



“A Comparative Study of Efficacy of Atorvastatin Alone and Atorvastatin with Omega-3 Fatty Acids Combination in Patients with Hyperlipidaemia Attending Tertiary Care Hospital”

C. Srinivasa¹, K. La kshminarayan¹, V. Srinivas¹ and B. V. S. Chandrasekhar^{2*}

¹Department of Pharmacology, VIMS, Bellary, India.

²Department of Pharmacology, GEMS & Hospital, Ragolu, India.

Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

Article Information

DOI: 10.9734/JPRI/2021/v33i45B32830

Editor(s):

(1) Dr. S. Prabhu, Sri Venkateswara College of Engineering, India.

Reviewers:

(1) Micheal Vincent Abiodun, Federal Polytechnic Bida, Nigeria.

(2) G. Krishna Kumar, JIPMER, India.

Complete Peer review History: <https://www.sdiarticle4.com/review-history/74791>

Original Research Article

Received 20 July 2021

Accepted 29 September 2021

Published 09 October 2021

ABSTRACT

Background: Current treatment with statins has become an integral part of vascular diseases but monotherapy has a significant residual event rate. Due to particularly one of the factor associated with atherogenic lipid phenotype that is characterized by a low high-density lipoprotein (HDL) cholesterol and increase in non-HDL cholesterol like Low-Density Lipoprotein (LDL). Omega-3 Fatty acids have demonstrated a preventiverole in primary and, particularly secondary cardiovascular diseases. Hence this study was planned to compare the efficacy of Atorvastatin alone with Atorvastatin and Omega-3 fatty acids in treatment in hyperlipidaemia patients.

Methods: The study was comparative, randomized, and prospective and open labeled conducted in MI patients. A total of 100 patients were selected based on inclusion and exclusion criteria. They were divided randomly into two Groups (Group-A and Group-B). Group-A was given Atorvastatin 10mg/day and Group-B was given Atorvastatin 10mg/day and Omega-3 fatty acids 600mg/day for 6 months. Follow up was done every month and efficacy was measured by assessing the lipoprotein levels in serum.

Results: The results were compared before treatment and after 6 months treatment. The levels

were significantly decreased Total Cholesterol (TC), LDL, Low-Density Lipoprotein (VLDL), Triglycerides (TG) and HDL levels were increased in Group-A and Group-B. When these results compared between two Groups the HDL levels were increased also it shown high significance (<0.001) but there were no significance changes in other cholesterol levels.

Conclusion: The present study results showed that Atorvastatin and Omega-3 fatty acids treatment was more effective than Atorvastatin alone treatment in improving HDL-C levels from base line and it may have a additive effect in major coronary artery diseases.

Keywords: Dyslipidemia; LDL; HDL; Atorvastatin; Omega-3 fatty acids.

1. INTRODUCTION

Hyperlipidemia patients have roughly twice the risk of developing Coronary Heart Disease (CHD) as compared to those with normal total cholesterol levels [1]. Over the past decade, Statins use has shown strong evidence in preventing cardiovascular morbidity and mortality but still there is controversy due to conflicting results in various types of studies [2-4] According to WHO, an estimated 7.2 million people died from CHD in 2008, representing approximately 12% of deaths worldwide [5].

Lipoproteins are classified into five types and these are responsible for synthesis of cell membrane, several biochemical functions like precursor for hormonal synthesis and fat-soluble vitamins [6]. Several studies have reported that Hyperlipidemia leads to several-fold increased risk of CHD. Among five lipoproteins LDL-C and HDL-C had a major role in increasing the risk of cardiovascular events, including myocardial infarction and stroke [7]. Pathological changes occurred in the setting of acute coronary syndrome (ACS), such as endothelial dysfunction, activation of inflammatory and coagulation cascades, and thrombus formation. The low HDL levels reflected disturbances in triglyceride metabolism. Recently anti-atherosclerotic properties of HDL have been discovered with the process of cholesterol clearance and named as Reverse Cholesterol Transfer (RCT) [8,9].

