Coronary Interventions

Incomplete Stent Apposition Causes High Shear Flow Disturbances and Delay in Neointimal Coverage as a Function of Strut to Wall Detachment Distance
Implications for the Management of Incomplete Stent Apposition

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Background—Lack of re-endothelialization and neointimal coverage on stent struts has been put forward as the main underlying mechanism leading to late stent thrombosis. Incomplete stent apposition (ISA) has been observed frequently in patients with very late stent thrombosis after drug eluting stent implantation, suggesting a role of ISA in the pathogenesis of this adverse event. The aim of this study was to evaluate the impact of different degrees of ISA severity on abnormal shear rate and healing response with coverage, because of its potential implications for stent optimization in clinical practice.

Methods and Results—We characterized flow profile and shear distribution in different cases of ISA with increasing strut-wall detachment distance (ranging from 100 to 500 μm). Protruding strut and strut malapposed with moderate detachment (ISA detachment distance <100 μm) have minimal disturbance to blood flow as compared with floating strut that has more significant ISA distance. In vivo impact on strut coverage was assessed retrospectively using optical coherence tomography evaluation on 72 stents (48 patients) sequentially at baseline and after 6-month follow-up. Analysis of coverage revealed an important impact of baseline strut-wall ISA distance on the risk of incomplete strut coverage at follow-up. Malapposed segments with an ISA detachment <100 μm at baseline showed complete strut coverage at follow-up, whereas segments with a maximal ISA detachment distance of 100 to 300 μm and >300 μm had 6.1% and 15.7% of their struts still uncovered at follow-up, respectively (P<0.001).

Conclusions—Flow disturbances and risk of delayed strut coverage both increase with ISA detachment distance. Insights from this study are important for understanding malapposition as a quantitative, rather than binary phenomenon (present or absent) and to define the threshold of ISA detachment that might benefit from optimization during stent implantation. (Circ Cardiovasc Interv. 2014;7:180-189.)

Key Words: angioplasty ■ blood flow velocity ■ stents ■ thrombosis

Drug eluting stents (DESs) have significantly reduced the incidence of stent restenosis and target vessel revascularization from 20.0% to 50.3% in the bare metal stent (BMS) era1 to 7.9% to 8.9%.2–4 However, these promising early results of DES have been undermined by concerns over a possible increase in late and very late stent thrombosis (LST, VLST) as compared with BMS.5–8 Pathological studies have revealed that delayed healing6–12 and incomplete re-endothelialization13 are common morphological findings in fatal cases of LST after DES.3–14 DES can interfere with this physiological healing process through different mechanisms: first, the antiproliferative drug released by the device prevents the cellular mitosis required to restore the endothelial continuity; second, the polymer carrying the drug exerts a proinflammatory effect itself15; finally, in
WHAT IS KNOWN

- In rheology studies, flow disturbances and high shear rates have been shown to influence biological processes and platelet activation.
- Incomplete stent apposition is observed frequently by intravascular imaging in patients affected with late stent thrombosis.
- Neointimal formation can reduce stent malapposition and the number of uncovered stent struts.

WHAT THE STUDY ADDS

- This study shows that the shear rate value and the area of blood affected by a high shear rate increase dramatically with increasing distance between a stent strut and vessel wall incomplete stent apposition distance.
- A 4-level grading scheme is outlined for the assessment of malapposition severity based on the impact on flow and a refined sequential optical coherence tomographic assessment of the healing process.
- Mildly malapposed struts affect flow patterns to a lesser extent and, in addition, neointimal healing process tends to completely correct for the malapposition, resulting in full integration of these struts within a year.
- More severely malapposed segments with maximal incomplete stent apposition distance >300 μm represent a greater concern as they affect not only larger areas of blood flow with higher shear but also have a higher likelihood of delayed healing.

