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TITLE PAGE

Article Title:

Risk of venous thromboembolism in outpatient parenteral antimicrobial therapy (OPAT): a systematic review and meta-analysis

Running Title: Systematic review of risk of VTE in OPAT

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ABSTRACT

The risk of venous thromboembolism (VTE) in outpatient parenteral antimicrobial therapy (OPAT) is not fully understood and the optimal strategy for thromboprophylaxis remains unclear. This systematic review investigated the incidence of VTE in OPAT settings (PROSPERO CRD42022381523). MEDLINE, CINAHL, EMCARE, EMBASE, Cochrane Library and grey literature were searched from earliest records to 18 January 2023. Eligible were primary studies reporting non-catheter-related or catheter-related thromboembolic (CRT) events in adults who received parenteral antibiotics in home or outpatient settings. In all, 43 studies involving 23,432 patient-episodes were reviewed. Four studies reported non-catheter related VTE while 39 included CRT. Based on generalised linear mixed-effects models, pooled risk estimates of non-catheter-related VTE and CRT were 0.2% (95% confidence interval [CI], 0.0 – 0.7%) and 1.1% (95% CI, 0.8 – 1.5%; prediction interval [PI], 0.2 – 5.4%), respectively. Heterogeneity was largely attributed to risk of bias by meta-regression (R^2 = 21%). Excluding high-risk studies, CRT risk was 0.8% (95% CI, 0.5 - 1.2%; PI, 0.1 - 4.5%). From 25 studies, pooled CRT rate per 1,000 catheter-days was 0.37 (95% CI, 0.25 – 0.55; PI, 0.08 – 1.64). Our findings do not support universal thromboprophylaxis nor routine use of inpatient VTE risk assessment model in the OPAT setting. However, high index of suspicion should be maintained, especially for patients with known risk factors for VTE. An optimised protocol of OPAT-specific VTE risk assessment should be sought.

KEYWORDS:

Complications; deep vein thrombosis; outpatient parenteral antimicrobial therapy; risk assessment; systematic review; thromboembolism; vascular access device

1. Introduction

Outpatient parenteral antimicrobial therapy (OPAT) programmes are widely used to administer intravenous (IV) antibiotics via vascular access device to facilitate early hospital discharge and admission avoidance of patients with infection. The effectiveness and safety of OPAT have been well documented [1-3]. Despite its benefits, patients receiving OPAT remain at risk of adverse events, including antibiotic-related and vascular access-related complications, which could result in unplanned hospital readmissions [4,5]. Venous thromboembolism (VTE) is a common complication of intravascular access devices, and is associated with interruption of antimicrobial therapy, unplanned readmission, increased healthcare costs, post-thrombotic syndrome, and pulmonary embolism (PE) [6,7]. The potential risk of VTE in OPAT is further increased by the presence of infection and restricted mobility [8]. VTE prophylaxis is an established standard of care for hospitalised patients after individualised risk assessment [9]. Appropriate thromboprophylaxis in at-risk hospitalised patients has been shown to reduce risk of VTE and related mortality [10]. However, the risk of VTE in OPAT is not fully understood and the optimal strategy for thromboprophylaxis for OPAT patients has not been established [11].

To guide strategy for optimal thromboprophylaxis in OPAT, this systematic review aims to examine the incidence of VTE in adult patients with infection treated with IV antimicrobials in home and outpatient settings.

2. Material and methods

The protocol for this systematic review was registered with the International Prospective Register of Systematic Reviews – PROSPERO (CRD42022381523) and complies with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist (Supplementary Table A.1) [12].

2.1. Search strategy and Information sources

The search strategy and source of evidence were developed after an initial review of existing literature. In this systematic review, a three-step search strategy was utilised. An initial limited search of MEDLINE (PubMed) and CINAHL was undertaken followed by an analysis of the text words contained in the titles and abstracts, and of the index terms used to describe the articles. A second search using all identified keywords and index terms was then conducted across CINAHL, EMBASE (Ovid), Ovid Emcare, MEDLINE (PubMed) and the Cochrane Library. The reference lists of all identified articles were then searched for additional sources.

Supplementary searches of clinical trial registries, Web of Science Conference Proceedings, Google/Google Scholar and the websites of the British Infection Association, European Society of Clinical Microbiology and Infectious Diseases, and Infectious Diseases Society of America were conducted to identify relevant unpublished work and grey literature. The search terms were generated based on the two main key terms (i.e., VTE and OPAT) and their corresponding alternative terms. The full search strategy is available in the Supplementary Table A.2. The search was not restricted by date of publication but was limited to studies published in English. The last electronic search was undertaken on 18 January 2023.