Currently statins are primarily used to lower cholesterol bio-synthesis and this will be protective against the cardiovascular disorders. The mode of action is via inhibition 3-Hydroxy-3-methyl glutaryl (HMG) CoA reductase - a rate limiting enzyme for cholesterol bio-synthesis pathway [10]. Based on risk of atherosclerosis, primary target is lowering LDL levels and secondary target is raising HDL levels [11,12]. Many clinical and meta-analysis studies have shown statins to be effective in approximately

lowering the LDL levels by 20 – 50% as well as TG levels by 10 – 20% and causing a possible net increase in HDL levels by 5 – 10%. Despite this, a large number of patients are still at high cardiovascular risk even after statin monotherapy. Emerging therapies for restoring the normal levels of lipoproteins is to target various pathways like clearance of cholesterol and pro-atherogenic lipoproteins modifications [13-18].

Many Clinical trials of prescription omega-3 fatty acids as monotherapy or as an adjunct to statin therapy have supported its efficacy for improving the lipid profile (reducing triglycerides and triglyceride-rich lipoproteins and raising HDL-C) in individuals with hypertriglyceridemia or mixed dyslipidemia [18,19]. This combination therapy may be preferable to drug combinations for treatment of combined hyperlipidaemia. Hence, the present study was planned to assess the safety and efficacy of Atorvastatin alone and Atorvastatin and omega-3 fatty acids in MI patients with Hyperlipidemia in the department of Medicine, in collaboration with department of pharmacology, Vijayanagara Institute of Medical Sciences (VIMS) a tertiary care hospital, Bellary.

2. MATERIALS AND METHODS

2.1 Study Design

The study was a comparative, prospective, randomized and open label study. The present study was conducted during the period March 2011 – April 2012. Patients with history of recent MI or post MI, attending the outpatient (OPD)/ inpatient (IPD) department of General Medicine, Vijayanagara Institute of Medical sciences (VIMS), Bellary. The study was started before 3 months of the treatment. During 3 months around 210 patients were came to OPD & IPD with history of MI. For selection of the participants by applying exclusion and inclusion criteria 84 patients were excluded. 26 patients were not shown interest to participate in the study.

Reaming 100 participants were included in the study.

A thorough clinical examination was done for all patients and the required laboratory investigations such as routine laboratory tests like Complete blood count, Hemoglobin%, blood sugar, serum creatinine, blood urea and liver function test (LFT), Lipid profile and Electrocardiogram. A total of One Hundred (100) patients were selected for the study by applying Inclusion - Exclusion criteria Fig. 1.

Also, patients who were taking medications, known to affect plasma lipid concentration or known to interact with study medications were excluded from the study. The participants randomly divided into two Groups and named as Group-A and Group-B by simple randomization using random numbers generated by computer software research randomizer. Group-A subjects were given Atorvastatin 10 mg tablet once daily (OD) orally and Group-B subjects were given

Atorvastatin 10 mg tablet OD along with Omega-3 fatty acids 300 mg capsule twice daily (BD) (600mg/day). For all the study participants the drugs were dispensed with free of cost during the treatment period (6 months) and were followed up every month till the end of the study Fig. 2.

Clinical Efficacy from week 0 (before the drug intervention) till the end of study (after drug intervention) was assessed by doing lipid profile. It was repeated every month to assessing the change in parameters like reduction in Total cholesterol (TC), Triglycerides (TGs), LDL cholesterol levels and rise in HDL cholesterol in each Group i.e., Group-A and Group-B. Also Liver function test was repeated at 3rd month and at the end of the study.

The data was collected and entered into a specially designed proforma (Case Recording Form) for the study. The data was analysed by t-test and P values for independent Groups.

