

Department of Veterans Affairs Cooperative Studies Program Clinical Trial Comparing Combined Warfarin and Aspirin With Aspirin Alone in Survivors of Acute Myocardial Infarction Primary Results of the CHAMP Study

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(CHAMP) Study Group*

Background—Both aspirin and warfarin when used alone are effective in the secondary prevention of vascular events and death after acute myocardial infarction. We tested the hypothesis that aspirin and warfarin therapy, when combined, would be more effective than aspirin monotherapy.

Methods and Results—We conducted a randomized open-label study to compare the efficacy of warfarin (target international normalized ratio 1.5 to 2.5 IU) plus aspirin (81 mg daily) with the efficacy of aspirin monotherapy (162 mg daily) in reducing the total mortality in 5059 patients enrolled within 14 days of infarction and followed for a median of 2.7 years. Secondary end points included recurrent myocardial infarction, stroke, and major hemorrhage. Four hundred thirty-eight (17.3%) of 2537 patients assigned to the aspirin group and 444 (17.6%) of 2522 patients assigned to the combination group died (log-rank $P=0.76$). Recurrent myocardial infarction occurred in 333 patients (13.1%) taking aspirin and in 336 patients (13.3%) taking combination therapy (log-rank $P=0.78$). Stroke occurred in 89 patients (3.5%) taking aspirin and in 79 patients (3.1%) taking combination therapy (log-rank $P=0.52$). Major bleeding occurred more frequently in the combination therapy group than in the aspirin group (1.28 versus 0.72 events per 100 person years of follow-up, respectively; $P<0.001$). There were 14 individuals with intracranial bleeds in both the aspirin and combination therapy groups.

Conclusions—In post-myocardial infarction patients, warfarin therapy (at a mean international normalized ratio of 1.8) combined with low-dose aspirin did not provide a clinical benefit beyond that achievable with aspirin monotherapy. (*Circulation*. 2002;105:557-563.)

Key Words: myocardial infarction ■ aspirin ■ anticoagulants ■ trials

During the past half-century, >100 clinical trials have described the merits and limitations of antiplatelet and anticoagulant agents in short- and long-term treatment after acute myocardial infarction (AMI).^{1,2} Although controversy exists over which form of therapy is superior in subgroups of survivors of AMI, it is clear that in the absence of contraindications, some form of antithrombotic therapy should be administered. Aspirin generally is preferred to warfarin in this setting because of its ease of administration, low cost, and comparable efficacy. However, this therapy is limited by only modest relative risk reductions in mortality and other vascular

end points.¹ More effective alternative antithrombotic regimens are needed.

Given that aspirin and oral anticoagulants inhibit thrombosis by different mechanisms, we proposed that the coadministration of these agents (combination hemotherapy) might have a synergistic antithrombotic effect. In the past, there has been reluctance to combine these agents in clinical trials and clinical practice. This view stems from the high bleeding rates observed in a series of older studies designed to reduce embolic stroke in patients with prosthetic heart valves.³

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TABLE 1. Reasons for Exclusion

Category	n
Patients excluded	14 977
Comorbidity limiting life expectancy to <2 yrs	2630
Screened >14 days after infarction	780
Incompetent to give informed consent	1050
Ongoing bleeding or bleeding risk	2079
Alternative indication for anticoagulant therapy	2824
Refusal to participate in trial	3175
Entered into a competing study	673
Treatment with high dose ASA or NSAID	517
Excessive travel distance to the VA	400
Died prior to randomization	424
Alcohol or drug dependency	656
Hypersensitivity to aspirin or warfarin	256
All other	2039

Total exclusions (17 503) exceeds the number of subjects excluded (14 977) because some patients fulfilled multiple criteria. VA indicates Veteran's Administration Medical Center; ASA, aspirin; and NSAID, nonsteroidal anti-inflammatory drug.

We hypothesized that by lowering the dose of aspirin to 81 mg daily and monitoring the effect of oral anticoagulants by use of the international normalized ratio (INR) at a range between 1.5 and 2.5 IU, the therapeutic benefit of combination hemotherapy would be preserved, and the major bleeding rate would be reduced.

