University of ULSTER

Nutrition and Blood Pressure: A role for B vitamins?

Mary Ward PhD, RD

Northern Ireland Centre for Food and Health,

University of Ulster, Coleraine.

Outline

- Hypertension – prevalence and consequences
- Diet and Blood Pressure
- Emergence of novel risk factors
- A role for riboflavin?
- Conclusions

Hypertension

- UK has one of the highest rates of death from cardiovascular disease (CVD)[1]
- Hypertension - most common medical condition in the UK that affects up to 40% of the population
- Positive and continuous relationship between blood pressure and CVD mortality[2]

1 Cannon *et al.* 2007 *GP Review*, 1-7.
2 Prospective Studies Collaboration 2002 *Lancet* 360,1903-1913.

Hypertension

- Hypertension is defined as a blood pressure (BP) of greater than 140/90 mmHg[3]

- Multiple lifestyle, genetic and nutritional factors known to affect BP yet it remains a global problem

3 National Institute for Health and Clinical Excellence 2004

Hypertension: risk factors

- Age
- Family history
- Race
- Gender
- Dietary factors
- Obesity
- Inactivity
- Smoking

Dietary approaches to lower BP

- Reduced Salt Intake
- Weight reduction
- DASH diet
- Alcohol

Salt

- An increased salt intake is positively associated with an increased risk of stroke and cardiovascular disease
- Decrease of 2mmHg in SBP / 1mmHg in DBP in response to a reduction in salt intake from 10 to 6g/d
- Evidence to support a modest benefit of salt reduction in terms of cardiovascular health

Dietary Approaches to Stop Hypertension

- High in fruit and vegetables, low fat dairy, wholegrain foods and low in saturated fat and refined sugar
- Rich in potassium, magnesium, calcium and fibre
- Associated with a decrease of 5mmHg SBP and 3.0mmHg in DBP – greater effect in hypertensive's

Weight reduction

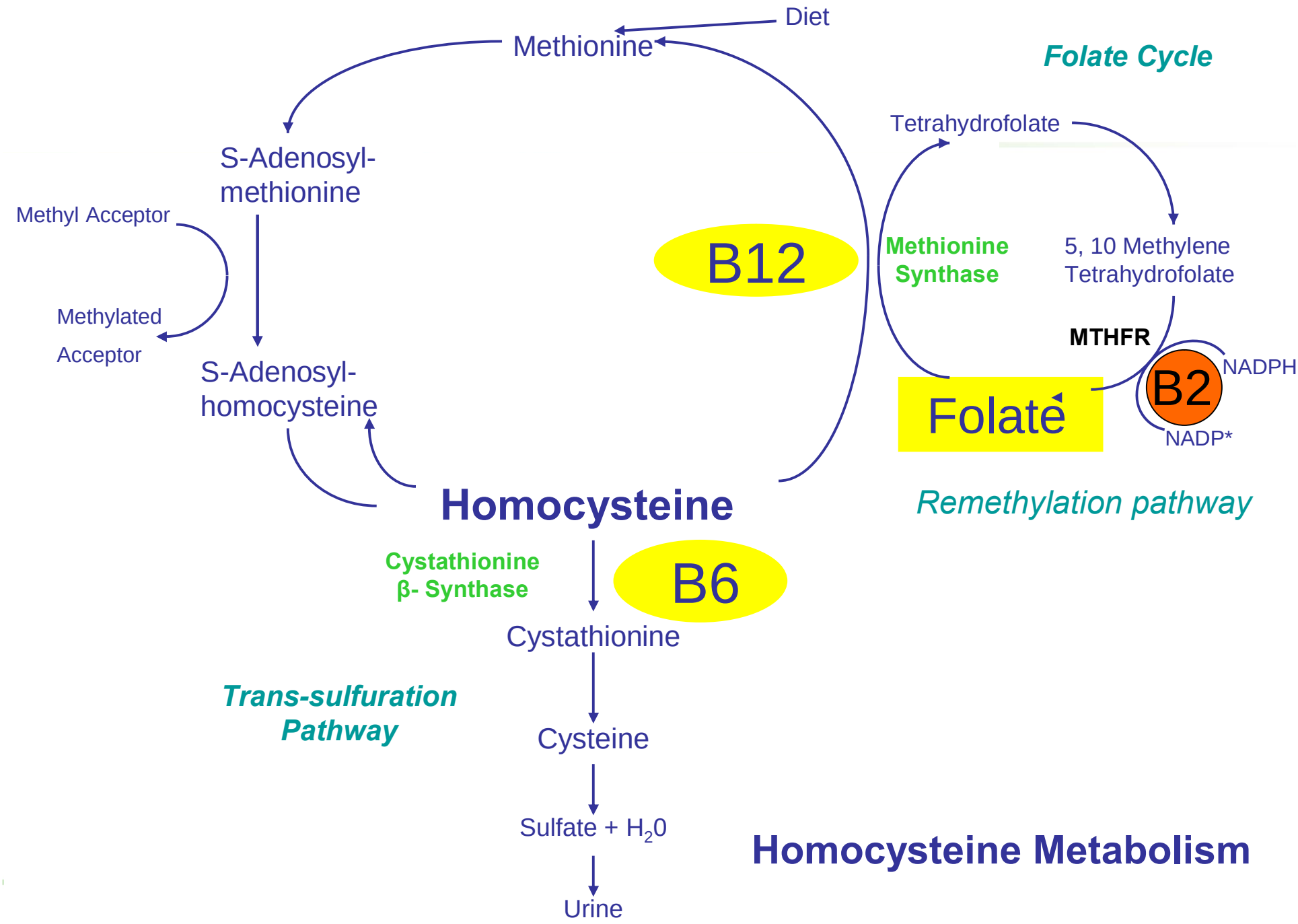
- Obesity remains a major public health challenge – approx 60% overweight / obese in NI
- Mean decrease of 4.4mmHg in SBP of 3.6mmHg in DBP in response to a weight decrease of 5kg
- Long term effects of sustained weight loss unknown

