

Derivation and validation of the ISAR score to predict the risk of repeat percutaneous coronary intervention for recurrent drug-eluting stent restenosis

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KEYWORDS

- prior percutaneous intervention
- restenosis

Abstract

Background: The treatment of drug-eluting stent (DES) in-stent restenosis (ISR) is challenging as it has a high risk of recurrence.

Aims: The aim of this analysis was to develop and validate a model to predict the risk of repeat percutaneous coronary intervention (PCI) for recurrent DES-ISR.

Methods: A retrospective, observational analysis was performed including consecutive patients treated with PCI for DES-ISR at two centres in Germany. Included patients were randomly divided into training and validation cohorts. Two regression analyses identified factors associated with repeat PCI for recurrent DES-ISR up to 1 year. The discriminative ability of the resultant model was then compared to a benchmark ISR classification model using bootstrap resampling. A classification and regression tree analysis and a numerical scoring system (the ISAR score) were used to predict the risk of repeat PCI for recurrent DES-ISR based on the identified predictors.

Results: We included 1,986 patients in the current analysis, divided randomly into training (1,471 patients, 1,778 lesions) and validation (515 patients, 614 lesions) cohorts. Four factor variables (a non-focal ISR pattern, a time interval to ISR of <6 months, ISR of the left circumflex artery and ISR in a calcified vessel) were associated with repeat PCI for recurrent DES-ISR at 1-year follow-up. On bootstrap resampling analysis, the C-statistic for the model including these four variables was 0.60 (95% confidence interval [CI]: 0.57-0.63), whereas the C-statistic for the benchmark ISR classification model was 0.54 (95% CI: 0.52-0.57), a difference that was statistically significant (delta C-statistic 0.062; 95% CI: 0.035-0.094; $p < 0.001$). The cumulative incidence of repeat PCI for recurrent DES-ISR was over three times higher in DES-ISR lesions with an ISAR score of ≥ 3 in comparison to lesions with an ISAR score of 0.

Conclusions: This study developed and validated a risk prediction model for repeat PCI for recurrent DES-ISR at 1-year follow-up. This model served to generate the ISAR score, a standardised tool that can be used to predict the 1-year risk of repeat PCI for recurrent DES-ISR.

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Abbreviations

ACS	acute coronary syndrome
BMS	bare metal stent
CABG	coronary artery bypass grafting
CART	classification and regression tree
CI	confidence interval
DCB	drug-coated balloon
DES	drug-eluting stent
HR	hazard ratio
IDI	integrated discrimination improvement
ISR	in-stent restenosis
LASSO	least absolute shrinkage and selection operator
LCx	left circumflex artery
MI	myocardial infarction
PCI	percutaneous coronary intervention
ST	stent thrombosis
TLR	target lesion revascularisation

Introduction

In-stent restenosis (ISR) is the most common cause of stent failure in the drug-eluting stent (DES) era¹⁻³. A commonly used ISR classification system, based on angiographic patterns of ISR, was developed in the bare metal stent (BMS) era and has been shown to provide prognostic information with respect to the risk of recurrent BMS-ISR requiring repeat percutaneous coronary intervention (PCI)⁴. Given that there are recognised differences between DES-ISR and BMS-ISR, the value of this classification system in the setting of DES-ISR is less certain⁵.

DES-ISR is challenging to treat, with a high risk of recurrence requiring repeat PCI after the initial treatment³. However, there are limited studies investigating the factors that are predictive of repeat PCI for recurrent DES-ISR in adequately sized patient populations. In fact, many of the previous studies on this topic reported on relatively small patient populations, which may have limited their ability to identify relevant predictors of repeat PCI for recurrent DES-ISR⁶⁻¹⁴.

The development of statistical models with the ability to predict repeat PCI for recurrent DES-ISR may be useful, both in order to risk stratify patients as well as to guide clinical follow-up after DES-ISR PCI. In this study, we report on the development and validation of a model to predict repeat PCI for recurrent DES-ISR.

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Methods

PATIENT SELECTION

Consecutive patients undergoing PCI for DES-ISR from September 2005 to December 2013 in two centres in Germany were included in the current analysis. Clinical, procedural and angiographic characteristics were analysed for consecutive patients undergoing PCI for DES-ISR. Relevant data were collected and entered into a computer database by specialised personnel of the clinical data management centre. Digitally recorded baseline, post-procedural, and follow-up coronary angiograms were sent to a centralised

imaging core laboratory (ISAResearch Center, Munich, Germany). The Mehran classification was used to classify the angiographic pattern of ISR⁴. This system classifies ISR into groups based on three characteristics: ISR length (≤ 10 mm: focal, > 10 mm: diffuse), ISR location (within or beyond stent margins) and occlusion (yes or no). Application of this classification system results in four groups: type I: focal; type II: diffuse, within stent; type III: diffuse, within and beyond stent; and type IV: occlusive. The presence or absence of coronary artery calcification was adjudicated by the angiographic core laboratory based on the system described by Mintz et al, with moderate or severe calcification classified as coronary artery calcification for the purposes of this analysis¹⁵. Full details of this system are provided in the **Supplementary Appendix 1**.

STUDY AIMS AND ENDPOINTS

The primary aim of this study was to develop and validate a risk model to predict repeat PCI for recurrent DES-ISR at 1-year follow-up. Accordingly, the main endpoint of interest for the current analysis was repeat PCI for recurrent DES-ISR, defined as any repeat percutaneous intervention of the initially treated target ISR lesion. Additional data were collected on other endpoints of interest, including all-cause mortality, myocardial infarction (MI), definite stent thrombosis (ST) and coronary artery bypass grafting (CABG) after PCI for DES-ISR. Myocardial infarction was defined as per the universal definition of myocardial infarction on the basis of clinical symptoms, electrocardiographic changes, and increases in cardiac biomarkers¹⁶⁻¹⁸. Stent thrombosis was defined as per the Academic Research Consortium (ARC) criteria¹⁹.

STATISTICAL ANALYSIS

For the purposes of this analysis, the patients were randomly divided into training and validation populations in a 3:1 ratio. Continuous variables are expressed as means \pm standard deviations and were compared using the Student's t-test or the non-parametric Wilcoxon rank-sum test. Categorical variables are reported as frequencies and percentages and were compared using the Chi-square test or Fisher's exact test. Data distribution was tested for normality by using the Kolmogorov-Smirnov test for goodness of fit. Adverse event rates were calculated with the use of the Kaplan-Meier method (for all-cause death) or cumulative incidence after accounting for the competing risk of death (for all events other than all-cause death) and compared using a Cox proportional hazards model. The cumulative incidences of repeat PCI for recurrent DES-ISR and definite ST were calculated at the lesion level, and the incidences of the remaining endpoints were calculated at the patient level.

Firstly, the least absolute shrinkage and selection operator (LASSO) method was used to select clinical, angiographic and procedural variables for the logistic regression analysis. Missing data were imputed using the multiple imputation by chained equations (R package mice) method. The use of LASSO regression was deemed appropriate in order to improve the prediction accuracy and interpretability of the regression model and to

prevent overfitting¹⁹. The complete list of variables considered for selection by the LASSO regression model are reported in the **Supplementary Appendix 2**.

Secondly, a logistic regression analysis was performed using the variables selected by LASSO to examine factors associated with repeat PCI for recurrent DES-ISR at 1-year follow-up²⁰. Regression coefficients were corrected for intracluster correlation in patients with multiple ISR lesions (R package *bootcov*)²¹. An exploratory analysis was also performed to predict repeat PCI for recurrent DES-ISR at longer-term follow-up (namely, from 1 to 5 years after the first reintervention for DES-ISR). The overall performance of the risk prediction model was assessed using the C-statistic. The training cohort was used to create the model with all LASSO variables, whilst the validation cohort was used to qualify the performance of the model. Using 400 cycles of bootstrap resampling, we performed an internal validation of the model (including only the significant variables) and repeated this analysis for a model based on the Mehran classification, after dichotomisation of the original four Mehran classification ISR categories into focal or non-focal (this latter group included diffuse intrastent, diffuse proliferative and total occlusion ISR lesions)⁴. This analysis allowed empirical bootstrap distributions of sample means and bootstrap confidence intervals of the C-statistics and integrated discrimination improvements (IDI) to be calculated. The C-statistic is a measure of the predictive accuracy of a model, and the IDI is a measure to quantify risk discrimination improvement²²⁻²³. We calculated the delta C-statistic and delta IDI to determine whether any differences in the predictive accuracy and the risk discrimination improvement between the two models were statistically significant.

