

Pharmacological measures to increase HDL-C among high risk isolated low HDL cases: A randomized study amongst north Indians

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Background & objectives: Low serum levels of high density lipoprotein cholesterol (HDL-C) is an established risk factor for coronary heart disease (CHD). Among a variety of lipid modifying drugs, the best single drug therapy to increase HDL-C levels, especially among high risk, isolated low HDL-C (ILHDL-C) cases is yet to be identified. The objectives of the present study were to evaluate the best pharmacological measure among atorvastatin, fenofibrate and niacin aimed to raise HDL-C and its effect in decreasing the estimated Framingham-10-year CHD risk percentage (CHD-RP) among high risk ILHDL-C cases in north India.

Methods: Two hundred CHD equivalent (CHD-RP \geq 20), ILHDL-C cases were randomly assigned for treatment either with atorvastatin 10 mg/day (n=70), micronized fenofibrate 160 mg/day (n=65) or niacin-extended release (ER) 750 mg/day (n=65). After 6 wk of treatment, the dosages of drugs were doubled and the patients were finally assessed after 12 wk for their lipid values.

Results: Baseline characteristics were similar in the three groups. Niacin therapy 750 mg and 1.5 g/day resulted in a significant rise in HDL-C by 8.10 ± 3.19 and 12.41 ± 4.39 per cent ($P < 0.001$), respectively. Fenofibrate 160 and 320 mg/day also resulted in a significant rise in HDL-C by 3.85 ± 3.48 and 6.24 ± 4.43 per cent ($P < 0.001$), respectively, while atorvastatin 10 and 20 mg/day resulted in a non-significant increase in HDL-C by 0.13 ± 2.92 per cent and 0.51 ± 2.63 per cent, respectively. By increasing HDL-C values, niacin was found to be most effective in reduction of 10-year CHD-RP ($P < 0.001$), followed by fenofibrate ($P = 0.010$), while atorvastatin had no effect.

Interpretation & conclusions: Our findings indicate that niacin rather than fibrates or statins seems to provide a safe and effective therapy for increasing HDL-C, thus reducing the cumulative CHD risk among ILHDL-C cases.

Key words Atorvastatin - coronary heart disease (CHD) - fenofibrate - isolated high density lipoprotein cholesterol (ILHDL-c) - niacin

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Coronary heart disease (CHD) is the leading cause of death and disability all around the world. Longitudinal population studies have confirmed that high density lipoprotein cholesterol (HDL-C) is inversely and independently associated with the risk of developing CHD¹. Among men and women aged 49 to 82 yr, who were free of CHD at baseline in the Framingham study (during a follow up period of 12 yr), the participants with high HDL-C levels (in the 80th percentile) were at 50 per cent lower risk of cardiovascular events compared with participants with low HDL-C levels (in the 20th percentile)². In the Prospective Cardiovascular Münster (PROCAM) study (~4,500 volunteers, aged 16-65 yr, followed up for 6 yr), individuals with HDL-C <35 mg/dl were found to have four times higher coronary risk than those with HDL-c ≥35 mg/dl³. Gordon *et al*¹ suggested that every 1 mg/dl increase in HDL-C results in a decrease of 2 to 3 per cent of composite cardiovascular risk to an individual. Results from Veterans Administration HDL Intervention Trial (VA-HIT) showed that in patients with initially low HDL-C, a modest increase of only 6 per cent of HDL-C significantly reduced both coronary morbidity and mortality upto 24 per cent⁴.

Mean HDL-C levels among Asian Indians is on an average 5 mg/dl lower than in white men, and 15 mg/dl lower than in black and Japanese men⁵. Isolated low HDL cholesterol (ILHDL-c), *i.e.* abnormally low HDL-C with desirable total cholesterol is substantially prevalent among Indians (39.6% in males and 39.3% in females) suffering with CHD⁶. Measures such as increasing physical activity⁷, decreasing alcohol intake⁸, smoking cessation⁹, and possibly losing body weight¹⁰ can elevate HDL-C. The use of pharmacological agents that increase HDL-C can also be considered in high risk ILHDL-C cases. Fibrates, nicotinic acids or statins can all reportedly be used for increasing HDL-C in high risk cases but their safety and efficacy in ILHDL-C cases is still to be investigated.