Methods

This Veterans Affairs Cooperative Study was conducted in 78 Department of Veterans Affairs medical centers in accordance with institutional guidelines. The Cooperative Studies Program Coordinating Center in West Haven, Conn, was responsible for data collection and analysis. All study medication was distributed by the Cooperative Studies Program Research Pharmacy in Albuquerque, NM. The Executive Committee was responsible for the overall conduct of the present study. The protocol was approved by the institutional review board at each participating center and by the Human Rights Committee at the Coordinating Center. Informed consent was obtained from each patient.

Patients

We have described the design of the present study in detail elsewhere.⁴ Briefly, veterans of either sex and of any age were eligible to participate in the study if they sustained a qualifying AMI within the preceding 14 days and fulfilled none of the exclusion criteria (Table 1). Each participating site was instructed to screen all patients with AMI for study eligibility.

Treatment Regimen and Follow-Up

After confirming the patient's eligibility with local site personnel by telephone, the Cooperative Studies Program Coordinating Center randomly assigned each patient to receive open-label combination hemotherapy or aspirin according to a permuted-block design with stratification by center. Patients in the aspirin monotherapy group received chewable aspirin (162 mg daily) as recommended by the Fifth American College of Chest Physicians Consensus Conference on Antithrombotic Therapy.⁵ Patients in the combination hemotherapy group received warfarin sodium (Coumadin, DuPont Pharmaceuticals) titrated to an INR of 1.5 to 2.5 IU along with chewable aspirin (81 mg daily, Bayer Pharmaceuticals). In the combination group, the 81-mg daily dose was chosen on the basis of other recent

studies of combination therapy.^{6–10} The dose of 81 mg was associated with lower rates of major gastrointestinal bleeding without compromising efficacy. Monitoring of the INR was performed locally by using a dose-adjustment protocol. Delay in the initiation of protocol-assigned therapy after randomization was permitted to allow subjects to undergo invasive procedures before receiving protocol-determined anticoagulant therapy.

A study coordinator saw patients 3 months after randomization and then every 6 months for the duration of the study. Subjects in the combination therapy group were seen between these scheduled visits either by the study coordinator or by the anticoagulation clinic staff to titrate their warfarin dosage. At each follow-up visit, the study staff provided counseling regarding adherence to the study regimen and asked about the occurrence of events and side effects since the previous visit.

Outcomes

The primary outcome of the present study was all-cause mortality. Secondary outcomes were recurrent myocardial infarction and stroke, as reported by local investigators using standardized definitions in the protocol.⁴ A composite secondary outcome of cardiovascular events was defined as vascular mortality, recurrent myocardial infarction, or stroke. Major hemorrhage was defined as any fatal, intracranial, or retroperitoneal bleed or any bleed that led to a hospitalization or transfusion and was accompanied by a fall in the hemoglobin of at least 2 g/dL. Cause of death and major hemorrhage were adjudicated by the end-points committee, which was blinded to treatment assignment. Secondary end points were not adjudicated.

Statistical Analysis

All analyses were conducted according to the intention-to-treat principle. Sample size was determined to detect a 15% reduction in annual mortality with combination therapy relative to aspirin alone. The target sample size to detect this effect size with 80% power and 5% type I error was 8000 patients and 1000 deaths. The trial was planned as a study of duration and not information. Differences in cumulative mortality rates between treatment groups were tested by the log-rank statistic. Interim monitoring of treatment mortality differences was performed by using the α spending method of Lan and DeMets¹¹ with sloped boundaries, with the "looks" at the data corresponding to the annual meetings of the Data Monitoring Board. Adverse event rates were expressed as the number of events per 100 person years of follow-up. The permutation test was used to test whether the rate ratio (combination/aspirin) was different from 1; 95% bootstrap confidence limits for rate ratio were determined.¹²

Analysis of secondary end points was tested at the 1% level of significance to provide some control for multiplicity. Two planned subgroup analyses were performed with patients stratified by age (younger or older than 60 years) and by myocardial function (severe, moderate, or mild/normal left ventricular dysfunction). Severe ventricular dysfunction was defined as a measured ejection fraction by angiography or radionuclide study of $\leq 25\%$ or a qualitative finding of "markedly depressed" myocardial function on echocardiographic assessment. Moderate ventricular dysfunction was defined as a measured ejection fraction $>25\%$ but $<40\%$ or a qualitative echographic finding of "moderately depressed" myocardial function. In addition, we evaluated the effects of treatment according to location, type of infarction, and the presence or absence of diabetes to determine whether adverse events, particularly stroke, were reduced in these high-risk subgroups.

