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Prevalence, management and outcomes of percutaneous coronary intervention for coronary in-stent restenosis: Insights from the France PCI Registry

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ABSTRACT

Background: Despite the evolution of stent technology, there is a non-negligible risk of in-stent restenosis (ISR) after Percutaneous coronary intervention (PCI). Large-scale registry data on the prevalence and clinical management of ISR is lacking.

Methods: The aim was to describe the epidemiology and management of patients with ≥1 ISR lesions treated with PCI (ISR PCI). Data on characteristics, management and clinical outcomes were analyzed for patients undergoing ISR PCI in the France-PCI all-comers registry.

Results: Between January 2014 and December 2018, 31,892 lesions were treated in 22,592 patients, 7.3 % of whom underwent ISR PCI. Patients undergoing ISR PCI were older (68.5 vs 67.8; $p < 0.001$), and more likely to have diabetes (32.7 % vs 25.4 %, $p < 0.001$), chronic coronary syndrome or multivessel disease. ISR PCI concerned drug eluting stents (DES) ISR in 48.8 % of cases. Patients with ISR lesions were more frequently treated with DES than drug eluting balloon or balloon angioplasty (74.2 %, 11.6 % and 12.9 %, respectively). Intravascular imaging was rarely used. At 1 year, patients with ISR had higher target lesion revascularization rates (4.3 % vs. 1.6 %; HR 2.24 [1.64–3.06]; $p < 0.001$).

Conclusions: In a large all-comers registry, ISR PCI was not infrequent and associated with worse prognosis than non-ISR PCI. Further studies and technical improvements are warranted to improve the outcomes of ISR PCI.

1. Introduction

Coronary heart disease (CHD) is a leading cause of death worldwide. Percutaneous coronary intervention (PCI) is established as the reference revascularization procedure. Plain old balloon angioplasty (POBA) was initially associated with complications such as elastic vessel recoil, constrictive remodeling and coronary

Abbreviations: BMS, bare metal stent; DAPT, dual antiplatelet therapy; DEB, drug eluting balloon; DES, drug eluting stent; ISR, in-stent restenosis; MACE, major adverse cardiac event; NSTEMI, non ST-segment elevation myocardial infarction; PCI, percutaneous coronary intervention; POBA, plain old balloon angioplasty; STEMI, ST-segment elevation myocardial infarction; TLR, target lesion revascularization.

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dissection. Subsequent developments of bare metal stents (BMS) and 1st and 2nd generation drug eluting stents (DES) led to a reduction in the risk of complications [1].

Despite the evolution of stent technology, in-stent restenosis (ISR) remains a clinical problem. Angiographic ISR is defined as luminal obstruction >50 % in the vessel segment within the area of the stent and/or within 5 mm proximal or distal to the stent [2]. The clinical incidence of BMS-ISR is around 30 % at 6 months, and rates of target lesion revascularization (TLR) for DES-ISR is around 7 % at 4 years [3,4]. Given the large number of PCI with stent implantation procedures performed in routine clinical practice, recurrence of CHD due to ISR is a highly relevant issue. Optimization of ISR management has been evaluated in randomized trials [5]. Current international guidelines suggest, when technically feasible, a new revascularization by PCI, with the use of everolimus-eluting stent or drug eluting balloon (DEB) as first line treatment in order to avoid the implantation of a new stent layer [6–8]. Both DES and DEB strategies have been associated with better outcomes than POBA in PCI of ISR (ISR-PCI) [5]. In case of failure or recurrence, coronary artery bypass surgery (CABG) should be considered. Intracoronary imaging may be of interest to understand the mechanism of restenosis and guide treatment [9].

However, little is known about the management of patients with ISR-PCI in daily clinical practice. The objective of this study was to describe the clinical presentation, patients' characteristics and management, as well as clinical outcomes of patients who underwent ISR angioplasty, by analyzing clinical, angiographic and PCI data from the prospective France-PCI registry.

2. Materials and methods

2.1. France PCI Registry

France PCI is an all-comers registry of all patients undergoing coronary angiography and/or PCI at French interventional cardiology centres since January 1st, 2014. The current study comprised data from six interventional cardiology centres in two regions in France: Auvergne Rhône Alpes and Centre Val de Loire. Prospective data are recorded on electronic files according to the standardized procedure of the hospitals (CardioReport, CVX medical, Croissy-Beaubourg, France; Hemolia, Paris, France; Atoutcoeur, Altilog, Caen, France). Epidemiological and procedural data are systematically collected. Coronary lesion characteristics such as artery involved, diameter, length, tortuosity, ISR or de novo lesion are recorded. Treatment strategies are also registered, including stent implantation, use of intracoronary imaging, or rotational atherectomy. Patients are followed-up by a clinical research assistant at each site with continuous data monitoring. One-year outcome is assessed for each patient who underwent PCI, by telephone call and/or medical record review. All data are anonymized and transferred daily to the France PCI national database. Written informed consent is obtained from all patients. The registry has been described in previous publications [10]. The registry is conducted according to contemporary clinical practice guidelines and French regulations (Advisory Committee on Information Processing in Material Research in the Field of Health no.13.245). The French Persons Protection Committee (IRB00003888) approved the study protocol (no. 15-231). Data collection and storage were approved by the French National Commission for Data Protection

