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Long-term outcomes of percutaneous coronary intervention for in-stent restenosis among Medicare beneficiaries

Hector Tamez[1], MD, MPH; Eric A. Secemsky[1], MD, MSc; Linda R. Valsdottir[1], MS; Issam D. Moussa[2], MD, MBA; Yang Song[3], MSc; Charles A. Simonton[4], MD; C. Michael Gibson[1,3], MD; Jeffrey J. Popma[5], MD; Robert W. Yeh[1,3]*, MD, MSc

1. Richard A. and Susan F. Smith Center for Outcomes Research in Cardiology, Division of Cardiology, Beth Israel Deaconess Medical Center, Boston, MA, USA; 2. Carle Health System, Carle Illinois College of Medicine, Beckman Institute for Advanced Science and Technology, University of Illinois, Urbana, IL, USA; 3. Baim Institute for Clinical Research, Boston, MA, USA; 4. Abiomed Inc., Danvers, MA, USA; 5. Medtronic, Santa Rosa, CA, USA

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KEYWORDS

- death
- in-stent restenosis
- myocardial infarction
- prior PCI
- stroke

Abstract

Background: In-stent restenosis (ISR) is highly prevalent and leads to repeat revascularisation. Long-term implications of ISR are poorly understood.

Aims: This study aimed to evaluate the long-term outcomes of patients undergoing percutaneous coronary intervention (PCI) for ISR.

Methods: National Cardiovascular Data Registry CathPCI records for individuals aged ≥65 years undergoing PCI from July 2009 to December 2014 were linked to Medicare claims. Baseline characteristics and long-term rates of death, myocardial infarction (MI), repeat revascularisation including target vessel revascularisation (TVR), and major adverse cardiovascular and cerebrovascular events (MACCE) were compared between ISR PCI versus *de novo* lesion PCI.

Results: Of 653,304 individuals, 10.2% underwent ISR PCI and 89.8% underwent *de novo* lesion PCI. The median duration of follow-up was 825 days (quartile 1: 352 days–quartile 3: 1,379 days). The frequency of MACCE (55.6% vs 45.0%; p<0.001), all-cause mortality (27.8% vs 25.5%; p<0.001), MI (19.0% vs 12.3%; p<0.001), repeat revascularisation (31.9% vs 18.6%; p<0.001), TVR (22.4% vs 8.0%; p<0.001), and stroke (8.8% vs 8.3%; p=0.005) was higher after ISR PCI. After multivariable adjustment, ISR PCI remained associated with worse long-term outcomes than after *de novo* lesion PCI (hazard ratio [HR] for MACCE 1.24 [95% CI: 1.22, 1.26], mortality 1.07 [95% CI: 1.05, 1.09], MI 1.44 [95% CI: 1.40, 1.48], repeat revascularisation 1.55 [95% CI: 1.51, 1.59], and TVR 2.50 [95% CI: 2.42, 2.58]).

Conclusions: ISR PCI was common and was associated with a significantly higher risk of recurrent long-term major ischaemic events compared to patients undergoing *de novo* lesion PCI. There remains a need for new strategies to minimise ISR.

**Corresponding author: Richard A. and Susan F. Smith Center for Outcomes Research in Cardiology, Division of Cardiology, Beth Israel Deaconess Medical Center, 375 Longwood Ave, 4th floor, Boston, MA 02215, USA. E-mail: ryeh@bidmc.harvard.edu*

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Abbreviations

BMS	bare metal stent
CABG	coronary artery bypass graft
CI	confidence interval
CMS	centres for Medicare and Medicaid Services
DES	drug-eluting stent
ISR	in-stent restenosis
MACCE	major adverse cardiovascular and cerebrovascular events
MI	myocardial infarction
PCI	percutaneous coronary intervention
TVF	target vessel failure
TVR	target vessel revascularisation
USA	United States of America

Introduction

Over half a million percutaneous coronary interventions (PCI) with metallic stents are performed annually in the United States of America (USA)[1]. These patients are at risk of in-stent restenosis (ISR) and development of recurrent symptoms. The incidence rate of ISR is reported to be between 5% and 20% with drug-eluting stents (DES) five years post procedure[2-4].

Despite improvements in short-term outcomes after DES placement, including low rates of stent thrombosis and one-year target vessel failure (TVF), patients receiving these stents have persistently rising rates of TVF over the long term[5,6]. Furthermore, the presence of stents may impact on future interventions such as repeat stenting and coronary artery bypass graft (CABG) surgery.

Despite the high annual number of PCIs performed worldwide, there is a poor understanding of the burden of ISR and the long-term outcomes associated with ISR PCI. In this study, we evaluated the frequency of ISR PCI in a large representative sample of older adults in the USA, the patient and procedural characteristics, and the associated long-term outcomes.

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Methods

STUDY POPULATION

Procedures in the American College of Cardiology National Cardiovascular Data Registry CathPCI Registry were considered for inclusion[7]. This registry includes data on PCIs from ~1,400 US catheterisation laboratories. Data elements are prospectively acquired using standardised forms and definitions.

Our analysis included all PCIs performed among patients aged ≥65 years between July 2009, the date of implementation of Version 4 of the CathPCI data collection form, and December 2014. Patients who underwent salvage PCI or presented with cardiogenic shock or cardiac arrest were excluded, as they have high mortality unrelated to their lesion characteristics. In patients with multiple PCIs, the first procedure was the index procedure. Patients were categorised as undergoing PCI for ISR if 1) the index lesion was identified as a restenotic lesion, and 2) they had a documented history of prior PCI in the CathPCI Registry.

To obtain long-term outcomes, patients were linked to centres for Medicare and Medicaid services (CMS) fee-for-service beneficiary claims data based on social security number, date of birth, and sex. Claims up to 31 December 2015 were used to ensure that each patient had ≥1 year of follow-up. CMS provides health insurance coverage for the majority of adults aged ≥65 years in the USA, and these claims data have been extensively used for health outcomes research.

COVARIATES AND OUTCOMES

The primary exposure was PCI for ISR versus PCI for a *de novo* lesion. These variables are specified in the CathPCI data collection instrument and are site reported. Covariates included demographic characteristics (including age, sex, and race/ethnicity), prior medical history (including diabetes mellitus, current dialysis, hypertension, and dyslipidaemia), and procedural and lesion characteristics (including PCI indication, bifurcation lesion, lesion in graft, chronic total occlusion, stent type, total stent length, and minimum stent diameter).

The primary outcome was the occurrence of major adverse cardiovascular and cerebrovascular events (MACCE), defined as the composite of death from any cause, MI, stroke and repeat revascularisation. Validated International Classification of Diseases, Ninth Revision codes were used to identify these endpoints **(Supplementary Table 1)**[8-10]. Secondary outcomes included the component outcomes of mortality, MI, repeat revascularisation (any vessel), target vessel revascularisation (TVR), and stroke. We extracted information on TVR by re-linking repeat revascularisation events found in CMS data to corresponding entries in the CathPCI Registry. We defined TVR as repeat PCI in a major epicardial vessel territory (left main, left anterior descending, left circumflex or right coronary artery) treated during the index admission.

STATISTICAL ANALYSIS

Baseline patient and procedural characteristics were obtained from the CathPCI Registry and compared using standardised differences. We used the Kaplan-Meier method to estimate the cumulative incidence of the primary and secondary outcomes and used the log-rank statistic to compare the differences between groups. A Cox proportional hazards regression model that included possible confounders selected *a priori* (age, sex, race, ethnicity, diabetes, chronic kidney disease stage, hypertension, dyslipidaemia, PCI indication, bifurcation lesion, lesion in graft, chronic total occlusion, stent type, total stent length, and minimum stent diameter) was used to perform an adjusted time-to-event analysis. A robust sandwich covariance matrix estimate was applied to account for the intracluster dependence of patients nested in hospitals.

Because patients with ISR PCI have a longer history of known coronary disease compared with those undergoing *de novo* lesion PCI, we performed a sensitivity analysis restricting the *de novo* lesion PCI group to patients with a history of prior PCI in another vessel. Additional subgroup and sensitivity analyses are provided

in **Supplementary Appendix 1**. Statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC, USA).

The institutional review board of the Beth Israel Deaconess Medical Center exempted this study from review.

Results

BASELINE CHARACTERISTICS

Of the 3,017,110 patients who had a PCI between July 2009 and December 2014, 1,568,783 (52.0%) were aged ≥65 years **(Figure 1)**. The main reasons for exclusion (4.5% of patients) were salvage PCI (0.4%), presence of cardiogenic shock (2.9%), cardiac arrest (0.9%) and inconsistent documentation of ISR PCI (ISR PCI listed at index but no prior history of PCI [0.3%]). Fifty-six percent of the remainder of patients were unable to be linked to CMS: 20.9% were enrolled in Medicare Advantage plans which are privately administered health plans for which fee-for-service data were not available, and 35.5% did not have sufficient data to be linked. The final cohort included 653,304 patients **(Figure 1)**. There were no clinically significant differences between linked and non-linked patients **(Supplementary Table 2)**.

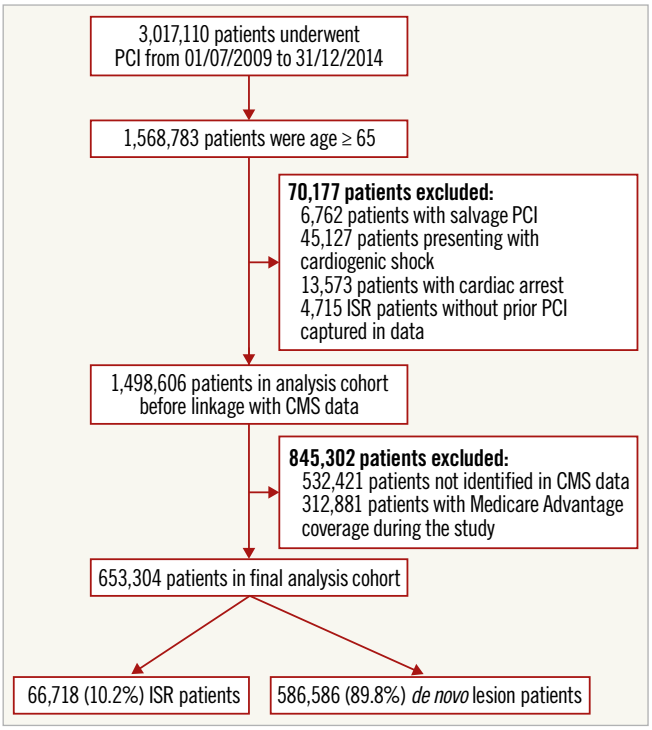

Figure 1. *Study flow diagram.*

Among this cohort, 66,718 patients (10.2%) underwent PCI for ISR and 586,586 (89.8%) underwent PCI for a *de novo* lesion. Patients undergoing ISR PCI were more likely to have diabetes mellitus (43.1% vs 36.1%), dyslipidaemia (92.7% vs 79.8%), prior MI (50.4% vs 24.7%) and prior CABG (30.6% vs 21.0%) compared to patients undergoing PCI to *de novo* lesions **(Table 1)**. The frequency table by stent characteristics is shown in **Supplementary Table 3**.

