Clinical Outcomes in type 2 Diabetes with in-stent Restenosis and Late/very Late Stent Thrombosis Undergoing Primary Percutaneous Coronary Intervention: A Single-center Observational Cohort Study

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Abstract

BACKGROUND: This study aimed to compare differences in the risk factors and clinical outcomes of type 2 diabetes mellitus (DM) and non-DM patients with de novo lesions (DNL), definite in-stent restenosis (ISR), and late or very late stent thrombosis (LST/VLST).

METHODS: A total of 4151 patients with acute coronary syndrome were screened angiographically to determine DNL, ISR, and LST/VLST. A total of 3976 patients were included in the analysis and divided into DM (n=1302) or non-DM (n=2674) group at admission. The primary endpoint was a composite of major adverse cardiovascular events (MACEs), defined as death, myocardial infarction, revascularization, and ischemic stroke within a 1-year follow-up period.

RESULTS: In the group with total white blood cell count >10 10^9/L (p=0.004), neutral granular cell count >7 10^9/L (p=0.030), neutrophil-lymphocyte ratio >1.5 (p=0.041), DNL outperformed LST/VLST lesions in terms of revascularization at a median follow-up of 698 days. Among patients with DNL, the incidences of MACEs (log-rank p=0.0002), all-cause death (log-rank p=0.00032), cardiac-related death (log-rank p=0.021), and revascularization (log-rank p=0.029) were significantly lower in the non-DM group than in the DM group. However, no difference was observed in the event rates of endpoints among patients with ISR and LST/VLST between the non-DM and DM groups. Furthermore, among DM patients, there was a critically higher cumulative incidence of revascularization (log-rank p=0.0002) in the subgroup with ISR lesions and higher rate of ischemic stroke (log-rank p=0.033) in the subgroup with LST/VLST lesions.

CONCLUSION: This study found that DM patients have a higher incidence of composite clinical outcomes than non-DM patients among patients with DNL. Compared with patients with DNL, patients with ISR lesions and LST/VLST lesions had more incidence of revascularization by long-term follow up. Thus, ISR and LST/VLST lesions are critical problems after coronary stenting, especially among DM patients.

Background

Type 2 diabetes mellitus (DM), a pro-inflammatory disease [1], exhibits an enhanced inflammatory reaction in the implantation site of second-generation drug-eluting stents (DESs). Compared with non-DM patients, DM patients undergoing stent implantation often present neointimal hyperplasia and diffusely diseased vessels including deleterious local phenomena[2], various healing responses, and arterial remodeling [3]. However, the long-term prognosis between de novo lesions (DNLs), in-stent restenosis (ISR) and very late stent thrombosis (LST/VLST) is still unclear among patients with DM who undergoing primary percutaneous coronary intervention (PCI). This study aimed to directly compare the difference in long-term prognosis of DNLs against ISR or LST/VLST in a retrospective, single-center, all-comer trial of DM and non-DM patients.

Methods

Study population and design

This retrospective observational study adhered to the Strengthening the Reporting of Observational Studies in Epidemiology statement. The study was conducted on patients who had undergone primary PCI at Fuwai Hospital (National Center for Cardiovascular Diseases, Peking Union Medical College and Chinese Academy of Medical Sciences) in Beijing, China, between January 2010 and June 2017. From a total of 4151 patients admitted for acute myocardial infarction (MI), 3976 patients were included in this study (Fig. 1) and were divided into the DM group (n = 1302) and non-DM group (n = 2674). The types of coronary lesions, including DNL (n = 3661), ISR (n = 35), and LST/VLST (n = 280), were identified angiographically. Patients (1) who were lost to follow-up, (2) whose coronary angiography parameters were not available, (3) and who refused participation were excluded from the analysis. This study was conducted according to the principles which were outlined in the declaration of Helsinki and has been approved by the Ethics Committee of Fuwai Hospital. All study subjects has written informed consent.

By using coronary angiography, ST was defined as a thrombus that originated in a segment 5 mm distal or proximal to the stent or in the stent in patients with acute coronary syndrome (ACS) [4]. The Academic Research Consortium (ARC) defined LST as stent thrombosis that occurs between 30 days and 1 year and VLST as stent thrombosis that occurs > 1 year after stent implantation [4]. Three cardiologists with > 5 years of experience screened the anonymous angiographic data independently and blindly and resolved disagreements.

Clinical outcomes

Clinical outcomes were obtained during follow-up via telephone call or confirmed from health records, and this method was approved by the Review Board of Fuwai Hospital. The primary endpoints were major adverse cardiovascular events (MACEs), all-cause death, cardiac-related

death, recurrent MI, revascularization, and ischemic stroke. MACE was the composite of all-cause death, recurrent MI, and ischemic stroke. The physicians in charge of the follow-up identified and extracted primary endpoints from hospital records, laboratory reports, and clinical notes in the event of death.

Statistical analyses

Time-to-event variables are presented as Kaplan–Meier (KM) curves by R language, and incidences of subgroups were compared using the log-rank test. Baseline patient characteristics were compared between patients with DNL, ISR, and LST/LVST among DM or non-DM patients.

Continuous variables are presented as means ± standard errors and categorical data as counts and percentages. Differences between continuous variables were compared using independent t-test, and those between categorical variables were compared using the $\chi 2$ test or Fisher test to assess the interaction between lesion types and baseline clinical, laboratory index, or angiographic characteristics. The Mantel-Cox method was used to calculate hazard ratios and 95% confidence intervals for comparisons of clinical outcomes including MACEs and all-cause death between groups, and the log-rank test was used to calculate corresponding p values. We conducted two-sided analysis of p values to allow conventional interpretation of results, and a $p < 0.05$ was considered statistically significant. Missing data were handled by single imputation. Most of the statistical analyses were conducted using the R language version I 386 3.6.2 (R Foundation for Statistical Computing, Vienna, Austria). Other analyses were performed using SPSS Statistics version 20.0 (SPSS, Inc., Chicago, IL).

Results

Table 1 presents the baseline demographic data, indicators of serum inflammation, lipids, angiographic features, and procedural characteristics of the entire study population. In total, 3976 patients were divided into the DM group (1178 DNL, 16 ISR lesions, and 108 LST/VLST lesions) or non-DM group (2483 DNL, 19 ISR lesions, and 172 LST/VLST lesions). The mean ages of the patients were 60.51 ± 0.33, 63.44 ± 3.09, and 62.44 ± 0.95 years in the DNL, ISR, and LST/VLST groups among DM patients, respectively. Compared with non-DM patients, DM patients were older (62.44 ± 0.95 years vs. 59.46 ± 0.80 years, p = 0.018), had less proportion of men (70.4% years vs. 82.6%, p = 0.013), and experienced PCI (89.8% vs. 80.8%, p = 0.003) among subgroups of patients with LST/VLST lesions.