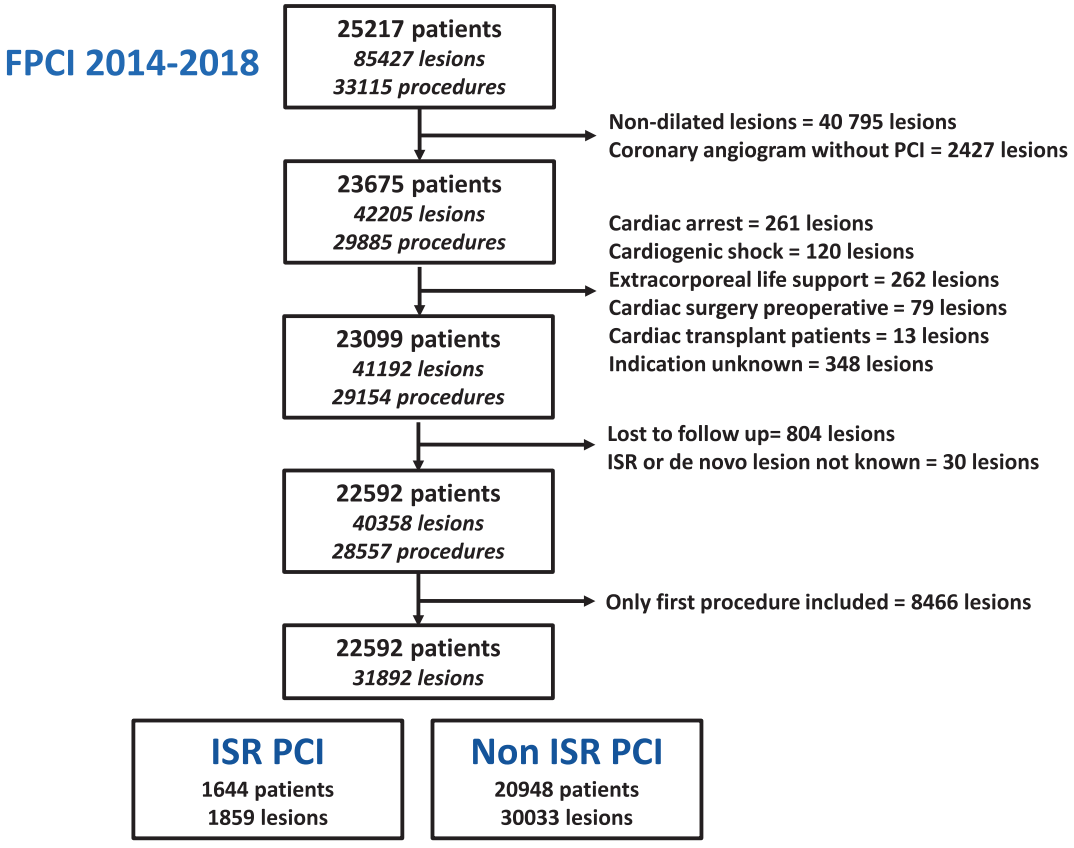

Fig. 1. Study flow chart.
Figure legend: France PCI Registry enrolled every patient undergoing angiography and/or percutaneous coronary intervention in a cath lab included in the registry. This study analyses data of every lesion registered, from 2014–01 to 2018–12.
Abbreviations: FPCI: France PCI; ISR: in-stent restenosis, PCI: percutaneous coronary intervention.

and Liberties (no. 2014-073). The France PCI study is registered on clinicaltrial.gov (NCT02778724).

2.2. Study population

All procedures with at least one angiographically significant identified lesion were included in the study. Non-dilated lesions, or procedures without PCI, were excluded. Patients with hemodynamic instability or in an emergency situation were excluded. In case of planned cardiac surgery, e.g. valve surgery, patients were also excluded as this may have affected the revascularization strategy. For patients with more than one procedure in the registry, only the index procedure was analyzed.

2.3. Primary objective

The primary objective was to describe the epidemiology, treatment strategies, and outcome of patients treated with ISR-PCI.

2.4. Definitions

Patients were included in the ISR-PCI group if they had at least one ISR lesion treated by PCI, whether or not they had undergone PCI for non-ISR lesions. Angiographic ISR was defined as luminal narrowing >50 % in the vessel segment within the area of the stent and/or within 5 mm proximal or distal to the stent.

Outcomes of interest were defined according to international recommendations: mortality, myocardial infarction (MI), TLR, bleeding complications according to the Bleeding Academic Research Consortium (BARC) classification, stroke [11]. TLR was defined as the occurrence of thrombosis or restenosis on the initially treated target lesion. Major adverse cardiovascular event (MACE) was defined as the occurrence of death, myocardial infarction, or TLR.

2.5. Statistical analysis

Categorical data are presented as numbers and percentages, and continuous variables as mean and standard-deviation. The assumption of normality was assessed by Shapiro-Wilks test. Comparisons of non-ISR PCI and ISR PCI groups used the chi-square or Fisher exact tests for categorical variables, and Student *t*-test or Mann-Whitney *U* test when t-test conditions were not fulfilled for continuous variables. Homoscedasticity was analyzed by the Fisher-Snedecor test for quantitative variables. For comparisons of correlated data (several measures for each patient: angiographic lesions findings, treatment strategies for lesions…) between non-ISR PCI and ISR PCI groups, random-effect models were used to model between and within patient variability as random-effect.

Estimates of censored data (MACE, all cause death, myocardial infarction, TLR, hemorrhage ≥ BARC3, stroke) were constructed using the Kaplan-Meier method. The Cox proportional hazards regression model was used to compare non-ISR PCI vs ISR PCI taking into account possible confounder covariates determined according to univariate results, and clinical features. The testing and parameter estimation used a statistical model which depends on the variables included in the model; it is therefore crucial for confounding adjustment that known clinically significant variables are included in the regression model. The following clinical variables were included in the multivariate analyses: sex, age, diabetes, past myocardial infarction, chronic kidney disease, clinical presentation, angiographic success, post PCI TIMI flow, lesion length, lesion diameter, PCI technique, DAPT duration, arterial access, thrombus aspiration. Particular attention was paid to multicollinearity and to the rules-of-thumb suggested for determining the minimum number of subjects required to conduct multiple regression analysis [12–14]. The proportional-hazard hypothesis was verified using Schoenfeld's test and plotting residuals. Results are shown as hazard-ratio (HR) and 95 % confidence interval.

