Original Article

Clinical and Applied Thrombosis/Hemostasis
Volume 27: 1-10

DOI: 10.1177/1076029620940046
journals.sagepub.com/home/cat
SAGE

The Net Clinical Benefit of Rivaroxaban Compared to Low-Molecular-Weight Heparin in the Treatment of Cancer-Associated Thrombosis: Systematic Review and Meta-Analysis

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Abstract

Cancer-associated thrombosis (CAT) carries significant morbidity and mortality. Low-molecular-weight heparin (LMWH) remains the standard of care, with recent systematic studies suggesting the efficacy and safety of rivaroxaban in the treatment of CAT. Uncertainty, however, remains regarding rivaroxaban efficacy and safety in real-world settings. We performed a systematic review and meta-analysis of studies comparing rivaroxaban to LMWH. We searched PubMed, MEDLINE, and EMBASE. The primary outcome was the net clinical benefit (NCB), while rates of major bleeding (MB), venous thromboembolism (VTE), clinically relevant nonmajor bleeding (CRNMB), and all-cause mortality events were secondary outcomes. Seventeen studies were included in the final analysis. Rivaroxaban had a better NCB (relative risk [RR] = 0.82; 95% CI = 0.75-0.89, Q = 10.51, I^2 = 0%), less VTE events (RR = 0.73, 95% CI = 0.65-0.82, Q = 6.76, I^2 = 0%), and lower all-cause mortality (RR = 0.72, 95% CI = 0.57-0.91, Q = 32.8, I^2 = 79%) compared to LMWH. Additionally, comparable MB events (RR = 1.07, 95% CI = 0.85-1.33, Q = 16.9, I^2 = 11%). However, CRNMB events were higher in the rivaroxaban group (RR = 2.02, 95% CI = 1.46-2.80, Q = 9.9, I^2 = 19%). Additional analyses demonstrated consistency of results. Our review encompassing data from randomized and real-world data suggested rivaroxaban superiority compared to LMWH in terms of a better NCB, fewer VTE events, lower all-cause mortality, and comparable MB risk while carrying a higher risk of CRNMB. These findings support the use of rivaroxaban in the treatment of CAT. Additionally, it warrants a sizable randomized controlled study testing the superiority of rivaroxaban versus LMWH formulation and ascertaining bleeding outcomes according to cancer type and site.

Keywords

cancer-associated thrombosis, CAT, DOAC, NOAC, malignancy

Date received: 03 April 2020; revised: 27 May 2020; accepted: 15 June 2020.

Background

Cancer carries up to a 7-fold increased risk of venous thromboembolism (VTE) development.[1] Additionally, it is estimated to account for up to one-fifth of community cases of VTE.[2] This increased risk is due to a composite of various factors such as immobility, surgical interventions, antineoplastic therapy, and the secretion of endogenous procoagulant factors by tumor cells (heparanase). There has been a recent interest in the latter

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with a recent review suggesting classifying cancer-related hypercoagulability into 2 types based on heparanase secretion.[3] Since the advent of the CLOT trial, which demonstrated the superior efficacy of low-molecular-weight heparin (LMWH) compared to vitamin K antagonists (VKA) in patients with cancer-associated thrombosis (CAT), LMWH attained the role of being the standard of care in the treatment of CAT.[4]

Use of LMWH in this vulnerable population is, however, not without complications; there have always been concerns of cost, the requirement of daily parenteral injections, weight-based dosage adjustments, lower adherence, and accumulation in patients with decreased glomerular filtration rate.[5,6] Consequent upon these challenges, attention has shifted to search for alternative orally bioavailable therapeutic options. Rivaroxaban, a direct oral anticoagulant (DOAC), has been investigated in the EINSTEIN trials and demonstrated excellent efficacy compared to VKA in treatment of VTE in the general population.[7] Prins et al performed a pooled analysis in patients with CAT from the same trials and concluded a better efficacy of rivaroxaban compared to VKA.[5] Since then, various observational studies testing rivaroxaban and LMWH in patients with CAT were conducted. A few of these were combined in a meta-analysis by Xing et al and consisted of 4 observational studies comprising a total of 667 patients; they concluded similar effectiveness and safety of rivaroxaban compared to LMWH.[8] Additionally, a single primary randomized controlled trial (RCT) showed that rivaroxaban was associated with lower VTE rates compared to LMWH without a significant increase in major bleeding (MB) risk.[9]

The beneficial effect of rivaroxaban (with respect to both clinical effectiveness and safety) from these reports resulted in its recommendation by recent CAT guidelines as a valid initial therapeutic option in patients with CAT.[10,11] However, given the growing number of observational studies, including real-world data evaluating rivaroxaban use in patients with CAT,[12] it will be important to determine the performance of rivaroxaban outside clinical trial environment (in the real world) and test the replicability of what has already been gleaned from RCT data. Consequent upon this, we aimed to quantitatively synthesize the overall effect of rivaroxaban (compared to LMWH only) estimated through overall net clinical benefit (NCB). We utilized data from controlled observational studies and real-world data. The result of this review will provide the clinicians, patients, and clinical guideline developers with a better understanding of the totality of the evidence regarding the utility of this agent in CAT.