Table 1
Baseline characteristics of entire population

Variables	DM Denovo lesion (N = 1178)	Non-DM Denovo lesion (N = 2483)	P_1	DM ISR (N = 16)	Non-DM ISR (N = 19)	P_2	DM LST/VLST (N = 108)	Non-DM LST/VLST (N = 172)	P3
Age (years)	60.51 ± 0.33	58.04 ± 0.25	< 0.001*	63.44 ± 3.09	62.95 ± 2.58	0.903	62.44 ± 0.95	59.46 ± 0.80	0.018*
Male [%(n)]	861(73.1%)	2027(81.6%)	< 0.001*	4(21.1%)	15(78.9%)	0.700	76(70.4%)	142(82.6%)	0.013*
Heart rate(beats/min)	78.68 ± 0.46	76.80 ± 0.32	0.177	72.75 ± 4.84	71.37 ± 2.68	0.796	76.36 ± 1.79	75.99 ± 1.18	0.859
SBP (mmHg)	125.56 ± 0.53	123.40 ± 0.38	0.001*	125.19 ± 3.33	121.79 ± 4.37	0.552	125.06 ± 2.52	124.98 ± 1.64	0.979
DBP(mmHg)	70.86 ± 0.46	71.27 ± 0.33	0.474	66.13 ± 5.33	62.53 ± 4.73	0.616	71.43 ± 1.74	72.53 ± 1.43	0.630
EF at admission	53.89 ± 0.52	54.16 ± 0.23	0.581	53.69 ± 2,14	55.78 ± 1.36	0.417	52.29 ± 0.84	51.40 ± 0.63	0.392
Risk factors									
Hypertension[%(n)]	769(65.3%)	1149(58.4%)	< 0.001*	11(68.8%)	15(78.9%)	0.700	65(37.8%)	107(62.2%)	0.172
Hyperlipidemia[%(n)]	997(94.0%)	2031(91.3%)	0.008*	14(87.5%)	17(89.5%)	0.496	91(95.8%)	143(91.7%)	0.158
Smoking[%(n)]	620(58.2%)	1553(69.3%)	< 0.001*	10(71.4%)	12(63.2%)	0.719	58(61.1%)	103(64.8%)	0.321
Previous PCI[%(n)]	122(10.4%)	164(6.6%)	< 0.001*	11(68.8%)	14(73.7%)	1.000	97(89.8%)	139(80.8%)	0.030*
Previous CABG[%(n)]	24(2.0%)	17(0.7%)	0.001*	0(0.00%)	2(10.5%)	0.489	1(0.9%)	1(0.6%)	0.624
AF[%(n)]	218(6.0%)	151(6.1%)	0.709	1(6.2%)	1(5.3%)	1.000	9(8.3%)	10(5.8%)	0.280
CKD[%(n)]	107(9.1%)	170(6.8%)	0.019*	3(18.8%)	0(0.0%)	0.086	11(10.2%)	12(7.0%)	0.231
Laboratory examinations									
HDL (mg/dl)	1.88 ± 0.04	1.62 ± 0.02	< 0.001*	1.63 ± 0.20	1.47 ± 0.22	0.622	1.80 ± 0.13	1.59 ± 0.07	0.118
LDL (mg/dl)	2.69 ± 0.03	2.81 ± 0.02	< 0.001*	2.38 ± 0.24	2.28 ± 0.16	0.731	2.32 ± 0.09	2.42 ± 0.09	0.417
Triglycerides (mg/dl)	1.03 ± 0.01	1.06 ± 0.01	0.027*	1.06 ± 0.06	1.16 ± 0.09	0.392	1.08 ± 0.04	1.09 ± 0.03	0.926
LPA (g/L)	252.88 ± 6.87	269.58 ± 4.95	0.052	342.94 ± 51.73	269.63 ± 47.91	0.718	264.44 ± 23.31	328.35 ± 23.82	0.056
hs-CRP	7.88 ± 0.15	7.54 ± 0.10	0.054	4.81 ± 1.22	7.05 ± 1.07	0.175	7.26 ± 0.46	6.55 ± 0.36	0.227
D-dimer of baseline	0.57 ± 0.05	0.53 ± 0.04	0.533	0.63 ± 0.24	0.66 ± 0.25	0.930	0.79 ± 0.21	0.61 ± 0.16	0.486
Peak level of D-dimer	0.97 ± 0.09	0.91 ± 0.05	0.524	2.14 ± 1.63	0.91 ± 0.42	0.490	1.36 ± 0.39	1.02 ± 0.23	0.421
Crea	82.70 ± 0.83	81.30 ± 0.45	0.138	82.31 ± 5.53	83.26 ± 4.17	0.890	82.52 ± 2.49	81.89 ± 1.69	0.829
eGFR (MDRD)	87.90 ± 0.83	91.78 ± 1.83	0.191	80.81 ± 5.62	80.32 ± 4.14	0.943	81.89 ± 2.16	91.48 ± 7.45	0.319

Variables	DM Denovo lesion (N = 1178)	Non-DM Denovo lesion (N = 2483)	P_1	DM ISR (N = 16)	Non-DM ISR (N = 19)	P_2	DM LST/VLST (N = 108)	Non-DM LST/VLST (N = 172)	P3
Peak level of TnI	3.44 ± 0.39	4.09 ± 0.28	0.177	3.00 ± 2.76	2.45 ± 1.24	0.850	2.33 ± 0.66	6.86 ± 1.78	0.019*
Discharge medication regimen									
Statin[%(n)]	1112(94.4%)	2316(93.3%)	0.218	15(93.8%)	18(94.7%)	1.000	102(94.4%)	159(92.4%)	0.349
Aspirin[%(n)]	1160(98.5%)	2467(99.4%)	0.015*	15(93.8%)	18(94.7%)	1.000	106(98.1%)	170(98.8%)	0.500
Clopidogrel[%(n)]	924(78.4%)	1912(77.0%)	0.352	8(50.0%)	12(63.2%)	0.506	75(69.4%)	121(70.3%)	0.488
Ticagrelor[%(n)]	244(20.9%)	553(22.4%)	0.303	8(50.0%)	7(36.8%)	0.506	31(29.2%)	50(29.1%)	0.540
ACEI[%(n)]	721(61.2%)	1547(62.3%)	0.536	9(56.2%)	13(68.4%)	0.503	61(56.5%)	105(61.0%)	0.263
ARB[%(n)]	124(10.5%)	195(7.9%)	0.008*	0(0.0%)	0(0.0%)	-	13(12.0%)	18(10.5%)	0.412
ACEI/ARB[%(n)]	843(71.6%)	1741(70.1%)	0.393	6(31.6%)	13(68.4%)	0.503	74(68.5%)	123(71.5%)	0.344
Beta-Blockers[%(n)]	1040(88.3%)	2150(86.6%)	0.154	15(78.9%)	14(87.5%)	0.666	89(82.4%)	161(93.6%)	0.003*
Diuretic[%(n)]	365(31.0%)	674(27.1%)	0.017*	16(100%)	19(100%)	1.000	35(32.4%)	66(38.4%)	0.189
Spironolactone[%(n)]	246(20.9%)	530(21.3%)	0.762	4(25%)	3(15.8%)	0.677	26(24.1%)	56(32.6%)	0.083
P2Y12 inhibitors	1167(99.1%)	2465(99.3%)	0.550	16(100%)	19(100%)	-	106(98.1%)	171(99.4%)	0.331
Lesion and Procedural Characteristics									
Total lesion length, mm	3.10 ± 0.02	3.21 ± 0.02	< 0.001*	3.13 ± 0.202	3.00 ± 0.23	0.690	3.06 ± 0.07	3.17 ± 0.06	0.192
Lesion diameter, mm	28.36 ± 0.48	26.95 ± 0.31	0.013*	20.13 ± 2.18	21.32 ± 3.10	0.764	26.01 ± 1.52	27.72 ± 1.17	0.369
Degree of lesion stenosis	97.00 ± 0.16	97.22 ± 0.11	0.249	93.06 ± 2.17	89.68 ± 5.31	0.586	98.63 ± 0.32	98.23 ± 0.35	0.431
Bifurcation lesion	405(34.4%)	862(34.7%)	0.853	5(31.2%)	8(42.1%)	0.727	27(71.5%)	49(28.5%)	0.310
TIMI after PCI			0.112			1.000			0.748
0	25(1.1%)	28(1.1%)	-	0(0.00%)	1(5.3%)	-	5(4.6%)	5(2.9%)	-
1	5(0.4%)	9(0.4%)	-	-	-	-	0(0.0%)	1(0.6%)	-
2	23(2.0%)	42(1.7%)	-	-	-	-	1(0.9%)	2(1.2%)	-
3	1125(95.5%)	2404(96.8%)	-	16(100%)	18(94.7%)	-	102(94.4%)	164(95.3%)	-
PTCA	1031(87.5%)	2176(87.6%)	0.915	16(100%)	16(84.2%)	0.234	100(92.6%)	158(91.9%)	0.509
Thrombus aspiration	456(38.7%)	1085(43.7%)	0.005*	3(18.8%)	3(15.8%)	1.000	39(36.1%)	76(44.2%)	0.113
Stent implantation	1043(88.5%)	2264(91.2%)	0.014*	10(62.5%)	10(52.6%)	0.734	61(56.5%)	118(68.6%)	0.027*
IABP	120(10.2%)	230(9.3%)	0.400	2(12.5%)	3(15.8%)	1.000	11(10.2%)	21(12.2%)	0.377
Endpoint events									
MACE	141(12.0%)	209(8.4%)	0.001*	16(100%)	19(100%)	-	15(13.9%)	30(17.4%)	0.269

