Risk of venous thromboembolism associated with peripherally inserted central catheters: a systematic review and meta-analysis

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Summary

Background Peripherally inserted central catheters (PICCs) are associated with an increased risk of venous thromboembolism. However, the size of this risk relative to that associated with other central venous catheters (CVCs) is unknown. We did a systematic review and meta-analysis to compare the risk of venous thromboembolism associated with PICCs versus that associated with other CVCs.

Methods We searched several databases, including Medline, Embase, Biosis, Cochrane Central Register of Controlled Trials, Conference Papers Index, and Scopus. Additional studies were identified through hand searches of bibliographies and internet searches, and we contacted study authors to obtain unpublished data. All human studies published in full text, abstract, or poster form were eligible for inclusion. All studies were of adult patients aged at least 18 years who underwent insertion of a PICC. Studies were assessed with the Newcastle–Ottawa risk of bias scale. In studies without a comparison group, the pooled frequency of venous thromboembolism was calculated for patients receiving PICCs. In studies comparing PICCs with other CVCs, summary odds ratios (ORs) were calculated with a random effects meta-analysis.

Findings Of the 533 citations identified, 64 studies (12 with a comparison group and 52 without) including 29 503 patients met the eligibility criteria. In the non-comparison studies, the weighted frequency of PICC-related deep vein thrombosis was highest in patients who were critically ill (13·91%, 95% CI 7·68–20·14) and those with cancer (6·67%, 4·69–8·64). Our meta-analysis of 11 studies comparing the risk of deep vein thrombosis related to PICCs with that related to CVCs showed that PICCs were associated with an increased risk of deep vein thrombosis (OR 2·55, 1·54–4·23, p<0·0001) but not pulmonary embolism (no events). With the baseline PICC-related deep vein thrombosis rate of 2·7% and pooled OR of 2·55, the number needed to harm relative to CVCs was 26 (95% CI 13–71).

Interpretation PICCs are associated with a higher risk of deep vein thrombosis than are CVCs, especially in patients who are critically ill or those with a malignancy. The decision to insert PICCs should be guided by weighing of the risk of thrombosis against the benefit provided by these devices.

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Introduction

The use of peripherally inserted central catheters (PICCs) in modern medical practice has increased rapidly for several reasons, including ease of insertion, many uses (eg, drug administration and venous access), perceived safety, and cost-effectiveness compared with other central venous catheters (CVCs).[1,2] Furthermore, the proliferation of nurse-led PICC teams has made their use convenient and accessible in many settings.[3,4]

Despite these benefits, PICCs are associated with deep vein thrombosis of the arm and pulmonary embolism.[5,6] These complications, which are often called venous thromboembolisms, are important because they not only complicate and interrupt treatment, but also increase cost, morbidity, and mortality.[7] Despite this effect, the burden and risk of PICC-related venous thromboembolism is uncertain and clinicians have scarce evidence on which to base choice of CVC. Existing data report wide estimates of this adverse outcome, ranging from less than 1% to as high as 38·5%, dependent on the population studied, method of diagnosis, and use of prophylaxis measures.[8,9] Furthermore, the precise incidence and risk of PICC-related venous thromboembolism relative to that of other CVCs is unknown. An understanding of this risk in the context of growing PICC use is an important cost and patient safety question. Up to now, no systematic review has been done to investigate these questions. Therefore, we did a systematic review and meta-analysis of the scientific literature to understand and quantitate this risk. Our key objectives were to define the frequency of PICC-related venous thromboembolism in specific populations and to compare the risk of venous thromboembolism between PICCs and CVCs.

Methods

Search strategy and selection criteria

We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) recommendations for this meta-analysis.[10] With the assistance

of a medical research librarian, we did serial literature searches for English and non-English articles (between Jan 12, 2012, and Dec 31, 2012). We searched Medline (1950–present, via Ovid), Embase (1946–present), Biosis (1926–present), the Cochrane Central Register of Controlled Trials (1960–present, via Ovid), and Evidence-Based Medicine Reviews (various coverage dates, via Ovid). We used Boolean logic with search terms including "peripherally inserted central catheter", "PICC", "deep vein thrombosis", "pulmonary embolism", and "venous thromboembolism". Controlled vocabularies (eg, Medical Subject Heading terms) were used to identify synonyms. The appendix provides a more detailed search strategy. All studies in human beings that were published in full text, abstract, or poster form were eligible for inclusion, with no restrictions on publication date, language, or status. Conference posters and abstracts were electronically searched through the Conference Papers Index provided by ProQuest (1982–present), Biosis (1926–present), and Scopus (1996–present). Ongoing clinical trials were identified from the clinicaltrials.gov website, and additional studies of interest were found through internet searches and hand searches of bibliographies.

See Online for appendix

Three authors (VC, SA, and AH) independently established study eligibility; any difference in opinion about eligibility was resolved by consensus. We included studies if they included participants 18 years of age or older; included patients with a PICC placed in the arm; and reported the development of deep vein thrombosis, pulmonary embolism, or both after PICC insertion. We excluded studies if they involved neonates or patients younger than 18 years; compared complications between different types of PICCs (eg, varying PICC gauge or lumens); reported catheter lumen thrombosis, superficial phlebitis, or thrombophlebitis but not venous thromboembolism; involved PICCs inserted into the leg; or were case reports of unusual complications.

Data extraction and validity assessment

Data were extracted from all included studies independently and in duplicate (by SA and AH) on a template adapted from the Cochrane Collaboration.[11] For all studies, we extracted the number of patients, population, number of deep vein thromboses or pulmonary embolisms or both, indication for PICC placement, whether the position of the PICC tip was ascertained after insertion, and use of pharmacological deep vein thrombosis prophylaxis, among other covariates. If any elements were missing, we contacted the study authors to obtain these data.

Included studies were divided into two categories: those reporting the incidence of PICC-related venous thromboembolism in a cohort of PICC recipients (non-comparison studies); and those in which PICCs were compared with other CVCs with respect to venous thromboembolism (comparison studies). Separate templates were created and inter-rater agreement statistics generated for abstraction of each of these distinct study types.

Assessment of bias risk

Two authors (VC and MB) assessed the risk of bias independently. Since all the included studies were non-randomised and had a cohort or case-control design, the Newcastle–Ottawa scale was used to judge study quality, as recommended by the Cochrane Collaboration.[12] This scale uses a star system to assess the quality of a study in three domains: selection of study groups; comparability of groups; and ascertainment of outcomes. Studies that received a star in every domain were judged to be of high quality.

Definition of comparison or treatment groups

Treatment groups were defined as patients who underwent PICC insertion for any indication. In studies with a comparison group, this group consisted of patients who received a CVC other than a PICC. When studies included both adults and children, we extracted only details for adult patients. Similarly, if studies included several types of CVCs, we extracted only data for PICCs.

