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Cost-Effectiveness of Fractional Flow Reserve–Guided Treatment for Acute Myocardial Infarction and Multivessel Disease

A Prespecified Analysis of the FRAME-AMI Randomized Clinical Trial

David Hong, MD; Seung Hun Lee, MD; Jin Lee, MPH; Hankil Lee, PhD; Doosup Shin, MD; Hyun Kuk Kim, MD; Keun Ho Park, MD; Eun Ho Choo, MD; Chan Joon Kim, MD; Min Chul Kim, MD; Young Joon Hong, MD; Myung Ho Jeong, MD, PhD; Sung Gyun Ahn, MD; Joon-Hyung Doh, MD; Sang Yeub Lee, MD; Sang Don Park, MD; Hyun-Jong Lee, MD; Min Gyu Kang, MD; Jin-Sin Koh, MD; Yun-Kyeong Cho, MD; Chang-Wook Nam, MD; Ki Hong Choi, MD; Taek Kyu Park, MD; Jeong Hoon Yang, MD; Young Bin Song, MD; Seung-Hyuk Choi, MD; Hyeon-Cheol Gwon, MD; Eliseo Guallar, MD, PhD; Juhee Cho, PhD; Joo-Yong Hahn, MD; Danbee Kang, PhD; Joo Myung Lee, MD, MPH, PhD; for the FRAME-AMI Investigators

Abstract

IMPORTANCE Complete revascularization by non–infarct-related artery (IRA) percutaneous coronary intervention (PCI) in patients with acute myocardial infarction is standard practice to improve patient prognosis. However, it is unclear whether a fractional flow reserve (FFR)–guided or angiography-guided treatment strategy for non-IRA PCI would be more cost-effective.

OBJECTIVE To evaluate the cost-effectiveness of FFR-guided compared with angiography-guided PCI in patients with acute myocardial infarction and multivessel disease.

DESIGN, SETTING, AND PARTICIPANTS In this prespecified cost-effectiveness analysis of the FRAME-AMI randomized clinical trial, patients were randomly allocated to either FFR-guided or angiography-guided PCI for non-IRA lesions between August 19, 2016, and December 24, 2020. Patients were aged 19 years or older, had ST-segment elevation myocardial infarction (STEMI) or non-STEMI and underwent successful primary or urgent PCI, and had at least 1 non-IRA lesion (diameter stenosis >50% in a major epicardial coronary artery or major side branch with a vessel diameter of ≥2.0 mm). Data analysis was performed on August 27, 2023.

INTERVENTION Fractional flow reserve–guided vs angiography-guided PCI for non-IRA lesions.

MAIN OUTCOMES AND MEASURES The model simulated death, myocardial infarction, and repeat revascularization. Future medical costs and benefits were discounted by 4.5% per year. The main outcomes were quality-adjusted life-years (QALYs), direct medical costs, incremental cost-effectiveness ratio (ICER), and incremental net monetary benefit (INB) of FFR-guided PCI compared with angiography-guided PCI. State-transition Markov models were applied to the Korean, US, and European health care systems using medical cost (presented in US dollars), utilities data, and transition probabilities from meta-analysis of previous trials.

RESULTS The FRAME-AMI trial randomized 562 patients, with a mean (SD) age of 63.3 (11.4) years. Most patients were men (474 [84.3%]). Fractional flow reserve–guided PCI increased QALYs by 0.06 compared with angiography-guided PCI. The total cumulative cost per patient was estimated as $1208 less for FFR-guided compared with angiography-guided PCI. The ICER was −$19 484 and the INB was $3378, indicating that FFR-guided PCI was more cost-effective for patients with acute myocardial infarction and multivessel disease. Probabilistic sensitivity analysis showed consistent results and the likelihood iteration of cost-effectiveness in FFR-guided PCI was 97%. When transition probabilities from the pairwise meta-analysis of the FLOWER-MI and FRAME-AMI trials were used,

(continued)

Key Points

Question Is fractional flow reserve (FFR)–guided treatment for non–infarct-related artery (IRA) percutaneous coronary intervention (PCI) more cost-effective than angiography-guided treatment for patients with acute myocardial infarction and multivessel disease?

Findings In this prespecified analysis of the FRAME-AMI randomized clinical trial with 562 patients, FFR-guided PCI increased quality-adjusted life-years by 0.06 and decreased the total cumulative cost per patient (in US dollars) by $1208 compared with angiography-guided PCI. The incremental cost-effectiveness ratio was −$19 484 and the incremental net monetary benefit was $3378.

Meaning This study found that FFR-guided PCI for non-IRA lesions saved medical costs and increased quality of life better than angiography-guided PCI in patients with acute myocardial infarction and multivessel disease.

+ Invited Commentary

+ Supplemental content

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Abstract (continued)

FFR-guided PCI was more cost-effective than angiography-guided PCI in the Korean, US, and European health care systems, with an INB of $3910, $8557, and $2210, respectively. In probabilistic sensitivity analysis, the likelihood iteration of cost-effectiveness with FFR-guided PCI was 85%, 82%, and 31% for the Korean, US, and European health care systems, respectively.

CONCLUSIONS AND RELEVANCE This cost-effectiveness analysis suggests that FFR-guided PCI for non-IRA lesions saved medical costs and increased quality of life better than angiography-guided PCI for patients with acute myocardial infarction and multivessel disease. Fractional flow reserve–guided PCI should be considered in determining the treatment strategy for non-IRA stenoses in these patients.

