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Original Research

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Cost-effectiveness of Fractional Flow Reserve Versus Intravascular Ultrasound to Guide Percutaneous Coronary Intervention: Results From the FLAVOUR Study

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AUTHOR'S SUMMARY

Fractional flow reserve (FFR) and intravascular ultrasound (IVUS) are representative physiologic and anatomic diagnostic modalities, and the addition of FFR or IVUS assessment to coronary

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Conflict of Interest
Bon-Kwon Koo has received institutional research grants from Abbott Vascular and Philips. All other authors declare no competing interests.

Data Sharing Statement
The data generated in this study is available from the corresponding authors upon reasonable request.

Author Contributions
Conceptualization: Hwang D, Koo BK; Data curation: Hwang D, Kim HL, Koo BK, Lee TJ; Formal analysis: Hwang D, Kim HL; Funding acquisition: Koo BK; Investigation: Hwang D, Kim HL, Ko J, Choi H, Jeong H, Jang SA, Hu X, Kang J, Zhang J, Jiang J, Hahn JY, Nam CW, Doh JH, Lee BK, Kim W, Huang J, Jiang F, Zhou H, Chen P, Tang L, Jiang W, Chen X, He W, Ahn SG, Kim U, Ki YJ, Shin ES, Kim HS, Tahk SJ, Wang J, Lee TJ, Koo BK; Methodology: Hwang D, Kim HL, Ko J, Choi H, Jeong H, Jang SA, Lee TJ, Koo BK; Supervision: Hu X, Kang J, Zhang

angiography demonstrated incremental information on treatment decision-making and better clinical outcomes. The current cost-effectiveness analysis based on the FLAVOUR trial demonstrated that FFR-guided percutaneous coronary intervention (PCI) was associated with a decrease in lifetime healthcare costs and an increase in quality-adjusted life-years compared to IVUS-guided PCI. The current results infer that FFR-guided PCI is a dominant treatment strategy compared to IVUS-guided PCI from the perspective of the Korean healthcare system.

ABSTRACT

Background and Objectives: The Fractional Flow Reserve and Intravascular Ultrasound-Guided Intervention Strategy for Clinical Outcomes in Patients with Intermediate Stenosis (FLAVOUR) trial demonstrated non-inferiority of fractional flow reserve (FFR)-guided percutaneous coronary intervention (PCI) compared with intravascular ultrasound (IVUS)-guided PCI. We sought to investigate the cost-effectiveness of FFR-guided PCI compared to IVUS-guided PCI in Korea.
Methods: A 2-part cost-effectiveness model, composed of a short-term decision tree model and a long-term Markov model, was developed for patients who underwent PCI to treat intermediate stenosis (40% to 70% stenosis by visual estimation on coronary angiography). The lifetime healthcare costs and quality-adjusted life-years (QALYs) were estimated from the healthcare system perspective. Transition probabilities were mainly referred from the FLAVOUR trial, and healthcare costs were mainly obtained through analysis of Korean National Health Insurance claims data. Health utilities were mainly obtained from the Seattle Angina Questionnaire responses of FLAVOUR trial participants mapped to EQ-5D.
Results: From the Korean healthcare system perspective, the base-case analysis showed that FFR-guided PCI was 2,451 U.S. dollar lower in lifetime healthcare costs and 0.178 higher in QALYs compared to IVUS-guided PCI. FFR-guided PCI remained more likely to be cost-effective over a wide range of willingness-to-pay thresholds in the probabilistic sensitivity analysis.
Conclusions: Based on the results from the FLAVOUR trial, FFR-guided PCI is projected to decrease lifetime healthcare costs and increase QALYs compared with IVUS-guided PCI in intermediate coronary lesion, and it is a dominant strategy in Korea.

Trial Registration: ClinicalTrials.gov Identifier: NCT02673424

Keywords: Coronary artery disease; Percutaneous coronary intervention; Cost; Quality-adjusted life year

INTRODUCTION

Even though coronary angiography is a standard method to evaluate coronary artery disease (CAD), various modalities are adjunctively used for deciding treatment strategies.[1)2)] Intravascular ultrasound (IVUS) is a representative intracoronary imaging device that can provide additive anatomical lesion severity and characteristics of underlying plaque and can be utilized for the optimization of percutaneous coronary intervention (PCI).[3-5)] Fractional flow reserve (FFR) is a standard invasive method to define the presence of myocardial ischemia, and FFR-guided PCI is currently recommended for treatment decision-making for CAD with intermediate lesion severity.[1)2)6-8)] These 2 methods have been developed based on different purposes with distinct strengths in guiding PCI.

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Recently, the Fractional Flow Reserve and Intravascular Ultrasound-Guided Intervention Strategy for Clinical Outcomes in Patients with Intermediate Stenosis (FLAVOUR) trial compared the clinical outcomes of FFR- and IVUS-guided PCI.[9] FFR-guided PCI was non-inferior to IVUS-guided PCI in terms of the composite of death, myocardial infarction, or revascularization at 24 months, and FFR-guided PCI resulted in the fewer use of stents and less frequent administration of dual antiplatelet therapy than IVUS-guided PCI. Considering the different required medical resources between FFR- and IVUS-guided PCI, we performed a cost-effectiveness analysis of FFR- and IVUS-guided PCI based on the results from the FLAVOUR trial in the Korean healthcare system.

