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# Acute Coronary Syndromes in the United States and United Kingdom: A Comparison of Approaches

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## Summary

*Background:* Patients with coronary artery disease are managed differently in different countries.

*Hypothesis:* These variations in patient management may affect clinical outcome, a possibility that should be taken into consideration in multicenter studies.

*Methods:* In a binational, 3 months study of antithrombotic treatment of patients with unstable angina and non-Q-wave infarction (ATACS), we compared the experience in the four enrollment centers in the United States (US) with the three centers in the United Kingdom (UK). The 59 US patients and the 299 UK patients were similar with regard to age, rates of prior revascularization, prior positive exercise tests, medication use, and aspirin use.

*Results:* US patients were more commonly women (45 vs. 28%), diabetic (30 vs. 4%), or hypertensive (52 vs. 31%), and had a prior coronary angiogram (30 vs. 18%). After enrollment, coronary angiography was performed more frequently in the US than in the UK (61 vs. 22%). Although the distribution of coronary disease was similar, revascularization without recurrent angina (19 vs. 4%, $p < 0.001$), or following recurrent angina (8 vs. 3%), was significantly more frequent in the US. Combined primary end points (recurrent angina, myocardial infarction, or death) did not differ between US (29%) and UK (25%) patients.

*Conclusion:* Therefore, international studies of acute coronary disease need to account for different treatments in different countries. These differences, in the small ATACS study, did not have a major impact on the composite primary outcome variables.

**Key words:** unstable angina, United States, United Kingdom

## Introduction

Many multicenter, clinical trials in acute coronary disease include patients from different countries, with different health care systems, resource bases, physician attitudes, and possibly different patterns of clinical practice. For example, physicians in the United States (US) judged more indications for catheterization and coronary artery bypass grafting as appropriate compared with those in the United Kingdom (UK).[1] These differences may impact on the overall outcome of a study and limit the applicability of the results in different clinical settings. For example, detailed analysis of the results from the Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries (GUSTO) trial[2] revealed a slightly better observed versus predicted mortality in the US patients. This may suggest that tissue plasminogen activator (TPA) is better than streptokinase only in the context of a higher rate of coronary angiography and revascularization procedures as seen in the US. To address this issue, we studied differences between populations randomized in the US and the UK in a multicenter, binational study of antithrombotic therapy in unstable angina and non-Q-wave infarction (ATACS).[3,4]

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## Methods

The ATACS study was a prospective, randomized, multicenter 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.[3,4] After approval by the hospital committees on human research, 358 eligible patients were randomized at four centers in the US and three in the UK. Recruitment started in December 1989 and ended in December 1991.

### Patient Selection; Inclusion/Exclusion Criteria

The inclusion/exclusion criteria for the study patients have been previously published,[3,4] and are presented in brief. Inclusion criteria: (1) over age 21; (2) presented to hospital with ischemic pain at rest caused by either unstable angina or non-Q-wave infarction; and (3) in addition to the above, evidence of underlying ischemic heart disease, for example, a positive stress test, prior percutaneous transluminal coronary angioplasty (PTCA) or coronary artery bypass graft (CABG), or electrocardiogram (ECG) changes. There were several exclusion criteria including but not limited to ischemic pain due to evolving Q-wave myocardial infarction (MI), left bundle-branch block, permanent pacemaker, or personal physician planning immediate intervention regardless of response to medication, and so forth.

Patients who were not taking aspirin prior to admission (Group A) were randomized to receive either aspirin alone 162.5 mg daily, or aspirin 162.5 mg daily plus anticoagulation with heparin and warfarin. Patients who were already taking aspirin (Group B) all received anticoagulation with heparin and warfarin, plus either controlled release aspirin 75 mg daily or conventional aspirin 75 mg daily. Anticoagulation was initiated with intravenous heparin to raise the activated partial thromboplastin time (aPTT) to twice normal for 3 to 4 days, followed by warfarin to raise prothrombin time to 1.3 to 1.5 times the control (international normalized ratio 2–3). In addition to trial antithrombotic therapy, antiantianginal therapy was administered to all patients according to a previously described algorithm,[3] and maximized as tolerated in order to titrate the systolic blood pressure to $\leq 130$ mmHg and the heart rate to $\leq 65$ beats/min. Patients were maintained on trial antithrombotic therapy for 12 weeks and were evaluated after hospital discharge at 3-week intervals for 12 weeks.

