**OSTEOGENIC DIFFERENTIATION IS A MECHANISM FOR BIOPROSTHETIC VALVE CALCIFICATION**

**N.M. Rajamannan**

Mayo Clinic, Rochester, MN, USA

*Background:*Bioprosthetic heart valve calcification is the major cause of structural valve deterioration (SVD).  The mechanism of valve degeneration is unknown. This study hypothesizes that bioprosthetic valve calcification is a stem cell mediated bone differentiation process.

*Method:*23 porcine valves removed from surgery were tested for SVD at and compared them to 6 control valves prior to implantation for stem cell marker and bone transcription factor for gene expression and MicroCT (Scanco). Next an *in vivo* model of prosthetic valve calcification by implanting normal bioprosthetic valves subcutaneously in 30 rabbits; 10 served as controls, 10 were fed  0.5% Cholesterol diet and 10 were fed 0.5% Cholesterol and were also given Atorvastatin for three months.  In these 30 rabbits we measured markers of osteogenic bone differentiation.

*Results:*Human bioprosthetic porcine valves removed at surgery demonstrated a four-fold increase in osteogenic markers and calcium burden by MicroCT. The control valves prior to implantation had no evidence of increase bone formation.

Bioprosthetic valve tissue explanted from the rabbits fed the cholesterol diets demonstrated atherosclerosis and had evidence of cells positive for cKit, macrophage, and osteopontin expression which was attenuated in those who also received atorvastatin (p < 0.05). Control valves demonstrated a mild increase in the markers.

*Conclusion:*Bioprosthetic valve calcification is a mesenchymal cKit mediated osteogenic process. These experimental data are the first to demonstrate the presence of cKit and Cbfa1 gene expression in *ex vivo* and *in vivo* analysis. These findings are the first to demonstrate a biological mechanism in bioprosthetic valve calcification and have implications for future therapy of patients with bioprosthetic valves in order to slow the progression of valve calcification.