Heart, Lung and Circulation (2020) **29**, 1433–1439
1443-9506/19/$36.00
https://doi.org/10.1016/j.hlc.2019.10.009

ORIGINAL ARTICLE

Incidence, Predictors and Clinical Outcomes of Stent Thrombosis Following Percutaneous Coronary Intervention in Contemporary Practice

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Received 25 July 2019; received in revised form 30 September 2019; accepted 14 October 2019; online published-ahead-of-print 27 November 2019

Background Stent thrombosis (ST) is an uncommon but serious complication of percutaneous coronary intervention (PCI). The reported rate of definite ST with new generation drug-eluting stents ranges from 0.5 to 1% at 30 days. We aimed to examine the incidence and outcomes of ST in a real-world setting.

Methods The Victorian Cardiac Outcomes Registry was established in 2012 as a state-wide clinical quality registry, with all PCI capable centres contributing in 2017. Data were collected on 41,137 consecutive PCI procedures from 2013 to 2017. We describe the patient characteristics and clinical outcomes in definite and probable ST at 30 days.

Results Stent thrombosis occurred in 225 patients (0.55%). Compared to patients without ST, these patients were more likely to be female (32.0% vs 23.4%, p≤0.01) and have a history of diabetes (28.6% vs 21.9%, p=0.02). ST was more common in patients with severely reduced left ventricular ejection fraction (14.9% vs 4.6%, p<0.001) and in patients presenting with ST-elevation myocardial infarction, cardiogenic shock and cardiac arrest for their index PCI (all p<0.001). Dual antiplatelet therapy at 30 days was less frequent in patients with ST (84.8% vs 92.0%, p<0.001), while 30-day mortality was more common: 23.6% versus 2.0% (p<0.001).

Conclusions Even with contemporary stents and adjunctive medications, ST still occurs following 1 in 200 PCIs, and is associated with increased mortality at 30 days.

Keywords Stent thrombosis • Percutaneous coronary intervention • Outcomes

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Introduction

Stent thrombosis (ST) is an uncommon but serious complication of percutaneous coronary intervention (PCI) [1], most frequently occurring within 30 days of the procedure [2]. Despite recent advances in stent implantation technologies and improvements in adjuvant antiplatelet therapy, the rate of ST with second and third generation drug eluting stents (DES) ranges from 0.5 to 1% and carries a mortality rate of 20–30%, with death often due to myocardial infarction [3–6].

Though a low incidence of ST has previously limited characterisation of specific risk factors, multiple observational studies have reported several clinical and procedural predictors for ST following PCI [1,4,7–11]. Early cessation of pharmacological antiplatelet therapy is strongly associated with an increased risk of ST [5,9]. Percutaneous coronary intervention conducted in patients presenting with ST-elevation myocardial infarction (STEMI) and non-ST segment myocardial infarction (NSTEMI) has also been linked with an increased risk [5,10]. Other predictors of ST are reported to include inappropriate stent length [11], poor renal function [12] and type II diabetes mellitus [13].

Given the significant consequences of complications associated with ST, the present study aimed to examine the incidence of ST in a contemporary population of Australian patients. Improved understanding of the incidence of ST and its complications may assist in earlier identification and management of high-risk patients.

Methods

The Victorian Cardiac Outcomes Registry (VCOR) is a state-based, multi-centre clinical quality registry, with the purpose to improve safety and quality of care provided to patients admitted to hospital for cardiovascular conditions. The VCOR methodology has been extensively described previously [14]. In brief, VCOR was established in 2012 and records data across public and private hospitals in Victoria, with all 30 PCI-capable centres contributing in 2017. VCOR is coordinated by Monash University and is governed by a steering committee comprised of representatives from contributing centres. We analysed data from all patients that underwent PCI between 1 January 2013 and 31 December 2017 following institutional ethics approval.

Stent thrombosis was defined according to the Academic Research Consortium (ARC) classification as: definite, the presence of acute coronary syndrome (ACS) with angiography or autopsy evidence of thrombus or occlusion; and, probable, an unexplained death following the procedure or acute myocardial infarction (MI) involving the target vessel territory without angiographic or autopsy confirmation [15]. STs classified as possible, defined as any unexplained death occurring at least 30 days following the procedure, were included in the "no ST" group. Baseline demographic characteristics were compared between those that recorded definite or probable ST and those that did not. Treatment strategies including adjuvant oral anticoagulant or antiplatelet therapy and procedural characteristics were also collected and compared between the two groups. Within procedural characteristics, lesion complexity was defined according to American College of Cardiology/American Heart Association (ACC/AHA) classification guidelines as A, B1, B2 or C [16].

