Characterizing the spectrum of in-stent restenosis: Implications for contemporary treatment

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BACKGROUND: Reports addressing treatment of in-stent restenosis (ISR) are principally derived from clinical trials.

OBJECTIVES: To characterize the spectrum of ISR in an unselected population, and to explore clinical and angiographic factors determining management.

METHODS: During a prespecified six-month period before the introduction of drug-eluting stents, consecutive cases of ISR that were identified during clinically driven cardiac catheterization at five hospitals offering all approved treatment modalities for ISR were prospectively registered.

RESULTS: ISR was identified in 363 patients; 301 (84%) had one ISR lesion and 62 (16%) had multiple lesions. Unstable clinical presentations accounted for 51%, including 15% with ST-elevation myocardial infarction. The median interval (25th, 75th percentiles) from stent insertion to angiographic diagnosis of ISR was eight months (Q1,Q3: 4,15), with a median stented length of 18 mm (Q1,Q3: 15,28). The majority of lesions (60%) displayed a diffuse ISR pattern (Mehran types 2 and 3). ISR type was independent of time to re-presentation, diabetes, arterial territory and total stent length. Treatment included percutaneous coronary intervention (PCI) alone (n=139 [38%]), PCI with brachytherapy (n=105 [29%]), medical therapy (n=60 [17%]) and coronary artery bypass graft surgery (n=59 [16%]). Medical therapy was associated with small vessel size and recurrent ISR, and coronary artery bypass graft surgery was associated with multiple lesions, as well as diffuse, occlusive and recurrent ISR. For patients treated percutaneously, PCI treatment alone was more common for focal restenosis and after ST-elevation myocardial infarction, and brachytherapy was the more common treatment for diffuse and recurrent ISR, and stable angina.

CONCLUSIONS: These data provide a benchmark description of the spectrum of ISR with which the impact of drug-eluting stents may be compared and better understood.

Key Words: *Coronary disease; Registries; Restenosis; Revascularization; Stents*

By the late 1990s, coronary stent use had been adopted as the standard of care for percutaneous coronary intervention (PCI) procedures (1-5). Routine stenting reduced the incidence of angiographic and clinical restenosis, compared with stand-alone balloon angioplasty, by establishing a larger initial lumen, and preventing early recoil and subsequent negative remodelling (6-9). However, restenosis within the stented seg-

La caractérisation du spectre des resténoses d'endoprothèse : Les répercussions sur le traitement contemporain

HISTORIQUE : Les comptes rendus portant sur le traitement des resténoses d'endoprothèse (REP) sont surtout dérivés d'essais cliniques.

OBJECTIFS : Caractériser le spectre de REP dans une population non sélectionnée et explorer les facteurs cliniques et angiographiques en déterminant la prise en charge.

MÉTHODOLOGIE : Pendant une période déjà établie de six mois avant l'installation d'endoprothèses à élution de médicament, des cas consécutifs de REP repérés pendant un cathétérisme cardiaque justifié cliniquement et exécuté dans cinq hôpitaux offrant toutes les modalités thérapeutiques approuvées de REP ont été consignés prospectivement.

RÉSULTATS : Trois cent soixante-trois patients ont souffert d'une REP. Trois cent un (84 %) avaient une lésion, et 62 (16 %), des lésions multiples. On a répertorié 51 % de présentations cliniques instables, y compris 15 % ayant un infarctus du myocarde avec surélévation du segment ST. L'intervalle médian (25^e et 75^e percentiles) entre l'installation de l'endoprothèse et le diagnostic angiographique de REP était de huit mois (Q1, Q3 : 4, 15), la longueur médiane de l'endoprothèse étant de 18 mm (Q1, Q3 : 15, 28). La majorité des lésions (60 %) comportaient un profil de REP diffus (Mehran de types 2 et 3). Le type de REP n'était pas corrélé avec le délai avant la nouvelle consultation, le diabète, le territoire artériel et la longueur totale de l'endoprothèse. Les traitements étaient une intervention coronaire percutanée (ICP) seule (n = 139 [38 %]), une ICP accompagnée d'une curiethérapie (n = 105 [29 %]), un traitement médical (n = 60 [17 %]) et un pontage aortocoronarien (n = 59 [16 %]). Le traitement médical s'associait à de petits vaisseaux et à une REP récurrente, et le pontage aortocoronarien, à des lésions multiples, ainsi qu'à une REP diffuse, occlusive et récurrente. Chez les patients traités par voie percutanée, l'ICP seule était plus courante en cas de resténose focale et après un infarctus du myocarde avec surélévation du segment ST, et la curiethérapie était le principal traitement d'une REP diffuse et récurrente, de même que d'une angine stable.

