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Short Communication

Minimizing Stent Thrombosis with Drug-eluting Stent and Dual-antiplatelet Therapy

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ABSTRACT

Stent Thrombosis (ST) is a rare but serious complication of coronary stents. Untreated cases have higher mortality and recurrence rate. However, the use of Drug–Eluting Stent (DES) and Dual Antiplatelet Therapy (DAPT) have shown to give auspicious reduction in the complication rate. The mechanisms contributing to Stent thrombosis are multifactorial. Addressing the specific underlying pathology with customized optimization of particular stent and antiplatelet usage can bring substantial reduction in ST after stent implantation. Furthermore, advances in preventive imaging modalities have proven to timely identify any unforeseen event of ST allowing early intervention. Additionally, novel medical therapies have been tested, taking into account genotypic factors and individualized risk assessment for both ischemic and bleeding events.

Keywords: Stent thrombosis; Drug-eluting stent; Dual-antiplatelet therapy; Clopidogrel

DESCRIPTION

Stent Thrombosis (ST) refers to the formation of blood clot that block a coronary stent, occurring because the stent doesn't have adequate endothelial coverage within the treated vessel following Percutaneous Coronary Intervention (PCI). This complication is concerning but relatively infrequent, especially with the development of Drug-Eluting Stent (DES) and Dual Anti-Platelet Therapy (DAPT) [1]. ST affects only around 0.5% to 1% of patients within a year, and there is 10% to 25% mortality rate within 30 days [2].

ST is a multifactorial process involving many pathophysiological factors ranging patient associated, lesion related, intra procedural or post procedural. Diabetes and kidney failure are considered strong independent predictors of the most prevalent type of ST with reference to time i.e. sub-acute ST (within 24 hours to 30 days) and Late ST-LST (up to a year). Furthermore ST is also classified on the basis of certainty. Definite ST is when angiographic or pathological confirmation of partial or total thrombotic occlusion within the persistent region is observed. Any unexplained death<30 days of stent implantation is called probable ST; whereas possible ST is defined with any unexplained death beyond 30 days [1].

DES are vascular prostheses with anti-proliferative drug-loaded polymeric matrix coating a metal platform stent Cobalt–Chromium (CoCr) or Platinum–Chromium (PtCr). These alloys provide good radial strength, reduces platelet and inflammatory cell adhesion being advantageous in minimizing in stent restenosis and ST [3].

Polymers used, carry drugs either in biodegradable or in durable form. Biodegradable polymers abolish the long-term implications of inflammation and hypersensitivity of permanent polymer. The anti-proliferative agents used in DES slows reendothelization which predisposes to the development of ST [1].

Second generation DES are preferred over first generation DES due to their superior mechanical performance. They are favored for their reduced risk of LST and VLST especially in high risk patients. They offer thinner, more biocompatible polymer with sustained anti-proliferative drug release which reduces inflammation allowing adequate neointimal growth and endothelization over stent sruts preventing development of ST. Among this class are Zotarolimus-Eluting Stent (ZES) and Everolimus-Eluting Stents (EESs). EES significantly reduce the incidence of MI and ST, making them the safest type of DES [1].

Type of DES used and the complexity of the lesion (unprotected left main disease, more than two lesions per vessel, lesion length ≥ 30 mm, bifurcation lesion with side branch ≥ 2.5 mm, vein bypass graft or thrombus-containing lesion) can influence the risk of events during or after DAPT. With the use of modern DES, early discontinuation of DAPT can be implemented, which provides

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the added benefit by reducing bleeding events in patients at high hemorrhagic risk. A shorter duration of DAPT or a switch from high-potency *P2Y12* inhibitors to clopidogrel might be associated with reduced bleeding without compromising the anti-ischemic protection [1,3]. Intracoronary imaging modalities e.g., *via* Intra Vascular Ultra Sound (IVUS) and Optical Coherence Tomography (OCT), minimize and thus prevent the ST occurrence by allowing early evaluation of risk factors contributing to future ST. Increased strut thickness influence the risk of early ST with definite certainty risk in small vessels and calcified lesions, malposition and evaginations determine the increased risk of late ST [1,3].

DAPT, which includes aspirin plus *P2Y12* inhibitors, is the most effective approach to reduce the risk of ST in the post procedural stage after PCI. Complexity of the lesion can influence the risk of adverse events but it can be modified by use of DAPT. The most important consideration to be done in selecting DAPT drug and duration is the particular patient risk of ischemia or bleeding. Furthermore, managing DAPT duration requires careful evaluation of risk factors involved in mechanism of ST. PRECISE-DAPT score has been formulated to identify DAPT duration considering bleeding risk. Similarly DAPT score helps to identify DAPT Continuation beyond 12 months (Table 1) [1].

Table 1: PRECISE-DAPT score to determine DAPT duration w.r.t bleeding risk.

