Cost-Effectiveness Analysis of Cardiovascular Disease Treatment in Japan

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Summary

The quality-adjusted life year (QALY) and incremental cost-effectiveness ratio (ICER) are important concepts in cost-effectiveness analysis, which is becoming increasingly important in Japan. QALY is used to estimate quality of life (QOL) and life years, and can be used to compare the efficacies of cancer and cardiovascular treatments. ICER is defined as the difference in cost between treatments divided by the difference in their effects, with a smaller ICER indicating better cost-effectiveness. Here, we present a review of cost-effectiveness analyses in Japan as well other countries. A number of treatments were shown to be cost-effective, e.g., statin for secondary prevention of cardiovascular disease, aspirin for primary prevention of cardiovascular disease, DOAC for high-risk atrial fibrillation, beta blockers, ACE inhibitors, and ARB for heart failure, sildenafil and bosentan for pulmonary hypertension, CABG for multi-vessel coronary disease, ICD for ventricular tachycardia, and CRT for heart failure with low ejection fraction, while others were not cost-effective, e.g., epoprostenol for pulmonary hypertension and LVAD for end-stage heart failure. Further investigations are required regarding some treatments, e.g., PCSK-9 inhibitors for familial hypercholesterolemia, PCI for multi-vessel coronary disease, catheter ablation for atrial fibrillation, and TAVI for severe aortic stenosis. Ethical aspects should be taken into consideration when utilizing the results of cost-effectiveness analysis in medical policy.

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Key words: ICER, Heart, QALY, Japanese

Medical costs are increasing in developed countries, including Japan, with the aging of the population and advances in technology. Although several drugs and devices have improved clinical outcomes, the increases in medical costs associated with these expensive options are placing pressure on national budgets. Efficient usage of medical budgets is crucial for maintenance of a sustainable medical system. Cost-effectiveness analysis was developed to make efficient use of medical budgets.¹⁾ Cost-effectiveness analysis evaluates not only the monetary costs of drugs or procedures, but also takes into account their effects on quality of life (QOL). Several countries, including the UK and Australia, introduced cost-effectiveness analysis to approve new drugs,²⁾ and Japan is planning to introduce cost-effectiveness analysis for health policy in 2018. Cost-effectiveness analysis is becoming increasingly important all around the world. Guidelines for the development, reporting, and evaluation of health care systems recommend the inclusion of cost-effectiveness analysis.³⁾ To understand cost-effectiveness analysis, it is necessary to understand key concepts, such as quality adjusted life year (QALY) or the incremental cost-effectiveness ratio (ICER). In the first part of this review, we will introduce

key concepts. In the second part, we will summarize cost-effectiveness data for cardiology drugs and cardiology devices. We have reviewed studies conducted in Japan as well as in other countries.

Key Concepts of Cost-Effectiveness Analysis

Definition of cost: Two types of cost are taken into consideration in cost-effectiveness analysis, i.e., direct costs and indirect costs.⁴⁾ Direct costs are all costs of resources used that are attributable to a health care intervention, and can be divided into direct medical costs and direct non-medical costs. Direct medical costs are the costs of inpatient and outpatient treatment, while direct non-medical costs are payments other than those for the medical institute, e.g., the costs of transportation to the hospital. Indirect costs represent opportunity loss, e.g., the loss of working opportunity because of disease. When performing cost-effectiveness analysis, we estimate the costs using real calculated costs, previously published data, or national data.

Analysis: Clarification of the analysis standpoint is necessary in cost-effectiveness analysis.⁵⁾ The Consolidated Health Economic Evaluation Reporting Standards

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Figure 1. Concept of quality of life (QOL) adjusted life year (QALY). For a patient with QOL 0.6 who lives for 2 years, QALY is $0.6 \times 2 = 1.2$.

(CHEERS) statement and Japanese guidelines recommend clarification of the analysis standpoint,^{6,7)} e.g., patient, medical system, and social. From the patient standpoint, costs include hospital payment, drug payment, transportation fees, and loss of working opportunity. From the standpoint of the medical system, costs include patient payments, insurance payments, and government payments. From the social standpoint, costs include patient payments, insurance payments, government costs, and opportunity loss. Most cost-effectiveness analyses use the medical system or social standpoint.