CONCLUSIONS : Ces données fournissent une description clinique du spectre de REP, grâce auquel il est possible de comparer et de mieux comprendre les répercussions des endoprothèses à élution de médicament.

ment (in-stent restenosis [ISR]) remained problematic. Patients with diabetes, long-target lesions and small-calibre reference vessels are at increased risk of developing ISR (10-12).

Reports that address treatment strategies for ISR are principally derived from populations undergoing protocol-specified angiography in clinical trials, or from patients enrolled in prospective trials testing specific ISR therapies. The resulting

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data are based on populations with selected characteristics and a limited extent of coronary artery disease (13-16). While these reports have described many important aspects of ISR, the spectrum of restenosis arising from unselected PCI populations has not been well characterized.

Drug-eluting stents (DES) have dramatically reduced the incidence of ISR in clinical trials that enrol limited patient and lesion subsets (17,18). Newer data obtained in more complex patients and lesions indicate that ISR, while proportionately reduced, remains a significant clinical challenge (19-28). Moreover, uncoated (bare metal) stents will be used in the foreseeable future in many centres worldwide in specific lesion subsets and to control PCI costs. Our aim, therefore, was to characterize the clinical spectrum and burden of ISR in an unselected pre-DES population, and to explore factors influencing therapeutic choices.

METHODS

Data acquisition

During a prespecified six-month period, from January 1, 2002, to June 30, 2002, all patients undergoing clinically driven cardiac catheterization were prospectively registered (approximately 5000 diagnostic coronary angiograms, including 3400 PCI procedures) in whom the angiographer identified ISR. Five high-volume centres in Canada participated. Participating centres were required to offer all approved treatment modalities for ISR, including on-site bypass surgery and intravascular brachytherapy. Sites recorded demographic, clinical, angiographic and laboratory characteristics of each ISR case, and obtained detailed information regarding the index PCI procedure directly from the original procedural record. Bifurcation stenting was narrowly defined, requiring the use of contiguous stents in both limbs of a previously treated bifurcation. Sites classified the ISR pattern according to the scheme of Mehran et al (10): type 1 (focal, less than 10 mm in length), type 2 (diffuse but within stent), type 3 (proliferative, extending beyond stent margins) and type 4 (occlusive). In patients with multiple ISR lesions, the catheterizing physician designated one primary ISR lesion by subjectively considering lesion location, localization of ischemia when available, as well as ISR severity. The catheterizing cardiologist also independently determined the choice of treatment for ISR, and registered the intended treatment categorically as medical, repeat PCI without brachytherapy (PCI), PCI with brachytherapy (PCI+B) or coronary artery bypass graft surgery (CABG).

Statistics

Descriptive clinical and angiographic statistics were tabulated. Continuous variables were summarized as a median value with 25th and 75th percentiles (Q1,Q3). In the case of a patient having multiple lesions, percentages were based on primary lesion characteristics. Clinical and angiographic characteristics that were thought likely to determine treatment decisions were prespecified. These included age, sex, history of diabetes, hypertension, prior myocardial infarction (MI), prior CABG, prior congestive heart failure, smoking status, kidney function (Cockcroft-Gault index), time to re-presentation, indication for repeat angiography, ISR morphology, ISR coronary segment, repetitive ISR and original stent deployment diameter. The χ^2 test for categorical variables or the Kruskal-Wallis test for continuous variables was used to compare and contrast clinical and angiographic characteristics in the medical, percutaneous and surgical

therapy groups. All hypotheses were tested with a two-sided test at a significance level of 0.05.