METHODS

Ethical statement

The study protocol was reviewed and approved by the Institutional Review Board (IRB) of Seoul National University Hospital (H-1602-134-744). The IRB had granted a waiver of consent. It was registered at www.ClinicalTrials.gov (NCT02673424). All personal information of the participants was anonymized and de-identified.

The FLAVOUR trial

The clinical and patient-reported outcomes between FFR- and IVUS-guided PCI in patients with intermediate coronary stenosis were compared in the FLAVOUR trial.[9][10] Briefly, the FLAVOUR trial was an investigator-initiated, prospective, randomized, open-label, multinational trial at 18 sites in Korea and China. The trial randomly assigned 1,682 patients with intermediate stenosis estimated as 40%–70% occlusion by visual estimation on coronary angiography to FFR- and IVUS-guided PCI from July 2016 through August 2019. The primary outcome was a composite of death, myocardial infarction, or revascularization at 24 months after randomization. The primary outcome events occurred in 8.1% of the FFR-guided PCI group and 8.5% in the IVUS-guided PCI group, demonstrating that FFR-guided PCI was non-inferior to IVUS-guided PCI (p for non-inferiority=0.01). The patient-reported Seattle Angina Questionnaire (SAQ) was similar in the 2 groups.

Analytic overview of cost-effectiveness analysis

A 2-part cost-effectiveness model, composed of a short-term decision tree and a long-term Markov model, was developed to compare the long-term cost-effectiveness of FFR- and IVUS-guided PCI from the perspective of the Korean healthcare system using TreeAge Pro 2020 (TreeAge Software, Williamstown, MA, USA). The model hypothesized a cohort of 65-year-old patients with intermediate stenosis receiving coronary angiography, where the age of the cohort was set based on the average age of participants in the FLAVOUR trial.[9] The health outcome was quality-adjusted life-years (QALYs), and all costs were expressed in 2021 U.S. dollars (USD; $1=1,188.8 Korean Won in 2021). The annual discount rate of future costs and QALYs was 4.5%, based on the economic evaluation guidelines of pharmaceuticals in Korea.[11] The primary outcome was the incremental cost-effectiveness ratio (ICER) calculated as incremental costs/QALY gained with the less expensive strategy as a reference. To explore the effects of parameter uncertainty on the results, one-way sensitivity analysis and probabilistic sensitivity analysis (PSA) were performed.

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Model

Figure 1 shows the schematic representation of a 2-part cost-effectiveness model in our study. The model structure was based on the natural course of the disease and key clinical outcomes in the FLAVOUR trial. The first part of the model is composed of a short-term decision tree for the first year. In the decision tree model, a decision was made on FFR or IVUS, and PCI was decided based on the results of the chosen test. Non-fatal myocardial infarction, revascularization, cardiac death, and non-cardiac death were considered events that could occur within one year. It was assumed that PCI was performed in all cases of non-fatal myocardial infarction or revascularization. The second part of the model is constituted of the Markov model to estimate the long-term cost-effectiveness for the next 29 years. Therefore, the total time horizon was 30 years, which was set to estimate lifetime cost-effectiveness at the age of the cohort. The cycle length of the Markov model was one year based on the natural course of the disease. Patients who survived in the one-year decision tree model entered into the Markov model, and the entering health state was determined according to the events that occurred in the decision tree model. Patients who did not undergo PCI as a result of FFR or IVUS and had no events for one year entered the "Well on medical treatment" state; patients who underwent PCI as a result of the test and had no events for one year entered the "Stable

