

The Prognostic Value of Residual Coronary Stenoses After Functionally Complete Revascularization



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on behalf of the FAME Study Investigators

ABSTRACT

BACKGROUND The residual SYNTAX score (RSS) and SYNTAX revascularization index (SRI) quantitatively assess angiographic completeness of revascularization for patients with multivessel coronary artery disease. Whether residual angiographic disease remains of prognostic importance after “functionally” complete revascularization with fractional flow reserve (FFR) guidance is unknown.

OBJECTIVES This study sought to investigate the prognostic value of the RSS and SRI after FFR-guided functionally complete revascularization.

METHODS From the FFR-guided percutaneous coronary intervention (PCI) cohort of the FAME (Fractional Flow Reserve Versus Angiography for Multivessel Evaluation) trial, the RSS and SRI were calculated in 427 patients after functionally complete revascularization. The RSS was defined as the SYNTAX score (SS) recalculated after PCI. The SRI was calculated as: $100 \times (1 - \text{RSS}/\text{baseline SS})$ (%). We compared differences in 1- and 2-year outcomes among patients with RSS of 0, >0 to 4, >4 to 8, and >8, and with SRI of 100%, 50% to <100%, and 0 to <50%.

RESULTS The mean baseline SS, RSS, and SRI were 14.4 ± 7.2 , 6.5 ± 5.8 , and $55.1 \pm 32.5\%$, respectively. Major adverse cardiac events (MACE) at 1 year occurred in 53 patients (12.4%). Patients with MACE had higher SS than those without (18.0 [interquartile range (IQR): 11.0 to 21.0] vs. 12.0 [IQR: 9.0 to 18.0], $p = 0.001$), but had similar RSS and SRI after PCI (RSS: 6.0 [IQR: 3.0 to 10.0] vs. 5.0 [IQR: 2.0 to 9.5], $p = 0.51$ and SRI: 60.0% [IQR: 40.9% to 78.9%] vs. 58.8% [IQR: 26.7% to 81.8%], $p = 0.24$, respectively). Kaplan-Meier analysis showed similar 1-year incidence of MACE with RSS/SRI stratifications (log-rank $p = 0.55$ and $p = 0.54$, respectively). Results were similar with 2-year outcome data analysis.

CONCLUSIONS After functionally complete revascularization with FFR guidance, residual angiographic lesions that are not functionally significant do not reflect residual ischemia or predict a worse outcome, supporting functionally complete, rather than angiographically complete, revascularization. (Fractional Flow Reserve Versus Angiography for Multivessel Evaluation [FAME]; [NCT00267774](https://doi.org/10.1016/j.jacc.2016.01.056)) (J Am Coll Cardiol 2016;67:1701-11)

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Angiographically complete revascularization is associated with improved long-term outcome after multivessel revascularization for stable coronary artery disease (CAD) compared with incomplete revascularization (1-5). However, complete revascularization is not always pursued or achievable in patients with multivessel CAD undergoing percutaneous coronary intervention (PCI).

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ABBREVIATIONS AND ACRONYMS

CAD = coronary artery disease

CI = confidence interval

FFR = fractional flow reserve

FSS = functional SYNTAX score

IQR = interquartile range

MACE = major adverse cardiac event(s)

PCI = percutaneous coronary intervention

RSS = residual SYNTAX score

SRI = SYNTAX revascularization index

SS = SYNTAX score

As such, the residual SYNTAX score (RSS) (6,7) was recently developed to quantitatively assess the degree and complexity of residual stenoses by recalculating the SYNTAX score (SS) after PCI (8,9). Similarly, the SYNTAX revascularization index (SRI) was introduced as another quantification tool to assess the proportion of CAD that has been treated by PCI (10,11).

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Recent studies have found that functional significance of a lesion on the basis of fractional flow reserve (FFR) is a more important determinant of future adverse cardiac events than the angiographic appearance of the lesions (12,13). PCI on angiographically significant lesions that are not functionally significant on the basis of FFR can be deferred safely with good long-term outcomes (14). Therefore, we hypothesized that after “functionally” complete revascularization with FFR guidance in patients with multivessel CAD (15), the residual angiographic disease, which is not functionally significant, would not be predictive of outcomes, as assessed by the RSS or SRI. Accordingly, the primary goal of the present study is to investigate the prognostic value of these 2 quantification systems in patients enrolled in the FFR-guided PCI cohort of the FAME (Fractional Flow Reserve Versus Angiography for Multivessel Evaluation) trial (16-18), who underwent functionally complete revascularization with FFR guidance.

METHODS

STUDY DESIGN AND PATIENT POPULATION. The detailed study protocol has been published previously (16,18,19). In brief, the FAME trial is a prospective, randomized, controlled, multicenter trial investigating the superiority of FFR-guided PCI over angiography-guided PCI in patients with multivessel CAD (NCT00267774). In patients with multivessel CAD amenable to PCI, the investigators indicated which lesions had at least 50% diameter stenosis and were thought to require PCI. Thereafter, patients were randomly assigned to either FFR-guided or angiography-guided PCI. In patients assigned to FFR-guided PCI, only functionally significant lesions with $FFR \leq 0.80$ were treated with PCI, and functionally insignificant lesions with $FFR > 0.80$ were intentionally left untreated; whereas in patients assigned to angiography-guided PCI, all indicated lesions were treated without measurement of FFR. Because patients assigned to angiography-guided PCI

did not undergo FFR assessment and calculation of the functional SYNTAX score (FSS), and because all patients assigned to angiography-guided PCI received “angiographically” complete revascularization, very little residual stenosis existed after PCI in these patients. Therefore, patients assigned to angiography-guided PCI were not included in this study.

