



Metformin Therapy and Circulating NT-proBNP Levels: The CAMERA Trial

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Although metformin therapy was initially contraindicated 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 (1). Previous small studies suggested metformin therapy may improve left ventricular function and other functional tests of status (2,3). By contrast, a recent trial of 500 patients showed no effect on left ventricular function over 4 months following myocardial infarction (4). Adding to this literature, our own Carotid Atherosclerosis: Metformin for Insulin ResistAnce (CAMERA) study unexpectedly demonstrated a small, borderline significant, increase in cardiac troponin-T on metformin versus placebo (5). We therefore sought to gain further insight into metformin's potential effect on cardiac function, using N-terminal prohormone brain natriuretic peptide (NT-proBNP) as a surrogate marker.

CAMERA was a randomized 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 (ClinicalTrials.gov identifier NCT00723307) (5). As previously reported, metformin therapy had no effect on carotid intima-media thickness but

improved measures of glycemia and insulin resistance and lowered weight by 3.2 kg. Plasma samples were quickly frozen at -80°C 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). The control coefficient of variation was $\leq 5.3\%$. As NT-proBNP data remained nonparametric 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 of <0.05 was selected to indicate statistical significance.

The average age of participants was 64 years. The median NT-proBNP was 92 pg/mL (interquartile range 47–166) for placebo-treated participants, whereas the median NT-proBNP was 88 pg/mL (59–203) for metformin-treated participants, which are relatively high levels as expected for a CHD population.

NT-proBNP data during the trial are provided in Fig. 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 (β -coefficient -0.69 [95% 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 (β -coefficient -1.99 [95% CI -7.33 to 3.35]; $P = 0.46$), 12 months (β -coefficient -3.0 [95% CI -9.90 to 3.82]; $P = 0.382$), or 18 months (β -coefficient -3.92 [95% CI -8.40 to 0.55]; $P = 0.085$), with no evidence of interaction by treatment group.

Metformin has no effect on NT-proBNP levels for 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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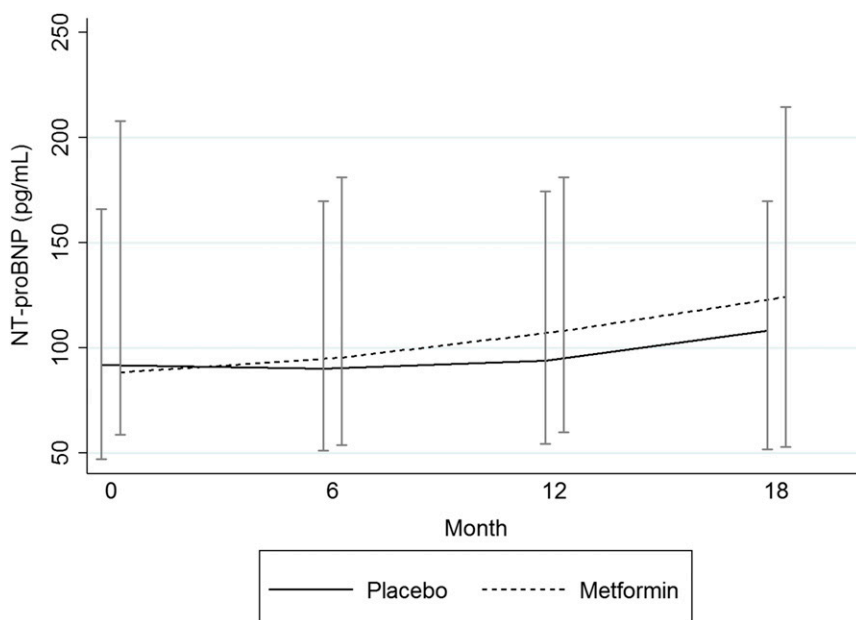


Figure 1—NT-proBNP levels in metformin- and placebo-treated participants in the CAMERA study.

Serono, which had no influence over the conduct of the trial or analysis of results. NT-proBNP assays were funded by an endowment grant from NHS Greater Glasgow and Clyde (CHO1/13).

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