# Homocysteine-lowering clinical trials in Norway

*Cardiovascular and cancer outcomes in the Western Norway B Vitamin Intervention Trial and the Norwegian Vitamin Trial*

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Dissertation for the degree philosophiae doctor (PhD)
at the University of Bergen

Institute of Medicine

2010

Dissertation date: September 17

## Scientific environment

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*"All scientific work is incomplete – whether it be observational or experimental. All scientific work is liable to be upset or modified by advancing knowledge. That does not confer upon us a freedom to ignore the knowledge we already have, or to postpone the action that it appears to demand at a given time."*

Austin Bradford Hill, 1965.(1)

# Acknowledgements

The present dissertation is based on the Western Norway B Vitamin Intervention Trial (WENBIT) and the Norwegian Vitamin Trial (NORVIT), two randomized controlled clinical trials conducted in the period from 1998 to 2005. I received a 3-year grant from The Norwegian Foundation for Health & Rehabilitation (2006 to 2008), and additional funding from the Institute of Medicine, University of Bergen and the Department of Heart Disease, Haukeland University Hospital in 2009.

In 2005, after ten years of hard work planning and running WENBIT, the WENBIT steering committee[a] decided to give me the confidence to finalize the study database, and to draft the article presenting the main results. In 2008, the NORVIT steering committee[b] entrusted me with the NORVIT data to be used in the combined analyzes and long-time follow-up of NORVIT and WENBIT.

I thank the steering committees, the 6837 patients who participated in the trials, the many recruiting physicians, the study personnel involved in follow-up, data collection and blood sampling, and the laboratory personnel who analyzed the blood. Their contributions made it possible to generate high-quality data for medical research.

I am deeply grateful to my principal supervisor, Professor Ottar Nygård, who introduced me to scientific work. He has generously given me great challenges and continuous support. My co-supervisor, Professor Per Magne Ueland, has inspired me with his vast scientific knowledge and working capacity, and has never been hard to ask. Professor Stein Emil Vollset has willingly shared his impressive epidemiological

[a] Ottar Nygård (chair, principal investigator), Jan Erik Nordrehaug, Per Magne Ueland, Dennis W. Nilsen, Stein Emil Vollset, Helga Refsum

[b] Knut Rasmussen (chair), Kaare Harald Bønaa (principal investigator), Egil Arnesen†, Inger Njølstad, Aage Tverdal, Jan Erik Nordrehaug, Per Magne Ueland

and statistical apprehension. I am also indebted to Professor Kaare Harald Bønaa for promoting the NORVIT-WENBIT collaboration, and for his sound skepticism and enthusiastic support.

I was privileged to work with Professor Egil Arnesen from September 2008 until he died December 3, 2009. He was always available online, and found solutions whenever I was overwhelmed by the complexity of the data and analyses. I miss him.

I thank all co-authors for their contributions in study conception, data collection and interpretation, and for sharing their expertise in the publication process.

Through regular research meetings and seminars at the Locus of Homocysteine at the University of Bergen, I have had the pleasure to discuss and work with skilful scientists within the disciplines of cardiology, nutrition, biochemistry, epidemiology and statistics. In addition, I have enjoyed input put from colleagues in the preventive cardiology research team.

Professor Jan Erik Nordrehaug has provided invaluable backing and excellent working conditions at the Department of Heart Disease. As the managing director of a large, busy hospital department, he shows by action how medical science is given priority.

With his broad experience from clinical research, Professor Per Lund Johansen was the perfect chair for the WENBIT end-points committee. I also thank him for being an encouraging roommate.

Janne Dyngeland, Gry Kvalheim, Marie Husa, Britt Gjellefall, Elfrid Blomdal, Reinhardt Seifert, Espen Nordrehaug and Alf Aksland gave technical assistance. Danuta T. Lund took care of my project account. Thank you all.

My loving parents Kari and Hans always believe in me, whatever choices I make.

I am endlessly fortunate to have Knut-Arne, Kristina and Nanna in my life. To them I owe the most.

Bergen, May 2010 Marta Ebbing

# Contents

# Abstract


## Introduction

Observational studies have reported associations between levels of the amino acid homocysteine in the circulation and risk of cardiovascular disease. Oral administration of the synthetic B vitamins folic acid and cyanocobalamin (vitamin B12) can lower plasma total homocysteine levels. In the Western Norway B Vitamin Intervention Trial (WENBIT) and the Norwegian Vitamin Trial (NORVIT), patients with ischemic heart disease were randomized to groups receiving folic acid plus vitamin B12, or no such treatment, to assess whether they would benefit from lowered homocysteine levels with respect to major adverse clinical events, such as myocardial infarction, stroke, cardiovascular death or all-cause death. Using a 2 x 2 factorial design, participants were also randomized to groups receiving vitamin B6 or no vitamin B6.

## Aims

The overall aim of the present dissertation was to investigate the clinical effects of B vitamin treatment in patients with established ischemic heart disease.

## Materials and methods

We used clinical and laboratory data on 6837 patients with ischemic heart disease, recruited from 36 hospitals in Norway (1998 to 2004) collected during in-trial follow-up, and data on cancer incidence and cause-specific and all-cause mortality on these patients collected during extended follow-up throughout the year 2007.

Clinical outcomes were analyzed for groups assigned to folic acid plus vitamin B12 treatment *vs* no folic acid/vitamin B12, and for groups assigned to vitamin B6 treatment *vs* no vitamin B6. Survival curves were constructed using the Kaplan-Meier

method, and estimates of hazard ratios with confidence intervals were obtained using Cox proportional hazards regression.

## Results

Folic acid plus vitamin B12 treatment lowered plasma total homocysteine substantially in both trial populations. In the WENBIT study population, this treatment was not associated with the incidence of major adverse cardiovascular events or all-cause mortality during in-trial follow-up of median 38 months. In the combined NORVIT-WENBIT study population, it was not associated with the incidence of major adverse cardiovascular events or any of its constituents (myocardial infarction, stroke or cardiovascular death) during in-trial follow-up of median 39 months, or associated with long-term cardiovascular mortality during extended follow-up of median 78 months. However, among NORVIT-WENBIT participants with hyperhomocysteinemia at baseline, treatment with folic acid plus vitamin B12 was associated with increased risk of in-trial major cardiovascular events, and of long-term cardiovascular mortality. Exploratory analyses in NORVIT-WENBIT showed that baseline plasma total homocysteine was not independently associated with cardiovascular outcomes, whereas homocysteine measured after 1-2 months of folic acid plus vitamin B12 treatment was a strong predictor of in-trial major cardiovascular events.

In the combined NORVIT-WENBIT study population, folic acid plus vitamin B12 treatment was associated with increased cancer incidence, cancer mortality and all-cause mortality during extended follow-up of median 78 months. These findings were consistent in both trial populations, among patients with age below or above the median, in both genders, among never and ever smokers and among patients with baseline serum folate level below or above the median. However, hazard ratios for folic acid plus vitamin B12 treatment *vs* no such treatment were higher among individuals with the TT genotype than among those with the CC or CT genotypes of the methylenetetrahydrofolate reductase 677C→T polymorphism.

Vitamin B6 treatment led to a 10-fold increase in plasma levels of pyridoxal 5' phosphate in both trial populations, but was not associated with outcomes during in-trial follow-up in the WENBIT study population, or with any outcomes during in-trial or extended follow-up of the combined NORVIT-WENBIT study population.

## Discussion and conclusions

Our findings with respect to cardiovascular outcomes are consistent with the null effects of homocysteine-lowering B vitamin treatment demonstrated in large randomized controlled trials to date. The increased risk of cardiovascular outcomes by folic acid plus vitamin B12 among patients with baseline hyperhomocysteinemia was contrary to what would be expected if homocysteine has a causal role in cardiovascular disease progression. Thus, B vitamins to lower homocysteine should not be recommended for patients with cardiovascular disease.

The increased cancer incidence and cancer mortality during extended follow-up observed in the groups who received folic acid plus vitamin B12 for median 39 months may be explained by the so-called acceleration phenomenon; that this treatment influenced growth in cancers that were silent at baseline or during trials, leading to excess subsequent clinical surfacing and diagnosis during extended follow-up. However, reports on cancer outcomes from other completed homocysteine-lowering B vitamin treatment trials to date do not support our findings, and our results need confirmation in other populations.

# List of publications

I M. Ebbing, Ø. Bleie, P. M. Ueland, J. E. Nordrehaug, D. W. Nilsen, S. E. Vollset, H. Refsum, E. K. Pedersen and O. Nygård. Mortality and cardiovascular events in patients treated with homocysteine-lowering B vitamins after coronary angiography: a randomized controlled trial. JAMA. 2008 August 20;300(7):795-804.

II M. Ebbing, K. H. Bønaa, E. Arnesen, P. M. Ueland, J. E. Nordrehaug, K. Rasmussen, I. Njølstad, D. W. Nilsen, H. Refsum, A. Tverdal, S. E. Vollset, H. Schirmer, Ø. Bleie, T. Steigen, Ø. Midttun, Å. Fredriksen, E. K. Pedersen and O. Nygård. Combined analyses and extended follow-up of two randomized controlled homocysteine-lowering B-vitamin trials. J Intern Med. 2010. August 4; doi:10.1111/j.1365-2796.2010.02259.x

III M. Ebbing, K. H. Bønaa, O. Nygård, E. Arnesen, P. M. Ueland, J. E. Nordrehaug, K. Rasmussen, I. Njølstad, H. Refsum, D. W. Nilsen, A. Tverdal, K. Meyer and S. E. Vollset. Cancer incidence and mortality after treatment with folic acid and vitamin B12. JAMA. 2009 November 18;302(19):2119-26.

# Abbreviations

| | |
|---|---|
| ACE | angiotensin-converting enzyme |
| AdoHcy | S-adenosylhomocysteine |
| AdoMet | S-adenosylmethionine |
| ARB | angiotensin receptor blocker |
| CABG | coronary artery bypass graft surgery |
| CAD | coronary artery disease |
| CI | confidence interval |
| CRP | C-reactive protein |
| CVD | cardiovascular disease |
| eGFR | estimated glomerular filtration rate |
| FA | folic acid |
| HDL | high-density lipoprotein |
| HR | hazard ratio |
| IHD | ischemic heart disease |
| IQR | interquartile range |
| LDL | low-density lipoprotein |
| LVEF | left ventricular ejection fraction |
| MI | myocardial infarction |
| MTHFR | methylenetetrahydrofolate reductase |

| | |
|---|---|
| NORVIT | Norwegian Vitamin Trial |
| p | probability |
| PCI | percutaneous coronary intervention |
| PLP | pyridoxal 5’ phosphate |
| RCT | randomized controlled trial |
| SD | standard deviation |
| SNP | single-nucleotide polymorphism |
| tHcy | total homocysteine |
| THF | tetrahydrofolate |
| TIA | transient ischemic attack |
| WENBIT | Western Norway B Vitamin Intervention Trial |

## Definitions

| | |
|---|---|
| Cardiovascular disease | Pathological conditions involving the cardiovascular system, including the heart, the blood vessels or the pericardium.(2) |
| Clinical trial | Any form of planned experiment which involves patients and is designed to elucidate the most appropriate treatment of future patients with a given medical condition.(3) |
| Confounding | The distortion of a measure of the effect of an exposure on an outcome due to the association of the exposure with other factors that influence the occurrence of the outcome. Confounding occurs when all or part of the apparent association between the exposure and outcome is in fact accounted for by other variables that affect the outcome and are not themselves affected by exposure.(4) |
| Coronary artery disease | Pathological processes of coronary arteries that may derive from a congenital abnormality, atherosclerotic, or non-atherosclerotic cause.(2) In the current dissertation, this term is used about the atherosclerotic disease. |
| Effect modification | Variation in the selected effect measure for the factor under study across levels of another factor (the modifier).(4) |

| | |
|---|---|
| Folate | Naturally occurring B vitamin, including 5-methyltetrahydrofolate prevailing in serum/plasma.(5) |
| Folic acid | Pteroylmonoglutamate, the synthetic fully oxidized form of folate used in fortified foods and vitamin supplements.(5) |
| Fortification | The deliberate addition of specific nutrient to foods as a means of providing the population with an increased level of intake. Generally synonymous with enrichment, supplementation, and restoration; in the USA enrichment is used to mean the addition to foods of nutrients that they do not normally contain, while fortification is the restoration of nutrients lost in processing.(6) |
| Ischemic heart disease | A disorder of cardiac function caused by insufficient blood flow to the muscle tissue of the heart. The decreased blood flow may be due to narrowing of the coronary arteries (coronary artery disease), to obstruction by a thrombus (coronary thrombosis), or less commonly, to diffuse narrowing of arterioles and other small vessels within the heart.(2) |
| Risk (bio)marker | A surrogate for an important biological process or (sub)clinical disease. The risk (bio)marker itself (as opposed to the process it represents) generally makes a poor target for therapy.(7) |
| Risk factor | An aspect of personal behavior or lifestyle, environmental exposure, or inborn or inherited |

| | |
|---|---|
| | characteristic, which, on the basis of epidemiologic evidence, is known to be associated with a health-related condition considered important to prevent. (2) |
| Vitamins | Organic substances that are required in small amounts for maintenance and growth, but which cannot be manufactured by the human body.(2) |

# 1. Introduction

## 1.1 Cardiovascular disease and cancer epidemiology

Worldwide, cardiovascular disease (CVD) is the leading cause of death. In 2004, an estimated 17.1 million people died from CVD, representing 29% of all global deaths. Of these, an estimated 7.2 million died from coronary artery disease (CAD) and 5.7 million from stroke.(8) Cancer is another leading cause of death, currently accounting for 13% of all global deaths, and being the second largest cause in most developed countries. In Norway, cardiovascular disease and cancer accounted for approximately 35% and 25% of all deaths, respectively, in 2007.(9)

## 1.2 Risk factors for coronary artery disease and cancer

A risk factor is generally defined as "an aspect of personal behavior or lifestyle, environmental exposure, or inborn or inherited characteristic, which, on the basis of epidemiologic evidence, is known to be associated with a health-related condition considered important to prevent".(2) When we refer to something as a "risk factor", we are implying that it plays an etiologic or causal role in the development of disease.(7) Whereas modifiable risk factors are subject to intervention, non-modifiable risk factors such as age, gender and other genetically determined characteristics are not.

The Framingham risk score is based on data from a cohort of white people aged 30-74 years, free of CAD, drawn from a free-living population of a suburb west of Boston, Massachusetts, US.(10) The risk factors are age, gender, total cholesterol, high-density lipoprotein (HDL) cholesterol, blood pressure, diabetes mellitus and current smoking. This score predicts a first coronary event (angina pectoris, coronary stenosis, myocardial infarction (MI), and coronary death), and has been found to be well calibrated for use in populations from the United States, Australia and New

Zealand.(11) The Systematic Coronary Risk Evaluation (SCORE) algorithm based on data from large European cohorts, was developed for clinical use to identify individuals in European populations at high risk of dying from CVD.(12,13) The SCORE variables include age, gender, total cholesterol, systolic blood pressure and current smoking. The SCORE has been found to overestimate the risk of fatal CVD in Norway. Therefore, a Norwegian score, NORRISK has been developed, based on more recent data from Norwegian cohorts and Statistics Norway.(14) NORRISK is currently recommended for individual risk assessment for primary prevention of CVD among Norwegians.(15)

Once people have been diagnosed with CVD, the aim of secondary prevention is to control the widely accepted modifiable risk factors by life-style and medical interventions.(13,16)

Common risk factors for cancer are smoking (active or passive), high alcohol consumption, overweight and obesity, physical inactivity, infection with certain micro-organisms, immunosuppressive treatment and family history of cancer.(17) It has been estimated that half of all cancer is preventable.(18) However, risk scores of cancer have not yet been developed.

## 1.3 Biomarkers of cardiovascular risk

A risk marker or biomarker of risk can be defined as a surrogate for an important biological process or subclinical disease. The risk (bio)marker itself (as opposed to the process it represents) generally makes a poor target for therapy. On the other hand, studying their potential role may improve knowledge of disease mechanisms.(7)

Emerging markers of cardiovascular risk have been identified by advances in laboratory medicine and imaging, and quite a few are made widely available for clinicians over the past 10 to 15 years.(19) However, the clinical relevance of these markers has been limited, as judged by their ability to improve risk stratification

performed by conventional risk scores.(20) Also, there is the question of how investigations of possible risk biomarkers should be performed.(21-23)

Among the most extensively examined biochemical markers for cardiovascular risk are high sensitive C-reactive protein (CRP), lipoprotein(a) and homocysteine.(19,24)

## 1.4 Homocysteine

Homocysteine is a sulfur-containing amino acid not found in foods that is produced from the metabolism of the essential amino acid methionine. It is a key intermediate in the process of generating methyl (CH3), or one-carbon, units for transmethylation reactions that are fundamental to all life forms. Adequate intake of methyl group sources (dietary choline, betaine, serine and methionine), and of coenzymes in one-carbon metabolism (folate, vitamins B12 [cobalamin], B6 [pyridoxal 5' phosphate, PLP] and B2 [riboflavin]), is necessary to ensure sufficient supply of methyl groups.(25)

The homocysteine metabolism is illustrated in Figure 1 (to the right). Methionine is adenosylated to form S-adenosylmethionine (AdoMet), which is used as a universal methyl donor, yielding S-adenosylhomocysteine (AdoHcy) as a side product. AdoHcy then undergoes hydrolysis to form homocysteine and adenosine. In most cells, homocysteine can be remethylated to methionine via the transfer of a methyl group from 5-methyl-tetrahydrofolate (5-methyl-THF). In hepatic and renal cells, homocysteine can alternatively be remethylated by the transfer of a methyl group from betaine. Ultimately, homocysteine can be irreversibly combined with serine to form cystathionine, which is further converted to cysteine by transsulfuration reactions. Abnormalities in any of the steps in these metabolic pathways may result in pathologically elevated homocysteine levels.(25)

Intracellular homocysteine concentration is kept low through remethylation, catabolism and export. In plasma a small (≤1%) amount of homocysteine is found in the reduced, non-protein-bound form, and the remainder in the oxidized forms, of

which 30% non-protein-bound, and 70% protein-bound. The sum of all homocysteine forms in plasma is denoted total homocysteine (tHcy).(26) The non-protein-bound homocysteine may be filtered by the renal glomeruli, but only a small fraction (≈1%) of the filtered load is subsequently excreted in the urine.(25)

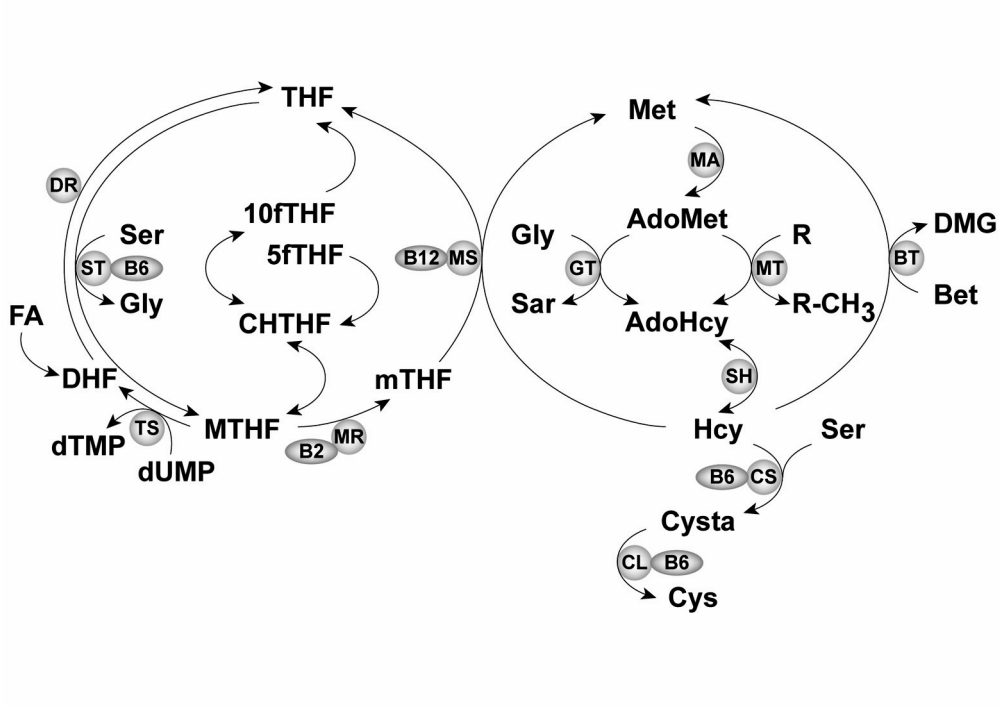


**Figure 1. The homocysteine and folate metabolism**

10fTHF, 10-formyltetrahydrofolate; 5fTHF,5-formyltetrahydrofolate; AdoHcy, S-adenosylhomocysteine; AdoMet, S-adenosylmethionine; B12, vitamin B12 (cobalamin); B2, vitamin B2 (riboflavin); B6, vitamin B6 (pyridoxal 5' phosphate); Bet, betaine; BT, betaine-homocysteine methyltransferase; CHTHF, methenyl tetrahydrofolate; CL, cystathionine gamma-lyase; CS, cystathionine beta-synthase; Cys, cysteine; Cysta, cystathionine; DHF, dihydrofolate; DMG, dimethylglycine; DR, dihydrofolate reductase; dTMP, deoxythymidine monophosphate; dUMP, deoxyuridine monophosphate; FA, folic acid; Gly, glycine; GT, glycine N-methyltransferase; Hcy, homocysteine; MA, methionine adenosyltransferase; Met, methionine; MR, 5,10-methylenetetrahydrofolate reductase (MTHFR); MS, methionine synthase; MT, methyltransferase; MTHF, 5,10-methylene-tetrahydrofolate (5,10-methylene-THF); mTHF, 5-methyltetrahydrofolate (5-methyl-THF); R, methyl acceptor; R-CH3, methylated molecule; Sar, sarcosine; Ser, serine; SH, S-adenosylhomocysteine hydrolase; ST, serine hydroxymethyltransferase; THF, tetrahydrofolate; TS, thymidylate synthase.
Modified from (27).

## 1.5 Folate and folic acid

Folate is the term used to describe a group of compounds derived from tetrahydrofolate (THF) which is a B vitamin mainly present in green leafy vegetables such as asparagus, spinach and broccoli, in legumes, whole grains and citrus fruits.(28,29) Naturally occurring folates predominantly exist as the reduced derivative 5-methyl-THF, which also is the main (>90%) circulating form of folate.(30)

Folic acid (pteroylmonoglutamate) is the synthetic and fully oxidized form of folate used in fortified foods and vitamin supplements.(31) The bioavailability of folic acid is probably higher than that of natural occurring folates.(32-36) Folic acid is readily transported though the intestinal brush border, and is reduced to THF by dihydrofolate reductase in the liver, before it enters the one-carbon metabolism within the cells.(37) However, due to the limited capacity of dihydrofolate reductase,(37) it can also be found as unmetabolized folic acid in the circulation.(38-41)

The folate metabolism is illustrated in Figure 1 (to the left). Intracellular folates function as a family of coenzymes that carry and activate methyl units, which are essential for DNA biosynthesis and methylation reactions. In DNA biosynthesis, the folate intermediate, 5,10-methylene-THF, serves as a methyl donor to convert deoxyuridine monophosphate into the DNA precursor deoxythymidine monophosphate. In methylation reactions, 5-methyl-THF acts as a substrate for the conversion of homocysteine into methionine catalyzed by methionine synthase (see above), and thus for the synthesis of the universal methyl group donor AdoMet.(42)

## 1.6 Vitamins B12, B6 and B2 in the one-carbon metabolism

Vitamin B12 is the coenzyme for methionine synthase in the remethylation of homocysteine to methionine. Vitamin B6 is the coenzyme for cystathionine beta-

synthase and for cystathionine gamma-lyase in the transsulfuration of homocysteine, in addition to being involved in a wide range of other metabolic pathways.(43,44) Vitamin B2 is the coenzyme for methylenetetrahydrofolate reductase (MTHFR) catalyzing the conversion of 5,10-methylene-THF to 5-methyl-THF.(45)

## 1.7 The methyltenetrahydrofolate reductase 677C→T polymorphism

Levels of B vitamins and homocysteine in the circulation are in part genetically determined. A common mutation in the gene encoding for MTHFR is the C to T substitution at nucleotide 677 (677C→T), which results in the amino acid change from alanine to valine in the catalytic domain of the protein. This creates a thermo labile enzyme with reduced catalytic activity.(46) People with the TT genotype have lower levels of serum/plasma folate and higher levels of plasma tHcy, especially in conditions with low serum/plasma folate.(45,47,48) Thus, the presence or absence of the T allele can be considered a random allocation – so-called Mendelian randomization (49) – into groups with life-long differences in plasma tHcy levels.

The prevalence of the TT genotype varies widely between regions and ethnic groups.(46) In Norway, the frequency of the T allele is approximately 28%, and the prevalence of TT homozygotes approximately 8% based on a large study of the general population.(50)

## 1.8 Homocysteine and cardiovascular disease

Homocysteine was first considered as pro-atherogenic (51) after the demonstration of vascular occlusive disease in autopsies of young adults with homocystinuria, an inborn error of metabolism in which cystathionine beta-synthase is deficient.(52)

Observational studies during the nineteen eighties and nineties demonstrated that circulating tHcy is associated with CVD.(53) This research was facilitated by the development of analysis methods of tHcy in plasma.(54) In cohort studies from

Norway, tHcy was an independent predictor of MI in the general population,(55) and a strong predictor of all-cause mortality in patients with angiographically confirmed CAD.(56)

In experimental settings, elevated levels of circulating homocysteine have been shown to induce endothelial dysfunction and injury, and activation of circulating platelets and leucocytes.(57)

Also, two meta-analyses of studies of CVD incidence across the MTHFR 677 genotypes up to 2001 supported that homocysteine may be causally related to CVD.(47,48)

## 1.9 Homocysteine-lowering B vitamin trials

Circulating B vitamin levels, particularly of folate and cobalamin, are inversely related to tHcy levels,(58,59) and tHcy can easily be lowered by oral administration of these B vitamins. Based on the findings of observational and experimental studies indicating that homocysteine may be causally related to CVD, there was a strong demand for clinical studies to assess the effect of such homocysteine-lowering treatment.(60-63) Folic acid typically lowers tHcy by 25%, and synthetic vitamin B12 (cyanocobalamin) additionally lowers tHcy by up to 7%.(53) These substances are affordable and were considered safe to be used in pharmacological doses to lower tHcy in clinical settings. Thus, during the late nineteen nineties a series of randomized controlled trials (RCTs) using folic acid alone or in combination with vitamin B12 were initiated in patients with cardiovascular and chronic kidney disease.(64) Table A1 in Appendix I shows characteristics of 11 large (each including more than 1000 participants) completed homocysteine-lowering RCTs.

