Combination Antithrombotic Therapy in Unstable Rest Angina and Non–Q-Wave Infarction in Nonprior Aspirin Users

Primary End Points Analysis From the ATACS Trial

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Background The purpose of this study was to compare combination antithrombotic therapy with aspirin plus anticoagulation versus aspirin alone, when added to conventional antianginal therapy in patients with unstable rest angina or non–Q-wave myocardial infarction who were nonprior aspirin users.

Methods and Results Two hundred fourteen patients were randomized; 109 were randomized to receive aspirin alone (162.5 mg daily) and 105 to receive a combination of aspirin plus anticoagulation, ie, aspirin 162.5 mg daily plus heparin (activated partial thromboplastin time, two times control) followed by aspirin 162.5 mg daily plus warfarin (international normalized ratio, 2 to 3). Trial therapy was begun by 9.5±8.8 hours of qualifying pain and was continued for 12 weeks. Primary end points were recurrent angina with ECG changes, myocardial infarction, and/or death. Analysis by intention to treat of primary events at 12 weeks was performed. At 14 days, there was a significant reduction in total ischemic events in the combination group versus aspirin alone (10.5% versus 27%, $P=.004$). An efficacy analysis of primary events at 12 weeks also revealed a large reduction in total ischemic events in the combination group versus aspirin alone (13% versus 25%, $P=.06$). Bleeding complications were slightly more common with combination therapy.

Conclusions In nonprior aspirin users, combination antithrombotic therapy with aspirin plus anticoagulation significantly reduces recurrent ischemic events in the early phase of unstable angina. (***Circulation*. 1994;89:81-88.**)

Key Words • ischemia • aspirin • anticoagulants

Patients with unstable angina pectoris represent a broad spectrum, ranging from progressive or accelerating angina to the higher-risk subset of rest angina with reversible ECG changes.[1] Biochemical studies in humans[2,3] and studies in an experimental animal model[4,5] suggested a major role for platelets and platelet-derived thromboxane A_2 in this syndrome. Randomized, therapeutic clinical trials have established a beneficial role for antiplatelet agents in unstable angina or non–Q-wave myocardial infarction.[6-9] In contrast, other clinical trials have demonstrated a beneficial effect with heparin or warfarin alone in patients with unstable rest angina.[10-12] Therefore, antithrombotic therapy with either antiplatelet agents alone or anticoagulants alone are of benefit in the acute coronary syndromes of unstable angina and/or non–Q-wave myocardial infarction.

Pathoanatomic and biochemical observations implicate platelet-rich thrombus overlying a ruptured plaque as the triggering mechanism for these acute coronary syndromes.[13-17] In an experimental model of deep arterial injury (mimicking plaque rupture), Lam et al[18] observed a significant reduction in platelet deposition and mural thrombus in animals pretreated with aspirin plus heparin versus heparin alone. The prior clinical trials have shown that failure of medical therapy in these syndromes most often occurs within the first few days after admission.[8,11,19] Therefore, in view of the dynamic intra-arterial processes precipitating unstable angina and non–Q-wave infarction, more aggressive antithrombotic therapy with platelet inhibition plus anticoagulation may offer more benefit than either agent alone. Based on the trend to lower mortality and morbidity with combination therapy in the RISC[8] study and in the small pilot study of Cohen et al,[19] a larger, multicenter, binational study was undertaken of combi-

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nation antithrombotic therapy in unstable angina and non–Q-wave infarction. The hypothesis tested was whether combination antithrombotic therapy with an antiplatelet agent and an anticoagulant reduced cardiac morbidity and mortality compared with an antiplatelet agent alone during a 12-week treatment period.

Methods

The study was a prospective, randomized, open-label, multicenter trial of antithrombotic therapy in the treatment of men and women (over age 21 years) admitted to the hospital with acute chest pain caused by unstable rest angina or non–Q-wave myocardial infarction. To select a high-risk population, patients with chest pain had to have definite evidence of ischemic heart disease but no evidence of evolving Q-wave infarction. After approval by the institutional committee on human research at each enrollment center, patient recruitment began in December 1989. The present study was designed as a pilot trial in the United States and in the United Kingdom. Based on enrollment and withdrawal statistics at the US centers, in the spring of 1991, enrollment was terminated on December 31, 1991. Two hundred fourteen patients gave informed consent and were randomized.