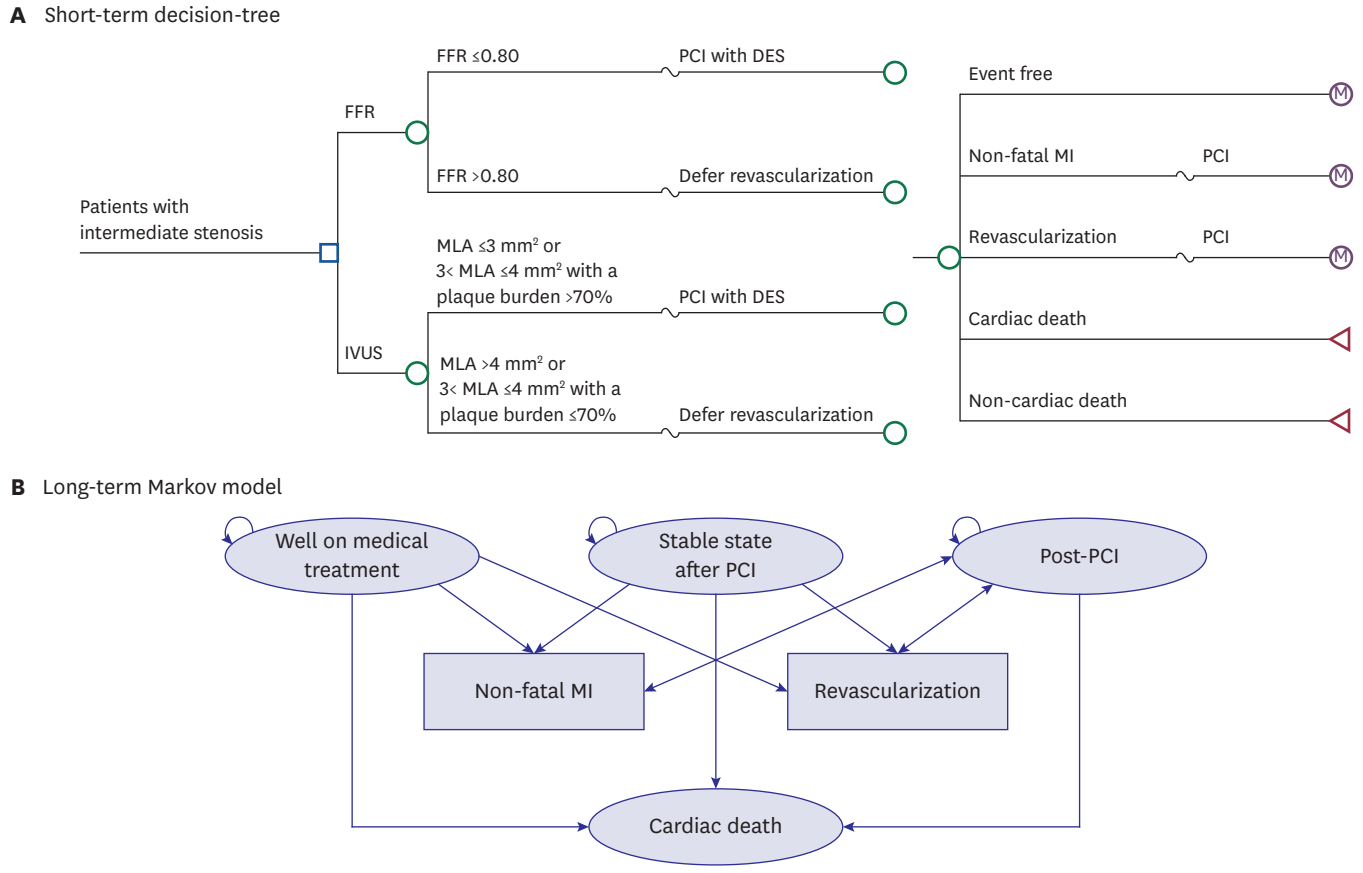

Figure 1. Model structure. A 2-part cost-effectiveness model, composed of a short-term decision tree (A) and a long-term Markov model (B), is shown. In the decision tree, a decision was made on FFR or IVUS, and PCI was decided based on the results of the chosen test. Thereafter, non-fatal MI, revascularization, cardiac death, and non-cardiac death could occur within one year. Patients who survived in the one-year decision tree entered into the Markov model, and the entering health state was determined according to the events that occurred in the decision tree. Yearly, patients were at risk of non-fatal MI, revascularization, cardiac death, and non-cardiac death. Non-cardiac death can occur at every state but not shown.
DES = drug-eluting stent; FFR = fractional flow reserve; IVUS = intravascular ultrasound; MI = myocardial infarction; MLA = minimal lumen area; PCI = percutaneous coronary intervention.

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state after PCI" state; and patients who underwent PCI for non-fatal MI or revascularization that occurred during the 1-year follow-up period entered the "Post-PCI" state, regardless of whether PCI was performed based on FFR or IVUS results. As in the decision tree, in the Markov model, patients were at risk of non-fatal myocardial infarction, revascularization, and cardiac and non-cardiac deaths during the follow-up. Patients in the "Well on medical treatment" or "Stable state after PCI" were moved to the "Post-PCI" state when they received PCI due to non-fatal myocardial infarction or revascularization. Patients entering the "Post-PCI" state were assumed to receive dual antiplatelet therapy for the first year and single antiplatelet therapy thereafter. Accordingly, the risk of clinical events, follow-up cost, and utility were applied differently for the first year and thereafter. When patients in the "Post-PCI" state underwent PCI again, dual antiplatelet therapy was restarted for one year as if they had newly entered the "Post-PCI" state, and the corresponding clinical event risk, cost, and utility were applied.

Model input

The base-case values and ranges of key model inputs are summarized in **Tables 1** and **2**.

