

ORIGINAL ARTICLE

A Comparison of Two Intensities of Warfarin for the Prevention of Recurrent Thrombosis in Patients with the Antiphospholipid Antibody Syndrome

Mark A. Crowther, M.D., M.Sc., Jeff S. Ginsberg, M.D., Jim Julian, M.Math., Judah Denburg, M.D., Jack Hirsh, M.D., James Douketis, M.D., Carl Laskin, M.D., Paul Fortin, M.D., David Anderson, M.D., M.Sc., Clive Kearon, M.D., Ph.D., Ann Clarke, M.D., William Geerts, M.D., Melissa Forgie, M.D., David Green, M.D., Lorrie Costantini, M.Sc., Wendy Yacura, Sarah Wilson, M.P.H., Michael Gent, D.Sc., and Michael J. Kovacs, M.D.

ABSTRACT

BACKGROUND

Many patients with the antiphospholipid antibody syndrome and recurrent thrombosis receive doses of warfarin adjusted to achieve an international normalized ratio (INR) of more than 3.0. However, there are no prospective data to support this approach to thromboprophylaxis.

METHODS

We performed a randomized, double-blind trial in which patients with antiphospholipid antibodies and previous thrombosis were assigned to receive enough warfarin to achieve an INR of 2.0 to 3.0 (moderate intensity) or 3.1 to 4.0 (high intensity). Our objective was to show that high-intensity warfarin was more effective in preventing thrombosis than moderate-intensity warfarin.

RESULTS

A total of 114 patients were enrolled in the study and followed for a mean of 2.7 years. Recurrent thrombosis occurred in 6 of 56 patients (10.7 percent) assigned to receive high-intensity warfarin and in 2 of 58 patients (3.4 percent) assigned to receive moderate-intensity warfarin (hazard ratio for the high-intensity group, 3.1; 95 percent confidence interval, 0.6 to 15.0). Major bleeding occurred in three patients assigned to receive high-intensity warfarin and four patients assigned to receive moderate-intensity warfarin (hazard ratio, 1.0; 95 percent confidence interval, 0.2 to 4.8).

CONCLUSIONS

High-intensity warfarin was not superior to moderate-intensity warfarin for thromboprophylaxis in patients with antiphospholipid antibodies and previous thrombosis. The low rate of recurrent thrombosis among patients in whom the target INR was 2.0 to 3.0 suggests that moderate-intensity warfarin is appropriate for patients with the antiphospholipid antibody syndrome.

From the Departments of Medicine (M.A.C., J.S.G., J. Denburg, J.H., J. Douketis, C.K.) and Clinical Epidemiology and Biostatistics (J.J., L.C., W.Y., M.G.), McMaster University, Hamilton, Ont.; the Department of Medicine (C.L., P.F., W.G.) and the Undergraduate Medical Program (S.W.), University of Toronto, Toronto; the Department of Medicine, Dalhousie University, Halifax, N.S. (D.A.); the Department of Medicine, McGill University, Montreal (A.C.); the Department of Medicine, University of Ottawa, Ottawa, Ont. (M.F.); and the Department of Medicine, University of Western Ontario, London, Ont. (M.J.K.) — all in Canada; and the Department of Medicine, Northwestern University, Chicago (D.G.). Address reprint requests to Dr. Crowther at St. Joseph's Hospital, Rm. L208, 50 Charlton Ave. E., Hamilton, ON L8N 4A6, Canada, or at crowthrm@mcmaster.ca.

N Engl J Med 2003;349:1133-8.

Copyright © 2003 Massachusetts Medical Society.

ANTIPHOSPHOLIPID ANTIBODIES, WHICH include anticardiolipin antibodies and lupus anticoagulant, are associated with both arterial and venous thrombosis.¹ After a first episode of thrombosis, patients with antiphospholipid antibodies have a higher risk of recurrent thrombosis than do patients without antiphospholipid antibodies.¹ Retrospective studies suggest that patients with antiphospholipid antibodies have a high risk of recurrent thrombosis while receiving moderate-intensity warfarin (target international normalized ratio [INR], 2.0 to 3.0) and that this risk is lower with a higher intensity of anticoagulant therapy (target INR, 3.1 to 4.5).²⁻⁴ However, these results must be interpreted with caution, because the studies were retrospective case series, recurrent thrombosis was not confirmed by independent adjudication, and the INR at the time of the thrombotic events was uncertain. Furthermore, the patients in these studies attended special clinics where the staff had an interest in the management of complex problems in patients with antiphospholipid antibodies and who were therefore likely to be in a selected subgroup of patients at high risk for recurrent thrombosis.