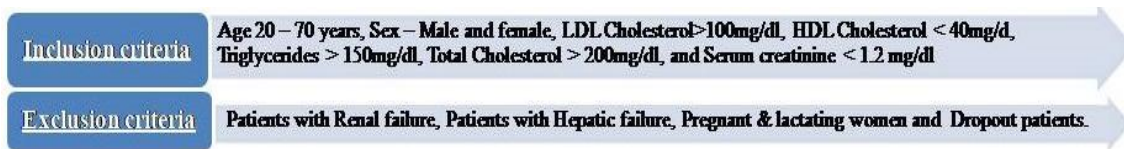


Fig. 1. Inclusion and exclusion criteria of the study participates

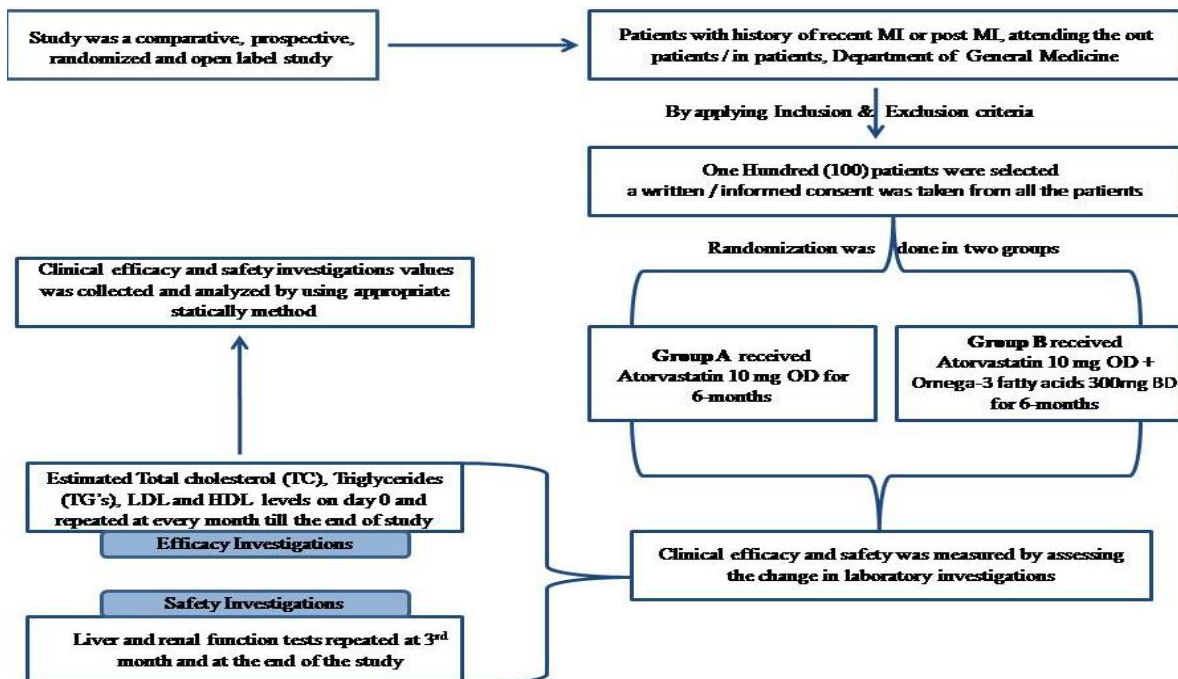


Fig. 2. Consort diagram describing the flow of participants in the study

3. RESULTS

3.1 Efficacy of Two Groups

3.1.1 Total cholesterol

After the treatment, total cholesterol levels were significantly ($p < 0.001$) reduced in both the Groups. In patients who were treated with Atorvastatin (Group A), the mean reduction of total cholesterol levels were 27.80 ± 12.88 and in those treated with Atorvastatin with Omega-3 fatty acids (Group-B) TC levels were 27.90 ± 15.91 . The percentage decrease of TC levels in Group-A was 12.66%, Group-B was 12.54%. The percentage decrease in of TC levels in Group-A was 11.5 % and in Group-B it was 13.5%. When Group-B was compared with Group-A the TC levels were not significantly decreased. The difference between them was 0.12%.

3.1.2 HDL cholesterol

After the treatment, in both the Group's total HDL levels were significantly ($p < 0.001$) increased as compared to the baselines levels. In patients who received Atorvastatin alone (Group-A), the mean increase in HDL - cholesterol levels was 2.16 ± 1.01 and in Atorvastatin with Omega-3 fatty acids treated patients (Group-B) it was 3.57 ± 1.26 . The percentage increase of HDL cholesterol levels in Group-A was 5.54% and in Group-B it was 9.27%. When Group-B was compared with Group-A the HDL levels were significantly increased. The difference between them was 3.7%.

3.1.3 LDL-cholesterol

After six months treatment, LDL cholesterol levels were significantly ($p < 0.001$) reduced in both the Groups. In Atorvastatin alone treated patients (Group-A), the mean reduction of LDL-levels were 25.63 ± 13.19 and in Atorvastatin with Omega-3 fatty acids treated patients (Group-B), levels were 26.30 ± 15.79 . The percentage decrease of LDL cholesterol levels in Group-A was 17.78% and in Group-B was 17.71%. The percentage decrease in LDL levels in Group-A was 11.5% and in Group-B was 13.5%. When Group-B was compared with Group-A the LDL levels were not significantly decreased. The difference between them was 0.7%.

