Determinants and prognostic implications of instantaneous wave-free ratio in patients with mild to intermediate coronary stenosis: Comparison with those of fractional flow reserve

Kyohei Onishi1, Heitaro Watanabe1, Kazuyoshi Kakehi1, Tomoyuki Ikeda1, Toru Takase1, Kenji Yamaji1, Masafumi Ueno1, Kazuhiro Kobuke1, Gaku Nakazawa1, Shunichi Miyazaki2, Yoshitaka Iwanaga1*

1 Division of Cardiology, Department of Internal Medicine, Kindai University Faculty of Medicine, Osaka-sayama, Japan, 2 Saiseikai-Tondabayashi Hospital, Tondabayasi, Japan
* Current address: Center for Cerebral and Cardiovascular Disease Information, National Cerebral and Cardiovascular Center, Suita, Japan
yiwanaga@kuhp.kyoto-u.ac.jp

Abstract

The instantaneous wave-free ratio (iFR) is used for assessing the hemodynamic severity of a lesion, as an alternative to the fractional flow reserve (FFR). We evaluated the relationship between iFR and FFR in detail and the clinical significance of iFR in patients with mild to intermediate coronary artery stenosis. We recruited consecutive 323 patients (421 lesions) with lesions exhibiting 30% to 80% diameter stenosis on angiography in whom FFR and iFR were measured. In the total lesions, mean diameter stenosis was 48.6% ± 9.0%, and physiological significance, defined by FFR of 0.80 or less or by iFR of 0.92 or less, was observed in 32.5% or 33.5%, respectively. Mismatch between iFR and FFR was observed in 18.1% of the lesions. Clinical factors did not predict FFR value; however, gender, diabetes mellitus, aortic stenosis, anemia, high-sensitivity CRP value, and renal function predicted iFR value. In multivariate logistic analysis after adjustment for FFR value, gender (p < 0.001), diabetes mellitus (p = 0.005), aortic stenosis (p = 0.005), high-sensitivity CRP (p < 0.001), and renal function (p = 0.003) were all independent predictors of iFR value. In Kaplan-Meier analysis, the baseline iFR predicted the subsequent major cardiovascular events (MACE) (hazard ratio, 2.40; 95% CI, 1.16–4.93; p = 0.018) and the results of the iFR-guided strategy for predicting rates of MACE and myocardial infarction/revascularization were superior to those of the FFR-guided strategy. In conclusion, significant clinical factors predicted iFR value, which affected the prognostic capacity. The iFR-guided strategy may be superior in patients with mild to intermediate stenosis.
Introduction

Fractional flow reserve (FFR) is defined as the ratio of distal coronary pressure divided by the proximal one (aortic pressure) in the stenosis at maximal hyperemia. This condition is induced by administration of a vasodilator agent in order to identify coronary stenosis that can induce reversible myocardial ischemia [1]. The FFR optimizes the risk stratification of patients with chest pain who are undergoing coronary angiography (CAG), and this use of the FFR has been supported by results of several trials and guideline recommendations [2]. The instantaneous wave-free ratio (iFR) is a recently introduced physiological index assessing the severity of stenosis without the administration of a vasodilator agent. It is defined as the ratio of resting distal coronary pressure to aortic pressure during the period of diastole in which microvascular resistance is minimized and constant (wave-free period) [3]. FFR and iFR have been demonstrated to show no significant differences in the prediction of myocardial ischemia from nitrogen-13–ammonia positron emission tomography [4]. A meta-analysis has shown excellent agreement of iFR with FFR without the undesired effects and cost of hyperemic agents [5]. In addition, it is also comparable with FFR in guiding revascularization according to two large randomized controlled trials [6, 7]. However, FFR-iFR mismatch has been recognized, and the reason for these discrepancies and those in clinical and angiographic characteristics of discordant lesions is not fully understood [8]. Because iFR is measured during resting status, whereas FFR is measured during hyperemic status, each index must represent a different aspect of pathophysiology in patients with coronary artery disease (CAD), especially in intermediate coronary lesions [9].

Watanabe et al. recently reported that not only the extent of local stenosis but also the amount of myocardial supply and the lesion location determined the physiological significance and may explain the visual–functional mismatch between CAG and FFR in mild to intermediate coronary stenosis [10]. Therefore, we evaluated the relationship of iFR with FFR in detail, and we determined the predictors for iFR and its prognostic potentials in 323 consecutive patients with CAD and mild to intermediate coronary artery stenosis. We further examined whether iFR-guided strategy for predicting cardiac events was clinically reasonable in this setting.

Materials and methods

Study protocol

Consecutive patients with stable CAD were enrolled between November 2013 and March 2017 at Kindai Hospital (Osakasayama, Japan). Patients eligible to participate had a lesion angiographically determined to be 30% to 80% diameter stenosis (DS) [11] and had undergone invasive physiological assessment before percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG). Patients were excluded when they had acute coronary syndrome, left main coronary artery stenosis, and coronary artery bypass grafted lesions. The measurements and analyses in quantitative coronary angiography (QCA), and iFR and the follow-up of clinical outcomes were performed retrospectively. The study was conducted in accordance with the 1964 Declaration of Helsinki and its later amendments and was approved by the Ethics Committee of Kindai University Faculty of Medicine, Osakasayama, Japan. The ethics committee waived the requirement for the informed consent and all data were fully anonymized before accessing them.

