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Trends in the outcomes of percutaneous coronary intervention with the routine incorporation of fractional flow reserve in real practice

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Aims We evaluated the impact of the routine use of fractional flow reserve (FFR) on the practice and outcomes of percutaneous coronary intervention (PCI).

Methods and results Between January 2008 and December 2011, the rate of FFR use during PCI increased from 1.9 to 50.7% after the introduction of routine FFR use ($P < 0.001$). A total of 5097 patients (2699 patients before and 2398 after the routine use of FFR) underwent PCI at an academic hospital in Korea; of those, stent implantation was deferred in 475 patients. We used propensity score (PS) matching to compare the rates of the primary endpoint [death, myocardial infarction (MI), or repeat revascularization] at 1 year the cohort before and after the routine use of FFR. In the PS-matched cohort (2178 pairs), the median number of lesions per patient was 2 [inter-quartile range (IQR) 1–2] before vs. 2 (IQR 1–2) after the routine FFR use ($P = 0.68$); the median number of stents implanted per patient was 2 (IQR 1–3) vs. 1 (IQR 1–2), respectively ($P < 0.001$). The rates of the primary endpoint at 1 year was significantly lower in patients after the routine FFR use vs. patients before the routine use of FFR (hazard ratio 0.55; 95% confidence interval 0.43–0.70; $P < 0.001$). This was primarily due to a reduction in peri-procedural MI and repeat revascularization.

Conclusion Routine measurement of FFR in daily practice appeared to be associated with less use of stents and an improvement in clinical outcomes.

ClinicalTrials.gov number NCT 01788592.

Keywords Coronary Disease • Stents • Fractional Flow Reserve • Prognosis

Introduction

During the past 30 years, percutaneous coronary intervention (PCI) has become one of the standard treatment strategies for patients with ischaemic heart disease since successful PCI of ischaemia-producing stenoses reduced cardiovascular events.[1–3] However, in a significant proportion of patients, PCI is performed without documentation of ischaemia,[4,5] which is not beneficial and is, instead, associated with increasing clinical risks and economic costs.[6,7]

Fractional flow reserve (FFR) is a pressure-wire-based index used during invasive procedure to identify ischaemia-producing coronary stenoses.[8] The accuracy of FFR has been validated in a wide variety of

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clinical and anatomic situations.[9] Moreover, several randomized and observational studies have documented the benefit of using FFR to select coronary stenoses for stent implantation.[1,6,10–12] Although contemporary guidelines recommend FFR measurements in the absence of clinical evidence of ischaemia,[13,14] the use of FFR during coronary intervention is reported to be only 6%.[15] Many operators still use angiography to decide whether and when to perform revascularization. In addition, there are limited large studies that reproduce the benefits of FFR in real-world practice.[11,12]

The ASAN PCI Registry is composed of two distinct periods separated by the introduction of mandated routine FFR use. The use of FFR in this prospective registry has increased from 1.9% between 2008 and 2009 to 50.7% between 2010 and 2011 (see Supplementary material online, *Figure S1*). This rapid adaptation of FFR within a relatively brief time frame provided a valuable opportunity to evaluate the overall benefit of FFR-guided PCI in real practice. Here, we report the changes in practice and outcomes of patients who underwent PCI before and after the routine use of FFR.

Methods

Study population

The ASAN PCI Registry (ClinicalTrials.gov number NCT 01788592) is a prospective, single-centre registry to assess the contemporary practice and outcomes of PCI in a tertiary, high-volume centre in Korea. The current analysis includes patients enrolled between January 2008 and December 2011 who had at least one coronary lesion with a visually estimated diameter stenosis of >50% in a vessel and in whom PCI was indicated clinically. We excluded patients who had myocardial infarction (MI) with ST-segment elevation or who presented with cardiogenic shock, and those who had a contraindication to the placement of drug-eluting stents (e.g. pregnancy, non-cardiac surgery within 6 months after PCI, or contraindication to the drugs eluting from stents, etc.). Only the first eligible PCI record for each patient was analysed. This study was approved by the institutional review board and written informed consent was obtained from all patients.

Study intervention

The study intervention was a systematic change in the assessment of coronary stenosis severity before performing a coronary intervention. Since January 2010, all operators have routinely used FFR in assessing the functional severity of intermediate coronary stenosis (visual estimated diameter stenosis between 50 and 80%) during coronary intervention without objective evidence of ischaemia prior to PCI. Fractional flow reserve measurements were first introduced at the Asan Medical Center in 2007 and, initially, were selectively used for research purposes. In 2009, the Fractional Flow Reserve versus Angiography for Guiding Percutaneous Coronary Intervention (FAME; NCT00267774) study validated the benefit of FFR-guided PCI in multi-vessel disease patients.[10] Accordingly, there was consensus about the need for routine FFR measurement in daily practice among the current investigators; and beginning in January 2010, clinical protocols were revised to mandate its use during coronary intervention. In the current analysis, we divided patients into two groups: (i) patients before the routine use of FFR (between January 2008 and December 2009) and (ii) patients after the routine use of FFR (between January 2010 and December 2011).