PROCEDURAL CHARACTERISTICS

Presentation with ST-elevation MI was less common in patients undergoing ISR PCI (7.1%) versus *de novo* lesion PCI (12.4%). Bare metal stents (BMS) were used in 7.2% of patients with ISR versus 21.2% of patients with *de novo* lesions; plain old balloon angioplasty was more common in patients with ISR (19.4%) versus *de novo* lesions (7.1%). Cutting or scoring balloon use was more frequent in patients with ISR (17.3%) versus *de novo* lesions (3.8%). Use of laser or rotational atherectomy was similar between groups. There was no difference in the ability to cross with a guidewire between groups.

UNADJUSTED COMPARISONS OF OUTCOMES AFTER ISR PCI AND DE NOVO LESION PCI

The median duration of follow-up was 825 days (quartile 1: 352 days–quartile 3: 1,379 days). The cumulative incidence of all-cause rehospitalisation at 30 days was 10.3% in the ISR group and 10.6% in the *de novo* lesion PCI group (p=0.02), and at 90 days was 20.4% in the ISR group and 20.3% in the *de novo* lesion PCI group (p=0.87). Patients undergoing ISR PCI had a higher cumulative incidence of MACCE compared to those undergoing *de novo* lesion PCI (55.6% vs 45.0% at 4 years; p<0.001) **(Figure 2)**. There was a higher cumulative incidence of all secondary outcomes at 4 years in patients undergoing ISR PCI compared to those undergoing PCI to *de novo* lesions: all-cause mortality (27.8% vs 25.5%; p<0.001), MI (19.0% vs 12.3%; p<0.001), repeat revascularisation (31.9% vs 18.6%; p<0.001), TVR (22.4% vs 8.0%; p<0.001), and stroke (8.8% vs 8.3%; p=0.005). Definite stent thrombosis requiring PCI in the same vessel as index PCI was 1.98% in the ISR group and 0.43% in the *de novo* group (p<0.001). For the results of the ISR subgroup comparisons, see **Supplementary Figure 1** for primary and secondary outcomes in the ISR group stratified by time to ISR, and **Supplementary Figure 2** for the cumulative incidence of events after PCI for ISR of different vessels.

ADJUSTED COMPARISON OF OUTCOMES AFTER ISR PCI WITH DE NOVO PCI

Multivariable adjustment showed that patients undergoing ISR PCI had an increased hazard of MACCE (hazard ratio [HR] 1.24 [95% CI: 1.22, 1.26]; p<0.001) **(Table 2)** versus *de novo* lesion PCI. Most components of MACCE were increased in patients undergoing ISR PCI compared with *de novo* lesion PCI, including all-cause mortality (1.07 [95% CI: 1.05, 1.09]; p<0.001), MI (1.44 [95% CI: 1.40, 1.48]; p<0.001), repeat revascularisation (1.55 [95% CI: 1.51, 1.59]; p<0.001) and TVR (2.50 [95% CI: 2.42, 2.58]; p<0.001). Adjusted rates of stroke were not significantly different between groups (1.03 [95% CI: 0.99, 1.07]; p=0.11). Findings were similar after excluding patients with unknown prior stent type **(Supplementary Table 4)**.

COMPARISON OF DE NOVO AND ISR PCI OUTCOMES AMONG PATIENTS WITH PRIOR PCI

After restricting the population to patients with a history of prior PCI in any vessel, baseline characteristics between groups were similar

Table 1. Baseline characteristics of patients undergoing PCI for in-stent restenosis versus de novo coronary lesions.

	ISR group (N=66,718)	De novo group (N=586,586)	Standardised difference
Demographics			
Age, mean±SD	74.2±6.8	74.6±7.0	–0.064
Male, n (%)	43,865 (65.7%)	367,550 (62.7%)	0.064
Race			
White	61,155 (92.5%)	538,583 (92.7%)	–0.006
Black	3,529 (5.3%)	29,695 (5.1%)	0.01
Other	1,414 (2.1%)	12,782 (2.2%)	–0.004
Ethnicity (Hispanic)	2,077 (3.1%)	19,376 (3.3%)	–0.011
Smoker (current/recent), n (%)	8,411 (12.6%)	80,201 (13.7%)	–0.032
Past medical history			
Diabetes mellitus, n (%)	28,773 (43.1%)	211,897 (36.1%)	0.143
Hypertension, n (%)	61,708 (92.5%)	503,326 (85.8%)	0.216
Dyslipidaemia, n (%)	61,789 (92.7%)	467,691 (79.8%)	0.38
Family history of premature CAD, n (%)	14,136 (21.2%)	112,167 (19.1%)	0.052
Prior myocardial infarction, n (%)	33,631 (50.4%)	144,656 (24.7%)	0.552
Prior PCI, n (%)	66,718 (100.0%)	161,501 (27.5%)	2.294
Prior CABG, n (%)	20,428 (30.6%)	123,139 (21.0%)	0.221
Dialysis (current), n (%)	2,187 (3.3%)	13,885 (2.4%)	0.055
LVEF <40%, n (%)	10,061 (21.3%)	88,111 (20.0%)	0.032
Procedural characteristics			
PCI indication, n (%)			
STEMI	4,735 (7.1%)	72,772 (12.4%)	–0.18
NSTEMI/unstable angina	37,911 (56.8%)	306,939 (52.3%)	0.09
Staged PCI	2,857 (4.3%)	23,287 (4.0%)	0.016
Stable angina	21,198 (31.8%)	183,393 (31.3%)	0.011
Stent type, n (%)			
DES	48,953 (73.4%)	421,007 (71.8%)	0.036
BMS	4,804 (7.2%)	124,148 (21.2%)	–0.409
POBA only	12,961 (19.4%)	41,431 (7.1%)	0.371
Atherectomy, n (%)	12,265 (18.4%)	31,791 (5.4%)	0.409
Laser	327 (0.5%)	875 (0.1%)	0.06
Rotational atherectomy	612 (0.9%)	9,492 (1.6%)	–0.063
Procedural characteristics			
Cutting or scoring balloon angioplasty	11,533 (17.3%)	22,576 (3.8%)	0.448
Lesion length, mm, mean±SD	18.46±11.22	18.40±10.57	0.005
Pre-procedure TIMI flow, n (%)*			
0	9,511 (10.0%)	89,377 (11.4%)	–0.046
1	6,735 (7.1%)	64,125 (8.2%)	–0.042
2	19,114 (20.0%)	156,254 (19.9%)	0.003
3	60,007 (62.9%)	475,191 (60.5%)	0.049
Chronic total occlusion, n (%)	2,503 (26.8%)	17,675 (20.2%)	0.157
Lesion in graft, n (%)	10,232 (10.7%)	52,397 (6.7%)	0.144
Bifurcation lesion, n (%)	11,337 (11.9%)	94,921 (12.1%)	–0.006
Thrombus present, n (%)	7,358 (7.7%)	77,898 (9.9%)	–0.078
Able to cross with guidewire, n (%)	94,424 (98.7%)	774,774 (98.4%)	0.026
Post-procedure TIMI flow, n (%)*			
0	633 (0.7%)	5,615 (0.7%)	–0.007
1	215 (0.2%)	2,400 (0.3%)	–0.016
2	886 (0.9%)	9,933 (1.3%)	–0.033
3	92,464 (98.2%)	754,987 (97.7%)	0.034
Prior stent type, n (%)			
DES	37,525 (51.2%)		
Non-DES	15,666 (21.4%)		
Type unknown	20,107 (27.4%)		
Stent type, n (%)			
BMS	7,876 (9.3%)	184,142 (22.3%)	–0.363
DES	76,939 (90.7%)	640,432 (77.7%)	0.363
Stent length, mm (mean±SD)	19.20±7.55	18.53±7.06	0.091
Stent diameter, mm (mean±SD)	2.99±0.50	2.96±0.52	0.062

Values are number (%) or mean±standard deviation (SD). *n reflects total number of lesions. BMS: bare metal stent; CABG: coronary artery bypass grafting; CAD: coronary artery disease; DES: drug- eluting stent; LVEF: left ventricular ejection fraction; NSTEMI: non-ST-segment elevation myocardial infarction; PCI: percutaneous coronary intervention; POBA: plain old balloon angioplasty; STEMI: ST-segment elevation myocardial infarction; TIMI: Thrombolysis In Myocardial Infarction

(Supplementary Table 5). Procedural characteristics included similar indications for PCI, lower BMS use (7.2% vs 17.0%) and higher use of cutting and scoring balloon angioplasty (17.3% vs 4.7%) in the ISR PCI versus the *de novo* lesion PCI group. The cumulative incidence of MACCE, all-cause mortality, MI, stroke, repeat revascularisation, and TVR is shown in **Figure 3**.

Multivariable adjustment showed an increased hazard of MACCE (1.19 [95% CI: 1.17, 1.21]; p<0.001), MI (1.25 [95% CI: 1.21, 1.30]; p<0.001), repeat revascularisation (1.48 [95% CI: 1.44, 1.53]; p<0.001), and TVR (2.16 [95% CI: 2.07, 2.24]; p<0.001), in patients undergoing ISR PCI compared to patients undergoing PCI to a *de novo* lesion in the group with a prior history of PCI **(Table 3)**. There continued to be no significant difference in all-cause mortality (1.02 [95% CI: 0.99, 1.04]; p=0.17) or stroke (0.98 [95% CI: 0.93, 1.03]; p=0.40) between groups after adjustment.

