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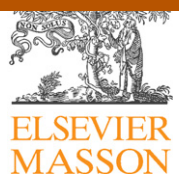

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CLINICAL RESEARCH

Comparative analysis of neointimal coverage with paclitaxel and zotarolimus drug-eluting stents, using optical coherence tomography 6 months after implantation

Analyse comparative de la réendothélialisation de stents actifs au paclitaxel et au zotarolimus en imagerie par cohérence optique six mois après implantation

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KEYWORDS
Drug-eluting stent;
Neointimal coverage;
Paclitaxel;
Zotarolimus

Summary
Background. — Intrastent thrombosis, while rare, has a poor prognosis. Strut non-coverage is one causal factor, especially in cases of resistance to or premature discontinuation of dual antiplatelet therapy.
Aim. — To compare neointimal coverage with paclitaxel and zotarolimus drug-eluting stents, using optical coherence tomography (OCT).
Methods. — Twenty-two drug-eluting stents (11 paclitaxel-eluting stents and 11 zotarolimus-eluting stents) were examined by OCT, 6 months after implantation. Mean neointimal strut-coverage thickness and percentage neointimal hyperplasia were measured every millimetre. On each OCT image, struts were classified into one of four categories: well-apposed to vessel wall with apparent neointimal coverage; well-apposed to vessel wall without neointimal coverage; malapposed to the vessel wall; or located on a major side branch.

Abbreviations: DES, Drug-eluting stent; LA, Lumen area; OCT, Optical coherence tomography; PES, Paclitaxel-eluting stent; SA, Stent area; ZES, Zotarolimus-eluting stent.

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Results. — OCT analysis showed a lower percentage of neointimal hyperplasia with paclitaxel-eluting stents than with zotarolimus-eluting stents (17% vs 38% and mean thickness 154 μm vs 333 μm, respectively; $p < 0.0001$). The rate of strut-coverage was greater with zotarolimus-eluting stents than with paclitaxel-eluting stents (99.1% vs 87.1%, respectively; $p < 0.0001$). A non-covered/covered strut ratio greater than 0.3 was observed in 0.5% of zotarolimus-eluting stent OCT images compared with 18% of paclitaxel-eluting stent OCT images ($p < 0.0001$).
Conclusion. — Six months after implantation, neointimal hyperplasia was greater with zotarolimus-eluting stents compared with paclitaxel-eluting stents. Conversely, neointimal strut-coverage was better with zotarolimus-eluting stents.

MOTS CLÉS
Paclitaxel ;
Réendothélialisation ;
Stents actifs ;
Tomographie par cohérence optique ;
Zotarolimus

Résumé
Contexte. — La thrombose de stent reste un évènement rare mais de mauvais prognostic. Un des facteurs est l'absence de réendothélialisation des stents, notamment en présence de résistance ou d'arrêt prématuré du traitement antiagrégant plaquettaire.
Objectif. — Comparer l'hyperplasie néointimale à six mois de stents actifs au paclitaxel et au zotarolimus en imagerie par cohérence optique.
Méthode. — Vingt-deux stents actifs ont été analysé en imagerie par cohérence optique : 11 au paclitaxel et 11 au zotarolimus six mois après leur implantation. L'épaisseur moyenne de la néo-intima est mesurée tous les millimètre ainsi que le pourcentage d'hyperplasie néointimale. Chaque maille est qualifiée de couverte, non couverte, malapposée ou en regard de collatérale.
Résultats. — L'analyse OCT retrouve un pourcentage d'hyperplasie néo-intimale moindre dans le groupe paclitaxel : 15 % versus 38 % avec une épaisseur moyenne de 154 μm versus 333 μm, respectivement; $p < 0{,}0001$. Les mailles sont plus souvent couvertes dans le groupe zotarolimus (99,1 % vs 87,1 %, $p < 0{,}0001$). Un ratio nombre de mailles non couvertes/couvertes supérieur à 0,3 est retrouvé sur 0,5 % des coupes de stents au zotarolimus (un des 11 stents) vs 18 % dans le groupe paclitaxel (sept des 11 stents) ($p < 0{,}0001$).
Conclusion. — La prolifération néo-intimale est plus importante après implantation d'un stent au zotarolimus qu'avec les stents au paclitaxel. Elle s'accompagne à six mois d'une meilleure couverture des mailles observée en tomographie par cohérence optique.

