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ORIGINAL RESEARCH

Prognostic Implications of Resistive Reserve Ratio in Patients With Coronary Artery Disease

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BACKGROUND: Resistive reserve ratio is a thermodilution-based index which integrates both coronary flow and pressure. Resistive reserve ratio represents the vasodilatory capacity of interrogated vessels including both epicardial coronary artery and microvascular circulation. We evaluated the prognostic potential of resistive reserve ratio compared with pressure-derived index (fractional flow reserve [FFR]) or flow-derived index (coronary flow reserve [CFR]).

METHODS AND RESULTS: A total of 1245 patients underwent coronary pressure and flow measurement using pressure-temperature wire. Resistive reserve ratio was calculated by CFR adjusted using the ratio between resting and hyperemic distal coronary pressure ([resting mean transit time/hyperemic mean transit time]×[resting distal coronary pressure/hyperemic distal coronary pressure]). Clinical outcome was assessed by patient-oriented composite outcome (POCO), a composite of any death, myocardial infarction, and revascularization at 5 years. At 5 years, the cumulative incidence of POCO was significantly different according to quartiles of resistive reserve ratio (9.9%, 11.3%, 17.2%, and 22.7% in quartiles 1 to 4, respectively, log rank $P<0.001$). Among patients with deferred revascularization, those with depressed resistive reserve ratio (<3.5) showed a significantly higher risk of POCO than those with preserved resistive reserve ratio (≥3.5) in patients with FFR>0.80 or patients with CFR>2.0. (FFR>0.80 group: 14.8% versus 6.0%; log rank $P=0.001$; CFR>2.0 group: 13.5% versus 7.1%; log rank $P=0.045$). Adding resistive reserve ratio into the model for 5-year POCO showed significantly higher global Chi square value than FFR or CFR ($P<0.001$, respectively, for FFR and CFR). Resistive reserve ratio <3.5 was significantly associated with the risk of POCO at 5 years in multivariable model (adjusted hazard ratio 1.597, 95% CI, 1.098–2.271, $P=0.014$).

CONCLUSIONS: Resistive reserve ratio, which integrated both coronary flow and pressure, showed incremental prognostic implications in patients with coronary artery disease undergoing elective percutaneous coronary intervention guided by invasive physiologic evaluation.

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Key Words: coronary artery disease ■ coronary flow reserve ■ fractional flow reserve ■ prognosis ■ resistive reserve ratio

In the treatment of ischemic heart disease, it is important to interpret how epicardial coronary arterial stenosis is related with functional significance, which is related to improving ischemic symptoms and prognosis.[1] The introduction of fractional flow reserve (FFR), an invasive physiologic index of functional stenosis severity that uses the trans-stenotic pressure ratio as a surrogate of myocardial blood flow impairment,

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For Sources of Funding and Disclosures, see page 11.

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CLINICAL PERSPECTIVE

What Is New?

- The current study demonstrated prognostic implication of resistive reserve ratio (RRR) as an integrated physiologic index of both pressure and flow. RRR showed an inverse relationship with the estimated risk of patient-oriented composite outcome.
- Among patients with deferred revascularization, those with depressed RRR (<3.5) showed a significantly higher risk of patient-oriented composite outcome than those with preserved RRR (≥3.5) in patients with coronary flow reserve >2.0 or patients with fractional flow reserve>0.80.
- Depressed RRR<3.5 was independently associated with higher risk of patient-oriented composite outcome and RRR showed superior discrimination of 5-year patient-oriented composite outcome than those with fractional flow reserve or coronary flow reserve on top of clinical variables.

What Are the Clinical Implications?

- Incremental prognostic impact of RRR imply that integration of both relative and absolute metrics of coronary circulatory indices would show more specific stratification of patients with myocardial ischemia and higher risk of future clinical events than flow-derived or pressure-derived indices alone.

Nonstandard Abbreviations and Acronyms

CFR	coronary flow reserve
FFR	fractional flow reserve
HR	hazard ratio
IMR	index of microcirculatory resistance
PCI	percutaneous coronary intervention
RRR	resistive reserve ratio
POCO	patient-oriented composite outcome

revolutionized decision-making on coronary revascularization in the cardiac catheterization laboratory, leading to improved patient outcomes compared with angiography-based decision making.[2–4]

Despite this, pressure-derived indices are not free from limitations in assessing coronary circulatory function, since disagreements between pressure-derived indices and flow measurements have been reported in several studies.[5,6] Coronary flow reserve (CFR) is an absolute ratio between resting and hyperemic coronary flow velocity or surrogate marker of flow velocity, and reflects the flow limitations of the entire coronary circulatory system, including both the epicardial and microvascular components.[2,7] Despite supportive study data on the prognostic impact of depressed CFR,[7–11] heterogenous mechanisms of depressed CFR and higher variability of CFR values according to hemodynamic status have limited its clinical applicability.[12] Considering both pressure-derived and flow-derived indices have their own limitations, integration of both coronary pressure and flow might provide superior discrimination of patient at higher risk of future clinical events. Since both coronary pressure and flow can be easily obtained using a pressure-temperature sensor guide wire, calculation of integrated index of both CFR and distal coronary pressure can be achieved.

Recently, the concept of resistive reserve ratio (RRR), which is an integrated index of both thermodilution-measured CFR and distal coronary pressure measured during resting and hyperemic status, has been suggested.[13] RRR represents the vasodilatory capacity of the coronary circulation and reflects cumulative functional disease burden throughout the interrogated vessel (Figure 1). We hypothesize that RRR might provide incremental prognostic stratification of patients at higher risk of clinical events at long-term follow-up than either pressure-derived (FFR) or flow-derived (CFR) indices. In this regard, we sought to evaluate the prognostic implications of RRR compared with FFR or CFR in patients with coronary artery disease.

METHODS

Anonymized patient level data will be made available after discussion in the executive committee for reasonable requests. Consent was not obtained for data sharing but the presented data are anonymized and the risk of identification is minimal.

Study Design and Population

The study population was derived from the International Collaboration of Comprehensive Physiologic Assessment Registry (NCT03690713). The registry was a patient-level pooled cohort of 3 prospective registries whose results have been previously published.[7,11,14–16] The registry was composed of 7 tertiary medical institutes in Korea (Seoul National University Hospital, Samsung Medical Centre, Inje University Ilsan Paik Hospital, Keimyung University Dongsan Medical Centre, and Ulsan University Hospital), Japan (Tsuchiura Kyodo General Hospital), and Spain (Hospital Clinico San Carlos). All patients were prospectively enrolled, and underwent clinically indicated invasive coronary angiography and comprehensive physiologic assessment for at least 1 vessel with intermediate stenosis.[7,11,14,15] In all studies, the same exclusion criteria

