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“direct Oral Anticoagulants Versus Low-molecular-weight Heparin for Acute Treatment of Venous Thromboembolism in Patients With Gastrointestinal Cancer: a Systematic Review and Meta-analysis”

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Research

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Abstract

Background

The association between gastrointestinal (GI) cancer and a high incidence of venous thromboembolism (VTE) is well known. Previous randomized controlled studies demonstrated that direct oral anticoagulants (DOACs) effectively treat cancer-associated VTE (CAT). However, some DOACs appeared to increase the risk of bleeding, particularly in patients with GI malignancies. Therefore, the current systematic review and meta-analysis was conducted to evaluate the safety and efficacy of DOACs in GI cancer-associated thrombosis.

Methods

All relevant studies that compared DOACs and low-molecular-weight heparin (LMWH) in GI cancer-associated thrombosis that were published before December 2020 were individually searched in two databases (MEDLINE and EMBASE) by two investigators. The effect estimates and 95% confidence intervals (CI) from each eligible study were combined using the Mantel-Haenszel method.

Results

A total of 1,418 patients were included in this meta-analysis. The rate of major bleeding was not significantly different between groups (relative risk [RR]: 1.57, 95% CI: 0.93-2.65, P=0.09, I^2=34%). However, the rate of clinically relevant non-major bleeding (CRNMB) was significantly higher in the DOACs group (RR: 1.98, 95% CI: 1.34-2.91, P=0.0005, I^2=0%). The risk of recurrent VTE was not significantly different between groups (RR: 0.72, 95% CI: 0.41-1.28, P=0.27, I^2=0%).

Conclusions

The current data suggests that treatment of GI cancer-associated thrombosis with DOACs significantly increases the risk of CRNMB, and a trend towards major bleeding risk in DOACs group. The efficacy of DOACs for preventing recurrent VTE in GI cancer was comparable to that of LMWHs.

Trial registration: INPLASY202180113

Background

The relationship between cancer and thrombosis is well recognized. Recent population-based study showed that the cumulative incidence of venous thromboembolism (VTE) after cancer diagnosis was 11.1-fold higher than non-cancer patients [1]. Moreover, VTE is among the leading cause of death in cancer patients [2]. The absolute rate of VTE in all cancers from a large United Kingdom database was 13.9 per 1,000 person-years [3, 4]. A study in East Asian population revealed an incidence of cancer-associated VTE of 9.9 per 1,000 person-years, particularly in hepatocellular and pancreatic cancer [5]. In addition to ethnicity and cancer stage, the type of cancer also influences the risk of thrombosis. Gastrointestinal (GI) cancer (cancers of the pancreas, stomach, liver, colon, and rectum) is among the top four most prevalent cancers in worldwide cancer statistics [6, 7]. A higher incidence of VTE was found in GI cancer patients compared to those with non-GI cancer [8, 9]. Singh R, *et al*. reported that 60 of 220 (27.3%) GI cancer patients experienced 83 thromboembolic events, including 38.6% deep vein thrombosis, and 20.5% pulmonary embolism [9]. Interestingly, some of those patients experienced more than one thrombotic event, and some thromboses were incidentally found [9].

Treatment of cancer-associated thrombosis has vastly improved in recent years. Direct oral anticoagulants (DOACs) have become a standard treatment for VTE in cancer patients based on evidence from recent randomized controlled studies that compared efficacy and safety between DOACs and low-molecular-weight heparin (LMWH) [10–13]. Even though the benefit of DOACs for preventing recurrent thrombosis has been clearly demonstrated in cancer patients, the risk of bleeding is a drawback– especially in patients with GI malignancies. The Hokusai VTE Cancer trial found major bleeding events among GI cancer patients treated with edoxaban to be significantly higher than the rate observed in the dalteparin arm (13.2% *vs.* 2.4%, $p = 0.0169$ [10]. In the SELECT-D study, patients with esophageal or gastroesophageal cancer receiving rivaroxaban tended to experience more major bleeding compared to those treated with dalteparin (36% *vs.* 5%) hence the recruitment of patients with this tumor type was stopped in the ongoing trial [11]. In contrast, the incidence of bleeding events, particularly in patients with GI malignancies, was not significantly different between the apixaban and dalteparin arms in the ADAM VTE and Caravaggio trials [12, 13].

The aim of this systematic review and meta-analysis was to improve our understanding of the efficacy and safety of DOACs for acute treatment of VTE in patients with GI cancer compared to low-molecular-weight heparin (LMWH) by comprehensively identifying all available studies, and summarizing and analyzing their data.

Methods

Data sources and searches

All relevant studies that compared DOACs and LMWH in GI cancer-associated thrombosis that were published before December 2020 were individually searched in two databases (MEDLINE and EMBASE). Two investigators (TR and WO) separately examined the included articles from the search terms 'DOACs', 'anticoagulants', and 'GI cancer' (**Additional file 1: Supplementary Data 1**). The Preferred Reporting Items for Systematic Reviews and Meta-Analyses Statement guided for this meta-analysis is shown in **Additional file 2: Supplementary Data 2** [14]. The study protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) (registration number INPLASY202180113).

Selection criteria and data extraction

The inclusion criteria for this meta-analysis were, as follows: 1) the type of study must have been a randomized controlled trial (RCT) or a cohort studies (either retrospective or prospective); 2) the study must have compared the efficacy between at least one DOAC and at least one LWMH in GI cancer-associated venous thromboembolism; 3) the study must have included the primary outcome of the study; and, 4) the study must have defined the definition of major bleeding according to the criteria of the International Society on Thrombosis and Haemostasis (ISTH) [15].

Selection of relevant articles and extraction of data was independently performed by the same two investigators (TR and WO). If there was any disagreement or question regarding the eligibility of an article, a third investigator (BS) intervened and made the final decision. The two investigators (TR and WO) examined the baseline characteristics data and the outcomes of all included studies, and the extracted data were cross-checked to avoid inaccuracy.

Outcome definitions

The primary outcome was either recurrent VTE or major bleeding after anticoagulant therapy according to the ISTH criteria [15]. The definition of major bleeding included fatal bleeding, symptomatic bleeding in a critical area or organ, or bleeding causing a decrease in hemoglobin level of 2 g/dL or more, or leading to transfusion of two or more units of whole blood or red cells [15].

