Effects of Toremifene and Tamoxifen on Lipid Profiles in Post-menopausal Patients with Early Breast Cancer: Interim Results from a Japanese Phase III Trial

Takeshi Tominaga1,*, Izo Kimijima2, Morihiko Kimura3, Yuichi Takatsuka4, Shigemitsu Takashima5, Yasuo Nomura6, Fujio Kasumi7, Akihiro Yamaguchi8, Norikazu Masuda9, Shinzaburo Noguchi10 and Nobuoki Eshima11

1Breast Cancer Center, Toyosu Hospital, Showa University, Tokyo, 2Breast Center, Northern Fukushima Medical Center, Date, 3Department of Surgery, Gunma Cancer Center, Ota, 4Department of Surgery, Kansai Rosai Hospital, Amagasaki, 5Department of Surgery, National Shikoku Cancer Center Hospital, Matsuyama, 6Department of Breast Surgery, Oikawa Hospital, Fukuoka, 7Department of Breast Oncology, Cancer Institute Hospital, Tokyo, 8Department of Surgery, Ogaki Municipal Hospital, Ogaki, 9Department of Surgery, National Hospital Organization Osaka National Hospital, Osaka, 10Department of Breast and Endocrine Surgery, Osaka University Graduate School of Medicine, Suita and 11Department of Medical Information Analysis, Faculty of Medicine, Oita University, Yufu, Japan

*For reprints and all correspondence: Takeshi Tominaga, Breast Cancer Center, Toyosu Hospital, Showa University, Tokyo, Japan. E-mail: t-tominaga@hkg.odn.ne.jp

Received November 9, 2009; accepted February 5, 2010

Objective: Toremifene and tamoxifen have been used for adjuvant therapy in post-menopausal patients with breast cancer in Japan. Dyslipidemias are common in post-menopausal women. However, limited data are available on the effects of these agents on lipid profiles in Japanese patients. The Japan Toremifene Cooperative Study Group has been conducting a Phase III randomized trial of post-menopausal patients with breast cancer. One of its secondary endpoints is to confirm the effects of these agents on serum lipid profiles.

Methods: The subjects were post-menopausal Japanese patients who had undergone surgery for early breast cancer. Toremifene or tamoxifen was administered for 2 years. Lipid levels were measured before and up to 24 months after initiation.

Results: Compared with baseline, at 24 months, the toremifene group (n = 123) showed significantly decreased total cholesterol (P < 0.001) and low-density lipoprotein cholesterol levels (P < 0.001), and significantly increased high-density lipoprotein cholesterol levels (P < 0.001). Their triglyceride levels were not affected (P = 0.677). The tamoxifen group (n = 120) also showed significantly decreased total cholesterol (P < 0.001) and low-density lipoprotein cholesterol levels (P < 0.001); no significant changes occurred in high-density lipoprotein cholesterol (P = 0.297) or triglyceride levels (P = 0.120).

Conclusions: Distinct differences between two selective estrogen receptor modulators on lipids were observed. Toremifene improved lipid profiles, particularly as an enhancer of high-density lipoprotein cholesterol. To a large extent, tamoxifen improved low-density lipoprotein cholesterol levels. The impact of these improved lipid profiles on the risk of cardiovascular diseases needs further confirmation.

Key words: breast cancer – lipid – post-menopausal patient – toremifene – tamoxifen

INTRODUCTION

Post-menopausal women experience significant alterations in estrogen levels that cause unfavorable effects on lipid and bone metabolism. These exacerbate problems associated with dyslipidemia, atherosclerosis and osteoporosis (1,2). Tamoxifen is a non-steroidal anti-estrogen agent that has...
Effects of toremifene and tamoxifen on lipid profiles

Lipid profiles in Japanese breast cancer patients. Here, we report the outcomes of the secondary endpoint is the effects of the agents on serum lipid profiles. The primary endpoint of the study is the survival rate. The secondary endpoint is the effects of the agents on serum lipid profiles. Here, we report the outcomes of the secondary endpoint to elucidate the effects of toremifene and tamoxifen on lipid profiles in Japanese breast cancer patients.

