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Stent thrombosis and platelet reactivity

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ABSTRACT

Stent thrombosis (ST) is a rare but potentially life-threatening event that can follow percutaneous coronary intervention (PCI) with stent implantation. Several factors related to procedure or patient features can favor thrombus formation and development of ST. Dual antiplatelet therapy (DAPT) with aspirin and $P2Y_{12}$ inhibitors is the cornerstone of strategy for reducing incidence of ST. Two main causes of DAPT failure have been identified: the inappropriately premature antiplatelet therapy discontinuation and hyporesponsiveness to antiplatelet drugs. There is growing evidence that a residual high on-treatment platelet reactivity (HPR) is associated with increased risk of thrombotic complications after PCI, including ST. In recent years numerous platelet function tests were developed and some of these have been extensively used in clinical studies to evaluate residual platelet reactivity, after antiplatelet drugs administration. The identification of patients with HPR is fundamental for optimization of antiplatelet treatment. Nevertheless first studies suggested that achieving a more intense platelet inhibition, switching from standard to an intensified treatment regimen on the basis of platelet reactivity, has failed to show any benefit in terms of clinical events. Certainly individualized pharmacological treatment of patients undergoing PCI remains one most important objective in order to prevent serious PCI complications, such as ST.

Klíčová slova:
Individualizovaná antiagregační léčba
Reaktivita krevních destiček
Trombóza stentu

SOUHRN

Trombóza stentu (stent thrombosis – ST) je sice vzácnou, ale potenciálně život ohrožující příhodou, s níž se lze setkat po perkutánní koronární intervenci (percutaneous coronary intervention – PCI) s implantací stentu. Ke vzniku trombu a rozvoji ST může přispívat několik faktorů souvisejících se samotným výkonem nebo charakteristikami pacienta. Základem strategie ke snížení výskytu ST je duální protidestičková léčba (dual antiplatelet therapy – DAPT) s kyselinou acetylsalicylovou a inhibitory $P2Y_{12}$. Byly zjištěny dvě hlavní příčiny neúspěšné DAPT: nevhodně předčasně ukončená protidestičková léčba a snížená odpověď na antiagregancia. Přibývá důkazů o tom, že reziduální vysoká reaktivita během léčby (high platelet reactivity – HPR) je spojena se zvýšeným rizikem trombotických komplikací včetně ST po PCI. V posledních letech byla vyvinuta řada testů na stanovení funkce krevních destiček; některé z těchto testů se ve velké míře používají v klinických studiích při stanovení reziduální reaktivity destiček po podání antiagregancií. Pro optimalizaci protidestičkové léčby je naprosto nezbytné vyhledávání pacientů s HPR. První studie nicméně naznačily, že dosažení intenzivnější inhibice krevních destiček po převedení pacienta ze standardního na intenzivní léčebný režim podle reaktivity destiček nezajistilo žádný přínos ve smyslu incidence příhod. Není pochyb o tom, že individualizovaná farmakoterapie u pacientů absolvujících PCI zůstává i nadále jedním z hlavních cílů v úsilí o předcházení vzniku závažných komplikací – včetně ST – v souvislosti s PCI.

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Introduction

Percutaneous coronary intervention (PCI) with stent implantation is currently the treatment of choice for coronary revascularization in patients affected by coronary artery disease (CAD). Although the introduction of dual antiplatelet therapy (DAPT) with aspirin and $P2Y_{12}$ inhibitors has resulted in a dramatic decrease in the incidence of recurrent ischemic complications after PCI [1–3], cardiovascular events following stent implantation still occur in a clinically significant proportion of patients [4,5]. Stent thrombosis (ST) is a potentially life-threatening event, most frequently associated with ST elevation myocardial infarction (STEMI) or sudden cardiac death, resulting from abrupt vessel closure. Mortality rates associated with ST vary from 20% to 45% [6–9].

