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) —

Satoshi Kodera, MD; Hiroyuki Morita, MD, PhD; Arihiro Kiyosue, MD, PhD;
Jiro Ando, MD; Issei Komuro, MD, PhD

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 icosapentate; 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

Editorial p 954

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

Received September 21, 2017; revised manuscript received December 11, 2017; accepted December 12, 2017; released online January 23, 2018 Time for primary review: 19 days

Department of Cardiovascular Medicine, Graduate School of Medicine, The University of Tokyo, Tokyo, Japan

Mailing address: Satoshi Kodera, MD, Department of Cardiovascular Medicine, Graduate School of Medicine, The University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113-8655, Japan. E-mail: kodera@tke.att.ne.jp

ISSN-1346-9843 All rights are reserved to the Japanese Circulation Society. For permissions, please e-mail: cj@j-circ.or.jp

and effectiveness of EPA in patients with hypercholesterolemia in Japan. The model evaluated quality-adjusted life-years (QALY) and cost of EPA (Epadel: 1,800mg/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.⁵ 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.^{6,7}

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,⁵ 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, 58.4mg/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 1,800mg EPA plus 10mg pravastatin or 5mg simvastatin daily, while statin monotherapy comprised 10mg pravastatin or 5mg 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.^{5,8-13} 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.⁵ Among patients receiving EPA in the JELIS,

Figure 1. Markov model of the effects of eicosapentaenoic acid (EPA) on cardiovascular disease (CVD) in patients with hypercholesterolemia. Patients are allocated to 1 of 6 health conditions (Baseline, New CAD, Post-CAD, New stroke, Post-stroke, Death) per cycle. Patients can move in the direction of any arrow. The model applies to each yearly cycle. CAD, coronary artery disease.

the mortality rate was approximately 0.6% annually.⁵ The annual CAD rates with statin monotherapy for primary prevention and secondary prevention were 0.4% and 2.5%, respectively.⁵ Both the EPA+statin combination therapy and statin monotherapy group had an annual stroke rate of 0.4%.¹⁰

Utility

Table 1 presents the utility value in each situation. Data from various previous trials were used to define QOL.¹⁴⁻¹⁸ In New CAD patients, QOL was 0.80,¹⁶ and we assumed that the QOL of New stroke patients was 0.52.¹⁴ Following the Japanese guidelines, the utility values were decreased by 2% annually.⁷

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 1,800mg 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,^{19,20} and the costs were decreased by 2% annually.⁷

Scenario Analysis

We performed 3 scenario analyses. The 1st scenario involved baseline usage of a strong statin (pravastatin 20mg, simvastatin 10mg, etc.) instead of a standard statin (pravastatin 10mg, simvastatin 5mg, 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.⁵ 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 <40mg/dL; TG >150mg/dL) were at the

Table 1. Key Parameters Used in the Model

	Primary prevention				Secondary prevention			
	EPA+statin	Ref.	Statin monotherapy	Ref.	EPA+statin	Ref.	Statin monotherapy	Ref.
Prob CAD (annual)	0.32%	[5]	0.4%	[5]	2.0%	[5]	2.5%	[5]
Prob stroke (annual)	0.4%	[5, 10]	0.4%	[5, 10]	0.4%	[5, 10]	0.4%	[5, 10]
Prob death (annual)	0.6%	[5]	0.6%	[5]	0.6%	[5]	0.6%	[5]
Follow-up cost	¥165,640	[19]	¥92,640	[19]	¥252,000	[19]	¥179,000	[19]
New CAD cost	¥2,852,000	[19]	¥2,780,000	[19]	¥2,852,000	[19]	¥2,780,000	[19]
New stroke cost	¥1,177,000	[20]	¥1,105,000	[20]	¥1,177,000	[20]	¥1,105,000	[20]
Stroke follow-up cost	¥331,000	[20]	¥259,000	[20]	¥331,000	[20]	¥259,000	[20]
Death cost	¥2,784,000	[19]	¥2,784,000	[19]	¥2,784,000	[19]	¥2,784,000	[19]
Base line utility	0.90	[17]	0.90	[17]	0.89	[16]	0.89	[16]
New CAD utility	0.8	[16]	0.8	[16]	0.8	[16]	0.8	[16]
Post-CAD utility	0.89	[16]	0.89	[16]	0.85	[16]	0.85	[16]
New stroke utility	0.52	[14]	0.52	[14]	0.52	[14]	0.52	[14]
Post-stroke utility	0.65	[14]	0.65	[14]	0.65	[14]	0.65	[14]

CAD, coronary artery disease; EPA, eicosapentaenoic acid; Prob, probability.

