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ORIGINAL ARTICLE

Safety and efficacy of anticoagulant treatment in patients with ovarian vein thrombosis: a systematic review and meta-analysis of observational studies

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Abstract

Background: The role of anticoagulation in ovarian vein thrombosis (OVT) is uncertain.

Objectives: We aimed to evaluate safety and efficacy of anticoagulant treatment in OVT patients.

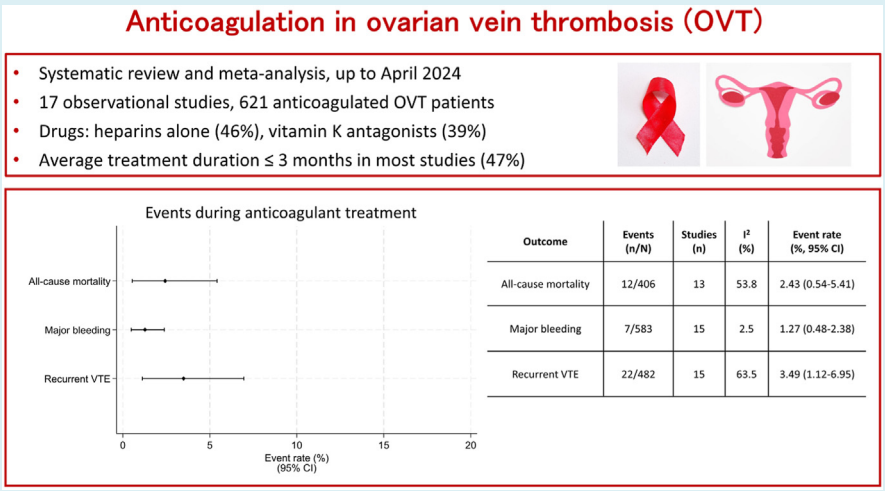
Methods: A systematic search was conducted in MEDLINE, EMBASE, and Cochrane Central Register of Controlled Trials databases up to April 2024. Eligible studies included randomized controlled trials and observational studies enrolling at least 10 adult patients with objectively diagnosed OVT and treated with any anticoagulants. The protocol was prospectively registered in the International Prospective Register of Systematic Reviews (CRD42021270883).

Alex Gatt and Jean Calleja-Agius are cosenior authors in this study.

Preliminary findings from this study were presented as a poster at the 2022 Congress of the International Society on Thrombosis and Haemostasis (ISTH).

Results: We included 17 observational studies (621 anticoagulated and 376 non-anticoagulated OVT patients); 9 studies enrolled mainly pregnancy/puerperium-related OVT. Most patients received heparins alone (45.7%) or proceeded to vitamin K antagonists (39.2%). The average treatment duration was ≤3 months in 8 studies (47.1%), >3 to ≤6 months in 6 studies (35.3%), and >6 months in 3 studies (17.6%). In treated patients, mortality rate was 2.43% (95% CI, 0.54%-5.41%; I^2 = 53.8%; 12/406 patients; 13 studies), major bleeding was 1.27% (95% CI, 0.48%-2.38%; I^2 = 2.5%; 7/583 patients; 15 studies), recurrent venous thromboembolism (VTE) was 3.49% (95% CI, 1.12%-6.95%; I^2 = 63.5%; 22/482 patients; 15 studies), and vessel recanalization was 89.4% (95% CI, 74.6%-98.6%; I^2 = 80.6%; 163/184 patients; 8 studies). The rate of recurrent VTE in untreated patients was 8.65% (95% CI, 2.61%-17.35%); however, the difference compared with treated patients was not statistically significant (risk ratio, 0.70; 95% CI, 0.36-1.37). At subgroup analyses, the rates of major bleeding and recurrent VTE were 0.80% (95% CI, 0.0-2%.17%) and 3.81% (95% CI, 0.42%-9.63%) in pregnancy/puerperium-related OVT, respectively, and 1.12% (95% CI, 0.32%-2.34%) and 1.78% (95% CI, 0.62%-3.46%), respectively, when analyzing only full-text studies.

Conclusion: There is paucity of literature regarding OVT. Our results suggest that anticoagulation is associated with low rates of major bleeding and recurrent VTE.



KEYWORDS
anticoagulants, meta-analysis, ovary, systematic review, venous thromboembolism

Essentials

- The role of anticoagulant treatment in patients with ovarian vein thrombosis is uncertain.
- We conducted a meta-analysis of 17 observational studies enrolling 621 anticoagulated ovarian vein thrombosis patients.
- Most patients received heparins or vitamin K antagonists, with average duration of up to 3 months.
- Anticoagulation was associated with low major bleeding and recurrent venous thromboembolism.

1 | INTRODUCTION

Ovarian vein thrombosis (OVT) is an unusual site of venous thromboembolism (VTE). Data from a single-institution case-control study suggests that OVT may be 60 times less frequent than lower extremity deep vein thrombosis (DVT) [1]. OVT can be a complication of pregnancy and the puerperium: it occurs in approximately 0.01% to 0.18% of pregnancies, and these cases more frequently involve the right ovarian vein [2–5]. OVT can also be secondary to genitourinary or gastrointestinal neoplasms, abdominopelvic surgery, or intra-abdominal infections [1,6–8].

The clinical presentation of OVT includes abdominal pain, tenderness, a palpable cord-like mass, as well as nonspecific symptoms, such as fever, anorexia, nausea, vomiting, and malaise [5]. The combination of pelvic pain, abdominal mass, and fever is considered the classical triad of OVT, which led to the original description of OVT as "septic pelvic thrombophlebitis."

Diagnosis nowadays relies on abdominal imaging techniques. Doppler ultrasound (US) is often the initial choice; however, visualization of the ovarian veins can be hindered by obesity or abdominal meteorism. Therefore, computed tomography (CT) or magnetic resonance imaging (MRI) is recommended [9,10].

With the increased use of abdominal imaging, OVT may also be an incidental finding discovered in asymptomatic patients. Studies evaluating women with gynecologic malignancies undergoing surgical treatment reported that incidental OVT was detected at follow-up CT scans in variable proportions, ranging from 13% to 80% of patients [7,11,12]. In 2 studies evaluating MRI screening in postpartum patients, asymptomatic pelvic vein thrombosis was detected in 46% of women at moderate-high thrombosis risk after cesarean section [13] and 30% of women at low thrombosis risk after vaginal delivery [14].

The optimal treatment for OVT is still debated. An open-label randomized controlled trial (RCT), published in 1999, enrolled 14 women with puerperal septic pelvic thrombophlebitis: 8 were assigned to antibiotic treatment alone, while 6 received antibiotic together with unfractionated heparin (UFH), which was given for a mean of 4.6 days [15]. This study aimed to assess the duration of fever ≥38 °C, which was not influenced by the concomitant administration of UFH. None of the patients in both arms of the study developed recurrent VTE at 3-month follow-up; however, the sample size was small [15]. More recently, an observational study showed that patients with OVT are less likely to receive anticoagulant treatment compared with patients with DVT of the lower extremities (54% vs 98%, respectively) [1].

The aims of this systematic review and meta-analysis were to evaluate the safety and efficacy of the anticoagulant treatment in patients with OVT and to compare the event rates with non-anticoagulated OVT patients.

2 | METHODS

This systematic review and meta-analysis is reported in accordance with the Preferred Reporting Items for Systematic reviews and Meta-Analyses 2020 Checklist [16]. The protocol was registered a priori in the International Prospective Register of Systematic Reviews (PROSPERO registration number: CRD42021270883).

2.1 | Study identification

A systematic search was conducted using the electronic databases MEDLINE/PubMed, EMBASE, and the Cochrane Central Register of Controlled Trials from their inception to April 23, 2024. The search strategy used the free text words and the subject headings (MeSH/EMTREE terms) reported in Supplementary Table S1. There was no language restriction. In addition, the reference lists of retrieved articles and a previous systematic review on postpartum OVT [4] were reviewed manually (snowballing).

To identify unpublished studies within the gray literature, the abstract books from the congresses of the International Society on Thrombosis and Haemostasis (ISTH, years 2015-2023), the American Society of Hematology (years 2015-2023), and the International Federation of Gynecology and Obstetrics (years 2015-2023) were hand-searched.