2.2. Eligibility criteria

Eligibility criteria were based on the PICO framework (population, intervention, comparator, and outcome) [13]. Studies were eligible if they reported catheter-related thromboembolism (CRT) and/or non-catheter-related VTE (outcome) in adult patients (>16 years old) with infection (population) who received parenteral antibiotics in home or outpatient settings (intervention). Studies of any research design were considered (with the exception of commentaries, editorials, reviews and guidelines). Studies which did not allow for calculation of incidence rate of VTE were excluded (Supplementary Table A.3).

Due to limited studies on non-catheter-related VTE in OPAT, we considered conference abstracts as recommended by Scherer et al [14]. Scherer et al suggested that conference abstracts should be considered in systematic reviews if available evidence is sparse or conflicting. Attempts were made to contact the authors of the abstracts to obtain further information on study methods and results. Conference abstracts meeting our eligibility criteria were included in this systematic review if there were no full-length publications or no response from the author.

2.3. Study selection and data extraction

All publications identified by the searches were imported into EndNote reference management software. After removing duplicate records, all identified articles were screened independently against the eligibility criteria by two reviewers (OCD and JC). Disagreements were resolved by consensus or with a third reviewer (EIK). Data were extracted independently from retrieved studies by all reviewers (OCD, JC, EIK) using a standardised and piloted data extraction spreadsheet. Extracted data included citation details (first author, year and type of publication), location, study purpose, design, sample size, number of CRT and non-catheter-related thromboembolic events, duration of follow-up and main findings. Any discrepancies in data extraction were discussed and resolved.

2.4. *Quality assessment*

Mixed Methods Appraisal Tool (MMAT) version 2018 was used to access the methodological quality of the included studies [15]. Quality appraisal was independently performed by two reviewers (OCD and JC). Any disagreement was resolved by discussion between the authors, and no studies were excluded based on the results of the evaluation. The developers of MMAT discourage the calculation of an overall numerical score, and exclusion of studies with low methodological quality [16]. Based on MMAT results, we assessed separately the risks of selection bias and information bias and produced a classification of overall risk as low, moderate or high as shown in Supplementary Table A.4. We used the latter to examine heterogeneity related to risk of bias in meta-regression and subgroup analyses.

2.5. *Meta-analysis*

The primary study outcome was incidence of CRT and non-catheter-related VTE. We estimated population-averaged incidence proportions pooled over the studies using a random intercept logistic regression model with maximum likelihood estimation [17]. The model assumed a Binomial distribution for the observed number of VTE cases in each study and a normal distribution for the random effects following the logit transformation. This approach correctly incorporates studies reporting zero cases and maintains confidence limits of pooled proportions within the zero to one range. The resulting confidence interval (CI) estimates the expected (average) VTE risk of all possible studies.

Higgin-Thompson's I^2 statistic was used as a summary index of the amount of variability of VTE incidence across studies that cannot be attributed to sampling error. Because I^2 is usually high and may not be discriminative for prevalence or incidence data [18], we additionally reported between-study variance (τ^2) with respective 95% prediction interval (PI). The PI describes the range of VTE risks that can be expected in new studies [19]. We constructed a forest plot to illustrate the distribution of VTE incidence across the studies along with 95% CIs calculated by Wilson's score method. To examine potential sources of variation in VTE incidence among the studies, we conducted multivariable meta-regression analysis with the Binomial-Normal mixed-effects model. Adjusted odds ratios (aORs) with respective 95% CI summarised the strength and direction of associations between study-level covariates and VTE incidence. For each covariate, a covariate-specific R^2 was calculated as the portion of between-study variance that was reduced after the inclusion of that covariate in the model (in the presence of all other variables). Moreover, for each covariate level we calculated pooled estimates of VTE incidence based on univariate subgroup analysis.

Candidate covariates for the regression analysis were decided a priori in our study protocol [20]. The following variables were examined: publication year, geographical location (WHO region), study design, and risk of bias (classified as either low-to-moderate or high).

Leave-one-out sensitivity analysis was carried out to assess the robustness of pooled estimates of VTE incidence against excessively influential studies. To address time-dependent confounding due to studies recording VTE incidence over different risk periods, we sought studies reporting OPAT duration statistics, calculated incidence density rates (expressed as number of events per 1,000 catheter-days) and estimated population-averaged incidence rates based on a Poisson-Normal mixed-effects model. All analyses were carried out in STATA (Version 17; Statcorp, College Station, TX, USA).