To our knowledge, there have been no randomized trials of the efficacy and safety of high-intensity versus moderate-intensity warfarin therapy in patients with the antiphospholipid antibody syndrome. Because increasing the target INR from a range of 2.0 to 3.0 to a range of 3.1 to 4.0 is likely to be associated with a doubling of the risk of major hemorrhage, it is important to know whether the higher-intensity treatment is more effective.^{5,6}

To determine whether high-intensity warfarin therapy is required in patients with antiphospholipid antibodies and a previous episode of thrombosis, we undertook a randomized, double-blind trial to compare long-term warfarin therapy targeted to an INR of 2.0 to 3.0 with therapy targeted to an INR of 3.1 to 4.0. Our hypothesis was that high-intensity warfarin would be more effective than moderate-intensity therapy.

METHODS

STUDY PATIENTS

Patients were recruited from tertiary care rheumatology and thromboembolism clinics. They were eligible if they had had an objectively confirmed arterial or venous thrombosis and a positive test for antiphospholipid antibodies on two occasions at

least three months apart. Testing for antiphospholipid antibodies was carried out in local clinical laboratories. Acceptable candidates included those whose tests showed the presence of lupus anticoagulant, as defined by the International Society on Thrombosis and Haemostasis,⁷ a moderate or high titer of IgG anticardiolipin antibody, or both. Patients who had only IgM anticardiolipin antibodies were not eligible for the study. Patients were also excluded if they had a clinically significant bleeding diathesis (e.g., refractory thrombocytopenia with a platelet count of less than 50,000 per cubic millimeter); a history of intracranial hemorrhage, stroke, or gastrointestinal bleeding within the previous three months; a contraindication to warfarin (e.g., allergy); a history of objectively confirmed recurrent thrombosis while receiving warfarin targeted to an INR of 2.0 or greater; pregnancy or a planned pregnancy during the study period; or a geographic location that would preclude follow-up.

RANDOMIZATION AND TREATMENT

The study was approved by the local institutional review board of each of the 13 participating centers, and all patients provided written informed consent before enrollment. Patients were randomized by means of telephone calls to the study coordinating center. Patients were stratified according to the presence or absence of previous arterial thromboembolism and according to the clinical center. The randomization sequence was generated with the use of a random-number table and was performed in blocks of two, four, or six patients.

To minimize bias, we tried to ensure that patients, treating physicians, and other study personnel and adjudicators were unaware of the treatment assignments. Hence, INR results were forwarded to the central warfarin monitors. The warfarin monitors instructed the clinical centers about the warfarin dosage and when to perform INR testing. Thus, physicians, nurse coordinators, and patients remained unaware of both the assigned intensity of warfarin and the INR achieved. To reduce the risk of unblinding, clinicians were discouraged from performing INR assessments when patients presented with suspected recurrent episodes of thrombosis until these were confirmed by testing.

After analysis of the trial data, unscheduled INR measurements that had been performed by the clinical centers during an episode of recurrent thrombosis were obtained from the patient's clinical record. If the INR had not been measured on the day

of the episode, the reported INR value was the value at the last scheduled visit before diagnosis of the episode. Similar strategies for masking warfarin therapy have been used successfully in previous clinical trials.^{8,9}

FOLLOW-UP AND OUTCOMES

Follow-up data were obtained in the clinic or by telephone at three-month intervals. Patients were seen in the clinic at least twice yearly and were asked about symptoms and signs of recurrent thrombosis. Patients were instructed to go to the local emergency department or to contact a study physician if symptoms or signs suggestive of recurrent thrombosis or major bleeding developed. Objective diagnostic testing was performed if a thrombotic event was suspected. If the test results were positive, they were forwarded to the coordinating center.

The primary outcome measure with respect to efficacy was an episode of recurrent thrombosis (a stroke or transient ischemic attack, myocardial infarction, peripheral arterial thrombosis, cerebral-vein thrombosis, deep-vein thrombosis, or pulmonary embolism) that was confirmed by adjudication. The primary outcome measure with respect to safety was bleeding.

