

The risk of catheter-related bloodstream infection with femoral venous catheters as compared to subclavian and internal jugular venous catheters: A systematic review of the literature and meta-analysis*

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Background: Catheter-related bloodstream infections are an important cause of morbidity and mortality in hospitalized patients. Current guidelines recommend that femoral venous access should be avoided to reduce this complication (1A recommendation). However, the risk of catheter-related bloodstream infections from femoral as compared to subclavian and internal jugular venous catheterization has not been systematically reviewed.

Objective: A systematic review of the literature to determine the risk of catheter-related bloodstream infections related to nontunneled central venous catheters inserted at the femoral site as compared to subclavian and internal jugular placement.

Data Sources: MEDLINE, Embase, Cochrane Register of Controlled Trials, citation review of relevant primary and review articles, and an Internet search (Google).

Study Selection: Randomized controlled trials and cohort studies that reported the frequency of catheter-related bloodstream infections (infections per 1,000 catheter days) in patients with nontunneled central venous catheters placed in the femoral site as compared to subclavian or internal jugular placement.

Data Extraction: Data were abstracted on study design, study size, study setting, patient population, number of catheters at each insertion site, number of catheter-related bloodstream infections, and the prevalence of deep venous thrombosis. Studies were subgrouped according to study design (cohort and randomized controlled trials). Meta-analytic techniques were used to summarize the data.

Data Synthesis: Two randomized controlled trials (1006 catheters) and 8 cohort (16,370 catheters) studies met the inclusion criteria for this systematic review. Three thousand two hundred thirty catheters were placed in the subclavian vein, 10,958 in the internal jugular and 3,188 in the femoral vein for a total of 113,652 catheter days. The average catheter-related bloodstream infections density was 2.5 per 1,000 catheter days (range 0.6–7.2). There was

no significant difference in the risk of catheter-related bloodstream infections between the femoral and subclavian/internal jugular sites in the two randomized controlled trials (i.e., no level 1A evidence). There was no significant difference in the risk of catheter-related bloodstream infections between the femoral and subclavian sites. The internal jugular site was associated with a significantly lower risk of catheter-related bloodstream infections compared to the femoral site (risk ratio 1.90; 95% confidence interval 1.21–2.97, $p = .005$, $I^2 = 35\%$). This difference was explained by two of the studies that were statistical outliers. When these two studies were removed from the analysis there was no significant difference in the risk of catheter-related bloodstream infections between the femoral and internal jugular sites (risk ratio 1.35; 95% confidence interval 0.84–2.19, $p = 0.2$, $I^2 = 0\%$). Meta-regression demonstrated a significant interaction between the risk of infection and the year of publication ($p = .01$), with the femoral site demonstrating a higher risk of infection in the earlier studies. There was no significant difference in the risk of catheter-related bloodstream infection between the subclavian and internal jugular sites. The risk of deep venous thrombosis was assessed in the two randomized controlled trials. A meta-analysis of this data demonstrates that there was no difference in the risk of deep venous thrombosis when the femoral site was compared to the subclavian and internal jugular sites combined. There was, however, significant heterogeneity between studies.

Conclusions: Although earlier studies showed a lower risk of catheter-related bloodstream infections when the internal jugular was compared to the femoral site, recent studies show no difference in the rate of catheter-related bloodstream infections between the three sites. (Crit Care Med 2012; 40:2479–2485)

KEY WORDS: catheter-related bloodstream infection; central venous catheter; femoral; jugular; meta-analysis; nosocomial infection; subclavian

Central venous catheters (CVCs) are ubiquitous in the intensive care unit (ICU). In the United States alone

15-million CVC days occur in ICU's each year (1). Central venous catheters are not without risk during both placement and while *in situ*. Recently,

much attention has been focused on catheter-related bloodstream infections (CRBI). Approximately 250,000 cases of CRBIs (80,000 in the ICU) occur in hospitals in the United States annually; an estimated 30,000 to 62,000 of these patients die as a result of this infection (1, 2). The cost of these infections is substantial, both in terms of morbidity and the financial resources expended (3). In order to improve patient outcome and reduce healthcare costs there

***See also p. 2528.**

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is currently considerable interest by healthcare providers, insurers, regulators and patient advocates in reducing the occurrence rate of these infections. Consequently, a number of healthcare organizations in the United States and Europe have published "Clinical Practice Guidelines" with the aim of reducing the frequency of CRBIs (2, 4–9). In common, these guidelines recommend "bundles of care" which include selection of catheter type, method of placement, care of the catheter, and timely removal of the catheter. With the institution of these bundles the occurrence rate of CRBI has been reduced to less than 3 per 1,000 catheter days in most hospitals in the United States and Europe (10).

