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

Sonia S. Anand, MD, MSc, FRCP; Salim Yusuf, DPhil, FRCP; Janice Pogue, MSc; Jeffrey I. Weitz, MD, FRCP; Marcus Flather, MBBS, MRCP; for the OASIS Pilot Study Investigators

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

A cute 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 effective1 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
hospitalization for unstable angina, 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. 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 anticoagulation (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. 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 (5) rehospitalization with unstable angina. Refractory angina was defined as a new episode of ischemic chest pain (with documented characteristic ECG changes during pain) lasting >5 minutes occurring 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 endpoints 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%. Because there were no differences in the estimates of the treatment effects using either the classification of the investigating physician or central adjudication, 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 χ² 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 with heparin or 1 of 2 doses of hirudin. Of these, 309 patients were randomized into the warfarin substudy, 155 to low fixed
TABLE 1. Major Reasons for Not Randomizing Patients Into the Warfarin Substudy

<table>
<thead>
<tr>
<th>Reason</th>
<th>Phase 1</th>
<th>Phase 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Planned interventional cardiac procedure (Cath/CABG/PTCA)*</td>
<td>97 (33%)</td>
<td>61 (55%)</td>
</tr>
<tr>
<td>No significant CAD</td>
<td>34 (11.6%)</td>
<td>5 (4.5%)</td>
</tr>
<tr>
<td>Concern about bleeding</td>
<td>18 (6.2%)</td>
<td>11 (9.9%)</td>
</tr>
<tr>
<td>Patient refusal</td>
<td>32 (11%)</td>
<td>5 (4.5%)</td>
</tr>
<tr>
<td>Physician refusal</td>
<td>20 (6.8%)</td>
<td>9 (8.1%)</td>
</tr>
<tr>
<td>Early discharge or transfer</td>
<td>29 (9.9%)</td>
<td>0</td>
</tr>
<tr>
<td>Suspected noncompliance</td>
<td>12 (4.1%)</td>
<td>1 (0.9%)</td>
</tr>
<tr>
<td>Difficult to monitor INR</td>
<td>10 (3.4%)</td>
<td>0</td>
</tr>
<tr>
<td>Missed randomization window</td>
<td>1 (0.3%)</td>
<td>8 (7.2%)</td>
</tr>
<tr>
<td>Event (including major bleed)</td>
<td>14 (4.8%)</td>
<td>3 (2.7%)</td>
</tr>
<tr>
<td>Indication for long-term warfarin</td>
<td>19 (6.5%)</td>
<td>5 (4.5%)</td>
</tr>
<tr>
<td>Other</td>
<td>6 (2.0%)</td>
<td>3 (2.7%)</td>
</tr>
</tbody>
</table>

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 2.

**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 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. 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 taking aspirin concomitantly. One major bleed occurred in a patient on aspirin whose INR was above the specified therapeutic range (INR, 10). The rate of minor bleeding was
14.2% in the warfarin group and 2.6% in the standard therapy group (RR, 5.46; 95% CI, 1.93 to 15.5; P = 0.001; Table 3).

**Compliance With Warfarin**

Of the 155 patients randomized to warfarin, 45 (29%) discontinued therapy before the end of the 6-month follow-up. Of these, 13 patients (29%) failed to continue warfarin after their initial hospital discharge (the reasons for this were not recorded), 11 (24%) had a planned interventional procedure, 7 (15%) experienced bleeding/medication intolerance, and 7 (15%) refused to continue with the study drug.

**Phase 2**

In phase 2, conducted from December 6, 1995, to May 22, 1996, 308 patients were randomized to intravenous therapy with heparin or 1 of 2 doses of hirudin. Of these, 197 patients were randomized to the warfarin substudy: 98 patients were randomized to moderate-intensity warfarin (INR, 2.0 to 2.5), and 99 patients received standard therapy. All patients were followed for 3 months. Eighty-five percent of patients received aspirin (median dose, 325 mg/d). The reasons for not entering the warfarin substudy are found in Table 1. The baseline characteristics of all patients are found in Table 2.

**Warfarin Dose and INR**

The median time from the start of the intravenous infusion to receipt of the first dose of warfarin (10 mg) was 26 hours (range, 12 to 48 hours). During the period when patients were on intravenous antithrombotic therapy and warfarin, 3 patients (4%) achieved INR values >4, and all of these patients were receiving medium-dose hirudin. None of these patients experienced bleeding complications. By the time of first hospital discharge, the mean INR was 1.7 (±0.7), and during the follow-up period, the mean INR was 2.3±0.6 (Figure 1). The mean daily dose of warfarin was 4 mg.

