49% (47% DCB, 50% DES). Paclitaxel DCBs and predominantly second-generation DES were used. Although DCBs showed a numerically higher number of target lesion revascularization (6.5% vs 2.7%, OR 2.51, 95% CI 0.76 to 8.25, p = 0.13), acute thromboses (2.9% vs 0%, OR 5.16, 95% CI 0.59 to 44.97, p = 0.14), and major adverse cardiac events) (6.5% vs 3.4%, OR 1.98, 95% CI 0.69 to 5.74, p = 0.21) (Figure 1), these results were not statistically significant. No significant difference was seen between DCB and DES for myocardial infarction (1.4% vs 1.3%, OR 0.97, 95% CI 0.13 to 7.29, p = 0.98), and all-cause mortality (0.7% vs 0%, OR 3.76, 95% CI 0.15 to 94.83, p = 0.42) (Figure 1). More type D or worse coronary dissections were seen with DCBs (14.5% vs 0%, OR 18.4, 95% CI 3.48 to 93.61, p = 0.0006). In the DCB group, bailout stenting with a bare-metal stent was required in 18 patients (13.0%) for type D or worse coronary dissection (13,9.4%), and residual coronary artery stenosis (4, 2.9%). One case (0.7%) was transitioned over to DES for unknown reasons.

Thus, all outcomes were statistically similar between DCBs and DES, except a significantly higher number of type D (or worse) acute coronary dissections with DCBs. This contributed to bail-out stenting procedures. Coronary artery dissections A-C are considered benign, while D-F are intervened upon urgently. A total of 14.5% DCB resulted in dissections D-F. Whether this number is reproduced in larger RCTs or is an acceptable number for bailout stenting remains to be determined. The use of DCB in STEMI may be considered in carefully selected patients, for example, to avoid jailing of a major side-branch, when the culprit vessel is too small, or in the presence of previous stents. The current evidence for the use of DCB in STEMI is not sufficient to recommend this modality routinely.

## Disclosures

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Khalid Changal, MD[a]
Mitra Patel, MD[a]
Tanveer Mir, MD[b]
Ahmed Elzanaty, MD[a]
Salik Nazir, MD[a]
Ehab Eltahawy, MD, MPH[a,*]
[a] Division of Cardiovascular Medicine, Department of Medicine, University of Toledo College of Medicine and Life Sciences, Toledo, Ohio
[b] Department of Medicine, Detroit Medical Center, Wayne State University, Detroit, Michigan
5 July 2020

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## Meta-Analysis Comparing Direct Oral Anticoagulants to Low Molecular Weight Heparin for Treatment of Venous Thromboembolism in Patients With Cancer

Low molecular weight heparin (LMWH) is considered the standard anticoagulant therapy for patients with cancer-associated Venous Thromboembolism (VTE).[1−3] Although the efficacy and safety of direct oral anticoagulants (DOACs) in the treatment of VTE in patients without cancer has been validated,[4] their role in cancer-associated VTE is still evolving. We conducted a meta-analysis of the published randomized controlled trial (RCTs) comparing DOACs with LMWH for the treatment of VTE in cancer patients.

We performed a comprehensive literature search of electronic databases (Embase, MEDLINE, and Cochrane Central) from inception to May 30, 2020 using a predefined search strategy. Two reviewers independently screened all results in successive stages: title/abstract followed by full-text review. Studies were selected if they were RCTs, included cancer patients with VTE, and compared clinical outcomes between DOACs and LMWH.

The principal efficacy outcome was recurrence of VTE, either symptomatic or incidentally discovered. None of the trials utilized serial surveillance imaging to assess for asymptomatic recurrent VTE. The principal safety outcome was incidence of major bleeding (defined as overt bleeding leading to a decrease in the hemoglobin level of ≥ 2 g/dl, transfusion of 2 or more units of blood, occurring at a critical site, or fatal bleeding). Secondary outcomes included clinically relevant nonmajor bleeding (CRNMB) and all-cause mortality. CRNMB was defined as clinically overt bleeding not meeting criteria for major bleeds, associated with impairment of daily living or requiring medical attention. All outcomes were assessed at 6 months.