Although some Indian studies have successfully demonstrated safety and efficacy of combination therapy *i.e.* extended release (ER) niacin+atorvastatin¹¹ and ER niacin+lovastatin¹² (both compared with statin monotherapy) among low HDL-C patients, but none of these explained the contribution of each drug, used in combination therapy group, affecting the increase of HDL-C. We thus hypothesized that if the HDL-C increasing effects (which also affect the decrease in cumulative CHD risk) from either of these single drug regimens (of atorvastatin, ER niacin and fenofibrate)

are comparable to that of combination therapy, it would obliterate the need to prescribe combination drug therapy especially in ILHDL-C subjects with no overt CHD, resulting in an overall reduction in the treatment costs (since combination drug regimens generally cost more than monotherapy). Also studies with a prospective and randomized approach, comparing the safety and efficacy of various lipid modifying single drug regimens among high risk ILHDL-C cases of Indian ethnicity have not been attempted. The present study was, therefore, aimed to evaluate the best pharmacological agent among atorvastatin, fenofibrate and niacin aimed to raise HDL-C and to study their extrapolated effect on Framingham 10-year CHD risk percentage (CHD-RP) among CHD risk equivalent ILHDL-C cases.

Material & Methods

Inclusion criteria and study design: The study was carried out on patients attending the out-patient clinics in the department of Cardiology, Sanjay Gandhi Post Graduate Institute of Medical Sciences (SGPGIMS), Lucknow, India. This study was a prospective, single centre study. Ethical approval for the study protocol was obtained from the institutional ethics committee and informed written consent was obtained from each participant.

Inclusion and exclusion criteria (CTRI No. CTRI/2012/003198) for the non-pharmacological phase of the study were as follows: isolated low HDL-C [abnormally low HDL-C with desirable total cholesterol (TC), low density lipoprotein cholesterol (LDL-C) and triglyceride (TG) levels] was defined in our study as subjects having TC and TG ≤200 mg/dl, LDL-C <130 mg/dl and HDL-C ≤35 mg/dl in men and ≤45 mg/dl in women. ILHDL-C cases who were CHD risk equivalent, *i.e.* with a predicted 10-year risk for developing CHD ≥20 per cent (employing Framingham CHD risk calculator)¹³, but had no overt history/symptoms of CHD were prospectively included in our study. Subjects with proven CHD (by history and consistent ECG findings, positive non-invasive test or angiographically proven CHD), secondary causes of dyslipidaemia (*e.g.* diabetes mellitus, hypothyroidism, nephrotic syndrome, cirrhosis, alcoholism, drugs like cyclosporine, *etc.*), abnormal liver function test (more than 3 times elevation of serum transaminase), abnormal renal function test (serum creatinine >2 mg/dl), abnormal creatinine phosphokinase (CPK) (more than 3 times the normal), pregnancy and known

sensitivity to statins, fibrates and niacin were excluded from the study.

Eligible subjects were selected consecutively from the outpatient department (OPD), who came to consult primarily for hypertension or dyslipidaemia management during the period from July 2005 to December 2010. Detailed clinical history assessment, risk factor profile, clinical examination with ECG were performed on selected ILHDL-C cases. These subjects were also investigated for fasting serum lipid levels, baseline biochemistry including a liver function test (LFT) to rule out other systemic illness or a secondary cause of dyslipidaemia. Based on the generated data, Framingham risk score (employing Framingham CHD risk calculator¹³) was calculated for each subject. ILHDL cases with 10-year CHD risk ≥ 20 per cent were included in the non-pharmacological phase of our study.