Variables	DM Denovo lesion (N = 1178)	Non-DM Denovo lesion (N = 2483)	P_1	DM ISR (N = 16)	Non-DM ISR (N = 19)	P_2	DM LST/VLST (N = 108)	Non-DM LST/VLST (N = 172)	P3
All caused mortality	82(7.0%)	106(4.3%)	0.001*	16(100%)	19(100%)	-	6(5.6%)	17(9.9%)	0.144
Cardiovascular death	50(4.2%)	71(2.9%)	0.037*	16(100%)	19(100%)	-	5(4.6%)	11(6.4%)	0.386
Recurrence MI	43(3.7%)	70(2.8%)	0.184	16(100%)	19(100%)	-	6(5.6%)	10(5.8%)	0.576
Ischemic stroke	21(1.8%)	42(1.7%)	0.892	16(100%)	19(100%)	-	5(4.6%)	3(1.7%)	0.149
Cerebral hemorrhage	3(0.3%)	11(0.4%)	0.569	16(100%)	19(100%)	-	0(0%)	0(0%)	-

The findings of revascularization were consistent across the stratified analyses of subgroups, including variables representing serum inflammation, lipids, and thrombus levels (Fig. 1). Especially, in the subgroup with total white blood cell (WBC) count > 10 10^9/L (p = 0.004, $P_{interaction}$=0.233), neutral granular cell count > 7 10^9/L (p = 0.030, $P_{interaction}$=0.847), neutrophil-lymphocyte ratio (NLR) > 1.5 (p = 0.041, $P_{interaction}$=0.662), peak D-dimer level < 0.5 mg/L (p = 0.042, $P_{interaction}$=0.001), and not currently smoking (p = 0.012, $P_{interaction}$=0.028), DNLs outperformed LST/VLST lesions in terms of revascularization at a median follow-up of 698 days. Outcomes related to components of all subgroups are presented in the Online Appendix.

Table 2 presents the cumulative incidence of clinical outcomes by KM analysis at 2 years. The cumulative incidences of MACEs (8.42% vs. 11.97%, log rank = 0.0002), all-cause death (4.27% vs. 6.91%, log rank = 0.00032), cardiac-related death (2.86% vs. 4.24%, log rank = 0.021), and revascularization (1.34% vs. 1.49%, log rank = 0.029) were lower in the non-DM group than in the DM group among patients with DNL. A trend toward superiority for the non-DM group, compared with the DM group, was apparent (Fig. 2). At approximately 5 years, the KM curves began to continually diverge for the primary endpoint in favor of the non-DM group up to 8.2 years. However, no differences were found in the cumulative incidences of clinical outcomes composite of MACEs, all-cause death, cardiac-related death, recurrent MI, revascularization, and ischemic stroke between the DM and non-DM groups among patients with ISR lesions and LST/VLST lesions.

Table 2
The cumulative incidence of clinical outcomes by Kaplan–Meier analysis at median 698 follow up days among all enrolled patients

Endpoints	DNL N = 2661			ISR N = 35			LST/VLST N = 280		
	DM N = 1178	Non-DM N = 2483	Log rank	DM N = 16	Non-DM N = 19	Log rank	DM N = 108	Non-DM N = 172	Log rank
MACE	141(11.97%)	209(8.42%)	0.0002*	0 (0.00%)	0 (0.00%)	-	15(12.89%)	30(17.44%)	0.94
All caused death	82(6.91%)	106(4.27%)	0.00032*	0 (0.00%)	0 (0.00%)	-	6(5.56%)	17(9.88%)	0.44
Cardiac caused death	50(4.24%)	71(2.86%)	0.021*	0 (0.00%)	0 (0.00%)	-	5(4.63%)	11(4.40%)	0.87
Recurrence MI	43(3.65%)	70(2.82%)	0.12	0 (0.00%)	0 (0.00%)	-	6(5.56%)	10(5.81%)	0.79
Revascularization	175(1.49%)	332(1.34%)	0.029*	4(25.00%)	4(21.05%)	0.11	21(19.44%)	27(15.70%)	0.085
Ischemic stroke	21(1.78%)	42(1.69%)	0.67	0 (0.00%)	0 (0.00%)	-	5(4.63%)	3(1.74%)	0.088

Results of the time-to-event analysis for the primary endpoint of MACEs, all-cause death, cardiac-related death, recurrent MI, revascularization, and ischemic stroke at follow-up between the DNL, ISR, and LST/VLST groups among DM patients are summarized in Table 3 and presented in Fig. 3. At a median follow-up of 698 days, the ISR group had inferior all-cause revascularization compared with the DNL and LST/VLST groups: 4 (25.00%) versus 175 (1.49%) and 21(19.44), log rank = 0.0002.

Table 3
The cumulative incidence of clinical outcomes by Kaplan–Meier analysis at 698 median follow up days among DM subjects

Endpoints	DNL N = 1178	ISR N = 16	LST/VLST N = 108	Log rank
MACE	141(11.97%)	0 (0.00%)	15(12.89%)	0.250
All caused death	82(6.91%)	0 (0.00%)	6(5.56%)	0.736
Cardiac caused death	50(4.24%)	0 (0.00%)	5(4.63%)	0.720
Recurrence MI	43(3.65%)	0 (0.00%)	6(5.56%)	0.320
Revascularization	175(1.49%)	4(25.00%)	21(19.44%)	0.0002*
Ischemic stroke	21(1.78%)	0 (0.00%)	5(4.63%)	0.033*

Discussion

Main findings

This study, which involved 3976 real-world consecutive patients who had undergone primary PCI in China, obtained the following major findings. First, the cumulative incidences of MACEs, all-cause death, cardiac-related death, and revascularizations were lower in the non-DM group than in the DM group among patients with DNL. Second, patients with ISR had inferior all-cause revascularization than those with DNL and LST/VLST.

