Cardiovasc Intervent Radiol (2014) 37:990–1008
DOI 10.1007/s00270-013-0771-3

CLINICAL INVESTIGATION VENOUS INTERVENTIONS

Centrally Inserted External Catheters and Totally Implantable Ports for the Delivery of Chemotherapy: A Systematic Review and Meta-Analysis of Device-Related Complications

S. Kulkarni · O. Wu · R. Kasthuri · Jon G. Moss

Received: 25 June 2013 / Accepted: 6 September 2013 / Published online: 13 November 2013

Abstract
Purpose This systematic review and meta-analysis aimed to evaluate the risks of complications (infectious and non-infectious) including the need for device removal associated with centrally inserted external catheters compared with totally implantable ports in patients undergoing chemotherapy.
Methods Relevant major electronic databases were searched from inception to December 2012. All randomized controlled trials (RCT) and observational studies that compared centrally inserted external catheters with totally implantable ports in patients undergoing chemotherapy were included in the systematic review. Meta-analysis was carried out to estimate the odds ratios of device-associated complications, including infection, non-infectious complications and device removal associated with external catheters relative to implantable ports.
Results Overall, five RCTs and 25 observational studies were included in the study. The studies were heterogeneous, and included adults and children, with different types of cancer, undergoing chemotherapy. Based on the pooled estimates from included studies, external catheters were associated with approximately a three to four-fold increase in the risks of infections, non-infectious complications and device removal compared implantable ports.
Conclusion The findings of this study showed that totally implantable ports are superior to external catheters in terms of catheter-associated complications. However, a formal health technology assessment on the clinical and cost-effectiveness of the use of implantable ports compared with external catheters is needed to inform policy makers of the relative value of investing in totally implantable devices compared with external catheters.

Keywords Central venous catheters · Totally implantable port · Complication rate · Infection rate · Systematic review · Meta-analysis

Introduction

Cancer requiring chemotherapy is common. The National Chemotherapy Advisory Group estimated ~65,000 programmes/year, and Hospital Activity Data for England reported 425,000 deliveries of chemotherapy for cancer during the year 2009–2010 [1]. Centrally inserted external venous catheters (CIEVCs) and totally implantable ports (TIPs) are devices commonly used in the delivery of chemotherapy to cancer patients. CIEVCs were introduced in the 1970s and modifications such as the Dacron cuff by Hickman in 1979 helped improve their durability. TIPs were introduced in the early 1980s offering an alternative strategy removing the need for an external catheter [2]. Infective and mechanical problems plaque any long-term venous access device, which can lead to interruption of treatment, increased patient morbidity, and the need for premature device removal and replacement [3]. There is a general perception that TIPs carry a lower risk of

S. Kulkarni · R. Kasthuri · J. G. Moss (✉)
Interventional Radiology Unit, Gartnavel General Hospital, 1053 Great Western Road, Glasgow G12 0YN, UK
e-mail: jonathan.moss@glasgow.ac.uk

S. Kulkarni
e-mail: shubhangkulkarni@nhs.net

O. Wu
Health Economics and Health Technology Assessment Unit, College of Medical, Veterinary and Life Sciences, University of Glasgow, 1 Lilybank Gardens, Glasgow, UK

complications than tunnelled central lines. There may also be other advantages resulting from the absence of an external line, such as patient acceptability and quality of life. However, TIPs are generally more complex to place requiring some tissue dissection and suturing. Each time a TIP is used, it must be needled for access, and the device is more costly than a CIEVC (prices vary from country to country but they are typically 3–10 times more expensive). Currently, there is no good evidence-based guidance to help health care providers and patients choose between these devices, and the decision is often based on local preference, availability of trained staff, cost pressures, duration of chemotherapy, and other unknown factors. This systematic review and meta-analysis aims to compare the complication profile and device-removal rate associated CIEVCs compared with TIPs in patients receiving chemotherapy for cancer.

Materials and Methods

A systematic review was performed according to the principles set out in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses [4]. The PRISMA checklist is provided in Table 2 in Appendix 1.

Eligibility Criteria

All prospective and retrospective studies that met the following criteria were included in the review:

- study population included patients who received chemotherapy through central venous access devices for the management of solid or haematological malignancies;
- studies that compared external catheters with internally implanted ports; and
- clinical outcomes included device-related complications, such as infection, mechanical failure and device removal.

No specific exclusion criteria and no limitations on language of publications were applied.

Data Sources

An extensive search was performed on MEDLINE and EMBASE from inception of the analysis to December 2012. Relevant keywords and permutations of search terms relating to CIEVCs and TIPs were combined with those relating to cancer and chemotherapy; subsequently, validated search filters for randomised controlled trials, and observational studies were applied to the search output [5]. An example of the electronic search strategy (used in MEDLINE) is presented in Appendix 2. In addition, the database search was supplemented by hand-searching of the reference lists of all for the studies meeting the inclusion criteria, and a citation search was performed to identify all articles that cited relevant original studies using the Web of Science database.

Study Selection, Data Items, and Data Extraction

Two reviewers (S. K., O. W.) screened all titles and abstracts of the studies retrieved from the search and excluded duplicates and studies that clearly did not meet the eligibility criteria. Full texts of the remaining studies were retrieved for further review. Data extraction of all included studies was performed according to a predefined protocol. One investigator performed the data extraction, and a second reviewer independently validated the data extraction. Where multiple publications referring to the same population and study time periods were found, only the publication reporting on the most up-to-date results was included. Data were extracted from each study for: (1) study design and follow-up period; (2) characteristics of the patient population; (3) type of intervention and comparator, including details on catheter placement; (4) prophylactic antibiotic use; (5) type of outcomes measured; and (6) all numerical data on device-related complications.

Risk of Bias in Individual Studies

The quality, including potential risk of bias, of the individual studies was assessed. To maintain a consistency of reporting, a validated generic checklist designed for quantitative studies (randomised and nonrandomised) was used to assess the quality of all studies included in the review [6]. Any disagreement relating to inclusion of studies, data extraction, or quality assessment between the reviewers was resolved by consensus.

Data Analysis

Different approaches have been used to estimate the incidence of device-related complications. In some studies, the number of patients was the chosen unit of measure, and the proportion of patients with complications was reported. In other studies, the number of devices was the chosen unit of measure, and the proportion of catheters resulting in complications was reported; this allows all data for patients who underwent multiple catheter placements during the study to be taken into account. In a few studies, catheter-days was used as the chosen unit of measure, and the number of patients who experienced device-related complications, or the total number of complication episodes observed per 1,000 catheter days, was reported; this takes into account the possibility of multiple complications (e.g.,

repeat infections) associated with one device. For the purpose of analysis, the number of devices was used as the unit of measure, and it was assumed that for studies that only provided data on patients, each patient received only one device during the study.

For each study, individual complication outcomes, including device removal if reported, was summarised by its risk ratio. Where appropriate, meta-analysis was performed based on the random effects model. Pooled risks of CIEVCs relative to TIPs were calculated for each complication outcomes. The results were expressed as odds ratios (ORs) with values >1.0 indicating an increased risk of complications associated with CIEVC. All analyses were stratified by patient population (adults or paediatric) and study design [randomized controlled trial (RCT), prospective cohort study, and retrospective studies]. Heterogeneity between the studies was examined with standard Chi square test. In addition, the I^2 statistic was also calculated. The association between study size and results was examined in funnel plots by plotting ORs against their SE, and asymmetry was measured by the asymmetry coefficient. All analyses were performed using Stata version 11.0 (StataCorp, College Station, TX, USA).

