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Review Article
Direct Oral Anticoagulants in Thromboembolism in Patients with Solid Cancer: Can They Be Privileged?

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Abstract

Pulmonary embolism and deep vein thrombosis are common and serious complications that take place in patients with concomitant malignant disease. Direct oral anticoagulants offer alternatives in prevention and treatment in comparison to traditional anticoagulants and therefore have been investigated by several studies. In patients with malignant disease these drugs, in particular apixaban, edoxaban and rivaroxaban, can be used for the prevention of recurrent deep vein thrombosis and pulmonary embolism. With safety being an important consideration in this vulnerable patient collective there is a natural concern regarding complications in anticoagulation treatment. The completed trials found an equivalent or lower risk of major bleeding events while using direct oral anticoagulants in comparison to traditional anticoagulants. There was an increased risk for gastrointestinal bleeding reported in patients with gastrointestinal cancer or metastases in the gastrointestinal tract. However, collectively, the risk of major bleeding was similar with direct oral anticoagulants compared to low molecular weight heparin or vitamin K antagonists. The efficacy of direct oral anticoagulants in the therapy of pulmonary embolism and deep vein thrombosis in tumor patients has also been investigated. Regarding patients with solid cancer, direct oral anticoagulants provide non-inferiority concerning efficacy and safety for the prevention and treatment of deep vein thrombosis and pulmonary embolism. They can offer an eligible oral alternative to the traditional treatment with vitamin K antagonists or low molecular weight heparin.

Key words: Thromboembolism, factor Xa inhibitors/therapeutic use, anticoagulants, embolism, cancer, hemorrhage

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Data Availability: All relevant data are within the paper and its supporting information files.

INTRODUCTION

Thromboembolism in cancer patients: Cancer patients face an up to seven times higher risk of venous thromboembolism (VTE) compared to patients without malignant disease[1,2]. Active cancer is therefore considered to be an independent risk factor for the appearance of venous thromboembolism, contributing to approximately one fifth of all cases[3-6]. The risk of cancer patients developing deep vein thrombosis with or without pulmonary involvement depends on the staging of the disease, localization of the primary tumor (highest risk being associated with the pancreas, brain, lung, kidney, ovary, stomach and bone), surgery and stationary treatment, as well as tumor-associated cancer treatments (chemotherapy, radiotherapy and pharmacological treatment)[7-10]. Recurrence of venous thromboembolism is more likely for patients with stage IV disease, tumors primarily localized to the lung, brain, pancreas or ovary and patients with recent progression of their disease[11]. Regarding mortality, venous thromboembolism ranks second on the list of causes of death in cancer patients[12].

The pathophysiology behind higher risk for thromboembolism in cancer patients is still uncertain, but likely several factors are contributing, including injury to vasculature that is induced by infiltrating cancer cells or pharmaceuticals, venous stasis due to pressure from the tumor tissue itself or prolonged bed rest, as well as endothelial damage and increased coagulation due to procoagulants released by cancer cells[13,14]. Tumor cell-derived factors directly inducing hypercoagulation include tissue factor, podoplanin, cancer procoagulant and plasminogen activation inhibitor-1[15-17]. Cytokine release from cancer cells into blood vessels may indirectly activate coagulation by inducing platelet aggregation. Furthermore, cancer cells express various adhesion molecules that allow them to attach to the endothelium and interact with immune cells circulating in the blood[18,19]. Due to this pathophysiological complexity, venous thromboembolism is still impossible to predict and hence effective treatment options are needed.

