



# Acute and sub-acute stent thrombosis: Frequency, predictors and features in patients undergoing primary percutaneous intervention at a tertiary care cardiac centre

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## ABSTRACT

**Objectives:** To assess the frequency of early (acute and sub-acute) stent thrombosis (ST) after primary percutaneous coronary intervention (pPCI) and to identify its potential predictors.

**Background:** ST is a serious clinical event associated with a high mortality rate. A very limited data are available regarding the incidence rate of early ST after pPCI and its predictors, especially for Pakistani population.

**Methods:** Study included consecutive patients who underwent primary PCI. Telephonic follow-ups were made to obtain 30-days outcomes including ST, mortality, and re-occurrence of symptoms. ST was defined as per the standardized definition proposed by the Academic Research Consortium and classified as acute (during the procedure) and sub-acute (within 30 days).

**Results:** A total of 569 patients were included with 80.5% (485) male patients. The stent thrombosis (acute or sub-acute) was observed in 33 (5.8%) patients out of which 3 (9.1%) were definite ST while remaining 30 (90.9%) were probable ST. Patients who develop ST were predominantly male, hypertensive, diabetic, with reduced pre PCI LVEF (%) and Killip Class. A significantly higher in-hospital mortality rate was observed in patients with ST as compared to without ST, 36.4% (12/33) vs. 0.2% (1/536); p-value < 0.001 respectively. Killip Class (III-IV) was found to be the independent predictor of ST with an adjusted odds ratio of 5.2 [1.76–15.32].

**Conclusions:** Early stent thrombosis (ST) is relatively frequent in patients undergoing primary PCI. Diabetic and hypertensive patients are at an increased risk of ST and presentation of patients in Killip Class III-IV is an independent predictor of early ST.

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## 1. Introduction

Stent thrombosis (ST) is a serious clinical event associated with high mortality rates and commonly presents as ST-segment elevation myocardial infarction (STEMI) [1]. Prior studies have demonstrated that ST is a rare occurrence with routine coronary intervention, with an incidence of less than 1% following percutaneous coronary intervention (PCI) [2]. However, its incidence is higher after acute myocardial infarction (AMI), with data from the HORIZONS-AMI trial reporting an incidence rate of 0.8% within 24 h (acute ST) and 1.2% within 30 days (sub-acute ST) in patients undergoing primary PCI for AMI [3]. Other studies have also demonstrated an acute and sub-acute ST rate of around 2.5% in patients with AMI [4–6]. The incidence of early ST (within 30 days)

may be even higher in patients with cardiac arrest and AMI, with some studies showing an incidence of around 5% [7,8].

Many clinical studies have been done in the past decades to evaluate the potential predictors of acute and sub-acute ST. Multiple factors seem to be involved in the pathophysiology of ST but the exact mechanism has not been completely understood. These factors have been classified into different categories, first and most important are device-related factors which include stent design, material, surface coating, number of stents per lesion, length of the stent, and interaction of stent with adjunctive treatment, for example, intracoronary brachytherapy. Another important category is related to lesion- or patient-specific factors, including vessel size, lesion length, acute coronary syndrome (ACS) or unstable angina, left anterior descending artery (LAD) involvement, presence of thrombus, plaque characteristics, coronary blood flow, local platelet/coagulation activity, advanced age, left ventricular ejection fraction, peripheral arterial disease, renal failure, diabetes mellitus,

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and non-adherence to dual antiplatelet therapy. Next category comprises procedural factors and includes stent malposition, stent under expansion, undersized stents, residual dissection, mechanical vessel injury and suboptimal antithrombotic therapy [9,10].

A very limited data are available regarding the incidence rate of early ST after primary PCI and its predictors, especially for Pakistani population. Therefore, the aim of this study was to assess the frequency of early (acute and sub-acute) stent thrombosis (ST) after primary PCI for ST-segment elevation myocardial infarction (STEMI) and to identify its potential predictors.