Epidemiological parameters

The probabilities of meeting the criteria for PCI as a result of FFR or IVUS, the probabilities of clinical events in the short-term decision tree, and the annual transition probabilities under "Stable state after PCI" or "Well on medical treatment" state in the Markov model were estimated from the FLAVOUR trial data. Specifically, the probabilities of clinical events in the decision tree model were estimated using data from the first year of the FLAVOUR trial. In the Markov model, the annual transition probabilities under the "Stable state after PCI" and "Well on medical treatment" states were estimated by converting the cumulative probabilities over the 2-year follow-up period of the FLAVOUR trial into annual probabilities (**Table 1**). For patients under the "Post-PCI" state, the transition probabilities of each clinical event while maintaining the dual antiplatelet therapy for the first year after PCI were derived from the Grand Drug-Eluting Stent registry, which enrolled 17,286 PCI patients from 55 participating centers in Korea[12][13]; the annual transition probabilities from the second year after PCI were estimated from the HOST-EXAM trial data, which prospectively compared the efficacy and safety of aspirin and clopidogrel at 37 centers in 5,438 patients who completed dual antiplatelet therapy after PCI, by converting the 2-year cumulative probabilities of the entire study population to annual probabilities (**Table 1**). Kaplan-Meier estimates were used to determine the cumulative probabilities for each clinical event in the clinical pathways. For non-cardiac mortality, age-specific mortality was estimated after excluding the probability of death due to heart disease from the cause-elimination life tables for 2020 in Korea.[14]

Costs

Costs were estimated to include those paid by the insurer and out-of-pocket paid by patients. For procedural costs of FFR measurement and IVUS assessment, excluding costs for accompanying hospitalization and coronary angiography, the ingredients approach was used by estimating the costs of each ingredient and adding them up. Specifically, the procedure cost for FFR was obtained from the Korean medical fee schedule (as of December 2021),[15] and the base-case value and the ranges were set considering the distribution by the level of medical institution where the FFR measurements were performed.[16] The cost of the pressure wire was obtained from the price list of medical devices (as of December 2021).[17] For the cost of drugs used in the FFR measurement, the base-case value was obtained using the 2021 drug prices of adenosine and nicorandil,[18][19] weighted by the ratio of adenosine to nicorandil use among

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Table 1. Model inputs for epidemiologic parameters

Parameters	Base-case values	Ranges	Sources
Related to test results			FLAVOUR trial
Proportion of FFR ≤0.80	0.3520	0.3197–0.3856	
Proportion of MLA ≤3 mm^2 or 3< MLA ≤4 mm^2 with a plaque burden >70%	0.5995	0.5665–0.6389	
Related to clinical events in the short-term model (1 year)			
Probability of nonfatal MI with revascularization in patients with			
PCI after FFR	0.0034	0.0000–0.0103	
Deferred PCI after FFR	0.0037	0.0000–0.0091	
PCI after IVUS	0.0000	0.0000–0.0034	
Deferred PCI after IVUS	0.0000	0.0000–0.0037	
Probability of revascularization without MI in patients with			
PCI after FFR	0.0375	0.0158–0.0604	
Deferred PCI after FFR	0.0112	0.0024–0.0206	
PCI after IVUS	0.0239	0.0106–0.0389	
Deferred PCI after IVUS	0.0149	0.0020–0.0298	
Probability of cardiac death in patients with			
PCI after FFR	0.0034	0.0000–0.0102	
Deferred PCI after FFR	0.0037	0.0000–0.0090	
PCI after IVUS	0.0000	0.0000–0.0034	
Deferred PCI after IVUS	0.0030	0.0000–0.0094	
Related to clinical events in the long-term model (annual probability)			
From stable state after PCI			
Probability of nonfatal MI with revascularization in patients with			
PCI after FFR	0.0034	0.0007–0.0117	
PCI after IVUS	0.0043	0.0014–0.0109	
Probability of revascularization without MI in patients with			
PCI after FFR	0.0386	0.0248–0.0578	
PCI after IVUS	0.0284	0.0193–0.0420	
Probability of cardiac death in patients with			
PCI after FFR	0.0017	0.0002–0.0091	
PCI after IVUS	0.0050	0.0019–0.0117	
From well on medical treatment			
Probability of nonfatal MI with revascularization in patients with			
Deferred PCI after FFR	0.0028	0.0008–0.0080	
Deferred PCI after IVUS	0.0000	0.0000–0.0028	
Probability of revascularization without MI in patients with			
Deferred PCI after FFR	0.0171	0.0104–0.0269	
Deferred PCI after IVUS	0.0169	0.0084–0.0290	
Probability of cardiac death in patients with			
Deferred PCI after FFR	0.0056	0.0023–0.0120	
Deferred PCI after IVUS	0.0090	0.0037–0.0200	
From post-PCI			
Probability of nonfatal MI with revascularization			
1st year	0.0034	0.0021–0.0053	Grand-DES registry
2nd year–	0.0034	0.0024–0.0047	HOST-EXAM trial
Probability of revascularization without MI			
1st year	0.0165	0.0133–0.0204	Grand-DES registry
2nd year–	0.0083	0.0067–0.0102	HOST-EXAM trial
Probability of cardiac death			
1st year	0.0273	0.0231–0.0321	Grand-DES registry
2nd year–	0.0040	0.0030–0.0054	HOST-EXAM trial

FFR = fractional flow reserve; IVUS = intravascular ultrasound; MI = myocardial infarction; MLA = minimal lumen area; PCI = percutaneous coronary intervention.