## 1.10 Folate, folic acid and cancer

Most observational studies have reported inverse associations between folate intake or plasma/serum folate and risk of colorectal cancer.(65-68) This has led to the

hypothesis that folate prevents cancer. However, associations of folate intake or levels have been inconsistent or absent for prostate,(69) lung (70,71) and breast cancer.(72-75) The proposed mechanisms behind folate prevention of cancer are that adequate folate supply ensures sufficient nucleotide synthesis and thereby genome stability, and supports proper global DNA methylation.(76,77)

On the other hand, once cellular transformation has occurred and a proliferating neoplasm is established, folate becomes essential for tumor growth. Premalignant and malignant cells often have a much faster rate of replication (and therefore DNA synthesis) than their normal counterparts, hence abundant folate is thought to accelerate their growth.(77) Based on the ground-breaking observation that administration of folic acid to children with acute leukemia led to a rapid worsening of the disease process, antifolate drugs such as aminopterin and methotrexate have been used in cancer treatment since the late nineteen forties.(78) In line with the observed “acceleration-phenomenon”,(79) findings from experimental,(80-83) epidemiological,(84) and clinical (85) studies have also led to the question whether folic acid administered through fortified foods and dietary vitamin supplements may enhance growth of established cancer.(76,86)

## 1.11 Folic acid food fortification and supplementation

In 1998, the US (87) and Canada (88) implemented mandatory folic acid fortification of flour and grain products to increase folate status in women of childbearing age in order to reduce the risk of neural-tube birth defects. There was also a hope that this public health intervention would reduce cardiovascular morbidity and mortality due to the homocysteine-lowering effect.(60,89) By 2009, 52 other countries worldwide have implemented mandatory folic acid fortification,(90,91) and the UK Food Standards Agency recently restated its position that adding folic acid to flour should be mandatory.(92) In addition, several countries currently permit voluntary folic acid fortification of foods such as breakfast cereals and fat spreads.(93,94)

In the North American population, fortification has resulted in a substantial increase in circulating folate (95-100) and unmetabolized folic acid (40) concentrations.

Two recent studies reported that 34.5% of the adult US population take dietary supplements containing folic acid, and that 2.7% of all and 5% of those older than 50 years consume more than the tolerable upper level of folic acid (1 mg per day) through mandatory fortified cereal grain products combined with ready-to-eat cereals and/or dietary supplements.(100,101)

In Norway there was no folic acid fortification of foods until 2007. Since then, small amounts of folic acid (20 µg per 100 kckal) may be added to foodstuffs after special permission from the Norwegian Food Safety Authority.(102) Presently, only a few products (cookies baked with fortified flour, energy bars and vitamin drinks) containing folic acid are marketed.(103)

Norwegian health authorities advice women to consume 0.4 mg per day of supplemental folic acid in addition to dietary folate when planning to get pregnant, and during the first trimester of pregnancy.(104) In 2007, 26.2% of birth giving mothers reported having taken folic acid supplements prior to conception and 60.5% reported having taken such supplements during pregnancy.(105) However, there are no recent studies documenting the use of over-the-counter dietary supplements containing folic acid in the general Norwegian population. The relatively low serum folate levels found among participants of the Hordaland Homocysteine studies, a large cohort of the general adult population, indicate that the consumption was modest during the nineteen nineties.(106,107) Also, the content of folic acid in supplements in Norway is low; at most 0.2 mg per recommended daily dose.(108)

# 2. Aims of the present study

The overall aim of the present dissertation was to investigate the clinical effects of B vitamin treatment in patients with established ischemic heart disease (IHD).

The specific aims were to

1. assess the effect of B vitamin treatment on cardiovascular morbidity and all-cause mortality in the Western Norway B Vitamin Intervention Trial (Paper I)
2. assess the effect of B vitamin treatment on cardiovascular morbidity and mortality in the populations of the Norwegian Vitamin Trial and the Western Norway B Vitamin Intervention Trial combined, and after extended follow-up (Paper II)
3. assess the effect of B vitamin treatment on cancer outcomes and all-cause mortality in the populations of the Norwegian Vitamin Trial and the Western Norway B Vitamin Intervention Trial combined, and after extended follow-up (Paper III)

# 3. Materials and methods

## 3.1 The Western Norway B Vitamin Intervention Trial

### Primary hypothesis

Among patients with CAD or aortic valve stenosis, daily treatment with homocysteine-lowering B vitamins would reduce the risk of serious adverse cardiovascular events (cardiovascular mortality, MI, unstable angina and thromboembolic stroke) with at least 20% during a follow-up of mean 4 years.(109)

### Design

Two-center, randomized, double-blind, placebo-controlled, clinical, secondary prevention study.

### Population

Patients eligible for randomization were men and women aged 18 years or older undergoing coronary angiography for suspected CAD and/or aortic valve stenosis at Haukeland University Hospital or Stavanger University Hospital in Western Norway. Exclusion criteria were inability to follow-up, participation in other trials, known alcohol abuse, serious mental illness or active cancer. All participants provided written informed consent. The consent form is shown in Appendix II.

From April 1999 to April 2004 a total of 3090 patients were included, of whom 2121 (68.6%) were randomized at Haukeland University Hospital and 969 (31.4%) at Stavanger University Hospital.

## Intervention and randomization

Participants were randomly assigned, using a 2 x 2 factorial design, to 1 of 4 groups receiving a daily oral dose of 1 of the following treatments: (1) folic acid (pteroylmonoglutamate) 0.8 mg, plus vitamin B12 (cyanocobalamin), 0.4 mg, and vitamin B6 (pyridoxine), 40 mg; (2) folic acid, 0.8 mg, plus vitamin B12, 0.4 mg; (3) vitamin B6, 40 mg; or (4) placebo. The study medication (Alpharma Inc, Copenhagen, Denmark), was given in a single capsule. For the first 2 weeks after randomization, the groups allocated to folic acid plus vitamin B12 received an extra capsule with a loading dose of 5 mg of folic acid per day, while the other groups received an extra capsule of placebo.

The randomization sequence was generated in blocks of 20 by Alpharma Inc, and study nurses assigned boxes of study capsules to participants in numerical order. The different capsules were indistinguishable by color, weight, or ability to dissolve in water. Participants, study and laboratory personnel, and the steering and end-point committees were unaware of the treatment allocation, and the randomization code was kept at Alpharma Inc until data entry was completed.

Participants were given conventional post-angiography medical treatment, and underwent myocardial revascularization procedures and/or valve surgery at the discretion of the treating physician. They were requested to abstain from taking dietary supplements containing B vitamins.

## Data collection

Demographic, clinical, and routine laboratory data were obtained by study personnel, and heart catheterization with coronary angiography was performed by cardiologists. Participants were scheduled for follow-up visits with interview, clinical examination and blood sampling at 1 month, 1 year and at a final study visit. If unable or unwilling to attend study visits, participants were interviewed by telephone or by letter. Also, participants provided information through self-administered questionnaires. Participants were asked about hospital admissions, and copies of

hospital records were retrieved by mail. The paper forms used in the data collection are shown in Appendix II.

In addition, archives of the hospitals in the West of Norway were searched for information on all participants' hospital admissions, and copies of records on possible events were collected. Data on deaths were obtained from the Cause of Death Registry and on incident cancer from the Cancer Registry in Norway, using the unique 11-digit person number for each participant.

Data were entered into to the computerized study database by trained study personnel, and data checks performed before the database was locked prior to the disclosure of the randomization code.

## Clinical end points

The primary clinical end point was a composite of all-cause death, non-fatal acute MI, acute hospitalization for unstable angina pectoris, and of non-fatal thromboembolic stroke (infarction). Secondary end points were fatal and non-fatal acute MI, acute hospitalization for angina pectoris, stable angina pectoris with angiographically verified progression, myocardial revascularization procedures, and fatal and non-fatal stroke. Incident cases of newly diagnosed cancer, except basal cell cancer, were recorded as a measure of safety. All clinical events were adjudicated by members of the end-points committee.

## Laboratory analyses

Blood samples obtained at baseline and 3 times during follow-up, were collected and processed by study personnel. Routine blood analyses were performed by the hospital laboratories. Blood samples for assessment of B vitamins and tHcy were usually immediately stored at –80°C until analyzed at Bevital AS by microbiological (110,111) and chromatography-mass spectrometry (112,113) methods.

### Organization and approvals

See Appendix III.

## 3.2 The Norwegian Vitamin Trial

### Primary hypothesis

Among patients having undergone an acute MI 1-7 days before inclusion, daily treatment with homocysteine-lowering B vitamins would reduce the risk of serious adverse cardiovascular events (cardiovascular mortality, recurrent MI or stroke) with at least 20% during a follow-up of mean 3.5 years.(114)

### Design

Multi-center, randomized, double-blind, placebo-controlled, clinical, secondary prevention study.

### Population

Patients eligible for randomization were men and women aged 30 to 85 years who had been hospitalized for an acute MI within 7 days before inclusion in one out of 35 hospitals in Norway. Exclusion criteria were the presence of coexisting disease associated with a life expectancy of less than 4 years, prescribed treatment with B vitamins or untreated vitamin B deficiency, or inability to follow the protocol, as judged by the investigator. All participants provided written informed consent. The consent form is shown in Appendix IV.

From December 1998 to March 2002 a total of 3749 patients were recruited, of whom 1902 (50.7%) were randomized from hospitals in the South-Eastern, 824 (22.0%) in the Western and Central, and 1023 (27.3%) in the Northern part of Norway.

## Intervention and randomization

The B vitamin intervention and the randomization procedure were identical as in WENBIT, see section 3.1.

Participants were given standard post-MI medical treatment, and underwent myocardial revascularization procedures at the discretion of the treating physician. They were requested to abstain from taking supplements containing B vitamins.

## Data collection

Demographic, clinical, and routine laboratory data were obtained by the investigators and study nurses at the 35 study centers. Participants were scheduled for follow-up visits with interview, clinical examination and blood sampling 1-2 months after randomization and at the end of the intervention. If unable or unwilling to attend study visits, participants were interviewed by telephone or by letter. Also, participants provided information through self-administered questionnaires. The paper forms used in the data collection are shown in Appendix IV.

Data on possible events were collected at the hospitals by study nurses, who filled in forms and submitted relevant discharge letters and medical record notes. For deaths that occurred outside the hospital, a copy of the death certificate was retrieved from the Cause of Death Registry. If deemed necessary by the end-points committee, additional information on the death was requested from the physician in charge.

Data were entered into to the computerized study database by trained study personnel, and data checks performed before the database was locked prior to the disclosure of the randomization code. Later, final data on incident cancer were obtained from the Cancer Registry in Norway, using the unique 11-digit person number for each participant.

### Clinical end points

The primary clinical end point was a composite of coronary death, non-fatal acute MI, and of fatal and non-fatal stroke. Secondary end points were acute MI, hospitalization due to unstable angina pectoris, myocardial revascularization procedures, stroke and all-cause death. Incident cases of newly diagnosed cancer, except basal cell cancer, were recorded as a measure of safety. All end points were adjudicated by members of the end-points committee.

### Laboratory analyses

Blood samples obtained at baseline and 2 times during follow-up, were collected and processed by laboratory personnel at the study centers. Routine blood analyses were performed by the hospital laboratories. Blood samples for assessment of B vitamins and tHcy were sent within 48 hours by mail to the laboratory of Bevital AS and stored at –80°C before analyzed by microbiological (110,111) and chromatography-mass spectrometry (112,113) methods.

### Organization and approvals

See Appendix V.

## 3.3 The NORVIT-WENBIT combined analyses and extended follow-up

### Background and objectives

NORVIT and WENBIT were planned as two separate but very similar trials; with similar patients, identical study design, identical study treatment regimen and doses, with similar follow-up routines and blood sampling procedures, to use the same central laboratory for blood analyses, and to have similar clinical end points. The principal investigators cooperated from the start of the planning of the two trials, the steering committees of both trials had overlapping representation, and there was an

intention to combine the results from the two trials when the separate results had been published. Also, both trials planned to extend the follow-up of the participants after the end of the intervention for the investigation of possible long-term effects.

The data collected during in-trial and post-trial follow-up on the close to seven thousand participants in NORVIT and WENBIT were combined to investigate

a) effects of the B vitamin treatment on incidence of major adverse cardiovascular events (MACE) and of cardiovascular mortality during the trial period and during post-trial follow-up, and whether there were certain subgroups that may benefit or suffer harm from the intervention

b) effects of the B vitamin treatment on risk of developing cancer, dying from cancer and all-cause mortality during the trial period and during post-trial follow-up

## Design

Combined analyses of data from the two RCTs NORVIT and WENBIT, and from post-trial observational follow-up of the trial cohorts through December 31, 2007.

## Population

A total of 6837 individuals who participated in NORVIT or WENBIT were included in the combined analyses.

## Post-trial observational follow-up

NORVIT was terminated in March, 2004, and WENBIT in October, 2005. When the primary results were available, participants were informed by letter that there was no apparent health benefit from the B vitamin intervention, and that such vitamin supplementation was not recommended as secondary prevention for patients with IHD. These letters are shown in Appendix VI. The post-trial follow-up did not imply any further personal contact or patients contributions.

## Data collection

Data from NORVIT and WENBIT were standardized and merged into one file containing demographic, clinical and laboratory data.

Data on incident cancer and on cause-specific mortality by December 31, 2007, were obtained by linkage of the unique personal identification numbers to the Cancer Registry of Norway and to the Cause of Death Registry at Statistics Norway in April 2009, when complete data were available.

## Clinical end points

The primary and secondary end points in the NORVIT-WENBIT combined analyses and extended follow-up are listed in Table 1 below.

**Table 1. End points in the NORVIT-WENBIT combined analyses and extended follow-up**

| Term | Definition |
|---|---|
| Primary cardiovascular end point during in-trial follow-up | A composite of major adverse cardiovascular events defined as cardiovascular death, non-fatal acute MI, except procedure related MIs, and of non-fatal stroke. |
| Secondary cardiovascular end points during in-trial follow-up | Fatal and non-fatal acute MI, including procedure related MIs. |
| | Fatal and non-fatal stroke. |
| | Acute hospitalization for angina pectoris. |
| | Myocardial revascularization procedures, except PCI and CABG performed within 6 months after index MI in NORVIT, or procedures determined by baseline coronary angiography in WENBIT. |
| Cardiovascular end point during extended follow-up | Cardiovascular death. |
| Primary cancer end point during extended follow-up | Incident new cancer registered in the Cancer Registry of Norway, except non-melanoma skin cancers. |
| | Cancer death. |
| Secondary cancer end point during extended follow-up | Incident new cancer subtypes registered in the Cancer Registry of Norway, except non-melanoma skin cancers. |
| | Cancer subtype death. |
| Cardiovascular death | Death with underlying cause of death coded as *International Statistical Classification of Diseases, 10$^{th}$ Revision*, codes I00 to I99, or code R96 by the Cause of Death Registry. |
| Cancer death | Death with underlying cause of death coded as *International Statistical Classification of Diseases, 10$^{th}$ Revision*, codes C00 to C97by the Cause of Death Registry. |
| Acute MI | NORVIT: As specified in (115), the online supplementary appendix. |
| | WENBIT: Following the definition of acute MI published by The Joint European Society of Cardiology/American College of Cardiology Committee in 2000.(116) |
| Stroke | NORVIT: As specified in (115), the online supplementary appendix. |
| | WENBIT: Following the definition of stroke published by the American College of Cardiology Committee in 2001.(117) |
| Cancer | Incident cancer registered in the Cancer Registry or Norway, excluding non-melanoma skin cancers. |

CABG, coronary artery bypass graft surgery; MI, myocardial infarction; PCI, percutaneous coronary intervention.

## Further laboratory analyses

Plasma cotinine, a biomarker for tobacco exposure,(118) was determined by tandem mass spectrometry.(119) Genotyping of the MTHFR gene (NCBI Entrez Gene 4524) 677C→T polymorphism, was performed using MALDI-TOF mass spectrometry.(120)

### Organization and approvals

The protocol for the NORVIT-WENBIT combined analyses and extended follow-up was approved by both steering committees and by the Regional Committee for Medical and Health Research Ethics, the Data Inspectorate, and the Norwegian Directorate of Health. The NORVIT-WENBIT study is authorized to obtain data from national health registries and hospitals extending to the end of 2014, and is registered with clinicaltrials.gov, Identifier: NCT00671346.

## 3.4 Statistical methods

Differences between groups were tested with Chi-squared test for categorical variables and parametric or non-parametric methods for continuous variables, as appropriate.(121) Pearson partial correlations were used to explore the relationship between baseline levels of plasma tHcy and serum or plasma B vitamins or serum creatinine, after logarithmical transformation of the skewed variables, and with adjustment for possible confounders (paper II).(121,122)

The 2 x 2 factorial design allowed separate assessments of effects from the folic acid plus vitamin B12 and the vitamin B6 interventions.(3,123) The main analyses were comparison of treatment effect between participants allocated to folic acid plus vitamin B12 (folic acid groups) *vs* no such treatment (non-folic acid groups) and between participants allocated to vitamin B6 (vitamin B6 groups) *vs* no such treatment (non-vitamin B6 groups). Comparisons were made according to the intention to treat principle, as well as according to the per protocol principle.(3)

We constructed survival curves using the Kaplan-Meier method, and analyzed the differences in survival between groups by the log-rank test. We estimated hazard ratios (HRs) and 95% confidence intervals (CIs) using Cox proportional hazard regression.(121) The Cox regression analyses were performed unstratified and unadjusted (paper I), or stratified for trial, unadjusted as well as adjusted for possible confounders (papers II and III). In the latter analyses, proportional hazards

assumptions were tested by Stata's estat phtest procedure based on Schoenfeld residuals,(124) and evidence of non-proportionality was not found.

Survival time was calculated for each participant from the date of randomization to the date of the first event included in any of the end points, or to the end of the intervention in NORVIT or WENBIT, or to December 31, 2007. For fatal events, the date of death was used to calculate survival times. Participants who declined post-trial follow-up (papers II and III) were censored at the date of their final study visit. Participants who emigrated were censored at the date of last contact (in-trial) or the date of emigration in the National Registry.

A two-sided statistical significance level of 0.05 was applied throughout, and the reported p values were not adjusted for multiple comparisons. We used the statistical software packages SPSS version 15.0 (SPSS Inc., Chicago, Illinois), S-PLUS, version 7.0-8.0 (TIBCO Software Inc, Palo Alto, California) (paper I and III), Stata version 10 (StataCorp LP, College Station, Texas) (paper II and III) and SAS version 9.2 (SAS Institute, Cary, North Carolina) (Paper III).

# 4. Summary of results

## 4.1 WENBIT population and primary outcomes (Paper I)

Mean (SD) age of the participants was 61.6 (10.0) years, ranging from 28 to 87 years, and the majority (n = 2458, 79.5%) were men. The reason for referral to baseline angiography was stable angina pectoris (n = 2585, 83.7%), acute coronary syndromes (n = 461, 14.9%) and aortic valve stenosis (n = 44, 1.4%). Most participants had 2- or 3-vessel disease (n = 1831, 59.3%). A total of 329 (10.8%) of participants reported regular use of over-the-counter supplements containing B vitamins prior to inclusion. The randomization procedure resulted in well-balanced intervention groups with no differences in baseline demographics or clinical characteristics. Table 2 shows baseline participant characteristics and treatment regimens following baseline angiography in WENBIT by gender.

A total of 2532 (81.9% of all) took 50 to 100% of their study medication throughout follow-up. Mean (SD) plasma tHcy level was lowered by 30%, from 10.8 (4.5) µmol/L at baseline to 7.6 (2.2) µmol/L after 1 year of follow-up in the groups receiving folic acid plus vitamin B12 ($p < 0.001$). Plasma tHcy remained unaltered in the groups receiving vitamin B6 alone or placebo.

During a median 38 months of follow-up, 422 participants (13.7% of all) experienced an event in the composite primary end point of death, acute MI, unstable angina pectoris, or thromboembolic stroke. There were no statistically significant differences between the folic acid and non-folic acid groups, or between the vitamin B6 and non-vitamin B6 groups in the survival analyses with respect to the primary end point.

**Table 2. Baseline characteristics in men and women in WENBIT**

| Characteristic | Men (n = 2458) | | Women (n = 632) | | P Value |
|---|---|---|---|---|---|
| Age, mean (SD), y | 61.0 | (9.8) | 64.0 | (10.3) | <0.001 |
| Age >75 y, No. (%) | 197 | (8.0) | 101 | (16.0) | <0.001 |
| Body-mass index, mean (SD)[a] | 27.0 | (3.5) | 26.7 | (4.5) | 0.18 |
| Systolic blood pressure, mean (SD), mm Hg | 141 | (20) | 140 | (21) | 0.53 |
| Diastolic blood pressure, mean (SD), mm Hg | 81 | (11) | 78 | (11) | <0.001 |
| LVEF <50%, No. (%) | 305 | (12.4) | 44 | (7.0) | <0.001 |
| Hemoglobin, mean (SD), g/dL | 14.6 | (1.1) | 13.4 | (1.1) | <0.001 |
| Creatinine, mean (SD), µmol/L | 94 | (16) | 81 | (15) | <0.001 |
| eGFR <60 mL/min/1.73m$^2$, No. (%) | 198 | (8.1) | 162 | (25.6) | <0.001 |
| Total cholesterol, mean (SD), mmol/L | 5.0 | (1.2) | 5.3 | (1.2) | <0.001 |
| HDL cholesterol, mean (SD), mmol/L | 1.2 | (0.3) | 1.4 | (0.4) | <0.001 |
| LDL cholesterol, mean (SD), mmol/L | 3.1 | (1.0) | 3.2 | (1.1) | 0.002 |
| CRP, median (IQR), mg/L | 1.9 | (3.3) | 2.1 | (3.8) | 0.02 |
| Cardiovascular history and risk factors, No. (%) | | | | | |
| MI | 1064 | (43.3) | 216 | (34.2) | <0.001 |
| PCI | 528 | (21.5) | 109 | (17.2) | 0.02 |
| CABG | 356 | (14.5) | 59 | (9.3) | 0.001 |
| Carotid-artery stenosis, TIA or stroke | 150 | (6.1) | 42 | (6.6) | 0.61 |
| Other peripheral-artery disease | 220 | (9.0) | 55 | (8.7) | 0.85 |
| Family history of premature CAD | 765 | (31.1) | 262 | (41.5) | <0.001 |
| History of hypercholesterolemia[b] | 1403 | (57.1) | 434 | (68.7) | <0.001 |
| Hypertension[c] | 1104 | (44.9) | 314 | (49.7) | 0.03 |
| Diabetes mellitus[d] | 279 | (11.4) | 77 | (12.2) | 0.56 |
| Ex smoker[e] | 1287 | (52.4) | 193 | (30.6) | <0.001 |
| Current smoker | 703 | (28.6) | 172 | (27.2) | 0.11 |
| CAD at baseline angiography, No. (%) | | | | | |
| No- or non-significant coronary stenosis[f] | 221 | (9.0) | 118 | (18.7) | <0.001 |
| 1-vessel disease | 699 | (28.4) | 221 | (35.0) | 0.001 |
| 2-vessel disease | 664 | (27.0) | 162 | (25.6) | 0.48 |
| 3-vessel disease | 874 | (35.6) | 131 | (20.7) | <0.001 |
| Medication following randomization, No. (%) | | | | | |
| Acetylsalicylic acid | 2229 | (90.7) | 558 | (88.3) | 0.07 |
| Clopidogrel | 622 | (25.3) | 150 | (23.7) | 0.42 |
| Warfarin | 123 | (5.0) | 29 | (4.6) | 0.67 |
| Statins | 2185 | (88.9) | 546 | (86.4) | 0.08 |
| Beta-blockers | 1916 | (77.9) | 500 | (79.1) | 0.53 |
| ACE inhibitors/ARB | 802 | (32.6) | 192 | (30.4) | 0.28 |
| Calcium channel blockers | 537 | (21.8) | 156 | (24.7) | 0.13 |
| Loop-diuretics | 221 | (9.0) | 87 | (13.8) | <0.001 |
| Oral antidiabetics | 156 | (6.3) | 43 | (6.8) | 0.68 |
| Insulin | 82 | (3.3) | 24 | (3.8) | 0.57 |
| Procedures following randomization, No. (%) | | | | | |
| PCI | 1103 | (44.9) | 256 | (40.5) | 0.05 |
| PCI with use of stent(s) | 980 | (39.9) | 228 | (36.1) | 0.08 |
| CABG | 629 | (25.6) | 107 | (16.9) | <0.001 |
| Valve surgery | 75 | (3.1) | 26 | (4.1) | 0.18 |

ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; CABG, coronary artery bypass graft surgery; CAD, coronary artery disease; CRP, C-reactive protein; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; LDL, low-density lipoprotein; LVEF, left ventricular ejection fraction; MI, myocardial infarction; PCI, percutaneous coronary intervention; TIA, transient ischemic attack.

[a]Body-mass index was calculated as weight in kilograms divided by height in meters squared. [b]Untreated total cholesterol values of ≥6.5 mmol/L. [c]Medically treated or started treatment at trial entry. [d]Included diabetes mellitus type 1 or 2. [e]Quit smoking >1 month before trial entry. [f]Normal vessels or plaque(s) with <50% luminal diameter narrowing.

## 4.2 NORVIT-WENBIT population and laboratory findings (Papers II and III)

A total of 6837 individuals were included in the combined analyses, of whom 6261 (98.7%) of participants alive at end of in-trial follow-up were included in the post-trial follow-up (Appendix Figure A1). Mean (SD) age was 62.3 (11.0) years, and 76.5% of participants were men. Median (25-75 percentiles) baseline plasma tHcy was 11.1 (9.1-13.7) μmol/L. Baseline plasma tHcy correlated with serum folate, serum creatinine and serum cobalamin (Table 3).

**Table 3. Pearson partial correlations between baseline total homocysteine, B vitamins and creatinine[a]**

| | tHcy | Folate | Cobalamin | PLP | Creatinine |
|---|---|---|---|---|---|
| **tHcy** | 1 | | | | |
| **Folate** | −0.325[b] | 1 | | | |
| **Cobalamin** | −0.197[b] | 0.160[b] | 1 | | |
| **PLP** | −0.124[b] | 0.386[b] | 0.160[b] | 1 | |
| **Creatinine** | 0.273[b] | −0.029[c] | 0.061[b] | 0.024 | 1 |

PLP, pyridoxal 5' phosphate; tHcy, plasma total homocysteine.
[a]After adjustment for age, gender, MTHFR 677C→T polymorphism, hypertension, obesity (body-mass index ≥30), diabetes mellitus, current smoking, prior myocardial infarction, prior percutaneous coronary intervention, prior coronary artery bypass graft surgery, prior carotid stenosis, transient ischemic attack or stroke, and indication for trial entry. [b]p <0.001. [c]p <0.05.

A total of 1179 (17.3%) of participants had hyperhomocysteinemia (plasma tHcy ≥15 μmol/L), as currently defined.(26) Baseline clinical and laboratory characteristics, risk factor levels and concomitant medication in the combined NORVIT-WENBIT population according to the presence or absence of hyperhomocysteinemia are presented in Table 4.