Novel risk factors

Homocysteine

- Homocysteine is an amino acid formed via the metabolism of dietary methionine
- Elevated total plasma homocysteine (>15µmol/l) has been observed to be an independent risk factor for CVD[4] and stroke[5]
- Homocysteine levels are determined by both nutritional and genetic factors

4 Wald *et al.* 2002 *BMJ* 325, 1202.
5 Yang *et al.* 2006 *Circulation* 113, 1335-1343.

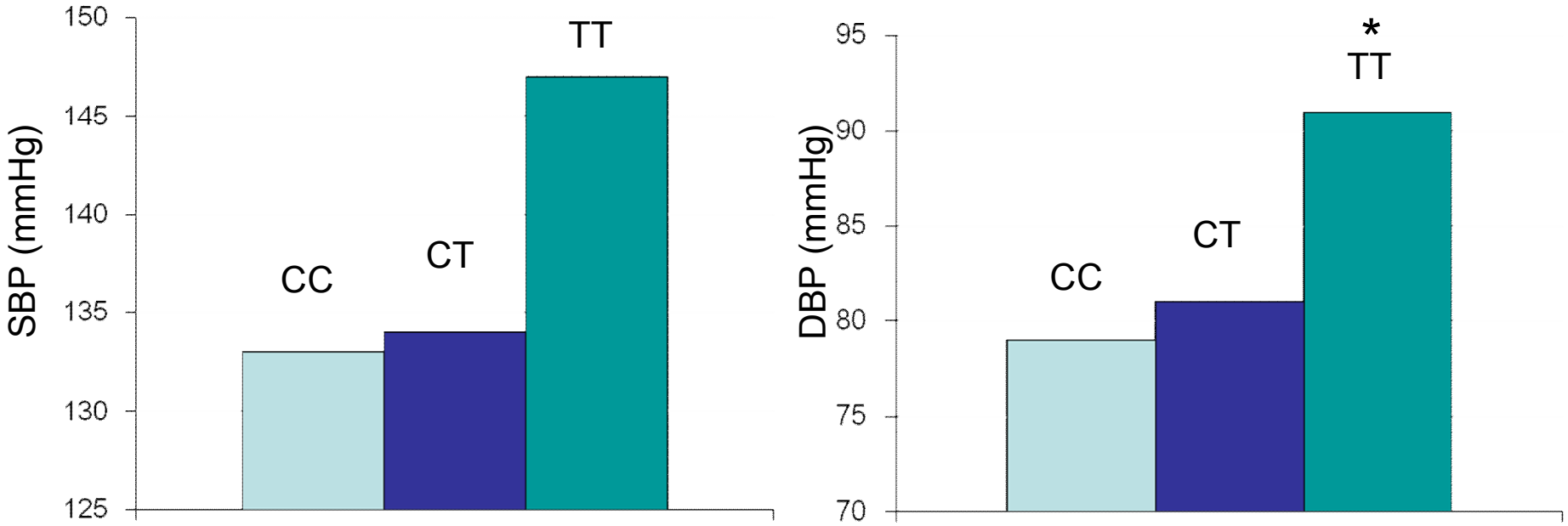

Diet
Methionine
Folate Cycle
Tetrahydrofolate
S-Adenosyl-
methionine
Methyl Acceptor
Methylated
Acceptor
B12
Methionine
Synthase
5, 10 Methylene
Tetrahydrofolate
MTHFR
NADPH
B2
NADP*
Folate
S-Adenosyl-
homocysteine
Homocysteine
Remethylation pathway
Cystathionine
β- Synthase
B6
Cystathionine
Trans-sulfuration
Pathway
Cysteine
Sulfate + H20
Urine
Homocysteine Metabolism

MTHFR

- Main genetic determinant of elevated homocysteine is the *677C→T* polymorphism in the enzyme methylenetetrahydrofolate reductase (MTHFR)
- Homozygosity (TT genotype) - present in 10% of Western populations and results in decreased enzyme activity and increased homocysteine levels
- Individuals with the TT genotype are at significantly higher risk of CVD and stroke[6] and emerging evidence suggests it may be independently linked with BP[7]

6 Lewis *et al.* 2005 *BMJ* 331, 1053.
7 Heux et al. 2004 *Hypertens Res* 27, 663–667.

MTHFR 677C→T and BP



Nishio *et al.* 1996 observed a graded relationship between BP and the number of T alleles [8]

8 Nishio *et al.* 1996 *Jpn J Hum Genet* 41(2), 247-251.

MTHFR 677C→T and BP

