Introduction
In-stent restenosis (ISR) develops due to the maladaptive response of the arterial tissue towards the injury caused by the stent. Balloon angioplasty and stent deployment denude endothelium and activate smooth muscle cells (SMC) to change their phenotype from quiescent to a more proliferative state thus giving rise to the development of neointima. The regeneration of endothelium is considered to involve either the homing of endothelial progenitor cells (EPC) from blood flow at the site of injury, where they convert into mature endothelial cells (EC), or endothelium regrowth from both sides of the stented part of the vessel [Hagensen, 2012]. In the current study, the effect of the origin of the ECs regeneration (EPC or regrowth from both sides of vessel) on ISR development is evaluated in-silico and their morphological differences in terms of tissue patterns are reported. Moreover, ISR response considering different ECs regeneration rates is also examined.

Material and Methods
Two-dimensional (2D) blood flow (lattice Boltzmann) and vascular tissue (agent based) models are coupled together [Caiazzo, 2011, Tahir, 2011]. A 4.5 mm long and 1.24 mm wide vessel with a vessel wall thickness of 120 μm is used as a benchmark geometry, where vessel injury is produced by deploying six square bare metal stent struts at a specific depth into the artery. Complete endothelium denudation is assumed after stent deployment. The SMCs from the medial layer start to proliferate inside the lumen. In the mean while, endothelium also starts to regenerate (either from random EPC seeding or from both sides of vessel) and if endothelium is present, the tissue model receives shear stress on the regenerated ECs and translates it in to nitric oxide (NO) production. If the NO concentration is higher than a certain predefined threshold, it causes a cell cycle arrest in the underlying SMCs and keeps them in a quiescent state.

Results
Quantitatively, random EPC seeding showed slightly higher neointimal growth when compared to EC growth from sides. However, ECs from sides tend to cause significantly lower luminal cross sectional area in the middle of the stented segment, whereas, a smoother tissue growth is observed in the case of random EPC seeding. Moreover, neointimal thickness measured on top of each strut tends to decrease with a faster endothelium recovery. The neointimal thickness also decreases with a faster endothelium growth assuming random EPC seeding.

Discussion
Results suggest a significant qualitative difference between both scenarios of ECs regeneration. A recent study showed that EPC does not play a role in the regenerated endothelium. Instead, the healthy endothelial cells near the injured sites (from both sides of the vessel) proliferate and generate an intact endothelium [Hagensen, 2012]. In order to verify similar tissue patterns in the histology; the work on obtaining longitudinal sections from porcine stented vessels showing restenosis is currently in progress. Such longitudinal stented data will allow us to compare our computational tissue patterns to those observed in animal experiments and may provide some insights to understand the question; where do the endothelial cells come from during the endothelium regeneration process following arterial injury.

References
Caiazzo et al, JOCS 2: 9-17, 2011.