ORIGINAL STUDIES

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Accuracy of the PARIS score and PCI complexity to predict ischemic events in patients treated with very thin stents in unprotected left main or coronary bifurcations

Guglielmo Gallone MD[1†] | Fabrizio D'Ascenzo MD[1†] | Federico Conrotto MD[1†] |
Francesco Costa MD[2] | Davide Capodanno MD[3] | Saverio Muscoli MD[4] |
Alaide Chieffo MD[5] | Imori Yoichi MD[6] | Mauro Pennacchi MD[7] |
Giorgio Quadri MD[8] | Ivan Nuñez-Gil MD[9] | Pier Paolo Bocchino MD[1] |
Francesco Piroli MD[1] | Ovidio De Filippo MD[1] | Cristina Rolfo MD[8] |
Wojciech Wojakowski MD[10] | Daniela Trabattoni MD[11] | Zenon Huczek MD[12] |
Giuseppe Venuti MD[3] | Andrea Montabone MD[13] | Andrea Rognoni MD[14] |
Radoslaw Parma MD[10] | Filippo Figini MD[15] | Satoru Mitomo MD[5] |
Giacomo Boccuzzi MD[13] | Alessio Mattesini MD[16] | Enrico Cerrato MD[8] |
Wojciech Wańha MD[10] | Grzegorz Smolka MD[10] | Bernardo Cortese MD[17] |
Nicola Ryan MB, BCh[9] | Mario Bo MD[18] | Carlo di Mario MD[16] |
Ferdinando Varbella MD[8] | Francesco Burzotta MD[19] | Imad Sheiban MD[15] |
Javier Escaned MD[9] | Gerard Helft MD[20] | Gaetano Maria De Ferrari MD[1]

[1]Division of Cardiology, Department of Internal Medicine, Città della Salute e della Scienza, University of Turin, Turin, Italy

[2]Department of Clinical and Experimental Medicine, Policlinic "G. Martino", University of Messina, Messina, Italy

[3]Division of Cardiology, Ferrarotto Hospital, University of Catania, Catania, Italy

[4]Department of Cardiovascular Disease, Tor Vergata University of Rome, Rome, Italy

[5]Unit of Cardiovascular Interventions, IRCCS San Raffaele Hospital, Milan, Italy

[6]Department of Cardiovascular Medicine, Nippon Medical School, Tokyo, Japan

[7]Department of Cardiovascular, Respiratory and Morphologic Sciences, Policlinico Umberto I, "Sapienza" University of Rome, Rome, Italy

[8]Department of Cardiology, Infermi Hospital, Rivoli, Italy

[9]Hospital Clínico San Carlos, IDISSC, and Universidad Complutense de Madrid, Madrid, Spain

[10]Division of Cardiology and Structural Heart Diseases, Medical University of Silesia, Katowice, Poland

[11]Department of Cardiovascular Sciences, Centro Cardiologico Monzino, IRCCS, Milan, Italy

[12]Medical University of Warsaw, Warsaw, Poland

[13]Department of Cardiology, S.G. Bosco Hospital, Torino, Italy

[14]Coronary Care Unit and Catheterization Laboratory, A.O.U. Maggiore della Carità, Novara, Italy

[15]Pederzoli Hospital, Peschiera del Garda, Italy

[16]Division of Structural Interventional Cardiology, Careggi University Hospital, Florence, Italy

[17]Interventional Cardiology Unit, ASST Fatebenefratelli-Sacco, Milan, Italy

[18]Section of Geriatrics, Department of Medical Sciences, Università degli Studi di Torino, A.O.U. Città della Salute e della Scienza di Torino, Turin, Italy

[19]Institute of Cardiology, Catholic University of the Sacred Heart, Rome, Italy

[20]Pierre and Marie Curie University, Paris, France

Correspondence
Guglielmo Gallone, Division of Cardiology, Department of Internal Medicine, Città della Salute e della Scienza, Corso Bramante 88/90, 10126, Turin, Italy.
Email: guglielmo.gallone@gmail.com,

Abstract

Background: The PARIS risk score (PARIS-rs) and percutaneous coronary intervention complexity (PCI-c) predict clinical and procedural residual ischemic risk following PCI. Their accuracy in patients undergoing unprotected left main (ULM) or bifurcation PCI has not been assessed.

Methods: The predictive performances of the PARIS-rs (categorized as low, intermediate, and high) and PCI-c (according to guideline-endorsed criteria) were evaluated in 3,002 patients undergoing ULM/bifurcation PCI with very thin strut stents.

Results: After 16 (12–22) months, increasing PARIS-rs (8.8% vs. 14.1% vs. 27.4%, $p < .001$) and PCI-c (15.2% vs. 11%, $p = .025$) were associated with higher rates of major adverse cardiac events ([MACE], a composite of death, myocardial infarction [MI], and target vessel revascularization), driven by MI/death for PARIS-rs and target lesion revascularization/stent thrombosis for PCI-c (area under the curves for MACE: PARIS-rs 0.60 vs. PCI-c 0.52, p-for-difference $< .001$). PCI-c accuracy for MACE was higher in low-clinical-risk patients; while PARIS-rs was more accurate in low-procedural-risk patients. ≥12-month dual antiplatelet therapy (DAPT) was associated with a lower MACE rate in high PARIS-rs patients, (adjusted-hazard ratio 0.42 [95% CI: 0.22–0.83], $p = .012$), with no benefit in low to intermediate PARIS-rs patients. No incremental benefit with longer DAPT was observed in complex PCI.