A sensitivity analysis was carried out to evaluate the possible impact of missing data on one year clinical outcomes. A representativeness analysis of the study sample with missing data vs. the complete cases in the multivariate analysis was conducted in order to confirm that missing data were random. Multivariate analyses were also carried

Table 1
Baseline characteristics.

	Overall	Non-ISR PCI	ISR PCI	p
	N = 22,592 (%)	*N* = 20,948 (%)	*N* = 1644 (%)	
Demographic data				
Age (yrs)	67.8 ± 12	67.8 ± 12	68.5 ± 11	<0.001
Male	16,928 (74.9)	15,564 (74.3)	1364 (82.9)	<0.001
BMI (kg/m^2)	27.5 ± 4.9	27.4 ± 4.9	27.6 ± 4.4	0.013
CV risk factors				
Diabetes mellitus	5830 (25.9)	5295 (25.4)	535 (32.7)	<0.001
Current/past smoking	10,877 (48.3)	9977 (47.7)	900 (54.9)	<0.001
Hypertension	12,828 (57)	11,828 (56.7)	1000 (61.1)	0.001
Dyslipidemia	11,206 (50.5)	10,055 (48.8)	1151 (71)	<0.001
Chronic kidney disease	394 (1.7)	359 (1.7)	35 (2.1)	0.021
Familial history	5296 (24)	4856 (23.7)	440 (27)	0.001
Medical history				
Previous CABG	1317 (5.8)	1089 (5.2)	228 (13.9)	<0.001
Previous myocardial infarction	2756 (12.2)	2084 (10)	672 (41)	<0.001
Previous stroke[a]	967 (4.3)	899 (4.29)	68 (4.1)	0.767
Previous PAD	2275 (10.1)	2029 (9.7)	246 (15)	<0.001
Clinical presentation				
Symptoms				
Asymptomatic	2468 (11.4)	2211 (11)	257 (15.8)	<0.001
Heart failure	1100 (5.1)	1034 (5.1)	66 (4.1)	
Stable angina	6569 (30.2)	5991 (29.8)	578 (35.6)	
Unstable angina	2685 (12.4)	2403 (11.9)	282 (17.3)	
NSTEMI	4825 (22.2)	4545 (22.6)	280 (17.2)	
STEMI	4079 (18.8)	3917 (19.5)	162 (9.97)	
Proven ischemia[b]	18,516 (82)	17,298 (82.6)	1218 (74.1)	<0.001
Anatomical severity				
Multivessel disease				
1-Vessel disease	8590 (38)	8122 (38.8)	468 (28.5)	<0.001
2-Vessel disease	8054 (35.7)	7446 (35.6)	608 (37)	
3-Vessel disease	5839 (25.9)	5274 (25.2)	565 (34.4)	
Left main disease alone	96 (0.4)	94 (0.4)	2 (0.1)	
Technical aspect				
Radial/ulnar access	20,906 (92.6)	19,473 (93)	1433 (87.3)	<0.001
Sheat size > 6F	644 (2.8)	596 (2.8)	48 (2.9)	0.859
Contrast volume, cc	152.1 ± 64	152.3 ± 64	149.7 ± 63	0.112
Fluoroscopy time, mn	11.9 ± 11	11.7 ± 10.8	13.6 ± 13	<0.001
Number of vessel PCI				
1-Vessel PCI	19,260 (85.3)	17,925 (85.7)	1335 (81.2)	<0.001
2-Vessel PCI	2952 (13.1)	2675 (12.8)	277 (16.8)	
3-Vessel PCI	358 (1.6)	325 (1.6)	32 (1.9)	
Medical treatment				
Aspirin	21,866 (97.9)	20,269 (97.9)	1597 (97.9)	0.814
AntiP2Y12				
None	295 (1.3)	275 (1.3)	20 (1.2)	<0.001
Clopidogrel	12,424 (55.6)	11,346 (54.8)	1078 (66)	
Ticagrelor	8894 (39.8)	8437 (40.7)	457 (28)	
Prasugrel	698 (3.1)	627 (3)	71 (4.3)	
Anticoagulant	2567 (11.5)	2379 (11.5)	188 (11.5)	0.976
DAPT duration				
0–6 months	4008 (18.8)	3665 (18.5)	343 (22.1)	<0.001
6–12 months	7098 (33.2)	6761 (34.1)	337 (21.8)	
>12 months	10,261 (48)	9392 (47.4)	869 (56.1)	

Data are expressed as absolute number/available data (%) and mean ± SD.
Abbreviations: BMI: body mass index; CABG: coronary artery bypass graft; DAPT: dual antiplatelet therapy; ISR: in-stent restenosis; NSTEMI: non ST-segment elevation myocardial infarction; STEMI: segment elevation myocardial infarction; PAD: peripheral artery disease; PCI: percutaneous coronary intervention; yrs: years.
[a] Transient ischemic attack or stroke.
[b] Confirmed on stress echocardiography, cardiac scintigraphy or FFR.

out excluding clinically relevant covariates for which too many data were missing. Accordingly and as only 5 % to 10 % missing data were observed, there was no imputation of missing data.

