The New England Journal of Medicine

VOLUME 347 SEPTEMBER 26, 2002 NUMBER 13

WARFARIN, ASPIRIN, OR BOTH AFTER MYOCARDIAL INFARCTION

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ABSTRACT

Background The role of antithrombotic therapy in secondary prevention after myocardial infarction is well established. Although the available literature suggests that warfarin is superior to aspirin, aspirin is currently the more widely used drug. We studied the efficacy and safety of warfarin, aspirin, or both after myocardial infarction.

Methods In a randomized, multicenter trial in 3630 patients, 1216 received warfarin (in a dose intended to achieve an international normalized ratio [INR] of 2.8 to 4.2), 1206 received aspirin (160 mg daily), and 1208 received aspirin (75 mg daily) combined with warfarin (in a dose intended to achieve an INR of 2.0 to 2.5). The mean duration of observation was four years.

Results The primary outcome, a composite of death, nonfatal reinfarction, or thromboembolic cerebral stroke, occurred in 241 of 1206 patients receiving aspirin (20.0 percent), 203 of 1216 receiving warfarin (16.7 percent; rate ratio as compared with aspirin, 0.81; 95 percent confidence interval, 0.69 to 0.95; P=0.03), and 181 of 1208 receiving warfarin and aspirin (15.0 percent; rate ratio as compared with aspirin, 0.71; 95 percent confidence interval, 0.60 to 0.83; P=0.001). The difference between the two groups receiving warfarin was not statistically significant. Episodes of major, nonfatal bleeding were observed in 0.62 percent of patients per treatment-year in both groups receiving warfarin and in 0.17 percent of patients receiving aspirin (P<0.001).

Conclusions Warfarin, in combination with aspirin or given alone, was superior to aspirin alone in reducing the incidence of composite events after an acute myocardial infarction but was associated with a higher risk of bleeding. (N Engl J Med 2002;347:969-74.)

THE importance of thrombosis in the pathogenesis of acute myocardial infarction is well recognized; the process involves both platelets and the coagulation system.[1-4] Patients who survive a myocardial infarction have a 15 to 20 percent risk of dying or having a reinfarction within two to five years[5,6] — a finding that substantiates the rationale for antithrombotic secondary prevention.

Two categories of long-term antithrombotic therapy are generally used today, oral anticoagulant agents and platelet-inhibiting drugs. A number of clinical trials have assessed the safety and efficacy of oral anticoagulant agents administered to patients who survive a myocardial infarction.[5,7-14] In comparison with placebo, these agents reduced the incidence of death,[5] reinfarction, and stroke.[5,14] Aspirin has been shown to reduce the incidence of composite end points[15,16] and, in meta-analyses, mortality[17] after a myocardial infarction. Earlier studies comparing aspirin with warfarin after myocardial infarction did not find statistically significant differences in the rate of death or reinfarction.[18-20] Theoretically, the combined use of warfarin and aspirin might have an additive effect by suppressing both the coagulation cascade and platelet function. Moreover, the combination might be effective with less intensive anticoagulation therapy. Two studies compared the use of aspirin alone with the combination of aspirin and low-dose warfarin in patients who survived a myocardial infarction. However, the international normalized ratio (INR) values were below the traditional therapeutic level, and there was no benefit of this combination as compared with aspirin alone.[21,22] A meta-analysis of the use of warfarin

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*The study participants are listed in the Appendix.

in patients with coronary artery disease[23] suggested that both high-intensity warfarin and moderate-intensity warfarin plus aspirin appeared to be superior to aspirin alone. The combination of low-dose aspirin and moderate-intensity warfarin in various patient categories has been shown to be safe, with a complication rate similar to that of treatment with warfarin alone.[24-26]

In the light of the inconsistency of the reported results, the aim of the present study was to compare the efficacy and safety of long-term treatment with warfarin alone, aspirin alone, or the two combined in patients who have survived acute myocardial infarction.

