

## Cost analysis of non-invasive fractional flow reserve derived from coronary computed tomographic angiography in Japan

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Received: 12 May 2014 / Accepted: 26 June 2014 / Published online: 17 July 2014  
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**Abstract** Percutaneous coronary intervention (PCI) based on fractional flow reserve (FFR<sub>cath</sub>) measurement during invasive coronary angiography (CAG) results in improved patient outcome and reduced healthcare costs. FFR can now be computed non-invasively from standard coronary CT angiography (cCTA) scans (FFR<sub>CT</sub>). The purpose of this study is to determine the potential impact of non-invasive FFR<sub>CT</sub> on costs and clinical outcomes of patients with suspected coronary artery disease in Japan. Clinical data from 254 patients in the HeartFlowNXT trial, costs of goods and services in Japan, and clinical outcome data from the literature were used to estimate the costs and outcomes of 4 clinical pathways: (1) CAG-visual guided PCI, (2) CAG-FFR<sub>cath</sub> guided PCI, (3) cCTA followed by CAG-visual guided PCI, (4) cCTA-FFR<sub>CT</sub> guided PCI. The CAG-visual strategy demonstrated the highest projected

cost (\$10,360) and highest projected 1-year death/myocardial infarction rate (2.4 %). An assumed price for FFR<sub>CT</sub> of US \$2,000 produced equivalent clinical outcomes (death/MI rate: 1.9 %) and healthcare costs (\$7,222) for the cCTA-FFR<sub>CT</sub> strategy and the CAG-FFR<sub>cath</sub> guided PCI strategy. Use of the cCTA-FFR<sub>CT</sub> strategy to select patients for PCI would result in 32 % lower costs and 19 % fewer cardiac events at 1 year compared to the most commonly used CAG-visual strategy. Use of cCTA-FFR<sub>CT</sub> to select patients for CAG and PCI may reduce costs and improve clinical outcome in patients with suspected coronary artery disease in Japan.

**Keywords** Fractional flow reserve · Non-invasive diagnosis · Cost-effectiveness · Computational fluid dynamics · Coronary computed tomographic angiography

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## Introduction

Prior studies have shown clinical and economic benefits from assessing and utilizing invasive fractional flow reserve (FFR<sub>cath</sub>) measurements to guide percutaneous coronary intervention (PCI). In the randomized controlled fractional flow reserve versus angiography for multivessel evaluation (FAME) study including 1,005 patients, it was demonstrated that deferring PCI in vessels not associated with myocardial ischemia based on FFR<sub>cath</sub> resulted in improved clinical outcomes and lower costs [1, 2]. Furthermore, the FAME II study involving 888 patients demonstrated that PCI in vessels associated with myocardial ischemia based on FFR<sub>cath</sub> significantly reduced urgent revascularization when compared to medical therapy alone [3]. In all studies published to date, invasive FFR has been assessed during angiography (FFR<sub>cath</sub>). While FFR<sub>cath</sub> is widely recommended and offers clinical and economic benefits, it is not yet widely used due to inconvenience and costs [4].

A new technology based on standard coronary computed tomographic angiography (cCTA) allows FFR to be estimated non-invasively (FFR<sub>CT</sub>) before sending a patient to angiography. Three prospective, multicenter, validation studies have been performed (DISCOVER-FLOW—diagnosis of ischemia-causing stenosis obtained via non-invasive fractional flow reserve [5]; DeFACTO—determination of fractional flow reserve by anatomic computed tomographic angiography [6]; and HeartFlowNXT—HeartFlow analysis of coronary blood flow using CT angiography: NeXT steps [7] to determine the diagnostic accuracy of FFR<sub>CT</sub> using FFR<sub>cath</sub> as the reference standard. Good concordance between FFR<sub>CT</sub> and FFR<sub>cath</sub> was found with high diagnostic accuracy of FFR<sub>CT</sub> for the detection or exclusion of hemodynamically significant stenosis using FFR  $\leq 0.80$  as the reference standard.

An analysis of potential costs and consequences of utilizing FFR<sub>CT</sub> to guide clinical decision-making in the United States has suggested the possibility of meaningful cost savings and clinical benefits [8]. In the present paper, we report a similar analysis, using data from the most recently published trial, HeartFlowNXT [7], as well as Japanese procedure and device cost information. The primary objective of this analysis is to determine the potential magnitude of cost savings and clinical benefit which could be expected in Japan through utilization of FFR<sub>CT</sub>.