Methods

This review was conducted in keeping with PRISMA guidelines.[13]

Study Eligibility Criteria

We included observational, real-world data, and RCTs comparing rivaroxaban to LMWH in patients with CAT. The studies that assessed at least VTE recurrence or MB episodes as an outcome were included. We excluded studies reporting on pediatric patient cohorts (<18 years of age) as well as studies not meeting the aforementioned inclusion criteria.

Search Strategy

We attempted a comprehensive literature search of PubMed, MEDLINE, and EMBASE. No language, date, or article type limitations were adopted in our search strategy. The search was last updated on February 20, 2020. Example of a database search strategy is: ((Thrombosis) OR (thromboembolism)) OR (VTE)) OR (venous thromboembolism)) OR (DVT)) OR (deep venous thrombosis)) OR (PE)) OR (pulmonary embolism)) OR (venous thromboembolism[MeSH Terms])) OR (deep venous thrombosis[MeSH Terms])) OR (deep venous thromboses[MeSH Terms])) OR (venous thromboses[MeSH Terms])) OR (pulmonary embolism[MeSH Terms])) OR (pulmonary embolisms[MeSH Terms])) AND (((((((cancer) OR (malignancy)) OR (malignancies)) OR (malignancy, hematologic[MeSH Terms])) OR (malignancy[MeSH Terms])) OR (malignancy[MeSH Subheading])) OR (Cancer[MeSH Subheading]))) AND ((rivaroxaban[Text Word]) OR (rivaroxaban)). Additionally, we performed a manual reference search utilizing retrieved studies and reviews.

Screening and Data Extraction

Initial title and abstract screening were attempted by 2 reviewers (M.F.H.M. and M.I.D.). Eligible articles were retrieved for full-text review and assessed for inclusion in our review. In case of disagreement, a third reviewer (M.N.E.) was called for adjudication guided by the protocol. Data extraction was performed utilizing preplanned templates. Examples of the data extracted are author, year of publication, study type, intervention, control, outcome assessed, type of malignancy, and so on.

Outcome

To capture the full effect of the anticoagulation strategy being studied, we opted to evaluate the NCB as the primary outcome in our review. Net clinical benefit is a composite of the VTE recurrence and MB episodes. Recurrence of VTE, MB, clinically relevant nonmajor bleeding (CRNMB) events, and all-cause mortality were also evaluated separately as secondary end points. We opted for 6 months whenever specified in the study, otherwise the longer duration of observation.

Additional Analysis

We further analyzed the secondary outcomes (VTE recurrence, MB, CRNMB, and mortality rates) in studies restricted to specific malignancies (gastrointestinal [GI] and genitourinary [GU]), studies utilizing various LMWH formulations, and studies of similar therapeutic duration. Moreover, we analyzed the data after the exclusion of registry-based studies.

