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Journal of Interdisciplinary Medicine

ORIGINAL RESEARCH

CARDIOLOGY // INTERNAL MEDICINE

# In-stent Flow Hemodynamics and the Risk of STent Failure Following Bioresorbable Vascular ScAFFolds Implantation – the STAFF Study

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**ARTICLE HISTORY**

Received: September 21, 2017
Accepted: Ocotber 17, 2017

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**ABSTRACT**

**Background:** Myocardial revascularization procedures have undergone important developments over the last decades, which led to a major shift in current clinical practice and therapeutic guidelines across the world. Bare metal and drug-eluting stents present several limitations, all centered on the concept of disturbed coronary hemodynamics after implantation, which can be surpassed by bioresorbable vascular scaffolds (BVS). BVSs are fourth-generation stents used in coronary revascularization procedures, but despite all the promising initial results published on their efficiency, several clinical trials have reported unsatisfactory results, and the main explanation was accredited to improper implantation method. Shear stress is a central element of intravascular homeostasis; it controls vascular remodeling, as well as the development, progression, and destabilization of atheromatous plaques. This study **aims** to assess the role of in-stent flow hemodynamics (evaluated by computational determination of shear stress via coronary CT imaging) in predicting the clinical evolution following BVS implantation. **Material and methods:** This case-control observational study will include patients with BVSs implanted at least 12 months prior to randomization. Each patient will undergo a complete evaluation of the demographic and clinical characteristics, cardiovascular risk factors, and imaging acquisitions via coronary CT angiography, based on which the endothelial shear stress will be calculated before and after BVS implantation. Post-processing of CT imaging data will evaluate the shear stress and the composition of the coronary plaques along the entire coronary tree. The primary endpoint will be the major adverse cardiovascular events (MACE) in patients with altered vs. non-altered BVS-related shear stress, and the secondary endpoints will comprise evaluating the rate of progression of stent resorption and progression of shear stress alteration. **Conclusions:** The findings of the STAFF study can be extremely useful in clinical practice for providing an answer to a key question that is still under debate: why do BVSs fail and how can we prevent this?.

**Keywords:** bioresorbable scaffolds, in-stent hemodynamics, shear stress, predilatation time, inflation pressures

## INTRODUCTION

### Study Rationale

Interventional myocardial revascularization procedures have undergone important developments over the last few decades, which led to a major shift in current clinical practice and therapeutic guidelines. Due to the substantial financial burden represented by the increased number of cardiovascular deaths, 50% (7.4 million) of which are being caused by atherosclerotic coronary artery disease (CAD), continuous efforts are made to develop novel methods for the therapeutic management of these patients.[1]

The most frequent therapeutic modality for the treatment of CAD is currently represented by percutaneous transluminal coronary angioplasty (PTCA), associated with stent implantation.[2]

Bare metal and drug-eluting stents, commonly used in percutaneous procedures, present several limitations, all centered on the concept of disturbed coronary hemodynamics after implantation, which can be surpassed by bioresorbable vascular scaffolds (BVS). Polymer-based BVSs are able to restore not only vessel patency, but also vascular motility, as the contained material will resorb in a few years, and no foreign material will be present anymore within the vascular wall.[3,4] BVSs are fourth-generation stents used in coronary revascularization procedures, which have been proposed to replace the first generations represented by bare metal stents and drug-eluting stents.[5] However, despite the promising initial results published on the efficiency of bioresorbable scaffolds, several clinical trials have reported unsatisfactory results, and the main explanation for this was accredited to improper implantation technique.[3,4,6]

On the other hand, stent angioplasty immediately restores blood flow in the obstructed artery; however, it has been demonstrated that stent struts can also provoke minor turbulence that can slow the endothelization process, as well as promote thrombosis.[7,8]

The growth of the fibroinflammatory lipid plaque is initiated and enhanced by the inflammatory processes regulated by shear stress. The local shear stress pattern at the endothelium level can be altered by a new atherosclerotic lesion.[9] In case of a significant stenosis, an increased flow velocity can create a disturbed flow downstream, distal from the plaque, which can contribute to the growth of the atherosclerotic plaque. In these circumstances, an increased atherosclerosis susceptibility, plaque growth, plaque instability, and an increased risk of thrombosis have been demonstrated by in vitro and in vivo studies on endothelial cells.[10–13]

Coronary computed tomography angiography (CCTA) can be used with high accuracy for the evaluation of luminal dimension and monitoring of BVS absorption after implantation.[14] The present study, based on noninvasive CCTA imaging and computational image post-processing, will attempt to answer a number of questions such as: (1) What is the influence of intraprocedural factors, mainly predilatation time and inflation pressures, on the permeability of bioresorbable scaffolds during follow-up? and (2) How does the in-stent flow hemodynamics, assessed by computational shear stress, influence the clinical evolution of patients with BVS?

## OBJECTIVES

The primary objective of this study is to assess the role of in-stent flow hemodynamics (evaluated by computational determination of the shear stress) in predicting the clinical evolution following BVS implantation.

