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Role of Endothelial Shear Stress in Stent Restenosis and Thrombosis

Pathophysiologic Mechanisms and Implications for Clinical Translation

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Restenosis and thrombosis are potentially fatal complications of coronary stenting with a recognized multifactorial etiology. The effect of documented risk factors, however, cannot explain the preponderance of certain lesion types, stent designs, and implantation configurations for the development of these complications. Local hemodynamic factors, low endothelial shear stress (ESS) in particular, are long known to critically affect the natural history of atherosclerosis. Increasing evidence now suggests that ESS may also contribute to the development of restenosis and thrombosis upon stenting of atherosclerotic plaques, in conjunction with well-appreciated risk factors. In this review, we present in vivo and mechanistic evidence associating ESS with the localization and progression of neointimal hyperplasia and in-stent clotting. Clinical studies have associated stent design features with the risk of restenosis. Importantly, computational simulations extend these observations by directly linking specific stent geometry and positioning characteristics with the post-stenting hemodynamic milieu and with the stent's thrombogenicity and pro-restenotic potential, thereby indicating ways to clinical translation. An enhanced understanding of the pathophysiologic role of ESS in restenosis and thrombosis might dictate hemodynamically favorable stent designs and deployment configurations to reduce the potential for late lumen loss and thrombotic obstruction. Recent methodologies for in vivo ESS profiling at a clinical level might allow for early identification of patients at high risk for the development of restenosis or thrombosis and might thereby guide individualized, risk-tailored treatment strategies to prevent devastating complications of endovascular interventions. (J Am Coll Cardiol 2012;59:1337–49) © 2012 by the American College of Cardiology Foundation

Intracoronary interventions have revolutionized the treatment of coronary artery disease, yet their clinical benefit may be compromised by in-stent restenosis (ISR) and stent thrombosis (ST). Several patient-specific characteristics including ubiquitous comorbidities, insufficient antiplatelet therapy, and lesion-related and procedural factors including extensive tissue injury and incomplete stent apposition or underexpansion can precipitate ISR and ST (1). These established factors, however, cannot entirely account for the proclivity of certain patients, lesions, or stent types to the development of complications. Local hemodynamic factors, low endothelial shear stress (ESS) in particular, critically affect the formation, progression, and heterogeneity of atherosclerotic plaque (2–7). Emerging preclinical (8–12), and clinical (13–16) evidence now suggests that low ESS may also contribute to the occurrence of complications upon stenting of atherosclerotic lesions, in conjunction with well-appreciated risk factors. Stent-induced changes in arterial geometry and, consequently, in flow and ESS patterns modify the arterial response to endothelial injury, thereby increasing the risk of ISR and ST.

The purposes of this review are to present in vivo and mechanistic evidence associating ESS with ISR and ST and to discuss potential clinical implications of these pathobiological associations. Enhanced understanding of the pro-restenotic and prothrombotic effect of adverse ESS patterns may guide stent designs and implantation configurations with improved hemodynamic performance, which might translate to improved anatomic and clinical outcomes.

Stent-Induced Changes in ESS

ESS, the tangential stress derived from the friction of flowing blood on the endothelial surface, is determined by flow velocity and by the presence of geometric asymmetries or obstructions (2). Implantation of rigid stent frameworks imposes acute alterations

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Abbreviations and Acronyms

BMS = bare-metal stent(s)
DES = drug-eluting stent(s)
ESS = endothelial shear stress
ISR = in-stent restenosis
MB = main branch
NIH = neointimal hyperplasia
SB = side branch
SMC = smooth muscle cell
ST = stent thrombosis

to the 3-dimensional arterial geometry and creates focal geometric irregularities related to strut protrusion (17). These vascular deformations modify flow velocity profiles, reduce the post-implantation ESS along the entire length of the stent, and alter the focal in-stent ESS distribution (18).

In addition to acute, stent-induced geometric and flow changes, subsequent neointimal hyperplasia (NIH) also alters arterial geometry and thereby the long-term hemodynamic milieu (19). With the progression of ISR, local ESS may exhibit temporal changes that are affected by, and in turn modulate, the neointimal response. This dynamic interplay resembles plaque-induced changes in ESS that dictate additional growth of native atherosclerotic plaque (Fig. 1) (4,20).

In Vivo Studies Associating Low ESS With ISR

Animal studies. Artificial ESS increase by application of a flow divider in stented rabbit iliac arteries provided direct mechanistic evidence that high ESS attenuates NIH through decreased inflammation, decreased elastic lamina fragmentation, and decreased smooth muscle cell (SMC) migration (8). Consistently, the most pronounced NIH developed in regions with decelerated flow velocity, low ESS, and elevated ESS gradients at implantation (9) (Fig. 2A). Focal distribution of ISR could thereby be predicted by the preceding ESS distribution, although the localization of NIH close to struts might also suggest the contribution of strut-induced tissue injury to the focal neointimal response. While these animal studies provide valuable mechanistic insights into the effect of low ESS on ISR, direct clinical extrapolation might be limited by differences in the histology of NIH between animal models and humans (21).

Human studies. Wentzel et al. (13) first showed an inverse relationship between ESS magnitude and the extent of ISR in bare-metal stent (BMS)–treated coronary arteries. In a serial study by Stone et al. (3), however, NIH at 6-month follow-up occurred at virtually all levels of baseline ESS. Methodological differences mainly regarding flow measurement might explain the contradictory results of these 2 pioneer studies. Later investigations consistently demonstrated an inverse relationship between ESS and ISR after BMS implantation (14,15,22) (Fig. 2B). Notably, ISR did not develop in all low-ESS sites, and, conversely, not all sites of ISR originated from low-ESS regions in these studies, likely indicating the contribution of other factors, such as lesion complexity, plaque inflammation, and the magnitude of direct tissue injury. Regarding drug-eluting stents (DES), ISR occurred more extensively in low-ESS regions after sirolimus-eluting stent (16) and paclitaxel-eluting stent (23) implantation. Only 1 relevant study found no relationship between ESS and neointimal thickening in sirolimus-eluting stent–treated lesions (24), which was likely related to the patients' diabetic status in that investigation.

Role of Low ESS in the Pathobiology of Restenosis

NIH represents an excessive healing response to endothelial injury. Migration of SMCs, the main cellular substrate of NIH, is dictated by injury-induced inflammation (25) and is affected by several risk factors of ISR (1). Low ESS likely exerts a synergistic pathobiological effect in this process (Fig. 1C). With BMS implantation, by which the endothelium is restored within weeks after implantation, low ESS conceivably promotes ISR through interactions of shear-sensing endothelial cells with SMCs (26). With DES implantation, by which re-endothelialization is retarded pharmacologically (27–30), ESS may act on SMCs directly via endothelium-independent mechanisms.

