

ISTITUTO DI RICERCHE FARMACOLOGICHE «MARIO NEGRI»

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RECOGNIZED AS A TAX EXEMPT
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AMERICA INTERNAL REVENUE CODE TAX
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ISO 9001 2000. ATTIVITA' DI FORMAZIONE
DI NUOVI RICERCATORI IN BIOMEDICINA

Milan. April 19 2004

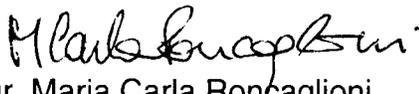
Division of Dockets Management
Food and Drug Administration
5630 Fishers Lane
Room 1061 (HFA-305)
Rockville, Maryland 20852 – USA

Re: Docket 77N-0094

ASPIRIN PRIMARY PREVENTION OF CHD

Please find enclosed the Study Synopsis and the documents requested of the Primary
Prevention Project (PPP).

On behalf of Dr. Tognoni (chairman)



Dr. Maria Carla Roncaglioni

for the Coordinating Centre of the PPP Study

77N-0094

SUPSI

ASPIRIN PRIMARY PREVENTION OF CHD STUDY SYNOPSIS

Re: Docket 77N-0094

Title of Study Primary Prevention Project (PPP)
Principal/Investigator(s): Gianni Tognoni, MD
Coordinating Center. Istituto di Ricerche Farmacologiche Mario Negri, Milan, Italy
Publication (reference): Collaborative Group of the Primary Prevention Project (PPP). Low-dose aspirin and vitamin E in people at cardiovascular risk: a randomised trial in general practice Lancet 2001; 357 : 89-95 (please attach publication)
Studied period (years): 1993-1998 (Date of first enrollment) June 8 1993 (Date of last completed) December 31 1998
Objectives To assess whether long term treatment with low-dose aspirin and vitamin E reduces the incidence of major cardiovascular events (vascular death and non fatal myocardial infarction or stroke) in subjects aged 50 years or greater, with at least one of the major recognised cardiovascular risk factors, but without previous cardiovascular events.
Methodology. controlled, centrally randomised, open-label 2x2 factorial clinical trial
Number of patients: Planned. at least 7,500 patients followed-up for 5 years were needed to verify the hypothesis of 25% reduction in the frequency rate of the cumulative endpoint with $\alpha=0.05$ and $1-\beta=0.90$. Analyzed 4495 patients were analysed. The trial was prematurely stopped on ethical grounds when newly available evidence from other trials on the benefit of aspirin in primary prevention was strictly consistent with the results of PPP interim analysis
Study population: 43% male 57% female Mean age. 64.4 years (SD 7.6) Cardiovascular risk at baseline: people aged 50 years or greater with <i>one or more of the following risk factors</i> : Old age (≥ 65 years): 50% Hypertension: 68% mean (SD) SBP mmHg 145.2 (16.0); DBP mmHg 85.4 (9) Hypercholesterolemia: 39% mean (SD) serum total cholesterol mmol/L 6.1 (1.2) Diabetes 17% mean blood glucose (mmol/L) 6.1 (2.0) Obesity (BMI >30 Kg/m ²): 23% Family history of premature myocardial infarction: 10% <i>Number of risk factors</i> One 31% Two 39% Three or more 29%
Test products, dose, and mode of administration: aspirin (one tablet of 100 mg enteric-coated a day); vitamin E (one capsule of 300 mg synthetic α -tocopherol a day)
Duration of treatment mean follow-up 3.6 (SD 1.0) years

Criteria for evaluation:

Efficacy: the main combined efficacy endpoint was the cumulative rate of cardiovascular death, non-fatal myocardial infarction, and non-fatal stroke. Predefined analysis included cardiovascular deaths, total deaths, total cardiovascular events (cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, angina pectoris, TIA, peripheral-artery disease, and revascularisation procedures).

Safety: all the events judged by the physicians to be clinically severe and unexpected, not necessarily drug-related, had to be documented in a standard form and promptly reported to the scientific and organising committee.