Aortic stenosis was defined as peak aortic velocity of 2.6 m/s or faster or an aortic valve area of less than 2.0 cm² according to echocardiography. Plasma B-type natriuretic peptide, hemoglobin, serum high-sensitive C-reactive protein (hs-CRP), creatinine, and hemoglobin A1c
levels were measured before CAG. The estimated glomerular filtration rate (eGFR) was calculated according to the equation specific to the Japanese population: eGFR = 194 × (serum creatinine) – 1.094 × (age) – 0.287 (× 0.739 for female patients).

CAG and QCA
CAG was performed with a standard technique involving the transradial or transfemoral approach [10]. Patients were administered intracoronal isosorbide dinitrate (1 to 5 mg) before initial angiography to achieve maximal vasodilation. CAG images were reviewed by independent physicians who were unaware of patients’ clinical characteristics and FFR value. QCA was performed to locate FFR measurement with the use of CAAS II (Pie Medical Imaging, Maastricht, The Netherlands) by an independent experienced physician who was unaware of the FFR result and other data [12]. Measurements included the minimum lumen diameter, reference vessel diameter, and lesion length at the target coronary segment before FFR was calculated. Percentage DS was calculated as the ratio of the minimum lumen diameter to the reference vessel diameter. Diffuse lesion was defined as stenotic lesions that were 20 mm in length or longer.

To evaluate the myocardial area supplied by the coronary artery distal to the stenosis, a modified version of the Bypass Angioplasty Revascularization Investigation (BARI) score was utilized, as in a previous study [10].

FFR and iFR measurements
Intracoronary pressure was measured with a 0.014-in. pressure guide wire (PressureWire; St. Jude Medical, St. Paul, MN, USA). It advanced to distal of the assessed area of stenosis. The proximal coronary pressure was measured via the guiding catheter. FFR was calculated as the mean distal coronary pressure divided by the mean aortic pressure at maximal hyperemia. Maximal hyperemia was induced by continuous intravenous infusion of adenosine 5’-triphosphate, administered at 140 μg/kg/min via the forearm vein in accordance with previous studies [13]. Subsequently, the pressure guide wire was manually pulled back slowly from the most distal part of the artery to the proximal part during induced steady-state maximal hyperemia in all patients. When the FFR value was 0.8 or lower, the coronary stenosis was considered functionally significant.

Coronary pressure recordings were extracted from a data storage system (RadiView, St. Jude Medical) and processed offline by our own algorithm. The iFR was defined as the ratio of distal coronary pressure to aortic pressure during the wave-free period (approximately 75% of late diastole) at rest [14]. We identified the dicrotic notch to recognize the onset of the diastolic phase, and the wave-free period (excluding the first 25% of diastole and ending 5 msec before the end of diastole) was evaluated.

Clinical follow-up
To monitor long-term clinical outcomes after FFR/iFR testing, patients completed a questionnaire, a telephone interview, or a chart review. Major adverse cardiovascular events (MACEs) were defined as the combination of all-cause death, myocardial infarction (MI), and the need for emergent revascularization. A secondary outcome was defined as the combination of MI and need for emergent revascularization. Clinical outcomes of patients who did not undergo subsequent revascularization because FFR exceeded 0.80 (the “FFR-defer” group) were compared with those of patients who did because FFR was 0.8 or less (the “FFR-perform” group) [15]. They were also compared on the basis of iFR: patients who did not undergo subsequent...
revascularization because iFR exceeded 0.92 (the “iFR-defer” group) and those who did because iFR was 0.92 or less (the “iFR-perform” group).

Statistical analysis
As part of the univariable analysis for continuous variables, comparisons among groups were performed with Student’s t test, one-way analysis of variance, and the Mann-Whitney U test. Pearson’s $\chi^2$ and Fisher’s exact tests were used to assess differences in categorical variables. A linear regression analysis with the Pearson correlation coefficient was used to assess the linearity of the relationship between two variables. Multiple logistic regression and univariable analyses were used to explore the significant predictors of FFR and iFR. Cutoff levels of iFR for physiological significance (FFR $\leq 0.8$) and the sensitivities and specificities of the cutoff levels were calculated in receiver operating characteristics (ROC) curve analysis. Event-free survival curves were analyzed according to the Kaplan-Meier method, and curves were compared in log-rank tests. Multivariable analysis of clinical outcomes was performed with Cox’s proportional hazards model, with the use of JMP V.14.3 (SAS Institute, Cary, NC, USA). Hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated. A $p$ value of less than 0.05 was considered significant. All results are expressed as means ± standard deviations.

Results
Baseline patient and lesion characteristics
CAG and FFR examinations were performed in 351 patients with 465 lesions. Of the lesions, 14 were excluded because they were left main coronary artery lesions, and 2 were excluded because they were CABG lesions. Another 16 lesions were excluded because they represented either less than 30% or more than 80% DS on angiography. In 12 lesions, iFR data was unavailable for the post hoc analysis. A total of 323 patients with 421 lesions were included in the analysis (S1 Fig).

