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Prospective Comparison of Patient Characteristics and Outcome of Non-prior Aspirin Users versus Aspirin Users with Unstable Angina or Non–Q-Wave Myocardial Infarction Treated with Combination Antithrombotic Therapy

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Abstract. **The objective of this study was to determine if aspirin users presenting with acute coronary syndromes are at higher risk for subsequent clinical events. In a trial evaluating combination antithrombotic therapy in resting angina or non–Q-wave myocardial infarction (MI), patients were prospectively dichotomized on admission into nonprior versus recent aspirin users. Then 105 nonprior users and 144 users were randomized to treatment with aspirin plus heparin/warfarin for 12 weeks. Recurrent myocardial ischemia occurring during the 12-week follow-up period was defined as recurrent angina (with electrocardiographic changes or prompting coronary revascularization), MI, or death. Prior aspirin users had a significantly higher incidence of previous MI, prior bypass grafting, beta-blocker use, or hypertension ($p \leq 0.003$) and were more likely to present with unstable angina as opposed to non–Q-wave MI. ($p \leq 0.008$). The cumulative probability of recurrent ischemic endpoints for nonprior versus recent users was 10% versus 21% at 14 days (log rank $p = 0.03$), and 19% versus 29%, at 12 weeks ($p = 0.06$). Using the Cox model, adjusting for variables significantly associated with outcome, aspirin use remained a significant predictor of 14-day outcome ($p = 0.04$) but not of 12-week outcome ($p = 0.06$). In conclusion, even after adjusting for significant differences in baseline variables, aspirin users presenting with rest angina or non–Q-infarction have a worse *short*-term prognosis in spite of maximal medical therapy.**

Key Words. **unstable angina, aspirin, non–Q-wave, myocardial infarction**

Randomized, placebo-controlled trials have established a benefit for antithrombotic therapy in patients with the acute coronary syndromes of unstable angina, and non–Q-wave myocardial infarction [1–3]. By design, all of these trials excluded prior aspirin (ASA) users. Nevertheless, the fraction of patients presenting with unstable angina or non–Q-wave infarction already taking aspirin is steadily increasing from 19% in 1988 [2] to 40% in the ATACS study completed in 1991 [4]. Are patients who have "failed" aspirin at higher risk for subsequent clinical events?

The original ATACS study [4,5] prospectively dichotomized patients with unstable angina or non–Q-wave myocardial infarction into nonprior versus prior ASA users. The present study presents a *post-hoc* analysis comparing these two groups with regard to their clinical characteristics and their 12-week clinical outcome on maximal medical and antithrombotic therapy.

Methods

The ATACS study was a prospective, randomized trial of antithrombotic therapy in the treatment of men and women (over age 21) with acute chest pain due to rest unstable angina or non–Q-wave myocardial infarction (MI). After approval by the institutional committee on human research at each enrollment center, 358 eligible patients were randomized:

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Table 1. Antithrombotic therapy in acute coronary syndromes—protocol

No prior ASA use: Trial A	
Group 1	*Group 2*
At randomization:	At randomization:
ASA 162.5 mg po heparin 100 U/kg iv push	ASA 162.5 mg po plus, loading
Maintenance:	Maintenance:
ASA 162.5 mg/day for 12 weeks	ASA 162.5 mg/day plus, heparin drip (PTT 2× control for 3 days) then warfarin (PT 1.3–1.5× control (INR 2–3) for 12 weeks
Prior ASA use: Trial B	
Group 1	*Group 2*
At randomization:	At randomization:
CR-ASA 75 mg po plus, loading heparin 100 U/kg iv push	Conventional ASA 75 mg po plus, loading heparin 100 U/kg iv push
Maintenance:	Maintenance:
CR-ASA 75 mg/day plus, heparin drip (PTT 2× control for 3 days) then warfarin (PT 1.3–1.5× control (INR 2–3) for 12 weeks	Conventional ASA 75 mg/day plus heparin drip (PTT 2× control for 3 days) then warfarin (PT 1.3–1.5× control (INR 2–3) for 12 weeks

ASA = aspirin; CR-ASA = controlled-release aspirin; INR = international normalized ratio.