Included patients were first subjected to non-pharmacological measures for six weeks. They were advised to reduce weight or maintain weight according to ideal body mass index, to stop smoking and to do aerobic exercise regularly about 30-45 min/day (at least 5 days a week). Dietary advice was also given to all selected subjects according to National Cholesterol Educational Programme (NCEP) step II diet plan¹⁴. Compliance to non-pharmacological measures, such as diet and exercise were ensured by issuing a telephonic reminder to all the enrolled subjects at days 7 and 15. After six weeks of non-pharmacological intervention, serum lipids and coronary risk factors were reassessed, subjects who had their HDL-C improved or total cholesterol or triglycerides changed and now failing to meet the inclusion criteria, were excluded. Using these data as baseline, recalculation of Framingham risk scoring was done for all subjects and those with a reduced predicted Framingham 10-year CHD risk (*i.e.* risk $< 20\%$) were also excluded.

CHD equivalent subjects (*i.e.* 10-year CHD risk $\geq 20\%$), who were not able to improve their HDL-C levels after the non-pharmacological phase, and still were ILHDL-C cases (*i.e.* had TC and TG ≤ 200 mg/dl, LDL-C < 130 mg/dl, HDL-C ≤ 35 mg/dl in men and ≤ 45 mg/dl in women) progressed to the pharmacological phase of the study. Using a random number generator, these subjects were randomly assigned to either of the three different, oral pharmacological therapies *viz.* atorvastatin (10 mg/day), micronized fenofibrate (160 mg/day) and extended release niacin (750 mg/day).

After six weeks these subjects were reassessed for change in lipid values and any adverse effect of assigned drugs. Dosages of the drugs assigned to the subjects were uptitrated (doubled) and they were finally assessed at the end of the study (after 6 more weeks of trial; *i.e.* after 12 wk from the start of pharmacological intervention). Appropriate amount of capsules/tablets of investigational drugs were dispensed to the subjects, free of cost at both the clinic visits. Compliance of study medication was assessed by the treating physician using both, a 7-day recall and pill count of the returned investigational drug. All subjects demonstrated $>95\%$ compliance to the drugs as calculated after both the follow up visits of the pharmacological phase. Serum transaminases and CPK were measured at baseline, after six weeks and after 12 wk. More than three times elevation from the upper normal limit (ULN) of these enzymes was taken as a criteria to withdraw drug therapy.

Lipid assessments: All lipid assessments were done in the laboratories of the department of Clinical Chemistry, SGPGIMS, Lucknow, India. Direct estimation of TC, and HDL-C levels was done from fasting serum samples employing CHOD-PAP method¹⁵. Triglycerides were also directly estimated from fasting serum samples employing a GPO-PAP method¹⁶. All lipid estimations were done using RX Imola benchtop clinical chemistry Analyzer (Randox Laboratories Ltd., Crumlin, UK). Low and very low density lipoprotein cholesterol (LDL-C and VLDL-C) were calculated employing the Friedewald's formula¹⁷. Non HDL cholesterol was calculated by using formula: TC-HDL cholesterol.

Sample size calculation and statistical analysis: Based on the data generated by a pilot study conducted by us (consisting of 10 high risk ILHDL subjects in each study group), the sample size for this study was calculated. It was assumed (based on our experience of the pilot study) that the use of atorvastatin (upto 20 mg/OD), extended release niacin (upto 1500 mg/OD) and micronized fenofibrate (upto 320 mg/OD) can cause a maximum decrease in the CHD risk percentage (by $3 \pm 5.3\%$) via an increase in the HDL-C levels (maximum increase in HDL-C levels by 4 ± 2 mg/dl) in our patients.

To test the null hypothesis of no difference in HDL-C level with alternative hypothesis of paired difference of 4.0 with standard deviation of 2 (in mg/dl), paired t test was applied with level of significance 0.05 and 95 per cent power of the test. The sample size for comparison of each drug was six, since it was a

hospital based study, we decided to use design effect 1.5. Thus, the total sample size was calculated to be nine subjects in each group. To test the null hypothesis of no difference in CHD risk percentage with alternative hypothesis of paired difference of -3.0 with standard deviation of 5.3 (both in %), paired t test was applied with level of significance 0.05 and 95 per cent power of the test. The sample size for comparison of each drug came out to be 43, since it was a hospital based study, we decided to use design effect of 1.5. Thus, the total sample size came out to be 65 for each study group. To fulfill both the study objectives the larger sample size, *i.e.* 65 subjects in each group was finalized as the sample size for this study.