A classification and regression tree (CART) analysis was performed with regression trees constructed using only the independent predictors of repeat PCI for recurrent DES-ISR. In addition, a numerical scoring system based on the four significant predictors served to help determine the risk of repeat PCI for recurrent DES-ISR at 1-year follow-up according to the number of predictor variables present. The risk of repeat PCI for recurrent DES-ISR was calculated as a cumulative incidence after accounting for the competing risk of death and compared using a Cox proportional hazards model with correction for intracluster correlation for lesions with increasing numbers of predictor variables compared to those without any predictor variables. These results are presented as hazard ratios (HR) and 95% confidence intervals (CI). Rates of repeat PCI for recurrent DES-ISR for patients as per the identified predictor variables were also calculated as cumulative incidences after accounting for the competing risk of death and compared using a Cox proportional hazards model with correction for intracluster correlation during two time periods (namely from 0 to 1 year and from 1 to 5 years after PCI). The results are presented as cumulative incidences, HRs and 95% CIs for both time periods. All analyses were in accordance with the TRIPOD statement (**Supplementary Table 1**)²⁴. Statistical significance was defined at a p-value of <0.05. Statistical analysis was performed using the R 3.6.0 Statistical Package (The R Foundation for Statistical Computing). All of the authors had access

to the data used in this study and take full responsibility for its integrity and the data analysis.

Results

We included 1,986 patients treated with PCI for DES-ISR. These patients were randomly divided into training (1,471 patients with 1,778 lesions) and validation cohorts (515 patients with 614 lesions). Overall, the median duration of follow-up (25th, 75th percentiles) after treatment with PCI for DES-ISR was 7.4 (4.2, 10.4) years.

Baseline clinical features for the overall population, as well as in the training and the validation populations, are shown in **Table 1**. Of note, most patients undergoing PCI for DES-ISR were male, and approximately one-quarter of patients presented with acute coronary syndrome (ACS). Lesion-level angiographic features in the overall population, as well as in the training and the validation populations, are shown in **Table 2**. The majority of the ISR lesions after DES implantation were focal as per the Mehran classification, and the initial repeat PCI type was comparable in the training and validation populations. The indication for repeat PCI for recurrent DES-ISR from 0-1 years and from 1-5 years is demonstrated in **Supplementary Table 2**.

CUMULATIVE INCIDENCES

Clinical outcomes at 1-year follow-up for the overall, training and validation populations are shown in **Table 3**. The cumulative incidence of repeat PCI for recurrent DES-ISR at 1-year follow-up in the training and the validation populations is shown in **Figure 1**.

PREDICTORS OF REPEAT PCI FOR RECURRENT DES-ISR FROM 0 TO 1 YEAR

The LASSO method selected the following variables for the logistic regression model from 0 to 1 year after PCI for DES-ISR: ISR type, age, hypercholesterolaemia, smoking, ACS, multivessel disease, left circumflex (LCx) coronary artery ISR, vessel calcification, ostial ISR lesion, bifurcational ISR, ISR severity (>90%), maximum device (stent/balloon) diameter and ISR interval. Of note, the variables ISR type and ISR interval were dichotomised (into non-focal/focal and <6 months/≥6 months, respectively) based on the analysis of the crude frequencies of repeat PCI at 1 year for DES-ISR in the training population as per groups identified by ISR type and ISR interval (**Supplementary Table 3**).

The logistic regression model including all the above-mentioned variables identified four independent predictors of repeat PCI for recurrent DES-ISR from 0 to 1 year: a non-focal ISR pattern, a time interval to restenosis of <6 months, ISR in the LCx coronary artery, and vessel calcification (**Table 4**). The C-statistic for the regression model including all variables identified by the LASSO analysis was 0.62 in the training population and 0.64 in the validation population.

BOOTSTRAP ANALYSIS

Internal validation was performed using bootstrapping with 400 resamples for the four-variable model in the training and validation

Table 1. Baseline characteristics.

Characteristic		All patients (N=1,986)	Training population (N=1,471)	Validation population (N=515)	p-value
Age, median [IQR], years		69.8 [61.6-76.2]	69.2 [60.8-76.1]	70.9 [63.5-76.7]	0.003
Sex, female – n (%)		398 (20.0)	295 (20.1)	103 (20.0)	>0.999
BMI, median [IQR], kg/m ²		27.2 [24.7-30.0]	27.2 [24.7-30.1]	27.2 [24.7-29.7]	0.453
First re-PCI interval, median [IQR], days		247 [197-840]	254 [197-886]	230 [196-744]	0.093
Restenosis interval – n (%)	<6 months	326 (16.4)	237 (16.1)	89 (17.3)	0.276
	6-12 months	833 (41.9)	603 (41.0)	230 (44.7)	
	>12-24 months	247 (12.4)	186 (12.6)	61 (11.8)	
	>24 months	580 (29.2)	445 (30.3)	135 (26.2)	
Short restenosis interval – n (%)		326 (16.4)	237 (16.1)	89 (17.3)	0.584
Diabetes – n (%)		748/1,980 (37.8)	586/1,468 (39.9)	162/512 (31.6)	0.001
Insulin-treated – n (%)		293/1,980 (14.8)	229/1,468 (15.6)	64/512 (12.5)	0.103
Arterial hypertension – n (%)		1,886/1,982 (95.2)	1,406/1,468 (95.8)	480/512 (93.4)	0.040
Hypercholesterolaemia – n (%)		1,505/1,971 (76.4)	1,115/1,461 (76.3)	390/510 (76.5)	0.992
Smoker – n (%)		302/1,981 (15.2)	231/1,468 (15.7)	71/513 (13.8)	0.339
ACS – n (%)		506/1,982 (25.5)	369/1,467 (25.2)	137 (26.6)	0.555
NYHA classification – n (%)	I	732 (36.9)	553 (37.6)	179 (34.8)	0.159
	II	964 (48.5)	709 (48.2)	255 (49.5)	
	III	241 (12.1)	179 (12.2)	62 (12.0)	
	IV	49 (2.5)	30 (2.0)	19 (3.7)	
Coronary artery disease – n (%)	Single-vessel	151 (7.6)	113 (7.7)	38 (7.4)	0.929
	Two-vessel	359 (18.1)	268 (18.2)	91 (17.7)	
	Three-vessel	1,476 (74.3)	1,090 (74.1)	386 (75.0)	
Multivessel disease – n (%)		1,835 (92.4)	1,358 (92.3)	477 (92.6)	0.899
Prior myocardial infarction – n (%)		830/1,979 (41.9)	608/1,466 (41.5)	222/513 (43.3)	0.509
Prior CABG – n (%)		275/1,984 (13.9)	192/1,469 (13.1)	83 (16.1)	0.099
Atrial fibrillation – n (%)		97 (4.9)	76 (5.2)	21 (4.1)	0.385
LVEF – n (%)	<35%	64 (3.2)	51 (3.5)	13 (2.5)	0.030
	35-50%	576 (29.0)	425 (28.9)	151 (29.4)	
	>50-55%	297 (15.0)	201 (13.7)	96 (18.7)	
	>55%	1,048 (52.8)	794 (54.0)	254 (49.4)	
Missing continuous data: Training Population: body mass index, 2 patients, Validation Population: body mass index, 1 patient. The remaining continuous data were complete. ACS: acute coronary syndrome; BMI: body mass index; CABG: coronary artery bypass grafting; IQR: interquartile range; LVEF: left ventricular ejection fraction; MI: myocardial infarction; NYHA: New York Heart Association; PCI: percutaneous coronary intervention					

populations and to compare the performance of the four-variable and the Mehran classification models. Of note, the model based on the Mehran classification included only the non-focal ISR morphology predictor variable.

