ORIGINAL RESEARCH

Stent and Dual Antiplatelet Therapy Duration Comparisons in the Setting of a Multicenter Randomized Controlled Trial: Can the Operator Experience Affect the Study Results?

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***Background*—**Operator experience influences outcomes after percutaneous coronary intervention, but this association in the controlled setting of a randomized, clinical trial is unclear.

***Methods and Results*—**We investigated operator-related outcomes (30-day and 2-year efficacy and safety end points) among patients undergoing percutaneous coronary intervention and randomized to different dual antiplatelet therapy durations and stent types. A total of 2003 patients were analyzed, and 7 operator groups were compared. The majority of preprocedural and postprocedural characteristics were imbalanced. The primary end point of the study, the composite of death, myocardial infarction, or cerebrovascular accidents, did not differ among operators at 30 days or 2 years. There were no significant differences also for all other individual and composite end points analyzed at 30 days and 2 years, except for 2-year stent thrombosis (P=0.048) and bleeding events (P=0.022 for Bleeding Academic Research Consortium type 2, 3, or 5). Adjusted comparisons for the main end points showed slight differences among operators at 30 days, but not at 2 years. There was no interaction of operator with dual antiplatelet therapy duration (P=0.112) or stent type (P=0.300). Results remained entirely consistent when operators were stratified by their experience.

***Conclusions*—**There was a weak signal of heterogeneity across study operators for the 30-day, but not the 2-year, main study outcomes. No clear effect of operator or operator experience was observed for the comparative efficacy and safety profile of the randomized stent types or dual antiplatelet therapy duration regimens.

***Clinical Trial Registration*—**URL: http://www.clinicaltrials.gov. Unique identifier: NCT00611286. **(*J Am Heart Assoc*. 2017;6: e007150. DOI: 10.1161/JAHA.117.007150.)**

Key Words: clinical outcomes • operator • percutaneous coronary intervention • randomized trial

Owing to innovations in device technology and improved operator techniques, percutaneous coronary intervention (PCI) has become a widely used and reproducible therapeutic procedure for the entire spectrum of coronary artery disease.[1,2]

Complications during and after PCI have dramatically declined during the past decades. Yet, periprocedural and postprocedural ischemic and bleeding adverse events still occur in a sizable proportion of patients. Although patient-related factors are known to play a key role for those

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Accompanying Tables S1 through S4 and Figures S1 through S5 are available at http://jaha.ahajournals.org/content/6/12/e007150/DC1/embed/inline-supplementary-material-1.pdf

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Clinical Perspective

What Is New?

- Observational studies suggest that operator volume/experience influences outcomes after percutaneous coronary intervention, but this is poorly explored in randomized, clinical trials, and there is ongoing debate on whether operator experience may influence reliability of trials findings.
- We compared operators in PRODIGY (Prolonging Dual Antiplatelet Treatment After Grading Stent-Induced Intimal Hyperplasia Study), a 4-by-2 randomized multicenter all-comer percutaneous coronary intervention trial comparing 4 stent types and 2 dual antiplatelet therapy duration regimens.
- We observed imbalances in the patient's and procedural characteristics and found weak differences in rates of clinical outcomes.
- After adjustment, there was a weak signal of heterogeneity across operators for 30-day, but not 2-year, main outcomes.
- When operators were stratified by their experience, no effect on clinical outcomes was observed.

What Are the Clinical Implications?

- No significant interactions were found between operators or operator experience and randomized dual antiplatelet therapy duration or stent type; thus, overall findings of the trial remained consistent.
- A prolonged dual antiplatelet therapy regimen failed to improve outcomes, irrespective of the operators.
- The routine collection of high-quality data sets should be encouraged to evaluate and improve operator competence and to allow investigation of operator as effect modifier of findings, especially for short-term outcomes after percutaneous coronary intervention, even in the controlled setting of a randomized, clinical trial.

occurrences, it is currently unknown to which degree these adverse events may be also operator dependent. Overall number of procedures performed and the operator experience may affect outcomes of patients undergoing PCI, but this evidence is mainly based on observational studies.[1–11] Randomized, controlled trials have played a major role in informing the community on the incidence, predictors, and implications of PCI-related adverse events. However, although the role of the center is often investigated or at least accounted for as a source of heterogeneity for the primary end point results, little is known on the potential impact of different operators on results of PCI studies. Operator expertise and the potential impact on outcomes has recently become a contentious topic for studies assessing access site.[12–16] Whether operators may also affect outcomes of studies assessing the performance of various stent platforms or durations of dual antiplatelet therapy (DAPT) after coronary stenting remains unclear. This analysis is frequently hampered by lack of proper data collection or inclusion of few cases by each single operator.

The aim of this study is to investigate whether an interoperator performance variation may exist in terms of efficacy and safety in the setting of the all-comer PRODIGY (Prolonging Dual Antiplatelet Treatment After Grading Stent-Induced Intimal Hyperplasia Study; NCT00611286) where patient recruitment was carried out by few interventional cardiologists, each recruiting a high number of patients.

Methods

The design and main findings of the PRODIGY trial have been previously reported.[17–19] PRODIGY is a 4-by-2 randomized, multicenter, open-label clinical trial designed to evaluate the efficacy and safety of prolonging the duration of clopidogrel therapy for up to 24 months in all-comer patients receiving a balanced mixture of stents with various anti-intimal hyperplasia potency and belonging to both first- and second-generation drug-eluting stent. Briefly, all-comer PCI patients (n=2013) were randomly allocated in a 1:1:1:1 fashion to 1 of 4 stent types, including everolimus-eluting stent, paclitaxel-eluting stent, zotarolimus-eluting Endeavor Sprint stent, or thin-strut bare metal stent. Patients alive at 30 days (n=1970) were then randomly allocated to either 6 or 24 months of DAPT. Selection criteria were broad, reflecting routine clinical practice. Randomization to 6- or 24-month DAPT was stratified by center, ongoing ST-segment-elevation myocardial infarction, presence of diabetes mellitus, and need for intervening for at least 1 in-stent restenotic lesion. The study was conducted in accord with the principles of the Declaration of Helsinki. The Ethics Committees of the 3 participating centers independently approved the protocol, and all participants gave written informed consent.

Operators

Interventional cardiologists of the 3 participating centers were trained operators, each with >500 cumulative PCI volume as first operator and all involved in the 24-hour on-call duty schedule at their referral institutions. During the trial, 6 operators performed PCI in the majority of patients enrolled, with each treating more than 50 patients. For the present study, each of them will represent an independent group. In order to explore the effect of PCI experience, operators were also further stratified in "More Experienced" and "Experienced" based on: (1) number of active years as first operator, (2) overall PCI volume, and (3) PCI volume/year in the 2 years before the trial initiation. "More experienced" operators were

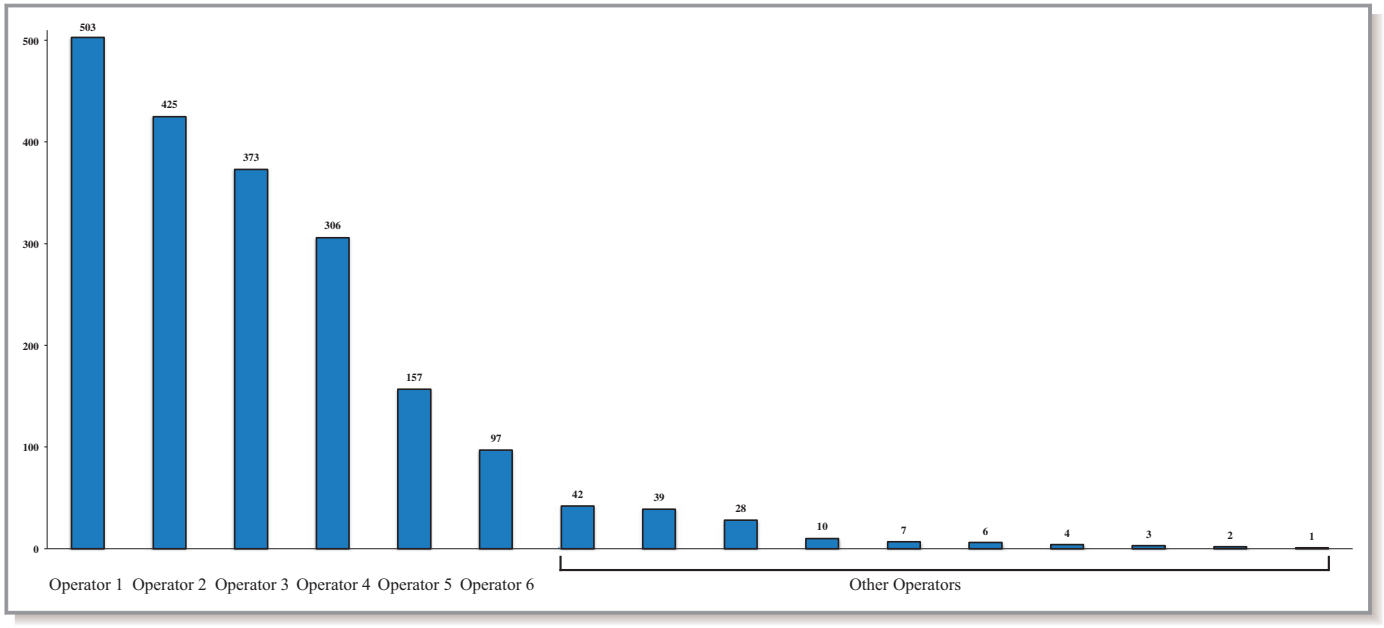

Figure 1. Operator procedure distribution.

those with >5 years, >1000 overall PCI, and >75 PCI/year, whereas "Experienced" were those with <5 years, 500 to 1000 overall PCI, and <75/year. Few other operators performed less than 50 procedures each, thus they were pooled in the seventh group named "other operators" overall including 142 patients/procedures (Figure 1).

