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A Strategy for the In-Silico Assessment of Drug Eluting Stents: A Comparative Study for the Evaluation of Retinoic Acid as a Novel Drug Candidate for Drug Eluting Stents

DIMITRIOS S. PLEOURAS [1,5], VASILEIOS S. LOUKAS [1,5], GEORGIA KARANASIOU [1,5], CHRISTOS KATSOURAS [2], ARSEN SEMERTZIOGLOU [3], ANARGYROS N. MOULAS [4], LAMBROS K. MICHALIS [5], AND DIMITRIOS I. FOTIADIS [1,5] (Fellow, IEEE)

[1]Unit of Medical Technology and Intelligent Information Systems, Department of Materials Science and Engineering, University of Ioannina, GR45110 Ioannina, Greece
[2]Department of Cardiology, Medical School, University of Ioannina, GR45110 Ioannina, Greece
[3]Rontis Corporation S.A., GR15125 Athens, Greece
[4]Department of Agricultural Technology, University of Thessaly, GR35100 Lamia, Greece
[5]Biomedical Research Institute – FORTH, University Campus of Ioannina, GR45110 Ioannina, Greece

CORRESPONDING AUTHOR: DIMITRIOS I. FOTIADIS (e-mail: fotiadis@uoi.gr).

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ABSTRACT In this work, a methodology for the in-silico evaluation of drug eluting stents (DES) is presented. A stent model developed by Rontis S.A. has been employed. For modeling purposes two different stent parts have been considered: the metal core and the coating. For the arterial models, we used animal specific imaging data and realistic geometries were reconstructed which were used as input to the drug-delivery model. More specifically, optical coherence tomography (OCT) imaging data from two coney iliac arterial segments were 3D reconstructed, and the preprocessed 3D stent was deployed in-silico. The deformed geometries of the in-silico deployed stents and the dilated arterial segments were used as input to the drug elution model. The same reconstructed arteries were used in three different cases: (i) Case A. The coatings contain retinoic acid at an initial concentration 49.2% w/w. (ii) Case B. The coatings contain retinoic acid at an initial concentration 1% w/w. (iii) Case C. The coatings contain sirolimus at an initial concentration 0.85% w/w. In each case, two different coatings were examined: (a) polylactic acid and (b) polylactic-co-glycolic acid. The results proved that retinoic acid is a very promising drug candidate for DES due to its binding time to the smooth muscle cells of the arterial wall that exceeds the corresponding time of sirolimus, while being non-toxic to the smooth muscle cells.

INDEX TERMS Drug eluting stents, computational modeling, controlled release. retinoic acid, sirolimus.

IMPACT STATEMENT A complete in-silico methodology for the evaluation of drug eluting stents is presented. The drug release rate of retinoic acid is much faster than other available drugs, however, it presents a prolonged effective time inhibiting restenosis.

I. INTRODUCTION

According to the World Health Organization (WHO), cardiovascular disease (CAD) remains the leading cause of death [1], [2]. Furthermore, over the past few years, there has been a progressive rise in the number of cases of CAD, which has been linked to various factors like high blood cholesterol, smoking, diabetes, obesity, and alterations in lifestyle [3], all of which are major contributors to atherosclerosis, the

predominant cause of CAD. Atherosclerosis is related to the development of plaque within the arterial walls causing arterial wall thickening and subsequently, lumen narrowing, which may lead eventually to cardiovascular events. Atherosclerosis can only be prevented either by regulating the patient's diet and physical activity, or by administering medications to lower the serum lipids. However, in the case of cardiovascular events, the immediate restoration of the blood flow on the obstructed arteries is necessary, which can be achieved exclusively by invasive techniques, such as percutaneous coronary revascularization (balloon angioplasty or stent deployment) or coronary artery bypass.

Percutaneous coronary revascularization using coronary stents was first realized in 1986 by Ulrich Sigwart [4], [5], as a way to prevent the arterial recoil of the throttled vessel and limit the arterial dissections that were observed in revascularization by balloon angioplasty. However, the first type of coronary stents, the bare metal stents (BMS), posed several risks to the arterial segment and did not prevent the proliferation of the smooth muscle cells, which causes the neointima formation and leads to restenosis [6], [4], [7], [8]. In particular, neointima formation is identified by the smooth muscle cells' accumulation in the intima region of the vessel, which is caused by inflammation within the arterial wall. To face those problems, a new generation of stents was developed; the drug eluting stents (DES). These stents can release medication locally, in a controlled manner, to the region around the deployed stent, targeting the reduction of the inflammatory response and restenosis inhibition [9].

Even though DES were superior to bare metal stents (BMS), several studies proved that the first generation of DES caused delayed reendothelialization up to 5 years, increasing the rates of myocardial infraction and late thrombosis after the end of the extended dual antiplatelet therapy (DAPT) [10]. Moreover, other studies identified the risks of the polymeric materials used in the first generation DES coatings, highlighting the increased inflammatory response [11], [12]. Several attempts were made to regulate the design and the materials of the DES stents, focusing on their safety and biocompatibility, which finally resulted in the development of the second generation of DES. Among the novel features, the most significant ones are the new polymeric materials of the coatings which contribute to less inflammatory responses, the thinner stent struts which enable faster reendothelialization, and the biocompatible stent core alloys [13].

