Because the Fractional Flow Reserve Versus Angiography for Multivessel Evaluation (FAME) study demonstrated that fractional flow reserve (FFR)–guided coronary revascularization results in better clinical outcomes compared with angiographic guidance, coronary pressure–based evaluation of the functional severity of coronary stenoses has emerged as a routine diagnostic strategy in clinical practice. Nonetheless, the impact of a coronary stenosis on myocardial perfusion may alternatively be quantified by the coronary blood flow–derived coronary flow velocity reserve (CFVR). Despite the fact that the diagnostic accuracy of FFR and CFVR is known to be equivalent, FFR and CFVR results are discordant in 30% to 40% of coronary stenoses: a phenomenon proposed to originate from divergent distribution of epicardial and microvascular involvement in coronary artery disease (Figure 1). Daily practice is likely governed by a combination of epicardial and microvascular involvement, where the extent of microvascular involvement remains elusive to the interventionalist when only coronary pressure is assessed. This diagnostic gap is important because microvascular disease is increasingly recognized as an essential component in the spectrum of ischemic heart disease, particularly its prognosis.

**Background**—Discordance between fractional flow reserve (FFR) and coronary flow velocity reserve (CFVR) may reflect important coronary pathophysiology but usually remains unnoticed in clinical practice. We evaluated the physiological basis and clinical outcome associated with FFR/CFVR discordance.

**Methods and Results**—We studied 157 intermediate coronary stenoses in 157 patients, evaluated by FFR and CFVR between April 1997 and September 2006 in which revascularization was deferred. Long-term follow-up was performed to document the occurrence of major adverse cardiac events: cardiac death, myocardial infarction, or target vessel revascularization. Discordance between FFR and CFVR occurred in 31% and 37% of stenoses at the 0.75, and 0.80 FFR cut-off value, respectively, and was characterized by microvascular resistances during basal and hyperemic conditions. Follow-up duration amounted to 11.7 years (Q1–Q3, 9.9–13.3 years). Compared with concordant normal results of FFR and CFVR, a normal FFR with an abnormal CFVR was associated with significantly increased major adverse cardiac events rate throughout 10 years of follow-up, regardless of the FFR cut-off applied. In contrast, an abnormal FFR with a normal CFVR was associated with equivalent clinical outcome compared with concordant normal results: ≤3 years when FFR <0.75 was depicted abnormal and throughout 10 years of follow-up when FFR ≤0.80 was depicted abnormal.

**Conclusions**—Discordance of CFVR with FFR originates from the involvement of the coronary microvasculature. Importantly, the risk for major adverse cardiac events associated with FFR/CFVR discordance is mainly attributable to stenoses where CFVR is abnormal. This emphasizes the requirement of intracoronary flow assessment in addition to coronary pressure for optimal risk stratification in stable coronary artery disease. (Circ Cardiovasc Interv. 2014;7:00-00.)

**Key Words:** coronary flow velocity reserve ■ coronary microcirculation ■ fractional flow reserve ■ stable coronary artery disease
WHAT IS KNOWN

- Fractional flow reserve (FFR) and coronary flow velocity reserve (CFVR) have an equivalent diagnostic accuracy for inducible myocardial ischemia.
- FFR and CFVR provide discordant results in 30% to 40% of cases, which was proposed to originate from a divergent distribution of epicardial and microvascular involvement in coronary artery disease, thus reflecting important coronary pathophysiology.

WHAT THE STUDY ADDS

- Discordance of CFVR with FFR is characterized by the magnitude of coronary microvascular resistance during basal and hyperemic conditions, implicating a pivotal role of the coronary microvasculature in the physiologically guided identification of coronary artery disease severity.
- Discordance of FFR and CFVR is associated with adverse outcome compared with cases where FFR and CFVR are concordantly normal.
- The adverse outcome of discordance between FFR and CFVR compared with cases in which FFR and CFVR are normal is particularly attributable to those cases where FFR is normal but CFVR is abnormal, whereas discordance with an abnormal FFR and a normal CFVR is predominantly associated with equivalent clinical outcome compared with concordantly normal FFR and CFVR.
major adverse cardiac events (MACEs). MACE was defined as the composite of cardiac death, acute myocardial infarction not clearly attributable to a nontarget vessel, and clinically driven (urgent) revascularization of the target vessel by means of coronary artery bypass graft surgery or percutaneous coronary intervention (PCI). All patient-reported adverse events were verified by evaluating hospital records or contacting the treating cardiologist or general practitioner.

