A Dissertation on

ASSOCIATION OF HELICOBACTER PYLORI INFECTION IN NON HAEMORRHAGIC STROKE PATIENTS

Submitted to

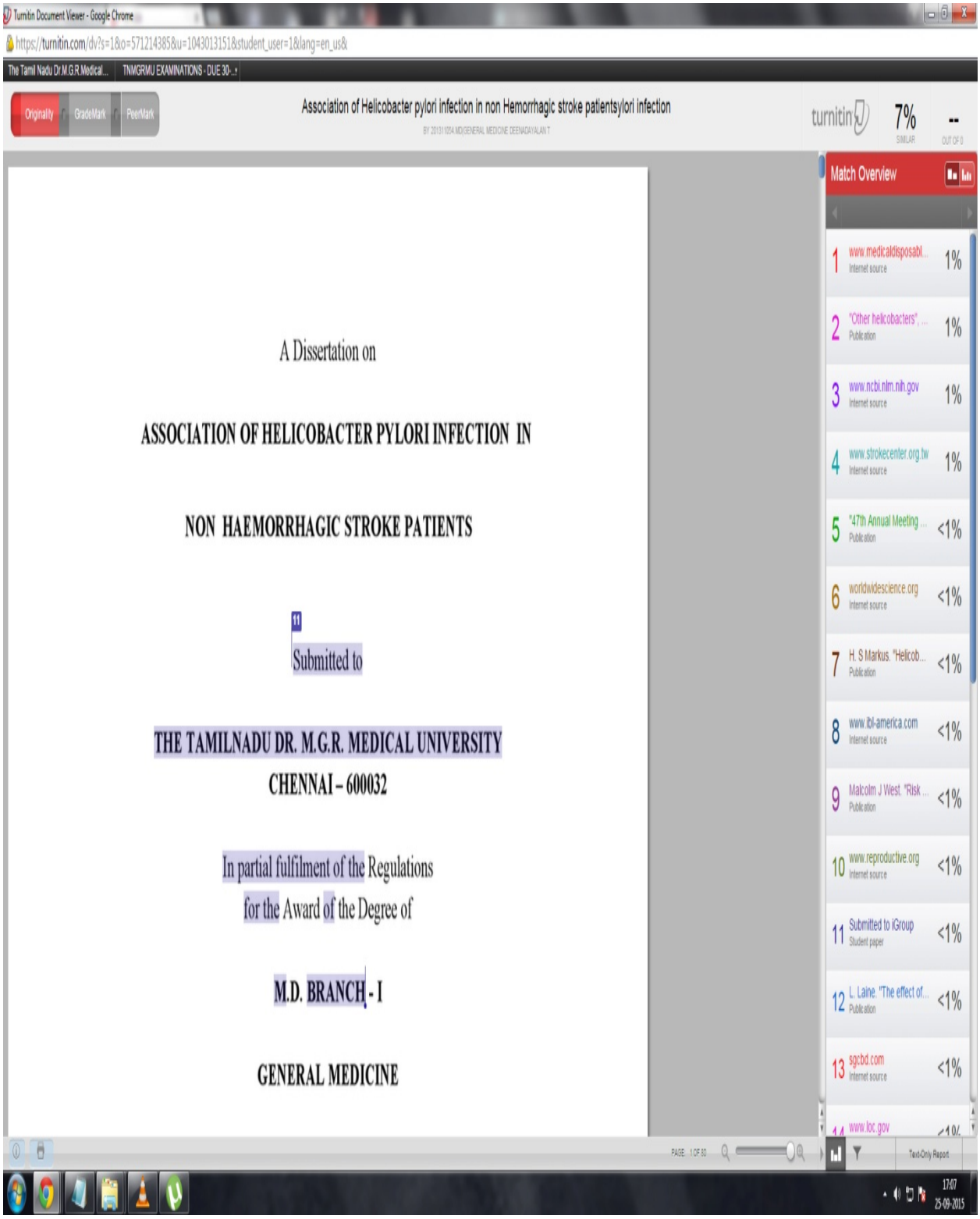
THE TAMILNADU DR. M.G.R. MEDICAL UNIVERSITY
CHENNAI – 600032

In partial fulfilment of the Regulations
for the Award of the Degree of

M.D. BRANCH - I

GENERAL MEDICINE

DEPARTMENT OF GENERAL MEDICINE
STANLEY MEDICAL COLLEGE
CHENNAI – 600 001
APRIL 2016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This is to certify that **DR. DEENADAYALAN .T,** Post - Graduate Student (2013 TO 2016) in the Department of General Medicine STANLEY MEDICAL COLLEGE, Chennai- 600 001, has done this dissertation on "**ASSOCIATION OF HELICOBACTER PYLORI INFECTION IN NON HAEMORRHAGIC STROKE PATIENTS"** under my guidance and supervision in partial fulfilment of the regulations laid down by the Tamil Nadu Dr. M.G.R. Medical University, Chennai, for M.D. (General Medicine), Degree Examination to be held in April 2016.

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DECLARATION

I **DR. DEENADAYALAN .T** declare that I carried out this work on "**ASSOCIATION OF HELICOBACTER PYLORI INFECTION IN NON HAEMORRHAGIC STROKE PATIENTS"** at the Medical OPD, Medical wards and Master Health Checkup OPD of Government Stanley Hospital during the period July 2014 to September 2015. I also declare that this bonafide work or a part of this work was not submitted by me or any other for any award, degree, or diploma to any other university, board either in India or abroad.

This is submitted to The Tamilnadu Dr. M.G.R. Medical University, Chennai in partial fulfilment of the rules and regulation for the M. D. Degree examination in General Medicine.

DR DEENADAYALAN .T

ACKNOWLEDGEMENT

At the outset I thank our Dean **Dr .ISAAC CHRISTIAN MOSES M.D.,FICP,FACP** for permitting me to carry out this study in our hospital.

I express my profound thanks to my esteemed Professor and Teacher **Dr. R. JAYANTHI, M.D.,** Professor and HOD of Medicine, Stanley Medical College Hospital, who is also my unit chief for encouraging and extending invaluable guidance to perform and complete this dissertation.

I wish to thank **Dr. C.S.Gauthaman M.D., Dr. K. RAJA M.D.,** Assistant Professors of my unit, Department of Medicine, Stanley medical college Hospital for their valuable suggestions, encouragement and advice.

I sincerely thank the members of Institutional Ethical Committee, Stanley Medical College for approving my dissertation topic.

I thank all my Colleagues, House Surgeons, and Staff nurses and other para medical workers for their support.

Last but not the least; I sincerely thank all those **patients** who participated in this study, for their co-operation.

TABLE OF CONTENTS

ABBREVIATIONS

CVA	CEREBRO VASCULAR ACCIDENT
HPYLORI	HELICOBACTER PYLORI
SHTN	SYSTEMIC HYPERTENSION
MS	MITRAL STENOSIS
AF	ATRIAL FIBRILLATION
SBP	SYTOLIC BLOOD PRESSURE
DBP	DIASTOLIC BLOOD PRESSURE
CHF	CONGESTIVE HEART FAILURE
CRP	C REACTIVE PROTEIN
ICH	INTRA CEREBRAL HAEMORRHAGE
SAH	SUB ARACHNOID HAEMORRHAGE
HSP	HEAT SHOCK PROTEIN
DALY	DISABILITY ADJUSTED LIFE YEARS
TIA	TRANSIENT ISCHEMIC ATTACK
CHD	CORONARY HEART DISEASE
SAH	SUB ARACHNOID HAEMORRHAGE
ICH	INTRA CEREBRAL HAEMORRHAGE

Introduction:

Helicobacter pylori is a gram negative organism which can cause chronic gastric inflammation[6]. This kind of gastritis is life long, unless eradicated by antibiotics. Helicobacter pylori has also been said to be associated with promotion of atherosclerosis. Some mechanisms are said to be linked between chronic infection with H pylori and promotion of atherosclerosis[1].

It[1] includes a small grade acute phase response, immune mediated mechanisms and free radical formation . Serum/Plasma markers of acute phase response such as, CRP, Total leucocyte count and serum Fibrinogen levels are elevated in those serologically positive for H pylori which points towards a small grade continuous inflammatory process. Cross reacting antibodies against human heat shock proteins have also been said to be a risk factor for carotid atherogenesis[2]. The heat shock protein produced by H pylori (60 kDa) has a high degree of resemblance in sequence with 60 kDa heat shock protein of humans[3].

Helicobacter pylori has been associated epidemiologically and pathologically with coronary artery disease[3]. Patel et al. pointed out that ECG with ischemic changes is very common in persons who are all show seropositivity with H. pylori which carried an Odds ratio of 3.82 even after adjustment with a various socioeconomic and risk factors for coronary heart disease. In another study Murray et

al. pointed that H. pylori sero positivity carries 1.51 times more risky for IHD (ischemic heart disease) with the Rose angina questionnaire even after giving adjustment to variety of social factors and other risk factors for coronary heart disease[25]. On comparing with ischemic heart disease (IHD), there is only a small database is available to support the relationship between seropositivity with H pylori and ischemic cerebro vascular accidents.

In a recent pilot study, Hugh and coworkers identified a significant association between seropositivity with Helicobacter pylori and ischemic stroke[20]. Heuschmann et al. noticed that seropositivity with H. pylori was carrying a significant risk of ischemic cerebro vascular events[4]. Since direct detection of H. pylori needs samples from vascular wall which is practically not a feasible approach, we can use the antibody levels to study the relationship between ischemic cerebro vascular events and chronic H.pylori infection in an indirect manner.

Another concern about this relationship is ,in chronic H.pylori infection often pathogen is acquired in childhood, which depends on socio economic status of that childhood time[6]. H.pylori infection has been demonstrated as more prevalent among poor socio economic status people and people with overcrowding[24]. So patient's Childhood socio economic status indirectly linked to present vascular dysfunction through chronic H.pylori infection.

Review of Literature:

H pylori is a gram-negative bacteria which is a spiral-shaped rod. This bacteria has significant association with chronic gastritis, gastric ulcer disease, ulcers in duodenum , antral gastritis, MALT lymphomas and gastric adenocarcinoma[6]. It is actively Motile with multiple flagella at one pole, *H.pylori* grows in a microaerophilic environment in 3–6 days when incubated at 37°C. The media for primary isolation include Skirrow's medium with, polymyxin B, vancomycin and trimethoprim, chocolate medium, and other selective media with antibiotics (eg, amphotericin, vancomycin, nalidixicacid,). The colonies are translucent and 1–2 mm in diameter and H. *pylori* is catalase positive and oxidase positive and it has a characteristic morphology, motile, and a strong producer of urease.

Epidemiology and Control of H.pylori infection:

H pylori presents on the gastric mucosa of less than 20% of persons younger than 30 years which increases in prevalence to 40–50% of persons aged more than 60 years, including persons who are asymptomatic. Mode of transmission is person-person which is indicated by intra familial clustering of H.pylori infection. Recent studies showing that there is definite relationship between chronic H.pylori infection and lower socio economic status.

Pathogenesis and Pathology behind H,pylori infection:

H pylori is better cultivated at an optimal pH of 6.0–7.0.It is found deep in the mucous layer near the epithelial surface. *H pylori* liberates proteolytic enzymes such as proteases which modifies the stomach mucus layer so that the diffusion of gastric acid through the mucus layer is restricted. It also produces urease which results in generation of ammonia which also buffers the acid. In human volunteers, infection of *H pylori* resulted in development of slowly progressive gastritis and hypochlorhydria. Significant relationship between chronic infection with *H.pylori* and duodenal ulcer disease also exists. Antibiotic therapy for H.pylori infection causes significant improvement in peptic ulcer disease. Though the mechanisms behind H. *pylori* mediated mucosal damage are not well understood, probably involves bacterial as well as host factors. Histologically, gastritis is characterized by acute and chronic inflammation. Neutrophils and mononuclear cell infiltrates are seen within the lamina propria and epithelium. Destruction of the epithelium and glandular atrophy may occur.

Immunity:

Patients infected with *H pylori initially* develop an IgM antibody response to the infection. Later, IgG and IgA are produced, and these persist, both systemically and at the mucosa, present in high titer in chronic infection. Early antimicrobial treatment will blunt this antibody response; these patients are said to be subject to repeat infection

Clinical Findings:

Acute infection can manifest with nausea and pain; vomiting and fever may also present. After colonization, the *H pylori* infection persists for long time perhaps decades or even a lifetime. About 80% of persons with duodenal ulcers and 50–70% patients with gastric ulcers have *H pylori* infection. *H pylori* is also a risk factor for lymphoma and gastric adenocarcinoma.

Diagnostic Laboratory Tests

A. Specimens:

Gastric biopsy specimens will be used for histopathologic examination and used for culture. Blood is collected for determination of serum antibodies. Stool samples may be collected for *H pylori* antigen detection.

B. Smears:

Histolopathological diagnosis of *H pylori* infection needs biopsy with an OGD scopy procedure. Silver stain or Giemsa stain will show H.pylori as spiral-shaped pathogens.

C. Culture:

Culture is performed when patients are not responding to treatment, and there is a need to assess susceptibility patterns..

D. Special Tests:

Rapid tests to detect urease activity are commonly used for presumptive diagnosis of *H pylori* infection. Here, gastric biopsy material is put into a media which contains urea as well as a color indicator. If there is H.pylori organism,as it produces urease ,there will be splitting of urea which will be sensed by the color indicator. In vivo tests for urease activity can also be done. In urea breath tests, patient will ingest 13C- or 14C-labeled urea., the urease activity of H.Pylori will give rise CO2 that can be detected in the patient's breath as it is labelled.

E. Antibody detection tests:

Enzyme linked immunosorbent assay(ELISA)[28] and Rapid H.pylori Antibody detection test are currently in use for H.pylori antibodies detection.

F.Rapid H.pylori Antibody detection test:

As this is rapid as well as easier to do, serological tests for *H. pylori* are better utilized for screening even a large population.It is also easier to perform compared to the invasive tests for H.pylori. With H.pylori infection patients will produce antibodieswhich correlate strongly with its histological confirmation.

This rapid screening test device is a chromatographic immunoassay which will detect antibodies against *H. pylori* in serum or plasma qualitatively. This rapid screening test utilizes particles coated with H.pylori antigen and antibody against

human IgG in order to specifically identify *H. pylori* antibodies of serum in short period.

Expected values of 'Rapid H.pylori Antibody detection test':

If this rapid antibody detection test is carried out along the Conventional ELISA, it can be comparable with Culture/Histology, which demonstrates an overall accuracy of 98.3%.

The majority of individuals exposed to H. pylori develop lgG antibodies against the organism. A relatively large proportion of patients who have positive levels of lgG antibodies arc asymptomatic even though they are colonized with the H. pylori. So lgG antibodies levels do not necessarily correlate with the severity of clinical symptoms.

Performance Characterstics:

The clinical trials were carried out to evaluate the H.pylori IgG antibody rapid screening test and its comparison with commercial H.pylori ELISA kit. Data was given as : In a comparison of H.pylori IgG antibody screening test results *gave* sensitivity of 95.9% (71/74) with specificity of 89.6% (43/48), and a total accuracy of 93.4% (l14/122) versus a commercial *H. pylori* lgG ELISA kit. On combining Conventional ELISA to this antibody screening test the accuracy is 98.3% on comparison to isolation of H.pylori either by Culture or Histology.

Treatment of infection with H.pylori:

Triple therapy with either of amoxicillin or tetracycline with metronidazole and bismuth subcitrate for 2 weeks will eradicate *H pylori* infection in 75–96% of patients[7]. Proton pump inhibitors (PPIs) have dual advantage as they have direct inhibition effect over H.pylori as well as they are inhibitors of urease. The preferred initial therapy is 7–10 days of a PPI plus amoxicillin and clarithromycin or a quadruple regimen of a PPI, metronidazole, tetracycline, and bismuth for 10 days.

Cerebrovascular Accident-Definition:

It is medical term for Stroke which results from ischemia followed by death of brain cells due to either vessel luminal blockage with clot or vessel rupture results in hemorrhage .

Epidemiology of stroke:

According to Feigin report (2009),for the past forty years, the annual CVA incidence rate has dropped by 1.1% in developed countries ,on other hand it has raised by 5.3% in developing countries[9].

- Stroke incidence and prevalence rates worldwide are shown as follow:
  - 400-800 strokes per 100,000 in a year (According to 'Banerjee 2005')
  - According to the report of 'Sridharan 2009',there are 5.7 million Deaths in a year

- 16 million new stroke cases every year
- according to WHO 2004,Stroke contributes for 27,650,000 DALYs

❖ Stroke Morbidity and Mortality in India[9]:

- Prevalence was 90-222 per 100,000 in a year (according to Dalal 2007)
- According to Nongkynrih 2004 report, 1.02 million deaths per year
- 1.34-1.54 million new cases of stroke occurring in a year (WHO 2005)
- According to WHO 2009 , Stroke contributes for 6,398,000 DALYs
- Shah and Mathur reported in 2006 that 12% of strokes were occurred in age <40 years population

Stroke burden in India

Though there is a decline in stroke mortality rates of high income countries, there is fear among experts regarding emergence of a stroke epidemic in India[12] . As life expectancy is increasing, India is predicted to face huge challenge to meet the economic burden in management of stroke . A recent analysis estimated that 8% of total medical and 46% of total neurological admissions were with stroke with a significant mortality rate of 20% at 30 days. A recent study calculated that 11% of overall strokes happen in younger population i.e <40years .Also it identified that one of prior cerebro vascular events is a important risk factor for stroke in less than 65 year population .

Worldwide 12.7 million people of stroke have severe disability .Of which, 8.9 million are from developing countries (Fisher 2011). That calculated DALYs due to cerebro vascular events was 5,288,435in 2004, which has an increase from estimate of 1998 i.e.4,917,631. Another recent analysis pointed that only the national per-capita income has strongest predictive value over mortality and disability in stroke patients[13] .It was notable that in 1998 worldwide 27.9 million DALYs were lost due to cerebro vascular events, it is approximately 7 times greater than of malaria . This is expected to increase as 60 million DALYs in 2020 of which 84% lose is expected in developing countries. Though economic burden of stroke is not separately explored , India is identified with loss of 8.6 billion dollars in 2005 cumulatively due to ischemic heart disease (IHD), Cerebro vascular accident and diabetes . This picture is expected a huge rise to 53 billion dollars by the year end of 2015 and India's GDP is calculated to fall by 1.1% because of the economic impact of CHD, stroke, and diabetes (WHO 2005). Another study stressing that among the stroke survivors of rural India ,73.2% have significant disability who are not at all meeting the needs of stroke care .

