Stent Thrombosis With Drug-Eluting Versus Bare-Metal Stents

Changing trends in the evolution of DES technology.

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The introduction of drug-eluting stents (DES) led to a significant advancement in the field of interventional cardiology by almost eradicating the problem of in-stent restenosis, the Achilles' heel of bare-metal stents (BMS). Randomized trials have demonstrated the superior efficacy of DES in terms of restenosis[1,2] but has raised a new concern over the potential for late and very late stent thrombosis (ST), a phenomenon that was not previously recognized with BMS.[3]

ST is a rare but catastrophic complication of coronary artery stenting, leading to a mortality and myocardial infarction (MI) rate of up to 64.4% at the time of the event and 8.9% at 6-month follow-up.[4] Recognizing the clinical importance of ST and the need for a novel classification, the Academic Research Consortium (ARC) defined ST in terms of timing after stent insertion and evidence of thrombosis (Table 1).[5] Early ST is further divided into acute (within 24 hours) and subacute (24 hours to 30 days). Late ST is defined as 30 days to 1 year, after which, it is considered "very late ST."

RISK FACTORS FOR ST

Many different factors contribute to the development of ST, but they can basically be divided into procedural factors, lesion characteristics, and patient characteristics. Procedural factors include stent underexpansion, malapposition, edge dissection, strut fracture, multiple stents, stent overlap, geographic miss, and residual stenosis and reduced TIMI flow after the procedure.[6-9] Lesion characteristics include long segment of disease, small-diameter vessels, saphenous vein graft lesions, chronic total occlusion, and bifurcation lesions.[6,10,11] Diabetes mellitus, chronic kidney disease, active smoking status, reduced ejection fraction, lack of adherence to or nonresponsiveness to dual-antiplatelet therapy (DAPT), thrombocythemia, advanced age, and hypersensitivity to the polymer or drug are a few of the patient characteristics that contribute to the development of ST.[12]

These established factors, however, cannot completely account for the proclivity of certain patient and lesion characteristics to the development of ST. Clinical and preclinical evidence suggests that after percutaneous coronary intervention (PCI), local hemodynamic factors and low endothelial shear stress contribute to, in conjunction with established factors, modifying arterial response to endothelial injury and increase the risk of ST.[13]

However, it is reasonable to assume that these risk factors and the acute arterial injury resulting from PCI are contributing factors to the development of ST predominantly in the early phase after PCI. Therefore, it is not surprising that initial reports of BMS use revealed an excessively high rate of subacute ST of approximately 20%.[14] As the stent struts endothelialize, the rate of ST declines significantly and becomes very uncommon beyond the initial 30 days.[15] With improvement in PCI techniques, the institution of DAPT, and further innovation in stent technology, the rate of subacute ST with BMS is exceedingly low at approximately 0.9%.[4] Consequently, late and very late ST cannot be attributed to the previously mentioned risk factors for ST and is only rarely observed in patients treated with BMS.[16]

LATE AND VERY LATE ST: A NEW PHENOMENON WITH DES

In 2003, first-generation DES became commercially available after randomized clinical trials demonstrated

TABLE 1. ARC CRITERIA FOR THE DIAGNOSIS OF STENT THROMBOSIS	
Type of ST	**Criteria**
Definite	Angiographic or pathologic evidence of ST
Probable	Unexplained death within 30 days of the procedure or MI at any time in the territory of previous PCI
Possible	Unexplained death occurring 30 days after the procedure

their superiority to BMS in the reduction of in-stent restenosis.[1,2,17-20] The principle mechanism of action for DES is the controlled release (via a polymer carrier on the stent) of either an antiproliferative or immunomodulatory compound that accumulates locally and inhibits the proliferative process that is responsible for in-stent restenosis. However, upon longer-term follow-up, a disturbing trend of an increased rate of late ST was observed. In one study, the incidence of late definite ST with paclitaxel-eluting stents (PES) compared to BMS was significantly higher, with a hazard ratio of 2.11 (1.19–4.23; $P < .017$).[3] Multiple other case reports and clinical studies indicate a small but measurable increase in the rate of late ST in patients receiving first-generation DES, with an estimated incidence of 0.2% to 0.5% per year.[17,21,22]