Conclusions: In the setting of ULM/bifurcation PCI, the residual ischemic risk is better predicted by a clinical risk estimator than by PCI complexity, which rather appears to reflect stent/procedure-related events. Careful procedural risk estimation is warranted in patients at low clinical risk, where PCI complexity may substantially contribute to the overall residual ischemic risk.

KEYWORDS
bifurcation, dual antiplatelet therapy, left main, risk stratification

1 | INTRODUCTION

Percutaneous coronary intervention (PCI) has proven to be safe and effective even in high-risk patients, such as those undergoing revascularization of unprotected left main (ULM) or coronary bifurcations.[1-4]

Improvement of technologies with ultrathin coronary stents reduced restenosis and stent thrombosis (ST) to less than 2% and to 1%, respectively, at 1 year in randomized controlled trials (RCT).[5] However, a considerable risk is still reported in real-life registries, as high as 5.5 and 2% for ULM lesions.[1] This recognition warrants a thorough assessment of the clinical-related and procedure-related residual ischemic risk following PCI, in order to identify clusters of patients for whom the threshold for invasive treatment might be higher and to tailor follow-up when PCI is performed. Indeed, high-risk patients may benefit from close follow-up immediately post-discharge, in order to reduce early readmission,[6] furthermore, accurate

prediction of recurrent event risk is pivotal to optimize the type and length of dual antiplatelet therapy (DAPT).[7-9] Recently, the Patterns of non-adherence to Antiplatelet Regimens In Stented patients (PARIS) score, developed to predict ischemic risk following PCI, showed an overall good performance in predicting thrombotic events in unselected patients.[10] However, only 158 of 5,018 patients (3%) had ULM revascularization and 595 (12%) bifurcation PCI in this study.[11] Similarly, Giustino et al. proposed a classification using validated and guideline-endorsed criteria[12-17] to evaluate the impact of procedural complexity on outcomes following PCI, this was demonstrated to have utility in tailoring DAPT duration.[18] Moreover, in this and a further study pooling patients from eight RCT to evaluate this classification, patients undergoing ULM or coronary bifurcation PCI were strongly underrepresented.[7]

The utility of the PARIS score and PCI complexity in assessing clinical and procedural residual ischemic risk following ULM/bifurcation

PCI remains undefined. Consequently, we evaluated the performance of the PARIS score and PCI complexity to predict ischemic events in a large real-life cohort of patients undergoing ULM or coronary bifurcation PCI with very thin strut stents.

2 | METHODS

The RAIN (veRy thin stents for patients with left mAIn or bifurcatioN in real life) registry is a multicenter study (see Appendix web only for sites of enrollment, NCT03622203) that retrospectively recruited patients from June 2015 to January 2017.[19]

All consecutive patients presenting with a critical lesion of an ULM or a coronary bifurcation (see Appendix web only for definition) and treated with a very thin stent in our centers were included in the RAIN registry. Study design details have been previously described.[19]

The PARIS score and PCI complexity risk grouping index were previously described.[10-12] Using the PARIS score, patients were classified as low risk: a score from 0 to 2, intermediate risk: a score between 3 and 4, and high risk: a score of more than 4, as previously reported.[10] According to the validated and guideline-endorsed criteria used in the definition proposed by Giustino et al., ULM/bifurcation PCI was considered complex if treated with two stents or if at least one of the following criteria was present at the index procedure: 3 vessels treated, ≥3 stents implanted, ≥3 lesions treated, total stent length >60 mm, or chronic total occlusion as target lesion.[18]

Major adverse cardiac events (MACE), a composite and mutual exclusive endpoint of death, myocardial infarction (MI) and target vessel revascularization (TVR), MACE single components, target lesion revascularization (TLR), and ST were the study outcomes. Rates of study outcomes at the last follow-up (16 [12–22] months) were assessed and compared in each risk group for both PARIS risk score and PCI complexity index. Accuracy of the two predictive tools was further evaluated. To evaluate if the combination of clinical and procedural risk indicators might result in improved risk stratification, PARIS score and PCI complexity were combined. Event rates and accuracy of the resulting score were then assessed.

To evaluate the potential role of the predictive tools to improve DAPT management, the interaction of DAPT duration (<12 months vs. ≥12 months) with MACE according to PARIS score and PCI complexity risk grouping was tested. Cox regression models were used to adjust for baseline confounders.

Categorical variables were reported as count and percentages, continuous variables as mean and SDs, or interquartile range. The presence of normal distribution was verified by the Kolmogorov–Smirnov test. The t-test or one-way analysis of variance test were used to assess differences between parametric continuous variables and Mann–Whitney U test or Kruskal–Wallis test for nonparametric variables, the chi-square test for categorical variables, and the Fisher exact test for 2×2 tables. Receiver operating characteristic (ROC) curves were elaborated for the PARIS score, PCI complexity, and the score resulting from their combination. The associated areas under the curve (AUCs) were calculated for the study endpoints and compared with DeLong et al. approach.[20] Cox

multivariate analysis was performed with MACE as a dependent variable and diabetes, STEMI as clinical presentation, reduced renal function (glomerular filtration rate < 60 ml/min/1.73 m^2 estimated by Cockroft–Gault formula), and DAPT ≥12 months as independent variables. A two-sided p-value <.05 was considered statistically significant; all analyses were performed with SPSS 21.0 (IBM, Armonk, NY) and MedCalc Statistical Software version 18.11.6 (MedCalc Software bvba, Ostend, Belgium; https://www.medcalc.org; 2019).

3 | RESULTS

A total of 3,002 patients were included, 792 with PCI in ULM and 2,210 in coronary bifurcations other than ULM.