Fractional flow reserve assessment and procedure

Fractional flow reserve was measured with a coronary pressure wire (St Jude Medical, Minneapolis, MN, USA) as described previously.[8,9] Percutaneous coronary intervention was performed in coronary stenoses with FFR < 0.75, if PCI was feasible, and deferred in those with FFR > 0.80. For FFR values between 0.75 and 0.80, the decision regarding revascularization was left to the operator's discretion. Percutaneous coronary intervention was performed with the use of standard techniques.[16] All patients undergoing PCI were prescribed aspirin plus clopidogrel (loading dose, 300 or 600 mg) before or during the coronary intervention. After the procedure, aspirin was continued indefinitely, and clopidogrel was prescribed for at least 12 months.

Study outcomes

The primary endpoint was the first occurrence of death from any causes, MI, or any repeat revascularization. The principal secondary endpoints were death, MI, stroke (of any cause), stent thrombosis, target vessel revascularization, target lesion revascularization, new lesion revascularization, composite of death or MI, and total number and length of implanted stents.

All deaths were considered cardiac unless an unequivocal non-cardiac cause could be established. The diagnosis of MI was based on the universal definition of MI.[17] In brief, procedure-related MI was based on the presence of new Q-waves or an elevation of creatine kinase-MB fraction or troponin I concentration more than three times the normal upper limit. In addition, an alternative criterion (an elevation of CK-MB more than five times the normal upper limit and ischaemic symptom or sign), defined *post hoc*, was also examined on the basis of recent arbitrary criteria of procedure-related MI.[18] Spontaneous MI was defined as any CK-MB or troponin increase above the upper range limit with or without the development of Q-waves on ECG. Stent thrombosis was defined as the definite or probable occurrence of a thrombotic event, according to the Academic Research Consortium classification.[19] Any repeat revascularization included any percutaneous or surgical revascularization procedure, irrespective of whether it was performed on a target or non-target lesion. Stroke, as detected by the occurrence of a new neurological deficit, was confirmed by a neurologist and imaging modalities. Total length of implanted stent was assessed by the manufacturer's specification and not on physical measurements made on site.

Clinical, angiographic, procedural, and outcome data were prospectively recorded in the dedicated PCI database by independent research personnel. Patients were clinically followed up at 1, 6, and 12 months, via office visits or telephone contact. For ensuring accurate assessment of clinical endpoints, additional information was obtained from visits or telephone contacts with living patients or family members and from medical records obtained from other hospitals, as necessary. Angiographic follow-up was not recommended unless ischaemic symptoms or signs were present during follow-up.

Statistical analysis

Continuous variables were compared with the Mann–Whitney test and categorical variables were compared with χ^2 statistics. Survival curves were constructed using Kaplan–Meier estimates and compared with the log-rank test.

To reduce the effect of selection bias and potential confounding in this observational study, we performed significant adjustment for differences in the baseline characteristics of patients with the use of propensity score (PS) matching. Propensity score was estimated non-parametrically using variables which are known to be related to both the group assignments and the outcome variables. In particular, we included age, sex, height,

weight, hypertension, diabetes mellitus, current smoker, hyperlipidaemia, previous bypass surgery, previous MI, previous coronary intervention, previous congestive heart failure, previous stroke, peripheral vascular disease, chronic renal failure, chronic lung disease, left ventricular ejection fraction, clinical presentation, extent of vascular disease, bifurcation, restenotic lesion, long lesion, thrombotic lesion, chronic total occlusion, and moderate-to-severe calcific lesion. Non-parametric PS estimation is used to eliminate possible bias due to the model dependence in the resulting parametric analysis stemming from the functional form specification and the curse of dimensionality.[20] It eliminates possible bias due to the model dependence in the resulting parametric analysis stemming from the functional form specification and the curse of dimensionality. 1:1 PS matching was performed by a nearest neighbour matching without replacement. The considered caliper size was 0.1. Pairs (before and after the routine incorporation of FFR) on the PS logit were matched within a range of 0.1 SD. Because the goal is to find well-matched groups, not well-matched pairs, greedy matching may be sufficient. The PS logit distributions for each cohort showed sufficient overlaps with caliper size 0.1. When we matched the individuals more tightly by decreasing the caliper size to 0.05, we obtained similar results as the caliper size 0.1. The balance of covariates was measured by their standardized differences in means. In general, it is considered that pre-treatment variable balancing can be achieved as long as the absolute standardized difference of means is <0.25. For the matched pair comparison, the Wilcoxon signed-rank test for continuous variables and McNemar's test for categorical variables were used. The Cox proportional hazards regression model was used to compare the clinical outcomes between the two groups in full cohort and PS-matched cohort with robust standard errors that accounted for the clustering of matched pairs.

