Insilico clinical trials for bioresorbable vascular stents

Marija Gacic*, Georgia Karanasiou**, Dimitris Fotiadis **and Nenad Filipovic*
*BIOIRC Research and Developed Center, Kragujevac, Serbia
**Foundation for Research and Technology Hellas, Ioannina, Greece
e-mails: marija.gacic@kg.ac.rs, g.karanasiou@gmail.com, fotiadis@uoi.gr, fica@kg.ac.rs

***Abstract*— The world stent market has an estimated value of €6.4 billion, of which 37% is generated in the US and 10% in the EU. Coronary stents are now the most commonly implanted medical devices, with more than 1 million implanted annually. Coronary stents are currently the most widely used for treating symptomatic coronary disease. This paper presents the innovative platform and its separate modules that can be used as a standalone tools developed within EU funded project InSilc, for designing, developing and assessing coronary stents. This integrated solution was developed by international consortium in H2020 project www.insilc.eu. After three years of intensive work on different modules, presented in this paper and their integration in the platform which will be offered as a service to interested stakeholders, consortium is planning the commercialization of the solution. In this paper the potential pathways for further exploitation and commercialization are presented together with market analysis, business plan and business model. The technological level of each module is also elaborated, as well as different business models for its market introduction. Future work will include testing and validation on larger databases, and improvement of the tool based on feedback from the users from different categories (stent industry, clinicians, researchers etc.). The main goal is commercialization of the InSilc solution and its fast market uptake.**

I. INTRODUCTION

Any medical device such as coronary or peripheral stent in the process of commercially released in the market, an appropriate level of scrutiny and rigorous testing must be undertaken. This testing is achieved through the clinical trials, a process that is carried out in three phases and targets the evaluation of the safety and efficacy of stent. The difference between the three phases is the number of the enrolled patients, as well as the variables of interest in each of these phases. In the first phase, only a small number of patients were enrolled while the ultimate objective is to ensure the safety of the medical device. In the other two phases, the medical device is tested on a larger number of patients towards evaluating its effectiveness and potential side effects (Phase II), and in multiple hospitals and countries (phase III) to demonstrate the efficacy in a larger population. After this testing and the approval of the stent, post-marketing multi-center studies are performed to estimate and assess the effectiveness of the new stent compared to already available in the market.

InSilc project aims to develop an *in-silico* clinical trial platform for designing, developing and assessing drug-eluting bioresorbable vascular scaffolds (BVS), by building on the comprehensive biological and biomedical knowledge and advanced modelling approaches, to simulate their implantation performance in the individual cardiovascular physiology [1].

In accordance with Directive 2010/63/EU, the principle of the 3Rs (Replacement, Reduction and Refinement) needs to be considered when selecting testing approaches to be used for regulatory testing of human and veterinary medicinal products. Testing of new models of vascular stents, scaffolds and balloons in real clinical trials is time consuming, expensive and highly inconvenient for the patients included in the study. Therefore, the intention is to replace, reduce and refine the real clinical study with the insilico clinical study and insilico testing of the innovative models of stents in order to decrease the costs and the time required to perform real clinical study. In this paper we are presenting the innovative solution for designing, developing and assessing coronary stents which is developed within the EU funded project InSilc. The main question that has been raised and answered in this work is what the benefits of using insilico trials are. Analyzing market of similar solutions has shown that there is no similar integrated solution on the market and that potential savings are significant

II. METHOD

The stent manufacturer provided the average results of uniaxial tensile tests performed on a number of dog-bone samples with a different gauge length, width and thickness. Tests are conducted at different temperatures. For each temperature, different curves were available referring to different strain rates: Results are in accordance with typical PLLA behavior: at each temperature, the curves show a common initial elastic response, a strain rate dependent yield point and plastic behavior ending with a strong hardening. At higher temperature or lower velocity, stress values decrease despite the increasing final strains [2].