## 2. Methods

After the approval of ethical review committee of National Institute of Cardiovascular Diseases (NICVD), Karachi, Pakistan, hospital records were obtained for the consecutive patients of acute myocardial infarction (MI) who underwent primary percutaneous coronary intervention (PCI). All the primary PCI procedures were performed by consultant cardiologist (with at least five years of interventional cardiology experience). Patients with periprocedural bleeding events (minor or major) were excluded from the analysis. All these included patients were preloaded with guideline-recommended medications including 300 mg soluble aspirin, 600 mg clopidogrel and unfractionated heparin as bolus (dose adjusted individually according to body weight as 70–100 units/kg) followed by glycoprotein IIb/IIIa inhibitor i.e tirofiban as bolus dose during the procedure. Also, these patients were kept on dual antiplatelet therapy (DAPT) i.e soluble aspirin 300 mg once daily and clopidogrel 75 mg twice daily for 1-month duration, followed by aspirin 75 mg indefinitely and colpidogrel 75 mg once daily for 12-month duration.

Data regarding baseline clinical and demographic characteristics, pre-procedure and angiographic characteristics, procedural characteristics, and in-hospital outcome were collected on a pre-designed structured questionnaire. The 30th day outpatient visit record were obtained to assess ST. And telephonic follow-ups were made for all the patients who underwent primary PCI within the study duration of 1st July 2017 to 31st December 2017. Follow-up outcomes included all-cause mortality, re-hospitalization, re-occurrence of MI, and re-intervention. Stent thrombosis (ST) was defined as per the standardized definition proposed by the Academic Research Consortium (ARC) comprises of definite and probable ST [11]. And ST was classified as acute (during the procedure) or sub-acute (within 30 days after the procedure).

The sample size for this study was calculated based on 3.5% [12] of the expected rate of stent thrombosis within 30 days after the index procedure, with 95% confidence interval, 1.5% margin of error, the required sample size for the study was calculated to be  $n = 577$ . IBM SPSS Statistics for Windows, Version 21.0. (IBM Corp., Armonk, NY, US) was used for the analysis of data. Shapiro-Wilk test was applied to check the hypothesis of normality for quantitative (continuous) variables. Appropriate descriptive statistics such as mean  $\pm$  SD or median (IQR) or frequency and percentages were calculated. Univariate and Multivariate logistic regression analysis were performed to identify the factors affecting stent thrombosis and odd ratios with 95% confidence interval were calculated for the potential predictors. Significant variables from the univariate analysis and clinically significant variables, such as age, positive family history, multi-vessel disease (MVD), culprit left main (LM), stent length (mm), and stent diameter (mm), were taken as explanatory variables in the multivariate analysis. All the significant variables from the univariate analysis were taken as explanatory variables for the multivariate analysis. A two-sided  $p$ -value of  $\leq 0.05$  was taken as criteria for significance.

## 3. Results

A total of 569 patients were included in this study, 80.5% (485) of the patients consisted of male patients. Age of the patients was in the range of 28–96 years. Hypertension was the common (40.8%) risk factor among the patients. The stent thrombosis (acute or sub-acute) was observed in 33 (5.8%) patients out of which 3 (9.1%) were definite ST while remaining 30 (90.9%) were probable ST.

Distribution of diseased vessels was 3VD in 26.4% (150), 2VD in 33.2% (189), and 38.1% (217) had single vessel diseased. Culprit artery was distributed as Mid-Distal LAD in 21.4% (122), proximal LAD in 28.3% (161), RCA in 38.7% (220), LCX in 10.5% (60), while left main was culprit in only 0.5% (3) patients. Patients who develop ST were predominantly male, hypertensive, diabetic, with reduced pre PCI LVEF (%) and Killip Class. Baseline clinical, demographic, and angiographic characteristics are presented in Table 1.

Procedural characteristics and the in-hospital outcome are presented in Table 2. Stent type was BMS for most, 52.9% (301), of the patients. Post-procedure TIMI flow was distributed as 0 in 0.4% (2), I in 0.5% (3), II in 3% (17), and 96.1% (547) had post procedure TIMI flow grade of III. Post-procedure in-hospital mortality rate was 2.3% (13) and it was significantly higher in patients with ST, 36.4% (12/33) vs. 0.2% (1/536);  $p$ -value  $< 0.001$  for patients with and without ST respectively.

