REVIEW

Management of venous thromboembolism in cancer patients and the role of the new oral anticoagulants

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ABSTRACT

Patients with cancer are at high risk for venous thromboembolism (VTE). Most clinical guidelines agree that low-molecular-weight heparins (LMWHs) are the preferred anticoagulants for the prevention and treatment of VTE in cancer patients. However, LMWHs require daily injections, weight-adjustment of dose, and can be associated with heparin-induced thrombocytopenia; all of which are important considerations in managing cancer-associated VTE. Comparatively, the new oral anticoagulants offer a more attractive option because of their oral administration, fixed-dose, and lack of routine laboratory monitoring. The results of phase III trials support the efficacy and safety of the new oral anticoagulants in the management of VTE. However, generalizing these findings to cancer patients with VTE is difficult since very few cancer patients were included. In this comprehensive review, we provide an overview of the current treatment of VTE, explore anticoagulant thromboprophylaxis in ambulatory cancer patients, and summarize existing evidence on the efficacy and safety of the new oral anticoagulants for the management of VTE in both non-cancer and cancer populations.

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1. Introduction

Venous thromboembolism (VTE), which includes deep vein thrombosis (DVT) and pulmonary embolism (PE), is a common complication of cancer patients. Approximately 15–20% of all VTE cases occur in patients with cancer [1,2]. In general, patients with cancer have a 4–7 fold increased risk for VTE as compared to non-cancer patients, and between 5 and 20% of patients diagnosed with cancer will develop VTE [3,4]. The risk of thrombosis is especially high during hospitalization, autochthonous chemotherapy, and following major cancer surgery. Patient characteristics, including advanced age, history of VTE, and poor performance status, as well as cancer-related factors, such as cancer type and disease stage, have been associated with an increased risk of VTE [3,5,6]. Furthermore, VTE in cancer patients is associated with important complications, including an 8–10% annual risk of bleeding with anticoagulant therapy and an annual 21–27% risk of VTE recurrence [3]. In addition, the occurrence of VTE may interfere with delivery of chemotherapy, reduce patient quality of life, and increase healthcare resource utilization [7,8]. Finally, cancer patients who develop VTE have an increased risk of death; combined arterial and venous thrombotic events are the second leading cause of death in cancer patients, accounting for 9% of cancer-related deaths [9–11].

In general, patients with VTE require anticoagulation to prevent thrombus extension and death acutely, and to prevent VTE recurrence in the long-term. In cancer patients, low molecular weight heparins (LMWHs) are the preferred anticoagulants, although vitamin K antagonists (VKAs) are used in patients where LMWH use is limited by severe renal dysfunction or cost. The inconvenience of daily injections, weight-adjustment of dose, and risk of heparin induced thrombocytopenia with LMWH and the frequent international normalized ratio (INR) monitoring and numerous food and drug interactions with VKAs, like warfarin, are important challenges in the care of the cancer patient with VTE. Of late, attention has turned to the new oral anticoagulants (NOACs) which include dabigatran, a direct thrombin inhibitor, and the factor Xa inhibitors rivaroxaban, apixaban, and edoxaban. The published trials to date, which are largely in non-cancer patient populations, have shown that these new agents are as efficacious and safe as standard anticoagulant therapies for the acute and the long-term treatment of VTE. Although data in cancer patients are sparse, these new agents are potentially attractive for use in patients with cancer because of their oral administration, fixed-dose, lack of a requirement for routine coagulation blood tests, and very little drug or food interactions. This review will briefly describe the management and prevention of VTE in cancer patients and summarize the published literature to date on the new oral anticoagulants and their potential role in the treatment and prevention of cancer-associated VTE.

2. Current treatment of venous thromboembolism in cancer patients

The initial treatment of acute VTE in cancer patients is similar to the treatment of VTE in non-cancer patients, with short-duration, weight-adjusted LMWH once or twice daily having largely replaced intravenous unfractionated heparin (UFH). The efficacy of parenteral anticoagulants...
for the initial treatment of VTE in cancer patients was assessed in a recent Cochrane review that incorporated data from 16 randomized controlled trials (RCTs) [12]. Meta-analysis showed a statistically significant reduction in mortality at 3 months follow-up with LMWH when compared to UFH (relative risk [RR] 0.71, 95% CI (0.52–0.98)), with a non-statistically significant advantage of LMWH over UFH in reduction of VTE recurrence (RR 0.78, 95% CI (0.29–2.08)). The reason for the survival benefit is unclear but may be secondary to antineoplastic effects of LMWH in certain cancer subgroups. Data on risk of bleeding and heparin-induced thrombocytopenia was insufficient to determine safety. Nonetheless, most clinical guidelines recommend LMWH over UFH for the initial treatment of acute VTE in cancer patients [13–16].

LMWH is also uniformly recommended across all guidelines for the long-term management of VTE in cancer patients [13–16]. A recent Cochrane review [17] included three open-label RCTs for a total of 1022 cancer patients comparing long-term LMWH (dalteparin, enoxaparin, and tinzaparin) to VKA for the treatment of cancer-associated VTE. In these trials, cancer patients with VTE were randomized to either weight-adjusted LMWH for 3–6 months or LMWH/UFH with VKA (dose adjusted to maintain an INR of 2–3) for 4–7 days, followed by VKA alone for 3–6 months [18–20]. There was a significant reduction in the incidence of recurrent VTE in patients receiving LMWH compared to VKA (hazard ratio [HR] 0.47, 95% CI (0.32–0.71)), with no significant differences in bleeding, thrombocytopenia or survival between the two groups. Each of the LMWHs has been studied in randomized controlled trials, however, only dalteparin is supported by the highest quality of evidence, and to date is the only LMWH with regulatory approval for the long-term treatment of cancer-associated VTE. Nonetheless, the three LMWHs are often considered therapeutically equivalent and many clinicians use them interchangeably. As a result, most major clinical guidelines do not recommend one LMWH over another for the treatment of thrombosis in cancer patients [13–16,21]. In addition to the superior efficacy of LMWH over VKAs, clinicians in general prefer LMWH because of its practical advantages over VKAs. These include the lack of food and few drug interactions, especially with chemotherapeutic agents; the avoidance of frequent venipunctures for monitoring of the anticoagulant effect; reliable delivery in patients with nausea, vomiting, and diarrhea; and a shorter half-life allowing for flexibility during invasive procedures and thrombocytopenia. However, the high cost and dependence on renal clearance may preclude use of LMWH in patients with renal insufficiency, and in these patients, VKAs are recommended [22].