Author	Study Design	n	TT	MTHFR & BP
Guillen *et al.* 2001	Observational	716	113	+ (SBP) & Graded
Inamoto *et al.* 2003	Observational	3247	508	+ (DBP)
Jiang *et al.* 2004	Intervention	444	106	+ (DBP)
Heux *et al.* 2004	Case:Control	500	60	+ (HTN)
Benes *et al.* 2001	Case:Control	1119	121	+(HTN-CAD)
Ravera *et al.* 2001	Observational	206	36	No relationship
Nakata *et al.* 1998	Case:Control	357	55	- (HTN)

MTHFR and B-vitamins

- Individuals with the TT genotype are particularly sensitive to B-vitamin statu[9]
- Decreased activity of the MTHFR enzyme seen in the TT genotype appears to be explained by the loss of the riboflavin cofactor[10]
- Riboflavin status is a potent modulator of homocysteine levels in individuals with the TT genotype[11]

9 Hustad *et al.* 2007 *The American Journal of Human Genetics,* 80(5), 846-855.
10 Guenther *et al.* 1999 *Nat Struct Biol* 6(4), 359-365.
11 McNulty *et al.* 2006 *Circulation* 113(1), 74-80

Genotype-specific response to riboflavin

	Mean homocysteine (µmol/L)		
	CC (n = 27)	CT (n = 26)	TT (n = 34)
Baseline	10.7	12.2	17.6
Riboflavin 1.6mg/d 12 weeks			
After intervention	10.9	11.8	13.0*

* p<0.05 denotes significance determined by independent t-tests split by treatment

12 McNulty *et al.* 2006 *Circulation* 113(1), 74-80

B-vitamins and BP

Author	n (TT)	B-vitamins	Duration	Hcy response	BP response
Williams *et al.* 2005	41 (5)	FA (5mg/d)	3 weeks	↓*	No effect (SBP:DBP) ↓* Pulse Pressure
Markan *et al.* 2007	153 (8)	FA (5mg/d)	4 weeks	↓*	No effect (SBP:DBP)

No published study to date has:

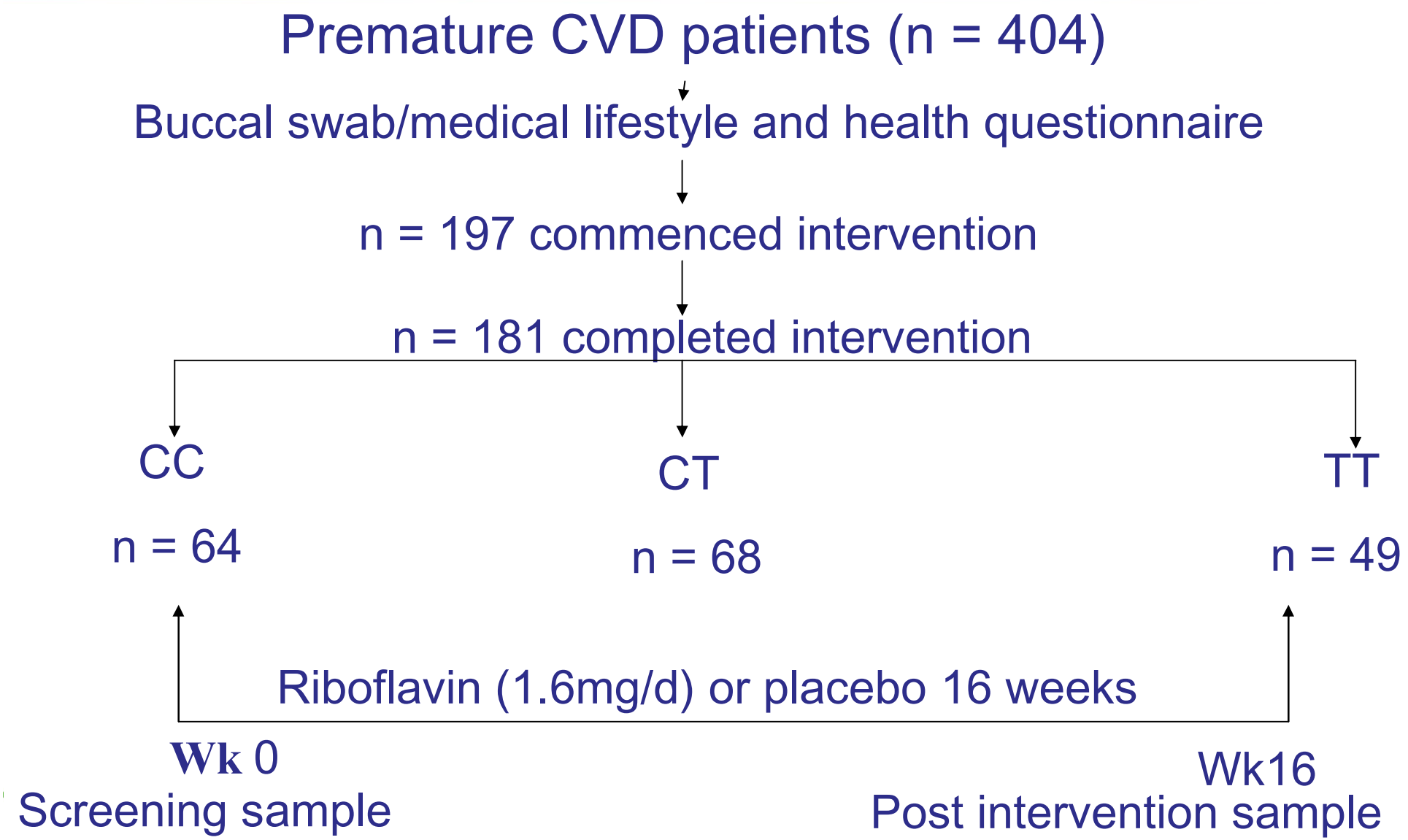
- Used TT genotype-driven recruitment

OR

- Considered the B-vitamin riboflavin

MTHFR and BP: a role for riboflavin

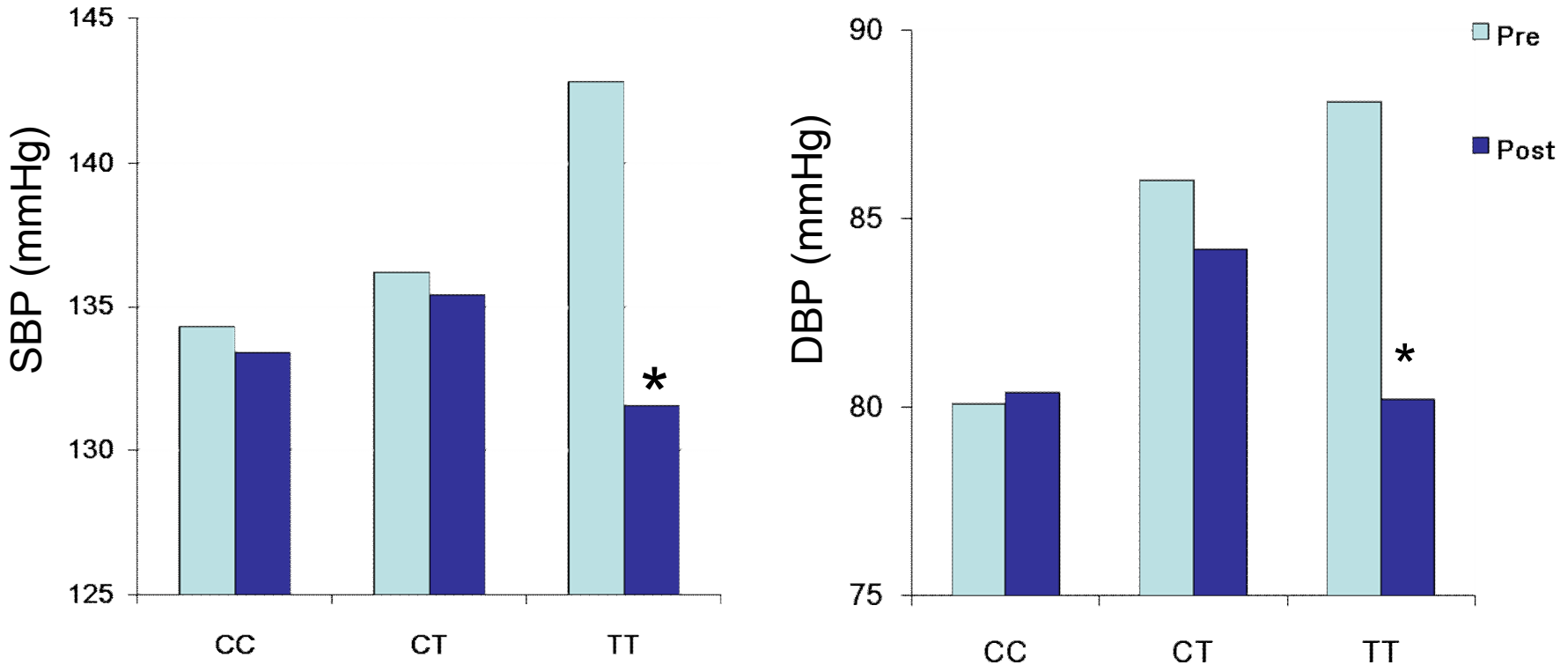
Study Design



Influence of the TT genotype on BP by status of riboflavin

		MTHFR 677C→T Genotype			
		CC n=67	**CT n=76**	**TT n=54**	**P[1]**
Systolic Blood Pressure (mmHg)	**Total**	131.1[a]	133.0 [a]	142.8 [b]	0.002
	Lower riboflavin[2]	131.2 [a]	135.8 [a]	147.4 [b]	0.005
	Higher riboflavin	131.0	129.6	138.6	0.172
Diastolic Blood Pressure (mmHg)	**Total**	80.3 [a]	83.3 [ab]	86.0 [b]	0.038
	Lower riboflavin	80.8	84.6	88.1	0.076
	Higher riboflavin	79.6	81.9	84.1	0.381

BP response to riboflavin intervention(1.6mg/d) split by genotype



* Statistical significance (p<0.05) determined by independent t-tests on BP change