Follow-up duration was  $18.08 \pm 1.76$  months. Mortality rate within 30 days of the procedure was found to be 4.4% (25) and re-admission rate within 30 days was found to be 2.3% (13). Mortality rate during the follow-up duration was 10.9% (62), re-infarction rate was 3% (17), and re-intervention was 2.5% (14). Rate of stent thrombosis was 5.8% (33), of which 0.5% (3) were acute stent thrombosis and 5.3% (30) were sub-acute stent thrombosis. The stent thrombosis was found to be associated with both in-hospital as well as post discharge adverse outcomes and complications which included in-hospital, early (within 30 days), and late (during follow-up) mortality, re admission, re-infarction, and re-intervention. Follow-up outcomes are presented in Table 3.

Unadjusted and adjusted odds ratio [95% CI] for the various determinants of stent thrombosis are presented in Table 4. Odds of stent thrombosis were significantly higher among patients with hypertension (2.35 [1.15–4.83]), diabetes (2.13 [1.04–4.35]), and patients who presented in Killip Class III or IV (6.4 [2.35–17.41]). Killip Class (III-IV) was found to be the independent predictor of acute and sub-acute stent thrombosis with an adjusted odds ratio of 5.2 [1.76–15.32].

## 4. Discussion

The principal findings from this retrospective study involving 569 patients undergoing primary PCI for STEMI are; the Academic Research Consortium Early Stent Thrombosis including acute and sub-acute ST within 30 days was not that uncommon event, occurring in around 5.8% of the patients with the rate of sub-acute stent thrombosis considerably higher than acute stent thrombosis. Stent thrombosis (ST), during any time interval up to one month, was not related to the type of stent implanted (BMS or DES). Early ST was observed more frequently in patients who were in Killip class III-IV. Hypertensive and diabetic patients were found to be at increased risk of early ST (within 30 days). However, among various risk factors, Killip class III-IV was found to be the only independent predictor of early ST. The mortality rate with early stent thrombosis was found to be 4.4% at 30 days.

However contrary to previous studies, we did not find any relationship between stent length and diameter with the frequency of stent thrombosis, nor did we observe any relation between lesion

**Table 1**  
Baseline clinical, demographic, and angiographic characteristics.

Characteristics	Total	Stent Thrombosis		p-value
		No	Yes	
<b>N</b>	569	536	33	–
<b>Gender</b>				
Male	80.5% (458)	80.4% (431)	81.8% (27)	0.039
Female	19.5% (111)	19.6% (105)	18.2% (6)	
<b>Age (years)</b>				
Range	96–28	96–28	85–34	0.256
Mean ± SD	55.57 ± 11.06	55.39 ± 10.91	58.45 ± 13.14	
Median [IQR]	56 [61–50]	56 [61–49]	56 [66–50]	
<b>Body Mass Index (kg/m<sup>2</sup>)</b>				
Range	54.08–15.04	54.08–15.04	31.64–18.43	0.786
Mean ± SD	25.59 ± 4.58	25.62 ± 4.64	25.13 ± 3.52	
Median [IQR]	25.01 [27.76–22.86]	25.01 [27.76–22.83]	25.1 [27.78–22.86]	
<b>Risk Factors</b>				
Hypertension	40.8% (232)	39.6% (212)	60.6% (20)	0.017
Diabetes mellitus	26.7% (152)	25.7% (138)	42.4% (14)	0.036
Smoking	23.6% (134)	23.9% (128)	18.2% (6)	0.454
Positive family history	3.7% (21)	3.4% (18)	9.1% (3)	0.09
Prior PCI	3% (17)	3.2% (17)	0% (0)	0.299
<b>Killip Class</b>				
I	86.3% (491)	87.5% (469)	66.7% (22)	<0.001
II	9.5% (54)	9.1% (49)	15.2% (5)	
III	2.3% (13)	2.1% (11)	6.1% (2)	
IV	1.9% (11)	1.3% (7)	12.1% (4)	
<b>Number of diseased vessels</b>				
None	2.3% (13)	2.2% (12)	3% (1)	0.594
Single vessel disease (SVD)	38.1% (217)	38.2% (205)	36.4% (12)	
Two vessels disease (2VD)	33.2% (189)	32.6% (175)	42.4% (14)	
Three vessels diseases (3VD)	26.4% (150)	26.9% (144)	18.2% (6)	
<b>Culprit artery</b>				
Mid-Distal LAD	21.4% (122)	21.3% (114)	24.2% (8)	0.447
Proximal LAD	28.3% (161)	28.5% (153)	24.2% (8)	
Right coronary artery (RCA)	38.7% (220)	38.6% (207)	39.4% (13)	
Circumflex (LCX)	10.5% (60)	10.6% (57)	9.1% (3)	
Left main (LM)	0.5% (3)	0.4% (2)	3% (1)	
Ramus	0.5% (3)	0.6% (3)	0% (0)	
<b>Dominance</b>				
Right	83.7% (476)	84.1% (451)	75.8% (25)	0.209
Left	9% (51)	9% (48)	9.1% (3)	
Co-dominance	7.4% (42)	6.9% (37)	15.2% (5)	
<b>Pre PCI LVEF (%)</b>				
Range	65–25	65–25	45–25	<0.001
Mean ± SD	44.7 ± 10.01	45.2 ± 9.95	35.71 ± 6.16	
Median [IQR]	45 [55–35]	45 [55–35]	35 [40–30]	
Not assessed	53.8% (306)	53.5% (287)	57.6% (19)	
<b>Lesion Length (mm)</b>				
Range	67–5	67–5	30–10	0.281
Mean ± SD	19.08 ± 8.07	19.04 ± 8.18	19.7 ± 6.07	
Median [IQR]	16 [24–13]	16 [24–13]	20 [25–14]	