Annually India is reporting nearly 1.7 million new stroke cases ,of which one-third are been disabled. Recently WHO calculates that by the year of 2050, eighty percentage of total stroke patients in the world will be contributed by developing countries especially China and India[12].

Recently India has brought out with its own guidelines in stroke management., this guidelines has complete coverage in the management of cerebro vascular event from onset of stroke to basic long term care need to be paid on patients

with first stroke or recurrent strokes. It also commented that increase in life expectancy , changing lifestyles, progressive urbanization, and progressive stress levels make India as a place of emerging epidemic of stroke.

Persons with hypertension, dyslipidemia and diabetes are particularly at risk of stroke. It is notable that more than 16% of persons over twenty years of age have hypertension in India . Among them 50% \are not aware of their high BP status. Among the population with awareness, only fifty percent take steps to control BP, and of them, only fifty percentage have control over BP.

Demographic transition of stroke in India

A recent research ('Feri 2012')which was carried out in India, Americo-Latine and China denoting that non communicable diseases such as heart disease, stroke, diabetes, malignancy and chronic respiratory disease as a whole, contributed for most of deaths which occurred in elder population. Also some other Indian studies have calculated that the prevalence of stroke ranges from 0.2-0.4/1000 among the population < 50 year to 13-21/1000 in the 76-85 year population group. Likewise, incidence rates also increase from 28-35/100,000 among the population < 50 year to 833-1107/100,000 in the 76-85 year population group. India has high prevalence of stroke among younger population on comparison with developed countries i.e 18-32% of all stroke cases. Prevalence of Stroke in the elder population of rural India was 1.2% comparable with urban India which had 1.8%. Also it is noted that

prevalence rate is directly proportional to age and inversely proportional to the level of education . Recent study (Tripathi 2011) also noted that the average age of patients with stroke in developing countries is 15 years lesser than that of developed countries. Indian studies estimated that about 11% to 16% of strokes occur in younger population (<40 years) . Around one in five patients with strokes admitted to hospitals belongs to younger age group(<40 years) in India. In India among CVA most common is ischemic stroke followed by haemorrhagic stroke and then by embolic stroke . Among stroke in young , 22-47% is due to large artery atherosclerotic disease .

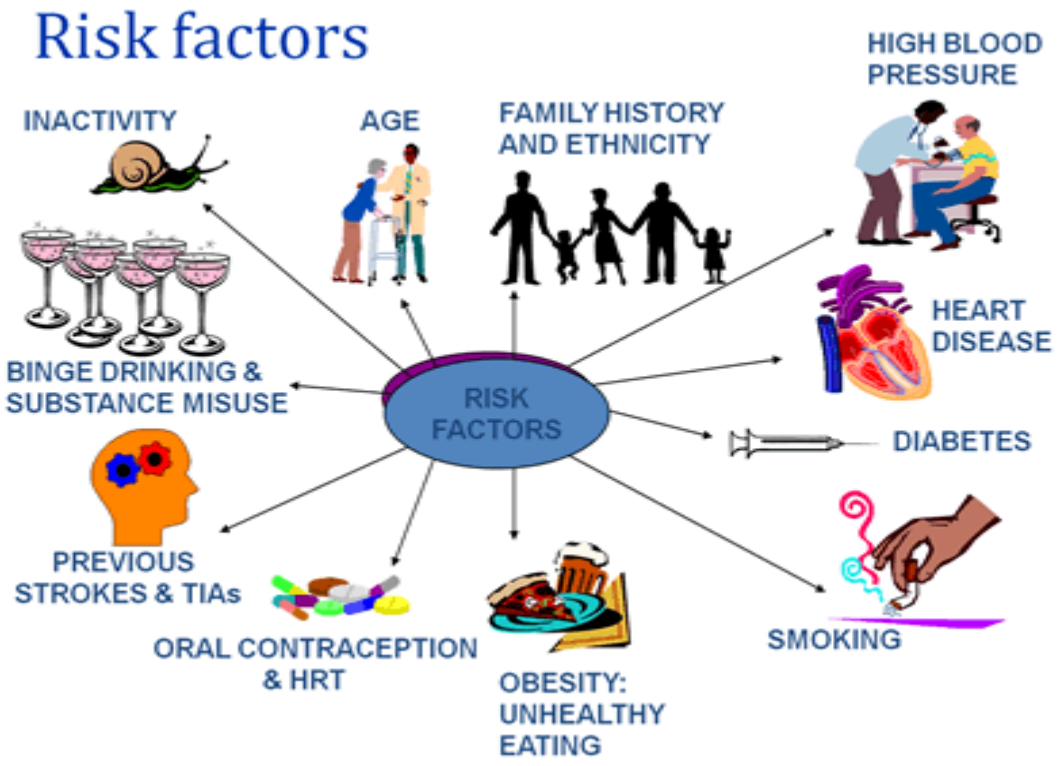
Recent analysis of (INSPIRE study) 3094 patients , carried out in India identified that around 28% (816) of stroke patients were belong to younger population (<50years) and 31% (938) were from lower economic status which suggested that higher stroke prevalence among younger and poor population in India . It coincides with Das et al study who noted that the stroke prevalence was huge among the slum dwellers of Kolkata than that of non-slum dwellers .In another study, Tripathy et al identified that the prevalence high BP and dyslipidemia were respectively 8% and 11% higher in the low socio economic population of Chennai compared with the high socio economic population .Men are at more risk to develop stroke with ratio of 2:1 comparing women .This kind of disparity is probably due to difference in prevalence of risk factors among men and women notably Smoking and Alcoholism. The mean age regarding stroke onset is for men ranges from 62-64 years and for women 58-67 years in India.

Risk factors for Ischemic stroke:

It can be classified as non modifiable and modifiable risk factors

NON MODIFIABLE RISK FACTORS	MODIFIABLE RISK FACTORS
❖ Age	-Hypertension
❖ Gender	-Atrial fibrillation
❖ Race	- Other cardiac diseases
❖ Family H/O Stroke	- Diabetes Mellitus
	-Dyslipidemia
	- Smoking
	-Acoholism
	- Illicit drug abuse
	- Obesity
	- Physical inactivity

❖ Beyond this risk factors , chronic low grade inflammation associated chronic infection is also found as a risk factor for atherosclerotic vascular events such as stroke and CAD. some of attributed pathogens are Chlamydia pneumoniae, Herpes simplex virus, Cytomegalovirus and Helicobacter pylori., of which the role of Herpes simplex virus and Cytomegalovirus in atherosclerotic events found to be insignificant on further studies.Still many studies are going on to explain the role of Helicobacter pylori and Chlamydia pneumonia on pathogenesis of vulnerable plaques.



Nonmodifiable Risk Factors for ischemic stroke:

Race , age , sex, heredity as well as ethnicity are called as nonmodifiable risk factors for ischemic cerebro vascular events. Though they are non modifiable, their merely presence alerts us the more possibility of vascular events, give thought about vigorous treatment of modifiable risk factors[13].

First we can see about age,one of non modifiable risk factors. It is said that for every ten years after 55 years of age , both male and female are at two times more risk regarding occurrence of new CVA event. Regarding sex, incidence of CVA is 1.35

times commoner in males than females, but the mortality rate is more among females than males gender because of longer life expectancy of females.

A significant family history is often notable in stroke. This is explainable by genetics, where same kind of genes who are all key in determining various risk factors of atherosclerosis shared by same family members. Framingham Study also concluded that both maternal and paternal history of stroke were have significant association with greater risk of cerebro vascular accident[13].

Race is also an important non modifiable risk factor. Regarding stroke incidence rate black people have two times more risk than that of white people. One comparison regarding stroke occurrence between African-American population and white population of 50 - 60 years, it was found that African-Americans had five times more risk for stroke than that of white people;In Asian population China, India and Japan are forerunners in CVA occurence. Especially in Japan stroke mortality and disability rates were very high in first half of 20th century, even proceeded that of cardiological issues. This picture was gradually altered after the end of second world war ,so now the stroke incidence rate of Japan is similar to that of United states of America.

Modifiable Risk Factors for Ischemic Stroke:

Hypertension

It is one of very important risk factor for any catastrophic vascular event especially stroke . Many studies revealed that hypertensives (defined as SBP ≥160 mm Hg and/or DBP ≥95 mm Hg)are four times more risky to develop stroke than non hypertensives. A meta analysis of seven studies intended to describe the role of blood pressure in CVA incidence revealed the relative risk of stroke is about 0.6 at a BP of 138/86 mm Hg and about 0.30 at BP of 124/74 mm Hg. Though it carries significance even in elder population the hypertension impact over stroke occurrence found to decrease with advancement of age: Let's see the odds ratio which is four at age of 50years, decreasing to one by age of ninety[13]. Population surveys revealed the hypertension prevalence which is around twenty percentage at 50years of age, nearly thirty percentage at 60 years of age, 40% at age of 70years, 55% at age of 80 years, and 60% at age of 90 years. If we use JNC 8 definition (i.e ≥140/90 mm Hg or on treatment with antihypertensives), hypertension prevalence rises to about forty five percentage at age of 50 years, >60% at age of 60 years, and >72% at age of 70years. Another notable fact that hypertension is more prevalent in black people than white population, which coincides with the fact that stroke prevalence is more common among black population than white population.

Many clinical trials also established the impact of treatment for hypertension (with anti hypertensives) over the stroke occurrence rate. A worldwide meta analysis of seventeen anti hypertensive treatment trials which involved nearly fifty thousand patients revealed that thirty eight percentage reduction in over all CVA occurrence and a forty percentage fall in occurrence of life threatening stroke events which indicates the necessity of appropriate treatment for SHTN. As worldwide meta analysis ,this impact is applicable in both black and white population of any age group.

Cardiac Diseases

Among heart diseases, Atrial fibrillation (AF) is one of the most important risk factor for ischemic stroke[14]. Incidence of Atrial fibrillation increases with advancement of age. For every 10 years after 55 years of age , AF incidence has two fold increase. Prevalence of Atrial fibrillation (AF) above age of sixty five years is calculated as 5.8%. Framingham Study suggests that the prevalence of atrial fibrillation in the United States population is in trend of increase[14].

Various studies indicated that 50% of cardio embolic stroke events are associated with atrial fibrillation. Framingham Study is indicating that non valvular atrial fibrillation carries 3 fold to 5 fold more risk for CVA. Unlike coronary heart disease, hypertension and cardiac failure,which has the impact over stroke occurrence which decline with advancement of age, atrial fibrillation impact on risk of stroke is persistent upto 90 years of age. The relative risk of atrial fibrillation for CVA rises from

2.8% in persons aged 51 to 60years to 22.6% in persons aged 81 to 90 years; i.e, around 1 in every 4 stroke patients of more than 80 year age group has atrial fibrillation[14] .

Recent meta analysis suggested that if atrial fibrillation is associated with congestive heart failure ,hypertension, increased age, DM, previous evidence of thrombo embolic manifestations like TIA, prior CVA and associated peripheral vascular disease there is more risk of embolic stroke. Investigators pointed out that patients who are all with less than 65years old who doesn't have any of this risk factors doesn't carry significant risk of embolic stroke. Another meta analysis of three different trials revealed that mitral annular calcification, chamber enlargement of left atrium and LV systolic dysfunction had strong association with development of embolic stroke in patients with atrial fibrillation

In a meta analysis of various Atrial fibrillation trials,it is noted that anticoagulation with Warfarin reduced the risk of stroke by sixty eight percentage[14]. Here annual incidence rate of embolic events was said to be 5.6% in the control group (i.e.without warfarin) and 1.5% in the study group (i.e.with warfarin) which also revealed that reduction of 3.1% ($P<.001$) events per year. On other hand incidence of bleeding was low for patients on aspirin or placebo (about 1%) which is comparable with warfarin group who has risk of 1.3%. According to SPAF (Stroke Prevention in Atrial Fibrillation) efficacy of aspirin in prevention of embolic stroke in patients with atrial fibrillation is uncertain. It also indicated that anticoagulants such as warfarin has significant efficacy over aspirin. Though Aspirin can reduce the incidence of

thrombotic(non-embolic) stroke, it doesn't carry significant efficacy in prevention of embolic stroke in persons with atrial fibrillation. Thus at present in prevention of embolic stroke in high risk group with atrial fibrillation ,warfarin is indicated. For those population belong to low risk group such as younger individuals and those in whom warfarin is contra indicated it is better to go with aspirin than warfarin. Even with this convincing evidence which support the efficacy of warfarin, it was estimated in 1992 that only twenty six percentage OP dept patients with atrial fibrillation were given the treatment with anticoagulants, among them elder population who received anticoagulant was very negligible only.

Regarding the association between cardiac valvular lesions and stroke,Mitral stenosis dominating the picture as it is often complicated by atrial fibrillation. Mitral valve prolapse unless complicated by atrial fibrillation or endocarditis, carries only minimal risk of stroke. Mitral annular calcification also carries significant risk for stroke. Mitral annular calcification is prevalent among 11% of men and 17% of women. Framingham Study revealed that those with mitral annular calcification carries two times more risk of stroke . Like MS, when mitral valvular calcification is complicated by atrial fibrillation, risk for embolic stroke is amplified. It is also depicted that combination of atrial fibrillation and mitral valvular calcification carries 5 time more risk for stroke, whereas on standing alone each carries only 2 times more risk for stroke. Valvular strands is a recent concept described as one of the risk factors for stroke. They

are identified with TEE as threadlike mobile strands that are attached to the aortic and mitral valve leaflets.

Left atrial chamber enlargement is also one of the risk factors for stroke. A recent Study concluded that for every 10mm increase in left atrial chamber size, stroke risk gets tripled. Atrial septal aneurysm (ASA) and Patent foramen ovale (PFO) also carries an increased risk for embolic events. Among these patent foramen ovale which is characterized with right-to-left shunt between two atrium, give rise the possibility of paradoxical embolism. Patent foramen ovale can be diagnosed by Trans esophageal echocardiography or trans thoracic echocardiography with help of agitated saline . Atrial septal aneurysm is characterized by an aneurysm of atrial septum which is bulged into either right or left atrium. Studies revealed that Atrial septal aneurysm is associated with cryptogenic stroke on comparision with control population. When both Atrial septal aneurysm and Patent foramen ovale exists together risk for embolic stroke gets doubled than when they present alone.

Myocardial pathologies also play an important role in stroke. Framingham Study revealed that coronary heart disease carries 2 times more risk of stroke, left ventricular hypertrophy carries 3 times more risk of stroke and congestive cardiac failure has 4 fold more risk of stroke. So it is obvious that in preventive strategies of embolic stroke ,prevention of CAD and LVH has an important role.

The interventional cardiology treatments and procedures are sometimes associated with complications such as stroke. Angioplasty and cardiac catheterization carries 0.3% to 0.4% risk for stroke. If intracardiac devices complicated by infection or thrombus there will be more risk of stroke. Cardioversion and electrophysiology procedures such as pacing, RFA carries significant risk for embolic stroke.

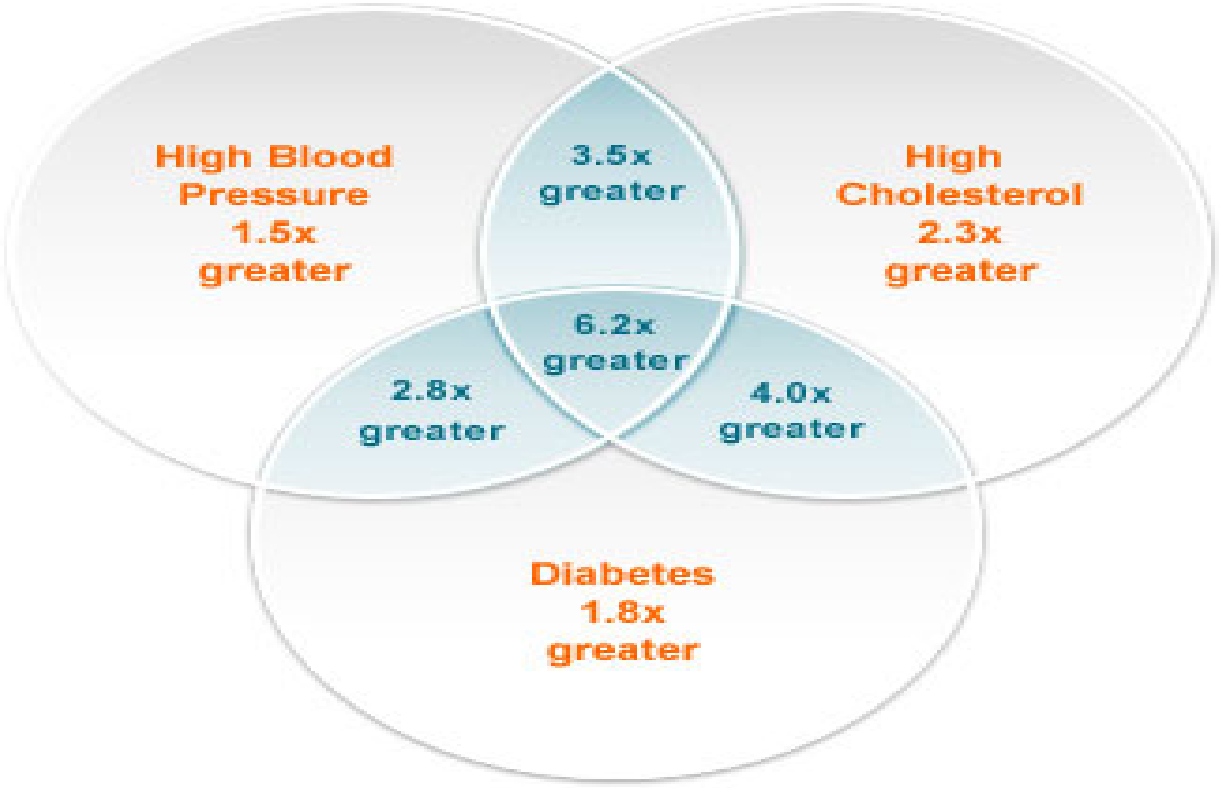
Diabetes Mellitus:

Diabetic patients have more tendency to have atherogenic risk factors like obesity, hypertension, and dyslipidemia[13] .various studies among stroke patients confirmed that DM carries relative risk of 1.7 to 3.1 regarding stroke occurrence. Studies also confirmed that diabetics are two times more risk to develop thrombo embolic events than non diabetics. Besides glycemic control ,hyperinsulinemia and increased insulin resistance also carries significant risk for thrombotic stroke.

