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## **TITLE PAGE**

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### **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

## 62 **1. Introduction**

63 Outpatient parenteral antimicrobial therapy (OPAT) programmes are widely used to administer  
64 intravenous (IV) antibiotics via vascular access device to facilitate early hospital discharge and admission  
65 avoidance of patients with infection. The effectiveness and safety of OPAT have been well documented [1-  
66 3]. Despite its benefits, patients receiving OPAT remain at risk of adverse events, including antibiotic-related  
67 and vascular access-related complications, which could result in unplanned hospital readmissions [4,5].  
68 Venous thromboembolism (VTE) is a common complication of intravascular access devices, and is  
69 associated with interruption of antimicrobial therapy, unplanned readmission, increased healthcare costs,  
70 post-thrombotic syndrome, and pulmonary embolism (PE) [6,7]. The potential risk of VTE in OPAT is further  
71 increased by the presence of infection and restricted mobility [8]. VTE prophylaxis is an established  
72 standard of care for hospitalised patients after individualised risk assessment [9]. Appropriate  
73 thromboprophylaxis in at-risk hospitalised patients has been shown to reduce risk of VTE and related  
74 mortality [10]. However, the risk of VTE in OPAT is not fully understood and the optimal strategy for  
75 thromboprophylaxis for OPAT patients has not been established [11].

76  
77 To guide strategy for optimal thromboprophylaxis in OPAT, this systematic review aims to examine the  
78 incidence of VTE in adult patients with infection treated with IV antimicrobials in home and outpatient  
79 settings.

80  
81

## 82 **2. Material and methods**

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

86

### 87 *2.1. Search strategy and Information sources*

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

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

101  
102 *2.2. Eligibility criteria*  
103 Eligibility criteria were based on the PICO framework (population, intervention, comparator, and outcome)  
104 [13]. Studies were eligible if they reported catheter-related thromboembolism (CRT) and/or non-catheter-  
105 related VTE (outcome) in adult patients (>16 years old) with infection (population) who received parenteral  
106 antibiotics in home or outpatient settings (intervention). Studies of any research design were considered  
107 (with the exception of commentaries, editorials, reviews and guidelines). Studies which did not allow for  
108 calculation of incidence rate of VTE were excluded ([Supplementary Table A.3](#)).

109  
110 Due to limited studies on non-catheter-related VTE in OPAT, we considered conference abstracts as  
111 recommended by Scherer et al [14]. Scherer et al suggested that conference abstracts should be considered  
112 in systematic reviews if available evidence is sparse or conflicting. Attempts were made to contact the  
113 authors of the abstracts to obtain further information on study methods and results. Conference abstracts  
114 meeting our eligibility criteria were included in this systematic review if there were no full-length  
115 publications or no response from the author.

116  
117 *2.3. Study selection and data extraction*  
118 All publications identified by the searches were imported into EndNote reference management software.  
119 After removing duplicate records, all identified articles were screened independently against the eligibility  
120 criteria by two reviewers (OCD and JC). Disagreements were resolved by consensus or with a third reviewer  
121 (EIK). Data were extracted independently from retrieved studies by all reviewers (OCD, JC, EIK) using a  
122 standardised and piloted data extraction spreadsheet. Extracted data included citation details (first author,  
123 year and type of publication), location, study purpose, design, sample size, number of CRT and non-  
124 catheter-related thromboembolic events, duration of follow-up and main findings. Any discrepancies in  
125 data extraction were discussed and resolved.

126  
127 *2.4. Quality assessment*  
128 Mixed Methods Appraisal Tool (MMAT) version 2018 was used to assess the methodological quality of the  
129 included studies [15]. Quality appraisal was independently performed by two reviewers (OCD and JC). Any  
130 disagreement was resolved by discussion between the authors, and no studies were excluded based on the  
131 results of the evaluation. The developers of MMAT discourage the calculation of an overall numerical score,  
132 and exclusion of studies with low methodological quality [16]. Based on MMAT results, we assessed  
133 separately the risks of selection bias and information bias and produced a classification of overall risk as  
134 low, moderate or high as shown in [Supplementary Table A.4](#). We used the latter to examine heterogeneity  
135 related to risk of bias in meta-regression and subgroup analyses.

136  
137 *2.5. Meta-analysis*  
138 The primary study outcome was incidence of CRT and non-catheter-related VTE. We estimated population-  
139 averaged incidence proportions pooled over the studies using a random intercept logistic regression model  
140 with maximum likelihood estimation [17]. The model assumed a Binomial distribution for the observed  
141 number of VTE cases in each study and a normal distribution for the random effects following the logit  
142 transformation. This approach correctly incorporates studies reporting zero cases and maintains confidence  
143 limits of pooled proportions within the zero to one range. The resulting confidence interval (CI) estimates  
144 the expected (average) VTE risk of all possible studies.