The C-statistic for the four-variable model was 0.61 (95% CI: 0.57-0.64) in the training population and 0.61 (95% CI: 0.55-0.67) in the validation population. The delta C-statistic was –0.003 (95% CI: –0.070 to 0.074; p=0.91) indicating that there was no difference in the discriminative performance of the four-variable model in the training and validation populations.

The C-statistic for the four-variable model developed to predict the likelihood of repeat PCI for recurrent DES-ISR at 1 year was 0.60 (95% CI: 0.57-0.63) and the C-statistic for the model based on the Mehran classification was 0.54 (95% CI: 0.52-0.57). The

IDI for the four-variable model was 0.021 (95% CI: 0.010-0.033) and the IDI for the model based on the Mehran classification was 0.005 (95% CI: 0.001-0.011). Both the delta C-statistic (0.062, 95% CI: 0.035-0.094) and delta IDI (0.016, 95% CI: 0.007-0.029) between the four-variable model and the model based on the Mehran classification were statistically significant (p<0.001).

CART MODEL AND PREDICTORS OF REPEAT PCI FOR RECURRENT DES-ISR FROM 0 TO 1 YEAR

The CART model (**Figure 2**) demonstrates the variables with an impact on the likelihood of repeat PCI for recurrent DES-ISR at 1-year follow-up. The likelihood of repeat PCI for recurrent DES-ISR ranged from 12.4% to 30.9% based on the presence or absence of the predictors identified in the final regression model.

Table 2. Angiographic characteristics.

Characteristic		All lesions (N=2,392)	Training population lesions (N=1,778)	Validation population lesions (N=614)	p-value
Restenosis morphology – n (%)	I (focal)	1,563 (65.3)	1,163 (65.4)	400 (65.1)	0.092
	II (diffuse intrastent)	581 (24.3)	420 (23.6)	161 (26.2)	
	III (diffuse proliferative)	57 (2.4)	40 (2.3)	17 (2.8)	
	IV (total occlusion)	191 (8.0)	155 (8.7)	36 (5.9)	
Vessel – n (%)	LCA	97 (4.1)	64 (3.6)	33 (5.4)	0.067
	LAD	870 (36.4)	645 (36.3)	225 (36.6)	
	LCx	700 (29.3)	540 (30.4)	160 (26.1)	
	RCA	725 (30.3)	529 (29.8)	196 (31.9)	
Initially implanted DES type	BP-BES	166 (6.9%)	119 (6.7%)	47 (7.7%)	0.51
	BP-SES	543 (22.7%)	402 (22.6%)	141 (23.0%)	
	PF-SES	465 (19.4%)	355 (20.0%)	110 (17.9%)	
	PP-EES	885 (37.0%)	664 (37.3%)	221 (36.0%)	
	PP-ZES	333 (13.9%)	238 (13.4%)	95 (15.5%)	
Initial repeat PCI type	DES	1,178 (49.2%)	862 (48.5%)	316 (51.5%)	0.219
	PTCA (DCB or POBA)	1,214 (50.8%)	916 (51.5%)	298 (48.5%)	
	DCB	635 (26.5%)	479 (26.9%)	156 (25.4%)	–
	POBA	579 (24.2%)	437 (24.6%)	142 (23.1%)	–
Scoring balloon	160 (6.7%)	122 (6.9%)	38 (6.2%)	0.630	
Rotational atherectomy	2 (0.1%)	2 (0.1%)	0 (0.0%)	0.628	
IVUS	4 (0.2%)	2 (0.1%)	2 (0.3%)	0.577	
OCT	59 (2.5%)	44 (2.5%)	15 (2.4%)	>0.999	
Calcification – n (%)	680 (28.5)	512 (28.9)	168 (27.4)	0.506	
Ostial lesion – n (%)	173 (7.3)	129 (7.3)	44 (7.2)	>0.999	
Bifurcation – n (%)	818 (34.3)	608 (34.3)	210 (34.2)	>0.999	
CTO – n (%)	169 (7.1)	135 (7.6)	34 (5.5)	0.101	
Restenosis \geq 90% – n (%)	343/2,387 (14.4)	270/1,773 (15.2)	73 (11.9)	0.049	
Device diameter, median [IQR] mm	3.00 [2.50-3.50]	3.00 [2.50-3.50]	3.00 [2.75-3.50]	0.054	

BES: biolimus-eluting stent; BP: biodegradable polymer; CTO: chronic total occlusion; DCB: drug-coated balloon; DES: drug-eluting stent; EES: everolimus-eluting stent; IQR: interquartile range; IVUS: intravascular ultrasound; LAD: left anterior descending; LCA: left coronary artery; LCx: left circumflex coronary artery; OCT: optical coherence tomography; PF: polymer-free; POBA: plain old balloon angioplasty; PP: permanent polymer; PTCA: percutaneous transluminal coronary angioplasty; RCA: right coronary artery; SES: sirolimus-eluting stent; ZES: zotarolimus-eluting stent

We also analysed the risk of repeat PCI for recurrent DES-ISR according to whether the DES-ISR lesions presented with one of the four significant predictors derived from the final regression model (**Table 5, Figure 3**).

THE ISAR SCORE

From the final regression model, including the significant predictors of repeat PCI for recurrent DES-ISR at 1 year, we developed a four-item score, namely the ISAR score, to estimate the 1-year incidence of repeat PCI for recurrent DES-ISR. The score is obtained by assigning 1 point to each DES-ISR lesion based on the following criteria: ISR location in the LCx coronary artery; non-focal stenosis morphology; presence of arterial calcification of the target vessel; Restenosis interval <6 months (ISAR). As such, the ISAR score for a DES-ISR lesion undergoing PCI

can range from 0 to 4 points. In the current study population, the 1-year incidences of repeat PCI for recurrent DES-ISR in lesions with ISAR scores of 0, 1, 2 and \geq 3 points were 12.1%, 15.9%, 24.2% and 30.5%, respectively (p for trend <0.001). Compared to lesions with an ISAR score of 0, the incidence of repeat PCI for recurrent DES-ISR was increased in lesions with an ISAR score of 1 (HR 1.37, 95% CI: 1.04-1.79), 2 (HR 2.27, 95% CI: 1.69-3.07) and \geq 3 (HR 3.11, 95% CI: 2.15-4.81). The cumulative incidences of repeat PCI for recurrent DES-ISR at 1-year as per the ISAR score are demonstrated in the **Central illustration**. Of note, the ISAR score was significantly correlated with the 1-year cumulative incidence of repeat PCI for recurrent DES-ISR in both the patient populations treated with stent- (p for trend=0.0016) and balloon-based (p for trend <0.001) modalities. There was no interaction between the ISAR score and ACS presentation with regard

Table 3. Clinical outcomes through to 1 year in the entire population, training population and validation population.

Lesion-level outcomes	All lesions (N=2,392)	Training (N=1,778)	Validation (N=614)	Hazard ratio (95% CI)
Repeat PCI for recurrent DES-ISR	402 (17.7)	299 (17.7)	103 (17.7)	1.01 (0.79-1.25)
Definite stent thrombosis	3 (0.1)	2 (0.1)	1 (0.2)	1.47 (0.00-9734.2)
Patient-level outcomes	All patients (N=1,986)	Training (N=1,471)	Validation (N=515)	Hazard ratio (95% CI)
All-cause mortality	90 (4.7)	63 (4.5)	27 (5.5)	1.23 (0.79-1.93)
Myocardial infarction	31 (1.6)	24 (1.7)	7 (1.4)	0.83 (0.36-1.94)
Coronary artery bypass grafting	18 (1.0)	15 (1.1)	3 (0.6)	0.57 (0.17-1.98)

Data are number of events with Kaplan-Meier estimates for all-cause mortality (%) or cumulative incidence (%) after accounting for competing risk of death for all other events. The hazard ratio and 95% confidence interval (95% CI) reported is for the comparison between the training and validation populations. DES: drug-eluting stent; ISR: in-stent restenosis; PCI: percutaneous coronary intervention

to repeat PCI for recurrent DES-ISR. The ISAR score was significantly correlated with the 1-year cumulative incidence of repeat PCI for recurrent DES-ISR in both the patient populations presenting with ACS (p for trend <0.001) and chronic coronary syndrome (CCS) (p for trend <0.001). The ISAR score was also significantly correlated with the incidence of repeat PCI for recurrent DES-ISR at 5-year follow-up (p for trend <0.001).

