

Incidence and prognosis of stent thrombosis following percutaneous coronary intervention in Middle Eastern patients: The First Jordanian Percutaneous Coronary Intervention Registry (JoPCR1)

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BACKGROUND: The incidence, risk factors, and outcome of stent thrombosis (ST) after percutaneous coronary intervention (PCI) in Middle Eastern patients are largely unknown.

OBJECTIVE: To determine the incidence, risk factors and outcome in our population.

DESIGN: Retrospective study of a prospective multicenter registry of consecutive patients who underwent PCI between January 2013 and February 2014 (JoPCR1).

SETTING: 12 tertiary care centers in Amman and Irbid, Jordan.

PATIENTS AND METHODS: We collected clinical baseline and follow-up data.

MAIN OUTCOME MEASURES: Incidence of stent thrombosis.

RESULTS: The mean (standard deviation) age of patients (n=2426) was 59.0 (10.1) years and 20.6% were women. Stents (n=3038) were drug eluting (89.6%), bare metal (9.4%) or bioabsorbable (1.0%). After 1 year, 47 patients (1.97%) had ST, including 44 (94%) definite and 3 (6%) probable ST. Patients who had ST presented with sudden death (n=6; 12.2%) or with a nonfatal event (n=43; 87.8%). Nonfatal events included non-ST-segment elevation acute coronary syndrome (26; 53%), acute ST segment elevation myocardial infarction (n=15; 31%) or heart failure (n=2; 4.1%). ST was associated with significantly higher one-month (22.0% vs. 0.7%) and one-year (12.3% vs. 0.73%) mortality rates compared with patients who did not have ST ($P<.001$). ST patients were younger (mean age 52.9 years vs. 58.4 years), had heart failure (64% vs. 18%), left ventricular ejection fraction (LVEF) <45% (36% vs. 13%), ST-segment deviation (70% vs. 48%), and elevated cardiac biomarkers blood levels (62% vs. 40%). In the multivariate analysis, the only factor that was significantly associated with ST was the heart failure (OR = 3.5, 95% confidence interval: 1.8, 6.6; $P<.0001$).

CONCLUSIONS: The incidence of ST was not different from that in other regions and was associated with an increased one-year mortality. Younger age, heart failure, low LVEF, ST-segment deviation, and elevated blood levels of cardiac biomarkers were predictors of ST.

LIMITATIONS: Possible selection bias, recall bias, and missing or incomplete information. The majority of patients were lost to follow up after the 6th month. The registry may not fully represent PCI practice and outcome in all areas in the country or region.

Stent thrombosis (ST) is a recognized complication of stent-based percutaneous coronary intervention (PCI) with an incidence that ranges between 0.5% and 2.2%.¹⁻³ Clinical consequences of ST are generally catastrophic, including death and major myocardial infarction (MI).²⁻⁶ The etiology of ST is multifactorial, including stent thrombogenicity and procedure-, lesion-, and patient-related factors.⁷⁻⁹ The incidence, risk factors, and outcome of stent thrombosis in Middle Eastern patients are largely unknown.

PATIENTS AND METHODS

JoPCR1 is a prospective multicenter registry of consecutive patients who undergo PCI at 12 tertiary care centers in Amman and Irbid, Jordan. In this study, data collected between January 2013 and February 2014 was analyzed. A case report form was used to record data prospectively at hospital admission, at discharge, and at 1, 6, and 12 months of follow-up. Data were collected during follow-up visits or phone calls to the patient, household relative or primary care physician. The study was approved by the institutional review board of each participating hospital, and patients signed informed consent.

Baseline data included clinical, laboratory, electrocardiographic, echocardiographic, and coronary angiographic features for each patient. The SYNTAX coronary diagram was used to define the involved arteries and their segments.¹⁰ Details of the PCI procedure and its outcome were also recorded. All PCI procedures were performed according to current standard guidelines. The arterial access site, dual antiplatelet therapy, and type of stent (drug-eluting stent [DES], bare-metal [BMS], or bioresorbable vascular scaffold [BVS]) were selected at operator's discretion. PCI was indicated for either acute coronary syndrome (ACS) or stable coronary disease. ACS was classified as (1) acute ST-segment elevation myocardial infarction (STEMI), defined by the presence of cardiac ischemic chest pain, ST-segment elevation of >2 mm in at least two contiguous leads on the 12-lead electrocardiogram (EKG), and elevated cardiac biomarkers (troponin or creatinine kinase-myocardial band) greater than the upper limit of the normal, or (2) non-ST-segment elevation ACS (NSTEMI). This included non-ST-segment elevation MI (NSTEMI), defined by the presence of cardiac ischemic chest pain, ST-segment depression, inverted T wave, or normal EKG and elevated cardiac biomarkers as above, and unstable angina (UA); defined by the presence of ischemic cardiac pain, ST-segment depression, inverted T wave or normal EKG and no elevation of cardiac biomarkers on admission and 8-12 hours later. Stable coronary dis-