Several studies have been conducted focusing on the DES drug release rates providing the necessary information to enable the regulation of the drug concentration within the arterial wall, which can lead either to local toxicity in case of drug excess, or to restenosis in case of drug deficiency [14], [15], [16], [17], [18], [19]. Several of those studies are based on computational modeling which enables the accurate prediction of DES drug diffusion over time. Zunino et al. [20] performed one of the first modeling approaches, and studied the 2D heparin drug release towards the adventitia layer of the arterial wall, using convection-diffusion equations for the drug release and Darcy's law for the momentum losses due to the arterial wall's porosity. Kolachalama et al. investigated the zotarolimus-drug elution in vitro and in vivo, allowing for the evaluation of various parameter values in a drug kinetics model that was employed in a 2D idealized artery model [21]. Pontrelli and de Monte [22], as well as, McGinty et al. [23], examined the drug release considering at least 3 different layers within the arterial wall, the intima, media and adventitia. A 2D analysis of the stent coating's drug release towards both the lumen and the arterial wall was performed by O'Brien et al. [24], considering a pulsatile blood flow. Zhu et al. refined the existed drug elution models, incorporating an analytical model for the coating's polymerization process, describing more accurately the dynamical porosity and the dynamical diffusivity of the drug within the coatings. Moreover, drug interactions within the arterial wall were also considered in their model [25]. Saha et al. [15], [16] performed a parametric analysis to investigate the drug distribution within the arterial wall using different strut distances, and extended their work in a second study, in which the pulsatile blood flow and an atherosclerotic area within the arterial wall were included. Sarifuddin et al. presented a model for the drug delivery of a drug-coated ballon (DCB) in a 2D reconstructed arterial segment, considering the drug binding, as well as, the lysosomal degradation of the drug [26]. Tzafriri et al. [14] considered drug interactions with specific and non-specific receptors within the arterial wall, while a very interesting approach was the one of Vo et al. [27], who incorporated a shrinking coating model within the drug elution model, accounting for the dynamical process of polymerization. Colombo et al. examined the elution of paclitaxel from a coated balloon into a 3D idealized arterial wall including a calcified area, as well as, the binding of paclitaxel on specific binding sites [28]. An 1D model for drug elution and distribution in a multilayered artery was created and utilized by Jain et al. [29]. It includes two consecutive processes, one during the deployment of the balloon and the other over the following period. Finally, a comprehensive model was presented by Escuer et al. , who examined drug elution from DES and DCBs toward an idealized 2D arterial wall consisted of three different layers [30]. However, the majority of the drug elution studies utilized either 2D or 3D idealized and non-realistic arterial geometries, while only a few included realistic geometries of reconstructed arterial segments, such as the study by Rikhtegar et al. [31].

This work focuses on the in-silico evaluation of retinoic acid as a candidate for DES for the effective treatment of cardiovascular disease. The stent coating consist of biodegradable polymers of either polylactic acid (PLA) or polylactic-co-glycolic acid (PLGA), which contain retinoic acid as a stenosis prohibitor drug, while the metal core of the stent consists of a Cobalt-Chromium alloy. The retinoic acid's interactions with the arterial wall differ from other available stent drugs as it is both immunosuppressive and non-destructive to the smooth muscle cells, which are partly responsible for the restenosis of the arterial segment. However, the retinoic acid's effect on the arterial wall are not fully understood, but

