

# Primary Prevention of Cardiovascular Events With Low-Dose Aspirin and Vitamin E in Type 2 Diabetic Patients

## Results of the Primary Prevention Project (PPP) trial

MICHELE SACCO, MD<sup>1</sup>  
 FABIO PELLEGRINI, MS<sup>1</sup>  
 MARIA C. RONCAGLIONI, MSc, BIOLs<sup>2</sup>  
 FAUSTO AVANZINI, MD<sup>2</sup>

GIANNI TOGNONI, MD<sup>2</sup>  
 ANTONIO NICOLUCCI, MD<sup>1</sup>  
 ON BEHALF OF THE PPP COLLABORATIVE  
 GROUP\*

**OBJECTIVE** — We investigated in general practice the efficacy of antiplatelets and antioxidants in primary prevention of cardiovascular events in people with type 2 diabetes.

**RESEARCH DESIGN AND METHODS** — The Primary Prevention Project (PPP) is a randomized, open trial with a two-by-two factorial design aimed to investigate low-dose aspirin (100 mg/day) and vitamin E (300 mg/day) in the prevention of cardiovascular events in patients with one or more cardiovascular risk factors. The primary end point was a composite end point of cardiovascular death, stroke, or myocardial infarction. A total of 1,031 people with diabetes in the PPP, aged  $\geq 50$  years, without a previous cardiovascular event were enrolled by 316 general practitioners and 14 diabetes outpatient clinics.

**RESULTS** — The PPP trial was prematurely stopped (after a median of 3.7 years) by the independent data safety and monitoring board because of a consistent benefit of aspirin compared with the control group in a population of 4,495 patients with one or more major cardiovascular risk factors. In diabetic patients, aspirin treatment was associated with a nonsignificant reduction in the main end point (relative risk [RR] = 0.90, 95% CI 0.50–1.62) and in total cardiovascular events (0.89, 0.62–1.26) and with a nonsignificant increase in cardiovascular deaths (1.23, 0.69–2.19). In nondiabetic subjects, RRs for the main end point, total cardiovascular events, and cardiovascular deaths were 0.59 (0.37–0.94), 0.69 (0.53–0.90), and 0.32 (0.14–0.72), respectively. No significant reduction in any of the end points considered could be found with vitamin E in either diabetic or nondiabetic subjects.

**CONCLUSIONS** — Our data suggest a lower effect of primary prevention of cardiovascular disease (CVD) with low-dose aspirin in diabetic patients as opposed to subjects with other cardiovascular risk factors. If confirmed, these findings might indicate that the antiplatelet effects of aspirin in diabetic patients are overwhelmed by aspirin-insensitive mechanisms of platelet activation and thrombus formation, thus making the balance between benefits and harms of aspirin treatment unfavorable. Further large-scale trials investigating the role of aspirin in the primary prevention of CVD in diabetic patients are urgently needed.

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From the <sup>1</sup>Department of Clinical Pharmacology and Epidemiology, Istituto di Ricerche Farmacologiche Mario Negri, Consorzio Mario Negri Sud, S. Maria Imbaro (CH), Italy; and the <sup>2</sup>Department of Cardiovascular Research, Istituto di Ricerche Farmacologiche Mario Negri, Milan, Italy.

Address correspondence and reprint requests to Antonio Nicolucci, MD, Department of Clinical Pharmacology and Epidemiology, Consorzio Mario Negri Sud Via Nazionale, 66030 S. Maria Imbaro (CH), Italy. E-mail: nicolucc@negrisud.it.

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\*Members of the Primary Prevention Project (PPP) Collaborative Group are listed in the APPENDIX.

**Abbreviations:** CVD, cardiovascular disease; ETDRS, Early Treatment of Diabetic Retinopathy Study; PPP, Primary Prevention Project; TIA, transient ischemic attack.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

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See accompanying editorial, p. 3349.

Diabetic macroangiopathy is the leading cause of mortality and morbidity in people with diabetes (1). In type 2 diabetic patients, mortality and morbidity for cardiac and cerebrovascular causes is two- to fourfold greater than in the general population (2). The alterations of hemostatic and thrombotic parameters are among the principal causes for the cardiovascular risk increase in diabetic patients (3). It has also been suggested that oxidative stress can contribute to diabetic vascular complications (4), and lower antioxidant defenses in diabetes have been described (5).

The benefits of aspirin in the primary prevention of cardiovascular disease (CVD) in high-risk patients without pre-existing CVD have been documented in five randomized clinical trials involving >50,000 individuals (6–10). A meta-analysis of pooled data from these studies showed that aspirin therapy reduced the risk for coronary heart disease by 28%, with no significant effects on total mortality and stroke (11). In addition, the Primary Prevention Project (PPP) (10) has recently shown that low-dose aspirin significantly reduced the risk of cardiovascular death by >40% in a population of 4,495 people with one or more cardiovascular risk factors after a median follow-up of 3.7 years.

Despite the high cardiovascular risk, clear evidence of benefit of antiplatelet therapy in diabetic people without previous CVD is still lacking. The main randomized evidence currently available comes from nine trials involving a total of ~5,000 patients, and the recent meta-analysis of their results indicates a much smaller proportional reduction in cardiovascular events than has been found in the secondary prevention setting (only 7% compared with 25%) (12). As for vitamin E, several randomized trials have recently failed to show a benefit deriving from its use in preventing cardiovascular events in

different high-risk groups, including diabetic patients (10,13–15).

The Primary Prevention Project (PPP) is a randomized, open-label trial with a factorial design testing whether chronic treatment with aspirin and vitamin E reduces the frequency of major cardiovascular events in patients without previous CVD and with one or more cardiovascular risk factors (10). We present the results relative to diabetic patients and compare the results of diabetic patients with those of nondiabetic patients who have other cardiovascular risk factors.