**Efficacy**

Five patients (5.1%) in the warfarin group compared with 12 (12.1%) in the standard therapy group experienced a primary outcome event (CV death, new MI, or refractory angina) (RR, 0.42; 95% CI, 0.15 to 1.15; P = 0.08; Figure 2). Ten patients (10.2%) in the warfarin group compared with 20 (20.2%) in the standard therapy group experienced a secondary event (CV death, new MI, or refractory or severe angina) (RR, 0.51; 95% CI, 0.25 to 1.02; P = 0.05). Seven patients (7.1%) in the warfarin group compared with 17 (17.2%) in the standard therapy group were rehospitalized for unstable angina over the 3-month follow-up period (RR, 0.42; 95% CI, 0.18 to 0.96).}

### Table 3. Results of the OASIS

<table>
<thead>
<tr>
<th>Event Cluster</th>
<th>Warfarin (n=155), n (%)</th>
<th>Standard (n=154), n (%)</th>
<th>RR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phase 1: Low-intensity warfarin (INR, 1.5) vs control</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CV death, MI, refractory angina*</td>
<td>10 (6.5)</td>
<td>6 (3.9)</td>
<td>1.66 (0.62–4.44)</td>
<td>0.31</td>
</tr>
<tr>
<td>CV death, MI, refractory angina, severe angina†</td>
<td>27 (17.4)</td>
<td>21 (13.6)</td>
<td>1.28 (0.76–2.16)</td>
<td>0.40</td>
</tr>
<tr>
<td>Rehospitalization for unstable angina†</td>
<td>32 (21)</td>
<td>32 (21)</td>
<td>0.99 (0.64–1.54)</td>
<td>0.97</td>
</tr>
<tr>
<td>Any stroke</td>
<td>0</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All death, MI, stroke</td>
<td>10 (6.5)</td>
<td>4 (2.6)</td>
<td>2.48 (0.80–7.75)</td>
<td>0.10</td>
</tr>
<tr>
<td>Major bleeds</td>
<td>4 (2.6)</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Minor bleeds</td>
<td>22 (14.2)</td>
<td>4 (2.6)</td>
<td>5.46 (1.93–15.5)</td>
<td>0.001</td>
</tr>
<tr>
<td>Phase 2: Moderate-intensity warfarin (INR, 2.3) vs control</td>
<td>(n=98)</td>
<td>(n=99)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CV death, MI, refractory angina*</td>
<td>5 (5.1)</td>
<td>12 (12.1)</td>
<td>0.42 (0.15–1.15)</td>
<td>0.08</td>
</tr>
<tr>
<td>CV death, MI, refractory angina, severe angina†</td>
<td>10 (10.2)</td>
<td>20 (20.2)</td>
<td>0.51 (0.25–1.02)</td>
<td>0.051</td>
</tr>
<tr>
<td>Rehospitalization for unstable angina†</td>
<td>7 (7.1)</td>
<td>17 (17.2)</td>
<td>0.42 (0.18–0.96)</td>
<td>0.03</td>
</tr>
<tr>
<td>Ischemic stroke‡</td>
<td>0</td>
<td>2 (2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All death/new MI/strokes§</td>
<td>5 (5.1)</td>
<td>13 (13)</td>
<td>0.39 (0.14–1.05)</td>
<td>0.05</td>
</tr>
<tr>
<td>Major bleeds</td>
<td></td>
<td></td>
<td>2 (2.0)</td>
<td>1 (1.0)</td>
</tr>
<tr>
<td>Minor bleeds</td>
<td>28 (28.6)</td>
<td>12 (12.1)</td>
<td>2.36 (1.37–4.36)</td>
<td>0.004</td>
</tr>
</tbody>
</table>

*Primary outcome.
†Secondary outcome.
‡There were no hemorrhagic strokes.
§Other outcome of interest.
||Need for transfusions.
0.96; P=0.03; Table 3). There was 1 noncardiac death in the standard therapy group. The rate of all deaths, MI, and stroke for patients in the warfarin group was 5.1% (5 of 98) compared with 13.1% (13 of 99) in the standard group (RR, 0.39; 95% CI, 0.14 to 1.05; P=0.05).

Interventional Procedures

The procedure rate (cardiac catheterization, PTCA, or CABG) was 52 of 98 (53%) in the warfarin group, 65 of 99 (66%) in standard group, and 81 of 111 (73%) in the nonrandomized group. In the warfarin group, 34 of 52 (65%) of the procedures were performed in hospital compared with 33 of 65 (51%) in the standard group and 59 of 81 (73%) in the nonrandomized group.

