**Tyumen Cardiology Research Center, Tomsk National Research Medical Center, Russian Academy of Science, Tomsk, Russia**

# Heterogeneity of Neointimal Healing Following Biodegradable-polymer Drug-Eluting Coronary Stent Implantation: a pilot randomized clinical trial (156)

**Study Protocol (version 1.1)**

03/08/2020

Drug-eluting stent (DES) implantation is regarded as an effective strategy for patients with narrowing of the coronary arteries. However, in-stent restenosis, one of the major events, which may cause late-stent failure, has imperiled the long-term clinical outcome after percutaneous coronary intervention (PCI). Several mechanisms have been revealed relating to the excessive neointimal healing including patient factors (diabetes), lesion factors (longer stent), or PCI procedure (stent under expansion), among others.

Therefore, additional information about neointimal hyperplasia is required to develop novel devices and improve stent therapy. Recently, optical coherence tomography (OCT) has been used to assess the morphologies of implanted coronary stents in detail in various clinical situations. With higher resolution than intravascular ultrasound, OCT can evaluate strut-level coverage and assess neointima more accurately.

Homogeneous neointima has uniform optical properties and does not show focal variations in backscattering pattern. Heterogeneous neointima has focally changing optical properties and shows various backscattering patterns. Layered neointima consists of concentric layers with different optical properties: an adluminal high scattering layer and an abluminal low scattering layer. Normal neointima, defined as smooth muscle cell-rich tissue with extracellular matrix containing collagens and proteoglycans, is seen as homogeneous and has a smooth luminal surface. The peak intensity of optical frequency domain imaging is in the moderate range, and the attenuation rate is mild to moderate. However, areas of fibrin deposition or inflammation (hypersensitivity) that appear during the development of neointima normally have a dark appearance. According to a histopathological validation study, a homogeneous pattern correlates most often with smooth muscle cells and a collagenous/proteoglycan matrix, while a heterogeneous pattern is frequently associated with stent-induced hypersensitivity vasculitis. A layered pattern is most commonly correlated to healed neointimal rupture/erosion. However, OCT pattern does not indicate a specific histologic finding even though OCT can visualize neointima in detail. Homogeneous neointima might be associated with better clinical outcomes after DES implantation, whereas non-homogeneous neointima or neoatherosclerotic change can be associated with poorer clinical outcomes. However, limited data are currently available, and further studies are required to comprehensively address these questions. The objective of this study is to investigate the formation and transformation of neointima after various types of DES implantation based on pathologic and OCT studies.

Planned work is a prospective pilot simple blind randomized study

Inclusion Criteria:

- Age > 18 years;

- Patients with symptoms of stable angina and/or presence of a positive functional test for ischemia;
- Patient is eligible for percutaneous coronary intervention (PCI);
- Patient has been informed of the nature of the study and agrees to its provisions and has provided written informed consent as approved by the Ethical Committee of the respective clinical site.

Exclusion Criteria:

- Target lesion involving a bifurcation with a side branch ≥2.0 mm in diameter;
- Target lesion located in the left main stem;
- Target lesion is located or supplied by an arterial or venous bypass graft;
- Lesion located very distally, difficult to be imaged by OCT;
- Co-morbidities that could interfere with completion of study procedures, or life expectancy less than 1 year;
- Participating in another investigational drug or device trial that has not completed the primary endpoint or would interfere with the endpoints of this study;
- Patient underwent target vessel revascularization with a DES;
- Patient presenting with acute myocardial infarction with ST elevation;
- Cerebrovascular accident within the past 12 months;
- Acute or chronic renal dysfunction (defined as creatinine greater than 2.0 mg/dl);
- Patient receiving oral anticoagulants

Patients will be randomized into two groups, depending on the type of DES by generating random numbers on a remote site just before the procedure. The main study group will be consisted of patients who underwent PCI using the Orsiro stent. The comparison group will be consisted of patients who underwent underwent PCI using the Resolute Integrity stent. DES implantation will performed using conventional techniques. Unfractionated heparin will administered as an initial bolus of 100 IU/kg. Dual antiplatelet therapy (aspirin and clopidogrel) will recommended to all patients for at least 12 months after DES implantation.

OCT will performed with either the Model M2 imaging system or the C7-XR imaging systems (LightLab Imaging, Inc./St. Jude Medical, St. Paul, Minnesota). The imaging wire will pulled from distal to proximal with a motorized pull-back system at 1.0 mm/s. The frequency-domain OCT system (Model C7-XR) will developed to generate frames at much higher rates, thereby allowing for faster pullback speeds. OCT images will generated at 100 frames/s, whereas the catheter will pulled back at 20 mm/s. A contrast medium will continuously flushed through a guiding catheter at a rate of 4 to 5 ml/s for 3 to 4 s. Continuous images will acquired and stored digitally for subsequent analysis.

All OCT images will analyzed at a core laboratory (Tyumen Cardiology Research center) by analysts who will blinded to both patient and procedural information. Cross-sectional OCT images will analyzed at 1-mm intervals for quantitative measurements. Stent area and luminal cross-sectional area (CSA) will measured, and neointimal CSA will calculated as the stent CSA minus the luminal CSA. The segment with minimal lumen area and greatest neointimal proliferation can be the representative site of the lesions for long-term clinical follow-up. Therefore, the stented segments at the minimal lumen CSA and greatest neointimal CSA will assessed qualitatively to characterize the neointimal tissue as: 1) homogeneous neointima, a uniform signal-rich band without focal variation or attenuation; 2) heterogeneous neointima, focally changing optical properties and various backscattering patterns; and 3) layered neointima, layers with different optical properties (i.e., an adluminal high-scattering layer and an abluminal low-scattering layer). The interobserver and intraobserver agreements for the assessment of neointimal tissue morphology in our laboratory will previously reported.

The primary endpoint of the study is endothelial coverage by heterogeneous neointima of the stent struts assessed by optical coherence tomography in the 4 ± 1 months after DES implantation. Secondary endpoints are: major adverse cardiac event, malapposed stent struts, uncovered stent struts, neointimal growth, angiographic reference vessel diameter, angiographic minimal lumen diameter, angiographic diameter stenosisstent thrombosis, binary restenosis puncture time, angiographic late lumen loss.

A major adverse cardiac event (MACE) was defined as cardiovascular death, nonfatal myocardial infarction, and target-lesion revascularization. Clinical events were defined according to the Academic Research Consortium. All deaths were considered cardiovascular deaths unless a definite noncardiovascular cause was established. Myocardial infarction was defined as the presence of clinical symptoms, electrocardiographic changes, or abnormal imaging findings of myocardial infarction combined with an increase in creatine kinase-myocardial band fraction >3 times the upper limit of the normal range or an increase in troponin T/troponin I to more than the 99th percentile of the upper limit of normal, all of which were unrelated to an interventional procedure . Stent thrombosis was defined according to the recommendations of the Academic Research Consortium. Target-lesion revascularization was defined as a repeat percutaneous intervention or bypass surgery of the target lesions with either of the following findings: ischemic symptoms or a positive stress test and an angiographic minimal lumen diameter stenosis ≥50% assessed by quantitative coronary angiographic analysis or an angiographic diameter stenosis ≥70% assessed by quantitative coronary angiographic analysis without either ischemic symptoms or a positive stress test.