PATIENTS AND METHODS

Ethics Review

The protocol was reviewed and approved by the respective Ethics Committee/Institutional Review Board of each participating institution and the study was conducted in accordance with the Helsinki Declaration of 1975. Prior to enrollment, all patients were provided written information about the study design and written informed consent was obtained from all patients for participation in the study.

PATIENTS

Between December 1998 and November 2001, a total of 253 patients were enrolled from 48 institutions throughout Japan. Patients who satisfied the following eligibility criteria were included: (i) post-menopausal primary breast cancer, (ii) ≤75 years of age, (iii) stage T1–2, N0, M0, (iv) estrogen receptor-positive or -unknown tumor and (v) underwent mastectomy or breast conserving resection. The TNM classification (1978 version) was used for the staging of breast cancer. Patients with estrogen receptor-unknown status were eligible, as the assay method for estrogen receptors was not available in some institutions at the time of trial planning.

Randomization and Treatment

Of the 253 patients, 243 were eligible for inclusion in this analysis. Enrolled patients were randomly assigned to one of the following two treatment groups: toremifene group (n = 123) and tamoxifen group (n = 120). The toremifene group received toremifene citrate tablets (40 mg/day) and the tamoxifen group received tamoxifen citrate tablets (20 mg/day). Subjects began taking these medicines within 6 weeks of surgery, which were continued on a daily basis for 2 years. At the time of trial planning, the standard treatment duration of toremifene and tamoxifen in the adjuvant setting for early breast cancer was 2 years in Japan.

Assessment of Serum Lipids

Although the timing of blood sampling has not been defined by the study protocol, no patient ate breakfast before sampling according to the clinical records. Thus, serum samples were collected after overnight fasting. Time points for blood collection were before the start of administration of adjuvant drugs and 3, 6, 12 and 24 months after the start of their administration. Serum lipids evaluated were total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C) and triglycerides (TG). Concentrations of serum lipids were measured by standard enzymatic methods. When an enzymatic method was not used, LDL-C values were calculated using the equation of Friedewald et al. (9).

Statistical Methods

Changes in lipid profiles were analyzed using Student’s paired t-test based on differences between mean values before administration (baseline) and mean values 24 months after administration of each agent (two-sided significance level = 0.05). Values measured 24 months after administration were compared between the groups by analysis of covariance, with the baseline values as covariates (two-sided significance level = 0.05).

RESULTS

Patient Characteristics

As shown in Table 1, there were no significant differences in background characteristics between the two groups. Five patients in the toremifene group and three in the tamoxifen group were eligible, as the assay method for estrogen receptors was not available in some institutions at the time of trial planning.

Randomization and Treatment

Of the 253 patients, 243 were eligible for inclusion in this analysis. Enrolled patients were randomly assigned to one of the following two treatment groups: toremifene group (n = 123) and tamoxifen group (n = 120). The toremifene group received toremifene citrate tablets (40 mg/day) and the tamoxifen group received tamoxifen citrate tablets (20 mg/day). Subjects began taking these medicines within 6 weeks of surgery, which were continued on a daily basis for 2 years. At the time of trial planning, the standard treatment duration of toremifene and tamoxifen in the adjuvant setting for early breast cancer was 2 years in Japan.

Assessment of Serum Lipids

Although the timing of blood sampling has not been defined by the study protocol, no patient ate breakfast before sampling according to the clinical records. Thus, serum samples were collected after overnight fasting. Time points for blood collection were before the start of administration of adjuvant drugs and 3, 6, 12 and 24 months after the start of their administration. Serum lipids evaluated were total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C) and triglycerides (TG). Concentrations of serum lipids were measured by standard enzymatic methods. When an enzymatic method was not used, LDL-C values were calculated using the equation of Friedewald et al. (9).

Statistical Methods

Changes in lipid profiles were analyzed using Student’s paired t-test based on differences between mean values before administration (baseline) and mean values 24 months after administration of each agent (two-sided significance level = 0.05). Values measured 24 months after administration were compared between the groups by analysis of covariance, with the baseline values as covariates (two-sided significance level = 0.05).

