Assessing the efficacy of anticoagulation therapy in the treatment of vascular Behçet's disease: a systematic review

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ABSTRACT

Objective. *Behçet's disease (BD) often presents with vascular complications, termed vascular Behçet's disease (VBD). While immunosuppression (IS) is the cornerstone of treatment, the role of anticoagulation (AC) is debated. This systematic review aims to consolidate and summarise the current evidence on the efficacy and safety of AC in VBD, especially considering emerging studies post-2018 European Alliance of Associations for Rheumatology (EULAR) recommendations.*

Methods. *We conducted a systematic search across PubMed, Embase, Web of Science, and Scopus up to January 2024, adhering to PRISMA guidelines. We included studies that investigated the impact of AC on VBD outcomes, using the Joanna Briggs Institute tools for data extraction and risk of bias assessment.*

Results. *Our search yielded 2,202 articles, with 34 studies meeting inclusion criteria. Results indicate variable AC coverage, from 10.8% to 98.6% across studies, with different anticoagulants employed. Some studies highlighted significant benefits of AC in reducing thrombotic events and improving surgical outcomes, whereas others showed neutral or limited effects. Safety profiles were generally favourable, with low incidences of significant bleeding.*

Conclusion. *AC therapy can be beneficial in certain contexts of VBD, particularly in reducing thrombosis recurrence and managing postoperative complications. However, the benefits of AC are not uniformly demonstrated across all patient settings, suggesting a tailored approach to AC use in VBD might be warranted. The findings underscore the necessity for randomised controlled trials to clarify the optimal therapeutic strategies for AC in conjunction with IS in BD.*

Introduction

Behçet's disease (BD) is a multisystem disease characterised by recurrent oral and genital ulcerations along with other systemic manifestations including, but not limited to, ophthalmic, dermatologic, neurologic and gastrointestinal involvements (1-7). One of the most important manifestations of BD is the vascular involvement (VBD), reported in up to 40% of patients according to some studies (7-10). BD can involve the entire vascular tree including arteries, veins and capillaries, hence the term 'variable vessel vasculitis' as described in the Chapel Hill classification (11). VBD is associated with significant morbidity and even mortality (12-14). VBD can be divided into venous and arterial subtypes, with the venous involvement being much more common (4). The venous involvement typically manifests in the form of thrombosis, most commonly as superficial and deep vein thrombosis in the lower limbs, although other sites may be involved with varying frequencies such as the superior and inferior vena cava, hepatic and portal veins and cerebral venous sinuses (15). The arterial involvement can manifest as thrombosis or aneurysms, with the pulmonary arteries being the most common site of arterial involvement (9). The thrombus in BD is strongly believed to be inflammatory in its nature, rather than due to the traditional hypercoagulable state seen in other conditions such as antiphospholipid syndrome (15). Indeed, it has been repeatedly reported that thrombotic event begins as an inflammation of the endothelium (endothelitis) that further propagates the thrombus formation, with a very low risk of embolism (16-19). Hence, it is widely accepted that immunosuppression is the main treatment in the case of thrombosis related to BD, rather than anticoagulation

(AC). According to the 2018 European Alliance of Associations for Rheumatology (EULAR) recommendations for the treatment of VBD, immunosuppressive treatments should be used in the case of acute deep vein thrombosis, and the addition of AC has no additional benefit (20). In the case of refractory venous thrombosis, it was stated that "Anticoagulants may be added, provided the risk of bleeding in general is low and coexistent pulmonary artery aneurysms are ruled out" (20).

Unlike the role of immunosuppressive treatment of VBD, which is a consensus, the role of AC in the treatment of VBD is still a major debate. Since the EULAR recommendations in 2018, several important papers have been published in this regard. To date, no randomised controlled trials (RCTs) have been published in this topic. Indeed, because of the various vascular manifestations, venous and arterial, it seems that a single RCT would not be able to solve the whole issue of VBD, but rather a very specific niche such DVT.

Therefore, we aimed to systematically review the up-to-date literature on the possible role of AC in the treatment of VBD, especially due to the emergence of some important studies, with emphasis on efficacy and safety of adding AC.

Methods

This systematic review was registered with the International Prospective Register of Systematic Reviews - PROSPERO (Registration code CRD42024509497). We adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (21, 22).

A systematic search was conducted across four databases: PubMed, Embase, Web of Science, and Scopus, up until January2024. To supplement our database searches, we also performed reference screening to identify additional relevant papers.

We tailored Boolean search strings for each database to ensure the retrieval of the relevant articles on Behçet's Disease and anticoagulation therapy. Key terms central to our search included 'Behcet', 'Anticoagulants', 'Warfarin', 'Heparin', 'Rivaroxaban', 'Apixaban', 'Dabigatran', 'Enoxaparin', and 'Fondaparinux'. These terms were integrated within the Boolean strings, with variations adjusted to align with the specific indexing and search capabilities of each database. The full Boolean strings, reflecting these tailored approaches for each database, are comprehensively detailed in the supplementary material of our review.

Study selection

Our systematic review targeted original research articles that scrutinised the effectiveness of anticoagulation therapy in BD. Considering the limited literature available on this topic, we expanded our inclusion criteria to encompass case series, recognising their prominence and significance in this field.

We excluded review papers, case reports, conference abstracts, editorials, preprints, and studies not written in English. Furthermore, any research not directly examining the application of anticoagulants in BD was also omitted.