Stent thrombosis and platelet inhibition

The Academic Research Consortium (ARC) has elaborated specific criteria for ST diagnosis, with the aim to propose a definition that could be uniformly applied in clinical trials and daily practice. According to the degree of certainty, ST is defined as "definite" in the presence of angiographic or pathologic confirmation; "probable" in case of unexplained death occurring within 30 days after the procedure, or myocardial infarction (MI) at any time in the territory of implanted stent; "possible" when unexplained death occurs beyond 30 days from procedure. According to the time of presentation, ST is defined as "acute" (within 24 h from stent implantation), "early" (occurring in the first 30 days after stent implantation), "late" (between 31 days and 12 months from the index procedure) and "very late" (after 12 months from angioplasty) [10]. Several factors can favor thrombus formation and development of ST [7–9,11–18]. Acute ST is generally associated to "procedure related" factors, such as stent underexpansion or malapposition, "edge" dissection, stent fracture, reduced TIMI (Thrombolysis in Myocardial Infarction) flow grade at the end of the procedure [7,9,13]. Early and late ST are usually related to lesion characteristics: long lesion length, small vessel diameter, treatment of saphenous vein graft, chronic total occlusion or bifurcation lesions are predictors of increased risk of ST [7–9,11,12]. Similarly, various clinical characteristics are strongly associated with the risk of ST: diabetes mellitus, acute coronary syndrome, neoplasms, advanced age, hypersentivity to polymer or drug, discontinuation of DAPT or hyposensitivity to antiplatelet drug [7–9,11,12,14–16]. Finally risk factors for very late stent thrombosis are still not well characterized, but instrumental and pathological evidences have underlined the fundamental role of incomplete stent healing and local inflammation in the development of ST also after several years from PCI [17,18].

Nowadays the maintenance of adequate platelet inhibition is the cornerstone of ST prevention and DAPT is the mainstay strategy for reducing incidence of ST. Two main causes of DAPT failure have been identified: the inappropriately premature antiplatelet therapy discontinuation and hyporesponsiveness to antiplatelet drugs. Many observational studies have shown a clear relation between premature DAPT discontinuation and poor clinical outcomes, especially in drug-eluting stent (DES) treated patients [8,19–21]. In the PREMIER registry, among 500 MI patients treated with DES, mortality rates at 1-year were significantly higher in patients who withdrew thienopydirine treatment than in those who continued appropriate therapy (7.5% vs 0.7%, $p < 0.0001$) [8]. In a series of 3021 DES treated patients, the rate of ST at 18 months was 1.9% (58 patients) and rate of ST within 6 months was 1.4 % (42 patients). Data from multivariable analysis identified $P2Y_{12}$ inhibitors discontinuation as a major independent predictor of ST within 6 months (HR 13.74; 65% CI, 4.04–46.68; $p < 0.001$) [21]. A retrospective analysis in 1293 patients treated with sirolimus eluting stent found no significant difference between treatment with DAPT withdrawn within or beyond 6 months (1.3% versus 2.6%, $p = 0.197$). However, patients treated with DAPT for longer than 6 months presented a significantly higher incidence of major bleeding (HR 3.623; 95% CI, 1.763–7.444; $p < 0.001$), including intracranial hemorrhage (HR 4.545; 95% CI; 1.083–19.068, $p = 0.039$) [22]. Concern about bleeding complications is also due to the evidence of their important clinical impact on outcomes of patients undergoing PCI [23,24]. A subsequent study on a population of 2701 patients treated with DES has shown that treatment with DAPT, for more than 12 months, was not significantly more effective than aspirin alone [25]. No difference in the incidence of ST was found in another study of 2013 patients randomized to receive DAPT for 6 versus 24 months [26]. Despite current guidelines recommending DAPT for 6–12 months after DES implantation and for 12 months after an acute coronary syndrome regardless of the type of stent implanted [27], data on optimal DAPT timing are not conclusive, and maybe definitive answers could come from several ongoing randomized clinical trials [28,29].

The role of platelet reactivity

Recently, the discussion about antiplatelet treatment has focused on the problem of responsiveness to drug treatment. Various investigations have shown that in patients with decreased response to clopidogrel, residual high platelet reactivity (HPR) is associated with increased risk of thrombotic complications after PCI [30–38]. Numerous platelet function tests are nowadays available, some of which have been extensively used in clinical studies to evaluate residual platelet reactivity after antiplatelet drugs administration [39]. Light transmittance aggregometry (LTA) is actually considered the gold standard method to assess platelet function. It is based on the measure of light transmission through platelet rich plasma after exposure to an agonist (i.e. adenosine diphosphate) with platelet poor plasma as reference. This method requires special training and it is time-consuming, therefore may not be suitable for routine clinical use [40,41]. Another method is the platelet vasodilator-stimulated phosphoprotein (VASP) phosphorylation assessment, which is based on the flow cytometry evaluation of $P2Y_{12}$ receptor inhibition. Similarly to LTA, this assay is not routinely used in clinical practice as it requires dedicated training and time-consuming laboratory procedures [40,42]. Currently, several tests are also available for a point of care evaluation of platelet reactivity: the VerifyNow P2Y12 (Accumetrics, Inc., San Diego, Cali-

Table 1 – Principal trials investigating role of tailored antiplatelet strategy with $P2Y_{12}$ inhibitors in percutaneous coronary intervention.

