Intrastent Thrombus – What You See Is What You Get? –

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Stent thrombosis following drug-eluting stent (DES) implantation is an uncommon but serious complication. Multiple factors such as stent thrombogenicity, patient/lesion factors, and procedural factors are considered to be involved in its development.¹ Dual antiplatelet therapy (DAPT) has been the cornerstone of prevention of this life-threatening event. However, clopidogrel, the most frequently prescribed thienopyridine, has to be processed twice by the CYP2C19 enzyme to become the active metabolite. Therefore, when clopidogrel is used as a DAPT agent, there has always been a concern over possible reduced efficacy in patients with the poor-metabolizer CYP2C19 genotype.

In this issue, Ichikawa et al² analyze 55 patients with intracoronary angiography, including genotyping of CYP2C19, a marker for clopidogrel metabolism. Among the 55 patients, there were 6 cases of intrastent mural thrombus as assessed by angiography. The authors found that the presence of intrastent thrombus was associated with sirolimus-eluting stent (SES) implantation, poor clopidogrel metabolism genotype, and in-stent yellow plaque. Although there would have been a significant risk of selection bias because of the number of intrastent thrombus patients being only 6, the study provides evidence that the poor-metabolizer genotype could be associated with local thrombus formation. These results are consistent with a previous optical coherence tomography (OCT) study showing high intrastent thrombus formation among patients with CYP2C19*2 allele carrier status.³

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Table 1. Angioscopic Studies of Thrombus Formation Following DES Implantation

Author	Stent	Months	Neointimal coverage grade	In-stent thrombus (%)	Yellow plaque (%)	DAPT
Ichikawa et al ²	SES etc	36 etc	1	13	26	ASA+Clo
Awata et al ⁴	BES vs. SES	9	–	20 vs. 31	80 vs. 69	ASA+Tic
Mitsutake et al ⁵	SES or PES	9	0–1	61	–	ASA+Clo
Yamamoto et al ⁶	SES	6	0–1	29	62	ASA+Tic

ASA, aspirin; BES, biolimus-eluting stent; Clo, clopidogrel; DAPT, dual antiplatelet therapy; DES, drug-eluting stent; PES, paclitaxel-eluting stent; SES, sirolimus-eluting stent; Tic, ticlopidine.

Table 2. OCT Studies of Thrombus Formation Following DES Implantation

Author	Stent	Months	Uncovered strut	In-stent thrombus	DAPT
Sawada et al ³	SES, PES	8	7.0 (non carrier) 6.2 (*2 carrier)	16 (non carrier) 52 (*2 carrier)	ASA+Clo
Choi et al ⁷	SES vs. EES	9	11 vs. 4.4	34 vs. 5	ASA+Clo
Inoue et al ⁸	EES	8	1.6	0	ASA+Clo
Kim et al ⁹	SES vs. ZES	9	12 vs. 0.3	28 vs. 0	ASA+Clo
Kubo et al ¹⁰	EES vs. BES	8–12	3 vs. 9	4 vs. 10	ASA+Clo
Nishinari et al ¹¹	ZES	2.5	0.8	0.04	ASA+Clo
Xie et al ¹²	SES vs. BMS	3	14 vs. 0.1	14 vs. 0	ASA+Tic

BMS, bare metal stent; EES, everolimus-eluting stent; OCT, optical coherence tomography; ZES, zotarolimus-eluting stent. Other abbreviations as in Table 1.

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Intracoronary imaging gives important information regarding thrombus formation following DES implantation. There have been previous studies using angioscopy^{2,4-6} (Table 1) or OCT^{3,7-12} (Table 2) attempting to elucidate that pathologic changes within DES. One of those studies has shown that the frequency of uncovered stent struts was higher, and incomplete stent apposition more frequently observed, in patients receiving SES than in those getting a bare metal stent (BMS).¹² Other OCT studies have shown that intrastent thrombus is more frequently observed in SES compared with second-generation DES.^{7,9} Such findings, including intrastent thrombus, incomplete vascular healing characterized by the presence of uncovered struts, and malapposed struts, were shown to be less common with everolimus-eluting stents than with biolimus-eluting stents;¹⁰ therefore, there may be a minor difference in thrombus formation among second-generation DES. However, it would be safe to say that second-generation DES have fewer uncovered stent struts as well as less thrombus formation as compared with first-generation DES, which is in line with the results of the current study.²

An advantage of angioscopy is its ability to distinguish plaque color behind the stent strut. Recent pathologic studies highlight the importance of neoatherosclerosis occurring early after DES implantation. Yellow plaque following DES implantation may reflect neoatherosclerotic change in the stented segment. The present study has shown that yellow plaque could be associated with intrastent thrombus formation. Because neoatherosclerosis is also reported in second-generation DES,¹³ there may be a risk of thrombus formation after newer generation DES implantation, especially in the longer term.

Although this study showed that intrastent thrombus formation was relatively common, it is important to recognize that this thrombus is different from clinically overt stent thrombosis. Despite the relatively high incidence of thrombus formation previously reported in DES patients,^{3-7,9,10} the presence of stent thrombus is not apparently associated with clinical presentation of thrombosis. In addition, recent clinical studies have found less and less instances of thrombosis with second-generation DES. The advent of new antiplatelet drugs, including prasugrel¹⁴ and ticagrelor, may have also changed the clinical relevance of CYP2C19 genotyping. More clinical data will be necessary to elucidate whether the results of this study have a clinical impact in the recent clinical milieu of newer antithrombotic agents.

