Anticoagulant treatment for isolated distal deep vein thrombosis: a systematic review and meta-analysis

Matteo Guarascio,[1] Emanuele Valeriani,[2,3] Laura Girardi,[4] Matteo Candeloro,[5] Arianna Pannunzio,[2] Ilaria Maria Palumbo,[2] Marcello Di Nisio[6] and Walter Ageno[4,7]

[1]Internal Medicine Unit, Vito Fazzi Hospital, Lecce, Italy; [2]Department of General Surgery, Surgical Specialties and Organ Transplantation "Paride Stefanini", Sapienza University of Rome, Rome, Italy; [3]Infectious Disease Department, Umberto I Hospital of Rome, Rome, Italy; [4]Department of Medicine and Surgery, Research Center on Thromboembolic Diseases and Antithrombotic Therapies, University of Insubria, Varese, Italy; [5]Department of Innovative Technologies in Medicine and Dentistry, "G. D'Annunzio" University, Chieti-Pescara, Italy; [6]Department of Medicine and Aging Sciences, "G. D'Annunzio" University of Chieti-Pescara, Chieti, Italy and [7]Department of Internal Medicine, Ospedale Regionale di Bellinzona e Valli, Bellinzona, Switzerland

Correspondence: M. Guarascio
guarasciomatteo@gmail.com

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Abstract

The optimal management of isolated distal deep vein thrombosis (IDDVT) is uncertain. To assess the efficacy and safety of anticoagulation in patients with IDDVT we performed a systematic review and meta-analysis of randomized and cohort studies on anticoagulation for IDDVT. Efficacy outcomes included recurrent deep vein thrombosis (DVT), pulmonary embolism (PE), proximal progression of IDDVT, post-thrombotic syndrome (PTS). Safety outcomes included major bleeding and clinically relevant non-major bleeding (CRNMB). Pooled incidence and risk ratios (RR) with 95% confidence intervals (CI) were calculated. Treatment duration was defined as short (<6 weeks), long (6-12 weeks), or extended (>12 weeks). Fifty-three studies (14,580 patients) were included. The incidence of recurrent DVT and proximal progression was 16% and 11% in untreated patients, 7% and 7% in short, 6% and 3% in long, and 4% and 2% in extended anticoagulation, respectively. The incidence of PE (2%) and major bleeding (2%) was low, with similar risk across groups of treatment duration. The incidence of PTS was 30% in untreated patients, 11% in short, and 0% in long anticoagulation. The incidence of CRNMB was respectively 2%, 1%, 4%, and 8%. Patients receiving short courses of anticoagulation had higher risk of recurrent VTE (RR=2.72; 95% CI: 1.19-6.23) and proximal progression (RR=3.86; 95% CI: 1.77-8.43) than patients receiving long anticoagulation, with similar bleeding risk in patients with IDDVT, anticoagulation seemed associated with lower risk of recurrent VTE and proximal progression, and similar bleeding risk compared to no anticoagulant treatment. Long-term treatment duration appeared to be more effective.

Introduction

Isolated distal deep vein thrombosis (IDDVT) refers to a lower extremity deep vein thrombosis (DVT) that occurs below the knee (i.e., below the popliteal vein) in the absence of concomitant thrombosis in other venous districts and represents the most common site of DVT presentation in the lower limbs.[1,2] With some interindividual variability, the distal deep veins of each leg, including the anterior and posterior tibial veins, the peroneal vein, and the muscular veins (soleus and gastrocnemius muscles), converge to form the trifurcation area, which drains into the popliteal vein. Due to its anatomical contiguity to the proximal deep veins and similar clinical features as proximal DVT, thrombosis at the level of the trifurcation is conventionally managed as proximal DVT.[3,4] Although IDDVT has long been considered a benign condition, several studies have reported non-negligible rates of complications, including extension to the proximal veins, thrombosis recurrence, pulmonary embolism (PE), and the post-thrombotic syndrome (PTS).[1,4] These rates are particularly evident in high-risk subpopulations, such as patients with active cancer.[5] A number of randomized controlled trials (RCT) have been carried out to compare different management strategies for IDDVT, but their findings have not always been consistent.[6] This has led to substantially weak and variable recommendations from clinical guidelines and to heterogeneous management strategies in daily clinical practice.[7-9]

To summarize the available evidence on anticoagulation for IDDVT, we performed a systematic review and meta-analysis of RCT and cohort studies evaluating the efficacy and safety of anticoagulant treatments, and assessed the in-

cidence of relevant outcomes in relation to the use, dose and duration of anticoagulation.

Methods

This meta-analysis was conducted following the PRISMA guidelines.[10] The PROSPERO registration ID is CRD42023437913.

Search strategy and study selection

We performed a systematic review of the literature using four electronic databases (MEDLINE, EMBASE, CINAHL, CENTRAL) up to March 2024 to identify all available RCT and cohort studies on IDDVT treatment (Figure 1). Two authors (MC and LG) independently screened the lists of records obtained by the search and performed the study selection based on titles and abstracts. The studies were included in the analysis if they met all the following criteria: (i) objective diagnosis of IDDVT; (ii) availability of data on relevant outcomes and (iii) inclusion of at least ten IDDVT patients. Any type and duration of anticoagulant treatment, as well as no anticoagulation, were considered acceptable for inclusion. Other therapeutic strategies and the relative studies were included if outcomes could be extracted in patients receiving anticoagulation treatment. Studies that met the inclusion criteria underwent independent full-text