The InSilc platform is based on the extension of existing multidisciplinary and multiscale models for simulating the drug-eluting BVS mechanical behaviour, the deployment and degradation, the fluid dynamics in the

micro- and macroscale, and the myocardial perfusion, for predicting the drug-eluting BVS and vascular wall interaction in the short- and medium/long term.

The developed InSilc platform consists of different simulation modules/tools - some of which can be considered as stand-alone modules and, therefore, can be used separately if there is such demand from the targeted users. These modules integrated in the InSilc platform are: Mechanical Modelling Module, 3D reconstruction and plaque characterization tool, Deployment Module, Fluid Dynamics Module, Drug Delivery Module, Degradation Module, Myocardial Perfusion Module, Virtual Population Physiology and Virtual Population database (Figure 1). These tools are applicable all types of coronary and peripheral stents, such as Bare Metal Stents (BMS), Drug-eluting Stents (DES) and Bioresorbable Stents. This is a great advantage of InSilc allowing this way the penetration of InSilc platform and modules to a wide range of market and interested stakeholders [3]. The paper presents the detailed comparative analysis of the costs and time required for the real clinical trial and insilico clinical trial performed using the presented solution.

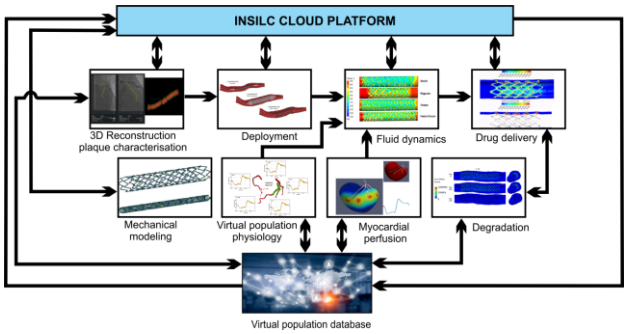

Figure 1. InSilc cloud platform

III. RESULTS

The purpose of the Deployment Module is the simulation of the coronary stent (DES or BVS) implantation within stenotic coronary artery models. This simulation provides detailed information of the short-term outcome after stenting, in terms of deployed stent and vessel configurations as well as the stresses and strains in the two elements. These data are useful in predicting the in vivo performances of a new device.

The Stent industry follows standard mechanical stent testing in the whole process of stent evaluation, i.e., according to ISO test standards. Mechanical tests are very time-consuming, expensive and require many cycles/iterations, while in some cases total redesign of the stent are required or even the examined stent design is abandoned. The Mechanical Modeling module assists in reducing the required number of real mechanical tests and the associated costs. In brief, the module provides the ability of the following mechanical tests to be simulated *in silico*: Simulated use – Pushability, Torquability, Trackability, Recoil, Crush resistance, Flex/kink, Longitudinal tensile strength, Crush resistance with parallel plates, Local Compression, Radial Force, Foreshortening, Dog Boning, Three-point bending, Inflation and Radial Fatigue test. The risk of fatigue failure is also predicted using fatigue criteria for metal stents with polymer.

The whole process for the Mechanical Module development includes the design, set up and implementation of several finite element simulations performed with the advanced and beyond the state-of-the-art in-house BIOIRC's solver PAK [4]. The solver achieves the simulation of nonlinear material and geometry problems, nonlinear contact problems, dynamics and statics with residual stress and strain analysis. The process that is followed, in general, includes the following steps: (i) creation of the 3D stent geometry (in case this is not available directly in a 3D format from the manufacturer), (ii) mesh generation, (ii) application of appropriate boundary conditions (depending on the test a variety of boundary conditions are applied). BIOIRC has developed a nonlinear material model that is applied in the finite element solver PAK for prescribing material property from uniaxial stress-strain experimental curves. It is an Open module used only in the Mechanical Modeling Module (Figure 2).