All thrombotic and bleeding events were adjudicated by a blinded central adjudication committee of two experts. The criteria for and classification of these events were prespecified.

STATISTICAL ANALYSIS

Estimation of the required sample size was based on two assumptions: first, that the risk of recurrent thrombosis would be approximately 15 percent per year in the group receiving moderate-intensity warfarin therapy and 2.5 percent per year in the group receiving high-intensity warfarin therapy²; and, second, that the average duration of follow-up would be approximately three years. With the use of a two-sided alpha error of 5 percent and a power of 80 percent, a total of 76 patients (38 per group) would be required to demonstrate that high-intensity warfarin was more effective than moderate-intensity warfarin. To protect against an underpowered comparison owing to either loss to follow-up or overestimation of the efficacy of high-intensity therapy, the originally planned sample size was increased to a total of 90 patients.

The primary analysis was based on the intention-to-treat principle. The time to a first recurrent thrombotic event in the two treatment groups was

compared with the use of the log-rank test. A similar analysis was planned for bleeding events. Hazard ratios for recurrent thrombosis were calculated with the use of the Cox proportional-hazards model.

As originally designed, the study called for a minimum of two years of follow-up for the 90th and final patient enrolled. Immediately before enrollment of the 90th patient, the steering committee reviewed the total number of thrombotic events that had been reported to the coordinating center. While remaining unaware of the treatment assignments, the steering committee noted that the overall rate of thrombosis was much lower than expected. To increase both recruitment and the number of patient-years of follow-up without prolonging the study, the steering committee extended enrollment for an additional 18 months and reduced the duration of follow-up for the final patient enrolled to six months.

RESULTS

Of 325 patients screened, 207 met the criteria for inclusion in the study, and of these, 42 were excluded. The reasons most frequently given for exclusion were pregnancy or planned pregnancy (in nine patients), a high risk of hemorrhage (eight), or previous failure of moderate-intensity warfarin (six). Fifty-one patients declined participation. Thus, a total of 114 patients were enrolled at 13 clinical centers between February 1998 and May 2001. The patients' characteristics were similar in the two groups except that there was a higher proportion of women in the moderate-intensity group (Table 1). The average duration of follow-up was 2.7 years in the moderate-intensity group and 2.6 years in the high-intensity group.

Eight patients (7.0 percent) from seven clinical centers had recurrent thrombosis: 6 (10.7 percent) of the 56 patients assigned to high-intensity warfarin therapy and 2 (3.4 percent) of the 58 patients assigned to receive moderate-intensity warfarin therapy (hazard ratio, 3.1; 95 percent confidence interval, 0.6 to 15.0; $P=0.15$) (Fig. 1 and Table 2). Of the two recurrences in the moderate-intensity group, one was a myocardial infarction in a patient with both previous myocardial infarction and previous deep-vein thrombosis, and the other was a deep-vein thrombosis in a patient with previous deep-vein thrombosis. The INR values in these two patients were 1.6 and 2.8, respectively.

The six recurrences in the high-intensity war-

Table 1. Base-Line Characteristics of the Patients.*

Characteristic	Target International Normalized Ratio		P Value
	3.1–4.0	2.0–3.0	
No. of patients	56	58	
Age — yr			0.45
Mean	43	41	
Range	20–80	21–81	
Female sex — no. (%)	27 (48)	41 (71)	0.01
Venous thrombosis — no. (%)	42 (75)	45 (78)	0.75
Systemic lupus erythematosus — no. (%)	10 (18)	6 (10)	0.24
Antiphospholipid antibodies — no.			0.98
IgG anticardiolipin antibody alone	22	22	
Lupus anticoagulant alone	24	25	
IgG anticardiolipin antibody and lupus anticoagulant	10	11	
Thromboembolism within 6 mo before randomization — no. (%)	16 (29)	21 (36)	0.26
Aspirin therapy at enrollment and throughout the study — no. (%)	8 (14)	6 (10)	0.52

* Patients assigned to high-intensity warfarin therapy had a target international normalized ratio (INR) of 3.1 to 4.0; those assigned to moderate-intensity therapy had a target INR of 2.0 to 3.0.