Definition of outcomes

The primary outcome was the occurrence of venous thromboembolism (deep vein thrombosis or pulmonary embolism) after PICC insertion. We defined deep vein thrombosis as thrombosis involving the deep veins of the arm (brachial, axillary, subclavian, or internal jugular veins) detected by compression ultrasonography, venography, or CT scan. Occurrence of pulmonary embolism was based on reports of diagnosis in each study. If study results reported catheter lumen occlusion or thrombosis and not deep vein thrombosis, we contacted the study authors to find out whether data for venous thromboembolism were available. If these data were not available, the study was excluded from the analysis.[2,13–16]

Statistical analysis

Studies were analysed according to whether or not they featured a comparison group. The unit of analysis was the number of patients with venous thromboembolism. Meta-analysis was used to pool the proportion of patients with venous thromboembolism in non-comparison studies, with variance estimates generated from the enhanced arcsine transformation for data with binomial distributions.[17]

In studies with both a PICC and a comparator group, data were extracted to calculate study-specific odds ratios (ORs). Treatment effect estimates were calculated as a weighted average so that an OR greater than 1 suggested a higher risk of venous thromboembolism with PICC than with CVC. All meta-analyses were done with a random-effects model, as described by DerSimonian and Laird.[18] The empirical continuity correction, a pseudo-Bayesian

approach, was used for studies in which no events were reported in either the treatment or control groups. As described by Sweeting and colleagues,[19] this correction is based on the pooled effect size from the studies with events and is less biased than is the typical 0·5 continuity correction. Taylor series were used to generate 95% CIs for the study with non-events. We investigated heterogeneity between studies with Cochrane's *Q* statistic and the I^2 statistic and classified heterogeneity as low, moderate, or high on the basis of an I^2 statistic of 25%, 50%, or 75%, respectively, according to the method suggested by Higgins and colleagues.[20] Publication bias for studies with a comparator group was assessed with Harbord's test; p values less than 0·05 indicated publication bias.

We did subgroup analyses to establish whether patient population (patients with cancer, those in the intensive care unit, patients admitted to hospital, and mixed patient groups), approach to venous thromboembolism diagnosis (asymptomatic screening *vs* symptomatic testing), PICC tip position ascertainment, or use of pharmacological venous thromboembolism prophylaxis affected our conclusions. Venous thromboembolism prophylaxis was defined as the use of unfractionated heparin, low-molecular-weight heparin, or warfarin for any indication in more than 50% of PICC recipients within a particular study. We also compared studies published before and after 2005, because important changes such as advances in PICC technology (polyurethane compounds), insertion techniques (modified Seldinger approach), and radiographic devices (bedside ultrasound) occurred between these years.

We did several sensitivity or influence analyses to test the robustness of our findings. All data management and analyses were performed with Stata SE/MP (version 11·2). Statistical tests were two-tailed.

Role of the funding source

VC and MAMR had full access to the data. VC, SS, and SAF had final responsibility for the decision to submit for publication.

Results

561 articles and conference abstracts were retrieved by our search (figure 1). Of 543 unique citations identified by our electronic and manual searches, 67 articles met the initial inclusion criteria.[5,6,9,21–84] Because of methodological differences, three studies that began by enrolling patients with deep vein thrombosis were excluded.[6,52,58] Furthermore, one study comparing PICCs with CVCs used lines, rather than patients, as the unit of analysis.[55] This study was excluded from meta-analyses, but was included in the systematic review. Thus, 64 articles involving 29 503 patients fulfilled the eligibility criteria (figure 1).[5,9,21–51,53–57,59–84] 12 studies compared PICCs with CVCs (n=3916),[23,24,28,32,37,43,55,61,70,71,79,81] whereas 52 included patients who underwent PICC placement without a comparison group (n=25 587).[5,9,21,22,25–27,29–31,33–36,38–42,44–51,53,54,56,57,59,60,62–69,72–78,80,82–84] Eligible studies ranged in size from 13 to 4223 patients and were done in various patient populations and care settings (tables 1 and 2). 42 studies were full-length reports published in peer-reviewed journals[5,21,23–26,28,29,32,34,37,39,42–44,46–48,50,51,53–55,57,59,61,62,67,69–72,74–79,81–84] and 22 were abstracts presented at scientific meetings.[9,22,27,30,31,33,35,36,38,40,41,45,49,56,60,63–66,68,73,80]

Except for five studies that used only venography,[5,21,24,29,53] and two that used a combination of ultrasound and venography,[34,70] all studies confirmed the presence of deep vein thrombosis with ultrasonography (non-compressibility of the vein, visible thrombus, or absence of Doppler-detected flow). Although five studies screened for deep vein thrombosis in asymptomatic patients,[5,21,33,59,63] most investigators did this test only if symptoms or signs suggested thrombosis. 37 of the included 64 studies (58%) did not report whether patients were on pharmacological venous thromboembolism prophylaxis (tables 1 and 2).[5,22,24,26,27,29–32,34–36,38,40,45,46,49,51,53,54,57,60,61,64–67,70,73,75–77,79,80,82–84] Similarly, 20 of 64 studies (31%) did not report

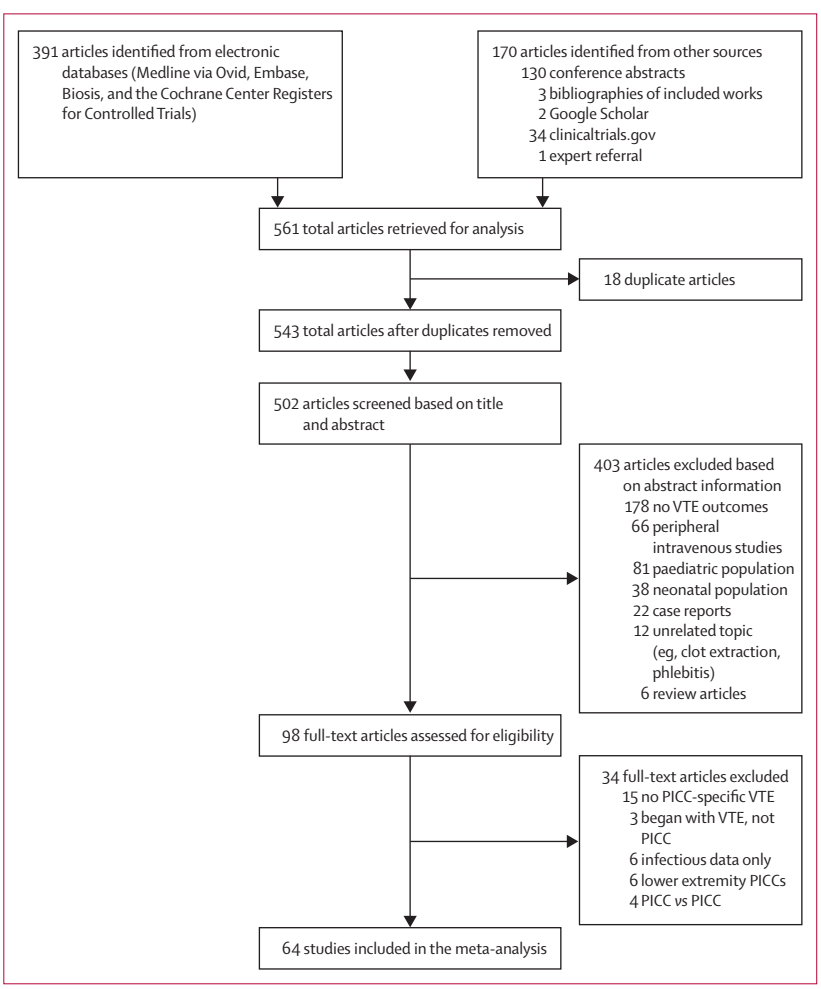

Figure 1: **Study selection**
VTE=venous thromboembolism. PICC=peripherally inserted central catheter.

