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Effects of Atorvastatin and Niacin, Alone and in Combination, On Lowering Serum LDL-Cholesterol and Lipoprotein (a) in Hyperlipidemia Patients

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Abstract

Background & objectives: Effects of statins on serum lipids in hyperlipidemia are not well defined. We compared the effects of atorvastatin and niacin, alone and combination, on lowering serum LDL-C and Lp (a) and increasing HDL-C in hyperlipidemia patients.

Patients and methods: A total of 150 adult patients (Group-A) with hyperlipidemia and 100 normal adults controls (Group-B) were included in the study. The fasting blood samples were taken and serum (I°) were stored frozen until analysed for TG, TC, LDL-C, HDL-C, and Lp (a). The 50 patients (Group A1) were prescribed Atorvastatin (10 mg once daily for 3 months), 50 patients (Group A2) were prescribed Niacin (50 mg twice daily for 3 months) and 50 patients (Group A3) were prescribed combination of the two drugs with same doses for 3 months. Blood samples were taken again at follow up and serum (II°) was stored frozen until analysed for lipids by biochemical methods.

Results: Lipid parameters (mg/dl), i.e. TG, TC, LDL-C, & Lp(a), were raised and HDL-C was reduced in patients (Group-A) compared to controls (Group-B); Atovastatin (10 mg/ day) and Niacin (50 mg/2day) significantly lowered TG,TC, LDL-C & Lp(a) and raised HDL-C in Group A1 and Group A2 respectively; Combination therapy (atorvastatin: 10 mg/day + Niacin : 50 mg*2/day) was much more effective in lowering TG, TC, LDL-C & LP(a) and raising HDL-C in Group A3.

Conclusions: The effects of combination therapy of the two drugs were much higher than their effects alone and therefore, can be adopted in hyperlipidemia patients.

Keywords: Atorvastatin; Niacin; LDL-Cholesterol; HDL-Cholesterol; Lipoprotein(a); Hyperlipidemia

Introduction

Atherosclerosis of the coronary and peripheral vasculature due to hyperlipidemia is the leading cause of death among men and women in the USA and rest of the world [1-4]. Recent evidences support the role of Low-Density Lipoprotein Cholesterol (LDL-C) in the pathogenesis of atherosclerosis and the risk of Coronary Artery /Heart Disease (CAD/CHD) events [5-7]. The development of the "statins" class of drugs provided a momentual leap in the management by pharmacotherapy of hyperlipidemia and CHD risk reduction. Randomised clinical trials have provided strong evidence that lowering plasma cholesterol with statins reduces the risk of cardiovascular/CHD events [5-7].

The recent update of the National Cholesterol Education Programme (NCEP) is the most aggressive approach to date for reducing CHD risk. A focal element of the report is the modification of LDL-C goal in high-risk patients to <70 mg/dL. This therapeutic option is valid (in high-risk patients) even if baseline LDL-C is <100 mg/dL. The report addressed high-risk patients with elevated total Triglycerides (TG) or lower High-Density Lipoprotein Cholesterol (HDL-C). It is recommended that patients in this category be given a combination of folic acid derivative or nicotinic acid in addition to an LDL-C lowering agent. When drug therapy is initiated in high-risk or moderately high-risk patients, the report recommends that such therapy be intensified to achieve reductions in LDL-C levels by at least 30–40%, if feasible [7,8].

In cases of exceptionally elevated LDL-C levels, a statin treatment alone may be insufficient to achieve optional LDL-C reduction. In such cases, a combination therapy such as statin plus exetimibe, statin plus niacin and statin plus cholestyramine may be considered keeping in mind intolerable adverse effects or drug interactions [7]. Although the principal focus is on plasma/serum LDL-C currently more rationale approach would be to reduce the concentrations of all cholesterol-bearing lipoproteins that contain apoprotein B. The lipoprotein (a) [Lp(a)] is the most important and relevant one in this regard [5-7].

