Stent Thrombogenicity Early in High-Risk Interventional Settings Is Driven by Stent Design and Deployment and Protected by Polymer-Drug Coatings

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Background—Stent thrombosis is a lethal complication of endovascular intervention. Concern has been raised about the inherent risk associated with specific stent designs and drug-eluting coatings, yet clinical and animal support is equivocal.

Methods and Results—We examined whether drug-eluting coatings are inherently thrombogenic and if the response to these materials was determined to a greater degree by stent design and deployment with custom-built stents. Drug/polymer coatings uniformly reduce rather than increase thrombogenicity relative to matched bare metal counterparts (0.65-fold; $P=0.011$). Thick-strutted (162 μm) stents were 1.5-fold more thrombogenic than otherwise identical thin-strutted (81 μm) devices in ex vivo flow loops ($P<0.001$), commensurate with 1.6-fold greater thrombus coverage 3 days after implantation in porcine coronary arteries ($P=0.004$). When bare metal stents were deployed in malapposed or overlapping configurations, thrombogenicity increased compared with apposed, length-matched controls (1.58-fold, $P=0.001$; and 2.32-fold, $P<0.001$). The thrombogenicity of polymer-coated stents with thin struts was lowest in all configurations and remained insensitive to incomplete deployment. Computational modeling–based predictions of stent-induced flow derangements correlated with spatial distribution of formed clots.

Conclusions—Contrary to popular perception, drug/polymer coatings do not inherently increase acute stent clotting; they reduce thrombosis. However, strut dimensions and positioning relative to the vessel wall are critical factors in modulating stent thrombogenicity. Optimal stent geometries and surfaces, as demonstrated with thin stent struts, help reduce the potential for thrombosis despite complex stent configurations and variability in deployment. (Circulation. 2011;123:1400-1409.)

Key Words: hemodynamics ■ malapposition ■ overlapping stents ■ stents ■ thrombosis

Stent thrombosis (ST) is a potentially lethal complication of endovascular intervention that arises early after implantation and can persist for years with drug-eluting stents (DES). The steady-state risk of ~0.6% to 1% annually is increased by ubiquitous comorbidities like diabetes mellitus, renal failure, and congestive heart failure, and by use in arterial bifurcations, long lesions, or overlap. Stent-wall malapposition has been observed with intravascular ultrasound in nearly 80% of patients presenting with ST. Importantly, ST incidence increases substantially when multiple risk factors occur simultaneously, exceeding 12% in some analyses.

Clinical Perspective on p 1409

The issue of device and material biocompatibility is not unique to stents; it is a grander issue and must be perceived as contextual rather than constitutive. Thus, stent geometry, material, and coatings can affect thrombogenicity, and it is incumbent on us to define when and how. Given a stent position adjacent to the injured vessel wall and within the flowing bloodstream, it is natural to consider the flow environment, vessel wall, and blood state as contextual elements influencing ST. We evaluated the thrombogenicity of bare and polymer/drug-coated stents using an integrated approach incorporating ex vivo, in vivo, and in silico insights. Well-deployed conformations were compared with high-risk scenarios in which stent-induced flow disruptions arise from increased strut dimension or device malapposition or overlap.

Methods

Ex Vivo Flow Setup

A modified Chandler loop evaluated endovascular device thrombosis. Motor-controlled rotors accelerate blood-filled silicone loops...
Flow loop, reactive sites, and stent configurations. A, Closed flow loop with a 2.5-cm reactive site. Stents are deployed within reactive sites in desired conformations. After a run, the stented segment is excised and flushed. Adherent clot is assessed visually and through lactate dehydrogenase (LDH) quantification. To determine the malapposition threshold, indigo dye was used to detect stent-wall contact. B, Proper stent deployment was modeled with apposed configurations. C, Incomplete stent deployment was modeled with underdeployed configurations. D, Overlapping stents were compared with length-matched controls.

Ex Vivo Comparisons of Basic Stent Design
Stent thrombosis was evaluated in well-deployed and high-risk scenarios in which flow disruptions arise from stent protrusion or device malapposition (see the online-only Data Supplement). Stents were premounted on balloon catheters (Abbott Vascular). Bare metal stents (BMS) with thin struts (81 to 818 m²) with a platform identical to clinical MULTILINK VISION (MLV) stents were compared with custom-built nonclinical stents of identical design but 2-fold thicker (thick-strut VISION [TSV]; 162 to 12 mm; n=8 per group). Apposed DES formulated on the thin MLV backbone (XIENCE V [XVS]; 96 to 96 m², 3.0 to 12 mm) ran concurrently (n=8) to examine the effect of drug/polymer coatings. A range of clinical-build BMS and DES was also tested; 3.0 to 12-mm BMS (MLV, Driver, TAXUS, Bx Velocity; n=6 each) were inflated to 3.2 mm and compared with similarly deployed 3.0 to 12-mm DES counterparts (XVS, Endeavor, TAXUS Liberte, Cypher; n=6 each). Lactate dehydrogenase values (in 485-nm absorbance) were normalized to MLV data.