The baseline characteristics of the patients and lesions are listed in Table 1. The mean age of the patients was 70.6 ± 9.0 years, and 76.5% were male. Furthermore, 48.2% of the lesions were located in the left anterior descending coronary artery (LAD), and the remaining were in the left circumflex artery (LCX) and right coronary artery. The mean FFR value was 0.84 ± 0.09, and physiological significance as defined by FFR of 0.8 or less was observed in 32.5% of the lesions. The minimum lumen diameter and reference vessel diameter in lesions of the right coronary artery were significantly larger than those in the LAD or LCX. In addition, lower FFR value was observed in LAD lesions as compared with that in LCX lesions or lesions of the right coronary artery ($p < 0.001$).

ROC analysis showed that the area under the ROC curve for iFR as an indicator of physiological significance (FFR $\leq 0.80$) was 0.876 (S2 Fig). The optimal cutoff value of iFR was 0.92 (sensitivity, 74%; specificity, 86%). In this cohort, the mean iFR value was 0.94 ± 0.06, and physiological significance as defined by iFR of 0.92 or less was observed in 33.5% of the lesions.

Relationship of iFR or FFR to patient and lesion characteristics
Although iFR was correlated with FFR ($R = 0.709, p < 0.001$; S3 Fig), mismatch between iFR and FFR (FFR $> 0.80$ and iFR $\leq 0.92$ or FFR $\leq 0.80$ and iFR $> 0.92$) was observed in 18.1% of the lesions. When the cutoff value of iFR was set to 0.89 [6, 7], the physiological significance defined by it and the mismatch between iFR and FFR were observed in 18.5% and 19.7%, respectively. The baseline clinical characteristics except hemoglobin A1c level did not predict
the FFR value; however, the clinical factors such as gender, diabetes mellitus, aortic stenosis, anemia, hs-CRP levels, and renal function, predicted the iFR value, as shown in Table 2.

The lesion characteristics, such as minimum lumen diameter, lesion location (LAD versus LCX or right coronary artery), diffuse lesion, proximal lesion, and BARI score FFR, was independently associated with FFR (fit of the model: $R^2 = 0.536$) [10]; those lesion characteristics was similarly associated with iFR (fit of the model: $R^2 = 0.391$). Hemoglobin A1c level was not associated with FFR independently with the multivariate analysis including the lesion

| Characteristic                          | Findings       |
|----------------------------------------|----------------|
| **Patients (n = 323)**                 |                |
| Age, years                             | 70.6 ± 9.0     |
| No. male                               | 247 (76.5%)    |
| BMI, kg/m$^2$                          | 23.9 ± 3.4     |
| No. currently smoking                  | 151 (46.7%)    |
| No. with diabetes mellitus             | 172 (53.4%)    |
| Hemoglobin level, %                    | 6.4 ± 0.9      |
| No. with hypertension                  | 279 (86.6%)    |
| No. with hypercholesterolemia          | 285 (88.5%)    |
| LDL-cholesterol, mg/dL                 | 91.0 ± 31.4    |
| No. with chronic kidney disease        | 148 (46.1%)    |
| eGFR, mL/min/1.73 m$^2$                | 59.1 ± 22.1    |
| No. on hemodialysis                    | 25 (7.8%)      |
| No. with anemia                        | 26 (8.1%)      |
| Hb, mg/dL                              | 13.4 ± 1.6     |
| Log (hs-CRP, mg/dL)                    | −2.28 ± 1.40   |
| No. with aortic stenosis               | 23 (7.3%)      |
| Peak aortic velocity, m/s              | 1.5 ± 0.6      |
| No. with old myocardial infarction     | 156 (48.4%)    |
| No. with prior PCI                     | 218 (67.7%)    |
| No. with prior CABG                    | 10 (3.1%)      |
| **Lesions (n = 421)**                  |                |
| Location                               |                |
| LAD                                    | 203 (48.2%)    |
| Non-LAD                                | 218 (51.8%)    |
| Diffuse lesion                         | 103 (24.5%)    |
| QCA findings                           |                |
| Lesion length, mm                      | 10.8 ± 6.0     |
| Minimum lumen diameter, mm             | 1.40 ± 0.41    |
| Reference vessel diameter, mm          | 2.72 ± 0.65    |
| DS, %                                  | 48.6 ± 9.0     |
| FFR $\leq 0.80$                        | 137 (32.5%)    |
| iFR $\leq 0.92$                        | 141 (33.5%)    |

Values are means ± standard deviations or numbers (%).

BMI, body mass index; CABG, coronary artery bypass grafting; DS, diameter stenosis; eGFR, estimated glomerular filtration rate; FFR, fractional flow reserve; Hb, hemoglobin; hs-CRP, high-sensitive C-reactive protein; iFR, instantaneous wave-free ratio; LAD, left anterior descending coronary artery; LDL, low-density lipoprotein; PCI, percutaneous coronary intervention; QCA, quantitative coronary angiography.

https://doi.org/10.1371/journal.pone.0237275.t001
characteristics ($p = 0.865$). After adjusting for the FFR value, a multivariable analysis showed that gender ($p < 0.001$), diabetes mellitus ($p = 0.005$), aortic stenosis ($p = 0.016$), hs-CRP level ($p < 0.001$), and eGFR ($p = 0.003$) were all independent predictors of iFR values (Table 3). The fit ($R^2$) of the model was 0.596.