The preferred site for placement of a nontunneled central venous catheter is complex and based on the skill and expertise of the operator, the availability and expertise of ultrasound-guided placement, the risk of bleeding and other complications (pneumothorax), as well as the urgency of placement. In emergent and high-risk situations, the femoral route is often chosen due to the ease and perceived lower insertion risk of this site (4, 11). While the Irish guidelines' recommendation is "to use the insertion site associated with the least likelihood of injury (jugular, femoral, subclavian)" (4) many of the clinical practice guidelines recommend that the femoral site be avoided due to the perceived higher risk of CRBI associated with this site. The 2011 recommendations from the "Healthcare Infection Control Practices Advisory Committee" of the Centers for Disease Control and Prevention state, "Avoid using the femoral vein for central access in adult patients" (class 1A recommendation) (2). This recommendation is echoed by the Infectious Disease Society of America (9). A class 1A recommendation (the highest level of evidence) refers to a recommendation supported by at least one randomized controlled trial (RCT) (12). As we were unaware that such evidence existed, we decided to perform a systematic review of the literature and perform a meta-analysis comparing the risk of CRBI for catheters placed in the femoral vs. the subclavian and internal jugular (IJ) veins. In order to improve the relevance and statistical power of our study we included RCT as well as cohort/observational studies.

MATERIALS AND METHODS

Identification of Trials. Our aim was to identify all relevant clinical trials that compared the risk of CRBI for nontunneled CVC placed in the femoral compared to either the subclavian and/or IJ sites. We included both RCT's as well as cohort studies. We restricted this analysis to human adults; however, there was no restriction as to the type of patient or the setting where the study was performed. Two of the authors (P.E.M. and M.F.) independently searched the National Library of Medicine's MEDLINE database for relevant studies in any language published from 1966 to October 2011 using the following medical subject headings and key words; catheterization, central venous AND catheter-related infection or sepsis AND femoral vein, subclavian vein or jugular vein, AND adult AND human. In addition, we searched Embase and the Cochrane Database of Systematic Reviews, the bibliographies of all selected articles and review articles that included information on CRBI's for other relevant articles. We also performed an Internet search (Google.com) to locate relevant data not published in peer-reviewed journals. This search strategy was done iteratively, until no new potential citations were found. We performed this meta-analysis according to the guidelines proposed by the Quality of Reporting of Meta-analyses group (13).

Study Selection and Data Extraction. Studies that reported/compared the rate of CRBI at the femoral and subclavian and/or IJ site were included in this review. Standardized criteria as published by National Nosocomial Infection Survey, the Centers for Disease Control and Prevention, and the Hospital in Europe Link for Infection Control through Surveillance were used to define CRBI (12, 14, 15). It should be noted that the Hospital in Europe Link for Infection Control through Surveillance definition includes local CVC infection (CR1) and general CVC infection (CR2) as well as "true" CRBI (CR3). Two of the authors (PEM, MF) independently abstracted data from all relevant studies using a standardized form. Data were abstracted on study design, study size, study setting, patient population, number of catheters at each insertion site, number of catheter days, number of CRBI's, and frequency of deep venous thrombosis (DVT). We recorded both the prevalence (percentage) and density (infections per 1,000 catheter days) at each site. The frequency of venous thrombosis of the cannulated vein (both symptomatic and asymptomatic) as diagnosed by screening ultrasonography was recorded.

Studies were sub-grouped according to study design (cohort and RCT). Summary data are presented as means (\pm SDs) and percentages as appropriate. Meta-analytic techniques were used to summarize the data. We compared the risk of CRBI for the femoral sites to the CRBI risk for the subclavian and IJ sites. We also compared the risk of infection between the subclavian and IJ sites. We used