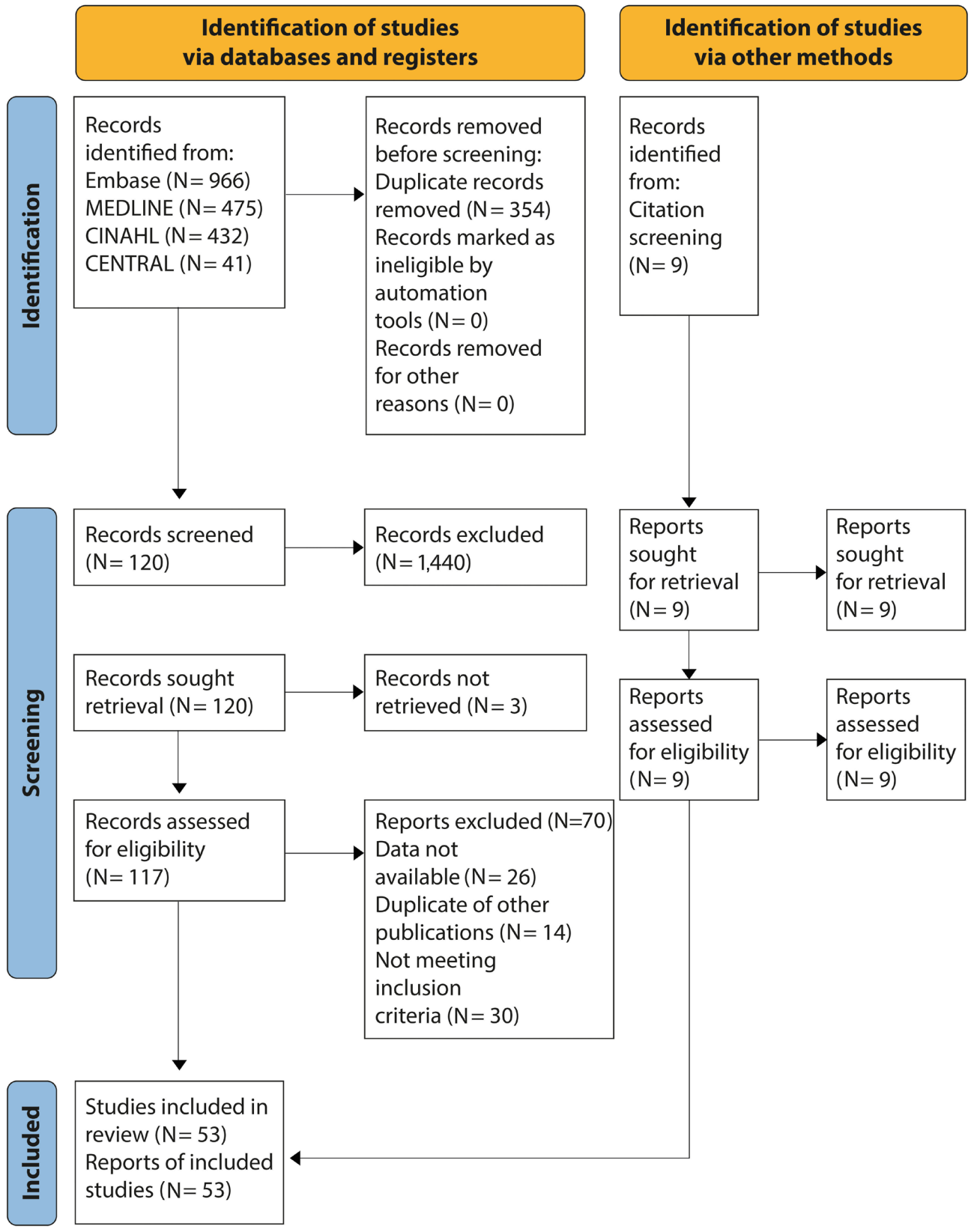

Figure 1. PRISMA flow diagram.

screening performed by the two authors (MC and LG) for final eligibility and data extraction.

Data extraction

Two authors (AP and IMP) reviewed eligible articles and extracted available data on each study (e.g., year of publication, design) and population characteristics (e.g., number and type of patients included, mean age, sex), method of diagnosis of IDDVT (i.e., ultrasonography), presence of symptoms, anticoagulant treatment (e.g., type, dose and duration), type of other management strategies (e.g., placebo, elastic compression, antiplatelet agents, anti-inflammatory drugs, or no treatment), and follow-up duration. The risk of bias was evaluated using the Cochrane tools for randomized (RoB 2) and non-randomized studies (ROBINS-I).[11,12]

Outcomes

The efficacy outcomes included the incidence of objectively confirmed recurrent DVT, PE, proximal progression of IDDVT, and PTS. Safety outcomes included the occurrence of major bleeding and clinically relevant non-major bleeding (CRNMB), as defined by the investigators of each study.

Statistical analysis and risk of bias assessment

Pooled risk ratios (RR) and pooled incidences (ES) with corresponding 95% confidence intervals (95% CI) were calculated in a random-effects model through the inverse variance method and DerSimonian-Laird method was used for T2 estimation. We used a continuity correction of 0.5 for studies with zero events. Heterogeneity was classified as follows: (i) 0% to 40% I^2 values indicate a level of heterogeneity that might not be important; (ii) 30% to 60% I^2 values may represent moderate heterogeneity, (iii) 50% to 90% I^2 values may represent substantial heterogeneity, (iv) 75% to 100% I^2 values indicate considerable heterogeneity.[13] The between-study heterogeneity was also evaluated by visual inspection of forest plots. The analysis was performed evaluating the duration of anticoagulation (i.e., short [<6 weeks], long [6-12 weeks], extended [>12 weeks], and mixed), therapeutic scheme (i.e., therapeutic, intermediate, prophylactic, and mixed doses) and the classes of venous thromboembolism (VTE) recurrence risk (i.e., high and low risk, as defined by the investigators of each study). A sensitivity analysis was conducted including only RCT and prospective cohort studies. Publication bias was assessed with Egger's test and represented graphically by funnel plots of the logit-transformed proportion *versus* the standard error.[14]

This study respect the ethical rules of the country in which it has been performed.

Results

The literature search identified 1,914 records. After removing 354 duplicates, 1,440 records were excluded after evaluation of the title and/or abstract. Of 120 studies evaluated in full-text, we excluded three studies as reports could not be retrieved, 26 as data were not available, 14 because they were duplicates of previous publications, and 30 records which did not meet the inclusion criteria. Nine additional studies were retrieved after manual search of the references of selected papers, of which three were excluded after full-text screening (Figure 1).

Overall, 53 studies were eventually included in the analysis, for a total population of 14,580 patients. Of these studies, 13 were RCT,[15-27] 21 prospective and 19 retrospective cohort studies. The complete list of references is provided in the *Online Supplementary Appendix*.

Online Supplementary Table S1 reports the main characteristics of the included studies. Anticoagulant treatments were given at prophylactic doses in four studies, at intermediate doses in two studies, at therapeutic doses in 30 studies, and at mixed doses in eight studies. The most commonly used anticoagulant drugs were low molecular weight heparins (LMWH), followed by vitamin K antagonists (VKA), unfractionated heparin (UFH), direct oral anticoagulants (DOAC), and fondaparinux. Treatment duration was short in 20 studies, long in 16 studies, extended in four studies and mixed in 16 studies. Twenty-three studies included patients presenting with symptomatic IDDVT only,[3,5,15,17,19,21-25,27-39] while the remaining included both patients with symptomatic IDDVT and patients with asymptomatic IDDVT at the time of enrolment. Follow-up duration ranged between 1 month and 8.4 years, for a median of 7.75 months.

