Original Article

Coronary in-stent restenosis in a real-world repeat-angiography cohort: frequency and clinical correlates from western kazakhstan

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ABSTRACT

Background

Coronary in-stent restenosis (ISR) remains clinically relevant in routine practice and is often detected in patients returning for repeat coronary angiography after prior percutaneous coronary intervention (PCI).

Objective

To determine the frequency of angiographically confirmed ISR and identify associated clinical and laboratory characteristics, including left ventricular ejection fraction (LVEF), in a real-world repeat-angiography cohort .

Methods

This multicenter retrospective registry included 1,005 adults from three PCI centers in Aktobe region (Kazakhstan) who underwent repeat coronary angiography in 2019-2023 and had a documented history of prior stent implantation. ISR was defined as ≥50% diameter stenosis within a previously implanted stent. Groups with and without ISR were compared using nonparametric and categorical tests; multivariable logistic regression assessed independent associations.

Results

ISR was identified in 138/1,005 patients (overall frequency 13.7%). Patients with ISR more often had diabetes, peripheral artery disease, prior CABG, and heart failure history, and more frequently underwent angiography in the setting of myocardial infarction. ISR was associated with higher creatinine and a higher prevalence of eGFR <60 mL/min/1.73 m², a more atherogenic lipid profile (higher LDL-C and non-HDL-C), and slightly lower LVEF. LDL-C target attainment (≤1.4 mmol/L) was low overall. Outpatient therapy patterns were broadly similar between groups; among patients with diabetes, SGLT2 inhibitor use was higher in the ISR group. In multivariable analysis, older age, obesity, and ACS presentation were associated with higher odds of ISR, while diabetes and eGFR <60 mL/min/1.73 m² showed inverse associations, interpreted cautiously in the repeat-angiography context (Nagelkerke R^2=0.070).

Conclusion

In a real-world repeat-angiography cohort after prior PCI, angiographically confirmed ISR (≥50%) was detected in 13.7% and was linked to a higher comorbidity burden, less favorable renal and lipid profiles, and slightly lower LVEF, with low LDL-C goal attainment in routine practice. These findings support intensified secondary prevention and further analyses incorporating procedural/anatomical determinants and timing from index PCI.

Keywords

Coronary Restenosis; Angiography, Coronary; Percutaneous Coronary Intervention; Risk Factors; Registries

INTRODUCTION

Coronary in-stent restenosis (ISR) continues to represent a clinically significant complication following percutaneous coronary intervention (PCI), despite the widespread adoption of drug-eluting stents[1]. In routine clinical practice, ISR is seldom regarded as merely an angiographic finding; rather, it frequently manifests as a recurrent clinical condition, leading to ischemic symptoms, repeat coronary angiography, and often subsequent revascularization procedures[1].

Concurrently, the population undergoing PCI is becoming increasingly complex, characterized by a higher prevalence of cardiometabolic comorbidities and chronic kidney disease. These factors may alter restenosis risk profiles and limit the generalizability of evidence derived from other healthcare settings[2]. This challenge is particularly pronounced in Central Asia, where available data on ISR remain scarce and are often based on selective cohorts, resulting in significant gaps in region-specific estimates of ISR prevalence and its clinical determinants[3–6].

Accordingly, the present study aimed to assess the frequency of angiographically confirmed ISR and to identify its associated clinical and laboratory characteristics, as well as left ventricular ejection fraction, using data from a retrospective, real-world registry of patients undergoing repeat coronary angiography after prior PCI.

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MATERIALS AND METHODS

Study design, setting, and study period

This multicenter retrospective observational study was based on a real-world repeat-angiography registry. The registry included patients from three PCI-capable centers in Aktobe region (Kazakhstan) who underwent coronary angiography between 2019 and 2023. Data were retrospectively extracted from hospital discharge summaries/medical records and coronary angiography reports.