Ex Vivo Comparisons of Stent Malapposition and Overlap
Devices were apposed to loop walls or underexpanded to a spectrum of stent:wall separation (0 to 60 μm [malapposition threshold], 150 to 210 [intermediate] or 350 to 400 [severe]; Figure 1B and 1C; see also the online-only Data Supplement). All stents were fixed within...
the loops through 15-atm edge inflation. Some MLV stents were fully expanded to 15 atm and compared with thin BMS (MLV), thick BMS (TSV), or thin DES (XVS) submaximally expanded at malaposition threshold (n=8 per group). Apposed MLV devices were compared with the full spectrum of malapposition (n=8 per group). Other stents were overlapped and compared with length-matched controls (Figure 1D). Three configurations were tested with 3.0×18-mm BMS (MLV and TSV) and DES (XVS) so that a 9-mm overlapped region was formed, 33% of the total stented 27-mm length (n=8 per overlap group). MLV (3.0×28 mm; n=8 each) served as single length-matched control.

In Vivo Testing: Effect of Strut Thickness
Four Yorkshire swine (40 to 44 kg) were maintained in accordance with Animal Welfare Act and institutional regulations. Pigs were anesthetized with inhaled isoflurane and local 2% lidocaine; 6F femoral arterial access was obtained. After heparinization, 3.0×12-mm stents were deployed into coronary arteries using standard techniques. Single stents (MLV or TSV) were deployed into the left anterior descending, left circumflex, or right coronary artery of each animal, 6 thin or thick stents in 12 vessels. Deployment was staggered with 2 stents of each type in the 3 arterial positions. Preprocedurally, animals were maintained on normal pig chow diet...
and daily aspirin (600 mg). Clopidogrel (300 mg) was administered before intervention. After the procedure, pigs were continued on aspirin (81 mg) and clopidogrel (75 mg).

After 3 days, the animals were euthanized. Stented segments were harvested (n=6 per stent type), fixed in 10% neutral buffered formalin, dehydrated in ethanol, xylene cleared, and methyl methacrylate resin embedded (see the online-only Data Supplement). Blocks were sawed at proximal, mid, and distal stent planes. Then, 5-μm thicknesses were sectioned and stained with hematoxylin/eosin-Y and Verhoeff–van Gieson elastin stains. Luminal thrombus area was quantified and fibrin content was scored (0=absent, 1=light, 2=moderate, 3=heavy with spans between struts) with Adobe Photoshop (Adobe Inc). Mean values were averaged over the stent length.

**Computational Modeling**

Flow perturbations induced by $81 \times 81$- or $162 \times 81$-μm$^2$ struts (identical to MLV/TSV platforms) were modeled within 3.0-mm lumen at graded wall separation (0 to 320 μm and the centerline flow) with 1.5-cm entrance and exit lengths. Separately, two 10-strut-long stents with 5 overlapping struts were considered. Overlapping struts were congruent (aligned) or noncongruent (offset), ie, struts positioned precisely on top of each other or phase shifted to various degrees with overlapping struts resting between the underlying, apposed struts.

A finite element–based non-Newtonian fluid dynamic module (COMSOL Inc.) solved the Navier-Stokes equations in the arterial lumen (see the online-only Data Supplement). Steady Poiseuille inlet conditions were characterized by typical coronary blood flow and symmetrical vessel characteristics (Reynolds number $\approx 242$). Zero-pressure outlet and no-slip blood-wall interface boundary conditions were imposed. Delaunay triangulation set mesh generation, and the Direct (PARDISO) algorithm solved the linear equations. Mesh density increased with successive simulation until <2% difference in the mean velocity in the distal recirculation zone. This convergence was achieved after 2 successive mesh refinements resulting in 35,648 triangular elements. Iterations for each simulation were performed until the weighted Euclidean norm for the estimated relative error became $<10^{-9}$.

**Statistical Analysis**

All experiments considered apposed MLV stents as a reference facilitating intergroup comparisons. Ex vivo lactate dehydrogenase data are thus provided as normalized ratios, expressed as mean±SD. The Anderson-Darling test for normality was performed on all observational groups (see the online-only Data Supplement). When sample normality was justified, statistical comparisons between observational groups were performed with the unpaired Student $t$ test assuming equal variances. When normality could not be supported, the Mann–Whitney test was used. The $P$ values provided were derived from the Student $t$ test unless otherwise indicated. Experimental differences were statistically significant at $P<0.05$.

**Results**

**Impact of Basic Stent Features**

Thicker stents were 49% more thrombogenic (1.49±0.20; $P<0.001$; Figure 2) and coated stents were less thrombogenic than matched MLV BMS (0.76±0.02 versus 1.00±0.15; $P=0.002$; Figure 2). These relationships held for stents of different designs. Clot mass remained significantly reduced when all DES were pooled as a group and compared with BMS (0.67±0.35 versus 1.03±0.54; $P=0.011$, Mann–Whitney test; Figure 3A and 3B). Thrombogenicity within the various BMS designs correlated with strut thickness (0.88±0.38 for struts <100 μm versus 1.44±0.65 for struts >100 μm; $P=0.036$, Mann–Whitney test; Figure 3C). These same results were observed in vivo. Radiographs of the excised stented coronary arteries confirmed uniform deployment (Figure 4A and 4B). Thick devices demonstrated significantly more thrombus after 3 days, (Figure 4C and 4D) with 62% more clot than with thinner versions (0.21±0.041 versus 0.13±0.019 mm$^2$; $P=0.004$; Figure 4E).