The secondary outcome was clinically relevant non-major bleeding (CRNMB). CRNMB was defined by the studies differently as provided in **Additional file 3: Supplementary Data 3**. Definitions of CRNMB that were used by studies included in this meta-analysis are shown in **Additional file 3: Supplementary Data 3**.

Quality assessment

The Jadad Quality Assessment Scale [16] and the Newcastle-Ottawa Scale [17] were used to evaluate the quality of the included randomized controlled trials and the non-randomized studies, respectively.

Statistical analysis

Review Manager 5.3 software from the Cochrane Collaboration (London, UK) was used to analyze all data. Two investigators (TR and WO) extracted all data from the selected studies using a standardized data extraction form. The effect was estimated and combined with 95% confidence intervals (CIs) using the Mantel-Haenszel method [18]. Cochran's Q test was calculated, and the statistical heterogeneity among the studies was estimated using the I^2 statistic. The four levels of heterogeneity were based on the value of I^2, as follows: 1) insignificant heterogeneity (I^2-value of 0–25%); 2) low heterogeneity (I^2-value of 26–50%); 3) moderate heterogeneity (I^2-value of 51–75%); and, 4) high heterogeneity (I^2-value of 76–100%) [19]. The random-effects model was applied based on the assumption that there was heterogeneity in each individual study due to individual patient characteristics, differences in the DOACs used among studies, and differences in the types of GI cancers [19]. A *p*-value less than 0.05 was considered statistically significant.

Results

Study identification and selection

Using electronic searches in the MEDLINE and EMBASE databases, 1,019 potentially relevant articles were collected until December 2020. One-hundred and forty-nine duplicated articles were excluded. Two investigators reviewed the titles and abstracts of the remaining 870 articles. Of those, 844 articles were excluded if they met at least one of the following three criteria: 1) the articles were reviews, meta-analyses, commentaries, or editorials, 2) the reports were irrelevant to the comparison between DOACs and LMWH, or 3) the reports described a study population different from that being evaluated in our study. A total of 26 full-length articles were identified. Of those, 20 articles were excluded due to insufficient data and/or lack of clinical outcomes. The remaining 6 articles (three RCTs and three retrospective studies) that collectively enrolled 1,418 patients were included in the present meta-analysis (one evaluating edoxaban, four evaluating rivaroxaban, and two evaluating apixaban). Figure 1 demonstrates the literature review and article selection process.

Baseline characteristics

A total of 1,418 patients were included from 6 studies. Among those, 165 patients were treated with edoxaban [20], 275 were treated with rivaroxaban [11, 21–23], 217 were treated with apixaban [23–24], and 761 were treated with LMWH (dalteparin (n = 647), enoxaparin (n = 113),

nadroparin (n = 1)). The characteristics of the patients included in the 6 studies included in this meta-analysis are described in Table 1. The number of patients enrolled in this study according to the type of GI cancer was 361 with upper GI cancer (cancer of the esophagus and/or stomach), 567 with lower GI cancer (cancer of colon and/or rectum), 483 hepato-biliary-pancreatic cancer (hepatocellular carcinoma, cholangiocarcinoma, cancer of the gallbladder, and/or pancreatic cancer), and 7 neuroendocrine tumors. GI cancer patients were further subdivided into the following three groups: group 1–928 patients with luminal GI cancer (cancer of the esophagus, stomach, colon, and/or rectum) [11, 20–24]; group 2–483 patients with non-luminal GI cancer (hepatocellular carcinoma, cancer of the gallbladder, and/or pancreatic cancer) [11, 20–24]; and, group 3–7 patients with neuroendocrine tumor [23]. The follow-up time in all studies was 6 months [11, 20–24].

Table 1
The characteristics of the patients included in the 7 studies included in this meta-analysis

Fist author and year of publication	Patients inclusion criteria	Group of treatment (No.)	Dose of anticoagulants	Type of GI cancers (No.)	Type of GI cancers (luminal VS non-luminal, others) (No.)	Follow up time in months (study period)	Type of study	Quality assessment (Jadad Quality score[16]/Newcastle-Ottaea scale (NOS)[17])
Young et al. 2018 [11]	Patients with active cancer (diagnosis or treatment within 6 months, recurrent or metastatic cancer receiving rivaroxaban or LMWH for symptomatic PE, DVT or incidental PE	Rivaroxaban (91)	15 mg BID for 3 weeks then 20 mg daily	Esophagus (11) Stomach (4) Colorectal (55) HB (2) Pancreas (19)	Luminal (70) Non-luminal (21)	6 months September 2013-December 2016)	Randomized controlled trial	-Showed method of randomization -No double blind -Withdrawal and dropout patients presented
		Dalteparin (86)	200 IU/Kg once daily for 30 days then 150 IU/Kg	Esophagus (19) Stomach (7) Colorectal (47) HB (2) Pancreas (11)	Luminal (73) Non-luminal (13)			
Recio-Boiles et al. 2019 [23]	Patients receiving DOACs or LMWHs with GI cancer and symptomatic or incidental VTE	Rivaroxaban (37)	15 mg BID for 3 weeks then 20 mg daily	Esophagus (3) Stomach (4) Colorectal (26) HB (1) Pancreas (28) NET (4)	Luminal (33) Non-luminal (29) NET (4)	6 months up (November 2013-February 2017)	Retrospective cohort study	Selection: 4 Comparability: 2 Outcome: 3
		Apixaban (29)	10 mg BID for 7 days then 5 mg BID					
		Enoxaparin (40)	1 mg/kg/dose twice daily or 1.5 mg/kg once daily	Esophagus (0) Stomach (5) Colorectal (11) HB (6) Pancreas (15) NET (3)	Luminal (16) Non-luminal (21) NET (3)			
Lee et al. 2019 [21]	Patients receiving rivaroxaban or LMWHs with GI cancer and confirmed PE or DVT	Rivaroxaban (78)	15 mg BID for 3 weeks then 20 mg daily	Stomach (19) Colorectal (21) Pancreato-biliary (38)	Luminal (40) Non-luminal (38)	6 months (January 2012-December 2016)	Retrospective cohort study	Selection: 4 Comparability: 2 Outcome: 3