## RESEARCH DESIGN AND METHODS

The PPP is a multicenter, centrally randomized, open-label clinical trial designed to test whether chronic treatment with aspirin (one tablet of 100-mg enteric-coated aspirin a day) and vitamin E (one capsule of 300-mg synthetic  $\alpha$ -tocopherol a day) reduces the frequency of major fatal and nonfatal cardiovascular events in patients with one or more major cardiovascular risk factors with no clinically relevant safety implications (10).

After the study was planned, we decided to specifically explore the effects of antiplatelet and antioxidant therapy in type 2 diabetic patients. For this purpose, in parallel with the main trial, which was conducted in general practice, we also involved 14 diabetes clinics with the aim of recruiting an additional sample of diabetic patients. After a median follow-up of 3.7 years, the main 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 the second, planned interim analysis. For this reason, even the enrollment of diabetic patients by diabetes clinics was stopped. Details on study design and main results of the trial have been reported elsewhere (10).

Briefly, patients were randomly allocated to receive aspirin or no aspirin and vitamin E or no vitamin E, following a two-by-two factorial design. Treatments were centrally assigned on telephone verification of the correctness of inclusion criteria with a separate computer-generated randomization table produced for each physician or center in random permuted blocks of 12, allowing stratification by physician or center. At the beginning, and repeatedly during the trial,

all patients received advice on compliance with background treatments and control of cardiovascular risk.

### Study population

Participants were diabetic patients (fasting venous plasma glucose concentration  $\geq 7.8$  mmol/l on at least two separate occasions or treated with antidiabetic drugs), aged  $\geq 50$  years, without history of major cardiovascular events. Exclusion criteria were severe pathology, treatment with antiplatelet drugs (history of vascular events or disease), chronic use of anti-inflammatory agents or anticoagulants, chronic use of aspirin or vitamin E, contra-indications to aspirin, disease with predictable poor short-term prognosis, and predictable psychological or logistical difficulties affecting compliance with the trial requirements.

### Follow-up

The trial procedures were planned to respect the conditions of routine care in patients with diabetes. Visits to renew drug supplies and to check tolerance and compliance to the trial treatments were arranged every 4 months. Follow-up clinical visits were scheduled yearly and included reassessment of the presence and level of cardiovascular risk factors and recording of outcome events. A compliance form was completed at 3 months after randomization.

### Efficacy end points

The primary study efficacy end point was the reduction of the incidence of major cardiovascular and cerebrovascular events (cardiovascular deaths, nonfatal myocardial infarction, and nonfatal stroke). Predefined analyses included cardiovascular deaths, total deaths, total cardiovascular events (cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, angina pectoris, transient ischemic attacks [TIAs], peripheral artery disease, and revascularization procedures). Details for the definition of the different end points are reported elsewhere (10).

### Statistical analysis

The study was designed to recruit up to 4,000 participants with diabetes. With the assumption of a constant event rate in participants with diabetes of 4% per year, this sample size would provide 90% power (two-sided  $\alpha = 0.05$ ) to detect a 25% RR reduction in the rate of myocar-

dial infarction, stroke, or cardiovascular death during the planned mean follow-up period of 5 years. The study was ended prematurely on the recommendation of the independent data safety and monitoring board. Therefore, we report results for a median follow-up period of 3.7 years.

Analyses were done according to the intention-to-treat principle. Treatment efficacy was expressed as RR estimates (given by the percentage of events in the treated group divided by the percentage of events in the control group) with 95% CIs. Kaplan-Meier survival curves were estimated for the main end point, and comparisons were made using the log-rank test. To take into account the slight imbalance in the number of cardiovascular risk factors and the proportion of subjects with hypertension and hypercholesterolemia between the groups treated and not treated with aspirin, treatment effect was also estimated by multivariate Cox analysis and expressed as hazard ratios (HRs) with 95% CIs, with number of cardiovascular risk factors, presence of hypertension, and presence of hypercholesterolemia forced in the model as covariates.

Patient characteristics according to the presence of diabetes were compared using the  $\chi^2$  test for categorical variables and the Mann-Whitney *U* test for continuous variables. The Breslow-Day  $\chi^2$  test for heterogeneity was used to compare the effect of aspirin in patients with and without diabetes.

**RESULTS**— Between 1994 and 1998, 4,784 patients were recruited, of whom 1,031 had diabetes. Among the latter, 744 (72.2%) were enrolled by 316 general practitioners and 287 (27.8%) by 14 diabetes outpatient clinics. Baseline patient characteristics according to the presence of diabetes are reported in Table 1.

Of the 1,031 diabetic patients enrolled, 519 were randomly assigned to receive 100 mg aspirin per day and 509 assigned to receive 300 mg vitamin E per day. Table 2 shows baseline characteristics of the population by treatment group. Patient characteristics were well balanced across the groups, with the only exception of a higher percentage of subjects with hypertension and hypercholesterolemia in the aspirin group compared with the no aspirin group.

Most patients with hypertension were given drug treatment, and 40% of the pa-

Table 1—Baseline patient characteristics according to the presence of diabetes

	Diabetes	No diabetes	P*
n	1,031	3,753	
Age (years)	64.2 ± 7.5	64.4 ± 7.7	0.7
Sex			
Male	497 (48.2)	1,557 (41.5)	<0.001
Female	534 (51.8)	2,196 (58.5)	
CV risk factors for inclusion			
Old age	496 (48.1)	1,870 (49.8)	0.3
Hypertension	643 (62.4)	2,580 (68.8)	<0.001
Family history	84 (8.2)	406 (10.8)	0.01
Obesity	340 (33.0)	790 (21.1)	<0.001
Hypercholesterolemia	308 (29.9)	1,498 (39.9)	<0.001
CV risk factors (n)			
One	109 (10.6)	1,344 (35.8)	<0.001
Two	309 (30.0)	1,560 (41.6)	
Three or more	613 (59.5)	849 (22.6)	
Smoking			
Ex	257 (25.2)	895 (24.0)	0.9
Current	168 (16.5)	555 (14.9)	
CV drugs			
Antihypertensive drugs	624 (60.5)	2,523 (67.2)	<0.001
Lipid lowering	131 (12.7)	595 (15.9)	0.01
BMI (kg/m <sup>2</sup> )	29.0 ± 5.0	27.3 ± 4.5	<0.001
Systolic blood pressure (mmHg)	148.7 ± 17.1	144.6 ± 16.0	<0.001
Diastolic blood pressure (mmHg)	84.9 ± 9.0	85.5 ± 8.4	0.03
Total cholesterol (mg/dl)	224.6 ± 44.0	237.8 ± 44.7	<0.001
HDL cholesterol (mg/dl)	49.8 ± 16.2	53.8 ± 17.0	<0.001
Triglycerides (mg/dl)	175.1 ± 105.9	149.7 ± 80.4	<0.001