Selection of Patients

Inclusion criteria. All patients enrolled in the study met all of the following three inclusion criteria: (1) over age 21, male or female (pregnant women were excluded) and (2) presented to hospital with ischemic pain caused by either unstable angina or non–Q-wave infarction defined as (a) recent onset of prolonged (≥10 minutes) or recurrent chest pain suggestive of acute myocardial ischemia, (b) pain occurring at rest with no provoking factors, and (c) the last attack of pain must have occurring within 48 hours of randomization. (3) In addition to the above, there must have been definite evidence of underlying ischemic heart disease, as shown by at least one or more of the following: (a) ECG changes during chest pain or on admission suggesting ischemia (if ST-segment elevation was present, it must have resolved within 30 minutes of relief of pain after nitroglycerin; patients with persistent ST elevation were not randomized), (b) previous documented myocardial infarction, (c) a previous positive exercise test or a previous coronary angiography showing a ≥50% luminal narrowing in any coronary artery, or (d) history of typical exertional angina, with chest pain precipitated by effort and relieved by rest and/or nitroglycerin.

Exclusion criteria. Exclusion criteria included (1) ischemic pain caused by evolving Q-wave myocardial infarction, (2) left bundle branch block or permanent pacemaker, (3) angina precipitated by congestive heart failure, tachyarrhythmia, hypertension (systolic blood pressure ≥160 mm Hg and/or diastolic blood pressure ≥100 mm Hg), valvular heart disease, Q-wave myocardial infarction within 4 weeks, anemia (hemoglobin <11 g/dL), or cocaine or other illicit drug use, (4) contraindications to anticoagulation, eg, allergy to heparin or aspirin, active peptic ulcer or other ulcerative disease of the gastrointestinal tract within 6 months, bleeding diathesis, or prior cerebral hemorrhage or nonhemorrhagic stroke within 2 months, (5) current need for anticoagulation, eg, pulmonary embolism, (6) chronic use of steroids or nonsteroidal anti-inflammatory drugs, (7) intravenous heparin therapy within 24 hours of randomization, (8) percutaneous transluminal coronary angioplasty (PTCA) within 6 months or coronary artery bypass grafting (CABG) within 1 year, (9) other serious disease, eg, severe liver disease or diabetes with proliferative retinopathy, (10) history of noncompliance or unlikely to return for follow-up, and (11) personal physician planning immediate intervention regardless of response to medical therapy.

Study Design

Once consent was obtained, patients were prospectively stratified into either nonprior aspirin users or prior aspirin users. Prior aspirin use was defined as ingestion of ≥150 mg of aspirin within 3 days of randomization, regardless of indication. Prior aspirin users were excluded from this study. Randomization and initiation of trial therapy was instituted as early as possible after admission to the emergency room. Trial therapy was continued for 12 weeks, after which continued administration of aspirin or anticoagulation was left to the discretion of the private physician.

Treatment Protocol: Trial Antithrombotic Therapy

Patients were randomized to receive one of two treatments.

Aspirin alone. Upon randomization, 162.5 mg aspirin PO as a loading dose followed by 162.5 mg aspirin daily.

Aspirin plus anticoagulation. Upon randomization, 162.5 mg aspirin PO and a loading dose of 100 U/kg heparin IV bolus. This was followed by 162.5 mg aspirin daily plus a continuous heparin infusion to maintain the activated partial thromboplastin time (aPTT) at two times control for 3 to 4 days. The aPTT tests were drawn 6 hours after the initial bolus and then once daily. Warfarin was to be started by the second or third day, presuming that coronary arteriography did not appear imminent. When the international normalized ratio (INR) reached 2.0 to 3.0 (prothrombin time, about 1.3 to 1.5 times control), heparin was discontinued.