	Study location	Total patients (n)	Study design	Patient population	Comparison device(s)	VTE events (n)				Method of VTE diagnosis	Pharmacological DVT prophylaxis?	PICC tip position verified?
						Comparison group		PICC group				
						No DVT	DVT	No DVT	DVT			
Al Raiy et al (2010)[23]	Detroit, MI, USA	1260	PC	Adults admitted to a single facility needing intravenous access	Triple lumen catheters	630	8	616	6	Symptomatic testing with compression US	Yes	Yes
Alhimyary et al (1996)[24]	Boston, MA, USA	231	RC	Adults needing total parenteral nutrition	Triple lumen catheters	105	0	124	2	Symptomatic testing with venography	NR	Yes
Bonizzoli et al (2011)[28]	Florence, Italy	239	PC	Critically ill adults in an ICU setting	Triple lumen catheters	113	12	83	31	Asymptomatic screening with compression US	Yes (LMWH)	Yes
Catalano et al (2011)[32]	Naples, Italy	481	PC	Adults with various malignancies	Tunnelled catheters, ports	437	15	27	2	Asymptomatic screening with CT	NR	Yes
Cortelezzia et al (2003)[37]	Milan, Italy	126	RC	Adults with haematological malignancies	Hickman and Bard dual lumen catheters	42	14	52	18	Symptomatic testing, CT, compression US, and V/Q scans	Yes (UFH and LMWH in all but 16 patients)	NR
Fearonce et al (2010)[43]	Salt Lake City, UT, USA	31	CC	Critically ill adults with burns in a burns ICU setting	Triple lumen catheters	82	0	30	1	Symptomatic testing with compression US	Yes (LMWH)	Yes
Mollee et al (2011)[55]*	Brisbane, NSW, Australia	727	PC	Adults with various malignancies	Triple lumen, tunnelled and non-tunnelled catheters	320	4	807	51	Symptomatic testing with compression US	No	Yes
Paz-Fumagalli et al (1997)[61]	Milwaukee, WI, USA	44	Prospective PICCs; retrospective CVCs	Adults with spinal cord injury	Triple lumen catheters, Hickman catheters	9	0	35	0	Symptomatic testing with compression US	NR	Yes
Smith et al (1998)[70]	Orlando, FL, USA	838	RC	Adults admitted to hospital	Tunneled Hickman and Groshong catheters	281	2	541	14	Symptomatic testing with compression US or venography	NR	Yes
Snelling et al (2001)[71]	Hamilton, Ontario, Canada	28	Hybrid RC and PC	Adults with gastrointestinal malignancies	Tunneled Hickman catheters	10	3	14	1	Symptomatic testing with compression US	No	Yes
Wilson et al (2012)[79]	Ann Arbor, MI, USA	572	RC	Neurosurgical patients in an ICU	Triple lumen catheters	36	395	2	139	Symptomatic testing with compression US	NR	Yes
Worth et al (2009)[81]	Melbourne, VIC, Australia	66	PC	Adults with haematological malignancies	Single, double, and triple lumen catheters; non-tunnelled Hickman catheters	29	2	21	14	Symptomatic testing with compression US	No	Yes

All events represent deep vein thrombosis; no pulmonary embolism was reported in any study. VTE=venous thromboembolism. DVT=deep vein thrombosis. PICC=peripherally inserted central catheter. PC=prospective cohort study. US=ultrasound. RC=retrospective cohort study. NR=not reported. ICU=intensive care unit. LMWH=low-molecular-weight heparin. CT=computed tomography. V/Q=ventilation perfusion. UFH=unfractionated heparin. CC=case-control study. CVC=central venous catheter. *The unit of analysis in this study was CVCs, rather than patients; thus, data from this study were not pooled for meta-analyses.

Table 1: **Characteristics of included studies with a comparison group**

whether position of the PICC tip was ascertained after PICC insertion (tables 1 and 2).[9,22,26,30,31,37–39,41,45,49,51,56,59,60,64,67,68,80,83] Only four studies provided data for time to deep vein thrombosis after PICC insertion; in these studies, the mean time to deep vein thrombosis was 8·7 days (range 3–22).[28,70,77,81] Inter-rater agreement of abstraction for comparison and non-comparison studies was excellent (κ=0·89 and 0·84, respectively).

Non-comparison studies were stratified into four groups on the basis of study population for the outcomes of deep vein thrombosis and pulmonary embolism. These groups were patients with cancer, patients in intensive care units, patients admitted to hospital, and studies that combined ambulatory and inpatient populations (figure 2).

18 studies (n=3430) reported PICC-related deep vein thrombosis outcomes in patients with cancer.[21,22,25,29,35,40,48,49,56,60,64,65,69,73,74,77,82,83] In these studies, the unweighted frequency of deep vein thrombosis was 6·8% (234/3430). Random effects meta-analysis showed that the weighted frequency of PICC-related deep vein thrombosis was 6·67% (4·69–8·64; figure 2). Nine studies tested for deep vein thrombosis in the presence of clinical signs,[25,29,35,48,56,64,69,74,82] one study did such testing in asymptomatic patients,[21] and eight did not report the trigger for deep vein thrombosis testing.[22,40,49,60,65,73,77,83] Only

	Publication type	Study design	Patient population	PICC indication	Total patients (n)	Total PICCs (n)	VTE events (n [% of events/total PICCs])	Method of VTE diagnosis	DVT prophylaxis?	PICC tip verified?	Key findings/ comments
Abdullah et al (2005)[21]	Peer-reviewed article	PC	Cancer	Long-term intravenous antibiotics (65%); chemotherapy (35%)	26	26	10 (38·5%)	Venography in all patients at time of PICC removal	No	Yes	Site of PICC (left/right), number of lumens, patient comorbidities (diabetes mellitus, hypertension, or coronary artery disease) did not predict VTE
Ahn et al (2011)[22]	Conference abstract	RC	Cancer	Chemotherapy administration	237	237	36 (15·2%)	NR	NR	NR	Hospital admission use of erythrocyte-stimulating drugs associated with VTE
Allen et al (2000)[5]	Peer-reviewed article	RC	Admitted to hospital	Long-term intravenous antibiotics, TPN, chemotherapy	119	354	32 (9·0%)	Venography before and after insertion in all patients	NR	Yes	Cannulation of the cephalic vein increases risk of thrombosis than basilic vein
Aw et al (2012)[25]	Peer-reviewed article	RC	Cancer	Chemotherapy	340	340	19 (5·6%)	Symptomatic testing with compression US	No	Yes	Diabetes, COPD, and metastatic cancer increased risk of PICC-related DVT
Bai and Hou (2010)[26]	Peer-reviewed article	RC	Ambulatory and admitted to hospital	NR	37	37	2 (5·4%)	Symptomatic testing with US	NR	NR	Chinese study designed to assess US-guided PICC insertion
Baxi et al (2008)[27]	Conference abstract	RC	Admitted to hospital	Venous access in patients admitted to hospital	1350	1350	24 (1·8%)	Symptomatic testing with US	NR	Yes	Increasing number of lumens was associated with increasing risk of VTE
Bottino et al (1979)[29]	Peer-reviewed article	PC	Cancer	Chemotherapy administration, intravenous fluids, intravenous access	81	87	13 (14·9%)	Venography in symptomatic patients	NR	Yes	One of the earliest reports of VTE in PICC recipients
Burg and Myles (2005)[30]	Conference abstract	RC	Antepartum	Venous access in antepartum patients	66	66	1 (1·5%), 1 PE	NR	NR	NR	The only DVT in this study was associated with PE
Cape et al (2007)[31]	Conference abstract	RC	Antepartum	Intravenous fluids, intravenous access	65	83	4 (4·8%)	NR	NR	NR	No patient comorbidity was associated with VTE
Chakravarthy et al (2005)[33]	Conference abstract	PC	Critically ill/ ICU	Venous access in ICU patients	31	31	20 (64·5%)	Compression US in asymptomatic patients	Yes	Yes	Despite high incidence of DVT, no PEs were reported
Chemaly et al (2002)[34]	Peer-reviewed article	RC	Ambulatory and admitted to hospital	Long-term intravenous antibiotics/antivirals	2063	2063	29 (1·4%), 2 PE	Compression US and venography for DVT; V/Q for PE	NR	Yes	Previous VTE and treatment with amphotericin B associated with VTE
Chu et al (2004)[35]	Conference abstract	PC	Cancer	Chemotherapy, intravenous fluids, TPN	41	44	3 (6·8%)	NR	NR	Yes	40% of PICCs overall had some complication, including VTE
Clemence (2011)[36]	Conference abstract	PC	Admitted to hospital	Variable; convenience sample requiring PICCs	203	203	13 (6·4%)	NR	NR	NR	Hypertension and arm circumference >3 cm at baseline risk factors for DVT
Curbelo-Irizarry et al (2006)[38]	Conference abstract	PC	Ambulatory and admitted to hospital	Intravenous antibiotics, chemotherapy, and parenteral nutrition	440	399	30 (7·5%)	Symptomatic testing with compression US	NR	NR	High rate of VTE in a population for whom indication for PICC in 50% of patients was intravenous antibiotics
DeLemos et al (2011)[39]	Peer-reviewed article	PC	Critically ill/ ICU	Venous access in neurosurgical ICU patients	33	33	1 (3·0%)	NR	Yes	NR	DVT occurred in an obese patient who was minimally responsive
Derudas et al (2009)[40]	Conference abstract	RC	Cancer	Chemotherapy	96	87	3 (3·4%)	NR	NR	Yes	Median dwell time of PICCs in this study was 120 days