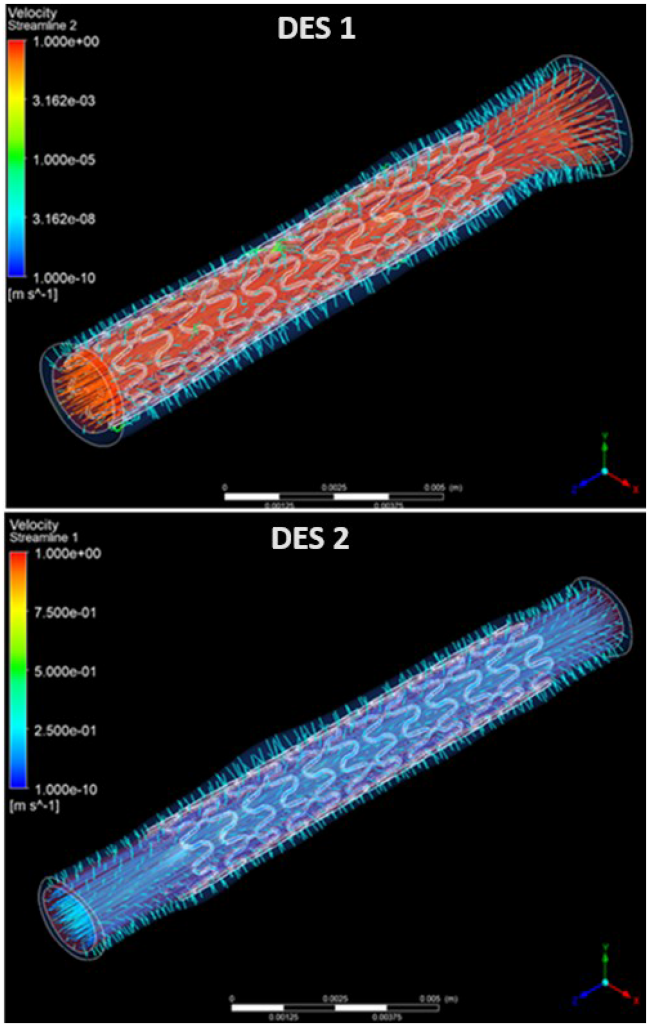

FIGURE 1. Blood flow streamlines in DES 1 and DES 2 cases.

there exist considerable experimental evidence to support that it causes the suppression of smooth muscle cell proliferation in cases of endothelial damage [32], [33].

We present a methodology that enables the in-silico analysis of the DES drug release from the stent coating using a three-step procedure. Specifically, we focus on the simulation of retinoic acid release from the stent coatings, considering two different cases for the coating thickness. The first step of the analysis includes the reconstruction of the coney arterial segments using the OCT imaging data. Subsequently, the in-silico stent deployment is performed in the realistic 3D reconstructed coney arterial segments, and drug elusion is simulated using the geometries of the deployed stents and the deformed arterial segments. To the best of our knowledge, this is the first study that examines in-silico the kinetics of retinoic acid as a candidate for DES drugs in animal reconstructed arterial segments, while using input from an in-silico stent deployment model. We are pioneering in our approach, by incorporating several features that enhance the model's prediction capability to ensure the realism of the results, such

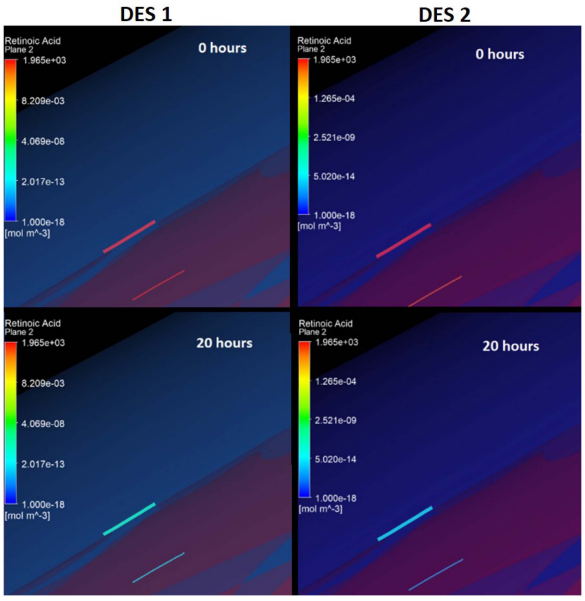

FIGURE 2. Distribution of retinoic acid concentration for 0 & 20 hours after deployment (case A: DES 1 & DES 2).

as the implementation of realistic 3D reconstructed arterial segments, the incorporation of the coatings' polymerization process, the implementation of drug kinetics based on advection and diffusion , the consideration of drug elusion towards the lumen domain in addition to the arterial wall domain, and finally the consideration of drug interactions within the arterial wall. We are validating the novel drug delivery model using sirolimus data, where experimental data exist [34].

II. RESULTS

After the implementation of the stent deployment model, the resulted geometries of the deployed stents and the dilated arterial segments were used in the drug elution model to analyze the release dynamics of retinoic acid in each case, considering an initial concentration of retinoic acid within the polymeric coatings 49.2% (Case A) and 1% (Case B), respectively. Moreover, additional simulations were performed to examine the release dynamics of the widely used DES drug sirolimus, using the initial concentration 0.85% (Case C) within the coatings. Therefore, a comparative analysis is performed for the kinetics of retinoic acid and sirolimus, focusing on the drug concentration, the coatings' polymerization and the drug interaction with the arterial wall over time.

Fig. 1 illustrates the blood flow streamlines, exhibiting maximum velocities in the order of magnitude of 10^{-1} m/s in the lumen, and 10^{-9} m/s in the arterial wall, which are in agreement with other computational studies [35]. Blood flow significantly affects the release of retinoic acid, which is drifting along with blood increasing, therefore, the gradient of the retinoic acid's concentration along the thickness of the coatings, thus favoring diffusion.

