Arch Pharm Res Vol 34, No 8, 1331-1337, 2011
DOI 10.1007/s12272-011-0813-9

Archives of Pharmacal Research
www.springer.com/12272

Retrospective Study on Antihyperlipidemic Efficacy and Safety of Simvastatin, Ezetimibe and their Combination in Korean Adults

Young-Hee Lee[1,2], Mi-Jeong Kim[2], Chang-Ik Choi[2], Jung-Woo Bae[2], Choon-Gon Jang[2], and Seok-Yong Lee[2]

[1]Department of Pharmacy, Ajou University Hospital, Suwon 443-721, Korea and [2]School of Pharmacy, Sungkyunkwan University, Suwon 440-746, Korea

(Received October 9, 2010/Revised December 30, 2010/Accepted March 23, 2011)

Antihyperlipidemic agents such as 3-hydroxymethyglutaryl-coenzyme A reductase inhibitors and cholesterol transporter inhibitors are used in coronary heart disease. However, controversy remains over the pharmacologic effects and safety of these drugs, especially when used in combination therapies. This retrospective study evaluated the therapeutic effect and safety of simvastatin 20 mg and ezetimibe 10 mg combination therapy compared to simvastatin 20 mg or ezetimibe 10 mg monotherapy in Korean patients according to gender, age, baseline low-density lipoprotein cholesterol, and cardiovascular risk factors. We observed significant differences among patient subgroups. Simvastatin and ezetimibe monotherapies and combination therapy reduced low-density lipoprotein cholesterol levels by 27.6%, 10.1%, and 36.8% ($p < 0.001$) and total cholesterol levels by 17.5%, 9.2%, and 25.3% ($p < 0.001$), respectively. Both monotherapy and combination therapy groups had similar incidences of all types of adverse events. However, one case of rhabdomyolysis was observed in the combination therapy group. These results suggest that, compared to monotherapy, combination therapy has an additive effect that is not influenced by risk factors. Despite the low incidence of adverse events, caution is required when using these drugs, especially in the context of musculoskeletal side effects.

Key words: Simvastatin, Ezetimibe, Combination therapy, Therapeutic effect, Adverse effect, Rhabdomyolysis

INTRODUCTION

Coronary heart disease (CHD) is a leading cause of death and hyperlipidemia, such as hypercholesterolemia, is a major risk factor for this disease. The correlation between plasma cholesterol level and CHD risk is continuous, positive, and graded (Stamler et al., 1986).

The current standard of treatment for hypercholesterolemia uses 3-hydroxymethyglutaryl-coenzyme A (HMG-CoA) reductase inhibitors, also known as statins, which block the rate-limiting step of cholesterol biosynthesis. HMG-CoA reductase inhibitors, such as simvastatin, are in widespread clinical use and have proven safe and effective for both primary prevention of CHD and secondary prevention of coronary events. Although statins are generally regarded as safe, some adverse effects have been reported. Liver toxicity, such as transaminase elevation, occurs in 0.1% to 0.9% of patients (Bhardwaj and Chalasani, 2007) and myopathy occurs in 1% to 5% of patients (Pasternak et al., 2002; Ahn, 2008). Rhabdomyolysis, a serious life-threatening adverse event (AE) with a 10% mortality rate, occurs in 1.6-6.5 persons per 100,000 on statin monotherapies and 5.98 persons per 10,000 on fibrate combination therapies (Graham et al., 2004). More recently, statins have been used in combination with other cholesterol targeting therapies, except fibrates, in an attempt to improve reductions in cholesterol levels. Ezetimibe inhibits the absorption of dietary and biliary cholesterol and is used with statins for an additive effect on low-density lipoprotein cholesterol (LDL-C) reduction. Combination therapy with ezetimibe reduces LDL-C levels by an additional 20% compared to statin monotherapy. The overall safety

Correspondence to: Seok-Yong Lee, School of Pharmacy, Sungkyunkwan University, Suwon 440-746, Korea
Tel: 82-31-290-7718, Fax: 82-31-290-7738
E-mail: sylee@skku.ac.kr

profile of ezetimibe is similar to placebo (Bays et al., 2001).