Data are means ± SD or n (%). CV, cardiovascular. \* $\chi^2$  for categorical variables, and Mann-Whitney *U* test for continuous ones.

tients with hypercholesterolemia received lipid-lowering drugs. Antidiabetic and lipid-lowering drugs were well balanced across the groups at baseline (Table 2), whereas the percentage of patients treated with antihypertensive drugs was higher in the aspirin group than in the no aspirin group. No differences between arms were found at the end of the study in terms of use of ACE inhibitors, other antihypertensive agents, and statins. HbA<sub>1c</sub>, lipids, and blood pressure levels were also comparable in the two arms throughout the study period (data not shown). At the end of study, 54 diabetic patients (11.9%) assigned to the control group were taking aspirin, whereas 135 (28.2%) assigned to aspirin had discontinued the treatment. The median duration of the follow-up was 3.7 years (interquartile range 3.1–4.3) for nondiabetic patients and 3.6 years (2.7–4.2) for diabetic patients.

Kaplan-Meier curves for the main combined end point according to the presence of diabetes are reported in Fig. 1,

showing a clear benefit of aspirin only in nondiabetic patients. The use of vitamin E was not associated with a better outcome in both groups. The efficacy profiles for aspirin and vitamin E in patients with and without diabetes are summarized in Fig. 2.

No significant reduction in any of the end points considered could be found with aspirin in diabetic patients, whereas in nondiabetic individuals, a significant reduction in the main combined end point, total cardiovascular events, cardiovascular deaths, and peripheral artery disease was documented. The  $\chi^2$  test for heterogeneity comparing the results in patients with and without diabetes reached the statistical significance for cardiovascular deaths ( $P = 0.03$ ).

As for vitamin E, no significant reduction in any of the end points considered could be found among diabetic patients, whereas a marginal reduction in the risk of peripheral artery disease was docu-

mented in nondiabetic individuals (Fig. 2).

Multivariate analyses confirmed a nonsignificant reduction in the hazards of the main cardiovascular end point for patients treated with aspirin (HR = 0.90, 95% CI 0.49–1.67) and a nonsignificant increase in those treated with vitamin E (1.21, 0.65–2.23).

### Safety

The rate of noncardiovascular deaths was similar in the treatment groups (Table 2). An excess of nonfatal events was reported for aspirin due to bleeding complications (1.9 vs. 0.2%;  $P = 0.007$ ). Overall, 10 episodes of bleeding were reported in the aspirin group (8 gastrointestinal) and 1 (gastrointestinal) in the control group. No intracranial hemorrhages were documented. The 38 new cancer diagnoses were evenly distributed in the treatment groups (20 cases in the aspirin group and 18 in the control group).

**CONCLUSIONS**— Diabetes is associated with a substantial increase in the risk of CVD, and the use of low-dose aspirin is thus recommended by existing guidelines (16,17). Despite the general consensus, the evidence supporting the use of aspirin for the prevention of CVD in diabetic patients is surprisingly scant. A recent meta-analysis failed to show a clear benefit of antiplatelet therapy in diabetic patients, with a nonsignificant 7% proportional reduction in serious vascular events (12). Within the meta-analysis, results relative to aspirin mainly derived from the Early Treatment of Diabetic Retinopathy Study (ETDRS), the only trial specifically conducted in diabetic patients (18). Even in this trial, there was a nonsignificant 9% reduction in serious vascular events. Our data are highly consistent with the existing evidence, showing a nonsignificant 10% reduction in the risk of the same end point, as compared with a 41% reduction in nondiabetic subjects. The positive effects of aspirin documented in the whole PPP population were even more evident when diabetic patients were excluded from the analysis, reaching the statistical significance for the main combined end point (RR reduction of 41%;  $P = 0.026$ ) and peripheral artery disease (RR reduction of 62%;  $P = 0.038$ ). Furthermore, the RR reduction for cardiovascular deaths rose to 69% and