3.1.4 VLDL cholesterol

At end of the treatment period, VLDL cholesterol levels were significantly ($p < 0.01$) reduced in both

the Groups. In patients who received Atorvastatin (Group-A), the mean reduction of VLDL-cholesterol levels was 4.34 ± 2.51 and in Atorvastatin with Omega-3 fatty acids treated patients (Group-B), it was 5.16 ± 2.62 . The percentage decrease in VLDL-C levels in Group-A was 11.57 % and in Group-B it was 13.50%. The percentage decrease in VLDL levels in Group-A was 11.5 % and in Group-B it was 13.5%. When Group-B was compared with Group-A the VLDL levels were not significantly decreased. The difference between them was 1.93% Table 1.

3.1.5 Triglycerides

After six months treatment, triglycerides levels were significantly ($p < 0.001$) reduced in both the Groups. In patients who received Atorvastatin (Group-A), the mean reduction of VLDL-cholesterol levels was 21.62 ± 12.65 and in Atorvastatin with Omega-3 fatty acids received patients (Group-B), it was 25.86 ± 13.14 . The percentage decrease in TG levels in Group-A was 11.5 % and in Group-B it was 13.5%. When Group-B was compared with Group-A the triglycerides levels were not significantly decreased. The difference between them was 2% Fig. 3.

3.2 Post Test Analysis to Compare Between Two Groups

3.2.1 Total cholesterol

In Atorvastatin Group (Group-A) the mean reduction of total cholesterol levels was 27.80 ± 12.88 and in combination Group (Group-B) it was 27.90 ± 15.91 . In Atorvastatin Group the mean \pm standard deviation (SD) of total cholesterol levels after treatment was reduced to 187.80 ± 12.47 mg/dl. In Atorvastatin + Omega-3 fatty acids Group reduction was 184.54 ± 13.58 mg/dl ($p > 0.05$).

3.2.2 HDL cholesterol

In Atorvastatin Group the mean increase in HDL - cholesterol levels was 2.16 ± 1.01 and in combination Group it was 3.57 ± 1.26 . In Atorvastatin Group the mean \pm standard deviation (SD) of HDL cholesterol levels after treatment was increased to 41.50 ± 1.67 mg/dl. In Atorvastatin + Omega-3 fatty acids Group increased to 42.78 ± 2.08 mg/dl ($p < 0.001$).

3.2.3 LDL-cholesterol

In Atorvastatin Group the mean reduction of LDL-cholesterol levels was 25.63±13.19 and in combination Group it was 26.30±15.79. In Atorvastatin Group the mean ± standard deviation (SD) of LDL cholesterol levels after treatment was reduced 114.36 ± 12.46mg/dl. In Atorvastatin + Omega-3 fatty acids Group the reduction was 110.20±13.36 mg/dl (p > 0.05).

3.2.4 VLDL cholesterol

In Atorvastatin Group the mean reduction of VLDL-cholesterol levels was 4.34±2.51 and in combination Group it was 5.16±2.62. In Atorvastatin Group the mean ± standard deviation (SD) of VLDL cholesterol levels after treatment was reduced to 31.69 ± 1.44mg/dl. In Atorvastatin + Omega-3 fatty acids Group it was 31.55±1.88 mg/dl (p > 0.05) Table 2.

3.2.5 Triglycerides

In Atorvastatin Group the mean reduction triglycerides levels was 21.62±12.65 and in combination Group it was 25.86±13.14. In Atorvastatin Group the mean ± standard deviation (SD) of triglycerides levels after treatment was reduced to 158.48 ± 7.24mg/dl. In Atorvastatin + Omega-3 fatty acids Group it reduced to 157.78±9.44 mg/dl (p > 0.05) Fig. 4.

3.3 Age and Sex

Among 100 patients, 82 were male patients and 18 were female patients. So, the incidence of coronary heart disease with Hyperlipidaemia is more in men than in women in our study Groups. Our study showed 26 patients were less than 40yrs of age, indicating increasing prevalence of CAD in younger population.

