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) era\(^1\) 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 healing\(^6\)–\(^11\) and incomplete re-endothelialization\(^11\) are common morphological findings in fatal cases of LST after DES.\(^9\)–\(^14\) 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 itself\(^15\); finally, in

**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 \(\mu\)m). Protruding strut and strut malapposed with moderate detachment (ISA detachment distance <100 \(\mu\)m) 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 \(\mu\)m at baseline showed complete strut coverage at follow-up, whereas segments with a maximal ISA detachment distance of 100 to 300 \(\mu\)m and >300 \(\mu\)m 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
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.11,16–20 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

Shear rate, defined as the local gradient of velocity 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

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Shear rate, defined as the local gradient of velocity between adjacent flow streamlines, affects biological arterial response25–28 and is a known modulator of platelet activation and thrombosis.29,30 Normal human shear rate (shear rate in large-to-medium-sized arteries) usually varies from 100 to 1000/s.22,23 However, protruding and malapposed strut struts create back-facing steps, which disturb the blood flow and 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

**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.27 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).

Computational mesh for the CFD studies was tested for its accuracy by comparing the velocity profiles around the 500-μm malapposed strut–computed meshes at various refinement levels. As a result of the sensitivity test, a 19604-node mesh provided 0.03% difference in velocity and 2.85% difference in maximum shear rate compared with a refined mesh with 78009 nodes.

**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.23 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),36,39 De Novo Pilot Study (NCT00934752),40 and Direct Implantation of a Rapamycin-Eluting Stent With Bio-Eroding 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.21,30–41 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,36 with angiographic and OCT follow-up scheduled at 13th month in a subgroup of patients.36 The De Novo Pilot Study (NCT00934752) assessed the performance of a paclitaxel-coated balloon (Moxxy, 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.36 The DIRECT study assessed the efficacy of the Svelte sirolimus-eluting coronary cobalt-chromium stent with fully
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 a dedicated OCT software (Lightlab Imaging) or Q-IVUS (version 2.1; Medis, Leiden, The Netherlands). Cross-sections were analyzed at 1-mm longitudinal intervals within the stented segment. The assessment of apposition and coverage was performed at baseline (apposition) and at the time of follow-up (apposition and coverage) according to previously described methodology.23,39-41 ISA distance was measured for each strut as the distance from the luminal leading edge of the strut reflection, at the midpoint of the strut long axis, to the vessel wall. To be consistent with the computational simulation models, detachment distances, defined as the distances between the abluminal leading edge of the strut and the vessel wall, were derived from OCT measures by subtracting the strut (and polymer) thickness for each device, namely: 89 μm for everolimus-eluting stent, 97 μm for zotarolimus-eluting stent, 81 μm for BMS in combination with drug-coated balloon, and 87 μm for sirolimus-eluting coronary cobalt-chromium stent (integrated delivery system).

ISA segments were defined as segments with ≥2 consecutive cross-sections containing ISA struts immediately post implantation (baseline, left) and at follow-up (right) in 3 clinical samples. Notice the different vascular healing patterns intended to cover the detached metallic struts with a neointimal layer. C. Closed-up from examples of B with ISA segments immediately post implantation (baseline, left) and at follow-up (right) illustrating cases of different ISA severity. The more severe is the strut detachment to the wall, the more likely is ISA to be still persistent at follow-up. Despite rims of neointimal tissue bridging between unapposed struts, remaining gaps can be observed at follow-up between ISA segments and the wall.

Figure 1. A, Definition and classification of strut apposition. Upper, Illustration of embedded and protruding but apposed struts. Lower, Illustration of progressive stent strut malapposition with increasing strut to wall incomplete stent apposition (ISA) detachment distance (ISA classification: mild, <100 μm; moderate, 100–300 μm; intermediate, 300–500 μm; and severe, >500 μm). B, Examples of ISA segments immediately post implantation (baseline, left) and at follow-up (right) in 3 clinical samples. Notice the different vascular healing patterns intended to cover the detached metallic struts with a neointimal layer. C. Closed-up from examples of B with ISA segments immediately post implantation (baseline, left) and at follow-up (right) illustrating cases of different ISA severity. The more severe is the strut detachment to the wall, the more likely is ISA to be still persistent at follow-up. Despite rims of neointimal tissue bridging between unapposed struts, remaining gaps can be observed at follow-up between ISA segments and the wall.

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Statistical Analysis

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 ($\leq$100 $\mu$m), moderate ($>100$, $\leq$300 $\mu$m), intermediate ($>300$, $\leq$500 $\mu$m), or severe ($>500$ $\mu$m) 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 $\leq$100 $\mu$m) 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 rate (Figure 3D) were found to both increase with detachment distance.
Table 1. Patients’ and Procedural Baseline Characteristics

<table>
<thead>
<tr>
<th>Patients (n=48)</th>
<th></th>
</tr>
</thead>
<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>
</tbody>
</table>

Antecedents

| Previous MI | 18 (37.5%)  |
| Previous PCI| 6 (12.5%)   |
| Previous CABG | 2 (4.2%)    |

Clinical presentation

| Silent ischemia | 4 (8.3%) |
| Stable angina   | 28 (58.3%) |
| Unstable angina | 12 (25.0%) |
| Myocardial infarction | 4 (8.3%) |

