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Treatment of venous thromboembolism in patients with cancer: A network meta-analysis comparing efficacy and safety of anticoagulants

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ABSTRACT

Introduction: Low-molecular-weight heparin (LMWH) and vitamin K antagonists (VKA) are current treatment options for cancer patients suffering from acute venous thromboembolism (VTE). The role of direct-acting oral anticoagulants (DOACs) for the treatment of VTE in cancer patients, particular in comparison with the current standard of care which is LMWH, remains unclear. In this network meta-analysis, we compared the relative efficacy and safety of LMWH, VKA, and DOAC for the treatment of cancer-associated VTE.

Methods: A pre-specified search protocol identified 10 randomized controlled trials including 3242 cancer patients. Relative risks (RR) of recurrent VTE (efficacy) and major bleeding (safety) were analyzed using a random-effects meta-regression model.

Results: LMWH emerged as significantly superior to VKA with respect to risk reduction of recurrent VTE (RR = 0.60, 95%CI:0.45-0.79, $p < 0.001$), and its safety was comparable to VKA (RR = 1.08, 95%CI:0.70-1.66, $p = 0.74$). For the DOAC vs. VKA efficacy and safety comparison, the relative risk estimates were in favor of DOAC, but had confidence intervals that still included equivalence (RR for recurrent VTE = 0.65, 95%CI:0.38-1.09, $p = 0.10$; RR for major bleeding = 0.72, 95%CI:0.39-1.37, $p = 0.32$). In the indirect network comparison between DOAC and LMWH, the results indicated comparable efficacy (RR = 1.08, 95%CI:0.59-1.95, $p = 0.81$), and a non-significant relative risk towards improved safety with DOAC (RR = 0.67, 95%CI:0.31-1.46, $p = 0.31$). The results prevailed after adjusting for different risk of recurrent VTE and major bleeding between LMWH vs. VKA and DOAC vs. VKA studies.

Conclusion: The efficacy and safety of LMWH and DOACs for the treatment of VTE in cancer patients may be comparable.

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1. Introduction

Venous thromboembolism (VTE) is a frequent complication and leading cause of death in patients with cancer [1]. The clinical course of cancer-associated VTE differs from VTE in non-cancer patients, most importantly because the risk of VTE recurrence and bleeding during anticoagulant therapy is substantially higher than in non-cancer patients [2]. Malignancy-associated morbidity and concurrent antineoplastic therapy further complicate the clinical management of VTE in patients with cancer [3].

The question on the optimal anticoagulation therapy for cancer patients with VTE is an ongoing area of research and debate [4,5]. Current guidelines of the major societies in the field agree in recommending a 3–6 months course of daily therapeutic doses of low molecular weight heparin (LMWH) as the first-line treatment for cancer-associated VTE [3,6–9]. For patients, the administration of LMWH therapy via daily subcutaneous injections over a course of several months is associated with considerable burden. Guidelines further recommend vitamin K antagonists (VKA) in a target International normalized ratio (INR) range of 2.0 to 3.0 as an alternative therapy given LMWH is unavailable or not possible [3]. Here, the necessity for frequent INR monitoring and the potential interactions of VKA with patient diet and anti-cancer drugs are important limitations [8,10].

Recently, direct-acting oral anticoagulants (DOACs) that directly inhibit either factor Xa (apixaban, edoxaban, and rivaroxaban) or thrombin (dabigatran) have been introduced as novel agents for treatment of VTE [11–14]. Importantly, these drugs can be administered orally in a fixed dose without the need for laboratory monitoring, and appear to have less potential drug and dietary interactions than VKA [15]. In randomized controlled trials comparing standard VTE therapy (initial LMWH followed by long-term VKA) to DOACs, all DOACs were non-inferior with respect to efficacy (i.e. prevention of VTE recurrence), and tended to be associated with a smaller risk of bleeding [4]. While

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these studies included only a small proportion of cancer patients, several subgroup analyses and four recent meta-analyses in the cancer subpopulation suggest that the efficacy and safety patterns of DOACs in cancer patients may be comparable to the patterns observed in non-cancer patients [4,16–18]. However, as head-to-head studies comparing DOACs with the currently recommended standard therapy for cancer-associated VTE, LMWH, have not been performed, the role of DOACs for the treatment of VTE in patients with cancer remains incompletely understood [3,4,19].

In the absence of real-world head-to-head studies, network meta-analyses (NMA) can provide indirect estimates of comparative effectiveness, and thus identify important trends in the data relevant for guideline makers, clinical practice, and the design of future trials [20]. In this study, we report a network meta-analysis on the efficacy and safety of DOACs, LMWH, and VKA for the treatment of VTE in patients with cancer. By performing an indirect comparison between DOACs and LMWH, we aim to explore DOACs in relation to the current standard therapy for cancer-associated VTE in terms of recurrent VTE and major bleeding.

2. Methods

2.1. Definition of Study Question

To compare the relative efficacy and safety of VKA, DOAC, and LMWH for the long-term treatment of VTE in patients with cancer.

