# Homocystein – hat die therapeutische Intervention einen Nutzen ?

**Symposium Prävention**
**8. Jahrestagung DGGG Freiburg 29.09.2006**

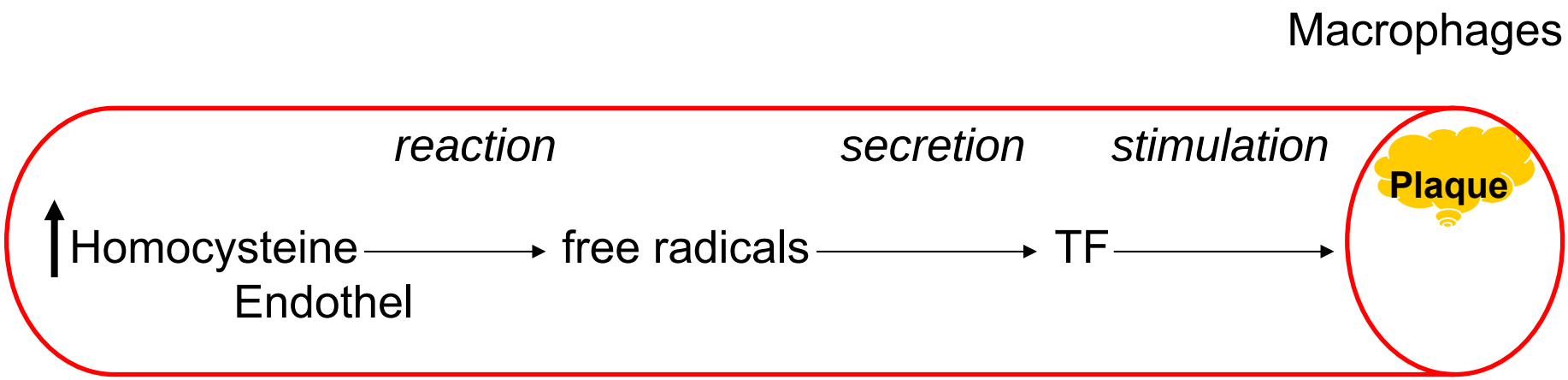
**Dr. M. Gogol**
**Klinik für Geriatrie**

KRANKENHAUS LINDENBRUNN

**Coppenbrügge**

# B-Vitamine und Homocystein

B-Vitamine (insbes. Folat, B6, B12 sind essentiell für die Synthese und den Metabolismus von Methionin zu Homocystein und Cystein.




**Homocystein-Serumspiegel↑ :**

- Angeborene Defekte
- Mangel an Folsäure / Vit. B12 / Vit. B6
- Niereninsuffizienz
- Medikamenten-NW (z.B. Methotrexat, Diuretika)

# Metaanalyse I

72 Studien → Mutation MTHFR Gen (n = 16.859)

20 Studien → prospektiv (n = 3.830)

Odds ratio bez. 5 µmol/l Seum-Homocysteinanstieg

| | | |
|---|---|---|
| Genetik | KHK | 1,42 (1,11 – 1,84) |
| Prospektiv | KHK | 1,32 (1,19 – 1,45) |
| Genetik | TVT/LE | 1,60 (1,15 – 2,22) |
| Genetik | Stroke | 1,65 (0,66 – 4,13) |
| Prospektiv | Stroke | 1,59 (1,29 – 1,96) |

Wald DS et al. Homocysteine and cardiovascular disease: evidence on causality from a meta-analysis. BMJ 2002;325:1202-6

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# Metaanalyse II

30 prosp. + retrospektive Studien

KHK n = 5.073

Stroke n = 1.113

Homecysteinspiegel ↓ 25 %

| | | | |
|---|---|---|---|
| RR ↓ | KHK | 11 % | 0,89 (0,83 – 0,96) |
| | Stroke | 19 % | 0,81 (0,69 – 0,95) |

JAMA®

The Homocysteine Studyies Collaboration – Homocysteine and risk ofcoronary heart disease and stroke. A meta-analysis. JAMA 2002;288:2015-22

# VISP

## Vitamin Intervention for Stroke Prevention

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n = 3.680, mittl. Alter 66 ± 11 a

63 % Männer

79 % Weisse, 15 % Farbige, 6 % andere

Prim. EP: Stroke

Sek. EP: KHK, Tod

Follow-up 2 a

**HD:** 25 mg pyridoxine, 0,4 mg cobalamine + 2,5 mg folic-acid

**ND:** 200 µg pyridoxine, 6µg cobalamine + 20 µg folic-acid

JAMA® Toole JF et al. Lowering homocysteine in patients with ischemic stroke to prevent recurrent stroke, myocardial infarction, and death. The Vitamin Intervention for Stroke Prevention (VISP) randomized controlled trial. JAMA 2004;291:565-75

# VISP – Basic characteristics I

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| Characteristics | Low-Dose Vitamin Group (n = 1853) | High-Dose Vitamin Group (n = 1827) | *P* Value |
|---|---|---|---|
| Age, mean (SD), y | 66.2 (10.8) | 66.4 (10.8) | .68 |
| Age group, y | | | |
| 35-54 | 300 (16.2) | 285 (15.6) | .91 |
| 55-64 | 463 (25.0) | 472 (25.8) | |
| 65-74 | 634 (34.2) | 617 (33.8) | |
| ≥75 | 456 (24.6) | 453 (24.8) | |
| Women | 690 (37.2) | 689 (37.7) | .77 |
| Race/ethnicity | | | |
| Black | 286 (15.4) | 259 (14.2) | .20 |
| White | 1452 (78.4) | 1473 (80.6) | |
| Other | 115 (6.2) | 95 (5.2) | |
| Mini-Mental State Examination[29] score, mean (SD) | 26.9 (3.3) | 26.9 (3.4) | .84 |
| Current smoker | 287 (15.5) | 334 (18.3) | .02 |
| Taking multivitamins† | 419 (22.6) | 407 (22.3) | .81 |

JAMA

Toole JF et al. Lowering homocysteine in patients with ischemic stroke to prevent recurrent stroke, myocardial infarction, and death. The Vitamin Intervention for Stroke Prevention (VISP) randomized controlled trial. JAMA 2004;291:565-75

# VISP – Basic characteristics II

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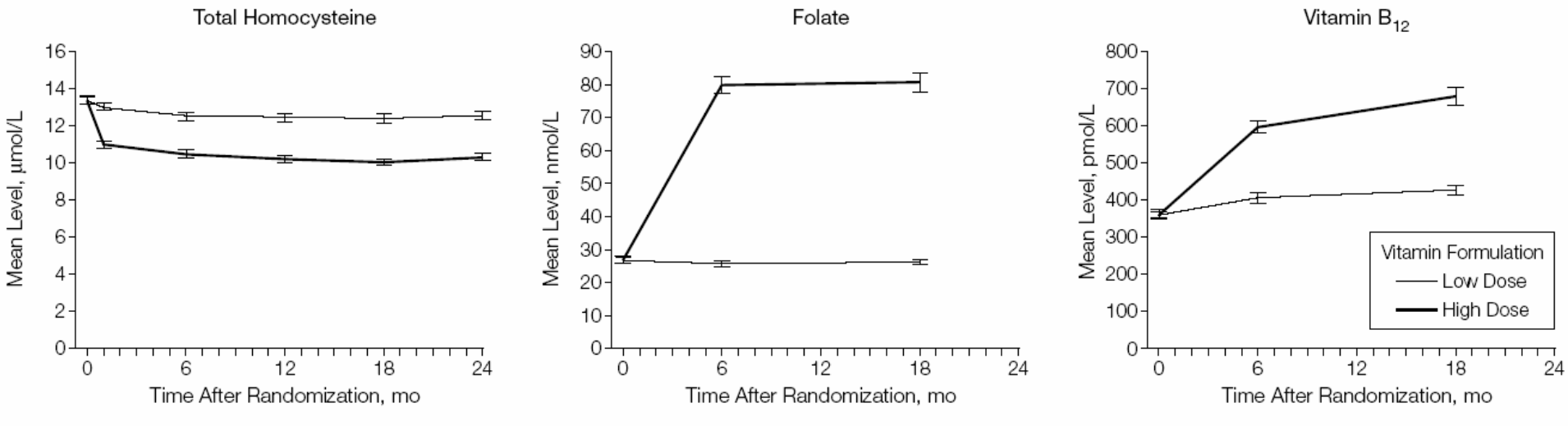
| | | | |
|---|---|---|---|
| Body mass index, mean (SD)‡ | | | |
| Men | 28.1 (5.3) | 28.1 (5.3) | .67 |
| Women | 28.5 (5.9) | 28.7 (6.7) | .66 |
| Blood pressure, mean (SD), mm Hg | | | |
| Systolic | 140.6 (18.9) | 141.1 (18.6) | .38 |
| Diastolic | 77.8 (10.1) | 78.0 (10.0) | .46 |
| Cholesterol level, mean (SD), mg/dL | | | |
| Total | 203.0 (46.5) | 200.8 (46.9) | .16 |
| High-density lipoprotein | 45.6 (15.7) | 45.2 (15.3) | .46 |
| Low-density lipoprotein | 123.3 (40.1) | 121.6 (40.2) | .22 |
| Triglyceride level, mean (SD), mg/dL | 172.7 (108.7) | 176.8 (190.1) | .44 |
| Serum creatinine level, mean (SD), mg/dL | 1.10 (0.54) | 1.13 (0.63) | .23 |
| History of | | | |
| Hypertension | 1358 (73.4) | 1354 (74.3) | .53 |
| Diabetes | 571 (30.8) | 500 (27.4) | .02 |
| Any cardiac disease§ | 438 (23.8) | 456 (25.1) | .37 |
| Chest pain | 646 (34.9) | 697 (38.1) | .04 |
| Smoking (ever) | 1205 (65.1) | 1239 (67.8) | .08 |
| Stroke prior to qualifying stroke | 428 (23.1) | 428 (23.4) | .81 |
| Carotid endarterectomy | 129 (7.0) | 118 (6.5) | .55 |
| Angina‖ | 130 (7.0) | 145 (7.9) | .29 |