3. Results

3.1. Selection results and characteristics of the studies

Our initial electronic search yielded 18,436 different publications, of which 39 met the eligibility criteria. An additional four articles were identified through hand-search of bibliographies and other sources. Hence, a total of 43 publications (two conference abstracts [21,22], and 41 full-length articles [4,7,23-61]) were included in our review (Fig. 1). Supplementary Table A.5 shows the details of the reviewed studies. The studies were published between 2001 and 2023; and were carried out in the United States (n = 21) [25, 27, 32-34,36,37,40,42-47,50,53-56,58,59], United Kingdom (n = 6) [21,22,24,28,49,60], Australia (n = 6) [7,29,48,51,52,57], New Zealand (n = 3) [30,31,61], Switzerland (n = 3) [26,37,39], Germany (n = 1) [23], Canada (n = 1) [35], Netherlands (n = 1) [4], and Japan (n = 1) [41]. We did not find any studies conducted in low-income countries. The period under study ranged from 6 months [17,33,36] to 13 years [49]. Study sample sizes ranged from 11 to 4160 [23,29]. Overall, the reviewed studies included 23,432 (mean 545; median, 231) patient-episodes, of whom 22,292 (mean 572; median, 247) and 1140 (mean 285; median, 154) were enrolled in studies that explored CRT and non-catheter-related thromboembolic events respectively.

3.2. Quality appraisal

An overview of the quality appraisal is provided in Supplementary Tables A.6 and A.7. 15 (35%) studies were categorised as quantitative non-randomised studies [4,7,25,31,32,34,37,42-44,49,52-54,56], and 28 (65%) as quantitative descriptive studies [21-24,26-30,33,35,36,38-41,45-51,55,57-61]. There were no qualitative

nor quantitative randomised controlled trials (RCTs). Using the MMAT tool, two studies [22,26] had one 'Yes' answer out of five criteria (weakest), while the strongest one [4] had five 'Yes' answers. Overall, six (14%) studies were assessed as having low risk of bias, 22 (51%) moderate, and 15 (35%) high risk of bias (Supplementary Table A.7). Inadequate information in the conference articles did not allow the rating questions to be adequately answered. Key quality issues were related to nonresponse bias, accounting for confounders, and appropriateness of the statistical analysis.

3.3. Incidence of VTE

Four studies (two full-length articles [24,52], and two conference abstracts [21,22]) examined the risk of non-catheter-related VTE in OPAT. Barr et al. carried out a retrospective review over a 3-year period of 780 OPAT episodes who did not receive thromboprophylaxis and reported two cases of proximal lower limb deep vein thrombosis (DVT) within 90 days of OPAT, giving a VTE incidence rate of 0.26% (95% CI, 0.03 – 0.92%) [24]. Kenyon et al. reported no VTE within 4 weeks of OPAT in their cohort of 94 patients over 40 years of age with cellulitis and who had no VTE prophylaxis [22]. Another study also reported zero incidence of VTE among 214 patient episodes (who had no thromboprophylaxis) within 90 days of OPAT [21]. Ong et al compared the outcomes of patients with cellulitis who received IV therapy in a Hospital in the Home (HITH) programme with those treated in the hospital. They recorded one case of PE in the hospital group but no VTE (PE/DVT) in the HITH group [52]. Pooling data from the four studies, the estimated incidence of non-catheter-related VTE was 0.2% (95% CI, 0.0 – 0.7%) – Table 1. Heterogeneity statistics could not reliably be estimated due to limited sample sizes, but heterogeneity should be considered low as the studies consistently reported near zero events of non-catheter-related VTE.