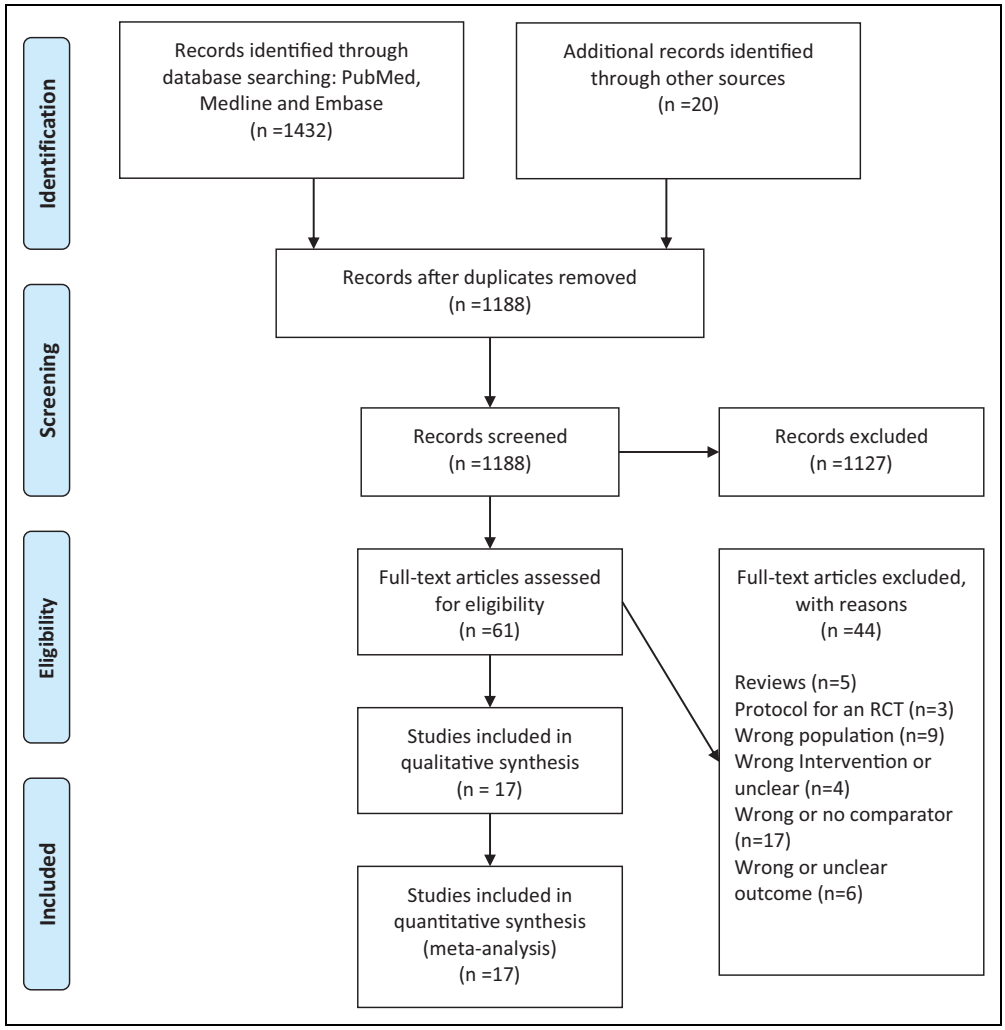

Figure 1. Flow diagram.

Study Quality and Risk of Bias Assessment

We used the validated Cochrane Collaboration's tool for assessing the quality and risk of bias in randomized trials.[14] Additionally, we utilized the New Castle Ottawa tool for the risk of bias assessment of observational studies[15] (Supplementary Table 1). Funnel plots were populated to screen for publication bias (Supplementary Figure 1).[16]

Statistical Analysis

Relative risks were computed as measures of the effect size. The Forest plot was displayed to summarize the results of the review. We planned and executed a sensitivity analysis. Subgroup analysis utilizing only the results from observational cohort studies, excluding real-world data utilizing registries, was performed observing for any inconsistency in the final point estimate. We also examined the effect of various LMWH formulations on the study outcomes. Moreover, we conducted a separate analysis to explore the study outcomes in studies exclusively done on GI and GU malignancies. The I^2 statistic was used to report heterogeneity. We considered an I^2 >50% to be indicative of a marked heterogeneity. The random effects model was used as our primary superiority meta-analytical technique. MetaXL software was used for statistical analysis (version 5.3; EpiGear International Pty Ltd).

Results

Our initial database search has retrieved 1432 potentially relevant articles, of which 17 studies were included in the meta-analysis (Figure 1). The included studies were comprised of 1 recent RCT,[9] 16 observational studies,[17-30] and 12 real-world data.[31] The total number of patients was 12 318 patients distributed between the intervention and the control arms (Tables 1 and 2).

The Net Clinical Benefit

The relative risk (RR) for the NCB was in favor of rivaroxaban compared to LMWH with a precise point estimate and confidence interval (RR = 0.82, CI = 0.75-0.89, Q = 10.51, I^2 =

Table 1. Showing Baseline Characteristics of Studies Included in the Review.