METHODS

Study Design

The trial was a randomized, open-label, multicenter study. The protocol was reviewed and approved by the institutional review boards at each center. The randomization was administered centrally with the use of permuted blocks. Data were stratified according to site. The investigators screened and registered patients after written informed consent had been obtained in accordance with the recommendation of the revised Declaration of Helsinki. All patients who had survived an acute myocardial infarction were screened and were randomly assigned to treatment before being discharged from the hospital. The three groups of patients received warfarin (Marevan, Nycomed) with the goal of achieving an INR of 2.8 to 4.2, 160 mg of aspirin (Albyl E, Nycomed) daily, or 75 mg of aspirin (Albyl E) daily combined with warfarin with the goal of achieving an INR of 2.0 to 2.5. The treatment was continued until a predetermined number of events had occurred. No interim analyses were performed.

Outcome Measures

The main study outcome was a composite of death, nonfatal reinfarction, or thromboembolic stroke, whichever came first, in an intention-to-treat analysis. Each of these outcomes was also analyzed separately. The number of therapeutic interventions, such as percutaneous coronary intervention and coronary-artery bypass grafting, was also recorded.

Study Population

Patients of either sex who were younger than 75 years of age were eligible for the study if they were hospitalized for acute myocardial infarction defined by the presence of two or more of the following criteria, according to the recommendations of the World Health Organization[27]: a history of typical chest pain; electrocardiographic changes typical of myocardial infarction; and a creatine kinase level greater than 250 U per liter, an aspartate aminotransferase level greater than 50 U per liter, or both, of probable cardiac origin. Patients were excluded if they had any indication for or contraindication against either of the study drugs, if they had a malignant disease, or if poor compliance was anticipated.

Follow-up

Clinical examinations were performed six weeks after myocardial infarction and at the end of the study. All patients received a questionnaire every six months that focused on new thromboembolic events, compliance, and possible adverse effects of the study medication.

Reinfarctions were defined by the World Health Organization criteria,[27] and strokes were verified by computed tomography. The medical records of patients who died during the study period were studied to verify any reported events. Causes of death were obtained from the medical records and from the official death certificates held by Statistics Norway. Control and adjustment of anticoagulant therapy were performed in the hospital outpatient clinics or in primary health care centers.

Adverse reactions to either of the study drugs were recorded throughout the study period. Major bleeding episodes were defined as nonfatal cerebral hemorrhage or bleeding necessitating surgical intervention or blood transfusion. All serious adverse events were reported to the National Drug Authority.

Compliance

At each visit and in the questionnaires, the compliance of the patients was investigated. In patients receiving warfarin, INR values were recorded both locally and centrally. Compliance in patients receiving aspirin was evaluated in a subpopulation by analyzing thromboxane B_2 levels in serum. The thromboxane assays were performed using a commercial enzyme immunoassay kit (code RPN 220, Amersham International).

Study Organization

The Warfarin, Aspirin, Reinfarction Study (WARIS II) was coordinated by a central project office at Ullevål University Hospital in Oslo, Norway; each participating hospital had a medical collaborator and a study nurse. The steering committee met regularly to assess the progress of the study and the quality of the data. An independent international ethics committee had access to the data base during the study to assess the quality of the data and to evaluate the number of adverse events. All end points and serious or fatal bleeding episodes were evaluated by an independent end-point and adverse events review committee, whose members were unaware of the patients' treatment assignments.

Statistical Analysis

The calculation of the sample size[28] was based on an assumed excess relative risk of 1.27 in patients receiving warfarin alone and an excess relative risk of 1.54 in patients receiving aspirin alone, as compared with patients receiving combined treatment and based on pairwise comparison with the combined-treatment group. The estimated total two-year event rate was 17 percent. The observation time was at least two years per patient, and the study was terminated when an overall event rate of 17 percent was reached. We used the log-rank test, which is equivalent to the score-test in Cox's regression analysis.[29-31] Given a two-sided probability of 0.05 and a power of 80 percent, the number of patients needed in each treatment group was calculated to be 1202. Thus, a total of 3606 patients were needed. Data at base line were compared with the use of a chi-square test for discrete variables and Student's t-test and a one-way analysis of variance for continuous variables. The main analysis was performed at the time of the occurrence of the first composite end point according to the intention-to-treat principle. All events were recorded until the closing date regardless of whether a patient stopped taking the study drug. We used rate ratios to estimate the crude efficacy of the three regimens.[32] Curves showing event-free survival were plotted with the use of the actuarial method. Differences in event-free survival were plotted with the use of the Breslow and log-rank tests when two curves were being compared and the Tarone–Ware test when several curves were being compared.[33] Stratification analysis was performed on major covariates and risk factors with the use of the Mantel–Haenszel method.[32] To quantify the confounding effect and estimate effect modification, Breslow and Day's test of heterogeneity was used.[34] All P values are two-tailed.

