Platelet-Mediated Thrombosis and Drug-Eluting Stents

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Stent thrombosis is an example of device-induced, platelet-mediated arterial thrombosis. Rates of stent thrombosis can vary from <1% to >10% depending on the patient population, genetic predisposition, device type, pharmacological choices, and duration of antiplatelet pharmacotherapy. The *Platelet Colloquium* is an annual academic–industry–governmental think-tank meeting devoted to identifying research challenges in platelet biology and clinical applications. The latest meeting was held in Washington, DC, on January 25 to 26, 2011, and this review summarizes the discussions of biocompatible stent design, platelet function assessment, and prevention of thrombosis via short- and long-term $P2Y_{12}$ platelet receptor antagonism.

Stent Design and Surface-Mediated Platelet Activation

The vascular injury induced by percutaneous coronary intervention (PCI) produces dynamic changes on the surface of human platelets.[1] Activated platelets are among the first cells to arrive at the site of injury. Stent thrombosis results from the interaction of several procedural, anatomic, and genetically determined factors.[2]

Early cellular and inflammatory events are influenced by the properties of the stent or its coating. First-generation drug-eluting stents (DES) used relatively thick struts and durable polymers.[3] Research efforts focused on development of nonerodable biocompatible materials that could control the release of antiproliferative medications over several weeks.[4] In vitro models showed that these devices appeared to be associated with increased platelet activation and adhesion compared with identical bare metal stents (BMS).[5] The continuous presence of a durable polymer and drug has been posited to be partly responsible for delayed arterial healing and enhanced stent thrombogenicity.[6]

Second-generation DES modified some of these components by reducing strut thickness and polymeric drug load.[3] In vitro data suggest that the lower polymeric drug load used in current everolimus-eluting stents may have a more favorable thrombogenic profile than BMS controls.[7] Recent data also suggest that these devices might favorably affect inflammation and vascular healing after DES implantation.[8] In clinical trials, second-generation DES appear to diminish some undesirable biological effects (thrombosis) seen with first-generation DES.[9,10] This finding is supported by recent clinical trial data in the setting of ST-segment elevation myocardial infarction, suggesting that everolimus-eluting stents reduce the risk of late stent thrombosis compared with identical BMS controls in this high-risk population (EXAMINATION trial).[11]

Further research in coating technologies has focused on bioerodable polymeric or polymer-free drug-releasing matrices, potentially allowing the drug-eluting platform to return to its bare metal backbone over several months.[12] Several clinical studies have studied the safety and efficacy of third-generation DES using bioabsorbable coatings (Table 1)[13–21] and polymer-free platforms (Table 2).[22–25] These studies have reported very low rates of late stent thrombosis (LST), while maintaining long-term efficacy.

However, no randomized trial has shown a clear reduction in stent thrombosis with bioabsorbable versus durable polymers. This does not necessarily disprove the concept of durable polymer-induced adverse events; the rates of stent thrombosis may be too low to compare within a randomized trial.[18] Thus, although the concept of complete polymer dissolution is attractive, questions about drug bioavailability, degradation profiles, and rebound inflammation remain.

One alternative strategy is to develop a drug elution vehicle that promotes healing and endothelialization. Although anti-CD34–coated stents have been shown to enhance stent coverage in vitro compared with sirolimus-eluting stents,[26] several clinical studies using this technology have shown restenosis and LST rates comparable to those with other BMS platforms. Thus, a further step would be to promote endothe-

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Table 1. Balloon-Expandable Stents Using Biodegradable Polymers

