MAYO CLINIC

ORIGINAL ARTICLE

Direct Oral Anticoagulants Compared With Dalteparin for Treatment of Cancer-Associated Thrombosis: A Living, Interactive Systematic Review and Network Meta-analysis

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Abstract

Objective: To maintain living, interactive evidence (LIvE) on the benefits and harms of different treatment options in adults with cancer-associated thrombosis (CAT).

Methods: We have used a novel LIvE synthesis framework to maintain this living, interactive systematic review since September 19, 2018. Randomized controlled trials evaluating the efficacy and safety of direct oral anticoagulants (DOACs) compared with low-molecular-weight heparin for CAT are included in this analysis. Details of LIvE synthesis framework are available at the website https://cat.network-meta-analysis.com.

Results: The results are constantly updated as new information becomes available (https://cat.network-meta-analysis.com/CAT.html). The living, interactive systematic review currently includes 4 randomized controlled trials (N=2894). Direct comparisons show that DOACs significantly decrease recurrent venous thromboembolism (VTE) events compared with dalteparin (odds ratio [OR], 0.59; 95% CI, 0.41 to 0.86; I^2, 25%) without significantly increasing major bleeding (OR, 1.34; 95% CI, 0.83 to 2.18; I^2, 28%). Mixed treatment comparisons show that apixaban (OR, 0.41; 95% credible interval [CrI], 0.16 to 0.95) and rivaroxaban (OR, 0.58; 95% CrI, 0.37 to 0.90) significantly decrease VTE recurrent events compared with dalteparin. Edoxaban significantly increases major bleeding compared with dalteparin (OR, 1.73; 95% CrI, 1.04 to 3.16), and rivaroxaban significantly increases clinically relevant nonmajor bleeding compared with dalteparin and other DOACs. There are no significant differences between DOACs in terms of VTE recurrences and major bleeding.

Conclusion: DOACs should be considered a standard of care for the treatment of CAT except in patients with a high risk of bleeding. Current evidence favors the use of apixaban for the treatment of CAT among other DOACs.

Registration: Open Science Framework (https://osf.io/dth86).

 ■ Mayo Clin Proc. 2021;■■(■):1-17

The landmark CLOT trial[1] established low-molecular-weight heparin (LMWH) as the preferred anticoagulant therapy for cancer-associated thrombosis (CAT). LMWH provided superior efficacy to vitamin K antagonists with similar bleeding rates. However, LMWH therapy has disadvantages, such as injection

Affiliations continued at the end of this article.

site discomfort, ecchymosis, and hematomas; it lowers the quality of life, which leads to poor compliance (median treatment duration of 3.3 months).[2] Direct oral anticoagulants (DOACs) are now considered the standard of care for treatment of venous thromboembolism (VTE) in noncancer patients for several reasons. Limited drug and food interactions, predictable pharmacokinetic and pharmacodynamic properties, rapid onset and offset of action, short half-life, and lack of the need for laboratory monitoring make this class of anticoagulants appealing for both patients and prescribers.[3]

The data related to DOACs for treatment of CAT are rapidly emerging and have challenged LMWH as the preferred option.[2,4-6] We previously published a network meta-analysis[7] on treatment of CAT including data from Hokusai VTE, SELECT-D, and ADAM VTE. There are several limitations to the conventional approach of evidence synthesis. In areas with rapidly moving evidence, many systematic reviews and meta-analyses (SRMAs) are outdated as soon as they are published.[8] There is usually little incentive for the original team to undertake the laborious updating process, and hence a completely new team will try to create (update) an SRMA from scratch. This duplication of effort not only is wasteful but often results in conflicted findings because of subtle differences in design or analysis strategy. Moreover, the presentation of results using conventional static tables and figures limits the depth of information that can be informative to clinicians and evidence users. To overcome these limitations, we developed a living, interactive systematic review (LISR) for treatment of CAT using a living, interactive evidence (LIvE) synthesis framework.

The publication of the Caravaggio trial[4] prompted an updated analysis. Given that contemporary guidelines—released before mature data on apixaban were published—have endorsed the use of rivaroxaban and edoxaban but not apixaban for treatment of CAT,[9] this update to include apixaban is timely and will inform the forthcoming guidelines for treatment of CAT. Hence, we present important details of individual trials (systematic review), the latest evidence for efficacy and safety of DOACs compared with dalteparin (pairwise meta-analysis) across multiple clinically important subgroups, and the comparative effectiveness of different DOACs (network meta-analysis) to help facilitate the choice of agent for treatment of CAT in clinical practice. Furthermore, we continue to maintain this LISR as the results of CANVAS (NCT02744092), CASTA-DIVA (NCT02746185), PRIORITY (NCT03139487), and CONKO-011 (NCT02583191) are awaited.

METHODS

LIvE Synthesis Framework

We have used a novel LIvE synthesis framework to maintain this LISR to update our previous systematic review and network meta-analysis (SRNMA).[10] The protocol was retrospectively registered at Open Science Framework (https://osf.io/dth86). This manuscript is reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) extension statement for network meta-analyses (Supplemental Methods 1, available online at http://www.mayoclinicproceedings.org).[11] A detailed description of "living" methods is available on our website (https://cat.network-meta-analysis.com).

Automated Search

The search strategy was designed with the assistance of an experienced medical librarian. The initial search was conducted on September 19, 2018, using standard databases. Subsequently, a living autosearch was created with monthly updates to identify new relevant randomized controlled trials (RCTs). The details of the search strategy and data sources used are provided in the Supplemental Methods 2 (available online at http://www.mayoclinicproceedings.org).

Semiautomated Study Selection

Randomized controlled trials evaluating the efficacy and safety of DOACs (factor Xa inhibitors including apixaban, rivaroxaban, and edoxaban; direct thrombin inhibitor dabigatran) compared with LMWH for

CAT were included. Nonrandomized trials and observational studies were excluded.

