



Is combined lipid-regulating therapy safe and feasible for the very old patients with mixed dyslipidemia?

Xiao Zou, Quan-Jin Si

The First Department of the Geriatric Cardiology, Chinese PLA General Hospital, NO. 28, Fuxing Road, Beijing 100853, China

Abstract

Objectives To detect the efficacy and safety of combined lipid-regulating therapies in the very old patients with mixed dyslipidemia and determine an appropriate therapy for them. **Methods** Four hundred and fifty patients aged over 75 with mixed dyslipidemia were divided into five groups according to different combination therapies. Lipid levels and drug related adverse events were tested during the study. **Results** Total cholesterol (TC) and low-density lipoprotein cholesterol (LDL-C) levels were reduced in every group compared to baseline: statin + ezetimibe: -30.0% and -55.5%; statin + policosanol: -31.1% and -51.2%; statin + fibrates: -23.7% and -44.6%; statin + niacin: -25.2% and -43.0%; and niacin + fibrates: -11.3% and -23.5%. The target achievement rates of LDL-C all exceeded 50%, except in niacin + fibrates (42.0%); statin + ezetimibe: 57.0%; statin + policosanol: 56.0%; statin + niacin: 52.0%; and statin + fibrates: 50.0%. However, overall, the niacin + fibrates group was the most effective in decreasing triglyceride (TG) and increasing high-density lipoprotein cholesterol (HDL-C) as follows: niacin + fibrates: -39.3% and 28.6%; statin + fibrates: -29.3% and 18.4%; statin + niacin: -18.5% and 16.7%; statin + ezetimibe: -17.1% and 7.1%; and statin + policosanol: -15.6% and 9.5%. The achievement rates of TG and HDL-C levels in niacin + fibrates (58.0% and 39.0%) were better than the other four groups: statin + niacin (34.0% and 34.0%), statin + fibrates (43.0% and 28.0%), statin + policosanol (30.0% and 24.0%) and statin + ezetimibe (28.0% and 25.0%). Patients in all five groups experiencing drug adverse events were only 2% and no severe adverse events occurred. **Conclusions** Statin + ezetimibe was the most effective group in lowering TC and LDL-C levels, while niacin + fibrates was the most effective in decreasing TG and increasing HDL-C levels. The commonly used combined lipid-regulating therapies with common dosages in this study were all quite safe and feasible for the very old patients with mixed hyperlipidemia.

J Geriatr Cardiol 2013; 10: 349–354. doi: 10.3969/j.issn.1671-5411.2013.04.014

Keywords: Elderly patients; Mixed dyslipidemia; Combination therapies; Safety

1 Introduction

Dyslipidemia, especially high low-density lipoprotein cholesterol (LDL-C) level with/or high-density lipoprotein cholesterol (HDL-C) level is the key risk factor(s) leading to coronary heart disease (CHD). It has been clearly documented that statins can significantly decrease serum LDL-C levels and the risk of cardiovascular events and mortality rates.^[1,2] However, mixed dyslipidemia is especially common in the very old patients and hypertriglyceridemia is strongly associated to postprandial hyperlipidemia, remnant accumulation, increased small dense LDL concentrations, low HDL-C, increased oxidative stress, endothelial dys-

function, leukocyte activation and insulin resistance. Furthermore, it is quite difficult to achieve optimal target lipid levels with only one kind of lipid-lowering agent. Actually, the combination therapy of different lipid-lowering drugs was often adopted in order to reach the new “stricter” cholesterol goals.^[3] On one hand, combination therapy with statin and one other lipid-lowering agent is useful in patients who are unable to achieve lipid goals on monotherapy. On the other hand, the combination therapy of lipid-lowering drugs may also cause some potential risks due to the specific physiological characteristics of the very old patients. For these high-risk patients, it is anticipated that these new options will optimize the management of dyslipidemia, thereby further reducing the morbidity and mortality of CHD.^[4] This study was designed to evaluate the efficacy and safety of different combined lipid-regulating therapies in the very old patients with mixed dyslipidemia and to determine an appropriate therapy for the very old patients with mixed dyslipidemia.