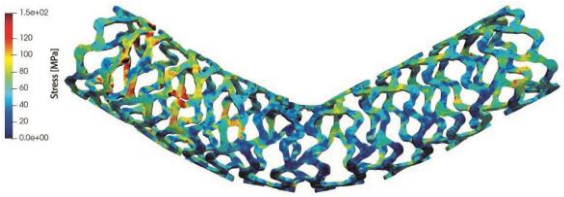

Figure 2. Mechanical Modeling module: Three point bending stent testing

The Deployment Module requires detailed information about the delivery systems to be simulated to create reliable and realistic virtual FE models of the devices involved in the stenting procedure. In silico simulations of the stenting procedure consists of the following steps, to be repeated for each device (stent or balloon): (i) device positioning, (ii) balloon inflation and, (iii) stent deployment. Most of the computational steps are automatized and this allows a significant reduction in preparing and performing the simulations. In turn, this allowed a reduction of the process to be sustained by the users of the Deployment Module (Figure 3).

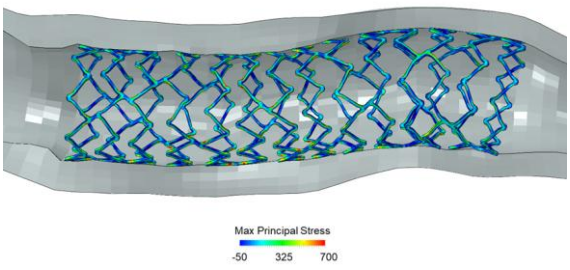

Figure 3. Deployment module

The Drug delivery Module (Figure 4) has been developed to model the in vivo release kinetics of the drug from the coating and its spatial distribution within the tissue over the course of weeks to months. Pharmacokinetics has been separately examined for the coating and the tissue. First, a mathematical empirical-trained model was developed to simulate release and extract the drug flux out of the drug-eluting surface, validated with the manufacturer's experiments. Then, a physics-based three-dimensional advection-diffusion-reaction model was developed wherein using continuum mechanics equations the convection of drug by the plasma infiltration, diffusion of the drug within the tissue, and binding/unbinding of the drug to the extracellular matrix and specific receptors have been considered. Drug delivery is modelled for a sustained period of time to monitor both the early burst of drug as well as long-term retention and ultimate clearance rate.

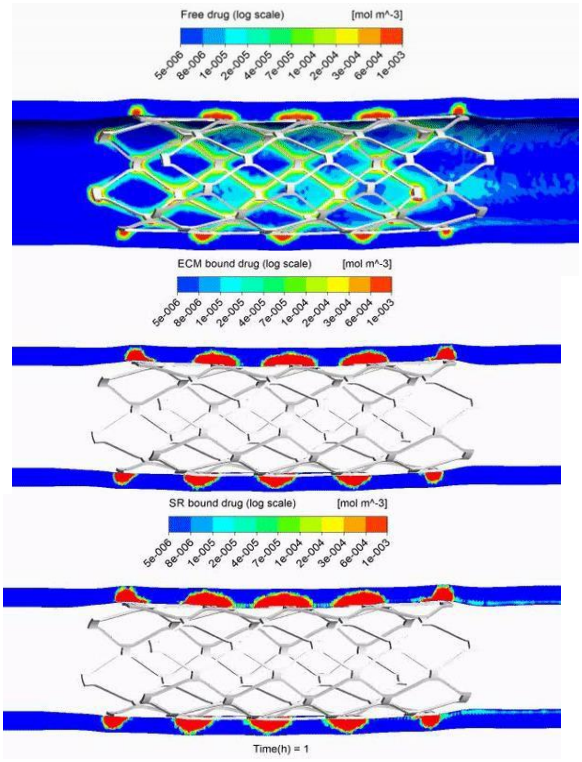

Figure 4 Drug delivery module

The Degradation Module (Figure 5) simulates the degradation pattern of implanted BVS. The InSilc degradation framework has been implemented within both Johnson-Cook and Parallel Rheological Framework (PRF) constitutive models, which have been found to form the basis for the mechanical behaviour of several commercial BVS.