Univariate and multivariate Cox regression analyses were used to identify predictors of the primary and secondary endpoints. Predictors were chosen by a backward stepwise Cox proportional hazard model using a threshold of 0.05 for variable elimination. Variables significantly associated with the primary endpoints and other clinical outcomes in univariate analyses listed in *Table 1* were entered into the final model. The proportional hazards assumption was confirmed by examination of log[−log (survival)] curves and by testing of partial (Schoenfeld) residuals. No relevant violations were found.

Analyses were performed with the use of R software, version 2.15.2 (R Foundation for Statistical Computing, Vienna, Austria) by an independent statistician (S.H.). R packages of survival and MatchIt were used to conduct the survival analysis and to construct the matched cohort/balance checking, respectively.[21,22] All reported *P*-values are two-sided, and *P*-values of <0.05 were considered statistically significance.

Results

Characteristics of the study population

Between January 2008 and December 2011, a total of 5097 patients were enrolled in the ASAN PCI Registry: 2699 patients before the routine use of FFR (January 2008 to December 2009) and 2398 after the introduction of the routine use of FFR (January 2010 to December 2011). As shown in Supplementary material online, *Figure S1*, the rate of FFR use rapidly increased up to 58% at the end of study patient enrolment.

Supplementary material online, *Table S1*, shows the baseline characteristics of the study patients before PS matching. After the introduction of the routine use of FFR, patients were generally older and male. More patients had hyperlipidaemia, peripheral vascular disease, chronic renal failure, chronic lung disease, and chronic total occlusions. Meanwhile, more patients before the routine use of FFR had previous bypass surgery and long lesions (lesion length $\geq$20 mm). Between the two groups, clinical presentation and distribution of the number of diseased vessels were not significantly different.

After PS matching, there were 2178 matched pairs of patients, and no significant differences were present between the two groups for any of the covariates (*Table 1*).

Procedural characteristics

Fractional flow reserve was successfully measured in 1267 patients (1551 lesions). The characteristics of the patients and FFR-assessed lesions are summarized in Supplementary material online, *Tables S2–S4*. In addition, the reasons for FFR not measured between 2010 and 2011, period of the routine FFR measurement, are summarized in Supplementary material online, *Table S5*. The tight stenosis or total occlusion was identified as the most frequent reason. In a total of 475 patients, stent implantation was deferred after FFR measurements; this comprised 37% of patients measured for FFR and 19% (461 out of 2398) of the cohort after introduction of the routine use of FFR. Fractional flow reserve was frequently measured in patients with stable angina, one-vessel disease, left anterior descending artery, and in lesions with diameter stenosis of 50–80%.

Procedural characteristics in *Table 2* show that during the period with the routine use of FFR, significantly fewer and shorter stents per patient were placed, although the number of lesions did not change. This effect was more pronounced in multi-vessel diseases ($P < 0.001$ for interaction). Furthermore, significant differences in the stent implantations according to the vascular territory were observed (*Figure 1*).

Outcomes

Complete 1-year follow-up data were obtained for 98.2% of the patients who received or deferred stent implantation; 44 (1.6%) and 48 (2.0%) patients were lost to follow-up before and after the introduction of the routine use of FFR, respectively ($P = 0.32$).

At 1 year of follow-up, 57 patients (1.1%) died, with 37 (0.7%) of these patients dying of a cardiovascular cause. One hundred and sixty-one patients (3.2%) had an MI, with 155 (3.0%) of those suffering from peri-procedural MI and 6 patients (0.1%) of those suffering from spontaneous MI, and 138 (2.8%) had a repeat revascularization.

Supplementary material online, *Figure S3*, shows the clinical outcomes of patients and lesions measured for FFR. Among 987 deferred lesions, 6 lesions (0.6%) were revascularized at 1-year follow-up. Particularly, among 475 PCI-deferred patients, only 1 non-cardiac death and 2 repeated revascularizations were occurred.

Supplementary material online, *Figure S4*, shows the unadjusted rates of clinical outcomes. The rate of death from any causes, MI, or repeat revascularization at 1 year (primary endpoint), the rate of death from any causes or MI, the rate of repeat revascularization were significantly lower among patients after the introduction of the routine use of FFR vs. before the routine use of FFR.