The Cox proportional hazards model¹³ was used to identify independent baseline predictors of mortality and to determine the relationship between the date of initiation of protocol therapy and mortality within each treatment arm. The fit of the model to the data was evaluated by examining residuals.¹⁴

Results

Follow-Up

Between October 20, 1992, and December 31, 1997, 20 036 patients with AMI were screened, and 5059 were entered into

TABLE 2. Baseline Characteristics of the Patients According to Treatment Group

Characteristic	ASA (n=2537)	Combo (n=2522)
Age, y	64±10	64±10
Male sex, %	98	98
Index MI type Q wave, %	42	41
Index MI involving anterior wall, %	28	28
Previous AMI, %	35	37
Diabetes, %	27	27
Hypertension, %	53	55
Prior CHF, %	8	8
Current smoker, %	45	42
Thrombolytic therapy for index MI, %	30	31
Peak CK		
Thrombolysis group	869	824
No thrombolysis group	1851	1699

Plus-minus values are mean±SD. Combo indicates combination therapy group; MI, myocardial infarction; CHF, congestive heart failure; and CK, creatinine phosphokinase.

No differences are significant at the $P=0.05$ level.

the study: 2537 were assigned to aspirin, and 2522 were assigned to combination therapy. The reasons for subject exclusion are listed in Table 1. Final follow-up visits occurred between April 1, 1998, and September 30, 1998. The number of total person-years of follow-up was 6940 years in the aspirin group and 6789 years in the combination group. The median follow-up was 2.7 years. During the study, 882 subjects died. Vital status was ascertained for all but 61 patients: 28 in the aspirin group and 33 in the combination group. In 555 subjects, vital status was determined by using the Veterans Affairs and National Credit Bureau administrative files. All other patients were seen at a final study exit visit.

Patients randomly assigned to the 2 treatment groups were similar at baseline with respect to demographic and clinical variables (Table 2). The population was characterized by high rates of hypertension, diabetes, and previous myocardial infarction. The median age was 62 years.

Cumulative initiation rates of protocol-assigned therapy in the aspirin and combination groups were 74% versus 61% at 1 month and 92% versus 84% at 1 year, respectively. Among patients initiated on therapy, 290 (12.6%) in the aspirin group and 517 (25.3%) in the combination group had therapy permanently discontinued during the study. Thus, the proportion of total follow-up time on protocol-assigned therapy was 86% for the aspirin group and 71% for the combination group. Patients who never had protocol therapy initiated or those who had it discontinued were treated at the discretion of their local physician.

Anticoagulation

INR values of patients in the combination therapy arm were measured and reported at each of the follow-up visit appointments and are displayed in Figure 1. The median INR for all values obtained at all scheduled follow-up visits was 1.8 IU.

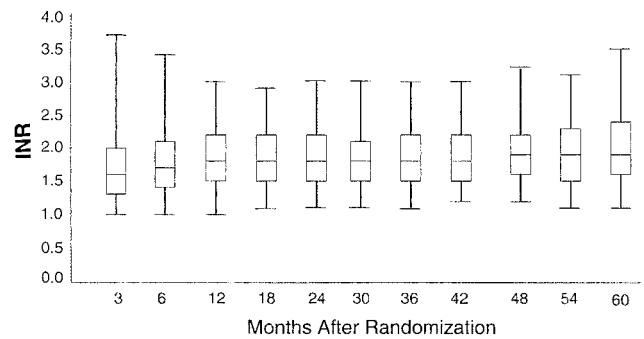


Figure 1. Distribution of INR values at specified follow-up visits for patients assigned to combination therapy. Box-whisker plot is shown. Box indicates 25th to 75th percentiles; horizontal line, median; and whiskers, 95th percentiles.

Values of 1.4 IU and 2.2 IU correspond to the lowest and highest quartiles, respectively, of measured INRs. These INR results reflect the intensity of anticoagulation only during the 71% of follow-up time during which patients randomized to combination therapy were receiving protocol-assigned treatment.