Patients with ST-segment elevation myocardial infarction could be enrolled if the infarction had occurred at least 5 days before PCI. By contrast, patients with unstable angina or non-ST-segment elevation myocardial infarction were allowed to enroll earlier than 5 days after myocardial infarction if the peak creatinine kinase was $< 1,000$ IU. Patients with prior PCI could be included. Patients were excluded if they had significant left main CAD, previous coronary artery bypass surgery, cardiogenic shock, or extremely tortuous or calcified coronary arteries. Patients were further excluded from the present substudy if the pre- and post-procedural angiogram data were not available. This study was approved by an institutional review committee from each participating site, and informed consent was obtained from all patients.

FFR MEASUREMENT AND TREATMENT. PCI was performed according to standard coronary interventional techniques, primarily with drug-eluting stents. In patients assigned to FFR-guided PCI, FFR was measured with a 0.014-inch pressure sensor guidewire (St. Jude Medical, Uppsala, Sweden). After equalization to the guide catheter pressure with the sensor positioned at the ostium of the coronary artery, the pressure guidewire was advanced down the target coronary artery. To induce maximal hyperemia, intravenous adenosine was administered at $140 \mu\text{g}/\text{kg}/\text{min}$ through a central vein. Simultaneous measurement of the mean proximal coronary pressure with the guide catheter and the mean distal coronary pressure with the pressure guidewire was performed. FFR was calculated as the ratio of the mean distal to proximal coronary pressure at hyperemia. All patients received dual antiplatelet therapy with aspirin and clopidogrel for at least 1 year after PCI (16,18,19).

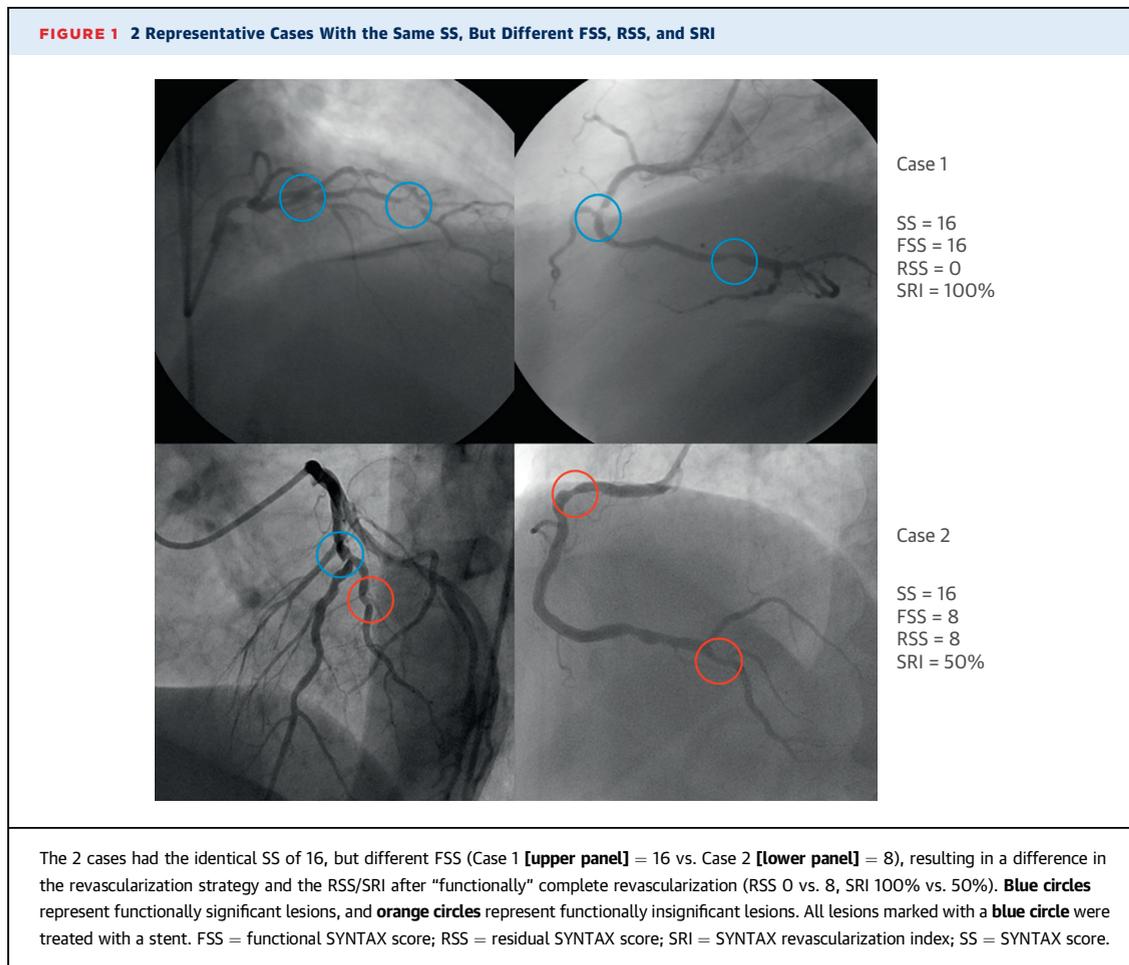
CALCULATION OF THE SS, FSS, RSS, AND SRI. The detailed methodology for calculating the SS and FSS can be found elsewhere (8,9,20). In brief, the SS was calculated from the pre-procedural angiogram, in which each coronary lesion producing $\geq 50\%$ diameter stenosis in vessels ≥ 1.5 mm by visual estimation was scored separately using the SS algorithm from the SYNTAX Score website and added to obtain the

overall SS (21). The FSS was calculated by deducting the individual score of lesions with an FFR >0.80. As previously reported from our dataset, the intra-observer variability of the SS using the intraclass correlation analysis was 0.95, 95% confidence interval (CI): 0.95 to 0.96 ($p < 0.001$), and that of the FSS was 0.96, 95% CI: 0.95 to 0.97 ($p < 0.001$). An inter-observer variability of the baseline SS using the intraclass correlation analysis was 0.59, 95% CI: 0.52 to 0.67 ($p < 0.001$), and that of the FSS was 0.71, 95% CI: 0.66 to 0.76 ($p < 0.001$) (20).