Clinical outcomes stratified by FFR and iFR

In the Kaplan-Meier analysis during a median follow-up of 978 days, the patients with baseline FFR of 0.80 or less did not show worse outcomes with regard to MACE and MI/need for emergent revascularization regardless of subsequent revascularization (Fig 1A). In contrast, those with iFR of 0.92 or less had significantly worse outcomes with regard to MACE (HR, 2.40; 95% CI, 1.16–4.93; $p = 0.018$) and a trend toward more MI and need for emergent revascularization (HR, 3.18; 95% CI, 0.93–10.87; $p = 0.065$) (Fig 1B). In the analysis of the relationship between FFR and iFR, the patients with mismatch between them showed frequent MACE (HR, 2.38; 95% CI, 1.09–5.19; $p = 0.030$) and those with FFR higher than 0.80 and iFR of 0.92 or less had

Table 2. Univariable analysis of FFR and iFR and baseline characteristics.

| Characteristics | Relationship to FFR ($p$) | Relationship to iFR ($p$) |
|-----------------|--------------------------|---------------------------|
| Patients        |                          |                           |
| Age             | 0.071                    | 0.358                     |
| Gender          | 0.809                    | 0.005                     |
| BMI             | 0.461                    | 0.238                     |
| Currently smoking | 0.785                  | 0.599                     |
| Diabetes mellitus | 0.149                | <0.001                    |
| Hemoglobin A1c level | 0.016               | 0.019                     |
| Hypertension    | 0.124                    | 0.080                     |
| Hypercholesterolemia | 0.259                | 0.202                     |
| LDL-cholesterol | 0.978                    | 0.929                     |
| Chronic kidney disease | 0.423             | 0.133                     |
| eGFR            | 0.182                    | 0.009                     |
| Hemodialysis    | 0.645                    | 0.062                     |
| Anemia          | 0.212                    | 0.008                     |
| Hemoglobin      | 0.865                    | 0.002                     |
| Log hs-CRP      | 0.070                    | <0.001                    |
| Aortic stenosis | 0.177                    | <0.001                    |
| Peak aortic velocity | 0.165            | <0.001                    |
| Lesions         |                          |                           |
| Location*       | <0.001                   | <0.001                    |
| Diffuse lesion  | <0.001                   | <0.001                    |
| QCA findings    |                          |                           |
| Lesion length   | <0.001                   | 0.046                     |
| Minimum lumen diameter | <0.001             | <0.001                    |
| Reference vessel diameter | <0.001   | <0.001                    |
| DS              | <0.001                   | <0.001                    |
| BARI score      | <0.001                   | <0.001                    |

*Lesion location indicates the distribution ratio of LAD to non-LAD.

BARI, Bypass Angioplasty Revascularization Investigation; BMI, body mass index; DS, percent diameter stenosis; eGFR, estimated glomerular filtration rate; FFR, fractional flow reserve; hs-CRP, high-sensitive C-reactive protein; iFR, instantaneous wave-free ratio; LAD, left anterior descending coronary artery; LDL, low-density lipoprotein; QCA, quantitative coronary angiography.

https://doi.org/10.1371/journal.pone.0237275.t002
more frequent adverse outcomes than did the other three groups (S1 Table). In Kaplan-Meier analysis, the baseline iFR with cut-off of 0.89 still predicted the MACE and MI/need for emergent revascularization (HR, 2.32; 95% CI, 1.10–4.88; \( p = 0.026 \) and HR, 4.79; 95% CI, 1.46–15.72; \( p = 0.010 \), respectively) (S4A Fig).

Of the 323 patients, 91 underwent target vessel revascularization (PCI or CABG). After excluding 67 patients who were not treated on the basis of the FFR value, we divided 256 patients into the FFR-defer group (\( n = 191 \)) and the FFR-perform group (\( n = 65 \); S5A Fig). Similarly, after excluding 91 patients, we divided 232 into the iFR-defer group (\( n = 177 \)) and the iFR-perform group (\( n = 55 \); S5B Fig). In the Kaplan-Meier analysis, the rates of MACE in

![Fig 1. Kaplan-Meier analysis for rates of MACE and MI/need for emergent revascularization according to baseline FFR and iFR values. (A) FFR of \( \leq 0.80 \) versus > 0.80. (B) iFR of \( \leq 0.92 \) versus > 0.92. FFR, fractional flow reserve; iFR, instantaneous wave-free ratio; MACE, major adverse cardiovascular event; MI, myocardial infarction.](https://doi.org/10.1371/journal.pone.0237275.g001)
the FFR-defer and FFR-perform groups were similar, and the FFR-defer group had lower rates of MI and need for emergent revascularization than did the FFR-perform group (Fig 2A). In contrast, significant differences in the rates of MACE and MI/need for emergent revascularization were observed between the iFR-defer and iFR-perform groups (Fig 2B). In multivariable Cox proportional analysis, after adjusting for age and sex, the FFR-defer group did not have fewer MACE and less MI/need for emergent revascularization than did the FFR-perform group. Moreover, the iFR-defer group had fewer MACE and less MI/need for emergent revascularization than did the iFR-perform group (S2 Table). When the cutoff value of iFR was set to 0.89, the iFR-defer group and the iFR-perform group consisted of 203 and 33 patients, respectively, and in the Kaplan-Meier analysis, significant differences in the rates of MACE and MI/need for emergent revascularization were still observed between the iFR-defer and iFR-perform groups (S4B Fig).

