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A novel clinical score to predict repeat coronary interventions in patients with drug-eluting stent restenosis

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Percutaneous coronary interventions (PCI) for in-stent restenosis (ISR) are usually considered as simple procedures from a technical standpoint and are associated with a low incidence of acute complications but they suffer from a significantly higher recurrence rate compared with PCI for *de novo* lesions[1,2]. Of note, although drug-eluting stents (DES) drastically reduced the occurrence of ISR as compared with bare metal stents (BMS), once ISR occurs, treatment of DES-ISR is more challenging and is associated with poorer long-term clinical and angiographic results than treatment of BMS-ISR[3]. Currently, both new-generation DES and drug-coated balloons (DCB) are recommended by the European guidelines on coronary revascularisation (Class I, level of evidence A) for the treatment of patients presenting with ISR[4]. Both strategies provide satisfactory long-term clinical outcomes although DES ensure superior late angiographic results that, in the particularly complex scenario of DES-ISR, eventually translate into a reduced need for repeat interventions[1-3]. The benefit of DES over DCB in patients with DES-ISR regarding clinically driven target lesion revascularisation, was confirmed by the DAEDALUS patient-level meta-analysis that included ~2,000 ISR patients from 10 randomised trials[3]. As "failing twice" is not clinically acceptable, a major emphasis has always been placed on the importance of optimising the final angiographic results during these reinterventions[1,2]. Intracoronary imaging is recommended in this setting, first to identify the underlying substrate (mechanical issues should be aggressively tackled), and then to optimise procedural results[1,2]. Notwithstanding its pathophysiological appeal, evidence supporting the value of intracoronary imaging to improve the clinical outcome of patients with ISR remains limited (Class IIa, level of evidence C)[4].

How can we identify patients with DES-ISR at higher risk for repeat PCI?

PRESENT STUDY

In this issue of EuroIntervention, Coughlan et al[5] present a novel clinical score (the ISAR score) to predict the risk of repeat PCI for recurrent DES-ISR. This prestigious group from Munich, with a time-honoured research interest in ISR (ISAR-DESIRE studies),

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retrospectively analysed 1,986 consecutive patients with DES-ISR (2,392 ISR lesions) from 2 centres. Patients were randomly divided (3:1 ratio) into training (1,471 patients, 1,778 lesions) and validation (515 patients, 614 lesions) cohorts, in order to develop and validate the predictive model. The median duration of clinical follow-up after DES-ISR treatment was 7.4 years. Four clinical variables, 1) a non-focal ISR pattern, 2) time interval to ISR <6 months, 3) ISR in the left circumflex coronary artery (LCx), and 4) ISR in a calcified vessel, were associated with repeat PCI for recurrent DES-ISR at 1 year. The C-statistic of the model (predictive accuracy) was modest (hazard ratio 0.60, 95% confidence interval: 0.57-0.63) but statistically superior (delta C-statistic, p<0.001) to previous models (i.e., the Mehran ISR classification). In addition, the numerical 4-item ISAR score (1 point for each variable) proved clinically useful to readily predict PCI for recurrent DES-ISR. In an exploratory analysis performed to predict repeat PCI from 1 to 5 years, the ISAR score retained its predictive value. Furthermore, the score maintained its value in patients receiving both stent- and balloon-based therapeutic modalities.

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The authors should be commended for providing novel and practical insights that are useful in predicting outcomes in these challenging patients by systematically analysing their uniquely large experience. However, discussing some methodological issues is of interest.

First, the statistical approach was sophisticated and robust yet pragmatic and clinically oriented. The least absolute shrinkage and selection operator method was selected for the logistic regression analyses to optimise accuracy and interpretability. A classification and regression tree selected variables impacting the likelihood of repeat PCI occurrence. Internal validation of the model was confirmed although the authors acknowledged that external validation should be pursued.

Second, the rate of repeat PCI at 1 year (17.7%) was higher than in previous studies[3] but we should keep in mind that 1/4 of patients were treated with plain balloon PCI. The primary endpoint was "any repeated PCI for the initially treated target ISR lesion" and, therefore, it would be important to confirm that all these interventions were clinically indicated and not a result of an oculostenotic reflex. This is relevant because during the last decade, these investigators performed several important trials on patients with ISR with mandated systematic angiographic surveillance to address different surrogate primary angiographic endpoints. In this regard, the cumulative frequency distribution curves of events presented in all the figures clearly showed a sharp increase in the number of repeat PCI procedures at 6-8 months, coincident with the time selected for the surveillance angiography in most research protocols. Curves of repeat PCI beyond the first year were flat and parallel and an exploratory analysis was unable to identify predictors of very late PCI. Reassuringly, a clinical indication (mainly stable angina) was confirmed in all patients requiring repeat PCI, suggesting that clinical symptoms were probably especially scrutinised during the early period.