**Impact of Suboptimal Stent Deployment: Malapposition**

Thin- and thick-strut stents with 0- to 60-μm wall separation were more thrombogenic than apposed thin-strut stents (1.58±0.17 and 1.64±0.17 versus 1.00±0.27; $P<0.001$; Figure 5A). The slightly malapposed thin-strut stents carried a thrombotic risk similar to apposed thick-strut stents ($P=NS$; Figures 2 and 5). DES coatings, which reduced BMS thrombogenicity when apposed, continued to limit thrombogenicity malapposed (0.73±0.007; $P=0.037$). There was no statistical difference between thin DES in apposed and malapposed configurations ($P=NS$; Figures 2 and 5).

Intriguingly, malapposition could not explain thrombogenicity until the extent and pattern of flow disruption associated with the strut and wall were introduced. Clot mass was greatest at mild (1.58±0.17) and severe (1.30±0.10) malapposition but less at intermediate strut-wall separation (0.85±0.17; Figure 5B). Strut-induced recirculation changed in size and location depending on wall apposition (Figure 5C and 5D). Recirculation could appear adjacent to the wall or stent; when the strut was close to the wall, they coincided. As strut-wall separation increased, recirculation zones initially remained on the wall, increasing in size. With further displacement, they shifted downstream, losing communication with the strut itself. Eventually, wall-contacting flow disturbances faded away altogether. With greatest wall separation, recirculation reemerged as strut-associated flow disruptions adjacent to and on the downstream aspect of the strut, now apart from the wall and within the flow field.

**Impact of Suboptimal Stent Deployment: Overlap**

Overlapped BMS were more thrombogenic than single-length matched controls, more so for thick struts than thin struts (2.32±0.96 and 3.25±0.11 versus 1.00±0.17; $P<0.001$, Mann–Whitney test; Figure 6A). Moreover, overlapped thin DES (0.51±0.019) were less thrombogenic than overlapped BMS ($P<0.001$) and even single BMS controls ($P<0.001$, both Mann–Whitney test). Overlap increases the amount of stent material and recirculation per unit length compared with nonoverlapped portions, more so for thicker struts. Flow was restored between thin struts and in noncongruent cases in which overlap allowed struts of upper stents to fall between struts of lower devices. When overlapping stents were congruent with struts piled one on top of the other, recirculation increased and was massive, spanning the entire overlapped interstrut regions in thick-strut cases (Figure 6B).
Discussion

Stent thrombosis is catastrophic, and it is feared that the addition of polymeric coatings and drugs increases thrombotic risk.\textsuperscript{6,17} We show here in a controlled model of early ST that clinically relevant polymer-coated stents are consistently less, not more, thrombogenic than matched bare metal platforms, especially in high-risk interventions. More important to ST in our models were the interaction of strut dimension and position relative to the vessel wall and the potential alterations in flow and recirculation imposed by the implanted device. In silico models allowed us to explore further a wide range of application scenarios and device use combinations, demonstrating how thrombogenicity could be modified by synergistic interactions between stent geometry and the local flow environment.

Effects of Strut Geometry

The importance of stent design and strut position relative to the vessel wall on thrombogenicity is not unexpected,\textsuperscript{12} yet not fully supported by clinical data. Stent implantation alters blood-exposed surfaces and luminal flow while creating a foreign stimulus and nidus for clot.\textsuperscript{1,2,18} Doubling the strut thickness nearly doubles foreign material and increases flow separation, stagnation, and reattachment (Figures 4F, 5F, and 6B). Such flow disruptions should enhance platelet deposition and thrombin and fibrin generation.\textsuperscript{19} In the Intracoronary Stenting and Angiographic Results: Strut Thickness Effect on Restenosis Outcome (ISAR-STEREO)\textsuperscript{20–22} trials, thin-strut (50\(\mu\)m) stents elicited less restenosis than thick-strut (140\(\mu\)m) BMS. Also, 96-\(\mu\)m everolimus-eluting devices (XVS) were less thrombogenic than 164- and 132-\(\mu\)m paclitaxel-eluting devices (3% to 0.7%, \(P=0.003\); and 1.1% to 0.3%, \(P=0.004\), respectively) in the Clinical Evaluation of the Xience V Everolimus Eluting Coronary Stent System in the Treatment of Patients with de novo Native Coronary Artery Lesions (SPIRIT) IV\textsuperscript{17} and the Second-Generation Everolimus-Eluting and
Paclitaxel-Eluting Stents in Real-Life Practice (COMPARE) trials. These latter studies implicate strut dimension in ST, but because they considered devices differing not only in thickness but also in delivered drug, elution kinetics, geometric design, material composition, and coating, they do not prove correlation. Indeed, when stents releasing rapamycin-like drugs were compared clinically, thin platforms with rapid elution were not consistently better than thicker, slow-release devices. Our work illuminates the impact of strut dimension on ST as an isolated parameter and begins to explain these seemingly ambiguous and even contradictory clinical findings by incorporating other aspects.