RESULTS

Recruitment was initiated in January 1994 and stopped in June 1998, when the required number of

patients had been enrolled. Twenty Norwegian hospitals participated in the study. The study was closed on September 1, 2000, when the predetermined number of composite events, 613, had occurred. A total of 3630 patients were included in the study; 1206 were assigned to aspirin, 1216 to warfarin, and 1208 to the combined therapy. The mean (±SD) duration of observation was 1445±592 days (approximately 4 years). Fourteen patients were lost to follow-up, all of whom were known to be alive at the closing date. The characteristics at base line were similar in the three treatment groups (Table 1). There were no intergroup differences in the rate of use of concomitant medical therapy during the study period: 76.5 percent of patients received statins, 73.8 percent beta-blockers, 28.5 percent angiotensin-converting–enzyme inhibitors, 12.9 percent calcium antagonists, 21.9 percent nitrates, 14.3 percent diuretics, and 2.3 percent digitalis. The mean INR was 2.8 in patients receiving warfarin alone and 2.2 in patients receiving combined therapy. An arbitrary cross-sectional evaluation of the dispersion of the INR values was performed: in the group that received warfarin alone, 34 percent of the INR values were below 2.8, and 4 percent were above 4.2. In the combined-therapy group, 23 percent of the values were below 2.0 and 30 percent above 2.5. The mean thromboxane B_2 level in 210 patients in the two groups receiving aspirin was 6.7±8.9 ng per milliliter for 160 mg of aspirin alone and 11.7± 15.2 ng per milliliter for 75 mg of aspirin combined with warfarin. The corresponding value in 25 patients receiving warfarin alone was 208.0±10.9 ng per milliliter.

Table 1. Clinical Characteristics of the Patients at Base Line.*

Characteristic	Aspirin (N=1206)	Warfarin (N=1216)	Aspirin plus Warfarin (N=1208)	P Value
Age (yr)	60.7±9.7	59.7±9.9	60.0±9.9	0.05
Male sex (%)	74.3	78.5	77.8	0.03
Smoking (%)	46.4	49.8	47.6	0.23
Diabetes (%)	9.0	6.8	8.7	0.22
Previous acute myocardial infarction (%)	12.5	13.1	13.2	0.41
Blood pressure (mm Hg)				
Systolic	124±19	123±19	124±20	0.91
Diastolic	74±13	75±13	75±14	0.63
Site of infarction (%)				
Anterior	39.2	36.6	39.7	0.23
Inferior	46.3	48.5	45.4	0.28
Q-wave acute myocardial infarction (%)	57.4	60.7	59.3	0.23
Peak creatine kinase level (U/liter)	1749±1894	1769±1722	1872±1767	0.13
Left ventricular ejection fraction (%)	53±12	52±13	52±13	0.37
Thrombolysis (%)	54.0	53.1	54.9	0.69

*Plus–minus values are means ±SD.

Table 2. Distribution of Events According to Treatment Group.*

Variable	Aspirin (N=1206)	Warfarin (N=1216)	Aspirin plus Warfarin (N=1208)
First events — no. (%)	241 (20.0)	203 (16.7)	181 (15.0)
Observation time — patient-yr	4669	4823	4927
No. of events per 100 patient-yr	5.16	4.21	3.67
Two or more events — no.	54	33	29
Events in conjunction with coronary-artery bypass grafting or percutaneous coronary intervention — no.	16	11	9

*According to the intention-to-treat analysis for the first event, the rate ratio for warfarin plus aspirin as compared with aspirin was 0.71 (95 percent confidence interval, 0.60 to 0.83; P=0.001), for warfarin as compared with aspirin it was 0.81 (95 percent confidence interval, 0.69 to 0.95; P=0.03), and for warfarin plus aspirin as compared with warfarin it was 0.87 (95 percent confidence interval, 0.73 to 1.03; P=0.18). According to the intention-to-treat analysis for the total number of events, the rate ratio for warfarin plus aspirin as compared with aspirin was 0.65 (95 percent confidence interval, 0.53 to 0.80; P<0.001), for warfarin as compared with aspirin it was 0.75 (95 percent confidence interval, 0.61 to 0.91; P=0.003), and for warfarin plus aspirin as compared with warfarin it was 0.87 (95 percent confidence interval, 0.71 to 1.08; P=0.20).

