Randomised trial of homocysteine-lowering with B vitamins for secondary prevention of cardiovascular disease after acute myocardial infarction

The Norwegian Vitamin Study (NORVIT)

Kaare Harald Bønaa, Tromsø/Trondheim, Norway

on behalf of the NORVIT study group

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The NORVIT study group

K Rasmussen, Tromsø	chair - executive committee
I Njølstad, Tromsø	chair - event committee
PM Ueland, Bergen	chair - core laboratory
Aa Tverdal, Oslo	statistical analysis
H Schirmer, Tromsø	event committee
T Steigen, Tromsø	event committee
H Wang, Tromsø	event committee
JE Nordrehaug, Bergen	executive committee
E Arnesen, Tromsø	executive committee
KH Bønaa, Tromsø	principal investigator

Background

- Many studies have shown that plasma homocysteine is a strong and independent risk factor for myocardial infarction and stroke
- Low dietary intakes of vitamin B-6 have been associated with increased risk
- Homocysteine can easily be lowered by treatment with folic acid, but
- it is not known whether lowering of homocysteine lowers the risk of myocardial infarction

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Study hypotheses

- Treatment with folic acid will lower the incidence of MI and stroke by 20 percent
- Treatment with vitamin B-6 will lower the incidence of MI and stroke by 20 percent

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Design

- Randomised, controlled, double blind, multicenter, secondary prevention trial
- Duration: 3.5 years
- No of patients: 3749
- Study drugs:
  - Folic acid 0.8 mg/day (+ vitamin B-12 0.4 mg/day)
  - Vitamin B-6 40 mg/day
- Financed by the Norwegian Research Council and other not-for-profit institutions

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Eligibility criteria

Inclusion

- Acute myocardial infarction within previous 7 days
- Age 30-84 years
- Informed consent

Exclusion

- Ongoing vitamin B therapy
- Life-threatening disease (other than CVD)
- Expected poor compliance

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Endpoints

Primary

Nonfatal and fatal MI (including sudden death) and nonfatal and fatal stroke (composite)

Secondary

Individual components of the primary EP

Total death

PCI and CABG

Hospitalization due to unstable angina

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2x2 factorial design

3749 patients randomised into 4 groups:

Group A: folic acid and vitamin B-6	n=937
Group B: folic acid	n=935
Group C: vitamin B-6	n=934
Group D: placebo	n=943

- Groups A + B **vs** C + D
- Groups A + C **vs** B + D
- Separate effects of A, B, and C

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Baseline characteristics

	Folic acid + vit B6	Folic acid	Vit B-6	Placebo
Age yr	64	63	63	63
Male %	73	74	73	75
Smoker %	46	43	49	48
History of MI %	18	17	16	16
Diabetes mellitus %	11	9	9	10
Hypertension %	30	27	29	29
Drugs at discharge				
ASA %	87	90	90	88
Beta-blockers %	91	92	90	91
Statins %	79	82	82	81

