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TAKE-HOME POINTS FROM LECTURES BY CLEVELAND CLINIC AND VISITING FACULTY

Issues in anticoagulant therapy: Recent trials start to answer the tough questions

ABSTRACT

Recent trials provide evidence to help guide the management of patients with recurrent episodes of venous thromboembolism, cancer patients with venous thromboembolism, and patients receiving anticoagulant therapy who must undergo surgery.

KEY POINTS

Patients with idiopathic or "unprovoked" venous thromboembolism require warfarin therapy tailored according to the risks and benefits.

Low-molecular-weight heparins are preferred for cancer patients for both acute and chronic therapy.

Low-molecular-weight heparins appear safe and effective for perioperative ("bridging") therapy in patients with mechanical heart valves, but randomized controlled trials are still needed.

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ANTICOAGULANT THERAPY has become more evidence-based in recent years, with randomized trials to provide guidance about the optimal care in specific situations.

This paper uses three brief clinical scenarios that clinicians are likely to encounter in everyday practice—idiopathic deep venous thrombosis (DVT), pulmonary embolism in a patient with cancer, and long-term anticoagulant therapy in a patient who is scheduled for surgery—to introduce discussions of how new evidence can be incorporated into clinical practice.

IDIOPATHIC DVT: HOW LONG TO TREAT? WHAT TARGET INR?

A 70-year-old African American woman with type 2 diabetes mellitus, hypertension, coronary artery disease, and a history of a stroke 3 years ago is admitted with a DVT in the proximal right common femoral vein. This appears to be unprovoked (idiopathic), and no major risk factors for venous thromboembolism (VTE) other than advanced age are identified.

She is treated in the hospital overnight with enoxaparin 1 mg/kg subcutaneously every 12 hours and discharged home taking enoxaparin and warfarin after she demonstrates the ability to give herself injections.

Which duration of warfarin therapy and target international normalized ratio (INR) do you recommend?

- 3 months at target INR 2–3
- 6 months at target INR 2–3
- 12 months at target INR 2–3
- 6 months at target INR 2–3, then indefinitely at target 1.5–2.0
- Indefinitely at target INR 2–3.

TABLE 1

Risk of major bleeding in outpatients taking warfarin

Which risk factors are present?

- Age > 65 years
- History of stroke
- History of gastrointestinal bleeding
- Recent myocardial infarction
- Hematocrit lower than 30%
- Diabetes mellitus

The sum of the risk factors determines the level of risk

INTERVAL	ESTIMATED RISK FOR MAJOR BLEEDING*		
	LOW (0 FACTORS)	INTERMEDIATE (1–2 FACTORS)	HIGH (≥ 3 FACTORS)
3 Months	2%	5%	23%
12 Months	3%	12%	48%

*At international normalized ratio (INR) 2–3

BEYTH RJ, QUINN LM, LANDEFELD CS. PROSPECTIVE EVALUATION OF AN INDEX FOR PREDICTING THE RISK OF MAJOR BLEEDING IN OUTPATIENTS TREATED WITH WARFARIN. AM J MED 1998; 105:91–99.

After an episode of VTE, the balance of risk and benefit favors treatment

Balancing the risks and benefits

In choosing the duration and intensity of warfarin therapy, one must weigh its risks and benefits, taking into account the risks of recurrent and fatal VTE and the risks of recurrent and fatal major bleeding, and tailor the therapy to the patient.

Traditional therapy for a first episode of VTE is with unfractionated heparin or low-molecular-weight heparin (LMWH) for at least 5 days, followed by warfarin for 3 to 6 months or more: 3 months for an episode caused by a transient risk factor (eg, immobilization following surgery), 6 months for idiopathic VTE, and more than 6 months for patients with a permanent risk factor such as cancer or deficiency of protein C, protein S, or antithrombin III.