Endothelium-mediated effect of low ESS. Low ESS up-regulates proinflammatory genes, including adhesion molecules, chemoattractant chemokines, and cytokines (2), thereby enhancing injury-induced inflammation. In addition, low ESS promotes the activation, proliferation, and migration of SMCs by increasing the expression of platelet-derived growth factor (31), endothelin-1, and vascular-endothelial growth factor and by attenuating endothelial expression of plasminogen activator inhibitor 1, an inhibitor of SMC migration (32).

Endothelium-independent effect of low ESS. SMCs per se are responsive to hemodynamic flow (33). Vasculoprotective laminar flow inhibits SMC proliferation and migration (34) by down-regulating platelet-derived growth factor and by promoting the autocrine effect of transforming growth factor-β, a potent SMC proliferation suppressor (35). Conversely, low ESS promotes SMC proliferation and migration, independently of the effect on endothelial cells (36).

Effect of low ESS on SMC phenotype. Neointimal SMCs shift from a quiescent, contractile phenotype to a synthetic phenotype. The phenotype of SMCs is clinically highly relevant because synthetic SMCs produce more extracellular matrix molecules and thus add more to the neointimal buildup. Low ESS favors synthetic SMCs (37) through up-regulation of the SMC differentiation repressors platelet-derived growth factor and KLF-4 (38) and thereby amplifies the naturally occurring synthetic state of neointimal SMCs.

Modifiable Factors That Influence the Pro-Restenotic Effect of Low ESS

Stent type: BMS versus DES. Evidence exists that low ESS exerts a differential pro-restenotic effect in BMS

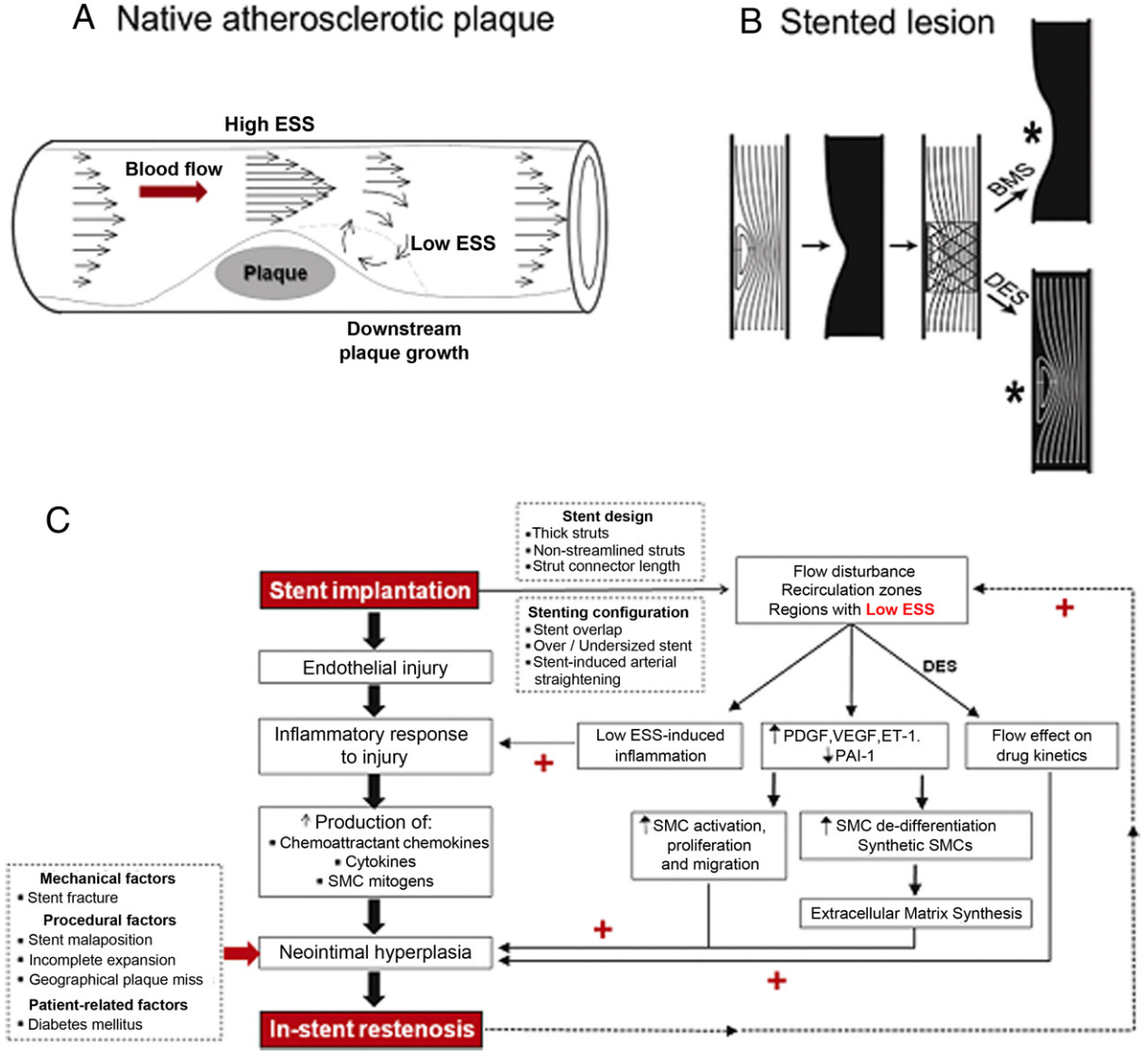

Figure 1 **Proposed Role of Low ESS in In-Stent Restenosis**

(A) Plaque-induced low ESS promotes plaque growth downstream of lumen-protruding atherosclerotic lesions. **(B)** Restenosis **(*)** imposes flow disturbance in BMS- and, to a lesser extent, DES-treated lesions. **(C)** Schematic presentation of the interrelationship between restenosis and low ESS that may promote additional restenosis. **(A)** Adapted, with permission, from Koskinas et al. (20). **(B)** Adapted, with permission, from Richter et al. (19). BMS = bare-metal stent(s); DES = drug-eluting stent(s); ESS = endothelial shear stress; ET = endothelin; PAI = plasminogen activator inhibitor; PDGF = platelet-derived growth factor; SMC = smooth muscle cell; VEGF = vascular endothelial growth factor.

compared with DES (39). The frequent development of extensive ISR with BMS placement likely sustains and amplifies disturbed flow and restenosis-induced low ESS, which might favor additional NIH (19). By inhibiting ISR pharmacologically, DES attenuate restenosis-related flow disturbances, thereby creating a hemodynamic environment with inherently lower pro-restenotic potential. In addition, the pro-restenotic effect of low ESS on DES may be abolished by the effect of flow on drug release (40). Recirculation zones with reduced flow and low ESS, typically distal to stent struts (18), prolong the residence time and increase local concentration of the eluted compound. In such regions with decelerated flow, the locally augmented antiproliferative drug effect might thereby antagonize the pro-restenotic effect of low ESS per se.