Fig. 2 shows the concentration of the retinoic acid within the inner coatings in several timesteps, which decreases at a

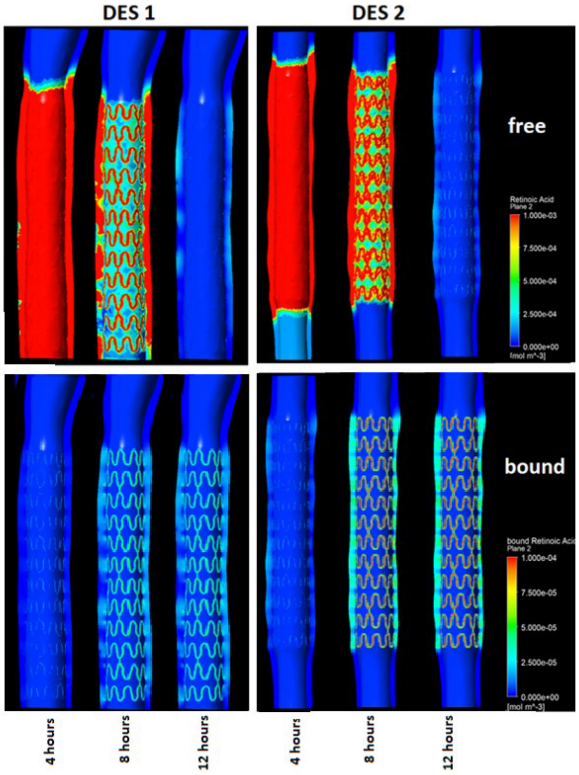

FIGURE 3. Distribution of free & bound retinoic acid concentration at 4, 8 & 12 hours after the stent deployment (case A: DES 1 & DES 2).

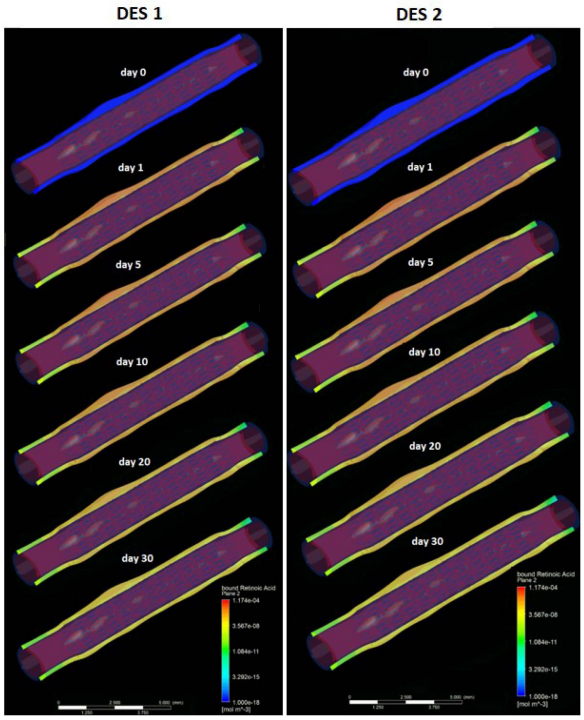

FIGURE 4. Distribution of bound retinoic acid concentration in the arterial wall domain (case A: DES 1 & DES 2).

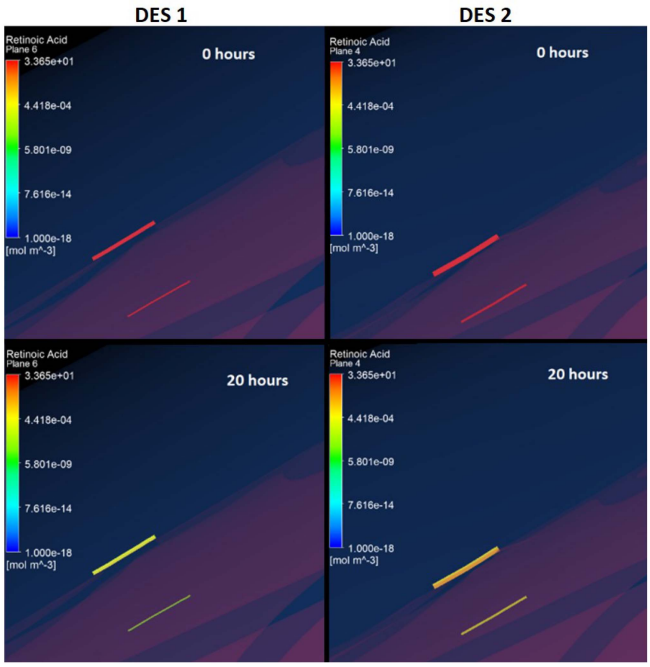

FIGURE 5. Distribution of retinoic acid concentration in the coating domain for 0 & 20 hours after deployment (case B: DES 1 & DES 2).

faster rate compared to the outer coatings for two reasons. The first reason is the reduced thickness of the inner coating compared to the outer, which means less medicine and faster depletion. The second reason is high blood velocity in the lumen compared to the arterial wall, which removes faster retinoic acid at the surface layer, therefore favoring its diffusion.