In addition, to obtain the RSS in all patients enrolled in this substudy, post-procedural angiograms were reviewed by a dedicated interventional cardiologist who was blinded to the baseline clinical characteristics, procedural data including FFR values, and clinical outcomes. From the post-procedural angiogram, each coronary lesion counted for the SS, but left untreated was scored separately, and individual scores were added to provide the RSS (6). For the RSS, a higher value suggests more CAD left untreated after PCI. After obtaining the RSS, the

SRI was calculated: $100 \times (1 - \text{RSS}/\text{baseline SS}) (\%)$. For the SRI, because this tool shows the proportion of CAD that has been treated by PCI, a lower value suggests more CAD left untreated after PCI. Two representative examples are presented in Figure 1. Post-procedural angiograms from 50 patients were randomly selected and reanalyzed by the same interventional cardiologist and a second independent interventional cardiologist to assess intraobserver and interobserver variability of the RSS.

ENDPOINTS. An independent clinical events committee whose members were blinded to treatment strategy adjudicated all events. The primary endpoint of this reanalysis was the same as that of the original FAME trial: major adverse cardiac events (MACE) (defined as a composite of all-cause death, myocardial infarction, or any repeat revascularization) and its components (all-cause death, myocardial infarction, repeat revascularization, and death or myocardial infarction) at 1 year after the index procedure among the RSS and SRI subgroups. The previously



mentioned analyses were repeated with 2-year follow-up data.

STATISTICAL ANALYSIS. All patients in the FFR-guided PCI cohort of the FAME trial were included in the reanalysis of the present study as long as the pre- and post-procedural angiograms were available. Categorical variables, including the primary endpoint and its individual components, are presented as counts and percentages. The Pearson chi-square test was used for comparisons of categorical variables. Continuous variables are presented as mean \pm SD, or median and interquartile range. Normality of the continuous variables was confirmed with the Shapiro-Wilk test. Depending on the result of the Levene test for homoscedasticity, 2 sets of variables with normal distributions were compared with the Student *t* test or Welch *t* test, as appropriate. If the normality test failed, 2 sets of variables were compared with the Mann-Whitney *U* test. The reproducibility of the RSS was evaluated by calculating intraobserver and interobserver variability using intraclass correlation. Correlations between scoring systems were tested with Spearman's correlation coefficient. An overall difference of variables among the RSS/SRI subgroups was determined using the 1-way analysis of variance test. Kaplan-Meier curves are shown for the time-to-event distributions of MACE stratified by the RSS and SRI. Patients were censored at 1 or 2 years (365 days or 730 days), or when events occurred. A *p* value <0.05 was considered statistically significant. All analyses were performed using SPSS version 21 software (SPSS, Chicago, Illinois).

RESULTS

Both pre- and post-procedural angiograms were available in 427 of 509 patients from the FFR-guided PCI cohort of the FAME trial database. The primary reason for exclusion was unavailability of a post-procedural angiogram. Patient characteristics, including age, sex, comorbidities, the number of lesions intended to treated, and the rate of MACE at 1 and 2 years, were similar between the included and excluded patients, except for a higher incidence of unstable angina in the included patients (31.9% vs. 17.2%, $p < 0.01$).

In 427 patients with both pre- and post-procedural angiograms, the mean SS, FSS, RSS, and SRI were 14.4 ± 7.2 , 10.8 ± 8.0 , 6.5 ± 5.8 , and $55.1 \pm 32.5\%$, respectively. The intraobserver variability of the RSS using the intraclass correlation analysis was 0.95, 95% CI: 0.92 to 0.97 ($p < 0.001$), and the interobserver variability of the RSS using the intraclass

correlation analysis was 0.92, 95% CI: 0.87 to 0.96 ($p < 0.001$).

