CLINICAL EVALUATION OF NAGARJUNABHRA RASA IN HRIDSHULA (STABLE ANGINA PECTORIS) AS COMPARED TO ISOSORBIDE MONONITRATE

A Thesis

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By

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UNDER THE GUIDANCE OF

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DEPARTMENT OF AYURVEDA

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CERTIFICATE OF THE SUPERVISOR

It is certified that work entitled **'Clinical Evaluation of Nagarjunabhra Rasa in Hridshula (Stable Angina Pectoris) As Compared to Isosorbide Mononitrate'** is an original research work done by **Dr. Dalal Naresh** under my supervision for the degree of Doctor of Philosophy in Ayurveda awarded by the Tilak Maharashtra Vidyapeeth, Pune. To the best of my knowledge this thesis

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I, Dr. Dalal Naresh Mange Ram, am Ph. D. Scholar of the Tilak Maharashtra Vidyapeeth in Ayurveda (Rasa Shastra) subject; thesis entitled 'Clinical Evaluation of Nagarjunabhra Rasa in Hridshula (Stable Angina Pectoris) as Compared to Isosorbide Mononitrate' under the supervision of Dr. V. A. Dole. I do solemnly affirm that the thesis submitted by me is my own work. I have not copied it from any source. I have gone through extensive review of literature of the published/unpublished research work and the use of such references made has been acknowledged in my thesis. The title and the content of research are original. I understand that, in case any complaint especially plagiarism, regarding my Ph.D. research from any party, I have to go through the inquiry procedure as decided by the Vidyapeeth at any point of time. I understand that, if my Ph.D. thesis (or part of it) is found duplicate at any point of time, my research degree will be withdrawn and in such circumstances, I will be solely responsible and liable for any consequences arises thereby. I will not hold the TMV, Pune responsible and liable in any case.

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INTRODUCTION

Ayurveda, the traditional ancient Indian science of life and health has described that its objective vests in the principle of preservation and promotion of health and treatment ofdiseases.[1] For that it prescribed not only herbs, plants, animal-products and minerals and metals based drugs but equally laid stress on dietary regimen, daily routine, hygiene and rejuvenation (*Rasayana*) therapies for longevity, cure and prevention of diseases. *Rasashastra*, the branch of Ayurveda deals with pharmacological characteristics of drug substances obtained from plants, metals and mineral, animals and marine materials with their processing, pharmaceutical manufacturing, uses and application in various disease conditions sometimes irrespective of *dosha* and *dushya* i.e. affected body materials and organs, patient's phenotype temperament, season, weather and drug administration time concepts etc.[2] It has offered many valuable herbo-mineral formulations for almost all kind of diseases. *Nagarjunabhra Ras*, an important formulation described under *hridroga prakarnam*, is indicated for treatment of heart diseases, all kind of pain, hyperacidity, piles, cachexia, injuries and chest diseases, bleeding disorders etc. so many diseases. It is also said as an adaptogenic and aphrodisiac drug.[3] Ayurvedic physicians usually prescribe this medicine for the treatment of *hridrogas* particularly *hridshula* which is akin to stable angina pectoris of contemporary modern medicine. *Nagarjunabhra Ras* is described in every classical *Rasashastra* compendium with its composition, method of preparation, properties, indications and dosage standards.

Nagarjunabhra Ras is composed of 1000 *puti abhraka bhasma* and decoction (Kwath) of bark of Terminalia Arjuna tree, classically.[4] These days in novel ayurvedic formularies it is described as made of 100 *puti abhraka bhasma* with seven *bhavana* of *Arjuna* bark's decoction.[5] In the market it is available in the same composition made by many registered ayurvedic pharmacies, in quantity of 250-300 mg tablet form.[6] Sometimes ayurvedic

physicians themselves make it in their settings in the same way. It is prescribed as1 tablet twice daily few hours before or after meals with different vehicles *(anupaan)* such as plain potable water or Arjuna bark's decoction, *arjunaksheerpak, arjunarishta* or honey.[7]In the present study it was advised to be taken 1 tablet twice daily 1-2 hours after meals with potable lukewarm water. In as much, an analytical study conducted by the scholar and published on Nagarjunabhra Ras found that the quality of the Terminalia Arjuna content was not up to the quantitative and qualitative standards in two drug samples procured from the market; this required standardised trial- drug for study; for which a quality control test was applied to the selected drug sample manufactured by a reputed and reliable Indian drug manufacturing company.[8]

Hridshula, the retrosternal precordial pain condition, in ayurveda, lies in the class of *hridroga*. On the basis of *doshas*' involvement there are five types of *hridrogas* viz. *vataja, pittaja, kaphaja, sannipataja and krimija*.[9]*Hridshula,* a characteristic chest pain, is *vata dosha* and *rasa dhatu* dominated manifestation with *kapha* and *pitta* involvement and participation; when they get vitiated cause obstruction within heart (vessels) and thus pain is anticipated.[10]Its Ayurvedic patho-physiology is explained in all premier *samhitas* viz. *Charaka, Sushruta, Vagbhatta, Sharangdhar and Madhava Nidana*.[11] Various symptoms of the diseases are explained on the basis of doshas' quantitative involvement and of *krimis* (pathogenic macro/micro-organisms) infestation.[11]*Hridshula* has been referred to, by Ayurvedists, Angina Pectoris of modern times.[12]According to modern medical science, in angina pectoris, coronary arteries are narrowed by spasm or blocked by atheromatous plaque formed within vascular lumen. Blood supply is obstructed and there is mismatch between demand and supply of oxygenated blood to the heart muscles. This manifest mild to severe anginal pain in the chest which is generally referred to left arm, jaws, neck and epigastrium whether at rest or on accustomed exertion and is generally relived by nitrates.[12] Causative

risk factors are unhealthy diet, intake of high calories and fat rich food with improper eating habits, tobacco smoking, sedentary lifestyle, hypertension, diabetes, stress and genetic predisposition.[13] In continuum of events of coronary artery diseases, in the inceptive stage when stabilised plaque narrowed coronaries cause discomfort to different nature of throbbing, piercing, twisting or burning pain in the mid or left side of chest with other classical signs like sweating, vomiting and referring pain, it is called stable angina which may further on rupture of plaque lead to unstable form of angina and acute myocardial infarction,[14] which is known as heart attack in common parlance. The prevalence of heart attacks in India was about 12.6% in urban areas and 4.6% in rural areas according to various reports published in 2015. In every 30 minutes one person dies owing to it and the burden of cardio vascular diseases is projected to be highest by the year 2020. This is the second largest killer in the world today.[15]In a recent study conducted by the National Institute of Nutrition under the Indian Council of Medical Research found that major increase in the incidents of non-communicable diseases among urban Indians attributed to nutrition transition, sedentary lifestyles and high risk behaviours. It showed that about 2.6 million Indians are predicted to dye due to coronary heart disease in India by 2020, which constitutes 54.1% of all heart and vascular diseases. In addition, the CHD in Indians occur prematurely, at least a decade or two earlier than that in developed countries.[16]Risk factors account for atherosclerosis i.e. thickening of coronary arteries by depositing cholesterol in their intimal layer which leads to narrowing of the vessels lumen and short supply of blood, nutrition and oxygen to the heart muscles as against demand.[13, 14]In cascade atherosclerosis plaques are formed within arteries lumen which may be stable or unstable. When plaque ruptures leads to thrombus / clot formation subsequently occlusion of the artery and acute myocardial infarction takes place leading to future events.[14] Stable angina is an intermediate clinical condition between narrowing of arteries due to plaque and unstable angina ahead of myocardial infarction.

Clinical presentation of stable angina is represented with symptoms of pain or discomfort in the chest. Other symptoms are extreme fatigue, pain and dyspnoea on exertion and relieved at rest or nitrates.[12]Sometimes this is asymptomatic and not recognized until acute myocardial infarction sets in. This may be easily recognized by electrocardiogram (ECG) with the ST segment depression and or inversion of T wave.[14] Treatment of stable angina consists of either approaches; medical and interventional therapy.[14, 17] Aim of the therapy is to dilate or open blocked arteries for smooth blood supply. Pharmaco-therapeutically nitrate therapy is mainstay to relieve chestpain.[12] Clinical effectiveness of nitrates was first described by Lauder Brunton, a British doctor, in 1867. The action of nitrates is to relax vascular smooth muscles facilitating vasodilatation. The vasodilatory effect of nitrates is evident in both systemic arteries and veins including coronaries in normal subjects and in patients with ischemic heart disease. While coronary vasodilatation leads to increased myocardial blood flow; the systemic venodilation leads to reduction in preload and after load which in turn reduces myocardial wall tension and oxygen demand making nitrates useful in angina pectoris. Nitrates are given either sublingually or by intravenous route or orally. Orally, Isosorbide dinitrate, a short acting nitrate drug, is used for immediate and for a short time period action, whereas isosorbide mononitrate is used for long time period action.[18]Additionally, anti-platelet aggregator acetyl salicylic acid (aspirin), anti hyperlipidemic statins, anti-hypertensive and hemodynamic effectors beta-blockers and cardiac metabolites are also recommended for primary and secondary prevention. All have definitive anti-anginal and disease regression efficacy. Thus, stable angina is completely manageable and reversible by pharmaceutical medicines and risk factors prevention; and quality of life is improved with thetreatment.[19]Yet, certain patients are left untreated due to serious side effects of certain anti-anginal drugs; developing resistance and tolerance to others remains a challenge to the physicians. Most common side effects of nitrate

preparations are headache, flushing, andhypotension.[20]Ayurveda offers a lot of formulations for the treatment of hridshula (stable angina pectoris). It offers both herbal and herbo-mineral Ras – medicines for different heart disease and hridshula i.e. angina conditions.[2,3,4,5] Nagarjunabhra Ras is an important preparation commonly used by ayurvedic physicians for the treatment of chronic stable angina.[21] Its Arjuna content has been tried by modern researchers a lot in cases of chronic stable angina.

Various pre-clinical and clinical studies are conducted on modern parameters establishing its anti-anginal, anti-ischemic, anti-hypertension, anti-hyperlipidemic, anti-platelet aggregating, cardio-active and anti-oxidant activity.[22-25] Its abhraka bhasma content has also been explored by modern scientists for various properties. Its nano-particles are found to be acting on cellular level and said to be cardio-active and protective.[26] It also improves myocardialischemia.[26,27,28]It also has a property of bio-activity enhancer of the other drug with which it is administered *(yogvahi)*. In classical literature both are said to be working in hridroga by special effect. Thus, in combination both ingredients work in synergy;[29,30,31] hence, in the present study their combination in form of Nagarjunabhra Ras was selected for initial study for evaluation of anti-anginal efficacy in terms of modern subjective and objective parameters. Now that, there is a huge demand of ayurvedic medicines in world market for cure and prevention of diseases, health and wellness promotion and a better living of healthy life, yet, due to lack of quality control and standardization, research and modernisation, packaging and dispensing, non-availability of ready to use formulations, clinical efficacy and toxicological and safety evidences; the rational and aware society hesitate to accept the time tested ayurvedic medicines. In this perspective, the Government of India has laid down certain GMP guidelines for clinical trials of these drugs and medicines, mandatory.[32]Further, treatment of stable angina still remains a challenge despite best treatment options available in modern times.[20] There is a group of patients which still remains

un treated due to various reasons. Post-MI, post-CABG, refractory angina patients and who have left –ventricular dysfunction with poor ejection fraction; high risk individuals unfit for intervention and coronary artery bypass grafting, economically poor which can't afford and patients of bad prognostic value; such patients may be tried by co-administration or singly on Ayurvedic medicines. For that purposes Nagarjunabhra Ras could be a drug of choice for the prevention and treatment of stable angina. Though Nagarjunabhra Ras has been used by Ayurvedic physicians extensively since a very long time for the treatment of angina; but it was not evaluated for its efficacy so far by any ayurvedic or modern physicians. No pre-clinical or clinical study was ever conducted on *Nagarjunabhra Ras* by any scholar on modern lines. Reverse pharmacology has made the Ayurvedic drugs' clinical study easier. This permits direct clinical trials. Similarly, toxicological, safety and dose determination preliminary data is not required.[118] Classical Ayurvedic drugs' doses and indications are prefixed. So, in the pursuit of search of newer effective and safer medicines this ayurvedic drug was tried in sufficient number of chronic stable angina patients in this study. Though this drug had millennium old human trials with known anti-anginal property yet its mechanism of action is to be searched out. Does it work on the principle of molecular reductionism or on biological complexities; either it could be used in combination with other ayurvedic or modern cardiovascular and cardio-active drugs; would it be effective in micro-vascular angina also? There could be many questions which are yet to be answered. The present study was done to evaluate efficacy of *Nagarjunabhra Ras* in chronic stable angina as compared to isosorbide mononitrate on modern parameters in association with modern medical experts.

A randomised controlled open-label, comparative add-on clinical study was carried out in a tiny sample of sixty patients from the population of chronic stable angina patients. Patients were divided into two groups with equal numbers in each; control group and trial group viz.

Group A i.e. ISMN group and Group B i.e. NAR group. Control A group patient were administered all modern drugs viz. aspirin, clopidogrel, metoprolol, atorvastatin and long acting nitrate isosorbide mononitrate while trial group patients were given aspirin, clopidogrel, metoprolol, atorvastatin and Nagarjunabhra Ras capsulated tablets. A sub-group of trial patients was without metoprolol. One single subject was without concomitant anti-anginal therapy in trial group where the test drug was given as monotherapy. All patients were examined on subjective as well as objective parameters before and after study. After a three months therapy mean values of the outcomes were compared with baseline values. UK's EMEA guidelines on clinical investigation of medicinal products in stable-angina pectoris, New York Heart Association and Indian Council of Medical Research Guidelines were followed. Statistical analysis was done to find out significant of difference.[74-78] Furthermore, contemporary world seeks evidences to recognise the science of Ayurveda in disease management. Can angina i.e. hridshula be cured with ayurvedic formulations as compared to modern medicines? This question is generally asked. Stable angina is effectively managed in modern medicine with the aim of relief in pain, normalization of ECG changes, and improvement in exercise tolerance and health related quality of life and overall survival. But still many patients are left untreated or improperly treated due to drug tolerance, serious adverse effects, un-affordable cost price of the treatment and poor accessibility despite best treatment modalities available. From the classical and contemporary literature we find that Terminalia arjuna bark extract and abhraka bhasma nano particles have all the properties of antiplatelet aggregation, antihypertensive, anti-hypercholesterolemia, cardio-protective, anti-oxidant and anti-diabetic, which are wanted for the treatment of hridshula i.e., chronic stable angina. Moreover abhraka bhasma has synergistic effects despite its own cardio-active and anti-oxidant action. And for a group of refractory angina patient a novel effective drug is required. Therefore, this study was undertaken.

AIM AND OBJECTIVES

Aim and objectives of the study was to evaluate clinical efficacy of Nagarjunabhra Ras in comparison to standard allopathic drug isosorbide mononitrate in hridshula (stable angina pectoris.

To assess anti-anginal efficacy of treatment protocol in each group.

After comparison of the results between two groups, to prove the efficacy of trial drug Nagarjunabhra Ras, statistically.

To study the effects of Nagarjunabhra Ras while added-on with anti-anginal conventional drugs.

HYPOTHESIS

- Vata, kapha and pitta dosha vitiate rasa-dhatu and when obstruct ras (rakta) vaha-srotsa (coronaries) of heart result in manifestation of hridshula (angina pectoris) which is chiefly a ras and vata consequence.
- For elimination of coronaries obstruction, vata-pitta-kapha ghna and ras treating dravya and aushdha are employed.
- Hridya dravya protect heart and act for normalization of blood circulation and heart's function.
- Nagarjunabhra Ras has both shula-hara and hridya properties.

REVIEW OF LITERATURE

AYURVEDIC VIEW

Hridrogas and hridshula have been suffering the humanity since old times. Its description is also available in ancient medicine. In 3500 B.C. Acharya Charaka has described its pathology and symptoms.1 Later from Sushruta to Vagbhatta and medieval text still 20th century literature five types of hridrogas and hridshula independently and discretely are explained with treatment.[3,9] Hridrogas' treatment with Terminalia arjuna bark is described in Ashtanghridya of Vagbhatta first of all.[31]

Hridroga:

Hridrogas and their treatment find adequate description in ayurvedic medicine literature since Vedic period.34 Present day heart diseases find their root in Samhitas. There, in Ayurveda, seems subjective and symptomatic approach in classifying heart diseases, diagnosis and management.

Hridaya[35, 36] is synonymous to heart. The terms hridaya, hridamaya, hridroga and hridshula have been found in Vedas. The earliest detailed description of hridroga and its treatment is available in Charaka Samhita Su. S. Ch. 17, Sushrut Samhita Ut.Ta. Ch.43 and Vagbhatta Samhita, Ashtang Hridya Nid. S. Ch. 5 and Chi. S. Ch. 6. Hridshula has been separately described in chapter 42, Su. S. Uttar Tantra. Later Madhavakar in Madhava Nidana in Hridroga chapter describes all kind of heart diseases from ayurvedic point of view. It appears that in various ayurvedic classical text books all the diseases explained that are presented in epigastrium and precordial region have included in hridrogas whether they are of upper gastro-intestine, respiratory system, chest trauma or heart and pericardium. Irrespective of above description when we find on account of vataja hridroga the symptoms described resemble with that of stable angina, acute myocardial infarction and heart failure in present times.[37, 38]

Hridroga Nidana: [39]

Nidana, the causative factors of hridroga according to ayurveda are described in Charaka Samhita, Sushrut Samhita and Madhava Nidana well versed. Modern day Ayurveda scholars try to classify these factors as 1. *Sharirik Karana* (Somatic factor) 2.*Mansikakarana* (Psychological factor) 3.*Aahar Karana* (Dietary factor) 4.*Vihara Karan* (Behavioural factor) 5.*Chikitsaka Karana* (Drugs and therapeutic factor) and 6.*AgantukaKarana* (External factor).

Acharya Charaka [75] explained that for weak persons by any cause *Javara* and *atisaara* (fever and diarrhoea), *aama vata* (rheumatism), *karshya* (wasting), *mada* (Intoxication by alcohol), *chhardi* (vomiting), *vegadharana* (suppression of natural urges), *nishwas dharana* (suppression of expiration), *vashpa nigrahan* (suppression of tears) will be predisposing factors of hridroga. (Ch. Su. S. 30/30-40 and Ch. Su. 7/21). *Chinta* (anxiety), *bhaya* (worry and fearfulness), *traasha* (frightening) (Ch. Su. 30/30-40) lead to hridroga. *Vyayam* (excessive exercise), *shrama* (strain and heavy work), *gurubharavahanam* (lifting heavy weight), *ushna* and *ruksha anna sevana* (consuming very hot and dry foods), *virudhaashan* (incompatible food intake), *adhyashana* (frequently overeating), *ajeeranashana* (polyphagia), *asatmaya bhojana* (eating allergic food substances), *guru annasevana* (eating late digesting foods), *kashaya* and *tiktarasa sevana* (eating astringent and bitter substances), *tikshana virechana* (purgation), *tikshana vasti* (enema) and improper performed *Panchkarama* therapy etc. *Abhighata* (injury), *bhutabhisangat* (external microorganisms)(Ch. Su.S. Ch. 30/30-40 and Madhava Nidana); and *gulma roga* (severe epigastric pain), (Ch. Ni. 3/11 and Su. Ut. T. 43/3 and Ch. Su. 30/30-40); these are causative factors of five kind of heart diseases viz. 1. Vaataja 2.Pittaja 3.Kaphaja 4.Tridoshaja and 5.Krimija.

In classical texts signs and symptoms of various hridrogas find explanation on the basis of Doshas' involvement and induction of Krimis. In agreement with the ayurvedic concept,

association of mental state (*manas bhava*) in coronary artery disease has been documented in two Pune studies using Ayursoft instrument recently.[40, 41]

Hridshula: [39, 42]

Shula (pain) is the main characteristic of vata; therefore, hridshula (chest pain) disease is described under vataja hridroga. In Charaka Samhita and Madhava Nidana vata aggravating causes such as *shoka* (woe), *upvasa* (starvation), *vyayam* (exercise), *shuska* and *ruksha bhojan* (dry and non-unctuous foods), *alpa bhojan* (mal-nutrition) etc. precipitate hridshula. Symptoms are described as severe to moderate to mild pain to feeling like nothing in chest, pocking pain, feeling of dryness, explosive pain, stiffness, dizziness, twitching, twisting, piercing and tearing pain sensation is felt in chest. (Su.Ut. T. 43 and Ma.Ni.)Hridshula [43, 44, 45] is separately mentioned in Sushruta Samhita chapter 42-43/4.Accordingly, the pathogenesis explained as that in hridshula the aggravated vata obstructed by kapha and pitta will combine with rasa dhatu and on reaching heart, thereby cause difficulty in respiration generating *badha* i.e. pain (jejjata commentary) in heart with different symptoms as described earlier.Dalhan[44] has emphasized that hridshula is a peculiar type of heart disease which is associated with pain and severe dyspnoea and thus it should be treated as a separate disease entity among the heart diseases.

Hridshula has not been described by Charaka separately. It is included in vataja hridroga. Sushruta described it under separate head due to typical symptoms and periodic nature of the disease. This is similar to modern time's angina pectoris pain in precordial area, an ischemic heart disease condition of coronary arteries.

Dr. VB Athavale[11] has presented a simple and exact explanation of hridshula that it is a severe pain in the heart usually characterised by difficulty in respiration. Its pathogenesis in ayurveda is detailed as that the increased and vitiated vata leads to spasm of the coronary vessels which results in temporary ischemia of heart and gives rise to severe pain. The

predisposing factors are the thickening of coronaries due to kapha (atherosclerosis) and pitta(inflammatory) and abnormality of rasa and rakta (hypercholesterolemia). All the factors which increase vata viz. exercise, exertion etc. act as predisposing factors. And for the treatment *vata shamak* and *kapha shamak* medicines should be administered as vata is dominant dosha and heart is situated in the region of kapha. From the ayurvedic point of view, degeneration of blood vessels is caused by increased vata molecules in the blood vessels, which make the blood vessels hard, thin, dry and rough. Deposits of lipids and calcium represent deposition of kapha molecules in the degenerated vessels resulting in irregular thickening of blood vessels. The disease thus is caused by increased and dominant vata dosha and vitiated kapha in the vessels walls. *Rasa* and *rakta dhatu sammurchhana* (conjugation), and *aam utpatti* are known factors for etio-pathogenicity according to the ayurvedic principles.

Treatment of Hridshula: [46 – 69]

Notwithstanding, the ayurvedic management of hridshula is done mainly with compounds which contain *vatahar* and *kaphahar* herbs like , *sunthi, bala, trikatu* , *hingu, puskarmula, Guggulu, lashuna, pippali* and specifically arjuna bark, arjunarishta and various ras-medicines viz. *mrigshringa bhasma, Prabhakar vati, Hridarnava Ras, Trinetra Ras* and Nagarjunabhra Ras etc. For treatment of Hridshula equally stress is also laid on *pathya-apathya* (dietary regimen), daily regimen (*vihar-sadachar*), and meditation (relaxation).

It has been identified these days that hridshula is identical to the angina pectoris of modern medicine and various ayurvedic medicines described in the texts have been tried successfully for the treatment of stable angina pectoris by ayurvedic physicians and modern research scholars. A lot of studies on hridshula treatment with ayurvedic drugs have been carried out at BHU Varanasi, GAU Jamnagar, NIA Jaipur, AIIMS Delhi, Delhi University, PGIMS

Chandigarh and Indore and at various Public and private ayurvedic and medical institutions of repute throughout the country.

Colabawalla HM in 1951 had ‘an evaluation of the cardio-tonic and other properties of Terminalia Arjuna’, Indian Heart Journal, Issue 3, Page 205-230; and held that the plant drug had significant effect on hemodynamic factors in patients with failing heart. Udupa K Net al (1987) in a clinical trial at Banaras Hindu University had proved Arjuna bark’s efficacy in Ischemic heart disease. Sharma SD and Tripathi SN studied management of hridroga (IHD) (1986) and found significant improvement in clinical and biochemical and ECG improvements with pushkar, gugulu and brahmi herbs compound in 50 patients. Vaid Tapan Kumar and Dr. Gurdip Singh (1988) have studied at GAU Jamnagar, yakuti guti and hridshoolaghanasava and notice significant changes in clinical parameters and exercise tolerance test. Jain V and Punia A et al (1992) in a clinical study administered bark powder of Terminalia Arjuna twice daily to 25 coronary artery disease (CAD) patients for 3 months. A reduction in the grade of positivity of treadmill test (TMT) response was observed in addition to improvement in exercise tolerance and a reduction in the frequency of anginal attacks and use of sublingual nitrates. Dwivedi S, Aggarwal MP (1994) tried clinically Terminalia Arjuna bark and noticed ‘anti-anginal and cardio-protective effects in coronary artery disease.’ Utmost work on effect of arjuna bark in atherosclerosis, coronary artery disease and angina was carried out by Dr. Sridhar Dwivedi, eminent professor and Director Principal of Hamdard Medical Institute, New Delhi between 1987 to 2014 in pre-clinical and clinical studies in various times explaining that most of the studies, both experimental and clinical, have suggested that the arjuna possesses anti-ischemic, anti-oxidant, hypo-lipidemic, and anti-atherogenic activities reference ‘Revisiting Terminalia arjuna –an ancient cardiovascular drug.’ Awasthi AK et al (1997) at NIA Jaipur clinically evaluated effect of Lashunadi Guggulu in management of chronic stable angina in 20 patients and after 2 months treatment

found marked improvement under CTMT and high reduction in lipid levels. Anil Bharani and Arun Ganguli (2002), Department of Medicine, Cardiology and Biostatics, MGM medical college and Hospital, Indore conducted study in 58 male patients on 'Efficacy of Terminalia arjuna in chronic stable angina: a double blind, placebo controlled, crossover study in comparison with Isosorbide Mononitrate and concluded that T.A. barks extract led to improvement in clinical and treadmill exercise parameters as compared to placebo therapy. These benefits were similar to those observed with isosorbide mononitrate 40 mg daily. Dwivedi S (2004), Asian Journal of Cardiology, illustrated that arjuna stem bark has been found to possess diuretic, antihypertensive, anti-anginal, hypolipidemic, anti-ischemic, and immune-modulating actions and bioflavonoids present in it act as anti-oxidants by virtue of their free radical scavenging action and preventing oxidation of LDL. SK Maulik and C K Katiyar (2010) explored pharmacological properties of T. arjuna bark and demonstrated animal studies and clinical studies reporting its beneficial effects in patients of chronic stable angina, endothelial dysfunction, heart failure and anti-ischemic coronary vasodilatory effects. Blumenthal, Foody, Wong; Preventive Cardiology (2012) reported 'A systemic review of studies of Terminalia arjuna bark extract demonstrating effectiveness in anginal pain, and coronary artery disease' with limited data which needs additional well-controlled comparative trials.