Discussion

FFR–iFR mismatch in intermediate coronary artery stenosis

On the basis of the FFR threshold of 0.80, the optimal cutoff of iFR in our cohort was 0.92. At this cutoff, the sensitivity was 74% and the specificity was 86%. Lower cutoff values were reported previously; for example, Göteborg et al., Petraco et al., and Ding et al. demonstrated optimal cutoff values of 0.89, 0.90 and 0.91, respectively [6, 16, 17]. The higher optimal cutoff value in our study cohort may be explained by the presence of lower grade ischemia than in the
previous studies. The theoretical adoption of a hybrid iFR-FFR strategy provided significantly better results than did a dichotomous cutoff value of 0.90 [18]. In this strategy, iFR values between 0.86 and 0.93 are considered the indeterminate range and values greater than 0.93 indicated nonsignificant ischemia. The latter value is similar to our cutoff value, and it may have resulted in better outcomes with the iFR-defer strategy. However, when the cutoff value of iFR was set to 0.89 in the present cohort, although the lesions with positive ischemia by iFR were decreased and the mismatch rate was slightly increased, the baseline iFR with cut-off of 0.89 still predicted the MACE and the iFR-guided strategy based on this value was still superior. It may suggest that iFR has associations with clinical outcomes regardless of the cutoff value.

FFR and iFR have been demonstrated to show no significant differences in the prediction of myocardial ischemia [4], and a meta-analysis demonstrated excellent agreement of iFR with FFR [5]. However, FFR-iFR mismatch has been recognized, and the reasons for the discrepancies between FFR and iFR remain unknown [8]. In our study, iFR did not match FFR (≤ 0.80) in 18.1% of patients at the optimal cutoff, 0.92. In exploring clinical factors that may explain the discordance between FFR and iFR, we found that gender, diabetes mellitus, hs-CRP level, aortic stenosis, and renal function were independently associated with iFR but not with FFR. Several researchers have explored the factors associated with the discordance [8, 9]; Lee et al. showed that female gender, diabetes mellitus, smaller reference vessel diameter, and higher percentage DS were associated with low iFR-high FFR discordance. Scarsini et al. reported that the best cutoff for iFR to predict FFR of 0.8 or less was lower in patients with aortic stenosis than in those with CAD [19], which was concordant with our result (optimal iFR cutoffs, 0.90 and 0.93 in patients with and without aortic stenosis, respectively).

**iFR and the physiological significance**

Petraco et al. explored the relationship of coronary flow reserve (CFR) with iFR and FFR [20]. iFR showed stronger correlation and better agreement with CFR than with FFR, particularly in the intermediate zone. Cook et al. reported that FFR did not match iFR in 14% of patients and that the disagreement was explained by differences in hyperemic coronary flow velocity and CFR [9]. As mentioned, we found that the clinical factors such as gender, diabetes mellitus, hs-CRP level, aortic stenosis, and renal function, were associated with iFR, independently of FFR. In view of the association of these conditions with impaired microvascular function [21–24], iFR may be more influenced by CFR and may not match FFR in such complex pathophysiological conditions. Another study demonstrated that discrepancies between FFR and iFR might be rationalized by differences in E/e´ on tissue Doppler echocardiography [25]. The diastolic dysfunction shown by increased E/e´ may also be associated with impaired microvascular function or impaired CFR.

**iFR and the clinical outcomes**

Two large randomized controlled trials recently demonstrated that revascularization guided by iFR was comparable with that guided by FFR with regard to rates of MACE 1 year later [6, 7]. Escaned et al. performed a post hoc analysis of the pooled data and showed that clinical outcomes for both iFR- and FFR-deferred populations were similar despite a higher rate of deferral with iFR (50% vs. 45% with FFR; p < 0.01) [26]. In contrast, Lee et al. investigated 2-year clinical outcomes of FFR- and iFR-guided deferral [27]. Both methods showed a significant association with 2-year rates of MACE. However, assessing the long-term clinical outcomes of the iFR-FFR discordant lesions according to treatment strategy has not been performed or warranted. This is of particular concern in patients with mild to intermediate lesions, such as our cohort. In this study, MACE was associated with lower iFR but not with lower FFR. The
patients in whom FFR was greater than 0.80 and iFR was 0.92 or less showed the worst prognosis, which suggests that iFR provided significant prognostic information apart from FFR.

In addition, deferral of revascularization on the basis of iFR greater than 0.92 was associated with fewer MACEs than revascularization that was based on iFR of 0.92 or less, in contrast to the findings with FFR. These findings may suggest that the treatment strategy (deferral or revascularization) should be based on iFR rather than FFR in patients with mild to intermediate coronary stenosis [28]. A prospective validation study is necessary for confirming our findings and their clinical relevance.

