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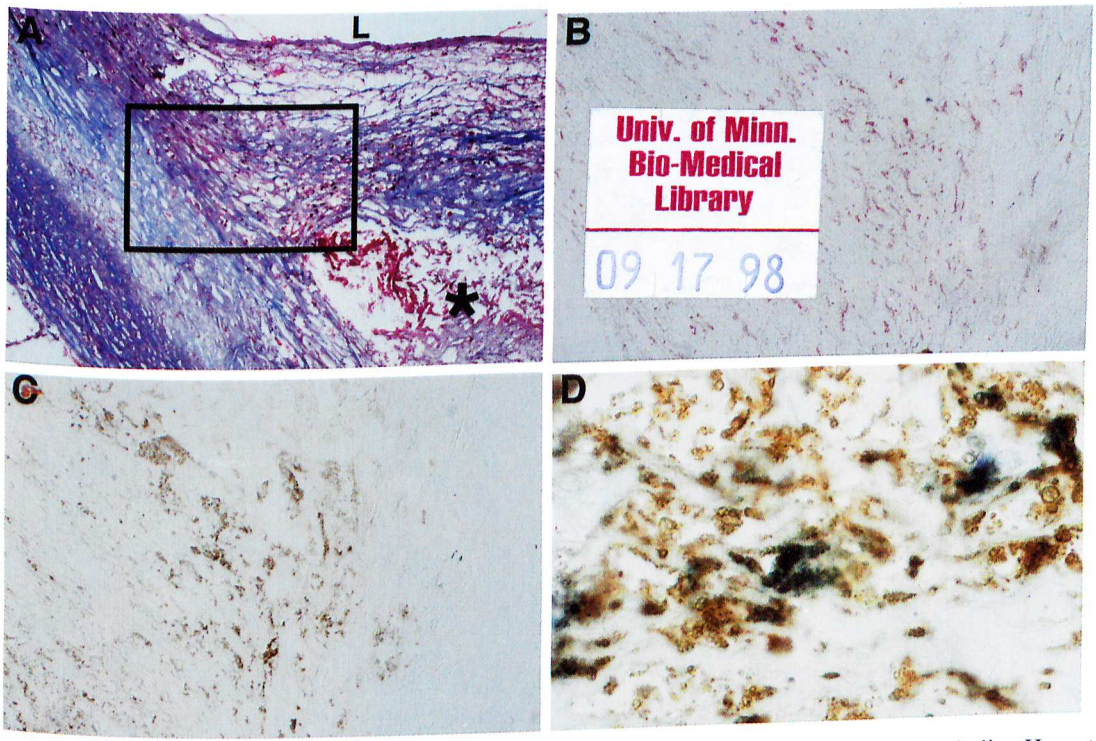

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Editorial

Brief Rapid Communication

Clinical Investigation and Reports*

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Long-Term Oral Anticoagulant Therapy in Patients With Unstable Angina or Suspected Non–Q-Wave Myocardial Infarction

Organization to Assess Strategies for Ischemic Syndromes (OASIS) Pilot Study Results

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Background—Patients with acute ischemic syndromes (AIS) suffer high rates of recurrent ischemic events despite aspirin treatment. Long-term therapy with oral anticoagulants in addition to aspirin may reduce this risk. We studied the effects of long-term warfarin at 2 intensities in patients with AIS without ST elevation in 2 consecutive randomized controlled studies.

Methods and Results—In phase 1, after the cessation of 3 days of intravenous antithrombotic therapy, 309 patients were randomized to receive fixed low-dose (3 mg/d) warfarin for 6 months that produced a mean international normalized ratio (INR) of 1.5±0.6 or to standard therapy. Eighty-seven percent of patients received aspirin in both groups. The rates of cardiovascular (CV) death, new myocardial infarction (MI), and refractory angina at 6 months were 6.5% in the warfarin group and 3.9% in the standard therapy group (relative risk [RR], 1.66; 95% CI, 0.62 to 4.44; $P=0.31$). The rates of death, new MI, and stroke were 6.5% in the warfarin group and 2.6% in the standard therapy group (RR, 2.48; 95% CI, 0.80 to 7.75; $P=0.10$). The overall rate of rehospitalization for unstable angina was 21% and did not differ significantly between the groups. Four patients in the warfarin group (2.6%) and none in the control group experienced a major bleed (RR, 2.48; 95% CI, 0.80 to 7.75), and there was a significant excess of minor bleeds in the warfarin group (14.2% versus 2.6%; RR, 5.46; 95% CI, 1.93 to 15.5; $P=0.001$). In phase 2, the protocol was modified, and 197 patients were randomized <48 hours from the onset of symptoms to receive warfarin at an adjusted dose that produced a mean INR of 2.3±0.6 or standard therapy for 3 months. Eighty-five percent received aspirin in both groups. The rates of CV death, new MI, and refractory angina at 3 months were 5.1% in the warfarin group and 12.1% in the standard group (RR, 0.42; 95% CI, 0.15 to 1.15; $P=0.08$). The rates of all death, new MI, and stroke were 5.1% in the warfarin group and 13.1% in the standard therapy group (RR, 0.39; 95% CI, 0.14 to 1.05; $P=0.05$). Significantly fewer patients were rehospitalized for unstable angina in the warfarin group than in the control group (7.1% and 17.2%, respectively; RR, 0.42; 95% CI, 0.18 to 0.96; $P=0.03$). Two patients in the warfarin group and 1 in the control group experienced a major bleed, and there was a significant excess of minor bleeds in the warfarin group (28.6% versus 12.1%; RR, 2.36; 95% CI, 1.37 to 4.36; $P=0.004$).