Fist author and year of publication	Patients inclusion criteria	Group of treatment (No.)	Dose of anticoagulants	Type of GI cancers (No.)	Type of GI cancers (luminal VS non-luminal, others) (No.)	Follow up time in months (study period)	Type of study	Quality assessment (Jadad Quality score[16]/Newcastle-Ottaea scale (NOS)[17])
		LMWH (203) -Dalteparin (177) -Enoxaparin (25) -Nadroparin (1)	Dalteparin: 200 IU/kg once daily Enoxaparin: 1 mg/kg/dose twice daily Nadroparin: 85.5 IU/kg twice daily	Stomach (98) Colorectal (11) Pancreato-biliary (94)	Luminal (109) Non-luminal (94)			
Ageno et al. 2020 [24]	Patients with active cancer or diagnosed within 2 years receiving apixaban or dalteparin for symptomatic or incidental PE/DVT	Apixaban (188)	10 mg BID for 7 days then 5 mg BID	Upper GI (23) Colorectal (121) HB or pancreas (44)	Luminal (144) Non-luminal (44)	6 months (April 2017-June 2019)	Randomized controlled trial (non-inferiority trial)	-No method of randomization -No double blind –Withdrawal and dropout patients presented
		Dalteparin (187)	200 IU/Kg once daily for 30 days then 150 IU/Kg	Upper GI (31) Colorectal (113) HB or pancreas (43)	Luminal (144) Non-luminal (43)			
Mulder et al. 2020 [20]	Cancer patients with symptomatic or incidental PE/DVT receiving edoxaban or LMWH	Edoxaban (165)	60 mg once daily after initial LMWH 5 days (30 mg once daily in creatinine clearance 30–50 mL/min, BM below 60 kg or concomitant treatment with potent P-glycoprotein inhibitors)	Esophagus (23) Stomach (10) Colorectal (83) HB (14) Pancreas (35)	Luminal (116) Non-luminal (49)	6 months (July 2015-December 2016)	Randomized controlled trial (non-inferiority trial)	-Showed method of randomization -No double blind -Withdrawal and dropout patients presented
		Dalteparin (140)	200 IU/Kg once daily for 30 days then 150 IU/Kg	Esophagus (11) Stomach (10) Colorectal (79) HB (12) Pancreas (28)	Luminal (100) Non-luminal (40)			

Fist author and year of publication	Patients inclusion criteria	Group of treatment (No.)	Dose of anticoagulants	Type of GI cancers (No.)	Type of GI cancers (luminal VS non-luminal, others) (No.)	Follow up time in months (study period)	Type of study	Quality assessment (Jadad Quality score[16]/Newcastle-Ottaea scale (NOS)[17])
Kim et al. 2020 [22]	Patients with upper GI tract and HBP cancer receiving LMWH or rivaroxaban (including unresectable or metastatic cancer)	Rivaroxaban (69)	15 mg BID for 3 weeks then 20 mg daily	Esophagus (1) Stomach (23) HB (18) Pancreas (27)	Luminal (24) Non-luminal (45)	6 months (January 2004-December 2014)	Retrospective cohort study	Selection: 4 Comparability: 2 Outcome: 3
		LMWH (105) -Dalteparin (57) -Enoxaparin (48)	Dalteparin: 200 IU/Kg once daily for 30 days then 150 IU/Kg Enoxaparin: 1 mg/kg twice daily	Esophagus (7) Stomach (52) HB (21) Pancreas (25)	Luminal (59) Non-luminal (46)			

Clinical bleeding outcome

Three randomized controlled trials and three retrospective studies compared DOACs with LMWH. Major bleeding was defined according to International Society on Thrombosis and Haemostasis (ISTH) criteria [15], which was combined with bleeding resulting in surgical intervention in the Caravaggio study [13]. Our pooled analysis showed a non-significantly higher risk of major bleeding in patients receiving DOACs compared to those receiving LMWH with the pooled relative risk (RR) of 1.57. However, the pooled effect estimate did not reach a statistically significant difference (95% CI: 0.93–2.65, $P = 0.09$). The heterogeneity of the meta-analysis was low with an I^2-value of 34% [11, 20–24] (**Fig. 2**).

A subgroup analysis evaluating major bleeding events in patients with luminal and non-luminal GI cancer revealed a trend toward non-statistically significant increased major bleeding in patients with luminal GI cancer treated with DOACs with a pooled RR of 1.58 (95% CI: 0.67–3.72, $P = 0.30$, $I^2 = 49\%$) (**Fig. 3A**) [11, 22, 24]. Similarly, among non-luminal GI cancer patients, major bleeding was not significantly different between groups, but the patients who received DOACs showed a trend towards more major bleeding with a pooled RR of 1.83 (95% CI: 0.6–5.56, $P = 0.29$, $I^2 = 0\%$) (**Fig. 3B**) [11, 22, 24].

In contrast, the incidence of CRNMB was significantly higher in the DOAC group than in the LMWH group with a pooled RR of 1.98 (95% CI: 1.34–2.91, $P = 0.0005$, $I^2 = 0\%$) (**Fig. 4**) [11, 21, 22, 24].

Locations of bleeding

Three studies reported the locations of major bleeding in patients with GI cancer treated with DOACs [22, 24, 25]. Thirty-three and 12 out of 65 bleeding events occurred in the upper and the lower GI tract, respectively. Other bleeding sites were the central nervous system, genitourinary tract, retro- and intra-peritoneal areas, upper airway, epistaxis, and muscle hematoma. Major bleeding details and the type of anticoagulant therapy are shown in **Table 2**.

Recurrent VTE outcome

The rate of recurrent VTE was not significantly different between those who received DOACs and those who received LWMH with a pooled RR of 0.72 (95% CI: 0.41–1.28, $P = 0.27$, $I^2 = 0\%$) (**Fig. 5**) [20, 21, 23].

Subgroup analysis of study outcomes according to the type of study

Both RCTs and cohort studies were included in this current systematic review and meta-analysis to analyze the bleeding outcomes separately based on the type of study [11, 20–24]. In RCT studies, the trend of bleeding outcomes was similar to the pooled analysis. The pooled RRs of major bleeding and CRNMB were 1.60 (95% CI: 0.82–3.15, $P = 0.17$, $I^2 = 25\%$) (**Fig. 2**) [11, 20, 24] and 3.07 (95% CI: 1.40–6.69, $P = 0.005$, $I^2 = 0\%$) (**Fig. 4**) [11, 24], respectively. Likewise, the pooled RRs of major bleeding and CRNMB in cohort studies were comparable to the results of full analysis (**Figs. 2 and 4**) [21, 22]. The pooled RR of VTE recurrence from cohort studies was not different between DOACs and LMWHs group [21, 23]; however, the pooled VTE recurrence outcome from RCT studies could not be performed due to limited number of the studies (**Fig. 5**) [20].

