Cost-Effectiveness of Statin Plus Eicosapentaenoic Acid Combination Therapy for Cardiovascular Disease Prevention in Japanese Patients With Hypercholesterolemia
— An Analysis Based on the Japan Eicosapentaenoic Acid Lipid Intervention Study (JELIS) —

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Background: The addition of eicosapentaenoic acid (EPA) to statin therapy has been shown to reduce cardiovascular events. This study examined the cost-effectiveness of EPA plus statin (EPA+statin) combination therapy compared with statin monotherapy for primary and secondary prevention of cardiovascular disease (CVD) in Japan.

Methods and Results: A Markov model was applied to assess the costs and benefits associated with EPA+statin combination therapy over a projected 30-year period from the perspective of a public healthcare funder in Japan. The incremental cost-effectiveness ratio (ICER), expressed as quality-adjusted life-years (QALY), was estimated for primary prevention and secondary prevention of CVD in patients with hypercholesterolemia. Impact on survival and number of events were based on the Japan EPA Lipid Intervention Study. Sensitivity analyses examined the influence of various input parameters on costs and outcomes of treatment. ICER was ¥29.6 million per QALY gained in primary prevention and ¥5.5 million per QALY gained in secondary prevention. The probabilities that EPA+statin combination therapy would be cost-effective compared with statin monotherapy were 39% in primary prevention and 49% in secondary prevention at a cost-effectiveness threshold of ¥5 million per QALY gained. Sensitivity analyses showed that EPA was cost-effective in secondary prevention.

Conclusions: EPA+statin combination therapy showed acceptable cost-effectiveness for secondary prevention, but not primary prevention, of CVD in patients with hypercholesterolemia in Japan.

Key Words: Cardiovascular disease; Coronary artery disease; Eicosapentaenoic acid; Hypercholesterolemia; Incremental cost-effectiveness ratio

Cardiovascular disease (CVD) is a major cause of death in Japan, with 196,113 cardiac deaths and 111,973 cerebrovascular deaths in 2015.1 The cost associated with CVD in Japan was ¥5,889 billion in 2013.2 Although statin therapy has been shown to reduce CVD risk,3 a residual risk for CVD remains. Eicosapentaenoic acid (EPA), an omega-3 fatty acid, is a useful treatment option to reduce the residual risk for CVD. Epadel (ethyl eicosapentate; Mochida Pharmaceutical, Tokyo, Japan) contains isolated and purified EPA. Compared with other omega-3 fatty acid drugs, Epadel has a higher concentration of EPA without docosahexaenoic acid.4 The manufacturing process for Epadel is of a high standard and does not result in the oxidation of EPA. The Japan Eicosapentaenoic Acid Lipid Intervention Study (JELIS), a prospective randomized study, reported a 19% reduction in cardiovascular events associated with EPA (Epadel) treatment in patients with hypercholesterolemia.5 However, the cost-effectiveness of EPA has not been determined. Health economics are important in Japan because of the low rate of economic growth and an increasing elderly population. Here, we report a cost-effectiveness analysis comparing the costs and benefits of EPA plus statin (EPA+statin) combination therapy vs. statin monotherapy for patients in Japan with hypercholesterolemia as primary and secondary prevention of CVD.

Methods
An economic model was developed to evaluate the costs
and effectiveness of EPA in patients with hypercholesterolemia in Japan. The model evaluated quality-adjusted life-years (QALY) and cost of EPA (Epadel: 1,800 mg/day) plus statin combination therapy and statin monotherapy (conventional therapy) over a 30-year time horizon. We constructed 2 models to compare the efficacy of EPA+statin combination therapy and statin monotherapy in primary and secondary prevention of CVD in patients with hypercholesterolemia. Various parameters were derived from the JELIS. The outcomes were calculated as the incremental cost-effectiveness ratio (ICER) per QALY gained and per life-year gained. The analysis was performed according to the Consolidated Health Economic Evaluation Reporting Standards statement and Japanese guidelines.

Model

A Markov model with Monte Carlo simulations was developed to evaluate the efficiency of EPA+statin combination therapy (Figure 1). The model had a yearly cycle, and in every cycle the patient could die, suffer from coronary artery disease (CAD), suffer from stroke, or be stable. We defined 6 conditions (Baseline, New CAD, Post-CAD, Death, New stroke, Post-stroke). All patients in primary and secondary prevention models started in the Baseline condition, and were then transferred to each condition annually according to each event. If a Baseline patient in the primary or secondary prevention models was stable, the patient’s condition remained as Baseline. If a Baseline patient experienced CAD, the patient was transferred to the New CAD condition. If a New CAD patient was stable, the patient was transferred to the Post-CAD condition. We distinguished the primary prevention model and the secondary prevention model with changing event rates, costs, and quality of life (QOL).