Trials	Design and study population	Antiplatelet strategies	Laboratory methods and HPR definition	Main results
GRAVITAS [52]	2214 patients with high platelet on-treatment platelet reactivity 12 to 24 h after PCI with drug-eluting stent	**Clopidogrel high dose** (600 mg load dose, 150 mg daily thereafter) or **clopidogrel standard dose** (no additional loading dose, 75 mg daily) for 6 months	VerifyNow Assay PRU ≥ 230	No significant difference in the incidence of cardiovascular death, nonfatal MI, or ST between two groups
Aradi et al. [54]	A total population of 200 patients screened for platelet reactivity and scheduled for elective PCI. Randomized 78 patients with high on-treatment platelet reactivity 12 to 24 h after 600 mg clopidogrel loading dose.	**Clopidogrel high maintenance dose** (150 mg daily) or **clopidogrel standard maintenance dose** (75 mg daily) for 4 weeks	ADP 5 µmol/L induced maximal aggregation values ≥ 34% (LTA)	CV death, MI or TVR was significantly higher in the HPR + 75 mg group compared to patients with high clopidogrel maintenance dose or to patients with normal platelet reactivity
EFFICIENT [55]	A population of 192 screened for platelet reactivity and scheduled for elective PCI. Randomized 94 patients with high on-treatment platelet reactivity after 5 days of treatment with ASA 100 mg and clopidogrel 75 mg.	**Clopidogrel high maintenance dose** (150 mg daily) or **clopidogrel standard maintenance dose** (75 mg daily) for 4 weeks	VerifyNow Assay percent of inhibition < 40%, ARU ≥ 550	6 months MACCE significantly higher in the HPR + 75 mg group compared to patients randomized to 150 mg clopidogrel or to patients with HPR
Bonello et al. [56]	162 randomized patients undergoing PCI screened for platelet reactivity 24 h after a 600-mg clopidogrel load	**VASP guided group** (three additional 600 mg clopidogrel loads in 24 h) or **control group** (clopidogrel standard dose without additional load)	VASP index > 50%	1-month MACCE significantly higher in clopidogrel control group
Bonello et al. [57]	429 randomized patients with a low clopidogrel response after a 600-mg LD undergoing PCI (screened for platelet reactivity within 24 h after load)	**VASP guided group** (three additional 600-mg clopidogrel loads in 24 h) or **control group** (clopidogrel standard dose without additional load)	VASP index > 50%	Rate of stent thrombosis was significantly lower in the VASP-guided group
TRIGGER-PCI [60]	423 randomized patients screened for HPR between 2 or 7 h after clopidogrel 75 mg maintenance dose the morning after PCI	**Clopidogrel** (75 mg daily) vs **prasugrel** (10 mg daily)	VerifyNow Assay PRU > 208	Prasugrel treatment was effective in reducing HPR but no clinical benefit for the low rate of adverse ischemic events
RESPOND [61]	2-way crossover design enrolling 98 patients	**Phase 1:** nonresponders (n = 41) and responders (n = 57) randomly received clopidogrel (600 mg/75 mg once daily) or ticagrelor (180 mg/90 mg twice daily) for 14 days **Phase 2:** all nonresponders switched treatment	ADP 20 µmol/L induced the absolute change in platelet aggregation (maximum extent) was ≤ 10%	Treatment with ticagrelor, regardless of clopidogrel response, induces a reduction of platelet reactivity below the cut-off point for ischemic events
ARCTIC [63]	2440 scheduled for elective PCI	**Monitoring group** (adjustment of antiplatelet therapy according to platelet function test) or **Conventional group** (conventional treatment not adjusted according to platelet function test)	VerifyNow Assay ARU ≥ 550 PRU ≥ 235	No difference in incidence of death, MI, ST, stroke or urgent revascularization at 1-year follow up

fornia), the Multiplate analyzer (Dynabyte, Munich, Germany), the Platelet Function Assay-100 (PFA-100 System; Dade Behring, Miami, Florida) and Plateletworks (Helena Laboratories, Beaumont, Texas) assays. In particular the VerifyNow P2Y12 assay is based on the measure of ADP-induced platelet aggregation, with results reported as $P2Y_{12}$ reaction units (PRU). The lower the PRU value, the greater the degree of $P2Y_{12}$ receptor inhibition by clopidogrel and vice versa [40,43]. The Multiplate analyzer is based on impedance multiple electrode platelet aggregometry (MEA) and results are reported as aggregation units (AU). Both assays do not require a particular training, are not time-consuming and require whole blood samples [40,44].