Treatment Protocol and Follow-up

All patients received aspirin (80–160 mg orally indefinitely) and clopidogrel (75 mg/day) according to the randomization scheme as follows: for either 6 months in the short DAPT arm or 24 months in the prolonged DAPT arm irrespective of the previously implanted stent type or indication for PCI.

The randomized patients returned for study visits at 30 days and then every 6 months up to 2 years. During follow-up visits, patients were examined and assessed for adverse events, asked for the antiplatelet therapy compliance, and 12-lead ECG recordings were obtained.

Study End Points

The primary efficacy end point of the PRODIGY trial was the composite of death, MI, or cerebrovascular accident, whereas the key safety end point included Bleeding Academic Research Consortium (BARC) type 2, 3, or 5 bleeding. The net effect on the combined ischemic and bleeding complications was obtained by 2 net adverse clinical event (NACE) end points that were generated by combining the primary efficacy end point of death, MI, or cerebrovascular accident with either the primary safety end point of BARC type 2, 3, or 5 bleeding or with BARC type 3 or 5 events. Other end points included each component of the primary efficacy end point, cardiovascular death, stent thrombosis (ST) defined on the basis of the Academic Research Consortium criteria, and BARC type 3 or 5 bleeding. Other safety end points included bleeding events adjudicated according to the thrombolysis in myocardial infarction and global use of strategies to open occluded coronary arteries scales. All study end point definitions were previously reported.

All end points were confirmed on the basis of documentation collected at each hospital and were centrally adjudicated by the clinical events committee, whose members were unaware of the patients' treatment-group assignments. The time frame of interest for the primary end point was from 30 days (ie, after the primary end point randomization) to 24 months.

Statistical Analysis

The PRODIGY trial was designed to enroll at least 1700 patients to detect a 40% reduction in the relative risk of the primary end point in the 24-month clopidogrel group compared with 6-month duration of clopidogrel therapy, with statistical power of >80% at a 2-sided significance level of 0.05. The planned sample size was finally increased up to 2000 to allow for fatalities occurring within the first 30 days, noncompliance, and loss to follow-up as previously described.[17–19]

Categorical variables were expressed as frequency (percentage), whereas continuous variables were expressed as mean and SD. Baseline and procedural characteristics among

the 7 groups were compared using chi-square test for categorical variables and ANOVA F test for continuous variables. Crude events among groups were compared with likelihood ratio *P* values testing the shared frailty effect across operators using an inverse gamma distribution in Weibull time-to-event regression. Estimation of the cumulative major adverse cardiovascular event (MACE) rate, as well as of BARC bleeding and NACE, was performed by the Kaplan–Meier method.

In order to compare clinical outcomes among groups, hazard ratios with 95% confidence intervals were calculated from adjusted Weibull time-to-event regression comparing each operator (operator 2 to operator 6) versus operator 1 who was elected as reference because of the highest number of patients/procedures performed. The adjustment was performed including the following variables: age, sex, body mass index, hypertension, dyslipidemia, current smoking, family history of coronary artery disease, previous PCI, previous coronary artery bypass graft, peripheral arterial disease, creatinine clearance, left ventricular ejection fraction, acute coronary syndrome, femoral access, multivessel PCI, PCI performed by 2 or more operators (versus 1 operator only), 1 or more complex lesions, 1 or more restenotic lesions, randomized stent (4 categories), total stent length, and CRUSADE (Can Rapid risk stratification of Unstable angina patients Suppress ADverse outcomes with Early implementation of the ACC/AHA Guidelines) score.

Proportional-hazards assumption was tested on the basis of Schoenfeld residuals after fitting a Cox regression model for each of the 4 end points ($P \geq 0.7$ in each case).

Univariate analysis was conducted to explore whether operator category may predict 2-year MACE, BARC type 2, 3, or 5, or NACE.

Interaction testing was performed to determine whether the effect of randomization to DAPT duration or to stent type on the primary end point was consistent irrespective of operator category or volume of PCI performed by each operator.

To explore the effect of operator experience, all the analyses were also computed contrasting “more experienced” versus “experienced” operators on study end points.

A 2-sided probability value of <0.05 was considered significant. All analyses were performed with Stata Statistical Software (release 14; StataCorp LP, College Station, TX).

Results

A total of 2013 patients were recruited into the study and randomly assigned to 1 of the 4 stent types. Ten patients withdrew consent. Thirty-three (1.6%) patients died within 30 days, thus 1970 patients were randomly allocated at 1 month to undergo 24-month versus 6-month duration of clopidogrel therapy. Seven operator groups were created by matching cases to first treating operator as follows: operator 1 (n=503), operator 2 (n=425), operator 3 (n=373), operator 4 (n=306), operator 5 (n=157), operator 6 (n=97), and other operators including 10 operators performing each less than 50 procedures and cumulatively recruiting 142 patients into the study (Figure 1).

Baseline and Procedural Characteristics

Table 1 reports baseline and procedural characteristics according to the operator groups. There were notable imbalances across operators that were mainly driven by the other operators group, which recruited patients who were slightly younger, more frequently affected by stable coronary artery disease (one fourth of patients in this group presented acute coronary syndrome as compared with three fourths of patients in all other operator groups), with preserved renal and left ventricular function, and lower bleeding risk. Operator 1 treated the highest rate of past MI or ST-segment-elevation myocardial infarction patients or those requiring more frequently left main coronary artery intervention, or presenting with the mean lowest mean left ventricular ejection fraction (Table 1). On the other hand, operator 6 treated the highest number of lesions per procedure, with at least 1 complex lesion per procedure as well as more patients with past coronary artery bypass graft. Multivessel or saphenous vein graft intervention was more frequently accomplished by operator 2, whereas operator 5 performed the lowest number of multivessel/multilesion interventions (Table 1). Radial access was the default access site across all operators.

Clinical Outcomes

At 30 days, there were no significant differences among operator groups for any analyzed individual or composite end points (Table 2). The highest rate of the primary end point was observed for operator 6, who experienced, however, the lowest number of any or access-site bleeding events. Operator 2 had the highest rate of cerebrovascular accident, BARC bleeding, as well as NACE. Operator 1 was the one experiencing the lowest rate of death and cerebrovascular accident, whereas operator 5 was associated with the lowest rate of MACE and NACE. Operator 1 and 2 were associated with the highest rate of access-site–related bleeding (Table 2). In the group of other operators, none of the patients died or had stroke or ST or target vessel revascularization or bleeding, and all events within 30 days were MI.

At 2-year follow-up, there were no significant differences among operators for the primary end point as well as the majority of secondary end points, except for ST, mainly driven by no event in the other operator group and for BARC type 2,