Treatment Protocol: Standard Medical Therapy

In addition to trial antithrombotic therapy, antianginal therapy was administered to all patients according to the following algorithm. Patients not taking a β-blocker were defined as low-risk or higher-risk. Low-risk patients had a normal ECG at the time of randomization and no previous myocardial infarction; therapy administered was metoprolol 50 mg PO immediately followed by 50 to 100 mg BID, plus oral isosorbide dinitrate (ISDN) 20 to 40 mg every 6 hours. Higher-risk patients received metoprolol 50 mg PO immediately followed by 50 to 100 mg BID, plus oral ISDN 20 to 40 mg every 4 to 6 hours, plus nifedipine 10 to 30 mg three times daily as tolerated. If β-blocker use was contraindicated, diltiazem 30 mg QID increasing to 60 to 90 mg QID as tolerated plus ISDN 20 mg every 4 to 6 hours was given. Patients already taking a β-blocker were given maximized β-blockade, maximized nitrates, and nifedipine 10 to 30 mg TID orally. If pain recurred in the hospital on the above regimen, oral nitrates were discontinued, and intravenous nitroglycerin (5 μg/min) or ISDN (2 mg/h) (increasing to maximum tolerated, as clinically indicated) was substituted.

The doses of the antianginal drugs were maximized as tolerated within 48 hours in order to titrate the systolic blood pressure to ≤130 mm Hg and the heart rate to ≤65 beats per minute. Aspirin-containing medication other than trial drug was prohibited, and a supply of acetaminophen was given. In the absence of a revascularization procedure, patients were discharged on their antianginal regimen plus their trial antithrombotic therapy.

Withdrawal of Trial Therapy

Trial therapy was discontinued for the following reasons: (1) major bleeding defined as transfusion of two or more units of blood, surgical correction, retroperitoneal or intracranial hemorrhage, or bleeding resulting in death or permanent disability, (2) minor bleeding that the study physician believed could not be remediated by adjusting the dose of antithrombotic therapy, (3) development of an end point (recurrent ischemia, myocardial infarction, or death) or of a cerebrovascular accident, (4) if after trial therapy was begun, a patient was found to have normal coronary arteries, nonobstructive coronary artery disease (no lesions ≥50%), or a negative maximal

exercise tolerance test, or there was a clear reason other than progressive ischemic heart disease for the qualifying pain, eg, severe anemia unrecognized at the time of randomization, trial therapy was discontinued; if a patient was determined to have had a transmural infarction as the qualifying event, eg, a true posterior infarction, trial therapy was also discontinued, (5) surgical revascularization or angioplasty, (6) noncompliance with trial medication or missing two consecutive follow-up visits.

Data Collected

Enrolled patients were seen by the study team upon admission, during their hospitalization, at the time of hospital discharge, 1 week after discharge, and thereafter at 3-week intervals for a total of 12 weeks. The following variables were recorded.

At baseline. Variables included demographic data including age, sex, race, and risk factors for coronary artery disease and a description of the present illness culminating in admission and prior medications.

At randomization. Variables included blood pressure and pulse; a 12-lead ECG before and after nitroglycerin, and an old baseline (if available); serum creatine kinase (CK) (total and MB fraction); hemoglobin/hematocrit and platelet count; aPTT and prothrombin time; and chest radiograph.

During hospital stay. Variables included daily 12-lead ECGs, including an ECG after coronary intervention such as PTCA or bypass surgery, and any ECG documenting a myocardial infarction after randomization or during recurrent chest pain; CK (total and MB) 12 hours after randomization and every 12 hours for 48 hours; serial serum CK determinations after recurrent ischemic chest pain lasting longer than 15 minutes; episodes of recurrent ischemic chest pain, major and minor bleeding, coronary arteriography, crossover to surgical revascularization or PTCA, and death were recorded; daily aPTT and prothrombin time (reported as INR) for those patients randomized to anticoagulant therapy (during each visit, patients receiving warfarin had a prothrombin time measured to ensure that the INR remained between 2 and 3.0 [prothrombin time, 1.3 to 1.5 times control]; the INR and prothrombin time were measured in all patients using the Coumatrak Protime Monitor manufactured by Biotrack Inc, Mountain View, Calif); and antianginal medications at time of discharge.