The frequency of the 677 T allele in the MTHFR gene was 28.9%, and 8.2% of individuals were homozygous for the TT genotype. Among individuals with the TT genotype, baseline median serum folate concentration was lower and plasma tHcy higher than among individuals with the CC or CT genotype (7.3 nmol/L *vs* 8.9 nmol/L; p <0.001, and 13.1 μmol/L *vs* 11.0 μmol/L, p <0.001, respectively).

**Table 4. Baseline characteristics and medication in NORVIT-WENBIT participants with or without hyperhomocysteinemia**

| Characteristic | tHcy ≥15 (n = 1179) | tHcy <15 (n = 5635) | P Value |
|---|---|---|---|
| Included in NORVIT, No. (%) | 883 (74.9) | 2850 (50.6) | <0.001 |
| Included in WENBIT, No. (%) | 296 (25.1) | 2785 (49.4) | <0.001 |
| Age, mean (SD), y | 67.4 (11.5) | 61.3 ±10.5 | <0.001 |
| Male gender, No. (%) | 915 (77.6) | 4293 (76.2) | 0.30 |
| Body-mass index, mean (SD)[a] | 26.1 (3.7) | 26.7 ±3.8 | 0.99 |
| Systolic blood pressure, mean (SD), mm Hg | 132 (22) | 132 ±22 | 0.70 |
| Diastolic blood pressure, mean (SD), mm Hg | 75 (14) | 76 ±13 | <0.001 |
| Total cholesterol, mean (SD), mmol/L | 5.6 (1.4) | 5.4 ±1.2 | 0.001 |
| Creatinine, median (25-75 percentiles), µmol/L | 97 (84-114) | 87 (78-97) | <0.001 |
| tHcy, median (25-75 percentiles), µmol/L | 17.7 (16.1-20.6) | 10.4 (8.8-12.1) | <0.001 |
| Folate, median (25-75 percentiles), µmol/L | 6.5 (4.9-8.9) | 9.3 (6.9-13.5) | <0.001 |
| Cobalamin, median (25-75 percentiles), pmol/L | 306 (239-391) | 360 (280-452) | <0.001 |
| PLP, median (25-75 percentiles), nmol/L | 27 (19-38) | 34 (24-48) | <0.001 |
| MTHFR 677 genotype, No./Total No. (%) | | | |
| CC | 487/1135 (42.9) | 2806/5397 (52.0) | <0.001 |
| CT | 460/1135 (40.5) | 2244/5397 (41.6) | 0.51 |
| TT | 188/1135 (16.6) | 347/5397 (6.4) | <0.001 |
| Vitamin supplements, No. (%)[b] | 265 (22.5) | 1310 (23.2) | 0.57 |
| Risk factors, No./Total No. (%) | | | |
| Hypertension | 495/1167 (42.4) | 1987/5606 (35.4) | <0.001 |
| Obesity[c] | 176/1173 (15.0) | 960/5631 (17.0) | 0.09 |
| Diabetes mellitus[d] | 129/1171 (11.0) | 590/5614 (10.5) | 0.61 |
| Smoking status and cotinine | | | |
| Never smoker, No./Total No. (%) | 328/1174 (27.9) | 1603/5626 (28.5) | 0.70 |
| Ex smoker, No./Total No. (%)[e] | 328/1174 (27.9) | 1875/5626 (33.3) | <0.001 |
| Current smoker, No./Total No. (%) | 518/1174 (44.1) | 2148/5626 (38.2) | <0.001 |
| History of CVD, No/Total No. (%) | | | |
| MI | 373/1163 (32.1) | 1527/5602 (27.3) | 0.001 |
| PCI | 106/1178 (9.0) | 708/5635 (12.6) | 0.001 |
| CABG | 103/1179 (8.7) | 489/5635 (8.7) | 0.95 |
| Carotid artery stenosis, TIA or stroke | 98/1172 (8.4) | 250/5610 (4.5) | <0.001 |
| History of cancer, No. (%)[f] | 69 (5.9) | 228 (4.0) | 0.006 |
| Indication for trial entry, No. (%) | | | |
| Acute MI | 912 (77.4) | 3142 (55.8) | <0.001 |
| Unstable angina | 14 (1.2) | 123 (2.2) | 0.03 |
| Stable angina | 244 (20.7) | 2335 (41.7) | <0.001 |
| Aortic-valve stenosis | 9 (0.8) | 35 (0.6) | 0.58 |
| Concomitant medication, No./Total No. (%) | | | |
| Acetylsalicylic acid | 932/1094 (85.2) | 4926/5462 (90.2) | <0.001 |
| Warfarin | 139/1086 (12.8) | 415/5455 (7.6) | <0.001 |
| Lipid-lowering drugs | 819/1091 (75.1) | 4725/5453 (85.2) | <0.001 |
| Beta-blockers | 940/1094 (85.9) | 4634/5461 (84.9) | 0.37 |
| Calcium antagonists | 180/1086 (16.6) | 812/5447 (14.9) | 0.16 |
| ACE inhibitors/ARBs | 469/1089 (43.1) | 1746/5447 (32.1) | <0.001 |
| Diuretics | 330/1088 (30.3) | 787/5450 (14.4) | <0.001 |

ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; CABG, coronary artery bypass graft surgery; MI, myocardial infarction; MTHFR, methylenetetrahydrofolate reductase; PCI, percutaneous coronary intervention; PLP, pyridoxal 5' phosphate; TIA, transient ischemic attack.

[a]Body-mass index was calculated as weight in kilograms divided by height in meters squared. [b]Daily or often use of vitamin supplements at trial entry. [c]Body-mass index ≥30. [d]Included diabetes mellitus type 1 or 2. [e]Quit smoking >1 month before trial entry. [f]Included any cancer except non-melanoma skin cancer.

Close to 85% of participants took ≥80% of the study-capsules throughout in-trial follow-up. In the folic acid groups, serum folate increased from a median 8.8 to 62.2 mmol/L, p <0.001, and serum cobalamin from a median 352 to 508 pmol/L, p <0.001 during the first 1-2 months of follow-up (Figure 2, Panels A and B). Treatment with folic acid plus vitamin B12 lowered plasma tHcy from a median 11.1 to 8.3 µmol/L (25%) after 1-2 months of follow-up, p <0.001 (Figure 2, Panel C). Among patients with baseline hyperhomocysteinemia, plasma tHcy was lowered from a median 17.7 to 11.2 µmol/L (37%), p <0.001, whereas among patients with no hyperhomocysteinemia, plasma tHcy was lowered from a median 10.4 to 8.0 µmol/L (23%), p <0.001. In the vitamin B6 groups, plasma PLP increased from a median 33.3 to 357.0 nmol/L, p <0.001 (Figure 2, Panel D).

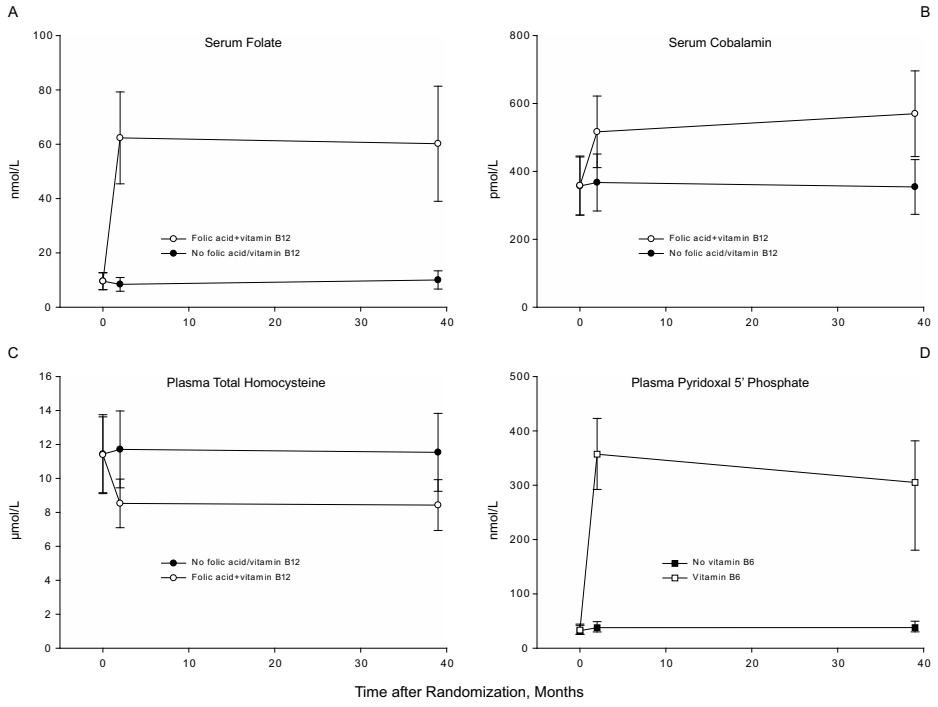


**Figure 2. Circulating levels of B vitamins and total homocysteine during trials.**

Median concentration of B vitamins and total homocysteine in serum or plasma. Error bars represent 25-75 percentiles.

## 4.3 NORVIT-WENBIT cardiovascular outcomes (Paper II)

During a median 39 months of in-trial follow-up, 531 (15.6%) of participants who received folic acid plus vitamin B12 *vs* 503 (14.7%) of those who did not receive such treatment experienced a MACE (HR, 1.07; 95% CI, 0.95-1.21; p = 0.28). In the vitamin B6 groups, a total of 524 (15.4%) of participants experienced a MACE *vs* 510 (14.9%) of participants in the non-vitamin B6 groups (HR, 1.04; 95% CI, 0.92-1.18; p = 0.53). During a median 78 months of extended follow-up, 317 (9.3%) of participants in the folic acid groups *vs* 287 (8.4%) of participants in the non-folic acid groups died from CVD (HR, 1.12; 95% CI, 0.95-1.31; p = 0.18). Long-term cardiovascular mortality was also similar in vitamin B6 groups and non-vitamin B6 groups with 308 (9.0%) *vs* 296 (8.6%) cardiovascular deaths (HR, 1.06; 95% CI, 0.90-1.24; p = 0.51).

There was no evidence of effect modification of folic acid plus vitamin B12 treatment, or of vitamin B6 treatment, by trial, age below or above the median (62.5 years), gender or current smoking. However, in patients with hyperhomocysteinemia, treatment with folic acid plus vitamin B12 was associated with increased risk of in-trial MACE (HR, 1.41; 95% CI, 1.12-1.77), and of long-term cardiovascular mortality (HR, 1.44; 95% CI, 1.11-1.86), p for interaction = 0.01 and 0.03, respectively. We could not demonstrate any effect modification by the MTHFR 677 genotype.

Figure 3 shows the results from the exploratory analyses of associations between plasma tHcy concentrations measured at baseline or at the follow-up visit 1-2 months later, and risk of in-trial MACE and long-term cardiovascular death, among participants assigned to folic acid plus vitamin B12 treatment. Baseline plasma tHcy was a significant predictor of in-trial MACE and long-term cardiovascular death in univariate analyses, but after adjustment for important confounders (age, gender, serum creatinine, hypertension, obesity, diabetes mellitus, current smoking, prior MI, prior PCI, prior CABG, prior carotid stenosis, transient ischemic attack or stroke, and indication for trial entry), baseline plasma tHcy was not associated with outcomes.

Notably, plasma tHcy measured at the follow-up visit after 1-2 months of folic acid plus vitamin B12 treatment, was significantly associated with increased risk of in-trial MACE (HR for every 5-µmol/L increment, 1.31; 95% CI, 1.09-1.56; p = 0.004), but not with long-term cardiovascular death (HR, 1.20; 95% CI, 0.96-1.50; p = 0.11), after adjustment for the aforementioned confounders (Figure 3).

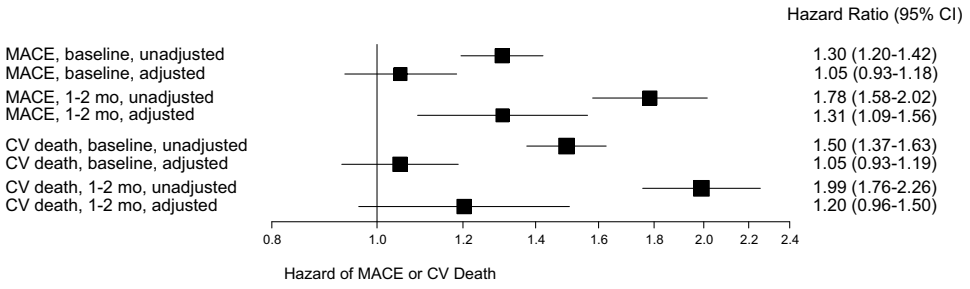


**Figure 3. Plasma total homocysteine as predictor of outcomes in folic acid groups**

CI, confidence interval; CV death, cardiovascular death; MACE, major adverse cardiovascular events. Hazard ratios are shown for every 5-µmol/L increment in plasma tHcy. Squares are proportional to the number of participants included in the analysis. Analyses were restricted to participants in the folic acid groups with plasma tHcy measurements at baseline and at the first follow-up visit which occurred 1-2 months after randomization (n = 3100). For the hazard ratios of MACE, participants who experienced a MACE between the two measurements were excluded from the analysis (n = 109). A total of 77 and 89 participants had missing values for one or several of the confounding covariates used in the adjusted analyses for MACE and CV death, respectively.

## 4.4 NORVIT-WENBIT cancer outcomes (Paper III)

A total of 629 participants (9.2%) were diagnosed with new cancers during (n = 292) or after (n = 337) the trials. Diagnoses were based on histological, cytological, or other diagnostic examinations in 90.5%, 4.9%, and 4.1% of the incident cases, respectively. Three cases of cancer were based on information from death certificates only. A total of 496 participants (7.3%) died during the trials and 525 (8.4%) died during post-trial follow-up. Of the total 1021 deaths through December 31, 2007, 236 (23.1%) were classified as cancer deaths.

After a median 39 months of treatment and an additional 38 months of post-trial observational follow-up, 341 participants (10.0%) who received folic acid plus vitamin B12 *vs* 288 participants (8.4%) who did not receive such treatment were diagnosed with cancer (HR, 1.21; 95% CI, 1.03-1.41; p = 0.02). A total of 136 (4.0%) who received folic acid plus vitamin B12 *vs* 100 (2.9%) who did not receive such treatment died from cancer (HR, 1.38; 95% CI, 1.07-1.79; p = 0.01). A total of 548 patients (16.1%) who received folic acid plus vitamin B12 *vs* 473 (13.8%) who did not receive such treatment died from any cause (HR, 1.18; 95% CI, 1.04-1.33; p = 0.01). Results were mainly driven by increased lung cancer incidence in participants who received folic acid plus vitamin B12. Vitamin B6 treatment was not associated with any significant effects. Figure 4 shows the Kaplan-Meier curves for cancer incidence, cancer mortality and all-cause mortality, and Figure 5 shows forest plots for cancer incidence according to cancer subtypes, for cancer mortality and all-cause mortality across folic acid plus vitamin B12 treatment.

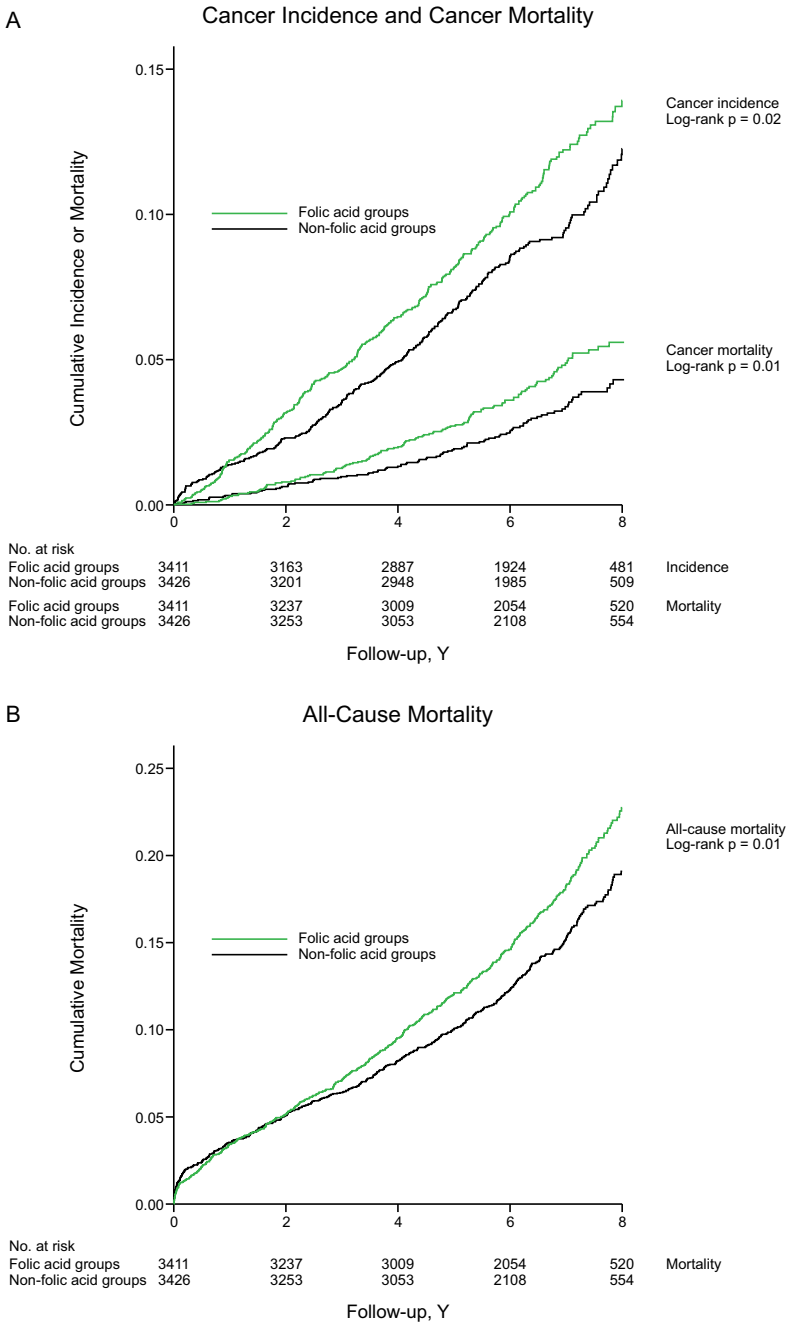


**Figure 4. Kaplan-Meier curves for cancer incidence, cancer mortality and all-cause mortality during extended follow-up for folic acid groups *vs* non-folic acid groups.**

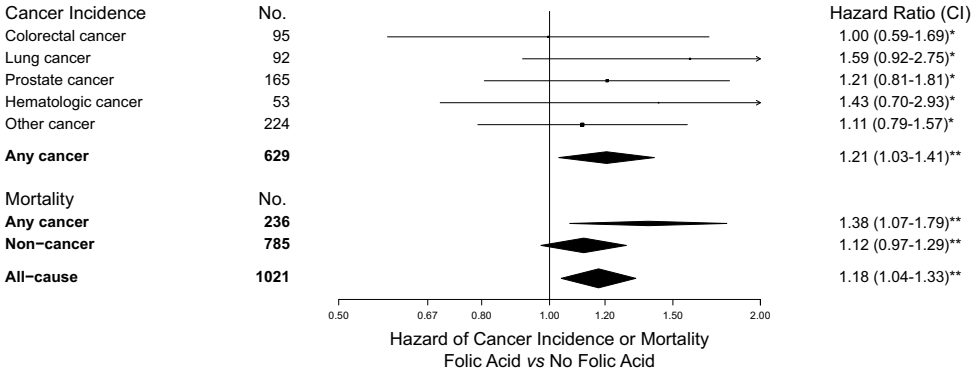


**Figure 5. Hazard ratios for cancer incidence according to cancer subtypes, cancer mortality and all-cause mortality across folic acid plus vitamin B12 treatment through extended follow-up.**

CI, confidence interval. Squares with horizontal lines indicate hazard ratios and the corresponding 99% confidence intervals. Diamonds indicate hazard ratios for total cancer incidence, cancer mortality, non-cancer mortality and all-cause mortality with 95% confidence intervals. *99% confidence intervals. **95% confidence intervals.

Results were consistent in both trial populations, among patients aged younger than or older than the median age, in both genders, among never and ever smokers, and among patients with baseline serum folate levels of less than or more than the median (8.8 mmol/L), (all p for interaction ≥0.06). HRs for folic acid *vs* non-folic acid groups were higher among individuals with TT genotype than among those with CC or CT genotypes of the MTHFR 677C→T polymorphism. For cancer mortality, we observed a statistically significant interaction (p = 0.03) between TT *vs* CC or CT genotypes and folic acid plus vitamin B12.

Table 5 shows the estimated HRs for the primary end points across strata defined by serum folate and serum cobalamin levels measured during study treatment. Participants in the second serum folate quartile (range 8.6-23.9 mmol/L) or in the second cobalamin quartile (range 338-440 pmol/L) had the lowest cancer incidence, cancer mortality and all-cause mortality through extended follow-up, thus quartile 2 was used as the reference category. HRs were statistically significantly higher for subjects in the fourth serum folate quartile (>62.7 mmol/L) as compared to those in

the second folate quartile. There were no such differences across quartiles of serum cobalamin.

**Table 5. Hazard ratios for cancer incidence, cancer mortality and all-cause mortality by serum levels of folate and cobalamin measured during study treatment**

| Serum Level, Quartiles | Total No.[a] | Cancer Incidence | | | Cancer Mortality | | | All-Cause Mortality | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | No. of Events | Hazard Ratio (95% CI) | P Value[b] | No. of Events | Hazard Ratio (95% CI) | P Value[b] | No. of Events | Hazard Ratio (95% CI) | P Value[b] |
| Folate[c] | | | | | | | | | | |
| Quartile 1 | 1592 | 143 | 1.08 (0.85-1.37) | 0.55 | 49 | 1.17 (0.76-1.78) | 0.48 | 222 | 1.33 (1.08-1.64) | 0.007 |
| Quartile 2 | 1592 | 130 | 1 | | 39 | 1 | | 152 | 1 | |
| Quartile 3 | 1592 | 141 | 1.10 (0.86-1.39) | 0.45 | 57 | 1.46 (0.97-2.19) | 0.07 | 165 | 1.08 (0.87-1.35) | 0.49 |
| Quartile 4 | 1591 | 169 | 1.30 (1.03-1.63) | 0.03 | 63 | 1.57 (1.05-2.34) | 0.03 | 272 | 1.71 (1.41-2.09) | <0.001 |
| All | 6367 | 583 | | 0.13 | 208 | | 0.10 | 811 | | <0.001 |
| Cobalamin[d] | | | | | | | | | | |
| Quartile 1 | 1592 | 142 | 1.15 (0.91-1.46) | 0.25 | 49 | 1.27 (0.84-1.93) | 0.25 | 194 | 1.12 (0.92-1.37) | 0.27 |
| Quartile 2 | 1592 | 128 | 1 | | 41 | 1 | | 188 | 1 | |
| Quartile 3 | 1593 | 171 | 1.32 (1.05-1.66) | 0.02 | 58 | 1.37 (0.92-2.04) | 0.13 | 208 | 1.06 (0.87-1.29) | 0.55 |
| Quartile 4 | 1590 | 142 | 1.08 (0.85-1.37) | 0.54 | 60 | 1.41 (0.95-2.09) | 0.09 | 221 | 1.12 (0.92-1.36) | 0.25 |
| All | 6367 | 583 | | 0.09 | 208 | | 0.35 | 811 | | 0.63 |

CI, confidence interval.
[a]A total of 6367 (93.1%) of participants had one or two measurements of serum folate and of serum cobalamin during study treatment with B vitamins or placebo. Folate and cobalamin quartiles were computed by using the mean of measurements from the study visit at 1 to 2 months after randomization and at the final study visit, or the actual value if only one sample was available after random treatment assignment. [b]P value for difference between quartiles with quartile 2 as reference, or for heterogeneity across all quartiles. [c]For serum folate, quartile 1, ≤8.6 nmol/L; quartile 2, 8.7 to 23.9 nmol/L; quartile 3, 24.0 to 62.7 nmol/L; quartile 4, >62.7 nmol/L. [d]For serum cobalamin, quartile 1, ≤337 pmol/L; quartile 2, 338 to 440 pmol/L; quartile 3, 441 to 567 pmol/L; quartile 4, >567 pmol/L.

# 5. Discussion and conclusions

## 5.1 Strengths and limitations

The strengths of WENBIT, and of the combined NORVIT-WENBIT study with extended follow-up, are first, the double-blinded randomized study design. A unique and important advantage of sufficiently large RCTs is that confounding variables, both known and unknown, will on average be distributed equally between intervention groups, and will therefore not bias the study results.(125) Furthermore, the analyses are based on a large number of well-described participants who adhered to the study medication, and biochemical treatment effects were corroborated through repeated measurements of circulating B vitamin and tHcy levels during the intervention. Third, the effect of the intervention was substantial with respect to serum folate and plasma tHcy, probably because of the relatively low serum folate levels at baseline. Finally, the study outcomes were either hard clinical end points occurring during trials with little loss to follow-up, adjudicated by professionals blinded for treatment allocation, or cancer and mortality end points throughout extended follow-up obtained from population based registries with almost 100% case coverage.

For the investigation on cardiovascular end points, NORVIT and WENBIT were initially powered to detect a 20% decreased risk of major adverse cardiovascular events in the groups allocated to homocysteine-lowering treatment.(109,114) However, the event rates were lower than anticipated in both trials, probably due to improvements in standard secondary prevention among patients with IHD. The intervention was prolonged and the number of participants increased in NORVIT, which achieved a statistical power of 0.87 to detect the hypothesized difference in the primary end point.(115) Given the media reports on the preliminary results from NORVIT September 2005 (126) indicating a possible increased cancer risk by folic acid treatment, the intervention in WENBIT, however, was somewhat prematurely

terminated. In the end, WENBIT had a 67% power to detect the hypothesized difference. By combining data from the two trials and prolonging follow-up for cancer incidence and cause-specific mortality, the statistical power was increased, and we could perform subgroup analyses according to participant baseline characteristics.

A limitation for the investigation of cancer outcomes was that the study design implied that all patients assigned to folic acid treatment also received vitamin B12. However, the observed associations between the primary end points and vitamin concentration measured during study treatment were confined to serum folate, suggesting that the adverse effects were mediated by folic acid.

For the investigation of clinical end points in the NORVIT-WENBIT study (papers II and III), we encountered the problem of multiple comparisons. We performed survival analyses for several primary end points across folic acid plus vitamin B12 treatment, and across vitamin B6 treatment, according to the 2 x 2 factorial design, which resulted in 4 comparisons in paper II and 6 comparisons in paper III.