3. The new oral anticoagulants and the treatment of venous thromboembolism

To date, results for dabigatran, rivaroxaban, apixaban, and, most recently, edoxaban for the treatment of acute VTE have been published. They hold promise of simplifying the management of VTE, including cancer-associated VTE. With predictable pharmacological profiles these agents are attractive alternatives to LMWH and VKAs. In particular, they are associated with minimal food and drug interactions, and can be taken orally in fixed-doses without the need for routine coagulation laboratory monitoring. Moreover, unlike VKAs, they have a shorter half-life and reach peak serum therapeutic levels within 2 to 4 h (Table 1). However, there are important considerations including their dependence on renal clearance, the lack of an antidote to reverse their anticoagulant effect in cases of bleeding, and the lack of a readily available assay to measure their anticoagulant effect if treatment failure or non-compliance is suspected.

3.1. Dabigatran for the acute and the long-term treatment of venous thromboembolism

Dabigatran has been compared with warfarin for the treatment of acute VTE in two phase III clinical trials: the RE-COVER [23] and

Table 1 Comparative pharmacology of the new oral anticoagulants and warfarin.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Rivaroxaban (Xarelto)</th>
<th>Dabigatran (Pradaxa)</th>
<th>Apixaban (Elisiqui)</th>
<th>Warfarin (Coumadin)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Target</td>
<td>Factor Va</td>
<td>Thrombin</td>
<td>Factor Va</td>
<td>VKORC1</td>
</tr>
<tr>
<td>Type of inhibition</td>
<td>Direct</td>
<td>Direct</td>
<td>Direct</td>
<td>Indirect</td>
</tr>
<tr>
<td>Prodrug</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Bioavailability</td>
<td>80–100%</td>
<td>6.5%</td>
<td>50%</td>
<td>100%</td>
</tr>
<tr>
<td>Dosing</td>
<td>q.d. (b.i.d.)</td>
<td>b.i.d.</td>
<td>b.i.d.</td>
<td>q.d.</td>
</tr>
<tr>
<td>Half-life</td>
<td>7–11 h</td>
<td>12–17 h</td>
<td>12 h</td>
<td>40 h</td>
</tr>
<tr>
<td>Tmax</td>
<td>2–4 h</td>
<td>1.5–3 h</td>
<td>3 h</td>
<td>2–8 h</td>
</tr>
<tr>
<td>Renal excretion</td>
<td>66%</td>
<td>80%</td>
<td>27%</td>
<td>None</td>
</tr>
<tr>
<td>Monitoring</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Drug interactions</td>
<td>CYP-3A4/P-gp</td>
<td>CYP-3A4</td>
<td>CYP-3A4</td>
<td>Multiple</td>
</tr>
</tbody>
</table>

Abbreviations: Tmax, time to maximum plasma concentration; q.d., once daily; b.i.d., twice daily; VKORC1, C1 subunit of the vitamin K epoxide reductase enzyme; P-gp, P-glycoprotein; CYP-3A4, cytochrome P450 3A4 enzyme.

RE-COVER II [24] trials. In both trials, patients were randomized to receive either fixed-dose dabigatran, 150 mg, twice-daily, or dose-adjusted warfarin (INR 2–3) for 6 months. The primary endpoint was non-inferiority in the 6-month incidence of recurrent VTE and VTE-related deaths. The results of both RE-COVER and RE-COVER II studies showed that dabigatran had similar efficacy as warfarin (HR 1.10, 95% CI (0.65–1.84) and HR 1.08, 95% CI (0.64–1.80), respectively) for the prevention of recurrent VTE with a similar safety profile (HR 0.82, 95% CI (0.45–1.48) and HR 0.69, 95% CI (0.36–1.32)) [23,24] (Table 2). Adverse events leading to drug discontinuation in RE-COVER were higher in the dabigatran group (7.9% vs. 6.5%, p = 0.05). However, there were no significant differences in the frequency of other adverse events, including number of deaths or acute coronary events, with the exception of dyspepsia (2.9% in the dabigatran group compared to 0.6% in the warfarin group, p < 0.001) [23].

Two complementary double-blind, randomized clinical trials were conducted to determine the efficacy and safety of dabigatran for the extended long-term treatment of VTE. These studies compared dabigatran (150 mg, twice daily) with warfarin (The RE-MEDY study [25]) or with placebo (The RE-SONATE study [25]) in patients with VTE after completing at least 3 months of initial treatment in the RE-COVER study. In the active-control study, dabigatran was shown to be non-inferior to warfarin in preventing recurrent VTE or VTE-related death (1.8% vs. 1.3%; HR 1.44, 95% CI (0.78–2.64), p = 0.01), with a trend toward a lower risk of bleeding compared to warfarin (0.9% vs. 1.8%; HR 0.52, 95% CI (0.27–1.02)). In the placebo-controlled study, recurrent VTE or VTE-related death occurred in 3 of 681 patients (0.4%) receiving dabigatran compared to 37 of 662 patients (5.6%) in the placebo group (HR 0.08, 95% CI (0.02–0.25), p < 0.001) and the risk of major bleeding with dabigatran was similar to that of placebo (0.3% vs. 0%). Although, there were more major or clinically relevant non-major bleeds in the dabigatran group compared to the placebo group (5.3% vs. 1.8%; HR 2.92, 95% CI (1.52–5.60), p < 0.001), there was no difference in the rate of acute coronary events among the groups.