ease was classified as (1) chronic stable angina, defined as ischemic cardiac pain on effort that did not change in severity for the previous 3 months, and absence of resting EKG ischemic changes or elevated cardiac biomarkers, or (2) silent ischemia, defined as absence of angina in the presence of signs of myocardial ischemia on EKG, echocardiography, or nuclear myocardial scan.

PCI for STEMI was (1) primary, i.e., PCI as reperfusion strategy with no thrombolysis, (2) rescue, i.e., PCI after failure of thrombolysis, or (3) elective, i.e., PCI after successful thrombolysis. PCI for NSTEMI/UA was (1) urgent, i.e., PCI done within 2 hours after admission for ongoing chest pain, hemodynamic instability, life-threatening ventricular arrhythmia or heart failure, (2) early invasive, i.e., PCI within 24 hours after admission, or (3) late invasive, i.e., PCI within 24-72 hours after admission.

Unfractionated heparin was given as an initial bolus of 70 IU/kg and added boluses were administered during the procedure to achieve an activated clotting time of 250-300 seconds. All patients who had not taken aspirin before presentation with ACS received 100 mg aspirin, followed by 100 mg/day indefinitely. Patients were given a loading dose of clopidogrel 300-600 mg or ticagrelor 180 mg according to the cardiologist's discretion, followed by 75 mg clopidogrel/day or 90 ticagrelor twice daily for at least one year for all patients except for patients with stable coronary disease who had a BMS implanted during the index admission. The use of glycoprotein IIb/IIIa inhibitors was left to the operator's discretion. Patients were observed after PCI in a coronary care or telemetry unit until the time of discharge.

Major events and adherence to prescribed medications were documented during follow-up calls or outpatient clinic visits. The major events of concern were death from cardiac causes (all deaths were considered cardiac unless a definite noncardiac cause could be established), ST, admission with ACS, repeat coronary angiography or revascularization. ST was defined according to the Academic Research Consortium as definite, probable or possible ST.¹¹ Only definite and probable ST cases were analyzed. Definite ST was defined as angiographic confirmation of a thrombus and presence of at least one of the following criteria within a 48-hour time window: acute onset of ischemic symptoms at rest, new ischemic EKG changes that suggested acute ischemia and/or typical rise and fall in cardiac biomarkers, or pathological confirmation of ST by a finding recent thrombus within the stent determined at autopsy or by examination of tissue retrieved following thrombectomy. Probable ST was defined as the occurrence of any

unexplained death within the first 30 days, or any MI that was related to documented acute ischemia in the territory of the implanted stent without angiographic confirmation of ST and in the absence of any other obvious cause, irrespective of the time after the index procedure. ST was considered as acute if it occurred 0 to 24 hours after stent implantation, subacute; if 24 hours to 30 days after stent implantation, and late if 31 days to 1 year after stent implantation.

Statistical analysis

Data were described and analyzed using IBM SPSS (version 20). Data were described using means, standard deviations, or percentages wherever appropriate. The independent t test was used to compare means and the chi-square test was used to compare proportions. Univariate and multivariate logistic regression was used to determine factors associated with ST. For the multivariate analysis, a forward approach in a multiple logistic-regression model was performed. In this model, all significant factors at alpha level of 0.1 from the univariate analysis were entered in the final model. The assumptions of logistic regression including collinearity were checked. The interaction terms between the variables in the final model were checked and none of them was shown to be significant. A *P* value of less than .05 was considered statistically significant.

RESULTS

Indications for PCI in the 2426 patients enrolled in the study were ACS (77.1%) and stable coronary disease (22.9%). ACS included STEMI (30.0%), NSTEMI (12.5%) and UA (34.5%). During hospitalization, dual antiplatelet therapy (DAPT) was administered to all patients. There were 47 cases (1.97%) of ST at 1 year of follow up, including 44 definite (94%) and 3 probable (6%) cases. **Table 1** shows the baseline characteristics of patients who had ST compared with those who did not. Most of the patients who developed ST (87%) had PCI for ACS. Among the ACS patients who had ST, PCI was indicated for STEMI (38%) and NSTEMI (49%).