Warfarin is very effective in decreasing the rate of VTE recurrence. However, after it is stopped, the chance of recurrence ranges from 6% to 20% in the first year. Kearon[1] calculated that the relative risk of recurrent VTE after stopping anticoagulant therapy ranges from 0.5 for patients with a transient risk factor to 4.1 for those homozygous for the factor V Leiden mutation. Moreover, 5% to 10% of recurrent episodes of VTE are fatal.[2]

On the other hand, the risks of bleeding with warfarin therapy are not trivial. Linkins et al[3] calculated that, in patients taking warfarin because of VTE (target INR 2–3), the incidence of intracranial bleeding is 0.65 to 1.5 per 100 patient-years, depending on the duration of therapy, and the mortality rate for patients with major bleeding events in this meta-analysis was 9% to 13%.

Evidence favors prolonged treatment

In a randomized trial called Long-Term, Low-Intensity Warfarin Therapy for the Prevention of Recurrent Venous Thromboembolism (PREVENT),[4] Ridker et al randomized patients who had experienced an episode of idiopathic VTE and who had been on full-dose warfarin therapy for a median of 6.5 months to either placebo or low-intensity warfarin (target INR 1.5–2.0).

The rate of recurrent VTE per 100 patient-years was 7.2 in the placebo group vs 2.6 in the warfarin group ($P < .001$). Major bleeding episodes per 100 patient-years occurred at a rate of 0.4 in the placebo group vs 0.9 in the warfarin group, but the difference was not statistically significant. The overall mortality rate was higher in the placebo group: 1.4 vs 0.7, although this difference was also not statistically significant.

The trial was stopped early after a mean follow-up of 2.1 years, due to the benefits seen in the warfarin group. The authors concluded that long-term low-intensity warfarin is highly effective in preventing recurrent VTE.

Conventional-intensity therapy is better than low-intensity therapy

In the Extended Low-intensity Anti-coagulation for Thromboembolism (ELATE) trial,[5] 738 patients who had received 3 or more months of warfarin therapy after an episode of idiopathic VTE were randomized to continue warfarin therapy with a target INR of either 2.0 to 3.0 (conventional intensity) or 1.5 to 1.9 (low intensity).

At an average of 2.4 years, the rate of recurrent VTE per 100 patient-years was 1.9 in the low-intensity group vs 0.7 in the conventional-intensity group ($P < .03$). The rate of major bleeding episodes was 1.1 with low-intensity treatment vs 0.9 with conventional-intensity

treatment (P = .76). The mortality rate was 1.9 with low-intensity treatment vs 0.9 with conventional intensity treatment (P = .09).

The authors concluded that conventional-intensity anticoagulation (INR 2.0–3.0) is superior to low-intensity anticoagulation (INR 1.5–1.9) for the long-term prevention of recurrent VTE without increasing the rate of major bleeding.

Predicting bleeding risk

The risk of major bleeding in clinical practice during warfarin treatment for secondary prevention of VTE is difficult to extrapolate from these trials, however, as they were not designed to detect this. Much larger trials that are applicable to the types of patients we see in clinical practice would be needed to study this appropriately.

Also, the patients in these trials were at low risk for bleeding: the risk of major bleeding ranged from 1% to 4% per year. These numbers are far lower than the risk we encounter in real life. If we apply the clinical prediction rule developed by Beyth et al[6] that stratifies patients as being at high, intermediate, or low risk of bleeding (TABLE 1), we would get a very different risk for bleeding.

Case revisited

This patient had an unprovoked episode of DVT, which according to the findings of the ELATE and PREVENT trials would call for warfarin therapy indefinitely (TABLE 2).[1] Based on the ELATE data, the target INR should be 2 to 3.

However, she has three of the seven risk factors identified by Beyth et al: advanced age, diabetes, and history of stroke (TABLE 1), and according to their index her risk of bleeding is high (48% at 12 months). Therefore, 6 months of therapy would be appropriate.

