# SREE CHITRA TIRUNAL INSTITUTE FOR MEDICAL SCIENCES AND TECHNOLOGY

## PROJECT REPORT

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**PROGRAMME: DM CARDIOLOGY**

**MONTH AND YEAR OF SUBMISSION: NOV 2003**

## CERTIFICATE

I, **Dr. Rajeev. E**, hereby declare that the projects included in this book were undertaken by me under the supervision of the faculty, Department of Cardiology, SCTIMST.

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1-11-2003

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Forwarded,

The candidate, **Dr. Rajeev. E** has carried out the minimum required procedure.

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## Contents

# Efficacy and Safety of Extended Release Niacin in Combination with Atorvastatin in Dyslipidemic Coronary Artery Disease Patients.

## Background and Review of Literature:

It has been suggested on the basis of epidemiological data[1,2] that each 1 percent reduction in the level of low-density lipoprotein (LDL) cholesterol results in a reduction of 1.0 to 1.5 percent in the risk of major cardiovascular events. In trials of LDL-lowering strategies, a reduction of 12 to 38 percent in the LDL level has resulted in a relative reduction in risk of 19 to 35 percent. Similarly in an epidemiologic analysis of risk related to high-density lipoprotein (HDL) cholesterol, an increment of 1 mg per deciliter in the HDL level has been associated with a reduction of 2 to 4 percent in the risk of cardiac events that is independent of the LDL level. If the benefits of raising the HDL level and lowering the LDL level are independent and of similar magnitude, as the results of several trials imply,[3-4] then simultaneous therapeutic alterations of 30 to 40 percent in the levels of these lipoproteins should theoretically reduce the risk of events by 60 to 80 percent.

Among lipid modifying drugs which acts beneficially towards all subfractions of lipids for varying extents, 3-hydroxy 3-methyl glutaryl co-enzyme A reductase inhibitors (the statins) and Niacin[6] have the best records for improving cardiovascular outcomes in clinical trials. Many well controlled trials have shown statins to produce dose dependent reduction in LDL cholesterol and modest elevations in HDL cholesterol. In major trials statins have shown to prevent cardiovascular events including myocardial infarction and death[5].

As there are robust evidences that LDL cholesterol lowering reduces risk for Coronary Heart Disease both in setting of primary and secondary prevention the primary goal of therapy is targetted to LDL cholesterol. This is reflected in the Adult Treatment Panel III (ATPIII)report on detection, evaluation and treatment of high blood cholesterol in adults[7]. ATPIII targets LDL cholesterol as primary goal of therapy and defines cut points for initiating treatment.

The ATPIII report has established the metabolic syndrome (Table 1)as the second target of therapy which represents a constellation of lipid and nonlipid risk factors of metabolic origin. The treatment approaches toward this include weight reduction and increased physical activity In patients with elevated triglycerides the Non-HDL cholesterol is targeted as a secondary target.

*Table. 1*

| Clinical Identification of the Metabolic syndrome | |
|---|---|
| Risk Factor | Defining Level |
| Abdominal Obesity<br>Waist circumference<br>Men<br>Women | <br><br>➢ 102cm (40 in)<br>➢ 88 cm (35 in) |
| Triglycerides | ➢ 150 mg/dL |
| HDL<br>Men<br>Women | <br>⋖ 40 mg/dL<br>⋖ 50 mg/dL |
| Blood Pressure | ➢ 135/85 mm Hg |
| Fasting glucose | ➢ 110 mg/dL |

Low HDL Cholesterol: Low HDL cholesterol is a strong independent predictor of CHD. In ATPIII this is defined as a level < 40 mg/dL. As per the present treatment guidelines there is *no targeted goal* for HDL raising (Table.2). Although clinical trials' results suggest that raising HDL will reduce risk, the evidence is insufficient to specifiy a goal of therapy. Also data showing currently available drugs to robustly raise HDL is found wanting.

***Table.2***

| **ATP III recommendations for low HDL** |
|---|
| 1. Primary target of therapy is LDL cholesterol |
| 2. Weight reduction and increase physical activity |
| 3. If Triglyceride elevated treat the non-HDL goal |
| 4. Consider drugs for HDL raising (Niacin or Fibrates)<br>Esp. In CHD/Risk equivalent patients. |

*Table.3* The effects different drug classes on lipid levels

| Drug Class | Lipid Effects | | Side-effects | Clinical trial results |
|---|---|---|---|---|
| HMG CoA reductase inhibitors (statins)* | LDL<br>HDL<br>TG | ↓18-55%<br>↑5-15%<br>↓7-30% | Myopathy,Increased liver Enzymes.Peripheral neuropathy. | Reduced major coronary events, CHD deaths, need for coronary procedures, stroke, and total mortality |
| Bile acid Sequestrants | LDL<br>HDL<br>TG | ↓15-30%<br>↑3-5%<br>No change or increase | Gastrointestinal distress Constipation Decreased absorption of other drugs | Reduced major coronary events and CHD deaths |
| Nicotinic acid | LDL<br>HDL<br>TG | ↓ 5-25%<br>↑15-35%<br>↓20-50% | Flushing,Hyperglycemia Hyperuricemia,(or gout) Upper GI,distress Hepatotoxicity, Rhinitis, Pruritus and rash. | Reduced major coronary events, and possibly total mortality* |
| Fibric acids | LDL<br>HDL<br>TG | ↓5-20%<br>↑10-20%<br>↓20-50% | Dyspepsia,Gallstones Myopathy,Unexplained non-CHD deaths in WHO study | Reduced major coronary events |

## Niacin (Nicotinic Acid)

Niacin was first introduced as a lipid lowering drug in 1954. Since then studies have shown data on reduction in non-fatal myocardial infarction and all cause mortality.[12] (The Coronary drug Project- JACC 1986) But two issues have prevented Niacin from being extensively used in present clinical practice. Niacin had a significant incidence of unpleasant side effects, the cutaneous reactions and flushing being the most common . Initial reports suggest flushing to be as common as 80-90%. Also this form of Niacin had to be dosed very frequently and hence compliance rates were low. Also the availability of statins, a potent class of drugs which promptly and predictably lowered LDL cholesterol with excellent safety and tolerability shifted the focus to statins.

Niacin functions in the body after conversion to nicotinamide adenine dinucleotide (NAD) in the NAD coenzyme system. The increase in HDL by Niacin is associated with a shift in the distribution of HDL subfractions (^ HDL2:HDL3 ratio) and an increase in lipoprotein a [Lp(a)] content. The mechanism of action of Niacin is not well defined. It may involve several actions including partial inhibition of release of free fatty acids from adipose tissue, and increased lipoprotein lipase activity, which may increase the rate of chylomicron triglyceride removal from plasma. Niacin decreases the hepatic synthesis of VLDL and LDL.

### Different forms of Niacin.

Basically there are two forms of Niacin preparations available. The 'immediate release' and the 'slow release' Niacin. The immediate release Niacin has to be taken frequently with meals and had reportedly more adverse reactions especially prostaglandin mediated flushing and leads to lesser compliance . Hence prolonged release forms were formulated. The sustained release forms were thought to have more of hepatic toxicity. A newer slow release preparation , the 'Extended Release' form which is an intermediate form which release over 8-10 hours is found to have less side effects with equal efficacy.[8] Table 4 summarises the features of different preparations.

| *Table.4* **Preparations of Niacin** | |
|---|---|
| Immediate Release | Delayed Release |
| Crystalline form | Sustained Release (SR) Controlled Release (CR) or Extended release.(ER) |
| Proven effectiveness on lipid lowering | New formulations. Studies on efficacy emerging. |
| Need for multiple daily dosing with food | Single daily dosing |
| Compliance low | Compliance Good |
| Flushing +++ | Flushing+ |
| | Concerns about Hepatotoxicity . Reportedly least with ER form. |
| | ? Less effect on lowering Triglycerides with SR/CR |

Precautions advised while considering Niacin therapy:

Patients with hepato-biliary disease are to be observed closely for worsening. Diabetic or pre-diabetic subjects may experience a dose related rise in glucose intolerance. In using for a patient with Acute Myocardial Infarction or unstable angina particularly when vasoactive drugs are simultaneously used, gradual dosing with observation is mandatory. In patients with Gout, disease worsening may occur. Very small proportion may have reduction in platelet count or prolongation of Prothrombin time on anticoagulants. Caution is advised in presence of renal dysfunction.[19]

## Treatment of Hyperlipidemia with combined Niacin Statin Regimens:

This approach provides marked LDL reduction and favourable changes in HDL and lipoprotein (a). Table 5 summarizes the present data on combined Niacin and Statin trials. There is paucity of data with Atorvastatin and Niacin combination.

Several case reports have suggested higher incidence of myopathy (As high as 2%) Recent prospecitve trials have not supported this and found combination to be safe.[9,11,15] Table 6 summarises the incidence of adverse reactions in the prospective trials with combination treatment.

| *Table. 5* | **Studies on Niacin and Statin combination therapy** | | | | | |
|---|---|---|---|---|---|---|
| Study | Statin | Niacin type | N | Duration of therapy Weeks | ⇓LDL-C % | ⇑ HDL-C % |
| Davignon et al[22] 1994 | Pravastatin 40mg | SR 1-2 g | 36 | 88 | 41 | 16 |
| Jacobson et al [23] 1994 | Fluvastatin 20mg | IR <3 g | 38 | 9 | 40 | 28 |
| Vacek et al [24] 1995 | Lovastatin 20mg | SR 1.2g | 25 | 12 | 37 | - |
| O keefe et al[25] 1995 | Pravastatin 20mg | IR 3g | 21 | 18 | 25 | 29 |
| Gardner et al[26] 1996 | Lovastatin 20mg | IR 1.5g | 14 | 4 | 30 | 27 |
| Pasternak et al[27] 1996 | Pravastatin 40mg | SR 1.5-3g | 40 | 30 | 39-44 | 17-20 |
| Gardner et al [28] 1997 | Pravastatin 20mg | IR 1.5g | 16 | 4 | 33.5 | 13 |
| Brown et al [29] 1997 | Lovastatin 40mg | IR/ SR 2g | 29 | 28 | 57 | 27 |
| Brown et al[19] 2001 | Simvastatin 10-20mg | IR 2-4 g | 160 | 144 | 42 | 26 |
| Capuzzi et al [30] 2003 | Rosuvastatin 40mg | ER 1-2g | 270 | 24 | 43 | 17-24 |
| | | | | | | |
| *SR- Sustained Release, IR- Immediate release, ER-Extended release.* | | | | | | |

***Table. 6*** **Incidence of Side-effects in Niacin-Statin combination**

| Side-effects | Percentage incidence * |
|---|---|
| Flushing | 10% (Delayed release) 8-80% (varied reports for IR forms) |
| Head-ache | 11% |
| Dyspepsia | 5% |
| Diarrhoea | 5% |
| Rhinitis | 4% |
| Nausea,vomiting | 4% |
| Rash | 4% |
| Pruritus | 3% |
| Biochemical: SGPT, SGOT elevation (>2 times.) | 1% |
| Hepatitis | Isolated reports only. |
| Low serum Phosphorus | 2-4% |
| Myopathy | Isolated reports. None reported in 8 recent trials (>300 patients) |
| Asymptomatic Rise in CPK | 2-4% |
| Fall in platelet count | 0.5% |
| Elevation in uric acid | 1% |

**At moderate doses of statin and 1.5 gm Niacin daily.*

## Lipoprotein (a)

A genetically determined lipoprotein in human blood, is one of the most powerful and independent risk factor for premature CAD as well as other arterial disease. The mean levels are reportedly three times higher in Asian Indians than in Chinese and Caucasians.A recent meta-analysis of reported prospective studies supports an independent predictive power for elevated Lp(a)[10]

Serum Lp(a) is relatively resistant to therapeutic lowering. Statin group of drugs are ineffective. Among currently available drugs only nicotinic acid reduces Lp(a) concentrations. In postmenopausal women, estrogen therapy also causes some reduction in Lp(a) concentrations. At present no clinical trial evidence supports a benefit from lowering Lp(a) levels with any particular agent.