Population

The study population reflected that of the JELIS with an average age of 61 years, 31% male patients, and rates of diabetes mellitus and hypertension of 16% and 35%, respectively. The average levels of low-density lipoprotein-cholesterol (LDL-C), high-density lipoprotein-cholesterol (HDL-C) and triglycerides (TG) were 181 mg/dL, 58.4 mg/dL and 153 mg/dL, respectively. We compared EPA+statin combination therapy and statin monotherapy for primary and secondary prevention of CVD in patients with hypercholesterolemia. EPA+statin combination therapy comprised 1,800 mg EPA plus 10 mg pravastatin or 5 mg simvastatin daily, while statin monotherapy comprised 10 mg pravastatin or 5 mg simvastatin daily.

Time Horizon

The time horizon was restricted to 30 years in our models. The study population had an average age of 61 years. A 30-year estimate was thought to be sufficient to evaluate the cost-effectiveness of the treatments. However, we changed the time horizon to 5, 10, 20, and 40 years in the sensitivity analysis.

Mortality and Hospitalization

Table 1 shows the annual rates of mortality and morbidity with each treatment, estimated from the JELIS and other studies. EPA+statin combination therapy was 19% superior to statin monotherapy in CAD prevention for both primary and secondary prevention, but did not improve the mortality rate. Among patients receiving EPA in the JELIS, the mortality rate was approximately 0.6% annually. The annual CAD rates with statin monotherapy for primary prevention and secondary prevention were 0.4% and 2.5%, respectively. Both the EPA+statin combination therapy and statin monotherapy group had an annual stroke rate of 0.4%.

Utility

Table 1 presents the utility value in each situation. Data from various previous trials were used to define QOL. In New CAD patients, QOL was 0.80, and we assumed that the QOL of New stroke patients was 0.52. Following the Japanese guidelines, the utility values were decreased by 2% annually.

Costs

We performed an economic evaluation from the perspective of a public healthcare funder in Japan. The costs included those associated with procedures, hospitalization, and drugs. A dose of 1,800 mg Epadel costs ¥210.8 in Japan. The cost data and their sources are listed in Table 1. We derived the follow-up and complication costs from previous studies, and the costs were decreased by 2% annually.

Scenario Analysis

We performed 3 scenario analyses. The 1st scenario involved baseline usage of a strong statin (pravastatin 20 mg, simvastatin 10 mg, etc.) instead of a standard statin (pravastatin 10 mg, simvastatin 5 mg, etc.). We hypothesized that the CAD event rate would be lower with strong statin use compared with the standard statin for both EPA+statin combination therapy and statin monotherapy. We hypothesized that the event reduction effect of EPA would be the same regardless of statin type. We estimated the ICER of EPA using a strong statin. In the 2nd scenario analysis, we evaluated hypercholesterolemic patients with low HDL-C and high TG in primary prevention. Subgroup analysis in the JELIS suggested that people with low HDL-C and high TG (HDL-C <40 mg/dL; TG >150 mg/dL) were at the
effects of uncertainty in the parameters on the results. We calculated the degree of uncertainty for all input parameters probabilistically. The distribution of the parameters was determined according to the type of parameter (β or γ distribution). We performed 100,000 simulations, and the outcomes are shown as the ICER per QALY gained and per life-year gained. One-way deterministic sensitivity analyses were performed to assess the effects of several parameters, and the results of one-way sensitivity analyses are shown as tornado plots. Threshold analyses were performed to evaluate the limits of each parameter, and we used a