Lipids

As hypercholesterolemia is an obvious risk factor for promotion of atherosclerosis, it is also an important modifiable risk factor for ischemic stroke. Many studies brought the positive relationship between total cholesterol and low density Lipoproteins(LDL) level with relative risk of stroke. These studies also didn't miss to mention the protective effects of HDL cholesterol over promotion of atherosclerosis.

One such study is Scandinavian Simvastatin Survival Study (4S Study) which revealed



that study group (i.e those on Simvastatin) has significant lower stroke incidence rate (46% lower)compared to placebo group .

Alcohol

Mild to moderate alcohol consumption will reduce cardiovascular disease as well as reduce the incidence of cerebro vascular accident. Recent meta analysis demonstrated a U-shaped relationship between alcoholism and thrombotic events i.e mild to moderate alcoholism is associated with low risk of thrombo embolic events[13]. However, profound alcoholism is associated with significant high risk for thrombo embolic events.

Illicit Drug Abuse

Among illicit drugs, cocaine is very well demonstrated with increased risk for stroke. Some other substances said to be associated with stroke are LSD, marijuana, amphetamines, and heroin. Some case studies demonstrated that nasal decongestants abuse(which have sympathomimetic activity) also associated with increased risk for stroke[13].

Lifestyle Factors

Obesity, sedentary lifestyle, over eating , and emotional stress are some of lifestyle factors have significant association with stroke. As obesity is one of modifiable riskfactors for hypertension,diabetes mellitus and dyslipidemia, the cumulative risk of stroke is amplified. Among the various patterns , central obesity which is characterized by fat deposition in and around abdomen carries significant risk for thrombotic events comparing with the gyanecoid obesity which is characterized by fat deposition around thigh and hip .

Physical inactivity is an another significant risk factor for atherosclerotic vascular events. Physical activity reduce overall risk of thrombotic events by reducing weight, Low Density Lipoprotiens, increase the insulin sensitivity and increasing High Density Lipoproteins. Regarding diet, at present fast food culture carries significant risk for stroke. Adding sufficient amounts of fish, green tea into the routine diet has beneficiary role in prevention of stroke.

Oral Contraceptives

Oral contraceptives with more estrogen content(such as >50 μg) which was used previously had significant association with stroke. But recent times studies showing that low-dose estrogen(<50 μg)contraceptives doesn't carry significant risk for stroke.

Migraine

Previously it was projected as an important risk factor of thrombotic stroke,but recent studies suggest that migraine is no longer a independent risk factor for thrombotic stroke after giving adjustment to other risk factors of stroke. Though there is some relationship between stroke and migraine, the overall relative risk is very small, often negligible. For example, it is identified that presence of migraine increases stroke risk from ten in 1 lakh woman years to eighteen in 1 lakh woman years .So finally it is concluded that the absolute risk regarding stroke occurrence in relation to migraine is negligible.

Hemostatic Factors

The association between hemostatic factors and stroke occurrence is explained by 2 different studies. Göteborg study demonstrated positive relationship between serum fibrinogen levels and stroke occurrence. Framingham Study also demonstrated this association in males, but in females it didn't carry the significance.

Serum fibrinogen level also positively correlated with development of carotid stenosis and stroke recurrence. Mechanisms behind the role of fibrinogen are: as it is a substrate for thrombus formation,there is direct evidence in clot formation. Other possible effects are: increases the blood viscosity ,promotion of platelet adherence and promotion of atherosclerosis.

The plasminogen activator system of human body also been demonstrated as having relationship with promotion of thrombotic events. Interestingly Physicians' Health Study demonstrated the positive relationship between plasminogen activator system and risk for stroke among men(between 40 to 85 years) . This paradoxical relationship of serum levels of tissue-type plasminogen activator with stroke occurrence was explained by a fact that within plasma majority of tissue-type plasminogen activator is in inactive form which was bound with plasminogen activator inhibitor-1 (PAI-1) and only a small part of tissue-type plasminogen activator is in active form(i.e.not bound with PAI-1). So that, elevated plasma tissue-type plasminogen activator level indicates only the elevated bound form which indirectly indicates impairment in fibrinolysis.

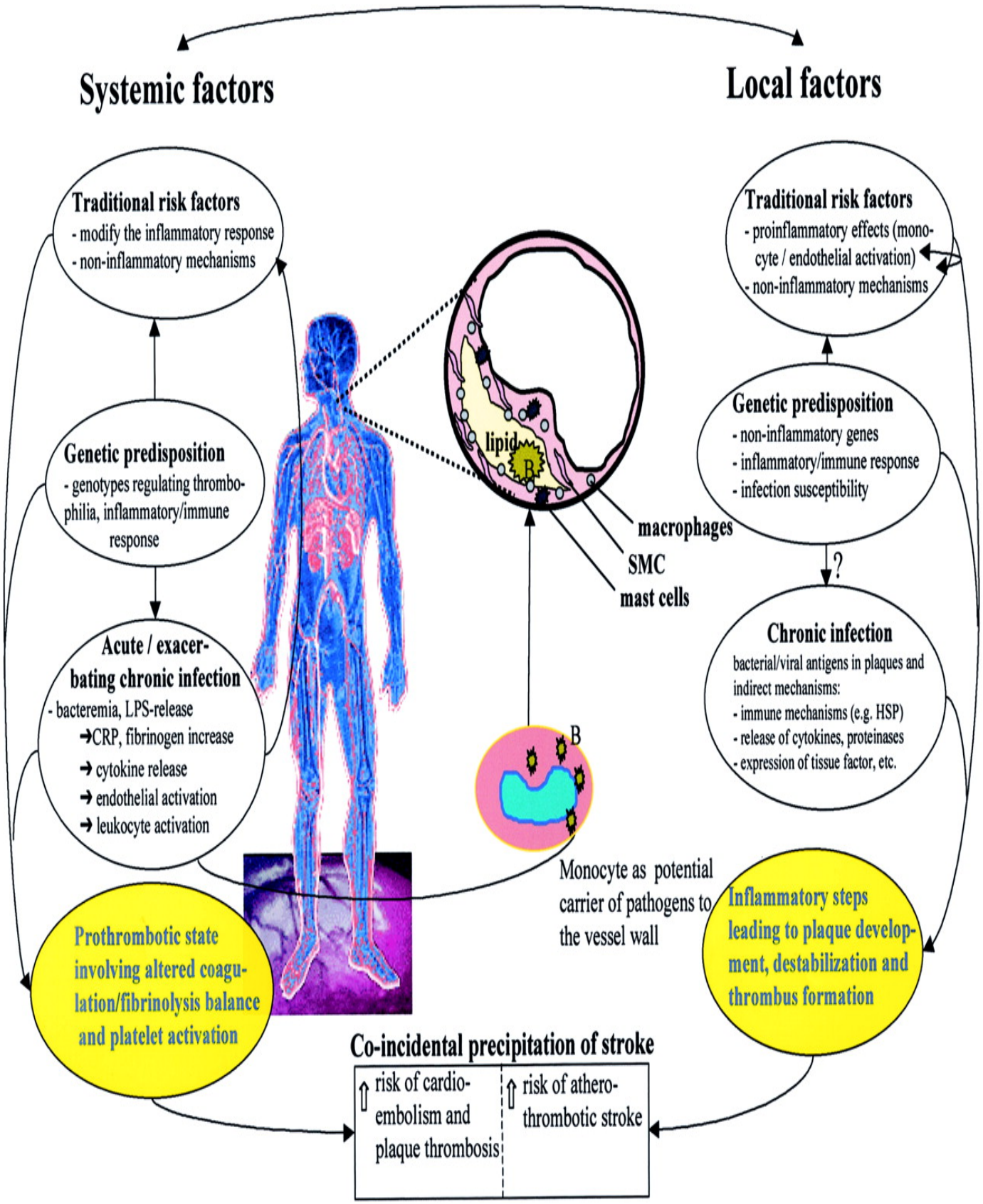
Homocysteine

It is synthesized from Methionine which is an essential amino acid. Blood levels of homocysteine depends on blood levels of vitaminB12, folic acid and vitamin B6,also determined by various genetic factors[15]. Many studies already showed

the strong positive relationship between hyperhomocysteinemia and stroke occurrence. Recently British Regional Heart Study demonstrated the positive relationship between hyperhomocysteinemia and stroke occurrence among middle aged women and men. Blood homocysteine level is inversely proportional to blood Vit B6 and folic acid level. Hyperhomocysteinemia is proven to be both atherogenic and prothrombotic by animal models. Also though supplementation of vitaminB12, folic acid and vitamin B6 will reduce homocysteine level, It doesn't been demonstrated that this approach will surely has impact on stroke incidence rate[15].

Other risk facors:

Chronic infections especially with Cytomegalovirus ,Chlamydia pnemoniae and H.pylori have been debated with pathogenesis of atheromatous plaques. All this organisms can infect blood vessel wall and exhibit chronicity and persistency .Of which Chlamydia pnemoniae and H.pylori bacterial components have already been isolated from atheromatous plaques. Some others arguing that secondary infection of plaques might aggravate the potency of known risk factors by 1) Chronic low grade inflammation 2)by altering vascular response to injury 3)by altering systemic lipid metabolism or through circulatory inflammatory mediators such as IL-6 which promote the activation of vascular wall cealls results in streak formation.


Systemic factors
Local factors
Traditional risk factors
- modify the inflammatory response
- non-inflammatory mechanisms
Genetic predisposition
- genotypes regulating thrombophilia, inflammatory/immune response
Acute / exacerbating chronic infection
- bacteremia, LPS-release
→CRP, fibrinogen increase
→ cytokine release
→ endothelial activation
→ leukocyte activation
Prothrombotic state involving altered coagulation/fibrinolysis balance and platelet activation
Traditional risk factors
- proinflammatory effects (monocyte / endothelial activation)
- non-inflammatory mechanisms
Genetic predisposition
- non-inflammatory genes
- inflammatory/immune response
- infection susceptibility
?
Chronic infection
bacterial/viral antigens in plaques and indirect mechanisms:
- immune mechanisms (e.g. HSP)
- release of cytokines, proteinases
- expression of tissue factor, etc.
Inflammatory steps leading to plaque development, destabilization and thrombus formation
lipid
B
macrophages
SMC
mast cells
B
Monocyte as potential carrier of pathogens to the vessel wall
Co-incidental precipitation of stroke
⇧ risk of cardio-embolism and plaque thrombosis
⇧ risk of athero-thrombotic stroke

In addition H.pylori produce heat shock protein which will activate macrophages to produce matrix metallo proteinases which might weak the atheromatous plaques so that they are susceptible to rupture followed by thrombus formation. Cross reacting antibody response to heats hock protein 60 also play an important role, because H.pylori HSP has very similar amino acid sequence as humans. Another significant opinion about this chronic infections is excessive acute phase reactants at a non vascular site of infection may worsen the thrombotic complications of atheroma by altering the balance between coagulation and fibrinolysis. This acute phase reactants which produces inflammatory processes have an important role at all stages of atherosclerosis from their streak to development of complications. It is better been depicted in the above diagram.

Special mention about Risk Factors among Indians:

Epidemiological experts already alerted Government of India regarding the emergence of stroke epidemic in India. Three transitions are said to be key for this epidemic in India :1) demographic2) socioeconomic factors and 3) lifestyle factors . This demographic transition is characterized with longer life expectancy, lifestyle transition is characterized with over eating with physical inactivity and finally about socioeconomic transition characterized by providing good living standards even

for rural population as well as adopting western life styles . Though these transitions are modifiable , they collectively increase the risk of stroke.

A recent study from Gujarat demonstrated that risk factors like hypertension (39%), smoking (36%), alcoholism (30%) and dyslipidemia (20%) are the important risk factors in elder population, all of this are modifiable. On the other hand increased BMI, smoking, alcoholism, hypertension and diabetes have significant association with young stroke. DM and dyslipidemia are well demonstrated risk factors for both large vessel and small vessel occlusive disease. A recent meta analysis involving ten thousand CVA patients from hundred Indian hospitals pointed out that stroke patients carried some modifiable risk factors more frequently such as tobacco consumption, alcoholism, hypertension, DM and hypercholesterolemia.

Patients with prior TIA and minor stroke have more susceptibility to develop newer thrombotic events . Prior experience with CAD and large artery occlusive disease are said to be independent risk factors for newer thrombotic events among stroke survivors. When Compared to US population , Indians carry more odds ratio with some of modifiable risk factors such as smoking and CAD in calculating the risk for stroke.

Anatomy of Cerebral Circulation

- **Anteriorly: Carotid Arteries** – middle & anterior cerebral arteries
  - Supply frontal, parietal, temporal lobes; part of the diencephalon (thalamus & hypothalamus)
- **Posteriorly: Vertebral Arteries** – basilar artery
  - Supply some parts of temporal & occipital lobes, cerebellum, brainstem, & part of the diencephalon
- **Circle of Willis** –It is the connection between the anterior & posterior cerebral circulation

Pathophysiology of Cerebrovascular Accident:

- **Ischemic Cascade**

  -characterised with series of metabolic events such as,

  - Free radical formation
  - Loss of ion homeostasis
  - Inadequate ATP adenosine triphosphate production
  - Release of glutamate like excitatory amino acids

- Finally Cell death

- **Border Zone**: is an area surrounding the main infracted area, characterized with restorable blood supply if stroke occurrence is within 3 hours

- **Transient Ischemic Attack**

  - TIA is nothing but a focal neurological deficit ,which lasts only for short period.

  - It is due to the transient blockade of any of vascular territories in brain.

    - Often this arterial blockade is due to formation of micro thrombi or emboli in small vessels

  - Clinical features of TIA will recover within one day – usually they will recover within fifteen minutes.

  - It should be taken as warning sign of progressive cerebrovascular disease

Classification of Stroke:

-depending on basic pathophysiologic findings, it can be broadly classified as ischemic and hemorrhagic stroke

- **Ischemic CVA**

-again based on underlying etiology it can be classified as

- **Embolic stroke**

and

- **Thrombotic stroke**

- **<u>Hemorrhagic CVA</u>**

-it may be either of

- **Subarachnoid Hemorrhage (SAH) or Intracerebral Hemorrhage(ICH)**

- Among these SAH may be aneurysmal rupture related(either of Saccular aneurysm or berry aneurysm)

- **<u>Ischemic Stroke</u>—**contributes 85% of total strokes due to sudden cessation of blood supply to particular area of brain results from super added thrombus formation over ruptured plaque results in complete occlusion of involved blood vessel.

- **Ischemic penumbra size is determined by:**
  - Size of the lesion
  - Rapidity of onset of event
  - Formation of collaterals in order to compensate the occluded blood vessel

- Since the cerebral edema gradually increases ,symptoms may get worsened during first 3 days.

- **Types of Ischemic Stroke:**

As already discussed it may be either one of Embolic Stroke or Thrombotic Stroke

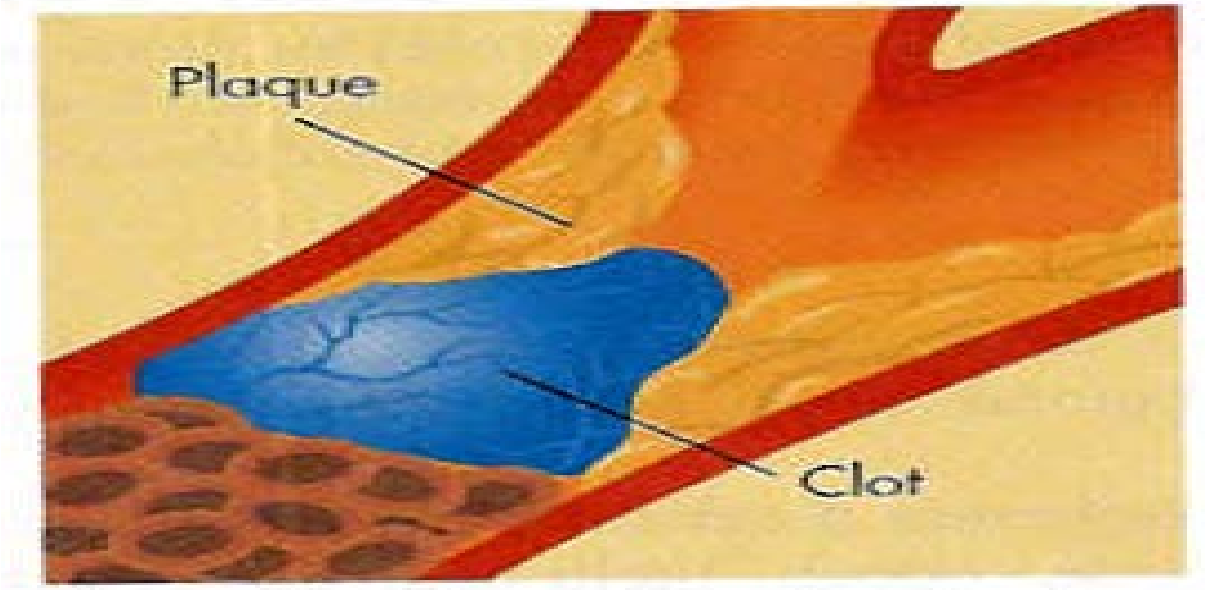
Ischemic – Thrombotic Stroke

-It accounts for >60% of strokes

-Here Lumen of vessel becomes occluded with thrombus proceeded by an abrupt change in vulneale plaques.,results in infarction.