FLAVOUR trial participants,[9] and the range was set based on individual drug prices in 2021.[19] Unlike the FFR measurement, the IVUS assessment was not covered by Korean National Health Insurance, so there was no officially determined unit cost. Thus, the procedure cost and material cost for the catheter included in the IVUS assessment were estimated from the average, minimum, and maximum values of costs disclosed by the Health Insurance Review and Assessment Service, which collects information on uncovered medical costs.[20]

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Table 2. Model inputs for costs, utilities and discount rate

Parameters	Base-case values	Ranges	Sources
Costs (2021 USD)			
Procedural costs			
FFR			
Procedure cost	88	88–100	[15]
Material cost (pressure wire)	763	763–778	[17]
Drug cost (adenosine or nicorandil)	12	7–21	[18][22]
IVUS			
Procedure cost	201	42–454	[20]
Material cost (catheter)	1,179	891–1,571	[20]
Inpatient costs (including coronary angiography)			NHIS-NHID, [21]
Inpatient costs with PCI	7,742	7,618–7,834	
Inpatient costs without PCI	1,473	1,408–1,506	
Annual follow-up costs			
1st year after PCI	274	254–293	
≥2nd year after PCI	264	246–282	
Deferred PCI	220	200–240	
Annual medication costs			NHIS-NHID, [18][22]
1st year after PCI	365	166–381	
≥2nd year after PCI	224	10–357	
Deferred PCI	127	10–357	
Treatment costs			NHIS-NHID, [21]
Nonfatal MI with revascularization	9,626	8,824–10,428	
Revascularization without MI	7,559	7,260–7,857	
Medical cost of cardiac death	9,344	3,044–15,645	
Health utility			
Utility of post-PCI (1st year after PCI)	0.805	0.766–0.844	FLAVOUR trial, [28]
Utility of stable state after PCI (≥2nd year after PCI)	0.850	0.842–0.857	
Utility of well on medical treatment (deferred PCI)	0.857	0.844–0.870	
Disutility of nonfatal MI with revascularization	0.095 for 14 days	0.08–0.267; 3–30 days	[23]_[26]
Disutility of revascularization without MI	0.095 for 7 days	0.08–0.267; 3–14 days	[23][25]_[27]
Discount rate (%)	4.5	0–5	[11]

For utility values, SAQ results from the FLAVOUR trial were converted using the equation that maps SAQ results to EQ-5D index.
EQ-5D = EuroQol-5 Dimension; FFR = fractional flow reserve; IVUS = intravascular ultrasound; MI = myocardial infarction; NHIS-NHID = National Health Insurance Service-National Health Information Database; PCI = percutaneous coronary intervention; SAQ = Seattle Angina Questionnaire; USD = U.S. dollars.

Inpatient costs for FFR or IVUS (including the cost of coronary angiography and, for patients undergoing PCI, also the cost of PCI), annual follow-up costs, treatment costs when clinical events occurred, and medical costs for one year before cardiac death were estimated through analysis of health insurance claims data using the National Health Insurance Service-National Health Information Database (approval No. for data access: NHIS-2022-1-346). Considering that FFR was covered by National Health Insurance for patients with intermediate stenosis, we analyzed the health insurance claims data for patients who underwent FFR from 2014 to 2020 and excluded patients with a history of coronary artery bypass graft surgery, PCI, stroke, or prescription of antiplatelet medication for more than 2 weeks in the 3 years prior to FFR, as well as patients who underwent coronary artery bypass graft surgery or died during the hospitalization for FFR. These patients were followed retrospectively to identify the inpatient care related to FFR, treatment according to the occurrence of clinical events, and follow-up care to estimate the costs thereof. To include the cost of uncovered services paid by patients, the proportions of such costs were applied to the estimated medical costs of inpatient care, annual follow-up, treatment, and cardiac death.[21] All costs obtained from the claims data were adjusted to 2021 using the Korean healthcare consumer price index. Annual medication costs were estimated by applying the weighted average price for each ingredient (as of 2021)[18] to the distribution of antiplatelet drug prescriptions for each health state and period (**Table 2**).[11][15][17][18][20-28]

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Health state utilities

To calculate QALYs, utility weights for each health state and disutility due to event occurrence were required. Considering that the health-related quality of life for patients with intermediate stenosis in Korea was measured using the SAQ in the FLAVOUR study,[9][10] the responses of Korean patients among the study participants were used to estimate the utility weight. Because the SAQ is a heart-specific measure, we used a mapping algorithm to convert it into a general preference-based measure. According to the database reporting the results of a systematic literature review conducted in March 2020 on mapping algorithms predicting EuroQol-5 Dimension (EQ-5D), there were 2 algorithms mapping SAQ to EQ-5D.[29][30] Among them, the mapping algorithm of Goldsmith et al,[28] which predicted values more similarly to previous studies reporting EQ-5D in Korean cardiovascular disease patients, was selected as the mapping algorithm for our study. Korean participants in the FLAVOUR trial were classified into each health state according to whether PCI was performed after FFR or IVUS and whether an event occurred thereafter, and the utility of each health state was estimated by mapping their responses to the EQ-5D. The value and duration of disutility due to the occurrence of each clinical event were taken from previous studies on similar study populations (**Table 2**).