Figure 5. Ex vivo and computational assessment of malapposition cases. A, Thrombogenicity of a thin bare metal stent (BMS) (MULTI-LINK VISION [MLV]), thick BMS (thick-strut VISION [TSV]), and drug-eluting stent (XIENCE V [XVS]) when deployed at their malapposition threshold (0 to 60 μm displacement) compared with apposed MLV controls. B, Clot mass in MLV platforms deployed in mild (0 to 60 μm), intermediate (150 to 210 μm), and severe (350 to 400 μm) malapposed configurations showing a variable response. C, Single-strut 2-dimensional simulations with various displacements showing stent-wall recirculation zones that first grow in size, shift downstream of the stent, lose stent communication, and then fade away altogether. D, Computed flow pattern with severe wall displacements (shown at centerline) depicting re-emergence of strut-associated recirculation; C, D color scale provided in cm/sec. E, Increased visual clot burden observed with severe stent-wall displacement. Depending on the relative thrombogenicities of the wall and stent, the shifting strut-wall recirculation patterns may help explain variability in malapposition-associated stent thrombosis events. LDH indicates lactate dehydrogenase.
of stent design and the context in which the designs are deployed.

Material Effects
Bare metal thrombogenicity has long been recognized. Metals may possess high surface potentials that promote thrombus formation, and corrosion can activate platelets and proinflammatory pathways. Well-designed polymer coatings serve as corrosive barriers and provide thromboresistance through modification of properties such as surface potential, wettability, and roughness. Yet, polymer coatings are often perceived to be less thrombore-sistant and less durable than metal and remain long after drug release is complete. That polymer coatings lowered thrombotic potential compared with BMS in our ST model, even in the face of challenging deployment, requires explanation.

In the era before DES, we found that hydrophobic polymer application to BMS reduced 14-day thrombotic occlusion rate from 15% to 0% (P<0.01) in a rabbit iliac artery. Fluoro-polymeric material and Dacron large artery bypass grafts offer clinical patency similar to venous conduits early in their

Figure 6. Ex vivo and computational assessment of overlap cases. A, Thrombogenicity of a thin bare metal stent (BMS) (MULTI-LINK VISION [MLV]), thick BMS (thick-strut VISION [TSV]), and drug-eluting stent (XIENCE V [XVS]) when deployed in overlapped configurations compared with single, length-matched MLV controls. B, Two-dimensional flow simulations over thin (81 μm) and thick (162 μm) overlapping stents in congruent and noncongruent configurations; color scale provided in cm/sec. Depending on strut alignment, flow disruptions can be augmented in susceptible geometries (as seen by the recirculation zone spanning the overlapped region in congruent thick cases).
Some analyses of clinical ST suggest a reduction in DES-related events compared with BMS shortly after implantation; other studies failed to show substantial differences between DES and BMS thrombosis rates. Despite a possible reduction in early thrombogenicity with polymeric material, fear of DES thrombosis is driven largely by late events in which poor reendothelialization, drug-induced tissue factor expression, inflammation, polymer degradation and hypersensitivity, and late acquired malapposition are observed. Richer definitions of biocompatibility must therefore be invoked to explain clinical DES findings. Although polymer coatings can be thromboreistant, thrombogenicity arises from the bioreponsiveness of time-variant environments, and longitudinal ST risk is a balance of material, flow, and vascular characteristics and responses. Considering the entire context is critical.

Effect of Poor Deployment

Strut malapposition and stent overlap are associated with ST. Intravascular ultrasound studies of older-generation stents reported stent-wall malapposition rates exceeding 20%; more recently, 88% of stented lesions had at least 1 malapposed strut when examined with optical coherence tomography. Malapposition can occur from inadequate deployment, regression of interposed thrombus, or positive tissue remodeling inferior to the strut. Despite efforts to reduce incomplete deployment, the asymmetrical and calcific nature of atherosclerotic lesions alone challenges stent positioning, and some variation in placement is inevitable. Although newer platforms, evolving implantation techniques, and imaging tools reduce malapposition, recent meta-analyses show that DES as a group have more late stent malapposition compared with BMS. When present, poor apposition increased ST risk >6-fold. Many cases of ST have some malapposition, but most malapposition does not result in thrombosis. In our models, malapposition alone could not account for thrombogenicity. Clot mass increased most when struts were displaced a distance similar to the overall strut height. As strut-wall separation grew, thrombogenicity fell and then increased again as struts were displaced far into the flow field. Computational models validated that strut position in the flow field significantly affects patterns of recirculation and stagnation. The shifting flow patterns observed, coupled with respective thrombogenicities of the stent material and vessel wall, may account for variable reports of ST. Large recirculating wall-contacting flows may promote clot when the vessel wall is prothrombotic, eg, when necrotic, poorly reendothelialized, or rich in tissue-factor expression. As struts move further into the free stream, flow recirculation between the strut and wall ceases, maximizing convective wall transport, and then ST is the balance of blood interaction with the stent material and flow alterations induced in the stream (Figure 5D).