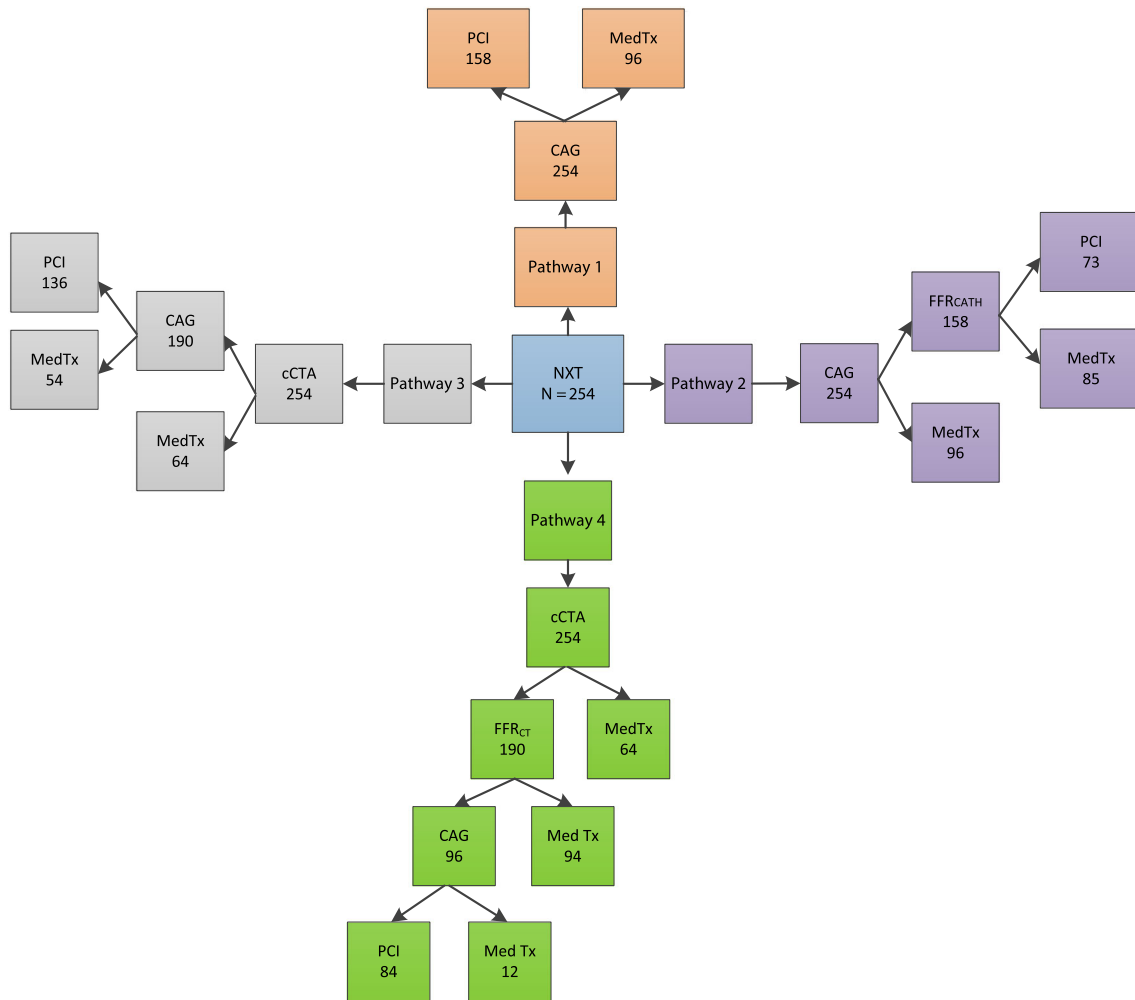
## Methods

We used data from 254 patients enrolled in the HeartFlowNXT trial [7]. All patients had known or suspected stable coronary artery disease (CAD) and were scheduled