Supplementary Appendix 2 shows the results of the ISR subgroup comparisons (outcomes for patients undergoing ISR PCI vs PCI to a *de novo* lesion adjusted for stent type used for the initial PCI **[Supplementary Table 6]**; baseline characteristics by treatment in ISR group **[Supplementary Table 7]**; outcomes for ISR patients treated with BMS or plain old balloon angioplasty vs DES **[Supplementary Table 8]**; ISR patient characteristics by stent type in the initial PCI **[Supplementary Table 9]**; outcomes for ISR patients with BMS vs DES in the initial PCI **[Supplementary Table 10]**; patient characteristics in a propensity matched cohort **[Supplementary**

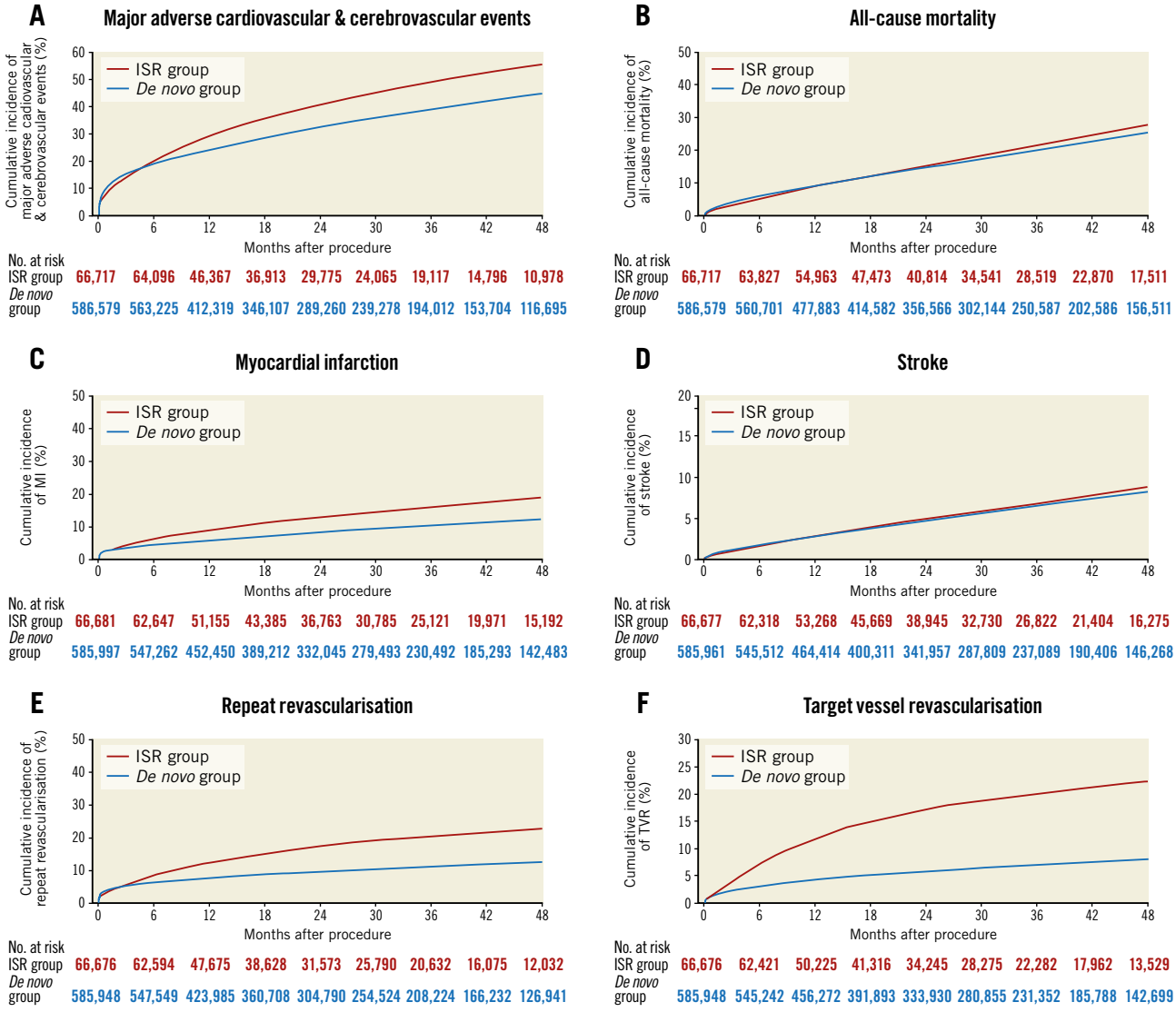

Figure 2. *Cumulative incidence of primary and secondary outcomes in patients undergoing ISR PCI and de novo lesion PCI. The cumulative incidence of major adverse cardiovascular and cerebrovascular events (A), all-cause mortality (B), myocardial infarction (C), stroke (D), repeat revascularisation (E) and target vessel revascularisation (F) in patients undergoing ISR PCI (red line) versus de novo lesion PCI (blue line).*

Table 2. Adjusted hazard ratios for primary and secondary outcomes of patients undergoing ISR PCI versus PCI to a de novo lesion.

Endpoint	Hazard ratio [95% CI]	*p*-value
MACCE	1.24 [1.22, 1.26]	<0.0001
All-cause mortality	1.07 [1.05, 1.09]	<0.0001
MI	1.44 [1.40, 1.48]	<0.0001
Stroke	1.03 [0.99, 1.07]	0.11
Repeat revascularisation	1.55 [1.51, 1.59]	<0.0001
TVR	2.50 [2.4, 2.58]	<0.0001

Hazard ratios were estimated from Cox regression models adjusted for age, sex, race, ethnicity, diabetes, chronic kidney disease stage, hypertension, dyslipidaemia, PCI indication, bifurcation lesion, lesion in graft, chronic total occlusion, stent type, total stent length, and minimum stent diameter. MACCE: major adverse cardiovascular and cerebrovascular events; MI: myocardial infarction; TVR: target vessel revascularisation

Table 11]; outcomes for ISR patients and *de novo* lesion PCI patients in a propensity matched cohort **[Supplementary Table 12]**).

Discussion

In this large national study of older US patients undergoing PCI based on a registry linked to long-term claims data for follow-up, we observed that PCI for ISR is strongly associated with worse long-term outcomes, including higher risk of MACCE, MI, repeat revascularisation, and TVR. To our knowledge, this is the first study evaluating long-term outcomes after ISR PCI using modern stent technologies in a large, comprehensive sample of elderly PCI patients in the USA. It highlights the importance of recognising the occurrence of restenosis as a prognostically meaningful event. Previous studies have used small cohorts and were designed to compare different stent iterations[11-15] or to compare drug-coated balloons with stents[16-18].

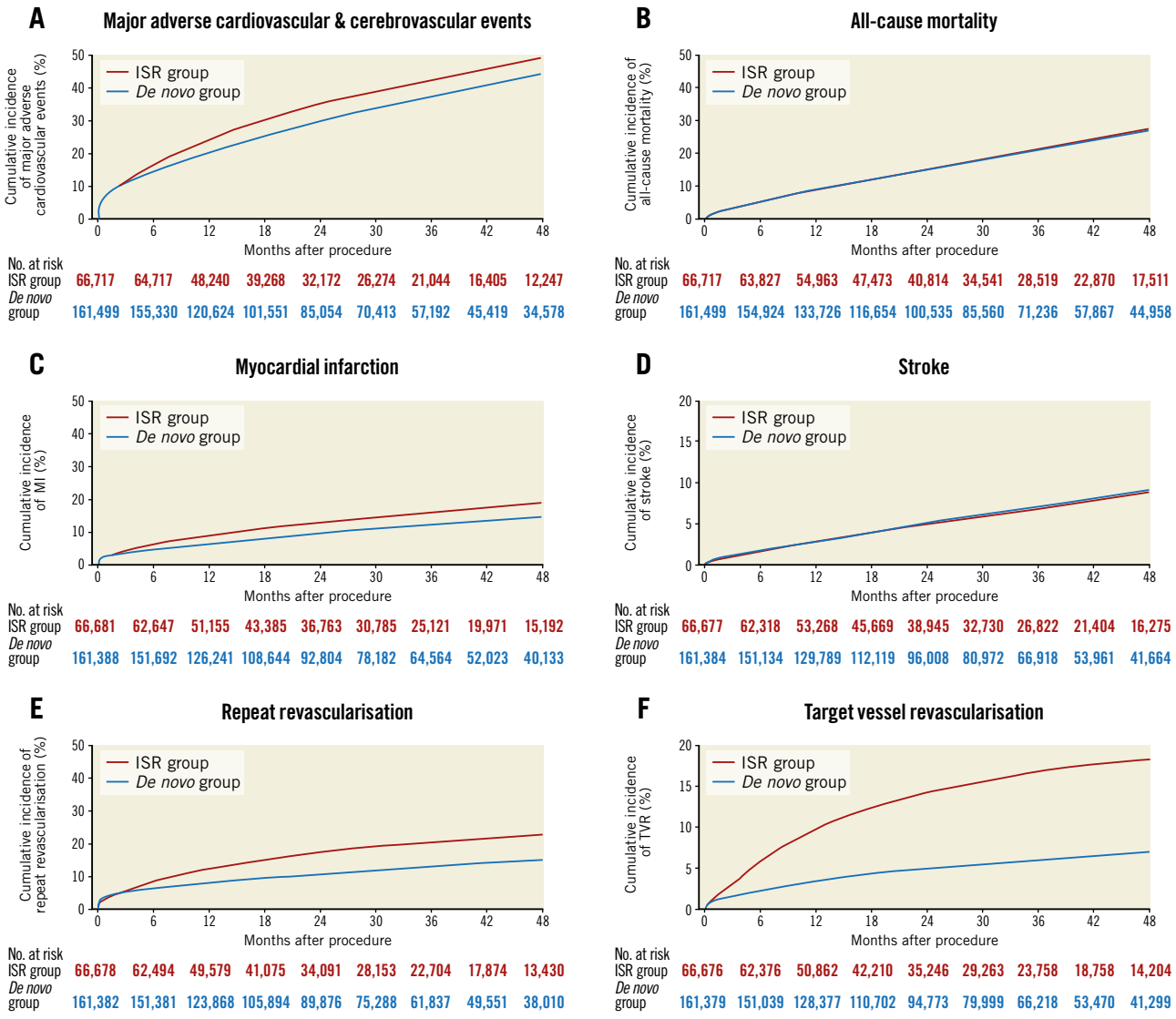

Figure 3. *Cumulative incidence of primary and secondary outcomes in patients undergoing ISR PCI and de novo lesion PCI with history of prior PCI. The cumulative incidence of major adverse cardiovascular and cerebrovascular events (A), all-cause mortality (B), myocardial infarction (C), stroke (D), repeat revascularisation (E) and target vessel revascularisation (F) in patients undergoing ISR PCI (red line) versus de novo lesion PCI (blue line).*

Table 3. Primary and secondary outcomes for patients undergoing ISR PCI versus PCI for a de novo lesion, restricted to patients with prior PCI.