In current times many ayurvedic scholars tried to elaborate ayurvedic treatment for hridshula – stable and unstable angina, atherosclerosis, acute myocardial infarction, occluded coronary arteries, dyslipidaemia, myocardial damage, heart failure, metabolic syndromes, genetic causes, hypertension and other risk factors either by way of modification of diet, lifestyle changes and regular exercises, yoga and meditation, literarily and experimentally. Shukla N, at GAU, Jamnagar (2012) has reported 'Management of Cardiac Emergencies in Ayurveda – A Clinico-literary Approach.' He described certain quick acting ayurvedic formulations.

Renu Rathi and Bharat J Rathi (2103) conducted a clinical study in coronary artery disease on a compound containing Arjuna bark and concluded that the compound had potent anti-anginal activity when tried upon exercise stress test and echocardiography, objective parameters. Sarvamangala et al (2014) in study 'Cardio-protective activity of Trinetra Ras in experimental animal model', and evaluated its cardio-protective activity against Isoprinaline induced cardiac damage in rats to understand mechanism of its therapeutic effect with respect to bio-chemical markers, ECG and histo-pathological changes and provided evidences. Trinetra Ras contains both the ingredients of Nagarjunabhra Ras; abhraka bhasma and Arjuna bark and additionally shuddha parad and shuddha gandhaka all in equal quantity. Hrinathachary B (2005) BRKR Govt. Ayurvedic College Hyderabad has conducted 'A clinical study on effects of Trinetra Ras in management of Hridroga' and showed efficacy in hridshoola.

As Nagarjunabhra Ras is composed of Terminalia Arjuna bark aqueous extract and nano-ash of krishanabharaka i.e., 100 puti black mica, abhraka bhasma, so, significance of mica in ayurvedic products has been illustrated in classical Rasashastra books and in modern scientific studies and its usefulness in heart diseases. Mishra Amrita (2011) overviewed Mica that after 100 – 1000 times repeated burning it is turned into abhraka bhasma which is an Ayurvedic medicine commonly used against many diseases. It is indicated in various chronic diseases as tuberculosis, COPD and heart diseases. It is a cellular regenerator and nerve tonic. Babita Bhatia (2013) in 'Analytical evaluation of an Ayurvedic formulation – Abhraka Bhasma' called it a wonder drug. In her study she authenticated Abhraka Bhasma by observing quality assurance methods and testing it through standard ayurvedic and modern analytical techniques like Energy dispersive X-ray fluorescence (EXDRF), field emission gun scanning electron microscopy (FEG – SEM) and Energy dispersive spectroscopy (EDS). The modern analytical method EXDRF revealed the presence of Fe (22%) as a major element and

Ca++, K+ and Si+ in low concentrations, 11%, 8% and 13% respectively. Mg (4%), Al (2%) and Ti (1%) were present as minor elements while Sodium, Chlorine and Phosphorus were present in traces (<1%). FEG – SEM studies showed that the grains in Abhraka Bhasma were heterogeneous and in aggregates of particle size between 19nm and 88nm. EDS analysis showed that major elements present were O (41%), Si (16%), K (13%) and iron (13%) and the minor elements were Al (6%), Mg (5%), Ca+ (4%), Cl- (1%), Sodium, Phosphorus and Titanium were present in traces (<1%). The analytical techniques used confirmed the absence of organic compounds and mercury.

Thus, in combination both the ingredients might be working in an increased efficacy. As Arjuna bark extract has all the qualities what an anti-anginal and anti-ischemic drug need for the treatment of stable angina and for primary and secondary prevention.[117] Abhraka Bhasma for being cardio-active and bio-availability enhancer and catalyst (*yogvahi*); it will be enhancing anti anginal activity in synergy. Therefore, Nagarjunabhra Ras may be a drug of choice for the ayurvedic treatment of chronic stable angina. Moreover this combination does not consist of any controversial heavy metal therefore it is a quite safe and effective drug. Hence this study was undertaken and presented here.

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MODERN VIEW[13, 14, 17, 18, 20]

Angina Pectoris:

Angina Pectoris is caused by transient episodes of myocardial ischemia. This is due to inadequate oxygen supply to the cardiac muscles relative to the demand. Due to reduction in coronary blood flow because of narrowing of the coronary arteries or their spasm heart muscles start aching. The increased myocardial oxygen demand is determined by heart rate, ventricular wall tension/stress and ventricular contractility. Simultaneously decreased myocardial oxygen supply is determined by inadequate coronary blood flow and occasionally by modified oxygen carrying capacity of the blood or both. Regardless of precipitating factor, the sensation of angina is similar in most patients. Pain is commonly experienced as a heavy, pressing, sub-sternal or precordial discomfort often radiating to the left shoulder, left arm, jaw and or epigastrium. This pain is caused by the metabolic consequences of myocardial ischemia; production and retention of acid metabolites leading to intracellular acidosis, intra-cellular ATP reduction and free fatty acid accumulation. Angina may occur in a stable pattern over many years or become unstable, increasing in frequency, severity and occurring at rest. Ischemic heart disease (IHD) synonym coronary artery disease (CAD) has a wide range of presentations. It may manifest as asymptomatic or symptomatic stable angina persisting for long period of time. The narrowing of the coronaries commences as a result of atherosclerosis. At times atheromatous plaque inside coronary arteries get ruptured and thrombus is formed which causes occlusion of coronary artery leading to myocardial infarction. Consequently cardiac muscles are damaged and arrhythmias take place. Ultimately cardiac failure or sudden death may occur.

Though angina pectoris is a clinical syndrome caused by imbalance between myocardial oxygen demand and supply, yet its salient feature is pain which is characterised by paroxysms of a distinctive pain sensation usually situated retrosternal and radiating

commonly to the precordial and left upper arm and occasionally to other adjacent areas. The pain is precipitated by effort or emotion or by a sudden change in the individual's temperament and rapidly relieved by rest or nitrates. The nature of pain is not constant; some may describe it as constricting, squeezing, pressing and crushing while to others it is stinging, burning sensation. It may be sharp, shooting or stabbing. It is constant for few minutes. The pain is of episodic nature which is momentary that does not continue for many hours. For diagnosis an electrocardiograph (ECG) during or immediately after the attack shows a T wave inversion in corresponding leads or depression of ST segment with or without inversion of T wave.

Different types of angina:

Angina Pectoris literarily is explained of many types based on its clinical presentation and different patho-physiological conditions as under:-

1. Variant angina (Prinzmetal angina)
2. Stable angina
3. Unstable angina (acute coronary insufficiency)
4. Acute myocardial-infarction
5. Micro-vascular angina

Atherosclerosis:

Atherosclerosis is defined as hardening of arteries due to deposition of lipids, blood constituents, fibrous tissue, and foam cells in the sub-intimal layers of the arteries. This is a degenerative disease of the large arteries in which aforesaid deposits are termed as atheromatous plaques. Later these plaques rupture and thrombotic clot is formed at ruptured site which travels to the terminal arteries facilitating occlusion of that vessels resulting blockage of the total blood oxygen and nutrition supply to that part of the cardiac muscles instituting pain, damage and myocardial infarction which may lead to death. This stage is

called unstable angina which electrocardiographically is classified in NSTEMI and STEMI. The damage and necrosis to the heart muscles develops ventricular dysfunction and heart failure which are irreversible.

Atherosclerosis has multiple pathogenic causal factors and starts in childhood only to produce lesions and clinical symptoms decade later. The disease process occurs mainly in the intimal tissue system in response to variety of physical and chemical stimuli. Some of the most important of these processes are the transport of plasma proteins into the intimal space, intimal fibro-muscular hyperplasia and internal lipid depositions. Lipids in the lesion are predominantly cholesterol and cholesterol esters. Atheroma thus formed may be either primary or secondary to sclerotic changes. In the early stages the lesions may be reversible, when they are limited to intima, but in the more advanced lesions the media and adventitia are also affected and at this point they may be irreversible.

Atherosclerosis is a chronic progressive rebuilding process in the arterial walls which may lead to arterial hardening, loss of elasticity and diminution of vessel lumen and thus impairment of function in the affected organ. The components which contribute to the fully developed atherosclerotic lesions are: 1) A necrotic lipid rich acellular centre. 2) Extra cellular lipid located interstitially and attached to fibre proteins. 3) Intracellular lipid deposits. 4) Proliferation of cells of the arterial media type. 5) Increased fibrosis in and around the lesion.6) Thickened intima due to a combination of the above factors. The lesions may also contain variable quantities of elastin and ground substance in the form of acid muco polysaccharides or proteoglycans, fibrin, calcium and crystalline cholesterol.

In atherosclerotic lesions endothelial cells and smooth muscle cells are also found but in addition a number of cells of haematogenous origin may be observed. These cells are monocytes, macrophages and lipophages. A characteristic feature is the presence of foam cells which are the lipid engorged smooth muscles cells. Most of the lipid in large human

plaques is derived directly from plasma lipoproteins. A grading of the atherosclerotic lesions is possible in the light of its pathology as: Grade I – Lipid streaks, spots, patches; Grade II– Fibrous and atheromatous plaques; Grade III – Necrotic, ulcerate, haemorrhagic or thrombotic plaques; Grade IV – calcified plaques.

Principles and Practice of Stable Angina Management:

In contemporary medicine Stable Angina is primarily managed medically. Primary goal of the treatment remains sufficient oxygenated blood supply to the heart muscles by vasodilation of coronaries. This is achieved by nitrate drugs. It is evident that nitrate drugs have vasodilation effect upon end arteries and veins thus facilitate blood flow through coronaries and reducing preload on the coronary vessels. Nitrates are classified into short acting nitrates e.g., isosorbide dinitrate and nitro-glycerine (glyceryl trinitrate) and long acting nitrates namely isosorbide -5- mononitrate etc. Apart from nitrates, beta-blockers, calcium channel blockers, anti-platelet aggregators, statins, cardio-metabolites are advised. They have their different beneficial treatment effects. Beta-blockers in angina work by slowing the heart rate thereby decreasing the oxygen demand. Calcium antagonists widen blood vessels by exerting affect upon arterial wall muscles. They prevent entering calcium ions into cells resulting in reduce force of heart and arterial muscle contraction. Antiplatelet aggregators have a role of primary and secondary prevention of atherothrombosis in chronic stable angina. Anti-ischemic and anti anginal effect of statins is evident from their lipid lowering role, hence, atherosclerosis reversibility and revascularisation. Cardiac metabolites e.g. Ranolazine, trimetazidine etc. inhibit angina pain producing stimuli and lessen the optimized energy metabolism in the ischemic myocardium; a different approach.

Aspirin and antiplatelet drugs:

Initial treatment of every angina should include aspirin. Ignatios Ikonomidis, MD et al(1999) proved that it reduces the circulating levels of pro-inflammatory atherogenic factors in the

blood in patients with chronic stable angina. Various other studies demonstrate beneficial effects of aspirin in chronic stable angina and coronary artery disease. Itsik Ben Dor and Alexander Battler, (2007)for the treatment of stable angina explained that Aspirin at a dose of75–325 mg per day reduces cardiovascular morbidity and mortality by 33% in patients with coronary artery disease. Another randomised placebo-controlled study of 479 patients addressed the acute phase of angina and documented a relative risk reduction of 39 % in the rate of future events. In Annals of Internal Medicine (1991), in a low-dose aspirin therapy for chronic stable angina a randomized placebo-controlled clinical trial Ridker PM, Manson JE, Gaziano JM, Buring JE, Hennekens CH from Harvard Medical School, Boston, Massachusetts the data indicated that alternate-day aspirin therapy greatly reduced the risk for first myocardial infarction among patients with chronic stable angina. The benefits and limitations of aspirin have stimulated the development of many new therapies targeting various platelet functions, including adhesion and aggregation. Clopidogrel, a thienopyridinederivative closely related to ticlopidine, has been in large trials. Patients with previous strokes, MI, peripheral vascular disease were randomised and similarly, in large trials of clopidogrel and aspirin in combination were shown to confer a great amount of reduction in strokes, MI and cardiovascular deaths. Antiplatelet drugs are valuable for the prevention of future events in chronic stable angina patients.

Beta-blockers:

The pharmacological agents that have ability to cause competitive inhibition of the effects of neuronally released and circulating catecholamines on beta adrenoreceptors are called beta adrenoreceptors blockers or beta-blockers. Beta blockers reduce myocardial oxygen requirement, primarily by slowing the heart rate. The slower heart rate in turn increases the fraction of the cardiac cycle occupied by the diastole, with a corresponding increase in the time available for coronary perfusion.

Beta blockers have become standard therapy by reducing frequency and severity of both stable and unstable angina. They are most useful in patients with high sympathetic tone manifested by sinus tachycardia and elevated blood pressure. Several placebo controlled trials have shown benefit of beta blockers in reducing subsequent MI and/or recurrent ischemia.

Calcium channel blockers:

Calcium antagonists are a heterogeneous group of compounds that inhibit calcium ion entry into cardiac and vascular smooth muscle cells via blockade of calcium channels. The efficacy of these agents is related to the reduction in myocardial oxygen demand and the increase in oxygen supply. They cause vascular smooth muscle relaxation and reduce coronary and peripheral vascular tone and afterload. These drugs have vasodilatory effects and lower blood pressure and slow heart rate. Diltiazem and verapamil are useful anti anginal and hypertensive. Amlodipine is used as antihypertensive and for stable angina due to coronary vasospasm.

Statins:

Statins are HMG-CoA reductase inhibitor class of cholesterol lowering agents possesses anti-anginal properties to a degree of efficacy that may be equivalent to the standard pharmacologic and mechanical therapies. Statins were introduced in1987 and revolutionized the management of coronary artery disease. Landmark statin trials have established the key role of statins for both primary and secondary prevention in combating and reversing atherosclerosis in chronic stable angina and in post-revascularised patients. They are adjunct to diet in primary, familial and mixed hypercholesterolemia. They reduce the risk of non-fatal MI and fatal and non-fatal strokes and angina in patients with established coronary artery disease. Cheol Whan Lee & Seung-Jung Park (2013) evidenced through a study that statins effect on plaque morphology and angina in patients with stable angina. J A. Lardizabal et al (2010) studied “the anti-ischemic and anti-anginal properties of statins’ and explored that the

mortality and morbidity benefit of statins in the management of coronary heart disease is established, both in the primary and secondary prevention conditions. In high risk individuals without prior history of CHD, statin therapy, on an average, reduces the risk of MI 27% and overall mortality 7%. In patients with known CHD it is estimated that statin treatment reduces total mortality 16%, CHD mortality 23%, and major CHD events 25%, irrespective of baseline cholesterol levels. Despite the novel state-of-the-art pharmacologic and mechanical therapies, chronic angina remains a major public health problem. Evidence is mounting on the anti-ischemic and anti anginal efficacy of statins in both experimental and clinical studies. John E. Deanfield (2010) elucidated that potent anti-ischaemic effects of statins in chronic stable angina has incremental benefit beyond lipid lowering.

Cardiac Metabolites: Trimetazidine and Ranolazine:

These are cyto-protective agents. Trimetazidine has a cellular approach to ischemia by directly counteracting all the major metabolic abnormalities occurring within the ischemic cell. These kinds of medicines including ranolazine decrease metabolic damage caused during ischemia by redirecting energy metabolism of myocardial cells from beta-oxidation of fatty acids to the glucose oxidative pathway, reducing intracellular acidosis, increasing ATP production and limiting the deleterious consequences of ischemia. The anti anginal effect of trimetazidine is not associated with alterations in hemodynamic determinants of myocardial oxygen consumption.

Nitrates:

Nitrates are most valuable class of drugs in the management of angina pectoris by causing systemic venodilation, thereby reducing preload, myocardial wall tension and oxygen requirement, as well as by dilating the epicardial coronary vessels and increasing blood flow in coronary vessels. They include amyl nitrite, glyceryl trinitrate (nitro-glycerine), PETN nitrate, isosorbide dinitrate and isosorbide mononitrate. They correct the supply-demand

imbalance in angina; metabolized to nitric oxide which relaxes vascular smooth muscles. Nitrates reduce afterload, left ventricular end diastolic pressure improving subendocardial perfusion. Adverse effects include postural hypotension, flushing and headaches. Most nitrates are available as sublingual preparations, well absorbed across the oral mucosa giving rapid short relief from symptoms. Isosorbide mononitrate or its pro-drug isosorbide dinitrate, are available as oral preparations, and may be effective for 12 hours. Isosorbide dinitrate tablets are short acting and available in strength of 5 mg – 10 mg; these are recommended as sublingual as and when required. Isosorbide mononitrate tablets are long acting and available in 20 – 30 mg in twice daily doses or 30 – 60 mg sustained released tablets.

Isosorbide-5-Mononitrate:

For this study primarily deals with efficacy of Nagarjunabhra Ras in comparison to Isosorbide Mononitrate (ISMN), therefore it is imperative to know pharmaco-therapeutics of this drug. ISMN is a drug principally used for the treatment of angina pectoris. It acts by vasodilation of coronaries and blood vessels facilitating blood flow and reducing blood pressure. This is used for primary as well as secondary prophylaxis of angina. This is an active metabolite of isosorbide dinitrate and has similar effect. It reduces preload and afterload of the heart by producing venous and arterial dilation, thus making improvement in the oxygen supply demand balance to the myocardium.

Adverse effects of the ISMN have been reported, very common. Headache predominates up to 30 % necessitating withdrawal of the drug. Fatigue, sleeplessness and gastrointestinal disturbances are also reported during clinical trials. Hypotension, dizziness, poor appetite, nausea are equally described as with other nitrate preparations in 1% to 5%patients. Other side effects are also reported include tachycardia, vomiting, diarrhoea, vertigo and heartburn making it not compliable. This preparation is available in instant release and extended release forms in dose of 20 mg BD or 30 – 60 mg ER tablets. This is a long acting nitrate metabolite

indicated for prevention and treatment of acute and chronic angina pectoris, hypertension and myocardial infarction.

Similar to other nitrites ISMN is converted into nitric oxide (NO) an active intermediate compound which activates atrial natriuretic peptide receptors enzyme guanylate cyclase. This stimulates the synthesis of cGMP which further activates protein kinase dependent phosphorylation in the smooth muscle cells eventually resulting in dephosphorylation of myosin light chain of cardiac muscle fibres. Subsequently release of calcium ions results in the relaxation of smooth muscles and vasodilation. This drug is absorbed 100% through gut. Phamacokinetically it has protein binding property. Primarily metabolized by liver it is excreted in urine; only 1% through faeces. Its half-life is 5 hours and is generally safe and is given in 40 mg – 120 mg daily in divided dosages. It interacts with certain drugs including which are used for hypertension treatment. This is taken without regard to meals.

A major problem with the use of nitrates is development of tolerance against them, which has been demonstrated with all forms of nitrates administration. Many studies and clinical trials were conducted in the past and evidenced their increasing tolerance and rebound effect. The phenomenon of vascular tolerance to organic nitrates has been recognised for many years. There has been increasing reports demonstrating that during sustained nitrate therapy, both the hemodynamic and the anti-anginal effects are attenuated.

Nitrate tolerance easily develops in patients receiving oral, topical or i.v. nitro-glycerine; and this attenuation of drug effects appears to limit its efficacy in patients with various kind of heart diseases.

Because of developing tolerance and other adverse effects, newer anti-anginal drugs come into place for treatment of angina pectoris and are being searched for. Many more contemporary drugs are concerned for going to lose their efficacy. Moreover the incidences of CAD and stable angina are increasing day by day. The modern medical science

community is pursuing for search of novel drugs. It looked towards traditional Ayurvedic Ras-Medicines with hope. The author saw many Ayurvedic physicians using Nagarjunabhra Ras for stable form of angina traditionally with pain reliving and sense of well-being effect. But they don’t have any clinical evidences. Hence this study was undertaken.

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RESEARCH METHODOLOGY

Materials and Methods:

The clinical study was conducted in 60 patients of pre-diagnosed chronic stable angina i.e. *hridshula* from both the sexes. Few were newly diagnosed. Others already on conventional treatment and few were post-PTCA. Their age was between 30 – 65 years. All were selected by cardiologist. They were randomly divided into two groups irrespective of age, sex and religion. They were studied in two sub-urban towns of National Capital Region Delhi in OPD clinics, between March 2016 and September 2018.

Design of study:

An open label randomised comparative clinical trial with active therapeutic control and add-on study was conducted.

Place of Study:

This study was conducted at Naresh Hospital, Jhajjar in Haryana at District H.Q. and Oxygen Multi-specialty Hospital Cath-Lab & Department of Cardiology situated at Rohtak City; both lying in National Capital Region of India; 30 & 35 KM away from West –Delhi.

Enrolment of Subjects:

Stable Angina patients were procured through advertisement in regional newspapers. All patients were examined and diagnosed by the cardiologist and judged eligible by inclusion and exclusion criteria. All were formally made aware of the study and those who agreed to participate in the study were enrolled and written consents were taken and randomly allotted to the different study groups. Sixty patients continued as per study protocol.

Randomisation Technique:

Selected patients were divided into treatment group and control group purely by chance with no regard to the will of researcher or patients' preference. It was a simple randomisation

technique, flipping a coin, and allocation concealment is followed to prevent influencing the subjects.

Inclusion Criteria:

1. Patients of adult age group between 30– 65 years of either sex.
2. Diagnosed cases of Chronic Stable Angina.
3. TMT positive cases.
4. Patient who met NYHA criteria.
5. Each patient was certified as of stable angina by the DM cardiologist.
6. Patients who are able to perform Treadmill Exercise Test.

Exclusion criteria:

1. Age below 30 and above 65 years.
2. Recent M.I. or PTCA less than three months.
3. Patients with conduction problem.
4. Uncontrolled hypertension.
5. Unstable Angina.
6. Serious concomitant disease of liver and kidney.
7. Malignancy.
8. Patients undergoing treatment for any other serious illness.

Assessment Criteria:

The confirmed cases of stable angina pectoris fulfilling the inclusion and exclusion criteria were assessed with subjective and objective criteria for the judgment of drug efficacy as under:

A. Subjective Parameters:

1. Pain (Borg Scale)
2. Dyspnoea

3. Burning Chest

4. Fatigue

5. NYHA (New York Heart Association) Score

6. EqoL-5D-Vas Score (European Quality of Life 5D Vas Score)

7. Number of Isosorbide Dinitrate 5 mg S/L tablets consumed daily.

Grading:

To assess the subjective tests of dyspnoea, burning of chest and fatigue gradation was done from 0 – 3 depending upon absence or presence of the same such as negative (0)and mild positive (1), moderate (2) and severe (3).

B. Objective parameters:

1. ECG (Electrocardiogram)

2. TMT (Treadmill Machine Exercise Stress Test)

3. Physical haemodynamic tests:

i. Body Mass Index (BMI)

ii. Heart Rate (HR)

iii. Systolic Blood Pressure (SBP)

iv. Diastolic Blood Pressure (DBP)

4. Laboratory Blood Chemistry Tests as under:

i. Haemoglobin

ii. Blood Sugar Random

iii. Lipid Profile:

a) Total Cholesterol (TC)

b) High Density Lipoprotein (HDL)

c) Low Density Lipoprotein (LDL)

d) Very Low Density Lipoprotein (VLDL)

e) Triglyceride (TG)

Methodology:

CRFs (Case Record Forms) were duly filled and signed by the research scholar. Sixtypatients were divided into two groups.

Group A: 30 patients (ISMN Control Group)

Group B: 30 patients (Nagarjunabhra Ras Trial Group) or NAR group

Group A control group patients received treatment orally as under:

1. Tab. Aspirin 150 mg OD i.e. once daily

2. Tab. Clopidogrel 75 mg OD i.e. once daily

3. Tab. Metoprolol XL 50 mg OD i.e. once daily

4. Tab. Isosorbide Mononitrate 20 mg BD i.e. twice daily

5. Tab. Atorvas 20 mg OD i.e. once daily

6. Tab. Isosorbide Dinitrate 5 mg S/L SOS i.e. when needed as rescue medicine

Group B trial group patients were given per oral as under:

1. Cap. Nagarjunabhra Ras BD i.e. twice daily

2. Tab. Aspirin 150 mg OD i.e. once daily

3. Tab. Clopidogrel 75 mg OD i.e. once daily

4. Tab. Metoprolol XL 50 mg OD i.e. once daily

5. Tab. Atorvas 20 mg OD i.e. once daily

6. Tab. Isosorbide Dinitrate 5 mg S/L SOS i.e. when required as rescue medicine

Study Period and Follow up Protocol:

A 90 days study was conducted to evaluate the anti anginal efficacy of Nagarjunabhra Ras in comparison to coronary vasodilator Isosorbide Mononitrate. Base line values were collected on 0 day of the study. Thereafter patients were revaluated for all parameters after every one month on 30th day, 60th day and finally on 90th day after the completion of the study.