Nonetheless, the authors should be commended for their meticulous work and careful observation. Although the event rate with current generation DES is fairly low, stent thrombosis remains a significant clinical issue because of its serious consequences. A recent randomized study showing lower adverse cardiac events with longer DAPT¹⁵ proves that controversies over optimal antiplatelet therapy are far from over. Invasive intracoronary imaging modalities, such as intravascular ultrasound, OCT, infrared spectroscopy, and angioscopy, will continue to provide valuable information in the field of interventional cardiology.

Disclosures

Conflict of Interest: J.A., speaking honorarium: Sanofi, Daiichi-Sankyo, Abbott Vascular, Terumo, Medtronic.

References

1. Honda Y, Fitzgerald PJ. Stent thrombosis: An issue revisited in a changing world. *Circulation* 2003; **108**: 2–5.
2. Ichikawa M, Takei Y, Hamasaki T, Kijima Y. Characterization of patients with angiographically-detected in-stent mural thrombi: Genetics of clopidogrel responsiveness and generations of drug-eluting stents. *Circ J* 2015; **79**: 85–90.
3. Sawada T, Shinke T, Shite J, Honjo T, Haraguchi Y, Nishio R, et al. Impact of cytochrome P450 2C19*2 polymorphism on intra-stent thrombus after drug-eluting stent implantation in Japanese patients receiving clopidogrel. *Circ J* 2011; **75**: 99–105.
4. Awata M, Uematsu M, Sera F, Ishihara T, Watanabe T, Fujita M, et al. Angioscopic assessment of arterial repair following biodegradable polymer-coated biolimus A9-eluting stent implantation: Comparison with durable polymer-coated sirolimus-eluting stent. *Circ J* 2011; **75**: 1113–1119.
5. Mitsutake Y, Ueno T, Yokoyama S, Sasaki K, Sugi Y, Toyama Y, et al. Coronary endothelial dysfunction distal to stent of first-generation drug-eluting stents. *JACC Cardiovasc Interv* 2012; **5**: 966–973.
6. Yamamoto M, Okamatsu K, Inami S, Takano M, Yokoyama S, Ohba T, et al. Relationship between neointimal coverage of sirolimus-eluting stents and lesion characteristics: A study with serial coronary angioscopy. *Am Heart J* 2009; **158**: 99–104.
7. Choi HH, Kim JS, Yoon DH, Hong KS, Kim TH, Kim BK, et al. Favorable neointimal coverage in everolimus-eluting stent at 9 months after stent implantation: Comparison with sirolimus-eluting stent using optical coherence tomography. *Int J Cardiovasc Imaging* 2012; **28**: 491–497.
8. Inoue T, Shite J, Yoon J, Shinke T, Otake H, Sawada T, et al. Optical coherence evaluation of everolimus-eluting stents 8 months after implantation. *Heart* 2011; **97**: 1379–1384.
9. Kim JS, Jang IK, Kim JS, Kim TH, Takano M, Kume T, et al. Optical coherence tomography evaluation of zotarolimus-eluting stents at 9-month follow-up: Comparison with sirolimus-eluting stents. *Heart* 2009; **95**: 1907–1912.
10. Kubo T, Akasaka T, Kozuma K, Kimura K, Fusazaki T, Okura H, et al. Vascular response to drug-eluting stent with biodegradable vs. durable polymer: Optical coherence tomography substudy of the NEXT. *Circ J* 2014; **78**: 2408–2414.
11. Nishinari M, Shimohama T, Tojo T, Shiono T, Shinagawa H, Kameda R, et al. Two-week interval optical coherence tomography: Imaging evidence on neointimal coverage completion after implantation of the Endeavor zotarolimus-eluting stent. *Catheter Cardiovasc Interv* 2013; **82**: E871–E878.
12. Xie Y, Takano M, Murakami D, Yamamoto M, Okamatsu K, Inami S, et al. Comparison of neointimal coverage by optical coherence tomography of a sirolimus-eluting stent versus a bare-metal stent three months after implantation. *Am J Cardiol* 2008; **102**: 27–31.
13. Otsuka F, Vorpahl M, Nakano M, Foerst J, Newell JB, Sakakura K, et al. Pathology of second-generation everolimus-eluting stents versus first-generation sirolimus- and paclitaxel-eluting stents in humans. *Circulation* 2014; **129**: 211–223.
14. Saito S, Isshiki T, Kimura T, Ogawa H, Yokoi H, Nanto S, et al. Efficacy and safety of adjusted-dose prasugrel compared with clopidogrel in Japanese patients with acute coronary syndrome: The PRASFIT-ACS study. *Circ J* 2014; **78**: 1684–1692.
15. Mauri L, Kereiakes D, Yeh R, Driscoll-Shempp P, Cutlip D, Steg G, et al. Twelve or 30 months of dual antiplatelet therapy after drug-eluting stents. *N Engl J Med* 2014; **371**: 2155–2166.