Endpoint	Hazard ratio [95% CI]	*p*-value
Death, MI or stroke (MACCE)	1.19 [1.17, 1.21]	<0.0001
All-cause mortality	1.02 [0.99, 1.04]	0.17
MI	1.25 [1.21, 1.30]	<0.0001
Stroke	0.98 [0.93, 1.03]	0.40
Repeat revascularisation	1.48 [1.44, 1.53]	<0.0001
TVR	2.16 [2.07, 2.24]	<0.0001

Hazard ratios were estimated from Cox regression models adjusted for age, sex, race, ethnicity, diabetes, chronic kidney disease stage, hypertension, dyslipidaemia, PCI indication, bifurcation lesion, lesion in graft, chronic total occlusion, stent type, total stent length, and minimum stent diameter. MACCE: major adverse cardiovascular and cerebrovascular events; MI: myocardial infarction; TVR: target vessel revascularisation

Not surprisingly, baseline characteristics differed between the groups, with patients who underwent ISR PCI having a higher prevalence of comorbidities. To minimise confounders, we performed an adjusted analysis and a subgroup analysis restricting the cohort to patients with a history of prior PCI, which ameliorated the differences in baseline characteristics. The association between ISR PCI and increased rates of MI and repeat revascularisation, including TVR, persisted even after this restriction, but there was no longer a difference in all-cause mortality or stroke. A small difference in all-cause mortality was still seen in the propensity-matched population. This could indicate that patients undergoing ISR PCI and PCI to a *de novo* lesion have significant differences in unmeasured confounders that are not captured by our multivariable or propensity score models. The similar mortality rates after matching on prior PCI suggest that, although ISR PCI portends a worse

prognosis with regard to the need for subsequent procedures, this may not influence more meaningful clinical outcomes such as death.

We also found that ISR PCI of a previously placed DES versus BMS was associated with more frequent subsequent MI and repeat revascularisation. This may be because patients with previously placed BMS had higher mortality, which may reflect that they are sicker and less likely to receive future invasive treatment. It is also plausible that patients who develop restenosis in a DES have more aggressive coronary disease than those with restenosis of a BMS. This is consistent with a recent meta-analysis which found higher rates of treatment failure in the treatment of ISR of a DES than ISR of a BMS[19].

The cumulative frequency of repeat revascularisation nearly doubled in patients undergoing ISR PCI compared with *de novo* lesion PCI. Most repeat revascularisations were explained by TVR (70% in ISR PCI vs 43% in *de novo* lesion PCI). The cumulative frequencies of MACCE and TVR were higher than described in randomised trials[16,20]. In a recent meta-analysis including data on >25,000 patients in randomised trials of metallic stents, patients were younger (62 vs 74 years) and had fewer comorbidities compared to our cohort. The five-year MACCE rate was lower in their study (9.4%) as compared to ours (45% in the *de novo* lesion PCI group and 55.6% in the ISR PCI group)[20]. Although our study was limited to older adults by design, these findings underscore how trial outcomes may differ from those in real-world practice.

Our study has important clinical implications. First, despite the technological advances of newer DES with lower incidence of ISR and the general impression of restenosis being benign, our study shows increased morbidity among patients who undergo ISR PCI. Our findings reinforce the importance of using all techniques available to reduce ISR, including adequate stent expansion and apposition and maximising luminal area[13,21]. Furthermore, use of intracoronary imaging can help to corroborate adequate lesion preparation and stent expansion before deployment of a second layer of stent, and has been shown to decrease the rate of MACCE[22]. Lastly, optimal medical therapy, novel stent technologies, and the emergence of drug-coated balloons may decrease the rate of ISR and change its treatment. Further research is needed to demonstrate whether improved treatments for restenosis can mitigate some of the late clinical events associated with ISR, and thus demonstrate that ISR is not only a strong marker of severe and aggressive coronary artery disease, but also causal of adverse outcomes.

Limitations

Our study has several limitations. This is an observational study so we cannot be certain that the association between restenosis and subsequent events is causal, and events may be missing or misclassified. Due to the nature of the data, for patients who underwent PCI to several vessels during the index procedure, we cannot distinguish which vessel had TVR, and we cannot determine if repeat revascularisation in the target vessels occurred in the same lesion. Similarly, because the data set lacks information on all prior PCIs for patients with ISR, other modelling approaches such as treating ISR PCI as a time-dependent covariate were not possible. Furthermore, MI could not be attributed to the treated lesion. We cannot rule out the potential for residual confounding, and we were unable to adjust for variables that were not present in the data. However, after limiting the *de novo* lesion PCI population to those with prior PCI in remote vessels, baseline characteristics between groups appeared balanced. Our study excluded 4,715 patients for whom we lacked information about prior PCI, and we were unable to link a large fraction of individuals in the CathPCI database to CMS claims. However, there were no clinically significant differences in measured variables between the linked and non-linked groups. Finally, we do not have information on concomitant medications which could differ and influence event rates between groups.

Conclusions

Patients who undergo ISR PCI are at higher risk of MACCE, MI, and repeat revascularisation, particularly of the target vessel, compared with patients undergoing PCI to *de novo* lesions. Novel devices and techniques to prevent the occurrence of restenosis and improve its treatment are needed.

Impact on daily practice

Patients who undergo PCI for in-stent restenosis are at higher risk of major adverse cardiovascular and cerebrovascular events such as myocardial infarction and the need for repeat revascularisation, including target vessel revascularisation, compared with patients undergoing the procedure for a *de novo* lesion. Practitioners should be aware of this increased risk and should use all available techniques to prevent the occurrence of restenosis and improve its treatment.

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Conflict of interest statement

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Supplementary data

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Supplementary Table 11. Patient characteristics - propensity score-matched cohort.

Supplementary Table 12. Primary and secondary outcomes for patients undergoing ISR PCI or PCI for a *de novo* lesion in a propensity score-matched cohort.

The supplementary data are published online at: https://eurointervention.pcronline.com/doi/10.4244/EIJ-D-19-01031

Supplementary data

Supplementary Appendix 1. Methods

We performed several subgroup analyses comparing outcomes based on the type of stent in the initial procedure (before ISR) for the ISR group, the type of stent used for the ISR PCI, and the vessel of the ISR.

As a sensitivity analysis, we performed a 1:1 propensity score match of ISR and de novo PCI patients including age, sex, race, ethnicity, diabetes, chronic kidney disease stage, hypertension, dyslipidaemia, PCI indication, bifurcation lesion, lesion in graft, total chronic occlusion, stent type, total stent length, and minimum stent diameter.

Supplementary Appendix 2. Results

Outcomes among ISR subgroups

There were no significant changes in outcomes after adjusting by the different stent types used for the initial PCI **(Supplementary Table 6)**. Patients whose ISR occurred a shorter time after the prior PCI also demonstrated worse unadjusted outcomes (cumulative incidence of MACCE after <1 month, 61.47%; after 1-5 months, 62.26%; after 6-12 months, 58.23%; after 1-2 years, 57.68%; after >2 years, 52.48%; p<0.001) **(Supplementary Figure 1)**.

There were significant differences in characteristics among patients who underwent PCI for ISR using DES vs BMS vs POBA **(Supplementary Table 7)**. ISR treatment with BMS had an increased hazard of MACCE (adjusted HR 1.29 [95% CI: 1.24, 1.34]; p<0.001), and all-cause mortality (adjusted HR 1.64 [95% CI: 1.55, 1.75]; p<0.001) as compared to DES treatment **(Supplementary Table 8)**. Similarly, ISR treatment with POBA had an increased hazard of MACCE (adjusted HR 1.18 [95% CI: 1.16, 1.23]; p<0.001), all-cause mortality (adjusted HR 1.25 [95% CI: 1.19, 1.31]; p<0.001), repeat revascularisation (adjusted HR 1.084 [95% CI: 1.037, 1.13]; p<0.001) and TVR (HR 1.27 [95% CI: 1.20, 1.33]; p<0.001) as compared to DES treatment.

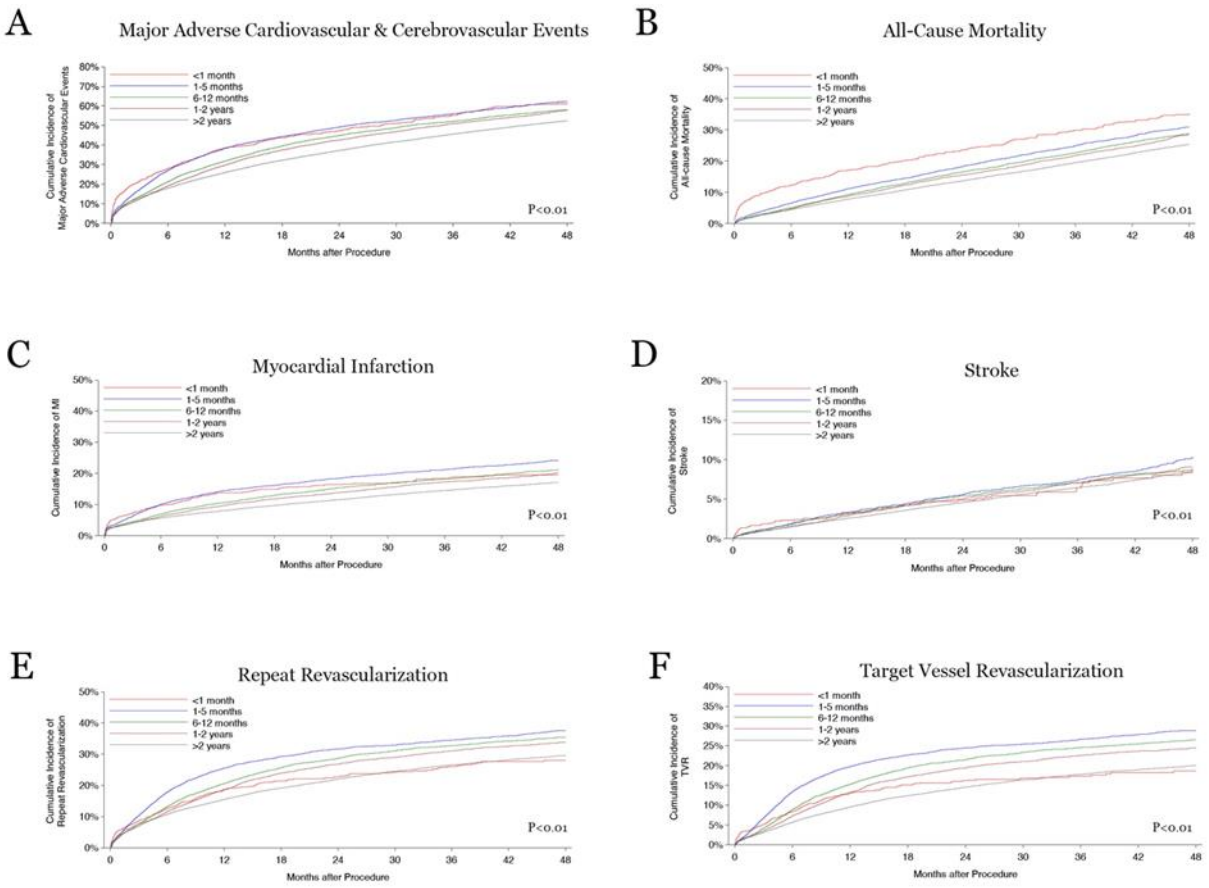
When comparing the subgroups of patients who had ISR PCI of a prior BMS versus prior DES we found differences in baseline characteristics **(Supplementary Table 9)**. Patients who received BMS at the initial PCI (before they developed ISR) were more likely to be older (74.8±7.0 vs 73.4±6.7; SD 0.13) and less likely to have a history of diabetes mellitus (39.5% vs 44.8%; SD -0.11) or history of CABG (25% vs

