ORIGINAL ARTICLE

Definite stent thrombosis among Malaysian population: predictors and insights of mechanisms from intracoronary imaging

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ABSTRACT

Introduction: Stent thrombosis (ST) is an uncommon, but significant complication following angioplasty. We aimed to examine the predictors, clinical outcomes and mechanism of definite ST cases among patients who underwent percutaneous coronary intervention (PCI).

Methods: This was a retrospective observational registry of 14,935 patients from the year 2011 till 2015. Clinical characteristics, clinical outcome and intracoronary imaging data were recorded in all the patients. The SPSS Statistic version 24 was used for statistical analysis. The Cox regression hazard model was used to report calculate the hazard ratio (HR) with a 95% confidence interval (95%CI). Independent predictors of ST were identified by univariate logistic regression analysis. Variables that showed a statistically significant effect in univariate analyses were entered in a multivariate Cox proportional hazards model. A p-value<0.05 was regarded as significant.

Results: The incidence of definite ST was 0.25% (37 out of 14935 patients). 75% of ST group patients presented with ST elevation myocardial infarction (75% vs. 19.8%, p<0.01). There was higher mortality among patients with ST when compared to the group without ST (Hazard Ratio, HR=10.69, 95%CI: 1.13, 100). Two independent predictors of ST were 1) previous history of acute myocardial infarction (HR=2.36, 95%CI: 1.19, 4.70) and 2) PCI in the context of acute coronary syndrome when compared to elective PCI (HR=37, 95%CI: 15.7, 91.5). Examination of 19 ST cases with intracoronary imaging identified nine cases (47%) of underexpanded stents and five cases (26%) of malopposition of stents.

Conclusions: ST is associated with high mortality. PCI in acute coronary syndrome setting and a previous history of acute myocardial infarction were significant predictors for ST. Intracoronary imaging identified stent underexpansion and malopposition as common reasons for ST. In cases where the risk of ST is high, the use of intracoronary imaging guided PCI is recommended.

KEYWORDS:
Stent thrombosis, Predictors, Intravascular ultrasound, Optical coherence tomography

INTRODUCTION

Stent thrombosis (ST) is a rare complication following coronary angioplasty. The incidence of ST ranges from 0.4% to 3%.[1-3] Despite the rare occurrence of ST following angioplasty the mortality rate is as high as 45%.[4] Studies have identified various risk factors for ST such as chronic kidney disease, diabetes mellitus, cardiogenic shock, small stent diameter, long stent length, calcified lesions, stent malapposition, stent underexpansion and stent edge dissection.[1-5] The risk of ST is also higher in cases of acute coronary syndrome (ACS) and ST-Elevation Myocardial Infarction (STEMI) compared with stable angina.[2,6]

The European Society of Cardiology guidelines for revascularisation has recommended the use of intravascular ultrasound (IVUS) or optical coherence tomography (OCT) in the assessment and management of stent failure.[7] The use of intracoronary imaging frequently identifies specific causes of ST. Stent underexpansion and malapposition are leading causes of acute ST and sub-acute ST.[8] Despite these risk factors, a significant group of patients develop ST in the absence or paucity of these risk factors. This explains the complex and often overlapping mechanisms of the ST pathophysiology.

The aim of this study was to examine the predictors, clinical outcomes, and mechanism of definite ST cases with a large registry of patients who underwent percutaneous coronary intervention (PCI).

MATERIALS AND METHODS

Study design

This study is a retrospective observational registry of 14,935 patients who underwent PCI at the National Heart Institute of Malaysia (NHIM) between the period of 2011 and 2015. All patients who underwent PCI were included in the study. The patients were followed up for a year after PCI from the records of clinic visits, hospital admission and telephone calls. The study was reviewed by the Research and Development department of the NHIM and was approved by the ethics committee.

Data Collection

Stent thrombosis was defined according to the Academic Research Consortium (ARC) criteria for "definite" ST where there were symptoms suggestive of an acute coronary

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syndrome and angiographic or pathologic confirmation of ST.9 The timing of ST was classified as acute (<24 hours of PCI), subacute (24 hours to 30 days), late (>30 days to 1 year), or very late (>1 year). Acute and subacute ST were also defined as early ST (within the first month).[9] Clinical characteristics, clinical data of patients were collected from the registry database, patient medical records and electronic medical information system. The context of PCI was recorded, including history of acute myocardial infarction, PCI for acute coronary syndrome or elective PCI. The term acute myocardial infarction was defined as ST elevation myocardial infarction (STEMI) and Non-ST elevation myocardial infarction (non-STEMI). Acute coronary syndrome (ACS) was defined as unstable angina, non-STEMI and STEMI. All angiographic characteristics for cases of definite ST were documented. Data from the PCI was documented, including the site and nature of the lesion, type and size of the stent used and the use of intracoronary imaging including IVUS and OCT.