It is worth mentioning, however brief, that there were significantly more cases of acute coronary events with dabigatran compared to warfarin (13 (0.9%) vs. 3 (0.2%), p = 0.02) in the RE-MEDY trial [25]. This lends support to the debate over whether use of dabigatran increases the risk of acute coronary events or if warfarin offers a cardio-protective effect through its multiple target effects on anticoagulation. When taking into consideration that dabigatran was not associated with a higher number of acute coronary events in the placebo-controlled RE-SONATE trial, it seems unlikely that dabigatran caused these events. Alternatively, the imbalance of baseline characteristics for cardiovascular risk factors (e.g., hypertension, diabetes), which favored the warfarin group, may have impacted the frequency of acute coronary events seen in the active-control study. Nonetheless, an
association between dabigatran and excess coronary events requires further study.

The efficacy and safety of dabigatran for the treatment of cancer-associated VTE have not been specifically studied. However, a subgroup analysis of the 121 cancer patients (4.7%) in the RE-COVER study showed that the frequency of recurrent events was similar in cancer patients treated with dabigatran versus warfarin (5.3% vs. 3.1%; p = 0.49) [23]. These results must be interpreted with caution as this was not a pre-specified analysis and patients with reduced life expectancy and end-organ dysfunction were excluded. As a result, cancer patients included had more favorable cancer diagnoses and therefore likely less prothrombotic.

3.2. Rivaroxaban for the acute and the long-term treatment of venous thromboembolism

Both the noninferiority designed EINSTEIN-DVT [26] and EINSTEIN-PE [27] trials compared rivaroxaban (15 mg twice daily for three weeks vs. 20 mg once daily thereafter for up to 12 months) with enoxaparin for 5 to 10 days followed by an oral vitamin-K antagonist for treatment of VTE. Overall, these studies showed that treatment of DVT and/or PE with rivaroxaban is similarly effective in preventing recurrence of VTE as standard therapy and may have a better safety profile (Table 2). Specifically, in the EINSTEIN-DVT trial, the primary outcome of VTE recurrence occurred in 2.1% of patients in the rivaroxaban groups and 3.0% of patients assigned to the VKA group (HR 0.68, 95% CI (0.44–1.04), p < 0.001). No differences in major or clinically relevant non-major bleeding were observed (HR 0.97, 95% CI (0.76–1.22), p = 0.77). As for the EINSTEIN-PE trial, the primary outcome of recurrent VTE occurred in 50 patients (2.1%) receiving rivaroxaban compared with 44 patients (1.8%) in the standard therapy group (HR 1.12, 95% CI (0.75–1.68), p = 0.003). The primary safety outcome of major or clinical relevant non-major bleeding occurred in 249 (10.3%) of patients in the rivaroxaban group and 274 patients (11.4%) in the standard therapy group (HR 0.90, 95% CI (0.76–1.07), p = 0.23) (Table 2).

In the EINSTEIN-Extension trial [26], treatment was continued for an additional 6 to 12 months to determine superiority of rivaroxaban (20 mg daily) to placebo for the treatment of symptomatic DVT or PE, after an initial 6–12 month period. Of the 602 patients taking rivaroxaban, 8 recurrent VTE events (1.3%) were observed compared to 42 events (7.1%) among those randomized to placebo (n = 594) (HR 0.18, 95% CI (0.09–0.39), p < 0.001). Major or clinically relevant non-major bleeds occurred more frequently in the rivaroxaban group compared to the placebo group (6.0% vs. 1.2%; HR 5.19, 95% CI (2.3–11.7)), although major bleeding was similar between both groups (0.7% vs. 0.8%, p = 0.11). The authors concluded that additional treatment beyond 6 months of rivaroxaban was effective in preventing recurrent events (82% risk reduction) with an acceptable risk of major bleeding (0.7%), and that this represented a favorable benefit-to-risk profile for long-term anticoagulation for secondary prevention of recurrent VTE.

The EINSTEIN-DVT [26] and PE [27] study included 207 (6%) and 223 (4.6%) patients with cancer, respectively. In the EINSTEIN-DVT study, 4 patients (3.4%) in the rivaroxaban group versus 5 patients (5.6%) in the standard therapy group experienced a recurrence. Major and clinically relevant non-major bleedings were similar between the two groups (Table 3). Among patients with cancer in the EINSTEIN-PE study, VTE recurrence occurred in 2 patients (1.8%) assigned to rivaroxaban compared to 3 patients (2.8%) assigned to standard therapy. Major and clinically relevant non-major bleeding occurred in 12.3% of patients in the rivaroxaban group compared to 9.3% of patients in the standard therapy group (Table 3). Data from a pooled analysis of EINSTEIN-DVT and EINSTEIN-PE showed that 2.6% of patients in the rivaroxaban group compared to 4% in the standard therapy group experienced recurrence of VTE (HR 0.62, 95% CI (0.22–1.8)) and that 2.6% of patients in the rivaroxaban group compared to 4.1% of patients in the standard therapy group experienced major bleeding (HR 0.61, 95% CI (0.21–1.77)) [28]. Although these results suggest that rivaroxaban may be as effective and safe as standard therapy for the treatment of VTE in cancer patients, the small number of cancer patients studied and the post priori nature of the analyses limits any definitive conclusions.