All statistical analyses were performed with Stata statistical software (version 15, StataCorp, College Station, TX). A p-value of <0.05 was considered significant. BP and BD had full access to all the data of the study and take responsibility for its integrity and the data analysis.

3. Results

3.1. Population

Between January 1st 2014 and December 31th 2018, 85,427 lesions were recorded, representing 25,217 patients and 33,115 procedures. A total of 22,592 patients with 31,892 treated lesions were included in the analysis, of whom 1644 (7.3 %) underwent ISR PCI (Fig. 1). 496 patients (2 %) were lost to follow-up and were excluded from the analysis.

Patients with ISR PCI were slightly older (68.5 vs. 67.8; $p < 0.001$) and mainly male (Table 1). Patients were more likely to have more risk factors, especially diabetes, adverse events such as myocardial infarction or previous CABG. The majority of patients with ISR had chronic coronary syndromes (55.5 %). Proven ischemia (confirmed on stress echocardiography, cardiac scintigraphy or FFR) was less frequent in non-ISR PCI compared to ISR patients (74.1 % vs 82.6 %, respectively; $p < 0.001$).

Procedures were more complex for ISR patients, with multivessel disease, less use of radial access, longer fluoroscopy time and additional angioplasty sites. There was a higher rate of clopidogrel use in ISR patients, and the duration of dual antiplatelet therapy was longer than with non-ISR procedures.

3.2. Lesion characteristics

Right coronary artery lesions were more frequent in ISR-PCI procedures (39.5 % vs. 32.1 %; $p < 0.001$). The majority of ISR lesions were intra-DES restenosis (48.8 %; Fig. 2). Lesions undergoing PCI for ISR were slightly more likely to have vessel diameter < 2.5 mm, lesion length > 2 0 mm and stenosis < 70 % (Table 2).

3.3. Treatment strategies

PCI management strategies are summarized in Table 3 and Fig. 2. Patients with ISR PCI were more likely to be treated with POBA (12.9 % vs 4.6 %; $p < 0.001$) and DEB (11.6 % vs 0.1 %; p < 0.001) compared to patients with non-ISR PCI. DES implantation was the main treatment option (74.2 %). When implanted, the cumulative stent length was greater in ISR PCI procedures. Intracoronary imaging was more frequently used for ISR PCI but remained rare (1.9 % vs 0.7 %; $p < 0.001$).

3.4. Clinical outcomes

At 1 year, there were no significant differences between ISR PCI and non-ISR PCI patients in terms of overall mortality rate (5.7 % vs 4.9 %; hazard ratio [HR] 1.15; 95 % confidence interval [CI] 0.93–1.42; $p =$

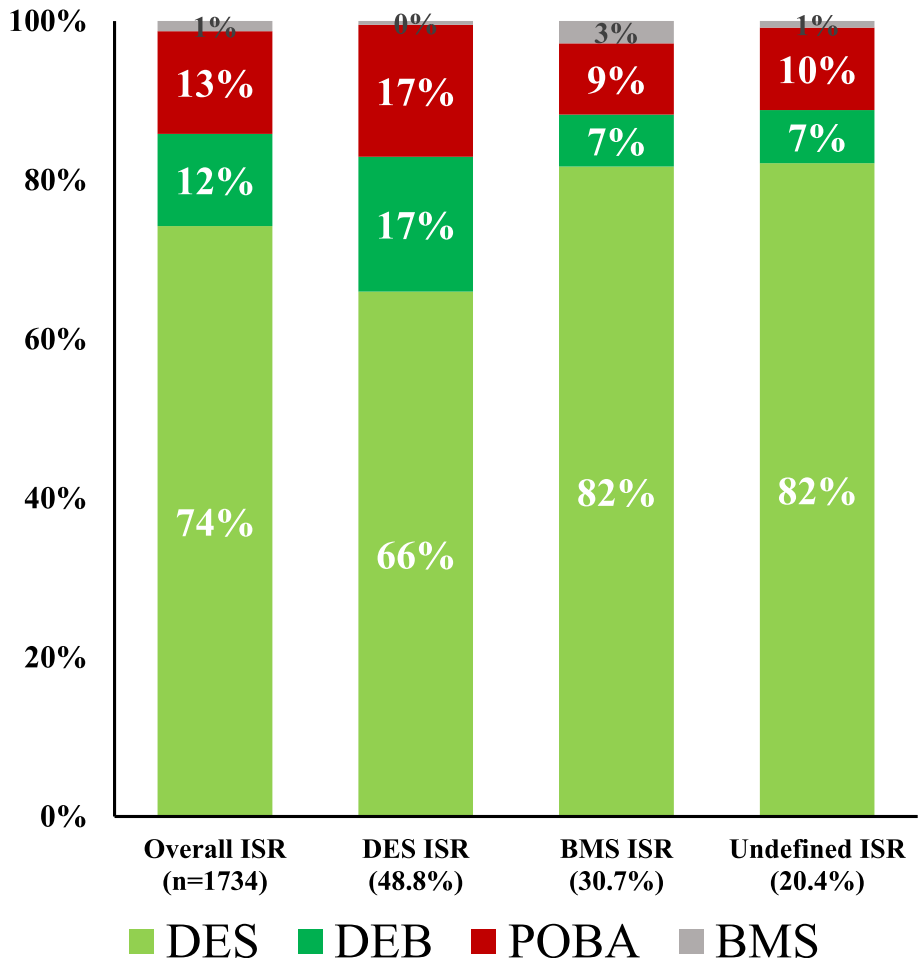

Fig. 2. Treatment modalities of ISR lesions based on stent type.
Figure legend: Histograms show modality of PCI according to stent type of in-stent restenosis.
Abbreviations: BMS: bare metal stent; DEB: drug eluting balloon; DES: drug eluting stent; POBA: plain old balloon angioplasty; ISR: in-stent restenosis.