A total of 1,892 (63.0%) patients were classified according to the PARIS score as low risk, 886 (29.5%) as intermediate, and 224 (7.5%) as high (Figure 1). Patients with higher PARIS scores were older, with more hypertension, hyperlipidemia, chronic kidney dysfunction, and diabetes mellitus both non-insulin-dependent (ID) and ID. History of MI or revascularization was more frequent in the high-risk group. Non-ST-segment elevation MI was the most common clinical presentation for both the high- and intermediate-risk groups, while low-risk patients presented more commonly with stable angina (Table 1).

In terms of procedural characteristics, distal left main was more frequently involved in the high-risk and intermediate-risk groups (71.7% vs. 69.6% vs. 62.0%, p = .022), while bifurcations (approximately 88% in all groups) and type C lesions (approximately 38% in all
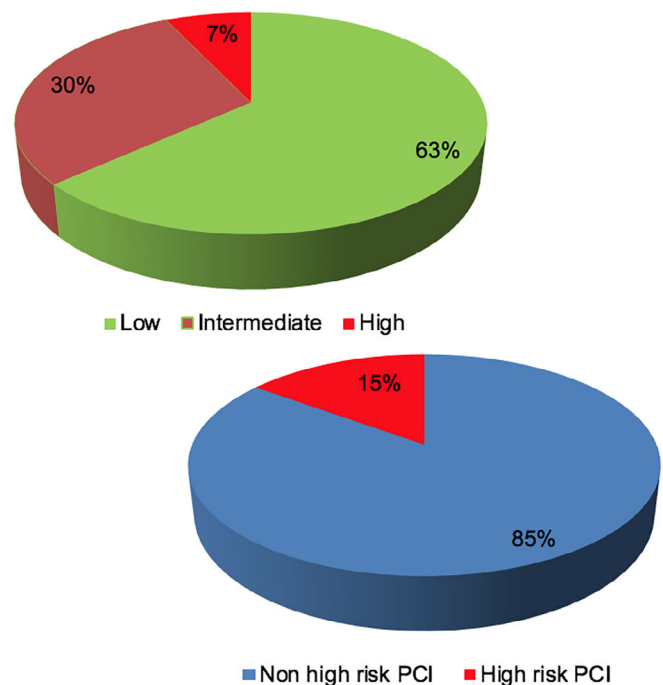

FIGURE 1 Stratification of patients according to Patterns of nonadherence to Antiplatelet Regimens In Stented patients (PARIS) risk score (top) and percutaneous coronary intervention (PCI) complexity (bottom) [Color figure can be viewed at wileyonlinelibrary.com]

TABLE 1 Distribution of baseline characteristics stratified by PARIS risk score and PCI complexity

	PARIS risk score categories				Complex PCI		
	Low n = 1,892	Intermediate n = 886	High n = 224	p-value	No n = 2,564	Yes n = 447	p-value
Age (years)	69 ± 11	67 ± 2	74 ± 10	.001	69 ± 10	68 ± 11	.100
Male	76.0	77.8	73.2	.943	76.3	76.3	.520
Smoker							
Previous	32.9	22.7	26.9		29.7	27.6	
Current	10.2	40.1*	31.1°§	<.001	21.2	18.3	.051
Arterial hypertension	72.0	76.6*	88.9°§	<.001	74.2	77.1	.112
Dyslipidemia	57.8	60.4	77.0°§	<.001	60.1	59.6	.442
Diabetes mellitus							
Non-ID	14.2	36.3	66.8		25.2	23.1	.197
ID	4.9	11.6*	15.6°§	<.001	7.7	6.8	.303
eGFR <60 ml/min/1.73 m^2	3.7	31.5*	91.2°§	<.001	18.6	16.3	.676
Prior MI	20.3	41.6*	55.1°§	<.001	29.8	26.3	.081
Prior PCI	26.0	38.5*	56.6°§	<.001	32.3	30.6	.256
Prior CABG	2.7	7.5*	13.3°§	<.001	5.2	3.4	.064
PCI indication							
STEMI	10.2	28.7	26.5		17.3	14.6	
NSTEMI	12.4	39.5	59.7		24.7	20.3	
UA	15.4	13.5	7.1		13.8	16.4	
Stable angina	35.1	10.9	4.4		24.9	29.5	
Pos. stress test	17.2	5.2	1.3		12.6	11.7	
Angio. FU	9.5	2.1*	0.9°§	<.001	6.5	7.4	.051

Note: Values are expressed as % patients or mean ± *SD*.

Abbreviations: CABG, coronary artery bypass graft; eGFR, estimated glomerular filtration rate; FU, follow-up; ID, insulin dependent; MI, myocardial infarction; NSTEMI, non-ST-elevation myocardial infarction; PCI, percutaneous coronary intervention; STEMI, ST-elevation myocardial infarction; UA, unstable angina.

Note: *p < .05 for low versus intermediate PARIS risk groups comparison.

Note: °p < .05 for intermediate versus high PARIS risk groups comparison.

Note: §p < .05 for low versus. high PARIS risk groups comparison.

groups) were evenly distributed. Patients in the high-risk group had more severe calcification, while diffuse disease was more frequent in the intermediate-risk group. Use of imaging and provisional versus 2-stent strategies did not differ among groups (Table 2). Twelve-months DAPT was the most common planned duration at discharge in all groups, with shorter DAPT more common in the high-risk and intermediate-risk groups (17.8% vs. 17.3% vs. 11.8% discharged with the therapy of <12 months [median 4.6], p < .001) (Table S1).

At 16 (12–22) months (no significant differences in follow-up length among PARIS score and PCI complexity groups), an increasing occurrence of MACE (8.8% vs. 14.1% vs. 27.4%), MI (2.7% vs. 4.7% vs.10.2%) and death (3.8% vs. 7.6% vs. 19.8%, all p < .001) was observed in the low-, intermediate-, and high-risk groups, while TVR, TLR, and ST rates were similar (Table 3).

