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https://doi.org/10.15017/19317
Original Article

Effect of Probucol on Elderly Hypercholesterolemic Patients in the FAST Study

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Abstract The present study involved a detailed post hoc comparison of the efficacy and safety of lipid-lowering therapy in elderly hypercholesterolemic patients from the Fukuoka Atherosclerosis Trial (FAST). The FAST cohort of 246 hypercholesterolemic patients included 76 patients who were 75 years old. Patients were randomized to receive probucol (500 mg/day) or pravastatin (10 mg/day) therapy, or to a control group (diet alone), and then were followed for 2 years. In patients ≥75 years old, either probucol or pravastatin achieved a significant reduction of carotid intima-media thickness (IMT). In patients <75 years old, lipid-lowering therapy also achieved a significant reduction of IMT. In patients ≥75 years old receiving probucol, the relative risk (95% confidence interval) of all-cause mortality was 0.15 (0.02 to 1.28) and that for major coronary events was 0.12 (0.02 to 1.04). In conclusion, probucol reduced the incidence of cardiovascular disease in elderly hypercholesterolemic patients as well as younger patients.

Key words: elderly hypercholesterolemic patients, probucol, pravastatin, intima-media thickness, carotid atherosclerosis, cardiovascular disease

INTRODUCTION

Atherosclerosis is a common disease in the elderly, and atherosclerotic lesions may cause myocardial infarction or stroke. Measurement of the carotid artery intima-media thickness (IMT) by high-resolution B-mode ultrasonography allows noninvasive detection of early carotid atherosclerosis, and the IMT is also a reliable end-point for trials assessing the effect of interventions on disease progression. Furthermore, ultrasonography can directly quantify early atherosclerotic changes and the response to risk factor modification3), allowing the use of a smaller patient population to determine the benefits of treatment or accurately assess the presence of early atherosclerosis. The Fukuoka Atherosclerosis Trial (FAST) was the first study to demonstrate the benefit of probucol therapy for patients with hypercholesterolemia and to also reveal an effect of probucol on the incidence of cardiovascular events2).

A direct relationship between the serum low-density lipoprotein (LDL)-cholesterol level and the risk of coronary heart disease (CHD) has been most clearly demonstrated in studies on middle-aged men. Although a similar relationship has also been observed
in middle-aged women and in some older populations (≥65 years), the relationship is reported to be weaker in the elderly and it has been less convincingly established for elderly women compared with elderly men⁴. This may be partly because women and elderly patients have been poorly represented in prior clinical trials of cholesterol-lowering therapy. Consequently, the value of screening the lipid profile and performing cholesterol-lowering therapy in these populations is still unclear⁴.

The aim of the present study was to perform a detailed post hoc assessment that compared the effect of lipid-lowering therapy on carotid atherosclerosis in younger and older patient subsets (≥75 and <75 years old) from the FAST population.

METHODS

Patient Selection and Study Protocol
The study design and the baseline characteristics of the patients have been described elsewhere². Briefly, between February 1996 and February 2000, men and women aged 30–89 years with hypercholesterolemia who met the following criteria were eligible to participate in the present study. Exclusion criteria included a serum triglyceride level >350 mg/dl, uncontrolled heart failure, recent myocardial infarction (<6 months), severe or unstable angina pectoris, hypothyroidism/hyperthyroidism or other endocrine diseases, secondary hyperlipidemia, uncontrolled diabetes mellitus, uncontrolled hypertension, heavy alcohol intake, obese patients on weight reduction programs, diseases that might interfere with drug absorption, any severe illness, and treatment with certain drugs (including corticosteroids, androgens, other lipid-lowering agents, or antiacids containing aluminum salts). Hospital visits for monitoring were scheduled after 2 weeks of therapy and then every 4 weeks thereafter. At each visit, a brief physical examination was performed, and the number of tablets was counted to assess compliance. In both groups, lipids, lipoproteins, and other laboratory parameters (to confirm safety) were also measured at each visit. Written informed consent was obtained from each patient, and this trial was approved by the Ethics Committee of Kyushu University Hospital.

