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COST-EFFECTIVENESS ANALYSIS OF IN SILICO CLINICAL TRIALS OF VASCULAR STENTS

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Abstract

Today, it takes ten to twelve years on average to complete a clinical trial before a new drug is approved and brought to market. Moreover, the evaluation of the efficacy and safety of drugs or devices has been performed in the linear and sequential manner with limited change over the past decade. The InSilc project is an EU funded project (www.insilc.eu) within which the InSilc platform was developed to design, develop and assess coronary stents. The InSilc platform contains the following modules: 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. We analysed the cost of three different in silico scenarios for clinical study. In Scenario 1, two different stent designs are compared according to the ISO standard for in silico mechanical tests. Scenario 2 predicts the stenting outcome for a virtual anatomy where design/material could be changed. Scenario 3 compares two stents using the same virtual anatomies from the Virtual vessel database. Cost-effectiveness analysis was performed for real clinical trials with metallic and BVS stent and in silico clinical trials. It was observed that in silico clinical trials are almost 90 times cheaper than real clinical trials for 1000 patients. In silico clinical trials will not completely replace real clinical studies, but the evidence shows that they can significantly reduce the cost of a real clinical study which will open a new avenue for future hybrid real and in silico clinical trials.

Keywords: Cost-effectiveness analysis, in silico clinical trials, InSilc project, vascular stents.

1. Introduction

Pharmaceutical and biotech companies conduct clinical trials for many reasons. The most important goal of clinical trials is to demonstrate safety and efficacy of new drugs to gain Food

and Drug Administration (FDA) or European Medical Agency (EMA) approval. FDA and EMA provide guidance to developers to ensure the awareness of acceptable clinical trials and appropriate outcomes. Health care costs continue to grow as a percentage of every country's gross domestic product (GDP). This has a direct influence on the governments and private payers to thoroughly examine the economic value of new treatments. On the other hand, regulatory bodies FDA or EMA demand clinical trials be as safe as possible for clinical trial participants.

As clinical trials progress, it is sometimes necessary to include more patients and this may also have influence on the suitability of the trial. Some patients are not able to participate in the study due to their medical history or opposite requirements for the trials. Moreover, some studies have showed that 18% of patients drop out after enrolling in the trials. It can create delays to the point that 86% of all trials do not meet enrolment timelines and 30% of Phase III trials fail due to enrolment challenges (NIH; Properezi et al. 2019). Therefore, patient recruitment is the largest cost driver of clinical trials, accounting for 32% of overall costs (Fig. 1).

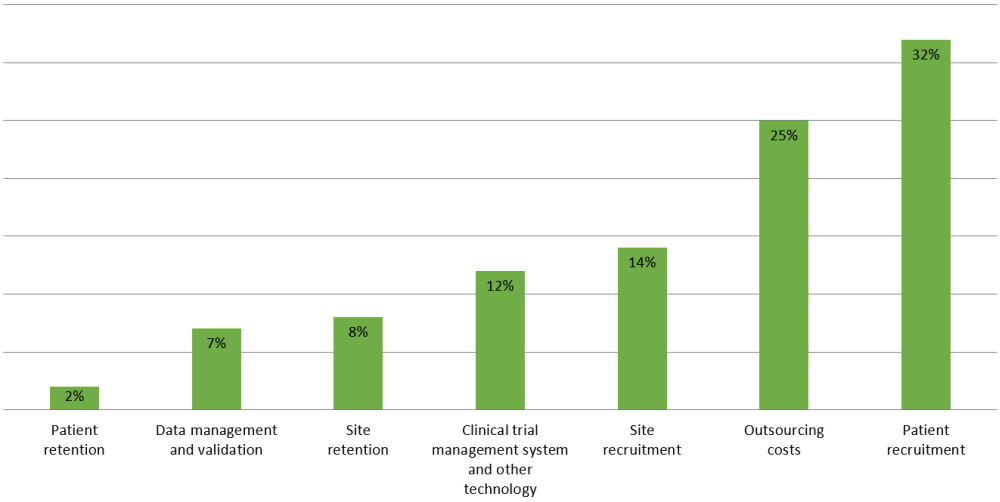

Fig. 1. Cost drivers in clinical trials 1.