Anticoagulants: Several heparin derivatives and vitamin K antagonists such as warfarin resemble classical anticoagulants to treat venous thromboembolism. Disadvantage of these conventional anticoagulants is difficulty of applying the appropriate dosage and their interactions with other pharmacologic substances. Therefore, these agents have recently been challenged by introduction of direct oral anticoagulants (DOACs), which directly inhibit factors involved in the blood clotting cascade instead of interfering with the synthesis of these factors like vitamin K antagonists[20]. Based on the target factor in the blood clotting cascade, two DOAC types are distinguished, factor Xa inhibitors (rivaroxaban, edoxaban, apixaban) and thrombin inhibitors (dabigatran)[21] (Fig. 1). They are administered orally in a fixed dose without need for additional blood testing for determination of their anticoagulatory efficacy in contrast to vitamin K antagonists. On the other hand, laboratory testing for kidney dysfunction is still needed and patients must be sensibilized that worsened function (e.g., concomitant infectious disease) may also inherit a higher risk for bleeding complications. Each DOAC may also induce specific adverse events and show relevant interactions with other pharmaceuticals[21-23]. The inhibition induced by some DOACs, e.g., dabigatran, is reversible by administration of counter regulatory agents such as idarucizumab[24]. European guidelines increasingly recommend replacing more conventional anticoagulation agents such as vitamin K antagonists with DOACs for prevention of thrombosis or treatment of thromboembolism. This also includes patients that are anticoagulated for prevention like in cases with concomitant atrial fibrillation[25]. As these are relatively novel agents, knowledge about their efficacy and safety in the treatment of venous thromboembolism in cancer patients is limited and subject of ongoing studies. The aim of the present review was to summarize the available data on the efficacy and safety of DOAC in treating venous thromboembolism in patients with different tumor entities.

Methods: A forward and reverse literature search was conducted in the PubMed database. Inclusion criteria were studies published on oral anticoagulants/DOACs in lung cancer, prostate cancer or breast cancer patients during the past 10 years in either German or English. Exclusion criteria were studies older than 10 years, studies with pediatric patients (under 18 years of age), studies on patients with high risk of bleeding (e.g., after surgery or persistent wounds) and studies on DOACs in gastrointestinal cancers. The search terms were oral anticoagulants, DOACs, vitamin K antagonists, pulmonary embolism and malignancy, deep vein thrombosis and malignancy. On PubMed® n = 330 records were screened, of which n = 298 studies were excluded due to the given criteria.

Anticoagulants in the prevention of thromboembolism in cancer patients

Apixaban

Efficacy and safety: Several clinical trials specifically evaluated the efficacy of DOAC in the prevention and treatment of thromboembolism in cancer patients.

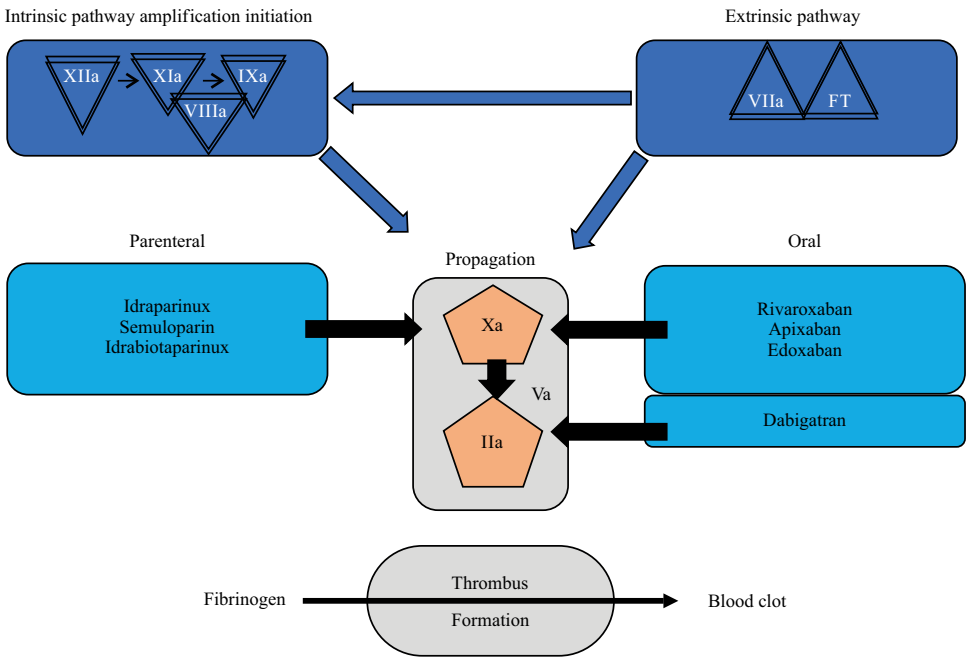

Fig. 1: Clotting cascade and intervention of anticoagulation

The placebo-controlled AVERT trial (apixaban for the prevention of venous thromboembolism in cancer patients; NCT02048865) assessed the efficacy of apixaban in administration with 2.5 mg twice daily for six months in cancer patients with a high VTE risk score according to Khorana score[26-28]. The incidence of venous thromboembolism was significantly reduced in the apixaban group compared to placebo[26].