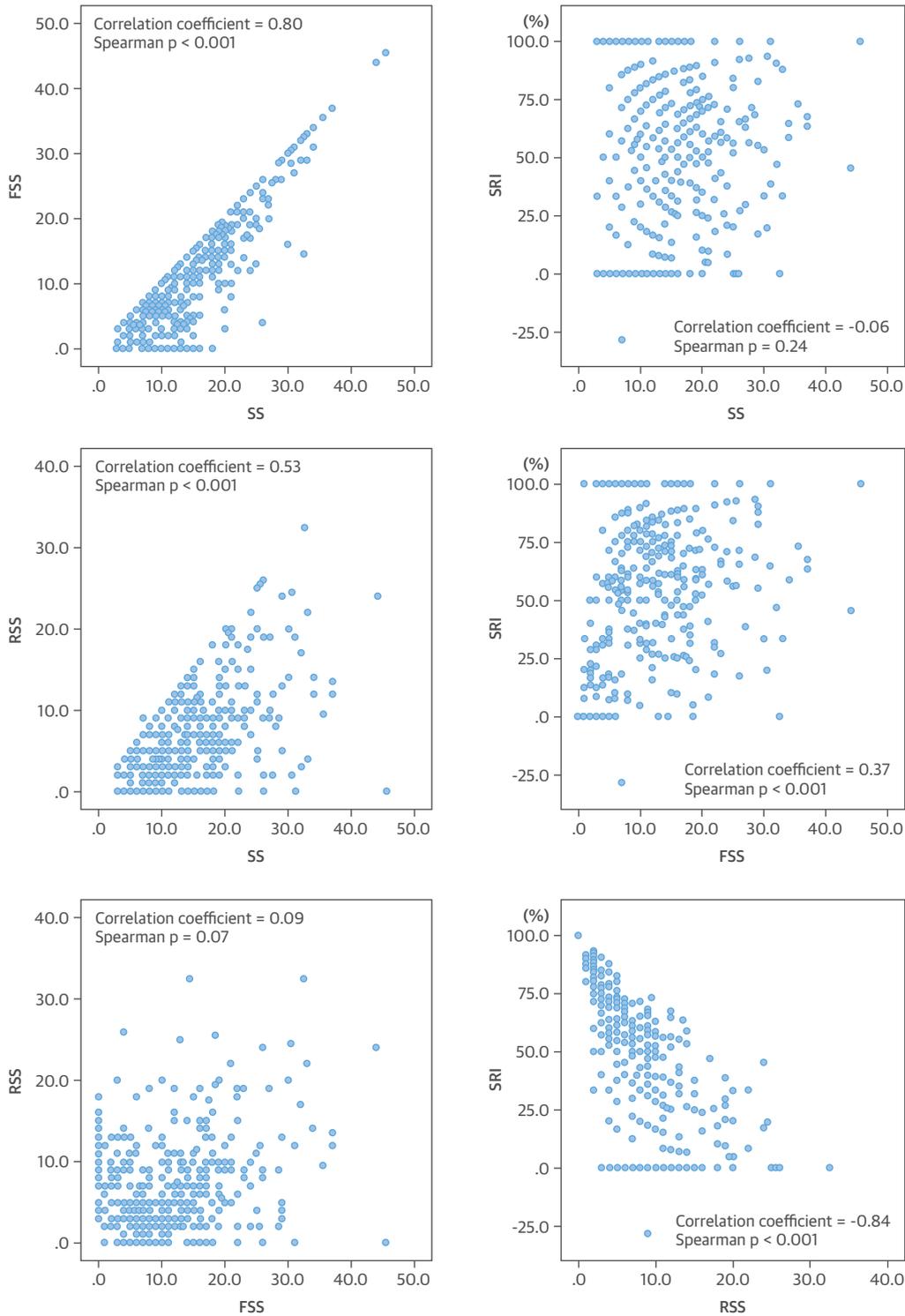
CORRELATIONS BETWEEN DIFFERENT SCORING SYSTEMS. Correlations between different scoring systems are shown in [Figure 2](#). The FSS and RSS were significantly correlated with the SS (correlation coefficient = 0.80 and Spearman $p < 0.001$ between the FSS and SS, and correlation coefficient = 0.53 and Spearman $p < 0.001$ between the RSS and SS, respectively), whereas the RSS was not correlated with the FSS (correlation coefficient = 0.09 and Spearman $p = 0.07$). The SRI was not correlated with the SS (correlation coefficient = -0.06 and Spearman $p = 0.24$). However, the SRI was positively correlated with the FSS (correlation coefficient = 0.37 and Spearman $p < 0.001$) and negatively correlated with the RSS (correlation coefficient = -0.84 and Spearman $p < 0.001$).

COMPARISONS OF BASELINE DATA AMONG THE RSS AND SRI SUBGROUPS. Comparisons of clinical, angiographic, and procedural characteristics among the RSS and SRI subgroups are summarized in [Table 1](#). Baseline patient clinical characteristics were similar among the RSS and SRI subgroups, except for the incidence of diabetes in the RSS and SRI subgroups ($p = 0.02$ and $p = 0.007$, respectively) and the history of myocardial infarction in the SRI subgroups ($p = 0.03$). The incidence of diabetes was lowest in patients with RSS = 0 and SRI = 100%, which represents angiographically complete revascularization.

With each increment of RSS, the SS increased (11.3 ± 6.9 for RSS = 0, 11.5 ± 5.7 for RSS >0 to 4, 13.3 ± 5.4 for RSS >4 to 8, and 19.2 ± 7.1 for RSS >8) and the number of lesions intended to treat increased (2.5 ± 0.8 for RSS = 0, 2.6 ± 0.8 for RSS >0 to 4, 2.8 ± 0.9 for RSS >4 to 8, and 3.0 ± 1.0 for RSS >8). By contrast, FSS did not vary with each increment of RSS value. Total number of stents per patient and total stented length per patient decreased with increasing RSS. The SS, FSS, and number of lesions intended to treat did not vary in a predictable fashion with each decrement of SRI. Total implanted stents per patient, total stented length per patient, and volume of contrast agent used decreased with each decrement of SRI (i.e., patients with SRI $<50\%$ had the smallest values).

CLINICAL OUTCOMES. MACE at 1 year occurred in 53 patients (12.4%). As shown in [Figure 3](#), patients with MACE had higher SS and FSS than patients without MACE, whereas RSS and SRI were similar between patients with and without MACE (RSS: 6.0 [interquartile range (IQR): 3.0 to 10.0] vs. 5.0 [IQR: 2.0 to

FIGURE 2 Correlations Between Different Scoring Systems



The FSS and RSS were significantly correlated with the SS, whereas the RSS was not correlated with the FSS. The SRI was not correlated with the SS. On the other hand, the SRI was positively correlated with the FSS and negatively correlated with the RSS. One patient had a higher RSS value than an original SS value due to a complication during PCI, resulting in a negative SRI value. Each point may represent >1 patient. Abbreviations as in Figure 1.

TABLE 1 Comparison of Clinical, Angiographic, and Procedural Characteristics Among the RSS and SRI Subgroups