Data Analysis
FFR was calculated as the ratio of mean distal coronary pressure to mean aortic pressure during maximal hyperemia and was evaluated at both the ischemic cut-off value of 0.75, where FFR <0.75 was considered abnormal,\textsuperscript{17} and the clinically adopted cut-off value of 0.80, where FFR ≤0.80 was considered abnormal.\textsuperscript{5,17} CFVR was calculated as the ratio of hyperemic to basal average peak blood flow velocity distal to the target stenosis, and CFVR <2.0 was considered abnormal.\textsuperscript{15} We additionally determined the hyperemic stenosis resistance index,\textsuperscript{6} defined as the ratio between the pressure drop across the stenosis and distal average peak blood flow velocity, as well as the microvascular resistance (MR) index,\textsuperscript{8} defined as the ratio of mean distal coronary pressure to distal average peak blood flow velocity, which was determined during basal conditions (basal MR [BMR]) and hyperemia (hyperemic MR [HMR]). The MR reserve was defined as the absolute difference between BMR and HMR.

Statistical Analysis
In the presence of multiple coronary stenoses of intermediate severity, one of the intermediate stenoses was randomly marked the index stenosis and was used for subsequent analyses. Event rates at 1, 3, 5, and 10 years of follow-up were estimated using the Kaplan–Meier method. Relative risks (RRs) were calculated as the ratio of Kaplan–Meier–estimated event rates at each time point. The 95% confidence interval for the RR was calculated by calculating the SE of the logarithm of the RR with a Taylor approximation, that is, as (SE(RR))\textsuperscript{2} (RR\textsuperscript{2}), and its 95% confidence interval. The latter was then exponentiated to obtain the 95% confidence limits of the RR. The statistical significance of differences in event rates between groups was assessed with the use of the log-rank test. The distribution of FFR and CFVR values was assessed using the Shapiro–Wilk statistic to assess normality of the distribution and the Hartigan dip test to assess unimodality of the distribution. Between groups, continuous variables were compared with Student t test or Mann–Whitney U test, according to their normal or skewed distribution, and categorical variables were compared with χ\textsuperscript{2} or Fisher exact test, as appropriate. Trend analyses across concordance and discordance groups were computed, where overall differences were compared with 1-way ANOVA, Kruskal–Wallis, χ\textsuperscript{2} or Fisher exact test, followed by post hoc t test, Mann–Whitney U or Fisher exact test, with Bonferroni-adjusted significance level. Variables are presented as mean (±SD), median (25th–75th percentile), or frequency (percentage), where appropriate. A P value below the 2-sided α-level of 0.05 was considered statistically significant. The STATA 13.1 statistical software package (StataCorp, College Station, TX) was used for all calculations.

Results

Patient Population
In a total of 214 patients, both coronary pressure and flow velocity were determined distal to 279 coronary stenoses. Follow-up was obtained in 209 of 214 patients (97.7%), with 273 of 279 stenoses (97.8%). In the other 5 patients (2.3%) no procedural and postprocedural data were available. PCI was deferred in 157 of 209 patients (75.1%), with 186 coronary stenoses (68.1%), 29 of which were considered nonindex stenoses and were discarded for the current analyses. Therefore, the final study population consisted of 157 patients, with 157 coronary stenoses in which revascularization was deferred.

The clinical characteristics of the final study population are shown in Table 1. Table I in the Data Supplement depicts the clinical, angiographic, and physiological characteristics of all patients in whom follow-up was obtained stratified by revascularization (PCI group) or deferral of revascularization (Defer group), as well as the angiographic and physiological characteristics of the index stenoses.

The mean age of the final study population was 60±13 years, and 71% of patients were men. The median follow-up duration amounted to 11.7 years (9.9–13.3 years). Figure 2A through 2C show the distribution of FFR and CFVR values across the study population. Both FFR and CFVR showed a normal (Shapiro–Wilk statistic: 0.97 and 0.94, respectively), and unimodal distribution (dip 0.026, P=0.75 and dip 0.022, P=0.91, respectively).

Frequency and Clinical Characteristics of FFR/CFVR Discordance
Using a cut-off value of <0.75 to indicate an abnormal FFR,\textsuperscript{18} a stenosis yielding discordant results between FFR and CFVR was present in 30.6% of patients (48 of 157), with FFR ≥0.75 and CFVR <2.0 in 16.6% of patients (26 of 157). Using the clinically adopted cut-off value of ≤0.80 to indicate an abnormal FFR,\textsuperscript{19,21} a stenosis yielding discordant results between FFR and CFVR was present in 36.9% of patients (58 of 157), with FFR ≤0.80 and CFVR ≥2.0 in 16.6% of patients (26 of 157). Using the clinically adopted cut-off value of ≤0.80 to indicate an abnormal FFR,\textsuperscript{19,21} a stenosis yielding discordant results between FFR and CFVR was present in 36.9% of patients (58 of 157), with FFR ≤0.80 and CFVR ≥2.0 in 16.6% of patients (26 of 157). Using the clinically adopted cut-off value of ≤0.80 to indicate an abnormal FFR,\textsuperscript{19,21} a stenosis yielding discordant results between FFR and CFVR was present in 36.9% of patients (58 of 157), with FFR ≤0.80 and CFVR ≥2.0 in 16.6% of patients (26 of 157). Table II in the Data Supplement depicts the demographic and clinical characteristics of the study population according to FFR and CFVR concordance and discordance at the 0.75 FFR level.
cut-off value, as well as at the 0.80 FFR cut-off value. No pertinent differences in clinical characteristics were present between groups, regardless of the cut-off value used to depict abnormal FFR.