Results

In total, 4,557 publications (1,812 RCTs and 2,745 observational studies) resulted from searching the electronic databases (Fig. 1) with 5 additional observational studies identified through hand-searching. After removing duplicate articles, 2,726 titles and abstracts were screened. Subsequently, the full text of the 39 potentially eligible studies were reviewed, of which 5 RCTs and 25 observational studies met the inclusion criteria and were included in the systematic review (Table 1).

In four of the RCTs included in the review, oncology patients were randomised to receive either a CIEVC or a TIP. The primary aim of the fifth RCT [7] was to compare heparin and urokinase as "locking agents" to maintain device patency. Although this study reported outcomes associated with CIEVC and TIP, urokinase was withdrawn from the market by the United States Food and Drugs Administration due to concerns regarding potential adverse outcomes, and this resulted in the trial terminating prematurely. Because patients were not randomised between the two devices, for the purpose of this systematic review, this study was categorised as a prospective cohort study.

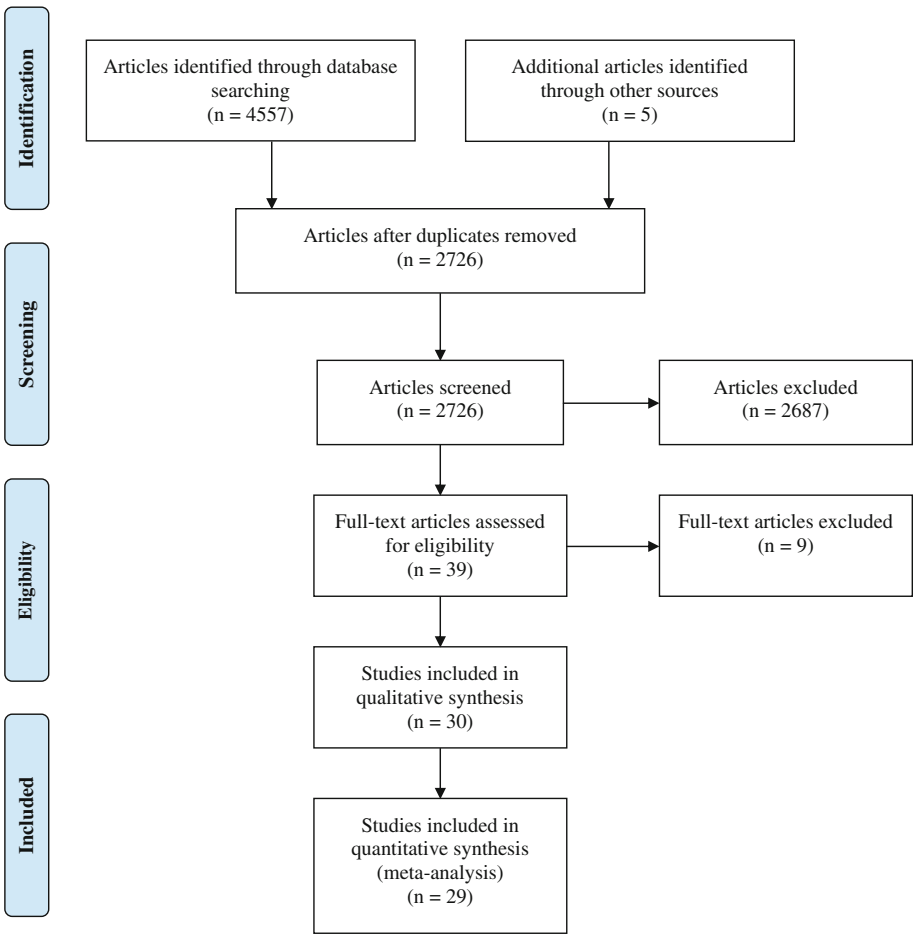

Fig. 1 PRISMA flow diagram of study identification and selection

Table 1 Characteristics of the included studies

Investigator/country/type of study	Patient population	Interventions	Antibiotic use	Outcome measures
Carde et al. [9]/France/single-centre RCT with 6-mo follow-up	Adults with solid and haematological malignancies undergoing intravenous chemotherapy for ≥6 months	Classical external catheter placed under local anaesthesia; majority placed by anaesthetists (n randomised = 53; n analysed = 46)	Adapted or broad-spectrum antibiotics given for treatment of infection	Device failure (complications leading to device removal)
		Port-a-Cath placed under general or local anaesthesia; majority placed by anaesthetists (n randomised = 53; n analysed = 50)		
				Functional duration (days between implantation and failure, death, or last consultation)
	Catheters used for drug administration and drawing blood			
				Patient acceptability
Kappers-Klunne et al. [10]/ Netherlands/single-centre RCT with follow-up until device removal or death	Adults with haematological malignancies (mainly acute leukaemia and some non-Hodgkin's lymphoma) with no adequate venous access	Double-lumen Hickman catheters placed by team of surgeons under local or general anaesthesia; flushed with heparinised saline weekly (n = 23)	Broad-spectrum antibiotics given when suspected of infection	Documented and suspected infection (positive cultures from catheter and/or peripheral vein with no demonstrable cause elsewhere)
	Catheters used for drug administration, drawing blood, and hyperalimentation			
				Complications leading to device removal
		Single-lumen Port-a-Caths placed by team of surgeons under local or general anaesthesia; flushed with heparinised saline at least every 4 weeks (n = 20)		Patient acceptability
Mueller et al. [11]/United States/ single-centre RCT with follow-up until device removal or death	Adults and children with solid and haematological malignancies undergoing chemotherapy for ≥1 month with anticipated difficult venous access	Hickman catheter placed by one of two surgeons; flushed after use or daily with diluted heparin solution (n randomised = 48; n analysed = 46)	Antibiotics given for treatment of clinically or microbiologically defined infection	Infection (exit site, tunnel with or without exit-site involvement, bacteremia, and bacteremia with exit-site and/or tunnel)
				Mechanical problems (breakage, displacement, inability to draw blood although infusion still possible)
				Complications leading to device removal
	Catheters used for chemotherapy or autologous bone marrow constitution			

Table 1 continued

Investigator/country/type of study	Patient population	Interventions	Antibiotic use	Outcome measures
		Port-a-Cath placed by one of two surgeons; flushed after use or monthly with heparinised saline if unused (n randomised = 52; n analysed = 46)		
Johansson et al. [8]/Sweden/ multicentre RCT prematurely terminated[b]	Patients (>15 years) with acute leukaemia	Double-lumen central venous catheters placed by surgeons and anaesthetists; flushed with heparinised saline after use or at least twice weekly (n = 20)	Antibiotics given for treatment of infection when clinically indicated	Device survival time
				Infection (tunnel and exit site)
	Catheters used for intensive induction chemotherapy			Local bleeding complications leading to device removal
		Double-lumen port placed by surgeons and anaesthetists; primed with heparinised saline after each use or monthly (n = 17)		
Ross et al. [18]/United States/ prospective cohort	Consecutive paediatric patients (median age 10 years) with solid and haematological malignancies; catheters were used for drawing blood	External catheters placed under general anaesthesia; flushed daily with heparin solution [n = 39 (41 catheters)]	Not reported	Complications child and parental acceptance
				Costs
	Sampling and administration of chemotherapy, fluids, antibiotics, hyperalimentation, and blood products			
		Ports placed under general anaesthesia, flushed every 4–6 weeks with heparin solution [n = 49 (50 catheters)]		
Wurzel et al. [20]/United States/ prospective cohort with follow-up for ≥30 days	Paediatric oncology patients with solid and haematological malignancies	Hickman lines placed by paediatric surgeons (33 catheters)	Preoperative antibiotics: 33 % Hickman and 47 % Port-a-cath	Infection
	Patient who failed one type of catheter often subsequently received the other type of catheter; patients in whom referral for bone marrow transplantation was anticipated received Hickman catheters			
		Port-a-Caths placed by paediatric surgeons (45 catheters)		
Mirro et al. [17]/United States/ prospective cohort with follow-up for a median of 376 days	Consecutive paediatric oncology patients with solid and haematological malignancies	Single-lumen Hickman or Broviac catheters placed under general anaesthesia; flushed twice daily (204 catheters)	Not reported	Infection (catheter exit site or port infection, tunnel infection, septicaemia)

