One-Year Outcome of Fractional Flow Reserve-Based Coronary Intervention in Japanese Daily Practice
—CVIT-DEFER Registry—

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**Background:** Clinical use of fractional flow reserve (FFR) has been rapidly increasing, but outcomes after FFR-based coronary intervention in Japanese daily clinical practice have not been well investigated.

**Methods and Results:** The prospective multicenter cardiovascular intervention therapeutics registry (CVIT)-DEFER enrolled consecutive patients for whom FFR measurement was clinically indicated. This study comprised 3,857 vessels in 3,272 patients. Lesions were categorized into 4 groups according to FFR result and revascularization strategy: group 1: FFR >0.8, and deferral of PCI (n=1992); group 2: FFR >0.8, then PCI (n=230); group 3: FFR ≤0.8, and deferral of PCI (n=506); and group 4: FFR ≤0.8, then PCI (n=1,129). The event rate for deferred lesions was significantly low compared with that for PCI lesions (3.5% vs. 6.6%; P<0.05). Vessel-related events occurred in 62 (3.1%), 11 (4.8%), 25 (4.9%), and 79 (7.0%) patients in groups 1, 2, 3, and 4, respectively. PCI for lesions in which FFR was >0.8 (group 2) showed no improvement in the event rate compared with a defer-strategy. On the other hand, deferred lesions with lower FFR values had a higher risk of vessel-related events.

**Conclusions:** A FFR-based revascularization strategy in daily clinical practice was safe with regard to vessel-related events.

**Key Words:** Fractional flow reserve; Japanese Association of Cardiovascular Intervention Therapeutics (CVIT); Percutaneous coronary intervention

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**Editorial p ???**

Cardiovascular Intervention Therapeutics (CVIT) has conducted the CVIT-DEFER registry, a prospective multicenter observational database, to survey the present situation of FFR use in daily clinical practice and its effect on patients’ outcomes.

FFR measurement had some effect on the selection of revascularization strategy. It has been shown that the revascularization strategy (medical/PCI/CABG) was changed after FFR measurement in 30–50% of patients. We also reported that the revascularization strategy was modified in 39% of patients, and the number of PCIs decreased by 22% in the CVIT-DEFER registry. In the present study, we investigated the 1-year outcome of FFR-based cardio-

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that included MI and revascularization were compared among the 4 groups.

**Statistical Analysis**
All statistical analyses were performed using SPSS version 22 (SPSS Inc., Chicago, IL, USA). Continuous variables are expressed as the mean ± standard deviation, and categorical variables are expressed as numbers and percentages. Continuous variables were compared using the ANOVA. The vessel-related event rates for defer-strategy lesions and PCI-treated lesions were compared using \( \chi^2 \) tests. We also performed multivariate logistic regression analysis adjusted for potential confounders (age, sex, FFR result, strategy (defer or PCI), coronary risk factors, ACC/AHA lesion type and measured vessel) to evaluate that included MI and revascularization.

**Methods**

**Study Patients**
The CVIT-DEFER registry is a prospective multicenter observational registry. All institutions belonging to CVIT were requested to enroll consecutive patients who underwent measurement of FFR. Thus, CVIT-DEFER was designed to include consecutive patients who had angiographically intermediate coronary stenosis and in whom FFR was clinically indicated. Between December 2012 and September 2013, 3,804 patients were enrolled at 168 institutions (Appendix S1) in Japan.

Patients with left main coronary artery disease and those for whom baseline or outcome data were unavailable were excluded. Therefore, the study comprised 3,857 vessels in 3,272 patients (86%). The study protocol was approved by the ethical review board of each institution, and written informed consent for clinical follow-up and use of their clinical data was given by all patients.

**FFR Measurement**
Coronary pressure was measured using a 0.014-inch sensor-tipped PCI guidewire (Pressure Wire Certus; St. Jude Medical, St. Paul, AK, USA or Prime Wire Prestige; Volcano Ltd., Cordova, CA, USA). Maximal hyperemia was induced by intravenous infusion of ATP (150–180 \( \mu \)g/kg body weight per minute) via the forearm or femoral vein or intracoronary injection of ATP (40–80 \( \mu \)g) or papaverine (8–12 mg). FFR was calculated as the ratio of the mean hyperemic distal coronary pressure to the mean aortic pressure during maximal hyperemia.

According to the FFR value and revascularization strategy, lesions were categorized into 4 groups (Figure 1): group 1: FFR >0.8, and deferral of PCI; group 2: FFR >0.8, then PCI; group 3: FFR ≤0.8, and deferral of PCI; and group 4: FFR ≤0.8, then PCI.