The overall quality of the 13 RCT was low in five, high in one, or with some concerns in seven studies (Figure 2). The overall quality of the 40 cohort studies was low in 14, high in eight, or with some concerns in 18 studies, respectively (Figure 3).

As detected by the Egger test, there was evidence of publication bias for studies evaluating major bleeding and CRNMB (*Online Supplementary Figures S28-S32*).

Efficacy outcomes

Figure 4 shows the incidence of the efficacy outcomes sorted by duration and dose of therapy, and baseline patients' risk.

The incidence of recurrent DVT was 16% (95% CI: 10-26%; I^2=84%) in patients receiving no anticoagulant therapy, and 7% (95% CI: 4-11%; I^2=85%), 6% (95% CI: 4-9%; I^2=86%), and 4% (95% CI: 2-7%; I^2=80%) in patients receiving short, long, and extended duration of anticoagulation. Corresponding RR were 0.21 (95% CI: 0.03-1.60) for short duration of treatment compared to no treatment and 0.40 (95% CI: 0.12-1.36) for long duration compared to no therapy (Figure 5). Overall, the risk of recurrent DVT was lower in patients receiving anticoagulant therapy than untreated patients (RR=0.36; 95% CI: 0.18-0.72; I2=57%). Specifically, the risk of recurrent DVT was significantly higher in patients receiving short *versus* long duration of anticoagulation (RR=2.72; 95% CI:

1.19-6.23; I2=52%) (*Online Supplementary Figures S1, S15* and *S16*). The incidence of recurrent DVT according to the dose of anticoagulant treatment was 13% (95% CI: 3-47%; I^2=90%) in patients receiving prophylactic dose, 7% (95% CI: 1-30%; I^2 93%) in patients receiving intermediate dose and 6% (95% CI: 4-9%; I^2=88%) in patients receiving therapeutic dose (*Online Supplementary Figures S2-S4*). According to the baseline patients' risk of VTE, this incidence was 9% (95% CI: 4-18%; I^2=93%) in patients at high risk and 3% (95% CI: 2-6%; I^2=45%) in low-risk ones (*Online Supplementary Figures S5* and *S6*).

The incidence of PE was similar in all subgroups of patients with a pooled incidence of 2% (95% CI: 2-3%) (*Online Supplementary Figures S7-S12, S17* and *S18*).

The incidence of proximal progression of IDDVT was 11% (95% CI: 7-16%; I^2=74%) in patients receiving no anticoagulant therapy, and 7% (95% CI: 2-18%; I^2=89%), 3% (95% CI: 1-6%; I^2=72%), and 2% (95% CI: 1-5%; I^2=NA) in patients receiving short, long and extended duration of anticoagulation, respectively. The risk of proximal progression of thrombosis was significantly higher in patients receiving short *versus* long duration of anticoagulation (RR=3.86; 95% CI: 1.77-8.43) (Figure 5; *Online Supplementary Figure S13*).

The pooled incidence of PTS was 30% in patients receiving no therapy (95% CI: 23-40%; I^2=0%), 11% in patients receiving short duration (95% CI: 2-44%; I^2=90%) and 0% in patients on long duration of anticoagulation (95% CI: 0-32%; I^2=NA) (*Online Supplementary Figure S14*).

A sub-analysis sorted on type of anticoagulant showed similar incidence of DVT recurrence and PE in DOAC, VKA and LMWH groups. The risk of proximal progression of thrombosis was higher in patients receiving VKA (12%; 95% CI: 5-28%) than in those on DOAC (2%; 95% CI: 1-5%) or LMWH (3%; 95% CI: 0-28%) (*Online Supplementary Table S2*).

A sensitivity analysis including only RCT and prospective cohort studies reported similar results in terms of proportion of efficacy outcomes, occurrences and risk ratios, when compared to those of the primary analyses. The incidence of recurrent DVT, PE and DVT proximal progression was 8% (95% CI: 6-11%; I^2=92%), 2% (95% CI: 2-3%; I^2=60%) and 7% (95% CI: 5-11%; I^2=77%), respectively (*Online Supplementary Tables S3* and *S4*).

Similarly, a sensitivity analysis including only high-quality studies published since 2009 reported comparable results: the incidence of recurrent DVT, PE and DVT proximal progression was 6% (95% CI: 4-10%; I^2=3%), 2% (95% CI: 1-3%; I^2=71%) and 8% (95% CI: 2-27%; I^2=86%) respectively (*Online Supplementary Table S5*).

Poor reporting did not allow any other subgroup analysis for these outcomes.

Safety outcomes

Figure 6 shows the incidence of the safety outcomes sorted by duration of therapy and baseline patients' risk.

