



Better Health By Food Supplements: The Example Cardiovascular Disease

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Prof. Dr. Georg Kojda
Approved Pharmacologist DGPT,
Official Commissary for Continuing Education
of Pharmacists in Cologne, Germany

Institut für Pharmakologie und Klinische Pharmakologie,
UniversitätsKlinikum, Düsseldorf
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(No conflict of interest)

Cardiovascular Prevention by Food Supplements

As for cardiovascular disease,
better health means

increased resistance against and
improved prevention of

the development of chronic diseases
associated with disability and premature death!

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Cardiovascular Prevention by Food Supplements



Why should health care providers participate in prevention programs ?



Prevention counseling is an important contribution to
public health care.

Prevention counseling expands and completes integrated
health care plans.

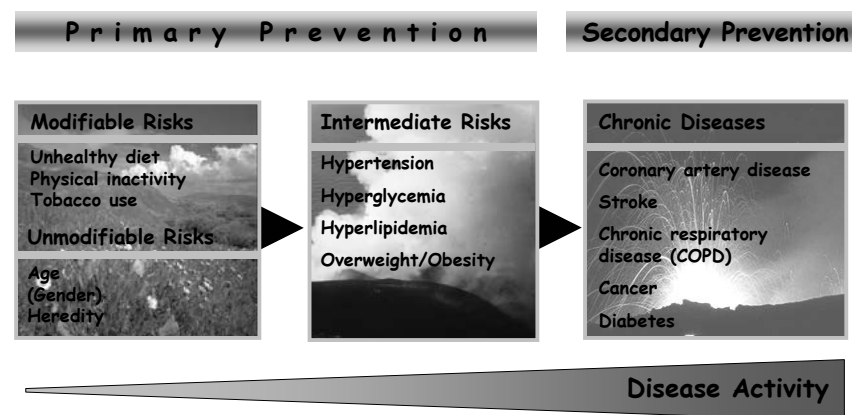
Prevention counseling supports communication among
different health care providers

Prevention counseling permits a rational and individual
self-medication concept for each patient.

Prevention counseling reduces the patient's risk to fall
for charlatans selling potentially hazardous medications
(e.g. via the internet)

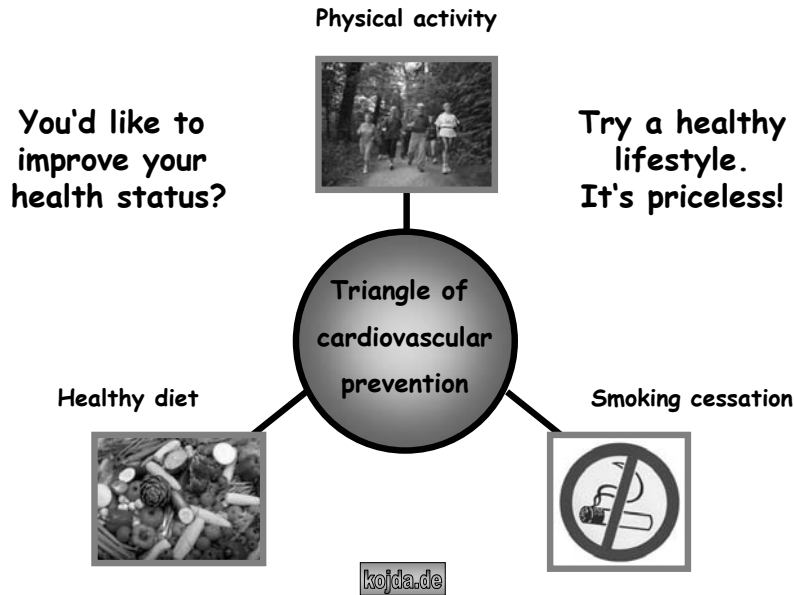
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Cardiovascular Prevention by Food Supplements



Scheme adopted from WHO: „Preventing Chronic Diseases: a vital investment“, 2004

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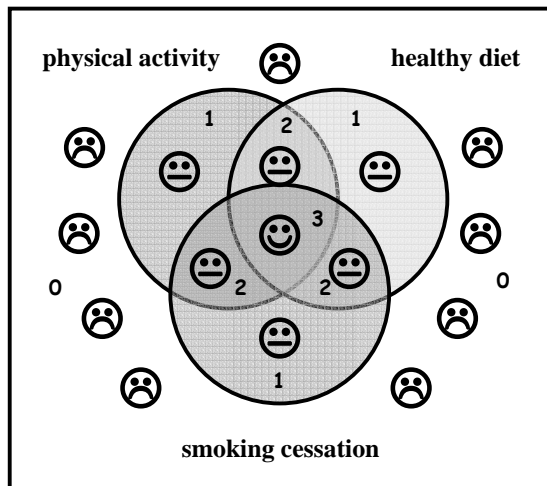
"The avoidance of modifiable risk factors for cardiovascular disease is a major challenge in the future."

(WHO: „Preventing Chronic Diseases: a vital investment“, 2004)



Selling any kind of food supplement should be accompanied by advices on a healthy lifestyle in over the counter consultations in pharmacies.

Simple scheme illustrating cardiovascular prevention



Step 0: maximal modifiable Risk

Step 1: high modifiable Risk

Step 2: moderate modifiable Risk

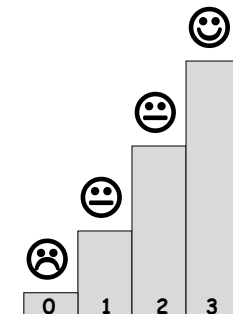
Step 3: low modifiable Risk



If health care providers don't support people to prevent cardiovascular disease, nobody does!

„In the clinician's world, most obese patients receive minimal lifestyle modification counseling, if any at all, because the offices of most primary care physicians are usually not staffed by dietitians, fitness experts, and those trained in behavioral issues related to weight management.“

Gadde K, Allison DB. Circulation 2006;114:974-984 (Obesity Trials Program, Duke University Medical Center Biostatistics and Clinical Nutrition Research Center, University of Alabama at Birmingham)



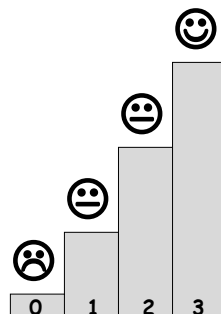
4 steps to keep vascular health



What can be done for prevention in short consultations by health care providers?