the random effects model (more conservative) using Review Manager 5.1.4 (Cochrane Collaboration, Oxford, UK) and Comprehensive Meta-analysis 2.0 (Biostat, Englewood, NJ) for the analyses and considered $p \leq .05$ (two sided) as significant. We report binary outcomes as the risk ratio (RR). Summary effects estimates are presented with 95% confidence intervals (CIs). We assessed heterogeneity between studies for each outcome using the Cochran Q statistic (16), with $p \leq .10$ indicating significant heterogeneity (17), and I^2 with suggested thresholds for low (25%–49%) moderate (50%–74%) and high (>75%) values (18, 19). In order to increase both the scientific and the clinical relevance of our meta-analysis, a sensitivity analysis was used to explain moderate-to-high heterogeneity (20–22). In particular, we assessed those studies that contributed to the excess heterogeneity (i.e., when heterogeneity could not be explained by chance alone, indicating a poor-quality/biased study (18, 22). We performed a funnel plot to determine publication and study bias (22–25). A funnel plot is a graph of study effect (log scale of odds ratio) plotted on the horizontal axis and a measure of within-study variance (usually standard error of log) on the vertical axis (24). Devoid of bias, the funnel plot should be symmetrical and appear like an inverted funnel (22, 24). As it was possible that the risk of infection at a particular site could change over time, we performed a meta-regression plotting the risk ratio vs. the year the study was reported.

RESULTS

A flow diagram outlining the search strategy and study selection is outlined in Figure 1. We included all published and unpublished studies that compared the risk of CRBI among any of the three sites. Our search strategy produced ten studies (two RCTs and eight cohort); these are listed in Table 1 (26–36). The Welsh Healthcare Associated Infection Program was located by an Internet search. The surveillance of CVC-related infections became mandatory in Wales in September 2007. The data for 2009 and 2010 are reported on their web site (33, 34). Additional data were provided by their lead investigator (Dr. Wendy Harrison), and the data from 2009 and 2010 combined. The Welsh study used the Hospital in Europe Link for Infection Control through Surveillance criteria (15) while the remaining studies used the National Nosocomial Infection Survey criteria (14) to define catheter-related infection.

One RCT compared the subclavian to the femoral site in 270 patients; the other RCT compared placement of a nontunneled dialysis catheter in the IJ vs. femoral site in 736 patients (35, 36).

Together, these two RCT's followed the patients for 7,511 catheter days (mean 8.3 ± 2.5 days/catheter). Screening Doppler ultrasonography was performed in both these studies. The eight cohort studies evaluated 16,370 catheters (3094

subclavian [19%], 10,592 IJ [65%] and 2684 femoral [16%]) for a total of 106,141 catheter days (mean 6.4 ± 1.8 days per catheter).

The average CRBI density was 2.5 ± 1.9 per 1,000 catheter days (range 0.6–7.2). The frequency of CRBI is presented in Table 1. One RCT each compared the risk of CRBI for the femoral compared to the either the subclavian or IJ site. There was no significant difference in the risk of CRBI between the two groups in both these studies (i.e., no level 1A evidence). Overall, there was no significant difference in the risk of CRBI for the femoral compared to the subclavian site (RR 1.75; 95% CI 0.80–3.8, $p = .16$). There was, however, significant heterogeneity between studies ($I^2 = 68\%$, $p = .002$). This heterogeneity was largely explained by the outlying studies of Lorente et al (28) and Nagashima et al (29). When these two studies were removed from the analysis, there was no heterogeneity between studies (RR 1.02; 95% CI 0.64–1.65, $p = .92$, $I^2 = 0\%$) (see Fig. 2). The funnel plot showing publication and study bias is shown in Figure 3. The funnel plot indicates some degree of publication bias; furthermore, the studies of Lorente et al (28) and Nagashima et al (29) are noted to be statistical outliers (the treatment effect is larger than expected by chance alone). Meta-regression showed a significant interaction between the risk of infection and the year of publication ($p = .05$), with the earlier studies favoring the subclavian site. Overall, the IJ site was associated with a significantly lower risk of CRBI compared to the femoral site (RR 1.90; 95% CI 1.21–2.97, $p = .005$, $I^2 = 35\%$; see Fig. 4). This difference was largely

