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Investigation of Drug Eluting Stents performance in human atherosclerotic artery through *in silico* modeling*

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Abstract— **Atherosclerosis is a chronic inflammatory disease associated with heart attack and stroke. It causes the growth of atherosclerotic plaques inside the arterial vessels, which in turn results to the reduction of the blood flow to the different organs. Drug-Eluting Stents (DES) are mesh-like wires, carrying pharmaceutical coating, designed to dilate and support the arterial vessel, restore blood flow and through the controlled local drug delivery inhibit neo-intimal thickening. *In silico* modeling is an efficient method of accurately predicting and assessing the performance of the stenting procedure. The present *in silico* study investigates the performance of two different stents (Bare Metal Stent, Drug-Eluting Stent) in a patient-specific coronary artery and assesses the effect of stent coating, considering that the same procedural approach is followed by the interventional cardiologist. The results demonstrate that even if small differences are obtained in the two models, the incorporation of the stent coatings (in DES) does not significantly affect the outcomes of the stent deployment, the stresses and strains in the scaffold and the arterial tissue. Nevertheless, it is suggested that regarding the DES expansion, higher pressure should be applied at the inner surface of the stent.**

I. Introduction

Cardiovascular disease (CVD) is, globally, the leading cause of mortality [1]. It has been estimated that approximately 17.9 million deaths are attributed to CVDs, which accounts for 31% of deaths internationally [1]. Coronary Artery Disease (CAD), the most prevalent type of CVD, is prominently manifested by the development of atherosclerotic plaque in heart vessels, ultimately leading to vessel occlusion and reduction of the blood flow to the heart muscle.

Percutaneous coronary revascularization has established minimally invasive clinical protocols with stent scaffolds towards treating the stenosed arterial vessels and restoring the blood flow. The purpose of such process is to create a consistent hemodynamic environment throughout the target lesion achieved by the insertion of an expandable wire-like mesh, which supports the surrounding arterial wall. Initially, Bare-Metal Stents (BMS) were used, however these scaffolds were linked with the onset of undesirable events, such as the early thrombosis (ST), due to platelet aggregation on the stent, and in-stent restenosis (ISR), due to failure in controlling the rate of neointimal hyperplasia. These adverse phenomena inevitably led to prescriptional post-operative medication for the patients, but most importantly triggered the emergence of the Drug Eluting Stents (DES). The rationale underpinning the development of DES scaffolds was that these devices can act as a medium for delivering medication directly to the intima layer of the artery and subsequently to the target lesion in whole, diminishing the challenges introduced by BMS, such as ISR [2], [3]. DES consist of the wire-like mesh surrounded by a biodegradable, polymer or non-polymer, coating containing the under-delivery medication that targets smooth muscle cell proliferation and suppresses neointimal hyperplasia. As the polymer degrades, the drug is released and absorbed by the arterial wall. Stents should provide a combination of performance aspects, such as high radial strength and minimal recoil, minimal foreshortening, radiopacity, flexibility, minimal metal to artery ratio (MTAR), non-toxicity, high resistance to thrombus formation, optimum scaffolding [4]. These performance criteria and additional safety and efficacy indicators are evaluated through: (i) *in vitro* testing, in a laboratory environment, (ii) *in vivo* testing, on animals and, (iii) clinical trials in humans. Currently, a plethora of DES are available in the market offering a range of different scaffold designs, coatings and drugs.

In silico methods combined with Finite Element Analysis (FEA) are considered the most agile and precise approaches for accurate predictions with respect to behavioral analysis of materials and structures, under different scenarios of use. *In silico* modeling has effectively stimulated research and development of new biomedical devices with optimal characteristics and performance. In this mindset, preceding efforts in the sector of FEA and *in silico* modeling of the stenting procedure showed that FEA is a reliable means of predicting the stent performance under several hypothetical scenarios [18]. In parallel, the ability of incorporating and integrating medical imaging knowledge from different imaging modalities (Optical Coherence Tomography – OCT, Intravascular Ultrasound - IVUS) and accurately representing

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the arterial tissue, opens the era for more realistic and accurate predictions.

Numerous studies investigating the stent deployment procedure, each with its own scope and limitations, are available. Several studies focused on the performance of individual stent designs, in terms of their biomechanical responses. Djukic *et al.* [5], studied the implantation of multiple stents within a patient-specific arterial segment. Karanasiou *et al*. [6] - [8] studied stent deployment in realistic arterial segments, focusing on the effect of strut thickness and materials. Geith *et al*. [9] and He *et al.* [10] investigated the type of folding and the role of the balloon in the stent expansion process, using idealized arterial segments. Schiavone *et al.* [11] studied the effects of the preliminary processes that a stent undergoes before the deployment procedure, such as the crimping and the balloon folding. Furthermore, the same authors [12], studied the effects of drug coating on the stent expansion.