Clinical outcomes collected at 30 days included all-cause mortality, new stroke, major bleeding, the need for emergency PCI, any target vessel revascularisation or target lesion revascularisation (TLR) and the need for emergency CABG or target vessel CABG. Patients were followed up at 30 days following discharge from the admission in which they underwent PCI. Where information could not be obtained from medical records, the patient or next of kin was contacted via telephone, or information sought from a general practitioner. Bleeding was defined according to the Bleeding Academic Research Consortium (BARC) classification [17], BARC 3 (overt haemorrhage with haemoglobin drop of >3 g/dL, intracranial bleeding, cardiac tamponade or transfusion requirement), or BARC 5 (probable or definite fatal haemorrhage).

Univariate analysis was undertaken to compare baseline, procedural, treatment characteristics and clinical outcomes in the ST group compared to the group without ST. Continuous variables are presented as means with standard deviations and categorical variables are expressed as the number of patients with percentages. The Chi-square, *t*-tests, or Mann-Whitney U test were used as appropriate to compare categorical and continuous variables and to assess statistical significance. All tests were two-tailed, and we considered a p value <0.05 statistically significant.

Results

A total of 41,137 consecutive PCI procedures were analysed with 225 definite and probable STs (0.55%) documented during the 5-year study period. Of the 225 STs analysed, 121 (53.8%) were recorded in hospital with the remaining 104 (46.2%) occurring within 30 days. The "no ST group" included 31 cases of possible ST. Baseline clinical characteristics are presented in Table 1. Patients with definite or probable ST at 30 days were more likely to be female (32.0% vs 23.4%; $p<0.01$) and present with a range of comorbid conditions, including medicated diabetes mellitus (28.6% vs 21.9%; $p=0.02$) and cerebrovascular disease (7.6% vs 3.7%; $p<0.01$). Severe left ventricular systolic dysfunction was more common in the ST group (14.9% vs 4.6%; $p<0.001$). Patients with ST were more likely to have presented for their index PCI with cardiogenic shock (13.3% vs 2.3%; $p<0.001$), out-of-hospital cardiac arrest (5.8% vs 2.3%; $p<0.001$) or for primary PCI for STEMI (42.7% vs 20.7%; $p<0.001$).

Procedural characteristics are described in Table 2 and medication characteristics are described in Table 3. There was no statistically significant difference in the route of access (radial vs femoral) between the ST and no ST

Table 1 Baseline clinical characteristics.

	All patients (n=41,137)	ST at 30 d (n=225)	No ST at 30 d (n=40,912)	P-value
Age (yr)	66.0±11.9	67.1±11.5	66.0±11.9	0.16
Female gender	9,656 (23.5)	72 (32.0)	9,584 (23.4)	<0.01
Year of PCI				0.08
2013	4,583 (11.1)	17 (7.6)	4,566 (11.2)	
2014	7,896 (19.2)	37 (16.4)	7,859 (19.2)	
2015	8,840 (21.5)	53 (23.6)	8,787 (21.5)	
2016	9,569 (23.3)	59 (26.2)	9,510 (23.2)	
2017	10,249 (24.9)	59 (26.2)	10,190 (24.9)	
Private hospital	16,175 (39.3)	89 (39.6)	16,086 (39.3)	0.94
Median length of stay, d (IQR)	2 (1, 4)	4 (2, 6)	2 (1, 4)	<0.001
BMI (kg/m^2)	28.8±5.4	29.0±5.7	28.8±5.4	0.52
Diabetes mellitus	9,010 (21.9)	64 (28.6)	8,946 (21.9)	0.02
Peripheral vascular disease	1,458 (3.5)	13 (5.8)	1,445 (3.5)	0.07
Cerebrovascular disease	1,532 (3.7)	17 (7.6)	1,515 (3.7)	<0.01
Previous PCI	13,553 (32.9)	99 (44.2)	13,454 (32.9)	<0.001
Previous CABG	3,212 (7.8)	10 (4.5)	3,202 (7.8)	0.06
LVEF				<0.001
Normal (>50%)	23,550 (66.3)	101 (48.6)	23,449 (66.4)	
Mild (45-50%)	6,686 (18.8)	44 (21.2)	6,642 (18.8)	
Moderate (35-44%)	3,599 (10.1)	32 (15.4)	3,567 (10.1)	
Severe (<35%)	1,662 (4.7)	31 (14.9)	1,631 (4.6)	
Renal function				0.51
eGFR >60 mL/min/1.73m^2	29,930 (72.8)	156 (69.3)	29,774 (72.8)	
eGFR=45-60 mL/min/1.73m^2	4,479 (10.9)	28 (12.4)	4,451 (10.9)	
eGFR=30-45 mL/min/1.73m^2	2,444 (5.9)	11 (4.9)	2,433 (5.9)	
eGFR >30 mL/min/1.73m^2	1,019 (2.5)	8 (3.6)	1,011 (2.5)	
Cardiogenic shock	982 (2.4)	30 (13.3)	952 (2.3)	<0.001
Out-of-hospital cardiac arrest	939 (2.3)	13 (5.8)	926 (2.3)	<0.001
Indication for PCI				<0.001
STEMI	8,547 (20.8)	96 (42.7)	8,451 (20.7)	
NSTEMI	9,647 (23.5)	45 (20.0)	9,602 (23.5)	
UAP	3,034 (7.4)	13 (5.8)	3,021 (7.4)	
Stable angina	11,105 (27.0)	30 (13.3)	11,075 (27.1)	
Other	8,804 (21.4)	41 (18.2)	8,762 (21.4)	