Figure 2 and *Table 3* show the rates of clinical outcomes in the 2178 PS-matched pairs. The risk of the primary endpoint was significantly lower in patients after the routine use of FFR. In addition, the risk of MI was significantly decreased, mainly due to the reduction of peri-procedural MI. The risks of any repeat revascularization and target

Table 1 Baseline characteristics of the propensity-score matched patients, according to the study group[a]

	Introduction of the routine use of FFR		*P*-value[b]
	Before (n = 2178)	After (n = 2178)	
Demographics			
Age, years	63 (56, 69)	63 (55, 70)	0.74
Male sex	1585 (72.8%)	1574 (72.3%)	0.73
Height, cm	165 (158, 170)	164 (157, 170)	0.75
Weight, kg	67 (60, 74)	67 (60, 74)	0.51
Cardiac or co-existing condition			
Hypertension	1328 (61.0%)	1333 (61.2%)	0.90
Diabetes mellitus	705 (32.4%)	705 (32.4%)	>0.99
Current smoker	634 (29.1%)	632 (29.0%)	0.97
Hyperlipidaemia	1388 (63.7%)	1396 (64.1%)	0.77
Previous bypass surgery	51 (2.3%)	44 (2.0%)	0.40
Previous myocardial infarction	106 (4.9%)	108 (5.0%)	0.95
Previous coronary intervention	369 (16.9%)	363 (16.7%)	0.84
Previous congestive heart failure	19 (0.9%)	22 (1.0%)	0.76
Previous stroke	131 (6.0%)	126 (5.8%)	0.79
Peripheral vascular disease	46 (1.9%)	44 (2.0%)	0.91
Chronic renal failure	57 (2.6%)	59 (2.7%)	0.92
Chronic lung disease	36 (1.7%)	30 (1.4%)	0.53
Left ventricular ejection fraction	60 (56, 64)	60 (57, 64)	0.42
Clinical presentation			0.10
Stable angina	1394 (64.0%)	1411 (64.8%)	
Unstable angina	582 (26.7%)	584 (26.8%)	
Non-ST-elevation myocardial infarction	202 (9.3%)	183 (8.4%)	
Extent of vascular disease			0.38
One-vessel disease	994 (45.6%)	1051 (48.3%)	
Two-vessel disease	637 (29.2%)	570 (26.2%)	
Three-vessel disease	313 (14.4%)	306 (14.0%)	
Left main disease	234 (10.7%)	251 (11.5%)	
Lesion characteristics			
Bifurcation	1205 (55.3%)	1200 (55.1%)	0.90
Restenotic lesion	155 (7.1%)	151 (6.9%)	0.86
Long lesion (>20 mm)	1742 (80.0%)	1748 (80.3%)	0.84
Thrombotic lesion	93 (4.3%)	92 (4.2%)	>0.99
Chronic total occlusion	141 (6.5%)	129 (5.9%)	0.48
Moderate-to-severe calcified lesion	147 (6.7%)	144 (6.6%)	0.90
Discharge medications			
Aspirin	2169 (99.6%) [2165 (99.6%)][c]	2142 (98.3%) [1767 (99.5%)]	<0.001 0.09
Clopidogrel	2160 (99.2%) [2156 (99.6%)]	1917 (88.0%) [1767 (99.5%)]	<0.001 0.87
Beta-blocker	1616 (74.2%) [1607 (74.2%)]	1566 (71.9%) [1334 (75.2%)]	0.09 0.51
ACE-I or ARB	701 (32.2%) [697 (32.2%)]	645 (29.6%) [539 (30.4%)]	0.07 0.22
Calcium channel blocker	1856 (85.2%) [1848 (85.4%)]	1799 (82.6%) [1493 (84.1%)]	0.019 0.28

Continued

Table 1 *Continued*

	Introduction of the routine use of FFR		*P*-value[b]
	Before ($n = 2178$)	After ($n = 2178$)	
Statin	1912 (87.8%)	2050 (94.1%)	<0.001
	[1899 (87.7%)]	[1647 (92.8%)]	<0.001

ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotension II receptor blocker; FFR, fractional flow reserve.
[a]Data are median (IQR) or number (%).
[b]*P*-values are based on the Wilcoxon signed-rank test for continuous variables and on McNemar's test for categorical variables.
[c]Only patients receiving stent implantation.

Table 2 Procedural characteristics of the propensity-score-matched patients, according to the study group[a]

	Introduction of the routine use of FFR		*P*-value[b]
	Before ($n = 2178$)	After ($n = 2178$)	
Fractional flow reserve	47 (2.2%)	1093 (50.2%)	<0.001
Intravascular ultrasound	1967 (90.3%)	2114 (97.1%)	<0.001
Number of lesions per patient	2 (1, 2)	2 (1, 2)	0.68
Number of treated lesions per patient	1 (1, 2)	1 (1, 1)	<0.001
Number of stents per patient	2 (1, 3)	1 (1, 2)	<0.001
Total stent length per patient, mm	46 (28, 72)	30 (18, 56)	<0.001
Stent diameter per patient, mm	3.29 (3.00, 3.50)	3.16 (2.83, 3.50)	<0.001
Multi-vessel stenting	772 (35.4%)	563 (25.8%)	<0.001

FFR, fractional flow reserve.
[a]Data are median (IQR) or number (%).
[b]*P*-values are based on the Wilcoxon signed-rank test for continuous variables and on McNemar's test for categorical variables.

vessel and target lesion revascularization were significantly decreased, but the risk of new lesion revascularization was not different. During the study period, the risk of death was not changed.