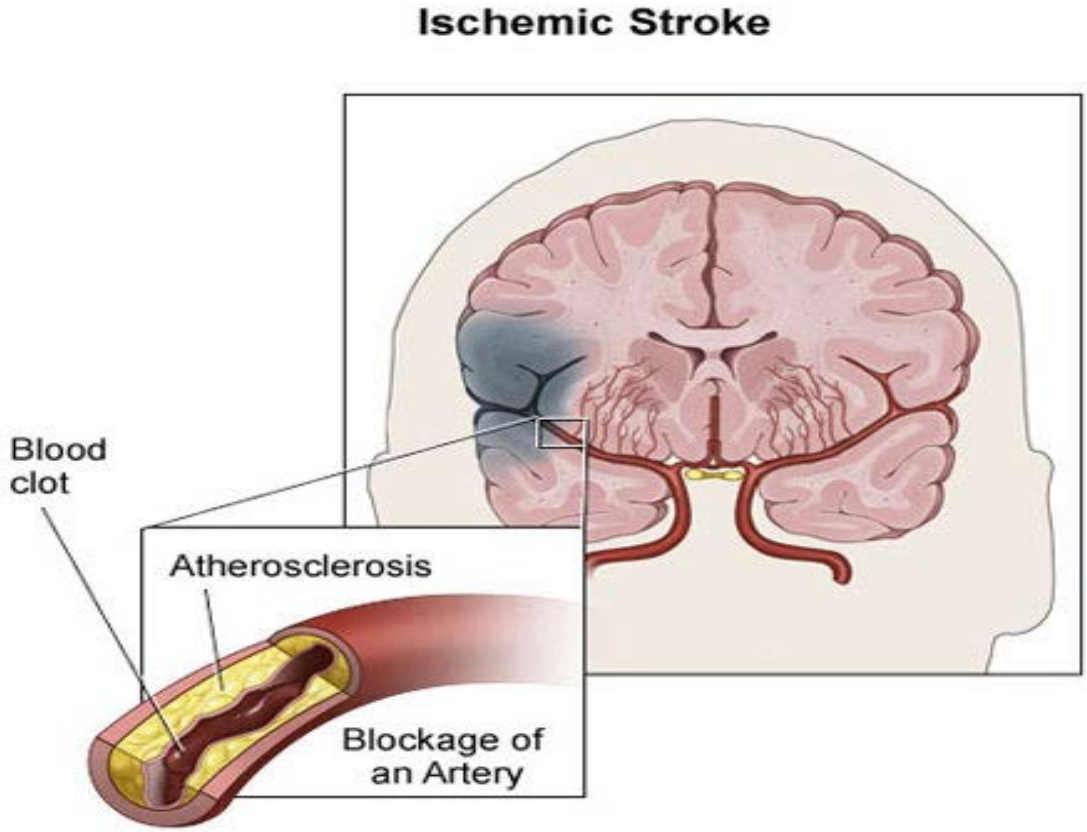
-Vulnerable plaques are nothing but plaques with large areas of foam cells,thin fibrous cap and few smooth muscle cells,they are more likely to rupture with either of extrinsic(Hypertension or platelet reactivity) or intrinsic(i.e. plaque structure

and composition) triggering factors.



Thrombotic stroke. Cerebral thrombosis is a narrowing of the artery by fatty deposits called *plaque*. Plaque can cause a clot to form, which blocks the passage of blood through the artery.

-That ‘abrupt change’ would be either one of 1)rupture of plaque 2)Hemorrhage into the plaque 3)ulceration of plaque.All this changes results in exposure of highly thrombogenic basement membrane to thrombogenic plaque constituents



Ischemic – Embolic Stroke

- Characterized by occlusion of any of cerebral arteries with emboli which is often originated from cardiac source,
- Which produces significant edema and ischemia of that particular vascular territory

- Contributes twenty four percent of all strokes
- Those with AF, Rhematic heart diseases ,prosthetic valves and Myocardial Infarction are particularly at risk of embolic stroke.
- Rapidity of symptomatology will determine the severity of stroke, because on a catastrophic embolic stroke, there won't be any time to form collaterals.
- Any age group can be affected.
- Recurrence is possible unless underlying cause is detected and properly treated.

Hemorrhagic Stroke

- It contributes to fifteen percent of total strokes.
- It is characterized by bleeding within brain parenchyma which eventually results in neuronal damage. It may be due to either of
  - Intracerebral or
  - Subarachnoid hemorrhage

Intracerebral Hemorrhage

- It is characterized by bleeding within brain parenchyma due to rupture of a blood vessel.
- Among the various risk factors of hemorrhagic stroke hypertension is significantly associated with hemorrhagic stroke
- Other causes includes: vascular malformations, trauma, brain tumor, ruptured aneurysms, anticoagulation and coagulation disorders.
- Usually there will be catastrophic onset of symptoms and rapid progression.
- Clinically characterized with neurological deficit, hypertension ,loss of consciousness, nausea, vomiting and headache.
- It carries grave prognosis with fifty percent mortality within few weeks
- Twenty percent of affected patients become functionally independent at 6 months
- Any age group can be involved,eventhough common in elderly patients
- Once patient recovers from the acute phase i.e after cerebral edema starts to subside the recovery is comparatively good. So in ICH mortality rate is high, but among the survivors morbidity rate is low when compared to thrombotic stroke.

- **Hemorrhagic Stroke with Subarachnoid Hemorrhage**

  - It is nothing but bleeding into the CSF filled subarachnoid space
  - It is often due to rupture of vascular aneurysm either of Saccular or berry aneurysm which is few mm to 15-25 mm in size
  - Other causes for Subarachnoid Hemorrhage: illicit drug abuse, trauma and Arteriovenous malformation (AVM)
  - Overall incidence of Subarachnoid Hemorrhage: 6-17/100,000
  - SAH is somewhat more commone in females
  - Its incidence increases with age
  - Warning Symptoms of Subarachnoid Hemorrhage: sudden onset of a severe headache which will usually be described by patient as "worst headache of his/her life"
  - Other clinical features: Neurological deficits, stiff neck , Loss of consciousness, seizures and nausea, vomiting.
  - Despite improvised surgical techniques for Subarachnoid Hemorrhage, SAH carries very poor prognosis with high mortality rate.

Clinical Manifestations of MCA territory involvement

Characterized with

- Opposite side focal deficits
- Opposite side hemianesthesia
- If dominant hemisphere is involved,aphasia is also possible.
- With non dominant hemisphere involvement, there will be neglect of opposite side; anosognosia may be there which is, unaware or denial of neuro deficit.
- Homonymous hemianopsia – is defective vision or blindness involving right or left halves of visual fields of both eyes

Clinical Manifestations of Anterior Cerebral Artery Involvement

Characterized with

- Contralateral
  - weakness of proximal upper extremity
  - lower extremity may have sensory & motor deficits

- ❖ Urinary incontinence
- ❖ Sensory loss (discrimination, proprioception)
- ❖ Contralateral grasp & sucking reflexes might be present
- ❖ Apraxia which is the inability to carry out familiar purposeful movements in the absence of gross motor or sensory impairment
- ❖ Personality change such as flat affect, loss of spontaneity, loss of interest in surroundings and Cognitive impairment

Clinical Manifestations of Posterior Cerebral Artery & Vertebrobasilar Involvement

Characterized with

- ❖ Altered mental status
- ❖ Unilateral or bilateral sensory loss
- ❖ Contralateral or bilateral weakness
- ❖ Dysphagia – which is difficulty in swallowing due to lower cranial nerve involvement
- ❖ Dysarthria

- Unilateral hearing loss
- Visual disturbances such as blindness, diplopia and homonymous hemianopsia,
- Ataxia, Vertigo

Cerebrovascular Accident-Diagnostic Studies

These are done to confirm CVA and to identify cause:

- Carotid Doppler studies (ultrasound study)-to identify the carotid plaques and also the intimae thickness of carotid arteries
- CT – immediate investigation which will differentiate between hemorrhagic stroke from ischemic stroke
- CT Angiography – visualizes cerebral vasculature
- MRI – has greater specificity than computed tomography
    - But it may not be possible in all patients,for reasons of availability, metal issues and claustrophobia.
- Angiography: It is gold standard for imaging carotid arteries

Cerebrovascular Accident Treatment Goals

- **Drug Therapy –**In early thrombotic CVA we have to attempt to remove the arterial blockade in order to get back perfusion in affected artery
- **Thrombolytic Drugs**: tPA (tissue plasminogen activator),which
  - Activate plasminogen into active form of fibrinolysin i.e plasmin
  - Promotes fibrinolysis as it selectively degrades the fibrin of thrombi
  - Enzymatic action digests fibrin & fibrinogen
  - Results is clot lysis
- But indicated only within 3 hours of symptoms of ischemic CVA
- Other lines of management:
  - Confirm Diagnosis with CT
  - Patient can be anticoagulated if it is an evolving stroke or embolic stroke
  - ASA and Statins also be indicated
  - Rehabilitation therapy also should be started simultaneously

Objectives

- To test the association between H.Pylori infection and Non haemorrhagic stroke
- To check the association between H.pylori infection and childhood socio economic status

Place of study

Dept of Medicine, Stanley Medical College and Hospital

Study population

100 consecutive ischemic cerebral infarct patients with age ,sex matched 100 control persons

Study design- Case control Study

Study period- July 2014 to Sept 2015

Operational Definitions:

- Case definition: Radiologically (either CT or MRI) proven ischemic cerebro vascular accident patients

Inclusion criteria

1)New onset radiologically proven ischemic Stroke patients

2)Age –more than 25 years

Exclusion criteria

1)Patient who have undergone Gastrectomy

2)Immuno compromised patients

3)Recurrent Cerebro vascular accident

4)Patients with previous H.pylori eradication therapy

Criteria for control- Healthy individuals with more than 25years age attending Master Health Checkup OPD in GSH

Methodology

A total of 200 subjects were included in this study. The subjects divided into 2 groups. Case group comprising patents who were radiologically proven to have new CVA , Control group comprising 100 healthy subjects attending Master Health Checkup OPD in GSH. Separate informed consent form was obtained from Control group participants.

BP and BMI were recorded in all subjects. With Standard Proforma the details regarding current and their childhood socio economic status were obtained..Relevant blood investigations like Lipid profile, ECG and CBC were sent. H.Pylori Serology status was checked by both Rapid enzyme linked immunosorbent assay (ELISA) and card (BIO-LINE) test and serology was said to be positive only if both tests are positive.

PRINCIPLE OF BIO-LINE CARD TEST

The Bio-LINE card test is a H. pylori rapid screening test device using patient's Serum/Plasma,which is a qualitative membrane strip based immunoassay for the detection of antibodies against H. pylori in serum or plasma. In this test procedure, anti•human IgG is immobilized in the test line area of the device. After a serum(or plasma) specimen is placed in the specimen well labeled as S, it reacts with *H. pylori* antigen coated particles in the device. This reacted mixture migrates along the length of the test strip chromatographically and interacts with the

above immobilized antihuman IgG. If the given sample contains antibodies against H. pylori, there will be a colored line in the test line region indicates a positive result. If the given sample does not contain *H. pylori* antibodies, a colored line wont be there indicates a negative result.

Reagents:

The test device contains a membrane coated with antihuman IgG and

H. pylori antigen coated particles.

SPECIMEN COLLECTION AND PREPARATION

- This rapid screening test is performed by using serum .
- To avoid hemolysis we separated the serum immediately after specimen collection .
- Normally procedure should be carried out immediately after the separation of serum. Specimens should not be left in room temp for longer time. Samples can be kept at 3-9°C for up to three days. Whereas it should be kept in minus twenty degree Celsius for long term storage. Just prior to testing the specimen and the test device should be brought to room temperature in order to equilibrate with room temperature**.**
- We collected the sample and freezed it below minus twenty degree Celsius. Just prior to testing we brought the samples to room temperature .

Directions -followed in use of BIO-LINE card:

1)Once the test device is removed from the pouch ,procedure should be carried out immediately as best results possible only if the assay is carried out within 2 hours .

2)After removing the test device from the foil pouch, place the device on a clean surface,then add 10 micro litre of serum into specimen well followed by we have to add three drops of sample diluent

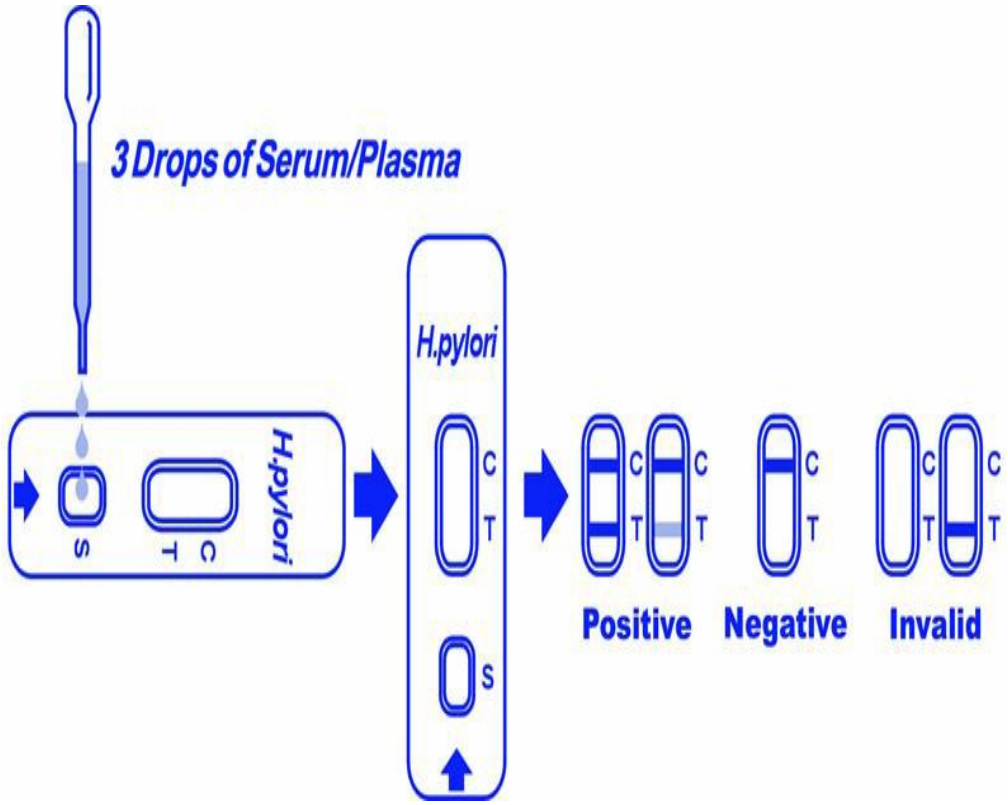
3)To read results, wait for 10 minutes. Appearance of two distinct red lines within ten minutes can be taken as positive result.Even low levels of H.pylori antibodies can give rise to faint red line,when time is prolonged,which should be avoided.

INTERPRETATION OF RESULTS

POSITIVE RESULT:

- if ther is appearance of 2 diffferent red lines.(1 redline on test region(T) ,another 1 in

control region)



NEGATIVE: if only 1 redline developed in region of (C) with absent redline in T region

INVALID: It may be due to insufficient specimen volume or incorrect procedural techniques characterized by absence of redline even in (C) region.

QUALITY CONTROL

A red line of control region (C) is used to make sure as adequate specimen volume and correct technique of procedure.

A picture from our patient's samples:

Principles of Helicobacter pylori IgG ELISA:

Diluted patient's serum sample is added to specimen well which is already coated with H.pylori specific antigen and IgG specific antibody. If the serum contains H.pylori specific antibody it will react with antigen. All the unbound forms get washed away .Now the enzyme conjugate is added which will selectively binds with antigen antibody complex, now the substrate is added and the plates are kept in incubator to allow

the hydrolysis of substrate by enzyme. Intensity of color produced is directionally proportion to serum level of IgG antibodies.

Interpretation of Helicobacter pylori IgG ELISA:

- It is based on Antibody index

Antibody index	Interpretation
<0.9	No detectable antibody to H.pylori IgG by ELISA
0.9-1.1	Borderline positive: follow-up test is needed
>1.1	Detectable antibody to H.pylori IgG by ELISA

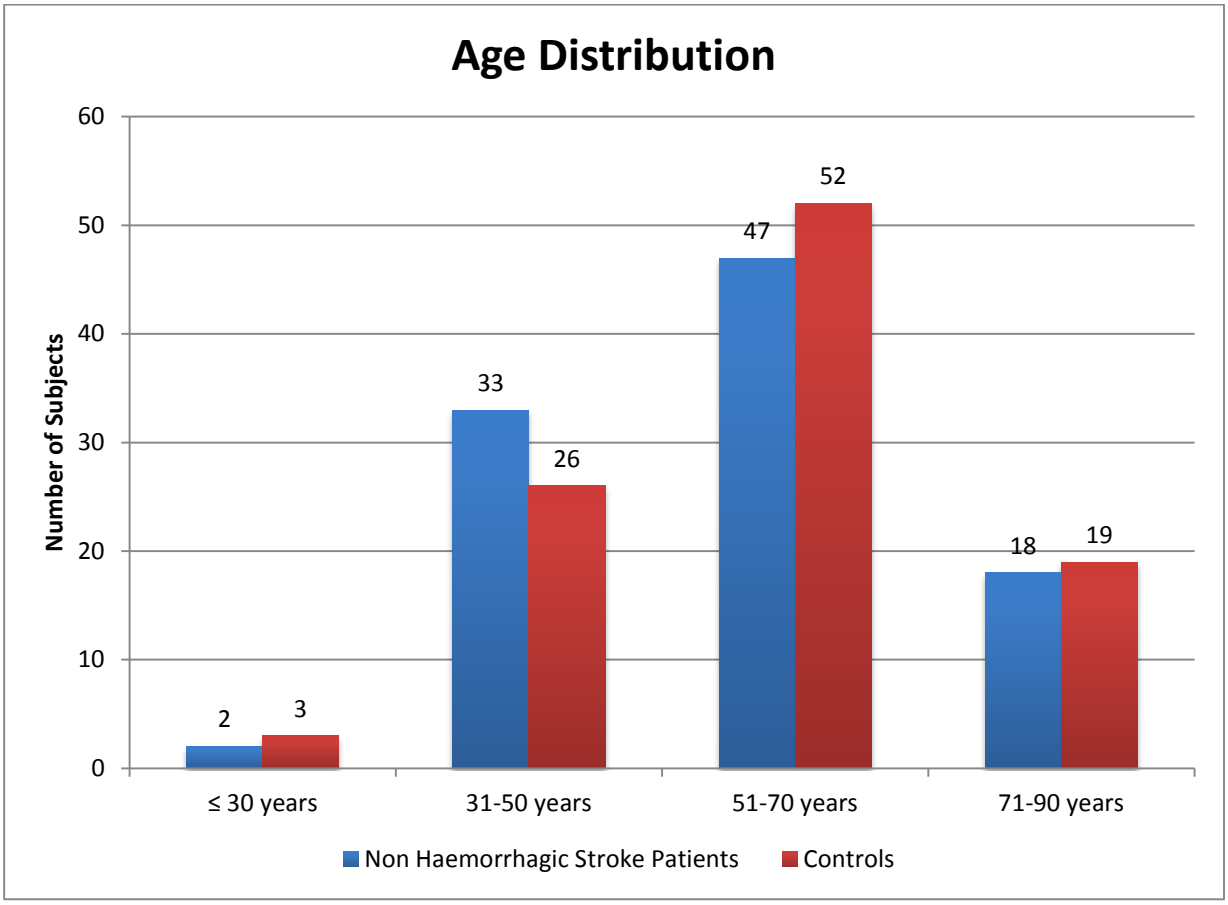
Part of kits we used:

Data Analysis

The patients were divided into two groups by Meperidine and Dexmedetomidine groups. Descriptive statistics was done for all data and were reported in terms of mean values and percentages. Suitable statistical tests of comparison were done. Continuous variables were analysed with the unpaired t test. Categorical variables were analysed with Fisher Exact Test. Statistical significance was taken as $P < 0.05$. The data was analysed using SPSS version 16 and Microsoft Excel 2007

Results and discussion

Age

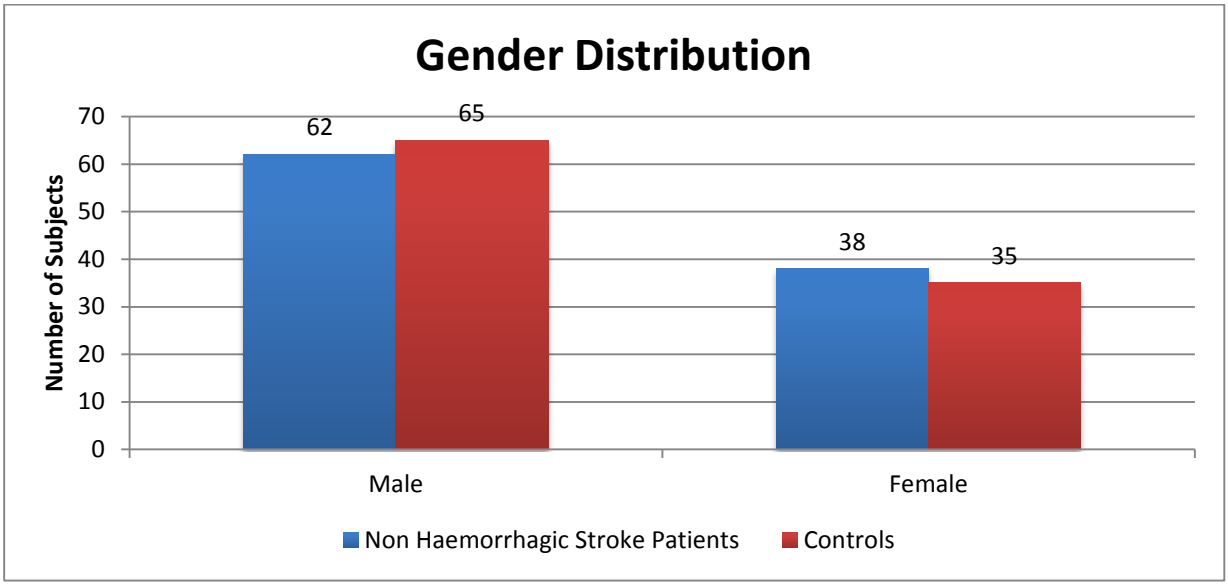


Age Distribution	Non Haemorrhagic Stroke Patients	%	Controls	%
≤ 30 years	2	2.00	3	3.00
31-50 years	33	33.00	26	26.00
51-70 years	47	47.00	52	52.00
71-90 years	18	18.00	19	19.00
Total	100	100	100	100

Age Distribution	Non Haemorrhagic Stroke Patients	Controls
N	100	100
Mean	57.49	57.50
SD	13.70	13.68
P value Unpaired t Test		0.9959

- Majority of the non hemorrhagic stroke patients group patients belonged to the 51-70 years age group (n=47, 47%) with a mean age of 57.49 years.
- In the control group patients, majority belonged to the same age group (n=52, 52%) with a mean age of 57.50 years.
- The association between the study groups and age distribution is considered to be not statistically significant since $p > 0.05$ as per unpaired t test.

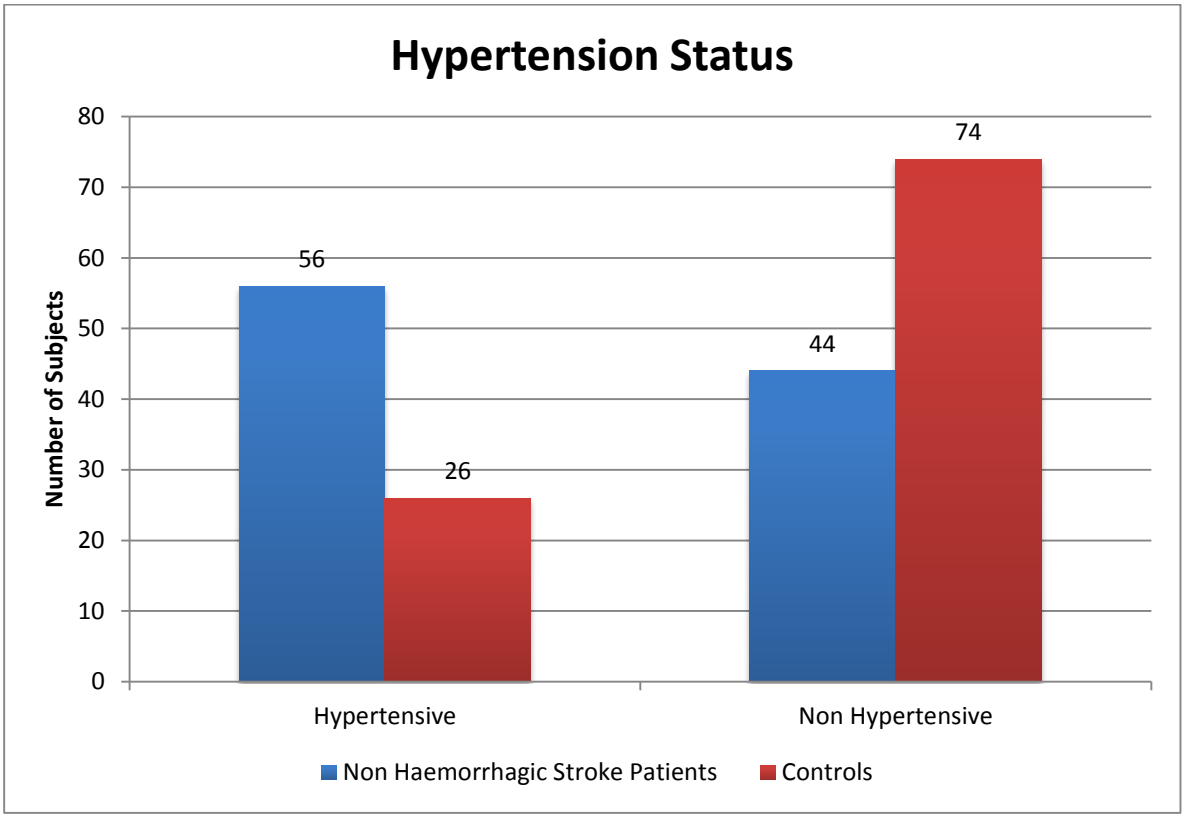
Gender



Gender Distribution	Non Haemorrhagic Stroke Patients	%	Controls	%
Male	62	62.00	65	65.00
Female	38	38.00	35	35.00
Total	100	100	100	100
P value Chi Squared Test			0.9999	

Majority of the non hemorrhagic stroke patients group patients belonged to the male gender class interval (n=62, 62%). In the control group patients, majority belonged to the same gender class interval (n=65, 65%). The association between the study groups and gender distribution is considered to be not statistically significant since $p > 0.05$ as per chi squared test.

Hypertension



Hypertension Status	Non Haemorrhagic Stroke Patients	%	Controls	%
Hypertensive	56	56.00	26	26.00
Non Hypertensive	44	44.00	74	74.00
Total	100	100	100	100
P value chi squared Test			0.0001	

Results

There is a true difference among study groups study groups in relation to hypertension status and this difference is considered to be statistically significant since $p < 0.05$ as per chi squared test. Most of the non haemorrhagic stroke patients were hypertensives (n=56, 56%). In the control group patients, majority were non hypertensives (n=74, 74%). This abnormality in hypertension incidence among the study groups is expressed with a p-value of 0.0001.

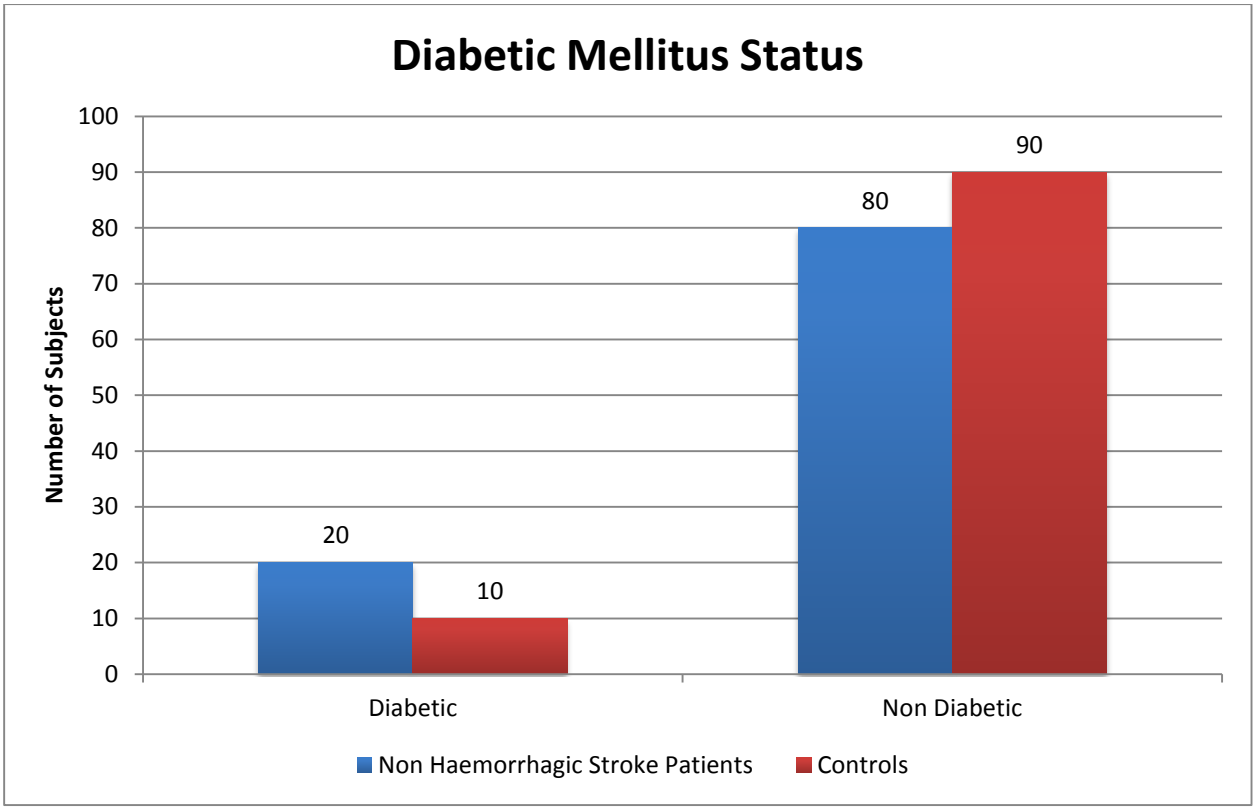
Discussion

The incidence of hypertension was meaningfully more in non haemorrhagic stroke patients group compared to control group by 30 percentage points. This significant difference of 2.15 times increase in incidence of hypertension in non haemorrhagic stroke patients group compared to control group is true and has not occurred by chance.

Inference

In this study we can safely conclude that hypertension is significantly associated with increased occurrence of non haemorrhagic stroke among our study patients.

DM



Diabetic Mellitus Status	Non Haemorrhagic Stroke Patients	%	Controls	%
Diabetic	20	20.00	10	10.00
Non Diabetic	80	80.00	90	90.00
Total	100	100	100	100
P value Chi Squared Test			0.0477	

Results

There is a true difference among study groups study groups in relation to diabetes status and this difference is considered to be statistically significant since $p < 0.05$ as per chi squared test. The incidence of diabetes among non haemorrhagic stroke patients was 20% (n=20). In the control group patients, the incidence of diabetes was 10% (n=10). This abnormality in diabetes incidence among the study groups is expressed with a p-value of 0.0477.

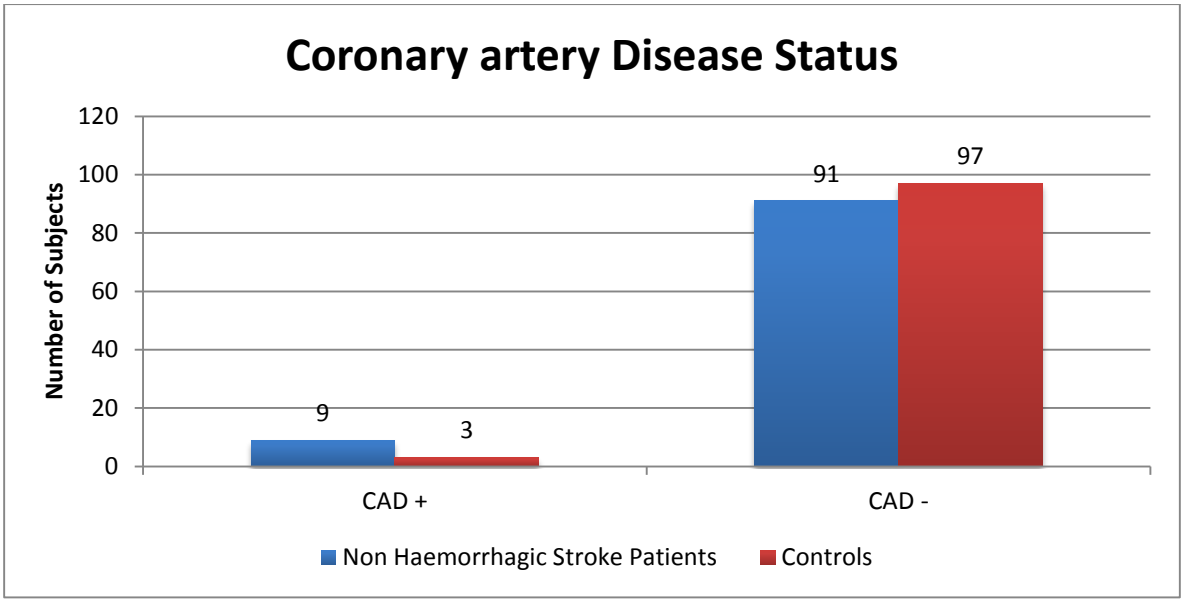
Discussion

The incidence of diabetes was meaningfully more in non haemorrhagic stroke patients group compared to control group by 10 percentage points. This significant difference of 2.00 times increase in incidence of diabetes in non haemorrhagic stroke patients group compared to control group is true and has not occurred by chance.

Inference

In this study we can safely conclude that diabetes is significantly associated with increased occurrence of non haemorrhagic stroke among our study patients.

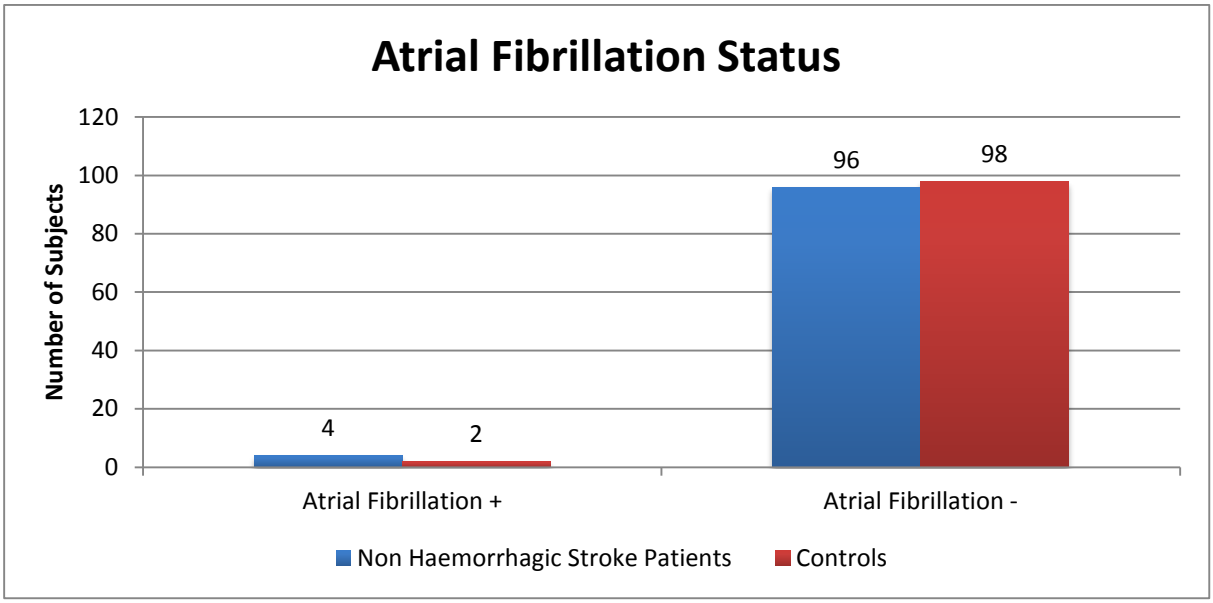
CAD



Coronary artery Disease Status	Non Haemorrhagic Stroke Patients	%	Controls	%
CAD +	9	9.00	3	3.00
CAD -	91	91.00	97	97.00
Total	100	100	100	100
P value Fishers Exact Test			0.0740	

Majority of the non haemorrhagic stroke patients group patients belonged to the CAD -ve class interval (n=91, 91%). In the control group patients, majority belonged to the same class interval (n=97, 97%). The association between the study groups and coronary artery disease status is considered to be not statistically significant since $p > 0.05$ as per fishers exact test.