Regarding safety, the AVERT trial showed that major bleeding episodes (any episode) occurred significantly higher in 6 patients (2.1%) who received apixaban in contrast to 3 patients (1.1%) who received placebo (hazard ratio, 1.89; 95% CI, 0.39-9.24) (Table 1). A *post hoc* analysis of the AVERT trial distinguished the patients between newly diagnosed and recurrent cancer[29]. Patients with newly diagnosed cancer had a significantly lower risk of venous thromboembolism but an increased risk of bleeding after start of apixaban administration, while the thromboembolism risk of patients with recurrent cancer was also significantly reduced without an increase in the risk of bleeding events. When patients were stratified by metastatic versus non-metastatic disease, both patient groups exhibited a significantly lower risk of venous thromboembolism due to apixaban administration, without a significant risk of bleeding in either group[30]. Another *post hoc* analysis of the AVERT trial identified patients with solid tumors, antiplatelet therapy and a body weight above 90 kg as those with a particular benefit from apixaban administration in terms of thromboembolism prevention. These results pointed towards a distinct efficacy profile of DOAC depending on the tumor stage, tumor progression and other patient characteristics. Since other studies have found an increased risk of bleeding for patients with gastrointestinal cancers[31,32] these cancer types are often considered as contraindications for DOAC usage. In controversy, the study from Ladha *et al.*[33] including patients with gastrointestinal cancer showed a lower risk of thromboembolism and bleeding in the apixaban group than in the placebo group.

Rivaroxaban

Efficacy and safety: The CASSINI trial (NCT02555878) was a placebo-controlled phase 3 trial to evaluate the efficacy of rivaroxaban in preventing symptomatic deep vein thrombosis and pulmonary embolism in cancer patients with different tumor entities[34-37]. Oral administration of rivaroxaban 10 mg once daily for 180 days reduced the incidence of proximal or distal deep vein thrombosis and pulmonary embolism compared to placebo, albeit the differences between both groups were not statistically significant for the entire cohort[35] and a subgroup of pancreatic cancer patients[38]. A *post hoc* analysis differentiating between patients with or without gastric and gastroesophageal junction cancers demonstrated that adverse events such as major bleeding were reduced by rivaroxaban in patients with other cancer types, but increased in patients with gastric/gastroesophageal junction cancer, indicating that the primary cancer type may affect both efficacy and safety[39].

Table 1: Venous thromboembolism and pulmonary embolism prophylaxis in clinical trials of oncology patients

Clinical trial	Treatment	Efficacy	NNT	Safety	NNH
AVERT[26]	Apixaban vs Placebo	Apixaban (4.2%) vs Placebo (10.2%) HR 0.41, 95% CI, 0.26-0.65, p = 0.001	17	Major bleeding: Apixaban (2.1%) vs Placebo (1.1%) HR 1.89, 95% CI 0.39-9.24	59
CASSINI[35]	Rivaroxaban vs Placebo	Rivaroxaban (6%) vs Placebo (8.8%) HR 0.66, 95% CI 0.40-1.09, p = 0.10	36	Major bleeding: Rivaroxaban (2%) vs Placebo (1%) HR 1.96, 95% CI, 0.59-6.49, p = 0.26	100

NNT: Number needed to treat, NNH: Number needed to harm, CI: Confidence interval and HR: Hazard ratio

Table 2: Venous thromboembolism and pulmonary embolism treatment in clinical trials of oncology patients

Clinical trial	Treatment	Efficacy	NNT	Safety	NNH
Hokusai-VTE[42]	Edoxaban vs Dalteparin	Dalteparin (13.5%) vs Edoxaban (12.8%) HR 0.97, 95% CI 0.70-1.36, p = 0.006 for noninferiority p = 0.87 for superiority	143	Major bleeding: Edoxaban (6.9%) vs Dalteparin (4.0%) HR 1.83, 95% CI 1.03-3.04, p = 0.04	35
SELECT-D[44]	Rivaroxaban vs Dalteparin	Rivaroxaban (4%) vs Dalteparin (11%) HR 0.43, 95% CI 0.19-0.99	14	Major bleeding: Rivaroxaban (6%) vs Dalteparin (4%) HR 1.83, 95% CI 0.68-4.96	50