A large proportion of patients treated with clopidogrel show an impaired response to this drug and high residual platelet reactivity [42,44–50], which has been extensively

demonstrated to result in increased rates of ischemic complications after PCI [28–36]. In the CREST study patients who experienced ST had significantly higher platelet reactivity in clopidogrel, as assessed with LTA, VASP, and greater incidence of HPR (defined as > 75th percentile for 5 and 20 μmol/L ADP induced aggregation in the group without ST and > 75th percentile of VASP values) [46]. Similarly, Hobson et al. found significantly higher platelet reactivity on clopidogrel in patients with ST, using the VerifyNow P2Y12 (PRU 183 ± 51 vs. 108 ± 31, $p = 0.02$) [47]. In a Swedish Registry, mean PRU levels during clopidogrel treatment was found to be higher in patients with ST than in control (246.8 ± 75.98 vs. 200.0 ± 82.7, $p = 0.001$). In this study, the optimal cut-off to predict ST was a PRU value ≥ 222 (AUC 0.69, $p < 0.0001$ in a receiver operating characteristic analysis) [48]. In another prospective observational study enrolling 804 patients, clopidogrel resistance (defined as platelet aggregation by 10 μmol/L ADP ≥ 90th percentile of controls [70%] at LTA) was associated with increased risk of ST (8.6% vs 2.3%, $p < 0.001$) and was identified as an independent predictor of ST (HR 3.08: 95% CI; 1.37–7.16, $p = 0.009$) [49]. In a series of 1608 DES treated patients, the 30-day incidence of definite ST and cumulative incidence of death and ST were higher in clopidogrel low responders (defined by MEA cut-off value of 416 AU·min) than in normal responders (respectively 2.2% vs 0.2%, $p < 0.0001$; 3.1% vs 0.6%, $p < 0.001$) [50]. More recently, in the POPULAR (Point-of-Care Platelet Function Assays Predict Clinical Outcomes in Clopidogrel Pre-Treated Patients Undergoing Elective PCI) study, which evaluated in a head-to-head comparison six different platelet function test (LTA, VerifyNow, Plateletworks, IMPACT-R, PFA ADP, PFA Innovance P2Y12), three tests (LTA, VerifyNow and Plateletworks) were found to be predictive of atherothrombotic events, however, none of the tests was identified to be predictive of ST [36]. Finally another important issue is related to the increased risk of ST associated to the presence of dual non-responsiveness to both clopidogrel and aspirin. An observational study involving 746 DES treated patients showed an incidence of dual non-responsiveness to clopidogrel and aspirin (evaluated by LTA) of 6%; in this group, the incidence of definite/probable ST (11.1%) was significantly higher than in patients responders to both clopidogrel and aspirin, or in patients with isolate clopidogrel or aspirin hyporesponsiveness (respectively 2.1%, $p < 0.001$; 2.2%, $p < 0.005$; and 2.3%, $p < 0.005$) [51].