The InSilc Degradation module depends on detailed input from the Deployment module, whereby the implanted configuration of the relevant device and artery has been predicted. The post-deployment stent-artery configuration and the material stress-strain history at all model integration points are imported and these form the starting point for the InSilc Degradation module. This approach ensures that model parameters remain consistent between the Deployment and Degradation modules, with continuity maintained in the discretisation/mesh, element type, underlying constitutive model and many of the numerical parameters that control the solution process (e.g., step times, mass scaling etc.) allowing for a consistent predictive mechanical framework. The InSilc degradation module predicts the spatiotemporal progression of degradation. Based on this, the predicted long-term biomechanical performance can be related to several clinical endpoints relevant to implanted stents, including, minimal stent area, malapposed stent struts, stent fracture or dismantling.

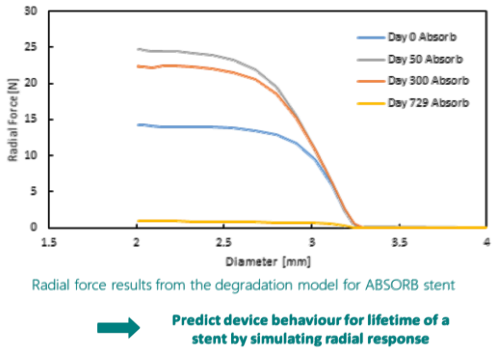

Figure 5. Degradation module

Fluid Dynamics Module (Figure 6) is developed to compute the velocity, pressure and shear stress patterns in stented segments of human coronary arteries. The Fluid Dynamics Module requires two main inputs: geometrical information and flow boundary conditions. The geometrical information consists of two STL-files, one describing the lumen of the vessel wall, the other the surface representation of the stent. These two STL-files are combined to form the mesh of the fluid domain by using a commercial platform (ICEM, ANSYS). The boundary conditions consist of time-dependent inflow and outflow curves. These data are used to feed in a commercial solver (FLUENT, ANSYS) to compute velocity, pressure and shear stress patterns. The output is formed by 2D maps of pressure and shear stress derived parameters in the stented region (**Error! Reference source not found.**6).

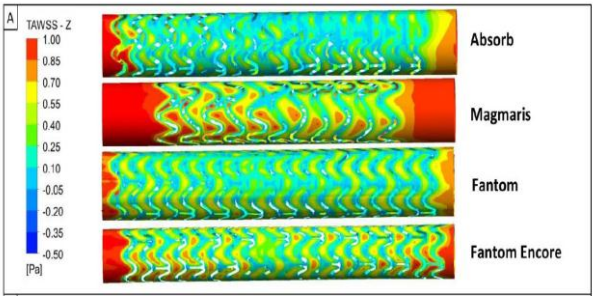

Figure 6. Fluid dynamics module solution

The Myocardial Perfusion Module (Figure 7) simulates the post-treatment performance of the drug-eluting BVS in improving myocardial perfusion distal from the treated vessel. The Myocardial Perfusion Module predicts the whole-heart perfusion in the cardiac muscle, and generates virtual myocardial perfusion maps. The module takes as inputs CT coronary angiography (CTCA) images, the model-generated pressure boundary conditions, and the outlet flow conditions from the Fluid Dynamics Module. Prediction of post-operative perfusion is then provided by solving a multi-compartment poroelastic flow model, from which the perfusion maps are estimated. By combining the Myocardial Perfusion Module with the boundary condition variability model, it is possible to simulate perfusion differences under both rest and stress. By varying the boundary conditions between rest and stress and computing the Summed Difference Score (SDS), a threshold value of SDS > 4 can be used to gauge whether the virtual patient is at risk of post-operative myocardial infarction and other major adverse cardiovascular events (MACE).