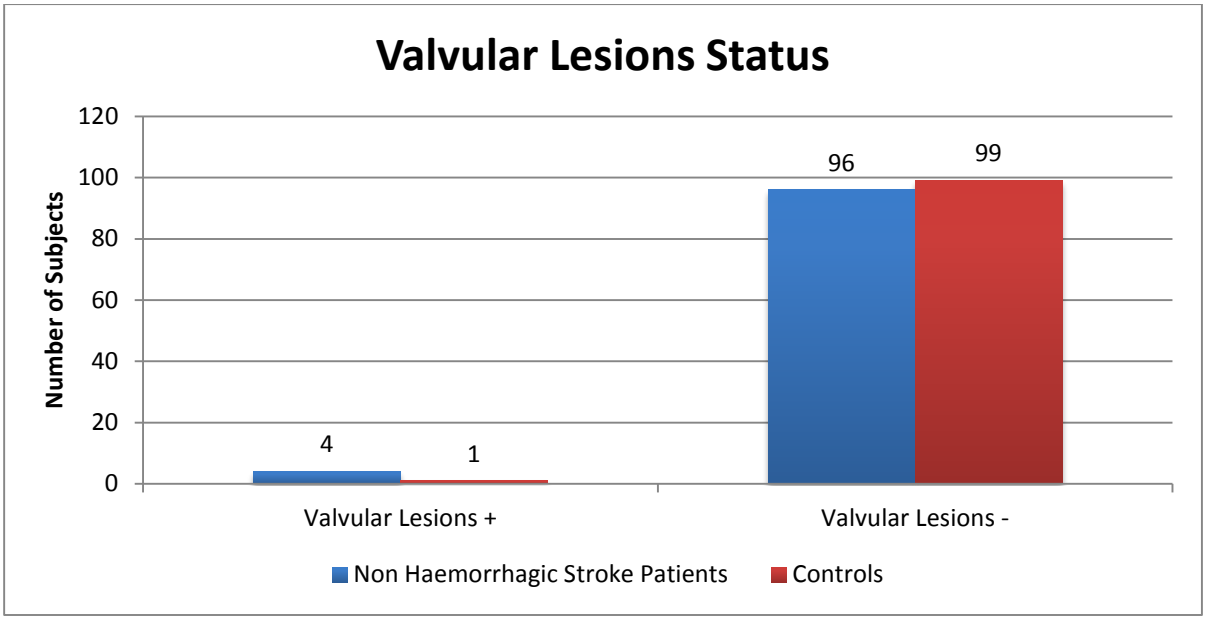
AF



Atrial Fibrillation Status	Non Haemorrhagic Stroke Patients	%	Controls	%
Atrial Fibrillation +	4	4.00	2	2.00
Atrial Fibrillation -	96	96.00	98	98.00
Total	100	100	100	100
P value Fishers Exact Test			0.4071	

Majority of the non haemorrhagic stroke patients group patients belonged to the atrial fibrillation -ve class interval (n=96, 96%). In the control group patients, majority belonged to the same class interval (n=98, 98%). The association between the study groups and atrial fibrillation status is considered to be not statistically significant since $p > 0.05$ as per fishers exact test.

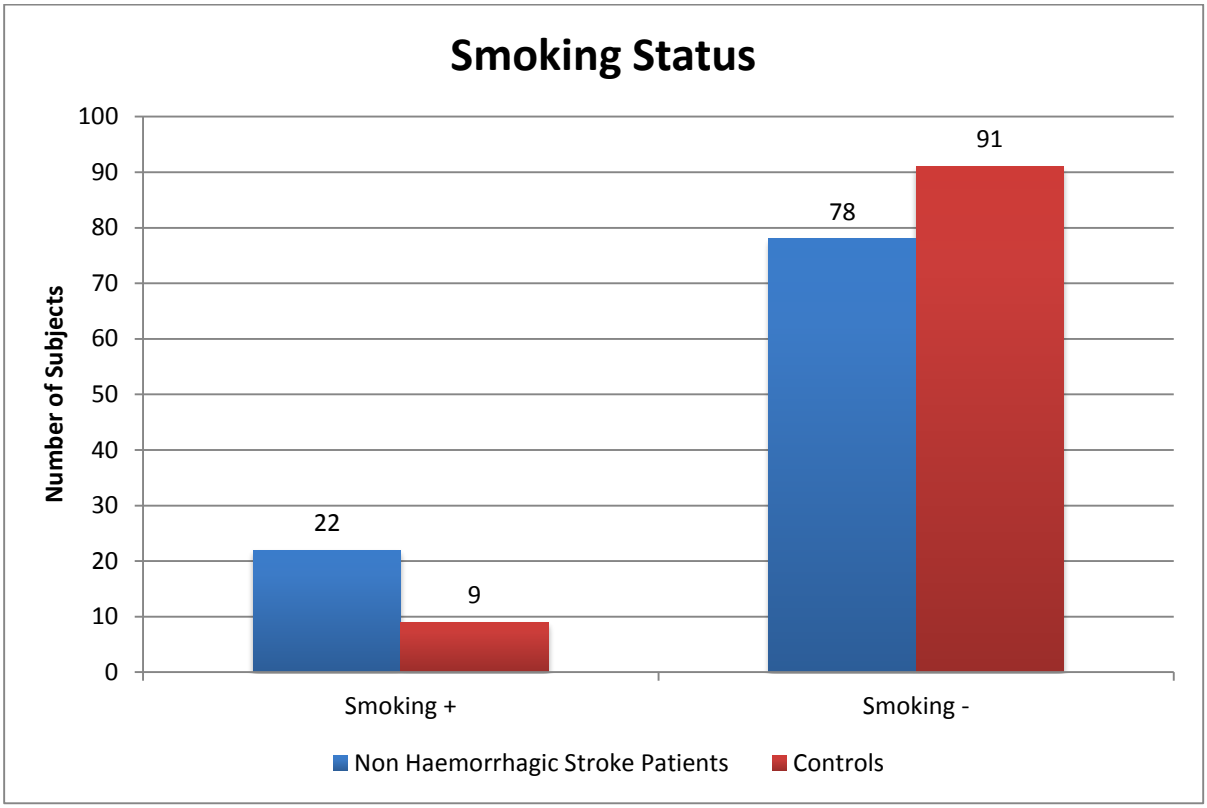
Valvular Lesions



Valvular Lesions Status	Non Haemorrhagic Stroke Patients	%	Controls	%
Valvular Lesions +	4	4.00	1	1.00
Valvular Lesions -	96	96.00	99	99.00
Total	100	100	100	100
P value Fishers Exact Test			0.1742	

Majority of the non haemorrhagic stroke patients group patients belonged to the valvular lesions -ve class interval (n=96, 96%). In the control group patients, majority belonged to the same class interval (n=99, 99%). The association between the study groups and valvular lesions status is considered to be not statistically significant since $p > 0.05$ as per fishers exact test.

Smoking



Smoking Status	Non Haemorrhagic Stroke Patients	%	Controls	%
Smoking +	22	22.00	9	9.00
Smoking -	78	78.00	91	91.00
Total	100	100	100	100
P value Chi Squared Test			0.0111	

Results

There is a true difference among study groups study groups in relation to smokingstatus and this difference is considered to be statistically significant since $p < 0.05$ as per chi squared test. The incidence of smokers among non haemorrhagic stroke patients was 22% (n=22). In the control group patients, the incidence of smokers was 9% (n=9). This abnormality in smoking incidence among the study groups is expressed with a p-value of 0.0111.

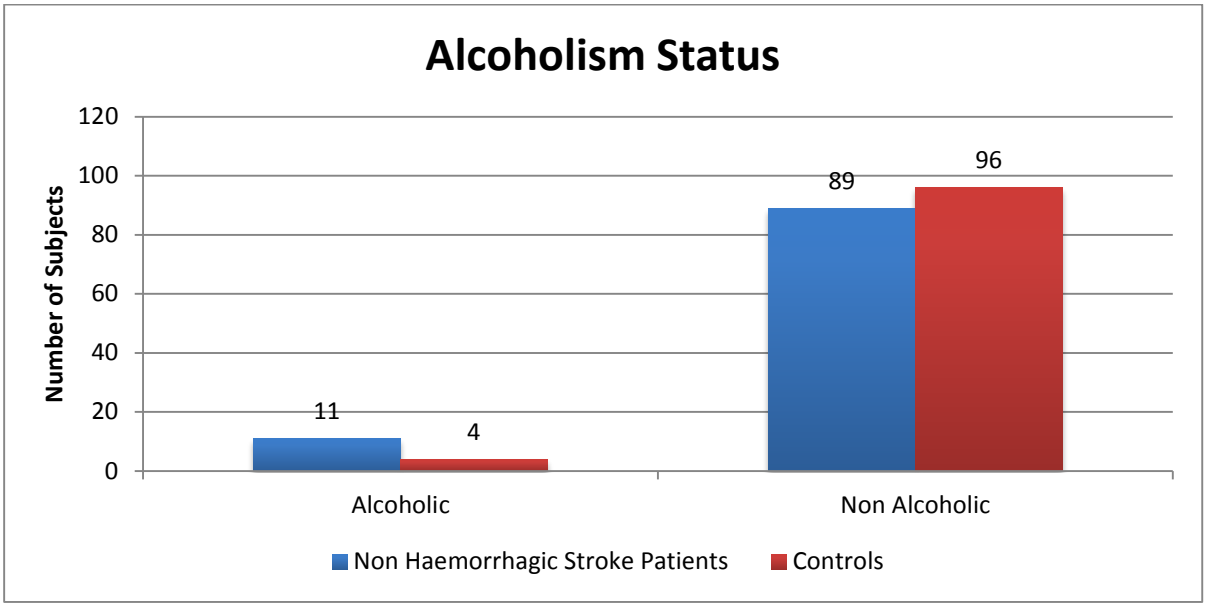
Discussion

The incidence of smoking was meaningfully more in non haemorrhagic stroke patients group compared to control group by 13 percentage points. This significant difference of 2.44 times increase in incidence of smoking in non haemorrhagic stroke patients group compared to control group is true and has not occurred by chance.

Inference

In this study we can safely conclude that smoking is significantly associated with increased occurrence of non haemorrhagic stroke among our study patients.

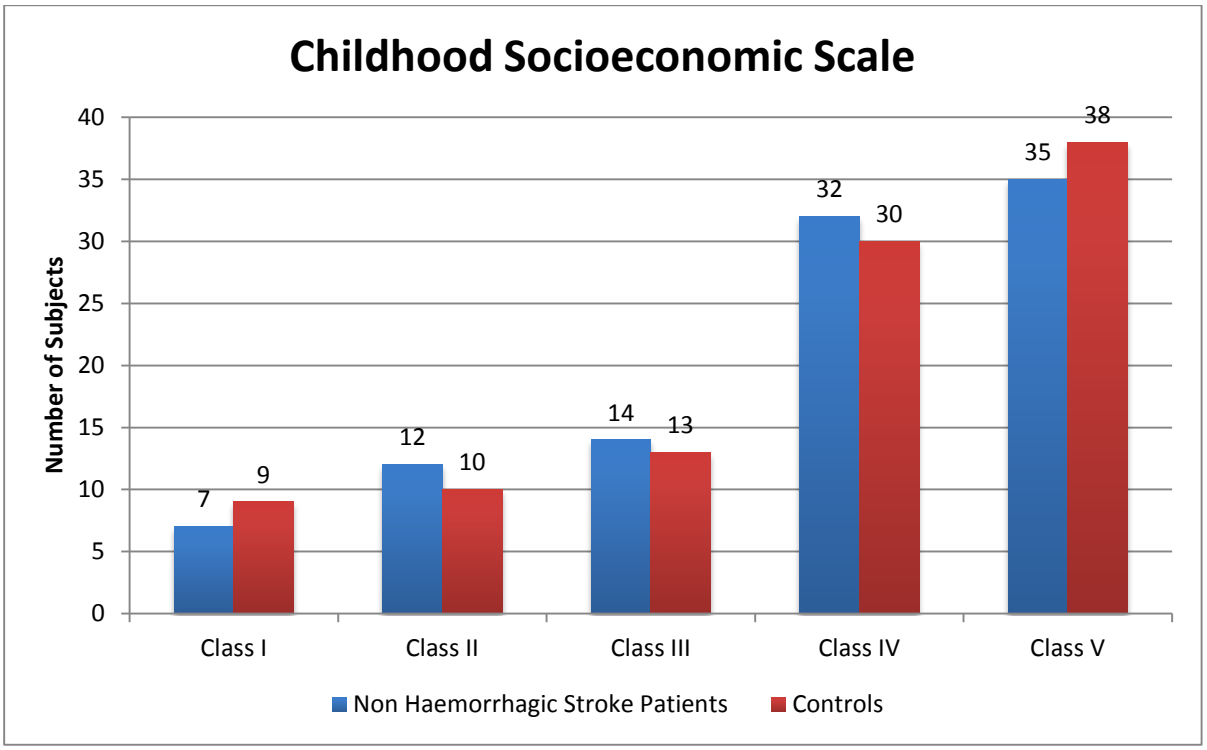
Alcohol



Alcoholism Status	Non Haemorrhagic Stroke Patients	%	Controls	%
Alcoholic	11	11.00	4	4.00
Non Alcoholic	89	89.00	96	96.00
Total	100	100	100	100
P value Fishers Exact Test			0.0602	

Majority of the non haemorrhagic stroke patients group patients belonged to the non alcoholic class interval (n=89, 89%). In the control group patients, majority belonged to the same class interval (n=96, 96%). The association between the study groups and alcohol intake status is considered to be not statistically significant since $p > 0.05$ as per fishers exact test.

Childhood Socioeconomic Scale

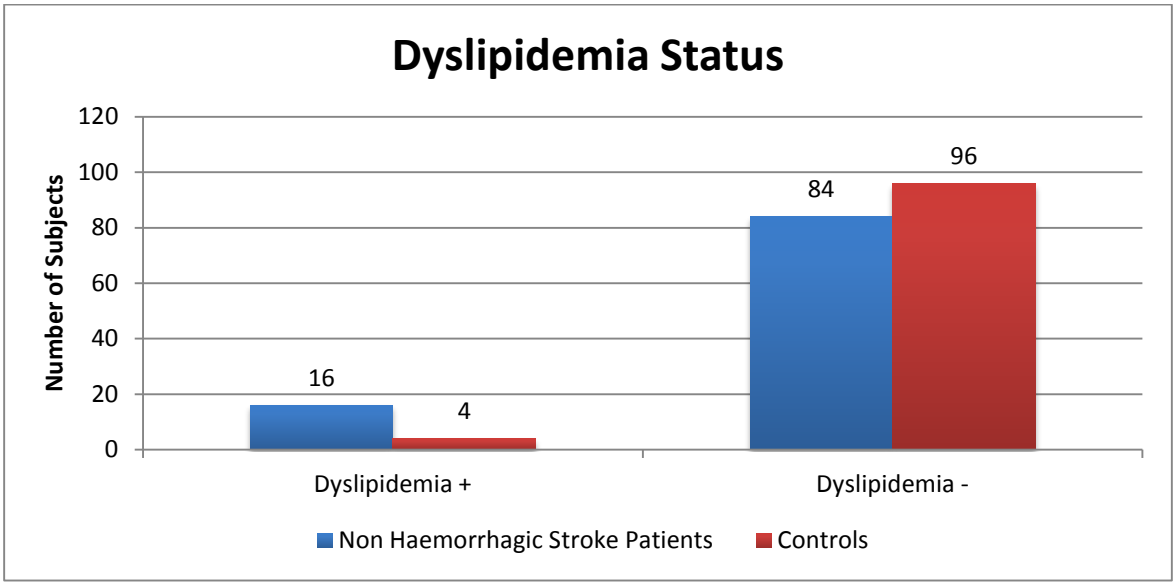


Childhood Socioeconomic Scale	Non Haemorrhagic Stroke Patients	%	Controls	%
Class I	7	7.00	9	9.00
Class II	12	12.00	10	10.00
Class III	14	14.00	13	13.00
Class IV	32	32.00	30	30.00
Class V	35	35.00	38	38.00
Total	100	100	100	100
P value Chi Squared Test			0.9999	

Results:

- Majority of the non haemorrhagic stroke patients group patients belonged to class V socioeconomic status (n=35, 35%).
- In the control group patients, majority belonged to the same class interval (n=38, 38%).
- The association between the study groups and socioeconomic status is considered to be not statistically significant since $p > 0.05$ as per chi squared test.

Dyslipidemia



Dyslipidemia Status	Non Haemorrhagic Stroke Patients	%	Controls	%
Dyslipidemia +	16	16.00	4	4.00
Dyslipidemia -	84	84.00	96	96.00
Total	100	100	100	100
P value Fishers Exact Test			0.0047	

Results

There is a true difference among study groups study groups in relation to dyslipidemia status and this difference is considered to be statistically significant since $p < 0.05$ as per fishers exact test. The incidence of dyslipidemia among non haemorrhagic stroke patients was 16% (n=16). In the control group patients, the incidence of dyslipidemia was 4% (n=4). This abnormality in smoking incidence among the study groups is expressed with a p-value of 0.0047.