It is not always clear how adjustments should be done. An often used method is simply to multiply the obtained p value with the number of comparisons being made.(127) However, because the primary end points (in-trial MACE and long-term cardiovascular death in paper II, and cancer incidence, cancer mortality and all-cause mortality in paper III) were strongly associated with one another, we thought that adjusting for multiple testing for these end points may attenuate and conceal true effects.(128,129)

In the subgroup analyses performed for the primary end points in paper II and III, resulting in a total of 24 and 18 comparisons, respectively, there was 70.8% and 60.3% probability that one or more statistically significant interaction tests ($p < 0.05$) could have appeared on the basis of chance alone. This was clearly stated in the methods sections. For the investigation on cancer subtypes, the end points were decided *post hoc* (after having received and analyzed the data). For these analyses, HRs with 99% CIs and no p values were presented, not to emphasize possible false

positive findings. We believe the above mentioned actions, including an emphasis on estimation rather than testing, should sufficiently alert the reader to the problem of multiple comparisons.

## 5.2 The results in papers I and II in relation to other studies

The null results of the homocysteine-lowering treatment on the primary end point in WENBIT are in line with results from two WENBIT substudies using intermediate end points. In a substudy among the 90 first participants randomized in WENBIT, none of the B vitamin interventions were associated with lowered inflammatory markers.(130) In another substudy among 348 WENBIT participants who underwent PCI at baseline, the homocysteine-lowering treatment was not associated with slower progression of the coronary atherosclerosis assessed by quantitative coronary angiography. A *post hoc* analysis of the latter study found that folic acid plus vitamin B12 treatment was associated with increased risk of rapid progression of the disease, expressed in percentage of diameter stenosis.(131)

In the NORVIT-WENBIT study on cardiovascular outcomes, we confirmed the finding of an increased risk of MACE in participants with high baseline plasma tHcy levels, as was observed in the NORVIT primary results.(115)

Our results are also fully in line with the results from other large homocysteine-lowering B vitamin treatment trials with hard clinical end points published to date,(132-138) of which none have found overall beneficial effects (Table AI in Appendix I). The meta-analysis by the B-Vitamin Treatment Trialists' collaboration using individual participant data from 8 (115,132-137,139,140) of these trials, has confirmed these findings.(141)

## 5.3 Why did homocysteine-lowering B vitamin treatment fail to prevent cardiovascular end points?

There are at least three possible explanations to why the homocysteine-lowering B vitamin treatment did not prevent cardiovascular events in NORVIT or WENBIT, or in any other large similar RCTs. First, homocysteine may not have a causal role in atherosclerosis or thrombosis. Second, homocysteine-lowering treatment in individuals who have already been diagnosed with CVD may not have an effect. Third, the B vitamins to lower homocysteine may have adverse effects that offset the possible benefits of the homocysteine-lowering.

The strongest evidence for a cause—effect relationship comes from consistent findings from different types of studies, preferably in diverse populations. After the initiation of NORVIT and WENBIT, there has been a rapid growth of prospective epidemiological evidence that circulating homocysteine is associated with the incidence (142) and prognosis (143-147) of CAD. A recent meta-analysis of cohort studies in healthy populations concluded that for each 5 μmol/L increment in tHcy level, the risk of coronary events increases by 18%, independently of traditional CAD risk factors.(142) Also, a later large prospective study conducted in a Swedish population not exposed to folic acid fortification, and with similar circulating folate and tHcy levels as in the current study population, found that plasma tHcy measured at baseline was strongly and independently associated with risk of MI after 13 years of follow-up.(148) Thus, the epidemiological evidence pointing towards a causal relationship between homocysteine and CVD cannot be disregarded. However, the evidence up to 2001 from Mendelian randomization studies pointing towards homocysteine being causally related to CVD,(47,48) has been weakened by a later meta-analysis of studies up to 2004, which found no association of the MTHFR 677C→T polymorphism and CAD in European, North-American or Australian populations.(149) Furthermore, a recent large study among healthy US women found no association between TT genotype and CVD after 10 years of follow-up.(150)

Elevated plasma tHcy concentration could result from deficiencies of folate, vitamin B12 or vitamin B6, or impaired functions of enzymes involved in the B vitamin and/or homocysteine metabolism,(151) but it is also associated with a variety of factors not reflecting B vitamin status. The latter include several risk factors for CVD such as smoking, low physical activity, high blood pressure, and high total cholesterol, impaired renal function and cellular immune activation.(152-154) In the current study population, self-reported current smokers had both higher plasma tHcy and lower serum folate at baseline than ex-smokers and never smokers.(155)

In the NORVIT-WENBIT folic acid groups, baseline tHcy was not an independent predictor, whereas the lowered tHcy after 1-2 months of folic acid and vitamin B12 treatment was a significant predictor of subsequent MACE. This may imply that when the homocysteine remethylation pathway is saturated with 5-methyl-THF (from folic acid) and vitamin B12 (from cyanocobalamin), the remaining plasma tHcy level reflects disturbances in other metabolic pathways that are in turn causally linked with disease progression. This is also in line with our main finding that lowering plasma tHcy with folic acid plus vitamin B12 did not lower the risk of cardiovascular events.

The increased risk of cardiovascular end points by folic acid plus vitamin B12 among NORVIT-WENBIT participants with baseline hyperhomocysteinemia could be a chance finding. Anyway, it was contrary to what would be expected if homocysteine has a causal role in CVD progression. Administration of pharmacological doses of these B vitamins could influence several biological systems, in addition to homocysteine remethylation.(151,156) One may therefore speculate that this intervention, which may promote DNA synthesis and cell proliferation, enhance neointimal proliferation in high-risk individuals with established atherosclerosis,(151,156) leading to an accelerated disease progression or vascular occlusion.

Ultimately, to purely test whether homocysteine causes cardiovascular disease, it would be necessary to use an intervention modality that lowered homocysteine without affecting other biomarkers or risk factors.(157)

## 5.4 Why did vitamin B6 treatment fail to prevent cardiovascular end points?

We found no separate effect of the vitamin B6 intervention on cardiovascular end points. This is in line with the results of recent observational studies demonstrating that low circulating levels of vitamin B6 may be a consequence of inflammation accompanying CAD and/or smoking, rather than being causally related to CAD.(158) Also two recent cross sectional studies in the general US (159) and older Puerto Rican US population,(160) observed inverse associations between CRP and PLP levels. Given the null results from the vitamin B6 intervention on levels of CRP and other inflammatory markers in the aforementioned WENBIT substudy,(130) the common cause for high levels of inflammation markers and low PLP levels in the circulation may be inflammation itself.

## 5.5 The results in paper III in relation to other studies

None of the other large homocysteine-lowering B vitamin trials that have reported cancer outcomes through in-trial follow-up found increased risk of cancer outcomes by the folic acid based homocysteine-lowering treatment.(134,137,161) In the aforementioned collaborative meta-analysis, the rate ratio for cancer incidence or cancer deaths during in-trial follow-up was 1.05 (95% CI, 0.97-1.10).(141) However, the adjudication method for cancer outcomes is not reported for all trials, and none of the trials in the collaboration (except for NORVIT and WENBIT) has prolonged the follow-up for cancer outcomes. Also, the baseline serum/plasma folate levels were higher in these trial populations than in the NORVIT and WENBIT populations, probably due to intake of folic acid fortified foods and/or a more common use of vitamin supplements than in the Norwegian trial populations. This may have obscured the effect of the additional folic acid through the intervention.

## 5.6 Why was folic acid treatment associated with cancer end points and all-cause mortality?

Epidemiological evidence suggests that large relative increase of incident solid cancers in humans over a short period by chemical causes is implausible.(127,162) Thus, the exposure time of median 39 months in NORVIT-WENBIT is considered short. However it is likely that the administration of pharmacological doses of folic acid during this time may have led to accelerated growth in cancers that were initially silent, and that this resulted in the statistically significantly increased cancer incidence and mortality observed through extended follow-up.(163)

Also, the finding of a dose/effect relationship across the second *vs* the fourth quartiles of on-treatment serum folate levels, and the increased risk of cancer mortality by folic acid treatment among participants with the TT genotype of the MTHFR 677C→T polymorphism, is compatible with a real biological effect.

The mechanisms may also include a direct effect of unmetabolized folic acid on cancer immune defense systems, although the *in vitro* findings of a folic acid associated disturbed function of natural killer cells published in 2006 (164) have not to our knowledge yet been confirmed by other research groups.

## 5.7 Conclusions

Despite the convincing epidemiological evidence that plasma tHcy predicts cardiovascular morbidity and mortality, the primary results from WENBIT and the combined results with extended follow-up of the NORVIT-WENBIT study population, add to the mounting proof that lowering homocysteine with folic acid based B vitamin treatment does not improve cardiovascular outcomes. This implies that homocysteine itself is probably not a causal factor in CVD, but rather a biomarker of increased risk. Routine measurement of tHcy in patients with CVD should not be performed unless there is clinical suspicion of folate (165) or vitamin

B12 deficiency,(166,167) or of cystathionine beta-synthase deficiency,(168) which should be treated with B vitamins.

Our data indicate that folic acid may promote cancer growth, thus folic acid should not be prescribed to patients unless they have proven folate deficiency. Moreover, folic acid in pharmacological doses should not be added to over-the-counter vitamin supplements for others than women planning to get pregnant or in their first 3 months of pregnancy.

# 6. Further perspectives

The hopes that a simple, affordable and presumably safe intervention with folic acid, vitamin B12 and/or vitamin B6 would reduce the risk of cardiovascular adverse events in patients with established cardiovascular or renal disease have been quashed by the null results from the portfolio of large B vitamin treatment trials with hard clinical end points published to date. Currently, only two such completed RCTs have not yet published their results; the VITAmins TO Prevent Stroke trial (169) and the SU.FOL.OM.3 trial.(170) In addition, a large primary prevention trial using enalapril with or without folic acid in patients with hypertension to evaluate the effects on incident strokes is under way, scheduled to be completed by March 2013.(171)

Just recently, a meta-analysis of cohort studies on vitamin B6 intake and/or blood levels, concluded that blood PLP levels are inversely associated with risk of colorectal cancer, and stated that these findings "…need to be confirmed in large RCTs of vitamin B6 supplementation."(172) However, the probability that new RCTs with adequate sample size (tens of thousands) and duration (decades) will be carried out to test the hypothesis that folic acid and other B vitamins prevent or promote CVD or cancer, is small, considering the high costs and low prospects of economic profits by such studies.

To further evaluate possible disease modifying, clinical effects of B vitamin treatment, the strategy should rather be to explore short- and long-term effects of the interventions in RCTs already completed or under way. Meta-analyses with use of individual participants' data will possibly provide some more answers,(64) especially if data from extended follow-up are obtained. A detailed analysis of cancer outcomes in 7 (115,133-137,139,140) of the RCTs in the B Vitamin Treatment Trialists' collaboration,(64) also including individual participants' data from 3 RCTs which used folic acid to prevent recurrent colorectal adenomas (85,173,174) is in progress.(109) Finally, when data from all 11 trials in the B Vitamin Treatment

Trialists' Collaboration (115,132-137,139,140,169,170,175) are available, new meta-analyses including data from more than 52000 participants should be performed.

Also, there is much more basic laboratory research to be accomplished. It will be important to investigate interrelationships between the different B vitamins, their metabolites and related compounds in the metabolic network of the one-carbon metabolism (45) in different populations, and to further explore these relationships when people are treated with high doses of synthetic B vitamins. The possible cancer promoting effects of folic acid and/or vitamin B12 should be examined by *in vitro* and animal experiments.

Furthermore, it will be necessary to perform more large-scale epidemiological research, especially concerning the ongoing folic acid fortification experiments that are currently being conducted in populations world wide.

As for the NORVIT and WENBIT populations, we will repeat analyses on cancer and mortality outcomes after 3 and 7 more years of post-trial follow-up. We will also use the data to investigate associations and correlations between baseline demographics and clinical characteristics, risk factor levels, biomarkers and metabolites, and clinical outcomes.

It is intriguing that lipid-modifying medications associated with on-treatment elevations in plasma tHcy (i.e. fibric acid derivatives and possibly niacin) (176) to a lesser extent than statins have demonstrated beneficial effects on hard clinical end points, despite having demonstrated presumably beneficial effects on HDL cholesterol and triglyceride levels.(177) Studies on mechanisms that may underlie these observations, and monitoring tHcy levels in future studies on novel lipid-modifying drugs, are encouraged.

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# Errata

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At page 58, bottom line, (109) in the text should refer to a new reference (175a)

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**Appendix I Table A Homocysteine-lowering B vitamin treatment trials**

**Table A. Completed homocysteine-lowering B vitamin treatment trials with more than 1000 participants**

| Trial | From year | To year | Patients | No | Follow-up | Primary Outcome | Result | Ref. | Comment |
|---|---|---|---|---|---|---|---|---|---|
| VISP<br>The Vitamin Intervention for Stroke Prevention | 1997 | 2002 | Men and women with recent non-disabling cerebral infarction | 3680 | Mean<br>20 mo | Recurrent cerebral infarction | RR 1.0<br>(0.8-1.3) | (133) | High-dose B vitamins *vs* low-dose B vitamin supplement |
| NORVIT<br>The Norwegian Vitamin trial | 1998 | 2004 | Men and women with recent AMI | 3749 | Median<br>40 mo | Composite of acute MI, stroke and sudden death | RR 1.08<br>(0.93-1.25) | (115) | 2 x 2 factorial design with vitamin B6 |
| WAFACS<br>Women's Antioxidant and Folic Acid Cardiovascular Study | 1998 | 2005 | Women at high risk of or with established CVD | 5442 | 7.3 y | Composite of acute MI, stroke, coronary revascularization, or cardiovascular death | RR 1.03<br>(0.90-1.19) | (136) | 2 x 2 x 2 x 2 factorial design with antioxidants |
| SEARCH<br>Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine | 1998 | 2008 | Men and women having undergone MI >3 mo. ago | 12064 | Mean<br>6.7 y | Composite of acute MI, coronary death, coronary revascularization, stroke or non-coronary revascularization | RR 1.04<br>(0.97-1.12) | (137) | 2 x 2 factorial design with 20 *vs* 80 mg simvastatin |
| VITATOPS<br>VITAmins TO Prevent Stroke trial | 1998 | 2009 | Men and women with recent (<7 mo.) stroke or TIA | 8000 | Not published | Composite of stroke, acute MI or cardiovascular death | Not published | (169) | |
| CHAOS-2<br>The second Cambridge Anti-Oxidant Heart Study | 1999 | 2002 | Men and women with recent MI, unstable angina or CAD verified by coronary angiography | 1882 | Median<br>1.7 y | Composite of acute MI, cardiovascular death or unplanned revascularization or | RR 0.97<br>(0.72-1.29) | (132) | |
| WENBIT<br>The Western Norway B Vitamin Trial | 1999 | 2005 | Men and women undergoing coronary angiography for suspected CAD or aortic-valve stenosis | 3090 | Median<br>38 mo | Composite of acute MI, unstable angina, thromboembolic stroke or all-cause death | HR 1.09<br>(0.90-1.32) | (139) | 2 x 2 factorial design with vitamin B6 |

**Table A. Completed homocysteine-lowering B vitamin treatment trials with more than 1000 participants (continued)**

| Trial | From year | To year | Patients | No | Follow-up | Primary Outcome | Result | Ref | Comment |
|---|---|---|---|---|---|---|---|---|---|
| HOPE-2<br>The Heart Outcomes Prevention Evaluation-2 trial | 2000 | 2005 | Men and women >55 y at high risk of or with established CVD | 5522 | Mean<br>5 y | Composite of acute MI, stroke or cardiovascular death | RR 0.95<br>(0.84-1.07) | (134) | |
| HOST<br>The Homocysteine Study | 2001 | 2006 | Men and women with advanced or end stage renal disease | 2056 | Median<br>3.2 y | All-cause death | HR 1.04<br>(0.91-1.18) | (135) | |
| FAVORIT<br>The Folic Acid for Vascular Outcome Reduction in Transplantation | 2002 | 2009 | Men and women with renal allograft for at least 6 mo. | 4110 | Median<br>3.5 y | Composite of acute MI, stroke, resuscitated sudden death, revascularization procedures or cardiovascular death | HR 1.0 | (138) | High-dose B vitamins *vs* standard vitamin supplement |
| SU.FOL.OM3<br>The SUpplementation with FOLate, vitamin B6 and B12 and/or OMega-3 fatty acids trial | 2003 | 2009 | Men and women with an acute coronary or cerebral ischemic event 1-12 mo. before inclusion | 2501 | Not published | Composite of acute MI, stroke or cardiovascular death | Not published | (170) | 2 x 2 factorial design with vitamin n-3 fatty acid |

# Appendix II WENBIT forms and questionnaires

**Pasientinformasjon**

# FORSØK MED B-VITAMINER MOT HJERTE- OG KARSYKDOM

Senere års forskning tyder på at enkelte B-vitaminer kan ha en viktig beskyttende effekt mot utvikling og komplikasjoner av hjerte- og karsykdom. Dette har aldri vært testet ut i vitenskapelige forsøk som er den eneste sikre måten for å få slik kunnskap.
Vi forespørr nå deg og alle andre som skal til hjertekateterisering ved Haukeland sykehus eller ved Sentralsykehuset i Rogaland om å delta i et slikt forsøk. Hovedhensikten med studien er å teste ut om ekstra inntak av B-vitamintabletter gir færre komplikasjoner og mindre plager senere enten du må fortsette med medisinsk behandling alene, blir behandlet med blokking (PTCA) eller må hjerteopereres. I forsøket vil tre fjerdedeler av deltakerne bli behandlet med B-vitaminene B6, B12 og folsyre i forskjellige kombinasjoner, mens en fjerdedel av deltakerne vil få placebo (narretablett). For at hverken legen eller pasienten skal kunne påvirke resultatene, vil dette gjøres såkalt blindt ved loddtrekning, og koden over hvem som får vitaminer blir ikke åpnet før forsøket avsluttes etter tre til fire år.

Før hjertekateteriseringen vil det bli tatt vanlige blodprøver for analyse av standardprøver som kolesterol etc. Spesielt for studien er at det i tillegg vil bli tatt blodprøve som skal fryses ned for senere analyser av andre risikofaktorer for hjerte- og karsykdom. Dette gjelder blant annet gener som styrer B-vitaminstoffskiftet og stoffer som gjenspeiler inntaket av B-vitaminene. Et av disse stoffene er homocystein som er en nyoppdaget og sannsynligvis viktig risikofaktor.

Du vil få utlevert studiemedisinen samtidig med at du blir informert om resultatet av hjertekateteriseringen. Om du videre skal behandles med medisiner, blokking eller operasjon, vil avgjøres uavhengig av studien. Studiemedisinen skal du ta en gang daglig. Alle som vil delta i forsøket får tilbud om ekstra kontroll og oppfølging etter en måned. Det vil da bli tatt nye blodprøver. Deretter vil det være årlige kontroller inntil forsøket avsluttes etter 3-4 år.

Noen pasienter som blir behandlet med blokking vil få tilbud om en ekstra kontroll et halvt år etter blokkingen. Vi ønsker da å utføre ny hjertekateterisering for å undersøke om B-vitaminene forebygger tilbakefall. Slike tilbakefall opptrer hos opptil en tredel av de som blir blokket. Dersom du ikke blir direkte forespurt om å delta i denne ekstraundersøkelsen, er dette ikke aktuelt for deg.

Det har ikke vært vist at de vitaminer og i de doser og kombinasjoner som her skal benyttes kan gi farlige bivirkninger. Selv om slike bivirkninger derfor er lite sannsynlige, kan de ikke helt utelukkes. Opplysninger om alle sykdommer som rammer deltakerne vil derfor bli innhentet fra sykehusene og det kan bli aktuelt å hente inn data fra kreftregisteret og dødsårsaksregisteret i Statistisk sentralbyrå. Vi ønsker også at du selv fyller ut et ekstra spørreskjema ved kateteriseringen og ved kontrollene.
Produsenten av studiemedisinen har for øvrig egen forsikringsordning for deltagerne.

Deltagelse i studien er frivillig og du har rett til å nekte å bli med. Du kan også når som helst trekke deg fra studien senere uten begrunnelse, men vi anbefaler at du først samrår deg med din lege.
Alle som har tilgang til persondata er underlagt taushetsplikt. Personnummer brukes kun til å kople opplysninger og all annen bruk av data vil foregå uten navn og personnummer. Vi gjør imidlertid oppmerksom på at kontrollmyndigheter vil kunne ha behov for å sjekke at opplysninger gitt i studien stemmer med opplysninger i din journal for å kontrollere studiens kvalitet. Alle data vil bli behandlet strengt fortrolig.

Ved spørsmål angående WENBIT kan du kontakte:

WENBIT sekretariat
Hjerteavdelingen SPU
Haukeland sykehus
Telefon: 55 97 2171/22 09/22 20
Telefax: 55 97 51 50
E-post: jady@haukeland.no

WENBIT sekretariat
Hjerteutredningen / Hjertelaget
Sentralsykehuset i Rogaland
Telefon:51 91 09 10
Telefax:51 91 09 01
E-post:

**WENBIT SAMTYKKEERKLÆRING**

Jeg har lest pasientinformasjonen og sier meg villig til å delta i forsøket
WENBIT – VESTNORSK STUDIE AV B-VITAMINER MOT HJERTE- OG KARSYKDOM.

Dato |_____|_____|_____|
dag måned år

_____
*underskrift av pasient*

Undertegnede lege bevitner at ovennevnte pasient har fått muntlig informasjon om WENBIT, at vedkommende har lest pasientinformasjonen og underskrevet samtykkeerklæringen.

_____
*underskrift av lege*

WENBIT-nummer

Blodprøvenummer

For sykehuset:
Navn- og adresselapp med strekkode skal limes på her *innenfor* feltet

Ved spørsmål angående WENBIT kan du kontakte:

WENBIT sekretariat
Hjerteavdelingen SPU
Haukeland sykehus
Telefon: 55 97 2171/22 09/22 20
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WENBIT sekretariat
Hjerteutredningen / Hjertelaget
Sentralsykehuset i Rogaland
Telefon:51 91 09 10
Telefax:51 91 09 01
E-post:

WENBIT-nummer

Blodprøvenummer

For sykehuset:
Navn- og adresselapp med strekkode skal limes på her *innenfor* feltet

# WENBIT undersøkelser og kontroller

**Vestnorsk studie av B-vitaminer mot hjerte- og karsykdom**
**Helseregion Vest**
**Sentralsykehuset i Rogaland, Stavanger**
**Haukeland Sykehus, Bergen**

Hovedprosjekt…….. ☐ PTCA subprosjekt… ☐
Aortastenoseprosjekt. ☐ Annet subprosjekt… ☐

| Tidspunkt | Dato | Kl | Sted | Prosedyrer | Skjema |
|---|---|---|---|---|---|
| Dag 00 | | | | Blodprøve<br>Andre undersøkelser | Pasientskjema<br>KF samtykkeerklæring |
| Dag 0 | | | | **Hjertekateterisering** | WENBITsamtykkeerklæring<br>WENBIT livsstil |
| Dag 1 | | | | **Start med studiemedisin** | HAD og Mestring<br>Kostskjema |
| 1 måned | | | | Blodprøve<br>Samtale | WENBIT pasientskjema |
| 6 måneder | | | | Gjelder kun deltakere i PTCA-studie: Hjertekat. | PTCA kontroll |
| 1 år | | | | Blodprøve Samtale EKG<br>Blodtrykk Høyde Vekt | WENBIT pasientskjema<br>WENBIT livsstil |
| 2 år | | | | Samtale EKG<br>Blodtrykk Høyde Vekt | WENBIT pasientskjema<br>WENBIT livsstil |
| 3 år | | | | Samtale EKG<br>Blodtrykk Høyde Vekt | WENBIT pasientskjema<br>WENBIT livsstil |
| 4 år | | | | Samtale EKG<br>Blodtrykk Høyde Vekt | WENBIT pasientskjema<br>WENBIT livsstil |
| 5 år | | | | Samtale EKG<br>Blodtrykk Høyde Vekt | WENBIT pasientskjema<br>WENBIT livsstil |

**Bruk av studiemedisin**
1) Én tablett daglig inntil studien avsluttes. Tabletten taes om morgenen, evt sammen med andre medisiner.
2) De første 14 dagene taes i tillegg én tablett daglig fra liten tablettboks som inneholder totalt 14 tabletter.

Dersom du glemmer å ta studiemedisinen én eller flere dager, kan du ta uteglemt mengde når du husker det. Du får tilsendt ny studiemedisin i posten hvert halvår. Bortsett fra tilleggsboksen for de første 14 dagene, inneholder hver boks 200 tabletter. Dette tilsvarer mer enn et halvt års forbruk. Når du mottar ny boks, skal du starte å bruke fra denne selv om du altså har tabletter til gode fra den gamle. Den gamle boksen må du imidlertid oppbevare, og ved de årlige kontrollene vil du få skriftlig informasjon om å ta med tablettboksen for innlevering.

**Annen informasjon**
Du må ikke bruke tilskudd av B-vitaminer eller multivitaminer. Dersom du eller legen din bestemmer at du skal starte med slikt tilskudd, må du kontakte oss da dette medfører at du trolig bør slutte i studien. Dersom du vurderer å slutte av andre årsaker, eller har spørsmål eller informasjon som gjelder WENBIT, kan du også kontakte prosjektsykepleier som vist nedenfor.
Utgifter til reise dekkes av trygden med vanlig egenandel. Ved evt innleggelser på sykehus må du huske å ta med studiemedisinen, fortsette å bruke denne under oppholdet og informere oss om innleggelsen.

Ved spørsmål angående WENBIT kan du kontakte:


WENBIT sekretariat
Hjerteavdelingen SPU
Haukeland sykehus
Telefon: 55 97 2171/22 09/22 20
Telefax: 55 97 51 50
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WENBIT sekretariat
Hjerteutredningen / Hjertelaget
Sentralsykehuset i Rogaland
Telefon:51 91 09 10
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E-post:

WENBIT-nummer

Blodprøvenummer

# PASIENTSKJEMA

**ved hjertekateteriseing**
**Helseregion III**
**Sentralsykehuset i Rogaland, Stavanger**
**Haukeland Sykehus, Bergen**

For sykehuset:
Navn- og adresselapp med strekkode skal limes på her *innenfor* feltet

Navn/dato ……..
underskrift

dag mnd år

**Les nøye:** For å få en god vurdering av din hjertesykdom, ber vi deg svare på dette skjemaet og ta det med til undersøkelsen. **Skjemaet må fylles ut nøyaktig da det benyttes til journalskriving og kvalitetssikring.** Er du usikker, notérer du i margen. Ved årstall noteres de to siste sifrene.