For statistical analysis, we calculated pooled risk ratios (RRs) with 95% confidence intervals (CI) using a random-effects model.[5,6] Stata version-15 was used for statistical analysis (StataCorp LLC). All p values were two-tailed with statistical significance specified at 0.05. Heterogeneity among studies was assessed using the Higgins $I^2$ value.[7]

The initial literature search yielded 1,662 citations. Four RCTs with a total of 2,894 patients were included in this study level meta-analysis.[8−11] Details of the study designs and baseline characteristics of patients are shown in Table 1. Of the 2,894 patients, 1,446 received a DOAC and 1,448 received LMWH. Almost all patients had active cancer (98% to 100%) and were receiving concurrent cancer treatment (57% to 73%). Patients with a poor functional status- Eastern Cooperative Oncology Group performance score >2, and those with basal cell or squamous cell skin cancer were excluded.

Recurrent VTE at 6 months was decreased in patients treated with DOACs compared to LWMH (5.2% vs 8.2%; RR 0.62, 95% CI 0.43 to 0.91; p = 0.01; $I^2$ = 30%; Figure 1A). CRNMB was higher with DOACs as compared to LMWH (10.3% vs 6.3%; RR 1.65, 95% CI 1.19 to 2.28; p = 0.002; $I^2$ = 29%;

Table 1
Study designs, treatment protocols and baseline characteristics of patients across randomized trials comparing DOACs versus LMWH

| Trial | HOKUSAI-VTE | SELECT-D | ADAM-VTE | CARAVAGGIO |
|---|---|---|---|---|
| Study Design | Randomized, open label, multi-center trial | Randomized, open label, multi-center trial | Randomized, open label, multi-center trial | Randomized, open label, multi-center trial |
| Treatment Arm | Edoxaban | Rivaroxaban | Apixaban | Apixaban |
| Treatment Arm Dose | LMWH x 5 days and then Edoxaban 60 OD | Rivaroxaban 15 mg BID x 3wks then 20 mg OD | Apixaban 10mg BID x 7 days then 5mg BID | Apixaban 10mg BID x 7 days then 5mg BID |
| Comparison | Dalteparin SC | Dalteparin SC | Dalteparin SC | Dalteparin SC |
| Comparison Arm Dose | 200 IU/Kg SC x 30 days than 150 IU/Kg SC | 200 IU/Kg SC x 30 days than 150 IU/Kg SC | 200 IU/Kg SC x 30 days than 150 IU/Kg SC | 200 IU/Kg SC x 30 days than 150 IU/Kg SC |
| Duration of Anticoagulation | 12 months | 6 months | 6 months | 6 months |
| Primary Outcome | Recurrent VTE or Major bleeding | Recurrent VTE | Any major bleeding | Recurrent VTE |
| Key Efficacy Outcome | Recurrent VTE | Recurrent VTE | Recurrent VTE | Recurrent VTE |
| Key Safety Outcome | Major bleeding and CRNMB | Major bleeding and CRNMB | Major bleeding and CRNMB | Major bleeding and CRNMB |
| Number of Patients Randomized | 1050 | 406 | 300 | 1170 |
| Baseline Characteristics of Trial Participants | | | | |
| | HOKUSAI-VTE | SELECT-D | ADAM-VTE | CARAVAGGIO |
| Type of cancer | | | | |
| Solid | 89.1% | 92.4% | 90.7% | 92.6% |
| Hematological | 10.9% | 7.6% | 9.3% | 7.4% |
| White | 84.1% | 95.8% | 92.7% | 80.2% |
| Mean Age (years) | 64 | 67 | 64 | 67 |
| Men | 52% | 53% | 48% | 49% |
| Mean Weight (kg) | 78.9 | NR (mean BMI-26.6) | 85.8 | 75.9 |
| Active Cancer | 97.8% | 100% | 100% | 97.3% |
| Metastatic Disease | 52.9% | 58.0% | 64.3% | 67.9% |
| Cancer Treatment in last 4 weeks | 72.4% | 69.5% | 72.7% | 56.4% |
| ECOG | | | | |
| 0 | 28.9% | 29.3% | 40.7% | 30.8% |
| 1 | 46.7% | 45.6% | 48.7% | 48.3% |
| 2 | 23.6% | 23.4% | 10.7% | 20.9% |
| CKD-Cr Clearance 30-50 ml/min | 6.8% | NR | 9.3% | 9.7% |
| Qualifying Diagnosis of Venous Thromboembolism | | | | |
| | HOKUSAI-VTE | SELECT-D | ADAM-VTE | CARAVAGGIO |
| PE | 62.8% | 71.6% | 52.0% | 55.2% |
| DVT | 37.2% | 27.1% | 47.0% | 44.8% |
| Symptomatic VTE | 67.5% | 47.5% | NR | 80.1% |
| Incidental VTE | 32.5% | 52.5% | NR | 19.9% |