Study population: inclusion and exclusion criteria

Patients were eligible if they met all of the following criteria:

1. age ≥18 years;
2. repeat coronary angiography performed during the index episode of care (elective evaluation for stable coronary artery disease or hospitalization for acute coronary syndrome [ACS], irrespective of ACS subtype);
3. documented history of prior index (primary) PCI with coronary stent implantation.

Exclusion criteria were:

1. absence of coronary angiography during the index episode;
2. absence of documented prior PCI with stent implantation.

Definitions and endpoint

The primary study endpoint was angiographically confirmed ISR, defined as ≥50% diameter stenosis within a previously implanted stent in any epicardial coronary artery segment on repeat coronary angiography. ISR was analyzed as a binary variable (present/absent).

The index clinical presentation was categorized as any myocardial infarction (MI), unstable angina, or non-ACS (elective/other), according to medical record documentation and registry coding.

Data sources and variables

Clinical and demographic data were obtained from discharge summaries and medical records, while coronary anatomy and ISR status were extracted from angiography reports. The following variables were analyzed:

- Demographics/anthropometrics: age, sex, body mass index (BMI); obesity defined as BMI ≥30 kg/m².
- Risk factors and comorbidities: current smoking; prior MI; prior coronary artery bypass grafting (CABG); type 2 diabetes mellitus (T2DM); heart failure (HF) history; atrial fibrillation (AF); ischemic stroke/transient ischemic attack (TIA); peripheral artery disease (PAD).
- Vital signs at admission: systolic blood pressure (SBP) and heart rate.
- Laboratory parameters: fasting glucose; creatinine; estimated glomerular filtration rate (eGFR, CKD-EPI); reduced renal function defined as eGFR <60 mL/min/1.73 m²; lipid profile including total cholesterol, high-density lipoprotein cholesterol (HDL-C), non-high-density lipoprotein cholesterol (non-HDL-C), low-density lipoprotein cholesterol (LDL-C), triglycerides; attainment of LDL-C ≤1.4 mmol/L.
- Echocardiography: left ventricular ejection fraction (LVEF).
- Outpatient (pre-admission) therapy; among patients with documented T2DM, glucose-lowering therapy was described separately.

Statistical analysis

All statistical analyses were performed using appropriate statistical software: IBM SPSS (IBM Corp. Released 2019. IBM SPSS Statistics for macOS, Version 26. Armonk, NY: IBM Corp.). Continuous variables were evaluated for distributional assumptions; normality was assessed using the Shapiro-Wilk test and visual inspection of histograms and Q–Q plots. Continuous variables are reported as median [interquartile range] and compared between groups using the Mann-Whitney U test. Categorical variables are presented as n (%) and compared using Pearson's χ^2 test; Fisher's exact test was used when χ^2 assumptions were not met (e.g., expected cell counts <5). All tests were two-sided, and $p<0.05$ was considered statistically significant.

The primary study endpoint (angiographically confirmed ISR ≥50%) was analyzed as a binary outcome (present/absent). To evaluate independent associations with ISR, multivariable logistic regression was performed. Covariates were selected a priori based on clinical relevance and included: age ≥65 years, sex, obesity (BMI ≥30 kg/m²), ACS presentation, T2DM,

reduced renal function (eGFR <60 mL/min/1.73 m²), PAD, and HF history. Results are reported as adjusted odds ratios (OR) with 95% confidence intervals (CI). Model explanatory performance was summarized using Nagelkerke R^2, and overall model significance was assessed using the likelihood-ratio test.

Ethiccal Clearence

The study was conducted in accordance with the Declaration of Helsinki and was approved by the Local Ethics Committee of the West Kazakhstan Marat Ospanov Medical University (Protocol No. 11, 24 November 2023). Participating centers provided de-identified discharge summaries and coronary angiography reports/protocols for analysis. The dataset contained no direct patient identifiers, and all analyses were performed on anonymized records in accordance with institutional and local data-protection requirements.

RESULTS

Among 1,005 patients with prior PCI undergoing repeat coronary angiography, angiographically confirmed ISR was detected in 138 cases, corresponding to an overall ISR frequency of 13.7% in this repeat-angiography cohort.