TABLE 2

Guidelines for duration of warfarin therapy (target INR 2-3) for VTE

RISK FACTOR	DURATION
Major transient risk factor	3 months
Surgery	
Hospitalization	
Immobilization of leg	
Minor risk factor	3 or 6 months
Air travel	
Pregnancy	
Estrogen therapy	
Less marked leg injuries	
Immobilization	
Unprovoked	Indefinite*
If unprovoked and also:	6 months
Isolated deep vein thrombosis in calf	
Anticoagulant therapy is burdensome	
Moderate to high risk of bleeding†	
Uncontrolled malignancy	Indefinite
If uncontrolled malignancy and also:	Consider 6 months
Very high risk of bleeding	
Additional reversible risk factor	

*Consider 6 months of therapy instead of indefinite if at high risk of bleeding. Factors favoring indefinite therapy include pulmonary embolism vs proximal deep vein thrombosis at presentation; more than one episode of unprovoked venous thromboembolism (VTE); antiphospholipid antibodies, protein C, protein S, or antithrombin deficiency; homozygous factor V Leiden mutation or G20210A prothrombin mutation; combined thrombophilic abnormalities; inferior vena cava filter; patient preference

†Risk factors for bleeding: age 65 or older, previous stroke, previous bleeding (eg, gastrointestinal), active peptic ulcer disease, renal impairment, anemia, thrombocytopenia, liver disease, diabetes mellitus, use of antiplatelet therapy, poor patient compliance, poor control of anticoagulation, structural lesions (including tumors) expected to be associated with bleeding. One or two risk factors suggest moderate risk and three or more risk factors suggest high risk of bleeding

KEARON C. LONG-TERM MANAGEMENT OF PATIENTS AFTER VENOUS THROMBOEMBOLISM. CIRCULATION 2004; 110(SUPPL 1):I-10–I-18.

VTE AND CANCER: WHICH ANTICOAGULANT IS OPTIMAL?

A 62-year-old African American man with recently diagnosed mucinous adenocarcinoma in the liver of unknown primary source presents with syncope. He undergoes helical computed tomography, which reveals bilateral pulmonary emboli. His troponin and brain natriuretic peptide levels are normal, he has no evidence of right ventricular dysfunction by echocardiography, and he is normotensive.

What is your preferred management strategy?

- Start LMWH in weight-based subcutaneous doses plus warfarin; stop the heparin when the INR is between 2 and 3, and continue warfarin indefinitely or until the patient is cured of cancer

TABLE 3

Risk of perioperative thromboembolic events

Patients at low risk (< 5%/year)
- Nonvalvular atrial fibrillation without multiple risk factors for cardioembolism
- Newer-model mechanical heart valves in the aortic position
- Venous thromboembolism more than 90 days before
- Intrinsic cerebrovascular disease without recurrent strokes or transient ischemic attacks

Patients at intermediate risk (5%–10%/year)
- Venous thromboembolism 1 to 3 months before
- Cerebrovascular disease with two or more strokes or transient ischemic attacks
- Newer-model mechanical valve (eg, St. Jude's) in the mitral position
- Older-model mechanical valve in the aortic position

Patients at high risk (>10%/year)
- Venous thromboembolism or arterial embolism within past month
- Valvular atrial fibrillation
- Atrial fibrillation with history of cardioembolism
- Atrial fibrillation with a mechanical valve
- Mechanical heart valve with a previous embolism
- Hypercoagulable state with a past life-threatening venous thromboembolism
- Older-model mechanical valve in the mitral position
- Acute intracardiac thrombus seen on echocardiography

- Give unfractionated heparin intravenously according to a nomogram and oral warfarin; stop the heparin when the INR is between 2 and 3 and continue warfarin indefinitely
- Give weight-based LMWH indefinitely
- Give weight-based LMWH for 6 months.

In cancer patients, low-molecular-weight heparins are better than unfractionated heparin or warfarin

Thrombosis and cancer

Thrombosis is a common complication of cancer, affecting about 1 in 200 cancer patients. In fact, thrombosis is a common presentation of cancer: 15% of patients with spontaneous VTE are diagnosed with cancer within 2 years. Screening for cancer in patients with spontaneous VTE has not yet been shown to improve survival, however.

Cancer patients with acute VTE have a fourfold to eightfold higher risk of dying than do patients without cancer. Standard therapy with unfractionated heparin and long-term warfarin is often associated with higher rates of bleeding and of recurrent VTE.[7–9]

Advantages of low-molecular-weight heparins

LMWHs are better than unfractionated heparin for initial DVT therapy in cancer patients. In two meta-analyses,[10,11] mortality rates were much lower for patients who received an LMHW for initial therapy for DVT than for those who received unfractionated heparin.