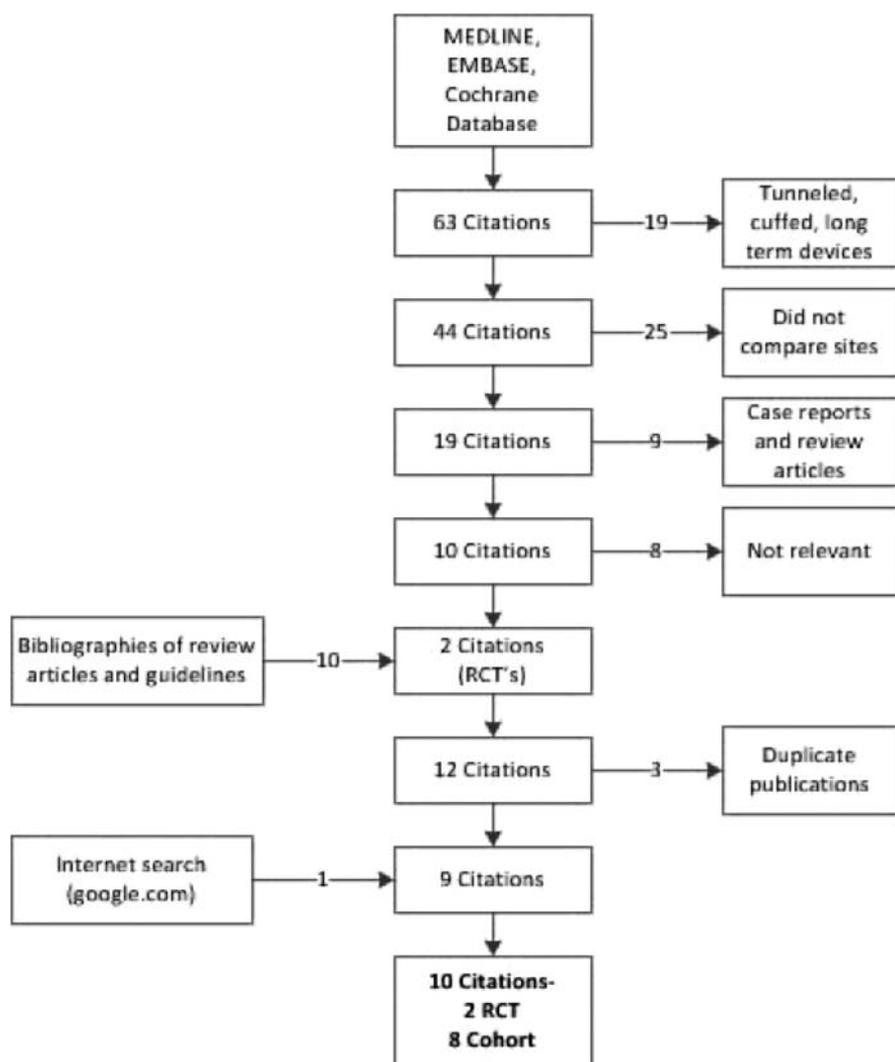


Figure 1. Flow-chart of study selection. RCT, randomized controlled trial.

Table 1. Summary of studies included in meta-analysis

First Author	Year	RCT/C	Country	Patients	Catheter Days	Number of Catheters			Catheter Related Bloodstream Infection n/1,000 Days		
						Subclavian	Internal Jugular	Femoral	Subclavian	Internal Jugular	Femoral
Goetz (26)	1998	C	USA	ICU/ward	2 700	137	72	91	2.6	1.4	6.3
Deshpande (27)	2005	C	USA	ICU	2 810	221	191	139	0.88	0.0	2.98
Lorente (28)	2005	C	Spain	ICU	18 943	917	1 390	288	0.97	2.99	8.34
Nagashima (29)	2006	C	Japan	ICU/ward	7 516	184	339	244	3.8	6.1	15.7
Garnacho-Mont (30)	2008	C	Spain	ICU	12 784	585	626	387	5.6	3.4	6.0
Gowardman (31)	2008	C	Australia	ICU	2 725	59	204	150	0.0	0.7	1.3
Lemaster (32)	2010	C	USA	emergency room	3 662	53	392	130	2.5	2.3	0.0
Harrison (33,34)	2010	C	Wales	ICU	55 039	938	7378	1255	0.74	0.54	0.56
Merrer (35)	2001	RCT	France	ICU	2 727	136	—	134	0.63	—	1.48
Parienti (36)	2008	RCT	France	ICU-ARF	4 784	—	366	370	—	2.3	1.5

RCT, randomized controlled trial; C, cohort study; ICU, intensive care unit; ICU-ARF, patients with acute renal failure in the ICU.