145  
146 Higgin-Thompson's  $I^2$  statistic was used as a summary index of the amount of variability of VTE incidence  
147 across studies that cannot be attributed to sampling error. Because  $I^2$  is usually high and may not be  
148 discriminative for prevalence or incidence data [18], we additionally reported between-study variance ( $\tau^2$ )  
149 with respective 95% prediction interval (PI). The PI describes the range of VTE risks that can be expected in  
150 new studies [19]. We constructed a forest plot to illustrate the distribution of VTE incidence across the  
151 studies along with 95% CIs calculated by Wilson's score method. To examine potential sources of variation  
152 in VTE incidence among the studies, we conducted multivariable meta-regression analysis with the  
153 Binomial-Normal mixed-effects model. Adjusted odds ratios (aORs) with respective 95% CI summarised the  
154 strength and direction of associations between study-level covariates and VTE incidence. For each  
155 covariate, a covariate-specific  $R^2$  was calculated as the portion of between-study variance that was reduced  
156 after the inclusion of that covariate in the model (in the presence of all other variables). Moreover, for each  
157 covariate level we calculated pooled estimates of VTE incidence based on univariate subgroup analysis.

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

161  
162 Leave-one-out sensitivity analysis was carried out to assess the robustness of pooled estimates of VTE  
163 incidence against excessively influential studies. To address time-dependent confounding due to studies  
164 recording VTE incidence over different risk periods, we sought studies reporting OPAT duration statistics,  
165 calculated incidence density rates (expressed as number of events per 1,000 catheter-days) and estimated  
166 population-averaged incidence rates based on a Poisson-Normal mixed-effects model. All analyses were  
167 carried out in STATA (Version 17; Statcorp, College Station, TX, USA).

168

169

### 170 **3. Results**

#### 171 *3.1. Selection results and characteristics of the studies*

172 Our initial electronic search yielded 18,436 different publications, of which 39 met the eligibility criteria. An  
173 additional four articles were identified through hand-search of bibliographies and other sources. Hence, a  
174 total of 43 publications (two conference abstracts [21,22], and 41 full-length articles [4,7,23-61]) were  
175 included in our review (Fig. 1). [Supplementary Table A.5](#) shows the details of the reviewed studies. The  
176 studies were published between 2001 and 2023; and were carried out in the United States ( $n = 21$ ) [25, 27,  
177 32-34,36,37,40,42-47,50,53-56,58,59], United Kingdom ( $n = 6$ ) [21,22,24,28,49,60], Australia ( $n = 6$ )  
178 [7,29,48,51,52,57], New Zealand ( $n = 3$ ) [30,31,61], Switzerland ( $n = 3$ ) [26,37,39], Germany ( $n = 1$ ) [23],  
179 Canada ( $n = 1$ ) [35], Netherlands ( $n = 1$ ) [4], and Japan ( $n = 1$ ) [41]. We did not find any studies conducted  
180 in low-income countries. The period under study ranged from 6 months [17,33,36] to 13 years [49]. Study  
181 sample sizes ranged from 11 to 4160 [23,29]. Overall, the reviewed studies included 23,432 (mean 545;  
182 median, 231) patient-episodes, of whom 22,292 (mean 572; median, 247) and 1140 (mean 285; median,  
183 154) were enrolled in studies that explored CRT and non-catheter-related thromboembolic events  
184 respectively.

185

#### 186 *3.2. Quality appraisal*

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

190 nor quantitative randomised controlled trials (RCTs). Using the MMAT tool, two studies [22,26] had one  
191 'Yes' answer out of five criteria (weakest), while the strongest one [4] had five 'Yes' answers. Overall, six  
192 (14%) studies were assessed as having low risk of bias, 22 (51%) moderate, and 15 (35%) high risk of bias  
193 (Supplementary Table A.7). Inadequate information in the conference articles did not allow the rating  
194 questions to be adequately answered. Key quality issues were related to nonresponse bias, accounting for  
195 confounders, and appropriateness of the statistical analysis.