Safety

Two patients (2.0%) randomized to warfarin suffered a major bleed compared with 1 patient (1.0%) in the standard therapy arm (RR, 2.02; 95% CI, 0.19 to 22; P=0.56). All patients were receiving aspirin. One patient suffered a retroperitoneal hemorrhage on day 3 after randomization while receiving intravenous heparin and had received an initial dose of warfarin, and the second patient suffered a spontaneous subdural hematoma after hospital discharge (day 26) while on warfarin (INR, 1.8). The major bleed in the standard therapy group occurred with the insertion of an intra-aortic balloon pump after a cardiac catheterization. The rates of minor bleeding were 28.6% in the warfarin group and 12.1% in the standard therapy group (RR, 2.44; 95% CI, 1.37 to 4.36; P=0.004, respectively; Table 3.

Compliance

Of those patients randomized to warfarin, 47 (48%) maintained treatment throughout the follow-up period of 3 months, i.e., the end of study, without interruption. By 3 months, 51 (52%) had discontinued warfarin permanently. The main reasons for discontinuing warfarin included planned interventional cardiac procedure in 19 (37%), concern about bleeding/medication intolerance in 12 (23%), or no objective evidence of coronary artery disease in 8 (16%).

Discussion

In phase 1, in which the effect of low-intensity, fixed-dose warfarin (INR, 1.5) and aspirin compared with standard therapy (aspirin alone) started after the cessation of intravenous heparin or hirudin and given for 6 months was studied, there were no apparent benefits of warfarin compared with standard therapy (aspirin alone). A trend toward increased major bleeds was observed in the warfarin-treated patients, and a substantial increase in the rate of minor bleeds (RR, 5.46; P<0.001) was observed with warfarin. The excess in bleeding rates despite only a modest mean INR prolongation may reflect inadequate INR monitoring in this phase of the study, which led to marked prolongation of the INR in a few patients.

Because of the disappointing results of phase 1 and similar results from 2 larger trials,2,3,10 4 modifications to the protocol were made in phase 2 of the OASIS pilot study. First, we evaluated the efficacy of moderate-intensity warfarin adjusted to an INR of 2 to 2.5 and aspirin compared with standard therapy (aspirin alone). Second, warfarin was started during the intravenous infusion of heparin or hirudin. Third, the recommended frequency of INR monitoring was increased. Fourth, the duration of treatment was reduced to 3 months. These differences likely accounted for the differences observed in the control event rate between phases 1 (3.9%) and 2 (12.1%). Despite the randomization of only 197 patients, promising trends in support of the efficacy of warfarin (INR, 2.3) in preventing recurrent ischemic events and rehospitalization for unstable angina over 3 months were observed. By 90 days, the relative reduction in risk of the primary outcome (composite of CV death, new MI, and refractory angina) was 58% (P=0.08). In addition, a 49% relative reduction in risk of CV death, new MI, and refractory and severe angina (P=0.05) and a 58% reduction of rehospitalization for unstable angina (P=0.05) were observed.

No significant difference in the rate of major bleeding was observed between the groups. However, the absolute rates of major bleeds were low, and even a 2-fold difference in major bleed rates may have been missed. A significant increase in the rate of minor bleeding in the warfarin-treated patients (RR, 2.4; P=0.003) was observed, although compared with phase 1, the excess risk was lower in patients treated with moderate-intensity than in those treated with low-intensity warfarin. The lower RR of bleeding in phase 2 may be a chance finding or alternatively may be related to the more frequent INR monitoring during the second phase of the pilot. Because the comparisons between the first and second phases were not randomized, any differences observed should be viewed with caution.

The results of the phase 1 comparison of low-intensity warfarin are consistent with the recent evidence from the CARS2 and Post-Coronary Artery Bypass Graft10 studies in which fixed doses of warfarin given together with aspirin were not found to be more effective than aspirin alone.

Previous trials of patients after MI indicate that moderate-intensity warfarin is both efficacious and safe.14-16 These trials were conducted without aspirin use but demonstrated a 35% to 40% RR reduction in major vascular events. Three randomized controlled trials have demonstrated the benefits of variable-intensity warfarin (INR range, 1.5 to 4.5) in the prevention of thromboembolic events and stroke in patients with atrial fibrillation.14-16 The recent SPAF-III trial in which high-risk patients with chronic atrial fibrillation were randomized to warfarin (INR, 2 to 3) or aspirin plus fixed low-dose warfarin (INR, 1.2 to 1.4) demonstrated that moderate-intensity warfarin alone was more effective than low-dose warfarin and aspirin and resulted in a 67% risk reduction in ischemic strokes.17

Furthermore, trials in patients with unstable angina in which moderate-intensity warfarin was combined with aspirin demonstrate promising results18,19 that are consistent with the results of phase 2 of the OASIS pilot study. The ATACS trial compared the combination of moderate-intensity warfarin (INR, 2 to 3) and aspirin with aspirin alone; the combination produced a 53% RR reduction in recurrent ischemic events (CV death, MI, and recurrent angina) at 3 months (P=0.06).18
Challenge of Warfarin Use in Patients With AIS