Table 2—Baseline patient characteristics according to treatment group

	Aspirin	Control	Vitamin E	Control
n	519	512	509	522
Age (years)	64.3 ± 7.6	64.2 ± 7.4	64.3 ± 7.5	64.1 ± 7.5
Sex				
Male	246 (47.4)	251 (49.0)	253 (49.7)	244 (46.7)
Female	273 (52.6)	261 (51.0)	256 (50.3)	278 (53.3)
CV risk factors for inclusion				
Old age	252 (48.6)	244 (47.7)	248 (48.7)	248 (47.5)
Hypertension	343 (66.7)*	300 (59.4)	312 (62.0)	331 (64.2)
Family history	49 (9.7)	35 (7.1)	38 (7.7)	46 (9.1)
Obesity	175 (34.2)	165 (33.1)	164 (32.7)	176 (34.5)
Hypercholesterolemia	179 (35.7)†	129 (26.3)	146 (30.1)	162 (32.0)
CV risk factors (n)				
One	53 (10.2)	56 (10.9)	58 (11.4)	51 (9.8)
Two	133 (25.6)	176 (34.4)	158 (31.0)	151 (28.9)
Three or more	333 (64.2)†	280 (54.7)	293 (57.6)	320 (61.3)
Smoking				
Ex	132 (25.6)	125 (24.8)	122 (24.1)	135 (26.3)
Current	83 (16.1)	85 (16.8)	86 (17.0)	82 (16.0)
CV drugs				
Antihypertensive drugs	335 (64.6)†	289 (56.5)	298 (58.6)	326 (62.5)
Lipid lowering	68 (13.3)	63 (12.6)	65 (13.0)	66 (12.9)
Diabetes treatment				
Diet alone	141 (27.2)	137 (26.8)	133 (26.1)	145 (27.8)
Sulphonylureas	133 (25.6)	135 (26.4)	147 (28.9)	121 (23.2)
Metformin	18 (3.5)	17 (3.3)	14 (2.8)	21 (4.0)
Sulphonylureas + metformin	169 (32.6)	166 (32.4)	162 (31.8)	173 (33.1)
Insulin + OHA	47 (9.1)	48 (9.4)	44 (8.6)	51 (9.8)
Other	11 (2.1)	9 (1.8)	9 (1.8)	11 (2.1)
BMI (kg/m <sup>2</sup> )	29.0 ± 5.2	29.1 ± 4.7	29.2 ± 5.3	28.9 ± 4.6
Systolic blood pressure (mmHg)	148.8 ± 17.0	148.6 ± 17.1	149.0 ± 16.7	148.4 ± 17.4
Diastolic blood pressure (mmHg)	84.9 ± 9.1	84.8 ± 8.9	85.1 ± 8.7	84.6 ± 9.2
Total cholesterol (mg/dl)	226.0 ± 46.2	222.2 ± 41.5	223.0 ± 42.1	226.1 ± 45.8
HDL cholesterol (mg/dl)	49.5 ± 16.8	50.2 ± 15.5	49.8 ± 16.5	49.9 ± 15.8
Triglycerides (mg/dl)	177.4 ± 111.2	172.8 ± 100.5	176.9 ± 110.9	173.3 ± 100.8
HbA <sub>1c</sub> (%)	7.6 ± 2.0	7.6 ± 2.1	7.6 ± 2.2	7.6 ± 2.0

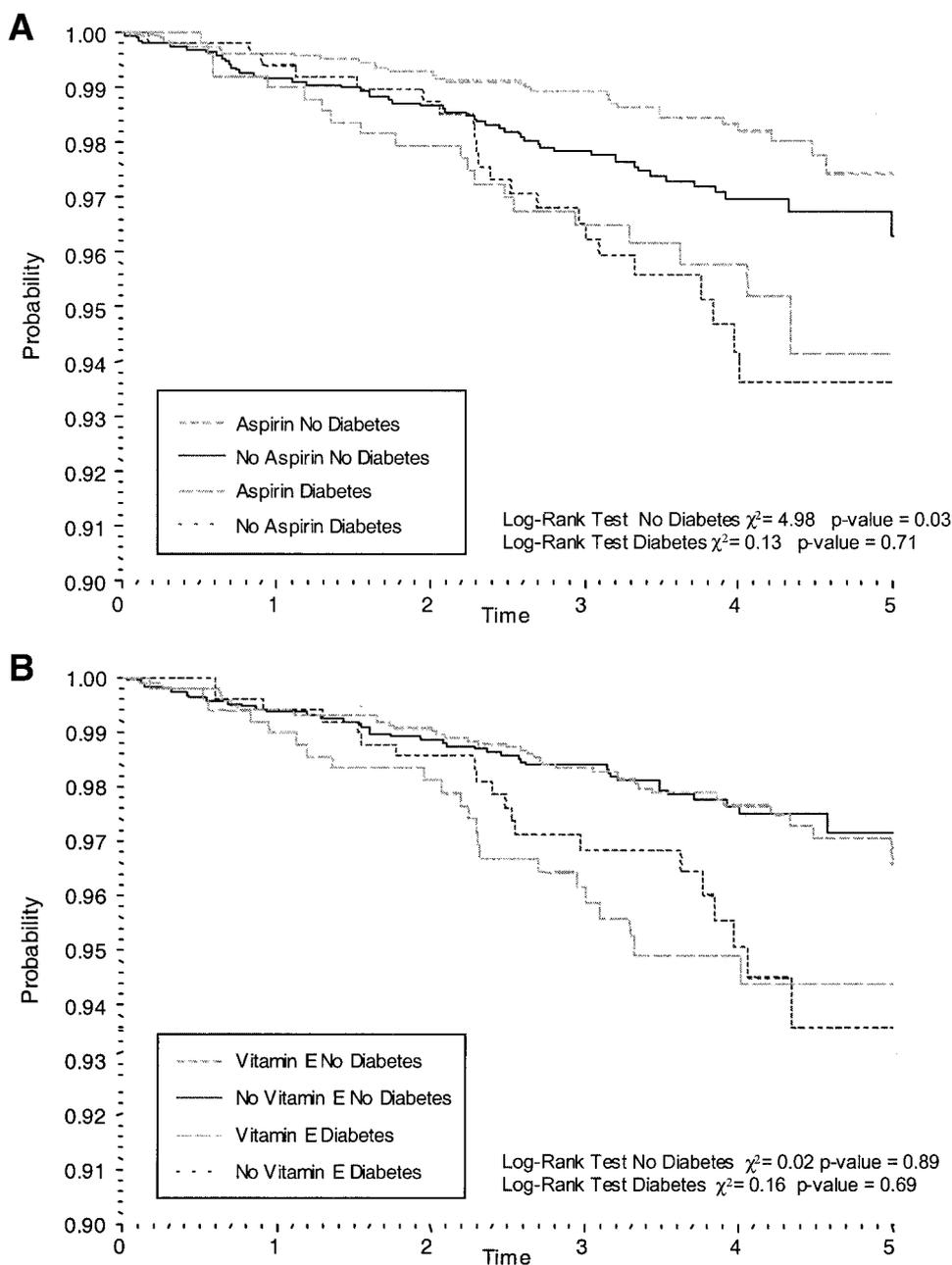
Data are means ± SD or n (%). CV, cardiovascular; OHA, oral hypoglycemic agents. \**P* < 0.05; †*P* < 0.01.

that for total cardiovascular events to 29%.

