Supplementary material

Search strategy

Medline via Pubmed

("peripherally inserted central catheter" OR "peripherally inserted central catheters" OR "peripherally inserted central venous catheter" OR "peripherally inserted central venous catheters" OR PICC OR PICCs OR "central venous access" OR "Catheterization, Peripheral"[Mesh] OR "Catheterization, Central Venous"[Mesh]) AND (thrombosis OR thrombotic OR thromb* OR "Venous Thromboembolism"[Mesh]) AND (("2010/01/01"[PDat] : "2018/12/31"[PDat]) AND adult[MeSH])

Cochrane

(“peripherally inserted central catheter” OR “peripherally inserted central catheters” OR “peripherally inserted central venous catheter” OR “peripherally inserted central venous catheters” OR PICC OR PICCs OR “central venous access”) AND (thrombosis OR thrombotic OR thromb*)

Embase

(“peripherally inserted central catheter” OR “peripherally inserted central catheters” OR “peripherally inserted central venous catheter” OR “peripherally inserted central venous catheters” OR PICC OR PICCs OR “central venous access”) AND (thrombosis OR thrombotic OR thromb*)

Supplementary methods

Details and operationalization of the risk of bias assessment

We found no established tool to assess the risk of bias of non-comparative studies investigating the occurrence of rare adverse events. We followed the methodology developed by Mantarro and colleagues to conduct a meta-analysis of the risk of cardiotoxicity after trastuzumab treatment for breast cancer.[1] Each study was eligible for a maximum of two stars per evaluation criterion, up to a total of eight stars. Studies assigned 6-8 points were considered as high quality, 4-5 as medium quality, and 1–3 as low quality. We assessed the risk of bias in the included studies according to the following key domains (table 1).

Lack of generalizability bias

We assessed the lack of generalizability bias based on the inclusion or exclusion of patients who met the indication for PICC insertion and that were likely representative of a large spectrums of patients, including those at high and low risk of developing deep vein thrombosis. Two variables were considered: oncologic diagnosis and anticoagulant therapy at the time of PICC insertion. We decided to assign two stars to studies on mixed samples including mostly oncologic patients that did not exclude patients on anticoagulant therapy at the moment of PICC insertion. We decided *a priori* to downgrade randomized controlled trials (RCTs) for lack of generalizability.

Detection bias

We judged a mean period of observation of at least 1 month after PICC insertion for a total of 6 months as optimal (two stars) to assess detection bias; at least two weeks for a total observation period of 1 month as intermediate (1 star); and less than two weeks as poor (zero stars). We assigned no stars to studies not reporting such data.

Attrition bias

The assessment of attrition bias was based on the rate of loss to follow-up: we assigned two stars if the proportion of withdrawals was less than 1%; one star if it was greater than or equal to 1%, but less than 3%; and no stars if the rate was greater than or equal to 3%. Because VTE is a rare event, we required that the cause of loss to follow-up was reported and that patients lost to follow-up did not differ from those observed. We assigned one or no stars to studies with a moderate or severe imbalance in patient characteristics concerning loss to follow-up and no stars to studies not reporting such data.

Reporting bias

Our assessment of reporting bias focused on outcome diagnosis modality. Accordingly, two stars were assigned to studies where PICC-related deep vein thrombosis was diagnosed by means of Doppler ultrasonography and where diagnostic criteria included the presence of intraluminal thrombus combined with a lack of vein compression and/or with an abnormal flow pattern in the segment of the vein distal to the thrombosis, as previously described.[2] One star was assigned to studies where PICC-related deep vein thrombosis was diagnosed by means of Doppler ultrasonography, but no diagnostic criteria were reported. No stars were assigned to studies which did not specify deep vein thrombosis detection modality.

References

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Table 1S. Quality assessment of included studies.

Study First Author	Year	Selection Bias	Attrition Bias	Detection Bias	Reporting Bias	Total
Bellesi et al[5]	2013	*	NA	*	*	4
Bertoglio et al[6]	2016	**	-	**	**	6
Cornillon et al[7]	2017	*	NA	**	*	4
Cotogni et al[3]	2015	**	NA	**	*	5
DeLemos et al[8]	2011	*	NA	*	-	2
Dupont et al[9]	2015	*	NA	*	*	3
Evans et al[10]	2010	*	NA	-	**	3
Evans et al[4]	2013	*	NA	-	**	3
Kang et al[11]	2017	**	NA	**	*	5
Mermis et al[12]	2014	*	NA	*	*	3
Pittiruti et al[13]	2014	*	NA	**	*	4
Sharp et al[14]	2015	*	-	**	*	4
Tian et al[15]	2010	**	NA	**	*	5
Zerla et al[16]	2017	*	NA	**	-	3
Liu et al[17]	2018	*	-	*	**	4

**, high quality; *, intermediate quality; –, low quality; NA, not assessable

Figure 1S. Forest plot showing weighted frequencies of PICC-related deep vein thrombosis rate.
Random effect meta-analysis for PICC-related deep vein thrombosis rate and subgroup stratification by tip location ascertainment.

