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Atherosclerotic plaque behind the stent changes after bare-metal and drug-eluting stent implantation in humans: Implications for late stent failure?

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ABSTRACT

Background and aims: The natural history and the role of atherosclerotic plaque located behind the stent (PBS) are still poorly understood. We evaluated the serial changes in PBS following bare-metal (BMS) compared to first-generation drug-eluting stent (DES) implantation and the impact of these changes on in-stent neointimal hyperplasia (NIH).

Methods: Three-dimensional coronary reconstruction by angiography and intravascular ultrasound was performed after intervention and at 6–10-month follow-up in 157 patients with 188 lesions treated with BMS (n = 89) and DES (n = 99).

Results: There was a significant decrease in PBS area (−7.2%; $p < 0.001$) and vessel area (−1.7%; $p < 0.001$) after BMS and a respective increase in both areas after DES implantation (6.1%; $p < 0.001$ and 4.1%; $p < 0.001$, respectively). The decrease in PBS area significantly predicted neointimal area at follow-up after BMS (β: 0.15; 95% confidence interval [CI]: 0.10–0.20, $p < 0.001$) and DES (β: 0.09; 95% CI: 0.07–0.11; $p < 0.001$) implantation. The decrease in PBS area was the most powerful predictor of significant NIH after BMS implantation (odds ratio: 1.13; 95% CI: 1.02–1.26; $p = 0.02$).

Conclusions: The decrease in PBS area after stent implantation is significantly associated with the magnitude of NIH development at follow-up. This finding raises the possibility of a communication between the lesion within the stent and the underlying native atherosclerotic plaque, and may have important implications regarding the pathobiology of in-stent restenosis and late/very late stent thrombosis.

1. Introduction

The predictive power of atherosclerotic plaque located behind the stent (PBS) on subsequent neointimal growth and restenosis has been a focus for research over the past two decades. In the early era of percutaneous coronary revascularization, ample evidence showed that the amount of residual atherosclerotic plaque after coronary balloon angioplasty or atherectomy correlates with restenosis rate [1,2]. In contrast, the role of PBS after coronary stenting remains controversial [3–6].

In-stent restenosis remains a major limitation of bare-metal stents (BMS). While drug-eluting stents (DES) drastically reduce its occurrence, they do not eliminate it [7]. It mainly results from aggressive neointimal hyperplasia (NIH), but recent data also indicate a shift in the underlying pathological substrate toward restenotic lesions with a higher proportion of in-stent atherosclerotic plaque or neoatherosclerosis [8]. The pathogenesis of in-stent atherosclerosis development is poorly understood.

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The present post hoc analysis of Prediction of Progression of Coronary Artery Disease and Clinical Outcome Using Vascular Profiling of Shear Stress and Wall Morphology (PREDICTION) study offers the opportunity to investigate the natural history of PBS after implantation of BMS compared to sirolimus-eluting (SES) and paclitaxel-eluting (PES) stents and provide insight into its role in neointimal formation.

2. Materials and methods

2.1. Study population

We analyzed the data of patients enrolled in the PREDICTION study [9], a prospective, multicenter study investigating the role of endothelial shear stress and vascular remodeling in the anatomic natural history of coronary atherosclerosis in patients presenting with an acute coronary syndrome. The patients underwent intracoronary vascular profiling with intravascular ultrasound (IVUS) and angiography of all major coronary arteries at the time of percutaneous coronary intervention. A large subset of consecutive, unselected patients underwent routine follow-up vascular profiling after 6–10 months to assess the anatomic natural history in relation to antecedent vascular characteristics. The study was performed in Japanese clinical sites because patients routinely undergo follow-up catheterization after successful percutaneous coronary intervention for an acute coronary syndrome, and this clinical practice facilitated the performance of a large natural history study. The PREDICTION study found that new cardiac events (primarily requirement of a percutaneous coronary intervention for rapid progression of luminal obstruction), were correlated with a large plaque burden, but observed as well that local low endothelial shear stress was also an independent determinant of new cardiac events. The study population of the present analysis consisted of 157 patients with available serial (post-stenting and at 6–10-month follow-up) angiographic and IVUS data, who underwent BMS, SES (Cypher, Cordis, Johnson & Johnson, Miami Lakes, FL), or PES (Taxus, Boston Scientific Corporation, Natick, MA) implantation for culprit or non-culprit native de novo lesions (study flowchart in Supplemental Fig. 1). The selection of stents depended on the operator's decision and local hospital policy. Inclusion criteria of PREDICTION study included age >18 years and presentation with an acute coronary syndrome requiring percutaneous coronary intervention. Exclusion criteria included heart failure New York Heart Association class III/IV, unstable clinical status, left main or 3-vessel coronary artery disease, significant coronary calcification precluding IVUS evaluation, renal failure such that additional contrast material would be contraindicated, clinically significant valvular disease, and life expectancy <12 months. The study protocol was approved by the ethics review committees at each participating center and all patients signed written informed consent before enrollment.