Outcomes

Overall, 438 patients (17.3%) assigned to the aspirin group and 444 patients (17.6%) assigned to the combination group died (log-rank $P=0.76$). Adjudicated cause of death is given in Table 3. Clinical characteristics of patients who died are presented in Table 4. Recurrent myocardial infarction occurred in 333 patients (13.1%) taking aspirin and 336 patients

TABLE 3. Cause of Death

Cause of Death	Aspirin		Combination	
	n	%	n	%
Vascular				
Sudden (<1 hour)	65	14.8	73	16.4
Sudden (>1 hour)	39	8.9	37	8.3
Definite AMI	61	13.9	55	12.4
Suspected AMI	8	1.8	8	1.8
Hemorrhage	7	1.6	10	2.3
Definite stroke	4	0.9	4	0.9
Probable stroke	2	0.5	0	0
CHF	35	8.0	36	8.1
Arrhythmia	12	2.7	2	0.5
Other AS	8	1.8	5	1.1
PE	2	0.5	2	0.5
Procedure related	23	5.3	35	7.9
Nonvascular				
Cancer	52	11.9	55	12.4
Accidental	11	2.5	10	2.3
Noncardiovascular	44	10.0	38	8.5
Unknown	65	14.8	74	16.7
Total	438	100	444	100

CHF indicates congestive heart failure; AS, atherosclerotic disease; and PE, pulmonary embolism. Sudden (<1 hour) denotes last seen less than 1 hour before death.

TABLE 4. Adjusted Hazard Ratios for Mortality by Patient Characteristics

Characteristic	Hazard Ratio	95% CI
Age, y	1.05	1.04, 1.06
Index MI type Q wave	0.78	0.67, 0.90
Previous MI	1.55	1.35, 1.79
Diabetes	1.41	1.22, 1.63
Prior CHF	1.75	1.44, 2.11
Previous CVA/TIA	1.27	1.04, 1.54
CHF with index MI	1.90	1.59, 2.27

CI indicates confidence interval; MI, myocardial infarction; CHF, congestive heart failure; CVA, cerebrovascular accident; and TIA, transient ischemic attack.

Hazard ratio and 95% CI were obtained from Cox proportional hazards model.

(13.3%) taking combination therapy (log-rank $P=0.78$). Of the total 789 reinfarctions (in 669 subjects) reported, 667 (85%) were classified as definite, and 122 (15%) were classified as probable. Stroke occurred in 89 patients (3.5%) taking aspirin and 79 patients (3.1%) taking combination therapy (log-rank $P=0.52$). The cumulative 5-year Kaplan-Meier curves were virtually identical for these outcomes as well as for the composite outcome of cardiovascular events (Figure 2). Hazard ratios for combination therapy relative to

aspirin therapy with 95% CIs for the primary and secondary outcomes by subgroups are given in Figure 3.

An exploratory analysis was performed to examine the relationship between the initiation of therapy and survival. Patients were stratified by the duration of the delay between randomization and the initiation of protocol-assigned therapy according to the following: initiation of protocol therapy within 14 days, initiation of therapy from 15 to 28 days, initiation of therapy after 28 days, or no initiation of protocol therapy. Patients for whom therapy was initiated within 14 days were used as the reference group. There was no association between delay in initiation of therapy and overall survival (Table 5). Patients for whom protocol-assigned therapy was never begun had an increased hazard ratio for mortality in both the aspirin and combination therapy groups.

Adverse Events

The annual incidence of major bleeding episodes (Table 6) was greater in the combination therapy group, with a rate ratio of 1.78 (95% bootstrap confidence limits 1.27 to 2.72). Major bleeds were primarily gastrointestinal in origin in both the combination therapy group (71%) and aspirin group (63%). Confirmed intracranial hemorrhage occurred with equal frequency in both groups, but 18 strokes in the aspirin group and 21 strokes in the combination therapy arm were not