Postdischarge follow-up visits. Variables included pill counts to assess compliance; hemoglobin, hematocrit, and stool for occult blood; for patients on warfarin, a prothrombin time to ensure the INR at 2 to 3.0; and an ECG recorded at 6 and 12 weeks or as clinically indicated.

All randomized patients in whom trial therapy was withdrawn were also followed as above.

Primary End Points

Recurrent angina. This was defined as recurrent chest pain at rest with ischemic ECG ST-T-wave changes occurring despite maximal antianginal therapy. Chest pain without acute ECG changes, even if suggestive of ischemia, was not considered an end point unless this pain prompted coronary revascularization.

Myocardial infarction. The presence of all three of the following was required for diagnosis: typical chest pain unrelieved by nitroglycerin and lasting 30 minutes or more; new and persistent ST-T-wave changes or Q waves, identified according to the criteria of the Minnesota code; and a rise in serum CK to two times above the upper limit of normal, or an increase of 50% or more in CK activity above the preceding sample but at least 1.5 times the upper limit of normal.

Perioperative myocardial infarction was identified by a combination of ECG criteria and enzyme criteria. In this setting, the CK MB must have been greater than 50 mU/mL when the normal reference was 15 to 16 mU/mL. Silent myocardial infarction was counted as an end point if new pathological Q waves appeared on the 12-lead ECG during a follow-up visit.

In identifying the occurrence of myocardial infarction, a judgment was made as to whether this event occurred before or after randomization. Only an infarction considered as an event clearly separate from the cardiac event qualifying the patient for randomization was considered an end point. Evidence of an increased CK at the time of randomization suggestive of an admission non–Q-wave evolving infarction was not considered an end point.

Total deaths. This included all deaths regardless of etiology. Fatal myocardial infarction or sudden death from which the patient was resuscitated was counted as a death.

Secondary End Points

Major bleeding, as described above, as well as coronary revascularization with either PTCA or CABG were prospectively recorded.

Protocol Deviations

Protocol deviations occurred in 65 patients. Analysis of serial ECGs and enzymes revealed that 16 patients had an evolving transmural myocardial infarction. One was anterior, and the remaining 15 were true posterior wall infarctions. In 17 patients, trial therapy was discontinued prematurely by the personal physician who referred the patients to a revascularization procedure even though there had been no recurrent ischemia on trial therapy. In 32 patients, trial therapy was discontinued prematurely by either the patient or the personal physician for miscellaneous reasons.

Statistics

Sample size estimate. Based on the data of Theroux et al[11] and Cohen et al,[19] a cumulative cardiac event rate (recurrent angina, myocardial infarction, and death) of at least 17% in the aspirin-alone group was expected. To perceive a 40% reduction in events (from 17% to 10%, with a power of 85%) by the addition of anticoagulation, 427 patients needed to be randomized into each cell. A pilot trial was begun in 1989 with interim analyses of patient enrollment and withdrawal rates planned. Based on enrollment and withdrawal statistics at the US centers, enrollment was terminated on December 31, 1991. End-points analysis was performed by the independent biostatistical center after enrollment was completed.

End-points analysis. Analyses of events were performed under the principle of intention to treat. In addition, a secondary analysis was performed censoring events at the time a patient withdrew from trial therapy (efficacy analysis). Comparison of time to event was displayed using Kaplan-Meier plots of percent free of event. Therapy groups were compared using a log rank statistic. Comparison of baseline characteristics was performed using a χ^2 statistic or t test as appropriate. A P value of $<.05$ was considered significant.

Results

Two hundred fourteen patients who had not been taking aspirin before admission were randomized; 109 were randomized to receive aspirin and 105 to receive a combination of aspirin plus anticoagulation (heparin followed by warfarin). The mean time from "qualifying pain" to randomization and treatment was 9.5±8.8 hours, with a median of 6.8 hours.