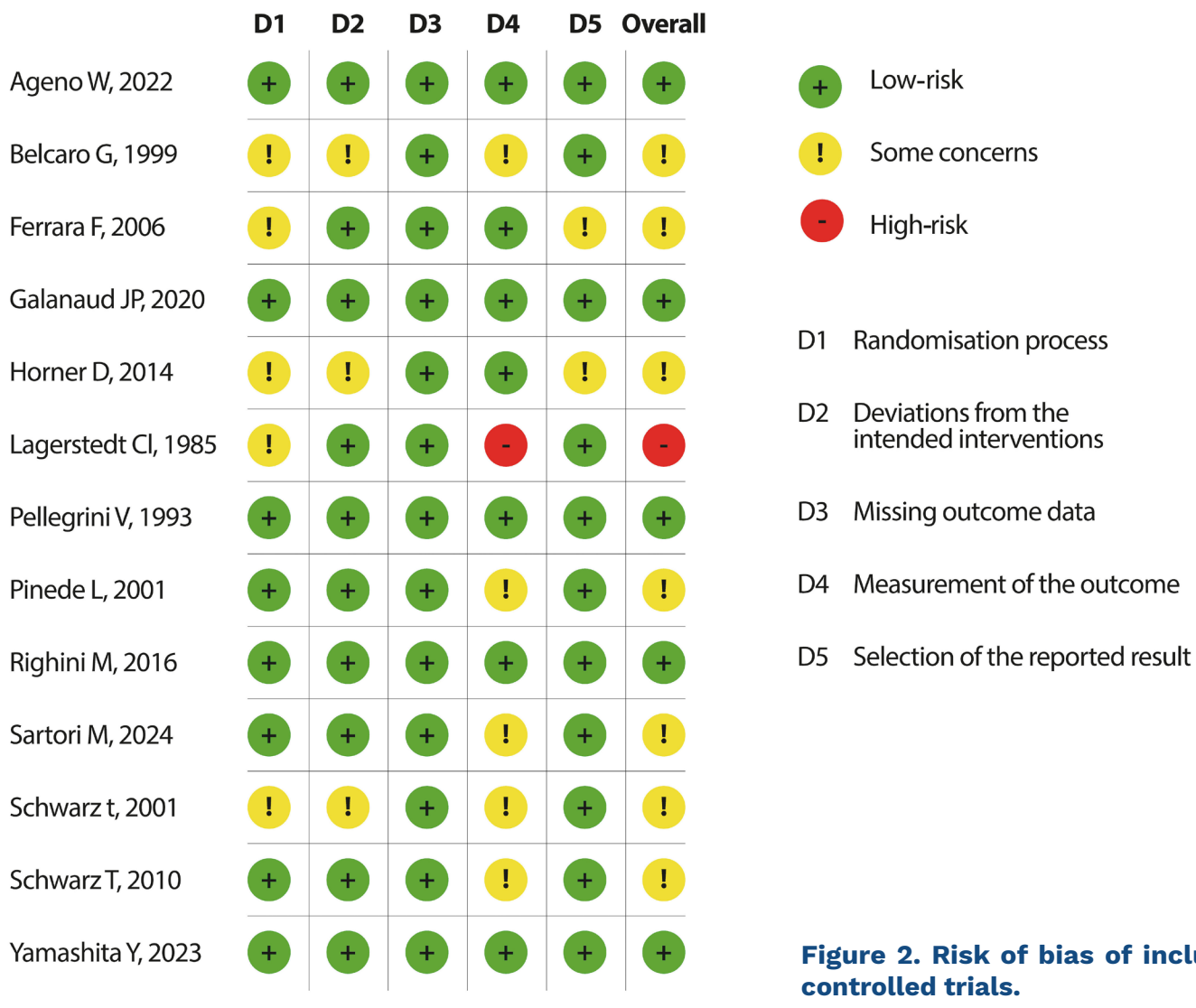

Figure 2. Risk of bias of included randomized controlled trials.

The incidence of major bleeding was similar among patients receiving different durations of anticoagulation with a pooled incidence of 2% (95% CI: 1-3%; I2 76%) (*Online Supplementary Figures S20* and *S26*). This incidence was 1% in patients receiving therapeutic dose of anticoagulation (95% CI: 1-3%; I^2=56%), no information was available for different schemes of treatments. Regarding the baseline patients' risk, the incidence of major bleeding was 1% in patients at low risk (95% CI: 0-2%; I^2=0%), compared to 4% in high-risk patients (95% CI: 2-10%; I^2=77%) (*Online Supplementary Figures S21* and *S22*).

The incidence of CRNMB was 2% in patients receiving no therapy (95% CI: 1-4%; I^2=0%), 1% in patients receiving short duration (95% CI: 1-3%; I^2=11%), 4% in patients receiving long duration (95% CI: 3-7%; I^2 77%), and 8% in patients receiving extended duration therapy (95% CI: 6-11%; I^2==not

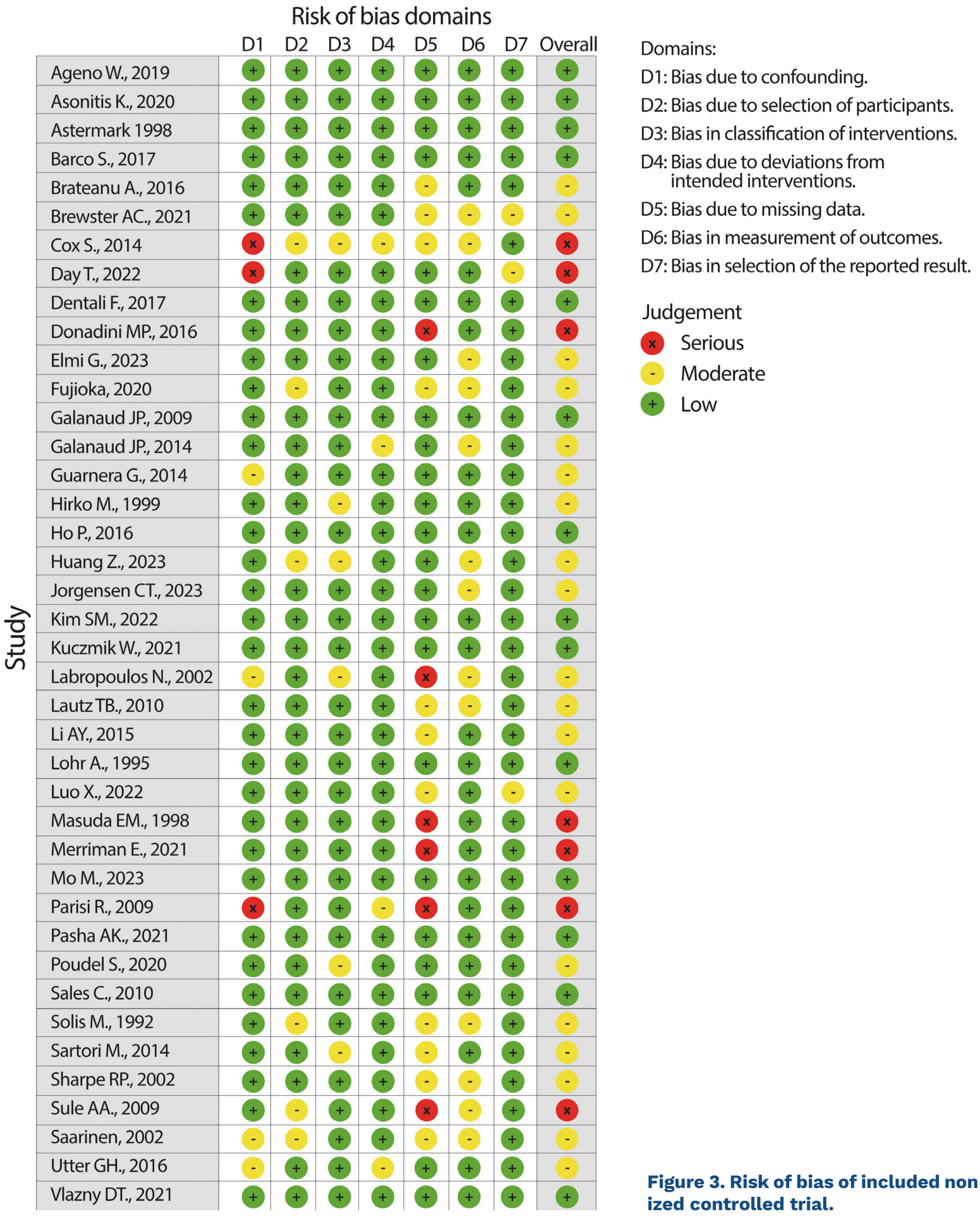

Figure 3. Risk of bias of included non-randomized controlled trial.

applicable [NA])) (*Online Supplementary Figures S23* and *S27*).