Despite limitations in measurement and therapy, some authorities believe that Lp(a) measurement is a useful addition to the major risk factors for identifying persons at still higher risk.[10]

## Aim of Study:

To assess the efficacy and safety of combination therapy of Niacin (Extended Release-Once daily) and Atorvastatin, and to compare the effects of this combination on various lipid sub fractions with respect to Atorvastatin monotherapy.

## Study Design:

The study design was presented in its full protocol before the Ethics committee of this institute and was started after the formal approval by the committee. This open labelled trial prospectively enrolled coronary artery disease patients who require treatment with a lipid lowering drug as per the National Cholesterol Education Programme -Adult Treatment Panel III guideline and who had a low HDL and elevated LDL. The low HDL was defined as per ATP III guideline of less than 40 mg/dl. All patients were on statin monotherapy for a minimum period of 6 months. For uniformity in interpreting data only patients on Atorvastatin were included and those who got changed over from another entered the trial after a run-in period of 8 weeks of atorvastatin with lipid checks before and after. The Atorvastatin was used in conventional dosages as would be required for target LDL levels .The atorvastatin dose was titrated as per lipid profile checks every 3 months or 2 weeks after a change in dosage. Niacin is dosed as per the recommended dose escalation regimen[17] for extended release Niacin. ***(Table 7)***

| WEEKS | NIACIN Dose | Total Daily Dose* |
|---|---|---|
| 1 | 375mg | 375mg |
| 2 | 500mg | 500mg |
| 3 | 375 - 2 tabs | 750mg |
| 4-7 | 500mg 2 tabs | 1000mg |
| Week 8 onwards | 500 X 3 | 1500mg |

*Given once daily at night.

All patients were motivated for life style changes like quitting smoking and increasing physical activity. Patients were adviced to refrain from alcohol use during period of study.

The primary dosage aim with respect to Niacin was to escalate the dose as per the schedule to the steady maximum of 1500 mg. In the group on combination therapy the atorvastatin dose was altered based on LDL level recommendations. As part of safety concerns it was never decided to increase both the drugs' dosages simultaneously at any occasion.

Study Population:

Included were men and women aged 30-75 yrs and followed up at the lipid clinic of SCTIMST. All were put on a lipid lowering diet conforming to step II NYHA diet. The inclusion and exclusion criteria is summarised in table 8.

| *Table 8* **Inclusion and Exclusion Crieteria** | |
|---|---|
| **Included** | **Excluded** |
| Age limit = 30-75 | Triglyceride level >300 |
| At least 6 months on statin | Hepatobiliary and renal disease |
| At least 2 months on Atorvastatin | IDDM or poorly controlled diabetes |
| HDL $\leq$ 39 ( on 2 different occasions) | Secondary forms of hyperlipidemia |
| Adhering to Diet (NYHA stepII) | Acute Myocardial infarction or Unstable angina (In-hospital phase) |
| Willingness for prompt followup | Hypothyroidism |
| | Gout and hyperuricemia. |
| | LV dysfunction. LVEF <40% |

Patients were assigned into 2 groups; and group1 patients (On Niacin and Atorvastatin) followed up with weekly visits initially for 1 month , then twice weekly for 2 months and then monthly. After any change in drug dosages patients were evaluated after a week or earlier if the patient has any new symptom to suggest intolerance. The group2 patients on Atorvastatin were followed up at 3 monthly intervals. LDL was checked in between if a change in atorvastatin dose was made.

Follow up: During each followup the patients were assessed clinically for any possible adverse effect of the drug. The compliance to the drug and dietary guidelines ensured and laboratory tests performed.

Safety and efficacy assessment.

Baseline fasting lipid profile with measurement of plasma lipoprotein-a and Aspartate aminotransferase(SGOT),Alanine Aminotransferase(SGPT). Creatine phosphokinase(CPK) and blood sugar were measured. At each visits CPK,SGPT,

SGOT were measured. Lipoproteins were measured at 3 monthly intervals. All patients had a baseline renal function test consisting of serum creatinine and Blood urea nitrogen. Estimation of serum uric acid and phosphorus were done in selective cases when patient had any prior history of elevated uric acid or joint pains occurred. Other less frequent evaluation included hemogram ,platelet count, and serum phosphorus.

Patients for combination therapy were given a full briefing about the proposed treatment and possible adverse effects reported by the drug manufacturer and previous trials. The need for symptom reporting and regular visits were emphasised and the drugs prescribed after obtaining an informed consent in the local language. Patients who continued on Atorvastatin monotherapy were followed in the usual follow-up pattern for Coronary artery disease patients on statins as proposed by the recent report of the ACC/AHA clinical advisory on statins.[21]

Patients on Niacin and Atorvastatin combination therapy were assessed at each visit for adverse effects as shown in table 6. Clinical events were elicited with direct and indirect questions and over the phone reporting.

At all review clinical and subclinical myopathy was assessed with symptom eliciting and laboratory measures of CPK. The definition of myopathy required unexplained persistent myalgia in presence of CPK elevation more than 3 times upper limit of normal. Any troubling symptom which can be attributed to the prescribed medication was noted and automatically led to withdrawal of drug. See table 9.

When subjective side effects like flushing and pruitus occurred, patient was told could be drug related and given the option to discontinue or continue with monitoring. On suspicion of myopathy the dose escalation was stopped and if clinical myopathy occurred or if sub-clinical myopathy detected from CPK elevation both statin and Niacin were discontinued.

Diabetic patients were included in the study after informed consent regarding probable worsening of diabetes and need for increasing anti diabetic drugs. Included were patients who had type2 diabetes and with OHA glycemic status well controlled. Periodic measurements of fasting and post prandial measurement of blood sugar was made and diabetic status controlled with modification of drug dosages or adding a second class of drug, Niacin was discontinued if blood sugar still was not controlled. For patients on Aspirin it was suggested that they take daily dose of aspirin along with

Niacin. Patients on Atorvastatin monotherapy was followed up with checks of CPK if patient had any muscle symptom and had atleast one liver enzyme screening once in the study period.

Efficacy checks:

Measurement of fasting lipid profile was done at baseline and every 3 monthly. Enzymatic methods were used for Total Cholesterol , Triglycerides and HDL measurements on an autoanalyser. (Dade Behring$^{TM}$) LDL was measured indirectly from the Friedwald equation. Due to inaccuracies in measuring LDL indirectly when TG is high, a cutoff for triglycerides was kept at 300mg/dl. Lp (a) was measured at baseline and after Niacin treatment . Lp (a) only single assay could be done in control group on Atorvastatin alone , which was done towards the end of study period. Lp(a) assessment was done using Immunoturbidimetric assays (CP Biomed inc.)

End points: A followup period of 6 months was planned. See table.9 for end points.

***Table 9.*** **End points**

- Completion of intended followup period (Minimum of 6 months)
- Any form of intolerance attributable to study drug which patient feels unable to continue.
- Rise in Liver enzymes (X2 ULN)
- Rise in CPK-Asymptomatic (X3 ULN)

  Rise in CPK with muscle symptom/fatigue.

  Significant muscle pain/tenderness.
- Worsening glucose tolerence/diabetic status
- Fall in S. Phosphorus levels <3 mg/dl or Platelets <1 Lakh/mm$^3$

*ULN - Upper Limit of Normal.*

Statistical Analysis:

All continuous variables were tabulated as mean ± standard deviation. The base-line lipid levels and those measured during the course of treatment were compared within groups by paired t-tests. Differences among groups and percentage difference between groups in the response of lipid parameters to therapy were compared by the two sample t-test. The significance was assessed by two-tailed P and Levene's Covariance methods. A P value of less than 0.05 was considered to indicate statistical significance. The difference in Lipoprotein-a between test and control groups were compared with Wilcoxon rank sum test. All analyses were carried out using Statistical Package for Social Sciences for Windows. ver.10.0.1 ©SPSS Inc.

## Results:

102 patients with CAD were given Extended Release Niacin along with Atorvastatin. 103 patients served as controls who were followed up on Atorvastatin monotherapy. The baseline characteristics are shown in table 10.

***Table 10***. Continuous Variables expressed as Mean± Std Deviation.

| | **Niacin + Atorvastatin**<br>N= 102 | **Atorvastatin**<br>N=103 |
|---|---|---|
| Age | 52.7 Years (29-69) | 52.3 Years(22-69) |
| Males | 100 (98%) | 101 (98.1%) |
| H/O ACS | 62 (60.8%) | 67 (65.1%) |
| BMI | 23.3 ± 4.3 | 22.7± 5.0 |
| Baseline CPK | 108 ± 43 | 103.2 ± 61 |
| Maximum CK | 138.7 ± 91 | |
| Baseline SGPT | 24.5 ± 13 | 20.1 ± 12 |
| Maximum SGPT | 32.6 ± 15 | |
| Atorvastatin dose<br>Least<br>Maximum | 13.2 ± 6<br>5 mg<br>40 mg | 15.8 ± 7.2<br>5 mg<br>40 mg |
| Niacin dose<br>Least<br>Maximum | 1.294g ± 257<br>1000 mg<br>1500mg | |

The baseline characteristics were similar in both the groups. Both groups were predominantly males. There were 62% and 67% of patients respectively in both groups who had an acute coronary syndrome in the past. This group represented a heterogenous group including patients who underwent revascularisation/arteriograms and who was on medical therapy for various reasons. The Niacin group had more of such patients who underwent revascularisation , esp percutaneously since they were more forthcoming for frequent clinic reviews. Baseline CPK and SGPT were similar in both the groups. In the Niacin combination therapy group , patients had experienced rise in average levels of CPK and SGPT but the final level fell within the specified laboratory range of normal. The patients on Atorvastatin monotherapy had a

higher mean dose of Atorvastatin.(15.8mg vs 13.2mg) The distribution of diabetic individuals and who characterised the 'metabolic syndrome' are tabulated below.(Table.11)

The dosage of Niacin was planned to be escalated to 1.5 gm but, this was not feasible in all patients. Only 61 (60%) had the full dose of 1.5 gm till the end of study period. Others were on 1000mg. The reason for this failure to escalate to maximum dose was mainly due to the fact that Niacin tablets were of 500 mg strength and patients found it inconvenient to swallow three such tablets and majority stuck to 1000g. on their own (mean dose=1.3g)

| *Table 11* | **Group 1(Niacin+Atorvastatin)** | **Group2 (Atorvastatin)** |
|---|---|---|
| Metabolic syndrome | 38 (37.3%) | 40 (38.8%) |
| Overweight (BMI > 25) | 29 (28%) | 29 (28.2%) |
| Diabetes Mellitus | 20 (19.6%) | 23 (22.3%) |
| Patients on full dose of Niacin (1500mg) | 61 (60%) | |

Both the groups had significant changes in the lipid variables compared to baseline. (All two-tailed P <0.05) The baseline lipid profile was comparable in both the groups. The percentage of patients who had attained LDL goal set by ATPIII were comparable at start of study (41%&40%)
Change in Lipid profile among groups before and at 6 months are given in table.12