Healthy diet

- Providing free leaflets (e.g. tables for food calories/cholesterol)
- PC-assisted diet consultation (needs qualification!)
- Bodyweight tables (compliance!)
- Body weight percentile tables (Kids)
- Advice on drugs and food supplements
- Cooperate activities with other health care providers



4 steps to keep vascular health

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Antiobesity Drugs



The ideal diet pill:

- Unfortunately not yet available
- Effective over the long term (no relapse)
- Simple administration (Compliance!)
- Low adverse-effect burden
- Few contraindications (preexisting disease)
- Low drug interaction potential
- Low costs

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Antiobesity Drugs



Diet pill reality:

OTC drugs:
Usually not evidenced based:
no prove for efficacy and safety
not recommendable

Prescription drugs:
Usually evidenced based:
prove for efficacy and safety
only partially recommendable:

Weight regain despite therapy
Often dangerous side effects
(e.g. Arrhythmias, Hypertension)
Significant interaction potential
High costs

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Prescription Antiobesity Drugs - Example 1



Sibutramin (Reductil®):

Central reuptake-inhibitor:
Reduces presynaptic uptake of noradrenaline, serotonin and dopamin

Much more effective when combined with diet:
Hypocaloric diet increases weight loss by 50 %
(4,5 kg after 1 year)

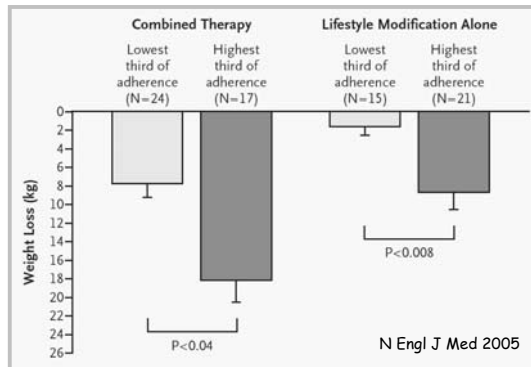
Side Effects (significant safety concerns):
(tachycardia, hypertension, arrhythmia)

Contraindications:
Epilepsia, Tics, con'comitant SSRI

High costs:
In Germany ca. 1,17 €/day)

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Prescription Antiobesity Drugs - An Example

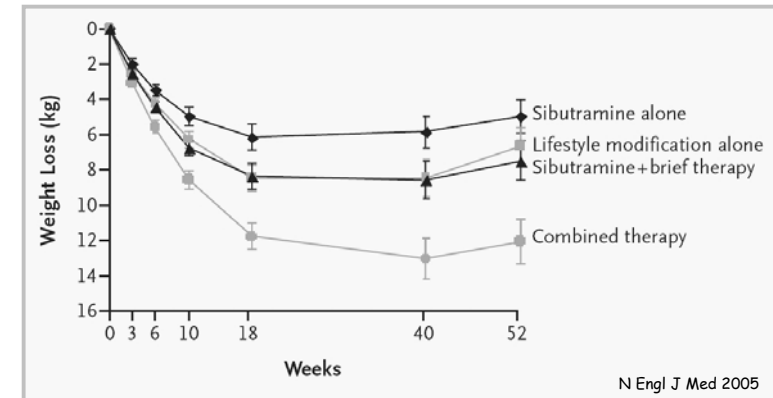


In clinical studies (somewhat artificial situation) the daily recording of food intake has an important impact on weight loss.

Pharmacists can encourage patients to perform such recordings to support both non-pharmacological and pharmacological antiobesity therapy

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„The results underscore the importance of prescribing weight-loss medications in combination with, rather than in lieu of, lifestyle modification.“ (Wadden TA, 2005)



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Prescription Antiobesity Drugs - Example 2



Rimonabant (Acomplia®)

Selektive Cannabinoid-Rezeptor Antagonist:
Blocks central und peripheral CB_1 -Receptors

Strong body weight reduction:
Together with diet minus 8,7 kg in one year effect remains in year 2

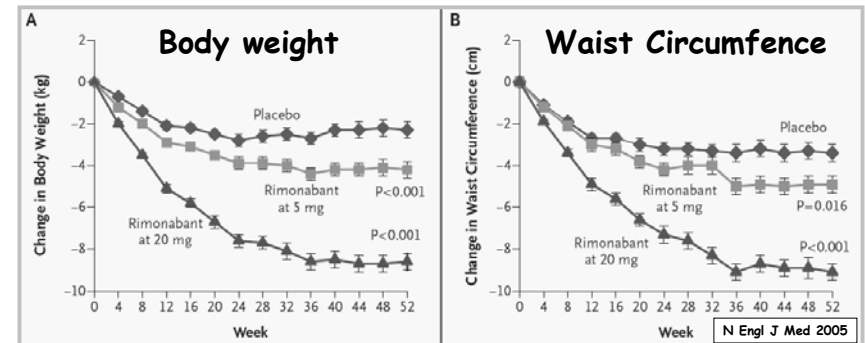
Side effects (use with caution!):
e.g. nausea, dizziness, anxiety, depression, insomnia, reduction of systolic and diastolic RR

Contraindications: (extrem cautious use)
hypersensitivity, lactation period (pregnancy, CYP3A4-metabolismus, cave: Interactions)

High costs:
In Germany the costs per day are about 3,00 €

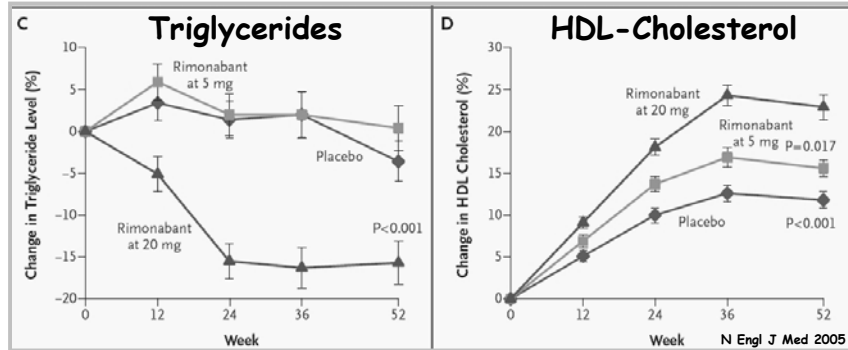
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Effect of Rimonabant in 1035 obese patients (BMI >34) with untreated Dyslipidemia



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Effect of Rimonabant in 1035 obese patients (BMI >34) with untreated Dyslipidemia



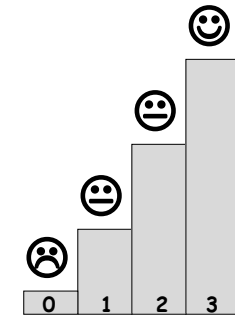
What can be done for prevention in general practitioner consultations and in over the counter consultations in pharmacies?