Main Outcome

There were 625 first events (17.2 percent) according to the intention-to-treat analysis: 283 deaths (7.8 percent), 276 reinfarctions (7.6 percent), and 66 thromboembolic strokes (1.8 percent). The distribution of these events in the three treatment groups is shown in Table 2. As compared with aspirin alone, the risk reduction in the patients receiving warfarin plus aspirin was 29 percent (P=0.001) and in those receiving warfarin alone it was 19 percent (P=0.03). The number needed to treat per year to prevent one event was 67 in the combined-therapy group and 100 in the warfarin group. The event-free survival curves are shown in Figure 1. The overall difference in effect yielded a P value of 0.003 (Tarone–Ware method). When the curves were compared pairwise, the results of significance tests were as follows: P<0.001 for warfarin plus aspirin versus aspirin alone, P=0.03 for warfarin alone versus aspirin alone, and P=0.21 for warfarin plus aspirin versus warfarin alone. The data on the separate events constituting the composite end point are shown in Table 3. The beneficial effect of warfarin, both in combination with aspirin and alone, was restricted to nonfatal reinfarction and thromboembolic stroke; there were no statistically significant differences in overall mortality among the groups.

The total number of events, including repeated events in some patients, was 741: 295 in the aspirin

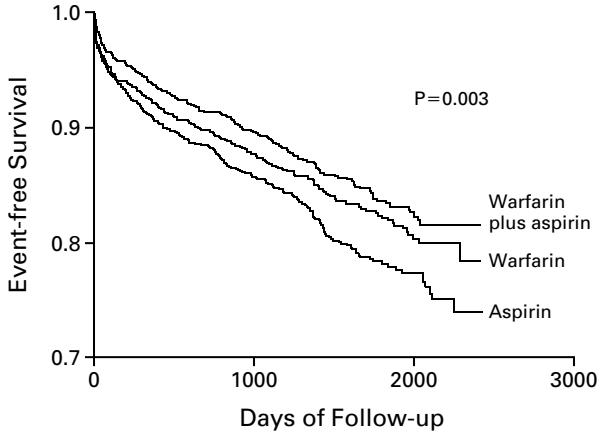

Figure 1. Event-free Survival Curves for the Composite End Point of Death, Nonfatal Reinfarction, and Thromboembolic Stroke.
The P value refers to the overall difference among the curves (Tarone–Ware method).

group (24.5 percent), 236 in the warfarin group (19.4 percent), and 210 in the combined-therapy group (17.4 percent) (Table 2). The total number of fatal events was 338 and the causes of death were as follows: sudden death, 67 patients; reinfarctions, 92; thromboembolic cerebral strokes, 6; hemorrhagic strokes, 14; other cardiovascular causes, 39; cancer, 69; and miscellaneous causes, 51. Of the 14 hemorrhagic cerebral strokes, 11 occurred during treatment with the assigned medication, 5 during warfarin therapy, and 6 during combined therapy.

A total of 1300 therapeutic interventions (coronary-artery bypass grafting or percutaneous coronary intervention) were performed during the study period. The numbers of procedures according to treatment group were 224 in the aspirin group, 204 in the warfarin group, and 188 in the combined-therapy group for coronary-artery bypass grafting and 230, 212, and 242, respectively, for percutaneous coronary intervention. The difference in the frequency of coronary-artery bypass grafting between patients receiving combined therapy and those receiving aspirin alone reached borderline significance with an odds ratio of 0.81 (95 percent confidence interval, 0.65 to 1.01; P=0.05). There were a few procedure-related events in each group (Table 2). Nonfatal reinfarction occurred in 10 patients receiving aspirin, 8 receiving warfarin, and 6 receiving combined therapy; and nonfatal thromboembolic stroke occurred in 6, 3, and 3 patients, respectively. These events were not included in the main analysis. At the end of the study, a total of 1058 patients had discontinued the assigned medication at some point during the study period of 80 months: 191 in the aspirin group, 387 in the warfarin group, and 480 in the combined-therapy group. The reasons for withdrawal in the three treatment groups are listed in Table 4. More patients in the two warfarin groups than in the aspirin group were withdrawn from therapy because of bleeding episodes.