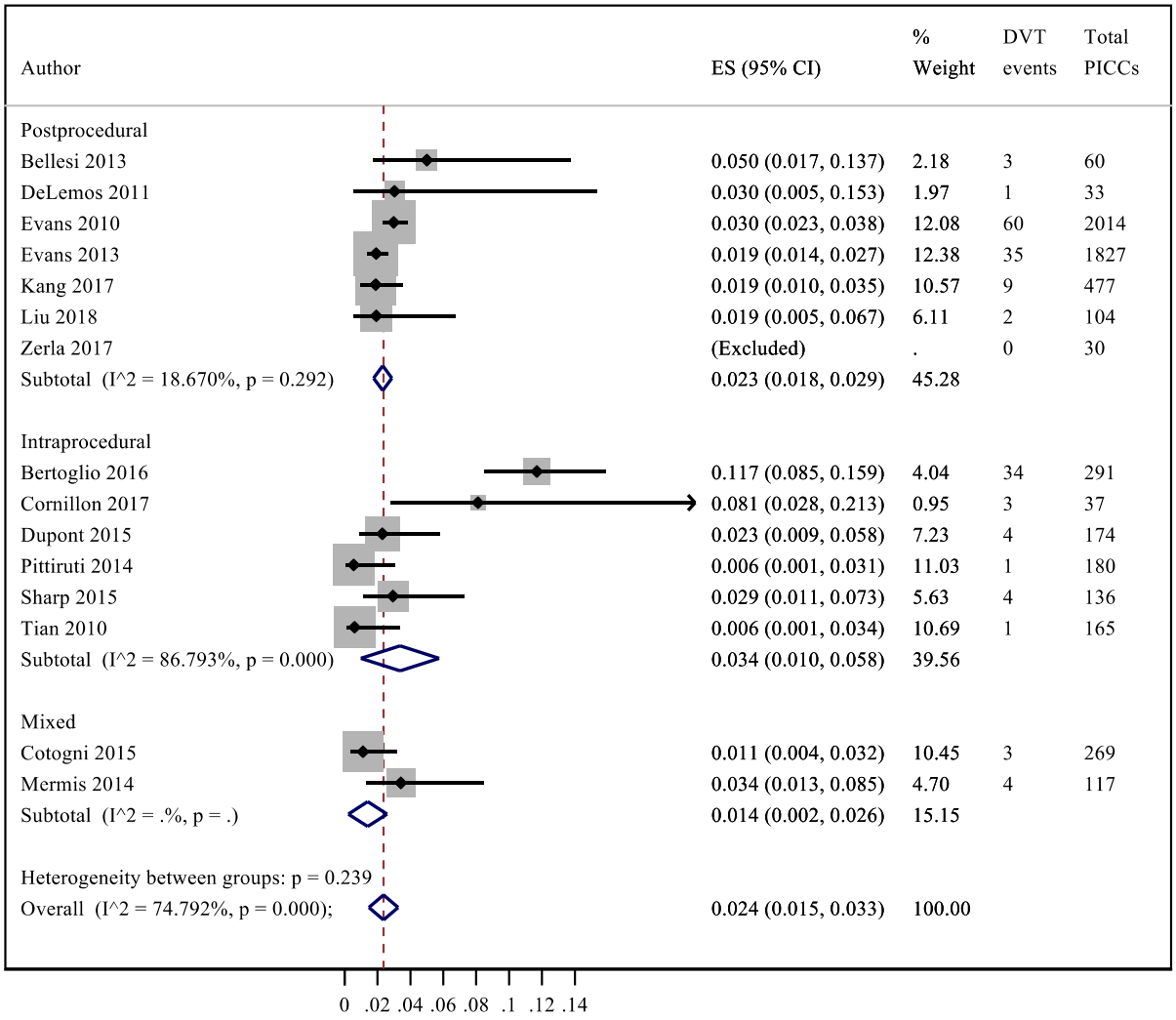


Figure 2S. Forest plot showing weighted frequencies of PICC-related deep vein thrombosis rate.
Random effect meta-analysis for PICC-related deep vein thrombosis rate and subgroup stratification by patient setting.