Conclusions—Long-term treatment with moderate-intensity warfarin (INR, 2.0 to 2.5) plus aspirin but not low-intensity warfarin (INR, 1.5) plus aspirin appears to reduce the rate of recurrent ischemic events in patients with AIS without ST elevation. (***Circulation***. **1998;98:1064-1070.**)

Key Words: warfarin ■ ischemia ■ thrombosis ■ angina

Acute ischemic syndromes (AIS) represent a continuum of acute myocardial ischemia (MI), which includes acute transmural MI with ST elevation, MI without ST elevation, and unstable angina. In patients with unstable angina, although short-term intravenous heparin and aspirin are effective[1] in reducing the incidence of cardiovascular (CV) death and new MI, patients continue to suffer recurrent ischemic events over the long term. It is believed that these recurrent ischemic events are a consequence of an ongoing thrombotic stimulus,[2] a concept supported by the long-term benefits of aspirin therapy.[3] Despite the use of aspirin, however, the rate of recurrent ischemic events remains high. For example, in the OASIS registry, 9.5% of patients suffered CV death, MI, or stroke in the 6 months after their initial

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hospitalization for unstable angina,[4] and an additional 7.2% were rehospitalized for unstable angina. Furthermore, markers of thrombin generation (F 1.2) remain elevated for months in patients with unstable angina, indicating an ongoing thrombotic stimulus.[5,6] Therefore, the combination of oral anticoagulants to suppress activation of the coagulation system and aspirin to block platelet activation may be better than aspirin alone for long-term reduction of ischemic events in patients with AIS.

Therefore, we tested first the efficacy, feasibility, and safety of fixed-dose low-intensity warfarin and then, in a second trial, the effects of moderate-intensity warfarin (international normalized ratio [INR], 2 to 2.5) in patients with AIS without ST elevation.

Methods

The 2 OASIS pilot studies were randomized trials of hirudin (low dose, 0.20-mg/kg bolus, 0.1-mg · kg^{-1} · h^{-1} infusion; medium dose, 0.4-mg/kg bolus, 0.15-mg · kg^{-1} · h^{-1} infusion) versus heparin (5000-U bolus, 1200 U/h) and warfarin versus standard therapy in patients with AIS without ST elevation using a partial 2×2 factorial design. Results of the safety and efficacy for heparin and different doses of hirudin have previously been published.[7] All eligible patients who participated in the OASIS pilot study were approached for consent to participate in the warfarin substudy. Patients were eligible if they were admitted to hospital within 12 hours of an episode of chest pain suspected to be due to unstable angina or MI without ST-segment elevation on their admission ECG. The diagnosis of unstable angina was based on symptoms of angina that were worsening or occurring with minimal activity associated with either current ECG evidence of ischemia or previously documented objective evidence of coronary artery disease. Patients who suffered major bleeding on or within 48 hours of the initial intravenous infusion, those who had a clear clinical indication for warfarin treatment, and those in whom CABG surgery was planned before or within 1 week of hospital discharge were excluded.

In phase 1 of the study, consenting patients were randomized to a fixed dose of warfarin (3 mg), which was aimed to achieve a low-intensity level of anticoagulation (target INR, 1.5) or standard therapy for 180 days. Warfarin therapy was started 5 to 7 days after randomization to the initial 72-hour intravenous infusion of heparin or hirudin because of concerns about potential hazards of combining hirudin with warfarin. The recommended loading dose for warfarin was 10 mg on day 1, followed by a maintenance dose of 3 mg/d for 6 months. Aspirin treatment was advised for all participants. INR monitoring was recommended at 3 to 6 days after initiation of warfarin and at 2 weeks and 1, 3, and 6 months or more frequently at the discretion of the responsible physician.