Demographic and clinical characteristics by ISR status

Demographic and clinical characteristics by ISR status are presented in Table 1.

Table 1. Demographic and clinical characteristics by ISR status

Variable	Overall	No ISR (n=867)	ISR (n=138)	p-value
Age, years	63 [57–70]	63 [57–70]	63 [58–68]	0.459
Age ≥65 years, n (%)	435 (43.3%)	384 (44.3%)	51 (37.0%)	0.106
Male sex, n (%)	750 (74.6%)	639 (73.7%)	111 (80.4%)	0.091
BMI, kg/m²	28.9 [26.8–31.0]	28.9 [26.7–31.1]	28.8 [27.0–30.7]	0.453
Obesity, n (%)	373 (37.1%)	328 (37.8%)	45 (32.6%)	0.238
Current smoking, n (%)	290 (28.9%)	242 (27.9%)	48 (34.8%)	0.098
SBP, mmHg	130 [120–150]	130 [120–150]	130 [120–150]	0.959
Heart rate, bpm	68 [60–79]	68 [60–79]	71 [65–81]	0.015
Prior MI, n (%)	755 (75.1%)	648 (74.7%)	107 (77.5%)	0.480
Prior CABG, n (%)	58 (5.8%)	45 (5.2%)	13 (9.4%)	0.048
T2DM, n (%)	210 (20.9%)	171 (19.7%)	39 (28.3%)	0.022
HF history, n (%)	116 (11.5%)	93 (10.7%)	23 (16.7%)	0.043
Ischemic stroke/TIA, n (%)	77 (7.7%)	61 (7.0%)	16 (11.6%)	0.061
PAD, n (%)	50 (5.0%)	38 (4.4%)	12 (8.7%)	0.030
AF, n (%)	77 (7.7%)	65 (7.5%)	12 (8.7%)	0.623
Index presentation category				
Any MI, n (%)	287 (28.6%)	231 (26.6%)	56 (40.6%)	<0.001
Unstable angina, n (%)	301 (30.0%)	257 (29.6%)	44 (31.9%)	
Non-ACS, n (%)	417 (41.5%)	379 (43.7%)	38 (27.5%)	

Continuous variables are presented as median [IQR]; categorical variables as n (%). Continuous variables were compared using the Mann-Whitney U test; categorical variables using Pearson's χ^2 test or Fisher's exact test, as appropriate. Two-sided $p<0.05$ was considered statistically significant.

The cohort was predominantly male (74.6%), with a median age of 63 years [57–70]. Baseline demographics were broadly comparable between patients with and without ISR, including age and BMI. (Table 1) However, patients with ISR presented with a higher heart rate at admission (71 [65–81] vs 68 [60–79] bpm; p=0.015) (Table 1).

Several comorbidities were more frequent in the ISR group. T2DM was observed in 28.3% vs 19.7% (p=0.022), HF history in 16.7% vs 10.7% (p=0.043), and PAD in 8.7% vs 4.4% (p=0.030). A history of CABG was also more common among patients with ISR (9.4% vs 5.2%; p=0.048) (Table 1).

The clinical context of the index presentation differed markedly by ISR status (overall distribution p<0.001). Angiographically confirmed ISR was identified more frequently among patients undergoing repeat angiography in the setting of MI (40.6% vs 26.6%). Conversely, in non-ACS (elective/other) referrals, repeat coronary angiography more often did not reveal ISR (43.7% vs 27.5%) (Table 1).