Physical and Laboratory Tests:

Following tests were done to assess test drug efficacy upon:

1. BMI (Body Mass Index) to judge effects on physical body mass.

2. SBP (Systolic Blood Pressure) to judge effect of the trial drug upon after -load pressure on heart.

3. DBP (Diastolic Blood Pressure) to see effect on preload pressure.

4. Herat Rate per minute at rest to find out effect on electrophysiology of heart.

5. Haemoglobin (Hb) % to nullify false anginal effect.

6. Blood Sugar Random which uncontrolled may affect study.

7. Lipid Profile values in blood to see effect of the drug in coronary artery disease patho-physiology.

Exercise stress test:

This is the most widely used test to establish or confirm the diagnosis of ischemic heart disease. It is also valuable in the assessment of anti-anginal efficacy of a therapy or the drug. There is recording of 12 leads ECG before, during and after exercise on a treadmill or a bicycle ergometer. It is employed to induce angina. The characterization of ST segment abnormalities suggesting angina is based on international standards of exercise protocol and accepted criteria. Due to its more objective character it is assumed that it provides evidence of drug mediated anti-ischemic effect. Improvement in total exercise time i.e. exercise capacity, maximum MET level achieved i.e. maximum work load achieved, maximum heart rate and the double product are standard parameters to prove the positive drug effects. Regression in ST segment depression in mm in chest leads and time taken to induce ischaemia i.e. time to 1 mm ST depression are indicative of restoration of health of heart muscles after administration of a drug.

Treadmill testing (TMT) methodology:

Patients were called for TMT at any time of the day with condition not had taken caffeinated drink, smoking, snacks or meal 3 hours before testing. Sports shoes and loose fitting wears were provided by the testing centre. Temperature of the testing room was kept comfortable with air-conditioning. Preliminary 12 leads ECG were performed on all subjects. After skin preparation electrodes were applied at right places as specified. Data of the patients such as name, age, sex, weight, BP and targeted heart rate were filled in the soft-ware programmer of the TMT machine; Allenger's Gemini-A-DX model. TMT was done according to Bruce protocol under the supervision of cardiologist at submaximal level when targeted heart rate achieved. BP was recorded at the end of every3 minute's stage and entered. At least 1 mm ST – segment depression after the J point was considered as positive indication. Patients were instructed if any of the following complaints occur during the test they are to switch off the emergency button or to tell immediately:

1. Severe dyspnoea or fatigue
2. Intolerable severe chest pain.
3. Severe sweating or sudden fall of BP
4. Tachycardia or bradycardia
5. Elevation of systolic BP.

Data of each patient was obtained on thermal ECG paper and analysed by the cardiologist.

TMT was done to evaluate exercise capacity for provocative ischemia, arrhythmia and fall in blood pressure if any, on following parameters:

1. Total exercise time taken.
2. MET level i.e. Maximum work load attained.
3. Time taken to 1 mm ST depression in any one lead.
4. Maximum Double Product i.e. Systolic Heart Rate x Blood Pressure (RPP) at peak.
5. Maximum ST segment depression in mm in chest leads v5 and v6.

6. Test End reasons.

Angina log:

Patient's experience of angina pain is recorded in an angina log sheet provided by the investigator. The daily frequency, severity, duration of anginal pain and concomitant use of short acting nitrates tablets are registered by the patient.

Ethical Consideration:

The study was conducted with Good Clinical Practices. Prior approval of the Tilak Maharashtra Vidyapeeth's Institutional Ethical Committee was taken. Provisions were specified for withdrawal from the study for any reason. Patients Information and written consents in local Hindi Language were taken. Consents were also signed by patients' attendants and witnesses were obtained. Patients' identity, medical condition and data were kept undisclosed maintaining strict confidentiality. Case record forms (CRF) and protocol had provisions for mention of adverse events during study in any case.

Statistical Analysis:

Data collected were compiled, tabled and subjected to appropriate statistical analysis using Wilcoxon Signed Rank for observations on gradation ordinal scale. For comparison between subjective parameters Mann Whitney U test was used. And for quantitative observations paired t-test was used to test significance between two groups. P-values less than 0.05 were considered as significant.

Medication plan:

Anti-anginal modern allopathic drugs – Aspirin, Clopidogrel, Metoprolol, Atorvas, Ismo and Sorbitrate were supplied by chemist. Ayurvedic Nagarjunabhra Ras tablets were procured from a well reputed renowned Ayurvedic Pharmacy. Quality control tests for Nagarjunabhra Ras tablets were performed at Naresh Hospital's Pharmacy Lab by the scholar himself. Tablets were grounded to fine powder and encapsulated to hide the identity, 300 mg each in

weight. 60 capsules were filled in each plastic vial viable for 30 days and encoded. All the medicines were administered as per dosages schedule prescribed by standard pharmacological and classical ayurvedic texts.

Nagarjunabhra Ras:

A classical mineral drug (Ras-medicine) is a compound of 100 puti Abhraka Bhasma and T. Arjuna bark's aqueous extract. Abhraka Bhasma is triturated till dry with decoction of Arjuna bark for seven times. Thereafter 250-300 mg of each tablet is prepared. One tablet twice daily is prescribed to be taken with potable lukewarm water or honey or with Arjuna bark's decoction twice daily, better two hours before or after meals.

Preparation of 100 puti abhraka bhasma:

Abhraka, Black Mica is Biotite mineral ore, formula $(HK)^2$ $(MgFe)^2$ $(AlFe)^2$ $(SiO4)^2$,is taken for bhasma preparation. Its clods are available at ayurvedic grocers, raw drug material suppliers in the market. The procedure of making nano-ash (bhasma) begins with abhraka purification (*shodhan*) i.e. making it liable for further processing. For that, 1 Kg of raw material was taken and heated till red then soaked in 7 litres of cow's milk for seven times in an earthen jar. After purification abhraka material is subjected to make powder by burning it in *gajaput* (cow-dung cakes' fire in a pit of size one *gaja* i.e. 3 X 3 X 3 feet) at a temperature of 750°-800° C with 4 litres of cow's urine in a sealed earthen casserole. Another method for purification is *dhanyabhraka* method. First method is followed by modern pharmacies and that too is acceptable and is authenticated by Rasacharyas. On self-cooling of the cooked Abhraka, a soft and fragile swollen abhraka material was obtained. Then it was powdered with pressure of palms or hammers and separated the trash material; sieved in a bucket full of water and left for 1 hour to settle the heavy material and dust in the bottom; the floating abhraka material was collected and dried in sun. That was finally further subjected to incineration (*bhasmikarana* i.e. *marana*); but this material was still lustrous hence first

subjected to making it lustreless; for that abhraka material was cooked for 7 times with equal quantity of *gur* (jaggery) plus ¼th of *navasadar* in gajaput agni. On becoming lustreless that material is triturated with different herbs' material which is specified for *abhraka marak – gana* (a group of substances used for abhraka incineration) e.g., trifala, aloe juice, gomutra, bhringraja, cow's milk, arka dugdha, vat-dugdha, vat-ankura, kaakmachi, ashwgandha,guduchi, kantakari, gokharu, mustaka, apamarg, vasapatra, kutaki, dhatura, tulasi, gur,erandmoola, palaka etc. 64 plants materials and bio-products. Methods of processing is triturating till dried. After each process the material was cooked in gajaput agni. This process was repeated 100 – 1000 times to make the nano-bhasma of abhraka. This bhasma is advised to be used for medicinal purpose. Improperly cooked bhasma is never recommended for use, not at all.

Preparation of T. Arjuna bark's decoction (kwath):

There is lot of adulteration in raw herbs' material; therefore it should be pharmacognostically examined by a trained chemist before use. Arjuna bark's coarse powder is soaked in potable water 8 times more in quantity and left for maceration, overnight. After12 hours that water and bark is boiled gently till left ¼ approximately. Later filtered and collected water is subjected to triturate with 100 puti abhraka bhasma till dry. This is called one bhavana of the Arjuna barks' kwath (decoction).

Quality Control and Standardisation of Trial Drug Nagarjunabhra Ras:

Before medication of Trial drug; Quality control and Standardisation of Nagarjunabhra Ras was necessary, though manufacturing company assures that. Yet, it was essential to ensure to have a good quality drug for the research work; therefore, scholar tried its best to get it tested in a government approved lab but unsuccessfully. Drug testing labs were unaware of the rasa-medicines test standards and either not ready to do in stipulated time limits. Scholar got it tested in one approved lab unsatisfactorily as that lab could not analyse except iron content

only. And while the scholar had in-house facility of preparing and testing drugs for clinical practice, hence it was decided to do it himself. Therefore prior to the clinical trial; procured drug was analysed here as under. A study for which was published elsewhere.[8] Separation of Terminalia Arjuna extract and Abhraka Bhasma from Nagarjunabhra Ras tablets was done by employing diffusion method and dry contents obtained by steam bath and hot air dryer.

Trial drug sample analysed for **Physico-chemical determinants** as under:

1. Moisture contents (Loss on Drying)
2. Total Ash
3. Acid insoluble ash
4. Water soluble ash
5. Alcohol soluble extractive
6. Water soluble extractive

Similarly **Primary Phyto-chemical screening** was done for presence of:

1. Tannins
2. Saponins
3. Terpenoids
4. Steroids
5. Flavonoids
6. Cardiac-glycosides
7. Combined Anthraquinones
8. Free Anthraquinones
9. Alkaloids
10. Reducing sugar.

All qualitative and quantitative values analysed as per API and WHO guidelines for herbal medicine standards.

ANALYSIS AND INTERPRETATION

Observation and Results

Total 60 cases of chronic stable angina were tried for the anti-anginal efficacy study of Nagarjunabhra ras in Delhi-NCR zone approved by the TMV, Pune ethical committee. All subjects fulfilling the criteria of inclusion and exclusion provisions of the study protocol were studied. They were randomly allocated in two groups i.e. 30 patients in each group.

Treatment Groups

Table I

	Group A Control Group Isosorbide Mononitrate	Group B Trial Group Nagarjunabhra RAS
No. of Patients (n=60)	30	30

Demographic Profile:

Table II

Showing Age and Sex Distribution

Age Group (Years)	**Total**	**Group A Control Group**			**Group B Trial Group**		
		M	**F**	**% age**	**M**	**F**	**% age**

≤50	27	12	00	40	12	02	47
51-60	30	14	02	53	11	02	43
>60	03	02	00	07	02	01	10
Total	60	28	02	100	25	05	100

Age:

In Group A, 40 % population was below 50 years of age, 53 % was between 51-60 years and 7 % was more than 60 years of age. In Group B, 47 % patients were below 50 years of age, 43 % were between 51-60 years and 10 % of the population was more than 60 years of age.

Sex:

In group A, out of 30 patients, 28 patients (93.3 %) were male and 2 (6.7 %) were female. And in Group B, 25 (83.3 %) were male and 5 (16.7 %) were female patients.

Table III

Showing Mean & Range of Age

Group	Range (Years)	Mean Age (Years)
Group A	30 – 61	50.43 ± 9.54 SD
Group B	35 – 65	51.36 ± 9.34 SD
Combined	30 – 65	50.89 ± 9.44 SD

In group A, the age varied from30 – 65 years; a mean of 50.43 ± 9.54 SD years. While in group B, the age varied from 35 – 65 years with a mean of 51.36 ± 9.34 SD years. Mean age for all patients was 50.89 ± 9.44 SD years and it ranged from 30 – 65 years.

Baseline Parameters:

Table IV

Showing Physical Parameters

Parameters	Range	Group A (Mean)	Group B (Mean)
BMI	17 – 34.2	24.4±3.9	24.7±3.6
Hear Rate (bpm)	55 – 132	82.4±12.5	85.5±16.3
SBP (mmHg)	80 – 170	126±31.3	131.3±19.4
DBP (mmHg)	60 – 110	84.3±13.0	87.6±14.7

BMI (Body Mass Index):

Table No. IV shows various baseline parameters. Minimum BMI was 17 and maximum BMI was 34.2. In group A, mean BMI was 24.4 ± 3.9 SD, while in group B, mean BMI was 24.7 ± 3.6.

Heart Rate:

In the sample minimum heart rate was 55 bpm and maximum HR was 132 bpm. In group A, mean HR was 82.4 ± 12.5 SD bpm; while in group B, it was 85.5 ± 16.3 bpm.

Blood Pressure:

Systolic blood pressure (SBP) ranged in the sample between 80 – 170 mmHg; minimum SBP noted being 80 mmHg and maximum SBP being 170 mmHg. Mean SBP in group A was 126 ± 31.3 SD; and in group B was 131 ± 19.4 SD.

Diastolic blood pressure (DBP) was ranged between 60 – 110 mmHg; lowest DBP was 60 mmHg and highest DBP was 110 mmHg. The mean DBP in group A was 84.3 ± 13.0 mmHg; and in group B was 87.6 ± 14.7 mmHg.

Table V

Showing Laboratory Parameters

Parameters	**Group A**		**Group B**	
	Range	Mean	Range	Mean
Hb (gm %)	9 – 14.7	12.6±1.4	10 – 15.2	12.3±1.5
Blood Sugar Random	78 – 175	113.9±28.8	65 – 235	109.6±32.4
Total Cholesterol	82 – 270	190.5±54.7	90 – 285	161.8±41.3
HDLC	17 – 66	34.2±13.1	16 – 49	29.3±10.3
LDLC	54 – 220	119.8±50.3	40 – 190	107.3±33.9
VLDLC	10 – 58	27.4±12.4	7 – 65	25.2±11.0
Triglyceride	50 – 420	160.2±80.3	65 – 217	128.5±35.1
S. Creatinine	0.5 – 1.6	0.9 ± 0.3	0.5 – 1.6	1.3±0.3
SGOT	22.7 – 54.1	32.6 ± 10.7	11.5 – 136.1	33.8 ± 29.2
SGPT	17.6 – 61.18	38.5 ± 13.3	15.7 – 95	32.6 ± 20.1

Haemoglobin (Hb):

Haemoglobin level in Group A ranged between 9 – 14.7 gm % with a mean value of 12.6±1.4 gm %, while in Group B it was 10 – 15.2 gm % and mean value was 12.3±1.5 gm %.

Random Blood Sugar (RBS):

Blood Sugar level at random in Group A was 78 – 175 mg % having a mean value of 113.9 ± 28.8 mg %. In Group B range of blood sugar level was 65 – 235 mg % with a mean blood sugar level of 109.6 ± 32.4 mg %.

Total Cholesterol (TC):

Total Serum Cholesterol varied from 82 – 270 with a mean of 190.5 ± 54.7 mg % in Group A. In Group B it was 90 – 285 mg %; mean 161.8 ± 41.3 mg %.

High Density Lipoprotein Cholesterol (HDLC):

High Density Lipoprotein Cholesterol in Group A was 17 – 66 mg % with a mean value of 34.2 ± 13.1 mg % and in Group B was 16 – 49 mg % and mean 29.3 ± 10.3 mg %.

Low Density Lipoprotein Cholesterol (LDLC):

LDLC was found between 54 mg % to 220 mg % in Group A patients with a mean value of 119.8 ± 50.3 mg %. In Group B, it was 40 – 190 mg % and a mean was107.3 ± 33.9 mg %.

Very Low Density Lipoprotein Cholesterol (VLDLC):

VLDLC in Group A was in a range of 10 – 58 mg % and mean was 27.4 ± 12.4 mg %. In Group B VLDL it was ranged from 7 mg % - 65 mg % and mean was 25.2 ± 11.0 mg %.

Triglycerides (TG):

TG level in Group A patients was varying from 50 – 240 mg %. Mean was 160.2 ± 80.3. And in Group B TG level was 65 – 217 mg % with a mean value of 128.5 ± 35.1 mg %.

Serum Creatinine:

Serum Creatinine value collected in Group A patients was between 0.5 – 1.6 mg % with a mean value of 0.9 ± 0.3 mg %; and in Group B it was 0.5 – 1.6 mg % and a mean of 1.3 ± 0.3 mg %.

Serum glutamic oxaloacetic transaminase (SGOT):

SGOT enzyme presented in selected patients of Group A was ranging between 22.7 – 54.1 mg % with a mean of 32.6 ± 10.7 mg %; and in group B patients it ranged between 11.5 – 136.1 mg % and a mean of 33.8 ± 29.2 mg %.

Serum glutamic pyruvic transaminase (SGPT):

SGPT levels in the serum of selective patients were ranging from 17.6 – 61.8 mg % with a mean value of 38.5 ± 13.3 Mg % in Group A. While in Group B patients it ranged from 15.7 – 95 mg %; and mean value was 32.6 ± 20.1 mg %.

Risk Factors:

Table VI

Showing Risk Factors

Risk Factors	Total	Group A	Group B
Smoking	**47 (78.3%)**	**24 (80%)**	**23 (76.6%)**
Fat Rich Diet	**58 (96.6%)**	**28 (93.3%)**	**30 (100%)**
Sedentary Lifestyle	**31 (51.6%)**	**15 (50%)**	**16 (53.3%)**
Diabetes	**7 (11.6%)**	**3 (10%)**	**4 (13.3%)**
Alcohol	**6 (10%)**	**5 (16.6%)**	**1 (3.3%)**

Hypertension	**32 (53.3%)**	**16 (53.3%)**	**16 (53.3%)**
Previous-MI/CAD	**24 (40%)**	**14 (46.6%)**	**10 (33.3%)**
Family History	**11 (18.3%)**	**5 (16.6%)**	**6 (20%)**
Stress	**39 (65%)**	**19 (63.3%)**	**20 (66.6%)**

Dietary factor i.e. fat rich diet was the major risk factor. From 60 patients, 58 (96.6%) were having abundant ghee or vegetables oil or tail in diet. Other risk factors in decreasing numbers were smoking 47 (78.3%), stress 39 (65%), hypertension 32 (53.3%), sedentary inactive leisure sitting life style 31 (51.6%), previous CAD 24 (40%), family history 11 (18.3%), DM 7 (11.6%) and alcohol 6 (10%).

Smoking:

In Group A, 24 (80%) and in Group B 23 (76.6%) patients had history of smoking. Overall in all 60 patients, 47 (78.3%) had smoking history.

Fat Rich Diet:*(Ahara)*

Ghee, tail and vegetable oil in rich quantities was found in 58 (96.6%) patients out of 60. In Group A there were 28 (93.3%) patients and in Group B, all 30 (100%) patients were found consuming one or the other form of fat in diet abundantly.

Sedentary lifestyle: (*Vihara*)

Out of total 60, 31 (51.6%) patients were living a leisurely inactive sedentary life style either at home or in office or at workplace. 15 (50%) in Group A and 16 (60%) in Group B subjects were at ease.

Diabetes Mellitus: (*Madhumeha*)

Three patients (10%) in Group A and four (13.3%) in Group B, thus making a total seven (11.6%) in number had diabetes mellitus.

Alcohol:

5 (16.6%) patients in Group A and 1 (3.3%) patient in Group B had history of alcoholism. In 60 patients alcoholism was found in 6 (10%) patients.

Hypertension:

16 (53.3%) patients in Group A were hypertensive whereas in equal number 16 (53.3%) subjects were found in Group B. A total of 32 (53%) patients out of 60 had history of HTN.

CAD/ Previous MI/Post-PTCA:

Total 24 (40%) out of 60 were having pre-diagnosed coronary artery disease who previously had CAG or MI or Post-PTCA. In Group A, they constitute 14 (36.6%) and 10 (13.3%), in Group B.

Family History:

Five (16.6%) patients in Group A and six (20%) in Group B had family history of ischemic heart disease; a total of eleven (18.3%) out of sixty patients had this.

Mental Stress:

This attributed the second most factor in coronary artery diseases having a big chunk of 39 (65%) out of 60 patients overall. In Group A 19 (63.3%); and 20 (66.6%) in Group B were found stress full in clinical subjective assessment.

Clinical Observations:

Data collected of individuals on subjective parameters for variable shown in tables as follow before study (on day 0) and after the completion of the study (on day 90). Baseline data was compared with the final result mean for statistical validation.

Table VII

Showing Subjective Observations

Variables	Group A	Group B	p-value
Relief of chest pain on Borg Scale	30 (100%)	30 (100%)	
Relief in dyspnoea	30 (100%)	30 (100%)	
Relief in burning chest	30 (100%)	29 (96.66%)	
Relief in fatigue	30 (100%)	30 (100%)	
NYHA score improved	30 (100%)	30 (100%)	
EQoL 5D VAS score improved	30 (100%)	30 (100%)	
Reduction in no. of ISDN tablets use	19 (63.33%)	19 (63.33%)	

All patients from both the groups got relief in chest pain 30 out of 30 i.e. 100%. All 30 patients out of 30 had 100% relief in dyspnoea; relief in burning chest was observed in all 30/30 (100%) in group A and in group B 29/30 (96.66%); all patients relieved of fatigue 30/30 (100%) in group A and 30/30 (100%) in group B; 30/30 (100%) patients showed improvement in NYHA scores and EQoL 5D VAS scores in both groups A and B. Reduction in consumption of ISDN tablets in numbers was equally found in both A and B groups i.e. 19 patients from total 30 patients in each group; 63.33 % in group A and 63.33 % in group B.

Table VIII

Showing Pain Scores on Borg Scale

Pain (Borg scale)	Median		Wilcoxon Signed Rank W	P-Value	% Effect	Result
	BT	AT				
Group A	3	0	-4.777[a]	0.000	92.7	Significant
Group B	3	0	-4.906[a]	0.000	96.4	Significant

Since observations are on ordinal scale (gradations), we have used Wilcoxon Signed Rank test to test efficacy in Group A and Group B. From above table we can observe that P-Values for Group A and Group B are less than 0.05. Hence we conclude that effects observed in both groups are significant.

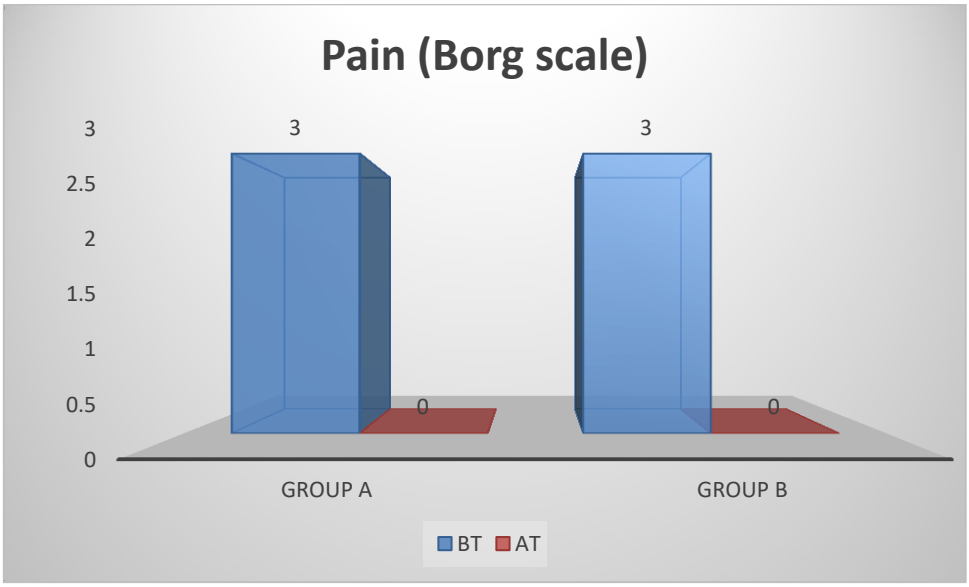

Fig. 1

Table IX

Showing Dyspnoea Scores

Dyspnoea score	Median		Wilcoxon Signed Rank W	P-Value	% Effect	Result
	BT	AT				
Group A	1	0	-5.014[a]	0.000	100.0	Significant
Group B	1	0	-4.983[a]	0.000	97.6	Significant

Since observations are on ordinal scale (gradations), we have used Wilcoxon Signed Rank test to test efficacy in Group A and Group B. From above table we can observe that P-Values for Group A and Group B are less than 0.05. Hence we conclude that effects observed in both groups are significant.

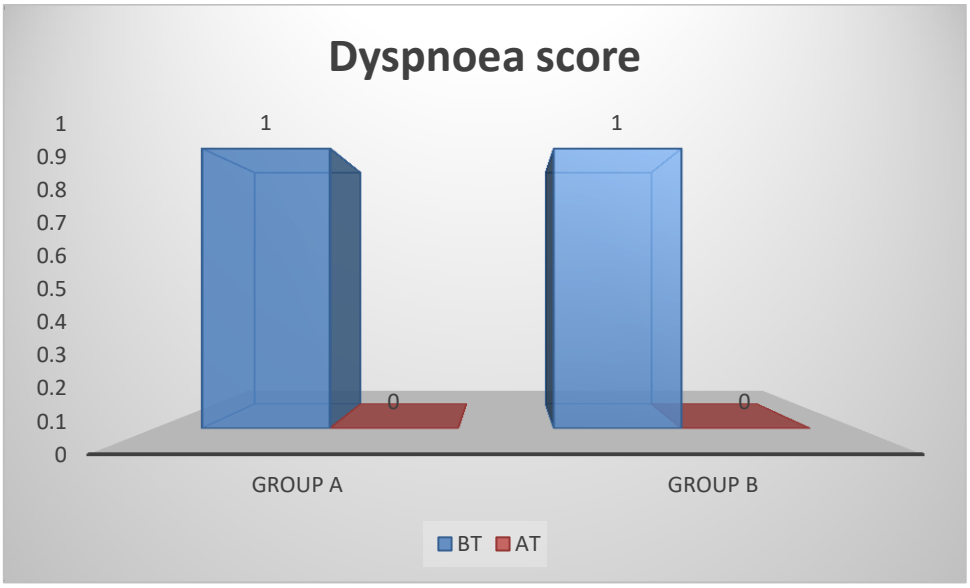

Fig. 2

Table X

Showing Burning Chest scores

Burning chest	Median		Wilcoxon Signed Rank W	P-Value	% Effect	Result
	BT	AT				
Group A	1	0	-5.303[a]	0.000	100.0	Significant
Group B	1	0	-5.108[a]	0.000	97.3	Significant

Since observations are on ordinal scale (gradations), we have used Wilcoxon Signed Rank test to test efficacy in Group A and Group B. From above table we can observe that P-Values for Group A and Group B are less than 0.05. Hence we conclude that effects observed in both groups are significant.