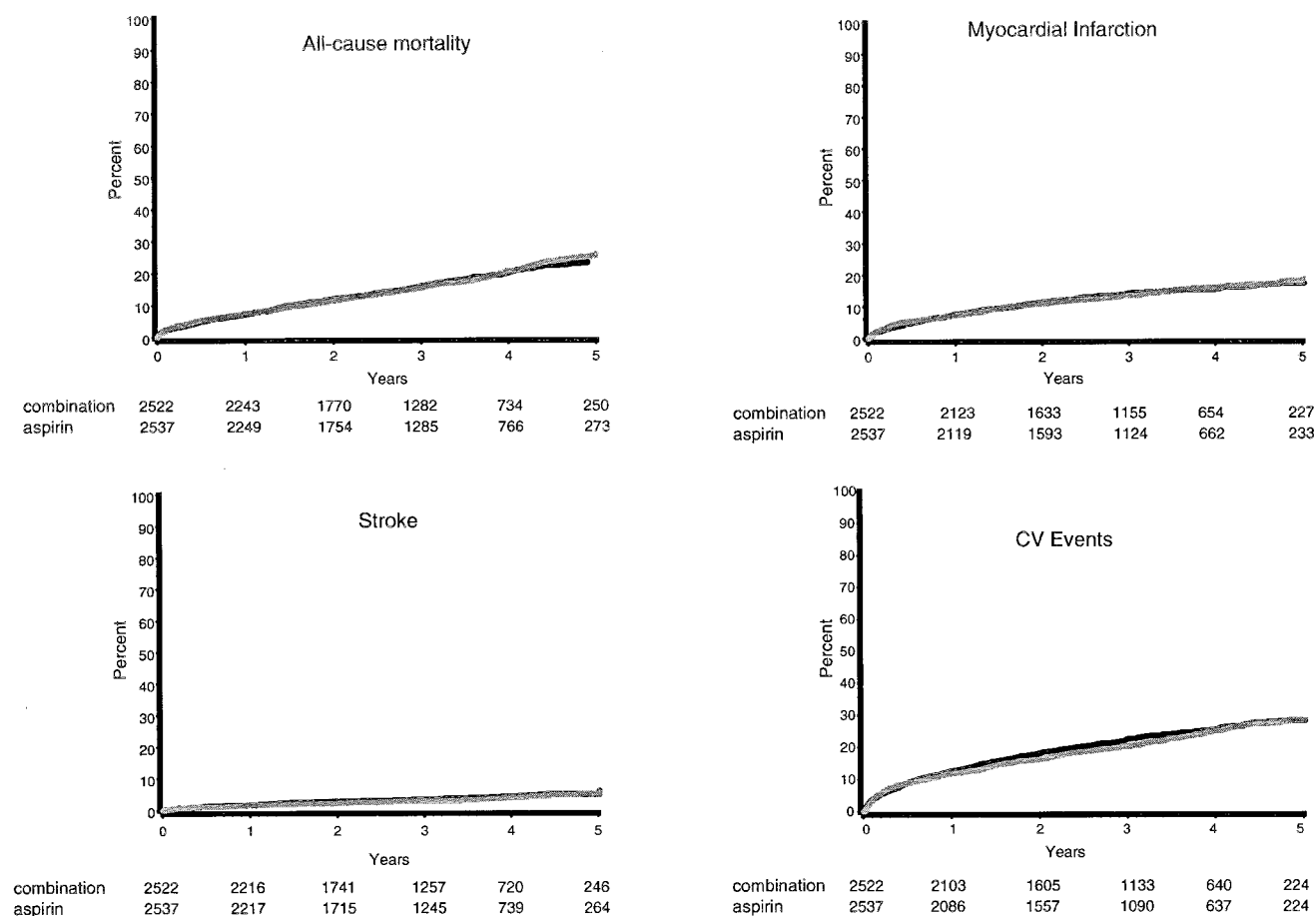


Figure 2. Kaplan Meier time-to-event curves for the primary and secondary outcomes. The numbers of patients at risk for each outcome and cumulative (percent) outcome rates are indicated by year of follow-up.

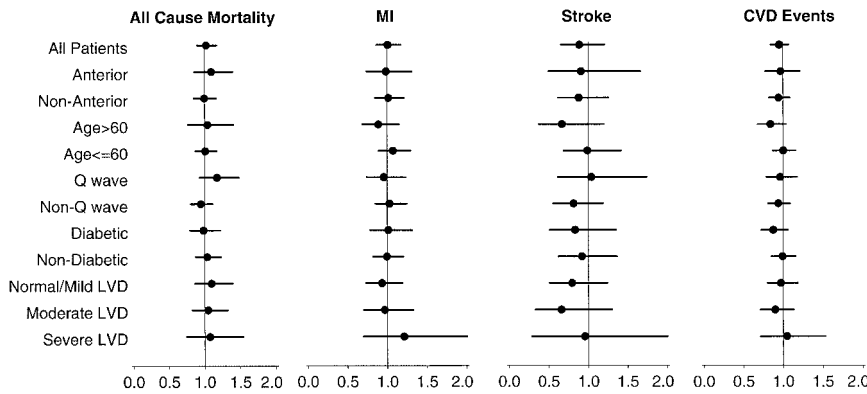


Figure 3. Relative risk and 95% CIs of primary and secondary outcomes by treatment group for all follow-up. Center circles to the left of the unity line indicate superiority of combination therapy over aspirin monotherapy.¹ LVD indicates left ventricular dysfunction.

evaluated for hemorrhagic or ischemic etiology. Fatal hemorrhage occurred in 7 patients in the aspirin group and 10 patients in the combination group.