214 patients were not using aspirin and 144 were ASA users.

Selection of patients: Inclusion and exclusion criteria

The inclusion and exclusion criteria for the study patients have been previously published [4,5] and are presented in brief here. Inclusion criteria were as follows: (1) age over 21 years, (2) presented to hospital with ischemic pain at rest caused by either unstable angina or non–Q-wave infarction, and (3) evidence of underlying ischemic heart disease, for example, a positive stress test or ECG changes. Exclusion criteria included: (1) ischemic pain due to evolving Q-wave MI; (2) left bundle branch block or permanent pacemaker; (3) angina precipitated by noncoronary causes, or contraindications to anticoagulation; (4) coronary angioplasty within 6 months or bypass surgery within 1 year; and (5) personal physician planning immediate intervention, regardless of response to medication.

Study design: ATACS

The original study design is outlined in Table 1. After informed consent, patients were prospectively stratified into either the nonprior ASA-use group (trial A) or the prior ASA-use group (trial B). Prior ASA use was defined as ingestion of ≥150 mg of ASA within 3 days of randomization. All trial therapy was instituted immediately on randomization in the emergency room. Trial therapy was continued for 12 weeks. Patients with no prior aspirin use were randomized to receive either ASA alone (n = 109) or ASA + anticoagulation (n = 105). Patients with prior aspirin use were randomized to receive either controlled-release (CR) aspirin + anticoagulation (n = 72) or conventional aspirin + anticoagulation (n = 72). Controlled-release aspirin acetylates platelet cyclooxygenase in the entero-hepatic circulation, but only minute levels of acetyl salicylic acid reach the systemic circulation, thereby preserving endothelial-cell prostacyclin synthesis [6,7].

In addition to trial antithrombotic therapy, anti-antianginal therapy was administered to all patients according to a previously described algorithm [4]. In summary, beta-blockers, nitrates, and calcium antagonists were maximized, as tolerated, in order to titrate the systolic blood pressure to ≤130 mmHg and the heart rate to ≤65 beats/min. Aspirin-containing medication other than the trial drug was prohibited and a supply of acetaminophen was given to each participant.

Study design: Current analysis

The current study presents a posthoc analysis of the 105 trial A (non–prior ASA) patients randomized to receive a combination of ASA plus anticoagulation versus the 144 trial B (prior ASA) patients randomized to receive a combination of ASA plus anticoagulation. The outcome of the 72 trial-B patients randomized to controlled-release ASA plus anticoagulation was identical to that of the 72 trial-B patients randomized to conventional ASA plus anticoagulation [5]. Therefore, the two groups of 72 patients were combined.

Primary endpoints

Recurrent angina. Recurrent angina 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 endpoint *unless* this pain prompted coronary revascularization.

Table 2. *Characteristics of patient population*

	Nonprior ASA (n = 105)	Prior ASA (n = 144)	Significance (p value)
Demographic characteristics			
Male (%)	72	73	ns
Mean age (years)	60	63	ns
Ethnic group, % white	95	92	ns
Current smoker (%)	34	23	.05
Baseline clinical history			
Hx of hypertension (%)	23	41	.002
Hx of diabetes (%)	9	9	ns
Hx stroke or TIA (%)	3	10	.05
Family hx or heart disease (%)	45	44	ns
Angina prior to last 4 wks (%)	53	74	.000
Hx myocardial infarction (%)	32	52	.003
Prior coronary angiogram (%)	11	35	.000
Prior PTCA (%)	2	5	ns
Prior CABG (%)	2	16	.000
Prior positive ETT (%)	48	40	ns
Baseline clinical characteristics			
Mean systolic BP (mmHg)	126	127	ns
Mean diastolic BP (mmHg)	73	75	ns
Cardiomegaly (%)	14	21	ns
LV hypertrophy on ECG (%)	6	6	ns
Admission diagnosis:			
Unstable angina (%)	70	87	.008
Non–Q-wave MI (%)	22	11	
Evolving Q-wave MI (%)	8	2	
Antianginal medications at study entry			
Beta-blockers (%)	21	52	.000
Calcium-channel blockers (%)	27	43	.012
Admission ECG findings			
Ischemic ST-T wave changes (%)	61	58	ns
New ST or T wave changes (%)	24	32	ns
New ST or T wave changes that reversed with NTG (%)	25	23	ns
Persistent ischemic ST-T wave changes (%)	36	33	ns