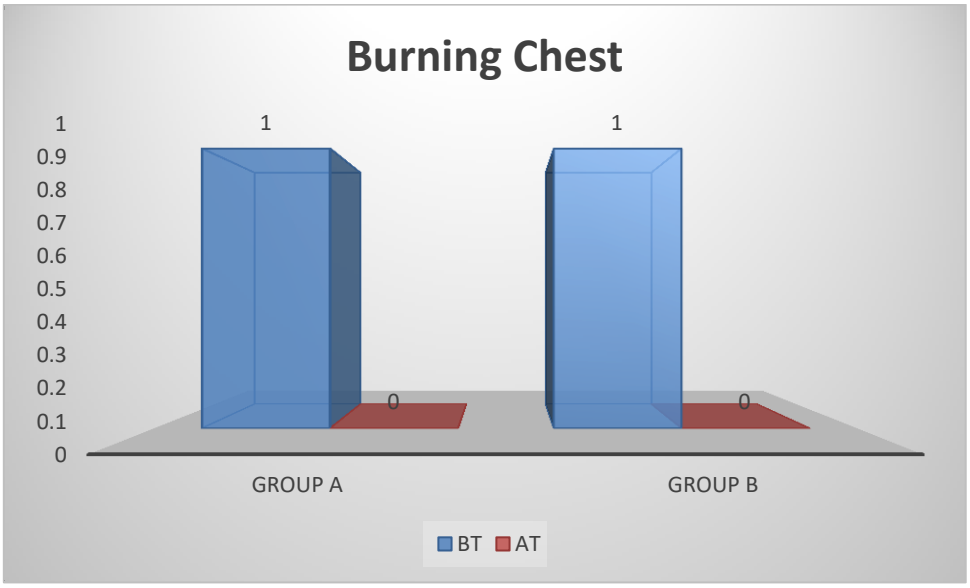

Fig. 3

Table XI

Showing Fatigue Score

Fatigue score	Median		Wilcoxon Signed Rank W	P-Value	% Effect	Result
	BT	AT				
Group A	1	0	-5.231[a]	0.000	100.0	Significant
Group B	1	0	-4.956[a]	0.000	100.0	Significant

Since observations are on ordinal scale (gradations), we have used Wilcoxon Signed Rank test to test efficacy in Group A and Group B. From above table we can observe that P-Values for Group A and Group B are less than 0.05. Hence we conclude that effects observed in both groups are significant.

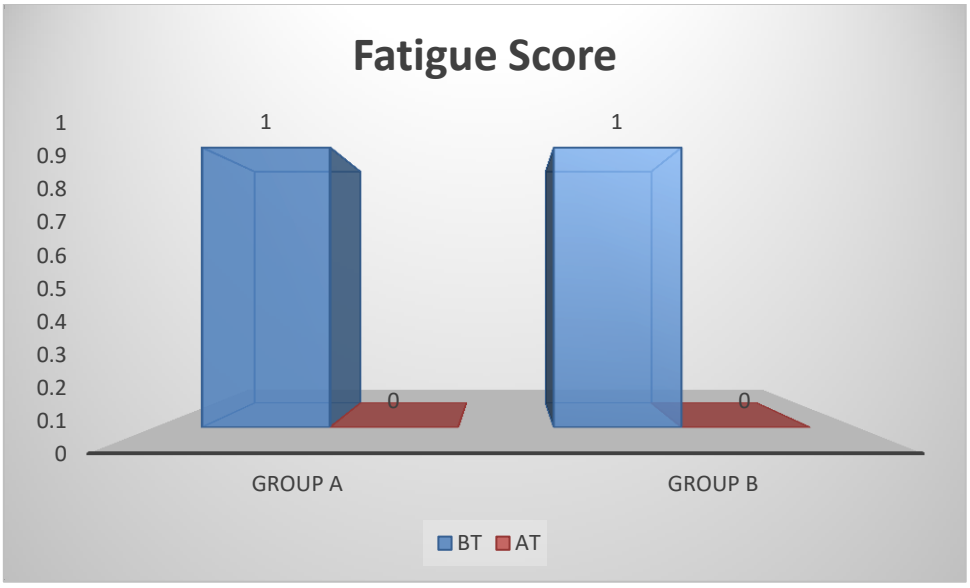

Fig. 4

Table XII

Showing NYHA Scores

NYHA Score	Median		Wilcoxon Signed Rank W	P-Value	% Effect	Result
	BT	AT				
Group A	2	1	-5.058[a]	0.000	55.6	Significant
Group B	2	1	-5.152[a]	0.000	53.8	Significant

Since observations are on ordinal scale (gradations), we have used Wilcoxon Signed Rank test to test efficacy in Group A and Group B. From above table we can observe that P-Values for Group A and Group B are less than 0.05. Hence we conclude that effects observed in both groups are significant.

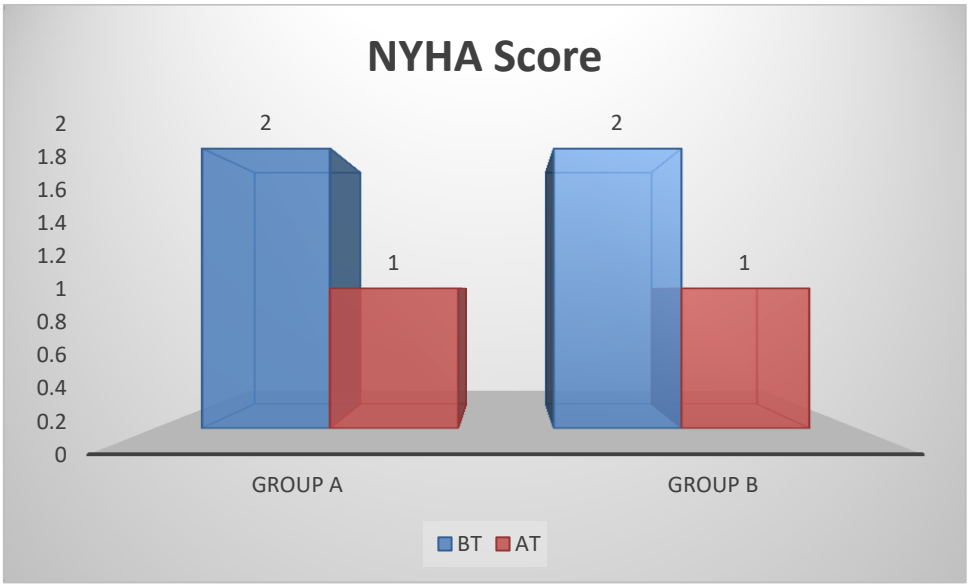

Fig. 5

Table XIII

Showing European Quality of Life 5 Dimensions VAS Scores

EQoL5DVAS Score	Median		Wilcoxon Signed Rank W	P-Value	% Effect	Result
	BT	AT				
Group A	2	1	-5.303[a]	0.000	50.0	Significant
Group B	2	1	-5.152[a]	0.000	51.5	Significant

Since observations are on ordinal scale (gradations), we have used Wilcoxon Signed Rank test to test efficacy in Group A and Group B. From above table we can observe that P-Values for Group A and Group B are less than 0.05. Hence we conclude that effects observed in both groups are significant.

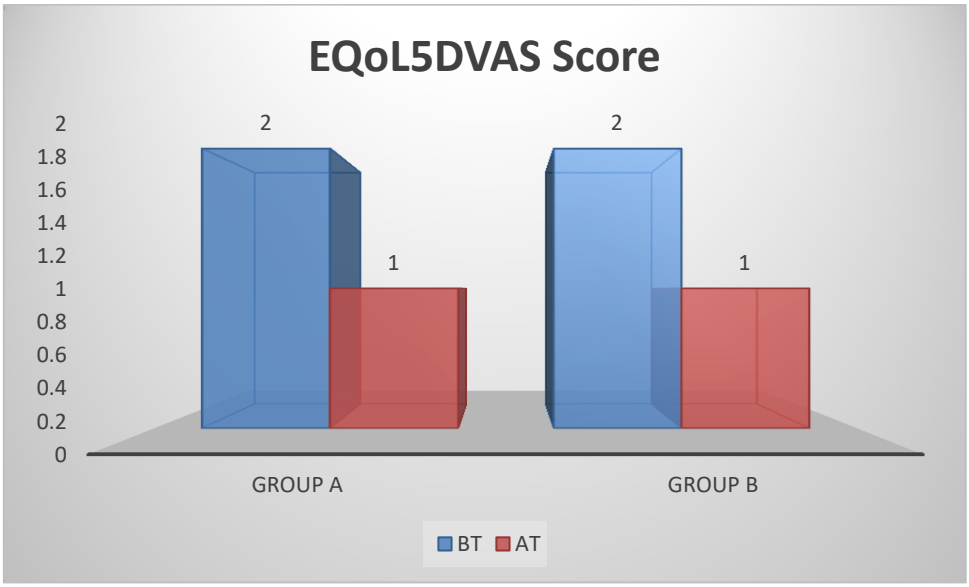

Fig. 6

Table XIV

Showing Number of Isosorbide Dinitrate 5 mg sub-lingual tablets consumption

No. of ISDN s/l tablets used	Median		Wilcoxon Signed Rank W	P-Value	% Effect	Result
	BT	AT				
Group A	1	0	-3.787[a]	0.000	97.2	Significant
Group B	1	0	-4.097[a]	0.000	97.4	Significant

Since observations are on ordinal scale (gradations), we have used Wilcoxon Signed Rank test to test efficacy in Group A and Group B. From above table we can observe that P-Values for Group A and Group B are less than 0.05. Hence we conclude that effects observed in both groups are significant.

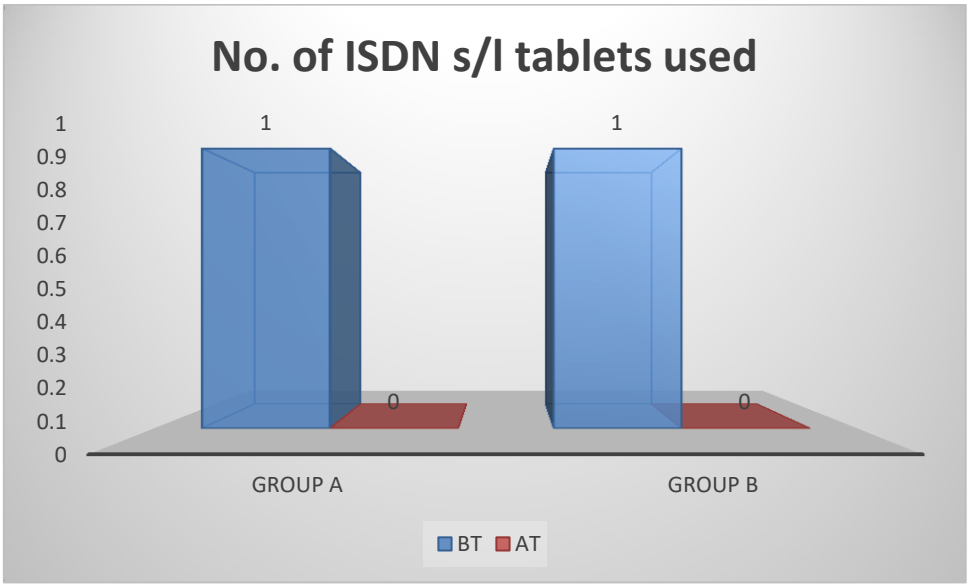

Fig. 7

Table XV: Comparison between Group A and Group B (Subjective Parameters):

	Group	N	Mean Rank	Sum of Ranks	Mann-Whitney U	P-Value
Pain (Borg scale)	Group A	30	27.55	826.50	361.500	0.157
	Group B	30	33.45	1003.50		
	Total	60				
Dyspnoea score	Group A	30	28.17	845.00	380.000	0.186
	Group B	30	32.83	985.00		
	Total	60				
Burning chest	Group A	30	27.60	828.00	363.000	0.059
	Group B	30	33.40	1002.00		
	Total	60				
Fatigue score	Group A	30	25.65	769.50	304.500	0.053
	Group B	30	35.35	1060.50		
	Total	60				

NYHA Score	Group A	30	30.08	902.50	437.500	0.783
	Group B	30	30.92	927.50		
	Total	60				
EQoL5DVAS Score	Group A	30	28.08	842.50	377.500	0.054
	Group B	30	32.92	987.50		
	Total	60				
No. of ISDN s/l tablets used	Group A	30	29.35	880.50	415.500	0.595
	Group B	30	31.65	949.50		
	Total	60				

For comparison between Group A and Group B, Mann -Whitney U test was applied. From above table we can observe that P-Values for all parameters are greater than 0.05. Hence we conclude that there is no significant difference in Group A and Group B.

Table XVI

Showing Body Mass Index

BMI		Mean	N	SD	SE	t-Value	P-Value	% Change	Result
Group A	BT	24.47	30	3.98	0.73	4.434	0.000	3.3	Sig
	AT	23.66	30	3.35	0.61				
Group B	BT	24.71	30	3.69	0.67	4.336	0.000	3.7	Sig
	AT	23.81	30	3.49	0.64				

Since observations are quantitative, we have used paired t-test to test significance in Group A and Group B. From above table we can observe that P-Values for Group A and Group B are less than 0.05. Hence we conclude that changes observed in both groups are significant.

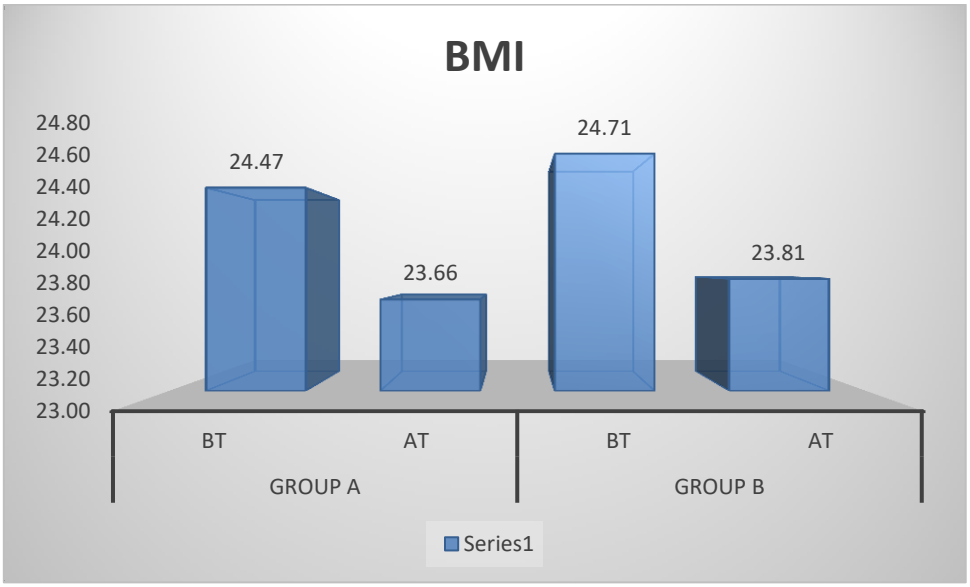

Fig. 8

Table XVII

Showing Systolic Blood Pressure

SBP		Mean	N	SD	SE	t-Value	P-Value	% Change	Result
Group A	BT	129.33	30	20.33	3.71	1.338	0.191	3.9	NS
	AT	124.33	30	10.73	1.96				
Group B	BT	132.33	30	19.60	3.58	4.168	0.000	8.8	Sig
	AT	120.67	30	11.43	2.09				

Since observations are quantitative, we have used paired t-test to test significance in Group A and Group B. From above table we can observe that P-Value for Group A is greater than 0.05 and Group B is less than 0.05. Hence we conclude that change observed in Group A is not significant while Group B is Significant.

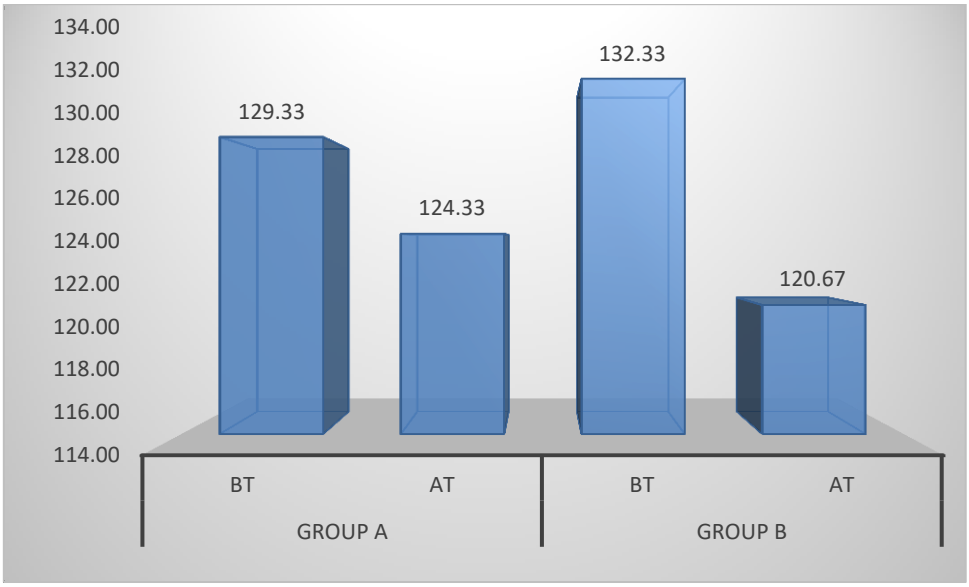

Fig. 9

Table XVIII

Showing Diastolic Blood Pressure

DBP		Mean	N	SD	SE	t-Value	P-Value	% Change	Result
Group A	BT	85.00	30	14.32	2.62	1.114	0.274	3.1	NS
	AT	82.33	30	8.98	1.64				
Group B	BT	88.33	30	15.33	2.80	3.102	0.004	7.9	Sig
	AT	81.33	30	10.42	1.90				

Since observations are quantitative, we have used paired t-test to test significance in Group A and Group B. From above table we can observe that P-Value for Group A is greater than 0.05 and Group B is less than 0.05. Hence we conclude that change observed in Group A is not significant while Group B is Significant.

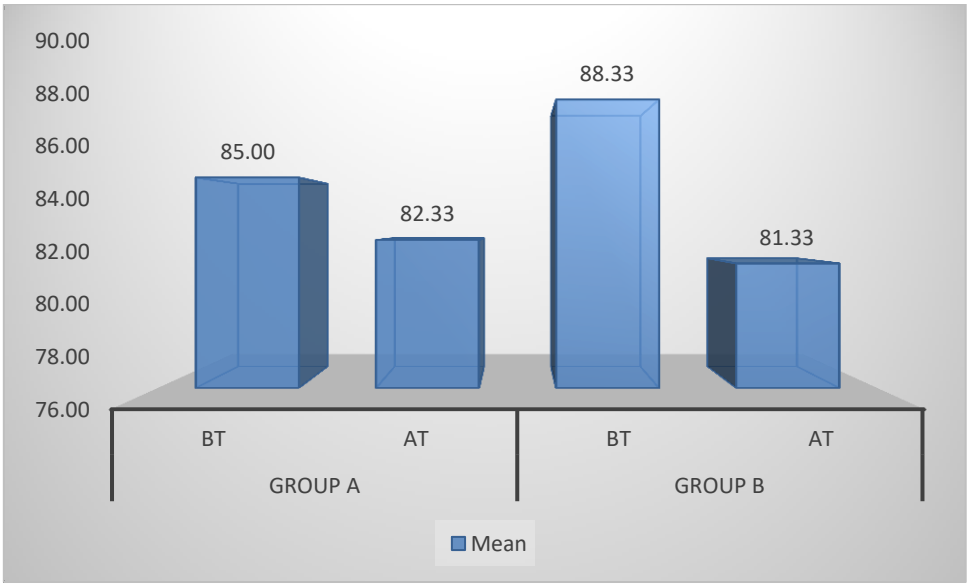

Fig. 10

Table XIX

Showing Heart Rate

HR		Mean	N	SD	SE	t-Value	P-Value	% Change	Result
Group A	BT	82.80	30	12.28	2.24	1.002	0.324	3.5	NS
	AT	79.87	30	13.93	2.54				
Group B	BT	84.57	30	16.24	2.97	2.290	0.029	9.0	Sig
	AT	76.97	30	9.77	1.78				

Since observations are quantitative, we have used paired t-test to test significance in Group A and Group B. From above table we can observe that P-Value for Group A is greater than 0.05 and Group B is less than 0.05. Hence we conclude that change observed in Group A is not significant while Group B is Significant.

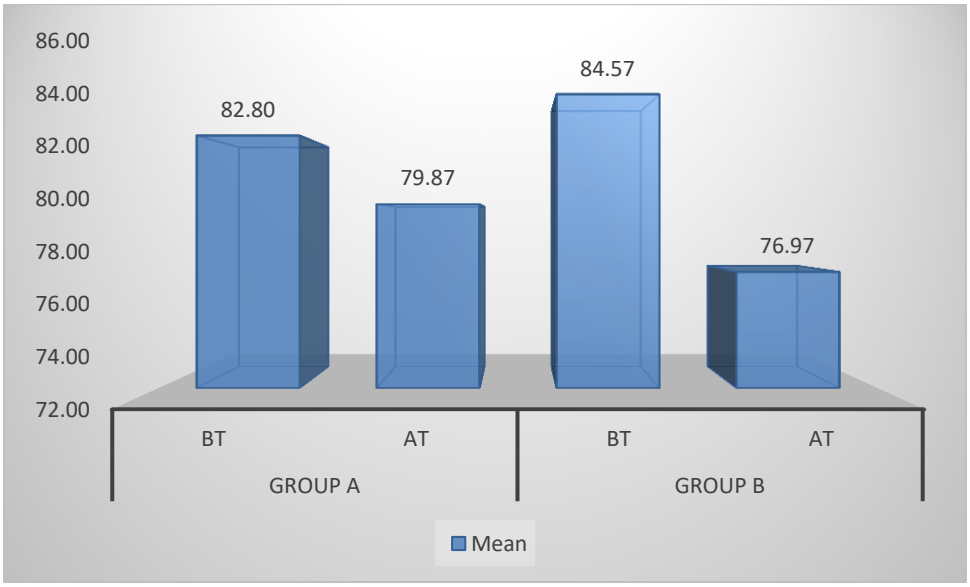

Fig. 11

Laboratory Parameters:

Table XX

Showing Haemoglobin

Hb		Mean	N	SD	SE	t-Value	P-Value	% Change	Result
Group A	BT	12.75	30	1.28	0.23	0.342	0.735	0.6	NS
	AT	12.67	30	1.33	0.24				
Group B	BT	12.29	30	1.51	0.28	-1.519	0.140	2.3	NS
	AT	12.58	30	1.09	0.20				

Since observations are quantitative, we have used paired t-test to test significance in Group A and Group B. From above table we can observe that P-Values for Group A and Group B are greater than 0.05. Hence we conclude that changes observed in both groups are not significant.

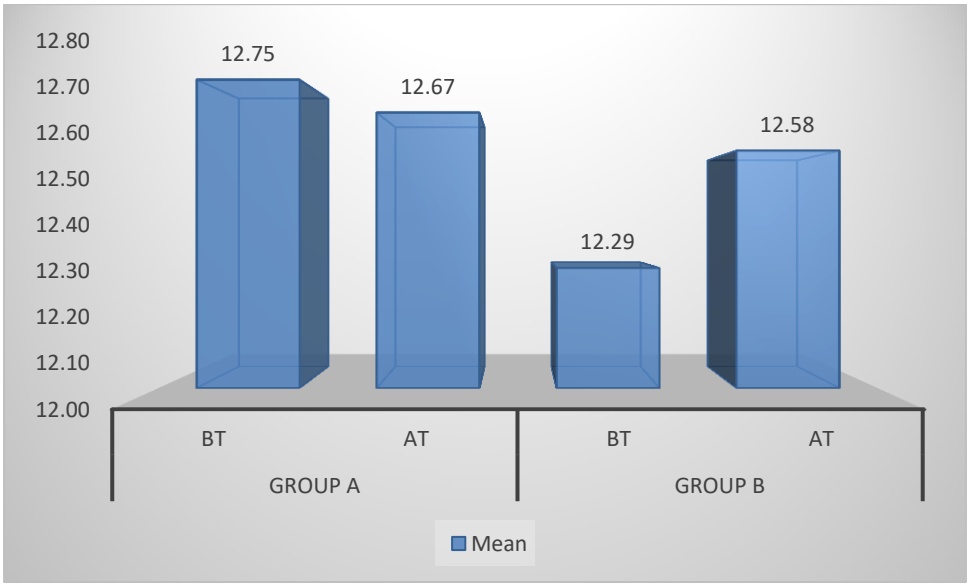

Fig. 12

Table XXI

Showing Blood Sugar Level

BSL		Mean	N	SD	SE	t-Value	P-Value	% Change	Result
Group A	BT	111.83	30	27.89	5.09	1.958	0.060	8.5	NS
	AT	102.30	30	23.63	4.31				
Group B	BT	109.73	30	32.35	5.91	0.316	0.755	2.1	NS
	AT	107.44	30	19.03	3.47				

Since observations are quantitative, we have used paired t-test to test significance in Group A and Group B. From above table we can observe that P-Values for Group A and Group B are greater than 0.05. Hence we conclude that change observed in both groups is not significant.