Recently, several clinical trials have demonstrated that increasingly aggressive cholesterol-lowering therapy might offer additional protection against CHD compared with less aggressive treatment (Pedersen, 2008; Strandberg et al., 2009). While higher doses of current statin therapies are capable of achieving these treatment goals, statin-induced myopathy, myalgia, and muscle pain or weakness are associated with statin therapy and these effects limit patient compliance (Pfefferkorn, 2009). One possible approach to overcoming this limitation is combination therapy. However, controversy exists regarding the pharmacologic effects and safety of combination therapy.

The safety and efficacy of ezetimibe and simvastatin combination therapy has been reported for Korean patients, especially in the treatment of primary hypercholesterolemia (Bae et al., 2005). However, the efficacy of ezetimibe and simvastatin combination therapy for certain subgroups of Korean patients has not been reported. As mentioned above, lipid-lowering therapy is applied in both primary and secondary prevention of CHD events. However, there is less information about the optimal treatment selection of lipid-lowering therapy. In addition, in secondary prevention, there is some discrepancy between the results of randomized controlled studies and retrospective analyses (Nevzorov et al., 2009). We assessed which patient subgroups showed the most response to treatment in terms of lipid-lowering effects and which patient subgroups were most susceptible to AEs. This retrospective study was conducted in order to evaluate the therapeutic effect and safety of simvastatin 20 mg and ezetimibe 10 mg combination therapy compared to simvastatin 20 mg or ezetimibe 10 mg monotherapy among certain subgroups of Korean patients.

MATERIALS AND METHODS

Study population

This study analyzed data for all outpatients with hyperlipidemia (total cholesterol above 240 mg/dL, LDL-C above 160 mg/dL, or triglyceride above 200 mg/dL in plasma) who began treatment with simvastatin 20 mg, ezetimibe 10 mg, or ezetimibe 10 mg and simvastatin 20 mg between January 2007 and June 2008 at Ajou University Hospital, Suwon, Republic of Korea. Efficacy assessments included only patients for whom laboratory data was available at 12 weeks after initiation of treatment. Patients who were taking other drugs for another primary disease, including diabetes mellitus, hypertension or coronary heart disease, were included in the study. Safety assessments included all patients who started these therapies during the study period, regardless of the presence of laboratory data. Patients were excluded if they were taking other lipid lowering drugs. This research protocol was approved by the Institutional Review Board of the School of Pharmacy, Sungkyunkwan University, Suwon, Republic of Korea (SKKUP-2008-008).

Subgroups of patients

Eligible patients were subgrouped according to gender, age (<66 or 66 years), and the presence of high risk factors, including diabetes mellitus, hypertension, and coronary artery disease. We analyzed LDL-C lowering efficacy for all three therapies within these subgroups. In addition, to evaluate the effects of baseline LDL-C levels on the pharmacological efficacy of three therapies, patients were subgrouped according to the previously reported criteria (Giraldez et al., 2008).

Efficacy assessments

Pharmacological efficacy was assessed by retrospective analysis of medical records. The primary efficacy variable was an absolute change in LDL-C (mg/dL) at end-point of study. The end-point value was defined as the last lipid measurement after 12 weeks of treatment. Secondary efficacy variables were the absolute changes in plasma concentration of total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), and triglycerides (TG).

Safety assessments

Safety was assessed by retrospective analysis of medical records of patients who were treated with simvastatin, ezetimibe or their combination over 9 months. The cases that the treatment was discontinued due to AEs were also included in safety assessments. Safety was evaluated by reviewing patient-reported AEs as well as the results of laboratory tests, including blood analyses. Safety variables were the incidences of any clinical or laboratory AEs, treatment-related AEs, serious AEs and the number of discontinuations due to AEs. AEs were classified according to type. Musculoskeletal AEs included muscle weakness, myalgia, myositis, and rhabdomyolysis. Hepatic AEs included alanine aminotransferase elevation and aspartate aminotransferase elevation. Laboratory test related AEs included creatine kinase elevation and blood urea nitrogen elevation. Cardiovascular AEs included chest pain. Gastrointestinal AEs included diarrhea, anorexia, abdominal pain, and flatulence. Other symptoms included headache, edema, dizziness, and insomnia.