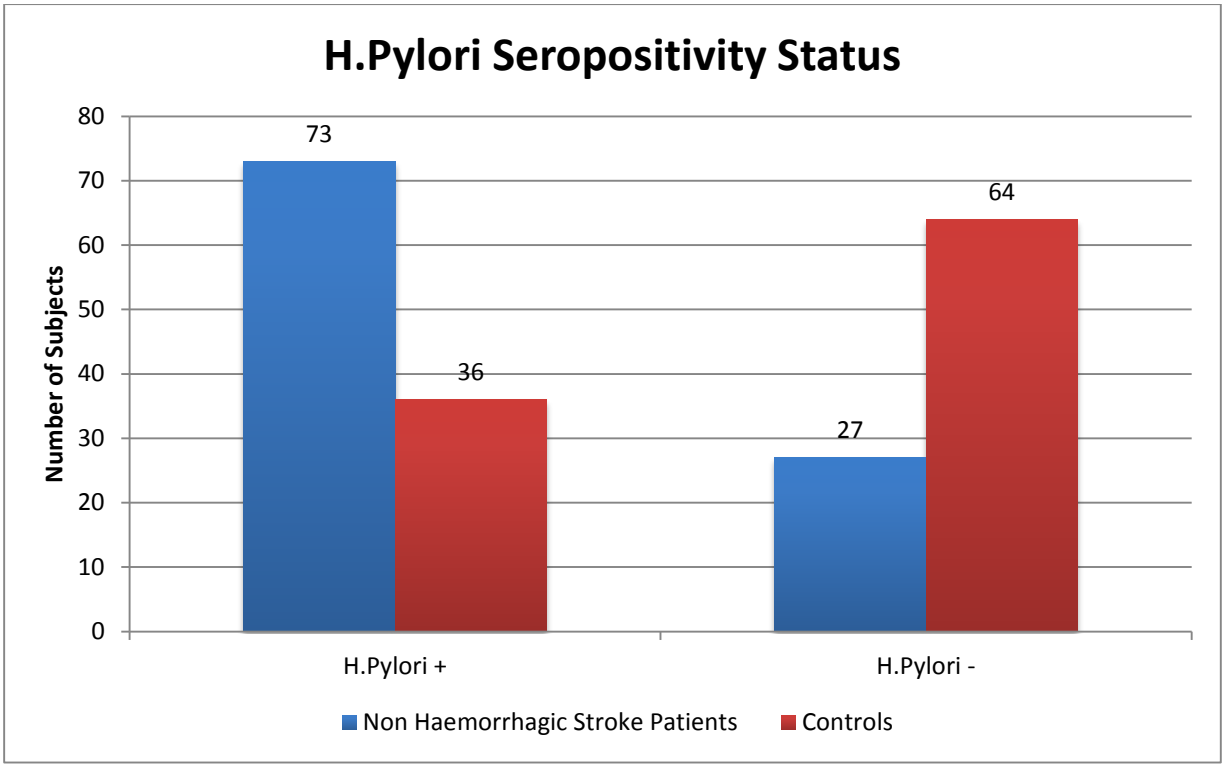
Discussion

The incidence of dyslipidemia was meaningfully more in non haemorrhagic stroke patients group compared to control group by 12 percentage points. This significant difference of 4.00 times increase in incidence of dyslipidemia in non haemorrhagic stroke patients group compared to control group is true and has not occurred by chance.

Inference

In this study we can safely conclude that dyslipidemia is significantly associated with increased occurrence of non haemorrhagic stroke among our study patients.

H Pylori



H.Pylori Seropositivity Status	Non Haemorrhagic Stroke Patients	%	Controls	%
H.Pylori +	73	73.00	36	36.00
H.Pylori -	27	27.00	64	64.00
Total	100	100	100	100
P value Chi Squared Test			0.0001	

Results

There is a true difference among study groups study groups in relation to H.Pylori seropositivity status and this difference is considered to be statistically significant since p < 0.05 as per chi squared test. The incidence of H.Pylori seropositivity among non haemorrhagic stroke patients was 73% (n=73). In the control group patients, the incidence of H.Pylori seropositivity was 36% (n=4). This abnormality in H.Pylori seropositivity incidence among the study groups is expressed with a p-value of 0.0001.

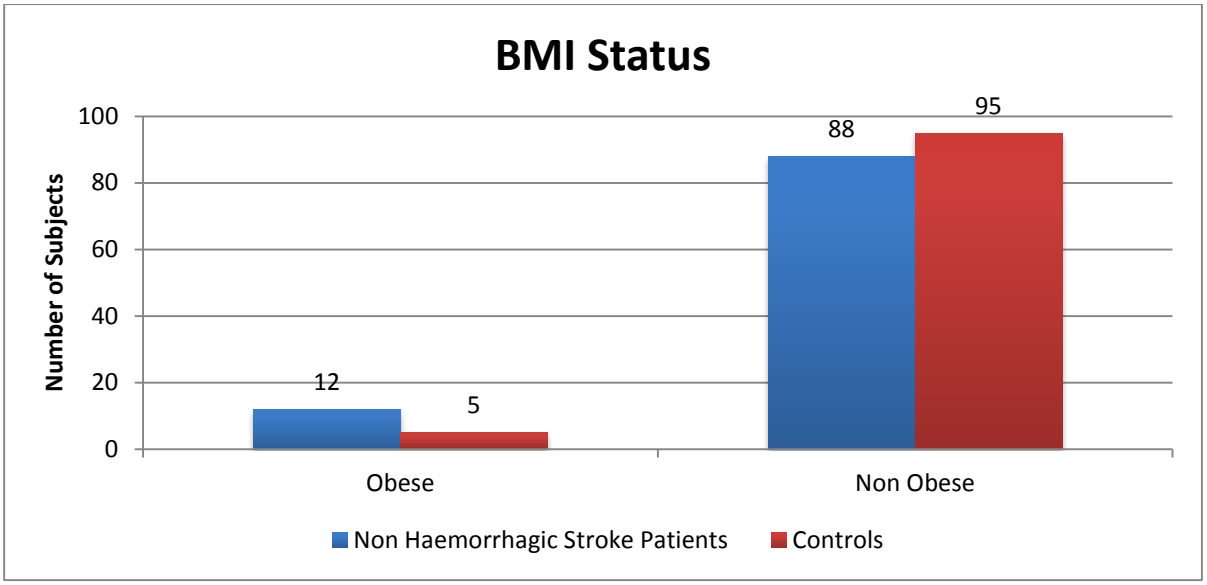
Discussion

The incidence of H.Pylori seropositivity was meaningfully more in non haemorrhagic stroke patients group compared to control group by 37 percentage points. This significant difference of 2.03 times increase in incidence of H.Pylori seropositivity in non haemorrhagic stroke patients group compared to control group is true and has not occurred by chance.

Inference

In this study we can safely conclude that H.Pylori seropositivity is significantly associated with increased occurrence of non haemorrhagic stroke among our study patients.

BMI



BMI Status	Non Haemorrhagic Stroke Patients	%	Controls	%
Obese	12	12.00	5	5.00
Non Obese	88	88.00	95	95.00
Total	100	100	100	100
P value Fishers Exact Test			0.0759	

Majority of the non haemorrhagic stroke patients group patients belonged to non obese BMI status (n=88, 88%). In the control group patients, majority belonged to the same class interval (n=95, 95%). The association between the study groups and BMI status is considered to be not statistically significant since $p > 0.05$ as per chi squared test.

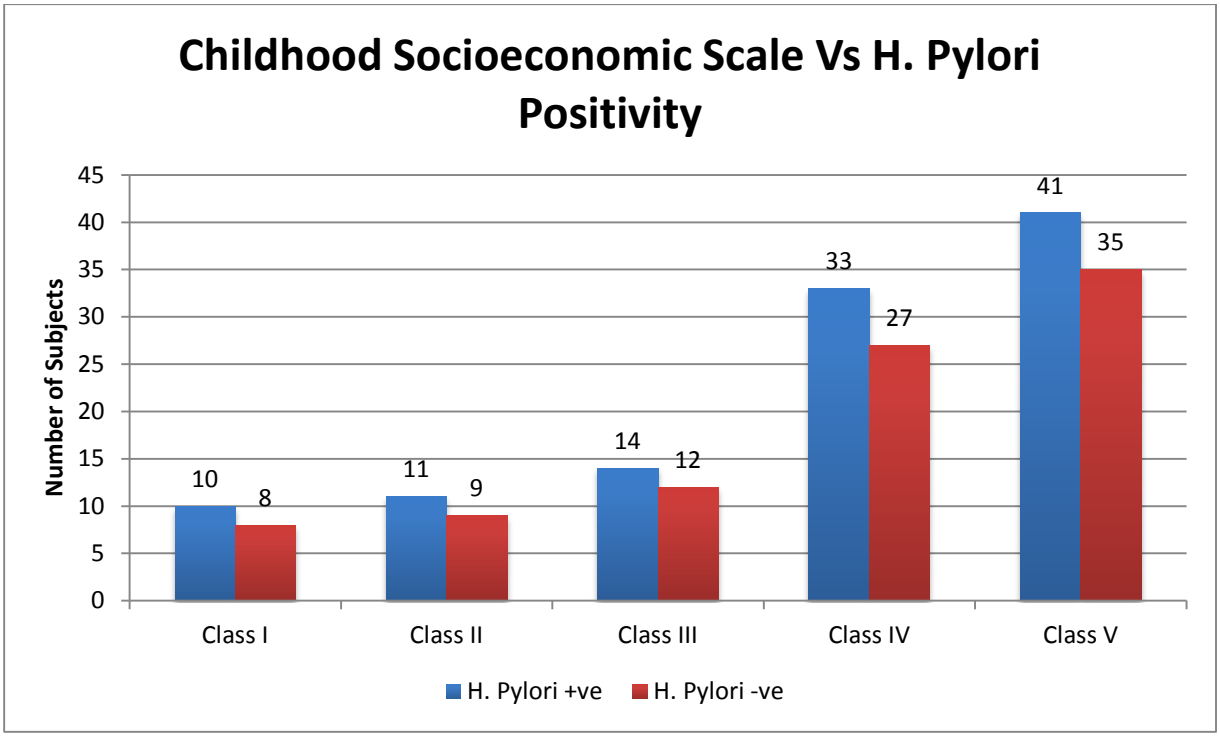
Multivariate logistic regression model for statistically Significant Predictor of Non Haemorrhagic Stroke adverse event

Independent Variables	Non Haemorrhagic Stroke		
	Odds Ratio	**95% Confidence Interval**	**P value**
Hypertensive	3.62	1.99-6.58	0.0001*
Diabetic	1.18	0.59-2.38	0.6342
Presence of CAD	3.20	0.84-12.18	0.0885
Presence of Atrial Fibrillation	2.04	0.37-11.41	0.4162
Presence of Valvular Lesions	4.13	0.45-37.57	0.2087
Smoker	2.85	1.24-6.56	0.0136*
Alcoholic	2.97	0.91-9.66	0.0710
Dyslipedemic	4.57	1.47-14.21	0.0086*
H.Pylori Seropositive	4.81	2.63-8.77	0.0001*
Obese	2.59	0.88-7.65	0.0849

Multivariate logistic regression model for statistically Significant Predictor of Non Haemorrhagic Stroke adverse event

- The risk of non heamorrhagic stroke in patients with hypertension is 3.62 times significantly more than patients without hypertension .It is statistically significant with a p-value of 0.0001
- The risk of non heamorrhagic stroke in patients who smoke is 2.85 times significantly more than patients who don't smoke .It is statistically significant with a p-value of 0.0136
- The risk of non heamorrhagic stroke in patients with dyslipedaemia is 4.57 times significantly more than patients without dyslipedaemia .It is statistically significant with a p-value of 0.0086
- The risk of non heamorrhagic stroke in patients with H.Pylori seropositivity is 4.81 times significantly more than patients with H.Pylori seronegativity .It is statistically significant with a p-value of 0.0001

Childhood Socioeconomic Scale Vs H. Pylori Positivity

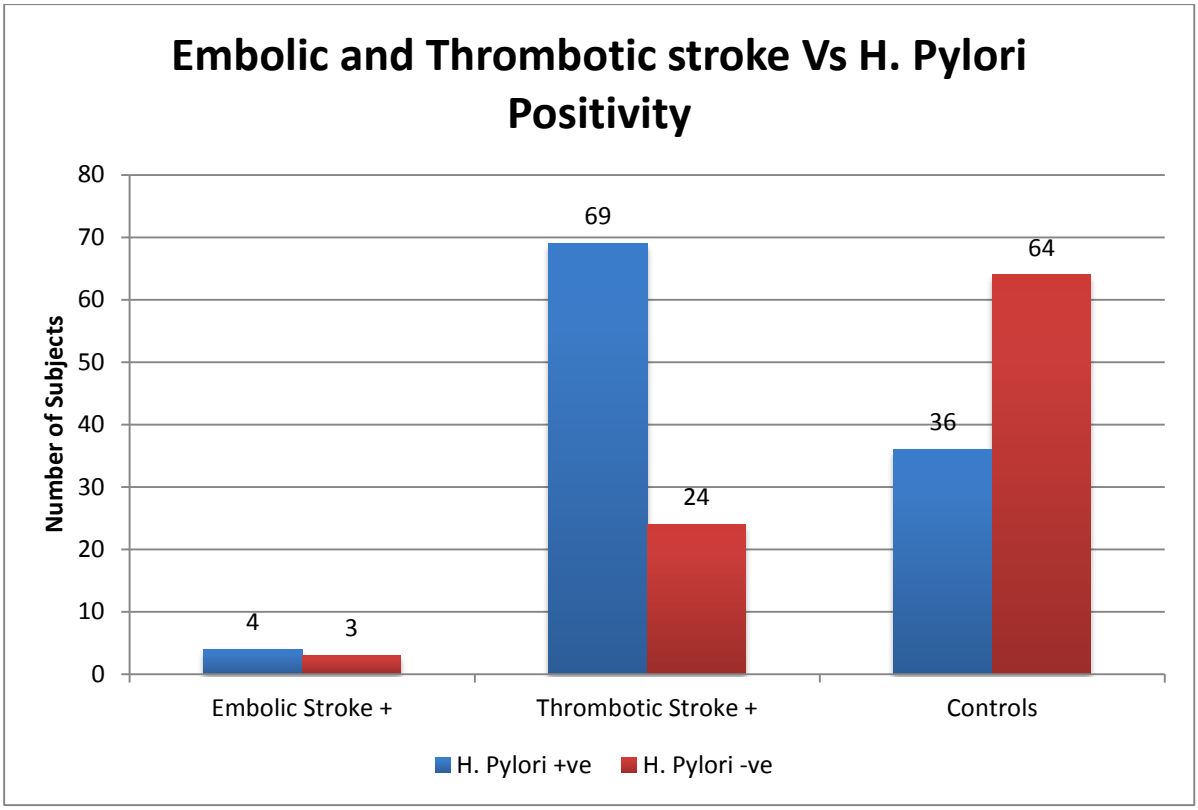


Childhood Socioeconomic Scale Vs H. Pylori Positivity	H. Pylori +ve	%	H. Pylori -ve	%
Class I	10	9.17	8	8.79
Class II	11	10.09	9	9.89
Class III	14	12.84	12	13.19
Class IV	33	30.28	27	29.67
Class V	41	37.61	35	38.46
Total	109	100	91	100
P value Chi Squared Test			0.4431	

Result:

Majority of the H. Pylori positive patients belonged to class V socioeconomic status (n=41, 37.61%). In the control group patients, majority belonged to the same class interval (n=35, 38.46%). The association between H. Pylori positivity and socioeconomic status is considered to be not statistically significant since $p > 0.05$ as per chi squared test.

Embolic and Thrombotic stroke Vs H. Pylori Positivity



Embolic and Thrombotic stroke Vs H. Pylori Positivity	H. Pylori +ve	%	H. Pylori -ve	%	P value Fishers Exact Test
Embolic Stroke +	4	3.67	3	3.30	0.3122
Thrombotic Stroke +	69	63.30	24	26.37	0.0001
Controls	36	33.03	64	70.33	NA
Total	109	100	91	100	

Results

There is a true difference among H pylori positivity groups in relation to Thrombotic stroke status and this difference is considered to be statistically significant since $p < 0.05$ as per fishers exact test. The incidence of Thrombotic stroke among H pylori positive patients was 69.30% (n=69). In the H pylori negative patients, the incidence of Thrombotic stroke was 26.37% (n=24). This abnormality in embolic stroke smoking incidence among the H pylori positivity groups is expressed with a p-value of 0.0001.

Discussion

The incidence of Thrombotic stroke was meaningfully more in H pylori positive patients group compared to H pylori negative group by 36.93 percentage points. This significant difference of 2.40 rimes increase in incidence of Thrombotic stroke among H pylori negative group is true and has not occurred by chance.

Inference

In this study we can safely conclude that H pylori positivity is significantly associated with increased occurrence of Thrombotic stroke among our study patients.

Conclusion:

- The risk of non haemorrhagic stroke in patients with H.Pylori seropositivity is 4.81 times significantly more than patients with H.Pylori seronegativity. H.Pylori seropositivity is significantly associated with increased occurrence of non haemorrhagic stroke among our study patients.
    - Among the non heamorrhagic stroke ,thrombotic stroke has significant association with H.pylori seropositivity.Embolic stroke doesn't have significant association with H.pylori seropositivity,though only7 cases had embolic stroke .
- Though majority of the H.Pylori positive patients belonged to class V socioeconomic status the association between H. Pylori positivity and socioeconomic status is not statistically significant .
- The risk of non heamorrhagic stroke in patients with hypertension is 3.62 times significantly more than patients without hypertension .
- The risk of non heamorrhagic stroke in patients who smoke is 2.85 times significantly more than patients who don't smoke .
- The risk of non heamorrhagic stroke in patients with dyslipidemia is 4.57 times significantly more than patients without dyslipedaemia .
- This is a small scale case control study;need large scale multicentric study to further consolidate this facts.

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PROFORMA

NAME: **AGE:** **SEX:** 1.M 2.F

LOCALITY: **CONTACT NO:**

NUMBER OF FAMILY MEMBERS:

OCCUPATION : 1. PROFESSIONAL

2. SEMI PROFESSIONAL

3. CLERICAL/SHOP OWNER/ FARMER

4. SKILLED WORKER

5. SEMI SKILLED WORKER

6. UNSKILLED WORKER

7. UNEMPLOYED

INCOME :

EDUCATIONAL STATUS:

KUPPUSWAMY's SOCIO-ECONOMIC STATUS SCALE-

NUMBER OF FAMILY MEMBERS AT 8th YEARS OF AGE-

COMPLAINTS :

PREVIOUS H/o CVA : 1. Yes 2. No

H/O CARDIAC DISEASE : 1. Yes 2. No; if yes specify _____

H/O RELATED TO PERIPHERAL VASCULAR DISEASE: 1. Yes 2. No

PREVIOUS H/o LAPAROTOMY : 1. Yes 2. No; if yes specify _____

IMMUNOCOMPROMISED : 1. Yes 2. No

H/O PREVIOUS H.pylori ERADICATION TREATMENT: _____

ANY H/O DRUG INTAKE FOR GASTRITIS: 1. Yes 2. No; if yes specify _____

H/O ANY OTHER CHRONIC DRUG INTAKE? : 1. Yes 2. No; If yes specify

SMOKING : 1. Yes 2. No

ALCOHOL INTAKE: 1. Yes 2. No

HYPERTENSION : 1. Yes 2. No

DIABETES : 1. Yes 2. No

RELEVENT CLINICAL EXAMINATION

HEIGHT : **WEIGHT:** **BMI:**

WAIST CIRCUMFERENCE:

BP: **PR:** **RR:**

CVS: **RS:** **PA:**

CNS:

INVESTIGATIONS

LIPID PROFILE :

Ig G H.pylori ELISA report:

Ig G H.pylori Ab with Card test: **1. Yes 2. No**

ECG FINDINGS:

ECHO FINDINGS:

RADIOLOGICAL REPORT:

COMMENT:

INFORMED CONSENT

A STUDY OF ASSOCIATION OF HELICOBACTER PYLORI INFECTION IN NON HAEMORRHAGIC STROKE PATIENTS

Place of study: Govt. Stanley medical college, Chennai

I ……. have been informed about the details of the study in my own language.