This study aims to assess the behavioral performance of two stents, (BMS and DES) during the *in silico* stenting process in a stenosed patient-specific arterial segment with the presence of two types of atherosclerotic plaque, i.e. Lipid Tissue (LT) and Calcified Tissue (CT). This study exploits FEA and assesses the mechanical performance of the two stents, as well as the biomechanical response of the arterial tissue.

II. Material Models and Methods

A. *3D Reconstruction*

For the 3D reconstruction of the mid Left Anterior Descending artery, OCT images and angiographic data were obtained, and a proprietary reconstruction tool was employed [14]. The OCT segmentation process includes: (i) the pre-processing of the images with noise and catheter artefact removal, (ii) the segmentation of the lumen and the outer border of adventitia and, (iii) the detection of the atherosclerotic plaque and characterization, through the application of a Convolutional-based (CNN) pixel classification technique. Afterwards, the segmented OCT frames are coupled with angiographic data, and the detected components are aligned and oriented in space perpendicularly to the centerline of the under-investigation branch, resulting in the patient-specific stenosed arterial segment, as illustrated in Fig. Figure *1*.

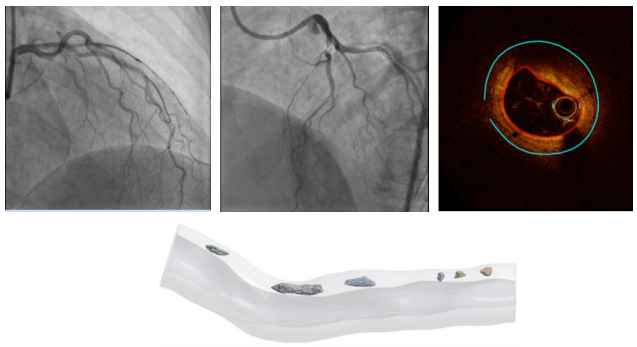

Figure 1 Angiographic data (top left & middle), OCT frame with detected lumen and adventitia borders (top right) and reconstructed 3D arterial model (bottom).

B. *Stent geometry and mesh creation*

The 3D Finite Element Models (Model A, Model B) include two components, both in their initial state i.e., the undeployed configuration: (i) stents (BMS for Model A, DES for Model B), both of which are based on the LeaderPlus stent, a commercially available stent by Rontis, (ii) the reconstructed arterial segment with the plaque components. All plaques are assigned the LT profile, besides Plaque 3 which is CT (Fig. 2). The stent geometrical specifications were provided by Rontis Corporation [15]. Both stents (BMS, DES) share the same design characteristics, however DES additionally carries the drug-coating; in the outer and inner surface of the stent, of approximate thickness 7μm and 3μm, respectively. The final FEMs and the respective geometrical details are presented in Figure 3 and Table I.

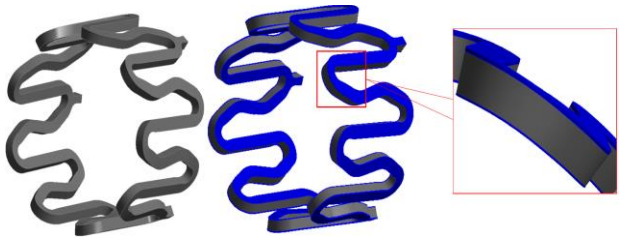

Figure 2 Cross-sectional view of one ring of the BMS (left) and DES with inner and outer coatings (middle & right).

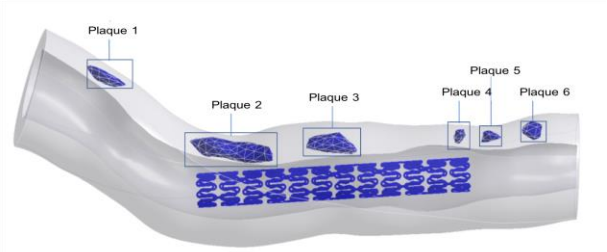

Figure 3 3D FEM model in pre-deployed configuration.