SD = standard deviation.

IQR = interquartile range.

PCI = percutaneous coronary intervention.

LAD = left anterior descending artery.

length and frequency of stent thrombosis. Smoking was not an independent risk factor for ST (acute or sub-acute) in our population.

There is an increased risk of MI and mortality associated with stent thrombosis. STEMI presentation is the most important predictor of ST according to emerging data. The Swedish Coronary Angiography and Angioplasty Registry (SCAAR) reported a 2.5 fold increased risk of ST in STEMI patients relative to patients without STEMI [13]. The incidence rate of early ST was reported to be ranging from 0.5 to 2.0% [14–17]. Various procedural factors and lesion-related factors such as stent under-expansion, tissue protrusion or residual thrombus, edge dissection, compromised flow individually

as well as in combination were thought to be related to these early events.

In our study, the rate of early ST (acute or sub-acute) after primary PCI was found to be 5.8%, of which 0.5% were acute and 5.3% were sub-acute. The rate of ST in our study is relatively higher than the reported incidence rate in the past studies, for example, the rate of early ST (acute and sub-acute) was reported to be 2.5% in the HORIZONS AMI trial [18]. Another study by Montalescot et al. reported an incidence rate of 2.5% for the STEMI patients undergone primary PCI [19]. Finally, definite early ST after primary PCI was reported in around 3.5% of the patients out of 5842 STEMI patients registered in the Dutch stent thrombosis registry [12].

**Table 2**  
Procedural characteristics and in-hospital outcome.

Characteristics	Total	Stent Thrombosis		p-value
		No	Yes	
<b>N</b>	569	536	33	–
<b>Stent Type</b>				
Drug-eluting stent (DES)	43.9% (250)	43.7% (234)	48.5% (16)	0.862
Bare metal stents (BMS)	52.9% (301)	53.2% (285)	48.5% (16)	
Plain old balloon angioplasty (POBA)	3.2% (18)	3.2% (17)	3% (1)	
<b>Stent Length (mm)</b>				
Range	38–6	38–6	30–8	0.293
Mean ± SD	16.83 ± 7.2	16.79 ± 7.27	17.45 ± 6.09	
Median [IQR]	15 [18–12]	15 [18–12]	15 [22–15]	
<b>Stent Diameter (mm)</b>				
Range	4.5–1.5	4.5–1.5	4–2	0.1
Mean ± SD	3.17 ± 0.63	3.17 ± 0.63	3.03 ± 0.59	
Median [IQR]	3.5 [3.5–3]	3.5 [3.5–3]	3 [3.5–2.75]	
<b>DAPT on discharge</b>	94.2% (536)	95.9% (514)	66.7% (22)	<0.001
Aspirin	95.6% (544)	97.4% (522)	66.7% (22)	<0.001
Clopidogrel	94.7% (539)	96.5% (517)	66.7% (22)	<0.001
<b>Post-procedure TIMI flow grade</b>				
0	0.4% (2)	0.4% (2)	0% (0)	0.698
I	0.5% (3)	0.6% (3)	0% (0)	
II	3% (17)	2.8% (15)	6.1% (2)	
III	96.1% (547)	96.3% (516)	93.9% (31)	
<b>In-hospital Mortality</b>	2.3% (13)	0.2% (1)	36.4% (12)	<0.001