Table 1. Baseline and Procedural Characteristics

Characteristic	Operator 1 (N=503)	Operator 2 (N=425)	Operator 3 (N=373)	Operator 4 (N=306)	Operator 5 (N=157)	Operator 6 (N=97)	Other Operators (N=142)	*P* Value	*P* Value Without Other Operators
Age, y	68.79±11.23	68.10±11.82	68.50±11.18	66.39±11.31	68.35±11.73	68.50±11.68	66.57±9.44	0.061	0.096
Male	380 (75.5%)	330 (77.6%)	277 (74.3%)	227 (74.2%)	119 (75.8%)	75 (77.3%)	124 (87.3%)	0.065	0.874
Body mass index, kg/m^2	27.51±4.42	26.67±3.72	27.07±3.97	26.54±3.64	27.86±4.70	28.74±5.12	27.36±2.68	<0.001	<0.001
Diabetes mellitus	128 (25.4%)	97 (22.8%)	93 (24.9%)	72 (23.5%)	39 (24.8%)	24 (24.7%)	35 (24.6%)	0.982	0.956
Insulin dependent	31 (6.2%)	28 (6.6%)	24 (6.4%)	17 (5.6%)	9 (5.7%)	8 (8.2%)	4 (2.8%)	0.687	0.955
Hypertension	372 (74.0%)	288 (67.8%)	274 (73.5%)	226 (73.9%)	101 (64.3%)	76 (78.4%)	101 (71.1%)	0.059	0.033
Hyperlipidemia	268 (53.3%)	222 (52.2%)	191 (51.2%)	180 (58.8%)	75 (47.8%)	43 (44.3%)	115 (81.0%)	<0.001	0.098
Current smoker	113 (22.5%)	121 (28.5%)	83 (22.3%)	73 (23.9%)	45 (28.7%)	21 (21.6%)	21 (14.8%)	0.022	0.172
Family history of CAD	159 (31.6%)	120 (28.2%)	119 (31.9%)	61 (19.9%)	32 (20.4%)	30 (30.9%)	36 (25.4%)	0.002	0.001
Past MI	150 (29.8%)	106 (24.9%)	103 (27.6%)	74 (24.2%)	40 (25.5%)	25 (25.8%)	37 (26.1%)	0.607	0.483
Past PCI	85 (16.9%)	84 (19.8%)	68 (18.2%)	38 (12.4%)	33 (21.0%)	16 (16.5%)	43 (30.3%)	0.001	0.122
Past CABG	44 (8.7%)	50 (11.8%)	45 (12.1%)	21 (6.9%)	14 (8.9%)	16 (16.5%)	23 (16.2%)	0.012	0.036
Peripheral arterial disease	75 (14.9%)	47 (11.1%)	49 (13.1%)	29 (9.5%)	20 (12.7%)	9 (9.3%)	23 (16.2%)	0.184	0.211
Creatinine clearance, mL/min	78.36±31.98	76.82±31.96	75.84±29.93	79.42±30.85	77.31±29.83	76.64±33.63	87.62±77.32	0.058	0.722
LVEF, %	49.53±10.86	49.78±10.44	51.20±9.98	50.70±10.18	50.32±9.35	48.61±10.40	56.75±8.83	<0.001	0.097
Clinical presentation									
Stable angina	90 (17.9%)	92 (21.6%)	111 (29.8%)	62 (20.3%)	33 (21.0%)	15 (15.5%)	103 (72.5%)	<0.001	0.001
ACS	413 (82.1%)	333 (78.4%)	262 (70.2%)	244 (79.7%)	124 (79.0%)	82 (84.5%)	39 (27.5%)	<0.001	0.001
STEMI	107 (21.3%)	71 (16.7%)	65 (17.4%)	50 (16.3%)	32 (20.4%)	19 (19.6%)	23 (16.2%)	0.464	0.398
NSTEMI	123 (24.5%)	93 (21.9%)	96 (25.7%)	80 (26.1%)	36 (22.9%)	21 (21.6%)	11 (7.7%)	0.001	0.722
Unstable angina	183 (36.4%)	169 (39.8%)	101 (27.1%)	114 (37.3%)	56 (35.7%)	42 (43.3%)	5 (3.5%)	<0.001	0.003
Access site								<0.001	<0.001
Radial	307 (61.0%)	254 (59.8%)	239 (64.1%)	264 (86.3%)	89 (56.7%)	88 (90.7%)	NA	<0.001	<0.001
Femoral	107 (21.3%)	96 (22.6%)	58 (15.5%)	29 (9.5%)	45 (28.7%)	6 (6.2%)	NA	<0.001	<0.001
Other or missing	89 (17.7%)	75 (17.6%)	76 (20.4%)	13 (4.2%)	23 (14.6%)	3 (3.1%)	NA	<0.001	<0.001
Angiographic features									
Multivessel disease	351 (69.8%)	303 (71.3%)	264 (70.8%)	201 (65.7%)	115 (73.2%)	66 (68.0%)	102 (71.8%)	0.628	0.534
No. of diseased vessels								0.815	0.693
Single-vessel disease	152 (30.2%)	122 (28.7%)	109 (29.2%)	105 (34.3%)	42 (26.8%)	31 (32.0%)	40 (28.2%)	0.628	0.534
Two-vessel disease	168 (33.4%)	150 (35.3%)	138 (37.0%)	111 (36.3%)	60 (38.2%)	33 (34.0%)	51 (35.9%)	0.917	0.846
Three-vessel disease	183 (36.4%)	153 (36.0%)	126 (33.8%)	90 (29.4%)	55 (35.0%)	33 (34.0%)	51 (35.9%)	0.549	0.437

Continued

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Table 1. Continued

Characteristic	Operator 1 (N=503)	Operator 2 (N=425)	Operator 3 (N=373)	Operator 4 (N=306)	Operator 5 (N=157)	Operator 6 (N=97)	Other Operators (N=142)	*P* Value	*P* Value Without Other Operators
Multivessel intervention	145 (28.8%)	131 (30.8%)	94 (25.2%)	73 (23.9%)	26 (16.6%)	28 (28.9%)	37 (26.1%)	0.02	0.010
No. of treated lesions								<0.001	<0.001
1 lesion	290 (57.7%)	260 (61.2%)	254 (68.1%)	196 (64.1%)	123 (78.3%)	52 (53.6%)	82 (57.7%)	<0.001	<0.001
2 lesions	150 (29.8%)	121 (28.5%)	98 (26.3%)	69 (22.5%)	25 (15.9%)	22 (22.7%)	33 (23.2%)	0.011	0.007
3 lesions	44 (8.7%)	28 (6.6%)	12 (3.2%)	27 (8.8%)	5 (3.2%)	14 (14.4%)	13 (9.2%)	<0.001	<0.001
≥4 lesions	19 (3.8%)	16 (3.8%)	9 (2.4%)	14 (4.6%)	4 (2.5%)	9 (9.3%)	14 (9.9%)	0.001	0.050
Treated vessel(s)									
LAD	286 (56.9%)	215 (50.6%)	169 (45.3%)	168 (54.9%)	83 (52.9%)	54 (55.7%)	78 (54.9%)	0.034	0.021
LCX	140 (27.8%)	153 (36.0%)	133 (35.7%)	98 (32.0%)	36 (22.9%)	32 (33.0%)	53 (37.3%)	0.009	0.009
Right coronary artery	191 (38.0%)	158 (37.2%)	127 (34.0%)	104 (34.0%)	59 (37.6%)	36 (37.1%)	47 (33.1%)	0.809	0.789
Left main artery	34 (6.8%)	27 (6.4%)	20 (5.4%)	18 (5.9%)	3 (1.9%)	6 (6.2%)	5 (3.5%)	0.318	0.348
Saphenous vein graft	6 (1.2%)	17 (4.0%)	7 (1.9%)	2 (0.7%)	4 (2.5%)	3 (3.1%)	3 (2.1%)	0.038	0.021
At least one complex lesion*	374 (74.4%)	289 (68.0%)	202 (54.2%)	185 (60.5%)	111 (70.7%)	73 (75.3%)	99 (69.7%)	<0.001	<0.001
At least 1 restenotic lesion	21 (4.2%)	28 (6.6%)	17 (4.6%)	9 (2.9%)	2 (1.3%)	4 (4.1%)	15 (10.6%)	0.002	0.069
Type of randomized stent								0.008	0.009
Bare metal stent	120 (23.9%)	109 (25.6%)	109 (29.2%)	84 (27.5%)	39 (24.8%)	16 (16.5%)	25 (17.6%)	0.046	0.146
Paclitaxel-eluting stent	125 (24.9%)	112 (26.4%)	100 (26.8%)	63 (20.6%)	34 (21.7%)	29 (29.9%)	37 (26.1%)	0.368	0.266
Zotarolimus-eluting stent	124 (24.7%)	115 (27.1%)	61 (16.4%)	82 (26.8%)	47 (29.9%)	30 (30.9%)	41 (28.9%)	0.002	0.001
Everolimus-eluting stent	134 (26.6%)	89 (20.9%)	103 (27.6%)	77 (25.2%)	37 (23.6%)	22 (22.7%)	39 (27.5%)	0.347	0.281
No. of implanted stents	1.97±1.22	1.93±1.19	1.62±0.95	1.87±1.32	1.39±0.78	2.15±1.33	2.20±1.81	<0.001	<0.001
Overall stent length, mm	42.65±31.75	40.82±28.57	34.32±22.41	39.95±30.41	28.56±16.94	44.58±29.44	47.02±40.34	<0.001	<0.001
Mean stent diameter, mm	2.93±0.43	3.06±0.45	2.95±0.41	2.98±0.46	2.95±0.44	3.00±0.48	3.11±0.48	<0.001	0.001
PCI performed by 2 senior operators	143 (28.4%)	109 (25.6%)	112 (30.0%)	17 (5.6%)	26 (16.6%)	9 (9.3%)	34 (23.9%)	<0.001	<0.001
CRUSADE score	27.43±12.87	27.41±13.13	27.21±13.07	26.36±12.86	25.44±12.61	27.61±15.14	22.22±10.86	0.001	0.543
Randomized DAPT regimen at 30 d								0.562	0.672
Short DAPT	245 (48.7%)	213 (50.1%)	176 (47.2%)	150 (49.0%)	78 (49.7%)	50 (51.5%)	71 (50.0%)	0.983	0.962
Long DAPT	254 (50.5%)	206 (48.5%)	186 (49.9%)	150 (49.0%)	75 (47.8%)	45 (46.4%)	71 (50.0%)	0.987	0.968
Not randomized	4 (0.8%)	6 (1.4%)	11 (2.9%)	6 (2.0%)	4 (2.5%)	2 (2.1%)	0 (0.0%)	0.135	0.245

P values are omnibus comparisons across the 7 operator categories (chi-square test for categories, ANOVA F test for continuous variables). ACC indicates American College of Cardiology; ACS, acute coronary syndrome; AHA, American Heart Association; CABG, coronary artery bypass graft; CAD, coronary artery disease; DAPT, dual antiplatelet therapy; LAD, left anterior descending artery; LCX, left circumflex artery; LVEF, left ventricle ejection fraction; MI, myocardial infarction; NSTEMI, non-ST-elevation myocardial infarction; PCI, percutaneous coronary intervention; RCA, right coronary artery; STEMI, ST-elevation myocardial infarction.