Laboratory and echocardiographic parameters by ISR status

Laboratory and echocardiographic parameters by ISR status are summarized in Table 2. Renal function markers suggested a less favorable profile in the ISR group. Creatinine was modestly higher (82.9 [71.3–102.0] vs 79.5 [68.8–92.2] µmol/L; p=0.022), and the proportion of patients with eGFR <60 mL/min/1.73 m² was greater (17.4% vs 10.8%; p=0.026) (Table 2). Lipid parameters were also less favorable in patients with ISR. Compared with those without ISR, they had higher LDL-C (2.97 [2.32–3.90] vs 2.86 [2.05–3.52] mmol/L; p=0.007) and higher non-HDL-C (3.61 [2.97–4.51] vs 3.45 [2.61–4.19] mmol/L; p=0.013), alongside a small but significant difference in total cholesterol (p=0.048) (Table 2). On echocardiography, patients with ISR had a slightly lower LVEF (49 [45–53] vs 51 [46–54]%; p=0.044) (Table 2).

Table 2. Laboratory and echocardiographic parameters by ISR status

Variable	Overall	No ISR (n=867)	ISR (n=138)	p-value
Creatinine, µmol/L	80.0 [69.0–93.5]	79.5 [68.8–92.2]	82.9 [71.3–102.0]	0.022
eGFR (CKD-EPI), mL/min/1.73 m²	88.5 [71.9–99.4]	89.1 [72.8–99.4]	86.7 [68.9–98.9]	0.203
eGFR <60 mL/min/1.73 m², n (%)	118 (11.7%)	94 (10.8%)	24 (17.4%)	0.026
Fasting glucose, mmol/L	6.05 [5.32–7.68]	6.00 [5.30–7.60]	6.50 [5.50–8.50]	0.071
Total cholesterol, mmol/L	4.60 [3.73–5.40]	4.59 [3.70–5.40]	4.64 [3.97–5.61]	0.048
HDL-C, mmol/L	1.13 [0.95–1.24]	1.13 [0.95–1.25]	1.11 [0.95–1.20]	0.244
Non-HDL-C, mmol/L	3.50 [2.64–4.25]	3.45 [2.61–4.19]	3.61 [2.97–4.51]	0.013
LDL-C, mmol/L	2.86 [2.10–3.57]	2.86 [2.05–3.52]	2.97 [2.32–3.90]	0.007
LDL-C ≤1,4 mmol/L, n (%)	77 (7.7%)	69 (8.0%)	8 (5.8%)	0.375
Triglycerides, mmol/L	1.40 [0.92–1.73]	1.40 [0.95–1.76]	1.40 [0.88–1.68]	0.441
LVEF, %	50 [46–54]	51 [46–54]	49 [45–53]	0.044

Continuous variables were compared using the Mann-Whitney U test; categorical variables using Pearson's χ^2 test or Fisher's exact test, as appropriate. Two-sided p<0.05 was considered statistically significant.

Outpatient (pre-admission) therapy by ISR status

Outpatient (pre-admission) therapy by ISR status is presented in Table 3.

Table 3. Outpatient (pre-admission) therapy by ISR status

Variable	Overall	No ISR (n=867)	ISR (n=138)	p-value
Aspirin, n (%)	718 (71.4%)	628 (72.4%)	90 (65.2%)	0.081
P2Y12 inhibitors: Clopidogrel, n (%) Ticagrelor, n (%)	195 (19.4%) 61 (6.1%)	176 (20.3%) 52 (6.0%)	19 (13.8%) 9 (6.5%)	0.197
Dual antiplatelet therapy, n (%)	235 (23.4%)	209 (24.1%)	26 (18.8%)	0.175
Renin-angiotensin system inhibitors, n (%)	574 (57.1%)	498 (57.4%)	76 (55.1%)	0.602
Beta-blockers, n (%)	671 (66.8%)	582 (67.1%)	89 (64.5%)	0.542
Calcium channel blockers, n (%)	265 (26.4%)	229 (26.4%)	36 (26.1%)	0.936
Statins, n (%)	470 (46.8%)	408 (47.1%)	62 (44.9%)	0.641
Ezetimibe, n (%)	37 (3.7%)	31 (3.6%)	6 (4.3%)	0.655
SGLT2 inhibitors, n (%)	46 (4.6%)	36 (4.2%)	10 (7.2%)	0.106
Antidiabetic therapy (patients with T2DM only; n=210)				
Metformin, n (%)	113 (36.7%)	58 (33.9%)	15 (38.5%)	0.591
Sulfonylureas, n (%)	60 (19.5%)	36 (21.1%)	5 (12.8%)	0.370
Insulin, n (%)	48 (15.6%)	26 (15.2%)	8 (20.5%)	0.470
SGLT2 inhibitors, n (%)	31 (14.8%)	21 (12.3%)	10 (25.6%)	0.045
DPP-4 inhibitors, n (%)	16 (5.2%)	9 (5.3%)	2 (5.1%)	1.000