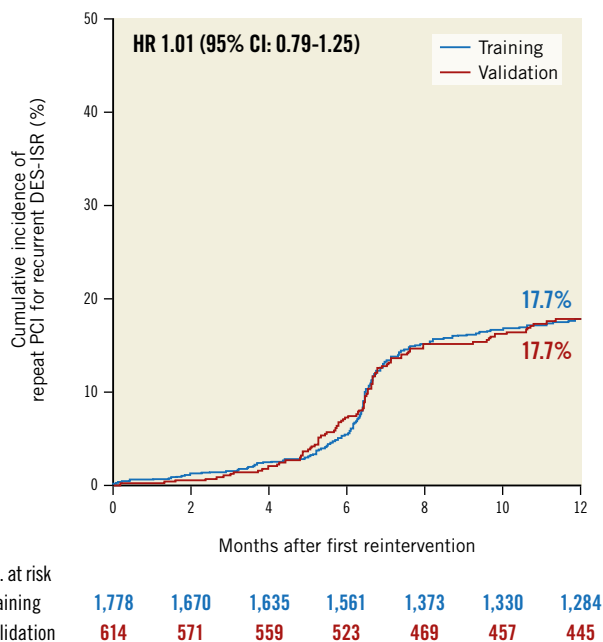


Figure 1. Repeat PCI for recurrent DES-ISR at 1 year in the training and validation populations. CI: confidence interval; DES: drug-eluting stent; HR: hazard ratio; ISR: in-stent restenosis; PCI: percutaneous coronary intervention

Table 4. Results of logistic regression analysis for repeat PCI for recurrent DES-ISR from 0 to 1 year after after the first reintervention for DES-ISR.

Variable	Regression coefficient	p-value
Non-focal ISR at index PCI	0.346	0.029
Age	-0.007	0.297
Hypercholesterolaemia	0.161	0.310
Smoking	0.197	0.328
Acute coronary syndrome	0.054	0.736
Multivessel disease	0.259	0.401
Left circumflex coronary artery	0.288	0.048
Vessel calcification	0.359	0.020
Ostial lesion	0.378	0.169
Bifurcation lesion	0.143	0.333
ISR severity >90%	0.178	0.383
Device diameter	-0.174	0.220
Restenosis interval <6 months	0.506	0.008

Significant correlates are in bold. DES: drug-eluting stent; ISR: in-stent restenosis; PCI: percutaneous coronary intervention

PREDICTORS OF REPEAT PCI FOR RECURRENT DES-ISR FROM 1 TO 5 YEARS

From 1 to 5 years, repeat PCI for recurrent DES-ISR occurred in 209 of 1,729 lesions.

An exploratory logistic regression model, searching for predictors of repeat PCI for recurrent DES-ISR from 1 to 5 years, did not identify any independent significant predictors of repeat PCI for recurrent DES-ISR from 1 to 5 years (**Supplementary Table 4**). In addition, a landmark analysis (from 0 to 1 year and from 1 to 5 years) explored a possible time dependence in the incidence of repeat PCI for recurrent DES-ISR according to whether the DES-ISR lesions presented with one of the four significant predictors derived from the final multivariable model at 1-year follow-up (**Supplementary Figure 1**).

Discussion

We studied nearly 2,000 patients treated with PCI for DES-ISR in order to develop and validate a risk prediction model for repeat PCI due to recurrent DES-ISR. As far as we are aware, the current study is the largest analysis of the predictors of repeat PCI for recurrent DES-ISR. The main findings of the present analysis are as follows:

- A non-focal DES-ISR pattern, a DES-ISR interval of <6 months, DES-ISR in the LCx coronary artery and DES-ISR in a calcified coronary vessel are independent predictors of repeat PCI for recurrent DES-ISR at 1-year follow-up.
- These four variables were used to develop and validate a risk prediction model for repeat PCI due to recurrent DES-ISR. Although the discriminative power of this risk prediction model was modest, it was stronger than a model based on a previous ISR classification system introduced in the BMS era.
- The four-variable model was then used to create the four-item ISAR score, a scoring system which allows for practical estimation of the risk of repeat PCI for recurrent DES-ISR.

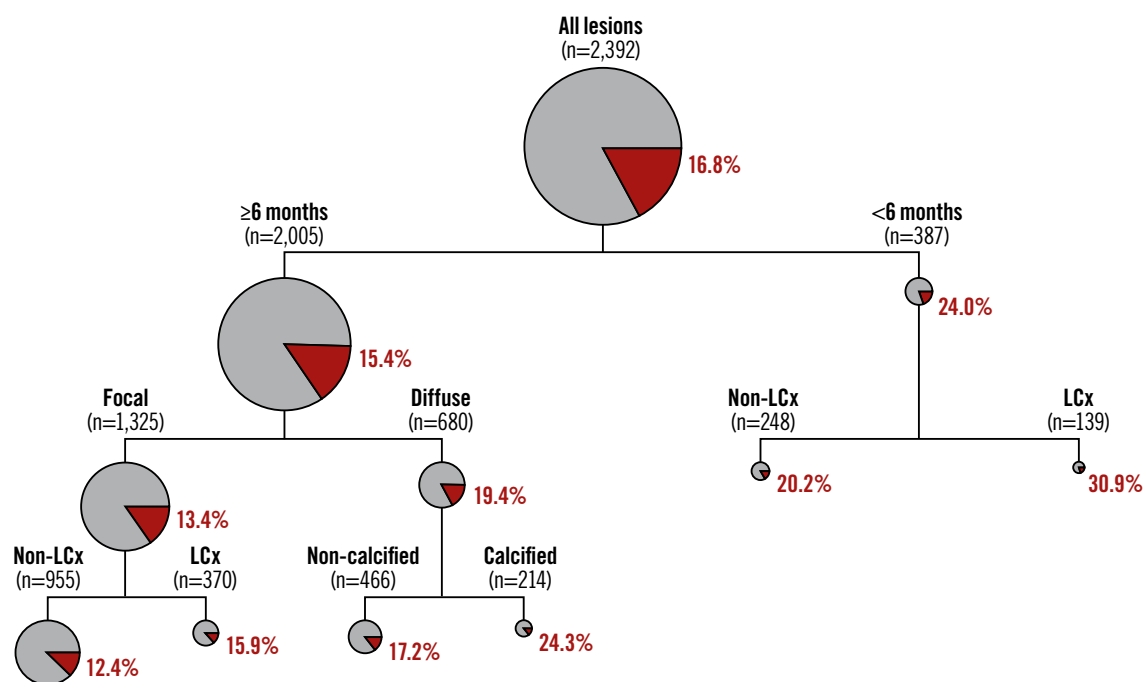


Figure 2. Classification and regression tree analysis. Classification and regression tree (CART) analysis demonstrating the variables which influence the likelihood of repeat PCI for recurrent DES-ISR at 1-year follow-up. The size of the circles are proportional to the size of the subgroup. The red segments of the circles indicate the percentage of DES-ISR lesions undergoing repeat PCI at 1-year follow-up. DES: drug-eluting stent; LCx: left circumflex coronary artery; ISR: in-stent restenosis; PCI: percutaneous coronary intervention

The present data demonstrate that patients with DES-ISR treated with PCI have a relatively high rate of recurrence, with repeat PCI for recurrent DES-ISR occurring in over one in six treated DES-ISR lesions at 1-year follow-up. This analysis focused on a follow-up duration of 1 year for two reasons. Firstly, a large proportion of trials dealing with a similar research topic were designed to capture major clinical endpoints up to 1-year follow-up^{2,25-27}. Secondly, the 1-year follow-up limit allowed us to compare the developed risk prediction model with a model based on the Mehran classification, which originally reported on clinical outcomes up to the same timepoint⁴.