Table 1 continued

Investigator/country/type of study	Patient population	Interventions	Antibiotic use	Outcome measures
	Catheters used to administer chemotherapy, blood products, and hyperalimentation when indicated			
				Other complications (obstruction)
		Port-a-Cath placed under general anaesthesia; flushed every 2 weeks (82 catheters)		Catheter removal
Ingram et al. [15]/Canada/ prospective cohort with follow-up >22 months	Paediatric haematology–oncology patients	Consecutive external catheters inserted under general anaesthesia; flushed daily with heparin solution (130 catheters)	Antibiotics given for treatment of infection	Device-related infection (blood/line infections, tunnel/exit site/pocket infections)
				Mechanical complications (occlusion, line rupture, and accidental dislodgement)
		Consecutive Port-a-Cath inserted under general anaesthesia; flushed every 4–6 weeks with heparin solution (144 catheters)		
				Device removal
La Quaglia et al. [16]/United States/prospective cohort with follow-up until first infection	Paediatric patients (≤16 years) with solid and haematological malignancies	Double-lumen external catheters; flushed daily with heparin solution (229 catheters)	Not reported	Infection (bacteremia, tunnel infection, pocket infection, and site infection)
		Ports; flushed monthly with heparin solution (42 catheters)		
				Time to first infectious complication
Wiener et al. [19]/United States/ multicentre prospective cohort	Paediatric oncology (≤21 years) patients with solid and haematological malignancies	External catheter; majority inserted under general anaesthesia (735 catheters)	Perioperative antibiotics given in 48 % of insertions	Removal due to infection, occlusion, and dislodgement
		TIP device; majority inserted under general anaesthesia (290 catheters)		
Groeger et al. [14]/United States/ prospective cohort followed-up until device removal or death (>500 days)	Consecutive patients with solid and haematological malignancies requiring chemotherapy	Hickman; flushed daily with heparinised saline [$n = 788$ (923 catheters)]	Not reported	Device-related infection (bacteremia or fungemia, tunnel infection, port-pocket infection, cutaneous site infection)
		Port-a-Cath; flushed every 4–6 weeks if not in use with heparinised saline [$n = 680$ (707 catheters)]		
Dillon et al. [7]/United States/ prospective cohort[a] planned for 3 years but prematurely terminated at 18 months (median 4.5)	Patients (≤21 years) with solid and haematological malignancies undergoing chemotherapy	All patients randomised to urokinase or heparin and stratified by type of catheter	Use of Bactrim or Septra or oral antifungal agents per institutional protocols	Time to first catheter occlusion (blockage of at least one catheter and inability to infuse fluid or withdraw blood)

Table 1 continued

Investigator/country/type of study	Patient population	Interventions	Antibiotic use	Outcome measures
	Patients were randomised to prophylactic urokinase or heparin every 2 weeks			
		Broviac or Hickman inserted according to individual institutional protocols and practices; flushed every 2 weeks ($n = 288$)		
		Ports inserted according to individual institutional protocols and practices; flushed every 2 weeks ($n = 281$)		
				Time to first catheter-related infection (positive blood culture from the catheter with no other source of infection)
Adler et al. [12]/Israel/prospective cohort; median duration 156.5 days	Paediatric haematology–oncology and haematopoietic stem cell transplant (HSCT) patients (general practice policy to use Hickman in those with HSCT and implantable ports in others)	Hickman lines placed by paediatric surgeon (173 catheters)	Antimicrobial therapy to treat infection	Infection (catheter-associated bloodstream infection, exit-site infection)
		Implantable ports placed by paediatric surgeon (246 catheters)		
				Total catheter days
Allen et al. [13]/United States/prospective cohort with follow-up for 12 months	Paediatric oncology patients (median age 6 years) with solid and haematological malignancies, including those who had received SCT	Tunnelled external; flushed daily with heparinised saline (n = not reported)	Antimicrobial therapy to treat infection	Infection (catheter-associated bloodstream infection)
		TIP device; flushed with heparin after use or every 4 weeks if not in use (n = not reported)		
		Overall cohort $n = 139$		
Handrup et al. [21]/Denmark/prospective cohort with follow-up until time of removal, death, or end of study (follow-up ≥12 months)	Paediatric patients with acute lymphoid leukaemia; only data on patients' first catheters were included	External catheters placed under general anaesthesia; flushed with heparin solution weekly ($n = 63$)	Antibiotics given for treatment of infection	Infection (catheter-associated bloodstream infection)
				Catheter removal (infection, mechanical complications)
		TIP device placed under general anaesthesia; flushed with heparin solution monthly when not in use ($n = 35$)		

Table 1 continued

Investigator/country/type of study	Patient population	Interventions	Antibiotic use	Outcome measures
Guenier et al. [27]/France/ retrospective cohort	Patients aged 3–78 years (mean age 44) with solid and haematological malignancies	Double-lumen Hickman placed under local anaesthesia except for very young patients ($n = 144$)	Not reported	Catheter removal due to complications
		Port-a-Cath placed under local anaesthesia except for very young patients ($n = 276$)		
Wacker et al. [35]/Switzerland/ retrospective cohort	Paediatric oncology patients with solid and haematological malignancies	External catheters placed by surgeon; flushed 3 times/wk with heparinised solution ($n = 44$; 59 catheters)	Some patients were given antibiotics	Complications (infection, obstruction, and other)
		Port-a-Cath placed by surgeon; flushed monthly with heparinised solution [$n = 33$ (34 catheters)]		
		Choice of catheters based on frequency of use, age, and ability of child or family to handle an external catheter		
	Catheters used for blood drawing, medication, blood products, hydration, and nutrition			
Pegues et al. [32]/United States/ retrospective matched case-controls	Adult oncology patients with solid tumours matched for primary solid tumour, presence of metastases, age, sex, and date of catheter insertion	Hickman placed by surgeons ($n = 47$)	Some patients were given prophylactic antibiotics	Catheter-associated infection
				Catheter removal
		Implanted port placed by surgeons ($n = 94$)		
Gleeson et al. [26]/United States/ retrospective cohort	Patients with gynaecological malignancies for chemotherapy, hyperalimentation, and supportive care	Externalised Groshong catheters placed by oncologists; flushed weekly when not in use with normal saline (67 catheters)	Not reported	Exit-site infection venous thrombosis (venography confirmed)
	Some patients had major surgery at time of placement			
		Hickman ports placed by oncologists; flushed monthly when not in use with heparin solution (37 catheters)		
Keung et al. [28]/United States/ retrospective cohort	Oncology patients who had central venous access device	Hickman and Groshong catheters placed by surgeons mostly under local anaesthesia; flushed daily with heparinised solution (69 catheters)	Prophylactic antibiotics given	Catheter-related infection (bacteremia and site infection)
		Subcutaneous ports placed by surgeons mostly under local anaesthesia; flushed every 4 weeks with heparinised solution (42 catheters)		