TABLE I. Stent and Arterial Geometrical Dimensions

Stent Configurations			
Model / Type	***Length (mm)***	***Inner Diameter (mm)***	***Strut Thickness (mm)***
Model A / BMS	12	1.222	0.0688
Model B / DES	12	1.219	0.0688
Artery			
Type	***Length (mm)***	***Minimum Inner Diameter (mm)***	***Degree of Stenosis (%)***
Mid LAD	54.1	1.43	36.3

ANSYS (Ansys Canonsburg, PA) [20], software was used for the implementation of the Finite Element Models. For both models (Model A, Model B), the stent/coatings and the artery have been meshed with solid lower-order hexahedral and higher-order tetrahedral elements, respectively. The final number of elements assigned to both geometries was based on a mesh sensitivity study, with the criterion being the differences in von Misses stresses captured not to exceed 5%, between each solution. The meshes that fell within this

margin were approximately 78,000 elements for the stent and 303,000 elements for the artery and plaques. For the DES mesh, 60,000 additional hexahedral elements were used due to the presence of the coating.

C. Material Properties

FEA modeling of the stent deployment procedure is a complicated process since large deformations, as well as non-linearities are involved with respect to the materials (i.e., plasticity and hyper-elasticity) and the realistic arterial geometry. In our models, in both stents, the metal core is made of Cobalt-Chromium (Co-Cr) MP35N alloy and the multi-linear isotropic hardening material model was used to represent the mechanical behavior. The drug coating is a porous material containing Polylactic acid (PLA) and the mechanical behavior was modeled as a linear elastic material. The artery was considered as a homogenous tissue and was modeled through the five-parameter Mooney–Rivlin material model [19]. The CT was assumed isotropic and linear elastic and the LT non-linear incompressible, both as suggested by Noble *et al.* [17]. The parameters used for the aforementioned material models are provided in Table II.

TABLE II. MATERIAL PROPERTIES

Stent				
Component	*Young Modulus (MPa)*	*Poisson Ratio*	*Yield Strength (MPa)*	*Tensile Strength (MPa)*
Stent	235,000	0.32	491	982
Coating	1,200	0,36	-	-
Artery				
C10	*C01*	*C20*	*C11*	*C30*
0.0189	0.00275	0.08572	0.5904	0
Plaques				
Tissue Type	*Young Modulus (MPa)*	*Poisson Ratio*	*Shear Modulus (MPa)*	*Incompressibility Parameter D1 (1/MPa)*
Calcified Tissue	1,000	0.3	-	-
Lipid Tissue	-	-	0.5	$1E^{-3}$

D. Boundary Conditions

Appropriate constrains were applied to both the artery and the stents, in order not to experience rigid body motions. The artery's ends were constrained in every direction and the stents were placed in the stenosed segment and were constrained so that only radial expansion was allowed. For the stent inflation (both in BMS and DES), direct pressure of 1.1MPa was applied at the inner surface (full expansion phase). After full expansion the pressure was removed (recoil phase). Frictional contact, with a friction coefficient 0.1, was considered between the artery and the stent.

III. Results and Discussion

Preliminary results of the models show that both stents perform in a similar way, in terms of the stresses and strains developed in the stent structure, as well as induced in the arterial wall and plaques. Both models exhibit stress induction at the stent strut crowns, as a result of the expansion of the stents and the developed strains. Small differentiations occur regarding stress induction at the arterial wall and plaques, for both models. The results are depicted in Figure *4*. Specifically, for the arterial wall the highest stresses are induced in the most stenosed part, at the thinnest fibrous cap, i.e., the cap beneath Plaque 2 and Plaque 3 (CT plaque). The plaque depth/dimensions of the fibrous cap are crucial to the stent deployment procedure, since thin atherosclerotic tissue caps are highly correlated with plaque rupture and Major Adverse Cardiovascular Events (MACE), post-operatively [16]. Additionally, Plaque 3 (CT plaque) experiences the heaviest stress induction, exhibiting the "protective role" of the respective arterial tissue cap, whereas the Plaques 2,4,5 (FT plaques) induce stresses to the tissue cap due to their incompressible nature. It is noticed that Plaques 1 and 6, located at a distance of the Region of Interest (ROI), are not affected by the stent deployment process.