SELECT-D = anticoagulation Therapy in Selected Cancer Patients at Risk of Recurrence of Venous Thromboembolism; ADAM VTE = Apixaban and Dalteparin in Active Malignancy-associated Venous Thromboembolism; LMWH = Low molecular weight heparin; SC = Subcutaneous; PE = pulmonary embolism; DVT = deep vein thrombosis; CRNMB = Clinically relevant nonmajor bleeding; CKD = chronic Kidney disease; Cr = Creatinine; Cl = clearance; ECOG = Eastern Cooperative Oncology Group; Kg =Kilograms; BMI = Body mass Index; NR = not reported.

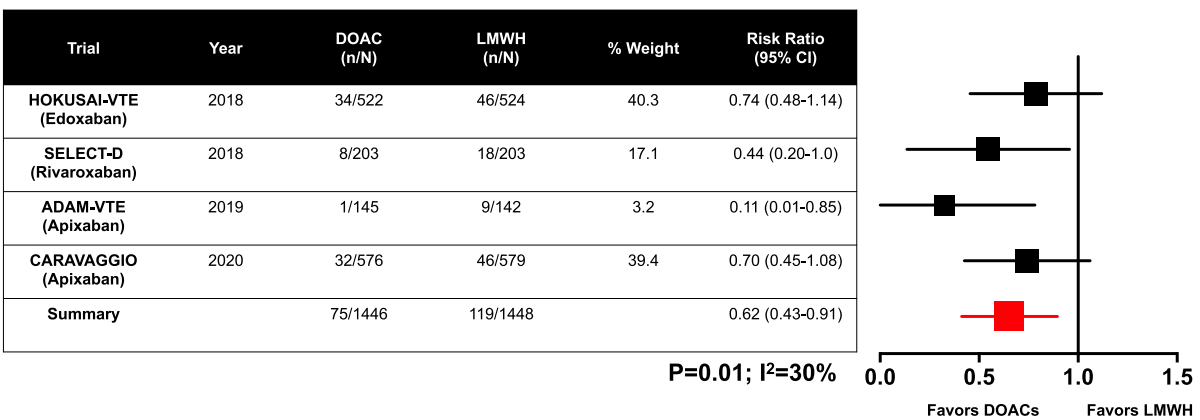


Figure 1A. Recurrent VTE at 6 months. DOAC = direct oral anticoagulant; LMWH = low molecular weight heparin; SELECT-D = anticoagulation Therapy in Selected Cancer Patients at Risk of Recurrence of Venous Thromboembolism; ADAM VTE = Apixaban and Dalteparin in Active Malignancy-associated Venous Thromboembolism.

| Trial | Year | DOAC (n/N) | LMWH (n/N) | % Weight | Risk Ratio (95% CI) |
|---|---|---|---|---|---|
| **HOKUSAI-VTE (Edoxaban)** | 2018 | 64/522 | 43/524 | 40.8 | 1.49 (1.04-2.16) |
| **SELECT-D (Rivaroxaban)** | 2018 | 25/203 | 7/203 | 13.3 | 3.57 (1.58-8.07) |
| **ADAM-VTE (Apixaban)** | 2019 | 9/145 | 7/142 | 10.0 | 1.26 (0.48-3.29) |
| **CARAVAGGIO (Apixaban)** | 2020 | 52/576 | 35/579 | 35.8 | 1.49 (0.99-2.26) |
| **Summary** | | 150/1446 | 92/1448 | | 1.65 (1.19-2.28) |