Correspondence to: Quan-Jin Si, MD, the First Department of the Geriatric Cardiology, Chinese PLA General Hospital, NO. 28, Fuxing Road, Beijing 100853, China. E-mail: quanjin2004@sohu.com

Received: June 4, 2013

Revised: August 5, 2013

Accepted: October 20, 2013

Published online: December 21, 2013

2 Methods

2.1 Study design

Four hundred and fifty mixed dyslipidemia patients aged 75 to 96 years old (80.92 ± 10.21 , mean \pm SD) from 2010 to 2012 in our hospital were included in the study. Inclusion criteria: (1) age over 75 years old; (2) mixed dyslipidemia; and (3) using two different kinds of lipid-regulating drugs. Patients were divided into five groups according to different combination therapies: niacin + fibrates ($n = 83$); statin + niacin ($n = 92$); statin + fibrates ($n = 90$); statin + policosanol ($n = 97$); and statin + ezetimibe ($n = 88$). All patients were given lipid-regulating drugs regularly as follows: atorvastatin, 20 mg/night; acipimox, 0.75 g/d; fenofibrate (III), 160 mg/d; policosanol, 20 mg/d; ezetimibe, 10 mg/d. The treatment lasted for 6 months. Patients were instructed to insist on their lipid-altering diet throughout the treatment period. Dyslipidemia criteria were based on the 2007 Chinese guidelines on the prevention and treatment of dyslipidemia in adults.^[5] LDL-C > 2.6 mmol/L, triglyceride (TG) > 2.26 mmol/L for high risk patients. Exclusion criteria included: (1) secondary dyslipidemia; (2) liver and renal dysfunctions; (3) could not maintain on lipid-altering diet; (4) acute myocardial infarction or stroke within six months; and (5) excessive alcohol drinking.

2.2 Data collection and measurements

The primary efficacy end point was the changes of TG, total cholesterol (TC), LDL-C and HDL-C levels from baseline to the end of the study. The percent changes were also measured to compare the effectiveness of different combination therapies. The safety was evaluated by clinical and statistical analysis, including clinical adverse reactions, laboratory indexes (such as liver function, kidney function and creatine kinase (CK) value) and vital signs. All clinical laboratory analysis was performed at the clinical bioche-

mistry lab using Roche's reagent with immunoturbidimetry method.

2.3 Statistical analysis

The measurement data of multiple groups, which were presented as mean \pm SD unless otherwise indicated, were compared with one-way ANOVA. The enumeration data were expressed as frequency and compared with chi-square test. The correlation analysis was done with logistic regression. Differences were considered significant with a $P < 0.05$. Statistical analysis was performed using the statistical software SPSS 13.0.

3 Results

3.1 Baseline conditions

Four hundred and fifty patients aged over 75 years old with mixed dyslipidemia were included in this study. Most of the baseline characteristics of the patients in five groups were comparable, except that baseline TG level was relatively higher and TC and HDL-C levels lower in niacin + fibrates group, than the other four groups, Table 1.

3.2 Changes in lipid profiles

After combination therapy, lipid levels were all improved markedly. Niacin + fibrates was the best group in decreasing TG level and elevating HDL-C level. Any one group of statin + niacin; statin + fibrates; statin + policosanol; and statin + ezetimibe was more effective than niacin + fibrates in decreasing TC and LDL-C, but statin + ezetimibe was the best group of them, see Table 2.

3.3 Target achievement rates

The target achievement rates of lipid levels were calculated with reference to the Chinese guidelines on the prevention

Table 1. Baseline conditions of five combination therapy groups (mmol/L).