Utility: Utility is defined as the expected value. Quality of life (QOL) includes physical value and psychological value, and is a useful parameter to evaluate the utility of a medical treatment. QOL evaluation can be divided into the profile type and the estimate type.⁸⁾ Profile type QOL, such as SF-36, evaluates health status in detail based on sufficient amounts of specific information regarding health and QOL. Estimate type QOL, such as EQ-5D, is often used in cost-effectiveness analysis. QOL 1.0 indicates perfect condition, while QOL 0 indicates death.

QALY: Quality-adjusted life year (QALY) is a parameter used to estimate QOL and life year gain,⁹⁾ and is calculated as: $\text{QALY} = \text{QOL} \times \text{Life year gain}$. Figure 1 shows the concept of QALY. For example, if a patient has QOL 0.6 and lives for 2 years, QALY is $0.6 \times 2 = 1.2$. QALY can be used to estimate QOL and life expectancy, and is a useful parameter to evaluate treatment efficacy. For example, QALY can be used to compare the efficacies of cancer treatment and cardiovascular treatment.

Definition of ICER: The incremental cost-effectiveness ratio (ICER) is an important parameter used for comparison of treatment efficacy,⁴⁾ and is defined as the difference in cost between treatments divided by the difference in effect. When comparing the cost-effectiveness of treatment

Figure 2. Estimation of incremental cost-effectiveness ratio (ICER). If the cost of treatment A is 60,000,000 yen and the cost of treatment B is 40,000,000 yen, the quality of life adjusted life year (QALY) of treatment A is 20 QALYs and that of treatment B is 15 QALYs. The ICER of treatment A over treatment B is 4,000,000 yen/QALY.

A and treatment B, $\text{ICER} = (\text{Cost A} - \text{Cost B}) / (\text{Utility A} - \text{Utility B})$. Figure 2 shows the estimation of ICER. If the cost of treatment A is 60,000,000 yen and the cost of treatment B is 40,000,000 yen, the QALYs of treatments A and B are 20 and 15 QALYs, respectively. The ICER of treatment A over treatment B is 4,000,000 yen/QALY. If the incremental cost is small or the incremental effect is large, ICER would be small. Therefore, a smaller ICER indicates better cost-effectiveness. ICER can be calculated by QALY and also life year. The Japanese guidelines recommend using ICER in cost-effectiveness analysis.⁷⁾

Cost-effectiveness threshold: The cost-effectiveness threshold is used to evaluate whether treatments are good or very good value for money.⁴⁾ Willing to pay (WTP) is a cost-effectiveness threshold of payment for treatment.¹⁰⁾ WTP is estimated using a questionnaire and is useful to evaluate whether ICER is cost-effective. The UK has ICER criteria of £20,000-£30,000 British pounds (GBP) per QALY.¹¹⁾ The cost-effectiveness of treatment A is good if its ICER over treatment B is less than GBP £20,000. Conversely, treatment A shows poor cost-effectiveness if its ICER over treatment B is more than GBP £30,000. The WTP in the United States is around \$50,000-\$100,000 per QALY,¹²⁾ and that in Japan is around 5,000,000-6,000,000 yen per QALY.¹²⁾ In Japan, treatment A would be considered to have good cost-effectiveness if its ICER over treatment B is less than 5,000,000 yen per QALY. In the case of life year gain, the threshold of cost-effectiveness would be 4,000,000-5,000,000 yen per life year in Japan.

Health economic analysis: The most common type of health economic analysis is cost-effectiveness analysis, which is a research method applied to estimate the incremental benefits and costs of a new treatment compared with the standard treatment.⁴⁾ Cost-effectiveness analysis is

Figure 3. Decision tree model. The decision tree includes all treatment choices and results of the treatments. The probability of cure with treatment A is PaCure. To compare the cost-effectiveness of treatments A and B, we calculate $(PaCure \times Cost\ A\ cure + PaDie \times Cost\ A\ die) / (PaCure \times QOL)$ versus $(PbCure \times Cost\ B\ cure + PbDie \times Cost\ B\ die) / (PbCure \times QOL)$.

