Rev Esp Cardiol. 2019;72(4):282–284

Editorial

Stent Thrombosis After ACS-PCI: Does Adherence to Antiplatelet Therapy Involve More Than Its Intensity?

Trombosis del *stent* tras la ICP por SCA: ¿la adherencia al tratamiento antiagregante implica más que su intensidad?

Zuzana Motovska*

Cardiocentre, Third Faculty of Medicine, Charles University, Prague, Czech Republic

MAGNITUDE OF THE PROBLEM

As a result of the increasing prevalence of risk factors, coronary heart disease (CHD) has become a leading cause of death, globally, among people aged 60 years and older. The worldwide burden of CHD is set to reach 47 million disability-adjusted life years by 2020.[1]

A substantial linear decrease in the rates of coronary artery bypass graft surgery has been observed over the past 2 decades. This decline has been accompanied by a corresponding increase in percutaneous coronary revascularization procedures such that most coronary artery lesions needing intervention are now treated with stents.[2] It has been projected that the total number of percutaneous coronary intervention (PCI) procedures performed in Europe will grow at a compound annual rate of 3.5% over the next half-decade, and the global market forecast for coronary artery stents is expected to increase from 2016 to 2020 by 2.9%.[3]

Stent thrombosis (ST) is an infrequent complication of PCI in the setting of effectively suppressed platelet reactivity with aspirin and a $P2Y_{12}$ inhibitor.[4] The rate of serious ST-associated events, however, is worrying; every fourth patient with ST dies and a consequential myocardial infarction (MI) occurs in almost every patient. Treatment for ST requires emergent, repeat coronary intervention, although optimal reperfusion is only achieved in two-thirds of patients. The risk of subsequent recurrent ST is high (5-year incidence = 24%).[5] The highest mortality risk is among those with early ST.

With the growth of the stented patient population, ST accounts for an increasing proportion of patients with ST-segment elevation MI. A study using a large population of all-comers treated with coronary stents showed that more than 60% of patients readmitted with ST-segment elevation MI within the 5-year follow-up had definite ST.[6]

Taking all this into consideration and given the current shift toward an aging demographic structure, stenting will continue to be in demand and the issue of ST and its prevention will become increasingly important.

PREVENTION

Risk Factor Identification

Several factors have been associated with the risk of ST. These factors can be divided into those related to patient profile, procedural characteristics, and antiplatelet therapy efficacy (Table 1). Higher patient thrombotic risk was confirmed in conjunction with acute coronary syndrome (ACS) as an indication of PCI, diabetes, chronic kidney disease, cigarette smoking, low left ventricular ejection fraction, and other prothrombotic comorbidities, such as cancer or thrombocytopathy. Lesion type and procedural factors can also influence in-stent vascular rheology. Interventions involving diffuse coronary artery disease, small vessel disease, anatomically complex lesions, the presence of a thrombus, bifurcational/ostial lesions, and suboptimal procedural results (eg, poor stent expansion, undersized stent, residual dissection, strut fractures), all increased the risk of ST.

Since the first use of stent implantation as a method of treating CHD, it has become clear that the risk of ST without effective suppression of platelet reactivity is unacceptable. At least 6 months of dual antiplatelet therapy (DAPT) should be maintained after PCI for stable CHD, and at least 12 months after stent implantation associated with ACS.[7] Earlier than recommended termination of DAPT, especially due to patient nonadherence, has been associated with an increased risk of ST.[8]

It is important to consider not only the predictive power but also the frequency of occurrence; less potent predictors might be clinically more meaningful if they commonly occur. Analysis of 153 350 patients and 2495 STs concluded that one of the most common and consistent predictors of ST was early antiplatelet therapy discontinuation, the extent of coronary disease, and stent number/length.[9] The factors differ depending on the time frame of ST, notably, in events that occur less than 30 days after PCI (acute or subacute ST), the most powerful factors are directly related to the stent implantation procedure.

Table 1
Factors Influencing Stent Thrombosis

Patient-related	Acute coronary syndrome
	Current cigarette smoker
	Diabetes requiring insulin therapy
	Chronic kidney disease
	Adherence to antiplatelet therapy
Procedure-related	Lesion characteristics
	Type of stent
	Stent diameter
	Total stent length
	Procedural result
Adjunctive antiplatelet drug-related	Inefficacy

* Corresponding author: Cardiocentre, Third Faculty of Medicine, Charles University, Ruská 87, 100 00 Prague 10, Czech Republic.
E-mail address: motovska.zuzana@gmail.com
Available online 27 November 2018

https://doi.org/10.1016/j.rec.2018.10.011

Score for ST Risk Prediction

The multifactorial nature of ST has been the basis for individual ST risk prediction. Optimally, risk prognostication should be calculated at the end of the procedure, and thereafter be used as a baseline for controlling clinical risk factors and personalization of adjuvant antithrombotic therapy.

Analyses of 2 large randomized clinical trials, which spanned the spectrum of ACS, resulted in the development and validation of a risk score consisting of 10 readily assessed variables.[10] The risk score can predict the occurrence of ST not only within the first year but also very late ST events.

Periprocedural Imaging

Endocoronary imaging, ie, intravascular ultrasound and optical coherence tomography both substantially improved our understanding of ST mechanisms. A major clinical use of the technique is to optimize stent placement and thus minimize stent-related adverse events, including ST. The use of intravascular imaging techniques for PCI guidance reduces the risk of ST by more than 50%.[11] The greatest benefit of periprocedural imaging can be expected especially in high-risk complex lesions. The second tool for preventing ST, through intracoronary imaging, is the identification of the postprocedural presence of ST mechanical risk factors.