Table 1 continued

Investigator/country/type of study	Patient population	Interventions	Antibiotic use	Outcome measures
Eastridge and Lefor [24]/United States/retrospective cohort	Adult patients with solid and haematological malignancies	Hickman lines placed by one single surgeon with majority under local anaesthesia; flushed daily with heparin (209 catheters)	No perioperative antibiotics	Infectious complications requiring removal
				Thrombotic complications requiring removal
		Ports placed by same surgeon majority under local anaesthesia; flushed with heparin after use or every 4 weeks if not in use (113 catheters)		
Silver et al. [34]/United States/retrospective cohort	Patients with gynaecological malignancies	External catheters placed in operating room by/supervised by attending physician (64 catheters)		Pneumothorax, bacteremia catheter removal
	Catheters used to administer chemotherapy, blood products, and hyperalimentation			
				Deep neck and thoracic vein thrombosis
		Ports placed in operating room by/supervised by attending physician (152 catheters)		
Minassian et al. [30]/United States/retrospective cohort	Patients with gynaecological malignancies	Single- or double-lumen Hickman placed under local anaesthesia; flushed 3 times/wk when not in use (68 catheters)	Not reported	Catheter-related complications (infections, venous thrombosis documented by venogram or Doppler, port extrusion, malposition, and migration)
		Port-a-Cath placed under local anaesthesia; flushed monthly when not in use (162 catheters)		
		Peripheral access system ports placed under local anaesthesia; flushed monthly when not in use (75 catheters)		
Koolen et al. [29]/Netherlands/retrospective cohort	Adult patients with advanced solid tumours requiring chemotherapy	Hickman catheters inserted under local anaesthesia by surgeons [$n = 114$ (128 catheters)]	Not reported	Catheter infection (high clinical suspicion with fever, necessitating removal)
				Catheter-related thrombosis (confirmed by ultrasound or phlebography) Pneumothorax
				Accidental removal
		Port-a-Cath inserted under local anaesthesia by surgeons [$n = 37$ (38 catheters)]		

Table 1 continued

Investigator/country/type of study	Patient population	Interventions	Antibiotic use	Outcome measures
Basford et al. [22]/Canada/ retrospective cohort	Paediatric patients with solid and haematological malignancies (48 % leukaemia) who had a central venous catheter placed for chemotherapy for >1 week; those <1 month and >18 year were excluded	External tunnelled catheters inserted by radiologists or surgeons (52 catheters)	Not reported	Infection (exit site or port pocket, tunnel infection and microbial colonisation of the catheter)
		Ports inserted by radiologists or surgeons (46 catheters)		Mechanical complications (dislodgement, catheter fracture, occlusion, venous thrombosis, and port-pocket dehiscence)
Estes et al. [25]/United States/ retrospective cohort	Patients with gynaecological malignancies receiving chemotherapy	External catheters placed by oncologist under local anaesthesia (65 catheters)	Antibiotics were not routinely given before procedure	Complications—mechanical, infectious, or thrombotic
		Ports placed by oncologist under local anaesthesia (51 catheters)		
Pracchia et al. [33]/Brazil/ retrospective cohort	Patients with haematological malignancies	Partially implanted catheters inserted by surgeons; flushed weekly with heparinised solution ($n = 54$)	Not reported	Infection rate
				First infection-free survival
	Catheters used for chemotherapy, transfusion of haemo-components, and collection of specimens for tests as required			
				Infection removal rate
				Time to removal due to infection
		Completely implanted catheters inserted by surgeons; flushed monthly with heparinised solution ($n = 42$)		
Ng et al. [31]/United Kingdom/ retrospective cohort	Adults with solid tumours for infusional chemotherapy	Hickman line placed by radiologists or surgeons; flushed weekly with heparinised saline ($n = 22$; 30 devices)	One Hickman line and two Port-a-cath patients received prophylactic antibiotics	Rate of complications (infection, blockage, leakage, and displacement)
		Port-a-Cath placed by radiologists or surgeons; flushed biweekly or monthly depending on dosing regimen [$n = 31$ (33 devices)]		
				Complication-free catheter duration
				Rate of catheter removal due to complications

Table 1 continued

Investigator/country/type of study	Patient population	Interventions	Antibiotic use	Outcome measures
Zganjer et al. [36]/Croatia/ retrospective cohort	Paediatric oncology patients (mean age 5 year) with solid tumours for chemotherapy	External catheters with most inserted by surgeons (121 catheters); Port-a-Cath with most inserted by surgeons (73 catheters)	Antibiotics given to treat infection	Complications (exit-site infections, tunnel or port-pocket infections, catheter sepsis, catheter thrombosis, deep venous thrombosis, catheter displacement or damage)
Beckers et al. [23]/Netherlands/ retrospective cohort	Adult patients with solid and haematological	Central venous catheters inserted by intensive care doctors and surgeons in operating room; flushed with heparin solution after use ($n = 15$)	Not reported	Infection (catheter related, suspected catheter related, and not catheter related; non-catheter related infections not included in analysis)
	Malignancies; central venous catheters were primarily indicated in patients with haematological cancers, with the exception of Hodgkin lymphoma; implanted access ports were primarily indicated in patients with solid cancers and Hodgkin lymphoma			
		Implanted access ports inserted by intensive care doctors and surgeons in operating room; flushed with heparin solution every 5–6 week if not in use ($n = 28$)		
				Thrombosis (catheter related)
	Catheters used for administration of chemotherapy and blood products			

n number randomised (may not equate to number analysed in the study), *LMWH* low molecular weight heparin

[a] Patients were randomised to urokinase or heparin and then stratified by type of central venous device. This study was classified as a prospective cohort study in this systematic review

[b] Patient recruitment was terminated early due to high rate of extensive local bleeding after port placement

A second trial was also closed prematurely due to excessive bleeding in the TIP arm [8]. The four RCTs were performed in adults (age >15 years). The devices were inserted by either anaesthetists [8, 9] or by surgeons [8, 10, 11]. The management of the devices regarding prophylactic antibiotics use and the frequency of anticoagulant "locking" varied amongst the trials, e.g., between twice weekly to every 2 weeks for anticoagulant "locking." The primary outcomes reported in these trials were catheter-associated complications, including infection, mechanical problems, thrombotic occlusion, and complications leading to device removal. Overall, the follow-up periods of the RCTs ranged from 13 to 30 months.

In terms of observational studies, 11 prospective (including the Dillon et al. RCT) [5, 12–21] and 15 retrospective studies [22–36] evaluated the use of venous catheters in different patient populations. 11 studies were in the adult population [14, 23–26, 28–34], of which 4 recruited only gynaecological patients [25, 26, 30, 34], 13 were performed in children (age ≤21 years) [7, 12, 13, 15–22, 35, 36], and 1 was performed in a mixed population (age 3–78 years); for the purpose of analysis, this study population was defined as adult [27]. Devices were inserted exclusively by surgeons in ten studies [12, 20, 23, 24, 28, 29, 32, 33, 35, 36], by surgeons or radiologists in two studies [22, 31], and by an oncologist or attending physician in 3 studies [25, 26, 34]. The primary outcomes of all of the studies were catheter-associated complications and complications leading to device removal with a particular emphasis on infection. Secondary outcomes included device-related anxiety and device acceptability by the patients and number of catheter days.

Assessment of Risk of Bias

Overall, the RCTs were well performed and fulfilled the majority of the quality assessment criteria partially or in full (Fig. 2). The major limitations were small sample sizes, particularly in two RCTs [8, 10], and the absence of any estimates of variance or uncertainty for the main results. Similarly, among the observational studies, ~50 % of the studies failed to report measures of uncertainty for the main results. Although the majority of the studies reported details of the analytical methods, only 40 % of the studies reported an estimate of variance and reported the results with sufficient details, and only 20 % of the studies controlled for potential confounding factors.