Items	N + F ($n = 83$)	S + N ($n = 92$)	S + F ($n = 90$)	S + P ($n = 97$)	S + E ($n = 88$)
Age, yrs	80.73 ± 10.70	81.56 ± 11.10	79.87 ± 10.56	81.20 ± 10.97	79.98 ± 10.0
Male/female (n)	79/4	88/4	86/4	92/5	85/3
CHD, n (%)	73 (87.95)	78 (84.78)	77 (85.56)	80 (82.47)	71 (80.68)
CI, n (%)	33 (39.76)	39 (42.39)	36 (40.00)	43 (44.33)	39 (44.32)
TC	5.04 ± 0.96	$5.23 \pm 1.09^{e*,d\#}$	$5.56 \pm 1.15^{b\#}$	$5.78 \pm 0.63^{b\#,c^*}$	$5.49 \pm 0.87^{b\#}$
Triglyceride	3.59 ± 1.81	$2.81 \pm 1.26^{b\#,c\#,d\#}$	$2.70 \pm 1.50^{b\#,c\#,d\#}$	$2.11 \pm 1.00^{b\#}$	$2.10 \pm 1.17^{b\#}$
HDL-C	0.77 ± 0.27	$0.84 \pm 0.23^{c\#,d\#}$	$0.87 \pm 0.34^{b^*,c^*,d\#}$	$1.05 \pm 0.30^{b\#}$	$0.99 \pm 0.42^{b\#}$
LDL-C	2.85 ± 0.77	2.91 ± 0.86	2.94 ± 0.80	2.97 ± 0.77	3.10 ± 0.90

Data are presented as mean \pm SD unless otherwise indicated. * $P < 0.05$, # $P < 0.01$. ^b: compared with N + F; ^c: S + N, S + F, S + P compared with S + E; ^d: S + N, S + F compared with S + P; ^e: S + N compared with S + F. CHD: coronary heart disease; CI: cerebral infarction; E: Ezetimibe; F: Fibrates; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; N: Niacin; P: Policosanol; S: Statin; TC: Total cholesterol.

and treatment of dyslipidemia in adults.^[3] The Niacin + Fibrates group was the best group in decreasing TG and elevating HDL-C. The LDL-C target achievement rates in

any one group of statin + niacin, statin + fibrates, statin + policosanol, and statin + ezetimibe could exceed 50%, but statin + ezetimibe was the best group of them, Figure 1.

Table 2. Lipid profiles changes from baseline to study end point in the 5 groups (mmol/L).

Groups	n	Total cholesteral	Triglyceride	HDL-C	LDL-C
Baseline, mean ± SD					
N + F	83	5.04 ± 0.96	3.59 ± 1.81	0.77 ± 0.27	2.85 ± 0.77
S + N	92	5.23 ± 1.09	2.81 ± 1.26	0.84 ± 0.23	2.91 ± 0.86
S + F	90	5.56 ± 1.15	2.70 ± 1.50	0.87 ± 0.34	2.94 ± 0.80
S + P	97	5.78 ± 0.63	2.11 ± 1.00	1.05 ± 0.30	2.97 ± 0.77
S + E	88	5.49 ± 0.87	2.10 ± 1.17	0.99 ± 0.42	3.10 ± 0.90
End point, mean ± SD					
N + F	83	4.47 ± 1.02 ^{##}	2.18 ± 1.06 ^{##}	0.99 ± 0.23 ^{##}	2.18 ± 0.64 ^{##}
S + N	92	3.91 ± 0.97 ^{##}	2.29 ± 1.32 ^{##}	0.98 ± 0.36 ^{##}	1.66 ± 0.61 ^{##}
S + F	90	4.24 ± 1.14 ^{##}	1.91 ± 1.12 ^{##}	1.03 ± 0.32 ^{##}	1.63 ± 0.64 ^{##}
S + P	97	3.98 ± 0.86 ^{##}	1.78 ± 0.89 ^{##}	1.15 ± 0.28 ^{a*}	1.45 ± 0.72 ^{##}
S + E	88	3.90 ± 0.89 ^{##}	1.74 ± 0.77 ^{##}	1.06 ± 0.30	1.38 ± 0.65 ^{##}
Percent changes (%)					
N + F	83	-11.3	-39.3	28.6	-23.5
S + N	92	-25.2 ^{b#,c#,d#}	-18.5 ^{b#,c#}	16.7 ^{b#,c#,d#}	-43.0 ^{b#,c#,d#}
S + F	90	-23.7 ^{b#,c#,d#}	-29.3 ^{b#,c#,d#}	18.4 ^{b#,c#,d#}	-44.6 ^{b#,c#,d#}
S + P	97	-31.1 ^{b#}	-15.6 ^{b#}	9.5 ^{b#,c#}	-51.2 ^{b#,c#}
S + E	88	-30.0 ^{b#}	-17.1 ^{b#}	7.1 ^{b#}	-55.5 ^{b#}

