InSilc: an *in silico clinical trials platform for advancing BVS design and development*

Karanasiou, G.S.[1], Fotiadis, D.I.[2]

[1]Department of Biomedical Research, Institute of Molecular Biology and Biotechnology, FORTH, GR 45110, Ioannina, Greece.

[2]Department of Biomedical Research, Institute of Molecular Biology and Biotechnology, FORTH, Ioannina, Greece and Dept. of Materials Science and Engineering, Unit of Medical Technology and Intelligent Information Systems, University of Ioannina, GR 45110, Ioannina, Greece.

Coronary Artery Disease (CAD) is the leading cause of death in Europe and worldwide with more than 17 million deaths [1]. Atherosclerosis, the major disease process of CAD, is a chronic inflammation driven by the build-up of atherosclerotic plaques inside the coronary arteries. Bioresorbable Vascular Scaffolds (BVS) revolutionised the field of interventional cardiology by providing targeted drug delivery, mechanical support and complete resorption overcoming the barriers of bare-metal and drug-eluting stents. *In vitro* and *in vivo* experiments followed by clinical trials are currently used in providing useful information on the safety and efficacy of BVS. However, these processes are time-consuming and costly. In parallel, they raise ethical considerations due to the uncertainty related to the extremely well performance in controlled laboratory experiments and pre-clinical studies, and potential under performance during or after clinical trials.

InSilc is an *in silico* clinical trial (ISCT) platform that accounts on the biological and biomedical knowledge and available advanced modelling approaches for simulating the short and medium/long term BVS performance. This is achieved by the integration of multidisciplinary and multiscale models that simulate the BVS mechanical behaviour, the deployment and degradation, the fluid dynamics and the myocardial perfusion. The development of the: (i) Mechanical Module, that reproduces the standard mechanical tests that are currently performed by the Stent Industry, (ii) 3D Reconstruction and plaque characterisation Module, that enables the reconstruction of the arterial tree (lumen, outer wall, calcified and non-calcified plaques) and the scaffold, (iii) Deployment Module, that simulates the post deployment BVS configuration, the stresses and strains within the BVS and the arterial wall, (iv) Fluid Dynamics Module, both in macroscopic and microscopic level, that provides the patient specific shear stress, the flow patterns and the process of in stent restenosis, (v) Myocardial perfusion Module, that captures ischemia and revascularization in the myocardium, (vi) Degradation Module, that predicts the degradation and long-term mechanical performance of the BVS, and their integration in the InSilc Cloud platform provides the final users (Stent Industry experts, Contract Research Organizations –CROs-, Interventional Cardiologists, Researchers) with fruitful information on the BVS behaviour assisting in BVS improved design and development. The concept of InSilc *in silico* clinical trials involves the execution of computational simulations on a large population of “virtual” patients” (Virtual Case

Repository) given a “virtual” BVS, allowing for the evaluation of the scaffold performance, quantifying its intended effect avoiding the presence of adverse effects and undesirable clinical outcomes, that could be potentially harmful for the patient.

Through InSilc platform, the stent industry experts can test the BVS using state-of-the-art *in silico* models and resources made available by high profile research organizations. CROs primary interest is the efficient clinical study design for achieving statistically sound study endpoints with the minimum number of patients. InSilc platform assists the CROs to efficiently define specific inclusion/exclusion criteria based on the Virtual Case repository and apply appropriate statistical and data analytics methods to minimize the number of required patients for specific endpoints. The Interventional Cardiologists use the InSilc platform for evaluating the performance of a specific BVS and decide on the scaffold that can minimize the post implantation complications. The Researchers have access to the Virtual Case repository and to a pool of BVS computer-aided design Models. These users may download high fidelity CAD models for research only purposes and through the platform available data, register a model/computational resource as a "under validation" model and use the InSilc with supported solvers to run the simulation on a number of pre-validated meshes (geometries and stents).

InSilc plays a key role in refining and reducing the cost of the preclinical assessment of BVS and complements the real clinical trials by offering the ability to examine the following “use-case scenarios”: (i) Scenario I: Compare existing stents, (ii) Scenario II: Compare anatomy configurations and patient conditions, (iii) Scenario III: Compare different clinical procedures, (iv) Scenario IV: Design entirely new stents.

The challenge of InSilc is two-fold: (i) validating the developed *in silico* models and addressing all the technological and cloud-based infrastructure requirements, (ii) facilitating the definition of a regulatory framework towards the successful application of InSilc in parallel with the real clinical trials. To accomplish this, the analysis and assessment of the diverse issues that should be taken into consideration for providing consolidated evidence for the need of adopting the InSilc platform in the usual practice of clinical trials is performed, and the steps and processes for addressing the regulatory and ethical issues and the new emerging standards are implemented.

This work is supported by the InSilc project that has received funding from the European Union’s Horizon 2020 research and innovation program under grant agreement No 777119 [2].

References

[1] WHO, Cardiovascular diseases (CVDs), http://www.who.int/mediacentre/factsheets/fs317/en/.

[2] InSilc: in silico trials for drug-eluting BVS design, development and evaluation, Cordis, European Commission, https://cordis.europa.eu/project/rcn/212941/factsheet/en.