Lp(a) has become a focus of research interest owing to the results of case-control and prospective studies linking elevated plasma levels of this lipoprotein with the development of CAD [9-11]. Lp (a) contains a Low-Density Lipoprotein (LDL)-like moiety, in which the apolipoprotein B-100 component is covalently linked to the unique glycoprotein Apolipoprotein (a) [Apo(a)]. Apo (a) is composed of repeated loop-shaped units called kringles, the sequences of which are highly similar to a kringle motif present in the fibrinolytic proenzyme plasminogen [10,12,13]. Based on the similarity of Lp(a) to both LDL and plasminogen, it has been hypothesized that the function of this unique lipoprotein may represent a link between the fields of

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atherosclerosis and thrombosis [9-13]. Serum Lp(a) levels are reported to be elevated in Diabetes Mellitus (DM) and an independent risk factor for CAD in DM, particularly non-insulin dependent DM (NIDDM) patients [9,10,14]. Elevated serum concentrations of Lp(a) (>30 mg/dl) were reported to confer an increased risk of CAD and, because of this association, the measurement of plasma Lp(a) is requested increasingly as part of CAD risk assessment [14-16].

However, it appears that the report of NCEP did not give due consideration about the role of Lp(a) in atherosclerosis. Does statins alone or in combination reduce the plasma levels of Lp(a)? The probable beneficial effects of lowing serum Lp(a) levels in CHD risk reduction by statins have not been considered which remained to be evaluated [7,8]. Although Lp(a) has been shown to accumulate in atherosclerotic lesions, its contribution to the development of atheromas is unclear. Regarding studies on Lp(a) with Bangladeshi patients only limited reports are available. One study on serum Lp(a) level in patients with Cerebrovascular Disease (CVD) was reported earlier [17]. Recently, another study showing elevation of serum Lp(a) level in patients with DM was reported [18]. Literature survey has indicated that no study about the effects of statins on serum Lp(a) and LDL-C levels in Bangladeshi patients has been reported. In the light of the NCEP report, we therefore planned the present study about the effects of pharmacotherapy with atorvastatin (statin) and niacin (vitamin), alone and in combination, in lowering serum LDL-C and Lp(a) levels and increasing HDL-C, in Bangladeshi patients with hyperlipidemia. The study is expected to reveal the probable role of Lp(a) in monitoring the lipid-lowering effects of atorvastatin and niacin and hence their efficacy in reducing risk for CAD events in patients with hyperlipidemias.

Patients and Methods

A total of 150 adult patients (Group-A) (Gender: males: 76, females: 74; Age range: 32-65 yrs; Mean age ± SD: 48.5 ± 10.5 yrs) with hyperlipidemia and 100 healthy adults (Group-B) (Gender: males: 54, females: 46; Age range: 30-65 yrs; Mean age ± SD: 45.5 ± 11.5) as normal controls (NCs) were included in the case-control prospective interventional study. The study was carried out at the Medical Research Unit (MRU), Medical College for Women & Hospital (MCW&H), Uttara, Dhaka-1230 and Bangladesh. The study was approved by the Ethical Review Committee (ERC) of MRU, MCW&H, Dhaka and BMRC, Dhaka, Bangladesh.

The patients were diagnosed as having hyperlipidemia without diabetes, hypertension, infections and thyroid diseases according to standard clinical and laboratory criteria [10,19-21]. After obtaining consent, clinical details and findings were recorded as per proforma designed for each patient. The fasting blood samples were taken as 1st degree samples (I^0), serum separated were aliquoted and stored frozen until analysed for serum lipid profile, i.e. TG, total cholesterol (TC), LDL-C, HDL-C, and Lp(a). The 50 patients (Group- A1) were prescribed Atorvastatin (10 mg once daily for 3 months), 50 patients (Group-A2) were prescribed Niacin (50mg twice daily for 3 months) and 50 patients (Group-A3) were prescribed combination of the two drugs with same doses for 3 months. Then 2nd degree blood samples (II^0) were taken at the end of 3 months period when patients reported for follow up. Our patients were not receiving any other lipid lowering drugs. The serum separated (II^0) were aliquoted and stored frozen, less than 3 months, until analyzed for the same lipid profile to see the effects of interventions on them. The lipid parameters were estimated by biochemical methods using research kits obtained from reputed commercial companies. Atorvastatin was chosen as it was reported to be the safest statin in terms of toxicity, particularly hepatotoxicity, nephrotoxicity, gastrointestinal upset, muscle aches, etc and secondly, atorvastatin was shown to have the highest effects in lowering serum TG and LDL-C concentrations [6-8]. Niacin was chosen as it was cheaper and readily available to the patients free of cost from our hospital (MCW&H); Secondly, Niacin is expected to facilitate in reducing atorvastatin dose. The results were analyzed statistically using standard statistical tests in computer [22,23].