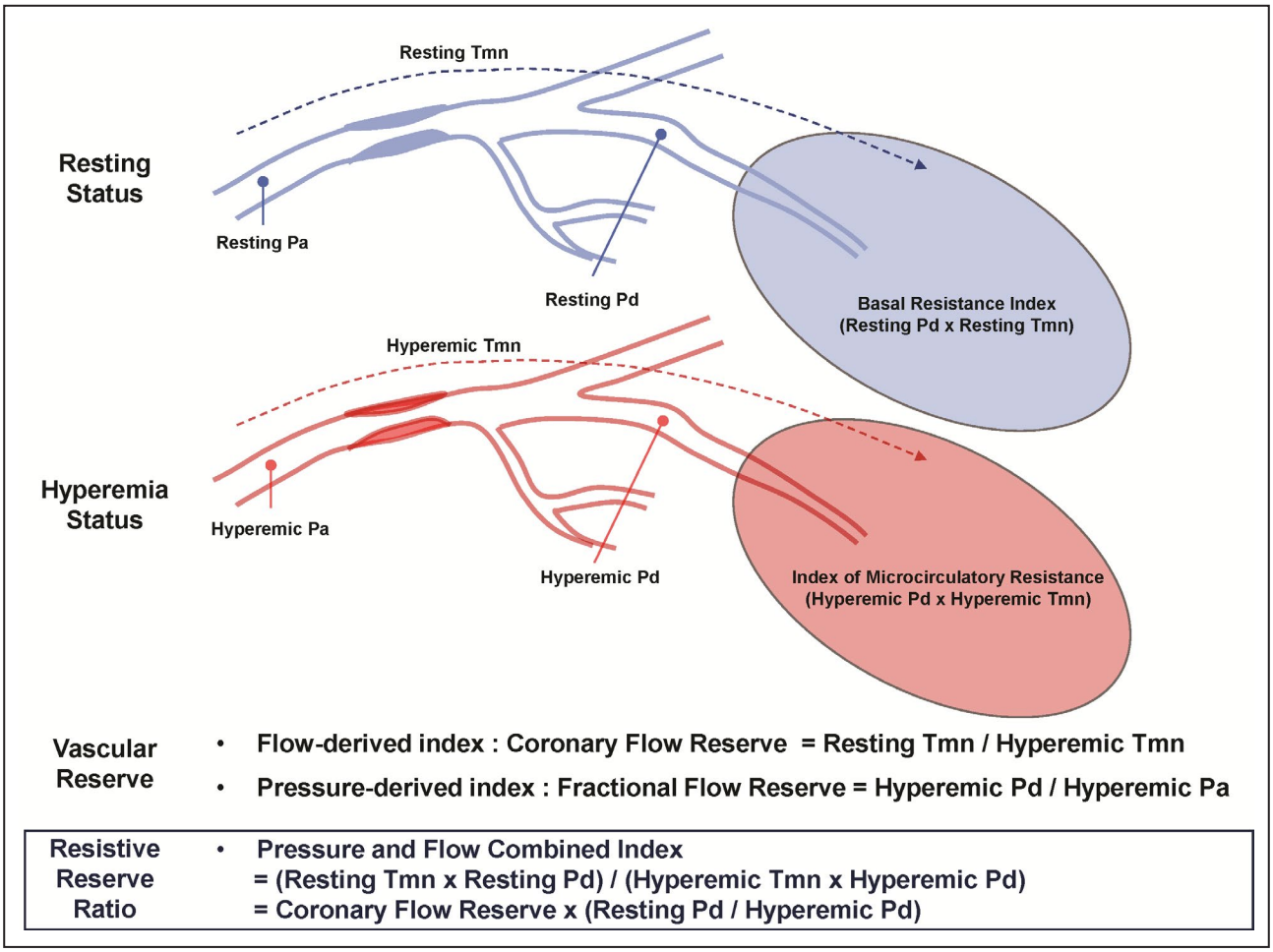

Figure 1. Concept of resistive reserve ratio.
In assessment of coronary circulatory function, coronary flow reserve can be calculated by ratio between resting and hyperemic mean transit time which is a surrogate marker of coronary flow. Fractional flow reserve is calculated as the ratio between hyperemic distal coronary pressure and hyperemic aortic pressure which is also surrogate marker of coronary flow at hyperemia. Resistive reserve ratio is an integrated index of both thermodilution-measured coronary flow reserve and distal coronary pressure measured during resting and hyperemic status and represents vasodilatory capacity of the coronary circulation and reflects cumulative functional disease burden throughout the interrogated vessel. Pa indicates aortic pressure; Pd, distal coronary pressure; and Tmn, mean transit time.

were applied, and patients with hemodynamic instability, left ventricular dysfunction (ejection fraction <30%), or a culprit vessel of acute coronary syndrome were excluded. Individual patient data were collected using standardized spreadsheets. For all variables included, standardized definitions were used. Invasive physiologic indices were also cross-checked and confirmed by each study's principal investigators.

Among the total 1694 vessels (1397 patients) enrolled overall, patients without available RRR were excluded from the current analysis, leaving 1484 vessels (1245 patients). Study protocols were designed in accordance with the Declaration of Helsinki (2013) and were authorized by the Institutional Review Boards or Ethics Committees at corresponding centers. The study protocol was registered at ClinicalTrials.gov (NCT03690713).

Angiographic Analysis and Coronary Physiologic Measurements

Coronary angiography was performed using standard techniques. Angiographic views were obtained following the administration of intracoronary nitrate (100 or 200 μg). All angiograms were analyzed at local core laboratories in masked fashion. Percent diameter stenosis (%DS), minimum luminal diameter, reference-vessel size, and lesion length were measured.

All coronary physiologic measurements were performed after diagnostic angiography and before revascularization was performed.[7,11,17] A guide catheter (5–7 Fr) without side holes was used to engage the coronary artery, and a pressure-temperature sensor

guide wire (Abbott Vascular, St. Paul, MN) was used to measure physiologic indices. After zeroing and equalizing the pressure sensor to the aortic pressure, the pressure sensor was positioned at the distal segment of the target vessel. Intracoronary nitrate (100 or 200 μg) was administered before each physiologic measurement. To derive resting mean transit time (Tmn), a thermodilution curve was obtained using 3 injections (4 mL each) of room-temperature saline. Hyperemia was induced by intravenous infusion of adenosine (140 μg/kg per min) through a peripheral or central vein. Hyperemic proximal aortic pressure (Pa), distal coronary pressure (Pd), and hyperemic Tmn were measured during sustained hyperemia after the pressure curve reached a nadir point.[18] The hyperemic period was recognized by a decreased Pd/aortic pressure pattern and a left shift in the Tmn. After measurements were complete, the guide wire was pulled back to the guide catheter, and the presence of a pressure drift was checked.

FFR was calculated as hyperemic Pd/aortic pressure, at the lowest average of 3 consecutive beats during maximal hyperemia. CFR was calculated as the resting Tmn/hyperemic Tmn.[11] Index of microcirculatory resistance (IMR) was calculated as the hyperemic Pd×hyperemic Tmn and was corrected using the Yong formula.[17] RRR was calculated as the ratio between basal resistance index (resting Tmn×resting Pd) and IMR, which can be transformed by CFR adjusted using ratio between resting and hyperemic distal coronary pressure ([resting Tmn/hyperemic Tmn]×[resting Pd/hyperemic Pd]).[13] For lesions with low FFR (≤0.80), percutaneous coronary intervention was recommended according to the current guidelines. However, the final decision for percutaneous coronary intervention was at the discretion of the operators. Current analysis used only pre-percutaneous coronary intervention physiologic indices.

Cut-Off Values and Patient Classifications

Cut-off values were FFR ≤0.80 (low FFR) and CFR ≤2.0 (low CFR), as previously described.[7,19–21] The cut-off value of RRR was determined by optimal cut-off value to predict the occurrence of POCO, which corresponded with the median value of RRR, and RRR <3.5 was defined as low RRR.

Patient Follow-Up, Outcome Measurements, and Clinical Event Adjudications

Clinical data were obtained at outpatient clinic visits or by telephone contact if needed. An independent clinical events committee whose members were unaware of the clinical, angiographic, and physiologic data adjudicated all events. The primary outcome was the patient-oriented composite outcome (POCO),[22] which includes all-cause mortality, any myocardial infarction, or any revascularization events during the 5-year follow-up. All clinical outcomes were defined according to the Academic Research Consortium, including the addendum to the definition of myocardial infarction.[22] All deaths were considered cardiac unless an undisputable non-cardiac cause was present. Repeat revascularization was also additionally adjudicated as to whether the event occurred in the initially interrogated vessel (target vessel-related repeat revascularization). Clinical outcomes were analyzed based on the worst hierarchical order (death > myocardial infarction >revascularization).

Statistical Analysis

All discrete or categorical variables are presented as numbers and relative frequencies (percentages), and continuous variables as means and SDs or medians with interquartile ranges according to their distributions, which were checked by the Kolmogorov-Smirnov test and visual inspection of Q-Q plots. Correlation coefficient among physiologic indices was analyzed using Pearson or Spearman method, according to the normality of variables. Data were analyzed on a per-patient basis for clinical characteristics and clinical outcomes at 5 years, and a per-vessel basis for comparison of vessel-related parameters. Among patients who underwent multivessel measurements, the vessel with the lowest FFR value was selected as a representative vessel of that patient for the per-patient analysis. For per-patient analyses, continuous variables were compared based on a 1-way analysis of variance, and dichotomous variables were compared using Chi-square tests or Fisher exact tests. For per-vessel analyses, a generalized estimating equation with an independent correlation structure was used to adjust for intra-subject variability among vessels from the same patient. Estimated means and SDs were presented as summary statistics. No post hoc adjustments were performed.

Event rates according to quartile and optimal cut-off value of RRR were calculated based on Kaplan–Meier censoring estimates and presented with cumulative incidence at 5-year follow-up, and the log-rank test or the Breslow test was used to compare survival curves between groups. The optimal cut-off value of RRR to discriminate the occurrence of POCO was calculated based on maximizing the sum of sensitivity and specificity of RRR, and the derived cut-off value was revalidated using a method using maximally selected log-rank statistics as a sensitivity analysis. A Cox proportional hazard regression was used to calculate hazard ratio (HR) and 95% CI. The assumption of proportionality was assessed

graphically by the log-minus-log plot, and the Cox proportional hazard models for all clinical outcomes satisfied the proportional hazards assumption. To explore the prognostic impact of RRR as continuous values, estimated event rates derived from the Cox proportional hazards regression model were plotted using the locally weighted scatterplot smoothing regression line according to RRR value, and the associations between RRR and estimated event rates were also adjusted by %DS, FFR, or multivariable analysis. Multivariable Cox proportional hazard models to identify independent predictors of POCO were constructed using all variables with a $P<0.05$ from the univariate analyses, and variables could be potentially relevant. Harrell c-statistics with 95% CI were calculated to validate the discriminant function of the model.

All analyses were 2-tailed, and clinical significance was defined as $P<0.05$. Statistical analyses were performed using R version 3.5.2 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Characteristics of the Study Population

The overall characteristics of 1245 patients (1484 vessels) are outlined in Table S1. The mean age of the study population was 64.7±10.3 years and 76.9% were men. Revascularization was performed in 464 vessels from 458 patients (36.8% of patients [31.3% of vessels]). The distribution of physiologic indices is shown in Figure S1. According to the quartile of RRR value, the study population was classified into 4 groups: quartile 1 (Q1: RRR ≥5), quartile 2 (Q2: RRR 3.5–4.9), quartile 3 (Q3: RRR 2.5–3.4), and quartile 4 (Q4: RRR <2.5). Patient and lesion characteristics, according to quartile of RRR, are summarized in Table 1.