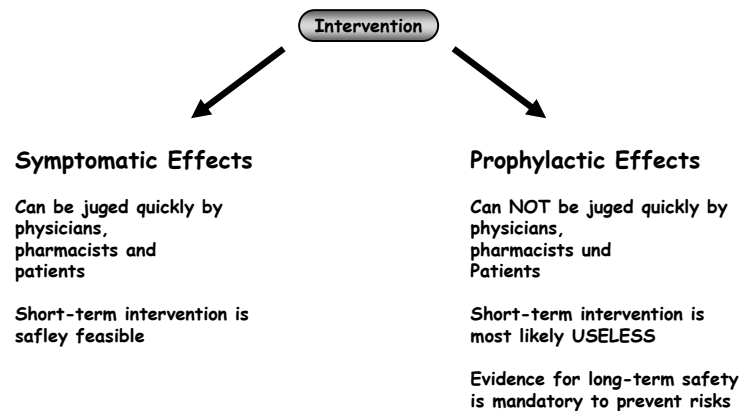
Preventive self-medication in over the counter consultations

Drugs
Acetylsalicylic acid (low-dose)

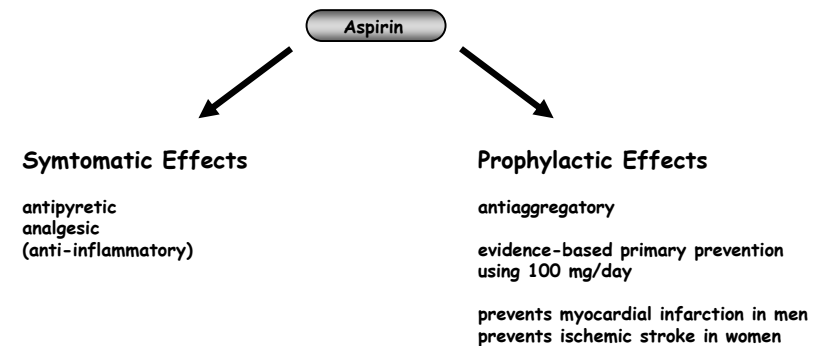
Food supplements
ω-3-fats (fish oils)
L-Arginine
Vitamines



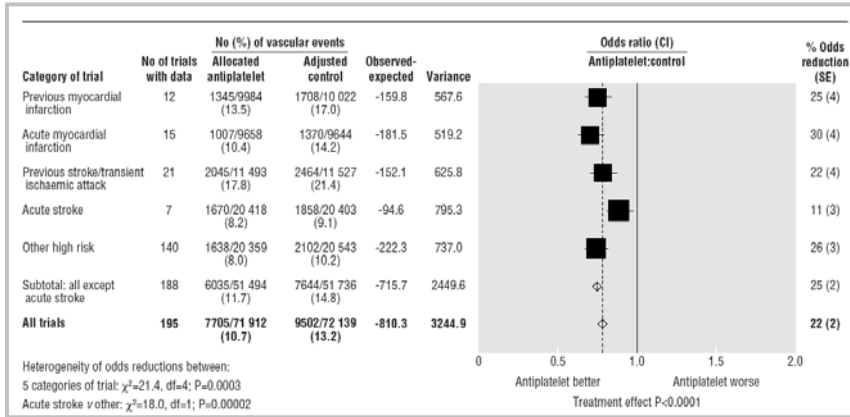
General considerations:
symptomatic vs. prophylactic effects



Prophylactic Effects of Aspirin*

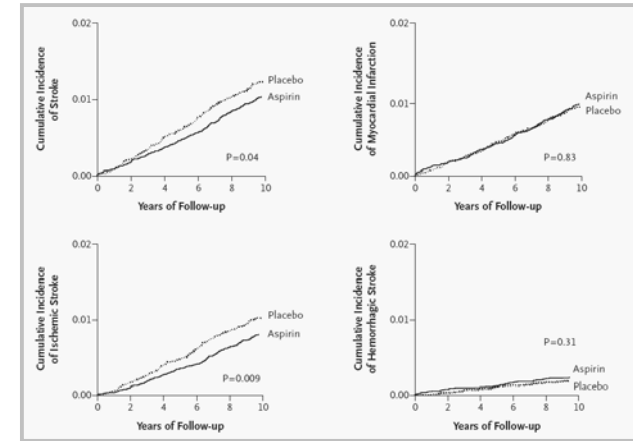


Prevention of vascular events by low-dose Aspirin*
Results of a meta-analysis



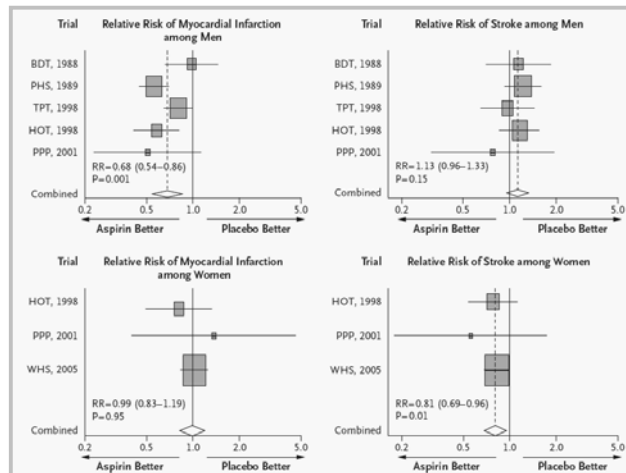
*acetylsalicylic acid

Effects of aspirin* in primary prevention among women
Women's Health Study, 39.876 healthy women at a mean age 54 years,
100 mg aspirin every other day for 10 years



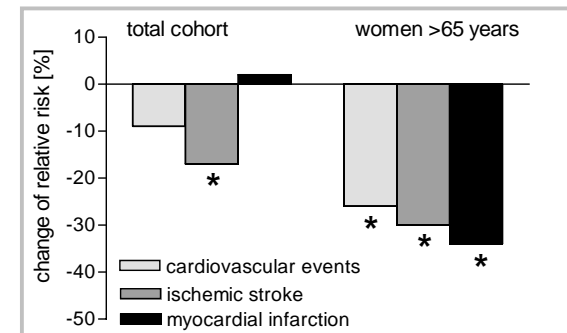
*acetylsalicylic acid

Effects of aspirin* in primary prevention
are dependent on gender!



