Comparison between direct factor Xa inhibitors and low-molecular-weight heparin for efficacy and safety in the treatment of cancer-associated venous thromboembolism: A meta-analysis

ABSTRACT

Aim of the Study: The role of direct-acting oral anticoagulants in the treatment of venous thromboembolism (VTE) in cancer patients compared with the current standard of low-molecular-weight heparin (LMWH) treatment remains unclear. This meta-analysis aimed to evaluate the efficacy and safety of direct factor Xa inhibitors compared with those of LMWH in the treatment of cancer-associated VTE.

Materials and Methods: We systematically searched PubMed, EMBASE, Cochrane library, and Web of Science for potential randomized controlled clinical trials and retrospective cohort studies. Data on recurrent VTE (efficacy) and major and minor bleeding events (safety) were extracted, and the odds risks (OR) were analyzed using a random-effect model.

Results: A total of nine studies involving 4208 cancer patients with VTE were included in these analyses. Pooled analysis showed that direct factor Xa inhibitors were significantly superior to LMWH in reducing the risk of recurrent VTE (OR = 0.67; 95% confidence interval [CI]: 0.54–0.82). There was no significant difference in the rate of major bleeding between the direct factor Xa inhibitor and LMWH treatments (OR = 1.25; 95% CI: 0.94–1.65). However, the rate of minor bleeding events was higher when a direct factor Xa inhibitor was used instead of LMWH (OR = 1.80; 95% CI: 1.05–3.07).

Conclusions: Direct factor Xa inhibitors are superior to LMWH in efficacy in the treatment of VTE in cancer patients, and the safety between the two regimens is comparable except for a slightly higher rate of minor bleeding when the former is used.

KEY WORDS: Cancer-related venous thromboembolism, direct-acting oral anticoagulants, efficacy, low-molecular-weight heparin, safety

INTRODUCTION

Cancer is a well-established hypercoagulable state with a 4–7-fold higher risk of venous thromboembolism (VTE) than the general population.[1,2] Although direct oral anticoagulants (DOACs) are the first-line treatment for VTE in patients without cancer,[3] low-molecular-weight heparin (LMWH) is recommended for those with cancer.[4,5] Direct Xa inhibitors have been approved because of their effectiveness and safety.[6-8] Additional benefits include fixed dosing, fewer interactions, and no requirement for blood monitoring compared with warfarin.[9-11] This study aimed to evaluate the efficacy and safety of direct factor Xa inhibitors in comparison with those of LMWH for the treatment of cancer-associated VTE.

MATERIALS AND METHODS

Data sources and search strategy
This analysis was conducted in line with the guidelines for the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA). The registration number in the PROSPERO

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database is CRD42018107438. PubMed, EMBASE, Cochrane library, and Web of Science were searched by two reviewers (Y. M. and L. J.) independently from each one’s inception until August 2018. The terms, such as rivaroxaban, apixaban, edoxaban, neoplasms, and LMWH, were searched as the Medical Subject Heading. Relevant reviews and meta-analyses were also reviewed.

**Study selection**

Two reviewers (Y. M. and L. J.) independently conducted the study screening, and disagreements were resolved through group discussion with a third person (S. R.). Studies were included if they met the following predetermined criteria: (a) they had analyzed cancer patients with VTE who underwent an anticoagulant therapy, (b) they had investigated the effect and bleeding risk of direct factor Xa inhibitors versus LMWH, (c) they were full studies reported in English, and (d) they were not limited to random controlled trials (RCTs) but also included eligible observational studies. Studies that met the following criteria were excluded: (a) those reported as letters, abstracts, conference summaries, case reports, reviews, or laboratory studies; (b) those published as duplicate data (only the most complete one was included); and (c) those in which a key information needed for further analysis was missing.

**Data extraction and quality assessment**

Data were extracted according to the PRISMA criteria. For each study, the following data were independently extracted by two authors (Y. M. and L. J.): country, year of publication, study design, treatment, comparator, follow-up months, and sample size. The following outcomes were collected for the two treatment groups where available: number of VTE recurrences, and major and minor bleedings. The outcomes were reported as defined in the individual studies.

The study quality was assessed by two reviewers (Y. M. and L. J.) using the JADAD score for RCTs and Newcastle-Ottawa Scale (NOS) for cohort studies. The disagreements about study data extraction and quality assessment were resolved by discussion with a third person (S. R.).