Computational Fluid Dynamic Simulation

We created models of stent strut malapposition: the models were based on a 2-dimensional midsection representative of a 3-mm-diameter straight coronary artery with parabolic steady inflow and peak velocity 50 cm/s (representative of the flow velocity in the human coronary circulation). We characterized blood flow patterns in different cases (Figure 1A) simulated using computational fluid dynamics (CFD) with finite volume method (CFX 12.1, ANSYS, Inc.). Blood was assumed to be a Newtonian fluid. Assessed struts were defined as struts in contact with the underlying vessel wall. Two different categories of apposed struts were considered in the simulation: (1) embedded struts, defined as those with ≥50% of the strut thickness inlaid into the vessel wall, (2) protruding struts, defined as those with <50% of the strut thickness inlaid into the vessel wall. Malapposed ISA struts were defined as struts detached from the vessel wall; ISA detachment distance was defined as the distance between the abluminal face of the strut and the vessel wall. Different levels of ISA were considered in the simulation with increasing maximal strut-wall ISA distances (distance from the abluminal side of malapposed strut to the vessel wall), ranging from 100 up to 500 μm.

Shear rate represents a measure of the local gradient of velocity in a flowing material (measured in inverse seconds). Velocity profiles, plot of shear rate, as well as quantification of the maximal shear and area of blood flow affected by abnormal shear rate were calculated from postprocessing of the CFD data for each case of ISA (Figures 1A and 2).

Clinical Optical Coherence Tomographic Study

Vascular healing response in ISA regions was evaluated by sequential optical coherence tomographic (OCT) analysis. Such an approach to assess natural healing of malapposed segments has been described previously by Gutierrez-Chico et al.30 OCT data from 3 different randomized trials were pooled and specifically reanalyzed to test the effect baseline ISA distance on strut coverage at follow-up. The trials combined were A Randomized Comparison of a Zotarolimus-Eluting Stent With an Everolimus-Eluting Stent for Percutaneous Coronary Intervention (RESOLUTE-all comers) trial (NCT00617084),38,39 De Novo Pilot Study (NCT00934752),40 and Direct Implantation of a Rapamycin-Eluting Stent With Bio-Erodable Carrier Technology Using an Integrated Delivery System (DIRECT) study (ACTRN12611001131943).41 Detailed description of the OCT substudies and method for baseline-follow-up sequential analysis have been described previously.23,39,44 Briefly, the RESOLUTE-All comers trial (NCT00617084) compared a zotarolimus-eluting stent with hydrophilic-polymer coating (Resolute, Medtronic Cardio Vascular, Santa Rosa, CA) versus an everolimus-eluting stent with fluoropolymer (Xience V, Abbott Vascular, Santa Clara, CA) in a nonselected-all-comers population,38 with angiographic and OCT follow-up scheduled at 13th month in a subgroup of patients.38 The De Novo Pilot Study (NCT00934752) assessed the performance of a paclitaxel-coated balloon (Moxly, Lutonix Inc, Maple Grove, MN) in combination with a bare metal stent (Multi-link Vision/MiniVision, Abbott Vascular, Santa Clara, CA) for the treatment of de novo coronary lesions, with angiographic and OCT follow-up scheduled at the 6th month. The DIRECT study assessed the efficacy of the Svelte sirolimus-eluting coronary cobalt-chromium stent with fully produce flow separation with eddies and larger shear rates.34-36

The aim of the present study was to investigate the influence of increasing malapposition severity on intracoronary flow disturbances and biological response in vivo.

Methods

Shear rate, defined as the local gradient in velocity between adjacent flow streamlines, affects biological arterial response and is a known modulator of platelet activation and thrombosis. Normal human shear rate (shear rate in large-to-medium-sized arteries) usually varies from 100 to 1000/s.23 However, protruding and malapposed stent struts create back-facing steps, which disturb the blood flow and some cases, the polymer may trigger a hypersensitivity reaction resulting in endothelial denudation and risk of VLST.11,16 The association between lack of stent strut coverage and LST/VLST has been revealed by histopathology studies,12,13 as well as in clinical setting by in vivo imaging studies.17

Several clinical and pathological studies have also shown an association between ISA and stent thrombosis in DES.31,37-39 Incidence of ISA has been reported in ≤77% of the cases of VLST and explained as the consequence of a delayed hypersensitivity reaction mediated by eosinophils and resulting in weakening of the vessel wall, positive remodeling of the vessel, late-acquired ISA, endothelial denudation, and VLST.11,16–20 Based on these observations, ISA has been suggested to be an important predisposing factor to stent thrombosis.21–24: asymptomatic incidentally discovered ISA at 8th month follow-up was shown to be associated with higher major adverse cardiac event and definite late stent thrombosis rates at 5-year follow-up.24 ISA struts exhibit delayed neointimal coverage as compared with well-apposed struts.21–23