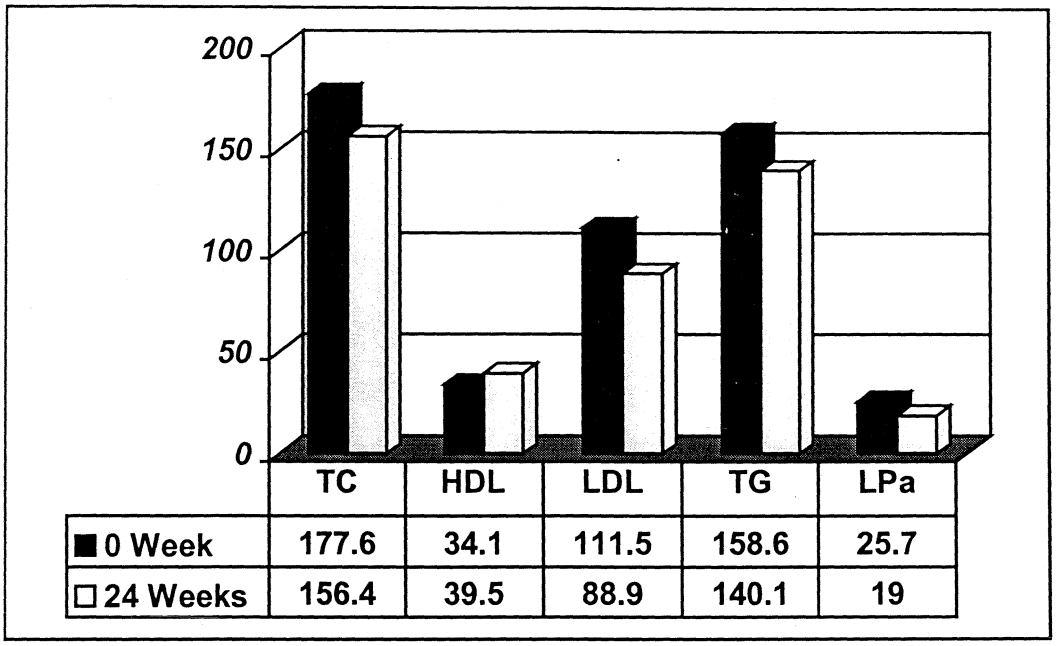
Due to technical reasons the values of baseline LP(a) in the control group could not be taken into analysis. However the values did not differ much from the final mean. 48% of patients had a final HDL level >40 in Niacin group where as only 16.5% had HDL above 40 in Atorvastatin only group.

*Table.12* **Both groups compared with respect to lipid parameters.**

| **Lipid parameters** | | **Niacin+Atorvastatin** | | **Atorvastatin** | |
|---|---|---|---|---|---|
| | | Pre-treatment | At 6 months | Pre-treatment | At 6 months |
| Total Cholesterol | Mean | 177.6 | 156.4 | 178.0 | 164.5 |
| SD | | 36.1 | 31.0 | 45.5 | 39.3 |
| Range | | 97-260 | 87-250 | 88-338 | 80-280 |
| HDL | Mean | 34.1 | 39.5 | 34.5 | 35.7 |
| SD | | 4.1 | 5.5 | 4.4 | 4.5 |
| Range | | 18-39 | 28-58 | 23-39 | 22-49 |
| LDL | Mean | 111.5 | 88.9 | 112.0 | 99.8 |
| SD | | 32.0 | 28.3 | 42.1 | 35.4 |
| Range | | 45-189 | 41-178 | 42-261 | 44-212 |
| Triglyceride | Mean | 156.6 | 140.1 | 157.2 | 145.2 |
| SD | | 53.0 | 40.4 | 56.1 | 46.5 |
| Range | | 67-300 | 50-248 | 62-300 | 60-310 |
| Lipoprotein(a) | Mean | 25.7 | 19.0 | 23.8 | |
| SD | | 15.5 | 9.0 | 14.1 | |
| Range | | 5-68 | 7-54 | 2.8-70.0 | |
| Number of patients achieving LDL goal <100mg/dl | | 42 (41%) | 84 (82%) | 41(39.8%) | 75 (72.8%) |
| Number of patients with HDL $\geq$ 40 | | 0 | 49 (48%) | 0 | 17 (16.5%) |
| No of patients with high LP-a* ($\geq$30mg/dl) | | 26 (28.8%) | 19 (21.1%) | | 23 (29.4%) |

The mean baseline and final lipid values are plotted in graph.1&2

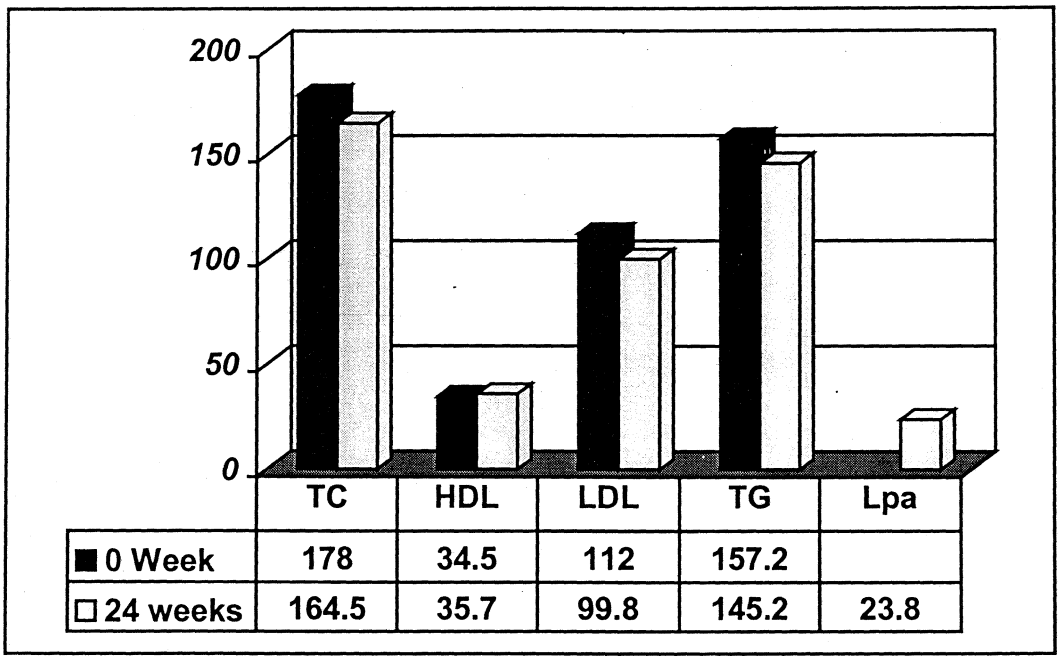
Group 1. Atorvastatin + Niacin




| | TC | HDL | LDL | TG | LPa |
|---|---|---|---|---|---|
| ■ 0 Week | 177.6 | 34.1 | 111.5 | 158.6 | 25.7 |
| □ 24 Weeks | 156.4 | 39.5 | 88.9 | 140.1 | 19 |

*All values expressed as arithmetic mean in mg/dl.*

Group 2. Atorvastatin only.

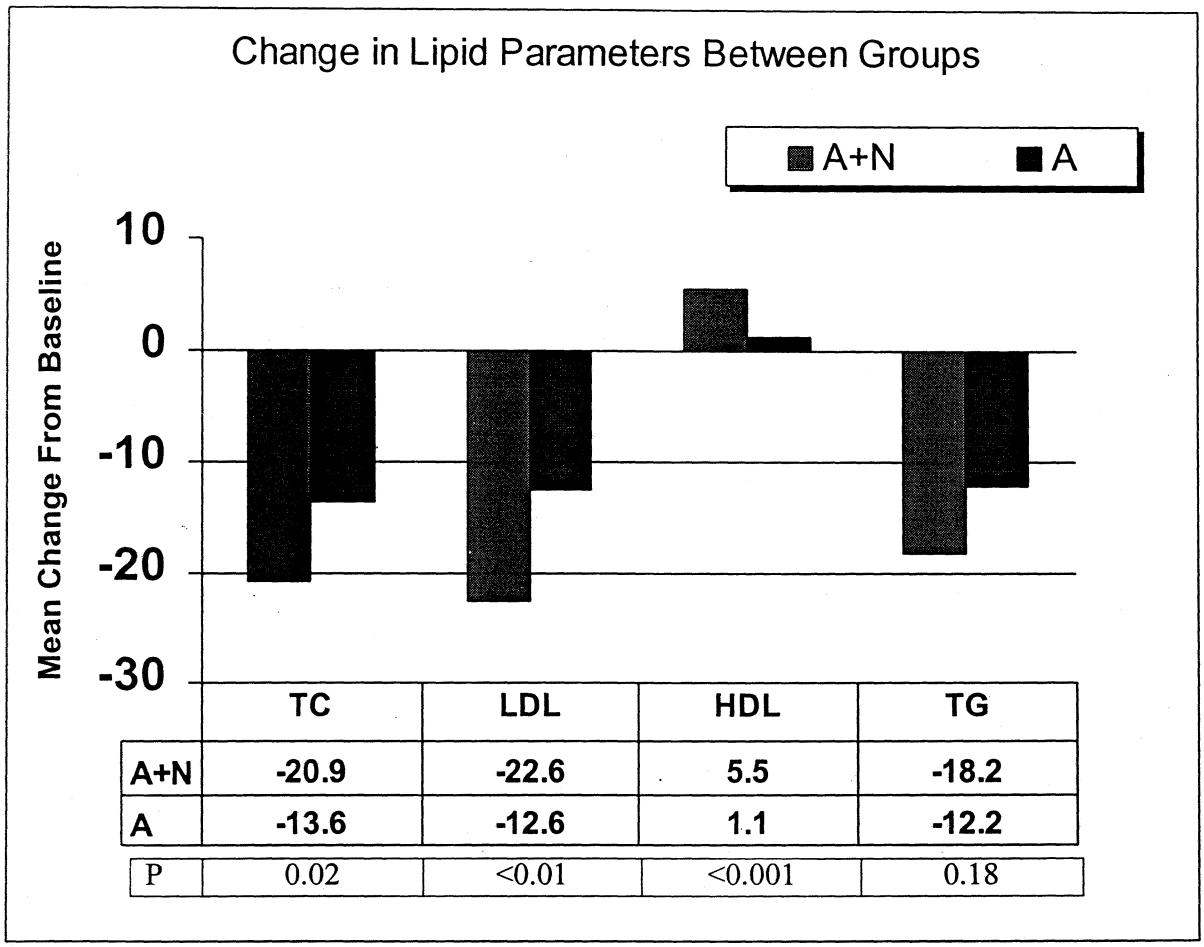



| | TC | HDL | LDL | TG | Lpa |
|---|---|---|---|---|---|
| ■ 0 Week | 178 | 34.5 | 112 | 157.2 | |
| □ 24 weeks | 164.5 | 35.7 | 99.8 | 145.2 | 23.8 |

The magnitude of change in Total Cholesterol, LDL and HDL were significantly higher in the Combination therapy group in comparison to Atorvastatin monotherapy group.(see graph3) The Triglyceride lowering was higher for the Combination therapy group, but this change was not statistically significant. Thus

the Atorvastatin and Niacin combination group was found to have produced significantly greater reduction in total Cholesterol, LDL Cholesterol and Significant rise in HDL. The LP (a) levels were also significantly reduced in Niacin arm compared to the post treatment levels in Atorvastatin monotherapy.

**Graph 3**




| | TC | LDL | HDL | TG |
|---|---|---|---|---|
| A+N | -20.9 | -22.6 | 5.5 | -18.2 |
| A | -13.6 | -12.6 | 1.1 | -12.2 |
| P | 0.02 | <0.01 | <0.001 | 0.18 |

## Subgroup Analysis

Effect of differing doses of Niacin: (Table .13)

61 patients (60%) who took Niacin had the full 1.5g for the whole duration of study. The rest had a dosage of 1 gm. Analyses were carried out to look for the changes in mean pre and post treatment lipid values and the safety parameters. The baseline lipid level were similar in both groups. The mean TC, LDL and TG reduced in both the groups and the magnitude of reduction was not significantly different between the groups. But the magnitude of HDL raising was significantly more in the 1.5g dose group ( +7.4 mg/dl vs +2.4mg/dl) Even though the rise in CPK was more in higher

dose group, this was not statistically significant. The change in SGOT, SGPT had no relation with the dosage given.

