Detection of very early stent healing after primary angioplasty: an optical coherence tomographic observational study of chromium cobaltum and first-generation drug-eluting stents. The DETECTIVE Study

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ABSTRACT

Background Lack of stent coverage appears to be associated with stent thrombosis, a problem of particular concern in patients with ST elevation myocardial infarction (STEMI).

Methods The DETECTIVE European Multicenter Registry was set up to address the early modality of stent healing in the setting of STEMI. The Registry compared, with an early optical coherence tomography (OCT) evaluation performed at 3–7 days, the patterns of coverage and apposition of the first generation of drug-eluting stents (DESs) and cobalt chromium non-drug-eluting stents (CCSs) that were deployed in culprit lesions and in non-culprit segments. The Registry included only patients with a multi-vessel disease to allow, at 3–7 days from the first angioplasty, a deferred OCT examination and a staged intervention in another vessel.

Results 28 stented lesions (15 patients) eventually entered the final OCT assessment. 13 stents were first-generation DESs, while the remaining 15 were CCSs. 18 stents (64%) were deployed at culprit STEMI lesions, and the remaining 10 (36%) were deployed at non-culprit sites. The distribution of clinical and procedural variables in DES and CCS as well as in culprit and non-culprit sites was not different. In total, 27 019 struts were analysed in 28 stents. The percentage of stent uncoverage in the overall analysis was 11.7%, while the percentage of malapposition and that of struts covered with thrombus were 4.8% and 2.2%, respectively. A low percentage of strut uncoverage was found in all the four studied subgroups: DES 12.8%, CCS 10.9%, stents deployed in culprit lesions 13.2% and stents deployed in non-culprit lesions 8.7%.

Conclusions In conclusion, our data show that in patients with STEMI, a very high percentage of stent struts is covered by an early thin rim of tissue within 7 days after stent positioning. The present data bring new insights in the mechanism and timing of strut coverage.

Acute and subacute stent thromboses occur in up to 5% of patients with acute coronary syndromes.3 They can occur in both bare and drug-eluting stents (DESs) and can be due to procedural complications but may be also related to stent characteristics such as scaffold surface or drug elution.2 3 On the other hand, late thrombosis represents a rare but threatening complication of DES.4–7 The latter is mainly related to the characteristics and release modality of antiproliferative drugs.

Optical coherence tomography (OCT) is nowdays an established technique for the evaluation of vessel wall response to stent implantation8 and to address strut uncoverage and/or malapposition.9 These features are likely related to stent thrombosis; in fact, anecdotic OCT data on late stent thrombosis showed a high rate of stent uncoverage.

While there are some data in the literature on OCT evaluation of bare metal stents and DES at 3, 6 and 9 months after deployment,10–14 there are no reports on the ‘early modality’ of stent healing.

This issue was prospectively addressed in the DETECTIVE European Multicenter Registry. The Registry addressed, in an early OCT evaluation performed at 3–7 days, the patterns of coverage and apposition of the first generation of DES and cobalt chromium non-drug-eluting stents (CCSs) in patients with ST elevation acute myocardial infarction (STEMI).

METHODS

Study design and patient population

This prospective Registry included only patients with acute STEMI and a multi-vessel disease, thus eligible for a two-step procedure (3–7 days apart). Accordingly, the stent deployed at the infarct-related site was imaged by OCT during the deferred intervention. The study was therefore conceived as a two-stage design. In the first step, patients received in the culprit STEMI lesions and in non-culprit segments, when needed, either CCS or first-generation DES. Based on the study design, 30 consecutive stented lesions (15 DESs and 15 CCSs) entered the Registry in the study period (from June 2008 to June 2009). Exclusion criteria were age <18 years, unprotected left main coronary artery disease, restenotic lesions and chronic renal failure (serum creatinine ≥2.5 mg/dl).