Sensitivity analyses

Two types of sensitivity analyses were performed to evaluate the effect of parameter uncertainty on the results. First, we performed one-way sensitivity analyses for the available range of each parameter (**Tables 1** and **2**). Regarding a specific parameter, the ICER value appeared to be infinite due to a shift in the direction of incremental effects. Therefore, we represented the tornado diagram using the incremental net monetary benefit. We also conducted a threshold analysis to identify the cut-off value at which the cost-effective strategy identified in the base-case results would still remain optimal at the willingness-to-pay (WTP) threshold in Korea. The WTP threshold was USD 28,642 per QALY gained based on the previous study and adjustment to 2021.[31] Second, we conducted PSA based on 10,000 second-order Monte Carlo Simulations, assigning distributions to parameters to evaluate the joint uncertainty of all parameters. The beta distribution was used for probabilities and utilities, and the gamma distribution was used for costs and disutilities.

RESULTS

Trial population and clinical outcomes

The FLAVOUR trial included 1,682 patients, with 838 patients in the FFR-guided PCI group and 844 patients in the IVUS-guided PCI group. The baseline characteristics were well-balanced between the 2 groups (**Supplementary Table 1**). More patients underwent PCI in the IVUS-guided PCI group than in the FFR-guided PCI group, and the procedural cost for FFR assessment was lower than for IVUS assessment (**Tables 1** and **2**). After 24 months of follow-up, the primary outcome events occurred in 8.1% of the FFR-guided PCI group and 8.5% in the IVUS-guided PCI group (p=0.779), demonstrating that FFR-guided PCI was non-inferior to IVUS-guided PCI (p for non-inferiority=0.01) (**Supplementary Table 2**). The cumulative incidences of cardiac deaths were 0.8% in the FFR-guided PCI group and 1.3% in the IVUS-guided PCI group (p=0.350). The cumulative incidences of myocardial infarction were 1.9% in the FFR-guided PCI group and 1.7% in the IVUS-guided PCI group (p=0.696), and those of revascularization were 5.7% and 5.3%, respectively (p=0.713) (**Supplementary Table 2**).

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Base-case analyses

In our 2-part cost-effectiveness model, FFR-guided PCI was associated with a decrease in healthcare costs of USD 2,451, from USD 15,585 to USD 13,133, compared to IVUS-guided PCI (**Table 3**). FFR-guided PCI increased QALYs of 0.178 from 11.084 QALYs to 11.262 QALYs compared to IVUS-guided PCI (**Table 3**). FFR-guided PCI was a dominant treatment strategy compared to IVUS-guided PCI under the base-case assumptions.

One-way sensitivity analyses

In the one-way sensitivity analyses, the results were most sensitive to the probabilities of cardiac death in the Markov model (**Figure 2**). However, except for the probability of cardiac death from "Well on medical treatment state" in patients with deferred PCI after FFR, the FFR-guided PCI strategy remained dominant in the one-way sensitivity analyses (**Figure 2**).

Table 3. Base-case results

Strategy	Cost (2021 USD)	Incremental cost (2021 USD)	Effectiveness (QALYs)	Incremental effectiveness (QALYs)	ICER
FFR	13,133	-	11.262	-	Dominant
IVUS	15,585	2,451	11.084	−0.178	Dominated

FFR = fractional flow reserve; ICER = incremental cost-effectiveness ratio; IVUS = intravascular ultrasound; QALY = quality-adjusted life-year; USD = U.S. dollars.