Device-Related Infectious Complications

All studies reported on device-related infectious complications, such as exit site, tunnel, port pocket, and catheter line infections as well as bacteraemia. However, one study did not report separate data for the two devices being compared and was excluded from the meta-analysis [13]. Overall all four RCTs, with the exception of the one terminated prematurely (due to bleeding complications) [8], reported a greater rate of infection in the CIEVC arm compared with the TIP arm. Meta-analysis of the data from the four RCTs showed that CIEVCs were associated with an increased risk of infection compared with TIPs; however, the difference was not statistically significant (OR 1.82; 95 % CI 0.93–3.55). Pooled analysis of the observational data supported the increased risk of infection with external catheters (Fig. 3). In particular, the increase in infection risk was greater among adult patients [OR 8.34; 95 % CI 6.14–11.32 (based on only one prospective study) and OR 3.45; 95 % CI 2.32–5.11 (based on pooled analysis of 12 retrospective studies)] than paediatric patients [OR 2.70; 95 % CI 1.91–3.82 (based on pooled analysis of nine prospective cohorts) and OR 1.74; 0.94–3.21 (based on pooled analysis of three retrospective studies)]. Overall, evidence of significant heterogeneity and moderate inconsistency was observed among retrospective studies of adult patients ($p = 0.035$, I^2 47 %) and among prospective studies of paediatric patients ($p = 0.011$, I^2 60 %).

Other Device-Related Complications

Only two of the four RCTs reported other device related complications [8, 11], and the pooled analysis showed that CIEVC were associated with a statistically significant increase in risk of these complications than TIPs (OR 3.27; 95 % CI 1.23–8.70). Similar findings were observed in paediatric patients, based on data from prospective cohort studies (OR 4.00; 95 % CI 2.00–8.01) [7, 17, 18, 21]. Although data from the retrospective studies showed an increased risk of other complications in both adult and paediatric groups in those with an CIEVC these results were not statistically significant, evidence of significant heterogeneity was also observed among retrospective studies of adult and paediatric patients.

Device Removal Due to Complications

Device removal due to infection and other complications was reported in the majority of studies. Most reported a statistically significant increase in the risk of device removal in patients with a CIEVC compared with a TIP. The risk associated with device removal was approximately three times greater in CIEVCs compared with TIPs in the four RCTs (OR 2.82; 95 % CI 1.06–7.52) (Fig. 4). The estimated magnitude of the risk observed was greater in the observational studies of adult patients, and one prospective cohort reported a six-fold increase (OR 6.36; 95 % CI 4.11–9.85). Retrospective studies reported an

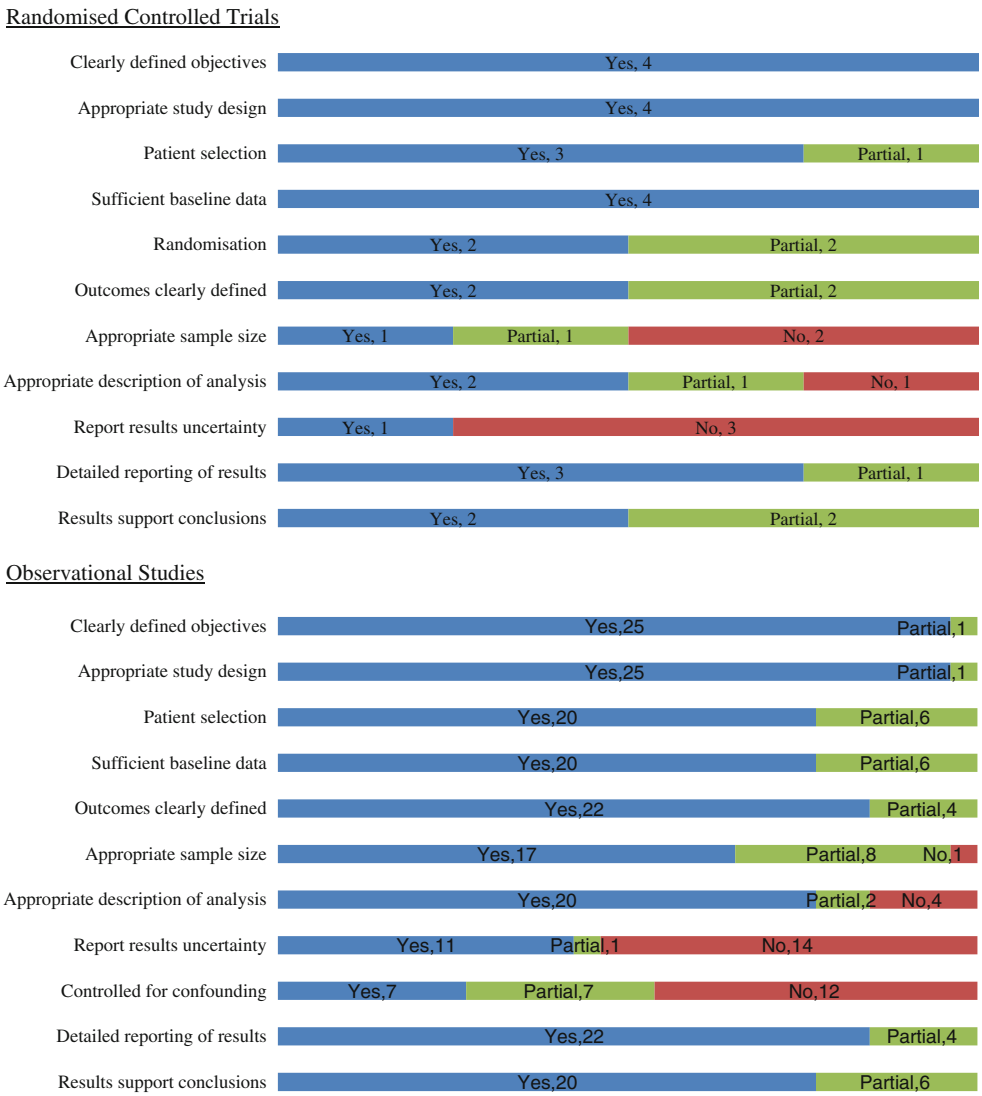

Fig. 2 Quality assessment of included studies

approximate fourfold increase (OR 3.79; 95 % CI 2.15–6.68). In the paediatric population, prospective cohort studies reported a three-fold increase in risk (OR 3.29; 95 % CI 2.24–4.82), and there was a two-fold increase in retrospective studies (OR 1.93; 95 % CI 0.84–4.43). Evidence of significant heterogeneity and inconsistency was observed among the randomised controlled trials ($p = 0.054$, I^2 61 %) and observational studies [$p = 0.005$, I^2 64 % (when pooling prospective studies in paediatrics); $p = 0.000$, I^2 74 % (when pooling retrospective studies in adults)].

Patient Acceptability

Only four studies (two RCTs and two observational cohorts) reported on patient acceptability in relation to the use of these devices. One trial (Carde et al.) reported that although patients generally accepted either device, the patient activity rate ($p = 0.02$) and hygiene ($p < 0.001$) were better showed within the TIP cohort [7]. Similarly, Kappers-Klunne et al. [10] commented on a general preference for TIPs due primarily to the absence of an external device and less maintenance. In the paediatric population, one study reported that 9 (7 %) of the CIEVCs were removed at the patient's request compared with none receiving a TIP [15]. Another study reported greater positive responses and fewer negative responses with TIPs than CIEVC when comparing ease of care, comfort, and overall acceptance [18].