CRT events were more commonly reported than were non-catheter-related VTE. The incidence risk of CRT ranged from 0% to 7.7% among the 39 reviewed studies [4,7,23,25-51,53-61]. Some studies also reported the incidence of CRT in events per OPAT/IV catheter days [7,29,34,36,42,43,55]. In these studies, the incidence rate ranged between 0 and 0.9 events per 1000 OPAT/IV catheter days. Only three studies directly assessed risk factors for CRT in the OPAT setting [7,25,32]. In other studies, CRTs were reported as an OPAT complication. A case-control study by Ingram et al. found malposition of catheter tip and complicated catheter insertion as risk factors for thrombosis [7]. Another study identified younger age, history of DVT, discharge to a skilled-nursing facility and therapy with amphotericin B as risk factors for peripherally inserted central catheter (PICC)-associated venous thrombosis [32]. Batayneh et al [25] did not identify a risk factor for PICC-related DVT among their cohorts but observed that patients with diabetic mellitus were

less likely to develop DVTs. The reason for this finding is unclear and needs further clarification. All but one studies differentiated between catheter-related superficial and deep vein thrombosis. Chemaly et al. [32] reported that 44% of upper extremity venous thromboses in their cohort were superficial but found no significant difference in mean time to diagnosis between deep and superficial thromboses.

Using the Binomial-Normal mixed-effects model, the estimated population-averaged risk of CRT was 1.1% (95% CI, 0.8 – 1.5%). However, accounting for heterogeneity, the 95% PI indicated that CRT incidence in future studies can be expected to range between 0.2% and 5.4%, pointing out considerable predictive uncertainty (Fig. 2). As seen in Table 2, multivariable meta-regression analysis showed no significant variation of CRT incidence of in relation to year of study, region, or study design. However, risk of bias was a main driver of heterogeneity, explaining 21% of the between-study variance. Studies with high risk of bias had significantly greater incidence of CRT than studies classified as low or moderate risk of bias (adjusted odds ratio, 2.48; 95% CI, 1.20 - 5.14; p = 0.019). Excluding the high-risk studies, estimated average risk of CRT was 0.8% (95% CI, 0.5 - 1.2%; 95% PI, 0.1 - 4.5%). Leave-one-out sensitivity analysis did not identify excessively influential (outlier) studies (Supplementary Fig. A.1).

We retrieved data on follow-up OPAT/IV catheter-days from 25 studies, which reported 169 CRT events over 431,911 catheter-days in total. Based on the Poisson-Normal mixed-effects model, the estimated population-averaged incidence rate of CRT was 0.37 events (95% CI, 0.25 – 0.55; PI, 0.08 – 1.64) per 1,000 catheter-days. Fig. 3 presents the respective forest plot. Leave-one-out sensitivity analysis did not identify outlier studies (Supplementary Fig. A.2). Meta-regression analysis of the time-adjusted incidence density rates produced compatible results as those from the previous analysis of cumulative incidence proportions (Supplementary Table A.8).

4. Discussion

The risk of VTE in hospitalised patients has been stratified into very low (< 0.5%), low (1.5%), moderate (3%) and high (6%) [62]. However, VTE risk in OPAT is not entirely clear. We present a systematic review of the current literature to establish the incidence of VTE in OPAT. The comprehensive analysis revealed a low incidence of thromboembolic events among patients who received OPAT. The pooled estimate for non-catheter-related VTE (0.2%) in our study is significantly lower than reported hospital-associated VTE

incidence proportions (1.0% - 1.3%) among hospitalised patients [63-65]; but comparable to the rates in very low-risk hospitalised medical patients for whom thromboprophylaxis is not recommended [10,62,66].

In our review, the incidence of CRT varied among the studies, depending on the type of vascular access device, indication for OPAT, antimicrobial agent administered, prior surgical intervention and underlying comorbidities. IV catheters can cause endothelial injury, vein wall inflammation and haemodynamic flow changes, which can lead to venous thrombosis [67]. The incidence risks of CRT we found in this review are lower than the reported risks (5% - 15%) for critically ill populations and hospitalised patients [6]. The relative low incidence of CRT in our review supports existing guidelines that do not recommend routine prophylactic anticoagulation nor heparin flushes to prevent catheter thrombosis [68]. Nevertheless, randomised controlled studies of the risks and benefits of pharmacological prophylaxis for CRT could provide more convincing data. To minimise the risk of CRT in the OPAT setting, careful consideration of modifiable risk factors and non-pharmacological methods such as type of vascular access device, insertion techniques, location of insertion, line care and early switch to oral therapy may be more relevant [6,69].