A total of 447 (14.8%) and 2,555 (85.2%) patients underwent a complex or a noncomplex PCI procedure, respectively (Figure 1). The clinical profile of the two groups, including age, the burden of cardiovascular risk factors, history of MI/revascularization, and clinical presentation, were similar (Table 1).

Regarding procedural features, ULM (38.2% vs. 25.1%, p < .001) and distal ULM (74.6 vs. 62.1%, p = .003) were more frequently treated in the complex PCI group, which also had higher rates of type C lesions (52.6% vs. 36.3%, p < .001), severe calcification (16.9% vs. 12.6%, p = .026), and diffuse disease (42.2% vs. 36.8%, p = .024). Use of imaging did not differ among groups, while postdilation (73.0% vs. 79.0%, p = .005) and final kissing balloon (73% vs. 35%, p < .001) were more commonly used in complex PCI procedures (Table 2). Following complex PCI, prasugrel and ticagrelor were prescribed more frequently, while length of DAPT did not differ, with 85.5% vs. 88.5% patients discharged with ≥12 months and 14.5% vs. 11.5% with less than 12 months (p = .086, median of 5.7 months) (Table S1).

At follow-up (Table 3), MACE were more frequent following complex PCI (15.2% vs. 11%, p = .025), mainly driven by TLR (2.5% vs. 6.7%, p < .001), while no differences were observed in death and MI rates. ST was more than doubled following complex PCI (3.8% vs. 1.4%, p = .001).

When integrating the PARIS score and PCI complexity (Table S2), PCI complexity significantly improved risk stratification for MACE (7.9%

TABLE 2 Distribution of lesion and procedure characteristics stratified by PARIS risk score and PCI complexity

	PARIS risk score categories				Complex PCI		
	Low risk n = 1,892	Intermediate risk n = 886	High risk n = 224	p-value	No n = 2,564	Yes n = 447	p-value
Radial access	70.6	67.2	59.6°§	.001	70.3	59.5	<.001
Main lesion vessel							
LM	27.8	24.3	30.5		25.1	38.2	
LAD	47.7	46.7	41.6		47.5	43.5	
LCx/OM	16.7	19.9	16.8		18.2	14.7	
RCA	5.9	7.8	9.7		7.4	3.0	
RI	1.8	1.1	1.3	.110	1.8	0.2	<.001
LM disease							
Ostial	14.9	16.6	16.7		17.3	7.7	
Mid	23.1	13.8	11.7		20.6	17.8	
Distal	62.0	69.6	71.7	.249	62.1	74.6	.001
Type C lesion	39.8	36.2*	40.3	.369	36.3	52.6	<.001
Severe calcification	11.7	13.9*	21.8°§	<.001	12.6	16.9	.018
Diffuse disease	31.8	55.9*	42.3°	<.001	36.8	42.2	.024
Bifurcation	87.2	88.0	89.4	.296	85.6	99.1	<.001
Treatment strategy							
Provisional	80.0	82.8	79.7		100.0	0.0	
2-stent	17.5	13.8	15.6	.307	0.0	100.0	<.001
Imaging							
IVUS	32.1	32.6	35.4		33.3	28.0	
OCT	0.9	1.0	1.8	.211	1.0	0.9	.080
Predilation	89.0	87.7	89.7	.726	87.5	94.6	<.001
Rotablator	2.2	2.1	6.5°	.016	2.3	3.4	.114
Postdilation	76.0	70.9*	70.6	.011	73.0	79.0	.005
Final kissing balloon	43.4	36.2*	40.1°	.008	34.8	73.1	<.001

Note: Values are expressed as percentage.
Abbreviations: LCx, circumflex; IVUS, intravascular ultrasound; LAD, left anterior descending; LM, left main; OCT, optimal coherence tomography; OM, obtuse marginal; PCI, percutaneous coronary intervention; RCA, right coronary artery; RI, ramus intermedius.
Note: *p < .05 for low versus intermediate PARIS risk groups comparison.
Note: °p < .05 for intermediate versus high PARIS risk groups comparison.
Note: §p < .05 for low versus high PARIS risk groups comparison.

TABLE 3 Clinical outcomes stratified by PARIS risk score and PCI complexity

	PARIS risk score categories				Complex PCI		
	Low n = 1,892	Intermediate n = 886	High n = 224	p-value	No n = 2,564	Yes n = 447	p-value
MACE	8.8	14.1*	27.4°§	<.001	11.0	15.2	.025
Death	3.8	7.6*	19.8°§	<.001	6.3	5.5	.312
MI	2.7	4.7*	10.2°§	<.001	3.8	3.6	.499
TVR	3.7	5.2	6.2§	.060	3.6	8.3	<.001
TLR	2.7	3.7	4.4	.120	2.5	6.7	<.001
ST	1.5	2.1	2.7	.122	1.4	3.8	.003