A model to predict repeat PCI for recurrent DES-ISR could potentially be used to identify patients at the highest risk of ISR recurrence and could help to stratify patients for the purposes of clinical follow-up. Overall, the model developed in our analysis had a relatively modest discriminative power for the prediction of repeat PCI for recurrent DES-ISR at 1-year follow-up. However,

the discriminative power of this model was greater than that of a model based on the Mehran classification system, which was developed in the BMS era⁴.

Our analysis confirms previous observations that the typical DES-ISR pattern is focal in morphology²⁸. A study which included a relatively small number of patients with a median follow-up of about 1 year reported that the ISR morphology (defined in that study as focal versus diffuse) retained prognostic importance in the early DES era with regard to both angiographic restenosis and repeat PCI for recurrent DES-ISR¹³. While that study excluded patients with occlusive restenosis, another smaller study subsequently reported that occlusive DES-ISR was also associated with an increased risk of both angiographic restenosis and recurrent target lesion revascularisation (TLR)⁶. A larger study, including 392 patients with a median follow-up of nearly 3 years, confirmed the importance of the initial DES-ISR morphology on longer-term outcomes after PCI for DES-ISR¹⁴. Our analysis, which includes

Table 5. Cumulative incidence of repeat PCI for recurrent DES-ISR from 0 to 1 year for lesions with and without the four predictor variables identified in the logistic regression model.

Predictor	Predictor present (n/N, KM%)	Predictor not present (n/N, KM%)	Hazard ratio (95% CI)
Restenosis interval <6 months	93/387 (24.4%)	309/2,005 (16.4%)	1.62 (1.22-2.10)
Non-focal in-stent restenosis morphology	173/829 (22.4%)	229/1,563 (15.3%)	1.56 (1.28-1.85)
Vessel calcification	134/680 (20.9%)	268/1,707 (16.5%)	1.35 (1.09-1.63)
Left circumflex artery	147/700 (21.9%)	255/1,692 (16.0%)	1.44 (1.19-1.80)

Data are number of events with cumulative incidence (%) after accounting for competing risk of death. CI: confidence interval; KM: Kaplan-Meier

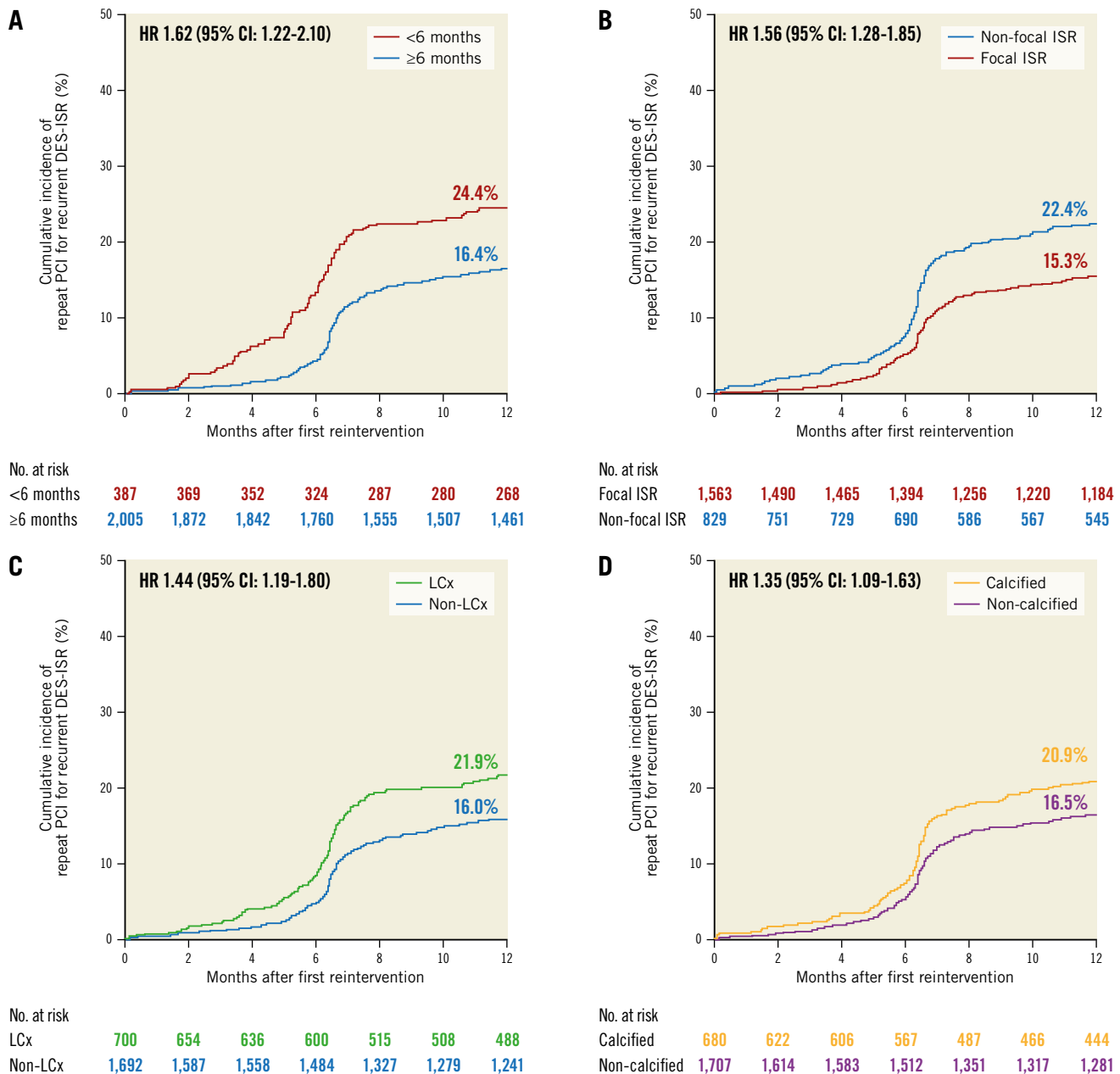
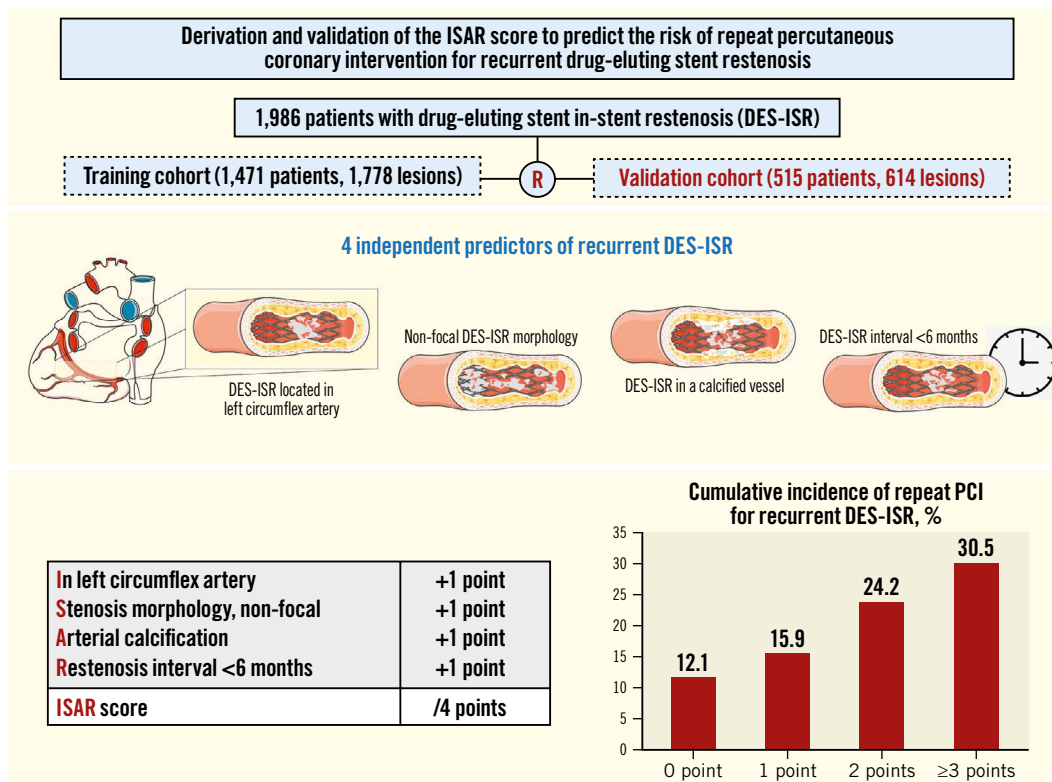