2.2 | Study selection

Studies that fulfilled all the following inclusion criteria were selected: 1) study design: RCT, retrospective or prospective observational cohort studies, or case series, enrolling at least 10 OVT patients treated with anticoagulants; 2) population: adult patients with objectively diagnosed OVT (at US, CT, MRI, or during surgery); 3) intervention: treatment with any anticoagulant drugs (eg, UFH, low-molecular-weight heparin [LMWH], vitamin K antagonists [VKAs], or direct oral anticoagulants [DOACs]); 4) comparator: no restrictions were applied (both studies with nonanticoagulated OVT patients and studies without a comparator group were included); and 5) outcomes: studies evaluating safety and/or efficacy outcomes (as defined in section 2.3). We excluded editorials, narrative reviews, studies with less than 10 anticoagulated OVT patients, studies with unclear OVT diagnostic criteria, studies not reporting clinical outcomes, and studies in which separate outcome data for anticoagulated vs nonanticoagulated OVT patients were not available (after contacting the original study authors).

After duplicate citations were removed, 3 investigators (L.M.B., C.V., and N.R.) independently screened titles and abstracts based on these inclusion and exclusion criteria. Citations deemed eligible by at least one of the investigators were retrieved as full-text reports. Only the reports meeting the prespecified inclusion and exclusion criteria were selected for data extraction.

2.3 | Data extraction and outcomes

From each report, 2 investigators (L.M.B. and C.V.) independently extracted the following study-level information using a standardized

Microsoft Excel spreadsheet: study characteristics (publication year, study design, and enrolment period), patient characteristics (number of anticoagulated patients, demographic data, and inclusion and exclusion criteria), details of the anticoagulant treatment (drug, dose, and treatment duration), follow-up duration, and outcome details (definition and number of patients).

Information regarding the following outcomes was collected: all-cause mortality; major bleeding during anticoagulant treatment; recurrent VTE (including recurrent OVT and other site VTE, such as DVT, pulmonary embolism [PE], and other abdominal vein thrombosis) during anticoagulant treatment; and vessel recanalization (partial or complete). Outcomes were collected as reported in the original studies without any attempt at reclassification. Data extraction was checked by a third investigator (N.R.). Due to missing or unclear outcome data in 16 of the included studies, the authors of these original studies (including corresponding author, first author, or any other author for whom an email address was available) were emailed for clarifications.

2.4 | Risk of bias assessment

Two investigators (L.M.B. and C.V.) independently assessed the risk of bias (RoB) of the included studies. In the protocol, it was planned to assess RCTs using the Cochrane Risk of Bias tool version 2 [17] and observational studies using the Risk Of Bias In Nonrandomised Studies of Interventions tool (ROBINS-I) [18]. However, all the included studies had an observational design; thus, only the ROBINS-I tool was used.

The ROBINS-I tool [18] includes 7 domains: bias due to confounding, bias in selection of participants into the study, bias in classification of interventions, bias due to deviations from intended interventions, bias due to missing data, bias in measurement of outcomes, and bias in selection of the reported result. A study is classified as low RoB if all domains are judged to be at low RoB. For domain 1 (bias due to confounding), the fact that anticoagulated OVT patients might have different comorbidities compared with nonanticoagulated OVT patients was considered a confounding bias. For domain 2 (bias in selection of participants into the study), the need for a certain follow-up duration or the need for follow-up imaging as inclusion criteria was considered as a selection bias. For domain 5 (bias due to missing data), we considered low RoB if patients without follow-up data were <5%, moderate if 5% to 10%, and serious if >10%. Domain 5 was assessed separately for clinical outcomes (ie, mortality, major bleeding, and recurrent VTE) and radiological outcomes (ie, partial or complete recanalization). The RoB assessment was reviewed by a third investigator (N.R.), and agreement was reached by consensus.

2.5 | Statistical analysis

The outcomes were expressed as weighted mean proportions with 95% CI, calculated by pooling the results of the included studies using an inverse-variance random-effects model. In order to normalize individual studies' proportions prior to pooling, proportions were transformed using the Freeman–Tukey double arcsine method [19,20]. As recommended in the Cochrane Handbook for Systematic Reviews of Interventions, statistical heterogeneity was evaluated using the I^2 statistic, where values from 0% to 40% may not be important, 30% to 60% may represent moderate heterogeneity, 50% to 90% substantial heterogeneity, and 75% to 100% considerable heterogeneity [21].

The outcomes were evaluated separately for anticoagulated vs nonanticoagulated patients, and a comparison between the 2 groups was performed by calculating the pooled risk ratio (RR) and 95% CI using the DerSimonian–Laird random-effects model [22]. However, since studies with zero outcome events in both arms are usually excluded from this calculation, a further analysis was performed using a 0.5 continuity correction added to every cell of each 2×2 table [23], where needed (ie, for the outcomes all-cause mortality, major bleeding, and recurrent VTE).

In the protocol for this systematic review and meta-analysis, a sensitivity analysis was planned by including only studies with low RoB, and subgroup analyses were planned by different risk factors for OVT and different anticoagulant treatments. However, since there were no studies at low RoB, this sensitivity analysis could not be performed. Subgroup analyses were performed by RoB (low/moderate vs serious/critical RoB); study design (retrospective vs prospective studies; single institution vs multicenter studies); publication details (published as full-text vs conference abstract only; published before the year 2000 vs after the year 2000); risk factors for OVT (studies enrolling ≥60% of the population with pregnancy/puerperium-related OVT vs cancer-associated OVT); and treatment details (≥60% of the population receiving parenteral vs oral anticoagulants; average treatment duration ≤3 months vs >3 months, and ≤6 months vs >6 months). The Cochrane Q statistic was used to evaluate the between-subgroups heterogeneity.

The presence of publication bias regarding the outcomes reported in anticoagulated patients was assessed through the creation of funnel plots of the Freeman–Tukey double arcsine-transformed proportion (horizontal axis) vs its SE (vertical axis). The Egger test was used to test the presence of funnel plot asymmetry [24].

The software STATA/BE version 18 (StataCorp LLC) and Review Manager (RevMan, version 5.4, The Cochrane Collaboration, 2020) were used for statistical analysis, considering P values < .05 statistically significant. RoB plots were created using the *robvis* tool [25].

3 | RESULTS

3.1 | Study identification and selection

We identified 5523 potentially relevant citations: 2326 from MEDLINE/PubMed, 3054 from EMBASE, and 143 from Cochrane Central Register of Controlled Trials; 1004 citations were identified as duplicates, while 4395 citations were excluded after titles and abstracts screening using the predefined inclusion and exclusion criteria. Thus,