A possible biological explanation was provided by angioscopy at 20 months of follow-up after implantation of first-generation DES, which demonstrated low-grade neointimal coverage of stent struts due to a delayed healing process well beyond a year.[15] Additionally, a direct relationship between low-grade neointimal coverage and thrombi formation was observed,[15] providing a possible biological explanation for the late ST events with first-generation DES. In addition to a lack of long-term endothelialization, positive arterial remodeling leading to late acquired incomplete stent apposition and persistent local hypersensibility reactions possibly secondary to residual polymer are potential contributing factors in late and very late ST in first-generation DES.[23]

Patient-level data from the major randomized trials of DES versus BMS have subsequently been analyzed to specifically address the incidence of ST and found a small, statistically nonsignificant increase in ST with DES.[24] However, the protocol definition of ST included only events related to the primary device used. In other words, only ST events of the initial stent used were included; if an ST occurred due to a repeat PCI for in-stent restenosis (which, of course, is much more common with BMS), the event was censored (ie, not counted as ST) because it did not occur from the original stent that was implanted.[25] This is the most likely explanation of why the mortality and MI rates are similar between BMS and DES in most studies.

In summary, first-generation DES were spectacularly successful in reducing the rate of in-stent restenosis but at a cost of delayed endothelialization and vessel healing due to increased inflammation secondary to the polymers utilized. This led to higher rates of late ST in the originally implanted stents, but because of a substantial reduction in restenosis, fewer target lesion revascularization procedures were necessary in the DES group. Because the risk of ST is highest immediately after PCI and within the first 30 days, more opportunities for ST as a consequence of repeat procedures were afforded to the BMS group, balancing the overall risk for ST.

SECOND-GENERATION DES: A PROMISE FOR LOWER RISK OF STENT THROMBOSIS?

Although effective in reducing the rates of clinical and angiographic restenosis, first-generation DES lacked many desirable characteristics, including a thin and biocompatible polymer, optimal flexibility, conformability, deliverability, freedom from structural fractures, and hypersensitivity reactions.[26] However, the main impetus for the development of newer DES was the relative bioincompatibility of the polymer, leading to incomplete vessel healing and the risk for ST.

The first of these second-generation DES devices was the zotarolimus-eluting stent (ZES), which has a cobalt chromium platform with a phosphoryl choline polymer. The stent was designed to release approximately 95% of the drug in 15 days. This device was tested in the ENDEAVOR I and II trials and showed a very favorable safety profile with few late and very late ST events compared to BMS.[27,28] In fact, in the ENDEAVOR II trial, a 1,000-patient study comparing ZES to BMS, the overall rate of ST was reduced, albeit not statistically, in the ZES group (0.9% vs 1.7%).[29] ENDEAVOR III, a comparison of the ZES to the first-generation sirolimus-eluting stent showed a significant reduction in cardiac death and MI at 5 years in favor of the ZES (1.3% vs 6.5%; $P = .003$).[30] Similarly, ENDEAVOR IV, which was a comparison with the PES, showed a significant reduction of

cardiac death and MI at 3 years (3.6% vs 7.1%; *P* = .004) and significant reduction in the cumulative incidence of very late ST (0.1% vs 1.6%; *P* = .004) (although the overall rate of ST was not significantly different).[31]