3.3. Apixaban for the acute and the long-term treatment of venous thromboembolism

Apixaban is another factor Xa inhibitor and has been studied in two phase III trials. The AMPLIFY study [29] was a double-blind study designed to show non-inferiority of apixaban (10 mg given twice daily for 7 days followed by 5 mg twice daily) compared to conventional therapy with LMWH followed by VKA (INR 2.0–3.0) for 6 months (N = 5395). The primary endpoint of recurrent symptomatic VTE and VTE-related deaths within the 6-month follow-up period occurred in 59 of the 2609 patients (2.3%) in the apixaban group and in 71 of the 2635 patients (2.7%) in the conventional therapy group (RR 0.84, 95% CI (0.60–1.18), p < 0.001 for non-inferiority). Apixaban compared to conventional therapy had a better safety profile. Major bleeding occurred in only 0.6% of patients receiving apixaban compared to 1.8% of patients receiving standard therapy (RR 0.31, 95% CI (0.17–0.55), p = 0.001 for superiority) (Table 2).

The AMPLIFY-EXT study [30] was a randomized, double-blind trial that compared two doses of apixaban (2.5 mg and 5 mg twice daily) with placebo for one additional year in 2486 patients with VTE who had completed 6 to 12 months of therapy in AMPLIFY. The primary efficacy outcome was symptomatic recurrent VTE or all-cause mortality. Compared to an 11.6% primary outcome risk in the placebo group, the risk was 3.8% and 4% in the 2.5 mg and 5 mg group, respectively (RR 0.33, 95% CI (0.22–0.48) and 0.36, 95% CI (0.25–0.35), respectively). There was no significant difference in major bleeding between the three groups (0.2% (placebo) versus 0.1% (2.5 mg) vs. 0.5% (5.0 mg)). Of note, the risk of clinically relevant non-major bleeding was higher with the 5.0 mg apixaban group compared to the 2.5 mg and placebo groups (4.2% vs. 3.0% and 2.3%, respectively), which suggests that the 2.5 mg dose may be the preferred dose when considering patients for continued therapy (Table 2).

Despite the enrollment of cancer patients into the AMPLIFY study (n = 143, 2.7%), and AMPLIFY-Ext study (n = 42, 1.7%), subgroup analyses among cancer patients were not conducted. The authors concluded that additional information is needed to adequately assess the safety and efficacy of apixaban for treatment of cancer-associated VTE [29,30].

3.4. Edoxaban for the acute treatment of venous thromboembolism

The Hokusai-VTE Investigators recently published results from their randomized, double-blind, noninferiority study comparing the oral factor Xa inhibitor, edoxaban, to warfarin for treatment of patients with acute VTE [31]. Of the 8240 patients, 4118 patients were randomized to receive 60 mg of edoxaban (once daily) while 4122 patients were randomized to receive LMWH followed by VKA (INR 2.0–3.0) for 3–12 months. The primary outcome of recurrent VTE occurred in 130 patients (3.2%) in the edoxaban group and in 146 (3.5%) in the warfarin group (HR 0.89, 95% CI (0.70–1.13)). The primary safety outcome of first major or clinically relevant non-major bleeding occurred less frequently in patients receiving edoxaban compared to those receiving warfarin (349 (8.5%) vs. 423 (10.3%), respectively; HR 0.81, 95% CI (0.71–0.92), p = 0.004 for superiority). Major bleeding occurred less often with edoxaban therapy compared to conventional therapy (56 (1.4%) vs. 66 (1.6%), respectively; HR 0.84, 95% CI (0.59–1.21), p = 0.35 for superiority) (Table 2). HOKUSAI-VTE included analyses of relative efficacy and safety in a pre-specified cancer patient subgroup. In total, 208 cancer patients were included, a relatively small fraction (2.5%) of all those randomized. Despite the small sample size, the results favored edoxaban with lower rates of recurrent VTE in those given edoxaban compared to those...
Table 2
Phase III randomized controlled trials comparing new oral anticoagulants versus conventional treatment after acute venous thromboembolism.