Most cases of hospital-associated VTE are diagnosed post-hospital discharge [63,64]. In our review, the highest incidence of VTE (7.7%) was observed in a small cohort of patients with osteomyelitis, most of whom had surgical interventions [26]. Surgery is a major risk factor for VTE [70,71]. Extending thromboprophylaxis in the outpatient period for up to 35 days post-operatively is recommended in selected patients who had major orthopaedic surgery [71]. However, extended thromboprophylaxis after hospital discharge in medical patients is not routinely recommended due to increased risk of adverse events and uncertainty about its benefit in preventing major or fatal thromboembolic events [72]. A systematic review of hospitalised medical patients found no significant effect of thromboprophylaxis on mortality but did result in more bleeding events (risk ratio, 1.34; 9 events per 1000 patients treated) [73]. Thus, the low risk of thromboembolic events found in our review indicates that extending thromboprophylaxis for all patients receiving OPAT may cause unnecessary harm. Apart from hospitalised patients, OPAT is also administered to patients with no prior hospitalisation to prevent admission.

The lower rate of non-catheter-related VTE in our review compared to hospital-associated VTE rates reported in literature [63-65] also suggests that validated risk assessment tools for VTE prevention in hospitalised patients may not be appropriate for patients receiving OPAT [24]. Hospitalised patients are often relatively less mobile and sicker than OPAT patients. Hence, there is need for an OPAT-specific VTE

risk assessment protocol based a robust analysis of the risk-benefit balance. It is possible that thrombotic events, especially CRT, are underdiagnosed in the OPAT settings due to lack of symptoms or signs to prompt a diagnostic test [32,74]. A high index of suspicion should be maintained, especially in patients with known risk factors, and appropriate diagnostic work-up should be performed. Confirmed cases should be treated promptly according to existing guidelines or standards of care [75], to minimise risk of embolisation and post-thrombotic syndrome without interrupting OPAT treatment.

The main strengths of this systematic review are its robust and iterative methodology approach to identify all relevant literature, the large sample size, and the sensitivity analysis to assess the robustness of pooled estimates of each outcome. However, there are a number of potential limitations. Since the relevant data were not consistently reported in the reviewed articles, we were unable to examine potential risk factors for VTE in OPAT (e.g., patient factors, history of VTE, catheter type and insertion techniques) [6,70]; concomitant anticoagulation in patients who had CRT; and CRT occurring after completion of OPAT. Moreover, it can be presumed that in studies with shorter mean follow-up, the number of thromboembolic events would be higher if the patients were followed for a longer duration; as most studies did not clearly report the risk period during which they sought for thromboembolic events, our pooled estimates of VTE risk are subject to confounding from this time-dependency. Nevertheless, our analysis of time-adjusted incidence density rates based on about 65% of the studies provides assurance that the risk of VTE is low even when considering duration of IV catheter use for OPAT. We were also unable to differentiate between superficial and deep vein catheter-related thrombosis; and between the incidence of VTE in patients with and those without prior hospitalisation. We included two conference abstracts due to limited publications on non-catheter-related VTE in OPAT. Conference abstracts are often not peer-reviewed and reported outcomes are often preliminary and/or based on limited analyses. However, inclusion of conference abstracts can provide a broader overview and reduce the potential impact of publication bias [14]. Non-English language articles were not assessed due to lack of language resources (i.e., professional translators), and it may have resulted in some language bias. The existing OPAT-VTE literature comprises mainly observational studies. The lack of high-quality RCTs comparing VTE in OPAT with hospital-associated VTE limits the conclusions of this review. Finally, as it is well known, the findings of meta-analyses of observational studies are limited by risk of systematic and random biases, unmeasured confounders, and high heterogeneity [76]. Our meta-regression and subgroup analyses may have mitigated some of these concerns.

4.1. Implications for research

Further research is needed to develop accurate VTE risk assessment tools appropriate for OPAT. Since a substantial proportion of hospital-associated VTE occur after hospital discharge [63,64], future studies should also differentiate between the risks of VTE in OPAT patients who had prior admission (early hospital discharge) and those who did not (admission avoidance). We encourage OPAT services (especially those in low-income countries) to publish their experiences to provide more prospective data on the risk of VTE. Decision-analytic modelling can be conducted using existing data to compare the benefits, risks and costs of thromboprophylaxis in OPAT. It would help determine the risk threshold at which prophylaxis provides optimal clinical benefit. The findings from decision-analytic modelling techniques would require validation.