All data were entered prospectively into a computerized database. Analysis was done using SPSS® statistical software (SPSS® ver.16.0, Chicago, IL, USA). Continuous variables were presented as mean \pm SD. Pearson's Chi square test, student t-test (paired or unpaired) and ANOVA (analysis of variance) were used as applicable. All hypothesis testing was done assuming a two tailed test.

Results

A total of 321 patients who had isolated low HDL and met the inclusion criteria gave informed

written consent. They were first subjected to non-pharmacological measures for six weeks. After six weeks 121 (37.69%) subjects were screen failed; 83 (25.86%) on account of improved HDL-C (>35 mg/dl in men and >45 mg/dl in women) and/or rise in TG or TC (*i.e.* >200 mg/dl), making them non-ILHDL cases; 31 (9.66%) on account of improved ($<20\%$) CHD risk percentage; and seven (2.18%) who did not report back after the non-pharmacological phase (lost to follow up). The remaining 200 patients were randomized to one of the treatment arms using a random number generator. Baseline characteristics including presence of conventional risk factors (age, gender, smoking, hypertension and family history of CHD) along with mean values of various lipid traits were similar among all the three treatment groups (Table I). As our subjects were of a high risk group, we had high percentage of smokers ($\sim 72\%$) in all the three treatment arms (Table I).

Niacin therapy (750 mg and 1.5 g/day) resulted in a significant rise in HDL-C by 8.10 ± 3.19 per cent ($P < 0.001$) and 12.41 ± 4.39 per cent ($P < 0.001$), respectively. After six weeks, significant reductions were recorded in TC, LDL-C, TG, VLDL-C, Non HDL-C levels and TC/HDL-C and LDL-C/HDL-C ratios ($P < 0.001$) (Table II). Mean baseline 10 year

Table I. Baseline characteristics of patients in the three study groups

Baseline characteristics	Niacin group (n=65)	Fibrate group (n=65)	Statin group (n=70)
Mean age (yr) (mean \pm SD)	64.43 \pm 6.73	64.09 \pm 6.56	66.31 \pm 6.87
Sex (Males) n (%)	53 (81.54)	61 (93.85)	61 (87.14)
Hypertension n (%)	45 (69.23)	43 (66.15)	58 (82.86)
Smokers n (%)	47 (72.31)	47 (72.31)	50 (71.43)
Family history of premature CAD n (%)	4 (6.15)	1 (1.53)	2 (2.86)
LV dysfunction n (%)	19 (29.23)	18 (27.69)	24 (34.29)
TC (mean \pm SD; mg/dl)	150.03 \pm 16.99	155.42 \pm 14.89	152.51 \pm 17.92
HDL-C (mean \pm SD; mg/dl)	33.65 \pm 2.08	32.86 \pm 2.89	33.01 \pm 2.71
LDL-C (mean \pm SD; mg/dl)	86.36 \pm 17.59	90.27 \pm 17.37	88.17 \pm 18.55
TG (mean \pm SD; mg/dl)	150.14 \pm 38.42	161.43 \pm 33.25	156.67 \pm 32.62
VLDL-C (mean \pm SD; mg/dl)	30.03 \pm 7.68	32.29 \pm 6.65	31.33 \pm 6.52
Non HDL-C (mean \pm SD; mg/dl)	116.38 \pm 16.86	122.55 \pm 15.81	119.50 \pm 17.46
TC/HDL ratio (mean \pm SD)*	4.47 \pm 0.54	4.78 \pm 0.72	4.64 \pm 0.61
LDL/HDL ratio (mean \pm SD)	2.58 \pm 0.55	2.79 \pm 0.70	2.69 \pm 0.61

* $P < 0.05$

LV, Left ventricle; TC, total cholesterol; HDL-C, high density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol; TG, triglycerides; VLDL-C, very low density lipoprotein cholesterol; Non HDL-C, non HDL cholesterol