Malapposition severity was categorized based on the impact of malapposition on flow and a refined sequential optical coherence tomographic assessment of the healing process.23,30,42,43 Malapposition severity was categorized based on the impact of malapposition on flow and a refined sequential optical coherence tomographic assessment of the healing process.23,30,42,43
bioabsorbable amino acid coating mounted on a fixed-wire, all-in-one integrated delivery system in patients with de novo coronary artery lesions (Svelte Medical Systems, New Providence, NJ). Angiographic and OCT follow-up were scheduled after 6-month follow-up.41

OCT pullbacks were obtained with M2, M3, or C7 systems (Lightlab Imaging, Westford, MA), according to the availability at the participating sites, using occlusive or nonocclusive technique where appropriate. All studies were approved by the institutional review board (Thoraxcentre, Rotterdam, The Netherlands). Tables 1 and 2 summarize the patients studied and the corresponding technical specifications.

OCT pullbacks were analyzed offline in a core laboratory (Cardialysis BV, Rotterdam, NL) by independent operators blinded to stent-type allocation and clinical and procedural characteristics of the patients, using occlusive or nonocclusive technique where appropriate. All studies were approved by the institutional review board (Thoraxcentre, Rotterdam, The Netherlands). Tables 1 and 2 summarize the patients studied and the corresponding technical specifications.

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Continuous variables are presented as the mean and SD or median with interquartile ranges. The association between ISA severity (detachment distance in the ISA segments at baseline) and the percentage of uncovered struts at follow-up was explored as the primary objective. Secondary objectives were the association between shear profile in the different malapposition categories at baseline with the presence of persistent malapposed struts at follow-up and thickness of coverage. Malapposition was categorized as mild (≤100 μm), moderate (>100, ≤300 μm), intermediate (>300, ≤500 μm), or severe (>500 μm) based on their maximal ISA detachment distance. The corresponding average values of the target variables were compared between categories by means of the Kruskal–Wallis nonparametric test, and a linear trend among the ranked categories was explored with the Jonckheere–Terpstra test (P value testing hypothesis that each ISA category results have the same distribution). Calculations were done with PASW version 17.0 (Chicago, IL.)

Results

CFD Simulation

Figure 3 shows the impact of strut-wall malapposition distance on blood flow velocity profiles (Figure 3A) and shear rate patterns (Figure 3B). CFD reconstruction showed that protruding struts and struts mildly malapposed (detachment distance ≤100 μm) only minimally disturb blood flow as compared with floating struts with larger detachment distance. Maximal shear rate (Figure 3C) and areas affected by abnormal shear above the preset threshold computed for each cases. E000, embedded; P000, protrusion; D100–D500, malapposition cases with ISA detachment distance ranging from 100 to 500 μm.
Shear rate profiles calculated for an embedded or protruding strut remain <3000/s with the high shear values confined to the edge of the strut. Maximal shear rate increases with malapposition distance; rates >10000/s were reached for a detachment distance >300 μm. Area of blood stream affected by the highest shear values (>1000/s threshold) increased gradually with ISA detachment distance (Figure 2D), revealing a critical difference between opposing or mildly malapposed struts close to the vessel wall as compared with ISA struts floating in the middle of the lumen.

Clinical OCT Study
A total of 48 patients (8 everolimus-eluting stent, 6 zotarolimus-eluting stent, 13 sirolimus-eluting coronary cobalt-chromium stent [integrated delivery system], and 21 drug-coated balloon), 52 lesions, and 72 stents from the 3 trials included in this study were analyzed sequentially at baseline and follow-up (Figure 3). Tables 1 and 2 summarize the baseline clinical and procedural characteristics of the patients and angiographic characteristics of the lesions, respectively. Seventy-eight segments with acute ISA were identified in the baseline OCT images. Matching with the OCT at follow-up was not possible in 6 segments, because of lack of fiduciary landmarks (2 cases), out-of-image artifacts (3 cases), or incomplete follow-up pulls not including the ISA segment (1 case). Five ISA segments were excluded from the quantitative analysis because the quality of the acquisition was deemed insufficient to yield reliable results, thus resulting in a total of 67 ISA segments included in the final quantitative analysis.