Intracoronary Imaging

OCT was performed with a frequency domain imaging system (C7XR, Ilumien or Ilumien Optis, St. Jude Medical).[10] The OCT images were obtained with motorised pullback at 1.0mm/s. An OCT pull-back of the segment of interest, including distal and proximal reference sites, was performed with contrast injection through the guiding catheter at 3 to 5mL/s. Intracoronary thrombus was identified as any abnormal mass protruding beyond the stent struts into the lumen.[11,12]

IVUS was performed after intracoronary administration of 0.1 to 0.2mg of nitroglycerin, with a commercially available iLab system (Boston Scientific, California). Imaging was acquired with a motorized pull-back at 0.5mm/s to include the stent. Stent, lumen, and malapposition cross-sectional areas (CSA) were measured at 1-mm axial increments throughout the length of the stent and 5-mm segments proximally and distally to the stent.

The main aetiologies of mechanical ST were classified as: stent underexpansion, stent malopposition and edge dissection. Stent underexpansion was defined as intra-stent minimal area ≤70% of the average reference lumen area.[13] Stent Malopposition (also known as incomplete stent apposition) was defined as separation of at least one stent strut from the vessel wall, where the distance from the endoluminal surface of the strut to the vessel wall was higher than the sum of the metal and polymer thickness.[14]

Statistics

Continuous data were presented as percentage or mean±standard deviation (SD). Tests of normalization were applied to continuous variables. Categorical variables were summarized as percentages and compared with the Chi square test. Parametric data was analysed with the independent sample t test. Non-parametric data was analysed with the Mann-Whitney test. The Cox regression hazard model was used to report calculate the hazard ratio (H R) with a 95% confidence interval (95%CI). Survival analysis was analysed by Kaplan-Meier Survival curve. Independent predictors of ST were identified by univariate logistic regression analysis. Variables that showed a statistically significant effect in univariate analyses were entered in a multivariate Cox proportional hazards model. A p value of <0.05 was regarded as significant. Software used for statistical analysis was SPSS Statistic version 24.

RESULTS

Baseline Characteristics

There were 14,935 patients included in the study with total 21,063 lesions treated with PCI. The mean age was 58.6±10.2years, 12,360 (82.8%) were males, 7,915 (53%) patients had diabetes mellitus, 949 (6.4%) had chronic kidney disease with serum creatinine level >200µmol/L and 7092 (53%) patients had a history of acute myocardial infarction (Table I).

Antiplatelet Therapy

The patients were on different combinations of dual antiplatelet therapy prior to PCI. There were a majority of 13,423 (89.9%) patients on a combination of aspirin/clopidogrel and 922 (6.1%) patients on a combination of aspirin/ticagrelor. There were also patients who were on combinations of any of aspirin, ticagrelor, clopidogrel, prasugrel, ticlodipine, cilostazol and triflusal. Majority of the patients with ST had aspirin/clopidogrel combination, 35 patients (95.6%) as compared to one patient (2.7%) each for the aspirin/ticagrelor group and triflusal/clopidogrel group (Table I). Post ST events, 19 patients had their clopidogrel switched to ticagrelor and one patient had aspirin re-challenge therapy.

Context of PCI

A total of 13,080 patients (87.8%) had elective PCI while 1855 patients (12.4%) had PCI for acute coronary syndrome. When comparing patients with ST and without ST, there were significantly more patients presented with acute myocardial infarction (75% vs. 19.8%, p<0.01) in the ST group (Table I). Similarly, there were significantly more acute coronary syndrome cases (83.8% vs. 12.2%, p<0.01) in the ST group. Conversely, there were significantly fewer patients having elective PCI in the ST group when compared to the group without ST (16.2% vs. 87.8%, p<0.01).