Figure 4. Markov model. The Markov model contains state transition probabilities.

expressed in terms of ICER, and the most commonly used outcome measure is QALY. Cost-effectiveness analysis is often presented on a 4-quadrant plane, with cost represented on the x-axis and effectiveness on the y-axis. Clinical trials are performed to estimate clinical effects, and a randomized control trial or meta-analysis of clinical trials is recommended for use of health economic analysis.⁷⁾

Analysis model and time horizon: Cost-effectiveness analysis is performed using two types of model, i.e., decision tree models and Markov models.⁴⁾ The decision tree model is suitable for an acute disease, and includes all treatment choices and results of treatments (Figure 3). A Markov model is suitable for a chronic disease, and is useful when the event examined has occurred repeatedly (Figure 4). When performing cost-effectiveness analysis, it is necessary to take into account long-term effects and costs. When limited data are available from published clinical trials, it is necessary to estimate the results over a longer time frame; therefore, a model capable of providing estimates over a longer time is required. A Markov

model contains state transition probabilities, and can be used to calculate long-term cost and effectiveness. The time horizon, i.e., the analysis period, should be long enough to estimate the effects of the treatment.

Sensitivity analysis: Cost-effectiveness analysis requires a number of parameters to be defined (cost, utility, event rate, etc.), and these parameters contain uncertainties. Sensitivity analysis, which is a statistical method to evaluate the robustness of results when parameters contain uncertainty,⁴⁾ is therefore necessary. In sensitivity analysis, the parameters are adjusted from the lowest to the highest number.

Medical ethics: Ethical aspects should be taken into consideration when utilizing the results of cost-effectiveness analysis in medical policy. Medical policy should take into account the following 3 ethical values: treating people equally, favoring the worse-off, and maximizing total benefits.¹³⁾ However, cost-effectiveness analysis only considers maximizing total benefits. The cost-effectiveness of device therapy for end-stage heart failure would be worse than use of sildenafil for erectile dysfunction.¹⁴⁾ However, this contravenes the ethical consideration of favoring the worse-off. Those with short life expectancy may achieve only little QALY with treatment. ICER of terminal care would be worse than pediatric treatments. In addition, ICER of expensive therapies for rare diseases would be worse than common disease treatments. This would mean that terminal patients and those with rarer diseases would not be treated equally. These examples indicate that cost-effectiveness analysis is insufficient for evaluating medical treatment in medical policy decision making.

Specific Cost-Effectiveness Analysis in the Field of Cardiology

Dyslipidemia: A Japanese study showed that the ICER of statin for primary prevention of cardiovascular disease compared with conventional therapy was 12,690,000-329,460,000 yen per QALY,¹⁵⁾ which suggested that primary prevention with statin was not cost-effective in Japan. A study performed in the United States indicated the ICERs of statins in primary prevention of cardiovascular disease for patients at high, intermediate, and low risk

were \$37,000, \$81,000, and \$140,000 per QALY, respectively.¹⁶⁾ These observations suggested that statins were cost-effective in primary prevention of cardiovascular disease for high-risk patients but not for low-risk patients.

The ICERs of protein convertase subtilisin/kexin type 9 (PCSK9) inhibitors over ezetimibe were reported to be \$503,000 per QALY for heterozygous familial hypercholesterolemia and \$414,000 per QALY for atherosclerotic cardiovascular disease in a study performed in the United States.¹⁷⁾ This study suggested that PCSK9 inhibitors are not cost-effective in the United States. However, there have been no Japanese studies regarding the cost-effectiveness of PCSK9 inhibitors.

Antithrombotic agents: A review article showed that aspirin was dominant in primary prevention of cardiovascular disease over no medication (less cost and more effect).¹⁸⁾ Adding aspirin improved QALY and reduced cost by reducing cardiovascular events. A Japanese study also showed dominance of aspirin over no medication in primary prevention of cardiovascular disease.¹⁹⁾ These data indicated that aspirin has very good cost-effectiveness in cardiovascular primary prevention all around the world. A study in the United States indicated that the ICER of clopidogrel over aspirin for secondary prevention of cardiovascular disease was more than \$130,000 per QALY.²⁰⁾ This study suggested that clopidogrel was not cost-effective for secondary prevention in the United States. A Canadian study showed an ICER of \$57,630 per QALY for prasugrel over clopidogrel.²¹⁾ In a study in Japan, the ICER of cilostazol over aspirin for secondary prevention of cerebral infarction was 1,800,000 yen per QALY,²²⁾ which suggested that cilostazol was cost-effective for secondary prevention of cerebral infarction in Japan.