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Introduction

Previous randomized clinical trials and registry data have shown that percutaneous coronary intervention (PCI) of non–infarct-related artery (IRA) lesions in patients with acute myocardial infarction with multivessel disease improves patient prognosis.[1-17] Based on these results, 2021 guidelines from the American College of Cardiology, American Heart Association, and Society for Cardiovascular Angiography and Interventions and 2018 guidelines from the European Society of Cardiology and European Association of Percutaneous Cardiovascular Interventions for myocardial revascularization recommend revascularization of non-IRA lesions before hospital discharge for patients with acute myocardial infarction with multivessel disease.[18-20]

The criteria for performing non-IRA PCI have not been clarified. Revascularization of non-IRA lesions based on angiographic severity assessed by visual estimation or quantitative coronary angiography[4,11,12] or functional significance assessed by fractional flow reserve (FFR)[7,9] had better clinical outcomes than IRA-only PCI. Two recent trials, FLOWER-MI (Flow Evaluation to Guide Revascularization in Multivessel ST-Elevation Myocardial Infarction)[14] and FRAME-AMI (Fractional Flow Reserve vs Angiography-Guided Strategy for Management of Non-Infarction Related Artery Stenosis in Patients With Acute Myocardial Infarction),[15] evaluated the comparative prognosis between FFR-guided vs angiography-guided PCI for non-IRA lesions in patients with acute myocardial infarction and multivessel disease. In both trials, FFR-guided PCI resulted in substantially lower rates of non-IRA PCI with fewer stents used than angiography-guided PCI. However, there were conflicting results regarding clinical outcomes between the 2 groups in both trials.[14,15] In the FLOWER-MI trial, FFR-guided PCI had similar risk in a composite of death, myocardial infarction, or unplanned hospitalization leading to urgent revascularization with angiography-guided PCI; in the FRAME-AMI trial, FFR-guided PCI substantially reduced risk in a composite of death, myocardial infarction, and repeat revascularization.

Given the heterogenous results in previous trials regarding which treatment provides better clinical outcomes, it is important to evaluate these strategies from a cost-effectiveness standpoint. Therefore, this prespecified analysis of the FRAME-AMI trial evaluated comparative cost-effectiveness between FFR-guided and angiography-guided PCI for non-IRA lesions among patients with acute myocardial infarction and multivessel disease.

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Methods

This prespecified analysis used data from the FRAME-AMI investigator-initiated, randomized, open-label, multicenter randomized clinical trial, which was conducted at 14 sites in Korea. The design and primary results of the FRAME-AMI trial have been published previously.[15] The trial protocol was approved by the institutional review board at each participating site (Supplement 1). All patients provided written informed consent before randomization. For patients presenting with conditions that precluded their understanding of the trial process, informed consent was obtained after stabilization by revascularization of IRA and a subsequent procedure for non-IRA was performed in a staged manner during the index hospitalization. Otherwise, informed consent was acquired before diagnostic coronary angiography and randomization was performed after successful primary or urgent PCI for IRA in patients that met the eligibility criteria.[15] eAppendices 1 to 4 in Supplement 2 provide detailed information on all participating centers and trial personnel, inclusion and exclusion criteria, definition of clinical events, and Seattle Angina Questionnaire analysis of FRAME-AMI. This study is reported according to the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) reporting guideline. The network and pairwise meta-analysis conducted both complied with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) reporting guideline.

Data Source

Briefly, patients aged 19 years or older with ST-segment elevation myocardial infarction (STEMI) or non-STEMI (NSTEMI) who underwent successful primary or urgent PCI of an IRA between August 19, 2016, and December 24, 2020, were candidates for enrollment. Patients were also required to have at least 1 non-IRA lesion with diameter stenosis greater than 50% in a major epicardial coronary artery or major side branch with a vessel diameter of 2.0 mm or greater by visual estimation judged to be amenable to PCI by operators. Key exclusion criteria were single-vessel disease, flow-limiting stenosis with a Thrombolysis in Myocardial Infarction flow grade of 2 or less in the non-IRA, target lesion located in the left main coronary artery, cardiogenic shock, and chronic total occlusion in non-IRA lesions. A total of 562 patients were randomly assigned to either FFR-guided PCI or angiography-guided PCI for non-IRA lesions. In the FFR-guided PCI group, FFR was measured in all non-IRA lesions with stenosis greater than 50% on visual estimation and only stenoses with an FFR of 0.80 or lower were treated with PCI. In the angiography group, any lesions with diameter stenosis greater than 50% on visual estimation were treated with PCI. The primary end point was a composite of time to death, MI, or repeat revascularization.

Statistical Analysis

Statistical analysis was planned in 2 ways. One analysis used actual individual patient data from the FRAME-AMI trial, and the other was based on the Markov model using previously published evidence.[12,14,15,21-31]

Cost-Effectiveness Analysis Using Trial Data

The primary economic evaluation was a within-trial cost-effectiveness analysis using the FRAME-AMI trial data undertaken from a health care system perspective. This cost-effectiveness analysis of the FRAME-AMI trial was prespecified and described in the trial protocol (Supplement 1) and at ClinicalTrials.gov (NCT02715518). A time horizon of 4 years was applied considering the median follow-up duration of the FRAME-AMI trial.

We calculated medical costs based on resource use during the index hospitalization and clinical events that occurred during subsequent follow-ups. Medical cost at the index hospitalization was calculated using the unit cost from the Korea Health Insurance Review and Assessment Service as well as from individual data regarding the number of guiding catheters, coronary guide wires, balloon catheters, stents, intravascular imaging devices, and hospital days for each patient in the trial log.

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Performance fees for IRA PCI, immediate non-IRA PCI, and staged non-IRA PCI from the Korea Health Insurance Review and Assessment Service were also included in the medical cost (**Table 1**). To calculate the medical cost at event, we assigned costs to postdischarge events based on previous studies (Table 1). Procedure-related myocardial infarction was not assigned a cost. In the analysis, costs are presented in US dollars (US$1 = ₩1200 and €1.07).