Table 1. Key Parameters Used in the Model

<table>
<thead>
<tr>
<th></th>
<th>Primary prevention</th>
<th>Secondary prevention</th>
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</thead>
<tbody>
<tr>
<td>Prob CAD (annual)</td>
<td>0.32% [5]</td>
<td>0.4% [5]</td>
</tr>
<tr>
<td>Prob stroke (annual)</td>
<td>0.4% [5, 10]</td>
<td>0.4% [5, 10]</td>
</tr>
<tr>
<td>Prob death (annual)</td>
<td>0.6% [5]</td>
<td>0.6% [5]</td>
</tr>
<tr>
<td>New stroke cost</td>
<td>¥1,177,000 [20]</td>
<td>¥1,105,000 [20]</td>
</tr>
<tr>
<td>Death cost</td>
<td>¥2,784,000 [19]</td>
<td>¥2,784,000 [19]</td>
</tr>
<tr>
<td>Base line utility</td>
<td>0.90 [17]</td>
<td>0.90 [17]</td>
</tr>
<tr>
<td>New CAD utility</td>
<td>0.8 [16]</td>
<td>0.8 [16]</td>
</tr>
<tr>
<td>Post-CAD utility</td>
<td>0.89 [16]</td>
<td>0.89 [16]</td>
</tr>
<tr>
<td>New stroke utility</td>
<td>0.52 [14]</td>
<td>0.52 [14]</td>
</tr>
<tr>
<td>Post-stroke utility</td>
<td>0.65 [14]</td>
<td>0.65 [14]</td>
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Table 2. (A) Cost-Effectiveness of EPA, (B) Scenario Analysis

<table>
<thead>
<tr>
<th>Arm</th>
<th>Cost</th>
<th>QALY</th>
<th>LY</th>
<th>ICER/QALY</th>
<th>ICER/LY</th>
</tr>
</thead>
<tbody>
<tr>
<td>EPA+statin vs. statin monotherapy (primary prevention)</td>
<td>EPA+statin (3,987,474 (1,579,711–7,865,812)</td>
<td>18.8 (13.6–21.6)</td>
<td>21.2 (19.6–22.3)</td>
<td>¥29,567,364</td>
<td>¥32,198,787</td>
</tr>
<tr>
<td>Statin monotherapy</td>
<td>¥2,517,209 (1,141,740–4,691,786)</td>
<td>18.7 (13.6–21.6)</td>
<td>21.1 (19.5–22.2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>EPA+statin vs. statin monotherapy (secondary prevention)</td>
<td>EPA+statin (6,551,407 (3,130,399–11,574,214)</td>
<td>18.1 (13.9–20.6)</td>
<td>20.8 (19.3–22.0)</td>
<td>¥5,450,831</td>
<td>¥5,410,598</td>
</tr>
<tr>
<td>Statin monotherapy</td>
<td>¥5,281,864 (2,670,345–8,991,695)</td>
<td>17.9 (13.8–20.4)</td>
<td>20.6 (19.0–21.8)</td>
<td></td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Arm</th>
<th>Cost</th>
<th>QALY</th>
<th>LY</th>
<th>ICER/QALY</th>
<th>ICER/LY</th>
</tr>
</thead>
<tbody>
<tr>
<td>Strong statin use</td>
<td>¥46,123,485</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low HDL-C, high TG population</td>
<td>¥35,165,604</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Life table estimate</td>
<td>¥18,778,012</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EPA+statin vs. statin monotherapy (secondary prevention)</td>
<td>Strong statin use (6,682,070)</td>
<td>17.9 (13.8–20.4)</td>
<td>20.6 (19.0–21.8)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Life table estimation</td>
<td>¥7,406,153</td>
<td></td>
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EPA, eicosapentaenoic acid; HDL-C, high-density lipoprotein-cholesterol; ICER, incremental cost-effectiveness ratio; LY, life-year; QALY, quality-adjusted life-year; TG, triglycerides.

**Sensitivity Analysis**

We performed a broad sensitivity analysis to evaluate the effects of uncertainty in the parameters on the results. We calculated the degree of uncertainty for all input parameters probabilistically. The distribution of the parameters was determined according to the type of parameter (β or γ distribution). We performed 100,000 simulations, and the outcomes are shown as the ICER per QALY gained and per life-year gained. One-way deterministic sensitivity analyses were performed to assess the effects of several parameters, and the results of one-way sensitivity analyses are shown as tornado plots. Threshold analyses were performed to evaluate the limits of each parameter, and we used a

The highest risk in primary prevention. We estimated the ICER of EPA in low HDL-C and high TG patients in primary prevention. In the 3rd scenario analysis, we used a life table to calculate mortality and event rates. The estimated mortality rate, CAD event rate, and stroke rate increased with age. EPA reduced CAD by 19% and stroke by 10% according to the JELIS. We estimated the ICER of EPA using the life table event rate.