N: Niacin; F: Fibrates; S: Statin; P: Policosanol; E: Ezetimibe; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; **P* < 0.05, [#]*P* < 0.01, ^a: compared with baseline; ^b: compared with N + F; ^c: S + N, S + F, S + P compared with S + E; ^d: S + N, S + F compared with S + P; ^e: S + N compared with S + F.

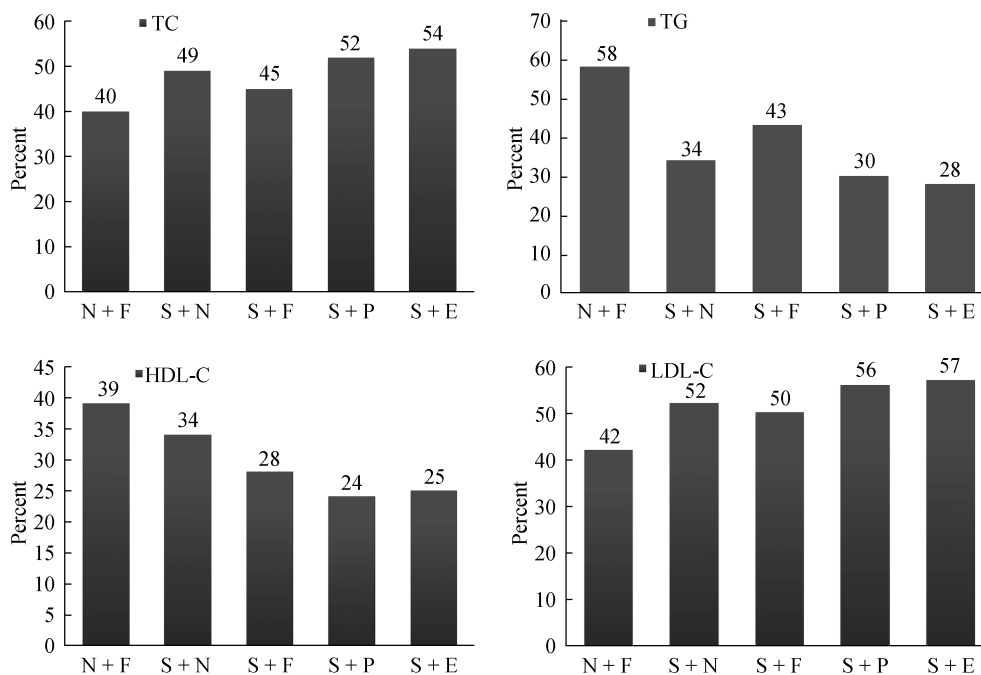


Figure 1. Lipid profile target achievement rates of different combination therapies. E: Ezetimibe; F: Fibrates; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; N: Niacin; P: Policosanol; S: Statin; TC: total cholesterol; TG: total triglyceride. In decreasing TG and HDL-C, *P* < 0.05 compared with S + N, S + F, S + P and S + E; in decreasing TC and LDL-C, *P* < 0.05 compared with N + F.

3.4 Safety

There was no significant difference in the proportions of adverse events in all five groups. There were no severe adverse events or deaths in this study, and the proportions of patients experiencing one, or more, adverse events in all five groups were 2%. In this study, four patients in all experienced drug-related abdominal pain and dyspnea, with one patient in each group: statin + niacin, statin + fibrates, statin + policosanol and statin + ezetimibe. There were also no reports of myopathy or rhabdomyolysis in this study. Two patients presented transient elevations with aspartate aminotransferase (AST) $< 3 \times \text{ULN}$ in group niacin + fibrates, and three patients presented CK increasing to 268 U/L, 249 U/L, 251 U/L without muscle symptoms in group statin + fibrates. There were no clinically meaningful changes in body weight, vital signs, and any other clinical and laboratory adverse events.

