CLINICAL RESEARCH
FINAL STUDY REPORT SUMMARY

Study Title:	Oral thiamine (Vitamin B1) supplementation in subjects with type 2 diabetes mellitus: a randomised, double-blind, placebo-controlled crossover trial assessing biophysical markers of endothelial function, oxidant stress, insulin sensitivity and vascular inflammation
REC Ref:	09/H0504/137
EudraCT No:	2009-017537-21
Chief Investigator:	Professor Mike Cummings
Sponsor:	Portsmouth Hospitals NHS Trust

List of Principal Investigators and Sites	Dr Georgina Page Single site at Portsmouth Hospitals NHS Trust.
List of Publications (or plans for publications) including those for patients (if applicable)	• MD Thesis. Submitted in April 2013 • An abstract entitled "*Thiamine supplementation in patients with Type 2 diabetes: effect on endothelial function and vascular inflammation*" has been accepted for poster presentation at Diabetes UK Annual Professional Conference 2013. • Further publication of the study in a peer-reviewed journal is planned for mid-2013. • The participants are to be informed of the findings via a personal letter following completion of the MD thesis.
Study Start and End Dates	Patient recruitment for this study commenced in June 2010 and was completed by March 2011. Patient follow-up continued until June 2011. The End of study declaration was submitted in July 2011.
Study Design	A randomised, double-blind, placebo-controlled crossover trial assessing biophysical markers of endothelial function, oxidant stress, insulin sensitivity and vascular inflammation.
No. of Patients (planned and analysed)	In total 49 patients expressed an interest in the study. Eleven were excluded as they did not meet the inclusion/exclusion criteria (already on insulin n=7; previous CABG n=1; on thiamine n=1; on other research intervention n=2). Following allocation two patients were withdrawn. One patient's initial bloods put them outside the inclusion criteria (HbA1c >10%) and another patient was excluded as we were unable to undertake photoplethysmography. Two patients discontinued the intervention, one because of side effects

	related to the medication (abdominal pain after ingestion) and one developed a chronic pain syndrome and felt unable to continue. 34 subjects successfully completed the study.
Main inclusion/exclusion criteria	Inclusion: • Individuals with a diagnosis of type 2 diabetes mellitus with a more than 30% chance of cardiovascular disease (ischaemic heart disease, cerebrovascular disease or peripheral vascular disease) over the next 10 years. • HbA1c less than 10% • Between the ages of 18 and 75 Exclusion: • Established cardiovascular disease (ischemic heart disease, cerebrovascular disease or peripheral vascular disease). • Allergy/intolerance to thiamine supplementation • Insulin treatment • Diuretic treatment • Current multivitamin/thiamine therapy • Abnormal thyroid function • Chronic excess alcohol consumption/impaired liver function (>21 units per week in females, >28 units per week in males; Department of Health Guidelines)
Investigational Medicinal Product(s) (including comparator, if applicable), mode of administration and batch number(s)	IMP: Thiamine hydrochloride (Trade name: Tyvera). Prescribed orally at a dose of 300mg a day given as 3 tablets. Treatment lasts for 8 weeks. Placebo: Manufactured matched placebo tablet identical to thiamine also given as 3 tablets for 8 weeks.
Duration of Treatment	8 weeks
Primary and Secondary Objective(s)	Primary endpoint measure: VCAM Secondary endpoints are: • Measurement of endothelial dysfunction determined by the reflection index of the digital volume waveform using phtoplethysmography • Measurement of insulin sensitivity (HOMA-B method) • Markers of oxidant stress (TAOS, LHP, cGMP, GSH/GSSG) • Markers of vascular inflammation (hsCRP and ACR) • Glycaemic control (HbA1c, Fructosamine) • Lipid parameters
Conclusions	The key findings of this study were: 1. A significant increase in serum thiamine diphosphate levels

across the treatment arm. This increase was not seen in the placebo arm.

Baseline mean TDP in the treatment arm was 183 + 28 nmol/l. Following treatment with thiamine it was 310 ± 82 nmol/l. In the placebo arm, baseline mean TDP was 196 ± 41 nmol/l. Following treatment with placebo it was 178 ± 32 nmol/l. The data was distributed parametrically. Repeated ANOVA testing (Greenhouse-Geisser treatment) with post hoc Bonferroni testing showed there was a significant increase in TDP levels in the treatment arm ($p < 0.001$

2. A statistically significant reduction in systolic blood pressure across the treatment arm compared with the placebo arm.

   Baseline mean systolic blood pressure in the treatment arm was 134.9 ± 18.7 mmHg. Following treatment with thiamine it was 121.7 ± 12.6 mmHg.

   In the placebo arm, baseline mean systolic blood pressure was 127.8 ± 17.7 mmHg. Following treatment with placebo it was 124.7 ± 17.8 mmHg.

   The data was distributed parametrically. Repeated ANOVA testing (Greenhouse-Geisser treatment) with post hoc Bonferroni testing showed there was a significant effect of treatment on systolic BP ($p = 0.001$).

3. Treatment with thiamine showed no significant reduction in biophysical markers of oxidative stress, endothelial dysfunction, vascular inflammation and insulin resistance.

The full study is currently being written up as an MD thesis and is to be submitted by April 2013. An abstract entitled "Thiamine supplementation in patients with Type 2 diabetes: effect on endothelial function and vascular inflammation" has been accepted for poster presentation at Diabetes UK Annual Professional Conference 2013. Further publication of the study in a peer-reviewed journal is planned for mid-2013. The participants are to be informed of the findings via a personal letter following completion of the MD thesis.

Sponsor Authorisation: Dr. Linda Hirndale

Signature: Linda Hirndale, Associate Research Manager

Date: 17th June 2013