

Is long-term anticoagulation after acute thromboembolic limb ischemia always necessary?

Thomas L. Forbes, MD; Guy DeRose, MD; Kenneth A. Harris, MD

Objective: After thromboembolectomy, patients with acute limb ischemia often receive anticoagulant therapy to prevent recurrent events. Patients with atrial fibrillation or cardiac thrombus have a higher risk of recurrent emboli than those without these risk factors. This study examines the importance of long-term anticoagulation in these 2 groups. **Design:** A review of patients presenting with acute limb ischemia over a 5-year period (1994–1999). **Setting:** A university-affiliated medical centre. **Patients:** Fifty patients divided into 2 groups: 19 (38%) patients with atrial fibrillation (group 1) and 31 (62%) patients with no atrial fibrillation or cardiac thrombus (group 2) as confirmed by transthoracic echocardiography. **Intervention:** All patients underwent surgical thromboembolectomy and received postoperative anticoagulant therapy. **Outcome measures:** Mortality, limb loss, further thromboembolic events and bleeding complications as determined by telephone survey. **Results:** There was a significant difference in 5-year survival (group 1, 84%; group 2, 64%) and early limb loss (group 1, 0%; group 2, 13%). Further thromboembolic events and bleeding complications were rare but were more common in group 1. In group 2 there were no instances of recurrent thromboemboli and no bleeding complications although only 39% of patients in this group were taking anticoagulants at the end of the study period. **Conclusions:** Patients with extremity thromboemboli without atrial fibrillation or cardiac thrombus may not be at the same risk for recurrent events as those with these risk factors, and long-term anticoagulant therapy may not be as necessary in this group.

Objectif : Après une thromboembolectomie, les patients atteints d'ischémie aiguë d'un membre reçoivent souvent une thérapie aux anticoagulants afin d'éviter les rechutes. Les patients qui ont de la fibrillation auriculaire ou un thrombus cardiaque présentent un risque plus élevé de récurrence des embolies que ceux qui n'ont pas ces facteurs de risque. Dans cette étude, on analyse l'importance de l'anticoagulation de longue durée dans ces deux groupes. **Conception :** Examen sur cinq ans (1994–1999) de patients présentant une ischémie aiguë d'un membre. **Contexte :** Centre médical affilié à une université. **Patients :** Cinquante patients répartis en deux groupes : 19 (38 %) patients ayant une fibrillation auriculaire (groupe 1) et 31 (62 %) patients sans fibrillation auriculaire ni thrombus cardiaque (groupe 2), tel que confirmé par échocardiographie transthoracique. **Intervention :** Tous les patients ont subi une thromboembolectomie chirurgicale et reçu une thérapie aux anticoagulants après l'intervention. **Mesures de résultats :** Mortalité, perte de membre, autres thromboembolies et complications hémorragiques déterminées par sondage téléphonique. **Résultats :** On a constaté une différence importante entre les groupes des taux de survie à cinq ans (groupe 1, 84 %; groupe 2, 64 %) et de perte précoce d'un membre (groupe 1, 1,0 %, groupe 2, 13 %). Les événements thromboemboliques et les complications hémorragiques ont été rares par la suite, mais plus fréquents chez les sujets du groupe 1. Chez ceux du groupe 2, on n'a enregistré aucun cas de récurrence de thromboembolie ni aucune complication hémorragique, même si 39 % seulement des patients de ce groupe prenaient des anticoagulants à la fin de la période d'étude. **Conclusions :** Les patients ayant une thromboembolie dans un membre et qui ne présentent aucune fibrillation auriculaire ni thrombus cardiaque ne sont peut-être pas aussi exposés aux récurrences que ceux qui présentent ces facteurs de risque, et une thérapie de longue durée aux anticoagulants n'est peut-être pas aussi nécessaire chez les sujets de ce groupe.

From the Division of Vascular Surgery, London Health Sciences Centre, University of Western Ontario, London, Ont.

Accepted for publication Jan. 2, 2002.

Presented at the 22nd annual meeting of the Canadian Society for Vascular Surgery, Banff, Alta., Sept. 29 and 30, 2000.