EPA, eicosapentaenoic acid; HDL-C, high-density lipoprotein-cholesterol; ICER, incremental cost-effectiveness ratio; LY, life-year; QALY, quality-adjusted life-year; TG, triglycerides.
Cost-Effectiveness Analysis of EPA in Japan

Circulation Journal Vol.82, April 2018

Cost-effectiveness analysis of EPA in Japan

Table 2A presents the main results. Over the 30-year time horizon, the expected costs of EPA+statin combination therapy and statin monotherapy were ¥4.0 million and ¥2.5 million, respectively. The expected QALY of EPA+statin combination therapy and statin monotherapy were 18.8 QALY and 18.7 QALY, respectively. The ICER of EPA+statin combination therapy compared with statin monotherapy was ¥29.6 million per QALY gained.

Secondary Prevention
Over the 30-year time horizon, the expected costs of EPA+statin combination therapy and statin monotherapy were ¥6.6 million and ¥5.3 million, respectively. The expected QALY of EPA+statin combination therapy and statin monotherapy were 18.1 QALY and 17.9 QALY, respectively. The ICER of EPA+statin combination therapy compared with statin monotherapy was ¥5.5 million per QALY gained (Table 2A).

Scenario Analysis
Table 2B shows the results of the scenario analyses. With the use of a strong statin in primary prevention and secondary prevention patients, the ICER for EPA+statin combination therapy over statin monotherapy was ¥46.1 million and ¥6.7 million per QALY gained, respectively. For patients with low HDL-C and high TG in primary prevention, the ICER for EPA+statin combination therapy over statin monotherapy was ¥35.2 million. Using life table event rate estimation among primary prevention and secondary prevention patients, the ICER for EPA+statin combination therapy over statin monotherapy was ¥18.8 million and ¥7.4 million per QALY gained, respectively.

Deterministic Sensitivity Analysis
Figure 2 presents the differences in cost-effectiveness ratios based on various one-way sensitivity analyses. The primary prevention model (Figure 2A) and secondary prevention

Figure 2. Tornado plots showing results of deterministic one-way analysis. EPA plus statin combination vs. statin monotherapy for primary prevention (A) and secondary prevention (B) of CVD. QOL, quality of life. Other abbreviations as in Figure 1.

Table 3. (A) Threshold Analysis, (B) Time Horizon (ICER/QALY)

<table>
<thead>
<tr>
<th></th>
<th>Primary prevention</th>
<th>Secondary prevention</th>
</tr>
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<tbody>
<tr>
<td><strong>A</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EPA 1,800 mg cost</td>
<td>¥24</td>
<td>¥201</td>
</tr>
<tr>
<td>EPA effect (mortality reduction)</td>
<td>11%</td>
<td>1.6%</td>
</tr>
<tr>
<td>EPA effect (CAD reduction)</td>
<td>Cannot estimate</td>
<td>22%</td>
</tr>
<tr>
<td><strong>B</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5 years</td>
<td>¥207,052,433</td>
<td>¥30,871,274</td>
</tr>
<tr>
<td>10 years</td>
<td>¥97,683,594</td>
<td>¥14,426,734</td>
</tr>
<tr>
<td>20 years</td>
<td>¥49,165,699</td>
<td>¥7,519,117</td>
</tr>
<tr>
<td>40 years</td>
<td>¥27,085,782</td>
<td>¥4,440,711</td>
</tr>
</tbody>
</table>

Abbreviations as in Tables 1,2.
5-year estimations were higher than the 30-year estimations. The ICER for EPA+statin combination therapy over statin monotherapy among primary prevention and secondary prevention patients with 40-year estimations were lower than the 30-year estimations. The ICER for EPA+statin combination therapy over statin monotherapy among primary prevention and secondary prevention with 40-year estimations were lower than the 30-year estimations.

**Probabilistic Sensitivity Analysis**

Figure 3 shows the distribution of simulated cost-effectiveness of EPA. Among primary prevention patients, the QALY were almost the same for EPA+statin combination therapy and statin monotherapy, and the cost of EPA+statin combination therapy was incrementally cost-effective relative to statin monotherapy in 39% of simulations. In secondary prevention, EPA+statin combination therapy was incrementally cost-effective relative to statin monotherapy in 49% of simulations. Abbreviations as in Figure 1.

![Figure 3](image)

**Figure 3.** Cost-effectiveness plots for EPA in (A) primary prevention and (B) secondary prevention of CVD from 100,000 simulations with a decision-analytic model. Ellipses show 95% confidence intervals. Solid lines show the willingness to pay with a slope of ¥5 million per quality-adjusted life-year (QALY) gain. (A) Similar QALY for EPA+statin combination therapy and statin monotherapy, and the cost of the EPA+statin combination is higher than that of statin monotherapy in primary prevention. EPA+statin combination therapy was incrementally cost-effective relative to statin monotherapy in 39% of simulations. (B) Cost of EPA+statin combination therapy is higher than that of statin monotherapy, and EPA+statin achieved more QALY than statin monotherapy in secondary prevention. EPA+statin combination therapy was incrementally cost-effective relative to statin monotherapy in 49% of simulations. Abbreviations as in Figure 1.