Stent drug. Certain eluted drugs may attenuate the neointimal response to low ESS. SMC cell cycle is regulated by a balance between positive regulators, including cyclins and cyclin-dependent kinases, and negative regulators, including cyclin-dependent kinase inhibitors. Sirolimus inhibits SMC migration by decreasing cyclin-dependent kinase and increasing cyclin-dependent kinase inhibitor activity (41). Importantly, low ESS may antagonize these sirolimus effects (42) by up-regulating cyclin-dependent kinase–mediated SMC proliferation (43). In

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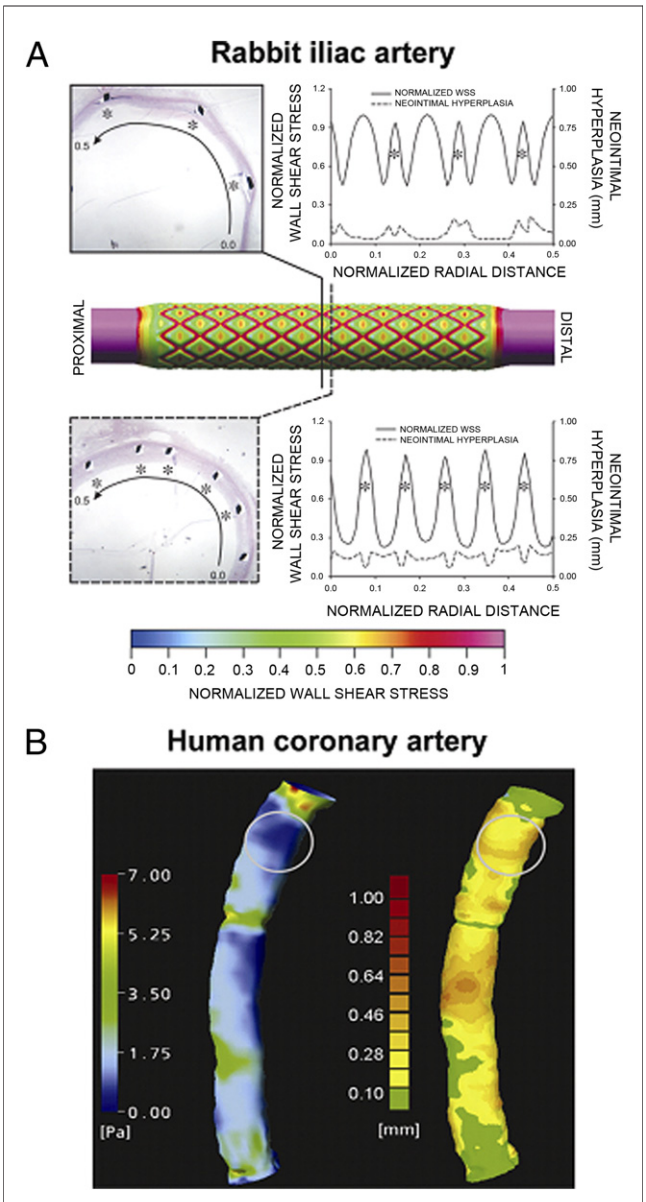

Figure 2 **In Vivo Evidence Associating Low ESS With In-Stent Restenosis**

(A) In-stent ESS distribution predicts subsequent localization of neointimal hyperplasia (NIH) in rabbit iliac arteries. Regions adjacent to struts are exposed to low ESS **(middle)**. Histological sections **(top and bottom)** colocalize low-ESS regions with pronounced NIH. **Asterisks** indicate locations of struts. Spatial plots of ESS and NIH display the correlation between ESS and NIH distribution. **(B)** 3-dimensional color-coded maps show in-stent ESS distribution **(left)** and neointima thickness **(right)** in a human coronary artery. Low-ESS regions **(circles)** colocalize with increased neointima thickness. ESS = endothelial shear stress; WSS = wall shear stress. **(A)** Adapted, with permission, from LaDisa et al. (9). **(B)** Adapted, with permission, from Papafaklis et al. (14).

contrast, paclitaxel inhibits SMC proliferation through centrosomal impairment, independently of ESS-related signaling pathways. Consistently, clinical restenosis is low ESS-related in lesions with BMS and paclitaxel-eluting stents, but not in lesions treated with sirolimus-eluting stents (39). Although the antiproliferative capacity of sirolimus is primarily related to its cytostatic impact on SMCs, attenuation of the pro-restenotic effect of low ESS in regions with restenosis-susceptible anatomy might represent an additional beneficial effect of sirolimus over paclitaxel.

Different DES types differentially affect the phenotype and thereby the matrix-producing capacity of neointimal SMCs. Sirolimus favors contractile SMCs, whereas paclitaxel promotes synthetic SMCs in vitro (44) and in vivo (45). Therefore, sirolimus likely attenuates, whereas paclitaxel amplifies, the low ESS–induced synthetic phenotype of SMCs. The interrelating effects of ESS and other DES types on SMC phenotype are unexplored and may merit investigation.

Stent design. Computational, experimental, and clinical investigations strongly support a critical impact of stent design on the in-stent ESS and on the development of ISR. The mere presence of struts imposes flow separation and recirculation zones downstream of struts. The magnitude of these stent-induced flow disruptions is largely dependent on strut design (10,18,46) and, in turn, substantially influences the arterial response to stenting in animal models (9,47,48). These observations become particularly important when coupled with clinical evidence concerning different rates of ISR attributed to different stent geometries. Strut shape, strut thickness, and the arrangement of strut-strut intersections have been associated clinically with the angiographic severity of ISR and with post-intervention clinical outcomes (49–54). Among different stents, those with hemodynamically favorable designs according to computational modeling–based simulations are robustly associated with reduced ISR in clinical practice (Figs. 3A to 3D) (55). Although these computational predictions underscore the impact of stent design on the ESS distribution and pro-restenotic potential (55), extrapolation to the in vivo setting may be limited by the effect of patient-specific characteristics on clinical restenosis.