SD = standard deviation.

IQR = interquartile range.

DAPT = dual antiplatelet therapy.

TIMI = thrombolysis in myocardial infarction.

**Table 3**  
Follow-up outcome.

Characteristics	Total	Stent Thrombosis		p-value
		No	Yes	
<b>N</b>	569	536	33	–
<b>Follow-up duration (months)</b>				
Range	22–16	22–16	21–16	0.259
Mean ± SD	18.08 ± 1.76	18.1 ± 1.76	17.76 ± 1.71	
Median [IQR]	18 [20–16]	18 [20–16.5]	18 [19–16]	
<b>Follow-up outcomes</b>				
Expired	10.9% (62)	6.9% (37)	75.8% (25)	<0.001
Re-admission within 30 days	2.3% (13)	1.3% (7)	18.2% (6)	<0.001
Expired within 30 days	4.4% (25)	0% (0)	75.8% (25)	<0.001
Re MI	3% (17)	0.4% (2)	45.5% (15)	<0.001
Re Intervention	2.5% (14)	0.7% (4)	30.3% (10)	<0.001
<b>Stent Thrombosis (ST)</b>	5.8% (33)	–	100% (33)	–
Definite	0.5% (3)	–	9.1% (3)	–
Probable	5.3% (30)	–	90.9% (30)	–
<b>Acute Stent Thrombosis</b>	0.5% (3)	–	9.1% (3)	–
<b>Sub-acute Stent Thrombosis</b>	5.3% (30)	–	90.9% (30)	–

SD = standard deviation.

IQR = interquartile range.

The rate of early ST (acute or sub-acute) for STEMI patients, observed in our study as well as reported in past studies, was substantially higher than the rates (0.1–1.4%) reported for the moderate to high-risk non-STEMI patients and stable coronary artery disease (CAD) patients [20–22].

Our study also observed that the implanted stent type, DES or BMS, was not associated with ST (acute or sub-acute). This finding is supported by various randomized trials and studies comparing first-generation BMS to DES. Studies reported no significant difference in the rate of stent thrombosis after implantation of BMS and DES [18,23–25]. The ACUITY trial also showed that there are no differences in the rate of early ST (acute or sub-acute) between patients with ACS treated with BMS and DES [26].

In our study, we observed that the risk of ST is higher among diabetic patients, however, diabetes mellitus failed to attain the required statistical significance to be an independent predictor of early stent thrombosis. Studies in the past have reported diabetes as an independent predictor for ST [27–29]. Significance of diabetes in prior studies can be attributed to the effects of confounders such as longer lesion length, smaller vessel size, increased platelet aggregation, and a higher rate of residual dissections [30–33].

Similarly, hypertensive patients were observed to be at higher risk of ST, but hypertension too failed to attain the required statistical significance to be an independent predictor. This is aligned with prior knowledge that no previous study has identified hyper-

