

Vitamin K Antagonists After 6 Months of Low-Molecular-Weight Heparin in Cancer Patients with Venous Thromboembolism

BACKGROUND:

- Venous thromboembolism is a common complication of malignancy positioning cancer patients with an increased risk of developing either deep vein thrombosis or pulmonary embolism.
- The treatment of choice for this population of patients is low-molecular-weight-heparin for initial and long-term therapy between three to six months.

OBJECTIVE:

- To assess whether switching to vitamin K antagonists after six months of LMWH therapy increases the risk of recurrent venous thrombosis or bleeding compared to continuing LMWH therapy.

METHODS:

- **Design:** Multicenter, unblinded, nonrandomized, propensity score-matched cohort; Duration: 12 months
- **Inclusion Criteria:** Patients with active cancer defined as new (<3 months before), diagnosed cancer, metastatic cancer, or cancer that was being treated (surgery, chemotherapy, radiotherapy, support therapy, or combined therapies); patients have been treated with LMWH for 6 months for symptomatic, objectively confirmed venous thrombosis.
- **Exclusion Criteria:** Patients currently participating in a therapeutic clinical trial with a blinded therapy; patients who stopped anticoagulation therapy prior to six months.
- **Primary Outcome Measure:** Time-to-the composite event of symptomatic, objectively confirmed recurrent deep vein thrombosis or recurrent pulmonary embolism.
- **Secondary Outcome Measures:** Major bleed, defined as a bleeding that required at least 2 unites of red blood cell transfusion, or bleeding into critical organ or site, or fatal bleeding.
- 964 patients (482 per group) either received
 - LMWH + assessment for signs and symptoms of venous thrombosis recurrence and for bleeding or other complications
 - or
 - LMWH-VKA + assessment for signs and symptoms of venous thrombosis recurrence and for bleeding or other complications
- Data handling method was intent-to-treat

RESULTS:

- Out of 964 patients initially enrolled in the study, 129 patients died; 79 from the LMWH groups and 50 from the LMWH-VKA group (2 were on LMWH and 3 were on VKA who died of bleeding). No patient died from recurrent venous thrombosis.
- **Primary Outcome Measure:** Patients who continued with LMWH had a similar rate of deep vein thrombosis recurrences (RR 1.41; 95% CI, 0.68-2.93) or pulmonary embolism recurrences than those who switched to VKA (RR 0.73; 95% CI, 0.34-1.58).
- **Secondary Outcome Measure:** Patients who continued with LMWH had a similar rate of major bleeding (RR 0.96; 95% CI, 0.51-1.79) or nonmajor bleeding (RR 1.15; 95% CI, 0.55-2.40) as compared with those who switched to VKA. Fatal bleeding occurred in 3 patients received LMWH and in 2 on VKA (RR 1.50; 95% CI, 0.25-8.93).
- **Author's Conclusions:** In cancer patients with venous thromboembolism who completed six months of anticoagulation therapy with LMWH, switching to VKA was not associated with any increase in recurrent venous thromboembolism, major bleeding, or total bleeding when compared to continuing LMWH.

STRENGTHS:

- Since they used a nonrandomized design, they performed a propensity score-based matching analysis using predefined potential confounding factors.

LIMITATIONS:

- Retrospective cohort study
- Choice of continuing LMWH or switching to VKA was confounded by patient's medical condition
- It was a nonrandomized design that included inherent bias due to prognostic imbalance

- Patients with more advanced cancer or patients who had ongoing treatments might have been selected by a treating physician to continue long-term LMWH, while switching lower-risk patients to VKA.
- No data on the status of the patient's cancer after 6 months from venous thromboembolism diagnosis
- No data was collected about compliance and patients' preferences
- Even with propensity score matching for the patient selection process, there can be remaining imbalances in terms of confounding
 - Because they observed a higher mortality rate with patients who continued on LMWH after 6 months and the most common cause of death in both groups was cancer-related, it suggests that patients who were treated with LMWH were more likely to have the worse cancer prognosis. This suggest that if patients with a higher-risk cancer were switched to VKA, they would have worse outcomes.
- No data on which LMWH therapy the patients were taking
- No data on what the INR goals were for people who switched to VKA therapy
- No data on any doses/strengths for either drug
- No data on additional medications (whether cancer or non-cancer related)

CONCLUSIONS:

- Although the study showed that VKA therapy was comparable to continuing LMWH therapy, the alternative treatment may not be comparable in actual practice.
 - The type of anticoagulation to use in cancer patients, whether LMWH or VKA, is dependent on multiple factors such as type, extent and rate of progression of cancer, type of concomitant chemotherapy, and whether or not additional medications are being used for concomitant disease states.
 - Factors like these were supposedly routinely recorded in the RIETE registry but were never reported in this study to form a clinical conclusion.
 - Even though the study concluded there is no more of an inherent risk when switching to VKA, one should not feel comfortable enough to agree that this should be done in clinical practice with all low-risk cancer patients.
 - There are too many variables left unsaid in this study, it would be difficult to extrapolate it to all cancer patients diagnosed with venous thrombosis.
- Future Research:
 - Since it was suggested in the study that patients who were treated with LMWH were more likely to have the worst cancer prognosis, a trial should be done to determine if the outcomes of patients who continued LMWH were different from those who switched to VKA after 6 months of anticoagulation therapy in a particular cancer; such as patients diagnosed with different stages of colorectal cancer.
 - A future study should also include a multicenter, blinded, randomized, placebo-controlled prospective cohort to address the need for LMWH or VKA therapy after the initial six-month treatment with LMWH for recurrent venous thrombosis.

Reference: Chai-Adisaksotha C, Iorio A, Crowther MA, Miguel J, et al. Vitamin K Antagonists After 6 Months of Low-Molecular-Weight Heparin in Cancer Patients with Venous Thromboembolism. *The American Journal of Medicine.* 2018; 131: 430-437.