33.5%; SD -0.16) compared to patients who previously received DES. Multivariable models revealed a lower risk of MACCE (0.94 [95% CI: 0.91, 0.97]; p<0.001), MI (0.86 [95% CI: 0.79, 0.93]; p<0.001), repeat revascularisation (0.78 [95% CI: 0.74, 0.82]; p<0.001), and TVR (0.72 [95% CI: 0.67, 0.77]; p<0.001) in patients who received a BMS as compared to DES in the initial PCI before the ISR. BMS use in the initial PCI was associated with increased hazard of all-cause mortality (1.09 [95% CI: 1.04, 1.14]; p<0.001) compared to patients who received DES **(Supplementary Table 10)**.

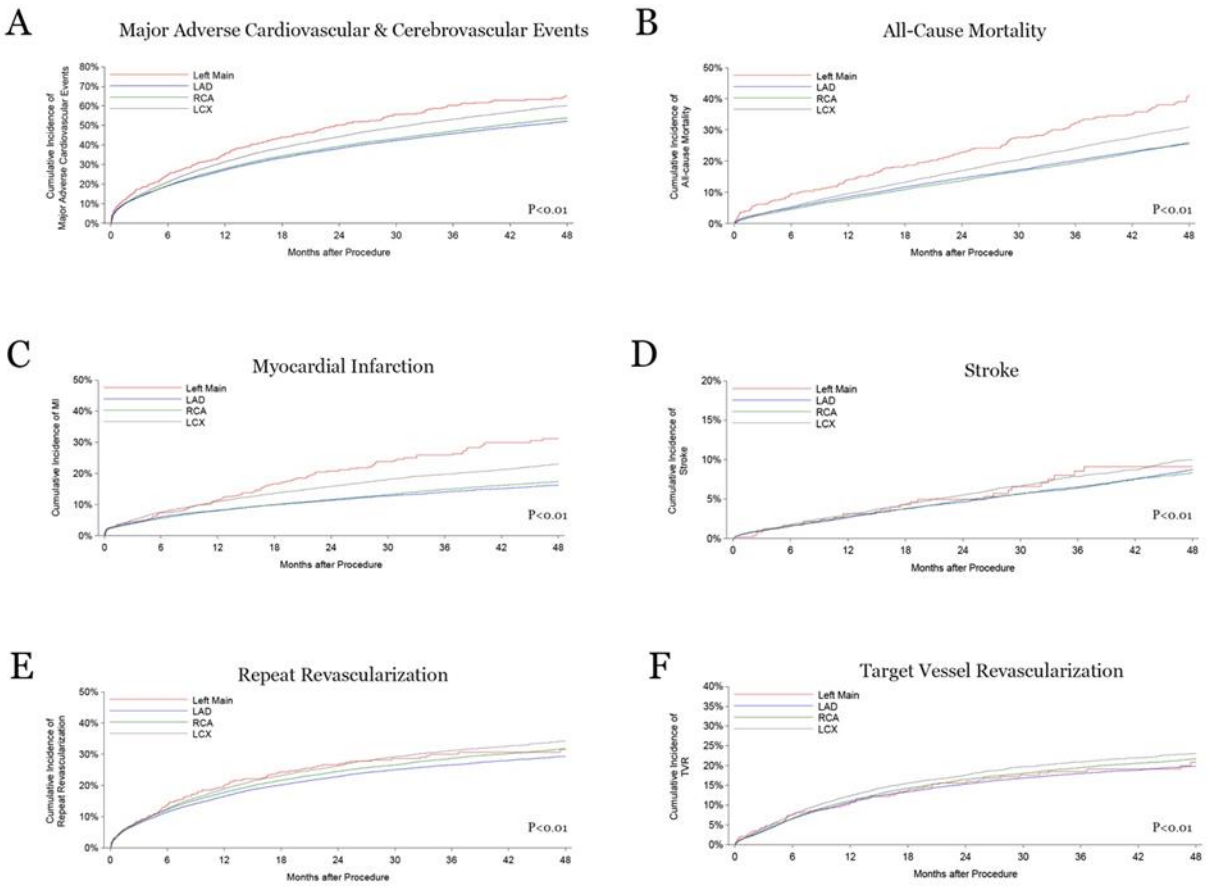
Among ISR patients, ISR of the left main coronary artery (LMCA) was associated with worse outcomes compared to other vessels (cumulative incidence of MACCE at 4 years for LMCA, 65.1%; left anterior descending coronary artery [LAD], 52.2%; circumflex coronary artery [Cx], 60.2%; and right coronary artery [RCA], 53.9%; p<0.001) **(Supplementary Figure 2)**.

Sensitivity analysis: propensity score-matched population

In the 1:1 propensity matched comparison of ISR PCI and *de novo* PCI patients, baseline characteristics were similar **(Supplementary Table 11)**. Associations between ISR PCI and outcomes were similar in magnitude and statistical significance to those in the primary analysis **(Supplementary Table 12)**. ISR PCI was associated with an increased hazard of MACCE (1.24 [95% CI: 1.22, 1.26]; p<0.001), all-cause mortality (1.06 [95% CI: 1.03, 1.09]; p<0.001), MI (1.41 [95% CI: 1.36, 1.46]; p<0.001), repeat revascularisation (1.58 [95% CI: 1.53, 1.63]; p<0.001), and TVR (2.44 [95% CI: 2.34, 2.54]; p<0.001), compared with PCI to a *de novo* lesion **(Supplementary Table 12)**. There continued to be no significant difference in stroke (0.99 [95% CI: 0.95, 1.04]; p=0.40) between groups after adjustment.



Supplementary Figure 1. Primary and secondary outcomes in the ISR group stratified by time to ISR.



Supplementary Figure 2. Cumulative incidence of events after PCI for ISR of different vessels.

Supplementary Table 1. ICD-9 diagnostic codes used for outcome adjudication in CMS claims data.

MI	410.x0-410.x1
Stroke	43411, 43491, 43311, 430, 431, 4321, 4329, 4359
Repeat revascularisation	3606, 3607, 0066, 3610, 3611, 3612, 3613, 3614, 3615, 3616, 3617, 3619
Bleeding	430, 431, 432, 459, 4230, 4233, 4320, 4321, 4329, 4560, 5314, 5693, 5780, 5781, 5782, 5783, 5784, 5785, 5786, 5787, 5788, 5789, 5997, 6262, 6270, 6271, 6288, 7191, 7670, 7703, 7847, 7848, 45620, 53021, 53082, 53100, 53101, 53120, 53121, 53140, 53141, 53160, 53161, 53200, 53201, 53220, 53221, 53240, 53241, 53260, 53261, 53300, 53301, 53320, 53321, 53340, 53341, 53360, 53361, 53400, 53401, 53420, 53421, 53440, 53441, 53460, 53461, 53501, 53511, 53521, 53531, 53541, 53551, 53561, 53784, 56202, 56203, 56212, 56213, 56681, 71910, 71911, 71912, 71913, 71914, 71915, 71916, 71917, 71918, 76711, 77210, 77211, 77212, 77213, 77214, 78630, 78639, 99702, 2851, 85221, 85300

CMS: Centres for Medicare and Medicaid Services; ICD-9: International Classification of Diseases, Ninth Edition; MI: myocardial infarction

Supplementary Table 2. Baseline characteristics of patients successfully linked to CMS versus those not able to be linked.

	Linked with CMS (N=653,304)	Not linked with CMS (N=845,302)	Standardised difference
Demographics			
Age, mean±SD	74.55±6.96	74.20±6.76	0.051
Male, n (%)	411,415 (63.0%)	525,336 (62.1%)	0.017
Race, n (%)			
White	599,738 (92.7%)	746,192 (89.3%)	0.117
Black	33,224 (5.1%)	61,286 (7.3%)	-0.091
Other	14,196 (2.2%)	27,808 (3.3%)	-0.069
Ethnicity			
Hispanic	21,453 (3.3%)	50,732 (6.0%)	-0.13
Smoker (current/recent), n (%)	88,612 (13.6%)	117,931 (14.0%)	-0.011
Past medical history			
Diabetes mellitus, n (%)	240,670 (36.8%)	330,360 (39.1%)	-0.046
Hypertension, n (%)	565,034 (86.5%)	735,729 (87.1%)	-0.017
Dyslipidaemia, n (%)	529,480 (81.1%)	689,283 (81.6%)	-0.013
Family history of premature CAD, n (%)	126,303 (19.3%)	153,484 (18.2%)	0.03
Prior myocardial infarction, n (%)	178,287 (27.3%)	243,599 (28.8%)	-0.034
Prior PCI, n (%)	228,219 (34.9%)	320,186 (37.9%)	-0.061
Prior CABG, n (%)	143,567 (22.0%)	190,264 (22.5%)	-0.013
Dialysis (current), n (%)	16,072 (2.5%)	17,699 (2.1%)	0.025
LVEF <40%, n (%)	98,172 (20.1%)	123,722 (19.7%)	0.011
Procedural characteristics			
PCI indication, n (%)			
STEMI	77,507 (11.9%)	106,265 (12.6%)	-0.022
NSTEMI/unstable angina	344,850 (52.8%)	450,820 (53.4%)	-0.011
Staged PCI	26,144 (4.0%)	33,815 (4.0%)	0
Stable angina	204,591 (31.3%)	254,120 (30.1%)	0.027
Stent type, n (%)			
DES	469,960 (71.9%)	615,540 (72.8%)	-0.02
BMS	128,952 (19.7%)	156,399 (18.5%)	0.031
POBA only	54,392 (8.3%)	73,363 (8.7%)	-0.013
Atherectomy, n (%)	44,056 (6.7%)	62,876 (7.4%)	-0.027
Laser	1,202 (0.2%)	1,496 (0.2%)	0.002