Stent Type (Manufacturer)	Drug	Stent Material	Polymer Type	Study Type (No. of Patients)	In-Stent Late Loss, mm	Binary Restenosis, %
CoStar (Conor Medical)[13]	Paclitaxel	CoCr	PLGA	Randomized controlled trial (CoStar n=989 vs Taxus n=686)	0.64 vs 0.26*	17.9 vs 4.1*
Supralimus (Sahajanand Medical)[14]	Sirolimus	SS	PLLA PLGA, PLC, PVP	First in man n=100	0.09	0.0
Excel Stent (JW Medical System)[15]	Sirolimus	SS	PLA	Registry n=2077	0.21	3.8
NEVO (Cordis)[16]	Sirolimus	CoCr	PLGA Reservoirs	Randomized controlled trial Nevo (n=202 vs PES n=192)	0.13 vs 0.36*	1.1 vs 8.0*
BioMatrix (Biosensors)[17]	Biolimus A9	SS	Abluminal PLA	Randomized controlled trial BES (n=857 vs SES n=850)	0.13 vs 0.19	20.9 vs 23.3*
NOBORI (Terumo)[18]	Biolimus A9	SS	Abluminal PLA	Randomized controlled trial BES (n=153 vs PES n=90)	0.11 vs 0.32*	0.7 vs 6.2†
SYNERGY (Boston Scientific; NCT01135225)	Everolimus	PtCr	PLGA Rollcoat Abluminal	Randomized controlled trial SD vs (LD vs PROMUS Element n=291)	NA	NA
Combo EPC+drug (OrbusNeich; NCT00967902)	Sirolimus	SS	Abluminal	Randomized controlled trial Combo (stent vs PES; n=180)	NA	NA
Elixir Myolimus (Elixir Medical)[19]	Myolimus	CoCr	Abluminal PLA	First in man n=15	0.15	0
Infinnium (Sahajanand)[20]	Paclitaxel	SS	PLLA PLGA, PLC PVP	Randomized controlled trial Infinnium (n=111 vs BMS n=57)	0.54 vs 0.90†	8.3 vs 25.5*
JACTAX Liberté (Boston Scientific)[21]	Paclitaxel	SS	JAC polymer Abluminal	First in man n=103	0.33	5.2

BES indicates biolimus-eluting stent; BMS, bare metal stent; CoCr, cobalt chromium; EPC, endothelial progenitor cell; JAC, juxtaposed abluminal coating; LD, low dose; NA, not available; PES, paclitaxel-eluting stent; PLA, poly-L-lactide; PLC, 75/25 poly L-lactide-co-caprolactone; PLGA, 50/50 poly DL-lactide-co-glycolide; PLLA, poly-L-lactic acid; PtCr, platinum chromium; PVP, polyvinyl pyrrolidone; SD, standard dose; SES, sirolimus-eluting stent; SS, stainless steel.

*$P \leq 0.001$.

†$P < 0.05$.

lialization by fixing antihuman-CD34 antibody to the DES surface.[26] In a porcine model of coronary restenosis, anti-CD34 antibody-coated sirolimus-eluting stents were associated with greater endothelialization at 3 and 14 days, compared with conventional sirolimus-eluting stents.[26] However, a clear clinical benefit of stents coated with this technology has not been shown. A randomized clinical trial using this dual approach (prohealing and sirolimus elution) is under development.

Preclinical modeling continues to provide meaningful insights regarding the potential for next-generation DES to improve clinical outcomes. For example, bench testing of stent thrombogenicity,[7] combined with computational modeling, appears to correlate with clinical outcomes seen in large randomized trials of second- versus first-generation DES.[9,10] If second-generation DES with durable polymers continue to produce excellent safety profiles, showing the additional value of newer technologies (ie, polymer free-coatings) or fourth-generation DES (bioabsorbable polymers on bioresorbable scaffolds) will become very difficult.

The concept of a fourth-generation, fully bioresorbable polylactide-everolimus DES is especially attractive as a potential way to restore vasomotion and endothelial function to potentially limit any hazard of LST. The challenge will be to show superiority to second- and third-generation DES with respect to major adverse cardiovascular events (MACE) or softer end points (measures of healing or endothelial function).[27,28] Based on likely low rates of clinical events in these future trials,

Table 2. Balloon-Expandable Stents Using Polymer-Free DES Platforms

Stent Type (Manufacturer)	Drug	Stent Material	Delivery Method	Study Type No. of Patients	In-Stent Late Loss, mm	Binary Restenosis, %
AmazoniaPax (Minvasys)[22]	Paclitaxel	CoCr	Abluminal microspray crystallization process	First in man Pax n=16 vs PES n=15	0.77 vs 0.42	NA
BioFREEDOM (Biosensors)[23]	Biolimus A9 (SD and LD)	SS	Microporous surface	First in man SD n=25 vs LD n=25 vs PES n=25	0.08 vs 0.37* 0.12 vs 0.37†	NA
VESTAsync (MIV Therapeutics)[24]	Sirolimus	SS	Nanoporous hydroxyapatite	First in man n=15	0.36	0
Yukon (Translumina)[25]	Rapamycin	SS	Microporous surface	Randomized controlled trial Yukon n=225 vs PES n=225	0.48 vs 0.48	12.6 vs 11.6