Fig. 3 shows the concentration of free and bound retinoic acid in a section of the domains at the timesteps of 4, 8 and 12 hours, respectively. We observe a sharp increase in the free retinoic acid concentration reaching 10 mol/m^3 during the first hours after the deployment of the stent, as well as a sharp decrease immediately after, that results to concentration values of the order of 10^{-4} mol/m^3. This is due to the abrupt depletion of the retinoic acid reserves within the coatings.

Fig. 4 illustrates the distribution of the bound retinoic acid concentration during the first 30 days after deployment. We observe a gradual increase in the concentration of retinoic acid having values in the order of magnitude of 10^{-4} mol/m^3 during the first day after the stent deployment, as well as, a gradual decrease within the first 30 days, where the mean concentration has a value in the order of magnitude of 10^{-6} mol/m^3. We also observe that the maximum concentration of the bound retinoic acid equals to the 20.34% of the available binding sites of the arterial wall.

To further support our results, we extend our analysis by examining the release of retinoic acid in the case of stent coatings with initial retinoic acid concentration 1% *w/w,* which represents an average drug concentration of the available DES (Fig. 5). We observe that the distribution and concentration of retinoic acid within the arterial wall differs considerably between both cases (with 49.2% and 1% *w/w*

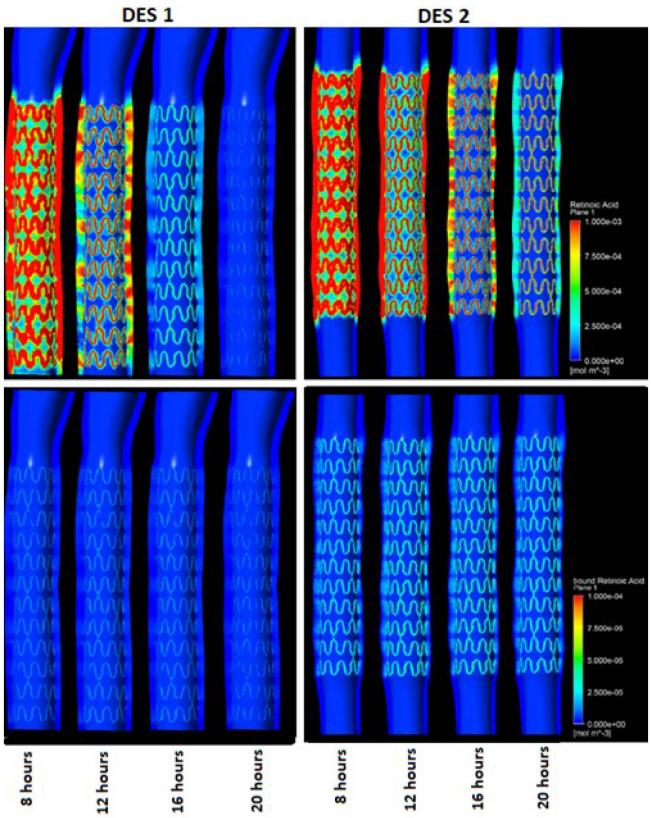

FIGURE 6. Distribution of free & bound retinoic acid concentration at 4, 8 & 12 hours after the stent deployment (case B: DES 1 & DES 2).

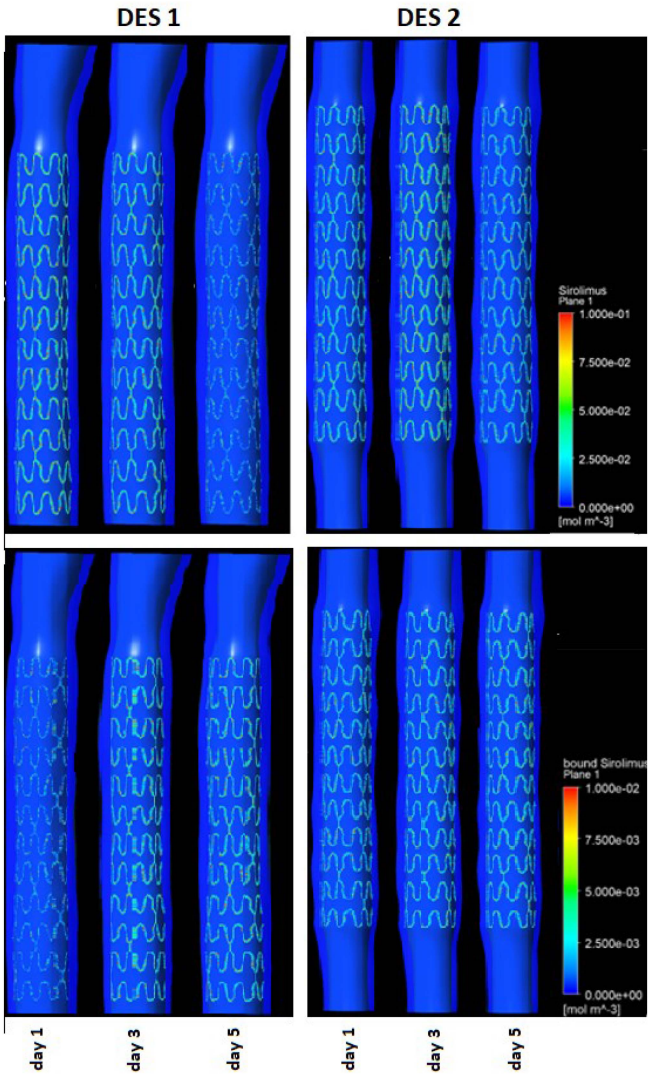

FIGURE 7. Distribution of free & bound sirolimus concentration at 1, 3 & 5 days after the stent deployment (case C: DES 1 & DES 2).

