Direct Oral Anticoagulants for Venous Thromboembolism in Patients with Brain Metastases: A Scoping Review of Intracranial Hemorrhage Risk

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BACKGROUND

- Direct oral anticoagulants (DOACs) are first-line for treatment of cancer-associated venous thromboembolism (VTE).[1]
- **No consensus exists on routine DOAC use in patients with brain metastases**. Clinical trials of DOACs and cancer often excluded brain metastases due to concern for intracranial hemorrhage (ICH). Studies allowing patients with brain metastases included small numbers.[2]
- Low-molecular-weight heparin (LMWH) has traditionally been favored in this population, but comparative ICH data is limited.[2]
- This scoping review characterizes the existing literature on ICH risk with DOACs for treatment of VTE in patients with brain metastases.

OBJECTIVE

To map and characterize the available **evidence on intracranial hemorrhage risk associated with DOAC use**, relative to other anticoagulants, for treatment of venous thromboembolism in patients with brain metastases.

METHODS

- Scoping review conducted per Joanna Briggs Institute (JBI) methodology.[3]
- Databases searched through 2024: Ovid MEDLINE, Ovid EMBASE, Cochrane Library, Web of Science, OAIster, Google Scholar, ProQuest Dissertations & Theses, ClinicalTrials.gov
- Final inclusion criteria required that study evaluate DOACs for treatment of cancer-associated VTE and discuss ICH in the context of brain metastases.
- Two reviewers independently screened abstracts, completed full text review, and extracted data per determined criteria. A third, independent reviewer resolved all conflicts.
- Cohort studies underwent quality appraisal using the revised JBI critical appraisal tool, with 9 standardized domains evaluated.[4]

RESULTS

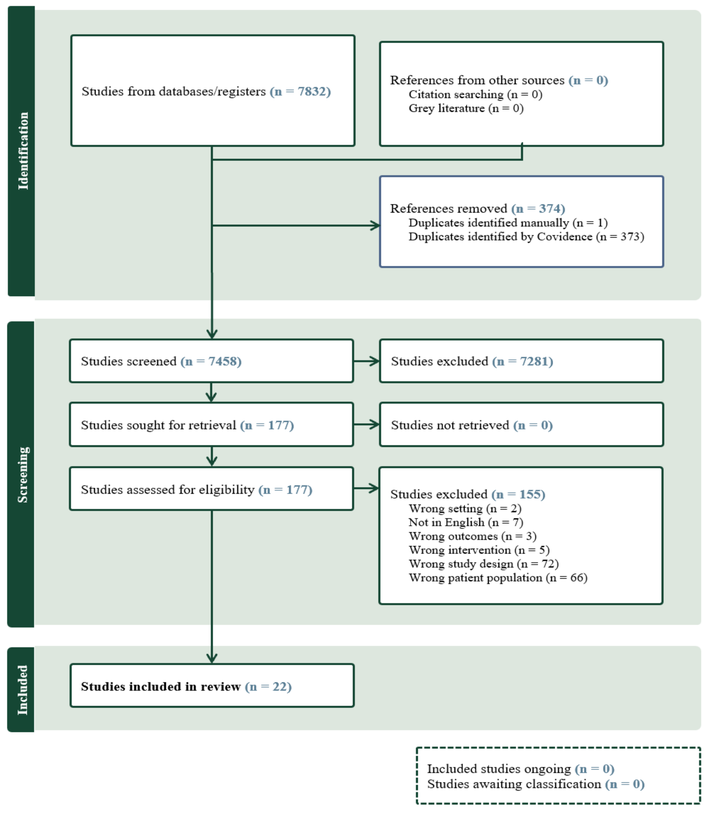


Figure 1. Study identification and selection process reported using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR) flow diagram.[5]