**FFR/CFVR Discordance in Relation to the Magnitude of Stenosis and Microvascular Resistance**

Table 2 depicts the angiographic and physiological characteristics of the study population according to concordance and discordance at the 0.75 FFR cut-off value, as well as at the 0.80 FFR cut-off value. Discordance between FFR and CFVR among stenoses with equivalent epicardial disease, as identified by FFR, was characterized by the magnitude of MR during basal conditions (BMR). Both among stenoses with FFR ≥0.75, and among stenoses with FFR <0.75, BMR was significantly lower when CFVR was abnormal compared with when CFVR was normal (P<0.001 for both; Table 2). Notably, a low BMR was associated with a high basal average peak blood flow velocity (Table 2). Similar results were observed at the 0.80 FFR cut-off value (Table 2).

Discordance between FFR and CFVR among stenoses with similar coronary flow reserve was characterized by the magnitude of MR during hyperemic conditions (HMR). Both among stenoses with CFVR ≥2.0, and among stenoses with CFVR <2.0, HMR was significantly lower when FFR <0.75 (P=0.015 and P=0.042, respectively; Table 2). Similar results were observed at the 0.80 FFR cut-off value (Table 2).

The 2 groups in which FFR and CFVR were discordant were characterized by divergence of hyperemic stenosis resistance index, BMR, HMR, and MR reserve (Table 2).
Table 2  Procedural Characteristics According to Concordant and Discordant Groups by the 0.75 and 0.80 FFR Cut-Off Value

