



BRIEF ANSWERS
TO SPECIFIC
CLINICAL
QUESTIONS

Q: Why shouldn't we use warfarin alone to treat acute venous thrombosis?

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A: Acute deep venous thrombosis (DVT) warrants acute therapy. Heparins produce desired levels of anticoagulation rapidly, within hours, whereas oral warfarin alone takes a minimum of 4 days. This delay, combined with the potential for warfarin-induced transient, paradoxical hypercoagulability, raises the risk of thrombus extension, embolization, and recurrence.

The following is a closer look at why we should not, and hopefully do not, use warfarin alone to treat acute DVT.

■ WARFARIN'S DRAWBACKS IN ACUTE THROMBOSIS TREATMENT

The primary goal of acute DVT management is achievement of therapeutic-intensity anticoagulation to prevent thrombus extension, embolization, and recurrence. Failure to surpass a minimum intensity of anticoagulation (defined as an activated partial thromboplastin time > 1.5 times control for heparin) within 24 hours of diagnosis of acute DVT increases the risk of late thrombosis recurrence.¹

Unfractionated heparin and low-molecular-weight heparins (LMWH) can rapidly achieve this degree of anticoagulation. Warfarin, on the other hand, promotes anticoagulation by inhibiting the normal hepatic posttranslational processing of vitamin K-dependent coagulation factors; therefore, there is a minimum 4-day delay in achieving

the needed reduction in factor activity to retard thrombin generation.² Brandjes et al³ showed 10 years ago that patients with acute DVT initially treated solely with a coumarin derivative (acenocoumarol) had a confirmed symptomatic recurrence rate of 20%, vs only 6% in those treated initially with heparin and acenocoumarol.

Warfarin's antithrombotic effect (ie, prevention of thrombosis) lags behind its anticoagulant effect (ie, prolongation of the prothrombin time). This lag time relates to the fact that factor VII has a significantly shorter half-life than the common pathway vitamin K-dependent factors, as will be discussed in greater detail later.

Paradoxically, warfarin may also promote an early, transient hypercoagulability by impairing production of fully functional vitamin K-dependent natural anticoagulant proteins (proteins C and S).

Yet despite its drawbacks in the acute treatment of DVT, warfarin, mainly prescribed in its oral form, is effective and convenient for chronic anticoagulation.

■ WARFARIN'S EFFECT ON THE COAGULATION CASCADE

Warfarin impairs the hepatic enzymes vitamin K-epoxide reductase and vitamin K reductase, which are required for the "recycling" of oxidized vitamin K into reduced vitamin K. Reduced vitamin K is required for the normal posttranslational gamma-carboxylation of select glutamic acid residues in the N-terminal domain of coagulation factors II (prothrombin), VII, IX, and X. In the presence of warfarin, dysfunctional coagulation factors—ie, partially carboxylated and non-gamma-carboxylated forms of these vitamin K-dependent coagulation factors—are produced and released into the circulation.²

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As fully functional circulating vitamin K-dependent factors are gradually replaced by the dysfunctional factors, a therapeutic level of anticoagulation is achieved. It takes at least 4 days to accomplish a sufficient depletion of factor activity to consider a patient anticoagulated. A stable international normalized ratio (INR) of 2.0 to 3.0 during warfarin therapy corresponds to factor activity levels of approximately 20%.⁴

Parenteral unfractionated heparin and LMWH, in contrast to warfarin, are rapidly effective, because they predominantly inactivate circulating activated factors II and X in an antithrombin-mediated process.⁵ Intravenous heparin and subcutaneous LMWH are suitable for acute management of thromboembolic events and should be utilized in addition to warfarin for at least 4 days and until a stable, target INR has been achieved.

■ ACUTE WARFARIN THERAPY: CAVEATS

INR is often deceptive in the first days

Achieving an INR between 2.0 and 3.0 during the initial several days of oral warfarin therapy does not mean that the degree of antithrombotic activity is adequate.⁶ Only a stable INR between 2.0 and 3.0 after at least 4 days (and maybe longer) of warfarin indicates an appropriate state of anticoagulation.

The reason is that prothrombin time and the INR (which is derived from the prothrombin time) primarily reflect factor VII activity. Because factor VII has a half-life of 6 to 8 hours, the initial increase in INR following the start of warfarin therapy reflects factor VII depletion rather than attainment of true systemic anticoagulation.