Baseline characteristics were similar between the two treatment groups with the exception of history of hypertension and diastolic blood pressure at entry (Table 1). More patients with a history of hypertension were assigned to aspirin alone than to aspirin plus anticoagulation (38% versus 23%, $P=.02$), and they had a higher diastolic blood pressure (79 mm Hg versus 75 mm Hg,

TABLE 1. Characteristics of Patient Population

	Aspirin (n=109)	Aspirin+ Heparin/Warfarin (n=105)	Significance
Demographic characteristics			
Men, %	63	72	NS
Mean age, y	63	60	.06
Ethnic group, %			
White	91	95	
Black	2	3	
Other	7	2	NS
Current smoker, %	36	34	NS
Baseline clinical history			
Hx of hypertension, %	38	23	.02
Hx of diabetes, %	7	9	NS
Hx of stroke or TIA, %	0	3	.07
Family hx of heart disease, %	45	45	NS
Angina before last 4 wk, %	45	53	NS
Hx of myocardial infarction, %	24	32	NS
Prior coronary angiogram, %	10	11	NS
Prior PTCA, %	1	2	NS
Prior CABG, %	4	2	NS
Prior positive ETT, %	61	48	NS
Baseline clinical characteristics			
Mean systolic BP, mm Hg	133	130	NS
Mean diastolic BP, mm Hg	79	75	.02
Cardiomegaly, %	11	14	NS
LV hypertrophy on ECG, %	2	6	NS
RBBB, %	2	5	NS
Admission diagnosis			
Unstable angina, n	76	71	NS
Non–Q-wave myocardial infarction, n	22	24	
Evolving Q-wave myocardial infarction, n	10	6	
Not classified	3	2	
Antianginal medications at study entry			
β-Blockers, %	31	21	.08
Calcium channel blockers, %	22	27	NS
Admission ECG findings			
Ischemic ST-T-wave changes, %	64	61	NS
New ST- or T-wave changes that reversed with NTG, %	22	25	NS

Hx indicates history; TIA, transient ischemic attack; PTCA, percutaneous transluminal coronary angioplasty; CABG, coronary artery bypass grafting; ETT, exercise tolerance test; BP, blood pressure; LV, left ventricular; RBBB, right bundle branch block; and NTG, nitroglycerin.

P=.02). The mean age of the 214 patients was 61 years. One hundred forty-seven patients were admitted for unstable angina, 46 with a non–Q-wave myocardial infarction, and 16 with an evolving Q-wave infarction. Five patients had no cardiac enzyme information at baseline.