Introduction

Randomized studies have shown that drug-eluting stents (DESs) reduce clinical restenosis rates significantly compared with bare-metal stents [1—4] due to inhibition of intimal neoproliferation [5]. Animal and autopsy studies, however, have shown this effect to be associated with delayed or deficient re-endothelialization. It is therefore advisable to continue dual antiplatelet therapy beyond the first month poststenting to avoid the extreme danger of late intrastent thrombosis [6]. In a series of 8000 DESs, Daemen et al. reported a consistent 0.6% late thrombosis rate over the first 3 years poststenting [7].

Intrastent thrombosis is a multifactorial phenomenon [8], but one significant factor is the failure of stent—strut re-endothelialization [9]. Postmortem studies of stented subjects [10] have reported that deficient re-endothelialization is associated more frequently with late intrastent thrombosis than with other causes of death [11,12].

Angioscopy has been the only in vivo imaging technique available for studying re-endothelialization, but it does not enable quantification [9,13]. Angiography sheds light only on restenosis, while intravascular ultrasound imaging lacks sufficient resolution to reveal stent coverage accurately. Optical coherence tomography (OCT) is a high-resolution (around 10 μm) imaging technology that is particularly well adapted for the study of the most superficial layers of the vessel wall and for strut-by-strut stent analysis. Several recent studies have focused on OCT analysis of neointimal coverage in bare-metal and first-generation drug-eluting (sirolimus) stents [14—17].

In this study, we used OCT to compare neointimal coverage at 6 months poststenting with two types of DES: a paclitaxel-eluting stent (PES) and a zotarolimus-eluting stent (ZES).

Methods

Study population

Between October 2006 and September 2007, 19 patients (16 men, 3 women) were included in the study. These patients were selected from the 790 patients treated in our centre, using the following inclusion criteria: consent, feasibility of OCT and DES indication. After randomization, the patients received a DES in a native coronary artery: 11 paclitaxel-eluting stents (PESs) and 11 zotarolimus-eluting stents (ZESs). Exclusion criteria were left main coronary artery stenosis, bypass lesion, ostial stenosis, renal insufficiency, acute-phase infarction and contraindication to a DES.

An angiographic control was scheduled at 6 months poststenting. Restenosis was defined as greater than 50% lumen narrowing on angiography.

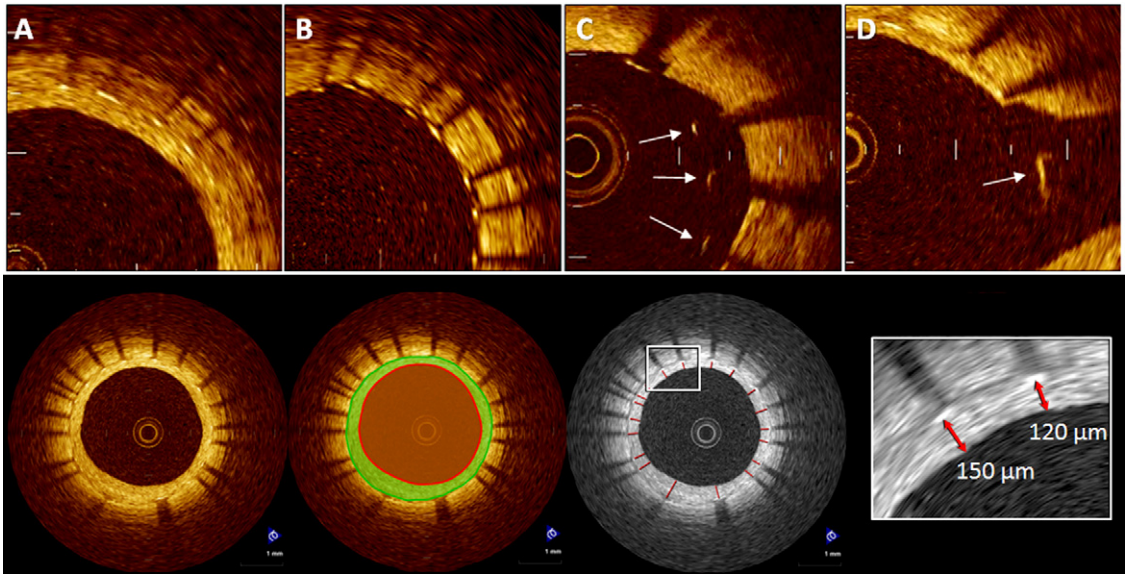

Figure 1. Drug-eluting stent analysis on optical coherence tomography millimetric images: top, qualitative strut analysis. A. Covered. B. Non-covered. C. Malapposed. D. Facing collateral. Bottom, quantitative analysis: intrastent area (green), lumen area (red), coverage thickness per strut (red arrows).