Rotational atherectomy	10,104 (1.5%)	14,795 (1.8%)	-0.016
Cutting & scoring balloon angioplasty	34,109 (5.2%)	48,846 (5.8%)	-0.024
Lesion length, mm (mean±SD)	18.41±10.64	18.49±10.81	-0.008
Pre-procedure TIMI flow, n (%)			
0	98,888 (11.2%)	134,016 (11.8%)	-0.017
1	70,860 (8.0%)	98,269 (8.6%)	-0.021
2	175,368 (19.9%)	232,291 (20.4%)	-0.012
3	535,198 (60.8%)	674,452 (59.2%)	0.032
Chronic total occlusion, n (%)	20,178 (20.8%)	26,986 (20.5%)	0.007
Lesion in graft, n (%)	62,629 (7.1%)	85,925 (7.5%)	-0.016
Bifurcation lesion, n (%)	106,258 (12.0%)	133,046 (11.6%)	0.012
Thrombus present, n (%)	85,256 (9.7%)	112,419 (9.8%)	-0.006
Able to cross with guidewire, n (%)	869,198 (98.4%)	1,124,573 (98.4%)	0.002
Post-procedure TIMI flow, n (%)			
0	6,248 (0.7%)	8,052 (0.7%)	0
1	2,615 (0.3%)	3,652 (0.3%)	-0.004
2	10,819 (1.2%)	13,541 (1.2%)	0.004
3	847,451 (97.7%)	1,096,719 (97.7%)	-0.001
Prior stent type, n (%)			
DES	37,525 (51.2%)		
Non-DES	15,666 (21.4%)		
Type unknown	20,107 (27.4%)		
Stent type, n (%)			
BMS	192,018 (21.1%)	231,956 (19.8%)	0.033
DES	717,371 (78.9%)	940,642 (80.2%)	-0.033
Stent length, mm (mean±SD)	18.59±7.11	18.74±7.22	-0.02
Stent diameter, mm (mean±SD)	2.96±0.52	2.95±0.52	0.025

BMS: bare metal stent; CABG: coronary artery bypass graft; CAD: coronary artery disease; CMS: Centres for Medicare and Medicaid Services; DES: drug-eluting stent; LVEF: left ventricular ejection fraction; NSTEMI: non-ST-elevation myocardial infarction; PCI: percutaneous coronary intervention; POBA: plain old balloon angioplasty; SD: standard deviation; STEMI: ST-elevation myocardial infarction; TIMI: Thrombolysis In Myocardial Infarction

Supplementary Table 3. Frequency of different stent types used for initial PCI.

Stent type	ISR group	De novo group
Bare metal stent	7,876 (9.29%)	184,142 (22.33%)
Cobalt-chromium everolimus-eluting stent	26,797 (31.59%)	223,337 (27.09%)
Cobalt-chromium zotarolimus-eluting stent	10,938 (12.9%)	93,662 (11.36%)
Platinum-chromium everolimus-eluting stent	24,436 (28.81%)	205,896 (24.97%)
Stainless steel drug-eluting stents*	7,372 (8.69%)	56,575 (6.86%)
Other stents**	7,396 (8.72%)	60,962 (7.39%)

*Stainless steel drug-eluting stents are first-generation drug-eluting stents.
**Other stents include: bioresorbable vascular scaffolds, cobalt-chromium paclitaxel-eluting stent, cobalt-chromium ultra-thin strut stent, platinum-chromium paclitaxel-eluting stent and tacrolimus-eluting stent.

ISR: in-stent restenosis; PCI: percutaneous coronary intervention

Supplementary Table 4. Primary and secondary outcomes for patients undergoing ISR PCI or PCI to a de novo lesion excluding patients with unknown type of prior stent.

Endpoint	Hazard ratio [95% CI]	*p*-value
Primary outcome	1.285 [1.263, 1.307]	<0.0001
All-cause mortality	1.124 [1.100, 1.149]	<0.0001
MI	1.504 [1.463, 1.547]	<0.0001
Stroke	1.074 [1.031, 1.119]	0.001
Repeat revascularisation	1.584 [1.542, 1.628]	<0.0001
TVR	2.921 [2.833, 3.013]	<0.0001

CI: confidence interval; ISR: in-stent restenosis; MI: myocardial infarction; PCI: percutaneous coronary intervention; TVR: target vessel revascularisation

Supplementary Table 5. Baseline characteristics in subgroup of patients with history of prior PCI.

	ISR group (N 66,718)	De novo group (N=161,501)	Standardised difference
Demographics			
Age, mean±SD	74.15±6.78	74.44±6.90	-0.042
Male, n (%)	43,865 (65.7%)	110,551 (68.5%)	-0.058
Race, n (%)			
White	61,155 (92.5%)	149,642 (93.5%)	-0.037
Black	3,529 (5.3%)	7,276 (4.5%)	0.037
Other	1,414 (2.1%)	3,182 (2.0%)	0.011
Ethnicity, n (%)			
Hispanic	2,077 (3.1%)	4,962 (3.1%)	0.002
Smoker (current/recent), n (%)	8,411 (12.6%)	20,421 (12.7%)	-0.001
Past medical history			
Diabetes mellitus, n (%)	28,773 (43.1%)	67,281 (41.7%)	0.03
Hypertension, n (%)	61,708 (92.5%)	147,816 (91.5%)	0.035
Dyslipidaemia, n (%)	61,789 (92.7%)	147,287 (91.2%)	0.052
Family history of premature CAD, n (%)	14,136 (21.2%)	34,961 (21.7%)	-0.011
Prior myocardial infarction, n (%)	33,631 (50.4%)	77,673 (48.1%)	0.046
Prior PCI, n (%)	66,718 (100.0%)	161,501 (100.0%)	0
Prior CABG, n (%)	20,428 (30.6%)	49,722 (30.8%)	-0.004
Dialysis (current), n (%)	2,187 (3.3%)	4,157 (2.6%)	0.042
LVEF <40%, n (%)	10,061 (21.3%)	24,246 (20.8%)	0.013
Procedural characteristics			
PCI indication, n (%)			
STEMI	4,735 (7.1%)	11,072 (6.9%)	0.009
NSTEMI/unstable angina	37,911 (56.8%)	88,528 (54.8%)	0.04
Staged PCI	2,857 (4.3%)	7,621 (4.7%)	-0.021
Stable angina	21,198 (31.8%)	54,239 (33.6%)	-0.039
Stent type, n (%)			
DES	48,953 (73.4%)	120,341 (74.5%)	-0.026
BMS	4,804 (7.2%)	27,509 (17.0%)	-0.305
POBA only	12,961 (19.4%)	13,651 (8.5%)	0.321
Atherectomy, n (%)	12,265 (18.4%)	9,948 (6.2%)	0.379
Laser	327 (0.5%)	266 (0.2%)	0.057
Rotational atherectomy	612 (0.9%)	2,482 (1.5%)	-0.056
Cutting & scoring balloon angioplasty	11,533 (17.3%)	7,516 (4.7%)	0.413

Lesion length, mm (mean±SD)	18.46±11.22	17.76±10.37	0.064
Pre-procedure TIMI flow, n (%)			
0	9,511 (10.0%)	17,435 (8.2%)	0.061
1	6,735 (7.1%)	15,807 (7.4%)	-0.015
2	19,114 (20.0%)	42,148 (19.9%)	0.005
3	60,007 (62.9%)	136,926 (64.5%)	-0.033
Chronic total occlusion, n (%)	2,503 (26.8%)	4,638 (27.2%)	-0.01
Lesion in graft, n (%)	10,232 (10.7%)	21,792 (10.2%)	0.015
Bifurcation lesion, n (%)	11,337 (11.9%)	24,425 (11.5%)	0.012
Thrombus present, n (%)	7,358 (7.7%)	15,667 (7.4%)	0.013
Able to cross with guidewire, n (%)	94,424 (98.7%)	209,540 (98.3%)	0.03
Post-procedure TIMI flow, n (%)			
0	633 (0.7%)	1,462 (0.7%)	-0.003
1	215 (0.2%)	595 (0.3%)	-0.011
2	886 (0.9%)	2,413 (1.2%)	-0.021
3	92,464 (98.2%)	204,517 (97.9%)	0.021
Prior stent type, n (%)			
DES	37,525 (51.2%)		
Non-DES	15,666 (21.4%)		
Type unknown	20,107 (27.4%)		
Stent type, n (%)			
BMS	7,876 (9.3%)	39,996 (18.4%)	-0.267
DES	76,939 (90.7%)	177,082 (81.6%)	0.267
Stent length, mm (mean±SD)	19.20±7.55	18.14±7.01	0.146
Stent diameter, mm (mean±SD)	2.99±0.50	2.96±0.53	0.064

BMS: bare metal stent; CABG: coronary artery bypass graft; CAD: coronary artery disease; DES: drug-eluting stent; ISR: in-stent restenosis; LVEF: left ventricular ejection fraction; NSTEMI: non-ST-elevation myocardial infarction; PCI: percutaneous coronary intervention; POBA: plain old balloon angioplasty; SD: standard deviation; STEMI: ST-elevation myocardial infarction; TIMI: Thrombolysis In Myocardial Infarction

Supplementary Table 6. Primary and secondary outcomes for patients undergoing ISR PCI versus PCI to a de novo lesion adjusted for stent type used for the initial PCI.