Traditional clinical trials are successful around 10%. A very comprehensive testing of the medical device is necessary for final outcome product in medical industry. There are three phases in the process of applied stents for the clinical study. The first phase considers smaller number of patients where only safety of the stent is important. The second phase includes a lot of patients where possible side effects and effectiveness are analysed. The third phase, which is conducted in the large population, analyses efficacy of the stent deployment. The aim of the multi-centre clinical studies is also to compare the evaluation stent with already existing stent in the market (Taylor 2019).

The InSilc project established computational platform for in silico clinical trial for design, development and evaluation of drug-eluting, bioresorbable vascular scaffolds (BVS) stent and simulation deployment in the relevant virtual arteries which are taken from real patients from medical images.

It has been estimated that total world stent market amounts to about €6.4 billion. Around 37% is produced in the United States and 10% in the European Union. Still, coronary stents are most dominant with more than 1 million deployments per year. More than 80 % of the sales are bare metal and drug-eluting coronary stents with Compound Annual Growth Rate (CAGR) of 2.0%. The biggest stents sales are presented in the US, France, Germany, Italy, Spain, UK, Japan, Brazil, China and India.

Older people are becoming more dominant in the global living. It is expected that the number of people who are 65 or older will increase from 605 million to 2 billion by 2050. This will be directly connected to the increase of the market for stents. Global market for coronary artery disease treatment devices from 2020 to 2030 is increasing with **CAGR of 6.4%. It shall increase from $49.80 billion in 2020** to **$92.51 billion by 2030 (Fig. 2).**

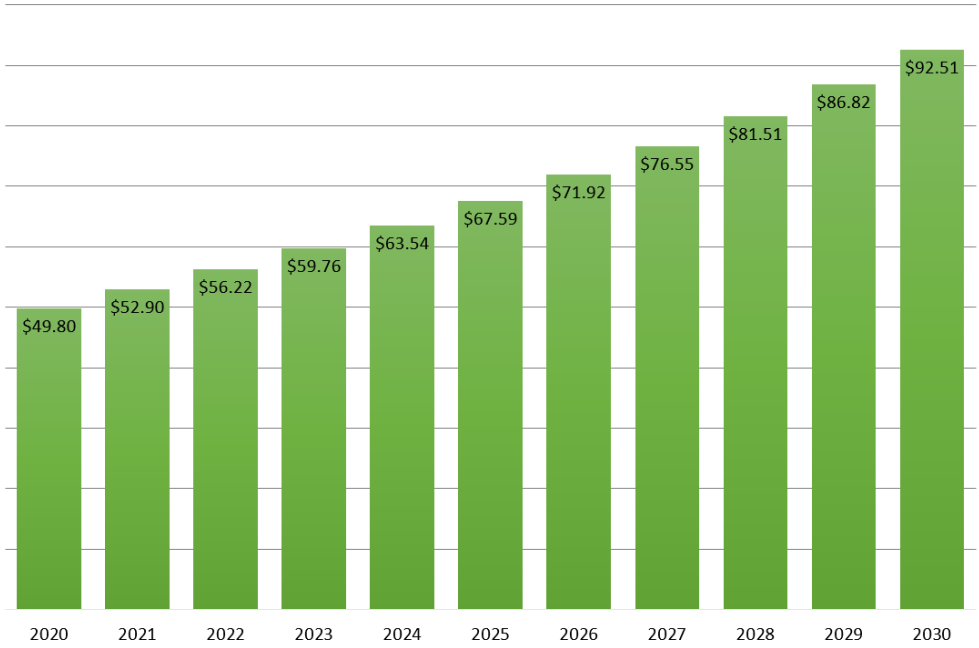

Fig. 2. Global market for coronary artery disease treatment devices 2020-2030.