Note: Values are expressed as percentage of patients. Median follow-up 16 (12–22) months.
Abbreviations: MACE, major adverse cardiac events; MI, myocardial infarction; ST, stent thrombosis; TLR, target lesion revascularization; TVR, target vessel revascularization.
Note: *p < .05 for low versus intermediate PARIS risk groups comparison.
Note: °p < .05 for intermediate versus high PARIS risk groups comparison.
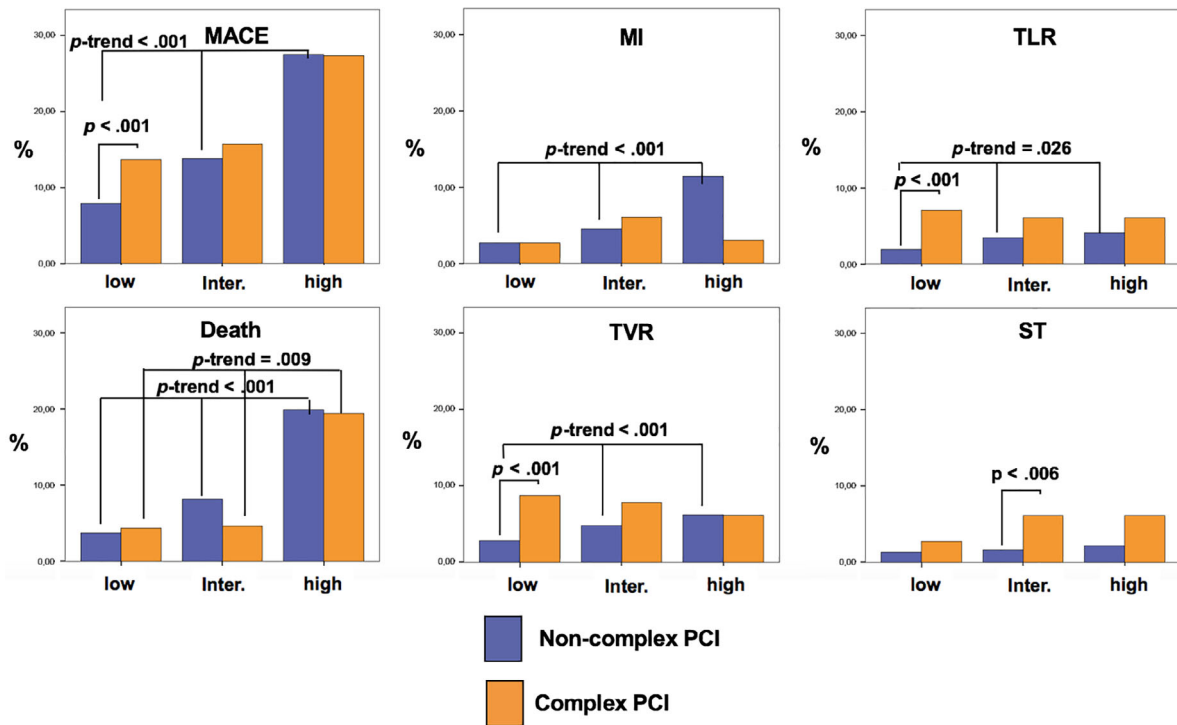Note: §p < .05 for low versus high PARIS risk groups comparison.

FIGURE 2 Improved risk stratification by combining clinical and procedural risk indicators to predict study endpoints. Event rates stratified according to Patterns of nonadherence to Antiplatelet Regimens In Stented patients (PARIS) score (low, intermediate, and high groups) and percutaneous coronary intervention (PCI) complexity are presented, with *p*-values denoting significant reclassification ability of the two scores. Procedural risk estimation (as assessed by PCI complexity) appears to be particularly relevant in patients at low clinical risk (as assessed by PARIS), while clinical risk seems to refine risk stratification in patients undergoing a low-risk procedure in particular. Abbreviations as in Table 3 [Color figure can be viewed at wileyonlinelibrary.com]

vs. 13.7%, *p* < .001), TLR (1.9% vs. 7.0%, *p* < .001), and TVR (2.8% vs. 8.7%, *p* < .001) among patients in the PARIS low-risk group and for ST (1.6% vs. 6.1%, *p* = .006) among patients in the intermediate-risk group. The PARIS score improved risk stratification for MACE, MI, TLR, and TVR among patients undergoing noncomplex PCI, and for death in both noncomplex and complex PCI groups (Figure 2).

In the overall population, AUCs for MACE, MI and death were higher for the PARIS score than for PCI complexity (MACE: 0.60 [0.57–0.64] vs. 0.52 [0.49–0.56], *p* < .001; death: 0.65 [0.61–0.70] vs. 0.49 [0.45–0.54], *p* < .001; MI: 0.62 [0.56–0.67] vs. 0.50 [0.44–0.55], *p* = .021), while PCI complexity displayed a numerically nonsignificant higher predictivity for TVR, TLR, and ST (Figure 3). In subgroup analyses, this trend was observed regardless of clinical presentation, in both patients presenting with acute coronary syndrome and stable coronary artery disease (Table S3).

Integrating the PARIS score and PCI complexity did not result in significantly improved accuracy in predicting outcomes in the overall population (Figure 3), however, a numerical trend toward better accuracy of PCI complexity to predict MACE was observed in patients in the lower as compared to higher PARIS risk groups. Similarly, a numerically greater AUC for the PARIS score was observed in patients undergoing noncomplex as compared to complex PCI (Table 4).

A graded increase in MACE rates was observed for higher PARIS risk score in both patients undergoing <12 months (10.3, 23.2, 71.4%,

p < .001) and ≥12 months DAPT (8.2, 14.1, 25.6%, *p* < .001). No interaction of DAPT with MACE was observed in the PARIS low-risk group (*p* = .219), while ≥12 months DAPT duration was associated with lower MACE rates in PARIS intermediate- (*p* = .015) and high-risk (*p* < .001) groups. After adjustment for baseline confounders (diabetes, STEMI as clinical presentation, chronic kidney disease), the association between <12 month DAPT and MACE remained significant in the high-risk (hazard ratio 2.36 [95% CI: 1.20–4.63], *p* = .012), but not the intermediate-risk (hazard ratio 1.05 [95% CI: 0.59–1.89], *p* = .848) PARIS groups (Table S4). Similar results were observed when considering only MACE occurring after DAPT discontinuation (Figure 1S).