13 Horigan *et al.* 2010 *J Hypertension*

TT genotype and Riboflavin: an emerging role in BP

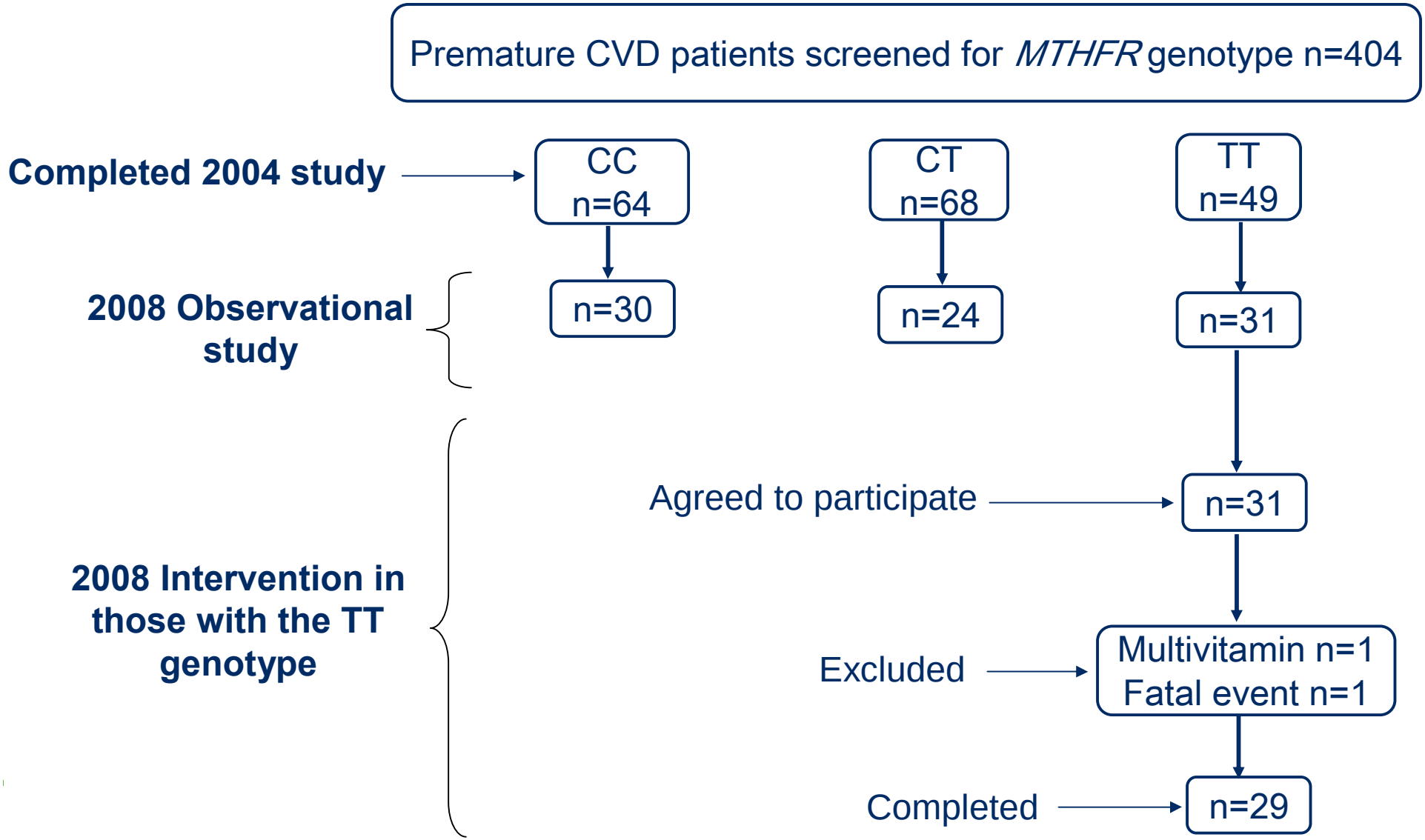
- At baseline individuals with the TT genotype had significantly higher BP compared to those with the CT or CC genotype

- Riboflavin supplementation (1.6mg/d) for 16 weeks produced a genotype-specific BP lowering

Follow-up study

- Reinvestigation of premature CVD patients with different *MTHFR* genotypes
  - Observational study
  - Cross-over intervention study