Data extraction

The data extraction for our review was conducted by two of our researchers, chosen from MO, FH, and MEN, utilising a standardised form. The extracted data included the first author's name, year of publication, study design, sample size, and the types of anticoagulants used. Additionally, we focused on the type of vascular involvement, the percentage of patients treated with anticoagulation therapy, and vascular outcomes. When available, we also compared the outcomes between groups treated with anticoagulants and those without such treatment. Further, data on any immunosuppressive treatments used alongside anticoagulants, clinical outcomes assessed, and the key findings of each study were extracted. Discrepancies between reviewers were resolved through discussion, and a third reviewer was consulted when necessary.

Risk of bias

To evaluate the robustness and reliability of the studies included in our review, we employed the Joanna Briggs Institute (JBI) Critical Appraisal tools. These tools are specifically designed for the quality assessment of observational cohort, case series, and cross-sectional studies. Each study was independently evaluated for risk of bias by two of our researchers, chosen from MO, FH, and MEN. In cases of discrepancies in their assessments, a consensus was reached through discussion and mutual agreement. The JBI tools allowed us to assess various aspects of each study, including methodological precision, potential for bias, and the overall validity of the findings (23).

Results

Search results and study selection

We searched four databases, PubMed, Embase, Scopus, and Web of Science, yielding a total of 2,202 articles, which were narrowed down through several steps. Automated filters removed 283 non-relevant articles such as reviews and editorials, and 629 duplicates were excluded. Titles and abstracts were independently screened by MO and MEN, removing a further 1,074 entries. Discrepancies were resolved through consultation with FH. Of the 216 articles assessed for eligibility, 34 met our inclusion criteria and were selected for detailed analysis (Fig. 1).

Summary of the included studies

Our systematic review analysed 34 studies published between 2003 and 2023, encompassing a total of 2,516 patients with VBD. The studies included 12 cohort studies, 17 case series, 3 case-control studies, and 2 cross-sectional studies (8-10, 14, 24-53). The coverage of anticoagulation therapy was predominantly high across studies, as seen in Desbois *et al*. (49) where 98.6% of the cohort received such therapy, and in Roriz *et al*. case series, all patients were on vitamin K antagonists (30). Various anticoagulation therapies were reported, including warfarin (8-10, 25-30, 32-36, 38, 42-46) and novel oral anticoagulants (41) (Table I).

The primary outcome measures reported across studies included relapse rates, remission rates, recanalisation, mortality, and post-thrombotic syndrome. Relapse rates were reported in 28 studies and ranged from 5.9% to 75%. Remission rates, reported in 18 studies, varied from

65.7% to 97.1%. Six studies reported on recanalisation, with rates ranging from 30% to 83%. Mortality rates, documented in 22 studies, spanned from 0% to 15%. Post-thrombotic syndrome was reported in 7 studies, with incidence rates between 25% and 51% (Table I).

Of the 2,516 patients, 1,876 (74.6%) received anticoagulation therapy, 2,138 (85.0%) received immunosuppressants, and 1,684 (66.9%) received both. Anticoagulation was used as initial therapy in 1,562 (62.1%) patients. The most common anticoagulant was warfarin (1,324 patients, 52.6%), followed by low molecular weight heparin (412 patients, 16.4%). The duration of anticoagulation therapy ranged from 3 months to indefinitely, with a median duration of 12 months across studies reporting this information.

Types of vascular involvement

Studies were grouped according to type of vascular involvement, as follows: arterial only, venous only, cardiac only, pulmonary only, cerebral sinus vein thrombosis only, and mixed vascular involvement according to the population included in each study (Table I). Only one study reported pure arterial involvement demonstrating that AC were associated with lower incidence of postoperative thrombosis (10). Ten studies addressed venous involvement only. Four studies showed favourable effect, 4 studies demonstrated that AC had no added value to IS and two studies did not report the effect of AC. Four studies examined the effect of AC among patients with cardiac involvement only and showed positive effect across all four studies. Five studies examined patients with CSVT only. Two of the five studies reported favourable outcome of AC, two other studies reported favourable outcome when AC were combined with IS and one study didn't report the effect of AC. Eleven studies in this SLR reported outcomes of mixed vascular involvement rather than a separate involvement, with mixed effects; some showed beneficial effects while others did not.

Quality and risk of bias

In our systematic review on anticoagulation therapy in vascular involvements of BD, we included a diverse range of studies: 12 cohort, 17 case series, 3 case-control, and 2 cross-sectional studies. Our rigorous assessment using the Joanna Briggs Institute Critical Appraisal Tools revealed varying levels of methodological quality.

In cohort studies (Supplementary Table S1), we observed a mix of methodological strengths and weaknesses. Several studies exhibited robust methodology, particularly in terms of group similarity and reliable outcome measurement. However, some faced challenges in clearly identifying and addressing confounding factors. The case series studies (Suppl. Table S2) mostly demonstrated high methodological quality, with clear criteria for inclusion and consistent measurement methods. Despite these strengths, certain studies showed a lack of clarity in the consecutive and complete inclusion of participants.