A meta-analysis examining the cost-effectiveness of direct oral anticoagulant (DOAC) use for stroke prevention in atrial fibrillation indicated that DOAC was cost-effective over warfarin.²³⁾ The ICER of rivaroxaban over warfarin was \$3,190-\$55,757 per QALY, that of dabigatran over warfarin was \$11,150-\$20,797 per QALY, and that of apixaban showed a gain of \$4,723-\$24,312 per QALY over warfarin. In a Japanese study, the ICER of apixaban over warfarin for atrial fibrillation was \$22,500 per QALY.²⁴⁾ These⁴⁾ data indicated that although DOACs were expensive, they showed acceptable cost-effectiveness for stroke prevention in atrial fibrillation.

Heart failure treatment:

Beta blockers: A study performed in the United States indicated an ICER of beta-blocker over no beta-blocker of \$7,043 per life year gain in patients with heart failure.²⁵⁾ In a study performed in the United Kingdom, carvedilol was shown to have a lower cost and better clinical effect over conventional therapy in patients with severe heart failure.²⁶⁾ A Japanese study showed that the 5-year costs of carvedilol versus conventional therapy were 3,500,000 yen versus 5,500,000 yen, respectively, and life expectancy with carvedilol versus conventional therapy was 121 months versus 88 months, respectively. This study showed that carvedilol had a lower cost and provided longer life expectancy than conventional therapy for chronic heart failure.²⁷⁾ These data showed that beta-blockers have good cost-effectiveness in heart failure patients all around the

world.

Angiotensin converting enzyme (ACE) inhibitor, angiotensin receptor blocker (ARB), and others: A study performed in the United States showed that the ICER of captopril over placebo was \$3,700-\$10,400 per QALY after myocardial infarction.²⁸⁾ In another American study, the ICER of enalapril over placebo was \$115 per QALY for symptomatic heart failure.²⁹⁾ A German study indicated an ICER of \$1,700-\$5,800 per life year gain for ramipril over placebo for heart failure after myocardial infarction.³⁰⁾ A study performed in the United States showed that valsartan was dominant over placebo for chronic heart failure (less cost and better effect),³¹⁾ and a British study showed that candesartan was dominant over placebo for heart failure (less cost and better effect).³²⁾ These data indicated that ACE inhibitors and ARBs are cost-effective for the treatment of heart failure in various countries. A Japanese study showed tolvaptan reduced the cost of treatment for heart failure in aquaporin-defined responders.³³⁾ Compared with conventional therapy, tolvaptan showed lower medical cost (1,120,000 yen/year versus 3,120,000 yen/year, respectively) and shorter hospital stay (30 days versus 70 days, respectively). Tolvaptan could be cost-effective in certain types of heart failure.

Drugs for pulmonary hypertension: In a British study, the ICERs of epoprostenol, iloprost, and bosentan over supportive care for functional class 3 pulmonary hypertension were GBP £277,000, GBP £101,000, and GBP £27,000 per QALY, respectively, and sildenafil was dominant (less cost and better effect).³⁴⁾ These data suggested that bosentan and sildenafil are cost-effective treatments for pulmonary hypertension, while epoprostenol is not. This is consistent with network meta-analysis indicating that bosentan and sildenafil had superior effectiveness over other oral medications for pulmonary artery hypertension.³⁵⁾ To date, there have been no cost-effectiveness analyses of pulmonary hypertension drugs in Japan.