In phase 2, consenting patients were randomized to moderate-intensity anticoagulation (target INR, 2 to 2.5) by adjusting the INR or standard therapy for 3 months. Warfarin therapy was initiated 12 to 24 hours after the initiation of the intravenous infusion of heparin or hirudin. The recommended dose was 10 mg on day 1, 3 mg on day 2, and 3 mg on day 3. Thereafter, dose adjustments of warfarin were left to the discretion of the treating physicians to target an INR value of 2 to 2.5. The goal was to increase the INR into the therapeutic range (INR, 2 to 2.5) by the time of hospital discharge. However, the intravenous infusion was not continued >72 hours if this target was not achieved. Aspirin treatment was advised for all patients. INR monitoring was done on days 2 and 3 after starting warfarin; on the day of hospital discharge; and at 2 weeks, 35 days, and 2 and 3 months or as often as indicated for clinical reasons. Data on the following outcomes were documented: (1) CV death, (2) new MI as evidenced by recurrent symptoms with either new ECG changes or new enzyme elevation, (3) refractory angina, (4)severe angina, and [illegible] ring despite "optimum" medical treatment and requiring an additional intervention such as thrombolytic therapy for threatened MI, insertion of an intra-aortic balloon pump, cardiac catheterization within 24 hours, or transfer to a tertiary care center within 48 hours of the onset of pain/symptoms. Optimum treatment was defined as at least 2 antianginal treatments, 1 of which should be an intravenous nitrate (unless contraindicated). After the initial hospitalization, refractory angina was defined as readmission to hospital with a primary diagnosis of unstable angina leading to a cardiac procedure. Severe angina was defined as recurrent ischemic chest pain lasting >5 minutes while the patient was on optimal therapy with documentation of new ECG changes associated with the episode of chest pain. Rehospitalization with unstable angina was defined as all readmissions to the hospital (after initial hospitalization for study entry) with a diagnosis of unstable angina that was associated with typical ECG changes on the admission ECG or was confirmed as the primary diagnosis on the discharge summary by the most responsible physician. The safety outcomes monitored included stroke and bleeding. Stroke was defined as the presence of a new focal neurological deficit thought to be vascular in origin with signs or symptoms lasting >24 hours, and strokes were further classified as intracranial hemorrhage or ischemic infarction. Bleeding was classified as major if the event was fatal or life threatening, was permanently or significantly disabling, or required transfusion of packed red blood cells or surgical treatment. All other bleedings were classified as minor.

Blinded Central Adjudication of Events

All major clinical end points up to 35 days, including death (classified by cause), MI, refractory angina, readmission for unstable angina, major bleed, and stroke, were initially adjudicated by a central committee of clinicians blinded to the treatment allocation using standard definitions. An overall agreement rate of 75% was observed between reported and adjudicated events for all outcomes. The rate of agreement for CV death, MI, and strokes was 95%.[8] Because there were no differences in the estimates of the treatment effects using either the classification of the investigating physician or central adjudication,[8] events that occurred after 35 days were not formally adjudicated in this pilot study.

Study Organization

Patients were recruited from 31 clinical centers in Canada. Data were transmitted by use of the DataFax system to the Canadian Cardiovascular Collaboration Project Office located at the Preventive Cardiology and Therapeutics Program of the Hamilton Civic Hospitals Research Center, McMaster University. All patients gave written informed consent, and the protocol was approved by the Institutional Review Board of each hospital. Key safety and efficacy data were reviewed by an independent Data and Safety Monitoring Board during the course of the study.

Statistical Analysis

The primary outcome for the comparison for efficacy was the composite of CV death, new MI, and refractory angina. Secondary comparisons included the composite of CV death, new MI, refractory and severe angina, and rehospitalization for unstable angina. The major safety outcomes were stroke and bleeding. Individual and cluster outcomes were compared by use of Mantel-Haenszel χ^2 tests. The main goal of the study was to explore feasibility, the safety effects on the INR, and the preliminary clinical efficacy of warfarin versus standard therapy. Therefore, the study was not formally powered to detect significant differences in clinical outcomes.

Results

Phase 1: Low-Intensity Fixed-Dose Warfarin

In phase 1, conducted from July 15, 1994, to August 30, 1995, 601 patients were randomized to intravenous therapy

TABLE 1. Major Reasons for Not Randomizing Patients Into the Warfarin Substudy

	Phase 1	Phase 2
Total randomized to first part of trial,* n	601	308
Randomized to warfarin substudy, n	309	197
Reasons among those not randomized, n	292	111
Planned interventional cardiac procedure (Cath/CABG/PTCA)*	97 (33%)	61 (55%)
No significant CAD	34 (11.6%)	5 (4.5%)
Concern about bleeding	18 (6.2%)	11 (9.9%)
Patient refusal	32 (11%)	5 (4.5%)
Physician refusal	20 (6.8%)	9 (8.1%)
Early discharge or transfer	29 (9.9%)	0
Suspected noncompliance	12 (4.1%)	1 (0.9%)
Difficult to monitor INR	10 (3.4%)	0
Missed randomization window	1 (0.3%)	8 (7.2%)
Event (including major bleed)	14 (4.8%)	3 (2.7%)
Indication for long-term warfarin	19 (6.5%)	5 (4.5%)
Other	6 (2.0%)	3 (2.7%)