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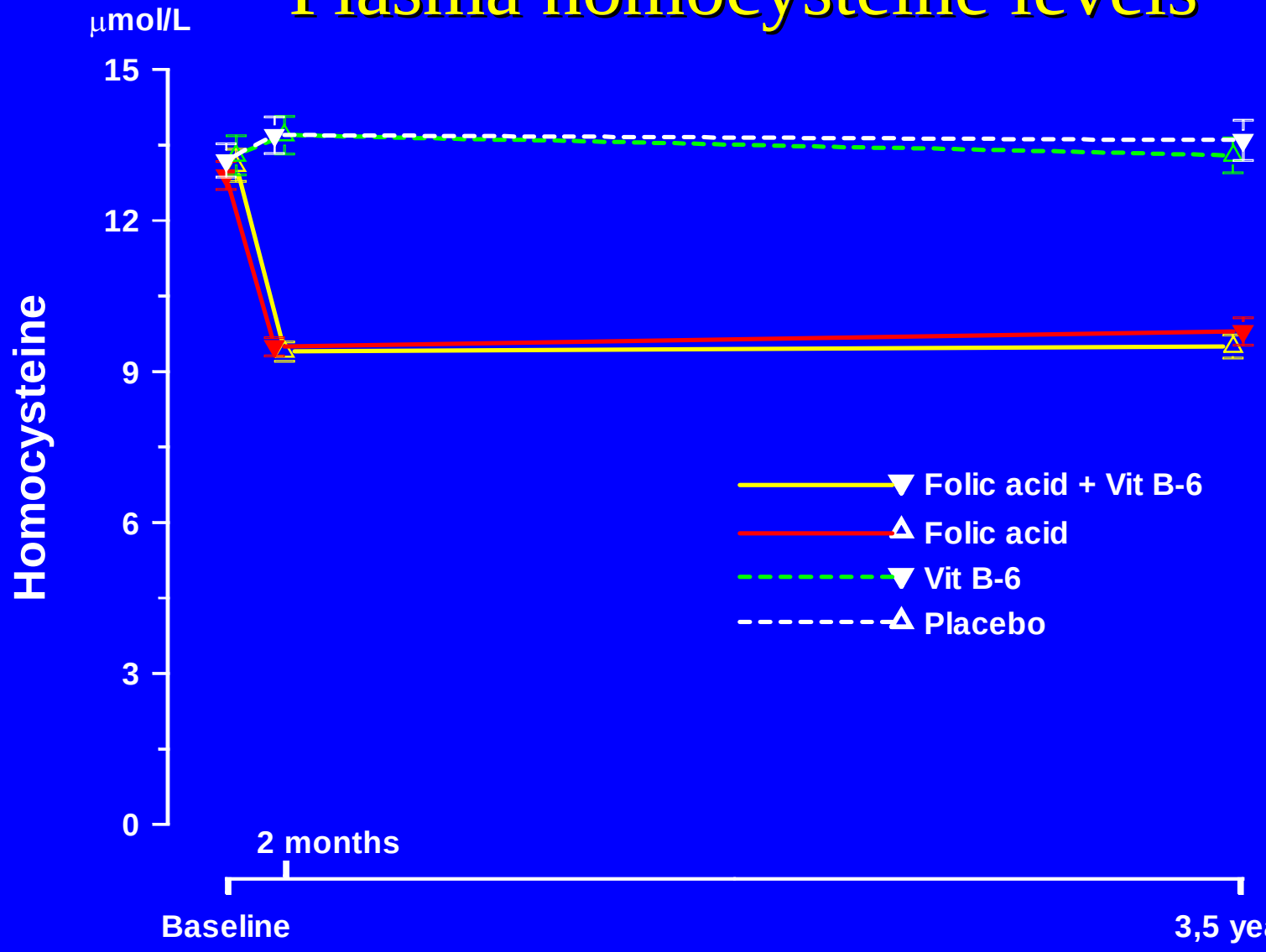
Plasma homocysteine levels