***Table.13 Effect*** of different dosage of Niacin on Lipid parameters (Between those who had targeted full dose of 1.5 gm vs others)

| Mean Difference (Basal to 6 months) | **Niacin dosage** | | P* |
|---|---|---|---|
| | 1.5 gm N=61 | 1gm N=40 | |
| Total Cholesterol | -22.2 | - 19.6 | 0.65 |
| HDL | + 7.4 | + 2.4 | **<0.01** |
| LDL | - 25.9 | - 17.6 | 0.12 |
| Triglycerides | - 16.1 | - 22 | 0.43 |
| LP-a | - 6.6 | -6.5 | 0.9 |

*All values in mg/dl .All differences non significant except change in HDL.

Effects of combination therapy in diabetic and non-diabetics (Table. 14)

20 Patients who received the combination therapy were diabetics on therapy. The effects of Niacin in this subgroup were assessed. The pre-treatment values for lipid parameters and other characteristics were equally distributed among both groups. The magnitude of Niacin effect was apparently more in diabetic group but this was not reaching levels of statistical significance.

***Table.14*** Diabetic subgroup- Efficacy of combination.

| Mean Difference (Basal to 6 months) mg/dL | **Type2 Diabetes** | |
|---|---|---|
| | No N=82 | Yes N=20 |
| Total Cholesterol | -29.5 | -19.1 |
| HDL | +5.2 | +5.4 |
| LDL | -30.3 | -20.7 |
| Triglycerides | -21.4 | -17.7 |
| LP-a | -7.8 | -6.3 |

*All differences non significant.

Effect of Combination therapy in subset with metabolic syndrome.

Of the patients on combination therapy, 38 (37%) could be categorized into metabolic syndrome. The mean BMI was 25.6 in metabolic syndrome group while that in others were 21.9. Lipid values were were slightly higher (Not significant) in those who exhibited the metabolic syndrome. The dosages of Atorvastatin and Niacin were nearly equal in both the groups. The average mean levels of change in lipid

subtractions is given in the table.15, which showed a trend for triglyceride lowering to be more in patients with metabolic syndrome. But these differences in TC,LDL,HDL and Triglycerides were not statistically significant. The baseline level of LP(a) was higher in the subset with metabolic syndrome and the extent of lowering (34% and 17% ) was higher in this subset.

***Table. 15*** Metabolic syndrome.

| Mean Difference (Basal to 6 months) | **Metabolic syndrome** | | P |
|---|---|---|---|
| | Present N=38 | Absent N=64 | |
| Total Cholesterol | -22.7 | -20.2 | NS |
| HDL | +5.6 | +5.2 | NS |
| LDL | -23.9 | -25.8 | NS |
| Triglycerides | -21.7 | -16.5 | NS |
| Lp-a | -10.0 | -4.1 | 0.02 |

All differences non-significant except Lp(a)

Overweight Patients ( BMI > 25).

Of the group which received combination therapy 29(28%) had a BMI of 25 or above. The baseline characteristics with respect to age, dosage of Atorvastatin, Niacin as well as lipid sub fractions were comparable among overweight and non-obese groups. The mean change in lipid parameters with combination therapy was similar with respect to the BMI.

Safety End-points.

At the end of 6 months Niacin was stopped in 4 patients and 4 others had minor side-effects but continued with both Niacin and Atorvastatin (8%incidence of events). In one patient niacin was stopped due to a rise in Creatine Kinase enzyme(Maximum CPK=890 IU). In this patient no clinical myopathy was noted. On subsequent followup the CK levels gradually came down over a period of 4-6 weeks after stopping both Niacin and Statin. In 2 patients Niacin had to be stopped in view of difficulty in controlling post prandial blood sugar with anti-diabetic drugs. 1 patient who had a history of quiscent acid peptic disease developed nocturnal stomach pains and upon discontinuing Niacin had symptom relief. No serious side-effects occurred. No patient had significant hepatic toxicity or rise in liver enzymes. Noncompliance to study drug was noted in 3 patients on Atorvastatin group where as none in Niacin

combination group. One patient in Atorvastatin group had drug discontinued due to a rise in liver enzymes.(SGPT=360) Table 16 gives an overview of adverse reactions.

**Table.16** Adverse reactions and compliance.

| **Niacin + Atorvastatin** | **Atorvastatin only.** |
|---|---|
| Noncompliance - 0 | Noncompliance - 3 |
| Niacin stopped during followup- 4 | Atorvastatin stopped-1 |
| *Reason for discontinuation:*<br>Peptic ulcer - 1<br>Worsening diabetes=2<br>Subclinical myopathy=1(X3 times ULN CK) | *Reason for discontinuation:*<br>Rise in liver enzymes =1 |
| Minor side-effects | |
| Flushing -2<br>GI sympoms-2 | GI symptoms 2 |

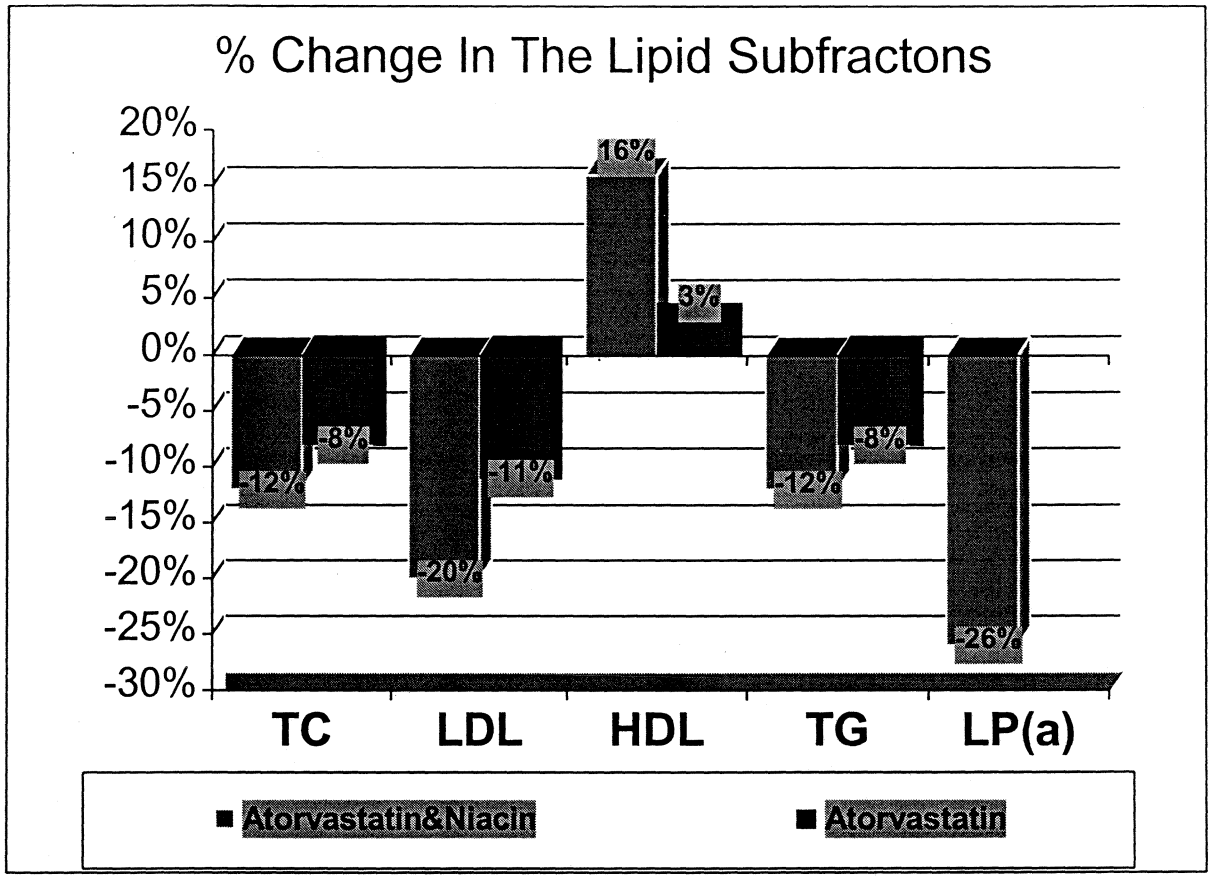
Two patients reported flushing , but both didn't feel it to be troublesome to stop the medication. One patient felt nasal congestion at night which may be due to mucosal capillary vasodilatationan as an eqivalent of flushing .

## Discussion

As recognised by the National Cholesterol Education Programme- ATP III report, it suggests that there may be more to achieve in lipid lowering than LDL lowering. And the focus shifts to the so called metabolic syndrome, the key feature being insulin resistance and atherogenic particles in excess in blood. This forms a second target of therapy. Also newer emerging risk factor like Lipoprotein (a) is being implicated in premature atherosclerotic vascular disease and is a marker of aggressive forms of disease. With proven benefits for HDL level raising in coronary artery disease patients, possible benefits with lowering triglycrides, and theoretical benefits in lowering LP(a), statins alone are insufficient to achieve these results. In this setting the ideal solution would be to combine the beneficial effects on Statins with that of Niacin by way of combination therapy. The intermediate/extended release form of niacin has convenience of once daily dosing and less of trouble some effects like flushing and major ill effects when used in combination with statin.

Previous studies suggest that bedtime niacin administration diminishes lipolysis and release of free fatty acids to the liver; this, in turn, leads to an abolition of the usual diurnal increase in plasma triglyceride, which may result in diminished formation and secretion of triglyceride in the very-low-density lipoprotein fraction.[20]

In this study both Atorvastatin monotherapy and Combination therapy of Niacin and atorvastatin effected significant lowering of TC, LDL,and Triglycerides as compared with the basal values and had elevations in HDL.(more in combination therapy group). The absolute changes among both groups when compared showed significant differences.(Graph 4) The combination therapy group exerted greater reductions in TC, LDL and Lp(a) . There was significant elevation in mean HDL levels when compared with monotherapy and 48% in combination therapy group had >40 mg/dl HDL. (16.5% only in atrovastatin group) The triglycerides were lowered by both treatment strategies but the absolute difference was not statistically significant. The percentage shift in lipid subclasses expressed as percentage of basal level is plotted in the graph.



