**DOWNREGULATION OF ENDOTHELIAL BETA-2 SPECTRIN BY INCREASED PLAQUE STIFFNESS INDUCES A LEAKY VESSEL PHENOTYPE IN ATHEROSCLEROTIC PLAQUE MICROVASCULATURE**

**E.A. Biessen**1,2

1Maastricht University, Maastricht, Netherlands

2Institute for Molecular Cardiovascular Research, RWTH Aachen, Aachen, Germany.

Intraplaque angiogenesis is a poorly understood process in atherosclerotic plaque destabilization. Seeking strategies to tackle the detrimental consequences of plaque vessel dysfunction, we investigated the molecular changes in plaque microvessels which correlated to a leaky vessel phenotype. From human atherosclerotic lesions’ transcriptome data, we reconstructed coexpression networks, identifying a network which showed high and selective correlation to plaque microvascular density, but not angiogenic endothelium or pericyte coverage. Five central module members were selected, including ZEB1 and SPTBN1. While the former gene has recently been implicated in angiogenic regulation in tumors, our study shows that loss of the latter resulted in enhanced leukocyte transmigration and vascular permeability *in vitro*. These effects of SPTBN1 could be linked to an increased number of focal adhesions, and reduced junctional VE-cadherin expression. Mechanistically, locally increased tissue stiffness downregulated SPTBN1 expression, an effect that was associated with enhanced presence of intraplaque haemorrhage. In summary, this study unveils SPTBN1 as a new regulator of plaque microvessel formation and patency. Moreover local stiffness-dependent regulation of SPTBN1 primes a leaky vessel phenotype in atherosclerotic plaque microvessels, thus aggravating the disease.