## Familiebelastning

*Har noen i nærmeste familie hatt angina/hjertekrampe/hjerteinfarkt før 70 års alder?* Nei…..☐ Ja…….. ☐

Far ……. ☐ Fars søsken.. ☐ Fars foreldre..☐ Egne søsken. ☐ Egne barn…… ☐
Mor……. ☐ Mors søsken..☐ Mors foreldre.☐ Søskenbarn...☐ Vet ikke…….. ☐

Alder til den med tidligst symptom…… alder i år

Alder til yngste som døde av hjertet…… alder i år

*Er det tilfeller av plutselig* uventet dødsfall i familien før *55 års alder hos menn eller 65 års alder hos kvinner?*
Nei…..☐ Ja…….. ☐

## Røyking

Aldri røkt…… ☐
Røker fortsatt ☐

Evt start ved alder alder i år

Ev sluttet ved alder alder i år

Vis du sluttet siste året, hvor mange mnd siden antall mnd

Røkt i total antall år….. antall år

Hvis du har røkt, hvor mange sigaretter har du røykt pr. dag i snitt? 0-10.. ☐ 11-20..☐ Mer enn 20… ☐
Hvis du fortsatt røker, hvor mange sigaretter røyker du nå pr. dag? 0-10…☐ 11-20..☐ Mer enn 20… ☐

## Alkohol

*Moderat inntak av alkohol kan muligens beskytte mot utvikling av hjertekarsykdom. Dersom 1 enhet alkohol = 1 liten flaske pils = 1 glass vin = 1 drink (brennevin), hvor mange enheter drikker du i gjennomsnitt pr uke? 1 fl vin = 6 enheter.*

Intet forbruk…☐ Mindre enn 1.☐ 1-3…. ☐ 4-6…. ☐ 7-12.. ☐ Mer enn 12 enheter pr dag. ☐

## Kaffe og te

| | *0* | *Ca 1* | *2-4* | *Minst 5* | *Evt hva slags kaffe drikker du oftest?* | |
|---|---|---|---|---|---|---|
| Hvor mange kopper kaffe drikker du per dag? | ☐ | ☐ | ☐ | ☐ | Filter...☐ | Kokekaffe…. ☐ |
| Hvor mange kopper te drikker du per dag? | ☐ | ☐ | ☐ | ☐ | Pulver ☐ | Koffeinfri…… ☐ |

## Fysisk aktivitet

Hvor ofte mosjonerer du i gjennomsnitt per uke?…… *Aldri* ☐ *Ca 1* ☐ *2-3* ☐ *Minst 4* ☐

Evt hva slags mosjon er dette?… *Går tur* ☐ *Jogger* ☐ *Sykler* ☐ *Svømmer* ☐ *Annet* ☐

## Kolesterol

Høyeste verdi målt (før evt medikam behandling) , kolesterolverdi
Vet ikke…… ☐

Hvilket år målt… årstall

År med kolesterol-senkende medisin , antall år

Evt år m full kostendring antall år

## Høyt blodtrykk

*Har du eller har du hatt høyt blodtrykk?*
Nei…… ☐ Ja….. ☐

*Har blodtrykket vært behandlet med tabletter?*
Nei…. ☐ Ja…….. ☐

Hvis ja, hvor lenge.. antall år

## Sukkersyke

*Har du sukkersyke?*
Nei…….. ☐ Ja, hvor lenge…. antall år

*Hvis ja, hva slags behandling får du nå?*
Kost…☐ Tabletter☐ Insulin ☐

*Vis insulin, har du tidl. hatt tablett-behandling?* Nei…. ☐ Ja ☐

## Hjertekarsykdom

| *Har du hatt følgende:* | *Nei* | *Ja* | *Antall ggr* | *Årstall* |
|---|---|---|---|---|
| Hjerteinfarkt | ☐ | ☐ | \|___\|\|_____\| | |
| Ballongblokking av kransåre i hjertet | ☐ | ☐ | \|___\|\|_____\| | |
| Bypass-operasjon | ☐ | ☐ | \|___\|\|_____\| | |
| Hjerneslag/drypp | ☐ | ☐ | \|___\|\|_____\| | |
| Operasjon på halsårene | ☐ | ☐ | \|___\|\|_____\| | |

| *Har du hatt følgende:* | *Nei* | *Ja* | *Antall ggr* | *Årstall* |
|---|---|---|---|---|
| Smerter i leggene ved gange som forsvinner når en er i ro (røykebein) | ☐ | ☐ | \|___\|\|_____\| | |
| Blodpropp i bena | ☐ | ☐ | \|___\|\|_____\| | |
| Operasjon/blokking årene til bena | ☐ | ☐ | \|___\|\|_____\| | |
| Operasjon på hovedpulsåren | ☐ | ☐ | \|___\|\|_____\| | |
| Blodpropp i lungene | ☐ | ☐ | \|___\|\|_____\| | |

## Andre sykdommer eller plager

| *Har du eller har du hatt følgende:* | *Nei* | *Ja* |
|---|---|---|
| Hjerteflimmer av og til | ☐ | ☐ |
| Hjerteflimmer kronisk | ☐ | ☐ |
| Astma, kronisk astmabronkitt/KOLS | ☐ | ☐ |
| Annen lungesykdom | ☐ | ☐ |
| Høyt stoffskifte | ☐ | ☐ |
| Lavt stoffskifte | ☐ | ☐ |
| Leddgikt | ☐ | ☐ |
| Annen reumatisk sykdom | ☐ | ☐ |
| Psoriasis | ☐ | ☐ |
| Utslett eller annen hudsykdom | ☐ | ☐ |
| Nyresykdom | ☐ | ☐ |

| *Har du eller har du hatt følgende:* | *Nei* | *Ja* |
|---|---|---|
| Kreftsykdom | ☐ | ☐ |
| Sår på magesekk, spiserør eller tolvfingertarm | ☐ | ☐ |
| Plager med sure oppstøt eller brystsvie | ☐ | ☐ |
| Kronisk tykktarmsykdom | ☐ | ☐ |
| Annen mage/tarmsykdom | ☐ | ☐ |
| Osteoporose/benskjørhet | ☐ | ☐ |
| Annen plage fra muskler/skjelettet (senebet. mm) | ☐ | ☐ |
| Søvnproblem | ☐ | ☐ |
| Depresjon | ☐ | ☐ |
| Angst eller annen psykisk plage | ☐ | ☐ |
| Redusert hukommelse | ☐ | ☐ |

Annen sykdom/plage eller annen kommentar: ……

## Vitaminer, tran og kosttilskudd

| *Hvor ofte bruker du* | *Aldri* | *Av og til* | *Ofte* | *Daglig* |
|---|---|---|---|---|
| Vitamin, tabletter | ☐ | ☐ | ☐ | ☐ |
| Vitamin, flytende | ☐ | ☐ | ☐ | ☐ |
| Tran | ☐ | ☐ | ☐ | ☐ |
| Jerntabletter | ☐ | ☐ | ☐ | ☐ |
| Annet kosttilskudd | ☐ | ☐ | ☐ | ☐ |

*Hvilke typer tar du (sett evt kryss i flere bokser)*

| | | | |
|---|---|---|---|
| Multivitamin | ☐ | B-vitamin | ☐ |
| C-vitamin | ☐ | E-vitamin | ☐ |
| A/D-vitamin | ☐ | Folsyre/folat | ☐ |
| Q-10 | ☐ | Selén | ☐ |
| Fiskeolje/Omega3 | ☐ | Hvitløk | ☐ |

## Medikamenter (også insulin, vitaminer, kosttilskudd) som du bruker nå

| *Navn på tablett* | *Tablett-styrke* | *Antall tabletter pr gg* | *X* | *Antall ggr pr dag* | *Navn på tablett* | *Tablett-styrke* | *Antall tabletter pr gg* | *X* | *Antall ggr pr dag* |
|---|---|---|---|---|---|---|---|---|---|
| …… | ……. | ……. | | ……. | …… | ……. | ……. | | ……. |
| …… | ……. | ……. | | ……. | …… | ……. | ……. | | ……. |
| …… | ……. | ……. | | ……. | …… | ……. | ……. | | ……. |
| …… | ……. | ……. | | ……. | …… | ……. | ……. | | ……. |
| …… | ……. | ……. | | ……. | …… | ……. | ……. | | ……. |

## Allergi

*Er du allergisk mot noen medisintyper?* Nei…..☐ Ja……☐ Usikker….☐

Evt hva slags reaksjon?…… Evt mot hvilke medisiner? ……
navn eller type medikament

## Infeksjon og antibiotika

*Har du hatt infeksjon med feber siste året?*
Nei…..☐ Ja……☐
Hvis ja, antall måneder siden siste infeksjon. ☐ antall

*Har du brukt antibiotika (f. eks. penicillin) siste året?*
Nei…..☐ Ja…..☐ Usikker….☐
Hvis ja, hvor mange antibiotikakurer har du tatt…… ☐ antall

## Bare for legen

| **ASA** | Warfa | Dipyri | **ACE-h** | AT-II-h | **Betabl** | Alfabl | **Ca-bl.** | **Nitro** | **Statin** | Resin | Amiodar | Digitalis | Insulin | **Metform** | Sulfon | An adiab |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| ☐ | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ |

| LM-Hep | **GPIIb/IIIa** | An akoag | **Loopdiur** | Thiazid | Spironol | NSAID | Prednis | Imurel | Metotrex | Cya | Antihist | B12-inj | Folsyre | Thyrox | Antidep | Østrogen |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| ☐ | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ |

Brukerkode lege

Skjemaversjon 11.12.2008 ON

Serienummer

# WENBIT I RESULTATER VED INKLUSJON

Vestnorsk studie av B-vitaminer mot hjerte- og karsykdom
Sentralsykehuset i Rogaland, Stavanger
Haukeland Sykehus, Bergen
Helseregion III

For sykehuset:
Navn- og adresselapp med strekkode skal limes på her *innenfor* feltet

Telefon privat arbeid eller mobil

## Sosial status, utdannelse og kjønn

Gift/samboer ☐ Ugift…… ☐ Skilt/separert… ☐ Enke/enkemann.. ☐ ***Kjønn:*** Mann ☐ Kvinne.. ☐
Grunnsskole ☐ Videreg…. ☐ Høyskole…….. ☐ Universitet…… ☐

## Indikasjon for utredning [1]

Stabil AP.. ☐ Stum iskemi.. ☐ UAP ØH ☐ Non-Q inf ØH.. ☐ Q-inf ØH…. ☐ UAP/Inf-nylig[2] ☐
Inf. tidligere[3] ☐ Suspekt CAD. ☐
AS……. ☐ AI…. ☐ MI. ☐ MS……. ☐ Annen klaff…. ☐ Medfødt vit. ☐ Endocarditt.. ☐
H(O)CM ☐ CCM ☐ Alv. arrytmi (VT/VF) ☐ Ao-disseksjon ☐ Preop vurd[4] ☐ Annet.. ☐

[1] Evt kryss i flere ruter. ØH defineres som utredning ved ØH sykehusinnleggelse
[2] < 4 uker, polikl. us.
[3] > 4 uker
[4] Også transplantasjonsutredning

## Symptom

| | | *NYHA-klasse* | | | | |
|---|---|---|---|---|---|---|
| Angina pectoris? | Nei ☐ | 1 ☐ | 2 ☐ | 3 ☐ | 4 ☐ | |
| Dyspnoe/utmattelse? | Nei ☐ | 1 ☐ | 2 ☐ | 3 ☐ | 4 ☐ | |
| Syncope? | Nei.. ☐ | Ja. ☐ | | | | |

*Canadian Cardiovascular Society-klasse*: 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4a ☐ 4b ☐ 4c ☐

*Vis ØH, antall dager siden symptomdebut* ____ , ____ antall

## Kardiovaskulær sykehistorie

| *Antall tidligere tilfeller av* | *0* | *1* | *2* | *>2* | *Antall tidligere tilfeller av* | *0* | *1* | *2* | *>2* |
|---|---|---|---|---|---|---|---|---|---|
| Hjerteinfarkt | ☐ | ☐ | ☐ | ☐ | Operasjon på halsårene | ☐ | ☐ | ☐ | ☐ |
| PTCA | ☐ | ☐ | ☐ | ☐ | Perifer emboli | ☐ | ☐ | ☐ | ☐ |
| CABG | ☐ | ☐ | ☐ | ☐ | Operesjon/PTA perifere kar | ☐ | ☐ | ☐ | ☐ |
| Sykehusinnl. for angina | ☐ | ☐ | ☐ | ☐ | Operesjon/PTA aorta | ☐ | ☐ | ☐ | ☐ |
| Sykehusinnl. for hjertesvikt | ☐ | ☐ | ☐ | ☐ | Lungeemboli | ☐ | ☐ | ☐ | ☐ |
| Hjerneslag | ☐ | ☐ | ☐ | ☐ | DVT | ☐ | ☐ | ☐ | ☐ |
| TIA | ☐ | ☐ | ☐ | ☐ | | | | | |

Tidspunkt for evt første hjerteinfarkt ____ årstall

Tidspunkt for evt siste hjerteinfarkt… ____ årstall

Dersom hjerteinfarkt i løpet av siste året, hvor mange måneder siden…… ____ antall

## Klinisk undersøkelse

| Høyde | Vekt | Midje | Hofte | Systol BT | Diastol BT | Hjertefrekvens[1] |
|---|---|---|---|---|---|---|
| cm | kg | cm | cm | mm Hg | mm Hg | BPM |

Stenoselyd over karotis….. Svekket lyskepuls… Svekket fotpuls……. [1]Må samsvare med EKG

## Spirometri og Rtg toraks

| ***Spirometri*** | VC | FVC%[1] | FEV-1/FVC | PEF%[1] | ***Rtg toraks***[2] | [2]Taes på alle >60 år |
|---|---|---|---|---|---|---|
| Spirometri verdier: | | | | | Utført…… | Ikke utført… |
| | | | | | Normalt……. | Patologisk.. |
| Ikke utført… | , liter | % | % | % | [1]Av forventet verdi | |

## EKG

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Normalt …. | RBBB… | LBBB…. | PQ-tid | S $V_1$ | S $V_3$ | R aVL | R $V_5$ | R $V_6$ |
| Sinusrytme | A. flimm | An. rytm | | | | | | |
| Q-infarkt[1]… | NVI…… | FVI……. | | | | | | |
| Hemiblokk.. | Iskemi… | | ms | mm | mm | mm | mm | mm |
| Hypertrofi… | Usp STT forandringer.. | | QRS | Mean QT | SD | | Min QT | Max QT |

[1] Q-bredde >0,04 sekund og dybde ≥25% av R-takk.

Sokolow-Lyon voltage = S V1 + R V5. V6/V5 ratio = R V6/R V5
Cornell voltage = R aVL + S V3. Cornell product = Cornell voltage x QRS.

| | | | , | | |
|---|---|---|---|---|---|
| ms | ms | ms | | ms | ms |

## AEKG

AEKG ikke utført. ☐
Normal AEKG…. ☐
Stum iskemi[1] ☐
Bare symptom ☐
Symptom+iskemi ☐

Maks belastning ____ Watt
Maks puls.. ____ BPM
Maks SBT.. ____ mm Hg
δ-SBT… ____ mm Hg

*Symptom*: Angina ☐ Dyspnoe ☐ Manglende BT-stigning ☐
*Iskemi lokalisert til veggomrode* Fremre ☐ Lateral ☐ Nedre ☐

[1] ≥ 1 mm ST-depresjon.

## Ekkokardiografi

| Aorta | LAD | LVEDD | LVESD | Septum | Bakre vegg | EF | Hjertefrekvens |
|---|---|---|---|---|---|---|---|
| mm | mm | mm | mm | mm | mm | % | BPM |

| E-maks | A-maks | dV/dt | IVRT | Ao V-maks cont | Ao V-maks LVOT[1] | LVOT-diam[1] |
|---|---|---|---|---|---|---|
| ,__ m/s | ,__ m/s | ,__ m/s2 | ,__ ms | ,__ m/s | ,__ m/s | ,__ cm |

Ingen inf.skade… ☐ *Infarktskade i* Septum ☐ Fremre ☐ Laterale ☐ Nedre ☐

AI grad: 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐
MI grad: 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐

[1] Kun på pasienter med aortastenose

*Ekkokardiografi ikke utført……..* ☐

LVM=0,83[(LVEDD+septum+bakre vegg)$^3$ -LVEDD$^3$]+0,6. LVMI=LVM/BSA. RWT=2xBakre vegg/LVEDD.

## Hjertekateterisering

| Dato utført | | | EF | EDT | Aortagradient[1] | Aortaklaff areal[2] | PWP | PVR |
|---|---|---|---|---|---|---|---|---|
| dag | måned | årstall | % | mm Hg | mm Hg | ,__ cm2/ m2 | mm Hg | __-5 dynsek cm |

AI grad: 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐
MI grad: 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐

[1] maks [2] korrigert for kroppsoverflate

Normale kar……. ☐ Veggforandringer ☐ 1-karsykdom ☐ 2-karsykdom ☐ 3-karsykdom. ☐
Normale kar etter tidligere utført PTCA…. ☐ Réstenose… ☐
Normale venegraft (SBG) etter tidl. CABG ☐ Stenos. SBG ☐ Åpen LIMA ☐ Stenos. LIMA ☐
LMS-stenose…. ☐ LAD-stenose…. ☐ CX-stenose… ☐ Intermed-stenose ☐ RCA-stenose ☐
Ingen inf.skade.. ☐ FVI-hypokinesi.. ☐ FVI akinesi… ☐ FVI aneurysme ☐
NVI-hypokinesi.. ☐ NVI akinesi… ☐ NVI aneurysme ☐

## Videre behandling

Ingen…… ☐ Medikamentell… ☐ PTCA…….. ☐ CABG…….. ☐ AVR……. ☐
Annen invasiv[1].. ☐ Annen operativ.. ☐

[1] Rotablator, TMR

***Evt årsak til at invasiv/operativ behandling ikke skal gjennomføres:***

Normale funn….. ☐ Små funn/sympt. ☐ Lav EF……. ☐ Perifere forandringer i koronararteriene ☐
Alvorlig hjertesykdom med høy risiko……. ☐ Inoperabel… ☐ Alvorlig, ikke-kardial sykdom…… ☐

## Rekruttérbarhet og randomisering i WENBIT

Rekruttérbar[1]….. Randomisert…… Ekskludert… Ikke rekruttérbar..
*Evt eksklusjonsgrunn:* Tidl. randomisert. Annen studie. Uegnet[2]. Uvillig. Annen sykd.[3]
*Evt randomiseringsgruppe:* Hovedgr PTCA gruppe[4] Aortastenose…..

[1] Suspekt eller kjent koronarsykdom eller aortastenose [2] Mentalt eller fysisk, inklusive misbruk siste 2 år. [3] Aktiv kreftsykdom, annen alvorlig sykdom [4] PTCA-skjema må utfylles

## Medikamenter videre

ASA Warfarin Dipyridamol ACE-hemmer AT-II-hemmer Betabl. Alfabl. Calciumbl. Nitroretard Statin Resin Amiodarone Digitalis Østrogen

Insulin Metformin Sulfonamid Andre antidiab. NSAIDS Prednison Imurel Metotrexat Cya Antihistamin B12-inj. Folsyre Thyroxin Antidepr

LM-Heparin GP-IIb/IIIa-hemmer Annen antikoag Loop diuretika Thiazid Spironolactone

## Lege

Overlege Overlege vikar Ass.l-D-stilling Ass.l-Utd Annen lege

Brukerkode:

Skjemaversjon
04 oktober 1999

+ +

# WENBIT pasientskjema

**Vestnorsk studie av B-vitaminer mot hjerte- og karsykdom**
**Helseregion Vest**
**Sentralsykehuset i Rogaland, Stavanger**
**Haukeland Sykehus, Bergen**

WENBIT-nummer

Blodprøvenummer

For sykehuset:
Navn- og adresselapp med strekkode skal limes på her *innenfor* feltet

**Navn** ..... Dato for underskrift: dag mnd år
underskrift

**Kontroll ved:** 6 mndr.. ☐ 1 år.. ☐ 2 år.. ☐ 3 år. ☐ 4 år.. ☐ 5 år.. ☐

**Til deg som deltar i WENBIT** For å sikre deg en god kontroll og oppfølging i studien, ønsker vi at du svarer på spørreskjemaet og tar det med til undersøkelsen. Skjemaet må fylles ut nøyaktig da det skal leses av en maskin. Bruk sort eller blå penn/tusj. Sett kryss i de rutene som passer for deg. Riktig markering av kryss i en rute er slik ☒. Er du uheldig og krysser i feil rute, skraverer du hele ruten ■. Notér evt i margen.

## Hjertekarsykdom

*Har du siden du sist ble undersøkt av oss i WENBIT-studien hatt (kryss av hvis ja)*

| | | | |
|---|---|---|---|
| Hjertekateterisering | ☐ | Hjerneslag/drypp | ☐ |
| Ballongblokking | ☐ | Operasjon på halsårene | ☐ |
| Bypass-operasjon | ☐ | Blodpropp i bena | ☐ |
| Sykehusinnleggelse for hjerteinfarkt | ☐ | Operasjon eller blokking av årene til bena | ☐ |
| Sykehusinnleggelse for hjertesvikt | ☐ | Operasjon på hovedpulsåren | ☐ |
| Sykehusinnleggelse for annen hjertesykdom | ☐ | Blodpropp i lungene | ☐ |

Evt hva slags hjertesykdom.....

## Diverse sykdommer og plager

*Etter at du ble med i WENBIT, har du fått sykdom eller plager som du ikke hadde tidligere, eller er du blitt bedre eller værre av plager som du hadde fra før?* ***Du må sette kryss i en av de fem første rutene for hver sykdom eller plage****. Dersom du har vært innlagt på sykehus for noe av dette siden du sist ble undersøkt av oss i WENBIT-studien, må du i tillegg sette kryss i det siste feltet. Gi gjerne kommentarer nederst på siden.*

| *Sykdom eller plage* | *Ingen plage* | *Blitt bedre* | *Uforandret* | *Blitt verre* | *Nyoppstått* | *Har vært innlagt på sykehus* |
|---|---|---|---|---|---|---|
| Angina/brystsmerter | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ |
| Tungpust/åndenød | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ |
| Hjerteflimmer | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ |
| Astma, kronisk astmabronkitt / KOLS | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ |
| Andre plager fra lungene | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ |
| Plager med stoffskifte | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ |
| Leddgikt | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ |
| Annen reumatisk sykdom | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ |
| Psoriasis | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ |
| Utslett eller annen hudsykdom | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ |
| Sår på magesekk, spiserør el tolvfingertarm | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ |
| Plager med sure oppstøt/brystsvie | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ |
| Kronisk tykktarmssykdom | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ |
| Annen mage / tarmsykdom | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ |
| Kreftsykdom | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ |
| Nyresykdom | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ |
| Osteoporose / benskjørhet | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ |
| Annen plage fra muskler / skjelettet (senebet. mm) | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ |
| Søvnproblemer | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ |
| Depresjon | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ |
| Angst eller annnen psykisk plage | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ |
| Redusert hukommelse | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ |
| Infeksjon, uansett lokalisasjon | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ |
| Generelt uvell eller kvalm | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ |
| Annen sykdom eller plage | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ |

Kommentar:.....

Evt ved hvilket sykehus har du vært innlagt (gjelder også hjertekarsykdom).....

## Røyking

Aldri røkt.. ☐ Sluttet mer enn Sluttet siste året, *Hvis du fortsatt røyker, antall sigaretter per dag i snitt:*
Røkr forts ☐ 1 år siden ☐ ant mndr siden… ☐ (antall) 0-10… ☐ 11-20 ☐ Mer enn 20…….. ☐

## Alkohol

*Moderat inntak av alkohol kan muligens beskytte mot utvikling av hjertekarsykdom. Dersom 1 enhet alkohol = 1 liten flaske pils = 1 glass vin = 1 drink (brennevin), hvor mange enheter drikker du i gjennomsnitt pr uke? 1 fl vin = 6 enheter.*

| Antall enheter alkohol | *0* | *0- 1* | *1-3* | *4-6* | *7-12* | *>12* |
|---|---|---|---|---|---|---|
| per uke i snitt…….. | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ |

Antall dager per måned
med inntak av alkohol…….. ☐ (antall)

## Kaffe og te

| *Hvor mange kopper* | *0* | *Ca 1* | *2-4* | *5-8* | *>8* |
|---|---|---|---|---|---|
| kaffe drikker du per dag….. | ☐ | ☐ | ☐ | ☐ | ☐ |
| te drikker du per dag..…… | ☐ | ☐ | ☐ | ☐ | ☐ |

*Evt hva slags kaffe drikker du oftest (sett evt to kryss)?*
Filterkaffe…….. ☐ Kokekaffe…….. ☐
Pulverkaffe…….. ☐ Koffeinfri…….. ☐

## Fysisk aktivitet

| Hvor ofte mosjonerer du | *Aldri* | *Ca 1* | *2-3* | *Minst 4* |
|---|---|---|---|---|
| i gjennomsnitt per *uke*…… | ☐ | ☐ | ☐ | ☐ |

Evt hva slags *Går tur* *Jogger* *Sykler* *Svømmer* *Annet*
mosjon er dette?…… ☐ ☐ ☐ ☐ ☐

*Mosjonerer du nå mer eller mindre enn for 1 år siden?*…….. Mosjonerer mer…… ☐ Mosjonerer mindre… ☐

## Vitaminer, tran og kosttilskudd utenom studiemedisinen

| *Hvor ofte bruker du* | *Aldri* | *Av og til* | *Ofte* | *Daglig* |
|---|---|---|---|---|
| Vitamin, tabletter…….. | ☐ | ☐ | ☐ | ☐ |
| Vitamin, flytende…… | ☐ | ☐ | ☐ | ☐ |
| Tran…… | ☐ | ☐ | ☐ | ☐ |
| Jerntabletter…….. | ☐ | ☐ | ☐ | ☐ |
| Annet kosttilskudd…… | ☐ | ☐ | ☐ | ☐ |

*Hvilke typer tar du (sett evt kryss i flere bokser)*
Multivitamin…… ☐ B-vitamin…… ☐
C-vitamin…….. ☐ E-vitamin…….. ☐
A/D-vitamin…… ☐ Folsyre/folat…. ☐
Q-10…… ☐ Selén…… ☐
Fiskeolje/Omega3… ☐ Hvitløk…….. ☐

## Infeksjon og antibiotika

*Har du hatt infeksjon med feber siden forrige kontroll?*
Nei…. ☐ Ja….. ☐

Hvis ja, antall måneder siden siste infeksjon.. ☐ (antall)

*Har du brukt antibiotika (etc penicillin) siden forr. kontroll*
Nei…. ☐ Ja… ☐ Usikker…… ☐

Hvis ja, hvor mange antibiotikakurer…….. ☐ (antall)

## Medikamenter (også insulin, vitaminer, kosttilskudd) som du bruker nå

| *Navn på tablett* | *Tablett styrke* | *Ant tabl pr gang* | *Anl ggr pr dag* | *Navn på tablett* | *Tablett-styrke* | *Ant tabl pr gang* | *Ant ggr pr dag* |
|---|---|---|---|---|---|---|---|
| …… | …….. | ……. | ……. | …… | …….. | ……. | ……. |
| …… | …….. | ……. | ……. | …… | …….. | ……. | ……. |
| …… | …….. | ……. | ……. | …… | …….. | ……. | ……. |
| …… | …….. | ……. | ……. | …… | …….. | ……. | ……. |
| …… | …….. | ……. | ……. | …… | …….. | ……. | ……. |
| …… | …….. | ……. | ……. | …… | …….. | ……. | ……. |