Patients in quartiles 3 to 4 (lower value of RRR) were of older age, were more frequently women, and had a higher incidence of diabetes mellitus than those of patients in quartiles 1 to 2 (higher value of RRR). There were significant differences in the severity of the stenoses and the physiologic indices of the lesions across all groups. The diameter stenosis tended to be higher when the RRR value was lower. Overall, patients with lower RRR showed lower FFR, lower CFR, and higher IMR. Figure S2 shows the correlation of RRR with %DS, FFR, CFR, and IMR. RRR showed a modest correlation with %DS ($R=-0.148$, $P<0.001$), FFR ($R=0.198$, $P<0.001$), IMR ($R=-0.268$, $P<0.001$). Although RRR showed significant correlation with CFR ($R=0.948$, $P<0.001$), the classification agreement between CFR and RRR was only modest (Kappa value 0.605, $P<0.001$) and 28.5% of patients with CFR>2.0 showed low RRR (<3.5) (Figure S3).

Clinical Outcomes of Patients According to RRR

Table 2 and Figure 2 present the cumulative incidence of POCO during 5 years of follow-up according to the quartile of RRR among total patients. Median follow-up duration was 1422.0 days (Q1–Q3, 566.0–1855.0 days). At 5 years, the cumulative incidence of POCO was significantly different according to quartiles of RRR (9.9%, 11.3%, 17.2%, and 22.7% in Q1 to Q4, respectively, log-rank $P<0.001$). Patients with low RRR had a higher risk of POCO than those with high RRR (Q3 versus Q1: HR 1.740, 95% CI, 1.004 to 3.014, $P=0.048$; Q4 versus Q1: HR 2.457, 95% CI, 1.482–4.072, $P<0.001$). Similarly, when patients were stratified into 2 groups by optimal cut-off value (RRR<3.5), those with low RRR showed a higher risk of POCO than those with high RRR (HR 1.941, 95% CI, 1.387–2.714, $P<0.001$) (Figure S4).

To evaluate the prognostic impact of RRR among deferred patients (n=787) with high FFR or high CFR, the risk of POCO was compared according to RRR in a subgroup of high FFR (n=643) or high CFR (n=597). Comparisons of baseline patient and vessel characteristics according to RRR in high FFR or high CFR groups are presented in Table S2. In the high FFR group, patients with RRR<3.5 showed significantly higher risk of POCO at 5 years (14.8% versus 6.0%, HR 2.556, 95% CI, 1.428–4.577, $P=0.001$) than those with RRR≥3.5. Similarly, patients with RRR<3.5 showed about a 2-fold higher risk of POCO than those with RRR≥3.5 in the high CFR group (13.5% versus 7.1%, HR 1.849, 95% CI, 1.003–3.408, $P=0.045$) (Table 3 and Figure 3).

Comparison of Additive Prognostic Impact of FFR, CFR, and RRR for Occurrence of POCO Among Patients With Deferred Revascularization

RRR showed significant association with the occurrence of POCO after adjustment with %DS or FFR. In addition, RRR was an independent predictor of POCO in the multivariable model and showed significant association with the estimated risk of POCO at 5 years (adjusted HR of RRR<3.5: 1.579, 95% CI, 1.098–2.271, $P=0.014$) (Table 4 and Figure 4).

In comparison of additive prognostic impact on top of clinical variables, models with FFR, CFR, or RRR showed significantly increased global Chi square value than model with clinical variables. However, model with RRR showed the highest global Chi square value than model with FFR or CFR ($P<0.001$ for both comparisons) (Figure 5).

DISCUSSION

The current study evaluated the prognostic implications of RRR as an integrated physiologic index of both

Table 1. Patient and Lesion Characteristics According to Quartile of Resistive Reserve Ratio

	Quartile 1 (RRR≥5)	Quartile 2 (RRR 3.5–4.9)	Quartile 3 (RRR 2.5–3.4)	Quartile 4 (RRR<2.5)	*P* Value
Per-patient analysis (n=1245)	258 (20.7%)	356 (28.6%)	276 (22.2%)	355 (28.5%)	
General characteristics					
Age, y	62.17±9.91	63.65±10.07	65.78±10.36	66.79±10.11	<0.001
Men	217 (84.1%)	285 (80.1%)	195 (70.7%)	261 (73.5%)	<0.001
BMI, kg/m^2	24.9±3.7	24.9±3.4	24.7±3.5	24.8±3.6	0.701
Clinical presentation					0.970
Stable ischemic heart disease	230 (89.1%)	321 (90.2%)	246 (89.1%)	318 (89.6%)	
Acute coronary syndrome	28 (10.9%)	35 (9.8%)	30 (10.9%)	37 (10.4%)	
Cardiovascular risk factors					
Hypertension	156 (60.5%)	231 (64.9%)	180 (65.2%)	250 (70.4%)	0.079
Diabetes mellitus	73 (28.3%)	107 (30.1%)	110 (39.9%)	155 (43.7%)	<0.001
Hypercholesterolemia	169 (65.5%)	225 (63.2%)	176 (63.8%)	214 (60.3%)	0.595
Current smoker	60 (23.3%)	67 (18.8%)	53 (19.2%)	86 (24.2%)	0.220
Obesity (BMI>25 kg/m^2)	115 (45.5%)	160 (45.1%)	119 (44.2%)	154 (44.6%)	0.993
Multivessel disease	77 (29.8%)	117 (32.9%)	100 (36.2%)	141 (39.7%)	0.060
Per-vessel analysis (n=1484)*	323 (21.8%)	416 (28.0%)	327 (22.0%)	418 (28.2%)	
Target vessel location					0.008
LAD	191 (59.1%)	270 (64.9%)	216 (66.1%)	273 (65.3%)	
LCX	41 (12.7%)	54 (13.0%)	52 (15.9%)	72 (17.2%)	
RCA	91 (28.2%)	92 (22.1%)	59 (18.0%)	73 (17.5%)	
Angiographic characteristics					
Reference diameter	3.0±0.6	2.9±0.6	2.9±0.7	2.8±0.6	<0.001
Diameter stenosis, %	42.9±15.6	45.3±16.4	45.9±16.4	49.5±17.8	<0.001
Lesion length, mm	11.7±8.1	12.4±8.1	12.2±8.3	13.7±9.6	0.003
Coronary physiologic parameters					
Resting Pd/Pa	0.96±0.04	0.94±0.05	0.93±0.06	0.89±0.11	<0.001
Fractional flow reserve	0.86±0.08	0.84±0.10	0.83±0.11	0.79±0.13	<0.001
Coronary flow reserve	4.8±0.8	3.3±0.5	2.4±0.4	1.5±0.4	<0.001
Resting Tmn, sec	1.10±0.45	0.90±0.41	0.76±0.44	0.62±0.44	<0.001
Hyperemic Tmn, sec	0.23±0.09	0.28±0.13	0.33±0.22	0.43±0.33	<0.001
IMR, U	16.8±7.6	19.0±9.2	21.8±12.6	25.6±19.9	<0.001
Resistive reserve ratio	6.2±1.0	4.2±0.4	3.0±0.3	1.9±0.4	<0.001

Values expressed as mean±SD or number (%). BMI indicates body mass index; IMR, index of microcirculatory resistance; LAD, left anterior descending artery; LCX, left circumflex artery; Pa, aortic pressure; Pd, distal coronary pressure; RCA, right coronary artery; and Tmn, mean transit time.

*Per-vessel analyses results (*P* values) were calculated from a generalized estimating equation.

pressure and flow. RRR represents the vasodilatory capacity of the coronary circulation and reflects cumulative functional disease burden throughout the interrogated vessel. We found that RRR is a valuable index in predicting POCO at 5 years, with an inverse relationship between RRR and POCO rates, both in the overall study population and in those patients in whom revascularization was deferred. The significant difference in the risk of POCO according to RRR was also maintained in high FFR or high CFR groups. Multivariable analysis confirmed that the prognostic value of RRR in predicting long-term POCO rates is independent of other indices. In addition, model with RRR showed significantly higher predictability for POCO at 5 years than the model with FFR or the model with CFR.