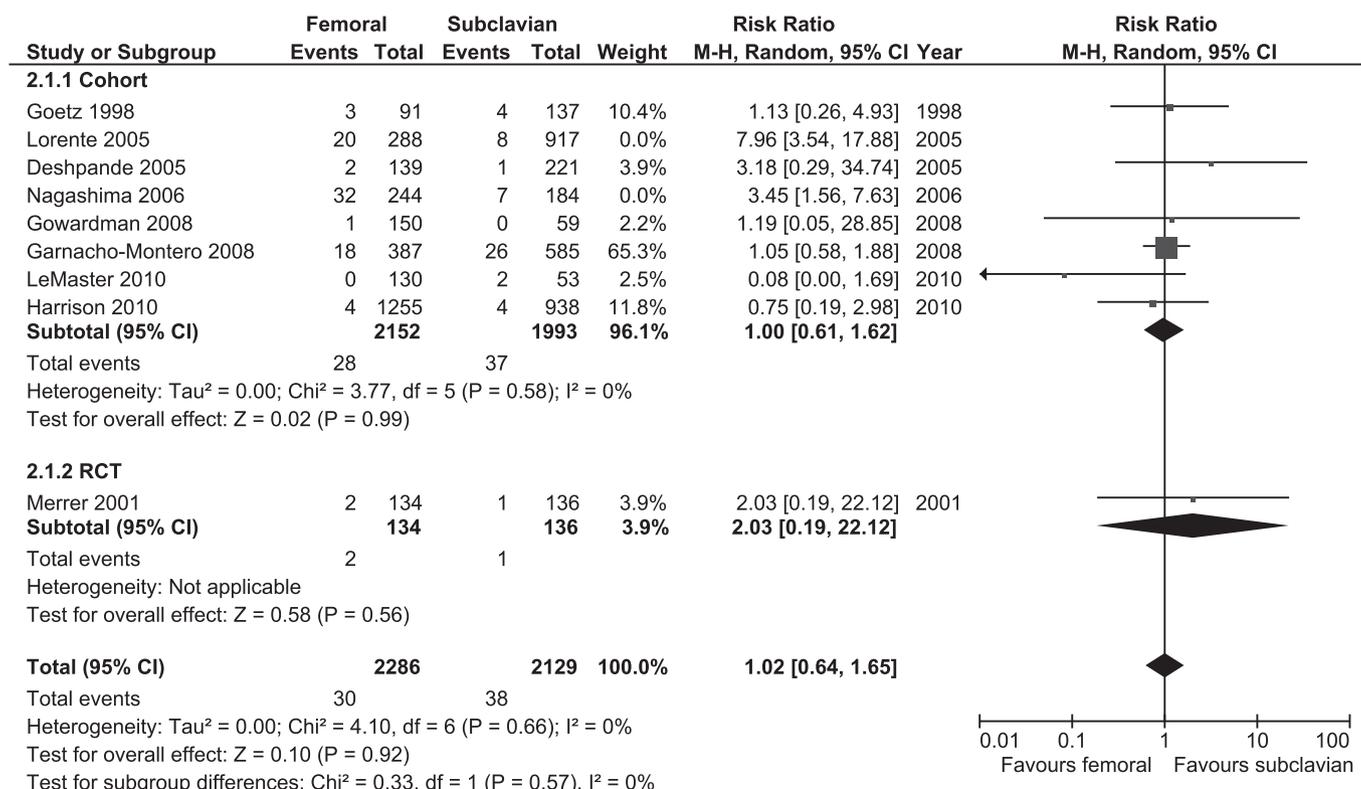


Figure 2. Comparison of the risk of catheter-related bloodstream infection for the femoral compared to the subclavian site. Studies are grouped by study type; randomized controlled trials (RCTs) and cohort studies. Weight is the relative contribution of each study to the overall treatment effect (risk ratio and 95% confidence interval [CI]) on a log scale assuming a random effects model. M-H, Mantel-Haenszel.