Statistical analysis

Data are expressed as mean ± S.D. or mean ± S.E.M. Statistical analysis was performed using SigmaStat 2.0 (SPSS). Multi-group comparisons were performed by one-way analysis of variance (ANOVA) and multiple post hoc comparison using the Student-Newman-Keuls test. The paired *t*-test was used to calculate changes from baseline. Patients experiencing AEs were compared between treatment groups using the chi–square (χ^2) test. p values < 0.05 were considered significant.

RESULTS

Patient characteristics

A total of 1,366 patients were screened for this study and were evaluated for safety and tolerability. Of these, 173 patients met the eligibility criteria for efficacy assessment and were grouped according to treatment type. These treatment groups were further divided according to age, gender, and the presence of cardiovascular risk factors. Baseline characteristics were not significantly different among the groups (Table I).

Efficacy results for LDL-C and additional parameters

When compared to baseline values, simvastatin, ezetimibe and simvastatin plus ezetimibe combination therapies significantly lowered LDL-C by 27.6%, 10.1%, and 36.8%, respectively ($p < 0.001$). This additive effect of simvastatin plus ezetimibe was also found in the reduction of TC levels by 17.5%, 9.2%, and 25.3%, respectively ($p < 0.001$). However, treatment with these drugs did not significantly change the concentrations of other lipids, including HDL-C and TG (Fig. 1).

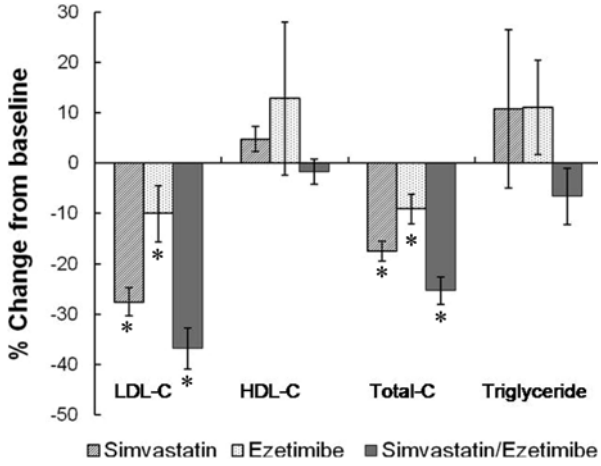

Fig. 1. Percent changes in LDL-C, HDL-C, total-C and triglycerides from baseline measurements after 12 weeks of treatment. Simvastatin (n = 74), ezetimibe (n = 39) and simvastatin/ezetimibe combination (n = 60) significantly lowered LDL-C and total-C. Data represent the mean ± S.E.M. *$p < 0.001$

We compared the effects of gender, age and presence of cardiovascular risk factors with the pharmacological efficacy of drugs, which lowered LDL-C independent of these variables (Table II). Additive effects of simvastatin and ezetimibe were also found regardless of these variables.

We also analyzed the contribution of baseline LDL-C to the anti-cholesterolemic effects of the drugs. The group with LDL-C levels less than 92 mg/dL maintained lower LDL-C levels but showed no further reductions from baseline with all three therapies. However, groups with LDL-C levels higher than 93 mg/dL showed LDL-C lowering effects that were proportional to baseline LDL-C levels. Treatment with simvastatin/

Table I. Baseline characteristics of patients

		Simvastatin (N=74)	Ezetimibe (N=39)	Simvastatin/Ezetimibe (N=60)	*p* value
Gender, No (%)	Female	45 (61)	12 (31)	26 (43)	-
	Male	29 (39)	27 (69)	34 (57)	
Age		57.2 ± 10.8	52.2 ± 13.0	58.6 ± 12.5	-
Diabetes mellitus[#], No (%)		33 (44.6)	29 (74.4)	7 (11.7)	1
Hypertension, No (%)		5 (6.8)	4 (10.3)	12 (20.0)	1
CHD[‡], No (%)		3 (4.1)	0 (0.0)	12 (20.0)	1
Total cholesterol (mg/dL)		207.9 ± 38.1	199.9 ± 40.4	217.0 ± 50.8	0.157
LDL cholesterol (mg/dL)		125.2 ± 34.9	118.3 ± 35.9	131.8 ± 43.2	0.226
HDL cholesterol (mg/dL)		50.9 ± 11.8	52.3 ± 10.5	49.5 ± 11.6	0.488
Triglyceride (mg/dL)		172.0 ± 111.9	170.7 ± 148.3	226.5 ± 268.5	0.190

Data are expressed as mean ± S.D.
[#]Diabetes mellitus includes type II diabetes and gestational diabetes.
[‡]CHD represents all coronary heart diseases, including myocardial infarction, angina pectoris and coronary artery artherosclerosis.