<table>
<thead>
<tr>
<th>Study</th>
<th>Intervention</th>
<th>Duration of treatment</th>
<th>Primary efficacy outcome(^a), n/N (%)</th>
<th>Main safety outcomes, n/N (%)</th>
<th>Conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dabigatran</strong></td>
<td>RE-COVER Dabigatran 150 mg BID vs. dose-adjusted warfarin (INR 2–3) (both treatments administered after initial treatment with enoxaparin of UFH)</td>
<td>6 months</td>
<td>30/1274 (2.4%) versus 27/1265 (2.1%) HR 1.10 (0.65–1.84)</td>
<td>MB: 20/1274 (1.6%) versus 24/1265 (1.9%) HR 0.82 (0.45–1.48) CRB: 71/1274 (5.6%) versus 111/1265 (8.8%) HR 0.63 (0.47–0.84)</td>
<td>Dabigatran is non-inferior to warfarin for recurrent VTE and VTE-related deaths. Trend toward less major bleeds with dabigatran than standard therapy.</td>
</tr>
<tr>
<td></td>
<td>RE-COVER II Dabigatran 150 BID vs. dose-adjusted warfarin (INR 2–3) (both treatments administered after initial treatment with enoxaparin of UFH)</td>
<td>6 months</td>
<td>30/1279 (2.4%) versus 28/1289 (2.2%) HR 1.08 (0.66–1.80)</td>
<td>MB: 15/1279 (1.2%) versus 22/1289 (1.7%) HR 0.69 (0.36–1.32) Any bleed: 200/1279 (15.6%) versus 285/1289 (22.1%) HR 0.67 (0.56–0.81)</td>
<td>Dabigatran is non-inferior to warfarin for recurrent VTE and VTE-related deaths. Less major bleeding with dabigatran vs. standard therapy</td>
</tr>
<tr>
<td></td>
<td>RE-MEDY Dabigatran 150 mg BID vs. dose-adjusted warfarin (INR 2–3)</td>
<td>3–36 additional months after an initial 3 months of treatment</td>
<td>26/1430 (1.8%) versus 18/1426 (1.3%) HR 1.44 (0.78–2.64), (p = 0.01)</td>
<td>MB: 13/1430 (0.9%) versus 25/1426 (1.8%) HR 0.52 (0.27–1.02) CRB: 80/1430 (5.6%) versus 145/1426 (10.2%) HR 0.54 (0.41–0.71) ACS: 13/1430 (0.9%) versus 3/1426 (0.2%)</td>
<td>Dabigatran is non-inferior to warfarin for recurrent VTE and VTE-related deaths. Fewer major bleeds with dabigatran than standard therapy.</td>
</tr>
<tr>
<td></td>
<td>RE-SONATE Dabigatran 150 mg BID vs. placebo</td>
<td>3–36 additional months after an initial 3 months of treatment</td>
<td>3/681 (0.4%) versus 37/867 (5.6%) HR 0.08 (0.02–0.25), (p = 0.001)</td>
<td>MB: 2/681 (0.3%) versus 0/667 (0%) CRB: 36/863 (5.3%) versus 12/662 (1.8%) HR 2.92 (1.52–5.60) ACS: 1/681 (0.1%) versus 1/662 (0.2%)</td>
<td>Dabigatran superior to placebo for recurrent VTE and VTE-related deaths.</td>
</tr>
<tr>
<td><strong>Rivaroxaban</strong></td>
<td>EINSTEIN-DVT Rivaroxaban 150 mg BID for 3 weeks followed by 20 mg OD vs. enoxaparin 1 mg/kg + dose-adjusted warfarin</td>
<td>3, 6, or 12 months</td>
<td>36/1731 (2.1%) versus 51/1718 (3.0%) HR 0.68 (0.44–1.04), (p = 0.001)</td>
<td>CRB: 139/1718 (8.1%) versus 138/1711 (8.1%) HR 0.97 (0.76–1.22), (p = 0.77)</td>
<td>Rivaroxaban is non-inferior to enoxaparin + warfarin for recurrent VTE-related death. Similar rates of CRB.</td>
</tr>
<tr>
<td></td>
<td>EINSTEIN-PE Rivaroxaban 150 mg BID for 3 weeks followed by 20 mg OD vs. enoxaparin 1 mg/kg + dose-adjusted warfarin</td>
<td>3, 6, or 12 months</td>
<td>50/2419 (2.1%) versus 44/2413 (1.8%) HR 1.12 (0.75–1.68), (p = 0.003)</td>
<td>MB: 26/2412 (1.1%) versus 52/2405 (2.2%) HR 0.49 (0.31–0.79), (p = 0.003) CRB: 249/2419 (10.3%) versus 274/2413 (11.4%) HR 0.90 (0.76–1.07)</td>
<td>Rivaroxaban is non-inferior to enoxaparin + warfarin for VTE recurrence and VTE-related death. Less major bleeds with rivaroxaban than standard therapy.</td>
</tr>
<tr>
<td></td>
<td>EINSTEIN-Extension Rivaroxaban 20 mg OD vs. placebo</td>
<td>6–12 months</td>
<td>8/602 (1.3%) versus 42/594 (7.1%) HR 0.18 (0.09–0.39), (p = 0.001)</td>
<td>MB: 4/598 (0.7%) versus 0/590 (0%) CRB: 36/602 (6%) versus 7/594 (1.2%) HR 5.19 (2.3–11.7)</td>
<td>Rivaroxaban is superior to placebo for VTE recurrence and VTE-related deaths.</td>
</tr>
<tr>
<td><strong>Apixaban</strong></td>
<td>AMPLIFY Apixaban 10 mg BID 7 days followed by 5 mg BID vs. enoxaparin 1 mg/kg + dose-adjusted warfarin</td>
<td>6 months</td>
<td>59/2609 (2.3%) versus 71/2635 (2.7%) RR 0.84 (0.17–0.55)</td>
<td>MB: 15/2676 (0.6%) versus 49/2689 (1.8%) RR 0.31 (0.17–0.55), (p = 0.001) CRB: 103/2691 (3.8%) versus 215/2704 (8%) RR 0.48 (0.36–0.60)</td>
<td>Apixaban was noninferior to conventional therapy for treatment of acute VTE and was associated with significantly less bleeding.</td>
</tr>
<tr>
<td></td>
<td>AMPLIFY-EXT Apixaban 2.5 mg or 5 mg BID vs. placebo</td>
<td>12 months</td>
<td>A2.5: 32/840 (3.8%) AS: 34/813 (4.2%) P: 96/829 (11.6%) RR (A2.5 vs. P) 0.33 (0.22–0.48) RR (AS vs. P) 0.36 95% CI (0.25–0.53)</td>
<td>MB: 25/840 (3%) AS: 25/813 (3%) P: 19/829 (2.3%) RR (A2.5 vs. P) 0.29 (0.72–2.33) RR (AS vs. P) 1.82 (1.05–3.18) RR (A2.5 vs. AS) 0.71 (0.43–1.18)</td>
<td>Apixaban in both doses is superior to placebo for recurrent VTE. Apixaban did not increase the rate of major bleeding or clinically relevant non-major bleeding.</td>
</tr>
</tbody>
</table>
nadirparin is not sufficient and the bleedings were comparable (4.1% vs. 3.5%), suggesting that cyclic use of nadroparin arm, subcutaneous nadroparin was administered for
refractory prostate cancer, or locally advanced pancreatic cancer. In the
in 503 patients with non-small-cell lung cancer (stage IIIB), hormone-
therapy up to a maximum of 4 months. The incidence of combined
symptomatic venous or arterial thrombotic events was 2% and 3.9%
in patients who received nadroparin versus placebo, respectively
(p = 0.02), with a nonsignificant increase in major bleeding. Van
Doormaal et al. compared nadroparin prophylaxis to no anticoagulant
in the observation group (p = 0.01); an 87% relative risk reduction with no difference in major bleeding or mortality. Similarly, an
85% risk reduction was seen in the FRAGEM study of dalteparin prophylaxis versus placebo in advanced pancreatic cancer
[35]. VTE during the 12-week treatment period was reduced from 23% to 3.4% (p = 0.002), with no difference in major bleeding. These
findings show that in patients with advanced pancreatic cancer receiving
gemcitabine-based chemotherapy. Patients were randomized to either
enoxaparin or observation for 3 months. Symptomatic VTE occurred in
5% of patients in the enoxaparin group compared to 14.5% of patients
in the observation group (p < 0.01); an 87% relative risk reduction with no difference in major bleeding or mortality. Similarly, an
85% risk reduction was seen in the FRAGEM study of dalteparin thromboprophylaxis versus placebo in advanced pancreatic cancer
[35]. VTE during the 12-week treatment period was reduced from 23% to 3.4% (p = 0.002), with no difference in major bleeding. These
findings show that in patients with advanced pancreatic cancer receiving chemotherapy, LMWH prophylaxis can safely reduce VTE rates.
The PRODIGE trial [36] tested the effect of LMWH thromboprophylaxis in 186 patients with newly diagnosed grade 3 or 4 malignant glioma. Patients received either dalteparin or placebo for 6 months, and therapy could continue for an additional 6 months. The primary outcome of symptomatic VTE occurred in 9 patients (9%) receiving dalteparin compared to 13 patients (15%) in the placebo group