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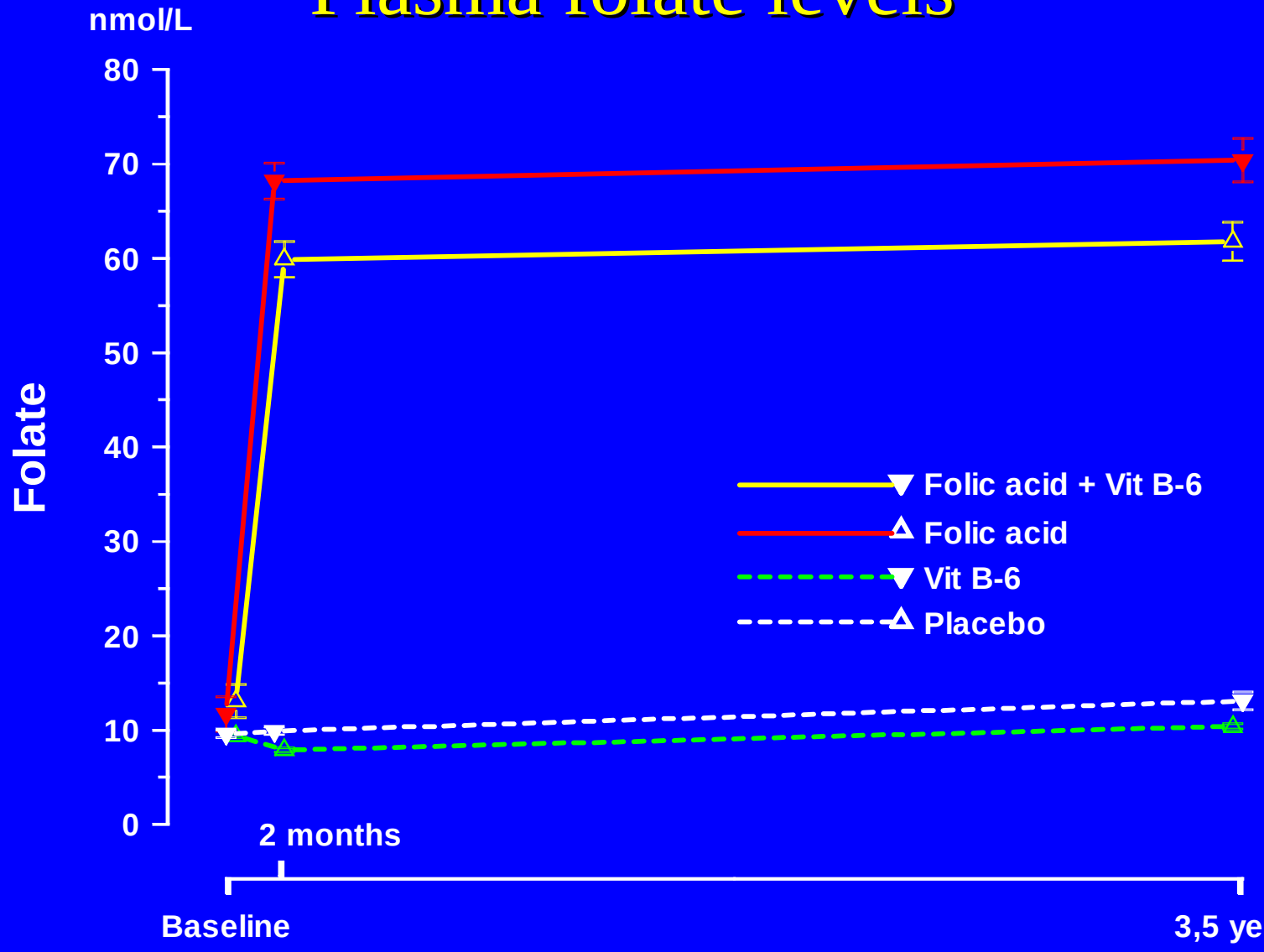
Plasma folate levels



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No. of events during 3.5 years of intervention

Primary endpoints	716
Secondary endpoints	
Myocardial infarction	643
Stroke	98
Death from any cause	365
PCI	1096
CABG	584
Cancer	113