Citations were initially screened through the conventional pathway using the EndNote software, and the structured results were uploaded to the LIvE platform to create an interactive PRISMA flowchart. Subsequently, citations identified through the automated search were pushed into the central data repository, in which a highly sensitive and a validated machine-learning filter was used to pull out RCTs.[12] Relevant citations were then annotated, screened, and reviewed for inclusion using a Web-assisted rule-based screener on an interactive graphical user interface, the scanner—human-in-the-loop pathway. The living interactive PRISMA is automatically updated to keep record of the study screening and selection process. This process is performed by 2 independent reviewers (I.B.R. and S.A.A.N.), and any disagreement is resolved by discussion and input from a senior author (R.D.M.).

Semiautomated Data Extraction and Quality Assessment

The data abstraction was initially done manually through the conventional pathway to create an interactive table on the website. The interactive table summarizes the trial characteristics, population characteristics, and main results. Subsequently, the new data were extracted through a Web-assisted rule-based extraction on an interactive graphical user interface, the extractor—human-in-the-loop pathway. The extracted data include the first author's last name, publication year, trial design, type of DOACs, type of LMWH, number of participants in the treatment and control arms, outcomes of interest, mean age of the participants, median treatment duration, follow-up duration, timing of analysis, discontinuation in treatment and control arms, type of cancers included, Eastern Cooperative Oncology Group (ECOG) scores of participants, number of participants with platelet count below 100,000/mm^3, and number of participants with creatinine clearance between 30 and 50 mL/min. This process is performed by 2 independent reviewers (I.B.R. and S.A.A.N.), and any disagreement is resolved by discussion and input from a senior author (R.D.M.).

The major efficacy outcome was recurrent VTE. The major safety outcomes were major bleeding (MB) and clinically relevant nonmajor bleeding (CRNMB). For the Caravaggio trial, MB was in accordance with the European Medicines Agency definition.[4] The other 3 trials used the International Society on Thrombosis and Hemostasis criteria.[2,5,6,13] Event definitions were provided in the Methods section of the original trials and are outlined in Supplemental Table 1 (available online at http://www.mayoclinicproceedings.org). Other patient-important end points included a composite of VTE and MB (net clinical benefit), fatal bleeding, and all-cause mortality. Odds of MB are further presented by site, including gastrointestinal (GI), genitourinary (GU), and intracranial bleeding.

The Cochrane Collaboration risk of bias assessment tool version 2 is used for evaluating the methodologic quality of the included studies.[14]

Automated Data Synthesis

The extracted data were initially uploaded to the analyzer module using a structured format and are now automatically exported from the extractor module to a fully automated analysis module, the analyzer. The analyzer was constructed with a hybrid approach. Functions from Python packages Pandas (version 1.0.3) and NumPy (version 1.18.4) were called for data format conversion and data preprocessing; functions from R packages meta (version 4.11.0), netmeta (version 1.2.0), and BUGsnet (version 1.0.3) were called to carry out automated pairwise meta-analysis, frequentist, and Bayesian network meta-analysis approaches, respectively. The raw analysis results generated through the analyzer were visually enhanced using JavaScript packages D3.js (version 5.15.0) and ECharts (version 4.1.2). The interactive features, such as dynamically updated comparator and measure of effect, were enabled on the basis of JavaScript packages Vue.js (version 2.6.12) and jQuery (version 3.4.1). The detailed description on choice of analytic parameters for this

living project is provided in the Supplemental Methods 3 (available online at http://www.mayoclinicproceedings.org).

Primary Analysis. Direct comparisons were made using conventional pairwise meta-analysis. DerSimonian and Laird (DL) random effects meta-analyses were used to compute weighted mean effect size. Effect sizes were expressed as odds ratio (OR) with their 95% CIs.

Mixed comparisons for each outcome of interest were made using Bayesian network meta-analysis. Markov chain Monte Carlo algorithms were applied to generate estimates with their 95% credible intervals (CrIs).[15] All networks were generated on the basis of uninformative prior distributions. The fit of random effect and fixed effect models and identification of any potential outliers were carried out a priori using the deviance information criterion and by generating leverage plots.[16-18] In the setting of a sparse network, a fixed effect model was used as between-study heterogeneity cannot be assessed reliably in such cases.[19] The relative rankings between DOACs for each outcome were assessed using the surface under the cumulative ranking curves based on cumulative posterior probabilities. Rankograms and cumulative distribution plots were generated to give a better visualization of ranking for each outcome. A sensitivity analysis was conducted using a frequentist approach.[20]

Subgroup and Sensitivity Analyses. The following subgroup analyses were planned a priori subject to availability of data to test for interactions (age $\geq$65 years vs age <65 years, male vs female, incidental vs symptomatic VTE, deep venous thrombosis [DVT] vs pulmonary embolism [PE], apixaban vs other DOACs, metastatic vs nonmetastatic cancer, active cancer vs history of cancer, solid vs hematologic cancer, performance status [ECOG] score 2 vs performance status [ECOG] score <2, stay in the study <3 months vs stay in the study >3 months). A formal test of interaction was performed, and the *P* value of heterogeneity (interaction) was used to establish the significance of differences between the subgroups.[21] Sensitivity analyses were planned a priori to check for consistency of results (outcomes reported at 6 months and VTE including only upper and lower extremities). Post hoc sensitivity analyses were performed using the Hartung-Knapp-Sidik-Jonkman (HKSJ) method and by applying Hartung-Knapp (HK) adjustment.[22,23]

Certainty of Evidence

Summary of findings (SoF) tables and evidence profiles were initially constructed manually using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach and used to assess confidence in estimates.[24] Direct estimates for all outcomes were assessed on risk of bias, inconsistency, indirectness, imprecision, and suspicion of publication bias. Network estimates for VTE, MB, and CRNMB were additionally assessed on incoherence and intransitivity. Now, we have implemented the tabulator module, which generates interactive SoF tables and evidence profiles.

Pairwise Meta-analysis SoF. Relative effect estimates with associated 95% CIs are exported from the analyzer module and translated into absolute effects using assumed comparator risk (either internal or external baseline risk) for each patient-important outcome. Each individual component contributing to certainty of evidence is assessed manually by 2 investigators (I.B.R. and S.A.A.N.) independently, and structured data are uploaded to the tabulator module, which adjudicates the level of certainty (high, moderate, low, and very low) by a rule-based algorithm. Individual cells in the SoF table are interactive and provide additional details when clicked.