Table 1. Total cholesterol, triglycerides and lipoproteins levels of before treatment and at end of the treatment with atrovastatin 10 mg

	Mean ± standard deviation of Baseline value		Mean ± standard deviation end of treatment value		Mean changes from base line	P value
	Mean	SD	Mean	SD	%	
Total Cholesterol(mg/dl)	215.60	±16.82	187.80	±12.47	12.66	< 0.001
HDL Cholesterol(mg/dl)	39.34	± 1.77	41.50	±1.67	5.54	< 0.001
LDL Cholesterol(mg/dl)	140.24	±16.83	114.60	±12.32	17.78	< 0.001
VLDL Cholesterol(mg/dl)	36.04	± 3.38	31.69	± 1.44	11.57	< 0.001
Triglycerides Cholesterol(mg/dl)	180.10	± 16.91	158.48	±7.24	11.5	< 0.001

Table 2. Total cholesterol, triglycerides and lipoproteins levels of before treatment and at end of the treatment with atrovastatin 10 mg and omega 3-fatty acids

	Mean ± standard deviation of Baseline value		Mean ± standard deviation end of treatment value		Mean changes from base line	P value
	Mean	SD	Mean	SD	%	
Total Cholesterol(mg/dl)	212.44	±22.75	184.54	±13.58	12.54	< 0.001
HDL Cholesterol(mg/dl)	39.20	±2.60	42.78	± 2.08	9.27%	< 0.001
LDL Cholesterol(mg/dl)	136.50	±22.48	110.20	± 13.36	17.71	< 0.001
VLDL Cholesterol(mg/dl)	36.72	± 4.08	31.55	± 1.88	13.50	< 0.001
Triglycerides Cholesterol(mg/dl)	183.64	±20.42	157.78	±9.44	13.5	< 0.001