196

### 197 3.3. Incidence of VTE

198 Four studies (two full-length articles [24,52], and two conference abstracts [21,22]) examined the risk of  
199 non-catheter-related VTE in OPAT. Barr et al. carried out a retrospective review over a 3-year period of 780  
200 OPAT episodes who did not receive thromboprophylaxis and reported two cases of proximal lower limb  
201 deep vein thrombosis (DVT) within 90 days of OPAT, giving a VTE incidence rate of 0.26% (95% CI, 0.03 –  
202 0.92%) [24]. Kenyon et al. reported no VTE within 4 weeks of OPAT in their cohort of 94 patients over 40  
203 years of age with cellulitis and who had no VTE prophylaxis [22]. Another study also reported zero incidence  
204 of VTE among 214 patient episodes (who had no thromboprophylaxis) within 90 days of OPAT [21]. Ong et  
205 al compared the outcomes of patients with cellulitis who received IV therapy in a Hospital in the Home  
206 (HITH) programme with those treated in the hospital. They recorded one case of PE in the hospital group  
207 but no VTE (PE/DVT) in the HITH group [52]. Pooling data from the four studies, the estimated incidence of  
208 non-catheter-related VTE was 0.2% (95% CI, 0.0 – 0.7%) – Table 1. Heterogeneity statistics could not reliably  
209 be estimated due to limited sample sizes, but heterogeneity should be considered low as the studies  
210 consistently reported near zero events of non-catheter-related VTE.

211

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

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

226  
227 Using the Binomial-Normal mixed-effects model, the estimated population-averaged risk of CRT was 1.1%  
228 (95% CI, 0.8 – 1.5%). However, accounting for heterogeneity, the 95% PI indicated that CRT incidence in  
229 future studies can be expected to range between 0.2% and 5.4%, pointing out considerable predictive  
230 uncertainty (Fig. 2). As seen in Table 2, multivariable meta-regression analysis showed no significant  
231 variation of CRT incidence of in relation to year of study, region, or study design. However, risk of bias was  
232 a main driver of heterogeneity, explaining 21% of the between-study variance. Studies with high risk of bias  
233 had significantly greater incidence of CRT than studies classified as low or moderate risk of bias (adjusted  
234 odds ratio, 2.48; 95% CI, 1.20 - 5.14; p = 0.019). Excluding the high-risk studies, estimated average risk of  
235 CRT was 0.8% (95% CI, 0.5 - 1.2%; 95% PI, 0.1 - 4.5%). Leave-one-out sensitivity analysis did not identify  
236 excessively influential (outlier) studies (Supplementary Fig. A.1).

237  
238 We retrieved data on follow-up OPAT/IV catheter-days from 25 studies, which reported 169 CRT events  
239 over 431,911 catheter-days in total. Based on the Poisson-Normal mixed-effects model, the estimated  
240 population-averaged incidence rate of CRT was 0.37 events (95% CI, 0.25 – 0.55; PI, 0.08 – 1.64) per 1,000  
241 catheter-days. Fig. 3 presents the respective forest plot. Leave-one-out sensitivity analysis did not identify  
242 outlier studies (Supplementary Fig. A.2). Meta-regression analysis of the time-adjusted incidence density  
243 rates produced compatible results as those from the previous analysis of cumulative incidence proportions  
244 (Supplementary Table A.8).

245  
246

#### 247 **4. Discussion**

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

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

255  
256 In our review, the incidence of CRT varied among the studies, depending on the type of vascular access  
257 device, indication for OPAT, antimicrobial agent administered, prior surgical intervention and underlying  
258 comorbidities. IV catheters can cause endothelial injury, vein wall inflammation and haemodynamic flow  
259 changes, which can lead to venous thrombosis [67]. The incidence risks of CRT we found in this review are  
260 lower than the reported risks (5% - 15%) for critically ill populations and hospitalised patients [6]. The  
261 relative low incidence of CRT in our review supports existing guidelines that do not recommend routine  
262 prophylactic anticoagulation nor heparin flushes to prevent catheter thrombosis [68]. Nevertheless,  
263 randomised controlled studies of the risks and benefits of pharmacological prophylaxis for CRT could  
264 provide more convincing data. To minimise the risk of CRT in the OPAT setting, careful consideration of  
265 modifiable risk factors and non-pharmacological methods such as type of vascular access device, insertion  
266 techniques, location of insertion, line care and early switch to oral therapy may be more relevant [6,69].