*acetylsalicylic acid

Age-dependent effects of aspirin* in primary
prevention among women
Women's Health Study, 39.876 healthy women at a mean age 54 years,
100 mg aspirin every other day for 10 years



*acetylsalicylic acid

Side effects of aspirin* in primary prevention among women

Women's Health Study, 39.876 healthy women at a mean age 54 years,
100 mg aspirin every other day for 10 years

Side Effect	Aspirin (N=19,934)	Placebo (N=19,942)	Relative Risk (95% CI)	P Value
<i>no. of events (%)</i>				
Gastrointestinal bleeding				
Any	910 (4.6)	751 (3.8)	1.22 (1.10–1.34)	<0.001
Requiring transfusion	127 (0.6)	91 (0.5)	1.40 (1.07–1.83)	0.02
Peptic ulcer	542 (2.7)	413 (2.1)	1.32 (1.16–1.50)	<0.001
Hematuria	3,039 (15.2)	2,879 (14.4)	1.06 (1.01–1.12)	0.02
Easy bruising	10,561 (53.0)	8,494 (42.6)	1.40 (1.37–1.45)	<0.001
Epistaxis	3,801 (19.1)	3,321 (16.7)	1.16 (1.11–1.22)	<0.001
Any report of gastric upset	11,856 (59.5)	11,915 (59.7)	0.99 (0.97–1.02)	0.59

* The presence of gastrointestinal bleeding or peptic ulcer was confirmed by a specific follow-up questionnaire. CI denotes confidence interval.

(Data from: Ridker PM et al., N Engl J Med 2005;352:1293)

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*acetylsalicylic acid

Recommendation for the use of aspirin* in primary prevention among women



Paul M Ridker, MD

„Thus, as with men, any decision about the use of aspirin in primary prevention among women must ultimately be made after a woman consults her physician or health care provider, so that the net absolute benefits and risks for the individual patient can be ascertained“

(Ridker PM et al., N Engl J Med 2005;352:1293)

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*acetylsalicylic acid

Recommendation for advices on the long-term use of aspirin* in primary prevention

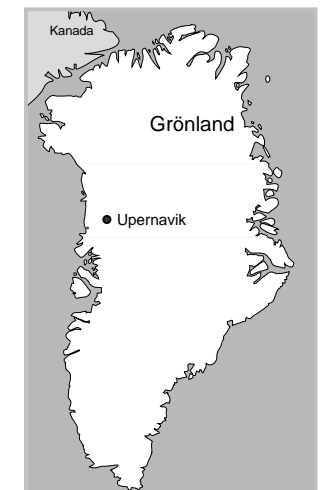
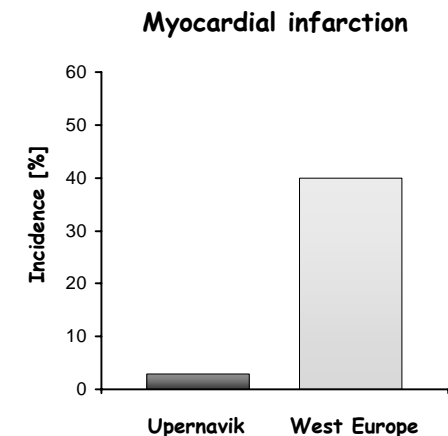


In general practitioner counselling and over the counter consultations in pharmacies on cardiovascular prevention potentially serious risks and contraindications of low dose aspirin have to be considered.

A general recommendation for the long-term use of low-dose aspirin as a self-medication should not be made without a discussion between the patient and his physician.

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*acetylsalicylic acid



Kromann N et al., Acta Med Scand 1980

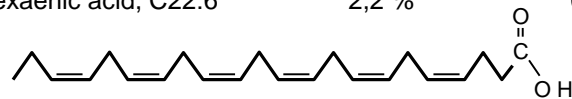
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Significant nutritional differences in between Eskimos and Danes

	Eskimos	Danes
Eicosapentaenic acid, C20:5	2,3 %	0,4 %

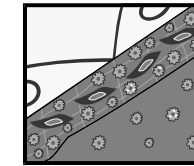
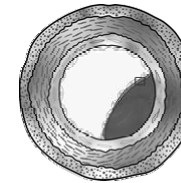


	Eskimos	Danes
Docosahexaenic acid, C22:6	2,2 %	0,3 %



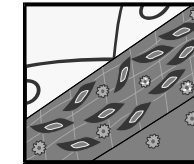
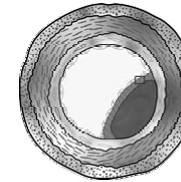
Bang H O et al., Am J Clin Nutr 1980; Kromann N et al., Acta Med Scand 1980

unstable Plaque



thin fibrous cap,
strong signs of
inflammation

stable Plaque



thick fibrous cap,
less signs of
inflammation

Endothelial cells

Smooth muscle cells

Makrophages

Thies et al., Lancet. 2003;361(9356):477-85.