Percutaneous coronary intervention (PCI) and coronary artery bypass grafting (CABG): A study performed in the United States showed an ICER of \$6,791 per QALY for coronary artery bypass graft (CABG) over percutaneous coronary intervention (PCI) with drug-eluting stents in diabetic multivessel disease.³⁶⁾ The Synergy between percutaneous coronary intervention with TAXUS and cardiac surgery (SYNTAX) trial showed an ICER of CABG over PCI of \$16,537 per QALY in left main coronary disease or 3-vessel disease.³⁷⁾ A meta-analysis to examine the cost-effectiveness of PCI versus CABG indicated a favorable ICER for CABG rather than PCI in multivessel coronary artery disease (CAD).³⁸⁾ A prospective observational study performed in the United Kingdom reported an ICER of GBP £47,000 per QALY for PCI over medical treatment in angina pectoris,³⁹⁾ and a Japanese study indicated an ICER of PCI over medical therapy in angina patients of \$7,000 per QALY.⁴⁰⁾ Drug-eluting stents showed better cost-effectiveness than bare metal stents in Japan.⁴¹⁾ These data suggested that PCI is more cost-effective than medical therapy for angina in Japan. Meta-analysis suggested that CABG would have better cost-effectiveness than PCI for multivessel disease in Japan as well as other countries.³⁸⁾

Catheter ablation: A meta-analysis indicated that catheter ablation was associated with high costs and high rates of complications.⁴²⁾ No evidence is available regarding important variables in ablation, and it is difficult to evaluate its cost-effectiveness. However, a Japanese analysis showed an ICER of ablation plus warfarin over warfarin of 1,692,399-2,747,037 yen per QALY for atrial fibrillation with CHADS₂ score 4-6. These data indicated that ablation was cost-effective for high-risk patients.⁴³⁾

Implantable cardioverter defibrillator (ICD) and cardiac resynchronization therapy (CRT): A meta-analysis and systematic review performed in the United Kingdom reported an ICER of GBP £14,231-GBP £29,756 per QALY for implantable cardioverter defibrillators (ICD) compared with optimal medical therapy,⁴⁴⁾ and the ICER of cardiac resynchronization therapy (CRT) compared with optimal therapy was GBP £27,584-GBP £27,899 per QALY. These data indicated that both ICD and CRT represent cost-effective treatments. However, there have been no cost-effectiveness analyses of ICD and CRT in Japan.

Transcatheter aortic valve implantation (TAVI): A meta-analysis showed controversial results of transcatheter aortic valve implantation (TAVI) ICER over surgical aortic valve replacement (AVR) for severe aortic stenosis.⁴⁵⁾ Two of 7 studies indicated that AVR was dominant (less cost and better effect), two studies showed that TAVI was dominant (less cost and better effect), and 3 studies showed ICERs of \$32,000-\$1,014,949 per QALY for TAVI over AVR in severe aortic stenosis. Thus, further cost-effectiveness analyses of TAVI are required.

Left ventricular assist device (LVAD): In a British study, the ICER of left ventricular assist devices (LVAD) over conventional therapy for end-stage heart failure was GBP £79,212 per QALY.⁴⁶⁾ Another meta-analysis showed an ICER of \$89,790-\$414,274 per QALY for LVAD over heart transplantation for end-stage heart failure.⁴⁷⁾ These data suggested that LVAD is not cost-effective for end-stage heart failure. All reports regarding the ICER of LVAD published to date were based on retrospective observational studies, and estimation of the cost-effectiveness may not be accurate. To date, there have been no Japanese studies regarding ICER of LVAD.

Conclusions

While some treatments are cost-effective (statins for secondary prevention of cardiovascular disease, aspirin for primary prevention of cardiovascular disease, DOAC for high-risk atrial fibrillation, beta blockers, ACE inhibitors, and ARB for heart failure, sildenafil and bosentan for pulmonary hypertension, CABG for multivessel coronary disease, ICD for ventricular tachycardia, CRT for severe heart failure with low ejection fraction), others are not (epoprostenol for pulmonary hypertension, LVAD for end-stage heart failure). Further investigations are required regarding some treatments (PCSK-9 inhibitors for familial hypercholesterolemia, PCI for multivessel coronary disease, catheter ablation for atrial fibrillation, TAVI for severe aortic stenosis). Ethical aspects should be taken into consideration when utilizing the results of cost-effectiveness analysis in medical policy.

Disclosures

Conflicts of interest: The authors declare that they have no conflicts of interest.

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