Subgroup analysis of bleeding risk according to the type of DOAC

Neither the rivaroxaban nor apixaban subgroups was associated with a significant increase in major bleeding events compared to the LMWH arm with a pooled RR of 1.61 (95% CI: 0.75–3.47, $P = 0.22$, $I^2 = 50\%$) in the rivaroxaban group (**Fig. 6A**) [11, 21–23], and a pooled RR of 1.06 (95% CI: 0.47–2.39, $P = 0.90$, $I^2 = 0\%$) in the apixaban group (**Fig. 6D**) [23, 24]. In contrast, CRNMB rates were significantly higher in GI cancer patients treated with rivaroxaban compared to those treated with LMWH (pooled RR: 1.82, 95% CI: 1.18–2.81, $P = 0.007$, $I^2 = 0\%$) (**Fig. 6B**) [11, 21, 22]. There was no significant difference in the rates of recurrent VTE between the two groups (pooled RR: 0.76, 95% CI: 0.25–2.32, $P = 0.63$, $I^2 = 0\%$) (**Fig. 6C**) [21, 23]. Due to the limited number of comparative studies between apixaban and LMWH in GI cancer patients, data specific to CRNMB and recurrent VTE could not be demonstrated. Likewise, the analysis of major bleeding, CRNMB, and recurrent VTE could not be performed in a subgroup of GI cancer patients receiving edoxaban due to insufficient data comparing edoxaban and LMWH. Figure 6 demonstrates forest plot of studies that compared major bleeding, CRNMB and recurrent VTE in patients who received each DOAC in comparison with LMWHs.

Table 2. Major bleeding details and the type of anticoagulant therapy reported from studies included in this meta-analysis

References	Group of treatment (No. of bleeding patients)	Number of events and the site of major bleeding						
		Upper GI tract	Lower GI tract	Central nervous system	Genitourinary tract	Retroperitoneal area	Intra-abdominal area	Other sites
Kraaipoel et al. 2018 [25]	Edoxaban (21)	16	3	-	-	1	-	1 Epistaxis
	Dalteparin (5)	1	-	2 intracerebral hemorrhage 1 thoracic spinal cord	-	-	-	1 Not mentioned
Kim et al. 2020 [22]	Rivaroxaban (12)	7	2	-	-	-	-	3 Unspecified GI tract
	LMWHs (8)	2	1	-	-	-	3 hemoperitoneum	1 Unspecified GI tract 1 Unspecified site
Ageno et al. 2020 [24]	Apixaban (9)	4	3	-	1	-	1	
	Dalteparin (9)	3	3	-	-	1	-	2 Upper airway 1 Muscle

Abbreviations: GI, gastrointestinal; LMWHs, low molecular weight heparins

Discussion

Several studies have demonstrated the efficacy and safety of DOACs in patients with cancer-associated venous thromboembolism [10–13]. DOACs have become an alternative to LMWH for the treatment of CAT. Despite the non-inferior efficacy of DOACs to LMWH for preventing recurrent VTE, a higher bleeding risk was found in certain DOACs in a subgroup analysis of patients with GI and genitourinary tract cancers compared to that of LMWH [25–27]. However, previous randomized controlled trials enrolled patients with various kinds of cancer. Thus, a systematic review and meta-analysis that focuses on the use of DOACs for acute treatment of venous thromboembolism in patients with gastrointestinal cancer is needed.

The pooled analysis in this study demonstrated no significant differences in major bleeding or recurrent VTE between patients who received DOACs and patients who received LMWH. Major bleeding was also found to be similar in subgroup analysis that compared luminal and non-luminal GI malignancy. It is possible that some luminal GI cancer patients were treated with surgical resection of the tumor before starting anticoagulant therapy, which would have reduced the risk of GI bleeding. In contrast, the rate of CRNMB was significantly higher in GI malignancy patients in the DOACs group than in the LMWH group.

A previous randomized controlled trial of VTE treatment in non-cancer patients demonstrated a higher incidence of GI bleeding among those treated with rivaroxaban compared to those treated with warfarin [26]. Moreover, the incidence of GI hemorrhage and CRNMB was significantly higher in the rivaroxaban group than in the LMWH group in the SELECT-D study [11]. A higher rate of major bleeding, but not CRNMB, was observed in cancer patients receiving edoxaban compared to those receiving dalteparin in the Hokusai VTE Cancer trial, and a higher rate of GI bleeding was observed in patients with GI cancer [10]. In contrast, two studies reported no significant difference in the risk of major GI bleeding in cancer patients compared between those receiving apixaban and those receiving LMWH [12, 13].

Interestingly, analysis for association between bleeding risk and the type of DOAC used for acute VTE treatment in GI cancer patients showed no significant difference in major bleeding in both the rivaroxaban and apixaban subgroups. This result suggests that the type of DOAC might not be the only risk factor for high bleeding risk in GI cancer patients. Nonetheless, higher CRNMB was observed in patients receiving rivaroxaban compared to those receiving LMWH in this meta-analysis.

The results of the meta-analysis are consistent with those of previous meta-analyses of DOAC use in cancer patients that reported higher CRNMB [27], but similar major bleeding events [28, 29] in DOAC users compared to those taking LMWH. Although major bleeding in the present meta-analysis was not significantly different between GI cancer patients receiving DOACs and GI cancer patients receiving LMWH, there was a trend towards increased major bleeding in the DOACs group. Moreover, the efficacy of DOACs for preventing recurrent VTE was not different from that of LMWH in GI cancer patients. The lack of significance was likely from the low number of events resulting in lower power of statistics. Therefore, DOACs should be considered an effective alternative treatment to LMWH for treating acute VTE, with no statistically significant difference in major bleeding among patients with GI malignancies. However, the significantly higher CRNMB that is associated with DOACs must be considered when deciding to use DOACs in GI cancer patients. The risk of bleeding should be disclosed and discussed with the patients before starting therapy.