Discussion

The present study found that when warfarin (target INR 1.5 to 2.5 IU) is added to aspirin (81 mg daily), no reduction in mortality, stroke, or recurrent myocardial infarction beyond that achievable with aspirin monotherapy (162 mg daily) was seen. The study ended after 6 years, as planned. At that time, we observed 882 of the projected 1000 deaths (88% of the total information in the trial). Based on the accumulated data, the conditional power of reaching a significant finding in favor of combination therapy with 1000 deaths was almost nil. Thus, the study was not continued beyond its planned duration.

Although the annual major bleeding complication rates were low, levels were higher in the combination group (1.28%) than in the aspirin group (0.72%, $P<0.001$). Intracranial hemorrhage was virtually identical in the 2 groups.

The protocol required randomization to occur within 2 weeks of the infarction. By 1 month after study entry, a proportion of patients had not begun protocol-assigned therapy (27.6% for aspirin and 40.6% for combination therapy). The primary reason for the delay in protocol-assigned therapy initiation was the reluctance of investigators to anticoagulate patients in whom invasive procedures were either anticipated or in whom procedures had been recently performed. The delay in study drug initiation in the combination therapy group, relative to the aspirin therapy group, was not responsible for the lack of difference in survival in the 2 groups. In

addition, survival was not associated with the length of delay between randomization and drug initiation.

Of the 444 deaths in the combination therapy group, 117 (26%) occurred in patients who had never begun warfarin therapy. Of the 438 deaths in the aspirin group, 86 (19.6%) occurred in patients who had never begun aspirin therapy. An exploratory analysis excluding randomized patients who had never begun study medication failed to show any difference in any of the outcome measures (data not shown).

Adherence to the treatment assigned is a major concern in trials using oral anticoagulant therapy. Despite the delay in initiation of the study drug in many individuals, the proportion of follow-up time spent on protocol-assigned therapy was high: 86% for the aspirin group and 71% for the combination group. Withdrawals from both the aspirin group (12.6%) and the combination therapy group (25.3%) were within the rates seen in other major secondary prevention studies using these agents.¹⁵ The proportion of INR values (74%) at or above the lower end of the specified therapeutic range (1.5 IU) was also typical.¹⁶

A potential limitation of the present study is open-label drug administration with resultant differential follow-up between treatment arms. Patients in the combination group were seen by study personnel more frequently, resulting in inherent informational biases, including detection, recall, and interviewer bias. Differential misclassification may result from these biases and affect the identification and classification of bleeding episodes and other secondary outcomes. These limitations were addressed by defining total mortality as the primary study end point and adjudicating all bleeding episodes by a blinded end-points committee.

The other published post-AMI trial evaluating warfarin and aspirin in combination, the Coumadin Aspirin Reinfarction

TABLE 5. Hazard Ratios for Mortality by Date of Initiation of Protocol Therapy

	Aspirin (n=2537)			Combination (n=2522)		
	n	HR	95% CI	n	HR	95% CI
Never initiated	240	3.30	2.58, 4.21	478	2.02	1.62, 2.53
Within 14 days	1614	1.00	...	1286	1.00	...
15 to 28 days	222	1.15	0.81, 1.62	213	0.94	0.65, 1.36
More than 28 days	461	0.77	0.57, 1.04	545	0.73	0.55, 0.97

n indicates sample size; HR, hazard ratio; and 95% CI, 95% confidence interval.

HR and 95% CI were obtained from Cox proportional hazards model within 14 days as the reference group.

TABLE 6. Bleeding Complications According to Treatment Assigned

Complication	Aspirin		Combination		P	Rate Ratio (95% CI)
	n	Rate	n	Rate		
Minor bleeding	77	1.11	349	5.14	<0.001	4.63 (3.78, 6.94)
Major bleeding	50	0.72	87	1.28	<0.001	1.78 (1.27, 2.72)
Intracranial bleeding	15	0.22	14	0.21	>0.972	0.95 (0.41, 2.06)

Bleeding rates are expressed as events per 100 patient-years of follow-up. CI indicates confidence limits.