As many as 30% of endovascular interventions receive multiple overlapping stents, increasing the mass of foreign material, surface area for clot formation, and likelihood of malapposition. Upper stents cannot be flush to the wall without excessive embedding of the lower device. If lower devices are apposed, the upper stent will protrude significantly into the flow field to an extent directly related to strut dimension. Our data confirm overlap-associated ST risk, correlate strut protrusion with flow alteration, and demonstrate the exacerbation of effect with precise stent overlap alignment. When stents align perfectly, struts lie precisely one on top of another and generate maximal flow disruption; when alignment is out of phase, the extent of flow separation is minimized. Real-life scenarios attain a spectrum of strut positions relative to other overlapped struts, and here the importance of dimensions emerges. As strut thickness increases, alignment can induce massive, global recirculation zones in contrast to the local disruptions associated with thin struts. The improvement provided by new-generation, thinner devices may be accentuated in such complex settings. In the SPIRIT IV trial, thinner devices performed better than thicker platforms as a whole (hazard ratio, 0.67) and twice as well in patients receiving multiple stents per lesion (hazard ratio, 0.33). The thrombogenicity in Context

Williams, among others, insists that biological implants can never be inherently biocompatible, but rather exhibit biocompatibility in specific scenarios. The former is a constitutive, intrinsic property of the implant; the latter is contextual and dependent on application space. Emerging paradigms require that we define biological reactivity on the basis of specific environments rather than material properties of the implants alone. Indeed, platelet activation on stents of different materials was determined by the flow imposed and drugs applied over the stents and to blood. We now extend this scheme to include feedback effects wherein the implant defines its own context by imposing specific flow disruptions. The size and position of stents struts relative to the wall and each other greatly affect the extent and position of recirculation and stagnation. This idea potentially explains how minor degrees of malapposition can be insidiously problematic and, in contrast, how struts can cross the ostium of a branch vessel unnoticed. It also implies that there may well be multiple modes of ST: those that arise by virtue of the thrombopathology associated with flow disruptions and the injured vessel wall, those that arise from flow alterations around stent struts, or those that are created by some combination of the two. With this in mind, endothelial toxicity, tissue factor activation, altered healing, and signaling take on added importance, and issues related to stent deployment become intimately entwined with stent design.

Study Limitations

Ex vivo and computational models add insight into the factors affecting device thrombosis, yet they are simplifications, and their relevance to clinical settings must be considered. Flow loops do not account for vascular wall response (eg, reendothelialization or inflammation), and noncompliant tubing cannot capture complex biomechanical strut-wall interactions. Future flow models incorporating endothelial and smooth muscle cell linings may offer further insight. Still, the models allow methodical examination of highly controlled environments not possible through animal or clinical testing alone. Two-dimensional simulations provide a glimpse of
3-dimensional, time-varying flow fields, the full characterization of which is beyond the scope of this article; elucidation of these flow fields should contribute greatly to future understanding. Our ex vivo flow studies were performed with porcine blood not exposed to antithrombotic agents to provide the greatest degree of control. Drugs can reduce clot formation in our system, but would cloud the central focus of these investigations. Moreover, assessment of thrombus was not fully blinded because quantifying a clot required stent handling and visualization. Finally, the lactate dehydrogenase–based assay provides a sensitive but not specific marker of cellular material. Although lactate dehydrogenase signal correlates with clot weight, the contribution from fibrin formation versus platelet accumulation is not characterized. Such mechanistic understanding could help tailor stent- and environment-specific drug therapies.

Conclusions
Stent thrombosis is a feared and fatal complication. Concerns that polymer/drug coatings are inherently thrombogenic, however, must be reconsidered, because early clotting is reduced by polymer/drug coatings. Strut dimensions are associated with ST, especially in high-risk deployment configurations, but inadequate deployment is not directly causal of ST or pathogenic until one appreciates the flow disruption imposed by strut position. Flow tracking can bring together seemingly disparate data regarding thrombosis and deployment, provide clinical tools for optimal placement, direct the choice of adjunctive medical therapy, and drive future stent design. Optimal designs are likely those that perform well despite inevitable variability in deployment, and characterizing the flow impact of device placement may more appropriately define thrombotic risk.

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References


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**CLINICAL PERSPECTIVE**

Concern remains that stent thrombosis is a price paid for reducing restenosis, particularly with drug-eluting stents. Fear of clotting dictates procedural protocols, adjunctive medication, and device selection. We show here that polymer/drug coatings reduce rather than increase thrombosis early after complex interventions and that stent design and deployment drive thrombogenicity. Thinner devices reduce clot formation, whereas coatings are protective, especially in malapposed and overlap scenarios. Indeed, thin polymer-coated devices exhibit low thrombogenicity even in the most complex settings. By defining clot relative to the flow regimes imposed by struts, our models further explain the lack of consensus in clinical trials that sought to correlate deployment and thrombosis. We show here how well-apposed devices create flow separation upstream and downstream of struts and that clot potential tracks with these zones. As struts move off the wall, the flow-separation zones increase and then reduce as flow is restored beneath struts—clotting peaks and falls synchronous with flow alterations. With further displacement, strut-associated disturbances reemerge, eliciting a different pattern of thrombosis. When struts overlap, displaced struts impose a high-risk flow regime, and small changes in strut dimension or stent configuration elicit global changes in flow. Stent thrombosis differs with the nature of flow disruption, and clinical focus on design or deployment alone must give way to a broader context considering their combined impact on flow. Given the inevitable variability in deployment, the choice of optimal design and/or antithrombotic therapies may now be dictated by these patterns of flow disruption.
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Supplemental Material