Primary angioplasty for STEMI was performed according to standard clinical practice, and the
stent type was selected at the discretion of the operator. Coadjuvant thrombectomy was not used. In total, 16 patients (30 lesions) were enrolled. They received dual antiplatelet drugs (clopidogrel bolus of 600 mg plus 75 mg/day and aspirin 100 mg/day). Glycoprotein IIb/IIIa inhibitors were given at physicians’ discretion.

OCT analysis

Acquisition
The target stented segment was assessed by OCT to address malapposition and coverage of stent struts. Both the time domain (TD) and frequency domain (FD) C7 systems were allowed. OCT images using TD-OCT were obtained with a non-occlusive technique. Full details on this methodology are described elsewhere. Briefly, the OCT system used in this study consisted of an interface unit (Model M2 Cardiology Interface System; LightLab Imaging, Inc., Westford, Massachusetts, USA) providing images at a longitudinal resolution of 15 μm and a 0.019-inch (0.0483-cm) wire-type imaging catheter (Image-Wire; LightLab Imaging, Inc.) that contains a 0.006-inch (0.0152-cm) fibre-optic imaging core and a distal radiopaque tip, like any other conventional guidewires. A motorised pull-back system at a speed of 3.0 mm/s was used, and OCT images were acquired at 15.6 frames/s.

The FD-OCT system (LightLab Imaging, Inc.) is equipped with a tunable laser light source with a sweep range of 1.250–1.370 nm. The optical fibre is encapsulated within a rotating torque wire built in a rapid-exchange 2.6-F catheter. The FD-OCT imaging catheters were delivered over a 0.014-inch (0.0356-cm) guidewire through a 6-F or larger guiding catheters. Images were obtained at a pull-back speed of 20 mm/s.

Core laboratory assessment

Quantitative coronary angiography and OCT
Quantitative coronary angiography (QCA) analysis was performed off-line with a computer-assisted system using an automated edge detection algorithm (MEDIS, Cardiovascular Angiography Analysis System II, Fie Medical Data, Maastricht, The Netherlands). QCA analyses were performed by observers who were unaware of the treatment allocation. The treated segment was analysed using two orthogonal views. Analyses were performed preintervention and postintervention.

FD-OCT images were calibrated adjusting the Z offset. This critical step was done before image acquisition to obtain accurate measurements. All OCT frames were digitally stored and independently analysed using an off-line software (LightLab Console) by personnel blinded to procedural data and clinical outcome. For the TD-OCT images, analyses were done at 0.16-mm intervals, while for the FD-OCT images, 0.20-mm intervals were adopted. Measured tissue thickness >0 μm was defined as coverage. A stent strut was classified as malapposed when the distance between its inner surface reflection and the vessel wall was ≥160 μm for the Cypher Select, 130 μm for the Taxus Liberté and between 60 and 80 μm for CCSs. Each stent strut was therefore classified into one of four categories: (1) malapposed to vessel wall without apparent tissue coverage (uncovered and malapposed), (2) well apposed to vessel wall without tissue coverage (uncovered), (3) malapposed to the vessel wall with tissue coverage (malapposed) and (4) well apposed and with tissue coverage (figure 1). Assessment of strut tissue coverage, malapposition and thrombus formation was done at an ‘overall level’ and at a ‘stent level’. In the overall-level analysis, the number of uncovered/malapposed struts and the number of
cross sections with \( \geq 5 \) uncovered struts were calculated after having added all the analysed struts or cross sections. At a stent-level analysis, the count of strut uncoverage/malapposition or cross sections with \( \geq 5 \) uncovered struts was done for each single stent, and therefore, the final value of uncoverage or malapposition was obtained as the average of measurements calculated for each stent.

All OCT analyses were deemed of sufficient quality if the percentage of cross sections (obtained along the whole stent length) with optimal assessment was greater than 80%.

All QCA and OCT frame analyses were performed in a validated core laboratory (Rome Heart Research, Italy) by personnel blinded to procedural data and clinical outcome.