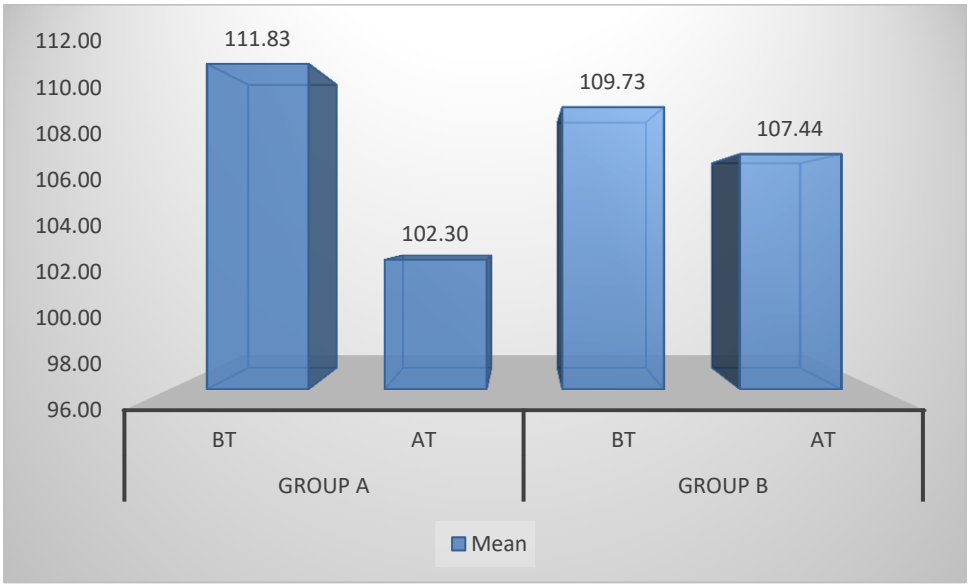

Fig. 13

Table XXII

Showing Total Cholesterol

Total cholesterol mg / dl		Mean	N	SD	SE	t-Value	P-Value	% Change	Result
Group A	BT	184.67	30	54.06	9.87	4.308	0.000	16.1	Sig
	AT	154.90	30	33.95	6.20				
Group B	BT	163.53	30	42.86	7.83	4.403	0.000	15.2	Sig
	AT	138.70	30	28.95	5.29				

Since observations are quantitative, we have used paired t-test to test significance in Group A and Group B. From above table we can observe that P-Values for Group A and Group B are less than 0.05. Hence we conclude that change observed in both groups is significant.

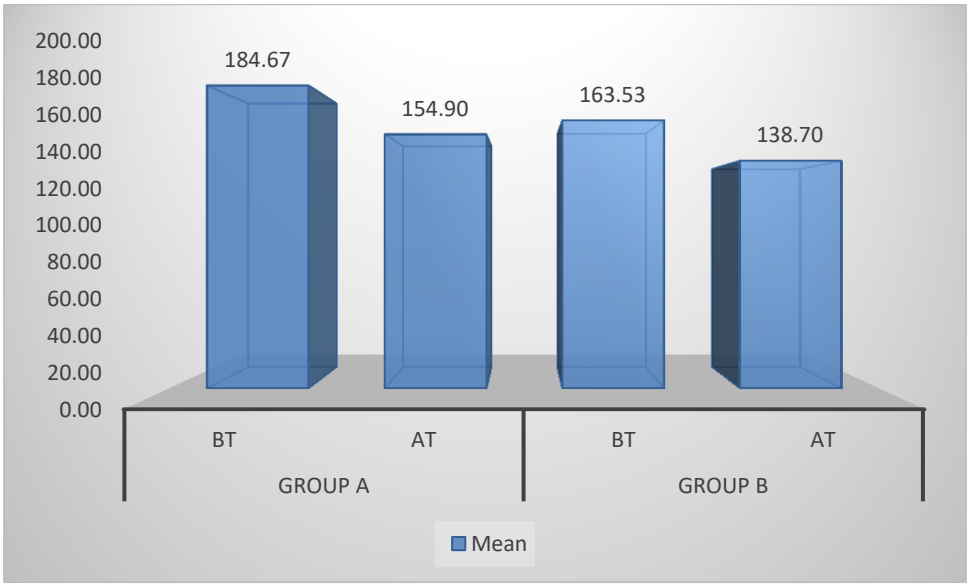

Fig. 14

Table XXIII

High Density Lipoprotein:

HDL		Mean	N	SD	SE	t-Value	P-Value	% Change	Result
Group A	BT	34.50	30	13.29	2.43	1.198	0.240	7.6	NS
	AT	31.87	30	8.78	1.60				
Group B	BT	29.77	30	11.20	2.05	-0.726	0.474	3.9	NS
	AT	30.92	30	9.11	1.66				

Since observations are quantitative, we have used paired t-test to test significance in Group A and Group B. From above table we can observe that P-Values for Group A and Group B are greater than 0.05. Hence we conclude that change observed in both groups is not significant.

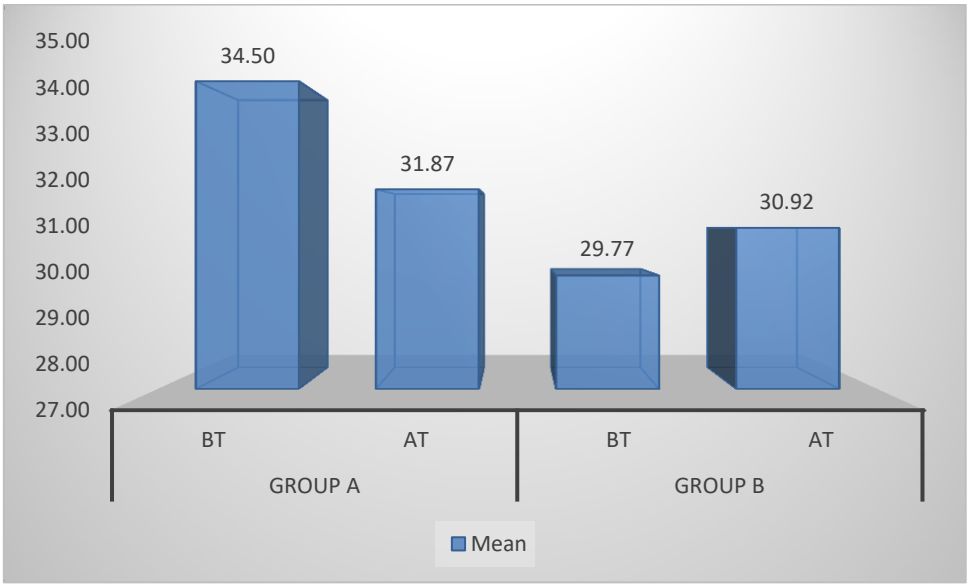

Fig. 15

Table XXIV

Showing Low Density Lipoprotein

LDL		Mean	N	SD	SE	t-Value	P-Value	% Change	Result
Group A	BT	112.40	30	50.16	9.16	2.658	0.013	14.7	Sig
	AT	95.83	30	35.31	6.45				
Group B	BT	108.07	30	37.71	6.89	3.694	0.001	18.0	Sig
	AT	88.57	30	25.08	4.58				

Since observations are quantitative, we have used paired t-test to test significance in Group A and Group B. From above table we can observe that P-Values for Group A and Group B are less than 0.05. Hence we conclude that change observed in both groups is significant.

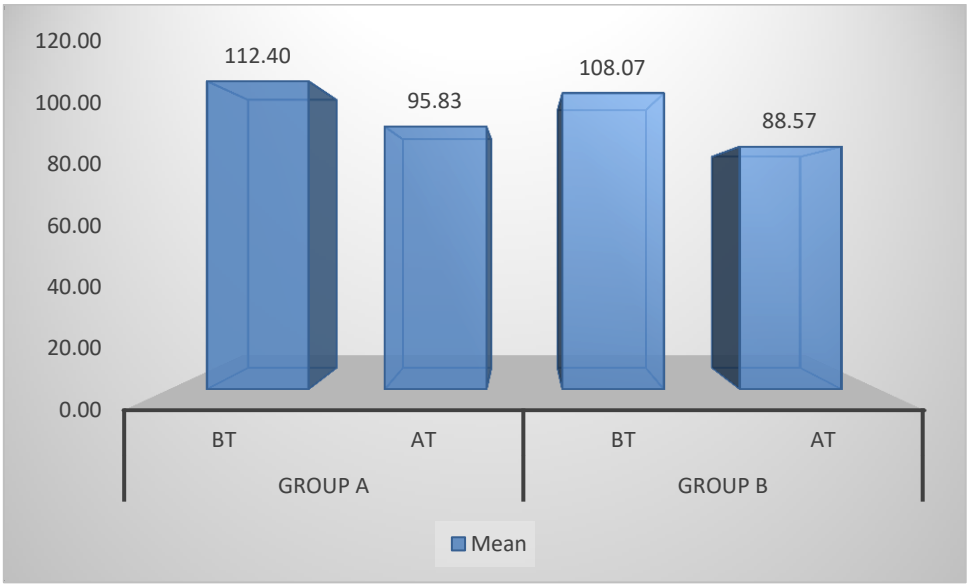

Fig. 16

Table XXV

Showing Very Low Density Lipoprotein

VLDL		Mean	N	SD	SE	t-Value	P-Value	% Change	Result
Group A	BT	29.94	30	18.60	3.40	1.975	0.058	18.2	NS
	AT	24.50	30	13.77	2.51				
Group B	BT	25.04	30	10.92	1.99	2.675	0.012	22.4	Sig
	AT	19.44	30	6.87	1.25				

Since observations are quantitative, we have used paired t-test to test significance in Group A and Group B. From above table we can observe that P-Value for Group A is greater than 0.05 and Group B is less than 0.05. Hence we conclude that change observed in Group A is not significant while Group B is Significant.

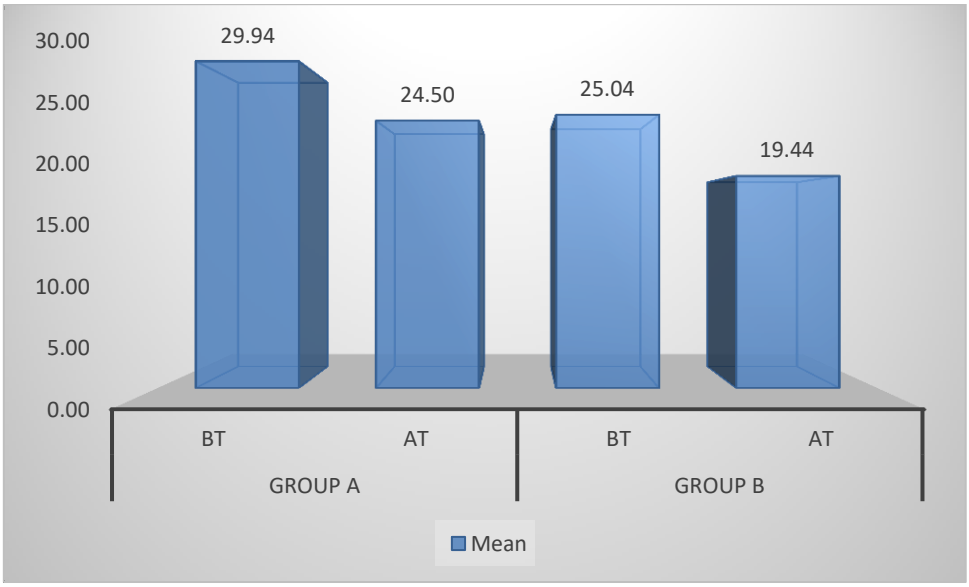

Fig. 17

Table XXVI

Showing Triglycerides

Triglycerides		Mean	N	SD	SE	t-Value	P-Value	% Change	Result
Group A	BT	161.90	30	83.39	15.23	2.785	0.009	22.5	Sig
	AT	125.53	30	38.05	6.95				
Group B	BT	128.10	30	34.51	6.30	2.968	0.006	14.9	Sig
	AT	109.01	30	35.00	6.39				

Since observations are quantitative, we have used paired t-test to test significance in Group A and Group B. From above table we can observe that P-Values for Group A and Group B are less than 0.05. Hence we conclude that change observed in both groups is significant.

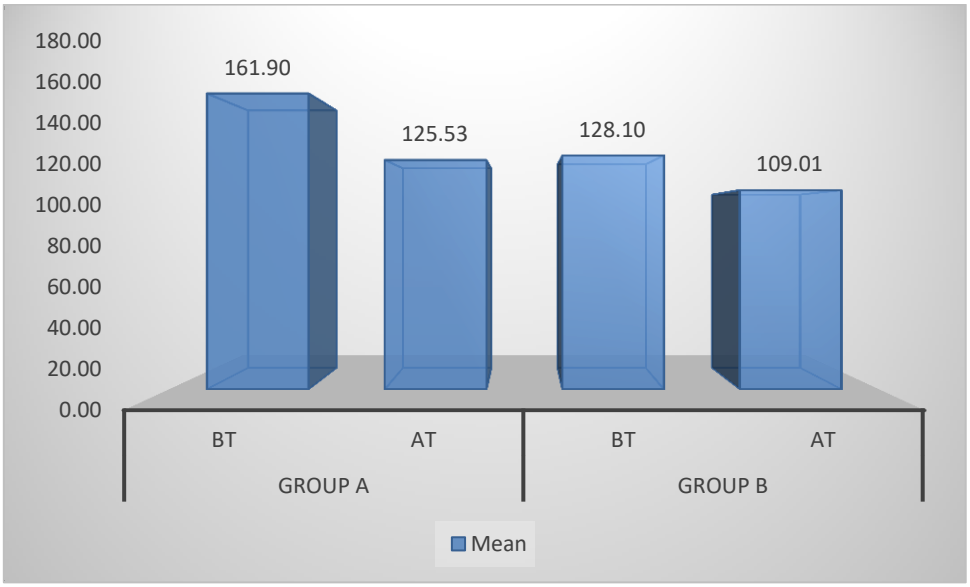

Fig. 18

Treadmill Exercise Test: Table XXVII

Showing Metabolic Equivalents (MET)

MET level at peak		Mean	N	SD	SE	t-Value	P-Value	% Change	Result
Group A	BT	8.54	29	2.65	0.49	-6.127	0.000	22.5	Sig
	AT	10.46	29	2.62	0.49				
Group B	BT	8.08	30	2.58	0.47	-8.464	0.000	28.4	Sig
	AT	10.37	30	2.75	0.50				

Since observations are quantitative, we have used paired t-test to test significance in Group A and Group B. From above table we can observe that P-Values for Group A and Group B are less than 0.05. Hence we conclude that change observed in both groups is significant.

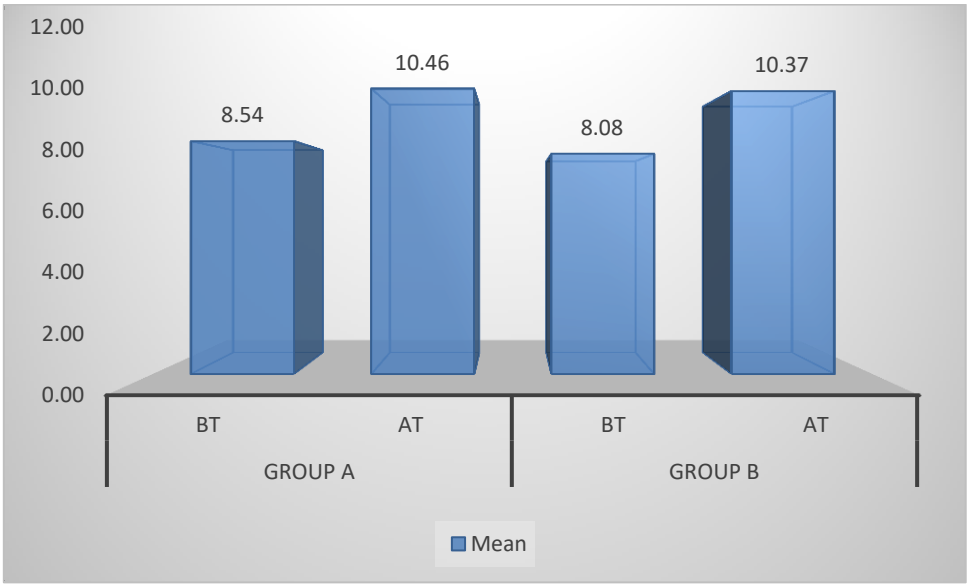

Fig. 19

Table XXVIII

Showing Double Product (Rate Pressure Product): HR X SBP

Double Product (Rate Pressure Product)		Mean	N	SD	SE	t-Value	P-Value	% Change	Result
Group A	BT	21760.00	30	7692.84	1404.51	-3.101	0.004	15.5	Sig
	AT	25133.33	30	7318.34	1336.14				
Group B	BT	23000.00	30	7150.89	1305.57	-0.019	0.985	0.1	NS
	AT	23020.00	30	7083.02	1293.18				

Since observations are quantitative, we have used paired t-test to test significance in Group A and Group B. From above table we can observe that P-Value for Group A is less than 0.05 and Group B is greater than 0.05. Hence we conclude that change observed in Group A is significant while Group B is not Significant.

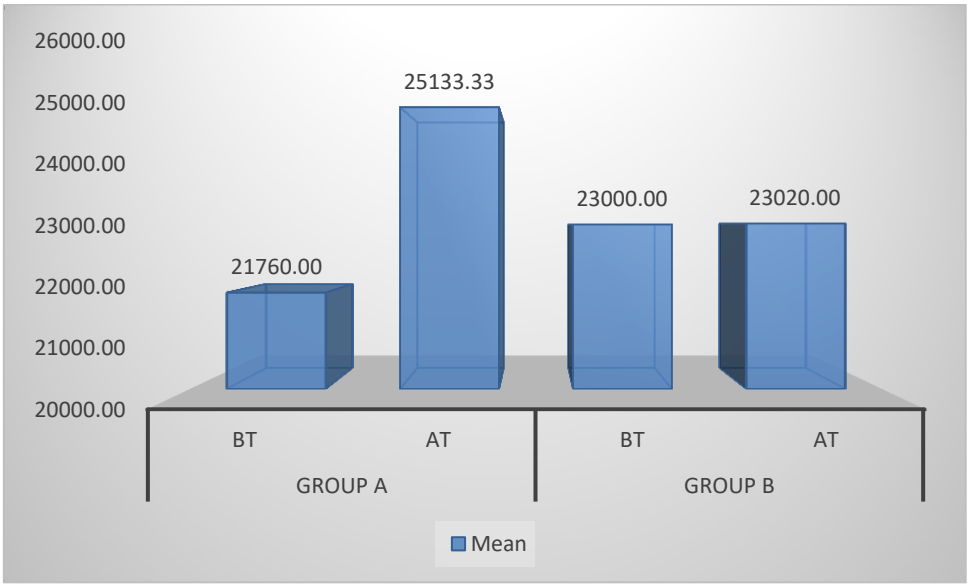

Fig. 20

Table XXIX

Showing Maximum ST Depression in V5 Chest Lead

Max. ST depression in lead V5 in mm		Mean	N	SD	SE	t-Value	P-Value	% Change	Result
Group A	BT	1.57	30	0.74	0.13	3.507	0.001	34.2	Sig
	AT	1.03	30	0.71	0.13				
Group B	BT	2.12	30	1.13	0.21	5.686	0.000	44.7	Sig
	AT	1.17	30	0.79	0.14				

Since observations are quantitative, we have used paired t-test to test significance in Group A and Group B. From above table we can observe that P-Values for Group A and Group B are less than 0.05. Hence we conclude that change observed in both groups is significant.

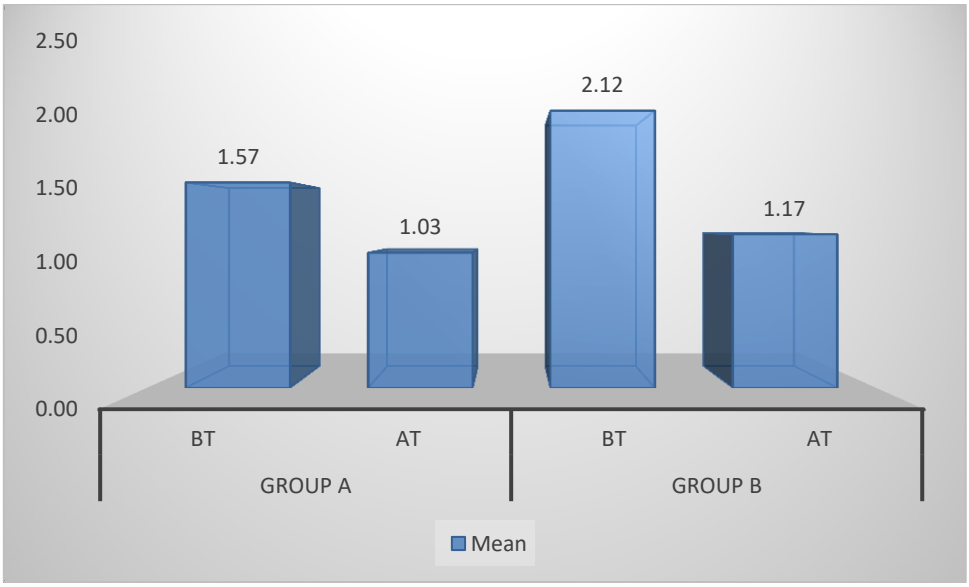

Fig. 21

Table XXX

Showing Maximum ST Depression in Chest Lead V6

Max. ST depression in lead V6 in mm		Mean	N	SD	SE	t-Value	P-Value	% Change	Result
Group A	BT	1.40	30	0.57	0.10	4.956	0.000	43.3	Sig
	AT	0.79	30	0.60	0.11				
Group B	BT	1.97	30	1.14	0.21	5.637	0.000	47.8	Sig
	AT	1.03	30	0.72	0.13				

Since observations are quantitative, we have used paired t-test to test significance in Group A and Group B. From above table we can observe that P-Values for Group A and Group B are less than 0.05. Hence we conclude that change observed in both groups is significant.

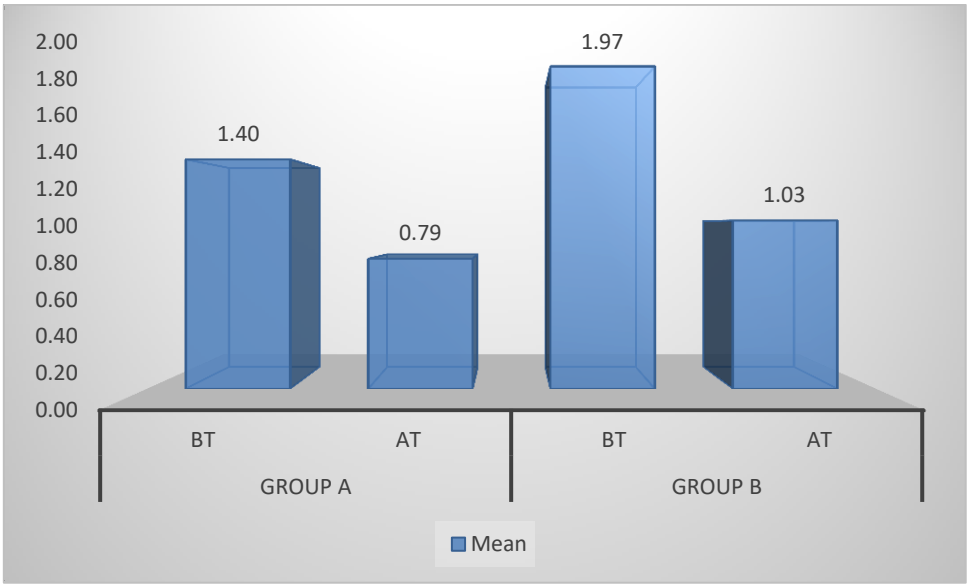

Fig. 22

Table XXXI

Showing Total Exercise Time

Total exercise time in seconds		Mean	N	SD	SE	t-Value	P-Value	% Change	Result
Group A	BT	429.97	30	180.23	32.90	-6.203	0.000	26.1	Sig
	AT	542.03	30	154.29	28.17				
Group B	BT	394.67	30	150.45	27.47	-7.730	0.000	34.9	Sig
	AT	532.43	30	166.84	30.46				

Since observations are quantitative, we have used paired t-test to test significance in Group A and Group B. From above table we can observe that P-Values for Group A and Group B are less than 0.05. Hence we conclude that change observed in both groups is significant.