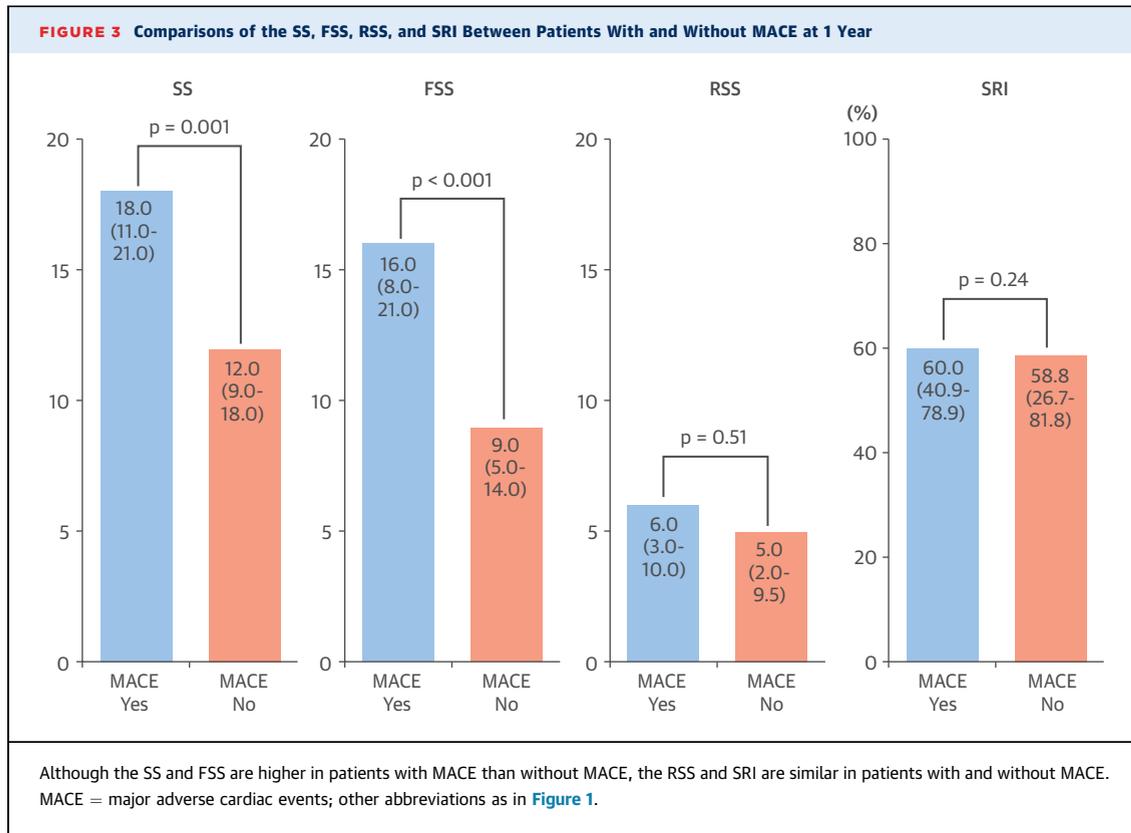
	Overall (N = 427)	RSS				p Value
		0 (n = 62)	>0 to 4 (n = 127)	>4 to 8 (n = 101)	>8 (n = 137)	
Clinical characteristics						
Age, yrs	64.7 ± 10.2	63.5 ± 10.0	64.9 ± 10.4	64.2 ± 9.4	65.4 ± 10.7	0.61
Male	318 (74.5)	53 (85.5)	96 (75.6)	73 (72.3)	96 (70.1)	0.13
Diabetes	107 (25.1)	6 (9.7)	31 (24.4)	28 (27.7)	42 (30.7)	0.02
Hypertension	263 (61.6)	33 (53.2)	74 (58.3)	70 (69.3)	86 (62.8)	0.17
Hypercholesterolemia	306 (71.7)	45 (72.6)	90 (70.9)	76 (75.2)	95 (69.3)	0.79
Family history of CAD	172 (40.3)	27 (43.5)	51 (40.2)	46 (45.5)	48 (35.0)	0.39
Current smoker	114 (26.7)	15 (24.2)	39 (30.7)	23 (22.8)	37 (27.0)	0.56
Previous myocardial infarction	156 (36.5)	22 (35.5)	39 (30.7)	35 (34.7)	60 (43.8)	0.16
Previous PCI	122 (28.6)	17 (27.4)	30 (23.6)	31 (30.7)	44 (32.1)	0.45
Unstable angina	136 (31.9)	19 (30.6)	40 (31.5)	28 (27.7)	49 (35.8)	0.61
Angiographic and procedural characteristics						
SS	14.4 ± 7.2	11.3 ± 6.9	11.5 ± 5.7	13.3 ± 5.4	19.2 ± 7.1	<0.001
FSS	10.8 ± 8.0	11.1 ± 7.0	9.8 ± 5.9	9.3 ± 7.0	12.9 ± 10.1	0.002
RSS	6.5 ± 5.8	0.0 ± 0.0	2.6 ± 0.9	6.2 ± 1.1	13.2 ± 4.8	<0.001
Lesions intended to treat, n	2.8 ± 0.9	2.5 ± 0.8	2.6 ± 0.8	2.8 ± 0.9	3.0 ± 1.0	<0.001
Total implanted stents per patient, n	1.9 ± 1.3	2.8 ± 1.2	2.0 ± 1.1	1.8 ± 1.2	1.4 ± 1.3	<0.001
Total stented length per patient, mm	36.1 ± 27.3	54.2 ± 34.0	40.4 ± 25.2	33.7 ± 22.8	25.8 ± 23.7	<0.001
Procedure time, min	67.7 ± 42.4	70.0 ± 31.4	68.9 ± 42.6	62.3 ± 30.3	69.5 ± 52.8	0.54
Volume of contrast agent used, ml	263.3 ± 120.0	295.0 ± 138.5	268.7 ± 117.9	253.3 ± 119.4	251.5 ± 111.8	0.09
SRI						
	Overall (N = 427)	100% (n = 62)	50% to <100% (n = 208)	<50% (n = 157)		p Value
Clinical characteristics						
Age, yrs	64.7 ± 10.2	63.5 ± 10.0	64.8 ± 9.9	65.1 ± 10.7		0.57
Male	318 (74.5)	53 (85.5)	154 (74.0)	111 (70.7)		0.08
Diabetes	107 (25.1)	6 (9.7)	61 (29.3)	40 (25.5)		0.007
Hypertension	263 (61.6)	33 (53.2)	128 (61.5)	102 (65.0)		0.27
Hypercholesterolemia	306 (71.7)	45 (72.6)	150 (72.1)	111 (70.7)		0.94
Family history of CAD	172 (40.3)	27 (43.5)	90 (43.3)	55 (35.0)		0.24
Current smoker	114 (26.7)	15 (24.2)	58 (27.9)	41 (26.1)		0.83
Previous myocardial infarction	156 (36.5)	22 (35.5)	64 (30.8)	70 (44.6)		0.03
Previous PCI	122 (28.6)	17 (27.4)	50 (24.0)	55 (35.0)		0.07
Unstable angina	136 (31.9)	19 (30.6)	66 (31.7)	51 (32.5)		0.97
Angiographic and procedural characteristics						
SS	14.4 ± 7.2	11.3 ± 6.9	15.1 ± 7.0	14.5 ± 7.3		0.001
FSS	10.8 ± 8.0	11.1 ± 7.0	12.8 ± 7.2	8.1 ± 8.6		<0.001
SRI	55.1 ± 32.5	100.0 ± 0.0	69.5 ± 12.2	18.5 ± 16.4		<0.001
Lesions intended to treat, n	2.8 ± 0.9	2.5 ± 0.8	2.8 ± 1.0	2.8 ± 0.9		0.08
Total implanted stents per patient, n	1.9 ± 1.3	2.8 ± 1.2	2.2 ± 1.1	1.1 ± 1.0		<0.001
Total stented length per patient, mm	36.1 ± 27.3	54.2 ± 34.0	43.0 ± 22.9	19.9 ± 20.6		<0.001
Procedure time, min	67.7 ± 42.4	70.0 ± 31.4	72.2 ± 41.0	60.8 ± 47.0		0.04
Volume of contrast agent used, ml	263.3 ± 120.0	295.0 ± 138.5	279.3 ± 121.5	230.0 ± 102.1		<0.001