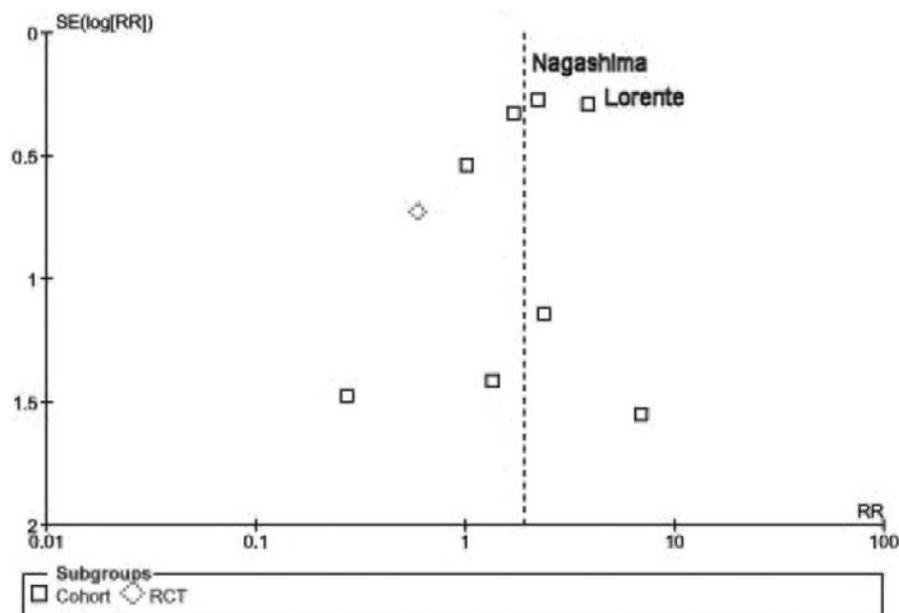


Figure 3. Funnel plot for potential publication bias for studies comparing the femoral and subclavian sites. RR, risk ratio; RCT, randomized controlled trial.

explained by the studies of Lorente et al (28) and Nagashima et al (29). When these two studies were removed from the analysis there was no significant difference in the risk of CRBI between the femoral and IJ sites (RR 1.35; 95% CI 0.84–2.19, $p = .2$, $I^2 = 0\%$). Meta-regression showed

a significant interaction between the risk of infection and the year of publication ($p = .01$), with the earlier studies favoring the IJ site (see Fig. 5). There was no significant difference in the risk of CRBI between the subclavian and IJ sites (RR 1.09; 95% CI 0.67–1.75, $p = .74$, $I^2 = 27\%$).

The risk of DVT was assessed only in the two RCT's. A meta-analysis of this data is presented in Figure 6. This demonstrates that there was no difference in the risk of DVT when the femoral site was compared to the subclavian and IJ sites combined. There was, however, significant heterogeneity between the studies ($I^2 = 94\%$, $p < .0001$). This heterogeneity is presumably explained by the divergent results of the two studies.

DISCUSSION

The main finding of our systemic review is that recent evidence demonstrates no difference in the risk of CRBI between the femoral, subclavian, and IJ sites. Furthermore, the 1A recommendation to avoid the femoral site for the placement of a nontunneled short-term central venous catheter is not supported by the literature (2, 7). It is not clear how the Centers for Disease Control and Prevention and Infectious Disease Society of America came to their recommendation, furthermore, they referenced only four of the studies included in our systematic review (26, 28, 35, 36). In our meta-analysis, the studies of Lorente et al (28) (performed in Santa Cruz

