New Oral Anticoagulants for Cancer Associated Venous-Thromboembolism: A Meta-Analysis

Satyanarayana R Vaidya MD, MRCP; Sonu Gupta MD; Santhosh R Devarapally MD, FACC.

Background

Venous thromboembolism (VTE) is the leading cause of mortality in patients with cancer and results in increased morbidity. The risk of VTE is fourfold to sevenfold in patients with malignancy compared to those without. The management of cancer-associated thrombosis poses many challenges due to the simultaneously increased risk of bleeding seen in patients receiving anticoagulation treatment.

The 2016 CHEST Guideline and Expert Panel Report advocates the use of low-molecular-weight heparin (LMWH) over a vitamin K antagonist (VKA) for the first three months after the diagnosis of VTE in cancer patients (Grade 2B recommendation). However, a recurrence rate of VTE as high as 15% per year in cancer patients has compelled practitioners to consider indefinite anticoagulation in this population.

The efficacy and safety of newer oral anticoagulants (NOA) compared to warfarin (VKI) in preventing the recurrence of VTE is well documented. However, it still needs to be determined whether this pattern holds when compared to the pooled data with low-molecular-weight heparin (LMWH) and Vitamin K antagonist VKA in patients with malignancy.

Objective

The purpose of the study is to compare safety and efficacy outcomes of NOA therapy with low molecular weight heparin (LMWH) alone or combination of LMWH/heparin and therapeutic doses of VKA in patients with VTE with active cancer (standard treatment).

Methods

We searched available databases for all randomized controlled trials comparing NOAs with LMWH alone or combination of LMWH/heparin and therapeutic doses of VKA. All these trials included patients with VTE and proportion of them had active cancer.

The efficacy outcomes included the number of VTE recurrences; safety outcomes included major or clinically relevant bleeding.

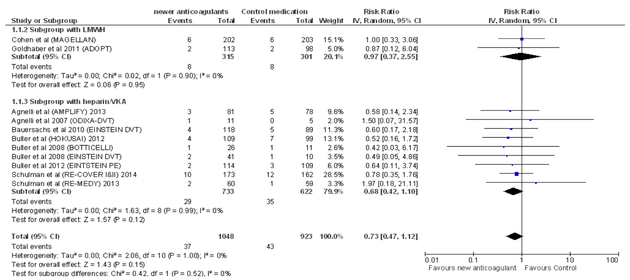
A meta-analysis of the efficacy and safety outcomes was conducted between the two groups.

The statistical analysis was conducted using Review Manager (RevMan) version 5.3 (Cochrane, Oxford, UK). The random effects model of DerSimonian and Laird was used. The relative risk ratios (RR) and 95% confidence intervals were calculated using the inverse variance method.

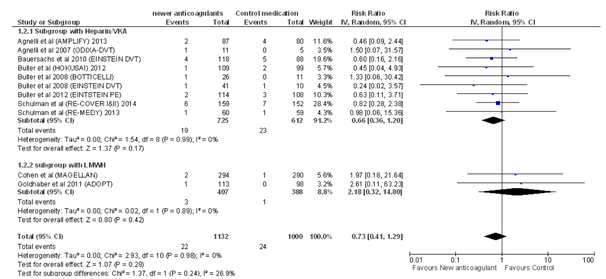
Results

Twelve studies fulfilled the inclusion criteria and were included in the meta-analysis. Of the twelve studies, ten compared NOAs with standard treatment of VTE (LMWH &VKA). Two studies compared NOAs with LMWH only in acutely ill hospitalized patients. In aggregate, all the above studies included a total of 2,054 active cancer patients. Compared to standard treatment, NOAs showed a non-significant reduction in VTE [Risk ratio (RR)=0.68; 95% confidence interval (CI)=0.42–1.10; P=0.12], major bleeding (RR=0.66; 95% CI=0.36–1.20; P=0.17), and in clinically relevant bleeding (RR=0.85; 95% CI=0.65–1.10; P=0.22).

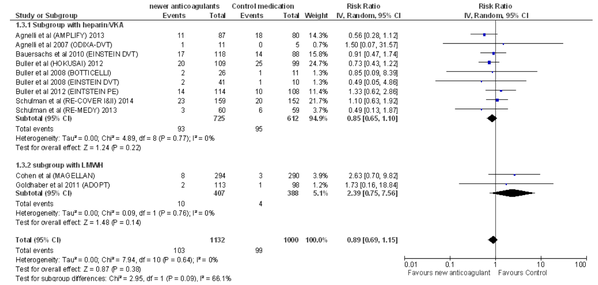
In a subgroup analysis of acutely ill hospitalized cancer patients, NOAs were comparable to LMWH in prevention of VTE (RR=0.97; 95% CI=0.37–2.55; P=0.95) however, their use was associated with higher major bleeding (RR=2.18; 95% CI=0.32–14.80; P=0.42) and clinically relevant bleeding (RR=2.39; 95% CI=0.75–7.56; P=0.14) rates.



Forest plot for Recurrence of VTE.



Comparison of Major bleeding.



Comparison of Clinically relevant bleeding

Conclusion

NOAs seem to be comparable to conventional treatment in both their efficacy and safety in patients with VTE and malignancy. However, increased rates of bleeding were observed with their use compared to the use of LMWH in acutely-ill hospitalized patients.

References

1. Blom JW, Doggen CJ, Osanto S, et al: Malignancies, prothrombotic mutations, and the risk of venous thrombosis. Jama 2005, 293(6):715-22.

2. Heit JA, Silverstein MD, Mohr DN, et al: Risk factors for deep vein thrombosis and pulmonary embolism: a population-based case-control study. Archives of internal medicine 2000, 160(6):809-15.

3. Khorana AA, Francis CW, Culakova E, et al: Thromboembolism is a leading cause of death in cancer patients receiving outpatient chemotherapy. Journal of thrombosis and haemostasis : JTH 2007, 5(3):632-4.

4. Gussoni G, Frasson S, La Regina M, et al: Three-month mortality rate and clinical predictors in patients with venous thromboembolism and cancer. Findings from the RIETE registry. Thrombosis research 2013, 131(1):24-30.

5. Khorana AA, Dalal MR, Lin J, et al: Health care costs associated with venous thromboembolism in selected high-risk ambulatory patients with solid tumors undergoing chemotherapy in the United States. ClinicoEconomics and outcomes research : CEOR 2013, 5:101-8.

Disclosure

None