Despite developments in drug-eluting stent (DES) technology, stent thrombosis (ST) continues to be one of the most feared complications, with high morbidity and mortality after percutaneous coronary interventions (PCI).\(^1\) In addition to procedural and patient-specific factors, the propensity for ST can be influenced by stent design, including features such as strut thickness, polymer coating, and type of antiproliferative drug used.\(^2\) Without question, antithrombogenicity is one of the most important and preferred characteristics for coronary stents. Oral pharmacologic therapy with dual antiplatelet therapy (DAPT; ie, aspirin in combination with a thienopyridine, such as clopidogrel) is the standard strategy after PCI to reduce the risk of ST while healing takes place after stent placement. According to the 2016 American College of Cardiology/American Heart Association guidelines, this standard strategy requires DAPT usage for at least 1 month after bare-metal stent (BMS) use and at least 6 months after DES use in patients with stable ischemic heart disease, whereas patients with acute coronary syndrome require at least 12 months of DAPT.\(^3\)

With decades of research into biomaterial-blood interactions, our understanding of the potential of antithrombotic stent coating technologies continues to evolve. Such an approach offers the possibility of greatly reducing the need for prolonged DAPT,\(^4\) which is associated with an increased risk of bleeding and overall higher mortality after PCI in some analyses.\(^5\)

In this article, we discuss in detail how different coating technologies (eg, durable polymer versus biodegradable polymer) used in DESs can play an important role in shaping the future of antiplatelet therapy after PCI. We examine preclinical and clinical data regarding the antithrombotic effect of stent coatings and summarize how differences in DES polymer coating design may modify DAPT duration.

**DEVELOPMENT IN STENT POLYMERS**

The first commercially available DESs employed durable polymers such as -SIBS (poly(styrene-b-isobutylene-b-styrene)) in paclitaxel-eluting stents (Taxus\(^1\), Boston Scientific Corporation) and polyethylene-co-vinyl acetate and poly(n-butyl methacrylate) (PBMA) in sirolimus-eluting stents (SESs) (Cypher\(^6\), Cordis).\(^6\) In porcine coronary arteries, Cypher\(^6\) implantation was associated with granulomatous and eosinophilic reaction, which is reported to have peaked at 3 months and remained high even at 6 months.\(^6\) Similar rare but overwhelming localized inflammatory reactions leading to ST have also been reported in humans who have received SES implants.\(^7,8\) The timeline of this phenomenon suggests a lack of biocompatibility because these findings tended to occur after the end of the elution of the immunosuppressive drug. Furthermore, along with ST, such inflammation at the stented site has been associated with greater neointimal growth and development of neatherosclerosis over time.\(^9,10\)

With continued evolution of DESs, different durable polymers were applied and side-chain modifications were made to the sirolimus molecule, resulting in analogues such as zotarolimus, with greater lipophilicity, and everolimus. Second-generation DESs, such as the cobalt-chromium everolimus-eluting stent (CoCr-EES) (XEFORE EES, Abbott) is covered by a base layer of PBMA encapsulated by a poly(vinylidene fluoride-co-hexafluoropropylene) (PVDF-HFP), whereas the polymer on Resolute Integrity\(^6\) zotarolimus-eluting stents (Medtronic) consists of a mixture of C10, C19, and polyvinylpyrrolidone polymers (BioLinx). The use of different polymers (in addition to changes in stent platforms) contributed to a reduction in late ST rates relative to earlier-generation DESs.\(^11,12\)

Despite these improvements, the association of durable polymers with potentially harmful effects lingered, and the assumption that BMS had a greater biocompatibility than durable-polymer DESs persisted. Biodegradable-polymer (eg, Synergy\(^9\), Boston Scientific Corporation) and polymer-free (eg, BioFreedom\(^9\), Biosensors International Group, Ltd.) DESs were developed under the assumption that a DES eventually becomes a BMS through polymer degradation and therefore should be more biocompatible.
than a durable-polymer DES. Most biodegradable polymers are synthetic polyesters from the poly (β-hydroxy acid) family, including poly(lactic acid), polyglycolic acid, and their copolymer poly(lactic-co-glycolic acid. The most important question with regard to DAPT duration for these different devices is the relative thromboresistance of these different polymers and whether any would allow shortening of DAPT because of its behavior in the setting of flowing blood.

**BLOOD-MATERIAL INTERACTIONS RELEVANT TO DES**

Stent surfaces are directly in contact with the blood after implantation until neointimal tissue fully covers the stent struts. The behavior and interactions of the stent surface with blood elements is important in understanding the performance of different stents with regard to thrombosis risk. Blood-biomaterial interactions for each stent are different, and these interactions influence whether the surface repels or attracts platelets and prothrombotic blood elements, such as fibrinogen and inflammatory cells. Inflammatory cell adhesion and activation can further promote thrombosis.