A higher rate of MACE was observed in patients undergoing complex versus noncomplex PCI prescribed ≥12 months DAPT (15.8% vs. 9.9%, *p* = .002), but not in patients with <12 months DAPT (16.3% vs. 21.4%, *p* = .304). An interaction of DAPT duration with MACE was observed for noncomplex PCI (*p* < .001), but not for complex PCI (*p* = .541) (Figure 4), which became not significant after adjustment (Table S5).

4 | DISCUSSION

The PARIS risk score and PCI complexity represent validated and effective tools to estimate clinical and procedural residual ischemic risk in unselected (with respect to anatomical and procedural features)
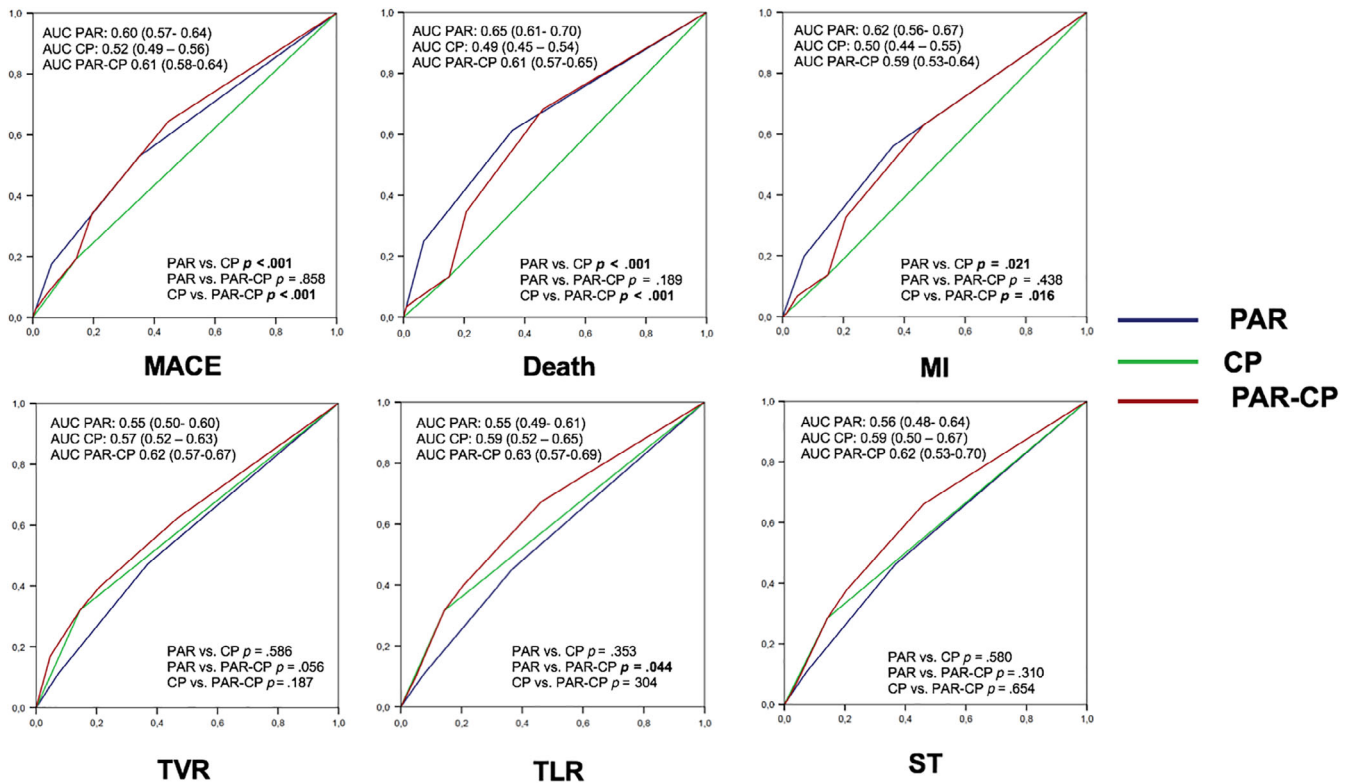
FIGURE 3 Accuracy of clinical and procedural risk indicators to predict study endpoints. The area under the curves (AUCs) for Patterns of nonadherence to Antiplatelet Regimens In Stented patients (PARIS) risk score (PAR, blue), percutaneous coronary intervention (PCI) complexity (PC, green), and their combination (PAR-PC, red) for different event types are reported. p-values for difference among AUCs are displayed. Abbreviations as in Table 3 [Color figure can be viewed at wileyonlinelibrary.com]

TABLE 4 Accuracy of PARIS risk score and PCI complexity in reciprocal subgroups

	Subgroups	AUC for MACE	95% CI
PCI complexity	Low PARIS	0.55	0.50–0.60
	Intermediate PARIS	0.51	0.45–0.56
	High PARIS	0.50	0.42–0.58
PARIS score	Noncomplex PCI	0.62	0.58–0.66
	Complex PCI	0.55	0.47–0.63

Note: p-values for AUC differences among subgroups are nonsignificant.
Abbreviations: AUC, area under the curve; PCI, percutaneous coronary intervention; MACE, major adverse cardiac events.