Of potential clinical value for integration of these concepts in interventional practice, the adverse hemodynamic consequences of stenting are amenable to stent design. Strut-induced flow disruption can be attenuated by the combination of reduced strut thickness and streamlined strut shape (10,11). Thick struts increase the in-stent area exposed to low ESS, whereas thinner struts and larger interstrut spacing restore ESS to physiologic levels (10). In addition, flow separation, low ESS, and spatial ESS gradients in the vicinity of struts are more pronounced with rectangular (nonstreamlined) struts, they are reduced with circular arc-shaped (streamlined) struts with a 2:1 width-to-height ratio, and virtually abolished by thinner streamlined struts with 4:1 and 8:1 width-to-height ratios (Fig. 3E) (10). Quantification of the effect of strut design on the in-stent ESS affirmed that streamlined struts >yielded only 4% of between-struts area exposed to low ESS, whereas nonstreamlined struts dramatically increased the low ESS area to 81% (11). Appreciating the synergistic beneficial effect of

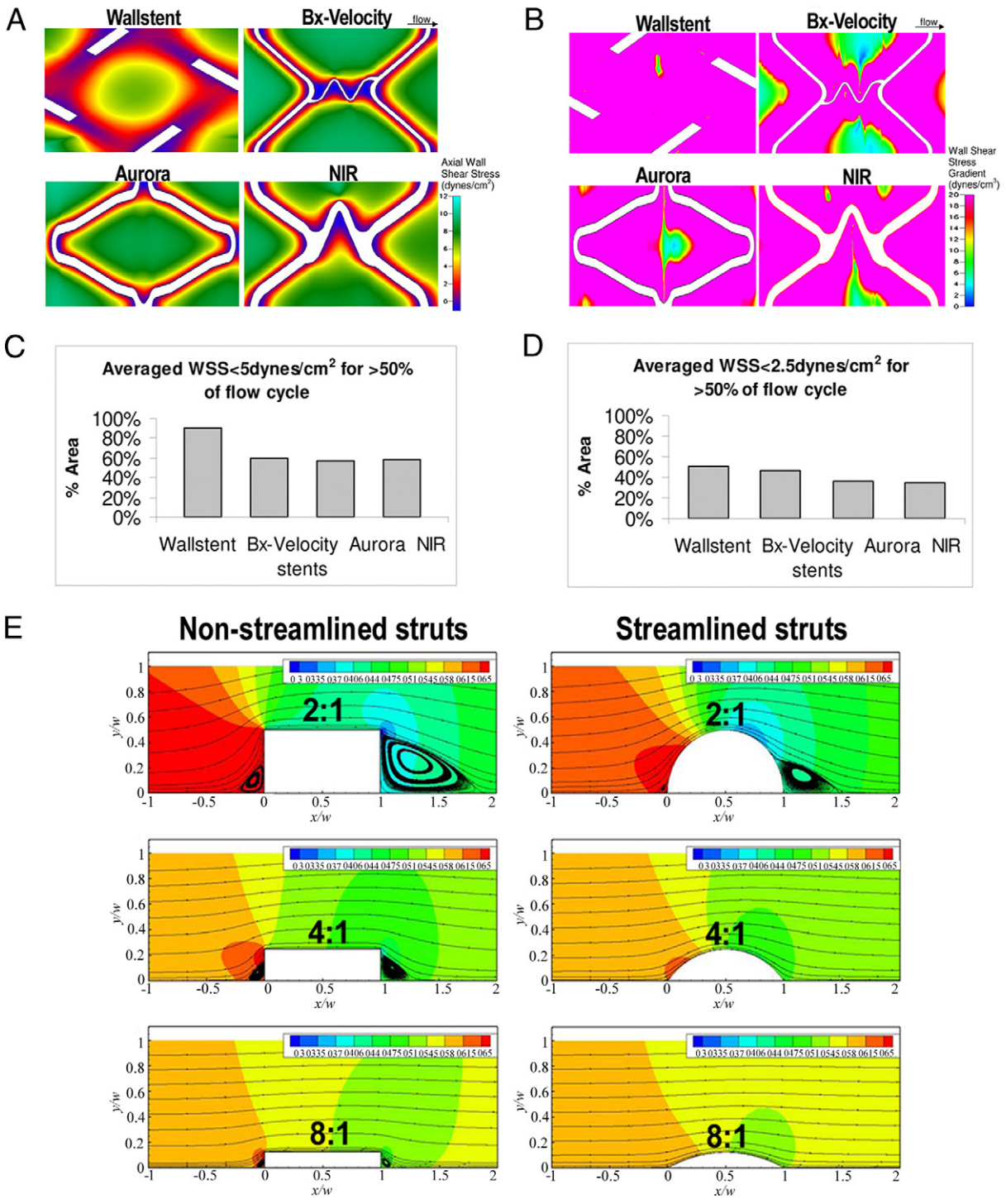

Figure 3 **Effect of Stent Design on the In-Stent ESS Distribution**

Wall shear stress (WSS) is lower **(A)**, WSS gradients are higher **(B)**, and the percentage of between-struts area with low WSS is greater **(C,D)** for the Wallstent compared with the BxVelocity, Aurora, and NIR stents. **(E)** Streamlines at the vicinity of rectangular (nonstreamlined) struts **(left)** and circular arc (streamlined) struts **(right)** for 2:1, 4:1, and 8:1 length-to-height ratios. Recirculation zones occur in rectangular struts for all aspect ratios, but only in thick circular-shaped struts with a 2:1 length-to-height ratio. **(A to D)** Adapted, with permission, from Duraiswamy et al. (55). **(E)** Adapted, with permission, from Jimenez and Davies (10).

strut thinning and streamlining on the in-stent ESS may have considerable implications in optimizing hemodynamically favorable stent designs because the maximal extent of strut thinning per se is limited by the need to maintain adequate material strength.

In addition to strut design, strut connectors also affect in-stent hemodynamics. Computational comparison of 5 clinically used stents showed that minimal connector length in the cross-flow direction and optimal alignment with flow decreased the percentage of in-stent area exposed to low ESS (56).

Stent diameter. Stents with increased diameter relative to the normal artery cross section pose a higher risk of clinical ISR (57). Although stent oversizing may induce ISR through marked arterial injury, oversized stents may also promote NIH by increasing the arterial cross section, reducing flow rate, and thus lowering ESS in the stented versus the proximal nonstented arterial segment.

Stent undersizing may also favor ISR by creating low-ESS zones near struts. Intriguingly, simulations comparing different scenarios of stent undersizing indicate more marked decrease in ESS for 5% stent undersizing compared with 20% undersizing (12). Mechanistically, minor stent undersizing creates small gaps between the struts and the arterial wall, thereby increasing flow resistance and lowering local ESS. In the case of more pronounced stent undersizing, the increased distance between stent struts and the wall may attenuate the effects of flow resistance and ESS lowering (12). These computational observations underscore the impact of optimal stent size selection on the post-stenting hemodynamic environment and likely account in part for the clinical association of underexpansion and incomplete stent apposition with ISR (58) and thrombotic complications (59).