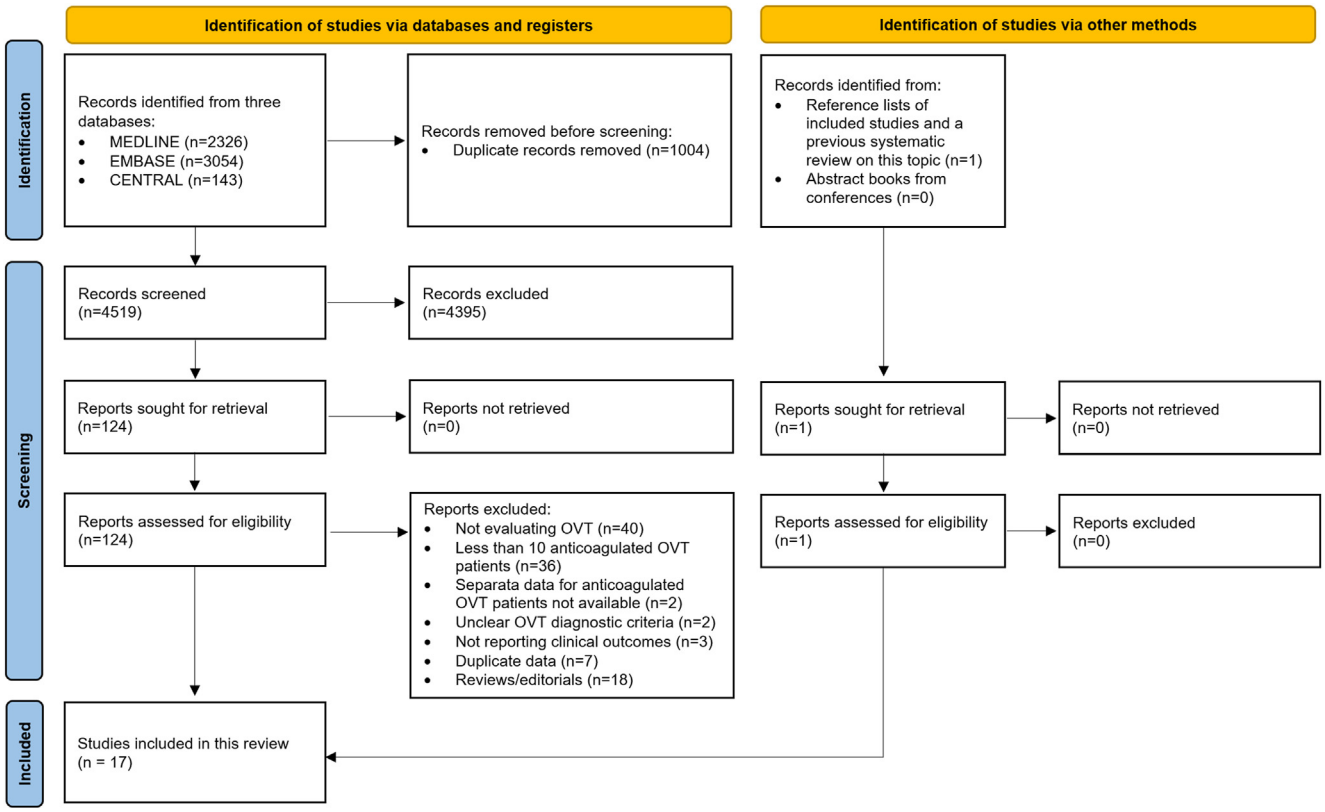


FIGURE 1 Preferred Reporting Items for Systematic reviews and Meta-Analyses flow diagram. CENTRAL, Cochrane Central Register of Controlled Trials; OVT, ovarian vein thrombosis. Source: adapted from Page et al. [16].

124 citations were chosen for detailed evaluation. Among these, 108 studies were excluded after full-text evaluation (the rationale for exclusion is provided in the Preferred Reporting Items for Systematic reviews and Meta-Analyses flow diagram, Figure 1, while the list of the excluded articles is available upon request). No additional studies were identified by searching conference abstract books; however, 3 conference abstracts [26–28] were already retrieved by the search into EMBASE. One additional study [29] was identified from the reference lists of a previous systematic review on this topic [4]. Finally, 17 studies were included in this systematic review [1,3,6,26–39].

3.2 | Studies and population characteristics

Study characteristics are summarized in Table 1 [1,3,6,26–39]. All studies had an observational design; 3 (17.6%) studies were prospective cohorts [31,32,39], and 5 (35.7%) studies were multicenter cohorts [3,29,31,33,36]. Studies were performed in 6 different countries: Canada, France, Israel, Italy, Saudi Arabia, and the United States. Three studies were only available as conference abstracts [26–28].

The number of subjects with OVT in the included studies ranged from 10 patients [29] to 223 patients [6], for a total of 1000 patients with OVT. Detailed OVT characteristics in the included studies are reported in Supplementary Table S2. Seven studies included only women with OVT related to pregnancy/puerperium [27,29–32,34,36]; one study included only women with gynecologic cancer [28]. In the other studies with mixed aetiopathogenesis, the proportion of women with pregnancy/puerperium-related OVT ranged from 8% to 81%, cancer-associated OVT from 1% to 61%, and unprovoked OVT from 4% to 16%.

The right ovarian vein was more frequently involved (432/757 patients, 57.1%), followed by the left ovarian vein (249/757 patients, 32.9%) and bilateral OVT (76/757 patients, 10.0%). Extension into the renal vein was reported in 53/508 (10.4%) patients and into the inferior vena cava in 62/508 (12.2%) patients; concomitant PE was present in 33/769 (4.3%) patients.

Three studies specified in the inclusion criteria that they enrolled only patients receiving anticoagulant treatment [33,37,39]. Among the other studies without any restrictions in the inclusion criteria, 8 studies also included a group of patients who were not treated with anticoagulants [1,3,6,26–28,35,36], for a total of 376 untreated OVT patients (for 3 patients, it was not reported whether they were anticoagulated or not).

The number of anticoagulated OVT patients in the included studies ranged from 10 patients [29] to 118 patients [1], for a total of 621 anticoagulated OVT patients. The proportion of anticoagulated OVT patients in the included studies ranged from 12.6% [6] to 100% [29–34,37–39]. Most patients received either LMWH/UFH only (251/549, 45.7%) or proceeded to receive VKA (215/549, 39.2%). DOACs were used only in a

TABLE 1 Characteristics of the included studies.

Author, year	Study design	Country	Years	Inclusion criteria	Exclusion criteria	No. of patients with OVT	Age of OVT patients, y
Witlin and Sibai, 1995 [30]	Retrospective, single-center	United States	July 1984 to August 1994	All patients with postpartum OVT (diagnosed at US, CT, intraoperatively) after uncomplicated vaginal delivery	OVT after cesarean, cases of undocumented (but presumed) septic pelvic thrombophlebitis	11	Mean, 25.5 (range, 16-40)
Giraud et al. 1997 [29]	Retrospective, multicenter	France	NR	Patients with postpartum OVT (diagnosed at US, CT, intraoperatively)	Lack of documentation	10	Mean, 29.2 (range, 23-36)
Salomon et al. 1999 [31]	Retrospective, multicenter	Israel	1990-1998	Consecutive patients with postpartum OVT (diagnosed at US, CT, MRI)	No traceability	22	Mean, 30.5 (range, 19-39)
Salomon et al. 2010 [32]	Prospective, single-center	Israel	January 2004 to December 2007	Consecutive patients with postpartum OVT (diagnosed at CT)	NR	13	Mean, 30.6 (range, 24-42)
Labropoulos et al. 2015 [33]	Prospective, multicenter	United States	9-y period (years not specified)	Patients with symptomatic OVT (diagnosed at US, CT), treated with anticoagulation, at least 3 mo follow-up	Patients without symptoms, without clinical and imaging follow-up, lost or died before 3 mo	23	Mean, 44 (range, 23-68)
Lerouge et al. 2016 [34]	Retrospective, single-center	France	January 2011 to May 2015	All patients with postpartum OVT (diagnosed at CT)	NR	13	Mean, 30 (range, 23-38)
Rottenstreich et al. 2016 [3]	Retrospective, multicenter	Israel	January 2000 to May 2015	All patients with OVT (diagnosed at US, CT, MRI)	NR	74	Mean, 32 (range, 19-68)
Assal et al. 2017 [6]	Retrospective, single-center	United States	January 2004 to January 2014	Adult patients with OVT (diagnosed at US, CT, MRI)	NR	223	Mean, 55.6 (range, 20-89)
Lenz et al. 2017 [1]	Case-control, single-center	United States	January 1990 to October 2015	Consecutive patients with OVT (diagnosed at US, CT, MRI, intraoperatively) Control group: randomly selected age-, diagnosis date-, and gender-matched patients diagnosed with lower limb DVT	NR	219	Mean, 50.8 (range, NR)
Plastini et al. 2017 [35]	Retrospective, single-center	United States	January 2010 to May 2015	Adult patients with OVT (diagnosed at US, CT, MRI)	NR	50	Mean, 43.4 (range, 20-87)
Allain Wouterlood et al. 2021 [36]	Retrospective, multicenter	Canada	July 2003 to June 2018	Consecutive patients with OVT (diagnosed at US, CT, MRI, intraoperatively) during pregnancy or puerperium	NR	47	Mean, 32.1 (range, NR)
Covut et al. 2021 [37]	Retrospective, single-center	United States	November 2012 to January 2018	Patients with OVT (diagnosed at CT), receiving therapeutic anticoagulation, available follow-up CT scan	Patients who did not receive therapeutic anticoagulation or without follow-up CT	36	Median, 47 (range, 25-86)
Alsheef et al. 2022 [38]	Retrospective, single-center	Saudi Arabia	2005-2016	All patients with OVT (diagnosed at US, CT, MRI)	NR	18	Mean, 39.2 (range, NR)
De Pascali et al. 2022 [26][a]	Retrospective, single-center	Italy	2007-2021	Consecutive adult patients diagnosed with OVT	NR	38	Mean, 57.6 (range, NR)
Greenman et al. 2022 [27][a]	Retrospective, single-center	United States	2012-2020	Patients diagnosed with OVT in the peripartum period	NR	37	NR
Greenman et al. 2022 [28][a]	Retrospective, single-center	United States	2012-2020	Patients with gynecologic cancer diagnosed with OVT	NR	116	NR
Wysokinski et al. 2023 [39]	Prospective, single-center	United States	March 2013 to April 2021	Consecutive patients with acute VTE treated with anticoagulation	NR	50	Mean, 53.5 (range, 20-79)