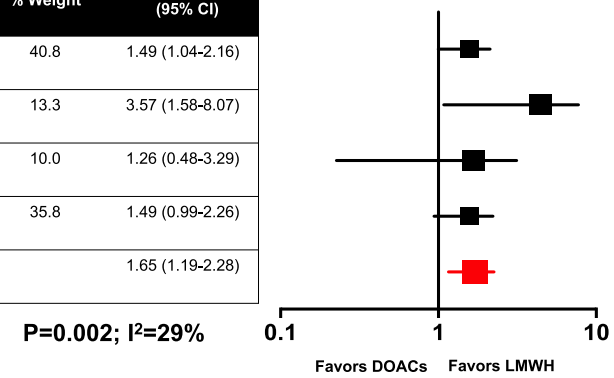


Figure 1B. Clinically relevant nonmajor bleeding at 6 months. DOAC = direct oral anticoagulant; LMWH = low molecular weight heparin; SELECT-D = anticoagulation Therapy in Selected Cancer Patients at Risk of Recurrence of Venous Thromboembolism; ADAM VTE = Apixaban and Dalteparin in Active Malignancy-associated Venous Thromboembolism.

| Trial | Year | DOAC (n/N) | LMWH (n/N) | % Weight | Risk Ratio (95% CI) |
|---|---|---|---|---|---|
| **HOKUSAI-VTE (Edoxaban)** | 2018 | 29/522 | 17/524 | 39.1 | 1.71 (0.95-3.08) |
| **SELECT-D (Rivaroxaban)** | 2018 | 11/203 | 6/203 | 18.4 | 1.83 (0.69-4.86) |
| **ADAM-VTE (Apixaban)** | 2019 | 0/145 | 2/142 | 2.3 | 0.20 (0.01-4.04) |
| **CARAVAGGIO (Apixaban)** | 2020 | 22/576 | 23/579 | 40.2 | 0.96 (0.54-1.71) |
| **Summary** | | 62/1446 | 48/1448 | | 1.31 (0.83-2.08) |

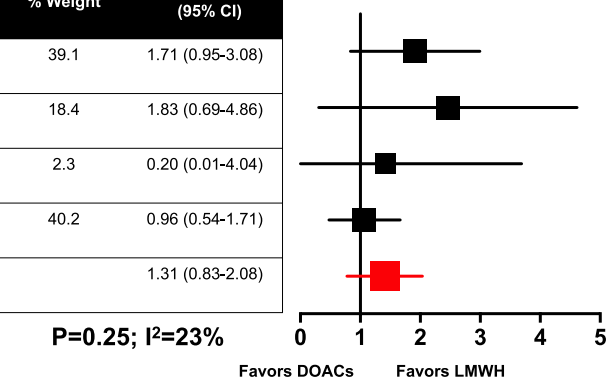


Figure 1C. Major bleeding at 6 months. DOAC = direct oral anticoagulant; LMWH = low molecular weight heparin; SELECT-D = anticoagulation Therapy in Selected Cancer Patients at Risk of Recurrence of Venous Thromboembolism; ADAM VTE = Apixaban and Dalteparin in Active Malignancy-associated Venous Thromboembolism.

| Trial | Year | DOAC (n/N) | LMWH (n/N) | % Weight | Risk Ratio (95% CI) |
|---|---|---|---|---|---|
| **HOKUSAI-VTE (Edoxaban)** | 2018 | 140/522 | 127/524 | 35.6 | 1.11 (0.90-1.36) |
| **SELECT-D (Rivaroxaban)** | 2018 | 48/203 | 56/203 | 20.2 | 0.86 (0.61-1.20) |
| **ADAM-VTE (Apixaban)** | 2019 | 23/145 | 15/142 | 7.6 | 1.5 (0.82-2.76) |
| **CARAVAGGIO (Apixaban)** | 2020 | 135/576 | 153/579 | 36.7 | 0.89 (0.73-1.08) |
| **Summary** | | 346/1446 | 351/1448 | | 0.99 (0.83-1.18) |