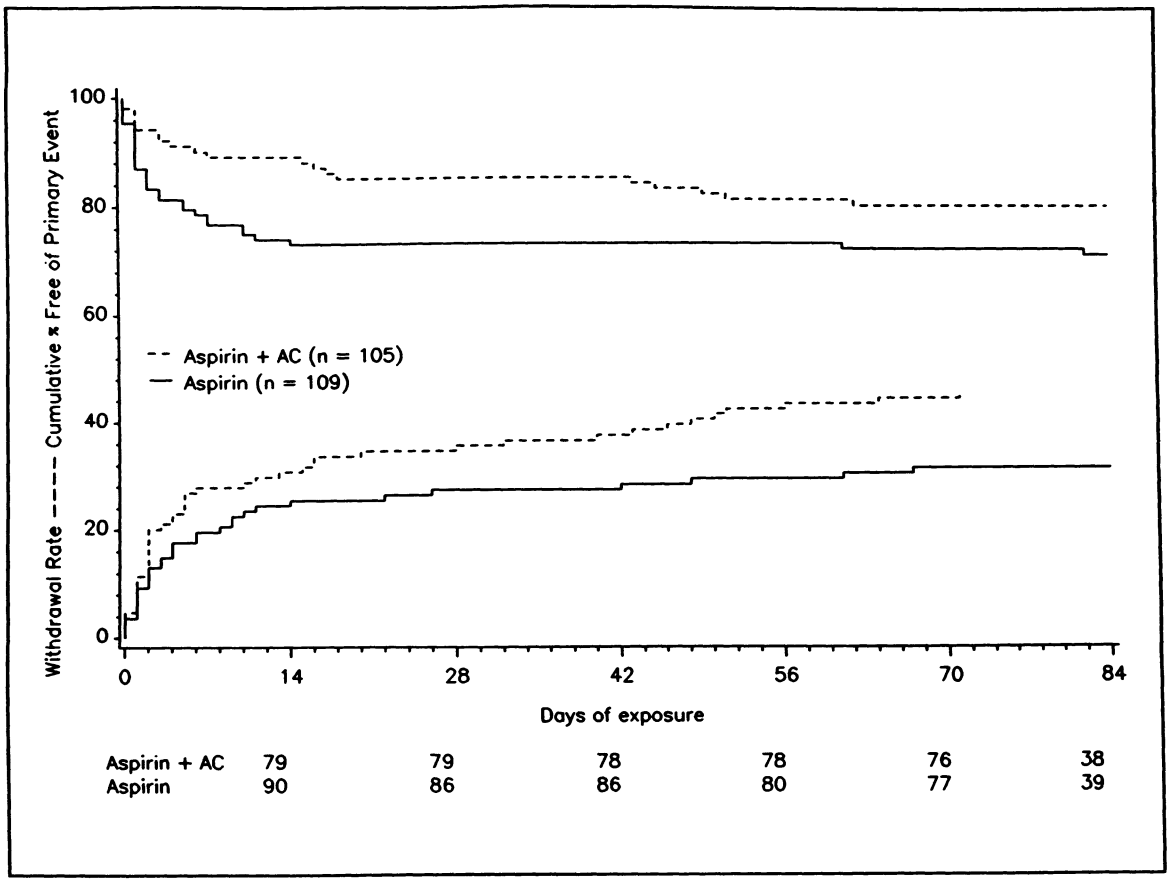
By the end of the 12-week follow-up period, 31 patients (28%) assigned to aspirin alone experienced a primary event compared with 20 patients (19%) assigned to aspirin plus anticoagulation (P=.09 by log rank statistic after adjusting for history of hypertension and diastolic blood pressure at entry) (Table 2 and Figure). When exposure was censored at the time that a patient discontinued trial therapy, 27 patients (25%) assigned to aspirin experienced a primary event compared with 14 patients (13%) assigned to aspirin plus

TABLE 2. Primary End Points

	Aspirin (n=109)		Aspirin+Heparin/ Warfarin (n=105)		
	n	%	n	%	Significance*
Primary end point					
No event	78	72	85	81	
Event	31	28	20	19	.09
Recurrent angina with ECG changes or prompting intervention					
No event	89	82	93	89	
Event	20	18	12	11	NS
Myocardial infarction					
No event	100	92	99	94	
Event	9	8	6	6	NS
All deaths					
No event	107	98	103	98	
Event	2	2	2	2	NS

*After adjustment for history of hypertension and diastolic blood pressure at entry.

anticoagulation (P=.06 by log rank statistic after adjusting for history of hypertension and diastolic blood pressure at entry). Post hoc analysis by intention to treat, limiting exposure to 14 days (as if the study had been designed as an acute phase trial), showed a significant benefit for combination therapy (Table 3): 27% of patients assigned to aspirin experienced a primary event versus 10% of patients assigned to combination therapy (P=.004 by log rank statistic, after adjusting for history of hypertension and diastolic blood



Graph shows cumulative percent of patients free of any primary end point. Also depicted in the bottom half of the panel is the withdrawal rate from trial therapy. AC indicates anticoagulant.

TABLE 3. Primary End-Points Analysis and Time to Event

	Aspirin (n=109)		Aspirin+Heparin/ Warfarin (n=105)		
	n	%	n	%	Significance*
Primary end point (12 weeks): intention to treat					
No event	78	72	85	81	
Event	31	28	20	19	.09
Primary end point (12 weeks): efficacy					
No event	82	75	91	87	
Event	27	25	14	13	.06
Primary end point (14 days): intention to treat					
No event	80	73	94	90	
Event	29	27	11	11	.004
Primary end point (30 days): intention to treat					
No event	80	73	90	86	
Event	29	27	15	14	.03

*After adjustment for history of hypertension and diastolic blood pressure at entry.

pressure at entry), yielding a relative risk of 0.35 (95% confidence interval, 0.17 to 0.72).