Supplementary material online, *Table S6*, shows the clinical outcomes in the PS-matched cohorts, excluding patients not receiving stent implantation ($n = 475$). The results are similar to the primary analysis. In addition, subgroup analysis showed the same trends (see Supplementary material online, *Figure S5*).

Predictors of the primary endpoint and other clinical outcomes are given in Supplementary material online, *Table S7*. Fractional flow reserve was identified as an important predictor related to the primary endpoint. In addition, FFR was significantly associated with the total number of treated lesions and the total number and length of implanted stents (see Supplementary material online, *Table S8*).

Discussion

The current study observed the benefit of FFR-guided PCI in a real-world patient population. Temporal comparison of two cohorts using PS matching showed that the routine use of FFR was associated with the lower risks of death, MI, or repeat revascularization at 1 year. It is primarily due to a reduced number of stents used per patients and a subsequent decreased risk of peri-procedural MI and repeat revascularization.

The quarterly rate of FFR use in our study increased up to 58% at the end of the enrolment period. One can criticize that this rate is low regarding the mandated use of FFR. However, FFR measurement is neither feasible nor necessary in a number of lesions, including tight stenoses or totally occluded lesions, stenoses evaluated by non-invasive functional study, stenoses with extreme vessel tortuosity or calcification, and the stenoses supplying small myocardium. To address this issue, we retrospectively evaluated the reasons for FFR not measured in the cohort between 2010 and 2011 and identified tight stenosis (visual estimated diameter stenosis >80%) or total occlusion as the most frequent reason. Only in 3.6% of those patients not measured FFR, no specific reasons were identified. Therefore, this rate could be considered as the rate of routine FFR measurement in real practice.

Consistent with FAME-I, we found a reduced risk of death or MI. However, most differences were derived from peri-procedural MI. Although the prognostic relevance of peri-procedural MI is still in debate,[23] it is evident that FFR-guided PCI results in the reduction of this stent-related complication causing myocardial damage. In addition, we applied the a strict criterion of the third universal definition of MI after adjudication of peri-procedural MI as *post hoc* analysis.[18] Although the overall incidence of MI was decreased, the benefit from FFR and the risk of increased stent use were consistently observed. On the other hand, the trend in mortality reduction