Of the polymers in medical applications, fluoropolymers have been well known to be capable of reducing platelet adhesion and activation and thrombosis as compared to nonfluorinated controls. Dependent on degree of fluorine substitution, suppression of platelet adhesion and activation increases accordingly. In the PVDF-HFP coating on CoCr-EESs, more than 50% of the carbon backbone is substituted with fluorine to form a hydrophobic surface. In addition to its role in PCI, fluorinated polymers have been used in vascular grafts to lower thrombogenicity and inflammatory reaction and to promote faster endothelialization, which are ideal properties for stent coatings and vascular devices.

There is considered to be a protective “cloaking” mechanism; when fluoropolymers contact blood, the surface becomes covered by a high concentration of albumin. This albumin binding to fluorinated surfaces prevents more reactive proteins, such as fibrinogen, from adsorbing. The main role of fibrinogen is to stimulate platelet adhesion and activation via their glycoprotein IIb/IIIa receptor at three different sites, resulting in the binding of platelets to fibrinogen.

Thus, through this mechanism of preventative binding, albumin-coated surfaces are thought to have antithrombotic effects. In this regard, Szott et al compared several different types of coating, including PVDF-HFP, PBMA, and polystyrene-b-polysobutylene-b-polystyrene (SIBS1—102T 15% styrene 85% isobutylene, molecular weight [MW] 100,000; SIBS2—103T 30% styrene 70% isobutylene, MW 100,000), and 316L stainless steel (SS). Albumin adsorption from a pure protein solution was higher in order of SIBS1, SIBS2, PBMA, PVDF-HFP, and SS. However, in the situation of flowing blood and removal by blood elements, albumin retention may be more important than its initial binding. When using a detergent (eg, sodium dodecyl sulfate [SDS]) in vitro to evaluate protein retention, the amount of albumin was greatest on PVDF-HFP among all test samples (Figure 1). Higher albumin:fibrinogen ratios are thought to correlate with lower thrombogenicity. In this regard, PVDF-HFP showed favorable results because the albumin:fibrinogen ratio was highest in PVDF-HFP, whereas SIBS2 showed a slightly higher amount of fibrinogen than albumin. When samples were preadsorbed using 1% plasma, adherent platelets were lower in order of PVDF-HFP, SIBS2, PBMA, and SIBS1, albeit without significant differences between them. Also, monocyte adhesion, as a marker of inflammation, is lowest in order of PVDF-HFP, PBMA, SIBS1, SIBS2, and SS, with no significant difference except between PVDF-HFP and SS and between PBMA and SS.

In addition, another type of fluorinated polymer showed similar data to that reported on PVDF-HFP. Poly[bis(trifluoroethoxy)phosphazene] was compared with polymethylmethacrylate, silicone, and other materials (hydroxylated glass, aldehyde-, alkyl-, or amino-terminated surfaces). Poly[bis(trifluoroethoxy)phosphazene] showed the highest human serum albumin on the surface and the
lowest amount of fibrinogen. Collectively, these data have contributed to a better understanding of the potential mechanisms behind the pro/antithrombotic mechanisms of different polymers. However, preclinical studies may provide greater insight into the behavior of different polymers because thrombus formation in vivo is a more complex process than just protein adsorption.

**PRECLINICAL DATA SUPPORTING THE IMPORTANCE OF FLUOROPOLYMERS IN BLOOD-MATERIAL INTERACTIONS**

Acute thrombogenicity of various stent designs and polymer coatings can be evaluated using models that better replicate the complexity of human conditions. An ex vivo porcine arteriovenous shunt model has been developed at CVPath institute. In this model, three DESs are consecutively deployed in Sylgard mock vascular phantoms, and blood flows through the shunt under low-dose heparin conditions for 90 to 120 minutes. In these models, the activated clotting time was targeted to be between 150 and 190 seconds. Stents are assessed for platelet and leukocyte adhesion through immunostaining and evaluation by confocal microscopy. The stents are also evaluated by scanning electron microscopy (SEM) for thrombus evaluation.