CT, computed tomography; DVT, deep vein thrombosis; MRI, magnetic resonance imaging; NR, not reported; OVT, ovarian vein thrombosis; US, ultrasonography; VTE, venous thromboembolism.
[a]Currently published as a conference abstract only.

small number of patients in more recent studies (83/549, 15.1%) and were mainly factor Xa inhibitors (apixaban *n* = 46, rivaroxaban *n* = 24, edoxaban *n* = 1, dabigatran *n* = 1, and anti-Xa not further specified *n* = 11). Information regarding the anticoagulant drug was not available for the remaining 72 patients. The average duration of anticoagulant treatment (Table 2) was ≤3 months in 8 studies (47.1%) [1,3,29,30,33,35,36,38], >3 months to ≤6 months in 6 studies (35.3%) [27,28,32,34,37,39], and >6 months in 3 studies (17.6%) [6,26,31].

3.3 | RoB

When considering clinical outcomes, the overall RoB was moderate for 15 studies and serious for 2 studies (Figure 2A). Out of 8 studies assessing radiological outcomes, the overall RoB was moderate for 1 study and serious for 7 studies (Figure 2B). The RoB was higher for the radiological outcomes because imaging results during follow-up were available only for a minority of patients. The detailed rationale for the RoB judgment is reported in Supplementary Table S3.

3.4 | Synthesis of results

The original data regarding the study outcomes in the included studies are reported in Supplementary Table S4. For 11 of these studies [3,26–28,31–34,36,38,39], additional information was provided by the original study authors.

3.4.1 | Outcomes in anticoagulated OVT patients

3.4.1.1 | *Mortality.* All-cause mortality was reported in 13 studies [3,26–34,36,38,39], in which 12 out of 406 anticoagulated OVT patients died. The cause of death was not VTE-related in 11 patients and unknown in 1 patient. The weighted mean mortality rate was 2.43% (95% CI, 0.54%-5.41%), and heterogeneity was substantial (I^2 = 53.8%, *P* = .011; Figure 3).

3.4.1.2 | *Major bleeding.* Major bleeding events during anticoagulant treatment were reported in 15 studies [1,3,26–28,30–39], with some variability in the definitions (Supplementary Table S5). Overall, 7 out of 583 anticoagulated OVT patients had major bleeding (4 events occurred during LMWH treatment, 2 during VKA treatment, and 1 during DOAC treatment). Major bleeding events included gastrointestinal bleeding (*n* = 3) and alveolar hemorrhage (*n* = 1); the location of major bleeding could not be retrieved for the other 3 events. The weighted mean rate of major bleeding on treatment was 1.27% (95% CI, 0.48%-2.38%), and heterogeneity was not relevant (I^2 = 2.5%; *P* = .42; Figure 4).

3.4.1.3 | *Recurrent VTE.* Recurrent VTE events during anticoagulant treatment were reported in 15 studies [3,6,26–28,30–39], with some variability in the definitions (Supplementary Table S5). Overall, 22 out of 482 anticoagulated OVT patients had recurrent VTE. Recurrent VTE included DVT (*n* = 18) and recurrent OVT (*n* = 3); 20 events occurred during UFH/LMWH treatment and 1 event during DOAC treatment; no information could be retrieved for 1 recurrent VTE. The weighted mean rate of recurrent VTE on treatment was 3.49% (95% CI, 1.12%-6.95%), and heterogeneity was considerable (I^2 = 63.5%; *P* < .001; Figure 5).

3.4.1.4 | *Vessel recanalization.* Ovarian vein recanalization was reported in 8 studies [3,26,29,31–33,35,37], in which 163 out of 184 anticoagulated OVT patients showed partial or complete recanalization (11 partial and 152 complete). Imaging modalities for follow-up assessment included US [33], CT scan [37], or both [3], but no information was reported in the remaining 5 studies. The weighted mean rate of recanalization was 89.4% (95% CI, 74.6%-98.6%), and heterogeneity was considerable (I^2 = 80.6%; *P* < .001; Figure 6).

3.4.1.5 | *Sensitivity and subgroup analyses.* When we considered only the 14 studies published as full texts in peer-reviewed journals [1,3,6,29–39], the weighted mean rate for all-cause mortality was 2.67% (95% CI, 0.28%-6.84%; 10 studies; 10/274 patients), for major bleeding 1.12% (95% CI, 0.32%-2.34%; 12 studies; 4/451 patients), for recurrent VTE 1.78% (95% CI, 0.62%-3.46%; 12 studies; 5/350 patients), and for vessel recanalization 89.6% (95% CI, 71.5%-99.7%; 7 studies; 142/161 patients).

In a subgroup analysis by OVT risk factors, the 9 studies enrolling mainly pregnancy/puerperium-related OVT [3,27,29–32,34,36,38] were compared with the 4 studies enrolling mainly cancer-associated OVT [6,26,28,39]. The average duration of anticoagulant treatment was shorter in the former (≤3 months in 5 studies, 55.6%; >3 months to ≤6 months in 3 studies, 33.3%; >6 months in 1 study, 11.1%) than the latter group (>3 months to ≤6 months in 2 studies, 50%; >6 months in 2 studies, 50%). Studies enrolling mainly pregnancy/puerperium-related OVT had nonsignificantly lower rates of adverse clinical outcomes and significantly higher rates of ovarian vein recanalization compared with studies enrolling mainly cancer-associated OVT. In detail, the weighted mean rates for all-cause mortality were 0.85% (95% CI, 0.0%-2.23%; 9 studies; 0/230 patients) vs 5.13% (95% CI, 0.0%-15.69%; 3 studies; 8/153 patients), respectively (heterogeneity between subgroups *P* = .20). The weighted mean rates for major bleeding were 0.80% (95% CI, 0.0%-2.17%; 8 studies; 0/220 patients) vs 2.01% (95% CI, 0.0%-7.51%; 3 studies; 3/153 patients), respectively (*P* = .54). The weighted mean rates for recurrent VTE were 3.81% (95% CI, 0.42%-9.63%; 8 studies; 9/220 patients) vs 4.67% (95% CI, 0.0%-14.46%; 4 studies; 13/170 patients), respectively (*P* = .75). The weighted mean rates for vessel recanalization were 99.3% (95% CI, 97.0%-100%; 4 studies; 87/87 patients) vs 91.3% (95% CI, 73.2%-97.6%; 1 study; 21/23 patients), respectively (*P* = .037).

Results of the other sensitivity and subgroup analyses performed in anticoagulated OVT patients are reported in Supplementary Table S6.

TABLE 2 Details of the anticoagulant treatment used in the included studies.