LMWHs have both antithrombotic and antineoplastic effects. The antithrombotic effects include activating antithrombin III, and variably inactivating factors IIa and Xa. Animal studies indicate antineoplastic effects by direct antitumor, antiangiogenic, and immune system modulatory actions. LMWHs also stimulate release of endothelial tissue factor path inhibitor, which is both antithrombotic and antineoplastic.[12]

LMWHs are better than warfarin for long-term VTE treatment in cancer patients. In a randomized, open-label multicenter trial, Meyer et al[13] gave 146 patients with VTE and cancer enoxaparin 1.5 mg/kg subcutaneously every day for a short bridging period and then randomized them to receive 3 months of either continued enoxaparin or warfarin. The combined rate of major bleeding and recurrent VTE events was 10.5% in the enoxaparin group compared with 21% in the warfarin group. This difference was not statistically significant. However, a higher rate of fatal bleeding in the warfarin group (8%

TABLE 4

Bridging studies of low-molecular-weight heparin

AUTHOR	NO. RECEIVING LMWH	NO. WITH VALVES	BLEEDING (%)		THROMBO-EMBOLISM (%)
			MAJOR	MINOR	
Spandorfer et al[16]	20	—	5	10	0
Tinmouth et al[17]	24	12	0	8.3	4.2
Dotan et al[18]	20	3	0	10	0
Ferreira et al[19]	74	74	1.35	10.8	0
Jaffer et al[20]*	69	21	2.8	1.3	
Spyropoulos et al[21]	84	27	3.5	3.5	0
Douketis et al[22]	650	215	0.74 (high-risk surgery) 1.85 (non-high-risk surgery)		0
Kovacs et al[23]	224	112	6.7	—	3.6 (0.9 cardioembolic)
PROSPECT[24]*	250	0	3.6†	—	1.6‡
REGIMEN[25]*	721	174	3.3	12	0.9

*Abstracts
†Rate of bleeding much higher (22%) in those undergoing major surgery
‡Rate of thromboembolism much higher (5.6%) in those undergoing major surgery

compared with 0% in the enoxaparin group) reached statistical significance.

In a study by Lee et al,[9] 672 patients with cancer and DVT or pulmonary embolism received dalteparin 200 IU/kg for 5 to 7 days and then were randomized to either continue dalteparin 200 IU/kg every day for 1 month followed by 150 IU/kg for 5 months or to receive an oral anticoagulant for 6 months. Those in the oral anticoagulant group had a 17% rate of recurrent VTE compared with 9% in the dalteparin group ($P = .002$). There was no difference in major bleeding.

Efficacy rates may not tell the whole story, however. Factors that may argue against the use of LMWHs are their cost and whether insurance companies will pay for them. Giving oneself daily injections may detract from quality of life. These drugs also increase the risk of osteopenia and of heparin-induced thrombocytopenia.

Case revisited

Based on the data discussed, this patient should receive LMWH indefinitely or until he is cured of cancer.

A SURGICAL PATIENT ON WARFARIN: PERIOPERATIVE ANTICOAGULATION MANAGEMENT

A 72-year-old woman with a history of rheumatic heart disease and atrial fibrillation had a St. Jude mechanical valve placed in the mitral position approximately 5 years ago. Now, she is scheduled for sigmoid resection for colon cancer. She is taking warfarin with a target INR of 2 to 3.

What are your recommendations for her preoperative anticoagulation management?

- Stop the warfarin 5 days before surgery and admit her to the hospital for intravenous unfractionated heparin for 3 days before surgery; stop the heparin 6 hours before surgery
- Stop the warfarin 5 days before surgery and start subcutaneous enoxaparin 1 mg/kg every 12 hours for 3 days before surgery. Give the last dose about 24 hours before surgery
- Stop warfarin 5 days before surgery without bridging therapy.