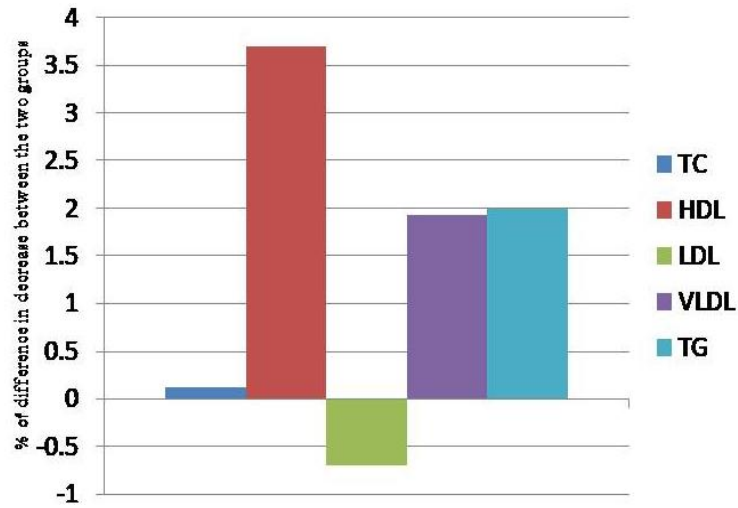


Fig. 1. The efficacy in % of difference in decrease between Group-A and Group-B

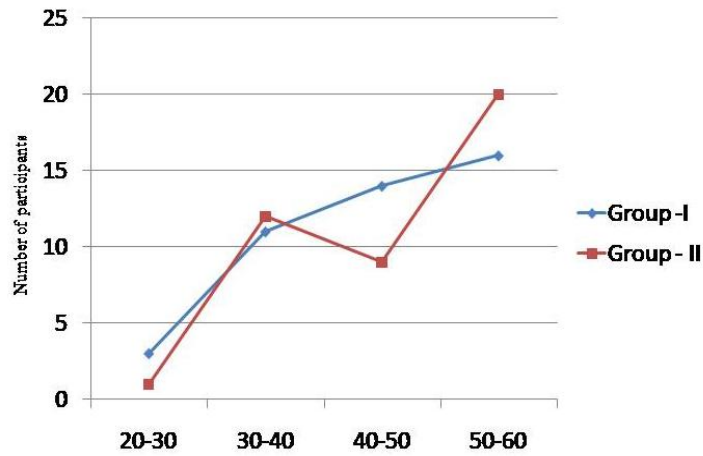


Fig. 2. Age distribution of study participants

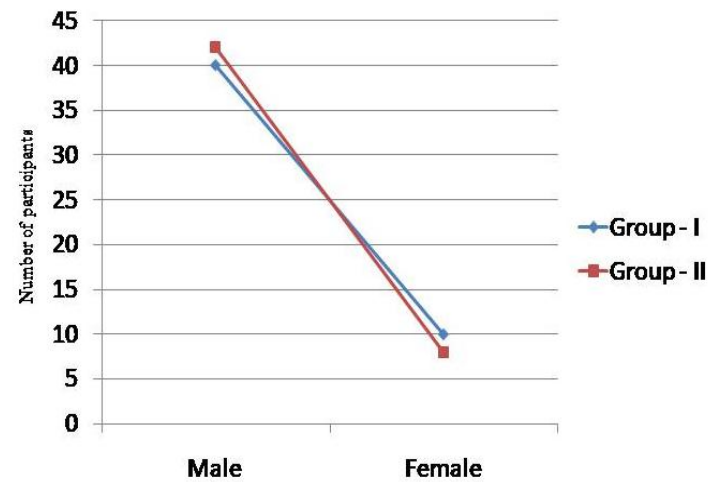


Fig. 3. Number of male and female participants in each group

4. DISCUSSION

Several prospective trials have demonstrated that the addition of Omega-3 fatty acid to statins improved cardiovascular mortality [19,20]. In the present study, we assessed the safety and efficacy of six months treatment with atorvastatin in 50 subjects and atorvastatin and Omega-3 fatty acids in 50 subjects with MI Fig. 5. The efficacy parameters - LDL, HDL and TG levels were significantly reduced in both the Groups. While comparing these parameters in between the Groups, the HDL levels were only significantly raised in Group-B as compared to Group-A. In CVD, improving HDL levels is a secondary target but several clinical studies concluded that reduction of HDL cholesterol could be a greater coronary risk factor than an increase in LDL cholesterol levels [8,9].

The therapeutic target of cardiovascular protective effect and its possible mechanisms have been discussed below. Elevation of HDL levels potentiates the biological properties including anti-atherogenic, anti-thrombotic and anti-inflammatory [21,22]. HDL has ability to uptake and return excess cholesterol from peripheral tissues back to the liver. It also promotes cholesterol removal through various efflux pathways from macrophages in the artery wall and has potential protective effect against arterial disease [23]. In peritoneal macrophages of mouse model Maria P A et al in 2007 demonstrated that around 34% of the total efflux was mediated by ABCA1, 20% by SRB1, 46% by ABCG1, small contribution by SR-BI and another pathway is aqueous. HDL and its subpopulations (ApoA-I, ApoA-II, ApoA-IV and ApoE) have antioxidant activity by preventing the proatherogenic oxidative modifications of LDL [24]. The important key role is activation of PON1 which diminishes the lipid peroxidation. It has a strong anti-inflammatory activity and in addition it down regulates the expression of adhesion molecules against monocytes release of inflammatory mediators and cytokines [25]. The HDL anti-thrombin effect is by reducing Platelet activating factor (PAF) which is a potent activator of platelets, monocytes, and leukocytes. PAF is metabolized by the PAF – acetyl hydrolase (AH) enzyme whose activity is associated with HDL [26]. By attenuating expression of tissue factor as well as selectins and by down regulation of thrombin generation through the C-reactive protein, the platelet activation will be inhibited. HDL activates the release of Prostacyclin-PGI2 and this will prevent the platelet aggregation and

promote the vascular smooth muscle relaxation [27].

At present, the pharmacological therapy for the various pathological conditions with fixed dose combinations are preferred for better patient compliance, potentiation of therapeutic response like synergism or additive or adjuvant effect and reduction of the side effects of one of the drugs. In the present study, MI patients were treated with statins and Omega-3 fatty acids and beneficial effects were observed. In our study, 4 patients complained of constipation and 2 patients complained of flatulence in Atorvastatin Group. In Omega Group 3 patients complained of constipation, 6 patients complained of flatulence and 2 patients complained of diarrhea during 1st month which gradually subsided over a period time.

5. CONCLUSION

Current trend of pharmacological approaches are the combination therapies for disorders or diseases to prevent resistance or tolerance development, improve the efficacy or reduce the unwanted effects and improve the patient compliance as well as cost benefit ratio of treatment. In our study, the pathological condition was treated with novel combination but still only minimal beneficial effects have been observed. Our research study was done in a small group of patients with six months duration. Our study suggest that by elevating HDL levels, normal levels of other lipoproteins may be obtained by longer term treatment of the statins with Omega-3 fatty acids. The study limitations are demonstrated short term effect of the drug Atorvastatin 10mg tablet OD along with Omega-3 fatty acids 300mg capsule twice daily (BD) (600mg/day) in small sample size and not proven the reduction cardiovascular abnormal events by improving the lipid profile.