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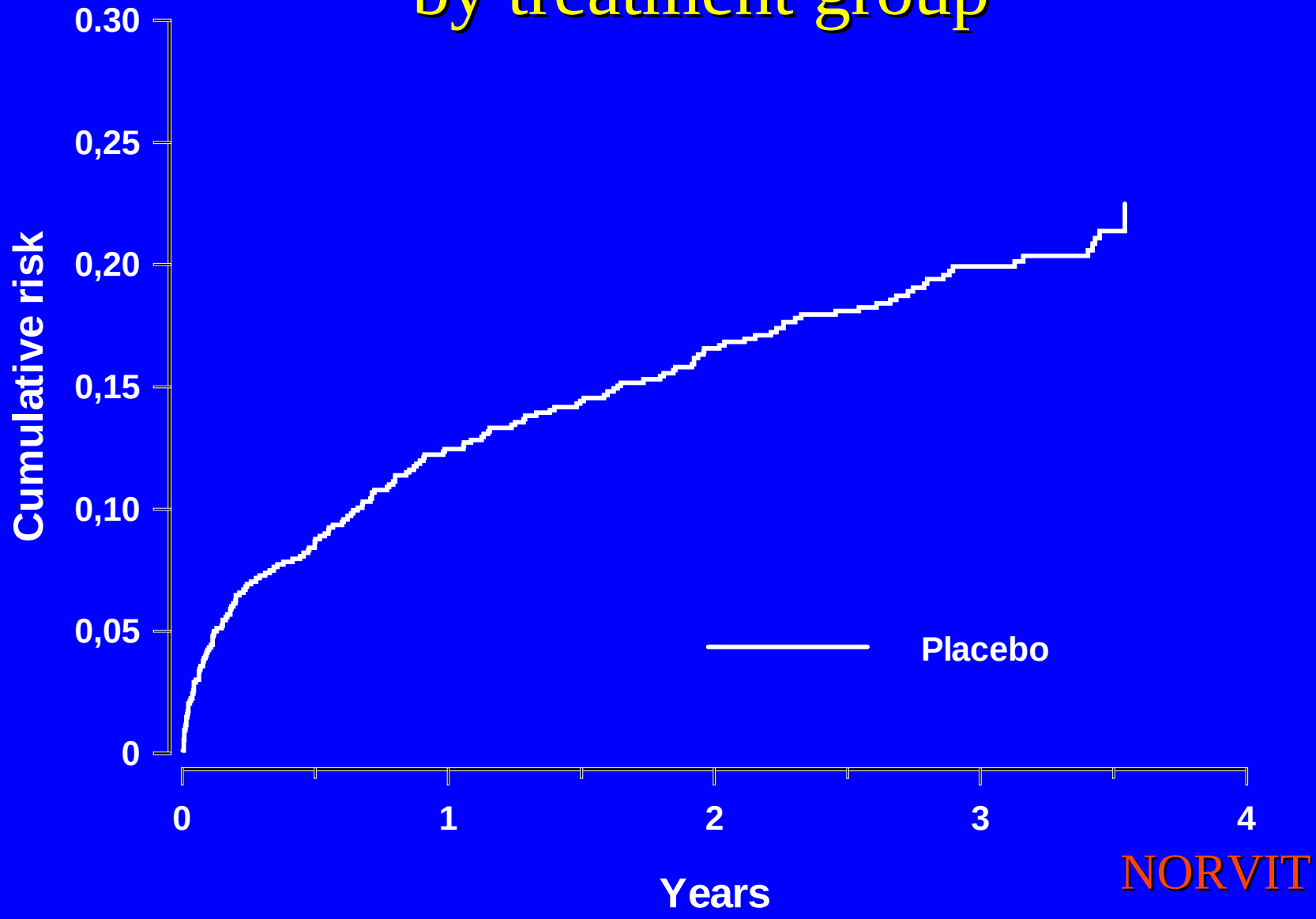
Cumulative risk of primary endpoint by treatment group