Values are expressed as mean±standard deviation or n (%).

Abbreviations: BMI, body mass index; CABG, coronary artery bypass graft; eGFR, estimated glomerular filtration rate; IQR, interquartile range; LVEF, left ventricular ejection fracture; NSTEMI, non-ST-elevation myocardial infarction; PCI, percutaneous coronary intervention; ST, stent thrombosis; STEMI, ST-elevation myocardial infarction; UAP, unstable angina pectoris.

groups. Placement of DES was found to be less common in those with ST at 30 days (75.1% vs 81.8%; p=0.01). Percutaneous coronary intervention to lesions located in the left anterior descending (LAD) or left main (LM) were more common in the ST group (47.6% vs 40.6% and 3.6 vs 1.9%; respectively; p=0.03). Patients with ST were significantly less likely to have been discharged from hospital on dual antiplatelet therapy (DAPT) (90.2% vs 95.2%; p<0.01) and were more commonly discharged on no antiplatelet agent (1.1% vs 0.1%; p<0.001). A similar finding was observed for both DAPT at 30 days following index procedure (84.2% vs 92.0%; p<0.001), as well as for the absence of antiplatelet therapy (6.7% vs 1.1%; p<0.001).

Clinical outcomes are presented in Table 4 and Figure 1. Stent thrombosis was associated with 23.6% mortality at 30 days, as compared to 2.0% in the no ST group (p<0.001). Major bleeding occurred at a rate of 8.4% in the ST group as compared to 1.1% (p<0.001) in the no ST group. In the 225 patients with ST at 30 days, there were 11 in-hospital major bleeding cases and a further eight major bleeding cases at 30 days (totalling 19 major bleeds at 30 days). DAPT was found to have been discontinued in 10 of the 19 major bleeding cases at 30 days (Table 5). Emergent PCI or CABG was

Table 2 Procedural characteristics.

	All patients	ST at 30 d	No ST at 30 d	P-value
PCI access				0.23
Brachial/radial	19,949 (48.5)	118 (52.4)	19,831 (48.5)	
Femoral	21,188 (51.5)	107 (47.6)	21,081 (51.5)	
Lesion location				0.03
RCA	12,694 (30.9)	62 (27.6)	12,632 (30.9)	
LAD	16,734 (40.7)	107 (47.6)	16,627 (40.6)	
LCx	10,076 (24.5)	47 (20.9)	10,029 (24.5)	
LM	799 (1.9)	8 (3.6)	791 (1.9)	
Graft	834 (2.0)	1 (0.4)	833 (2.0)	
Lesion complexity				0.38
A or B1	17,286 (42.0)	88 (39.1)	17,198 (42.0)	
B2 or C	23,851 (58.0)	137 (60.9)	23,714 (58.0)	
Any DES	33,617 (81.7)	169 (75.1)	33,448 (81.8)	0.01
BMS only	4,708 (11.4)	31 (13.8)	4,677 (11.4)	0.27
Total stent number	1.3±0.8	1.4±0.9	1.3±0.8	0.20
Total stent length (mm)	25.3±16.9	26.7±19.0	25.3±16.9	0.22
Intravascular ultrasound	487 (1.2)	8 (3.6)	479 (1.2)	0.01

Values are expressed as mean±standard deviation or n (%).