### Statistical analysis

Continuous data were expressed as mean±SD, and categorical data were expressed as proportions (%). Comparisons were performed using the \( \chi^2 \) test and unpaired t test as appropriate. All tests were two sided, and an \( \alpha \) level of 0.05 was considered statistically significant. To address whether demographic, clinical and procedural variables were related to the percentage of uncoverage, we applied an analysis of variance (ANOVA) at a stent-level analysis. The following variables were considered: age, sex, treated vessel, hypertension, hypercholesterolaemia, smoking habit, diabetes, ejection fraction, culprit versus non-culprit lesions and DES versus CCS.

### RESULTS

Two stented lesions (one patient) out of the 30 that entered the Registry were not studied by OCT at 3–7 days. One patient with two DESs (the first in a left anterior descending culprit lesion and a second in a non-culprit left circumflex) refused the deferred intervention and, as a consequence, did not undergo the OCT follow-up study. Therefore, 28 stented lesions (14 patients) eventually entered the final OCT assessment. Thirteen stents were DESs (6 Taxus Libertè, Boston Scientific (Boston – Natick, MA, USA); 4 Protaxx, Vascular Concepts (Little Maplestead, Halstead, UK); and 3 Cypher Select, Cordis Corp. Johnson & Johnson), while the remaining 15 were CCSs (8 Driver, Medtronic (Minneapolis, MN, USA); 3 Catania, Celonova (Peachtree City, GA, USA); 2 Minivision, Abbott (Abbott Park, IL, USA); 1 vCorollex, B. Braun (Melsungen, Germany); and 1 Multilink, Abbott). Eighteen stents (64%) were deployed at culprit STEMI lesions and the remaining 10 (36%) were deployed at non-culprit sites. The distribution of clinical and procedural variables for DES and CCS was not different. Likewise, there were no differences in the clinical and procedural variables of stent deployment in the culprit and non-culprit segments. Also, the time lag between stent deployment and OCT assessment did not differ (7.17±1.34 days for the DES group and 6.71±1.07 days for the CCS (\( p = 0.35 \)). Tables 1 and 2 show the demographic, clinical and procedural variables.

### Overall analysis

Data on the reproducibility of OCT measurements performed by the used core laboratory (Rome Heart Research, Italy) have been already published.

In total, 27'019 struts were analysed in 28 stents. The percentage of stent uncoverage at the overall analysis was 11.7%, while the percentage of malapposition and that of struts covered with thrombus were 4.8% and 2.2%, respectively.

Table 3 shows the amount of strut coverage, malapposition and presence of in-stent thrombotic formations in the population groups studied. A low percentage of strut uncoverage was found in all of the four subgroups: DES 12.8%, CCS 10.9%, stents deployed in culprit lesions 13.2% and stents deployed in non-culprit lesions 8.7%. The percentage of struts covered with thrombus was higher for DES and for stents deployed in culprit lesions.

The percentage of cross section having \( \geq 3 \) uncovered struts was 17.9% for DES, 18.0% for CCS, 20.7% for culprit stents and 9.3% for non-culprit stents.

### In-stent analysis

The stent-level analysis showed an overall percentage of uncovered struts of 11.0±8.9%. The percentage of uncovered struts was 12.5±3.9% in the DES group, 9.7±8.5% in the CCS group, 12.5±10.3% in culprit stents and 8.3±4.9% in non-culprit stents.

The distribution of strut coverage was non-homogeneous, as shown in figure 1. Five stents showed a percentage of uncovered struts greater than 20%; all of them (three DESs and two CCSs) were deployed in culprit lesions (figure 2).

None of the demographic clinical and procedural variables, including the stent type (DES vs CCS) and presence of culprit lesions, was found to be related to the uncoverage rate at the ANOVA.