Another second-generation DES is the everolimus-eluting stent (EES), which is also based on a cobalt chromium platform and an acrylic and fluoropolymer. The EES was designed to release 25% of the drug in the first day and 75% by 1 month, with complete release by 4 months. Not only was the polymer more biocompatible, it also retained the deliverability, flexibility, and low strut thickness of its BMS predecessor. The SPIRIT clinical trial program was designed to show the clinical efficacy of the EES. In the SPIRIT FIRST and SPIRIT II trials, the EES showed superiority to BMS[32] and PES,[33] respectively, with consistent reduction in clinical events in favor of EES throughout the 2 years of follow-up. The pivotal SPIRIT IV randomized clinical trial versus the PES demonstrated significant reduction in target lesion failure (6.9% vs 9.9%; *P* = .003), all MI (2.5% vs 3.9%; *P* = .02), Q-wave MI (0.1% vs 0.8%; *P* = .002), and ischemia-driven target lesion revascularization (4.5% vs 6.9%; *P* = .004).[34] Comparisons of ST events between first- and second-generation DES, as well as BMS, on long-term follow-up of major trials are illustrated in Table 2.

In terms of ST thrombosis, the SPIRIT First trial demonstrated no difference in ARC-defined ST events in either arm at up to 5 years of follow-up, with the caveat that the total number of patients enrolled was only 60. The SPIRIT II trial showed no ARC (definite/probable) ST at 1 year of follow-up and only 1% at 2 years, with no subsequent events at up to 4 years. Results of SPIRIT III were consistent with the data from previous trials and showed a numerically low rate of all ST at up to 4 years of follow-up (1.51% vs 1.71% with EES and PES, respectively). The SPIRIT IV results were also in favor of EES, with overall 2-year ST rates of 0.42% versus 1.23% (*P* = .008).[34] Other large trials also looked at ST rates for DES. The BASKET PROVE trial compared EES versus BMS and randomized 2,314 patients for 2-year follow-up. Definite, definite or probable, and possible ST rates were lower with EES (although not statistically significant), with hazard ratios of 0.33, 0.62, and 0.96, respectively.[35]

CAN SECOND-GENERATION DES ACTUALLY REDUCE ST RATES, AND ARE STUDIES POWERED TO DETECT A DIFFERENCE?

Almost all clinical studies comparing different stent types are vastly underpowered to allow estimations of the real ST rates with any degree of confidence secondary to the rare nature of ST events. As previously outlined, if one were to design a clinical trial to demonstrate a doubling of the ST rate with one device over another, the trial would have to enroll at least 8,000 patients to adequately detect a 50% relative increase (1% absolute increase) in the rate of ST, assuming a baseline rate of 2%.[25] There is only one randomized clinical trial comparing first-generation DES with second-generation DES that is adequately powered to detect a difference in ST rates, and the results are currently pending.[36]

A recently published network meta-analysis,[37] including 49 randomized trials comprising 50,000 patients, compared differences in ST between first- and second-generation DES and between DES and BMS. The primary endpoint was prespecified as definite ST at 1 year according to the ARC criteria. Secondary prespecified endpoints included the 1-year rate of definite or probable ST; early, late, and very late ST; and 2-year definite or probable ST. Of note, if multiple episodes of ST occurred in the same patient over a period of time, that patient was counted only once in the cumulative analysis of the 1- and 2-year ST rate. The authors found that EES was statistically superior when compared with BMS

TABLE 2. MAJOR TRIALS OF SECOND-GENERATION DES VS BMS AND FIRST-GENERATION DES FOR ARC-DEFINED DEFINITE/PROBABLE ST

Study	Design	Follow-Up	Incidence of ST	*P* Value
ENDEAVOR II[28]	ZES vs BMS	270 days	0.5% vs 1.2%	*P* = .224
ENDEAVOR III[30]	ZES vs SES	5 years	0.7% vs 0.9%	*P* = 1
ENDEAVOR IV[31]	ZES vs PES	3 years	1.1% vs 1.7%	*P* = .38
SPIRIT First[38]	EES vs BMS	5 years	No events in either arm	NA
SPIRIT II[39]	EES vs PES	3 years	1% vs 2.9%	*P* = .28
SPIRIT III[40]	EES vs PES	2 years	1.3% vs 1.7%	*P* = .77
SPIRIT IV[34]	EES vs PES	2 years	0.42% vs 1.23%	*P* = .008

for all endpoints except definite or definite/probable very late ST. EES was also associated with significantly lower early definite ST when compared with the first-generation DES.