Abbreviations: BMS, bare metal stent; DES, drug-eluting stent; LAD, left anterior descending artery; LCx, left circumflex artery; LM, left main artery; PCI, percutaneous coronary intervention; RCA, right coronary artery; ST, stent thrombosis.

undertaken in the ST group in 20.0% and 4.0% of cases respectively ($p<0.001$).

Discussion

Stent thrombosis is defined by the development of occlusive or partially occlusive thrombus within or adjacent to a stent placed during or after PCI [18]. This may be precipitated by several factors that promote slow coronary blood flow, endothelial injury or hypercoagulability [18]. These factors may broadly be defined as patient-, procedural-, lesion-, and medication-related. This study investigated the incidence, predictors and clinical outcomes of ST across a large patient cohort undergoing PCI in Victoria from 2013 to 2018. The results highlight that definite or probable ST still occurs in contemporary practice in 0.55% of PCI cases before 30 days post PCI. Despite improved PCI technology and practices, ST is an infrequent but nonetheless important complication of PCI.

We found that those with ST were more likely to be female, more likely to suffer from a range of medical comorbidities and less likely to be on DAPT at 30 days. While major bleeding was at a significantly higher rate in the ST group, only 19 of 225 ST patients were found to have a major bleeding event. This study reports a mortality rate of 23.6% in those with ST, and adds to growing understanding of patient and procedural risk factors for ST.

The results of this study are in keeping with previous registry analyses. A German-Italian registry of 2,229 patients with first generation DES reported an incidence of 0.6% of definite and probable STs at 30 days [8]. Analysis of an Australian cohort of 2,919 patients from 2004 to 2006 found an incidence of 0.5% of definite and probable ST at 30 days [6]. Pooled clinical trial and registry data reflect an incidence of 0.9% at 30 days in patients with bare metal stent (BMS) implantation in 2001 [19] and 0.6% in patients with first generation DES in 2005 [20] (0.7% and 0.5% in the present study, respectively). We found that 42.7% of patients with ST had presented for their index PCI with STEMI, as opposed to 20.7% of patients without ST at 30 days. This disparity is in keeping with investigation of 3,405 moderate and high risk ACS patients included in the Acute Catheterization and Urgent Intervention Triage StrategY (ACUITY) trial, an analysis that demonstrated an incidence of ST in this population of 1.4% at 30 days, and increased risk of patients with high-risk ACS [21]. Potential mechanisms for the increased incidence of ST following primary PCI for STEMI are platelet activation [22] and impaired absorption of adjuvant antiplatelet therapy in this setting [23].

We showed that factors associated with ST included female gender ($p<0.01$), cerebrovascular disease ($p<0.01$) and previous PCI ($p<0.001$). In view of emerging data suggesting that female gender is an independent predictor for mortality following PCI [24], a statistically significant difference in the percentage of females within the ST group and no-ST group is notable. Stent thrombosis was more common in patients with left ventricular systolic dysfunction ($p<0.001$), a result consistent with previous data on BMS use [25]. Not dissimilar to findings of a recent meta-analysis of patients with type 2 diabetes undergoing PCI with DES implantation [13], type 2 diabetes was present at a higher percentage in patients with ST than without. Angiographic and procedural features

Table 3 Medication characteristics.

	All patients	ST at 30 d	No ST at 30 d	P-value
24 hours prior to PCI				
Oral anticoagulation	2,349 (5.7)	15 (6.7)	2,334 (5.7)	0.52
Aspirin	37,313 (90.7)	208 (92.4)	37,105 (90.7)	0.37
Thienopyridine	18,782 (45.7)	88 (39.1)	18,694 (45.7)	0.05
Ticagrelor	15,204 (37.0)	96 (42.7)	15,108 (36.9)	0.08
No antiplatelet	1,650 (4.0)	7 (3.1)	1,643 (4.0)	0.49
Single antiplatelet	7,866 (19.1)	47 (20.9)	7,819 (19.1)	0.50
Dual antiplatelet	31,603 (76.8)	171 (76.0)	31,432 (76.8)	0.77
On discharge from hospital				
Oral anticoagulation	2,806 (6.9)	21 (11.5)	2,785 (6.9)	0.10
No antiplatelet	45 (0.1)	2 (1.1)	43 (0.1)	<0.001
Single antiplatelet	1,901 (4.7)	16 (8.7)	1,885 (4.7)	0.01
Dual antiplatelet	38,330 (94.7)	165 (90.2)	38,165 (95.2)	<0.01
At 30 d				
Aspirin	37,666 (95.6)	160 (96.4)	37,506 (95.6)	0.85
Thienopyridine	21,802 (55.3)	72 (43.4)	21,730 (55.4)	<0.01
Ticagrelor	16,450 (41.7)	88 (53.0)	16,362 (41.7)	0.01
No antiplatelet	455 (1.1)	12 (6.7)	443 (1.1)	<0.001
Single antiplatelet	2,728 (6.9)	14 (7.9)	2,714 (6.9)	0.60
Dual antiplatelet	36,522 (91.9)	151 (84.8)	36,371 (92.0)	<0.001