retinoic acid) in the timesteps beyond 20 hours of the stent deployment. The concentration of retinoic acid in the first case decreases by 8 orders of magnitude within the first 20 hours of stent deployment, while in this case a decrease of 3 orders of magnitude is observed within the corresponding period. Moreover, in both cases, we observe a slow decrease in the concentration of the bound retinoic acid, due to the release rate of the bound retinoic acid being relatively low compared to other drugs [23] (Fig. 6).

For comparison reasons, we also examined the kinetics of the well-known drug sirolimus using the geometries of the deployed stents and the reconstructed arterial segments. This was achieved using the sirolimus parameters presented in the study of Zhu et al. [25], considering an initial concentration 0.85% *w/w* within the coatings.

Fig. 7 illustrates the distribution of the free and bound sirolimus concentrations in slices of the arterial segments for both cases (PLGA and PLA) at successive timesteps within the first 5 days, which comply with other published models and experimental results. There is a gradual change in the sirolimus concentration within the coatings, that decreases by an order of magnitude after four days. This corresponds to a 95% decrease of the sirolimus concentration within the coating during the first four days. The corresponding decrease of the coatings' retinoic acid concentration (considering the initial retinoic acid concentration 49.2% w/w within the coatings) occurs within the first eight hours after stent deployment. Moreover, we observe a slow decrease in the concentration of the bound sirolimus, which reaches values that have an order of magnitude 10^{-2} mol/m^3 *with*in 3 days' time after stent deployment. In the retinoic acid case, the concentration of the bound retinoic acid shows an increase within the first 3 days, due to the slow rate of the retinoic acid binding to the smooth muscle cells (0.0416 h^{-1}) compared to that of sirolimus (10 s^{-1} [25]).

III. DISCUSSION

In this work a complete in-silico approach is presented regarding the evaluation of novel DES using 3D reconstructed arterial segments. Our methodology is divided in three steps, which include the 3D reconstruction of the arterial segments, the in-silico stent deployment and the in-silico drug elusion. This methodology was designed for the assessment of retinoic

acid as a novel drug candidate in DES. For comparison reasons, sirolimus, the widely applied DES drug was also examined.

The stent deployment and drug delivery models are both subject to the study's limitations. Regarding the first, there was no consideration given to endothelium damage during stent deployment, and the lack of balloon geometry resulted in a more straightforward deployment technique. Due to the lack of experimental data, a number of assumptions were made for the drug delivery model, including those for the plasma flow within the artery wall, the drug release parameters, and the boundary conditions [34], [36]. Additionally, as the layers of the artery wall could not be distinguished in the 3D reconstruction of the animal arterial segments, a homogeneous arterial wall was utilized for each model. In reference to the drug delivery model, the implemented geometries are not the actual reconstructed geometries—we were unable to precisely reconstruct the stents—but rather the output of the stent deployment model. Furthermore, we ignored the retinoic acid's comprehensive impact on the artery wall in favor of analyzing the retinoic acid's impact on the smooth muscle cells based on existing experimental evidence.

Regarding retinoic acid, two different coating concentrations were examined: 49.2% w/w and 1% w/w. For 49.2% retinoic acid concentration, the results demonstrated the rapid release of retinoic acid, that depleted within the first day. This can be justified due to the large porosity of the polymeric coatings, which is caused by the high concentration of the drug resulting to its rapid diffusion. Moreover, the immediate binding of a large percentage of the released retinoic acid was observed within the arterial wall, which was later reduced slowly. Nevertheless, after a twenty-day period, the maximum concentration of the bound retinoic acid occupied only 0.1% of the available arterial wall binding sites, while after thirty days it decreased to such an extent that it occupied only 0.01% of the available binding sites, which are both considered negligible. For 1% w/w retinoic acid concentration, our approach demonstrated a slower release rate of retinoic acid, however we observed only a slight increase in the effective time of the bound retinoic acid (from 7 days to 10 days). Finally, we compared the results of the retinoic acid release model, to the results of a drug elution model for sirolimus DES, using both arterial segments of this project. The results exhibited the slower release (of up to 10 times) of the sirolimus drug compared to the retinoic acid, which was also justified by the initial porosity of the coatings in the retinoic acid cases.