The secondary objectives of the study are:

- to assess the role of various factors that could influence the permeability of BVS. The studied factors will include: (1) procedural aspects during stent implantation (such as pre-dilatation time and inflation pressures); (2) imaging-derived biomarkers (such as global and local calcium score, Syntax score, location and severity of associated coronary lesions); (3) clinical data (age, gender, comorbidities, left ventricular function); and (4) hemodynamic factors such as shear stress in the coronary tree and at the level of the stented lesion;
- to assess the correlation between the evolution of shear stress at the site of the implanted BVS and the degree of BVS resorption in the follow-up period.

## STUDY DESIGN

This is a case-control observational study that will take place in the Laboratory of Advanced Research in Cardiac Multimodal Imaging of the Cardio Med Medical Center of Tîrgu Mureş, Romania.

**Baseline:** Baseline is defined as the date of enrollment in the study of each patient; patient enrollment will commence on January 1, 2019.

**Follow-up period:** Patient follow-up will be regularly performed at 1, 3, 6, and 12 months after randomization.

### Groups and interventions

The study lot will consist of 50 patients with implanted BVS, in whom the implantation procedure occurred

at least 12 months prior to randomization, divided in 2 groups:

- group 1 – patients with implanted BVS in whom imaging tests (CT or angiography) reveal signs of stent failure (stent occlusion or severe restenosis);
- group 2 – patients with implanted BVS in whom imaging tests (CT or angiography) reveal patent BVS stents.

Inclusion criteria:

- patients aged at least 18 years;
- patients who have signed the written informed consent;
- patients with BVS implanted at least 12 months prior to the procedure.

Exclusion criteria:

- patient's refusal to take part in the study;
- pregnant women;
- any malignancy within the last 5 years;
- any disease or comorbidity that reduces life expectancy under 1 year;
- non-compliant patients who, in the opinion of the investigators, will not undergo the follow-up process.

Written informed consent will be obtained from all eligible patients to allow collection and statistical analysis of patient's data.

## STUDY PROCEDURES

For each patient enrolled in the study, a dedicated database will be created, storing:

1. demographic and clinical data (background, age, personal history etc.);
2. electrocardiography;
3. echocardiography;
4. coronary CT angiography;
5. technical data related to the implantation procedure (predilatation parameters), which will be recorded using patient data files.

Computational processing of CT imaging data will be performed in the laboratory of computational medicine of the Cardio Med Medical Center, using complex simulations and advanced post-processing techniques for the analysis of shear stress and the composition of the coronary plaques along the entire coronary tree. Shear stress will be assessed at the level of all significant (>50%) coronary artery stenoses and BVS-related shear stress will be calculated at three levels: inside the BVS, proximal to the BVS, and distal to the BVS.

For each CT imaging dataset, the following parameters will be analyzed: global calcium score and local calcium score of the stented coronary artery, Syntax score, the presence of co-existing lesions and their severity, the degree of stent resorption, the presence of in-stent restenotic tissue and severity of restenosis, the volume of epicardial fat, and the presence of vulnerability markers in the coronary tree.

For each angiographic imaging dataset, the following parameters will be analyzed: the Syntax score, the presence of co-existing lesions and their severity, the severity of restenosis and the TIMI flow. During invasive imaging (performed when indicated), an intracoronary imaging procedure consisting of optical coherence tomography will be associated, to quantify the amount of stent resorption.

Statistical analysis will be performed in the laboratory of medical statistics of the Advanced Cardiac Multimodal Imaging Research Center SC Cardio Med SRL.

## STUDY ENDPOINTS/OUTCOME MEASURES

The primary endpoint of the study will be represented by the rate of major adverse cardiovascular events (MACE) in patients with altered vs. non-altered BVS-related shear stress and in relation to procedural aspects related to predilatation.

MACE will be defined as cardiac death, need for target vessel revascularization (with target vessel defined as the vessel with a vulnerable plaque), or reinfarction.

Secondary endpoints will be represented by: (1) the rate of progression of stent resorption and (2) the rate of progression of shear stress alteration.

## ETHICS

All study procedures are in line with the principles in the Declaration of Helsinki. All patients will sign an informed consent prior to be enrolled in the study. The study received Ethics approval from both institutional boards (approval no. 29/28.12.2017 from the Ethics Committee of Cardio Med Medical Center, and approval no. 338/17.11.2017 from the Ethics Committee of the University of Medicine and Pharmacy of Tîrgu Mureş).

## CONCLUSIONS

The aim of this study is to assess the role of two major factors that could influence the evolution of BVS: in-stent hemodynamics, as assessed by the calculation of shear stress, and procedural aspects related to the stenting procedure, in order to identify factors that could be associated with a lower rate of stent failure following BVS implantation.

The findings of the STAFF study can be extremely useful in clinical practice for providing an answer to a key question that is still under debate: why do BVSs fail and how can we prevent this?

## ACKNOWLEDGEMENT

This clinical trial is a part of the project entitled 'Increasing the research capacity in the field of vulnerable plaque imaging, based on advanced nanoparticles, fusion imaging and computational simulation – PlaqueImage' financed by the National Authority of Scientific Research and Innovation and the Romanian Ministry of European Funding, through the Competitivity Operational Program, contract number 26/01.09.2016, SMIS code:103544. The research is also receiving funding from the University of Medicine and Pharmacy Tîrgu Mureș, Romania, via governmental funds for PhD studies, contract number 14057114/07.10.2014.

## CONFLICT OF INTEREST

Nothing to declare.

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