Utility is expressed as the difference in quality-adjusted life-years (QALYs) between the 2 strategies. Quality-adjusted life-years represent patient survival time weighted by quality of life, represented by a utility function. Quality-of-life indexes (utilities) were evaluated at 12 months using the Seattle Angina Questionnaire. Questionnaire scores were translated to European Quality of Life–5 Dimensions scores using a mapping algorithm.[32] The trial protocol did not mandate Seattle Angina Questionnaire completion, and 60% of patients completed the questionnaire at 1-year follow-up. We performed multiple imputations to account for the missing values. To estimate Seattle Angina

Table 1. Key Inputs in the Model

	Korean population		US population		European population	
Input	Value, $	Source	Value, $	Source	Value, $	Source
Cost[a]						
Medical cost at index hospitalization						
Angiography-guided PCI	9842	Lee et al,[15] 2023	14 878	Fearon et al,[21] 2010	7226	Le Bras et al,[29] 2022
FFR-guided PCI	9326		13 182		7647	
Unit cost per service or product, $						
IRA PCI performance fee	2126	Lee et al,[15] 2023	2005	Fearon et al,[23] 2013	202	Le Bras et al,[29] 2022
Immediate non-IRA PCI performance fee	435		796	Fearon et al,[26] 2018	202	
Staged non-IRA PCI performance fee	1357		567	Fearon et al,[22] 2013	194	
Drug-eluting stent, 1 each	1431		1656		613	
Pressure wire	709		650	Fearon et al,[21] 2010	428	
Guide wire	16		85		50	
Intensive care unit cost per day	74		2877		346-863	
Hospitalization cost per day	15		2000		578-820	
Medical cost at event						
Death from any cause	9235	Hwang et al,[30] 2023	35 818	Kazi et al,[24] 2014	1586	Le Bras et al,[29] 2022
Nonfatal MI	7338		16 544	Fearon et al,[21] 2010	5370	
Repeat revascularization	7292		12 780		4633	
Utility						
After PCI	0.79	Kodera et al,[27] 2019	0.92	Shaw et al,[31] 2008	0.85	Pocock et al,[28] 2021
Recurrent MI (disutility)	−0.06	Lewis et al,[25] 2014	−0.06	Lewis et al,[25] 2014	−0.06	Lewis et al,[25] 2014
Transition probability						
Death						
Angiography-guided PCI	0.02	Lee et al,[15] 2023	0.02	Mehta et al,[12] 2019	0.02	Puymirat et al,[14] 2021
FFR-guided PCI	0.007		0.01		0.01	
Angiography-guided vs FFR-guided PCI, HR (95% CI)	0.30 (0.11-0.83)		0.86 (0.50-1.83)	eFigure in Supplement 2	0.89 (0.36-2.20)	
Recurrent MI						
Angiography-guided PCI	0.01	Lee et al,[15] 2023	0.02	Mehta et al,[12] 2019	0.02	Puymirat et al,[14] 2021
FFR-guided PCI	0.008		0.03		0.03	
Angiography-guided vs FFR-guided PCI, HR (95% CI)	0.32 (0.13-0.75)		1.31 (0.51-4.21)	eFigure in Supplement 2	1.77 (0.82-3.84)	
Repeat revascularization						
Angiography-guided PCI	0.01	Lee et al,[15] 2023	0.005	Mehta et al,[12] 2019	0.02	Puymirat et al,[14] 2021
FFR-guided PCI	0.009		0.004		0.03	
Angiography-guided vs FFR-guided PCI, HR (95% CI)	0.61 (0.28-1.34)		0.87 (0.37-2.09)	eFigure in Supplement 2	1.34 (0.62-2.92)	

Abbreviations: FFR, fractional flow reserve; HR, hazard ratio; IRA, infarct-related artery; MI, myocardial infarction; PCI, percutaneous coronary intervention.

[a] Exchange rate calculated with ratios between $1 and ₩1200 and between $1 and €1.07.

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Questionnaire scores, a linear regression model was constructed among patients who were measured for utility and did not experience recurrent myocardial infarction until 1-year follow-up with the following variables: assigned treatment group (FFR-guided or angiography-guided PCI), intended timing of non-IRA PCI (immediate or staged non-IRA PCI during index hospitalization), location of non-IRA (left anterior descending artery or non-left anterior descending artery), initial presentation (STEMI or NSTEMI), sex (male or female), age (<65 or ≥65 years), diabetes, left ventricular ejection fraction (<50% or ≥50%), and $P2Y_{12}$ inhibitor type (clopidogrel, ticagrelor, or prasugrel). The estimated coefficients were used to generate utility values for patients who did not have utility data. If the patient experienced recurrent myocardial infarction, the score was adjusted using disutility. Both utilities estimated from trial data and from the previous study were used.[27] The disutility weight of the state after recurrent myocardial infarction was obtained from a previous study in both analyses (Table 1).[25]

The cost-effectiveness of FFR-guided PCI was expressed as the incremental cost-effectiveness ratio (ICER), defined as the difference in cumulative costs divided by the difference in cumulative QALYs. We computed CIs for differences in costs and QALYs and in ICERs using the bootstrap technique with the percentile method with 25 000 replications. We also calculated the incremental net monetary benefit (INB).[33] The INB can be computed as the difference between incremental QALYs multiplied by the willingness-to-pay (WTP) threshold and incremental cost: $INB = (\Delta QALY \times WTP) - \Delta Cost$.[33] A positive INB (>0) indicates that the FFR-guided PCI is cost-effective compared with angiography-guided PCI at the given threshold of WTP, whereas a negative INB indicates that FFR-guided PCI is not cost-effective relative to angiography-guided PCI.[33]

Multiple sensitivity analyses were conducted to assess the robustness of the findings. First, probabilistic sensitivity analysis using Monte Carlo simulation was performed to further assess intraindividual and parameter uncertainties.[34] In the probabilistic sensitivity analysis, patients were randomly sampled and simulations were repeated 25 000 times. Using bayesian statistical principles, we used a prior distribution that is commonly specified depending on the characteristics of the model parameters. As for the input variable ranges in the simulation, a log-normal distribution was used for transitional probabilities with a 95% CI from the previous literature (Table 1), a β distribution for utilities with values between 0 and 1 and a range variation of 10%, and a γ distribution for costs (ie, costs could not be <0), with a range variation the same as the mean, to accurately represent cost variability.[35] Second, utility data were extrapolated from previous studies and the same analysis was performed to compensate for the incompleteness of calculating utility through the Seattle Angina Questionnaire.[25,27] Third, planned subgroup analyses regarding cost-effectiveness of FFR-guided PCI were performed according to the intended timing of non-IRA PCI, location of non-IRA, initial presentation, sex, age, diabetes, left ventricular ejection fraction, and $P2Y_{12}$ inhibitor type.