<table>
<thead>
<tr>
<th></th>
<th>FFR 0.75 Cut-Off</th>
<th></th>
<th>FFR 0.80 Cut-Off</th>
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<th>Overall P Value</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Concordant Normal</td>
<td>Discordant</td>
<td>Concordant Normal</td>
<td>Discordant</td>
<td>Concordant</td>
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<tr>
<td></td>
<td>FFR ≥0.75</td>
<td>FFR ≥0.75</td>
<td>FFR &lt;0.75</td>
<td>FFR ≥0.75</td>
<td>FFR &lt;0.75</td>
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<td></td>
<td>CFVR ≥2.0</td>
<td>CFVR &lt;2.0</td>
<td>CFVR ≥2.0</td>
<td>CFVR &lt;2.0</td>
<td>CFVR &lt;2.0</td>
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</tr>
<tr>
<td>(n=100)</td>
<td>(n=22)</td>
<td>(n=26)</td>
<td>(n=9)</td>
<td>(n=78)</td>
<td>(n=10)</td>
<td>(n=48)</td>
</tr>
<tr>
<td>LAD</td>
<td>50 (50)</td>
<td>8 (36)</td>
<td>18 (69)</td>
<td>6 (67)</td>
<td>35 (45)</td>
<td>4 (40)</td>
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<td>(mm)</td>
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<td></td>
<td></td>
<td>10 (48)</td>
</tr>
<tr>
<td>LCX</td>
<td>22 (22)</td>
<td>10 (45)*†</td>
<td>3 (12b)</td>
<td>0 (0)§</td>
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<td>RCA</td>
<td>28 (28)</td>
<td>4 (18)</td>
<td>5 (19)</td>
<td>3 (33)</td>
<td>23 (29)</td>
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<td>10 (21)</td>
</tr>
<tr>
<td>Diameter stenosis, %</td>
<td>53 (45–57)</td>
<td>52 (47–56)</td>
<td>54 (52–57)</td>
<td>61 (55–66)</td>
<td>52 (45–57)</td>
<td>53 (48–53)</td>
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<td>54 (50–57)</td>
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<tr>
<td>Reference diameter, mm</td>
<td>3.0 ± 0.7</td>
<td>2.9 ± 0.4</td>
<td>2.8 ± 0.6</td>
<td>2.6 ± 0.7</td>
<td>0.70 ± 0.4</td>
<td>0.70 ± 0.4</td>
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<tr>
<td>Overall P Value</td>
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<td></td>
<td></td>
<td>1.5 (1.1–1.7)†</td>
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<td></td>
<td></td>
<td>1.3 (1.1–1.5)†</td>
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<td>FFR</td>
<td>0.86 (0.81–0.91)*†§</td>
<td>0.80 (0.78–0.87)*†§</td>
<td>0.70 (0.68–0.73)*†§</td>
<td>0.66 (0.60–0.71)*†§</td>
<td>0.69 (0.60–0.73)*†§</td>
<td>0.74 (0.70–0.78)‡§</td>
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<td>(mm)</td>
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<td></td>
<td>0.76 (0.67–0.78)‡§</td>
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<tr>
<td>CFVR</td>
<td>2.6 (2.3–3.0)†§</td>
<td>1.8 (1.6–1.9)*†</td>
<td>2.7 (2.2–3.1)†§</td>
<td>1.6 (1.4–1.8)*†§</td>
<td>1.7 (1.5–1.9)*†§</td>
<td>1.8 (1.5–1.9)†§</td>
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<td>0.001</td>
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<tr>
<td>HSR, mmHg/cm per second</td>
<td>0.31 (0.19–0.48)*†§</td>
<td>0.52 (0.36–0.70)*†§</td>
<td>0.79 (0.67–0.89)*†§</td>
<td>0.78 (0.61–0.94)*†§</td>
<td>0.26 (0.16–0.39)*†</td>
<td>0.34 (0.25–0.49)*†</td>
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<td>(mm)</td>
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<td></td>
<td></td>
<td>0.70 (0.50–0.81)‡§</td>
</tr>
<tr>
<td>BMR, mmHg/cm per second</td>
<td>6.29 (5.00–6.00)†§</td>
<td>4.71 (3.81–6.07)†§</td>
<td>6.52 (4.25–7.45)†</td>
<td>3.60 (2.80–4.18)‡,‡</td>
<td>0.001</td>
<td>6.50 (5.06–7.92)†§</td>
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<td>(mm)</td>
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<td></td>
<td></td>
<td>4.91 (4.15–5.29)*†</td>
</tr>
<tr>
<td>HMR, mmHg/cm per second</td>
<td>2.08 (1.67–2.63)*</td>
<td>2.29 (1.83–2.81)†</td>
<td>1.73 (1.43–1.99)†§</td>
<td>1.52 (1.31–1.88)‡</td>
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<td>2.08 (1.78–2.63)*</td>
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<td>2.51 (2.05–2.96)</td>
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<tr>
<td>MR reserve, mmHg/cm per second</td>
<td>4.17 (3.06–5.39)†§</td>
<td>2.26 (1.91–2.99)*†§</td>
<td>4.61 (3.23–5.38)†§</td>
<td>2.06 (1.40–2.21)‡,‡</td>
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<td>4.27 (3.23–5.37)†§</td>
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<td>(mm)</td>
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<td></td>
<td></td>
<td>2.26 (1.98–2.74)*</td>
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<tr>
<td>h-Pa, mmHg</td>
<td>93 (86–102)</td>
<td>93 (85–100)</td>
<td>91 (82–99)</td>
<td>97 (90–100)</td>
<td>93 (86–103)</td>
<td>90 (85–101)</td>
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<td>b-Pa, mmHg</td>
<td>92 (85–102)</td>
<td>91 (79–99)</td>
<td>86 (80–96)</td>
<td>90 (71–98)</td>
<td>94 (87–102)</td>
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<td>87 (82–97)</td>
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<tr>
<td>h-Pm, mmHg</td>
<td>81 (74–89)*†§</td>
<td>74 (68–81)*†§</td>
<td>64 (60–70)*‡</td>
<td>61 (50–71)*‡</td>
<td>0.01</td>
<td>82 (76–91)*†§</td>
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<td>(mm)</td>
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<td>79 (75–88)*†§</td>
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<tr>
<td>h-AP, mmHg</td>
<td>12.9–18)*†§</td>
<td>17 (12–22)*†§</td>
<td>27 (24–31)*†§</td>
<td>31 (28–36)*†§</td>
<td>0.001</td>
<td>11 (7–14)*†§</td>
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<td>(mm)</td>
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<td></td>
<td></td>
<td>12 (10–15)*‡§</td>
</tr>
<tr>
<td>b-APV, cm/s</td>
<td>15 (11–19)*†§</td>
<td>19 (14–26)*‡</td>
<td>14 (11–18)*‡</td>
<td>25 (21–31)*‡</td>
<td>0.001</td>
<td>15 (12–18)*‡</td>
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<tr>
<td>(mm)</td>
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<td></td>
<td>20 (16–27)*‡</td>
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<tr>
<td>h-APV, cm/s</td>
<td>38 (31–49)</td>
<td>34 (26–43)</td>
<td>38 (31–46)</td>
<td>39 (33–53)</td>
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<td>(mm)</td>
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<td>36 (25–45)</td>
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</table>
| APV indicates average peak flow velocity; BMR, basal microvascular resistance; CFVR, coronary flow velocity reserve; FFR, fractional flow reserve; HMR, hyperemic microvascular resistance; HSR, hyperemic stenosis resistance index; LAD, left anterior descending coronary artery; LCX, left circumflex coronary artery; Pa, aortic pressure; Pd, distal coronary pressure; AP, pressure drop across the stenosis; and RCA, right coronary artery. *P<0.05 versus discordant CFVR normal FFR abnormal; † P<0.05 versus discordant abnormal; ‡ P<0.05 compared with concordant normal; and § P<0.05 versus discordant CFVR abnormal and FFR normal.
Clinical Outcome After Deferral of Revascularization in Lesions With FFR/CFVR Discordance