Coronary Circulation and Physiologic Indices

The coronary artery system has 3 components with different functions: conductive epicardial coronary arteries, arterioles, and capillaries, although the borders of each compartment cannot be clearly defined anatomically.[23] In any condition wherein coronary blood flow fails to meet myocardial oxygen demand, myocardial ischemia can occur. Physiological interrogation of epicardial vessels

Table 2. Clinical Outcomes of Patients According to Quartile of Resistive Reserve Ratio

	Quartile 1 (RRR≥5)	Quartile 2 (RRR 3.5–4.9)	Quartile 3 (RRR 2.5–3.4)	Quartile 4 (RRR<2.5)	*P* Value
Per-patient analysis (n=1245)	258 (20.7%)	356 (28.6%)	276 (22.2%)	355 (28.5%)	
All-cause death	1.3% (3)	2.7% (8)	5.3% (10)	6.6% (16)	0.042
Cardiac death	0.9% (2)	1.3% (4)	2.2% (4)	3.4% (8)	0.338
Myocardial infarction	1.4% (3)	2.3% (6)	1.1% (2)	4.1% (11)	0.086
Any revascularization	8.8% (17)	9.2% (26)	12.6% (25)	16.3% (42)	0.029
Target vessel-related revascularization*	6.7% (11)	5.8% (12)	10.9% (15)	13.8% (26)	0.041
Death or myocardial infarction	2.2% (5)	4.9% (14)	6.0% (11)	10.4% (27)	0.003
Patient-oriented composite outcome†	9.9% (20)	11.3% (33)	17.2% (35)	22.7% (61)	<0.001

Data expressed as cumulative incidence of clinical outcomes and numbers of events. Cumulative incidence of clinical outcomes represents Kaplan–Meier estimates during median follow-up of 1422.0 days (Q1–Q3, 566.0–1855.0 days). *P* values for log-rank or Breslow test in survival analysis. RRR indicates resistive reserve ratio.

*Target vessel-related revascularization denotes ischemia-driven revascularization occurred in initially interrogated vessel.

†Patient-oriented composite outcomes include all-cause mortality, any myocardial infarction, and any revascularization.

with stenoses is typically performed with FFR, a well-validated approach to set the indication of coronary revascularization to improve both angina symptoms and clinical outcomes.[19,24] However, lack of a functionally significant epicardial coronary stenosis does not exclude the possibility of microvascular disease as another potential

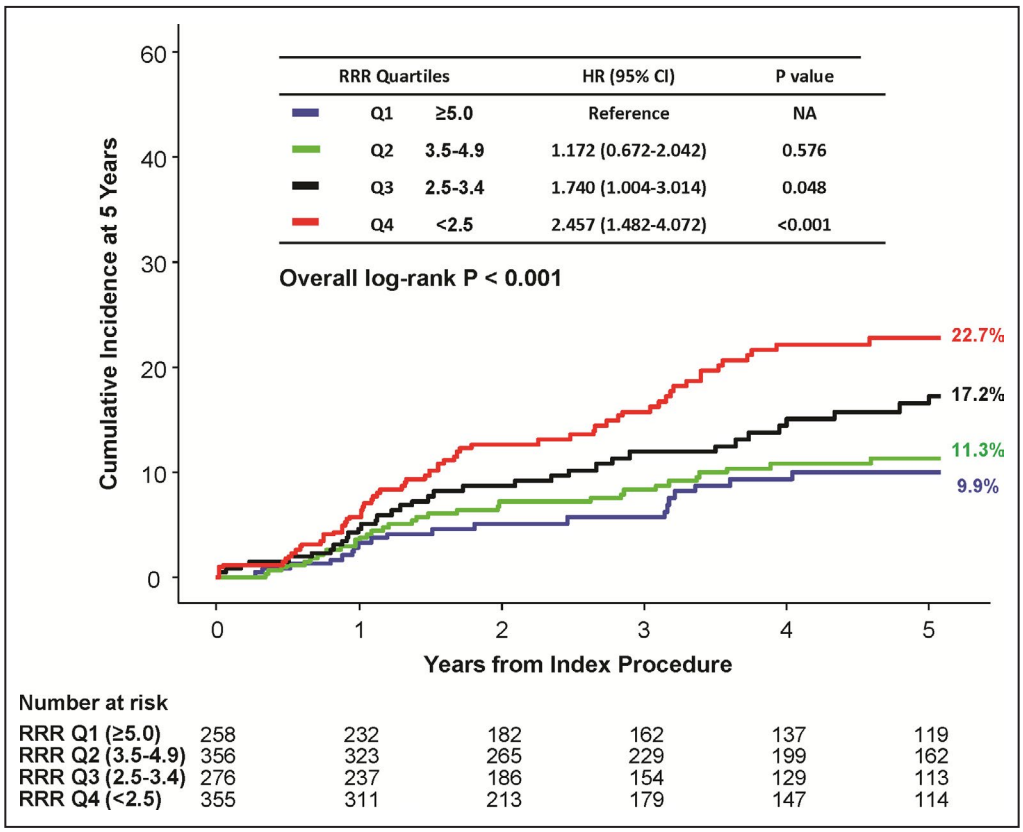

Figure 2. Comparison of patient-oriented composite outcome according to quartiles of resistive reserve ratio.

The cumulative incidence of patient-oriented composite outcome at 5 years is compared according to quartile of resistive reserve ratio. There was a significant trend of higher RRR and lower risk of patient-oriented composite outcome, and vice versa. HR indicates hazard ratio; Q1 to Q4, quartile 1 to 4; and RRR, resistive reserve ratio.

Table 3. Clinical Outcomes of Patients With Deferred Revascularization According to Resistive Reserve Ratio in High FFR or High CFR Subgroups

	High FFR Population				High CFR Population			
	RRR≥3.5	RRR<3.5	HR (95% CI)	*P* Value	RRR≥3.5	RRR<3.5	HR (95% CI)	*P* Value
Per-patient analysis	349/643 (54.3%)	294/643 (45.7%)			416/597 (69.7%)	181/597 (30.3%)		
All-cause death	1.3% (4)	5.0% (11)	3.483 (1.109–10.94)	0.023	1.7% (6)	5.3% (7)	2.857 (0.959–8.502)	0.048
Cardiac death	0.6% (2)	4.2% (9)	5.709 (1.233–26.44)	0.012	1.1% (4)	3.3% (4)	2.460 (0.615–9.839)	0.188
Myocardial infarction	1.1% (3)	1.6% (4)	1.663 (0.372–7.435)	0.501	1.4% (5)	0.0% (0)	NA	NA
Any revascularization	4.7% (13)	10.3% (23)	2.270 (1.149–4.482)	0.015	5.5% (18)	8.7% (11)	1.511 (0.714–3.201)	0.277
Target vessel-related revascularization*	2.5% (7)	6.6% (14)	2.568 (1.036–6.366)	0.035	3.6% (12)	5.7% (7)	1.434 (0.565–3.644)	0.448
Death or myocardial infarction	2.4% (7)	6.2% (14)	2.527 (1.020–6.265)	0.038	2.8% (10)	5.3% (7)	1.713 (0.652–4.502)	0.269
Patient-oriented composite outcome†	6.0% (17)	14.8% (34)	2.556 (1.428–4.577)	0.001	7.1% (24)	13.5% (18)	1.849 (1.003–3.408)	0.045

Data expressed as cumulative incidence of clinical outcomes and numbers of events. Cumulative incidence of clinical outcomes represents Kaplan–Meier estimates during median follow-up of 1422.0 days (Q1–Q3 566.0–1855.0 days). *P* values for log-rank or Breslow test in survival analysis. CFR indicates coronary flow reserve; FFR, fractional flow reserve; HR, hazard ratio; and RRR, resistive reserve ratio.
*Target vessel-related revascularization denotes ischemia-driven revascularization occurred in initially interrogated vessel.

domain of myocardial ischemia.[7,11,25] Previous studies presented that the additional stratification using flow-based index (CFR or coronary flow velocity reserve) with FFR could discriminate patients with myocardial ischemia but FFR>0.80.[7,10,11,15,26,27] However, heterogenous mechanism of depressed CFR and higher variability of flow-based indices according to hemodynamic status have limited its clinical applicability.[12]

Rationale of Integrated Physiologic Index With Both Pressure and Flow

The concept of coronary flow capacity has been introduced to overcome the potential limitations of flow-derived or pressure-derived indices.[14,28,29] Coronary flow capacity is a 2-step stratified approach using CFR and absolute measure of hyperemic coronary blood flow. Previous studies indicated that coronary flow capacity is an effective way to define myocardial ischemia using non-invasive measurement using positron emission tomography, and invasive measurement using Doppler or pressure-temperature sensor guidewires.[14,28,29] Because of additional stratification using absolute hyperemic coronary blood flow, coronary flow capacity essentially ruled out that depressed CFR originated from elevated resting coronary blood flow, and therefore, provides less sensitivity to changes in systemic hemodynamics during resting status than CFR alone. In addition, previous studies also presented that coronary flow capacity showed better risk stratification for patient's clinical outcomes than CFR or FFR alone.[14,28,29] These results imply that integration of both relative and absolute metrics of coronary circulatory indices would show more specific stratification of patients with myocardial ischemia and higher risk of future clinical events than flow-derived or pressure-derived indices alone. However, coronary flow capacity requires 2-dimensional mapping for interpreting its significance and the cut-off value of absolute hyperemic coronary blood flow has not been clarified.

In this regard, the current study used the concept of RRR. RRR was proposed by Layland et al.[13] They defined the RRR as the ratio between basal resistance index (resting Tmn×resting Pd) and hyperemic resistance index, IMR (hyperemic Tmn×hyperemic Pd). However, this equation can be transformed into CFR divided by ratio between resting and hyperemic Pd, and thus can be interpreted as CFR, adjusted by a surrogate marker of hyperemic coronary flow which was normalized by resting value. Therefore, this transformation enables the interpretation of RRR as a single surrogate value of coronary flow capacity. Using both pressure and flow measured in the target vessel, RRR represents cumulative inducible flow limitations and functional disease burden from epicardial coronary arteries and the microvasculature.