Statistical methods: Analysis were done according to the intention-to-treat principle. Treatment efficacy on the main combined endpoint, on its single components, and on total deaths was assessed by fitting a Cox's regression model, and the results were expressed as relative-risk estimate with 95% CIs. The analysis on other endpoint were done with the Mantel-Haenszel procedure. Kaplan-Meier survival curves were censored at 4 years –ie, the median follow-up of the population- since the proportion of patients at risk at 5 years was only 5.3% of the original population

STUDY SYNOPSIS

SUMMARY – CONCLUSIONS

In women and men at risk of having a cardiovascular event because of the presence of at least one major risk factors low-dose aspirin given in addition to treatment of specific risk factors contributes an additional preventive effect, with an acceptable safety profile. The results on vitamin E's cardiovascular primary preventive efficacy are not conclusive per se, although the results are consistent with the negative results of other large published trial on secondary prevention

EFFICACY RESULTS:

The efficacy profile of aspirin and vitamin E is reported in Table 1 (see attach)

SILENT MI INCLUSION OR EXCLUSION RATIONALE:

Silent myocardial infarction was not included as endpoint. In a pragmatic trial run in the context of general practice it was not feasible to collect ECG at baseline and at the end of the trial for each patients enrolled.

SAFETY RESULTS:

The rate of non-cardiovascular death was similar in the treatment group. Severe and unexpected non-fatal events were more frequent in the aspirin group than in the no-aspirin group. A large proportion of the excess of non-fatal events reported for aspirin was, as expected, due to bleeding complications (mainly gastrointestinal) - 1.1% vs 0.3% $p=0.0008$. Out of the four deaths caused by haemorrhage, three were in the no-aspirin group and one in the aspirin group.
See Table 2 (attach)

CONCLUSIONS.

PPP was set up to provide an assessment of antiplatelet and antioxidants as cardiovascular primary preventive strategies in the context of care were they are expected to be decided and practised, on people of both sexes identified as being at cardiovascular risk on the basis of at least one of the major recognised risk factor.

Aspirin lowered the frequency of all the endpoints, being significant for cardiovascular deaths (from 1.4 to 0.8%; relative risk 0.56 - 95%CI 0.31-0.99) and total cardiovascular events (from 8.2 to 6.3%; relative risk 0.77 - 95%CI 0.62-0.95)

Vitamin E showed no effect on any prespecified endpoint

Protocol and Protocol Amendments Attached (Executive Summary)

on behalf of Dr. Topucan

M. Paule Roussel
Signature

20 April 2004
Date

Study Contact for FDA follow-up:

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Table 1 Efficacy profile of aspirin and vitamin E treatment

	Aspirin (n=2226)		Relative risk (95% CI)	Vitamin E (n=2231)		Relative risk (95% CI)
	n	(%)		n	(%)	
Main combined endpoint (cardiovascular death, non-fatal myocardial infarction and non-fatal stroke)	45	(2.0)	0.71 (0.48-1.04)	56	(2.5)	1.07 (0.74-1.56)
Total cardiovascular events or diseases #	141	(6.3)	0.77 (0.62-0.95)	158	(7.1)	0.94 (0.77-1.16)
All deaths	62	(2.8)	0.81 (0.58-1.13)	72	(3.2)	1.07 (0.77-1.49)
cardiovascular	17	(0.8)	0.56 (0.31-0.99)	22	(1.0)	0.86 (0.49-1.52)
non cardiovascular	45	(2.0)	0.98 (0.65-1.46)	50	(2.2)	1.21 (0.80-1.81)
All myocardial infarction	19	(0.8)	0.69 (0.38-1.23)	22	(1.0)	0.89 (0.52-1.58)
non-fatal myocardial infarction	15	(0.7)	0.69 (0.36-1.33)	19	(0.8)	1.01 (0.56-2.03)
All stroke	16	(0.7)	0.67 (0.36-1.27)	22	(1.0)	1.24 (0.66-2.31)
non-fatal stroke	15	(0.7)	0.84 (0.42-1.67)	20	(0.9)	1.56 (0.77-3.13)
Angina pectoris	54	(2.4)	0.82 (0.58-1.17)	66	(3.0)	1.22 (0.86-1.73)
Transient ischaemic attack	28	(1.3)	0.71 (0.44-1.15)	33	(1.5)	0.96 (0.60-1.53)
Peripheral artery disease	17	(0.8)	0.60 (0.33-1.08)	16	(0.7)	0.54 (0.30-0.99)
Revascularisation procedure	20	(0.9)	0.70 (0.40-1.24)	27	(1.2)	1.25 (0.71-2.18)