<table>
<thead>
<tr>
<th>Study</th>
<th>Intervention</th>
<th>Duration of treatment</th>
<th>Primary efficacy outcome, n/N (%)</th>
<th>Main safety outcomes, n/N (%)</th>
<th>Conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Edoxaban HOKUSAI-VTE</td>
<td>Edoxaban 60 mg OD vs. warfarin</td>
<td>3–12 months</td>
<td>130/4118 (3.2%) versus 146/4122 (3.5%) HR 0.89 (0.70–1.13)</td>
<td>MB 56/4118 (1.4%) versus 66/4122 (1.6%) HR 0.84 (0.59–1.21)</td>
<td>Edoxaban was noninferior to warfarin and caused significantly less bleeding in patients with acute VTE.</td>
</tr>
</tbody>
</table>

* The primary efficacy outcome was recurrent VTE or VTE-related death.

Table 2 (continued)

<table>
<thead>
<tr>
<th>Study</th>
<th>Intervention</th>
<th>Duration of treatment</th>
<th>Primary efficacy outcome, n/N (%)</th>
<th>Main safety outcomes, n/N (%)</th>
<th>Conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rivaroxaban</td>
<td>EINSTEIN-DVT</td>
<td>207/3449 (6%)</td>
<td>15 BID → 20 OD</td>
<td>INR 2.0–3.0</td>
<td>3.4 (vs. 5.6) 14.4 (vs. 15.9)</td>
</tr>
<tr>
<td></td>
<td>EINSTEIN-PE</td>
<td>223/4832 (4.6%)</td>
<td>15 BID → 20 OD</td>
<td>INR 2.0–3.0</td>
<td>1.8 (vs. 2.8) 12.3 (vs. 9.3)</td>
</tr>
<tr>
<td></td>
<td>EINSTEIN-extension</td>
<td>54/1196 (4.5%)</td>
<td>20 OD</td>
<td>Placebo</td>
<td>n/a</td>
</tr>
<tr>
<td></td>
<td></td>
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<td></td>
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<td></td>
</tr>
<tr>
<td>Dabigatran</td>
<td>RE-COVER</td>
<td>121/2539 (4.8%)</td>
<td>n/a</td>
<td>Placebo</td>
<td>n/a</td>
</tr>
<tr>
<td></td>
<td>RE-COVER II</td>
<td>150 BID</td>
<td>INR 2.0–3.0</td>
<td>n/a</td>
<td></td>
</tr>
<tr>
<td></td>
<td>RE-MEDY</td>
<td>150 BID</td>
<td>INR 2.0–3.0</td>
<td>n/a</td>
<td></td>
</tr>
<tr>
<td></td>
<td>RE-SONATE</td>
<td>n/a</td>
<td>Placebo</td>
<td>n/a</td>
<td></td>
</tr>
<tr>
<td>Apixaban</td>
<td>AMPLIFY</td>
<td>143/5395 (2.7%)</td>
<td>10 BID → 5 BID</td>
<td>Enoxaparin 1 mg/kg; INR 2.0–3.0</td>
<td>n/a</td>
</tr>
<tr>
<td></td>
<td>AMPLIFY-EXT</td>
<td>42/2482 (1.7%)</td>
<td>2.5 BID</td>
<td>Placebo</td>
<td>n/a</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>5.0 BID</td>
<td>n/a</td>
<td></td>
</tr>
<tr>
<td>Edoxaban</td>
<td>Hokusai-VTE</td>
<td>208/8240 (2.5%)</td>
<td>60 OD</td>
<td>INR 2.0–3.0</td>
<td>3.7 (vs. 7.1) 18.3 (vs. 25.3)</td>
</tr>
</tbody>
</table>

Table 3

Cancer subgroup analysis from phase III randomized controlled trials comparing new oral anticoagulants versus conventional treatment after acute venous thromboembolism.
(HR 0.51, 95% CI (0.19–1.40)). At 6 months, there were 5 patients (5.1%) with intracranial bleeds in the dalteparin arm compared to one (1.2%) in the control arm (HR 4.2, 95% CI (0.48–36.0)). Trends suggest that thromboprophylaxis with dalteparin reduced VTE, but was also associated with increased intracranial bleeding, which raises doubt of the benefit of LMWH in glioma patients.