To the best of our knowledge, this is the first systematic review and meta-analysis to gather current available comparative data between DOACs and LMWH for acute treatment of venous thromboembolism in GI cancer patients. Analysis for consistency among studies based on visual inspection of forest plots and the low I^2 values showed no or low level of heterogeneity.

This study has some limitations. First, the low number of events and included patients may preclude demonstrating statistically significant differences in some outcomes such as recurrent VTE. Second, the data of specific baseline characteristics of the patients which might affect the risk of thrombosis, such as gender, age, cancer treatment, are lacking. Third, the definition of the primary outcome varied among included studies. Fourth, there were only three studies that included recurrent thrombosis as the primary outcome. Fifth and last, publication bias could not be assessed due to the limited number of studies included in this meta-analysis.

Conclusions

The pooled data from this meta-analysis suggest that the efficacy of DOACs for prevention of recurrent VTE in patients with GI malignancies is comparable to that of LMWH. However, CAT treatment with DOACs is associated with significantly increased risk of CRNMB. Therefore, the benefits and risks of DOAC treatment in CAT should be discussed with the patients with GI cancer before commencing the therapy.

Abbreviations

CI: confident interval; CRNMB: clinically relevant non-major bleeding; DOACs: direct oral anticoagulants; GI: gastrointestinal; ISTH: International Society on Thrombosis and Haemostasis; LMWH: low-molecular-weight heparin; MB: major bleeding; RCT: randomized controlled trial; RR: relative risk; VTE: venous thromboembolism

Declarations

Ethics approval and consent to participate

The need for ethics approval by institutional board review was waived as this study does not directly involve human subjects.

Consent for publication

Not applicable because this study does not directly involve human subjects.

Availability of data and material

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

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Authors' Contributions

All authors designed the study. T.R.(1) and W.O. collected the data. W.O. performed the statistical analyses. T.R.(1) and B.S. drafted the manuscript and prepared the final version. Y.C., B.S., and T.R.(2) made critical revisions. All authors read and approved the final manuscript.

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Figures

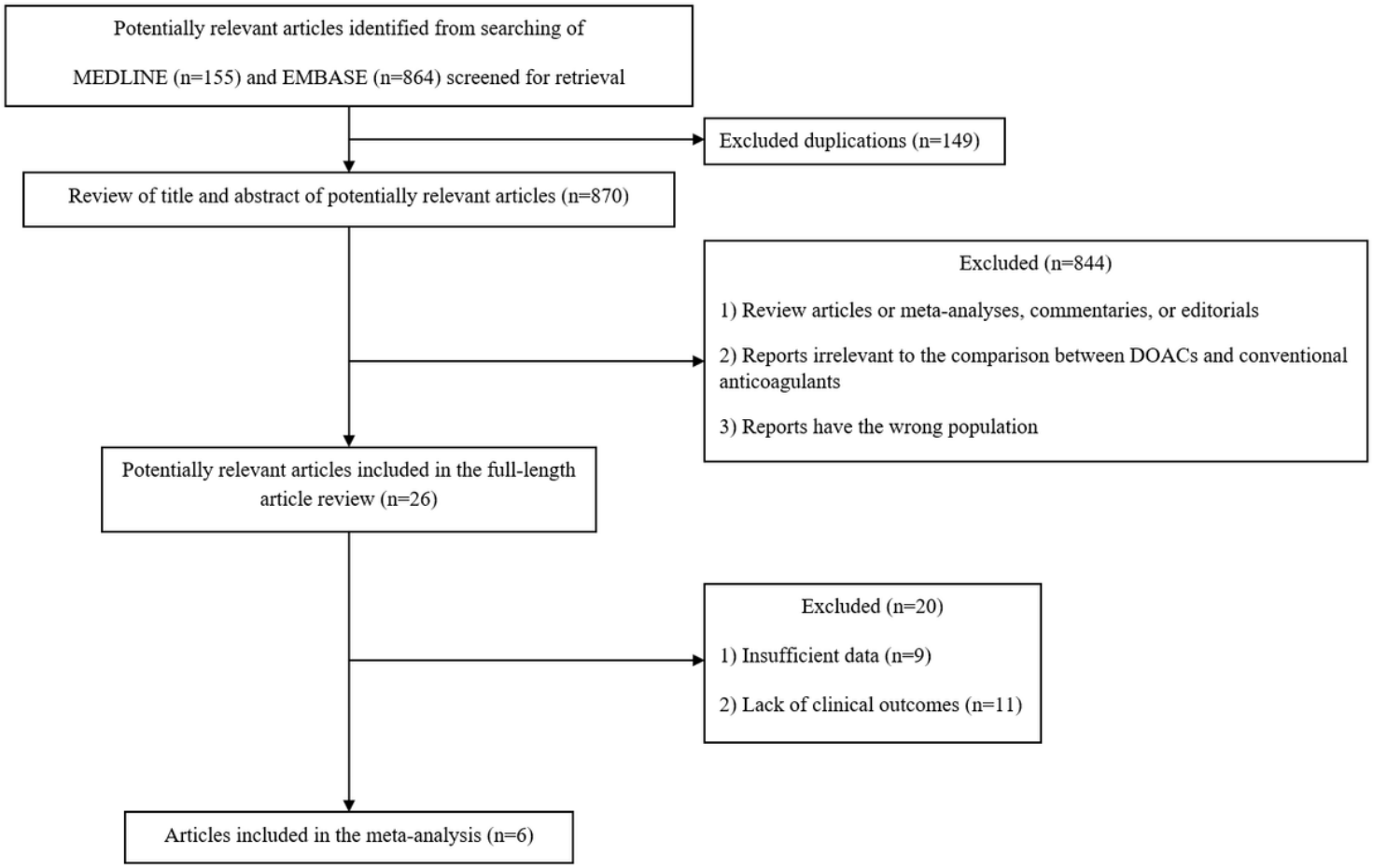

Figure 1

Demonstrates the literature review and article selection process.