Table 1. Patients’ and Procedural Baseline Characteristics

<table>
<thead>
<tr>
<th>Patients (n=48)</th>
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<tbody>
<tr>
<td>Age, y</td>
<td>59.3 (10.7)</td>
</tr>
<tr>
<td>Men</td>
<td>39 (81.3%)</td>
</tr>
<tr>
<td>Cardiovascular risk factors</td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>24 (50.0%)</td>
</tr>
<tr>
<td>DM</td>
<td>10 (20.8%)</td>
</tr>
<tr>
<td>Insulin-requiring</td>
<td>1 (2.1%)</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>36 (75.0%)</td>
</tr>
<tr>
<td>Smoking</td>
<td>18 (37.5%)</td>
</tr>
<tr>
<td>Current smoker (&lt;30 d)</td>
<td>9 (18.8%)</td>
</tr>
<tr>
<td>Antecedents</td>
<td></td>
</tr>
<tr>
<td>Previous MI</td>
<td>18 (37.5%)</td>
</tr>
<tr>
<td>Previous PCI</td>
<td>6 (12.5%)</td>
</tr>
<tr>
<td>Previous CABG</td>
<td>2 (4.2%)</td>
</tr>
<tr>
<td>Clinical presentation</td>
<td></td>
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<tr>
<td>Silent ischemia</td>
<td>4 (8.3%)</td>
</tr>
<tr>
<td>Stable angina</td>
<td>28 (58.3%)</td>
</tr>
<tr>
<td>Unstable angina</td>
<td>12 (25.0%)</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>4 (8.3%)</td>
</tr>
<tr>
<td>Procedural characteristics</td>
<td></td>
</tr>
<tr>
<td>No. of vessels treated</td>
<td>1.31 (0.59)</td>
</tr>
<tr>
<td>No. of lesions treated</td>
<td>1.21 (0.41)</td>
</tr>
<tr>
<td>No. of stents implanted</td>
<td>1.56 (1.24)</td>
</tr>
<tr>
<td>Total stented length, mm</td>
<td>29.6 (28.5)</td>
</tr>
<tr>
<td>Small vessel (&lt;2.5 mm diameter)</td>
<td>14 (29.2%)</td>
</tr>
<tr>
<td>Overlap</td>
<td>4 (8.3%)</td>
</tr>
<tr>
<td>Type of stent</td>
<td></td>
</tr>
<tr>
<td>EES</td>
<td>8 (16.7%)</td>
</tr>
<tr>
<td>ZES</td>
<td>6 (12.5%)</td>
</tr>
<tr>
<td>SES (IDS)</td>
<td>13 (27.1%)</td>
</tr>
<tr>
<td>DCB-BMS</td>
<td>21 (43.8%)</td>
</tr>
</tbody>
</table>

Table 2. Angiographic Characteristics of the Lesions

<table>
<thead>
<tr>
<th>Lesions (n=52)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Target vessel</td>
<td></td>
</tr>
<tr>
<td>LAD</td>
<td>23 (44.2%)</td>
</tr>
<tr>
<td>LCX</td>
<td>7 (13.5%)</td>
</tr>
<tr>
<td>RCA</td>
<td>22 (42.3%)</td>
</tr>
<tr>
<td>TO</td>
<td>3 (5.8%)</td>
</tr>
<tr>
<td>Bifurcation</td>
<td>13 (25.0%)</td>
</tr>
<tr>
<td>Moderate or severe calcific</td>
<td>8 (15.4%)</td>
</tr>
<tr>
<td>QCA characteristics</td>
<td></td>
</tr>
<tr>
<td>Lesion length, mm</td>
<td>12.5 (7.4)</td>
</tr>
<tr>
<td>Pre-stenting</td>
<td></td>
</tr>
<tr>
<td>RV, mm</td>
<td>2.62 (0.44)</td>
</tr>
<tr>
<td>MLD, mm</td>
<td>0.90 (0.42)</td>
</tr>
<tr>
<td>Percentage of diameter stenosis</td>
<td>66 (15)</td>
</tr>
<tr>
<td>Post-stenting in-stent</td>
<td></td>
</tr>
<tr>
<td>RV, mm</td>
<td>2.76 (0.39)</td>
</tr>
<tr>
<td>MLD, mm</td>
<td>2.33 (0.43)</td>
</tr>
<tr>
<td>Percentage of diameter stenosis</td>
<td>14 (7)</td>
</tr>
</tbody>
</table>