Author, year	Median age (rivaroxaban group), years	Sample size (rivarox-aban/ LMWH)	Study design	Type of cancer	Intervention (Dose)	Control (type of LMWH dose)	Follow-up duration	Therapeutic duration (rivar-oxaban vs LMWH), months
Young[9]	67	406 (203/203)	Primary RCT (open label)	GI 35%, pancreas 7%, breast 10%	Rivaroxaban (15 mg BID for 21 days >20 mg OD)	Dalteparin (200 IU/kg OD for 1 month>150 IU/kg OD for 5 months)	24 months	Median duration of 5.9 vs 5.8
Chaudhury[22]	62	157	Retrospective cohort	Hematological malignancy 23%	Rivaroxaban (NS)	Dalteparin (NS)	6 months	NS (56.1% vs 54.2% completed >6 months of treatment)
Ageno[23]	69.3	369	Prospective cohort	Not restricted (GI 13.7% in Riva/ 29.1% in LMWH/ GU 26% in both groups)	Rivaroxaban (NS)	LMWH (NS)	2 months	Median duration 5.1-5.5
Boiles[21]	66.5	77 (37/40)	Retrospective cohort	Gastrointestinal malignancies (pancreatic 38%, colon ca 34%, stomach/esophagus 18%	Rivaroxaban (15 mg BID for 21 days >20 mg OD)	Enoxaparin (1 mg/kg/dose BID or 1.5 mg/kg OD)	6 months	Median duration 6 vs 4
Nicklaus[25]	57.9	90 (45/45)	Retrospective cohort	Solid tumor 92%, metastatic cancer Riva 44%, Enox 62% (Subtypes NS)	Rivaroxaban (Appropriate therapeutic dose)	Enoxaparin (Appropriate therapeutic dose)	—	Mean duration of 5.6 vs 3.7
Signorelli[27]	60.4	44 (18/26)	Retrospective cohort	Gynecologic malignancies	Rivaroxaban (NS)	Enoxaparin (NS)	6 months	NS (Majority of LMWH shifted therapy with only 23% remaining on LMWH at the end of the study)
Ross[26]	64	153 (30/123)	Retrospective cohort	Not restricted	Rivaroxaban (NS)	LMWH (Enoxaparin 1 mg SC BID was the most common agent used)	12 months	NS
Simmons[24]	62.6	266 (98/168)	Retrospective cohort	Not restricted (GI & GU 29%)	Rivaroxaban (NS)	Enoxaparin (NS)	12 months	NS
Lee-1[18]	66.7	204 (131/73)	Retrospective cohort	Primary lung malignancies (Majority adenocarcinoma)	Rivaroxaban (15 mg BID for 21 days>20 mg OD)	Dalteparin (200 IU/kg OD for 1month>150 IU/kg OD for 5 months)	—	Mean duration of 3.6 vs 1.7
Lee-2[17]	66.5	281 (78.203)	Retrospective cohort	Gastrointestinal (53%) and pancreatobiliary Cancer (47%)	Rivaroxaban (15 mg BID for 21 days >20 mg OD)	LMWH (87% Dalteparin 200 IU/kg once daily)	6 months	Mean duration of 4 vs 3.1
Lee-3[19]	68.05	124 (63/61)	Retrospective cohort	Urologic malignancies (bladder 36%, Prostate 26%)	Rivaroxaban (15 mg BID for 21 days>20 mg OD)	Dalteparin (200 IU/kg once daily)	—	Mean duration 4 vs 2.2 ($P < .001$)
Lee-4[30]	56.9	162 (102/60)	Retrospective cohort	Gynecological malignancies	Rivaroxaban (NS)	Dalteparin (NS)	6 months	Mean duration 4 vs 3.45
Wysokinski[29]	62	526 (163/363)	Prospective cohort	GI, GU, and pancreatic cancer were the most common (45%)	Rivaroxaban (15 mg BID for 21)	Enoxaparin (200 IU/kg once daily)	6 months	NS (3-6 months completions (41.1% in Riva vs 47.4%)
Hummert[28]	65	182 (85/97)	Retrospective cohort	Not specified (metastatic disease 53%)	Rivaroxaban (NS)	Enoxaparin	—	Median duration 7.1 vs 3.1 months ($P < .000$)
Angelini[20]	63	190 (24/166)	Prospective cohort	Hematological malignancy 28.8%	Rivaroxaban (NS)	LMWH (NS)	—	NS
Khorana[12]	61.3	7683 (3370/4313)	Retrospective cohort	Not specified	Rivaroxaban (NS)	LMWH	12 months	Median duration of 3.6 vs 2
Streiff[31]	72.7	1367 (685/682)	Retrospective cohort	Not restricted (Lung CA 20%, GI & GU 13%)	Rivaroxaban (NS)	LMWH (all types allowed)	12 months	Median duration of 3 vs 1

Abbreviations: BID, twice daily; CA, cancer; LMWH, low-molecular-weight heparin; GI, gastrointestinal; GU, genitourinary; NS, not significant; OD, once daily; RCT, randomized controlled trial; SC, subcutaneously.

Table 2. Summary of Relevant Events and Outcomes in the Included Studies.

Author, year	VTE recurrence		Major bleeding		CRNMB		Mortality		Outcome duration
	Rivaroxaban % (n = events/total)	LMWH % (n = events/total)	Rivaroxaban (events/total)	LMWH % (n = events/total)	Rivaroxaban % (n = events/total	LMWH % (n = events/total)	Rivaroxaban % (n = events/total	LMWH % (n = events/total)	
Young[9]	4% (8/203)	8.9% (18/203)	5.5% (11/203)	3% (6/203)	12.3% (25/203)	3.5% (7/203)	23.6% (48/203)	27.5% (56/203)	6 months
Chaudhury[22]	4.9% (3/60)	11.1% (11/97)	2.8% (3/107)	1.1% (2/179)	9.3% (10/107)	4.5% (8/179)	-	-	6 months
Ageno[23]	3.6% (5/146)	4.5% (10/223)	1.4% (2/146)	3.6% (8/223)	-	-	4.8% (7/146)	24.7% (55/223)	-
Boiles[21]	2.7% (1/37)	7.5% (3/40)	21.6% (8/37)	5% (2/40)	-	-	-	-	6 months
Nicklaus[25]	8.8% (4/45)	13.3% (6/45)	2.2% (1/45)	4.4% (2/45)	-	-	-	-	-
Signorelli[27]	0% (0/18)	4% (1/26)	17% (3/18)	8% (2/26)	-	-	-	-	6 months
Ross[26]	3.3% (1/30)	5.6% (7/123)	13% (4/30)	11% (14/123)	6.7% (2/30)	7.3% (9/123)	-	-	6 months
Simmons[24]	1% (1/98)	4.2% (7/168)	5.1% (5/98)	3.6% (6/168)	6.1% (6/98)	0.6% (1/168)	4.1% (4/98)	8.6% (15/168)	3 months
Lee-1[18]	5.3% (7/131)	2.7% (2/73)	6.1% (8/131)	2.7% (2/73)	17.6% (23/131)	11% (8/73)	80.9% (106/131)	87.7% (64/73)	6 months
Lee-2[17]	3.8% (3/78)	3.9% (8/203)	5.1% (4/78)	8.9% (18/203)	24.4% (19/78)	15.3% (31/203)	37.2% (29/78)	68% (138/203)	6 months
Lee-3[19]	3.2% (2/63)	4.9% (3/61)	4.8% (3/63)	6.6% (4/61)	15.9% (10/63)	11.5% (7/63)	72.1% (41/63)	65.1% (44/61)	-
Lee-4[30]	5.9% (6/102)	6.7% (4/60)	7.8% (8/102)	5% (3/60)	16.7% (17/102)	10% (6/60)	69.6% (71/102)	65% (39/60)	6 months
Wysokinski[29]	3.7% (5/163)	4.3% (12/363)	6.6% (9/163)	6.5% (18/363)	8.8% (12/163)	2.2% (6/363)	14.7% (20/163)	28.1% (78/363	6 months
Hummert[28]	1.1% (1/85)	2% (2/97)	8.2% (7/85)	7.2% (7/97)	-	-	-	-	-
Angelini[20]	0% (0/24)	10% (17/166)	-	-	-	-	-	-	-
Khorana[12]	8.7% (293/3370)	11.7% (505/4313)	4.4% (148/3370)	4.9% (211/4313)	-	-	-	-	6 months
Streiff[31]	13.3% (90/685)	17.6% (120/682)	6.7% (46/685)	4.1% (28/682)	-	-	-	-	6 months