Figure 3. Cumulative incidence of repeat PCI for recurrent DES-ISR at 1-year follow-up for lesions with and without the four predictor variables identified in the logistic regression model. A) Restenosis interval <6 months versus restenosis interval ≥6 months. B) Restenosis morphology: non-focal versus restenosis morphology: focal. C) Artery involved: left circumflex artery versus non-left circumflex artery. D) Vessel calcification: calcified vessel versus non-calcified vessel. CI: confidence interval; DES: drug-eluting stent; HR: hazard ratio; ISR: in-stent restenosis; LCx: left circumflex coronary artery; PCI: percutaneous coronary intervention

a population that is between 6 to 10 times larger than in previous studies and with approximately 2,500 DES-ISR lesions, demonstrates that in addition to the DES-ISR morphology, the restenosis interval, the involved vessel and the presence of arterial calcification are predictors of repeat PCI for recurrent DES-ISR at 1-year follow-up.

Some studies have previously suggested that these factors may be associated with an increased risk of TLR in the setting of DES-ISR. We previously reported that ISR occurring <12 months after DES implantation is associated with an increased risk of adverse

events in DES-ISR treated with drug-coated balloon (DCB) angioplasty²⁹. While the development of early DES-ISR may suggest a more aggressive ISR phenotype, definitive data in this regard are limited. It has been reported that early DES-ISR is mainly caused by neointimal hyperplasia, whereas DES-ISR that occurs later tends to be caused by neoatherosclerosis, and this may also be relevant in this regard³⁰. It has been previously suggested that ostial ISR lesions in the LCx coronary artery have an increased TLR rate in comparison to non-LCx lesions³¹. Similar findings were reported in another study assessing patients with ostial

CENTRAL ILLUSTRATION The ISAR score to estimate the risk of repeat PCI for recurrent DES-ISR at 1-year follow-up.

The ISAR score can range from 0-4 based on the presence or absence of the four identified predictors of repeat PCI for recurrent DES-ISR. Patients receive +1 point for each of the following criteria they meet: DES-ISR In the LCx coronary artery, non-focal Stenosis morphology, Arterial calcification and Restenosis interval of <6 months (ISAR). The cumulative incidence of repeat PCI for recurrent DES-ISR increases with an increasing ISAR score, from 12.1% for patients with an ISAR score of 0 to 30.5% for patients with an ISAR score of ≥ 3 . DES: drug-eluting stent; LCx: left circumflex coronary artery; ISR: in-stent restenosis; PCI: percutaneous coronary intervention; R: Patients were randomly divided into training (1,471 patients with 1,778 lesions) and validation (515 patients with 614 lesions) cohorts

ISR treated with DCB therapy, with an increased risk of TLR in patients treated for LCx DES-ISR³². Both vessel and lesion calcification have also been previously associated with an increased risk of DES-ISR^{33,34}. In addition, another small study including 276 patients noted that patients undergoing repeat PCI of recurrent DES-ISR commonly had moderate to severe target lesion calcification³⁵.

While several risk prediction models have been proposed for the prediction of developing ISR after PCI with DES implantation, our current analysis is the first risk prediction model that has been developed and validated in a large number of patients for repeat PCI for recurrent DES-ISR⁶⁻⁹. The overall modest discriminative power of our model may reflect the heterogeneous nature of DES-ISR. In our study, this was particularly evident from 1 to 5 years after PCI for DES-ISR, a time period in which we were unable to identify any significant predictor of repeat PCI for recurrent DES-ISR. The risk of recurrent DES-ISR PCI may be increased because of multiple factors, relating not only to the patient, lesion and initial procedure but also to the initial treatment of the DES-ISR¹⁰⁻¹². This complexity may become

even more apparent at longer-term follow-up, and this may have contributed to the inability of our model to identify predictors of repeat PCI for recurrent DES-ISR beyond 1 year.

Overall, these results highlight that it remains challenging to accurately predict the likelihood of a patient requiring repeat PCI for recurrent DES-ISR. In this context, the ISAR score may be a prediction tool of certain relevance. An ISAR score of 0 was associated with a 12.1% risk of repeat PCI for recurrent DES-ISR at 1-year follow-up, while an ISAR score of ≥ 3 was associated with a risk of 30.5%. From a practical perspective, an advantage of the ISAR score is that it can be quickly calculated in the cardiac catheterisation laboratory using readily available angiographic and clinical information. Vessel calcification, DES-ISR morphology and ISR vessel location can all be assessed angiographically, while the restenosis interval can be identified from the clinical history, clinical referral report or previous angiogram report in the majority of cases. The ISAR score may be useful not only to guide clinical follow-up but also when counselling patients regarding their risk of requiring repeat PCI for recurrent DES-ISR within the first year. However, these data also demonstrate that even the lowest risk DES-ISR patients (with an

ISAR score of 0) are still at a relatively high risk of repeat PCI for recurrent DES-ISR at 1-year follow-up, highlighting the challenge that remains in treating DES-ISR in real-world practice.

Limitations

This study has several limitations which warrant consideration. This is a retrospective analysis of patient data from a registry database and so carries the inherent limitations associated with this form of analysis. Although we used randomly assigned training and validation populations, an external prospective validation of the ISAR score is still missing. Therefore, while the model was internally validated, it lacks external validation. Most patients presented with stable coronary artery disease at the time of PCI for DES-ISR, with only 25% of the entire cohort presenting with ACS. In this regard, the predictive performance of the ISAR score in a population different from that investigated here remains to be addressed, although there was no interaction between the ISAR score and clinical presentation with regard to repeat PCI for recurrent DES-ISR. This point also holds true regarding the DES platforms studied, given that the latest-generation DES were not included in the present analysis. The presence of coronary artery calcification, one of the significant predictors of repeat PCI for recurrent DES-ISR at 1 year, was evaluated only at coronary angiography, which may have led to underreporting or to underestimation of calcification. Similarly, given the low use of intravascular imaging in this analysis, it was not possible to assess imaging parameters for inclusion into our model. Indeed, despite encouragement from consensus documents³⁶, the use of intravascular imaging in clinical practice in Europe and the US remains relatively low³⁷⁻³⁸. We had no information regarding antithrombotic medications and other secondary prevention measures at the time of PCI for DES-ISR. In this regard, the possible impact of common cardioactive drugs and risk reduction pathways on a subsequent repeat PCI for recurrent DES-ISR cannot be determined in this context and should be the subject of future investigations. This analysis does not have detailed procedural data demonstrating the mechanism of the initial DES-ISR or regarding lesion preparation techniques used prior to the index PCI. The identification of recurrent ISR after a first reintervention for ISR may be dependent on the nature of follow-up. A final important potential limitation of the ISAR score is that in some cases it may not be possible to determine the restenosis interval at the time of the repeat PCI procedure.