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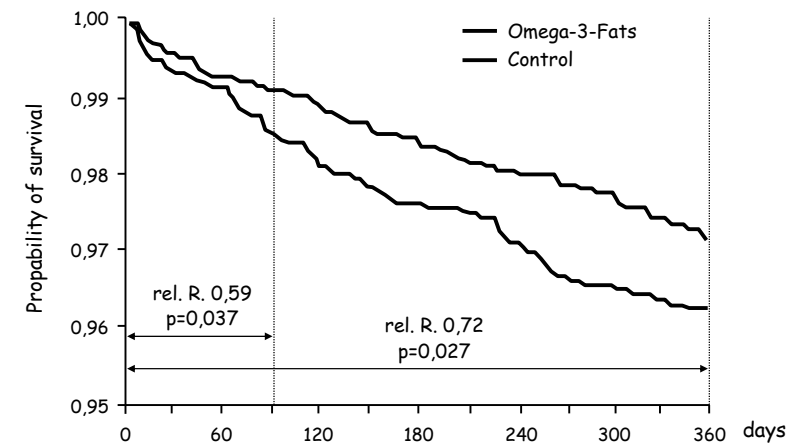
GISSI-Prevenzione Trial

Study characteristics

- ➔ Inclusion of 11.324 patients with MI (last 3 months)
- ➔ Randomized controlled trial
- ➔ Total mortality, cardiovascular mortality, non-fatal MI, non-fatal stroke as primary end points
- ➔ Optimal guideline therapy in all patients
- ➔ Data analysis after 6, 12, 18, 30, 42 months
- ➔ All patients were advised to adhere to a healthy lifestyle

(GISSI-Prevenzione, Lancet 1999;354:447-455)

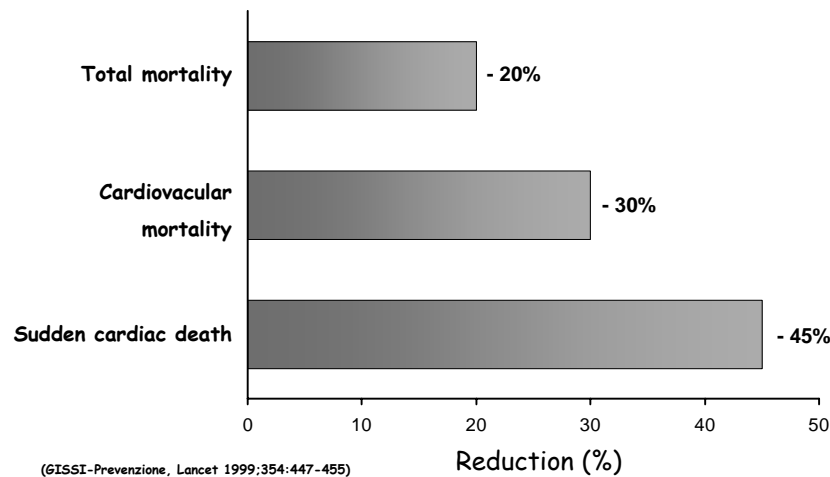
The effect of standardized ω -3-fats among patients with myocardial infarction



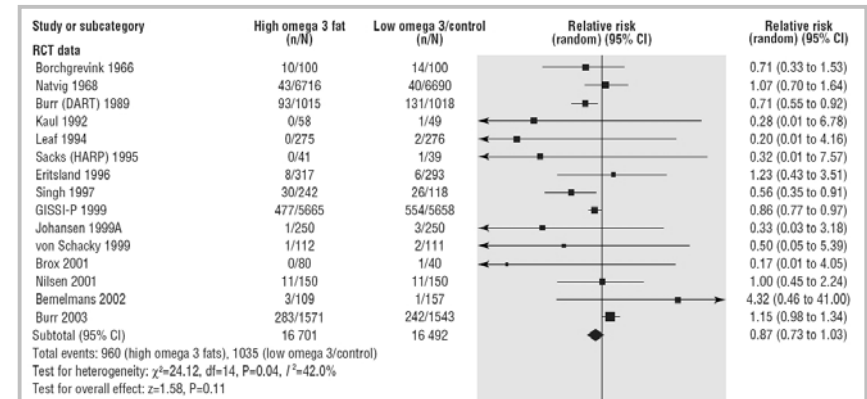
(GISSI-Prevenzione, Lancet 1999;354:447-455)

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The effect of standardized ω -3-fats among patients with myocardial infarction, subgroup analysis



No significant effect of standardized ω -3-fats among patients with low, medium or high cardiovascular risk.



Hooper et al., BMJ 2006;332(7544):752-60

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Recommendation for advices on the long-term use of ω -3-fats in cardiovascular prevention



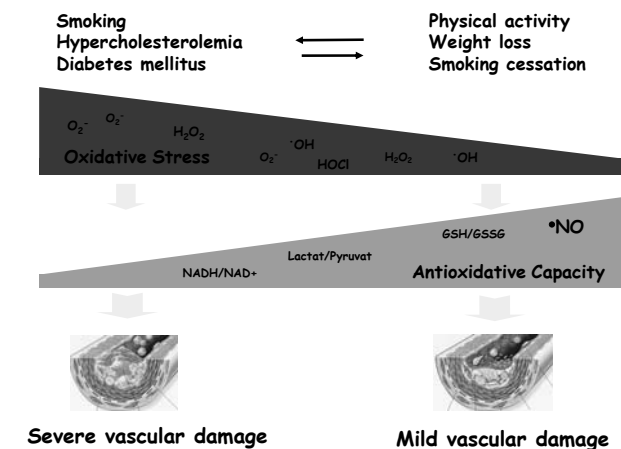
In general practitioner counselling and over the counter consultations in pharmacies on cardiovascular prevention ω -3-fats may be recommended to post-MI patients, but a discussion between the patient and his physician appears necessary to avoid any interference with standard guideline pharmacotherapy, particularly replacement of first choice evidenced-based drugs.

A general recommendation for the long-term use of ω -3-fats among low-risk patients cannot be made, since no clear benefit has been demonstrated in RTCs. On the other hand, there appears to be no serious side effects.

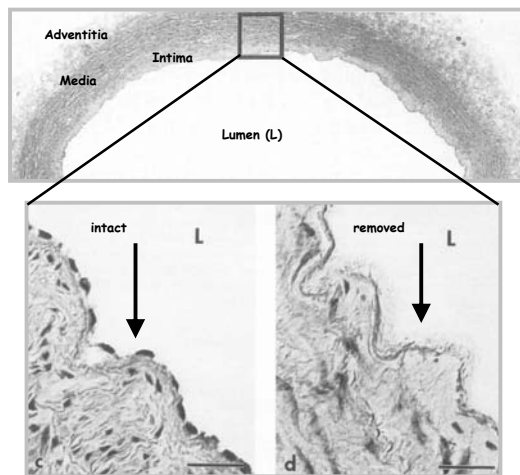
Further RCTs are needed.