Overall, evidence for routine primary LMWH thromboprophylaxis in general ambulatory cancer patients is insufficient because of varying patient, cancer, and treatment-related factors. A recent Cochrane Collaboration systematic review [37] reported on the efficacy and safety of LMWH or UFH anticoagulant thromboprophylaxis in outpatients with cancer, and included nine randomized controlled trials (RCTs) enrolling 2857 cancer patients with metastatic or locally advanced solid cancers of different tissue types. Anticoagulant prophylaxis reduced symptomatic VTE (RR 0.55; 95% CI 0.37–0.82) and mortality at 48 months compared to placebo or control (RR 0.92; 95% CI 0.88–0.97). No definitive conclusion could be made on the effect of anticoagulant prophylaxis on major and minor bleedings due to the lack of statistical power. As a result, the latest ACCP clinical guidelines suggest that LMWH or UFH should be considered in cancer outpatients with solid tumors undergoing chemotherapy and at high risk for VTE (e.g., immobilization, angiogenesis inhibitors, hormonal therapy, prior thalidomide, lenalidomide, and prior VTE) [37]. The most recent ASCO guidelines [16] concluded that the available clinical trial data to-date is too limited to justify offering all patients with solid malignancies anticoagulation for thromboprophylaxis, especially given the heterogeneity of the patient populations. However, they have added to their recommendations that clinicians may consider LMWH prophylaxis on a case-by-case basis in highly selected outpatients with solid tumors receiving chemotherapy accompanied by a discussion with the patient about the uncertainties involved.

Anticoagulant thromboprophylaxis may be effective in reducing VTE in certain cancer populations, particularly those with pancreatic cancer, but it remains unclear whether thromboprophylaxis provides significant benefit to unselected cancer outpatients. Risk assessment and stratification can help identify cancer patients at highest risk for VTE and as a result, most likely to benefit from thromboprophylaxis. Several risk stratification methods have been developed that use scoring systems, based on clinical parameters and biomarkers, to identify high risk patients [38–40]. The Khorana risk assessment score was the first to be developed and was derived from a cohort of 2701 non-select cancer patients undergoing chemotherapy. Five predictive variables were identified to assess VTE risk: 1) primary site of cancer; 2) pre-chemotherapy platelet count; 3) hemoglobin level and/or use of erythropoiesis-stimulating agents; 4) pre-chemotherapy leukocyte count; and 5) body mass index [37]. Observed rates of VTE in the derivation and validation cohorts, respectively, were 0.8% and 0.3% in the low risk group (score = 0), 1.8% and 2% in the intermediate risk group (score = 1 to 2), and 7.1% and 6.7% in the high risk group (score ≥ 3). The Khorana score has been externally validated by independent groups [39–41]. In a paper by Verso et al.[41], the authors present a post hoc subgroup analysis of 1,150 patients from the PROTECHT study. These patients were separated by risk category: 12% of the patients were classified as high risk. Among these patients, rate of VTE events was 4.5% in the nadroprarin arm compared to 11.1% in the placebo arm (Verso 2012). This reduction in VTE events indirectly supports the use of the Khorana model in identifying high risk patients and shows a clinical benefit of thromboprophylaxis in these patients. Further support for the model comes from a subgroup analysis from the SAVE-ONCO study, which showed that when the risk score was applied to the patient population, the greatest risk reduction was seen in high risk patients (5.4% in placebo arm vs. 1.5% in the semuloparin arm; HR 0.27, 95% CI (0.09–0.82)) [42].

Overall, the Khorana score is simple enough to be used in the clinical setting, but must first be studied in clinical trials that will specifically determine the efficacy and safety of stratifying non-select cancer patients by risk for anticoagulant prophylaxis. Ongoing studies are assessing the Khorana risk assessment score in conjunction with LMWH prophylaxis in ambulatory cancer patients undergoing chemotherapy and future studies with the new oral anticoagulants are expected.

4.1. New oral anticoagulant for thromboprophylaxis in ambulatory cancer patients

To date, there has been only one study using a NOAC for primary prophylaxis in cancer patients [43]. In this placebo-controlled pilot study, 125 patients undergoing first-line or second-line chemotherapy for advanced or metastatic lung, breast, gastrointestinal, bladder, ovarian or prostate cancer, myeloma, or selected lymphomas randomized to 5 mg, 10 mg or 20 mg once daily apixaban or placebo for 12 weeks [43]. The primary outcome was major bleeding or clinically relevant non-major bleeding. The rate of bleeding among the apixaban group was 2.2% (95% CI (0.26%–7.5%)). Although there were no fatal bleeds and bleeding rates were low in all three apixaban groups, there was a trend for the highest rate of bleeding in the 20 mg group. Nonetheless, it was not possible to draw inferences on the safest dose. It is important to note that the study selected patients with low risk of bleeding since patients taking antiplatelet agents or with prolonged coagulation times were excluded. The authors concluded that apixaban was well tolerated and future studies were warranted to determine a safe prophylactic VTE regimen in ambulatory cancer patients receiving chemotherapy.