LAD indicates left anterior descending; LCX, left circumflex; MLD, minimal lumen diameter; QCA, quantitative coronary angiography; RCA, right coronary artery; RV, reference vessel diameter; and TO, total occlusion.
The association with the thickness of coverage is less clear: either considering the mean thickness of coverage or the maximal thickness of coverage measured in each ISA segment; there seems to be an inverse relation between detachment distance and thickness of coverage along the 3 inferior ISA categories. However, coverage in the category of >500 μm detachment is thicker than in the precedent categories, resulting in a u-shaped distribution and no significant linear association (Table 3; Figures 1C and 4).

**Discussion**

The main findings of this study are as follows: (1) protrusion and detachment of stent struts from the vessel wall create disturbances in the coronary flow, translated into higher shear rates around the strut boundaries. (2) The magnitude and area affected by higher shear augment gradually with the degree of malapposition. (3) The delay in neointimal healing is related to the degree of ISA severity measured immediately post implantation by OCT, meaning that the more severely a strut is detached, the less likely it is to heal and integrate within the artery wall.

Our analysis indicates that shear rate is affected by the degree of malapposition. The parallel between shear and delayed coverage as a function of the detachment distance might be interpreted in terms of a causative relation. Flow disturbances and high shear rates are present in the coronary artery from the moment of stent implantation, therefore they precede the neointimal healing process and might determine its progress to some extent. Previous work showed that shear stress modulates the neointimal healing after stenting, and the thickness of the neointimal hyperplasia layer covering the struts is inversely related to the local level of shear stress.25–28 The similarity in dose–response relations suggests that the more detached the strut, the larger its distance from the existing endothelial layer and the higher the shear stress on the strut wall, and subsequently the more hampered the neointimal reaction intended to cover the detached struts.

**Shear Stress as a Mechanism to Explain the Delayed Healing of Acute ISA Regions**

Several investigators have described previously how protruding or detached struts can alter normal coronary flow and affect drug distribution and recirculation,35,42,43 and the larger the strut, the more severe its impact on flow,35 but the intrinsic dependence of shear rate on the detachment distance and delayed coverage as a function of the detachment distance might be interpreted in terms of a causative relation. Flow disturbances and high shear rates are present in the coronary artery from the moment of stent implantation, therefore they precede the neointimal healing process and might determine its progress to some extent. Previous work showed that shear stress modulates the neointimal healing after stenting, and the thickness of the neointimal hyperplasia layer covering the struts is inversely related to the local level of shear stress.25–28 The similarity in dose–response relations suggests that the more detached the strut, the larger its distance from the existing endothelial layer and the higher the shear stress on the strut wall, and subsequently the more hampered the neointimal reaction intended to cover the detached struts.

**Table 3. Optical Coherence Tomographic Analysis of the Matched ISA Segments**

<table>
<thead>
<tr>
<th>ISA Categories According to the Maximal Detachment Distance in the Segment at Baseline</th>
<th>≤100 μm</th>
<th>&gt;100 μm ≤300 μm</th>
<th>&gt;300 μm ≤500 μm</th>
<th>&gt;500 μm</th>
<th>KW (P Value)</th>
<th>JT (P Value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of ISA segments</td>
<td>7</td>
<td>38</td>
<td>17</td>
<td>5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Percentage of uncovered struts</td>
<td>0 (0–0)</td>
<td>6 (0–9)</td>
<td>15 (0–24)</td>
<td>18 (8–25)</td>
<td>0.010</td>
<td>0.001</td>
</tr>
<tr>
<td>Percentage of persistent ISA struts</td>
<td>0 (0–0)</td>
<td>1 (0–0)</td>
<td>11 (0–17)</td>
<td>13 (11–19)</td>
<td>0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mean thickness coverage, μm</td>
<td>143 (73–198)</td>
<td>132 (68–188)</td>
<td>91 (52–95)</td>
<td>106 (65–157)</td>
<td>0.342</td>
<td>0.101</td>
</tr>
<tr>
<td>Maximal thickness coverage, μm</td>
<td>357 (290–445)</td>
<td>243 (163–310)</td>
<td>196 (110–280)</td>
<td>370 (280–390)</td>
<td>0.011</td>
<td>0.372</td>
</tr>
</tbody>
</table>