for coronary angiography (CAG). Each patient in the trial was evaluated with cCTA, FFR<sub>CT</sub>, clinically-indicated CAG and FFR<sub>cath</sub>. Calculation of FFR<sub>CT</sub> from standard acquired cCTA images and evaluation of FFR<sub>cath</sub> were performed independently at core laboratories [7]. The study results demonstrated that FFR<sub>CT</sub> provided high per-patient diagnostic accuracy (81 %) for the detection of hemodynamically significant CAD with a sensitivity of 86 % (95 % CI 77–92 %) and specificity of 79 % (95 % CI 72–84 %) using FFR<sub>cath</sub> as the reference standard. FFR<sub>CT</sub> also provided excellent discrimination of patients with and without lesion-specific ischemia with an area under the receiver-operating characteristics curve of 0.90 (95 % CI 0.87–0.94 %) [7]. Using patient-specific data from this study, we modeled four hypothetical diagnostic/treatment pathways for patients with known or suspected CAD who are scheduled for coronary angiography (Fig. 1):

1. Pathway 1: CAG-visual: all patients undergo coronary angiography as scheduled. Those with  $\geq 50$  % stenosis by visual assessment of angiographic images undergo PCI.
2. Pathway 2: CAG-FFR<sub>cath</sub>: all patients undergo angiography as scheduled. Those patients with  $\geq 50$  % stenosis undergo FFR<sub>cath</sub> and only those with FFR<sub>cath</sub>  $\leq 0.80$  undergo PCI.
3. Pathway 3: cCTA-CAG: all patients undergo cCTA. Only those with  $\geq 50$  % cCTA stenosis undergo CAG. Those with  $\geq 50$  % stenosis by visual assessment of the angiogram undergo PCI.
4. Pathway 4: cCTA-FFR<sub>CT</sub>-CAG: all patients undergo cCTA. Those with  $\geq 50$  % stenosis by cCTA undergo FFR<sub>CT</sub>. Only those with FFR<sub>CT</sub>  $\leq 0.80$  undergo CAG and PCI is performed after visual angiographic confirmation of the stenosis.

For each pathway, we estimated the costs in Japan in accord with the Japanese Ministry of Health, Labour and Welfare (MHLW) medical insurance medical expense database [9]. We considered cost data from the detailed economic analysis in the 2 years follow-up report of the FAME study [1] and applied the conversion rate of 93.42 Yen/Dollar. The peri-procedural costs utilized in this study are shown in Table 1. While the actual cost of FFR<sub>CT</sub> analysis has not yet been determined, for the purposes of this analysis, we sought the cost of FFR<sub>CT</sub> which produced equivalence between the costs of Pathway 2 and Pathway 4. This was calculated to be \$2,000, which is comparable to the FFR<sub>cath</sub> disposable costs + CAG procedure fee as reimbursed by the MHLW medical insurance. The analysis of each pathway involved totaling the costs for each test and procedure described for all patients in that pathway and dividing by the total number of patients (254) giving the average cost per patient.



**Fig. 1** Outline of 4 hypothetical diagnostic/treatment strategies applied to the 254 patient population from the HeartFlowNXT clinical trial

**Table 1** Procedural costs used in the analysis

	Costs per procedure	Procedure fee	Device cost	Hospital stay			Total costs
				Per night	Avg nights	Total	
Angio		\$420	\$60	\$1,500	1.4	\$2,100	\$2,580
PCI-1 vessel		\$2,550	\$5,789	\$1,500	2.0	\$3,000	\$11,339
PCI-2 vessel		\$2,550	\$9,802	\$1,500	2.0	\$3,000	\$15,352
PCI-3 vessel		\$2,550	\$13,815	\$1,500	2.0	\$3,000	\$19,365
cCTA		\$400	–	–	0.0	–	\$400
FFR		\$42	\$1,800	–	0.0	–	\$1,842
Price FFRct		–	\$2,000	–	0.0	–	\$2,000