DISCLAIMER

The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

CONSENT

The patients were explained about the details of the study and a written informed consent was taken from all the patients before including them in the study.

ETHICAL APPROVAL

Ethical clearance was obtained from the Institutional Ethics committee (IEC) of VIMS, Bellary, before the start of study.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. Mozaffarian D, Benjamin EJ, Go AS, et al. Heart disease and stroke statistics—2016 update: A report from the American Heart Association. *Circulation*. 2016;133(4):e38-e360. DOI: 10.1161/CIR.0000000000000350
2. Postmus I, Trompet S, Deshmukh HA, Barnes MR, Li X, Warren HR, et al. Welcome Trust Case Control Consortium. Pharmacogenetic meta-analysis of genome-wide association studies of LDL cholesterol response to statins. *Nat Commun*. 2014;5:5068. DOI: 10.1038/ncomms6068
3. Postmus I, Warren HR, Trompet S, Arsenault BJ, Avery CL, Bis JC, et al. Meta-analysis of genome-wide association studies of HDL cholesterol response to statins. *J Med Genet*. 2016;53:835–845. DOI: 10.1136/jmedgenet-2016-103966
4. Chu AY, Giulianini F, Barratt BJ, Ding B, Nyberg F, Mora S, Ridker PM, Chasman DI. Differential genetic effects on statin-induced changes across low-density lipoprotein-related measures. *Circ Cardiovasc Genet*. 2015;8:688–695. DOI: 10.1161/CIRCGENETICS.114.000962
5. WHO, The World Health Report 2002. Reducing Risks, Promoting Healthy Life. Geneva: World Health Organization; 2002.
6. Jacobs WR. Ejection Clicks. In: Walker HK, Hall WD, Hurst JW, editors. *Clinical Methods: The History, Physical, and Laboratory Examinations*. 3rd edition. Boston: Butterworths; 1990. Chapter 28.
7. Pérez-Méndez Ó, Pacheco HG, Martínez-Sánchez C, Franco M. HDL-cholesterol in coronary artery disease risk: function or structure? *Clin Chim Acta*.
8. Ramirez, A, Hu PP. Low High-Density Lipoprotein and Risk of Myocardial Infarction. *Clinical Medicine Insights. Cardiology*. 2015;9:113-7. DOI: 10.4137/CMC.S26624
9. Vergeer M, Holleboom AG, Kastelein JJ, Kuivenhoven JA. The HDL hypothesis: does high-density lipoprotein protect from atherosclerosis? *J Lipid Res*. 2010;51(8):2058-73. DOI: 10.1194/jlr.R001610 Epub 2010 Apr 6. PMID: 20371550; PMCID: PMC2903818.
10. Buhaescu I, Izzedine H. Mevalonate pathway: A review of clinical and therapeutical implications. *Clin Biochem*. 2007;40:575–584. DOI: 10.1016/j.clinbiochem.2007.03.016
11. Expert Panel on Detection Evaluation, and Treatment 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 treatment of high blood cholesterol in adults (Adult Treatment Panel III). *JAMA*. 2001;285:2508–2509.
12. Bezafibrate Infarction Prevention (BIP) study. Secondary prevention by raising HDL cholesterol and reducing triglycerides in patients with coronary artery disease. *Circulation*. 2000;102(1):21-7. DOI: 10.1161/01.cir.102.1.21 PMID: 10880410.
13. Adams SP, Sekhon SS, Wright JM. Lipid-lowering efficacy of rosuvastatin. *Cochrane Database Syst Rev*. 2014;2014(11):CD010254. Published 2014 Nov 21. DOI: 10.1002/14651858.CD010254.pub
14. Jan Borén, M John Chapman, Ronald M Krauss, Chris J Packard, Jacob F Bentzon, Christoph J Binder, et al. Low-density lipoproteins cause atherosclerotic cardiovascular disease: Pathophysiological, genetic, and therapeutic insights: A consensus statement from the European Atherosclerosis Society Consensus Panel, European Heart Journal. 2020V;41(24): 2313–2330. Available: <https://doi.org/10.1093/eurheartj/ehz962>