The coronary stents make about 90% penetration of interventional cardiology procedures. Stent sales will grow with double-digit rates because of innovations and emerging market uptake.

Different types of software on the market are declared an in silico platform. Their users can run some specific tasks and obtain outputs from the platform. However, those software packages differ from the InSilc platform in terms of purpose and complexity. For example, the InSilico trials platform[1] offers users the possibility of selecting the model of choice from the digital library, developing or uploading their own model.

The InSilc platform as a whole and each of its separate modules have been offered to stent industry key players as a service for competitive price, compared to real clinical trials. The use of the platform reduces the time needed for conducting in vitro experiment or clinical trial. For instance, Mechanical Module only can significantly reduce costs and time by performing all

[1] https://insilicotrials.com

mechanical stent tests in silico. Similarly, the rest of the modules can be used as a partial replacement of clinical trials.

In this paper, we first introduce the InSilc platform as a whole and present some of the modules. Next, we analyze the costs of three different scenarios related to the use of the InSilc platform for different types of stent testing or deployment in the virtual patient anatomy. Financial analysis of each module as well as of the total platform per one stent simulation is performed. The average cost per patient for the execution of a real clinical trial is presented. Finally, the calculated price for in silico trials per one stent is compared with the cost of the real clinical trial.

2. Method

2.1 Insilc cloud platform

InSilc cloud platform refers to the development of patient-specific models for different stent testing and deployment in the virtual cohorts. It could complement a clinical trial with reducing the number of enrolled patients and improving statistical significance, and/or advise clinical decisions (Pappalardo et al. 2019).

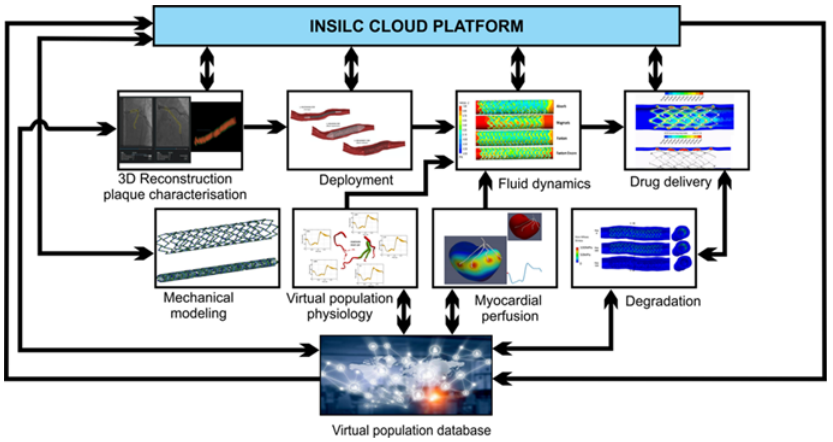

Fig. 3. InSilc cloud platform.

The InSilc platform consists of different modules which simulate drug-eluting BVS stents and their deployment in the virtual arteries. Also, degradation process is simulated in the micro and macro level together with computational fluid dynamics and myocardial perfusion.

The computational modules developed and 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 (Fig. 3). All types of coronary and peripheral stents can be simulated with these modules, such as Bare Metal Stents (BMS), Drug-eluting Stents (DES) and Bioresorbable Stents. InSilc platform and its modules are trying to enter market and reach interested stakeholders (Filipovic et al. 2021; Fotiadis and Filipovic 2021). In this cost-effective study we compare the costs and time required for a real clinical trial and in silico clinical trial.

2.2 Description of the modules

For development of a new stent, corresponding ISO standard mechanical tests are used for evaluation of different mechanical behaviour. These tests could be very time consuming and expensive. For example, fatigue tests can use a lot of cycles and can take up to several months, 24 hours per day. InSilc platform can mimic these mechanical tests virtually. These sets of tests are: Pushability, Trackability, Torquability, Recoil, Crush resistance, Longitudinal tensile strength, Flex/kink, Crush resistance with parallel plates, Local Compression, Radial Force, Three-point bending, Foreshortening, Dog Boning, Inflation and Radial Fatigue test.