Due to the low statistical power, our data cannot be considered conclusive. Nevertheless, they are coherent with the existing literature in suggesting the hypothesis that low-dose aspirin might be less effective in diabetic patients as compared with the general population. Several mechanisms have been suggested that can act in combination and be responsible for these findings. First of all, diabetes might represent a particular case of aspirin resistance. In fact, in diabetic patients, platelets could be activated through different mechanisms that can lead to thrombosis despite aspirin therapy. The involvement of aspirin-

insensitive Cox-2, an inducible enzyme mainly expressed in monocyte-macrophages under inflammatory stimuli, as an additional source of TxA<sub>2</sub> is one of these possible mechanisms (19). Interestingly, circulating levels of different endothelial-derived adhesive molecules, which indicate the inflammatory phenotype of endothelial cells, are increased in diabetes (20,21). The upregulated inflammatory response present in diabetic patients could therefore be responsible for aspirin resistance. It has also been suggested that hyperglycemia can lead to the generation of a relevant quantity of thromboxane and endoperoxides bypassing the cyclooxygenase step (22), thus contributing to aspirin resistance.

Diabetes is also often associated with other cardiovascular risk factors, such as hypertension and hypercholesterolemia. It has been recently suggested (23) that aspirin may be less effective in subjects with systolic blood pressure values >145 mmHg. In the PPP trial, 54.5% of diabetic patients had baseline values >145 mmHg. As for hypercholesterolemia, it has been shown (24) to be associated with reduced responsiveness of platelets to aspirin. A lower effect of aspirin in the presence of elevated values of total cholesterol was also described in the Physicians' Health Study (7) and the Thrombosis Prevention Trial (23). Dyslipidemia, present in >30% of the patients in our study, could thus contribute in determining the results.



**Figure 1**—Kaplan-Meier survival curves for main end point (cardiovascular death, nonfatal myocardial infarction, and nonfatal stroke) according to aspirin and diabetes status (A) and to vitamin E and diabetes status (B).

Another explanation for the lower-than-expected effect of aspirin can be represented by the low dose used. In fact, in diabetic patients, platelets have an increased turnover, and higher doses of aspirin may be necessary to achieve the same levels of thromboxane inhibition as in nondiabetic subjects (25). Nevertheless, it should be noted that the results of the ETDRS were very similar to ours, despite an aspirin dose of 650 mg/day (18).

Finally, recent studies have suggested

that the benefits of aspirin and ACE inhibitors may be attenuated when both agents are used together (26), but a recent meta-analysis (27) showed no such interaction. In our study, we did not find any differential effect of aspirin in patients treated or not with ACE inhibitors.

Results relative to vitamin E are highly consistent with those of the main trial as well as with the existing literature, showing a substantial lack of effect of antioxidant vitamin supplementation in

preventing major cardiovascular events in patients at risk. In particular, the recent results of the Heart Protection Study, involving ~6,000 individuals with diabetes (13), showed that vitamin supplementation did not produce any significant reduction in the 5-year incidence of major cardiovascular events in patients with and without prior coronary heart disease. Similarly, in the Microalbuminuria Cardiovascular Renal Outcomes (MICRO)-Heart Outcomes Prevention Evaluation