Table II. Effect of different pharmacological interventions on lipid parameters (n=200)

Lipids	Baseline (mg/dl)	After initial dose (mg/dl)	% age change	<i>P</i> value	After uptitrated dose (mg/dl)	% age change	<i>P</i> value
Lipid values after niacin therapy 750 and 1500 mg/day							
TC	150.03±16.99	146.08±16.89	-2.65±2.03	<0.001	145.00±15.34	-3.26±1.93	<0.001
HDL-C	33.65±2.08	36.33±1.91	8.10±3.19	<0.001	37.78±2.19	12.41±4.39	<0.001
LDL-C	86.36±17.59	82.39±17.29	-4.65±4.28	<0.001	81.40±15.97	-5.46±4.51	<0.001
TG	150.14±38.42	136.74±34.82	-8.76±4.14	<0.001	129.08±32.50	-13.66±5.42	<0.001
VLDL-C	30.03±7.68	27.35±6.96	-8.76±4.14	<0.001	25.82±6.50	-13.66±5.42	<0.001
Non HDL-C	116.38±16.86	109.74±16.90	-5.81±2.85	<0.001	107.22±15.25	-7.81±2.40	<0.001
TC/HDL ratio	4.47±0.54	4.03±0.50	-9.87±3.12	<0.001	3.84±0.43	-13.82±3.49	<0.001
LDL/HDL ratio	2.58±0.55	2.28±0.50	-11.68±5.23	<0.001	2.16±0.44	-15.73±5.66	<0.001
Lipid values after fenofibrate therapy 160 and 320 mg/day							
TC	155.42±14.89	150.95±14.52	-2.81±3.49	<0.001	149.37±13.27	-3.76±3.32	<0.001
HDL-C	32.86±2.89	34.08±2.64	3.85±3.48	<0.001	34.86±2.78	6.24±4.43	<0.001
LDL-C	90.27±17.37	90.64±16.27	0.85±6.41	0.605	90.57±14.48	1.32±8.70	0.745
TG	161.43±33.25	131.17±24.24	-18.22±5.17	<0.001	119.68±19.98	-25.07±6.59	<0.001
VLDL-C	32.29±6.65	26.23±4.85	-18.22±5.17	<0.001	23.93±3.99	-25.07±6.59	<0.001
Non HDL-C	122.55±15.81	116.88±15.16	-4.52±4.40	<0.001	114.51±14.27	-6.41±4.19	<0.001
TC/HDL ratio	4.78±0.72	4.46±0.62	-6.33±4.26	<0.001	4.32±0.60	-9.26±4.98	<0.001
LDL/HDL ratio	2.79±0.70	2.69±0.62	-2.78±6.97	<0.001	2.63±0.56	-4.38±9.99	<0.001
Lipid values after atorvastatin therapy 10 and 20 mg/day							
TC	152.51±17.92	134.41±30.23	-11.67±17.49	<0.001	129.96±29.52	-14.77±15.45	<0.001
HDL-C	33.01±2.71	33.04±2.71	0.13±2.92	0.805	33.16±2.53	0.51±2.63	0.160
LDL-C	88.17±18.55	74.66±29.99	-14.34±32.15	<0.001	70.98±30.05	-19.19±28.15	<0.001
TG	156.67±32.62	133.56±30.09	-14.06±13.11	<0.001	129.11±24.49	-16.66±10.04	<0.001
VLDL-C	31.33±6.52	26.71±6.02	-14.06±13.11	<0.001	25.82±4.90	-16.66±10.04	<0.001
Non HDL-C	119.50±17.46	101.37±29.59	-14.73±22.74	<0.001	96.80±28.88	-18.90±19.76	<0.001
TC/HDL ratio	4.64±0.61	4.08±0.88	-11.70±17.65	<0.001	3.92±0.84	-15.18±15.39	<0.001
LDL/HDL ratio	2.69±0.61	2.27±0.89	-14.35±32.09	<0.001	2.14±0.88	-19.58±28.07	<0.001
Values are mean ± SD							
TC, Total cholesterol; HDL-c, high density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol; TG, triglycerides; VLDL-C, very low density lipoprotein cholesterol; Non HDL-C, non HDL cholesterol							
Dosages used: Niacin-sustained release 750 mg/day uptitrated to 1500 mg/day after 6 weeks of treatment; Fenofibrate 160 mg/day uptitrated to after six weeks 320 mg/day; Atorvastatin 10 mg/day uptitrated to 20 mg/day after 6 weeks of treatment							