**Clinical Follow-up**
Individual patient data on clinical outcome at 1 year were requested. Clinical outcome included death, stroke, myocardial infarction (MI), and revascularization (either PCI or CABG) within 1 year. The rate of vessel-related events that included MI and revascularization were compared among the 4 groups.
the association between vessel-related events and categorized FFR results in defer-strategy lesions. In all analyses, \( P < 0.05 \) was considered to be statistically significant.

**Results**

**Patient and Lesion Characteristics**

Patient and lesion characteristics are shown in Table 1. The average age of the patients was 70±10 years, and 74% were men. Approximately half of the patients had a history of PCI, and the majority had stable coronary artery disease, including 63% with stable angina pectoris.

**FFR Measurements**

FFR was measured in 3,857 vessels and multivessel measurement was performed in 16% of the cases (mean, 1.2 vessels per patient). The investigated lesion was located in the left anterior descending artery (LAD) in 2,357 cases (61.1%), left circumflex artery (LCX) in 484 (12.5%), and right coronary artery (RCA) in 1,016 (26.3%).

Mean FFR result was 0.79±0.09 in the LAD, 0.85±0.10 in the LCX, and 0.86±0.10 in the RCA. FFR was >0.8 in 2,222 vessels (57.6%) and ≤0.80 in the remaining 1,635 (42.4%). Lesions were allocated to the 4 categorized groups: group 1 (n=1,992); group 2 (n=230); group 3 (n=506); and group 4 (n=1,129). The revascularization strategy was decided according to the FFR result in 81% (groups 1 and 4), but against the FFR result in 19% (groups 2 and 3).

The prevalence of lesions in the LAD was higher in the groups with FFR ≤0.8 (groups 3 and 4) than in the groups with FFR >0.8 (groups 1 and 2).

**Patient Events**

There were 60 patient events (1.8%; death in 34, stroke in 26). The prevalence of lesions in the LAD was higher with the association between vessel-related events and categorized FFR results in defer-strategy lesions. In all analyses, \( P < 0.05 \) was considered to be statistically significant.

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**Table 2. Lesion Characteristics in 4 Groups Categorized by FFR Result and PCI Strategy (CVIT-DEFER Registry)**

<table>
<thead>
<tr>
<th></th>
<th>Group 1</th>
<th>Group 2</th>
<th>Group 3</th>
<th>Group 4</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>No. of lesions</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FFR &gt;0.8 PCI</td>
<td>1,992</td>
<td>230</td>
<td>506</td>
<td>1,129</td>
<td></td>
</tr>
<tr>
<td>FFR ≤0.8 PCI</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Vessel measured</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LAD</td>
<td>972 (49%)</td>
<td>106 (46%)</td>
<td>410 (81%)</td>
<td>869 (77%)</td>
<td></td>
</tr>
<tr>
<td>LCX</td>
<td>326 (16%)</td>
<td>44 (19%)</td>
<td>35 (7%)</td>
<td>79 (7%)</td>
<td></td>
</tr>
<tr>
<td>RCA</td>
<td>694 (35%)</td>
<td>80 (35%)</td>
<td>61 (12%)</td>
<td>181 (16%)</td>
<td></td>
</tr>
<tr>
<td><strong>Lesion severity</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>50%</td>
<td>1,171 (57%)</td>
<td>50 (24%)</td>
<td>149 (39%)</td>
<td>253 (21%)</td>
<td></td>
</tr>
<tr>
<td>75%</td>
<td>839 (41%)</td>
<td>129 (62%)</td>
<td>203 (53%)</td>
<td>803 (66%)</td>
<td></td>
</tr>
<tr>
<td>90%</td>
<td>42 (2%)</td>
<td>28 (14%)</td>
<td>32 (8%)</td>
<td>152 (13%)</td>
<td></td>
</tr>
<tr>
<td><strong>ACC/AHA classification</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Type A/B1</td>
<td>1,488 (73%)</td>
<td>118 (57%)</td>
<td>207 (54%)</td>
<td>541 (45%)</td>
<td></td>
</tr>
<tr>
<td>Type B2/C</td>
<td>558 (27%)</td>
<td>89 (43%)</td>
<td>177 (46%)</td>
<td>667 (55%)</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations as in Table 1.

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**Table 3. FFR Results in 4 Groups Categorized by FFR Result and PCI Strategy (CVIT-DEFER Registry)**

<table>
<thead>
<tr>
<th></th>
<th>Group 1</th>
<th>Group 2</th>
<th>Group 3</th>
<th>Group 4</th>
<th>P value (vs. non-event)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>No. of lesions</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>NS</td>
</tr>
<tr>
<td>Event (−)</td>
<td>1,992</td>
<td>230</td>
<td>506</td>
<td>1,129</td>
<td>NS</td>
</tr>
<tr>
<td>Event (+)</td>
<td>1,930</td>
<td>219</td>
<td>481</td>
<td>1,050</td>
<td>NS</td>
</tr>
<tr>
<td><strong>FFR result</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>NS</td>
</tr>
<tr>
<td>Event (−)</td>
<td>0.88±0.05</td>
<td>0.85±0.05</td>
<td>0.73±0.06</td>
<td>0.70±0.08</td>
<td>NS</td>
</tr>
<tr>
<td>Event (+)</td>
<td>0.87±0.05</td>
<td>0.85±0.04</td>
<td>0.71±0.08</td>
<td>0.70±0.08</td>
<td>NS</td>
</tr>
</tbody>
</table>