Procedural characteristics

| No. of vessels treated | 1.31 (0.59) |
| No. of lesions treated | 1.21 (0.41) |
| No. of stents implanted | 1.56 (1.24) |
| Total stented length, mm | 29.6 (28.5) |
| Small vessel (<2.5 mm diameter) | 14 (29.2%) |
| Overlap              | 4 (8.3%)    |
| Type of stent        |           |
| EES                  | 8 (16.7%)  |
| ZES                  | 6 (12.5%)  |
| SES (IDS)            | 13 (27.1%) |
| DCB-BMS             | 21 (43.8%) |

CABG indicates coronary artery bypass graft; DCB-BMS, combination of drug-coated balloon with bare metal stent; DM, diabetes mellitus; EES, everolimus-eluting stent; MI, myocardial Infarction; PCI, percutaneous coronary intervention; SES (IDS), sirolimus-eluting stent on integrated delivery system; and ZES, zotarolimus-eluting stent.

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 pullbacks 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 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>
</tbody>
</table>

QCA characteristics

<table>
<thead>
<tr>
<th>Lesion length, mm</th>
<th>12.5 (7.4)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Poststenting</td>
<td></td>
</tr>
<tr>
<td>RVD, 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>Poststenting in-stent</td>
<td></td>
</tr>
<tr>
<td>RVD, 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; RVD, reference vessel diameter; and TO, total occlusion.

Table 3 and Figure 4 show the results of the quantitative OCT analysis. Seven ISA segments at baseline had maximal detachment distances ≤100 μm immediately post implantation (mild), 38 ISA segments had maximal detachment distances between 100 and 300 μm (moderate), 17 ISA segments between 300 and 500 μm (intermediate), and in 5 ISA segments the maximal detachment distances were >500 μm (severe), corresponding to the largest disturbances and shear value in the blood stream. The percentage of uncovered struts and persistent ISA struts at follow-up showed significant differences between the categories (P value=0.010 and 0.001, respectively) and a statistically significant linear trend (P value=0.001 and <0.001, respectively), with values increasing from 0% to 18% uncovered struts and from 0% to 13% persistent ISA struts over the different categories of malapposition. As shear rate increases with malapposition distance, so does the rate of uncovered struts and incidence of persistent ISA at follow-up. Correlation between baseline shear rate (lower boundary obtained from the idealized responses in Figure 2) and mean percentage of uncovered struts and rate of persistent ISA at follow-up in each ISA category is shown in Figure 5.
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. 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, and the larger the strut, the more severe its impact on flow, 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. 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>No. of ISA segments</th>
<th>Percentage of uncovered struts</th>
<th>Percentage of persistent ISA struts</th>
<th>Mean thickness coverage, μm</th>
<th>Maximal thickness coverage, μm</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>≤100 μm</td>
<td>&gt;100 μm ≤300 μm</td>
<td>&gt;300 μm ≤500 μm</td>
<td>&gt;500 μm</td>
<td>KW (P Value)</td>
</tr>
<tr>
<td>No. of ISA segments</td>
<td>7</td>
<td>38</td>
<td>17</td>
<td>5</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>
</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>
</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>
</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>
</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 BMS25and DES.26,27 It has also been advocated to explain the differences in coverage between the luminal and abluminal sides of the struts in bioresorbable scaffolds.44 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 BMS25and DES.26,27 It has also been advocated to explain the differences in coverage between the luminal and abluminal sides of the struts in bioresorbable scaffolds.44

**Figure 4.** Impact of detachment distance on neointimal coverage in a clinical setting. Mean values of percentage of uncovered struts at follow-up (FUP; primary objective), percentage of persistent malapposed (incomplete stent apposition [ISA]) struts at follow-up, mean and maximal thickness of coverage measured in the ISA segment. Bars, 95% confidence intervals.

**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 blood stream, 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,11,17–19 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.11,16–20

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.24 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 inci-
dently 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 impair-
ing the neointimal coverage of ISA struts, shear is known in
rheology to activate platelets.29–33 High shear rate activates
platelets (>1000/s) in a dose-dependent manner through von
Willebrand factor binding to glycoprotein Ib and glycopro-
tein IIb/IIIa receptors.29–33 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.29–32 In
a recent study relevant to stent malapposition, Kolandaivelu
et al35 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, poten-
tially 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 war-
thant 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,21–23 thus raising con-
cerns 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 hap-
pens 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 car-
diologist. 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 inde-
pendent predictor of persistent ISA and delayed coverage
at follow-up.23 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 lamellar 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 findings on the evolution of acute ISA, and its relationship with disturbed rheology, have to be therefore interpreted with caution 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 thrombogenic effects (ie, platelet activation), it can also reduce others through increased transport (ie, wash out of thrombin).

OCT has consistently shown good correlation with histology 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 sensitivity and specificity for this aim are <100% and still poorly known. In particular, OCT can hardly be used to discriminate 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 organization responsible for the analysis (Cardiodynamics BV, Rotterdam, The Netherlands) received grants from the corresponding sponsors to run the trials, but the content of this article is an investigator-driven independent post hoc analysis.

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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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