A reluctance by physicians to treat patients with AIS with long-term warfarin therapy was observed in this trial. The primary reason for this was the possibility that patients may undergo an interventional cardiac procedure such as cardiac catheterization, PTCA, or CABG surgery. Starting warfarin in this group of patients is considered by many physicians to be inconvenient, particularly if the effects of warfarin need to be reversed. The belief that revascularization may obviate the need for future warfarin therapy by reducing the risk of future death or myocardial infarction may also be relevant. However, in 3 moderate-sized randomized trials—TIMI-IIb,\textsuperscript{20} TIMI-IIIB,\textsuperscript{21} and VanQWISH\textsuperscript{22}—there was no impact in the prevention of death or MI with a strategy of routine cardiac catheterization with liberal revascularization compared with a more conservative strategy. Second, poor compliance of patients who were randomized to warfarin was observed. The main reasons for discontinuation of warfarin therapy were planned invasive cardiac procedures, minor bleeding episodes, and patient inconvenience. The proportion of withdrawals in our study is similar to the rate of warfarin withdrawals reported in the ATACS trial, in which 45% of patients withdrew from warfarin before the 3-month follow-up.\textsuperscript{16}

Study Limitations

Both of these studies were pilot studies conducted to assist in the design of a more definitive and larger study. Despite the small numbers of patients, the lack of benefit with warfarin in the first study is consistent with the results of 2 larger trials.\textsuperscript{7,8} The promising results of our second pilot are consistent with trials of moderate-intensity warfarin in unstable angina.\textsuperscript{16} Nevertheless, the apparent large treatment effect sizes in both studies in unstable angina may be exaggerated by the play of chance, and it may be prudent to expect more moderate differences in a larger study. A second caution is that these studies were open, and all of the events were not adjudicated. However, a detailed analysis of the results indicated no differences in effects between the adjudicated and unadjudicated analyses, with $>95\%$ concordance for important outcomes such as death, MI, or stroke.\textsuperscript{6}

Our promising experience in phase 2 of the OASIS pilot study justifies more extensive evaluation of the moderate-intensity warfarin. Therefore, we have embarked on a larger study (OASIS-2) in which we expect 4000 patients to be randomized to moderate-intensity warfarin (INR, 2 to 3) and aspirin versus aspirin alone after receiving intravenous anti-thrombin therapy.

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Appendix

List of Investigators: Clinical Centers

Camp Hill Medical Center, Halifax: I. Bata, M. MacFarlane; CHR de l’Amiante, Thefford Mines: J. Campeau, F. Ouimet; Chedoke-McMaster Hospital, Hamilton: A. Panju, G. Woodcock; General Hospital Health Science Center, St John’s: B. Sussex, L. St Croix; General Hospital/St Joseph’s Hospital, Thunder Bay: C. Lai, K. Kwiatkowski; Greater Niagara General Hospital, Niagara Falls: Y.K. Chan, D. Zanio; Hamilton General Hospital, Hamilton: J. Gill, C. Odell; Henderson General Hospital, Hamilton: T. Boyne, G. Cappelli; Hospital de Sept-Iles, Sept Iles: G. Bouchard, M. Fournier; Hotel-Dieu de Levis, Levis: P. Auger, F. Dumont; Lebidge Regional Hospital, Lethbridge: R. Schuld, M. Bartoshyk; Lions Gate Hospital, North Vancouver: K. Woo, R. Moore; Montreal Heart Institute, Montreal: P. Theroux, A.M. Rouette; Plains Health Center, Regina: N. Habib, Denis Jones; Royal Columbian Hospital, New Westminster: D. Rupka, D. Hilbich; Royal University Hospital, Saskatoon: J. Lopez, P. Kuny; St Boniface Hospital, Winnipeg: A. Morris, M. Schillberg; St Joseph’s Hospital, London: G. Wisenberg, J. Occhipinti; Sudbury Memorial Hospital, Sudbury: S. Nawaz, L. Chomey; Sunnybrook HSC, North York: C. Joyner, K. Freskiv; Surrey Memorial Hospital, Surrey: P. Polasek, L. Breakwell; Toronto Hospital, Toronto: P. Daly, C. Johnson; University Hospital, London: W. Kostuk, R. Osalkin; University of Ottawa Heart Institute, Ottawa: J.F. Marquis, S.A. Kerns; General Hospital of Port Arthur, Port Arthur: C. Lai, K. Kwiatkowski; St Joseph’s Hospital, Hamilton: M. Sullivan, M. Lawrence; Concordia Hospital, Winnipeg: H. Smith, M. Sokulski; McKeller General Hospital, Thunder Bay: A. Weeks, C. Girard; Foothills Hospital, Calgary: J. Warnica, B. Smith; and Welland County General Hospital, Welland: G. Venkatesh, S. Demers.

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