267  
268 Most cases of hospital-associated VTE are diagnosed post-hospital discharge [63,64]. In our review, the  
269 highest incidence of VTE (7.7%) was observed in a small cohort of patients with osteomyelitis, most of  
270 whom had surgical interventions [26]. Surgery is a major risk factor for VTE [70,71]. Extending  
271 thromboprophylaxis in the outpatient period for up to 35 days post-operatively is recommended in selected  
272 patients who had major orthopaedic surgery [71]. However, extended thromboprophylaxis after hospital  
273 discharge in medical patients is not routinely recommended due to increased risk of adverse events and  
274 uncertainty about its benefit in preventing major or fatal thromboembolic events [72]. A systematic review  
275 of hospitalised medical patients found no significant effect of thromboprophylaxis on mortality but did  
276 result in more bleeding events (risk ratio, 1.34; 9 events per 1000 patients treated) [73]. Thus, the low risk  
277 of thromboembolic events found in our review indicates that extending thromboprophylaxis for all patients  
278 receiving OPAT may cause unnecessary harm. Apart from hospitalised patients, OPAT is also administered  
279 to patients with no prior hospitalisation to prevent admission.

280  
281 The lower rate of non-catheter-related VTE in our review compared to hospital-associated VTE rates  
282 reported in literature [63-65] also suggests that validated risk assessment tools for VTE prevention in  
283 hospitalised patients may not be appropriate for patients receiving OPAT [24]. Hospitalised patients are  
284 often relatively less mobile and sicker than OPAT patients. Hence, there is need for an OPAT-specific VTE

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

291  
292 The main strengths of this systematic review are its robust and iterative methodology approach to identify  
293 all relevant literature, the large sample size, and the sensitivity analysis to assess the robustness of pooled  
294 estimates of each outcome. However, there are a number of potential limitations. Since the relevant data  
295 were not consistently reported in the reviewed articles, we were unable to examine potential risk factors  
296 for VTE in OPAT (e.g., patient factors, history of VTE, catheter type and insertion techniques) [6,70];  
297 concomitant anticoagulation in patients who had CRT; and CRT occurring after completion of OPAT.  
298 Moreover, it can be presumed that in studies with shorter mean follow-up, the number of thromboembolic  
299 events would be higher if the patients were followed for a longer duration; as most studies did not clearly  
300 report the risk period during which they sought for thromboembolic events, our pooled estimates of VTE  
301 risk are subject to confounding from this time-dependency. Nevertheless, our analysis of time-adjusted  
302 incidence density rates based on about 65% of the studies provides assurance that the risk of VTE is low  
303 even when considering duration of IV catheter use for OPAT. We were also unable to differentiate between  
304 superficial and deep vein catheter-related thrombosis; and between the incidence of VTE in patients with  
305 and those without prior hospitalisation. We included two conference abstracts due to limited publications  
306 on non-catheter-related VTE in OPAT. Conference abstracts are often not peer-reviewed and reported  
307 outcomes are often preliminary and/or based on limited analyses. However, inclusion of conference  
308 abstracts can provide a broader overview and reduce the potential impact of publication bias [14]. Non-  
309 English language articles were not assessed due to lack of language resources (i.e., professional translators),  
310 and it may have resulted in some language bias. The existing OPAT-VTE literature comprises mainly  
311 observational studies. The lack of high-quality RCTs comparing VTE in OPAT with hospital-associated VTE  
312 limits the conclusions of this review. Finally, as it is well known, the findings of meta-analyses of  
313 observational studies are limited by risk of systematic and random biases, unmeasured confounders, and  
314 high heterogeneity [76]. Our meta-regression and subgroup analyses may have mitigated some of these  
315 concerns.

316

317 *4.1. Implications for research*

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

326

327 *4.2. Implications for practice*

328 Our findings of low risk of VTE among patients receiving OPAT do not support universal  
329 thromboprophylaxis, nor anticoagulation and heparin flushes for routine prevention of CRT in this setting.  
330 A validated risk assessment model for inpatients identifies one bleeding event in 52 (1.9%) low-risk medical  
331 patients who had pharmacological thromboprophylaxis [66]. Thus, the risk of bleeding may outweigh the  
332 benefits of thromboprophylaxis in OPAT settings. Furthermore, in agreement with Barr et al. [24], we  
333 suggest that OPAT patients should not be routinely assessed for VTE risk using inpatient risk assessment  
334 tools due to differences in risk profile. Risk assessment models appropriate to OPAT have been proposed  
335 [22]. In the interim, as recommended by the UK OPAT guidelines [11], patients deemed at high risk of VTE  
336 during hospitalisation (e.g., post-major orthopaedic surgery) should be carefully considered for extended  
337 thromboprophylaxis during OPAT after an individualised risk-benefit assessment if the risk persists. OPAT  
338 clinicians should maintain a high index of suspicion for prompt diagnosis and appropriate treatment of  
339 VTE/catheter-related thrombosis, especially in high-risk patients.