JAMA

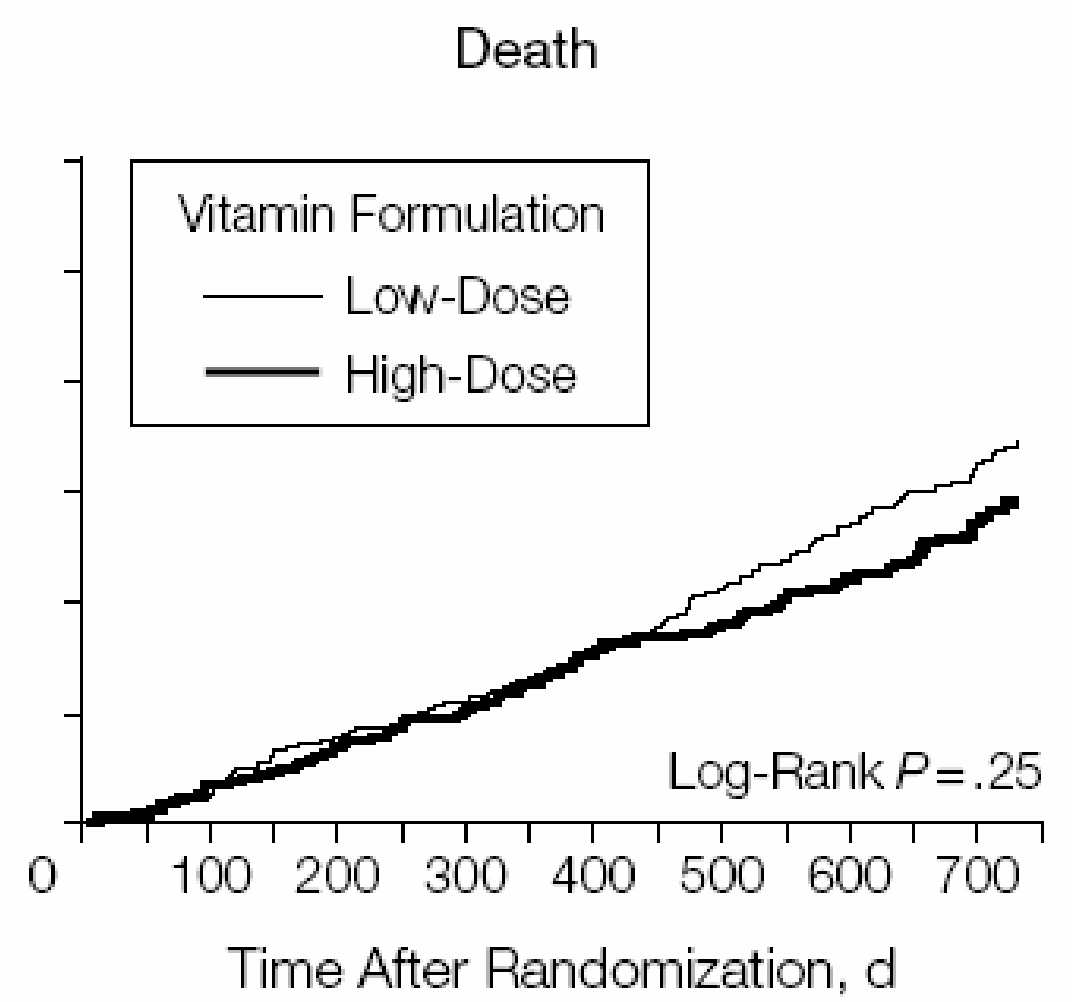
Toole JF et al. Lowering homocysteine in patients with ischemic stroke to prevent recurrent stroke, myocardial infarction, and death. The Vitamin Intervention for Stroke Prevention (VISP) randomized controlled trial. JAMA 2004;291:565-75

# VISP - Vitaminspiegel



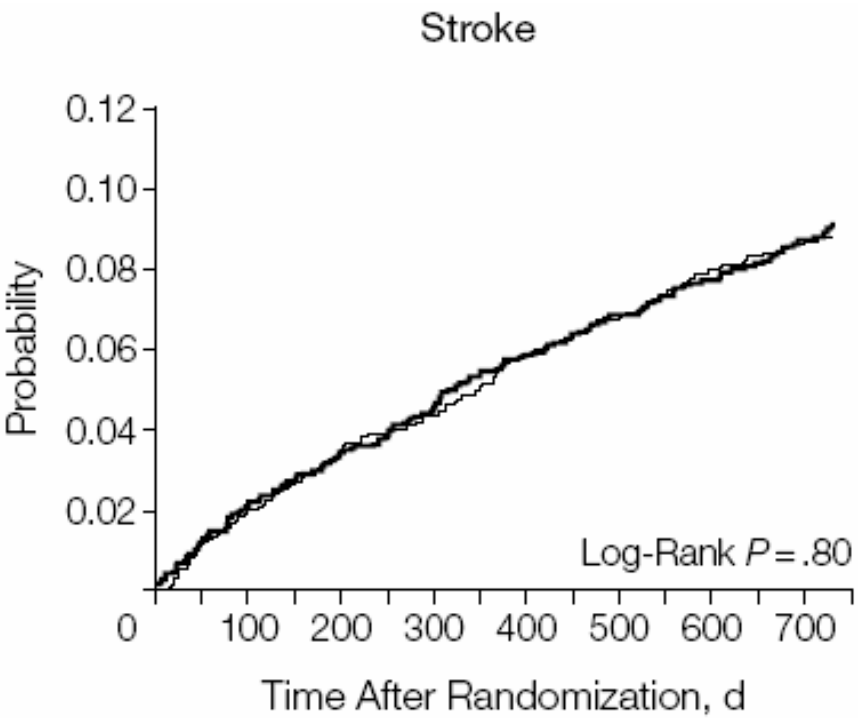

Toole JF et al. Lowering homocysteine in patients with ischemic stroke to prevent recurrent stroke, myocardial infarction, and death. The Vitamin Intervention for Stroke Prevention (VISP) randomized controlled trial. JAMA 2004;291:565-75

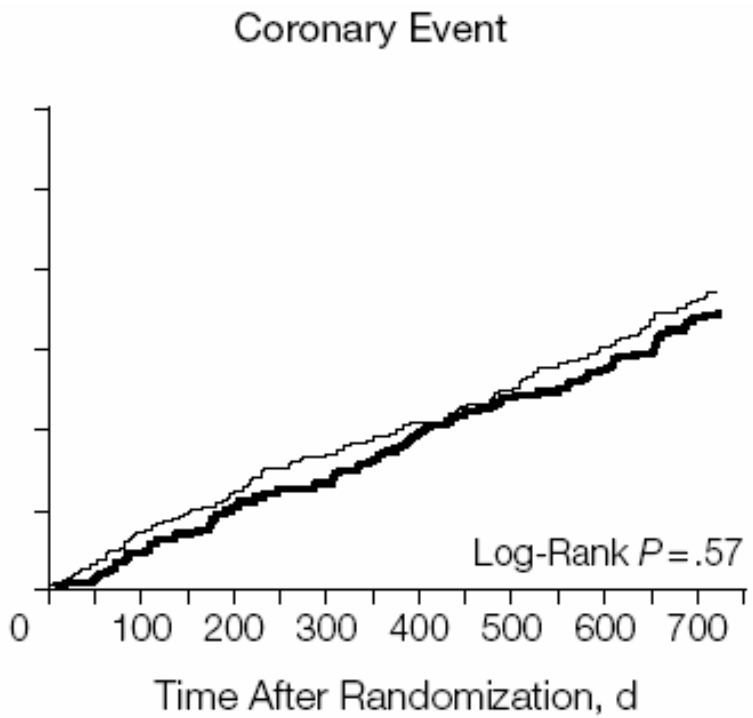
# VISP – Endpunkte I




Toole JF et al. Lowering homocysteine in patients with ischemic stroke to prevent recurrent stroke, myocardial infarction, and death. The Vitamin Intervention for Stroke Prevention (VISP) randomized controlled trial. JAMA 2004;291:565-75

# VISP – Endpunkte II




Toole JF et al. Lowering homocysteine in patients with ischemic stroke to prevent recurrent stroke, myocardial infarction, and death. The Vitamin Intervention for Stroke Prevention (VISP) randomized controlled trial. JAMA 2004;291:565-75