Primary end points (failure of trial therapy, MI, and death) were recorded throughout the 12-week study period. Trial therapy was considered to have failed if patients suffered recurrent angina at rest associated with ischemic ST-segment and T-wave changes on the ECG, or if recurrent pain resulted in an urgent intervention irrespective of ECG changes. Myocardial infarction was diagnosed if three criteria were fulfilled: (1) typical pain lasting more than 30 min, (2) a rise in serum creatinine kinase to twice normal or a rise of $\geq 50\%$ above the preceding sample to at least 1.5 times normal, and (3) new and persistent ST-T-wave changes or Q waves on the resting ECG. Perioperative infarction was diagnosed from new ECG changes and a rise in cardiac enzymes.

## Statistical Analysis

All analyses were performed on an intention-to-treat basis. Time to event for the different groups was displayed using Kaplan-Meier plots and a log rank statistic used to compare differences between patients treated in the US and UK. Categorical variables were compared with a chi-squared statistic and continuous variables with an unpaired *t*-test.

## Results

### Baseline Patient Demographics

Fifty-nine patients were recruited from four centers in the US and 299 from three centers in the UK. There were several significant differences in baseline patient demographics between the two countries (Table I). Patients recruited in the US were more likely to be female (45 vs. 28%), non-white (39 vs. 1%), and to have a prior history of hypertension (52 vs. 31%), diabetes (30 vs. 4%), or a previous coronary angiogram (30 vs. 18%). In addition, ischemic ECG changes on admission were more commonly found in US than in UK patients (75 vs. 58%), The remaining baseline characteristics analyzed were similar (Table I).

### End Points

Of the total of 358 patients, 93 (26%) experienced a primary end point. Similar proportions of patients in the US and in the UK reached a primary end point (Table II). In addition, the US and UK patients were also similar with respect to the nature and timing (Fig. 1) of these end points. Four (6.7%) US patients versus 26 (8.7%) UK patients experienced MI or death. In the US, the one death occurred after the patient stopped his trial antithrombotic therapy; in the UK, one of four deaths occurred after noncompliance with trial medication.

There were significant differences in the rates of withdrawal from trial therapy (Fig. 1) and coronary diagnostic and revascularization procedures (Table II) between the US and the UK. Significantly more patients underwent diagnostic coronary angiography in the US than in the UK (61 vs. 22%, $p < 0.001$); however, the extent of coronary disease was similar in the two countries (Table II). US patients were significantly more likely to undergo revascularization, in particular, to be revascularized in the absence of recurrent pain [11/16 (69%) vs. 7/17 (41%), $p < 0.001$]. These differences occurred for both PTCA and CABG. Both ischemic end points and coronary revascularization occurred "early" after presentation (Fig. 2); however, the majority of ischemic events had already occurred by Day 4, 1 to 2 days before most revascularizations.

The prescription of antianginal medication after randomization did not differ between the US and the UK with respect

TABLE I Baseline characteristics of patient population

| | UK (n = 299) | US (n = 59) | p Value |
|---|---|---|---|
| Demographics | | | |
| Male (%) | 72 | 55 | 0.01 |
| Mean age (years) | 62 | 63 | NS |
| Race (%): | | | |
| White | 99 | 61 | <0.001 |
| Black | 0 | 11 | |
| Other | 1 | 29 | |
| Prior clinical history (%) | | | |
| Family history of heart disease | 44 | 47 | NS |
| Current smoker | 30 | 32 | NS |
| Hypertension | 31 | 52 | 0.003 |
| Diabetes mellitus | 4 | 30 | <0.001 |
| Prior MI | 38 | 36 | NS |
| Prior angina | 59 | 57 | NS |
| Prior coronary angiogram | 18 | 30 | 0.04 |
| Prior PTCA or CABG | 10 | 14 | NS |
| Prior positive exercise test | 46 | 40 | NS |
| Characteristics on admission (%) | | | |
| Medication | | | |
| Current aspirin use | 60 | 59 | NS |
| Beta blockers | 38 | 29 | NS |
| Calcium-channel blockers | 31 | 39 | NS |
| Diagnosis | | | |
| Unstable angina | 75 | 85 | NS |
| Non-Q-wave MI | 19 | 13 | |
| Evolving Q-wave MI | 6 | 2 | |
| Systolic blood pressure (mmHg) | 130 | 122 | 0.02 |
| Diastolic blood pressure (mmHg) | 76 | 74 | NS |
| Cardiomegaly on x-ray (%) | 17 | 13 | NS |
| Admission electrocardiogram | | | |
| Ischemic ST-T-wave changes (%) | 58 | 75 | 0.02 |

*Abbreviations:* CABG = coronary artery bypass grafting, MI = myocardial infarction, PTCA = transluminal coronary artery angioplasty, UK = United Kingdom, US = United States, NS = not significant.