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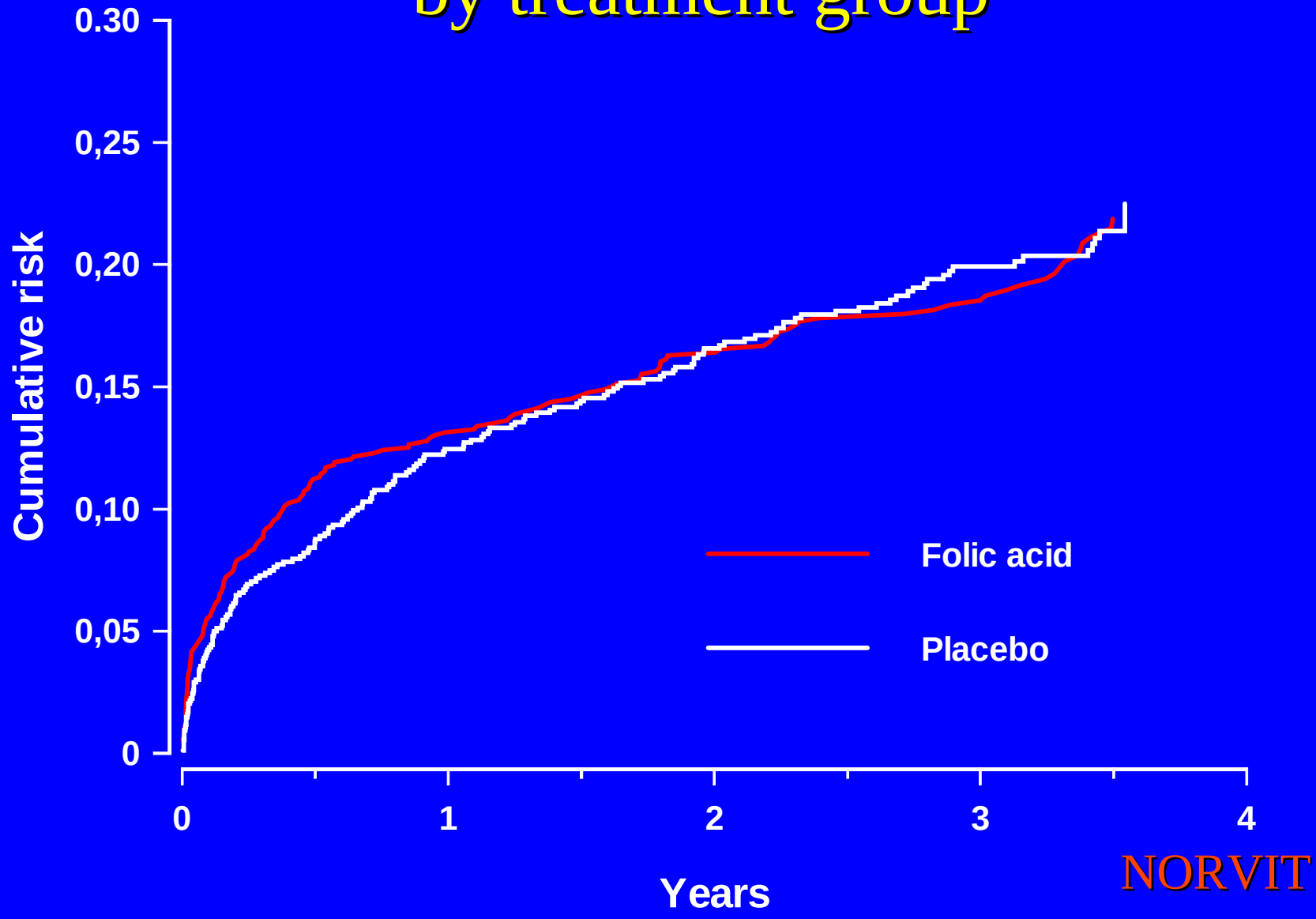
Cumulative risk of primary endpoint by treatment group