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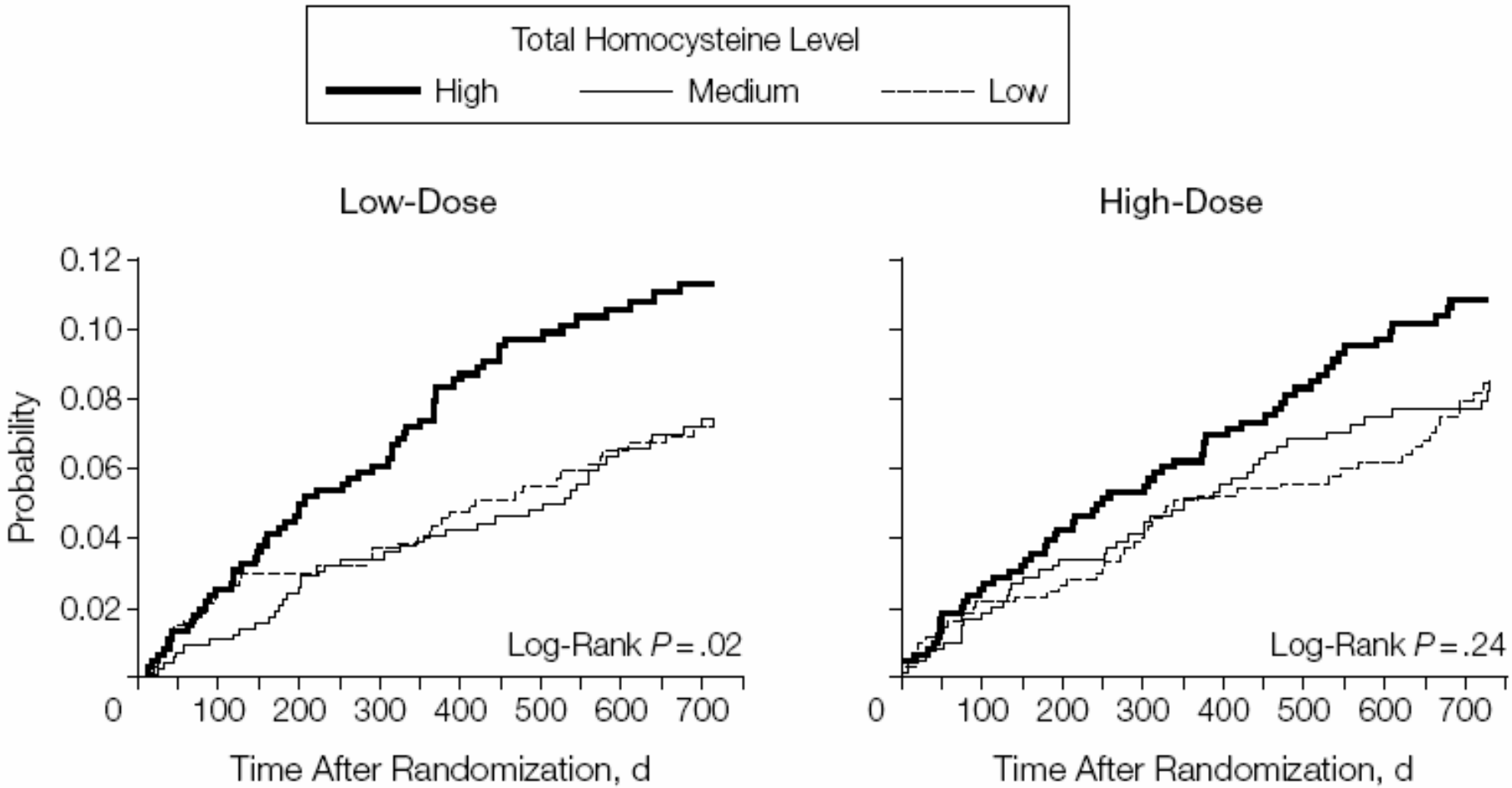
# VISP – Schlaganfallrisiko

**Wahrscheinlichkeit Stroke in Korrelation zum anfänglichen Homocysteinspiegel und Behandlungsgruppe**




**↓ 3 µml/l HC level RR ↓ Stroke 10 % (p = 0,05), KHK 26 % (p < 0,001) und Tod 10 % (p = 0,001)**

**↓ 3 µml/l HC level RR ↓ Stroke 2 %, KHK 7 % und Tod 7 % (alle n.s.)**


JAMA® Toole JF et al. Lowering homocysteine in patients with ischemic stroke to prevent recurrent stroke, myocardial infarction, and death. The Vitamin Intervention for Stroke Prevention (VISP) randomized controlled trial. JAMA 2004;291:565-75

# VISP - Kommentar

- Statistische Power ?
- Geringe Ereignisrate in beiden Gruppen
- Laufzeit zu kurz
- Geringe Homocysteinspiegel-Senkung → Nahrungssupplementierung in den USA
- Vitamin B12-Gabe in der HD-Gruppe zu niedrig und in der LD-Gruppe zu hoch

Stroke Hankey GJ, Eikelboom JW. Folic acid-based multivitamin therapy to prevent stroke. The jury is still out. Stroke 2004;35:1995-8

# Homocystein
## and In-Stent restenosis

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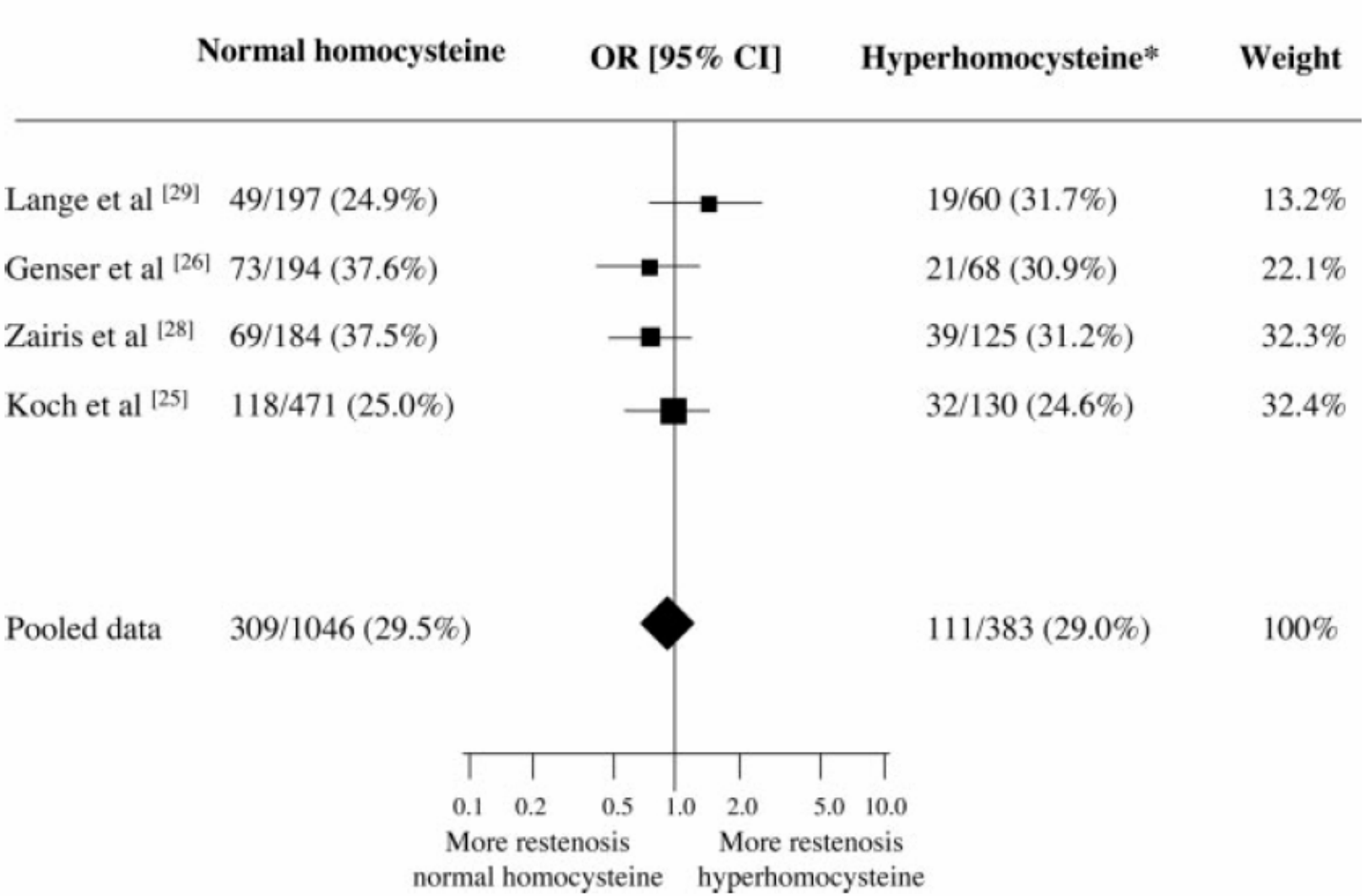


Circulation

De Luca G et al. Homocysteine ans ist effects on in-stent restenosis. Circulation 2005;112:e307-11

# HOPE 2

## Heart Outcomes Prevention Evaluation 2

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5.522 Patienten — Alter > 55 a (69 ± 7)

Männer 71 % — Rasse k.A.