Optical coherence tomography procedure

OCT was conducted 6 months after stenting, immediately after the control angiography. Unfractionated heparin (30 IU/kg) was injected intra-arterially via a 6F catheter. A 0.014-inch guide was introduced into the vessel and positioned distally to the stent. A Helios™ coaxial occlusion balloon catheter (LightLab Imaging, Westford, MA, USA) was then introduced along the guide across the vessel until the balloon marker was at the distal extremity of the stent. The guide was withdrawn and replaced by a 1.4F optic fibre, connected to the occlusion balloon catheter and inserted through the balloon until distal to the stent. The occlusion balloon was then withdrawn until proximal to the DES and inflated to between 0.4 and 0.7 atm. Physiological saline was injected downstream of the occlusion balloon catheter via its coaxial catheter; 30 mL were injected during each pullback. OCT gives a clear image once the medium is sufficiently transparent. Automatic light-source pullback then began (1 mm/s, with 15 images per second acquisition). A 30 mm DICOM-format video recording was made of the artery, including the stented segment. The balloon was then deflated and the saline injection stopped. Several pullbacks may be needed for analyses exceeding 30 mm. The pullbacks were repeated until perfect visualization of the whole length of all stents was obtained.

Optical coherence tomography analysis

OCT images were selected from the DICOM pullback recordings every millimetre (every 15 images) over the entire stented segment and analysed by two independent operators. Lumen area (LA, in mm^2) and stent area (SA, in mm^2) were measured on each image, to enable calculation of the percentage neointimal hyperplasia area (SA-LA/SA $\times$ 100). Neointimal hyperplasia thickness was measured on each strut (Fig. 1). The struts visible in each image were classified into four categories:A: well-apposed to the vessel wall with apparent neointimal coverage;B: well-apposed to the vessel wall but without neointimal coverage (non-coverage defined as the absence of any visible structure between the lumen and vessel on OCT, with strut reflection);C: malapposed to the vessel wall without neointimal coverage (malapposition defined as > 110 µm between the reflection of the stent strut and the vessel wall, corresponding to OCT axial resolution + thickness of stent strut);D: in a bifurcation.

The percentage of covered struts per OCT image was noted.

Statistical analysis

The data had a multilevel hierarchical structure. The PES group comprised 11 patients with 11 stents and the ZES group eight patients with 11 stents; three patients in the ZES group with two stents each were individualized for analysis. In terms of OCT images, there were 200 PES items and 195 ZES items; in terms of struts, there were 2511 PES items and 2615 ZES items.

Quantitative variables are presented as mean $\pm$ standard deviation for the two groups. For qualitative variables, contingency tables were drawn up for the study population as a whole. The rates for each coverage category were calculated for the total of 5126 struts and were treated as continuous quantitative variables. The PES and ZES groups were compared in terms of the various variables by the non-parametric Wilcoxon test for quantitative variables and Fisher's exact test for the 2×2 tables of qualitative variables. All tests were conducted with a bilateral formulation, with first-degree risk set at 5%, using SAS v9 software (SAS Institute, Cary, NC, USA).

Table 1 Population characteristics.