Study limitations

This study had several limitations. First, this was a single center study with a retrospective analysis. Especially, some bias may affect the results of clinical outcomes since some target-vessel revascularizations were performed not on the basis of the FFR value, but on the operators’ decision in some patients. Second, it was up to the operator to decide whether to perform the FFR measurement. The selection bias might be an important limitation. However, in this study, only consecutive lesions of 30% to 80% DS demonstrated on angiography were analyzed, and for such lesions, FFR is routinely measured in our cath lab. Finally, whereas FFR value was calculated on site, iFR value was calculated on a post hoc basis in this study. Although the calculation and analysis were performed in a blind manner, this might have affected the difference in the clinical outcomes by the treatment strategies. Also, iFR was calculated by our own algorithm and not validated with commercially available ones in the present study. It may have had some impact on the threshold of iFR or the match rate with FFR.

Conclusions

In 323 consecutive patients with CAD and mild to intermediate coronary artery stenosis, iFR-FFR mismatch was observed to a certain extent, and the predictors of iFR, which included clinical factors such as gender, diabetes mellitus, hs-CRP level, renal function, and aortic stenosis, were different from those of FFR. The baseline iFR showed prognostic capacity regardless of subsequent revascularization, and the iFR-guided strategy for predicting cardiac events was clinically superior to the FFR-guided strategy in this setting. These findings may be explained, at least in part, by contribution of the clinical factors on iFR value. The iFR may provide more information about coronary flow status with regard to ischemia and prognostic information than does FFR in patients with mild to intermediate CAD.

Supporting information

S1 Fig. Patient enrollment in this study. CAG, coronary angiography; FFR, fractional flow reserve; iFR, instantaneous wave-free ratio.
(TIF)

S2 Fig. Receiver operating characteristics analysis for iFR as an indicator of ischemia on the basis of FFR value no more than 0.80. AUC, area under the curve; FFR, fractional flow reserve; iFR, instantaneous wave-free ratio.
(TIF)

S3 Fig. Relationship between FFR and iFR. Each red dot denotes a patient with a major cardiac event; each black dot denotes a patient with no major cardiac event. FFR, fractional flow reserve; iFR, instantaneous wave-free ratio; N, number.
(TIF)
S4 Fig. Kaplan-Meier analysis for rates of MACE and MI/need for emergent revascularization according to baseline iFR values and the treatment strategy on the basis of the cutoff value of iFR: 0.89. (A) iFR of ≤ 0.89 versus > 0.89. (B) iFR-perform group versus iFR-defer group. FFR, fractional flow reserve; iFR, instantaneous wave-free ratio; MACE, major adverse cardiovascular event; MI, myocardial infarction.

(TIF)

S5 Fig. Patient enrollment in the prognosis analysis. “FFR-defer” and “iFR-defer” groups consisted of patients who did not undergo subsequent revascularization; “FFR-perform” and “iFR-perform” groups consisted of patients who did, on the basis of FFR or iFR values. FFR, fractional flow reserve; iFR, instantaneous wave-free ratio; MACE, major adverse cardiovascular event.

(TIF)

S1 Table. Clinical outcomes according to FFR and iFR values. FFR, fractional flow reserve; iFR, instantaneous wave-free ratio; MACE, major adverse cardiovascular event; MI, myocardial infarction.

(DOCX)

S2 Table. Cox multivariable models to identify hazard ratio of clinical outcomes. * Adjusted for age and sex. “FFR-defer” and “iFR-defer” groups consisted of patients who did not undergo subsequent revascularization; “FFR-perform” and “iFR-perform” groups consisted of patients who did, on the basis of FFR or iFR values. FFR, fractional flow reserve; iFR, instantaneous wave-free ratio; MACE, major adverse cardiovascular event; MI, myocardial infarction.

(DOCX)

S1 Dataset. 
(XLSX)

S2 Dataset. 
(XLSX)

Author Contributions

Conceptualization: Heitaro Watanabe, Tomoyuki Ikeda, Kenji Yamaji, Masafumi Ueno, Shunichi Miyazaki.

Data curation: Kyohei Onishi, Heitaro Watanabe, Kazuyoshi Kakehi, Tomoyuki Ikeda, Toru Takase.

Formal analysis: Heitaro Watanabe, Kazuhiro Kobuke.

Funding acquisition: Yoshitaka Iwanaga.

Investigation: Kenji Yamaji, Masafumi Ueno, Yoshitaka Iwanaga.

Supervision: Gaku Nakazawa, Shunichi Miyazaki.

Writing – original draft: Kyohei Onishi, Heitaro Watanabe.

Writing – review & editing: Yoshitaka Iwanaga.