Table III in the Data Supplement shows the incidence of MACE and its components among patients in the different concordance and discordance groups at 1, 3, 5, and 10 years of follow-up. In general, MACE was governed by coronary revascularizations.

Figures 3A, 3B, 4A, and 4B show the Kaplan–Meier curves for MACE among patients in the concordant normal and discordant groups, Kaplan–Meier estimates and statistical comparison of which are presented in Tables 3 through 5. Overall, discordance between FFR and CFVR was associated with a significantly increased MACE rate throughout follow-up compared with concordant normal FFR and CFVR results, regardless of whether the 0.75 (Figure 3A and Table 3) or 0.80 (Figure 3B and Table 3) cut-off was used to depict an abnormal FFR.

Importantly, the combination of a normal FFR and an abnormal CFVR, indicating predominant microvascular disease (Figure 1), was associated with a high MACE rate early after deferral of revascularization. This high early MACE rate remained significantly higher throughout 10-year follow-up compared with concordantly normal FFR and CFVR results, regardless of whether FFR <0.75 or FFR ≤0.80 was depicted as abnormal (Figure 4A and 4B and Tables 4 and 5). In contrast, an abnormal FFR with a normal CFVR, indicating predominant focal but nonflow-limiting epicardial disease (Figure 1), was associated with equivalent clinical outcome compared with concordant normal FFR and CFVR results for up to 3 years after deferral of revascularization when FFR <0.75 was depicted abnormal (Figure 4A and Table 4), and up to 10 years after deferral of revascularization when FFR ≤0.80 was depicted abnormal (Figure 4B and Table 5). Moreover, the MACE rate associated with a normal FFR and abnormal CFVR was significantly higher than that associated with an abnormal FFR and normal CFVR: up to 3 years of follow-up when FFR <0.75 was depicted abnormal (Figure 4A and Table 4), and up to 10 years of follow-up when FFR ≤0.80 was depicted abnormal (Figure 4B and Table 5).

Discussion

The main finding in this study is that discordance with a normal FFR and abnormal CFVR is associated with adverse long-term clinical outcome compared with stenoses in which FFR and CFVR are concordantly normal, whereas discordance with an abnormal FFR and a normal CFVR is predominantly associated with equivalent clinical outcome compared with concordantly normal FFR and CFVR. Because discordance is a frequent phenomenon, occurring in 31% to 37% of intermediate coronary stenoses, its substantial clinical impact that contrasts with the information derived from FFR implicates a necessity of coronary flow assessment in addition to coronary pressure for optimal physiological evaluation of stable coronary artery disease.
According to our observations, coronary flow plays a dominant role in the functional consequences of stable coronary artery disease, which is not identified by solitary measurement of coronary pressure–derived FFR. Nonetheless, after 3 years of follow-up, an increase in MACE was observed in patients with a normal CFVR and an abnormal FFR, particularly at the 0.75 cut-off; this is likely attributable to disease progression. Because FFR <0.75 distal to these stenoses indicates that epicardial conductance is substantially impaired relative to vessels in which both FFR and CFVR are normal, it is likely that these initially nonflow-limiting stenoses more frequently lead to a flow-limiting stenosis at long-term follow-up as part of progression of obstructive coronary artery disease and are therefore associated with a long-term increase in MACE. This is supported by the finding that the observed increase in MACE was substantially more pronounced when FFR <0.75, than when FFR ≥0.80, suggesting that the extent of epicardial disease is indeed a contributing factor to the occurrence of MACE at long-term follow-up. In addition, coronary flow reserve decreases with advancing age, and a progressive decrease in CFVR associated with aging during a 10-year follow-up period may alternatively explain the long-term gain in MACE in these patients. Nonetheless, these findings strongly indicate that a favorable clinical outcome after deferred revascularization in stenoses of intermediate severity can only be assumed in the presence of a normal CFVR, even when FFR is normal. Hence, our current observations emphasize the need for combined assessment of coronary flow and pressure in clinical practice.