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	Publication type	Study design	Patient population	PICC indication	Total patients (n)	Total PICCs (n)	VTE events (n [% of events/ total PICCs])	Method of VTE diagnosis	DVT prophylaxis?	PICC tip verified?	Key findings/ comments
(Continued from previous page)											
Durrani et al (2009)[41]	Conference abstract	RC	Admitted to hospital	Variable	623	623	22 (3·5%)	Symptomatic testing with US	Yes	NR	Antiplatelet treatment with aspirin+clopidogrel non-significantly decreased risk of DVT
Evans et al (2010)[42]	Peer-reviewed article	PC	Admitted to hospital	Variable; venous access, antibiotics, chemotherapy, and TPN	1728	2014	60 (3·0%), 6 PE	Symptomatic testing with compression US	No	Yes	6 patients (11%) had PE in the 90 days after DVT; 968 (48%) received DVT prophylaxis
Fletcher et al (2011)[44]	Peer-reviewed article	RC	Critically ill/ ICU	Variable; central venous access, vesicant medications, etc	479	479	39 (8·1%), 6 PE	Symptomatic testing with compression US	Yes	Yes	6 of 39 DVTs (15%) associated with PE
Grant et al (2008)[45]	Conference abstract	RC	Ambulatory and admitted to hospital	Variable; intravenous access, antibiotics, chemotherapy, and TPN	4223	6513	189 (2·9%)	Symptomatic testing with compression US	NR	NR	Four-fold increase in risk of DVT in those who received several PICCs
Grove and Pevec (2000)[46]	Peer-reviewed article	RC	Ambulatory and admitted to hospital	Variable; intravenous access, antibiotics, chemotherapy, and TPN	678	813	32 (3·9%), 0 PE	Symptomatic testing with compression US	NR	Yes	PICC diameter directly related to risk of thrombosis: risk least for 3 Fr, greatest for 6 Fr
King et al (2006)[47]	Peer-reviewed article	CC	Admitted to hospital	Variable; intravenous access, antibiotics, chemotherapy, and TPN	27 cases, 54 controls	1296	27 (2·1%)	Symptomatic testing with compression US	Yes	Yes	Cancer was the strongest risk of PICC DVT; VTE prophylaxis did not reduce this risk
Lee et al (2006)[48]	Peer-reviewed article	PC	Cancer	Variable; intravenous access, chemotherapy, blood products	444	297	15 (5·1%)	Symptomatic testing with compression US	Yes	Yes	Patients with ovarian cancer or >1 attempt at insertion were at greater risk of DVT
Lin and Walker (2004)[49]	Conference abstract	RC	Cancer	Variable; patients with cancer	190	244	9 (3·7%)	Symptomatic testing with US	NR	NR	Risk of DVT greater in patients with cancer than in patients without cancer
Lobo et al (2009)[50]	Peer-reviewed article	RC	Admitted to hospital	Variable; intravenous access, intravenous antibiotics, intravenous fluids, TPN, chemotherapy	777	954	38 (4·0%), 8 PE	Symptomatic testing with compression US	No	Yes	PICCs in location others than SVC, previous VTE, and length of stay >10 days was associated with DVT; 8 patients had a PE
Loupus et al (2008)[51]	Peer-reviewed article	RC	Admitted to hospital with cervical spine injury	Intravenous antibiotics; blood product administration	44	56	4 (7·1%)	Symptomatic testing with compression US	NR	NR	No PICC or patient-related characteristics were associated with DVT (small sample size)
Merrell et al (1994)[53]	Peer-reviewed article	PC	Admitted to hospital	Variable; chemotherapy, TPN, intravenous access	460	389	2 (0·5%)	Venography in symptomatic patients	NR	Yes	Most patients in the study were men; despite low DVT rates, 3·6% had catheter occlusion
Meyer (2011)[54]	Peer-reviewed article	RC	Admitted to hospital	Variable; intravenous access	1307	879	30 (3·4%)	Symptomatic testing with compression US	NR	Yes	PICC-related DVT rates dropped after US guidance and vein measurement before insertion started
Mukherjee (2001)[56]	Conference abstract	RC	Cancer	Variable; patients with cancer	NR	385	20 (5·2%)	Symptomatic testing with compression US or venography	No	NR	Dual lumen catheters were more likely to be associated with DVT
Nash et al (2009)[57]	Peer-reviewed article	RC	Cystic fibrosis	Intravenous access for antibiotics	147	376	17 (4·5%)	Compression US in symptomatic patients (12); venography in asymptomatic patients (5)	NR	Yes	5 patients had asymptomatic DVT during subsequent PICC insertion