ASA = acetyl salicylic acid; Hx = history; TIA = transient ischemic attack; PTCA = percutaneous transluminal coronary angioplasty; CABG = coronary artery bypass graft; ETT = ; BP = blood pressure; LV = left ventricular; ECG = electrocardiogram; MI = myocardial infarction; NS = not significant; NTG = nitroglycerin.

Myocardial infarction. MI was defined as chest discomfort unrelieved by nitroglycerin and lasting 30 minutes or more, accompanied by new and persistent ST-T wave changes or Q waves, *and* a rise in serum CK to 2 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 15–16 mU/ml. Silent MI was counted as an endpoint if a new pathologic Q wave appeared on the 12-lead ECG during a follow-up visit.

In identifying the occurrence of MI, a judgement was made as to whether this event occurred before or after randomization. Only those infarctions considered as events clearly separate from the cardiac event qualifying the patient for randomization were considered to be endpoints. Evidence of an increased creatine kinase at the time of randomization suggestive of an admission non–Q-wave evolving infarction was not considered to be an endpoint.

Total deaths. All deaths, regardless of etiology, were included.

Statistics

Comparison of baseline characteristics was performed using a chi-square test for categorical variables and a t-test for continuous variables. 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 with-

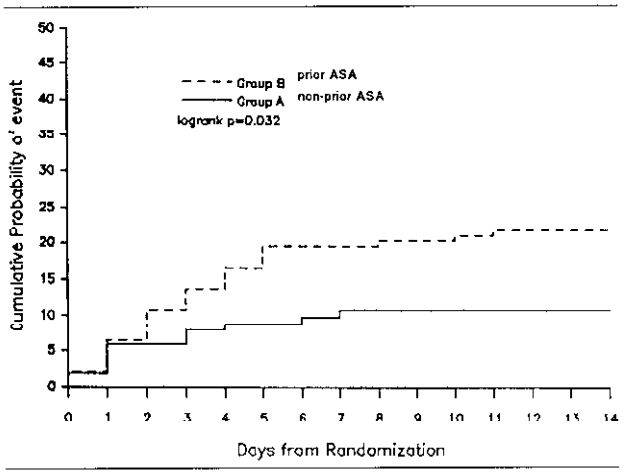

Fig. 1. The cumulative percent of patients free of any primary endpoint in nonprior aspirin users (group A) versus prior aspirin users (group B).

drew from trial therapy (efficacy analysis). Time to event was displayed using Kaplan-Meier plots of percent free of events. Adjustments for covariates that differed significantly between prior aspirin users and nonprior users was performed using a Cox proportional hazards model. The two groups were compared using a log rank statistic. A p value of less than 0.05 was considered significant.

Results

The mean time from "qualifying pain" to randomization and treatment was 12.2 ± 11.8 hours. The baseline characteristics of the 105 nonprior ASA patients randomized to receive ASA plus anticoagulation are compared with the 144 prior ASA users who received ASA plus anticoagulation in Table 2. There were no significant differences between nonprior aspirin users and prior aspirin users with respect to age, gender, or the presence of ischemic changes on the admission electrocardiogram. However, a significantly larger fraction of prior ASA users had a history of hypertension, prior stroke, or transient ischemic attack, or previous MI or coronary bypass surgery. Thirty-nine patients presented with non–Q-wave infarction as opposed to unstable angina. A significantly larger fraction of nonprior ASA users (22%) presented with non–Q-wave infarction compared with only 11% of prior ASA users. Eighty-one (33%) of the entire cohort (n = 249), had coronary revascularization after admission.