Network Meta-analysis SoF. An additional feature for network meta-analysis SoF tables is application of multiple comparisons by dynamic selection of reference treatment (comparator). A color scheme (details on website) indicates certainty of evidence for each comparison, and additional details for each comparison (such as number of RCTs included, number of events/total number of

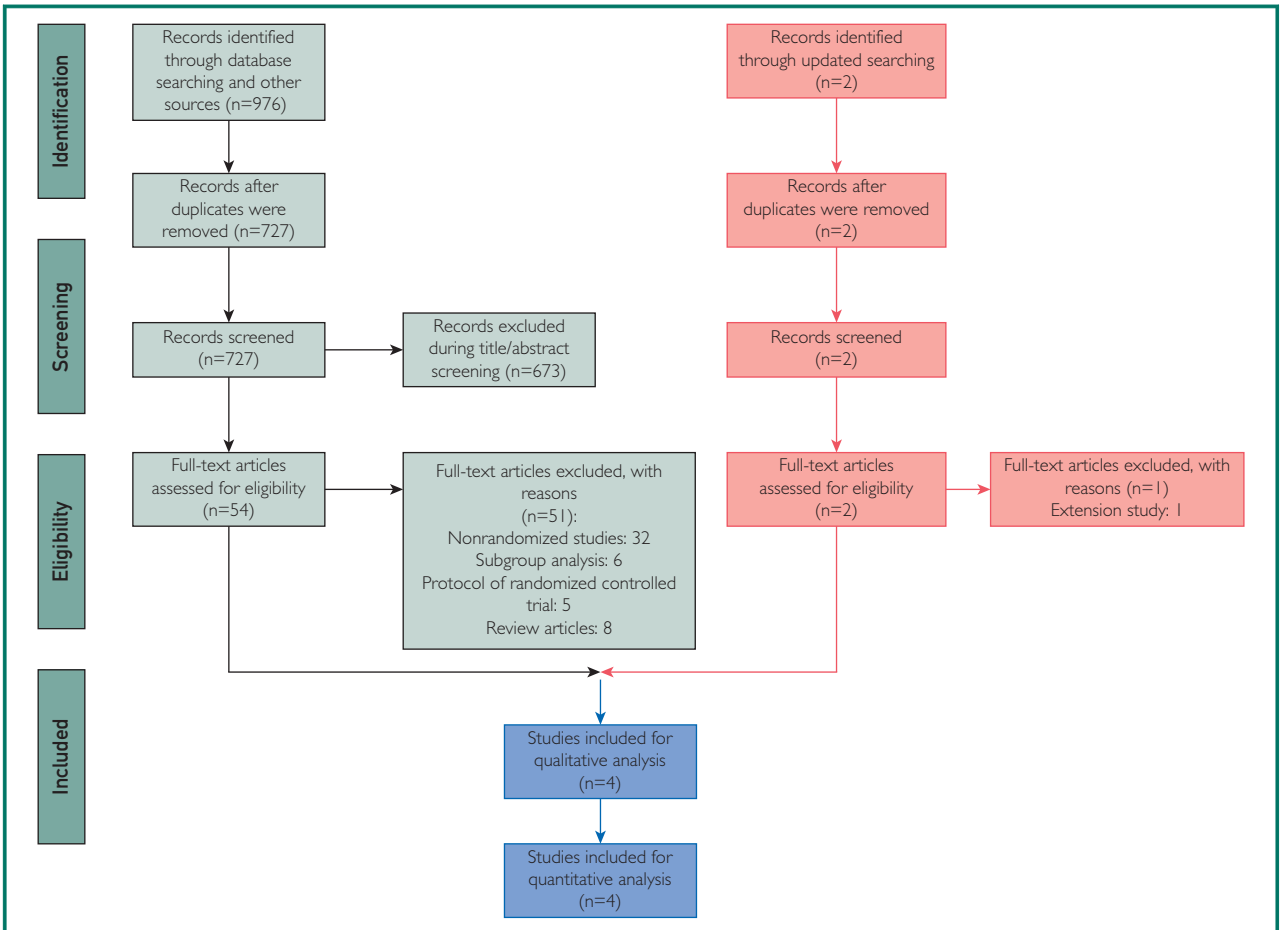

FIGURE 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram illustrating evidence search and selection. The green limbs on the left side of the flow diagram correspond to the original (initial) search conducted on September 19, 2018. The red limbs on the right side of the flow diagram correspond to the relevant results of the updated (living) search that is programmed to be conducted at monthly intervals after the original (initial) search. The blue limbs in the lower center of the flow diagram correspond to the studies included in the living systematic review (upper) and living meta-analysis (lower) to date.

participants in each arm, absolute risk, and absolute risk difference in numbers and percentage points) become available by clicking the corresponding cell.

Reconciliation Table

A reconciliation table was constructed to reconcile the trials included and conclusions from previous SRMAs comparing DOACs vs LMWH.

RESULTS

Two relevant citations[4,25] were considered since the publication of our initial meta-analysis through living autosearch.[7] The Caravaggio trial[4] met the inclusion criteria and was included in the SRNMA. An update of the SELECT-D trial[25] was excluded because it focused on extended DOAC treatment. A total of 4 RCTs[2,4-6] comparing DOACs with LMWH were included in this SRNMA as shown in Figure 1. The living interactive results of this updated SRNMA are outlined in the form of an interactive table (configurable summary table highlighting the trial and population characteristics), interactive forest plots (configurable plots according to primary, subgroup, and sensitivity analysis), and interactive evidence profiles (configurable tables with multiple filters). The living interactive results are available on our website (https://cat.network-meta-analysis.com/CAT.html).

Trial Characteristics

In total, 4 eligible RCTs (N=2894) compared DOACs against a common comparator, LMWH (dalteparin 200 IU/kg daily for a month followed by 150 IU/kg daily thereafter), administered subcutaneously. DOAC comparators included edoxaban (60 mg once daily),[5] rivaroxaban (15 mg twice daily for 3 weeks followed by 20 mg once daily),[6] and apixaban (10 mg twice daily for a week followed by 5 mg twice daily)[2,4] for efficacy and safety in patients with CAT (Figure 2). The treatment duration was 6 months in all trials[2,4,6] except the Hokusai VTE trial,[5] in which it was 6 to 12 months. Table 1 outlines the summary of trial characteristics.