Table 2
Angiographic lesion findings.

	Overall		Non-ISR PCI		ISR PCI		p
	N = 31,892 (%)		N = 30,033 (%)		N = 1859 (%)		
Target coronary vessel							
Left main	956	(3)	921	(3.1)	35	(1.9)	<0.001
LAD	12,042	(37.8)	11,389	(37.9)	653	(35.1)	
Circumflex	4251	(13.3)	4027	(13.4)	224	(12)	
Right coronary artery	10,372	(32.5)	9638	(32.1)	734	(39.5)	
Secondary branches	4050	(12.7)	3879	(12.9)	171	(9.2)	
Artery graft	37	(0.12)	30	(0.1)	7	(0.4)	
Venous graft	184	(0.58)	149	(0.5)	35	(1.88)	
Lesion length							
<10 mm	5719	(18)	5462	(18.2)	257	(13.9)	<0.001
10–20 mm	18,723	(58.8)	17,655	(58.8)	1068	(57.9)	
>20 mm	7399	(23.2)	6881	(22.9)	518	(28.1)	
Lesion diameter							
<2,5 mm	15,121	(47.5)	14,146	(47.1)	975	(52.6)	<0.001
≥2,5 mm	16,741	(52.5)	15,863	(52.9)	878	(47.4)	
% lesion stenosis							
<70 %	7875	(24.7)	7299	(24.3)	576	(31)	<0.001
≥70 %	24,017	(75.3)	22,734	(75.7)	1283	(69)	
TIMI flow							
≤2	6979	(21.9)	6545	(21.8)	434	(23.5)	0.487
3	24,870	(78.1)	23,454	(78.2)	1416	(76.5)	
Stent type							
DES	–	–	–	–	907	(48.8)	–
BMS	–	–	–	–	571	(30.7)	–
BVS	–	–	–	–	2	(0.1)	–
Unknown	–	–	–	–	379	(20.4)	–

Data are expressed as absolute number/available data (%) and mean ± SD.
Abbreviations: BMS: Bare metal stent; BVS: Bioabsorbable vascular scaffold; DES: Drug eluting stent; ISR: In-stent restenosis; LAD: Left anterior descending; PCI: percutaneous coronary intervention; TIMI: thrombolysis in myocardial infarction flow.

0.190). However, patients in the ISR PCI group had a poorer prognosis with a significantly higher risk of TLR (4.3 % vs 1.6 %; HR 2.61; 95%CI 2.01–3.38; $p < 0.001$) and MI (2.3 % vs 1.3 %; HR 1.83; 95 % CI 1.30–2.58; $p = 0.001$) (Fig. 3). No significant differences in rates of hemorrhage and stroke were observed. The results were consistent after adjustment for conventional confounders (Table 4).

Among patients undergoing ISR PCI, those treated with DES implantation had a better prognosis in terms of TLR (3.3 %) compared to POBA (8 %), DEB (8.3 %), or BMS (15.8 %) ($p < 0.001$). No significant differences between POBA, DEB and BMS were found (Fig. 4).

Table 3
Treatment strategies for lesions.

	Overall		Non-ISR PCI		ISR PCI		p
	N = 31,892 (%)		N = 30,033 (%)		N = 1859 (%)		
POBA alone	1548	(5.1)	1324	(4.6)	224	(12.9)	<0.001
DEB	237	(0.8)	69	(0.1)	201	(11.6)	
DES	26,895	(88.2)	25,608	(89.1)	1287	(74.2)	
BMS	1809	(5.9)	1787	(6.2)	22	(1.3)	
Stent count	1.85 ± 1.1		1.87 ± 1.1		1.53 ± 1.2		<0.001
Stent length. mm	21.5 ± 11.6		21.4 ± 11.5		24.6 ± 12.7		<0.001
Additional techniques							
Intravascular imaging	244	(0.8)	208	(0.7)	36	(1.9)	<0.001
FFR	746	(2.3)	688	(2.3)	58	(3.1)	0.028
Thrombus aspiration	1920	(6)	1827	(6.1)	93	(5)	0.059
RA	389	(1.2)	377	(1.3)	12	(0.6)	0.029
Angiographic success							
Yes	30,670	(96.2)	28,901	(96.3)	1769	(95.3)	0.076
No or intermediate	1.206	(3.8)	1119	(3.7)	87	(4.7)	
Post PCI TIMI flow							
≤2	1001	(3.1)	944	(3.1)	57	(3.1)	0.715
3	30,842	(96.9)	29,043	(96.8)	1799	(96.9)	

Data are expressed as absolute number/available data (%) and mean ± SD.
Abbreviations: BMS: Bare metal stent; BVS: Bioabsorbable vascular scaffold; DEB: Drug eluting balloon; DES: Drug eluting stent; FFR: Fractional flow reserve; ISR: In-stent restenosis; LAD: Left anterior descending; PCI: percutaneous coronary intervention; POBA: Plain old balloon angioplasty; RA: Rotational atherectomy; TIMI: thrombolysis in myocardial infarction flow.