Using this model, we examined the acute thrombogenicity of CoCr-EES coated by PVDF-HFP fluoropolymer relative to four different CE Mark-approved biodegradable-polymer DESs: (1) BioMatrix Flex biolimus-eluting stent (BES) (Biosensors International Group, Ltd.); (2) Nobori BES (Terumo Interventional Systems); (3) platinum-chromium EES (Synergy); and (4) Orsiro SES (Biotronik, Inc.). Stents were bisected and stained against specific platelet markers: CD61 as a marker of platelet aggregation (Immunotech, IM0540, dilution 1:100; Beckman Coulter) and CD42b as a marker of platelet adhesion (sc-7070, dilution 1:40; Santa Cruz Biotechnology) to capture both originating and propagated platelet thrombus. Positive staining was visualized using a secondary antibody conjugated to an Alexa Fluor 488 fluorophore (Life Technologies). Fluorescence area indicating platelet aggregation and propagation was least in the CoCr-EES relative to all four biodegradable-polymer DESs (Figure 2). Also, the number of platelet aggregate clots (> 0.1 mm²) was the least in the CoCr-EES. Inflammatory cells that attach to strut surfaces also affect clot formation via platelet-leukocyte interactions. The number of cell nuclei on strut surfaces, as assessed through 4',6-diamindino-2-phenylindole staining and likely indicative of immune cell deposition, was the least in the CoCr-EES. BMSs, which lack a surface coating, were identified as the most thrombogenic stent. Regardless of whether the polymer coatings and/or drug has some protective effect relative to a metal surface, the effects were most pronounced for the CoCr-EES.

In another study, the polymer-free DES (BioFreedom) showed higher platelet adherence relative to CoCr-EES (Figure 3). The abluminal surface of the polymer-free DES may be a contributing factor in the higher acute thrombogenicity that was observed. Higher strut thickness and lack of drug in a luminal side can contribute to higher thrombogenicity in polymer-free DESs. Biolimus A9 is coated only on the abluminal surface of polymer-free DES. When using inflammatory markers for neutrophils (PM-1) and monocytes (CD-14), the inflammatory effect of polymer-free DES was significantly greater than that of CoCr-EES and similar to that of BMS (Figure 4). Aggregated thrombus can provoke inflammatory cell adherence because platelet aggregation on the surfaces is recognized as a trigger to recruit circulating leukocytes (eg, neutrophils and monocytes). In the same study, fluoropolymer-only stents without drugs showed significantly less platelet aggregation as compared to BMS. Interestingly, anti-inflammatory effects in fluoropolymer-only stents without drugs were comparable to BMS, although CoCr-EES with drugs showed significantly lower inflammation relative to BMS. Thromborelaxation due to fluoropolymer coating and anti-inflammatory effect due
to the drug can thus each play an important role in blood-material interactions.

**CLINICAL IMPLICATIONS OF BLOOD-MATERIAL INTERACTIONS ON STENT THROMBOGENICITY IN HUMANS**

The results of the collective experimental findings described thus far indicate that the fluoropolymer coating serves as a protective barrier against acute thrombus formation, and this protective effect of the fluoropolymer is further illustrated through clinical outcomes. Clinical trials and a network meta-analysis reported by Palmerini et al have shown a lower prevalence of ST with CoCr-EES as compared to BMS and early DES use. When analyzing data from 13 randomized clinical trials, CoCr-EES showed significantly lower ST, target lesion revascularization, and myocardial infarction as compared to other stents. In a network meta-analyses conducted by Palmerini et al, the use of biodegradable polymer BES had higher rates of definite ST compared with CoCr-EES at 1 year. The increased risk for definite ST with biodegradable-polymer BES compared with CoCr-EES was apparent both before 30 days as well as between 30 days and 1 year. In another network meta-analysis, Bangalore et al confirmed these findings, demonstrating lower rates of definite ST with CoCr-EES compared to several biodegradable-polymer DESs. Although conformal polymer coatings may have lower thromboresistance than BMS, biodegradable polymer coatings may also have disadvantages in terms of platelet aggregation because of the eventual loss of polymer.

However, when directly comparing the durable fluoropolymer CoCr-EES with biodegradable polymer DES, significant differences in terms of safety have not yet been demonstrated. In the BIOFLOW-II trial (n = 452) comparing CoCr-EES and an ultra-thin strut (61 μm) biodegradable-polymer SES (O-SES, Orsiro†), definite/probable ST was not significantly different (0% vs 0%; O-SES vs CoCr-EES). In unselected populations enrolling 7,640 patients, CoCr-EES was compared with O-SES with propensity score matching and the final study population consisted of 2,902 matched patients. The rate of definite ST did not differ significantly between them (CoCr-EES, 0.8% vs O-SES, 0.8%; \( P = 1.00 \)). Recent meta-analysis enrolling 19,886 patients from 16 randomized controlled trials showed that there were no significant differences of ST between the two DESs. Also, biodegradable-polymer DESs and durable-polymer...
DESs showed similar clinical outcomes regardless of the DAPT duration (≥6 months vs ≥12 months). These trials, however, were all conducted using relatively long periods of DAPT (6–12 months).