Table II. Effects of gender, age and cardiovascular risk factors on the LDL-C lowering efficacies of simvastatin, ezetimibe, and simvastatin/ezetimibe combination

			Simvastatin	Ezetimibe	Simvastatin/Ezetimibe
Gender	Female	N	45	12	26
		Baseline	126.8 ± 6.1	122.4 ± 12.0	145.2 ± 8.4
		At 12 wk	89.9 ± 4.8	99.4 ± 7.3	81.0 ± 8.0
		% change	−25.2 ± 3.8	−7.9 ± 13.7	−42.3 ± 5.0
	Male	N	29	27	34
		Baseline	122.9 ± 4.4	116.4 ± 6.5	121.5 ± 7.1
		At 12 wk	81.3 ± 3.6	98.1 ± 5.1	74.6 ± 5.7
		% change	−31.3 ± 4.0	−11.0 ± 5.4	−32.6 ± 6.0
Age	Age < 66Y	N	58	32	44
		Baseline	129.2 ± 4.3	120.8 ± 6.4	131.0 ± 6.7
		At 12 wk	87.9 ± 3.8	97.6 ± 4.7	80.8 ± 5.9
		% change	−29.6 ± 3.1	−14.3 ± 4.9	−33.6 ± 5.1
	Age 66Y	N	16	7	16
		Baseline	110.8 ± 10.0	106.6 ± 12.9	134.0 ± 10.4
		At 12 wk	81.6 ± 6.2	102.6 ± 8.5	67.9 ± 6.7
		% change	−20.4 ± 6.3	9.3 ± 20.5	−45.6 ± 5.9
Cardiovascular risk	High	N	49	33	39
		Baseline	125.3 ± 5.3	119.9 ± 6.0	126.8 ± 6.5
		At 12 wk	84.3 ± 3.2	98.5 ± 4.7	77.3 ± 6.6
		% change	−28.4 ± 3.1	−12.1 ± 6.0	−34.5 ± 5.5
	Low	N	25	6	21
		Baseline	125.1 ± 6.3	109.3 ± 18.7	141.1 ± 10.3
		At 12 wk	91.0 ± 7.5	98.3 ± 9.0	77.4 ± 6.0
		% change	−26.0 ± 5.7	1.0 ± 13.8	−41.1 ± 5.6

Data are expressed as mean ± S.E.M.