### Discordance Between FFR and CFVR: Is Only One of Them Correct?

It is often implied that discordance between FFR and CFVR stems from inaccuracy in the determination of one of these parameters, whereby the inaccuracy is typically attributed to limitations of CFVR. However, FFR and hyperemic flow reserve are both valuable clinical tools, and understanding the mechanisms underlying discordance is crucial for optimizing patient care.
velocity, as an important factor in CFVR, are intrinsically related by a curvilinear pressure drop—flow velocity relationship resulting from the combined effect of Poiseuille’s and Bernouilli’s Law on stenosis hemodynamics.14 As a result, the pressure drop across a stenosis increases with increasing flow through the stenosis. Consequently, for a given stenosis, FFR and CFVR per definition move in opposite directions with changing hyperemic flow through the stenosis.14 Hence, discordance between FFR and CFVR can be explained from basic physiological principles, and neither FFR nor CFVR can be considered incorrect in case of discordant results.

**Coronary Microvasculature Characterizes Discordance Between FFR and CFVR**

Meuwissen et al first described the pivotal role of the functional status of the coronary microvasculature during hyperemic conditions in the occurrence of both extremes of the discordance spectrum.8 Our observations expand on the role of the coronary microvasculature as a pivotal component not only in the extremes of the discordance spectrum but as the main determinant of discordance of CFVR with FFR and indicate that its functional status during basal conditions provides substantial additional information.

The 4 major quadrants in which the relationship between FFR and CFVR can be divided (Figure 1), as proposed by Johnson et al,9 are individually characterized by the status of the coronary microvasculature, where the magnitude of BMR and HMR in vessels with concordant normal FFR and CFVR results (Figure 1, blue area) can be considered normal in the absence of a stenosis inducing a pressure drop, or microvascular disease reducing myocardial blood flow (Table 2). In comparison, in vessels with a normal FFR and abnormal CFVR (Figure 1, green area), BMR is low, whereas HMR is relatively high (Table 2), despite epicardial disease of equivalent severity. This probably results from predominant microvascular disease, as the low BMR indicates compensatory microvascular vasodilation during basal conditions, and the relatively high HMR may indicate impaired hyperemic vasodilator response of the coronary microvasculature. Apparently, more extensive microvascular disease not only limits the vasodilatory capacity of the coronary microcirculation but also necessitates compensatory vasodilation of the coronary resistance vessels, and thus a decrease in BMR, to accommodate equivalent myocardial demand during basal conditions.12,14,23

In vessels with an abnormal FFR and a normal CFVR (Figure 1, orange area), BMR is normal, and HMR is low compared with vessels with discordant normal FFR and CFVR (Table 3). This probably results from predominant focal, but nonflow-limiting, epicardial disease in the absence of microvascular abnormalities, because the normal BMR indicates that myocardial perfusion is preserved in basal conditions, which allows BMR to remain unaltered,24 and HMR indicates that the vasodilatory response of the microvasculature is intact. In these stenoses with a substantial pressure drop, the low HMR may be attributed to chronic deprivation of distal perfusion pressure, leading to structural adaptation of the coronary vasculature and a reduced vascular tone at maximal hyperemia.25,26

Vessels with discordant abnormal FFR and CFVR (Figure 1, red area) are characterized by a low BMR and a relatively low HMR (Table 3), most likely indicating extensive epicardial disease yielding similar structural adaptation to a loss of perfusion pressure, but additionally limiting blood flow to such extent necessitating compensatory microvascular vasodilation already during basal conditions.24 However, a combination of epicardial and microvascular disease cannot be excluded in this setting, although this is unlikely in the presence of a low HMR, which indicates a normal physiological vasodilatory response of the microvasculature during hyperemia.

**Disturbed Coronary Autoregulation May Drive Discordance of CFVR With FFR**

We observed that discordance of CFVR with FFR among stenosis with equivalent epicardial disease is particularly characterized by abnormalities in BMR (Table 2). Notably, in patients in whom CFVR was abnormal, a decreased

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**Table 5.** Cumulative Major Adverse Cardiac Event Rate at 1, 3, 5, and 10 Years of Follow-Up Stratified by the Specific Accordance and Discordance Groups According to the 0.80 FFR Cut-Off Value