2.2. Definition of Study Population, Interventions, and Study Designs

Adult cancer patients with any type of solid or hematologic malignancy suffering from an objectively-confirmed acute episode of VTE (i.e. deep vein thrombosis [DVT] and/or pulmonary embolism [PE]) represent the study population of this analysis. Eligible interventions were pharmacological agents from the groups of VKAs, DOACs, and LMWHs. These interventions had to be tested in randomized controlled trials (RCTs) comparing two or more of the above interventions with a minimum treatment period of 3 months. Studies comparing the above interventions against placebo, unfractionated heparin (UFH), or pentasaccharides such as idra- or fondaparinux were ineligible.

2.3. Definition of Outcomes

The efficacy and safety outcomes of this analysis were recurrent VTE and major bleeding, respectively. Recurrent VTE (DVT and/or PE) was defined according to Carrier et al. as a new non-compressible segment on leg vein sonography, new filling defect on venography, new high probability ventilation/perfusion scan, or a new pulmonary artery filling defect on chest computed tomography or pulmonary angiography [4]. Major bleeding was defined according to ISTH criteria as a bleeding episode that was clinically overt and associated with one or more of the following criteria: (1) a fall in the hemoglobin level ≥2 g/dL, (2) clinical indication for transfusion of ≥2 units of packed red blood cells, (3) bleeding located intracranially, in major joints, or the retroperitoneum, and (4) fatal bleeding [21].

2.4. Search Strategy and Study Selection

A pre-specified online literature search protocol identified 840 articles, which were independently reviewed by two authors (FP and CA, Supplemental Table 1). One RCT that was not identified by the literature search but presented recently as an abstract (the CATCH trial) was manually added [22]. Finally, 10 studies were included in this meta-analysis (Table 1, Supplemental Fig. 1). Cancer-specific data for 5 of these studies could be identified by including four congress abstracts and one published manuscript [4,23–25].

2.5. Statistical Analysis

All statistical analyses were performed using STATA (Windows Version 13.0, STATA Corp., TX, USA). The trial network was graphically visualized using the user-contributed `networkplot` function [26]. We expressed the efficacy and safety endpoints as relative risks with 95% CIs, and pooled them using a random-effects pairwise meta-analysis model (Stata routine `metan`). The I^2 statistic was calculated as a quantitative measure of heterogeneity. The network meta-analysis (NMA) was carried out within a frequentist setting, using the multivariate random-effects meta-regression routine `mvmeta` [27]. Here, we compared strategies (i.e. LMWH vs. VKA) rather than individual drugs (e.g. tinzaparin vs. acenocoumarol). To gauge the potential results of future trials on VTE therapy in cancer, we calculated 95% predictive intervals and graphically presented them on forest plots in combination with meta-analysis estimates and their 95% CIs (Stata command `intervalplot`) [26]. A surface under the cumulative ranking curve (SUCRA) analysis was performed to compare the ranks of the treatments with respect to efficacy and safety, with higher SUCRA values indicating better treatments (Stata command `sucra`) [26]. To explore the extent of clinical heterogeneity resulting from differing between-study definitions of cancer status, we calculated the 6-month risk of recurrent VTE and major bleeding in the VKA arms of the included trials, and weighed them according to the total number of patients in the VKA arm (Table 1). We then used meta-regression to adjust our NMA and SUCRA results for each study's six-month risk of VTE or bleeding in the VKA group, respectively. The dataset and full analysis code is available on request from the authors. Results are reported according to PRISMA criteria (Supplemental Table 4, Supplemental Fig. 1).

3. Results

3.1. The Evidence Base

Three-thousand-two-hundred-forty-two cancer patients from 10 two-arm RCTs were included in this analysis (Table 1). Six studies compared VKA with LMWH (n = 2078 patients), and five studies compared VKA with DOAC (n = 1164 patients). Two network plots graphically represent the evidence base (Fig. 1A+B). Most evidence existed for VKA, followed by LMWH and DOAC.

3.2. Assessment of Bias and Design Differences in Selected Studies

The risk of bias in the selected studies was assessed using Cochrane criteria (Supplemental Table 2). While all 10 studies only included patients with objectively-confirmed acute symptomatic VTE, the criteria for defining patients' cancer status at baseline were more heterogenic (Table 1). In comparison to the VKA arm of DOAC trials, the VKA arms of LMWH trials experienced both a higher risk of recurrent VTE (weighted 6-month risk: 12.6% vs. 5.5%) and major bleeding (6.1% vs. 4.0%, Table 1).

None of the selected studies actively screened for DVT and/or PE. Nine out of the 10 selected studies defined symptomatic recurrent VTE as the efficacy endpoint, while one study, the CATCH trial, also included incidental VTE events. The definition of the safety endpoint (major bleeding) appeared to be highly consistent across all 10 included studies.

3.3. Recurrent VTE and Major Bleeding – Pairwise Meta-Analysis

As compared to VKA, the relative risk of recurrent VTE was highly in favor of LMWH (Relative Risk (RR) = 0.60, 95%CI: 0.45-0.79, $p < 0.001$, Fig. 2A). The risk of major bleeding did not differ significantly between LMWH and VKA (RR = 1.07, 95%CI: 0.66-1.73, $p = 0.80$, Fig. 3A). Comparing DOACs to VKA, the relative risks were non-significantly in favor of DOACs for both recurrent VTE (RR = 0.65, 95%CI: 0.38-1.09, $p = 0.10$, Fig. 3A) and major bleeding (RR = 0.72, 95%CI: 0.39-1.35, $p = 0.31$,