Author, y	No. of nonanticoagulated OVT patients	No. of anticoagulated OVT patients	Anticoagulant treatment drugs	Anticoagulant treatment duration	Follow-up duration	Other treatments
Witlin and Sibai, 1995 [30]	0	11	• UFH (*n* = 7) • UFH → VKA (*n* = 4)	• UFH: 12 d (mean), 7-26 d (range) • VKA: 3 mo	NR	• Antibiotics (*n* = 11)
Giraud et al. 1997 [29]	0	10	• UFH (*n* = 8) • LMWH (*n* = 2)	10 d to 2 mo (range)	NR	• Antibiotics (*n* = 10) • Surgery (*n* = 1)
Salomon et al. 1999 [31]	0	22	• Heparin → VKA (*n* = 22)	8.9 mo (mean), 1-60 mo (range)	NR	NR
Salomon et al. 2010 [32]	0	13	• LMWH (*n* = 12) • LMWH → VKA (*n* = 1)	3.5 mo	6 mo after delivery	NR
Labropoulos et al. 2015 [33]	Not included	23	• LMWH (*n* = 6) • LMWH → VKA (*n* = 17)	3 mo	27 mo (median)	NR
Lerouge et al. 2016 [34]	0	13	• UFH (*n* = 1) • LMWH (*n* = 4) • LMWH → VKA (*n* = 8)	6 mo (mean)	NR	• Antibiotics (*n* = 11)
Rottenstreich et al. 2016 [3]	1	73	• LMWH (*n* = 53) • LMWH → VKA (*n* = 19) • DOAC (*n* = 1)	3 mo (median), 3-6 mo (IQR)	40 mo (mean)	• Antibiotics (*n* = 39)
Assal et al. 2017 [6]	195 (all patients with OVT), 182 (if considering only patients with isolated OVT)	28 (all patients with OVT), 17 (if considering only patients with isolated OVT)	Patients with isolated OVT only: • LMWH/UFH (*n* = 6) • LMWH/UFH → VKA (*n* = 11)	NR	28.2 mo (median) 38.0 mo (mean)	NR
Lenz et al. 2017 [1]	101	118	• LMWH (*n* = 24) • VKA (*n* = 83) • DOAC (*n* = 11)	3.0 mo (median), 3-6 mo (IQR)	14.8 mo (median)	• IVC filter (*n* = 1)
Plastini et al. 2017 [35][a]	15	33	• VKA or LMWH (*n* = 33)	3.0 mo (mean)	23.7 mo (mean)	• IVC filter (*n* = 2) • Antiplatelet (*n* = 1) • Antibiotics (*n* = 3)
Allain Wouterlood et al. 2021 [36][a]	5	41	• UFH/LMWH (*n* = 14) • LMWH/UFH → VKA (*n* = 26) • DOAC (*n* = 1)	2.8 mo (median), 1.4-2.8 mo (IQR)	NR	• Antibiotics (*n* = 38)

(Continues)

TABLE 2 (Continued)

Author, y	No. of nonanticoagulated OVT patients	No. of anticoagulated OVT patients	Anticoagulant treatment drugs	Anticoagulant treatment duration	Follow-up duration	Other treatments
Covut et al. 2021 [37]	Not included	36	• LMWH (*n* = 15) • LMWH/UFH → VKA (*n* = 11) • LMWH/UFH → DOAC (*n* = 10)	• LMWH: 6 mo (median), 1-12 mo (range) • VKA: 4 mo (median), 2-31 mo (range) • DOAC: 4 mo (median), 3-42 mo (range)	14 mo (median)	• Antiplatelet (*n* = 3)
Alsheef et al. 2022 [38]	0	18	• LMWH (*n* = 18)	• 1-3 mo (*n* = 13) • 3-6 mo (*n* = 1) • 6-12 mo (*n* = 2) • Lifelong (*n* = 2)	NR	NR
De Pascali et al. 2022 [26][b]	5	33	• LMWH (*n* = 23) • LMWH → VKA (*n* = 3) • LMWH → DOAC (*n* = 7)	• <6 mo (*n* =12) • >6 mo (*n* = 21)	32.7 mo (mean)	NR
Greenman et al. 2022 [27][b]	8	29	• LMWH/UFH (*n* = 23) • UFH → VKA (*n* = 2) • DOAC (*n* = 4)	6 mo (mean)	NR	NR
Greenman et al. 2022 [28][b]	46	70	• UFH (*n* = 21) • LMWH (*n* = 8) • LMWH/UFH → VKA (*n* = 5) • DOAC (*n* = 8) • Not available (*n* = 28)	6 mo (mean)	NR	NR
Wysokinski et al. 2023 [39]	Not included	50	• LMWH (*n* = 6) • LMWH/UFH → VKA (*n* = 3) • DOAC (*n* = 41)	5.1 mo (mean), 4.1 mo (median), 3.0-6.1 mo (IQR)	24 mo	NR

DOAC, direct oral anticoagulants; INR, international normalized ratio; IVC, inferior vena cava; LMWH, low-molecular-weight heparin; NR, not reported; OVT, ovarian vein thrombosis; UFH, unfractionated heparin; VKA, vitamin K antagonists.

[a]For 2 patients in the study by Plastini et al. [35] and 1 patient in the study by Allain Wouterlood et al. [36], it was not reported whether they were anticoagulated or not.

[b]Currently published as conference abstract only.

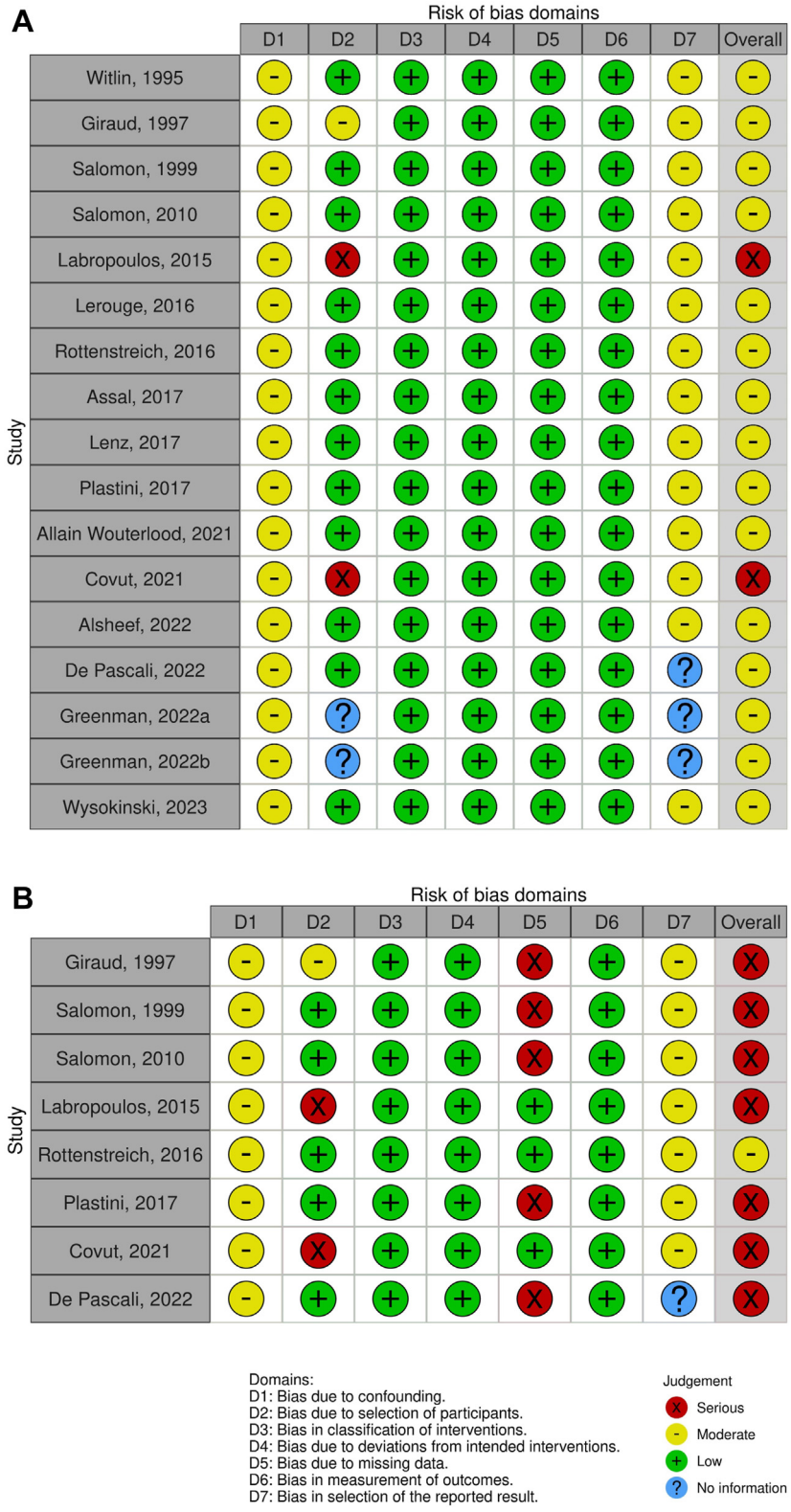


FIGURE 2 Risk of bias of the included studies when considering clinical outcomes (A) and radiological outcomes (B).