For Mechanical Module we used advanced and beyond the state-of-the-art in-house solver PAK developed by BIOIRC [PAK]. Nonlinear material and geometry problems, nonlinear contact problems, dynamics and statics with residual stress and strain analysis have been used in this solver PAK. Firstly, three-dimensional stent geometry is generated. Then, finite element mesh is built. Boundary condition are prescribed together with nonlinear material properties defined from uniaxial stress-strain experimental curves. Three-point bending stent testing for A and B different BVS models has been presented for Mechanical Modelling Module in Fig. 4.

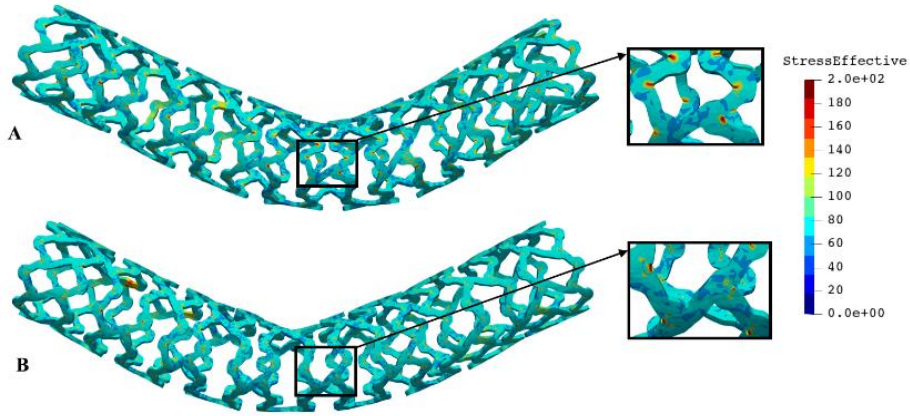

Fig. 4. Mechanical Modeling Module: Three-point bending stent testing for A and B different BVS models.

For stent deployment in the coronary artery Deployment Module is used. Basic information what we can get from this Module are stresses and strains in the stent material, but also in the arterial wall. What can also be detected and analysed is short-term outcome after stent deployment in the artery. The procedure for stent implantation contains from positioning, balloon inflation and deployment. Fully automatized procedure makes this process easy for users. An example of stent deployment with maximal stress distribution in the stent is presented in Fig. 5.

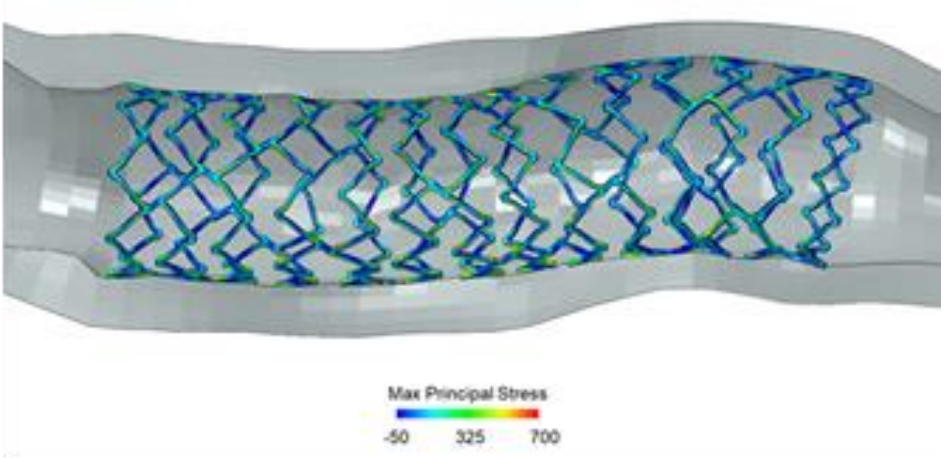

Fig. 5. Deployment Module. Stress distribution in the stent deployed in the coronary artery.