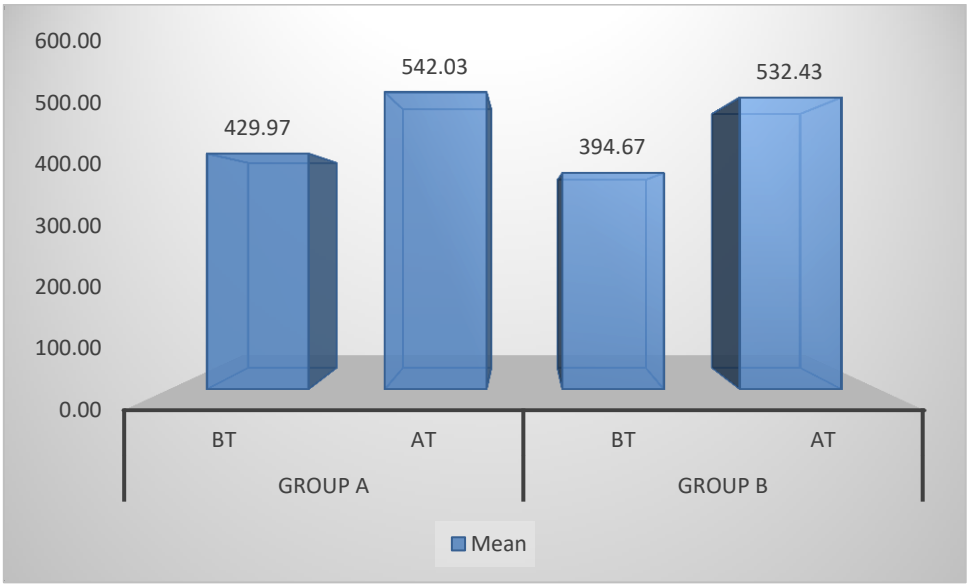

Fig. 23

Table XXXII

Showing Time Taken to 1 mm ST Depression

Time to 1 mm ST depression in seconds		Mean	N	SD	SE	t-Value	P-Value	% Change	Result
Group A	BT	265.40	30	124.96	22.81	-4.734	0.000	56.7	Sig
	AT	415.90	30	130.58	23.84				
Group B	BT	230.70	30	120.60	22.02	-8.318	0.000	82.3	Sig
	AT	420.47	30	118.45	21.63				

Since observations are quantitative, we have used paired t-test to test significance in Group A and Group B. From above table we can observe that P-Values for Group A and Group B are less than 0.05. Hence we conclude that change observed in both groups is significant.

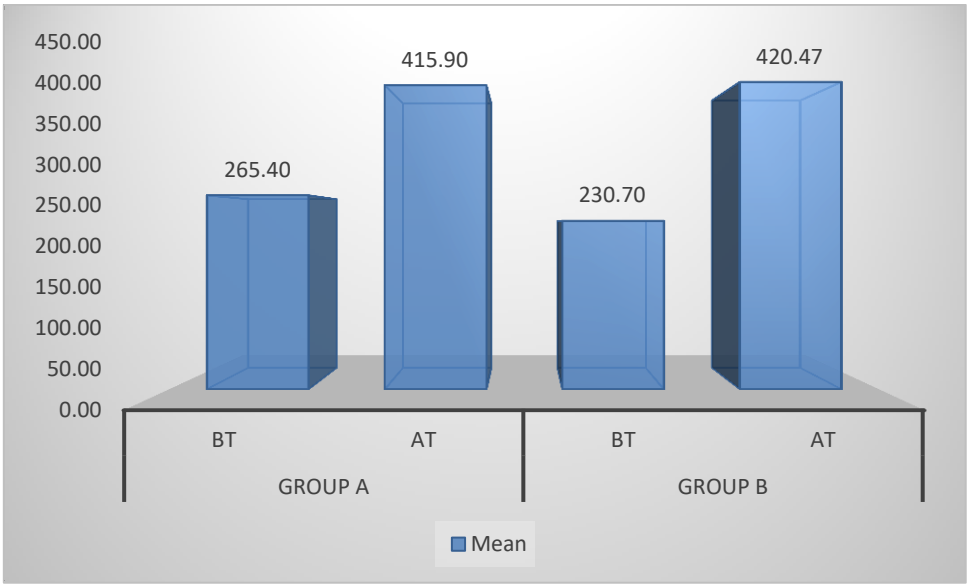

Fig. 24

Table XXXIII: Comparison between Group A and Group B (Objective Parameters)

Variable	Group	N	Mean	SD	SE	t-Value	P-Value
BMI	Group A	30	0.99	0.81	0.15	-1.065	0.292
	Group B	30	1.21	0.79	0.14		
SBP	Group A	30	16.33	12.99	2.37	0.214	0.831
	Group B	30	15.67	11.04	2.02		
DBP	Group A	30	9.33	9.44	1.72	-0.705	0.483
	Group B	30	11.00	8.85	1.62		
HR	Group A	30	13.27	9.15	1.67	-0.198	0.844
	Group B	30	13.87	13.83	2.52		
Hb	Group A	30	1.00	0.78	0.14	1.012	0.316
	Group B	30	0.81	0.69	0.13		
BSL	Group A	30	22.20	17.19	3.14	-0.552	0.583
	Group B	30	25.69	30.03	5.48		
Total cholesterol mg / dl	Group A	30	38.63	28.37	5.18	1.262	0.212
	Group B	30	29.77	26.00	4.75		
HDL	Group A	30	8.37	8.92	1.63	0.986	0.328
	Group B	30	6.44	5.88	1.07		
LDL	Group A	30	26.83	26.54	4.85	0.246	0.807
	Group B	30	25.23	23.88	4.36		
VLDL	Group A	30	11.65	10.85	1.98	1.212	0.231
	Group B	30	8.47	9.48	1.73		
Triglycerides	Group A	30	59.43	53.20	9.71	2.815	0.007
	Group B	30	28.58	27.80	5.07		
MET level at peak	Group A	30	2.51	2.41	0.44	0.321	0.749
	Group B	30	2.35	1.40	0.26		
Double Product (Rate Pressure Product)	Group A	30	5426.67	4100.46	748.64	0.947	0.347
	Group B	30	4500.00	3448.74	629.65		
Max. ST depression in lead V5 in mm	Group A	30	0.88	0.44	0.08	-1.038	0.303
	Group B	30	1.05	0.78	0.14		
Max. ST depression in lead V6 in mm	Group A	30	0.73	0.52	0.10	-2.102	0.040
	Group B	30	1.08	0.74	0.13		
Total exercise time in seconds	Group A	30	112.07	87.20	15.92	1.614	0.109
	Group B	30	137.77	67.20	12.27		
Time to 1 mm ST depression in seconds	Group A	30	150.50	92.60	16.91	1.982	0.057
	Group B	30	189.77	78.40	14.31		

For comparison between Group A and Group B we have used unpaired t-test. From above table we can observe that P-Values for almost parameters are greater than 0.05. Hence we conclude that there is no significant difference between Group A and Group B.

Table XXXIV

Showing Results of Physico-chemical Analyses of different samples:

Sample	Moisture-content	Total – Ash	Acid-insoluble Ash	Water soluble Ash	Alcohol soluble extractive	Water soluble extractive
TABark	4.2% (<8.0%)	24% (≤25%)	15.5% (≤1%)	0.5%	20.8% (≥20%)	22.4% (≥20%)
NAR	8.0% (<8.0%)	53%	47.5%	2%	Nil	20%
TAE-NAR	5.6% (<8.0%)	16%	4.5%	11%	0.2%	85.6%

***TABark**=Terminalia Arjuna Bark; **NAR**= Nagarjunabhra Rasa; **TAE-NAR**= Terminalia Arjuna dry Extract obtained from Nagarjunabhra Rasa.

*** API reference values are given in brackets with sample values.**

Table XXXV

Showing Results of phyto-chemical screening of different samples:

Constituent	TA Bark	NAR	TAE-NAR
Tannins	+	+/-	+/-
Saponins	+	+/-	+/-
Terpenoids and Steroids	+ -	+ -	+ -
Flavonoids	+	-	-
Cardiac –glycosides	+	+	+
Combined Anthraquinones	+	+/-	+
Free Anthraquinones	-	-	-
Alkaloids	+	+	+
Reducing sugars	+	+/-	+/-

Note: + ve = present; - ve = absent

Above results in both tables showed compatible values of good quality trial drug Nagarjunabhra rasa in terms of presence of Terminalia Arjuna bark's extractive.

Photo showing Trial Drug

Discussion

Hridshula, specified as Angina Pectoris in contemporary medicine and recognised by Ayurvedic scholars, has been a major health concern all over the world. As per WHO it has emerged as an epidemic for few decades.[80] In developing countries including India it is rising steadily with severe complications.[79,80] Hridshula has a wide and variable presentation – from stable angina to acute coronary syndrome. In Modern medicine there have been developed various treatment modalities for different conditions in continuum for cure and secondary prevention. In Ayurveda system there has been a limited approach. Chronic stable angina and refractory angina has been successfully treated with various formulations either herbal or herbo-mineral Ras compounds, but without any documentary proof. Given the serious side effects of drugs, drug-drug interactions, tolerance to almost all modern allopathic drugs, associated morbidity and mortality with the coronary diseases,[20,113] there has been need of improved therapeutic strategies. There has always been a search of newer anti-anginal drug and a longing of ayurvedists for comparatively effective medical management of stable angina patients within their own system. Here it is worth mentioning that one should not be confused with acute hridshula (unstable acute coronary syndrome) and chronic hridshula (stable form of angina). The present study deals with only stable form of chronic angina and the drug is tried in such patients.

Nagarjunabhra Ras, which contains 100 puti Abhraka nano-bhasma and aqueous extract of bark of Terminalia arjuna plant, has been often prescribed by ayurvedic physicians irrespective of *dosha, dhatu, desh, kaal, prakriti, agni* and *mal kalpana*[77] (views on physical constituent characteristics, disease patho-physiology and co-administered drugs etc.). Classically its both ingredients are said to be useful in all kind of hridroga and *shula* (pain).[115] In Ayurvedic theories Arjuna works by special effect (Prabhava). It is also explained Kapha-pitta-hrut (Ref. *Bhavaprakash Nighantu*). And Abhraka works by synergy (yogvahi)

accentuating action of Arjuna. Abhraka also has anti-tridosha property and relieves pain *(prashmitrujam)*[2] classical reference Rasratanasamuchchaya chapter 2/2. Thus, Nagarjunabhra Ras is said to be effective in hridshula.

Classically pharmaceutical composition of Nagarjunabhra ras varies as 100 puti and 1000 puti abhraka bhasma ingredients with seven bhavna of Terminalia Arjuna bark's kwath. Present formulation contains 100 puti abhraka bhasma. Rasacharyas has specified that for disease cure purpose 100 puti abhraka bhasma will suffice whereas for longevity, yoga samadhi and moksha attainment 1000 puti is wanted.[30]

Mode of action of Nagarjunabhra Ras in hridshula in terms of modern pharmacology is not known. There are no documental evidences available so far in this regard except classical ayurvedic references. According to Ayurveda it checks and cures *tridoshajanya* diseases and acts as *rasayana.* Probably biological effect of essential minerals, metabolites and phytochemicals found in Nagarjunabhra ras; in synchronic to its rasayana, tridoshghna, hrudya properties exhibits shoolhar parbhava. Arjuna and abhraka both work in synergy. Hrudya action of arjuna by special effect and prashmita ruja[2] property of abhraka combined work as hridshula hara.

Therefore, present study was undertaken to evaluate the clinical efficacy of Nagarjunabhra Ras in comparison to modern allopathic coronary vasodilator drug Isosorbide Mononitrate. Total 69 patients were enrolled for the study acknowledging 15–20 % drop-out rate. Out of which 9 patients left and could not continue; attrition for being lack of faith in the drug efficacy, unwillingness to pursue, fear of side effects and due to poor compliance. There was 13% drop out. Sixty patients continued as per study protocol. They were randomly divided into two groups of thirty in each **(Table I)**. Group A was given control drug Isosorbide Mononitrate 20 mg twice daily along with conventional drugs Aspirin 150 mg +

Clopidogrel 75 mg + and Metoprolol XL 50 mg + Atorvas 20 mg, all once daily. As a rescue medicine Isosorbide Dinitrate 5 mg sub-lingual tablet was also prescribed to take on onset of angina pain. Group B was administered trial drug Nagarjunabhra Ras encapsulated 300 mg tablet twice daily with lukewarm potable water along with Aspirin 150 mg + Clopidogrel 75 mg + Metoprolol XL 50 mg + Atorvas 20 mg all once daily with rescue medicine tablet ISDN 5 mg sun-lingual as and when needed to control angina pain.

The mean age in ISMN treated group A was 50.43±9.54 years (Range 30-61 years) while the NAR treated group B had a mean age of 51.36 ± 9.34 years (Range 35 – 65 years) **(Table III)**. Patients aged between 51 – 60 years constituted the main bulk i.e. 48.33 % of all patients **(Table II)**. Park K et al also reported that the peak period of coronary heart disease is attained between 51 – 60 years. Kocher et al done study also showed mean age 52 ± 9 years. Both are comparable to our study.[20]

In Group A there were 28 male patients and 2 were female out of total 30 patients while in group B there were 25 male and 5 female patients out of 30. This showed that 88.33 % were male and 11.66 % were female in the test population. This showed that there was male dominance in chronic stable angina coronary artery disease. Overall male female ratio in the study population was found 8.8:1.2. This was corresponding to results of studies conducted by Park et al and Kocher et al.[20]

Table IV was showing Physical parameters. In Group A mean **BMI** was 24.4±3.9 whereas in Group B 24.7±3.6. There was a range 0f 17 – 34.2 in all age groups. This showed that higher BMI patients have more inclination towards the CADs. Average **heart rate** of the patients in Group A was 82.4±12.5 bpm and in Group B patients mean HR was 85.5±16.3 bpm. Range in total study population was 55 – 132 bpm. This showed a trend of little higher

heart rate in CADs is related to higher incidences of angina pain, and slower heart rate may be seen due to myocardial dysfunction or effects of drugs being taken.

Blood pressure – systolic ranged between 80 – 170 mmHg. Mean systolic blood pressure in Group A was 126 ± 31.3 and in Group B was 131± 19.4. Diastolic blood pressure ranged between 60 – 110 mmHg. In Group A DBP was 84±13.0 and in Group B it was 87±14.7. This showed a high BP is directly proportional to CADs.

Table V showed baseline **Haemoglobin** range in total population was 9 – 15.2 gm %, while mean Hb in Group A was 12.6 ± 1.4 gm% and 12.3 ± 1.5 gm% in group B. This indicated within normal limits of Hb mean. **Random Blood Sugar** level range in total population was 65 – 235 mg %. Mean RBS in group A was 113.9 ± 28.8 mg % and in group B was 109.6 ± 32.4 mg%. It showed that angina and CAD patients have links with high sugar in the blood while in both the groups mean values were within normal limits feasible for finding the effects of the drug upon sugar level in the blood. **Total cholesterol** level in the blood ranged from 82 – 285 mg %; and mean TC in group A was 190.5 ± 54.7 mg % and 161.8 ± 41.3 mg % in group B showing that high cholesterol level in the blood is reason for CADs and angina while within normal limits of mean values will help in to judge the effects of the drugs if any in cholesterol. The **High Density Lipoprotein Cholesterol** (HDLC), the good cholesterol, ranged from 16 - 66 mg % in the test population with an average mean of 32.4 ± 13.1 mg % in group A and 29.3 ± 10.3 mg % in group B subjects. This showed a trend of low HDL level (<40 mg %) which is compatible to the finding in various studies in Indian population. **Low Density Lipoprotein (LDL) Cholesterol** level was in a range of 40 – 220 mg % with a mean of 119.8 ± 50.3 mg % in group A and 107.3 ± 33.9 mg % in group B which showed higher level of LDL, bad cholesterol, in the blood which said to be chiefly responsible for atherosclerosis and targeted to be controlled < 100 mg %. **Very Low Density Lipoprotein (VLDL)** ranged from 7 – 65 mg % and a mean of 27.4 ± 12.4 mg % in group A

and 25.2 ± 11.0 mg % in group B while **Triglyceride (TG)** was ranged between 50 – 420 mg% with mean 160.2 ± 80.3 mg% in group A and in group it ranged from 65 mg % - 217 mg % mean 128.5 ± 35.1 mg %. Both VLDL and TG, and in both groups A and B, were in consistence with the general concept that TG is generally five times higher to VLDL. **Serum Creatinine** was measured to judge adverse or toxic effects upon kidneys. Whole the test population in this study was ranged between 0.5 – 1.6 mg % mean in group A 0.9 ± 0.3 mg% and in group B 1.3 ± 0.3 mg% of Serum Creatinine showing normal kidney function. **Serum glutamic oxaloacetic transaminase (SGOT)** level in group A population was ranged between 22.7 mg % - 54.1 mg % mean of 32.6 ± 10.7 mg % and in group B it ranged between 11.5 mg % - 136.1mg %; a mean of 33.8 ± 29.2 mg %. Similarly **Serum glutamic pyruvic transaminase(SGPT)**test in group A was measured in a range of 17.6 mg % - 61.18 mg % mean 38.5 ± 13.3 mg %; and in group B it ranged between 15.7 – 95 mg% with a mean of 32.6±20.1 mg%; all within normal limit showing normal liver function test.

Table VI showed Risk Factors involved in Coronary artery disease and angina. These are found to be major causative factors in modern times. 78.3 % of the subject population was smoking *hukka* or *bidi* - cigarettes. 96.6 % of the subjects were having diet rich in ghee, oil or trans fats. Among the test population 51.6 % of people were living a sedentary life style. This showed that the people of above habits are more prone to have CAD. 53.3 % of the population was having hypertension. 65 % stress factor and 42 % previous MI or CAD are exceptional contributory factor to the CAD angina. 18.3 % of the cases were having family history of the CAD. 11.6 % people were diabetic and 10 % were alcoholic in the study population.

Table VII had clinical data showing response of the therapy group wise on subjective parameters. It showed that in all the parameters taken for trial there was excellent positive drug response in both groups A and B. There was 100 % relief in chest pain on Borg scale.

100 % relief was obtained in dyspnoea in all the patients in both groups A and B. Relief in burning chest sensation was also 100 %. There was 100 % relief in fatigue also. On NYHA score there was 100 % improvement in all subjects. Patients falling under Grade II and Grade III; all went back to grade I. Similarly 100 % of the test population improved to normal EQoL-5D-Vas values. Reduction in number of Isosorbide dinitrate (Sorbitrate) 5 mg sub-lingual tables reduced to zero in all patients who were having these tablets SOS. 63.33 % of the patients in A group and 63.33% in B group had consumed ISDN sub-lingual tablets.

Table number VIII showed subjective response of reduction in chest pain measured on Borg scale. Significant 92.7% effect was obtained in group A (p-value 0.000) and 96.4 % (p-0.000) effect in Group B. This showed both control and trial drugs are equally significantly effect in controlling chest pain.

In **table IX** dyspnoea score was shown 100 % ($p<0.05$) efficacy in Group A and 97.6 % ($p < 0.05$) efficacy in group B. There were equal and significant results in both groups.

Burning chest was recorded in **table X** showing 100 % ($p < 0.05$) reduction of the symptom in group A and 97.3 % ($p < 0.05$) reduction in group B; equal and significant effects.

Table XI showed Fatigue score. 100 % ($p < 0.05$) significant reduction was found in both groups; equal efficacy.

On NYHA score scale **table XII** showed 55.6 % effect in (p 0.000) in group A and 53.8 % (p 0.000) effect in group B. Significant and equal effect $p < 0.05$ in both groups.

Similarly EQoL 5D VAS score shown in **table XIII** found that in group A effect of the treatment was 50% (p 0.000) and in group B patients treatment efficacy was obtained

51.5 % (p 0.000). Effect observed in both groups was significant as p value < 0.05. Result was equal in both treatment models.

Table XIV showed reduction in number of consumption of rescue medicine tablets of ISDN. In group A there was 97.2 % (p 0.000) reduction in use of number of tablets while in group B reduction in use of ISDN tablets was 97.4% (p 0.000). Effects observed in both groups were equal and significant.

Table XV showing when comparison between Group A and Group B was made on subjective parameters we found that p values for all parameters were > 0.05 which concluded that there is no difference in group A and group B results.

Table XVI showed BMI reduction occurred in both groups were equally significant. It was observed that p values in each group were less than 0.05, hence significant.

In **table XVII** we found that SBP in group A reduced 3.9 % p value > 0.05 non-significant while in group B with 8.8 % reduction p was < 0.05 significant. Hence we can interpret that trial drug in groups has scored over control drug in terms of systolic blood pressure control.

In table **XVIII** in case of DBP there was reduction of 3.1 % (p > 0.05) in group A non-significant and in group B reduction was significant 0f 7.9 % (p < 0.05). Here we found that trial drug B was superior to control drug.

Table XIX showed that control and reduction in heart rate was found significant in group B 9 %. Change in mean was from 84.57 ± 16.24 SD to 76.97 ± 9.77 SD, p 0.029 (< 0.05) significant while in group A it was mean 82.80 ± 12.28 SD to 79.87 ± 13.93 SD, p 0.324 (>0.05) non-significant. Group B drug was tested superior to Group A.

From **table XX** we found that the effects and changes in haemoglobin levels were not significant in either of the groups A and B. There was a change in mean 12.75 ± 1.28 SD to 12.67 ± 1.33 SD p 0.342 (> 0.05) in group A, non-significant, while change of mean in group B was found 12.29 ± 1.51 SD to 12.58 ± 1.09 SD p 0.140 (> 0.05), non-significant. But a trend noticed in group A there was little reduction in Hb and in group B there was a little rise which may be due to iron moiety in Nagarjunabhra Ras.

Table XXI showed that there were non-significant changes in random blood sugar levels in either of the groups A and B. In group A, before treatment (BT) RBS mean was 111.83 ± 27.89 SD and after treatment (AT) it was mean 102.30 ± 23.63 SD, p value 0.060 (> 0.05) as non-significant. And in Group B change in RBS was noted BT 109.73 ± 32.35 SD to AT 107.44 ± 19.03 p value 0.755 (> 0.05), non-significant. This showed no effect over RBS by drugs of both groups.

Table XXII showed total cholesterol levels in the blood before treatment and after treatment. It showed in group A, BT mean TC was 184.67 ± 54.06 SD and AT was a54.90 ± 33.95 SD, p 0.000 (< 0.05) and in group B, BT mean TC was 163.53 ± 42.86 SD, p 0.000 (< 0.05). In both cases reduction in cholesterol level was significant and equal.

In **table XXIII**, mean HDL level was seen BT in group A 34.50 ± 13.29 SD and AT it was 31.87 ± 8.78 SD p 0.240 (> 0.05) non-significant low. And BT in group B level of HDL was 29.77 ± 11.20 SD and AT was 30.92 ± 9.11mg%; non-significant rise. Value of difference expressed in p 0.474 (> 0.05) non-significant. Equal effect in both groups as compared.

From **table XXIV** in group A level of LDL was noted BT mean 112.40 ± 50.16 SD and reduced AT mean 95.83 ± 35.31 SD p value 0.013 (< 0.05) significant. In group B mean

value BT was 108.07 ± 50.16 and AT 95.83 ± 35.31 SD difference in p 0.001 (< 0.05), significant. Hence it was concluded that changes were equal in both groups, statistically.

Table XXV showed that in case of VLDL mean value was 29.94 ± 18.60 SD and AT mean was 24.50 ± 13.77 SD, p 0.058 > 0.05 non-significant and in group B mean VLDL, BT was 25.04 ± 10.92 SD and AT was 19.44 ± 6.87 p 0.012 < 0.05, significant.

From **table XXVI** we found that TG level in Group A, BT mean was 161.90 ± 83.39 SD and AT mean was 125.53 ± 38.05 SD. Difference value p 0.009 < 0.05, significant and in group B was mean TG, BT 128.10 ± 34.51 SD and AT mean 109.01 ± 35.00 SD p 0.006 < 0.05, hence significant.

From the above tables we found that the treatment regimens in both the groups had significant reduction effect upon all types of cholesterol. It was not evident that there was inverse i.e. reciprocal relationship between VLDL and LDL and or HDL. Direct proportional decrease in VLDL and TG was evident.[109]

On objective treadmill exercise stress test (TMT) parameters, **table no. XXVII** showed that MET (Metabolic Expenditure of Task), a ratio of metabolic rate during TMT exercise, is measured to find cardiovascular health is the rate of energy consumption. The higher the MET value higher is fitness of heart muscles. MET level in group A mean was 8.54 ± 2.65 SD, BT and AT was 10.46 ± 2.62 SD with an increase of 22.5% and p 0.000 (<0.05) significant. In group B values of MET were 8.08 ± 2.58 SD, BT and AT with increase MET was 10.37 ± 2.75 SD with a change of 28.4 % showing p 0.000 (<0.05), significant.

Table XXVIII showed double product values. DP is rate pressure product measured by multiplying SBP x HR. This is used for risk stratification in cardiovascular disease. By

measuring high in treadmill exercise stress test it predicts high mortality in CAD.[114] Therefore it is said to be beneficial in decreasing order. In the present study in group A patients it increased by 15.5 % in mean values and non-significant increase in group B patients. This showed better efficacy of the treatment regimen given to the group B over group A. In group A, BT, DP was 21760 ± 7692.84 SD and AT, DP was 25133.33 ± 7318.34 SD, a significant 15.5 % increase p 0.004 (<0.05). While in group B, BT, DP was 23000 ± 7150.89 SD and AT was 23020 ± 7083 SD an increase by 0.1 % a non-significant p 0.985 (> 0.05).

ST depression in ECG refers to where in the trace ST segment is abnormally low below the baseline. It is significant if it is more than 1 mm in leads V5 and V6. This indicates reversible myocardial ischaemia during treadmill exercise test of which coronary insufficiency in CAD is a major cause.[115]

From **table XXIX** we found that in group A patients BT, mean ST depression in lead V5 was 1.57 ± 0.74 and AT 1.03 ± 0.71 change in percentage 34.2 % with p 0.001 (<0.05) as significant. In group B, BT mean ST depression in lead V5 was 2.12 ± 1.13 SD and AT was 1.17 ± 0.79, reverse change 44.7 % with p value 0.000 (<0.05) which is significant. Both group drugs exhibited significant effect but group B drug effect was greater in terms of percentage. Statistically was equal effect.