CHD risk of 21.57 ± 2.74 per cent was also significantly reduced after both 750 mg and 1.5 g/day of niacin therapy to 17.15 ± 7.05 per cent ($P < 0.001$) and 15.46 ± 5.99 per cent ($P < 0.001$), respectively (Table III).

Micronized fenofibrate 160 and 320 mg/day therapy, for six weeks each, resulted in a significant increase in HDL-C levels by 3.85 ± 3.48 per cent ($P < 0.001$) and 6.24 ± 4.43 per cent ($P < 0.001$), respectively. Significant decreases in serum levels of

TC, TG, VLDL-C, non HDL-C levels and TC/HDL-C and LDL-C/HDL-C ratios were also recorded both after six weeks each of 160 and 320 mg/day therapy of fenofibrate ($P < 0.001$). However, a non-significant change in LDL-C values was recorded after fenofibrate therapy of both dose regimens (Table II). Fibrate therapy of 160 mg/day for six weeks resulted in a non significant decrease in mean baseline 10 year CHD risk (21.80 ± 2.81 to $20.66 \pm 10.02\%$). However, the

Table III. Change in 10-year Framingham CHD risk percentage after use of different pharmacological agents to increase HDL-c (n=200)

Therapy group	Baseline 10-year CHD risk%	Risk % after use of initial dose	P value	Risk % after use of uptitrated dose	P value
Niacin	21.57±2.74	17.15±7.05	<0.001	15.46±5.99	<0.001
Fenofibrate	21.80±2.81	20.66±10.02	0.378	18.66±9.14	0.010
Statin	20.79±1.83	23.69±7.83	0.003	21.59±5.74	0.240

Values are mean ± SD
 Dosages used: Niacin-sustained release 750 mg/day uptitrated to 1500 mg/day after 6 weeks of treatment; Fenofibrate 160 mg/day uptitrated to after six weeks 320 mg/day; Atorvastatin 10 mg/day uptitrated to 20 mg/day after 6 weeks of treatment

decline rose to a significant level after subsequent six weeks of 320 mg/day fenofibrate therapy to 18.66 ± 9.14 per cent ($P=0.010$) (Table III).

On the other hand, atorvastatin 10 and 20 mg/day therapy for six weeks resulted in a non-significant modest increase in HDL-C levels ($0.13 \pm 2.92\%$, $P=0.805$ and 0.51 ± 2.63). After six weeks each of atorvastatin 10 and 20 mg/day therapy, significant fall was seen in serum TC, LDL-C, TG, VLDL-C, non HDL-C levels and TC/HDL-C and LDL-C/HDL-C ratios ($P<0.001$) (Table II). Meanwhile, mean baseline 10 year CHD risk of subjects was significantly increased after six weeks of 10 mg/day atorvastatin therapy; 20.79 ± 1.83 to 23.69 ± 7.83 per cent, $P=0.003$. A 20 mg/day dose of atorvastatin for six weeks induced a non-significant increase, rendering the mean risk to 21.59 ± 5.74 per cent (Table III).

None of the subjects required discontinuation of therapy, minor elevation of AST/ALT (<3 times) were observed in two cases (2.86%) in atorvastatin arm. Niacin therapy was also well tolerated, flushing was reported by seven (10.77%) patients, but there was no need of discontinuation of therapy. No significant gastrointestinal (GI) or other side effects were observed due to fenofibrate therapy. There were no reported incidences of myalgia or any other muscular discomfort in our patients.