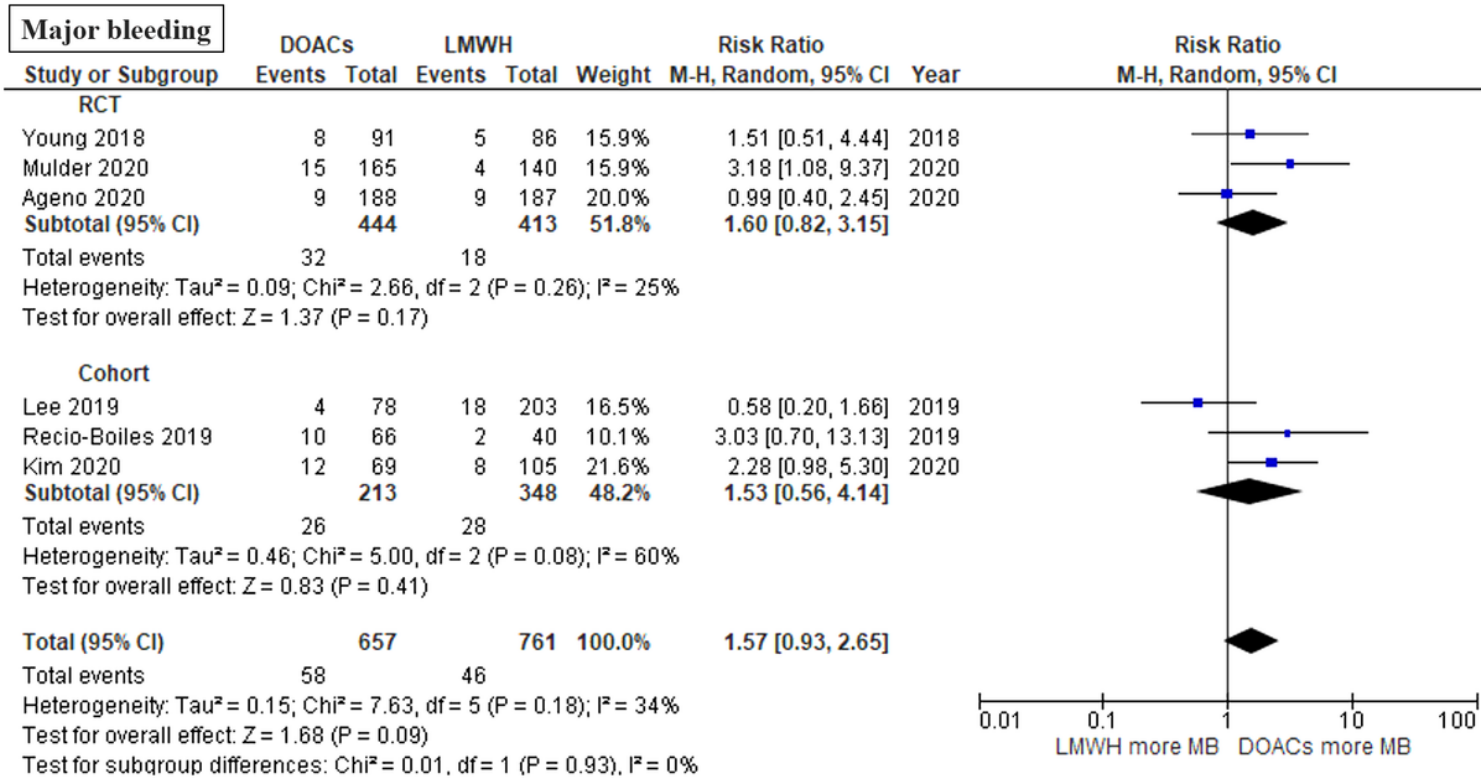

Figure 2

The heterogeneity of the meta-analysis was low with an I2-value of 34% [11, 20-24]