subjects with one or more of the following events: cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, angina pectoris, transient ischaemic attack, peripheral artery disease, revascularisation procedure.

Table 2 Safety profile of aspirin and vitamin E treatments: severe and unexpected non-fatal events according to treatment group

	Aspirin (n=2226)	No aspirin (n=2269)	Vitamin E (n=2231)	No vitamin E (n=2264)
Total	154	110	138	126
<u>Cancer</u>	86	80	86	80
<u>Bleeding</u>	24	6	16	14
gastrointestinal	17	5	11	11
intracranial (not parenchymal)	2	0	2	0
ocular	1	1	1	1
epistaxis	2	0	1	1
other	2	0	1	1
<u>Gastrointestinal disease (except bleeding)</u>	8	3	6	5
<u>Other events</u>	36	21	30	27

PRIMARY PREVENTION PROJECT (PPP)

**EFFICACY OF VITAMIN E AND ASPIRIN IN THE PREVENTION OF VASCULAR EVENTS
IN SUBJECTS AT HIGH CARDIOVASCULAR RISK**

Executive Summary

- **Istituto di Ricerche Farmacologiche "Mario Negri"**
- **Centro Studi e Ricerche in Medicina Generale (CSERMEG)**

December 1994

1. **BACKGROUND**

Vascular diseases are mostly due to the progression of atherosclerosis, which eventually results in acute thrombotic episodes, leading to different clinical events (e. g. myocardial infarction, stroke, sudden death).

Apart the control and correction of modifiable risk factors, the prevention of atherosclerosis process is still orphan of specific means.

Experimental, as well as epidemiological and clinical evidences accumulated over the last several years have suggested a possible preventive role of antioxidant vitamins with respect to development of atherosclerosis (1).

On the other hand, at variance with the secondary prevention (2), the role of aspirin for the primary prevention of cardiovascular morbidity and mortality is still debated (3).

Moreover, epidemiological data suggest an effect of aspirin and antioxidant vitamins in reducing morbidity due to cataract (4,5) and of aspirin on mortality due to colon cancer (6).

The whole body of evidences so far available suggests the need of formal clinical test of the efficacy of antioxidant vitamins and aspirin in the prevention of cardiovascular disease and/or other clinical events possibly caused by altered antioxidant processes.

2. **AIM OF THE STUDY**

The main object of the study is to assess whether long-term treatment with vitamin E and low-dose aspirin reduces the incidence of major vascular events (vascular death and non-fatal myocardial infarction or stroke) in subjects with cardiovascular risk factors, but without previous cardiovascular events.

Further objectives are the prevention of minor vascular events and the reduction of incidence of colon cancer and cataract.

3. **STUDY POPULATION**

The study population will be recruited among people seen by general practitioners or attending the hospital diabetic clinics or the centers for the treatment of hypertension.

