**Targeting hypoxia in atherosclerosis in diabetes.**

**Aims.** Atherosclerosis is a major cause of cardiovascular disease (CVD)-related deaths in diabetes. Residual risk of CVD remains even after treatment of standard risk factors including hyperglycaemia. Therefore, additional mechanism-based therapeutic options are urgently needed. Although diabetes is associated with tissue hypoxia across multiple organs, hypoxic responses are impaired due to defective activation of hypoxia-inducible factor (HIF) signalling. Daprodustat is the first FDA approved small molecule inhibitor of HIP prolyl hydroxylase for anaemia in chronic kidney disease that can activate HIF, however, its role in CVD in diabetes in not known.

**Methods.** *In vitro* studies involving cell culture models, mimicking diabetes-induced foam cell formation in human THP-1 monocytes and murine bone marrow derived macrophages (BMDMs), were conducted to investigate anti-atherogenic properties of Daprodustat. Moreover, atheroprone Apoe-/- mice made diabetic with streptozotocin, were treated with Daprodustat in an intervention study.

**Results.** HIF activation with Daprodustat attenuated foam cell formation in THP-1-derived macrophages and BMDMs.This was linked to the regulation of genes critical in cholesterol efflux including *FABP5* and *ABCA1*. Complete blood count showed increased number of red blood cells in Daprodustat treated mice compared to vehicle treated mice. Critically, treatment with Daprodustat attenuated atherosclerosis in diabetic *Apoe-/-* mice with more than 2-fold reduction in plaque size compared to vehicle treated mice.

**Conclusion**. This study implicate that Daprodustat is a potential candidate for drug repurposing in diabetes associated atherosclerosis.