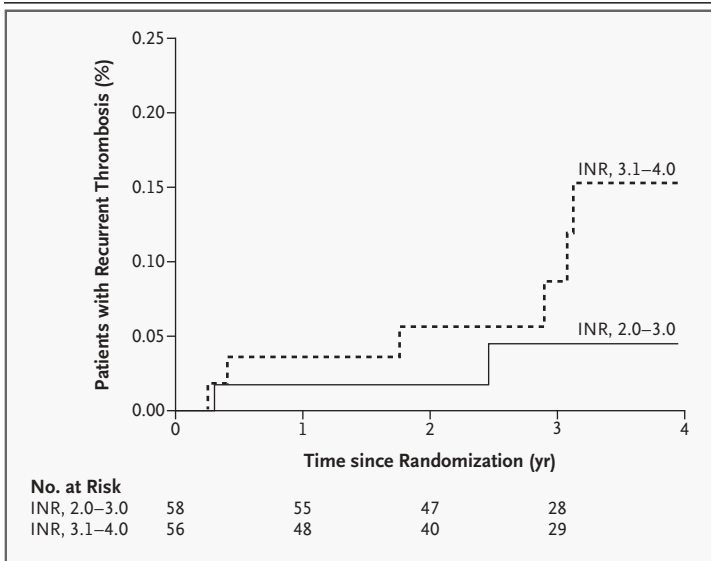


Figure 1. Time to First Recurrent Thrombosis for All Patients Enrolled in the Study.

INR denotes international randomized ratio. Patients assigned to high-intensity warfarin therapy had a target INR of 3.1 to 4.0; those assigned to moderate-intensity therapy, a target INR of 2.0 to 3.0.

farin group included a deep-vein thrombosis in a patient with both previous peripheral arterial thrombosis and previous deep-vein thrombosis, a stroke in a patient with a previous deep-vein thrombosis, a deep-vein thrombosis in a patient with previous stroke, a pulmonary embolism in a patient with previous pulmonary embolism, a myocardial infarction in a patient with previous myocardial infarction, and a deep-vein thrombosis in a patient with previous pulmonary embolism. Five of these six patients continued to receive high-intensity warfarin; their INR values were 3.1, 1.0, 0.9, 1.9, and 3.9, respectively. The sixth patient had discontinued the warfarin 137 days before the recurrent event.

Thirteen patients treated with moderate-intensity warfarin discontinued the drug prematurely. Of these, five stopped at the time of a suspected thrombotic event (confirmed on adjudication in two patients), one stopped because of a major hemorrhage, and seven withdrew consent. Of the seven who withdrew consent, two could not be followed to the end of the study, and data on these patients were censored 69 and 414 days after enrollment.

Twenty-one patients treated with high-intensity warfarin discontinued the drug prematurely. Of these, 5 stopped at the time of a suspected thrombotic event (confirmed on adjudication), 3 stopped because of a major hemorrhage, 1 became pregnant, clinically significant thrombocytopenia developed in 1, and 11 withdrew consent. Of these 21 patients, 1 had a confirmed deep-vein thrombosis three months later. Of the 11 patients who withdrew consent, 4 could not be followed to the end of the study, and data on these patients were censored at 60, 148, 657, and 726 days.

The average INR values in the moderate- and high-intensity warfarin groups were 2.3 and 3.3, respectively. In the moderate-intensity group, the INR was above the target range 11 percent of the time, within the range 71 percent of the time, and below it 19 percent of the time. In the high-intensity group, the corresponding figures were 17, 40, and 43 percent. Eighty-six percent of the time that the INR in patients assigned to high-intensity warfarin was “subtherapeutic,” it was between 2.0 and 3.1.

Major bleeding occurred in four patients assigned to moderate-intensity warfarin and in three assigned to high-intensity warfarin (Table 2). The annual risk of major bleeding was 2.2 percent with moderate-intensity warfarin and 3.6 percent with high-intensity warfarin. Eleven patients (19 percent) in the moderate-intensity group and 14 pa-

Table 2. Outcomes and Duration of Follow-up in the High-Intensity and Moderate-Intensity Warfarin Groups, According to Subgroup.*