Categorical variables were compared using Pearson's χ^2 test or Fisher's exact test, as appropriate. Two-sided $p<0.05$ was considered statistically significant.

Before admission, the most commonly used medications were aspirin (71.4%), beta-blockers (66.8%), renin-angiotensin system inhibitors (RASi) (57.1%), and statins (46.8%) (Table 3). Outpatient treatment patterns were largely similar between groups, with no statistically significant differences in antiplatelet regimens, RASi, beta-blockers, calcium channel blockers, statins, ezetimibe, or SGLT2 inhibitors in the overall cohort (all $p>0.05$) (Table 3).

In the subgroup of patients with documented T2DM (n=210), most glucose-lowering therapies were used at similar rates between groups; however, SGLT2 inhibitor use was higher among patients with ISR (25.6% vs 12.3%; $p=0.045$) (Table 3).

Multivariable regression analysis

A multivariable logistic regression model was used to assess factors independently associated with angiographically confirmed ISR within this repeat-angiography cohort. The model was statistically significant but showed modest explanatory power (Nagelkerke $R^2=0.070$), indicating that additional unmeasured clinical, anatomical, and procedural determinants likely contribute to ISR risk (Table 4).

After adjustment, older age (≥65 years), obesity, and an ACS presentation remained associated with higher odds of ISR, whereas T2DM and reduced renal function (eGFR <60 mL/min/1.73 m²) demonstrated inverse associations; PAD showed a borderline inverse

association (Table 4) .Sex and HF history were not independently associated with ISR in the multivariable model (Table 4).

Given that the analysis was restricted to patients undergoing repeat coronary angiography, the observed inverse associations should be interpreted cautiously and may reflect selection effects and residual confounding within a repeat-angiography cohort rather than a protective biological effect.

Table 4. Multivariable logistic regression for angiographically confirmed ISR

Predictor	Adjusted OR	95% CI	p-value
Age ≥65 years	1.50	1.00–2.23	0.048
Male sex	1.51	0.94–2.44	0.090
Obesity	1.56	1.04–2.36	0.032
ACS presentation	1.29	1.11–1.49	0.001
T2DM	0.54	0.35–0.84	0.006
eGFR <60 mL/min/1.73 m²	0.56	0.33–0.95	0.033
PAD	0.50	0.25–1.02	0.056
HF history	0.68	0.40–1.14	0.142

Outcome: ISR ≥50% (yes/no) in the repeat-angiography cohort; Model: multivariable logistic regression; ORs adjusted for all covariates listed.

DISCUSSION

In this multicenter real-world registry of patients with prior PCI who underwent repeat coronary angiography, angiographically confirmed ISR was found in 13.7%. This frequency is higher than in many contemporary series of unselected post-PCI populations, and the difference is plausibly explained by our denominator: we studied a repeat-angiography cohort enriched with symptomatic referrals and ACS presentations, where the pre-test probability of clinically relevant stent failure is intrinsically higher than in routine post-PCI follow-up cohorts. Contemporary syntheses and expert statements emphasize that the "observed" ISR rate depends strongly on the clinical pathway that leads to repeat angiography, as well as on the definitions and ascertainment strategy used for restenosis[1,7]. In addition, our registry includes patients with prior PCI performed across different years and technologies; without explicitly modeling the time from index PCI to repeat angiography, early and late presentations may be mixed, which can influence both the measured ISR frequency and its correlates.