Values are mean ± SD or n (%).
FSS = functional SYNTAX score; PCI = percutaneous coronary intervention; RSS = residual SYNTAX score; SRI = SYNTAX revascularization index; SS = SYNTAX score.

9.5], $p = 0.51$ and SRI: 60.0% [IQR: 40.9% to 78.9%] vs. 58.8% [IQR: 26.7% to 81.8%], $p = 0.24$, respectively).

Comparisons of outcomes at 1 year among RSS and SRI subgroups are summarized in [Table 2](#). MACE and each component of MACE were not different among the RSS and SRI subgroups at 1 year. Kaplan-Meier curves at 1 year stratified by

RSS and SRI showed no significant separation (log-rank $p = 0.55$ for the RSS subgroups and log-rank $p = 0.54$ for the SRI subgroups) ([Figure 4](#)). Similarly, when stable and unstable patients were analyzed separately or when patients with SS 0 to 22 and with SS >23 were analyzed separately, Kaplan-Meier curves at 1 year, stratified by RSS



and SRI, showed no significant separation (Online Tables 1 and 2).

2-YEAR CLINICAL OUTCOME DATA. To test the durability of the results with longer-term follow-up, the same analyses were repeated with 2-year outcome data. MACE occurred in 74 patients (17.3%) at 2 years. As shown in Online Figure 1, patients with MACE had higher SS and FSS than patients without MACE, whereas RSS and SRI were similar between patients with and without MACE (RSS: 6.0 [IQR: 3.0 to 9.0] vs. 5.0 [IQR: 2.0 to 10.0], $p = 0.47$ and SRI: 58.9% [IQR: 33.3% to 78.6%] vs. 59.1% [IQR: 26.3% to 81.8%], $p = 0.57$, respectively).

Comparisons of outcomes at 2 years among RSS and SRI subgroups are summarized in Online Table 3. MACE and each component of MACE were not different among the RSS and SRI subgroups at 2 years. Kaplan-Meier curves at 2 years, stratified by RSS and SRI, showed no significant separation (log-rank $p = 0.87$ for the RSS subgroups and log-rank $p = 0.93$ for the SRI subgroups) (Online Figure 2). Similarly, when stable and unstable patients were analyzed separately or when patients with SS 0 to 22 and with SS >23 were analyzed separately, Kaplan-Meier curves at 2 years, stratified by RSS and SRI, showed no significant separation (Online Tables 1 and 2).

DISCUSSION

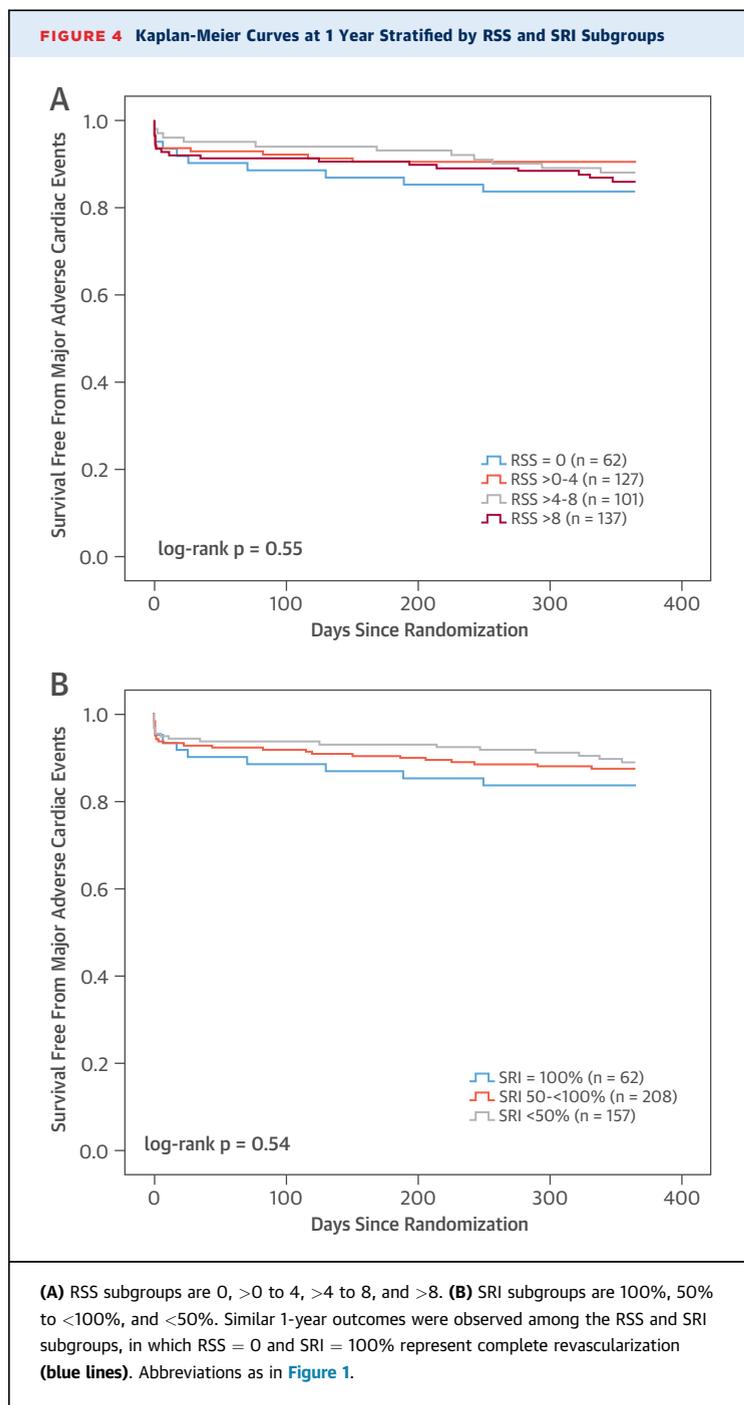
The principal finding of the present study is that the RSS and the SRI do not predict MACE at 1- and 2-year follow-up in patients with multivessel CAD after

