Coronary artery disease (CAD) is the most common form of heart disease and affects the health of millions of individuals worldwide.\(^1,2\) In patients with CAD, coronary artery narrowing, or stenosis, restricts blood flow and reduces the amount of oxygen to the heart.\(^3\) When stenosis causes insufficient oxygen supply to the heart – a condition called myocardial ischemia – patients with CAD may benefit from percutaneous coronary intervention (PCI), such as stenting partially occluded vessels.\(^4,5\)

In recent years, the use of PCI for CAD has been called into question.\(^6\) Research suggests no benefit to adding stenting of partially occluded vessels to standard medical treatment. Data from the COURAGE (Clinical Outcomes Utilizing Revascularization and Aggressive drug Evaluations) trial brought into question the benefit of PCI for patients with CAD.\(^6\) Although stenting can be helpful for many patients with stenosis, it was not beneficial when administered to all patients. Furthermore, an economic analysis of COURAGE data showed that PCI added approximately $10,000 to per-patient treatment costs, with no significant improvement in outcomes.\(^7\)

Fractional flow reserve (FFR) is a technique used to assess the severity of blood flow blockages in patients with CAD.\(^3\) FFR technology can help physicians identify ischemia-inducing stenosis with greater than 90 % accuracy – this facilitates treatment decision-making that improves patient outcomes, and helps to avoid unnecessary medical procedures.\(^3,5\) In addition to contributing to improved patient outcomes, PressureWire™ FFR can also decrease costs to providers and healthcare facilities.\(^3,9\)

Fractional flow reserve technology is the key to distinguishing which patients will benefit from PCI. Two landmark studies using the St. Jude Medical PressureWire FFR technology have demonstrated that although PCI is not necessary for all patients with CAD, it is beneficial for those with ischemia-inducing stenosis.\(^8\)

Benefits for those with Ischemia-inducing stenosis

**FAME**

The FAME (Fractional Flow Reserve [FFR] vs. Angiography for Multivessel Evaluation) trial showed a benefit of FFR-guided PCI, with approximately 30 % reduced risk of death, myocardial infarction (MI) and revascularization compared with angiography-guided PCI.\(^3,5\) During a 2-year follow-up, patients continued to show decreased mortality risk and MI rates.\(^10\)

**FAME 2**

The FAME 2 (FFR-guided Percutaneous Coronary Intervention [PCI] plus Medical Treatment vs. Medical Treatment Alone in Patients with Stable Coronary Artery Disease) trial found that use of FFR-guided PCI led to an 86 % decrease in risk of unplanned hospitalization for urgent revascularization, compared with medical treatment alone.\(^8\)
Fractional Flow Reserve (FFR) — Shown to Improve Patient Outcomes and Reduce Costs

The Role of Fractional Flow Reserve (FFR) in Coronary Artery Disease (CAD) Management

Coronary artery disease (CAD) is the most common form of heart disease and affects the health of millions of individuals worldwide. Treatment for CAD involves medical therapy, including lifestyle changes and the use of various drugs; additionally, patients with insufficient oxygen supply to the heart, or myocardial ischemia, may benefit from coronary intervention (PCI), such as stenting of partially occluded vessels. The course of treatment for patients with CAD depends on disease severity. While coronary angiography is always performed prior to PCI, it may underestimate or overestimate the severity of specific cardiac lesions. In contrast, FFR provides a quantitative ratio of the actual blood flow in a narrowed artery, compared with the normal achievable blood flow and is more accurate in diagnosing ischemic lesions than angiography alone. Using this functional or morphological measurement, FFR can quantify the severity of specific stenoses, as shown in Figure 1.

- A measurement of 1.0 indicates normal, healthy blood flow.
- A measurement of 0.75 or lower indicates with 100 % specificity the lesion(s) is causing ischemia.

Patients with an FFR ≤0.80 are recommended for PCI. The 0.80 cutoff for PCI has been validated in several clinical trials – these outcomes are summarized in this document.