Therefore, the question arises of whether the newer-generation DES can actually have a lower ST rate than BMS. New, more thromboresistent polymers with better coating technology and thinner polymer coats can potentially lead to faster endothelialization and lower rates of late acquired incomplete stent apposition.[41] In addition, newer thin-strut stent designs can potentially reduce the development of adverse hemodynamic factors. Thicker struts produce low endothelial shear stress distal to the stented segment (leading to decreased endothelialization) and high shear stress within the stent (leading to increased platelet activation). The thinner and more streamlined struts of second-generation DES are thought to play a role in the decreased thrombogenicity associated with this type of stent.[13]

Most importantly, however, even if the new-generation DES does not actually reduce ST compared with BMS, the overall ST rate should still be reduced. The reason for this is very similar to the argument of why first-generation DES did not cause an overall increase in ST. Assuming that the ST rate per implanted stent is similar between second-generation DES and BMS, the restenosis rate will be greatly decreased with DES. Therefore, there will be much fewer repeat revascularizations in the DES group and, consequently, less opportunity for ST from repeat procedures. This becomes even more apparent with longer follow-up as repeat revascularization procedures continue to accumulate predominantly in the BMS group. In conjunction with the decreased thrombogenicity of second-generation DES, the results of the previously mentioned meta-analysis indicating lower ST rates with EES versus BMS and first-generation DES can be reasonably explained.

THE ROLE OF DAPT IN PREVENTING ST

The optimal duration of DAPT after stent implantation remains unknown at present. There is conflicting evidence in the literature regarding the benefit of long-term DAPT for reducing ischemic events, given the risk of increased bleeding complications. In one study of approximately 3,000 patients, discontinuation of DAPT was found to be the most powerful predictor of ST in the first 6 months after DES implantation (hazard ratio, 13.74; 95% confidence interval, 4.04–46.68; $P < .001$). Discontinuation of DAPT after 6 months did not however predict the occurrence of ST (hazard ratio, 0.94; 95% confidence interval, 0.3–2.98; $P = .92$).[42]

Similarly, Schulz et al also noted that in a 4-year follow-up of 6,800 patients after DES implantation, the benefit of DAPT was largely confined to the first 6 months after stent implantation.[43] Conversely, patients who were enrolled in the 2-year TYCOON registry had fewer ST events in the 24-month group compared with the 12-month group (0.4% vs 3.0%; $P = .02$), which was largely driven by fewer incidents of very late ST (0% vs 2%; $P = .03$).[44] However, there was no significant difference noted in long-term survival rates with either duration of DAPT.

According to current recommendations from the America College of Cardiology/American Heart Association/Society for Cardiovascular Angiography and Interventions, following DES implantation, DAPT should be continued for at least 12 months after DES implantation unless there is a high bleeding risk.[45] There is a need for larger randomized controlled trials to find a more definitive recommendation. The results of ongoing clinical trials (ie, ISAR SAFE, OPTIMIZE, SECURITY, etc.) will hopefully shed some light on this clinical challenge. Until further results become available, it seems reasonable to continue DAPT for a minimum of 1 year after DES implantation, in particular, in patients with a low risk of bleeding.

CONCLUSION

ST is a rare but catastrophic complication of PCI. Second-generation DES seem to be at least similar to BMS in terms of ST rates and, according to some studies, superior for this outcome. Lower rates of in-stent restenosis, and subsequently fewer repeat revascularization procedures, in addition to a more thromboresistent profile of second-generation DES, could account for this observation. Available data suggest that, in suitable patients, second-generation DES seem to be highly beneficial, with fewer adverse events seen when compared with BMS and with first-generation DES. ■

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