The procedure for measurement of carotid IMT and its reproducibility have been described elsewhere⁹. In brief, ultrasonography was done with the patient in the supine position using an Aloka SSD-2000 (Aloka, Tokyo, Japan) with a 7.5 MHz transducer. The IMT of the far wall of both the right and left common carotid arteries was measured at 2, 2.5, and 3 cm proximal to the carotid bifurcation. The IMT was defined as the distance between two echogenic lines separated by a hypoechoic or anechoic space, with the outer line corresponding to the medial-adventitial border and the inner line representing the luminal-intimal border. The mean IMT was calculated as the average value of the measurements obtained at 6 sites (3 per vessel) in the bilateral carotid arteries. Stenosis was defined as plaque (IMT ≥1.10 mm) occupying more than half of the luminal circumference of the artery on a transverse scan.

Laboratory Tests
Blood samples were collected between 8 and 9 am after a 12-hour fast. Serum cholesterol and triglyceride levels were measured by enzymatic methods. Using the calcium heparin method, high-density lipoprotein (HDL) cholesterol was measured in
the supernatant obtained after precipitation of apolipoprotein B-containing lipoproteins by and LDL cholesterol was calculated using Friedewald’s formula. Measurements were done on the day of blood collection, or else the blood was stored at -4°C for no longer than 3 days until assay.

Statistical Analysis

All data were recorded on standard forms and were entered into a database. Results are expressed as percentages or as the mean (SD). The mean values of numerical variables were compared by the Mann-Whitney U test, while categorical variables were compared by the chi-square test, as appropriate.

The endpoint was the effect of each treatment on the incidence of major atherosclerotic events. The relative risk and 95% confidence interval were calculated with the Cox regression model. In all analyses, P<0.05 was considered to indicate statistical significance. All data were analyzed on an intention-to-treat basis.

RESULTS

Baseline Characteristics

The baseline characteristics of the subjects have been summarized elsewhere. Briefly, the mean age of the patients was 66.1 years and 31.3% were men. The average systolic blood pressure and diastolic blood pressure were 130.8 and 77.1 mm Hg, respectively. Of the 246 patients, 59.3% were recent or former smokers, 42.5% had a history of hypertension, and 22.9% had diabetes mellitus. Baseline serum total cholesterol and LDL-cholesterol levels were 253.0 mg/dL and 166.1 mg/dL, respectively, while the HDL-cholesterol level was 57.0 mg/dL and the serum triglyceride level was

<table>
<thead>
<tr>
<th>Table 1 Baseline characteristics (including lipids) for the two subgroups of interest (patients &gt;75 years old and patients &lt;75 years old)</th>
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<tr>
<td><strong>Probuloc</strong></td>
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CVD: cerebrovascular disease  BMI: body mass index  IHD: ischemic heart disease  IMT: intima-media thickness  HT: hypertension  LDL: LDL-cholesterol  aSBP: systolic blood pressure  dSBP: diastolic blood pressure

The baseline characteristics of the subjects have been summarized elsewhere. Briefly, the mean age of the patients was 66.1 years and 31.3% were men. The average systolic blood pressure and diastolic blood pressure were 130.8 and 77.1 mm Hg, respectively. Of the 246 patients, 59.3% were recent or former smokers, 42.5% had a history of hypertension, and 22.9% had diabetes mellitus. Baseline serum total cholesterol and LDL-cholesterol levels were 253.0 mg/dL and 166.1 mg/dL, respectively, while the HDL-cholesterol level was 57.0 mg/dL and the serum triglyceride level was
149.2 mg/dL. The mean IMT was 1.308 mm. There were no statistically significant differences in any of these baseline characteristics among the three treatment groups (probucol, pravastatin, and diet alone).