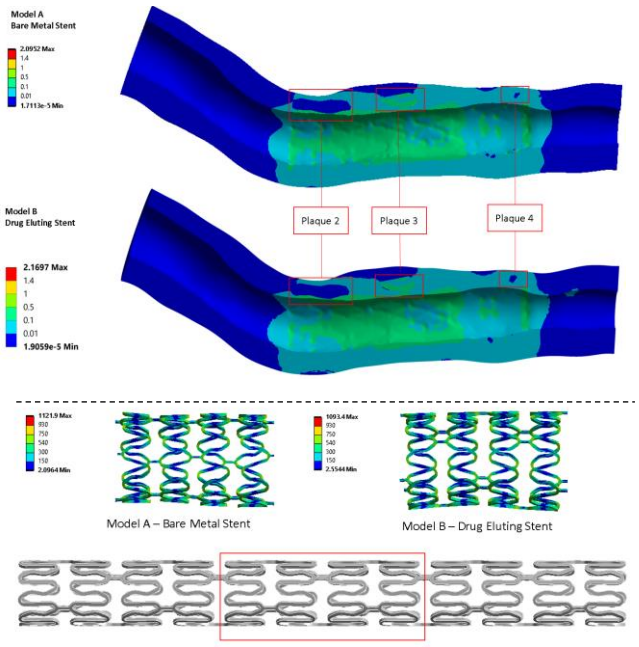

Figure 4. von Mises stresses in arterial wall and stents, in full expansion phase.

Figure 5 illustrates the total strains developed on the stents against the pressure applied on their inner surface, during the expansion and recoil phase. The strains developed in the stents indicate the deformation of the structure itself and are produced as a result of the applied pressure. It is observed that the strains exhibited on the DES are marginally smaller than those in the BMS. This is the result of the incorporation of the drug coating at the inner and outer surfaces of the DES. The additional forces applied at the DES structure for the coatings lead to a slight under-expansion. This phenomenon can be alleviated with the application of additional pressure during the inflation phase, so that the exact same order of expansion in achieved.

Figure 6 accurately depicts the impact of the drug coatings in the immediate recoil of the DES stent in comparison to the BMS. The immediate stent recoil was calculated as following:

$$\text{Recoil} = \frac{D_0 - D_1}{D_0}\ x\ 100\%\ , \qquad (1)$$

where D_0 and D_1 is the diameter in the middle part of the stent at the end of the expansion phase and after the recoil phase, respectively. Specifically, in Fig. Figure *6*, it is shown that the DES has a higher recoil rate than the BMS, i.e., approximately 0.4%, attributed to the additional forces exerted in the stent structure from the inclusion of the drug coating.

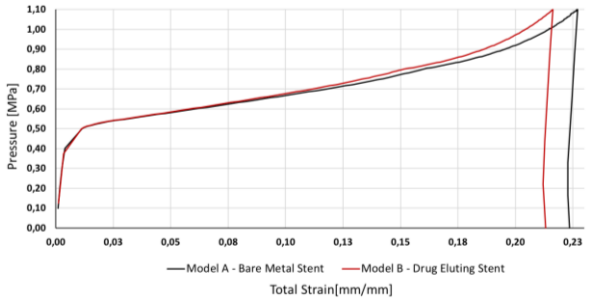

Figure 5. Total strain (elastic and plastic) against pressure applied on the inner surface of the stents.

Based on the aforementioned results, it is revealed that the DES inflation should occur with marginally higher pressure than the BMS. The reasoning behind this outcome is two-fold: (i) the under-expansion of the DES, as well as (ii) the higher recoil rate, which essentially leads to smaller diameter after the recoil phase.

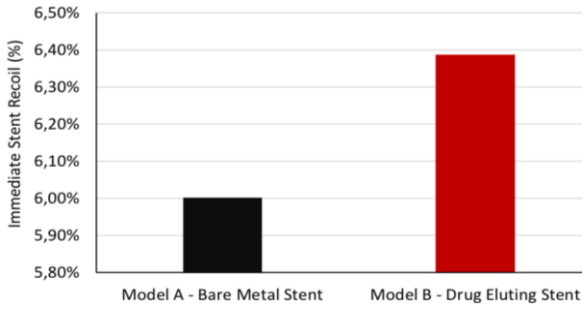

Figure 6 Immediate Stent Recoil.

IV. Conclusion

This study has demonstrated that both stents behave in a similar manner achieving almost the same performance. Although, the effects of the drug coating on the stent expansion and immediate recoil are evident, the differences, with respect to the overall performance in widening the lesion, are small. These *in silico* models constitute an initial approach in assessing the mechanical performance of stents, in realistic arterial tissues, during the stenting procedure, focusing on the effect of stent coating. In turn, the post-stenting configuration alters the hemodynamics of the arterial environment as well as the drug-delivery patterns. Therefore, in addition to the validation of the proposed approach with data from animal studies, in which the predicted lumen gain will be compared against the lumen gain from post-operative OCT images, our future work will focus on investigating the effect of the stent coatings on the restenosis and drug-diffusion mechanisms.

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