**Statistical analysis**

We determined pooled odds ratios (ORs) and 95% confidence intervals (CIs) for VTE recurrences in patients with cancer treated with direct Xa inhibitors or LMWH. We also assessed the pooled ORs of major or minor bleeding. Data were pooled by using the Mantel–Haenszel method. Results were reported according to a fixed-effects model in the absence of significant heterogeneity and to a random-effects model in the presence of significant heterogeneity. The appropriateness of pooling data across the studies was assessed using the I² test for heterogeneity. In addition, we conducted sensitivity and subgroup analyses. The meta-analyses were performed using Stata software (version 14.0, Stata Corp, College Station, Texas).

**RESULTS**

**Literature search**

As shown in Figure 1, a total of 654 pieces of literature were identified from database searches. Nine studies met the inclusion criteria and were included in this meta-analysis. No publication bias was detected [Figure 2].

**Characteristics of the eligible studies and quality assessment**

The characteristics of the nine studies included are listed in Table 1. This meta-analysis involved 4208 patients from studies that included 44–1367 patients. Seven (77.78%) studies were from the USA, one study (11.11%) was from the UK, and one study (11.11%) was from Spain. Two studies (22.22%) were RCTs and seven studies (77.78%) were retrospective cohort studies. The regimens of the study treatment group included rivaroxaban, edoxaban, and apixaban, while those of the comparator group included dalteparin, LMWH, and enoxaparin. Results of quality assessment (NOS/JADAD) are shown in Table 1. The basic outcomes, including VTE recurrence and major and minor bleeding, are presented in Table 2.

**Efficacy outcomes**

**Venous thromboembolism recurrence**

The rates of VTE recurrence in the nine studies are reported in two groups [Table 2]. The aggregated rate of VTE recurrence was 10.41% (179 of 1720 patients) and 12.72% (300 of 2359 patients) in the direct factor Xa inhibitor and LMWH groups, respectively. A significantly lower rate of VTE recurrence was found in the direct factor Xa inhibitor group than that of the LMWH group (OR = 0.67; 95% CI: 0.54–0.82) with no heterogeneity ($I^2 = 0$%; $P = 0.472$) [Figure 3].
Table 1: Main characteristics of studies included in the meta-analysis

| Study                        | Country | Age (years) | Primary cancer type, n (%)                         | Co-morbidities                              | Study design | Study treatment | Metastatic cancer, n (%) | Comparator | Follow-up (months) | Sample size | Quality assessment (NOS/JADAD) |
|------------------------------|---------|-------------|---------------------------------------------------|---------------------------------------------|--------------|-----------------|--------------------------|------------|---------------------|------------|------------------------------|
| Young et al., 2018[12]       | UK      | 67.0        | Colorectal (25.1), lung (11.6), esophageal/gastroesophageal (7.4), ovarian (7.4), pancreatic (7.4), other/unknown (31.3) | NA                                           | RCT          | Rivaroxaban     | 236 (58.1)               | Dalteparin | 6                   | 406         | 3 (JADAD)                         |
| Streiff et al., 2018[13]     | USA     | 73.0        | Lung (19.9), gynecologic (6.9), pancreatic (6.9), lymphoma (6.7), other/unknown (60.6) | Hypertension (69.3), diabetes (29.7), COPD (29.3), obesity (11.8) | Retrospective cohort study | Rivaroxaban | NA                                          | LMWH       | 3, 6, 12               | 1367        | 9 (NOS)                         |
| Simmons et al., 2018[14]     | USA     | Study treatment: 62.6 | GI (19.9), pancreatic (10.9), GU (9.4), lung (8.3), other/unknown (51.5) | NA                                           | Retrospective cohort study | Rivaroxaban | 148 (55.6)               | Enoxaparain | 3                   | 266         | 8 (NOS)                         |
| Nicklaus et al., 2018[15]    | USA     | Study treatment: 57.9 | NA                                               | NA                                           | Retrospective cohort study | Rivaroxaban | 48 (53.3)                | Enoxaparain | 3                   | 90          | 7 (NOS)                         |
| Raskob et al., 2018[16]      | USA     | Study treatment: 64.3 | NA                                               | NA                                           | RCT          | Edoxaban        | 554 (53.0)               | Dalteparin | 12                  | 1046        | 3 (JADAD)                         |
| Chaudhury et al., 2018[17]   | USA     | Study treatment: 62.2 | NA                                               | Hypertension (49.0), diabetes (13.3), coronary artery disease (13.3) | Retrospective cohort study | Rivaroxaban | 146 (51.0)               | Dalteparin | 1, 3, 6               | 286         | 8 (NOS)                         |
| Alzghari et al., 2018[18]    | USA     | Study treatment: 62.0 | Lung (25.4), gynecologic (16.9), breast (15.5), colorectal (12.7), other/unknown (29.6) | NA                                           | Retrospective cohort study or apixaban | Rivaroxaban | 32 (45.1)                | Enoxaparain | >6                  | 71          | 8 (NOS)                         |
| Signorelli and Gandhi 2017[19] | USA     | Study treatment: 60.4 | Gynecologic malignancies                         | NA                                           | Retrospective cohort study | Rivaroxaban | 15 (34.1)                | Enoxaparain | 6                   | 44          | 8 (NOS)                         |
| Xavier et al., 2017[20]      | Spain   | 62.5        | Colon (26.8), pancreatic (17.1), rectal (7.3), other/unknown (39.1) | Hypertension (39.0), diabetes (24.4), COPD (0.0) | Retrospective cohort study | Rivaroxaban | 36 (87.8)                | LMWH       | 5.5                  | 632         | 7 (NOS)                         |