Population Characteristics

Two trials included both patients with active cancer and patients with a history of cancer[4,5]; the remaining trials included only patients with active cancer.[2,6] More than one-third of patients (n=1122 [38.8%]) had DVT only as the qualifying thrombus. Nearly all patients (n=2648 [91.5%]) had solid cancers, and more than half (n=1768 [61.1%]) had locally advanced or metastatic disease (Appendix Table, available online at http://www.mayoclinicproceedings.org). Similarly, more than one-third (n=965 [33.3%]) of the patients had GI cancer, whereas only about one-sixth of patients (n=323 [11.1%]) had GU cancer. The most common cancer in the trial arms was colorectal cancer (n=545 [18.8%]). The breakdown of the number of each cancer type is provided in Supplemental Table 2 (available online at http://www.mayoclinicproceedings.org). About one-fifth (n=615 [21.3%]) of patients had an ECOG score of 2. Few patients (n=121 [4.2%]) had a platelet count below 100,000/mm^3, whereas less than one-tenth (n=212 [7.3%]) of patients had creatinine clearance between 30 and 50 mL/min.

Pairwise Meta-analysis

A total of 214 (7.3%) VTE recurrent events were observed during the trial duration, 82 (5.6%) events in the DOACs arm and 132 (9.1%) events in the dalteparin arm. DOACs significantly decreased VTE recurrences compared with dalteparin (OR, 0.59; 95% CI, 0.41-0.86; I^2, 25%; Supplemental Figure 1, available online at http://www.mayoclinicproceedings.org). A total of 121 (4.2%) MB events occurred, 69 (4.8%) events in the DOACs arm and 52 (3.6%) events in the dalteparin arm. DOACs were not significantly different from dalteparin in terms of MB (OR, 1.34; 95% CI, 0.83 to 2.18; I^2, 28%; Supplemental Figure 1). A total of 269 (9.2%) CRNMB events were observed, 162 (11.2%) events in the DOACs arm and 107 (7.3%) events in the dalteparin arm. DOACs significantly increased CRNMB events compared with dalteparin (OR, 1.69; 95% CI, 1.13 to 2.42; I^2, 41%; Supplemental Figure 1). The analysis of major GI and major GU bleeding was limited to 3 trials,[4-6] excluding the ADAM VTE trial,[2] which reported no MB events. Similarly, in analyzing intracranial bleeding, the ADAM VTE[2] and SELECT-D[6] trials were excluded. The results of a pairwise meta-analysis are summarized in Table 1.

Subgroup Analysis

All 4 trials with a total of 2894 patients were included in the subgroup analysis involving each study as a unit of analysis, whereas only 2 trials (Hokusai VTE and Caravaggio)[4,5] reported data on independent subgroups within the studies (Supplemental Figure 2, available online at http://www.mayoclinicproceedings.org). The results of the subgroup analysis are outlined in Supplemental Table 3 (available online at http://www.mayoclinicproceedings.org).

Sensitivity Analysis

The results of sensitivity analysis and primary analysis were consistent. The sensitivity analysis, which excluded the ADAM VTE trial, included a total of 2607 patients; additional analysis with outcomes reported at 6 months for all trials included a total of 2894 patients (Supplemental Figure 3, available online at http://www.mayoclinicproceedings.org). Supplemental Table 4 (available online at http://www.mayoclinic

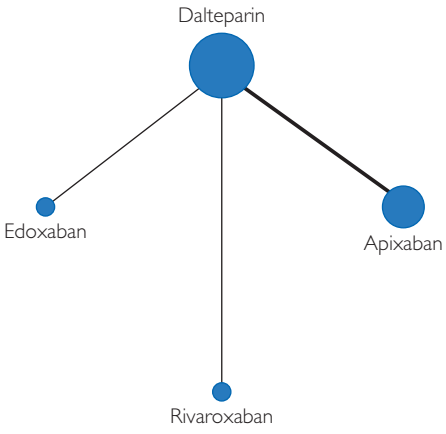

FIGURE 2. Network plot of eligible trials. This illustration shows a network plot (graph) of included trials evaluating efficacy and safety of direct oral anticoagulants in the treatment of cancer-associated venous thromboembolism compared with dalteparin. Nodes (circles) depict intervention (edoxaban, rivaroxaban, and apixaban) and comparator (dalteparin). Edges (lines) illustrate head-to-head comparisons between 2 nodes (intervention and comparator). The numbers of trials comparing each pair are indicated by diameter of nodes and width of edges. Greater number of each comparison is scaled as a larger node and a thicker edge.

proceedings.org) summarizes the results of sensitivity analyses.

Network Meta-analysis

Mixed treatment comparisons are reported from a model with the lower deviance information criterion. In case of a sparse network, the fixed effect model is used. The details of fit of both models are provided in Supplemental Table 5 (available online at http://www.mayoclinicproceedings.org).

