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Incidence and predictors of outcomes after a first definite coronary stent thrombosis

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KEYWORDS

- ACS/NSTE-ACS
- adjunctive pharmacotherapy
- coronary occlusion
- other technique
- stent thrombosis

Abstract

Aims: Stent thrombosis (ST) is a rare but potentially fatal complication of coronary artery stenting. Little is known about the optimal treatment strategy at the time of an ST event. We aimed to identify the incidence and predictors of adverse cardiac events after treatment of a definite ST.

Methods and results: A total of 695 patients with definite ST were included between 1996 and 2017 in two academic medical centres. The primary endpoint was MACE, the composite of cardiac death, myocardial infarction (MI) and target vessel revascularisation (TVR). Mean age was 62.8±12.1 years and 76.3% were male. ST occurred at a median of 22 days (IQR 3-551 days); 50.8% were early and 49.2% were late/very late ST. At 60-month follow-up, the MACE rate was 43.7%, cardiac death 19.5%, MI 17.9%, TVR 24.8%, and repeat definite ST was 12.1% (10.5% in target vessel). Independent predictors of MACE were cardiogenic shock (HR 2.54, 95% CI: 1.75-3.70; p<0.001), ST in the LAD (HR 1.76, 95% CI: 1.32-2.35; p<0.001), prior CVA/TIA (HR 1.68, 95% CI: 1.08-2.62; p=0.020), peripheral vascular disease (HR 1.55, 95% CI: 1.00-2.39; p=0.046), multivessel disease (HR 1.53, 95% CI: 1.12-2.08; p=0.007), and final TIMI flow 2-3 (HR 0.54, 95% CI: 0.34-0.85; p=0.009). No specific treatment of ST influenced MACE; however, new-generation $P2Y_{12}$ inhibitors reduced the risk of MI (HR 0.56, 95% CI: 0.32-0.99; p=0.049).

Conclusions: The incidence of adverse events remains high after a first episode of ST. New-generation $P2Y_{12}$ inhibitors reduce the risk of MI. Additional stenting, GP IIb/IIIa inhibitors and thrombectomy did not improve outcomes following ST.

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Abbreviations

BMS	bare metal stent
CABG	coronary artery bypass graft
DAPT	dual antiplatelet therapy
DES	drug-eluting stent
MACE	major adverse cardiac events
MI	myocardial infarction
PCI	percutaneous coronary intervention
ST	stent thrombosis
TIMI	Thrombolysis In Myocardial Infarction
TVR	target vessel revascularisation

Introduction

Over the years, improvements in stent technology have reduced the incidence of future target lesion failure[1]. Conversely, stent thrombosis (ST) has emerged as a safety concern associated with high rates of death and myocardial infarction (MI)[2]. Amongst others, the problem has been linked to stent-related factors such as underexpansion, malapposition, polymer-related hypersensitivity reactions, neoatherosclerosis and incomplete stent coverage, and patient-related factors such as premature discontinuation of antiplatelet therapy[3-5].

The risk of early or late ST appeared to occur at a rate of 0.6% per year after the implantation of a first-generation drug-eluting stent (DES)[6], and up to 0.3% per year in novel-generation DES[7,8]. The latter triggered the development of more biocompatible and bioresorbable polymers and pushed guideline committees to review dual antiplatelet therapy (DAPT) strategies[9]. At the same time, exhaustive attempts were made to identify baseline patient and procedural characteristics associated with an increased risk for ST[10-13].

To date, little is known about ST treatment strategies applied in daily clinical practice and their impact on adverse events. Therefore, the purpose of our study was to identify the incidence and predictors of future adverse cardiac events after treatment of a first definite ST.

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Methods

POPULATION

This is a retrospective study including two academic hospitals (Erasmus University Medical Center, the Netherlands, and Bern University Hospital, Switzerland). All patients who presented with a first definite ST between 1996 and 2017 were included.

ENDPOINTS AND DEFINITIONS

The primary endpoint was major adverse cardiac events (MACE), a composite of cardiac death, non-fatal MI, and ischaemia-driven target vessel revascularisation (TVR) at 60-month follow-up after the first ST event. Death was classified as cardiac or non-cardiac. Secondary endpoints included the components of MACE and repeat definite ST in the target vessel (ST-TV). Cardiac death was defined as any death due to a clear cardiac cause, unwitnessed death or death of unknown cause, and all procedure-related deaths, including those related to concomitant treatment. Coronary artery bypass grafting (CABG) revascularisation was considered an event if not part of the initial ST treatment. TVR, MI and ST were defined according to the Academic Research Consortium definitions[14]. Repeat ST-TV was identified as any new definite ST in the target vessel after the successful treatment of the index ST.

CLINICAL FOLLOW-UP

Survival data were obtained from municipal civil registries. A health questionnaire was sent to all living patients with questions on readmission and MACE. For patients who had an adverse event at another centre, medical records or discharge summaries were systematically reviewed. General practitioners, referring cardiologists, and patients were contacted as necessary for additional information. There was no independent or external monitoring of data entry. We performed censoring at 60 months with 14 patients lost to follow-up. Clinical events were adjudicated by trained study personnel not involved in the specific procedures during the course of the study. All patients provided written informed consent for the procedure and the use of anonymised data sets for research purposes in alignment with the Dutch Medical Research Acts and the appropriate Health Insurance Portability and Accountability Act waiver/authorisation or the appropriate informed consent documentation per institutional policy for the collection of data in Switzerland.

STATISTICAL ANALYSIS

Categorical variables are expressed as numbers and frequencies and compared using the χ^2 test or Fisher's exact test when appropriate. Continuous variables are presented as the mean±standard deviation (SD) and tested using the Student's t-test or as the median and interquartile range (IQR: 25^{th}-75^{th} percentile) and tested with the Mann-Whitney rank-sum test.