TABLE II End-points analysis: 12 weeks

| | UK (n = 299) | US (n = 59) | p Value |
|---|---|---|---|
| Primary end points | | | |
| Intention to treat (%) | 76 (25.4) | 17 (28.8) | NS |
| Recurrent pain with | | | |
| ECG changes | 41 (13.7) | 8 (13.6) | |
| Recurrent pain leading | | | |
| to revascularization | 9 (3.0) | 5 (8.5) | |
| Myocardial infarction | 17 (5.7) | 3 (5.1) | |
| Death | 9 (3.0) | 1 (1.7) | |
| Primary end points | | | |
| Efficacy (%) | 65 (21.7) | 16 (22.0) | NS |
| Secondary end-points | | | |
| Coronary revascularization (%) | 17 (5.7) | 16 (27) | |
| Prompted by pain (%) | 10 (59) | 5 (31) | |
| Not prompted by pain (%) | 7 (41) | 11 (69) | |
| PTCA | | | |
| Prompted by pain | 4 | 3 | |
| Not prompted by pain | 3 | 5 | |
| CABG | | | |
| Prompted by pain | 6 | 2 | |
| Not prompted by pain | 4 | 6 | |
| Diagnostic angiography | | | |
| No | 234 (78) | 23 (39) | |
| Yes | 65 (22) | 36 (61) | |
| >70% stenosis | | | |
| No vessel | 2 (3) | 6 (17) | |
| 1 Vessel | 26 (40) | 11 (31) | |
| 2 Vessels | 18 (28) | 8 (22) | |
| 3 Vessels | 12 (18) | 7 (19) | |
| Left main stem | 7 (11) | 4 (11) | |

Abbreviations as in Table I.

to beta blockers, calcium antagonist, and nitrates. The level of anticoagulation achieved, both on heparin and warfarin, was also similar in the two countries.

## Discussion

The ATACS study was designed to determine the role of different antithrombotic agents in the treatment of unstable angina and non-Q-wave infarction.[3,4] The present analysis focuses on differences in management and outcomes between patients recruited in the US and the UK. While antithrombotic medication and the prescription of antianginal medication was similar in the two countries, the decision to perform coronary angiography and revascularization procedures was left to the discretion of the individual cardiologist. Patients in the US were investigated with invasive coronary angiography and were revascularized more frequently than patients in the UK. However, this more aggressive invasive approach in the US had little impact on the cumulative end point event rate observed during the 12-week follow-up period.

While there were some differences in baseline demographic characteristics, such as more women and more diabetic patients in the US, the extent of disease as seen in the 101 patients who were catheterized was similar between the two countries.

The Veterans Administration Cooperative Study of medical versus surgical treatment for unstable angina also suggested that, overall, patients undergoing surgery showed no long-term advantage.[5] However, patients were not treated with aggressive antithrombotic therapy during the follow-up, and more recent analyses suggest a better outcome in the subset of patients with left ventricular dysfunction who had coronary bypass. The Thrombolysis in Myocardial Infarction (TIMI) IIIB investigators[6] randomized patients with unstable angina and non-Q-wave infarction to either early (18–48 h after presentation) coronary angiography and revascularization, or to a conservative strategy in which invasive interventions were only performed after failure of medical therapy. Recurrent in-

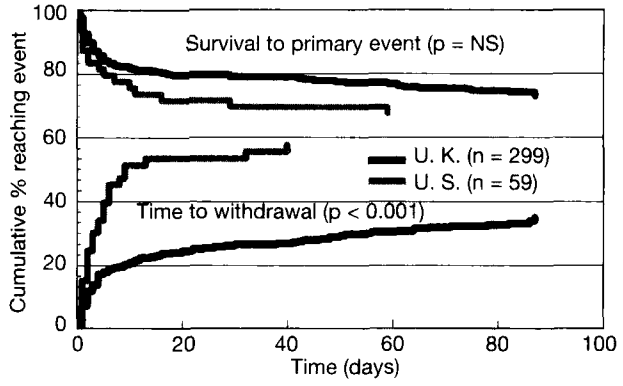


FIG. 1 Cumulative percent of patients free of any primary end point (upper panel), relative to the withdrawal rate from trial therapy (bottom half of the panel). NS = not significant.