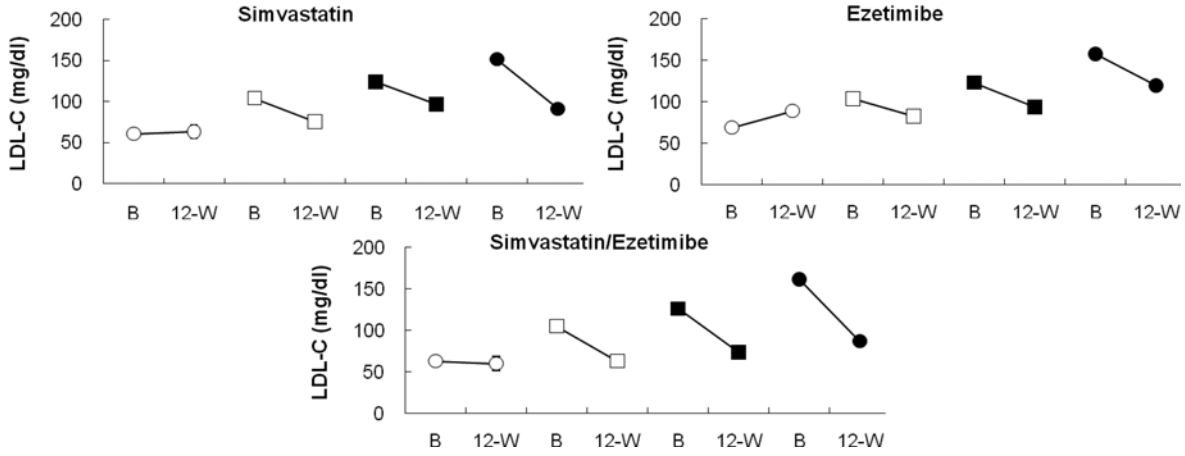

Fig. 2. Changes in LDL-C level after 12 weeks of treatment in patient groups with different basal LDL-C. Data represent the mean ± S.E.M. ○, patients with a basal LDL-C below 92 mg/dL; □, patients with a basal LDL-C between 92 and 112 mg/dL; ■, patients with a basal LDL-C between 112 and 132 mg/dL; ●, patients with a basal LDL-C above 132 mg/dL

ezetimibe combination therapy showed additive effects that maintained LDL-C levels at less than 100 mg/dL in all cases (Fig. 2).

Safety and tolerability

All 1,366 patients that were treated during the study period were analyzed for safety comparisons. Treatment with simvastatin, ezetimibe, or the combi-

Table III. Rates of clinical adverse events in the musculoskeletal, hepatic, laboratory measurement, general symptom, cardiovascular and gastrointestinal systems

	Simvastatin			Ezetimibe			Simvastatin/ Ezetimibe		
	Total	Drug-related		Total	Drug-related		Total	Drug-related	
	[N]	[N]	(%)	[N]	[N]	(%)	[N]	[N]	(%)
Total patients	**798**	**–**	**–**	**152**	**–**	**–**	**416**	**–**	**–**
Total adverse events	**67**	**21**	**(2.63)**	**17**	**8**	**(5.26)**	**42**	**17**	**(4.09)**
Musculoskeletal	**12**	**5**	**(0.63)**	**3**	**1**	**(0.66)**	**10**	**8**	**(1.92)**
Muscle weakness	2	1	(0.13)	1	0	(0.00)	3	3	(0.72)
Myalgia[a]	10	4	(0.50)	2	1	(0.66)	3	2	(0.48)
Myositis[b]	0	0	(0.00)	0	0	(0.00)	3	2	(0.48)
Rhabdomyolysis[c]	0	0	(0.00)	0	0	(0.00)	1	1	(0.24)
Hepatic	**23**	**4**	**(0.50)**	**2**	**2**	**(1.32)**	**8**	**3**	**(0.72)**
ALT elevation	16	3	(0.38)	0	2	(1.32)	5	2	(0.48)
AST elevation	7	1	(0.13)	0	0	(0.00)	3	1	(0.24)
Lab	**18**	**8**	**(1.00)**	**10**	**5**	**(3.29)**	**9**	**5**	**(1.20)**
CK elevation	14	7	(0.88)	9	5	(3.29)	9	5	(1.20)
BUN elevation	4	1	(0.13)	1	0	(0.00)	0	0	(0.00)
Symptoms	**10**	**3**	**(0.38)**	**1**	**0**	**(0.00)**	**12**	**0**	**(0.00)**
Headache	5	2	(0.25)	0	0	(0.00)	1	0	(0.00)
Edema	2	1	(0.13)	0	0	(0.00)	0	0	(0.00)
Dizziness	3	0	(0.00)	0	0	(0.00)	3	0	(0.00)
Insomnia	0	0	(0.00)	0	0	(0.00)	1	0	(0.00)
Others	0	0	(0.00)	1	0	(0.00)	7	0	(0.00)
Cardiovascular	**1**	**0**	**(0.00)**	**0**	**0**	**(0.00)**	**1**	**0**	**(0.00)**
Chest pain	1	0	(0.00)	0	0	(0.00)	1	0	(0.00)
Gastrointestinal	**3**	**1**	**(0.13)**	**1**	**0**	**(0.00)**	**2**	**1**	**(0.24)**
Diarrhea	1	0	(0.00)	0	0	(0.00)	1	0	(0.00)
Anorexia	1	0	(0.00)	0	0	(0.00)	0	0	(0.00)
Abdominal pain	1	1	(0.13)	1	0	(0.00)	0	0	(0.00)
Flatulence	0	0	(0.00)	0	0	(0.00)	1	1	(0.24)