4. Discussion

The present study is the first work describing the management of ISR PCI in France. The main results can be summarized as follows (Graphical abstract): (1) ISR PCI accounted for 7.3 % of all PCI procedures in a contemporary routine clinical practice setting and comprised DES ISR in at least 48.8 % of cases; (2) ISR PCI patients were more likely to present with cardiovascular risk factors, comorbidities and angiographically complex lesions than non-ISR PCI patients; (3) approximately 10–20 % of ISR were treated with POBA although this is not recommended in European guidelines on myocardial revascularization [8]; (4) patients with ISR PCI had a worse 1-year prognosis than patients with non-ISR PCI with higher rates of TLR and MI.

PCI with stenting has overcome most of the limitations of POBA. However, the rate of long-term complications after PCI procedures including ISR and thrombosis remains relevant. In the United States, a retrospective analysis of a national PCI registry reported a 10 % prevalence of ISR PCI, similar to our findings [15]. As in our study, cardiovascular risk factors and comorbidities such as diabetes were associated with need for ISR PCI [15]. Most ISR PCI in this study occurred after DES PCI, which can be attributed to DES being the more implanted type of stent, in accordance with guidelines' recommendations of DES preferred over BMS in all clinical situations and the equal strength of recommendations for DES and DEB for treatment of DES- or BMS-ISR (recommendation class Ia [8]). Meta-analyses of randomized studies showed a benefit in terms of TLR with first generation DES (sirolimus-eluting stent or paclitaxel-eluting stent) compared to BMS, yet there were concerns about late thrombosis [16–18]. Second generation DES (everolimus-eluting stent) maintained the positive outcomes with first-generation DES in term of TLR, and reduced the risk of late and very late thrombosis to a level similar to BMS [19,20].

Our analysis indicates that the majority of guidelines are followed in French clinical practice, but the high use of POBA (12.9 % of ISR PCI), particularly in the DES-ISR group (16.6 %) is noteworthy. Furthermore, despite a similar immediate success rate, the 1-year rate of TLR after ISR PCI remains generally higher than after non-ISR PCI. The TLR survival curves start to separate after 2 months. A higher rate of TLR at 1 year (8–11 %) was observed in randomized studies on ISR angioplasty [5]. Of note, ISR PCI involved smaller vessels and longer lesions than non-ISR PCI, which were associated with increased TLR when using first-generation DES [21]. Besides, a recent meta-analysis demonstrated that implantation of a new-generation DES to treat DES ISR is more effective than the use of a DEB, reducing 3-year TLR, without difference in mortality [5]. This may be a way to improve the outcome of these patients.

Both intravascular ultrasound and optical coherence tomography (OCT) imaging techniques are recommended in the European guidelines for the management of ISR (class IIa recommendation [8]). Intracoronary imaging may allow an individualized treatment of ISR and there are indications that its use improves long-term patient outcomes [7,22]. In particular, OCT can provide details on the characteristics of the tissue covering stent struts, revealing the nature of restenosis, neoatherosclerosis or fibrous hyperplasia (according to the inhomogeneity of the signal) and guide choice of treatment (DES or DEB) [22]. ISR may also be caused by mechanical issues such as malapposition, underexpansion, or stent fracture. This is often not apparent on coronary angiography but revealed by OCT. Treatment of stent underexpansion requires the use of noncompliant balloons inflated at high pressure,