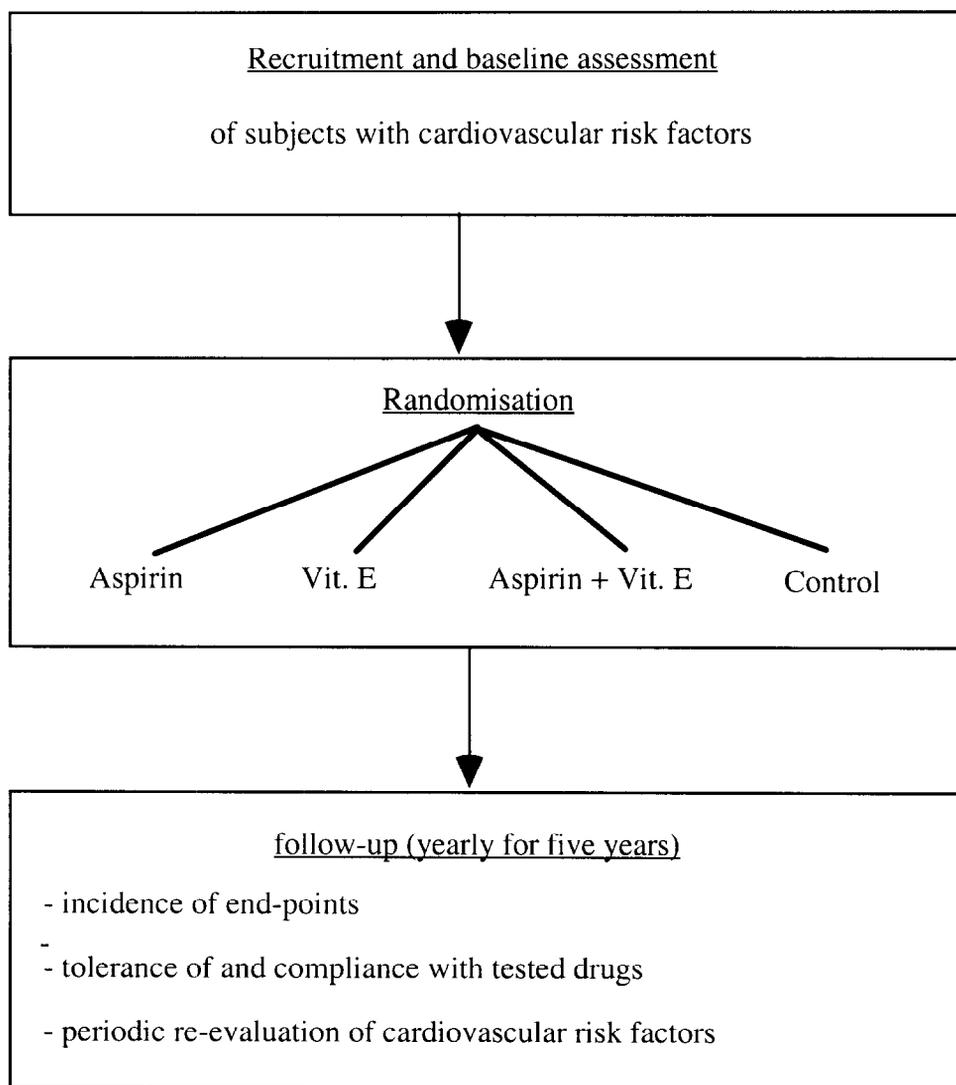
Inclusion criteria: subjects of both sexes, ≥ 50 years old, with no history of cardiovascular disease or cancer, willing to cooperate and presenting at least one of the following risk factors: age ≥ 65 , family history of premature myocardial infarction, obesity, arterial hypertension, diabetes mellitus and hypercholesterolemia.

Exclusion criteria include concomitant disease(s) with a poor short-term prognosis, likely unsuitability to comply with trial requirements, indications or

contraindications to aspirin treatment.

4. STUDY DESIGN

The study will be conducted as a multicenter, controlled, centrally randomised, open clinical trial, with a 2 x 2 factorial design and planned as shown below:



4.1 Baseline assessment

Each patient will be assessed for the presence and level of cardiovascular risk factors by family and medical history, physical examination and laboratory tests.

4.2 Randomisation

All eligible patients will be centrally randomised by telephone to aspirin (100 mg/die) or vitamin E (300 mg/die) or aspirin plus vitamin E or to a control group. The randomisation will be stratified by participating doctor.

4.3 Experimental treatment

Aspirin: low dose enteric coated aspirin (100 mg daily) is adopted. This dose of aspirin has been chosen as the minimum dose of commercially available formulation able to inhibit completely cyclo-oxygenase dependent platelet aggregation.

Vitamin E: vitamin E will be taken at the dose of 300 mg daily. This dosage has been selected on the basis of the assumption, derived from the observational data, that lower doses unlikely exert a greater biological effectiveness.