Clinically, ISR clustered with a more adverse cardiometabolic and atherosclerotic phenotype (T2DM, PAD, prior CABG) and with less favorable renal function markers—patterns consistent with the established concept that ISR reflects both local vascular response and systemic risk milieu [1]. The more atherogenic lipid profile in the ISR group further reinforces the importance of aggressive secondary prevention. Importantly, LDL-C goal attainment was strikingly low in our cohort, underscoring a substantial, actionable treatment gap relative to current European Guidelines for very-high-risk patients[8]. This finding is clinically relevant regardless of ISR status, because contemporary evidence shows that substantial residual cholesterol risk can persist even with intensive LDL-lowering and may be further mitigated by additional lipid-lowering strategies[9].

Beyond lipids, an important (and often underappreciated) contributor to post-PCI prognosis is residual risk that is not routinely quantified in everyday practice, particularly residual inflammatory risk. Large analyses demonstrate that elevated inflammatory markers identify patients with persistent risk despite effective LDL-C lowering, including in intensively treated cohorts [9,10]. Conceptual and clinical reviews also highlight that residual atherosclerotic risk is multidimensional—encompassing inflammatory, thrombotic, and metabolic pathways that are frequently under-recognized in routine care [11]. In the context of ISR, such unmeasured residual risk domains may partly explain why clinical recurrence and repeat angiography occur even when conventional risk factors appear reasonably controlled, and they represent an important direction for future registry development in our setting.

Our multivariable model confirmed that age, obesity, and ACS presentation were independently associated with ISR, while the direction of some adjusted associations differed from unadjusted comparisons. In a cohort defined by repeat angiography, such patterns may reflect selection effects and residual confounding rather than protective biology—an interpretation consistent with methodological cautions in contemporary ISR consensus documents[7]. The modest explanatory performance of the model supports the notion that

important determinants were not captured, particularly lesion-, stent-, and procedure-related characteristics and the use of intravascular imaging, which are central to mechanistic ISR phenotyping and treatment selection [1,7]. In parallel, contemporary consensus efforts in the drug-coated balloon era stress the need for standardized lesion assessment and harmonized endpoints to enable meaningful comparisons across studies and regions[12,13].

Limitations

This study has several limitations. First, its retrospective observational design precludes causal inference and leaves the possibility of residual confounding. Second, the analysis was restricted to a repeat-angiography cohort (elective evaluation or ACS-related angiography), which may introduce selection effects and limits generalizability to all patients after index PCI; therefore, the reported ISR frequency should not be interpreted as population-level post-PCI incidence. Third, ISR was assessed from routine angiography reports without a centralized core laboratory or quantitative coronary angiography, and inter-operator variability across centers cannot be excluded. Fourth, key lesion-, stent-, and procedure-related characteristics (e.g., stent type/length/diameter, lesion complexity, optimization strategy, intravascular imaging) were not available, and the time interval from index PCI to repeat angiography was not analyzed. Finally, outpatient medication data reflect documented therapy at presentation and do not capture adherence or dose intensity.

CONCLUSION

In a multicenter real-world repeat-angiography cohort, angiographically confirmed ISR was detected in 13.7% of patients with prior PCI. ISR was more frequently observed in patients with a higher burden of comorbidity and a less favorable cardiometabolic profile, alongside low LDL-C target attainment in routine practice. These findings support strengthening secondary prevention and motivate future analyses incorporating procedural/anatomical determinants and timing from index PCI to repeat angiography to refine risk stratification for clinically relevant ISR.

Conflict of interest

The authors declare no conflict of interest.

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Authors' contributions

Data gathering and idea owner of this study: Kurmanalina Gulnara, Medovchshikov Vadim, Zholdin Bekbolat;

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Editing and approval of final draft: Boshanov Zhantilek, Kurmanalina Gulnara, Medovchshikov Vadim, Yeshniyazov Nurlan, Mussin Nadiar, Zholdin Bekbolat.

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Data Availability Statement

All data generated or analyzed in this study can be obtained from the corresponding author upon inquiry.

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