Discussion

Our study was a single centre, randomized, interventional study which investigated both the efficacy of different pharmacological agents to increase HDL-C among ILHDL-C cases and their effect in terms of reducing the predicted 10-year Framingham risk.

The underlying mechanism of HDL-C lowering effects of niacin was largely unclear until recently. Zhang *et al*¹⁸ demonstrated that cell surface expression of the ATP synthase beta chain is inhibited by niacin

which leads to reduced hepatic removal of HDL protein and increase in levels of serum HDL-C. Niacin has also been reported to modestly decrease the risk of cardiovascular events¹⁸.

Three niacin formulations are available *viz.* immediate-release (IR), sustained-release/long-acting (SR/LA), and extended-release (ER)¹⁹. Both IR and SR preparations of niacin have been found to be associated with increased incidences of hepatotoxicities (in the form of mild liver enzyme elevations, steatosis, hepatitis, abnormal liver biopsies, or fulminant hepatic failure)^{20,21}. Because of the unfavourable risk-benefit ratio of IA and LA/SR formulations compared with ER formulation, production and marketing of many IA and LA/SR niacin brands have ceased. The ER formulation, available only by prescription, has a balanced metabolism resulting in less hepatotoxicity (<1%)^{22,23}, and was thus used in the present study.

In a meta-analysis of 30 niacin trials, Birjmohun *et al*²⁴ found that niacin treatment significantly increased HDL-C by 6.7 mg/dl or 16 per cent. Among the different niacin formulations, immediate release-niacin (23%) had the strongest HDL-C increasing capacity than the sustained release-niacin (13%). Our results showed a significant increase in HDL-C with 1.5 g/day extended release-niacin. A higher dose could have possibly resulted in greater improvement.

Among different formulations, subjects treated with Immediate release-niacin showed the most incidences of flushing (up to 85%), whereas flushes seemed to occur less in sustained release-niacin (26%)²⁴. The incidences of flushing and hepatotoxicity have been demonstrated to be lower in extended release formulation^{22,23}. In contrast to earlier reports, very few cases with flushing were seen in our trial (10.77%), probably because of use of a low dose (1.5 g/day). In previous studies, gastrointestinal symptoms had a prevalence of 35 per

cent with immediate release-niacin vs. 15 per cent with sustained release-niacin²⁴. Also the subject withdrawal rate was distributed as 20 per cent in the immediate release-niacin and 2.9 per cent in the sustained release-niacin²⁴. In the present study, GI side effects subject withdrawal were not seen, probably due to the fact that maximum dose of extended release niacin used was 1.5 g/day as compared to upto 3 g/day in other niacin trials.

Recently, the sale of extended release niacin has been severely hit after the results of AIM-HIGH trial²⁵ were published. This study, among 3,414 proven CHD patients with a mean follow up of 3 years, although showed a significant rise in HDL-C coupled with lowering of TG levels in the group treated with 1.5-2.0 g/day of ER niacin (in addition to 40-80 mg/day of simvastatin and 10 mg/day of ezitamibe), but showed no increments in terms of clinical benefits (*i.e.* no significant reduction in rates of composite of death from coronary heart disease, non-fatal myocardial infarction, ischaemic stroke, hospitalization for an acute coronary syndrome, or symptom-driven coronary or cerebral revascularization)²⁵. The subjects randomized in the AIM-HIGH trial²⁵ were treated with combinations of either niacin + simvastatin + ezitamibe or placebo + simvastatin + ezitamibe (*i.e.* combination therapy), whereas in our study the effectiveness of single drug regimen (*i.e.* either niacin, atorvastatin or fenofibrate) was investigated, among high risk-ILHDL subjects. Thus, our results cannot be compared with the results reported in AIM-HIGH study²⁵.