Table 2. (A) Cost-Effectiveness of EPA, (B) Scenario Analysis

A						
Arm	Cost	QALY	LY	ICER/QALY	ICER/LY	
EPA+statin vs. statin monotherapy (primary prevention)						
EPA+statin	¥3,987,474 (1,579,711–7,865,812)	18.8 (13.6–21.6)	21.2 (19.6–22.3)	¥29,567,364	¥32,198,787	
Statin monotherapy	¥2,517,209 (1,141,740–4,691,786)	18.7 (13.6–21.6)	21.1 (19.5–22.2)			
EPA+statin vs. statin monotherapy (secondary prevention)						
EPA+statin	¥6,551,407 (3,130,399–11,574,214)	18.1 (13.9–20.6)	20.8 (19.3–22.0)	¥5,450,831	¥5,410,598	
Statin monotherapy	¥5,281,864 (2,670,345–8,991,695)	17.9 (13.8–20.4)	20.6 (19.0–21.8)			
B						
EPA+statin vs. statin monotherapy (primary prevention)						
Strong statin use				¥46,123,485		
Low HDL-C, high TG population				¥35,165,604		
Life table estimate				¥18,778,012		
EPA+statin vs. statin monotherapy (secondary prevention)						
Strong statin use				¥6,682,070		
Life table estimation				¥7,406,153		

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

highest risk in primary prevention.²¹ 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.⁵ We estimated the ICER of EPA using the life table event rate.

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

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

Abbreviations as in Tables 1,2.

cost-effectiveness cutoff point of ¥5 million per QALY gained, based on a previous report.²² Cost-effectiveness acceptability curves were plotted to evaluate the probability that EPA+statin combination therapy was more cost-effective than statin monotherapy. Our models were developed using commercial software (TreeAge Pro 2016; TreeAge, Williamstown, MA, USA).

Results

Primary Prevention

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 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. 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.

model (Figure 2B) were constructed. Both primary prevention and secondary prevention models were most sensitive to the EPA cost. The mortality rate and QOL of CAD were also important in both models, but the stroke rates and stroke costs were not sensitive to changes in either model. Table 3A shows the results of threshold analyses. The threshold for EPA 1,800mg cost was <¥24 among primary prevention patients, while that among secondary prevention patients was <¥201. The threshold for the effect of EPA on mortality reduction was >11% among primary prevention patients, and among secondary prevention patients it was >1.6%. The results with different time horizons are shown in Table 3B. The ICER for EPA+statin combination therapy over statin monotherapy among primary prevention and secondary prevention patients with

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 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 higher than that of statin monotherapy (Figure 3A). In secondary prevention patients, the cost of EPA+statin combination therapy was higher than that of statin monotherapy, and EPA+statin combination

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.^{23,24} A low EPA/AA ratio is reported to be associated with an increased risk for CVD.²⁵ The JELIS reported that Epanol 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.²⁶ Although the degree of cost-effectiveness of EPA in secondary prevention was different between Japan and the USA, our study is consistent with the results of the US study,²⁶ in that EPA was cost-effective in secondary prevention of CVD. The cost-effectiveness analysis in the US study also included subanalysis of primary prevention of CVD using data from the JELIS, and EPA was found not to be cost-effective, similar to our own analyses. It is suggested that EPA did not show good cost-effectiveness because of the low event rate in primary prevention even in the USA. Our scenario analysis suggested that EPA was not cost-effective in primary prevention even in high-risk populations with low HDL-C and high TG levels. It is difficult to achieve good cost-effectiveness in primary prevention of CVD, and even statins have been reported to be not cost-effective in primary prevention in Japan,²⁷ in which an ICER of ¥76.2 million per QALY for statins over conventional therapy was indicated.

Highly purified EPA (e.g., Epanol) needs to be distinguished from other omega-3 fatty acid drugs.²⁸ Some studies indicated that omega-3 fatty acid was unable to prevent

CVD.^{29–31} After the JELIS, Kromhout et al reported the results of a large prospective randomized trial that indicated no reduction in the rate of major cardiovascular events by low-dose EPA and docosahexaenoic acid.²⁹ The Outcome Reduction with an Initial Glargine Intervention trial showed that daily supplementation with omega-3 fatty acids did not reduce vascular events in patients at high risk for cardiovascular events.³⁰ However, it should be noted that only a high-purity EPA product would reduce cardiovascular events.²⁸ Epanol has shown dramatic event reduction even in patients who started strong statin use after acute coronary syndrome.³²