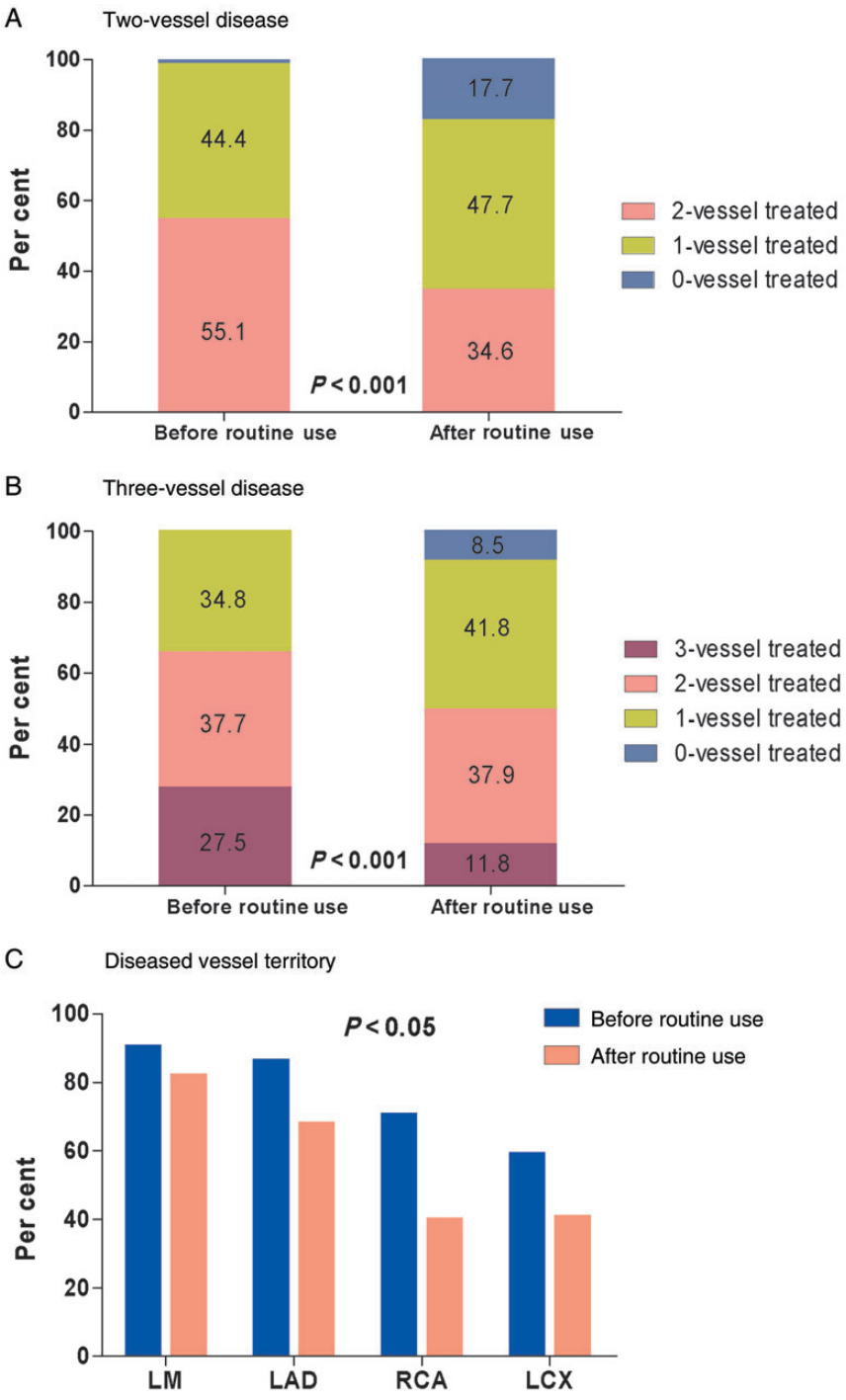

Figure 1 The rate of stenting and the number and territory of the diseased vessels in propensity-score-matched patients. Angiographically two-vessel disease (*A*), three-vessel disease (*B*), and diameter stenosis >50% in the left main, left anterior descending, left circumflex, and right coronary arteries (*C*).

could not be observed in the present study even with much larger study population.

The overall event rate was relatively low in the current study. The 1-year event rates for death, spontaneous MI, and revascularization were 1.1, 0.1, and 2.8% during study periods, lower than that reported previously.[10,24] The relatively infrequent occurrence of an event was not easily explained, but the routine use of intravascular ultrasound-guided PCI could be an important contributing factor. We used IVUS to assess the lesion morphology and to optimize the stent implantation in as high as 98% of the procedure. As shown in a recent