**Evt hvilke medisiner er nye siden siste kontroll i WENBIT:** ……
**Evt hvilke medisiner har du sluttet med siden sist:** ……

## Bare for legen

**Ingen endring……..** ☐ **Ingen medisin……..** ☐

| **ASA** | Warfa | Dipyri | **ACE-h** | AT-II-h | **Betabl** | Alfabl | **Ca-bl.** | **Nitro** | **Statin** | Resin | Amiodar | Digitalis | Insulin | Metform | Sulfon | An adiab |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| ☐ | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ |
| LM-Hep | **GPIIb/IIIa** | An akoag | **Loopdiur** | Thiazid | Spironol | NSAID | Prednis | Imurel | Metotrex | Cya | H2-bl | **Prot-ph** | B12-inj | Thyrox | Antidep | Østrogen |
| ☐ | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ |
| Ur-h | Antihist | | | | | | | | | Simva | Lova | Atorva | Prava | Ceriva | Fluva | Annet |
| ☐ | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ |

Brukerkode lege

Skjemaversjon 22.05.2000 ON

+ +

# WENBIT kontroll

**Vestnorsk studie av B-vitaminer mot hjerte- og karsykdom**
**Helseregion Vest**
**Sentralsykehuset i Rogaland, Stavanger**
**Haukeland Sykehus, Bergen**

WENBIT-nummer

Blodprøvenummer

For sykehuset:
Navn- og adresselapp med strekkode skal limes på her *innenfor* feltet

Mnd-kontroll 1☐ 6☐
Årlig kontroll 1☐ 2☐ 3☐ 4☐ 5☐

## 1 Bruk av studiemedikasjon og Status

**Som foreskr** ☐ Glemt av & til ☐ Brukt lite/intet ☐ **Ved årlig kontroll**; antall tabletter som ikke er brukt siste året…… antall
Brukt for mye ☐

*Vis sluttet, årsak:* Trukk samtyk ☐ Advers event ☐ Annen årsak……☐

## 2 Klinisk undersøkelse (ikke v 1 mnd)

| Høyde | Vekt | Midje | Hofte | SBT | DBT | Hjertefrekv |
|---|---|---|---|---|---|---|
| cm | kg | cm | cm | mm Hg | mm Hg | BPM |

**Kvinner**: Hvis nyoppstått menopause…. alder

## 3 Symptom

| | *Ingen plage* | *Blitt bedre* | *Uforandret* | *Blitt verre* | *Nyoppstått* | *Innlagt sykehus* |
|---|---|---|---|---|---|---|
| Angina/brystsmerter…… | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ |
| Tungpust/åndenød…… | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ |

| | | *NYHA-klasse* | | | | | *Canadian Cardiovascular Society Angina-klasse (CCSA)*[1] | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| ***Angina pectoris*** | Nei ☐ | 1☐ | 2☐ | 3☐ | 4☐ | | 0☐ | 1☐ | 2☐ | 3☐ | 4a☐ | 4b☐ | 4c☐ |
| ***Dyspnoe/utmattelse*** | Nei ☐ | 1☐ | 2☐ | 3☐ | 4☐ | | | | | ***Syncope?*** | | Nei☐ | Ja☐ |

[1] 0 Ingen angina. 1 Angina kun ved store fys anstreng. 2 Angina ved normale dagligdagse fys anstreng (etc rask trappegang, fysisk anstreng etter måltid, i kulde eller i vind). 3 Betydelig angina ved vanlig lettere fysiske anstrengelser (gange flat vei/opp 1 etage i trapp). 4a Angina også i hvile (ustabil), stabilisert på per oral medikasjon 4b Angina også i hvile (ustabil), stabilisert på intravenøs medikasjon. 4c Angina også i hvile (ustabil), *ikke* stabilisert på intravenøs medikasjon

## 4 EKG (ikke v 1 mnd)

| | | | | |
|---|---|---|---|---|
| **Normalt EKG**☐ | **Sinusrytme..** ☐ | Atrieflimmer…..☐ | PM-rytme…….. ☐ | An rytme…… ☐ |
| Nytt RBBB ☐ | Nytt LBBB ☐ | Nytt hemiblokk ☐ | Ny/økt iskemi…….. ☐ | Ny/økt hypertrofi……☐ |
| Nytt Q-FVI ☐ | Nytt Q-NVI ☐ | Nye uspes for.. ☐ | Red tidligere forandr ☐ | ***Uforandret EKG….*** ☐ |

## 5 Hendelser siden forrige kontroll? (Aktuell arbeidssituasjon ikke v 1 mnd)

**Nei**… ☐ Planl beh v inklusjon utført uten komplik[1].. ☐
**Ja**……☐ Planl beh v inklusjon utført med komplik[2] ☐ Annet endepunkt[3]…. ☐ SAE[4]……☐

***Akt arb.sit:*** Hj.vær☐ Fullt arb☐ Delvis sykmeldt☐ Fult sm☐ Uføretr☐ Pensjn☐ Arb.led..☐

***Sykmeldt*** *pga hjertet siste året?*
Nei…..☐ Ja……☐ Antall dager…….. antall

*Sykmeldt av an årsak siste året?*
Nei…. ☐ Ja……☐ Antall dager antall

[1] ikke endepunkt i WENBIT. [2] Komplikasjon/forlenget sykehusopphold regnes som endepunkt. [3] Skjema *WENBIT hendelser* utfylles [4] Serious adverse event, skjema *WENBIT-SAE* utfylles

## 6 Blod- og urinprøve

| Dato | og | klokkeslett | *Fastende?* Tid siden måltid | *Fryseprøve?* | *Urinprøve?* | *Morgenurin?*[1] | *U-fryseprøv?* |
|---|---|---|---|---|---|---|---|
| | | | Nei... | Nei… | Nei… | Nei…. | Nei…. |
| | | | Ja…. | Ja…… | Ja…… | Ja….. | Ja….. |
| dag | mnd | år nærm time | timer | | | 1 Første vannlating | |

**Prøven tatt ved:** HS….. SiR FiH…. SSSF. An SH Primærlege……

## 7 Medikamenter videre

**Ingen endring……..** **Ingen medisin……..**

| | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **ASA** | Warfa | Dipyri | **ACE-h** | AT-II-h | **Betabl** | Alfabl | **Ca-bl.** | **Nitro** | **Statin** | Resin | Amiodar | Digitalis | Insulin | **Metform** | Sulfon | An adiab |
| LM-Hep | **GPIIb/IIIa** | An akoag | **Loopdiur** | Thiazid | Spironol | NSAID | Prednis | Imurel | Metotrex | Cya | H2-bl | **Prot-ph** | B12-inj | Thyrox | Antidep | Østrogen |
| Ur-h | Antihist | | | | | | | | | Simva | Lova | Atorva | Prava | Ceriva | Fluva | Annet |

**Ny medisin**…… **Sluttet med** ……

+ + +

Brukerkode lege

Skjemaversjon 22.05.2000 ON

WENBIT-nummer

Blodprøvenummer

# WENBIT hendelser

**Vestnorsk studie av B-vitaminer mot hjerte- og karsykdom**
**Helseregion Vest**
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For sykehuset:
Navn- og adresselapp med strekkode skal limes på her *innenfor* feltet

Det må fylles ut 1 skjema for hvert endepunkt.
Ved alvorlige hendelser (SAE)[1] må skjemaet WENBIT-SAE også utfylles.

[1] Alle hendelser som er dødelige, livstruende, medfører hospitalisering eller forlenget hospitalisering for tilstand som ikke var tilstede før studien ble iverksatt, eller som medfører vedvarende fysisk funksjonsnedsettelse.

## Utført behandling planlagt ved randomisering

| | Nei | Ja | | Nei | Ja |
|---|---|---|---|---|---|
| PTCA planlagt ved randomisering…….. | ☐ | ☐ | Annen beh. planlagt v. randomis. | ☐ | ☐ |
| CABG planlagt ved randomisering…… | ☐ | ☐ | | | |

## Endepunkt-type

| | Nei | Ja | | Nei | Ja |
|---|---|---|---|---|---|
| Død…….. | ☐ | | Ny CABG…… | ☐ | ☐ |
| Hjerteinfarkt…… | ☐ | ☐ | Hjerneslag eller TIA…… | ☐ | ☐ |
| Innleggelse for ustabil angina…….. | ☐ | ☐ | Subarachnoidalblødning…… | ☐ | ☐ |
| Residivangina etter PTCA…… | ☐ | ☐ | Lungeemboli…… | ☐ | ☐ |
| Restenose etter PTCA…….. | ☐ | ☐ | DVT…… | ☐ | ☐ |
| Ny PTCA pga réstenose…… | ☐ | ☐ | Perifer karsykdom[1]…… | ☐ | ☐ |
| Ny PTCA, ny sykdom…… | ☐ | ☐ | Innl. for annen hjertesykdom…… | ☐ | ☐ |
| PTCA etter CABG…… | ☐ | ☐ | Annen årsak til innleggelse…… | ☐ | ☐ |
| Angina etter CABG…… | ☐ | ☐ | | | |

[1] Tromboemboli, PTA eller operasjon på aorta eller perifere kar

Evt kommentar: ……

## Generelt

*Dato for debut hendelse* dato mnd år

*Dato evt sykehusinnleggelse* dato mnd år

*Dato for evt utskrivning* dato mnd år

***Prosedyrerelatert: hendelse***

< 2 minutt….. ☐ < 1 time… ☐ 1-6 t……. ☐ 6-24 t ☐ ≥ 24 timer ☐

Prosedyrekode

## Død

Bevitnet……..☐ Ikke bevitnet død…… ☐ Plutselig/uventet død…….. ☐ Kard sjokk/svikt☐

## Akutt hjerteinfarkt

Nytt LBBB…. Q-infarkt…. Non-Q….. Brystsmerter >20 minutt….. ST-hevning…

*Positive enzymer?* Nei……. Ja…….

Maksimums-verdier av enzymer:

| CK | CKMB | ASAT | Troponin T | Troponin I |
|---|---|---|---|---|
| | | | | |

## Ustabil angina

*Nyoppst EKG-for?* Nei……. Ja……..
*Positive enzymer?* Nei……. Ja…….

Maksimumsverdier enzymer vis forhøyet:

| CK | CKMB | ASAT | Troponin T | Troponin I |
|---|---|---|---|---|
| | | | | |

## PTCA / CABG

| | *LMS* | *Prox/Øvr LAD* | *CX* | *RCA* |
|---|---|---|---|---|
| POBA…… | ☐ | ☐ | ☐ | ☐ | ☐ |
| Stent…… | ☐ | ☐ | ☐ | ☐ | ☐ |
| LIMA…….. | ☐ | ☐ | ☐ | ☐ | ☐ |
| SBG…….. | ☐ | ☐ | ☐ | ☐ | ☐ |

Antall nye stenter….. ☐ antall

Antall gamle stenter……. ☐ antall

## Klaffeop

| | *AS* | *AI* | *MI* | *MS* | *Annen* |
|---|---|---|---|---|---|
| Klaffefeil:…….. | ☐ | ☐ | ☐ | ☐ | ☐ |

Protese/op:…….. ☐ *Mek* ☐ *Biol* ☐ *An graft* ☐ *Plastikk*

## Karsykdom

Utf angio/ultralyd/dopler Nei…. ☐ Ja….. ☐ Utført oper? Nei…….. ☐ Ja…… ☐

Evt operasjon lokalisasjon: Intracb ☐ Hals.. ☐ Ao asc ☐ Ao abd ☐ Perif kar……. ☐

## Cerebrovaskulær hendelse

*Utført CT eller MR?* Nei…. ☐ Ja….. ☐ Lammelse ☐ Talevansk ☐ Perm sequele ☐

SAH… ☐ Intrac blø ☐ Cerebralt infarkt…… ☐ Usp slag.. ☐ TIA…… ☐ RIND…… ☐

## DVT eller Lungeemboli

**DVT**: Utført UL/venografi? Nei…. ☐ Ja….. ☐

**L-emboli**: CT/scintegrafi? Nei…. ☐ Ja……☐ Utført ekko? Nei…… ☐ Ja…… ☐

## Diagnosenummer

☐ Diagnose 1 ☐ Diagnose 2 ☐ Diagnose 3 ☐ Diagnose 4

## Prosedyrenummer og lege

☐ Prosedyre 1 ☐ Prosedyre 2 ☐ Prosedyre 3 ☐ Prosedyre 4

Brukerkode lege ☐

Skjemaversjon 22.05.2000 ON

## Appendix III WENBIT organization and approvals

**WENBIT organization and approvals**

**Steering Committee:** Ottar Nygård (chair), Per Magne Ueland, Jan Erik Nordrehaug, Dennis W. Nilsen, Stein Emil Vollset, Helga Refsum.

**End-Points Committee:** Per Lund-Johansen, MD (chair), Section for Cardiology, Institute of Medicine, University of Bergen; Leik Woie, MD, Department of Cardiology, Stavanger University Hospital; Marta Ebbing MD, Department of Heart Disease, Haukeland University Hospital.

**Safety Committee:** Rolv T. Lie, PhD (chair), Section for Epidemiology and Medical Statistics, Department of Public Health and Primary Health Care, University of Bergen; Terje R. Pedersen, MD, Centre for Preventive Medicine, Ullevål University Hospital, Oslo, Norway.

**Funding/Support:** WENBIT was funded by the Advanced Research Program and Research Council of Norway, the Norwegian Foundation for Health and Rehabilitation, the Norwegian Heart and Lung Patient Organization, the Norwegian Ministry of Health and Care Services, the Western Norway Regional Health Authority, the Department of Heart Disease at Haukeland University Hospital, Locus for Homocysteine and Related Vitamins at the University of Bergen, Locus for Cardiac Research at the University of Bergen, the Foundation to Promote Research Into Functional Vitamin B12 Deficiency, and Alpharma Inc.

**Role of the Sponsors:** The main sponsors were nonprofit organizations with no participating role in the trial. Alpharma Inc provided the study capsules, generated the randomization sequence, and concealed the randomization code free of charge and rendered a limited grant to finance the initial phase of the trial. However, Alpharma Inc had no role in the design or implementation of the trial, had no access to study data, and did not participate in data analysis or interpretation or in the preparation, review, or approval of the manuscript.

**Approvals:** The study protocol was in accordance with the principles of the Declaration of Helsinki, and the trial was approved by the Regional Committee for

Medical and Health Research Ethics, the Norwegian Medicines Agency, and the data handling by the Data Inspectorate. WENBIT was registered with clinicaltrials.gov, Identifier: NCT00354081.

# Appendix IV NORVIT forms and questionnaires

NORVIT

Norsk multisenterstudie: Effekt av vitaminer ved hjerteinfarkt

# Forespørsel om å delta i forskningsprosjekt

Etter et hjerteinfarkt er det viktig å hindre tilbakefall. Vi kjenner noen behandlinger som reduserer denne risikoen, men flere av disse har dessverre uønskete bivirkninger. I denne undersøkelsen vil vi se om en enkel behandling med vitaminer kan forebygge tilbakefall. De som deltar vil kunne bidra vesentlig til den fremtidige behandling av hjertepasienter og til forebygging av sykdom.

## Bakgrunn for undersøkelsen

Det finnes grunn til å undersøke om B-vitaminer kan forebygge tilbakefall hos pasienter som har hatt hjerteinfarkt. En rekke norske sykehus har derfor gått sammen om NORVIT-undersøkelsen der noen pasienter får B-vitaminer i forskjellige doser og noen får en juksetablett. Ingen har undersøkt dette før, og vi vet ikke om behandlingen er effektiv. Alle deltakere får i tillegg alle de behandlinger som sykehuset mener er nødvendig og riktig. Du kan delta hvis du er i alderen 30-84 år og har hatt hjerteinfarkt i løpet av de siste 7 dager og ikke har annen alvorlig sykdom.

## Hvordan foregår undersøkelsen?

Undersøkelsen varer i ca. 3 år. De første to uker tar man to kapsler daglig, deretter en daglig. Verken du eller legen vet om kapselen inneholder vitaminer. Studien krever en kontroll på sykehuset etter ca. to måneder og ytterligere en etter ca. 3 år. For øvrig følges kontrollrutinene ved sykehuset og din faste lege.

Hver 6. måned får du tilsendt kapsler for neste halvår fra Regionsykehuset i Tromsø. Samtidig får du et spørreskjema som skal returneres i en vedlagt, frankert konvolutt. Du vil bli spurt om helsetilstanden og om du har husket å ta kapslene. Hvis du har vært syk eller innlagt på sykehus siden sist, vil vi be om å få lov til å innhente opplysninger fra sykehuset, fra din egen lege eller fra helseregistre. Dette er viktig fordi de som leder studien og kontrollerer den (Statens legemiddelkontroll) vil ha behov for å sjekke at det ikke oppstår misforståelser om hvilke sykdommer du har hatt. Ingen opplysninger vil komme på avveie.

## Følgende forhold er viktig å kjenne til:

1. Deltakelse er frivillig. De som ikke ønsker å delta, får ikke dårligere behandling enn de som deltar. Det er ikke nødvendig å begrunne hvorfor man eventuelt ikke ønsker å delta.
2. Det er viktig at deltakerne tar kapslene og returnerer spørreskjemaene.
3. De som underveis i studien ikke ønsker å delta videre, kan slutte uten å begrunne dette og uten at det får innvirkning på behandling og oppfølging fra sykehuset. Opplysninger som ble gitt før man sluttet, vil inngå i undersøkelsen.
4. Det er svært sjelden at de vitaminmengdene som skal brukes i denne studien gir bivirkninger. Deltakerne er forsikret gjennom pasientskadeordningen og egen forsikring tegnet av det firma som produserer vitaminene.
5. Vitaminene kan påvirke effekten av noen få legemidler, bl.a. midler som brukes ved epilepsi og Parkinsons sykdom. Det er derfor viktig at du forteller legen din at du er med i denne studien.
6. Deltakerne får informasjon om resultatene ved avslutning av studien. Dersom du har spørsmål underveis, kan du kontakte

Navn på kontaktperson ved sykehuset _____

## Vitaminer og hjernefunksjon

Det er teoretisk mulig at vitaminer kan ha en viss gunstig effekt på hukommelse og andre hjernefunksjoner. Noen sykehus vil forsøke å kartlegge dette ved å stille en del spørsmål til deltakerne. Dette tar ca. 10 minutter, og spørsmålene vil av mange oppfattes som svært enkle.

## Samtykke

Jeg har lest informasjonen om undersøkelsen og samtykker i å delta. Jeg gir tillatelse til at det kan hentes opplysninger om meg fra sykehus-journalen, helseregistre, folkeregisteret (adresseendring), min faste lege og meg selv.

❑ Kryss her hvis du ikke ønsker å besvare spørsmål om hukommelse og hjernefunksjon

Fødselsdato _____ Navn _____

Bruk blokkbokstaver

Sted _____ Dato _____

Underskrift _____

**Vennligst undertegn to eksemplarer av samtykket. Det ene beholdes av deltaker. Det andre eksemplaret arkiveres ved sykehuset.**

# NORVIT

Norsk multisenterstudie: Effekt av vitaminer ved hjerteinfarkt

# Skjema ved inklusjon

Dette skjema fylles ut så snart pasienten er stabil og senest 7 dager etter akutt hjerteinfarkt.

## Hva er NORVIT?

NORVIT er en randomisert, dobbelt blind, norsk sekundærprofylaktisk multisenterstudie som undersøker om behandling med B-vitaminer kan forebygge tilbakefall av kardiovaskulær sykdom etter akutt hjerteinfarkt. Ca. 40 norske sykehus deltar. I alt 3500 pasienter randomiseres til tre forskjellige B-vitamin tilskudd eller placebo. Alle deltakerne gis i tillegg standard postinfarktbehandling på vanlig klinisk indikasjon. Studien vil pågå i ca. tre år.

NORVIT har en enkel design med inklusjon så snart pasienten er stabil etter gjennomgått akutt hjerteinfarkt og kontroll etter ca. to måneder (1-3 avhengig av sykehusets rutiner) og ved avslutning av studien. Fordi B-vitaminer i de doser som gis ikke har kjente bivirkninger, vil en stor andel av infarktpasientene kunne inkluderes i NORVIT.

NORVIT er en forskerinitiert studie med et trangt budsjett som gjennomføres takket være betydelig ekstra innsats ved norske sykehus.

NORVIT er den første studien som tester effekten av forskjellige B-vitaminer. Studien vil kunne gi ny kunnskap om behandling og forebygging av kardiovaskulær sykdom.

## Denne inklusjonspakken inneholder

1. Skjema ved inklusjon (dette skjema) og ferdig frankert konvolutt for retur av utfylt skjema til NORVIT
2. Orientering til sykepleier/lege om NORVIT
3. Forespørsel til pasient om å delta i forskningsprosjekt med samtykke-erklæring
4. Brev til pasientens faste lege (orientering om pasient som deltar i NORVIT-undersøkelsen)

## Lykke til!

## Trenger du flere opplysninger om NORVIT?

Dette skjema med innlegg inneholder de opplysninger du trenger for å inkludere pasienter i NORVIT. Ved sykehuset er det en koordinerende lege og sykepleier for NORVIT. Disse har komplett protokoll for studien og kan gi ytterligere opplysninger. Du kan også kontakte NORVIT direkte.

Sykehusets koordinerende lege og sykepleier:

_____

_____

NORVIT v/Sissel Andersen, Institutt for samfunnsmedisin, Universitetet i Tromsø, 9037 Tromsø
Telefon 77 64 48 16. Telefaks 77 64 48 31. E-post norvit@ism.uit.no

Sykehus _____

Pasientens navn _____

Fødselsdato og personnr. (11 siffer) I____I____I____I_____
DAG MND ÅR PERSONNUMMER

Adresse _____

Post nr _____ Telefon _____

Fast primærlege/navn _____

Adresse _____

*Randomiseringsnr (klistrelapp) festes her*

**Dato for det hjerteinfarkt som fører til inklusjon i NORVIT**
**Dato for ekstra blodprøve til NORVIT**
**Dato for første dose med NORVITs studiemedikasjon**

DAG MND ÅR

## Kriterier for inklusjon/eksklusjon

| | | |
|---|---|---|
| 1. Gjennomgått akutt hjerteinfarkt i løpet av de siste 7 dager? | Ja | Nei |
| 2. Alder 30-84 år? | Ja | Nei |
| 3. Har pasienten undertegnet samtykke-erklæringen? | Ja | Nei |
| 4. Forventet manglende evne eller motivasjon til å følge forsøksplanen? | Ja | Nei |
| 5. Alvorlig sykdom unntatt hjertesykdom (f.eks. kreft, nyresvikt som krever dialyse, eller gjennomgått organtransplantasjon) med forventet levetid mindre enn 4 år? | Ja | Nei |
| 6. Indikasjon for behandling med B-vitaminer? | Ja | Nei |

Dersom «Ja» for spørsmål 1-3 og «Nei» for spørsmål 4-6, kan pasienten delta i NORVIT

## Tidligere sykdommer, vitamin-tilskudd, røyk

| | | | |
|---|---|---|---|
| Tidligere hjerteinfarkt? | Ja | Nei | Usikker |
| Tidligere angina pectoris? | Ja | Nei | Usikker |
| Tidligere hjerneslag? | Ja | Nei | Usikker |
| Diabetes mellitus? | Ja | Nei | Usikker |
| Tidligere koronaroperert (CABG)? | Ja | Nei | |
| Tidligere percutan koronar angioplastikk (PTCA)? | Ja | Nei | Usikker |
| Tar pasienten vitamin-tilskudd regelmessig? | Ja | Nei | Usikker |

Hvis ja, hvilke? _____

| | | | |
|---|---|---|---|
| Var pasienten under medikamentell behandling for høyt blodtrykk ved innleggelse? | Ja | Nei | Usikker |
| Røyker pasienten sigaretter/tobakk daglig? | Ja | Nei | Usikker |

Hvis pasienten ikke røyker nå, men har røykt daglig tidligere, hvor lenge er det siden røykestopp? _____

## Opplysninger om det aktuelle hjerteinfarkt

Fikk pasienten fibrinolytisk behandling? Ja Nei

SYMPTOM

Brystsmerter? Ja Nei

Varighet av brystsmerter_____ minutter

Eventuelle andre symptom _____

EKG

Nye EKG forandringer? Ja Nei Usikker

Ny Q-takk? Ja Nei

Bredde av ny Q-takk: ≥0.04 sekund <0.04 sekund

Amplityde av ny Q-takk ≥25% av R-takk <25% av R-takk

Nytilkommet eller sekvensiell ST-T hevning eller senkning? Ja Nei

Lokalisasjon? Fremre vegg (≥1mm)

Nedre vegg (≥0.5mm)

Nytilkommet eller sekvensiell utvikling av persisterende negativ T-bølge? Ja Nei

Hvilke avledninger? _____

ENZYMER

Angi hvilke enzymer eller andre biokjemiske markører som ble målt. Oppgi resultat av inntil 4 målinger hvorav en verdi må være den høyeste som ble registrert. Oppgi dato for hver måling.

| ENZYM/MARKØR | DAG MND | DAG MND | DAG MND | DAG MND |
|---|---|---|---|---|
| | | | | |
| | RESULTAT | | | |
| 1. _____ | | | | |
| 2. _____ | | | | |
| 3. _____ | | | | |

## Kolesterol, kreatinin, blodtrykk, høyde og vekt

S-kolesterol ved innleggelse , mmol/L

S-kreatinin ved innleggelse mmol/L

Blodtrykk ved inklusjon (NB) systolisk mmHg

diastolisk mmHg

Spør pasienten om høyde og vekt høyde cm

, vekt kg

**Se neste side for opplysning om rutiner i forbindelse med inklusjon av pasient til NORVIT. Kopier side 2 og 3 av dette skjema til sykehusets NORVIT-arkiv. Dette skjema sendes i ferdig frankert konvolutt til NORVIT.**

Dato _____Underskrift_____

## Rutiner ved inklusjon av pasient i NORVIT (kryss av)

- [ ] Orientér pasienten om NORVIT og be pasienten lese «Forespørsel om å delta i forskningsprosjekt» og undertegne samtykkeerklæringen på samme ark.
  Pasienten skal beholde et eksemplar, det andre oppbevares i sykehusets NORVIT-arkiv.

- [ ] Fyll ut side 2 og 3 av dette skjema.

- [ ] Ta ut en av de nummererte klistrelappene fra plastposen som inneholder de to boksene med studiemedikasjon. Påse at nummeret på lappen er identisk med nummeret på boksene.
  Fest klistrelappen øverst til høyre på side to av dette skjemaet.
  *Dette er svært viktig fordi nummeret angir behandlingskoden.*

- [ ] Gi pasienten medikamentboksene.
  *NB: Første dose (1 kapsel fra hver boks) skal ikke tas før etter at det er tatt ekstra blodprøve til NORVIT.*

- [ ] Rekvirèr ekstra blodprøve til NORVIT. Sykehuset har lokale rutiner for dette.