Characteristic	Paclitaxel ($n=11$)	Zotarolimus ($n=8$)	p
Patients			
Age (years)	55.4 ± 11.9	59.4 ± 10.8	0.30
Men	9	7	1.00
Risk factors			
Smoking	9	5	0.60
Diabetes	2	2	1.00
Hypertension	1	1	1.00
Hyperlipidaemia	7	5	1.00
Obesity	1	4	0.11
Heredity	2	1	1.00
Coronary history	2	2	1.00
Angina	1	1	1.00
Acute coronary syndrome	10	7	
Glycoprotein IIb/IIIa inhibitor treatment	4	1	0.34
Location of stent	($n=11$)	($n=11$)	
Left anterior descending coronary artery	6	4	0.75
Left circumflex coronary artery	3	4	
Right coronary artery	2	3	
Lesion type (American College of Cardiology/American Heart Association)			
A	3	2	1.00
B1	5	5	
B2	3	4	
C	0	0	
Reference lumen diameter (mm)	2.9 ± 0.3	3.0 ± 0.3	0.82
Minimal lumen diameter (mm)	0.7 ± 0.4	0.6 ± 0.4	0.60
Lesion length (mm)	14.6 ± 5.1	14.4 ± 6.3	0.77
Stent diameter (mm)	2.9 ± 0.2	3.1 ± 0.3	0.11
Stent length (mm)	18.2 ± 5.2	17.7 ± 6.9	0.79
Inflation pressure (atm)	12.7 ± 2.1	13.3 ± 2.2	
Direct stenting	11	9	
Postdilatation	0	1	
Postangioplasty reference lumen diameter (mm)	3.0 ± 0.2	3.0 ± 0.3	
Postangioplasty minimal lumen diameter (mm)	2.9 ± 0.2	2.9 ± 0.4	
Final success	11	11	

Values are numbers or mean ± standard deviation. p = non-significant.

Results

Population characteristics

Population characteristics are given in Table 1. Most patients underwent angioplasty after a non-ST-segment elevation acute coronary syndrome (17 patients). The two groups did not differ significantly in terms of clinical characteristics or lesion type and all lesions were de novo. Stent diameters ranged from 2.5 to 4.0 mm and lengths from 9 to 32 mm. There were no complications secondary to angioplasty during the 6-month follow-up period under dual antiplatelet therapy or during the OCT procedure.

Angiographic analysis

Before angioplasty, there were no significant intergroup differences in reference or minimum diameter: 2.9 ± 0.3 mm and 0.7 ± 0.4 mm, respectively, in the PES group and 3.0 ± 0.3 mm and 0.6 ± 0.40 mm, respectively, in the ZES group ($p=0.82$ and $p=0.60$, respectively). Mean lesion length was 14.6 ± 5.1 mm in the PES group and 14.4 ± 6.3 mm in the ZES group ($p=0.77$). At 6 months, there was no intrastent restenosis requiring further revascularization.

Optical coherence tomography analysis

OCT was performed in all 22 patients. Thirty-five pullbacks were performed to analyse the 22 stents. In all, 395 mm of stent were studied and 5126 struts were visualized (200 PES OCT cross-sectional images, for 2511 struts; 195 ZES OCT cross-sectional images, for 2615 struts). Strut coverage thickness was estimated by two independent operators. Concordance with quantitative measurements was virtually perfect, with an intraclass correlation coefficient of 0.99. The value submitted to analysis was the mean of the two observers' estimates. Strut coverage was likewise classified in the four exclusive categories by the two independent observers, again with

Table 2 Neointimal hyperplasia and strut coverage.

	Paclitaxel	Zotarolimus	*p*
OCT images	(*n* = 200)	(*n* = 195)	
Lumen area (mm^2)	6.53 ± 2.20	5.09 ± 2.80	< 0.0001
Intrastent area (mm^2)	7.78 ± 1.78	7.89 ± 2.83	0.64
Neointimal hyperplasia area (mm^2)	1.25 ± 1.23	2.81 ± 1.09	< 0.0001
Proliferation rate (%)	17 ± 16	38 ± 15	< 0.0001
OCT images with > 70% covered struts	82.0	99.5	< 0.0001
Mean strut-cover thickness (mm)	0.154 ± 0.133	0.333 ± 0.147	< 0.0001
Struts (%)	(*n* = 2511)	(*n* = 2615)	
Covered	87.1	99.1	< 0.0001
Non-covered	9.9	0.2	< 0.0001
Malapposed	1.8	0.4	0.012
Facing collateral	1.2	0.3	0.011

Values are mean ± standard deviation or percentage.

virtually perfect agreement (kappa = 0.99). In cases of disagreement, the category adopted for analysis was determined by a third observer. Results are shown in Table 2.

Neointimal thickness

Mean endothelial thickness was 154 ± 133 μm in the PES group and 333 ± 147 μm in the ZES group ($p < 0.0001$) (Fig. 2).