Issues on tailored antiplatelet therapy

Once established HPR as a risk factor for development of ST, the issue remains to find a strategy to prevent this condition. One possibility to achieve a greater platelet inhibition resides in the administration of higher dose of clopidogrel. In the GRAVITAS (Gauging Responsiveness with A VerifyNow assay – Impact on Thrombosis And Safety) trial, 2214 patients with HPR after coronary stenting were randomized to receive clopidogrel high dose (600-mg loading dose plus 150 mg daily thereafter) versus a standard dose (no additional loading dose plus conventional 75 mg daily). Platelet reactivity after PCI was assessed by VerifyNow P2Y12 assay (Accumetrics, Inc., San Diego, California). At 6-month follow up no significant difference in the incidence of composite primary endpoint (cardiovascular death, nonfatal MI, or ST) was observed between patients who received clopidogrel high dose and standard dose (2.3% vs. 2.3%, HR 1.01, 95% CI 0.58–1.76; $p = 0.97$) [52]. These disappointing results suggested the scarce effectiveness of tailoring antiplatelet treatment on the basis of bedside platelet function test. However, different aspects of GRAVITAS need to be discussed. One potential problem is the timing of platelet reactivity assessment (12–24 h after PCI), as during the first 24 h after the procedure platelet reactivity could increase in reason of PCI itself [53]. Another important point is the low risk profile of the population enrolled, which was unlike to additionally benefit from a more aggressive antiplatelet treatment. Other trials have tested the assumption to achieve a better outcome with a more aggressive use of antiplatelet drug in patients with on clopidogrel HPR (Table 1). Aradi et al. in a small study found a significant decrease in platelet reactivity, assessed by LTA, with the administration of one month of clopidogrel 150-mg maintance dose in HPR patients. The primary composite endpoint (cardiovascular death, MI or target vessel revascularization – TVR) was higher in HPR patients receiving clopidogrel standard dose versus HPR patients receiving double clopidogrel dose (24.6% vs. 3.1%, $p = 0.01$) or versus patients with normal platelet reactivity (9.4%, $p = 0.01$) [54]. In the EFFICIENT (EFFect of hIgh-dose ClopIdogrel treatmENT) trial in elective PCI patients with clopidogrel resistance (defined as a percent of inhibition lower than 40% at VerifyNow P2Y12 Assay), the administration of higher clopidogrel dose (150 mg) was more effective than standard dose in preventing MACCE [55]. Bonello et al. showed better clinical outcomes by using incremental clopidogrel loads to overcome HPR as assessed by VASP [56,57]. The advent of new more potent $P2Y_{12}$ inhibitors has offered new options to reduce the rate of patients with inadequate inhibition of $P2Y_{12}$ receptor [58,59]. The TRIGGER-PCI (Testing platelet Reactivity In patients underGoing elective stent placement on clopidogrel to Guide alternative thErapy with pRasugrel) trial investigated the effectiveness and the safety of prasugrel versus clopidogrel in patients with HPR after non-urgent PCI with DES implantation [60]. This study demonstrated the efficacy of switching from clopidogrel to prasugrel to achieve greater platelet inhibition, however, no clinical benefit was observed with this tailored antiplatelet strategy for HPR. Similarly the RESPOND (Response to Ticagrelor in Clopidogrel Nonresponders and Responders and the Effect of Switching Therapy) trial [61] has shown that treatment with ticagrelor, regardless of clopidogrel response, induces a reduction of platelet reactivity below the cut-off point for ischemic events (defined as > 59% 20 μmol/L ADP-induced maximal platelet aggregation, ≥ 235 PRU based on the VerifyNow P2Y12 assay, and > 50% Platelet Reactivity Index based on the VASP phosphorylation assay). Recently a meta-analysis of 10 randomized trials testing the efficacy of intensified antiplatelet therapy on the basis of platelet reactivity shows the effectiveness of a tailored treatment in reducing cardiovascular mortality. Interestingly the net clinical benefit of the tailored therapy was found to be greater in patients at higher risk for ST [62].

More recently, the ARCTIC (Assessment by a Double Randomization of a Conventional Antiplatelet Strategy versus a Monitoring-guided Strategy for Drug-Eluting Stent Implantation and of Treatment Interruption versus Continuation One Year after Stenting) trial [63] showed no significant improvement in clinical outcome in patients with an adjustment of treatment strategy guided by platelet reactivity assessed with VerifyNow. 2440 scheduled for PCI were randomly assigned to a treatment based on platelet reactivity or a conventional therapy. Treatment strategies in HPR patient were the following: intravenous aspirin in case of aspirin resistance and administration of glycoprotein IIb/IIIa inhibitors, and an additional loading dose of clopidogrel (at a dose of ≥ 600 mg) or a loading dose of prasugrel (at a dose of 60 mg) for clopidogrel resistance. Subsequently patients received daily dose of clopidogrel 150 mg or prasugrel 10 mg. Other adjustments of treatment were evaluated with platelet function tests at 14 and 30 days after procedure. At 1-year follow-up the incidence of primary endpoint (death from any cause MI, ST, stroke or transient ischemic attack, or urgent revascularization) was 31.1% in conventional group and 34.6% in the monitoring group ($p = 0.10$); in the same way no difference was found in incidence of ST between two groups (0.7% vs 1.0%, $p = 0.51$).

Conclusions

ST is currently considered one of most serious and life-threatening events following PCI with stent implantation. Possible strategies to reduce the incidence of these complications could reside in the improvement of stent and device technology, and in the optimization of periprocedural and maintenance drug treatment. Although high residual platelet reactivity has been demonstrated to be a predictor of ST, no evidence thus far exists on the effectiveness of tailoring antiplatelet therapy on the basis of platelet function tests. Although achieving a more intense platelet inhibition, switching from standard to an intensified treatment regimen has failed to show any benefit in terms of clinical events. The reasons for this lack of benefit are not clear; however, may be related to the selection of antiplatelet strategy or patient population. The option of selecting patients on the basis of genetic profile is also open, although no relevant data are available yet on-treatment tailoring based on genetic testing. Nevertheless, individualized pharmacological treatment in PCI patients represents one major aim in order to prevent ischemic and bleeding complication following percutaneous procedure.

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