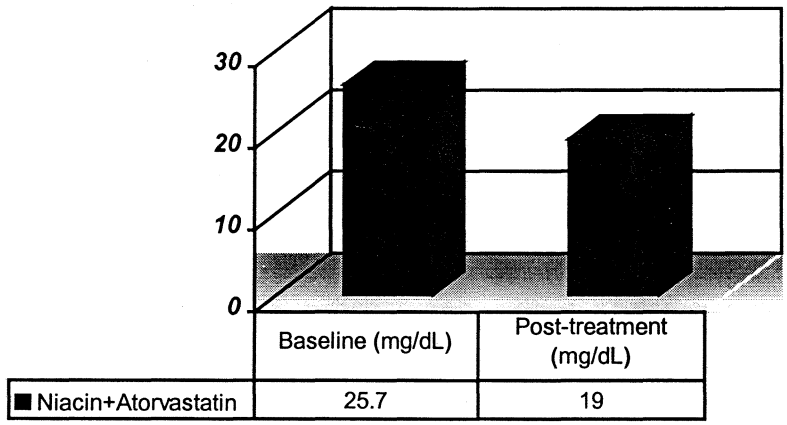

As per large studies Niacin would be expected to cause 15-35% rise in HDL and 20-50% fall in triglycerides[9]. The reduction of LDL and total cholesterol is contributed by statins as well in this study. The expected effect on Triglyceride is not seen in this study (reduction of 12% ) but HDL shows a rise of 16% (as compared with 3% rise with monotherapy). Also the difference in Triglyceride lowering is lesser than would be expected (12% vs 8%)

The rationale for the lack of triglyceride effects may be multiple. In this study the upperlimit of 300mg/dL cutoff point is set. This may have excluded patients with higher triglycerides , in whom magnitude of triglyceride lowering would be more. Also confounding factors in sampling may have influenced the estimation of triglycerides.[14] Triglyceride levels would fluctuate with respect to the precise timing of sampling after the last meal. This may not be uniform among subjects. Also patients with coronary artery disease may exhibit a greater post-prandial delay in the removal of chylomicron particles. Two triglyceride surges have been demonstrated in some individuals , 1 approximately 2-4 hours after a fat containing meal, and the other between 8-10 hours later. Postural state at sampling also has shown to produce

variations in level of triglycerides. Sampling in bed results in lower levels and levels increase after a period of standing. In present study which has a smaller sample size, the effects of any of the above mentioned problems may have resulted in exaggerated effects. These inconsistencies in sampling and differing values may be the explanation for the apparent absence of a significant lowering of plasma triglycerides.

Effect on Lipoprotein(a) : Niacin and atorvastatin combination lowered the LP (a) levels significantly, compared to basal levels. The basal Lp(a) was high in 29% of subjects and at 6 months only 21% had levels >30mg/dl.(29% in control group) The mean Lp(a) showed significant reduction of 26%.(See graph 4)

**Effect of NIACIN + ATORVASTATIN on Plasma LP(a) (Mean Levels)**




Reported data shows LP(a) lowering to the extent of about 20% with Niacin and statin combination[14].Statins have not shown to change LP(a) levels significantly.

Safety of the combination therapy:

No serious adverse events occurred with addition of Niacin. In 4% Niacin had to be discontinued , reason being worsening of diabetes in 2. This is a known effect of niacin and caution has to be exercised while using in diabetic subjects. But this does not contraindiacte its use in the diabetic population who have a higher prevalence of atherogenic dyslipidemia with low HDL. Only one (1%)patient had significant elevation in creatine kinase, which was unassociated with muscle pain or tenderness. No rhabdomyolysis occurred. The incidence of significant myopathy from various studies on combination therapy have placed statin-fibrate combination at highest risk

(Approx 1%) and statin-niacin combination a little lower. Flushing incidence as per this study is only 2%. This low incidence may be due to the controlled release of active drug as well as night time dosing. In our population with predominantly dark complexion flushing may not be easily noticed. Also nearly all patients in this study were on concomitant aspirin therpy , which patients took along with niacin would have contributed to the low incidence of troublesome flushing. 3% Had GI symptoms (Upper GI tract) and in 1 patient worsening of acid peptic disease warranted withdrawal of niacin(two of these patients were on 1.5g and one patient on1g dose). The CPK and SGPT showed rise in niacin group but this rise was not reaching statistical significance. No patient significant rise in liver enzymes or uric acid in niacin group. One patient on atorvastatin therapy was found to have elevated SGPT and SGOT with fatty changes in liver and atorvastatin was stopped.The liver enzyme rise in this setting could not be clearly attributed to Atorvastatin. Since patients were followed up regularly with an element of bias towards inclusion of more motivated patients in niacin group the compliance to niacin therapy was complete. 3% on Atorvastatin monotherapy were non-compliant.

The Niacin dose was escalated to 1.5 gm in majority and Atorvastatin was used in modest doses. Maximum Atorvastatin dose used in this study is 40mg which is lower than other reports when used as monotherapy.

The effect of 1.5 g and 1g when analysed separately showed that HDL elevation was more marked in the higher dose group. The effect on HDL by niacin is dose dependent. Also the maximum CK values occurred in patients taking full prescribed dose of Niacin.The liver enzymes did not correlate with dosage. But since none had elevation in SGPT/SGOT this was to be expected. The reported beneficial effects on LP(a) is dose dependent, but present data did not show significant difference between levels of final LP(a) in the 1g and 1.5 g dosage strata.This may be due to the small sample size of study.

The effect of Niacin and Atorvastatin on patients with metabolic syndrome was similar to those without this. Niacin was equally efficient in beneficially modifying lipids in those with metabolic syndrome. The mean level of LP(a) was higher in (29.8mg.dl vs 23 mg/dl) patients with metabolic syndrome. Lowering of Lp(a) is better (34% vs 17%)in patients with metabolic syndrome.

Niacin and Atorvastatin combination therapy was found to be equally effective in diabetic and overweight subsets.

Effect on attaining ATPIII LDL goal.

This study addressed a common and clinically relevant issue : in patients taking a stable dose of statin who have not achieved their LDL Cholesterol goal with a persistent low HDL cholesterol: what are the beneficial effects of adding another drug-'Extended Release Niacin' to statin?

At start of study the number of patients who had reached ATP III LDL cholesterol goal was 41% in combination therapy group and 40% in monotherapy group. Both groups had atorvastatin dosage adjusted by checking LDL cholesterol levels. The group on combination therapy at the end of study had 82% who reached LDL cholesterol goal whereas only 73% reached LDL-cholesterol goal in Atorvastatin monotherapy. This difference is highly significant especially in the setting of a population of patients with CHD..This beneficial effect on LDL goal on adding Niacin has been shown in other studies as well.[18]

**Limitations of study:**

1. Open labelled and non-placebo-controlled nature.
2. Short duration of followup.

## Conclusions:

1. Combination therapy with Atorvastatin and Niacin caused significantly greater lowering of Total Cholesterol and LDL Cholesterol and Lipoprotein(a) when compared to a similar group on Atorvastatin monotherapy, also addition of Niacin significanty raised the HDL levels. The combination effected lowering of triglycerides which was not significantly higher than Atorvastatin alone.
2. Addition of Extended Release Niacin to a stable moderate dose of Atorvastatin is safe.
3. The most common reported adverse reaction for Niacin-'flushing'- occurred in only 2% of subjects and that too was not troublesome.Major side-effects Clinical myopathy and Hepatic dysfunction are extremely uncommon.
4. Niacin-Extended Release at a dose of 1.5 gm is superior to 1 gm in raising HDL levels
5. In patients with diabetes combination therapy was equally effective in modifying lipid profile favourably when compared with non-diabetics. 10% with type 2 diabetes had worsening of diabetes. Diabetic subjects need to be monitored for this problem during therapy with Niacin.
6. Patients with metabolic syndrome has higher levels of LP(a) and Niacin and Atorvastatin combination therapy lowers LP(a) to a greater extent in this subset.

## References.


1. Wilson PW, Anderson KM, Castelli WP. Twelve-year incidence of coronary heart disease in middle-aged adults during the era of hypertensive therapy: the Framingham Offspring Study. Am J Med 1991;90:11-6. [Erratum, Am J Med 1991;90:537.]
2. Assmann G, Cullen P, Schulte H. The Munster Heart Study (PROCAM): results of follow-up at 8 years. Eur Heart J 1998;19:Suppl A: A2-A11.
3. Phillips NR, Waters D, Havel RJ. Plasma lipoproteins and progression of coronary artery disease evaluated by angiography and clinical events. Circulation 1993;88:2762-70.
4. Robins SJ, Collins D, Wittes JT, et al. Relation of gemfibrozil treatment and lipid levels with major coronary events: VA-HIT: a randomized controlled trial. JAMA 2001;285:1585-91.
5. Gould LA, Rossouw JE, Santanello NC. Cholesterol reduction yield Clinical benefit-Impact of statin trials. Circulation 1998;97:946-952
6. Martin JR, Tato F, Mostaza JM et al. Effectiveness of low dose crystalline Nicotinic acid in men with low high density lipoprotein cholesterol levels. Arch of Int Med. 1996; 156:1081-88.
7. Expert panel on detection, Evaluation and tratment of High Blood Cholesterol in Adults. Executive summary of the third report of the National Cholesterol Education program (NCEP) Expert panel on detection, Evaluation and tratment of High Blood Cholesterol in adults (Adult Treatment Panel III) JAMA 2001;285:2486-2497.
8. Knopp RH, Ginsberg J, Albers JJ Contrasting effects of unmodified and time-release forms of niacin on lipoproteins in hyperlipidemic subjects: clues to mechanism of action of niacin. *Metabolism* 1985;34:642-50.
9. Guyton JR, Goldberg AC, Kreisberg RA.Effectiveness of once-nightly dosing of extended release niacin alone and in combination for hypercholesterolemia. *Am J Cardiol* 1998;82:737-43.
10. Danesh J, Collins R, Peto R. Lipoprotein(a) and coronary heart disease. Meta-analysis of prospective studies. *Circulation* 2000;102:1082-5.

11. Wolfe ML, Vartanian SF.Safety and effectiveness of Niaspan when added sequentially to a statin for treatment of dyslipidemia.Am J Cardiol 2001 Feb 15;87(4):476-9
12. Canner PL, Berge KG, Wenger NK. Fifteen year mortality in Coronary Drug Project patients: long-term benefit with niacin. *J Am Coll Cardiol* 1986;8:1245-55.
13. Miller M. Differentiating the effects of Railsing low levels of High density lipoprotein cholesterol versus lowering of normal triglycerides;Further insights from the VA-HIT trial. Am J Cardiol 2000;86(suppl):23L-27L
14. Bays HE. Lipoprotein effects of a new dual component drug(niacin externded release and lovastatin) compared with starting doses of atorvastatin and lovastatin. J Am Coll of Cardiol 2002;39 suppl A :245A
15. Stein EA, Davidson MH, Dujovne CA et al.Efficacy and Tolerability of Low-dose Simvastatin and Niacin, Alone and in Combination, in Patients With Combined Hyperlipidemia: A Prospective Trial.J Cardiovasc Pharmacol Ther 1996 Apr;1(2):107-116
16. Capuzzi DM, Guyton JR et al.Efficacy and safety of an extended-release niacin (Niaspan): a long-term study. Am J Cardiol 1998 Dec 17;82(12A):74U-81U
17. Goldberg AC.Clinical trial experience with extended-release niacin (Niaspan): dose-escalation study. Am J Cardiol 1998 Dec 17;82(12A):35U-38U
18. Wolfe ML, Vartanian SF.Safety and effectiveness of Niaspan when added sequentially to a statin for treatment of dyslipidemia.Am J Cardiol 2001 Feb 15;87(4):476-9
19. Brown BG, Zhao X-Q, Chait A, et al. Simvastatin and niacin, antioxidant vitamins, or the combination for the prevention of coronary disease. N Engl J Med 2001;345:1583-1592
20. Knopp RH. Clinical profiles of plain versus sustained-release niacin (Niaspan) and the physiologic rationale for nighttime dosing.Am J Cardiol. 1998 Dec 17;82(12A):24U-28U
21. Writing Committee members. ACC/AHA/NHLBI Clinical advisory on the use and safety of statins. J Am Coll of Cardiol 2002;40:567-72.
22. Davignon J, Roederer G et al. Comaprative efficacy and safety of Pravastatin, Nicotinic acid and the two combined in patients with hypercholesterolemia. Am J Cardiol 1994; 73: 339-345.