Correspondence to: Dr. Thomas L. Forbes, Division of Vascular Surgery, London Health Sciences Centre, University of Western Ontario, Ste N380, 375 South St., London ON N6A 4G5; fax 519 667-6853; Tom.Forbes@lhsc.on.ca

Arterial thromboembolism is a common cause of acute extremity ischemia. In an elderly patient population this can result in a significant risk of limb loss and death.¹ Various therapeutic regimens commonly include long-term anticoagulation to prevent further adverse events.² Anticoagulation is not always innocuous, with local bleeding complications occurring in up to 17% of cases.³ Although there is evidence to support the long-term use of anticoagulants in patients with atrial fibrillation and acute limb ischemia,^{4,5} there are few reports supporting its use in other patients with limb ischemia. Those reports that do exist are often conflicting. Green and associates⁶ showed a definite short-term reduction in the risk of recurrent emboli in those taking warfarin. However, Jivegard and associates³ were unable to show any benefit of warfarin over placebo in reducing limb loss, mortality or recurrent emboli in their randomized controlled trial, even in patients with atrial fibrillation or an identifiable cardiac source of emboli. Campbell and associates⁷ did show some benefit of longer term anticoagulation in reducing the risk of further emboli and amputation. Although not statistically significant, there was a trend for patients with thrombosis in situ taking warfarin to have reduced mortality and limb loss.

Recognizing the clearer evidence supporting the use of long-term anticoagulation in patients with a cardiac source of emboli (atrial fibrillation or intracardiac thrombus), this study attempted to determine whether in the absence of these risk factors there remained a benefit of anticoagulation after acute thromboembolic limb ischemia.

Patients and methods

All patients who presented to our institution between 1994 and 1999 with acute limb ischemia were identified. Those with a history of chronic lower extremity ischemia, thrombosis of previous vascular grafts, traumatic

limb ischemia or thrombosed aneurysms were excluded. All patients were treated with surgical thromboembolectomy and postoperative anticoagulation with heparin intravenously. Warfarin was started in the early postoperative period. We obtained from the charts demographic data from the time of the initial presentation. Risk factors for thromboembolism, including atrial fibrillation, myocardial infarction, malignant disease, previous episodes of thromboembolism and anticoagulation status, were documented. Transthoracic echocardiography (TTE) reports were reviewed for evidence of valvular lesions, intracardiac thrombus and left ventricular dysfunction.

Following the episode of acute ischemia, the patient was followed up by telephone interview or their surrogate if the patient was dead. The telephone survey asked the following questions:

- Is the patient alive (cause of death if known)?
- Were there further thromboembolic occurrences?
- Were there further revascularization procedures?
- Was the affected limb amputated?
- Is the patient still taking warfarin?
- Have there been complications of anticoagulation?

This telephone survey took place over several weeks in March 2000 giving a follow-up period ranging from 3 to 60 months. The χ^2 test for proportions was used for statistical analysis, and a *p* value of 0.05 was considered significant.

Results

Fifty patients (17 [34%] men) with acute thromboembolic extremity ischemia were identified during the study period. All patients, or their surrogates if the patient had died, were contacted by telephone, giving a response rate of 100%. The mean age of the 50 patients was 71.9 (range from 37–99) years. The demographics of the study patients are

shown in Table 1. The majority (75%) of those taking warfarin had subtherapeutic INR levels (< 2). On presentation all patients underwent surgical thromboembolectomy and were investigated postoperatively for an intracardiac source of emboli by TTE in 82% of cases.

All patients without atrial fibrillation underwent TTE, which revealed an intracardiac thrombus in 2 patients. These patients were placed in group 1 with those having atrial fibrillation as patients who had significant cardiac risk factors for peripheral arterial embolism (Table 2). Thirty-one (62%) of the patients did not have either of these cardiac risk factors and were placed in group 2). Both groups were equivalent with respect to gender ratio, age and incidence of previous emboli. Those in group 1 were more likely to be already taking anticoagulants than those in group 2 (42% v. 13%, *p* < 0.05). One-third of the patients in group 2 had known malignant disease at the time of initial presentation, indicative of a possible hypercoagulable state. No patients in group 1 were known to have malignant disease.

Table 3 summarizes the data from the follow-up telephone survey. The length of follow-up did not differ between the 2 groups. In both groups, patients were equally likely to be taking warfarin at the time of discharge after their acute event and there was no difference in the risk of bleeding complications. Although it was rare,

Table 1

Demographics in 50 Patients With Acute Limb Ischemia

Category	No. (and %)*
Males	17 (34)
Age, yr	
Mean	71.9
Range	37–99
Lower/upper extremity	31/19 (62/38)
Previous emboli	12 (24)
Present warfarin use	12 (24)
Malignant disease	10 (20)
Transthoracic echocardiography	41 (82)

*Except where indicated

patients with one of the cardiac risk factors were more prone to recurrent arterial thromboembolism than group 2 patients without these risk factors (16% v. 0%, $p < 0.05$). Those in group 1 were more likely to be taking anticoagulants at the time of follow-up (79% v. 39%, $p < 0.05$). Four patients (13%) in group 2 underwent lower extremity amputation during the initial hospitalization for acute ischemia. There were no further instances of limb loss during the follow-up period. Group 2 patients had a significantly higher death rate than group 1 (36% v. 16%, $p < 0.05$) during the follow-up, with all deaths related to the higher incidence of malignant disease. When patients with malignant disease in group 2 were compared with those with no malignant disease in this group, there was no statistical difference in outcome.