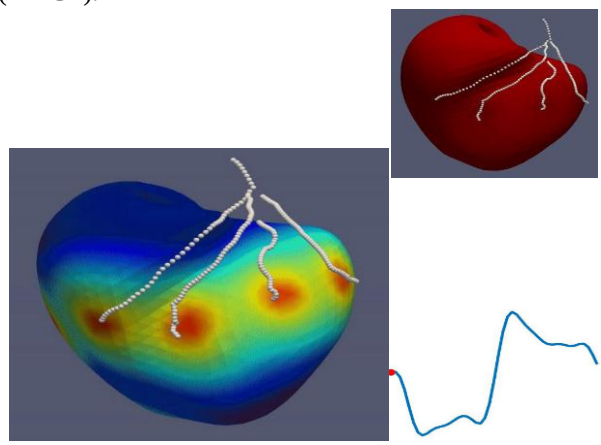

Figure 7. Myocardial perfusion model solution

IV. CONCLUSIONS

The main exploitable products of InSilc are the Mechanical Modelling Module, the 3D reconstruction and plaque characterization tool, the Deployment Module, the Fluid Dynamics Module, the Drug Delivery Module, the Myocardial Perfusion Module, the Degradation Module, the Virtual Physiology Module, the Virtual Population Database and the integrated InSilc cloud platform. The refinement and further development and validation activities enabled the achievement of advanced TRL(s). In more detail, all Modules achieved to reach the promised according to the work plan TRL(s) that are TRL3 for the Virtual Population Physiology Module, TRL4 for the Degradation Module and the Myocardial Perfusion Module, TRL5 for the Fluid Dynamics Module and the Drug Delivery Module, TRL6 for the 3D reconstruction and plaque characterization tool and the Deployment Module. The Mechanical Modeling Module achieved to reach a higher TRL (TRL 7) compared to the planned in the DoA (TRL5 to TRL 6). Finally, the TRL of the integrated InSilc Cloud platform is TRL5. Considering the achieved TRL(s), the costs and time required to execute an in silico experiment by each in silico module, an updated pricing strategy has been prepared with a reduction of more than 50% compared to the initial pricing strategy. It should be also highlighted that InSilc partners share the same vision and would be very interested in further exploiting InSilc after the project's end by being involved in other in silico projects and new collaborations, participating in academic research fundings, innovation programmes and industry-oriented grants, clustering with other projects, the Avicenna Alliance and the task force for Good Simulation Practices, organising educational and training activities, capitalising on the gained knowledge and developed technology and further explore in to other endovascular devices, such as drug-coated balloons.

ACKNOWLEDGMENT

This paper is supported by the projects that have received funding from the European Union's Horizon 2020 research and innovation programme under grant agreements No 777119 (InSilc project). This article reflects only the author's view. The Commission is not responsible for any use that may be made of the information it contains.

REFERENCES

[1] H2020 InSilc project: In-silico trials for drug-eluting BVS design, development and evaluation, www.insilc.eu

[2] Nenad Filipovic, Dalibor Nikolic, Velibor Isailovic, Miljan Milosevic, Vladimir Geroski, Georgia Karanasiou, Martin Fawdry, Aiden Flanagan, Dimitris Fotiadis and Milos Kojic, In vitro and in silico testing of partially and fully bioresorbable vascular scaffold, J Biomech 2021 Jan 22;115:110158. doi: 10.1016/j.jbiomech.2020.110158. Epub 2020 Dec 2.

[3] D. Fotiadis and N. Filipovic, In-silico trials for drug-eluting BVS design, development and evaluation, The Project Repository Journal January 2021 – Volume 8, 2021

[4] PAK Finite element program, BIOIRC, Research and Development Center, 34000 Kragujevac, Serbia http://www.bioirc.ac.rs/index.php/software/5-pak
.