Third, information on classical "quantitative" coronary angiography findings, including minimal lumen diameter and percentage diameter stenosis, before and after the procedure, was not provided. It would have been useful to assess whether repeat PCI was more frequently required in patients with suboptimal angiographic results[1,2]. Similarly, information on angiographic findings at follow-up was not provided, probably because late angiographic surveillance was not available in all patients. Nevertheless, it remains possible that other variables might be better suited to predict recurrent "angiographic" ISR. In this regard, minimal lumen diameter, % diameter stenosis, late lumen loss, and loss index are well-established angiographic surrogates of efficacy[1,2]. This could be interesting from a mechanistic or pathophysiological standpoint but would have more elusive clinical implications.

Fourth, some issues related to the 4 identified predictive "clinical" variables are also worth discussing. An "early" presentation and a "diffuse" angiographic pattern are well-established predictors of recurrences in patients with ISR and are also classically considered markers of an aggressive adverse vessel response[1,2]. The selected cut-offs are also well accepted (<6 months and >10 mm, respectively) and were dichotomised based on event frequencies, but it remains unclear whether different cut-off values (i.e., using receiver operator characteristic curves) would have provided a better predictive value. The 2 other clinical factors are of particular interest because they have not been detected as independent predictors of adverse outcomes in most previous studies on ISR. Calcification of the vessel wall is always of concern in *de novo* lesions because it may prevent achieving optimal PCI results and has a clear influence on long-term outcomes[4]. Importantly, stent underexpansion remains a major cause of ISR and resistant underexpansion, due to severe vessel wall calcification, is a common cause of recalcitrant ISR[1,2]. Nevertheless, in patients with ISR, the presence of calcification at the vessel wall may be difficult to assess, particularly in those with several layers of metal. Reassuringly, despite the use of a definition developed for *de novo* lesions, the presence and severity of coronary calcification was adjudicated at a core laboratory. It would have been of interest to know whether the final procedural results were indeed poorer in severely calcified vessels. Ablation of calcium at the vessel wall is no longer possible after stenting (although it may be still effective in calcified neoatherosclerosis), but simpler, currently available alternatives for dilating resistant lesions (super-high-pressure balloons or lithotripsy) are of help in improving final results in selected patients with ISR in heavily calcified vessels[1,2]. Finally, the predicted value of the LCx location may be considered surprising. However, the ostium of this vessel is always difficult to treat[6]. ISR confined to the LCx ostium usually develops after a simple (stent cross-over) or complex (2-stent technique) intervention at the left main. This represents a well-known challenging substrate that has been systematically excluded from most trials on ISR[6]. To avoid injuring the nearby left main stem, interventions at this location tend to avoid additional stents and suboptimal results are frequently considered acceptable. Accordingly, this uniquely

complex anatomical scenario may be considered a "different animal" and separated from other ISR lesions[6]. In this regard, data on whether ISR at other LCx locations kept the same predictive value would have been of interest.

Finally, other factors classically considered as adverse prognostic markers, including the number of ISR recurrences and the presence of multiple metal layers were not identified in the present study[1,2]. Notably, diabetes was also not identified in previous studies as a predictor of recurrences in these patients[1,2]. The analysis of the potential benefit of using intracoronary imaging during these procedures was strongly limited by a low (<3%) use[4]. Likewise, although the ISAR score was equally valuable irrespective of the selected therapeutic modality, the use of treatment strategies different from new-generation DES did not emerge as a predictor of repeat PCI. This is in apparent contradistinction with recent findings by this group in the meta-analysis including all available randomised trials on ISR[3]. Considering that the present retrospective analysis comes from an observational all-comers registry, unmeasured confounders or treatment selection biases may help to explain the results[5].

FINAL REMARKS

The newly developed ISAR score provides an attractive and easy to implement clinical tool to predict the need for recurrent revascularisation in patients with DES-ISR. Further studies are required to confirm whether its prospective use in the clinical setting may help to optimise the clinical decision-making process and eventually the outcome of these challenging patients.

Conflict of interest statement

The authors have no conflicts of interest to declare.

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