For the case-control studies (Suppl. Table S3), there was notable methodological consistency. Most of these studies ensured comparability of groups and appropriate matching of cases and controls, yet some ambiguity was noted in the identification and handling of confounding factors. The cross-sectional studies (Suppl. Table S4) particularly excelled in defining clear inclusion cri-

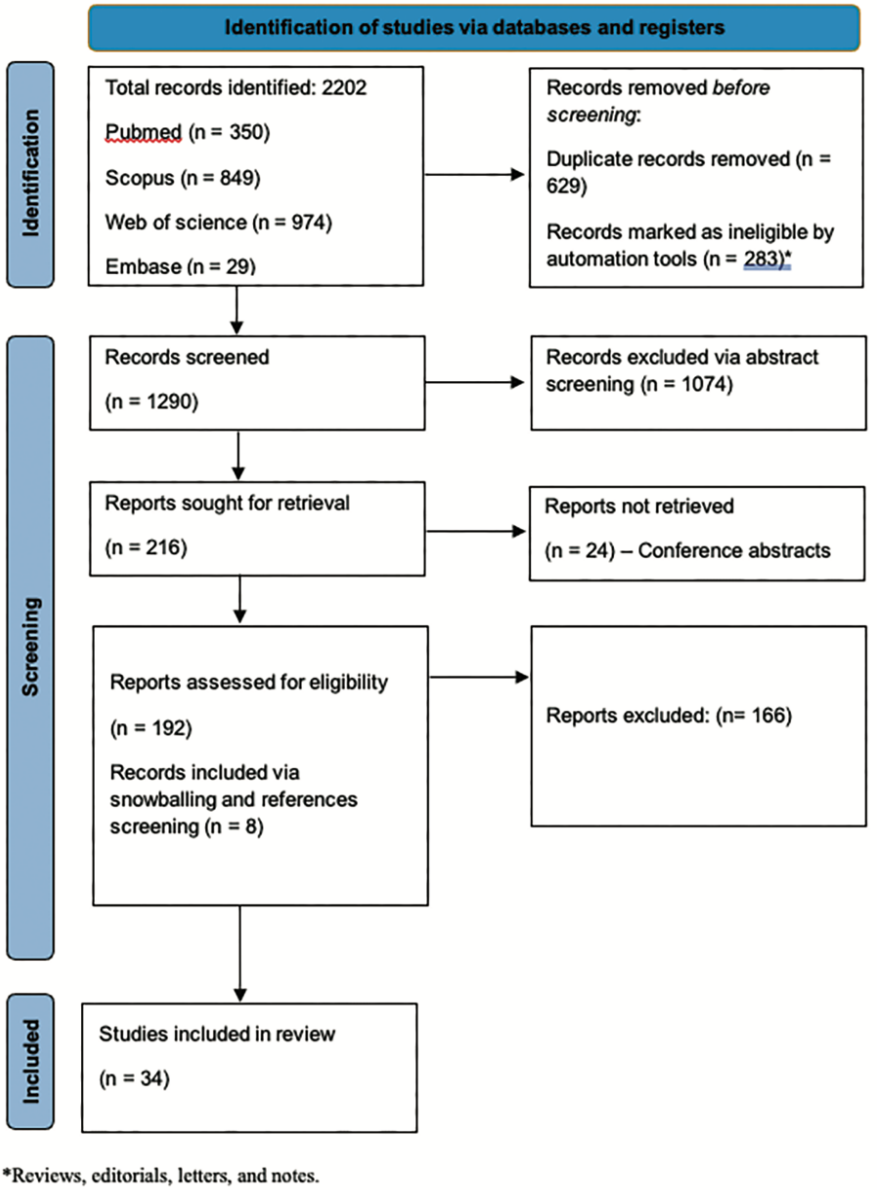

Fig. 1. PRISMA flowchart.

Table I. Summary of the included studies.