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### Table 1 Demographical and clinical characteristics

<table>
<thead>
<tr>
<th>Patients, n</th>
<th>15</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (mean±SD)</td>
<td>57±13</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>12 (80)</td>
</tr>
<tr>
<td>Diabetes mellitus, n (%)</td>
<td>2 (13)</td>
</tr>
<tr>
<td>Dyslipidaemia, n (%)</td>
<td>9 (60)</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>11 (73)</td>
</tr>
<tr>
<td>Smokers, n (%)</td>
<td>4 (26)</td>
</tr>
<tr>
<td>Previous smokers, n (%)</td>
<td>4 (26)</td>
</tr>
<tr>
<td>EF (%)</td>
<td>52±10</td>
</tr>
</tbody>
</table>

**EF**, ejection fraction.
DISCUSSION
To our knowledge, this is the first study on very early OCT evaluation of CCSs and DESs in patients with STEMI. Our data show a fast pattern of coverage; in fact, a very high percentage of stent struts (88.3%) was found to be already covered with a thin layer at 3–7 days since stent positioning.

The literature provides data on the coverage of sirolimus-eluting stents at follow-up. The amount of strut uncoverage was about 15% at 3 months since deployment, while a slightly lower number (11%) was reported at 6 months. In the present study, the DES group showed a percentage of strut uncoverage at 3–7 days that was less than 15%.

Our findings bring further strength to the concept that stent strut coverage is a very early phenomenon that occurs in the first few days after stent positioning. The present data corroborate the conclusions from van Beusekom et al., who showed, in a porcine model, a high early incidence of strut coverage after DES positioning, with endothelial cells being present in over 60% of cases at 5 days after deployment. No human studies, however, have previously analysed stent coverage during this critical early period.

The mechanism of DES thrombosis remains unclear as it is likely a multi-factorial phenomenon. The low incidence of strut uncoverage at OCT in the very early phase supports two different theories on stent thrombosis. Stent thrombosis after DES positioning may be triggered by malfunctioning endothelial cells that, despite their presence in the early postintervention period, cannot exert a protective action against vessel thrombosis. Alternatively, stent thrombosis may occur due to the complete absence of endothelial cell coverage. This second pathophysiological scenario is sustained by some anecdotic cases of stent thrombosis, showing a much higher rate of strut uncoverage, as compared with follow-up studies performed in asymptomatic patients.

Our data add information to the mechanism and timing of strut coverage. It is likely that the stent portions that do not

<table>
<thead>
<tr>
<th>Total struts (n)</th>
<th>Uncoverage n</th>
<th>%</th>
<th>Malapposition n</th>
<th>%</th>
<th>Thrombus coverage n</th>
<th>%</th>
<th>Total CS (n)</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>DES</td>
<td>11547</td>
<td>1479</td>
<td>12.8</td>
<td>556</td>
<td>4.8</td>
<td>351</td>
<td>3.0</td>
<td>1184</td>
</tr>
<tr>
<td>CCS</td>
<td>15463</td>
<td>1680</td>
<td>10.9</td>
<td>732</td>
<td>4.7</td>
<td>253</td>
<td>1.6</td>
<td>1616</td>
</tr>
<tr>
<td>Stents in culprit lesions</td>
<td>17868</td>
<td>2360</td>
<td>13.2</td>
<td>1126</td>
<td>6.3</td>
<td>550</td>
<td>3.1</td>
<td>1732</td>
</tr>
<tr>
<td>Stents in non-culprit lesions</td>
<td>9142</td>
<td>798</td>
<td>8.7</td>
<td>163</td>
<td>1.8</td>
<td>54</td>
<td>0.6</td>
<td>1068</td>
</tr>
</tbody>
</table>

CCS, chromium cobaltum stent; CS, cross section; DES, drug-eluting stent.
heal in the early phase tend to not be covered later on, as the percentage of strut coverage slightly increases over time. As an uneven distribution of strut coverage can be appreciated in the early phase, it is likely that stents with a high rate of uncoverage (18% in our population) are those at risk of thrombosis. Assuming that strut coverage protects from thrombosis,6–8 12 15 presence of tissue coverage in the early phase should contribute to reducing the risk of thrombosis even in the acute–subacute phase. Obviously, other components, including procedural factors, exert an additional role.