RESULTS

Patient Characteristics

As shown in Table 1, there were no significant differences in background characteristics between the two groups. Five patients in the toremifene group and three in the tamoxifen group were eligible, as the assay method for estrogen receptors was not available in some institutions at the time of trial planning.

Randomization and Treatment

Of the 253 patients, 243 were eligible for inclusion in this analysis. Enrolled patients were randomly assigned to one of the following two treatment groups: toremifene group (n = 123) and tamoxifen group (n = 120). The toremifene group received toremifene citrate tablets (40 mg/day) and the tamoxifen group received tamoxifen citrate tablets (20 mg/day). Subjects began taking these medicines within 6 weeks of surgery, which were continued on a daily basis for 2 years. At the time of trial planning, the standard treatment duration of toremifene and tamoxifen in the adjuvant setting for early breast cancer was 2 years in Japan.

Assessment of Serum Lipids

Although the timing of blood sampling has not been defined by the study protocol, no patient ate breakfast before sampling according to the clinical records. Thus, serum samples were collected after overnight fasting. Time points for blood collection were before the start of administration of adjuvant drugs and 3, 6, 12 and 24 months after the start of their administration. Serum lipids evaluated were total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C) and triglycerides (TG). Concentrations of serum lipids were measured by standard enzymatic methods. When an enzymatic method was not used, LDL-C values were calculated using the equation of Friedewald et al. (9).

Statistical Methods

Changes in lipid profiles were analyzed using Student’s paired t-test based on differences between mean values before administration (baseline) and mean values 24 months after administration of each agent (two-sided significance level = 0.05). Values measured 24 months after administration were compared between the groups by analysis of covariance, with the baseline values as covariates (two-sided significance level = 0.05).

RESULTS

Patient Characteristics

As shown in Table 1, there were no significant differences in background characteristics between the two groups. Five patients in the toremifene group and three in the tamoxifen group were eligible, as the assay method for estrogen receptors was not available in some institutions at the time of trial planning.

Randomization and Treatment

Of the 253 patients, 243 were eligible for inclusion in this analysis. Enrolled patients were randomly assigned to one of the following two treatment groups: toremifene group (n = 123) and tamoxifen group (n = 120). The toremifene group received toremifene citrate tablets (40 mg/day) and the tamoxifen group received tamoxifen citrate tablets (20 mg/day). Subjects began taking these medicines within 6 weeks of surgery, which were continued on a daily basis for 2 years. At the time of trial planning, the standard treatment duration of toremifene and tamoxifen in the adjuvant setting for early breast cancer was 2 years in Japan.

Assessment of Serum Lipids

Although the timing of blood sampling has not been defined by the study protocol, no patient ate breakfast before sampling according to the clinical records. Thus, serum samples were collected after overnight fasting. Time points for blood collection were before the start of administration of adjuvant drugs and 3, 6, 12 and 24 months after the start of their administration. Serum lipids evaluated were total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C) and triglycerides (TG). Concentrations of serum lipids were measured by standard enzymatic methods. When an enzymatic method was not used, LDL-C values were calculated using the equation of Friedewald et al. (9).

Statistical Methods

Changes in lipid profiles were analyzed using Student’s paired t-test based on differences between mean values before administration (baseline) and mean values 24 months after administration of each agent (two-sided significance level = 0.05). Values measured 24 months after administration were compared between the groups by analysis of covariance, with the baseline values as covariates (two-sided significance level = 0.05).

RESULTS

Patient Characteristics

As shown in Table 1, there were no significant differences in background characteristics between the two groups. Five patients in the toremifene group and three in the tamoxifen group were eligible, as the assay method for estrogen receptors was not available in some institutions at the time of trial planning.

