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THE INTERACTION OF BLOOD FLOW AND DRUG RELEASE FOR CARDIOVASCULAR DRUG ELUTING STENTS.

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ABSTRACT

A stent is a small mesh tube that is inserted permanently into a stenotic artery. The stent restores the original value of the arterial section to ensure the physiological flow rate. One of the problems caused by the stent insertion is the re-narrowing of the treated vessel. To overcome this phenomenon drug-eluting stents (DES) have been recently introduced. Referred to as a *coated* or *medicated* stent, a DES is a normal metal stent that has been coated with a pharmacological agent (drug) that is known to interfere with the process of restenosis (reblocking). The design of such devices is a very complex task because their performance in widening the arterial lumen and preventing further restenosis is influenced by many factors such as the geometrical design of the stent, the mechanical properties of the materials and the chemical properties of the drug that is released. Mathematical models and numerical simulation techniques are appropriate to study such phenomena with the aim to be used as a predictive tool for the effective design of drug eluting stents.

In this work, we will focus on the interaction between several factors, as the geometry of the stent, the blood flow and the drug release process, to determine the performance of the device. These topics have been already analyzed separately, see [1,2] and references therein, but the study of their interplay is still rather new in literature. For example, in most cases the blood flow is assumed to have a minor influence on the distribution of the drug into the walls. In particular, it is common to consider that the arterial lumen acts as a perfect sink with respect to the drug concentration, because it is rapidly transported away from the location of the stent. Recently, the analysis pursued in [3] suggested that this assumption is not really justified. Indeed, the drug that is apparently lost in the blood stream significantly affects the drug deposition in the portion of the arterial walls downstream to the stent. For these reasons, we aim to analyze the interaction of the blood flow and the drug deposition into the artery in the case of a realistic geometry of the stent and of the arterial walls deformed after the stent expansion.

To this purpose, we set up and discuss suitable models to describe the fluid dynamics, the drug release and the consecutive transport phenomena. In particular, observing that the arteries treated with cardiovascular stents are large enough to apply a Newtonian model for blood rheology, we consider the Navier-Stokes equations for the fluid dynamics in the arterial lumen. However, the flow is not restricted

to the arterial lumen because blood plasma filtrates from the inner to the outer part of the arterial walls under the action of blood pressure. We describe this process by means of the Darcy's law of filtration.

The drug release and transport is described by a system of advection-diffusion equations that are coupled by means of suitable transmission conditions at the interface between the lumen and the wall of the artery, representing the so called endothelial layer. This model can be enriched to account for several phenomena as the chemical interaction between the drug and the arterial tissue and the dependence of the endothelial permeability and drug diffusivity form the shear forces induced by blood flow.

Furthermore, particular attention should be dedicated to the condition at the interface between the stent and surrounding environment, because it is primarily responsible to determine the drug release rate. We remind that DES for cardiovascular applications are miniaturized metal structures that are coated with a micro-film containing the drug that will be locally released into the arterial walls for healing purposes. The thickness of this film generally lays within the range of microns. Owing to the fact that the stent coating is extremely thin, we apply the reduced model proposed in [4], where the diffusion equation governing the drug release form the stent is condensed into a boundary condition applied on the stent surface.

For the space discretization of the partial differential equations at hand, we apply the finite element method. In particular, for what concerns the coupling between Oseen and Darcy equations we consider the unified formulation proposed in [5] while for the advection-diffusion equations we apply Lagrangian elements that are stabilized in the transport dominated case by means of the continuous interior penalty scheme proposed in [6]. We also analyze suitable iterative methods in order to split the coupled heterogeneous problems into a sequence of independent ones.

These mathematical models and numerical methods allow us to analyze the interaction of blood flow and drug release for a realistic cardiovascular stent.

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