<table>
<thead>
<tr>
<th>FFR 0.80 Cut-Off‡</th>
<th>FFR &gt;0.80 CFVR ≥2.0</th>
<th>FFR &gt;0.80 CFVR &lt;2.0</th>
<th>FFR ≤0.80 CFVR ≥2.0</th>
<th>Relative Risk†</th>
<th>P Value‡</th>
<th>Relative Risk†</th>
<th>P Value‡</th>
<th>Relative Risk†</th>
<th>P Value‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-year follow-up</td>
<td>1%</td>
<td>60%</td>
<td>6%</td>
<td>46.2 (6.1–349.4)</td>
<td>&lt;0.001</td>
<td>4.9 (0.5–45.6)</td>
<td>0.124</td>
<td>9.5 (2.9–31.7)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>3-year follow-up</td>
<td>3%</td>
<td>77%</td>
<td>13.5 (4.8–37.6)</td>
<td>&lt;0.001</td>
<td>1.6 (0.4–6.1)</td>
<td>0.465</td>
<td>8.4 (3.0–23.6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>5-year follow-up</td>
<td>9%</td>
<td>80%</td>
<td>8.8 (4.1–19.1)</td>
<td>&lt;0.001</td>
<td>2.5 (1.0–6.1)</td>
<td>0.035</td>
<td>3.5 (1.9–6.4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>10-year follow-up</td>
<td>28%</td>
<td>80%</td>
<td>2.8 (1.8–4.6)</td>
<td>&lt;0.001</td>
<td>1.4 (0.9–2.4)</td>
<td>0.130</td>
<td>2.0 (1.3–3.2)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

CFVR indicates coronary flow velocity reserve; FFR, fractional flow reserve; and MACE, major adverse cardiac event.

*Event rates were estimated with the Kaplan–Meier method.

†Relative risks and their 95% confidence intervals were calculated with the use of the Kaplan–Meier estimated MACE rates and their respective SEs.

‡P values are log-rank P values.
resistance of the microvasculature during basal conditions coexisted with an increased basal coronary flow velocity. Because normal coronary autoregulatory function would provide compensatory vasodilation only to the point necessary to maintain stable coronary flow, an increase in basal coronary flow in this setting suggests that coronary autoregulation is disturbed. Such disturbed autoregulation is consistent with an important role of microvascular (dys)function in the discordance between FFR and CFVR and may be attributed to structural vascular adaptation in the setting of microvascular disease or in the setting of chronic deprivation of perfusion pressure in the presence of substantial epicardial disease.

**Focal or Diffuse Epicardial Coronary Artery Disease in FFR/CFVR Discordance**

Because it cannot be inferred from an FFR value at a single location whether a pressure drop occurs from focal or diffuse disease of the epicardial conduit artery, which would require a distal-to-proximal pressure pullback, the epicardial component of coronary artery disease summarized by FFR includes the hemodynamic effect of both focal and diffuse epicardial atherosclerosis. Nonetheless, diffuse disease is in general less likely to induce an abnormal FFR because of a lack of convective acceleration of blood flow, limiting the resulting pressure drop over the diseased epicardial artery. Therefore, as suggested by Johnson et al, diffuse coronary artery disease may particularly provide a coexisting or alternative explanation for a reduction in CFVR, which may also be associated with adverse clinical outcome. Nonetheless, we have attributed the reduction in CFVR to a predominance of microvascular abnormalities. Complementary to the study by Johnson et al, our study allowed detailed evaluation of the relative distribution of epicardial and MRs. Our interpretation was therefore governed by the observation that abnormality of CFVR in our study population was generally associated with alterations in the resistance induced by the microvascular compartment instead of the epicardial compartment (Table 2). Nonetheless, in individual cases both diffuse epicardial and microvascular disease may provide coexisting explanations for a reduction in CFVR.

**Comparison With Previous Studies**

Information on the prognostic value of discordance between invasively assessed FFR and CFVR for long-term clinical outcome is limited. Our report is the first to identify a dominant role of invasively measured CFVR over FFR at its contemporary 0.80 cut-off value in the long-term prognosis of stable coronary artery disease patients. Moreover, this study is the first to identify a pivotal role of microvascular function in basal conditions in the discordance of CFVR and FFR and its important implications for clinical outcome of coronary stenoses of intermediate severity. Thereby, our results extend the observations of Meuwissen et al, whom showed that 1-year MACE rate after deferral of coronary revascularization of stenoses with FFR ≥0.75 was substantially higher when CFVR was abnormal than when CFVR was normal. Moreover, these results are consistent with studies using noninvasive imaging modalities to assess coronary flow reserve. In patients with normal hyperemic myocardial perfusion (as a surrogate for a normal FFR), Herzog et al reported an abnormal CFR to be associated with a significantly increased MACE rate compared with when CFR was normal (6.3% versus 1.4% per year; P<0.05). Similarly, Murthy et al identified an impaired CFR to be associated with a 3.2- and 4.9-fold increase in cardiac mortality rates among diabetic and nondiabetic patients, respectively, when hyperemic myocardial perfusion was normal.