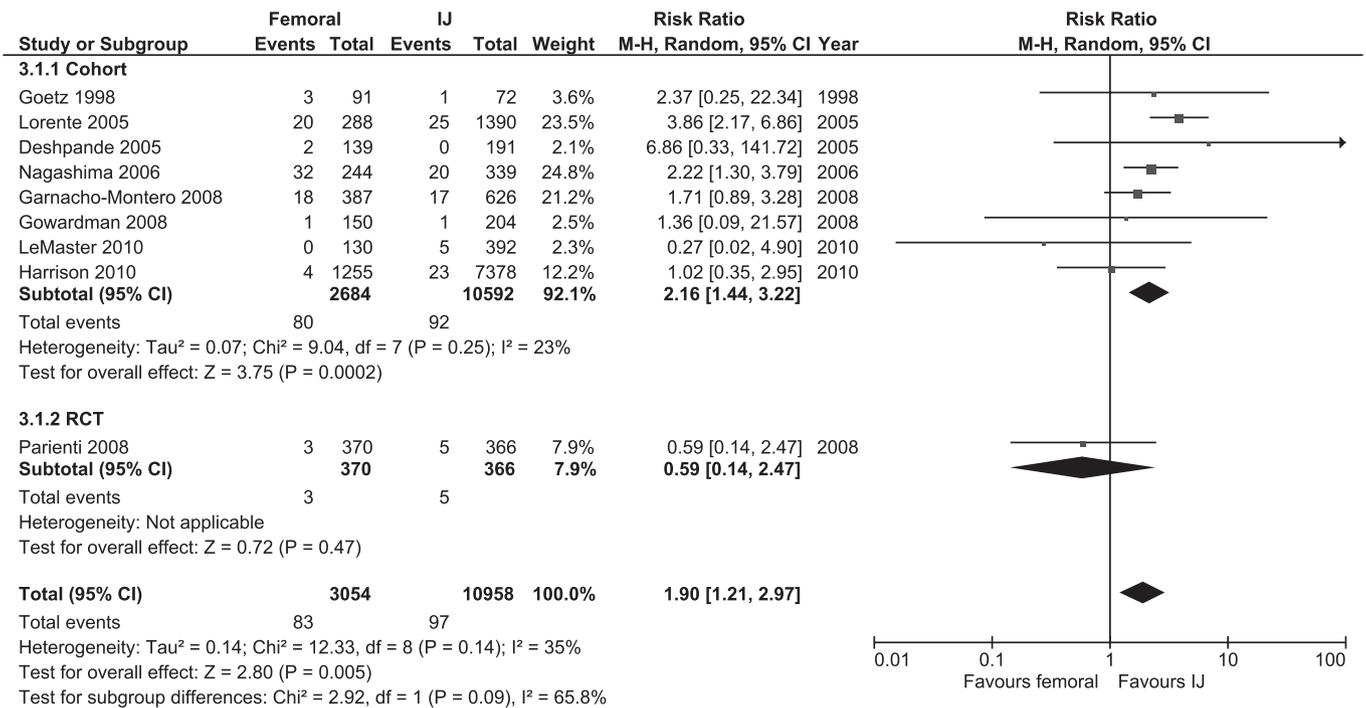


Figure 4. Comparison of the risk of catheter-related bloodstream infection for the femoral compared to the internal jugular (IJ) site. Studies are grouped by study type; randomized controlled trials (RCTs) and cohort studies. Weight is the relative contribution of each study to the overall treatment effect (risk ratio and 95% confidence interval) on a log scale assuming a random effects model. *M-H*, Mantel-Haenszel.

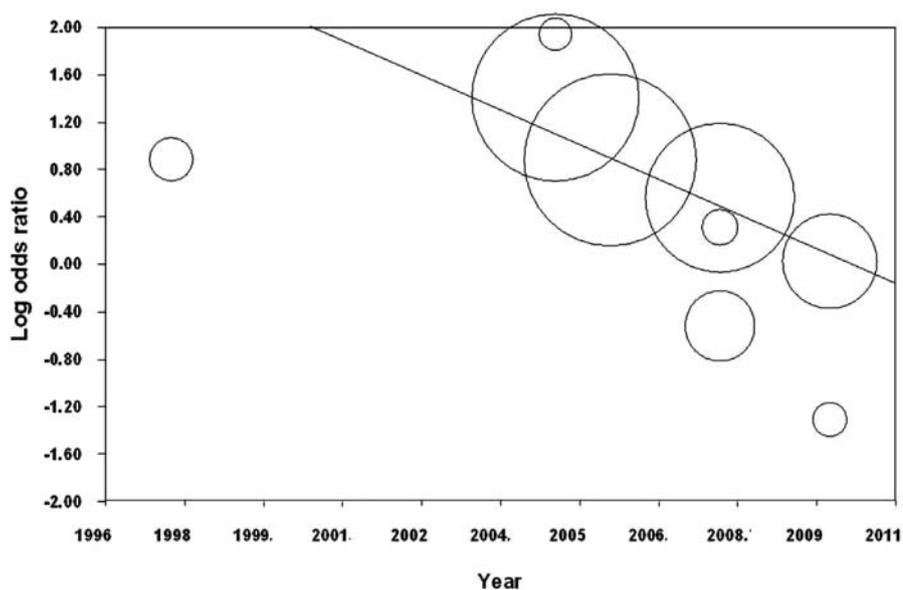


Figure 5. Regression of the year of publication vs. the log odds ratio of catheter-related bloodstream infections. A log odds ratio above zero favors the internal jugular site while a log odds ratio below zero favors the femoral site. The size of the circle indicates the statistical influence of each study.

de Tenerife, Spain) and Nagashima et al (29) (performed in Yokohama, Japan) were statistical outliers. It is possible that the “situational circumstances” of these ICUs/hospital were significantly different or unique from that of the other ICUs/hospitals included in this systematic review limiting the generalizability of their findings.

When comparing the subclavian and IJ site to the femoral site we noted an important interaction over time, with earlier studies showing a higher rate of infection at the femoral site. Furthermore, the overall risk of CRBI has decreased over time. In 1998, the rate of bloodstream infection in the United States was 5.32/1,000 catheter days (37).