Both rivaroxaban (OR, 0.41; 95% CrI, 0.16 to 0.95) and apixaban (OR, 0.58; 95% CrI, 0.37 to 0.90) significantly decreased VTE recurrence compared with dalteparin. There were no statistically significant differences between the DOACs with regard to reducing VTE recurrence. Both apixaban and rivaroxaban ranked higher than dalteparin. (Supplemental Figure 4, available online at http://www.mayoclinicproceedings.org). Edoxaban significantly increased MB compared with dalteparin (OR, 1.73; 95% CrI, 1.04 to 3.16). However, edoxaban was not significantly different from apixaban (OR, 2.04; 95% CrI, 0.91 to 4.64) and rivaroxaban (OR, 0.93; 95% CrI, 0.93 to 2.94) with regard to MB. Both apixaban and dalteparin ranked higher than edoxaban and rivaroxaban (Supplemental Figure 5, available online at http://www.mayoclinicproceedings.org). Rivaroxaban significantly increased CRNMB compared with dalteparin (OR, 4.09; 95% CrI, 1.79 to 10.59), apixaban (OR, 2.73; 95% CrI, 1.08 to 7.71), and edoxaban (OR, 2.99; 95% CrI, 1.21 to 8.26). Dalteparin was ranked higher than the others and rivaroxaban was ranked the least safe drug in terms of CRNMB (Supplemental Figure 6, available online at http://www.mayoclinicproceedings.org). Apixaban significantly decreased combined VTE recurrence and MB events (net clinical benefit) compared with dalteparin (OR, 0.66; 95% CrI, 0.46 to 0.95). Apixaban did not significantly differ from edoxaban (OR, 0.69; 95% CrI, 0.42 to 1.43) or rivaroxaban (OR, 0.86; 95% CrI, 0.41 to 1.81). Apixaban was ranked higher than the others (Supplemental Figure 7, available online at http://www.mayoclinicproceedings.org). No statistically significant comparisons were observed for mortality between DOACs and dalteparin or between the DOACs. DOACs ranked higher than dalteparin (Supplemental Figure 8, available online at http://www.mayoclinicproceedings.org).

Certainty of Evidence

The risk of bias of all studies and across all outcomes was low as shown in the risk of bias summary and graph (Supplemental Figure 9, available online at http://www.mayoclinicproceedings.org). Publication bias could not be statistically assessed because of a small number of included studies. Network coherence (consistency) assessment was not possible because of a lack of closed loops in our network geometry. Bayesian and frequentist approaches showed similar results. Certainty in evidence for direct estimates such as the reduction in VTE recurrence and increase in MB with DOACs was high and low, respectively. The SoF tables for direct and network estimates are provided in Table 2 and

Table 3, respectively. Evidence maps illustrating harms and benefits of DOACs using direct and network estimates are shown in Appendix Figure 1 (available online at http://www.mayoclinicproceedings.org).

Reconciliation With Previous Systematic Reviews

Reconciliation of trials included and conclusions from previous SRMAs[7,26-30] comparing DOACs vs LMWH is illustrated in Appendix Figure 2 (available online at http://www.mayoclinicproceedings.org).

DISCUSSION

The major findings of this meta-analysis are as follows: cancer patients with acute VTE treated with DOACs experience a decreased rate of VTE recurrence by 41% compared with dalteparin (high certainty); whereas MB rates did not differ between treatment classes (low certainty), CRNMB was more frequent with DOACs compared with dalteparin (moderate certainty); GU bleeds were more frequent with DOACs; and GI bleed, intracranial bleed, fatal bleeding, and mortality rates were similar between groups. Taken together, these data suggest that DOAC therapy may improve efficacy compared with dalteparin without sacrificing safety in many cases. This improved efficacy appears to be particularly evident for apixaban and rivaroxaban, whereas apixaban is the only DOAC that does not increase the risk of MB (seen with edoxaban) and CRNMB (seen with rivaroxaban) compared with dalteparin. Multiple a priori sensitivity and subgroup analyses were conducted to mitigate the differences in clinical trial design and primary end points. The definitions of recurrent VTE and MB differed slightly across the studies but are unlikely to account for significant differences in results. The decreased VTE recurrence with DOACs is consistent across sensitivity analyses (excluding rare site thrombosis for VTE recurrence by excluding data from the ADAM VTE trial and restricting analyses to the on-treatment period by using Hokusai VTE trial data at 6 months) and including multiple subgroups regardless of the type of VTE event (incidental, symptomatic) or location (DVT, PE).

VTE recurrence may carry an increased risk of mortality for cancer patients, particularly if the recurrent event type is a PE.[31,32] In this meta-analysis, we show that as a class, DOACs have an efficacy advantage over LMWH. This translates into more than 40% reduction of recurrent thrombosis (OR, 0.59; 95% CI, 0.41 to 0.86). Both apixaban and rivaroxaban stand out as particularly effective agents. Decreased VTE recurrence with DOACs is consistent with previous data.[7,28-30,33-36] Further subgroup analysis showed that the benefits of DOACs are consistent by type of VTE event (DVT or PE), by presentation (symptomatic vs incidental), and by characteristics of the patient (such as age, cancer stage, or performance status). Whereas the risk of incident and recurrent VTE is likely to vary by tumor type, important future directions must include cancer-specific outcomes both for the initial treatment and for long-term management.[37,38]

Bleeding outcomes, especially in patients with GI and GU malignant neoplasms, are of special interest.[2-6,39] Indeed, these patients tended to have increased bleeding outcomes in both the Hokusai VTE Cancer and SELECT-D trials.[5,6] These outcomes have prompted guidelines to endorse caution in considering DOACs for these types of patients, with a preference for LMWH.[40-42] In this meta-analysis, DOACs did not differ significantly compared with dalteparin in terms of major GI bleeding, but GU bleeding rates were increased. However, the CI around the ORs of GU and GI bleeding is wide, especially for GU bleed, and larger data sets specific to these patients would be welcomed. Another important subset is patients with primary intracranial tumors, with intracranial metastasis, or simply at risk of intracranial hemorrhage. These patients were excluded from participating in the Caravaggio trial,[4] with limited recruitment in the other 3 trials.[2,5,6] It is reassuring that the rates of intracranial bleeding were extremely low overall at 0.3% with no difference between treatment arms. Until further data become available, it is probably safe to consider DOAC therapy for these patients. Subgroup analysis did not identify safety advantages when stratified by age or cancer stage.