Stent area did not differ significantly between groups (7.78 ± 1.78 mm^2 in the PES group vs 7.89 ± 2.83 mm^2 in the ZES group; $p = 0.64$).

Neointimal proliferation was greater in the ZES group, with a mean lumen area of 5.09 ± 2.80 mm^2 vs 6.53 ± 2.20 mm^2 in the PES group ($p < 0.0001$) and a percentage neointimal hyperplasia of 38 ± 15% versus 17 ± 16% in the PES group ($p < 0.0001$).

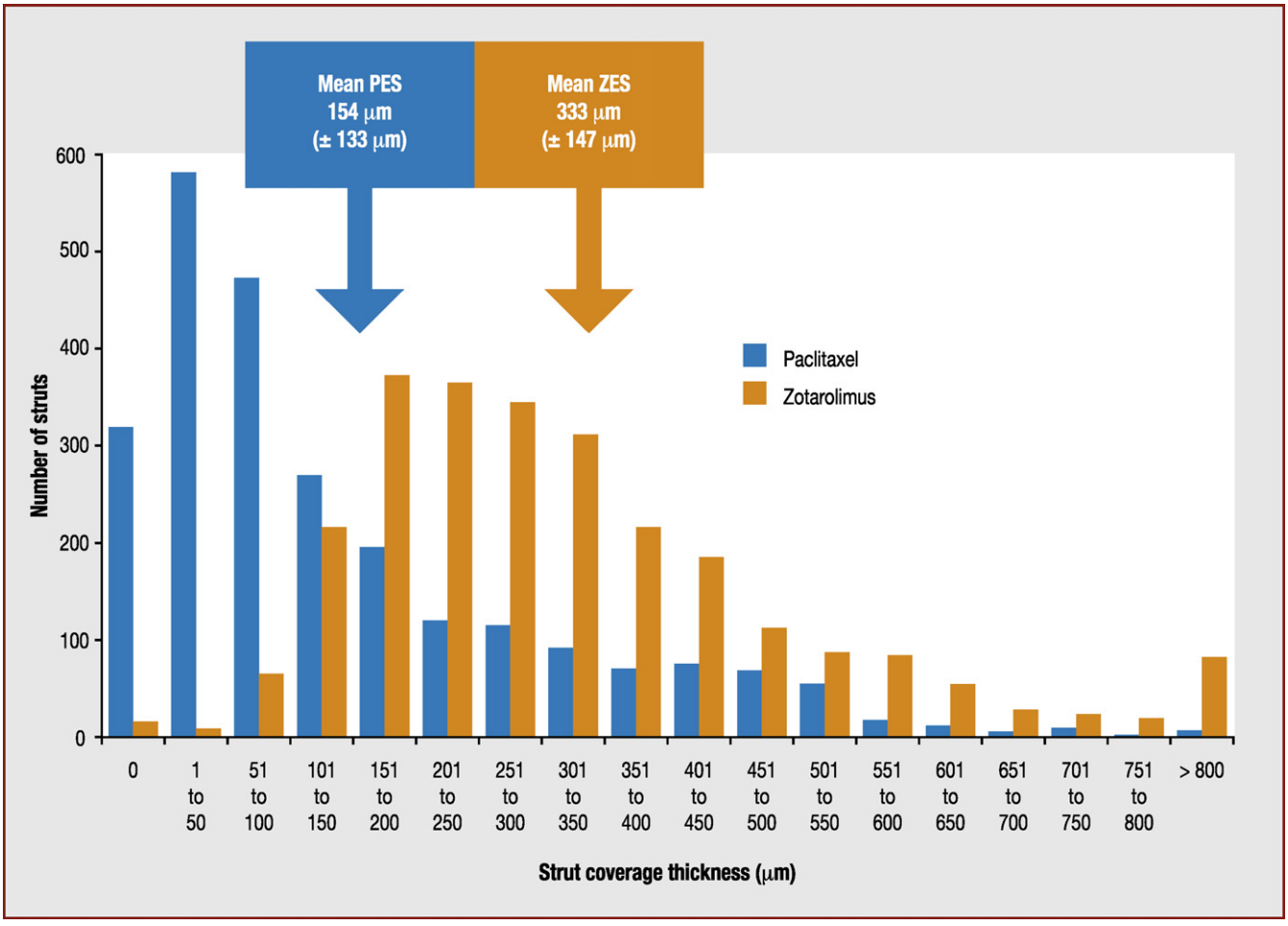

Figure 2. Distribution of strut coverage thickness in paclitaxel-eluting stent (PES) and zacrolimus-eluting stent (ZES) groups.