Author (ref.)	Year	Sample size	Population	Vascular involvements	Anticoagulation (type and %)
Wu (8)	2014	93	Adults	Extremity vein thrombosis, vena cava thrombosis (venous)	Warfarin (88.2%)
Alibaz-Oner 2015(9)	2015	936 (260 with VBS)	Adults	Thrombosis, Thrombophlebitis (venous)	Warfarin (59.8%)
Saadoun *et al*. (10)	2012	101	Adults	Aneurysms, occlusions, stenosis, aortitis (arterial)	Warfarin (46.5%)
Emmungil (25)	2014	22	Adults	Intracardiac thrombus, DVT (cardiac and venous)	Warfarin (36.3%)
Emmi *et al*. (26)	2018	70	Adults	Venous thrombosis (venous)	Warfarin (31.4%)
Shengguang Li (27)	2014	161 (27 with lesions)	Adults	Venous involvement, arterial lesions (venous and arterial)	Warfarin (96.3%)
Ozen (28)	2010	7	Paediatric	Various vascular involvements	LMWH, warfarin (not specified)
Akyol (29)	2021	61	Adults	Budd-Chiari syndrome, other thromboses (venous)	Warfarin/enoxaparin (50%)
Roriz (30)	2018	7	Adults	Cerebral venous thrombosis (venous)	Vitamin K antagonists (100%)
Shi (31)	2018	21	Adult	CSVT, various thrombosis (venous)	Not specified type of AC (95.2%)
Saadoun (32)	2009	64	Adults	Cerebral venous thrombosis (venous)	Warfarin (96.9%)
Oumerzouk (33)	2022	24	Adults	Cerebral venous thrombosis (venous)	Vitamin K antagonists (100%)
Ideguchi (34)	2011	412 (26 with involvement)	Adults	Various arterial and venous lesions (venous and arterial)	Warfarin (34.3%)
Lee (35)	2020	34	Adults	DVT (venous)	Warfarin (55.8%), NOAC's (11.7%)
Guzelkucuk (36)	2021	46 (10 with thrombosis)	Paediatric	Various thrombosis (venous)	Heparin, Warfarin (100%)
Seyahi (37)	2015	78	Adults	Lower-extremity vein thrombosis (venous)	Not specified
Eroglu (38)	2021	61	Adults	PAT, various venous thrombosis (pulmonary and venous)	Warfarin/LMWH (49.2%)
Samaniego (39)	2020	57	Adults	VTE (venous)	Heparin, acenocoumarol (100%)
Girgin (40)	2021	78	Adult	DVT, PAT, PAA (pulmonary and venous)	Not specified type of AC (32.2%)
Vautier (41)	2021	44	Adult	Various thrombosis (venous)	DOACs (100%)
Desbois 2018 (42)	2018	18	Adult	Major vessel involvement	Warfarin (94.4%)
Desbois 2012 (43)	2012	296	Adults	Venous thrombosis events (venous)	Warfarin (98.6%)
Kehribar (44)	2020	18	Adult	Vascular Behcet's disease	Warfarin (22.2%)
Wang (45)	2015	12	Adult	Intracardiac thrombus (cardiac)	Warfarin (100%)
Demir (46)	2019	12	Paediatric	Sinus venous thrombosis (venous)	Enoxaparin, warfarin (100%)
Alkaabi (47)	2011	9	Adult	Stroke, DVT, ICT, PAA (cardiac, venous, pulmonary)	Not added
Reşit Yıldırım (48)	2023	28	Adults	DVT, pulmonary vasculitis (venous and pulmonary)	Warfarin (65%)
Geri (49)	2012	52	Adults	Cardiac lesions (cardiac)	Warfarin (59.6%)
Zhu (50)	2012	20	Adults	Intracardiac thrombus, aortic valvular involvement (cardiac and arterial)	Warfarin (100%)
Ahn (51)	2008	37	Adult	Venous thrombosis (venous)	Warfarin (10.8%)
Alibaz-Oner 2022 (52)	2022	291	Adult	Various thromboses (venous)	Not specified type of AC (64%)
Tohmé (53)	2003	18	Adult	Various vascular involvements	Not specified type of AC (94.4%)

BD: Behçet's disease; IVC: inferior vena cava; DVT: deep vein thrombosis; SVT: superficial vein thrombophlebitis; PAT: pulmonary artery thrombosis; CSVT: cerebral sinus venous thrombosis; ICT: intracardiac thrombus; PAA: pulmonary artery aneurysm; LMWH: low-molecular-weight heparin; VTE: venous thromboembolism; DOACs: direct oral anticoagulants; NOACs: novel oral anticoagulants; PE: pulmonary embolism.