From **table XXX** it was evident that ST depression in lead V6 in group A patients BT was mean 1.40 ± 0.57 SD and AT mean 0.79 ± 0.60 SD with a reverse change of 43.3 % p 0.000 (<0.05), significant. In group B, BT, ST depression was 1.97 ± 1.14 SD and AT was 1.03 ± 0.72 SD, p value 0.000 (<0.05), reverse change 47.8 % as significant. Greater change was observed in group B in terms of % age.

From **table XXXI** we noticed that total exercise time in seconds taken in group A patients BT mean was 429.97 ± 180.23 SD seconds and AT was increased to 542.03 ± 154.39 SD seconds with a p 0.000 < 0.05 which is significant. While in group B total exercise time BT was 394.67 ± 150.45 SD seconds and AT total exercise time was increased to 532.43 ± 166.84 seconds, highly significant as p 0.000 < 0.05. There was 34.9 % of time increase in group B more than the time increased in group B patients i.e. 26.1 %.

Similarly from **table XXXII** we found that AT time taken to 1 mm ST depression was higher in percentage in group B in comparison to group A; showing more effect of the treatment regimen of group B. In group A patients mean time taken to 1 mm ST depression BT was 265.40 ± 124.96 SD in second and AT was increased to 450.90 ± 130.58 SD in seconds with a p value 0.000 < 0.05 which is significant efficacy of the drugs. In group B patients mean time taken to 1 mm ST noted BT was 230.70 ± 120.60 SD seconds and AT was 420.47 ± 118.45 SD increased with p 0.000 < 0.05 which is significant in value of difference. We also noticed that percentage of change was 82.3 % in group B greater than 56.7% in group A. This proved greater efficacy by group B drugs.

Table XXXIII showed that P-values for almost parameters are greater than 0.05. Hence there was no significant difference between Group A and group B.

Table XXXIV and XXXV showed analytical values in the test drug sample; were compatible with values of good quality dry extract of T. Arjun bark.

Along with efficacy, safety and adverse effects of a drug and drug-drug interactions in multidrug therapy are important consideration in clinical study. Ayurvedic medicines are in practice since very long and in anyway trial drug Nagarjunabhra Ras is not reported unsafe. Scholar himself is prescribing it since many years. No untoward effects were ever observed or reported till date. Though safety study was out of preview of the present study, yet, it was

carried out in limited subject by chance on hepatic and renal function test parameters. In few cases in both groups A and B; SGOT, SGPT and Serum Creatinine test were done before and after completion of study. Data could not be tabulated for being insufficient. Any inference would be void.

Dietary and life style regimens (Pathya-Apathya) play documented role in the treatment of Hridshul advised in Ayurvedic as well as modern medicine. Pathya – apathya modifies the risk factors and protects individuals from disease progression. Active life style, 30 minutes regular exercise, quitting of tobacco smoking, fat free diet, alcohol abstinence, yoga and meditation, prayers for relieving of stress, patient education for strict compliance and regular follow up all were advised for secondary prevention during this study.

Risk factors which cause *tridosha* and *rasa (rakta)-dhatu dushti* (vitiation); which in conjugation generate *badha* (pain, reference *jejjata*) in heart (*srotsa*), presenting various signs and symptoms of stable and unstable angina alias hridshula, were noted by their concomitant and conspicuous presence, as specified in modern medicine.

Thus, from the above discussion we found that baseline haemodynamic parameters including heart rate, systolic and diastolic blood pressures were comparable as were the laboratory parameters viz. Hb, blood sugar, total cholesterol, high density cholesterol, low density cholesterol, very low density cholesterol, triglyceride and treadmill parameters, total exercise time, time to 1 mm ST depression, MET values, double product and maximum ST depression in chest leads V5 and V6. Mean values in both groups were compared.

Comparative results in both groups showed greater efficacy of the drugs on subjective parameters in group B than group A in terms of percentages in pain scores on Borg scale, fatigue, EQoL 5D VAS score, reduction in use no. of ISDN tablets, while greater, in group A,

than group B in dyspnoea burning chest, NYHA scores. Relatively there was no significance of difference in efficacy on statistical analysis between both groups.

Physical and laboratory chemical values obtained from both groups we observed that reduction in BMI, systolic blood pressure, diastolic blood pressure, low density cholesterol, very low density cholesterol in percentage were greater in group B than group A, while blood sugar level, total cholesterol, high density cholesterol and triglyceride values reduction was greater in group A than group B. After treatment changes in both groups were significant except in Hb, BSL and HDL. On comparing both groups values changed were equally significant in all parameters statistically.

On TMT parameters we found that percentage wise changes were higher in group B in MET values, maximum ST segment depression in chest leads, total exercise time and time taken to 1 mm ST depression, while mean double products was significantly higher after treatment in group A, a bad prognosis, while marginal and non-significant increase was seen in group A showing better efficacy comparatively. Statistically changes were equally significant in both groups showing equal efficacy of the drugs in both groups.

Thus, we analysed that trial drug Nagarjunabhra Ras is no-inferior to the control drug ISMN in anti anginal property and efficacy. Though mode of action of Nagarjunabhra Ras on modern pharmacological parameters are yet to find out nevertheless from the present study we observed that quality of life has certainly been improved after course of the drug. Results were compatible to the efficacy of Terminalia Arjuna in modern literature.

Few scholars opined that anti-anginal efficacy seen may be a result of placebo effect or due to haemodynamic effect of metoprolol and reversible anti atherogenic effects of statins or antiplatelet effects of aspirin and clopidogrel or risk factors modification. We refuted the charges as we found that comparative changes in values of different parameters in

Nagarjunabhra Ras group B were greater than the values in ISMN control group A in terms of percentage. These differences may be said due to Nagarjunabhra Ras.

Though meticulous attention had been paid to proper methodology in preparing the patients, performing the tests and interpreting the results, yet study protocol, experimental design, selection of subjects, randomisation and controversy regarding accuracy and diagnostic power of subjective and objective parameters remain in question.

Adverse Effects:

No adverse effects and any drug-drug interaction particularly of Nagarjunabhra Ras were observed during the study. Nitrates commonly have side effects like headache, hypotension and flushing resulted their withdrawal which were not evident in Group B patients. In few patients nitrate rebound phenomenon[116] was seen in group A patients. Drug Nagarjunabhra Ras was well tolerated and safe. No casualty or MI had occurred in either of the group.

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CONCLUSION

Clinically Nagarjunabhra Ras efficacy was compared to Isosorbide Mononitrate in patients of chronic stable angina i. e. hridshula in ayurvedic parlance. Nagarjunabhra Ras not only relieved pain symptoms but improved quality of life.

Treatment regimens in two groups of patients A and B showed anti-anginal efficacy. On comparison of results of subjective and objective measurements, statistically, between two groups, p-values were > 0.05 in all parameters. No significant difference of means was found.

From the present study it was concluded that anti-anginal efficacy of Nagarjunabhra Ras was found equivalent to control drug. All patients showed clinical improvement in all parameters. Quality of life was seen improved well. During the treatment period patients had experienced good tolerance of the drug with no untoward effects. According to present study Nagarjunabhra Ras in one tablet twice daily dose may be prescribed or added to modern drugs. It is quite effective anti-anginal drug which can be used safely in patients of chronic stable angina i.e. Hridshula.

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APPENDICES

CRF (Case Record Form) Visiting Day:

C R. No.: Date/Time:

NAR/ISMN **Baseline/Follow-up Data**

Name/Age/Sex/address/ Phone No.:

C/O:

H/O:

Rx/H:

Risk Factor:

O/E: Temp/HR/BP: Height/Weight:

Hb: BMI:

BS(R):

Lipid Profile: TC: HDL: LDL: VLDL: TG:

S. Creatinine:

SGOT/SGPT:

Subjective Parameters: **Objective Parameters:**

Pain (Borg scale): ECG:

Dyspnoea: TMT:

Burning chest: **Rx:**

Fatigue:

NYHA Score

EQoL 5D Vas Score:

No. of Sorbitrate 5 mg S/L tabs used daily:

Physician's sign

Treatment:

NAR Group:

1. …….
2. …….
3. …….
4. …….
5. ……
6. …….

Control Group:

1. ……..
2. ……
3. …….

Issue all medicines for 30 days only **Signature**

Tables For Clinical evaluation of Nagarjunabhra RAS in hridshula (stable angina)

Table 1: Subjective parameters

Variable	**Baseline characteristics (Before Treatment)**	**Findings (After Treatment)**
Clinical symptoms		
Pain Borg scale		
Dyspnea		
Burning chest		
Fatigue		
NYHA grading score		
EQoL 5D VAS score		
No. of ISDN tablets used		

Table 2: Physical and laboratory values

Variable	**During Treatment**					**After Treatment Mean (SE)**	**P-value**
	Visit1 Day 0	**Visit 2 Day30**	**Visit 3 Day60**	**Visit 4 Day90**	**X**		
BMI					X		
SBP					X		
DBP					X		
Heart rate					X		
Hb					X		
BSR					X		
Total cholesterol					X		
HDL					X		
VLDLC					X		
LDL					X		
Triglyceride					X		

Note: P-value consider as significant (<0.05), SBP (Systolic blood pressure), DBP (Diastolic Blood pressure), SE (Standard Error)

Table 3: TMT values

Variable	During Treatment				After Treatment Mean (SE)	P-value
	Visit 1 Day 0	**Visit 2 Day 30**	**Visit 3 Day 60**	**Visit 4 Day 90**		
Total exercise time (min)						
MET level at peak						
Time to 1 mm ST depression						
Max double product at peak						
Max ST segment depression in mm (V_5) (V_6)						
Test end reasons						

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INFORMED CONSENT FORM

(To be filled up by Parents/Guardians on behalf of subject)

Clinical evaluation of Nagarjunabhra RAS in the treatment of hridshula (Angina Pectoris) as compared to Isosorbide mononitrate

The contents of the information sheet dated ……..version……...that was provided have been read carefully by me / explained in detail to me, in a language that I comprehend, and I have fully understood the contents. I confirm that I have had the opportunity to ask questions.

The nature and purpose of the study and its potential risks / benefits and expected duration of the study, and other relevant details of the study have been explained to me in detail. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal right being affected.

I understand that my participation in this research and sections of any medical notes may be looked at by responsible individuals. I give permission for these individuals to have access to records.

I agree to participate in the above study.

---------- ---------- ---------- ---------- Name of the patient Signature Date

---------- ---------- ---------- ---------- Name of the Attendant Signature Date

---------- ---------- ---- ---------- Name of the witness Signature Date

---------- ----------

Signature of the Research Scholar **Signature of the Guide**

BORG SCALE

Grade	Symptoms (chest pain)
0	Nothing at all
0.5	Extremely weak(just noticeable)
1	Very weak
2	Weak(light)
3	Moderate
4	Somewhat strong
5	Strong (heavy)
6	.
7	Very strong
8	
9	Extremely strong (almost maximal)
10	Maximal

New York Heart Association Functional Classification

Class I: - Cardiac disease, but no symptoms and no limitation in ordinary physical activity, e.g. no shortness of breath when walking, climbing stairs etc. (Score-1)

Class II: - Mild symptoms (mild shortness of breath and/or angina) and slight limitation during ordinary activity. (Score-2)

Class III: - Marked limitation in activity due to symptoms, even during less-than-ordinary activity, e.g. walking short distances (20–100 m). Comfortable only at rest. (Score–3)

Class IV: - Marked severe limitations. Experiences symptoms even while *at rest*. Mostly bedbound patients. (Score-4)

EQoL 5-D VAS SCORE

MOBILITY

I have no problems in walking about
I have slight problems in walking about
I have moderate problems in walking about
I have severe problems in walking about
I am unable to walk about

SELF-CARE

I have no problems washing or dressing myself
I have slight problems washing or dressing myself
I have moderate problems washing or dressing myself
I have severe problems washing or dressing myself
I am unable to wash or dress myself

USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*

I have no problems doing my usual activities
I have slight problems doing my usual activities
I have moderate problems doing my usual activities
I have severe problems doing my usual activities
I am unable to do my usual activities

PAIN / DISCOMFORT

I have no pain or discomfort
I have slight pain or discomfort
I have moderate pain or discomfort
I have severe pain or discomfort
I have extreme pain or discomfort

ANXIETY / DEPRESSION

I am not anxious or depressed
I am slightly anxious or depressed
I am moderately anxious or depressed
I am severely anxious or depressed
I am extremely anxious or depressed

Date	Number of angina attacks	Numbers of tablet intake of GTN/ISDN	Trigger	Intensity of angina pain				Duration of pain/Min.			Response
				Mild	Mod	Severe	Nil	Short	Medium	Long	

रूग्ण सूचना पत्रक

अध्ययन का शीर्षकः

नागार्जुनाभ्ररस का हृद्यशूल, स्टेबल एंजाईना, में आइसोसोरबाइड मोनोनाइटरेट से तुलनात्मक चिकित्सीय अध्ययन।

परिचयः

हृद्यशूल एंजाईना – हृद्य की कोरोनरी धमनियों में रूकावट होने या बंद होने से रह रह कर छाती और आसपास में दर्द होने लगता है जो बढ़ कर हार्ट अटैक हो जाता है। यह जान लेवा भी हो सकता है। इसका समयोचित उपचार औषधिय चिकित्सा तथा एंज्योप्लास्टि शल्यक्रिया से संभव है। परंतु कई कारणों से इस चिकित्सा में असमर्थ होते हैं। इनमें आर्थिक, सर्जरी व औषधियों के प्रति असहिष्णुता का कारण प्रमुख है। आयुर्वेदिक चिकित्सा में इसके अनेक प्रभावी योग बताए गए हैं। अनेक योग घरेलु उपचार व लोक चिकित्सा के रूप में प्रसिद्ध व प्रचलन में हैं तथा बिना किसी कुप्रभाव के सालों से प्रयोग किए जाते रहे हैं। आयुर्वेदिक चिकित्सक भी इनका प्रयोग करते हैं जैसे अर्जुन छाल चूर्ण, अर्जुन क्षीर पाक, नागार्जुनाभ्र रस, प्रभाकर वटी, हृद्यार्णव रस आदि प्रमुखता से बिना किसी हानि के प्रयोग किए जाते हैं।

लक्ष्यः

इस अध्ययन का उद्देश्य नगार्जुनाभ्र रस के प्रभाव का तुल्नात्मक आंकलन तथा परिणाम की जांच करना है। स्टेबल एंजाइना में प्रयोग की जा रही अंग्रेजी दवाइयों के साथ प्रयोग करके इसके प्रभाव का आंकलन करना है।

विधिः

मरीजों को स्वतः अथवा रेफर किए होने पर उनकी सहमति से ही इस प्रायोगिक अध्ययन में शामिल किया जाएगा।किसी दुष्प्रभाव अथवा अनिच्छा के कारण रोगी को इस अध्ययन कोर्स को छोड़ने की स्वतंत्रता रहेगी। 90 दिन तक निःशुल्क औषधियां दी जाएंगी व प्रोटोकोल में निर्देशित आवश्यक लैब जांचें व टीएमटी टेस्ट किए जाएंगे। रोगी व उसके घर उपचारक अभिभावकों को उनकी सरल मातृभाषा में उनके लाभ की दृष्टि से यह जानकारी प्रदान की गई है।

श्लोक

हृद्रोगमिति वा शोकस्यत्र रोगेषु इति परे हृदयस्य हृद्भावः अथवा हृदोरोगो

हृद्रोगः। (मधुकोष)

शोकोपवासव्यायामरूक्षशुष्काल्पभोजनैः।**वायुराविश्यहृदयंजनत्युत्तमांरूजम्**।।

(च सं0 सू0 17/30)

दुषयित्वारसंदोषाविगुणाहृदयंगताः।**कुर्वन्तिहृदयेबाधां**हृद्रोगंतंप्रचक्षते।।

(सु0सं0उ0तं0 43/3,4)

कफपित्तावरूद्धस्तुमारूतोरसमूर्च्छितः।हृदिस्थः कुरुतेशूलमुच्छ्वासावरोधकंपरम्।।

सहृद्शूलइति ख्यातोरसमारूतसम्भवः।। (सु0सं0उ0तं042/132)

अत्युष्णगुर्वन्नकषायतिक्तश्रमाभिघाताध्यशनप्रसंगैः।**संचिन्तनै**र्वेगविधारणैश्चहृदामयः

पंचविधः प्रदिष्टः।। (मा0नि0हृ0नि0/1)

ककुभःशीतलो हृद्यः क्षतक्षयविषम्रजित्।मेदोमेहव्रणान् हन्ति**तुवरः कफपित्तहृत्।।**

(भा0प्र0)

अर्जुनस्य त्वचासिद्धं क्षीरं योज्यंहृदामये।सितयापंचमूल्यावाबलयामधुकेनवा।।

घृतेनदुग्धेनगुडाम्भसावापिबन्तिचूर्णककुभत्वचोये।हृद्रोगजीर्णज्वररक्तपित्तंहत्वाभवेयुश्चिरजी

विनस्ते।। (भैषज्यरत्नावली 33/11–12)

सहस्रपुटनैः शुद्ध वज्राभ्रमर्जुनत्वचः।सत्त्वैविमर्दितंसप्तदिनंखल्लेविशोषितम्।

हृद्रोगंसर्वशूलार्शोहृल्लासच्छर्द्यरोचकान्।हन्त्यन्यानपिरोगांश्चबल्यंवृष्यं रसायनम्।।

(भैषज्यरत्नावली 33/36–38)

गौरीतेजः परममृतं**वातपित्त**क्षयघ्नं।प्रज्ञाबोधि**प्रशमितरूजं** वृष्यमायुष्यग्रयम्।।

बल्यंस्निग्धंरूचिद**मकफं**दीपनंशीतवीर्यं।तत्तद्योगैः **सकलगदहृद्**व्योमसूतेंद्रबन्धि।।

(र0र0स02/2)

अभ्रंकज्जलिकोपेतमर्जुनक्वाथभावितम्।कृमितंश्लैष्मिकंवापिविनिहन्तिहृदामयम्।।
(रसतरंगिणी 10/87)

MASTERCHART

GROUP A - DATA SUBJECTIVE PARAMETERS

S.No.	CRNo.	Name	Age	Sex	Address	Pain (Borg scale)		Dyspnoea score		Burning chest		Fatigue score	
						BT	AT	BT	AT	BT	AT	BT	AT
1	4	JJ	40	M	Jhajjar	3	0	1	0	1	0	1	0
2	5	SG	55	F	Jhajjar	3	0.5	1	0	1	0	1	0
3	9	Pawan	40	M	Jhajjar	2	0	1	0	1	0	1	0
4	14	RKC	56	M	Jhajjar	3	0	2	0	1	0	1	0
5	15	SB	60	M	Jhajjar	3	0	1	0	1	0	1	0
6	18	RDT	35	M	Jhajjar	4	0.5	1	0	1	0	1	0
7	21	SSK	58	M	Jhajjar	3	0	2	0	1	0	2	0
8	23	SV	35	M	Jhajjar	3	0.5	1	0	1	0	1	0
9	24	OP	61	M	Jhajjar	2	0	1	0	1	0	1	0
10	25	VB	30	M	Jhajjar	3	1	1	0	1	0	1	0
11	26	RKG	45	M	Jhajjar	2	0	1	0	1	0	1	0
12	27	RCH	41	M	Jhajjar	3	1	1	0	1	0	1	0
13	28	DNC	59	M	Jhajjar	3	0	1	0	1	0	1	0
14	29	ANK	46	M	Jhajjar	3	0.5	1	0	1	0	1	0
15	30	MK	40	M	Jhajjar	3	0.5	1	0	1	0	1	0
16	32	SDB	56	F	Jhajjar	3	0	1	0	1	0	1	0
17	33	BS	60	M	Rohtak	2	0	1	0	1	0	1	0
18	34	SC	57	M	Rohtak	3	0.5	2	0	2	0	2	0
19	35	KDD	59	F	Rohtak	3	0	1	0	1	0	1	0
20	37	JD	61	M	Rohtak	4	1	2	0	1	0	1	0
21	41	NCD	52	M	Rohtak	2	0	1	0	1	0	1	0
22	42	BSL	53	M	Rohtak	2	0	1	0	1	0	1	0
23	43	IS	60	M	Rohtak	3	0	2	0	1	0	1	0
24	44	RP	38	M	Jhajjar	2	0	1	0	1	0	1	0
25	45	MR	60	M	Rohtak	3	0.5	2	0	1	0	1	0
26	50	RKS	60	M	Jhajjar	2	0	1	0	1	0	1	0
27	51	NKJ	45	M	Jhajjar	2	0	1	0	1	0	1	0
28	52	HV	60	M	Jhajjar	3	0	2	0	1	0	1	0
29	53	RS	57	M	Rohtak	2	0	1	0	1	0	1	0
30	59	SKB	46	M	Jhajjar	3	0	1	0	1	0	1	0

MASTERCHART

GROUP B - DATA

1	1	Ramesh	48	M	Rohtak	3	1	1	0	1	0	1	0
2	2	Kaushlya	60	F	Jhajjar	3	0	1	0	1	0	1	0
3	3	SD	50	F	Jhajjar	2	0	1	0	1	0	1	0
4	6	DB	60	M	Jhajjar	4	0.5	2	0	1	0	2	0
5	7	AKK	35	M	Jhajjar	3	0	2	0	1	0	1	0
6	8	Rajender	37	M	Jhajjar	3	0	1	0	1	0	1	0
7	10	ND	60	M	Jhajjar	3	0	1	0	1	0	1	0
8	11	AKS	36	M	Jhajjar	2	0	1	0	1	0	1	0
9	12	SBG	59	M	Jhajjar	3	0	2	0	1	0	1	0
10	13	BL	45	M	Jhajjar	3	0	2	0	1	0	2	0
11	16	RW	50	F	Jhajjar	3	0	2	0	1	0	2	0
12	17	Anil	52	M	Rohtak	3	0	2	0	1	0	2	0
13	19	RCW	54	F	Jhajjar	3	0	1	0	1	0	1	0
14	20	HS	65	M	Jhajjar	3	0.5	2	0	1	0	2	0
15	22	KD	65	F	Rohtak	3	0.5	3	1	2	0	2	0
16	31	SDJ	45	M	Jhajjar	3	0	1	0	1	0	1	0
17	36	Sheela	50	F	Jhajjar	2	0	1	0	1	0	1	0
18	38	Angoori	60	F	Rohtak	3	0.5	2	0	1	0	1	0
19	39	HB	60	M	Rohtak	2	0	1	0	1	0	1	0
20	40	OPR	62	M	Jhajjar	3	0	2	0	2	0	2	0
21	46	JS	59	M	Rohtak	2	0	1	0	1	0	1	0
22	47	RKB	55	M	Rohtak	2	0	1	0	1	0	1	0
23	48	AKDG	38	M	Jhajjar	2	0	1	0	1	0	1	0
24	49	KS	47	M	Jhajjar	3	0	1	0	1	0	1	0
25	54	SM	37	M	Jhajjar	3	0	1	0	1	0	1	0
26	55	PR	57	M	Jhajjar	3	0	1	0	2	0	2	0
27	56	SW	50	M	Jhajjar	3	0	1	0	1	0	2	0
28	57	Jitender	48	M	Jhajjar	2	0	1	0	2	0	2	0
29	59	KT	60	M	Jhajjar	3	0	1	0	3	1	3	0
30	60	HO	37	M	Jhajjar	3	0	1	0	2	0	1	0

MASTERCHART

PHYSICAL PARAMETERS

NYHA Score		EQoL5DVAS Score		No. of ISDN s/l tablets used		BMI				SBP		
BT	AT	BT	AT	BT	AT	0 day	30 day	60 day	90 day	0 Day	30 day	60 day
2	1	22222	11111	0	0	18.3	17.5	18.7	19.1	110	110	110
2	1	22233	11111	3	1	31.25	31.25	31.25	30	140	120	150
2	1	22223	11111	0	0	23.1	22.7	22.4	21.5	150	130	140
2	1	22222	11111	2	0	23	23	22.9	22.6	130	130	110
2	1	22222	11111	2	0	24.2	24.5	23.7	24	110	120	110
2	1	21232	11121	0	0	23.7	24.3	24.6	24.3	120	140	130
2	1	32222	11111	3	0	19.1	18.8	19	19	110	130	130
2	1	22222	11111	0	0	28.7	28.4	28	28	110	110	110
2	1	22222	11111	1	0	26.7	25.6	26.1	25.6	140	140	140
2	1	22232	11111	0	0	27	26.8	26	25.6	130	110	110
2	1	22222	11111	1	0	18.6	18.9	19	19	130	140	130
2	1	22222	11111	0	0	27.3	27.3	27.5	27	130	120	140
2	1	22222	11111	2	0	24.8	24.8	25.5	25.5	150	150	150
2	1	22232	11111	0	0	23.8	23.9	24.2	24	120	120	110
2	1	22222	11111	1	0	17	16.6	17	17	100	90	100
2	1	22232	11111	2	0	27.1	26.7	26	25.5	150	140	120
2	1	22232	11111	2	0	24.9	24.2	24	23.5	160	150	140
3	1	32232	11111	4	0	22.1	22	22	22	160	140	110
2	1	22232	11111	1	0	29.1	28.7	28.3	27.4	170	140	130
3	1	32332	11111	1	0	22.7	22	22	21.8	110	120	110
2	0	22222	11111	0	0	23.4	23	22	22	90	120	130
2	0	22222	11111	1	0	28.5	28	28	27.1	140	130	120
3	1	22332	11111	3	0	34.2	34	33	30	110	130	130
2	1	22222	11111	1	0	27.6	27	26	26	130	120	110
3	1	32232	11111	1	0	22.7	22.6	22	22	140	140	110
2	1	21223	11111	2	0	18	17.8	17.6	18	100	110	110
2	1	22222	11111	0	0	26.6	25.6	26	25	150	140	110
2	1	22222	11111	1	0	23.1	22.8	22.1	22.1	140	130	120
2	1	22222	11111	0	0	21.1	20.7	20.5	20	130	120	120
2	1	22232	11111	2	0	25.4	25	24.5	24.1	120	110	110