Several studies support our current observations on the pertinence of microvascular function in basal conditions. We have reported recently that abnormalities in microvascular function under basal autoregulation conditions, in the absence of hyperemic blood flow impairment, impart a particularly important risk for long-term adverse events, both in patients with stable coronary artery disease and in patients after primary PCI for ST-segment–elevation myocardial infarction. Moreover, the previously mentioned noninvasive imaging studies support this hypothesis, because both studies indicate that an abnormal coronary flow reserve in the presence of normal hyperemic perfusion, indicating alterations in basal flow, is an important marker for adverse outcome. Apparently, substantial risk for long-term MACE is attributable to abnormalities in basal coronary flow regulation, implicating that indeed microvascular dysfunction is an elementary component in the diagnosis and prognosis of patients with coronary artery disease.

Finally, a recent study by Jespersen et al reported that patients with stable chest pain syndromes and coronary arteries without focal epicardial obstructive disease, considered indicative of diffuse epicardial narrowing, are at an 1.85-fold increased risk for MACE at long-term follow-up. Because diffuse epicardial narrowing may provide a coexisting explanation for a reduction in CFVR, or angina in the absence of focal epicardial disease may alternatively indicate microvascular disease, our observations are also consistent with those of Jespersen et al. Generally, the observations in these studies implicate that a normal epicardial coronary artery, documented either angiographically, noninvasively, or by FFR, does not imply a normal coronary vasculature. The presence of microvascular disease is an important element in coronary artery disease, which imposes an important risk for adverse outcome, and its identification may allow more accurate risk stratification in the setting of stable coronary artery disease.

**Future Perspectives**

The results of the present study emphasize the implications of discordance between coronary pressure and flow-derived parameters for clinical outcome in patients with stable coronary artery disease and indicate the importance of its recognition in clinical practice. Recent data have indicated that discordance with CFVR may be less frequent with the use of a basal pressure-derived index, the instantaneous wave-free ratio, compared with FFR. This was particularly relatable to the relative insensitivity of instantaneous wave-free ratio toward nonflow-limiting coronary stenoses, where the large pressure gradient during hyperemia, responsible for a positive FFR, results from a large increase in coronary flow during hyperemia: particularly those stenoses where we documented that clinical outcome is favorable. Hence, in
contrast to current assumptions, it may be speculated that basal conditions could provide an advantage over hyperemia in some cases, prompting further evaluation of this phenomenon in future studies.

Limitations

The results from the present study should be interpreted in consideration of some limitations. First, the relatively small sample size limits the statistical power and the strength of the conclusions. However, the present study comprises the largest cohort of stenoses with discordant FFR and CFVR results reported to date and the first to report long-term clinical follow-up of discordance at the 0.80 FFR cut-off value. Moreover, the differences between normal and abnormal CFVR results are large, indicating an important role of coronary flow for long-term MACE. Nonetheless, our results warrant evaluation in a larger discordance cohort, in particular, to identify the pertinence of revascularization in patients with discordant FFR and CFVR results.

Second, consistent with the era in which the data were obtained, the composition of the study population was based on the operator’s decision not to intervene. As a result, coronary stenoses in which revascularization was deferred were angiographically less severe, compared with stenoses in which PCI was performed. Secondary to the well-known discrepancy between the angiographic and physiological severity of a coronary stenosis, the stenoses in which revascularization was deferred included stenoses that are considered physiologically significant and would have been treated in contemporary clinical practice. However, as a corollary, the study population of deferred coronary stenoses represented a clinical population routinely referred for FFR assessment before intervention in contemporary clinical practice (Figure 2B and 2C). This allowed to study the natural (untreated) clinical course of FFR and CFVR discordance in a representative patient population, which can be considered a strength for the extrapolation of our results and conclusions to contemporary clinical practice.

Finally, this study is limited by the assessment of adverse events at long-term follow-up partly performed by means of a telephone survey. Such an approach is sensitive toward a possible patient recall bias, which may have resulted in under-reporting of adverse events. Nonetheless, the long-term MACE rates reported in the present study are generally comparable with those reported by Li et al.

Conclusions

Discordance between FFR and CFVR with a normal FFR but reduced CFVR, indicating predominant microvascular disease, is associated with a particularly unfavorable prognosis, whereas a preserved CFVR in the presence of an abnormal FFR, indicating nonflow-limiting epicardial coronary artery disease, yields a long-term clinical outcome comparable with concordantly normal FFR and CFVR. Our observations indicate a dominant role of coronary flow in the functional severity of coronary stenoses and implicate a necessity for identification of stenoses with discordance between coronary pressure and flow-derived parameters for optimal distinction between functionally significant and nonsignificant coronary stenoses.

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Disclosures

None.

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