[a]Myalgia is defined as muscle aches and pains without CK elevation.
[b]Myositis is defined as muscle discomfort with CK elevation.
[c]Rhabdomyolysis is defined as muscle complaints with a CK elevation greater than 10 times the upper limit of normal (ULN).

nation was well tolerated in all patient groups and there were similar overall safety profiles between the treatment groups. Although liver and musculoskeletal AEs were pre-specified as AEs of special interest in the main study, there were no significant differences among the three treatment groups. One case of drug-related rhabdomyolysis was reported in the simvastatin /ezetimibe combination group (Table III).

DISCUSSION

Administration of ezetimibe and simvastatin lowered LDL-C by inhibiting intestinal cholesterol absorption and hepatic cholesterol biosynthesis, respectively, in our study sample of Korean adults. This result coincides with previous results (Bae et al., 2005). TC levels were also significantly reduced due to LDL-C reductions. However, these three treatments did not change HDL-C levels and TG levels were only reduced by the combination therapy. These results may be due to higher baseline TG levels or greater efficacy at lowering LDL-C. Statins are more effective in decreasing LDL-C levels and were also more effective in decreasing TG levels in patients with hypertriglyceridemia (Stein et al., 1998).

Gender, age and the presence of cardiovascular risk

factors such as CHD, hypertension, or diabetes mellitus did not significantly affect pharmacological efficacy. As a result, these therapies could be applied without significant modifications in dosing patterns. For high-risk patients, the recommended LDL-C goal is less than 100 mg/dL and for very high-risk patients an LDL-C goal of less than 70 mg/dL is recommended (Grundy et al., 2004; O'Keefe et al., 2006; Wierzbicki, 2007). In patients with the lowest LDL-C levels at baseline, therapies that maintain LDL-C levels could prevent future cardiovascular events (O'Keefe et al., 2006).

The overall occurrences of total and drug-related AEs were not significantly different among the treatment groups. Although liver and musculoskeletal AEs were of the greatest concern due to the targeting of statins to these organs, there was no increase in AEs in these groups. However, the combination therapy group did show a higher frequency of musculoskeletal AEs, including one case of drug-related rhabdomyolysis. Rhabdomyolysis is a syndrome involving the breakdown of skeletal muscle. Statins are a well-known cause of rhabdomyolysis (Antons et al., 2006). Patients with certain metabolic abnormalities are predisposed to statin rhabdomyolysis (Qari, 2009).

These results suggest that (1) combination therapy has additive effects compared to monotherapy, (2) this effect is not influenced by risk factors, (3) these pharmacologic effects are not prominent in patients with low LDL-C levels at baseline, and (4) even though these therapies were generally tolerable with low incidences of AEs, caution is required regarding musculoskeletal side effects.

There are no significant differences observed among the patient subgroups regarding the efficacy and safety of all three treatments. This indicates that simvastatin, ezetimibe, or combination therapy can all be used in the primary and secondary prevention of CHD events regardless of patient characteristics.

Although this analysis was performed with a relatively large cohort of patients, the results are specific for the selected patient population and generalizations to other populations should be applied with caution.

REFERENCES

Ahn, S. C., Neuromuscular complications of statins. *Phys. Med. Rehabil. Clin. N. Am.*, 19, 47-59 (2008).

Antons, K. A., Williams, C. D., Baker, S. K., and Phillips, P. S., Clinical perspectives of statin-induced rhabdomyolysis. *Am. J. Med.,* 119, 400-409 (2006).

Bae, J. W., Kim, H. S., Lee, S. C., Han, K. H., and Jeon, E. S., The safety and efficacy of ezetimibe and simvastatin combination therapy in Korean patients with primary hypercholesterolemia. *Kor. J. Int. Med.*, 68, 487-497 (2005).

Bays, H. E., Moore, P. B., Drehobl, M. A., Rosenblatt, S., Toth, P. D., Dujovne, C. A., Knopp, R. H., Lipka, L. J., Lebeaut, A. P., Yang, B., Mellars, L. E., Cuffie-Jackson, C., and Veltri, E. P., Effectiveness and tolerability of ezetimibe in patients with primary hypercholesterolemia: pooled analysis of two phase II studies. *Clin. Ther.*, 23, 1209-1230 (2001).