Cath indicates cardiac catheterization.
*Initial randomization to heparin or hirudin.

dose of warfarin, and 154 to standard therapy. Approximately 87% of these patients received aspirin (median dose, 325 mg/d). Two hundred ninety-two patients were not randomized into the warfarin substudy. The reasons for not randomizing patients into the warfarin substudy are found in Table 1. The baseline characteristics of all patients are found in Table .

Warfarin Dose and INR

The median time to receipt of the first dose of warfarin was 6 days (range, 5 to 8 days) after initial entry into the study. At

TABLE 2. Baseline Characteristics of Patients

Variable	Standard Therapy	Warfarin	Not Randomized
Phase 1			
Number	154	155	292
Mean age, y	65±12	63±10	65±11
Women	49 (32%)	53 (34%)	98 (34%)
Unstable angina*	128 (83%)	129 (83%)	257 (88%)
Non–Q-wave MI*	26 (17%)	26 (17%)	35 (12%)
Abnormal ECG	134 (87%)	136 (88%)	237 (81%)
IV heparin given†	56 (36%)	54 (35%)	77 (26%)
Phase 2			
Number	99	98	111
Mean age, y	64±12	64±12	62±12
Women	30 (30%)	36 (37%)	34 (31%)
Unstable angina*	79 (80%)	82 (84%)	96 (86%)
Non–Q-wave MI*	13 (13%)	9 (9%)	9 (8%)
Abnormal ECG	79 (80%)	73 (74%)	60 (72%)

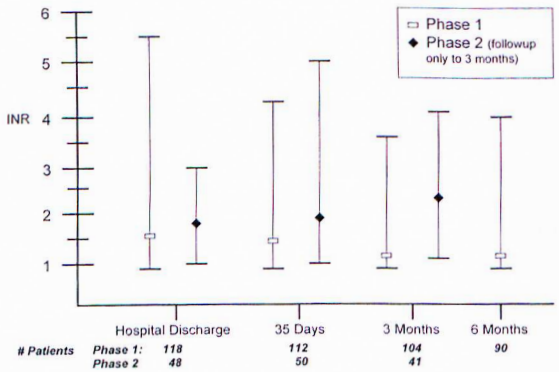

Figure 1. Distribution of INR values at follow-up visits: median and interquartile range.

hospital discharge, the mean INR was 1.68 (±0.67). Over the 6 months of follow-up, the mean INR was 1.48 (±0.63) (Figure 1). Of the patients who continued warfarin throughout the study, the mean dose was 3 mg/d.

Efficacy

Ten patients (6.5%) in the warfarin group compared with 6 (3.9%) in the standard therapy group experienced a primary outcome event (CV death, new MI, or refractory angina; relative risk [RR], 1.66; 95% CI, 0.62 to 4.44; $P=0.31$). During the follow-up period, 27 patients (17.4%) in the warfarin group suffered a secondary outcome event (CV death, new MI, or refractory or severe angina) compared with 21 patients (13.6%) in the standard therapy group (RR, 1.28; 95% CI, 0.76 to 2.16; $P=0.40$). Thirty-two patients in both the warfarin group (21%) and standard therapy group (21%) were rehospitalized for unstable angina over the 6 months of follow-up (RR, 0.99; 95% CI, 0.64 to 1.54; $P=0.97$). The rate of all deaths, new MI, and stroke was 6.5% (10 of 155) in the warfarin group compared with 2.6% (4 of 154) in the standard therapy group (RR, 2.48; 95% CI, 0.80 to 7.75; $P=0.10$; Table 3).

Interventional Procedures

Before randomization into the warfarin substudy, 44 of 155 patients (28%) randomized to warfarin had an interventional procedure (cardiac catheterization, PTCA, or CABG) compared with 42 of 154 (27%) in the standard group. After randomization, procedures were performed on 29 (18.7%) of 155 patients in the warfarin group (3 in hospital and 26 during the 6-month follow-up) compared with 35 (23%) of 154 in the standard group (4 in hospital and 31 during the 6-month follow-up). The procedure rate in the nonrandomized group was 207 (71%) of 292 overall, with 153 occurring during the initial hospitalization and 54 occurring during the 6-month follow-up.

Safety

Four patients (2.6%) randomized to warfarin suffered a major bleed compared with no patients in the standard therapy arm. Of the 4 major bleeds, 2 were gastrointestinal hemorrhages and 2 were macroscopic hematuria. Three patients were

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