

FAST FACTS AND CONCEPTS #236
PHARMACOLOGIC TREATMENT OF ACUTE VENOUS THROMBOEMBOLISM IN PATIENTS WITH ADVANCED CANCER

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Background Venous thromboembolism (VTE) is a common complication of malignancy which carries a poor prognosis (1). This *Fast Fact* discusses the approach to VTE in patients with advanced cancer.

Does anticoagulation for VTE improve outcomes? There is little randomized, placebo controlled data on anticoagulation for the treatment of VTE (2). The only study comparing heparin and warfarin for acute pulmonary embolism (PE) versus no treatment found a decrease in mortality with a number needed to treat (NNT) of four (3). Data from non-placebo controlled trials shows anticoagulation for acute VTE decreases recurrence (4) and clot propagation (5). Based on this evidence and clinical consensus, anticoagulation is recommended to decrease mortality and VTE recurrence in patients with a new VTE.

What is the best treatment for VTE for cancer patients? Current evidence-based guidelines recommend LMWH instead of oral vitamin K antagonists (e.g. warfarin) for at least 6 months in the treatment of acute VTE for advanced cancer patients, even if the patient has a primary CNS malignancy (6). The CLOT trial (7) demonstrated a decreased risk for recurrent VTE in patients maintained on LMWH versus oral anticoagulation with a number needed to treat (NNT) of 13. The major risk of anticoagulation is bleeding. In the CLOT trial major bleeding occurred in ~5% of patients regardless of the type of anticoagulation. A Cochrane review of LMWH versus oral anticoagulants for VTE in patients with cancer showed a statistically significant decrease in recurrent VTE in favor of LMWH (8). There is emerging evidence that novel anticoagulants like dabigatran (a direct thrombin inhibitor) and rivaroxaban (a direct factor Xa inhibitor) may be equally effective at treating acute VTE in cancer but with less overall associated bleeding (though perhaps more GI bleeding) and less need for serum monitoring (9). Although the use of these agents has greatly increased in the last several years, the role of these novel oral anticoagulants vs more established agents such as LMWH is not yet clearly established (6).

Does the evidence supporting the use of anti-coagulation for treatment of VTE apply to cancer patients with short prognoses? Unfortunately, most studies exclude patients with increased creatinine, those in bed greater than 50% of the day, and those with less than a three-month prognosis (see *Fast Fact* #13). Thus, there are no research data to guide clinicians on the efficacy (does it prolong life or reduce symptoms?), safety (what is the bleeding risk?), and tolerability of treating acute VTE in cancer patients with prognoses of weeks to a few months.

What other considerations should be made in the decision to treat acute VTE in cancer patients with short prognoses?

1. Decide whether to anticoagulate or treat symptomatically. This decision is largely empiric and should be based on clinical judgment about prognosis, symptom burden, and patient preference. For instance, for a patient with a prior history of VTE who remains ambulatory and who develops symptomatic VTE (e.g. a painful, swollen leg), providing anti-coagulation may be appropriate to prevent additional symptomatic events. If this same patient was already bedbound with a prognosis of weeks, it is doubtful anti-coagulation would provide substantial benefit. Though current evidence-based guidelines recommend anticoagulation for incidental VTE in advanced cancer (6), there is no strong rationale for this recommendation when a patient has a prognosis of weeks and the patient's primary goal of treatment is comfort.
2. If anticoagulation is chosen, then determine whether to use an oral vitamin K antagonists like warfarin, LMWH, or a novel oral anticoagulant such as dabigatran or rivaroxaban. LMWH and the newer oral anticoagulants do not require routine laboratory testing, have

fewer drug-drug interactions, and are less diet dependent for safe administration than warfarin. In addition, a patient's INR is highly diet dependent and can rise dangerously in patients with diminishing oral intake, which is common for advanced cancer patients. Hence warfarin may require frequent laboratory monitoring of the INR. However, LMWH and new oral anticoagulants are far more expensive than warfarin; furthermore, unlike warfarin, there is no effective antidote for these agents if the anticoagulant effect as needs to be reversed. Warfarin costs approximately \$0.11/day compared to about \$20/day for generic enoxaparin. However, this comparison does not take into account the cost of laboratory tests to monitor a patient's INR or the administration costs for patients unable to self-administer LMWH. Given its high cost LMWH may not be available for many patients receiving hospice care.

Bottom Line The patient's prognosis and preferences should be considered prior to starting anticoagulation therapy. Clinicians should work with hospice agencies to determine an affordable plan to safely administer and monitor anticoagulation for acute VTE in hospice patients. Clinicians should prepare patients who decide to initiate anticoagulation for discontinuing it once expected survival is short or worsening risks such as uncontrolled INR become apparent.

*Major bleeding includes any bleeding associated with death, located at a critical site (intracranial, intraspinal, intraocular, retroperitoneal or pericardial area), resulting in the need for a transfusion of at least two units of blood or leading to a drop in hemoglobin of at least 2.0 g per deciliter.

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