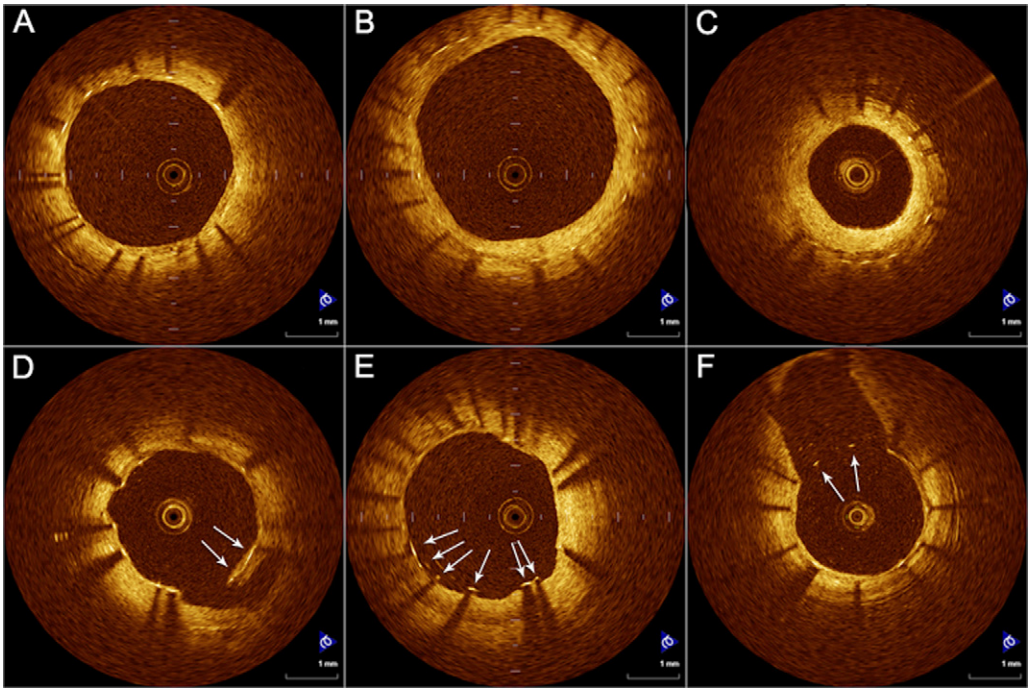

Figure 3. Examples of optical coherence tomography images. A. Paclitaxel-eluting stent, 3.0 × 20 mm, neointimal hyperplasia area 13%, mean neointimal hyperplasia thickness 95 μm, 100% covered struts. B. Zacrolimus-eluting stent, 4.0 × 9 mm, neointimal hyperplasia area 26%, mean neointimal hyperplasia thickness 270 μm, 100% covered struts. C. Zacrolimus-eluting stent, 2.5 × 8 mm, neointimal hyperplasia area 47%, mean neointimal hyperplasia thickness 375 μm, 100% covered struts. D. Paclitaxel-eluting stent, 2/11 struts malapposed. E. Paclitaxel-eluting stent, 6/19 struts non-covered, 68% covered. F. Paclitaxel-eluting stent, 2/12 struts facing collateral branch.

Neointimal coverage

The incidence of non-covered struts was greater in the PES group (12.9% vs 0.9%; $p < 0.0001$); there was also a higher rate of malapposition in the PES group (1.8% vs 0.4%; $p < 0.0001$) (Fig. 3). Non-coverage of more than 30% of struts per OCT image also occurred more frequently in the PES group (18% vs 0.5%; $p < 0.0001$). Seven PESs but only one ZES were associated with a covered/non-covered strut ratio of greater than 0.3 on at least one OCT image. No thrombi were observed in any of the 22 examinations.