23. Jacobson TA, Chin MM et al. Fluvastatin with and without Niacin for hypercholesterolemia. AMJ Cardiol 1994; 74:149-154
24. Vacek. JL, Dietmeir G et al. Comparison of Lovastatin 20mg and Nicotinic acid 1.2 G with either drug alone for type2 Hyeperlipoproteinemia Am j Cardiol ; 76:182-184
25. O'Keefe JH Jr, Harris WS et al. Effects of Pravastain with Niacin or Magnesium of lipid levels and post prandial lipemia. AMJ Cardiol 1995; 76:480-484
26. Gardner SF,Schneider EF et al. Combination therapy with low dose lovastatin and Niacin is as effective as higher dose lovastatin. Pharmacotherapy 1996;16:490-423
27. Pasternak RC, Brawn LE et al. Effect of combination therapy with lipid reducing drugs in patients with CAD and "normal" cholesterol levels.A randomized placebo controlled trial. Ann Int Med. 1996;125:529-540
28. Gardner SF, Marx MA et al. Combination of low dose Niacin and Pravastatin improves the lipid profile in diabetic patients without compromising glycemic control. Ann Pharma Other 1997;31:677-682
29. Brown BG, Bardsley J et al. Moderate dose, three drug therapy with Niacin, Lovastatin and Cholestipol to reduce low density lipoprotein cholesterol less than 100mg/dl In patients with hyperlipidemia and CAD. Am J Cardiol 1997; 80:111-115
30. Capuzzi DM, Morgan JM et al. Beneficial effects of Rosuvastatin alone and in combination with extended release Niacin in Patients with a combined hyperlipidemia and low high density lipoprotein levels. Am J Cardiol 2003;91:1304-1310

# Clinico-epidemiological Profile and Intermediate Term Follow-up of Patients with Angiographically Normal or Mild Coronary Artery Disease and Structurally Normal Heart.

**Background**

A significant proportion of patients undergoing diagnostic coronary catheterization because of chest pain, has normal or near normal coronary arteries. Although the heterogeneous nature behind symptoms in this group of patients should be emphasized, the overall prognosis in terms of life expectancy and cardiac pathology is excellent. This group of patients, before a definite demonstration of coronary anatomy has considerable morbidity and use of medical resources in terms of medications and hospitalisations.

Patients presenting with history of chest pain in absence of acute coronary syndrome with a structurally normal heart fall into two categories, those with significant intraluminal coronary artery disease and those without. The further management and prognosis depends on this key issue. The prediction whether a single patient would fall into either of these categories by non-invasive diagnostic tests may not be accurate in many instances. The approach to such a patient would commonly include a characterization of symptoms, evaluation of risk factors for coronary artery disease and stress electrocardiogram.

Patients with CAD may become symptomatic in many different ways but most commonly develop angina pectoris. Typical angina means a chest discomfort due to myocardial ischemia, often described as a transient squeezing, pressure-like precordial discomfort. Not all stable chest pain syndromes are truly anginal. Various authors have subdivided stable chest pain syndromes in an attempt to link the quality of symptoms with the prevalence of significant CAD. Diamond and Forrester[1] found significant CAD at angiography in 89% of patients with typical angina but in only 50% with atypical angina and merely 16% of patients with non anginal chest Pain. Inclusion of coronary risk factors strengthened the predictability of such models. In CASS, (Coronary Artery Surgery Study) 8,157 patients with chronic stable chest pain who underwent coronary angiography were characterized by type of symptoms reported. The CASS definitions of anginal type have become standards for much subsequent literature[2] . "Typical angina" or "Definite angina" was defined as substernal discomfort precipitated by exertion and relieved by rest or nitroglycerin in 10 minutes. Most patients reported typical radiation to the shoulders, jaw or inner aspect of the arm. Patients with probable angina had most of the features of definite angina, but the features were atypical in some respects (e.g., radiation, unpredictable relief with nitroglycerin or duration up to 15 to 20 min). The third group had

34 percent of patients at low risk with a treadmill score +5 or greater.

Aim of study: To study the clinical features, epidemiological factors, non-invasive risk assessment and angiographic characteristics of patients who underwent coronary angiogram as part of diagnostic workup for Coronary artery disease. (CAD). Patients with coronary angiograms showing only mild coronary lesions (defined as <50% diameter stenosis) or normal coronary arteries without a prior history or definite evidence of acute coronary syndromes and/structural heart disease are selected.

Methods:

Angiographic data of this hospital from January 1999 to Dec 2002 were examined and angiograms of patients who had no prior history of acute coronary syndromes without (clinical and Echocardiographic) structural heart abnormalities are reviewed. Excluded are epicardial lesions or lesions in large branches with more than 50%diameter stenosis, assessed visually and if borderline by quantitative coronary angiography (QCA). Patients with history of Acute Coronary Syndrome (ACS), Myocardial infarction or abnormal echocardiographic anatomy (Except milder degrees of LV hypertrophy and relaxation abnormalities) were excluded. Also those with any lesion of left main stem were excluded. All patients who had assessment of cardiac risk as part of non-cardiac surgery were excluded.

The epidemiological, exercise test and echocardiographic data were obtained from the hospital records and patients were followed up till September 2003. The referring physician's diagnosis and details of data on hospitalisations were sought and any hospitalisation with acute coronary syndrome with documented serial electrocardiographic changes or cardiac enzyme elevation was taken as prior ACS and such patients were excluded. Data on lipid parameters were taken from the laboratory records. Basal ECG at the time of admission for coronary angiography was evaluated and categorized into normal or abnormal resting ECG, and abnormality qualified. Echocardiographic data were also noted, particularly for left ventricular hypertrophy, diastolic dysfunction.

The exercise test was done in standard Bruce Protocol and Interpreted into positive, Negative or Inconclusive for inducible ischemia. Duke score was calculated in all instances except in cases with Left bundle branch block.

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The exercise test was done in standard Bruce Protocol and Interpreted into positive, Negative or Inconclusive for inducible ischemia. Duke score was calculated in all instances except in cases with Left bundle branch block.

## Results:

316 patients were included in the study after going through the reports of over 4200 coronary angiograms performed over 4 years. All had normal or near normal coronary arteries as defined earlier. The demographic and symptom characteristics are given in table 1.

The average age was 51.8 years and majority fell in the 45-60 years age group (66%). 55% of the cases were females. Angina was the predominant symptom in 298 patients (94%). Majority of the patients were assessed to have typical angina (51%) at the time of admission for coronary angiography, 20% had atypical chest pain and 24% had probable angina, that is symptoms were akin to anginal pain with odd features. The average NYHA class was 2.1. 45% had history of hospitalisation and 23(8%) had two or more hospitalisations. Patients were on various medications before coronary angiogram, number ranging from 0 to 7, per person average of 3.8 drugs. The most common drug was Aspirin (98%).

Other symptoms were reported in 80 patients (25%), dyspnoea being the commonest (21%) 3% had fatigue as symptom.

Risk factors for atherosclerosis were present in 89.2%. The most prevalent were hypertension and dyslipidemia in 62%&61% each. (Table. 2)

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| **Table 1.** | | **N= 316** |
|---|---|---|
| Age (Mean ± Standard Deviation) | | 51.8 ± 8.9 (27-78 years) |
| Male: Female | | 0.45:0.55 |
| Angina | Typical | 160 (51%) |
| | Atypical chest pain | 63 (20%) |
| | Probable angina | 75 (24%) |
| NYHA class | | 2.1 ± 0.34 |
| Occurrence of Rest angina /symptoms at rest | | 176 (62%) |
| Patients who had Hospitalisations before CAG | | 126 (45%) |
| Duration of symptoms (months) | | 11.2 ± 12.5 |
| No of Medications before angiogram Mean & Range | | 3.8 (0-7) |
| **Symptoms other than chest pain** | | |
| Dyspnea on effort | | 64(21%) |
| Fatigue | | 9 (3%) |
| Palpitations | | 6(2%) |
| Others- Neurological, claudication etc. | | 1 |
| **Medications before angiogram** | | **(percentage)** |
| Aspirin | | 98.1 |
| Nitrates | | 51 |
| Beta-blocker | | 45.5 |
| Ca channel blockers | | 38.3 |
| Statins | | 30 |
| ACE Inhibitors | | 13.6 |

**Table. 2 Risk Factors for coronary artery disease:**

| | | |
|---|---|---|
| No identifiable risk factors | | 34 (10.8 %) |
| Hypertension | | 196 (62%) |
| *Dyslipidemia | | 193 (61%) |
| | High LDL | 106 (42%) |
| | Low HDL | 153(40.7%) |
| | High LDL & Low HDL | 56 (22%) |
| | High Triglycerides | 30 (11.5%) |
| Smoking | | 73 (23.1%) |
| Diabetes mellitus /IFG | | 82 (24.7%) |
| Family history | | 54 (17%) |
| Hypothyroidism | | 9 (3%) |
| Post menopausal status (female n=173) | | 111 (64%) |

*LDL as per Adult treatment panel III defined targets for risk category. HDL low if less than 40 mg/dl. Triglycerides high if >200 mg/dl.

80% of patients had multiple risk factors. 25% had diabetes mellitus. The average lipid parameters are shown in table. 3

| | | | |
|---|---|---|---|
| 2 or more risk factors present | | | 80.4 |
| 3 or more risk factors present | | | 28.1 |
| Duration of diabetes mellitus N=82 (Mean± SD) Months | | | 61.5 ± 48.1 |
| Lipids Elevated | | | 151 (51%) |
| Total Cholesterol | HDL | LDL | Triglycerides |
| 199± 48 | 41± 10 | 129± 45 | 142± 81 |

All Values in mg/dl

The resting ECG was normal in majority, abnormal in 37.7%, and the commonest abnormality being repolarization abnormalities. (Table. 4)

**Table.4 Electrocardiographic findings**

| | |
|---|---|
| Normal | 192 (60.8%) |
| Abnormal | 119 (37.7%) |
| | ST/T changes 99 |
| | LBBB 7 |
| | RBBB 4 |
| | Early Repolarization 3 |
| | AF 2 |

The echocardiographic characteristics were as follows. (**Table. 5**)

| LVDD | LVDS | IVSD | IVSS | PWD | PWS | LA | AO | EF |
|---|---|---|---|---|---|---|---|---|
| 44.5 | 27.6 | 9.6 | 12.6 | 9.4 | 12.8 | 34.6 | 28.5 | 69.3 |
| Diastolic dysfunction | | | | LVH | | | | |
| 60 (20.9%) | | | | 37 (12.3%) | | | | |

Exercise stress testing result was available in 75% of patients. 71% were reported to be positive for inducible ischemia. 74% had attained 85% or more of maximum predicted heart rate. Test was reportedly negative in 9.2% and inconclusive in 20%. Average Duke score was 1.6. Only 2.2% were noted to have high-risk score of less than -10. Majority (74%) had an intermediate risk score. (See Table .6)

**Exercise test characteristics: Table 6** {TMT Done in N=217 (75%)}

| | |
|---|---|
| Mean ET | 7.1 min |
| METs | 8.5 |
| **P**ositive: **N**egative: **I**nconclusive | 154(71%) 20 (9.2%) 43 (20%) |
| Duke score | Mean +1.6 Range(-12 - +12) |
| Low risk (>5) | 42 (23%) |
| Intermediate risk (4 to -9) | 134 (74%) |
| High risk (< -10) | 4 (2.2%) |

The reported indication for Coronary angiogram is shown in table.7. The most common indication was a positive or inconclusive stress test.

| **Table. 7 Indication for coronary angiography** | |
|---|---|
| Positive or inconclusive TMT | 138 (43.6%) |
| Suspected Unstable angina | 65 (20.7%) |
| ECG abnormalities | 18 (5.6%) |
| Multiple risk factors | 15.5 (4.9%) |
| Referral or patient preference | 8 (2.5%) |