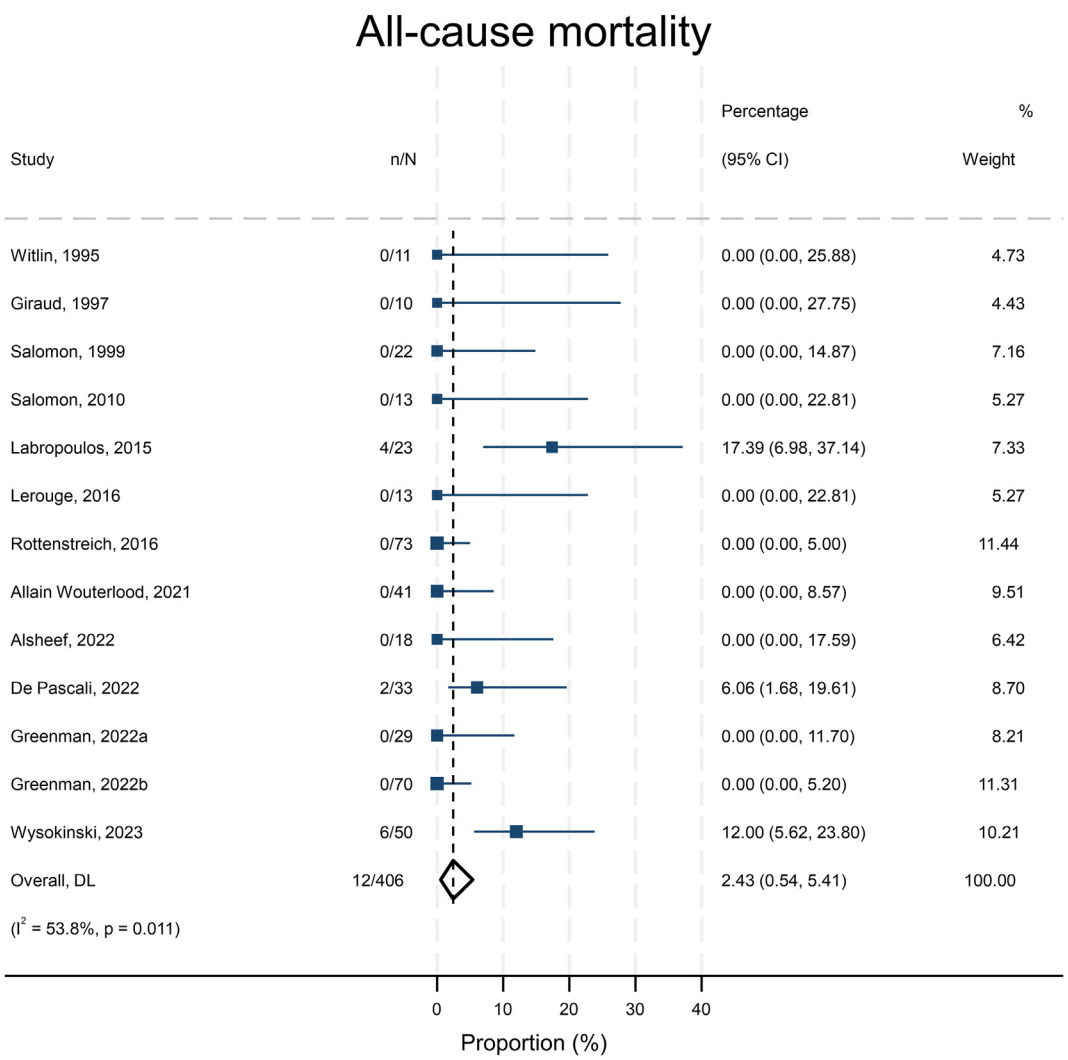


FIGURE 3 Rate of all-cause mortality in anticoagulated ovarian vein thrombosis patients.

3.4.2 | Outcomes in nonanticoagulated OVT patients

3.4.2.1 | *Mortality.* Five studies reported all-cause mortality in untreated OVT patients [3,26–28,36]. In these studies, the weighted mean mortality rates were 0.96% (95% CI, 0.0%-2.60%; 2/246 patients) in treated patients vs 1.17% (95% CI, 0.0%-4.51%; 0/65 patients) in untreated patients (Supplementary Figure S1A). There was no statistically significant difference between the 2 groups (RR, 0.88; 95% CI, 0.05-16.19; Supplementary Figure S2A).

3.4.2.2 | *Major bleeding.* Seven studies reported major bleeding in untreated OVT patients [1,3,26–28,35,36]. In these studies, the weighted mean rates of major bleeding were 0.94% (95% CI, 0.08%-2.49%; 4/397 patients) in treated patients vs 1.09% (95% CI, 0.02%-3.27%; 1/181 patients) in untreated patients (Supplementary Figure S1B). There was no statistically significant difference between the 2 groups (RR, 1.02; 95% CI, 0.14-7.39; Supplementary Figure S2B).

3.4.2.3 | *Recurrent* VTE. Seven studies reported recurrent VTE in untreated OVT patients [3,6,26–28,35,36]. In these studies, the weighted mean rates of recurrent VTE were 4.24% (95% CI, 0.18%-11.80%; 19/296 patients) in treated patients vs 8.65% (95% CI, 2.61%-17.35%; 29/262 patients) in untreated patients (Supplementary Figure S1C). There was no statistically significant difference between the 2 groups (RR, 0.70; 95% CI, 0.36-1.37; Supplementary Figure S2C).

3.4.2.4 | *Vessel recanalization.* Three studies reported ovarian vein recanalization in untreated OVT patients [3,26,35]. In these studies, the weighted mean rates of recanalization were 90.0% (95% CI, 65.1%-100%; 104/111 patients) in treated patients vs 24.7% (95%

