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A randomised controlled trial to investigate ambulatory blood pressure response to riboflavin supplementation in adults with the *MTHFR* 677TT genotype

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Hypertension is the leading cause of preventable premature death, estimated to affect over 1 billion adults worldwide. Meta-analyses of epidemiological studies suggest that the C677 T polymorphism in the gene *MTHFR* encoding the folate metabolising enzyme methylenetetrahydrofolate reductase (MTHFR) is associated with an increased risk of hypertension by 24–87%[(1)]. Supplementation with riboflavin (a cofactor for MTHFR) can modify this phenotype as demonstrated in a series of randomised controlled trials conducted at this centre[(1)]. Compared with clinic blood pressure measured at one time-point only, ambulatory blood pressure monitoring (ABPM) measures BP over a 24hr period and provides a more reliable assessment of an individual's BP[(2)]. The aim of this study was to utilise ABPM to investigate the effect of riboflavin supplementation on BP in adults with the *MTHFR* 677TT genotype.

Adults 18–65yrs recruited across Northern Ireland to the RIBOGENE study (NCT02463513) were screened for the *MTHFR* TT genotype and those who were eligible and willing to participate (n = 81), were stratified by baseline systolic BP and randomised to receive either riboflavin treatment (10 mg/day) or placebo for 16 weeks. Biomarker status of riboflavin was measured using the erythrocyte glutathione reductase activation coefficient (EGRac) assay and BP was measured by both clinic BP and ABPM, in accordance with NICE guidelines[(3)].

BP response to riboflavin was found to be strongly dependent on baseline BP. Participants with a baseline systolic BP of less than 125 mmHg showed no response to riboflavin supplementation (data not shown). In participants with a baseline systolic BP ≥125 mmHg, riboflavin supplementation resulted in a significant BP lowering of daytime systolic BP by 3·8 mmHg compared to 0·2 mmHg in the placebo group (see Table).

	Riboflavin n23		Placebo n26		
	Mean	SD	Mean	SD	P-value
Age	48·6	11·3	47·8	12·0	0·823
Male n(%)	17	73·9	12	46·2	0·093
BMI	28·8	3·8	27·2	3·1	0·131
Riboflavin status[†]	**Mean**	**95% CI**	**Mean**	**95% CI**	
Pre	1·33	1·28–1·38	1·29	(1·24–1·34)	
Post	1·20	1·14–1·25	1·31	(1·25–1·36)	<0·001
Change		−0·12		0·02	
Daytime BP mmHg[≠]	**Mean**	**95% CI**	**Mean**	**95% CI**	
Pre	137·1 ()	132·7–141·3	134·7	130·3–139·1	
Post	133·0	128·9–138·1	134·8	130·6–139·1	0·036
Change		*−3·8*		*−0·2*	

Response to intervention analysed by repeated measures ANCOVA, adjusting for sex. [†] Higher EGRac values are indicative of lower riboflavin status. [≠] mean of participant daytime/awake hrs which was personalised for each participant.

This is the first study to use ABPM to show that riboflavin supplementation, targeted at adults with the MTHFR 677TT genotype, results in significant lowering of mean day and night BP. It is also the first demonstration of this genotype specific effect of riboflavin on BP in non-hypertensive and younger adults. Given the frequency of this genotype worldwide (approximately 10%, but as high as 30% in some populations) and the global burden of blood pressure-related disease, these findings could offer a personalised approach for BP management in these at risk sub-populations.

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