Outcome and Subgroup	INR of 3.1–4.0			INR of 2.0–3.0			Hazard Ratio (95% CI)	P Value
	No. of Patients	No. with Outcome	Patient-Years of Follow-up	No. of Patients	No. with Outcome	Patient-Years of Follow-up		
Recurrent thrombosis								
All patients	56	62	148	58	2	158	3.1 (0.6–15.0)	0.15
Patients with previous arterial thrombosis	14	3	35	13	1	38	3.1 (0.3–30.0)	0.30
Patients with previous venous thrombosis	42	3	113	45	1	119	2.9 (0.3–28.0)	0.34
Patients with systemic lupus erythematosus	10	2	30	16	1	52	3.5 (0.3–38.0)	0.28
Patients with lupus anticoagulant	34	4	86	36	2	100	2.1 (0.4–12.0)	0.37
Bleeding								
Any	56	14	97	58	11	126	1.9 (0.8–4.2)	0.13
Major	56	3	111	58	4	133	1.0 (0.2–4.8)	0.96

* Hazard ratios are for high-intensity as compared with moderate-intensity warfarin. INR denotes international normalized ratio, and CI confidence interval. Patients assigned to high-intensity warfarin therapy had a target INR of 3.1 to 4.0; those assigned to moderate-intensity therapy, a target INR of 2.0 to 3.0.

tients (25 percent) in the high-intensity group had at least one episode of bleeding (Table 2). No patient died during the study.

Multivariable analyses with the use of the Cox model did not reveal any statistically significant confounding due to the base-line characteristics or stratification factors for any of the study outcomes. The small number of recurrent events precluded a meaningful analysis of the relation between base-line prognostic factors and the risk of recurrent thrombosis.

DISCUSSION

In this study, we found that high-intensity warfarin therapy is not more effective than moderate-intensity warfarin for the prevention of recurrent thrombosis in patients with antiphospholipid antibodies. Our results also showed that the absolute risk of recurrent thrombosis was low if warfarin therapy was targeted to an INR of 2.0 to 3.0.

The findings of this study are different from those of previous studies in which patients with the antiphospholipid antibody syndrome had a high risk of recurrent thrombosis when treated with moderate-intensity warfarin.^{2,3} There are several reasons for these differences. Most important, the previous studies were retrospective, and, as a con-

sequence, neither the rates of recurrent thrombosis nor the intensity of anticoagulant therapy received at the time of the recurrent events could be accurately determined. In contrast, we enrolled patients prospectively, evaluated recurrent events objectively, and obtained accurate data on the intensity of anticoagulant therapy for all patients. In addition, previous studies enrolled patients at a few highly specialized clinics that had an interest in managing complex problems related to antiphospholipid antibodies.

Our results are likely to be valid and generalizable, because the study was randomized and double-blinded, central adjudication was used, and patients were enrolled at 13 clinical centers. Positive results of two consecutive antiphospholipid-antibody tests performed three months apart were required for enrollment in order to reduce the likelihood that patients whose test results were transiently positive, and therefore potentially less clinically important, would be included.¹⁰ Base-line variables were evenly distributed between the two groups, with the exception that the moderate-intensity group had a higher proportion of women. This imbalance occurred as a result of chance and did not confound the results of the study.

This study has several limitations. Because we required all patients to have two positive antiphos-

pholipid-antibody tests three months apart, we did not examine the effectiveness of warfarin in the initial three months after a first episode of thrombosis. We excluded patients with a high risk of bleeding and those who had had a thrombosis while taking warfarin, and thus we cannot comment on how warfarin therapy for such patients should be managed. Because only 14 patients (8 of whom were assigned to high-intensity warfarin) were also treated with aspirin, it is not possible to draw meaningful conclusions about the concomitant use of aspirin and its influence on the frequency of recurrent thrombosis or bleeding. In addition, the rate of recurrent thrombosis might have been lower if the INRs in patients assigned to high-intensity warfarin had been in the desired range during a greater portion of the study period. However, this failing is unlikely to have had a major influence on the results, given that only one of the recurrent

thrombotic episodes in the high-intensity warfarin group occurred in a patient who had prematurely discontinued the assigned treatment. Furthermore, the average INR value was fully 1 point higher in the high-intensity group than in the moderate-intensity group. Finally, because the rate of recurrent thrombosis in the moderate-intensity group was very low, it is unlikely that strict maintenance of an INR greater than 3.0 in the high-intensity group would have improved this result.