4 Discussion

Dyslipidemia is an important risk factor for CHD and ischemic stroke including high LDL-C, TG and low HDL-C level.^[6] Adequate control of hyperlipidemia is of paramount importance for prevention of vascular events and statin is generally considered as the first drug if a medication is necessary for hyperlipidemia.^[7] Despite the excellent benefit/risk profile of statins, their use is limited by a dose-related risk of adverse events, particularly those related to muscle toxicity. One of the problems associated with reaching the LDL-C target level during statin treatment is the emergence of laboratory or clinical side effects.^[8,9] In addition, mixed dyslipidemia is usually so common in the very old patients, and so often very difficult to get satisfactory control of the lipid levels with only with one kind of lipid-regulating drugs.^[10] Low levels of HDL-C (< 1.03 mmol/L or < 40 mg/dL) are an independent risk factor for cardiovascular diseases, and most of the previous studies indicated that raising levels of HDL-C is a major treatment strategy for regressing atherosclerosis and enhancing CVD risk reduction.^[11-13] Therefore, presently, niacin and fibrates were always added to statin for increasing HDL-C level.^[9] While there were still some studies insisted that HDL-C preventing cardiovascular events based on its unique lipid particle biology and not only its level.^[14] Whether the level of HDL-C, or its function, is important for the prevention of cardiovascular events is still in dispute.

Effective treatment to achieve target lipid parameters in high-risk patients may require combination drug therapies. It could theoretically have a better effect on lipid-regulating than single drug therapy. However, concerns regarding risks

associated with such combination therapies may limit their use, particularly for the very old patients due to their age-related specific characteristics.^[15] There were some previous studies about combination therapy for mixed dyslipidemia.^[16-20] However, these studies only compared the efficacy of combination therapies and monotherapy, and failed to compare the efficacy of different combination therapies in the very old patients.

In the present study, five different combination therapies were adopted to manage mixed dyslipidemia. The results showed each type of the five combination therapies were quite effective for the very old patients with mixed dyslipidemia. TC and LDL-C levels were all reduced by different percentages in every group compared to baseline. The target achievement rates of LDL-C all exceeded 50%, except in the niacin + fibrates group. Statin + ezetimibe was the best group in target achievement rates of LDL-C level. Also, statin + ezetimibe was obviously the best group in decreasing TC and LDL-C levels. However, niacin + fibrates was the best group in decreasing TG and increasing HDL-C. The achievement rates of TG and HDL-C levels in niacin + fibrates were better than the other four groups.

According to the previous studies, atorvastatin monotherapy (10 mg/d for 12 weeks) only reduced TC by 27% and LDL-C by 35%.^[21] However, this study showed that LDL-C level were reduced by over 40% in any combination group, except in niacin + fibrates group, and it was even over 50% in the groups: statin + ezetimibe and statin + policosanol. The combination of niacin + fibrates in the very old patients could also better enhance their lipid-regulating efficacy, but didn't increase the adverse reactions such as the risk of myopathy or other incidences, similar to some studies done in the non-old patients.^[12] It suggested that the combination of statin + niacin, statin + fibrates could not only get better comprehensive lipid-regulating effects, but didn't increase the occurrence of myopathy and liver toxicity.^[16,17,22] So statin + niacin or statin + fibrate therapy should be considered if monotherapy did not achieve lipid targets or is impractical. Fibrates and niacin added to statins could reduce TG, increase HDL-C, and reduce non-HDL cholesterol to a greater extent than statin monotherapy. Ezetimibe and statin combination therapy could produce more benefits on lowering LDL-C level.^[18,23,24] Compared to monotherapy, the statin and ezetimibe combination therapy has an additive effect that is not influenced by risk factors. They reduced LDL-C levels by 36.8% and TC levels by 25.3%, respectively.^[25] And it has also been proved in this study. Previous studies showed addition of policosanol to atorvastatin succeeded to produce some further reduction in lipid levels above that of atorvastatin

alone,^[19,26] which was in accordance with the present study.