Values are expressed as n (%).

Abbreviations: PCI, percutaneous coronary intervention; ST, stent thrombosis.

including lesion complexity (such as bifurcation lesions with DES), stent number, stent length and stent underexpansion have previously been linked to ST [5,25–28]. Discrepancies in lesion complexity, stent number, and stent length between the two groups did not reach statistical significance in the present study, however.

We observed that 84.8% of patients with ST at 30 days remained on DAPT as compared to 92.0% of those without ST (p<0.001). Fewer patients were found to remain on a thienopyridine in the ST group (43.4% vs 55.4%, p<0.01) but there was no difference in the frequency of aspirin use (96.4% vs 95.6%, p=0.85). The results of this study build on the results of large observational and registry studies reporting discontinuation of antiplatelet therapy as the most important predictor of ST, with one study publishing a hazard ratio of 36.53 (95% confidence interval 7.96–167.77, p<0.01) for ST with cessation of clopidogrel within 30 days in patients with DES [5]. The relationship observed between major bleeding and ST, despite a lower rate of DAPT may be due to the withdrawal of antiplatelet medication in a response to a

Table 4 Clinical outcomes at 30 d.

	All patients (n=41,137)	ST at 30 d (n=225)	No ST at 30 d (n=40,912)	P-value
Mortality	889 (2.2)	53 (23.6)	836 (2.0)	<0.001
Stroke	158 (0.4)	7 (3.1)	151 (0.4)	<0.001
Major bleed	487 (1.2)	19 (8.4)	468 (1.1)	<0.001
Emergency PCI	233 (0.5)	45 (20.0)	178 (0.4)	<0.001
Emergency CABG	37 (0.1)	9 (4.0)	28 (0.1)	<0.001
Any TVR	258 (0.6)	43 (19.1)	215 (0.5)	<0.001
Any TLR	165 (0.4)	42 (18.7)	123 (0.3)	<0.001
Target vessel CABG	133 (0.3)	9 (4.0)	104 (0.3)	<0.001

Values are expressed as n (%).

Abbreviations: CABG, coronary artery bypass graft; PCI, percutaneous coronary intervention; ST, stent thrombosis; TLR, target lesion revascularisation; TVR, target vessel revascularisation.