FIGURE 4 Interaction of DAPT duration with MACE according to risk grouping. MACE occurrence stratified by DAPT duration (light blue: <12 months vs. red: ≥12 months) and according to PARIS risk categories (left) and PCI complexity (right) is illustrated. Abbreviations: DAPT, dual antiplatelet therapy; PCI, percutaneous coronary intervention [Color figure can be viewed at wileyonlinelibrary.com]
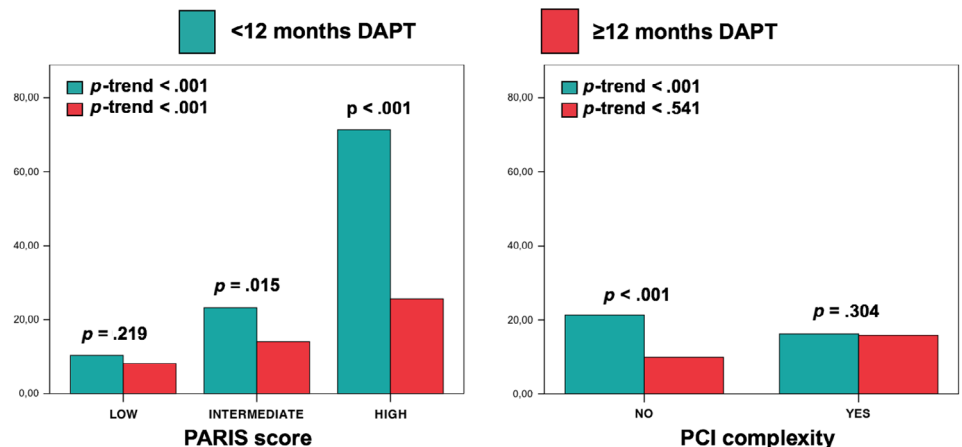
patients undergoing PCI.[10,18] The aim of this study was to assess whether the PARIS risk score and PCI complexity remain effective tools to predict future events in the high-risk subset of ULM/bifurcation PCI, evaluating their predictive performance in a large, real-life prospective cohort of patients undergoing ULM/bifurcation PCI. Importantly, the study population was exclusively treated with new-generation very thin strut DESs, thus reflecting the most contemporary real-world practice and the associated clinical outcomes.

Our main findings can be summarized as follow:

1. In patients undergoing ULM or coronary bifurcation PCI with very thin strut DESs, the PARIS risk score is associated with a moderate accuracy to predict MACE at a median of 16 (12–22) months follow-up, outperforming PCI complexity.
2. In line with the rationale underlying the respective predictive tools, the PARIS score displayed better predictive value for patient-related ischemic events; while PCI complexity showed a numerical nonsignificant trend toward a higher predictivity for procedure-related events (i.e., TLR and ST).
3. Although combining the PARIS score and PCI complexity did not result in better predictive accuracy in the overall population, high PCI complexity was associated with higher MACE occurrence (mainly driven by TLR) among patients with a low PARIS score, while a high PARIS score was associated with higher MACE occurrence among patients undergoing noncomplex PCI. These observations suggest that procedural risk estimation might be particularly relevant in patients at low clinical risk, as in this subset it may account for the majority of the overall residual ischemic risk post PCI.
4. Longer (≥12 months) DAPT yielded high MACE reduction in patients with a high PARIS score, while no benefit was observed in patients with a low PARIS score.
5. No incremental benefit of longer DAPT was observed in patients undergoing complex PCI.

ULM and bifurcation lesions account for 4–7% and 20%, respectively, of all coronary lesions treated with PCI.[21-23] Among segments of the coronary tree, ULM disease represents the highest-risk lesion subset, associated with poorer clinical outcomes compared with the non-ULM disease.[24] On the other hand, bifurcation lesions represent a challenging procedural setting, burdened by a lower rate of procedural success and a higher risk of complications.[25] The evolution of stent technologies, resulting in reduced rates of restenosis and repeated revascularization,[24,26] has allowed the expansion of PCI indications to more complex procedural, cardiovascular, and lesion morphological settings, with favorable procedural and clinical outcomes. However, in these high-risk subsets, clinical- and procedural-related ischemic events may still occur at unacceptably high rates, warranting a precise risk assessment to guide appropriate management. This is particularly relevant in real-world clinical practice, where event rates may differ compared to RCTs, due to unselected complex populations, resource restraints, and DAPT adherence.

In our study population, we observed an increasing burden of cardiovascular risk factors and higher-risk clinical features with higher PARIS score values, while no such association was observed with PCI complexity. An opposite relationship was observed for higher-risk procedural features, which were associated with PCI complexity, but not with the PARIS score. These observations highlight the profoundly different rationale underlying the two stratification tools, developed to predict the overall patient-related ischemic risk (PARIS) as opposed to the procedure and stent-related ischemic risk (PCI complexity).

Consistently, we observed that even though both scores were significantly associated with MACE, this was mainly driven by death and MI for PARIS, while, for PCI complexity, TLR and ST were the main drivers. Importantly, PARIS demonstrated a better performance than PCI complexity, highlighting the importance of a patient's clinical profile in determining the overall residual ischemic risk in patients undergoing ULM/bifurcation PCI.[27]

Moreover, we observed that the predictive ability of the PARIS score for MACE, MI, and TLR was driven by the subgroup of patients undergoing noncomplex PCI; while, conversely, that of PCI complexity was mainly driven by patients with lower clinical risk (low PARIS subgroup for TLR, MI, and MACE; intermediate PARIS group for ST, Figure 2). This observation stresses the importance of an individualized risk assessment balancing clinical and procedural considerations. Moreover, it suggests that the risk/benefit trade-off of a complex PCI procedure may vary considerably according to the clinical profile of the patient and that there should be a higher threshold-to-treat in low clinical risk patients.