CoCr indicates cobalt chromium; DES, drug-eluting stents; LD, low dose; NA, not available; PES, paclitaxel-eluting stent; SD, standard dose; SS, stainless steel.

*$P = 0.001$.

†$P = 0.002$.

Table 3. Completed and Ongoing Randomized Trials of Individualized Antiplatelet Therapy During or After Percutaneous Coronary Intervention

Trial Name	n	Population	Intervention	Control	Primary End Point	Follow-Up	Treatment Effect
GRAVITAS[29] (NCT00645918)	2214	Stable CAD/ACS with high OTR to standard clopidogrel after PCI	Clopidogrel 600 mg LD/150 mg MD+ASA	Clopidogrel 75 mg MD+ASA	CV death, non-fatal MI, stent thrombosis	6 mo	HR 1.01 (95% CI: 0.58–1.76); P=0.97
TRIGGER-PCI (NCT00910299)	2150	Elective PCI with high OTR to standard clopidogrel	Prasugrel 60 mg loading; then 10 mg daily+ASA	Clopidogrel 75 mg MD+ASA	CV death or MI	6 mo	Stopped for insufficient events after 250 patients completed follow-up
ARCTIC[30] (NCT00827411)	2466	Stable CAD/NSTE-ACS undergoing PCI	Platelet function-guided: GPI, high- dose clopidogrel or prasugrel in patients with high OTR)	Conventional: GPI, clopidogrel, prasugrel at doctor discretion	Death, MI, stent thrombosis, stroke, or urgent revascularization	12 mo	NA
TARGET-PCI (NCT01177592)	1500	Nonemergent PCI	Therapy guided by platelet function and/or CYP2C19 genotype: prasugrel in patients with high reactivity or LOF allele carrier	Conventional therapy	CV death, MI, ischemic stroke, urgent revascularization	6 mo	NA

ACS indicates acute coronary syndromes; ASA, aspirin; CAD, coronary artery disease; CI, confidence interval; CV, cardiovascular; GPI, glycoprotein IIb/IIIa inhibitor; HR, hazard ratio; LD, loading dose; LOF, loss of function; MI, myocardial infarction; MD, maintenance dose; NA, not available; NSTE, non-ST-segment; OTR, on-treatment reactivity; PCI, percutaneous coronary intervention.

pooling of several randomized studies likely will be needed to evaluate the long-term efficacy and safety of emerging technologies, including the practical question of whether new designs will allow shorter courses of dual antiplatelet therapy (DAPT).

In Vivo Testing With Platelet Function Assays

Currently, all DES aim to prevent surface-mediated platelet activation through at least 12 months of DAPT—aspirin and a $P2Y_{12}$ receptor antagonist. Clopidogrel is the most commonly used $P2Y_{12}$ antagonist, but its pharmacodynamic effects are variable. As a result, various platelet function tests have been proposed to monitor and guide DAPT in this setting. One potential mechanism for limiting the risk of platelet activation and device thrombosis is to individualize the pharmacological approach according to patient-mediated (not device-mediated) risk.

Previous studies in this regard are limited in several important ways. First, the cutoff values derived from the studied populations (primarily at single centers) were not prospectively confirmed in independent validation cohorts. Further, multivariable models showing independent associations between on-treatment reactivity (OTR) while receiving clopidogrel and outcomes were likely "overfitted"; they included too many covariates for too few events. Finally, these studies did not address whether OTR truly is a modifiable risk factor for future cardiovascular events.