Parameter (mg/dl)	Subjects		Student's t-test* (A vs B)
	Group-A (n=150)	Group-B (n=100)	
TG	Range: 110-375 Mean ± SD: 170 ± 50	50-170 90 ± 15	t = 15.384, df =248 p<0.001
TC	Range: 170 – 250 Mean ± SD: 210 ± 16	135-200 150 ± 15	t = 12.723, df =248 p<0.001
LDL-C	Range: 80-150 Mean ± SD: 105 ± 15	70-125 80 ± 11	t = 2.524, df =248 p<0.005
HDL-C	Range: 15-60 Mean ± SD: 38 ± 10	32-66 48 ± 12	t = 2.681, df =248 p<0.025
Lp(a)	Range: 35.5-95.5 Mean ± SD: 55.4 ± 16.3	9.5 – 41.5 23.7 ± 10.4	t = 12.613, df =248 p<0.001

Table 1: Lipid parameters in patients (Group-A) before intervention with atorvastatin and niacin and in normal control (Group-B) and their statistical analysis by Student's t-test.

Results

Table 1 shows the lipid parameters and their statistical analyses in patients (Group A) before intervention with atorvastatin and niacin and in normal controls (Group-B). Among the lipid parameters, TG, TC, LDL-C and Lp(a) were elevated and HDL-C was reduced in patients significantly ($p<0.05$). The effects of atorvastatin alone (10 mg/day) in patients with hyperlipidemia are stated in Table 2. TG, TC, LDL-C and LP (a) levels were lowered by 30%, 30% and 29% respectively, while HDL-C was raised by 15%, which were significant by Paired t test ($P<0.05$). Table 3 shows the effects of niacin alone (50 mg* 2/day) in patients with hyperlipidemia. TG, TC LDL-C and Lp(a)

Parameter (mg/dl)	Patient (Group-A1)		Percent Reduction	Paired t-test* (A1-I0 vs A1-II0)
	A1-I0(n=50)	A1-II0(n=50)		
TG	Range: 115-350 Mean ± SD: 170 ± 55	110-301 150 ± 45	30%	t = 2.332, df =49 p<0.025
TC	Range: 175-240 Mean ± SD: 205 ± 15	170 – 230 180 ± 16	15%	t = 12.128, df =49 p<0.05
LDL-C	Range: 80-150 Mean ± SD: 101 ± 20	68-135 71 ± 14	30%	t = 2.475, df =49 p<0.025
HDL-C	Range: 20-65 Mean ± SD: 40 ± 12	28-70 46 ± 12	15%↑	t = 2.115, df =49 p<0.05
Lp(a)	Range: 38.5 – 90.5 Mean ± SD: 58.5 ± 18	30.4-70.5 45.6 ± 15	20%	t = 2.214, df =49 p<0.05

* P ≤ 0.05: Significant; P > 0.05: Not Significant

Table 2: Effects of atorvastatin alone (10 mg/day) on lipid parameters in patients (Group-A1) with hyperlipidemia and their statistical analysis by Paired t- test.

were lowered significantly by 25%, 25%, 25% respectively, (P<0.05). However, reduction of Lp(a) by 10% and increase of HDL-C by 10% were not significant by paired t-test (p>0.05). Table 4 shows the effects of combination therapy (atorvastatin 10 mg/day + Niacin 50 mg* 2/ day) on lipid parameters in patients with hyperlipidemia. Interestingly the combination therapy was much more effective in reducing Lp(a) by 30% and increasing HDL-C by 25% compared to treatments singly by paired t-test (p<0.01). Table 5 shows the comparison by Z-test of the

Parameter (mg/dl)	Patient (Group-A2)		Percent Reduction	Paired t-test* (A2-I0 vs A2-IIo)
	A2-I0(n=50)	A2- II0 (n=50)		
TG	Range: 120-375 Mean ± SD: 185 ± 55	100-305 140 ± 22	25%	t = 2.229, df =49 p<0.05
TC	Range: 180-235 Mean ± SD: 210 ± 15	140 – 205 165 ± 17	25%	t = 2.208, df = 49 p<0.05
LDL-C	Range: 80-150 Mean ± SD: 110 ± 15	72-120 88 ± 12	25%	t = 2.214, df = 49 p<0.05
HDL-C	Range: 16-60 Mean ± SD: 40 ± 11	22-72 45 ± 10	10%↑	t = 2.014, df =49 p<0.05
Lp(a)	Range: 38 – 98 Mean ± SD: 60 ± 18	32-75 51 ± 15	10%	t = 2.012, df =49 p>0.05

* P ≤ 0.05: Significant; P > 0.05: Not Significant

Table 3: Effects of niacin alone (50 mg×2/day) on lipid parameters in patients (Group-A2) with hyperlipidemia and their statistical analysis by Paired t-test.