5. Discussion

Overall, the current data indicate that the NOACs have non-inferior therapeutic efficacy and similar or better safety profiles in comparison to short-term LMWH for 5–7 days followed by warfarin for the treatment of acute VTE in the general population. Moreover, all four new agents demonstrate low adverse events during extended therapy, beyond 3–6 months. Although demonstrating non-inferiority is arguably not sufficient to change standard of care, the predictable pharmacological profile, ease of administration, lack of required monitoring or dose adjustments, very few drug–drug interactions, and lack of food interactions make the new oral agents attractive for the treatment of VTE in cancer patients.

However, there is insufficient data in support of these new agents in the management of VTE in cancer patients. Primarily, there have been no studies specifically investigating the role of these agents in the treatment of cancer-associated VTE. Moreover, all trials to date included very few patients with malignant disease: RE-COVER study of dabigatran: 4.8% [23]; RE-MEDY: 2.1% [25]; EINSTEIN trials of rivaroxaban: 6% (DVT) [26], 4.6% (PE) [27], and 4.5% (extended VTE treatment) [26]; AMPLIFY study of apixaban: 2.7% [29]; AMPLIFY-EXT trial of apixaban: 1.8% (2.5 mg) and 1.1% (5 mg) [30] and HOKUSAI-VTE: 2.5% [31]. While cancer subgroup analyses suggest clinical benefit for rivaroxaban, dabigatran and edoxaban, the small sample size and exploratory nature of these analyses limit any definitive conclusions. The strict inclusion criteria in these trials limited patients with end-organ dysfunction (e.g., renal and liver dysfunction) and elevated risk of bleeding from enrolling, resulting in an overall study population likely not-representative of patients with advanced cancer who compared to the general population have a higher risk of recurrent thrombosis and major bleeding with anticoagulation [3,44]. Lastly, while the new agents demonstrated non-inferiority against warfarin, this does not necessarily equate to non-inferiority over LMWH, which is the preferred VTE treatment method in cancer patients. As a result, the efficacy and safety of the new oral anticoagulants in cancer patients has not been adequately assessed to date in this population. Further research is needed to understand the effect of these agents in cancer patients, including trials directly comparing NOACs with LMWH, before adopting them for the treatment of cancer-associate VTE.
Several other potential concerns regarding the use of these agents in cancer patients have yet to be addressed. Although few drug interactions have been reported to date, the NOACs can inhibit or induce either the CYP 3A4 (rivaroxaban, apixaban) system or the p-glycoprotein (dabigatran and apixaban) system. The CYP 3A4 system is integral to the metabolism of several chemotherapeutic agents (e.g., capetabine and imatinib) [45,46] and targeted biologics including tyrosine kinase inhibitors (e.g., sorafenib, sunitinib, and imatinib) [45]. Moreover, p-glycoprotein is a transporter protein that is exploited by cancerous cells to extrude cytotoxic drugs that usually enter the cell by passive diffusion and as a result is implicated in multidrug chemotherapy resistance [47]. It is unknown what role if any the new oral agents may have on efflux-mediated chemotherapy resistance. Though these drugs undoubtedly also interact with warfarin, the ability to monitor warfarin’s anticoagulant effect somewhat mitigates the risks of concomitant therapy.

Another concern is the cancer population’s predisposition to bleeding while on standard anticoagulant therapy [48,49]. The risk of major bleeding with use of warfarin among cancer patients is estimated to be approximately three times greater than placebo recipients [50] and while low molecular weight heparin is associated with a lower risk of bleeding [51], the risk is not negligible. Although the more reliable pharmacokinetics of the new oral agents compared to warfarin may offset some of the risk of bleeding, features unique to the cancer population, including cancer-induced and chemotherapeutic-associated thrombocytopenia, chemotherapy-induced mucositis/enteritis, and use of anti-angiogenic therapy, can theoretically increase the risk of bleeding with use of these new agents. Moreover, cancer patients are susceptible to renal dysfunction either directly from cytotoxic effects of chemotherapeutic agents or indirectly as a result of dehydra tion from chemotherapy-induced gastrointestinal toxicity. Dabigatran and rivaroxaban are mostly dependent on renal clearance for elimination, and both agents are contraindicated in patients with severe renal impairment (creatinine clearance < 30 ml/min). Through apixaban is less dependent on renal elimination, apixaban is not recommended in patients with creatinine clearance < 15 ml/min or in those undergoing dialysis, and caution should be used in patients with severe renal impairment. Accumulation of apixaban has been shown in patients with severe renal impairment and dabigatran accumulation has been observed with mild to moderate renal impairment [52–54]. As a result, use of these medications, including apixaban, requires frequent monitoring of renal function in cancer patients who may experience impairment of renal function during chemotherapy in addition to a thorough assessment of bleeding. A subgroup analysis that combined the bleeding data from the EINSTEIN-DVT and PE trials reported less bleeding with rivaroxaban than the standard therapy group (2.6% vs. 4.1%; HR 0.61, 95% CI (0.21–1.77)) [28]. Although this is encouraging safety data, further larger studies in non-select cancer patients are needed to confirm these preliminary findings.

Finally, although the oral administration of the new anticoagulants is undoubtedly more convenient than the injectable administration of the LMWHs, chemotherapy-related gastrointestinal toxicities resulting in nausea and vomiting, difficulty swallowing and diarrhea may limit oral intake and absorption of the new agents. The effect of missed doses on the risk of recurrence is not known, although use of low molecular weight heparin is a bridging option during periods of limited oral intake.

6. Conclusion

In conclusion, the are promising for the treatment of VTE in the general population, but there are limited data on the use of these agents in cancer patients to determine their efficacy and safety in the management of cancer-associated VTE. Dedicated studies of cancer patients with VTE are needed in order to clarify the role of the new oral anticoagulants before these agents can be recommended for treatment and possibly prevention of VTE in this important patient population.

Conflict of interest

The authors declare no conflicts of interest.

References