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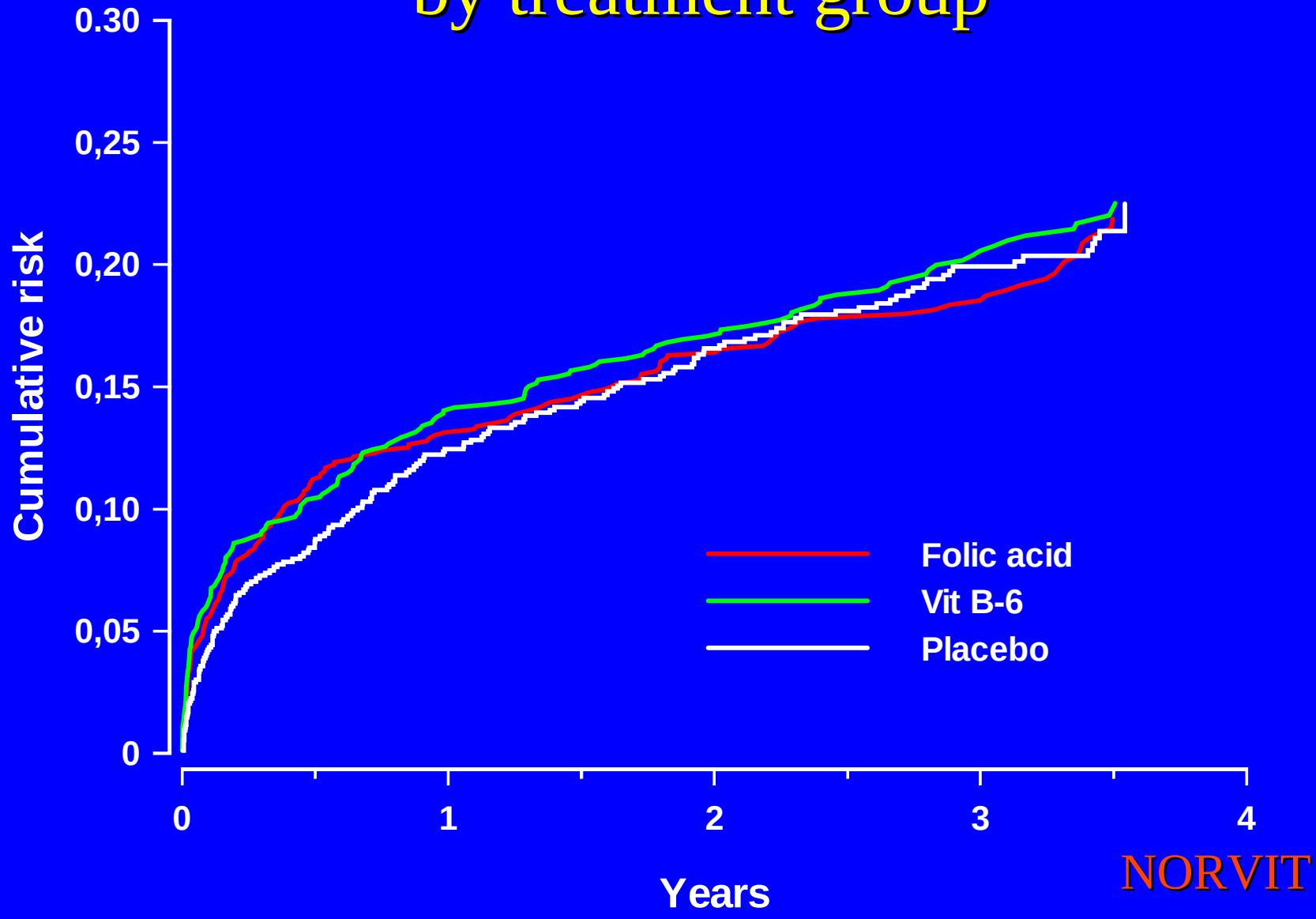