Randomization and Treatment

Of the 253 patients, 243 were eligible for inclusion in this analysis. Enrolled patients were randomly assigned to one of the following two treatment groups: toremifene group (n = 123) and tamoxifen group (n = 120). The toremifene group received toremifene citrate tablets (40 mg/day) and the tamoxifen group received tamoxifen citrate tablets (20 mg/day). Subjects began taking these medicines within 6 weeks of surgery, which were continued on a daily basis for 2 years. At the time of trial planning, the standard treatment duration of toremifene and tamoxifen in the adjuvant setting for early breast cancer was 2 years in Japan.
group had histories of angina pectoris. Among eligible patients, one in the toremifene group and two in the tamoxifen group had histories of myocardial infarction. One patient in the tamoxifen group had a history of cerebral infarction. Among the patients with dyslipidemia, medication was administered to 14 in the toremifene group (11 received statins and 3 received fibrates) and 13 in the tamoxifen group (12 received statins and 1 received fibrate).

**Effects of Toremifene and Tamoxifen on Serum Lipids**

As shown in Fig. 1, TC levels in both the toremifene and tamoxifen groups began to decline in the 3rd month and continued to decline until the 24th month. Compared with baseline levels, the TC values had decreased significantly in the 24th month in both groups (toremifene group, $P < 0.001$; tamoxifen group, $P < 0.001$). LDL-C levels in both groups also began to decrease in the 3rd month and continued to decrease until the 24th month. In the third month, the mean values of LDL-C in both groups decreased sufficiently from borderline levels to normal levels. The LDL-C values were decreased significantly compared with baseline in the 24th month in both groups (toremifene group, $P < 0.001$; tamoxifen group, $P < 0.001$).

HDL-C levels in the toremifene group began to increase in the 3rd month and continued to increase until the 24th month, at which point the increase was 18.0%. The HDL-C values increased significantly compared with baseline in the 24th month in the toremifene group ($P < 0.001$). In the tamoxifen group, the HDL-C increase peaked in the 6th month and had increased by 1.7% in the 24th month. Compared with baseline values, the HDL-C increase in the tamoxifen group was not significant in the 24th month ($P = 0.297$).

TG levels in the toremifene group showed a transient increase in the 3rd month and decreased thereafter, with a 4.7% decrease in the 24th month. Compared with baseline, the decrease in TG in the toremifene group was not significant in the 24th month ($P = 0.001$). In the tamoxifen group, the TG levels increased, peaked in the 3rd month and achieved an 11.8% increase in the 24th month. However, the increase in TG from baseline in the toremifene group was not significant in the 24th month ($P = 0.120$).

Table 2 shows the changes in the number of patients with dyslipidemia following treatment with SERMs. Toremifene decreased the prevalence of hyper-LDL-C, hypo-HDL-C and hyper-TG. Although tamoxifen decreased the prevalence of hyper-LDL-C, it failed to decrease the prevalence of hypo-HDL-C and hyper-TG. The effect of SERMs on TC was not assessed because the diagnostic criteria for TC were replaced by LDL-C in Japan.

Several indices have been used to assess the risk of atherosclerosis and coronary heart disease (7). The influence of toremifene and tamoxifen on the indices for these risks is shown in Table 3. Both TC to HDL-C and LDL-C to HDL-C ratios decreased in the toremifene and tamoxifen groups. The TG to HDL-C ratio decreased in the toremifene group, whereas this index increased slightly in the tamoxifen group.

**DISCUSSION**

Hypercholesterolemia and hypertriglyceridemia are more common in post-menopausal women compared with pre-menopausal women, and the primary cause is thought to be decreased blood estrogen concentrations. A relationship between serum lipid levels and heart disease has been established previously. In many industrialized countries, coronary heart disease is the major cause of death in post-menopausal women. A Caucasian post-menopausal woman in the USA is 10 times more likely to die of heart disease than of breast cancer (10). Thus, the effects on lipid metabolism of SERMs that are used as adjuvant therapy for post-menopausal breast cancer patients have attracted particular attention.
One study showed that both toremifene and tamoxifen decreased TC and LDL-C levels after 12 months of adjuvant therapy, and that toremifene also increased HDL-C (7). Another study found similar effects for both agents, although it failed to show an increase in HDL-C in their toremifene group (6). In general, the present results are consistent with previous reports based on short-term treatments (11–14).