Study (CARS), also failed to demonstrate the superiority of combination therapy compared with aspirin monotherapy.⁶ In that trial, 8803 patients were randomized within 21 days of qualifying infarct to 1 of 3 arms: aspirin monotherapy (160 mg daily) or a combination of aspirin (80 mg) and warfarin at a fixed dose of either 1 or 3 mg daily. The intensity of anticoagulation was considerably lower than that in the Combination Hemotherapy and Mortality Prevention (CHAMP) trial; the median INR was 1.04 IU in the 1 mg warfarin group and 1.19 IU in the 3 mg warfarin group. No differences in the primary event rates of reinfarction, nonfatal ischemic stroke, or cardiovascular death were observed after a median follow-up of 14 months. Major bleeding rates were similar in the 2 studies and higher in the combination therapy groups for both studies. Thus, it appears that the combination of aspirin and warfarin at a mean INR of ≤ 1.8 is no better than aspirin alone.

In addition to these 2 studies, 3 trials have failed to demonstrate the superiority of combination therapy using low-intensity warfarin (mean INR <2.0 IU) compared with control treatment in the settings of unstable angina and non-Q-wave AMI,⁹ stroke prevention in nonvalvular atrial fibrillation,⁷ and prevention of atherosclerosis in aortocoronary saphenous vein bypass grafts.⁸ Two small studies that evaluated combination therapy with the use of moderate-intensity warfarin (INR 2.0 to 2.5 IU)⁹ and high-intensity warfarin (INR 3.0 to 4.5 IU)¹⁰ have shown improved short-term outcomes (3 months) in patients with acute coronary ischemia compared with outcomes in patients after control treatment. The question of the efficacy of higher intensity warfarin in combination with aspirin for long-term secondary prevention after AMI is being addressed by ongoing studies, including the Warfarin Reinfarction Study II (WARIS II) and the Anticoagulants in the Secondary Prevention of Events in Coronary Thrombosis II (ASPECT II).

Appendix

The following persons participated in the CHAMP trial (asterisks indicate principle investigators): Albany, NY: J. Sacco* and M.B. Tschinkel; Albuquerque, NM: C.A. Roldan* and J.E. Jones; Alexandria, La: J. Sampson* and J. Schmitt; Allen Park, Mich: R. Reher* and F.N. Talmers*; Amarillo, Tex: W. Allison*, S. Tirmizi*, B. Escaler*, C. Sivaram*, and J. Periman; Asheville, NC: B.A. Omar*, M. Moten*, N. Patel*, D. Moniz*, G. Patel*, and G. Ely; Atlanta, Ga: D.J. Bower*, M. Aguayo, J. Guidot, and N. Griffith; Augusta, Ga: V.C. Sridharan*, M.R. Sridharan*, and J. Hubbard; Baltimore, Md: N.H. Carliner* and J. Scheck; Bay Pines, Fla: U.R. Shettigar*, R. Diemer, and D.O. Appunn; Biloxi, Miss: A. Kanade* and W. Jackson; Birmingham, Ala: G.J. Perry*, E. Brown, and B. Sanders; Boise, Idaho: C. Eriksson* and J. Gieselmann; Boston, Mass: M. Brophy*; Brooklyn, NY: N. El-Sherif*, N. Aladhamy*, and G. El-attar; Charleston, SC: M. Zile*, M.J. Miller*, A. Wriggins, J.K. Busted, D. Lee, and K. Miller; Cincinnati, Ohio: L. Wexler*; Cleveland, Ohio: A. Taylor*; Columbia, Mo: M. Krishnan*, I.E. Ijahja*, and S. Beattie; Columbia, SC: A. Saenz* and D. Hart; Danville, Ill: A. Morrobel* and S. Shammo*; Dayton, Ohio: A.G. Suryaprasad* and D. Williams; Denver, Colo: C. McBryde*, T. Meyer*, and J. Mignoli; Des Moines, Iowa: R. Loungani* and T. Pierson; Dublin, Ga: A.C. Pradhan* and L. Kight; Durham, NC: K. Morris* and S. Dougherty; Fargo, ND: P. Czernek* and E. Garten; Fayetteville, NC: F. Maher* and L. Fritz; Grand Island, Neb: M. Nangia*; Hines, Ill: R. Hariman* and M. Tully; Hot Springs, SD: A. Kumar* and J. Johnston; Houston, Tex: A. Blaustein*, D.L. Mann*, and C. Rowe; Huntington, WV: S. Canisico*, R. Stevenson*, R. Touchon*, C. Harless, and K. Roe; Jackson, Miss: N. Srivastava*