*Type B2 or C lesion according to the ACC/AHA coronary lesion classification.

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Table 2. Clinical Outcomes at 30 Days

Event	Operator 1 (N=503)	Operator 2 (N=425)	Operator 3 (N=373)	Operator 4 (N=306)	Operator 5 (N=157)	Operator 6 (N=97)	Other Operators (N=142)	*P* Value	*P* Value Without Other Operators
Primary efficacy end point									
All-cause death, MI, or CVA	46 (9.1)	54 (12.7)	35 (9.4)	38 (12.4)	13 (8.3)	13 (13.4)	18 (12.7)	0.420	0.401
Secondary efficacy end points									
All-cause death or MI	45 (8.9)	47 (11.1)	34 (9.1)	37 (12.1)	12 (7.6)	12 (12.4)	18 (12.7)	1.000	1.000
All-cause death	4 (0.8)	6 (1.4)	11 (2.9)	6 (2.0)	4 (2.5)	2 (2.1)	0 (0.0)	0.211	0.279
Cardiovascular death	4 (0.8)	6 (1.4)	11 (2.9)	6 (2.0)	4 (2.5)	2 (2.1)	0 (0.0)	0.211	0.279
Stroke or TIA	1 (0.2)	8 (1.9)	2 (0.5)	1 (0.3)	3 (1.9)	1 (1.0)	0 (0.0)	0.057	0.074
Myocardial infarction	43 (8.5)	43 (10.1)	27 (7.3)	32 (10.5)	8 (5.1)	10 (10.3)	18 (12.7)	1.000	1.000
Definite ST	5 (1.0)	4 (0.9)	1 (0.3)	4 (1.3)	0 (0.0)	0 (0.0)	0 (0.0)	1.000	1.000
Definite or probable ST	7 (1.4)	6 (1.4)	4 (1.1)	7 (2.3)	1 (0.6)	1 (1.0)	0 (0.0)	1.000	1.000
Definite probable or possible ST	7 (1.4)	6 (1.4)	5 (1.4)	7 (2.3)	1 (0.6)	1 (1.0)	0 (0.0)	1.000	1.000
TVR	6 (1.2)	5 (1.2)	3 (0.8)	4 (1.3)	1 (0.7)	0 (0.0)	0 (0.0)	1.000	1.000
Safety end points									
Access-site related bleeding*	8 (1.6)	7 (1.6)	2 (0.5)	2 (0.7)	1 (0.6)	0 (0.0)	1 (0.7)	0.065	0.047
BARC classification									
Key safety end point—type 2, 3, or 5	12 (2.4)	10 (2.4)	5 (1.4)	5 (1.6)	3 (2.0)	0 (0.0)	0 (0.0)	1.000	1.000
Type 3 or 5	4 (0.8)	4 (0.9)	2 (0.5)	2 (0.7)	1 (0.7)	0 (0.0)	0 (0.0)	1.000	1.000
TIMI classification									
Minor	3 (0.6)	1 (0.2)	2 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1.000	1.000
Major	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)	0.145	0.153
Minor or major	3 (0.6)	1 (0.2)	2 (0.5)	2 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)	1.000	1.000
GUSTO classification									
Moderate	2 (0.4)	3 (0.7)	1 (0.3)	0 (0.0)	1 (0.7)	0 (0.0)	0 (0.0)	1.000	1.000
Severe	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)	0.145	0.153
Moderate or severe	2 (0.4)	3 (0.7)	1 (0.3)	2 (0.7)	1 (0.7)	0 (0.0)	0 (0.0)	1.000	1.000
Net clinical adverse events (NACE)									
All-cause death, MI, CVA, or BARC 2, 3, or 5	58 (11.5)	63 (14.8)	40 (10.7)	41 (13.4)	16 (10.2)	13 (13.4)	18 (12.7)	1.000	1.000
All-cause death, MI, CVA, or BARC 3 or 5	50 (9.9)	58 (13.6)	37 (9.9)	39 (12.7)	14 (8.9)	13 (13.4)	18 (12.7)	0.453	0.419

Likelihood ratio *P* value testing the shared frailty effect across operators using an inverse gamma distribution in Weibull time-to-event regression. BARC indicates Bleeding Academic Research Consortium; CVA, cerebrovascular accident; GUSTO, global use of strategies to open occluded coronary arteries; MI, myocardial infarction; ST, stent thrombosis; TIA, transient ischemic attack; TIMI, thrombolysis in myocardial infarction; TVR, target vessel revascularization.
*Access-site related bleeding analyzed with mixed effects logistic regression.

3, or 5, mainly driven by difference for BARC 2 across operator groups (Table 3). ST was more frequently observed with operator 2, whereas operator 5 was associated with the highest rate of overall and most severe bleeding events. On the other hand, operator 5 was associated with the lowest rate of MI, ST, and target vessel revascularization. Operator 6 was the one with highest rate of the primary end point, as well as NACE, predominantly driven by the highest rates of death and MI (Table 3), whereas the primary end point was lowest for operator 3. Overall, the group of other operators who treated more stable patients was associated with lowest rates of death, bleeding, and composite end points (Table 3).

Adjusted comparisons for the main efficacy and safety end points at 30 days and 2 years are shown in Table 4. At 30 days, MACE and NACE were significantly increased with operator 2 compared with operator 1. Trends toward higher risk of MACE (49–56%) and NACE (45–52%) were also noted for Operator 4 and 6 as compared with operator 1, mainly attributable to increased risk of ischemic events. At 2 years, there was, however, no notable difference in operators'

Table 3. Clinical Outcomes at 2 Years

Event	Operator 1 (N=503)	Operator 2 (N=425)	Operator 3 (N=373)	Operator 4 (N=306)	Operator 5 (N=157)	Operator 6 (N=97)	Other Operators (N=142)	*P* Value	*P* Value Without Other Operators
Primary efficacy end point									
All-cause death, MI, or CVA	108 (21.5)	93 (21.9)	64 (17.2)	61 (20.0)	28 (17.8)	25 (25.8)	24 (17.0)	1.000	1.000
Secondary efficacy end points									
All-cause death or MI	100 (19.9)	83 (19.5)	62 (16.6)	58 (19.0)	28 (17.8)	24 (24.8)	23 (16.2)	1.000	1.000
All-cause death	40 (8.0)	36 (8.5)	33 (8.8)	21 (6.9)	16 (10.2)	11 (11.4)	6 (4.3)	1.000	1.000
Cardiovascular death	29 (5.8)	23 (5.5)	23 (6.2)	10 (3.3)	10 (6.4)	8 (8.4)	3 (2.2)	1.000	1.000
Stroke or TIA	14 (2.9)	15 (3.6)	6 (1.7)	4 (1.4)	5 (3.2)	3 (3.2)	1 (0.7)	0.386	0.486
Myocardial infarction MI	75 (15.1)	61 (14.5)	38 (10.3)	41 (13.5)	13 (8.4)	15 (15.9)	18 (12.7)	0.349	0.300
Definite ST	11 (2.2)	10 (2.4)	2 (0.5)	6 (2.0)	0 (0.0)	0 (0.0)	0 (0.0)	0.042	0.126
Definite or probable ST	18 (3.7)	17 (4.1)	5 (1.4)	9 (3.0)	1 (0.6)	3 (3.3)	0 (0.0)	0.048	0.195
Definite probable or possible ST	35 (7.1)	31 (7.4)	15 (4.1)	14 (4.7)	6 (3.9)	6 (6.5)	3 (2.2)	0.158	0.310
TVR	70 (14.4)	47 (11.5)	50 (14.1)	26 (8.7)	11 (7.4)	9 (10.0)	10 (7.1)	0.054	0.115
Safety end points									
BARC classification									
Key safety end point—type 2, 3, or 5	39 (8.0)	40 (9.7)	25 (7.0)	16 (5.4)	16 (10.6)	5 (5.7)	1 (0.7)	0.022	0.421
Type 3 or 5	13 (2.7)	20 (4.9)	15 (4.2)	8 (2.7)	7 (4.6)	2 (2.3)	1 (0.7)	0.340	0.494
TIMI classification									
Minor	9 (1.9)	7 (1.7)	6 (1.7)	1 (0.3)	1 (0.7)	2 (2.3)	0 (0.0)	1.000	1.000
Major	3 (0.6)	8 (2.0)	5 (1.4)	3 (1.0)	4 (2.6)	0 (0.0)	1 (0.7)	0.467	0.449
Minor or major	12 (2.5)	15 (3.7)	11 (3.1)	4 (1.3)	5 (3.3)	2 (2.3)	1 (0.7)	1.000	1.000
GUSTO classification									
Moderate	8 (1.6)	9 (2.2)	8 (2.2)	5 (1.7)	2 (1.4)	2 (2.3)	0 (0.0)	1.000	1.000
Severe	5 (1.0)	9 (2.2)	5 (1.4)	3 (1.0)	4 (2.6)	0 (0.0)	1 (0.7)	1.000	1.000
Moderate or severe	13 (2.7)	18 (4.4)	13 (3.7)	8 (2.7)	6 (4.0)	2 (2.3)	1 (0.7)	1.000	1.000
Net clinical adverse events (NACE)									
All-cause death, MI, CVA, or BARC 2, 3, or 5	136 (27.1)	120 (28.3)	77 (20.6)	72 (23.6)	40 (25.5)	28 (29.0)	24 (17.0)	0.120	0.227
All-cause death, MI, CVA, or BARC 3 or 5	116 (23.1)	101 (23.8)	69 (18.5)	66 (21.6)	32 (20.4)	26 (26.9)	24 (17.0)	1.000	1.000