References

1. Tonino PA, De Bruyne B, Pijls NH, Siebert U, Ikeno F, van’t Veer M, et al. Fractional flow reserve versus angiography for guiding percutaneous coronary intervention. N Engl J Med. 2009; 360:213–224. https://doi.org/10.1056/NEJMoa0807611 PMID: 19144997
1. De Bruyne B, Pijls NH, Kalesan B, Barbato E, Tonino PA, Pirolo Z, et al. Fractional flow reserve-guided PCI versus medical therapy in stable coronary disease. *N Engl J Med*. 2012; 367:991–1001. https://doi.org/10.1056/NEJMoai1205361 PMID: 22924638

2. Patel MR, Calhoon JH, Dehmer GJ, Grantham JA, Maddox TM, Maron DJ, et al. ACC/AATS/AHA/ASE/ASNC/SCAI/SCCT/STS 2017 Appropriate use criteria for coronary revascularization in patients with stable ischemic heart disease: A report of the American College of Cardiology Appropriate Use Criteria Task Force, American Association for Thoracic Surgery, American Heart Association, American Society of Echocardiography, American Society of Nuclear Cardiology, Society for Cardiovascular Angiography and Interventions, Society of Cardiovascular Computed Tomography, and Society of Thoracic Surgeons. *J Am Coll Cardiol*. 2017; 69:2212–2241. https://doi.org/10.1016/j.jacc.2017.02.001 PMID: 28291663

3. Petraco R, Al-Lamee R, Gotberg M, Sharp A, Hellig F, Nijjer SS, et al. Real-time use of instantaneous wave-free ratio versus fractional flow reserve to guide PCI. *J Am Coll Cardiol*. 2017; 70:1813–1823. https://doi.org/10.1016/j.jacc.2017.02.001 PMID: 28317438

4. Hwang D, Jeon KH, Lee JM, Park J, Kim CH, Tong Y, et al. Diagnostic performance of resting and hyperemic invasive physiological indices to define myocardial ischemia: validation with 13N-ammonia positron emission tomography. *JACC Cardiovasc Interv*. 2017; 10:751–760. https://doi.org/10.1016/j.jcin.2016.12.015 PMID: 28365268

5. Maini R, Moscona J, Katigbak P, Fernandez C, Sidhu G, Saleh Q, et al. Instantaneous wave-free ratio as an alternative to fractional flow reserve in assessment of moderate coronary stenoses: A meta-analysis of diagnostic accuracy studies. *Cardiovasc Revasc Med*. 2018; 19:613–620. https://doi.org/10.1016/j.carrev.2017.12.014 PMID: 29371084

6. Götberg M, Christiansen EH, Gudmundsdottir U, Sandhall L, Danielewicz M, Jakobsen L, et al. Instantaneous wave-free ratio versus fractional flow reserve to guide PCI. *N Engl J Med*. 2017; 376:1813–1823. https://doi.org/10.1056/NEJMoai1616540 PMID: 28317438

7. Davies JE, Sen S, Dehi HM, Al-Lamee R, Petraco R, Nijjer SS, et al. Use of the instantaneous wave-free ratio or fractional flow reserve in PCI. *N Engl J Med*. 2017; 376:1824–1834. https://doi.org/10.1056/NEJMoai1700445 PMID: 28317458

8. Lee JM, Shin ES, Nam CW, Doh JH, Hwang D, Park J, et al. Discrepancy between fractional flow reserve and instantaneous wave-free ratio: clinical and angiographic characteristics. *Int J Cardiol*. 2017; 245:63–68. https://doi.org/10.1016/j.ijcard.2017.07.099 PMID: 28789845

9. Cook CM, Jeremias A, Petraco R, Sen S, Nijjer S, Shun-Shin MJ, et al. Fractional flow reserve/instantaneous wave-free ratio discordance in angiographically intermediate coronary stenoses: an analysis using Doppler-derived coronary flow measurements. *JACC Cardiovasc Interv*. 2017; 10:2514–2524. https://doi.org/10.1016/j.jcin.2017.09.021 PMID: 29268881

10. Watanabe H, Onishi K, Kakehi K, Takase T, Yamaji K, Ueno M, et al. Clinical and angiographic factors predicting fractional flow reserve and explaining the visual-functional mismatch in patients with intermediate coronary artery stenosis. *Coron Artery Dis*. 2020; 31:73–80.

11. Yonetsu T, Murai T, Kanaji Y, Lee T, Matsuda J, Usui E, et al. Significance of microvascular function in visual-functional mismatch between invasive coronary angiography and fractional flow reserve. *J Am Heart Assoc*. 2017; 6:e005916. https://doi.org/10.1161/JAHA.117.005916 PMID: 28566295

12. Suga T, Iwanaga Y, Kobuke K, Morimoto K, Ikuta S, Ueno M, et al. Clinical utility of low-pressure implantation of drug-eluting stent into very small vessels. *J Cardiol*. 2014; 63:218–222. https://doi.org/10.1016/j.jcc.2013.06.006 PMID: 24646655

13. De Bruyne B, Pijls NH, Barbato E, Bartunek J, Bech JW, Wijns W, et al. Intracoronary and intravenous adenosine 5'-triphosphate, adenosine, papaverine, and contrast medium to assess fractional flow reserve in humans. *Circulation*. 2003; 107:1877–1883. https://doi.org/10.1161/01.CIR.0000061950.24940.88 PMID: 12668522

14. Sen S, Escaned J, Malik IS, Mikhail GW, Foale RA, Mira R, et al. Development and validation of a new adenosine-independent index of stenosis severity from coronary wave-intensity analysis: results of the ADVISE (ADenosine Vasodilator Independent Stenosis Evaluation) study. *J Am Coll Cardiol*. 2012; 59:1392–1402. https://doi.org/10.1016/j.jcc.2011.11.003 PMID: 22154731