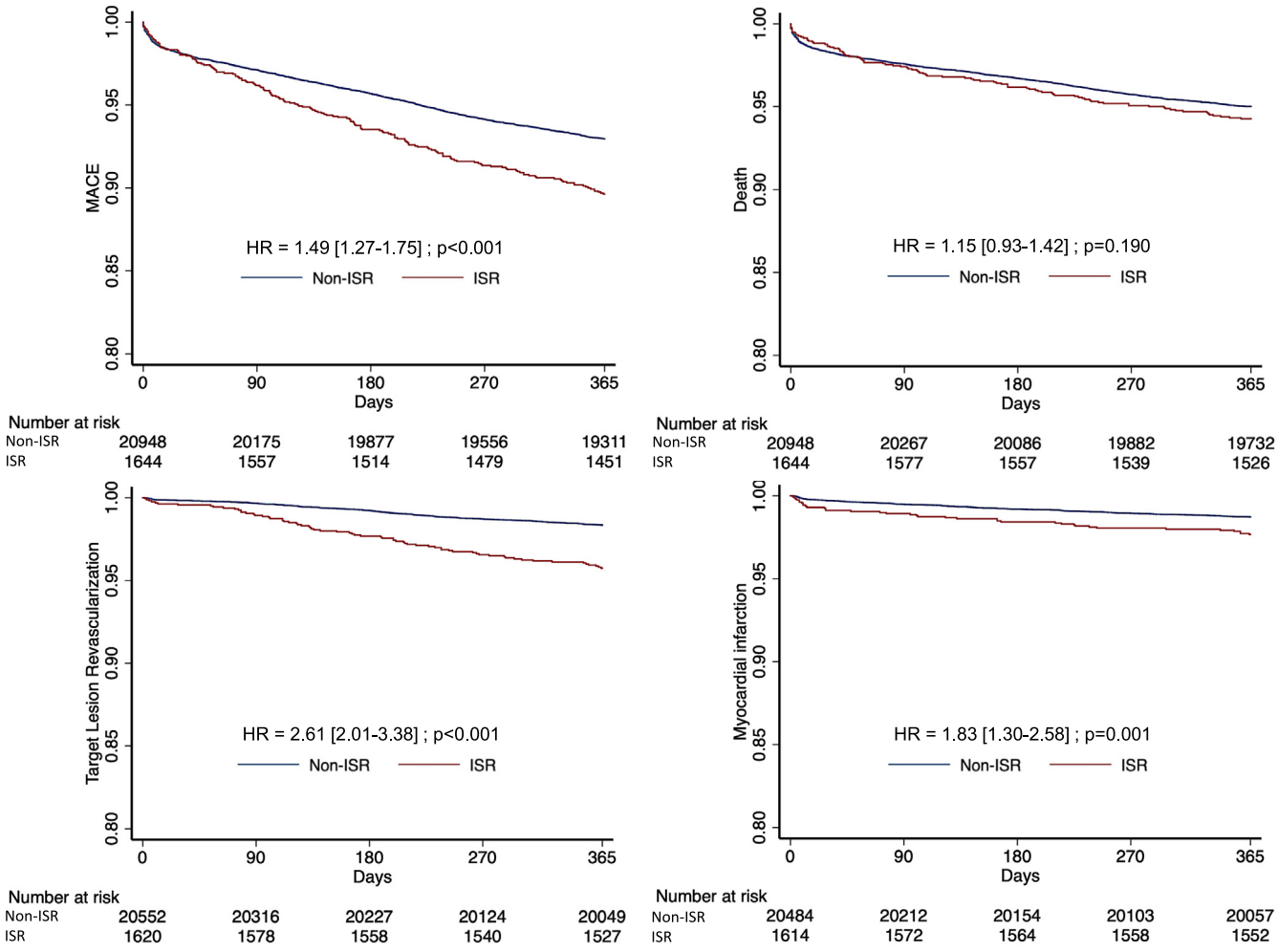

Fig. 3. Clinical outcomes at 1-year follow-up according to ISR and non-ISR PCI.
Figure legend: Kaplan-Meier curves showing occurrence of MACE, death, target lesion revascularization and myocardial infarction after PCI according to ISR and non-ISR PCI group.
Abbreviations: HR: Hazard ratio; ISR: In-stent restenosis; MACE: Major adverse cardiac event.

Table 4
1 year clinical outcomes according to the presence of ISR lesions.

ISR patients vs non ISR patients	Univariate		Multivariate	
	HR [95%CI] p-value		HR [95%CI], p-value	
MACE	1.49 [1.27–1.75]	<0.001	1.39 [1.15–1.68]	0.001[b]
All cause death	1.15 [0.93–1.42]	0.190	1.08 [0.86–1.35]	0.490[c]
Myocardial Infarction	1.83 [1.30–2.58]	0.001	1.41 [0.94–2.10]	0.093[d]
TLR	2.61 [2.01–3.38]	<0.001	2.24 [1.64–3.06]	<0.001[e]
Stent thrombosis[a]	1.74 [1.03–2.93]	0.038	1.29 [0.70–2.37]	0.413[e]
Hemorrhage ≥ BARC3	1.09 [0.78–1.54]	0.600	0.94 [0.59–1.51]	0.811[f]
Stroke	1.09 [0.61–1.98]	0.755	1.03 [0.46–2.30]	0.938[g]

Abbreviations: BARC: Bleeding Academic Research Consortium; DAPT: dual antiplatelet therapy; MACE: Major adverse cardiac event; PCI: percutaneous coronary intervention; TIMI: thrombolysis in myocardial infarction flow; TLR: Target lesion revascularization.

[a] Definite, probable or possible.

[b] Model included sex, age, diabetes, past myocardial infarction, chronic kidney disease, clinical presentation, angiographic success, post PCI TIMI flow, lesion length, lesion diameter, PCI technique.

[c] Model included sex, age, diabetes, past myocardial infarction, chronic kidney disease, clinical presentation, angiographic success, post PCI TIMI flow, lesion length, lesion diameter.

[d] Model included sex, age, diabetes, past myocardial infarction, chronic kidney disease, clinical presentation, angiographic success, post PCI TIMI flow, lesion length, lesion diameter, PCI technique.

[e] Model included sex, age, diabetes, past myocardial infarction, chronic kidney disease, clinical presentation, angiographic success, post PCI TIMI flow, lesion length, lesion diameter, PCI technique.

[f] Model included sex, age, diabetes, past myocardial infarction, chronic kidney disease, clinical presentation, angiographic success, post PCI TIMI flow, lesion length, lesion diameter, PCI technique, DAPT duration.

[g] Model included sex, age, diabetes, past myocardial infarction, chronic kidney disease, clinical presentation, angiographic success, post PCI TIMI flow, lesion length, lesion diameter, PCI technique, DAPT duration, arterial access, thrombus aspiration.