Conclusions

Restenosis morphology and interval, vessel calcification and involvement of the LCx coronary artery are independent predictors of repeat PCI for recurrent DES-ISR at 1-year follow-up. A four-variable model for risk prediction of repeat PCI for recurrent DES-ISR at 1-year follow-up demonstrated a modest discriminative performance overall, although superior to that of the current benchmark for ISR classification. Based on the four-variable prediction model, we developed the ISAR score, a four-item scoring system that can be used to estimate the risk of repeat PCI for recurrent DES-ISR at 1-year follow-up.

Impact on daily practice

At 1-year follow-up after the first DES-ISR intervention, four factor variables (a non-focal ISR pattern, a time interval to ISR of <6 months, ISR of the left circumflex artery and ISR in a calcified vessel) are associated with an increased risk of repeat PCI for recurrent DES-ISR. These four factors were used to generate the ISAR score, a scoring system which was significantly correlated with the 1-year cumulative incidence of repeat PCI for recurrent DES-ISR. The 1-year risk of repeat PCI for recurrent DES-ISR can be predicted using the ISAR score, a standardised tool that can be quickly calculated in the cardiac catheterisation laboratory using readily available angiographic and clinical information.

Conflict of interest statement

J. Wiebe reports lecture fees from AstraZeneca and lecture fees and an institutional grant from Abbott Vascular. The other authors have no conflicts of interest to declare.

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Supplementary data

Supplementary Appendix 1. Methods.

Supplementary Appendix 2. List of variables considered by the LASSO model.

Supplementary Table 1. TRIPOD checklist: prediction model development and validation.

Supplementary Table 2. Indications for repeat PCI for recurrent DES-ISR at 1- and 5-year follow-up.

Supplementary Table 3. Repeat PCI for recurrent DES-ISR from 0 to 1 year and from 1 to 5 years as per ISR interval and morphology.

Supplementary Table 4. Results of logistic regression analysis for repeat PCI for recurrent DES-ISR from 1 to 5 years after first re-intervention for DES-ISR.

Supplementary Figure 1. Landmark analysis demonstrating the cumulative incidence of repeat PCI for recurrent DES-ISR from 0-1 years and from 1-5 years for lesions with and without the four predictor variables identified in the logistic regression model.

The supplementary data are published online at:
<https://eurointervention.pcronline.com/doi/10.4244/EIJ-D-22-00860>



Supplementary data

Supplementary Appendix 1

Methods.

Angiographic classification system for coronary vessel calcification

Coronary vessel calcification grade	Angiographic findings
None	No radiopacity
Mild	Faint radiopacities noted during the cardiac cycles
Moderate	Dense radiopacities noted only during the cardiac cycle
Severe	Dense radiopacities noted without cardiac motion before contrast injection generally compromising both sides of the arterial lumen

Supplementary Appendix 2

List of variables considered by the LASSO model

Age, body mass index (BMI), sex, diabetes mellitus, hypertension, hypercholesterolaemia, smoking status, acute coronary syndrome (ACS) presentation, multi-vessel disease, previous MI, previous CABG, restenosis morphology (focal or non-focal), left circumflex (LCx) coronary artery, ostial LCx coronary artery, distal vessel, vessel calcification, ostial lesion, bifurcation lesion, chronic total occlusion (CTO) lesion, restenosis severity $\geq 90\%$, maximum device diameter (stent or balloon) and short restenosis interval (< 6 months between the initial DES implantation and the initial treatment of the DES-ISR)

Supplementary Table 1. TRIPOD Checklist: Prediction Model Development and Validation

Section/Topic	Checklist Item			Page
Title and abstract				
Title	1	D;V	Identify the study as developing and/or validating a multivariable prediction model, the target population, and the outcome to be predicted.	1
Abstract	2	D;V	Provide a summary of objectives, study design, setting, participants, sample size, predictors, outcome, statistical analysis, results, and conclusions.	2
Introduction				
Background and objectives	3a	D;V	Explain the medical context (including whether diagnostic or prognostic) and rationale for developing or validating the multivariable prediction model, including references to existing models.	4
	3b	D;V	Specify the objectives, including whether the study describes the development or validation of the model or both.	4
Methods				
Source of data	4a	D;V	Describe the study design or source of data (e.g., randomized trial, cohort, or registry data), separately for the development and validation data sets, if applicable.	4,5
	4b	D;V	Specify the key study dates, including start of accrual; end of accrual; and, if applicable, end of follow-up.	4
Participants	5a	D;V	Specify key elements of the study setting (e.g., primary care, secondary care, general population) including number and location of centres.	4
	5b	D;V	Describe eligibility criteria for participants.	4
	5c	D;V	Give details of treatments received, if relevant.	22
Outcome	6a	D;V	Clearly define the outcome that is predicted by the prediction model, including how and when assessed.	5
	6b	D;V	Report any actions to blind assessment of the outcome to be predicted.	NA
Predictors	7a	D;V	Clearly define all predictors used in developing or validating the multivariable prediction model, including how and when they were measured.	6, 33
	7b	D;V	Report any actions to blind assessment of predictors for the outcome and other predictors.	6
Sample size	8	D;V	Explain how the study size was arrived at.	4
Missing data	9	D;V	Describe how missing data were handled (e.g., complete-case analysis, single imputation, multiple imputation) with details of any imputation method.	6
Statistical analysis methods	10a	D	Describe how predictors were handled in the analyses.	5-7
	10b	D	Specify type of model, all model-building procedures (including any predictor selection), and method for internal validation.	5-7
	10c	V	For validation, describe how the predictions were calculated.	5-7
	10d	D;V	Specify all measures used to assess model performance and, if relevant, to compare multiple models.	5-7
	10e	V	Describe any model updating (e.g., recalibration) arising from the validation, if done.	5-7
Risk groups	11	D;V	Provide details on how risk groups were created, if done.	5-7
Development vs. validation	12	V	For validation, identify any differences from the development data in setting, eligibility criteria, outcome, and predictors.	5-7
Results				
Participants	13a	D;V	Describe the flow of participants through the study, including the number of participants with and without the outcome and, if applicable, a summary of the follow-up time. A diagram may be helpful.	8, 23
	13b	D;V	Describe the characteristics of the participants (basic demographics, clinical features, available predictors), including the number of participants with missing data for predictors and outcome.	8, 20
	13c	V	For validation, show a comparison with the development data of the distribution of important variables (demographics, predictors and outcome).	20, 21, 22
Model development	14a	D	Specify the number of participants and outcome events in each analysis.	23
	14b	D	If done, report the unadjusted association between each candidate predictor and outcome.	8, 24
Model specification	15a	D	Present the full prediction model to allow predictions for individuals (i.e., all regression coefficients, and model intercept or baseline survival at a given time point).	24
	15b	D	Explain how to use the prediction model.	8-10
Model performance	16	D;V	Report performance measures (with CIs) for the prediction model.	9
Model-updating	17	V	If done, report the results from any model updating (i.e., model specification, model performance).	9
Discussion				
Limitations	18	D;V	Discuss any limitations of the study (such as nonrepresentative sample, few events per predictor, missing data).	14
Interpretation	19a	V	For validation, discuss the results with reference to performance in the development data, and any other validation data.	9
	19b	D;V	Give an overall interpretation of the results, considering objectives, limitations, results from similar studies, and other relevant evidence.	12-14
Implications	20	D;V	Discuss the potential clinical use of the model and implications for future research.	14
Other information				
Supplementary information	21	D;V	Provide information about the availability of supplementary resources, such as study protocol, Web calculator, and data sets.	15
Funding	22	D;V	Give the source of funding and the role of the funders for the present study.	15

Supplementary Table 2. Indication for repeat PCI for recurrent DES-ISR through to 1 year and 5 years follow up*