PRECISE-DAPT score	
Hemoglobin (1 g/dl decrease)	0-15
WBC (10^3 units/µl increase)	0-15
Age (10 years increase)	0-19
Cr clearance (10 ml/min decrease)	0-25
Prior bleeding	0-26
Total	0-100

Note: Baseline hemoglobin was truncated>12g/dland <10g/dl,WBCs countwas truncated >20x103 /µLand <5x103 /µL.Agewas truncated>90 years and<50years.Creatinine clearancewas truncated >100ml/min.
Interpretation:Hemoglobinof10g/dlandWBCs of20,000=15 points each.Cr clearanceof 0=25points.Age>90years=19 points.Priorbleeding has26points.
Score <25-no high risk bleeding=standard DAPT; Score >25-high risk bleeding-short term DAPT

American guidelines for DAPT after PCI, especially considering newer generation DES, recommends continued reduced six months DAPT in the non-ACS group and three months DAPT in patients at risk for bleeding or in low-risk patients with stable angina. High risk patients for ischemia should be kept on 12 months of DAPT. In a study absolute risk reduction of 0.25% in major bleeding with the short DAPT group was observed in comparison to standard term DAPT (0.32% versus 0.57%) [1].

Drug-drug interactions impact the effect of anti-platelet agents. Proton-pump inhibitors (especially omeprazole), lipophilic statins (especially atorvastatin), Ca2+-channel blockers (especially amlodipine), morphine have all been associated with interaction with *P2Y12* inhibitors, which mostly inhibits their antiplatelet activity. Interactions between clopidogrel and parathyroid hormone levels, serum uric acid levels, mean platelet volume and chronic obstructive pulmonary disease, among other factors, have also been reported, leading to high on therapy platelet reactivity, which can potentially lead to increased risk of thrombotic events, including ST [3]. Patients with CYP2C19 Loss-Of Function (LOF) alleles cannot metabolize clopidogrel. This requires optimization with alternative *P2Y12* inhibitor antiplatelet therapy, such as prasugrel and ticagrelor. Although this is not done as routine testing and is limited to patients with high-risk anatomy, high-risk heart failure Killip class IIb patients or in patients with diabetic complications [1].

TAILOR-PCI trial conducted over 12 months follow-up period, focused on genotype-guided selection of *P2Y12* inhibitors in patients carrying *CYP2C19* LOF gene. These patients presented with Acute Coronary Syndrome (ACS) or stable Coronary Artery Disease (CAD) and underwent PCI. The study compared conventional clopidogrel therapy in patients who did not have point-of-care genotyping and found that there was no statistically significant difference in the outcome of ST prevention in comparison to the group undergoing genotype testing [4].

A post-hoc analysis of the TAILOR-PCI trial extracted (*ABCD*-gene) score which ranges from 0 to 38 and includes factors such as Age, Body Mass Index, Chronic Kidney Disease, Diabetes, and Genotyping, to identify patients who are at increased risk of High Platelet Reactivity (HPR) when taking clopidogrel (a score of 10 points or more is considered high risk for ischemia identification). After 12 months the study found that patients with high *ABCD*-gene score had significantly higher rates of primary and secondary adverse ischemic events in comparison to low scorers. This suggests that *ABCD*-gene score helps in identifying individuals who are more likely to experience adverse outcomes e.g., ST, when taking clopidogrel after PCI. This suggests the potential benefits of genotype guided therapy at 3 months in consideration with individual patient factors aiding to select most desired anti-platelet to be continued after PCI (Table 2) [5].

Table 2: ABCD-GENE score to determine clopidogrel use.

ABCD-GENE Score	
Age>75 years	4
Body mass index >30 kg/m^2	4
CKD(GFR<60 ml/min)	3
Diabetes mellitus	3
1 *CYP2C19* LOF allele	6
2 *CYP2C19* LOF alleles	24

DAPT use to reduce the risk of ST, requires optimal duration of DAPT to be continued related to individual risk factors. Numerous randomized, controlled trials and meta-analyses have compared different durations and intensities of DAPT while studying the effects of DAPT discontinuation over time, as a predictor of ST [1] Following are some trials discussing different DAPT durations (Table 3) [1,6-8].

Table 3: Illustrates trials discussing different DAPT durations.

Trials conducted to study DAPT duration	Duration of DAPT used in the trials	Outcomes related to different durations of DAPT