Lesion Characteristics

There were 21,063 coronary lesions treated with PCI. Left anterior descending artery (LAD) was the vessel treated the most (44.7%), followed by right coronary artery (29.9%), left circumflex artery (19.9%), left main stem (LMS) artery (2.4%) and bypass graft (1.9%). There were 1893 ostial lesions (9%), 1534 (7.3%) total occlusion lesions, 758 (3.6%) calcified lesions and 1548 (20%) bifurcation lesions treated. There were no significant differences in the characteristics of lesions when comparing patients with ST and no ST (Table II).

Procedural Characteristics

There were 19,418 lesions (80.2%) treated with drug eluting stents (DES), compared to 1797 lesions (7.4%) treated with bare metal stents (BMS), and 1560 lesions (6.4%) treated with Drug Eluting Balloon (DEB). 497 (2.4%) of the lesions involved stents to the LMS artery, 3922 lesions (18.6%) were treated with stent length 31.5mm and above, 9382 (44.5%) lesions had stent diameter less than 3mm, and 6939 (32.9%) lesions had maximum balloon dilatation size less than 3mm,

Table I: Baseline characteristics and Antiplatelet therapy comparing stent thrombosis (ST) and no ST groups

Patient and Clinical Characteristics	No ST (n = 14,898)	ST (n = 37)	p-value
Age, Mean±SD years	58.6±10.2	58.2±10.4	0.62
Male	12,332 (82.8%)	28 (77.8%)	0.38
Diabetes Mellitus, %	7891 (53.0%)	24 (66.7%)	0.13
Hypertension, %	11,022 (74.0%)	30 (83.3%)	0.20
Dyslipidaemia, %	10,380 (69.7%)	24 (66.7%)	0.69
Family history of cardiovascular disease, %	1753 (11.8%)	3 (8.3%)	0.52
Chronic Kidney Disease (>200µmol/L), %	948 (6.4%)	1 (2.8%)	0.72
History of Myocardial infarction, %	7069 (47.4%)	23 (63.9%)	0.049
ST elevation Myocardial Infarction as presentation, %	2953 (19.8%)	27 (75.0%)	<0.01
Dual Antiplatelet Therapy			
Aspirin + Clopidogrel, %	13,388 (89.9%)	35 (95.6%)	-
Aspirin + Ticagrelor, %	921 (6.2%)	1 (2.7%)	-
Clopidogrel + Triflusal, %	34 (0.2%)	1 (2.7%)	-
Other dual antiplatelet drugs*	555 (3.7%)	-	
Context of PCI			
PCI in Acute Coronary Syndrome	1824 (12.2%)	31 (83.8%)	<0.01
Elective PCI	13,074 (87.8%)	6 (16.2%)	<0.01

*Other dual antiplatelet drugs depicts a combination of two of either ticagrelor, clopidogrel, aspirin, prasugrel, cilostazol, triflusal or ticlodipine

Table II: Type of Lesions and Procedural Characteristics

Lesion and Procedural Characteristics	No ST (n=21,063)	ST (n=37)	p-value
Lesion Characteristics			
Left main stem	496 (2.4%)	1 (3.1%)	0.77
Left anterior descending	9413 (44.7%)	23 (62.2%)	0.06
Left circumflex	4181 (19.9%)	7 (18.9%)	0.75
Right coronary artery	6288 (29.9%)	7 (18.9%)	0.09
Bypass graft vessel	400 (1.9%)	0	0.45
Ostial Lesion	1891 (9%)	2 (6%)	0.59
Total Occlusion Lesion	1532 (7.2%)	2 (6%)	0.82
Calcified Lesion	758 (3.6%)	0	0.27
Procedural Characteristics			
Drug Eluting Stent	19,388 (92%)	33 (89.2%)	0.75
Bare Metal Stent	1794 (8.5%)	3 (8.1%)	0.95
Bioabsorbable scaffold	205 (1%)	1 (2.7%)	0.27
Stent Length 31.5 mm and above	3918 (18.6%)	4 (12.5%)	0.26
Stent diameter less than 3 mm	9371 (44.4%)	11 (34%)	0.90
Maximum Balloon size less than 3mm	6922 (32.9%)	14 (44%)	0.28
Overlapping stent	4282 (20.3%)	7 (21.9%)	0.82
Bifurcation stenting	1546 (7.3%)	2 (6.3%)	1.00
Multi-vessels angioplasty	8229 (64.8%)	20 (55.6%)	0.29
Slow intracoronary flow post PCI (<TIMI III flow)	807 (3.8%)	0	0.63
Intracoronary Imaging			
IVUS used	880 (4.2%)	14 (51.2%)	<0.01
OCT used	262 (1.2%)	7 (18.9%)	0.01

*ST-Stent thrombosis

4289 (20%) lesions had overlapped stenting and 8249 (7.3%) lesions involved ≥2 vessels angioplasty (multi-vessels angioplasty).