NNT: Number needed to treat, NNH: Number needed to harm, CI: Confidence interval and HR: Hazard ratio

Some data is also available from smaller, prospective studies and retrospective analyses. Lee *et al.*[40] retrospectively evaluated the efficacy of rivaroxaban compared with dalteparin regarding prevention of venous thromboembolism recurrence in lung cancer patients. They found no significant difference between low molecular heparin and rivaroxaban usage. Faqah *et al.*[41] retrospectively assessed the efficacy of rivaroxaban in comparison to enoxaparin in terms of the incidence rates of deep vein thrombosis and pulmonary embolism and also found no significant differences between both antithrombotic agents, pointing towards no inferiority of rivaroxaban in thromboembolism treatment.

Anticoagulants in the treatment of thromboembolism in cancer patients

Edoxaban

Efficacy and safety: The Hokusai trial assessed the efficacy of edoxaban (60 mg/day for 3-12 months) compared to warfarin in the treatment of venous thromboembolism[42]. The patient population included patients with and without cancer. The results were not stratified by the cause of thromboembolism and showed that edoxaban was not inferior to warfarin in terms of thromboembolism treatment in patients who had received heparin as a previous anticoagulant therapy. A follow-up analysis of the Hokusai trial that specifically assessed the efficacy of edoxaban in cancer patients (NCT02073682) demonstrated that the DOAC was non-inferior to dalteparin. Meanwhile in the Hokusai trial, 6.9% of cancer patients receiving edoxaban experienced major bleeding events, compared to 4.0% in the heparin group[43].

Rivaroxaban

Efficacy and safety: In the SELECT-D trial, the efficacy of rivaroxaban as an option for treatment of cancer patients with symptomatic deep vein thrombosis or pulmonary embolism was compared to efficacy of dalteparin[32,44]. Rivaroxaban administration resulted in a reduced recurrence of venous thromboembolism but was associated with a higher frequency of bleeding events[32] (Table 2).

Additional data on DOACs in general: In addition to the aforementioned study, further systematic reviews and meta-analyses assessed the efficacy of DOAC against thromboembolism in cancer patients based on the currently available data. Song *et al.*[45], identified four randomized controlled trials and 14 retrospective analyses investigating the efficacy of DOACs in cancer patients in comparison to heparins and found an overall diminished risk of venous thromboembolism and the recurrence of deep vein thrombosis, while neither the risk of pulmonary embolism nor the mortality from this complication was significantly affected by DOAC administration. In comparison to other DOAC, the authors identified rivaroxaban as a particularly effective DOAC in reducing the thromboembolism risk in cancer patients. Samaranayake *et al.*[46] conducted a meta-analysis of the data from four available randomized controlled trials and found recurrence of venous thromboembolism to be significantly reduced by usage of DOACs in comparison to heparins in cancer patients. In contrast to Song *et al.*[45], the authors identified the highest efficacy for apixaban compared to the other DOACs. Moik *et al.*[47] also assessed efficacy of DOACs compared to heparins in the treatment of venous thromboembolism in cancer patients in a meta-analysis and confirmed a significantly reduced recurrence of venous thromboembolism.

Haykal *et al.*[48] compared the efficacy of DOAC with that of heparins as a treatment option for venous thromboembolism in cancer patients as assessed in randomized controlled trials.

They identified four randomized controlled trials[32,43,49,50] also found a decreased recurrence of venous thromboembolism and deep vein thrombosis, while no differences in pulmonary embolism recurrence were observed. In contrast, Wang *et al.*[51] concluded from their literature evaluation that DOACs reduced the incidence of pulmonary embolism and of venous thromboembolism significantly. Sabatino *et al.*[52] assessed data on DOACs in comparison to dalteparin in terms of preventing venous thromboembolism in cancer patients and observed that DOAC administration significantly reduced the incidence of venous thromboembolism compared to low molecular heparin.

Despite these positive results on DOACs for the prevention, treatment and avoidance of recurrence of venous thromboembolism in cancer patients, all systematic reviews and meta-analyses that are available to date are based on the four randomized controlled trials described above. Therefore, it is not surprising that they come to the same conclusions on DOAC efficacy.