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	Publication type	Study design	Patient population	PICC indication	Total patients (n)	Total PICCs (n)	VTE events (n [% of events/ total PICCs])	Method of VTE diagnosis	DVT prophylaxis?	PICC tip verified?	Key findings/ comments
(Continued from previous page)											
Nunoo et al (2011)[9]	Conference abstract	RC	Admitted to hospital	Variable; patients who underwent major bowel resection	1648	205	12 (5·9%)	NR	Yes	NR	PICCs associated with 11-fold increased risk of VTE in a postoperative population
Paauw et al (2008)[59]	Peer-reviewed article	PC	Admitted to hospital	Intravenous access for antibiotics and TPN	56	56	21 (37·5%), 1 PE	Compression US in asymptomatic patients	Yes	NR	Use of VTE prophylaxis was associated with nearly half the rate of DVT
Pari et al (2011)[60]	Conference abstract	PC	Cancer	Intravenous access for chemotherapy, palliative, and TPN; medical and surgical patients	70	70	1 (1·4%)	NR	NR	NR	Abstract outlined a pathway for shared decision making; no details available about VTE
Pittiruti et al (2009)[63]	Conference abstract	RC	Critically ill/ ICU	Intravenous access; measurement of CVP	15	16	1 (6·3%)	Compression US in asymptomatic patients	No	Yes	Power injectable PICCs were associated with low rates of DVT in this study
Pittiruti (2012)[62]	Peer-reviewed article	RC	Critically ill/ ICU	Intravenous access; TPN; drugs that need CVC; CVP monitoring	65	65	2 (3·1%)	Symptomatic testing with compression US	Yes	Yes	Included adult and child patients; data shown are for adults only
Romagnoli et al (2010)[64]	Conference abstract	RC	Cancer	Chemotherapy; patients with cancer	49	52	3 (5·8%)	Symptomatic testing with US	NR	NR	All DVTs occurred in PICCs placed at the basilic vein
Ros et al (2005)[65]	Conference abstract	RC	Cancer	Chemotherapy; patients with head and neck cancer	36	36	4 (11·1%)	NR	NR	Yes	DVT noted only in patients with cervical lymphadenopathy
Sansivero et al (2011)[66]	Conference abstract	PC	Ambulatory and admitted to hospital	Variable; ambulatory and patients admitted to hospital included	50	50	2 (4·0%)	NR	NR	Yes	Mainly examined infectious complications related to a securement device
Seeley et al (2007)[67]	Peer-reviewed article	RC	Admitted to hospital	Variable; patients in hospital	233	233	17 (7·3%)	Symptomatic testing with US	NR	Yes	Osteomyelitis identified as a risk factor for PICC-related DVT in this group
Shea et al (2006)[68]	Conference abstract	RC	Admitted to hospital with inflammatory bowel disease	Variable; intravenous access	15	15	3 (20%)	Symptomatic testing with US	Yes	NR	Underpowered to assess associations between PICC, patient variables, and VTE
Simcock (2008)[69]	Peer-reviewed article	RC	Cancer	Chemotherapy	375	312	33 (10·6%)	Symptomatic testing with compression US	Yes	Yes	VTE rates were high but decreased with use of US guidance during PICC insertion
Sperry et al (2012)[72]	Peer-reviewed article	RC	Admitted to hospital	Intravenous access, intravenous antibiotics, TPN	672	798	10 (1·3%)	Symptomatic testing with compression US	No	Yes	Arm of PICC insertion was not associated with VTE; oedema of the arm was the most common presentation of DVT
Strahilevitz et al (2001)[73]	Peer-reviewed article	RC	Cancer	Chemotherapy in patients with acute myeloid leukaemia	40	52	2 (3·8%)	NR	NR	Yes	Although small, the risk of VTE was similar to other catheters in this single-centre study
Tran et al (2010)[74]	Peer-reviewed article	RC	Cancer	Chemotherapy in patients with haematological malignancies	498	899	39 (4·3%)	Symptomatic testing with compression US	No	Yes	Risk of PICC-related DVT decreased when PICCs were inserted by a tunnelled approach into the internal jugular vein
Trerotola et al (2010)[75]	Peer-reviewed article	PC	Critically ill/ ICU	Chemotherapy, intravenous antibiotics, venous access, TPN, CVP monitoring	50	50	26 (52·0%)	Compression US surveillance in asymptomatic patients; venography in symptomatic patients	NR	Yes	High rate of VTE in this study was attributed to the new 6 Fr triple lumen catheter tested

(Continues on next page)

	Publication type	Study design	Patient population	PICC indication	Total patients (n)	Total PICCs (n)	VTE events (n [% of events/ total PICCs])	Method of VTE diagnosis	DVT prophylaxis?	PICC tip verified?	Key findings/ comments
(Continued from previous page)											
Vidal et al (2008)[76]	Peer-reviewed article	PC	Ambulatory and admitted to hospital	TPN, intravenous antibiotics and chemotherapy	115	127	3 (2·4%)	Symptomatic testing with US	NR	Yes	Mechanical complications were the most frequent event in this French study
Walshe et al (2002)[77]	Peer-reviewed article	PC	Cancer	Chemotherapy, intravenous antibiotics, intravenous access, hydration, TPN	335	366	12 (3·3%)	NR	NR	Yes	Thrombosis occurred within 1 week in most patients
Wilson et al (2012)[78]	Peer-reviewed article	RC	Critically ill/ ICU	Variable; neurosurgical ICU patients	431	431	36 (8·4%)	Symptomatic testing with compression US	Yes	Yes	Previous VTE, placement in a paretic arm, and mannitol infusion associated with increased risk of DVT
Worley et al (2007)[80]	Conference abstract	RC	Admitted to hospital	Variable; drug administration, venous access	468	468	2 (0·4%)	Symptomatic testing with compression US	NR	NR	Clopidogrel conferred no advantages to DVT prevention in PICC recipients
Xing et al (2011)[82]	Peer-reviewed article	RC	Cancer	Chemotherapy; intravenous access	187	188	4 (2·1%)	Symptomatic testing with compression US	NR	Yes	PICCs thought to be safe for use in patients with breast cancer
Yue et al (2010)[83]	Peer-reviewed article	RC	Cancer	Chemotherapy; intravenous access	400	400	8 (2·0%)	NR	NR	NR	Chinese study assessing safety of PICCs; catheter obstruction was the most common complication (38/400)
Zhu et al (2008)[84]	Peer-reviewed article	RC	Ambulatory and admitted to hospital	Chemotherapy; intravenous access, blood product administration	2170	2170	6 (0·3%)	Symptomatic testing with compression US	NR	Yes	All patients with PICC-related DVT had advanced cancer; article in Chinese

PICC=peripherally inserted central catheter. VTE=venous thromboembolism. DVT=deep vein thrombosis. PC=prospective cohort study. RC=retrospective cohort study. NR=not reported. TPN=total parenteral nutrition. US=ultrasound. COPD=chronic obstructive pulmonary disease. PE=pulmonary embolism. ICU=intensive care unit. V/Q=ventilation–perfusion scan. CC=case-control study. SVC=superior vena cava. CVP=central venous pressure.

Table 2: **Characteristics of included studies without a comparison group**

one study explicitly reported use of pharmacological deep vein thrombosis prophylaxis;[69] four reported no use of any pharmacological prophylaxis,[21,25,56,74] whereas 13 did not obtain data for this treatment.[22,29,35,40,48,49,60,64,65,73,77,82,83] The most common indications for PICC placement in these studies were administration of chemotherapy, intravenous antibiotics, and blood products.

Eight studies (n=1219) featured patients with PICCs in intensive care units.[33,39,44,62,63,75,76,78] In these studies, the unweighted frequency of deep vein thrombosis was 10·5% (128 of 1219). The weighted frequency of PICC-related deep vein thrombosis was 13·91% (7·68–20·14; figure 2). In six studies, investigators reported use of pharmacological deep vein thrombosis prophylaxis,[33,39,44,62,63,78] whereas two did not comment about the use of this treatment.[75,76] Five studies tested for deep vein thrombosis in the presence of symptoms;[44,62,75,76,78] two screened for asymptomatic deep vein thrombosis,[33,63] and one did not report the trigger for testing of deep vein thrombosis.[39] The most common indications for PICC placement in this population were intravenous antibiotic administration, central venous access, and haemodynamic monitoring.

18 studies (n=11476) reported venous thromboembolism outcomes related to PICCs in patients admitted to hospital (non-intensive care unit).[5,9,26,27,36,38,41,42,47,50,51,53,54,59,67,68,72,80] The unweighted frequency of PICC-related deep vein thrombosis in these patients was 3·0% (349 of 11476) and the weighted frequency of PICC-related deep vein thrombosis was 3·44% (2·46–4·43). Five studies explicitly reported use of pharmacological deep vein thrombosis prophylaxis,[9,41,47,59,68] three used it in less than 50% of their population,[42,50,72] and ten did not report use of this treatment.[5,26,27,36,38,51,53,54,67,80] 13 studies tested for deep vein thrombosis in the presence of clinical signs suggestive of this development;[26,27,38,41,42,47,50,51,53,54,68,72,80] two screened for deep vein thrombosis in asymptomatic patients,[5,59] and three did not report the trigger for testing.[9,36,67] The most common indications for PICC placement in this subset were intravenous antibiotic administration, venous access, and total parenteral nutrition.