15. Guyton JR, Goldberg AC, Dreisberg RA, et al. Effectiveness of once-nightly dosing of extended-release niacin alone and in combination for hypercholesterolemia. *Am. J. Cardiol.* 1998;8:737–743.
16. Bays HE, Dujovne CA, McGovern ME, et al. Comparison of once-daily, niacin extended-release/lovastatin with standard doses of atorvastatin and simvastatin (The Advicor Versus Other Cholesterol-Modulating Agents Trial Evaluation [ADVOCATE]). *Am. J. Cardiol.* 2003;9:667–672.
17. Kashyap ML, McGovern ME, Berra K, et al. Long-term safety and efficacy of a once-daily niacin/lovastatin formulation for patients with dyslipidemia. *Am. J. Cardiol.* 2002;8:672–678.
18. Bradberry JC, Hilleman DE. Overview of omega-3 Fatty Acid therapies. *P T.* 2013;38(11):681-691.
19. Ann C Skulas-Ray, Peter WF Wilson, FAHA Chair, William S Harris, Eliot A Brinton, Penny M. Kris-Etherton, et al. On behalf of the American Heart Association Council on Arteriosclerosis, Thrombosis and Vascular Biology; Council on Lifestyle and Cardiometabolic Health; Council on Cardiovascular Disease in the Young; Council on Cardiovascular and Stroke Nursing; and Council on Clinical Cardiology. Omega-3 Fatty Acids for the Management of Hypertriglyceridemia: A Science Advisory from the American Heart Association. 2019;140(12):e673-e691. Available: <https://doi.org/10.1161/CIR.00000000000709>
20. Brown GB, Zhao G, Chait A. et al. Simvastatin and niacin, antioxidant vitamins, or the combination for the prevention of coronary disease. The HDL atherosclerosis Treatment Study (HATS). *N. Engl. J. Med.* 2001;345:1583–1592.
21. Camont L, Lhomme M, Rached F, Le Goff W, Nègre-Salvayre A, Salvayre R, et al. Small, dense high-density lipoprotein-3 particles are enriched in negatively charged phospholipids: Relevance to cellular cholesterol efflux, antioxidative, antithrombotic, anti-inflammatory, and antiapoptotic functionalities. *Arterioscler Thromb Vasc Biol.* 2013;33(12):2715-23. DOI: 10.1161/ATVBAHA.113.301468 Epub 2013 Oct 3. PMID: 24092747.
22. Rye KA, Bursill CA, Lambert G, Tabet F, Barter PJ. The metabolism and anti-atherogenic properties of HDL, *Journal of Lipid Research.* 2009;50:S195–S200.
23. Daniil G, Phedonos PA, Holleboom AG, et al, Characterization of antioxidant/anti-inflammatory properties and apoA-I-containing subpopulations of HDL from family subjects with monogenic low HDL disorders, *Clinica Chimica Acta.* 2011; 412(13-14):1213–1220.
24. Adorni MP, Zimetti F, Billheimer JT, et al. The roles of different pathways in the release of cholesterol from macrophages, *Journal of Lipid Research.* 2007;48(11):2453–2462.
25. Jaouad L, Milochevitch C, Khalil A. PON1 paraoxonase activity is reduced during HDL oxidation and is an indicator of HDL antioxidant capacity, *Free Radical Research.* 2003;37(1):77–83.
26. McCall MR, La Belle M, Forte TM, Krauss RM, Takanami Y, Tribble DL. Dissociable and nondissociable forms of platelet-activating factor acetylhydrolase in human plasma LDL: implications for LDL oxidative susceptibility. *Biochim Biophys Acta.* 1999;1437(1):23-36.
27. Escudero I, Martínez-González J, Alonso R, Mata P, Badimon L. Experimental and interventional dietary study in humans on the role of HDL fatty acid composition in PGI2 release and Cox-2 expression by VSMC. *Eur J Clin Invest.* 2003;33(9):779-86. DOI: 10.1046/j.1365-2362.2003.01221.x PMID: 12925037.

© 2021 Srinivasa et al.; This is an Open Access article distributed under the terms of the Creative Commons Attribution License (<http://creativecommons.org/licenses/by/4.0>), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Peer-review history:
The peer review history for this paper can be accessed here:
<https://www.sdiarticle4.com/review-history/74791>