Acute ST occurred in 7 (0.29%), subacute in 26 (1.10%), and chronic in 14 (0.58%) of the patients who had ST. Compared with patients who did not have ST, those who had this event had higher in-hospital, 1-month and 1-year mortality (**Table 2**). Only 4 patients (8.5%) presented with death, and the other 43 patients (91.5%) had nonfatal events, including NSTEMI (60.3%), STEMI (35.0%) or heart failure (4.7%).

Most of the stents used (n=3038) were DES (90%). BMS and BRS comprised 9% and 1%, respectively. Thrombosis occurred in 45 DES (92% of all ST cases), 3

Table 1. Baseline features of patients who had stent thrombosis compared with those who did not.

Feature	Stent thrombosis n=47	No stent thrombosis n=2379	P value
Mean age (years)	52.9	58.4	.05
Men (n,%)	37 (79)	1893 (80)	.487
Hypertension (n, %)	26 (62)	1483 (62)	.473
Hypercholesterolemia (n, %)	21 (45)	1164 (49)	.336
Current smokers (n, %)	23 (49)	1035 (44)	.277
Mean BMI	30.2	28.0	.44
Mean CrCl (mL/min)	129	100	.46
Mean serum creatinine (mg/dL)	0.84	1.01	.077
Diabetes mellitus (n, %)	30 (64)	1273 (54)	.105
Prior history of CAD/MI (n, %)	16 (34)	848 (35.6)	.47
Prior history of PCI (n, %)	14 (29.8)	527 (24)	.227
DAPT at discharge (n, %)			
Aspirin	46 (97.9)	2356 (99)	.76
Clopidogrel/Ticagrelor	45 (95.7)	2347 (98.7)	.33
Major bleeding event (n, %)	0	23 (0.97)	.47

ACS=acute coronary syndrome; BMI=Body mass index (weight in kg/height in m²); CAD=coronary artery disease; CrCl=creatinine clearance (mL/min); DAPT=dual antiplatelet therapy; MI=myocardial infarction; PCI=percutaneous coronary intervention.

Table 2. Cardiac death in patients who had or did not have stent thrombosis.

Timing of cardiac mortality	Cardiac mortality		P value
	Patients who had ST	Patients who did not have ST	
In-hospital	2/9 (22.2%)	17/2417 (0.70%)	<.0001
1 month	3/33 (9.1%)	26/2380 (1.1%)	<.0001
12 months	4/47 (8.5%)	43/2292 (1.9%)	<.0001

ST=stent thrombosis

(6%) BMS, and 1 (2%) BRS. Only one patient reported stopping the DAPT.

In the univariate analysis, the factors that were associated with ST were heart failure, ST-segment deviation and elevated serum cardiac biomarkers. Gender, past history of MI or PCI, chronic renal disease or severity of coronary artery disease were not associated with an increased risk for ST (**Table 3**). In the multivariate analysis (**Table 4**), the only factor that was significantly associated with ST was the heart failure. Heart failure was

Table 3. Univariate predictors of stent thrombosis.

Feature	Stent thrombosis (n=47)	No stent thrombosis (n=2379)	P value
Heart failure (n, %)	30 (61)	436 (19)	<.0001
ST-segment deviation (n, %)	33 (67)	1151 (49)	.008
Elevated cardiac biomarkers (n, %)	31 (63)	943(40)	.001
ACS (n, %)	43 (88)	1830 (77)	.05
PCI for multivessel CAD (n, %)	14 (29)	668 (28)	NS

ACS=acute coronary syndrome; CAD=coronary artery disease.

Table 4. Multivariate analysis of factors associated with stent thrombosis.

Variable	OR	95% confidence interval		P value
Heart failure	3.5	1.8	6.6	<.001
ST-segment deviation	1.5	0.7	3.3	.290
Acute coronary syndrome	1.4	0.5	3.6	.523
Elevated cardiac markers	1.2	0.5	2.5	.705
PCI for multivessel CAD	1.0	0.5	2.0	.913

CAD=coronary artery disease; PCI=percutaneous coronary intervention. Coefficient of determination ($r^2=.047$).

associated with an increased odds of ST (OR=3.5, 95% confidence interval: 1.8, 6.6, $P<.0001$).

DISCUSSION

The main findings of this study of Middle Eastern patients were: (1) incidence of ST after 1 year of follow up was similar to that observed in studies from other regions, (2) ST was associated with significantly higher in-hospital and 1-year mortality compared with patients who did not have this complication, and (3) catastrophic presentations in patients who had ST were lower than those reported in most similar studies, i.e., death in <1/10 and STEMI in <4/10 patients.