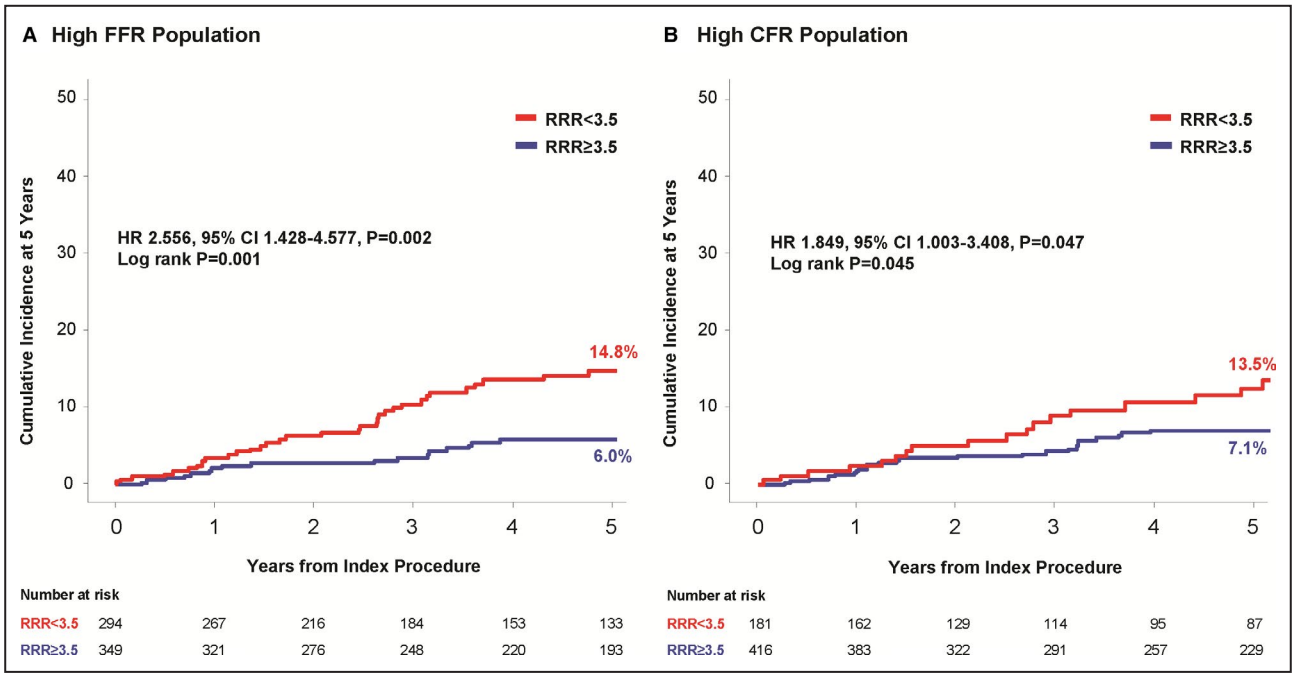

Figure 3. Comparison of patient-oriented composite outcome between preserved or depressed resistive reserve ratio, among high fractional flow reserve or high coronary flow reserve population with deferred revascularization.
The cumulative incidence of patient-oriented composite outcome at 5 years is compared between preserved (≥3.5) and depressed resistive reserve ratio (<3.5) in subgroup of (**A**) high fractional flow reserve (>0.80) or (**B**) high coronary flow reserve (>2.0) among patients with deferred revascularization. CFR indicates coronary flow reserve; FFR, fractional flow reserve; HR, hazard ratio; and RRR, resistive reserve ratio.

Clinical Relevance of Resistive Reserve Ratio

When physiologic characteristics according to quartiles of RRR were compared, patients with lower RRR showed lower FFR and CFR, higher diameter stenosis and IMR than those with higher RRR. In addition, RRR had a modest positive correlation with FFR, and a negative correlation with %DS and IMR. Although RRR showed significant correlation with CFR, the classification agreement between CFR and RRR was modest, and about one third of patients with preserved CFR showed depressed RRR (<3.5). In a comparison of the risk of POCO according to quartiles of RRR, there was a significant trend of higher RRR and lower POCO risk, and vice versa. These results were consistent when the patients were classified by an optimal cut-off value of RRR (<3.5).

More importantly, patients with depressed RRR showed a significantly higher risk of POCO than those with preserved RRR among patients with high FFR and deferred revascularization. Similarly, patients with depressed RRR also showed significantly higher risk of POCO than those with preserved RRR among deferred patients with high CFR. Furthermore, RRR showed superior discrimination of 5-year POCO than those with FFR or CFR on top of clinical variables. The current results support the improved risk stratification by RRR in patients with high FFR or high CFR after deferral of revascularization. Therefore, when revascularization was deferred based on FFR or CFR, RRR can be used as additional prognostic indicator. Further study is warranted to clarify the potential role of RRR in guiding treatment decision-making in patients with stable ischemic heart disease.

Although previous studies indicated that only one physiologic index such as FFR, CFR, or IMR cannot fully discriminate patients at higher risk of clinical events, it is unclear how can we integrate multiple coronary physiologic indices. In this regard, the current study proposed the concept of RRR as an integrated physiologic index of both coronary flow and pressure. RRR can be discriminated from flow-derived index (CFR), pressure-derived index (FFR), or the lowest possible passive microvascular resistance (IMR). Compared with CFR alone, RRR can integrate the severity of epicardial coronary disease by incorporating distal coronary pressure, as with the concept of coronary flow capacity. Compared with FFR alone, RRR integrates the concept of coronary flow reserve, which cannot be reflected by pressure-derived indices. In addition, as RRR reflects the dynamic nature of coronary arterial tone, it is less influenced by the amount of myocardium subtended to the location of the pressure-temperature sensor, which was the shortcoming of IMR.[30]

Table 4. Association of Resistive Reserve Ratio for Occurrence of Patient-Oriented Composite Outcomes at 5 Years Among Patients With Deferred Revascularization

Models	HR (95% CI)	*P* Value	Harrell C-index
Unadjusted Model			0.611 (0.554–0.668)
RRR<3.5	2.496 (1.531–4.068)	<0.001	
Adjusted by Diameter stenosis			0.672 (0.608–0.735)
RRR<3.5	2.543 (1.544–4.190)	<0.001	
%DS	1.028 (1.012–1.044)	<0.001	
Adjusted by FFR			0.652 (0.589–0.715)
RRR<3.5	2.415 (1.480–3.940)	<0.001	
FFR (per 0.01 increase)	0.946 (0.918–0.976)	<0.001	
Full multivariable adjustment*			0.713 (0.670–0.756)
RRR<3.5	1.579 (1.098–2.271)	0.014	
FFR (per 0.01 increase)	0.972 (0.955–0.989)	0.001	
Age (per 1.0 increase)	1.031 (1.011–1.051)	0.002	
Diabetes mellitus	1.479 (1.054–2.075)	0.025	

FFR indicates fractional flow reserve; and RRR, resistive reserve ratio.

*Adjusted covariates included age, sex, hypertension, diabetes mellitus, hyperlipidemia, acute coronary syndrome, multivessel disease, fractional flow reserve, and % diameter stenosis.

Study Limitations

Some limitations of the current study should be noted. First, we could not compare non-invasive stress tests according to the low or high RRR groups. Second, although the decision to perform percutaneous coronary intervention for target lesions was made based on the FFR value, the participating investigators were not masked to the physiologic indices and therefore may have been influenced in their decision-making strategy. Nevertheless, all clinical events were independently adjudicated by the clinical events adjudication committee. Third, further investigations, including the external validation of cut-off value and a longer follow-up period, are needed to confirm our findings. Fourth, the majority of the current study population presented with stable ischemic heart disease, therefore, the results cannot be extrapolated to patients with ST-segment–elevation myocardial infarction. However, there has been no previous study which evaluated prognostic implication of RRR in patients with stable ischemic heart disease. Fifth, 15.1% of deferred vessels showed an FFR ≤0.80 and were deferred revascularization based on operator's discretion. However,