Cost-Effectiveness Analysis Using a Markov Model

In the secondary analysis, we performed a cost-effectiveness analysis of FFR-guided PCI in 3 different health care systems (Korean, US, and European) using a Markov model. We used a 2-state Markov model in which the simulated patients can exist in either (1) myocardial infarction or (2) death. Patients initially allocated to myocardial infarction could either remain in that same state or transition to death in every cycle, according to transition probability. Patients who experienced recurrent myocardial infarction or repeat revascularization remained in the same state, and disutility was only applied in the case of recurrent myocardial infarction. A time horizon of 4 years was applied for the model, as done for the within-trial cost-effectiveness analysis.

Medical costs at index hospitalization were obtained from the FRAME-AMI trial[15] for the Korean population, the FAME and FAME 2 (Fractional Flow Reserve Versus Angiography for Multivessel Evaluation) trials[21,26] for the US population, and the FLOWER-MI trial[14] for the European population. We assigned costs to postdischarge events based on previous studies (Table 1). Cost and utility data were discounted by an annual rate of 4.5%, according to the Korean Guidelines of Methodological

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Standards for economic evaluation, and by 3.5% for US and European cost and utility based on previous literature.[36] We projected the discounted lifetime health care cost by multiplying the number of patients with the sum of the costs in every health status. Total QALYs were accumulated from the QALY values in each cycle. In the Korean, US, and European health care systems, values of $35 000, $60 000, and $40 000 per QALY were considered a reasonable WTP threshold based on the gross domestic product per capita.

Transition probability for the Korean population was acquired from the FRAME-AMI trial.[15] Since there was no head-to-head trial comparing FFR-guided and angiography-guided PCI in patients with acute myocardial infarction and multivessel disease in the US, transition probabilities for the US population were obtained from the COMPLETE trial (Complete Versus Culprit-Only Revascularization Strategies to Treat Multivessel Disease After Early PCI for STEMI) for angiography-guided PCI.[12] The transition probability of FFR-guided PCI was obtained by multiplying the transition probability of angiography-guided PCI and the odds ratio (OR) between FFR-guided and angiography-guided PCI calculated from a network meta-analysis of 14 trials. For the European population, transition probabilities were obtained from the FLOWER-MI trial.[14] To confirm the robustness of cost-effectiveness analysis, 2 models with different transition probabilities were constructed: model 1 used transition probabilities from the network meta-analysis of 14 trials (eTable 1 in Supplement 2),[1-15] and model 2 used transition probabilities from a pairwise meta-analysis of the FRAME-AMI and FLOWER-MI trials.

For the network meta-analysis, a bayesian random-effects model was used to calculate ORs with 95% credible intervals (CRIs), which were calculated with the gemtc package in R, version 4.1.0 (R Project for Statistical Computing). We ran Markov chain Monte Carlo samplers, running 4 chains with different starting values. A burn-in phase of 10 000 iterations was followed by 50 000 updates, in which the number of burn-in iterations was chosen according to the Brooks-Gelman-Rubin method for convergence checks.[37] For the pairwise meta-analysis, pooled ORs with 95% CIs were calculated using the DerSimonian and Laird method for the random-effects model. The probabilistic sensitivity analysis was conducted with the same method as the within-trial cost-effective analysis. All analyses were performed using R, version 4.1.0, and Stata, version 16 (StataCorp LP). Data analysis was performed on August 27, 2023.

Results

A total of 562 FRAME-AMI patients with acute myocardial infarction and multivessel disease underwent randomization: 284 to receive FFR-guided PCI and 278 to receive angiography-guided PCI for non-IRA lesions. Their mean (SD) age was 63.3 (11.4) years, and there were 474 men (84.3%) and 88 women (15.7%). A total of 265 patients (47.2%) presented with STEMI and 297 patients (52.8%) presented with NSTEMI. Non-IRA lesions were treated with immediate PCI after successful treatment of IRA in 337 patients (60.0%) and with a staged procedure during the same hospitalization in 225 patients (40.0%). In the FFR-guided PCI group, PCI was performed in 182 patients (64.1%) and deferred in 102 patients (35.9%) with non-IRA lesions, whereas 270 patients (97.1%) underwent PCI for non-IRA lesions in the angiography-guided PCI group. In the FFR-guided PCI group, FFR was measured in 83.2% of non-IRA lesions and the treatment decision was made based on the FFR value. Among the non-IRA lesions evaluated with FFR, 49.5% of interrogated lesions had an FFR greater than 0.80 and 50.5% had an FFR of 0.80 or less. In 16.8% of non-IRA lesions, PCI was performed without FFR measurement due to diameter stenosis greater than 90% in non-IRA lesions. The mean (SD) number of stents used per patient for non-IRA lesions was 0.9 (0.9) in the FFR-guided PCI group and 1.3 (0.7) in the angiography-guided PCI group ($P < .001$). The total mean (SD) number of stents used per patient for both IRA and non-IRA PCI was 2.2 (1.1) in the FFR-guided PCI group and 2.5 (0.9) in the angiography-guided PCI group ($P < .001$).