4.2. Implications for practice

Our findings of low risk of VTE among patients receiving OPAT do not support universal thromboprophylaxis, nor anticoagulation and heparin flushes for routine prevention of CRT in this setting. A validated risk assessment model for inpatients identifies one bleeding event in 52 (1.9%) low-risk medical patients who had pharmacological thromboprophylaxis [66]. Thus, the risk of bleeding may outweigh the benefits of thromboprophylaxis in OPAT settings. Furthermore, in agreement with Barr et al. [24], we suggest that OPAT patients should not be routinely assessed for VTE risk using inpatient risk assessment tools due to differences in risk profile. Risk assessment models appropriate to OPAT have been proposed [22]. In the interim, as recommended by the UK OPAT guidelines [11], patients deemed at high risk of VTE during hospitalisation (e.g., post-major orthopaedic surgery) should be carefully considered for extended thromboprophylaxis during OPAT after an individualised risk-benefit assessment if the risk persists. OPAT clinicians should maintain a high index of suspicion for prompt diagnosis and appropriate treatment of VTE/catheter-related thrombosis, especially in high-risk patients.

5. Conclusions

This study gives insight into the risk of VTE in OPAT. Within its constraints, this review suggests that patient receiving OPAT are at low risk of VTE and adds to the growing evidence that OPAT is a safe alternative to inpatient care. The current findings provide a strong rationale and foundation for future studies on the optimal assessment strategy for OPAT thromboprophylaxis. In the interim, a mindful individualised approach that weighs the pros and cons of prophylaxis seems prudent.

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Competing Interests

None.

Ethics Approval

Not applicable.

Sequencing

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None.

Author Contributions

OCD: Conceptualisation, Data curation, Formal analysis Investigation, Methodology, Visualisation, Writing – original draft preparation. **JC:** Investigation, Validation, Writing – review & editing. **EIK:** Data curation, Formal analysis, Methodology, Validation, Writing – review & editing.

Ethics Approval

Not applicable.

Sequencing

690 Not applicable.

691

692 ## Consent to Participate

693 Not applicable.

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695 ## Consent to Publish

696 Not applicable.

TABLES

Table 1. Results of random-effects meta-analysis of the incidence of non-catheter-related thromboembolic events in outpatient parenteral antimicrobial therapy

Study	n/N	VTE Incidence, %	95% CI
Barr et al 2014	2/780	0.3	0.0 - 0.9
Keeley et al 2020	0/214	0.0	0.0 - 1.7
Kenyon et al 2011	0/94	0.0	0.0 - 3.8
Ong et al 2019	0/52	0.0	0.0 - 6.8
Population-averaged estimate	2/1140	0.2	0.0 - 0.7

CI, confidence interval; n/N, number of non-catheter-related thromboembolic events over the total number of patients at risk in each study; VTE, venous thromboembolism.

Table 2. Multivariable meta-regression analysis of the associations between study-level characteristics and the incidence of catheter-related venous thromboembolism in outpatient parenteral antimicrobial therapy

Study characteristic	Levels	n	CRT incidence (CI; PI), %	Adjusted OR (CI)	*P*-value	R^2
Year of publication	≤2019	22	1.3 (0.8 - 1.9; 0.3 - 6.0)	Ref.	0.942	0.0%
	≥2020	17	0.9 (0.5 - 1.4; 0.1 - 5.6)	0.98 (0.51 - 1.88)		
Region	Europe	8	0.7 (1.9 - 2.9; 1.9 - 3.0)	Ref.	0.657	6.5%
	N. America	22	1.3 (1.9 - 2.9; 1.9 - 2.9)	1.45 (0.66 - 3.16)		
	Western Pacific	9	0.9 (1.9 - 2.9; 1.9 - 3.0)	1.27 (0.52 - 3.12)		
Study design	Descriptive (single arm)	25	1.0 (0.7 - 1.4; 0.3 - 3.6)	Ref.	0.282	9.0%
	Comparative non-randomised	14	1.1 (0.6 - 2.0; 0.1 - 9.3)	1.39 (0.77 - 2.49)		
Risk of bias	Low/moderate	26	0.8 (0.5 - 1.2; 0.1 - 4.5)	Ref.	0.019	21.2%
	High	13	2.4 (1.9 - 2.9; 1.9 - 2.9)	2.48 (1.20 - 5.14)		

CI, 95% confidence interval; CRT, catheter-related venous thromboembolism; n, number of studies; OR, odds ratio; PI, 95% prediction interval.

FIGURE CAPTIONS

Fig. 1. Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) 2020 flow diagram of the systematic review process [13].