Discussion

During the last three decades, many studies have suggested that CIEVCs are associated with an increased risk of device-related complications compared with TIPs. The

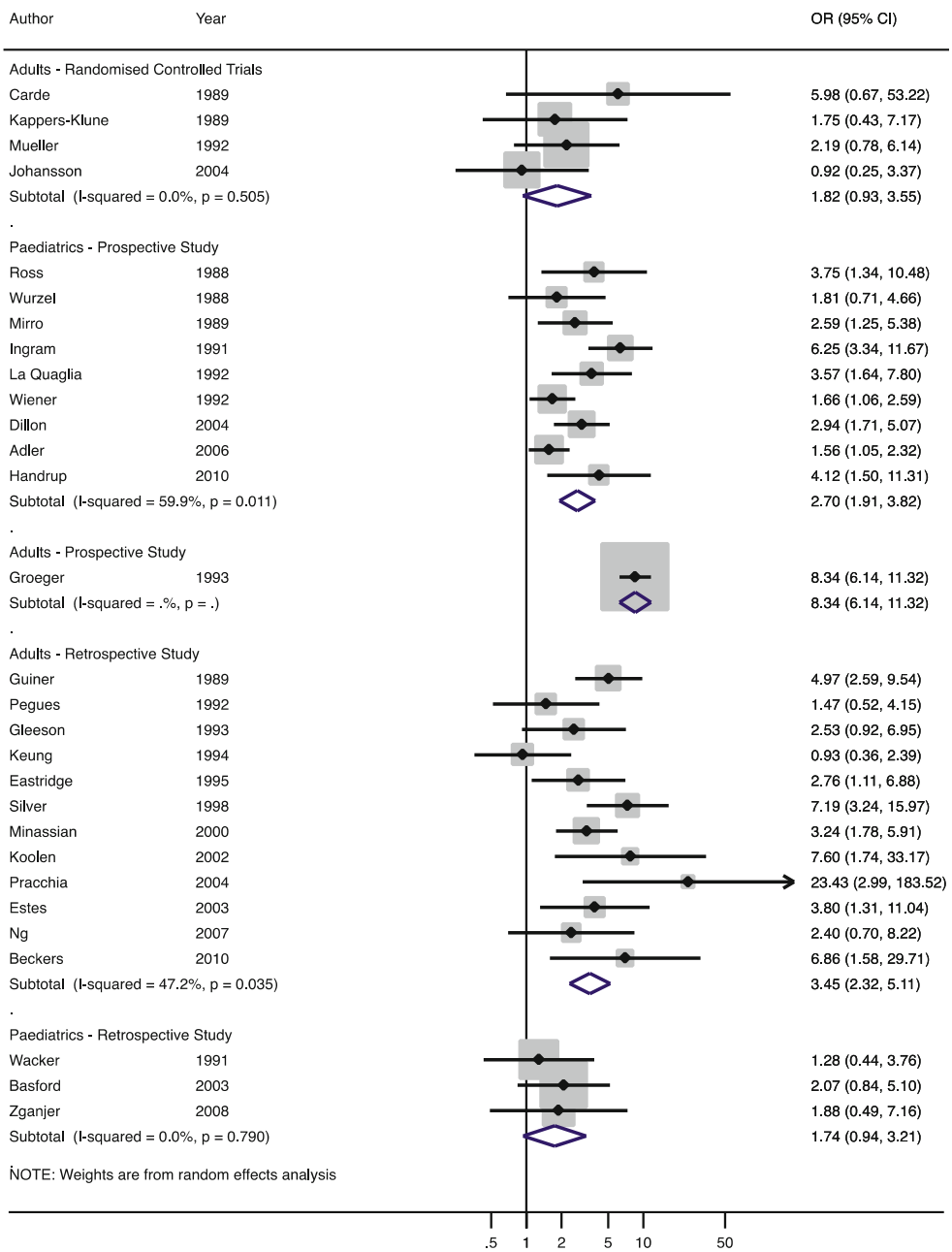

Fig. 3 Risk of infection

validity of this "opinion" has until now not been confirmed by a systematic review or meta-analysis and may explain why the use of TIP use varies widely across the world. This systematic review and meta-analysis generally supports the view that there is an increased risk of infection, noninfectious complication, and complication-related device removal among patients with CIEVC compared with those with TIPs albeit with some caveats.

The reported risk of infection varied substantially between individual studies, and this remained the case irrespective of study type and population. One explanation may be the wide variance in the definition of infection across individual studies, e.g., some studies only included catheter-associated bloodstream infections, whereas others included bloodstream infection, bacteraemia, and exit-site infections. The pooled ORs from the meta-analysis of the RCTs were approximately two-fold; however, this did not achieve statistical significance. However, this may be the result of the small samples sizes (largest reported $n = 106$). Observational studies showed an approximate three-fold increase in the risk of infection among adult and paediatric patients (prospective studies only) with CIEVCs