Missing values for covariates were present in less than 5%, except for smoking (6.6% missing values), statin prescription (6.8% missing values), index stent type (15.5% missing values), multivessel disease (MVD) (17.6% missing values), and estimated glomerular filtration rate <60 ml/min/1.73 m² (34.2% missing values). Therefore, we applied multiple imputation to handle missing values. Values were imputed using a regression approach based on patients' clinical data. Results from five imputed data sets were pooled to obtain risk estimates.

Univariate predictors of outcomes were identified using Cox proportional hazards models. Predictors with a p-value <0.1 were introduced into the multivariate Cox proportional hazards model using the "enter" method. In case of outcomes with an insufficient number of events, the most strongly associated covariates were included in the model. Data are presented as hazard ratios (HRs) with 95% confidence intervals (95% CI). All tests were two-tailed and a p-value <0.05 was considered statistically significant. The Kaplan-Meier method was applied to show the cumulative incidence of the primary and secondary endpoints.

SPSS software, Version 24.0 for Windows (IBM Corp., Armonk, NY, USA) was used to perform all the analyses.

Results

CLINICAL PRESENTATION

A total of 695 patients presenting with a first episode of definite ST were included. Mean age was 62.8±12.1 years and 76.3% were male. The first ST occurred at a median of 22 days (25th-75th percentile: 3-551 days; min 0, max 5,859 days) after the index percutaneous coronary intervention (PCI). Early ST (0-30 days) and late/very late ST (>30 days) occurred in 50.8% and 49.2% of the cases, respectively. MI was the presenting symptom in 87.2% of the cases and accompanied by cardiogenic shock in 11.8%. Aspirin was used by 88.9% of the patients at baseline and 53.8% used $P2Y_{12}$ inhibitors **(Table 1, Table 2)**.

According to the timing of ST (early vs late/very late), patients with early ST were older (64.1±12.1 vs 61.4±11.9 years, respectively, p=0.004), presented more often with MI (93.4% vs 80.6%, respectively, p<0.001) and haemodynamic instability (16.9% vs 6.9%, respectively, p<0.001), had multivessel ST (5.2% vs 1.5%, p=0.007) or left coronary system as culprit (for LAD 58.6% vs 48.5%, p=0.009; for left circumflex artery 21.2% vs 14.1%, respectively, p=0.015) **(Supplementary Table 1, Supplementary Table 2)**.

Table 1. Baseline characteristics.

Characteristics		Patients (N=695)
Age		62.8±12.1
Male		530/695 (76.3)
Prior myocardial infarction		368/692 (53.2)
Prior cerebrovascular accident/transient ischaemic attack		52/685 (7.6)
Peripheral vascular disease		60/685 (8.8)
Coronary artery bypass graft		54/685 (7.9)
Dyslipidaemia		415/692 (60)
Hypertension		367/692 (53)
Diabetes mellitus		152/693 (21.9)
Current smoking		203/649 (31.3)
Estimated glomerular filtration rate <60 ml/min/1.73 m²		91/457 (19.9)
Family history of cardiovascular disease		248/691 (35.9)
Index stent	Bare metal stent	76/587 (12.9)
	Drug-eluting stent	446/587 (76)
	Bare metal stent+drug-eluting stent	4/587 (0.7)
	Bioresorbable scaffold	15/587 (2.6)
	Bioresorbable polymer	46/587 (7.8)
Aspirin		576/648 (88.9)
$P2Y_{12}$ inhibitor	Clopidogrel	286/648 (44.1)
	Ticagrelor	33/650 (5.1)
	Prasugrel	30/650 (4.6)
Anticoagulation		40/672 (6)
Presentation	Myocardial infarction	592/679 (87.2)
	Unstable angina	69/679 (10.2)
	Stable angina	18/679 (2.7)
Cardiogenic shock		82/693 (11.8)
Stent thrombosis timing	Acute	104/679 (15.3)
	Subacute	241/679 (35.5)
	Late	115/679 (16.9)
	Very late	219/679 (32.3)

Categorical data are presented as counts and percentages. Continuous data are presented as mean±SD or median and interquartile range (IQR 25th-75th percentile).

TREATMENT

Thrombectomy and glycoprotein IIb/IIIa (GP IIb/IIIa) inhibitors were used in 47.9% and 57.6% of the patients, respectively. In 27.6% of the patients, intracoronary imaging was used to assess the mechanism of the ST, with neoatherosclerosis (31.8%), malapposition (25.5%) and underexpansion (17.7%) as the main findings **(Table 2)**. Additional stenting was performed in 59.8% of the patients with the use of DES in 90.8%. Plain old balloon angioplasty (POBA) alone was performed in 34.4% of the cases and CABG in 0.9%. DAPT was prescribed in 95.7% of the patients, 28.1% of whom received either prasugrel or ticagrelor. The remaining patients were treated with a combination of an oral anticoagulant (OAC) and one antiplatelet therapy (APT) (1.1%), one APT (1.8%) or OAC alone (0.3%); in 1.1% of the cases no APT or OAC was prescribed due to concomitant major bleeding **(Table 2)**.

As compared to late/very late ST, patients with early ST more often received treatment with POBA (45.6% vs 24.3%, respectively, p<0.001) and GP IIb/IIIa inhibitors (66.6% vs 47.9%, p<0.001), but fewer patients with early ST underwent intracoronary imaging assessment as compared to those with late/very late ST (24.3% vs 30.8%, respectively, p=0.058) **(Supplementary Table 2)**.

OUTCOMES

At 60 months, the cumulative incidence of the primary composite endpoint was 43.7% (238 cases). Cardiac death occurred in 19.5% (111 cases), MI in 17.9% (82 cases) and TVR in 24.8% (118 cases). Repeat definite ST occurred in 12.1% (58 cases) and repeat definite ST-TV in 10.5% (51 cases) (acute 9.8% [5 cases], subacute 27.5% [14 cases], late 23.5% [12 cases], and very late 39.2% [20 cases]) **(Figure 1)**.