A. Experimental Overview

B. Controlling and Quantifying Malapposition

C. Histology Specimen Preparation

D. Computational Modeling Equations

E. Normality Testing

F. Supplemental References
A. Experimental Overview

Figure S1. SCHEMA OF EXPERIMENTAL FLOW  We used ex vivo, in silico (computational), and in vivo models to investigate stent design and deployment effects on thrombogenicity. Shown is a flowchart of the various experiments performed, categorized by the different approaches. Each box represents a specific comparison as detailed in the manuscript. Notably, while in vivo techniques offer highly relevant settings, they are complex and cannot be fully controlled, making detailed parametric investigation difficult. Combined approaches that integrate multiple perspectives can
provide a richer understanding of relevant phenomena by allowing isolation, perturbation, and parameterization of complex biological and physical environments.

**B. Controlling and Quantifying Malapposition**

To guide stent deployment within malapposed samples, stents were deployed in different flow loop segments over a range of inflation pressures (8-16 atm in 1 atm increments). Strut position relative to the wall was imaged with indigo dye injection (see Manuscript Figure 1b-c). Full or incomplete stent apposition was determined by presence or absence of stent contact with the reactive segment wall. The malapposition threshold (MT) for a given stent formulation was defined by the first inflation pressure that failed to achieve full apposition, and found to be 10 atm, 12 atm, and 10 atm for the MLV, TSV, and XVS platforms respectively. In these conformations, strut bends (e.g. the “vertices” of conjoined straight strut elements; Figure S2.A) are wall contacting while the straight strut elements themselves remain as yet unapposed and displaced from the wall.

Given the cylindrical silicone reactive segments into which the stents were deployed, it is possible to estimate the range of strut-wall displacements through geometric considerations; recognizing that real arteries depart significantly from these ideal cases. The MLV, TSV, and XVS stents were chosen because they share a similar platform whose circumference is traversed by 12 diagonal strut elements (Figure S2.A). Assuming the elements are uniformly arranged, an axial projection will yield a polygon (dodecahedron) whose 12 vertices are the strut bends and whose 12 edges are the
straight strut elements (Figure S2.B). This polygon just fits inside a circle of radius $R_{\text{max}}$. At the malapposition threshold (MT), $R_{\text{max}}$ is equivalent to the silicone tube radius, $R_{\text{wall}}$ (3.2 mm / 2 = 1.6 mm). The radius of the inscribed circle that fits within the polygon, $R_{\text{min}}$, the minimum wall displacements, $D_{\text{min}}$, and the maximal wall displacements, $D_{\text{max}}$, are then given by

$$R_{\text{min}} = R_{\text{max}} \cos \left( \frac{\theta}{2} \right) \quad \text{(S1)}$$

$$D_{\text{min}} = R_{\text{wall}} - R_{\text{max}} \quad \text{(S2)}$$

$$D_{\text{max}} = R_{\text{wall}} - R_{\text{min}} \quad \text{(S3)}$$

where $\theta$ is the angle between adjacent struts, or $2\pi/12$.

To consider additional wall displacements, MLV stents were further under expanded using an inflation pressure of 2 atm less than the malapposition threshold pressure (8 atm). This reduced the overall expansion diameter to 2.9 mm as determined from the standard pre-mounted MLV balloon compliance characteristics, yielding an $R_{\text{max}}$ of 1.45 mm in these intermediate cases. Severe strut:wall separation was achieved by expanding MLV slightly to just above their opening pressure (~2 atm), carefully removing the stents from the pre-mounted 3.0 mm balloon, and remounting them on separate 2.5 mm balloons for a uniform 2.5 mm expansion, yielding an $R_{\text{max}}$ of 1.25 mm. It should be noted that in all malapposition cases, the edges were tacked down at 15 atm to keep the stent in a fixed position within the reactive site.

Using the derived values for $R_{\text{max}}$ in the malapposition threshold, intermediate, and severe cases, the estimated ranges of wall displacements are given in Table S1.
Table S1. Estimated strut:wall separation ranges for various malapposition conformations.

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<tr>
<th>MALAPPOSITION DEGREE</th>
<th>$R_{\text{max}}$</th>
<th>$R_{\text{min}}$</th>
<th>$D_{\text{min}}$</th>
<th>$D_{\text{max}}$</th>
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</thead>
<tbody>
<tr>
<td>Threshold (MT)</td>
<td>1.6mm</td>
<td>1.54mm</td>
<td>0.0mm</td>
<td>0.06mm</td>
</tr>
<tr>
<td>Intermediate</td>
<td>1.45mm</td>
<td>1.39mm</td>
<td>0.15mm</td>
<td>0.21mm</td>
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<tr>
<td>Severe</td>
<td>1.25mm</td>
<td>1.20mm</td>
<td>0.35mm</td>
<td>0.40mm</td>
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</table>
Figure S2. Strut:wall separation may be calculated from geometric considerations, assuming (A) symmetric struts comprised of 12 edges and 12 bends (vertices) as in the MLV platform shown in the radiograph. (B) Axial projections of the polygonal stent within a vessel of radius $R_{\text{wall}}$. $R_{\text{max}}$ is the maximal radius circumscribing the polygon and $R_{\text{min}}$ is the radius of the circle fitting within the polygon. $\theta$ is the angle subtended by a strut. The difference between $R_{\text{wall}}$ and $R_{\text{max}}$ and $R_{\text{min}}$ yield an estimated range of strut:wall separations.
C. Histology Specimen Preparation