15. Zimmermann FM, Ferrara A, Johnson NP, van Nuenen LX, Escaned J, Albertsson P, et al. Deferral vs. performance of percutaneous coronary intervention of functionally non-significant coronary stenosis: 15-year follow-up of the DEFER trial. *Eur Heart J*. 2015; 36:3182–3188. https://doi.org/10.1093/eurheartj/ehv182 PMID: 26400925

16. Petraco R, Al-Lamee R, Gotberg M, Sharp A, Hellig F, Nijjer SS, et al. Real-time use of instantaneous wave-free ratio: results of the ADVISE in-practice: an international, multicenter evaluation of instantaneous wave-free ratio in clinical practice. *Am Heart J*. 2014; 168:739–748. https://doi.org/10.1016/j.ahj.2014.06.022 PMID: 25440803

17. Ding WY, Nair S, Appleby C. Diagnostic accuracy of instantaneous wave free-ratio in clinical practice. *J Interv Cardiol*. 2017; 30:564–569. https://doi.org/10.1111/jic.12422 PMID: 28853190
18. Petraco R, Park JJ, Sen S, Nijjer SS, Malik IS, Echavarria-Pinto M, et al. Hybrid iFR-FFR decision-making strategy: implications for enhancing universal adoption of physiology-guided coronary revascularisation. *EuroIntervention*. 2013; 8:1157–1165. https://doi.org/10.4244/EIJV8A179 PMID: 23256988

19. Scarsini R, Pesarini G, Zivelonghi C, Piccoli A, Ferrero V, Lunardi M, et al. Coronary physiology in patients with severe aortic stenosis: comparison between fractional flow reserve and instantaneous wave-free ratio. *Int J Cardiol*. 2017; 243:40–46. https://doi.org/10.1016/j.ijcard.2017.05.117 PMID: 28610962

20. Petraco R, van de Hoef TP, Nijjer S, Sen S, van Lavieren MA, Foale RA, et al. Baseline instantaneous wave-free ratio as a pressure-only estimation of underlying coronary flow reserve: results of the JUSTIFY-CFR Study (Joined Coronary Pressure and Flow Analysis to Determine Diagnostic Characteristics of Basal and Hyperemic Indices of Functional Lesion Severity–Coronary Flow Reserve). *Circ Cardiovasc Interv*. 2014; 7:492–502. https://doi.org/10.1161/CIRCINTERVENTIONS.113.000926 PMID: 24987048

21. Wu KY, Timmerman NP, McPhedran R, Hossain A, Beanlands RSB, Chong AY, et al. Differential association of diabetes mellitus and female sex with impaired myocardial flow reserve across the spectrum of epicardial coronary disease. *Eur Heart J Cardiovasc Imaging*. 2019; pii: jez163.

22. Vaccarino V, Khan D, Votaw J, Faber T, Veledar E, Jones DP, et al. Inflammation is related to coronary flow reserve detected by positron emission tomography in asymptomatic male twins. *J Am Coll Cardiol*. 2011; 57:1271–1279. https://doi.org/10.1016/j.jacc.2010.09.074 PMID: 21392641

23. Niizuma S, Takiuchi S, Okada S, Horio T, Kamide K, Nakata H, et al. Decreased coronary flow reserve in haemodialysis patients. *Nephrol Dial Transplant*. 2008; 23:2324–2328. https://doi.org/10.1093/ndt/gfm954 PMID: 18234846

24. McConkey HZR, Marber M, Chiribiri A, Pibarot P, Redwood SR, Prendergast BD. Coronary microcirculation in aortic stenosis. *Circ Cardiovasc Interv*. 2019; 12:e007547. https://doi.org/10.1161/CIRCINTERVENTIONS.118.007547 PMID: 31416359

25. Arashi H, Yamaguchi J, Ri T, Otsuki H, Nakao M, Kamishima K, et al. The impact of tissue Doppler index E/e’ ratio on instantaneous wave-free ratio. *J Cardiol*. 2018; 71:237–243. https://doi.org/10.1016/j.jjcc.2017.09.003 PMID: 29054592

26. Escaned J, Ryan N, Mejia-Renteria H, Cook CM, Dehbi HM, Alegria-Barrero E, et al. Safety of the deferral of coronary revascularization on the basis of instantaneous wave-free ratio and fractional flow reserve measurements in stable coronary artery disease and acute coronary syndromes. *JACC Cardiovasc Interv*. 2018; 11:1437–1449. https://doi.org/10.1016/j.jcin.2018.05.029 PMID: 30093050

27. Lee JM, Shin ES, Nam CW, Doh JH, Hwang D, Park J, et al. Clinical outcomes according to fractional flow reserve or instantaneous wave-free ratio in deferred lesions. *JACC Cardiovasc Interv*. 2017; 10:2502–2510. https://doi.org/10.1016/j.jcin.2017.07.019 PMID: 29198458

28. Johnson NP, Tóth GG, Lai D, Zhu H, Açar G, Agostoni P, et al. Prognostic value of fractional flow reserve: linking physiologic severity to clinical outcomes. *J Am Coll Cardiol*. 2014; 64:1641–1654. https://doi.org/10.1016/j.jacc.2014.07.973 PMID: 25323250