TABLE 1. Characteristics of Eligible Trials[a]

Study	Trial design	Treatment arm	Control arm	Treatment arm dose	Control arm dose	Median treatment duration (mo)	Primary end points	Secondary end points	Type of cancers excluded
Raskob et al[5] Hokusai VTE 2018	Randomized, open-label, noninferiority trial	Edoxaban (n=522)	Dalteparin (n=524)	60 mg qd	200 IU/kg qd 150 IU/kg qd	6.93[b]	Composite of recurrent VTE or MB	NR	Squamous cell carcinoma Basal cell carcinoma (skin)
Young et al[6] SELECT-D 2018	Randomized, open-label, pilot trial	Rivaroxaban (n=203)	Dalteparin (n=203)	15 mg bid 20 mg qd	200 IU/kg qd 150 IU/kg qd	5.9	Recurrent VTE	MB CRNMB	Squamous cell carcinoma Basal cell carcinoma (skin)
McBane et al[2] ADAM VTE 2020	Randomized, open-label, superiority trial	Apixaban (n=145)	Dalteparin (n=143)	10 mg bid 5 mg bid	200 IU/kg qd 150 IU/kg qd	5.78	MB	Recurrent VTE CRNMB	Nonmelanoma skin cancers (not specified)
Angelli et al[4] Caravaggio 2020	Randomized, investigator-initiated, open-label, noninferiority trial	Apixaban (n=576)	Dalteparin (n=579)	10 mg bid 5 mg bid	200 IU/kg qd 150 IU/kg qd	5.84[b]	Recurrent VTE MB	CRNMB	Primary brain tumors Intracerebral metastases Acute leukemia Squamous cell skin carcinoma Basal cell carcinoma (skin)

[a]CRNMB, clinically relevant nonmajor bleeding; MB, major bleeding; n, number of patients in an arm; NR, not reported; VTE, venous thromboembolism.
[b]Median treatment duration in months was calculated by dividing the given days by 30.436875.

TABLE 2. GRADE Summary of Findings Using Pairwise (Direct) Estimates[a,b]

Certainty assessment							No. of patients, n/N (%)		Effect		
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	DOACs	LMWH (dalteparin)	Relative (95% CI)	Absolute (95% CI)	Certainty
Venous thromboembolism recurrence											
4	Randomized trials	Not serious	Not serious	Not serious	Not serious	None	82/1446 (5.7)	132/1448 (9.1)	OR, 0.59 (0.41-0.86)	35 fewer per 1000 (from 52 fewer to 12 fewer)	⊕⊕⊕⊕ High
Major bleeding											
4	Randomized trials	Not serious	Not serious	Not serious	Very serious[c]	None	69/1446 (4.8)	52/1448 (3.6)	OR, 1.34 (0.83-2.18)	12 more per 1000 (from 6 fewer to 39 more)	⊕⊕◯◯ Low
Clinically relevant non-major bleeding											
4	Randomized trials	Not serious	Not serious	Not serious	Serious[d]	None	162/1446 (11.2)	107/1448 (7.4)	OR, 1.65 (1.13-2.42)	42 more per 1000 (from 9 more to 88 more)	⊕⊕⊕◯ Moderate
Net clinical benefit											
4	Randomized trials	Not serious	Not serious	Not serious	Very serious[c]	None	151/1446 (10.4)	184/1448 (12.7)	OR, 0.78 (0.53-1.14)	25 fewer per 1000 (from 55 fewer to 15 more)	⊕⊕◯◯ Low
Mortality											
4	Randomized trials	Not serious	Not serious	Not serious	Very serious[c]	None	412/1446 (28.5)	416/1448 (28.7)	OR, 0.99 (0.79-1.24)	2 fewer per 1000 (from 46 fewer to 46 more)	⊕⊕◯◯ Low
Major gastrointestinal bleeding											
3	Randomized trials	Not serious	Not serious	Not serious	Very serious[e]	None	39/1301 (3.0)	20/1306 (1.5)	OR, 1.94 (0.96-3.95)	14 more per 1000 (from 1 fewer to 43 more)	⊕◯◯◯ Very low
Major genitourinary bleeding											
3	Randomized trials	Not serious	Not serious	Not serious	Very serious[f]	None	10/1301 (0.8)	1/1306 (0.1)	OR, 5.03 (1.08-23.34)	3 more per 1000 (from 0 fewer to 17 more)	⊕⊕◯◯ Low
Fatal bleeding											
2	Randomized trials	Not serious	Not serious	Not serious	Very serious[e]	None	0/1098 (0.0)	4/1103 (0.4)	OR, 0.20 (0.02-1.72)	3 fewer per 1000 (from 4 fewer to 3 more)	⊕◯◯◯ Very low

Continued on next page

TABLE 2. Continued

Certainty assessment							No. of patients, n/N (%)		Effect		
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	DOACs	LMWH (dalteparin)	Relative (95% CI)	Absolute (95% CI)	Certainty
Intracranial bleeding											
2	Randomized trials	Not serious	Not serious	Not serious	Very serious[e]	None	2/1098 (0.2)	6/1103 (0.5)	OR, 0.40 (0.09-1.77)	3 fewer per 1000 (from 5 fewer to 4 more)	⊕◯◯◯ Very low

[a]DOACs, direct oral anticoagulants; GRADE, Grading of Recommendations Assessment, Development, and Evaluation; LMWH, low-molecular-weight heparin; OR, odds ratio.

[b]This table provides a summary of relative and absolute risks for pairwise (direct) comparisons of DOACs vs LMWH using 4 levels of certainty: high (further research is very unlikely to change our confidence in the estimate of effect), moderate (further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate), low (further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate), and very low (very uncertain about the estimate).

[c]Very serious imprecision due to wide confidence intervals that include clinically meaningful benefit and harm.

[d]Serious imprecision due to wide confidence intervals.

[e]Very serious imprecision due to very wide confidence intervals that include clinically meaningful benefit and harm.

[f]Very serious imprecision due to very wide confidence intervals.