I have completely understood the details of the study.

I am aware of the possible risks and benefits, while taking part in the study.

I agree to collect samples of blood/saliva/urine/tissue if study needs.

I understand that I can withdraw from the study at any point of time and even then, I can receive the medical treatment as usual.

I understand that I will not get any money for taking part in the study.

I will not object if the results of this study are getting published in any medical journal, provided my personal identity is not revealed.

I know what I am supposed to do by taking part in this study and I assure that I would extend my full cooperation for this study.

Volunteer:	Witness:
Name and address	Name and address
Signature/thumb impression:	Signature/thumb impression
Date:	Date:

Investigator Signature and date

INFORMED CONSENT

A STUDY OF HELICOBACTER PYLORI INFECTION PREVALENCE IN NON HAEMORRHAGIC STROKE PATIENTS

AT GOVERNMENT STANLEY HOSPITAL, CHENNAI.

நான் இந்த ஆராய்ச்சியில் விவரங்களை முற்றிலும் புரிந்து கொண்டேன்.

ஆய்வில் பங்கு எடுத்து போது, சாத்தியமான அபாயங்கள் மற்றும் பயன்களை பற்றி நான் அறிந்துள்ளேன்.

நான் எந்தவொரு வேளையிலும் ஆய்வில் இருந்து திரும்ப முடியும், அதன் பின்னர், நான் வழக்கம் போல் மருத்துவ சிகிச்சை பெற முடியும் என்று புரிந்துகொள்கிறேன்

நான் ஆய்வில் பங்கு எடுத்து பணம் எதையும் பெற முடியாது என்று அறிந்துள்ளேன்.

இந்த ஆய்வின் முடிவுகள் எந்த மெடிக்கல் ஜர்னலில் வெளியிடப்பட இருந்தால் நான் எதிர்க்கவில்லை, என் தனிப்பட்ட அடையாளத்தை வெளிப்படுத்தப்பட்டு இருக்க கூடாது.

நான் இந்த ஆய்வில் பங்கெடுப்பதன் மூலம் நான் என்ன செய்ய போகிறேன் என்று தெரியும்

நான் இந்த ஆய்வில் என் முழு ஒத்துழைப்பையும் கொடுப்பேன் என்று உறுதியளிக்கிறேன்.

தன்னார்வளர்	சாட்சி
பெயர் மற்றும் முகவரி	பெயர் மற்றும் முகவரி
கையொப்பம் / விரல் ரேகை:	கையொப்பம் / விரல் ரேகை:

ஆராய்ச்சியாளராக

கையொப்பம் மற்றும் தேதி

INSTITUTIONAL ETHICAL COMMITTEE, STANLEY MEDICAL COLLEGE, CHENNAI-1

Title of the Work : Association of Helicobacter pylori infection in non Hemorrhagic stroke patients..

Principal Investigator : Dr. Deenadayalan. T

Designation : PG in MD (General Medicine)

Department : Department of General Medicine
Government Stanley Medical College,
Chennai-01

The request for an approval from the Institutional Ethical Committee (IEC) was considered on the IEC meeting held on 02.07.2014 at the Council Hall, Stanley Medical College, Chennai-1 at 2PM

The members of the Committee, the secretary and the Chairman are pleased to approve the proposed work mentioned above, submitted by the principal investigator.

The Principal investigator and their team are directed to adhere to the guidelines given below:

1. You should inform the IEC in case of changes in study procedure, site investigator investigation or guide or any other changes.
2. You should not deviate from the area of the work for which you applied for ethical clearance.
3. You should inform the IEC immediately, in case of any adverse events or serious adverse reaction.
4. You should abide to the rules and regulation of the institution(s).
5. You should complete the work within the specified period and if any extension of time is required, you should apply for permission again and do the work.
6. You should submit the summary of the work to the ethical committee on completion of the work.

K Vasanthi
MEMBER SECRETARY,
IEC, SMC, CHENNAI

CASE LIST																	
SEX	AGE	Htn	DM	CAD	Atrial fibrillation		Valvular Lesions		Smoking	Alcoholic	Childhood SES		Dyslipidemia		H.Pylori Seropositivity			BMI>25
M	73	1	2	2	2		2		1	1	I		2		2			2
F	58	1	2	2	2		2		2	2	III		2		1			2
M	60	2	2	2	2		2		1	2	IV		2		1			2
M	68	1	1	2	1		1		2	2	I		1		2			1
M	70	1	2	1	2		2		2	2	V		2		1			2
M	53	1	2	1	2		2		2	2	IV		2		1			2
F	58	1	2	2	2		2		2	2	II		2		1			2
M	66	1	1	2	2		2		2	2	V		1		1			1
M	60	1	1	2	2		2		2	2	IV		1		1			1
M	68	1	1	2	2		2		2	2	III		1		1			1
M	82	1	1	2	2		2		2	2	I		2		2			2
M	75	2	2	2	2		2		1	2	IV		1		1			1
M	66	1	2	2	1		1		2	2	IV		2		2			2
M	42	1	2	2	2		2		2	2	II		2		1			2
M	56	1	1	1	2		2		2	2	V		1		1			1
M	52	1	2	2	2		2		2	2	III		2		1			2
M	45	2	2	2	2		2		1	1	II		2		2			2
M	42	2	2	2	2		2		1	2	V		2		1			2
M	34	2	2	2	2		2		1	1	IV		2		2			2
M	70	1	1	2	2		2		2	2	V		1		1			1
M	40	1	2	2	2		2		2	2	V		2		1			2
M	70	1	2	2	2		2		2	2	IV		2		1			2
M	68	2	2	2	2		2		1	2	V		2		1			2
M	37	2	2	2	2		2		1	2	III		2		1			2
M	50	2	1	2	2		2		2	2	V		2		1			2
M	62	1	1	2	2		2		2	2	IV		1		1			1
M	45	1	2	2	2		2		2	2	I		2		1			2
M	54	2	1	2	2		2		2	2	V		1		1			1
M	55	2	2	2	2		2		1	1	IV		2		1			2
M	50	1	2	2	2		2		2	2	V		2		1			2
M	60	1	2	2	2		2		2	2	III		2		1			2

M	60	1	2	2	2		2		2	2	V		2		1			2
M	45	1	2	2	2		2		2	2	IV		2		1			2
M	58	2	2	2	2		2		1	2	II		2		2			2
F	77	1	2	2	2		2		2	2	V		2		1			2
CASE LIST																		
M	60	1	2	2	2		2		2	2	IV		2		1			2
M	60	1	2	2	2		2		2	2	I		2		2			2
M	61	2	2	2	2		2		1	1	V		2		1			2
M	60	2	2	2	2		2		2	2	IV		2		1			2
M	56	2	2	2	2		2		2	2	III		2		1			2
M	80	2	2	2	2		2		1	1	V		2		1			2
M	48	2	2	2	2		2		1	1	V		2		1			2
M	40	2	2	2	2		2		2	2	IV		2		2			2
F	31	2	1	2	2		2		2	2	V		1		1			1
M	40	2	2	2	2		2		1	2	V		2		1			2
M	85	1	2	2	2		2		2	2	I		2		2			2
F	70	1	1	2	2		2		2	2	IV		1		1			1
F	27	2	2	2	1		1		2	2	V		2		2			2
M	65	2	1	2	2		2		2	2	IV		2		1			2
F	2	2	2	2	2		2		2	2	III		2		2			2
F	81	2	2	2	1		1		2	2	V		2		1			2
M	74	2	2	2	2		2		1	2	IV		2		1			2
F	75	1	2	2	2		2		2	2	II		2		1			2
F	60	2	2	2	2		2		2	2	V		2		1			2
F	70	2	2	2	2		2		2	2	V		2		1			2
M	43	2	2	2	2		2		1	1	IV		2		2			2
F	40	1	2	2	2		2		2	2	V		2		1			2
F	60	1	2	1	2		2		2	2	IV		2		1			2
F	47	1	2	2	2		2		2	2	III		2		2			2
M	73	1	2	2	2		2		2	2	V		2		1			2
F	70	1	1	2	2		2		2	2	IV		1		2			2
M	85	1	2	2	2		2		2	2	V		2		1			2
F	27	2	2	2	2		2		2	2	IV		2		2			2

M	64	2	2	1	2		2		1	2	II		2		2		2
F	48	1	2	2	2		2		2	2	V		2		1		2
M	41	2	2	2	2		2		2	2	I		2		2		2
M	73	2	2	2	2		2		1	1	V		2		1		2
M	61	2	2	2	2		2		2	2	III		2		1		2
F	73	1	2	2	2		2		2	2	V		2		1		2
F	60	2	2	2	2		2		2	2	II		2		2		2
F	70	2	2	2	2		2		2	2	V		2		1		2
CASE LIST																	
F	77	1	2	2	2		2		2	2	IV		2		2		2
F	50	1	2	2	2		2		2	2	V		2		1		2
F	65	1	2	1	2		2		2	2	IV		2		2		2
F	57	1	2	2	2		2		2	2	III		2		1		2
M	65	1	2	2	2		2		2	2	V		2		1		2
M	47	1	2	2	2		2		2	2	IV		2		1		2
M	54	1	1	1	2		2		2	2	V		1		1		1
M	54	1	2	2	2		2		2	2	IV		2		1		2
F	50	2	2	2	2		2		2	2	III		2		2		2
M	44	2	2	2	2		2		2	2	V		2		1		2
M	37	2	2	2	2		2		2	2	IV		2		1		2
M	72	1	1	2	2		2		2	2	V		1		1		2
F	48	1	2	2	2		2		2	2	V		2		1		2
M	72	1	2	2	2		2		2	2	IV		2		1		2
M	66	2	2	2	2		2		1	1	II		2		2		2
M	39	2	2	2	2		2		1	2	V		2		1		2
F	76	1	2	2	2		2		2	2	IV		2		1		2
M	64	1	1	2	2		2		2	2	V		1		1		2
M	47	1	2	2	2		2		2	2	III		2		1		2
M	52	2	1	2	2		2		2	2	I		2		2		2
F	71	1	2	2	2		2		2	2	IV		2		1		2
M	43	2	2	2	2		2		1	2	II		2		2		2
F	60	2	2	2	2		2		2	2	V		2		1		2
M	60	2	1	2	2		2		2	2	III		2		2		2

F	42	1	2	2	2		2		2	2	IV		2		1			2
F	61	1	2	1	2		2		2	2	II		2		2			2
M	42	1	2	2	2		2		1	1	V		2		1			2
F	48	1	2	2	2		2		2	2	I		2		1			2
F	52	2	1	1	2		2		2	2	IV		1		1			2

CONTROL LIST																	
SEX	AGE	Htn	DM	CAD	Atrial fibrillation		Valvular Lesions		Smoking	Alcoholic	Childhood SES		Dyslipidemia		H.Pylori Seropositivity			BMI>25
M	70	1	2	2	2		2		1	2	V		2		1			2
M	40	2	2	2	1		1		2	2	IV		2		2			2
M	70	2	2	2	2		2		2	2	II		2		2			2
M	68	1	1	2	2		2		2	2	V		1		1			1
M	37	2	2	2	2		2		2	2	IV		2		2			2
M	50	2	2	2	2		2		2	2	I		2		2			2
M	62	2	2	2	2		2		2	2	V		2		1			2
M	45	2	2	2	2		2		2	2	IV		2		2			2
M	54	1	2	2	2		2		2	2	III		1		2			1
M	55	2	1	2	2		2		2	2	V		2		1			2
M	50	1	2	2	2		2		2	2	V		2		1			2
M	60	2	2	2	2		2		2	2	IV		2		1			1
M	60	2	2	2	2		2		2	2	V		2		1			2
M	45	1	2	2	2		2		2	2	V		2		2			2
M	58	2	1	1	2		2		1	2	I		2		2			2
F	77	2	2	2	2		2		2	2	IV		2		2			2
M	60	2	2	2	2		2		2	2	V		2		1			2
M	60	2	2	2	2		2		1	1	IV		2		2			2
M	61	2	2	2	2		2		2	2	III		2		2			2
M	60	1	1	2	2		2		2	2	V		2		2			2
M	73	2	2	2	2		2		2	2	IV		2		1			2
F	58	2	2	2	2		2		2	2	II		2		2			2
M	60	2	2	2	2		2		2	2	V		2		2			2
M	68	1	1	2	2		2		2	2	V		1		1			1
M	70	1	2	2	2		2		2	2	IV		2		2			2
M	53	2	2	2	2		2		2	2	V		2		1			2
F	58	2	2	2	2		2		2	2	IV		2		2			2
M	66	2	2	2	2		2		2	2	III		2		2			2
M	60	2	2	2	2		2		2	2	V		2		2			2
M	68	1	1	2	2		2		2	2	IV		2		2			2
M	82	1	2	2	2		2		2	2	V		2		2			2

M	75	2	1	2	2		2		2	2	IV		2		2			2
M	66	1	2	2	2		2		2	2	II		2		1			2
M	42	2	2	2	2		2		2	2	V		2		2			2
M	56	2	2	2	2		2		2	2	I		2		2			2
M	52	2	2	2	2		2		2	2	V		2		2			2
M	45	2	2	2	2		2		2	2	III		2		2			2
CONTROL LIST																		
M	42	2	2	2	2		2		2	2	V		2		1			2
M	34	2	2	2	2		2		2	2	II		2		2			2
F	50	2	2	2	2		2		2	2	V		2		2			2
M	44	2	1	2	2		2		2	2	IV		2		2			2
M	37	2	2	2	2		2		2	2	V		2		1			2
M	72	1	2	2	2		2		2	2	IV		2		2			2
F	48	2	2	2	2		2		2	2	III		2		2			2
M	72	2	2	2	2		2		2	2	V		2		1			2
M	66	2	2	1	2		2		2	2	IV		2		2			2
M	39	2	2	2	2		2		2	2	V		2		1			2
F	76	2	2	2	2		2		2	2	IV		2		2			2
M	64	2	2	2	2		2		2	2	III		2		2			2
M	47	2	2	2	2		2		2	2	V		2		2			2
M	52	2	2	2	2		2		2	2	IV		2		1			2
F	71	2	2	2	2		2		2	2	V		2		1			2
M	43	2	2	2	2		2		1	2	V		2		1			2
F	60	1	2	2	2		2		2	2	IV		2		2			2
M	60	1	2	2	1		2		2	2	II		2		2			2
F	42	2	2	2	2		2		2	2	V		2		1			2
F	61	1	2	2	2		2		2	2	IV		2		2			2
M	42	2	2	2	2		2		1	2	V		2		1			2
F	48	2	2	2	2		2		2	2	III		2		2			2
F	52	2	2	1	2		2		2	2	I		2		2			2
F	47	2	2	2	2		2		2	2	IV		2		1			2
M	73	2	2	2	2		2		2	2	II		2		2			2
F	70	2	2	2	2		2		2	2	V		2		1			2

M	85	2	2	2	2		2		2	2	III		2		2			2
F	27	2	2	2	2		2		2	2	IV		2		2			2
M	64	2	2	2	2		2		2	2	II		2		2			2
F	48	2	2	2	2		2		2	2	V		2		1			2
M	41	2	2	2	2		2		2	1	I		2		2			2
M	73	1	2	2	2		2		1	2	IV		2		1			1
M	61	2	2	2	2		2		2	2	I		2		2			2
F	73	2	1	2	2		2		2	2	III		2		2			2
F	60	2	2	2	2		2		2	2	IV		2		1			2
F	70	2	2	2	2		2		2	2	I		2		2			2
F	77	2	2	2	2		2		2	2	V		2		1			2
F	50	1	2	2	2		2		2	2	IV		2		2			2
CONTROL LIST																		
F	65	2	2	2	2		2		2	2	II		2		2			2
F	57	2	2	2	2		2		2	2	V		2		1			2
M	65	2	2	2	2		2		2	2	IV		2		2			2
M	47	2	2	2	2		2		1	2	III		2		1			2
M	54	1	2	2	2		2		2	2	I		2		2			2
M	54	2	2	2	2		2		2	2	IV		2		2			2
M	56	2	2	2	2		2		2	2	IV		2		1			2
M	80	1	2	2	2		2		2	2	II		2		2			2
M	48	2	2	2	2		2		2	2	V		2		2			2
M	40	2	2	2	2		2		1	2	III		2		2			2
F	31	2	2	2	2		2		2	2	II		1		2			2
M	40	2	2	2	2		2		2	1	V		2		1			2
M	85	1	2	2	2		2		2	2	IV		2		2			2
F	70	2	1	2	2		2		2	2	V		2		2			2
F	27	2	2	2	2		2		2	2	V		2		1			2
M	65	1	2	2	2		2		1	1	IV		2		2			2
F	28	2	2	2	2		2		2	2	V		2		1			2
F	81	1	2	2	2		2		2	2	III		2		2			2
M	74	1	2	2	2		2		2	2	V		2		2			2
F	75	2	2	2	2		2		2	2	IV		2		1			2

F	60	1	2	2	2		2		2	2	I		2		2			2
F	70	1	2	2	2		2		2	2	V		2		1			2
M	43	1	2	2	2		2		2	2	IV		2		2			2
F	40	2	2	2	2		2		2	2	V		2		1			2
F	60	2	2	2	2		2		2	2	III		2		2			2
				1-Yes														
				2-No														
				Childhood SES-patient's Childhood Socio Economic Status according to Modified Kuppusamy scale														