As for the therapeutic scheme of anticoagulation, the incidence of CRNMB was 2% in patients receiving therapeutic doses (95% CI: 1-5%; I^2=64%), no data were available for other therapeutic schemes. Finally, depending on the patients' baseline risk, the incidence of CRNMB was 8% (95% CI: 6-10%) and 2% (95% CI: 1-4%) in patients at high and low risk, respectively (*Online Supplementary Figures S24* and *S25*).

Figure 7 reports the risk ratios for safety outcomes in patients receiving different anticoagulant treatment durations. A sensitivity analysis was conducted for safety outcomes as well, including only RCT and prospective cohort studies, and reported similar results to those of the primary analyses. The incidence of major bleeding and CRNMB was 2% (95% CI: 1-4%; I^2=88%) and 5% (95% CI: 3-7%; I^2=73%) respectively (*Online Supplementary Tables S3* and *S4*).

Another sensitivity analysis including only high-quality

	N/N patients	N of studies	ES (95% CI)
RECURRENT DVT			
Random effects model, I2 = 91%	**759/11871**	**33**	**7 (5-9)**
Duration of therapy			
Short (< 6 weeks), I2 = 85%	164/1851	14	7 (4-11)
Long (6-12 weeks), I2 = 86%	277/3907	16	6 (4-9)
Extended (> 12 weeks), I2 = 80%	65/1975	4	4 (2-7)
No therapy, I2 = 84%	128/869	10	18 (10-26)
Dose of therapy			
Therapeutic, I2 = 88%	231/3991	18	8 (4-9)
Intermediate, I2 = 93%	47/451	2	7 (1-30)
Prophylactic, I2 = 90%	18/134	2	13 (3-47)
Baseline patients' risk			
High-risk patients, I2 = 93%	103/1227	3	9 (4-18)
Low-risk patients, I2 = 45%	15/493	2	3 (2-6)
PULMONARY EMBOLISM			
Random effects model, I2 = 53%	**193/11134**	**41**	**2 (2-3)**
Duration of therapy			
Short (< 6 weeks), I2 = 45%	24/1634	16	2 (1-4)
Long (6-12 weeks), I2 = 37%	75/3463	14	3 (2-3)
Extended (> 12 weeks), I2 = 76%	9/889	2	1 (0-4)
No therapy, I2 = 84%	32/1233	17	3 (2-6)
Dose of therapy			
Therapeutic, I2 = 13%	35/2506	18	2 (2-3)
Intermediate, I2 = 74%	13/451	2	2 (0-20)
Prophylactic, I2 = 0%	2/147	3	3 (1-9)
Baseline patients' risk			
High-risk patients, I2 = 86%	10/825	2	1 (0-8)
Low-risk patients, I2 = 23%	8/865	5	2(1-3)
PROXIMAL PROGRESSION			
Random effects model, I2 = 84%	**229/3882**	**24**	**7 (5-10)**
Duration of therapy			
Short (< 6 weeks), I2 = 89%	51/624	6	7 (2-18)
Long (6-12 weeks), I2 = 72%	35/1198	5	3 (1-6)
Extended (> 12 weeks), I2 = NA	7/288	1	2 (1-5)
No therapy, I2 = 74%	84/884	11	11 (7-16)
POST-THROMBOTIC SYNDROME			
Random effects model, I2 = 80%	**63/332**	**3**	**16 (8-31)**
Duration of therapy			
Short (< 6 weeks), I2 = 90%	30/215	3	11 (2-44)
Long (6-12 weeks), I2 = NA	0/8	1	0 (0-32)
No therapy, I2 = 0%	33/109	2	30 (23-40)

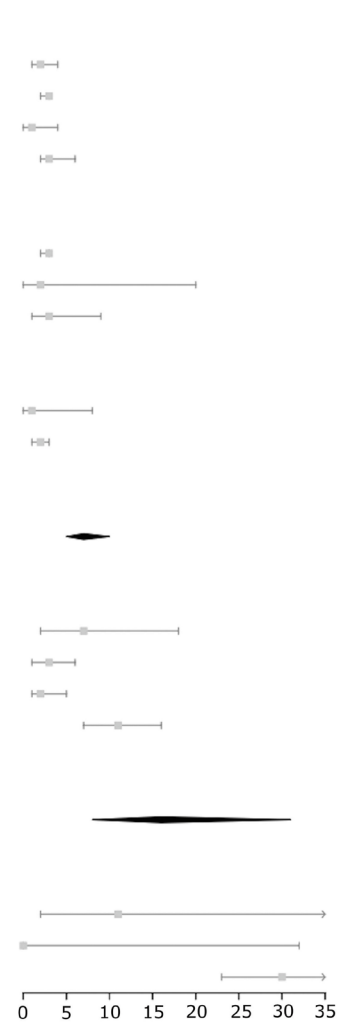

Figure 4. Incidence of efficacy outcomes sorted by the duration and dose of anticoagulant therapy and by the classes of risk. The gray squares indicate the individual study estimates (ES) of the proportion of best-corrected visual acuity improvement, whereas the gray horizontal lines indicate the 95% confidence intervals (CI) of the individual studies. The diamonds indicate the summary estimates with 95% CI. DVT: deep vein thrombosis; NA: not applicable.

studies published since 2009 was performed and reported similar results: the incidence of major bleeding and CRNMB was 2% (95% CI: 1-3%; I^2=77%) and 3% (95% CI: 2-5%; I^2=75%), respectively. (*Online Supplementary Table S5*). Poor reporting did not allow any other subgroup analysis for these outcomes.