Bhardwaj, S. S. and Chalasani, N., Lipid-lowering agents that cause drug-induced hepatotoxicity. *Clin. Liver Dis.*, 11, 597-613 (2007).

Giraldez, R. R., Giugliano, R. P., Mohanavelu, S., Murphy, S. A., McCabe, C. H., Cannon, C. P., and Braunwald, E., Baseline low-density lipoprotein cholesterol is an important predictor of the benefit of intensive lipid-lowering therapy: a PROVE IT-TIMI 22 (Pravastatin or Atorvastatin Evaluation and Infection Therapy-Thrombolysis In Myocardial Infarction 22) analysis. *J. Am. Coll. Cardiol.*, 52, 914-920 (2008).

Graham, D. J., Staffa, J. A., Shatin, D., Andrade, S. E., Schech, S. D., La Grenade, L., Gurwitz, J. H., Chan, K. A., Goodman, M. J., and Platt, R., Incidence of hospitalized rhabdomyolysis in patients treated with lipid-lowering drugs. *JAMA*, 292, 2585-2590 (2004).

Grundy, S. M., Cleeman, J. I., Merz, C. N., Brewer, H. B. Jr., Clark, L. T., Hunninghake, D. B., Pasternak, R. C., Smith, S. C. Jr., and Stone, N. J., Implications of recent clinical trials for the National Cholesterol Education Program Adult Treatment Panel III guidelines. *Circulation*, 110, 227-239 (2004).

Nevzorov, R., Novack, V., Henkin, Y., Kobal, S. L., Jotkowitz, A., and Porath, A., Discrepancy between results of randomized control studies and retrospective analysis: the case of statin therapy effect on one-year mortality in patients with decompensated heart failure. *Eur. J. Intern. Med.*, 20, 494-498 (2009).

O'Keefe, J. H. Jr., Cordain, L., Jones, P. G., and Abuissa, H., Coronary artery disease prognosis and C-reactive protein levels improve in proportion to percent lowering of low-density lipoprotein. *Am. J. Cardiol.*, 98, 135-139 (2006).

Pasternak, R. C., Smith, S. C. Jr., Bairey-Merz, C. N., Grundy, S. M., Cleeman, J. I., and Lenfant, C., ACC/AHA/NHLBI Clinical Advisory on the Use and Safety of Statins. *Stroke*, 33, 2337-2341 (2002).

Pedersen, T. R., Intensive lipid-lowering therapy for patients with aortic stenosis. *Am. J. Cardiol.*, 102, 1571-1576 (2008).

Pfefferkorn, J. A., 'Muscle-sparing' statins: preclinical profiles and future clinical use. *Curr. Opin. Investig. Drugs*, 10, 245-252 (2009).

Qari, F. A., Severe rhabdomyolysis and acute renal failure secondary to use of simvastatin in undiagnosed hypothyroidism. *Saudi J. Kidney Dis. Transpl.*, 20, 127-129 (2009).

Stamler, J., Wentworth, D., and Neaton, J. D., Is relationship between serum cholesterol and risk of premature

death from coronary heart disease continuous and graded? Findings in 356,222 primary screenees of the Multiple Risk Factor Intervention Trial (MRFIT). *JAMA*, 256, 2823-2828 (1986).

Stein, E. A., Lane, M., and Laskarzewski, P., Comparison of statins in hypertriglyceridemia. *Am. J. Cardiol.*, 81, 66B-69B (1998).

Strandberg, T. E., Holme, I., Faergeman, O., Kastelein, J. J., Lindahl, C., Larsen, M. L., Olsson, A. G., Pedersen, T. R., and Tikkanen, M. J., Comparative effect of atorvastatin (80 mg) versus simvastatin (20 to 40 mg) in preventing hospitalizations for heart failure in patients with previous myocardial infarction. *Am. J. Cardiol.*, 103, 1381-1385 (2009).

Wierzbicki, A. S., Newer, lower, better? Lipid drugs and cardiovascular disease – the continuing story. *Int. J. Clin. Pract.*, 61, 1064-1067 (2007).