Abbreviations: CRNMB, clinically relevant nonmajor bleeding; LMWH, low-molecular-weight heparin; VTE, venous thromboembolism.

0%), indicating the absence of heterogeneity (Figure 2). Sensitivity analysis revealed overall consistency, except with the exclusion of the largest study (registry-based real-world data; n = 7683),[12] where there was a trend toward a protective effect but with uncertainty in the final point estimate (RR = 0.87, CI = 0.75-1.02; Supplementary Table 2). The funnel plot showed no evidence of publication bias (Supplementary Figure 1).

Recurrent VTE

Recurrent VTE events were significantly less in the rivaroxaban group (RR = 0.73, CI = 0.65-0.82, Q = 6.76, I^2 = 0%; Figure 2). Sensitivity analysis showed overall consistency in the final point estimate upon ordered exclusion of the constituent studies (indicating the absence of a small study effect; Supplementary Table 3). The funnel plot indicated a publication bias possibility (Supplementary material Figure 1).

Major Bleeding

Sixteen studies reported on MB outcomes; there was no evidence of a significant difference between rivaroxaban and LMWH in terms of MB episodes overall (RR = 1.07, CI = 0.85-1.33, Q = 16.9, I^2 =11%; Figure 2). Sensitivity analysis did not affect the results significantly (Supplementary Table 4). The funnel plot did not show evidence of publication bias (Supplementary material Figure 1).

Clinically Relevant Nonmajor Bleeding

Nine studies evaluated CRNMB events. There was a significantly higher rate of CRNMB events in the rivaroxaban group (RR = 2.02, CI = 1.46-2.80, Q = 9.93, I^2 = 19%). The results were homogeneous and consistent on sensitivity analysis (Supplementary Table 5).

All-Cause Mortality

Results from 8 studies revealed lower mortality in the rivaroxaban group (RR = 0.72, CI = 0.57-0.91, Q = 32.8, I^2 = 79%). The results showed marked heterogeneity. Nonetheless, only one study had a point estimate that is greater than 1 (Figure 2). Sensitivity analysis depicted consistency despite ordered removal of the constituent studies (Supplementary Table 6).

Subgroup Analysis

Studies restricted to GI and GU malignancies. Bleeding events (MB or a composite of MB and CRNMB) were trending higher in the rivaroxaban group upon analyzing the GI/GU restricted studies (RR = 1.36, CI = 0.82-2.24, Q = 6.8, I^2 = 41%). The results were consistent upon pooling the non-GI/GU restricted studies, with rivaroxaban causing more bleeding events (RR = 1.41, CI = 1.03-1.92, Q = 26.5, I^2 = 59%) compared to LMWH (Supplementary Figures 2 and 3).