NS, not significant. Other abbreviations as in Table 1.
Vessel-Related Events

A deferral strategy was selected for 2,498 lesions (64.8%). The event rate for defer-strategy lesions was significantly low compared with that for PCI-treated lesions (3.5% vs. 6.6%; P<0.05, Figure 1). We compared the event rate among the 4 groups categorized by FFR result and revascularization strategy (Figure 2).

Vessel-related events occurred in 177 FFR-measured vessels (4.6% of FFR measurements) and in 107 non-FFR-measured vessels. Vessel-related events for FFR-measured vessels occurred in 62 (3.1%), 11 (4.8%), 25 (4.9%), and 79 (7.0%) vessels in groups 1, 2, 3, and 4, respectively (Tables 2, 3). PCI for lesions in which FFR was >0.8 (group 2) did not improve the event rate compared with the defer-strategy (group 1).

Association Between FFR Results and Vessel-Related Events in Deferred Lesions

A histogram of the FFR results for the defer-strategy lesions is shown in Figure 3. Most had FFR >0.80, but 506 lesions had a FFR ≤0.80. Figure 4 shows the association between FFR results and vessel-related events in the defer-strategy lesions. Lesions with a lower FFR had a higher risk of a vessel-related event. FFR result (odds ratio [OR]: 0.157; 95% confidence interval [CI]: 0.038–0.643; P=0.010), defer-strategy (OR: 0.708; 95% CI: 0.527–0.951; P=0.022) and dyslipidemia (OR: 0.685; 95% CI: 0.532–0.746; P=0.003) were found to be significant predictors of vessel-related events (Table 4).

Discussion

In the CVIT registry, FFR was measured in 3,857 moderately stenotic lesions in 3,272 patients and PCI was deferred in 2,498 lesions (64%). On the basis of an analysis during registry enrollment, with regard to the revascularization strategy for each patient, the number of PCIs that had been scheduled before FFR measurement decreased by 22%, medical therapy increased by 41%, and the revascularization strategy was changed in 39% of patients.8 Thus, FFR measurement had a great effect on treatment selection by physicians in Japan. It is also clear that a medical expense-reducing effect was obtained using FFR measurement, but the most important factor the patients’ outcomes following the change in revascularization strategy. The present analysis of prognosis at 1 year demonstrated that the incidence of the composite endpoint (death, MI, and stroke) for all cases was 1.8%. FFR measurement was not necessarily performed in all lesions, and cases of moderate stenosis in which FFR was measured in the residual vessels that were not the vessels with the most severe lesions were included, which prevented us from analyzing the direct correlation between FFR result and clinical events in the patient concerned. However, our data showed major events can occur with some frequency in cases of lesions in which the physician considered FFR should be measured.

With regard to the FFR-measured vessels, we analyzed

Table 4. Multivariate Logistic Regression Model Estimates for Vessel-Related Events in FFR-Based Coronary Intervention in Japanese Daily Practice (CVIT-DEFER Registry)

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Odds ratio</th>
<th>95% CI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>FFR result</td>
<td>0.157</td>
<td>0.038–0.643</td>
<td>0.010</td>
</tr>
<tr>
<td>Defer strategy</td>
<td>0.708</td>
<td>0.527–0.951</td>
<td>0.022</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>0.685</td>
<td>0.532–0.746</td>
<td>0.003</td>
</tr>
</tbody>
</table>

CI, confidence interval; FFR, fractional flow reserve.
the FFR result, treatment option, and subsequent vessel-related events. FFR measurement is now common practice in Japan, but the extent to which decision-making is based on the measured FFR is as yet unclear. In the present analysis, treatment selected on the basis of the FFR result accounted for 3,121 lesions (80.9%), and in the remaining 19.1% PCI was selected or deferred against the FFR result. The reason why these physicians disregarded the FFR result in each patient is unknown; however, the incidence was high compared with French registry data of 4.3%. Most importantly, for lesions with FFR \( \leq 0.80 \), a defer-strategy was selected in 30% of cases. A prevalence of lesions in the LAD was higher in the groups with FFR \( >0.80 \), and in the groups with FFR \( \leq 0.80 \) (groups 3 and 4) than in the groups with FFR \( >0.80 \) (groups 1 and 2). Reverse mismatch findings, which indicate that FFR is significantly low even though the angiographic degree of stenosis is not so severe, are more frequent in the LAD. Such visual information might have some influence on decision-making of PCI indication. Conventionally, revascularization strategy decision-making is based on the presence or absence of subjective symptoms, together with multimodal ischemic evaluation results; thus, we believe that the physicians did not necessarily select treatment solely on the basis of FFR result.