Independent predictors of MACE were cardiogenic shock (HR 2.54, 95% CI: 1.75-3.70; p<0.001), ST in the LAD (HR 1.76, 95% CI: 1.32-2.35; p<0.001), prior cerebrovascular accident (CVA)/transient ischaemic attack (TIA) (HR 1.68, 95% CI: 1.08-2.62; p=0.020), peripheral vascular disease (HR 1.55, 95% CI: 1.00-2.39; p=0.046) and MVD (HR 1.53, 95% CI: 1.12-2.08; p=0.007). Final Thrombolysis In Myocardial Infarction (TIMI) flow 2-3 was inversely associated with MACE (HR 0.54, 95% CI: 0.34-0.85; p=0.009) and cardiac death (HR 0.33, 95% CI: 0.18-0.60; p<0.001) at 60 months. Treatment with new-generation $P2Y_{12}$ inhibitors was inversely associated with future MI events (HR 0.56, 95% CI: 0.32-0.99; p=0.049), and the use of intracoronary imaging was associated with an increased risk for repeat ST-TV (HR 1.85, 95% CI: 1.06-3.23; p=0.032). No other modifiable procedural characteristics predicted any of the outcomes **(Table 3)**.

Table 2. Periprocedural characteristics.

Characteristics		Patients (N=695)
Multivessel disease		257/573 (44.9)
Multivessel stent thrombosis		23/695 (3.3)
Stent thrombosis location	Left main	14/695 (2)
	Left anterior descending coronary	372/695 (53.5)
	Left circumflex coronary	124/695 (17.8)
	Right coronary artery	194/695 (27.9)
	Bypass graft	24/695 (3.5)
Bifurcation involved		144/695 (20.7)
TIMI flow pre	0	475/683 (69.5)
	1	65/683 (9.5)
	2	67/683 (9.8)
	3	76/683 (11.1)
TIMI flow post	0	28/683 (4.1)
	1	13/683 (1.9)
	2	36/683 (5.3)
	3	606/683 (88.7)
Intracoronary imaging		192/695 (27.6)
IVUS		117/695 (16.8)
OCT		80/695 (11.5)
Intracoronary imaging findings	Underexpansion	34/192 (17.7)
	Malapposition	49/192 (25.5)
	Edge dissection	27/192 (14.1)
	Edge disease	17/192 (8.9)
	Neoatherosclerosis	61/192 (31.8)
	Uncovered struts	2/192 (1)
	Gap	9/192 (4.7)
	Broken stent	2/192 (1)
Glycoprotein IIb/IIIa inhibitor		392/680 (57.6)
Overall thrombectomy		322/672 (47.9)
Rheolytic thrombectomy		77/283 (27.2)
Aspirin prescribed		649/666 (97.4)
$P2Y_{12}$ inhibitor prescribed	Clopidogrel	431/666 (64.7)
	Ticagrelor	76/666 (11.4)
	Prasugrel	139/666 (20.9)
Anticoagulation prescribed		43/666 (6.5)
Statins prescribed		635/648 (98)
Treatment of stent thrombosis	Additional stent	415/694 (59.8)
	POBA alone	239/694 (34.4)
	Coronary artery bypass graft	6/694 (0.9)
	Conservative	34/694 (4.9)
Additional stent characteristics	Direct stenting	102/410 (24.9)
	Bare metal stent	35/413 (8.5)
	Drug-eluting stent	375/413 (90.8)
	Drug-eluting stent+bare metal stent	3/413 (0.7)
	Number of stents	1 (1-2)
	Average diameter (mm)	3 (2.75-3.5)
	Length (mm)	28 (16-40)
	Overlapping	190/415 (45.8)
POBA characteristics	Non-compliant	54/236 (22.9)
	Plain (no drug-eluting balloon)	177/236 (75)
	Cutting	3/236 (1.3)
	Drug-coated	3/239 (1.3)

Categorical data are presented as counts and percentages. Continuous data are presented as mean±SD or median and interquartile range (IQR 25^{th}-75^{th} percentile). IVUS: intravascular ultrasound; OCT: optical coherence tomography; POBA: plain old balloon angioplasty; TIMI: Thrombolysis In Myocardial Infarction

According to the timing of the ST, similar predictors were found for MACE following early ST as for the total population. Cardiogenic shock and final TIMI flow 2-3 were the only independent predictors for MACE in patients with late/very late ST. Intracoronary imaging increased the risk for future MI, TVR and ST-TV in patients with early ST, and index stent type DES reduced future MI events in patients with late/very late ST. No procedural characteristics predicted any of the outcomes in patients presenting with late/very late ST **(Supplementary Table 3, Supplementary Table 4)**.

When considering the time point of the index ST (years 1996-2007 and 2008-2017), similar predictors of MACE were found for both groups as for the total population, except for additional stenting which increased the risk of adverse events in the first group (HR 1.82, 95% CI: 1.16-2.86; p=0.008) **(Supplementary Table 5)**.

Discussion

Patients presenting with ST have a significantly increased risk for morbidity and mortality following PCI. While extensive research has been performed on finding predictors of ST[10-13], little to no evidence is available on the optimal treatment strategy for those presenting with the event. Furthermore, the low incidence of ST and the lack of systematic follow-up entail great difficulty in recognising the real incidence of adverse events and their predictors. In the present investigation we assessed the incidence and predictors of future MACE after the treatment of a first definite ST in the largest series of patients thus far.

At first, we quantified the incidence of MACE after the index ST. At 60 months, almost every second ST patient suffered from MACE (43.7%), mainly driven by a high mortality rate (25.8%), 75% of which were cardiac. Furthermore, the incidence of TVR was as high as 24.8%. Interestingly, 51 out of 118 TVR (43.2%) resulted from a repeat ST-TV event, indicating that the applied ST treatment was ineffective in a substantial proportion of patients. Looking for baseline predictors, we found that cardiogenic shock, ST in the LAD and post-procedural TIMI flow were strong predictors of MACE; similar patient and lesion-related factors have been found in previous studies with smaller patient cohorts and shorter follow-up[15-19].