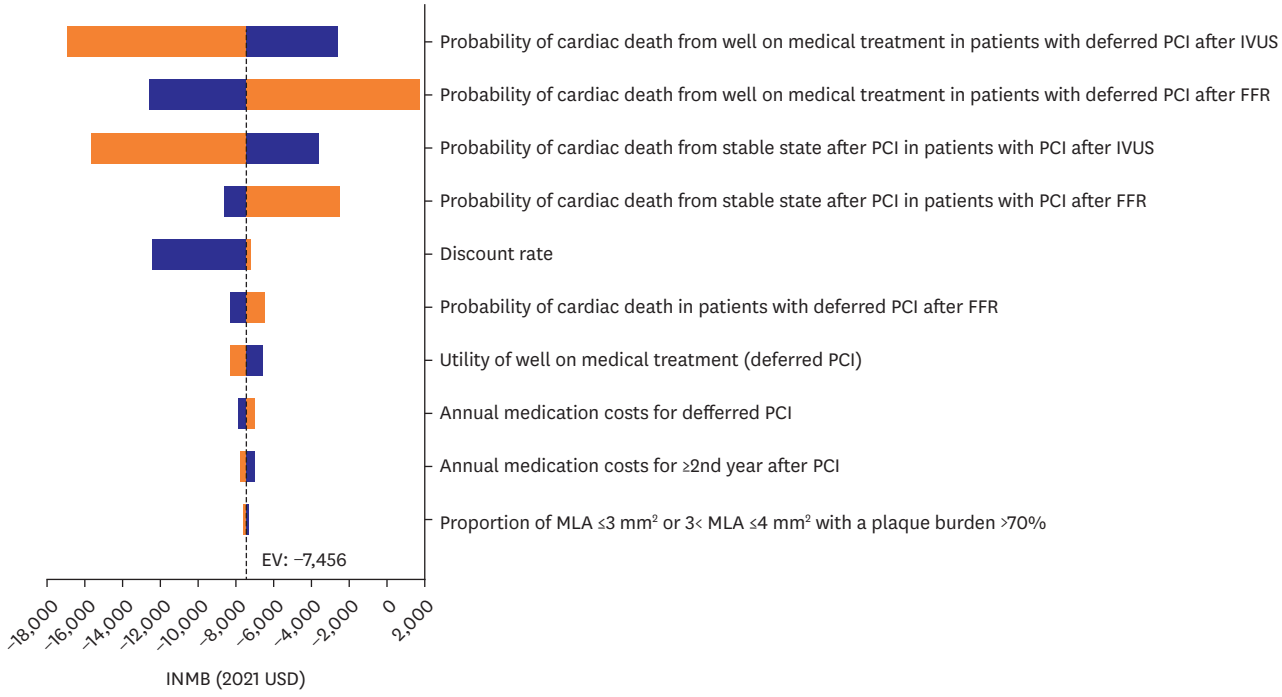

Figure 2. Selected results of one-way sensitivity analysis. A tornado diagram for FFR- vs. IVUS-guided PCI is presented to visualize the one-way sensitivity analysis. The top 10 variables with considerable INMB variation are shown. The vertical line represents the base-case INMB. The x-axis represented the ranges of INMB when the parameter values were varied over plausible ranges. A value of INMB greater than 0 indicates that IVUS-guided PCI is more cost-effective than FFR-guided PCI under the WTP threshold. Blue color indicates when each parameter has values lower than the base-case value within the range, and orange color indicates when each parameter has higher values.
EV = expected value; FFR = fractional flow reserve; INMB = incremental net monetary benefit; IVUS = intravascular ultrasound; MLA = minimal lumen area; PCI = percutaneous coronary intervention; USD = U.S. dollar; WTP = willingness-to-pay.

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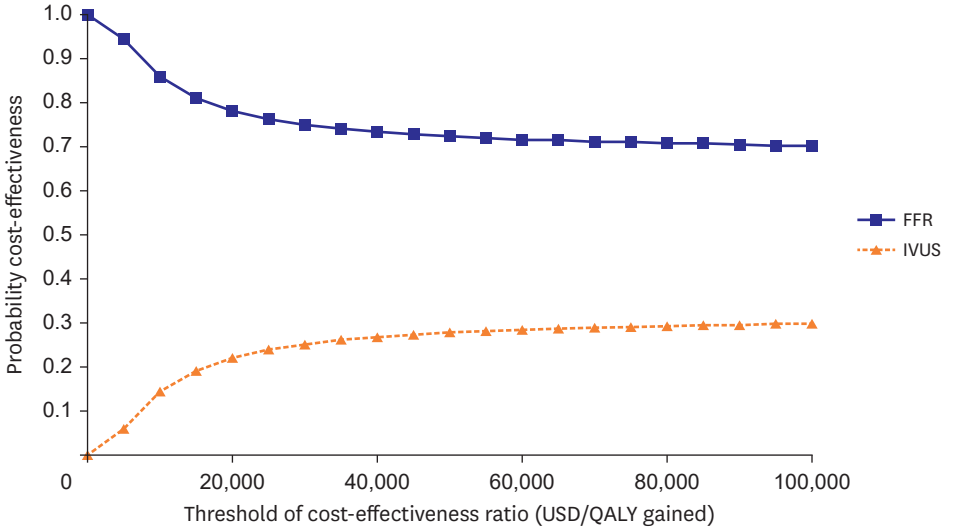

Figure 3. Cost-effectiveness acceptability curves. The results of the probabilistic sensitivity analysis are shown. The curves show the probabilities that each strategy is cost-effective at varying cost-effectiveness threshold ratios. Even as the willingness-to-pay threshold increased, the higher probability that FFR-guided percutaneous coronary intervention would be cost-effective was maintained.
FFR = fractional flow reserve; IVUS = intravascular ultrasound; QALY = quality-adjusted life-year; USD = U.S. dollar.

Probabilistic sensitivity analyses

In the PSA, FFR-guided PCI was cost-effective over a wide range of threshold cost-effectiveness ratios. Specifically, the probability that FFR-guided PCI would be cost-effective under a WTP of USD 28,642/QALY gained was 75.3%. Even as the WTP threshold increased, the higher probability that FFR-guided PCI would be cost-effective was maintained (**Figure 3**). From the results of PSA as an incremental cost-effectiveness scatter plot, FFR-guided PCI was the dominant strategy in 67.9% of the simulation results (**Supplementary Figure 1**).