FFR Technology

FFR ratio is determined using a pressure guidewire system, such as the St. Jude Medical PressureWire, to measure the pressure inside the coronary arteries. Coronary interventionists insert the pressure guidewire through the stenosed artery, as seen in Figure 2. Following this, maximum blood flow is pharmacologically induced, and the FFR ratio of the lesion is calculated.

FFR Use in Clinical Practice

Clinical research has shown that FFR is effective in patients with stable ischemic CAD who are candidates for revascularization (PCI). FFR is particularly useful in the assessment of coronary lesions prior to PCI or CABG surgery, to identify the lesions responsible for ischemia and inform the treatment decision-making process. Patients found by angiography to have obstructive CAD, or CAD of indeterminate severity, can also benefit from FFR.

FFR: Relevant Clinical Data

The benefit of PCI for CAD treatment was recently called into question by research suggesting no benefit of stenting of partially occluded vessels compared to standard medical treatment. However, this

FFR improves health outcomes and decreases costs.

ECONOMIC EVALUATION – FAME

An economic evaluation of data collected during the FAME clinical study showed that using PressureWire FFR versus angiography alone to assess the need for PCI in patients with multivessel CAD saved more than $2,000 per patient. In this study, 1-year per-patient healthcare costs associated with angiography-guided PCI were $16,700, whereas costs associated with FFR-guided PCI were $14,315.

- These cost savings were attributable to a decrease in unnecessary PCI procedures, as well as fewer rehospitalizations and adverse cardiac events.
- This analysis found that PressureWire FFR was a dominant treatment choice – meaning that it is both more effective and less expensive – for patients with CAD.

ECONOMIC EVALUATION – FAME 2

Economic analysis of the FAME 2 study demonstrated that over a 3-year cost projection, use of PressureWire FFR-guided PCI was associated with a cost of increased utility of $32,000 per quality-adjusted life year (QALY) gained. This is well below the cost effectiveness benchmark of $50,000 per QALY gained.

ECONOMIC EVALUATION – FAME 3

In Asia, economic evaluations found expected cost-per-patient savings ranging from USD $1,055 in Korea to $2,407 in Japan.

- These cost savings were attributable to a decrease in unnecessary PCI procedures, as well as fewer rehospitalizations and adverse cardiac events.
- This analysis found that PressureWire FFR was a dominant treatment choice – meaning that it is both more effective and less expensive – for patients with CAD.

For the treating physician, the new guidelines mean that FFR is recommended before making a decision to perform PCI or sending the patient to surgery. This assumes the patient has come to the cath lab without a prior functional test and with a stenosis of 50-90 % as shown by angiography.
Fractional Flow Reserve

Research did not use FFR to determine which lesions were causing ischemia.

Two subsequent landmark studies used the St. Jude Medical PressureWire FFR technology to demonstrate the benefit of targeting ischemia-inducing stenoses. These studies demonstrated that utilizing FFR results in improved outcomes for patients, including reduced rates of death, myocardial infarction (MI) and – in particular – revascularization.5,8

COURAGE Study

In 2007, evidence from the Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE) trial, questioned the necessity of PCI in patients with myocardial ischemia and substantial CAD. Figure 3 shows outcomes of patients in the PCI and medical therapy groups, none of which showed any significant differences.