Adverse Events

There were 69 nonfatal major bleeding episodes in patients receiving treatment with the study medication: 8 receiving aspirin (0.17 percent per year), 33 receiving warfarin (0.68 percent per year), and 28 receiving combined therapy (0.57 percent per year). The difference was significant, with a rate ratio of 0.25 (95 percent confidence interval, 0.10 to 0.60) for the comparison of aspirin and warfarin. The incidence of minor bleeding episodes was 0.84 percent, 2.14 percent, and 2.70 percent per year, respectively. The organ-specific numbers of hemorrhages are shown in Table 5.

TABLE 3. DISTRIBUTION OF SEPARATE EVENTS ACCORDING TO TREATMENT GROUP.*

EVENT	ASPIRIN (N=1206)	WARFARIN (N=1216)	ASPIRIN PLUS WARFARIN (N=1208)	RATE RATIO (95% CI)	P VALUE
		no. of events			
Reinfarction	117	90	69	0.56 (0.41–0.78)†	<0.001
				0.74 (0.55–0.98)‡	0.03
Thromboembolic stroke	32	17	17	0.52 (0.28–0.98)†	0.03
				0.52 (0.28–0.97)‡	0.03
Death	92	96	95		0.82

*CI denotes confidence interval, and NS not significant.

†The rate ratio is for aspirin plus warfarin as compared with aspirin.

‡The rate ratio is for warfarin as compared with aspirin.

TABLE 4. REASONS FOR WITHDRAWAL ACCORDING TO TREATMENT GROUP.

REASON	ASPIRIN (N=1206)	WARFARIN (N=1216)	ASPIRIN PLUS WARFARIN (N=1208)
		no. of patients	
Patient unwilling to continue	3	42	63
Bleeding	20	60	89
Adverse reaction	43	24	81
Coronary-artery bypass grafting or percutaneous coronary intervention	10	148	97
Indication for change in antithrombotic treatment	91	20	9
Lack of compliance	1	25	36
Other	23	68	105
Total	191	387	480

TABLE 5. NONFATAL BLEEDING COMPLICATIONS ACCORDING TO TREATMENT GROUP.

COMPLICATION	ASPIRIN	WARFARIN	ASPIRIN PLUS WARFARIN
		no. of patients	
Major bleeding			
Cerebral	1	5	3
Gastrointestinal	6	18	21
Urinary	—	2	—
Muscle or skin	—	1	—
Other	1	7	4
Total	8	33	28
Minor bleeding			
Nose or airways	7	20	30
Gastrointestinal	18	30	45
Urinary	7	24	27
Muscle or skin	—	8	16
Other	7	21	15
Total	39	103	133

The number needed to treat per year to cause one major bleeding episode was 250 for warfarin plus aspirin and 200 for warfarin alone, as compared with treatment with aspirin alone.

DISCUSSION

In this study, we found a statistically significant superiority of warfarin in combination with aspirin (relative risk reduction, 29 percent) as well as of warfarin alone (relative risk reduction, 19 percent) as compared with aspirin for the reduction in the composite end point. The event rate was lower than in previous studies,[5,6] with an annual rate of the composite end point of 4.3 percent, probably because of the generally improved secondary prevention.

The follow-up throughout the study period was rigorous, with regular contacts maintained with the patients, collaborating hospitals, and general practitioners. Thus, all events were carefully recorded. Nevertheless, the study closely simulated regular clinical practice, with decentralized treatment and follow-up, largely performed in general-practice settings. Therefore, the study results may be extrapolated to the everyday care of patients after myocardial infarction. The mean INR was within the target range in both warfarin groups, although it was at the lower margin in the group receiving warfarin alone.