PEGASUS-TIMI 54 trial in patient population with prior MI/PCI (Only study to allow re-introduction of DAPT after period of discontinuation to combat ischemic events). From 2010-2013.	Compared six months and 24 months DAPT(studying specifically used ticagrelor)	Higher major bleeding risk in 24 months group using DAPT, but reduced ischemic events
PRODIGY trial with majority ACS and remaining stable CAD population and various different stent types tested. (Used BMS,EES,PES,ZES)	Compared six months and 24 months DAPT	Higher major bleeding risk in 24 months group using DAPT, especially in CAD patients. PES only showed reduced ST with extended DAPT, contrary to EES which favored shorter DAPT for ST, MACE reduction
ITALIC trial. From 2008-2010 at French sites. From 2012-2013 at European and middle eastern sites. (UsedEES)	Compared six months DAPT to 12 or 24 months DAPT	No difference in ischemic event reduction and major bleeding
DAPT study. From 2009-2011. (UsedE-ZES compared withSES andEES).	Patients treated with prasugrel within 12 months after PCI randomly allocated to stop drugs or allowed to continue till 30 months	Higher mortality and fatality along with moderate/major bleeding with extended DAPT but reduced ST (0.4% *vs.* 1.4%; p-value<0.001) and MACE
RESET trail [6]. (Real Safety and Efficacy of 3-Month Dual Antiplatelet Therapy Following Endeavor Zotarolimus-Eluting Stent Implantation). From 2009-2010	three-month versus 12-month DAPT regimens	EES is non-inferior to SES for TLR at 12 months, with no difference in clinical endpoints, including stent thrombosis. This was maintained at 7 years of follow-up.
OPTIMIZE trial [7]. (Optimized Duration of Clopidogrel Therapy Following Treatment With the Zotarolimus-Eluting Stent in Real-World Clinical Practice). From 2010-2012.	three-month versus 12-month DAPT regimens	Stable coronary artery disease or low-risk ACS treated with zotarolimus-eluting stents, 3 months of dual antiplatelet therapy was noninferior to 12 months for NACCE, without significantly increasing the risk of stent thrombosis.
SECURITY trial [8]. (Second Generation Drug-Eluting Stent Implantation Followed by Six- Versus Twelve-Month Dual Antiplatelet Therapy). From 2009-2014	Six months versus 12 month DAPT durations with second-generation DES	Low-risk population, stable or unstable angina. No differences were observed in definite or probable stent thrombosis at 12 months and BARC type 3 or 5 bleeding at 12 months.

Newer *P2Y12* inhibitors prasugrel was studied in TL-PAS trial. The results showed reduced MI/ ST ischemic events but severe bleeding was documented. Older age (≥75 years), body weight<60 kg, and previous stroke or Transient Ischemic Attack (TIA) were most susceptible population. This paradoxical bleeding risk with use of antithrombotic is called trade-off between bleeding and thrombosis. PLATO trial, a cohort, studied ticagrelor with clear superiority over clopidogrel, with lower incidence of ST. No significant difference in bleeding risk was observed between the two groups [1].

To combat the bleeding risk associated with aspirin, SMART-CHOICE trial, the STOPDAPT-2 trial, and the TWILIGHT study supported the idea of *P2Y12* antagonist monotherapy following a short duration of three months of DAPT with aspirin [1].

CONCLUSION

Intracoronary imaging offers valuable insight in predicting ST development risk. This complication can further be reduced by personalizing DAPT specific to patient ischemia and bleeding risk according to recommended guidelines, along with selection of efficient DES favoring patient outcomes.

REFERENCES

1. Sohail M, Patel P, Midha S, Shukla S, Dhamija D, Bello AO, et al. Identifying the incidence, predictors, outcomes, and prevention of Stent Thrombosis (ST) in post-percutaneous coronary revascularization patients with drug-eluting stents (des): A systematic review. Cureus. 2023. 13; 15(9). C
2. Kirtane AJ, Stone GW. How to minimize stent thrombosis. Circulation. 2011; 124(11):1283-1287.
3. Gori T, Polimeni A, Indolfi C, Räber L, Adriaenssens T, Münzel T. Predictors of stent thrombosis and their implications for clinical practice. Nat Rev Cardiol. 2019; 16(4):243-256.
4. Pereira NL, Bavry AA, Eagle KA. Tailored antiplatelet initiation to lessen outcomes due to decreased clopidogrel response after percutaneous coronary intervention-TAILOR PCI. In Proceedings of the ACC 2020.
5. Capodanno D, Angiolillo DJ, Lennon RJ, Goodman SG, Kim SW, O'Cochlain F, et al. ABCD-GENE score and clinical outcomes following percutaneous coronary intervention: Insights from the TAILOR-PCI trial. J Am Heart Assoc. 2022; 11(4):e024156.
6. Kumbhani D, Bhatt D. Randomized evaluation of Sirolimus-eluting versus Everolimus-eluting stent trial–reset. ACC. 2019
7. Feres F, Costa RA, Abizaid A, Leon MB, Marin-Neto JA, Botelho RV, et al. Three *vs.* twelve months of dual antiplatelet therapy after zotarolimus-eluting stents: The OPTIMIZE randomized trial. Jama. 2013; 310(23):2510-2522.
8. Colombo A, Chieffo A, Frasheri A, Garbo R, Masotti-Centol M, Salvatella N, et al. Second-generation drug-eluting stent implantation followed by 6-versus 12-month dual antiplatelet therapy: The SECURITY randomized clinical trial. J Am Coll Cardiol. 2014; 64(20):2086-2097.