Discussion

The results of this systematic review and meta-analysis suggest that patients with IDDVT who are managed without anticoagulation have a higher risk of recurrent DVT, proximal progression of thrombosis, and PTS compared with patients receiving anticoagulant treatments. Long-term anticoagulation regimen (i.e., between 6 and 12 weeks) appears to be more effective than short-term treatment durations (i.e., up to 6 weeks). Furthermore, there is a trend towards a reduced risk of recurrent DVT in extended treatment (i.e., over 12 weeks) compared to long treatment duration. The incidence of recurrent DVT was higher in patients defined at high risk than in those defined at low risk and the benefit of anticoagulant treatment appeared to be greater in patients receiving either intermediate or therapeutic doses of anticoagulant agents as compared with patients receiving prophylactic doses. There were no differences in PE across groups of different treatment duration or dose. Globally, the incidence of major bleeding was low (ranging from 1% to 4%) and similar across the considered groups; moreover, the risk for major bleeding was lower in patients treated with anticoagulants. CRNMB rates were higher in patients at high risk for recurrent DVT and in those receiving long or extended treatment duration.

Despite previous studies claimed IDDVT to be a benign disease associated with a low incidence of proximal DVT and PE,[38,40-42] other studies reported a similar long-term risk of recurrence as more proximal DVT.[3,34] Furthermore, a significant proportion of patients presenting with acute PE are found to have concomitant IDDVT as the sole possible source of embolization.[43] Unfortunately, patients with IDDVT were excluded from the majority of RCT evaluating the efficacy of therapeutic approaches for VTE. Therefore, the available data remain scarce to make a definitive judgement on the optimal therapeutic management for this patients population.

The findings of our study support the use of anticoagulant therapy in IDDVT, confirming its efficacy and relative safety in a very large population. A previous meta-analysis by Franco and colleagues included 4,072 patients diagnosed with IDDVT from 24 studies.[6] The use of anticoagulation was associated with a significant reduction in VTE recurrence compared to no treatment, without a statistically significant increase in the risk of major bleeding.[6] The analysis sorted by dose of therapy showed a trend toward a lower risk of recurrent VTE in patients on therapeutic dose of anticoagulant treatment compared to prophylactic or intermediate doses, although

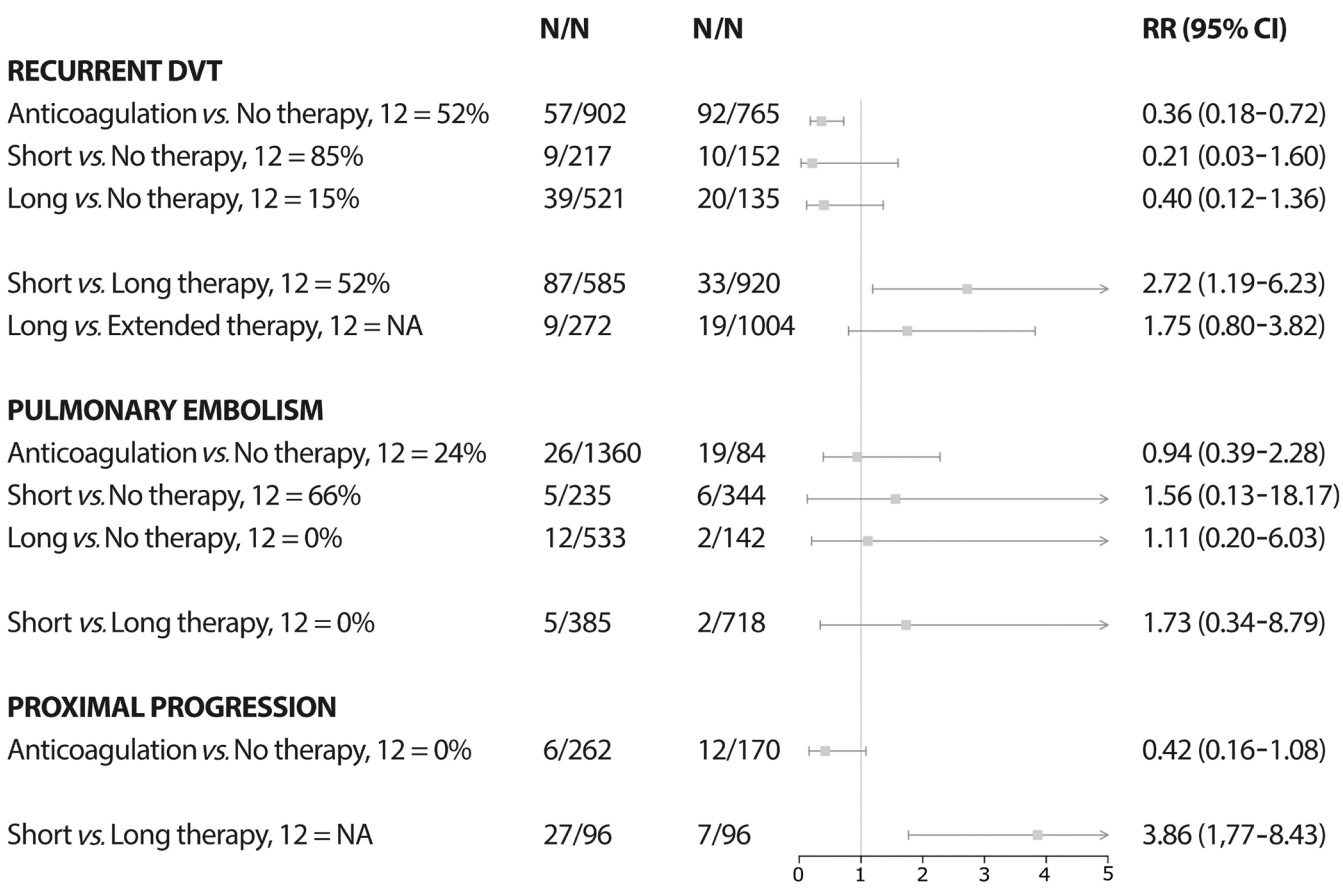

Figure 5. Risk ratios of efficacy outcomes sorted by the duration of anticoagulant therapy (short, <6 weeks of therapy; long, 6-12 weeks of therapy; extended, >12 weeks of therapy; mixed, mixed duration of therapy). The vertical line indicates the null estimate value. The gray squares indicate the individual study estimates of the proportion of best-corrected visual acuity improvement, whereas the gray horizontal lines indicate the 95% confidence interval (CI) of the individual studies. DVT: deep vein thrombosis; NA: not applicable; RR: risk ratios.

there was evidence for significative heterogeneity.[6] Our meta-analysis aligns with the results of the previous one, and further corroborates and extends its insights in a larger population, providing data for specific subgroups of patients according to the type and dose of treatments, as well as underlying patients' risks. Our results confirmed the benefit of anticoagulant treatment as compared to no treatment, although this difference was not statistically significant. Extending treatment duration beyond 6 weeks seemed to be more beneficial than shorter treatment durations, however, once again the significant heterogeneity limited strong conclusions. At variance with the study by Franco *et al.*, we found similar incidence of recurrent DVT in patients treated with intermediate or high dose of anticoagulant drugs.