DM and DNL

This study showed that DM patients have significantly higher incidences of MACEs (11.97% vs. 8.42%, p = 0.0002), all-cause death (6.91% vs. 4.27%, p = 0.00032), cardiac-related death (4.24% vs. 2.86%, p = 0.021), and revascularization (1.49% vs. 1.34%, p = 0.029) than non-DM patients among patients with DNL. Owing to microvascular dysfunction, thrombus burden, unstable plaque, and diffuse distribution of atherosclerotic lesions, DM patients with ACS generally had higher incidences of LST/VLST and ISR [5, 6]. Inflammation and accumulation of reactive oxygen species and metabolic cytokines are primary mechanisms of vascular remodeling and progression of adverse myocardial diseases resulting from glycemic variability and hyperglycemia [7–11]. Furthermore, a previous study has reported that insulin resistance is higher in patients with cardiovascular disease [12]. Various biomarkers are proposed to play a role in the stratification of ACS. Cyr61, which predicts primary endpoints in patients with ACS, is involved in cell adhesion, proliferation, migration, and inflammation [13]. Indeed, glycemic variability has previously been shown as an outcome predictor of patients with ACS undergoing PCI [14]. Furthermore, the risk for repeat revascularization has been related to DM severity, with insulin-dependent DM having the highest risk factor for repeat revascularization [15]. Elevated glucose level is markedly related to sympathetic stimulation, and catecholamine can stimulate glucose release and control hyperglycemia [16–18]. Mechanistically, an increase in the incidence of MACE, mortality, and stroke among DM patients might be a result of direct glucotoxic effects, which lead to the attenuation of endothelium-dependent vasodilatation and myocardial perfusion damage [19–21]. Furthermore, hyperglycemia can cause conformational changes in platelet glycoproteins and affect platelet function and intraplatelet signaling pathways; as a result, more solid coronary clots are formed [22–23].

DM and LST/VLST

In the implantation of first-generation DES, the incidence of LST/VLST was correlated with incomplete stent apposition and delayed endothelial coverage, thereby leading to chronic inflammation [24]. However, second-generation DES, which is characterized with durable, biodegradable and biocompatible polymers, is not resistant to LST/VLST [25]. The mechanisms of thrombosed stent segments are fibrin deposition and chronic inflammation leading to strut malapposition, delayed healing, and heart remodeling, which are distinct from early ST [26–32]. Previous studies [33–36] have identified DM as an important clinically independent predictor of poor outcome in ST in the real world of mixed use of bare-metal stents (BMS) and DES. Longer lesion length, smaller vessel size, a higher rate of residual dissections, increasing thrombus burden, and bifurcation lesions might be the underlying reasons for a predisposition of DM patients to ST [37, 38]. This study highlights that total WBC count (p = 0.021) and neutral granular cell count (p = 0.018) were independent risk factors of LST/VLST among DM patients. This is consistent with the severe inflammation status of DM patients with LST/VLST. In addition, this study found a significant increase in the incidence of ischemic stroke in patients with LST/VLST compared with those with DNL and ISR (log rank = 0.033). A previous study has reported that neovascularization, fibrin accumulation, and thrombus burden are accompanied by inflammation, which correlated with the early healing of thrombus [39]. Occasional accumulation of macrophages, giant cells, and lymphocytes is a main

characteristic of the inflammatory response after percutaneous coronary stenting [40, 41]. Presence of peristrut eosinophilic material in the plasma might be a marker of endothelial cell leakage. Therefore, it is necessary to compare the effects of hypercholesterolemia using a healthy model.

DM and in-stent thrombosis

DM patients have a two- to four-fold higher risk of developing ISR after PCI than non-DM patients and thus deserve additional attention. Although new-generation DES have greatly decreased neointimal proliferation, ISR and late stent failure are common complications and crucial after coronary stenting. A recent study [42] confirmed that a higher hemoglobin A1c (HbA1c) variability in type 2 DM patients was more likely to cause higher incidences of neointimal hyperplasia and ISR and hypothesized that postprandial glucose variability might be more important than fasting glucose in the development of ISR. Compelling evidence from a notable study [43] has confirmed a significantly increased rate of ISR in DM patients undergoing PCI irrespective of specific treatment modalities, such as BMS, DES, and balloon angioplasty. Another study reported that endothelial dysfunction and impaired bioavailability of endothelium-derived nitric oxide play a critical role in the pathogenesis of post-PCI restenosis [44].

The possible mechanisms of glycemic and HbA1c variabilities that affect the progression of ISR in DM patients remain unclear. Previous studies concluded that hyperglycemia [45, 46], insulin resistance [47], and glycemic variability [48] result in adverse vascular and myocardial remodeling directly and indirectly by stimulating the production of inflammatory factors, metabolic cytokines, and reactive oxygen species. This is consistent with our finding that the prognosis DNL outperformed ISR, especially in the subgroup with total WBC count > 10 10^9/L, neutral granular cell count > 7 10^9/L, and NLR > 1.5. Furthermore, accumulating evidence confirmed that delayed re-endothelialization [49] and endothelial dysfunction [50] play major roles in the development of ISR and are significant predictors of ISR after stent implantation. Among patients with re-stenosis of the stent, insulin resistance was an established and acknowledged contributory element. The higher incidence of MACEs was correlated with endothelial dysfunction and dysregulated glucose homeostasis, which play a significant role in restenosis [51]. Therefore, delayed re-endothelialization and endothelial dysfunction are potential mechanisms in the progression of ISR under the setting of high glycemic variability [52]. Previous studies have reported [53] that endothelial vasomotor function in the systemic artery tree is significantly related to the pathobiological process of ISR by suppressing the proliferation of smooth muscle and inhibiting intimal hyperplasia. Endothelial vasomotor function has been shown to reflect nitric oxide-mediated dilation [54]. Furthermore, asymmetric dimethylarginine has been shown to be correlated with the pathogenesis of atherosclerosis and endothelial dysfunction [55]. A previous study [56] revealed that serum soluble triggering receptor expressed on myeloid cells-1 (sTREM-1) level, which is considerably affected by DM, is a predictive biomarker of ISR and an important mediator of migration, cellular inflammation, vascular smooth muscle cell proliferation, and sTREM-1 concentration. A high ISR rate may be related to dyslipidemia in DM, mainly due to increased remnant-like particle cholesterol, which is identified as lipoproteins rich in triglycerides, and in the fasting state, very low density lipoproteins are major components [57].

Insight from optical coherence tomography (OCT)

OCT has shown micro- and high-resolution intra-vascular imaging of culprit vessels to meet better understanding of mechanisms of underlying pathophysiological process of stent thrombosis. 1) Patients with acute/subacute ST suffer from high incidence of underexpansion of stent which was identified as key morphological features of ST by OCT. Furthermore, it has been shown that flow disturbance and non-streamlined flow along malapposed stent struts are in keeping with the known association between acute thrombogenicity of stents and acute procedural results [58]. 2) Malapposed struts and uncovered struts were commonly found in the patients with ST. 3) In patients with LST and VLST, neoatherosclerosis [59] and uncovered struts were relatively frequent findings. Furthermore, a heterogeneous profile has been observed [60] that malapposed, uncovered, underexpansion and severe restenosis are predominant features among patients with LST/VLST within the first year and in-stent neoatherosclerosis phenomenon, residual edge dissection and plaque rupture within the proximal or distal edge segment are more commen among patients with LST/VLST beyond 1 year. In addition, severe ISR has underlying association with VLST/LST and the linkage could be interpreted by a procoagulant state resulted from deceleration of flow within the restenotic stented segment. Representative images of dominant findings for very late ST in patients with DM are shown in Fig. 4.

Limitation

This study has some limitations. First, we retrospectively collected clinical data on definite ST of patients who underwent primary PCI, as self-reported by site investigators in this study. Furthermore, the trial was conducted in a single-center in China. Therefore, we cannot exclude geographical variations in PCI practice outside China or in higher-volume centers. Third, we did not enroll patients with ST in terms of probability, possibility, or secondary to chance, which may lead to underestimation of definite ST incidence. However, ST according to the definitions of ARC (26) was a pre-specified endpoint. All ST events were adjudicated independently by a blinded clinical events committee according to established criteria, and the incidence of definite ST continued to diverge between the two investigated devices up to 5 years,

which would render chance unlikely. Thus, it is necessary to closely evaluate demographic covariates and longitudinal management of therapeutic options.