Likelihood ratio *P* value testing the shared frailty effect across operators using an inverse gamma distribution in Weibull time-to-event regression. BARC indicates Bleeding Academic Research Consortium; CVA, cerebrovascular accident; GUSTO, global use of strategies to open occluded coronary arteries; MI, myocardial infarction; ST, stent thrombosis; TIA, transient ischemic attack; TIMI, thrombolysis in myocardial infarction; TVR, target vessel revascularization.

performances. Operator category did not predict 2-year MACE (*P*=0.74), BARC type 2, 3, or 5 (*P*=0.31), or NACE (*P*=0.66 and 0.85 for NACE with BARC 2, 3, or 5, and BARC 3 or 5, respectively).

Operator Interaction With DAPT and Stent Randomized Groups for the Primary Outcome

When the primary end point of all-cause death, MI, or cerebrovascular accident was stratified according to the operators, no significant interaction emerged between operator and DAPT randomization (*P*=0.112; Figure 2), and this was confirmed at 6-month landmark analysis (from 6 months to 2 years: *P*=0.425; Figure S1).

Similarly, interaction testing between operator and stent type (*P*=0.300; Figure 2) was negative. Also, no interaction was observed between operator and DAPT or randomized stent at stratified analysis by operator volume (Figures S2 and S3). Three-way interaction among operator-randomized DAPT duration-randomized stent was similarly negative (*P*=0.210).

Table 4. Adjusted Hazard Ratios

Event	Operator n vs Operator 1 (Reference)												Overall *P* Value*
	Operator 1 (N=503)	*P* Value	Operator 2 (N=425)	*P* Value	Operator 3 (N=373)	*P* Value	Operator 4 (N=306)	*P* Value	Operator 5 (N=157)	*P* Value	Operator 6 (N=97)	*P* Value	
At 30 d													
All-cause death, MI, or CVA	1	Ref.	1.58 (1.05–2.37)	0.029	1.38 (0.86–2.21)	0.179	1.56 (0.97–2.53)	0.069	1.09 (0.54–2.21)	0.802	1.49 (0.76–2.92)	0.245	0.224
BARC 2, 3, or 5	1	Ref.	0.82 (0.33–2.04)	0.672	0.95 (0.30–2.95)	0.923	0.72 (0.22–2.37)	0.593	0.57 (0.14–2.28)	0.431	…	0.231†	1.000
All-cause death, MI, CVA, or BARC 2, 3, or 5	1	Ref.	1.42 (0.98–2.05)	0.064	1.28 (0.83–1.96)	0.267	1.31 (0.84–2.04)	0.240	0.95 (0.51–1.76)	0.858	1.32 (0.69–2.53)	0.409	0.435
All-cause death, MI, CVA, or BARC 3 or 5	1	Ref.	1.57 (1.06–2.33)	0.024	1.36 (0.86–2.14)	0.189	1.52 (0.95–2.44)	0.078	1.07 (0.54–2.09)	0.849	1.45 (0.74–2.82)	0.280	0.244
At 2 y													
All-cause death, MI, or CVA	1	Ref.	1.10 (0.83–1.48)	0.504	0.96 (0.69–1.33)	0.791	1.18 (0.84–1.68)	0.342	0.91 (0.57–1.46)	0.700	1.37 (0.85–2.20)	0.199	1.000
BARC 2, 3, or 5	1	Ref.	1.14 (0.72–1.80)	0.573	0.98 (0.58–1.68)	0.954	0.73 (0.39–1.38)	0.340	1.40 (0.75–2.63)	0.291	0.73 (0.27–1.95)	0.527	1.000
All-cause death, MI, CVA, or BARC 2, 3, or 5	1	Ref.	1.11 (0.86–1.44)	0.415	0.89 (0.66–1.21)	0.466	1.07 (0.78–1.46)	0.687	1.01 (0.68–1.50)	0.949	1.17 (0.75–1.82)	0.487	1.000
All-cause death, MI, CVA, or BARC 3 or 5	1	Ref.	1.11 (0.84–1.46)	0.480	0.95 (0.69–1.30)	0.731	1.19 (0.85–1.67)	0.303	0.98 (0.63–1.52)	0.927	1.27 (0.79–2.02)	0.322	1.000

Hazard ratios from adjusted Weibull time-to-event regression comparing each operator n (2–6) vs Operator 1. Adjusted for: PCI performed by 2 or more operators (vs 1 operator only), age, sex, body mass index, hypertension, dyslipidemia, current smoking, family history coronary artery disease, previous percutaneous coronary intervention (PCI), coronary artery bypass graft, peripheral arterial disease, creatinine clearance, LVEF, acute coronary syndrome, femoral access, multivessel PCI, 1 or more complex lesions, 1 or more restenotic lesions, randomized stent (4 categories), total stent length, and CRUSADE (Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes With Early Implementation of the ACC/AHA Guidelines) score. BARC indicates Bleeding Academic Research Consortium; CVA, cerebrovascular accident; GUSTO, global use of strategies to open occluded coronary arteries; MI, myocardial infarction; PCI, percutaneous coronary intervention; ST, stent thrombosis; TIA, transient ischemic attack; TIMI, thrombolysis in myocardial infarction; TVR, target vessel revascularization.

*Likelihood ratio *P* value testing the shared frailty effect across operators using a Gaussian distribution in Adjusted Weibull time-to-event regression.

†No BARC 2, 3, or 5 bleedings in Operator 6: Fisher's exact test *P* value on raw counts reported instead comparing Operator 6 vs 1.

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Operator Experience

When analyses were conducted comparing "More experienced" with "Experienced" operators, no significant effect emerged on clinical outcomes at 30-day or 2-year and no interaction was noted with respect to randomized DAPT duration or stent type (Tables S1 through S4; Figures S4 and S5).

Discussion

The present study explored the interoperator impact on clinical outcomes of patients undergoing PCI in the setting of a randomized, clinical trial. Across each operator stratum, there were several differences for patient and procedural characteristics, making interpretation of unadjusted clinical outcomes problematic. After adjustment, there were some differences for 30-day outcomes, mainly owing to different risks of ischemic events across operators. However, adjusted analyses failed to show heterogeneous outcomes across operator groups at 2 years, and operators did not impact on the comparative efficacy or safety profile of different DAPT durations or stent types. Therefore, the present analysis provides reassurance that operator per se or operator experience/operator volume was not a significant effect modifier of our study findings.

The optimal duration of DAPT after PCI is a matter of ongoing discussion, attributed to a clear trade-off between benefits and risks. A prolonged DAPT regimen prevents recurrent or new MI related or not to stent thrombosis. Furthermore, procedural complexity has emerged as an important driver of DAPT duration, with prolonged DAPT being beneficial in more-complex procedures.[20] Accordingly, it is plausible that different operators with different technical skills, expertise, and case volume, as well as different procedural tactics (predilatation and postdilatation, duration and pressure of dilatation, stent implantation sizing and technique, use of intravascular imaging modalities, etc) may be associated with different clinical outcomes. In this respect, however, we did not find significant interaction between operator, type of stent, and DAPT regimen, suggesting that our overall study results were consistent across operators, which has notable implications for the external validity of our findings. There was, however, signal that operator may impact

	events/nr of patients	events/nr of patients	Hazard Ratio (95% CI)	p-value	interaction p-value
Randomized DAPT*:	**Short DAPT**	**Long DAPT**	**Long vs Short**		
All-cause Death, MI or CVA from 30 to 720 days					**0.112**
Operator 1	36/254	28/245	0.79 (0.48-1.29)	0.340	
Operator 2	16/206	27/213	1.68 (0.91-3.12)	0.099	
Operator 3	17/186	14/176	0.87 (0.43-1.76)	0.692	
Operator 4	16/150	7/150	0.41 (0.17-1.01)	0.052	
Operator 5	7/ 75	10/ 78	1.42 (0.54-3.73)	0.476	
Operator 6	5/ 45	8/ 50	1.51 (0.49-4.63)	0.468	
Other Operators***	3/ 71	4/ 71	1.36 (0.31-6.10)	0.684	
Randomized to any DES or BMS:**	**DES**	**BMS**	**DES vs BMS**		
All-cause Death, MI or CVA from 0 to 720 days					**0.300**
Operator 1	75/383	33/120	0.69 (0.46-1.04)	0.079	
Operator 2	65/316	28/109	0.80 (0.51-1.24)	0.314	
Operator 3	45/264	19/109	0.98 (0.57-1.67)	0.937	
Operator 4	49/222	12/ 84	1.59 (0.85-2.99)	0.150	
Operator 5	20/118	8/ 39	0.79 (0.35-1.80)	0.575	
Operator 6	19/ 81	6/ 16	0.61 (0.24-1.52)	0.287	
Other Operators***	20/117	4/ 25	1.05 (0.36-3.06)	0.936	