Coronary angiogram was done via the femoral route, except in one patient when it was done via the Radial route. The Judkin's technique was used usually. Calcification on the coronary tree was noted in 24 (7.5%) of cases. The mean age of those with calcification was 62.1 years and 2/3$^{rd}$ were males and seen almost exclusively in those with diseased coronaries (21 of 24 had intraluminal lesions). Coronary artery ectasia as defined by more than 50% diameter of a reference non-affected artery, was found in 15 angiograms. (4.7%) (Table.8)

**Table. 8A Coronary angiographic characteristics**

Coronary Angiogram N=316

| | |
|---|---|
| Calcium on Fluoroscopy | 24 (7.5%) |
| Ectasia | 15 (4.7%) |
| Diseased Coronaries | 110 (35%) |
| Complications | 10 (3.2%) |
| Access site complications : Pseudoaneurysm =3, AV fistula= 1<br>Arrhythmia (SVT, AF) 1 each. LBBB =1, TIA=1<br>Coronary dissection=1<br>Angina with borderline cardiac enzyme rise =1 | |

**Table.8.B** Diseased Coronaries- Distribution of disease and mean diameter of stenosis:

| LAD | Circumflex | RCA | Branch Lesions (Diagonal, OM, |
|---|---|---|---|
| 74 (23%) | 21 (6.4%) | 37 (12%) | Ramus, PDA) 44 (14%) |
| Mean Diameter of Stenoses | | | |
| 18% | < 10% | 10% | |

In 110 (35%) patients, coronary angiogram showed mild disease and the rest had no luminal abnormalities detectable. The Left anterior descending artery was diseased in 74 (23%) patients, the circumflex in 21 (6.4%) Right coronary artery in 37 (12%) and Branch lesions occurred in 44 patients

The complications of cardiac catheterization occurred in 10 patients (3.2%). The most common occurrence was access-site complications, 3 instances of pseudo-aneurysm and 1 AV fistula. All patients with local complications were females and 3 of 4 were obese.

One patient had a catheter-induced dissection of right coronary artery without significant flow limitation. There was no peri-procedure angina or cardiac enzyme elevation. On follow up patient was doing well.

Arrhythmias occurred in 2. One patient had SVT and other had atrial fibrillation. SVT was self-limited, AF persisted at discharge, but when seen 1 month later the patient was noted to be in sinus rhythm. One patient developed left bundle branch block, which resolved after 6 hours.

One patient had chest discomfort after procedure and on monitoring had mild elevation cardiac enzymes without electrocardiographic changes. This patient had mild disease with ectatic coronary segments.

One patient had a transient ischemic attack involving the posterior cerebral circulation presenting as vertigo. A computed tomogram of head was normal.

No major complications like myocardial infarction, death, massive cerebro-vascular accident or life threatening arrhythmias occurred. The patients with pseudo-aneurysm underwent ultrasound probe guided compression and 2 out of three were noted to have regression on follow-up vascular Doppler studies. One patient required blood transfusion and had repair of pseudo-aneurysm. Patient with AV fistula was operated without events.

Follow-up data was obtained from 230 patients. (72.8%) 124 had $\geq$ 2 visits. 86 patients were lost to follow up. The events and follow-up data are as given in table. 9.

The mean duration of follow up was 22.4 months. 7.8% had any form of events during follow up. 17 patients had hospitalisations at follow up for presumed unstable angina; no patient had multiple hospitalisations. (Total 19 hospitalisations including 1 MI and 1 Stroke) Of these 15 had atypical symptoms and got hospitalized, 2 had non-

Q wave MI with ECG changes. Both of them underwent repeat coronary angiogram after 18 months and 48 months respectively. Both had initially diseased coronaries but only one patient had disease progression. In this patient the LAD disease had progressed from 40% to 70%. One patient developed acute Inferior wall myocardial infarction. This patient had mild (30%) LAD disease, which on repeat angiogram after MI was shown to be tight (90%) along with total occlusion of Right coronary artery. This patient underwent coronary bypass surgery.

2 patients were noted to be in atrial fibrillation (Both had systemic hypertension and VH) and one had normal coronaries and other had mild disease. One patient had ischemic stroke (3years after angiogram) and another had a transient ischemic attack (1-year after angiogram- in a patient with atrial fibrillation)

All major events: myocardial infarction, stroke and unstable angina with arteriographic progression of disease occurred in patients who had diseased coronaries. Of subset with normal coronaries, 3 patients had atypical chest pain requiring hospitalisation and one had atrial fibrillation. The patient who had an iatrogenic coronary dissection had no events during follow up. Also patients who had local complications during angiogram had no events.

**Table. 9 Follow-up N=230 (72.8%)**

| | |
|---|---|
| Duration followed up (Mean ± sd Months) | 22.4 ± 12.2 |
| Events on followup | 21 (9 %) |
| **Major Events n=4** | **Minor events n=17** |
| Death=0<br>Myocardial infarction=1<br>ACS- Unstable angina/NQMI =2<br>Stroke=1<br>Worsening of lesions on repeat angiogram =2 | Hospitalisations for atypical symptoms= 15<br>TIA=1<br>Atrial fibrillation =2 |
| Mean NYHA class | 1.31 |
| Asymptomatic status | 147 (78%) |
| Medications on followup (mean no) | 2.6 |
| Risk factor modification | |
| Optimum | 171 (76%) |
| Suboptimal | 47 (21%) |
| Poor | 6 (2.7%) |

78% were found to be asymptomatic on followup. The rest 22% had typical or atypical symptoms. Previous symptom status, hospitalisations or risk factors could not predict the continued presence of symptoms. Also the symptomatic status was similar in both diseased as well as normal coronries.76% had optimum risk factor modification at followup. The use of medications at followup is shown in table 10.

**Use of Medications post angiogram:Table 10**

| | |
|---|---|
| Aspirin | 57.2% |
| Statins | 43% |
| Ca channel blockers | 40.7% |
| Beta-blocker | 28.4% |
| Nitrates | 14.6% |
| ACE Inhibitors | 9.3% |
| Others | 9.8% |

**Discussion**

Coronary atherosclerosis is a slowly progressive process that can be clinically inapparent for long periods of time. A single patient may undergo a coronary angiogram for either definite coronary artery disease (acute coronary syndrome or previous angiographic disease) or "Suspected coronary disease". This means that a patient's symptoms or other clinical characteristics suggest a high likelihood for significant CAD and its related adverse outcomes, but that evidence of CAD has not yet been documented as defined above.

Although the extent of coronary disease defined by coronary angiography does predict outcome, use of coronary angiography as a "screening tool" in unselected populations is neither prudent nor cost-effective.[4]

This study included 316 patients with suspected coronary artery disease and found non-significant CAD on angiogram. The indication for coronary angiogram most commonly being a positive or inconclusive non-invasive test- exercise ECG. 20% were thought to have an acute coronary syndrome in recent past and angiogram was done. In this study most of the patients were in 45-60 age group, which in the presence of symptoms with risk factors the likelihood of significant CAD is maximal. The number of females exceeded males, which suggests the more prevalence of atypical symptoms and inconclusive exercise tests in females.

Half of patients were thought to have typical angina (51%) This finding suggest that from nature of symptoms it may not be able to predict presence or absence of significant CAD. 45% of patients had hospitalisations before angiogram and were on mean 3.8 medications. 89.2% of patients in present study had risk factors for coronary artery disease and in 80% more than 2 risk factors were present. In 51% of patients, the lipid profile was abnormal. 42% had elevated LDL and 41% had low HDL. The presence of abnormal lipids was similarly distributed in patients with mild disease and normal coronaries.

The ACC-AHA statement on cornary angiography state that those who are intolerant of medical therapy, who fail to respond adequately to medical therapy, or in whom chest pain limits their lifestyle significantly despite taking >2 anti anginal medications should be considered for coronary angiography. Patients who repeatedly present to the hospital with nonspecific chest pain, but who fail to have high-risk markers for ischemia, may also benefit from coronary angiography. The findings of a normal

coronary angiogram in such patients indicate a good long-term prognosis that is reassuring to both the patient and the physician.

In 75% of patients, exercise stress test was performed. In majority this was reported as positive (71%) in view of ST changes. But only extremely rarely patients had angina as a symptom during treadmill test. The Duke score showed an average of 1.6. Only 2.2% had a high-risk score. The fact that majority of patients in present study (74%) fell into intermediate score group and only few falls in high rlsk group suggests that such a scoring would still be useful to predict significant CAD.

The coronary angiogram showed calcification on fluoroscopy in 7.4% patients. This had a strong association with advanced age and presence of luminal disease. Coronary artery ectasia was noted in 4.7%. This represents atherosclerotic involvement of coronaries resulting in negative remodelling of arteries. The distribution of disease suggests more often LAD to be affected.

The complications of cardiac catheterisation:

There were 10 (3.2%) instances of complications in in present study. No death/life threatening complication occurred. The reported incidence of death and lifethreatening complications during cardiac catheterization is up to 0.5%. The most common complication encountered was vascular access problems. (3 Pseudo-aneurysm and 1 AV fistula) Only one patient had significant hematoma with psudo-aneurysm requiring blood transfusion. Although in 2 patients arrhythmias occurred, no major or life threatening arrhythmias occurred. The incidence of local complications and neurologic complications in the present study is similar to reported incidences of 1.6% and 0.3%.[6] One patient had a catheter induced coronary dissection. This caused no flow limitting flap. The catheter related complications are most often reported in patients with significant disease burden, especially ostial disease.

Follow-up

72.8 % were followed up after angiogram and rest were lost to follow up. The mean duration of follow up was 22.4 months. 9% had occurrence of any form of events during follow up. 147 patients (78%) were asymptomatic at follow up. The rest continued to have typical/atypical angina, but the number of repeat hospitalisations were much fewer. Only 17 patients had hospitalisations for probable unstable angina (As compared to 126 cases prior to angiogram) and of these only 2 had truly unstable

angina/non-Q MI as assessed by electrocardiograhic changes and enzyme measures. There was only one instance of myocardial infarction, and this patient had significant disease progression on repeat angiogram. Of the 2 patients who had unstable angina, only one had significant disease progression on repeat angiogram. The continued presence of symptoms or hospitalisations was not predicted by risk factors, ECG abnormalities , hospitalisations or symptom status before angiogram.

In study by Pasternak et al, which had 175 patients with follow up data on 90% for median $3^{1/2}$ Years, no deaths were reported and only one myocardial infarction occurred. This is in concordance with the present study. But Pasternak et al[8] reports 54% to be symptomatic and 17% had hospitalisation on follow up. Continuing chest pain was significantly more common in women and in patients who had experienced chest pain for more than one year before angiography. Present study had much lower incidence of hospitalisation and there was no difference in events between both sexes

76% had optimum risk factor modification on follow up, which reflects more awareness of coronary artery disease among patients who had prior angiography. Kemp et al have reported the seven year survival of 4051 patients from the CASS database with normal and near normal coronary arteries and found excellent prognosis in general[16]. The subset with risk factors (smoking and hypertension) had increased risk of mortality. Since the number of events were low, no such conclusion could be drawn from this present study. The optimum risk modification in a good proportion those who were followed up would have contributed to the event free survival.

There are few reported studies on long term survival of patients who have normal or mildly abnormal coronary angiogram. The longevity is found to be the same as normal population. In one study, which followed up 521 of such patients for 10 years, found significant events including death/MI in 2.1%[7].The event rate was much lower in (0.6%) patients with normal coronaries than in mildly diseased ones. In present study major events were 1.4% and all of them occurred in patents with diseased arteries. This suggests the disparity in survival without events in those with normal and mildly diseased coronaries. The incidence of myocardial infarction in normal coronaries in previous studies has been 0.9 - 0.6 % respectively. The lower incidence found in present study might be due to shorter follow up duration and loss of follow up in 27%.