We estimated future event rates for appropriately and inappropriately treated patients using the FFR cutoff value of  $<0.80$  drawing on data from the deferral versus performance of PTCA in patients without documented ischemia (DEFER) [10], FAME [11, 12] and providing regional observations to study predictors of events in the coronary tree (PROSPECT) [13] studies. We considered a coronary

lesion to be significant by visual assessment of the CAG or cCTA if lumen stenosis was  $\geq 50\%$  and defined functional significance of a lesion as either an  $FFR_{cath}$  or  $FFR_{CT}$  of  $\leq 0.80$ . Accordingly, we used the following assumptions to estimate the combined 1 year death/MI rate for: (a) PCI in patients with  $FFR_{cath} \leq 0.80$ : 3%; (b) PCI in patients with  $FFR_{cath} > 0.80$ : 3%; (c) medical therapy in patients with

FFR<sub>cath</sub> >0.80: 1 %; (d) medical therapy in patients with FFR<sub>cath</sub> ≤0.80: 5 %; (e) invasive measurement of FFR<sub>cath</sub>: 0.4 % [7, 14].

**Results**

A total of 254 patients from the international, multicenter HeartFlowNXT trial had complete information and were included in the analysis. Fifty-seven patients (22 %) in the study were from Japanese clinical sites. Patient characteristics are shown in Table 2. One-third of the patients (80/254) had ischemia-causing stenoses with FFR ≤0.80 and 21 % of the 484 vessels in which invasive FFR was measured had FFR<sub>cath</sub> ≤0.80.

**Utilization and costs**

In this analysis, we modeled the expected cost to treat each patient. The overall cost for each patient is dependent on the test(s) utilized in a given pathway, the lesion measurements for each test, the order in which tests are performed and the treatment performed in accord with the test results. As discussed above, in this analysis we included four hypothetical clinical pathways. The average per-patient cost, for each clinical pathway is shown on Table 3.

In the most commonly used clinical strategy, CAG visual (Pathway 1), all patients would undergo CAG, 62 % would undergo PCI and 80 vessels per 100 patients would be treated based on visual assessment of the angiogram

with an average cost of \$10,360 per patient. In Pathway 2, FFR<sub>cath</sub> was used to select patients for PCI and only 29 % of patients would undergo PCI with 37 vessels per 100 patients requiring PCI, assuming strict adherence to the recommended threshold of FFR<sub>cath</sub> ≤0.80. This 54 % reduction in PCI would result in a potential average cost of \$7,222 per patient corresponding to a 30 % savings per patient when compared to Pathway 1. In Pathway 3, cCCTA was used to select patients for CAG reducing the number of angiograms by 25 % and the number of patients undergoing PCI by 13 % compared to Pathway 1 (CAG visual). PCI was guided by visual CAG and the number of vessels treated was reduced by only 10 % with average cost savings of 12 % relative to Pathway 1. In Pathway 4, the strategy of initial cCCTA with FFR<sub>CT</sub> in patients with ≥50 % stenosis and CAG only in those with FFR<sub>CT</sub> ≤0.80 reduced the number of angiograms by 62 % and number of patients undergoing PCI by 47 %. Only 48 vessels per 100 patients needed PCI with an average cost per patient of \$7,222, a 30 % cost savings per patient compared to Pathway 1.

**Clinical events**

The estimated one-year rate of death or MI for the CAG visual-guided strategy (Pathway 1) was 2.4 % (Table 3). Use of cCTA to select patients for CAG (Pathway 3) reduced the death/MI rate to 2.2 % due to the reduction in number of CAG. The use of FFR<sub>cath</sub> or FFR<sub>CT</sub> to guide PCI treatment (Pathways 2 and 4) resulted in the greatest reduction (21 %) in death/MI rate to 1.9 % compared to visual angiography-guided treatment. The combined effects of cost and clinical event rate are shown in Fig. 2.

**Discussion**

Three prospective, multicenter clinical trials, comprising 609 patients and 1,050 vessels have evaluated the diagnostic accuracy of FFR<sub>CT</sub> using FFR<sub>cath</sub> as the reference standard [5–7]. Each study has shown FFR<sub>CT</sub> to have high diagnostic accuracy for the diagnosis of lesion-specific