Baseline characteristics (including lipids) for the two subgroups of interest (patients ≥75 years old and patients <75 years old) are shown in the Table 1. In general, the three treatment groups were well matched for age and sex at baseline. The elderly subgroup (≥75 years old) included a higher proportion of women, and more patients had cerebrovascular disease compared with the younger subgroup (<75 years old) (p<0.01 for probucol, p<0.01 for pravastatin, and p<0.01 for diet alone; chi-square test). The potential importance of chance differences in baseline characteristics between any of the four subpopulations receiving either of the two active treatments was evaluated by assessing the relationship of all listed baseline variables to total mortality or major coronary events.

Drug Treatment and Serum Lipids
The percent changes of serum lipids after 2 years of treatment are displayed in Fig. 1. Mean between-group differences (intention-

Fig. 1 Percent changes of serum lipids after 2 years. Among patients ≥75 years old, there was a significant decrease of serum total cholesterol in each of the three subgroups (by 25.0%, 26.6%, and 13.2% compared with baseline, respectively). There was also a significant decrease of serum LDL-cholesterol by 29.2%, 31.3%, and 9.8%, respectively, while the HDL-cholesterol levels of the probucol and control groups were significantly lower after 2 years. Patients <75 years old from the probucol and pravastatin groups showed a significant decrease of serum total and LDL-cholesterol levels (by 23.6% and 21.0% or 23.3% and 25.5% compared with baseline, respectively). In the probucol group, HDL-cholesterol was significantly reduced after 2 years (21.9%, p<0.01).
to-treat) of the percent change from baseline over the full duration of the trial are shown for total cholesterol, LDL cholesterol, and HDL cholesterol.

**Patients ≥ 75 Years Old**

After 2 years of treatment, there was a decrease of serum total cholesterol in each of the three groups, which showed a significant reduction of 25.0%, 26.6%, and 13.2% compared with baseline, respectively. After 2 years, there was also a significant decrease of serum LDL-cholesterol in the three groups, with the reduction being 29.2%, 31.3%, 9.8%, respectively. The serum HDL-cholesterol level of the pravastatin group was increased by 1.0% after 2 years, but this change was not significant. On the other hand, the HDL-cholesterol level showed a significant decrease in the probucol and control groups by 21.9% and 9.6%, respectively (Mann-Whitney U test). Triglyceride levels showed no significant changes throughout the study.

**Patients < 75 Years Old**

After 2 years of treatment, there was a significant decrease of serum total cholesterol and LDL-cholesterol levels in the probucol and pravastatin groups, with a reduction of 23.6% and 21.0% versus 23.3% and 25.5% compared with baseline, respectively. In the control group, total cholesterol and LDL-cholesterol levels were also lower at the end of the study, but the changes were not significant. The HDL-cholesterol level of the probucol group was significantly reduced after 2 years (21.9%, p<0.01). In the pravastatin group and the control group, however, HDL-cholesterol showed no significant changes throughout the study. Triglyceride levels also showed no significant changes throughout the study in any of the groups.

**Intima-Media Thickness**

The percent change of carotid IMT after 2 years is shown in Fig. 2. The decrease of IMT in patients ≥75 years old from the
probucol and pravastatin groups was significant compared with that in patients <75 years old (both p<0.01; Mann-Whitney U test). In the control group, however, IMT showed a significant increase of 19.9% after 2 years (p<0.05; Mann-Whitney U test). The changes of IMT in the probucol and pravastatin groups were significantly different compared with that in the control group (both p<0.001; Mann-Whitney U test), while there was no significant difference in the change of IMT between the probucol and pravastatin groups at 24 weeks after the completion of treatment. There was no significant increase of IMT in the probucol group after 2 years of treatment.

**Total and CHD Mortality**

Among the 82 patients in the probucol group, two suffered a major cardiovascular event (2 deaths from coronary heart disease). Major events occurred in 4 of the 83 patients from the pravastatin group (3 deaths from coronary heart disease and 1 nonfatal myocardial infarction) and 11 of the 81 patients from the control group (8 deaths from coronary heart disease and 3 nonfatal myocardial infarctions). Of the 16 deaths that occurred during this study, two were in the probucol group, 5 were in the pravastatin group, and 9 were in the control group. Among these 16 patients, 13 deaths were from cardiovascular causes, while the others were due to gastrointestinal bleeding and infection. Total mortality and CHD mortality in the patients ≥75 years old are shown in Table 2.