Stepwise logistic regression was used to identify which prespecified characteristics independently predicted treatment choices (a significance level of 0.20 was used to enter variables, and a level of 0.25 was used to remove variables) while adjusting for total stent length for the primary lesion and the presence of multisite lesions. First, factors were examined that predicted selection of medical therapy versus any form of revascularization (PCI, PCI+B or CABG). Among those undergoing revascularization, variables were examined that predicted selection for each type of revascularization by using a baseline logit model in which PCI served as the reference treatment choice (29). The interaction of ISR morphology and total stent length for the primary lesion were also tested. Statistically significant factors were presented using OR and 95% CI.

RESULTS

Clinical characteristics

During the six-month period of registration, ISR was diagnosed in 366 patients – approximately 7% of all patients undergoing clinically driven coronary angiography at participating centres during this time. Three patients were excluded due to incomplete data regarding treatment of the primary ISR lesion, leaving 363 patients for analysis. Seventy per cent of patients were male, median age was 61 years (Q1,Q3: 53,69), diabetes was present in 32%, prior MI in 48%, prior CABG in 22% and 11% were active smokers. Unstable clinical presentations drove cardiac catheterization in 51% of patients, including 15% with recent or acute ST-elevation MI (STEMI).

Angiographic characteristics

Angiographic characteristics are summarized in Table 1. The left anterior descending artery was the most common ISR location, accounting for approximately 40% of the overall burden of restenosis. Sixty-two patients had more than one lesion (54 patients with two lesions and eight patients with three lesions). The median final balloon diameter used at the time of initial stent deployment in the presenting lesion was 3.0 mm (Q1,Q3: 2.75,3.5), with only 6% involving stents deployed at 4.0 mm or more in diameter. The ISR pattern was not related to time to presentation, diabetic status, vessel territory, number of stents or even to total stent length. Furthermore, there appeared to be no interlesion correlation of the ISR pattern among patients with more than one ISR lesion (Figure 1). Recurrent ISR was observed in 67 patients (68 lesions), representing nearly one-fifth of the overall burden of restenosis. The frequency of ISR patterns observed in recurrent ISR lesions was not different from that observed in patients with de novo ISR ($\chi^2_{(3)}=3.98$, $P=0.26$). Of the 55 patients whose primary ISR lesions were occlusive (type 4), recent or acute thrombotic occlusion was suspected clinically in only eight patients, three of whom presented within 30 days, two within two months and the remaining three within one year of stent insertion.

Interval from stent insertion

The interval from stent insertion to diagnosis of ISR could be determined in 355 patients (98%) and varied from less than one month to more than three years (median eight months [Q1,Q3: 4,15]) (Figure 2). Those re-presenting with STEMI had the shortest median time from stent insertion, and those with stable angina had the longest. Female patients had a shorter median time to re-presentation, as did patients with

TABLE 1
Angiographic characteristics

	Primary lesion (n=363)	Ancillary lesions		ISR lesions (n=433)
		Lesion 2	Lesion 3	
ISR site				
Left anterior descending artery	147 (41%)	13	1	161 (37%)
Circumflex artery	80 (22%)	20	0	100 (23%)
Right coronary artery	113 (31%)	27	7	147 (34%)
Saphenous vein graft	23 (6%)	2	0	25 (6%)
Flow in ISR				
TIMI 3	254 (70%)	44	6	304 (70%)
TIMI 2	42 (12%)	7	1	50 (12%)
TIMI 1	12 (3%)	1	0	13 (3%)
TIMI 0	55 (15%)	10	1	66 (15%)
ISR pattern				
Type 1 (focal)	89 (25%)	11	1	101 (23%)
Type 2 (diffuse)	132 (36%)	25	4	161 (37%)
Type 3 (proliferative)	87 (24%)	16	2	105 (24%)
Type 4 (occlusive)	55 (15%)	10	1	66 (15%)
Details of original PCI		n=350		n=417
Number of stents				
1	260 (74%)	53	6	319 (76%)
2	61 (17%)	3	2	66 (16%)
3	18 (5%)	2	0	20 (5%)
4+	11 (3%)	1	0	12 (3%)
Total stented length (mm)		n=337		n=401
median (Q1,Q3)	18 (15,28)	18 (13,24)	15.5 (12.5,22)	18 (15,28)
Final balloon size (mm)		n=338		n=402
median (Q1,Q3)	3.0 (2.75,3.5)	2.8 (2.5,3.0)	2.5 (2.5,2.65)	3.0 (2.75,3.0)