![Figure 4](image)

**Figure 4.** Cost-effective acceptability curves of EPA. (A) Primary prevention and (B) secondary prevention of CVD in patients with hypercholesterolemia in Japan. Abbreviations as in Figure 1.
therapy achieved more QALY than statin monotherapy (Figure 3B). The cost-effectiveness acceptability curves for EPA+statin combination therapy are presented in Figure 4. With a cost-effectiveness threshold of ¥5 million per QALY gained, the cost-effectiveness probability of EPA+statin combination therapy was 39% in primary prevention patients (Figure 4A) and 49% in secondary prevention patients (Figure 4B).

Discussion

The results of this study indicated that EPA+statin combination therapy has acceptable cost-effectiveness for secondary prevention of CVD in patients with hypercholesterolemia, with an ICER of approximately ¥5 million per QALY. The CVD reduction effect of EPA showed an acceptable cost performance for secondary prevention. For primary prevention of CVD, EPA did not show good cost-effectiveness in patients with hypercholesterolemia. The CVD event rate was too low in primary prevention to achieve an acceptable cost-effectiveness. Threshold analysis showed that the cost-effectiveness of EPA for primary prevention would be acceptable in Japan for an EPA 1,800mg cost <¥24. Thus, EPA would need to become much cheaper to be cost-effective for primary prevention in Japan.

The cost-effectiveness of EPA might be better in Western countries than in Japan, because the Japanese population typically eats more fish than Western populations and the Japanese ratio of EPA to arachidonic acid (AA) (EPA/AA) is higher than that in Western countries. A low EPA/AA ratio is reported to be associated with an increased risk for CVD. The JELIS reported that Epadel reduced cardiovascular events in the Japanese cohort. It is possible that EPA could be more effective in Western populations with a low EPA/AA ratio, compared with Japanese populations with a high EPA/AA ratio. The cost-effectiveness of a drug depends on the basal risk profiles of the target population.

In the current situation, the higher the event rate, the better the cost-effectiveness of EPA would have been. A cost-effectiveness analysis performed in the USA using data from the JELIS reported that EPA had excellent cost-effectiveness in secondary prevention of CVD. Although the degree of cost-effectiveness of EPA in secondary prevention was different between Japan and the USA, our data from the JELIS reported that EPA showed acceptable cost-effectiveness for secondary prevention. Although a study performed in the USA provided some data regarding the cost-effectiveness of EPA for primary prevention, the data were from subanalyses. We reported the cost-effectiveness for EPA for primary prevention as the results of the main analysis as well as from sensitivity analysis. EPA is used not only for secondary prevention but also for primary prevention in daily practice, and analysis of the cost-effectiveness of EPA for primary prevention has practical importance. Third, this study was based on the JELIS, a large Japanese clinical trial, so the patient population, event rate, and mortality rate were consistent with those in Japanese patients with hypercholesterolemia, and our data should be applicable to clinical practice in Japan.

Study Limitations

The first is related to the various assumptions made in the study design. We developed our models under certain assumptions, including complication rate, follow-up cost, and QOL. To overcome this limitation, we took these differences into account using scenario and sensitivity analyses. Our sensitivity analysis indicated that our results would be robust despite the assumptions. The second limitation is in regard to hypercholesterolemia severity and its treatment. In the present study, hypercholesterolemia severity and its treatment were based on the JELIS, in which the average LDL-C level was 181mg/dL and standard statins were used for treatment. Therefore, we conducted scenario analyses of patients with hypercholesterolemia and those on a strong statin. EPA addition appeared to be less cost-effective in the current era of strong statin use.

Conclusions

EPA showed acceptable cost-effectiveness for secondary prevention but not primary prevention of CVD in patients with hypercholesterolemia in Japan.

Acknowledgments

We thank Mr. Alexander Pshieff, LLB, BBmedSc, from Edanz Group (www.edanzediting.com/ac) for editing a draft of this manuscript.

Disclosures

The authors declare that they have no conflicts of interest.
Funding
This study received no grants from any funding agency in the public, commercial, or not-for-profit sectors.

References