In Japan, the effects of toremifene and tamoxifen following 1-year administration have been reported on lipid profiles in breast cancer patients (8). On the basis of the outcomes of this study, a crossover trial was performed. In patients who switched from toremifene to tamoxifen, HDL-C levels decreased and TG levels increased significantly. Conversely, in patients who switched from tamoxifen to toremifene, HDL-C levels increased significantly, whereas TG levels decreased significantly (15). The previously cited results and the outcomes of this study confirm that the effects of toremifene and tamoxifen on lipid profiles are different, especially their effects on HDL-C. Furthermore, our data showed that the favorable effects of toremifene and tamoxifen on lipid profiles were maintained throughout the treatment period.

The Framingham heart study established that TC was a risk factor for coronary artery disease (16). In recent years, LDL-C has also become recognized as an important risk factor for coronary heart disease. In Japan, guidelines for the prevention of arteriosclerotic cardiovascular disease were revised in 2007 by incorporating LDL-C > 140 mg/dl into the diagnostic criteria for coronary artery disease in high-risk groups. Concomitantly, TC was eliminated from the diagnostic criteria (17).

Many randomized trials have shown the benefits of agents that lower LDL-C levels, such as statins, in women who are at a high risk for atherosclerosis and its associated complications. The present study showed that LDL-C levels were markedly decreased in both the toremifene and tamoxifen groups, suggesting that both agents could lower the risk of atherosclerotic cardiovascular diseases. Hypertriglyceridemia is also a known risk factor for atherosclerosis (18). Decreasing the levels of LDL-C and TG using statins has been the standard therapy for dyslipidemia. However, the residual cardiovascular risk for patients treated with statins remains high, indicating that there are lipid targets other than LDL-C or TG to be considered (19).
It is well known that the occurrence of coronary heart disease is lower in Japanese compared with Caucasians (20). A recent epidemiologic study showed that Japanese had worse TC and LDL-C levels and better HDL-C levels compared with Caucasians (21). Another study reported a much lower prevalence of coronary calcium in Japanese, in spite of a less favorable profile of other major independent factors. The study authors assumed that this might imply that there are strong protective factors against atherosclerosis in the Japanese (22). These observations suggest that HDL-C might play a key role for the prevention of cardiovascular disease in the Japanese population.

HDL-C is known to play a central role in reverse cholesterol transport and to have antioxidant, anti-inflammatory and anti-thrombotic effects. These roles of HDL-C have been studied both epidemiologically and clinically, and it has been shown that there is an inverse correlation between the HDL-C level and the risk of coronary artery disease (23). The results of many trials have shown that a low HDL-C level is a strong independent risk factor of coronary heart disease (24). Our data demonstrated that toremifene decreased the number of patients with low HDL-C levels, suggesting that toremifene may reduce the risk for coronary heart disease.

In many studies, the ratio of TC to HDL-C or LDL-C to HDL-C has been used as indices of coronary heart disease risk. In the present study, administrations of both agents

### Table 2. Changes in the number of patients with dyslipidemia following treatment with SERMs

<table>
<thead>
<tr>
<th>Group</th>
<th>Serum lipids</th>
<th>Lipid level</th>
<th>Number of patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Baseline</td>
<td>3 months</td>
</tr>
<tr>
<td>Toremifene</td>
<td>LDL-C</td>
<td>Hyper a</td>
<td>58 (47.2)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Normal</td>
<td>65 (52.8)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Total</td>
<td>123 (100.0)</td>
</tr>
<tr>
<td></td>
<td>HDL-C</td>
<td>Hypo b</td>
<td>16 (13.0)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Normal</td>
<td>107 (87.0)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Total</td>
<td>123 (100.0)</td>
</tr>
<tr>
<td></td>
<td>TG</td>
<td>Hyper c</td>
<td>50 (40.7)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Normal</td>
<td>73 (59.3)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Total</td>
<td>123 (100.0)</td>
</tr>
<tr>
<td>Tamoxifen</td>
<td>LDL-C</td>
<td>Hyper a</td>
<td>48 (40.0)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Normal</td>
<td>72 (60.0)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Total</td>
<td>120 (100.0)</td>
</tr>
<tr>
<td></td>
<td>HDL-C</td>
<td>Hypo b</td>
<td>3 (2.5)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Normal</td>
<td>117 (97.5)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Total</td>
<td>120 (100.0)</td>
</tr>
<tr>
<td></td>
<td>TG</td>
<td>Hyper c</td>
<td>45 (37.5)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Normal</td>
<td>75 (62.5)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Total</td>
<td>120 (100.0)</td>
</tr>
</tbody>
</table>

SERMs, selective estrogen receptor modulator; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; TG, triglycerides.