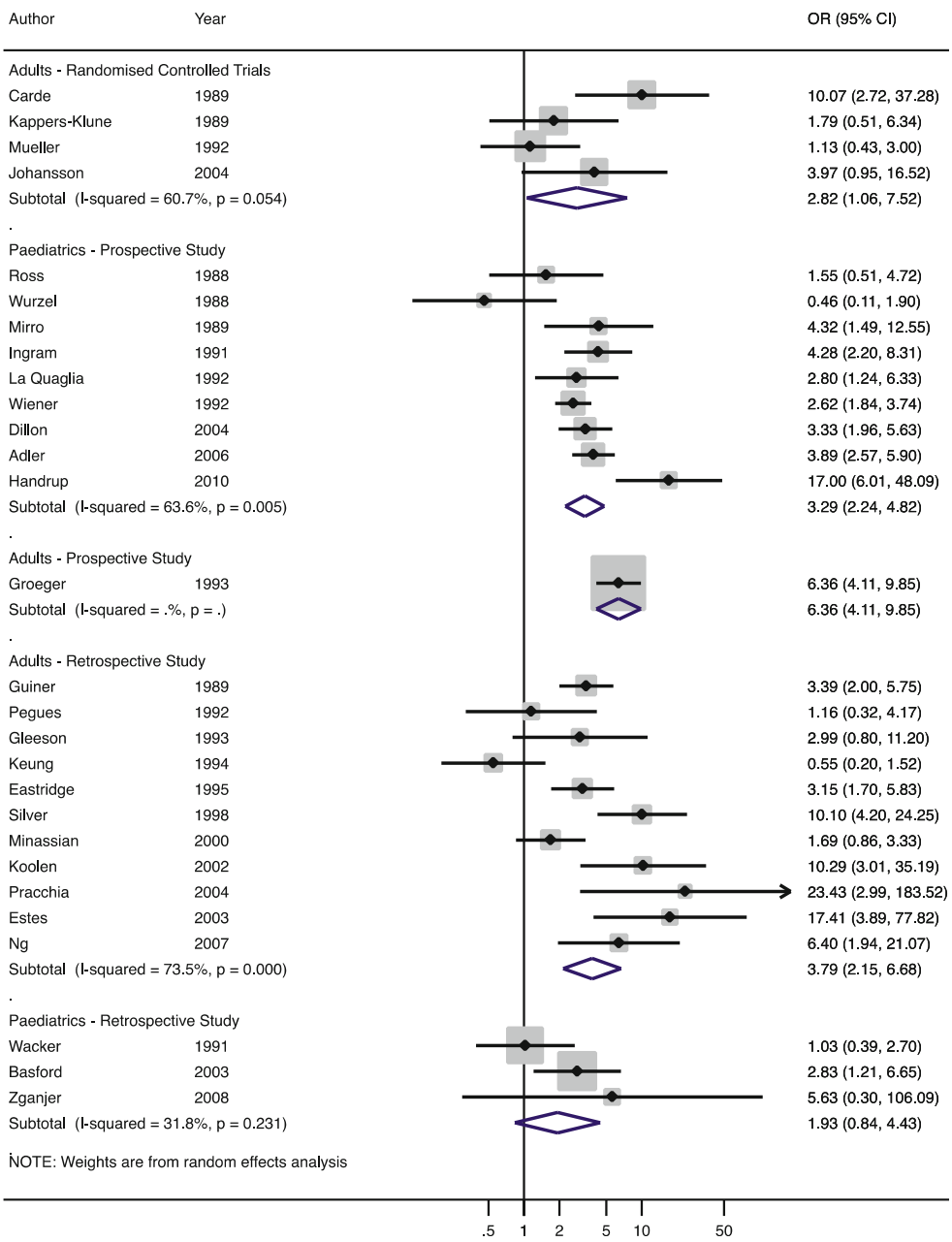

Fig. 4 Risk of device removal due to complications

compared with TIPs. However, there is evidence of substantial heterogeneity among these studies.

Due to the limited data available, noninfectious complication described in this study is a composite outcome that included mechanical complications, thrombosis, and bleeding. Therefore, unsurprisingly, the reported risk of noninfectious complications varied between studies, and the pooled analysis was associated with substantial heterogeneity. Nonetheless, it is interesting to note that the risk of noninfectious complications associated with CIEVC use relative to TIP use is similar to that of infection. Similarly, device removal included removal as a result of any complications (i.e., infectious and noninfectious complications). In the adult population, regardless of study type, the evidence is consistent in showing a statistically significant three- to four-fold increase in the risk of device removal among CIEVC patients compared with to those receiving TIPs. Similar findings were found in the prospective studies of the paediatric population but not in the retrospective studies.

The main limitation of this study is the heterogeneity of the evidence base; therefore, the pooled estimate should be

interpreted with caution. Although it is reasonable to conclude that the existing studies support that the risks of infectious, noninfectious complications, and device removal are greater with CIEVC compared with TIPs, the precise magnitude of these risks is less conclusive. As noted previously, studies included in this study vary in terms of population (e.g., age group, cancer type, and disease severity) and device-management protocols. An additional potential limitation is the 24-year time span (1988–2012) used for the literature search. However, there has been little significant modification of these devices since their inception. What has changed is the use of imaging to access the target vein and an expanding group of staff groups who now place these devices (anaesthetists, radiologists, nurse practitioners). However, we found no evidence that the age of participants in the studies (a surrogate for the age of the device) had any effect on the relative complication rates.

In the United States, TIP devices are the preferred choice for long-term venous access in oncology patients, whereas in the United Kingdom and continental Europe, CIEVCs play a central role. The decision-making processes behind this are complex and ill understood. In the United Kingdom, CIEVC placement is largely a nurse-led service, whereas TIPs are usually placed by doctors. A move away from CIEVC use to a TIP strategy will have an initial impact on both training and service delivery, which will need to be addressed. Interventional radiologists, anaesthetists, and surgeons will need to embrace change and support other groups (mainly nurse practitioners) in placing TIPs. The other major factor is the cost of the device itself; the purchasing costs of TIPs are substantially greater than the costs of CIEVCs. However, total costs associated with using a certain device should include not only the purchasing cost of the device but also the costs associated with device placement, management of complications, and replacement devices if necessary. Ng et al. [31] performed a simple cost analysis that compared total cost for both devices in the United Kingdom and estimated total costs of £1512/catheter for a CEIVC and £1483 for a TIP. In another study, Ross et al. [18] reported that the costs of both devices are comparable during the short-term, but potential cost savings may be achieved when TIPs are in use for >6 months. However, the decisions on adoption of health care interventions (pharmaceuticals and medical devices) should be informed by an extensive health technology assessment when both clinical benefits and cost-effectiveness are formally assessed.

This systematic review and meta-analysis has shown that CEIVC use is associated with an increased risk of infections, noninfectious complications, and need for device removal due to complications compared with TIPs. However, a formal health technology assessment on the clinical and cost-effectiveness of the use of TIPs compared with CEIVCs is needed to inform policy-makers on the relative value of investing in totally implantable devices compared with external catheters.

Conflict of interest All the authors declared that they have no conflict of interest.

Appendix 1

See Table 2.

Table 2 PRISMA checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known	3
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS)	3
METHODS			

Table 2 continued

Section/topic	#	Checklist item	Reported on page #
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number	None
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale	4
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study investigators to identify additional studies) in the search and date last searched	4
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated	4
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis)	4
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators	4
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made	4–5
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was performed at the study or outcome level), and how this information is to be used in any data synthesis	5
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means)	5
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if performed, including measures of consistency (e.g., I^2) for each meta-analysis	5–6
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies)	6
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if performed, indicating which were prespecified	6
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram	6, Figure 1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations	Table 1
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12)	7, Figure 2
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot	Figures 3, 4
Synthesis of results	21	Present results of each meta-analysis performed, including confidence intervals and measures of consistency	8–9, Figures 3, 4
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15)	9
Additional analysis	23	Give results of additional analyses, if performed (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16])	8–9, Figures 3, 4
DISCUSSION			

Table 2 continued

Section/topic	#	Checklist item	Reported on page #
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy-makers)	10
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias)	10
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research	12
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review	Title page

From Moher et al. [4]

For more information, visit: www.prisma-statement.org

Appendix 2: MEDLINE Search for Randomised Controlled Trials

1. (central venous adj8 (catheter* or access)).tw
2. percutaneouscateter*.tw.
3. (venous adj8 (catheter* or access)).tw.
4. vascular access.tw
5. hickman*.tw.
6. (implant* adj8 catheter*).tw.
7. (venous adj8 port*).tw.
8. port?a?cath*.tw.
9. (implant* adj8 port*).tw.
10. (implant* adj8 reservoir*).tw.
11. (port adj8 advice*).tw.
12. (subcutaneous* adj8 port*).tw.
13. (tunnel* adj8 catheter*).tw.
14. or/1-13
15. chemotherapy.tw.
16. tumo?r.tw.
17. cancer.tw.
18. malignan*.tw.
19. oncolg*.tw.
20. or/15-19
21. 14 and 20
22. randomized controlled trial/
23. random allocation/
24. double blind method/
25. single blind method/
26. clinical trial/
27. clinical trial, phase i.pt
28. clinical trial, phase ii.pt
29. clinical trial, phase iii.pt
30. clinical trial, phase iv.pt
31. controlled clinical trial.pt
32. randomized controlled trial.pt
33. multicenter study.pt
34. clinical trial.pt
35. exp clinical trials/
36. or/22-35
37. (clinical adj trial$).tw
38. ((singl$ or doubl$ or treb$ or tripl$) adj (blind$3 or mask$3)).tw
39. placebos/
40. randomly allocated.tw
41. (allocated adj2 random$).tw
42. or/37-41
43. 36 or 42
44. case report.tw
45. letter/
46. historical article/
47. or/44-46
48. 43 not 47
49. 21 and 48

