**Semaglutide provides superior cardioprotection compared to pravastatin and offsets pravastatin-induced cardiac impairment in obesity**

**Aim:** This study investigated the effects of semaglutide and pravastatin monotherapy and when combined on cardiometabolic risk factors, cardiac structure and function, and tolerance to ischaemia/reperfusion in an obese murine model.

**Methods:** Mice were fed standard rodent chow (CON; n=15) or an obesogenic diet (OB; n=60) for sixteen weeks to induce obesity. OB mice were randomly subdivided and treated with semaglutide (SEM; n=15), pravastatin (STA; n=15), combination therapy (SEMSTA; n=15) or vehicle (OB; n=15) for six weeks. Outcome measures included cardiometabolic risk factors,cardiac structure and function (echocardiography), and ischaemic tolerance (Langendorff heart perfusions).

**Results:** Compared to controls, OB mice gained weight (OB: 2.94±0.29g vs. CON: 0.52±0.14g; p<0.0001) and became insulin resistant - increased HOMA-IR (OB: 32.92 ± 6.43 vs. CON: 14.27±0.27; p<0.01). Weight gain was limited by semaglutide (SEM: 0.84±0.21g; p<0.001), pravastatin (STA: 1.54±0.34 g; p<0.01), and the combination (SEMSTA: -0.62±0.37g, p<0.0001). HOMA-IR was lowered by semaglutide monotherapy (SEM: 10.50±2.38; p<0.01) and combination therapy only (15.67±1.56; p<0.05). Echocardiographic myocardial performance index (MPI) was increased with pravastatin monotherapy (STA: 0.70±0.05; p<0.05), suggesting mild impairment in global cardiac function. A finding not observed when combined with semaglutide (SEMSTA: 0.66±0.04; p>0.05). *Ex-vivo* Langendorff perfusion demonstrated improved post-ischaemic recovery of left ventricular developed pressure in OB mice treated with semaglutide monotherapy (SEM: 71.50±2.21mmHg; p<0.05) and combination therapy (SEMSTA: 74.0±3.05mmHg; p<0.01). Effluent LDH activity was increased in OB mice treated with pravastatin (STA: 23.5±1.08IU/g, p>0.05), but was reduced with combination therapy (SEMSTA: 13.8±2.34IU/g, p<0.05), indicating cardioprotection by semaglutide in pravastatin-treated OB mice.

**Conclusions:** Semaglutide improved metabolic outcomes and ischaemic tolerance. Pravastatin monotherapy showed modest metabolic impairment, evidence of mild cardiac dysfunction and reduced tolerance to ischaemia-reperfusion. Combination therapy was most effective in preventing weight gain, preserved semaglutide’s benefits and mitigated pravastatin-associated risks suggesting therapeutic synergy in obesity-related cardiovascular disease management.