- 2,287 patients with significant CAD and myocardial ischemia were randomized to receive either optimal medical therapy with PCI (n=1,149), or optimal medical therapy alone (n=1,138).6
- After a mean follow-up of 4.6 years, use of PCI in addition to optimal medical therapy was associated with no significant difference in outcomes related to death, MI, stroke or rehospitalization due to acute coronary syndrome, compared with optimal medical therapy alone.6

DEFER Study

The DEFER study was undertaken in patients with stable chest pain and a functionally nonsignificant coronary stenosis to investigate if percutaneous coronary intervention (PCI) of such stenosis is justified. Published in 2001, the DEFER trial was the first prospective study that used FFR to determine the benefit of percutaneous transluminal coronary angioplasty (PTCA) among patients with an FFR score ≥0.75.4

- Patients with a single stenosis recommended for PTCA based on angiographic results (FFR ≥0.75) were randomized to either receive or defer PTCA.
- All patients with an FFR <0.75 received PTCA, regardless of randomization (n=144); this group was known as the reference group.
- Of patients with an FFR ≥0.75 (n=181), 90 received PTCA and 91 were deferred, based on randomization; these were the performance and deferral groups.4
- At 2 years follow-up, 89% of patients in the deferral group experienced no adverse events. This outcome was statistically similar to the performance group (83%) and significantly superior to the reference group (78%; P=0.03).4
- Patients in the deferral and performance groups had a similar incidence of MI or revascularization, while these events were more common in the reference group (P<0.001 compared with deferral group and P<0.05 compared with performance group).4
- There was no significant difference in mortality rates among the three groups.

This study indicated that the outcomes of patients referred for PTCA without objective proof of ischemia might vary depending on the severity of coronary stenoses detected by FFR. In patients with FFR scores ≥0.75, PTCA did not appear to improve patient outcomes compared to medical treatment alone.4 A 5-year follow-up of DEFER patients showed that these outcomes were maintained over time. Data were obtained for 98% of patients from the original DEFER trial.4

- There was no significant difference in event-free survival between the deferral (80%) and performance (73%) groups; however, the reference group had significantly lower event free survival (63%; P=0.03).
• The combined rates of cardiac death and acute MI were 3.3 % in the deferral group, 7.9 % in the performance group, and 15.7 % in the reference group; this difference was significant only for the reference group (p=0.003).
• No differences in chest pain were experienced by patients in the deferral or performance groups.15
• PCI of a stenosis with an FFR score >0.75 provides no benefit for the patient and should be discouraged.14
• The lesions at greatest risk of causing cardiac death or AMI are those that are functionally significant as identified by an FFR ≤0.75.16

FAME Study
The FAME study, Fractional Flow Reserve versus Angiography for Multivessel Evaluation, published in 2009, was designed to demonstrate whether patients with multivessel disease had better outcomes with FFR-guided PCI compared to angiography guided PCI.5

• A total of 1,005 patients with multivessel CAD, recruited from 20 centers in Europe and the U.S., were randomized to undergo angiography-guided PCI or FFR-guided PCI.
• Angiography-guided PCI involved the stenting of all indicated lesions, and FFR-guided PCI involved the stenting of lesions with FFR measurements ≤0.80.1
• Patients in the angiography group had an average of 2.7 lesions per patient, which was similar to the average of 2.8 in the FFR group (P=0.34). However, the number of stents used per patient was significantly different between the two groups, with 2.7 used in the angiography group and 1.9 used in the FFR group (P<0.001).
• At 1-year after stenting, a total of 91 patients (18.3 %) in the angiography group had experienced an event (death, nonfatal MI or repeat revascularization) compared with 67 patients (13.2 %) in the FFR group; these results were statistically significant (P=0.02).5

As shown in Figure 4, the FAME study showed that the improved patient outcomes observed in the PressureWire group were likely based on targeting the specific lesions most likely to cause ischemia, rather than simply the number of stents used to treat CAD.