TABLE 2 Comparison of Outcomes at 1 Year Among the RSS and SRI Subgroups

	Overall (N = 427)	RSS				p Value
		0 (n = 62)	>0 to 4 (n = 127)	>4 to 8 (n = 101)	>8 (n = 137)	
MACE	53 (12.4)	10 (16.1)	12 (9.4)	12 (11.9)	19 (13.9)	0.55
Death	8 (1.9)	3 (4.8)	1 (0.8)	2 (2.0)	2 (1.5)	0.27
Myocardial infarction	24 (5.6)	3 (4.8)	8 (6.3)	4 (4.0)	9 (6.6)	0.82
Repeat revascularization	25 (5.9)	4 (6.5)	4 (3.1)	8 (7.9)	9 (6.6)	0.45
Death or myocardial infarction	31 (7.3)	6 (9.7)	9 (7.1)	5 (5.0)	11 (8.0)	0.69

	Overall (N = 427)	SRI			p Value
		100% (n = 62)	50 to <100% (n = 208)	<50% (n = 157)	
MACE	53 (12.4)	10 (16.1)	26 (12.5)	17 (10.8)	0.56
Death	8 (1.9)	3 (4.8)	3 (1.4)	2 (1.3)	0.18
Myocardial infarction	24 (5.6)	3 (4.8)	14 (6.7)	7 (4.5)	0.62
Repeat revascularization	25 (5.9)	4 (6.5)	12 (5.8)	9 (5.7)	0.98
Death or myocardial infarction	31 (7.3)	6 (9.7)	16 (7.7)	9 (5.7)	0.57

Values are n (%).
 MACE = major adverse cardiac events (defined as a composite of all-cause death, myocardial infarction, or any repeat revascularization); MI = myocardial infarction; other abbreviations as in Table 1.



functionally complete revascularization (Central Illustration). These results reinforce that an FFR-guided PCI strategy offers sufficient revascularization because PCI of angiographically significant, but not functionally significant, lesions can be safely deferred. Moreover, they raise the question of whether RSS and SRI scores should be applied without accounting for the FFR result of specific lesions.

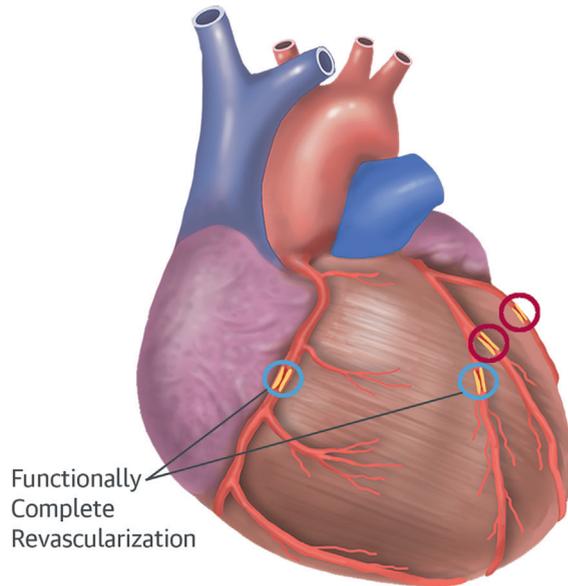
As shown in a previous FAME trial substudy, the FSS, which, compared with the SS, counts only functionally significant lesions on the basis of FFR assessment, better stratified the risk of MACE in patients undergoing multivessel FFR-guided PCI (20). Therefore, the fact that the RSS correlated significantly with the SS, but not with the FSS, may explain why the RSS had no prognostic value after functionally complete revascularization. This finding was similar when the SS and FSS were compared among the 4 RSS subgroups. With each decrement of the RSS, the number of lesions intended for treatment increased; however, the actual number and length of stents implanted decreased. In other words, patients with an RSS >8 had the highest baseline SS, but received the fewest number and shortest length of stents; nevertheless, the long-term outcome was similar compared with the other subgroups.

Similarly, the finding that the SRI was positively correlated with the FSS explains that the SRI had no prognostic value because the SRI should be negatively correlated with the FSS to be prognostic. With each decrement of the SRI, the number of lesions indicated tended to increase; however, the actual number/length of stents implanted decreased, and the long-term outcome was similar. These findings suggest that a scoring system with a purely anatomic approach may be insufficient, not only for the pre-procedural assessment, but also for the post-procedural assessment for predicting outcome after PCI.