Indication for Repeat PCI for recurrent DES-ISR	All Patients (N=341)	Training Population (N=250)	Validation Population (N=91)	p value
Through to 1-year follow-up				0.27
<i>STEMI</i>	4 (1.2%)	2 (0.8%)	2 (2.2%)	
<i>NSTEMI</i>	43 (12.6%)	27 (10.8%)	16 (17.6%)	
<i>Unstable Angina</i>	44 (12.9%)	35 (14.0%)	9 (9.9%)	
<i>Stable Angina</i>	232 (68.0%)	174 (69.6%)	58 (63.7%)	
<i>Positive Ischemia Stress Testing</i>	18 (5.3%)	12 (4.8%)	6 (6.6%)	
Indication for Repeat PCI for recurrent DES-ISR				p value
From 1- to 5-year follow-up				0.35
<i>STEMI</i>	4 (2.3%)	4 (3.1%)	0 (0.0%)	
<i>NSTEMI</i>	19 (10.7%)	12 (9.3%)	7 (14.3%)	
<i>Unstable Angina</i>	34 (19.1%)	26 (20.2%)	8 (16.3%)	
<i>Stable Angina</i>	111 (62.4%)	78 (60.5%)	33 (67.3%)	
<i>Positive Ischemia Stress Testing</i>	10 (5.6%)	9 (7.0%)	1 (2.0%)	

*Indication for repeat PCI for recurrent DES-ISR is reported at a patient level. Some patients had repeat PCI for recurrent DES-ISR in more than one lesion.

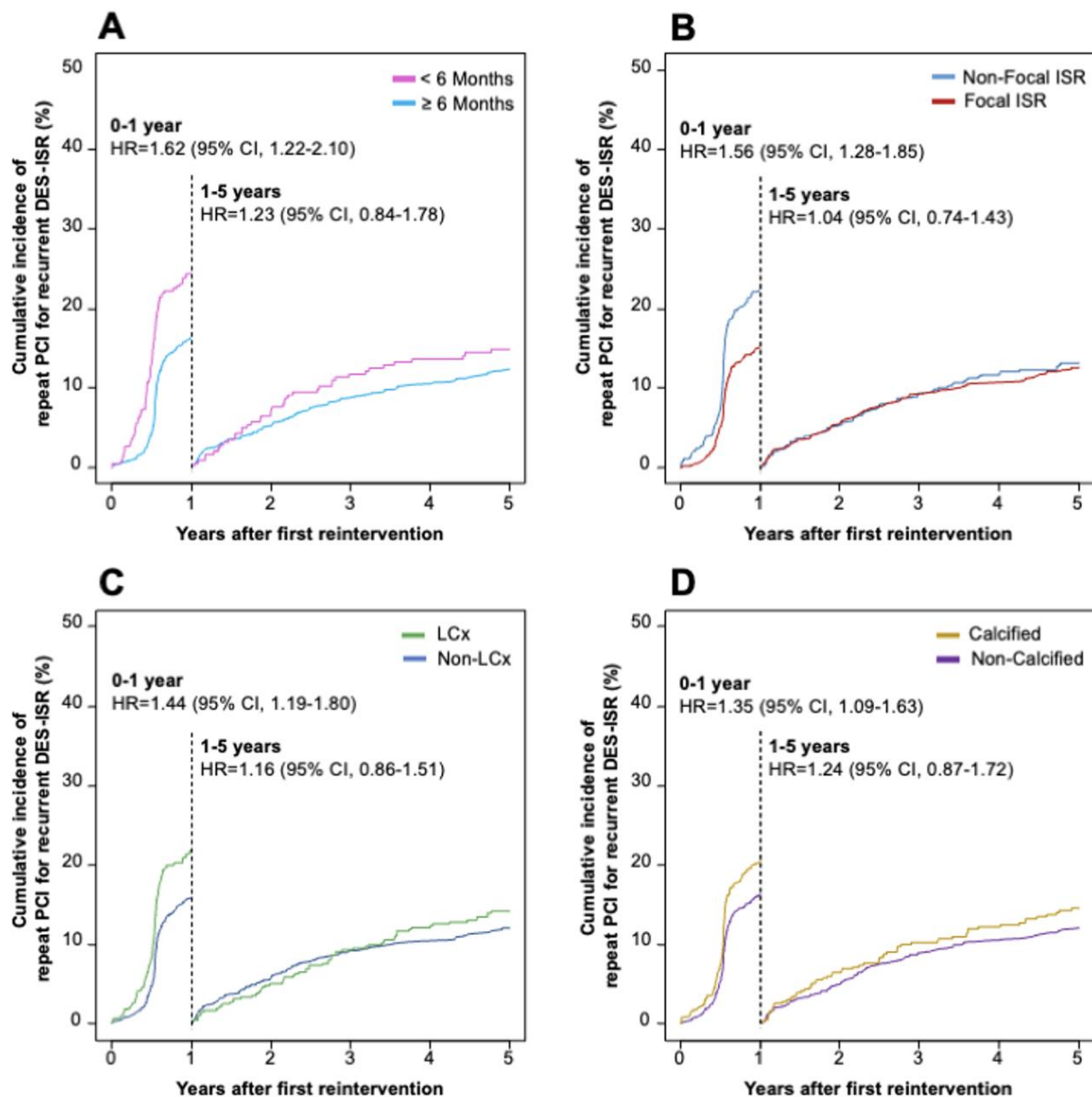
DES = drug-eluting stent, ISR = in-stent restenosis, NSTEMI = non-ST-segment elevation myocardial infarction, PCI = percutaneous coronary intervention, STEMI = ST-segment elevation myocardial infarction

Supplementary Table 3. Repeat PCI for recurrent DES-ISR from 0 to 1 year and from 1 to 5 years as per ISR interval and morphology

		Restenosis Interval				
	All Training Population Lesions (N=1,778)	6 months (N=284)	6-12 months (N=711)	>12-24 months (N=238)	>24 months (N=545)	P value
Repeat PCI for recurrent DES-ISR from 0 to 1 year – no. (%)	299 (16.8)	69 (24.3)	117 (16.5)	45 (18.9)	68 (12.5)	<0.001
Repeat PCI for recurrent DES-ISR from 1 to 5 years – no. (%)	155/1,284 (12.1)	29/195 (14.9)	62/546 (11.4)	12/176 (6.8)	52/367 (14.2)	0.050
		ISR Morphology				
	All Training Population Lesions (N=1,778)	Focal (N=1,163)	Diffuse intra-stent (N=420)	Diffuse proliferative (N=40)	Total occlusion (N=155)	P value
Repeat PCI for recurrent DES-ISR from 0 to 1 year – no. (%)	299 (16.8)	165 (14.2)	90 (21.4)	11 (27.5)	33 (21.3)	0.001
Repeat PCI for recurrent DES-ISR from 1 to 5 years – no. (%)	155/1,284 (12.1)	108/886 (12.2)	37/279 (13.3)	1/22 (4.6)	9/97 (9.3)	0.475

Supplementary Table 4. Results of logistic regression analysis for repeat PCI for recurrent DES-ISR from 1 to 5 years after first reintervention for DES-ISR.

Variable	Regression coefficient	p value
Age	-0.018	0.060
Diabetes	0.195	0.376
Hypertension	0.822	0.809
Hypercholesterolemia	0.256	0.308
Acute coronary syndrome	-0.056	0.801
Multivessel disease	0.258	0.512
Previous myocardial infarction	0.033	0.873
Left circumflex coronary artery	0.004	0.984
Chronic total occlusion	-0.111	0.774
Vessel calcification	0.336	0.143
Bifurcation lesion	0.273	0.136
Restenosis interval <6 months	0.263	0.322



Supplementary Figure 1. Landmark analysis demonstrating the cumulative incidence of repeat PCI for recurrent DES-ISR from 0 to 1 year and from 1 to 5 years for lesions with and without the four predictor variables identified in the logistic regression model.

(Panel A) Restenosis interval <6 months versus restenosis interval \geq 6 months, (Panel B) Restenosis morphology: non-focal versus restenosis morphology: focal (Panel C) Artery involved: left circumflex artery versus non-left circumflex artery, (Panel D) Vessel calcification: calcified vessel versus non-calcified vessel.