A 2-year follow-up of FAME study participants showed that this benefit was maintained over time.10 At 2 years:

• Mortality or MI in the angiography-guided group were significantly higher than in the FFR-guided group (12.9 % and 8.4 %, respectively; P=0.02).
• No significant between-group differences were seen in the rates of PCI or coronary artery bypass surgery, or in the combined rates of death, nonfatal MI and revascularization.
• Patients with lesions with an FFR >0.80 (for which stenting was deemed unnecessary) had a MI rate of 0.2 % and a revascularization rate of 3.2 %, showing very little risk associated with deferral of stenting in these specifically identified lesions.12

These follow-up data demonstrate the benefit of FFR measurement in patients with multivessel CAD. When FFR is used prior to PCI, patient outcomes are improved and unnecessary stenting is also prevented.10

FAME 2 Study
The FAME 2, FFR-guided Percutaneous Coronary Intervention plus Medical Treatment vs. Medical Treatment Alone in Patients with Stable Coronary Artery Disease, study was designed to investigate the outcomes of stable angina patients receiving FFR-guided PCI compared with patients who received optimal medical therapy alone.4 The COURAGE study, which used angiography-guided PCI to study stable angina patients, showed no advantage of PCI over optimal medical therapy. FAME 2 was designed to assess whether FFR-guided PCI would result in improved outcomes for a composite endpoint of death, MI or urgent revascularization.

• Of 1,220 enrolled patients:
  - 888 (73 %) patients with ≥1 lesion with an FFR score of <0.80 were randomly assigned to receive FFR-guided PCI plus optimal medical therapy (FFR group), or optimal medical therapy alone (medical therapy group).
  - 332 (27 %) patients in whom all stenoses had an FFR ≥0.80 received optimal medical therapy alone (registry group).4
• Patients in the medical therapy group showed a significantly higher need for urgent revascularization, compared to patients in the FFR group (11.1 % vs. 1.6 %, P<0.001).
• Patients in the medical therapy group were more likely to have revascularizations triggered by MI or evidence of ischemia (P<0.001).

In patients with FFR results of ≥0.80 in all lesions, only 3 % experienced a primary endpoint, indicating the safety of medical therapy alone in these patients.4 However, in patients with lesions likely to induce ischemia, FFR-guided PCI significantly reduced patient risk for urgent revascularization, compared with medical management alone. Figure 5 shows the outcomes in patients who did have lesions with an FFR ≥0.80.

Recruitment for the FAME 2 study was halted in January 2012, when an independent Data and Safety Monitoring Board (DSMB) recommended early termination of the study. The preliminary results were considered so compelling that research was stopped so patients with FFR <0.80 randomized to optimal medical therapy only could also receive the benefits of PCI.5

These data support the idea of treating patients with “Functionally Complete Revascularization.” With this approach, only ischemia-inducing lesions require stenting.7 When used in patients indicated...
**Clinical Guidelines and Appropriate Use Criteria**

**Clinical Guidelines**

FFR is included in the U.S. guidelines recommended by the American College of Cardiology Foundation (ACCF), the American Heart Association (AHA), and the Society for Cardiovascular Angiography and Interventions (SCAI). The ACCF/AHA/SCAI guidelines give the use of FFR for guiding revascularization in patients with ischemic CAD a Class IIa recommendation, with Level A evidence. Due to the positive results of the DEFER and FAME studies, FFR has been incorporated into recent European Society of Cardiology (ESC) and European Association for Cardio-Thoracic Surgery (EACTS) guidelines on myocardial revascularization. These guidelines acknowledge the difficulty in making accurate assessments of stenosis using visual assessments or quantitative coronary angiography, and suggest the use of FFR when functional information is lacking (i.e., when noninvasive stress imaging is contraindicated, nondiagnostic or unavailable).

**Appropriate Use Criteria**

A 2012 report prepared by multiple cardiology medical societies* addressed the use of FFR in appropriate use criteria for diagnostic catheterization. These appropriate use criteria recommend FFR for diagnostic evaluation of most CAD cases determined by angiography to be of intermediate, obstructive/significant or indeterminate severity. In the same year, various societies including the ACCF, SCAI, STS, AATS, AHA, ASNC, HFSA, and SCCT released a targeted appropriate use criteria update for coronary revascularization. The panel indicated that:

- Patients may be appropriately referred for coronary angiography based on symptom presentation and a high pretest probability of CAD.
- However, for patients with coronary narrowing of uncertain severity, FFR is recommended as an additional invasive measurement to determine the need for PCI.
- The FFR cutoff point of the severity of lesions for which PCI was considered necessary was set at 0.80, to reflect data showing patient risk.