Q1,Q3 25th, 75th percentiles; ISR In-stent restenosis; PCI Percutaneous coronary intervention; TIMI Thrombolysis In Myocardial Infarction

Figure 1) The in-stent restenosis (ISR) pattern for patients with multiple lesions is shown (n=62, eight patients with three lesions). The total height of each stacked bar indicates the percentage of patients with the possible ISR patterns observed as their primary ISR lesion. The component bars within each stacked bar indicate the percentage of patients with each ISR pattern in their ancillary ISR lesion. Note that the distribution of ancillary ISR lesion types does not appear to be related to the primary lesion type

multiple lesions (Table 2). Conversely, those with recurrent ISR and ISR involving stented vein grafts had longer median

Figure 2) Length of interval between diagnosis of in-stent restenosis (ISR) and previous percutaneous coronary intervention according to nature of re-presentation. ACS Acute coronary syndrome; STEMI ST-elevation myocardial infarction

TABLE 2
Comparison of days from stent insertion to in-stent restenosis (ISR) identification for selected characteristics*

Characteristic	Median (Q1,Q3)	P†
Sex		0.03
Male (n=248)	244 (140,507)	
Female (n=107)	208 (96,381)	
Diabetes (n=346)		0.88
No (n=236)	232 (129,430)	
Yes (n=110)	232 (132,487)	
Multiple ISR lesions		0.02
No (n=294)	246 (133,497)	
Yes (n=61)	176 (105,301)	
Primary ISR vessel		0.04
SVG (n=21)	338 (196,735)	
RCA (n=112)	258 (132,507)	
LAD artery (n=144)	216 (132,359)	
CIR artery (n=78)	213 (117,436)	
Repetitive ISR (n=352)		<0.0001
No (n=287)	211 (117,364)	
Yes (n=65)	488 (210,907)	
Indication for angiography		<0.0001
Stable angina (n=177)	266 (162,504)	
Other ACS (n=126)	184 (97,416)	
STEMI (n=52)	142 (69,287)	
ISR pattern		0.32
Type 1 (focal [n=89])	266 (140,497)	
Type 2 (diffuse [n=128])	210 (126,345)	
Type 3 (proliferative [n=83])	226 (122,436)	
Type 4 (occlusive [n=55])	271 (140,641)	

*Number of patients is 355 unless otherwise stated; †Comparisons between groups are based on the Kruskal-Wallis test. ACS Acute coronary syndrome; CIR Circumflex; LAD Left anterior descending; RCA Right coronary artery; STEMI ST-elevation myocardial infarction; SVG Saphenous vein graft

times to re-presentation. The median time to re-presentation did not differ among various patterns of ISR.