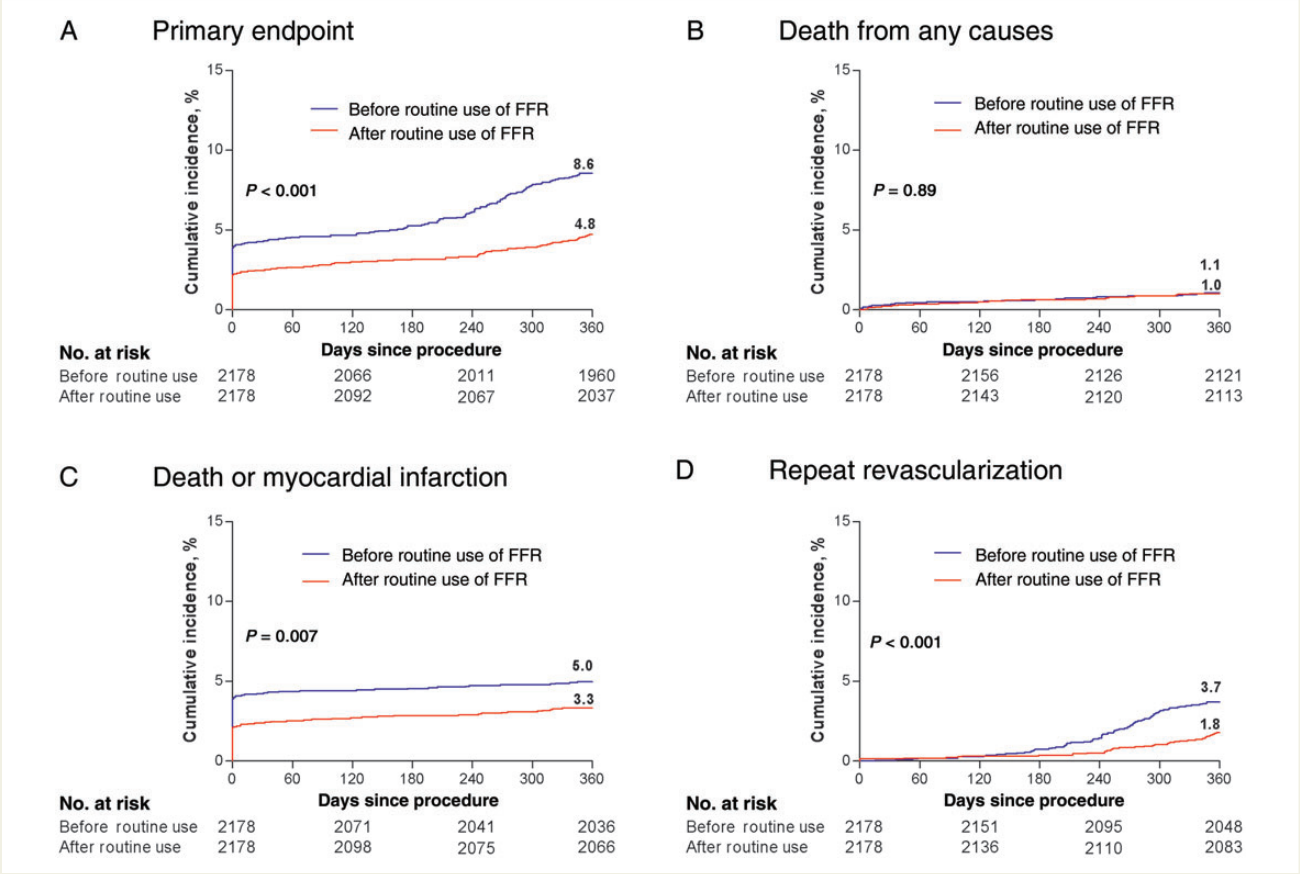

Figure 2 Adjusted curves for the primary endpoint and selected secondary endpoint before and after the introduction of the routine use of fractional flow reserve in propensity-score-matched patients. The primary endpoint of death from any causes, myocardial infarction, or any repeat revascularization (*A*); death from any causes (*B*); death from any causes or myocardial infarction (*C*); and any repeat revascularization (*D*).

meta-analysis, intravascular ultrasound-guided PCI in a drug-eluting stent era is associated with the reduction of death, MI, and stent thrombosis.[25] In addition, a higher rate of deferral of stent implantation after FFR measurement, which can avoid the stent-related unnecessary complications, could be another reason. In the current study, 63% of FFR-measured lesions were deferred, comparable with a recent observational study,[11] but higher than FAME-I, in which 37% of FFR-measured lesions were deferred. Only 0.6% out of deferred lesions received repeat revascularization at 1-year follow-up. Such favourable prognosis of deferred lesions may be related to the absolute lower rate of primary endpoints (death, MI, and repeat revascularization) in our study. Third, in the current study, ~45% of the population had one-vessel disease. Finally, our study involved an Asian population, and there may be a racial or ethnic difference in the propensity for ischaemic or thrombotic complications. In fact, the rate of primary endpoint in the cohort before the routine FFR measurement was similar to that of a prospective PCI registry study conducted in Asia with similar inclusion/exclusion criteria.[26]

Interestingly, profound reduction of stent use was observed in the territory of right coronary artery and left circumflex artery, which can be explained by the higher incidence of 'visual–functional mismatch' in this territory.[27] The stenosis-supplied smaller myocardial territories may have a higher chance to have a negative FFR, and subsequently a less chance to receive stent implantation.

It should be recognized that the impact of routine FFR measurement could be varied according to the threshold to PCI based on the visual estimation. The impact of FFR is likely higher in centres with low thresholds to PCI based on visual estimates, but may be less impactful on those that incorporate non-invasive stress testing prior to catheterization or have higher thresholds to PCI based on visual anatomical criteria (for example those who have retrained their assessment based on prior experience with IVUS or FFR).

The efficacy of revascularization in patients with stable ischaemic heart disease has been debatable. Large randomized clinical trials comparing the revascularization and the optimal medical treatment such as the Clinical Outcomes Utilizing Revascularization and Aggressive drug Evaluation (COURAGE) failed to demonstrate the benefit of stent implantation for the prevention of death, non-fatal MI, unplanned revascularization, or angina.[28] However, in this study, non-invasive testing was performed in 85% of the patients, and less than one-third of the patients had >10% ischaemia on myocardial perfusion imaging,[29] thus the benefit of PCI cannot be expected. On the other hand, FAME-II (Fractional Flow Reserve-

Table 3 Hazard ratios for 1-year clinical outcomes of patients before vs. after the introduction of the routine use of fractional flow reserve among propensity-matched patients[a]