- [ ] *Etter* at ekstra blodprøve til NORVIT er tatt skal pasienten ta første dose av NORVITs studiemedikasjon. Det skal tas 1 kapsel daglig fra *hver* av de to boksene i 14 dager (altså 2 kapsler daglig i 14 dager), deretter skal pasienten fortsette med 1 kapsel daglig fra den store boksen så lenge studien varer. Pasienten vil få tilsendt ny forsyning fra NORVIT hver 6. måned.

- [ ] Merk pasientjournalen med NORVIT-logoen (klistrelapp).

- [ ] Send NORVITs ferdig formulerte brev «Orientering om pasient som deltar i NORVIT-undersøkelsen» til pasientens faste lege.

- [ ] Kopier side 2 og 3 av dette skjemaet til sykehusets lokale arkiv over deltakere i NORVIT.

- [ ] Vennligst send dette skjema så snart som mulig til NORVIT i ferdig frankert konvolutt.

- [ ] Bestill poliklinisk kontroll om ca. 2 (1-3) måneder.

- [ ] Vennligst send kopi av epikrisen til NORVIT.

Se «Orientering til sykepleier/lege» for opplysninger om videre oppfølging av deltakerne i NORVIT.

# NORVIT

Norsk multisenterstudie: Effekt av vitaminer ved hjerteinfarkt

# Skjema ved kontroll

Fylles ut ved kontroll ca. 2 (1-3) måneder etter at pasienten ble inkludert i NORVIT

## Hva er NORVIT?

NORVIT er en randomisert, dobbelt blind, norsk sekundærprofylaktisk multisenterstudie som undersøker om behandling med B-vitaminer kan forebygge tilbakefall av kardiovaskulær sykdom etter akutt hjerteinfarkt. Ca. 40 norske sykehus deltar. I alt 3500 pasienter randomiseres til tre forskjellige B-vitamin tilskudd eller placebo. Alle deltakerne gis i tillegg standard postinfarktbehandling på vanlig klinisk indikasjon. Studien vil pågå i ca. tre år.

NORVIT har en enkel design med inklusjon så snart pasienten er stabil etter gjennomgått akutt hjerteinfarkt og kontroll etter ca. to måneder (1-3 avhengig av sykehusets rutiner) og ved avslutning av studien. Fordi B-vitaminer i de doser som gis ikke har kjente bivirkninger, vil en stor andel av infarktpasientene kunne inkluderes i NORVIT.

NORVIT er en forskerinitiert studie med et trangt budsjett som gjennomføres takket være betydelig ekstra innsats ved norske sykehus.

NORVIT er den første studien som tester effekten av forskjellige B-vitaminer. Studien vil kunne gi ny kunnskap om behandling og forebygging av kardiovaskulær sykdom.

## Trenger du flere opplysninger om NORVIT?

Skjemaet er selvforklarende. Baksiden innholder ytterligere opplysninger om rutiner ved kontroll av pasienter som er med i NORVIT. Ved sykehuset er det en koordinerende lege og sykepleier for NORVIT. Disse har komplett protokoll for studien og kan gi ytterligere opplysninger. Du kan også kontakte NORVIT direkte.

Sykehusets koordinerende lege og sykepleier:

_____

_____

NORVIT v/Sissel Andersen, Institutt for samfunnsmedisin, Universitetet i Tromsø, 9037 Tromsø
Telefon 77 64 48 16. Telefaks 77 64 48 31. E-post norvit@ism.uit.no

Sykehus_____

Pasientens navn _____

Fødselsdato og personnr. (11 siffer) |____|____|____|_____
DAG MND ÅR PERSONNUMMER

Adresse_____

Post nr_____ Telefon _____

Fast primærlege/navn _____

Adresse _____

## Hendelser/symptom etter inklusjon i NORVIT

| | | | |
|---|---|---|---|
| Reinnlagt på sykehus etter inklusjon? Hvilket sykehus?_____ | Ja | Nei | Usikker |
| Nytt hjerteinfarkt? | Ja | Nei | Usikker |
| Nytt hjerneslag? | Ja | Nei | Usikker |
| Angina pectoris? | Ja | Nei | Usikker |
| Koronar operasjon (CABG)? | Ja | Nei | Usikker |
| Percutan koronar angioplastikk (PTCA)? | Ja | Nei | Usikker |
| Lungeemboli? | Ja | Nei | Usikker |
| Dyp venetrombose? | Ja | Nei | Usikker |
| Transitorisk ischemisk atakk (TIA)? | Ja | Nei | Usikker |
| Annen kardiovaskulær hendelse? *Spesifiser på neste side.* | Ja | Nei | Usikker |

*Husk å fylle ut NORVITs meldeskjema for hendelse dersom det er inntruffet en hendelse etter inklusjon.*

## Studiemedikasjon

| | | | |
|---|---|---|---|
| Har pasienten tatt studiemedikasjonen? (2 kapsler/dag de første to uker, deretter 1 kapsel/dag) | Ja, som foreskrevet | | |
| | Av og til glemt | | |
| | Ofte glemt | | |
| | Mer enn foreskrevet | | Usikker |
| Bivirkninger av studiemedikasjon? *Spesifiser på neste side.* | Ja | Nei | Usikker |
| Fortsetter med studiemedikasjon? *Spesifiser på neste side.* | Ja | Nei | Usikker |
| Eventuell dato sluttet med studiemedikasjon. | | | |
| | DAG | MND | ÅR |

## Andre medikamenter som skal brukes i fortsettelsen etter kontrollen

| | | | |
|---|---|---|---|
| Acetyl salicyl | Ja | Nei | Usikker |
| Kolesterol senkende | Ja | Nei | Usikker |
| Betablokker | Ja | Nei | Usikker |
| ACE (angiotensin converting enzyme)-hemmer | Ja | Nei | Usikker |
| Angiotensin II-reseptor antagonist | Ja | Nei | Usikker |
| Calciumantagonist | Ja | Nei | Usikker |
| Diuretika | Ja | Nei | Usikker |
| Isosorbide mono/dinitrate | Ja | Nei | Usikker |
| Marevan | Ja | Nei | Usikker |

## Blodtrykk og pulsfrekvens

| | | |
|---|---|---|
| Systolisk | | mmHg |
| Diastolisk | | mmHg |
| Pulsfrekvens | | slag/min |

## Eventuelle kommentarer

Spesifiser eventuell annen kardiovaskulær hendelse

_____

_____

Spesifiser eventuelle bivirkninger av NORVITs studiemedikasjon

_____

_____

*NB: Ved mistanke om alvorlige bivirkninger skal SLKs skjema om bivirkninger fylles ut. Send kopi av SLK-skjemaet til NORVIT*

Andre kommentarer

_____

_____

_____

## Andre rutiner ved denne kontroll

1. Rekvirér ekstra blodprøve til NORVIT. Sykehuset har egen rutine for dette. Kontakt laboratoriet eller kontaktperson for NORVIT.

2. Presiser for pasienten at studiemedikasjonen må tas slik foreskrevet (1 kapsel daglig). Videre oppfølging/kontroll skjer på vanlig klinisk indikasjon. Bortsett fra sluttkontroll (etter ca. 3 år) inngår ingen videre kliniske kontroller i NORVIT. Sykehus og pasient vil få beskjed om tidspunkt for sluttkontroll fra NORVIT som også vil sende ny forsyning av studiemedikasjon og et spørreskjema til pasienten hver 6. måned mens studien pågår.

3. Ta kopi av side 2 og 3 av dette skjema til sykehusets arkiv over deltakere i NORVIT. Utfylt skjema sendes i ferdig frankert konvolutt til NORVIT.

*Se neste side for ytterligere opplysninger om NORVIT*

Dato _____ Underskrift _____

## Nærmere opplysninger om NORVIT

NORVIT tar sikte på å inkludere ca. 3500 pasienter i løpet av 1 1/2 år. Studien vil pågå til det har inntrått 750 primære endepunkt. Dette oppnås ved at alle pasienter følges inntil sist inkluderte pasient har vært fulgt i ca. 3 år. Det primære endepunkt er alvorlig kardiovaskulær hendelse, definert som kardiovaskulær død (død av koronarsykdom eller hjerneslag), non-fatalt hjerteinfarkt eller non-fatalt hjerneslag. Sekundære og tertiære endepunkt er angitt i NORVITs protokoll.

## Inklusjonskriterier

1. Inklusjon innen 7 dager etter gjennomgått akutt hjerteinfarkt.
2. Alder ≥30 år og <85 år ved inklusjon.
3. Undertegnet skriftlig samtykke.

## Eksklusjonskriterier

1. Forventet manglende evne eller motivasjon til å følge forsøksplanen.
2. Alvorlig livstruende sykdom (bortsett fra kardiovaskulær sykdom) med forventet levetid mindre enn 4 år, som f.eks. kreft, nyresvikt som krever dialyse, eller gjenomgått organtransplantasjon.
3. Indikasjon for behandling med Vitamin $B_{12}$, Vitamin $B_6$ eller folat (e.g. perniciøs anemi og vitamin $B_{12}$ mangel).

## Dosering av NORVITs studiemedikasjon

Ved inklusjon i NORVIT fikk pasienten utdelt NORVITs studiemedikasjon pakket i en stor og en mindre boks. Den store boksen inneholder ca. 200 kapsler og den mindre inneholder 14 kapsler. Pasienten ble bedt om å 1 kapsel fra hver boks daglig de første 14 dager etter inklusjon (2 kapsler per dag), og deretter fortsette med 1 kapsel daglig fra den store boksen. Hver 6. måned vil pasienten få tilsendt ny forsyning av kapsler fra NORVIT. Pasienten skal fortsette med 1 kapsel daglig så lenge studien varer.

## Videre oppfølging av pasienter etter denne kontroll

Etter denne kontroll skal pasienten følges opp på vanlig klinisk indikasjon. Hver 6. måned vil pasienten få tilsendt et spørreskjema om helsetilstanden som skal returneres til NORVIT. Dersom det fremgår at pasienten har vært innlagt på sykehus for kardiovaskulær sykdom eller gjennomgått kardiovaskulær operasjon eller behandlingsprosedyre, vil koordinerende lege eller sykepleier få melding om dette fra NORVIT og anmodet om å fylle ut NORVITs meldeskjema for hendelse. Dersom sykehuset på annen måte får opplysning om at en deltaker har vært innlagt på sykehus for kardiovaskulær sykdom eller er død skal NORVITs meldeskjema for hendelse fylles ut. Ved avslutning av NORVIT etter ca. 3 år vil pasienten bli innkalt til kontroll ved sykehuset. NORVIT vil sende melding til sykehuset om tidspunkt for denne kontrollen.

Det er viktig at NORVIT så snart som mulig får melding om kardiovaskulære hendelser som inntreffer hos deltakerne. NB! Deltakerne skal fortsette med NORVITs studiemedikasjon etter non-fatale hendelser.

## Melding av eventuelle bivirkninger

De vitaminer som benyttes i NORVIT har ingen kjente bivirkninger. Dersom det oppstår mistanke om bivirkninger skal melding om dette sendes Statens legemiddelkontroll (SLK) på ordinært skjema («Melding om bivirkning ved normal dosering av legemiddel»). Kopi av SLK-skjemaet skal sendes NORVIT.

SENDT UT ETTER 6 MND.

**SPØRRESKJEMA - NORVIT-UNDERSØKELSEN**

6

***Vennligst oppgi ny adresse og telefonnummer dersom det som står ovenfor ikke er korrekt***

Ny adresse: .....

Telefon ..... ..... .....

***Vennligst sett kryss!***

1. *Har du vært innlagt på sykehus etter at du begynte med NORVIT-kapselen?*
   ___ Nei
   ___ Ja

   Hvis ja, hvilken sykdom eller sykdommer førte til innleggelse?
   ___ Hjerteinfarkt
   ___ Angina pectoris (hjertekrampe)
   ___ Hjerteoperasjon
   ___ Utblokking av blodårer til hjertet
   ___ Hjerneslag eller drypp
   ___ Blodpropp
   ___ Annen sykdom, hvilken?.....

   Hvis ja, ved hvilket sykehus var du innlagt?.....

   Når var du innlagt? .....

2. *Bruker du medisinen i NORVIT studien som foreskrevet, det vil si 1 kapsel hver dag?*
   ___ Ja
   ___ Har av og til glemt/hoppet over
   ___ Har ofte glemt/hoppet over
   ___ Har brukt mer enn jeg skulle

3. *Har du hatt noen plager etter at du begynte med NORVIT- kapselen?*
   ___ Nei
   ___ Ja Hvis ja, hvilke plager er det?.....

   .....(fortsett ev på baksiden)

Returneres i svarkonvolutten til *NORVIT*, Universitetet i Tromsø, 9037 Tromsø

SENDT UT ETTER 12+18+24+30+36 MND.

**SPØRRESKJEMA - NORVIT-UNDERSØKELSEN**

12

***Vennligst oppgi ny adresse og telefonnummer dersom det som står ovenfor ikke er korrekt***

Ny adresse: .....

Telefon .....

Du har fått en ny boks med kapsler som du skal ta fra nå av.

***Vennligst skriv opp dato når du startet å ta kapsler fra den nye boksen: .....***

***Hvor mange kapsler er igjen i den gamle boksen: .....***

***Vennligst sett kryss!***

1. *Har du vært innlagt på sykehus i løpet av det siste halve året?*

___ Nei
___ Ja

*Hvis ja, hvilken sykdom førte til innleggelse?*

___ Hjerteinfarkt
___ Angina (hjertekrampe)
___ Hjerteoperasjon
___ Utblokking av blodårer til hjertet
___ Hjerneslag eller drypp
___ Blodpropp
___ Annen sykdom, hvilken? ..... .....

*Hvis ja, ved hvilket eller hvilke sykehus var du innlagt?*.....

*Når var du innlagt?* .....

2. *Hvordan er helsetilstanden din nå?* Kryss av for et alternativ

___ Meget dårlig

___ Dårlig

___ Verken god eller dårlig, middels

___ Bra

___ Utmerket

**VENNLIGST SNU ARKET!** **NORVIT 12**

3. *Bruker du medisinen i NORVIT studien som foreskrevet, det vil si 1 kapsel hver dag?*

___ Ja
___ Har av og til glemt/hoppet over
___ Har ofte glemt/hoppet over
___ Har brukt mer enn jeg skulle

4. *Har du hatt noen plager etter at du begynte med kapselen som du får i NORVIT-studien?*

___ Nei
___ Ja Hvis ja, hvilke plager er det? .....

.....

.....

5. *Røyker du daglig for tiden?*

___ Nei

___ Ja

*Hvis du ikke røyker nå, men har røykt tidligere, når sluttet du?* .....

***Vennligst returner skjemaet i den frankerte svarkonvolutten til***

***NORVIT, Universitetet i Tromsø, 9037***

# SPØRRESKJEMA VED AVSLUTNING AV NORVIT STUDIEN

*Navn og randnr*

Vi ber om at du fyller ut skjemaet hjemme og tar det med til sluttkontrollen på sykehuset. Hvis du er usikker på hvordan du skal svare, kan du be om hjelp på sykehuset. Noen av spørsmålene vil du kjenne igjen fra tidligere spørreskjemaer, men vi ber deg allikevel svare på disse nå ved avslutning av studien.

**Du ble med i NORVIT-studien den _____ da du var innlagt ved**

**_____ sykehus.**

**Har du vært innlagt på andre sykehus etter at du ble i NORVIT studien?**

Ja ☐ Nei ☐

**Hvis ja, ved hvilke sykehus har du vært innlagt og når var du innlagt (årstall)?** Hvis du har var innlagt ved samme sykehus flere ganger, er det tilstrekkelig å føre opp sykehuset en gang. Etter navnet på sykehuset føyer du til et eller flere årstall da du var innlagt

| Sykehus | Hvilke år var du innlagt? |
|---|---|
| _____ | _____ |
| _____ | _____ |
| _____ | _____ |
| _____ | _____ |
| _____ | _____ |
| _____ | _____ |
| _____ | _____ |
| _____ | _____ |

Hva heter din faste primærlege?

Navn:_____

Kontoradresse:_____

**Har du – eller har du hatt – noen av følgende sykdommer eller operasjoner <u>etter at du ble med i NORVIT-studien?</u>** Det hjerteinfarktet du hadde da du ble med i NORVIT regnes ikke med (Sett kryss)

| | | | |
|---|---|---|---|
| Hjerteinfarkt (sår på hjertet) | Ja ☐ | Nei ☐ | Usikker ☐ |
| Hjerneslag eller hjernedrypp | Ja ☐ | Nei ☐ | Usikker ☐ |
| Angina pectoris (hjertekrampe) | Ja ☐ | Nei ☐ | Usikker ☐ |
| Blodpropp i lungen (lungeemboli) | Ja ☐ | Nei ☐ | Usikker ☐ |
| Blodpropp i beina (venetrombose) | Ja ☐ | Nei ☐ | Usikker ☐ |
| Hjerteoperasjon | Ja ☐ | Nei ☐ | Usikker ☐ |
| Utblokking av blodårer til hjertet | Ja ☐ | Nei ☐ | Usikker ☐ |
| Operasjon av blodåre på halsen | Ja ☐ | Nei ☐ | Usikker ☐ |
| Operasjon av hovedpulsåre | Ja ☐ | Nei ☐ | Usikker ☐ |
| Operasjon av blodåre til beina | Ja ☐ | Nei ☐ | Usikker ☐ |
| Sukkersyke | Ja ☐ | Nei ☐ | Usikker ☐ |
| Kreftsykdom | Ja ☐ | Nei ☐ | Usikker ☐ |
| Sår på magesekken eller tolvfingertarmen | Ja ☐ | Nei ☐ | Usikker ☐ |
| Psykiske plager som du har søkt hjelp for | Ja ☐ | Nei ☐ | Usikker ☐ |
| Kronisk bronkitt | Ja ☐ | Nei ☐ | Usikker ☐ |
| Nyresykdom | Ja ☐ | Nei ☐ | Usikker ☐ |
| Hjerterytmeforstyrrelse | Ja ☐ | Nei ☐ | Usikker ☐ |

Har du i løpet av det siste året vært plaget med smerter og/eller stivhet i muskler og ledd? Ja ☐ Nei ☐

Hvis ja; har plagene vart sammenhengende i 3 måneder eller mer? Ja ☐ Nei ☐

Hvis ja; har plagene ført til redusert fysisk aktivitet? Ja ☐ Nei ☐

Har du i løpet av det siste året vært plaget med eksem eller utslett? Ja ☐ Nei ☐

Har du siden du ble med i studien merket endringer med ditt hår? (fargeendring, volumendring eller lignende) Ja ☐ Nei ☐

Hvis ja, hva slags endring .....

**Hvordan er helsen din nå?**

| | |
|---|---|
| Dårlig | ☐ |
| Ikke helt god | ☐ |
| God | ☐ |
| Svært god | ☐ |

**Har du de siste to ukene følt deg:**

| | Nei | Litt | En god del | Svært mye |
|---|---|---|---|---|
| Nervøs og urolig? | ☐ | ☐ | ☐ | ☐ |
| Plaget av angst? | ☐ | ☐ | ☐ | ☐ |
| Trygg og rolig? | ☐ | ☐ | ☐ | ☐ |
| Glad og optimistisk? | ☐ | ☐ | ☐ | ☐ |
| Nedfor/deprimert? | ☐ | ☐ | ☐ | ☐ |

**Hvordan har din fysiske aktivitet i fritiden vært det siste året?** Angi bevegelse og kroppslig anstrengelse i din fritid. Hvis aktiviteten varierer meget for eksempel mellom sommer og vinter, så ta et gjennomsnitt. Spørsmålet gjelder bare det siste året. Sett kryss i den ruten som passer best.

Leser, ser på fjernsyn eller annen stillesittende beskjeftigelse? ☐

Spaserer, sykler eller beveger deg på annen måte minst 4 timer i uka? ☐
(Her skal du også regne med gang eller sykling til arbeidsstedet, søndagsturer m.m)

Driver mosjonsidrett, tyngre hagearbeid eller lignende? ☐

Trener hardt eller driver konkurranseidrett regelmessig og flere ganger i uka? ☐

**Har du deltatt i organisert hjertetrening/hjerterehabilitering etter at du ble med i NORVIT studien?**

Ja ☐ Nei ☐

**Synes du hukommelsen er blitt dårligere etter at du ble med i NORVIT-studien?**

Nei ☐
Litt dårligere ☐
Mye dårligere ☐
Vet ikke ☐

**Hvis hukommelsen har endret seg, hvordan skjedde det?**

Plutselig ☐
Gradvis ☐

**Røyker du daglig?** Ja ☐ Nei ☐

**Hvor mange ganger i måneden drikker du vanligvis alkohol?** Regn ikke med lettøl.

Sett 0 hvis mindre enn 1 gang i måneden Antall ganger _____

**Hvilken utdanning er den lengste du har fullført?**

Grunnskole, 7-10 år, framhaldsskole, folkehøgskole ☐
Realskole, middelskole, yrkesskole, 1-2 årig videregående skole ☐
Artium, øk.gymnas, allmennfaglig retning i videregående skole ☐
Høgskole/universitet, mindre enn 4 år ☐
Høgskole/universitet, 4 år eller mer ☐

**Har du tatt NORVIT-medisinen som foreskrevet, det vil si 1 kapsel hver dag?**

Ja ☐
Har av og til glemt/hoppet over ☐
Har ofte glemt/hoppet over ☐
Har brukt mer enn jeg skulle ☐

**Skriv ned navn, styrke og dose på alle medisiner som du tar daglig eller regelmessig**

| Navn | Styrke | Dose (hvor ofte tar du medisinen) |
|---|---|---|
| | | |
| | | |
| | | |
| | | |
| | | |
| | | |
| | | |
| | | |
| | | |
| | | |

**Bruk av helsevesenet**

Hvor mange ganger har du i løpet av de siste 12 månedene, på grunn av egen helse eller sykdom, vært (sett 0 hvis du **ikke** har hatt slik kontakt):

| | Antall ganger siste 12 måneder |
|---|---|
| Hos vanlig lege/legevakt | |
| Hos psykolog eller psykiater | |
| Hos annen legespesialist utenfor sykehus | |
| På poliklinikk | |
| Innlagt i sykehus | |
| Hos fysioterapeut | |

**Forespørsel om helseopplysninger etter avsluttet behandling med NORVIT-medisinen.**

Du har nå deltatt i siste kontroll i NORVIT-studien. Fra nå av skal du ikke ta NORVIT-medisinen. Du vil få informasjon om resultatene av studien, og hvilken behandling du fikk, etter at alle deltakere har vært til sluttkontroll. Denne informasjonen vil bli sendt ut høsten 2004.

Vi vet ikke om behandling med vitaminer har langtidseffekter etter at behandlingen er avsluttet. For å undersøke om dette er tilfellet er det nødvendig med informasjon om helsetilstanden til deltakerne i NORVIT-studien. Vi spør derfor om tillatelse til å få informasjon om eventuelle sykdommer i inntil 10 år etter at behandling med NORVIT-medisinen ble avsluttet. De opplysninger som vil bli innhentet er navn på sykdommen (diagnose) og om det er utført hjerteoperasjon eller utblokking av blodårer. Opplysningene vil bli hentet fra sykehusjournal, primærlege og nasjonale helseregistre. Opplysningene behandles konfidensielt av NORVITs egne prosjektmedarbeidere som har taushetsplikt.

Det er frivillig å delta i oppfølgingen. Deltakere kan når som helst trekke seg fra oppfølgingen uten begrunnelse. De opplysninger som er samlet inn før man eventuelt slutter, vil inngå i undersøkelsen etter at navn og personnummer er slettet. Dersom man ikke ønsker å delta, eller senere trekker deg fra oppfølgingen, vil det ikke få konsekvenser for forholdet til helsevesenet. Etter prosjektslutt, som beregnes til å være i 2014, vil alle opplysninger anonymiseres. Deltakerne får tilsendt informasjon om konklusjonene fra prosjektet når det avsluttes.

Spørsmål om prosjektet kan rettes til NORVIT, Institutt for Samfunnsmedisin, Universitetet i Tromsø, 9037 Tromsø, telefon 77 64 48 16.

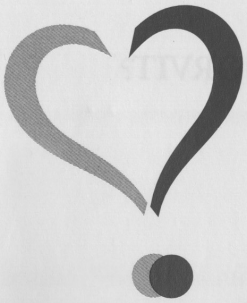
**Samtykke**

Jeg samtykker i at NORVIT-studien innhenter opplysninger om sykdom og sykdomsinnleggelser i inntil 10 år etter at jeg er sluttet med NORVIT-medisinen.

Ja ___ Nei ___

_____ _____

Dato Underskrift



NORVIT

Norsk multisenterstudie: Effekt av vitaminer ved hjerteinfarkt

# Skjema ved sluttkontroll

Sykehus som inkluderte pasienten: _____

## Veiledning ved sluttkontroll:

Skjemaet kan fylles ut av sykepleier eller lege. Den viktigste oppgaven ved sluttkontrollen er å sikre at alle opplysninger som kan bidra til å belyse om pasienten har hatt et endepunkt blir sendt til NORVIT. Den enkleste måten er å sende kopi til NORVIT av alle relevante epikriser for innleggelser som har funnet sted etter at pasienten ble med i NORVIT. Det er bedre å sende en epikrise for mye enn en for lite. Husk: alle epikriser – også for innleggelser for andre tilstander enn NORVITs endepunkter – kan inneholde informasjon som kan bidra til å belyse om pasienten har hatt et endepunkt. Det er ikke nødvendig å sende ny kopi av epikriser som allerede er sendt (se neste side). Den endelige klassifikasjon av endepunkt blir foretatt av NORVIT. Det innebærer at dersom du er usikker på om en hendelse/innleggelse fyller kriteriene for et endepunkt, så skal du sende epikrisen til NORVIT. NORVIT må ha alle epikriser om følgende tilstander:

*Hjerteinfarkt*
*Hjerneslag*
*Angina pectoris*
*Hjertesvikt eller kardiogent sjokk*
*By-pass operasjon (ACB)*
*Utblokking av koronar arterier (PTCA/PCI)*
*TIA (transitorisk ichemisk attakk)*
*Lungeemboli*
*Dyp venetrombose (DVT)*
*Operasjon eller stenting for aortaaneurysme*
*Operasjon eller stenting for claudicatio intermittens*
*Operasjon for carotis stenose*
*Kreft*
*Alvorlig ventrikkelarytmi*
*Atrieflimmer*
*Alvorlig depresjon/demens*

Ta imot spørreskjemaet "Spørreskjema ved avslutning av NORVIT studien" som pasienten skal ha fylt ut hjemme. Bruk eventuelt ekstra skjema hvis pasienten ikke har tatt med det tilsendte. Sluttkontrollen er ikke fullført før spørreskjemaet og dette sluttkontroll skjemaet er utfylt! Kontroller at alle spørsmål er besvart. Vær eventuelt behjelpelig med avkrysning på ubesvarte spørsmål. Sjekk spesielt om pasienten har krysset av og undertegnet på siste side for tillatelse til videre oppfølging.