References

1. http://www.hscic.gov.uk/searchcatalogue. Accessed 24 Mar 2013
2. Peters JL (2009) The history of central venous access. In: Hamilton H, Bodenham AR (eds) Central venous catheters. Wiley, Oxford
3. Boersma RS, Jie KSG, Verbon A, Van Pampus ECM, Schouten HC (2008) Thrombotic and infectious complications of central venous catheters in patients with hematological malignancies. Ann Oncol 19(3):433–442
4. Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009) Preferred reporting items for systematic reviews and meta-analysis: the PRISMA statement. PLos Med 6(7):e1000097
5. Scottish Intercollegiate Guidelines Network (2013) Search filters. http://www.sign.ac.uk/methodology/filters.html. Accessed 24 Mar 2013
6. Kmet LM, Lee RC, Cook LS (2004) Standard quality assessment criteria for evaluating primary research papers from a variety of

fields. Alberta: Alberta Heritage Foundation for Medical Research, 2004 HTA Initiative no. 13
7. Dillon PW, Jones GR, Bagnall-Reeb HA, Buckley JD, Wiener ES, Haase GM (2004) Prophylactic urokinase in the management of long-term venous access devices in children: a children's oncology group study. J Clin Oncol 22(13):2718–2723
8. Johansson E, Bjorkholm M, Bjorvell H, Hast R, Takolander R, Olofsson P et al (2004) Totally implantable subcutaneous port system versus central venous catheter placed before induction chemotherapy in patients with acute leukaemia: a randomized study. Support Care Cancer 12(2):99–105
9. Carde P, Cossetdelaigue MF, Laplanche A, Chareau I (1989) Classical external indwelling central venous catheter versus totally implanted venous access systems for chemotherapy administration: a randomized trial in 100 patients with solid tumors. Eur J Cancer Clin Oncol 25(6):939–944
10. Kappers-Klunne MC, Degener JE, Stijnen T, Abels J (1989) Complications from long-term indwelling central venous catheters in hematologic patients with special reference to infection. Cancer 64:1747–1752
11. Mueller BU, Skelton J, Callender DPE, Marshall D, Gress J, Longo D et al (1992) A prospective randomized trial comparing the infectious and noninfectious complications of an externalized catheter versus a subcutaneously implanted device in cancer-patients. J Clin Oncol 10(12):1943
12. Adler A, Yaniv I, Steinberg R, Solter E, Samra Z, Stein J et al (2006) Infectious complications of implantable ports and Hickman catheters in paediatric haematology–oncology patients. J Hospital Infect 62(3):358–365
13. Allen RC, Holdsworth MT, Johnson CA, Chavez CM, Heideman RL, Overturf G et al (2008) Risk determinants for catheter-associated blood stream infections in children and young adults with cancer. Pediatr Blood Cancer 51(1):53–58
14. Groeger JS, Lucas AB, Thaler HT, Friedlander-Klar H, Brown AE, Kiehn TE et al (1993) Infectious morbidity associated with long-term use of venous access devices in patients with cancer. Ann Intern Med 119(12):1168–1174
15. Ingram J, Weitzman S, Greenberg ML, Parkin P, Filler R (1991) Complications of indwelling venous access lines in the pediatric hematology patient: a prospective comparison of external venous catheters and subcutaneous ports. Am J Pediatr Hematol Oncol 13(2):130–136
16. La Quaglia MP, Caldwell C, Lucas A, Corbally M, Heller G, Steinherz L et al (1994) A prospective randomized double-blind trial of bolus urokinase in the treatment of established Hickman catheter sepsis in children. J Pediatr Surg 29(6):742–745
17. Mirro J Jr, Rao BN, Stokes DC, Austin BA, Kumar M, Dahl GV et al (1989) A prospective study of Hickman/Broviac catheters and implantable ports in pediatric oncology patients. J Clin Oncol 7(2):214–222
18. Ross MN, Haase GM, Poole MA, Burrington JD, Odom LF (1998) Comparison of totally implanted reservoirs with external catheters as venous access devices in pediatric oncologic patients. Surg Gynecol Obstet 167(2):141–144
19. Wiener ES, McGuire P, Stolar CJ, Rich RH, Albo VC, Ablin AR et al (1992) The CCSG prospective study of venous access devices: An analysis of insertions and causes for removal. J Pediatr Surg 27(2):155–163 (discussion 163–164)
20. Wurzel CL, Halom K, Feldman JG, Rubin LG (1988) Infection rates of Broviac–Hickman catheters and implantable venous devices. Am J Dis Child 142(5):536–540
21. Handrup MM, Moller JK, Frydenberg M, Schroder H (2010) Placing of tunneled central venous catheters prior to induction chemotherapy in children with acute lymphoblastic leukemia. Pediatr Blood Cancer 55(2):309–313
22. Basford TJ, Poenaru D, Silva M (2003) Comparison of delayed complications of central venous catheters placed surgically or radiologically in pediatric oncology patients. J Pediatr Surg 38(5):788–792
23. Beckers MM, Ruven HJT, Seldenrijk CA, Prins MH, Biesma DH (2010) Risk of thrombosis and infections of central venous catheters and totally implanted access ports in patients treated with cancer. Thrombosis Res 125:318–321
24. Eastridge BJ, Lefor AT (1995) Complications of Indwelling venous access devices in cancer-patients. J Clin Oncol 13(1):233–238
25. Estes JM, Rocconi R, Straughn JM, Bhoola S, Leath CA, Alvarez RD et al (2003) Complications of indwelling venous access devices in patients with gynecologic malignancies. Gynecol Oncol 91(3):591–595
26. Gleeson NC, Fiorica JV, Mark JE, IPinelli DM, Hoffman MS, Roberts WS et al (1993) Externalized Groshong catheters and Hickman ports for central venous access in gynecologic oncology patients. Gynecol Oncol 51:372–376
27. Guenier C, Ferreira J, Pector JC (1989) Prolonged venous access in cancer-patients. Eur J Surg Oncol 15(6):553–555
28. Keung YK, Watkins K, Chen SC, Groshen S, Silberman H, Douer D (1994) Comparative study of infectious complications of different types of chronic central venous access devices. Cancer 73(11):2832–2837
29. Koolen DA, van Laarhoven HWM, Wobbes T, Punt CJA (2002) Single-centre experience with tunnelled central venous catheters in 150 cancer patients. Neth J Med 60(10):397–401
30. Minassian VA, Sood AK, Lowe P, Sorosky JI, Al-Jurf AS, Buller RE (2000) Longterm central venous access in gynecologic cancer patients. J Am Coll Surg 191(4):403–409
31. Ng F, Mastoroudes H, Paul E, Davies N, Tibballs J, Hochhauser D et al (2007) A comparison of Hickman line- and Port-a-Cath-associated complications in patients with solid tumours undergoing chemotherapy. Clin Oncol 19(7):551–556
32. Pegues D, Axelrod P, McClarren C, Eisenberg BL, Hoffman JP, Ottery FD et al (1992) Comparison of infections in Hickman and implanted port catheters in adult solid tumor patients. J Surg Oncol 49(3):156–162
33. Pracchia LF, Dias LCS, Dorlhiac-Llacer PE, DdAF Chamone (2004) Comparison of catheter-related infection risk in two different long-term venous devices in adult hematology-oncology patients. Rev Hospital Clin 59(5):291–295
34. Silver DF, Hempling RE, Recio FO, Piver MS, Eltabbakh GH (1989) Complications related to indwelling caval catheters on a gynecologic oncology service. Gynecol Oncol 70(3):329–333
35. Wacker P, Bugmann P, Halperin DS, Babel JF, Le Coultre C, Wyss M (1992) Comparison of totally implanted and external catheters in paediatric oncology patients. Eur J Cancer 28A(4–5):841–844
36. Zganjer M, Cizmic A, Butkovic D, Matolic M, Karaman-Ilic M, Stepan J (2008) Central venous catheters for chemotherapy of solid tumors: our results in the last 5 years. Coll Antropol 32(3):767–770