Eight studies (n=9462) featured a mixed cohort of ambulatory and inpatients.[30,31,34,45,46,57,66,84] This group was distinct in that it included the largest retrospective cohort

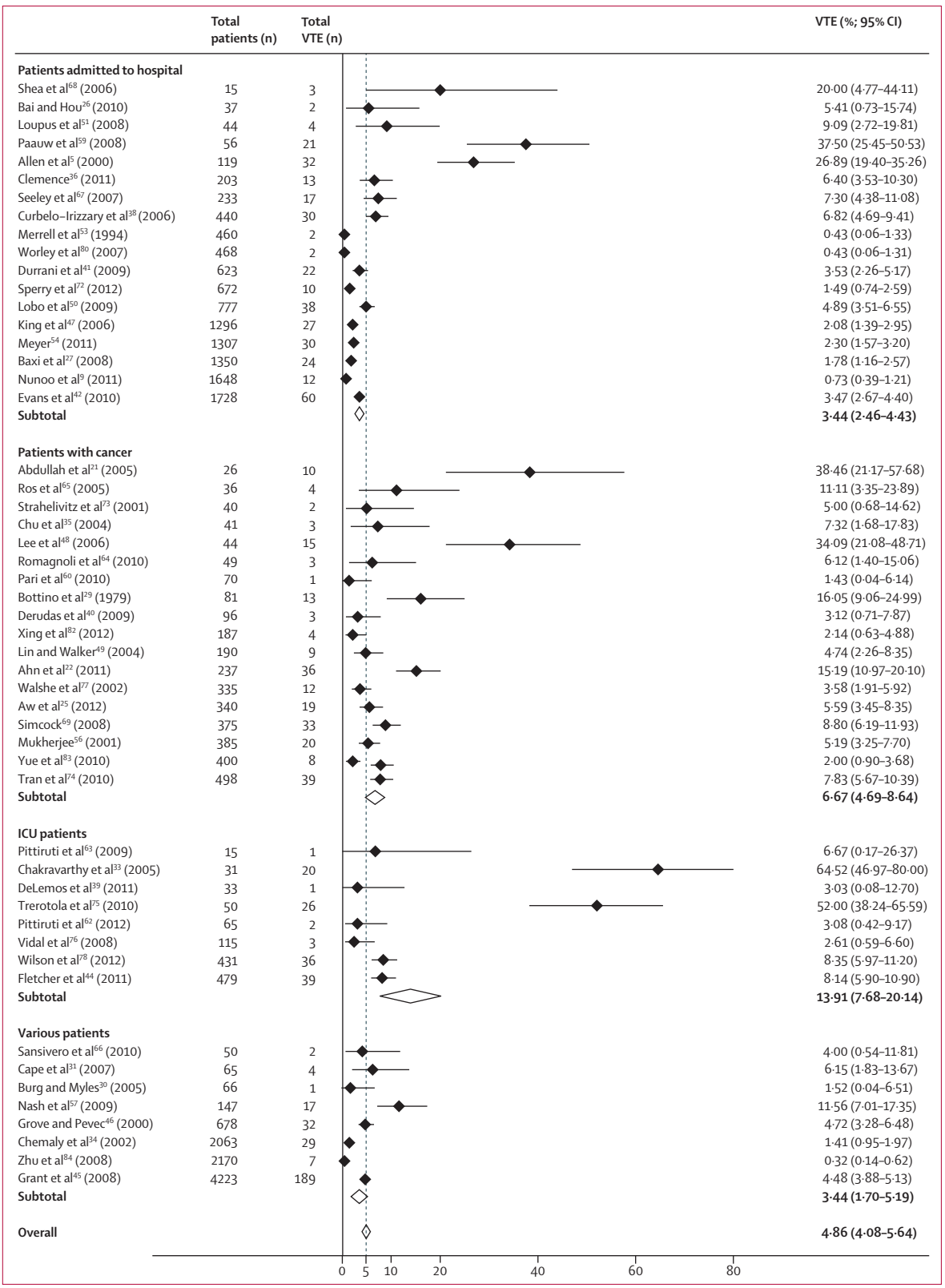

Figure 2: **Forest plot showing the pooled, weighted frequency of patients with peripherally inserted central catheter VTE in studies without a comparison group**
Random effects meta-analysis showing the individual and pooled weighted frequency of peripherally inserted central catheter-related VTE in studies without a comparison group, stratified by patient population. VTE=venous thromboembolism. ICU=intensive care unit.

study investigating the incidence of PICC-related venous thromboembolism[45] and unique populations such as antepartum patients[30,31] and those with cystic fibrosis.[57] In this varied population, the unweighted frequency of PICC-related deep vein thrombosis was 3·0% (281 of 9462). The weighted frequency of PICC-related deep vein thrombosis was 3·44% (95% CI 1·70–5·19). None of the included studies in this group reported on the use of deep vein thrombosis prophylaxis, presumably because they mainly included outpatients in whom this practice is uncommon. Four studies tested for deep vein thrombosis in the presence of clinical signs suggestive of this development,[34,46,57,84] whereas four did not report the trigger for deep vein thrombosis testing.[30,31,45,66] The most common reasons for PICC placement in this population were long-term intravenous antibiotic treatment, total parenteral nutrition, and intravenous hydration.

Comparisons across critically ill patients, those admitted to hospital, patients with cancer, and mixed subgroups showed important differences in PICC-related deep vein thrombosis. Notably, patients cared for in intensive care unit settings and those with cancer were reported to have the greatest risk of deep vein thrombosis (figure 3).

Of the 52 included studies without a comparison group, only six reported the development of pulmonary embolism associated with PICCs.[9,30,34,42,44,50] Five studies were retrospective[9,30,34,44,50] and one was prospective.[42] From a patient perspective, the frequency of pulmonary embolism in these studies was low at 0·5% (24 of 5113). However, of the 179 total venous thromboembolism events within these studies, pulmonary embolism represented 13·4% (24 of 179) of all thromboembolisms. The frequency of pulmonary embolism was highest in critically ill patients (those in the neurosurgical intensive care unit), where pulmonary embolism represented 15·4% (six of 39) of all venous thromboembolism events.[44]

12 studies (n=3916) reported venous thromboembolism rates in PICC recipients and those with CVCs and were published in peer-reviewed journals.[23,24,28,32,37,43,55,61,70,71,79,81] One study reported rates of deep vein thrombosis relative to the number of CVCs, rather than the number of patients.[55] Although we did not pool outcomes from this study for meta-analyses, deep vein thrombosis related to PICCs was frequent in this study compared with that associated with CVCs (51 of 807 PICCs [6·3%] *vs* 4 of 320 CVCs [1·3%]). Only one study noted retrospective evidence of pulmonary embolism by imaging;[32] otherwise, pulmonary embolism was not reported in any study. In all but two studies,[28,32] clinical symptoms (eg, arm swelling or pain) prompted radiological testing to