The Degradation Module simulates the degradation pattern of implanted BVS, as it is presented in Fig. 6. The InSilc degradation framework was implemented within both Johnson-Cook and Parallel Rheological Framework (PRF) constitutive models, which have been found to form the basis for the mechanical behavior of several commercial BVS.

Degradation Module in the InSilc platform uses input data from Deployment Module. It uses geometry of the deployment stent artery system and stress-strain history. In this way consistence between Deployment and Degradation has been achieved during solution process in time.

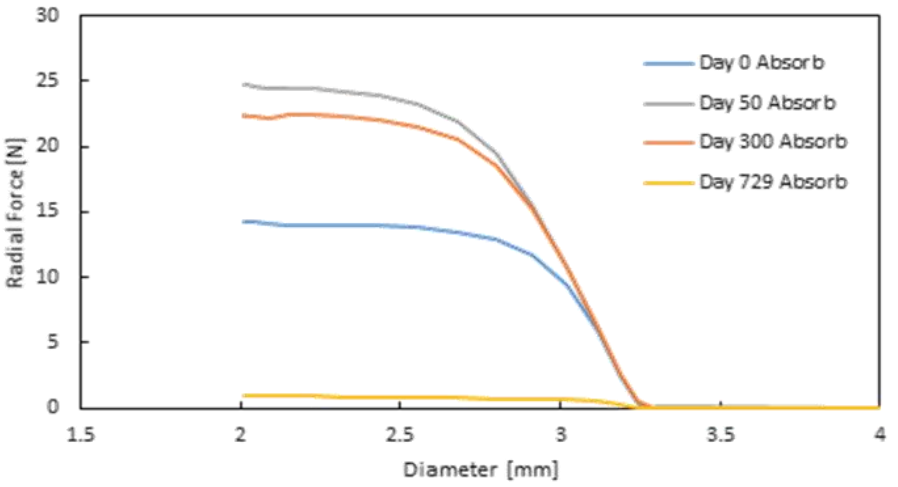

Fig. 6. Degradation Module. Radial force distribution vs diameter in different time during degradation.

3. Results

3.1. Cost-effectiveness analysis of different in silico scenarios

3.1.1. Scenario 1 – pre-clinical testing assessment

Stent manufacturers have the obligation to perform standard mechanical stent testing according to ISO standards. The objective of Scenario 1 is to simulate in silico all the tests required by the ISO. In this scenario, we performed the following tests: 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. All of these in silico tests are used to compare the performance of two stents with different stent designs. The cost and time required is presented in Table 1. It can be seen that in silico stent testing for 8 standard tests amounts to €5,800 while the same testing with in vitro amounts to €64,000. Moreover, time in days for in silico test is 1 day, and all 8 tests could be run in parallel. In vitro stent testing will take 84 days. Actual cost/time concerns the testing of minimum 10-15 samples per test.

Mechanical Module	**Cost €**	**Actual Cost €**	**Time (in days)**	**Actual Time (in days)**
Radial	800	6,000	1	6
Inflation	800	10,000	1	42
Three-point bending	800	6,000	1	6
Crush	400	6,000	1	6
Local Compression	400	6,000	1	6
Longitudinal Tensile Strength	600	6,000	1	6
Kinking	1,000	12,000	1	6
Flex	1,000	12,000	1	6
Total €	**5,800**	**64,000**	**1 (all parallel)**	**84**

Table 1. Cost and time required to perform Scenario 1.

3.1.2. Scenario 2 - design new stents

Scenario 2 aims to predict the stenting outcomes, for a virtual anatomy, when parameters such as design or material change in a specific stent. In this example, the following modules/tools are included: 3D reconstruction and plaque characterization tool, Deployment Module, Fluid dynamics Module, Drug Delivery Module, Degradation Module and Myocardial Perfusion Module.