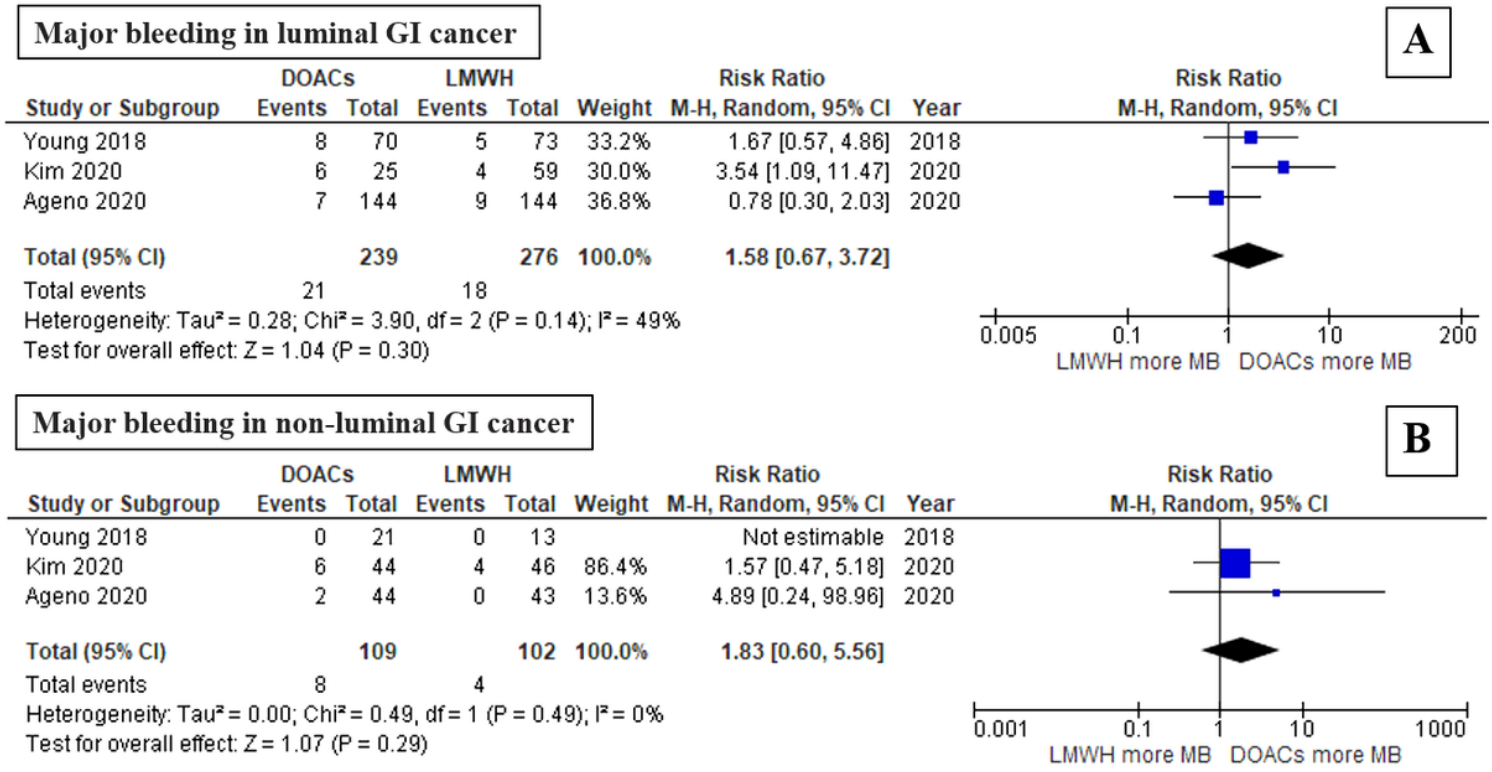

Figure 3

A subgroup analysis evaluating major bleeding events in patients with luminal and non-luminal GI cancer revealed a trend toward non-statistically significant increased major bleeding in patients with luminal GI cancer treated with DOACs with a pooled RR of 1.58 (95% CI: 0.67-3.72, P=0.30, I2=49%)

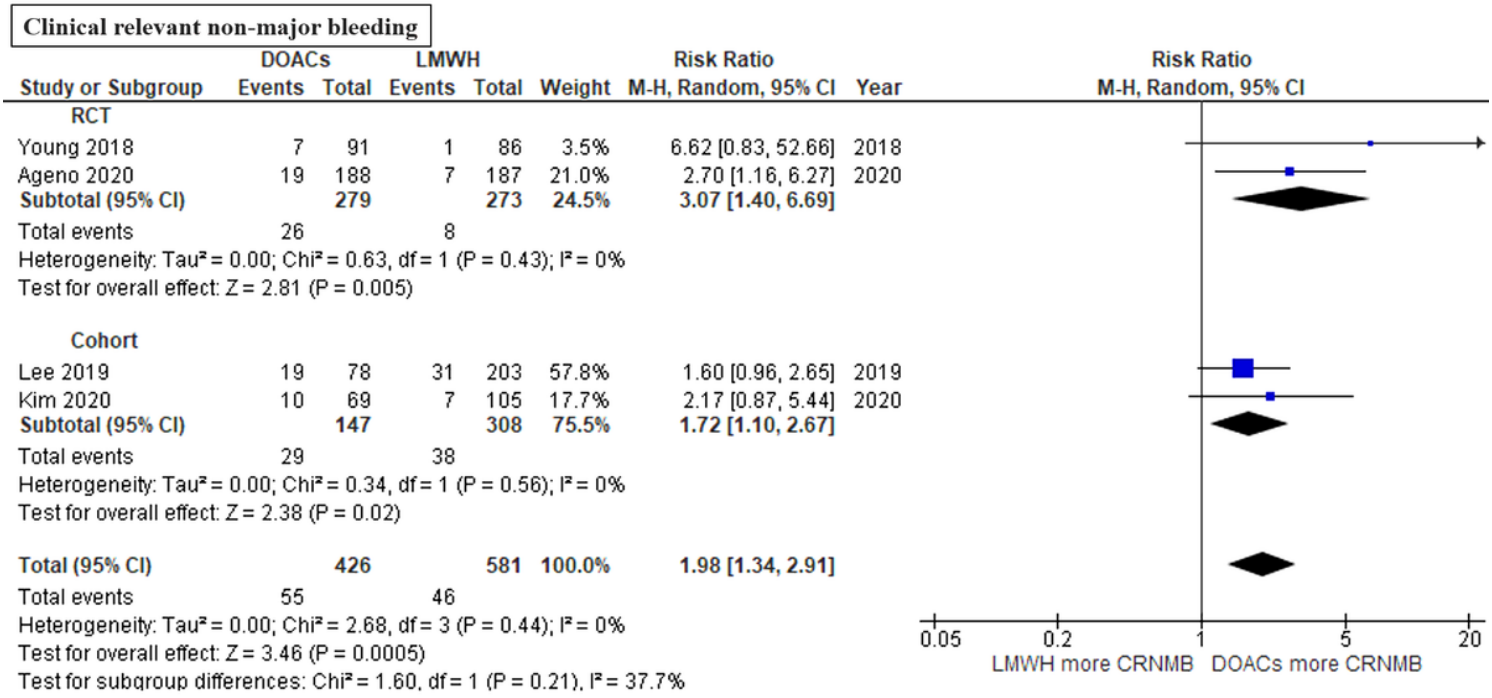

Figure 4

In contrast, the incidence of CRNMB was significantly higher in the DOAC group than in the LMWH group with a pooled RR of 1.98 (95% CI: 1.34-2.91, P=0.0005, I2=0%)