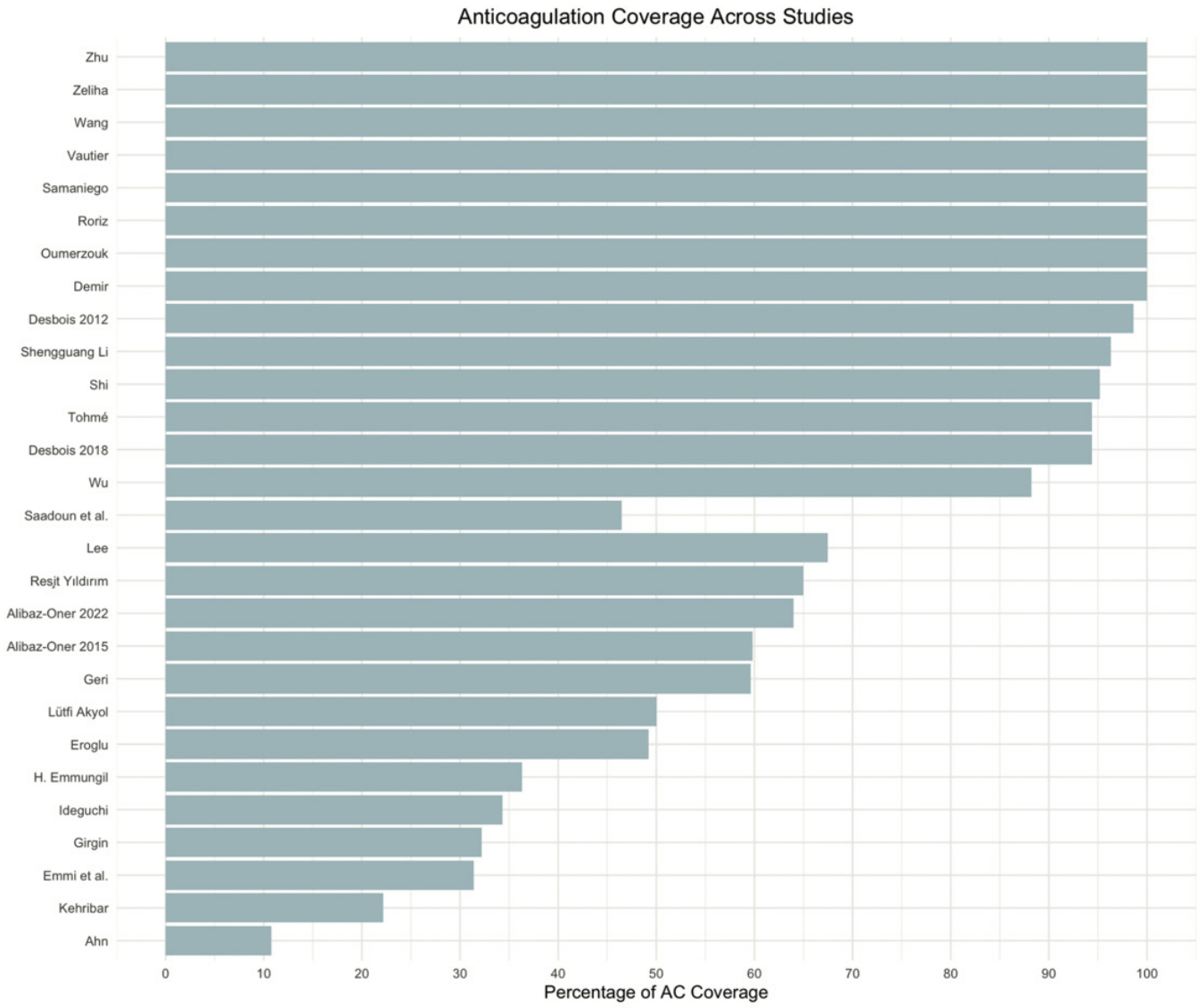

Fig. 2. Anticoagulation coverage across the included studies.

teria and detailed descriptions of study subjects. Nevertheless, there were instances where the use of appropriate statistical analysis was questionable.

Coverage and types of anticoagulation

The use of anticoagulation (AC) therapy varied widely across studies. Ahn *et al*. (51) reported the lowest coverage at 10.8% while Desbois *et al*. (43) and Li et al. (27) reported the highest at 98.6% and 96.3% respectively.

Warfarin was the most commonly used anticoagulant. Seyahi *et al*. (14) and Eroglu *et al*. (38) reported Warfarin or its combination with low molecular weight heparin in 33% and 49.2% of patients respectively. Vautier *et al*. (41) exclusively used direct oral anticoagulants (DOACs) in their study cohort (Table I, Fig. 2).

Indications

AC was used for various vascular complications in BD. Eroglu *et al*. (38) reported a 30% risk reduction in vascular relapses in pulmonary artery involvement with AC use. Seyahi *et al*. (14) described AC use in Budd-Chiari syndrome management. Lee *et al*. (35) reported AC as part of treatment regimens for deep vein thrombosis.

Efficacy

Seven out of 34 studies directly assessed the effect of AC. Saadoun *et al*. (10) found a reduction in postoperative thrombosis rates from 75% without AC to 40% with its use. Desbois *et al*. (43) reported that AC, used in 98.6% of their cohort, significantly reduced venous thrombosis relapse.

Oumerzouk *et al*. (33) observed that 70% of patients with cerebral venous thrombosis experienced poor outcomes despite universal AC administration. Vautier *et al*. (41) reported a lower risk of thrombotic recurrence with DOACs (hazard ratio: 0.11, p=0.002).

Emmi *et al*. (26) found that adalimumab-based regimens effectively managed venous thrombosis without being influenced by concurrent AC use. Ahn *et al*. (51) reported a 75% relapse rate with AC-only treatment compared to a lower rate when combined with immunosuppressive therapy (Fig. 3).