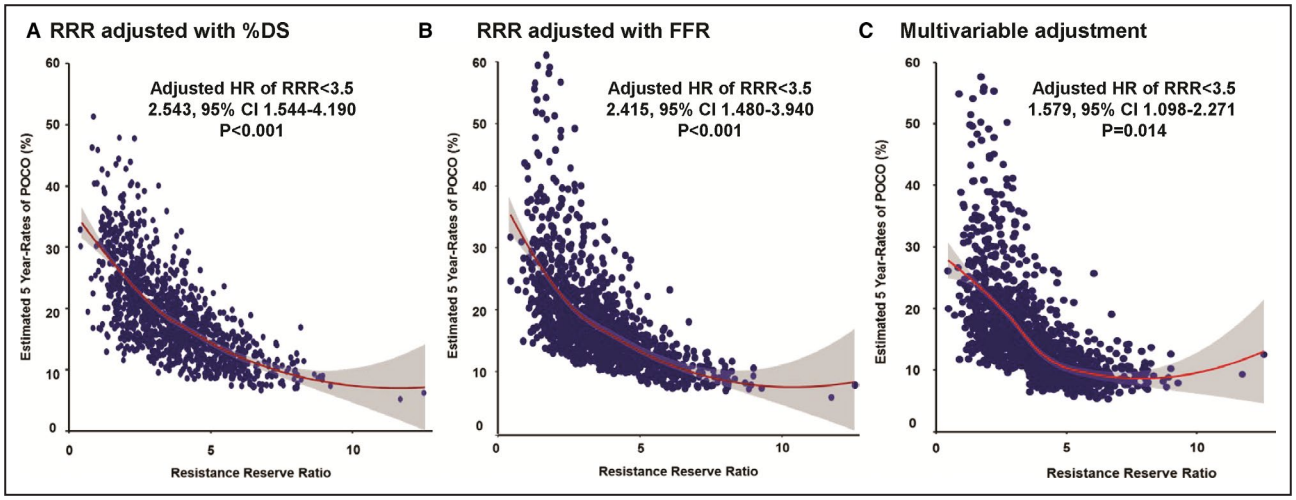

Figure 4. Association of resistive reserve ratio with estimated risk of patient-oriented composite outcome at 5 years among patients with deferred revascularization.

The non-linear relationship between resistive reserve ratio and the estimated risk of patient-oriented composite outcome at 5 years was plotted after adjustment with (**A**) percent diameter stenosis (%DS), (**B**) fractional flow reserve, or (**C**) multivariable adjustment. Adjusted covariates in the multivariable model are age, sex, hypertension, diabetes mellitus, hyperlipidemia, acute coronary syndrome, multivessel disease, fractional flow reserve, and % diameter stenosis. %DS indicates percent diameter stenosis; FFR, fractional flow reserve; and RRR, resistive reserve ratio.

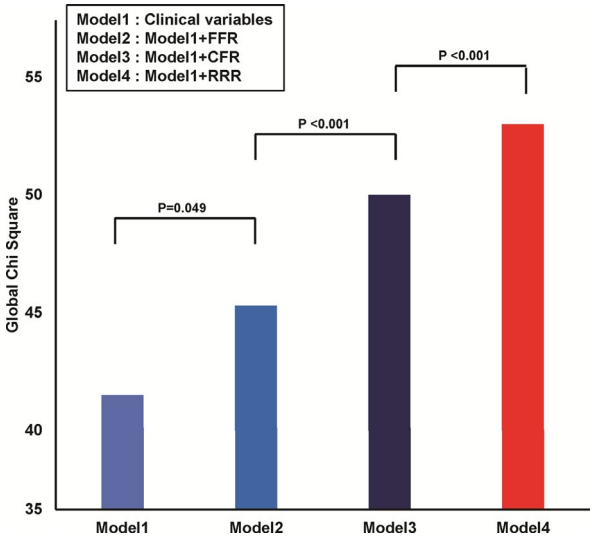

Figure 5. Comparison of additive prognostic impact of FFR, CFR, and RRR for risk of patient-oriented composite outcome at 5 years among patients with deferred revascularization.
In addition to model with clinical variables, additive prognostic impact of fractional flow reserve, coronary flow reserve, or resistive reserve ratio was compared. Model 4 (clinical variables with resistive reserve ratio) showed significantly higher global Chi square value than Model 2 (clinical variables with fractional flow reserve) or Model 3 (clinical variables with coronary flow reserve). Included clinical variables were age, sex, hypertension, diabetes mellitus, hyperlipidemia, acute coronary syndrome, multivessel disease, and % diameter stenosis. CFR indicates coronary flow reserve, FFR, fractional flow reserve; and RRR, resistive reserve ratio.

time to target vessel revascularization was not different according to FFR value at the index procedure (FFR ≤0.80 at index procedure: 876.2±518.3 days versus FFR >0.80 at index procedure: 780.6±469.9 days, *P*=0.583) and clinical events were defined according to objective criteria. Sixth, the discrimination ability of multivariable model was relatively low, probably because of a limited number of clinical events. Therefore, a further validation study would be warranted.

CONCLUSIONS

Resistive reserve ratio which integrates both coronary flow and pressure showed incremental prognostic implications in patients with coronary artery disease undergoing elective percutaneous coronary intervention guided by invasive physiologic evaluation.

ARTICLE INFORMATION

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Supplementary Materials

Appendix S1
Tables S1 and S2
Figures S1–S4

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Supplemental Material

Appendix

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Table S1. Characteristics of Patients According to the Registries.

	Total population	Korea registry	Japan registry	Spain registry
Per-patient analysis	**n=1,245**	**n=552**	**n=631**	**n=62**
General characteristics				
Age, years	64.7 ± 10.3	61.6 ± 10.3	67.4 ± 9.4	65.6 ± 10.8
Male	958 (76.9%)	389 (70.5%)	520 (82.4%)	49 (79.0%)
BMI, kg/m^2	24.8 ± 3.5	24.6 ± 3.0	24.8 ± 3.8	28.5 ± 4.4
Clinical presentation				
Stable ischemic heart disease	1115 (89.6%)	454 (88.2%)	631 (100%)	30 (48.4%)
Acute coronary syndrome	130 (10.4%)	98 (17.8%)	0 (0%)	32 (51.6%)
Cardiovascular risk factors				
Hypertension	817 (65.6%)	328 (59.4%)	444 (70.4%)	45 (72.6%)
Diabetes mellitus	445 (35.7%)	160 (29.0%)	260 (41.2%)	25 (40.3%)
Hypercholesterolemia	784 (63.0%)	350 (63.4%)	400 (63.4%)	34 (54.8%)
Current smoker	266 (21.4%)	105 (19.0%)	142 (22.5%)	19 (30.6%)
Obesity (BMI>25 kg/m^2)	548 (44.8%)	234 (42.7%)	280 (44.4%)	34 (79.1%)
Multivessel disease	435 (34.9%)	273 (49.5%)	113 (17.9%)	49 (79.0%)
Per-vessel analysis	**n=1,484**	**n=772**	**n=631**	**n=81**
Vessel location				
LAD	950 (64.0%)	463 (60.0%)	442 (70.1%)	45 (55.6%)
LCX	219 (14.8%)	136 (17.6%)	67 (10.6%)	16 (19.7%)

RCA	315 (21.2%)	173 (22.4%)	122 (19.3%)	20 (24.7%)
Target vessel PCI performed	464 (31.3%)	96 (12.4%)	338 (53.6%)	30 (37.0%)
Angiographic characteristics				
Reference diameter	2.9 ± 0.6	3.0 ± 0.6	2.8 ± 0.7	2.8 ± 0.7
Diameter stenosis, %	46.0 ± 16.8	42.5 ± 17.5	49.7 ± 15.2	53.2 ± 12.5
Lesion length, mm	12.6 ± 8.6	11.6 ± 8.3	12.6 ± 7.5	23.0 ± 13.0
Physiologic parameters				
Resting Pd/Pa	0.93 ± 0.08	0.95 ± 0.06	0.90 ± 0.09	0.89 ± 0.09
Fractional flow reserve	0.83 ± 0.11	0.86 ± 0.10	0.79 ± 0.11	0.80 ± 0.10
Coronary flow reserve	2.9 ± 1.3	3.1 ± 1.3	2.8 ± 1.3	2.1 ± 1.4
IMR, U	21.0 ± 13.9	19.4 ± 9.7	22.9 ± 17.1	20.9 ± 18.5
Resistive reserve ratio	3.7 ± 1.7	3.8 ± 1.6	3.6 ± 1.7	2.7 ± 1.9

Values expressed as mean ± SD or number (%).

BMI, body mass index; IMR, index of microcirculatory resistance; LAD, left anterior descending artery; LCX, left circumflex artery; Pa, aortic pressure; Pd, distal coronary pressure; RCA, right coronary artery; Tmn, mean transit time.

Table S2. Characteristics of Patients with Deferred Revascularization According to Resistive Reserve Ratio in High CFR or High FFR Subgroups.

