PROJECT PROPOSAL

2025/6 Academic Entry Year – Cohort 4

Supervisory Team

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Project Details

Title: A pilot randomized controlled trial of semaglutide in people living with multiple long-term and stage B heart failure

Summary: Heart failure costs the NHS an estimated **£2 billion** annually, which constitutes about **2% of the total NHS budget**. 1-2% of the population are affected but disproportionately affects ethnic minorities and those from lower socio-economic classes due to the higher prevalence of risk factors such as obesity, diabetes and hypertension. Despite advances in treatment for heart failure the prognosis remains dismal and worse than most cancers. In this pilot trial you will randomise 60 participants with early heart failure (structural abnormalities but no symptoms) and obesity with an additional co-morbidity (diabetes, hypertension, chronic kidney disease, atrial fibrillation) to semaglutide or standard care to assess the effect on cardiac structure, function (using cardiac MRI) and objective exercise capacity (peak Vo2). Blinded Imaging outcomes, functional capacity and

quality of life will be assessed after 6 months. This study will provide pilot data for a larger efficacy study that could pave the way for anti-obesity therapies for the prevention of heart failure in those at greatest risk.

Aim: To provide proof of concept that semaglutide improves cardiac remodelling, exercise capacity and quality of life in people living with obesity and multiple long-term conditions.

Background: Heart failure (HF) affects around 920,000 people in the UK and accounts for ~2% of the NHS budget (~£2Billion per annum). HF disproportionately affects people from ethnic minorities and those from lower socio-economic classes due to the higher prevalence of risk factors such as obesity, diabetes and hypertension and chronic kidney disease, which complicates management. The prognosis of HF following a heart failure diagnosis is appalling with 30-40% of patients dying within a year of diagnosis. To improve diagnosis and management of patients at risk of HF the American Heart Association has classified patients at risk of HF as stage A and those with evidence of structural or functional abnormalities as stage B (SBHF). Whilst those with SBHF are at high risk of progressing to symptomatic HF, interventions may be more effective as cardiac abnormalities are likely to be more effective early in the disease process. Recently the GLP1-receptor agonist semaglutide has been shown to improve symptoms and exercise capacity in people with HF with preserved ejection fraction and obesity, with or without diabetes.[1, 2] This PhD proposal will now assess whether semagluditde can lead to reverse cardiac remodelling, improved functional capacity and quality of life in people with SBHF and multiple long-term conditions

Research Plan:
Year 1: The PhD candidate will undertake a systematic review on the effects of weight loss on cardiac remodelling in patients at risk of but without symptomatic HF (SA/B). Design and get approvals (year 1) for a: Prospective randomized open-label blinded end-point pilot trial of semaglutide in SBHF (year2-3), figure 1. Population- Adults with SBHF and obesity and at least 1 additional comorbidity (diabetes, hypertension, atrial fibrillation) will be recruited from our clinics and primary care, targeting under-represented groups. Intervention- semaglutide2.4mg weekly by subcutaneous injection for 6 months. Comparator- standard care for comorbidities as directed by responsible clinicians. Outcomes- Primary: cardiac MRI (left ventricular mass, global longitudinal strain). Secondary: Peak Vo2 and Quality of life (EQ-5D-5L). Exploratory- circulating biomarkers (NT-proBNP, inflammation (hsCRP). As a pilot study no power calculation has been performed as the aim is to assess the likely effect size of the intervention and the sample size is that indicated for pilot studies

Expected outcomes and impact: The student will receive training in systematic reviews, design and conduct of clinical trials including interaction with the MHRA (Phase IV cTIMP) and cardiac phenotyping (MRI, Cardiopulmonary exercise testing) and QoL assessment. The trial will provide pilot data for a larger powered phase II efficacy trial (aiming at NIHR EME) that could pave the way for for anti-obesity therapies for the prevention of heart failure in those at greatest risk

References:
1. Kosiborod, M.N., et al., *Semaglutide in Patients with Heart Failure with Preserved Ejection Fraction and Obesity.* N Engl J Med, 2023.
2. Kosiborod, M.N., et al., *Semaglutide in Patients with Obesity-Related Heart Failure and Type 2 Diabetes.* N Engl J Med, 2024. **390**(15): p. 1394-1407.