**Economic Impact of FFR**

In addition to improving patient outcomes, data show that the use of FFR technology is an economically viable – and in many cases, preferred – option for patients with multivessel coronary disease. The COURAGE trial called into question the effectiveness of PCI; an economic evaluation of these same data showed a lack of cost-effectiveness using PCI without FFR. Figure 6 shows the costs of initial treatment, costs within and beyond the trial, and lifetime costs for each group.

- The COURAGE trial did not show any benefit of PCI compared to medical therapy alone; cost-effectiveness data also did not show a benefit to...
Fractional Flow Reserve

Radcliffe caRdiology

PCI. These data were expressed as the ratio of the cost of PCI to the life-years gained and quality-adjusted life years (QALYs) gained.7

- The total in-trial cost for the PCI group was $10,125 higher than the medical therapy group ($34,843 and $24,718, respectively).7
- The PCI group had a $9,450 higher lifetime cost than the medical therapy group ($99,820 versus $90,370).7
- Due to these high costs, nearly all estimates of QALYs gained totaled >$50,000 per QALY gained; with an incremental cost-effectiveness ratio (ICER) point estimate of $168,019 per QALY gained.7
- These cutoffs are generally accepted benchmarks of cost effectiveness; therefore, PCI was not found to be a cost effective treatment.7

However, as discussed, the COURAGE study likely included the use of PCI in patients with an FFR ≥0.80. The use of PCI only for patients with more severe stenoses could likely change this cost-effectiveness analysis.8 Coronary interventionists can use FFR measurements to determine the patients who will benefit most from PCI. Treating the right patient, at the right time, can improve patient outcomes while maintaining cost-effectiveness.

**FAME Study: U.S. Economic Data**

The FAME study used FFR to determine the patients who would benefit most from PCI, and found PCI to improve health outcomes for patients with ischemia-inducing stenoses. An economic analysis of FAME data, performed in the context of the U.S. healthcare system, demonstrated the cost-effectiveness of using FFR to guide treatment decisions for the use of PCI in patients with multivessel CAD.9

- A cost-utility analysis compared costs and QALYs using FAME data, with a 1 year timespan, including medical costs associated with treatment, PCI and follow-up.
- At 1 year, average overall costs were significantly less in patients who received FFR ($14,315 vs. $16,700, P<0.001).
- FFR-guided PCI was found to be cost saving in 91 % of patients, and was cost-effective at a threshold of U.S. $50,000 per QALY in nearly 100 % of patients.6

As shown in Figure 7, this economic evaluation of FAME data demonstrated that, in addition to improving health outcomes, FFR-guided PCI in patients with multivessel CAD also reduces treatment costs.6

**FAME: Global Economic Data**

Cost-effectiveness analyses of the FAME study are currently available for 12 countries worldwide: Australia, Belgium, Canada, China, France, Germany, India, Italy, Japan, Korea, Switzerland and United Kingdom.3 Data evaluated include patient outcomes (cardiac events), quality of life and resources used, within the context of various markets.15 The use of FFR to determine PCI in patients with multivessel CAD makes both medical and financial sense. Based on data from the FAME clinical study, FFR-guided PCI has been shown to be cost-effective in every market in which they have been analyzed.15 In the European markets, FFR-guided PCI has been shown to improve health outcomes over a 2-year timeframe (Figure 8). Additionally, Figure 9 shows the expected total 2-year cost savings associated with the improved health outcomes that result from using FFR-guided PCI.