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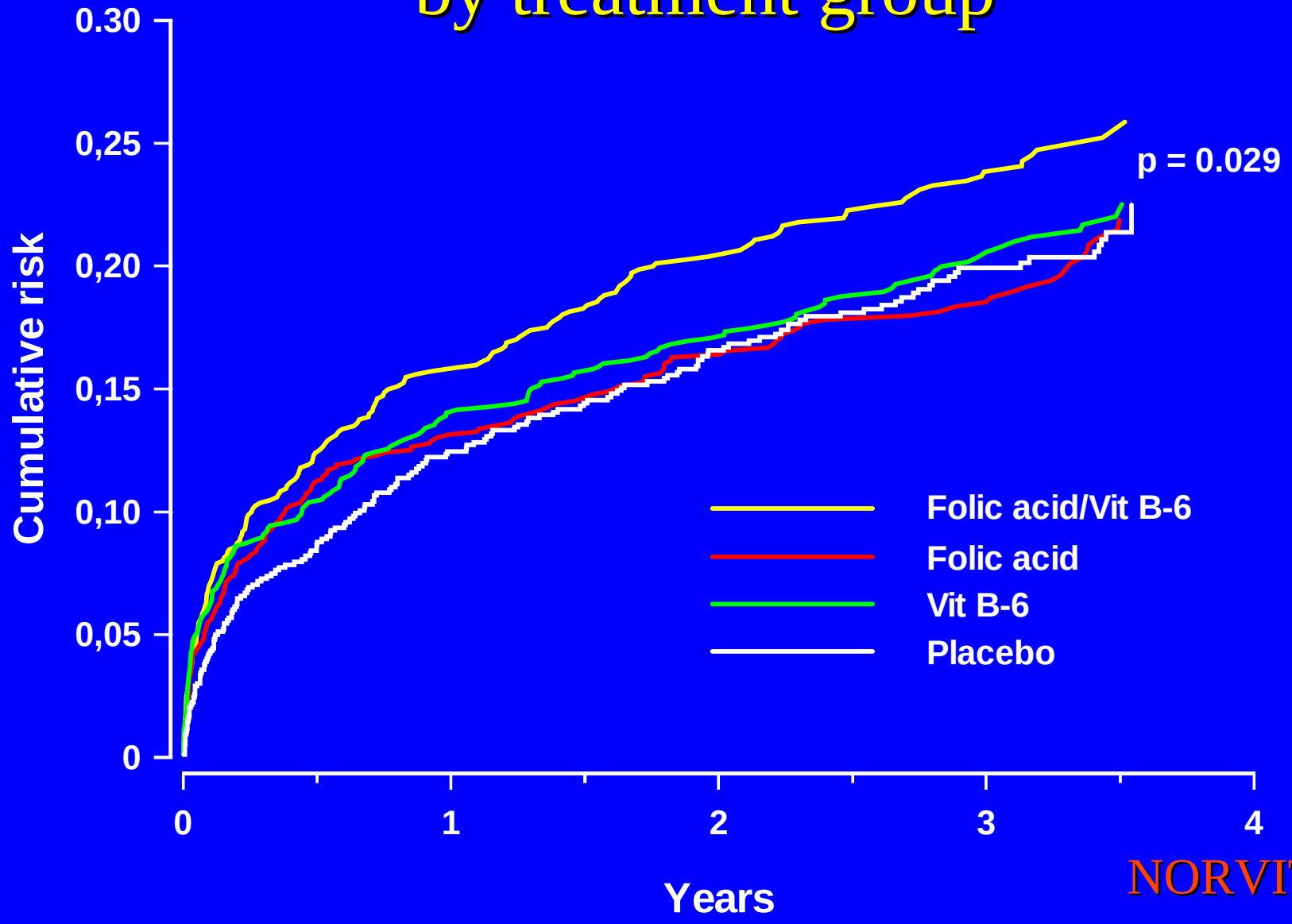
Cumulative risk of primary endpoint by treatment group



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Event rates

	Folic acid + vit B-6	Folic acid	Vit B-6	Placebo
Primary endpoint	81.6	66.9	70.1	67.2
MI	73.0	57.5	64.0	59.2
Death	37.5	28.7	33.4	31.7
Cancer	12.0	11.9	8.0	9.0

Rate per 1000 person-years

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Rate ratios

	Folic acid vs control[1]			Vitamin B-6 vs control[2]		
	RR	95% CI	*p*	RR	95% CI	*p*
MI and stroke	1.1	(0.9 – 1.3)	0.3	1.1	(1.0 – 1.3)	0.09
MI	1.1	(0.9 – 1.2)	0.5	1.2	(1.0 – 1.4)	0.04
Death	1.0	(0.8 – 1.3)	0.8	1.2	(1.0 – 1.5)	0.11
Cancer	1.4	(1.0 – 2.0)	0.08	1.0	(0.7 – 1.4)	0.3

[1] Groups A+B vs C+D

[2] Groups A+C vs B+D

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Rate ratios

	Folic acid + vitamin B-6 vs control[1]		
	RR	95% CI	*p*
MI and stroke	1.2	(1.0 – 1.4)	0.03
MI	1.2	(1.0 – 1.4)	0.03
Death	1.2	(1.0 – 1.5)	0.10
Cancer	1.3	(0.8 – 1.9)	0.3

[1] Group A vs B+C+D

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Summary of findings - I

In NORVIT plasma homocysteine levels were lowered by 28% with no reduction in risk of MI or stroke

Homocysteine is not a causal risk factor, but an ”innocent by-stander”

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Summary of findings - II

Folic acid alone:

- No significant effect on risk of CVD
- Increased risk of cancer?