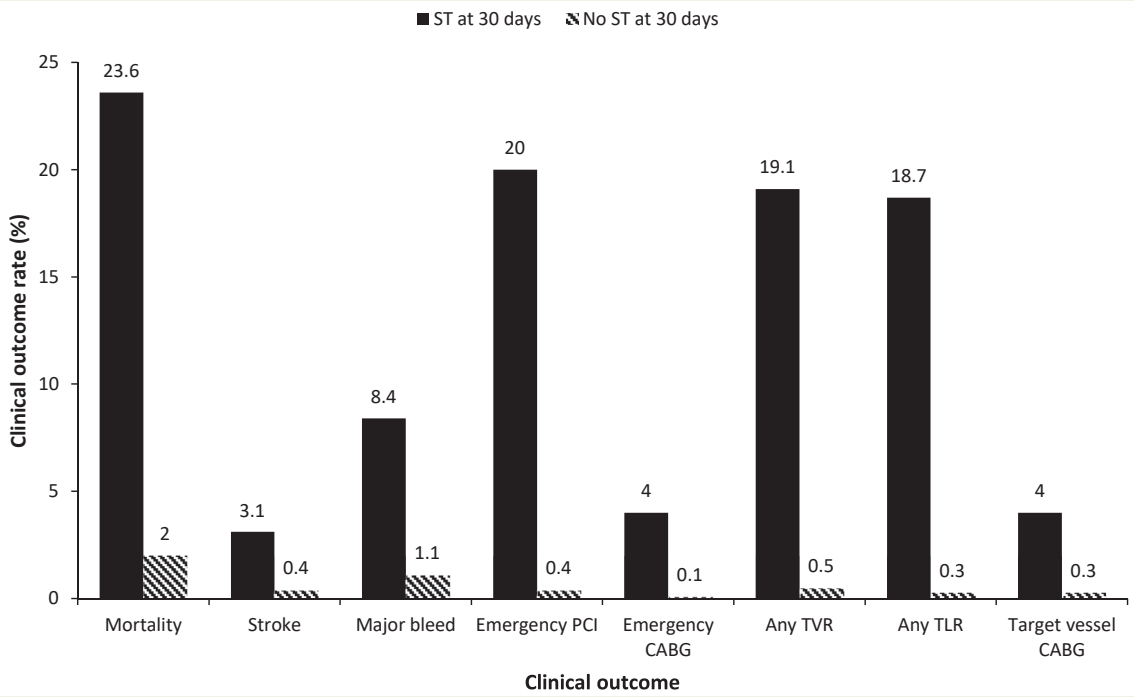

Figure 1 Clinical outcomes at 30 days.
Abbreviations: PCI, percutaneous coronary intervention; CABG, coronary artery bypass graft; TVR, target vessel revascularisation; TLR, target lesion revascularisation; ST, stent thrombosis.

major bleeding event, subsequently placing the patient at higher risk of ST. This is supported by the discontinuation of DAPT in seven of the 11 patients that had an inpatient major bleeding event and went on to develop ST at 30 days. In patients that had a major bleed by 30 days and developed ST, over half had discontinued DAPT (10 of 19). Alternative reasons for the lower rate of DAPT seen in the stent thrombosis group include medication non-adherence, concurrent therapy with oral anticoagulation whereby the patient continued single antiplatelet therapy.

There are several limitations and strengths of this study worth noting. This study provides a contemporary analysis of stent thrombosis in the era of third generation drug-eluting stents. As most cases of ST occur within 30 days of placement [2], complete 30-day follow-up of medication prescription and clinical outcomes was one further advantage. Thirty (30)-day outcomes included both definite and probable STs. We believe the reported incidence of ST is likely to be closer to the true incidence as patients suffering silent stent occlusion were included in the analyses. This has been a limitation of previous studies [5,7].

While analyses of a large cohort enable examination of uncommon events such as ST, a limitation of the present study is its retrospective, non-randomised design and subsequent vulnerability to multiple sources of potential bias. Furthermore, given that ST was an uncommon outcome, there was not enough power to conduct a multivariate analysis. Despite this, this descriptive study was able to establish several associations in demographic and procedural data for ST. However, due to its retrospective design, causality cannot be inferred. Second, while use of third generation stents is standard of care in Victoria, VCOR does not collect data detailing specific DES generation; therefore, a comparative safety analysis of stent generation was not possible. Third, while most ST occur within 30 days, late and very-late ST were not captured by this study. One final

Table 5 **Major bleeding and dual antiplatelet therapy in patients with ST.**

	ST at 30 d (n=225)	No DAPT 30 d (n=74)	DAPT 30 d (n=147)	P-value
Inpatient major bleed	11 (4.9)	7 (9.5)	4 (2.6)	0.03
30-day major bleed	19 (8.4)	10 (13.5)	9 (6.0)	0.06

Values are expressed as n (%).
Abbreviations: DAPT, dual antiplatelet therapy; ST, stent thrombosis.

limitation is that while data regarding medication prescription was collected at 30 days, it is difficult to ascertain prevalence of true medication adherence in this population in a registry of this size.

Conclusions

Stent thrombosis remains an uncommon but important complication of PCI. The results of this registry-based study of a large cohort of unselected patients undergoing PCI suggest that, even with new generation stent technology and adjunctive medication, ST occurs following approximately one in every 200 PCIs. In the contemporary setting, ST is associated with increased risk of mortality at 30 days.

Acknowledgements

The Victorian Cardiac Outcomes Registry (VCOR) was funded by the Victorian Department of Health and Human Services and by a one-off grant from Medibank Private from 2011 to 2014. It is currently funded by the Department of Health and Human Services, Monash University and Victorian Cardiac Clinical Network. Professor Duffy's work is supported by a NHMRC grant (reference no. 1111170). Professor Reid is supported by a NHMRC Principal Research Fellowship (reference no. 11136372). Associate Professor Stub is supported by a NHF Future Leader Fellowship (reference no. 101908), and a Viertel Foundation Clinical Investigator award. The authors declare no conflicts of interest.

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