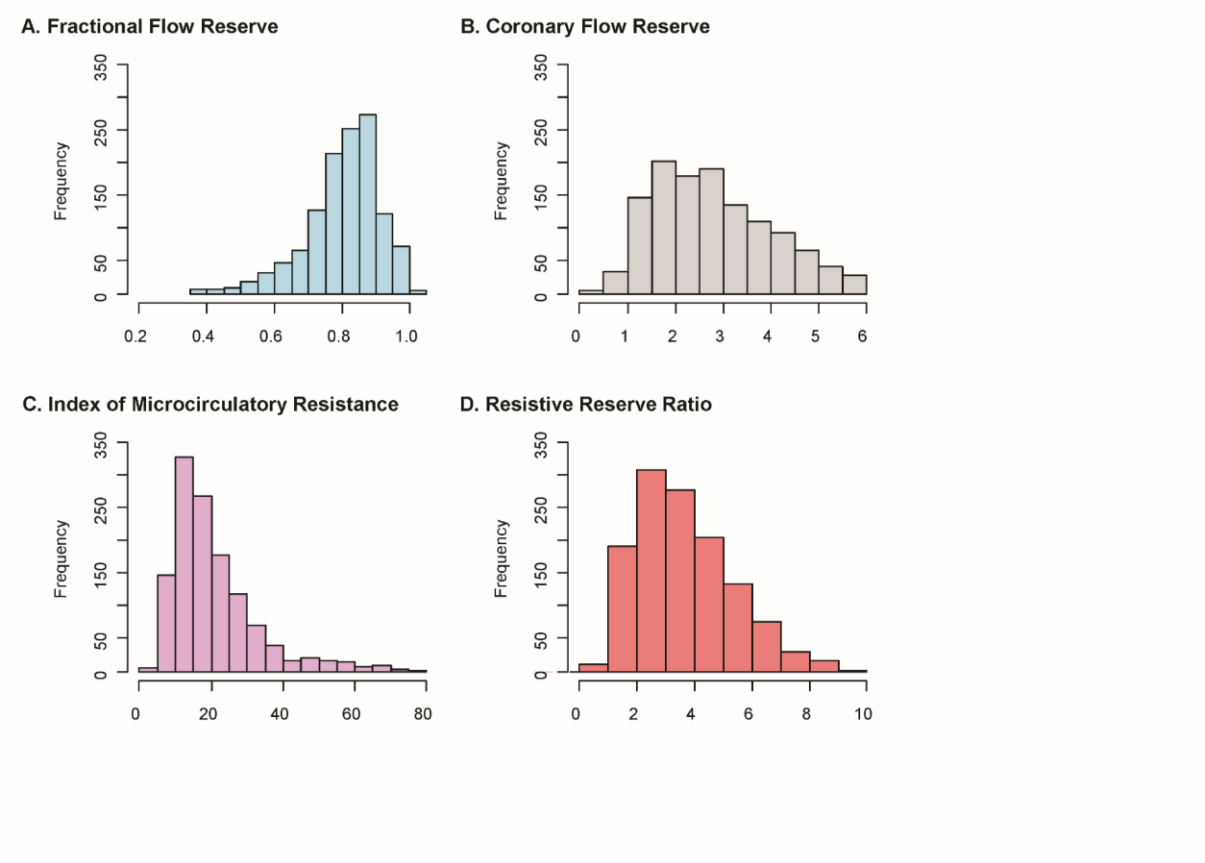
	High FFR Population			High CFR Population		
	RRR≥3.5	**RRR<3.5**	**P value**	**RRR≥3.5**	**RRR<3.5**	**P value**
Per-patient analysis (n=787)	**349/643 (54.3%)**	**294/643 (45.7%)**		**416/597 (69.7%)**	**181/597 (30.3%)**	
General characteristics						
Age, years	62.4 ± 10.5	65.8 ± 10.0	<0.001	62.3 ± 10.3	65.0 ± 10.2	0.003
Male	268 (76.8%)	193 (65.7%)	0.002	331 (79.6%)	118 (65.2%)	<0.001
BMI, kg/m^2	24.8 ± 3.9	24.7 ± 3.5	0.911	24.9 ± 3.8	24.6 ± 3.5	0.476
Clinical presentation			**0.827**			**1.000**
Stable ischemic heart disease	308 (88.2%)	262 (89.1%)		366 (88.0%)	159 (87.9%)	
Acute coronary syndrome	41 (11.8%)	32 (10.9%)		50 (12.0%)	22 (12.1%)	
Cardiovascular risk factors						
Hypertension	213 (61.0%)	187 (63.6%)	0.556	262 (63.0%)	109 (60.2%)	0.584
Diabetes mellitus	99 (28.4%)	115 (39.1%)	0.005	114 (27.4%)	74 (40.9%)	0.002
Hypercholesterolemia	219 (62.8%)	170 (57.8%)	0.233	263 (63.2%)	114 (63.0%)	1.000
Current smoker	74 (21.2%)	64 (21.8%)	0.938	87 (20.9%)	41 (22.7%)	0.713
Obesity (BMI>25 kg/m^2)	154 (44.4%)	126 (43.9%)	0.968	189 (45.8%)	79 (44.9%)	0.916
Multivessel disease	120 (34.4%)	129 (43.9%)	0.017	155 (37.3%)	73 (40.3%)	0.536
Per-vessel analysis (n=1,020)	**470/866 (54.3%)**	**396/866 (45.7%)**		**540/767 (70.4%)**	**227/767 (29.6%)**	
Vessel location			**0.071**			**0.132**

LAD	261 (55.5%)	231 (58.3%)		324 (60.0%)	144 (63.4%)	
LCX	77 (16.4%)	79 (20.0%)		79 (14.6%)	40 (17.6%)	
RCA	132 (28.1%)	86 (21.7%)		137 (25.4%)	43 (18.9%)	
Angiographic characteristics						
Reference diameter	3.1 ± 0.6	2.9 ± 0.6	0.001	3.0 ± 0.6	2.9 ± 0.7	0.007
Diameter stenosis, %	39.0 ± 14.9	39.6 ± 14.8	0.501	40.2 ± 15.0	39.9 ± 14.6	0.789
Lesion length, mm	10.9 ± 7.0	10.9 ± 6.9	0.988	11.3 ± 7.6	10.5 ± 6.3	0.126
Physiologic parameters						
Resting Pd/Pa	0.96 ± 0.04	0.96 ± 0.04	<0.001	0.96 ± 0.04	0.95 ± 0.04	0.141
Fractional flow reserve	0.90 ± 0.05	0.90 ± 0.05	0.757	0.88 ± 0.07	0.88 ± 0.07	0.383
Coronary flow reserve	4.1 ± 0.9	2.0 ± 0.6	<0.001	4.0 ± 0.9	2.5 ± 0.3	<0.001
Resting Tmn, sec	0.99 ± 0.44	0.62 ± 0.40	<0.001	0.98 ± 0.43	0.72 ± 0.38	<0.001
Hyperemic Tmn, sec	0.25 ± 0.11	0.31 ± 0.21	<0.001	0.25 ± 0.11	0.29 ± 0.16	<0.001
IMR, U	18.9 ± 8.7	24.0 ± 18.3	<0.001	18.3 ± 8.5	22.3 ± 12.8	<0.001
Resistive reserve ratio	5.1 ± 1.2	2.4 ± 0.7	<0.001	5.1 ± 1.2	3.0 ± 0.3	<0.001

Values expressed as mean ± SD or number (%).

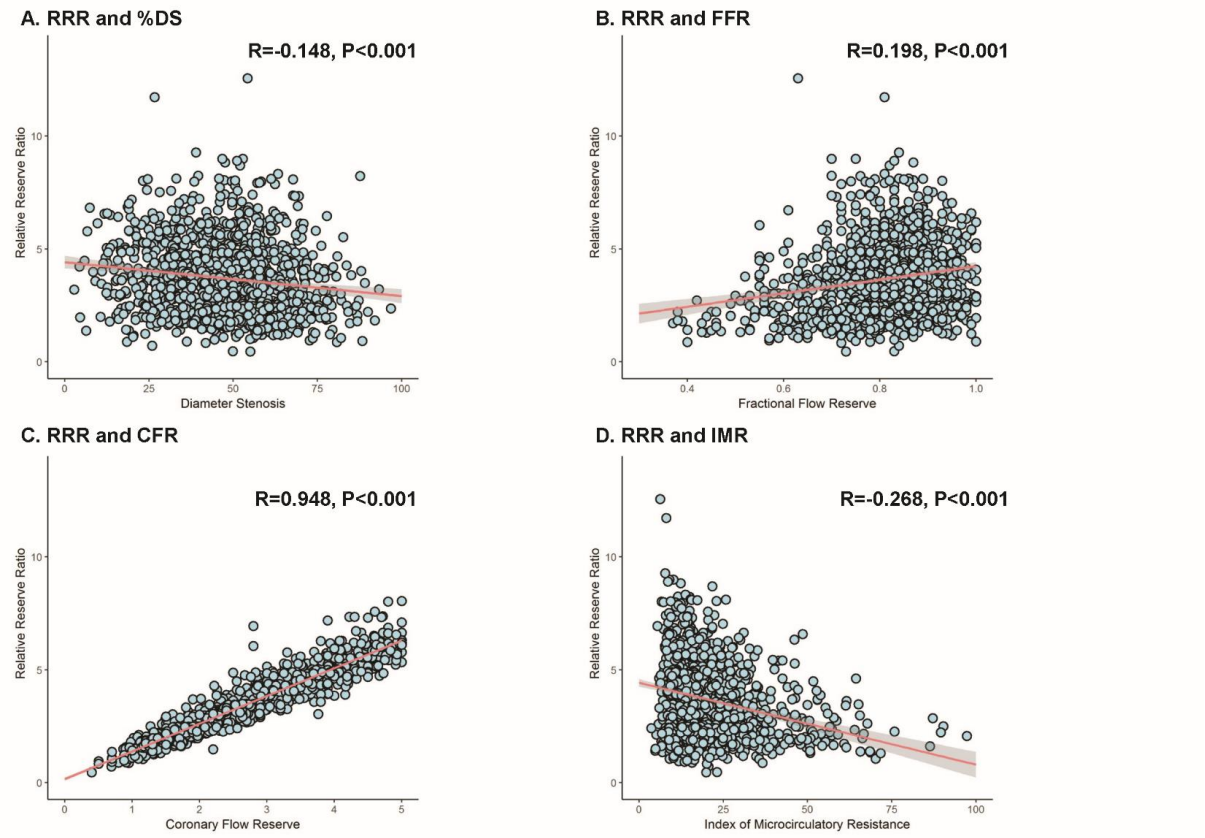
BMI, body mass index; IMR, index of microcirculatory resistance; LAD, left anterior descending artery; LCX, left circumflex artery; Pa, aortic pressure; Pd, distal coronary pressure; RCA, right coronary artery; RRR, resistive reserve ratio; Tmn, mean transit time.