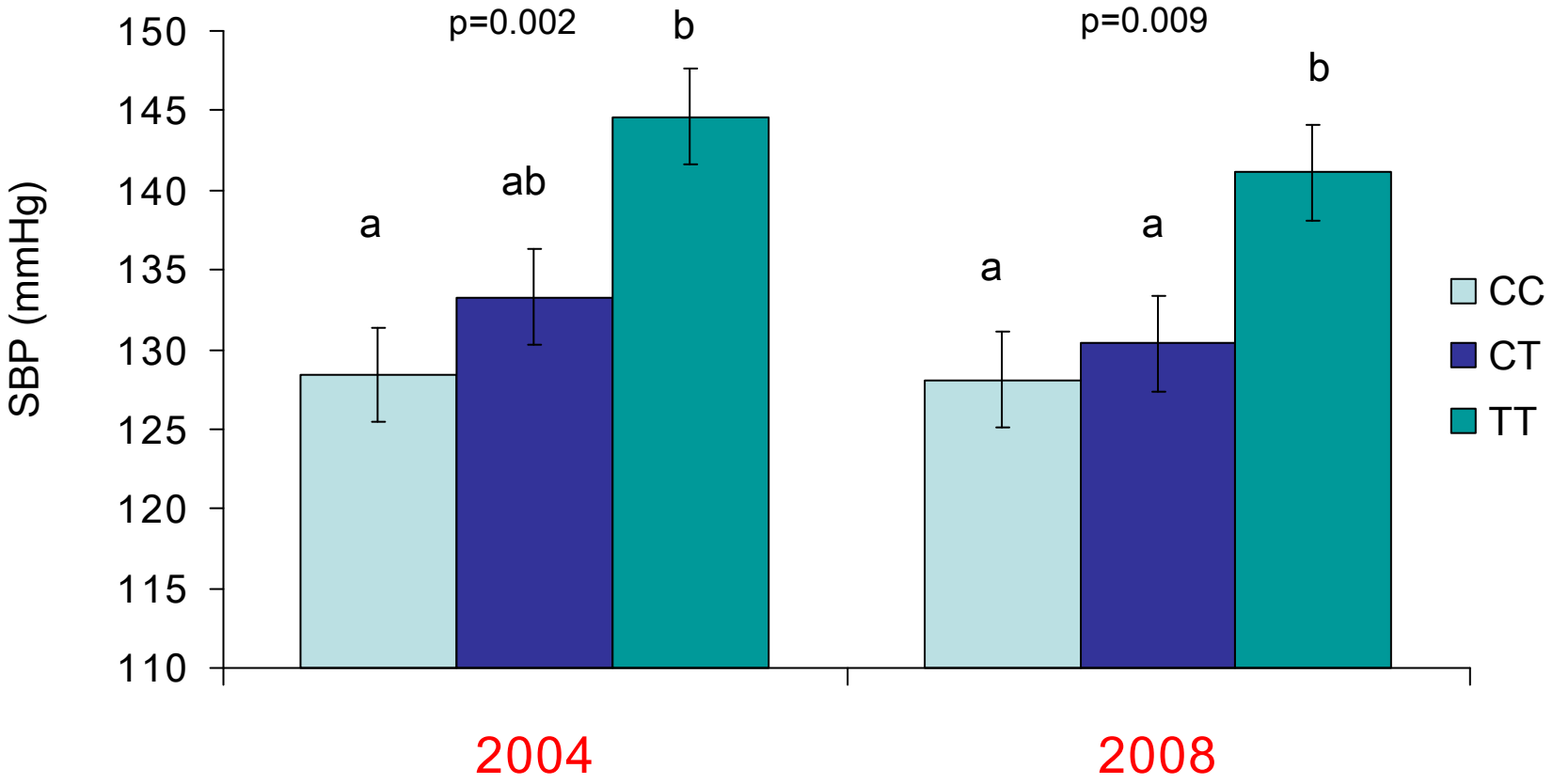
Study design and completion rates



Baseline characteristics of follow-up cohort

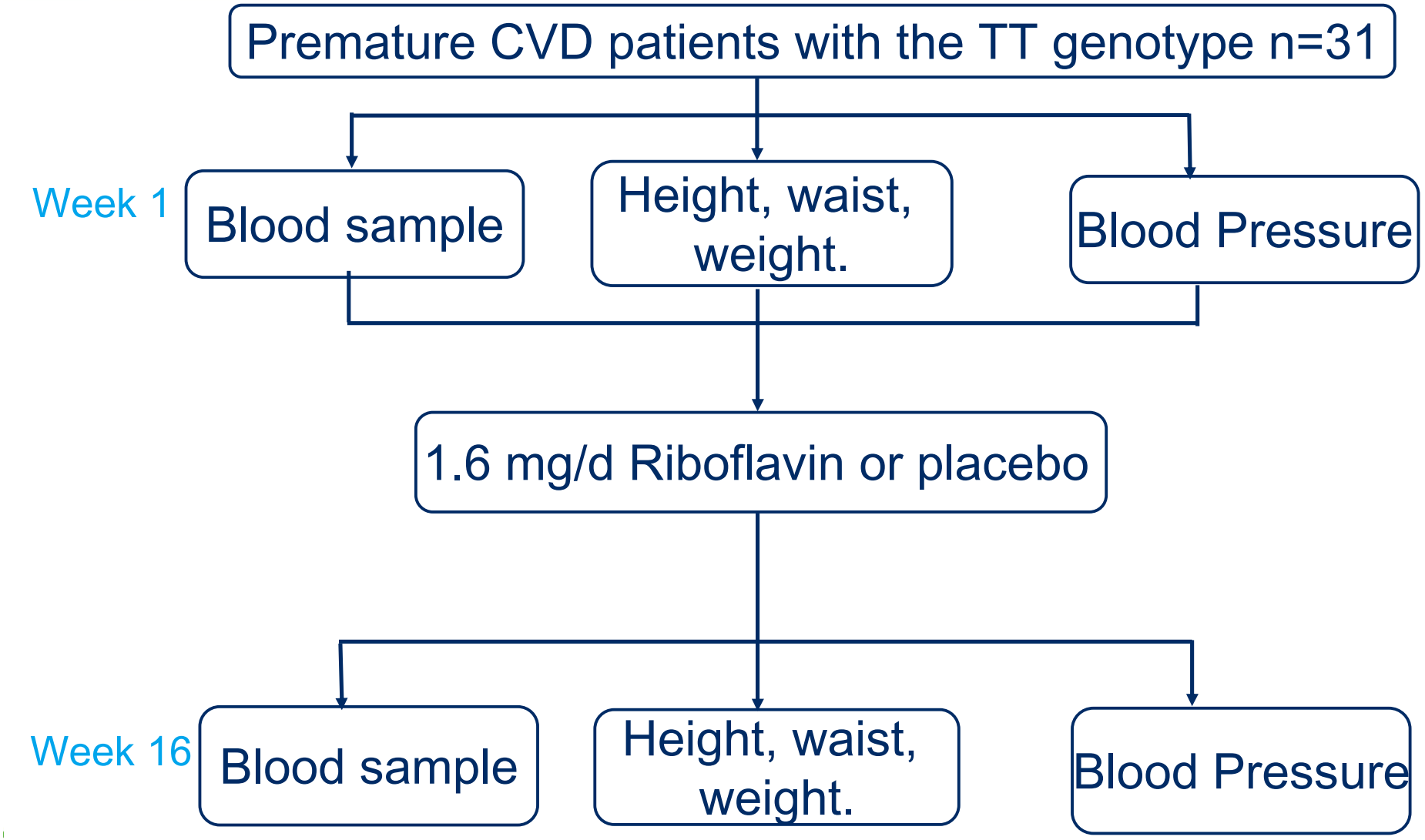
	2004 All n=83	2008 All n=83
Age (y)	53.9 (5.6)	58.2 (5.6)
BP (mmHg)	136 / 82	133 / 79
BMI (kg/m^2)	29.2 (4.9)	29.8 (5.2)
Waist (cm)	96.4 (13.0)	104.8 (13.6)
Smoker (%)	25	22

Baseline SBP by MTHFR genotype



Differences between genotype groups at each time point determined by 1-way ANOVA and Tukey post hoc test ($p<0.05$)

Intervention Protocol



Results / discussion

- TT genotype was confirmed as a genetic risk factor for hypertension in this high-risk cohort
- CVD patients with the *MTHFR* 677 TT genotype remained hypertensive at follow-up despite marked changes in antihypertensive therapy;
- Only riboflavin treatment significantly decreased BP (*by* 9mmHg SBP and 6mmHg DBP) over the 4-year period;
- A 2 mmHg decrease in SBP is estimated to decrease stroke mortality by 10%[2]

2 Prospective Studies Collaboration 2002 *Lancet* 360,1903-1913.

Implications for the food industry

- Dietary sources of riboflavin
- Fortified foods
- Personalised nutrition

Conclusions: Diet and Blood Pressure

- In *Obese* individuals clear benefits of weight reduction
- In *Hypertensive's* a reduced salt intake and DASH diet are proven to be effective
- In this *genetically at-risk group* riboflavin is an important determinant of blood pressure

Research Team

NICHE

Dr Geraldine Horigan
Dr Carol Wilson
Prof Sean Strain
Prof Helene McNulty

Collaborators in TCD

Prof John Scott
Dr Anne Molloy

Clinical Collaborators in Cardiovascular Research

Dr Tom Trouton, Antrim Area Hospital
Dr John Purvis, Altnagelvin Area Hospital

Partly funded by NI Chest Heart and Stroke Association