54	132	91.6	88.4	2	CAD	Nil	24.52
47	44	M	N	N	N	N	N	173	65	21.72	85	127	179	58	132	94.6	70.72	2	CAD	Nil	23.3
48	57	M	Y	N	N	N	N	170	65	22.49	93	134	172	46	140	98.0	97.24	3	CVA	Nil	23.05

49	50	F	N	N	Y	Y	N	164	58	21.56	97	130	167	57	142	81.6	79.56	5	CAD	Nil	23.6
50	44	F	N	N	Y	Y	N	159	56	22.15	95	137	163	51	135	85.0	79.56	3	CAD	Nil	24.4
51	60	M	Y	N	Y	Y	Y	169	68	23.81	90	128	167	42	138	97.4	70.72	5	CAD	Nil	23.06
52	51	F	N	N	N	N	N	159	53	20.96	83	124	176	53	133	96.4	61.88	4	CVA	Nil	24.06
53	58	M	Y	Y	Y	Y	Y	169	73	25.56	126	211	203	35	175	133.0	97.24	3	CAD	Nil	24.67
54	50	M	Y	N	Y	Y	N	174	64	21.14	95	134	174	49	139	97.2	88.4	4	CAD	Nil	24.22
55	45	F	N	N	Y	Y	N	162	59	22.48	88	118	173	52	142	92.6	97.24	3	CAD	Nil	24.15
56	41	M	N	N	Y	Y	Y	177	67	21.39	90	131	165	58	148	77.4	79.56	2	CAD	Nil	23.55
57	56	M	Y	N	N	N	N	168	59	20.90	94	138	172	53	135	92.0	70.72	4	CAD	Nil	23.78
58	55	M	N	N	Y	Y	N	174	65	21.47	95	128	172	46	131	99.8	70.72	3	CAD	Nil	23.65
59	51	F	N	Y	Y	N	Y	165	60	22.04	129	213	165	58	137	79.6	150.28	3	CAD	Nil	24.66
60	46	F	N	Y	N	N	N	158	63	25.24	115	145	195	45	169	116.2	79.56	2	CAD	Nil	25.14
61	43	M	Y	N	Y	N	N	174	68	22.46	95	135	175	59	138	88.4	79.56	2	CAD	Nil	24.29
62	50	M	Y	N	Y	N	N	175	62	20.24	91	134	172	52	134	93.2	61.88	5	CVA	Nil	24.89
63	42	F	N	N	Y	N	N	163	61	22.96	90	132	178	52	143	97.4	88.4	2	CVA	Nil	22.76
64	49	F	N	N	Y	Y	Y	165	59	21.67	96	125	167	56	137	83.6	88.4	4	CAD	Nil	25.4
65	54	M	Y	N	N	N	N	173	67	22.39	87	116	163	43	144	91.2	97.24	2	CAD	Nil	24.4
66	51	F	N	N	Y	Y	N	163	56	21.08	85	129	176	55	138	93.4	70.72	3	CAD	Nil	24.03
67	41	M	N	N	N	N	N	171	64	21.89	90	129	172	48	143	95.4	61.88	2	CVA	Nil	24.69
68	44	F	N	N	N	N	N	157	55	22.31	93	130	170	55	141	86.8	97.24	3	CAD	Nil	23.88

69	50	F	N	N	N	Y	N	159	54	21.36	91	136	168	52	138	88.4	88.4	3	CAD	Nil	25.01
70	52	M	Y	N	Y	N	N	169	59	20.66	90	132	164	41	132	96.6	79.56	3	CAD	Nil	23.69
71	55	M	Y	Y	Y	N	Y	171	68	23.26	98	140	191	36	168	121.4	141.44	3	CAD	Nil	22.79
72	49	M	N	N	N	Y	N	170	62	21.45	88	124	162	58	139	76.2	70.72	4	CVA	Nil	24.43
73	51	F	N	Y	Y	N	Y	160	59	23.05	133	217	194	44	171	115.8	70.72	2	CAD	Nil	22.55
74	43	M	Y	N	Y	Y	N	174	63	20.81	83	123	168	44	136	96.8	70.72	3	CAD	Nil	22.55
75	49	F	N	N	N	N	N	156	52	21.37	95	126	162	58	134	77.2	61.88	4	CVA	Nil	23.08
76	45	M	Y	N	N	N	N	173	66	22.05	93	137	179	52	140	99.0	88.4	3	CAD	Nil	24.52
77	57	M	Y	N	Y	N	Y	170	63	21.80	91	134	173	57	136	88.8	97.24	4	CVA	Nil	25.23
78	42	M	N	N	N	N	N	172	64	21.63	86	130	170	42	148	98.4	88.4	2	CAD	Nil	24.34
79	49	F	N	N	N	N	N	161	54	20.83	90	133	167	56	142	82.6	79.56	3	CAD	Nil	23.97
80	46	F	N	N	Y	N	N	158	53	21.23	94	130	170	51	134	92.2	79.56	2	CAD	Nil	23.31