Follow-up 5 a

Drug Adherence 96,5 → 90,8 % (Verum)

96,0 → 88,5 % (Placebo)

2,5 mg Folsäure
50 mg Vitamin B6
1 mg Vitamin B12

} vs. Placebo

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# HOPE 2 – Basic characteristics

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**Table 1. Baseline Characteristics of the Patients.***

| Characteristic | Active Group (N=2758) | Placebo Group (N=2764) |
|---|---|---|
| Age — yr | 68.8±7.1 | 68.9±6.8 |
| Female sex — no. (%) | 796 (28.9) | 763 (27.6) |
| Vascular disease history — no. (%) | | |
| Coronary artery disease | 2285 (82.8) | 2315 (83.8) |
| Myocardial infarction | 1501 (54.4) | 1498 (54.2) |
| Stable angina | 1651 (59.9) | 1636 (59.2) |
| Unstable angina | 709 (25.7) | 730 (26.4) |
| Coronary-artery bypass grafting | 722 (26.2) | 779 (28.2) |
| Percutaneous coronary intervention | 565 (20.5) | 546 (19.8) |
| Stroke | 241 (8.7) | 251 (9.1) |
| Stroke or transient ischemic attack | 341 (12.4) | 343 (12.4) |
| Intermittent claudication | 73 (2.6) | 60 (2.2) |
| Peripheral-artery surgery or percutaneous intervention | 157 (5.7)† | 119 (4.3) |
| Carotid endarterectomy | 82 (3.0) | 64 (2.3) |

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# HOPE 2 – Basis characteristics II

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| | | |
|---|---|---|
| Risk factors — no. (%) | | |
| Hypertension | 1542 (55.9) | 1497 (54.2) |
| Diabetes mellitus | 1122 (40.7) | 1087 (39.3) |
| Elevated total cholesterol | 1333 (48.3) | 1306 (47.3) |
| Low HDL cholesterol | 432 (15.7) | 454 (16.4) |
| Current smoking | 306 (11.1) | 327 (11.8) |
| Medication use — no. (%) | | |
| Aspirin or antiplatelet agents | 2148 (77.9) | 2224 (80.5) |
| Beta-blockers | 1270 (46.0) | 1294 (46.8) |
| Lipid-lowering drugs | 1627 (59.0) | 1690 (61.1) |
| ACE inhibitors | 1818 (65.9) | 1827 (66.1) |
| Angiotensin II–receptor blockers | 124 (4.5) | 131 (4.7) |
| Calcium-channel blockers | 1045 (37.9) | 1012 (36.6) |
| Diuretics | 756 (27.4) | 696 (25.2) |
| Oral hypoglycemic agents | 653 (23.7) | 647 (23.4) |
| Insulin | 406 (14.7) | 361 (13.1) |
| Hormone-replacement therapy‡ | 137 (17.2) | 130 (17.0) |
| Multivitamins | 331 (12.0) | 307 (11.1) |

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# HOPE 2 – Basic characteristics III

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**Table 1. (Continued.)**

| Characteristic | Active Group (N=2758) | Placebo Group (N=2764) |
|---|---|---|
| Findings on physical examination | | |
| Heart rate — beats/min | 68.7±11.2 | 68.9±11.5 |
| Systolic blood pressure — mm Hg | 138.8±21.7 | 138.9±23.4 |
| Diastolic blood pressure — mm Hg | 77.4±11.8 | 77.5±11.7 |
| Body-mass index | 29.6±16.4 | 29.7±21.1 |
| Waist-to-hip ratio | 0.95±0.3 | 0.94±0.1 |
| Ankle–brachial index | 1.0±0.2 | 1.0±0.2 |
| Laboratory results — mg/dl§ | | |
| Total cholesterol | 186.8±38.8 | 184.8±38.0 |
| LDL cholesterol | 105.7±33.2 | 103.9±31.9 |
| HDL cholesterol | 46.8±14.0† | 45.8±13.0 |
| Triglycerides | 178.6±119.7 | 181.1±113.8 |
| Plasma glucose | 128.8±57.6 | 125.7±51.7 |
| Creatinine | 1.0±0.3 | 1.0±0.3 |

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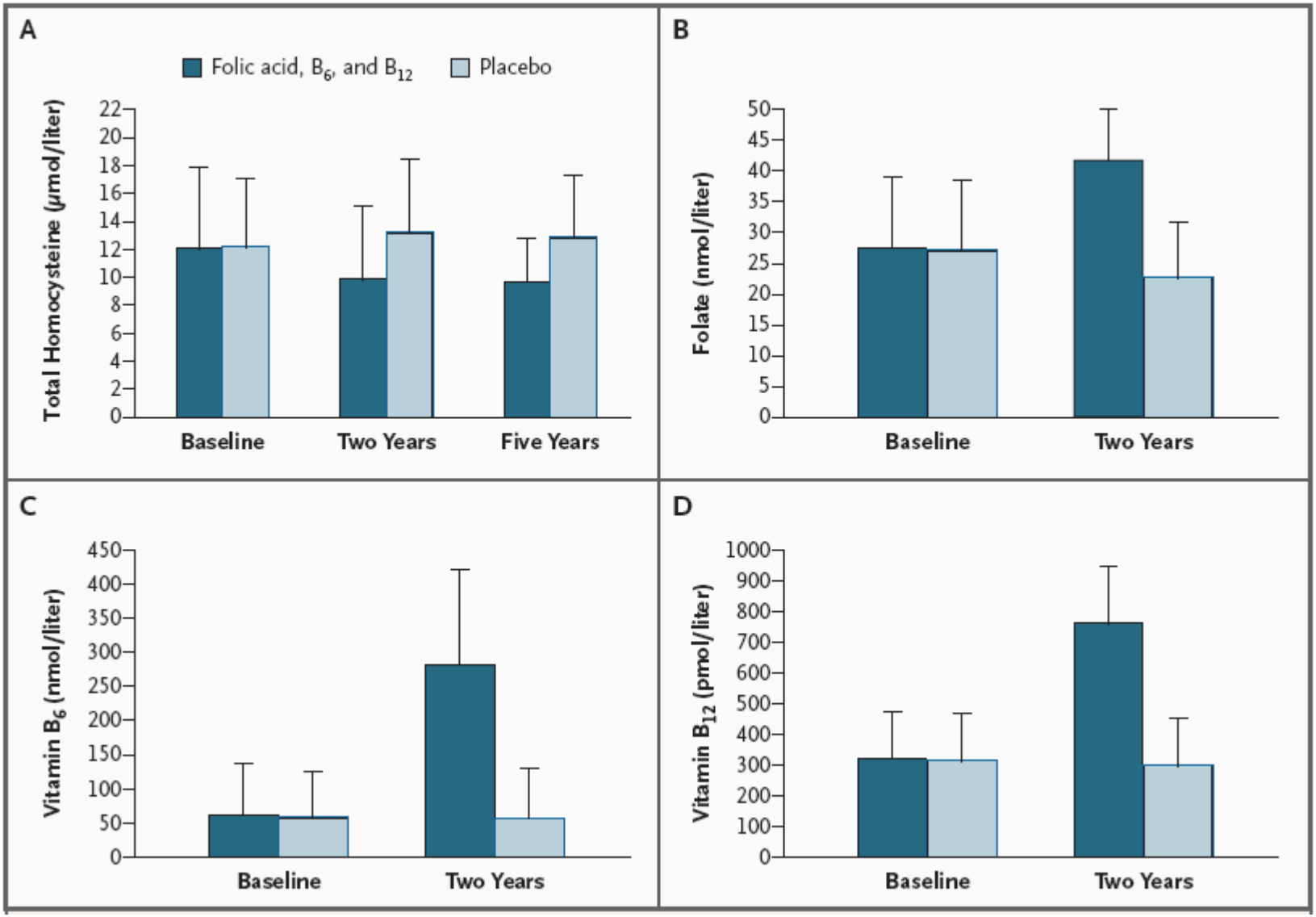
# HOPE 2 - Vitaminspiegel