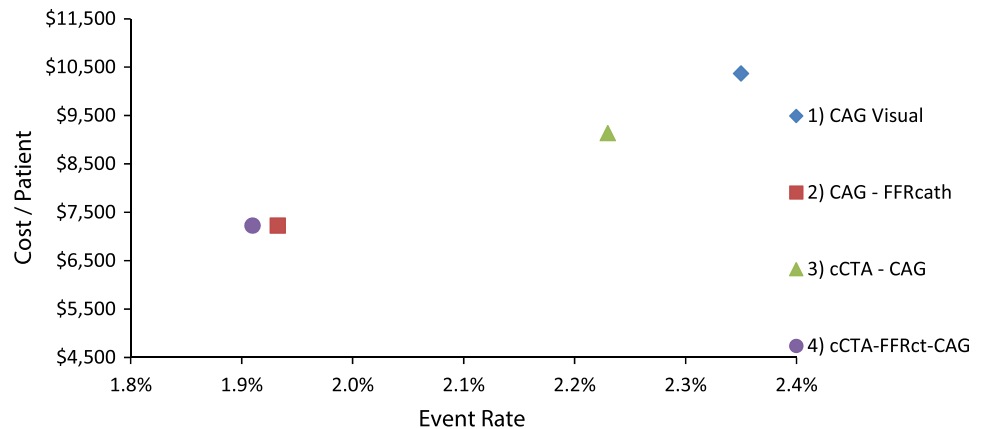
**Table 2** Characteristics of study population (n = 254)

Age ± SD (range)	64 ± 10 years (32–84 years)
Men:women (%)	162:92 (64:36 %)
Asian:Caucasian (%)	86:163 (34:64 %)
Hyperlipidemia (%)	200 (79 %)
Hypertension (%)	174 (69 %)
Diabetes (%)	58 (23 %)
Current smoking (%)	46 (18 %)
Prior myocardial infarction (%)	5 (2 %)
Angina within past month (%)	197 (78 %)

**Table 3** Peri-procedural costs and 1 year clinical event rates

	CAG visual	CAG-FFR <sub>cath</sub>	cCTA-CAG	cCTA-FFR <sub>CT</sub> -CAG
No. of patients undergoing CAG (per 100 pts)	100	100	75	38
No. of patients undergoing PCI (per 100 pts)	62	29	54	33
Vessels treated by PCI (per 100 pts)	80	37	72	48
Costs per patient	\$10,360	\$7,222	\$9,128	\$7,222
1 year event rate	2.4 %	1.9 %	2.2 %	1.9 %

**Fig. 2** Combined per-patient cost and projected 1 year event rate (death/MI) for 4 clinical pathways modeled in this study. FFR<sub>cath</sub> and FFR<sub>CT</sub> guided clinical pathways demonstrated the lowest cost and clinical event rate compared to visual-guided treatment strategies



ischemia using FFR<sub>cath</sub> as the reference standard with significant improvement in the ability to discriminate patients with and without ischemia when compared to cCTA [5–7] and CAG [7]. The use of invasive FFR<sub>cath</sub> to identify lesion-specific ischemia and guide coronary intervention is now well-established and has been shown to not only improve patient outcome but also reduce costs [1]. It has been suggested that non-invasive FFR<sub>CT</sub> may be poised to assume the role of gatekeeper to the interventional catheterization laboratory, especially for intermediate stenosis [15], and a previously modeled analysis based on US data has suggested that the use of FFR<sub>CT</sub> may improve patient outcomes while reducing healthcare costs [8].

In this study we based our analysis on the most recently published experience with FFR<sub>CT</sub> which incorporates the latest refinements in software technology with automated image processing and improved physiologic modeling of coronary flow parameters [7]. The results show that the diagnostic performance of non-invasive FFR<sub>CT</sub> compares favorably to invasive FFR<sub>cath</sub> and can discriminate ischemia-causing stenoses from non-functional stenoses. According to European Society of Cardiology [16] and American Heart Association [17] practice guidelines, FFR<sub>cath</sub> is the gold standard for assessing the hemodynamic significance of coronary lesions and for interventional clinical decision-making; however, FFR<sub>cath</sub> is not practical in many cases for reasons of safety and time. FFR<sub>CT</sub> has potential value in selecting patients for CAG and interventional treatment with the potential of achieving significant reduction in costs and improving outcomes compared to visual angiography-guided treatment. As indicated by the model in this study, the utilization of FFR<sub>CT</sub> in Japan may result in fewer diagnostic catheterizations, fewer inappropriate PCI treatments, improved patient outcomes, and a 30 % reduction in average cost per patient relative to standard care (Pathway 1) if fully implemented.