Fig. 2. Forest plot of the results of the random-effects meta-analysis of the risk of catheter-related venous thromboembolism in outpatient parenteral antimicrobial therapy (OPAT). n/N denotes the number of catheter-related thromboembolic (CRT) events over the total number of patients at risk in each study. The diamond's centre is the population-averaged CRT incidence proportion. The diamond's length and the respective grey vertical area indicate the 95% confidence interval of the pooled average estimate. The extended blue line continuing through the confidence interval and the respective bluish-grey vertical area indicate the 95% prediction interval of CRT incidence expected in new studies.
Abbreviations: CI, confidence interval; CRT, catheter-related venous thromboembolism.

Fig. 3. Forest plot of the results of the random-effects meta-analysis of the incidence density rate of catheter-related venous thromboembolism in outpatient parenteral antimicrobial therapy. n/N denotes the number of CRT cases over the total number of OPAT/IV catheter-days in each study. The diamond's centre is the population-averaged CRT incidence rate. The diamond's length and the respective grey vertical area indicate the 95% confidence interval of the pooled average estimate. The extended blue line continuing through the confidence interval and the respective bluish-grey vertical area indicate the 95% prediction interval of CRT incidence expected in new studies.
Abbreviations: CI, confidence interval; CRT, catheter-related venous thromboembolism

Figure

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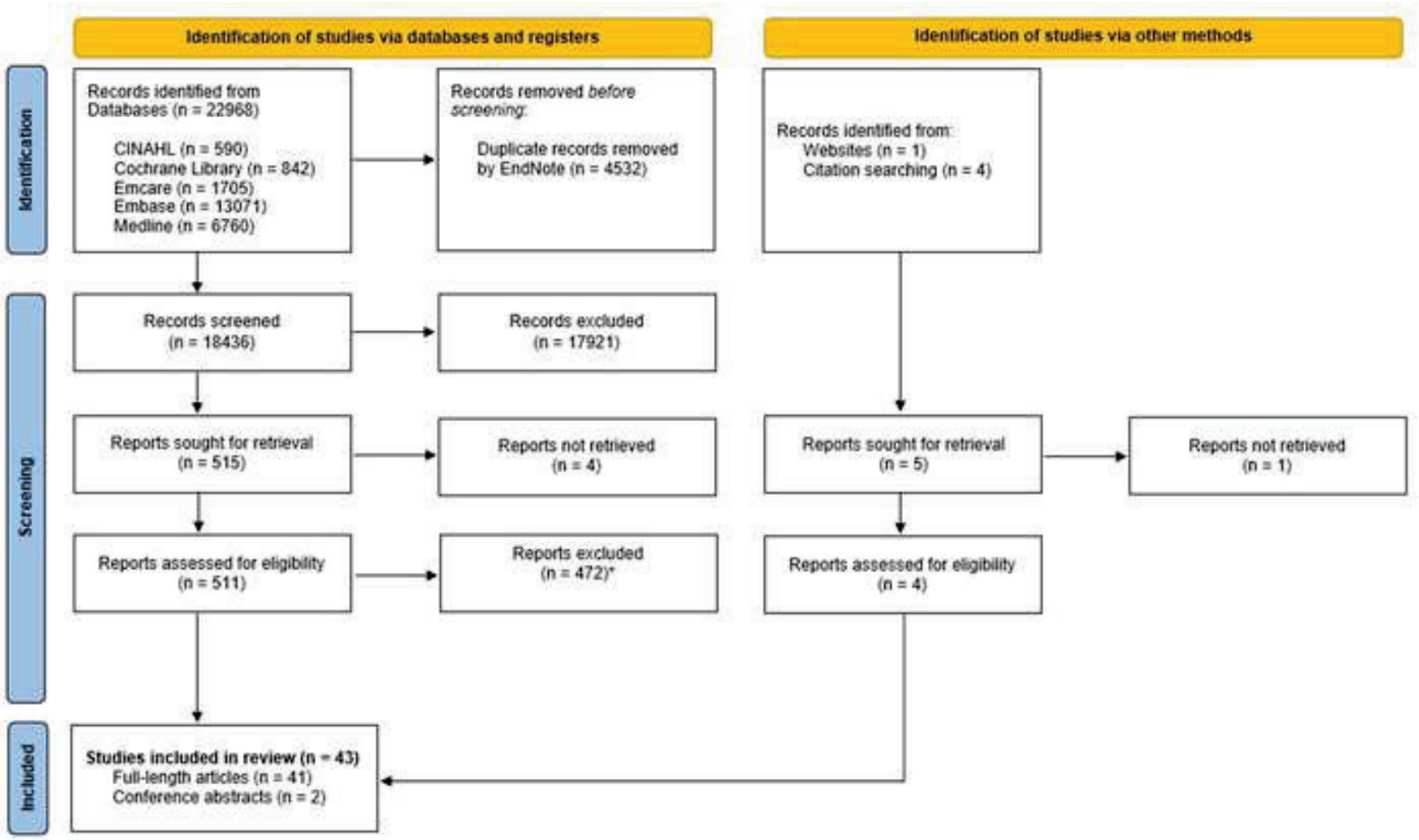

*Reasons for exclusion are stated in Supplementary Material S3.