Figure 3) Treatment strategies selected by attending cardiologist by numbers (table) and percentage (bar chart) according to lesion type, length and multiplicity. CABG Coronary artery bypass graft surgery; MED Medical therapy; PCI Percutaneous coronary intervention; PCI+B PCI with brachytherapy

Treatment

The treatment of ISR is shown in Figure 3. Most patients were treated percutaneously (244 patients [67%]). Among the 244 patients undergoing any PCI by intention, the primary ISR lesion could not be crossed with a coronary guidewire in 11 cases (4.5%). PCI alone was used in 139 patients (159 lesions) and PCI+B in 105 patients (126 lesions). Cutting balloons were used in 142 patients. Debulking with any form of atherectomy or ablation was rare (seven lesions). A new bare metal stent was deployed in 48 patients (50 lesions), eight of whom received coincident brachytherapy. CABG (59 patients [16%]) and medical therapy (60 patients [17%]) were less commonly recommended as the initial form of management. The database of the present study did not capture treatment choices following unsuccessful PCI.

On univariate analysis, the choice of therapy was related to lesion types ($P < 0.0001$): patients selected for medical therapy more often had total occlusions (32%), those selected for PCI/PCI+B more often had diffuse ISR (41%) and those selected for CABG surgery had proliferative ISR (46%) (Table 3). A statistically significant difference in final balloon size was noted, but appeared to be attributable to a small variability rather than a large difference in median values. CABG was associated with multiple ISR lesions, as well as proliferative and occlusive ISR. However, there were no statistically significant differences between clinical characteristics (including diabetes) and choice of therapy.

Factors from the multivariable model that predicted repeat revascularization (of any type) rather than medical treatment were increasing vessel diameter (OR 2.6 [95% CI 1.2 to 5.8] per 1 mm increment) and previous therapy for ISR (OR 7.1 [95% CI 1.6 to 31.4]). Neither stent length nor ISR pattern predicted repeat revascularization, and neither did their interaction term. Among patients selected for any form of revascularization ($n = 274$), factors that distinguished the selection of PCI+B versus PCI alone were repeat treatment for ISR (OR 4.2 [95% CI 2.0 to 8.9]), types 2 and 3 versus type 1 ISR (OR 3.9 [95% CI 1.9 to 8.3] and OR 2.6 [95% CI 1.1 to 6.1], respectively), and presentation with stable ischemia versus STEMI (OR 3.2 [95% CI 1.3 to 8.0]). CABG surgery was more likely used than simple PCI for patients with multiple lesions (OR 3.2

TABLE 3
Selected patient characteristics comparing treatments ($n = 363$)

Characteristic	Medical (n=60)	PCI/PCI+B (n=244)	CABG (n=59)	P*
Age (Q1,Q3), years	64 (53,72)	62 (56,72)	57 (53,66)	0.07
Men, n (%)	44 (73)	168 (69)	42 (71)	0.78
Diabetes, n (%)	23 (40)	69 (29)	22 (37)	0.20
ISR pattern, n (%)				<0.0001
Type 1 (focal)	17 (28)	68 (28)	4 (7)	
Type 2 (diffuse)	14 (23)	100 (41)	18 (31)	
Type 3 (proliferative)	10 (17)	50 (21)	27 (46)	
Type 4 (occlusive)	19 (32)	26 (11)	10 (17)	
Multiple ISR lesions, n (%)	8 (13)	38 (16)	16 (27)	0.07
Prior CABG, n (%)	11 (19)	58 (24)	9 (16)	0.32
ISR in LAD, n (%)†	18 (38)	80 (44)	28 (58)	0.11
ACS-driven angiography, n (%)	27 (45)	119 (49)	38 (64)	0.06
Total stent length (mm) median (Q1,Q3)	22 (16.5,28)	18 (15,28)	18 (15,30)	0.49
Final balloon size (mm) median (Q1,Q3)	3 (2.5,3)	3 (2.75,3.5)	3 (3,3)	0.04
Interval to ISR diagnosis (days) median (Q1,Q3)	330 (126,619)	233 (128,416)	185 (133,378)	0.36

*Comparisons tested using either the χ^2 or Kruskal-Wallis test, as appropriate; †Excluded patients with previous coronary artery bypass surgery (CABG). Q1,Q3 25th, 75th percentiles; ACS Acute coronary syndrome; ISR In-stent restenosis; IQR Interquartile range; LAD Left anterior descending artery; PCI Percutaneous coronary intervention; PCI+B PCI with brachytherapy

[95% CI 1.3 to 7.6]), lesion types 2, 3 and 4 versus type 1 (OR 4.7 [95% CI 1.4 to 15.8], OR 10.6 [95% CI 3.1 to 36.0], OR 6.6 [95% CI 1.7 to 26.2], respectively) and for previously treated ISR (OR 2.9 [95% CI 1.1 to 7.3]).