Vitamin B-6 alone:

- No significant effect on risk of CVD

Folic acid and vitamin B-6 in combination:

- 21 percent increased risk of MI

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Conclusions – NORVIT

1. High doses of B vitamins should not be prescribed for secondary prevention of cardiovascular disease
2. Folic acid and vitamin B-6 in combination may increase the risk of cardiovascular disease
3. Further studies are needed to find out whether folic acid accelerates growth of cancer cells

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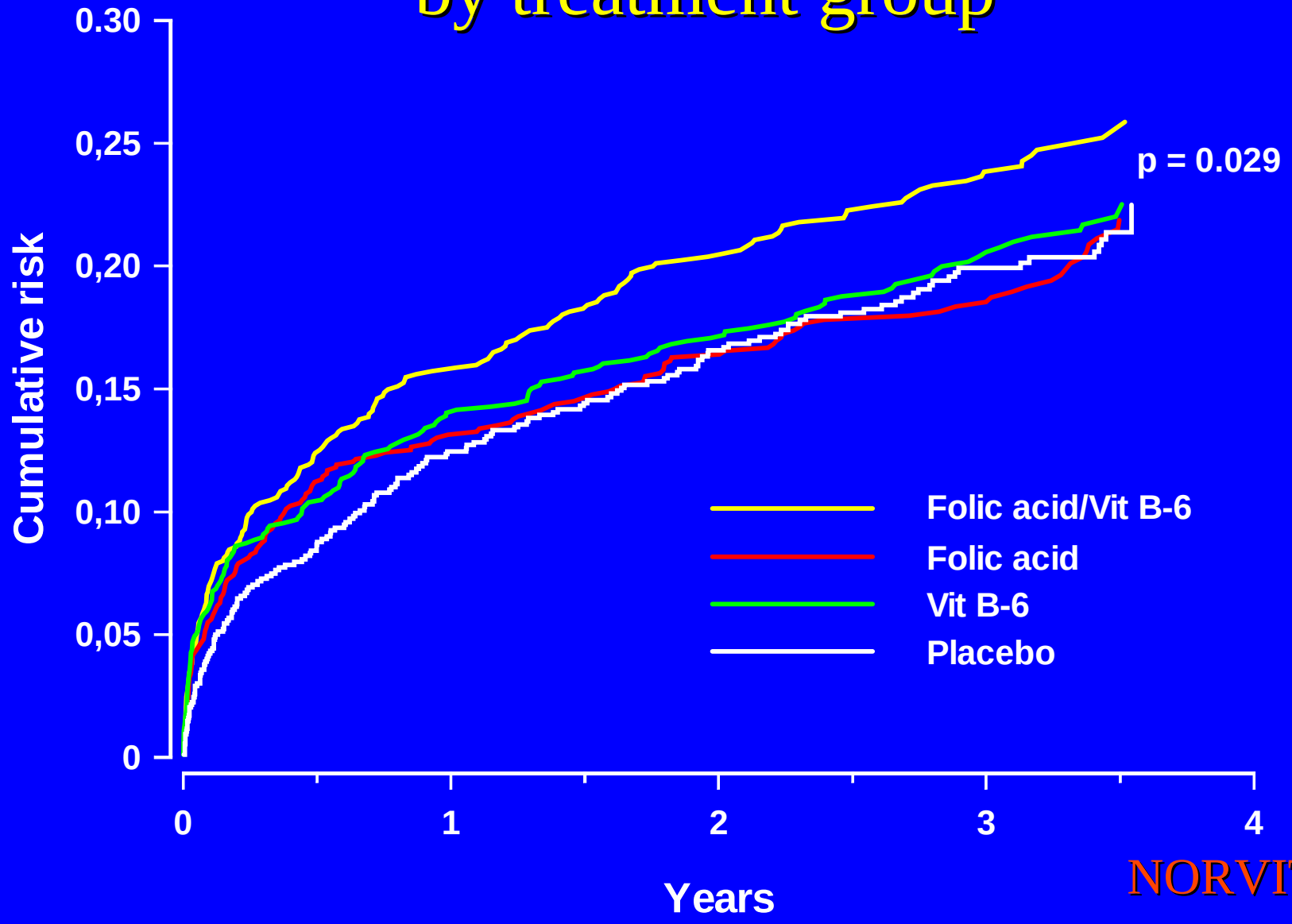
Cumulative risk of primary endpoint by treatment group



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