Following excision, the stented segments were dehydrated though serial submersions in graded ethanol baths (75%, 90%, 95%, then three incubations in 100%). Following clearance in 100% xylene, the segments were infiltrated with a methyl methacrylate (MMA) resin (50% xylene / 50% MMA, then two cycles of a mix of MMA, butyl methacrylate, polyethylene glycol 400, and benzoyl peroxide) and polymerized using dimethyl-p-toluidine as described in detail elsewhere.\(^2\)

D. Computational Modeling Equations

The continuity and momentum equations

\[
\nabla \cdot \mathbf{v}_f = 0 , \quad \text{and} \\
\rho \left[ \frac{\partial \mathbf{v}_f}{\partial t} + \mathbf{v}_f \cdot \nabla \mathbf{v}_f \right] = -\nabla P + \nabla \cdot (\mu \nabla \mathbf{v}_f)
\]

\[(S4) \quad (S5)\]

were solved in the arterial lumen, where \(\mathbf{v}_f, \rho = 1060 \text{ kg/m}^3, P\) and \(\mu\) are the velocity, density, pressure and effective viscosity of blood, respectively. Stent implantation causes local flow separation and re-attachment regions juxtaposed to the stent struts characterized by low shear rates. With the aim of capturing such non-Newtonian flows, the simulation accounted for dynamic blood viscosity using the Carreau model

\[
\mu = \mu_\infty + (\mu_0 - \mu_\infty) \left[1 + (\lambda \dot{\gamma})^2\right]^{-0.375}.
\]

\[(S6)\]
Here $\mu$ is the effective blood viscosity, $\mu_w = 0.0035$ kg/m.s and $\mu_0 = 2.5$ kg/m.s are the blood viscosities at infinite and zero shear rates, respectively, $\dot{\gamma}$ is the shear rate, and $\lambda = 25$ s is a time constant.\textsuperscript{3, 4}

**E. Normality Testing**

Normality testing was performed on all sample groups. Table S2 lists the various groups and their associated p-value as determined using the Anderson-Darling test. A level of significance ($\alpha$-level) of 0.10 was selected to increase the likelihood of rejecting the hypothesis that the data fit a normal distribution (null hypothesis). Statistical comparisons using groups where $p \leq \alpha$ (as highlighted in the table) were performed using the nonparametric Mann-Whitney test. When the normality hypothesis was not rejected, the unpaired Student's t-test was used.
Table S2. Anderson-Darling derived p-values for experimental data.

<table>
<thead>
<tr>
<th>FIGURE</th>
<th>SAMPLE GROUP</th>
<th>P-VALUE</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>ML VISION™</td>
<td>0.26</td>
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<tr>
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<td>TS Vision</td>
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<tr>
<td></td>
<td>XIENCE™ V</td>
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<tr>
<td>3A</td>
<td>BMS (Pooled)</td>
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<tr>
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<td>0.069</td>
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<tr>
<td>3C</td>
<td>Thin BMS (&lt;100um)</td>
<td>0.060</td>
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<tr>
<td></td>
<td>Thick BMS (&gt;100um)</td>
<td>0.75</td>
</tr>
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<td>4E</td>
<td>ML VISION™; Thrombus area</td>
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</tr>
<tr>
<td></td>
<td>TS Vision; Thrombus area</td>
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<tr>
<td></td>
<td>ML VISION™; Fibrin Score</td>
<td>&lt;0.005</td>
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<td></td>
<td>TS Vision; Fibrin Score</td>
<td>0.409</td>
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<td>In-Vivo Data</td>
<td>ML VISION™; Apposed Control</td>
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<td>ML VISION™; Malapposed (0-60µm)</td>
<td>0.56</td>
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<tr>
<td></td>
<td>TS Vision; Malapposed (0-60µm)</td>
<td>0.34</td>
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<tr>
<td></td>
<td>XIENCE™ V; Malapposed (0-60µm)</td>
<td>0.88</td>
</tr>
<tr>
<td>5B</td>
<td>ML VISION™; Malapposed (0-60µm)</td>
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<tr>
<td></td>
<td>ML VISION™; Malapposed (150-210µm)</td>
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<td></td>
<td>ML VISION™; Malapposed (350-400µm)</td>
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<td>ML VISION™; Apposed (Not shown)</td>
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<tr>
<td>6A</td>
<td>ML VISION™; Apposed Control</td>
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<tr>
<td></td>
<td>ML VISION™; Overlap</td>
<td>0.009</td>
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<td></td>
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<tr>
<td></td>
<td>XIENCE™ V; Overlap</td>
<td>0.58</td>
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F. Supplementary References


초기 스텀트 혈전은 스텀트 strut의 두께가 작으면 덜 생기며, 폴리머와 약물 코팅에 의해서는 오히려 예방된다

조 상호 교수 한림대학교 성심병원 순환기내과

Summary

배경
스템트 혈전증(stent thrombosis)은 혈관 중재술에서 약 5~10%의 합병증으로, 스텀트 내 전단과 약물 코팅의 두께와 관계가 있는 것으로 알려져 있다. 본 연구에서는 약물 코팅 스텀트의 혈전 생성을 증가시킨다고 할 수 있는 결과를 얻는 데에 있어, 폴리머와 strut의 두께가 혈전 생성에 미치는 영향을 알아냈다.