Stenting configuration. In addition to stent design, stenting configuration decisively influences in-stent hemodynamics. Virtual implantation of an everolimus-eluting stent (XCIENCE-V, Abbott Vascular, Santa Clara, California) in 5 configurations yielded marked heterogeneity of ESS distribution among different implantation scenarios (60). Implantation of 2

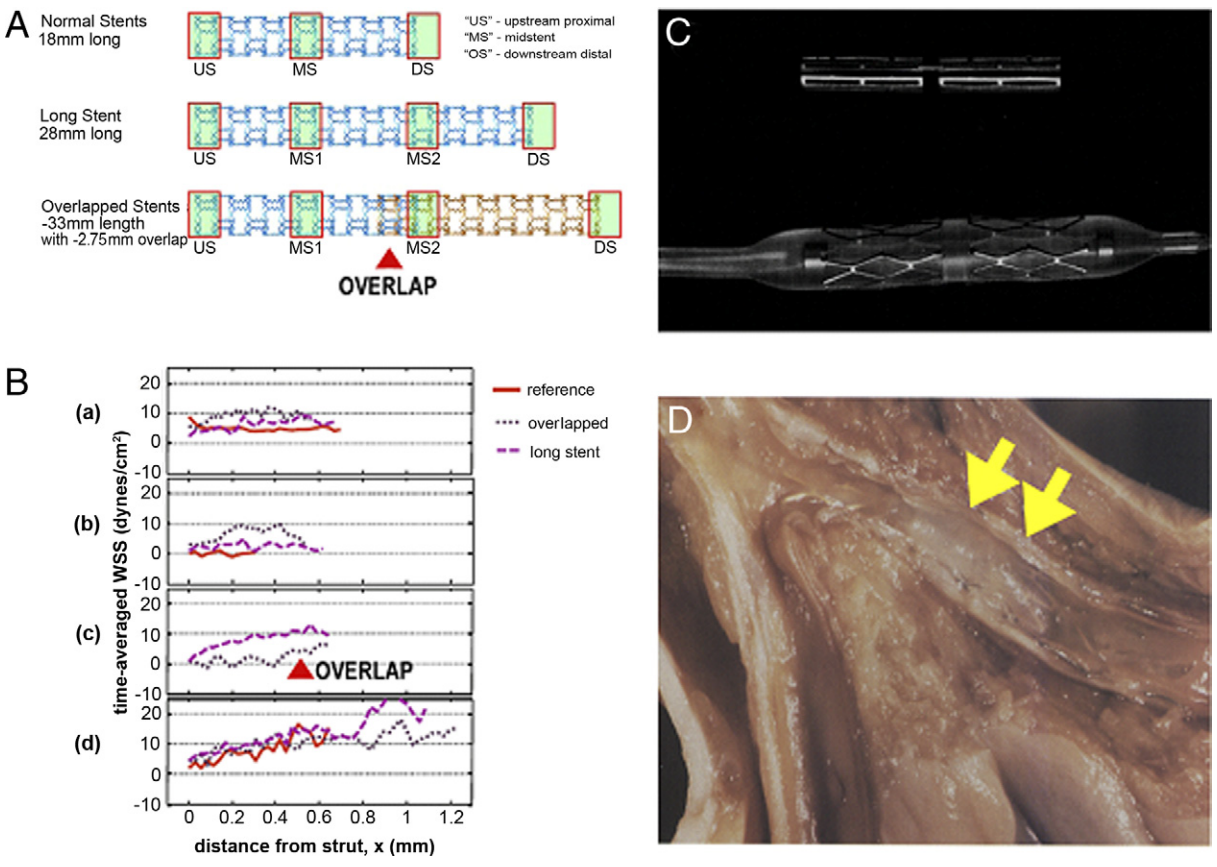

Figure 4 **Effect of Stenting Configuration on the Post-Stenting ESS**

(A) Different implantation configurations of an everolimus-eluting (XCIENCE) stent: normal, long, and 2 overlapping stents. **(B)** Stenting configuration differentially affects ESS magnitude at the upstream **(a)**, mid stent 1 **(b)**, mid stent 2 **(c),** and downstream **(d)** locations. ESS is substantially lower distal to the stent overlap **(arrowheads)** compared with the same location in the single long stent. **(C)** Photomicrograph of a Palmaz-Schatz BMS. **(D)** Autopsy specimen from an artery previously treated with 2 overlapping Palmaz-Schatz stents. Note the enhanced NIH at the region of stent overlap **(arrows)**. **(A, B)** Adapted, with permission, from Charonko et al. (60). **(C, D)** Adapted, with permission, from Ellis et al. (63). Abbreviations as in Figures 1 and 2.