Supported by a grant from the Canadian Institutes for Health Research (MCT 14390). Dr. Crowther holds a Research Scholarship from the Canadian Institutes for Health Research. Dr. Ginsberg is a Career Investigator of the Heart and Stroke Foundation of Ontario. Drs. Douketis and Kearon each hold Research Scholarships from the Heart and Stroke Foundation of Canada. Dr. Kovacs is an Internal Scholar of the Department of Medicine at the University of Western Ontario, Canada. Dr. Clarke is a Career Investigator of the Canadian Institutes for Health Research. Dr. Fortin is a Scientist of the Arthritis Society/Canadian Institutes for Health Research and is supported in part by the Arthritis Center of Excellence of the University of Toronto. DuPont Pharma provided the warfarin used in the study.

REFERENCES

1. Crowther MA, Ginsberg JS. Antiphospholipid antibody syndrome. In: Goldhaber SZ, Ridker PM, eds. *Thrombosis and thromboembolism*. Vol. 44 of *Fundamental and clinical cardiology*. New York: Marcel Dekker, 2002:49-66.
2. Khamashta MA, Cuadrado MJ, Mujic F, Taub NA, Hunt BJ, Hughes GRV. The management of thrombosis in the antiphospholipid-antibody syndrome. *N Engl J Med* 1995;332:993-7.
3. Rosove MH, Brewer PM. Antiphospholipid thrombosis: clinical course after the first thrombotic event in 70 patients. *Ann Intern Med* 1992;117:303-8.
4. Ruiz-Irastorza G, Khamashta MA, Hunt BJ, Escudero A, Cuadrado MJ, Hughes GR. Bleeding and recurrent thrombosis in definite antiphospholipid syndrome: analysis of a series of 66 patients treated with oral anticoagulation to a target international normalized ratio of 3.5. *Arch Intern Med* 2002;162:1164-9.
5. Palareti G, Leali N, Coccheri S, et al. Bleeding complications of oral anticoagulant treatment: an inception-cohort, prospective collaborative study (ISCOAT): Italian Study on Complications of Oral Anticoagulant Therapy. *Lancet* 1996;348:423-8.
6. Oden A, Fahlen M. Oral anticoagulation and risk of death: a medical record linkage study. *BMJ* 2002;325:1073-5.
7. Brandt JT, Barna LK, Triplett DA. Laboratory identification of lupus anticoagulants: results of the Second International Workshop for Identification of Lupus Anticoagulants. *Thromb Haemostasis* 1995;74:1597-603.
8. Crowther MA, Clase CM, Margetts PJ, et al. Low-intensity warfarin is ineffective for the prevention of PTFE graft failure in patients on hemodialysis: a randomized controlled trial. *J Am Soc Nephrol* 2002;13:2331-7.
9. Kearon C, Gent M, Hirsh J, et al. A comparison of three months of anticoagulation with extended anticoagulation for a first episode of idiopathic venous thromboembolism. *N Engl J Med* 1999;340:901-7. [Erratum, *N Engl J Med* 1999;341:298.]
10. Wilson WA, Gharavi AE, Koike T, et al. International consensus statement on preliminary classification criteria for definite antiphospholipid syndrome: report of an international workshop. *Arthritis Rheum* 1999;42:1309-11.

Copyright © 2003 Massachusetts Medical Society.

CORRECTION

A Comparison of Two Intensities of Warfarin for the Prevention of Recurrent Thrombosis in Patients with the Antiphospholipid Antibody Syndrome

A Comparison of Two Intensities of Warfarin for the Prevention of Recurrent Thrombosis in Patients with the Antiphospholipid Antibody Syndrome . On page 1136, in Table 1, the number (percentage) of patients who had systemic lupus erythematosus in the group with a target international normalized ratio of 2.0 to 3.0 should have been 16 (28), rather than 6 (10), as printed, and the corresponding P value should have been 0.21, rather than 0.24, as printed.

CORRECTION

A Comparison of Two Intensities of Warfarin for the Prevention of Recurrent Thrombosis in Patients with the Antiphospholipid Antibody Syndrome

A Comparison of Two Intensities of Warfarin for the Prevention of Recurrent Thrombosis in Patients with the Antiphospholipid Antibody Syndrome . On page 1137, in the first row of Table 2 ("All patients"), under "INR of 3.1–4.0," the number of patients with recurrent thrombosis should be 6, rather than 62, as printed. We regret the error.