Along with drug occupancy of the arterial wall's available binding sites, drug protection against restenosis (proliferation of smooth muscle cells) is assessed by comparing the bound drug concentration with the IC50 value [37], which represents the drug concentration required to reduce SMC proliferation by 50%. Retinoic Acid and Sirolimus both have IC50 values listed in Table 1, while Fig. 8 demonstrates the maximal inhibition of SMC proliferation over time for the retinoic acid cases. Sirolimus is much more effective against restenosis than retinoic acid since its IC50 value is over 522 times lower.

TABLE 1. IC50 of Sirolimus & Retinoic Acid

Sirolimus	Retinoic Acid
4.1E-9 M [50]	2.14E-6 M

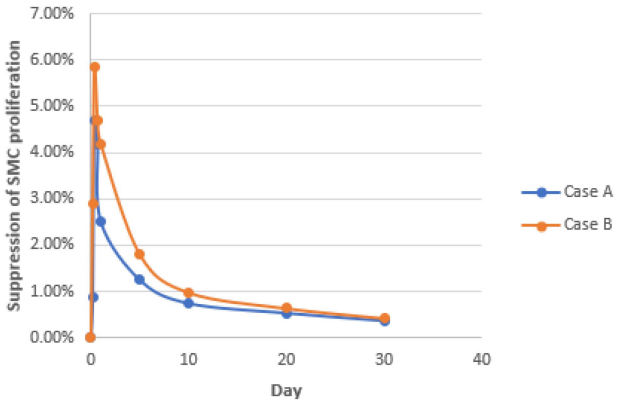

FIGURE 8. Suppression of SMC proliferation over time (case A & B).

According to the findings of Fig. 8, sirolimus is effective for six months while retinoic acid is only effective for the first ten days [38].

Many models that can forecast arterial wall thickening in actual arterial segments have been presented in recent years [35], [39]. By applying a model like this, one can forecast the actual restenosis; however, this is outside this work's scope.

The proposed approach not only exploits the latest computational models of drug elusion and delivery, but also incorporates several novel features to further optimize the accuracy of the results. The work of Zhu et al. includes a very sophisticated model for drug release, which is not based on empirical or experimental equations but incorporates an analytical model for the polymerization process of the stent coatings, which enables the release of the drug from enclosed micro-cavities. However, their model was only applied in an idealized 2D cross-section of a stent strut and the arterial wall, while both blood flow and plasma flow were not considered, which significantly affect the drug dispersion within the arterial wall. Moreover, Rikhtegar et al. presented a complete methodology regarding the examination of drug release in deployed stents, that included the ex vivo stent deployment in porcine coronary arteries, the scanning of the resulted segments using micro-computer tomography (μCT), the 3D reconstruction of the imaging and the drug release simulation [31]. Even though this is an excellent approach, a very simple model was used to describe both the blood flow and the drug kinetics, without describing the release process. In our approach, we present a complete methodology for the in-silico evaluation of a DES performance, which is enabled using real imaging data of arteries, an in-house arterial segment 3D reconstruction tool, a stent deployment model and a novel drug

elusion model for retinoic acid. Specifically, we developed a complex model that includes several discrete models that are combined into one. Our approach includes a model for blood flow in the lumen, a model for plasma flow in the arterial wall considering the momentum losses due to the porosity, a model for the polymerization process, a model for the variable drug diffusivity according to the polymerization index, a model for the drug kinetics, and a model for the drug interactions within the arterial wall resulting to its binding or unbinding to the smooth muscle cells.

The contemporary model of drug delivery is validated only for the sirolimus case, where experimental data exist. The outcomes for the sirolimus case are presented in Fig. 7, which are in agreement with other scientific reports [34]. Given that a drug delivery model can be parameterized to describe the release of different drugs, we suppose that the retinoic acid.

To our knowledge, this is the first study to investigate retinoic acid as a drug candidate for DES. We incorporated into the presented model, some of the most accurate mathematical models regarding the polymerization process, the drug release dynamics as well as the drug interactions within the arterial wall. The use of 3D realistic animal artery geometries in the stent deployment model and the supply of the resulting geometry as input to the drug delivery model are among the novel aspects of this work. Other novel aspects include the consideration of 3D drug release towards the wall and lumen domains allowing drug infiltration in successive wall regions, the consideration of 3D polymer degradation, and the implementation of a drug-artery interaction model for the retinoic acid. Our research will eventually expand to include this model combined with a plaque growth model, which describes a number of species linked to atherosclerosis. This will enable a more thorough examination of the drug's effects on an evolving arterial wall.