4.4 Follow-up

Subjects will be followed for five years with quarterly visits. Once a year a follow-up form will be completed, including re-evaluation of level of cardiovascular risk, incidence of end-points, tolerance and compliance with the test treatment.

4.5 End-point

The major end-point of the study is the combination of the following events: vascular mortality, non-fatal myocardial infarction, non-fatal stroke.

Total mortality, the incidence of clinical manifestation of atherosclerosis, cancer and cataract will be evaluated as well.

5. **SIZE OF TRIAL POPULATION**

Assuming that half the patients enrolled will be 65 years of age or older and half will be male, the estimated annual event rate among control subjects would be about 1.5%. Based on this estimate, the 5-year rate in the control group is assumed to be about 7.5%. A population of about 20,000 subjects is needed to verify the hypothesis of a 25% reduction (from 7.5% to 5.6%) in the incidence of the end-point in the treatment group (aspirin or vitamin E).

6. **STATISTICAL ANALYSIS**

Statistical analysis will be done according to the "intention to treat" principle, thus including drop-out and drop-in patients.

The primary objective of the analysis will be the incidence of major end-point (combination of vascular mortality, non-fatal myocardial infarction and stroke) in the treatment groups as compared with the control groups in the overall trial population.

Secondary analysis will include the evaluation of treatment efficacy:

- in subgroups of subjects stratified according to the kind and number of risk factors,

- with regard to particular end-points: vascular mortality, myocardial infarction (fatal and/or non- fatal), cerebral stroke (fatal and/or non fatal, ischemic or hemorrhagic, disabling or not), and other events (e.g., peptic ulcer, haemorrhagic events, cancer incidence and death, cataract, etc.).

6.1 Interim analyses

The Data Monitoring Committee will conduct two formal interim analyses, when 500 and 1000 major events will be recorded, in order to evaluate the incidence of the events considered as the major end-point of the study in the treatment and control groups.

7. **ETHICAL ASPECTS**

The study protocol has been submitted to and approved by the Committees foreseen for the purpose by the Italian legislation, present at either regional or local level. The "Good Clinical Practice" (GCP) criteria are adopted as established by the current legislation (D.M. 27.04.1992).

All the eligible patients will be informed about the aims of the study and asked for their consent to participate.

8. **TIME FOR STUDY COMPLETION**

The study will start in April 1994 and recruitment is foreseen to be completed by the end of 1995. The trial will be stopped upon achievement of 1500 major events, what is foreseen to be reached within a five-year follow-up period.

9. **STUDY ORGANIZATION**

The Scientific Group of the study consists of the following groups:

- Principal investigators: all the participating doctors.
- Scientific and Organizing Secretariat and Randomisation Centre (F. Avanzini, V.Bertele', V.Caimi, F.Colombo, I.Pangrazzi, M.C. Roncaglioni, G. Tognoni).
- External Safety and Efficacy Monitoring Committee (A. De Carli, A. Del Favero, E. Geraci).
- Clinical Reviewing Committee (C. Alli, D. Coen, A. Volpi).

References

- 1) Steinberg D, Workshop Participants. Antioxidants in the prevention of human atherosclerosis. *Circulation* 1992,85:2338.
- 2) Antiplatelet Trialists'Collaboration. Collaborative overview of randomised trial of antiplatelet therapy. *Br Med J* 1994, 308: 159.
- 3) Manson JE, Tosteson H, Ridker PM, Satterfield S, Hebert P, O'Connor GT, Buring JE and Hennekens CH. The primary prevention of myocardial infarction. *N Engl J Med* 1992,326: 1406.
- 4) Editorial. Preventing cataract. *Lancet* 1992, 340:883.
- 5) Knekt P, Heliövaara M, Rissanen A. Serum antioxidant vitamins and risk of cataract. *Br Med J* 1992, 305:1392.
- 6) Thun MJ, Namboodiri MM, Heath CW. Aspirin use and reduced risk of fatal colon cancer. *N Engl J Med* 1991, 325:1593.