- a ≥ 140 mg/dl.
- b < 40 mg/dl.
- c ≥ 150 mg/dl.

### Table 3. Improvement of HDL-C-associated indices for coronary heart disease risk

<table>
<thead>
<tr>
<th>Index</th>
<th>Treatment group</th>
<th>Value at % change</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>24 months</td>
</tr>
<tr>
<td>TC to HDL-C ratio</td>
<td>Toremifene</td>
<td>4.04</td>
</tr>
<tr>
<td></td>
<td>Tamoxifen</td>
<td>3.85</td>
</tr>
<tr>
<td>LDL-C to HDL-C ratio</td>
<td>Toremifene</td>
<td>2.51</td>
</tr>
<tr>
<td></td>
<td>Tamoxifen</td>
<td>2.33</td>
</tr>
<tr>
<td>TG to HDL-C ratio</td>
<td>Toremifene</td>
<td>2.76</td>
</tr>
<tr>
<td></td>
<td>Tamoxifen</td>
<td>2.62</td>
</tr>
</tbody>
</table>

TC, total cholesterol.
resulted in improvements of the TC to HDLC and LDL-C to HDL-C ratios, although toremifene showed superior changes compared with tamoxifen. Furthermore, toremifene administration improved the TG to HDLC ratio, whereas tamoxifen failed to improve this index.

Unfortunately, the number of HDL-C-enhancing agents available for clinical practice is limited. The results of a meta-analysis of randomized controlled trials showed 10% and 16% increases in HDL-C levels for fibrates and niacin, respectively (25). Toremifene has been reported as the only SERM that significantly increased HDL-C (26). On the basis of the available data, toremifene is considered to be one of the most potent HDL-C-enhancing agents available for clinical practice. Unlike other HDL-C-enhancing agents, toremifene provides dual actions both as an HDL-C enhancer and as a therapeutic agent for breast cancer, thus providing additional benefits for post-menopausal breast cancer patients.

The present results suggest that SERMs provide favorable effects by lowering the risk of arteriosclerosis and coronary heart disease. In fact, no coronary events were recorded in the toremifene group and only one angina pectoris case was recorded in the tamoxifen group in the present study. A significantly lower incidence of cerebrovascular damage and thrombosis has been reported for patients who were given toremifene compared with those who were given tamoxifen in a previous study (27). In fact, no incidence of cerebral infarction was observed in the present study. Thus, serum lipid profile analysis could be a useful tool for selecting drugs for the treatment of post-menopausal breast cancer patients who are at a risk for dyslipidemia or atherosclerosis.

The results of the present study confirmed the beneficial effects of toremifene and tamoxifen on lipid profiles of post-menopausal women with early breast cancer. The favorable effects of these SERMs might offer benefits for patients with dyslipidemias or with histories of atherosclerosis and ischemic heart disease.

In conclusion, toremifene and tamoxifen show distinct differences in their effects on lipid profiles of post-menopausal women with early breast cancer. Toremifene improves the overall lipid profiles, particularly as a potent HDL-C enhancer. Tamoxifen improves the profiles for a limited set of lipids. Overall, toremifene shows better effects on the lipid profiles compared with tamoxifen. Additional studies are needed to confirm the impact of these improved lipid profiles on the risks for arteriosclerosis and cardiovascular disease.

Acknowledgements
The authors would like to acknowledge the patients, physicians, nurses and clinical research coordinators who participated in the trial.

Funding
This work was supported by Nippon Kayaku Co. Ltd.

Conflict of interest statement
None declared.

References
19. Choi BG, Vilahur G, Yadegar D, Viles-Dzalez JF, Badimon JJ. The role of high-density lipoprotein cholesterol in the prevention and