Of the patients who had ST, there were 33 (89.2%) DES, three (8.1%) BMS and one (2.7%) bio-absorbable scaffold complicated with ST (Table II). There were 807 (3.8%) lesions without TIMI III coronary flow (slow intracoronary flow) post angioplasty. Interestingly, all lesions with ST had TIMI III coronary blood flow post index PCI (Table II).

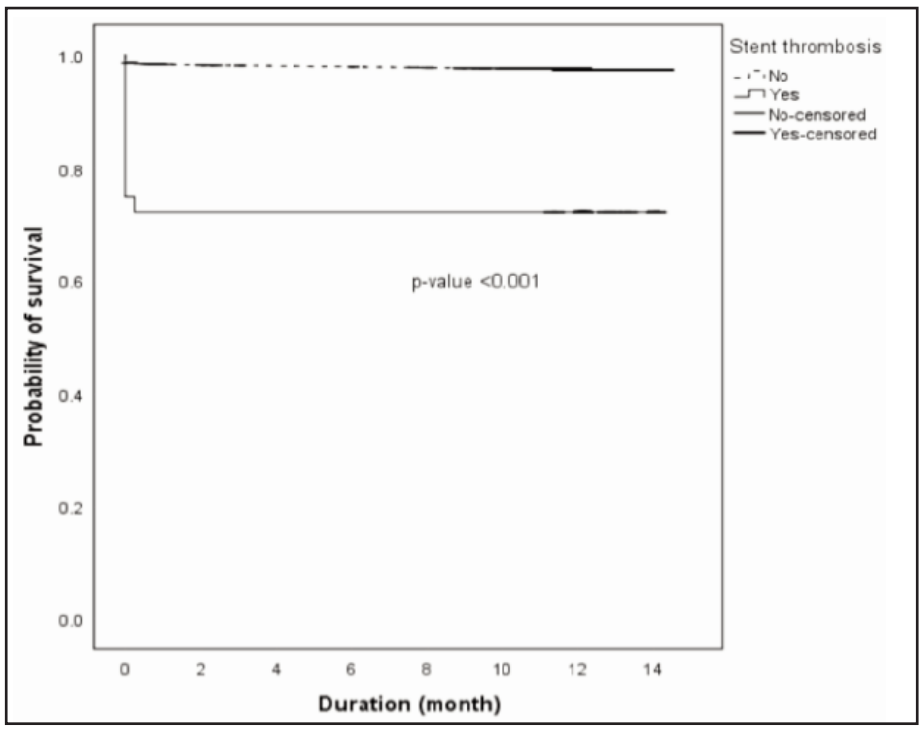
There were no significant differences in procedural characteristics comparing patients with ST and without ST (Table II).

Intracoronary Imaging

There were higher numbers of patients where intracoronary imaging was used among the ST group (Table II) for both IVUS (51.2% vs. 4.2%, p<0.001) and OCT (18.9 vs. 1.2%, p=0.011). This finding was explained the use of the intracoronary imaging to investigate the cause of ST.

Table III: Univariate and Multivariate Analysis of predictors of ST

Univariate	Hazard Ratio	95% CI	p value
Clinical Predictors			
Diabetes Mellitus	1.52	0.76-3.02	0.22
Chronic Kidney Disease (Sr. Creatinine level >200μmol/L)	1.32	0.40-4.39	0.64
History of Myocardial Infarction	2.00	0.99-3.87	0.05
PCI Status (acute coronary syndrome vs Elective)	35.8	14.9-86.22	<0.01
Primary PCI	1.65	0.57-4.73	0.35
No Aspirin Use	1.38	0.18-10.38	0.74
Type of Lesion & Procedural Predictors			
Ostial lesion	0.50	0.06-3.75	0.50
Total occlusion lesion	0.65	0.08-4.88	0.67
Bifurcation stenting	1.31	0.30-5.61	0.71
Overlapping stent	0.85	0.28-2.53	0.77
Stent length ≥31.5mm	0.64	0.18-2.16	0.47
Stent diameter less than 3mm	0.76	0.30-1.94	0.57
Maximum Balloon size less than 3mm	1.70	0.66-4.35	0.26
Multivariate			
History of Myocardial Infarction	2.36	1.1929-4.70	0.014
PCI context (acute coronary syndrome vs Elective)	37.97	15.76-91.51	<0.01