**DAPT DURATION**

It remains uncertain whether fluoropolymer coating might provide an advantage relative to biodegradable-polymer DES in curtailing DAPT because of their superior thromboresistant profile, as seen in the preclinical studies referenced previously. In the field of current commercially available DES, the optimal duration for very short (<3 months) DAPT remains unknown. A comprehensive meta-analysis from 10 clinical trials enrolling a total 32,287 patients evaluated the benefits of <12 months of DAPT relative to extended (>12 months) DAPT. The most frequently used stent was CoCr-EES. Short-duration DAPT (3 or 6 months) was associated with lower rates of major bleeding relative to long-duration DAPT (>12 months) (odds ratio, 0.58; 95% confidence interval, 0.36–0.92; P = .02). Also, ischemic or thrombotic outcomes were statistically comparable. Thus, the specific properties of CoCr-EES discussed previously may mean that when implanted in noncomplex lesions, it is feasible to safely shorten the DAPT duration to 3 to 6 months.

However, the conversation regarding DAPT has moved to even shorter durations (<3 months). Within this period of time, stent struts may not be fully covered by endothelium. In animal models, endothelialization of BMSs occurs quicker than with DESs. Therefore, within this early period (<3 months after PCI) the feature of thromboresistance imparted by polymer coatings may be even more important in helping to curtail the need for DAPT. Because of its superior thromboresistant profile, CoCr-EES equipped with fluoropolymer coating may be the most favorable for a short duration of DAPT as compared to other types of DESs.

The first conducted randomized study to assess 1-month DAPT after implanting DES was the landmark LEADERS FREE trial. This study, which included 2,466 patients at high risk of bleeding treated with polymer-free DES or BMS, showed a significantly favorable primary safety endpoint (defined as a composite of cardiac death, myocardial infarction, or stent thrombosis) for polymer-free DES relative to BMS at 1 year (9.4% vs 12.9%, respectively; P = .005), although there was no significant difference of definite or probable ST between them. Additionally, the 2-year results in the same study still showed a favorable primary safety endpoint for polymer-free DES (12.6% vs 15.3%, respectively; P = .039). However, it must be acknowledged that polymer-free DES showed a relatively high rate of definite or probable ST (2%) at 1 year; while comparable to BMS (2.2%), this rate is higher than what is reported for other DESs that use polymers for drug elution. Whether this was due to thick struts or other patient-specific characteristics remains uncertain. One would hope that we could improve on this rate of ST with DES use (such as CoCr-EES) because, as mentioned previously, polymer-free DESs showed greater thrombogenicity than CoCr-EES in the ex vivo pig arteriovenous shunt model.

To date, CoCr-EES has shown promising results for short-term DAPT. The STOP-DAPT study was a prospective, multicenter, single-arm study evaluating 3-month DAPT duration after CoCr-EES implantation. The primary endpoint was a composite of cardiovascular death, myocardial infarction, stroke, definite ST, and TIMI major/minor bleeding at 1 year; 1,525 patients were enrolled from 58 Japanese centers, with complete 1-year follow-up in 1,519 patients (99.6%). Thienopyridine was discontinued within 4 months in 94.7% of patients. The event rates beyond 3 months were very low (cardiovascular death, 0.5%; MI, 0.1%; ST, 0%; stroke, 0.7%; and TIMI major/minor bleeding, 0.8%). These data suggest very promising results for reducing DAPT duration after CoCr-EES implantation.

Additional studies are being conducted to further refine the optimal duration of DAPT. In this regard, the XIENCE 28 Global Study is a prospective, single-arm, multicenter, open-label, nonrandomized trial to further evaluate the safety of 1-month DAPT in subjects at high risk of bleeding who are undergoing PCI with XIENCE EESs. The XIENCE 90 study is a prospective, single-arm, multicenter, open-label trial to evaluate the safety of 3-month DAPT in subjects at high bleeding risk who are undergoing PCI with XIENCE EESs within the United States. Overall, these data will help us to understand whether short duration of DAPT is truly safe in combination with a stent that has consistently demonstrated a favorable thromboresistant profile.

**CONCLUSION**

Despite advances in DES technology, ST is still not infrequent and is associated with high morbidity and mortality. Such data continue to influence physicians to use DAPT for long periods of time, which is associated with an increased risk for bleeding. It is increasingly being recognized that stent related factors, especially coating technologies, have the potential to reduce the risk for ST through favorable blood-material interactions and thus perhaps allow for a shortened duration of DAPT. Fluorinated polymers have shown significant promise in modifying this risk through their interaction with specific plasma proteins, which prevents the adhesion and aggregation of platelets to the stent surface, thus minimizing thrombus formation. Clinical data supporting a role for fluorinated polymers in reducing ST are especially convincing. Thus, it seems likely that CoCr-EES coated by a fluoropolymer may be the most suitable DES for a short-duration DAPT strategy.