Study Strengths

First, it was a non-industry-based study. Bell et al reported that cost-effectiveness analysis contains bias and industry-based analyses tend to show good results for certain companies.³³ The degree of bias in this study was low because it was a non-industry-based study. Second, this is the first study to evaluate the cost-effectiveness of EPA in primary 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.²⁶ 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 181 mg/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 Pishief, LLB, BMedSc, 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

- Jinkoudoutai-Chosa (Vital Statistics 2015). <http://www.mhlw.go.jp/toukei/saikin/hw/jinkou/geppo/nengai15/index.html> (accessed May 3, 2017).
- Iryouhinodoukou-Chosa (Survey on the Trend of Medical Care Expenditures). <http://www.mhlw.go.jp/toukei/saikin/hw/k-iryohi/14/dl/kekka.pdf> (in Japanese) (accessed May 3, 2017).
- Chou R, Dana T, Blazina I, Daeges M, Jeanne TL. Statins for prevention of cardiovascular disease in adults: Evidence report and systematic review for the US Preventive Services Task Force. *JAMA* 2016; **316**: 2008–2024.
- Brinton EA, Mason RP. Prescription omega-3 fatty acid products containing highly purified eicosapentaenoic acid (EPA). *Lipids Health Dis* 2017; **16**: 23.
- Yokoyama M, Origasa H, Matsuzaki M, Matsuzawa Y, Saito Y, Ishikawa Y, et al. Effects of eicosapentaenoic acid on major coronary events in hypercholesterolaemic patients (JELIS): A randomised open-label, blinded endpoint analysis. *Lancet* 2007; **369**: 1090–1098.
- Anderson JL, Heidenreich PA, Barnett PG, Creager MA, Fonarow GC, Gibbons RJ, et al. ACC/AHA statement on cost/value methodology in clinical practice guidelines and performance measures: A report of the American College of Cardiology/American Heart Association Task Force on Performance Measures and Task Force on Practice Guidelines. *J Am Coll Cardiol* 2014; **63**: 2304–2322.
- Fukuda T, Shiroyai T, Ikeda S, Igarashi A, Akazawa M, Ishida H, et al. Guideline for economic evaluation of healthcare technologies in Japan. *J Natl Inst Public Health* 2013; **62**: 625–640.
- Yasue H, Ogawa H, Tanaka H, Miyazaki S, Hattori R, Saito M, et al. Effects of aspirin and ticlopidine on cardiovascular events after acute myocardial infarction: Japanese Antiplatelets Myocardial Infarction Study (JAMIS) Investigators. *Am J Cardiol* 1999; **83**: 1308–1313.
- Hata J, Tanizaki Y, Kiyohara Y, Kato I, Kubo M, Tanaka K, et al. Ten year recurrence after first ever stroke in a Japanese community: The Hisayama study. *J Neurol Neurosurg Psychiatry* 2005; **76**: 368–372.
- Tanaka K, Ishikawa Y, Yokoyama M, Origasa H, Matsuzaki M, Saito Y, et al. Reduction in the recurrence of stroke by eicosapentaenoic acid for hypercholesterolemic patients: Subanalysis of the JELIS trial. *Stroke* 2008; **39**: 2052–2058.
- Shiomi H, Nakagawa Y, Morimoto T, Furukawa Y, Nakano A, Shirai S, et al. Association of onset to balloon and door to balloon time with long term clinical outcome in patients with ST elevation acute myocardial infarction having primary percutaneous coronary intervention: Observational study. *BMJ* 2012; **344**: e3257.
- Shigematsu K, Nakano H, Watanabe Y, Sekimoto T, Shimizu K, Nishizawa A, et al. Characteristics, risk factors and mortality of stroke patients in Kyoto, Japan. *BMJ Open* 2013; **3**: e002181.
- Hata J, Nagai A, Hirata M, Kamatani Y, Takamashi A, Yamagata Z, et al. Risk prediction models for mortality in patients with cardiovascular disease: The BioBank Japan project. *J Epidemiol* 2017; **27**: S71–S76.
- Tengs TO, Lin TH. A meta-analysis of quality-of-life estimates for stroke. *Pharmacoeconomics* 2003; **21**: 191–200.
- Hattori N, Hirayama T, Katayama Y. Medical care for chronic-phase stroke in Japan. *Neurol Med Chir (Tokyo)* 2012; **52**: 175–180.
