Introduction Matrix Metalloproteinase 14 (MMP14) is expressed in atherosclerotic plaques, with a potential role in matrix protein degradation and neovascularisation. The MMP14 gene is upregulated by hypoxia and contains a possible Hypoxic-Inducible Factor (HIF) recognition sequence (5’-RCGTG-3’). Simvastatin is commonly prescribed as treatment for cardiovascular disease, and is known to stabilise atheromas through preventing rupture and neovascularisation. We hypothesised that HIF1α binds to the MMP14 gene promoter, enhancing MMP14 expression, and that simvastatin acts to attenuate this effect.

Methods Chromatin Immunoprecipitation (ChIP) assays were performed on cultured human umbilical vein endothelial cells (HUVEC), either in hypoxia (1% oxygen) or normoxia, with or without 0.1 μM simvastatin to assess HIF1α interaction with the MMP14 promoter. Western Blots and FACS analysis were used to detect changes in HIF1α and MMP14 expression of HUVEC cells cultured either in hypoxia (1% oxygen) or normoxia, with or without 0.1 μM simvastatin.

Results HIF1α bound to the MMP14 gene promoter in hypoxia but this was significantly decreased with the addition of simvastatin. There was no HIF1α and MMP14 interaction in cells that were cultured in normoxic conditions. HIF1α expression was substantially upregulated after 4 hours of hypoxic incubation but this was significantly attenuated by the addition of simvastatin. MMP14 expression was significantly increased in hypoxic conditions and the addition of simvastatin reduced this effect.

Conclusion Our results showed that MMP14 is upregulated in hypoxic conditions and that this occurs by the interaction of HIF1α and the MMP14 gene promoter region. The upregulation of MMP14 is attenuated by the addition of simvastatin which reduces the interaction of HIF1α with the MMP14 gene promoter. These results suggest that simvastatin may stabilise atheromas through inhibiting MMP14.