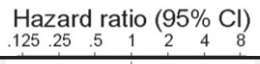

Figure 2. Stratified effect of operators on the primary comparisons of the primary outcome in the PRODIGY trial. Hazard ratios from Weibull time-to-event regression on the composite of all-cause death, MI, or CVA comparing the randomized DAPT durations or randomized stents and testing for effect modification by the Operators n (1–6). *Short DAPT randomized to 6 months of DAPT, Long DAPT randomized to 24 months of DAPT. **ZES-S (zotarolimus-eluting Endeavor Sprint stent), PES (paclitaxel-eluting stent), and EES (everolimus-eluting stent) combined. ***The Other Operators are shown for completeness, but not used for interaction testing. BMS indicates bare metal stent; CVA, cerebrovascular accidents; DAPT, dual antiplatelet therapy; DES, drug-eluting stent; MI, myocardial infarction.

on outcomes in the early period after PCI when indeed operator and procedural factors are more likely to play a role. On the contrary, at 2 years, we did not observe significant differences across operator groups, likely as a reflection that procedural technicalities adopted by each operator have limited impact on long-term outcomes.

Physician competence is a critical component in the provision of optimal health care. All physicians must have the appropriate training, fund of knowledge, clinical decision making, and technical skills. In the setting of PCI, operators must perform these procedures at a requisite level of proficiency and competency.

Patients treated by high-volume operators and at high-volume centers have been shown to experience a higher rate of procedural success and lower rates of mortality and postprocedural complications.[1–11] As a consequence, standards of assistance have been recommended for PCI operators.[1,2,6] Recently, in an observational study, operator experience has emerged as an important prognostic factor in a complex intervention, such as left main PCI, where patients treated by high-volume and experienced operators had better outcomes.[9] Operators were shown to impact on outcomes in the setting of different complex procedures, such as chronic total occlusions,[21] the implantation of specific devices as bioresorbable vascular scaffolds,[22] and structural interventions.[23]

During the past decades, the cardiology community has been largely informed in terms of clinical practice by the results of many randomized trials. In order to achieve enough of a number of observations, and to reduce the bias related to single-center studies, multicenter studies are frequently performed and currently regarded as the study design allowing for the greatest external validity. Multicenter PCI studies can, however, also critically depend on expertise and proficiency of the multiple operators involved. Although subgroup analyses are frequently performed to explore the consistency of study results across different geographical locations, and sometimes randomization is stratified by center, the role of each operator within each center is almost never appropriately investigated. Operators are very rarely matched with the corresponding treated patients within each multicenter study, and even when this information is available, each study operator generally contributes with a limited number of patients within each study. There are, however, relevant exceptions. Interoperator variation was previously investigated in 1071 patients enrolled in the TAPAS (Thrombus Aspiration During Percutaneous Coronary Intervention in Acute Myocardial Infarction Study) trial.[16] The primary end point of the study, which was myocardial blush grade 3, was analyzed across 6 operator groups, and it was shown to significantly differ across operators after adjustment for baseline and procedural imbalances. This post-hoc analysis suggested that, even in a controlled setting, significant interoperator variation might exist in the efficacy of primary PCI.[16] Interestingly, however, no data on patient outcomes were available across operators at long-term follow-up.

More recently, the operator experience, and its potential impact on outcomes, has become a matter of debate in the comparison of radial versus femoral access site for PCI. In the MATRIX-Access (Minimizing Adverse Haemorrhagic Events by TRansradial Access Site and Systemic Implementation of angioX),[12] the benefit of radial versus femoral access appeared consistent across major patient subgroups including tertiles of the centers' annual volume of PCI. However, positive tests for trend were found across tertiles of the centers' percentage of radial PCI for both co-primary end points and all-cause mortality at 30 days, suggesting a more-pronounced benefit of radial access in centers that did 80% or more-radial PCI,[12] and this generated great interest.[13–15,24,25] Whether these differences will remain detectable also at longer-term follow-up remains currently unclear.

All together, our results are consistent with previous observations that operators may impact on procedural or PCI short-term (ie, 30-day) clinical outcomes whereas such an effect seems to vanish at time frames more remote from the index intervention. This may reflect the existence in contemporary practice of well-standardized percutaneous techniques and improved biomedical technologies for the treatment of patients with coronary artery disease. In this context, factors, which are largely unrelated to the revascularization procedure per se, such as adherence to and optimal titration of secondary prevention medication as well as comorbidities and disease progression, may affect long-term outcomes more than procedural technical features. On the other hand, the effect of operator on PCI outcomes seemed to be, at best, minimal, and when operators were stratified for their volume/experience before the trial initiation, this effect disappeared. The absence of a definite experience-outcome relationship for individual operators should not be regarded as surprising in such a context where centers and operators were at high volume of PCI. However, volume per se might not be an appropriate marker of quality (high volume may not correspond to high quality because practice/volume by itself is of little value if the procedure is not properly executed).[2,26]

Therefore, our current findings extends previous results of the PRODIGY trial by suggesting that the impact of stent selection or DAPT durations on ischemic and bleeding outcomes remained consistent across study operators.

Limitations

This is a post hoc analysis sharing limitations of other not prespecified and not powered analyses. PRODIGY is a

3-center trial, and it cannot be excluded that, in larger trials with many different centers and operators involved, a certain degree of interoperator variation may exist and may have a significant interaction with safety and efficacy end points.

Although the comparisons between operators were adjusted for main variables, it cannot be excluded that other confounders may affect these findings.

The number of events in some cases (ie, stroke or ST) was too low to allow an appropriate adjusted comparison among 6 or 7 groups.

Conclusions

After adjustment for multiple patient- and procedure-related imbalances, there was a weak signal of heterogeneity across individual study operators for the 30-day, but not the 2-year, main study outcomes, and no differences were observed across operators' past PCI volumes. Accordingly, no clear effect of the operator was observed for the comparative efficacy and safety profile of the randomized stent types or DAPT duration regimens in our study, which has notable implications for the external validity of the PRODIGY study results.

Disclosures

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Supplemental Material

Table S1. Baseline and procedural characteristics according to operator experience.

Characteristic	More experienced operators (N=798)	Experienced operators (N=1063)	p-value
Age (yr)	68.28 ± 11.52	68.01 ± 11.40	0.606
Male	607 (76.1%)	801 (75.4%)	0.743
Body Mass Index (kg/m^2)	26.86 ± 3.84	27.40 ± 4.37	0.006
Diabetes	190 (23.8%)	263 (24.7%)	0.663
Insulin-dependent	52 (6.5%)	65 (6.1%)	0.772
Hypertension	562 (70.4%)	775 (72.9%)	0.252
Hyperlipidemia	413 (51.8%)	566 (53.2%)	0.542
Current smoker	204 (25.6%)	252 (23.7%)	0.384
Family history of CAD	239 (29.9%)	282 (26.5%)	0.106
Prior MI	209 (26.2%)	289 (27.2%)	0.634
Prior PCI	152 (19.0%)	172 (16.2%)	0.109
Prior CABG	95 (11.9%)	95 (8.9%)	0.037
Peripheral arterial disease	96 (12.0%)	133 (12.5%)	0.776
Creatinine Clearance (ml/min)	76.37 ± 31.01	78.35 ± 31.47	0.175
LVEF (%)	50.44 ± 10.24	49.90 ± 10.42	0.261
Clinical presentation			
Stable angina pectoris	203 (25.4%)	200 (18.8%)	0.001
ACS	595 (74.6%)	863 (81.2%)	0.001
STEMI	136 (17.0%)	208 (19.6%)	0.184
NSTEMI	189 (23.7%)	260 (24.5%)	0.743
Unstable Angina	270 (33.8%)	395 (37.2%)	0.143
Access site			<0.001
radial	493 (61.8%)	748 (70.4%)	<0.001
femoral	154 (19.3%)	187 (17.6%)	0.364
other or missing	151 (18.9%)	128 (12.0%)	<0.001
Angiographic features			
Multivessel Disease	567 (71.1%)	733 (69.0%)	0.333
No. of diseased vessels			0.621
Single-vessel disease	231 (28.9%)	330 (31.0%)	0.333
Two-vessel disease	288 (36.1%)	372 (35.0%)	0.625
Three-vessel disease	279 (35.0%)	361 (34.0%)	0.658
Multivessel intervention	225 (28.2%)	272 (25.6%)	0.223
No. of treated lesions			0.012
1 lesion	514 (64.4%)	661 (62.2%)	0.332
2 lesions	219 (27.4%)	266 (25.0%)	0.241
3 lesions	40 (5.0%)	90 (8.5%)	0.004
≥4 lesions	25 (3.1%)	46 (4.3%)	0.221
Treated vessel(s)			
LAD	384 (48.1%)	591 (55.6%)	0.001
LCX	286 (35.8%)	306 (28.8%)	0.001