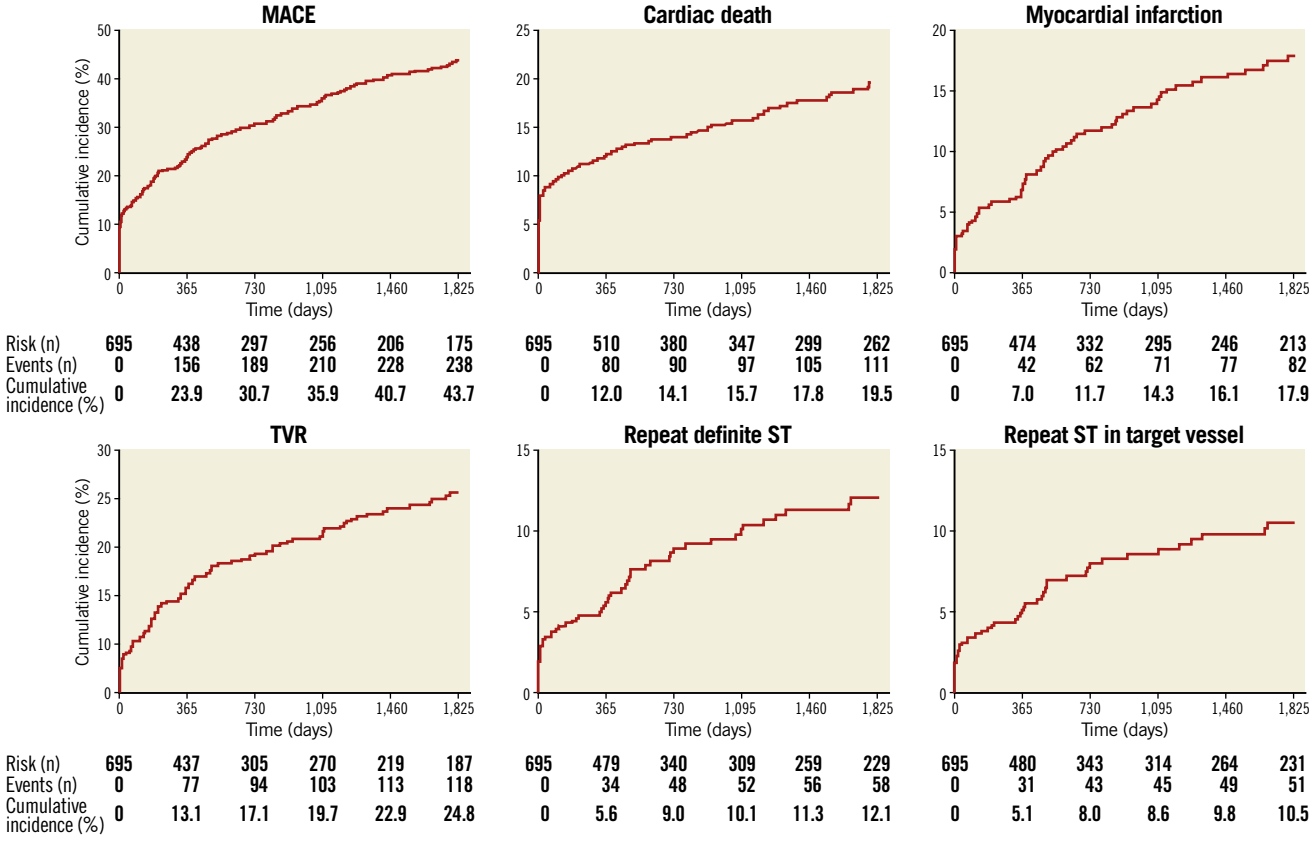

Figure 1. *Outcomes at 60-month follow-up. MACE: major adverse cardiac events; ST: stent thrombosis; TVR: target vessel revascularisation*

Table 3. Independent predictors of outcomes at 60 months.

Events		HR (95% CI)	*p*-value
Major adverse cardiac events	Cardiogenic shock at ST	2.54 (1.75-3.70)	<0.001
	ST in LAD	1.76 (1.32-2.35)	<0.001
	Prior CVA/TIA	1.68 (1.08-2.62)	0.020
	Peripheral vascular disease	1.55 (1.00-2.39)	0.046
	Multivessel disease	1.53 (1.12-2.08)	0.007
	TIMI flow 2-3 post	0.54 (0.34-0.85)	0.009
Cardiac death	Cardiogenic shock at ST	3.41 (2.17-5.38)	<0.001
	ST in LAD	1.76 (1.16-2.67)	0.007
	eGFR <60 ml/min/1.73 m²	1.64 (1.02-2.63)	0.040
	Age	1.04 (1.02-1.06)	<0.001
	TIMI flow 2-3 post	0.33 (0.18-0.60)	<0.001
Myocardial infarction	Multivessel ST	2.54 (1.09-5.94)	0.031
	Peripheral vascular disease	2.22 (1.17-4.22)	0.014
	Male	1.84 (1.03-3.28)	0.039
	ST in LAD	1.72 (1.08-2.72)	0.021
	Prasugrel/ticagrelor prescribed	0.56 (0.32-0.99)	0.049
Target vessel revascularisation	Prior CVA/TIA	1.97 (1.11-3.51)	0.021
Stent thrombosis in target vessel	Prior coronary artery bypass graft	4.02 (1.72-9.39)	0.001
	ST in LAD	2.50 (1.28-4.89)	0.007
	Intracoronary imaging	1.85 (1.06-3.23)	0.032

Data are presented as hazard ratios (HR) and 95% confidence intervals (CI). CVA/TIA: cerebrovascular accident/transient ischaemic attack; eGFR: estimated glomerular filtration rate; LAD: left anterior descending coronary; ST: stent thrombosis; TIMI: Thrombolysis In Myocardial Infarction

With a specific focus on modifiable procedural characteristics, we found that 59.8% of the patients were treated with additional stents (90.8% were DES). Their use, however, did not impact on future MACE. The latter puts the findings of the Dutch Stent Thrombosis registry (DSR), in which the use of additional stents increased cardiac death and repeat ST up to 73% at three years, into perspective[17]. Merely 26% of the patients in the DSR presented with late or very late ST as compared to 49.2% in our study - an important difference given the substantially higher incidence of neoatherosclerosis in patients with late or very late ST as compared to early ST. Furthermore, the difference in timing between both studies should be taken into account, resulting in a significant difference in the use of bare metal stents (BMS) and new $P2Y_{12}$ inhibitors (±50% and 0%, respectively, in the DSR).