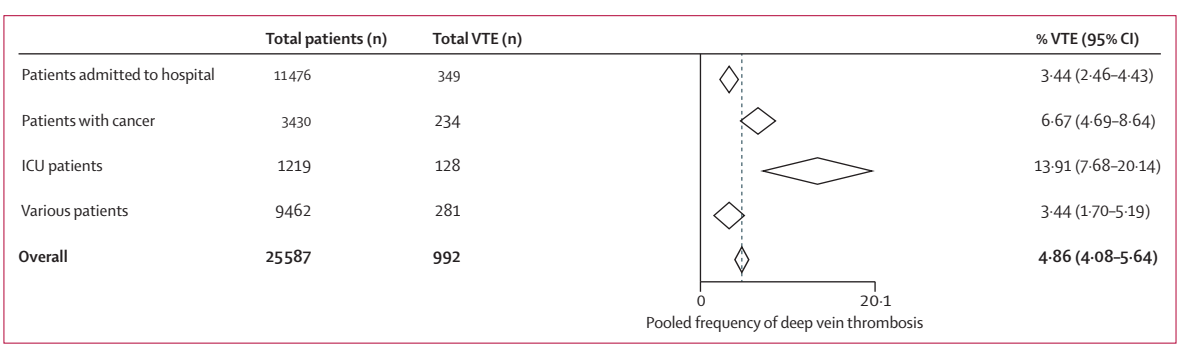

Figure 3: **Forest plot showing weighted frequency of peripherally inserted central catheter-related VTE risk, stratified by patient population**
VTE=venous thromboembolism. ICU=intensive care unit.

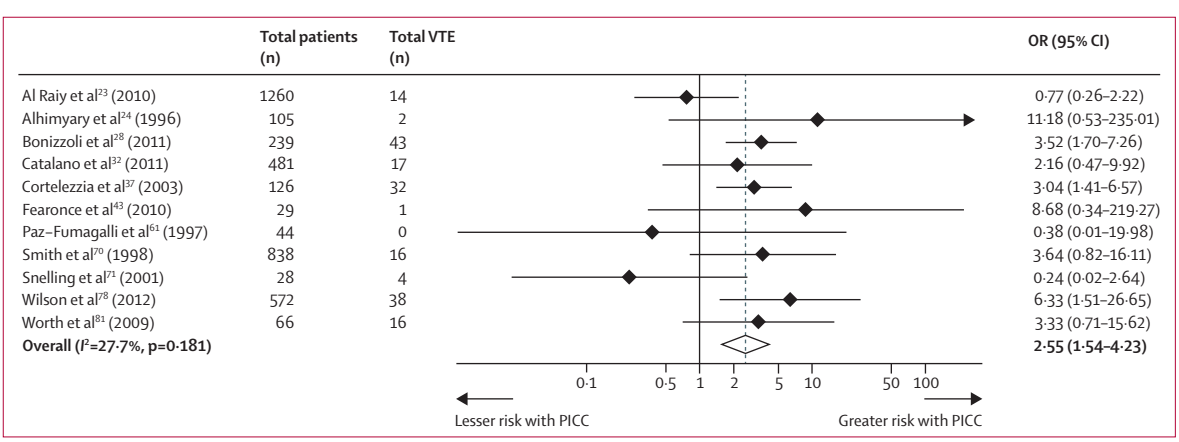

Figure 4: **Risk of venous thromboembolism between peripherally inserted central catheters and central venous catheters in studies with a comparison group**
Forest plot showing odds of development of upper-extremity DVT in patients with peripherally inserted central catheters versus central venous catheters. VTE=venous thromboembolism. OR=odds ratio. PICC=peripherally inserted central catheter.

	Comparison studies (OR, 95% CI)	Non-comparison studies (% VTE, 95% CI)
Base-case scenario	2·55 (1·54–4·23)[23,24,28,32,37,43,55,61,70,71,79,81]	4·86 (4·08–5·64)[5,9,21,22,25–27,29–31,33–36,38–42,44–51,53,54,56,57,59,60,62–69,72–78,80,82–84]
Study design		
Retrospective	3·12 (1·35–7·24)[24,37,70,71,79]	4·52 (3·66–5·39)[5,9,22,25,27,30,31,34,40,41,44–46,49–51,54,56,57,62–65,67–69,72–74,78,80,82,84]
Prospective	2·11 (0·96–4·63)[23,28,32,81]	8·32* (5·95–10·69)[21,26,29,33,35,36,38,39,42,48,53,59,60,66,75–77,83]
Case–control	2·26 (0·11–47·22)[43,61]	4·99 (4·19–5·80)[47]
Patient population		
Cancer	2·24 (1·01–4·99)[32,37,71,81]	6·67 (4·69–8·64)[21,22,25,29,35,40,48,49,56,60,64,65,69,73,74,77,82,83]
Admitted to hospital	1·75 (0·50–6·08)[23,24,61,70]	3·44 (2·46–4·43)[5,9,26,27,36,38,41,42,47,50,51,53,54,59,67,68,72,80]
Intensive care unit	4·08 (2·17–7·70)[28,43,79]	13·91* (7·68–20·14)[33,39,44,62,63,75,76,78]
Various	NA	3·13 (1·56–4·70)[30,31,34,45,46,57,66,84]
Approach to VTE diagnosis		
Asymptomatic screening	3·22 (1·67–6·18)[28,32]	34·15* (17·92–50·37)[5,21,33,59,63]
Symptomatic testing only	2·37 (1·18–4·76)[23,24,37,43,61,70,71,79,81]	4·30 (3·44–5·17)[25–27,29,34,35,38,41,42,44,46–48,50,51,53,54,56,57,62,64,68,69,72,74–76,78,80,82,84]
Not reported	NA	4·34 (2·79–5·89)[22,30,31,36,39,40,45,49,59,60,65–67,73,77,83]
Use of DVT prophylaxis		
Yes	2·37 (1·10–5·09)[23,28,37,43]	7·94 (5·42–10·46)[9,33,39,41,44,47,48,59,62,63,68,69,78]
No	1·05 (0·08–13·66)[71,81]	4·93 (3·02–6·84)[21,25,42,50,56,72,74]
Not reported	3·69 (1·65–8·26)[24,32,61,70,79]	4·26 (3·32–5·19)[5,22,26,27,29–31,34–36,38,40,45,46,49,51,53,54,57,60,64–67,73,75–77,80,82–84]
PICC tip verification		
Yes	2·43 (1·30–4·53)[23,24,28,32,43,61,70,71,79,81]	5·13 (4·13–6·13)[5,21,25,27,29,33–36,40,42,44,45,47,48,50,53,54,57,62,63,65,66,69,72–78,82,84]
Not reported	3·04 (1·41–6·57)[37]	4·69 (3·26–6·11)[9,22,26,30,31,38,39,41,45,49,51,56,59,60,64,67,68,80,83]

All subgroup analyses were done with random-effects meta-analyses. References indicate studies pooled for specific outcome. OR=odds ratio. VTE=venous thromboembolism. NA=not applicable. DVT=deep vein thrombosis. PICC=peripherally inserted central catheter. *Denotes statistically significant difference.

Table 3: **Subgroup analysis**

diagnose deep vein thrombosis. Deep vein thromboses were detected by venography in one study,[24] CT scan in another,[32] and compression ultrasound in the remaining ten.[23,28,37,43,55,61,70,71,79,81] Four studies[23,28,37,43] reported use of pharmacological deep vein thrombosis prophylaxis, three did not use this treatment,[55,71,81] and five did not report on this practice (table 1).[24,32,61,70,79] Meta-analysis of 11 studies of 3788 patients showed that PICCs were associated with an increase in the odds of deep vein thrombosis compared with CVCs (OR 2·55, 95% CI 1·54–4·23, p<0·0001; figure 4). With an estimated baseline rate of 2·7% for PICC-related deep vein thrombosis and a pooled OR of 2·55, the number needed to harm relative to CVCs was calculated to be 26 (95% CI 13–71). Minimal heterogeneity was noted across studies (I^2=27·7%, p=0·181; figure 4). Harbord's test statistic did not suggest publication bias (p=0·94).