Endpoint	Hazard ratio [95% CI]	*p*-value
Primary outcome	1.321 [1.299, 1.344]	<0.0001
All-cause mortality	1.125 [1.100, 1.150]	<0.0001
MI	1.501 [1.459, 1.545]	<0.0001
Stroke	1.076 [1.032, 1.122]	0.0006
Repeat revascularisation	1.586 [1.548, 1.625]	<0.0001
TVR	2.637 [2.563, 2.713]	<0.0001

CI: confidence interval; ISR: in-stent restenosis; MI: myocardial infarction; PCI: percutaneous coronary intervention; TVR: target vessel revascularisation

Supplementary Table 7. Baseline characteristics by treatment in ISR group.

Characteristics	DES group (N=48,953)	BMS group (N=4,804)	POBA group (N=12,961)	*p*-value
Demographics				
Age, mean	74.0±6.7	75.8±7.3	74.3±6.9	<0.001
Male, n (%)	32,545 (66.5%)	3,135 (65.3%)	8,185 (63.2%)	<0.001
Race, n (%)				<0.001
White	45,012 (92.8%)	4,421 (92.7%)	11,722 (91.3%)	
Black	2,422 (5.0%)	273 (5.7%)	834 (6.5%)	
Other	1,058 (2.2%)	74 (1.6%)	282 (2.2%)	
Hispanic	1,502 (3.1%)	132 (2.8%)	443 (3.4%)	0.039
Current/recent smoker (<1 year)	6,028 (12.3%)	753 (15.7%)	1,630 (12.6%)	<0.001
Past medical history				
Diabetes	21,127 (43.2%)	1,936 (40.3%)	5,710 (44.1%)	<0.001
Hypertension	45,281 (92.5%)	4,387 (91.3%)	12,040 (92.9%)	0.002
Dyslipidaemia	45,516 (93.0%)	4,318 (89.9%)	11,955 (92.3%)	<0.001
Family history of premature CAD	10,544 (21.6%)	935 (19.5%)	2,657 (20.5%)	<0.001
Prior MI	24,428 (49.9%)	2,631 (54.8%)	6,572 (50.7%)	<0.001
Prior PCI	48,953 (100.0%)	4,804 (100.0%)	12,961 (100.0%)	
Prior CABG	14,770 (30.2%)	1,442 (30.0%)	4,216 (32.5%)	<0.001
Currently on dialysis	1,499 (3.1%)	200 (4.2%)	488 (3.8%)	<0.001
Reduced LVEF (<=40%)	6,950 (20.1%)	1,010 (28.7%)	2,101 (23.1%)	<0.001
Chronic kidney disease				<0.001
eGFR >=90	4,053 (8.7%)	319 (7.0%)	1,077 (8.8%)	
60 <= eGFR <90	22,013 (47.4%)	1,917 (42.3%)	5,568 (45.4%)	
30 <= eGFR <60	17,428 (37.5%)	1,871 (41.2%)	4,686 (38.2%)	
15 <= eGFR <30	1,679 (3.6%)	261 (5.8%)	519 (4.2%)	
eGFR <15	1,294 (2.8%)	168 (3.7%)	420 (3.4%)	
PCI indication				<0.001
STEMI	2,651 (5.4%)	870 (18.1%)	1,214 (9.4%)	
NSTEMI or unstable angina	28,265 (57.8%)	2,531 (52.7%)	7,115 (54.9%)	
Staged PCI	2,187 (4.5%)	200 (4.2%)	470 (3.6%)	
Other	15,838 (32.4%)	1,202 (25.0%)	4,158 (32.1%)	
Stent type (patient-based)				<0.001
DES	48,953 (100.0%)	0 (0.0%)	0 (0.0%)	

BMS	0 (0.0%)	4,804 (100.0%)	0 (0.0%)	
No stents	0 (0.0%)	0 (0.0%)	12,961 (100.0%)	
Atherectomy	7,249 (14.8%)	635 (13.2%)	4,381 (33.8%)	<0.001
Laser	219 (0.4%)	10 (0.2%)	98 (0.8%)	<0.001
Rotational atherectomy	492 (1.0%)	34 (0.7%)	86 (0.7%)	<0.001
Cutting balloon angioplasty	6,677 (13.6%)	602 (12.5%)	4,254 (32.8%)	<0.001
Time between ISR PCI and previous implantation of restenosed stent				<0.001
<1 month	1.1%	3.4%	3.0%	
1-5 months	9.0%	7.0%	9.8%	
6-12 months	10.9%	6.9%	12.8%	
1-2 years	12.7%	10.2%	15.6%	
>2 years	58.6%	63.1%	49.9%	
Time unknown	7.8%	9.4%	9.0%	
Lesion characteristics				
Lesion length, mm	19.3±11.7	17.7±10.2	14.7±7.8	<0.001
Pre-procedure TIMI flow				<0.001
0	5,873 (8.0%)	1,154 (16.2%)	2,484 (16.3%)	
1	5,118 (7.0%)	522 (7.3%)	1,095 (7.2%)	
2	14,706 (20.1%)	1,386 (19.5%)	3,022 (19.9%)	
3	47,342 (64.8%)	4,058 (57.0%)	8,607 (56.6%)	
Chronic total occlusion (if pre-procedure DS=100%)	1,554 (27.2%)	143 (12.7%)	806 (32.2%)	<0.001
IVUS (if pre-procedure DS 40-70%)	2,127 (19.0%)	153 (15.1%)	682 (27.1%)	<0.001
Lesion in graft	7,712 (10.5%)	1,016 (14.2%)	1,504 (9.9%)	<0.001
Bifurcation lesion	8,800 (12.0%)	679 (9.5%)	1,858 (12.2%)	<0.001
Thrombus present	4,596 (6.3%)	1,136 (15.9%)	1,626 (10.7%)	<0.001
Guidewire across lesion	72,900 (99.5%)	7,092 (99.3%)	14,432 (94.5%)	<0.001
Post-procedure TIMI flow				<0.001
0	254 (0.3%)	39 (0.6%)	340 (2.4%)	
1	83 (0.1%)	15 (0.2%)	117 (0.8%)	
2	463 (0.6%)	93 (1.3%)	330 (2.3%)	
3	71,948 (98.9%)	6,924 (97.9%)	13,592 (94.5%)	
Prior stent type for ISR				<0.001
DES	28,345 (52.3%)	1,560 (30.3%)	7,620 (54.5%)	

Non-DES	11,320 (20.9%)	1,814 (35.2%)	2,532 (18.1%)	
Type unknown	14,498 (26.8%)	1,776 (34.5%)	3,833 (27.4%)	
Stent characteristics				
Stent type				<0.001
BMS	795 (1.0%)	7,081 (100.0%)		
DES	76,939 (99.0%)	0 (0.0%)		
Stent length, mm	19.3±7.6	17.7±6.5		<0.001
Stent diameter, mm	3.0±0.5	3.1±0.6		<0.001

BMS: bare metal stent; CABG: coronary artery bypass graft; CAD: coronary artery disease; CMS: Centres for Medicare and Medicaid Services; DES: drug-eluting stent; eGFR: estimated glomerular filtration rate; ISR: in-stent restenosis; IVUS: intravascular ultrasound; LVEF: left ventricular ejection fraction; NSTEMI: non-ST-elevation myocardial infarction; PCI: percutaneous coronary intervention; POBA: plain old balloon angioplasty; SD: standard deviation; STEMI: ST-elevation myocardial infarction; TIMI: Thrombolysis In Myocardial Infarction

Supplementary Table 8. Cox regression of outcomes for ISR PCI patients when treated with BMS or POBA versus DES.

BMS versus DES		
Endpoint	**Hazard ratio [95% CI]**	***p*-value**
Primary outcome	1.289 [1.236, 1.345]	<0.0001
All-cause mortality	1.648 [1.551, 1.751]	<0.0001
MI	1.098 [0.985, 1.224]	0.0921
Stroke	0.884 [0.734, 1.065]	0.1941
Repeat revascularisation	0.842 [0.783, 0.905]	<0.0001
TVR	0.940 [0.865, 1.021]	0.1434
POBA versus DES		
Endpoint	**Hazard ratio [95% CI]**	***p*-value**
Primary outcome	1.197 [1.161, 1.234]	<0.0001
All-cause mortality	1.251 [1.194, 1.310]	<0.0001
MI	1.038 [0.963, 1.118]	0.3349
Stroke	0.966 [0.869, 1.074]	0.5215
Repeat revascularisation	1.084 [1.037, 1.134]	0.0004
TVR	1.270 [1.208, 1.334]	<0.0001

Adjusted for age, gender, race, ethnicity, diabetes, chronic kidney disease stage, hypertension, dyslipidaemia, PCI indication, bifurcation lesion, lesion in graft, total chronic occlusion, total stent length, and minimum stent diameter.
BMS: bare metal stent; CI: confidence interval; DES: drug-eluting stent; ISR: in-stent restenosis; MI: myocardial infarction; PCI: percutaneous coronary intervention; POBA: plain old balloon angioplasty; TVR: target vessel revascularisation

Supplementary Table 9. Patient characteristics by stent type in the initial PCI for patients in the ISR group.

Characteristics	ISR PCI		Standardised difference
	Prior stent BMS (N=14,196)	Prior stent DES (N=33,968)	
Demographics			
Age, years			
Mean±SD	74.8±7.0	73.9±6.7	0.13
Male	9,336 (65.8%)	22,201 (65.4%)	0.01
Race			
White	13,083 (92.8%)	31,150 (92.6%)	0.01
Black	774 (5.5%)	1,735 (5.2%)	0.02
Other	243 (1.7%)	752 (2.2%)	-0.04
Hispanic	384 (2.7%)	1,023 (3.0%)	-0.02
Current/recent smoker (<1 year)	1,908 (13.4%)	3,691 (10.9%)	0.08
Past medical history			
Diabetes	5,605 (39.5%)	15,230 (44.8%)	-0.11
Hypertension	13,017 (91.7%)	31,660 (93.2%)	-0.06
Dyslipidaemia	13,105 (92.3%)	31,850 (93.8%)	-0.06
Family history of premature CAD	2,897 (20.4%)	7,472 (22.0%)	-0.04
Prior MI	7,709 (54.3%)	16,753 (49.3%)	0.10
Prior PCI	14,196 (100.0%)	33,968 (100.0%)	0.00
Prior CABG	3,692 (26.0%)	11,363 (33.5%)	-0.16
Currently on dialysis	461 (3.3%)	1,173 (3.5%)	-0.01
Reduced LVEF (<=40%)	2,155 (21.8%)	4,844 (20.5%)	0.03
Chronic kidney disease			
eGFR >=90	1,094 (8.1%)	2,707 (8.4%)	-0.01
60 <= eGFR <90	6,314 (46.7%)	15,088 (46.8%)	0.00
30 <= eGFR <60	5,183 (38.4%)	12,194 (37.8%)	0.01
15 <= eGFR <30	529 (3.9%)	1,229 (3.8%)	0.01
eGFR <15	389 (2.9%)	1,017 (3.2%)	-0.02
PCI indication			
STEMI	876 (6.2%)	2,124 (6.3%)	0.00
NSTEMI or unstable angina	8,144 (57.4%)	19,243 (56.7%)	0.01
Staged PCI	537 (3.8%)	1,399 (4.1%)	-0.02