Relevant modules, their prices and time required are presented in Table 2. In can be seen that all in silico modules cost €8,600, while real clinical trial cost for metallic stent is €11,788 and for BVS €14,400 per patient. Also, time in days for in silico study is 18 days if all simulations are running sequentially or maximum 7 days if they are running in parallel, while real clinical studies are running up to 2 years.

Tool/Module used in Scenario 2	Cost €	Actual cost of clinical trials	Time (in days)	Time required to execute a clinical study
3D Reconstruction Tool	200	**Metallic stent** clinical study cost per stent: **€11,788** **BVS** clinical study cost per stent: **€14,400**	2	Up to 2 years (enrollment + 9-12 months FU) for first-in-man study
Deployment Module	2,000		3	
Fluid Dynamics Module	1,000		2	
Drug Delivery Module	3,800		7	
Degradation Module	1,000		2	
Myocardial Perfusion Module	600		2	
Total €	**8,600**		**18 sequentially or 7 days in parallel**	

Table 2. Costs and time required to perform Scenario 2.

3.1.3. Scenario 3 - compare existing stents

The aim of this scenario is to compare two stents using the same virtual anatomies, available in the Virtual vessel database. In this example, the following modules/tools are included: 3D reconstruction and plaque characterization tool, Deployment Module, Fluid Dynamics Module, Drug Delivery Module and Degradation Module. The cost and time for performing this scenario are presented in Table 3. It can be seen that in silico costs are around €8,000 and maximum duration is 18 days. If we consider including the whole pipeline up to degradation for real clinical studies, the duration can be up to 5 years (patient enrolment + follow-up for degradation). Otherwise, 2-3 years are needed for restenosis (enrolment + 12 months FU).

Tool/Module used in Scenario 3	Cost €	Actual cost of clinical trials	Time (in days)	Time required to execute a clinical study
3D Reconstruction Tool	200	**Metallic stent** clinical study cost per stent: **€11,788** **BVS** clinical study cost per stent: **€14,400**	3	Duration of a clinical trial depends upon the study design. 1)If we consider including the whole pipeline up to degradation, the duration can be up to **5 years** (patient enrolment + follow-up for degradation). 2) If we limit to restenosis, **2-3 years** are needed (enrolment + 12 months FU)
Deployment Module	2,000		3	
Fluid Dynamics Module	1,000		2	
Degradation Module	1,000		3	
Drug Delivery Module	3,800		7	
Total €	**8,000**		**18**	

Table 3. Cost and time required to perform Scenario 3.

3.2. Financial analysis

Detailed prices of each module are presented (Gacic 2022) in Table 4.

Module	Price €	Base for calculation of in silico trial
Virtual Database Module	200	Per simulation.
Deployment Module	1,000	Per simulation with the deployment of one stent in a single vessel. More complex procedures should be considered separately. 3D geometry of the stent has been generated in the previous step.
Fluid Dynamics Module	900	Per simulation.
Drug Delivery Module	1,900	Per simulation. The geometry of artery and stent has been generated from previous module. The pharmacokinetics model of the release for the stent device has already been developed.
Degradation Module	500	Per simulation.
Myocardial Perfusion Module	300	Per patient with some additional automatization.
Virtual Population Physiology Module	200	Per patient.
InSilc Platform	150	Per simulation.
Total	**5,150**	

Table 4. Detailed prices of each module and total price for in silico stent deployment.