Conclusion

In conclusion, the study found that DM patients have a higher incidence of composite clinical outcomes than non-DM patients with DNL. Further, compared with patients with DNL, patients with ISR lesions and LST/VLST lesions had more long-term composite clinical outcomes. Thus, ISR and LST/VLST lesions are critical problems after coronary stenting, especially among DM patients.

Strengthen antithrombotic therapy may provide favorable effects to reduce the incidence of ISR /ST and improve clinical outcomes in patients with type 2 diabetes after PCI.

Declarations

Ethics approval and informed consent

It is from the ethics committee of the department of Cardiology, Fuwai Hospital, National Center for Cardiovascular Diseases, Peking Union Medical College, China.

Data Availability

The datasets used and/or analyzed during this study are available from the corresponding author on reasonable request.

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Competing interests

1. We have received funding from Chinese Academy of Medical SciencesInnovation Fund for Medical Sciences (2016-I2M-1–009).

2. Non-financial competing interests.

3. Non-financial competing interests include family associations, political, religious, academic or any other.

Author Contributions

1. Substantial contributions to conception and design, data acquisition, or data analysis and interpretation: Hongbing Yan, Xiaoxiao Zhao, Jinying Zhou, Runzhen Chen, Ying Wang, Tan Yu, Chen Liu, Peng Zhou, Zhaoxue Sheng, Jiannan, Yi Chen, Li Song, Hanjun Zhao.

2. Drafting the article or critically revising it for important intellectual content: Hongbing Yan, Xiaoxiao Zhao, Jinying Zhou, Runzhen Chen, Ying Wang, Tan Yu, Chen Liu, Peng Zhou, Zhaoxue Sheng, Jiannan, Yi Chen, Li Song, Hanjun Zhao.

3 Final approval of the version to be published: Hongbing Yan, Xiaoxiao Zhao, Jinying Zhou, Runzhen Chen, Ying Wang, Tan Yu, Chen Liu, Peng Zhou, Zhaoxue Sheng, Jiannan, Yi Chen, Li Song, Hanjun Zhao.

4. Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of the work are appropriately investigated and resolved: Hongbing Yan, Xiaoxiao Zhao, Jinying Zhou, Runzhen Chen, Ying Wang, Tan Yu, Chen Liu, Peng Zhou, Zhaoxue Sheng, Jiannan, Yi Chen, Li Song, Hanjun Zhao.

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Consent for publication

Written informed consent for publication was obtained from all participants.

Disclosures

No conflicts of interest, financial or otherwise, are declared by the authors.

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Figures

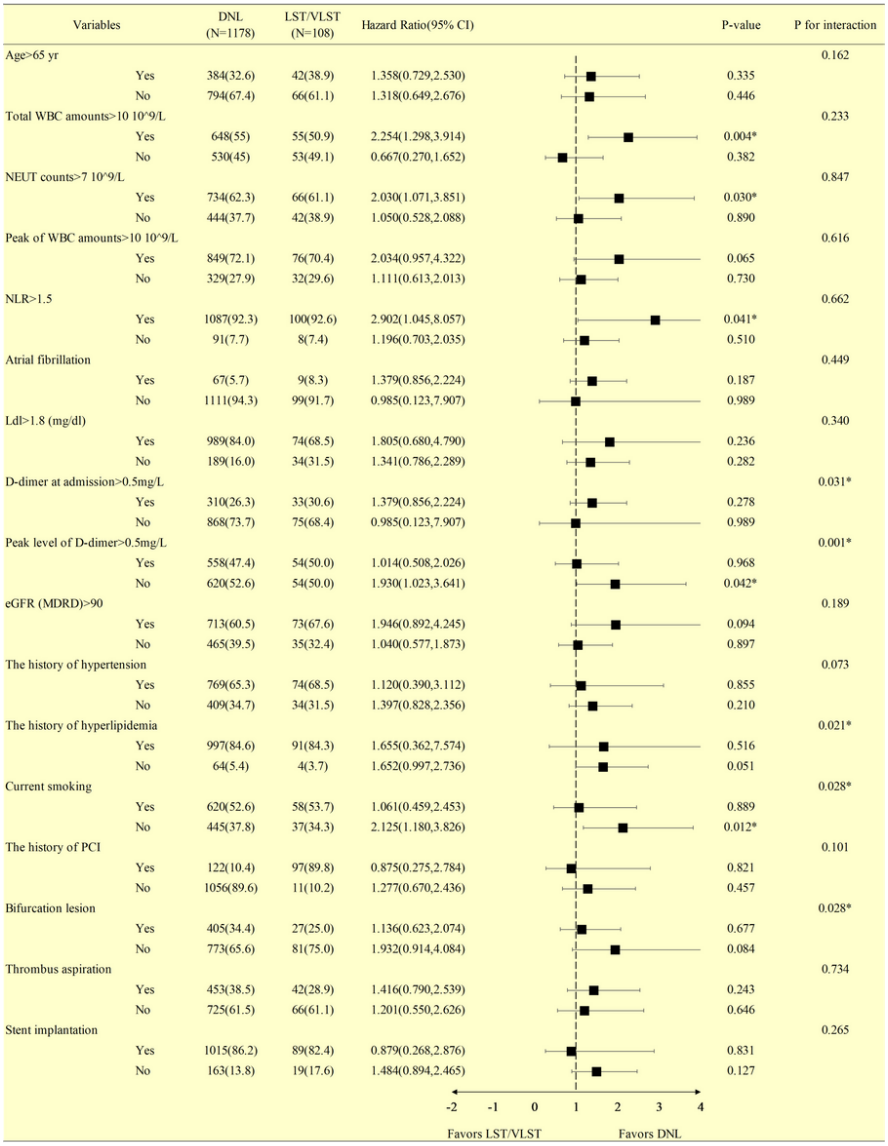
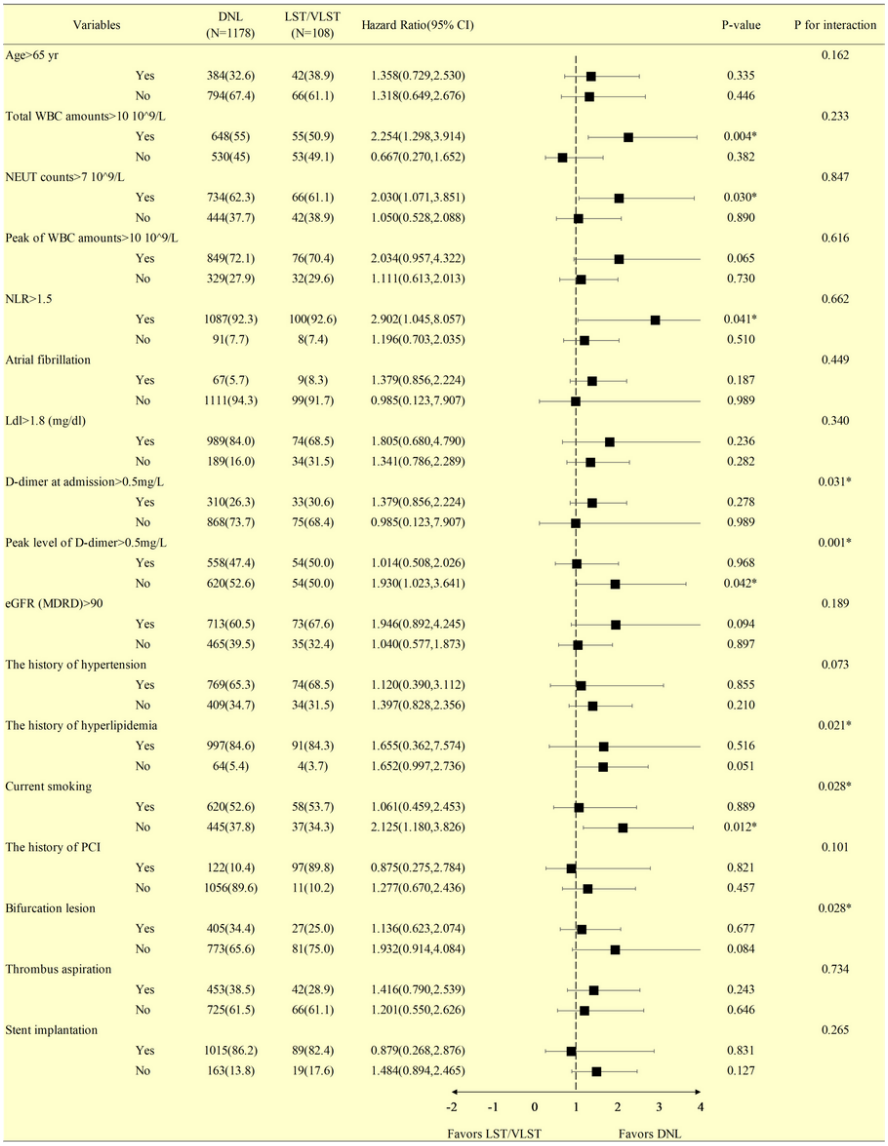