The efficacy of DOAC in the prevention or treatment of thromboembolism in cancer patients may also depend on the location of the thrombosis. Davies *et al.*[53] assessed the efficacy of rivaroxaban in treating upper extremity deep vein thrombosis of cancer patients due to central venous catheter placement. The authors demonstrated that rivaroxaban was associated with preserved line function. Interestingly, most patients in this study were breast cancer patients and it is therefore one of the few studies addressing a specific cancer type in comparison to other tumor entities.

One issue with the available efficacy data is the lack of conclusive stratification by cancer type. An exception is the subgroup analysis of gastrointestinal cancers versus other cancer entities mentioned above and individual studies including only patients with a specific cancer type. Some information may be drawn from venous thrombosis registries such as the GARFIELD (global anticoagulant registry in the field) registry, in which thrombosis data was stratified by active cancer versus cancer-free and by tumor entity[54]. This analysis revealed differences in the incidence of venous thrombosis by cancer type and showed that thrombosis patients with cancer less frequently received DOACs than those without active cancer.

In the CASSINI trial, 2.0% of patients who had received rivaroxaban experienced major bleeding events compared to 1.0% in the placebo group[35] (Table 2). Rivaroxaban administration was associated with major bleeding events in 6% of patients and clinically relevant non-major bleeding events in 4 % of the patients analyzed as part of the SELECT-D trial, while these events did not occur in the placebo by Marshall *et al.*[44] (Table 1). The pathophysiological mechanism of such bleeding events is related to the interference of the DOAC with the blood coagulation cascade. Moreover, the risk of bleeding is associated with the primary tumor location, with gastrointestinal tumors posing a particular risk for such adverse events. Because the results of cancer-related venous thromboembolism studies in terms of DOAC safety are rarely stratified by tumor entity, patients with other cancers than gastrointestinal cancers may face a particular risk of major and non-major bleeding, which has yet to be investigated in more detail in future trials.

Due to the potentially increased risk of bleeding DOAC are contraindicated for certain patients who face an intrinsically elevated risk of bleeding that may be related to or independent of the cancer[20]. These include patients with highly malignant and dynamic cancer entities such as myeloid leukemia, lymphoma, advanced brain and colon tumors, that require tumor-specific measures including chemotherapy, patients with primary or metastatic tumors in locations that are critical for bleeding events such as colorectal carcinomas, lung tumors, brain tumors and gastric carcinomas and patients with an impaired hematopoiesis[20].

In addition to bleeding, DOACs may skew the results of standard blood tests performed to assess thrombolysis such as biochemical analysis of blood clotting parameters including prothrombin time and International Normalized Ratio (INR). For example, dabigatran raises activated partial thromboplastin time, prothrombin time, thrombin time, ecarin clotting time and anti-factor Xa activity[55]. Rivaroxaban and apixaban increase prothrombin time, activated partial thromboplastin time, anti-factor Xa activity and international normalized ratio[55].

CONCLUSION

The DOACs emerge more and more as potential replacements for conventional anticoagulants such as heparins and vitamin K antagonists. Nonetheless, their efficacy in preventing and treating deep vein thrombosis and pulmonary embolism in cancer patients has only been demonstrated in a few large randomized clinical trials. These trials found DOACs to be at least not inferior to heparins or vitamin K antagonists, both in the prevention and treatment of thromboembolism and its recurrence.

Nonetheless, certain safety concerns with DOACs remain, particularly the increased risk of major and non-major bleeding events associated with these pharmaceuticals. Moreover, the individual DOACs show distinct efficacy and safety profiles, which complicate their selection in the treatment of cancer patients in clinical practice. Future studies should investigate the distinct effect of DOACs on patients with different tumor entities to allow for a treatment algorithm by tumor entity and tumor stage. A recent meta-analysis found no survival benefit from DOAC administration in such patients, yet this point should be investigated beyond mortality risk in the future.

SIGNIFICANCE STATEMENT

Thrombosis and embolism are relevant comorbidities in patients with cancer. This systematic review was conducted to assess differences between different treatment modalities with focus on direct oral anticoagulants in comparison to vitamin K antagonists and low molecular weight heparin. Although oral intake of a fixed dosage is more feasible for patients than subcutaneous administration or measuring of coagulation parameters, they are not as frequently prescribed in cancer patients as for other indications. Direct oral anticoagulants offer equivalent efficacy in comparison to other medication while also providing a comparable amount of side effects, especially clinical-relevant bleeding episodes. Further studies should investigate direct oral anticoagulants with stratification for different solid tumor entities.

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