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Vascular oxidative stress in atherosclerosis



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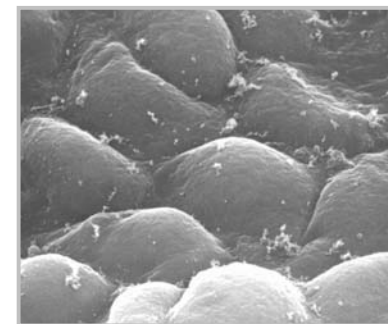


The most vulnerable cells are damaged first.
In the vascular system these are endothelial cells.

Kojda, Eur J Pharmacol 1993; 250:385-394

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Electron microscopy scan of human endothelial cells

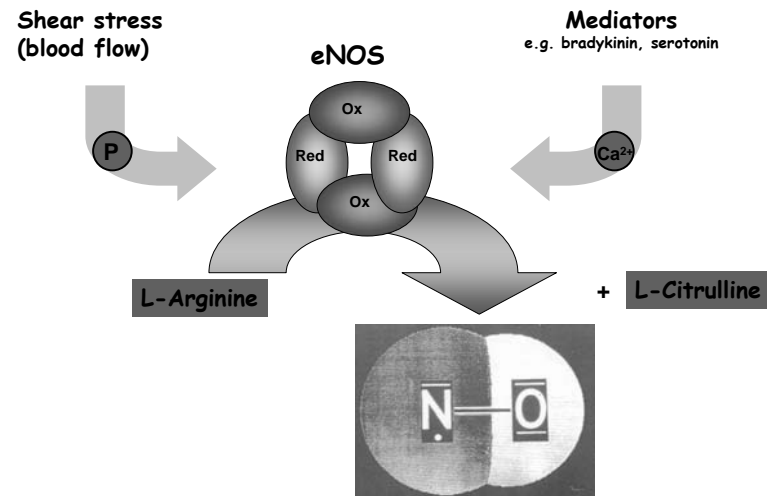
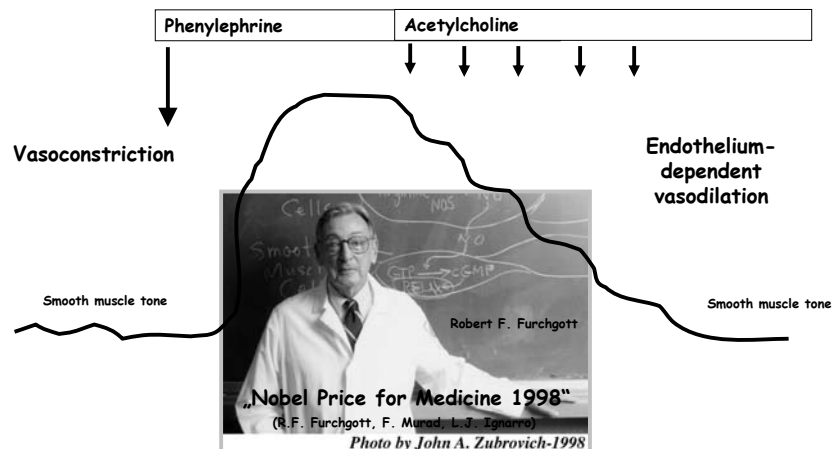


Human V. Saphena Explant
(Coronary Artery Bypass Graft)

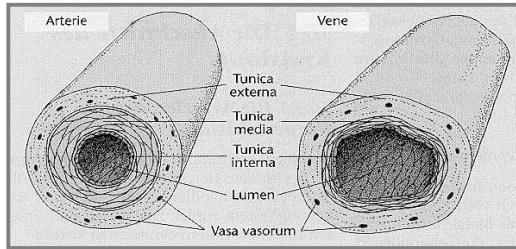
aus Kojda, Naunyn-Schmiedeberg's Arch Pharmacol 361(Suppl):R117

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„The discovery of endothelium-dependent vasodilation uncovered an entirely new principle for signalling in the human organism“

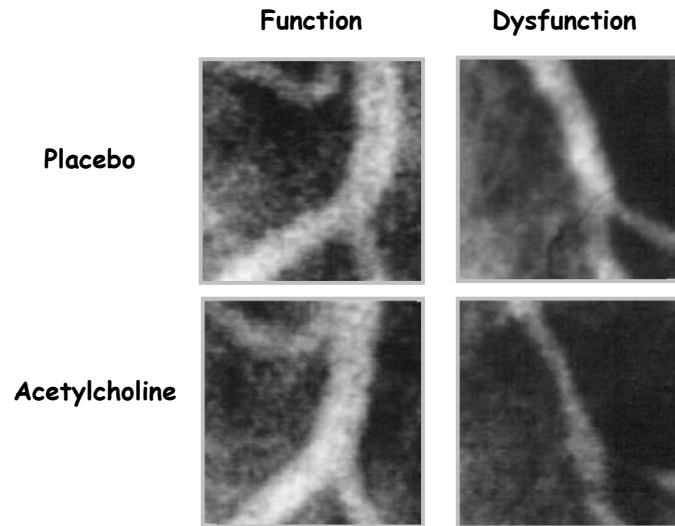


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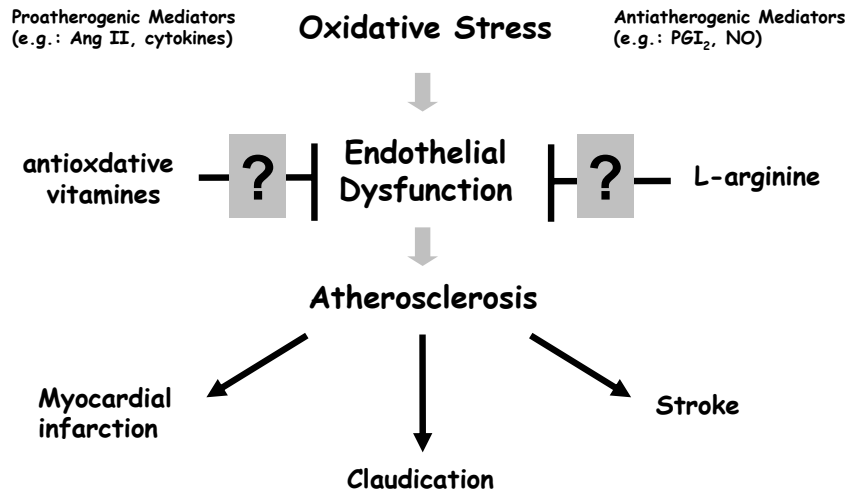


Effects of NO in the vascular system

- vasodilatatory
- antiaggregatory
- antiadhesive
- antioxidative
- antiproliferative
- antiapoptotic



(From: Treasure et al., NEJM 1995)



Prophylactic Efficacy of L-Arginine?