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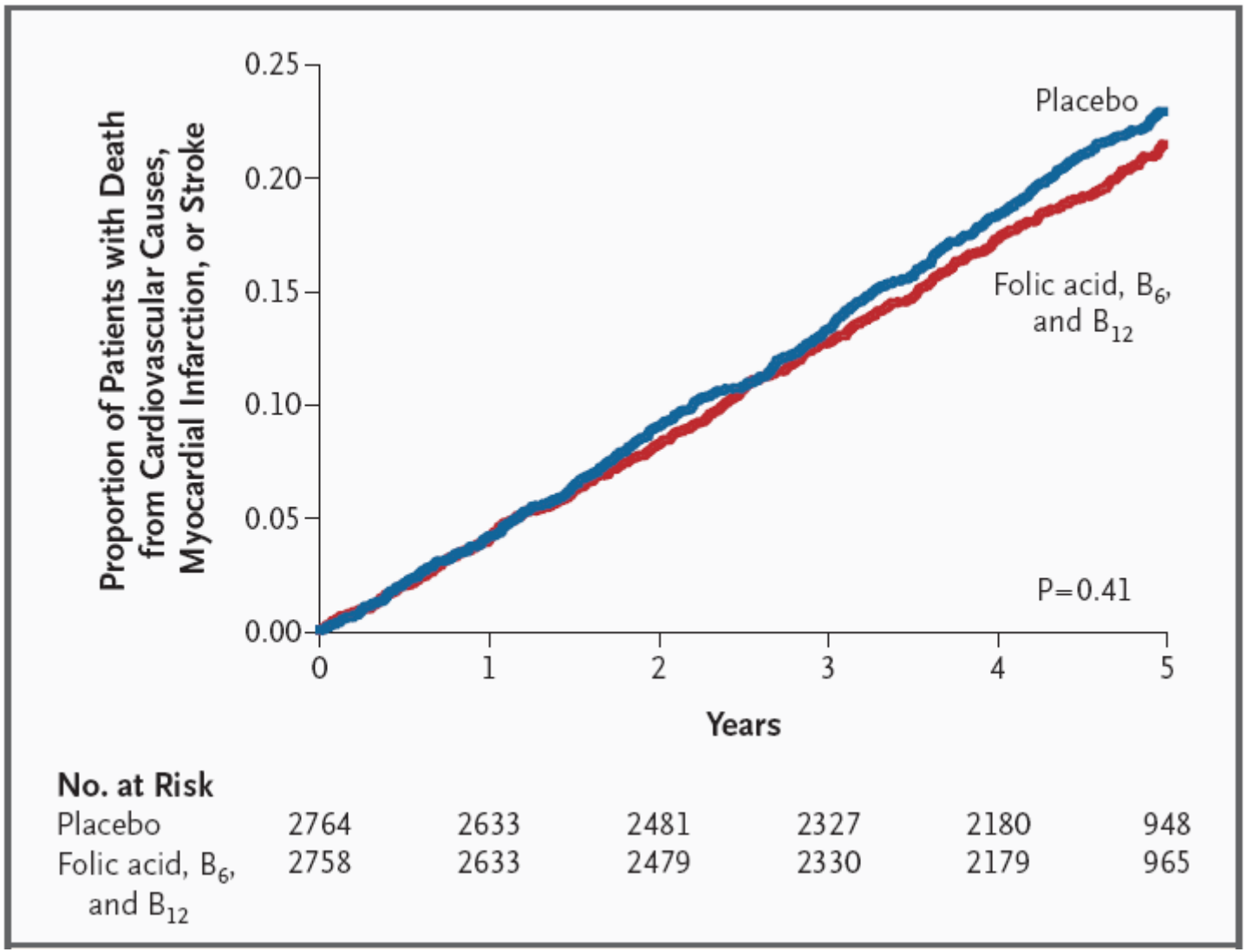
# HOPE 2 – Primärer EP kombiniert

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# HOPE 2 – Primäre EP

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**Table 2. Outcomes.**

| Outcome | Active Group (N=2758) | Placebo Group (N=2764) | Relative Risk (95% CI)* | P Value† |
|---|---|---|---|---|
| | *no. of patients (%)* | | | |
| **Primary outcome and its components** | | | | |
| Composite of death from cardiovascular causes, myocardial infarction, or stroke | 519 (18.8) | 547 (19.8) | 0.95 (0.84–1.07) | 0.41 |
| Death from cardiovascular causes‡ | 276 (10.0) | 291 (10.5) | 0.96 (0.81–1.13) | 0.59 |
| Myocardial infarction‡ | 341 (12.4) | 349 (12.6) | 0.98 (0.85–1.14) | 0.82 |
| Stroke‡ | 111 (4.0) | 147 (5.3) | 0.75 (0.59–0.97) | 0.03 |

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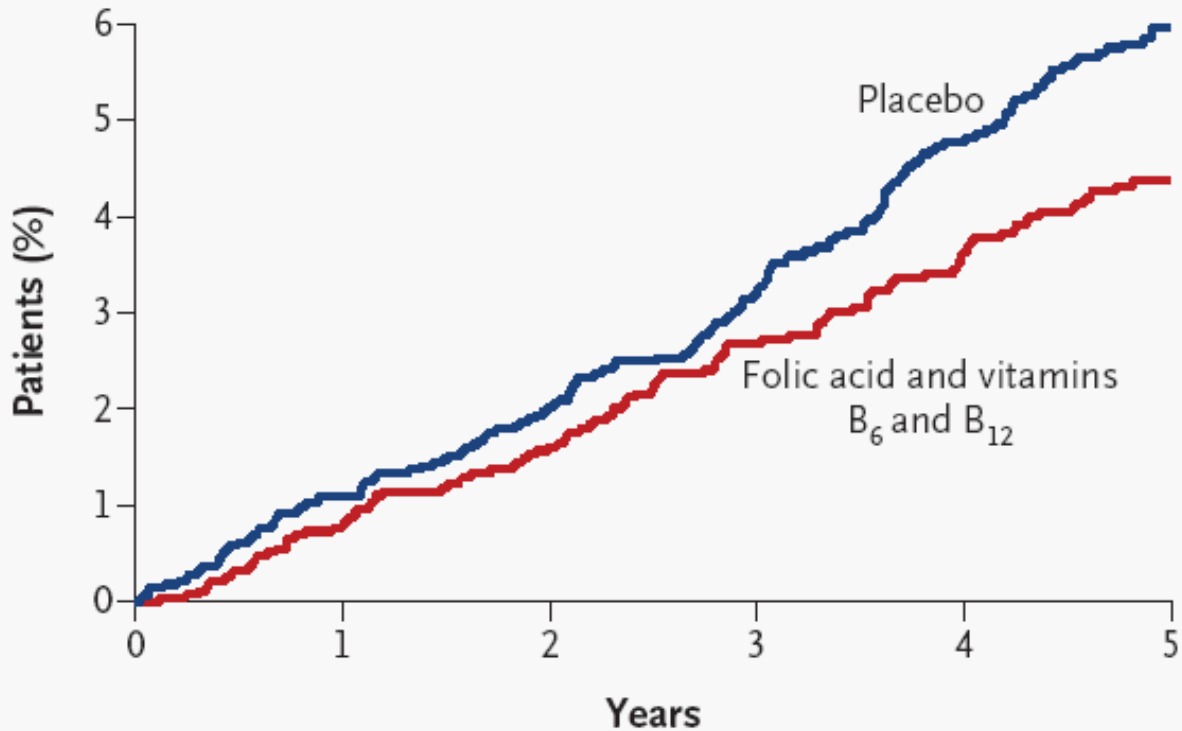
# HOPE 2 – EP Stroke




| No. at Risk | | | | | | |
|---|---|---|---|---|---|---|
| Placebo | 2758 | 2685 | 2558 | 2441 | 2324 | 1026 |
| Folate | 2764 | 2670 | 2561 | 2439 | 2312 | 1044 |

**Figure 1. Kaplan–Meier Estimates of the Percentage of Patients with Stroke during a Trial of Homocysteine Lowering.**

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Quinlivan EP, Gergory III, JE. Homocysteine, B vitamins, and cardiovascular disease. Letter. N Engl J Med 2006;355:205-11

# HOPE 2 – Sekundäre EP

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| Secondary outcomes | | | | |
|---|---|---|---|---|
| Total ischemic events§ | 900 (32.6) | 890 (32.2) | 1.03 (0.94–1.13) | 0.57 |
| Death from any cause | 470 (17.0) | 475 (17.2) | 0.99 (0.88–1.13) | 0.94 |
| Hospitalization for unstable angina | 268 (9.7) | 219 (7.9) | 1.24 (1.04–1.49) | 0.02 |
| Hospitalization for heart failure | 202 (7.3) | 174 (6.3) | 1.18 (0.96–1.44) | 0.12 |
| Revascularization | 458 (16.6) | 422 (15.3) | 1.10 (0.96–1.26) | 0.16 |
| Incident cancer | 358 (13.0) | 340 (12.3) | 1.06 (0.91–1.23) | 0.47 |
| Site-specific cancers | | | | |
| Colon | 50 (1.8) | 37 (1.3) | 1.36 (0.89–2.08) | 0.16 |
| Lung | 52 (1.9) | 45 (1.6) | 1.16 (0.78–1.73) | 0.47 |
| Breast | 11 (0.4) | 10 (0.4) | 1.11 (0.47–2.61) | 0.81 |
| Prostate | 70 (2.5) | 58 (2.1) | 1.21 (0.86–1.72) | 0.28 |
| Melanoma | 5 (0.2) | 12 (0.4) | 0.42 (0.15–1.19) | 0.10 |
| Death due to cancer | 94 (3.4) | 95 (3.4) | 0.99 (0.74–1.33) | 0.94 |
| Other outcomes | | | | |
| Transient ischemic attack | 131 (4.7) | 120 (4.3) | 1.11 (0.87–1.42) | 0.42 |
| Venous thromboembolism (pulmonary embolism and deep-vein thrombosis) | 37 (1.3) | 40 (1.4) | 0.96 (0.61–1.50) | 0.86 |
| Fractures | 246 (8.9) | 235 (8.5) | 1.06 (0.88–1.26) | 0.55 |