**Table 4**  
Determinants of stent thrombosis.

Characteristics	Unadjusted		Adjusted	
	OR [95% CI]	p-value	OR [95% CI]	p-value
Male	0.91 [0.37–2.27]	0.843	–	–
Age (years)	1.02 [0.99–1.06]	0.122	1.03 [0.99–1.06]	0.157
Body Mass Index (kg/m <sup>2</sup> )	0.98 [0.9–1.06]	0.549	–	–
Hypertension	2.35 [1.15–4.83]	0.02*	1.63 [0.75–3.52]	0.215
Diabetes mellitus	2.13 [1.04–4.35]	0.039*	2 [0.9–4.43]	0.087
Smoking	0.71 [0.29–1.75]	0.456	–	–
Positive family history	2.88 [0.8–10.31]	0.105	2.08 [0.52–8.21]	0.298
Prior PCI	0 [0–0]	0.998	–	–
Killip Class (III–IV)	6.4 [2.35–17.41]	<0.001*	5.2 [1.76–15.32]	0.003*
Left dominance	1.02 [0.3–3.45]	0.979	–	–
Lesion length (mm)	1.01 [0.97–1.05]	0.651	–	–
MVD	1.05 [0.51–2.15]	0.901	0.76 [0.35–1.66]	0.493
Mid-Distal LAD	1.18 [0.52–2.7]	0.687	–	–
Proximal LAD	0.8 [0.35–1.81]	0.595	–	–
Right coronary artery (RCA)	1.03 [0.5–2.12]	0.929	–	–
Circumflex (LCX)	0.84 [0.25–2.84]	0.78	–	–
Left main (LM)	8.34 [0.74–94.47]	0.087	7.19 [0.43–121.14]	0.171
Bare metal stents (BMS)	0.83 [0.41–1.67]	0.601	–	–
Stent length (mm)	1.01 [0.97–1.06]	0.605	1.01 [0.96–1.07]	0.601
Stent diameter (mm)	0.71 [0.42–1.2]	0.203	0.72 [0.4–1.29]	0.268

OR = odds ratio.

CI = confidence interval.

PCI = percutaneous coronary intervention.

MVD = multi-vessel disease.

LAD = left anterior descending artery.

\* statistically significant at 5%.

tension as an independent risk factor for ST. A final and the only independent predictor of ST that has been demonstrated in our study is the presentation of patients in Killip Class III–IV. Stone et al. in the HORIZON-AMI trial, demonstrated that presentation with acute heart failure (Killip class  $\geq 2$ ) was an important independent predictor of subsequent re-infarction in patients who have undergone primary PCI. Killip Class III–IV indicate greater myocardium at risk with reduced systolic left ventricular function. This trial demonstrated that 76.3% of re-infarctions occurred due to early stent thrombosis hence supporting a correlation between Killip class at presentation and rate of stent thrombosis [34]. Brodie et al, also found that Killip class III–IV was a significant univariable correlate of increased incidence of early ST (30 days) [6].

Stent thrombosis is most feared complication of any successful PCI, strict attention to the patients risk factor and ability to adhere and tolerate DAPT is necessary before proceeding PCI with stenting. Assiduous care to technical details is necessary to optimize the stent implantation and deployment particularly in complex disease and novel stents are emerging with potential to inherently lower the risk of ST. Any elective surgery after stent implantation (six weeks after BMS, 6 to 12 months after DES) should be avoided without discontinuation of DAPT (if possible). Finally, use of more potent anti-platelet agents like ticagrelor in patient with ACS with low bleeding risk to be used. It is therefore essential to carefully evaluate the patients individual risk for ST to prevent or at least minimize the most devastating complication of stent implantation.

## 5. Study limitations

This is a single center based retrospective study lacking data on late stent thrombosis. Secondly, we cannot be sure about the exhaustive use of potential predictors of stent thrombosis in multivariate analysis. One of the key finding of this study was that the Killip Class (III–IV) was found to be an independent predictor of ST, whoever, underlying mechanism behind higher risk of ST in heart failure patients is not studied and it cannot be confirmed whether or not it is simply but not purely due to definite stent thrombosis.

## 6. Conclusion

In conclusion, our study has demonstrated that early stent thrombosis (acute or sub-acute) is a relatively frequent occurrence in patients undergoing primary PCI for acute MI, with a frequency of about 5.8 per 100 patients with a 30 days mortality rate of 75.8%. The type of stent implanted, BMS or DES had no impact on the frequency of stent thrombosis. Diabetic and hypertensive patients are at an increased risk of stent thrombosis and presentation of patients in Killip Class III–IV is an independent predictor of early stent thrombosis.

## Disclaimer

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## Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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