The prices for real clinical study for metallic and BVS stent per patient are €11,788 and €14,400, respectively. The price for in silico clinical study per stent is €5,150. For calculation of the price for more patients, real clinical studies are calculated as linear function which is multiplied with the number of patients. The price for in silico clinical study is not calculated as linear function, because it can be speed up with parallel calculation on supercomputer or high-performance computing in parallel with divided of square root for number of patients. Comparison for the price for real and in silico clinical trials for both metallic and BVs stents is presented in Table 5. Variation of the price for real and in silico clinical trials for metallic and BVS stent with logarithms scale for number of patients has been graphically shown in Fig. 7. It can be seen that real clinical study for 1000 patients is amounting to 12-14.5 million euros, while in silico clinical trials for the same number of patients are up to €163,000 (Gacic et al.2021; Gacic 2022; Gacic 2023).

Number of patients	Price for real clinical study with metallic stent (€)	Price for real clinical study with BVS stent (€)	Price for in silico clinical study with virtual stent (€)
1	11,788	14,400	5,150
10	117,880	144,000	16,286
100	1,178,800	1,440,000	51,500
1000	11,788,000	14,400,000	162,857

Table 5. Comparison of the price for real and in silico clinical trials.

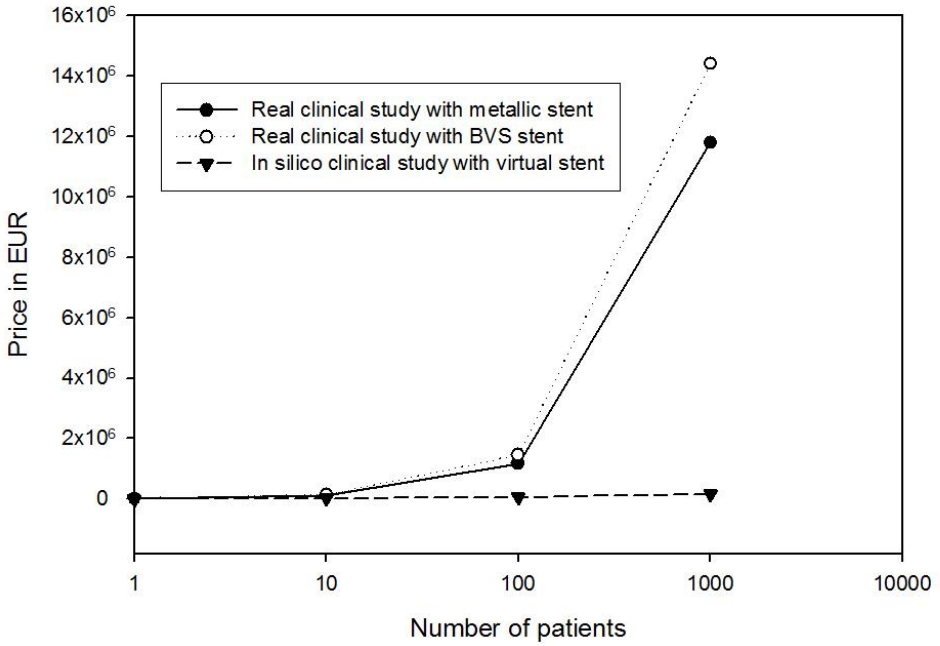

Fig. 7. Variation of the price for real and in silico clinical trials for metallic and BVS stent.

4. Discussion and conclusions

The main exploitable products of the InSilc project 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 (Gacic 2022).

A detailed cost analysis of five different in silico scenarios defined in the InSilc project has been described.

Scenario 1 compared in silico two different stent designs for all ISO mechanical tests. The outcomes of virtual anatomy with different design and material have been analysed in Scenario 2. Two stents in the same virtual anatomies from virtual coronary database have been compared in Scenario 3.

Financial analysis has taken into account the prices per each InSilc module as a total of €5,150. It has been shown that the cost of real clinical study including 1000 patients can be very expensive amounting to 12-14.5 million euros, while in silico clinical trials for the same number of patients are up to €163,000. It is almost 90 times cheaper than real clinical study. The perspective of in silico clinical trials is very promising. It will not completely replace real clinical studies, but it will significantly reduce the cost of real clinical studies and become standard complementary part of future hybrid clinical study (real and in silico).

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