The Newcastle–Ottawa scale was used to assess study quality and risk of bias in both comparison and non-comparison studies. Studies with a comparison group were generally of high quality, with the exception of four studies in which follow-up, exposure, and ascertainment of diagnosis of venous thromboembolism were not reported (appendix).[24,61,71,81] Non-comparison studies suffered in quality owing to the inclusion of many scientific abstracts that did not report all quality domains (appendix).

Subgroup analyses were done to assess the risk of PICC-related venous thromboembolism by patient population, approach to venous thromboembolism diagnosis, and use of pharmacological venous thromboembolism prophylaxis. Within the comparison studies, these analyses showed no differences as judged by the overlap in the confidence intervals between subgroups (appendix). However, in the non-comparison studies, the frequency of deep vein thrombosis was substantially greater in prospective studies, studies that used asymptomatic surveillance for diagnosis of deep vein thrombosis, and studies done in intensive care unit settings (table 3).

Sensitivity analyses by study design, quality, sample size, and year of publication were done for comparison and non-comparison studies. All meta-analytic conclusions remained robust to this testing.

Discussion

Although deep vein thrombosis of the arm is infrequent in the general population, the same disorder related to indwelling devices such as CVCs is common.[85] With increasing use of CVCs, recognition and prevalence of this complication have risen in recent years.[86] Although recent evidence suggests that PICCs are associated with venous thromboembolism, the precise incidence and risk of this outcome remain uncertain.[7,87,88] In our meta-analysis of 12 comparison and 52 non-comparison studies, we showed that PICCs were associated with greater risk of deep vein thrombosis of the arm than

were CVCs. The incidence of PICC-related deep vein thrombosis seemed to be highest in critically ill patients and those with cancer (figure 4), and was more frequent in studies that used prospective designs and screened for deep vein thrombosis in the absence of clinical symptoms. These findings suggest that PICC-related deep vein thrombosis is a complication that might be more prevalent than clinically perceived or more evident when robust study designs are used.

Several nuances unique to PICCs could explain the raised risk of thrombosis inherent with these devices. For example, PICCs are inserted into peripheral veins that are more likely to occlude in the presence of a catheter that occupies much of the luminal diameter.[89] Conversely, when PICCs are inserted above the elbow into larger vessels or when the vein diameter is checked before PICC insertion, the risk of deep vein thrombosis decreases.[54,74,90] Similarly, site of PICC insertion affects risk of thrombosis. Various explanations have been suggested, including differences in the anatomical approach to the superior vena cava and more frequent mechanical trauma to the vessel intima in right-handed people.[5,42,91] The finding that PICCs placed in the internal jugular, rather than arm veins, are associated with a lower incidence of deep vein thrombosis supports the theory that intimal injury from repeated arm movements could be associated with PICC-related deep vein thrombosis.[74] Finally, an increased frequency of mechanical complications coupled with longer dwell times of PICCs compared with CVCs might raise the risk of deep vein thrombosis.[50,92]

Despite the prevalence of deep vein thrombosis, pulmonary embolism was an infrequent occurrence in those who received PICCs. Although the paucity of PICC-related pulmonary embolism might merely represent the natural history of deep vein thrombosis of the arm,[93] several factors unique to PICCs and their insertion could explain these findings. For example, more frequent development of thrombophlebitis with PICCs might form a physiological barrier against proximal embolisation of a clot.[92] Alternatively, practices such as verification of PICC tip positioning and use of smaller-gauge PICCs could mitigate pulmonary embolism.[94] Deep vein thrombosis of the arm might also be more clinically apparent than that of the leg, leading to earlier institution of treatment and consequent decrease in risk of embolisation.

In view of the heightened risk of deep vein thrombosis, should PICC recipients routinely receive pharmacological deep vein thrombosis prophylaxis? Although we recorded no significant difference in the frequency of deep vein thrombosis between studies that used prophylaxis and those that did not, our ability to discern benefit is limited by the scarcity of systematic reporting about prophylaxis. Although our findings agree with previous reviews in this regard,[95,96] our results also suggest that PICC-related deep vein thrombosis is more common than is clinically realised, remaining undetected in many cases. In this context, non-pharmacological methods such as early catheter removal and guidance to appropriately place PICCs might be relevant in the prevention of PICC-associated deep vein thrombosis.[97] Importantly, the clinical relevance of asymptomatic thrombosis and the optimum approach to manage such events is unknown. Although randomised studies to assess the risk of PICC-associated deep vein thombosis have begun to emerge,[98,99] only a randomised controlled study of the risk and benefits associated with pharmacological deep vein thrombosis prophylaxis can resolve this important concern.

Our results should be considered in the context of several limitations. First, no randomised trials were included, and roughly a third of the studies included in our analysis (22 of 64) were published in abstract form only; inclusion of these studies could affect the robustness of our findings and might not assuage concerns about publication bias.[100] However, none of the studies published in abstract form included a comparison group, sensitivity and subgroup analyses effectively isolated effects from these groups, and authors were contacted directly for additional data; therefore, we believe that the inclusion of this grey literature strengthens, rather than weakens, our report. Second, most of the included studies did not have a comparison group, which reduces our ability to generate pooled ORs of PICC-related venous thromboembolism. Third, data for deep vein thrombosis prophylaxis were scarce, and only four studies included data for duration of catheterisation; the absence of these data limits our understanding of the effect of this confounder on frequency of venous thromboembolism. Fourth, stratification of non-comparison studies into patient populations has the problem of overlap of patient types (eg, patients with cancer in the intensive care unit). Despite this limitation, this approach is the most pertinent method to frame our analysis in a clinical context. Finally, as is the case with all meta-analyses of observational data, the limits of epidemiological inference, including systematic and random biases, measurement error, and unmeasured confounding (eg, important patient covariates), should be remembered in the interpretation of our analysis,[101] although the use of sensitivity and subgroup analyses helps to mitigate this problem.

Our study also has notable strengths. First, because we included comparison and non-comparison studies, the study is the largest and most comprehensive review so far of the incidence, patterns, and risk of PICC-related venous thromboembolism. Second, unlike previous studies, we did not restrict our analysis to a particular patient population, PICC type, or venous thromboembolism definition; thus, this report is the most externally valid and generalisable estimate of PICC-related venous thromboembolism published so far. Third, our analysis is the first to isolate both deep vein thrombosis and pulmonary embolism outcomes, practices associated with

these events (deep vein thrombosis prophylaxis and tip verification), and method or approach to their diagnosis. Consequently, our study holistically informs clinicians, researchers, and policy makers about many aspects of PICC-related venous thromboembolism. Last, our results are strengthened by the inclusion of a large amount of unpublished data obtained through direct author contact.

In conclusion, we found that PICCs are associated with a raised risk of deep vein thrombosis, but not pulmonary embolism, when compared with CVCs. A thoughtful consideration of this risk weighed against the benefits of a PICC is important, especially when PICCs are placed in patients with critical illness or cancer.

Contributors

VC created the figures; designed the study; gathered, analysed, and interpreted data; and wrote the report. SA helped to gather data and write the report. AH did the literature search, data gathering, and writing of the report. MB contributed to study design, data gathering, and writing of the report. MAMR, SS, and SF helped with study design, data analysis and interpretation, and writing of the report.

Conflicts of interest

We declare that we have no conflicts of interest.

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