Practically, most of the very old patients were in very high cardiovascular risk conditions and should benefit from strict control of lipid levels to prevent major adverse cardiovascular events. However, it was so usually difficult to get better target achievement rates of LDL-C level with statin or other lipid-regulating agent alone. This study showed the currently common combination therapies could greatly increase the target achievement rates and almost every combination therapy could exceed 50% of target, except in the niacin + fibrates group.

The combination therapy strategies included in the study were most common in clinical practice presently,^[20] and results confirmed there were no severe adverse events or deaths occurred in this study. Incidences of drug-related adverse events were all relatively low in the five combination groups. There was also no significant difference in the proportions of adverse events among five groups. The proportions of patients in all five groups experiencing one or more drug-related adverse events were only 2%, similar to statins used alone, which was in agreement with previous studies.^[27]

This study suggested that all of the five combination groups in the study could produce better beneficial effects in improving lipid levels and did not increase adverse events. The commonly used combined lipid-regulating therapies with the recommended dosages in this study were all quite safe and feasible for the very old patients. The combination lipid therapy is recommended to produce a favorable risk to benefit ratio if the global coronary heart disease risk of the patient is high.

Acknowledgments

The authors are grateful to the Department of statistics and the Department of Biochemistry of Chinese PLA General Hospital for assistance. The funding institutes had no role in the design, methods, subject recruitment, data collection, analysis, and preparation of manuscript or in the decision to submit the manuscript for publication. The authors declare no conflicts of interest.

References

- Natarajan P, Ray KK, Cannon CP. High density lipoprotein and coronary heart disease: current and future therapies. *J Am Coll Cardiol* 2010; 55: 1283–1299.
- Chapman MJ, Redfern JS, McGovern ME, *et al.* Niacin and fibrates in atherogenic dyslipidemia: pharmacotherapy to reduce cardiovascular risk. *Pharmacol Ther* 2010; 126: 314–345.
- Daskalopoulou SS, Mikhailidis DP. Reaching goal in hypercholesterolaemia: dual inhibition of cholesterol synthesis and absorption with simvastatin plus ezetimibe. *Curr Med Res Opin* 2006; 22: 511–528.
- Stein EA. Managing dyslipidemia in the high-risk patient. *Am J Cardiol* 2002; 89 (5A): 50C–57C.
- Joint Committee for Developing Chinese Guidelines on Prevention and Treatment of Dyslipidemia in Adults. Chinese guidelines on prevention and treatment of dyslipidemia in adults. *Chin J Cardiol* 2007; 35: 390–419.
- Wu YF, Liu XQ, Li X, *et al.* USA-PRC Collaborative Study of Cardiovascular and Cardiopulmonary Epidemiology Research Group; China Multicenter Collaborative Study of Cardiovascular Epidemiology Research Group. Estimation of ten-year risk of fatal and non-fatal isehemic cardiovascular diseases in Chinese. *Circulation* 2006; 114: 2217–2225.
- LaRosa JC, Pedersen TR, Somaratne R, *et al.* Safety and effect of very low levels of low-density lipoprotein cholesterol on cardiovascular events. *Am J Cardiol* 2013; 111: 1221–1229.
- Kashani A, Phillips CO, Foody JM, *et al.* Risks associated with statin therapy: a systematic overview of randomized clinical trials. *Circulation* 2006; 114: 2788–2797.
- Silva M, Matthews ML, Jarvis C, *et al.* Meta-analysis of drug-induced adverse events associated with intensive-dose statin therapy. *Clin Ther* 2007; 29: 253–260.
- Kashani A, Sallam T, Bheemreddy S, *et al.* Review of side-effect profile of combination ezetimibe and statin therapy in randomized clinical trials. *Am J Cardiol* 2008; 101: 1606–1613.
- Hausenloy DJ, Yellon DM. Enhancing cardiovascular disease risk reduction: raising high-density lipoprotein levels. *Curr Opin Cardiol* 2009; 24: 473–482.
- Sprecher DL. Raising high-density lipoprotein cholesterol with niacin and fibrates: a comparative review. *Am J Cardiol* 2000; 86: 46L–50L.
- Mureddu GF, Brandimarte F, De Luca L. High-density lipoprotein levels and risk of cardiovascular events: a review. *J Cardiovasc Med (Hagerstown)* 2012; 13: 575–586.
- Taylor AJ. Evidence to support aggressive management of high-density lipoprotein cholesterol: implications of recent imaging trials. *Am J Cardiol* 2008; 101: 36B–43B.
- Da-Yi Hu. Advance in dyslipidemia treatment in 2010. *Chin J New Drugs* 2011; 20: 1358–1361.
- McKenney JM. Combination treatment with atorvastatin plus niacin provides effective control of complex dyslipidemias: a literature review. *Postgrad Med* 2012; 124: 7–20.
- Mohiuddin SM, Thakker KM, Setze CM, *et al.* Evaluating optimal lipid levels in patients with mixed dyslipidemia following short- and long-term treatment with fenofibric acid and statin combination therapy: a post hoc analysis. *Curr Med Res Opin* 2011; 27: 1067–1078.
- Bays HE, Ose L, Fraser N, *et al.* A multicenter, randomized, double-blind, placebo-controlled, factorial design study to evaluate the lipid-altering efficacy and safety profile of the ezetimibe/simvastatin tablet compared with ezetimibe and