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**Table 2: The medical and economic impact of using FFR-guided PCI for patients with multivessel CAD**

<table>
<thead>
<tr>
<th>Country</th>
<th>QALYs Gained</th>
<th>Deaths Avoided</th>
<th>MI Avoided</th>
<th>MACE Avoided</th>
<th>PCI Avoided</th>
<th>CABG Avoided</th>
<th>Savings per Patient</th>
</tr>
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<tr>
<td>Australia*</td>
<td>27</td>
<td>36</td>
<td>84</td>
<td>85</td>
<td>49</td>
<td>41</td>
<td>$1,812</td>
</tr>
<tr>
<td>Australia**</td>
<td>23</td>
<td>29</td>
<td>70</td>
<td>70</td>
<td>42</td>
<td>35</td>
<td>$1,812</td>
</tr>
<tr>
<td>China</td>
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<td>70</td>
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<td>286</td>
<td>97</td>
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</tr>
</tbody>
</table>

QALY = quality-adjusted life years; MI = myocardial infarction; MACE = major adverse cardiovascular events; PCI = percutaneous coronary intervention; CABG = coronary angiography bypass graft. *Public sector of Australia health care **Private sector of Australia health care

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**Table 2** The medical and economic impact of using FFR-guided PCI for patients with multivessel CAD

**Figure 7: Costs associated with FFR-guided PCI in the FAME trial**

**Figure 8: The health impact of using FFR-guided PCI in selected European markets**

**Figure 9: The expected total 2-year cost savings associated with the improved health outcomes that result from using FFR-guided PCI**
Fractional Flow Reserve

Figure 11: The budget impact of using FFR-guided PCI in selected European markets

Figure 10: Cumulative cost over 12 months: FFR-guided PCI vs. medical therapy

Figure 9: The budget impact of using FFR-guided PCI in selected European markets

FAME 2 Study: U.S. Economic Data
An economic analysis of FAME 2 data was presented at the 2012 Transcatheter Cardiovascular Therapeutics (TCT) conference on October 24, 2012, and concluded that:

• The incremental cost-effectiveness ratio (ICER) for FFR guided PCI was calculated at $32,000 per QALY gained based on 3-year projections, well below the commonly accepted threshold of $50,000 per QALY gained.
• Angina and quality of life are significantly improved by FFR-guided PCI compared to medical therapy.
• FFR-guided PCI has higher initial cost than medical therapy, but the cost gap narrows >50% by 1 year.

At baseline, patients in the FFR-guided PCI group had higher costs than patients who received optimal medical therapy. This was due to the initial procedure and hospitalization. However, at 1 year, cost estimates of follow-up expenditures for the FFR guided PCI group were statistically significantly lower compared with the medical therapy group, primarily due to the increased revascularization costs in the medical therapy group as shown in Table 3. Cost differences between the two groups over 1 year are shown in Figure 10.

Table 3: Cost estimates, baseline and follow-up

In addition, study results showed that FFR-guided PCI improved angina and quality of life. Patients in the FFR group also experienced an increase in utility* of 0.054, compared with 0.003 in the medical therapy group (p<0.001). In-trial results showed $53,000 per QALY gained. This is in line with the common QALY threshold of $50,000. In addition, because the FAME 2 study was stopped early, a 3-year projection was completed to determine a more realistic QALY calculation. The results of this analysis showed $32,000 per QALY gained, well below the $50,000 QALY threshold.

Figure 11 shows how FFR-guided PCI is cost-effective compared with angio-guided PCI or medical therapy, based on multiple study outcomes.

Summary
Fractional flow reserve has contributed to physician decision-making and improved patient and economic outcomes. FFR remains one of the most validated and accurate lesion assessment tools and is supported by an unprecedented legacy of randomized outcome trials, including DEFER, FAME and FAME 2.

Similar economic outcomes were found in the context of multiple Asian countries (i.e., Japan, China, Korea, India) and Australia. Cost-effectiveness and budget impact analyses were performed for these five countries (Table 2). These analyses used FAME data to identify the overall per-person costs of using angiography- vs. FFR-led PCI, as well as expected overall outcomes after 2 years of follow-up.

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