Overall, we found only moderate accuracy for the PARIS risk score to predict the study outcomes (AUCs for MACE 0.60, for death 0.65, for MI 0.62), in line with what was observed in the PARIS validation cohort and a recent observational registry (AUC for thrombotic events 0.64 in both studies).[10,28] PCI complexity showed poor performance in predicting MACE, death, and MI, while fair accuracy—numerically but nonsignificantly superior to PARIS—was observed for TLR (AUC: 0.59) and ST (AUC: 0.59). Moreover, even if complex PCI resulted in better risk stratification in patients at low clinical risk, this did not translate into improved accuracy beyond the PARIS score to predict the ischemic risk in the overall population of patients undergoing ULM/bifurcation PCI.

A tailored DAPT duration is paramount to maximize treatment benefits over risks, however, the optimal strategy to guide DAPT treatment across different clinical scenarios remains uncertain.[29-31] Thus, we evaluated whether clinical and procedural risk features modified the benefit in terms of MACE reduction associated with different DAPT durations in this high-risk study subset.

Consistent with the PARIS validation study, we found that a longer (≥12 months) DAPT duration was associated with a considerable benefit in MACE occurrence (71.4% vs. 25.6%, $p < .001$) in the high PARIS risk group, which was lost in patients at intermediate and low PARIS risk.[10] This observation should be interpreted with caution as bias in DAPT duration selection might have occurred, with patients at higher bleeding (and therefore overall) risk likely to have received shorter DAPT durations. However, the result was consistent also after

adjustment for baseline predictors of both ischemic and bleeding risks that might have directed the physician's choice on DAPT duration and interestingly also when considering only events occurring after DAPT discontinuation.

Our study focused on ischemic endpoints; accordingly, we cannot elaborate on the risk/benefit trade-off of different DAPT durations in terms of ischemia-bleeding net benefit. However, this finding suggests that in patients with intermediate to low clinical PARIS risk, a ≥12 months DAPT duration may not be associated with further ischemic events reduction, exposing patients to an unjustified bleeding risk. This concept is also supported by the results of the DAPT study in which longer (30 months) as compared to 12-month DAPT duration following PCI was associated with a benefit on ischemic endpoints in patients at high ischemic risk exclusively (as defined by a DAPT score ≥2), while associating with increased bleeding among patients at low ischemic risk (DAPT score <2).[32,33]

Conversely, we found no association between PCI complexity and MACE reduction with longer DAPT duration. This result fuels the ongoing debate regarding the potential role of complex PCI features in guiding DAPT duration.[34] Giustino et al. found MACE reduction in complex PCI patients treated with longer as compared to shorter DAPT (adjusted HR: 0.56; 95% CI: 0.35–0.89), while no such benefit was observed in patients undergoing noncomplex PCI (p-int = .01).[18] Conversely, in the DAPT trial, no interaction between complex PCI (as defined by one of: ULM, >2 lesions per vessel, lesion length ≥30 mm, bifurcation lesion with side branch ≥2.5 mm, lesion located in a saphenous vein graft, and thrombus-containing lesion) and DAPT duration (30 months vs. 12 months) was found for ischemic endpoints occurring between 12 and 30 months following PCI.[35] Regardless of a potential, still uncertain, incremental benefit of longer DAPT in complex lesion scenarios, our results together with a consistent body of evidence seem to point toward patient-related factors better predicting the need to reduce events related to all the coronary vessels as opposed to the single stented segment.[34]

The findings of this observational study should be interpreted with caution because of the presence of some limitations. First, we identified clinical variables on the basis of documentation in medical records, and the completeness of that documentation may not have been consistent either across hospitals or over time. Second, we calculated the evaluated predictive tools retrospectively, and management was as per clinical practice; whether a PARIS risk score- or PCI complexity-driven management of patients undergoing ULM/bifurcation PCI may influence outcomes is thus beyond the scope of the analysis. Third, the follow-up window width was quite large ranging from 12 to 22 months and outcomes analysis stratified by subgroups and ROC curves were not performed in a time-dependent manner. However, even if a deriving bias cannot be excluded, the follow-up length was well balanced among PARIS score and PCI complexity groups limiting this possibility. Fourth, as already discussed, the association of longer DAPT duration with better outcomes in patients at high PARIS risk should be interpreted in light of the fact that duration of DAPT therapy was as per clinical practice and selection bias might have occurred. Finally, the limited predictive accuracy of PCI complexity in our study may have been influenced by the overall high-risk PCI population included in the RAIN registry.

In the setting of ULM/bifurcation PCI, despite an overall low accuracy, the residual ischemic risk is better predicted by a clinical risk estimator (PARIS) than by PCI complexity, which rather appears to reflect stent/procedure-related events. Careful procedural risk estimation is warranted in patients at low clinical risk, where PCI complexity may substantially contribute to the overall residual ischemic risk. Clinical and procedural risk predictors should be prospectively tested to finally accrue their potential in real-world decision making.

CONFLICT OF INTEREST
The authors declare no potential conflict of interest.

ORCID
Guglielmo Gallone https://orcid.org/0000-0001-8011-6844
Fabrizio D'Ascenzo https://orcid.org/0000-0002-6646-9317
Giorgio Quadri https://orcid.org/0000-0003-4164-2758
Francesco Piroli https://orcid.org/0000-0001-6817-2923
Ovidio De Filippo https://orcid.org/0000-0002-4915-9501
Giuseppe Venuti https://orcid.org/0000-0003-3486-1039
Andrea Montabone https://orcid.org/0000-0002-0954-8254
Radoslaw Parma https://orcid.org/0000-0002-7304-7315
Satoru Mitomo https://orcid.org/0000-0001-8972-4352
Enrico Cerrato https://orcid.org/0000-0002-1260-7534
Wojciech Wańha https://orcid.org/0000-0003-1220-9496
Bernardo Cortese https://orcid.org/0000-0002-5808-7810
Francesco Burzotta https://orcid.org/0000-0002-6569-9401

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.