TABLE 3. GRADE Summary of Findings Using Network Estimates[a,b]

		DOACs					
LMWH		Edoxaban		Rivaroxaban		Apixaban	
Venous thromboembolism recurrence							
Trial duration: 6 to 12 months							
Dalteparin		OR, 0.67 (0.44-1.02)	28 fewer per 1000 (49 fewer to 2 more)	OR, 0.41 (0.16-0.95)	52 fewer per 1000 (75 fewer to 4 fewer)	OR, 0.58 (0.37-0.90)	36 fewer per 1000 (55 fewer to 8 fewer)
91 per 1000[g]		●●○○ Low[c]		●●●○ Moderate[d]		●●●● High	
Rank 4		Rank 3		Rank 1		Rank 2	
		Based on 1046 participants (1 RCT)		Based on 406 participants (1 RCT)		Based on 1442 participants (2 RCTs)	
Major bleeding							
Trial duration: 6 to 12 months							
Dalteparin		OR, 1.78 (1.04-3.16)	26 more per 1000 (1 more to 69 more)	OR, 1.93 (0.71-5.80)	31 more per 1000 (10 fewer to 142 more)	OR, 0.88 (0.48-1.58)	4 fewer per 1000 (18 fewer to 20 more)
36 per 1000[g]		●●●○ Moderate[d]		●○○○ Very low[e]		●●○○ Low[e]	
Rank 2		Rank 4		Rank 3		Rank 1	
		Based on 1046 participants (1 RCT)		Based on 406 participants (1 RCT)		Based on 1442 participants (2 RCTs)	
Clinically relevant nonmajor bleeding							
Trial duration: 6 to 12 months							
Dalteparin		OR, 1.37 (0.95-1.98)	25 more per 1000 (3 fewer to 63 more)	OR, 4.09 (1.79-10.59)	172 more per 1000 (51 more to 384 more)	OR, 1.50 (1.00-2.27)	33 more per 1000 (0 fewer to 79 more)
74 per 1000[g]		●●○○ Low[c]		●●○○ Low[f]		●●○○ Low[c]	
Rank 1		Rank 2		Rank 4		Rank 3	
		Based on 1046 participants (1 RCT)		Based on 406 participants (1 RCT)		Based on 1442 participants (2 RCTs)	

[a]DOACs, direct oral anticoagulants; GRADE, Grading of Recommendations Assessment, Development, and Evaluation; LMWH, low-molecular-weight heparin; OR, odds ratio; RCT, randomized controlled trial.

[b]This table provides a summary of relative and absolute risks for mixed treatment comparisons of DOACs vs LMWH derived from Bayesian network meta-analysis using 4 levels of certainty: high (further research is very unlikely to change our confidence in the estimate of effect), moderate (further research is likely to have an important impact on our confidence in estimate of effect and may change the estimate), low (further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate), and very low (very uncertain about the estimate).

[c]Serious imprecision due to wide confidence intervals that include clinically meaningful benefit and harm.

[d]Serious imprecision due to wide confidence intervals.

[e]Very serious imprecision due to very wide confidence intervals that include clinically meaningful benefit and harm.

[f]Very serious imprecision due to very wide confidence intervals.

[g]The absolute baseline risk with dalteparin for each outcome was calculated by averaging the absolute baseline risk with dalteparin compared with each treatment.

Last, fatal bleeding was also infrequent with an overall rate of 0.3%, which did not differ by treatment. In considering bleeding as an outcome, intracranial bleeding and fatal bleeding are foremost on the minds of patients, their families, and providers.[43] The low rates are therefore reassuring and should help discussion and decision-making efforts.

The increase in CRNMB by 65% with the use of DOACs deserves consideration. Although neither major nor life-threatening, this type of bleeding can result in anticoagulation interruptions, possibly increasing the risk of subsequent thrombosis recurrence. Inconvenience and resource utilization are other variables to consider. In the 4 clinical trials,[2,4-6] each of the DOACs increased the rate of this event relative to dalteparin. How this type of event should be factored into management decision-making is complex and difficult to know with certainty. Patients experiencing CRNMB events may have an increased propensity for MB events in the future. Extremes of weight and drug interactions with cancer treatment are other situations that warrant caution with the use of DOACs.[43-45]

Thrombotic outcomes increase mortality in cancer patients and are the second most common cause of death after cancer progression.[46] To date, there has not been an anticoagulation strategy shown to improve mortality rates.[1,29,30,47-49] The DOAC trials are not unique in this finding.[2,4-6] Whereas there were mortality differences across trials, these rates did not differ within any specific trial whether patients received a DOAC or dalteparin. The reason for neutral survival outcomes is not readily apparent and does not appear to be explained by differences in either VTE recurrence or MB rates. It is possible that cancer-associated VTE portends a more aggressive tumor that may not be affected by anticoagulation therapy alone. The lack of overall mortality benefit despite lower VTE recurrence and fatal bleeds may not be surprising, given the high risk of death from advanced cancer. Individual patient meta-analysis focusing on patients with localized risk of cancer with longer follow-up may be insightful, but it may be limited by lack of power to detect such a difference. Future trials devoted to specific tumor types may be able to tease out survival differences that are not apparent in the current data set.

The results of our primary analysis are consistent with those of Giustozzi et al[27] but differ from those of Mulder et al.[26] Whereas our results are consistent with those of Giustozzi et al,[27] this analysis has several advantages, such as use of the GRADE approach, additional sensitivity analyses to harmonize the definition of VTE and timing of analysis, and true subgroup analysis with formal statistical testing to test for interactions as opposed to concluding a difference in effect in distinct subgroups on the basis of differences in the level of statistical significance within subgroups, which can be misleading.[21] The results of our direct SRMA differ from those of Mulder et al,[26] which reported that DOACs neither significantly reduce the risk of VTE nor increase the risk of bleeding. This is an intriguing example of how the choice of studies included, time point of treatment (on treatment vs follow-up), and estimator used in a random effects model (DL vs Sidik-Jonkman) and application of HK adjustment can alter the significance of mean effect size and subsequently influence clinical decision-making, which relies heavily on the paradigm of statistical significance. Whereas the HKSJ method or simply applying HK adjustment has been proposed as a more robust method, especially with a small number of studies, DL continues to be the most popular approach to conduct random effects meta-analysis. Nevertheless, the HKSJ method or HK adjustment produces CIs wider than those from the DL procedure with a substantial improvement in coverage accuracy.[21-23,50,51] An evidence map, illustrating differences in direct estimates when different estimation methods are used, is shown in Supplemental Figure 10 (available online at http://www.mayoclinicproceedings.org).