Studies have shown that patients who undergo PCI for ACS have a higher incidence of ST than those in who undergo PCI for stable coronary disease.¹² The majority of patients in our study (77%) had PCI for ACS. Low ST incidence rates were mainly reported in clinical trials that enrolled patients who had elective PCI.¹³ Higher ST rates (2.9-3.7%) were observed in patients who had PCI for NSTEMI and STEMI.¹⁴ In registries

representing "real world" practice of patients with PCI for STEMI and NSTEMI, rates of ST ranged between 1.2 and 1.9%.^{15,16} The 1-year incidence of 1.97% observed in our study was not different from the ST rate noted in "real world" registries and was lower than that observed in some clinical trials.

Studies have demonstrated that up to 90% of patients who sustain ST present with death or STEMI;^{1,2} more than 2-fold the rate observed in our study (44%). The fact that 60% of our ST patients presented with NSTEMI indicates that the thrombus was not completely occlusive in more than half of these patients. Potential factors that may explain this finding include the relatively younger age of our patients, the low prevalence of high-risk features on admission (chronic renal disease, heart failure, prior history of MI, and multivessel CAD), the high rate of use of drug-eluting stents, and a high DAPT compliance rate.

Factors associated with increased risk of ST in the univariate analysis were heart failure, ST-segment deviation and elevated cardiac biomarkers. Several mechanical and patient-, disease-, lesion-related factors have been shown by many studies to be associated with an increased risk for ST. Stent underexpansion, malapposition, residual dissection and inflow/outflow disease are well established mechanical causes related to early ST.¹⁷⁻²¹ Mechanical factors may be inadequate to explain ST in all cases. Clinical, angiographic, procedure and hematological factors include diabetes mellitus, baseline renal insufficiency, smoking, higher baseline haemoglobin level, previous PCI, ejection fraction <30%, ACS, greater overall burden of coronary atherosclerosis, primary PCI for STEMI, presence of thrombus, small stent diameter, longer stented segment, stenting in restenotic, complex, or bypass graft lesions, per cent stenosis before and after the procedure, final minimal lumen diameter within the stent, Thrombolysis In Myocardial Infarction (TIMI) flow grade <3, presence of intermediate coronary lesions proximal and distal to the culprit lesion, bifurcation lesions, no pre-procedural antiplatelet agents administration, increased platelet activity, aspirin resistance, impaired response to antiplatelet therapy, and acute post procedural renal failure.²²⁻²⁶

Discontinuation of dual antiplatelet therapy is a strong predictor of ST. The presence of other coexisting factors, however, makes the risk of ST not limited only to interruption of DAPT.²⁷⁻³¹ Only one patient with ST in our study reported discontinuation of DAPT. However, validation of adherence to therapy among other patients who had ST and those who did not have ST was not possible, making it difficult to make conclusions about the complex interplay of DAPT interruption and

ST. Our study evaluated the incidence of ST up to 1 year after PCI; hence, the relationship between DAPT discontinuation and very late ST (>1 year) needs further follow up.

This registry has limitations inherent to observational studies.³² It may be subject to selection bias, collection of non-randomized data, and missing or incomplete information. Participation was voluntary and the enrolment of consecutive patients was encouraged, but this was not verified, as it is the case with other registries.^{33,34} ACS patients who died before or shortly after admission and those who did not undergo angiography were not represented in the group of patients we enrolled. The accuracy of the recall of the patients or their relatives of major events, such as death, major bleeding, readmission, or revascularization, is unlikely to be underreported. Less than 1.5% of patients could not be followed up until the end of the study period; however, the majority of those patients were lost to follow up af-

ter the 6th month, making the number of missed diagnosis of ST from the 6th month to the end of the study minimal. The registry included high volume tertiary care centers and may not fully represent PCI practice and outcome in all areas in the country or region.

Despite these limitations, our study is unique in that it evaluated short- and long-term outcomes of PCI in the Middle East, a region in the world that is not well represented in cardiovascular interventional studies and registries.

The incidence of stent thrombosis at 12 months after successful stent implantation in consecutive real-world patients was 1.9%. Young, ST-segment deviation, elevated cardiac marker, acute coronary syndrome, heart failure, and low ejection fraction were identified as independent predictors of stent thrombosis. The clinical consequences were death in 8.5% of patients and nonfatal MI in the majority of the others. Most of these events (50%) occurred in hospital before discharge.

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