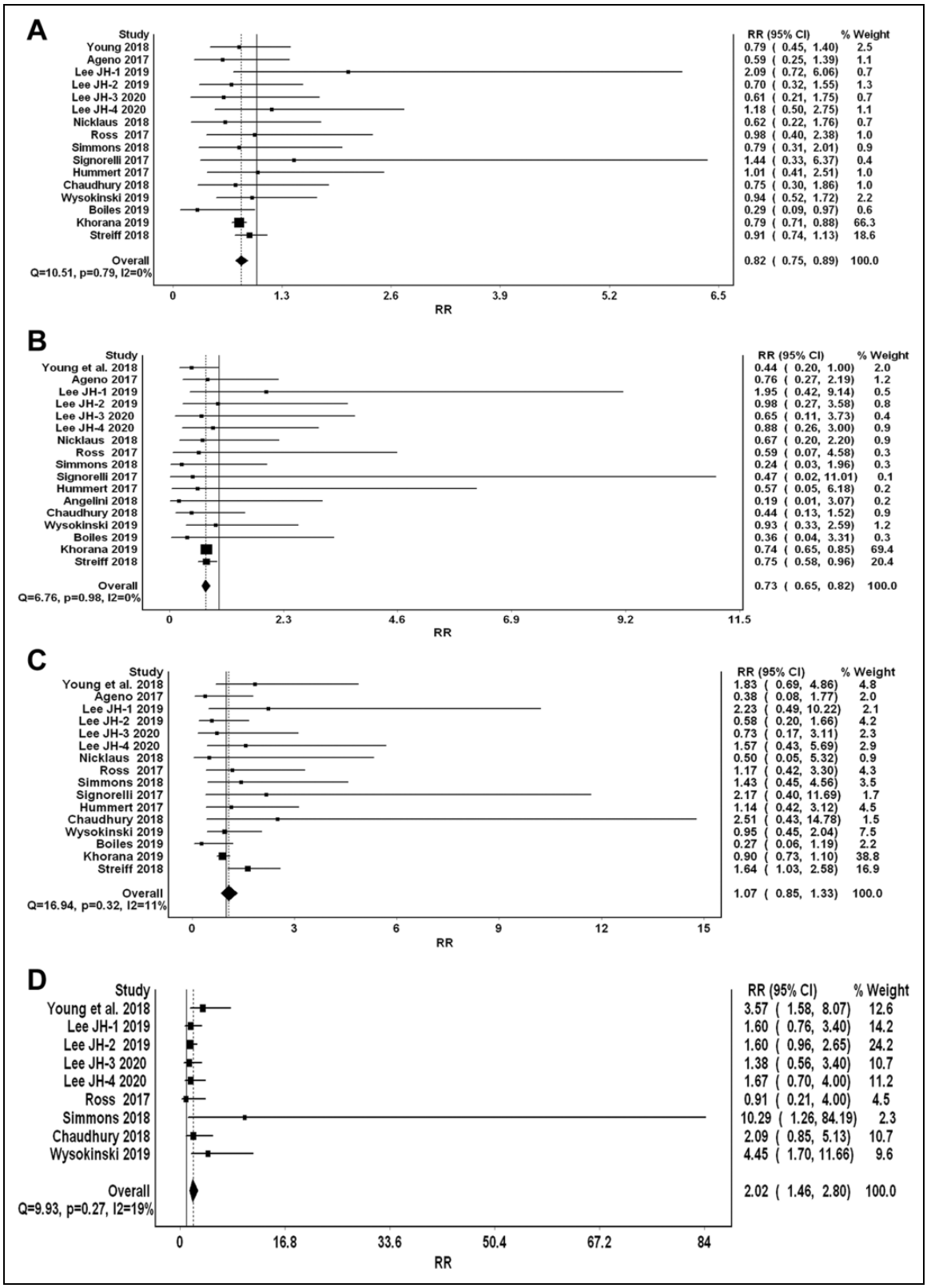

Figure 2. Forest plot comparing the (A) net clinical benefit (NCB), (B) VTE recurrence, (C) MB, (D) CRNMB, and (E) mortality among rivaroxaban and LMWH users. The results demonstrate no or mild heterogeneity (A-D) depicted by the low I^2. Mortality data (E) I^2 value (79%) indicates a marked heterogeneity; however, as depicted by the forest plot, the heterogeneity of the effect was regarding the extent of the protective effect with most point estimates below 1. CRNMB indicates clinically relevant nonmajor bleeding; LMWH, low-weight-molecular heparin; MB, major bleeding; NCB, net clinical benefit; VTE, venous thromboembolism.

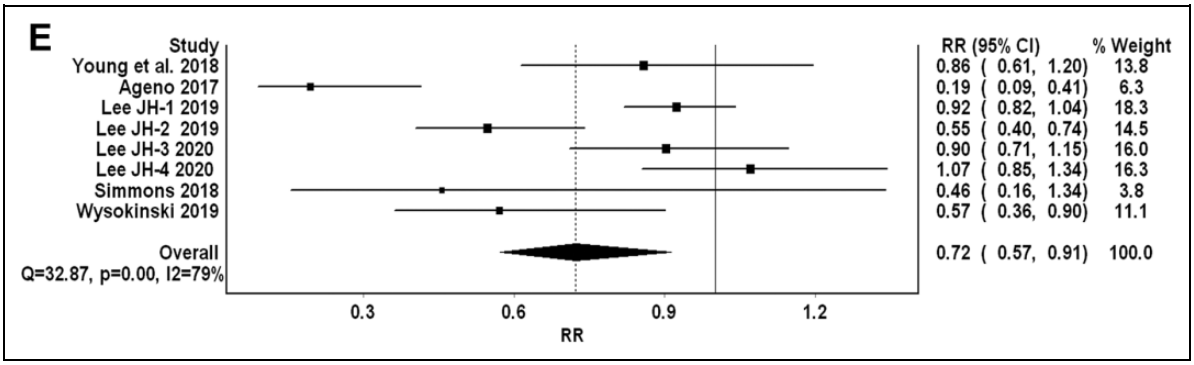

Figure 2. (continued)