To our knowledge, this is the first meta-analysis assessing anticoagulation for IDDVT that provides information on pooled incidence rates of IDDVT according to the baseline patients' risk. We believe this may be relevant since different management approaches are currently suggested for high- and low-risk patients.[7,8] In the OPTIMEV study, patients over 50 years old, those with an unprovoked IDDVT, or with multiple veins involvement had a 3-fold increased risk of VTE recurrence compared to those without these risk factors.[3] In the articles selected for the present analysis, the definitions of high and low risk varied considerably among studies (*Online Supplementary Table S6*). Certainly, patients with cancer-associated IDDVT, such as those enrolled in the ONCO-DVT study, are considered to be at high risk.[5,18,44] In other studies, patients with cancer were excluded because they were considered at very high risk, and different definitions of the level of risk were provided.[22,23] We found that the incidence of recurrent DVT tended to be higher in patients defined as high risk than in those defined as low risk (9% *vs*. 3%). While limited by the relative low number of patients and events, this analysis seems to support the need for anticoagulant therapy in high-risk patients, while its relevance remains less clear for low-risk patients. Hence, further studies should standardize the definition of low-risk patients and determine the optimal management strategy for these patients.

Of interest, our study reports a lower incidence of PTS in patients receiving anticoagulant therapy compared to pa-

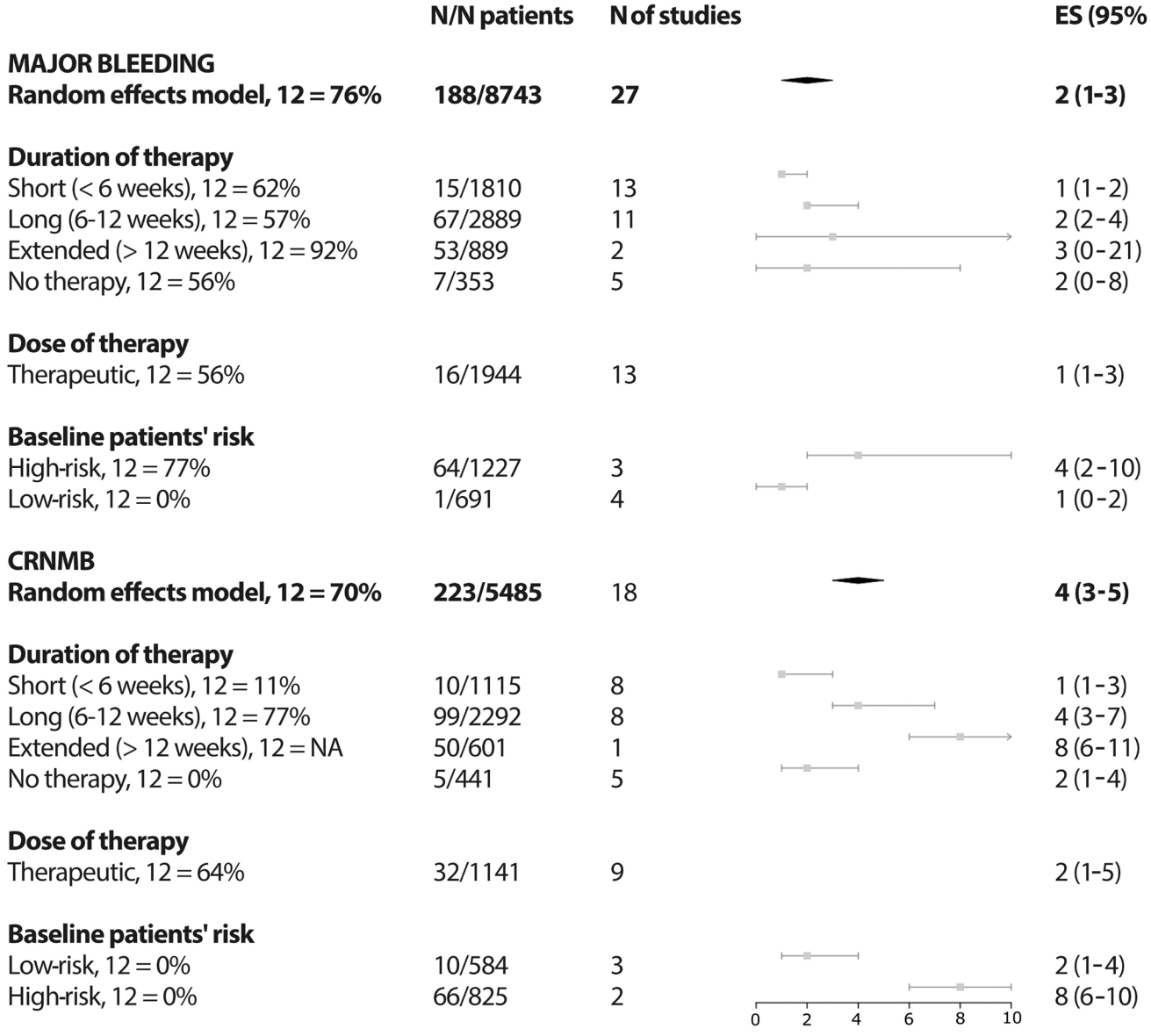

Figure 6. Incidence of safety outcomes sorted by the duration and dose of anticoagulant therapy and by risk classes. The gray squares indicate the individual study estimates of the proportion of best-corrected visual acuity improvement, whereas the gray horizontal lines indicate the 95% confidence interval (CI) of the individual studies. The diamonds indicate the summary estimates (ES) with 95% CI.