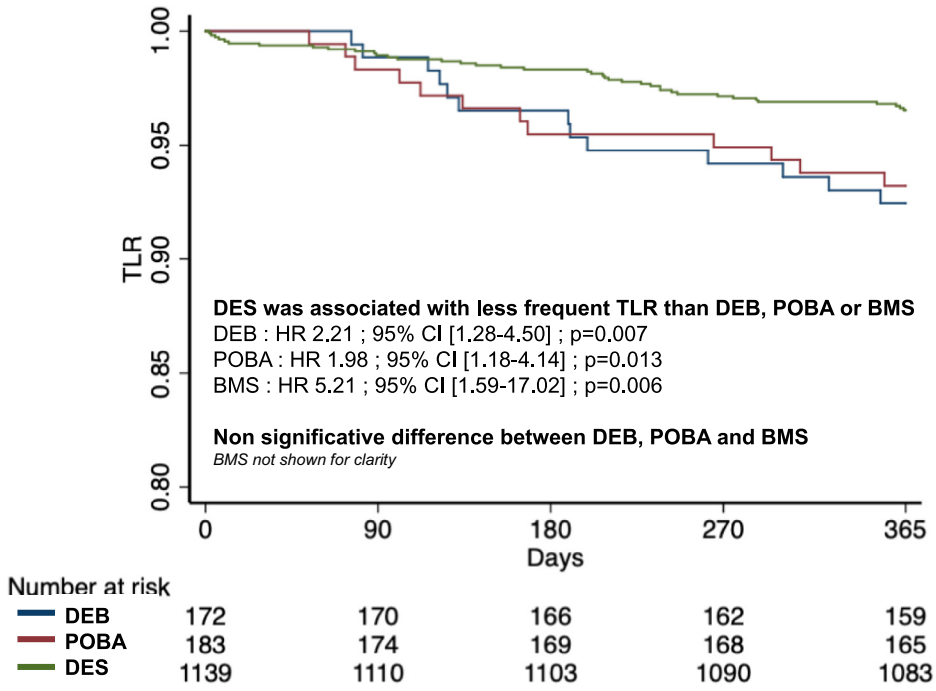

Fig. 4. TLR incidence according to treatment strategy in ISR PCI patients.
Figure legend: Kaplan-Meier curves showing occurrence of target lesion revascularization after PCI in ISR PCI group according to treatment strategy.
Abbreviations: BMS: bare metal stent; CI: confidence interval; DEB: drug eluting balloon; DES: drug eluting stent; PCI: percutaneous coronary intervention; POBA: plain old balloon angioplasty; HR: Hazard ratio; ISR: In-stent restenosis; TLR: Target lesion revascularization.

rotational or orbital atherectomy, laser or intravascular lithotripsy [23]. Repeat stent implantation within an underdeployed stent is not an appropriate treatment for underexpansion [24]. The low rate of use of imaging may be explained by reimbursement issues. In particular, imaging by IVUS or OCT adds major costs to the procedure and are not reimbursed in France.

Several limitations in this report should be considered. The numbers of recurrent restenosis within the same stent, stent layers, and restenosis timing are not known. However, by limiting the analysis to the first recorded procedure for each patient, we believe to have assessed and interpreted the first episodes of restenosis. The registry includes no data on the cause of restenosis, whether mechanical causes (underexpansion, malapposition, or stent fracture) or the presence of neoatherosclerosis. If identified, these abnormalities might have changed the treatment option chosen. Missing data such as treatment modality or unknown outcome, may have affected some analyses. This is an issue inherent to most registry analyses. We performed sensitivity and representativeness analyses to evaluate the possible impact of missing data and found no impact on the main conclusions drawn (Supplementary Tables 1 and 2). Thus we believe that the results reflect the clinical reality described in this work. Moreover, data about ISR patients treated with CABG or medical treatment without revascularization were not captured in the registry. Finally, we performed only an exploratory analysis of lesion-related predictors of TLR within the ISR group, since the evaluation of predictors of target lesion failure has already been reported in randomized studies (e.g. DES or DEB use).

5. Conclusions

ISR PCI represented 7.3 % of PCI in a French all-comers registry and was associated with a worse prognosis than non-ISR PCI. Further, prospective studies are needed to improve the management of ISR PCI patients.

CRediT authorship contribution statement

Benjamin Duband: Conceptualization, Data curation, Formal analysis, Methodology, Validation, Visualization, Writing – original draft, Writing – review & editing. **Géraud Souteyrand:** Conceptualization, Data curation, Investigation, Methodology, Project administration, Supervision, Validation, Visualization, Writing – review & editing. **Jean Michel Clerc:** Data curation, Investigation, Methodology, Validation, Visualization, Writing – review & editing. **Stephan Chassaing:** Data curation, Investigation, Methodology, Validation, Visualization, Writing – review & editing. **Olivier Fichaux:** Data curation, Investigation, Methodology, Validation, Visualization, Writing – review & editing. **Pierre Marcollet:** Data curation, Investigation, Methodology, Validation, Visualization, Writing – review & editing. **Ronan Deballon:** Data curation, Investigation, Methodology, Validation, Visualization, Writing – review & editing. **Laurent Roussel:** Data curation, Investigation, Methodology, Validation, Visualization, Writing – review & editing. **Bruno Pereira:** Conceptualization, Formal analysis, Investigation, Methodology, Project administration, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. **Jean-Philippe Collet:** Data curation, Investigation, Methodology, Validation, Visualization, Writing – review & editing. **Philippe Commeau:** Data curation, Investigation, Methodology, Validation, Visualization, Writing – review & editing. **Guillaume Cayla:** Data curation, Investigation, Methodology, Validation, Visualization, Writing – review & editing. **Rene Koning:** Data curation, Investigation, Methodology, Validation, Visualization, Writing – review & editing. **Pascal Motreff:** Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. **Hakim Benamer:** Funding acquisition, Data curation, Investigation, Methodology, Validation, Visualization, Writing – review & editing. **Gregoire Rangé:** Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Supervision, Validation, Visualization, Writing – review & editing.

Declaration of competing interest

GS and PM declare consulting fees for Terumo and Abbott. BD declares lecture fees for Organon and Amgen. JPC declares research funding or fees from Astrazeneca, Boston Scientific, Bristol-Myers Squibb, Cor2ed, Lead-Up, Medtronic, WebMD. GC declare research funding or fees from Abbot, Amgen, Astrazeneca, Bayer, Biotronik, Bristol-Myers Squibb, Medtronic, Microport, Pfizer, Sanofi-Aventis. PC declares consulting fees for Terumo, Bsci, Abbott, Edwards.

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Ethical aspects

- Advisory Committee on Information Processing in Material Research in the Field of Health (no. 13.245)
- French Persons Protection Committee (IRB00003888): study protocol (15-231)
- French National Commission for Data Protection and Liberties (no. 2014-073)

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.carrev.2023.02.006.

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