Thrombus aspiration did not emerge as a protective measure against future MACE. The latter extends the findings of several recent randomised trials in which thrombus aspiration failed to reduce future events in STEMI patients[17,20,21].

Significant improvement in the risk of future MI was also found with the use of either prasugrel or ticagrelor in patients presenting with ST, a finding that adds to previous studies including ACS populations[22-24].

Differences in treatment profiles were found in patients presenting with early versus late/very late ST. Patients with an early ST event were more likely to receive treatment with POBA and GP IIb/IIIa inhibitors, which is in line with the assumption that

stent deployment-related issues and an initial impaired response to ADP-receptor antagonist therapy during a prothrombotic state mostly explain an early ST event[2,25]. Intravascular imaging findings confirmed a higher incidence of procedure-related issues (underexpansion and edge dissections) in this population. Moreover, additional stenting was more frequent in patients with late or very late ST, which could suggest a higher incidence of neoatherosclerosis.

A stratified analysis following either early or late/very late ST revealed one remarkable finding: the risk for future MI, TVR and repeat ST-TV appeared to be significantly increased when intravascular imaging was performed. Intravascular imaging was performed more frequently in younger and male patients, cases where the index stent was bioresorbable, the LAD was the culprit, and the presentation of the ST was "very late". Furthermore, those patients more often received treatment with GP IIb/IIIa inhibitors, thrombectomy, and direct stenting, with a larger stent number and length. However, we were not able to identify a consistent and significantly higher risk profile of patients receiving imaging versus those who did not **(Supplementary Table 6)**. Finally, a play of chance could not be excluded.

It is essential to remark that including patients over almost 20 years is both our strength and our main limitation. Several important changes have taken place in the coronary field, entailing great difficulty in finding individual predictors of future outcomes. Periprocedural treatment strategies have been influenced by novel insights, the availability of pharmacological and technical resources, and improvements in stent technology; as such, optical coherence tomography was only introduced in 2008, the new-generation $P2Y_{12}$ inhibitors became available in 2009, and stents have evolved from BMS to DES (first and second generations) to platforms with bioresorbable polymers/backbone. Nevertheless, a sensitivity analysis regarding the time of presentation showed similar predictors as for the whole population; of note, additional stenting was a strong predictor of MACE only in the population 1996-2007, which could be explained by a higher use of earlier stent technologies[26].

Limitations

This is a retrospective study including patients over a long period of time; changes in treatment strategies over the years might have influenced our results. An important selection bias might be present concerning the use of intracoronary imaging. Information on lesion complexity was not available. Data on compliance to antiplatelet agents were not accessible. Finally, given the retrospective nature of the study analysis, there were some missing baseline data and a multiple imputation technique was used. Hence, our results are hypothesis-generating only and must be confirmed in larger-scale randomised studies.

Conclusions

The incidence of adverse events remains high after a first episode of ST. Treatment with new-generation $P2Y_{12}$ inhibitors reduces the risk of future MI. The use of new stents, GP IIb/IIIa inhibitors and thrombectomy was not associated with improved cardiovascular outcomes following ST.

Impact on daily practice

There is a significantly increased risk for morbidity and mortality following the treatment of a first ST episode. While placing stents and using GP IIb/IIIa inhibitors was not shown to improve outcome, treatment with new-generation $P2Y_{12}$ inhibitors might be preferable to clopidogrel in order to reduce the risk of myocardial infarction. Larger and randomised studies are needed to compare the effect of procedural and medical treatment strategies for ST in the current era.

Conflict of interest statement

J. Daemen has received institutional grant/research support from Abbott Vascular, Boston Scientific, ACIST Medical, Medtronic and PulseCath, and consultancy and speaker fees from Pythagoras Medical, ACIST Medical, Medtronic and PulseCath. S. Windecker has received research grants from Amgen, Abbott Vascular, Bayer, Boston Scientific, Biotronik, Medtronic, Edwards Lifesciences, St. Jude and Terumo. L. Räber has received speaker fees from Abbott, Amgen, and Sanofi, and research grants from Abbott, Sanofi, Regeneron and HeartFlow. T. Zanchin has received a grant from the Swiss National Science Foundation (grant no. 323530_171146). The other authors have no conflicts of interest to declare.

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Supplementary data

Supplementary Table 1. Baseline characteristics according to ST timing.

Supplementary Table 2. Periprocedural characteristics according to ST timing.

Supplementary Table 3. Independent predictors of outcomes up to 60 months in patients presenting with early ST.

Supplementary Table 4. Independent predictors of outcomes up to 60 months in patients presenting with late/very late ST.

Supplementary Table 5. Independent predictors of MACE up to 60 months according to the time point of the ST event.

Supplementary Table 6. Differences between patients with and without intravascular imaging (IVUS/OCT) during the index stent thrombosis event.

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Supplementary data

Supplementary Table 1. Baseline characteristics according to ST timing.