Figure 1

Stratified Analysis of the Revascularization at median Follow-up of 698 days in Patients with DNL or LST/VLST lesion Values are n (%). The primary endpoint is revascularization. *Interaction is for risk ratio -2 to 1 year and risk ratio 1 to 4 years for LST/VLST and DNL. DNL, denovo lesion; LST, late stent thrombosis; VLST, very late stent thrombosis; CI, confidence interval; WBC, white blood cell; NEUT, neutral granular cell counts; NRL, neutrophil lymphocyte ratio; Ldl, low densith lipoprotein; eGFR, estimated glomerular filtration rate; PCI, percutaneous coronary intervention



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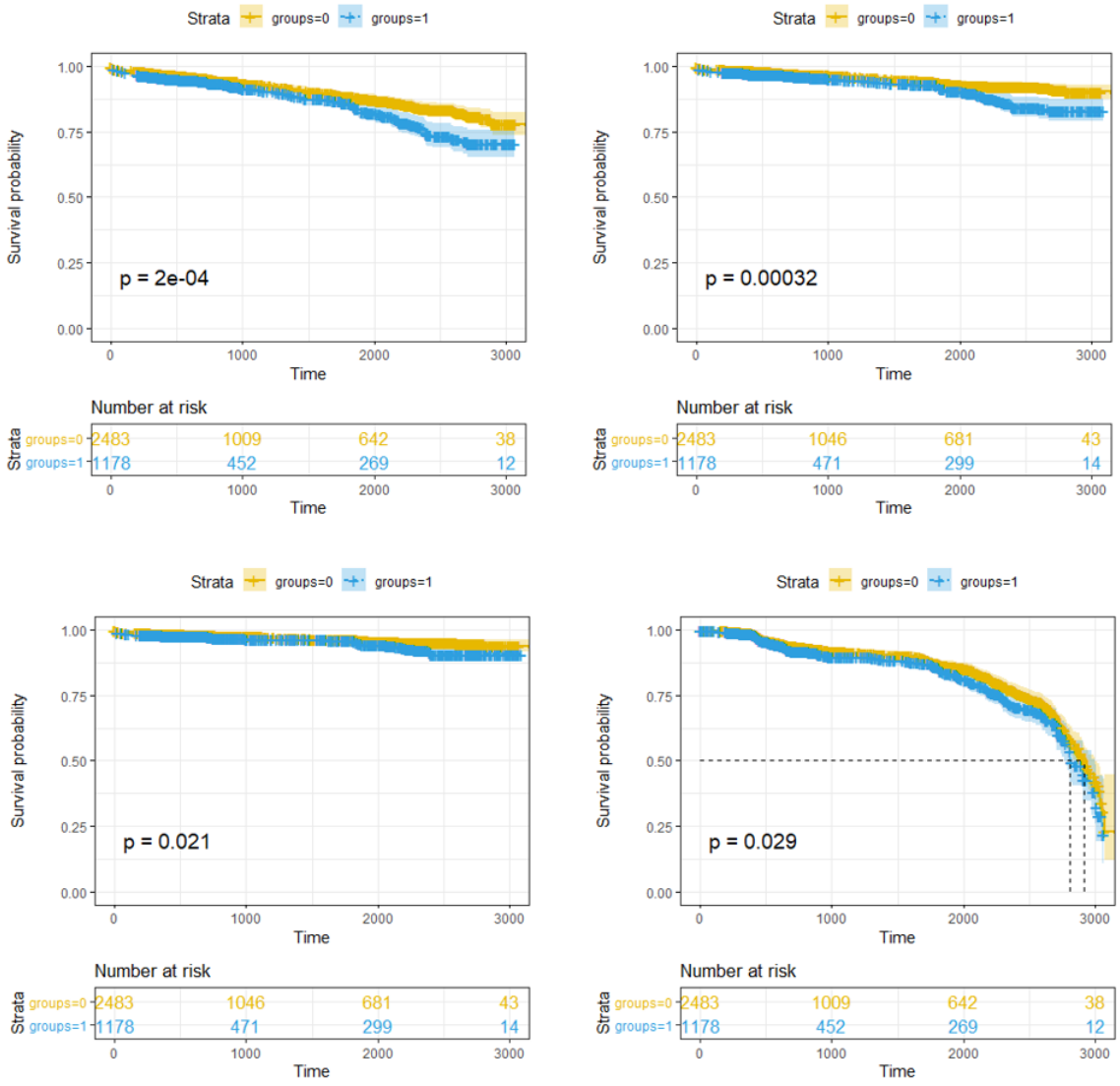
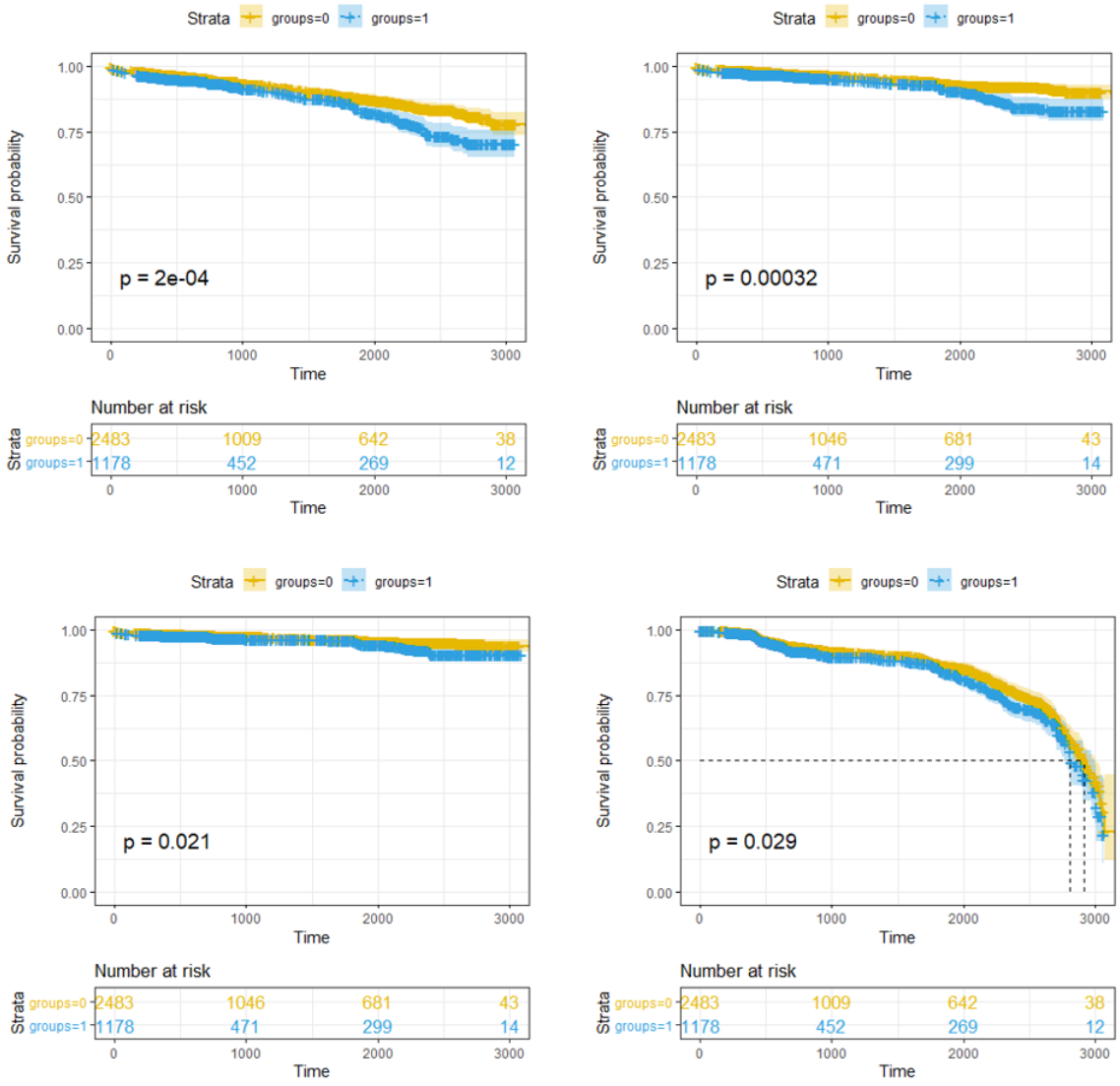