Number at Risk	1-month	6-month	1-year
No ST	12083	12023	10220
ST	26	26	26

Fig. 1: Kaplan Meier survival curve for showing mortality in patients with and without ST

Incidence of Stent Thrombosis

There were 37 cases of definite ST, the incidence of ST was 0.25%. Of the 37 cases of ST, 13 (36%) had acute ST, 16 (43%) had sub-acute ST, four patients (11%) had late ST and the remaining four patients (11%) had very late ST. The majority of cases were early ST, 29 (78.3%) cases occurring within the first month after PCI.

Mortality Rate

The in-hospital mortality rate was 24.3% (9 out of 37 patients). The Kaplan Meier curve (Figure 1) showed that there was higher mortality among patients with ST when compared to the group without ST (HR=10.69, 95%CI: 1.13, 100). Although the follow up period was 1 year, all cases of mortality among the patients with ST occurred early (within the first month). Patients who had PCI for acute coronary

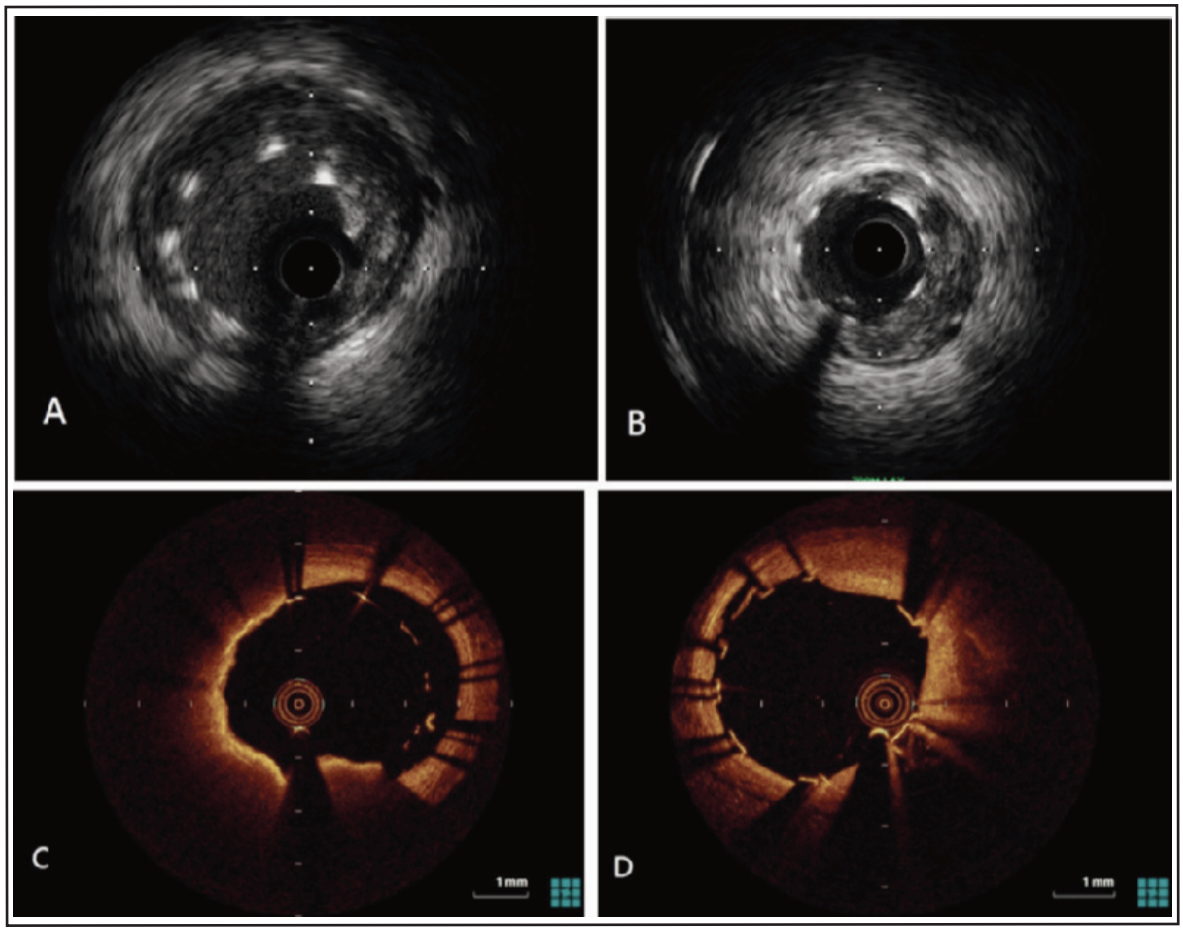


Fig. 2: A: IVUS image of malopposed stent demonstrating separation of stent strut from the vessel wall; B: IVUS image of underexpanded stent, where the reference artery area and diameter are substantially larger than within stented segment; C: OCT images of malopposed stent where bright, reflective stent struts are visualized and are not in contact with the intima of the artery; D: OCT image of underexpanded stent, intra-stent minimal area is ≤70% of the average reference lumen area

syndrome had a significantly higher mortality risk than the elective PCI group (HR=4.6, 95%CI: 3.65, 5.78).

Predictors of ST

Univariate analysis was used to identify clinical, lesion and procedural predictors for ST (Table III). A history of acute myocardial infarction was a significant predictor for ST (HR=2.00, 95%CI: 0.99, 3.87). PCI in the context of acute coronary syndrome was another significant clinical predictor for ST when compared to elective PCI (HR=35.8, 95%CI: 14.9, 86.22).