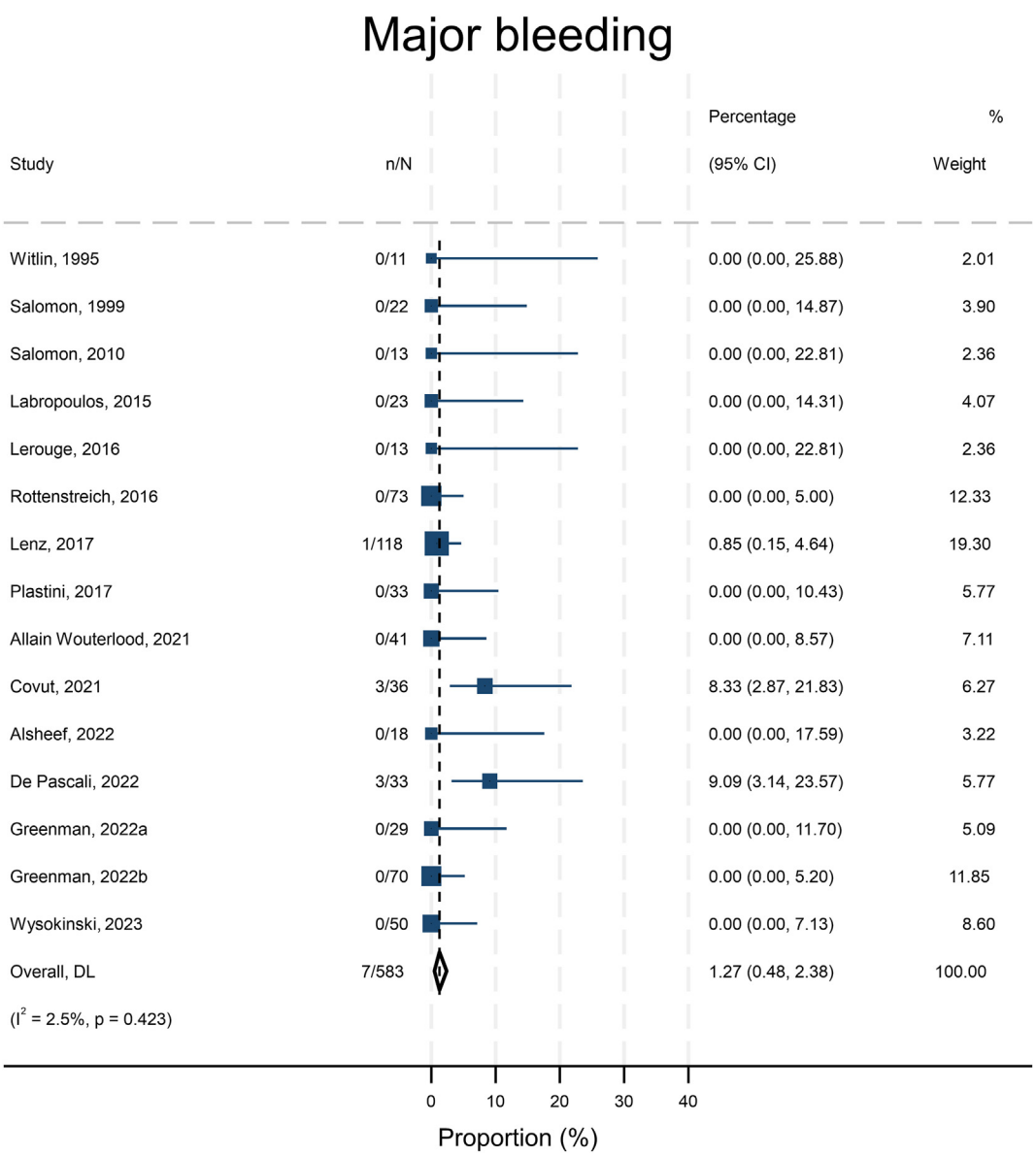


FIGURE 4 Rate of major bleeding in anticoagulated ovarian vein thrombosis patients.

CI, 1.1%-59.7%; 3/9 patients) in untreated patients (Supplementary Figure S1D). There was no statistically significant difference between the 2 groups (RR, 1.59; 95% CI, 0.59-4.25; Supplementary Figure S2D).

3.5 | Publication bias

There was no evidence of publication bias for any of the analyzed outcomes in anticoagulated OVT patients (Egger's test for overall mortality P = .54; major bleeding P = .35; recurrent VTE P = .98; and vessel recanalization P = .41; Supplementary Figure S3).

4 | DISCUSSION

In this systematic review and meta-analysis, we assessed the safety and efficacy of anticoagulant treatment for patients with OVT. From a systematic search within the published and gray literature, we retrieved 17 observational studies enrolling 621 anticoagulated OVT patients. We found that the weighted mean rates of major bleeding and recurrent VTE during anticoagulant treatment were 1.27% and 3.49%, respectively; however, they were 1.12% and 1.78%, respectively, when considering only the 14 studies published as full texts. Overall, partial or complete ovarian vein recanalization was reported in 89.4% of treated patients, with a nonsignificant better trend compared with untreated patients.

In studies enrolling mainly pregnancy/puerperium-related OVT, adverse clinical outcomes (all-cause mortality, major bleeding, and recurrent VTE) were nonsignificantly less common, while vessel recanalization occurred more frequently compared with studies enrolling mainly cancer-associated OVT. Our results suggest that pregnancy/puerperium-related OVT carries a better prognosis: no mortality events, no major bleeding during anticoagulant treatment, and all

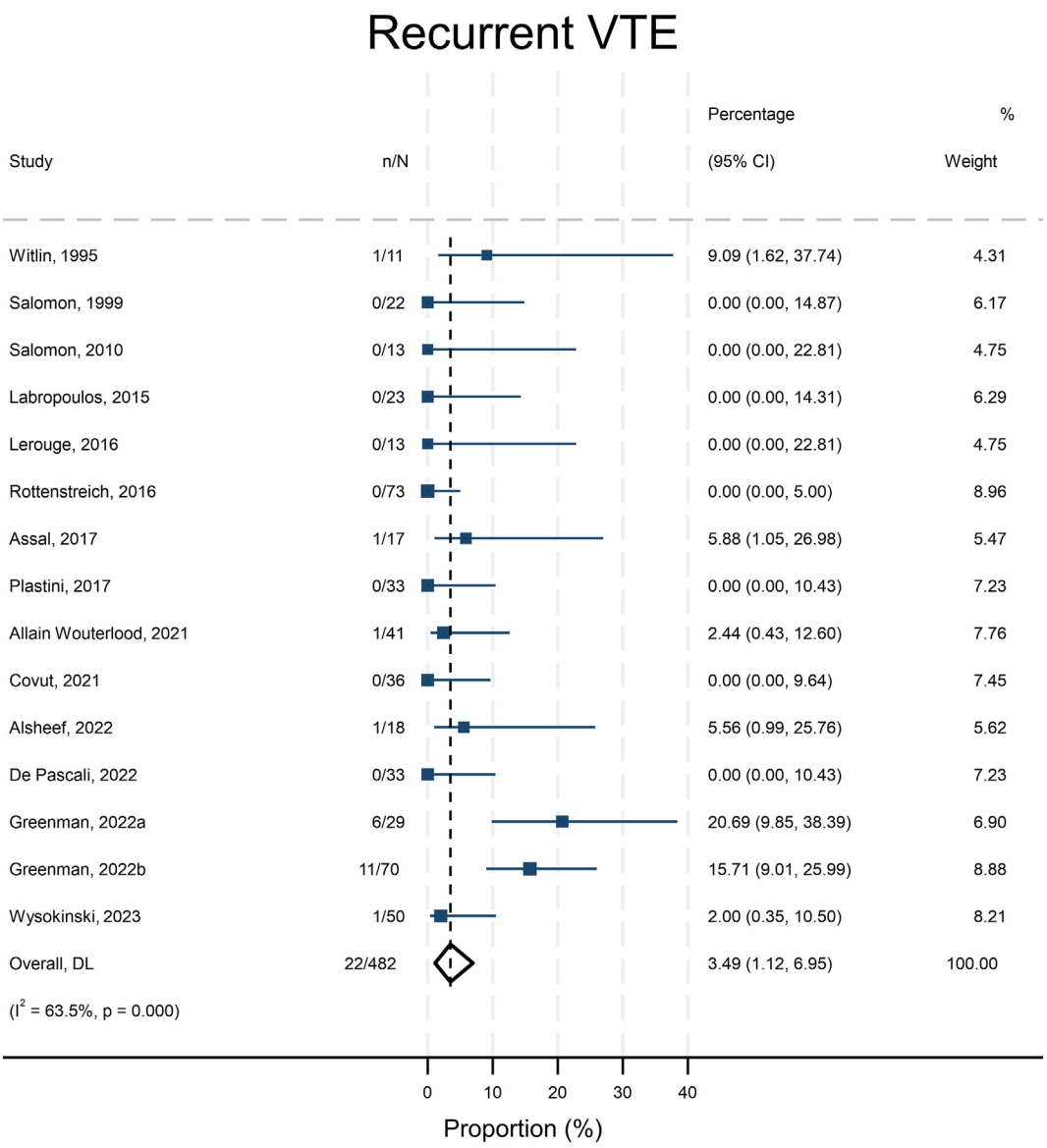


FIGURE 5 Rate of recurrent venous thromboembolism in anticoagulated ovarian vein thrombosis patients.

patients achieving a certain degree of ovarian vein recanalization (which was complete in 96.6% and partial in 3.4%); however, 3.8% of these women developed recurrent VTE on treatment (either DVT or recurrent OVT), but we were unable to state whether symptomatic or incidentally detected.