Studies evaluating different formulations of LMWH (enoxaparin and dalteparin). There was a trend of fewer VTE events in the rivaroxaban group compared to both dalteparin (RR = 0.62, CI = 0.37-1.05, Q = 3.38, $I^2 = 0\%$) and enoxaparin (RR = 0.64, CI = 0.33-1.22, Q = 1.63, $I^2 = 0\%$). Compared to dalteparin, MB events trended to be higher among rivaroxaban users (RR = 1.62, CI = 0.90-2.93, Q = 1.64, $I^2 = 0\%$), and CRNMB events were significantly higher among rivaroxaban users (RR = 1.82, CI = 1.34-2.46, Q = 3.48, $I^2 = 0\%$). Major bleeding events were not different in rivaroxaban users compared to enoxaparin users (RR = 0.97, CI = 0.60-1.56, Q = 4.55, $I^2 = 0\%$; Supplementary Figure 4). The absence of data limited the comparison of CRNMB between rivaroxaban and enoxaparin users.

Studies of similar therapeutic duration. All-cause mortality was reported in 3 studies that had similar therapeutic duration. Mortality was nondifferent between rivaroxaban (RR = 0.85, CI = 0.61-1.18, Q = 6.13, $I^2 = 67\%$) and LMWH users, however, with marked heterogeneity. Rates of VTE recurrence (RR = 0.63, CI = 0.40-1.00, Q = 2.00, $I^2 = 0\%$), MB (RR = 1.19, CI = 0.72-1.95, Q = 4.04, $I^2 = 1\%$), and CRNMB (RR = 2.71, CI = 1.74-4.21, Q = 2.97, $I^2 = 0\%$) in the rivaroxaban group versus LMWH were consistent with that of the primary analysis (Supplementary Figure 5).

Excluding registry-based analysis. In subgroup analysis excluding 2 registry-based studies,[12,31] the NCB of rivaroxaban compared to LMWH favored rivaroxaban, however, with uncertainty in the final point estimate (RR = 0.82, CI = 062-1.04). Recurrence of VTE (RR = 0.62, CI = 0.42-0.91) and MB episodes (RR = 1.05, CI 0.76-1.46) were consistent and were not affected by the exclusion of these studies.

Risk of bias assessment

Most of the included studies were of at least moderate quality (Supplementary Table 1). The funnel plot showed no evidence of publication bias with regard to the reviews' primary outcome (Supplementary Figure 1).

Discussion

This is the first systematic review attempting to combine data from multiple sources and multiple designs (controlled trials, observational, and real-world data) encompassing a plethora of patients (over 12 000), examining the combined effectiveness and safety of rivaroxaban in patients with CAT. We found that compared to LMWH, rivaroxaban has less risk of VTE recurrence, lower all-cause mortality, and a better overall NCB (VTE events and MB). Although CRNMB events were consistently higher in the rivaroxaban group, MB events were comparable between the 2 groups. Overall, the results were consistent across studies with no significant changes identified on subsequent additional analysis. Adding the real-world data gives assurance to frontline clinicians, patients, policy, and guidelines makers about not only the efficacy but also the effectiveness of rivaroxaban in a pragmatic manner.

A recent study by Guo et al found that LMWH has very low adherence compared to DOACs.[6] At least 8 constituent studies in our review had a significant difference in the therapeutic duration between LMWH (consistently less) and rivaroxaban (Table 1). This prompted us to consider LMWH nonadherence in real-world data as a possible reason for its lower efficacy and seemingly better safety (lower CRNMB). However, our additional analysis of studies with similar therapeutic duration revealed the consistency of the reviews' findings (with mortality as an exception limited by a small number of studies). Nonetheless, we cannot rule out the effect of nonadherence to daily doses (skipping doses) to explain this discrepancy. Subgroup analysis comparing rivaroxaban to LMWH formulations suggested a trend of increased MB events among rivaroxaban users (RR = 1.62, CI = 0.90-2.93, Q = 1.64, $I^2 = 0\%$) compared to dalteparin but not to enoxaparin; this may support using dalteparin when opting for an LMWH formulation in the treatment of CAT patients with a higher bleeding risk, till further data accrue.

The mortality benefit with rivaroxaban is a remarkable finding that could potentially change the therapeutics of CAT. It is known that thromboembolism is a leading cause of death in patients with cancer.[32] Moreover, rivaroxaban, in our review, demonstrated consistently superior efficacy in terms of lower VTE events. Hence, a postulated mechanism by which

rivaroxaban could lead to lower mortality is by preventing fatal undiagnosed VTE events. Another explanation is the proposed anticancer properties of rivaroxaban unrelated to its anticoagulant effect.[33] While a good number of the constituent studies had balanced baseline characteristics, the possibility of confounding by indication where patients with less favorable risk profile received the standard therapy (LMWH) cannot be ruled out in these observational studies.