Parameter (mg/dl)	Patient (Group-A3)		Percent Reduction	Paired t-test* (A3-Io vs A3-IIo)*
	A3-I0(n=50)	A3- II0(n=50)		
TG	Range: 110-375 Mean ± SD: 175 ± 45	100-300 130 ± 35	30%	t = 2.423, df = 49 p=<0.025
TC	Range: 170-250 Mean ± SD: 210 ± 17	140 – 230 160 ± 20	25%	t = 2.534, df = 49 p=<0.025
LDL-C	Range: 80-150 Mean ± SD: 115 ± 16	60-115 78 ± 14	3%	t = 2.612, df = 49 p=<0.025
HDL-C	Range: 15-60 Mean ± SD: 35 ± 12	30-80 45 ± 14	25%↑	t = 2.456, df = 49 p=<0.025
Lp(a)	Range: 40 – 98 Mean ± SD: 62 ± 18	22-70 44 ± 12	30%	t = 2.724, df = 49 p=<0.010

* P ≤ 0.05: Significant; P > 0.05: Not Significant

Table 4: Lipid lowering effects of combination therapy with Atorvastatin: (10 mg/day) & Nacin (50 mg×2/day) in patients (Group-A3) with hyperlipidemia and their statistical analysis by Paired t-test.

Parameter (mg/dl)	Effects according to intervention % reduction (↓); %Increase (↑)			Z-test for proportion
	Group-A1	Group-A2	Group-A3	
TG	30% (↓)	25% (↓)	30% (↓)	A1 vs A2 Z = 1.35 (< 1.96); NS (p>0.05) A2 vs A3 Z = 1.35 (< 1.96); NS (p>0.05) A3 vs A1 Z = 0.00 (< 1.96); NS (p>0.05)
TC	15% (↓)	25% (↓)	25% (↓)	A1 vs A2 Z = 3.32 (> 3.0); HS (p<0.005 A2 vs A3 Z = 0.00 (< 1.96); NS (p>0.05) A3 vs A1 Z = 3.32 (> 3.0); HS (p<0.005)
LDL-C	30% (↓)	25% (↓)	31% (↓)	A1 vs A2 Z = 1.35 (< 1.96); NS (p>0.05) Gr A2 vs Gr A3 Z = 1.76 (< 1.96); NS (p>0.05) A3 vs A1 Z = 0.28 (< 1.96); NS (p>0.05)
HDL-C	15% (↑)	10% (↑)	25% (↑)	A1 vs A2 Z = 1.66 (< 1.96); NS (p>0.05) A2 vs A3 Z = 6.01 (> 3.0); HS (p<0.005) A3 vs A1 Z = 3.84 (> 3.0); HS (p<0.005)
Lp(a)	20% (↓)	10% (↓)	30% (↓)	A1 vs A2 Z = 3.84 (> 3.0); HS (p<0.005) A2 vs A3 Z = 7.65 (> 3.0); HS (p<0.005) A3 vs A1 Z = 2..1 (> 1.96); S (p>0.05)

A1: Patients treated with atorvastatin alone (10 mg/day); A2: Patients treated with niacin alone (50 mg×2/day); A3: Patients treated with atorvastatin (10 mg/day) plus niacin (50 mg×2/day); NS: Not significant; S: significant; HS: Highly significant.

Table 5: Comparison by Z- test for proportion of the effects on reducing or increasing the individual components of the lipid profile according to intervention.

percentages (proportions) of the effects on reducing or increasing the individual components of the lipid profile according to intervention.