and J. Voelkel; Kansas City, Mo: W. Emmot* and C. Perkins; Lake City, Fla: G. Bhaskar*, J. Thomas, and K. Herbert; Leavenworth, Kan: R. Nanda*, R. Miles*, M. Luse, and L. Woods; Lexington, Ky: D. Booth*, G.B. Clarke*, P. Frazier, and J. Jasper; Loma Linda, Calif: A. Jacobson* and D. Wielenga; Long Beach, Calif: H. Olson* and S. Saniga-Parker; Louisville, Ky: S. Wagner*, A. Joseph*, and N. Zettwoch; Madison, Wis: J.H. Thomsen*, A. Patel*, and L.E. Williams; Manchester, NH: P.L. Grich*; Memphis, Tenn: J.C. Riddle*, L. Johnson, and Z. Qualls; Milwaukee, Wis: J. Wynsen* and C. Hanson; Minneapolis, Minn: C. Gornick* and J. Johnson; Murfreesboro, Tenn: S. Cacodcar*, S. Sharma*, D. Gupta*, and R. Cassidy; Muskogee, Okla: K. Danisa* and S. Westbrook; Nashville, Tenn: D.M. Kerins* and B. Roberts; Newington, Conn: M.J. Radford* and N. Najarian; New York, NY: J. Lorin* and M. Keary; Northampton, Mass: N. Raheb* and C. Modrzakowski; Northport, NY: G.I. Mallis* and J. Gustavson; North Chicago, Ill: H. Deshmukh* and R. Singh*; Oklahoma City, Okla: U. Thadani* and B. Parker; Pittsburgh, Pa: M. Amidi*, M. DiTommaso, J. Klein, and M. Bell; Phoenix, Ariz: J.V. Felicetti* and K. Young; Portland, Ore: E. Murphy*, H. Demots*, and K. Avalos; Prescott, Ariz: S. Achacoso*, J. Sampson*, and J. Rindone; Providence, RI: S. Sharma* and L. Coulter; Reno, Nev: J.P. Johns* and L. Cieszko; Richmond, Va: R. Jesse* and C. Murphy; Salem, Va: N. Jarmukli*, D.C. Russell*, and D. Atkins; Salisbury, NC: D. Katzin*, M.N. Khan*, and D.G. Redfern; San Antonio, Tex: R.A. O'Rourke*, A. Jain*, D. Berg, and P. Baker; San Diego, Calif: A. Maisel*, Selpulveda, Calif: B.J. Cohen*; Sheridan, Wyo: M. Hiller*; St. Louis, Mo: H. Stratmann*, G.A. Williams*, and M. Whitson; Syracuse, NY: T.L. Anthony*, L. Koilowski, and J. Regan; Tampa, Fla: H. Fontanet*, G.B. Cintron*, and S. Thomas; Tomah, Wis: S.W. Babcock*; Tucson, Ariz: S. Goldman*, A. Warner*, J. Ohm, E. Gregorio, and P. Martinez; Washington, DC: D. Lu* and B. Gregory; West Haven, Conn: I. Cohen* and L. Canestri; West Los Angeles, Calif: M. Bersohn* and C. Silbar; West Roxbury, Mass: G.V.R.K. Sharma* and D. Lapsley; Wilkes-Barre, Pa: M. O'Reilly*; and White River Junction, Vt: C. Nice* and M. Garcia.*

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The following persons are located at VA Headquarters, Washington, DC: J.R. Feussner (Chief Research and Development Officer) and D. Deykin (Former Chief, Cooperative Studies Program).

Committees are as follows: Data Monitoring Board: B. Weksler (Chair), M. Dunn, S. Kelsey, G. Raskob, and G. Beck; Executive Committee: L. Fiore, M. Brophy, P. Peduzzi, M. Ezekowitz, J. Sacco, D. Lu, C. Colling, and D. Collins; and End Points Committee: J. Plehn (Chair), P.S. Rahko, M. Cohen, R. Homer, E. Benjamin, and L. Mendes.

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