When the operator makes a decision about the indication and procedural strategy of PCI, the coronary pressure pullback recording may give them useful information. If the pressure gradient is focal in the pullback curve, stent implantation will be effective, but if it is gradual throughout the entire coronary artery, it might be difficult to obtain complete recovery of coronary flow even with long stenting. Therefore, the operator’s decision should be based not only on the FFR result but also on the pressure gradient pattern.

Although events occurred in 3.5% of defer-strategy lesions overall, the rate was significantly lower than that of events that occurred in lesions that had undergone PCI. However, FFR results for the defer strategy showed great variation (Figure 3), and in cases where intervention had been deferred at lower FFR values, the incidence of subsequent events was high. In lesions with FFR \( \leq 0.80 \), physicians judged the risks associated with PCI to be high and deferred the intervention. However, it is important to judge the risk of events between performing PCI and deferral. Furthermore, if the defer-strategy was selected, the FFR result should be considered carefully, and intensive medical therapy might be mandatory.

Among the lesions for which treatment was deferred on the basis of FFR \( >0.80 \) (group 1), vessel-related events occurred in 3.1%. In the group that underwent PCI despite FFR \( >0.80 \) (group 2), subsequent events occurred in 4.8%. Although there was no significant difference compared with the deferral group, the incidence was high, which suggested that PCI treatment, at least, did not inhibit the onset of events. This result is comparable with that found in the Defer trial. Furthermore, MI arising from a lesion for which intervention was deferred occurred in only 1 patient (0.05%), which is extremely rare. In the 15-year follow-up report of the Defer study, the risk of MI onset 1–15 years after deferral of PCI was considered to be low; therefore, in the present registry, a deferral strategy based on FFR was considered to be safe.

**Study Limitations**

The registry was conducted by CVIT, with the participation of numerous institutions that performed PCI irrespective of FFR experience, and each institution was requested to enroll consecutive patients who underwent FFR measurement. Therefore it was possible to observe the state of FFR use in actual clinical practice. On the other hand, enrollments included a broad spectrum of patients, such as those with multivessel disease and in whom FFR was measured in moderate stenosis after treatment for the most severe lesions. With regard to evaluation of the correlation between measured FFR and patient prognosis, this is a major issue. However, even with subjects including severe cases, a FFR-based deferral strategy resulted in good prognosis, which we believe has great significance.

The main findings of this study were the pattern of use of FFR and its relation to vessel-related events in a nationwide registry. It was not possible to analyze the direct relation between FFR result and patients’ outcomes. However, the vessels with good FFR results had lower vessel-event rates, regardless of the treatment strategy, and the vessels with lower FFR results had higher event rates including MI. Furthermore, the patients’ outcomes in this study were very good, indicating a FFR-based treatment strategy can be considered as safe. To validate the role of FFR in improvement of clinical outcomes of patients, a randomized prospective trial is necessary.

Many patients in which the treatment was not necessarily selected on the basis of FFR values were enrolled. This enabled us to analyze prognosis when treatment not based on FFR was selected. However, unlike prospective studies, PCI for cases of FFR \( >0.80 \) was performed at the discretion of the physician, which could have caused a bias in patient selection, and therefore attention should be paid when interpreting the results.

The decision of target lesion revascularization during the follow-up period was determined by each physician. Deterioration of FFR or a positive result of non-invasive exercise test was not necessarily ascertained. In cases of moderate stenosis, even if the physician knew the FFR result was negative at the previous catheterization, the bias in the physician’s decisions may have contributed to an indication of revascularization in such cases. It is important to continue to report the clinical importance of FFR-based intervention.

Intracoronary injection of ATP was used for inducing maximal hyperemia in 5.4% of the measurements, but there is some risk of insufficient hyperemia because it is short acting. It is important to know the practical details of FFR measurement and thus establish the precise methodology for confidence in FFR-guided procedures in the daily clinical setting.

**Conclusions**

A FFR-based revascularization strategy in daily clinical practice was safe with regard to vessel-related events.

**Acknowledgments**

The authors thank Dr. Chisa Matsumoto, MD, for her advice on the statistical analysis, and Crimson Interactive Pvt. Ltd. (Ulatus – www.ulatus.jp) for their assistance in manuscript translation.

**Conflict of Interest Statement**

N.T. serves as a consultant for St. Jude Medical, Volcano Japan and Boston Scientific. The other authors report no conflicts.
References


Supplementary Files

Supplementary File 1

Appendix S1

Please find supplementary file(s):