Table 3 shows completed and ongoing randomized studies of individualized antiplatelet therapy during or after percutaneous coronary intervention (PCI).[29,30] Gauging Responsiveness with A VerifyNow assay-Impact on Thrombosis And Safety (GRAVITAS; NCT00645918) was designed to assess whether high-dose clopidogrel would be superior to standard-dose clopidogrel in preventing MACE at 6 months among patients with high OTR after DES implantation.[29] Of 5429 patients screened with the VerifyNow $P2Y_{12}$ test after PCI, 2214 (41%) had high OTR while receiving clopidogrel, defined as >230 $P2Y_{12}$ reaction units. They were randomized to receive either a 75-mg daily maintenance dose of clopidogrel, or another 600-mg loading dose, followed by 150-mg daily maintenance dosing.

The incidence of MACE at 6 months (primary end point) was 2.3% in both groups (hazard ratio [HR], 1.01; 95% CI, 0.58 to 1.76; P=0.97).[29] Stent thrombosis developed in 0.5% of patients in the higher-dose group and 0.7% of the standard-dose group (P=0.42). Bleeding rates did not differ significantly, although the proportions of patients with persistently high OTR were modestly but significantly reduced from baseline at 30 days and 6 months.

A separate observational analysis compared GRAVITAS patients assigned to standard-dose clopidogrel after PCI by the presence (n=1105) or absence (n=586) of persistently high OTR.[31] Patients with high OTR had a nonsignificantly higher rate of MACE than patients without high OTR (HR, 1.68; 95% CI, 0.76 to 3.72; P=0.20).[29] In post hoc analysis, patients with lower levels of OTR after PCI or during follow-up had a significantly lower risk of MACE.[31]

A more recent trial illustrates the difficulty of showing differences between therapies when event rates are low. In July 2009, the Testing platelet Reactivity In patients undergoing elective stent placement on clopidoGrel to Guide alternative thERapy with prasugrel (TRIGGER-PCI; NCT00910299) began enrollment of its 2150 expected patients with stable coronary artery bypass surgery undergoing successful, elective PCI with DES. On March 18, 2011, the sponsor stopped the study after a preliminary, blinded analysis of the first 250 patients to complete follow-up revealed that the trial would not generate enough primary end point events (cardiovascular death or myocardial infarction [MI] at 6 months) for analysis. The study had been designed assuming a 7% incidence of the primary end point for this interval.

Although GRAVITAS did not support treatment with high-dose clopidogrel when 1 platelet function test identified

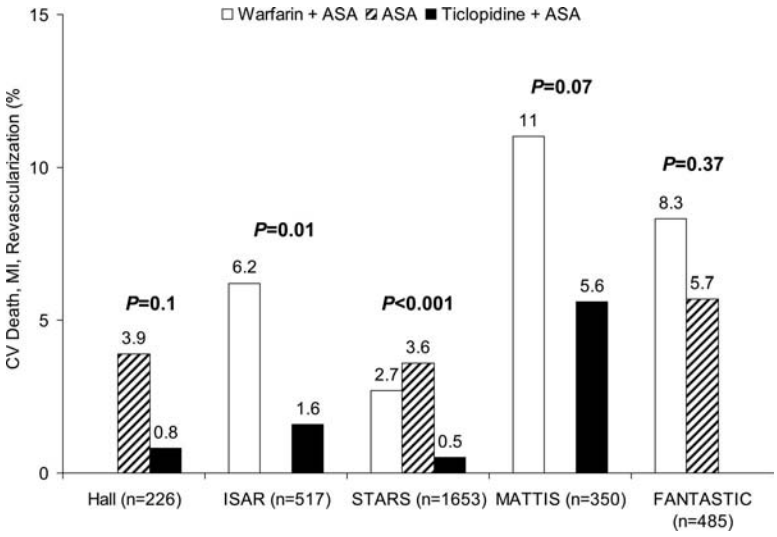

Figure 1. Composite incidence of cardiovascular death, myocardial infarction, or revascularization among randomized trials of warfarin or ticlopidine versus aspirin.[34–38]

high OTR after PCI, it did illustrate some important phenomena. First, OTR was shown to be dynamic for the first month after PCI.[31] Second, the pharmacodynamic effect of the higher maintenance dose was marginal relative to standard dosing in patients with high OTR. Third, the 6-month MACE rate was relatively low with modern DES and techniques used in patients with stable coronary artery bypass surgery. Therefore, very large cohorts will be required to show independent associations between OTR and outcomes, given the multitude of clinical predictors of high OTR and the infrequency of events.