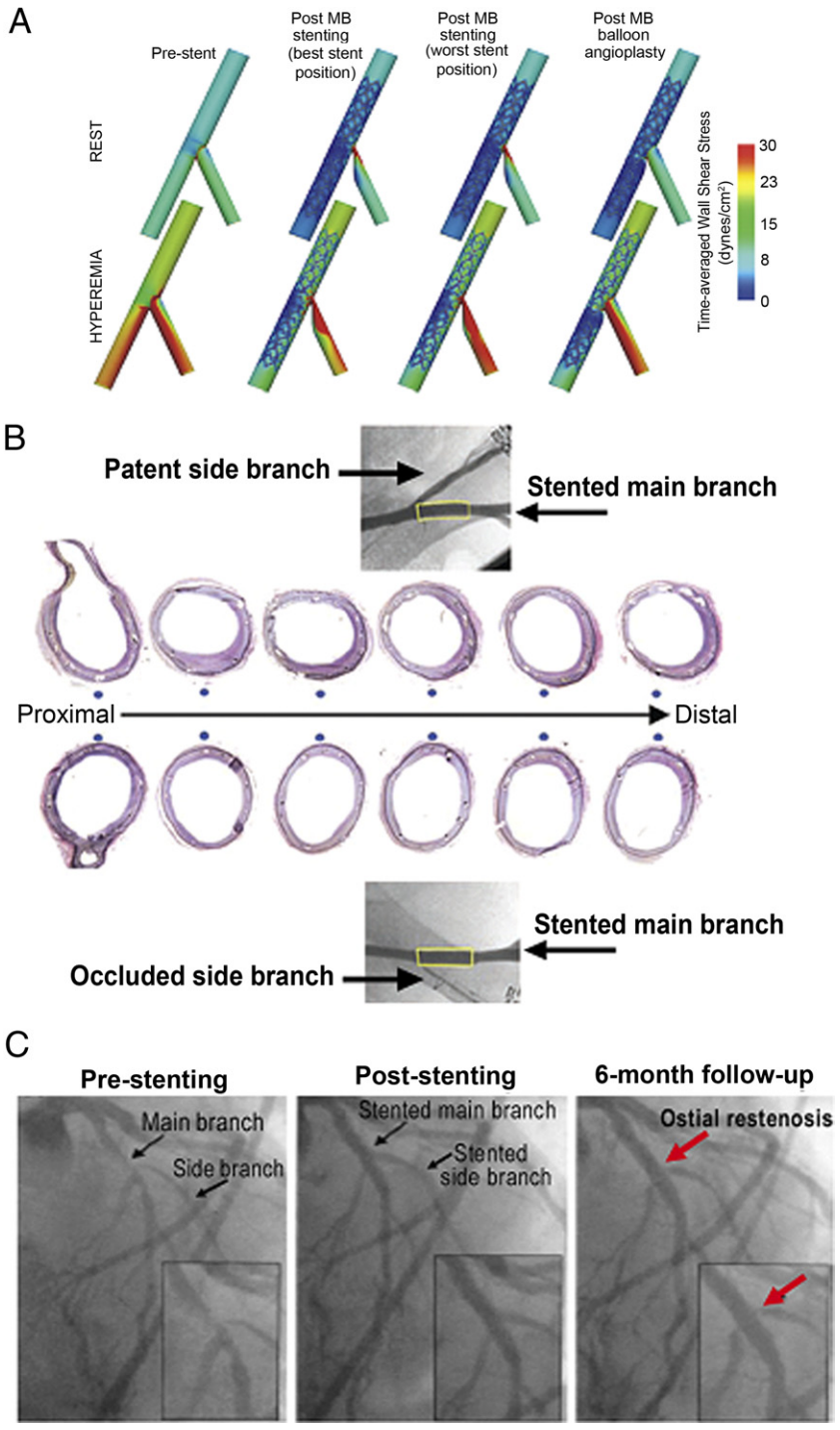

Figure 5 Hemodynamic and Neointimal Responses to Single Versus Double Stenting in Coronary Bifurcations

(A) Computational model of ESS distributions under resting **(top)** and hyperemic flow **(bottom)** in the main branch (MB) and side branch (SB) of a bifurcation treated with different stenting configurations. Best and worst stent position indicate the least and the greatest number of struts obstructing the SB ostium, respectively. SB angioplasty after MB stenting **(right)** does not significantly modify the area with low WSS compared with MB stenting alone. **(B)** Serial sections along the stented MB in a pig coronary bifurcation. NIH is more pronounced in the case of a patent SB (**upper panels** and in vivo corresponding angiogram) compared with the occluded SB case **(lower panels). (C)** Pre-stenting **(left)** and post-stenting **(middle)** angiographic images in a human coronary bifurcation treated with 2 stents. Six-month follow-up **(right)** shows restenosis at the ostium of the SB. **(A)** Adapted, with permission, from Williams et al. (71). **(B)** Adapted, with permission, from Richter et al. (70). **(C)** Adapted, with permission, from Colombo et al. (74). Abbreviations as in Figure 2.

overlapping stents substantially reduced ESS downstream of the junction compared with a single longer stent, likely indicating a region prone to renarrowing at the overlap zone (60) (Fig. 4). Stent overlap has been associated with marked inflammation and poor endothelialization (61) and with unfavorable angiographic and clinical outcomes (62,63). Although the increased drug and polymer concentration at the site of double-stent layers may locally increase tissue toxicity and precipitate neointimal growth (64), the adverse hemodynamic sequelae of stent overlapping might also contribute to the higher risk of ISR in this setting (60).

Long coronary stents have also been linked to late lumen loss and worsening clinical prognosis (49,65). Long stents do not impose significant flow disruption compared with shorter stent lengths (60). The higher ISR rates observed clinically with longer stents might therefore relate to lesion complexity, greater vascular injury, or adverse clinical characteristics of patients presenting with longer lesions rather than to the hemodynamic effect of long stents. From a hemodynamic perspective, a single longer stent rather than multiple overlapping stents might therefore be preferable, if technically feasible, for the treatment of long or diffuse plaques.

Arterial curvature. Inflexible stents that do not conform to the natural arterial curvature impose skewing of velocity profiles (13,17) and decrease ESS along the myocardial aspect of the stented segment (18). These adverse hemodynamic sequelae of implanting inflexible stents in curved coronary segments might account for the clinical association of stent-imposed arterial straightening with angiographic ISR and adverse clinical events (66). Importantly, resorption of the stent polymer in recently introduced bioabsorbable vascular scaffolds gradually restores arterial curvature to the pre-implantation state (67). These promising platforms might thereby in the long-term ameliorate the adverse ESS changes of arterial straightening imposed at implantation.

Bifurcation stenting. Bifurcation lesions predispose to ISR (1), likely due to the inherently complex geometry and flow patterns that are further complicated by the intervention itself (68). NIH in DES-treated coronary