Characteristics	Early ST (N=345)	Late/very late ST (N=334)	*p*-value*
Age	64.1±12.1	61.4±11.9	0.004
Male	256/345 (74.2)	267/334 (79.9)	0.076
Prior MI	159/343 (46.4)	203/333 (61)	<0.001
Prior CVA/TIA	24/338 (7.1)	26/331 (7.9)	0.711
Prior PVD	24/338 (7.1)	36/331 (10.9)	0.087
Prior CABG	21/338 (6.2)	33/331 (10)	0.075
Dyslipidaemia	185/342 (54.1)	221/334 (66.2)	0.001
Hypertension	175/342 (51.2)	183/334 (54.8)	0.346
Diabetes mellitus	81/343 (23.6)	69/334 (20.7)	0.354
Current smoking	89/312 (28.5)	109/321 (34)	0.141
eGFR <60 ml/min/1.73 m²	38/213 (17.8)	51/237 (21.5)	0.328
Family history of CVD	113/341 (33.1)	132/334 (39.5)	0.085
Index stent			
BMS	38/321 (11.8)	38/266 (14.3)	0.379
DES	240/321 (74.8)	206/266 (77.4)	0.450
BMS+DES	2/321 (0.6)	2/266 (0.8)	1.000
BRS	8/321 (2.5)	7/266 (2.6)	0.915
BRP	33/321 (10.3)	13/266 (4.9)	0.016
Aspirin	297/329 (90.3)	270/309 (87.4)	0.245
$P2Y_{12}$ inhibitor			
Clopidogrel	221/329 (67.2)	65/309 (21)	<0.001
Ticagrelor	29/330 (8.8)	4/310 (1.3)	<0.001
Prasugrel	21/330 (6.4)	9/310 (2.9)	0.038
Anticoagulation	20/330 (6.1)	20/327 (6.1)	0.976

Presentation			
MI	311/333 (93.4)	266/330 (80.6)	<0.001
Unstable angina	19/333 (5.7)	49/330 (14.8)	<0.001
Stable angina	3/333 (0.9)	15/330 (4.5)	0.004
Cardiogenic shock	58/344 (16.9)	23/333 (6.9)	<0.001
ST timing			
Acute	104/345 (30.1)	N/A	N/A
Subacute	241/345 (69.9)	N/A	N/A
Late	N/A	115/334 (34.4)	N/A
Very late	N/A	219/334 (65.6)	N/A

* p-values represent early versus late/very late ST.

Categorical data are presented as counts and percentages. Continuous data are presented as mean±SD or median and interquartile range (IQR 25^{th}-75^{th} percentile).

BMS: bare metal stent; BRP: bioresorbable polymer; BRS: bioresorbable scaffold; CABG: coronary artery bypass graft; CVA/TIA: cerebrovascular accident/transient ischaemic attack; CVD: cardiovascular disease; DES: drug-eluting stent; DM: diabetes mellitus; eGFR: estimated glomerular filtration rate: MI: myocardial infarction; PVD: peripheral vascular disease; ST: stent thrombosis

Supplementary Table 2. Periprocedural characteristics according to ST timing.

Characteristics	Early ST (N=345)	Late/very late ST (N=334)	*p*-value*
Multivessel disease	113/249 (45.4)	136/308 (44.2)	0.772
Multivessel ST	18/345 (5.2)	5/334 (1.5)	0.007
2-vessel ST	17/345 (4.9)	5/334 (1.5)	0.012
3-vessel ST	1/345 (0.3)	0/334 (0)	1.000
ST location			
LM	6/345 (1.7)	8/334 (2.4)	0.548
LAD	202/345 (58.6)	162/334 (48.5)	0.009
LCX	73/345 (21.2)	47/334 (14.1)	0.015
RCA	85/345 (24.6)	105/334 (31.4)	0.048
Bypass graft	3/345 (0.9)	21/334 (6.3)	<0.001
Bifurcation involved	78/345 (22.6)	62/334 (18.6)	0.193
TIMI flow pre			
0	250/338 (74)	215/329 (65.3)	0.015
1	25/338 (7.4)	39/329 (11.9)	0.051
2	30/338 (8.9)	33/329 (10)	0.610
3	33/338 (9.8)	42/329 (12.8)	0.220
TIMI flow post			
0	19/338 (5.6)	9/329 (2.7)	0.063
1	8/338 (2.4)	5/329 (1.5)	0.429
2	20/338 (5.9)	14/329 (4.3)	0.329
3	291/338 (86.1)	301/329 (91.5)	0.027
Intracoronary imaging	84/345 (24.3)	103/334 (30.8)	0.058
IVUS	58/345 (16.8)	57/334 (17.1)	0.930
OCT	26/345 (7.5)	51/334 (15.3)	0.001
Intracoronary imaging findings			
Underexpansion	18/84 (21.4)	15/103 (14.6)	0.221
Malapposition	19/84 (22.6)	30/103 (29.1)	0.314
Edge dissection	24/84 (28.6)	3/103 (2.9)	<0.001

Edge disease	1/84 (1.2)	15/103 (14.6)	0.001
Neoatherosclerosis	2/84 (2.4)	55/103 (53.4)	<0.001
Uncovered struts	0/84 (0)	2/103 (1.9)	0.503
Gap	5/84 (6)	4/103 93.9)	0.733
Broken stent	1/84 (1.2)	1/103 (1)	1.000
GP IIb/IIIa inhibitor	221/332 (66.6)	159/332 (47.9)	<0.001
Circulatory support	29/340 (8.5)	21/330 (6.4)	0.286
Thrombectomy	147/332 (44.3)	164/324 (50.6)	0.104
Rheolytic	42/114 (36.8)	33/158 (20.9)	0.004
Aspirin prescribed	312/322 (96.9)	321/328 (97.9)	0.438
$P2Y_{12}$ inhibitor prescribed			
Clopidogrel	200/322 (62.1)	219/328 (66.8)	0.215
Ticagrelor	41/322 (12.7)	33/328 (10.1)	0.284
Prasugrel	71/322 (22)	66/328 (20.1)	0.547
Anticoagulation prescribed	25/322 (7.8)	18/328 (5.5)	0.243
Statins prescribed	314/321 (97.8)	307/313 (98.1)	0.815
Treatment of ST			
Additional stent	165/344 (48)	235/334 (70.4)	<0.001
POBA	157/344 (45.6)	81/334 (24.3)	<0.001
CABG	1/344 (0.3)	5/334 (1.5)	0.118
Conservative	21/344 (6.1)	13/334 (3.9)	0.187
Additional stent characteristics			
Direct stenting	32/162 (19.8)	64/233 (27.5)	0.079
BMS	20/164 (12.2)	15/234 (6.4)	0.045
DES	141/164 (86)	219/234 (93.6)	0.011
DES+BMS	3/164 (1.8)	0/234 (0)	0.069
Number of stents	1 (1-2)	1 (1-2)	0.814
Av. diameter (mm)	3 (2.5-3.25)	3 (2.75-3.5)	<0.001
Length (mm)	23.5 (14-37.5)	28 (20-43)	0.001
Overlapping	81/165 (49.1)	101/235 (43)	0.227
POBA characteristics			
NC	35/156 (22.4)	19/79 (24.1)	0.781
Plain (no DEB)	120/156 (76.9)	56/79 (70.9)	0.313