Figure S1. Distribution of Physiologic Indices.



Distributions of (A) fractional flow reserve, (B) coronary flow reserve, (C) index of microcirculatory resistance, (D) resistive reserve ratio are shown.

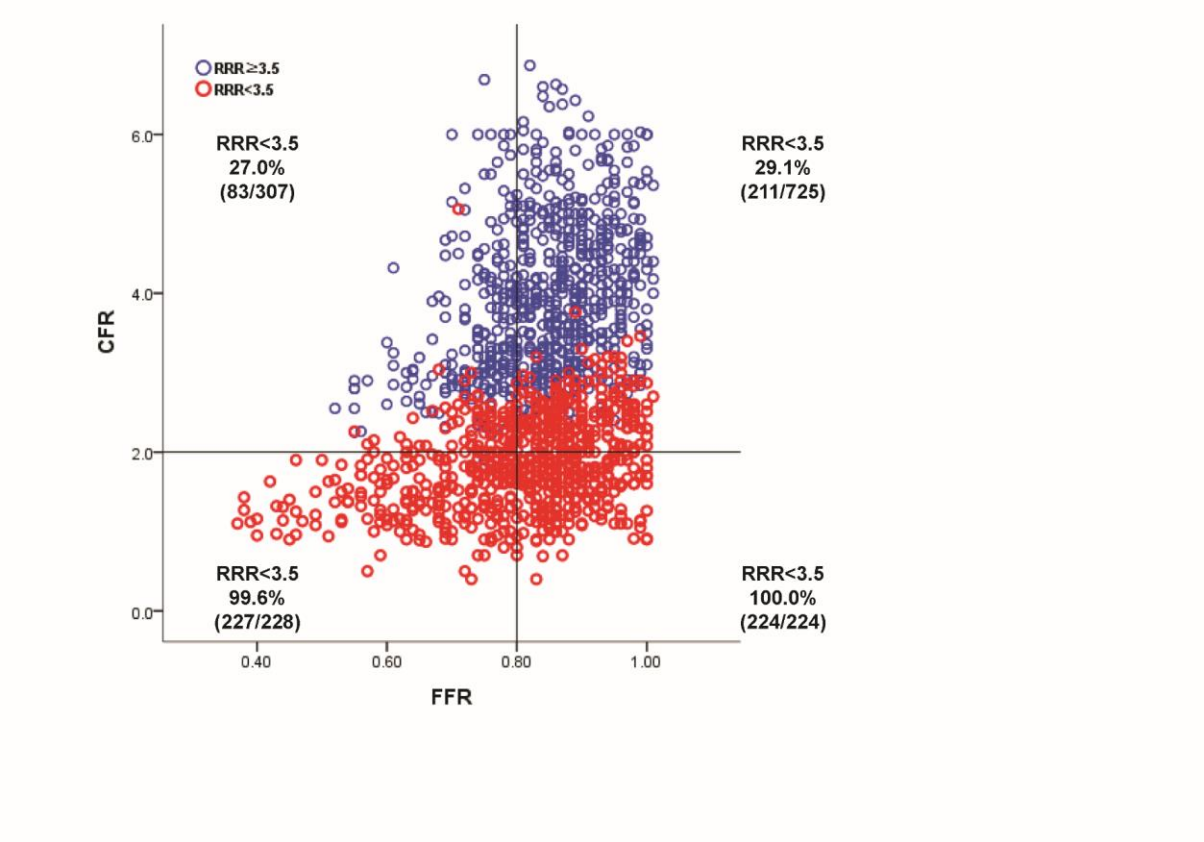
Figure S2. Correlation of Resistive Reserve Ratio with Diameter Stenosis or Other Physiologic Indices.



Correlation of RRR with **(A)** percent diameter stenosis, **(B)** FFR, **(C)** CFR, and **(D)** IMR.

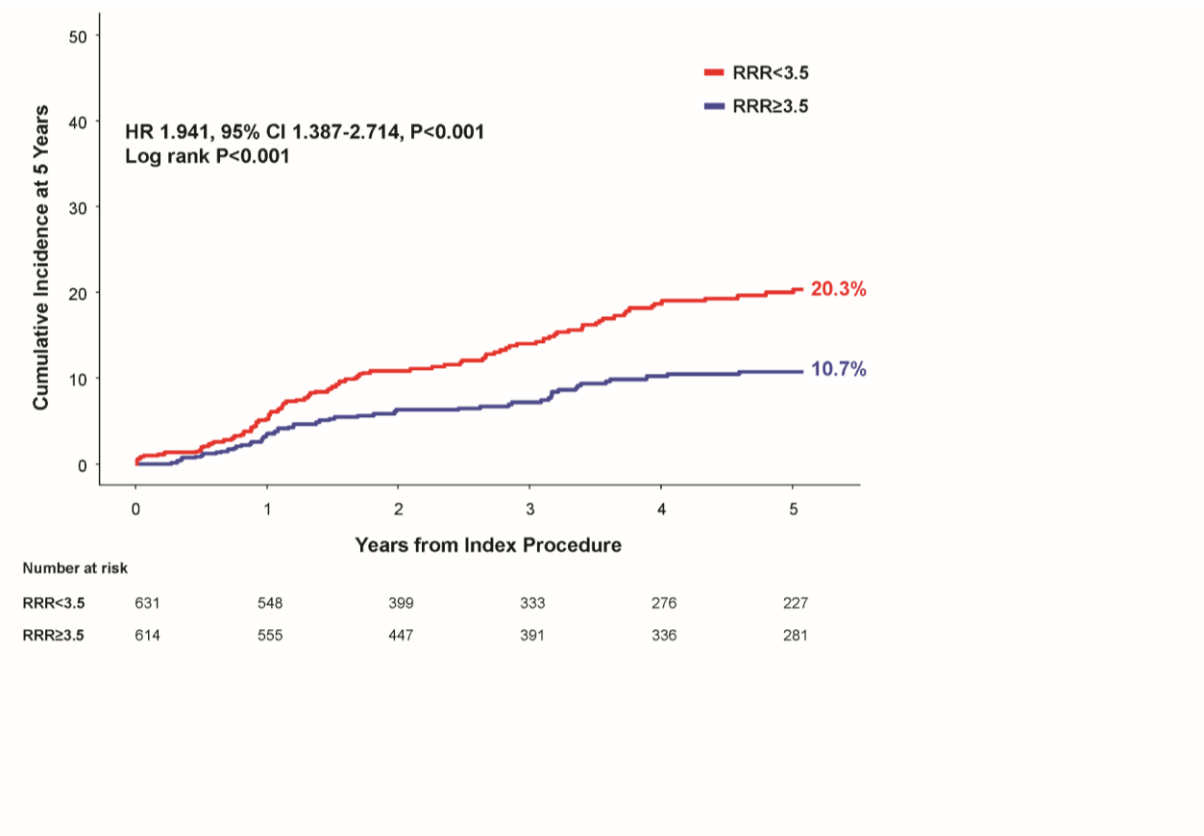
CFR, coronary flow reserve; FFR, fractional flow reserve; IMR, index of microcirculatory resistance; %DS, percent diameter stenosis; RRR, resistive reserve ratio.

Figure S3. Distribution of CFR, FFR and Resistive Reserve Ratio.



Distribution of vessels according to CFR and FFR values. Red dots represented vessels with depressed resistive reserve ratio (RRR) <3.5 and blue dots represent those with preserved RRR≥3.5. Although RRR showed high correlation with CFR (R=0.948, p<0.001), the classification agreement between CFR and RRR was only modest (Kappa value 0.605, p<0.001) and 28.6% of patients with CFR>2.0 showed low RRR (<3.5). Numbers represent the number of vessels in each quadrant.

Figure S4. Comparison of Patient-Oriented Composite Outcome According to Resistive Reserve Ratio.



Cumulative incidence of patient-oriented composite outcomes (POCO) is shown according to cut-off value of resistive reserve ratio (RRR). Unadjusted hazard ratio and 95% confidence intervals are presented._CI, confidence intervals; HR, hazard ratios; RRR, resistive reserve ratio.