IV. CONCLUSION

In this study, we examined the kinetics of retinoic acid, which is a novel DES drug candidate that inhibits restenosis by regulating smooth muscle cell proliferation by avoiding their apoptosis. The underlying mechanism of existing DES drugs rely on the destruction of the smooth muscle cells that leads to the generation of necrotic cores and subsequently to calcification, whereas in the use of retinoic acid smooth muscle cell proliferation is hindered [40]. For the retinoic acid kinetics a contemporary model was developed by capitalizing on experimental data [32], [33], [41], [42]. Our findings indicate that the drug release rate is much faster in retinoic acid than the drugs of DES available in the market, where drug depletion requires three to six months (Table 2) [27]. In relation to other DES studies, our study is not limited to the analysis of the case with 1% retinoic acid initial concentration, which is an average DES drug concentration [25], but also includes the analysis of the DES with retinoic acid initial concentration 49.2%. To the best of our knowledge, this is the only approach in which a large drug concentration in the DES coatings has been examined, to evaluate the possibility of prolongating the drug elution period. However, such a high drug concentration is prohibitive to be used in the existing DES, since it contributes to the onset of cardiotoxicity, when in abundance within the arterial wall. Moreover, our results show that the high initial drug concentration reduces the polymer concentration in the mixture, resulting in a highly porous coating, which favors the drug release rates. Therefore, the high drug concentration leads to rapid release, instead of a prolonged one in homogeneous coating mixtures. In contrast to other DES drugs, retinoic acid presents an increased binding period to the arterial wall. Therefore, with an appropriate polymer selection that prolongs the release period, retinoic acid protection period could be much larger than this of sirolimus and of other drugs. The proposed study enables the design and development of a complete in-silico pipeline integrating 3D realistic coney arterial models, advanced computational approaches for simulating the implantation of the scaffold, the drug release kinetics, as well as, the polymer degradation mechanism in the arterial micro-environment, namely the lumen and the arterial wall.

TABLE 2. The Three Cases Features

Case	Drug	w/w Initial Drug Concentration	Release Period	Effective Period
Case A	Retinoic Acid	49.2%	2-4 hours	~7 days
Case B	Retinoic Acid	1%	16-20 hours	~10 days
Case C	Sirolimus	0.85%	36-72 hours	~5 months [47]

V. MATERIALS & METHODS

The study presents a comprehensive methodology for the computational analysis of retinoic acid eluting stents to prevent restenosis post-implantation. While existing studies focus on drug elution in drug-eluting stents (DES), few utilize realistic data such as 3D arterial segments and in-silico deployed stent models. Our approach addresses this gap by providing a realistic investigation into retinoic acid kinetics as a DES drug candidate. This work involves collecting and reconstructing OCT imaging data from two coronary arterial segments, developing the stent deployment model, and creating the drug elution model. Three drug cases were examined: (i) retinoic acid at 49.2% w/w initial concentration, (ii) retinoic acid at 1% w/w initial concentration, and (iii) sirolimus at 0.85% w/w initial concentration. Each case includes two coating materials: polylactic-co-glycolic acid and polylactic acid (DES 1 & 2).

A. STENT DESIGN

The stent design is based on the LeaderPlus stent geometry, processed from 2D to 3D. The pharmaceutical/polymer coating's 3D geometry is designed based on provided input.

B. 3D RECONSTRUCTION OF ARTERIES

OCT pullback sequences are converted to grayscale and processed using the Polar space. The Harris-Stephens detector detects the OCT catheter. The reconstruction involves drawing a rectangle around the guidewire, lumen border detection using bilateral filtering and the Fast-Marching algorithm, and adventitia layer extraction and surface fitting.

C. IN-SILICO STENT DEPLOYMENT

A computational model simulates 3D stent deployment in reconstructed arteries. Arterial tissue is modeled as a hyperelastic material. Coatings are linear elastic materials with specified stiffness coefficients. Boundary conditions and contact modeling between artery surfaces and stent are implemented.

D. DRUG DELIVERY MODEL

The model includes 3D polymerization of coatings, drug diffusion, transport due to blood flow, and retinoic acid's effect on smooth muscle cells proliferation. Coatings consist of PLA or PLGA biodegrading materials with retinoic acid. Polymerization assumptions simplify computational complexity. Drug diffusion and transport in lumen and arterial wall are described using convection-diffusion equations, considering porosity effects.

E. INITIAL AND BOUNDARY CONDITIONS

Inlet and outlet conditions are set based on average blood velocity and pressure. Initial conditions include specified drug concentrations in stent coatings and zero concentration elsewhere.

F. NUMERICAL IMPLEMENTATION

ANSYS software is used for simulations, with meshing techniques employed to ensure accuracy.

Overall, the study provides a detailed methodology for computationally analyzing retinoic acid eluting stents, addressing key aspects of stent design, artery reconstruction, stent deployment, and drug delivery modeling.

F. AUTHOR CONTRIBUTIONS

Dimitrios S. Pleouras: Methodology; Validation; Formal Analysis; Writing - Original Draft; Visualization. **Vasileios S. Loukas:** Methodology; Writing - Review & Editing. **Georgia Karanasiou:** Conceptualization; Writing - Review & Editing; Supervision. **Christos Katsouras:** Investigation; Data Curation. **Arsen Semertzioglou:** Resources. **Anargyros N. Moulas:** Resources. **Lambros K. Michalis:** Investigation; Data Curation. **Dimitrios I. Fotiadis:** Conceptualization; Writing - Review & Editing; Project administration; Funding acquisition.

F. CONFLICT OF INTEREST

There are no conflicts of interest to declare.

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