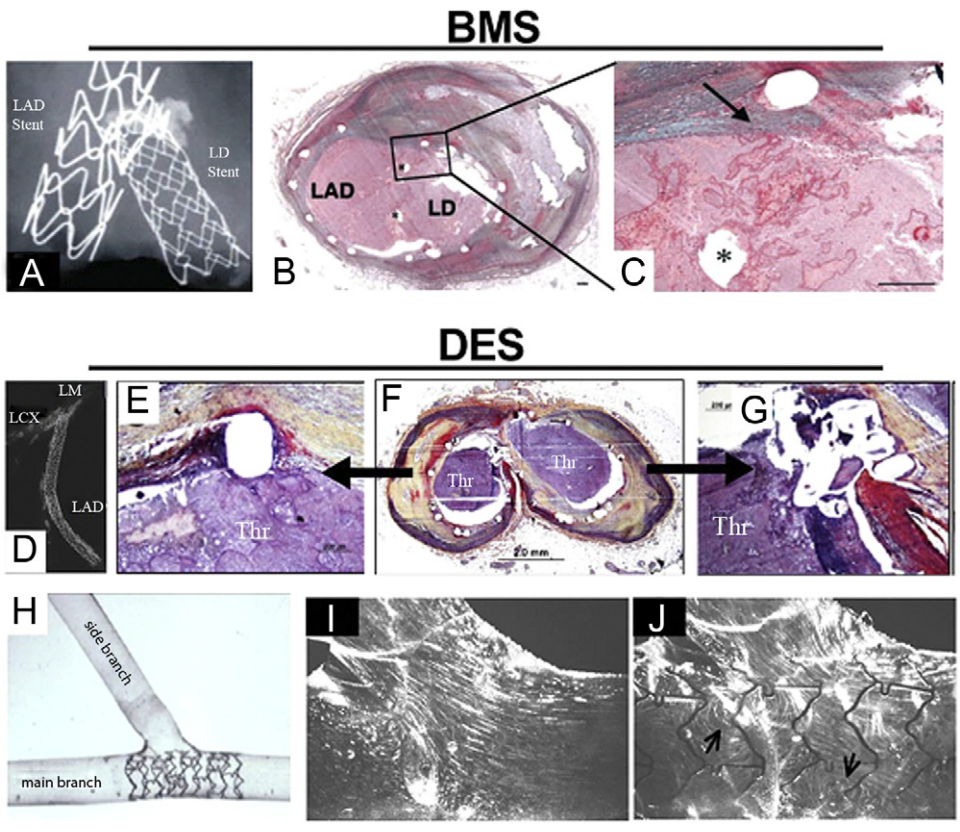

Figure 6 **Stent Thrombosis Localizes in Regions With Disturbed Flow**

(A) Postmortem angiogram of a BMS-stented left anterior descending (LAD)–left diagonal (LD) bifurcation. **(B, C)** Histopathology shows thrombosis with neointima **(arrow)** and platelet-rich thrombus around an uncovered strut **(*)**. **(D)** Bifurcation lesion treated with 2 DESs in the LAD and left circumflex (LCX) ostia. **(E to G)** Both stents are occluded with thrombus (Thr) adherent to uncovered struts at the flow divider. **(H to J)** In vitro model in the same study shows undisturbed flow in the non-stented model **(I)** versus vortical structures **(arrows)** at the flow divider in the stented model **(J)**. **(A to C)** Adapted, with permission, from Farb et al. (27). **(D to J)** Adapted, with permission, from Nakazawa et al. (69). LM = left main; other abbreviations as in Figure 1.

bifurcations is more pronounced at the low-ESS lateral walls compared with the high-ESS flow divider in autopsy registries (69). Consistently, leukocyte accumulation and subsequent neointimal buildup localize at the lateral walls of stented coronary bifurcations in pigs (70), clearly suggesting a link among local low ESS, inflammation, and focal ISR.

Of clinical importance, the hemodynamic sequelae of different bifurcation stenting techniques may appreciably affect local ESS and the proclivity to ISR. Although the widely applied side-branch (SB) angioplasty after main-branch (MB) stenting is beneficial in terms of restoring flow patency, there may not be a benefit to this approach compared with MB stenting alone from a hemodynamic perspective (Fig. 5A) (71). Consistently, experimental ISR in the stented MB of a coronary bifurcation was more pronounced with concomitant dilation of the occluded SB compared with the untreated SB scenario (Fig. 5B) (70). Mechanistically, flow in the obstructed MB may be optimized functionally in the occluded SB state. Consequently, flow disruption imposed on the stented MB by concomitantly opening the SB might in the long-term outweigh the immediate benefit of restoring flow patency in both branches (70). The lack of hemodynamic benefit by SB angioplasty compared with MB stenting alone might, at least in part, account for the lack of significant clinical benefit of double versus single stenting of bifurcation lesions with BMS (72) or DES (73,74) (Fig. 5C).

In bifurcations treated with DES, relative stent positioning may modify the neointimal response by altering flow-mediated drug kinetics within the bifurcation. Computational simulations indicate higher drug delivery in the stented MB for the mid-and downstream compared with the upstream position of the stent relative to the bifurcation entrance. The clinically relevant increase in drug elution in the former scenario of stent positioning is likely related to the overlap of the drug-coated stented segment with the region of boundary layer separation (75).

Overall, although decision making for the treatment of individual bifurcation lesions is clearly dictated by anatomic and functional lesion characteristics and by patient-specific criteria (76), consideration of hemodynamic parameters may optimize local drug delivery and might guide stenting configurations with improved long-term outcomes.

Role of ESS in ST

Clinical evidence associating ESS with ST. Contrary to the progressive nature of ISR, the abrupt occurrence of clotting hampers the prospective assessment of ST in relation to local hemodynamics. Pathologic studies suggest that stenting across branch ostia and bifurcations (i.e., regions with disturbed flow) precipitate ST in BMS (27) and DES (28) (Figs. 6A to 6C). Clotting occurs at sites with delayed arterial healing and incomplete strut coverage that colocalize with vortical flow structures, mainly at the flow divider (69) (Figs. 6D to 6J). Overall, although arterial regions exposed to nonphysiologic ESS appear conducive to ST in autopsy registries, associations with in vivo responses are indirect and therefore cannot establish causality.

Potential role of ESS in the pathobiology of ST. The pathobiology underlying ST is multifaceted. Although systemic factors, including patient-specific characteristics and inadequate antiplatelet therapy, play a major role (1), certain local stent-related and procedural factors may also precipitate ST, in part via their adverse effect on local ESS (Table 1). Notably, stent thrombogenicity may be augmented by low ESS–induced endothelial dysfunction and also by high ESS–induced platelet activation.

ENDOTHELIUM-RELATED PRO-THROMBOTIC EFFECT OF ESS. Thrombosis is prevented in normal arteries by a balance among prothrombotic and antithrombotic factors. Low ESS attenuates the endothelial expression of nitric oxide, prostacyclin I_2, and tissue plasminogen activator, shifting the balance toward a prothrombotic state (2). Additionally, low ESS may promote ST by inhibiting endothelial cell proliferation and retarding re-endothelialization of the arterial and strut surface

Table 1 Risk Factors of Late Stent Thrombosis and Potential Role of ESS

Risk Factor	Effect on In-Stent ESS/ Endothelial Response to ESS
Patient factors	
Diabetes	
Renal failure	
Acute coronary syndrome	
Stent factors	
Incomplete endothelialization	→ Attenuation of physiologic ESS-induced endothelial production of PGI_2, tPA, eNOS (2)
Hypersensitivity to the drug or polymer	
Procedural factors	
Bifurcation stenting	→ Adverse hemodynamic impact on the inherently complex ESS environment (68–70)
Lesion complexity	
Multivessel disease	
Excessive stent length	
Stent undersizing	→ Gaps between stent struts and arterial wall → increased flow resistance → low ESS (12)
Incomplete stent expansion (underexpansion)	
Overlapping stents	
Expansive vascular remodeling	→ Reduced flow rate → low ESS (2,4)
Antiplatelet therapy	
Premature discontinuation	
Clopidogrel resistance	

Certain recognized risk factors of late stent thrombosis, indicated in **bold**, likely act in part by adversely modulating the in-stent ESS or by affecting the response of the endothelial substrate to the local ESS.

eNOS = endothelial nitric oxide synthase; ESS = endothelial shear stress; PGI_2 = prostacyclin I_2; tPA = tissue plasminogen activator.

(77). Incomplete endothelial coverage, the main pathological correlate of ST (27–29), favors ST by exposing thrombogenic arterial components (metallic stent material, lipid core) to circulating prothrombotic factors. Although DES, in particular, delay re-endothelialization pharmacologically, low ESS might exert a synergistic effect and may thereby extend the timeframe during which DES are prone to ST.