Kontrollen består for øvrig av:
1. Utfylling av dette skjemaet
2. Blodprøvetaking (NORVIT-prøver som ved inklusjon og kontroll – sendes Haukeland)
3. Blodprøve til lokalt laboratorium for analyse av kolesterol og kreatinin
4. Registrering av BT, puls, vekt og EKG

NORVIT v/Sissel Andersen, Institutt for samfunnsmedisin, Universitetet i Tromsø, 9037 Tromsø
Telefon 77 64 48 16. Telefaks 77 64 48 31. E-post norvit@ism.uit.no

## Blir sluttkontroll utført ved samme sykehus som inkluderte pasienten i NORVIT?

Ja ☐ Nei ☐

Hvis nei, oppgi navn på sykehus som utfører sluttkontrollen:

_____

## NORVIT har registrert følgende innleggelser og diagnoser for denne pasienten

Dato for innleggelsen:

| | Hjerteinfarkt | Hjerneslag | Annet |
|---|---|---|---|
| _____ | ☐ | ☐ | ☐ |
| _____ | ☐ | ☐ | ☐ |
| _____ | ☐ | ☐ | ☐ |
| _____ | ☐ | ☐ | ☐ |
| _____ | ☐ | ☐ | ☐ |
| _____ | ☐ | ☐ | ☐ |
| _____ | ☐ | ☐ | ☐ |
| _____ | ☐ | ☐ | ☐ |
| _____ | ☐ | ☐ | ☐ |
| _____ | ☐ | ☐ | ☐ |

## Har pasienten, etter at han/hun ble inkludert i NORVIT, flere innleggelser enn de som er nevnt ovenfor ved det sykehus hvor han/hun ble inkludert? Vær spesielt oppmerksom på innleggelser ved andre avdelinger enn medisin/kardiologi – som for eksempel nevrologisk avd., geriatrisk avd., kirurgisk avd. m.fl.

Ja ☐ Nei ☐ Usikker ☐

Hvis ja, ta kopi av alle aktuelle epikriser og send dem til NORVIT!

## Har pasienten, etter at han/hun ble inkludert i NORVIT, vært innlagt ved andre sykehus enn det sykehus som inkluderte pasienten i NORVIT?

Ja ☐ Nei ☐ Usikker ☐

Hvis ja, kontroller at navn på aktuelle sykehus og årstall for innleggelser er ført opp på første side på pasientens spørreskjema. Send kopi av eventuelle epikriser hvis de er i pasientens journal.

## Har pasienten symptomer på angina pectoris for tiden? Spør om typiske symptomer

Ja ☐ Nei ☐ Usikker ☐

## Kryss for medikamenter som pasienten bruker for tiden

| | | | |
|---|---|---|---|
| Acetyl salicyl | Ja | Nei | Usikker |
| Kolesterolsenkende | Ja | Nei | Usikker |
| Betablokker | Ja | Nei | Usikker |
| ACE (angiotensin converting enzyme) - hemmer | Ja | Nei | Usikker |
| Angiotensin II-receptor antagonist | Ja | Nei | Usikker |
| Calcium-antagonist | Ja | Nei | Usikker |
| Diuretika | Ja | Nei | Usikker |
| Langtidsvirkende nitroglycerin | Ja | Nei | Usikker |
| Marevan | Ja | Nei | Usikker |
| Bruker pasienten korttidsvirkende nitroglycerin for tiden? | Ja | Nei | Usikker |

## NORVIT studiemedikasjon

Har pasienten tatt NORVIT studiemedikasjon inntil sluttkontroll?

Ja Nei Usikker

Hvis nei, når sluttet pasienten med studiemedikasjonen? Redegjør for eventuell usikkerhet knyttet til om pasienten har tatt studiemedikasjonen.

_____

_____

_____

_____

_____

## Blodtrykk, puls og vekt

Systolisk _____ mmHg

Diastolisk _____ mmHg

Puls _____ slag/min

Vekt _____ kg

## Blodprøver

Total kolesterol _____ mmol/L

Kreatinin _____ mmol/L

## Ta EKG!

**Med de epikriser som NORVIT allerede har mottatt (jfr. ovenfor) og de som eventuelt sendes ved denne sluttkontrollen, tror du da at NORVIT har mottatt alle relevante epikriser for denne pasienten?**

☐ Ja ☐ Nei ☐ Usikker

Hvis nei, vennligst gi opplysninger om eventuelle innleggelser du tror vi mangler epikrise for:

_____

_____

_____

_____

_____

_____

_____

_____

_____

_____

_____

_____

_____

_____

_____

_____

_____

Dato for sluttkontroll _____

Underskrift av sykepleier eller lege_____

Følgende sendes NORVIT:

Dette skjemaet
Spørreskjema til pasienten
Eventuelle epikriser
Dagens EKG

NORVIT

Norsk multisenterstudie: Effekt av vitaminer ved hjerteinfarkt

# Meldeskjema for kardiovaskulær hendelse eller død

## Vennligst meld følgende hendelser til NORVIT snarest mulig:

NB! Gjelder både sikre og sannsynlige hendelser/diagnoser.

**Dødsfall**

**Akutt hjerteinfarkt** - non-fatalt og fatalt

**Annen koronar hendelse,** inkludert

Innleggelse for ustabil angina pectoris eller langvarige brystsmerter uten påvist akutt hjerteinfarkt
Akutt hjertesvikt/kardiogent sjokk uten påvist akutt hjerteinfarkt
Koronar bypass operasjon (CABG) eller percutan transluminal coronar angioplastikk (PTCA)

**Hjerneslag** - non-fatalt og fatalt hjerneslag, og transitorisk ischemisk attakk (TIA)

**Annen kardiovaskulær hendelse,** inkludert

Dyp venetrombose
Lungeemboli
Primær hjertearytmi
Aortaaneurisme
Carotis-endarterektomi
Andre hjerte-sykdommer eller arteriosklerotisk sykdom

1. Vennligst fyll ut ett skjema for hver hendelse.
2. Sikre og sannsynlige hendelser (diagnoser) skal meldes. NORVIT vil foreta endelig klassifikasjon.
3. Ved innleggelse: send kopi av epikrise til NORVIT.
4. Returner utfylt skjema til NORVIT i ferdig frankert konvolutt. Ta kopi av sidene 2-4 til sykehusets NORVIT-arkiv.

## Trenger du flere opplysninger om NORVIT?

Ved sykehuset er det en koordinerende lege og sykepleier for NORVIT. Disse har komplett protokoll for NORVIT og kan gi ytterligere opplysninger. Du kan også kontakte NORVIT direkte.

Sykehusets koordinerende lege og sykepleier:

_____

_____

NORVIT v/Sissel Andersen, Institutt for samfunnsmedisin, Universitetet i Tromsø, 9037 Tromsø
Telefon 77 64 48 16. Telefaks 77 64 48 31. E-post norvit@ism.uit.no

Pasientens navn _____

Fødselsdato og personnr. (11 siffer) |____|____|____|_____
DAG MND ÅR PERSONNUMMER

Dato for symptomdebut (hvis ukjent: dato for diagnose):

| | DAG | MND | ÅR |
|---|---|---|---|
| Ble pasienten innlagt på sykehus? | Ja | Nei | |
| Hvilket sykehus?_____ | | | |
| Hvis ja: | DAG | MND | ÅR |
| Dato for innleggelse | | | |
| Dato for utskrivning | | | |
| Tilstand ved utskrivning | i live | død | |

*Sett kryss for diagnose*

## Akutt hjerteinfarkt

| | | |
|---|---|---|
| Fikk pasienten fibrinolytisk behandling? | Ja | Nei |

### SYMPTOM

| | | |
|---|---|---|
| Brystsmerter? | Ja | Nei |
| Varighet av brystsmerter_____ minutter | | |

Eventuelle andre symptom _____

### EKG

| | | | |
|---|---|---|---|
| Nye EKG forandringer? | Ja | Nei | Usikker |
| Ny Q-takk? | Ja | Nei | |
| Bredde av ny Q-takk: | ≥0.04 sekund | <0.04 sekund | |
| Amplityde av ny Q-takk | ≥25% av R-takk | <25% av R-takk | |
| Nytilkommet eller sekvensiell ST-T hevning eller senkning? | Ja | Nei | |
| Lokalisasjon? | Fremre vegg (≥1mm) | | |
| | Nedre vegg (≥0.5mm) | | |
| Nytilkommet eller sekvensiell utvikling av persisterende negativ T-bølge? | Ja | Nei | |
| Hvilke avledninger? _____ | | | |

### ENZYMER

Angi hvilke enzymer eller andre biokjemiske markører som ble målt. Oppgi resultat av inntil 4 målinger hvorav en verdi må være den høyeste som ble registrert. Oppgi dato for hver måling.

| ENZYM/MARKØR | DAG MND | DAG MND | DAG MND | DAG MND |
|---|---|---|---|---|
| | RESULTAT | | | |
| 1. _____ | | | | |
| 2. _____ | | | | |
| 3. _____ | | | | |

## Annen koronar hendelse *(Sett kryss)*

Ustabil angina pectoris eller langvarige brystsmerter uten påvist ferskt hjerteinfarkt

Akutt hjertesvikt/kardiogent sjokk uten påvist ferskt hjerteinfarkt

Koronar bypass operasjon (CABG)

Percutan transluminal coronar angioplastikk (PTCA)

## Hjerneslag *(Sett kryss)*

Subarachnoidalblødning

Cerebralt infarkt

Intracerebral blødning

Uspesifisert hjerneslag

Transitorisk ischemisk attakk (TIA)

Annen diagnose, spesifiser: _____

**Ved hjerneslag:** Diagnosen er basert på *(kryss av for ett eller flere alternativer)*

Symptomer

Varighet mer enn 24 timer? Ja Nei

Spinalvæske-undersøkelse

CT

MR

Angiografi

**Ved TIA:** Diagnosen er basert på (*sett ett kryss*)

Kun sykehistorie

Sykehistorie og kliniske tegn

## Annen kardiovaskulær hendelse *(Sett kryss)*

Dyp venetrombose

Lungeemboli

Primær hjertearytmi

Aortaaneurisme

Carotis-endarterektomi

Annen hjertesykdom eller arteriosklerotisk sykdom

Spesifiser annen sykdom_____

_____

Dato _____Underskrift_____

Adresse_____

**NB! Fyll ut neste side ved dødsfall.**

# Fylles ut ved dødsfall

## Dato for dødsfall

DAG MND ÅR

## Hvor skjedde dødsfallet?

Sykehus

Navn og avd._____

Utenfor sykehus

Sted_____

**Behandlende lege,** navn og adr. _____

## Klinisk hoveddiagnose *(sett ett kryss)*

Akutt hjerteinfarkt
Annen hjertesykdom, akutt hjerteinfarkt ikke verifisert*
Hjerneslag*
Aortaaneurisme
Lungeemboli
Annen kardiovaskulær sykdom*
Malign sykdom*
Voldelig død (suicid, drap, ulykke)
Annen diagnose*
Ukjent diagnose

*Spesifikk diagnose/Eventuell ICD-kode_____

## Kilde for opplysninger *(sett ett eller flere kryss)*

Pasientjournal
Dødsmelding
Muntlig informasjon
Annet, spesifiser _____

**Ble det foretatt obduksjon?** Ja Nei Vet ikke

Dato _____Underskrift_____

Adresse_____

# Appendix V NORVIT organization and approvals

**NORVIT organization and approvals**

**Steering Committee:** Knut Rasmussen, MD, PhD (chair); Kaare Bønaa, MD, PhD (principal investigator); Egil Arnesen, MD; Per Magne Ueland, MD, PhD; Jan Erik Nordrehaug, MD, PhD; Inger Njølstad, MD, PhD; Aage Tverdal, PhD.

**End-Points Committee:** Inger Njølstad, MD, PhD (chair); Henrik Schirmer, MD, PhD; Terje Steigen, MD, PhD; Harald Wang, MD.

**Data and Safety Monitoring Board:** Terje R. Pedersen, MD, PhD, Centre for Preventive Medicine, Ullevål University Hospital; Dag S. Thelle, MD, PhD, Department of Biostatistics, Institute of Basic Medical Science, University of Oslo; Aage Tverdal, PhD, Division of Epidemiology, the Norwegian Institute of Public Health; Oslo, Norway.

**Funding/Support:** NORVIT was funded by the Norwegian Research Council, the Council on Health and Rehabilitation, the University of Tromsø, the Norwegian Council on Cardiovascular Disease, the Northern Norway Regional Health Authority, the Norwegian Red Cross, the Foundation to Promote Research into Functional Vitamin B12 Deficiency, and an unrestricted private donation.

**Role of the Sponsors:** The main sponsors were nonprofit organizations with no participating role in the trial. Alpharma Inc provided the study capsules free of charge. However, Alpharma Inc had no role in the design or implementation of the trial, had no access to study data, and did not participate in data analysis or interpretation or in the preparation, review, or approval of the manuscript.

**Approvals:** The study protocol was in accordance with the principles of the Declaration of Helsinki and the trial was approved by the Regional Committee for Medical and Health Research Ethics and the Norwegian Medicines Agency. NORVIT was registered with clinicaltrials.gov, Identifier: NCT00266487.

## Appendix VI Letters to NORVIT and WENBIT participants

NORVIT

Tromsø, 1.september 2005

Kjære **NORVIT-pasient,**

Det er nå gått flere år siden du ble med i NORVIT-studien og over ett år siden studien ble avsluttet. Du har også fått brev med informasjon om hvilken av de fire behandlingsgruppene du selv hørte til. Vi skriver nå for å fortelle deg hovedresultatene av studien. Disse blir lagt frem på et stort europeisk hjertemøte i Stockholm 5. september og det vil i den forbindelse også bli sendt ut en pressemelding. Vi ønsker at alle NORVIT-pasienter skal få informasjonen direkte fra oss på en så forståelig måte som mulig og sender derfor dette brevet samtidig med foredraget.

Som du husker var de 3749 pasientene delt i fire grupper: A, B, C og D. Gruppe A hadde fått alle tre B-vitaminene, gruppe B bare folinsyre og B12, gruppe C bare B6 og gruppe D juksetablett (placebo). Fordi fordelingen mellom gruppene var gjort tilfeldig var det ca. 937 pasienter i hver gruppe.

Gjennomføringen av studien har skjedd helt etter styringsgruppens intensjoner. Pasientene har fulgt opplegget meget godt og alle er blitt sluttkontrollert på en eller annen måte. Organisasjonen har maktet å ta seg av alle opplysningene som har strømmet inn. Resultatene viser at B-vitaminene har senket kroppens homocysteine på en meget effektiv måte, slik vi forventet. Det var dette som skulle være den mest sannsynlige virkningsmekanisme for en gunstig effekt av B-vitaminene.

Studiens hovedresultater når det gjelder antall pasienter med ny sykdom i de fire gruppene er som følger:

| | A | B | C | D |
|---|---|---|---|---|
| Nytt hjerteinfarkt | 182 | 147 | 161 | 153 |
| Hjerneslag | 21 | 25 | 22 | 27 |
| Død | 104 | 80 | 92 | 89 |

Det er vanskelig å beregne om de små forskjellene som fins mellom gruppene er tilfeldige eller ikke. Dette krever kompliserte statistiske beregninger, som vi selvfølgelig har gjort. Hovedresultatet er klart: Det er ingenting som tyder på en positiv effekt hos pasientene som har fått B-vitaminer. Det er litt større dødelighet i gruppe A, men ikke mer enn hva som kan være en tilfeldighet. Det er også en tendens til at pasientene i gruppe A har noen flere nye hjerteinfarkter, dette gir en viss mistanke om at pasientene som har fått alle tre vitaminene faktisk har fått en meget liten økning av sin risiko.

For den enkelte av dere betyr dette dessverre at dere ikke har hatt noen personlig medisinsk nytte av å delta. Det er til og med en liten mulighet for at NORVIT-prosjektet har utsatt noen av dere for en liten ekstra risiko i tillegg til den som skyldes sykdommen. Hvis dette har skjedd, beklager vi det sterkt. Det er ikke mulig å si hvem av dere som eventuelt har vært utsatt for denne risiko. En eventuell slik risiko vil sannsynligvis meget raskt opphøre når vitamintilførselen er stoppet. Hvis du har fortsatt på egen hånd med å ta B-vitamin, råder vi deg til å slutte.

Vi som har organisert NORVIT-studien regnet med at B-vitaminene enten ville vise seg positive eller ikke ha noen virkning. Muligheten for en beskjeden negativ effekt er derfor høyst overraskende. Slike overraskelser ligger i kontrollerte kliniske undersøkelsers natur. Man vet ikke svaret på forhånd, nettopp derfor er det riktig å gjøre undersøkelsen.

Dessverre har vi altså ikke oppfylt vår drøm om å løse hjerteinfarktproblemet med enkle og billige B-vitaminer. Likevel er det ingen tvil om at NORVIT-studien har vært meget nyttig og at dere som NORVIT-pasienter har gjort menneskeheten en stor tjeneste ved å delta. Vi vet nå mye mer om virkningen av B-vitaminer hos hjerteinfarktpasienter og kan på grunnlag av studien slå fast at B-vitaminer ikke har noe for seg, selv om homocysteinenivået reduseres. Det brukes i dag millioner og sannsynligvis milliarder på B-vitaminer verden over på dette grunnlag og dette kan nå opphøre. Fremtidig forskning kan også finne nye veier pga. resultatene. Kanskje kan effektive behandlingsformer utvikles på grunnlag av denne informasjonen på lengre sikt.

Siden dette er det siste du hører fra oss vil vi på vegne av NORVIT-organisasjonen enda en gang takke deg for at du ville hjelpe oss med å avklare denne viktige medisinske hypotese. En slik avklaring har vi oppnådd, selv om svaret ikke ble slik vi håpet.

For NORVIT-organisasjonen

| Knut Rasmussen | Kaare H. Bønaa | Sissel Andersen |
|---|---|---|
| Styreleder | Prosjektleder | Prosjektkoordinator |

HELSE BERGEN
Haukeland Universitetssykehus

**Hjerteavdelingen**

Bergen, 3. september 2007

# Resultater fra WENBIT studien

Kjære deltaker!

Først og fremst vil vi få takke deg for at du var med i WENBIT studien. Vi takker også for at du har vært tålmodig i forhold til resultatet, som har latt vente på seg.

I alt 3090 pasienter, de aller fleste med kransåresykdom, deltok i WENBIT. Totalt 969 deltakere ble fulgt opp ved Stavanger Universitetssykehus og 2121 ble fulgt opp ved Haukeland Universitetssykehus. Studien ble avsluttet litt før planen oktober 2005. En del pasienter møtte til siste studiekontroll utpå nyåret 2006.

Hovedspørsmålet i WENBIT studien var om det å ta B-vitaminer kunne forebygge utvikling av hjerte-karsykdom og påvirke dødeligheten hos pasienter med kransåresykdom. Pasientene fikk en av fire ulike typer studiemedisin (kapsler), som skulle tas en gang daglig. Det var tilfeldig hvilke pasienter som fikk hvilken studiemedisin, og verken pasienter eller studiepersonell (sykepleiere og leger) visste hvem som fikk hva undervegs.

1. Pasienter i gruppe 1 fikk folsyre, vitamin B12 og vitamin B6
2. Pasienter i gruppe 2 fikk folsyre og vitamin B12
3. Pasienter i gruppe 3 fikk vitamin B6
4. Pasienter i gruppe 4 fikk placebo, det vil si ”narremedisin”

Vi har nå åpnet koden for hvem som fikk hvilken studiemedisin og undersøkt om det å ta B-vitamin tilskudd var gunstig for deltakerne.

Du var i gruppe

Blodprøvene viste som forventet at pasientene i gruppe 1 og 2 fikk høyere verdier av folsyre og vitamin B12, og lavere verdier av homocystein. Homocystein er et stoff som blant annet markerer risiko for hjerte-kar sykdom.

Vi fant vi ingen holdepunkt for at det å ta de ulike B-vitamin tilskuddene var gunstig eller ugunstig når det gjelder sykdomsutviklingen og risiko for død. Slik sett er WENBIT resultatet ”nøytralt”. Selv om dette kanskje var litt skuffende, er også et ”nøytralt” vitenskapelig resultat viktig. Vi har nå ingen grunn til å anbefale B-vitamin tilskudd for pasienter med kransåresykdom.

Som du kanskje husker, var det i forbindelse med en annen tilsvarende norsk studie (NORVIT) spørsmål om B-vitamin tilskudd kunne være farlig, og kanskje øke risikoen for kreft. Vi har ikke funnet holdepunkt for dette i WENBIT.

WENBIT sekretariat
Hjerteavdelingen, Haukeland Universitetssykehus
Telefon: 55 97 21 71
Telefax: 55 97 21 50
E-post: janne.dyngeland@helse-bergen.no

HELSE BERGEN
Haukeland Universitetssykehus

**Hjerteavdelingen**

Resultatene fra WENBIT studien blir første gang presentert offentlig 4. september 2007 på den europeiske hjertekongressen, som i år arrangeres i Wien. Vi vil også publisere resultatet i et anerkjent vitenskapelig medisinsk tidskrift, men det kan ta tid før en slik artikkel foreligger.

Mer informasjon om WENBIT studien kan du finne på internettsiden til Haukeland Universitetssykehus på www.helse-bergen.no

Hvis du lurer på noe vedrørende din deltakelse i studien, kan du ta kontakt med WENBIT sekretariatet, se nedenfor.

Nok en gang: Takk for at du har bidratt til medisinsk forskning!

Med hilsen

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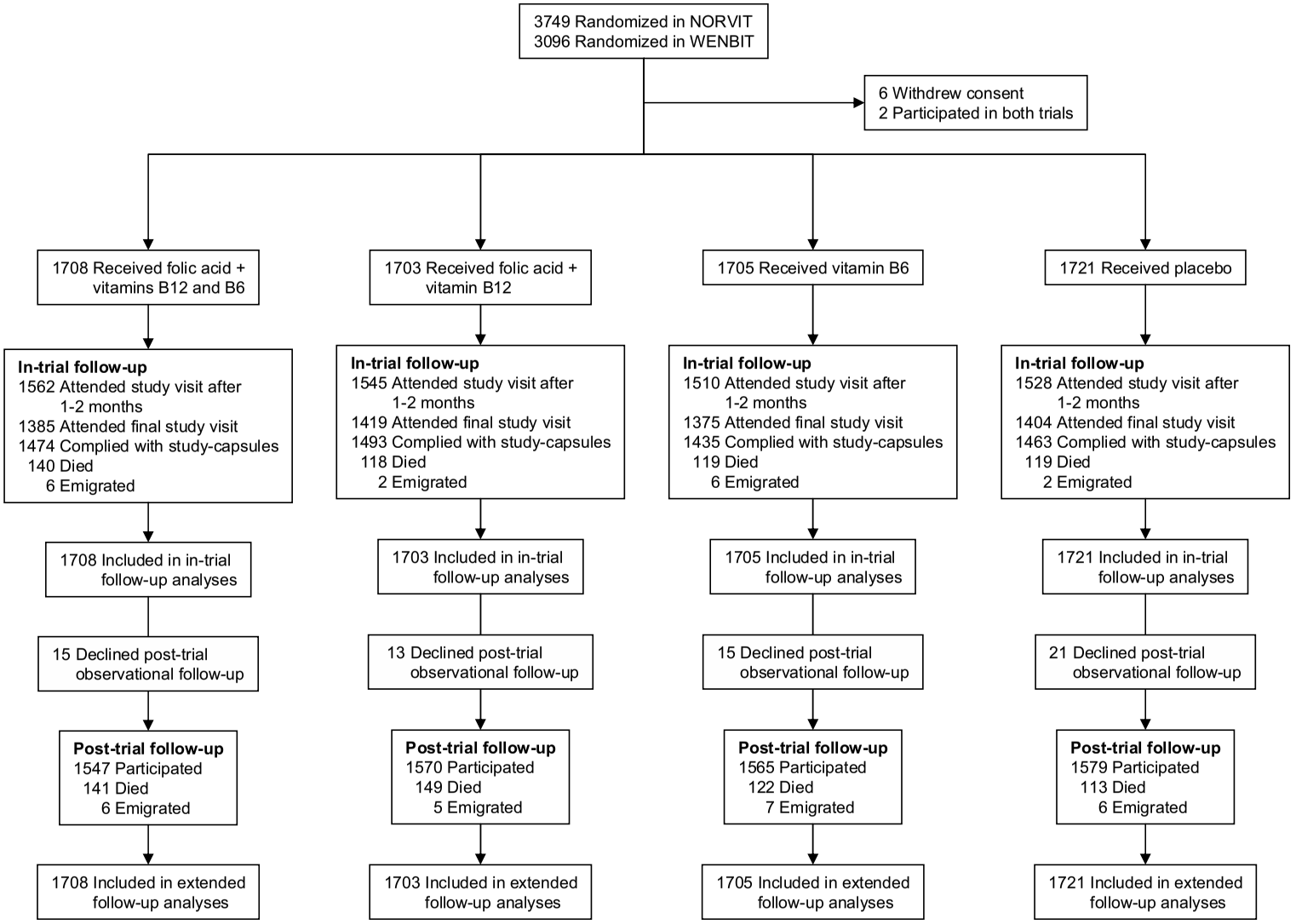
**Appendix VII Figure A. Flow of participants through NORVIT and WENBIT**


3749 Randomized in NORVIT
3096 Randomized in WENBIT
6 Withdrew consent
2 Participated in both trials
1708 Received folic acid + vitamins B12 and B6
1703 Received folic acid + vitamin B12
1705 Received vitamin B6
1721 Received placebo
In-trial follow-up
1562 Attended study visit after 1-2 months
1385 Attended final study visit
1474 Complied with study-capsules
140 Died
6 Emigrated
In-trial follow-up
1545 Attended study visit after 1-2 months
1419 Attended final study visit
1493 Complied with study-capsules
118 Died
2 Emigrated
In-trial follow-up
1510 Attended study visit after 1-2 months
1375 Attended final study visit
1435 Complied with study-capsules
119 Died
6 Emigrated
In-trial follow-up
1528 Attended study visit after 1-2 months
1404 Attended final study visit
1463 Complied with study-capsules
119 Died
2 Emigrated
1708 Included in in-trial follow-up analyses
1703 Included in in-trial follow-up analyses
1705 Included in in-trial follow-up analyses
1721 Included in in-trial follow-up analyses
15 Declined post-trial observational follow-up
13 Declined post-trial observational follow-up
15 Declined post-trial observational follow-up
21 Declined post-trial observational follow-up
Post-trial follow-up
1547 Participated
141 Died
6 Emigrated
Post-trial follow-up
1570 Participated
149 Died
5 Emigrated
Post-trial follow-up
1565 Participated
122 Died
7 Emigrated
Post-trial follow-up
1579 Participated
113 Died
6 Emigrated
1708 Included in extended follow-up analyses
1703 Included in extended follow-up analyses
1705 Included in extended follow-up analyses
1721 Included in extended follow-up analyses