Cutting	0/156 (0)	3/79 (3.8)	0.037
Drug-coated	1/157 (0.6)	2/81 (2.5)	0.268

* p-values represent early versus late/very late ST.

Categorical data are presented as counts and percentages. Continuous data are presented as mean±SD or median and interquartile range (IQR 25^{th}-75^{th} percentile).

Av.: average; BMS: bare metal stent; CABG: coronary artery bypass graft; DEB: drug-eluting balloon; DES: drug-eluting stent; IVUS: intravascular ultrasound; LAD: left anterior descending coronary artery; LCX: left circumflex coronary artery; LM: left main; NC: non-compliant; OCT: optical coherence tomography; POBA: plain old balloon angioplasty; RCA: right coronary artery; ST: stent thrombosis; TIMI: Thrombolysis In Myocardial Infarction

Supplementary Table 3. Independent predictors of outcomes up to 60 months in patients presenting with early ST.

Early ST (0-30 days)	Hazard ratio (95% CI)	*p*-value
MACE		
Cardiogenic shock at ST	2.07 (1.30-3.31)	0.002
ST in LAD	1.87 (1.22-2.87)	0.004
Multivessel disease	1.65 (1.01-2.72)	0.046
TIMI flow 2-3 post intervention	0.43 (0.24-0.77)	0.005
Cardiac death		
Cardiogenic shock at ST	2.69 (1.55-4.66)	<0.001
ST in LAD	2.16 (1.25-3.73)	0.005
Multivessel disease	2.13 (1.14-3.97)	0.018
Age	1.04 (1.02-1.06)	<0.001
TIMI flow 2-3 post intervention	0.32 (0.15-0.65)	0.002
MI		
Multivessel ST	4.73 (1.83-12.20)	0.001
ST in LAD	3.15 (1.99-4.98)	0.012
Intracoronary imaging at ST	2.24 (1.11-4.53)	0.024
TVR		
Multivessel ST	3.17 (2.20-4.58)	0.022
Intracoronary imaging at ST	2.37 (1.29-4.37)	0.005
Diabetes mellitus	2.03 (1.10-3.74)	0.023
ST in LAD	2.02 (1.06-3.87)	0.041
ST-TV		
Multivessel ST	7.68 (2.33-25.31)	0.001
Intracoronary imaging at ST	5.36 (2.07-13.89)	0.001

Data are presented as hazard ratio (HR) and 95% confidence interval (CI).

CVA/TIA: cerebrovascular accident/transient ischaemic attack; CVD: cardiovascular disease; LAD: left anterior descending coronary artery; MACE: major adverse cardiac events; MI: myocardial infarction; ST: stent thrombosis; ST-TV: stent thrombosis in target vessel; TVR: target vessel revascularisation

Supplementary Table 4. Independent predictors of outcomes up to 60 months in patients presenting with late/very late ST.

Late/very late ST (>30 days)	Hazard ratio (95% CI)	*p*-value
MACE		
Cardiogenic shock at ST	3.03 (1.67-5.51)	<0.001
TIMI flow 2-3 post intervention	0.46 (0.21-0.99)	0.047
Cardiac death		
Cardiogenic shock at ST	10.06 (4.69-21.61)	<0.001
Age	1.06 (1.03-1.10)	<0.001
MI		
ST in RCA	0.32 (0.14-0.74)	0.007
Index stent DES	0.46 (0.22-0.94)	0.035
TVR		
Peripheral vascular disease	2.04 (1.04-4.00)	0.038
ST-TV		
No predictors found	N/A	N/A

Data are presented as hazard ratio (HR) and 95% confidence interval (CI).

MACE: major adverse cardiac events; MI: myocardial infarction; RCA: right coronary artery; ST: stent thrombosis; ST-TV: stent thrombosis in target vessel; TVR: target vessel revascularisation

Supplementary Table 5. Independent predictors of MACE up to 60 months according to the time point of the ST event.

Predictors of MACE	HR (95% CI)	*p*-value
ST between 1996 and 2007 (296 patients)		
ST in LAD	1.99 (1.29-3.09)	0.002
Cardiogenic shock at ST	1.77 (1.03-3.04)	0.039
Additional stent	1.82 (1.16-2.86)	0.008
TIMI flow 2-3 post intervention	0.34 (0.16-0.70)	0.004
ST between 2008 and 2017 (399 patients)		
Cardiogenic shock	3.22 (1.90-5.46)	<0.001
Multivessel disease	1.66 (1.03-2.68)	0.037
Age	1.02 (1.00-1.03)	0.015
TIMI flow 2-3 post intervention	0.47 (0.25-0.87)	0.016

Data are presented as hazard ratio (HR) and 95% confidence interval (CI).

LAD: left anterior descending coronary artery; MACE: major adverse cardiac events; ST: stent thrombosis; TIMI: Thrombolysis In Myocardial Infarction

Supplementary Table 6. Differences between patients receiving intravascular imaging (IVUS/OCT) during the index stent thrombosis event.