2.2. Three-dimensional coronary artery reconstruction procedure and analysis

The vascular profiling procedure was performed to reconstruct the coronaries arteries in three-dimensional (3D) space [9]. In brief, the 3D anatomy of the stented coronary artery was reconstructed from two planes of coronary angiography and electrocardiographically gated IVUS images (Galaxy IVUS system with the Atlantis 40 MHz SR Pro IVUS catheter, Boston Scientific, Natick, MA) performed with automated pullback at 0.5 mm/s. The arterial lumen and outer vessel wall (area within the external elastic membrane [EEM]) were reconstructed from digitized and segmented end-diastolic IVUS frames, using a semi-automated system to trace the lumen and EEM borders. Each frame was aligned perpendicular to the catheter core. The boundary points of each frame were connected by spline curves to rebuild the luminal and outer vessel wall geometry in 3D space. In the stented regions, the stent borders were manually traced in digitized and segmented end-diastolic IVUS frames and the 3D geometry of the stent was then reconstructed. The 3D geometry of the neointima was taken as the difference between the stent and the lumen. We divided the entire 3D-reconstructed stented artery into consecutive 1.5-mm segments. For analysis of serial anatomic changes, each arterial segment at baseline was compared with the identical segment at follow-up. Segments with incomplete apposition, defined as a separation of at least one stent strut from the intimal surface of the arterial wall, were excluded from analysis (193 segments). The following measurements were obtained for each segment: (i) lumen area, (ii) stent area, (iii) vessel (EEM) area, (iv) neointimal area (stent area minus lumen area), and (v) PBS (plaque plus media) area (vessel area minus stent area). Change (Δ) in each parameter was provided as follow-up minus baseline measurement. Due to the very low rate of adverse events in our low-risk population we used significant NIH (defined as neointimal area >50% of stent area) as a binary anatomic outcome. Reproducibility and validation of IVUS measurements have been previously reported [10].

2.3. Statistical analysis

Continuous variables with normal and non-normal distribution are expressed as mean ± SD and median and interquartile range (IQR), respectively. Categorical variables are presented as counts (percentages) and compared using the chi-square test. Analyses of area comparisons were performed on a per-segment basis. The association of continuous response variables with categorical variables was evaluated by implementing mixed-effects analysis of variance with the patient designated as random effects to account for within-subject correlation due to the analysis of multiple segments in a single patient. Probability values were adjusted for multiple comparisons with the use of the Scheffé method. Linear mixed modeling was used to investigate the relationship between continuous response variables and continuous predictors. The association of binary response variable with baseline variables was evaluated by mixed-effects logistic regression. Factors entered into the univariable analysis included baseline vessel, lumen, and PBS areas and their respective changes from baseline to follow-up. Variables associated with anatomic outcomes on univariable analysis at p level <0.1 were considered for entry in the respective multivariable models, and non-significant variables were dropped by means of backward selection. Clinical variables (e.g., diabetes mellitus, statin use) were not associated with ΔPBS area and were, therefore, excluded from multivariable models. A value of $p < 0.05$ was considered statistically significant.

3. Results

3.1. Patient and lesion characteristics

Patient characteristics are summarized in Table 1. Age, gender, and coronary risk factors were not different among stent groups. Moreover, comparable baseline demographic data indicate that the data in the present analysis are representative of the PREDICTION population. As shown in Table 2, the prevalence of underlying culprit lesion was higher in BMS than in SES and PES groups (89.9% *vs.* 54.4% *vs.* 48.4%, respectively; $p < 0.001$). Stent lengths were shorter in BMS compared to SES and PES groups (19 mm [IQR: 16–26 mm] *vs.* 22 mm [IQR: 17–29 mm]) *vs.* 21 mm [IQR: 17–28 mm], respectively; $p = 0.02$).