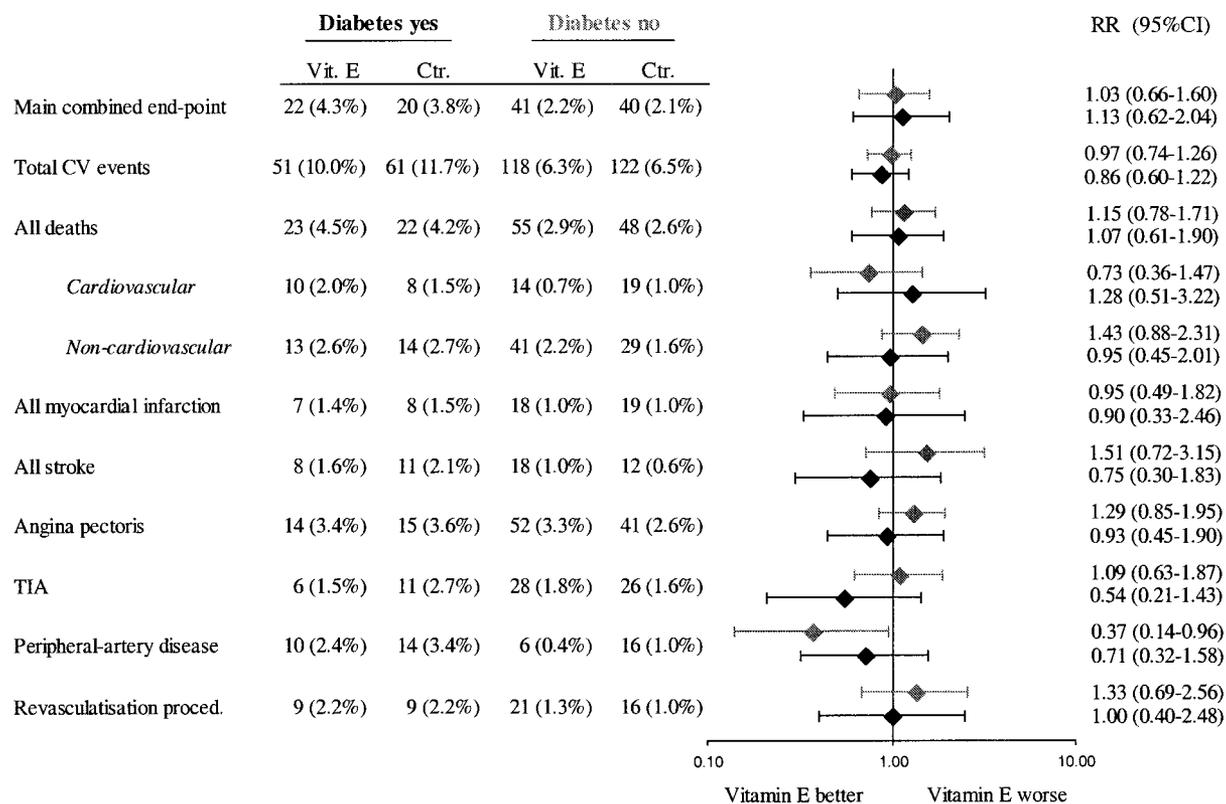
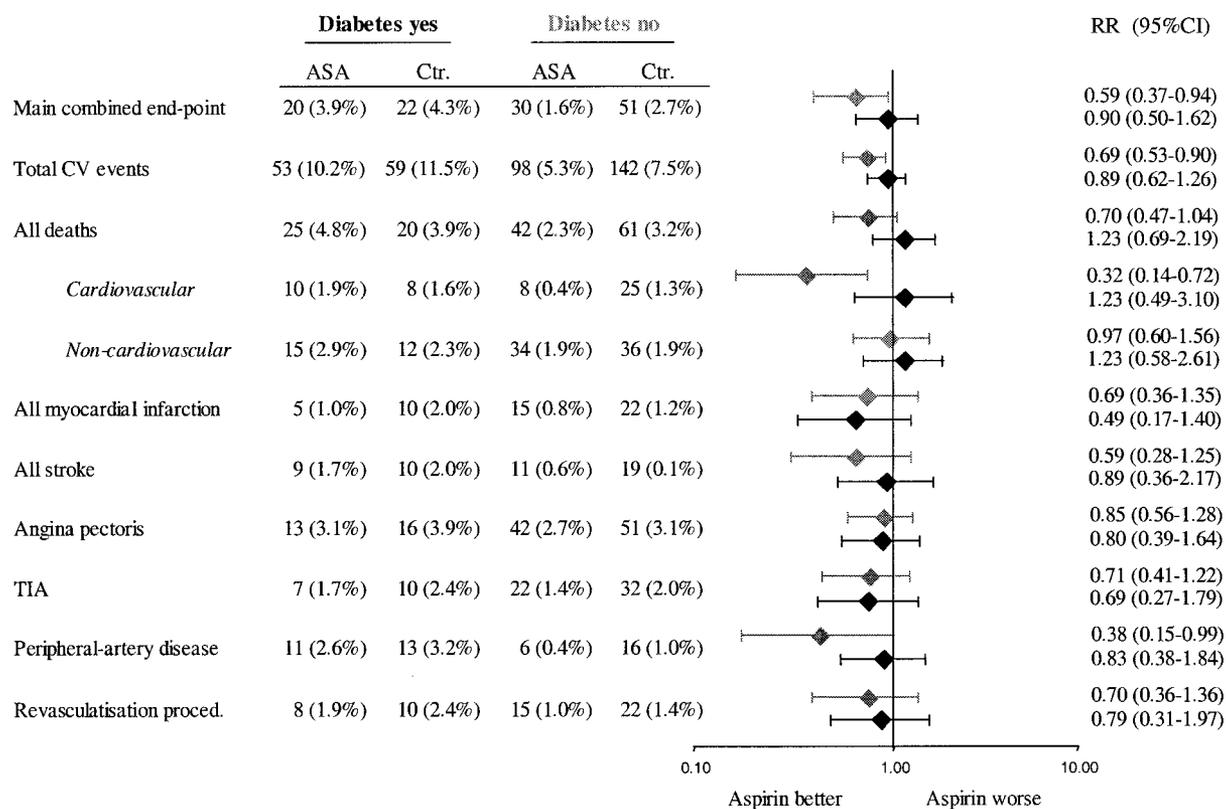


Figure 2— Efficacy profile of aspirin and vitamin E in subjects with (n = 1,031; in black) and without (n = 3,753; in gray) diabetes.

(HOPE) study the daily administration of 400 IU vitamin E for an average of 4.5 years to 3,654 people with diabetes had no effect on cardiovascular outcomes or nephropathy (14). On this ground, the recommendation of antioxidant vitamin supplementation in diabetic patients is hardly justified.

Finally, some of the potential limitations of our study need to be discussed. First, the study is underpowered due to its premature stop, as well as to a rate of events (1% per year) significantly lower than that hypothesized (4% per year). Therefore, the efficacy of aspirin in the primary prevention of CVD in patients with diabetes cannot be ruled out.

Second, the study was open label. The choice not to use a blinded design is related to the pragmatic nature of the trial, which was mainly conducted in general practice; in other words, we wanted to test the efficacy and safety of preventive strategies while respecting the conditions of routine care in patients with cardiovascular risk factors. The open design did not lead to overtreatment in one group at the expense of the other. In fact, study arms did not differ for the entire study period in terms of antihypertensive and lipid-lowering treatments, and the two groups showed superimposable values in terms of HbA<sub>1c</sub>, lipid profile, and blood pressure levels. Furthermore, only a few patients in the control group were treated with aspirin, thus confirming that the open design did not affect the interpretation of the results.

In conclusion, our data seem to show a lower effect of primary prevention of CVD with low-dose aspirin in diabetic patients as opposed to subjects with other cardiovascular risk factors. If confirmed, these findings may suggest that in diabetic patients the antiplatelet effects of aspirin are overwhelmed by aspirin-insensitive mechanisms of platelet activation and thrombus formation, thus making the balance between benefits and harms of aspirin treatment unfavorable. Further large-scale trials investigating the role of aspirin in the primary prevention of CVD in diabetic patients are urgently needed, together with studies aimed at identifying the mechanisms by which diabetic patients may fail aspirin therapy.

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## APPENDIX

### The Primary Prevention Project (PPP) Collaborative Group

Scientific and organizing committee: G Tognoni, F Avanzini, J Pangrazzi, MC Roncaglioni (Istituto di Ricerche Farmacologiche Mario Negri, Milano); V Berlete', G de Gaetano (Consortio Mario Negri Sud, Santa Maria, Imbaro); V Caimi, M Tombesi (CSeRMEG Centro Studi e Ricerca in Medicina Generale, Monza).

Data management: F Colombo, S Barlera (Istituto di Ricerche Farmacologiche Mario Negri, Milano).