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# HOPE 2 – Subgruppen I

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| Group | No. of Patients | Incidence of Primary Outcome in Placebo Group % | Relative Risk (95% CI) in the Folic Acid, $B_6$, and $B_{12}$ Group | P Value for Interaction |
|---|---|---|---|---|
| Overall | 5522 | 19.8 | | |
| Sex | | | | 0.57 |
| Female | 1559 | 21.0 | | |
| Male | 3963 | 19.3 | | |
| Age | | | | 0.37 |
| <69 yr | 2664 | 16.2 | | |
| ≥69 yr | 2858 | 23.1 | | |
| Regions with folate fortification | | | | 0.33 |
| Yes | 3982 | 18.0 | | |
| No | 1540 | 24.5 | | |
| Homocysteine level | | | | 0.70 |
| Lower third (<10 μmol/liter) | 1086 | 14.1 | | |
| Middle third (≥10 and <12.7 μmol/liter) | 1085 | 16.2 | | |
| Upper third (≥12.7 μmol/liter) | 1134 | 24.0 | | |
| Creatinine level | | | | 0.94 |
| <Median (0.98 mg/dl) | 1622 | 14.7 | | |
| ≥Median | 1689 | 21.5 | | |
| Total cholesterol | | | | 0.93 |
| <Median (182 mg/dl) | 1649 | 16.5 | | |
| ≥Median | 1662 | 19.9 | | |

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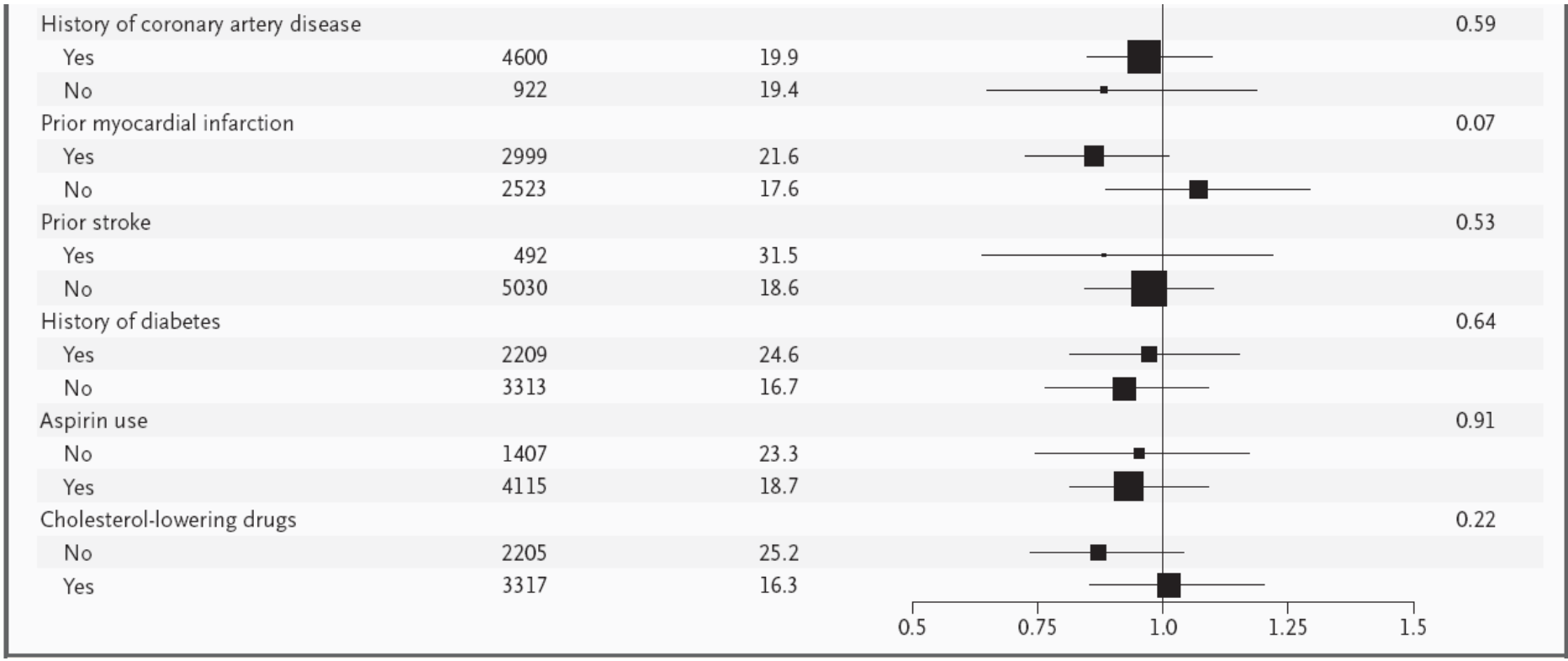
# HOPE 2 – Subgruppen 2

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# NORVIT

## NORwegian VITamin Trial

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n = 3.749 Post-Myokardinfarkt

Männer 74 %

Mittl. Alter 63 ± 12 a

Follow-up 40 Monate

**4 Gruppen**

1. 0,8 mg Folsäure, 0,4 mg Vit. B12, Vit. 40 mg B6
2. 0,8 mg Folsäure, Vit. 0,4 mg B12
3. 40 mg Vit. B6
4. Placebo

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Bonaa KH et al. – Homocysteine lowering and cardiovascular events after acute myocardial infarction. N Engl J Med 2006;354:1578-88

# NORVIT – Basic characteristics I

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**Table 1. Baseline Characteristics of the Patients and Use of Concomitant Medications.***

| Characteristic | Folic Acid, $B_{12}$, and $B_6$ (N=937) | Folic Acid and $B_{12}$ (N=935) | $B_6$ (N=934) | Placebo (N=943) | P Value |
|---|---|---|---|---|---|
| Age — yr | 63.6±11.9 | 63.2±11.6 | 62.5±11.7 | 62.6±11.4 | 0.11 |
| Male sex — no. (%) | 684 (73) | 696 (74) | 686 (73) | 705 (75) | 0.80 |
| Total cholesterol — mmol/liter | 5.8±1.2 | 5.8±1.2 | 5.8±1.3 | 5.7±1.3 | 0.49 |
| Creatinine — μmol/liter | 91±27 | 91±26 | 90±25 | 91±24 | 0.57 |
| Systolic blood pressure — mm Hg | 126±21 | 126±20 | 125±20 | 125±20 | 0.27 |
| Diastolic blood pressure — mm Hg | 73±13 | 73±13 | 72±13 | 72±13 | 0.25 |
| Body-mass index† | 26.5±4.0 | 26.2±3.5 | 26.3±3.8 | 26.3±3.8 | 0.66 |
| Medical history — no. (%) | | | | | |
| Myocardial infarction | 171 (18) | 155 (17) | 149 (16) | 153 (16) | 0.54 |
| Angina pectoris | 262 (28) | 225 (24) | 243 (26) | 240 (26) | 0.28 |
| Stroke | 50 (5) | 36 (4) | 38 (4) | 33 (3) | 0.21 |
| Diabetes mellitus | 103 (11) | 83 (9) | 86 (9) | 96 (10) | 0.40 |
| Coronary-artery bypass surgery | 55 (6) | 40 (4) | 38 (4) | 44 (5) | 0.26 |
| Percutaneous coronary intervention | 44 (5) | 45 (5) | 43 (5) | 49 (5) | 0.94 |

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# NORVIT – Basic characteristics II

| | | | | | |
|---|---|---|---|---|---|
| Receiving treatment for hypertension — no. (%) | 281 (30) | 250 (27) | 268 (29) | 275 (29) | 0.46 |
| Current smoker — no. (%) | 429 (46) | 405 (43) | 460 (49) | 453 (48) | 0.05 |
| Use of vitamin supplements — no./total no. (%) | 271/931 (29) | 275/930 (30) | 257/928 (28) | 263/935 (28) | 0.78 |
| Qualifying myocardial infarction | | | | | |
| Received primary or rescue PCI — no.(%) | 59 (6) | 61 (7) | 54 (6) | 54 (6) | 0.86 |
| Received thrombolysis — no./total no. (%) | 383/932 (41) | 403/931 (43) | 405/929 (44) | 381/942 (40) | 0.42 |
| Q-wave — no./total no. (%) | 403/906 (44) | 420/906 (46) | 411/894 (46) | 417/904 (46) | 0.85 |
| Peak creatine kinase — U/liter‡ | | | | | |
| Median | 969 | 1043 | 1004 | 929 | 0.62 |
| Interquartile range | 425–2156 | 461–2136 | 489–2084 | 457–2095 | |
| Concomitant medication — no./total no. (%) | | | | | |
| Acetylsalicylic acid | 757/874 (87) | 789/880 (90) | 764/853 (90) | 778/880 (88) | 0.16 |
| Beta-blockers | 797/873 (91) | 808/879 (92) | 768/853 (90) | 802/881 (91) | 0.58 |
| Statins | 690/873 (79) | 721/879 (82) | 704/856 (82) | 712/880 (81) | 0.30 |
| ACE inhibitors | 283/868 (33) | 264/875 (30) | 263/851 (31) | 262/880 (30) | 0.59 |
| Angiotensin II–receptor antagonists | 38/866 (4) | 46/873 (5) | 37/849 (4) | 48/879 (6) | 0.60 |
| Diuretics | 162/869 (19) | 153/874 (18) | 147/851 (17) | 152/879 (17) | 0.86 |
| Warfarin | 123/868 (14) | 89/873 (10) | 88/851 (10) | 104/879 (12) | 0.04 |