NA=Not reported, COPD=Chronic obstructive pulmonary disease, GI=Gastrointestinal, GU=Genitourinary, RCT=Random controlled trial, LMWH=Low-molecular-weight heparin, NOS=Newcastle-Ottawa Scale
Yang, et al.: A meta-analysis of treatment for cancer-associated venous thromboembolism

Table 2: Rates of efficacy and safety in the original studies

| Author                  | Years | Study treatment versus comparator                   | Recurrent VTE (%) | Major bleeding (%) | Minor bleeding (%) |
|-------------------------|-------|-----------------------------------------------------|-------------------|--------------------|--------------------|
| Young et al[12]         | 2018  | Rivaroxaban versus dalteparin                       | 3.94 versus 8.87  | 5.42 versus 2.96   | 12.32 versus 3.45  |
| Straiff et al[13]       | 2018  | Rivaroxaban versus LMWH                            | 16.50 versus 22.14| 8.18 versus 8.36   | NA                 |
| Simmons et al[14]      | 2018  | Rivaroxaban versus enoxaparin                      | 1.02 versus 4.17  | 5.10 versus 3.57   | 6.12 versus 0.60   |
| Nicklaus et al[15]      | 2018  | Rivaroxaban versus enoxaparin                      | 8.89 versus 13.33 | 2.22 versus 4.44   | 28.89 versus 22.22 |
| Raskob et al[16]       | 2018  | Edoxaban versus dalteparin                         | 7.65 versus 11.26 | 6.90 versus 4.01   | 14.56 versus 11.07 |
| Chaudhry et al[17]     | 2018  | Rivaroxaban versus dalteparin                      | 5.00 versus 11.34 | 2.80 versus 1.12   | 9.35 versus 4.47   |
| Alzghari et al[18]    | 2018  | Rivaroxaban or apixaban versus enoxaparin          | 8.33 versus 21.74 | 6.25 versus 4.35   | NA                 |
| Signorelli and Gandhi[19] | 2017  | Rivaroxaban versus enoxaparin                      | 0.00 versus 3.85  | 16.67 versus 7.89  | NA                 |
| Xavier et al[20]       | 2017  | Rivaroxaban versus enoxaparin                      | 12.20 versus 7.11 | 0.00 versus 6.65   | 12.20 versus 16.55 |

NA=Not reported, LMWH=Low-molecular-weight heparin, VTE=Venous thromboembolism

Figure 2: Funnel plot showing the absence of publication bias

Safety outcomes

Major bleeding

The numbers of the major bleeding events in the nine studies are reported in Table 2. The meta-analysis results showed similar rates of major bleeding between the direct factor Xa inhibitor and LMWH treatment groups (OR = 1.25; 95% CI: 0.94–1.65) with no heterogeneity (I² = 0%; P = 0.488) [Figure 4].

Minor bleeding

Minor bleeding data were available from six studies [Table 2]. In the direct factor Xa inhibitor treatment group, 13.29% (135/1016) patients presented with minor bleeding events, significantly higher than that observed in the LMWH treatment group (10.51% [176/1675]) (OR = 1.80; 95% CI: 1.05–3.07) with a moderate heterogeneity (I² = 55.8%; P = 0.045) [Figure 5].