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At a median follow-up of 3.5 years (IQR, 2.7-4.1 years), the FFR-guided PCI group had a significantly lower risk of the primary end point than the angiography-guided PCI group (Kaplan-Meier event rates at 4 years, 7.4% vs 19.7%; hazard ratio [HR], 0.43 [95% CI, 0.25-0.75]; *P* = .003). Kaplan-Meier event rates for death at 4 years were 2.1% vs 8.5% (HR, 0.30 [95% CI, 0.11-0.83]; *P* = .02) and those for myocardial infarction were 2.5% vs 8.9% (HR, 0.32 [95% CI, 0.13-0.75]; *P* = .009) in the FFR-guided and angiography-guided PCI groups, respectively. There was no significant difference in repeat revascularization between the 2 groups (4.3% vs 9.0%; HR, 0.61 [95% CI, 0.28-1.34]; *P* = .22) (Table 1).

Within-Trial Cost-Effectiveness Analysis

The 4-year QALY was 3.46 vs 3.40 for the FFR-guided and angiography-guided PCI groups, respectively. Regarding the effectiveness, there was a gain of 0.06 QALYs in the FFR-guided PCI group compared with the angiography-guided PCI group at 4 years. The total cumulative cost per patient in the FFR-guided PCI group was estimated as $1208 less than that for the angiography-guided PCI group. Consequently, the INB was $3378, suggesting that FFR-guided PCI was more cost-effective than angiography-guided PCI. Overall, the ICER was −$19 484, indicating that FFR-guided PCI was the dominant strategy for patients with acute myocardial infarction and multivessel disease (**Table 2**). The probabilistic sensitivity analysis showed consistent results and the likelihood iteration of cost-effectiveness in FFR-guided PCI was 97% (**Figure 1**). Similar results were also shown, with an INB of $4253 and ICER of −$13 885 when different utilities from the previous literature were applied

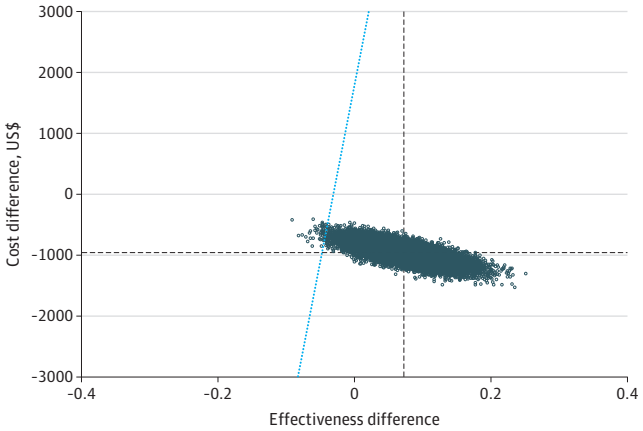
Table 2. Cost-Effectiveness of FFR-Guided PCI Relative to Angiography-Guided PCI in the FRAME-AMI Trial

Utilities	Cost, $[a]		QALYs		Cost-effectiveness, ICER ($/QALY)	INB, $
	Total	Incremental	Total	Incremental		
Estimated from data						
Angiography-guided PCI	11 057	Reference	3.40	Reference	NA	NA
FFR-guided PCI	9849	−1208	3.46	0.062	−19 484	3378
Extrapolated						
Angiography-guided PCI	11 057	Reference	3.12	Reference	NA	NA
FFR-guided PCI	9849	−1208	3.21	0.087	−13 885	4253

Abbreviations: FFR, fractional flow reserve; FRAME-AMI, Fractional Flow Reserve vs Angiography-Guided Strategy for Management of Non-Infarction Related Artery Stenosis in Patients With Acute Myocardial Infarction; ICER, incremental cost-effectiveness ratio; INB, incremental net monetary benefit; NA, not applicable; PCI, percutaneous coronary intervention; QALY, quality-adjusted life-year.

[a] Exchange rate calculated with ratio between $1 and ₩1200.

Figure 1. Cost-Effectiveness of Fractional Flow Reserve (FFR)–Guided vs Angiography-Guided Percutaneous Coronary Intervention (PCI) in the FRAME-AMI Trial



Replications of incremental cost-effectiveness of FFR-guided PCI compared with angiography-guided PCI. The incremental cost-effectiveness plane presents the impact of FFR-guided compared with angiography-guided PCI on the difference in quality-adjusted life-years (QALYs; until 4 years after PCI) and accompanying medical costs within this 4-year time period. Each of the 25 000 dots represents the results of 1 bootstrap replication. The diagonal dotted blue line indicates the willingness-to-pay (WTP) threshold of $35 000 per QALY added. The vertical dashed line represents the mean effectiveness difference; the horizontal dashed line, the mean cost difference.

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(Table 2). The cost-effectiveness of FFR-guided PCI relative to angiography-guided PCI was consistent across various subgroups (eTable 2 in Supplement 2).

Cost-Effectiveness Analysis Using a Markov Model

The network meta-analysis of 14 previous trials showed that there was no significant difference in the risk of death (OR, 0.86 [95% CRI, 0.50-1.83]), myocardial infarction (OR, 1.31 [95% CRI, 0.51-4.21]), and repeat revascularization (OR, 0.87 [95% CRI, 0.37-2.09]) between FFR-guided and angiography-guided PCI (eFigure in Supplement 2). When transition probabilities from the network meta-analysis were applied, FFR-guided PCI was accompanied by higher QALYs and lower medical costs in the Korean and US health care systems, represented by an INB of $1114 and $2451, respectively (**Table 3**). Conversely, FFR-guided PCI resulted in higher medical costs and similar QALYs with angiography-guided PCI in the European health care system. In probabilistic sensitivity analysis, the likelihood iteration of cost-effectiveness in FFR-guided PCI was 75%, 71%, and 40% in the Korean, US, and European health care systems, respectively (**Figure 2**).

In the pairwise meta-analysis of the FLOWER-MI and FRAME-AMI trials, pooled ORs for death, MI, and repeat revascularization were 0.53 (95% CI, 0.18-1.54), 0.76 (95% CI, 0.14-4.07), and 0.99 (95% CI, 0.42-2.37), respectively (eFigure in Supplement 2). When transition probabilities from the pairwise meta-analysis of the FLOWER-MI and FRAME-AMI trials were used, FFR-guided PCI was the dominant treatment in all 3 health care systems, with an INB of $3910, $8557, and $2210, respectively (Table 3). In the probabilistic sensitivity analysis, the likelihood iteration of cost-effectiveness in FFR-guided PCI was 85%, 82%, and 31% in the Korean, US, and European health care systems, respectively (Figure 2).