Secretariat and data input: F Clerici, A Palumbo, G Sgaroni (Istituto di Ricerche Farmacologiche Mario Negri, Milano), B Di Nardo (Consortio Mario Negri Sud, S Maria Imbaro).

External safety and efficacy monitoring committee: E Geraci (Chairman, Ospedale Cervello, Palermo); A Del Favero (Università di Perugia), A Decarli (Università di Milano).

Committee for event validation: C Alli (Ospedale Niguarda, Milano); E Beghi (Ospedale S Gerardo, Monza); D Coen (Ospedale di Rho), A Volpi (Ospedale di Magenta).

Participating general practitioners: P Accattoli (Macerata); A Agneta (Montalbano Jonico); S Alberino (Chiusdino); U Amoroso (Pescara); M Angeletti (Senigallia); G Antiga (Conegliano); R Ariutti (Berra); F Armani (Udine); G Bacci (Sanfaticchio); C Balzan (Trichiana); G Banchi (Borgo S Lorenzo); G Barba (Taranto); P Baron (Palmanova); A Barone (Albano di Lucania); M Bartoli (Marina di Carrara); PL Bartoli (Cesenatico); G Barucca (Monte S Pietro); R Bedon (Casale Monferrato); M Bellini (Rimini); A Bencivenni (S Giovanni in Persiceto); R Benetti (Casale sul Sile); E Beretta (Concorezzo); L Bertini (Monzuno); S Bertolissi (Udine); G Berton (Castelfranco Veneto); E Besozzi (Castelletto Ticino); S Bevilacqua (Viterbo); A Bianchi (Monopoli); D Bigotto (Gonars); MI Bini (Rovereto); G Bizzarri (Cannara); L Boldini (Torbole Casaglia); M Bosisio Pioltelli (Monza); S Bossi (Curtatone); RM Bozzetto (Breganze); A Brizzi

(Terlizzi); B Bruno (L'Aquila); A Bussotti (Sesto Fiorentino); A Buzzatti (Sedico); T Cadioli (Carpi); V Caimi (Monza); FP Calciiano (Grassano); L Caldarini (Limbiato); S Calienno (Monza); P Caltaginone (Castelnovo di Isola Vicentina); M Cancian (Conegliano); GL Cantamessa (Casale Monferrato); N Caporali (Piombo); M Carli (Novate Milanese); G Cascini (Chieti); P Casella/M Casella (Caserta); C Caso (Merceto S Severino); M Cassanelli (Castelfranco Emilia); A Catalano (S Leucio del Sannio); M Cavallini (Milano); F Cazzaniga (Monza); P Cedaro (Moggio Udinese); M Celia (Montebelluna); L Cella (Gossolengo); P Chiara (Torino); AV Ciardullo (Meta di Sorrento); G Ciccone (Stornara); C Ciociano (Sarno); A Cipolla (Mogliano Veneto); E Ciprietti (Nereto); L Cocco (Cellore); F Cocconi (Gazoldo); S Conio (Torino); F Corasaniti (Marina di Davoli); L Cozzani (Ponte di Arcola); ML Cressotti (Milano); E Cuzzo (S Antimo); L Cusmai (Foggia); GB D'Errico (Foggia); G D'Innocente (Pescara); C De Angelis (S Ferdinando di Puglia); C De Chirico (Sernaglia della Battaglia); M De Grandi (Novara); E De Maria (Napoli); C De Matteis (Paola); D De Matteis (Belvedere Spinello); R Della Vedova (Sagrado); E Di Giovambattista (Magnano in Riviera); M Di Giuseppe (Carnate); M Di Santi (Erba); MG Dionette (Scano di Montiferro); A Egitto (Carnate); V Emma (Pietraperzia); T Ermacora (Maiano); P Esposito (Udine); M Falcoz (Bessica di Loria); U Felice Civitillo (Napoli); FN Ferrara (Marconia di Pisticcio); V Ferrari (Parabita); A Ferreri (Cigoli San Miniato Basso); M Ferroni (Verona); S Filippo (Cosenza); S Fortunato (Montoro Inferiore); B Fossati (Monza); G Frapporti (Fumane); A Frascati (Chioggia); R Fucili (Pesaro); MA Fumagalli (Senago); P Gadducci (Pisa); G Galli (Licciana Nardi); O Galvani (Guidizzolo); V Gamberini (Imola); F Gangi (Pasian di Prato); R Gasparri (Mansuè); F Gazzetta (Varese); W Gentile (Foggia); S Germano (Avola); F Germini (Perugia); F Ghionda (Lecce); M Giaretta (Vicenza); U Giommoni (Macchie); R Giugliano (Pozzuoli); F Giusta (Borgo San Dalmazzo); P Giusti (Silvi); P Grilli (Pianello); G Groppelli (Pandino); S Gualtieri (Napoli); A Guerrini (Piangipane); B Guillaro (Pozzuoli); L Ibello (Aversa); MA Ingletti (Bari); MG Klavara (Gemona del Friuli); G Lattuada (Uboldo); D Lauri (Milano); M Lenotti (Varese); L Lepore (Recanati); G Licursi