Sensitivity analysis

“One-by-one study removed” method was used for the sensitivity analysis. The results are stable in the summary OR estimates of the outcomes [Supplementary Figure 1].

Subgroup analysis

Subgroup analyses for the different types of direct factor Xa inhibitors showed that the ORs of the rates of recurrent VTE for rivaroxaban, edoxaban, and rivaroxaban/apixaban groups were 0.67 (95% CI: 0.49–0.93), 0.67 (95% CI: 0.44–1.02), and 0.33 (95% CI: 0.08–1.36), respectively [Figure 6].

DISCUSSION

The objective of this meta-analysis was to compare direct Xa inhibitors with LMWH for the treatment of VTE in patients with cancer by pooling data from all the available RCTs and retrospective cohort studies. We analyzed data from nine studies including >4000 patients. Our analysis suggested that the use of direct Xa inhibitors was associated with a 33% reduction compared with the use of LMWH in the risk of VTE recurrence in cancer patients. There was no significant difference in the occurrence of major bleeding between the two treatments although direct Xa inhibitors might increase the risk of minor bleeding events. Subgroup analyses showed that only rivaroxaban was associated with a lower rate of recurrent VTE and different direct Xa inhibitors did not significantly differ in terms of bleeding events.
Based on our knowledge, this study is the first that has systematically collected data to directly compare the efficacy and safety outcomes of the use of direct Xa inhibitors and LMWH in the treatment of VTE in cancer patients. A meta-analysis by Brunetti et al. have previously reported no advantageous effect of direct Xa inhibitors compared with LMWH in terms of the recurrence of VTE (OR = 0.96; 95% CI: 0.52–1.75). However, their latest meta-analysis including both direct Xa inhibitors and dabigatran have found a similarly reduced risk of VTE recurrence, as our findings in comparison with that observed with LMWH or warfarin (relative risk [RR] = 0.64; 95% CI: 0.46–0.88). The guidelines recommend the use of direct Xa inhibitors in preventing the recurrence of VTE based on evidence from patients with no cancer. The findings in our study provide updated evidence to support the use of direct Xa inhibitors in cancer patients as well.

The occurrence of bleeding events is the main side effect of direct Xa inhibitors. Our study found no significant difference in major bleeding events between the uses of direct Xa inhibitors and LMWH in both overall and subgroup analyses, consistent with the comparisons between all DOACS and LMWH or warfarin in cancer patients (RR = 1.31; 95% CI: 0.71–2.44). However, Brunetti et al. have reported that the OR of major bleedings is 2.72 (95% CI: 1.05–7.01) with direct Xa inhibitors relative to LMWH. Notably, our study found that the rate of minor bleeding events in the use of direct Xa inhibitors was significantly higher than that in the LMWH group, while the significance disappeared in the subgroup analyses. The reason could be attributed to the moderate heterogeneity of the included studies. In addition, the dose of direct Xa inhibitors may make a difference in the efficacy and safety outcomes. A previous meta-analysis has demonstrated that, in comparison with LMWH, low doses of oral factor Xa inhibitors can achieve a small absolute risk reduction in venous thrombosis without increasing bleeding, whereas high doses increase bleeding.

There are some limitations when interpreting the findings in our study. All the studies included in this meta-analysis were from Post hoc analyses of RCTs or retrospective cohort studies. It is noteworthy that there were differences in the enrollment of the participants, follow-up period, and definition of major and minor bleedings, potentially causing the heterogeneity of our findings. Second, although the original aim of this study was to analyze the effects of all the direct Xa inhibitors, seven of the nine studies included in our study adopted rivaroxaban as the treatment therapy, and thus somewhat limited us to analyze the rivaroxaban treatment. Third, only patients from the USA, UK, and Spain were enrolled in these nine studies, hampering a global generalization. Last but not least, even though we systematically searched the electronic databases and also investigated the references in the included studies, we may have nevertheless missed some studies.

CONCLUSIONS

This meta-analysis suggests that direct Xa inhibitors are superior to LMWH in reducing the incidence of VTE recurrence in cancer patients without putting the patients at high risk for major bleeding. Meanwhile, our findings should be interpreted...
Yang, et al.: A meta-analysis of treatment for cancer-associated venous thromboembolism

with caution because rivaroxaban has been adopted in most studies. Future studies might assess the efficacy and safety data of other direct Xa inhibitors for the treatment of VTE in patients with different types of cancer.

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Conflicts of interest
There are no conflicts of interest.

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