Discussion

This prespecified analysis of the FRAME-AMI trial showed that FFR-guided PCI saved medical costs and increased quality of life better than angiography-guided PCI in patients with acute myocardial infarction and multivessel disease. The greater cost-effectiveness of FFR-guided PCI was similarly observed across various planned subgroup analysis. A sensitivity analysis with Markov models using medical costs from individual trials and transition probabilities from meta-analyses suggested that FFR-guided PCI would be more cost-effective than angiography-guided PCI across the Korean, US, and European health care systems.

Table 3. Cost-Effectiveness of FFR-Guided PCI Relative to Angiography-Guided PCI Across 3 Different Health Care Systems

Health care system	Cost, $			QALYs[a]			INB, $
	Angiography-guided PCI	FFR-guided PCI	Incremental	Angiography-guided PCI	FFR-guided PCI	Incremental	
Model 1[b]							
Korea	12 437	11 956	−480	2.68	2.70	0.02	1114
US	22 718	21 156	−1562	3.24	3.25	0.01	2451
Europe	8288	8916	627	2.99	3.00	0.01	−154
Model 2[c]							
Korea	12 437	10 928	−1509	2.68	2.75	0.07	3910
US	22 718	18.014	−4703	3.24	3.30	0.06	8557
Europe	8288	8405	116	2.99	3.05	0.06	2210

Abbreviations: FFR, fractional flow reserve; INB, incremental net monetary benefit; PCI, percutaneous coronary intervention; QALY, quality-adjusted life-year.

[a] In the Korean, US, and European health care systems, values of $35 000, $60 000, and $40 000 per QALY were considered a reasonable willingness-to-pay threshold based on the gross domestic product per capita.

[b] Transition probabilities were estimated from a network meta-analysis of 14 trials, including FLOWER-MI (Flow Evaluation to Guide Revascularization in Multivessel ST-Elevation Myocardial Infarction) and FRAME-AMI (Fractional Flow Reserve vs Angiography-Guided Strategy for Management of Non-Infarction Related Artery Stenosis in Patients With Acute Myocardial Infarction).

[c] Transition probabilities were estimated from pairwise meta-analysis of the FLOWER-MI and FRAME-AMI trials.

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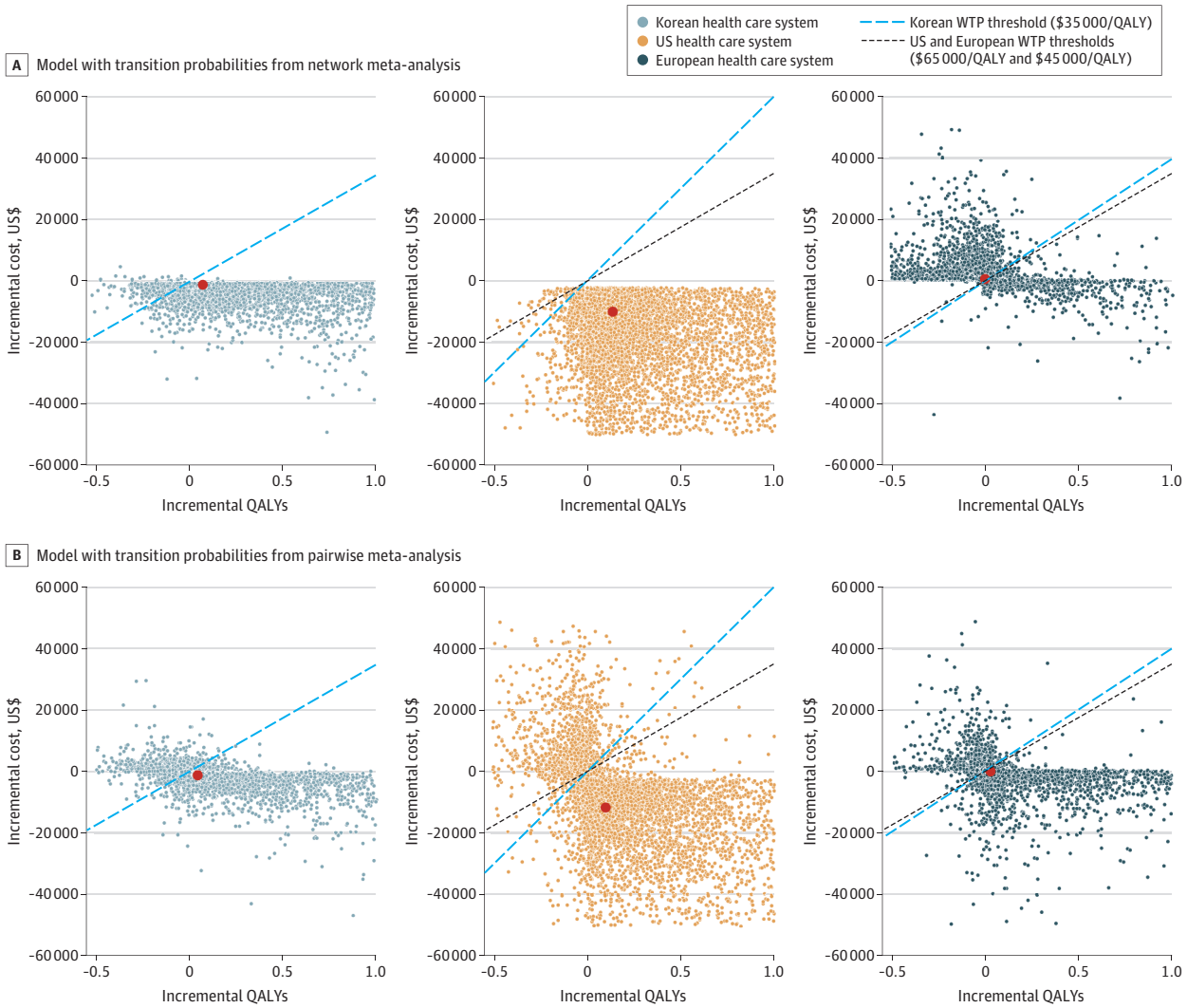
Complete revascularization for non-IRA decreases adverse clinical events compared with IRA-only PCI in patients with acute myocardial infarction and multivessel disease. However, whether selective FFR-guided non-IRA PCI or routine non-IRA PCI based on angiographic findings is better for patient prognosis is still debated. Previous studies have consistently shown that most intermediate coronary artery stenoses viewed with angiography do not have functional significance,[38] and the angiographic severity of non-IRA lesions can be overestimated in the acute phase of MI, leading to stenting hemodynamically insignificant lesions.[39] Furthermore, the prognostic benefit of non-IRA PCI was observed only in patients with non-IRA stenosis with diameter stenosis of 80% or greater by visual assessment or 60% or greater on laboratory assessment in the COMPLETE trial.[12] Moreover, total infarct size and ischemic burden were similar between angiography-guided complete revascularization and IRA-only PCI in the cardiac magnetic resonance