DISCUSSION

The current cost-effectiveness analysis based on the FLAVOUR trial demonstrated that FFR-guided PCI was associated with a decrease in lifetime healthcare costs and an increase in QALYs compared to IVUS-guided PCI. This finding was robust in most one-way sensitivity analyses. In the PSA, FFR-guided PCI was cost-effective over a wide range of threshold cost-effectiveness ratios. These results infer that FFR-guided PCI is a dominant treatment strategy compared to IVUS-guided PCI from the perspective of the Korean healthcare system.

FFR and IVUS are representative physiologic and anatomic diagnostic modalities, respectively, for deciding treatment strategies for CAD.[1)2)] Compared with coronary angiography alone, adding FFR or IVUS assessment demonstrated incremental information on treatment decision-making and better clinical outcomes.[3-8)] Furthermore, FFR-guided PCI and IVUS-guided PCI have demonstrated their cost-effectiveness compared to angiography-guided PCI.[32-34)] However, head-to-head comparison of FFR-guided PCI and IVUS-guide PCI has scarcely been performed. We recently reported the non-inferiority of FFR-guided PCI to IVUS-guided PCI in terms of the composite of death, myocardial infarction, or revascularization at 24 months.[9)] FFR-guided PCI resulted in the less frequent use of stents and administration of dual antiplatelet therapy than IVUS-guided PCI. Considering these

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marked differences in required medical resources between FFR- and IVUS-guided PCI, a cost-effectiveness comparison is needed.

In this cost-effectiveness analysis based on the FLAVOUR trial, FFR-guided PCI decreased lifetime healthcare costs from the perspective of the Korean healthcare system. This might be associated with a lower rate of PCI in the FFR-guided PCI group than in the IVUS-guided group, leading to less stent use and medication prescriptions. Also, the procedural cost of the FFR assessment is much lower than that of the IVUS assessment in Korea. For QALYs, FFR-guided PCI increases QALYs by 0.178 from 11.084 to 11.262 compared to IVUS-guided PCI. Even though the FLAVOUR trial showed similar patient-reported outcomes based on the SAQ at 24 months between FFR-guided PCI and IVUS-guided PCI,[9] the difference in QALYs can be attributed to a decrease in quality of life due to a higher proportion of PCI in the IVUS-guided PCI group and a decrease in life years due to a higher probability of cardiac death in the IVUS-guided PCI group in the long-term model.

Even though several assumptions and external data sources are inevitably applied to estimate this long-term cost-effectiveness, several sensitivity analyses showed consistent findings from the base-case analysis. From the one-way sensitivity analysis, cardiac death rates in the FFR-guided PCI group markedly affected the ICER, but the threshold of this probability affecting ICER toward the opposite direction was higher than in previous studies.[6][7] Other parameters could not change ICER toward the opposite direction. Notably, the PSA showed that the probability that FFR-guided PCI would be cost-effective under a WTP of USD 28,642/QALY gained was 75.3%, and FFR-guided PCI was dominant in 67.9% of the simulations. Combined with the base-case analysis, these results of sensitivity analyses support that FFR-guided PCI is a dominant treatment strategy compared to IVUS-guided PCI from the perspective of the Korean healthcare system.

Even though the current study showed consistent results, this study had several limitations. First, the health utilities used in this study had the advantage of being estimated from data collected from patients with intermediate stenosis in the FLAVOUR trial, but it had a limitation in that the SAQ responses were mapped to the EQ-5D rather than directly examining the EQ-5D. Second, we utilized most transition probabilities from the FLAVOUR trial, but several transition probabilities were from the previous registries. Third, we assumed that the risks of clinical events were consistent over 30 years in our model. Fourth, the current model reflected disutilities whenever an event occurred but did not consider the increase in the value of disutilities as the event was repeated. Fifth, the results of cost-effective analysis are affected by the economy, healthcare system, and medical costs in a given country. Therefore, the current results are confined to the Korean healthcare system. Sixth, unlike the FFR measurement, the IVUS assessment was not covered by Korean National Health Insurance. Therefore, the cost of IVUS assessment varied by hospital, and there is a possibility that the results may have been affected accordingly. However, this study used relatively reliable cost information collected from the Health Insurance Review and Assessment Service and also examined the impact of cost variations on the results by using the minimum and maximum values of this data. At least within the cost range of IVUS that we identified, cost variations did not significantly affect the results.

Based on the economic evaluation using the results of the FLAVOUR trial, FFR-guided PCI was found to be dominant compared to IVUS-guided PCI in Korea in intermediate coronary lesion, with lower costs and higher QALY gained.

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SUPPLEMENTARY MATERIALS

Supplementary Table 1

Baseline characteristics

Supplementary Table 2

Clinical outcomes based on intention to treat analysis

Supplementary Figure 1

Incremental cost-effectiveness ratio scatter plot. Probabilistic sensitivity analyses were performed on the base-case. This figure represented the results of probabilistic sensitivity analysis as an incremental cost-effectiveness scatter plot of intravascular ultrasound-guided percutaneous coronary intervention vs. fractional flow reserve-guided percutaneous coronary intervention.

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