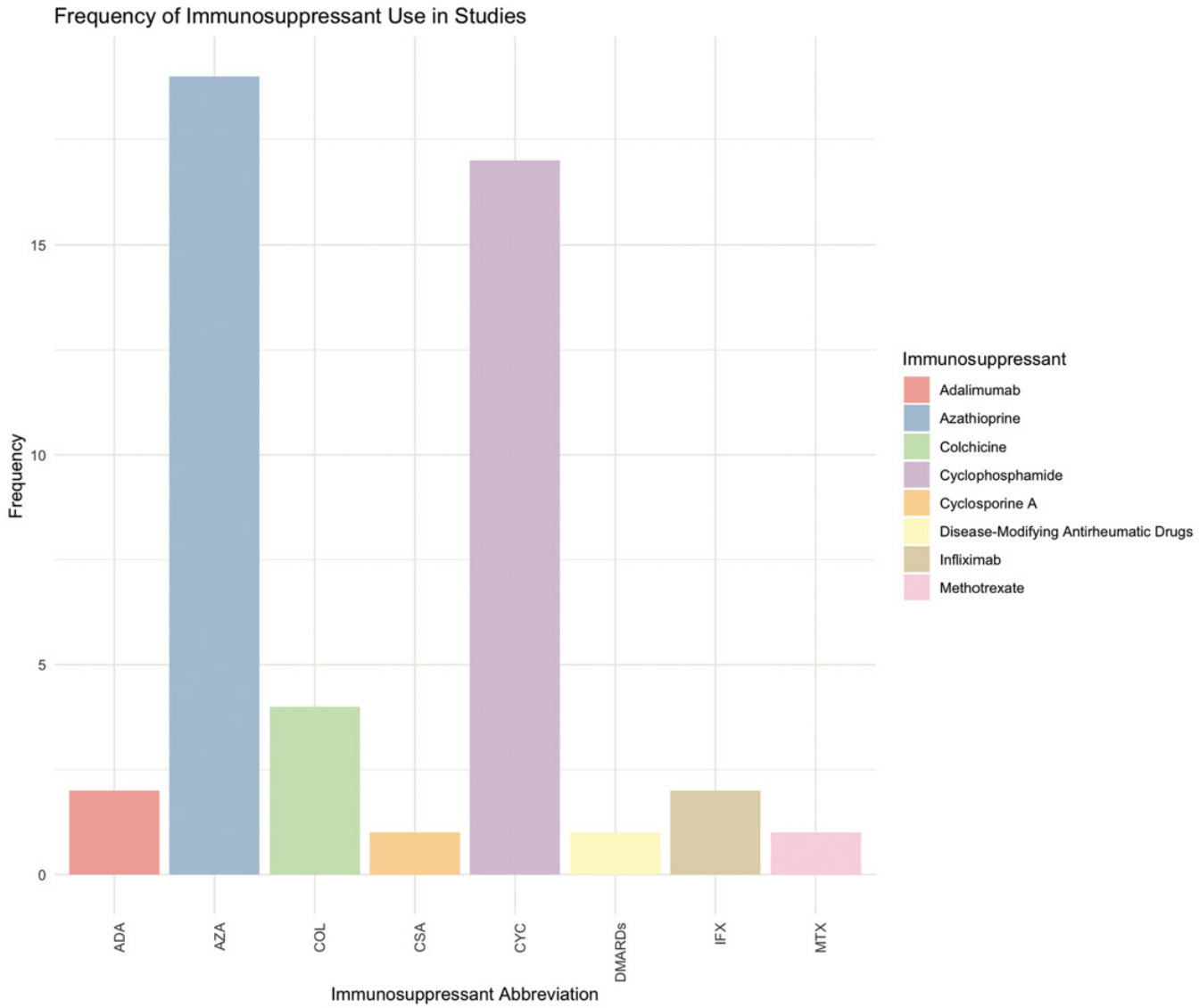

Fig. 3. Frequencies of the different immunosuppressants used in the included studies.

Overall, 21 out of 34 studies (62.5%) reported positive outcomes regarding AC efficacy, 10 (31.2%) presented neutral results, and 2 (6.2%) found negative implications. Only 7 out of 34 studies (20.5%) directly assessed the net effect of AC on treatment outcomes (Table II).

Very recently, October 2024, Alibaz-Oner *et al*. reported that anticoagulant treatment might decrease the relapse rate of pulmonary arterial involvement (PAI) in BD (54). Their study included 110 patients with PAI. Pulmonary artery thrombosis was evident in 104 patients and pulmonary artery aneurysm in 9 patients. In multivariate analysis, not starting anticoagulants independently increased the PAI relapse risk.

Safety profile

In the reviewed studies, haemorrhagic complications associated with AC therapy in BD occurred in 0–8.6% of patients. For instance, Lee *et al*. (35) reported 0 major bleeding events or deaths related to AC treatment in their cohort. Similarly, Coşkun *et al*. (24) observed 0 bleeding incidents in paediatric patients with vascular involvement receiving AC therapy for intracardiac thrombi management. Alibaz-Oner *et al*. (52) documented minor haemorrhages in 2.4% of their Turkish cohort, with 0 major adverse events attributed to AC treatment. Oumerzouk *et al*. (33) noted poor outcomes in 70% of their patient cohort, without specifying AC-related complications (50). Vautier *et al*. (41) reported 1 case of serious uterine bleeding requiring transfusion among patients using DOACs.

The incidence of major bleeding events ranged from 0% to 4.7% across studies. Minor bleeding events occurred in 2.4% to 8.6% of patients receiving AC therapy. The mortality rate due to bleeding was 0% in all studies (Table III).

Discussion

This systematic review examined AC therapy in VBD across 34 studies involving 2,516 patients. The results show AC use with immunosuppressants (IS) is generally safe and can reduce thrombotic events. However, its additional benefit over IS alone varies across studies. The efficacy and safety

Table II. Summary of the conclusions of the included studies on anticoagulation use in vascular Behçet's.

Author	Net effect of AC checked	Conclusion on AC use	Summary of why
Wu (8)	No	Supportive	High use of Warfarin, effectiveness not directly analysed
Alibaz-Oner (9)	No	Neutral	No additional positive effect of AC with IS
Saadoun *et al*. (10)	Yes	Supportive	Suggests considering AC for patients with arterial involvement
H. Emmungil (25)	No	Neutral	Focuses on effectiveness of immunosuppressants rather than AC
Emmi *et al*. (26)	Yes	Neutral	Found no significant modification of treatment efficacy by AC
Shengguang Li (27)	No	Positive	Mentions use of AC without specific conclusion on efficacy
Ozen (28)	No	Supportive	Suggests short-term use of AC
Lütfi Akyol (29)	No	Neutral	Mentions use of AC but concludes its role remained controversial
Roriz (30)	No	Positive	Safe to stop AC during optimal BD treatment
Shi (31)	No	Cautious	Suggests careful consideration before using AC
Saadoun (32)	Yes	Supportive	AC was safe and effective in managing CVT in BD
Oumerzouk (33)	No	Neutral	High use of AC but poor outcomes in a significant percentage
Ideguchi (34)	No	Neutral	Use of Warfarin noted, no specific conclusions on AC's net effect
Lee (35)	No	Supportive	No major bleeding events, suggests utility of AC
Guzelkucuk (36)	No	Positive	No complications detected from AC therapy
Seyahi (37)	Yes	Supportive	Associated with less severe post-thrombotic syndrome
Eroglu (38)	Yes	Supportive	Highlights importance of AC in preventing relapses
Samaniego (39)	No	Supportive	General safety noted with AC and protective role of immunosuppressants
Girgin (40)	Yes	Neutral	No demonstrated effect on relapse rates
Vautier (41)	No	Highly supportive	Significant reduction in relapse with DOACs
Desbois (42)	No	Supportive	Suggests a beneficial role in conjunction with anti-TNF-α therapy
Desbois (43)	No	Supportive	High use of AC, related to reduced relapse rates
Kehribar (44)	No	Neutral	Focuses on immunosuppressives over AC
Wang (45)	No	Supportive	Effective management with anticoagulants
Demir (46)	No	Positive	Focuses on immunosuppressive treatment efficacy
Alkaabi (47)	No	Negative	Focuses on efficacy of immunosuppressive therapy without AC
Reşit Yıldırım (48)	No	Supportive	Mentions potential adjunctive role of AC
Geri (49)	No	Supportive	Mentions beneficial role of AC in cardiac lesions
Zhu (50)	No	Supportive	Mentions effectiveness in conjunction with immunosuppressants
Ahn (51)	No	Negative	AC alone not effective
Alibaz-Oner 2022 (52)	Yes	Neutral	Addition of AC to IS did not show extra benefits
Tohmé (53)	No	Supportive	Effective in managing venous thrombosis and severe conditions

