

## **Metformin therapy and circulating NT-proBNP levels: the CAMERA trial**

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While metformin therapy was initially contra-indicated in patients with diabetes and heart failure (HF), its use in patients with HF has gradually expanded and it has been claimed that metformin therapy may be beneficial in patients with diabetes and stable HF<sup>1</sup>. Previous small studies suggested metformin therapy may improve left ventricular (LV) function and other functional tests of status<sup>2,3</sup>. By contrast, a recent trial of 500 patients showed no effect on LV function over 4 months following myocardial infarction<sup>4</sup>. Adding to this literature, our own CAMERA trial unexpectedly demonstrated a small, borderline significant, increase in cardiac troponin-T on metformin versus placebo<sup>5</sup>. We therefore sought to gain further insight into metformin's potential effect on cardiac function, using N-terminal of the prohormone brain natriuretic peptide (NT-proBNP) as a surrogate marker.

CAMERA was a randomised placebo-controlled trial studying the effect of metformin over 18 months on surrogate markers of cardiovascular disease in 173 participants with coronary heart disease (CHD) and elevated waist circumferences, but without diabetes (NCT00723307)<sup>5</sup>. As previously reported, metformin therapy had no effect on carotid-intima media thickness but did improve measures of glycaemia and insulin resistance, and lowered weight by 3.2kg. Plasma samples were quickly frozen at -80 degrees Celsius at baseline and subsequently every 6 months. For this post-hoc analysis, NT-proBNP was measured using an automated clinically validated assay with the manufacturer's calibrators and quality control material (e411, Roche Diagnostics, UK). The control coefficient of variation was  $\leq 5.3\%$ . As NT-proBNP data remained non-parametric after transformation, change in NT-proBNP on placebo and metformin at 6, 12 and 18 months was compared by Mann-Whitney U test. Given the potential relationship between adiposity and NT-proBNP we compared associations between baseline weight and NT-proBNP, and between change in weight and change in NT-proBNP, in the entire population by linear regression after confirming that the residuals were normally distributed. Analyses were performed using STATA (version 13.1) and a threshold p-value  $< 0.05$  was selected to indicate statistical significance.

Average age of participants was 64 years. For placebo-treated participants, median NT-proBNP was 92mg/mL (interquartile range [IQR] 47-166pg/mL) while for metformin-treated participants median NT-proBNP was 88pg/mL (IQR 59-203pg/mL), relatively high levels as expected for a CHD population. NT-proBNP data during the trial are provided in **Figure 1**. There was no difference between treatment arms at 6 months ( $p=0.20$ ), 12 months ( $p=0.61$ ) or 18 months ( $p=0.17$ ). There was no association between baseline weight and NT-proBNP (beta coefficient [B] -0.69 [95% confidence intervals (CI) -3.56 to 2.17];  $p=0.63$ ). There was also no relationship between change in weight and change in NT-proBNP at 6 months (B -1.99 [95%CI -7.33 to 3.35];  $p=0.46$ ), 12 months (B -3.0 [95%CI -9.90 to 3.82];  $p=0.382$ ) or 18 months (r -3.92 [95%CI -8.40 to 0.55];  $p=0.085$ ) respectively with no evidence of interaction by treatment group.

Metformin has no effect on NT-proBNP levels over up to 18 months in individuals with CHD, suggesting no detrimental or beneficial impact on cardiac function in such individuals. Any effect on clinical outcomes in patients with HF, if confirmed, is unexplained.

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## Figure Legend

**Figure 1.** NT-proBNP levels in metformin- and placebo-treated participants in CAMERA

Footnote: data displayed as median (interquartile range) for each timepoint

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