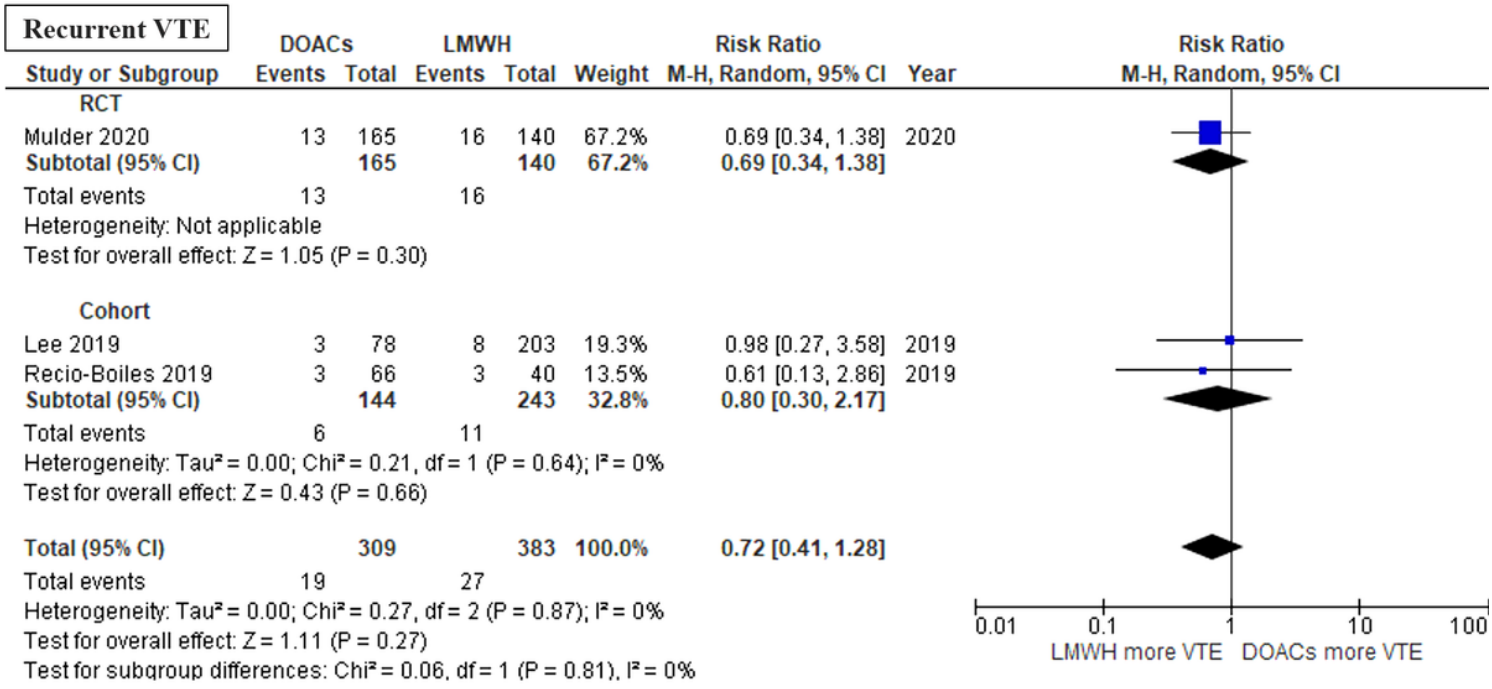

Figure 5

The rate of recurrent VTE was not significantly different between those who received DOACs and those who received LWMH with a pooled RR of 0.72 (95% CI: 0.41-1.28, P=0.27, I2=0%)

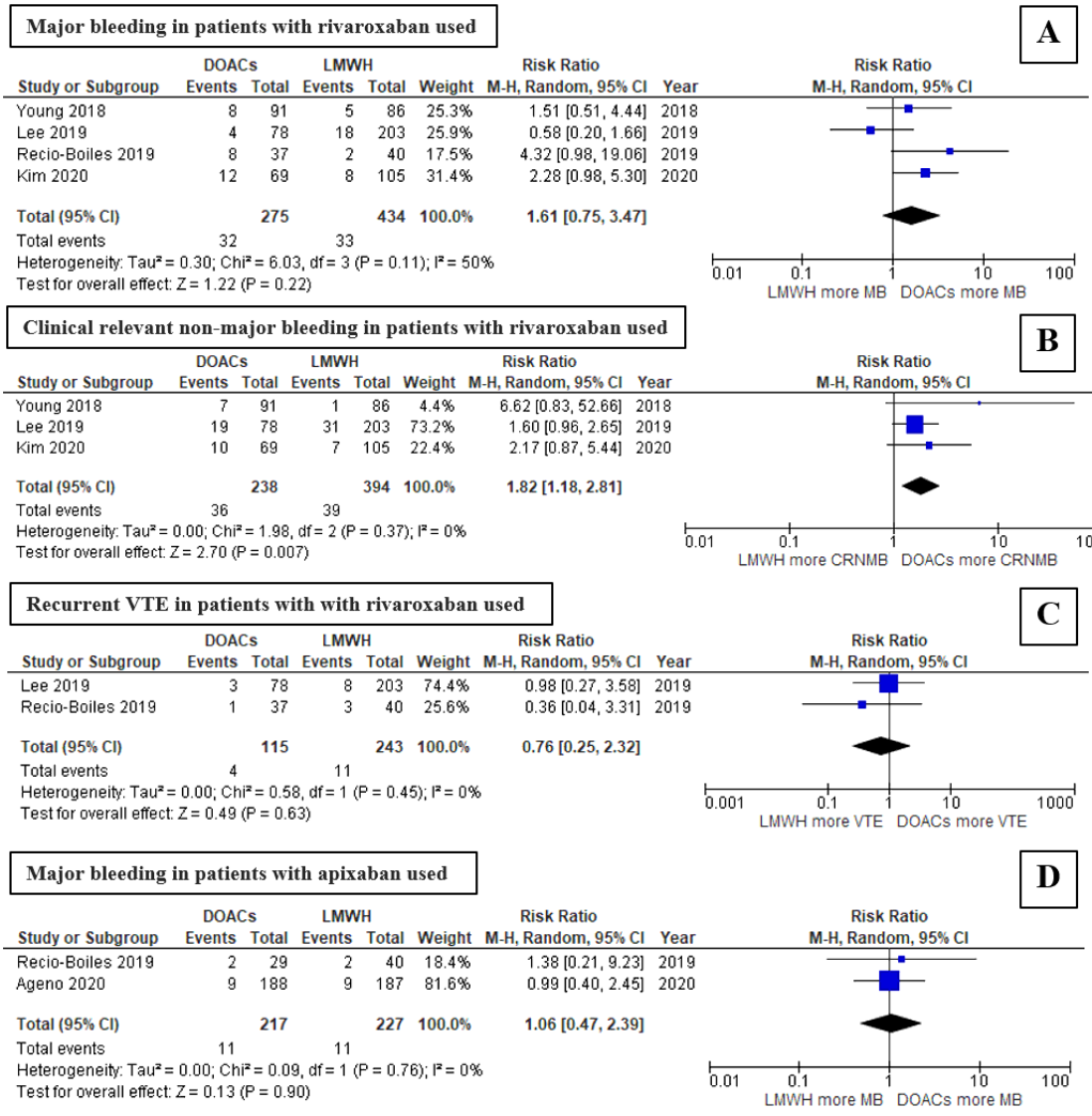

Figure 6

Neither the rivaroxaban nor apixaban subgroups was associated with a significant increase in major bleeding events compared to the LMWH arm with a pooled RR of 1.61 (95% CI: 0.75-3.47, P=0.22, I2=50%) in the rivaroxaban group

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Supplementarydata1Searchingstrategy2.docx
- Supplementarydata2PRISMAchecklist2.docx
- Supplementarydata3CRNMBdefinition.docx