(see also Kojda G, „Mehr Gesundheit durch dietätische Lebensmittel? Das Beispiel L-Arginin“ Apothekenmagazin 2006;24(3):36-37)



The biological ratio: L-arginine

- is the substrate of endothelial NO-synthase.
- inhibits atherosclerosis in animal experiments.
- improves endothelial function in animal experiments.
- improves endothelial function in small clinical trials

Prophylactic Efficacy of L-Arginine?



Taking a look at published randomised controlled trials leaves little room for speculation!

So far, there is no clinical evidence suggesting that L-arginine reduces the progression of cardiovascular disease or cardiovascular mortality.

Published RCTs showed no benefit!

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Prophylactic Efficacy of L-Arginine?



Great caution in post-MI patients!

- L-Arginine has no effect on ejection fraction and myocardial stiffness.
- L-Arginine-treatment did not increase the plasma concentration of L-arginine
- L-Arginin showed no increased rate of low and medium risk side effects.
- **6 deaths** in the L-Arginine group, no death in the placebo group!

(Vintage MI Study, JAMA 2006;295:58-64)

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Prophylactic Efficacy of L-Arginine?

Rigorous clinical data are limited

"Further studies will be of considerable interest, since such supplements are not accepted uniformly and rigorous clinical data are limited. Although the results of biochemical studies and studies in animals provide strong support for the use of such supplements, well-designed, controlled clinical trials are in the early stages."

Ferid Murad,
(NEJM 2006;295:58-64)



Ferid Murad, MD, PhD,
Nobel Laureate 1998

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Recommendation for advices on the use of L-arginine in cardiovascular prevention



In general practitioner consultations and over the counter consultations in pharmacies on cardiovascular prevention L-arginine should currently NOT be recommended to post-MI patients.

A general recommendation for the long-term use of L-arginine among low-risk patients cannot be made, since no benefit has been demonstrated in RTCs.

Further RCTs are needed.

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Prophylactic efficacy of folic acid/B-vitamines?

(see also Kojda G, „Mehr Gesundheit durch diätätische Lebensmittel? Das Beispiel L-Arginin“
Apothekenmagazin 2006;24(3):36-37)



Biological Ratio: folic acid, B₆, B₁₂

- reduces plasma homocysteine, a cardiovascular risk factor, by about 30 %
- animal studies suggested reduction of vascular oxidative stress
- animal studies and small clinical trials suggested improved endothelial function
- small clinical studies suggested benefit in overt cardiovascular disease

(Loscalzo J, N Engl J Med 2006; 354(15):1629-32)

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Prophylactic efficacy of folic acid/B-vitamines?

(see also Kojda G, „Mehr Gesundheit durch diätätische Lebensmittel? Das Beispiel L-Arginin“
Apothekenmagazin 2006;24(3):36-37)



The efficacy of folic acid/B-vitamines was investigated in two large RCTs.

The NORVIT trial included 3.749 patients (73 % males) who had an acute myocardial infarction within 7 days of randomization.

The HOPE-2 trial included 5.522 patients (72 % males) with a history of vascular disease (coronary, cerebrovascular, peripheral) or diabetes with additional risk factors for atherosclerosis

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Prophylactic efficacy of folic acid/B-vitamines?

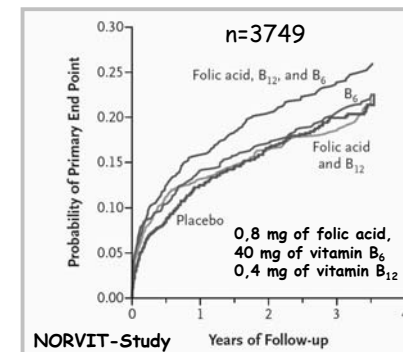
Table 2. Plasma Levels of Total Homocysteine and B Vitamins at Baseline, after Two Months, and at the End of the Intervention.*

NORVIT - Study Variable	Folic Acid, B ₁₂ , and B ₆ (N=937) †	Folic Acid and B ₁₂ (N=935) ‡	B ₆ (N=934) §	Placebo (N=943) ¶
Total homocysteine (µmol/liter)				
Baseline	13.1±5.0	12.9±4.3	13.3±6.1	13.2±5.2
2 Mo	9.4±3.0	9.5±2.8	13.7±5.7	13.7±5.6
End of intervention	9.5±3.6	9.8±4.0	13.3±5.4	13.6±6.2
Folate (nmol/liter)				
Baseline	13.1±27.5	11.7±28.4	9.4±6.6	9.6±6.0
2 Mo	59.9±29.5	68.2±30.0	7.9±7.1	9.9±6.3
End of intervention	61.8±31.7	70.4±36.4	10.4±9.6	13.1±14.5
Vitamin B₁₂ (pmol/liter)				
Baseline	388±161	400±311	388±167	383±182
2 Mo	571±212	578±372	398±158	393±143
End of intervention	638±370	648±414	398±320	390±171

(N Engl J Med 2006; 354(15):1578-88)

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Prophylactic efficacy of folic acid/B-vitamines?

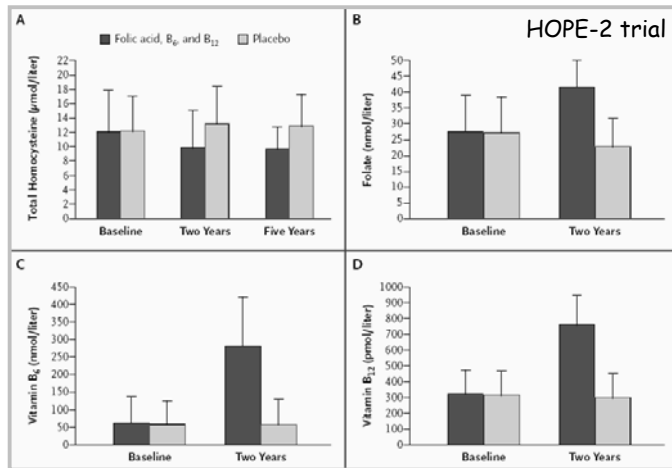


(N Engl J Med 2006; 354(15):1578-88)

Despite substantially reduced plasma homocysteine in the NORVIT trial, treatment with folic acid, B₆, B₁₂ was NOT beneficial, but potentially harmful among post-MI patients!