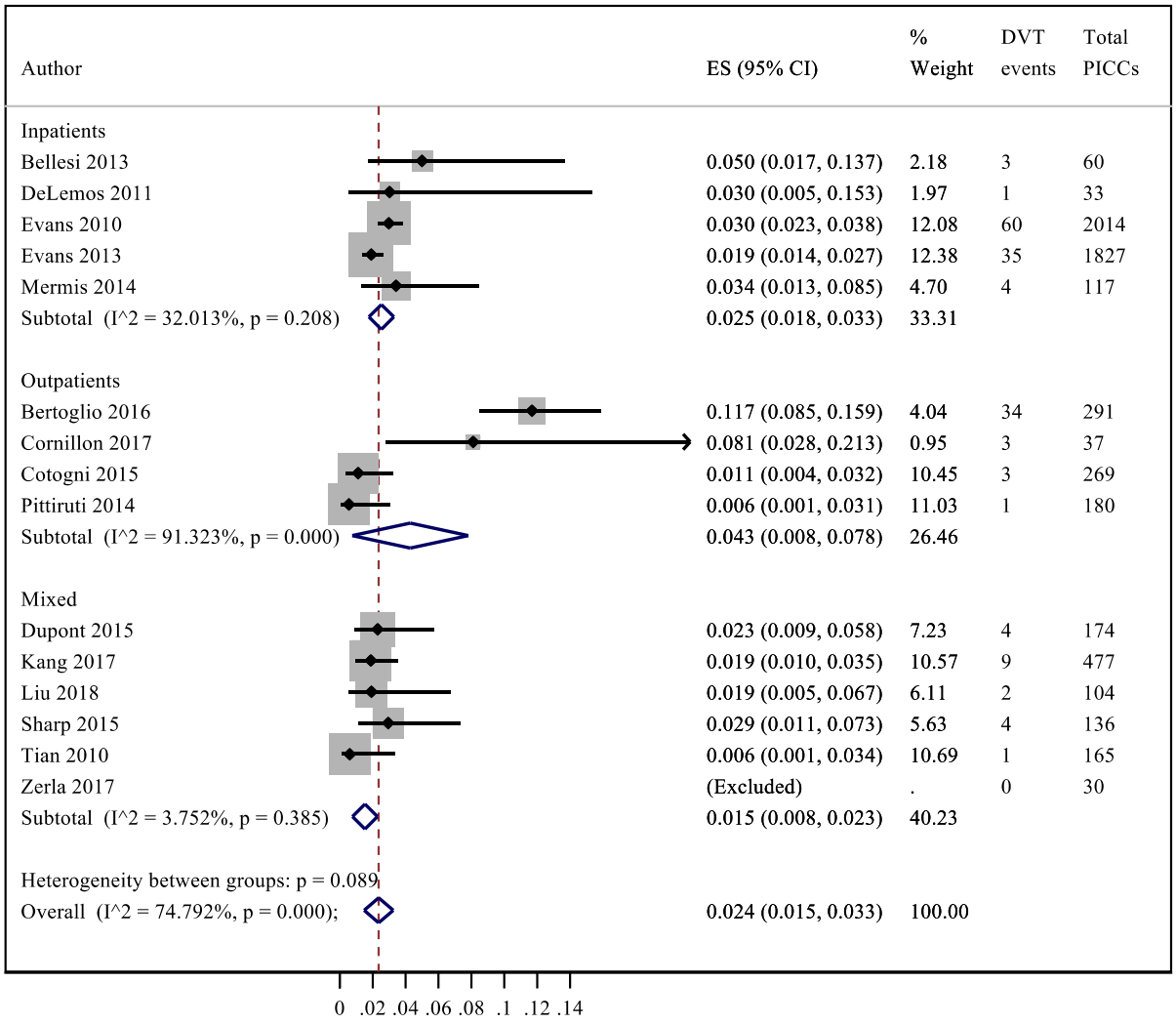
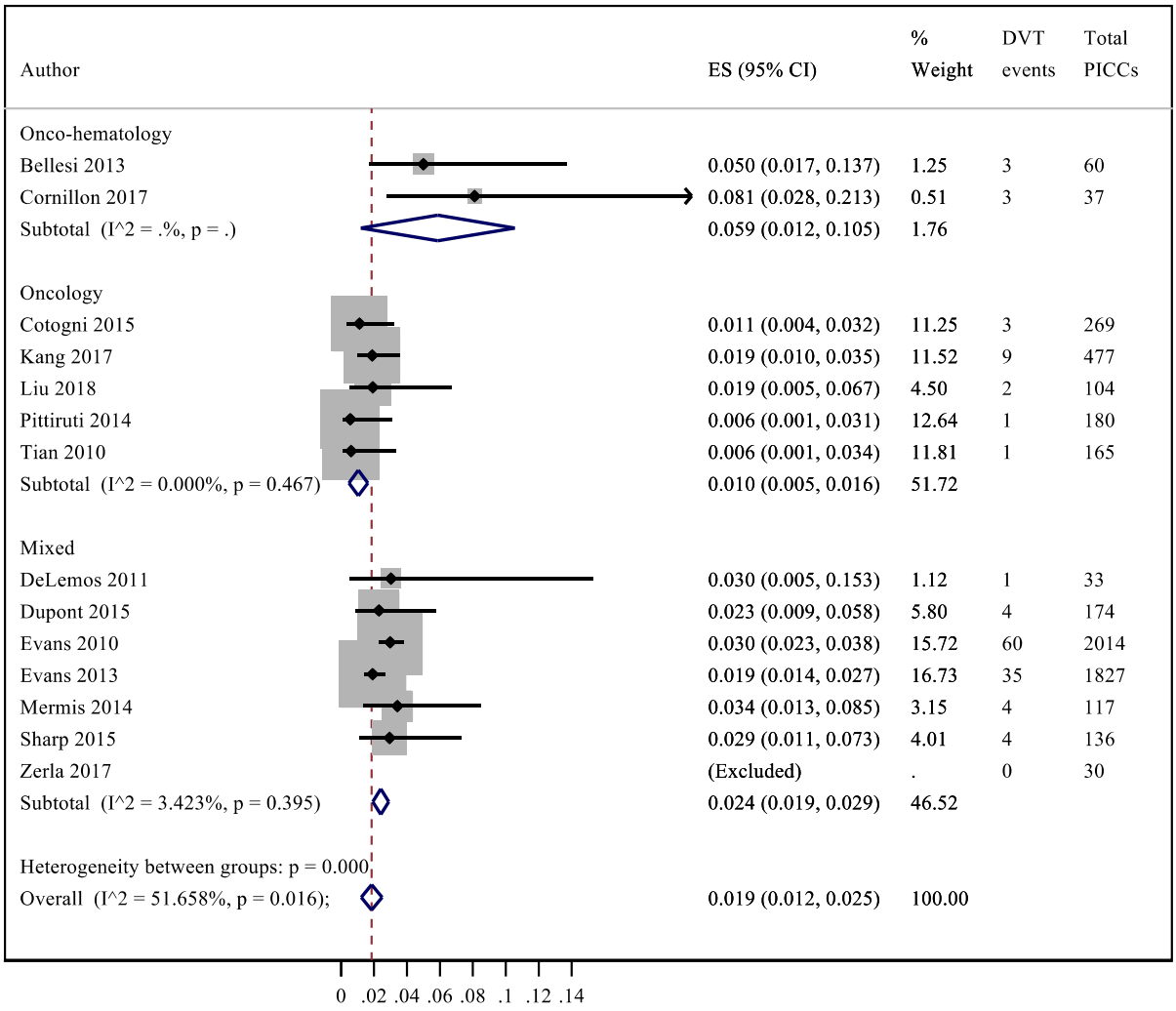