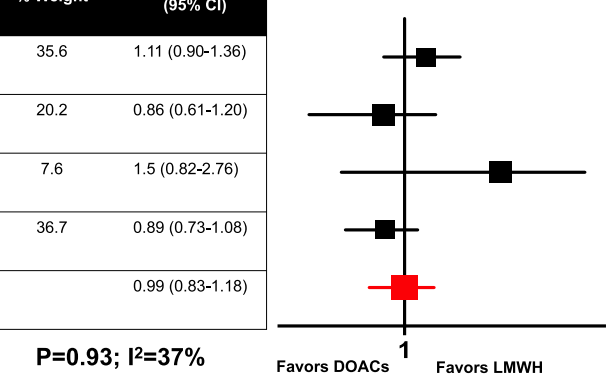


Figure 1D. All-cause mortality at 6 months. DOAC = direct oral anticoagulant; LMWH = low molecular weight heparin; SELECT-D = anticoagulation Therapy in Selected Cancer Patients at Risk of Recurrence of Venous Thromboembolism; ADAM VTE = Apixaban and Dalteparin in Active Malignancy-associated Venous Thromboembolism.

Figure 1B), driven largely by increased gastrointestinal and genitourinary bleeding. There was no difference in major bleeding between DOACs and LMWH (4.3% vs 3.3%; RR 1.31, 95% CI 0.83 to 2.08; p = 0.25; $I^2$ = 23%; Figure 1C). There was no difference in all-cause mortality between the 2 groups (23.9% vs 24.2%; RR 0.99, 95% CI 0.83 to 1.18; p = 0.93; $I^2$ = 37%; Figure 1D). The degree of heterogeneity between the studies ranged from low to moderate.

Our meta-analysis supports the use of DOACs as an effective alternative to LMWH for the treatment of VTE in

patients with cancer. The pooled analysis of study level data shows a statistically significant reduction in recurrent VTE at 6 months with DOACs as compared to LMWH. However, this decrease in recurrent VTE occurred at the cost of increased bleeding events, largely driven by CRNMB, with no difference in major bleeding or mortality.

The HOKUSAI-VTE,[8] and SELECT-D[9] trials compared edoxaban and rivaroxaban, respectively, to LMWH. The ADAM-VTE trial was the first trial to compare apixaban to LMWH in cancer-associated VTE and showed lower risk of recurrent VTE with apixaban.[10] However, these individual trials were not powered to detect superiority for efficacy outcomes. Subsequently the CARAVAGGIO study[11] compared apixaban with LMWH for the treatment of VTE in patients with cancer. This trial randomized 1,170 patients, the largest study to date and demonstrated that apixaban was noninferior to LMWH for the prevention of cancer-associated recurrent VTE, major bleeding, CRNMB, and all-cause mortality.

We found low to moderate heterogeneity in these studies which may be related to the use of different DOACs, varying proportions of underlying cancers, cancer treatment modalities and subtle differences in the defined outcomes. Furthermore, all 4 studies are limited by their open label design and small-moderate patient populations.

In conclusion, DOACs appear to be a reasonable alternative to LMWH for the treatment of cancer-associated VTE. If these agents are prescribed for patients with gastrointestinal or genitourinary malignancy, careful monitoring, and mitigation of bleeding risk should be performed.

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Kirtipal Bhatia, MD[a]
Guneesh Uberoi, MD[a]
Navkaranbir S. Bajaj, MD[b]
Vardhmaan Jain, MD[c]
Sameer Arora, MD[d]
Alfonso Tafur, MD MS[e]
Sripal Bangalore, MD, MHA[f]
Jeffrey W. Olin, DO[g]
Gregory Piazza, MD, MS[c]
Samuel Z. Goldhaber, MD[c]
Muthiah Vaduganathan, MD, MPH[f]
Arman Qamar, MD MPH[e,f,*]

[a] Department of Medicine, Icahn School of Medicine at Mount Sinai, New York, New York
[b] Division of Cardiology, University of Alabama School of Medicine, Birmingham, Alabama
[c] Division of Cardiovascular Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts
[d] Division of Cardiology, University of North Carolina School of Medicine, Chapel Hill, North Carolina
[e] Section of Vascular Medicine, NorthShore University Health System, University of Chicago, Evanston, Illinois
[f] Leon H. Charney Division of Cardiology, New York University Grossman School of Medicine, New York, New York
[g] Zena and Michael A. Wiener Cardiovascular Institute, and Marie-Josée and Henry R. Kravis Center for Cardiovascular Health, Icahn School of Medicine at Mount Sinai, New York, New York

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