Figure 2

Kaplan–Meier curve analysis for MACE/all caused death/cardiac caused death/revascularization at follow up between DM group and non DM group. DNL, denovo lesion; ISR, in stent restenosis; LST, late stent thrombosis; VLST, very late stent thrombosis groups=0,non-diabetes mellitus group; groups=1, diabetes mellitus group



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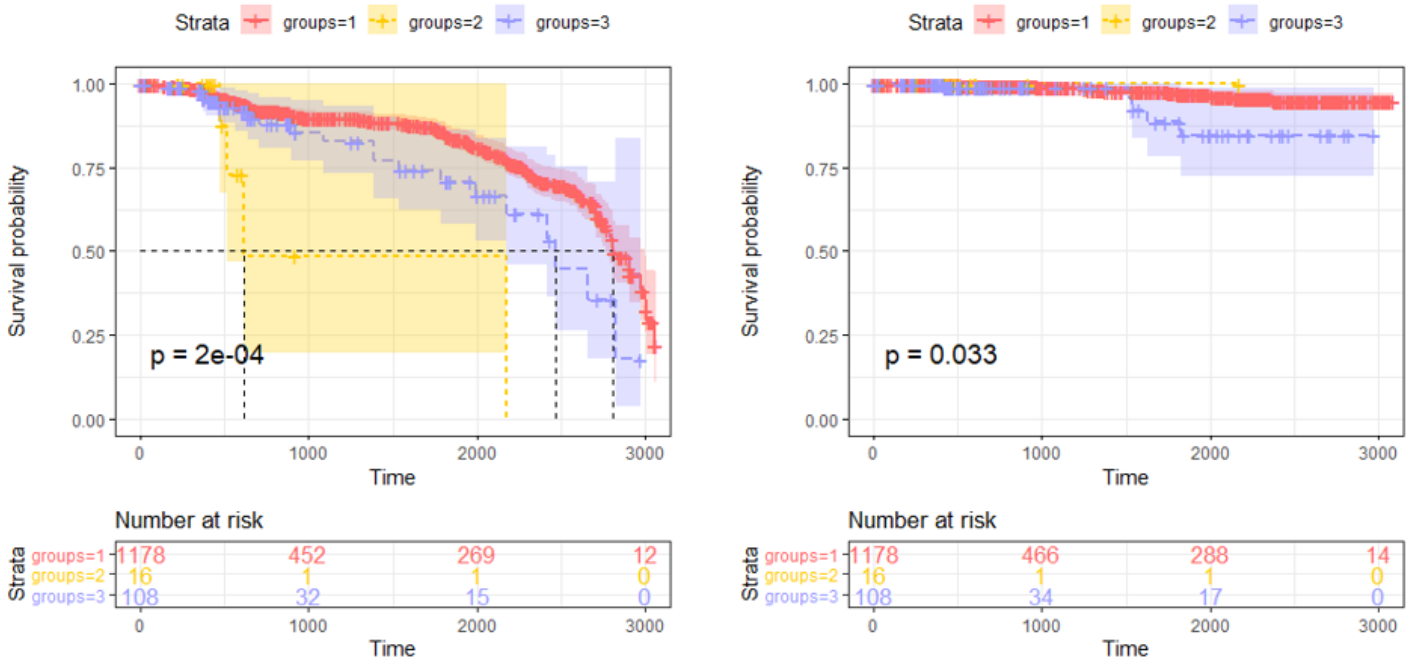
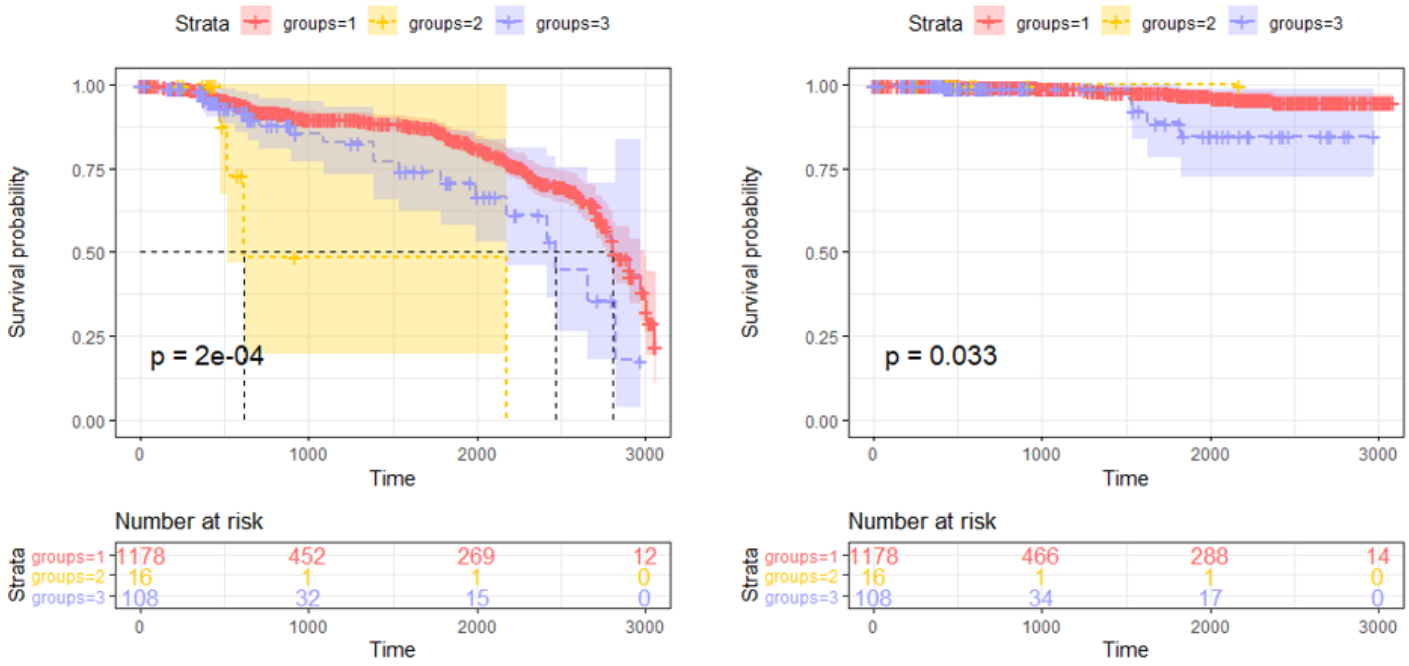