The effect of various classes of fibrates on serum HDL-C levels has been a subject for investigation for researchers over the years. Van der Hooft *et al*²⁶ suggested that fenofibrate increases HDL-C by reducing the cholesterylester transfer protein (CETP)-dependent transfer of cholesterol from HDL-C to VLDL-C. In a meta-analysis of 47 fibrates trial²⁴, all fibrates with the exception of clofibrate, significantly increased HDL-C concentration by 4.1 mg/dl or 10 per cent. Among the different fibrates; bezafibrate (11%), gemfibrozil (11%) and fenofibrate (10%) showed substantial increases in HDL-C levels²⁴. Since, no significant difference in efficacy was seen among the available classes of fibrates, we decided to use micronized fenofibrate in our study, as it was readily available in the market in a generic form. Also, since higher rate of liver-related adverse effects are associated with fenofibrate whereas a higher rate of muscle-related adverse effects are associated with gemfibrozil²⁷, we chose the former as our subjects had

no underlying liver disease at screening (as confirmed by normal LFTs of our subjects during the screening process) that could possibly be aggravated during the trial period, thus proving to be a safer option. Our results of the fenofibrate arm indicated a lesser efficacy than published studies, demonstrating a 6.24 ± 4.43 per cent increase in HDL-C with fenofibrate at six weeks of therapy. None of the subjects reported any serious GI or muscular side effects.

In randomized, controlled, head-to-head comparative studies, rosuvastatin elevated HDL-C by approximately 6 to 12 per cent compared with about 2 to 8 per cent for atorvastatin, 5 to 7 per cent for simvastatin, and 3 to 6 per cent for pravastatin^{28,29}. Our study demonstrated a mild and non-significant increase in HDL-C with six weeks of atorvastatin therapy each at doses of 10 and 20 mg/day, respectively.

Among all three pharmacological therapies tested in the present study, niacin therapy was found to be the most predictable and effective both in significantly increasing HDL-C levels and reducing the predicted Framingham 10-year CHD risk among the ILHDL-C cases. Fenofibrate therapy had a lesser effect compared to niacin, but was also successful in significantly increasing the levels of HDL-C and reduced CHD risk percentage, especially when given in an uptitrated dose of 320 mg/day. Atorvastatin on the other hand, proved to be largely ineffective in significantly increasing HDL-C levels together with an increase in the predicted 10-year CHD risk.

It is well known that patterns of dyslipidaemia are different in subjects of Indian origin and that CHD manifests among Indians at low total cholesterol and triglyceride levels³⁰. Thus in Indian scenario, lower HDL-C levels should be pharmacologically tackled, on priority as it can prove out to be the most important determinant for CHD, even if all other cholesterol sub-fractions (especially LDL-C and TC) are well within the normal limits (as in the case with ILHDL-C cases).

ATP III guidelines¹⁴ (Adult Treatment Panel III) recommend for an intensive statin regimen to achieve LDL-C goals among high risk cases. These guidelines may not be of much use in the high risk ILHDL-C cases as statin therapy could rather decrease the HDL-C levels. Therefore, our opinion is that statins should not be the drug of choice for increasing HDL-C, at least in subjects with no overt signs/symptoms of CHD.

The change in the predicted Framingham CHD risk percentage amongst our subjects was brought

about only due to drug supported increase in HDL-C values. If these drug(s) are coupled with other non-pharmacological measures such as diet, exercise and smoking cessation for a longer period of time, this could bring about further decrease in CHD-RP of the trial subjects.

This was a study of small sample size with a limited follow up period. It is true that using a surrogate measure (in our case increasing HDL-C and reducing CHD-RP) may or may not translate into clinical effects in the long run, and this may qualify to be a limitation of our study. A prospective study with a long term follow up (recording each and every cardiac event) in high risk ILHDL patients may be the best way to validate our hypothesis. Given a limited time frame and resources, using a risk calculator (as in the present study) seems to be the only way to provide the best estimate of the effectiveness of these drugs (in question) in primary prevention of CHD.

In conclusion, niacin rather than fibrates or statins seems to provide a safe and most effective way of increasing HDL-C, in high risk isolated low HDL cases. Niacin therapy aimed to increase HDL-C can significantly decrease the cumulative CHD risk in patients with isolated low HDL.

Niacin therapy coupled with lifestyle modification can be expected to further reduce the cumulative CHD risk of an individual.

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