The choice of DOACs is not an easy decision in the absence of direct clinical trial evidence. Both apixaban and rivaroxaban significantly reduce the risk of VTE recurrence compared with dalteparin. Both rivaroxaban and edoxaban appear to increase bleeding outcomes, which was not seen with apixaban. Balancing bleeding and thrombotic outcomes through an assessment

of net clinical benefit will be important for future comparisons. On the basis of the available data, we have either low or very low confidence in the certainty of these estimates based on low precision for a specific DOAC choice (Tables 2 and 3).

The included trials[2,4-6] were a fair representation of patients with localized and metastatic disease and are therefore a reasonable representation of real-world clinical practice. There are a few caveats where we have limited data to inform clinical practice. It is important to highlight clinical criteria for which patients were excluded from trial participation. First, we have limited data regarding the treatment of atypical VTE (upper extremity, cerebral venous sinus, and splanchnic veins). Only 1 trial included these indications as the qualifying thrombus.[2] Second, these data do not include populations of pediatric patients. Third, all patients with poor performance status (ECOG status >2) were excluded. Only about one-fifth (n=615) of patients had an ECOG score of 2, and patients with higher scores were excluded. Fourth, we do not know what to do with patients with limited life expectancy. Most trials excluded those patients expected to live less than 2 or 3 months. Fifth, we do not know how prolonged pretreatment with other anticoagulants affects either safety or efficacy outcomes. Sixth, we have limited information for cancer patients who have undergone adjunctive therapies, including inferior vena cava filter placement, thrombolysis, and mechanical thrombectomies. Seventh, these combined data provide no guidance for patients with cancer who have coexistent severe liver or kidney disease. Eighth, the interaction between cancer and heparin-induced thrombocytopenia is unexplored. Ninth, there are cancer patients who have suffered VTE but also have atrial fibrillation, mechanical heart valves, or prosthetic cardiovascular grafts who require anticoagulants for other reasons. Whether these patients would be better served with warfarin is not clear as there has been no head-to-head trial of DOACs with warfarin in cancer patients. Clearly, patients with mechanical heart valves deserve special attention.[43]

An additional area of interest is the patient with cancer and secondary antiphospholipid antibody syndrome. Recent trials have raised concern for the use of rivaroxaban and antiphospholipid syndrome, yet the interaction between antiphospholipid syndrome and cancer and VTE is unclear.[52,53] We have limited information about the management of patients with severe thrombocytopenia. Less than 10% of patients with thrombocytopenia (defined by platelet count of $<100{,}000/mm^3$) and patients with borderline creatinine clearance (30-50 mL/min) were included in the trials,[2,4,5] except the SELECT-D,[6] which did not report the number of patients with thrombocytopenia and borderline creatinine clearance. Last, effect modification by the type of solid tumor, renal failure, and body mass index could not be assessed because of unavailability of outcome data based on these parameters.

This analysis was limited by a small number of trials and examination of only study-level data. The small number of trials precluded the formal assessment of publication bias and consistency and led to imprecision (wide CIs); a network with sparse direct evidence and lack of consistent reporting for results by subgroups led to decreased credibility of subgroup analysis. Similarly, ranking probabilities are not reliable and should be interpreted on the basis of their congruence with pairwise ORs.[54] The key outcomes (recurrent VTE and MB) with slightly different definitions were meta-analyzed. However, sensitivity analyses were consistent with primary analyses, and subtle differences are unlikely to result in a change of conclusions. In the direct analysis, we assumed that all DOACs are comparable and meta-analyzed DOACs as a single group. However, to overcome this limitation, we conducted a network meta-analysis. It was assumed that dalteparin is representative of all LMWH products. However, these results may not be translated to other LMWH preparations. Indeed, trials of enoxaparin and tinzaparin did not show superiority over warfarin for this indication[47-49,55] (Supplemental Table 6, available online at http://www.mayoclinicproceedings.org). Therefore, indirectness should be considered in applying the results in clinical practice. The strengths of this analysis include using the GRADE approach to summarize the evidence for each

patient-important outcome. We provided estimates of both absolute and relevant benefit as well as certainty of the evidence for each estimate of effect size, provided results with both standard and more conservative models for analysis, performed sensitivity analyses using both Bayesian and frequentist approaches for network meta-analysis, and created evidence maps and reconciliation tables to summarize and to contextualize all previous SRMAs on this topic. One of the key strengths is our commitment to maintain LISRs and to incorporate new evidence as it becomes available.[10] Thus, we continue to monitor for results of CANVAS (NCT02744092), CASTA-DIVA (NCT02746185), PRIORITY (NCT03139487), and CONKO-011 (NCT02583191).

CONCLUSION

DOACs should be considered a standard of care for the treatment of CAT, with caution in patients with high risk of bleeding. Current evidence favors the use of apixaban for the treatment of CAT among other DOACs.

ACKNOWLEDGMENTS

Drs Riaz and Fuentes contributed equally as first authors.

SUPPLEMENTAL ONLINE MATERIAL

Supplemental material can be found online at http://www.mayoclinicproceedings.org. Supplemental material attached to journal articles has not been edited, and the authors take responsibility for the accuracy of all data.

Abbreviations and Acronyms: **CAT** = cancer-associated thrombosis; **CRNMB** = clinically relevant nonmajor bleeding; **DOAC** = direct oral anticoagulant; **DL** = DerSimonian and Laird; **GI** = gastrointestinal; **GU** = genitourinary; **HK** = Hartung-Knapp; **HKSJ** = Hartung-Knapp-Sidik-Jonkman; **GRADE** = Grading of Recommendations Assessment, Development, and Evaluation; **LISR** = living interactive systematic review; **LIVE** = living, interactive evidence; **LMWH** = low-molecular-weight heparin; **MB** = major bleeding; **OR** = odds ratio; **PRISMA** = Preferred Reporting Items for Systematic Reviews and Meta-Analyses; **RCT** = randomized controlled trial; **SoF** = summary of findings; **SRMA** = systematic review and meta-analysis; **SRNMA** = systematic review and network meta-analysis; **VTE** = venous thromboembolism

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Potential Competing Interests: Robert D. McBane 2nd declares research funding from Bristol-Myers Squibb related to the EVE trial. All the other authors have no conflicts of interest to declare.

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