340

341

342 **5. Conclusions**

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

348

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352

353 **Competing Interests**

354 None.

355

356 **Ethics Approval**

357 Not applicable.

358

359 **Sequencing**

360 Not applicable.

361

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673

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677

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679 None.

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### 681 **Author Contributions**

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

685

### 686 **Ethics Approval**

687 Not applicable.

688

### 689 **Sequencing**

690 Not applicable.

691

692 **Consent to Participate**

693 Not applicable.

694

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

<b>Study</b>	<b>n/N</b>	<b>VTE Incidence, %</b>	<b>95% CI</b>
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 <sup>2</sup>
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)		

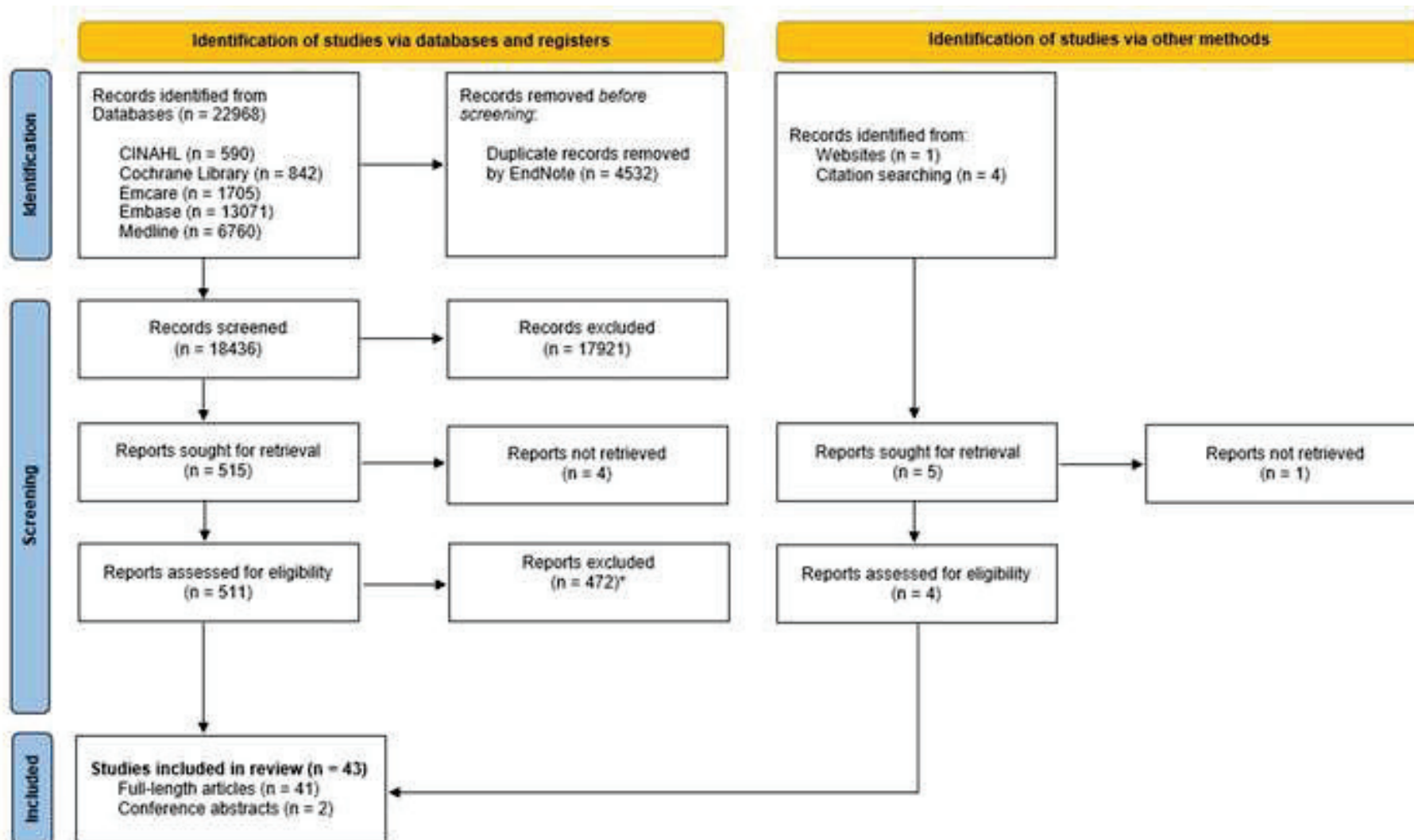
CI, 95% confidence interval; CRT, catheter-related venous thromboembolism; n, number of studies; OR, odds ratio; PI, 95% prediction interval.

## **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



\*Reasons for exclusion are stated in Supplementary Material S3.