AC: anticoagulation; BD: Behçet's disease; CVT: cerebral venous thrombosis; DVT: deep vein thrombosis; IS: immunosuppression; DOACs: direct oral anticoagulants; TNFα: tumour necrosis factor alpha.

of AC in VBD appear to depend on specific vascular involvements and individual patient factors. The overall safety profile of AC was acceptable, with minor complications reported, supporting its continued use under careful clinical supervision.

Of note, the study be Vautier *et al*. that reported the role of DOACS on preventing relapses of DVT, has impressively shown that DAOCs can significantly reduce the risk of relapse even when used alone, although the combination with immunosuppression is more effective (41). It should be emphasised that Vautier *et al*. used the time-dependent Cox regression method that accounts for the change in hazard over time (on-AC *vs*. off-AC) rather than the 'regular' Cox regression that assumes that the hazard is constant over time, as used in previous studies.

While the addition of AC therapy in VBD is typically not standard practice according to EULAR guidelines, specific circumstances highlight its potential utility (55). Notably, studies like those

Table III. Summary table of corticosteroid use, immunosuppression, and outcomes in the included studies.

Author (ref.)	% Patients administered corticosteroids	Immunosuppression (Type)	Main outcome	Complications
Wu (8)	100%	CYC, THL	High AC coverage with significant thrombosis resolution.	Minor complications reported, no detailed specifics.
Alibaz-Oner 2015 (9)	100%	AZA, CYC	Relapse rates lower in IS+AC treatments; AC crucial for new event reduction.	Minor haemorrhage noted; overall low complication rate.
Saadoun (10)	86.1%	CYC, AZA	AC associated with lower incidence of postoperative thrombosis.	No haemorrhagic complications noted.
Emmungil (25)	100%	CYC, AZA	AC effective in preventing cardiac thrombosis with no major complications.	No significant complications related to AC.
Emmi (26)	100%	ADA, DMARDs	AC did not alter the efficacy of ADA or DMARDs treatments for venous complications.	No significant impact on complication rates.
Li (27)	89%	MTX, CYC	AC used broadly for DVT and vena cava occlusion with positive outcomes.	No major bleeding or significant AC complications.
Ozen (28)	100%	COL, AZA	AC role not detailed; outcomes focused on IS effectiveness in paediatric cases.	No specific complications reported for AC group.
Akyol (29)	92%	CYC, AZA	AC's role in Budd-Chiari syndrome remained controversial.	One pulmonary haemorrhage reported, not AC-specific.
Roriz (30)	100%	AZA, STS	AC was safely discontinued with minimal relapse during follow-up.	One relapse noted after AC withdrawal.
Shi (31)	100%	CSA, CYC	High use of AC with cautious consideration due to potential complications.	Two cases of intracranial haemorrhage reported.
Saadoun (32)	84.4%	CYC, AZA	High AC effectiveness in CVT with no severe haemorrhagic complications.	Haemorrhagic complications were minor and managed without sequelae.
Oumerzouk (33)	25%	CYC	AC alongside immunosuppressants showed improved outcomes in CVT management.	Favourable outcomes with few sequelae noted.
Ideguchi (34)	54%	PRD, various IS	Low incidence of vascular complications with AC showing effectiveness.	No serious bleeding episodes reported with AC.
Lee (35)	100%	Various IS	DVT management with AC led to fewer post-thrombotic syndromes.	No major bleeding events; recurrence in some cases.
Guzelkucuk (36)	Not specified	COL, STS	AC used in all thrombotic cases with no major complications.	Thrombosis recurrence in one patient.
Seyahi (37)	95%	AZA	AC's role not detailed; significant post-thrombotic syndrome observed.	Increased frequency of PTS and venous claudication.
Eroglu (38)	83.6%	AZA, CYC	AC showed potential efficacy in preventing vascular relapses.	No haemorrhagic complications observed with AC use.
Samaniego (39)	91.2%	Various, not detailed	VTE management with AC showed low complication rates.	Low rates of side effects, no deaths reported.
Girgin (40)	75%	AZA	AC did not demonstrate a significant effect on relapse rates.	Leukopenia and hepatotoxicity reported in one patient each.
Vautier (41)	59%	Various, including IFX and ADA	AC associated with a reduced risk of thrombotic recurrence.	One serious uterine bleeding event requiring transfusion.
Desbois 2018 (42)	62.7%	Various IS	Significant reduction in venous thrombosis relapse with AC.	Bleeding complications in 2.4% of patients.
Desbois 2012 (43)	61%	CYC, AZA	AC highly effective with almost universal coverage.	Minimal complications, no major haemorrhagic events.
Kehribar (44)	100%	IFX, various	AC considered unnecessary in some cases due to effective IS.	One case of congestive heart failure reported.
Wang (45)	100%	Various, including CYC and AZA	AC effective in managing intracardiac thrombus with low recurrence.	No major complications reported with AC use.
Demir (46)	100%	COL, AZA	AC alongside IS showed effectiveness in paediatric sinus venous thrombosis.	No intracranial haemorrhage or significant adverse events.
Alkaabi (47)	Not specified	Not specified	Aggressive IS without AC effective for managing severe cases.	PAA rupture leading to death; AC not used.