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Prophylactic efficacy of folic acid/B-vitamines?



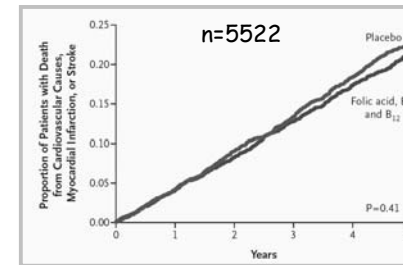
(N Engl J Med 2006; 354(15):1567-77)

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Prophylactic efficacy of folic acid/B-vitamines?

No beneficial effect among high-risk patients!

Intervention group (n=2,758)
 Coronary artery disease: 2,285 (82.8 %)
 Myokardial infarction: 1,501 (54.4 %)
 Stroke: 241 (8.7 %)
 Diabetes mellitus: 1,122 (40.7 %)



(N Engl J Med 2006; 354(15):1567-77)

Despite substantially reduced plasma homocysteine in the HOPE-2 trial, treatment with folic acid, B₆, B₁₂ was NOT beneficial among high-risk patients!

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NO prophylactic efficacy of folic acid/B-vitamines on cardiovascular outcomes!



".....there is no clinical benefit of the use of folic acid and vitamin B12 (with or without the addition of vitamin B6) in patients with established vascular disease."

Prof. Dr. Joseph Loscalzo, MD
 Brigham and Women's Hospital
 Harvard Medical School
 Boston, MS, USA

(N Engl J Med 2006; 354(15):1629-32)

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Recommendation for advices on the long-term use of folic acid/B-vitamines in cardiovascular prevention



In general practitioner counselling and over the counter consultations in pharmacies on cardiovascular prevention folic acid/B-vitamines should currently not be recommended to patients at high cardiovascular risk.

A general recommendation for the long-term use of folic acid/B-vitamines among low-risk patients cannot be made, since no RTC has demonstrated a benefit.

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Prophylactic efficacy of vitamin E?

(see also Kojda G, „Vitamin E bei koronarer Herzkrankheit? Erkenntnisse und Grenzen der klinischen Prüfung.“
Apothekenmagazin 2002;20(10):4-5)



Biological Ratio: vitamin E

- is reduced in patients with cardiovascular risk factors or overt disease
- animal studies suggested reduction of vascular oxidative stress by vitamin E
- pharmacologic doses appeared safe
- small clinical studies suggested benefit in overt cardiovascular disease

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Prophylactic efficacy of vitamin E?

The efficacy of vitamin E was investigated in several large RCTs.

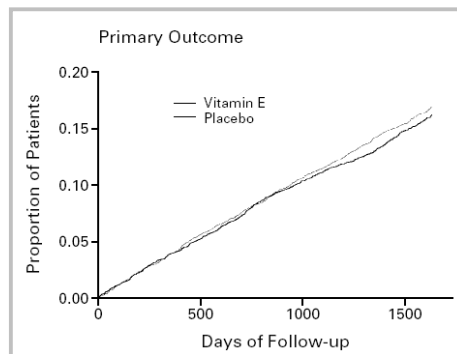


The HOPE trial included 9.541 patients (73 % males) with a high risk for cardiovascular events, e.g. 81 % had a history of coronary artery disease and 52 % had a myocardial infarction.

The 4.761 patients of the verum group received 400 IU/day of vitamin E from natural sources for 4-6 years (mean 4.5 years).

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Prophylactic efficacy of vitamin E?



(N Engl J Med 2002;342:154-60)

400 IU/day of vitamin E had no effects on on the composite outcome of nonfatal myocardial infarction, stroke, or death from cardiovascular causes.

Similar results were obtained for myocardial infarction, stroke and death from any cause.

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NO prophylactic efficacy of vitamin E on cardiovascular outcomes!



„In conclusion, 400 IU of vitamin E administered daily for four to six years had no beneficial effects on cardiovascular outcomes in a high-risk population of patients who were 55 years of age or older.

Vitamin E was well tolerated, with no significant adverse events as compared with placebo.“

Prof. Dr. Salim Yusuf, MD
Canadian Cardiovascular Collaboration Project Office
Hamilton General Hospital
Hamilton, Canada

(N Engl J Med 2002;342:154-60)

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Effects of food supplements in cardiovascular prevention

Evidenced-based efficacy in cardiovascular prevention

- AP Aspirin (low-dose, primary and secondary prevention)
- RP Statins (primary and secondary prevention)
- RP ω -3-fats (Omacor®, secondary prevention)

NO firm evidence for efficacy in cardiovascular prevention

- AP Vitamin E (potentially harmful at doses > 400 IU/day)
- AP Folic acid/B-vitamines (potentially harmful in post-MI patients)
- AP L-Arginine (potentially harmful in post-MI patients)
- AP L-Arginine/folic acid/B-vitamines (potentially harmful in post-MI patients)

Recommendation for advices on the use of food supplements in cardiovascular prevention



A patient's request for food supplements signals the wish to improve the current health condition and is, therefore, an excellent starting point for initiation of cardiovascular prevention counselling.

Recommendation for advices on the use of food supplements in cardiovascular prevention



In counselling on cardiovascular prevention patients should learn that the use of food supplements should **ALWAYS** be accompanied by a healthy lifestyle.

Recommendation for advices on the use of food supplements in cardiovascular prevention



Health care providers should be aware that there are some results from clinical trials suggesting that certain food supplements may actually increase cardiovascular risk.

Recommendation for a pharmacist's advice on the long-term use of food supplements in cardiovascular prevention



In general practitioner consultations and over the counter consultations in pharmacies on cardiovascular prevention ω -3-fats may be recommended to post-MI patients.

Regularly consumption of the food supplements

L-arginine,
folic acid/B-vitamins,
vitamin E (<400 IU/day) or
RDA-doses of mixed vitamins

shows no evidenced-based efficacy but appears at least safe among low risk patients.

Thank you for your attention



The lecture will be available as a small size PDF-file at www.kojda.de.

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