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2	1	22222	11111	2	0	24.9	24.2	24	24	150	150	130
2	1	22233	11111	1	0	21.6	22.2	23.4	23.4	160	150	150
2	1	22222	11111	0	0	25	25.3	25	25	140	120	120
3	1	32332	11111	3	0	24.6	23.1	22.8	23.1	150	130	130
2	1	32222	11111	1	0	26.1	25.5	25.2	24.9	150	130	160
2	1	32232	11111	3	0	19.46	19.56	19.08	19.08	130	130	140
2	1	22222	11111	1	0	24.5	24.5	24.2	24.2	130	130	130
2	1	22222	11111	1	0	26.6	25.6	26	25.4	150	140	110
2	1	22222	11111	0	0	23.5	23.8	23.8	24.5	150	130	130
3	1	33332	11111	2	0	24.3	24.6	24.3	24	160	150	130
2	1	22222	11111	0	0	19.85	20.95	20.58	20.95	110	100	110
2	1	22222	11111	2	0	33.4	33	32.7	32	90	130	110
2	1	22232	11111	3	0	25.7	25.7	25	25.8	130	120	120
3	1	33332	21111	3	0	21.2	20.9	20.7	20.3	140	110	100
3	1	33333	11111	3	0	19.5	19	19	16.6	140	90	100
2	1	21332	11111	0	0	26.8	25.6	25.3	24.8	140	130	120
2	1	22222	11111	0	0	22.2	21.3	21	20.9	80	80	90
3	1	32232	11111	1	0	24.1	24	22	21	160	140	130
2	1	22222	11111	1	0	28.8	28	27.6	26	140	140	130
2	1	22332	11111	4	1	21.4	21.7	22	22	110	130	110
2	1	22222	11111	0	0	25.9	25.5	25.1	25	150	140	120
2	1	22222	11111	0	0	29.5	29.1	28.3	27.9	130	120	120
2	1	22222	11111	1	0	31.4	31.8	31	30	120	110	120
2	1	21132	11111	1	0	28.9	28.2	28	27.9	140	140	110
2	1	22232	11111	0	0	28.1	28	27.7	27.5	120	120	110
2	1	22232	11111	1	0	18.1	18	18	18	110	110	100
2	1	22232	11111	1	0	25.9	25.3	25	25	140	130	130
2	1	22222	11111	0	0	25.5	25	24	24	130	130	120
2	1	32232	11111	2	0	20.8	20	19.5	19	110	100	120
2	1	22232	11111	0	0	22.1	21.8	21.6	21.1	130	120	110

MASTERCHART

								LABORATORY VALUES					
DBP				HR				Hb				Blood sugar	
90 day	0 day	30 day	60 day	90 day	0 day	30 day	60 day	90 day	0 day	30 day	60 day	90 days	0 day
110	70	70	70	70	79	83	87	48	11.9	12.3	11.9	11.4	84
130	80	80	90	90	62	64	66	90	10.2	10.4	12.6	11	112
140	100	100	90	100	80	90	91	98	14	15	13.3	12.7	135
130	80	90	80	80	68	83	73	71	12.9	11.5	10.4	12.2	98
130	70	80	70	80	95	100	105	97	13.6	12	10.8	11.7	100
130	80	100	100	100	90	91	88	108	13	13.6	13.7	16	80
110	70	90	80	80	77	89	90	91	11	12.3	13.6	13.6	78
130	80	70	70	80	75	79	75	100	11.7	11.3	12.1	13.6	90
150	90	80	90	100	80	72	74	85	11.9	12.8	11.2	11.2	175
110	90	80	80	80	95	95	60	73	13.6	14.1	13.5	14.6	77
140	90	90	90	90	97	83	117	106	12.8	12	11.9	10.7	99
140	110	90	100	100	104	115	103	107	14.5	14.7	14	14.2	85
140	70	60	70	70	80	82	77	67	11	11.4	10	10.6	118
120	80	80	80	80	100	86	84	80	12	11.8	12.1	12.1	120
110	60	60	60	70	55	57	73	77	12	12.4	11	12.2	124
120	110	90	80	80	96	81	80	80	11	11	12	12	105
130	100	100	80	80	84	81	70	70	13.5	13	12	12	112
130	90	90	90	90	72	81	70	72	11	11	12	12	120
120	110	90	80	80	66	72	70	72	12.9	12.8	12	12	112
120	70	80	90	80	88	81	90	80	14	13	12	12.4	70
130	70	80	90	70	92	68	72	78	14	13	12	12	120
120	100	90	80	90	80	72	70	72	13.4	13	13	14	118
120	70	90	80	80	100	80	72	72	11	11.2	12	12	180
120	90	90	90	80	80	70	60	72	12.2	13	12	12	114
120	90	90	90	80	72	80	60	70	9	10	12	11	150
120	70	80	80	80	80	81	70	72	13.1	13	13.2	13	86
120	110	90	90	80	79	81	70	72	13	13	12	13	79
110	90	90	80	80	70	80	72	72	12	12	12.1	12	154
110	90	80	80	70	100	80	72	70	14.2	14	13	13	140
120	80	70	80	80	78	72	72	72	14.7	14	14	15	122

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140	100	90	90	80	81	87	74	78	13	12.7	13	13.8	90
130	100	90	90	90	81	82	75	81	10.6	10	10.1	10.7	99
120	90	80	90	90	92	89	87	90	10.1	10	10.1	11	100
130	80	80	80	80	60	53	58	67	14.1	14.1	15	14.9	65
120	110	110	120	100	62	71	69	103	13	13	13	13.4	81
120	100	100	100	90	102	96	105	98	13.5	14.2	13.2	13	105
130	90	90	90	90	70	70	76	72	13.2	14.4	14.4	13.5	131
150	110	90	90	110	79	81	60	79	13	13	12	12	70
110	100	80	90	80	79	77	99	97	13	12.9	11.6	12.6	94
130	110	100	80	100	132	85	96	85	15.2	11.8	13.2	12.5	235
120	70	70	80	80	88	96	86	72	10	10.6	10.8	10.2	118
110	60	80	60	70	76	82	76	66	13	13.1	14	13.7	140
120	90	80	80	80	90	84	85	80	11.1	11.3	10.9	11.3	144
110	80	80	70	70	72	60	68	76	12.7	13.4	12.7	13.4	107
140	80	60	60	80	86	112	90	90	10.3	10	10	12	135
110	110	90	90	70	73	70	68	72	12.4	12.4	12.6	12.9	93
100	50	60	70	70	62	70	70	72	10	9.7	11	12	120
130	100	90	90	80	90	80	75	70	11	11	11.5	12	70
130	100	90	90	90	88	81	80	72	13.5	13	12	12	109
120	70	70	90	80	80	81	70	72	10	10.3	12	12	70
120	90	90	80	80	84	80	72	72	14	13	12.5	13	140
110	90	80	80	70	72	70	70	80	13.8	14	14	14	151
120	90	80	80	80	84	81	72	72	13.2	13	13.6	13	105
120	100	90	90	80	80	81	72	72	14	14	14.2	14	101
110	80	80	70	60	72	70	68	65	14	13	14	13.5	104
100	70	70	70	70	100	80	70	70	12.8	13	13	12	99
120	90	90	80	80	96	80	72	72	10	11	12	12	116
120	80	70	80	80	80	72	72	70	10.8	11	12	12	126
110	70	80	80	80	120	75	72	72	12	12	13	12	92
120	90	80	70	80	110	80	72	72	13.3	14	14	14	108

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r random mg/dl			Total cholesterol mg / dl				High density lipoprotien (HDL) mg /dl				Low density lipoprotien (LDL) mg /		
30 day	60 day	90 day	0 day	30 day	60 day	90 day	0 day	30 day	60 day	90 day	0 day	30 day	60 day
80	106	95	100	169	112	151	19	24	18	27	70	130	72
105	110	90	130	117	112	160	17	27	26	27	80	70	61
97	153	179	270	320	256	256	21	27	22	19	220	269	209
90	97	116	130	167	122	120	20	27	24	22	86	107	83
74	91	98	82	95	90	88	18	18	25	18	54	65	65
105	81	71	120	165	185	144	22	20	20	28	83	83	141
101	125	125	131	145	140	143	28	25	24	24	85	105	80
118	122	125	190	143	191	143	66	25	38	24	40	68	101
93	114	108	95	98	141	105	17	18	33	23	55	49	81
122	158	74	234	191	139	153	34	38	26	28	184	131	79
120	115	86	190	180	141	182	36	30	23	36	110	100	91
108	114	110	253	262	217	210	58	53	48	45	170	182	147
126	100	93	137	150	120	118	60	70	40	26	62	60	61
110	115	108	260	250	200	156	30	32	36	24	50	52	44
130	100	95	231	202	200	212	39	40	45	42	42	39	40
100	95	78	226	209	230	180	46	41	48	40	150	140	160
90	95	100	212	216	180	140	29	24	18	20	152	170	140
90	95	78	149	135	145	120	31	34	38	20	99	79	90
90	95	100	178	178	168	155	40	38	42	45	119	117	106
90	95	78	205	208	190	170	52	44	48	40	129	140	110
130	100	78	162	160	160	140	32	34	38	36	109	104	98
122	126	120	217	200	195	160	51	50	48	40	140	138	127
160	150	140	230	220	210	200	34	36	36	40	180	170	150
120	95	78	206	200	150	160	41	44	40	42	130	130	100
142	123	78	250	236	210	160	31	34	40	39	178	170	142
90	95	80	191	190	160	144	27	28	30	38	145	141	102
81	70	72	129	116	125	122	21	24	35	30	89	70	80
150	140	112	246	216	200	166	30	4	38	41	174	142	130
100	118	120	223	199	150	165	36	38	40	41	132	117	80
132	130	120	181	170	157	150	42	44	40	41	81	84	76

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85	100	86.3	157	205	150	137	55	41	46	40.7	74	135	60
102	82	90	146	126	115	155	19	24	22	18	120	85	85
90	80	105	194	195	175	190	26	34	22	30	140	126	120
93	86	102	130	164	190	164	26	22	11	22	80	99	140
110	80	102	263	200	187	183	45	14	26	24	182	138	117
117	160	153	142	100	136	143	16	11	15	16	111	80	110
81	85	114	145	120	122	136	24	26	32	28	96	77	84
90	95	78	129	116	100	100	21	24	18	20	89	70	60
100	96	127	160	110	141	175	28	21	31	26	112	75	91
85	98	77	143	90	135	100	26	15	29	22	93	50	71
112	139	140	90	121	98	105	16	22	24	25	50	71	48
150	135	140	132	140	110	110	49	52	39	38	44	50	39
112	80	76	129	120	115	99	22	20	18	18	94	86	87
88	90	118	143	156	128	106	20	24	22	23	95	110	98
126	139	93	156	149	144	141	30	38	38	40	106	96	90
87	102	114	150	130	120	105	20	29	37	32	112	73	53
90	95	108	154	116	116	135	24	24	28	20	114	70	86
90	95	102	241	215	176	160	31	34	40	40	198	160	110
119	105	122	169	164	166	161	46	42	48	40	103	100	98
90	95	100	121	100	134	100	19	20	28	20	66	55	80
90	95	100	257	216	200	144	37	24	18	30	201	170	160
150	120	100	285	200	185	160	30	40	38	40	190	115	100
110	120	108	197	200	180	170	16	28	45	40	149	140	97
112	95	100	169	160	150	155	18	24	18	30	138	114	110
110	105	120	194	186	178	177	35	36	40	40	130	123	113
112	110	106	172	170	160	150	44	40	41	42	102	100	94
120	122	120	123	120	110	104	46	44	40	41	58	58	50
112	110	104	140	140	126	120	34	40	41	40	80	80	73
100	124	120	136	130	120	110	26	30	32	30	86	80	70
112	122	120	190	180	164	150	40	41	44	40	120	115	100

MASTERCHART

′ dl		Very low density lipoprotien (VLDL) mg%			Trigycerides mg / dl				TREADMILL MACHINE EXERCISE TEST (TMT) Total exercise time in seconds			
90 day	0 day	30 day	60 day	90 day	0 day	30 day	60 day	90 day	0 day	30 day	60 day	90 day
111	11	15	22	13	55	75	110	65	707	698	805	785
97	33	20	25	33	165	100	175	165	408	413	334	419
220	29	24	25	17	145	120	125	85	525	567	625	600
80	24	33	15	18	120	165	75	90	420	544	498	556
58	10	12	10	12	50	60	50	60	208	259	296	297
90	15	25	24	26	75	125	120	130	728	784	589	666
83	18	15	22	36	90	75	102	100	96	214	233	224
83	84	50	22	36	420	250	210	180	505	507	523	554
55	23	31	27	21	115	155	135	135	479	450	547	559
93	16	22	34	32	80	110	170	160	554	555	610	640
152	44	40	27	12	220	170	135	160	381	394	375	497
144	25	27	22	21	125	153	110	105	669	720	675	777
58	15	20	30	34	75	80	100	170	436	367	328	290
50	74	80	70	82	180	170	160	210	309	379	391	384
42	22	25	20	28	104	115	107	140	696	808	613	625
125	30	28	22	15	146	140	110	75	329	338	408	478
105	31	22	22	15	195	110	110	115	420	458	587	598
85	19	22	17	15	165	150	110	145	212	278	407	478
95	19	23	20	25	260	160	110	150	329	399	467	490
105	23.8	24	32	25	119	110	130	95	269	278	301	358
89	21	22	24	15	170	160	110	155	390	518	540	540
105	26.4	22	20	15	132	110	130	100	369	458	480	530
140	16	14	24	20	255	200	180	160	213	270	360	480
103	35	26	10	15	175	110	110	153	703	698	707	718
106	41	32	28	15	230	180	160	145	180	243	340	360
91	19	21	28	15	95	100	90	86	745	720	786	840
77	19	22	10	15	95	120	100	90	393	520	593	660
100	41	40	32	25	230	200	160	108	364	452	520	542
100	55	44	30	24	200	180	140	115	274	338	424	540
71	58	42	40	38	290	200	189	160	588	662	720	776

MASTERCHART

54.02	28	32	34	36.2	140	160	162	181.4	559	669	613	757
125	7	17	8	12	135	85	140	80	235	249	372	383
130	28	35	33	22	140	175	165	200	328	485	484	419
117	24	43	39	25	120	215	195	125	219	284	457	257
126	36	48	44	33	180	240	220	165	471	565	470	940
107	15	9	11	20	75	45	55	100	347	448	272	441
95	25	19	23	24	125	95	115	120	589	623	603	605
65	19	22	22	15	95	110	110	75	569	578	587	598
135	20	14	19	14	85	70	95	70	310	376	434	525
60	24	25	35	18	120	125	355	90	418	512	619	594
60	24	28	26	20	120	140	130	100	199	196	513	381
55	40	56	32	17	172	167	160	84	408	546	512	547
69	13	14	10	12	65	70	50	60	386	452	399	331
66	28	22	8	17	140	110	90	85	149	209	256	248
86	20	25	16	15	138	125	140	124	236	242	275	295
55	18	28	30	18	90	110	150	90	382	475	470	490
100	16	22	12	15	80	110	90	75	369	384	467	530
105	12	21	26	15	115	110	95	75	182	253	287	305
96	19.2	22	20	25	96	106	110	95	303	398	467	478
65	36	25	26	15	125	125	110	75	133	218	347	418
100	19	22	22	14	196	110	110	97	410	496	540	546
100	65	45	47	20	217	182	150	102	644	660	681	725
95	32	32	38	35	160	100	190	150	470	511	557	600
100	13	22	20	25	165	110	105	95	311	358	400	480
110	29	27	25	27	145	140	140	156	492	480	540	600
88	26	30	25	20	130	140	133	120	540	600	610	720
54	19	18	20	19	95	90	92	95	593	600	600	660
70	26	20	12	10	130	120	113	110	686	780	720	720
70	24	20	18	10	120	132	112	100	478	540	600	720
96	30	24	20	14	150	140	128	120	424	508	540	660

MASTERCHART

MET level at peak				Time to 1 mm ST depression in seconds				Double Product (Rate Pressure Product)				Max. ST depression in l	
0 day	30 day	60 day	90 day	0 day	30 day	60 day	90 day	0 day	30 day	60 day	90 day	0 day	30 day
13.3	13.1	14.2	14.4	180	540	540	540	8300	19700	23500	20900	1.5	2.1
7.9	8	6.8	8.1	180	180	333	360	20400	17400	20000	23600	3.2	2.9
9.9	10.7	11.8	11.3	360	540	540	540	31600	39000	29700	33100	0.5	2.5
8.1	10.3	9.5	10.5	360	540	497	360	23600	25900	26200	24100	1	1.9
5.1	5.8	6.2	6.3	180	180	180	180	24200	21900	29000	26300	1.5	1
13.6	14	11.1	12.5	360	360	540	360	30000	35700	30200	33200	1.9	2
3	5	6	5.3	95	203	180	180	11800	18000	12800	8400	0	0
9.6	9.6	9.9	10.5	180	180	180	360	24800	28200	26700	32100	1	2
9.1	8.6	10.3	10.5	360	360	360	360	34000	30200	29400	28500	1	1
10.5	10.5	11.5	13	540	540	540	540	33400	29400	31200	33300	2	2
7.5	7.7	7.4	9.5	360	360	360	360	22300	27000	31700	33400	1	1.5
12.6	13.5	12.7	13.9	540	360	360	360	33800	33000	34400	33600	2	2
8.4	7.2	6.7	6.2	360	366	327	180	31700	25200	25200	18500	3.4	1
6.4	7.4	7.6	7.5	308	360	360	360	29000	26000	27900	33100	1	1
13.1	14.2	11.5	19:12	360	360	360	360	15100	15900	19800	29400	2.2	1.9
7.7	7.9	8.1	8.3	180	180	360	360	17400	26300	23000	23500	1.7	1.5
8.7	9	11.1	11.3	180	360	360	540	23700	23600	23000	23500	1.5	1.2
5.2	7.9	9.1	10.3	180	180	360	360	7700	10400	12600	15000	2	2
8.7	9	9.4	9.3	180	180	360	480	27000	36300	33000	35000	1.5	1.5
7.7	8	8.1	8.3	180	180	360	360	17400	16300	13000	15000	2	2
7.7	8.9	9.1	9.3	180	360	360	540	17000	26300	23000	25000	1.5	1
7	7.9	9	9.3	180	180	360	360	20000	20400	23700	23000	1.5	1.5
5.2	6.2	8	9	180	180	359	360	11000	11700	15000	23000	1.4	1
13.2	12.9	13.1	13.3	180	360	360	717	27600	26300	28000	30000	1.5	1
5.2	6.9	8	9.3	179	180	180	360	10700	13600	13000	15000	2	1.4
13.7	12.9	14	14.3	360	360	360	540	25800	25600	24600	30000	2	1.6
7.7	9	11	12	180	360	540	660	28000	28300	32000	35000	1.1	1
7.2	8.7	9.4	10.2	180	360	360	360	20500	23100	24000	25000	3	4
6	7.4	9	10.5	180	360	360	540	13000	13600	15800	16000	1	1
11.1	12	14	15	540	540	540	540	17900	17000	16400	15000	1.1	1

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10.4	12.8	12.3	13.5	179	359	359	359	26400	21700	23900	23500	4	3
5.4	5.6	7.3	7.5	180	180	360	360	29700	27000	29000	25700	2	2
6.7	9.3	9.2	8.1	180	360	360	360	28600	30000	33800	23600	2	0
5.2	6.1	8.8	5.7	180	180	180	256	22400	18800	23400	20900	1.5	0.9
9	10.7	9	10.9	470	360	360	540	24100	33400	26300	34600	1.1	2.1
6.9	8.6	5.9	8.5	60	60	180	360	24100	26800	19300	25000	1.4	3.2
11.1	11.7	11.4	11.4	180	360	540	540	28900	33800	28900	32200	2	2
10.7	10.9	11.1	11.3	180	360	360	540	37400	36300	23000	35000	1.8	2.5
6.4	7.4	8.4	9.9	309	360	360	360	25400	24400	27800	28100	1.5	1.5
8.1	9.7	11.6	11.2	180	360	360	360	28200	31000	34200	30500	0.9	0.7
5	4.9	8	7.5	60	60	180	420	18000	20500	26400	21700	2	1.9
7.8	10.1	9.5	10.1	359	359	512	389	10700	19100	11900	13000	1.6	1
7.5	8.7	7.9	6.7	180	180	360	330	25000	19000	21400	18900	0.3	0.3
4.1	5.1	5.7	5.6	148	180	180	180	17600	11000	11000	13200	3.8	3.3
6	6.5	7	7.3	180	180	180	240	13000	10000	9000	12600	3	2
7.5	9.1	8.8	10	180	180	360	540	37800	40400	23000	35000	1.9	2
7	7.5	9.1	10.3	180	180	360	360	17400	17000	23000	25000	3	2.5
5.7	6	7.1	7.7	180	180	180	180	17400	18000	23000	32000	3	2.5
6.3	7.9	9	9.3	180	180	360	360	18600	26300	23000	23500	1.5	1
3.7	5.9	7.1	8	132	217	346	360	10900	16300	18000	19000	1.1	1.2
7.9	9	11	11.7	409	495	439	540	14500	16000	23000	23500	1.5	1
12.3	13	3.1	14.3	180	360	360	540	18900	18000	16600	16000	3	2.4
9	9.9	10.5	11	180	360	360	540	23100	23600	24400	15000	1.6	1.3
6.4	7	8.1	9.2	180	180	360	360	20500	20600	23000	25000	6.1	5.5
9.4	9	11	13	180	180	360	540	33100	29700	23400	20000	3	2
10	12	13	15	180	360	540	540	20700	20000	17800	18000	2.2	1
11.1	12	13	13.7	539	540	540	540	17600	17000	16000	15000	1	0.5
13.2	14	13.9	14	359	360	540	540	20800	20000	17800	17000	1.8	1
9.1	11	12	13.2	477	539	540	540	13700	13000	14000	13200	2	1
8.1	9.6	11	14	360	539	540	540	32400	30900	30000	28400	2	1

MASTERCHART

lead V5 in mm		Max. ST depression in lead V6 in mm			
60 day	90 day	0 day	30 day	60 day	90 day
1.9	0.9	2	3	2.3	1.3
1.9	1.4	2.5	4	2.2	1.2
0.6	1.9	0.8	2.1	1.4	2
0.5	1	0.7	1.1	0.6	0.5
1.7	1.6	0.7	0.7	0.9	0.6
1	0.8	1	1	1	1.3
1.7	0	0	0	1.9	0
2	1.8	2	2	2.6	1.1
1.6	2	2	1	1.5	2
2.6	1	1	2	3	0.5
1	1.5	1	1	1	1
2.2	2.2	1	1	1	1
2.2	2.4	1.9	1	1.4	2
0.9	2.2	1	1.1	0.8	1.3
1.4	1	1.5	0.6	0.4	0
1.4	1	1.6	1	1.4	1
1.4	1	2	2	1	0.9
1.4	1	2	2	1.4	1
1.4	1	1.7	1	1.4	0.9
1.4	1	1.5	1	1.4	1
1	0	2	1	0.5	0
1	0.6	1.4	1	1	0
1	0.5	1.9	1	1	0.5
0.4	0.1	1	1	0.4	0
1	0.8	2	2	1	0.4
1	0.6	1	1	0.5	0.5
0.4	0	1	0.8	0.4	0
3	1.6	2	4	2	1
0.5	0	1	1	0.4	0
0.5	0.2	1	0.8	0.4	0.2

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3	3	4	4	3	3.2
1	1	4	3	1	1
1	1	2	1	1	1
0	1.9	2.6	1.1	0	1.9
2	1.1	1	2.2	1.7	0.5
1.2	2.5	0.5	0.2	1.1	1.2
1.6	0.8	2	2	1.6	0.8
2.4	1.6	1.7	2	2.4	1.9
1	1.1	1	1	1	0.7
0.4	1	1.7	0.7	0.5	1
0.5	1.8	0.5	1.9	0.8	1.7
0.7	1	1.6	1.5	0.2	1
0	0	1.4	0.5	0	0.2
3.3	2.6	2.9	2.2	2.2	2
2	1	3	2	2	1
2	1.5	1.7	1.2	1	1
2	1.6	2	2	1.4	1
2.4	1.8	3.5	3	2.6	1.9
0.9	0.6	1.3	1	0.8	0.5
1	0.9	1.8	2	1.4	1
1	0.6	1.8	1.2	1	0.8
2	1	4	2	2	1
1.1	1	1.3	1.3	1.1	1
4.4	2.6	4.8	4	2.4	2
1.5	1	2	1.5	1.2	1
0.5	0.5	1	1	0.5	0.5
0.5	0.5	1	0.5	0.5	0.5
0.8	0.5	1.2	1	0.5	0.2
1	0	1	0	0.5	0
0.5	0.2	1.5	0.5	0.4	0.1