Right coronary artery	285 (35.7%)	390 (36.7%)	0.697
Left main artery	47 (5.9%)	61 (5.7%)	0.920
Saphenous vein graft	24 (3.0%)	15 (1.4%)	0.021
At least one complex lesion*	491 (61.5%)	743 (69.9%)	<0.001
At least one restenotic lesion	45 (5.6%)	36 (3.4%)	0.021
Type of randomized stent			0.062
Bare-metal stent	218 (27.3%)	259 (24.4%)	0.163
Paclitaxel-eluting stent	212 (26.6%)	251 (23.6%)	0.159
Zotarolimus-eluting stent	176 (22.1%)	283 (26.6%)	0.026
Everolimus-eluting stent	192 (24.1%)	270 (25.4%)	0.516
Number of implanted stents	1.79 ± 1.09	1.87 ± 1.23	0.118
Overall stent length, mm	37.78 ± 26.07	39.96 ± 29.78	0.100
Mean stent diameter, mm	3.01 ± 0.44	2.96 ± 0.45	0.011
PCI performed by 2 or more operators	221 (27.7%)	195 (18.3%)	<0.001
CRUSADE score	27.32 ± 13.09	26.86 ± 13.06	0.456
Randomized DAPT regimen at 30 days			0.599
Short DAPT (6 months)	389 (48.7%)	523 (49.2%)	0.851
Long DAPT (24 months)	392 (49.1%)	524 (49.3%)	0.963
Not randomized	17 (2.1%)	16 (1.5%)	0.375

p-values are chi-square test for categories, t-test for continuous variables).

* Type B2 or C lesion according to the ACC/AHA coronary lesion classification.

Abbreviations: ACC=American College of Cardiology; ACS= Acute Coronary Syndrome; AHA=American Heart Association; CABG=Coronary Artery Bypass Graft; CAD=Coronary Artery Disease; LAD=Left Anterior Descending Artery; LCX=Left Circumflex Artery; LVEF=Left Ventricle Ejection Fraction; MI=Myocardial Infarction; NSTEMI=Non-ST-Elevation Myocardial Infarction; PCI=Percutaneous Coronary Intervention; RCA= Right Coronary Artery; STEMI= ST-Elevation Myocardial Infarction.

Table S2. Clinical outcomes at 30 days according to operator experience.

Event	More experienced operators (N=798)	Experienced operators (N=1063)	p-value
Primary Efficacy Endpoint			
All-cause Death, MI or CVA	89 (11.2)	110 (10.3)	0.603
Secondary Efficacy Endpoints			
All-cause Death or MI	81 (10.2)	106 (10.0)	0.919
All-cause Death	17 (2.1)	16 (1.5)	0.315
Cardiovascular Death	17 (2.1)	16 (1.5)	0.315
Stroke or TIA	10 (1.3)	6 (0.6)	0.119
Myocardial infarction MI	70 (8.8)	93 (8.8)	1.000
Definite ST	5 (0.6)	9 (0.9)	0.591
Definite or Probable ST	10 (1.3)	16 (1.5)	0.652
Definite, Probable or Possible ST	11 (1.4)	16 (1.5)	0.825
TVR	8 (1.0)	11 (1.0)	0.950
Safety Endpoints			
Access-site related bleeding*	9 (1.1)	11 (1.0)	0.847
BARC classification			
Key safety endpoint - Type 2, 3 or 5	15 (1.9)	20 (1.9)	0.997
Type 3 or 5	6 (0.8)	7 (0.7)	0.806
TIMI classification			
Minor	3 (0.4)	3 (0.3)	0.724
Major	0 (0.0)	2 (0.2)	0.996
Minor or major	3 (0.4)	5 (0.5)	0.761
GUSTO classification			
Moderate	4 (0.5)	3 (0.3)	0.450
Severe	0 (0.0)	2 (0.2)	0.996
Moderate or severe	4 (0.5)	5 (0.5)	0.921
Net Clinical Adverse Events (NACE)			
All-cause Death, MI, CVA or BARC 2, 3 or 5	103 (12.9)	128 (12.0)	0.596
All-cause Death, MI, CVA or BARC 3 or 5	95 (11.9)	116 (10.9)	0.523

Wald chisquare p-value testing the more experienced vs the experienced operators in Weibull time-to-event regression.

*Access-site related bleeding analyzed with Logistic regression.

Abbreviations: BARC=Bleeding Academic Research Consortium; CVA=Cerebrovascular Accident; GUSTO= Global Use of Strategies to Open Occluded Coronary Arteries; MI=Myocardial Infarction; ST=Stent Thrombosis; TIA=Transient Ischemic Attack; TIMI=Thrombolysis in Myocardial Infarction; TVR=Target Vessel Revascularization.

Table S3. Clinical outcomes at 2 years according to operator experience.

Event	More experienced operators (N=798)	Experienced operators (N=1063)	p-value
Primary Efficacy Endpoint			
All-cause Death, MI or CVA	157 (19.7)	222 (20.9)	0.575
Secondary Efficacy Endpoints			
All-cause Death or MI	145 (18.2)	210 (19.8)	0.421
All-cause Death	69 (8.7)	88 (8.3)	0.758
Cardiovascular Death	46 (5.8)	57 (5.4)	0.694
Stroke or TIA	21 (2.7)	26 (2.5)	0.769
Myocardial infarction MI	99 (12.5)	144 (13.8)	0.486
Definite ST	12 (1.6)	17 (1.6)	0.877
Definite or Probable ST	22 (2.8)	31 (3.0)	0.849
Definite, Probable or Possible ST	46 (5.9)	61 (5.9)	0.967
TVR	97 (12.7)	116 (11.3)	0.409
Safety Endpoints			
BARC classification			
Key safety endpoint - Type 2, 3 or 5	65 (8.5)	76 (7.4)	0.422
Type 3 or 5	35 (4.6)	30 (2.9)	0.071
TIMI classification			
Minor	13 (1.7)	13 (1.3)	0.455
Major	13 (1.7)	10 (1.0)	0.189
Minor or major	26 (3.4)	23 (2.2)	0.149
GUSTO classification			
Moderate	17 (2.2)	17 (1.7)	0.390
Severe	14 (1.8)	12 (1.2)	0.260
Moderate or severe	31 (4.0)	29 (2.8)	0.166
Net Clinical Adverse Events (NACE)			
All-cause Death, MI, CVA or BARC 2, 3 or 5	197 (24.7)	276 (26.0)	0.618
All-cause Death, MI, CVA or BARC 3 or 5	170 (21.3)	240 (22.6)	0.593

Wald chisquare p-value testing the more experienced vs the experienced operators in Weibull time-to-event regression.

Abbreviations: BARC=Bleeding Academic Research Consortium; CVA=Cerebrovascular Accident; GUSTO= Global Use of Strategies to Open Occluded Coronary Arteries; MI=Myocardial Infarction; ST=Stent Thrombosis; TIA=Transient Ischemic Attack; TIMI=Thrombolysis in Myocardial Infarction; TVR=Target Vessel Revascularization.

Table S4. Unadjusted and adjusted hazard ratios for main clinical outcomes according to operator experience.

Event	Hazard Ratio (95% CI)	p-value	Adjusted Hazard Ratio (95% CI)	Adjusted p-value
At 30 days				
All-cause Death, MI or CVA	1.08 (0.81-1.42)	0.603	1.16 (0.87-1.54)	0.321
BARC 2, 3 or 5	1.00 (0.51-1.96)	0.997	1.02 (0.51-2.04)	0.947
All-cause Death, MI, CVA or BARC 2, 3 or 5	1.07 (0.83-1.39)	0.596	1.15 (0.88-1.50)	0.299
All-cause Death, MI, CVA or BARC 3 or 5	1.09 (0.83-1.43)	0.523	1.18 (0.89-1.56)	0.253
At 2 years				
All-cause Death, MI or CVA	0.94 (0.77-1.16)	0.575	0.99 (0.80-1.23)	0.945
BARC 2, 3 or 5	1.15 (0.82-1.59)	0.422	1.17 (0.84-1.65)	0.354
All-cause Death, MI, CVA or BARC 2, 3 or 5	0.95 (0.80-1.15)	0.618	1.00 (0.82-1.20)	0.966
All-cause Death, MI, CVA or BARC 3 or 5	0.95 (0.78-1.15)	0.593	0.99 (0.80-1.21)	0.886

Hazard ratios from Adjusted Weibull time-to-event regression comparing More experienced operators vs Experienced operators, adjusted for: PCI performed by two or more operators (vs. one operator only), age, gender, BMI, hypertension, dyslipidemia, current smoking, family history CAD, previous PCI, CABG, peripheral arterial disease, creatinine clearance, LVEF, ACS, femoral access, multivessel PCI, one or more complex lesions, one or more restenotic lesions, randomized stent (4 categories), total stent length, CRUSADE score.