Xing et al performed the first meta-analysis in 2018 comparing rivaroxaban to enoxaparin. A total of 667 patients from 4 observational studies were included in their review.[8] They found that rivaroxaban has a trend (or be it not statistically significant) toward less VTE recurrence and lower mortality. They claimed that this is likely to be due to the small sample size and that the results are likely to be significant once more data on rivaroxaban in CAT are made available.[8] Our review, with excellent power, confirmed their findings. While conducting our review, we found about another planned meta-analysis examining the utility of rivaroxaban in patients with CAT; however, their registered planned review will be limited to RCTs only.[34] Although we think that their planned review will provide additional information, as it will encompass the results of EINSTEIN DVT and PE trials and any additional trial that is underway.[5] We felt the urgent need to acknowledge and include the abundant observational studies and real-world data in order to provide the medical community with a pragmatic perspective of the utility of rivaroxaban in patients with CAT. We did not include studies that evaluated warfarin only as a comparator, given the abundance of evidence suggesting LMWH as the standard of care in patients with CAT.[11]

The result of our review is concordant with already reported primary and secondary data, thus adding strength to the pool of available evidence. The recently published guidance by the International Initiative on Thrombosis and Cancer and the American Society of Clinical Oncology suggested LMWH as the first-line therapy. The guidance suggested a role for rivaroxaban and edoxaban in both the initial and the early maintenance treatment of CAT.[10,11] In both guidelines, the authors stated that the use of DOACs is to be limited to patients not exhibiting high-risk features of GI bleeding, GU bleeding, or strong drug–drug interaction. They also advised caution when using rivaroxaban or edoxaban in the setting of GI malignancy. In our review, we analyzed bleeding events in a small number of studies that were restricted to GI and GU malignancies, and the results were consistent with the primary analysis. However, we suggest adhering to current guidelines (with regards to cautions) until additional prospective data from RCTs and matched cohorts becomes available.

Our review has several limitations. First, we included observational studies and real-world data, which are usually confounded by inevitable bias. This was derived primarily for our intention to evaluate rivaroxaban in real-world settings. The fact that our review findings were consistent with those of RCTs suggested the consistency of the rivaroxaban effect, strengthening the recommendation of the recently published guidelines. We did not involve trials testing warfarin as a comparator; as a result, we have missed the subgroup analysis from 2 relevant RCTs (EINSTEIN-DVT and EINSTEIN-PE). Although the results of these 2 RCTs may have been relevant, the fact that warfarin is not considered the standard of care anymore by many authorities, as explained earlier, makes any comparison with it less relevant to the frontline clinicians and guidelines makers. Nevertheless, the point estimates from the composite of the 2 RCTs were in favor of rivaroxaban in both efficacy and safety compared to warfarin. And an attempt to account for this in our review would have resulted in a likely consistent or even a better overall effect of rivaroxaban against a composite standard of care (LMWH or warfarin).[5]

Our review encompassed interventional and noninterventional data. It will help both the clinicians and patients better understand the totality of evidence with regard to the rivaroxaban effect in patients with CAT. It will also have essential guideline implications supporting the current guidance. Keeping that notion in mind, we have noted an emerging pool of evidence from big real-world data suggesting a better efficacy (VTE recurrence) and safety (MB) of apixaban in patients with cancer having atrial fibrillation.[35] Additionally, the recently published RCTs by McBane et al and Agnelli et al concluded a comparable efficacy and safety of apixaban versus LMWH.[36,37] With these data, we believe apixaban will likely attain a role in the treatment of VTE in patients with CAT. We suggest direct head-to-head trials between the various DOAC analogs and also with LMWH to ascertain the ranks of various DOAC analogs in the treatment of CAT. Additionally, this proposed trial should explore long-term outcomes, such as mortality, to validate our results.

Conclusion

Our review, encompassing data from an RCT and a pool of real-world data, suggested the superiority of rivaroxaban compared to LMWH in terms of VTE recurrence, lower mortality, and a better NCB without significantly increased risk of MB in the subset of patients with CAT. Only CRNMB events were higher in the rivaroxaban group. A limited analysis revealed findings' consistency regardless of the cancer site. However, it is prudent to continue exercising caution when prescribing rivaroxaban to patients with GI and GU malignancies. The reviews' findings support the use of rivaroxaban in this group of patients. A sizable superiority RCT is imperative to confirm our findings (especially the mortality and the bleeding data).

Authors' Note

The first and last author contributed equally to this article. M.F.H.M. and M.I.D. conceived the reviews' idea. M.F.H.M devised the search strategy; M.F.H.M. and M.I.D. performed the initial and final article screening. L.O.A. and M.F.H.M. performed data extraction. M.F.H.M. wrote the initial draft, M.I.D. reviewed and updated the initial draft. The data used in this review are available upon reasonable request. All authors were actively involved in the review, and all approved the final manuscript for publication. No ethical approval was needed as this a secondary synthesis of the available literature.

Acknowledgments

The authors acknowledge the Qatar National Library for funding the open access publication of this review. The authors also acknowledge the peer reviewers for their valuable comments and feedback that led to significantly enhancing the manuscript.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: The authors thank Qatar National Library for funding the open access publication of this paper.

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Supplemental Material

Supplemental material for this article is available online.

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