Discussion

Intrastent thrombosis is rare, but has an extremely serious prognosis and a reported mortality reaching 45% [6,18,19]. Strut non-coverage is one causal factor, especially in cases of resistance to or premature discontinuation of dual antiplatelet therapy. There is, however, a lack of tools for the in vivo study of re-endothelialization. For these purposes, OCT would seem to be reliable, providing precise, reproducible, strut-by-strut measurements. Our experience was that interobserver variability was negligible and that all images were analysable in an appropriately selected population. At 10 μm, resolution is excellent, individualizing each strut.

Initial OCT studies focused on endothelialization of sirolimus-eluting stents. Takano et al., studying 31 sirolimus-eluting stents 3 months poststenting, reported a mean neointimal thickness of 29 μm. The percentages of non-covered and malapposed struts were 15 and 6%, respectively [16]. Matsumoto et al., with 57 sirolimus-eluting stents 6 months poststenting, reported a mean neointimal thickness of 52.5 μm and 8% non-covered struts, including 1% malapposed [15]. Takano et al., after 2 years of follow-up of 21 patients with a sirolimus-eluting stent, reported a mean neointimal thickness of 71 μm, with 5% of struts remaining non-covered [17].

Our present study is the first OCT comparison of neointimal coverage between two types of DESs. The data show greater neointimal hyperplasia at 6 months in the ZES group (333 μm vs 154 μm in the PES group). In this short series, neointimal hyperplasia did not lead to angiographic restenosis, but did result in almost total strut coverage in the ZES group, in agreement with previous angiographic findings based on late-loss. Pocock et al., in 11 randomized trials, reported less than 0.21 mm late-loss with sirolimus-eluting stents, between 0.30 mm and 0.49 mm with PESs, between 0.60 and 0.61 mm with ZESs, and between 0.80 and 1.06 mm with bare-metal stents [20]. There is a curvilinear correlation between late-loss and reintervention rates, with a low incidence of clinical events when late-loss is less than 0.65 mm [21]. This may account for the lack of observed clinical benefit in studies that compared different DESs. Like angiography, OCT disclosed greater neointimal hyperplasia with ZESs than with PESs. On the other hand, significantly fewer non-covered struts were found with ZESs than with PESs. Postmortem series confirm that lack of endothelial strut coverage is the prime histological predictor of late thrombosis: the relative risk of intrastent thrombosis increases ninefold in cases of non-coverage of greater than 30% of struts per OCT image [11]. Takano et al. [17], applying this prognostic index in an OCT study, found 38% of

patients with a sirolimus-eluting stent presenting with this thrombosis risk factor, 2 years poststenting. In our present study, this was the case in 64% of PES patients and 9% of ZES patients, 6 months poststenting.

In the literature, there was a significant difference between the rate of late thrombosis in the DES era (< 1% per year) and the rate of deficient coverage observed in vivo on OCT, even at 2-year follow-up. Thus, non-coverage is not a sufficient condition for the development of late thrombosis, but may be a determining risk factor when associated with others, such as premature discontinuation of antiplatelet therapy. These findings lead us to continue dual antiplatelet therapy beyond the first 6 months after DES stenting in patients who do not have a high risk of haemorrhage, in line with the latest guidelines [22—24]. Some studies have indeed reported that termination of clopidogrel treatment at 6 months post-DES-stenting was associated with increased late thrombosis and elevated mortality rates [24,25]. Our present study and previous studies show OCT to be an adapted tool for quantifying stent re-endothelialization and partial strut coverage with safety [26]. Future randomized comparative OCT trials may provide prognostic factors shedding light on poststenting healing and help to determine the optimal course of dual antiplatelet therapy. The correlation between the number of non-covered struts and the risk of late thrombosis still requires validation, however, in a larger prospective study.

Our study has a number of limitations. The sample size was small and from a single centre. OCT itself involves certain limitations: it requires transitory occlusion of the coronary artery, precluding analysis of the most proximal segments; currently, it does not have sufficient resolution to rule out the beginnings of re-endothelialization in the form of a 5-μm thick cellular monolayer; finally, tissue characterization is not always straightforward, hence the structure covering certain struts may be taken for neoproliferation, when it is, in fact, simply fibrin. Technological progress can be expected to alleviate these limitations.

Conclusion

OCT provides precise measurement of intimal hyperplasia volume and neointimal coverage of stent struts. The present comparative study found better strut re-endothelialization with zotarolimus stenting than with paclitaxel stenting, at the cost of greater mean hyperplasia — although not enough to cause restenosis.

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