Figure S1. Stratified effect of operators on the DAPT randomization by landmark approach.

	events/nr of patients	events/nr of patients	Hazard Ratio (95% CI)	Hazard ratio (95% CI) .125 .25 .5 1 2 4 8	p-value	interaction p-value
Randomized DAPT*:	**Short DAPT**	**Long DAPT**	**Long vs Short**			
All-cause Death, MI or CVA from 30 to 180 days						**0.132**
Operator 1	14/254	8/245	0.59 (0.25-1.40)		0.229	
Operator 2	6/206	13/213	2.12 (0.80-5.57)		0.129	
Operator 3	5/186	4/176	0.84 (0.23-3.12)		0.792	
Operator 4**	3/150	0/150	4.00 (0.45-35.37)		0.081	
Operator 5**	2/ 75	5/ 78	2.47 (0.48-12.74)		0.279	
Operator 6**	0/ 45	6/ 50	0.16 (0.02-1.25)		0.560	
Other Operators**	1/ 71	0/ 71				
All-cause Death, MI or CVA from 180 to 720 days						**0.425**
Operator 1	22/240	20/236	0.91 (0.50-1.67)		0.764	
Operator 2	10/200	14/199	1.42 (0.63-3.20)		0.397	
Operator 3	12/181	10/172	0.88 (0.38-2.03)		0.762	
Operator 4	13/145	7/150	0.51 (0.20-1.27)		0.147	
Operator 5**	5/ 73	5/ 73	1.00 (0.29-3.45)		0.998	
Operator 6**	5/ 45	2/ 44	0.38 (0.07-1.94)		0.244	
Other Operators**	2/ 70	4/ 69				

Hazard ratios from Weibull time-to-event regression on the composite of all-cause death, MI or CVA comparing the randomized DAPT durations and testing for effect modification by the Operators n (1 to 6).

* Short DAPT randomized to 6 months of DAPT, Long DAPT randomized to 24 months of DAPT

** Operators with less than 10 events and Other Operators are shown for completeness but not used for interaction testing.

Abbreviations: CVA=Cerebrovascular Accidents; DAPT=Dual Antiplatelet Therapy; MI=Myocardial Infarction.

Figure S2. Stratified effect of operator volume of procedures (2 strata) on the DAPT and stent type randomizations.

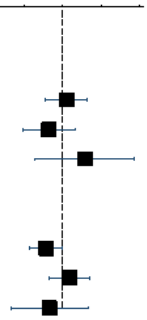
	events/nr of patients	events/nr of patients	Hazard Ratio (95% CI)	Hazard ratio (95% CI) .5 1 2 4	p-value	interaction p-value
Randomized DAPT:	**Short DAPT**	**Long DAPT**	**Short vs Long**			
All-cause Death, MI or CVA from 30 to 720 days						**0.195**
High volume (>300 PCIs)	85/796	76/784	0.90 (0.66-1.23)		0.512	
Medium or Low volume (≤300 PCIs)	15/191	22/199	1.45 (0.75-2.80)		0.267	
Randomized to any DES* or BMS:	**DES***	**BMS**	**DES vs BMS**			
All-cause Death, MI or CVA from 0 to 720 days						**0.697**
High volume (>300 PCIs)	234/1185	92/422	0.90 (0.71-1.15)		0.406	
Medium or Low volume (≤300 PCIs)	59/316	18/ 80	0.81 (0.48-1.37)		0.423	

* ZES-S, PES and EES combined.

Abbreviations: BMS=Bare Metal Stent; CVA=Cerebrovascular Accidents; DAPT=Dual Antiplatelet Therapy; DES=Drug-Eluting Stent; MI=Myocardial Infarction.

Figure S3. Stratified effect of operator volume of procedures (3 strata) on the DAPT and stent type randomizations.

	events/nr of patients	events/nr of patients	Hazard Ratio (95% CI)	Hazard ratio (95% CI) .25 .5 1 2 4	p-value	interaction p-value
Randomized DAPT:	**Short DAPT**	**Long DAPT**	**Short vs Long**			
All-cause Death, MI or CVA from 30 to 720 days						**0.381**
High volume (>400 PCIs)	52/460	55/458	1.07 (0.73-1.56)		0.743	
Medium volume (150-400 PCIs)	40/411	31/404	0.78 (0.49-1.25)		0.297	
Low volume (<150 PCIs)	8/116	12/121	1.48 (0.61-3.63)		0.387	
Randomized to any DES* or BMS:	**DES***	**BMS**	**DES vs BMS**			
All-cause Death, MI or CVA from 0 to 720 days						**0.196**
High volume (>400 PCIs)	140/699	61/229	0.74 (0.55-1.00)		0.047	
Medium volume (150-400 PCIs)	114/604	39/232	1.13 (0.79-1.62)		0.511	
Low volume (<150 PCIs)	39/198	15250	0.79 (0.39-1.58)		0.500	

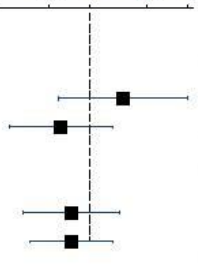


* ZES-S, PES and EES combined.

Abbreviations: BMS=Bare Metal Stent; CVA=Cerebrovascular Accidents; DAPT=Dual Antiplatelet Therapy; DES=Drug-Eluting Stent; MI=Myocardial Infarction.

Figure S4. Stratified effect of operator experience on the DAPT randomization.

	events/nr of patients	events/nr of patients	Hazard Ratio (95% CI)	Hazard ratio (95% CI) .5 .75 1 1.5 2	p-value	interaction p-value
Randomized DAPT*:	**Long DAPT**	**Short DAPT**	**Short vs Long**			
All-cause Death, MI or CVA from 30 to 720 days						**0.136**
More experienced operators	33/392	41/389	1.27 (0.80-2.01)		0.304	
Experienced operators	64/524	53/523	0.82 (0.57-1.18)		0.276	
Randomized to any DES or BMS:**	**DES****	**BMS**	**DES vs BMS**			
All-cause Death, MI or CVA from 0 to 720 days						
More experienced operators	110/580	47/218	0.88 (0.62-1.23)		0.453	**0.976**
Experienced operators	163/804	59/259	0.88 (0.65-1.19)		0.403	



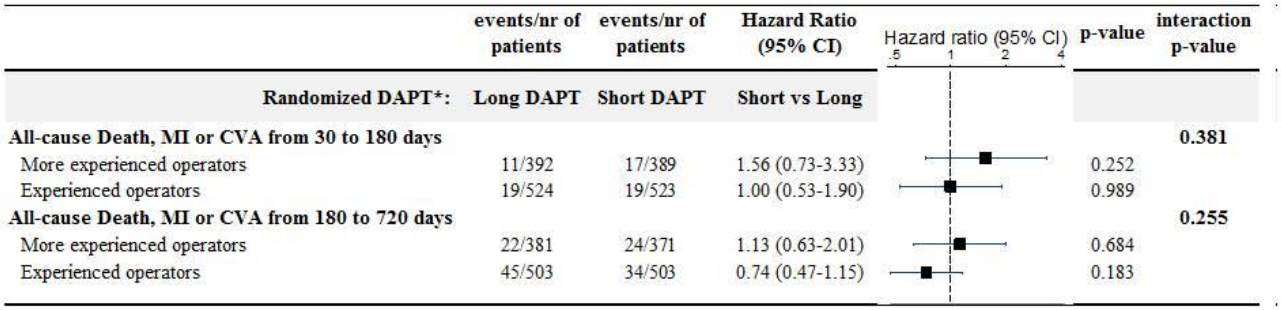
Hazard ratios from Weibull time-to-event regression on the composite of all-cause death, MI or CVA comparing the randomized DAPT duration or comparing the randomized stents and testing for effect modification by the Operator experience (More experienced or Experienced). Three-way interaction Operator experience x randomized DAPT (short or long) x randomized stent group (DES or BMS): $\chi = 1.05$, df=1, p=0.94

* Short DAPT randomized to 6 months of DAPT, Long DAPT randomized to 24 months of DAPT

** ZES-S, PES and EES combined.

Abbreviations: BMS=Bare Metal Stent; CVA=Cerebrovascular Accidents; DAPT=Dual Antiplatelet Therapy; DES=Drug-Eluting Stent; MI=Myocardial Infarction.

Figure S5. Stratified effect of operator experience on the DAPT randomization by landmark approach.



	events/nr of patients	events/nr of patients	Hazard Ratio (95% CI)	p-value	interaction p-value
Randomized DAPT*:	**Long DAPT**	**Short DAPT**	**Short vs Long**		
All-cause Death, MI or CVA from 30 to 180 days					**0.381**
More experienced operators	11/392	17/389	1.56 (0.73-3.33)	0.252	
Experienced operators	19/524	19/523	1.00 (0.53-1.90)	0.989	
All-cause Death, MI or CVA from 180 to 720 days					**0.255**
More experienced operators	22/381	24/371	1.13 (0.63-2.01)	0.684	
Experienced operators	45/503	34/503	0.74 (0.47-1.15)	0.183	

* Short DAPT randomized to 6 months of DAPT, Long DAPT randomized to 24 months of DAPT
Abbreviations: BMS=Bare Metal Stent; CVA=Cerebrovascular Accidents; DAPT=Dual Antiplatelet Therapy; DES=Drug-Eluting Stent; MI=Myocardial Infarction.

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