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# NORVIT - Vitaminspiegel

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**Table 2.** Plasma Levels of Total Homocysteine and B Vitamins at Baseline, after Two Months, and at the End of the Intervention.*

| Variable | Folic Acid, $B_{12}$, and $B_6$ (N=937)† | Folic Acid and $B_{12}$ (N=935)‡ | $B_6$ (N=934)§ | Placebo (N=943)¶ |
|---|---|---|---|---|
| **Total homocysteine (μmol/liter)** | | | | |
| Baseline | 13.1±5.0 | 12.9±4.3 | 13.3±6.1 | 13.2±5.2 |
| 2 Mo | 9.4±3.0 | 9.5±2.8 | 13.7±5.7 | 13.7±5.6 |
| End of intervention | 9.5±3.6 | 9.8±4.0 | 13.3±5.4 | 13.6±6.2 |
| **Folate (nmol/liter)** | | | | |
| Baseline | 13.1±27.5 | 11.7±28.4 | 9.4±6.6 | 9.6±6.0 |
| 2 Mo | 59.9±29.5 | 68.2±30.0 | 7.9±7.1 | 9.9±6.3 |
| End of intervention | 61.8±31.7 | 70.4±36.4 | 10.4±9.6 | 13.1±14.5 |
| **Vitamin $B_{12}$ (pmol/liter)** | | | | |
| Baseline | 388±161 | 400±311 | 388±167 | 383±182 |
| 2 Mo | 571±212 | 578±372 | 398±158 | 393±143 |
| End of intervention | 638±370 | 648±414 | 398±320 | 390±171 |

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# NORVIT - Outcome

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**Table 3.** Clinical Outcomes and Rate Ratios.

| Variable | Total No. | Folic Acid, $B_{12}$, and $B_6$ (N=937) | Folic Acid and $B_{12}$ (N=935) | $B_6$ (N=934) | Placebo (N=943) | Folic Acid and $B_{12}$ vs. No Folic Acid and $B_{12}$* | | $B_6$ vs. No $B_6$† | | Folic Acid, $B_{12}$, and $B_6$ vs. Placebo‡ | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | Rate Ratio (95% CI)§ | P Value | Rate Ratio (95% CI)§ | P Value | Rate Ratio (95% CI)§ | P Value |
| | | *no. of cases (rate/1000 observation-yr)* | | | | | | | | | |
| Primary end point¶ | 716 | 201 (81.6) | 168 (66.9) | 175 (70.1) | 172 (67.2) | 1.08 (0.93–1.25) | 0.31 | 1.14 (0.98–1.32) | 0.09 | 1.22 (1.00–1.50) | 0.05 |
| Myocardial infarction‖ | 643 | 182 (73.0) | 147 (57.5) | 161 (64.0) | 153 (59.2) | 1.06 (0.91–1.24) | 0.47 | 1.17 (1.00–1.37) | 0.05 | 1.23 (0.99–1.52) | 0.06 |
| Fatal** | 235 | 68 (24.5) | 47 (16.8) | 61 (22.1) | 59 (21.0) | 0.96 (0.74–1.24) | 0.75 | 1.24 (0.96–1.61) | 0.10 | 1.19 (0.84–1.69) | 0.34 |
| Nonfatal | 462 | 132 (53.0) | 113 (44.2) | 113 (44.9) | 104 (40.2) | 1.14 (0.95–1.37) | 0.16 | 1.15 (0.96–1.38) | 0.14 | 1.30 (1.00–1.68) | 0.05 |
| Stroke | 98 | 21 (7.7) | 28 (10.2) | 22 (8.1) | 27 (9.7) | 1.02 (0.68–1.51) | 0.94 | 0.81 (0.54–1.20) | 0.29 | 0.83 (0.47–1.47) | 0.52 |
| Death from any cause | 365 | 104 (37.5) | 80 (28.7) | 92 (33.4) | 89 (31.7) | 1.02 (0.83–1.26) | 0.82 | 1.19 (0.96–1.46) | 0.11 | 1.21 (0.91–1.61) | 0.19 |
| Hospitalization for unstable angina pectoris | 488 | 125 (50.5) | 126 (50.6) | 105 (41.6) | 132 (53.0) | 1.06 (0.89–1.27) | 0.50 | 0.88 (0.74–1.05) | 0.17 | 0.93 (0.73–1.19) | 0.57 |
| Coronary-artery bypass surgery | 584 | 138 (57.1) | 139 (57.0) | 150 (63.3) | 157 (65.0) | 0.90 (0.76–1.05) | 0.18 | 0.99 (0.84–1.17) | 0.91 | 0.89 (0.71–1.13) | 0.34 |
| Percutaneous coronary intervention | 1096 | 257 (122.6) | 270 (129.4) | 279 (135.0) | 290 (141.6) | 0.92 (0.82–1.03) | 0.16 | 0.94 (0.83–1.05) | 0.27 | 0.86 (0.72–1.02) | 0.08 |
| Cancer | 144 | 40 (15.5) | 39 (14.9) | 25 (9.8) | 40 (15.2) | 1.22 (0.88–1.70) | 0.23 | 0.84 (0.60–1.16) | 0.29 | 1.02 (0.65–1.58) | 0.94 |

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# NORVIT - Subgroups

**Table 4.** Rate Ratios for the Primary End Point in Various Subgroups.*

| Characteristic | Total No. | Folic Acid and $B_{12}$ vs. No Folic Acid and $B_{12}$† | $B_6$ vs. No $B_6$‡ | Folic Acid, $B_{12}$, and $B_6$ vs. Placebo§ |
|---|---|---|---|---|
| | | *rate ratio (95% confidence interval)* | | |
| Sex | | | | |
| Male | 2771 | 1.06 (0.89–1.27) | 1.14 (0.96–1.36) | 1.23 (0.96–1.57) |
| Female | 978 | 1.07 (0.82–1.41) | 1.11 (0.85–1.46) | 1.10 (0.75–1.61) |
| Age | | | | |
| ≤65 yr | 2068 | 1.17 (0.92–1.51) | 1.11 (0.87–1.42) | 1.26 (0.89–1.80) |
| >65 yr | 1681 | 0.97 (0.80–1.16) | 1.12 (0.93–1.34) | 1.05 (0.81–1.36) |
| Total homocysteine | | | | |
| ≤13 μmol/liter | 2237 | 0.97 (0.79–1.20) | 1.03 (0.84–1.27) | 1.02 (0.75–1.37) |
| >13 μmol/liter | 1496 | 1.27 (1.02–1.66) | 1.26 (1.02–1.55) | 1.56 (1.16–2.09) |
| Creatinine | | | | |
| ≤100 μmol/liter | 2845 | 1.05 (0.88–1.25) | 1.04 (0.87–1.25) | 1.09 (0.85–1.46) |
| >100 μmol/liter | 891 | 1.13 (0.87–1.47) | 1.32 (1.01–1.71) | 1.44 (0.98–2.11) |
| History of CVD or diabetes¶ | | | | |
| No | 1641 | 1.28 (0.95–1.73) | 0.92 (0.68–1.24) | 1.15 (0.76–1.75) |
| Yes | 2108 | 1.04 (0.88–1.23) | 1.22 (1.03–1.45) | 1.28 (1.01–1.62) |
| Current smoker | | | | |
| No | 2002 | 1.08 (0.90–1.30) | 1.06 (0.88–1.27) | 1.12 (0.86–1.45) |
| Yes | 1747 | 1.04 (0.81–1.32) | 1.28 (1.01–1.63) | 1.34 (0.95–1.88) |
| Qualifying myocardial infarction | | | | |
| No ST-segment elevation | 1959 | 1.25 (1.03–1.51) | 1.12 (0.92–1.35) | 1.40 (1.07–1.82) |
| ST-segment elevation | 1651 | 0.90 (0.71–1.15) | 1.11 (0.87–1.41) | 1.07 (0.76–1.51) |

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# Homocystein und Demenz I

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276 Patienten, mittl. Alter 73 Jahre, 65 % Frauen
Follow-up 2 Jahre

| | |
|---|---|
| Folsäure | 1.000 µg |
| Vitamin B12 | 500 µg |
| Vitamin B6 | 10 mg |

Kognitive Teste zeigten nach 1 und 2 Jahren
**keinen** Unterschied

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# Homocystein und Demenz II

**Table 1. Baseline Characteristics of the Participants.***

| Characteristic | Placebo Group (N=126) | Vitamin Group (N=127) | P Value |
|---|---|---|---|
| **Demographic characteristics** | | | |
| Age — yr | 73.4±5.7 | 73.6±5.8 | 0.79 |
| Female sex — no. (%) | 65 (52) | 47 (37) | 0.02 |
| Current smoker — no. (%) | 1 (1) | 6 (5) | 0.12 |
| Education attained — no. (%) | | | |
| <3 yr secondary | 41 (33) | 48 (38) | |
| ≥3 yr secondary | 11 (9) | 16 (13) | 0.31 |
| Tertiary | 74 (59) | 63 (50) | |
| History of hypertension — no. (%)† | 51 (40) | 56 (44) | 0.56 |
| Body-mass index‡ | 26.6±3.7 | 26.9±4.3 | 0.49 |
| Apolipoprotein E *ε4* carrier — no. (%)§ | 26 (24) | 36 (31) | 0.21 |
| Reading ability — no. of words pronounced correctly/ 50 words on the National Adult Reading Test | 36.8±6.8 | 35.6±6.5 | 0.13 |
| **Biochemical measures** | | | |
| Plasma total homocysteine — μmol/liter | 16.3±4.4 | 16.8±5.4 | 0.43 |
| Plasma folate — ng/ml | 10±5 | 10±5 | 0.78 |
| Plasma vitamin $B_{12}$ — pg/ml | 385±138 | 380±136 | 0.74 |
| Plasma cholesterol — mg/dl | 232±50 | 247±46 | 0.03 |