Figure

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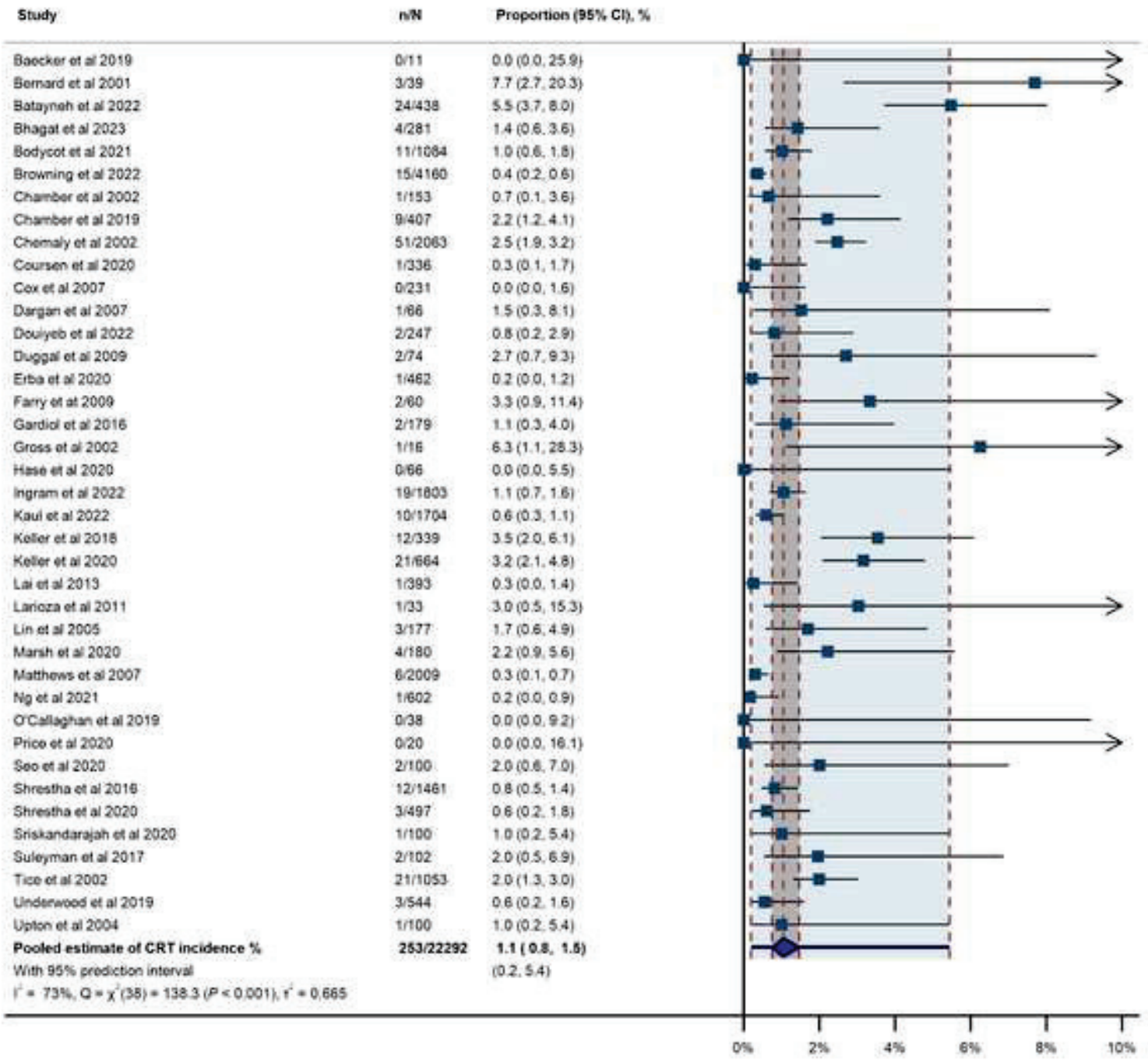

Figure

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