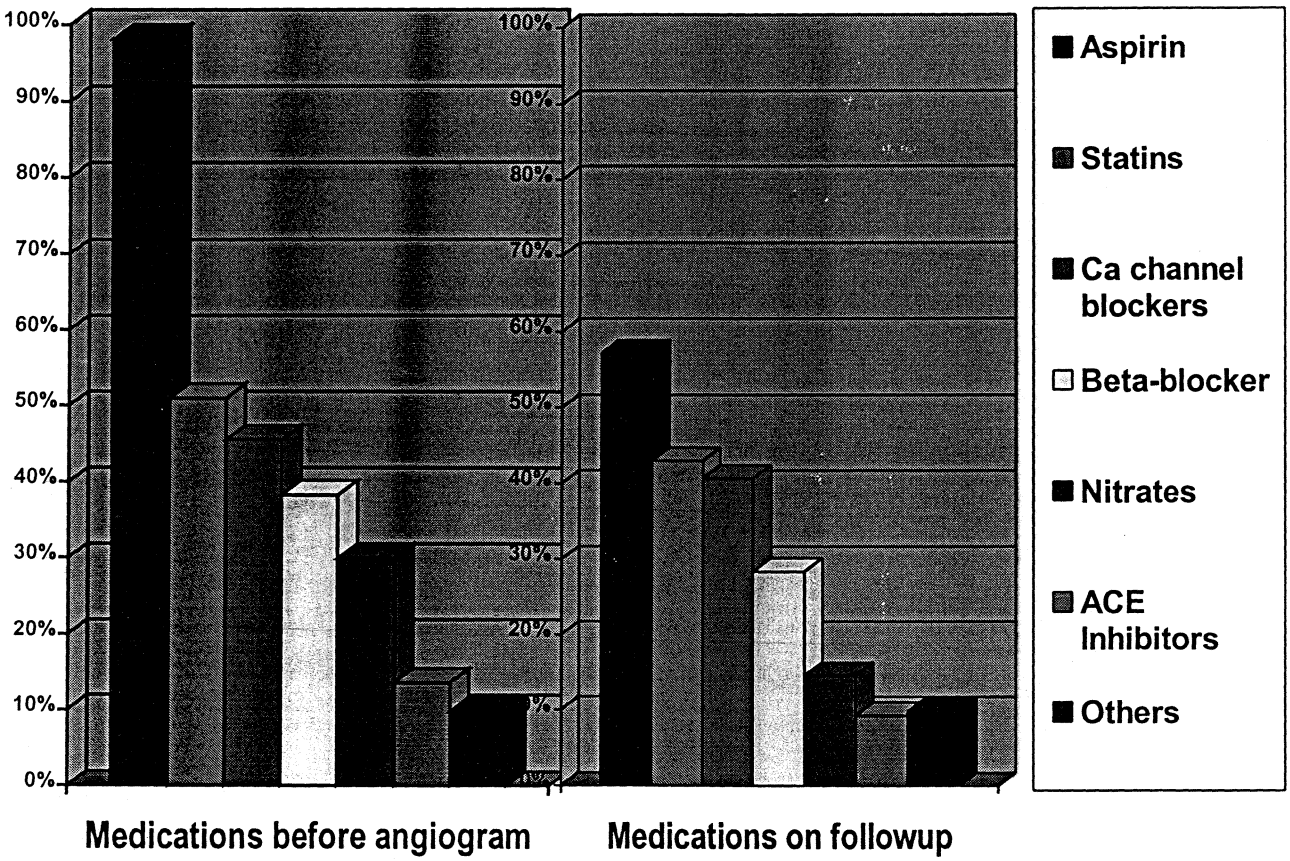
Follow up for events and repeat coronary angiogram done only in patients with subsequent events may not give the real incidence of disease progression. In this study only 3 patients underwent a repeat catheterization. The ideal study would entail repeated coronary arteriography for all, but this approach is neither practical nor ethical.

Angina with normal coronary arteries:

This condition has a reported incidence of 10-20% in persons undergoing coronary angiography because of clinical suspicion of angina. In this condition termed the syndrome-X, the prognosis is excellent. The cause of this syndrome is unclear. This may result from coronary microvascular dysfunction or spasm. In some subsets this may be due to abnormal pain perception and some may have a combination of these factors. It is difficult to determine patients with syndrome X in whom chest pain is due ischemia from patients with non-cardiac chest pain. This is most common in females, especially pre-menopausal females and majority have atypical chest pain.[17] The resting ECG may be normal or show nonspecific ST-T changes. 20% of patients have positive exercise stress tests. Metabolic studies during angiogram such as lactate extraction coefficient during atrial pacing may document ischemia in some patients[11]. In this study many of the patients would qualify for a diagnosis of syndrome -X. But it was not attempted to delineate this subset and no metabolic studies during angiogram were done. This is due to the fact that survival patterns of those with syndrome-X is similar to that of any cohort without significant obstructive disease on coronary angiogram[12]. The possibility of syndrome-X was considered in many of patients in the present study as reflected by more prevalent use of calcium channel blockers (41%) and Nikorandil (6%) post angiogram which have reported beneficial effects in coronary microvascular dysfunction.[13]

Morbidity and use of medical resources:

Requirment of hospitalisation describes the morbidity since this could be an expression of severe or disabling chest pain as well as other severe symptoms. Ockene et al reported that use of medical facilities decreased from 1.6 to 0.16 visits per year after diagnostic procedure[10]. This was a smaller proportion for patients who had normal coronaries demonstrated. Data from our present study shows a significant reduction in need for hospitalisation from 45% to 8.3%. This is entirely due to reduction of hospitalisation due to cardiac causes. The explanation for this could be an improvement in symptoms that have been reported in 78% after procedure. Similar studies also have reported less number of hospitalisations and reported well being




without symptoms in 20%-80% of patients with non-significant coronary arteriograms. [7,9] Another major explanation for the reduction in hospitalisation could be reassurance, for both the patient and the physician. This implies a major cost reduction in terms of repeat hospitalisation and use of medical resources.

Also there is a reduction in the number of drugs prescribed. A person was on an average 3.8 medication before angiogram, which could be reduced to 2.6 at follow up. (See Graph) This is a significant reduction, which would offset the cost considerations of cardiac catheterization in the long term. 135 (42%) patients were on 2 or less number of drugs. There was significant reduction in usage of nitrates.

This suggests that early catheterization would be a long-term cost effective approach to most patients with undiagnosed/suspected coronary artery disease.

**Limitations:**

1. Retrospective nature of the study.
2. Limited duration of follow-up.
3. Only very few patients underwent a repeat coronary angiogram during follow up.
4. No Intra vascular Ultrasound was used to further characterize diseased coronaries. Also no metabolic studies or provocative testing were done for evaluation of micro vascular dysfunction and to delineate syndrome-X
5. Even though 73% of patients had follow up, 27% were lost to follow up. Considering the relatively low expected occurrence of late significant events especially death, the follow up has to be near 100% to give exact incidence of significant adverse events.

**Conclusions:**

1. Coronary angiography when performed in such a population with no significant coronary artery disease is a safe procedure with virtually 'zero' mortality and lack of major complicatons. Majority of the complications are vascular access complications, which are more common in elderly and obese.

2. Symptom status in such patients at time of assessment at least in a sizeable proportion of patients would suggest typical anginal pain. So based on symptom assessment alone delineating significant CAD may be difficult.

3. A significant majority in this study had multiple risk factors for CAD. The most common indication for coronary angiogram was a positive or inconclusive treadmill exercise test.

4. Exercise electrocardiogram did not exclude significant CAD in 70% of subjects. However the Duke treadmill score was found to be useful, in that majority (97%) fell into low risk or intermediate risk category, and very few having a high-risk score.

5. Follow up of these patients showed low event rate and majority were asymptomatic and free of hospitalisations. Excluding significant lesions on arteriogram would reassure patients and reduce further hospitalizatons and number of medications. This would reduce morbidity and be a cost-effective strategy

6. However, typicality of chest pain for angina or the occurrence of electrocardiographic changes of ischemia prior to angiography did not predict continued chest pain during the follow-up period.

7. Coronary angiogram is a reasonable tool to identify those without risk of significant coronary events in the future, despite the fact that good number of ACS occurs in minor lesions, and doubtful value of angiogram to identify vulnerable plaques.

## REFERENCES


1. Diamond GA, Forrester JS. Analysis of probability as an aid in the clinical diagnosis of coronary-artery disease. N Engl J Med 1979;300: 1350–8.
2. Chaitman BR, Bourassa MG, Davis K, et al. Angiographic prevalence Of high-risk coronary artery disease in patient subsets (CASS). Circulation 1981;64:360 –7.
3. Mark DE, Shaw L, Harrell FE Jr, et al: Prognostic value of a treadmill exercise score in outpatients with suspected coronary artery disease. N Engl J Med 325:849, 1991. Copyright Massachusetts Medical Society.
4. Patterson RE, Eisner RL, Horowitz SF. Comparison of costeffectiveness and utility of exercise ECG, single photon emission computed tomography, positron emission tomography, and coronary angiography for diagnosis of coronary artery disease. Circulation 1995; 91:54–65.
5. Shaw LJ, Peterson ED, Shaw LK, et al: Use of a prognostic treadmill score in identifying diagnostic coronary disease subgroups. Circulation 98:1622, 1998
6. Wyman RM, Safian RD, Portway V et al. Current complications of diagnostic and therapeutic cardiac catheterization. J Am Coll Cardiol 1988;12:1400
7. Proudfit WL, Bruschke VG, Sones FM Jr Clinical course of patients with normal or slightly or moderately abnormal coronary arteriograms: 10-year ollow-up of 521 patients. Circulation. 1980 Oct;62(4):712-7
8. Pasternak RC, Thibault GE, Savoia M. Chest pain with angiographically insignificant coronary arterial obstruction. Clinical presentation and long-term follow-up. Am J Med. 1980 Jun;68(6):813-7.
9. Isner J, Salem D, Banas J. Long term clinical course of patients with normal coronary arteriography:followup study of 121 patients with normal or nearly normal coronary arteriograms. Am Heart J 1981;102; 645-653.
10. Ockene I, Shay M, Alpert J. Unexplained chestpain in patients with normal coronary arteriograms. A followup studyof functional status. N Engl J Med 1980; 303:1249-1252, Nov 27, 1980
11. Berland J, Cribier A, Cazor JL Angina pectoris with angiographically normal coronary arteries: a clinical, hemodynamic, and metabolic study. Clin Cardiol. 1984 Sep;7(9):485-92.
12. Romeo F, Rosano GM, Martuscelli E, et al: Long-term follow-up of patients initially diagnosed with syndrome X. Am J Cardiol 71:669, 1993
13. Heart Disease 6th Edition Ed E. Braunwald. . ©WB Saunders 2001.
14. Albertsson P, Emanuelson H, Karlsson T. Morbidity and use of medical resources in patients with chestpain and normal or near normal coronary arteries. Am J Cardiol. 1997 Feb 1;79(3):299-304.
15. ACC/AHA Guidelines for Coronary Angiography. A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on Coronary Angiography) J of Am Coll of Card Vol. 33, No. 6, 1999

16. Kemp HG, Kronmal RA, Vlietstra RE, Frye RL. Seven year survival of patients with normal or near normal coronary arteriograms: a CASS registry study. J Am Coll Cardiol 1986;7:479-483
17. Chambers J, Bass C. Chest pain with normal coronary anatomy: a review of natural history and possible etiologic factors. *Prog Cardiovasc Dis* 1990; 33: 161-184