Figure 3S. Forest plot showing weighted frequencies of PICC-related deep vein thrombosis rate after leave-one-out analysis and the exclusion of the study by Bertoglio and colleagues[6].
Random effect meta-analysis for PICC-related deep vein thrombosis rate and subgroup stratification by diagnosis.


Author
ES (95% CI)
% Weight
DVT events
Total PICCs
Onco-hematology
Bellesi 2013
0.050 (0.017, 0.137)
1.25
3
60
Cornillon 2017
0.081 (0.028, 0.213)
0.51
3
37
Subtotal (I^2 = .%, p = .)
0.059 (0.012, 0.105)
1.76
Oncology
Cotogni 2015
0.011 (0.004, 0.032)
11.25
3
269
Kang 2017
0.019 (0.010, 0.035)
11.52
9
477
Liu 2018
0.019 (0.005, 0.067)
4.50
2
104
Pittiruti 2014
0.006 (0.001, 0.031)
12.64
1
180
Tian 2010
0.006 (0.001, 0.034)
11.81
1
165
Subtotal (I^2 = 0.000%, p = 0.467)
0.010 (0.005, 0.016)
51.72
Mixed
DeLemos 2011
0.030 (0.005, 0.153)
1.12
1
33
Dupont 2015
0.023 (0.009, 0.058)
5.80
4
174
Evans 2010
0.030 (0.023, 0.038)
15.72
60
2014
Evans 2013
0.019 (0.014, 0.027)
16.73
35
1827
Mermis 2014
0.034 (0.013, 0.085)
3.15
4
117
Sharp 2015
0.029 (0.011, 0.073)
4.01
4
136
Zerla 2017
(Excluded)
.
0
30
Subtotal (I^2 = 3.423%, p = 0.395)
0.024 (0.019, 0.029)
46.52
Heterogeneity between groups: p = 0.000
Overall (I^2 = 51.658%, p = 0.016);
0.019 (0.012, 0.025)
100.00
0 .02 .04 .06 .08 .1 .12 .14