Descriptive results presented as mean (interquartile range). Differences among categories explored by means of Kruskal–Wallis nonparametric test; lineal trend explored by means of Jonckheere–Terpstra test. ISA indicates incomplete stent apposition; JT, Jonckheere–Terpstra; and KW, Kruskal–Wallis.
its effect on coverage has not been shown previously hitherto. This information is relevant to understand the problem of acute ISA properly, that is, ISA that appears as a consequence of suboptimal stent implantation during the coronary intervention, therefore at the moment when optimization is still possible. The results of our current study are consistent with previous evidences and propose increase in shear rate as a plausible mechanism to explain the incomplete coverage of malapposed struts with ISA. Shear stress has been shown to modulate the neointimal healing after stenting in BMS and DES. It has also been advocated to explain the differences in coverage between the luminal and abluminal sides of the struts in bioresorbable scaffolds. The increase in shear rate as a function of the detachment distance might well explain the incomplete coverage of ISA regions with ISA. Shear stress has been shown to modulate the neointimal healing after stenting in BMS and DES. It has also been advocated to explain the differences in coverage between the luminal and abluminal sides of the struts in bioresorbable scaffolds.

**Shear as a Mechanism to Explain the Thrombogenicity of Acute ISA Regions**

The delayed coverage of acute ISA regions, leaving metallic surfaces on the stent exposed to the bloodstream, has raised concerns about an eventual higher risk of stent thrombosis, but this suspicion has not been confirmed clinically hitherto. Several studies have suggested an association between late ISA with stent thrombosis in DES, and this association has been explained as the consequence of a delayed hypersensitivity reaction triggered by the polymer, mediated by eosinophils and resulting in vascular inflammation, weakening of the vessel wall, positive remodeling, late-acquired ISA, endothelial denudation, and finally VLST.

A recent study reported that incidentally detected ISA at the 8th month after stent implantation in asymptomatic patients was associated with higher risk of VLST and myocardial infarction as compared with well-apposed stents. Although this finding does not properly confirm the clinical
consequences of acute ISA, it is consistent with the suspicion that ISA entails a higher risk of stent thrombosis because incidentally discovered ISA in asymptomatic patients is unlikely to be the consequence of a hypersensitivity reaction.

The mechanism underlying the link between ISA struts and thrombosis is not fully understood yet. The increase in shear rate at ISA struts surfaces might partially explain its propensity to thrombotic phenomena. In addition to impairing the neointimal coverage of ISA struts, shear is known in rheology to activate platelets. High shear rate activates platelets (>1000/s) in a dose-dependent manner through von Willebrand factor binding to glycoprotein Ib and glycoprotein IIb/IIIa receptors. Several experiments have shown in vitro the influence of shear on clot formation and high shear rate is actually a prerequisite to reproduce the mechanisms of thrombus formation in both in vitro and in vivo models. In a recent study relevant to stent malapposition, Kolandaivelu et al. showed an increased amount of clot with underdeployed bare stent versus well deployed bare stent using an in vitro chandler loop system perfused with porcine blood. Therefore, the detachment of a strut from the vessel wall not only leads to higher levels of shear stress on the strut surface, potentially affecting neointimal coverage process, but the higher flow disturbances around its edges also increase the risk of platelet activation and thrombi aggregation. Under the shear rate hypothesis, the thrombogenicity of malapposed struts is a function of the detachment distance as well, which may warrant further exploration in future studies. This flow hypothesis has been only rarely considered in previous studies about ISA and stent thrombosis. Nonetheless, there are no compelling in vivo evidences yet about different thrombosis propensity in ISA regions depending on their detachment distance hitherto. This point must be specifically addressed in the future.

**Practical Implications**

Recent OCT studies have demonstrated consistently higher risk of delayed (or incomplete) coverage in acute ISA regions as compared with well-apposed struts, thus raising concerns about an eventual higher risk of stent thrombosis. In this series, we did not observe cases of late-acquired ISA, which has been suggested to be one of the hallmarks of VLST. In contrary to acute ISA, late-acquired ISA cannot be optimized during the interventional procedure because it usually happens in stents optimally deployed and apposed to the vessel wall, getting subsequently malapposed and thrombosed as a consequence of the inflammatory process. Evidence about the consequences of acute ISA on neointimal healing and clinical outcome is still scarce, and the question about whether it is worth spending time and resources in the optimization of apposition remains an open issue for the interventional cardiologist. Still, correction of ISA documented at the time of a DES deployment can be justified not only on the grounds of preventing risk of delayed coverage but also for ensuring adequate drug delivery to the vessel wall.