Since OVT is an uncommon location of VTE, the optimal anticoagulant treatment is still debated. The guidelines of the British Committee for Standards in Haematology, published in 2012, recommended conventional anticoagulation for 3 to 6 months for postpartum OVT, while no treatment was suggested for isolated OVT when incidentally detected in oncological patients after abdominal surgery [9]. The guidelines of the Canadian Society of Obstetricians and Gynaecologists, published in 2014, recommended therapeutic dose anticoagulation for 1 to 3 months for pregnancy-related OVT [10]. Some experts suggested anticoagulating symptomatic postpartum OVT for 3 months and avoiding anticoagulation in asymptomatic postpartum OVT unless there is thrombus extension or evidence of PE [4]. Other experts suggested considering anticoagulation in all OVT patients, using parenteral and/or oral anticoagulants, similar to the management of VTE in commoner anatomical sites [1,40].

The relatively low incidence rate of major bleeding complications during treatment (1.27%) reported in our meta-analysis suggests that the anticoagulant treatment for OVT patients is safe and seems to be comparable with the anticoagulant treatment for DVT and PE, while the rate of recurrent VTE during treatment (3.49%) showed considerable heterogeneity among the different studies. A meta-analysis reported that anticoagulant treatment with UFH, LMWH, or VKA in patients with DVT or PE is associated with an expected rate of recurrent VTE ranging from 1.28% to 1.84% and an expected rate of major bleeding ranging from 0.63% to 1.05% at 3 months follow-up [41]. This finding was also confirmed in the case-control study by Lenz et al. [1], which compared 219 patients with OVT vs 220 patients

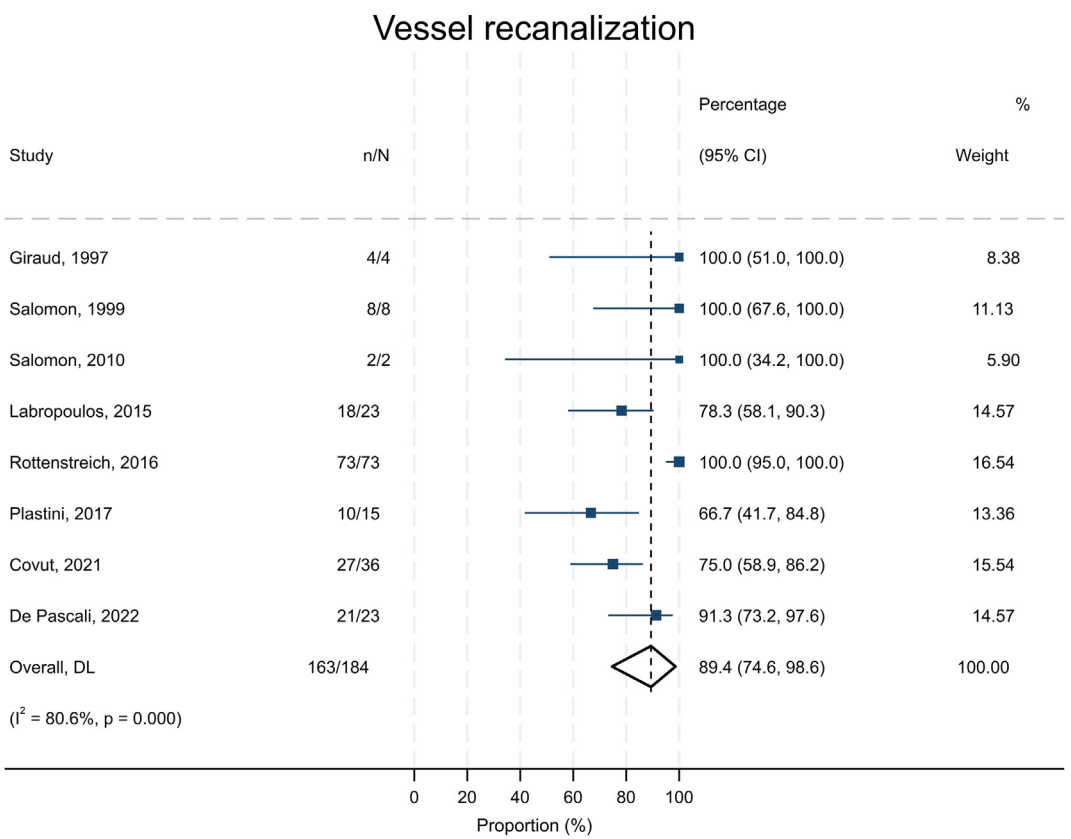


FIGURE 6 Rate of vessel recanalization in anticoagulated ovarian vein thrombosis patients.

with DVT, matched by female patients, age, and date of diagnosis. In this study, despite only 54% of OVT being anticoagulated (compared with 98% of DVT), the incidence of clinical outcomes was similar between the 2 groups: major bleeding rates were 2.1 per 100 patient-years in OVT patients vs 2.3 per 100 patient-years in DVT patients (P = .95), while VTE recurrence rates were 2.3 per 100 patient-years vs 1.8 per 100 patient-years (P = .49), respectively [1].

Due to the scarcity of data regarding nonanticoagulated patients (available only in 8 out of 17 studies), the comparisons between treated and untreated patients did not reach statistical significance. Nevertheless, this meta-analysis showed a trend toward a reduction of recurrent VTE in anticoagulated (∼4.2%) vs nonanticoagulated (∼8.7%) OVT patients (RR, 0.70; 95% CI, 0.36-1.37). Similarly, there was a trend toward better recanalization rates in anticoagulated (∼90%) vs nonanticoagulated (∼25%) OVT patients (RR, 1.59; 95% CI, 0.59-4.25). Previously, Assal et al. [6] showed a nonsignificant reduction of recurrent VTE with the anticoagulant treatment. In that study, 199 patients with isolated OVT were enrolled, and it was found that VTE recurrence rates were 5.9% in 17 anticoagulated women vs 9.9% in 182 nonanticoagulated women (P = .59) [6].

To the best of our knowledge, this is the first meta-analysis on the safety and efficacy of anticoagulant treatment in OVT. The main strengths of this study include the rigorous methodological approach, with preregistration of the protocol, independent abstracts/full texts screening, data extraction, and quality assessment. In addition, by contacting the original study authors, we managed to significantly reduce the amount of missing information on study outcomes, as we retrieved additional data for 11 out of 17 included studies.

However, this study has also some limitations. First, since all the included studies were observational studies, the selection of which patients were anticoagulated was not randomized, thus creating a high risk of confounding bias and selection bias. For instance, more comorbid OVT patients or those who developed clinical complications early after the OVT diagnosis might not have been considered eligible for anticoagulation, while patients with more extensive thrombosis or concomitant PE might have been more likely to be anticoagulated. Second, being a study-level meta-analysis, subgroup analysis had certain limitations. Since the included studies did not provide separate data according to different risk factors, different anticoagulant drugs, or different anticoagulant treatment duration, we could not provide precise estimates in these patient subgroups. Instead, we grouped studies in which the majority of the populations had a certain risk factor, received a certain anticoagulant drug, or had a certain average treatment duration. Of note, most of the studies had a relatively short follow-up duration; thus, the reported weighted mean rates might not be applicable to the long-term management of OVT, as more outcome events might occur with a longer follow-up duration. Third, our estimates on ovarian vein recanalization should be interpreted with caution since only 8 studies reported these data, and the RoB was serious in most of them. Furthermore, various imaging modalities, with different sensitivity and specificity for OVT detection [5], were used during follow-up.

In conclusion, the use of anticoagulant therapy in OVT seems to be associated with relatively low rates of recurrent VTE and major bleeding during treatment. However, more well-conducted studies (ideally RCTs or prospective cohort studies) are needed to confirm these findings and better delineate the optimal management strategy for OVT patients.

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AUTHOR CONTRIBUTIONS

N.R., A.G., and J.C.-A. were responsible for the conception and design of the study. N.R., L.M.-B., C.V., W.A., A.R., N.S., W.W., G.L.G., O.S., N.L., A.F., and M.A. acquired the data. N.R., L.M.-B., and C.V. drafted the manuscript. N.R. performed the statistical analysis. All authors interpreted the data, made critical revisions to the manuscript for important intellectual content, and provided final approval of the manuscript.

RELATIONSHIP DISCLOSURE

The authors have no conflicts of interest to declare in relation to this study.

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SUPPLEMENTARY MATERIAL

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