Discussion

Definitive conclusions are difficult

to draw from any retrospective study. However, when retrospectively obtained information is combined with contemporarily obtained follow-up data, strong suggestions can be made. Although the present study suffers from the shortcomings of any retrospective review, it is strengthened by a 100% follow-up through the telephone survey. The present series involves a small number of patients. Despite this, certain trends are clear. Although there were few instances of recurrent thromboembolic complications overall, patients without the risk factors of atrial fibrillation or an intracardiac thrombus appeared to be at less risk for recurrent events even though fewer patients in this group received long-term anticoagulation.

There is little published information supporting the long-term use of warfarin in patients without atrial fibrillation or an intracardiac thrombus who have acute extremity ischemia resulting from thromboembolism. In

this series they were more likely to have underlying malignant disease contributing to a hypercoagulable state. Although there is little published prospective data it is estimated that 15% of cancer patients will suffer a thromboembolic complication during their lifetime.⁸ The hypercoagulable state in cancer patients is thought to result from a combination of procoagulant release by tumour cells, chemotherapeutic drugs and comorbid risk factors.⁹

The difference between the 2 groups in this study with respect to the risk of recurrent thromboembolism may be the result of distinct pathologic processes. Presumably, acute limb ischemia in patients with atrial fibrillation or intracardiac thrombus is the result of a purely embolic phenomenon. But patients without these risk factors and possibly an underlying malignant disease are more prone to acute arterial thrombosis. In some of these latter patients this thrombotic process appears to be irreversible despite appropriate surgical intervention and anticoagulation, and can result in limb loss. The results of this study suggest that in most cases this acute thrombotic process abates sufficiently that these patients are not subjected to the same risk of further thrombotic episodes as those with cardiac risk factors. This is despite the observation that these patients are much less likely to be receiving long-term anticoagulation.

The 28% overall mortality in our study is similar to that found in other series and is not unexpected in predominantly elderly patients with cardiovascular risk factors and malignant disease.^{7,10} The difference in mortality between the 2 groups was directly associated with cancer-related deaths. Complications of long-term anticoagulation were rare in this study. Generally, these can be minimized with good control of anticoagulation and patient compliance. In this series, the control of anticoagulation was left to the discretion of the fam-

Table 2
Demographic Data on 19 Patients in Group 1 (Atrial Fibrillation or Intracardiac Thrombus) and 31 Patients in Group 2 (No Cardiac Risk Factors)

Category	Group 1, no. (and %)* (n = 19)	Group 2, no. (and %)* (n = 31)	p value
Males	5 (26)	12 (39)	NS
Mean age, yr	76.1	69.4	NS
Previous emboli	5 (26)	7 (23)	NS
Present warfarin use	8 (42)	4 (13)	< 0.05
Malignant disease	0	10 (32)	< 0.05
Transthoracic chocardiology	10 (53)	31 (100)	< 0.05

*Except where indicated
NS = not significant.

Table 3
Follow-up Data (Ranging from 3 to 60 Months) for 50 Patients With Acute Ischemia: Group 1 versus Group 2

Category	Group 1, no. (and %) (n = 19)	Group 2, no. (and %) (n = 31)	p value
Taking warfarin at the time of discharge	17 (90)	29 (94)	NS
Recurrent emboli	3 (16)	0	< 0.05
Complications of warfarin	2 (10)	0	NS
Current anticoagulation	15 (79)	12 (39)	< 0.05
Amputation (all occurred acutely)	0	4 (13)	< 0.05
Died	3 (16)	11 (36)	< 0.05

NS = not significant.

ily physicians with a recommendation to maintain the INR between 2 and 3. Long-term anticoagulation was maintained in 54% of our patients, a higher rate than that reported in other series.⁷ This may explain why recurrent thromboembolic events were rare in our series. As might be expected, patients with atrial fibrillation or an intracardiac thrombus were more likely to be maintained on warfarin than patients without these risk factors.