PLATELET-RELATED PRO-THROMBOTIC EFFECT OF ESS. Stenting creates regions with accelerated flow and high ESS on top of the struts and low ESS downstream of the struts; both sites of nonphysiologic ESS may enhance stent thrombogenicity. ESS peaks over the strut surface edges activate platelets to release thromboxane A_2 and adenosine diphosphate, which are potent mediators of platelet aggregation. Erythrocytes exposed to high ESS also release adenosine diphosphate. Activated platelets enter flow separation zones downstream of struts, reach high concentrations due to delayed flow, and, assisted by the low ESS–mediated attenuation of native anticoagulants, may trigger the coagulation cascade.

Modifiable factors that influence the prothrombotic effect of ESS. **STENT TYPE: BMS VERSUS DES.** DES have been perceived to inherently increase the likelihood of late ST based on extensive clinical (58,78) and autopsy findings (27–29,69). This notion has been challenged, however, by some contradictory clinical results (79). Intriguingly, DES may actually decrease early thrombogenicity compared with BMS in experimental (80) and clinical settings (81). The synergistic effects of adverse stent design features, particularly greater strut thickness, and stent positioning, such as malapposition and overlapping, rather than drug coating per se, are likely the key determinants of stent thrombogenicity (80).

STENT DESIGN. The creation and localization of thrombosis-prone regions are dictated by, and therefore amenable to, certain stent design characteristics. Thicker and nonstreamlined stent designs, such as currently applied rectangular geometries, may precipitate ST by: 1) magnifying high ESS–induced platelet activation on top of struts; and 2) impeding re-endothelialization, thus attenuating the endothelial production of anticoagulants in low-ESS regions downstream of struts (Fig. 7). The extent of de-endothelialization downstream of struts is proportional to strut thickness (28), likely due to more intense flow disturbance and greater flow separation distance induced by

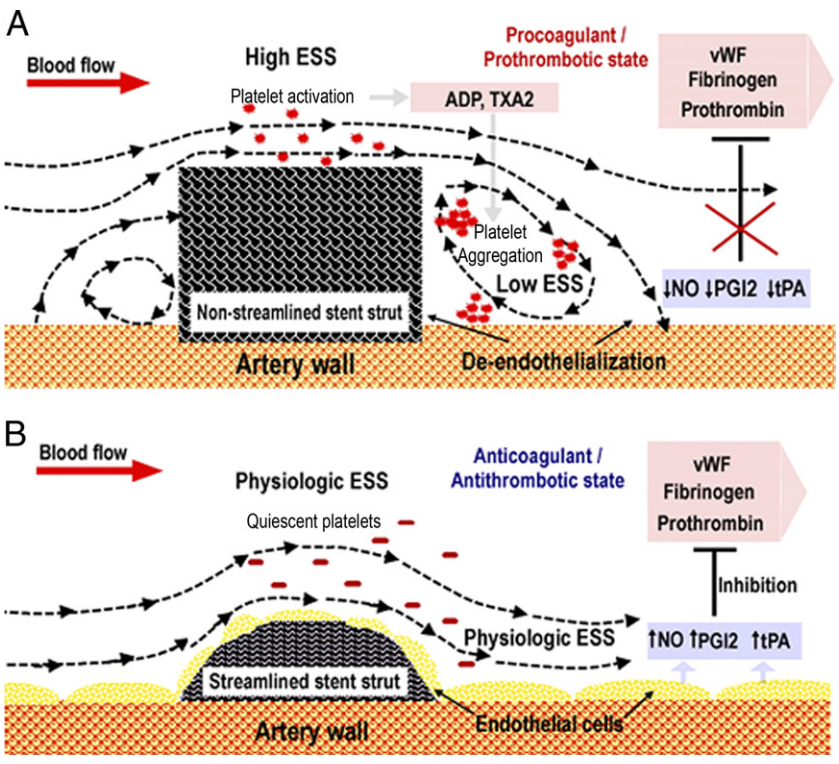

Figure 7 **Effect of Strut Design on Stent Thrombogenicity**

(A) Thick, rectangular struts promote stent thrombogenicity. High ESS on top of struts activates platelets to release adenosine diphosphate (ADP), a potent platelet aggregation promoter. Recirculation zones with low ESS downstream of the strut increase local concentration of activated platelets, retard re-endothelialization, and attenuate the production of natural anticoagulants. **(B)** Thin, circular struts retain physiologic ESS, which favors platelet quiescence on top of struts and enhances re-endothelialization and production of antithrombotic factors downstream of struts. **Red circle** = activated platelet; **Red line** = quiescent platelet. ESS = endothelial shear stress; NO = nitric oxide; PGI2 = prostacyclin; tPA = tissue plasminogen activator; vWF = von Willebrand factor. Modified, with permission, from Jimenez and Davies (10).

thicker struts (10). Computational predictions comparing clinically used stents affirm increased platelet deposition in nonstreamlined strut designs that produce complex flow patterns (82).

Clinical Implications of Applying In Vivo ESS Profiling and Hemodynamically Favorable Stent Designs

Several patient-specific, lesion-related, and procedural factors are known to precipitate ISR and ST (1), yet the identification of patients at highest risk of experiencing these complications remains a major clinical challenge. Multiple lines of experimental and clinical evidence extend our current understanding of low ESS as a proatherogenic stimulus (2–7) to a factor that also contributes to ISR and ST, clearly in conjunction with established risk factors. Appreciation of stent design and implantation configuration as critical determinants of the post-implantation hemodynamic milieu in a given local anatomy might therefore have significant implications in guiding individualized interventions with improved anatomic and clinical outcomes. In BMS, attenuation of restenosis-prone flow disruptions by integration of hemodynamically favorable stent design and positioning might reduce NIH in the early post-stenting period. In DES, optimal design properties could minimize disturbed flow patterns that likely retard re-endothelialization and precipitate late ST. Consideration of local hemodynamic as well as anatomic parameters in bifurcation lesions might optimize the post-stenting ESS distribution and in-stent drug kinetics in this challenging lesion subset. Recent bioabsorbable vascular scaffolds that gradually restore native arterial geometry might attenuate the stent-imposed adverse changes in ESS and might thereby improve long-term outcomes.

Early investigations of the role of ESS in vascular behavior were limited at the in vitro and ex vivo levels. Methodological advances have now enabled in vivo profiling of in-stent ESS in large-scale clinical studies (PREDICTION trial) (83), suggesting that these methods might become suitable for clinical purposes (84). In vivo characterization of in-stent regions with particularly low ESS might enable identification of individual patients and individual stented lesions prone to subsequent development of ISR or ST. In the emerging era of tailoring post-stenting adjunctive therapy (85), integration of intracoronary hemodynamics in the catheterization laboratory might allow for risk-tailored stenting strategies to avert the rare yet devastating complications of coronary interventions.

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