Demonstrating a benefit of antiplatelet therapy tailored to platelet function will be similarly challenging, given the large sample sizes required to provide adequate power to detect outcome differences between treatment groups. Ongoing randomized clinical trials, Thrombocyte Activity Reassessment and GEnoTyping for PCI (TARGET-PCI; n=1500; NCT01177592) and Assessment with a double Randomization of (1) a fixed dose versus a monitoring-guided dose of aspirin and Clopidogrel after DES implantation, and (2) Treatment Interruption versus Continuation, 1 year after stenting (ARCTIC; n=2500),[30] are likely underpowered in this regard. In addition, given the low event rates observed in stable coronary artery bypass surgery patients, the net clinical benefit of potent $P2Y_{12}$ inhibitors in patients with high OTR likely will be narrow. Future studies should focus on larger, "enriched" patient populations (eg, acute coronary syndromes) and longer follow-up. For now, the roles of platelet function testing to determine patient-mediated risk and to tailor antiplatelet therapy to prevent platelet-mediated device thrombosis remain unproven.

The American College of Cardiology/American Heart Association guidelines state that physicians may consider platelet function testing to determine platelet inhibitory response in patients receiving thienopyridine therapy if the results of testing might alter management (Class IIb, level of evidence, B).[32] Similarly, the European Society of Cardiology guidelines state that platelet function testing may be considered in selected cases when clopidogrel is used (Class IIb, level of evidence, B).[33]

Pharmacological Choices and Platelet Activation in DES Thrombosis

In the early stent experience, 5-drug antithrombotic regimens were not uncommon and included aspirin, dipyridamole, dextran, and prolonged heparin followed by warfarin. Despite this intensive therapy, stent thrombosis rates were routinely at or above 5%, with major bleeding rates 2 to 4 times higher. Several randomized trials showed substantial decreases in thrombotic complications with aspirin plus thienopyridine therapy versus either aspirin alone or aspirin plus warfarin (Figure 1).[34–38] These studies highlighted the critical role of using inhibitors of platelet activation (aspirin and $P2Y_{12}$ receptor antagonists) to prevent stent thrombosis. The fact that DAPT not only was a more effective antithrombotic but also significantly reduced bleeding risk compared with a warfarin-based regimen is an important lesson; there needs to be a tradeoff of increased bleeding for improved thrombosis prevention when the correct thrombotic pathway is targeted.

Platelet activation occurs almost immediately after stenting and appears to peak ≈2 to 4 hours afterward.[39] In addition to aspirin, platelet $P2Y_{12}$ antagonists have been the primary agents used to minimize platelet activation. Although clopidogrel has been the gold standard, it has several limitations.[40] Specifically, it was never designed to maximize inhibition of the platelet $P2Y_{12}$ receptor; in fact, it is thought to routinely inhibit only ≈80% of the ≈800 $P2Y_{12}$ receptors on the platelet surface. In contrast, the newer thienopyridine prasugrel and the nonthienopyridine ticagrelor were specifically designed to achieve higher levels of inhibition. These agents appear to block 100% of platelet surface $P2Y_{12}$ receptors.[40] This enhanced antiplatelet effect is likely explained by the more efficient generation of prasugrel's active metabolite compared with clopidogrel's.[41]

Similarly, ticagrelor is a nonthienopyridine $P2Y_{12}$ receptor antagonist with greater potency and more rapid achievement of therapeutic levels compared with clopidogrel. The platelet inhibition and patient outcomes trial showed a significant 16% reduction in the primary end point (death from vascular causes, MI, or stroke) and reductions in stent thrombosis and all-cause mortality with ticagrelor compared with clopidogrel