Discussion

Statins are well known to reduce adverse cardiovascular outcomes in patients with cardiovascular disease (CVD) and slow the progression of coronary atherosclerosis in proportion to their ability to reduce LDL-C. However, residual cardiovascular risk persists despite the achievement of target LDL-C levels with statin therapy in patients with established CVD [24,25]. The recent update of the NCEP is the most aggressive approach to date for reducing CHD risk [7,8]. When drug therapy is initiated in high risk or moderately high risk patients, the report recommended that such therapy be intensified to achieve reduction in LDL-C levels by at least 30-40% if feasible [7,8]. Secondly, a combination therapy such as statin plus ezetimibe, statin plus niacin and statin plus cholestyramine may be considered keeping in mind intolerable adverse effects or drug interaction [7].

The present study showed that TG, TC, LDL-C and Lp(a) were elevated, while HDL-C was reduced significantly ($p< 0.05$) indicating hyperlipidemia in our patients (Table 1). Either atorvastatin (10 mg/day) alone or niacin (50 mg×2/day) alone reduced TG (25-30%), TC (15-25%), LDl-C (25-30%) and Lp(a) (10-20%) and raised HDL-C (10-15%) significantly ($P<0.05$) (Tables 2 and 3). Our interventional study revealed that combination therapy with atorvastatin (10 mg/day) plus niacin (50 mg×2/ day) was much better in reducing the lipid levels, ie. TG (30%), TC (25%), LDL-C (30%) and Lp(a) (30%) and in elevating HDL-C (25%) significantly ($p<0.05$) (Tables 4 and 5). Atorvastatin was chosen as it was reported to be the safest statin in terms of toxicity, particularly hepatotoxicity, nephrotoxicity, gastrointestinal upset, muscle aches, etc and secondly, atorvastatin was shown to have the highest effects in lowering serum TG and LDL-C concentrations [6-8].

Our findings were interesting particularly in relation to reducing LDL-C and Lp(a) and elevating HDL-C. It appears that the report of NCEP did not give proper consideration about the role of Lp(a) in atherosclerosis [8,9]. Lp(a) has become a focus of research interest owing to the results of case-control and prospective studies linking elevated plasma levels of this lipoprotein with the development of CAD [9-11]. Two long term follow-up studies reported that the combination therapy with statin (simvastatin) to niacin and statin (simvastatin) to fenofibrate did not reduce the rate of fatal cardiovascular events, nonfatal myocardial infarction or nonfatal stroke as compared with simvastatin alone [24,25]. These non-incremental clinical benefits for addition of niacin to statin therapy during a 36 months follow-up period were observed, despite significant improvements in the LDL-C and HDL-C levels [24-26]. Our findings as well as other reports clearly suggested that some other factor or factors are responsible for continued clinically fatal events. One of the most important contenders for this factor is possibly Lp (a). As Lp(a) has structures similar to both LDL and plasminogen, it has been hypothesized that the function of Lp(a) may represent a link between the field of atherosclerosis and thrombosis [11-13]. The fact that plasma Lp(a) levels are largely genetically determined and vary widely among different ethnic groups, adds scientific interest to the ongoing study of this enigmatic molecule. Only limited studies have been reported on serum levels of Lp(a) in some populations including Indian subcontinent [14,27,28]. Further studies are warranted with combination therapy involving other statins also and following-up for a longer period to evaluate in terms of occurrence of fatal and non-fatal cardiovascular and other related events. Meanwhile, combination therapy with atorvastatin and niacin for hyperipidemias, particularly with CHD/CAD, can be adopted keeping in mind the tolerance and acceptability by patients.