It is likely that, in the future, OCT will have a role in identifying patients with high uncoverage rate and therefore at a higher risk of thrombosis. In this respect, as our study showed a high overall level of coverage within a week after stent positioning, OCT assessment may be encouraged in the early phase (1–3 months) to decide whether to interrupt the treatment with dual antiplatelet treatment.22 However, further studies are needed to select the appropriate timing and the pattern of uncoverage of patients at risk of stent thrombosis.

Uncover age ratio in the analysed groups

In all the explored groups, we found a percentage of coverage greater than 86%. Of note, a limited absolute difference in strut uncoverage (1.9%) was found between DES and CCS.

It is likely that this 1.9% difference in strut uncoverage in the two groups does not have any clinical implication. We also analysed those sites that have a large amount of uncovered metal and therefore may lead to a greater thrombogenic risk; the number of cross sections with ≥3 uncovered struts did not differ in the two groups. Of note, none of the demographic, clinical and procedural variables, including the stent type (DES vs CCS) and presence of culprit lesions, was related to the uncoverage rate at the ANOVA. These findings are in line with the well-known clinical concept that acute–subacute thrombosis is not higher for DES.

Of interest, the comparison between stents positioned in culprit STEMI lesions and those positioned in non-culprit STEMI lesions showed a higher rate of uncoverage in the culprit group, with an absolute difference of 4.5%. Our findings corroborate recent data, obtained at 6 months of follow-up, and reveal that incomplete stent apposition and the absence of OCT tissue coverage are more frequently detected by OCT in patients presenting with acute coronary syndromes. This finding is likely due to the presence of thrombus, a milieu that facilitates stent malapposition and hampers the process of vessel healing.23

Thrombotic depositions and malappositions

Thrombotic depositions on stent struts and malappositions were very uncommon (<1% and 2%, respectively) in non-culprit segments and were more frequent in DESs and culprit stents. Although the clinical significance of the thrombotic depositions on stent struts is still unknown, it is reasonable to hypothesise that the presence of thrombus after stenting elevates the risk for acute and subacute stent thrombosis.

In patients with acute coronary syndrome, the mechanism for malapposition likely involves the absorption of mural thrombus. Previous angiographic studies brought further strength to this concept, by showing that lesions leading to acute coronary syndromes are frequently associated with thrombus formation and that the thrombotic volume decreases serially.24

The tissue coverage we identified at OCT in the early phase can be due to residual thrombus encroachment instead of early vessel ‘healing’. Had we acquired OCT images immediately after stent positioning, we could have related residual thrombosis to the process of tissue coverage. However, in patients with acute coronary syndrome, the percentage of struts covered with thrombus at OCT immediately after intervention is much less than the percentage of coverage reported in our study.23

LIMITATIONS

A major limitation resides in the inability of OCT to differentiate the endothelial cells. Therefore, the layer of tissue that is shown by OCT may be made of tissue such as fibrin or other extracellular/cellular components without endothelial cells.

Other limitations of our study are in the small number of patients we evaluated and in the inclusion of different kinds of stents.

In the present, study some OCT acquisitions were done with a novel FD C7 OCT, having a better resolution in comparison with the previous TD-OCT. It is therefore possible that the previous TD-OCT underestimated the amount of strut coverage. This may bias any comparison with previous findings of follow-up stent assessment at OCT. However, FD-OCT analysis was done in a limited number of cases (four stents) and was well distributed between the two groups (one for CCS and three for DES).

Statistical assessments to address the relationship between stent type and presence of culprit lesions were performed at a stent-level analysis. As only 28 lesions (stents) entered the model, other studies addressing larger populations are needed to further elucidate this issue.

CONCLUSIONS

In conclusion, our data show that in patients with STEMI, a very high percentage of stent struts is covered by an early thin rim of tissue within 7 days after stent positioning. The present data bring new insights in the mechanism and timing of strut coverage.

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Competing interests None.

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Interventional cardiology


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