Baseline and procedural characteristics	No imaging (N=503)	Imaging (N=192)	*p*-value*
Age	63.7±12.1	60.6±11.8	0.002
Male	373/503 (74.2)	157/192 (81.8)	0.035
Prior MI	265/500 (53)	103/192 (53.6)	0.879
Prior CVA/TIA	36/493 (7.3)	16/192 (8.3)	0.647
Prior PVD	47/493 (9.5)	13/192 (6.8)	0.251
Prior CABG	44/493 (8.9)	10/192 (5.2)	0.105
Dyslipidaemia	300/500 (60)	115/192 (59.9)	0.980
Hypertension	268/500 (53.6)	99/192 (51.6)	0.631
Diabetes mellitus	109/501 (21.8)	43/192 (22.4)	0.856
Current smoking	148/457 (32.4)	55/192 (28.6)	0.348
eGFR <60 ml/min/1.73 m²	66/319 (20.7)	25/138 (18.1)	0.527
Family history of CVD	167/499 (33.5)	81/192 (42.2)	0.032
Index stent			
BMS	53/435 (12.2)	23/152 (15.1)	0.351
DES	332/435 (76.3)	114/152 (75)	0.743
BMS+DES	2/435 (0.5)	2/152 (1.3)	0.277
BRS	6/435 (1.4)	9/152 (5.9)	0.005
BRP	42/435 (9.7)	4/152 (2.6)	0.006
Aspirin	406/466 (87.1)	170/182 (93.4)	0.022
New $P2Y_{12}$ inhibitor	43/468 (9.2)	20/182 (11)	0.486
Anticoagulation	35/483 (7.2)	5/189 (2.6)	0.023
Presentation			
MI	421/487 (86.4)	171/192 (89.1)	0.359
Unstable angina	50/487 (10.3)	19/192 (9.9)	0.885
Stable angina	16/487 (3.3)	2/192 (1)	0.101
Cardiogenic shock	73/501 (14.6)	9/192 (4.7)	<0.001
ST timing			

Acute ST	80/492 (16.3)	24/187 (12.8)	0.268
Subacute ST	181/492 (36.8)	60/187 (32.1)	0.253
Late ST	87/492 (17.7)	28/187 (15)	0.400
Very late ST	144/492 (29.3)	75/187 (40.1)	0.007
Year of ST			0.043
1996-2007	226/503 (44.9)	70/192 (36.5)	
2008-2017	277/503 (55.1)	122/192 (63.5)	
Multivessel disease	200/389 (51.4)	57/184 (31)	<0.001
Multivessel ST	19/503 (3.8)	4/192 (2.1)	0.264
ST location			
LM	8/503 (1.6)	6/192 (3.1)	0.198
LAD	255/503 (50.7)	117/192 (60.9)	0.015
LCX	94/503 (18.7)	30/192 (15.6)	0.346
RCA	149/503 (29.6)	45/192 (23.4)	0.104
Bypass graft	22/503 (4.4)	2/192 (1)	0.031
Bifurcation involved	98/503 (19.5)	46/192 (24)	0.193
TIMI flow 0-1 pre	400/492 (81.3)	140/191 (73.3)	0.021
TIMI flow 2-3 post	454/492 (92.3)	188/191 (98.4)	0.002
GP IIb/IIIa inhibitor	249/488 (51)	143/192 (74.5)	<0.001
Thrombectomy	191/481 (39.7)	131/191 (68.6)	<0.001
Aspirin prescribed	457/474 (96.4)	192/192 (100)	0.008
New $P2Y_{12}$ inhibitor prescribed	150/474 (31.6)	65/192 (33.9)	0.581
Anticoagulation prescribed	34/474 (7.2)	9/192 (4.7)	0.237
Statins prescribed	454/467 (97.2)	181/181 (100)	0.023
Treatment of ST			
Additional stent	292/502 (58.2)	123/192 (64.1)	0.156
POBA	186/502 (37.1)	53/192 (27.6)	0.019
CABG	6/502 (1.2)	0/192 (0)	0.195
Conservative	18/502 (3.6)	16/192 (8.3)	0.010
Additional stent characteristics			
Direct stenting	57/287 (19.9)	45/123 (36.6)	<0.001

BMS	26/290 (9)	9/123 (7.3)	0.582
DES	263/290 (90.7)	112/123 (91.1)	0.906
DES+BMS	1/290 (0.3)	2/123 (1.6)	0.213
Number of stents	1 (1-2)	1 (1-2)	0.043
Av. diameter (mm)	3 (2.75-3.50)	3.12 (2.88-3.50)	0.006
Length (mm)	26 (16-40)	31 (18-43)	0.041
Overlapping	133/292 (45.5)	57/123 (46.3)	0.882
POBA characteristics			
NC	33/184 (17.9)	21/51 (40.4)	0.001
Plain (no DEB)	146/184 (79.3)	31/52 (59.6)	0.004
Cutting	3/184 (1.6)	0/52 (0)	1.000
Drug-coated	3/186 (1.6)	0/53 (0)	1.000

Categorical data are presented as counts and percentages and tested by χ^2 test or Fisher's exact test when appropriate. Continuous data are presented as mean±SD and tested by the Student's t-test or median and interquartile range (IQR 25^{th}-75^{th} percentile) and tested by Mann-Whitney rank-sum test.

Av.: average; BMS: bare metal stent: BRP: bioresorbable polymer; BRS: bioresorbable scaffold; CABG: coronary artery bypass graft; CVA/TIA: cerebrovascular accident/transient ischaemic attack; CVD: cardiovascular disease; DES: drug-eluting stent; eGFR: estimated glomerular filtration rate; IVUS: intravascular ultrasound; LAD: left anterior descending coronary artery; LCX: left circumflex coronary artery; LM: left main; MI: myocardial infarction; NC: non-compliant; OCT: optical coherence tomography; POBA: plain old balloon angioplasty; PVD: peripheral vascular disease; RCA: right coronary artery; ST: stent thrombosis; TIMI: Thrombolysis In Myocardial Infarction