Total cardiovascular events were significantly reduced in patients ≥75 years old from the probucol group compared with the control group (relative risk: 0.12; p<0.05). The reduction of relative risk was slightly greater than that observed for patients <75 years old (relative risk: 0.20; p=N.S.), but there were overlapping 95% confidence intervals. The relative risk of total death was similarly reduced by probucol in both age groups (86% reduction for patients ≥75 years old), and this decrease was statistically significant. Although the relative risk of total death was also reduced by pravastatin in both age groups (43% reduction for patients ≥75 years old), the change was not significant. The total cardiovascular event rate and total death rate over the duration of the study were more than three times higher in control group patients ≥75 years old (27.3% and 22.7%, respectively) compared with patients <75 years old (8.5% and 6.8%, respectively). Conse-

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<th>Table 2: Effect of probucol and pravastatin on clinical events in hypercholesterolemic patients</th>
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<td><strong>Patients, n (%)</strong></td>
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<td><strong>Probucol</strong></td>
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<tr>
<td><strong>Age≥75</strong></td>
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<td>All cardiovascular events</td>
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<td>Fatal MI</td>
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<td>All cerebrovascular events</td>
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quently, the absolute risk reduction for patients ≥75 years old was more than three times that for patients <75 years old in the case of both total cardiovascular events and total deaths.

DISCUSSION

FAST was the first clinical trial to clearly demonstrate the benefit of probucol for elderly hypercholesterolemic patients and to also demonstrate an effect of probucol on the incidence of cardiovascular events. FAST showed that probucol therapy could achieve a significant reduction in the risk of major coronary events in patients ≥75 or < 75 years old, as well as significant improvement of all the tertiary CHD and atherosclerosis-related study end-points that were positive in the entire FAST cohort. The magnitude of the observed risk reduction in these subgroups was very similar to that reported for the entire study cohort and for other clinically relevant subgroups that have been analyzed. Although FAST was not specifically designed to assess changes of mortality in elderly subjects, high event rates combined with the substantial percentage of patients in this subgroup allowed us to detect a significant reduction of both all-cause mortality and CHD mortality. Safety and tolerability showed no important differences between the two age groups and were largely consistent with the findings for the entire study cohort.

In the subjects ≥75 versus <75 years old, LDL cholesterol showed similar changes (26% vs. 22%). This finding is consistent with other data suggesting that the cholesterol-lowering effect of 3-hydroxy-3-methylglutaryl coenzyme A (HMG CoA) reductase inhibitors is enhanced as patients become older. Baseline total cholesterol, LDL-cholesterol, and HDL-cholesterol levels showed no significant relationship with the response to treatment (reduction in relative risk) in any of the subpopulations examined (data not shown), as was also the case for the entire study cohort. The reduction of LDL cholesterol was more significant in the pravastatin group than in the probucol or control groups. Although the control group showed a significant reduction of LDL cholesterol with diet alone, an increase of carotid IMT still occurred, unlike the outcome in the active treatment groups. After 2 years of therapy, there was a significant decrease of serum LDL-cholesterol in all three groups compared with baseline. It was interesting that probucol had an antiatherogenic effect and caused a reduction of CHD events in patients ≥75 years old.

Lipid peroxidation of LDL has been demonstrated to be an important risk factor for the development of atherosclerosis. There are several possible reasons, including the increased susceptibility of LDL to oxidation with aging, which can be partly explained by modification of its fatty acid composition and a decrease of the antioxidant (vitamin E) content. Recently, Napoli et al. reported that resistance of LDL to peroxidative modification was lower in elderly men than in young men. Furthermore, age was correlated with the extent of lipid peroxidation, supporting the hypothesis that LDL contributes to the increment of plasma lipid peroxides with aging. Since oxidation of LDL is considered to be a key event in atherogenesis, it could be an additional reason why atherosclerosis is related to aging.