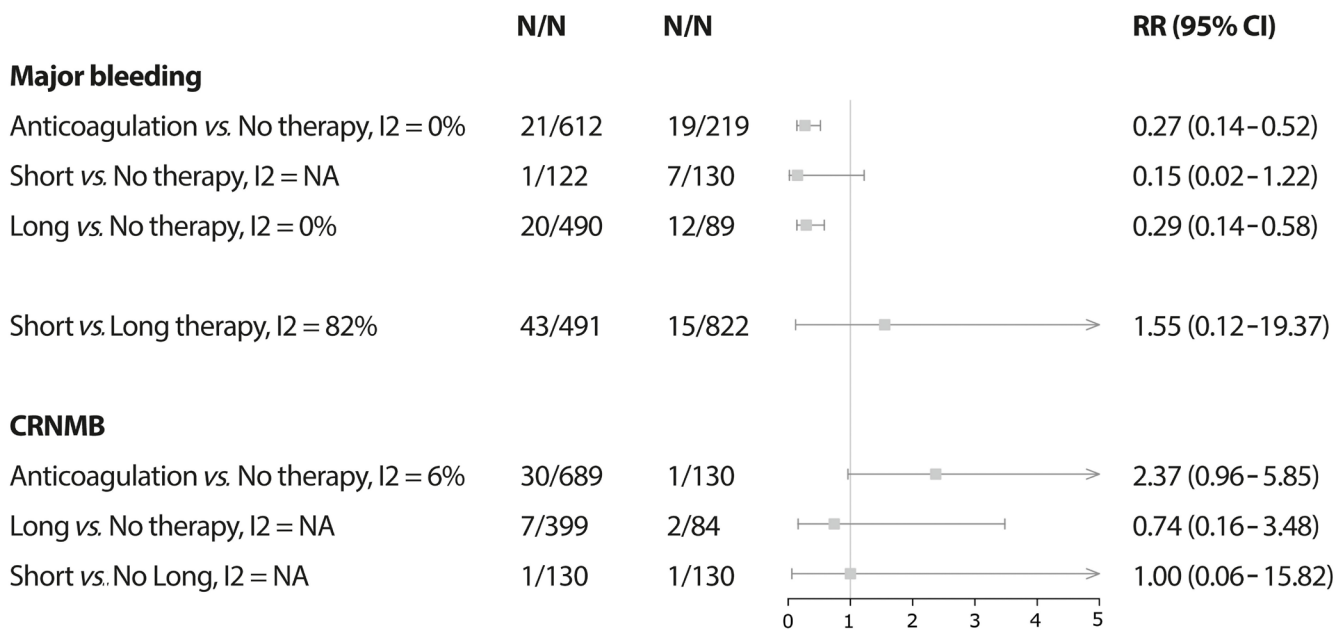

Figure 7. Risk ratios of safety outcomes sorted by the duration of anticoagulant therapy (short, <6 weeks of therapy; long, 6-12 weeks of therapy; extended, >12 weeks of therapy; mixed, mixed duration of therapy). The vertical line indicates the null estimate value. The gray squares indicate the individual study estimates of the proportion of best-corrected visual acuity improvement, whereas the gray horizontal lines indicate the 95% confidence interval (CI) of the individual studies. CRNMB: clinically relevant non-major bleeding; NA: not applicable; RR: risk ratios.

tients receiving no treatment. PTS appears to be a relatively frequent complication affecting also patients diagnosed with IDDVT. As shown by recent evidence from the international GARFIELD-VTE registry, 21.2% of patients with IDDVT developed PTS over a 3-year follow-up period.[45] The reduction of PTS with anticoagulant treatment could be related to higher rates of vessel recanalization obtained with adequate anticoagulation, as also suggested by the results of the RIDTS study.[23] Although limited by the small sample size, these findings further support the use of anticoagulation to lower the overall burden of IDDVT in terms of its short- and long-term complications.

The similar rates of major bleeding events observed in our study suggest a favorable clinical benefit of anticoagulant treatment, even when administered for longer durations, and are consistent with previous observations.[6] However, these results should be considered with caution since only approximately half of the included studies reported data on bleeding, and the definitions of major bleeding and CRNMB were heterogeneous across different papers. Notably, the incidence of major bleeding and CRNMB was higher in high-risk patients as compared to low-risk patients, suggesting the need for more careful and case-by-case evaluation for decision making in this subgroup of patients.

It is important to consider that a meta-analysis is inherently constrained by the limitations of the individual studies and the heterogeneity of the data. Our meta-analysis has some specific limitations that need to be acknowledged. Only a few studies included symptomatic events, and the low methodological study quality may have influenced the results, contributing to a certain degree of heterogeneity. The type (LMWH, UFH, fondaparinux, VKA, and DOAC), as well as the regimen (dose and duration) of anticoagulant agents varied across studies. The definitions of anticoagulant dose varied considerably among studies (*Online Supplementary Table S7*). Since this is a study-level meta-analysis, we could not adjust for the duration of treatment, which was insufficiently reported in many studies. The analysis focusing on treatment durations showed a borderline heterogeneity (I^2=52%) that was almost entirely limited to the pooled analysis of retrospective cohort studies. Indeed, the cohort studies included in the analysis were rather heterogenous in terms of study population (surgical patients undergoing screening for IDDVT or patients with symptomatic IDDVT), site of IDDVT (muscular or axial veins), diagnostic procedures to confirm recurrent or progressive thrombosis during follow-up, efficacy outcomes, and regimens of anticoagulants. Additionally, there was considerable variation in type of treatments provided for patients not receiving anticoagulants, which included placebo, elastic compression, antiplatelet agents, anti-inflammatory drugs, or no treatment at all. Concomitant therapies varied considerable even among anticoagulated patients. Due to these limitations, our results should be considered as a hypothesis rather than conclusive.

Despite these limitations, our study has also several strengths. In particular, by including a substantial number of studies (53 studies with over 14,000 patients), we were able to perform several sensitivity analyses.

In conclusion, this meta-analysis suggests that anticoagulant therapy is an effective approach for patients with IDDVT as it may reduce the risk of recurrent DVT, proximal progression of thrombosis and PTS, without increasing the risk of bleeding complications. Our findings also suggest the potential benefit of extending treatment beyond 6 weeks using intermediate to therapeutic doses of anticoagulation. Further studies are needed to define the optimal management strategy for patients defined at low risk and

the duration of treatment for high-risk patients, in particular those with permanent risk factors (e.g., cancer) or unprovoked IDDVT.

Disclosures

MDN has served as a consultant and has received honoraria from Daiichi Sankyo, Janssen, Leo Pharma, and Mylan. WA has participated in advisory boards for Astra Zeneca, Bayer, BMS-Pfizer, Norgine, Sanofi and Viatris. All other authors have no conflicts of interest to disclose.

Contributions

MC and LG independently screened the lists of records obtained by the search and performed study selection. AP and IMP reviewed eligible articles and extracted available data on each study. EV performed data analysis. MG wrote the manuscript. WA and MDN supervised the study.

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Data-sharing statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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