Table 4. Registries Assessing Outcomes Relative to DAPT Adherence

Study	n	Population	Study Duration	Findings
Airoldi[63]	3021	DES	18 mo	DAPT protective for ST only during first 6 mo; median time to ST with DAPT cessation <6 mo=14 d; 90 d thereafter
Park[64]	2873	Event-free DES	3 y	No reduction in death, MI, ST with DAPT after 1 y
j-Cypher[65]	10 778	SES	2 y	Discontinuation of DAPT, but not of aspirin alone, associated with ST at any time points
Schulz[66]	6816	DES	4 y	DAPT protective for ST only during first 6 mo; median time to ST with DAPT discontinuation <6 mo=9 d; 104 d thereafter
Roy[67]	2889	DES	1 y	DAPT not protective for ST after 6 mo
Van Werkum[68]	21 009	DES, BMS	30.9 mo	ST associated with DAPT discontinuation within 1 y; risk greatest if discontinued <30 d
Petersen[69]	9256	DES	1 y	Prolonged DAPT use associated with greater bleeding risk but lower risk of death or nonfatal MI
e-SELECT[70]	15 147	SES	1 y	ST associated with any DAPT discontinuation within 30 d

BMS indicates bare metal stent; DAPT, dual antiplatelet therapy; DES, drug-eluting stents; MI, myocardial infarction; ST, stent thrombosis.

in patients with acute coronary syndromes. Prasugrel and ticagrelor have different pharmacokinetics and side effect profiles, but both agents increase non-coronary artery bypass surgery related bleeding compared with clopidogrel.[42] The benefit of both prasugrel and ticagrelor with respect to prevention of stent thrombosis has led to US (prasugrel)[32] and European (ticagrelor and prasugrel)[33] Class I guideline recommendations for these more potent agents. Thus, the clinical trial data are consistent with the concept that higher levels of $P2Y_{12}$ inhibition translate into greater protection from thrombotic events compared with clopidogrel.[42,43]

Clinical trials of newer $P2Y_{12}$ inhibitors and novel inhibitors of other platelet thrombin receptors (such as protease activated receptor-1) offer the possibility of enhanced inhibition of platelet activation in various clinical scenarios. Cangrelor and elinogrel are both intravenous nonthienopyridine $P2Y_{12}$ inhibitors (elinogrel also has an oral form). In vitro and ex vivo data show that they provide high levels of inhibition against adenosine diphosphate-induced platelet aggregation, but Phase 3 trials of cangrelor were disappointing.[44] Elinogrel is now entering Phase 3 study, after earlier clinical trials showed promising results.[45] Protease activated receptor-1 inhibitors offer a novel mechanism for minimizing platelet activation with encouraging Phase 2 data,[46–49] but definitive Phase 3 data have yet to be published.

Blocking Platelet-Mediated Thrombosis Over the Long Term

Although devices, pharmacological therapies, patient testing strategies, and development have focused on the general prevention of device-mediated thrombosis, the specific issue of LST has been most readily addressed by extending the duration of PCI pharmacotherapies. Whether new biocompatible/nondurable polymer DES will obviate this need remains to be determined. For the immediate future, the question is not whether extended DAPT is needed to prevent late platelet-mediated thrombosis, but for how long.

Early studies of sirolimus-eluting stents and paclitaxel-eluting stents mandated 2 or 6 months of DAPT.[50,51] In 2006, however, registry data raised concern about the risk of LST-related death and MI.[52,53] A prospective cohort study also had identified premature DAPT discontinuation as an independent predictor of stent thrombosis within the first 9 months among 2229 patients who had been prescribed DAPT for 3 to 6 months after DES implantation.[54] Another large cohort study reported that LST can occur at an annual rate of 0.6% up to 3 years after DES implantation.[55] Long-term concern about LST has been highlighted by findings from the recent SIRolimus-eluting versus pacliTAXel-eluting stents for coronary revascularization (SIRTAX) LATE trial, in which the annual rate of stent thrombosis was 0.65% between 1 and 5 years after implantation of first-generation DES.[56,57] Although careful examination of patient-level data has refuted initial fears of increased mortality after DES implantation, concerns remain about the risk of LST beyond 1 year.