DISCUSSION

In a multicentre registry of the pre-DES era, we prospectively identified and characterized an unselected cohort of 363 patients with ISR as they presented for clinically driven cardiac catheterization. While ISR may not have independently driven repeat cardiac catheterization and revascularization in all cases, our findings confirm the substantial clinical burden imposed by ISR, and for the first time, they express this burden as a proportion of overall cardiac catheterization laboratory activity (approximately 7% of all contemporaneous coronary procedures). Repetitive ISR accounted for one-fifth of this burden.

Clinical trials incorporating protocol-specified follow-up angiography have established three factors that independently increase the risk for ISR: longer stent or lesion length, smaller post-PCI lumen diameter and presence of diabetes (7,11,12,30,31). Specific lesion subtypes often excluded from clinical trials, particularly bifurcation lesions and nonacute total occlusions, also have inherently high rates of restenosis (32). The prevalence of these factors in our registry was not, however, particularly high: 68% were not diabetic, 71% had stent lengths less than 28 mm (12% less than 13 mm) and 72% had a final balloon size of 3.0 mm or larger.

These data indicate that the characteristics of a cohort composed of patients with clinically detected ISR are influenced by factors beyond those that prospectively predict angiographic

restenosis in clinical trials. First, the baseline prevalence of various clinical and angiographic characteristics in the unselected population undergoing PCI (and therefore at risk for ISR) is likely to be a major determinant. If, for instance, the majority of stent-treated lesions are short, the lesions will constitute a larger fraction of the overall burden of ISR despite an inherently low per-patient risk. Second, the capacity of a lesion to manifest ischemia when ISR develops is also likely to be important. ISR in vessels that subtend small or nonviable territories, or in patients prone to silent ischemia, is less likely to prompt clinically driven angiography if ISR develops.

Timing of ISR diagnosis

Most cases of ISR (69%) were diagnosed within 12 months, in keeping with the known time course of the vascular response to PCI. However, almost one-third of cases were diagnosed more than one year after the index procedure, including approximately 10% being detected beyond two years (Figure 2). These data indicate a generally later time course for detection of ISR in clinical practice than reported in clinical trials. In practice, patients with recurrent angina due to ISR likely experience delays in recognizing symptoms, seeking medical attention, obtaining specialist referral, and undergoing confirmatory non-invasive tests and elective angiography. Our observation of the diagnosis of ISR being made earlier in those with acute coronary syndromes (ACS) and STEMI within the first year – cohorts that receive expedited access to care – supports this hypothesis. In some cases, however, late diagnosis of ISR is probably a manifestation of investigations triggered by disease progression in other coronary segments. Indeed, 47 of 54 patients with STEMI had culprit lesions remote from the ISR lesion, and contemporary restenosis studies examining rates of revascularization over predetermined follow-up periods demonstrate significant rates of nontarget lesion revascularization (13,14,31,33). Clinicians and patients should nevertheless be aware that a significant minority of patients with ISR present to cardiac catheterization more than one year following initial stent placement.

Previous studies have also noted a higher incidence of type 3 ISR in patients who re-present early following stenting, although any relationship between lesion type and sex is disputed (34-36). We found no such relationship in our unselected cohort. We found that women had a shorter interval from their previous procedure, but did not observe a relationship between time to re-presentation and type of ISR lesion.