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# Homocystein und Demenz III

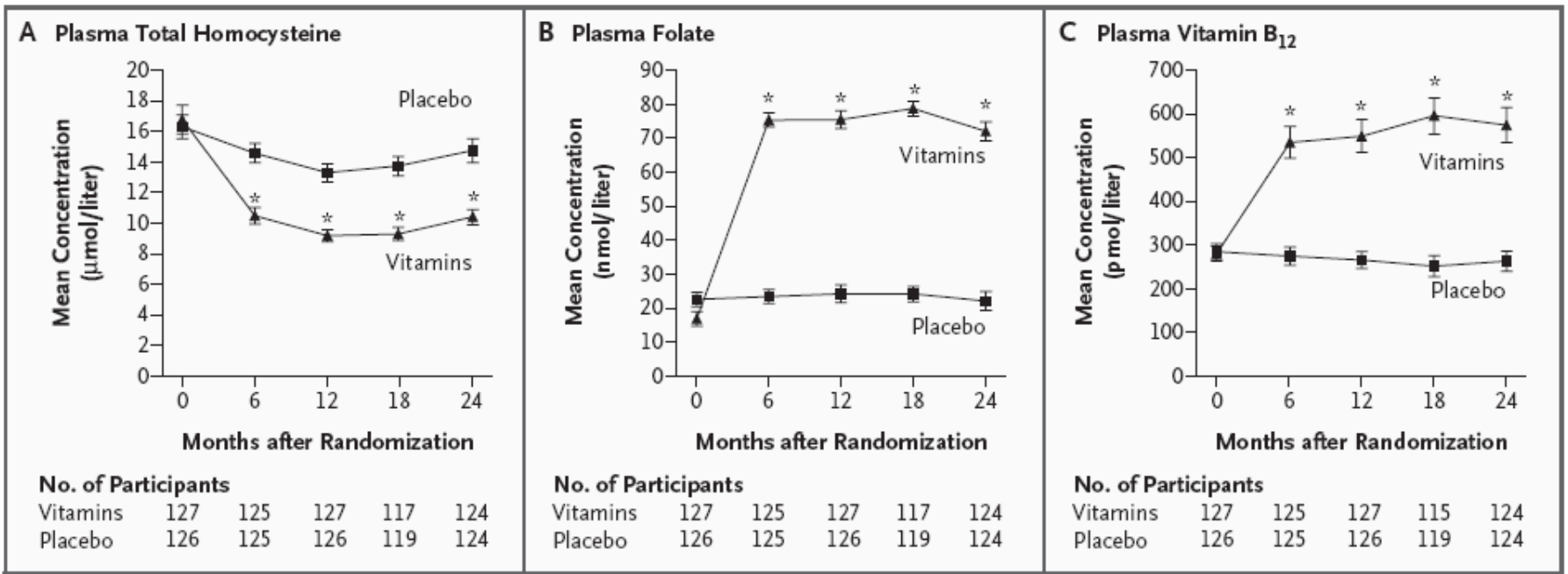


**Figure 2. Effect of Vitamins on Biochemical Measurements.**

I bars represent 95 percent confidence intervals. Asterisks indicate a significant difference from the placebo group ($P<0.001$). To convert the values for folate to nanograms per milliliter, divide by 2.266. To convert the values for vitamin $B_{12}$ to picograms per milliliter, divide by 0.738.

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# Homocystein und Demenz IV

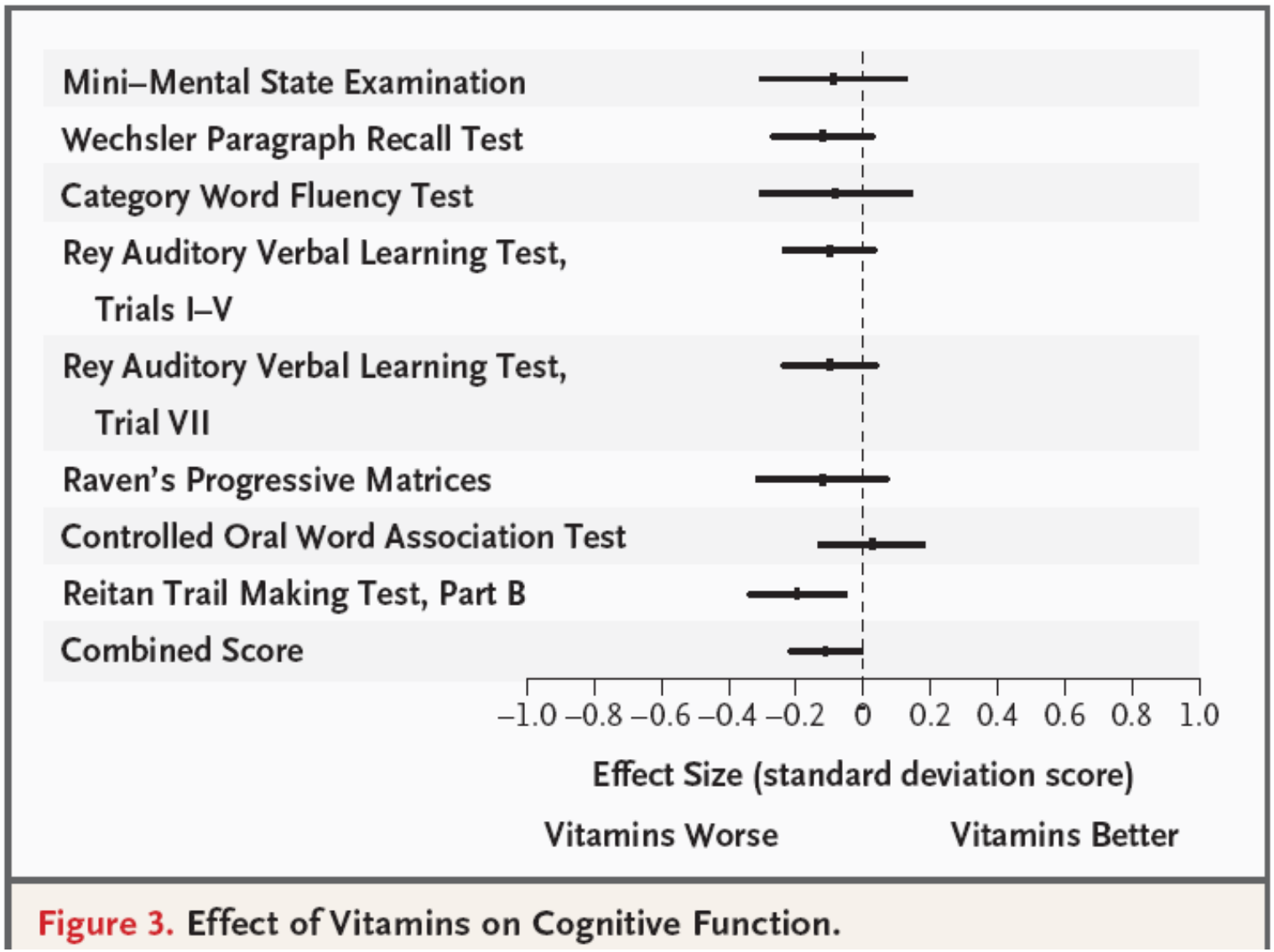


**Figure 3.** Effect of Vitamins on Cognitive Function.

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# Cockrane Library

- No evidence of benefit from vitamin B6 supplementation on mood or cognition of older people with normal vitamin B6 status or with vitamin B6 deficiency. **(1)**

- No evidence that folic acid with or without vitamin B12 improves cognitive function of elderly healthy people or people with dementia. **(2)**

THE COCHRANE COLLABORATION®


1. Malouf R, Grimley Evans J. Vitamin B6 for cognition. The Cochrane Database of Systematic Reviews 2006 Issue 3
2. Malouf R, Grimley Evans J, Areosa Sastre A.Folic acid with or without vitamin B12 for cognition and dementia. The Cochrane Database of Systematic Reviews 2006 Issue 3

# Take Home Message

- Homocystein-These als eigenständiger Risikofaktor zunehmend strittig
- Eine routinehafte Vitaminsubstitution kann nicht empfohlen werden
- Effekte auf Kognition nicht belegt
- Der Anteil älterer und hochaltriger Patienten in den Studien gering bis nicht vorhanden
- Daten für Patienten > 80 a nicht existent

**E-Mail:** gogol@krankenhaus-lindenbrunn.de
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