Current guideline recommendations reflect ongoing uncertainty: one set of recommendations calls for 12 months of DAPT after placement of a DES,[58] and the other recommends 6 to 12 months.[59] Clinical practice also varies considerably. In 1 US-based trial comparing everolimus- and paclitaxel-based DES, compliance with DAPT at 2 years was 69%,[60] whereas a European study of the same 2 stents revealed a 15% compliance rate at 2 years.[61] Contrary to US practice, a European Society of Cardiology statement on bleeding complications after PCI recommends that use beyond 12 months after DES placement be the exception, not routine practice.[62] Registry data have not shown a clear benefit for extending DAPT beyond 6 months (Table 4)[63–70] in all patients treated with DES. Clarification of the benefits of 6 versus 12 months of DAPT in stable PCI patients is being investigated in the Intracoronary Stenting and Antithrombotic Regimen: Safety and Efficacy of a 6-month DAT After Drug-eluting Stenting trial (NCT00661206).

In 2006, the US Food and Drug Administration agreed that at least 12 months of DAPT should be recommended for "off-label uses of DES."[71] Simultaneously, the Food and Drug Administration began asking DES manufacturers for studies of the optimal duration of DAPT as a condition of approval. The Food and Drug Administration's Critical Path Initiative created a public–private collaboration, the DAPT

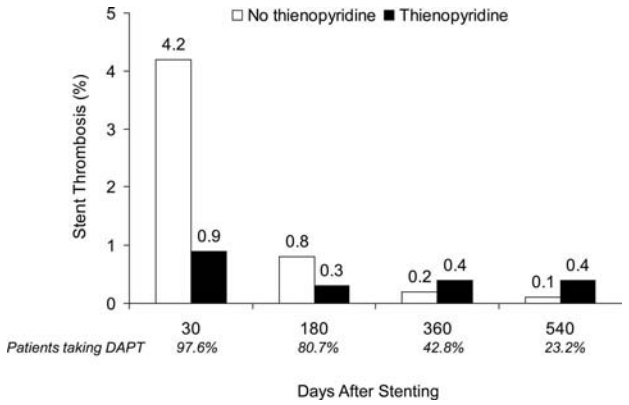

Figure 2. Incidence of stent thrombosis by use of thienopyridine at 30, 180, 360, and 540 days. The proportion of patients taking dual antiplatelet therapy at each time point is shown in italics. Adapted with permission from Airoldi et al.[63]

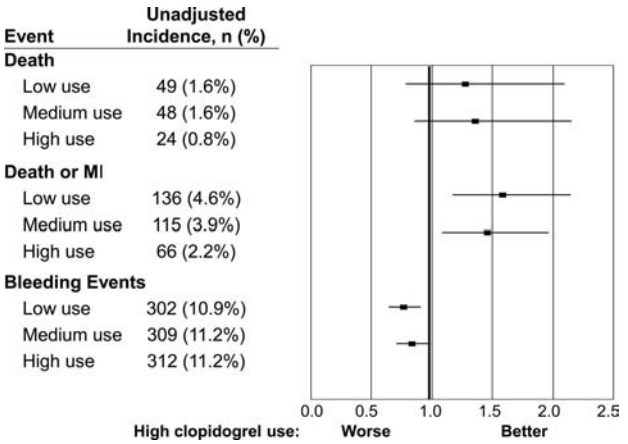

Figure 3. Unadjusted event rates and adjusted hazard ratios (with 95% confidence intervals) for the risks of death, death or myocardial infarction, and bleeding events by level of dual antiplatelet therapy use during the first year after drug-eluting stents implantation. Data derived from Petersen et al.[69]

study (NCT00977938), to address this issue.[72] Four device manufacturers, as well as international government and academic centers, are conducting a randomized, placebo-controlled trial of DAPT (clopidogrel or prasugrel with aspirin) among 20 645 patients who are (1) free from death, MI, stroke, repeat coronary revascularization, major bleeding, or stent thrombosis 12 months after implantation of a DES or BMS, and (2) already compliant with 12 months of DAPT after stent implantation. Eligible patients will be randomized to receive another 18 months of DAPT or begin taking placebo with aspirin. The primary end points are the composite incidence of death, MI, or stroke up to 33 months after stent implantation, stent thrombosis over the same interval, and major bleeding over this interval.