The beneficial effect of warfarin as compared with placebo in preventing new events after myocardial infarction is well established.[5,14] In the present study, we found that warfarin was superior to aspirin alone. We also found that the combination of moderate-intensity warfarin and a low dose of aspirin was the most effective therapy for the prevention of events after myocardial infarction. The fact that the Coumadin Aspirin Reinfarction Study and the Combination Hemotherapy and Mortality Prevention study[21,22] failed to demonstrate a beneficial effect of combining warfarin and aspirin is probably due to the insufficient level of anticoagulation, with a median INR of 1.2 and 1.8, respectively.

The main benefit of warfarin plus aspirin and warfarin alone was the prevention of nonfatal reinfarction and nonfatal thromboembolic stroke. Thus, our data did not show an effect on mortality; the reason for this is not easily explained. It is possible that the protective effect of aspirin against death in recurrent acute coronary syndromes, as observed in the Second International Study of Infarct Survival trial,[35] may explain the present observation.

A large number of patients in the two warfarin groups had warfarin withdrawn, most frequently in conjunction with coronary-artery bypass grafting, percutaneous coronary intervention, or bleeding episodes; these withdrawals may have lessened the effects of warfarin.

There were approximately four times as many major bleeding episodes in the two groups receiving warfarin than in the group receiving aspirin alone. Major bleeding episodes were not more frequent among patients receiving aspirin plus warfarin than among those receiving warfarin alone, but the incidence of minor bleeding episodes was higher in the combined-therapy group. This corresponds with the findings of a study on adverse events during treatment with warfarin plus aspirin.[24] The frequency of minor bleeding episodes may have been underreported, although the regular correspondence with the patients probably ensured a thorough record. All bleeding episodes requiring hospitalization were recorded.

In conclusion, as compared with aspirin alone, ther-

apy with moderate-intensity warfarin combined with aspirin and high-intensity warfarin alone resulted in a reduced risk of reinfarction and ischemic stroke but a higher risk of bleeding.

Supported in part by the Norwegian Council on Cardiovascular Disease.

We are indebted to all study nurses at the participating hospitals, to Eva Wedén and Lill Torjesen for excellent administrative help, and to Ingebjørg Seljeflot, Ph.D., for skillful laboratory work.

APPENDIX

The following centers and investigators (all in Norway) participated in this study: *Steering Committee* — H. Arnesen, P. Smith, J. Erikssen, G. von der Lippe (deceased), J. Godtfredsen, M. Abdelnoor, and H. Ekeli; *Ethics Committee* — J. Dale (deceased), J. Hampton, and G. Jensen; *End-Point and Adverse Events Committee* — Ø. Skjæggestad and F. Verheugt; Central Hospital of Akershus — J. Erikssen; Bærum Hospital — P. Smith and P. Vanberg; Haukeland University Hospital — G. von der Lippe, K. Breivik, E. Søgnen, and J.E. Norderhaug; Regional Hospital of Tromsø — K. Andersen and A. Iqbal; Central Hospital of Norland — R. Røde and B. Kvamme-Haug; Orkdal Hospital — K. Selsås and A. Tromsdal; Central Hospital of Vest-Agder — A. Tveiten, Ø. Bleie, and O. Eggen; Molde Hospital — E. Riise and A. Heskestad; Central Hospital of Østfold — M. Ljosland; Regional Hospital of Trondheim — J. Bathen, A. Støylen, A. Lied, and A. Sæterhaug; Central Hospital of Møre og Romsdal — T. Hole; Central Hospital of Vestfold — G. Frøland; Lillehammer Hospital — M. Dale and H.P. Dørum; Kongsberg Hospital — K. Berget; Larvik Hospital — P. Urdahl, S. Nyhus, and H. Tjønndal; Sandefjord Hospital — K. Nordlie, G. Noer, and R. Lødøen; Kongsvinger Hospital — E. Anker, T. Jensen, and S. Solheim; Notodden Hospital — N.O. Lid; Central Hospital of Telemark — P. Urdahl; and Ullevål University Hospital — M. Hurlen and K. Andersen.

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