

Title of proposed research: Low calorie diets as a treatment for microvascular angina and /or heart failure: Pilot studies to test safety, feasibility and potential efficacy prior to progression to large-scale trials

Brief summary: why this area, why Glasgow and why now? In clinical medicine, whilst real progress in preventing cardiovascular disease and lessening chances of premature mortality has occurred, the impact obesity on many conditions and on disease trends is beginning to be better appreciated; obesity rates have skyrocketed worldwide over the last three decades. Traditionally obesity is seen as a main player in conditions such as diabetes, fatty liver disease and hypertension. However, evidence that is more recent shows obesity in early and midlife is linked strongly to the risk for future heart failure,(1) particularly preserved ejection heart failure (HFpEF), a condition marked in around 60% with increased left atrial size(2) for which there is yet no proven therapy. This is a devastating condition with considerable morbidity and mortality. Notably, the reverse epidemiology in advanced heart failure when *unintentional* weight loss as a marker of severe illness is seen, and so some mistakenly consider intentional weight loss might be harmful. Yet, large-scale weight loss as seen with bariatric surgery is associated with lower occurrence of heart failure in obese patients(3) and emerging genetic data suggests obesity is a causal factor in heart failure.(4). We also have pilot data to show bariatric surgery in diabetes patients with heart failure is associated with a substantially lower mortality compared to BMI matched patients who do not undergo surgery (to be submitted to *Circulation*).

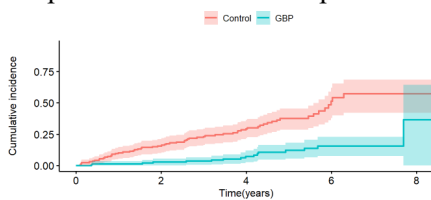
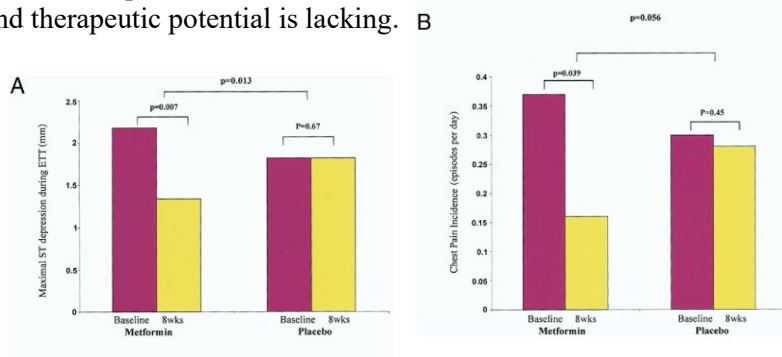


Figure: Novel and exciting unpublished data on mortality after Gastric Bypass (GBP) vs controls in Swedish patients with HF and diabetes (n=308). **HR 0.23 (0.12 to 0.43).**

We also now appreciate that obesity-driven haemodynamic abnormalities may be key drivers for this link. Even so, whilst several ongoing pharmacotherapy agents are being trialled in this condition, robust, adequately designed randomised trials of large weight loss in HFpEF that use MRI are lacking but needed.

Obesity is also common in individuals who suffer angina due to microvascular dysfunction yet have normal coronary arteries, microvascular angina [MVA], a condition which leads to considerable impairment in quality of life. Over 15 years ago, we showed in a small-scale randomised placebo-controlled trial (n=33) metformin led to less occurrence of angina, a significant reduction in maximal ST depression during an exercise test, with improvements related significantly to weight reduction.(5) Others have noted around half of subjects admitted to emergency unit with symptomatic chest pain which turns out to be MVA are obese,(6) whereas obesity has been directly related to vascular dysfunction in this condition, leading authors to speculate it may be causally related.(7) Uncontrolled studies using lower fidelity measures (Doppler Echo) also hint at low calorie diets significantly improving coronary flow reserve.(8) However, to date a *randomised* trial of substantial weight loss in such patients with blinded ascertainment of ischaemia and mvocardial blood flow to advance causality and therapeutic potential is lacking. B



Figures The effects of metformin relative to placebo on Maximal ST depression, Chest pain Incidence by diary.

Fortunately, we now have randomised trial proven lifestyle methods to help people lose considerable weight (~10-15kg) and sustain most of this weight loss at least for 2 years. In a seminal trial (DIRECT), we showed

low calorie diets followed by carefully worked methods to help lessen weight regain could help around one third of people with diabetes to undergo and sustain remission for up to two years.^(9,10) We now wish to use this same weight loss strategy to test the potential of big weight loss to treat HFpEF and MVA in state-of-the-art randomised trials, trials that the proposed PI and others have argued are needed (Sattar et al, Nature Medicine, In press). However, before we can undertake these, there is a **need for pilot studies to test acceptability and potential efficacy and to help determine sample size for definitive studies.** Should future major trials show promise, these studies would be truly ground breaking and could lead the way to new ways to manage these two important cardiac conditions that are rising in prevalence.

Potential roles and value of project for clinical fellow in cardiology and for ICAMS

- To gain and understanding of relevance of obesity in common CV conditions, including working on some epidemiological and genetic data for some early publication wins.
- To help develop protocols for feasibility trials of low calorie diet in MVA and HfPEF, liaising with world experts in each condition and in weight loss strategies.
- To help write and gain project grant funding from BHF for one of both of the above efficacy trials. Note: both grant applications can be submitted rapidly, even before fellow formally starts job. Chances of success improve substantially if fellows funding already in place, or partial funding in place. CSO funding will also be sort.
- To develop detailed study protocols and liaise with all relevant parties to undertake feasibility studies
- To learn all relevant methods including process of low calorie diets, MRI imaging, exercise testing, blood biomarkers, including reporting of complex MRI data.
- To lead on ethics proposals for both feasibility studies.
- To lead on recruitment for studies and for study conduct, liaising with relevant staff as required and ensuring patient safety, and quality measurements are made, recorded and analysed.
- This work would help Glasgow maintain and strengthen its position as world leading obesity trial centre, with important and timely extension to cardiovascular medicine.

References

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