Multivariate analysis showed that patients with history of acute myocardial infarction was a significant predictor of ST (HR=2.36, 95%CI: 1.19, 4.70). PCI in the context of acute coronary syndrome was another significant clinical predictor for ST when compared to elective PCI (HR=37, 95%CI: 15.7, 91.5). Both predictors were also significantly predict early ST, history of AMI (HR=2.23, 95%CI 1.02, 4.84) and PCI for acute coronary syndrome (HR=8.71, 95%CI: 4.13, 18.38). However, there was no identifiable predictor for late ST. The only predictor for very late ST was PCI for acute coronary syndrome statistics (HR=29.46, 95%CI 3.28, 264.7).

Intracoronary Imaging and Management of Stent Thrombosis

A total of 19 cases of ST were examined by Intravascular Ultrasound (IVUS) or Optical Coherence Tomography (OCT) and of these there were nine cases (47%) due to underexpanded stents, five cases (26%) related to malopposition of stents and two cases (11%) due to stent edge dissection. Four other cases (21%) which were examined by IVUS/OCT showed no identified aetiology for ST.

In all 31 (83.8%) of the ST cases had thrombus aspiration, while 13 (35.1%) received additional intracoronary GpIIb/IIIa receptor antagonist infusion. All of the ST cases had treatment in the form of noncompliance (NC) balloon post-dilatation. When compared to the first angioplasty, during subsequent angioplasty when ST occurred, there was higher pressure for the NC balloon dilatation, with an increase in previous mean pressure from 16.5±4 to 19±4.5atm (mean difference=2.71atm, 95%CI 0.45, 4.97). All of the ST cases were also subsequently treated with higher balloon diameter size, with an increase from mean balloon diameter of 2.95±0.49 to 3.23±0.65mm (mean difference=0.28mm, 95%CI: 0.12, 0.43). Seventeen (46%) of the ST cases had one new stent deployed, while three (8.1%) cases had two new stents, one (2.7%) case was treated with DEB.

DISCUSSION

The main findings of the study are, firstly the majority of ST cases occurred early, and ST was associated with higher mortality; secondly a significant proportion of ST cases occur in the context of acute coronary syndrome; and finally intracoronary imaging identified the common causes of ST to be underexpansion and malopposition of stents.