TTE was successful in identifying intracardiac thrombus in 2 patients. This is in keeping with the experience of other centres with TTE.¹¹ In our series this investigation was limited to the heart. The Mayo Clinic has published their experience, including the abdominal aorta in patients who present with acute lower extremity ischemia.¹² This revealed mobile thrombi in several patients and had an impact on the choice of treatment. Several groups are beginning to show that transesophageal echocardiography (TEE) has a greater ability to reveal intracardiac thrombus than the transthoracic technique,¹³ which could be replaced by TEE as the preferred study when the presence or absence of an intracardiac thrombus is an important factor in determining the need for long-term anticoagulation.

The overall limb loss rate of 8% in this study is comparable to that found in other studies.⁷ All amputations occurred during the acute presentation in patients with underlying malignant disease despite postoperative anticoagulation. There were no instances of limb loss during the follow-up period. Although these patients have an increased risk of limb loss in the acute phase, presumably as a result of a hypercoagulable

state, there were no instances of recurrent thromboemboli or amputation in the follow-up period that would have indicated a definite need for long-term anticoagulation.

Conclusions

This retrospective study suggests that patients without atrial fibrillation or an intracardiac thrombus may not have the same risk of recurrent thromboembolic events as those having these risk factors. Early heparinization appears valuable because of the higher risk of acute limb loss, but long-term anticoagulation appears to confer little additional benefit. Despite this, we continue to recommend long-term anticoagulation of both groups of patients until further evidence is obtained. This remains an area in which complete understanding of the role of anticoagulation awaits a properly designed multicentre prospective randomized trial that considers cardiac risk factors as well as the presence or absence of malignant disease.

Acknowledgement: We thank Dr. E.S. Woodford for her assistance in data collection and manuscript preparation.

References

1. Stallone RJ, Blaisdell FM, Cafferata HT, Levin SM. Analysis of morbidity and mortality from arterial embolectomy. *Surgery* 1969;65:207-17.
2. McPherson GA, Wolfe JH. ABC of vascular diseases. Acute ischaemia of the leg. *BMJ* 1992;304:169-72.
3. Jivegard L, Holm J, Bergqvist D, Björck CG, Björkman H, Brunius U, et al. Acute lower limb ischemia: failure of anticoagulant treatment to improve one-month results of arterial thromboembolectomy. A prospective randomized multi-center study. *Surgery* 1991;109:610-6.
4. Petersen P, Boysen G, Godtfredsen J, Andersen ED, Andersen B. Placebo-controlled, randomised trial of warfarin and aspirin for prevention of thromboembolic complications in chronic atrial fibrillation. The Copenhagen AFASAK study. *Lancet* 1989;1:175-9.
5. Ezekowitz MD, Bridgers SL, James KE, Carliner NH, Colling CL, Gornick CC, et al. Warfarin in the prevention of stroke associated with nonrheumatic atrial fibrillation. Veterans Affairs Stroke Prevention in Nonrheumatic Atrial Fibrillation Investigators. *N Engl J Med* 1992;327:1406-12.
6. Green RM, DeWeese JA, Rob CG. Arterial embolectomy before and after the Fogarty catheter. *Surgery* 1975;77:24-33.
7. Campbell WB, Ridler BM, Szymanska TH. Two-year follow-up after acute thromboembolic limb ischaemia: the importance of anticoagulation. *Eur J Vasc Endovasc Surg* 2000;19:169-73.
8. Sallah S, Ahmad O, Kaiser HE. Pathogenesis of thrombotic disorders in patients with cancer. *In Vivo* 2000;14:251-3.
9. Levine M. Treatment of thrombotic disorders in cancer patients. *Haemostasis* 1997;27(Suppl 1):38-43.
10. Aune S, Trippstad A. Operative mortality and long-term survival of patients operated on for acute lower limb ischemia. *Eur J Vasc Endovasc Surg* 1998;15:143-6.
11. Fanning WJ, Vaccaro PS, Satiani B, Smead WL, Das BM. The role of echocardiography in patients with acute peripheral arterial embolization. *Ann Vasc Surg* 1986;1:316-20.
12. Spittell PC, Seward JB, Hallet JW Jr. Mobile thrombi in the abdominal aorta in cases of lower extremity embolic arterial occlusion: value of extended trans thoracic echocardiography. *Am Heart J* 2000;139(2 Pt 1):241-4.
13. Lagatolla NR, Burnand KG, Stewart A. Role of transoesophageal echocardiography in determining the source of peripheral arterial embolism. *Br J Surg* 1995;82:1651-4.