- Magnuson EA, Farkouh ME, Fuster V, Wang K, Vilain K, Li H, et al. Cost-effectiveness of percutaneous coronary intervention with drug eluting stents versus bypass surgery for patients with diabetes mellitus and multivessel coronary artery disease: Results from the FREEDOM trial. *Circulation* 2013; **127**: 820–831.
- Shiroyai T, Fukuda T, Ikeda S, Igarashi A, Noto S, Saito S, et al. Japanese population norms for preference-based measures: EQ-5D-3L, EQ-5D-5L, and SF-6D. *Qual Life Res* 2016; **25**: 707–719.
- Kang K, Gholizadeh L, Inglis SC, Han HR. Correlates of health-related quality of life in patients with myocardial infarction: A literature review. *Int J Nurs Stud* 2017; **73**: 1–16.
- Tsutani K, Igarashi A, Fujikawa K, Evers T, Kubin M, Lamotte M, et al. A health economic evaluation of aspirin in the primary prevention of cardiovascular disease in Japan. *Intern Med* 2007; **46**: 157–162.
- Kimura T, Igarashi A, Ikeda S, Nakajima K, Kashimura S, Kunitomi A, et al. A cost-utility analysis for catheter ablation of atrial fibrillation in combination with warfarin and dabigatran based on the CHADS2 score in Japan. *J Cardiol* 2017; **69**: 89–97.
- Saito Y, Yokoyama M, Origasa H, Matsuzaki M, Matsuzawa Y, Ishikawa Y, et al. Effects of EPA on coronary artery disease in hypercholesterolemic patients with multiple risk factors: Sub-analysis of primary prevention cases from the Japan EPA Lipid Intervention Study (JELIS). *Atherosclerosis* 2008; **200**: 135–140.
- Shiroyai T, Sung YK, Fukuda T, Lang HC, Bae SC, Tsutani K. International survey on willingness-to-pay (WTP) for one additional QALY gained: What is the threshold of cost effectiveness? *Health Econ* 2010; **19**: 422–437.
- Ninomiya T, Nagata M, Hata J, Hirakawa Y, Ozawa M, Yoshida D, et al. Association between ratio of serum eicosapentaenoic acid to arachidonic acid and risk of cardiovascular disease: The Hisayama Study. *Atherosclerosis* 2013; **231**: 261–267.
- Lin C, Rajalahti T, Mjøs SA, Kvalheim OM. Predictive associations between serum fatty acids and lipoproteins in healthy non-obese Norwegians: Implications for cardiovascular health. *Metabolomics* 2016; **12**: 6.
- Domei T, Yokoi H, Kuramitsu S, Soga Y, Arita T, Ando K, et al. Ratio of serum n-3 to n-6 polyunsaturated fatty acids and the incidence of major adverse cardiac events in patients undergoing percutaneous coronary intervention. *Circ J* 2012; **76**: 423–429.
- Philip S, Chowdhury S, Nelson JR, Benjamin Everett P, Hulme-Lowe CK, Schmier JK. A novel cost-effectiveness model of prescription eicosapentaenoic acid extrapolated to secondary prevention of cardiovascular diseases in the United States. *J Med Econ* 2016; **19**: 1003–1010.
- Kawakami K, Hinotsu S, Urushihara H, Onishi Y. Cost effectiveness analysis of dyslipidemia in Japan. 2011 [cited 15 July 2017]. http://www.esri.go.jp/jp/prj/int_prj/prj-si2010/sem_ps.html (in Japanese) (accessed July 15, 2017).
- Bowen KJ, Harris WS, Kris-Etherton PM. Omega-3 fatty acids and cardiovascular disease: Are there benefits? *Curr Treat Options Cardiovasc Med* 2016; **18**: 69.
- Kromhout D, Giltay EJ, Geleijnse JM. n-3 fatty acids and cardiovascular events after myocardial infarction. *N Engl J Med* 2010; **363**: 2015–2026.
- Bosch J, Gerstein HC, Dagenais GR, Diaz R, Dyal L, Jung H, et al. n-3 fatty acids and cardiovascular outcomes in patients with dysglycemia. *N Engl J Med* 2012; **367**: 309–318.
- Roncaglioni MC, Tombesi M, Avanzini F, Barlera S, Caimi V, Longoni P, et al. n-3 fatty acids in patients with multiple cardiovascular risk factors. *N Engl J Med* 2013; **368**: 1800–1808.
- Nosaka K, Miyoshi T, Iwamoto M, Kajiya M, Okawa K, Tsukuda S, et al. Early initiation of eicosapentaenoic acid and statin treatment is associated with better clinical outcomes than statin alone in patients with acute coronary syndromes: 1-year outcomes of a randomized controlled study. *Int J Cardiol* 2017; **228**: 173–179.
- Bell CM, Urbach DR, Ray JG, Bayoumi A, Rosen AB, Greenberg D, et al. Bias in published cost effectiveness studies: Systematic review. *BMJ* 2006; **332**: 699–703.