Figure 2. Cost-Effectiveness of Fractional Flow Reserve (FFR)–Guided vs Angiography-Guided Percutaneous Coronary Intervention (PCI) in 3 Health Care Systems



Transition probabilities from the network meta-analysis of 14 trials, including the FLOWER-MI and FRAME-AMI trials (A) and with pairwise meta-analysis of the FLOWER-MI and FRAME-AMI trials (B), were used in the cost-effectiveness analysis. The incremental cost-effectiveness plane illustrates the impact of FFR-guided PCI compared with angiography-guided PCI on the difference in quality-adjusted life-years (QALYs; up to 4 years after PCI) and the associated medical costs within this 4-year period. A Monte Carlo simulation was conducted, in which patients were randomly selected and simulations were repeated 25 000 times to generate the outcomes (represented as dots). The difference in cumulative costs is displayed on the vertical axis, and the difference in QALYs is displayed on the horizontal axis. Graphs display the Korean willingness-to-pay (WTP) thresholds for the Korean ($35 000/QALY), US ($65 000/QALY), and European ($45 000/QALY) health care systems. Red dots represent mean incremental cost-effectiveness ratios.

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substudy of the CvLPRIT trial (Complete Versus Lesion-Only Primary PCI Pilot Study).[40] Therefore, routine angiography-guided PCI for all non-IRA lesions with diameter stenosis greater than 50%, even without inducible myocardial ischemia, may be accompanied by unnecessary procedures with additional stents, greater contrast media use, and increased risk of procedure-related complications, which may result in worse long-term patient prognosis. In this regard, FFR-guided PCI would reduce unnecessary PCI for functionally insignificant stenosis and would be superior to angiography-guided PCI for patients with stable ischemic heart disease and for those with acute myocardial infarction and multivessel disease.[18-20] However, 2 recent trials that directly compared FFR-guided and angiography-guided PCI in patients with acute myocardial infarction and multivessel disease showed conflicting results.[14,15] Based on the heterogenous results from these 2 trials, it is important to clarify the cost-effectiveness of each strategy.

This study evaluated the cost-effectiveness of FFR-guided PCI in multiple ways. By using actual medical cost and utility values in the FRAME-AMI trial data, FFR-guided PCI was deemed the dominant strategy compared with angiography-guided PCI. Consistent results were observed when utility values were extrapolated from a previous study,[27] probabilistic sensitivity analysis, and multiple subgroup analyses. In addition, cost-effectiveness of FFR-guided PCI was also shown across 3 different health care systems using Markov models. The cost-effectiveness of FFR-based PCI was more remarkable for the US health care system, which has higher medical costs than the Korean and European health care systems. This difference in cost-effectiveness was mainly attributable to relatively higher medical costs incurred when adverse clinical events were treated in the US. It should be noted that the results of the network meta-analysis and pairwise meta-analysis were slightly different for the European health care system; this was due to the different transition probability, especially for myocardial infarction, between the network meta-analysis (OR, 1.31 [95% CRI, 0.51-4.21]) and pairwise meta-analysis (OR, 0.76 [95% CI, 0.14-4.07]), originating from the discordant results between the FLOWER-MI and FRAME-AMI trials.

Nevertheless, the overall analysis results support that FFR-guided PCI was the dominant strategy compared with angiography-guided PCI. Of note, deferral of PCI for non-IRA based on FFR provided at least comparable clinical outcomes in the FLOWER-MI trial or superior clinical outcomes in the FRAME-AMI trial compared with angiography-guided PCI. Considering that FFR-guided PCI resulted in much lower rates of non-IRA PCI than angiography-guided PCI in both trials, it should be noted that FFR-guided PCI would save additional medical resources and costs without an apparent safety signal for patient prognosis. Further trials with larger sample sizes, such as FULL REVASC,[41] OPTION-STEMI,[42] and COMPLETE 2,[43] would further clarify the role of FFR-guided PCI in patients with acute myocardial infarction and multivessel disease.

Limitations

The following limitations of this study should be considered. First, the results of the cost-effectiveness analysis were dependent on key input values, such as transition probability, medical costs, and utilities, which were obtained through limited previous studies. Therefore, application of our results to other health care systems is limited. Second, all of the previous trials excluded patients with left main coronary artery disease or chronic total occlusion in non-IRA lesions. Further trials are required to clarify whether complete revascularization, including chronic total occlusion in non-IRA, would have prognostic benefit and cost-effectiveness over IRA-only PCI in patients with acute myocardial infarction and multivessel disease. Third, the FRAME-AMI trial was terminated earlier than initially planned due to the COVID-19 pandemic; therefore, potential overestimation of the treatment effect as well as a resulting loss of power should be considered in interpreting our results. Fourth, we used a published approach to convert Seattle Angina Questionnaire scores to quality-of-life measures, but these instruments measure different aspects of quality of life.