More recent data have shown that this rate has been reduced to 2.05/1,000 catheter days (10). It is likely that the use of full drapes, gowns, masks, gloves, hand-hygiene, chlorhexidine for skin preparation together with strict adherence to aseptic precautions, antimicrobial-coated catheters, the use of ultrasound guidance, and vigilant management of the catheter and exit site account for both these findings (2, 38). The Welsh Healthcare Associated Infection Program is the largest (55,039 catheterday) and most recent (2009 and 2010) analysis of the risk of CVC-related infection (33, 34). It is noteworthy that in this analysis, the overall risk of CVC related infection was 0.6/1,000 catheter days with no difference in the risk of infection between insertion sites. Furthermore, it should be noted that as a consequence of the Hospital in Europe Link for Infection Control through Surveillance definitions of CVC related infection (15), only 48% of these infections were blood-culture-positive, yielding a “true” CRBI rate (according to the Infectious Disease Society of America criteria (14)) of 0.22/1,000 catheter days. Our findings are supported by the prospective study of Casanegra et al who evaluated the risk of CRBI and DVT associated with CVC’s in their medical ICUs between September

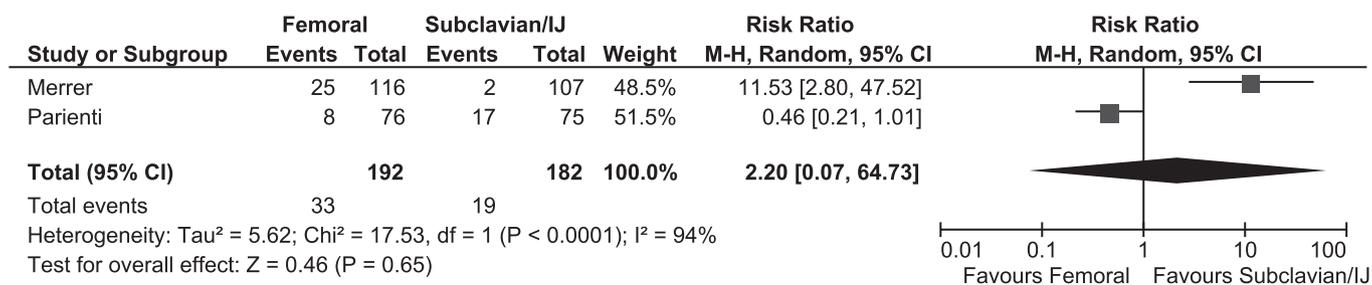


Figure 6. Comparison of the risk of deep venous thrombosis according to site of placement; femoral vs. combined subclavian/internal jugular (IJ). Weight is the relative contribution of each study to the overall treatment effect (risk ratio and 95% confidence interval [CI]) on a log scale assuming a random effects model. M-H, Mantel-Haenszel.

2008 and March 2009 (39). Two hundred and seventeen catheters (49% femoral, 38% IJ, and 13% subclavian) for a total of 1,200 catheter days were evaluated. No CRBIs or DVTs were identified. It should be noted that in this study 97% of patients studied received routine thromboprophylaxis. In a noncomparative prospective study, Joynt and colleagues reported that 9.6% of femoral CVC's were associated with DVT's; the use of thromboprophylaxis was not reported in this study (40). Furthermore, when comparing the risk of DVT according to site, it should be acknowledged that in the study of Pariente et al only dialysis catheters, which are associated with a higher risk of venous thrombosis, were used.

On the basis of the results of our systematic review and a review of the literature, we suggest the following pragmatic approach to site selection for central venous cannulation. The site of preference should depend on the expertise and skill of the operator and the risks associated with placement. In an emergent situation or in high-risk patients femoral placement may be preferred. All catheters that are placed under less-than-ideal emergency circumstances should be removed and resited within 24–48 hrs. Catheters placed in the IJ and femoral site should be placed under direct ultrasound guidance as this technique reduces the risk of placement complications (11, 41–43). The subclavian site should be avoided in patients with chronic renal failure to preserve the arm veins and subclavian vein for possible fistula placement (8). The femoral veins should be avoided in renal transplant patients. Another potential reason to avoid the femoral site is to allow early mobilization, this is particularly true for dialysis catheters. CVC placement is somewhat of a daunting task in massively obese patients (44); a subgroup analysis of the Parienti study suggests a higher risk of CRBI with femoral placement in these patients, hence this site should be avoided (36).

CONCLUSIONS

Although earlier studies showed a lower risk of CRBI when the IJ was compared to the femoral site, recent studies show no difference in the rate of CRBI among the three sites. In keeping with the Irish guidelines, we recommend the insertion site associated with the least likelihood of injury (4).

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