방법 및 결과
약물방출스템트(drug-eluting stent, DES) 코팅이 태생적으로 혈전 생성을 조장하는지, 만약 이 물질에 대한 반응이 스텀트 디자인과 약물 도포 방법에 많이 좌우되는지 여부를 알아낼 목적으로 시행하였다. 약물/폴리머 코팅은 오히려 혈전 생성을 감소시킨 결과를 보였고, 폴리머 코팅은 strut의 두께와 스텀트의 혈관 벽에 대한 상대적인 위치가 스텀트 혈전증 발생의 매우 중요한 위험인자였다. 이는 스텀트의 코팅과 입상 방법의 이상성에도 불구하고 스텀트 혈전증을 감소시키는 데 도움이 될 것임을 드러냈다.

결론
이미 알려진 개념과는 달리 약물/폴리머 코팅은 그 자체가 태생적으로 급성 스텀트 혈전 생성을 조장하지 않으나, 약물 코팅의 두께와 스텀트의 혈관 벽에 대한 상대적인 위치가 스텀트 혈전증 발생의 매우 중요한 위험인자이다. 이는 스텀트의 코팅과 입상 방법의 이상성에도 불구하고 스텀트 혈전증을 감소시키는 데 도움이 될 것이다.
Commentary

급성 관동맥주 aprox. 안정형 혈심증 치료에 많이 이용하는 스텐트 삽입술의 가장 큰 단점이자 이슈는 스텐트 절착증이다. 스텐트 절착증의 유발 원인으로는 환자가 지닌 요인(예: 안정 심부전, 당뇨병, 심부전, 약물 복용)과 병변 자체의 특성(예: 분지부 병변, 긴병변, 급성 심근경색) 및 스텐트 자체의 요인(polymet, drug, stent material, stent geometry)을 들 수 있는데, 본 연구는 스텐트 자체의 요인이 무엇인지에 대해 보다 세부적 분석한 연구이다.

주요 결론은 스텐트 strut의 두께가 두꺼울수록 혈전 생성이 잘 일어나서 두꺼운 일반금속스텐트가 없는 일반 금속스텐트보다 절착 생성이 적었고, 금속과 약물 스텐트의 비교에서는 약물방출스텐트에서 가장 적었다.(Figure 1, 2). 2세대 약물방출스텐트인 Xience-V가 기존의 스텐트 절착증을 적게 일으켰다고 알려진 일반금속스텐트에 비해서 오히려 초기 절착 생성이 적다는 사실은 매우 놀라운 결과이다(Figure 1). 약물방출스텐트의 약물과 polymer가 오히려 초기 혈전 발생을 억제시킨다는 것이다. 또한, 잘 알려진 대로 급변환 스텐트나 혈관벽에 밀착한 등이 스텐트가 끼지 않는 경우(malapposition)에도 절

Figure 1. 생체 외에서 얻은 일반금속스텐트(ML Vision, MIV)와 두꺼운 일반금속스텐트(TS Vision, TSV) 그리고 약물 방출스텐트인 Xience V의 혈전 생성 경향

![Figure 1](image_url)

[Bar graph showing the adherence of stents of different materials to the vessel wall]
한 개념으로만 알고 있었던 여러 내용에 대한 구체적 증거를 마련했다는 데에 큰 의미가 있는 성과이다. 본 연구를 고려한다면 biodegradable polymer, thin strut drug-eluting stent이 현재 가장 이상적인 스테트일 아론적 가능성이 있다. 즉, 초기 혈전증은 polymer로 막고 후기 혈전증은 polymer가 사라지면서 감소하며 동시에 thin strut으로 혈전의 위험을 극소화 시킬 수 있기 때문이다. 또한 혈전증의 예방을 위해서는 스테트 삽입 시에 좀 더 정확하게 혈관벽에 달착시키는 시술자의 노력도 함께 필요하다고 하겠다. 후후 발전이 잘 부분으로는 스테트 strut의 모양, 약물방출이 혈관벽으로만 이루어지는 경우 및 스테트의 디자인이 혈류 변화와 혈전 생성에 미치는 영향들이 있겠다.

Figure 2. 생체내 혈전 생성 경향의 대비 관찰등록에서 얻은 MULTI-LINK VISION(ML Vision, MLV) 스테트와 두꺼운 thick-strut VISION(TS Vision, TSV)의 비교. AE일 FU로 확장된 MLV와 TSV 스테트 C와 D의 삽입 후 3일째의 H&E 염색. E: 스테트에 부착된 혈전 분석. F: 각 스테트의 혈류 역학의 변화 모델.