Unstable Angina Versus Non–Q-Wave Myocardial Infarction

One hundred forty-seven patients were classified as being admitted with unstable angina, and 46 patients were classified as having an admission non–Q-wave myocardial infarction. In the unstable angina subset, 22 of 76 patients assigned to aspirin alone had a primary event (29%) versus 15 of 71 assigned to aspirin plus anticoagulation (21%). In the non–Q-wave infarction subset, 7 of 22 patients assigned to aspirin alone had a primary event (32%) versus 4 of 24 assigned to aspirin plus anticoagulation (17%). However, all of the primary events experienced by the non–Q-wave infarction patients occurred within the first 14 days.

Secondary End Points

In the aspirin-alone treatment group, 16 patients (15%) underwent revascularization with either PTCA or CABG versus 12 (11%) in the aspirin-plus-anticoagulation group. With reference to major bleeding complications, there were no spontaneous (unrelated to coronary revascularization) major bleeds in the patients assigned to aspirin alone. In contrast, in the patients assigned to combination therapy, the major bleeding rate was 2.9%. The frequency of minor bleeds or medication intolerance in patients assigned to aspirin alone versus combination therapy was 2.8% and 6.7%, respectively.

Withdrawals

Withdrawal from therapy or occurrence of a secondary end point occurred in 31% of patients assigned to aspirin alone and in 45% of patients assigned to combination therapy before the end of the 12 weeks of follow-up. The reasons for withdrawal of therapy varied (Table 4). Compliance to aspirin therapy was adequate; patients took their tablets, on average, 80% of the time. Monitoring the level of anticoagulation in patients assigned to aspirin plus warfarin revealed a median INR value of 2.3 over the 12-week period. Fifty percent of the INR values fell between 2.0 and 2.7 and 90% between 1.4 and 3.5.

TABLE 4. Reasons for Withdrawal of Trial Therapy

	Aspirin (n=109)		Aspirin+ Heparin/ Warfarin (n=105)	
	n	%	n	%
Withdrawal or secondary end point				
No	81	74	62	59
Yes	28	26	43	41
Evolving Q-wave infarct	10	9.2	6	5.7
Major bleed	0	0	3	2.9
PTCA not prompted by recurrent pain	3	2.8	3	2.9
CABG not prompted by recurrent pain	4	3.7	1	1.0
Stroke	1	.9	0	0
Normal coronary arteries	2	1.8	4	3.8
Medication intolerance	3	2.8	7	6.7
Poor compliance	0	0	3	2.9
Patient request	0	0	4	3.8
Physician request	3	2.8	6	5.7
Other exclusions	2	1.8	6	5.7

PTCA indicates percutaneous transluminal coronary angioplasty; CABG, coronary artery bypass grafting.

TABLE 5. Pooled Analysis of Relative Risk of Combination Therapy Versus Aspirin Alone

	ATACS		RISC[8]		Theroux et al[11]		
	Aspirin (n=109)	Aspirin + Heparin (n=105)	Aspirin (n=189)	Aspirin + Heparin (n=210)	Aspirin (n=121)	Aspirin + Heparin (n=122)	RR_{mh} (CI)
Myocardial infarction/death	9 (8.3%)	4 (3.8%)	7 (3.7%)	3 (1.4%)	4 (3.3%)	2 (1.6%)	.44 (.21-.93)

CI indicates 95% confidence interval.

Discussion

Despite several large-scale, placebo-controlled trials in patients with the acute coronary syndromes of unstable rest angina or non–Q-wave myocardial infarction, several issues remain unresolved. (1) Is combination antithrombotic therapy with an antiplatelet agent and an anticoagulant better than the established benefit of either of these agents alone? (2) What is the impact of combination therapy on the acute coronary syndrome of non–Q-wave infarction? (3) If combination antithrombotic therapy is better, is it an effective and safe medical regimen over the long term (after hospital discharge)?