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References

1. Rosamond WD, Chambless LE, Folsom AR, Cooper LS, Conwill DE, et al. (1998) Trends in the incidence of myocardial infarction and in mortality due to coronary heart disease, 1987 to 1994. N Engl J Med 339: 861-867.
2. Murray CJ, Lopez AD (1997) Mortality by cause for eight regions of the world: Global Burden of Disease Study. Lancet 349: 1269-1276.
3. Coresh J, Kwiterovich PO Jr (1996) Small, dense low-density lipoprotein particles and coronary heart disease risk: A clear association with uncertain implications. JAMA 276: 914-915.
4. American Heart Association (2005) Heart Disease and Stroke Statistics Update. Dallas, Texas.
5. Havel RJ, Rapaport E (1995) Management of primary hyperlipidemia. N Engl J Med 332: 1491-1498.
6. Knopp RH (1999) Drug treatment of lipid disorders. N Engl J Med 341: 498-511.
7. Balbisi EA (2006) Management of hyperlipidemia: new LDL-C targets for persons at high-risk for cardiovascular events. Med Sci Monit 12: RA34-39.
8. Grundy SM, Cleeman JI, Merz CNB, Brewer Jr HB, Clark LT, et al. (2004) Implications of recent clinical trials for the National Cholesterol Education Program Adult Treatment Panel III guidelines. Circulation 110: 227-239.
9. Danesh J, Collins R, Peto R (2000) Lipoprotein(a) and coronary heart disease. Meta-analysis of prospective studies. Circulation 102: 1082-1085.
10. Fujiwara F, Ishii M, Taneichi H, Miura M, Toshihiro M, et al. (2005) Low incidence of vascular complications in patients with diabetes mellitus associated with liver cirrhosis as compared with type 2 diabetes mellitus. Tohoku J Exp Med 205: 327-334.
11. Marcovina SM, Koschinsky ML (1998) Lipoprotein(a) as a risk factor for coronary artery disease. Am J Cardiol 82: 57U-66U.
12. BERG K (1963) A NEW SERUM TYPE SYSTEM IN MAN--THE LP SYSTEM. Acta Pathol Microbiol Scand 59: 369-382.
13. Scanu AM, Fless GM (1990) Lipoprotein (a). Heterogeneity and biological relevance. J Clin Invest 85: 1709-1715.
14. Devanapalli B, Lee S, Mahajan D, Bermingham M (2002) Lipoprotein (a) in an immigrant Indian population sample in Australia. Br J Biomed Sci 59: 119-122.
15. Gaw A, Brown EA, Gourlay CW, Bell MA (2000) Analytical performance of the Genzyme LipoPro Lp(a) kit for plasma lipoprotein(a)-cholesterol assay. Br J Biomed Sci 57: 13-18.
16. Barghash NA, Elewa SM, Hamdi EA, Barghash AA, El Dine R (2004) Role of plasma homocysteine and lipoprotein (a) in coronary artery disease. Br J Biomed Sci 61: 78-83.
17. Hoque MM, Sultana P, Arslan MI (2005) Lipoprotein-a: a laboratory tool for clinical categorization of CVD. Mymensingh Med J 14: 75-79.
18. Giasuddin ASM, Jhuma KA, Mujibul Haq AM (2008). Lipoprotein(a) status in Bangladeshi patients with diabetes mellitus. J Med Coll Women Hosp 6: 74-82.
19. Alberti KG, Zimmet PZ (1998) Definition, diagnosis and classification of diabetes mellitus and its complications. Part 1: diagnosis and classification of diabetes mellitus provisional report of a WHO consultation. Diabet Med 15: 539-553.
20. Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, et al. (2003) The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: the JNC 7 report. JAMA 289: 2560-2572.
21. Rifai N, Bachorik PS, Albers JJ (2001) Lipids, Lipoproteins and Apolipoproteins. In: Burtis CA, Ashwood ER, (eds.), Tielz Fundamentals of Clinical Chemistry, (5thedn), Saunders Company, Philadelphia, USA, 462-493.
22. Kirkwood BR, Sterne JAC (2008). Essential Medical Statistics (2ndedn) Oxford: Blackwell Science Ltd.

23. Prabhakara GN (2008). Biostatiscs (1stedn) Jaypee Brothers, Medical publishers, New Delhi, India.

24. ACCORD Study Group, Ginsberg HN, Elam MB, Lovato LC, Crouse JR 3rd, et al. (2010) Effects of combination lipid therapy in type 2 diabetes mellitus. N Engl J Med 362: 1563-1574.

25. AIM-HIGH Investigators, Boden WE, Probstfield JL, Anderson T, Chaitman BR, et al. (2011) Niacin in patients with low HDL cholesterol levels receiving intensive statin therapy. N Engl J Med 365: 2255-2267.

26. Nicholls SJ, Ballantyne CM, Barter PJ, Chapman MJ, Erbel RM, et al. (2011) Effect of two intensive statin regimens on progression of coronary disease. N Engl J Med 365: 2078-2087.

27. Scanu AM (2003) Lp(a) lipoprotein--coping with heterogeneity. N Engl J Med 349: 2089-2090.

28. Scanu AM (2003) Lipoprotein(a) and the atherothrombotic process: mechanistic insights and clinical implications. Curr Atheroscler Rep 5: 106-113.