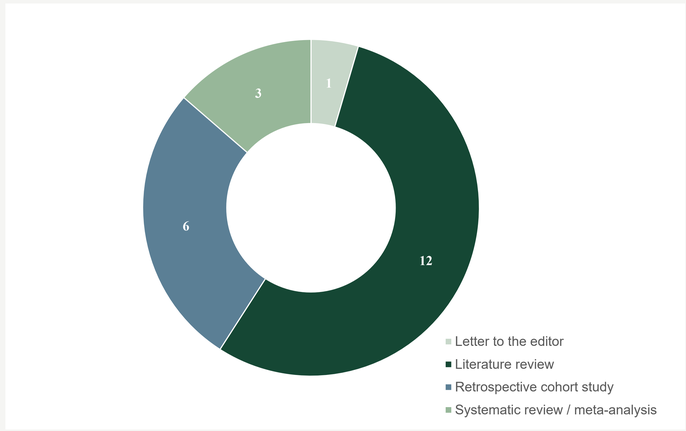


Figure 2. Distribution of the included study designs (n = 22).

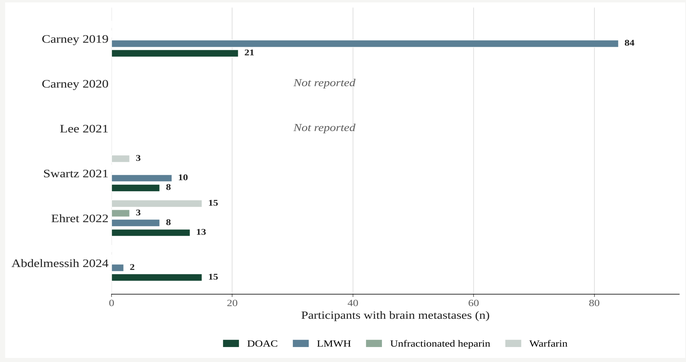


Figure 3. Anticoagulant used among participants with brain metastases, by retrospective cohort study. "Not reported" indicates studies that did not report anticoagulant-specific counts for the brain metastases subgroup.

Study	Brain metastases, n	Key Findings	Critical Appraisal
Carney 2019 [6]	105	Any ICH: 27.8% DOAC vs 52.9% LMWH. Major ICH: 11.1% DOAC vs 17.8% LMWH.	High
Carney 2020 [7]	58	Recurrent ICH after anticoagulation was associated with high mortality. Too few DOAC patients for comparison by anticoagulant type.	Moderate
Lee 2021 [8]	85	ICH: 4.9% DOAC vs 2.3% LMWH. Difference was not statistically significant.	Moderate
Swartz 2021 [9]	21	4 ICH events. No significant difference by anticoagulant (1 DOAC, 2 LMWH, 1 warfarin).	High
Ehret 2022 [10]	41	ICH occurred in 12.2%; prior hemorrhage and melanoma associated with higher risk. ICH not evaluated by anticoagulant type.	High
Abdelmessih 2024 [11]	17	Overall ICH in patients with brain tumors at 3 months: 4.1% DOAC vs 15.6% enoxaparin. Brain metastasis specific data unavailable.	High

Table 1. Key findings and risk-of-bias appraisal for the 6 included retrospective cohort studies. DOAC = direct oral anticoagulant; LMWH = low-molecular-weight heparin; ICH = intracerebral hemorrhage.

KEY RESULTS

- 7,458 abstracts screened, 177 full-text reviewed**, 22 studies included**, among which were 6 retrospective cohort studies.
- 16 studies focused exclusively on brain cancer (primary and metastatic). **Only 1 study focused exclusively on brain metastases**, and it did not compare ICH by anticoagulant class.
- **ICH incidence in brain metastases ranged from 4.9-27.8% with DOACs and 2.3-52.9% with LMWH** across studies reporting a comparison; no statistically significant differences reported.
- Fatal ICH was infrequently discussed.
- On critical appraisal, 4 cohort studies were rated high and 2 were rated moderate risk of bias.

DISCUSSION

- Available evidence does not suggest a significantly increased ICH risk with DOACs relative to LMWH in patients with brain metastases.
- Evidence is sparse, retrospective, and at risk of confounding. Few studies were designed to isolate this population.
- Cohort studies often differed in baseline risk factors that were not consistently adjusted for across groups.

CONCLUSIONS

Limited, retrospective evidence suggests no significant increase in ICH with DOACs compared with LMWH in patients with brain metastases treated for VTE. Prospective studies are needed to define ICH risk in this population.

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