Extent of acute ISA has been shown to be the only independent predictor of persistent ISA and delayed coverage at follow-up. If shear is one of the key mechanisms for delayed coverage and higher thrombogenicity associated with malapposition, then the clinical relevance of acute ISA might depend directly on how distant the strut is from the vessel wall. According to this model, the classical question of whether we should optimize acute ISA might be reformulated as to what degree of acute ISA should we optimize. We are still far from a definite answer to this question. In this study, we used OCT series in exploring predictors of the lack of coverage at follow-up with 4 different grades of ISA severity. Data were analyzed to test consistency with the shear stress hypothesis, and sequential OCT quantitative analysis could be performed on 67 ISA stent segments. Results from this shear calculation and sequential OCT analysis using the classification proposed here suggest that the optimization of malapposition when the ISA detachment distance is <300 μm (moderate ISA) and particularly when the ISA distance is <100 μm (mild ISA) might be less critical as ISA in this case will be corrected over...
time by the vascular healing reaction, restoring smooth lami-
lar flow with complete strut coverage as evidenced in >98% of
cases within a year. Severely malapposed segments with
maximal ISA distance >300 μm represent a greater concern
as these segments are affecting not only larger areas of blood
flow with high shear rate but also have a higher likelihood of
delayed healing with ISA struts persistent at follow-up.

Although this strategy has not been evaluated clinically
hitherto, future research on this topic would certainly benefit
from this approach.

Limitations
This study is only hypothesis generating: shear values have
been simulated based on a simple idealized computational
model and the correspondence between the computed shear
rate and the coverage measured by OCT in a clinical scenario
only suggests the differences in the local flow patterns as a
plausible mechanism to explain the incomplete coverage of
ISA and a possible link to stent thrombogenicity. These find-
ings on the evolution of acute ISA, and its relationship with
disturbed rheology, have to be therefore interpreted with
cautions and results must be replicated in different and larger
series. Although these results suggest shear alterations as a
mechanism underlying the delayed coverage, this hypothesis
still needs to be demonstrated on a large clinical population.

Thrombogenicity is a complex biological process involving
a mixture of the persistent flow disruption (stagnant flow or
high shear rate), platelet activation, and vessel surface injury/
inflammation. Also, although shear is known to augment some
thrombotic effects (ie, platelet activation), it can also reduce
others through increased transport (ie, wash out of thrombin).

OCT has consistently shown good correlation with histol-
ogy for the assessment of neointimal coverage after stenting
in different studies, so it should be considered a valid in vivo
proxy for neointimal coverage. Nonetheless, its sensitiv-
ity and specificity for this aim are <100% and still poorly
known. In particular, OCT can hardly be used to discrimi-
nate whether healthy endothelium is present at its surface.
We have considered the coverage assessed by OCT as a reliable
estimate for the neointimal coverage, but this approach entails
some degree of inaccuracy.

Conclusions
This study shows that flow disturbances and risk of delayed
strut coverage both increase with ISA detachment distance.
Risk of persistent malapposed struts in a clinical scenario
also depends on their detachment from the vessel wall. These
insights are important for understanding malapposition as a
quantitative phenomenon and to define threshold of ISA
detachment that might benefit from optimization during stent
implantation. Additional studies are required to determine the
exact impact of ISA severity on patient outcomes.

Disclosures
The study pools optical coherence tomographic data from 3 different
clinical trials sponsored by Medtronic (Santa Rosa, CA), Lutonix Inc
(Maple Grove, MN), and Svelte Medical Systems (New Providence,
NJ), respectively. The core laboratory and clinical research organi-
ization responsible for the analysis (Cardialysis BV, Rotterdam, The
Netherlands) received grants from the corresponding sponsors to run
the trials, but the content of this article is an investigator-driven inde-
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Incomplete Stent Apposition Causes High Shear Flow Disturbances and Delay in Neointimal Coverage as a Function of Strut to Wall Detachment Distance: Implications for the Management of Incomplete Stent Apposition

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