Stent Technology

Recent developments in stent technology, and improvements in drug elution and stent design have resulted in further reductions in the stent thrombosis rate.[2]

ANTITHROMBOTICS

Intensification of DAPT by adding potent $P2Y_{12}$ inhibitors in combination with aspirin significantly decreases the incidence of ST after PCI in ACS (Table 2). Treatment with prasugrel or ticagrelor might also be an option in high-risk patients after stent implantation for stable coronary artery disease. For identification of high-risk ST patients, a relevant score can be used, such as the Syntax score or a score for predicting ST. Tailoring DAPT to more intensive inhibition of platelet reactivity in patients after ST is imperative. Intensive antiplatelet therapy is, of course, limited by the increased bleeding risk. Mitigating this risk is essential to minimize subsequent premature DAPT cessation.

Prehospital initiation of ticagrelor in patients with ST-elevation myocardial infarction (STEMI) and a primary PCI strategy can reduce the incidence of early ST (Table 2).

In triple therapy with aspirin, the use of clopidogrel and low doses of a direct oral anticoagulant significantly lowered the risk of ST.[18] Among stented patients with ACS treated with DAPT, twice-daily rivaroxaban 2.5 mg was associated with a reduction in ST and mortality. The benefit of rivaroxaban appeared early and was maintained over time. The other oral anticoagulant, apixaban, demonstrated a similar reduction in ST in the study, which was terminated prematurely. Factor Xa inhibitors affect the coagulation cascade through the inhibition of thrombin generation; furthermore, because thrombin is a potent stimulant of platelet reactivity, these drugs also inhibit platelet aggregation. However, the benefits from ST reduction are at least partially offset by a 3-fold increase in the risk of major bleeding. Therefore, triple therapy is reserved only for patients with at high risk of ST and low risk of bleeding.

Adherence to DAPT, which includes following the recommended duration, is the most affordable, and generally the most effective preventative measure against ST.[9] Premature termination of DAPT, due to patient nonadherence, especially in the early phase after stent implantation, increases the risk of ST and mortality.[8,19] In addition to shortening DAPT duration, ignoring guidelines on the use of newer $P2Y_{12}$ inhibitors can also be considered nonadherence to recommended antiplatelet therapy (in the absence of high bleeding risk). Patient adherence to $P2Y_{12}$ therapy decreased after the introduction of newer, more expensive drugs. Prasugrel and

Table 2
Incidence of Stent Thrombosis

	Publication year	Indication	N	Drug	Occurrence of ST 12-15 mo after PCI
Randomized studies					
TRITON[12]	2007	Primary PCI	1188	Clopidogrel	Definite NA Definite/probable 2.7%
PLATO[13]	2009	Primary PCI	2486	Clopidogrel	Definite 2.3% Definite/probable 3.4%
TRITON[12]	2007	Primary PCI	1152	Prasugrel	Definite NA Definite/probable 1.5%
PLATO[13]	2009	Primary PCI	2463	Ticagrelor ± clopidogrel pretreatment	Definite 1.4% Definite/probable 2.3%
ATLANTIC[14]	2014	Primary PCI	953 909	In hospital ticagrelor Prehospital ticagrelor	Definite 1.2% (at 30 d) Definite 0.2% (at 30 d)
PRAGUE -18[15]	2017	Primary PCI	596	Ticagrelor ± selective switch to clopidogrel	Definite 1.5% Definite/probable NA
			634	Prasugrel ± selective switch to clopidogrel	Definite 1.1% Definite/probable NA
Registries (no adjustment for baseline differences)					
Sheffield, UK[16]	2017	Primary PCI	1654 1136	Ticagrelor Prasugrel	Definite 1.0% Definite 1.6%
SWEDEHEART[17]	2018	Primary PCI	1995 5438	Ticagrelor in hospital Ticagrelor pretreatment	Definite 0.4% at 30 d Definite 0.5% at 30 d
RENAMY[4]	2018	ACS-PCI	2604	Ticagrelor	Definite 1.2%
			1519	Prasugrel	Definite 0.9%

ACS, acute coronary syndrome; PCI; percutaneous coronary intervention; ST, stent thrombosis.

ticagrelor had higher out-of-pocket patient costs, which contributed significantly to lower adherence rates compared with clopidogrel.[20] Selective de-escalation to clopidogrel in patients with low ischemic risk may be a real opportunity to ensure the continuation of DAPT. Patient copayment is now part of DAPT personalization after ACS-PCI.[21]

IMPORTANCE OF OTHER DRUGS

High-intensity statin treatment can prevent delayed vascular healing processes and chronic vascular inflammation, which are predisposing factors for very late ST after drug-eluting stent implantation. The benefits of statins are not only due to their ability to lower low-density lipoprotein cholesterol, but also to other benefits that include improving endothelial function, reducing vascular inflammation, and reducing platelet adhesion and thrombus formation.

CONCLUSIONS

ST is a devastating complication, whose occurrence is proportionally rare. However, because of the increasing population of stent implanted patients, it is an attention-worthy event. The most important approach to deal with ST after ACS-PCI is its prevention. With respect to its multifactorial etiology, efforts at ST prevention focus on optimizing stent deployment, the use of new-generation stents, and maximizing adherence to effective antiplatelet therapy.

CONFLICTS OF INTEREST

Z. Motovska has received speaker's fees from AstraZeneca, and outside the area of work commented on here. She is also an Advisory Board member for AstraZeneca, Bayer, and Boehringer Ingelheim.

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