- simvastatin monotherapy in patients with primary hypercholesterolemia. *Clin Ther* 2004; 26: 1758–1773.
- 19 Backes JM, Gibson CA, Ruisinger JF, *et al.* Modified-policosanols does not reduce plasma lipoproteins in hyperlipidemic patients when used alone or in combination with statin therapy. *Lipids* 2011; 46: 923–929.
 - 20 Reiner Z. Combined therapy in the treatment of dyslipidemia. *Fundam Clin Pharmacol* 2010; 24: 19–28.
 - 21 Cubeddu LX, Cubeddu RJ, Heimowitz T, *et al.* Comparative lipid-lowering effects of policosanols and atorvastatin: a randomized, parallel, double-blind, placebo-controlled trial. *Am Heart J* 2006; 152: 982.e1–e5.
 - 22 Watts GF, Karpe F. Republished review: Triglycerides and atherogenic dyslipidaemia: extending treatment beyond statins in the high-risk cardiovascular patient. *Postgrad Med J* 2011; 87: 776–782.
 - 23 Uemura Y, Watarai M, Ishii H, *et al.* Atorvastatin 10 mg plus ezetimibe 10 mg compared with atorvastatin 20 mg: impact on the lipid profile in Japanese patients with abnormal glucose tolerance and coronary artery disease. *J Cardiol* 2012; 59: 50–56.
 - 24 Efrati S, Averbukh M, Dishy V, *et al.* The effect of simvastatin, ezetimibe and their combination on the lipid profile, arterial stiffness and inflammatory markers. *Eur J Clin Pharmacol* 2007; 63: 113–121.
 - 25 Lee YH, Kim MJ, Choi CI, *et al.* Retrospective study on antihyperlipidemic efficacy and safety of simvastatin, ezetimibe and their combination in Korean adults. *Arch Pharm Res* 2011; 34: 1331–1337.
 - 26 Berthold HK, Unverdorben S, Degenhardt R, *et al.* Effect of policosanols on lipid levels among patients with hypercholesterolemia or combined hyperlipidemia: a randomized controlled trial. *JAMA* 2006; 295: 2262–2269.
 - 27 Davidson MH, Maccubbin D, Stepanavage M, *et al.* Striated muscle safety of Ezetimibe/Simvastatin (Vytorin). *Am J Cardiol* 2006; 97: 223–228.