For the entire cohort of 249 patients, primary endpoints occurred in 41 (16%) patients by 14 days and in 62 (25%) by the end of the 12-week follow-up period. Comparison of 14-day outcome between nonprior versus prior ASA users is depicted in Figure 1. There is a significantly higher event rate in the prior ASA users, with on unadjusted difference of p = .03. Twenty-one percent of prior ASA-use patients experienced a primary event, versus 11% of nonprior ASA use patients (Table 3). Only two other variables were significantly associated with 14-day outcome. History of hypertension and use of calcium channel blockers were both associated with a higher event rate. No variables were significantly associated with 12-week outcome. Using the Cox model, adjusting for covariates hypertension and the use of calcium-channel blockers at baseline, revealed that prior ASA remained a significant predictor of poorer outcome at 14 days (log rank statistic p = 0.032); see Table 3. Prior ASA use, however, was not significantly associated with 12-week outcome (p = 0.06).

Discussion

The fraction of patients presenting with unstable angina or non–Q-wave infarction already taking aspirin has increased steadily, 48% in the TIMI-IIIB trial [8] and 64% in the more recent TIMI-7 study [9]. Despite several comparisons of the clinical characteristics and outcome of nonprior versus prior aspirin users [5,9–13], the implications of presenting with unstable angina or non–Q-wave myocardial infarction having "failed" ASA remain controversial. Early comparisons suggested that ASA users had similar clinical and angiographic characteristics [10,11]. In a large primary prevention trial, Ridker et al. [11] compared patients experiencing a nonfatal MI after randomization to ASA versus those having an event who were randomized to placebo. There were no differences between the treatment groups with regard to infarct size (measured by CK and left ventricular ejection fraction) nor in the number of vessels obstructed.

More recent analyses [5,9] suggest that patients who have "failed" aspirin have a higher risk profile. In the TIMI-7 cohort [9], prior ASA users were significantly older and were more likely to have had a prior infarction or coronary revascularization procedure. In addition, they observed that ASA users were *less* likely to present with non–Q-wave myocardial infarction.

Present study

The current analysis comparing the two arms of the ATACS study [4,5] provides the first prospective comparison of short and intermediate clinical outcome of prior versus nonprior aspirin users with unstable angina or non–Q-wave infarction followed on similar medical regimens. In parallel with Borzak et al. [9], our prior ASA users also had a higher risk profile, with more users having prior hypertension and being on calcium-channel blockers. However, in spite of a higher risk profile, our prior aspirin users also were *less* likely to present with non–Q-wave myocardial infarction and more likely to present with rest angina. This is in keeping with the findings of Borzak et al.

Table 3. *Primary endpoints*

	Nonprior ASA (n = 105)		Prior ASA (n = 144)		Significance (p value)
	No.	(%)	No.	(%)	
Primary endpoint (12 weeks)					
Intention to treat					
No event	85	(81)	102	(71)	
Event	20	(19)	42	(29)	0.06
Primary endpoint (14 days)					
Intention to treat					
No event	94	(90)	114	(79)	
Event	11	(11)	30	(21)	0.032[a]

[a]Adjusted for covariates hypertension and calcium-channel blocker use at baseline.

[9], as well as observations made by Col et al. [12] and Garcia-Dorado et al. [13].

Borzak et al. [9], using stepwise regression analysis, observed that prior ASA use was not a predictor of recurrent ischemia or death. In contrast, the present analysis suggests that even after correcting for imbalances in risk profile, prior ASA users have a significantly worse short-term prognosis (14 days) and a trend to a worse intermediate (12 week) prognosis. Explanations for this difference compared with the TIMI-7 cohort [9] may be that our population had a larger number of non–Q-wave infarctions (16% vs, 8%). In addition, only 33% of our patients underwent revascularization. It is likely that there were a higher number of interventions in the TIMI-7 group, which was based entirely in the United States.

Limitations

The present analysis was based on combining the two treatment limbs within the prior ASA use arm of the ATACS study [5]. Since there were no significant difference between the prostacyclin-sparing combination antithrombotic regimen versus the conventional ASA combination regimen, we do not think this biased the analysis. Also, the dose of ASA in the non-prior-use arm was 162.5 mg, but in the prior-use limb it was 75 mg. Because the RISC study [3] established a beneficial effect for 75 mg ASA in unstable angina, the difference in the ASA dose is probably not of clinical significance.

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Appendix

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