Author (ref.)	% Patients administered corticosteroids	Immunosuppression (type)	Main outcome	Complications
Yıldırım (48)	93%	CYC, AZA	AC adjunct to IS showed beneficial effects in managing DVT.	One death from pulmonary artery aneurysm bleeding; AC status unclear.
Geri (49)	Not specified	AZA, CYC	AC used in over half of patients with positive outcomes.	Cardiac-related deaths and myocardial infarctions noted.
Zhu (50)	100%	Various, including prednisone	AC critical in reducing cardiac thrombus and improving heart failure.	Recurrence of thrombus and severe valvular complications after surgery.
Ahn (51)	100%	COL, AZA	AC alone not effective; combined with IS, it showed better outcomes.	No major complications related to AC reported.
Alibaz-Oner 2022 (52)	59.2%	AZA, CYC	Combined AC and IS did not demonstrate additional benefits; early cessation linked to higher relapse rates.	Minor haemorrhage related to AC treatment.
Tohmé (53)	72%	COL, CYC	Effective management with AC in severe cases, suggesting a combined therapy approach for best outcomes.	No major complications noted; further research on AC needed.

AC: anticoagulation; IS: immunosuppression; AZA: azathioprine; CYC: cyclophosphamide; IFX: infliximab; ADA: adalimumab; DVT: deep vein thrombosis; CVT: cerebral venous thrombosis; PAA: pulmonary artery aneurysm; PTS: post-thrombotic syndrome; COL: colchicine; THL: thalidomide; MTX: methotrexate; STS: steroids; PRD: prednisone; CSA: cyclosporine A.

by Saadoun *et al*. (32) and Geri *et al*. (49) demonstrate that AC can be as effective as IS therapy or beneficial when combined with IS in cases such as cerebral sinus vein thrombosis and cardiac involvement. This suggests the need for a tailored approach in VBD management, where therapy is customised based on detailed patient assessments and specific vascular involvement.

The global diversity in managing VBD is evident from findings by Tayer-Shifman *et al*., where the use of AC varied significantly among rheumatologists from Turkey, Israel, and the USA, reflecting differences in clinical experience and disease prevalence (56). This variation underscores the urgent need for controlled studies to establish more definitive guidelines.

Furthermore, Korkmaz's critique (57) on Ahn *et al*. (51) study regarding deep venous thrombosis in BD emphasises the importance of considering underlying prothrombotic conditions, such as Factor V Leiden mutation. Such conditions may necessitate long-term AC alongside IS, suggesting that treatment regimens should account for both the inflammatory nature of BD and individual thrombotic risk profiles.

As long as no randomised controlled trials (RCTs) assessing the use of IS combined with AC compared to IS alone in the treatment of VBD, the use of AC will continue to be a major debate, and the decision whether to add AC or not will be considered on each single-case basis and according to the existence of risk factors for bleeding, the treating physician's approach and experience and the patient's preferences.

RCTs comparing the use of combined IS and AC *versus* AC alone would not be appropriate in the case of VBD as it is quite clear that the principal treatment in VBD is IS as suggested repeatedly by many studies. Indeed, because of the various vascular manifestations of BD, no single RCT will be able to solve this debate, as each single RCT will be able to address only one specific manifestation (*e.g*. DVT). Moreover, some manifestations, such as Budd-Chiari, are very rare, thus limiting the possibly of conducting RCTs to answer the question whether AC are effective in the treatment of this manifestation. We believe it is of paramount importance to launch a multi-centre, multinational initiative aiming to collect the available data from each participating centre on the role of AC in each single vascular manifestation, in order to include the maximum number of patients with the specific manifestation. Such initiative will be able to provide more valuable, and hopefully homogenous, data that might shed more light on the role of AC in the various manifestations of VBD.

As the thrombus in BD is inflammatory in its nature, IS, with or without glucocorticoids, should be the principal treatment of VBD (15, 18, 58). AC might be added in cases where IS might not be sufficient or effective such as the coexistence of other hypercoagulable state, niche indication (cerebral sinus vein thrombosis or cardiac involvement), refractory thrombosis or other indications that necessitate the introduction of AC (venous thromboembolism after surgery).

Conclusion

This review suggests that AC may have a role in VBD treatment, particularly in specific vascular involvements. However, its use requires careful consideration alongside IS therapy, accounting for individual patient factors and potential underlying prothrombotic conditions. The decision to use AC in VBD should be made on case-by-case basis, balancing potential benefits and risks. More research is needed to establish definitive guidelines for AC use in this complex vasculitic disorder.

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