Other	4,636 (32.7%)	11,192 (33.0%)	-0.01
Stent type (patient-based)			
DES	10,172 (71.7%)	25,485 (75.0%)	-0.08
BMS	1,681 (11.8%)	1,451 (4.3%)	0.28
No stents	2,343 (16.5%)	7,032 (20.7%)	-0.11
Atherectomy	2,527 (17.8%)	6,466 (19.0%)	-0.03
Laser	39 (0.3%)	196 (0.6%)	-0.05
Rotational atherectomy	113 (0.8%)	287 (0.8%)	-0.01
Cutting balloon angioplasty	2,414 (17.0%)	6,091 (17.9%)	-0.02
Time between ISR diagnosis and original implantation of the restenosed stent			
<1 month	262 (1.8%)	740 (2.2%)	-0.02
1-5 months	2,630 (18.5%)	3,052 (9.0%)	0.28
6-12 months	1,881 (13.3%)	4,926 (14.5%)	-0.04
1-2 years	1,654 (11.7%)	5,905 (17.4%)	-0.16
>2 years	7,447 (52.5%)	18,616 (54.8%)	-0.05
Time unknown	317 (2.2%)	708 (2.1%)	0.01
Lesion characteristics			
Lesion length, mm			
Mean±SD	19.4±11.4	17.9±11.0	0.14
Pre-procedure TIMI flow			
0	1,808 (9.0%)	4,654 (9.6%)	-0.02
1	1,391 (6.9%)	3,217 (6.6%)	0.01
2	4,028 (20.0%)	9,389 (19.4%)	0.02
3	12,933 (64.2%)	31,147 (64.3%)	0.00
Chronic total occlusion	450 (24.7%)	1,233 (26.9%)	-0.05
Lesion in graft	2,044 (10.1%)	5,708 (11.8%)	-0.05
Bifurcation lesion	2,513 (12.4%)	6,173 (12.7%)	-0.01
Thrombus present	1,455 (7.2%)	3,698 (7.6%)	-0.02
Guidewire across lesion	19,953 (98.8%)	47,958 (98.8%)	0.00
Post-procedure TIMI flow			
0	117 (0.6%)	292 (0.6%)	0.00
1	41 (0.2%)	107 (0.2%)	0.00
2	160 (0.8%)	433 (0.9%)	-0.01
3	19,609 (98.4%)	47,037 (98.3%)	0.01
Stent characteristics			

Stent type			
BMS	2,649 (14.0%)	2,446 (5.8%)	0.28
DES	16,305 (86.0%)	39,418 (94.2%)	-0.28
Stent length, mm	20.0±7.5	18.8±7.5	0.16
Stent diameter, mm	3.0±0.5	3.0±0.5	0.07

BMS: bare metal stent; CABG: coronary artery bypass graft; CAD: coronary artery disease; DES: drug-eluting stent; eGFR: estimated glomerular filtration rate; ISR: in-stent restenosis; IVUS: intravascular ultrasound; LVEF: left ventricular ejection fraction; NSTEMI: non-ST-elevation myocardial infarction; PCI: percutaneous coronary intervention; POBA: plain old balloon angioplasty; SD: standard deviation; STEMI: ST-elevation myocardial infarction; TIMI: Thrombolysis In Myocardial Infarction

Supplementary Table 10. Primary and secondary outcomes for patients undergoing ISR PCI comparing BMS versus DES use in the initial PCI.

Endpoint	Hazard ratio [95% CI]	*p*-value
Primary outcome	0.94 [0.91, 0.97]	<0.001
All-cause mortality	1.09 [1.04, 1.14]	<0.001
MI	0.86 [0.79, 0.93]	<0.001
Stroke	0.99 [0.89, 1.11]	0.92
Repeat revascularisation	0.78 [0.74, 0.82]	<0.001
TVR	0.72 [0.67, 0.77]	<0.001

BMS: bare metal stent; CI: confidence interval; DES: drug-eluting stent; ISR: in-stent restenosis; MI: myocardial infarction; PCI: percutaneous coronary intervention; TVR: target vessel revascularisation

Supplementary Table 11. Patient characteristics - propensity score-matched cohort.

Characteristics	ISR group (N=63,099 patients)	De novo group (N=63,099 patients)	Standardised difference
Demographics			
Age, years (mean±SD)	74.2±6.8	74.1±6.7	0.017
Male	41,472 (65.7%)	41,445 (65.7%)	0.001
Race			
White	58,344 (92.5%)	58,972 (93.5%)	-0.039
Black	3,395 (5.4%)	2,982 (4.7%)	0.03
Other	1,360 (2.2%)	1,145 (1.8%)	0.024
Hispanic	1,807 (2.9%)	1,530 (2.4%)	0.027
Current/recent smoker (<1 year)	7,949 (12.6%)	8,216 (13.0%)	-0.013
Past medical history			
Diabetes	27,329 (43.3%)	26,713 (42.3%)	0.02
Hypertension	58,427 (92.6%)	58,518 (92.7%)	-0.006
Dyslipidaemia	58,517 (92.7%)	58,554 (92.8%)	-0.002
Family history of premature CAD	13,355 (21.2%)	13,152 (20.8%)	0.008
Prior MI	31,869 (50.5%)	18,316 (29.0%)	0.45
Prior PCI	63,099 (100.0%)	20,938 (33.2%)	2.007
Prior CABG	19,414 (30.8%)	17,571 (27.8%)	0.064
Currently on dialysis	2,086 (3.3%)	1,829 (2.9%)	0.023
Reduced LVEF (<=40%)	9,518 (21.3%)	9,030 (19.3%)	0.047
Chronic kidney disease			
eGFR >=90	5,431 (8.6%)	5,484 (8.7%)	-0.003
60 <= eGFR <90	29,415 (46.6%)	29,812 (47.2%)	-0.013
30 <= eGFR <60	23,920 (37.9%)	23,941 (37.9%)	-0.001
15 <= eGFR <30	2,456 (3.9%)	2,172 (3.4%)	0.024
eGFR <15	1,877 (3.0%)	1,690 (2.7%)	0.018
PCI indication			
STEMI	4,185 (6.6%)	4,144 (6.6%)	0.003
NSTEMI or unstable angina	36,316 (57.6%)	36,697 (58.2%)	-0.012
Staged PCI	2,689 (4.3%)	2,352 (3.7%)	0.027
Other	19,909 (31.6%)	19,906 (31.5%)	0
Stent type (patient-based)			
DES	46,340 (73.4%)	46,214 (73.2%)	0.005
BMS	4,525 (7.2%)	4,414 (7.0%)	0.007
No stents	12,234 (19.4%)	12,471 (19.8%)	-0.009
Atherectomy	11,631 (18.4%)	4,082 (6.5%)	0.368

Laser	312 (0.5%)	112 (0.2%)	0.055
Rotational atherectomy	580 (0.9%)	1,119 (1.8%)	-0.074
Cutting balloon angioplasty	10,933 (17.3%)	2,998 (4.8%)	0.41
Lesion characteristics			
Lesion length, mm	18.5±11.2	18.4±10.8	0.007
Pre-procedure TIMI flow			
0	8,818 (9.8%)	8,019 (9.6%)	0.004
1	6,334 (7.0%)	6,778 (8.1%)	-0.043
2	18,153 (20.1%)	16,949 (20.3%)	-0.006
3	57,078 (63.2%)	51,567 (61.9%)	0.026
Chronic total occlusion (if pre-procedure DS=100%)	2,380 (27.5%)	1,833 (23.4%)	0.094
IVUS (if pre-procedure DS 40-70%)	2,838 (20.3%)	1,797 (18.3%)	0.053
Lesion in graft	9,759 (10.8%)	8,591 (10.3%)	0.016
Bifurcation lesion	10,785 (11.9%)	9,364 (11.2%)	0.022
Thrombus present	6,810 (7.5%)	6,618 (7.9%)	-0.015
Guidewire across lesion	89,500 (98.7%)	80,773 (96.6%)	0.138
Post-procedure TIMI flow			
0	603 (0.7%)	896 (1.1%)	-0.046
1	207 (0.2%)	451 (0.6%)	-0.052
2	818 (0.9%)	1,364 (1.7%)	-0.069
3	87,658 (98.2%)	77,851 (96.6%)	0.097
Prior stent type for ISR			
DES	35,550 (51.2%)	-	.
Non-DES	14,891 (21.5%)	-	.
Type unknown	18,940 (27.3%)	-	.
Stent characteristics			
Stent type			
BMS	7,411 (9.2%)	7,160 (9.2%)	0.002
DES	73,004 (90.8%)	70,950 (90.8%)	-0.002
Stent length, mm	19.2±7.6	18.9±7.3	0.037
Stent diameter, mm	3.0±0.5	3.0±0.5	0.012

BMS: bare metal stent; CABG: coronary artery bypass graft; CAD: coronary artery disease; DES: drug-eluting stent; eGFR: estimated glomerular filtration rate; ISR: in-stent restenosis; IVUS: intravascular ultrasound; LVEF: left ventricular ejection fraction; NSTEMI: non-ST-elevation myocardial infarction; PCI: percutaneous coronary intervention; POBA: plain old balloon angioplasty; SD: standard deviation; STEMI: ST-elevation myocardial infarction; TIMI: Thrombolysis In Myocardial Infarction

Supplementary Table 12. Primary and secondary outcomes for patients undergoing ISR PCI or PCI for a de novo lesion in a propensity score-matched cohort.

Endpoint	Hazard ratio [95% CI]	*p*-value
Primary outcome	1.24 [1.22, 1.26]	<0.001
All-cause mortality	1.06 [1.03, 1.09]	<0.001
MI	1.41 [1.36, 1.46]	<0.001
Stroke	0.996 [0.95, 1.04]	0.88
Repeat revascularisation	1.58 [1.53, 1.63]	<0.001
TVR	2.44 [2.34, 2.54]	<0.001

MI: myocardial infarction; TVR: target vessel revascularisation