In fact, factor VII depletion has been shown to contribute little to warfarin's antithrombotic effect,⁷ venous thrombosis has been reported in individuals with congenital factor VII deficiency,⁸ and factor VII activity levels between 0.05 and 0.10 IU/mL (5–10%) are adequate for surgical hemostasis in some patients.⁹ Factor VII deficiency impairs the initiation of coagulation but not the amplification of coagulation.

Furthermore, the ability of thrombin to activate components of the intrinsic pathway

The coagulation cascade: Thrombin begets more thrombin

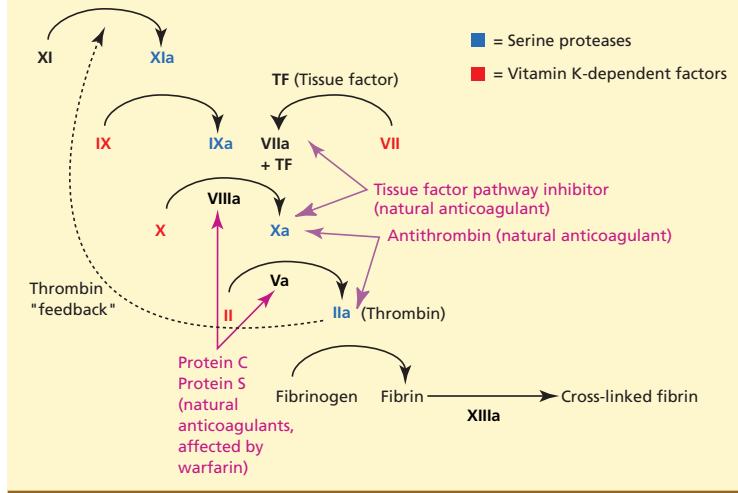


FIGURE 1. Contemporary coagulation cascade with inhibitors (natural anticoagulants).

of coagulation provides a feedback mechanism that perpetuates coagulation activation (FIGURE 1).

Factor II and X depletion takes 4 to 5 days

Experimental studies have demonstrated that depletion of factors II and X, the vitamin K-dependent factors in the common pathway of coagulation, protects against tissue factor-induced intravascular coagulation, and depletion of factors II and X is a more accurate indication of true systemic anticoagulation.⁷ Factor II has a half-life of approximately 72 hours, factor X has a half-life of approximately 36 hours, and it takes roughly 4 to 5 days of warfarin therapy to depress factor II and X levels to below 25%.

Warfarin can paradoxically cause a transient prothrombotic state

Warfarin affects the gamma-carboxylation and functional levels of the natural anticoagulants protein C and protein S, in addition to the procoagulant vitamin K-dependent factors.

Activated protein C is instrumental in regulating coagulation by inactivating cofactors Va and VIIIa in protein S-supported reactions. Protein C also can inhibit the binding

Heparin acts rapidly because it inactivates factors II and X



of factor Xa to platelets and can promote fibrinolysis by increasing levels of plasminogen activators.¹⁰ Protein C has a half-life comparable to that of factor VII (ie, 6–8 hours). Therefore, protein C levels fall in response to warfarin therapy during the period before factors II and X reach desired levels.

Without the concomitant use of heparin or LMWH, this warfarin-induced protein C deficiency can paradoxically result in a transient prothrombotic state. A large initial “bolus” dose of warfarin (≥ 10 mg) can produce a precipitous decrease in protein C activity and an even greater temporary disruption in the hemostatic balance in favor of thrombosis.⁶

Furthermore, the early protein C deficiency caused by warfarin may contribute to the development of warfarin-induced skin necrosis,¹¹ and warfarin therapy in the absence of concomitant administration of a direct

thrombin inhibitor in patients with heparin-induced thrombocytopenia is associated with venous limb gangrene.¹²

Parenteral anticoagulation with a heparin during the initiation of warfarin therapy appears to protect against the transient hypercoagulability induced by warfarin.

CONCLUSION

In patients with acute thrombosis, warfarin should be begun following the achievement of a therapeutic intensity of anticoagulation with a rapidly effective agent such as heparin or LMWH. Physicians should avoid the temptation to discontinue heparin and LMWH if the INR surpasses 2.0 prior to a minimum 4-day overlap with warfarin. Heparin and LMWH “bridging” to warfarin improves the efficacy and safety of oral warfarin therapy. ■

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Giving heparin appears to prevent warfarin-induced hypercoagulability at the start of therapy

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