Present Study

In patients not taking aspirin, our data suggest that combination antithrombotic therapy significantly reduces the incidence of primary ischemic events in the early phase (first 14 days). However, by 90 days, there is only a trend favoring combination therapy. It is possible that the power to detect a significant difference at 90 days using an intention-to-treat analysis was too small, given our sample size.

Comparison With Prior Studies

Combination therapy for unstable angina or non–Q-wave infarction has been prospectively evaluated in only three studies.[8,11,19] The trial by Theroux et al[11] was the first randomized comparison of different antithrombotic regimens including combination therapy with aspirin plus heparin in patients with unstable angina. Trial therapy was terminated after a mean follow-up of 6 days. Combination therapy with aspirin plus heparin was significantly better than placebo; however, there were no statistically significant differences in recurrent ischemic events between the combination group versus the heparin-alone or aspirin-alone treatment limbs.[11]

The RISC Study Group[8,20] conducted a 90-day study of combination low-dose aspirin (75 mg daily) and heparin versus aspirin alone or versus heparin alone in patients with either unstable angina or non–Q-wave infarction. The heparin treatment was only continued for 5 days. The combination of aspirin and short-term heparin resulted in the lowest rate of events at 5 days, but there were no significant differences in recurrent ischemic events between the combination group versus the aspirin-alone treatment limbs.[8]

The relative risk reduction in infarction or death occurring within the first 5 days in patients on combination therapy versus aspirin alone was similar for these two trials (Theroux et al,[11] RISC[8]) as well as the present ATACS study (Table 5). The pooled estimate of the relative risk combining observed results from the three studies (calculated using the method of Mantel-Haenszel[21]) for infarction or death among patients treated with combination antithrombotic therapy compared with aspirin alone was 0.44 (95% confidence interval, 0.21 to 0.93).

Combination antithrombotic therapy with aspirin plus anticoagulants has also been shown to be more effective than anticoagulants alone in reducing thromboembolism in patients with prosthetic heart valves.[22-24] The recent randomized trial of Turpie et al[25] demonstrated a highly significant reduction in thromboembolism with combination therapy.

The higher ischemic event rate experienced in our study, compared with RISC or Theroux et al, may be partially explained by the fact that randomization and treatment in our study occurred at the time of admission in the emergency room. In the RISC Study,[8] randomization was allowed up to 72 hours after hospital admission. In the Theroux study,[11] only the events occurring within the first 5 days were counted, and patients with non–Q-wave infarction were excluded. Our data indicate that recurrent ischemic events may occur within days of onset of pain. Therefore, any delay in randomization may overlook patients with early recurrent ischemia and artificially reduce the total number of events.

Non–Q-Wave Myocardial Infarction

The impact of combination therapy on the subset of patients with non–Q-wave infarction paralleled that for patients with unstable rest angina in that there appeared to be a trend in favor of combination therapy. It has been suggested that the stimulus for clot propagation in these patients is greater than in patients with unstable angina.[17] This may explain why, despite initiating trial antithrombotic therapy within 24 hours, even in combination, almost all recurrent ischemic events in patients with non–Q-wave infarction occurred within the first 14 days.[26]

Clinical Implications

In summary, the dynamic intra-arterial process precipitating the acute coronary syndromes of unstable rest angina and non–Q-wave myocardial infarction necessitates prompt and aggressive antithrombotic therapy with aspirin plus an anticoagulant. In the absence of trials showing that urgent revascularization with either PTCA[27] or urgent CABG[28,29] reduces acute morbidity or improves long-term survival compared with aggressive medical management, we believe that the combination antithrombotic regimen added to antianginal medication should become the standard, early-phase medical regimen for these acute coronary syndromes. A more effective antithrombotic therapy must be identified for prior aspirin users and for patients with non–Q-wave infarction.

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