Randomization to prolonged versus 12-month DAPT duration in the DAPT study is expected to be complete in May 2012, and results are expected to be available in the spring of 2014. The study already has had to overcome some challenges, however. For example, the trial design assumed that 80% of patients would be eligible for randomization, but only 60% have satisfied all criteria and agreed to randomization to date. Two further caveats: the study data cannot answer questions about outcome differences by stent type (first- versus second-generation DES) or individual thienopyridine agent, and the trial will have only limited ability to assess the relation between short-term interruptions in DAPT and outcomes.

In the meantime, current practice may be best defined by large registry data (Table 4).[63–70] Most of these analyses identified a protective benefit of DAPT during the first 6 months after DES implantation, but the data conflict regarding subsequent benefit (Figure 2).[63] In addition, benefits at all time points must always be weighed against the potential increase in bleeding risk (Figure 3).[69] Finally, type and duration of DAPT therapies are not the only issues pertaining to this debate; bleeding risk and antithrombotic benefits of DAPT might vary according to aspirin dose[73,74] or regional variations in care.[75]

Once we reach 2014, will we no longer need to rely on postapproval surveillance data and registry studies to determine the optimal duration of DAPT to prevent coronary stent thrombosis? This seems unlikely; pharmacological agents, polymers, stent designs, and practice patterns continue to evolve far more rapidly than does the randomized evidence. It is unlikely that we can perform 20 000-patient clinical trials for each new generation of DES, and it might be false to assume a class effect with respect to device-mediated thrombosis. Thus, preclinical testing and assessment of patient-related risk will continue to be critical. Well-organized registries can continue to offer useful information in this regard, keeping in mind the observational nature of the data collected.

Conclusions

In summary, stent thrombosis cannot be viewed from a singular device, patient, or pharmacological perspective; prevention of platelet-mediated stent thrombosis requires a 3-fold approach focusing on the development of improved polymer systems, assessment of individual patient-related platelet pathophysiology, and optimization of the dose and duration of platelet receptor antagonist therapy:

- Stent thrombosis is an example of acute and delayed device-induced, platelet-mediated device thrombosis.
- Emerging DES platforms are moving toward biocompatible and bioerodable polymers, which aim to prevent potential platelet activation and inflammation associated with early earlier-generation DES designs.
- Although comparative clinical trials will provide an important evidence base, distinguishing the potential advantages of iterative changes in DES design will likely hinge on in vitro testing methods, soft end points (stent healing, endothelial function), and well-designed registry analyses.
- The scientific community still faces the challenges of treating patient-specific risks of platelet-mediated stent thrombosis with point-of-care testing.
- DAPT focusing on $P2Y_{12}$ receptor antagonism has a proven role in preventing platelet-mediated stent thrombosis. The role of newer agents in preventing stent thrombosis is proven, but the optimum treatment duration of DAPT therapy remains uncertain.

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Disclosures

Dr Granada has received grants from Abbott Vascular, Boston Scientific, and Medtronic. Dr Price has received grants from Accumetrics, BMS/sanofi-aventis, and Quest Diagnostics; has had speaker's bureau appointments for Daiichi/Lilly; has received honoraria from BMS/sanofi-aventis, Medtronic, St. Jude Medical, Boston Scientific, and AstraZeneca; and has consulted for Accumetrics, BMS/sanofi-aventis, Daiichi/Lilly, and Medicure. Ms. French has consulted for Regado Biosciences. Dr Steinhubl is a former employee of The Medicines Company. Dr Cutlip has received grants from Medtronic and has consulted for AstraZeneca. Dr Becker has received grants from AstraZeneca, Bayer, and Regado Biosciences; has received honoraria from Johnson & Johnson and Regado Biosciences; and has consulted for Daiichi/Lilly and Boehringer-Ingelheim. Dr Smyth has received grants from AstraZeneca and The Medicines Company, and has consulted for BMS/sanofi-aventis. Dr Dauerman has consulted for Abbott Vascular, Medtronic, and MDS Scientific; has consulted for Abbott Vascular, Medtronic, MDS Scientific, Novartis, The Medicines Company, Gilead, and St. Jude Medical; and has served as an expert witness for the defense in New Hampshire.

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KEY WORDS: platelets ■ stents ■ blood flow ■ thrombosis ■ antiplatelet agents

Supplemental Material

Appendix. Participants in the 2011 *Platelet Colloquium*

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