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Conclusions

This cost-effectiveness prespecified analysis of the FRAME-AMI randomized clinical trial suggests that FFR-guided PCI for non-IRA lesions saved medical costs and increased quality of life compared with angiography-guided PCI in patients with acute myocardial infarction and multivessel disease. In conclusion, FFR-guided PCI should be considered when determining the treatment strategy for non-IRA stenoses in these patients.

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Corresponding Authors: Danbee Kang, PhD, Department of Clinical Research Design and Evaluation, Samsung Advanced Institute for Health Sciences and Technology, Sungkyunkwan University, and Center for Clinical Epidemiology, Samsung Medical Center, 115 Irwon-ro, Gangnam-gu, Seoul 06335, South Korea (dbee.kang@g.skku.edu); and Joo Myung Lee, MD, MPH, PhD, Department of Internal Medicine and Cardiovascular Center, Heart Vascular Stroke Institute, Samsung Medical Center, 50 Irwon-dong, Gangnam-gu, Seoul 135-710, Republic of Korea (drone80@hanmail.net or joomyung.lee@samsung.com).

Author Affiliations: Heart Vascular Stroke Institute, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea (D. Hong, K. H. Choi, T. K. Park, Yang, Song, S.-H. Choi, Gwon, Hahn, J. M. Lee); Chonnam National University Hospital, Gwangju, Korea (S. H. Lee, M. C. Kim, Y. J. Hong, Jeong); Center for Clinical Epidemiology, Samsung Medical Center, Sungkyunkwan University, Seoul, South Korea (J. Lee, J. Cho, D. Kang); Department of Clinical Research Design and Evaluation, Samsung Advanced Institute for Health Sciences and Technology, Sungkyunkwan University, Seoul, South Korea (J. Lee, J. Cho, D. Kang); College of Pharmacy, Ajou University, Suwon, South Korea (H. Lee); Division of Cardiology, Department of Internal Medicine, Duke University Medical Center, Durham, North Carolina (Shin); Chosun University Hospital, University of Chosun College of Medicine, Gwangju, Korea (H. K. Kim, K. H. Park); Seoul St Mary's Hospital, The Catholic University of Korea, Seoul, Korea (Choo); Uijeongbu St Mary's Hospital, The Catholic University of Korea, Seoul, Korea (C. J. Kim); Yonsei University Wonju College of Medicine, Wonju Severance Christian Hospital, Wonju, Korea (Ahn); Department of Medicine, Inje University Ilsan Paik Hospital, Goyang, Korea (Doh); Chung-Ang University College of Medicine, Chung-Ang University Gwangmyeong Hospital, Gwangmyeong, Korea (S. Y. Lee); Inha University Hospital, Incheon, Korea (Don Park); Sejong General Hospital, Bucheon, Korea (H.-J. Lee); Gyeongsang National University School of Medicine, Gyeongsang National University Hospital, Jinju, Korea (M. G. Kang, Koh); Keimyung University Dongsan Medical Center, Daegu, Korea (Y.-K. Cho, Nam); Department of Epidemiology and Medicine, Welch Center for Prevention, Epidemiology and Clinical Research, Johns Hopkins Medical Institutions, Baltimore, Maryland (Guallar).

Author Contributions: Drs D. Kang and J.M. Lee had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Drs D. Hong and S.H. Lee contributed equally to this work as co–first authors.

Concept and design: D. Hong, S.H. Lee, K.H. Park, T.K. Park, Yang, Gwon, D. Kang, J.M. Lee.

Acquisition, analysis, or interpretation of data: D. Hong, S.H. Lee, J. Lee, H. Lee, Shin, H.K. Kim, Choo, C.J. Kim, M.C. Kim, Y.J. Hong, Jeong, Ahn, Doh, S.Y. Lee, S.D. Park, H.-J. Lee, M.G. Kang, Koh, Y.-K. Cho, Nam, K.H. Choi, T.K. Park, Song, S.-H. Choi, Guallar, J. Cho, Hahn, D. Kang, J.M. Lee.

Drafting of the manuscript: D. Hong, S.H. Lee, Jin Lee, Yang, D. Kang, J.M. Lee.

Critical review of the manuscript for important intellectual content: D. Hong, S.H. Lee, H. Lee, Shin, H.K. Kim, K.H. Park, Choo, C.J. Kim, M.C. Kim, Y.J. Hong, Jeong, Ahn, Doh, S.Y. Lee, S.D. Park, H.-J. Lee, M.G. Kang, Koh, Y.-K. Cho, Nam, K.H. Choi, T.K. Park, Yang, Song, S.-H. Choi, Gwon, Guallar, J. Cho, Hahn, D. Kang, J.M. Lee.

Statistical analysis: D. Hong, S.H. Lee, J. Lee, H. Lee, Guallar, J. Cho, D. Kang, J.M. Lee.

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Administrative, technical, or material support: K.H. Park, Ahn, S.D. Park, M.G. Kang, T.K. Park, Song, Gwon, Hahn, J.M. Lee.

Supervision: S.H. Lee, H.K. Kim, C.J. Kim, M.C. Kim, Y.J. Hong, Jeong, Doh, S.Y. Lee, Koh, K.H. Choi, T.K. Park, Yang, S.-H. Choi, Gwon, J. Cho, Hahn, J.M. Lee.

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Data Sharing Statement: See Supplement 3.

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SUPPLEMENT 1.
Trial Protocol

SUPPLEMENT 2.
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eAppendix 3. Definition of Clinical Events
eAppendix 4. Seattle Angina Questionnaire Analysis
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eReferences

SUPPLEMENT 3.
Data Sharing Statement

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