Figure 3

Time-to-Event Curves for the Primary Endpoint of revascularization and ischemic stroke at follow up between DNL group, ISR group and LST/VLST group among patients with DM. DNL, denovo lesion; ISR, in stent restenosis; LST, late stent thrombosis; VLST, very late stent thrombosis groups=1, denovo lesion group; groups=2, in stent restenosis group; groups=3, late stent thrombosis or very late stent thrombosis group



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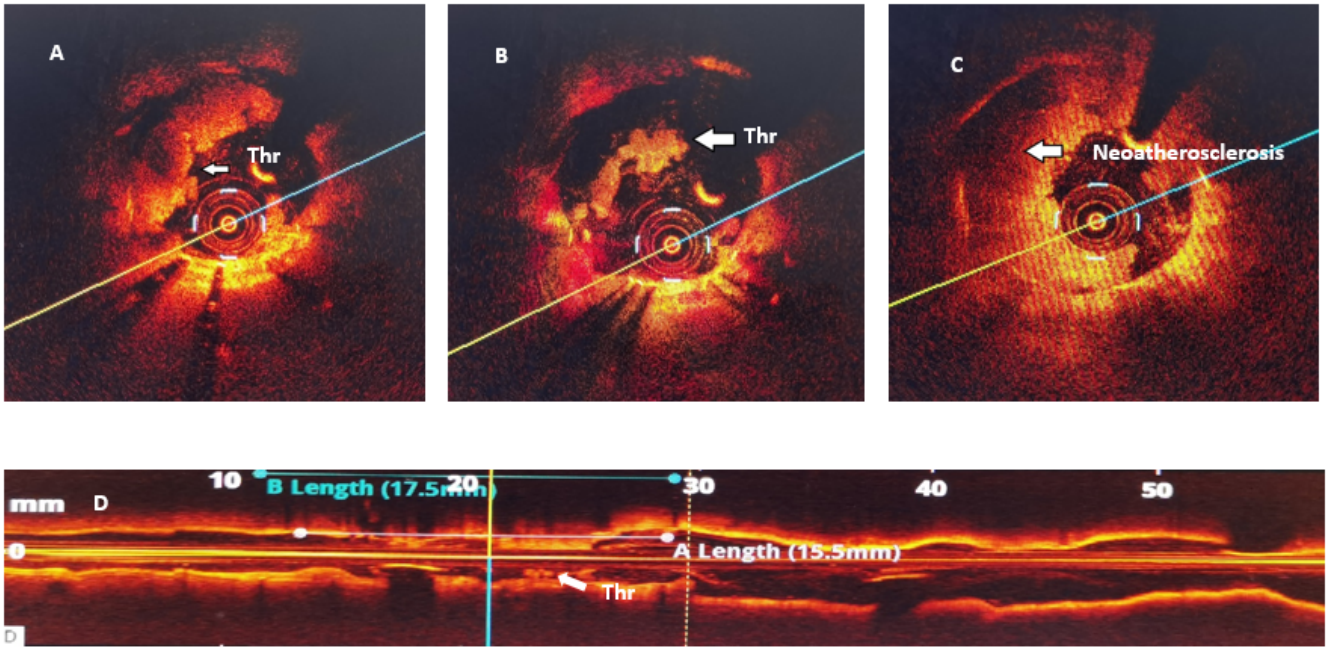
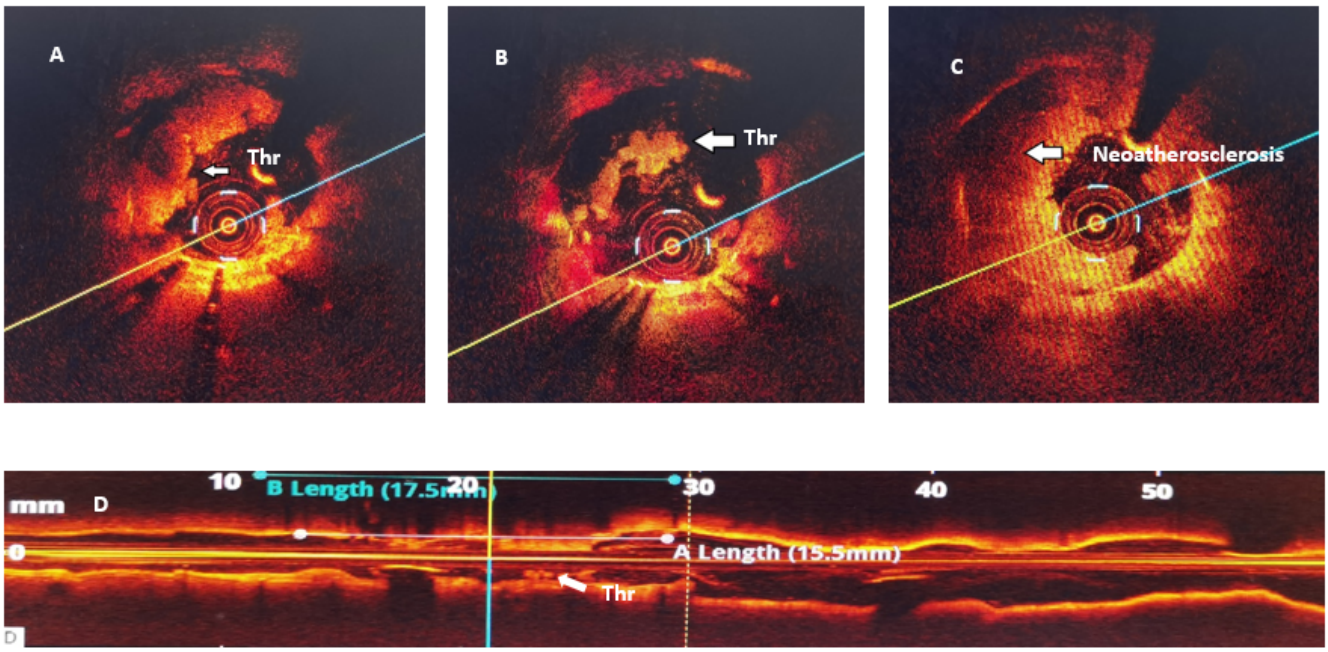


Figure 4

Representative images of optical coherence tomography (OCT) findings in patients presenting with very late stent thrombosis (VLST) with DM. (A) Neoatherosclerosis with a lipid-rich plaque (white arrows), accompanied by thrombus formation (thr). (B) Corresponding longitudinal view of the patient with stent thrombosis (white arrows). (C) Neoatherosclerosis with a lipid-rich plaque (white arrows). (D) Corresponding longitudinal view of the DM patient with stent thrombosis.



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