The risk of embolism is higher with mechanical valves in the mitral than in the aortic position

TABLE 5

Bridging therapy protocol

Before surgery

If the preoperative INR is 2 to 3, stop warfarin 5 days before surgery (eliminate 4 doses)
If the preoperative INR is 3 to 4.5, stop warfarin 6 days before surgery (eliminate 5 doses)
Thirty-six hours after the last warfarin dose, start enoxaparin 1 mg/kg subcutaneously or dalteparin 100 IU/kg every 12 hours
The last dose of low-molecular-weight heparin should be taken about 24 hours before the procedure

After surgery

Restart low-molecular-weight heparin at full dosage about 24 hours following the procedure
Consider prophylactic dosage of low-molecular-weight heparin on the first few days for patients at high risk for bleeding; this is determined in consultation with surgeon
Restart warfarin at the preoperative dosage on the first postoperative day
Monitor the prothrombin time or INR daily until the patient is discharged, and periodically thereafter until the therapeutic range is reached
Discontinue low-molecular-weight heparin when the INR is 2 to 3 for two consecutive days
Take a complete blood cell count with platelets on days 3 and 7 to screen for heparin-induced thrombocytopenia

Bridging therapy before and after surgery

The need for bridging therapy for a patient on warfarin undergoing a nonemergent procedure depends on several factors (TABLE 3), including:

- The underlying indication for anticoagulation with warfarin
- The risk of thrombosis—eg, the patient's risk factors for thromboembolism, the risk inherent in the procedure, and the likely time off of anticoagulation
- The risk of bleeding from the procedure.

Always discuss plans for bridging therapy with the surgeon, anesthesiologist, and patient

Without anticoagulation therapy, patients with mechanical heart valves have a risk of thromboembolism of about 8% annually. This risk is slightly higher with older mechanical valves (eg, Starr-Edwards) than with newer-generation valves (eg, St. Jude). Heparin decreases that risk by about 75%. In this patient, who also has atrial fibrillation and rheumatic heart disease, the risk of thromboembolism is higher.

The consequences of thromboembolism and bleeding must also be considered. Recurrent VTEs are fatal in about 6% of cases.[2] Arterial thromboemboli are fatal in 20% of cases, and another 40% result in permanent disability.[14] Major bleeding events rarely result in permanent disability but are fatal in 3% of cases.[15]

Various options are available to maintain anticoagulation perioperatively. One option may be to use a nomogram to reduce the warfarin dose to keep the INR less than 2.0.

Other options include the use of unfractionated heparin or LMWH for bridging. Although we may have more clinical experience with unfractionated heparin and it has been around much longer than LMWH, neither drug is approved by the US Food and Drug Administration for bridging. However, there are more published abstracts and studies with the use of LMWH as a bridge for patients on warfarin for various conditions, including mechanical heart valves, than unfractionated heparin. With LMWH in this setting, the risks of thromboembolism were low, but the risk of major bleeding ranged from 0 to 6.7% (TABLE 4).[16–25]

Patients undergoing bridging therapy for surgery or a procedure should be handled very cautiously postoperatively. For major surgery, the protocol delineated in TABLE 5 can be used. For minor surgery or a procedure such as colonoscopy, full-dose anticoagulation can be resumed on the first postoperative day.

For our patient with a mechanical heart valve who is scheduled for colon resection, we would stop the warfarin 5 days before surgery and prescribe an LMWH (self-administered subcutaneously at home) starting 36 hours after the last warfarin dose. The last heparin dose should be about 24 hours before surgery. Both drugs are restarted after surgery; the

LMWH can be stopped when the INR has returned to the range of 2 to 3 for 2 consecutive days.

In all cases, the bridging therapy and plans to resume full anticoagulation should be discussed with the surgeon, the anesthesiologist, and the patient. Because the potential for litigation is high in this area, discussions should be documented.

Managing a patient with LMWH is also less expensive than with unfractionated heparin. The true mean cost savings was more than $13,000 per patient in a managed care setting in New Mexico, taking into account inpatient, outpatient, and pharmacy costs ($P < .01$).[26]

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