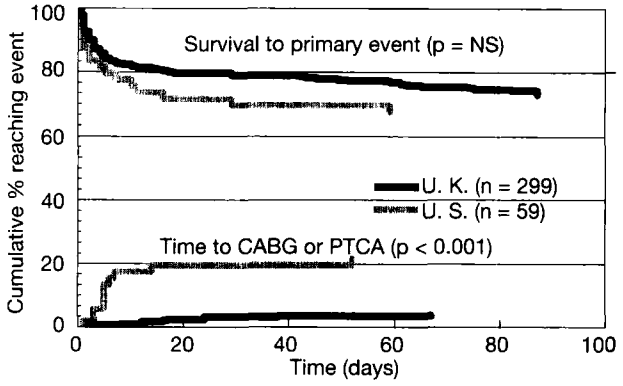


FIG. 2 Cumulative percent of patients free of any primary end point (upper panel), relative to the rate of coronary revascularization (bottom half of the panel). Both ischemic end points and coronary revascularization occurred early after presentation; however, the majority of ischemic events had already occurred by Day 4. CABG = coronary artery bypass grafting, PTCA = percutaneous transluminal coronary angioplasty, NS = not significant.

farction and mortality occurred with equal frequency in the two groups, and the investigators concluded that an early invasive strategy did not yield a more favorable outcome. However, after failure of initial therapy, a significant number of patients randomized to the conservative strategy did cross over to invasive interventions. More recently, Naylor *et al.*[7] analyzed outcomes in 8,517 patients waiting for CABG and concluded that patients "rarely (0.4% deaths) suffered critical events." There was no mention, however, of myocardial infarctions or rehospitalization, and many patients had stable angina. In the present ATACS analysis, six patients suffered MI after their primary end point of recurrent chest pain. Thus, the merits of early invasive versus conservative strategies remains unclear.

In the acute coronary syndrome of MI, Rouleau *et al.*[8] studied patients treated in the US or Canada and found that more US patients had revascularization procedures (31 vs. 12%), but that this had no influence on either the rate of reinfarction (13 vs. 14%), nor survival (77 vs. 78%). Patients in Canada, however, did have more angina during follow-up.[8] In contrast, Lotan *et al.*[9] observed an 86% decrease in recurrent infarction over 3 years of follow-up, using an early invasive rather than conservative approach in patients presenting with anterior non-Q-wave MI.

Based on the increased number of US patients with adverse risk factors (hypertension, diabetes, admission ischemic ST-T-wave changes), one would expect more US patients to experience recurrent ischemic end points and to require more revascularization. However, the subset of patients who underwent coronary angiography demonstrated no differences in the extent of coronary artery disease between the US versus the UK. Therefore, differences in revascularization rates in patients, either with or without recurrent angina, were not due to patients in the US having more extensive disease. It has already been observed that physicians in the US are more likely than UK physicians to feel that coronary angiography and coronary interventions are appropriate in patients whose angina has stabilized.[1] Differences in the availability of coronary angiography and revascularization in the US compared with the UK may be one explanation for the different rates of invasive procedures. Availability of on-site cardiac catheterization facilities was associated with higher rates of coronary angiography and revascularization in patients after MI treated in different regions in the US.[10–12] However, in spite of regional differences in procedures rates, there was no difference in outcome (reinfarction or death).[11,12]

## Limitations

It is possible that events occurring after the 12-week follow-up were missed. However, Wallentin and the RISC group[13,14] found that the risk of recurrent MI or death was highest early after presentation with unstable angina, particularly in the first 5 days. Although there was some difference in the rate of MI or death, no conclusions can be drawn because of the relatively small total number of patients enrolled. There was a disparity in the number of patients enrolled in the UK versus the US, but the nature of these hospitals was quite comparable: all were major teaching hospitals with long track records in clinical trials of patients with coronary artery disease. While there was a waiting time of several months for UK patients stabilized after unstable angina who were referred for elective surgery, there were no deaths in this subgroup. Finally, it is possible that the early revascularizations done in the US were not performed early enough to affect the clinical outcome.

## Conclusions

This study of patients with acute coronary syndromes has confirmed that patients receive different management in different countries despite a uniform study protocol. A more intensive diagnostic and therapeutic approach, however, may

have little impact on primary outcome variables. The interpretation of multicenter studies should take these differences into account.

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