Mode of presentation

Our data confirm that ACS frequently precede the diagnosis of ISR (37). Moreover, of 178 patients in our registry who presented in an acute phase, 170 (96%) did so beyond 30 days. Our cross-sectional method did not allow precise calculation of a stent thrombosis rate. However, stent thrombosis was clinically suspected in only 18 cases during a period when the participating centres performed approximately 3400 PCI procedures. Of these cases, stent thrombosis was confirmed angiographically in eight patients, four of whom presented with STEMI. These data extend previous reports, confirming low rates of thrombosis in bare metal stents to an unselected cross-sectional population (38,39).

Treatment

Practice patterns regarding treatment choices seen in our registry were consistent with contemporaneous evidence. Most

patients were treated with simple repeat balloon inflation PCI, a simple and low-cost approach easily undertaken in combination with the diagnostic procedure during which ISR was identified. Apart from DES (which were not available during the period of registration) and brachytherapy, no percutaneous technology has proven to be superior to balloon redilation alone (40-44). Brachytherapy treatment implied a more expensive and complex intervention, and was less suited to ad hoc interventions coupled with diagnostic angiography. Its targeted use in long, diffuse or proliferative lesions, elective procedures (in stable angina) and repetitive restenosis likely reflected these considerations. Moreover, clinicians may have been concerned about an associated late hazard (38,44). CABG surgery was second only to brachytherapy as the choice for diffuse or proliferative ISR patterns and was rarely used in patients with single-focal ISR lesions.

Implications for targeted use of DES

DES technology has markedly reduced the risk of ISR in patients undergoing PCI, and DES devices have rapidly replaced bare metal stents in some jurisdictions, notably in the United States (23-28,40,45-49). However, in many publicly funded health care systems (including Canada and much of Europe), cost and regulatory considerations have restricted DES usage to varying degrees. This has led interventional cardiologists to target DES devices to patients at increased risk for ISR. Our registry demonstrates, however, that the majority of the burden of bare metal stent restenosis occurs in patients who were individually at low risk for developing ISR. Our data indicate that eliminating ISR in all patients with diabetes, for example, would reduce the overall burden of ISR by less than one-third. Similarly, eliminating ISR in all lesions with a stented length exceeding 28 mm or in all left anterior descending artery lesions would reduce the burden of restenosis by only 23% and 41%, respectively. It is worthy to note that these projections overestimate the actual effect that would be obtained with DES, which reduce, but do not eliminate, the incidence of ISR.

Study limitations

The present study used a descriptive registry, and the findings must be interpreted accordingly. Neither the clinical nor angiographic incidence of ISR can be calculated due to the cross-sectional nature of the data. Moreover, not all patients with ISR are referred for repeat angiography due to absent symptoms, patient or physician preference, comorbidity or fatal outcome. Our methods did not allow clear determination of the causal relationship between ISR and repeat angiography. Identification of a primary ISR lesion in patients with multiple ISR lesions is subjective and fraught with difficulty (13,50); we did not capture the reasons for designating primary ISR lesions in these cases. Therapeutic decisions were entirely at the discretion of the attending cardiologist; neither a predefined treatment algorithm nor recommendations for management were used. Relationships between the investigated variables are therefore associations, reflecting application of evidence and judgment in clinical practice.

CONCLUSIONS

In the pre-DES era, ISR was observed in 7% of consecutive diagnostic coronary angiograms performed in five high-volume interventional centres. Re-presentation typically occurred

between four and 14 months following the initial procedure. However, one-third of patients with ISR were diagnosed more than one year after their index procedure. The clinical presentation associated with the angiographic finding of ISR was an ACS in just over one-half of cases. Occlusive ISR accounted for 15%. The treatment of nonocclusive ISR was largely in concordance with literature, with 67% receiving a percutaneous intervention and 16% receiving CABG. Focal ISR tended to be treated with PCI alone, while types 2 and 3 were associated with an increased use of adjunctive brachytherapy or surgical revascularization. Although brachytherapy was the only available percutaneous therapy proven to be more effective than balloon angioplasty, only 43% of those having a repeat percutaneous procedure received brachytherapy. These data provide a benchmark of the current spectrum of ISR with which comparison may be made in the new era of DES technology.

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