	Cumulative event rate at 1 year		Hazard ratio (95% CI)[b]	*P*-value
	Introduction of the routine use of FFR			
	Before (n = 2178)	After (n = 2178)		
Primary endpoint	185 (8.6)	103 (4.8)	0.55 (0.43–0.70)	<0.001
Death				
Death from any cause	23 (1.1)	22 (1.0)	0.96 (0.53–1.72)	0.89
Cardiac death	14 (0.7)	15 (0.7)	1.08 (0.52–2.23)	0.84
Non-cardiac death	8 (0.4)	6 (0.3)	0.75 (0.26–2.18)	0.60
Myocardial infarction				
Any myocardial infarction	85 (3.9)	50 (2.3)	0.59 (0.42–0.83)	0.003
Peri-procedural myocardial infarction				
CK-MB > 3 times UNL	85 (3.9)	46 (2.1)	0.54 (0.38–0.78)	0.001
CK-MB > 5 times UNL	56 (2.1)	34 (1.4)	0.59 (0.37–0.94)	0.025
CK-MB > 5 times UNL plus ischaemic symptom or sign[c]	37 (1.4)	17 (0.7)	0.38 (0.20–0.72)	0.003
Spontaneous myocardial infarction	0	4 (0.2)	NA	NA
Death or myocardial infarction	108 (5.0)	72 (3.3)	0.66 (0.49–0.90)	0.007
Repeat revascularization				
Any repeat revascularization	79 (3.7)	39 (1.8)	0.49 (0.34–0.71)	<0.001
Target vessel	59 (2.8)	28 (1.3)	0.47 (0.30–0.74)	0.001
Target lesion	54 (2.5)	19 (0.9)	0.35 (0.21–0.59)	<0.001
New lesion	26 (1.2)	20 (1.0)	0.77 (0.43–1.39)	0.39
Stent thrombosis				
Definite	2 (0.1)	2 (0.1)	1.00 (0.14–7.13)	0.99
Definite or probable	5 (0.2)	2 (0.1)	0.40 (0.08–2.07)	0.28
Stroke	15 (0.7)	8 (0.4)	0.53 (0.23–1.26)	0.15

[a]For the total number of events for each type of endpoint, first events only are counted. Cumulative rates of events are based on Kaplan–Meier estimates. FFR, fractional flow reserve; NA, not applicable; UNL, upper normal limit.
[b]Hazard ratios are for patients after the routine use of FFR, compared with patients before the routine use of FFR.
[c]Either (i) symptoms suggestive of myocardial ischaemia, or (ii) new ischaemic ECG changes or new left bundle branch block, or (iii) angiographic loss of patency of a major coronary artery or a side branch or persistent slow- or no-flow or embolization, or (iv) imaging demonstration of new loss of viable myocardium or new regional wall motion abnormality.

Guided Percutaneous Coronary Intervention plus Optimal Medical Treatment versus Optimal Medical Treatment Alone in Patients with Stable Coronary Artery Disease) trial showed that revascularization for the stenosis of FFR $\leq$ 0.80 in a large epicardial artery suggesting that there were large areas of myocardium that were at risk for ischaemia may have benefit over optimal medical treatment regarding the reduction of urgent re-admission and revascularization treatment.[1] In this context, the routine use of FFR in daily practice could generalize the ischaemia-guided PCI using FFR in daily practice and will ultimately lead to an improvement of PCI outcomes.

From a methodological standpoint, this temporal comparison, observational study has some differences in outcomes, which might be a function of secular changes in the patient characteristics or of uncaptured practice patterns. However, the time frame encompassed by our study was relatively brief, with few differences in baseline clinical or angiographic characteristics between the time periods. Further, we used PS matching to make the patient groups comparable according to the measured confounders. Second, the time horizon for the clinical outcome analysis was limited to 1 year. Therefore, further long-term follow-up is necessary. Third, the implanted stent types were different according to the two different enrolment periods. However, in our multivariate analysis, stent type was not identified as a predictor of clinical outcomes. In addition, we did not use the paclitaxel eluting stent, which shows a higher rate of thrombotic events when compared with other drug-eluting stents, and other second generation drug-eluting stents showed comparable safety and efficacy profiles.[30] Fourth, to reproduce the same results, interventional cardiologists need to perform FFR to assess the functional impact of the stenosis and IVUS to optimize DES implantation, which is not feasible to a large number of catheterization laboratories in different medical systems even in industrialized countries mainly due to economical and reimbursement issues. In addition, we did not consider the reduction of angina, which is the main effect of stenting in patients with stable or unstable angina and did not evaluate the cost-effectiveness.

In conclusion, the routine measurement of FFR in daily practice appeared to be associated with less use of stent implantation and improvement in clinical outcomes at 1 year.

Supplementary material

Supplementary material is available at *European Heart Journal* online.

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