In addition to advancing patient care, utilizing FFR<sub>CT</sub> technology in Japan may provide significant cost savings for the overall Japanese Healthcare System by safely deferring unnecessary CAG and identifying patients who would benefit from PCI. In 2011 it is estimated that 504,476 coronary angiographies and 181,991 non-emergent PCIs were performed in Japan [18]. If our analysis can be extrapolated to the larger population, the utilization of FFR<sub>CT</sub> might decrease coronary angiographies by as much as ~60 % and PCI procedures by ~40 %. Based on the results in this study, we estimate that widespread implementation of FFR<sub>CT</sub> in Japan has the potential to result in considerable cost savings to the Japanese Healthcare System while improving the clinical outcome for patients.

### Study limitations

This study has several important limitations. First, this study is a simulation of possible costs and outcomes rather than documentation of costs incurred and outcomes experienced utilizing FFR<sub>CT</sub> in actual clinical practice. While direct assessment of cost-efficacy is not yet available for FFR<sub>CT</sub> or other non-invasive testing modalities in stable CAD, the source data for this study represents the largest clinical experience of any non-invasive testing modality using FFR<sub>cath</sub> as the reference standard. FFR<sub>CT</sub> has close direct correlation to measured FFR, which has well-documented outcome and cost data in more than 1,005 patients [11], but independent confirmation with actual outcome data utilizing FFR<sub>CT</sub> for clinical decision making is needed. The extent to which patients analyzed in this report may not precisely reflect the spectrum of patients undergoing CAG in Japan may limit the ability to extrapolate directly to expected outcomes in Japan. A prospective longitudinal study evaluating clinical outcomes, resource utilization and quality of life of FFR<sub>CT</sub>-guided evaluation

and treatment of patients with suspected CAD is currently underway (PLATFORM trial, clinical trials.gov NCT01943903). Second, this study did not include patients with acute coronary ischemia, patients with prior PCI or CABG, and patients who are not suitable candidates for cCTA. Thus, the usefulness of FFR<sub>CT</sub> in this broader population of patients with CAD is unknown. Third, costs related to clinical adverse events during follow-up were not considered; however, the FFR<sub>CT</sub> guided pathway had the lowest event rate during follow-up. Fourth, FFR<sub>CT</sub> is not yet widely available and market pricing for this test has not yet been determined. This analysis uses an FFR<sub>CT</sub> price of \$2,000, the price at which the costs of Pathways 2 and 4 were equivalent. The resulting average total cost of treating a patient in Pathway 4 (cCTA-FFR<sub>CT</sub>-CAG) is \$7,222. If the price of FFR<sub>CT</sub> is modeled as \$1,500, the average cost of treating a patient in this pathway decreases to \$6,848, a 34 % savings compared to standard care (Pathway 1). If the price of FFR<sub>CT</sub> is modeled as \$2,500, the average cost for a patient in this pathway is \$7,596, a 27 % reduction compared to standard care (Pathway 1). Finally, this analysis does not consider the possibility of only partial or limited adoption of the FFR<sub>CT</sub> decision pathway, which inherently would limit the potential cost savings of this approach. For example, the decision to send a patient to CAG is made by comprehensive evaluation of the patient's symptoms and physical findings, risk profile, and results of other non-invasive tests for myocardial ischemia and may cause the physician to override the results of the FFR<sub>CT</sub>. Similarly, physicians in Pathway 2 may choose to—not measure FFR in the cath lab or may override the results of FFR<sub>cath</sub> thus reducing the potential economic and outcome benefit. Thus, actual savings achieved may be limited by physicians' adherence to the clinical decision making pathway. Further evaluations including prospective outcome studies are underway to better understand and quantify the potential clinical and economic improvements identified in this simulation.

## Conclusion

Analysis of data from the HeartFlowNXT trial and using Japanese costs of goods and services suggest that utilization of non-invasive FFR<sub>CT</sub> for clinical decision making could improve clinical outcomes and decrease costs by more accurately identifying patients for CAG and PCI.

**Acknowledgments** The NXT trial was funded by the HeartFlow, Inc.

**Conflict of interest** Ben Forrest and Christopher K. Zarins are employees of HeartFlow, Inc.

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