(Ururi); P Lombardi (Milano); M Lombardo (Catania); M Lorello (Napoli); E Lovisa (Sambughé-Preganziol); G Luisetto (Sedico); P Luvisi (Torre del Lago); P Maestri (Ferrara); R Maggioni (Legnago); P Malavasi (Carpi); M Mao (Torino); A Marcello (Casapulla); S Marinacci (Orta Nova); E Marini (Limbiate); M Marolla (Torremaggiore); C Martini (Vinadio); C Marulli (Martinsicuro); M Masperi (Abbiategrosso); M Mastella (Foza); M Mastrocola (Loro Piceno); A Matteucci (Osimo); M Mazzù (Torino); A Mellace (Catanzaro); GM Mezzacapo (Veroli); D Migaldi (Cosenza); A Miluzio (Stornarella); R Miradoli (Milano); V Misiani (Reggio Calabria); M Monina (Giulianova); U Montanari (Val Canneto di Cerveteri); S Moretti (Caserta); M Morini (Cotignola); A Moro (Preganziol); S Moscardini (Soiana); P Moschitta (Firenze); V Mossa (Bari); G Mureddu (Quartu S Elena); R Murgia (Cagliari); AM Mussini (Vigevano); G Nafra (Silvi); R Nasorri (Terontola); G Nati (Roma); L Nicoletti (Parabita); S Nicoli (Borgo di Terzo); S Nuccioni (Castiglione del Lago); C Paci (Bari); S Pagliani (Milano); A Palatella (Foggia); E Palmieri (Reggio Calabria); G Panarese (Pescara); M Panigada (Bergamo); EG Panza (Bollate); E Parma (Monza); G Paroli (Galleno); R Patricelli (Ravenna); GB Perego (Treviolo); G Perone (Trepuzzi); I Perugini (Capranica); V Petracchini (Torino); L Petrerà (Castellana); R Petrucci (Fossombrone); G Piazza (Santorso); F Piccolo (Bisceglie); M Pignatti (S Giovanni in Persiceto); DE Pignotti (Borgo San Dalmazzo); D Pinto (Monopoli); E Pirovano (Novate Milanese); D Pirrotta (Scilla); F Pizzolon (Godega Sant'Urbano); D Poggi (Imola); G Principe (Monte S Angelo); S Quinterio (Milano); P Rafanelli (Firenze); L Ragone (Vigevano); A Ramunni (Conversano); BM Ribetto (Villar Perosa); N Rinaldi (Monte S Angelo); MG Riva (Monza); M Rocca (Bollate); A Rossitto (Taranto); C Sagnelli (Maddaloni); G Saitta (Fabriano); S Salvi (Ascoli Piceno); G Salvio (S Giovanni Teatino); G Sampaolo (Ancona); A Santangelo (Vaglio Basilicata); S Sbrenna (Collepepe); P Schianchi (Felino); G Schirosa (Montalbano Jonico); A Schirra (Ghilarza); C Scolarin (Altavilla Vicentina); R Serni (Firenze); O Serra (Quartu S Elena); MP Seveso (Garbagnate); G Silvestre (Garbagnate); C Simone (Castelvenere); R Simonetti (Spresiano); F Sissa (Virgilio); E Sizzano (Pratrivero); P Soave

(Arcugnano); N Stafflano (Mosciano S Angelo); M Stranges (Caserta); F Suzzi (Imola); M Suzzi (Imola); AC Tazza (Piedimonte Matese); D Telleschi (Pontedera); G Titta (Torino); M Tognolo (Loreggia); A Tomasi (Recoaro Terme); A Tomba (Valdagno); M Tombesi (Macerata); P Tonello (Castelgomberto); R Tonon (Padova); M Torella (Napoli); P Tornari (Alzate Brianza); M Uberti (Torino); G Ursini (Basciano); A Varriale (Villanterio); R Vece (Eboli); R Ventriglia (Magione); O Venturini (Palmanova); I Veramonti (Civitella del Tronto); G Veronelli (Pusiano); L Verrengia (Sessa Aurunca); A Villa (Limbiate); F Villa (Villa d'Adda); G Vincenti (Sarzana); MR Visca (Imola); E Visonà (Valdagno); F Vitali (Castiglione del Lago); A Vitanza (Gravina di Catania); P Zappone (Palmi); G Zorzetti (Casale Monferrato).

Participating diabetes outpatient clinics: M Iorini (Asola); MD'Aurizio (Atessa); A Aiello, M Cristofaro (Campobasso); C Mazzi, N Buzzoni (Gallarate); N Mangano, S Rovelli (Gravedona); M Pupillo, D Antenucci (Lanciano); A Venezia, R Morea (Matera); U Ronchini, R Toniato (Montefiascone); D Fedele, A La Polla (Padova); E Scafidi (Palermo); E Vitacolonna, E Ciccarone, F Capani (Pescara); MV Sacco (Potenza); A Pagano (Roma); G Monesi, G Lisato (Rovigo).

Participating hospital hypertension units: A Autolitano, M Artusa (Ospedale Asilo Vittoria, Mortara); I Berto, P Bajardi (Ospedale Degli Infermi, Biella); R Beretta, C Costantini (Ospedale di Legnano); P Caldorola, N Barile (Ospedale M Sarccone, Terlizzi); C Cavaliere (Ospedale F Ferrari, Casarano); M Cristofari (Ospedale di Desio); S D'Amico (Ospedale S Luca, Trecenta); AM Fiorenza, A Torri (Ospedale G Salvini, Garbagnate Milanese); G Garavelli (Ospedale di Cremona); M Giardinieri, L Nosotti (Ospedale S Filippo Neri, Roma); M Guglielmi, R Pietrofeso (Ospedale San Giovanni di Dio e Ruggi D'Aragona, Salerno); M Mattarei, S Rossi (Ospedale di Rovereto); C Pasotti, A Capra (Ospedale Civile, Voghera); E Ronchi, G Palombo (Ospedale San Carlo Borromeo, Milano); B Stagni (Ospedale S Orsola Malpighi, Bologna).

Other participants: G Cappellari, PP Faronato, P Lagomanzini (Ospedale Civile, Feltre); V Capuano (Ospedale Curteri, Mercato S Severino); G Castiglioni, R Fantasia (Ospedale di Busto Arsizio); F Cosmi (Ospedale di Cortona); L De Vivo,

G De Caro, G Pepe (Ospedale S Leonardo, Castellammare di Stabia); G Di Mauro (Ospedale Curteri, Mercato S Severino); FE Gifuni (A S L Napoli 4 e 5, Napoli); A Magliaro (Centro Diagnostico Magliaro, Avellino); F Muzio (Ospedale S Corona, Garbagnate Milanese); FR Piantadosi (Ospedale Antonio Cardarelli, Napoli); GF Scarlini, G D'Aguanno (Ospedale Civile, Cassino); G Sodano (ARCA, Napoli); L Vicari (Ospedale Ferro Brandiforti, Leonforte).

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