FAST showed that probucol therapy could delay the increase of IMT independently of its LDL or HDL cholesterol-lowering effect, and a reduction of IMT occurred
earlier with probucol than with pravastatin. In the present study, patients ≥75 years old showed a significantly smaller change of IMT after probucol therapy compared with patients <75 years old irrespective of the cholesterol-lowering effect. However, it was clearly demonstrated that probucol could reduce the risk of all-cause mortality and major coronary events in CHD patients ≥75 years old. The above findings suggest that there may be another mechanism involved in the effect of probucol. Other investigators have shown that suppression of atherogenesis by probucol is independent of its cholesterol-lowering action and is presumably due to an antioxidant effect on lipids. Because mortality and CHD events increase with age, the absolute reduction of the death rate and event rate was substantially greater for patients ≥75 years old compared with those <75 years old. The relationship between serum cholesterol and the development of CHD has been observed in various epidemiological studies, but is reported to be weaker in elderly persons compared with middle-aged subjects, so the above findings may be unexpected. However, limited data are available about the predictive value of cholesterol in elderly patients with established CHD. Taken together with the results of the present study, the above findings may indicate the importance of ancillary effects of probucol other than cholesterol lowering for reducing the incidence of cardiovascular events. In fact, our data suggest that probucol may have multiple actions, but further studies are needed to investigate the relative contribution of each effect of this drug.

A difference between the effect of probucol and pravastatin on the IMT was not demonstrated by the present study, perhaps because the sample size was small. A large-scale investigation would be necessary to determine whether probucol and pravastatin therapy have a different influence on the IMT. Lack of a placebo control group was another limitation of our study. However, the use of quantitative B-mode ultrasound allowed us to obtain unbiased data. Although FAST was not specifically designed to assess the influence of lipid-lowering therapy on mortality in the elderly, high event rates combined with the substantial percentage of elderly patients in the study population provided the power to demonstrate a significant reduction of both all-cause mortality and CHD mortality among elderly patients receiving probucol. Safety and tolerability showed no important differences related to age or sex, and were generally consistent with the results for the entire study cohort.

In conclusion, the present findings suggest that hypercholesterolemia in the elderly is a morbid state requiring treatment and that probucol is a useful drug for reducing the incidence of cardiovascular disease in hypercholesterolemic elderly persons.

ACKNOWLEDGEMENTS

We thank Naoko Kinukawa, MS, for providing advice about the statistical analysis.

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(Received for publication December 27, 2005)

This study was supported by a grant from the Japanese Ministry of Education, Science, and Culture (Tokyo, Japan).
(和文抄録)

高齢者の高コレステロール血症に対する Probucol の効果

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【目的】高齢者 (75 歳以上) の高コレステロール血症患者に対して、積極的な脂質低下療法が頸動脈硬化の進展抑制および主要冠動脈イベントリスク低下が認められるか否かについて検討した。

【方法】FAST の対象患者 (246 例) のうち、75 歳以上 (76 例) と 75 歳未満 (168 例) について、脂質低下療法（Probucol Pravastain）および食事療法により、その有効性について頸動脈エコーを用いて評価した。頸動脈の内膜中膜複合体厚 (IMT) を測定し、左右 6 点の IMT の平均値を IMT 値とした。1 次エンドポイントは 2 年間の IMT 値の変化率とし、2 次エンドポイントは主要冠動脈イベントとした。

【結果】Probucol 群及び Pravastain 群では、年齢に関係なく、高齢者においても動脈硬化の進展抑制を認め、Probucol 群における高齢者の Control 群に対する各臨床イベントの相対リスク（95%信頼期間）は総死亡が 0.15 (0.02-1.28)，総冠動脈イベント 0.12 (0.02-1.04) 有意な進展を認めめた。一方、Pravastain 群との間では、各臨床イベントの相対リスクに有意差は認められなかった。Probucol 群と Pravastain 群との間では、各臨床イベントの相対リスクに有意差は認められなかった。

【結論】75 歳以上の高齢者に対しても Probucol は、頸動脈硬化の進展抑制効果が認められ、さらに主要冠動脈イベントの相対リスクの低下作用を認められる可能性が示唆された。