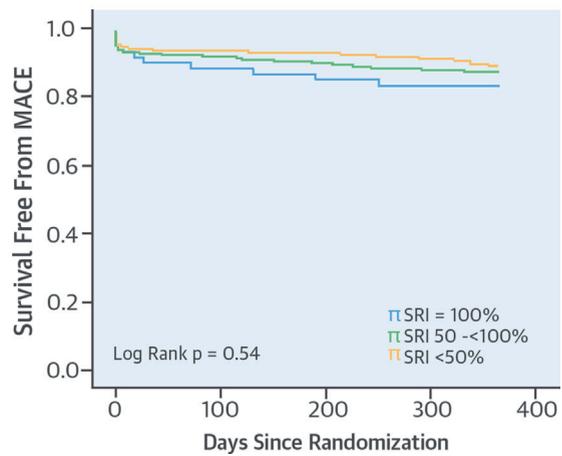
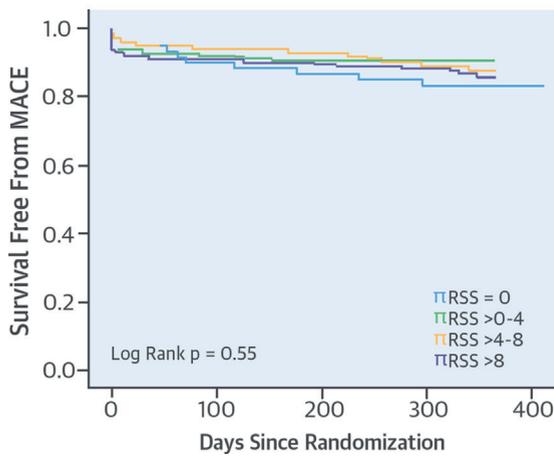
The RSS and SRI have been shown to be associated with worse long-term outcomes after angiography-guided PCI, suggesting the importance of angiographically complete revascularization in managing patients with stable angina and multivessel CAD (6,7,11,22-26). Given that functionally insignificant lesions do not tend to contribute to outcome when left untreated, the integration of functional information into the RSS and SRI should improve the prognostic value, just as was seen with the relationship between the SS and FSS (20), and as we document in this report. Although angiographically complete revascularization may be better than angiographically incomplete revascularization, our study supports the concept that functionally complete revascularization is as good as angiographically complete revascularization, if not better.

STUDY LIMITATIONS. First, because patients with ST-segment elevation myocardial infarction within 5 days were excluded, our results may not be applicable for patients with ST-segment elevation myocardial infarction and with multivessel CAD undergoing PCI.

CENTRAL ILLUSTRATION Untreated Lesions After FFR-Guided PCI: The Concept of “Functionally Complete Revascularization



- FFR ≤ 0.80: PCI improves outcome (FSS)
- FFR > 0.80: No impact on outcome, irrespective of residual CAD (RSS) or the extent of revascularization (SRI)



Kobayashi, Y. et al. J Am Coll Cardiol. 2016;67(14):1701-11.

“Angiographically” complete revascularization results in PCI of all angiographically significant lesions, which include both functionally significant and insignificant lesions. “Functionally” complete revascularization focuses on PCI of only functionally significant lesions, leaving functionally insignificant CAD for medical treatment, and in this manner, optimizing the benefit of PCI while minimizing its risk. Studies have shown that functionally significant lesions result in increased cardiac events without PCI, whereas functionally insignificant disease is treated more effectively with medical therapy. In this study, we found that functionally insignificant lesions have no prognostic value, irrespective of the untreated CAD assessed by the RSS or the extent of revascularization assessed by the SRI. CAD = coronary artery disease; FFR = fractional flow reserve; FSS = functional SYNTAX score; MACE = major adverse cardiac events; PCI = percutaneous coronary intervention; RSS = residual SYNTAX score; SRI = SYNTAX revascularization index.

Second, we do not have a control arm in this substudy because all angiographically significant lesions of patients enrolled in the angiography-guided PCI cohort were treated with PCI. Third, although the intention was for functionally complete revascularization in all patients, a small proportion of functionally significant lesions may have been left untreated due to the complexity of CAD anatomy, procedural failure, or the operator's discretion. Fourth, because the baseline complexity of CAD is relatively low in this population, our results may not apply to patients with more extensive CAD. However, the outcomes at 1 and 2 years did not differ among the RSS and SRI subgroups, irrespective of baseline SS stratification, suggesting the applicability of our results to patients with more complex CAD. Finally, because this study is a post hoc analysis of the FFR-guided PCI arm of the FAME trial, which was not designed to assess the impact of residual lesions or the extent of revascularization after FFR-guided PCI, the results of the present study should be interpreted as hypothesis-generating.

CONCLUSIONS

After functionally complete revascularization with FFR guidance, the residual functionally insignificant lesions do not increase the risk for MACE. For these reasons, the angiography-based RSS and SRI do not

predict a worse long-term outcome in these patients. Our study supports the concept of functionally complete revascularization, rather than angiographically complete revascularization.

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PERSPECTIVES

COMPETENCY IN PATIENT CARE AND

PROCEDURAL SKILLS: After functionally complete coronary revascularization on the basis of assessment of FFR, residual lesions that are angiographically, but not hemodynamically, significant are not associated with subsequent ischemic events.

TRANSLATIONAL OUTLOOK: Future studies should address whether selective coronary revascularization on the basis of FFR measurements apply as well to patients with ST-segment elevation myocardial infarction and patients with multivessel disease undergoing coronary artery bypass graft surgery.

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KEY WORDS fractional flow reserve, multivessel revascularization, residual SYNTAX score, SYNTAX revascularization index

APPENDIX For supplemental figures and tables, please see the online version of this article.