Incidence of Stent Thrombosis

The incidence of definite ST in our study is 0.24%. This figure is comparable to other registries in Europe and Asia. There was a 1.2% definite ST seen in the Swedish Coronary Angiography and Angioplasty Registry (SCAAR)[15] and 1.3% definite ST in the Spanish Registry (ESTROFA),[3] whilst in the setting of stable coronary artery disease, the incidence of ST is reported to be approximately 1% to 2% from other Asian registries.[16,17]

Significant proportion of ST cases occur in the context of Acute Coronary Syndrome

In our patients, almost 80% of the ST occurred within 30 days and the majority of patients with ST were in the context of acute coronary syndrome (83%) as opposed to elective PCI cases (17%). This finding is important as it was shown in the ACUITY trial in 2011 that patients with ST in NSTEMI-ACS had poor prognosis. The increased risks of death were observed in cases of early and late ST with a 1-year all-cause mortality rate was 16% after definite ST compared to 3% in patients without ST.[18] Another study of ST in acute myocardial infarction showed significantly higher all-cause mortality rate after ST of 29% compared to 17% for patients without ST.[19]

Among our patients, despite a high in-hospital mortality rate, only 8% of the stents with thrombosis had repeat revascularization in long term follow up. This number is relatively low compared to 27% of target vessel revascularization reported by Kubo et.al.[20]

PCI for acute coronary syndrome is the strongest predictor of ST in our study. Other studies have shown that ST is more likely to occur in the context of acute coronary syndrome.[21,22] Cardiogenic shock and STEMI were the strongest predictors of ST in one registry of 5,833 patients who underwent PCI, highlighting the need for careful consideration when deciding on PCI with stent in non-culprit lesions in STEMI patients.[23]

APOLLO investigators found that the survivors of 1-year post AMI had an observe risk of AMI, stroke and all cause death up to 36.2% at three years follow up[24]. Our predictors of history of AMI probably explain the mechanism of APOLLO findings. This could be explained by pathophysiologic factors such as persistent slow coronary blood flow and low shear stress leading to activation of the intrinsic pathway, the presence of a systemic prothrombotic state related to acute coronary syndrome.[25]

Importance of Intracoronary imaging in Stent Thrombosis

The use of intracoronary imaging (IVUS/OCT) guided angioplasty was low in our centre, 5.5%. However, its use was more frequent after stent complication as it was crucial in identifying the mechanisms of ST. Important procedural specific risk factors for early and late ST include mechanical issues such stent underexpansion, malapposition, undersizing, and stent edge.[26] In our patients, the majority of cases were due to malopposed stents (Figure 2A, 2C) or underexpanded stents (Figure 2B, 2D). A high proportion of the cases presented early as acute and subacute ST, consistent with other studies, which where ST is attributed to mechanical issues.[27] Additionally, uncovered stent struts and neoatherosclerosis have been identified as a risk factors for very late ST.[28,29]

It is possible that there is an association for higher mechanical issues in the context of acute coronary syndrome. The mechanisms for the stent malopposition or stent underexpansion for example, in the context of acute coronary syndrome may be due to the presence of thrombus confined between struts and vessel wall that dissolves over time, difficulties to achieve correct culprit lesion sizing or plaque coverage.[29] Hence, the high percentage of stent malapposition and stent underexpansion among acute coronary syndrome patients with ST, is a sign of a need for early detection and correction these anomalies during initial PCI, guided by intracoronary imaging.

In the context where intracoronary imaging is not accessible due to availability or cost constraint, simple steps to reduce the mechanical mismatch of stent size in ACS are 1) achieving maximal vasodilatation with intra-coronary nitroglycerine before the stent size selection and 2) post-dilatation of the stent with appropriate size non-compliant balloon.

Establishing a precise diagnosis for the cause of ST is important in order to implement appropriate therapy.29 Such therapy may include stent implantation, balloon angioplasty alone for severe underexpansion or subsequent stent placement for neoatherosclerosis or edge-related disease progression.[25]

STUDY LIMITATIONS

This is a non-randomised observational study using the registry data and thus the incidence of ST may have been underestimated. Only the angiographically definite ST were included in our registry, but not cases with probable and possible ST. Furthermore, these cases were only limited to patients who were still warded during the events, patients who presented to our facilities during the events and those referred back to our centre during or after the events.

There was a disproportionate number of IVUS cases compared to OCT cases as the choice of intracoronary imaging depended on physician preference. Some of the patients in the group with ST did not have intracoronary imaging, hence the cause of ST was not documented.

It was also not possible to determine retrospectively compliance with antiplatelet treatment among patients who had ST and this may serve as a confounding factor.

CONCLUSION

ST is associated with significantly higher mortality. PCI for acute coronary syndrome and a previous history of acute myocardial infarction were significant predictors for ST. Intracoronary imaging identified stent underexpansion and malopposition as common causes of ST. In cases where the risk of ST is high, the use of IVUS/OCT guided PCI is recommended.

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