ORIGINAL ARTICLE

Intravascular Complications of Central Venous Catheterization by Insertion Site

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ABSTRACT

BACKGROUND

Three anatomical sites are commonly used to insert central venous catheters, but insertion at each site has the potential for major complications.

METHODS

In this multicenter trial, we randomly assigned nontunneled central venous catheterization in patients in the adult intensive care unit (ICU) to the subclavian, jugular, or femoral vein (in a 1:1:1 ratio if all three insertion sites were suitable [three-choice scheme] and in a 1:1 ratio if two sites were suitable [two-choice scheme]). The primary outcome measure was a composite of catheter-related bloodstream infection and symptomatic deep-vein thrombosis.

RESULTS

A total of 3471 catheters were inserted in 3027 patients. In the three-choice comparison, there were 8, 20, and 22 primary outcome events in the subclavian, jugular, and femoral groups, respectively (1.5, 3.6, and 4.6 per 1000 catheter-days; P=0.02). In pairwise comparisons, the risk of the primary outcome was significantly higher in the femoral group than in the subclavian group (hazard ratio, 3.5; 95% confidence interval [CI], 1.5 to 7.8; P=0.003) and in the jugular group than in the subclavian group (hazard ratio, 2.1; 95% CI, 1.0 to 4.3; P=0.04), whereas the risk in the femoral group was similar to that in the jugular group (hazard ratio, 1.3; 95% CI, 0.8 to 2.1; P=0.30). In the three-choice comparison, pneumothorax requiring chest-tube insertion occurred in association with 13 (1.5%) of the subclavian-vein insertions and 4 (0.5%) of the jugular-vein insertions.

CONCLUSIONS

In this trial, subclavian-vein catheterization was associated with a lower risk of bloodstream infection and symptomatic thrombosis and a higher risk of pneumothorax than jugular-vein or femoral-vein catheterization. (Funded by the Hospital Program for Clinical Research, French Ministry of Health; ClinicalTrials.gov number, NCT01479153.)

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Subclavian, jugular, and femoral central venous catheterization are associated with infectious, thrombotic, and mechanical complications.[1] Catheter-related bloodstream infection has a significant effect on morbidity, mortality, and health care costs.[2-4] The risk of short-term catheter-related bloodstream infection is influenced mainly by extraluminal microbial colonization of the insertion site,[5] and such colonization is also associated with thrombosis.[6,7] Although the importance of catheter-related deep-vein thrombosis has been debated,[1] all thromboses have the potential to embolize. In addition, catheter-related deep-vein thrombosis[7-9] and pulmonary embolism[10] may remain undiagnosed in critically ill patients undergoing mechanical ventilation.[11]

We conducted the 3SITES multicenter study to evaluate the risk of catheter-related bloodstream infection or symptomatic catheter-related deep-vein thrombosis in adult patients who had been admitted to an intensive care unit (ICU). On the basis of our previous meta-analysis,[12] we hypothesized that the risk of these major complications would differ according to the site of catheter insertion.

Methods

Study Design and Oversight

The 3SITES study was a multicenter randomized, controlled trial conducted in four university-affiliated hospitals and five general hospitals, representing 10 ICUs, in France from December 2011 through June 2014. The study was supported by funds from the French Ministry of Health Programme Hospitalier de Recherche Clinique National to the Délégation de la Recherche Clinique et de l'Innovation of the Caen University Hospital. The first author designed the study. CareFusion provided chlorhexidine products free of charge; no other commercial entity contributed to this trial. The research ethics committee at Caen University approved the study protocol (available with the full text of this article at NEJM.org) for all the participating centers. The first author analyzed the data and vouches for the accuracy and completeness of the reported data and for the fidelity of the study to the protocol.

Patients and Randomization

Patients 18 years of age or older were eligible for the study if they were admitted to the ICU, required nontunneled central venous vascular access through a new venipuncture, and were considered by the physician inserting the catheter to be suitable candidates for venous catheterization in at least two of the following three sites: the subclavian veins, the jugular veins, or the femoral veins. The determination that a venous access site was suitable (or usable) for catheterization was based on clinician judgment. More than one catheter per patient could be included in the trial. Written informed consent was obtained from all participants or from their proxies in cases of impaired decision-making capacity at the time of enrollment.

If all three venous access sites (subclavian, jugular, and femoral) were considered suitable for catheter placement, the catheterization site was assigned in a 1:1:1 randomization scheme (three-choice scheme). If one of the three sites was not suitable on both the left and right sides of the body, the catheterization site was assigned in a 1:1 randomization scheme for the other two sites (two-choice scheme), an approach termed "selective exclusion."[13] If only one site was suitable, that catheterization procedure was not included in the study. Randomization was stratified according to ICU and according to the use of antibiotic therapy versus no use of antibiotic therapy[14]; it was implemented by means of a centralized 24-hour, web-based or telephone interactive computerized response system (EOL, MedSharing), with the use of permuted-block randomization with varying block sizes.

Trial Procedures

All participating ICUs followed the French Haute Autorité de Santé checklist[15] and U.S. guidelines for preventing catheter-related infections.[16] Residents or staff physicians who had performed at least 50 previous procedures inserted the catheters or supervised the catheterization in the ICU. Maximal sterile barrier precautions were used, including surgical hand antisepsis,[17] sterile gloves, surgical long-sleeved gowns, caps, and masks. Patients were covered by sterile drapes. Antiseptics, dressing, and catheter products are listed according to participating ICU in Table S1 in the Supplementary Appendix, available at NEJM.org. None of the study catheters were antiseptic-impregnated, antibiotic-impregnated, or tunneled.

Catheterization was achieved by means of the Seldinger technique with the use of anatomical landmarks or ultrasonographic guidance. After

jugular and subclavian catheterizations, chest radiography was used to confirm the position of the catheter tip inside the superior vena cava and to assess for pneumothorax. Catheters were not used for routine blood sampling or renal replacement therapy.

Decisions to remove catheters were made independently by the physicians caring for each patient. After aseptic removal, the catheter tips were sent for quantitative culture.[18] Peripheral blood for culture was systematically drawn at the time of catheter removal (details are provided in the Supplementary Appendix). Patients discharged from the ICU with the catheter in place had blood drawn for culture simultaneously from a peripheral vein and the central venous catheter to determine the differential time to positivity.

Within 2 days after removal of the catheter, compression ultrasonography was performed at the insertion site to confirm symptomatic catheter-related deep-vein thrombosis and to detect asymptomatic deep-vein thrombosis. Cases of symptomatic deep-vein thrombosis and cases of asymptomatic deep-vein thrombosis were combined for some analyses and referred to as total deep-vein thrombosis. Data on asymptomatic deep-vein thrombosis were missing for all patients who died or were discharged from the ICU with the catheter in place.

External, independent clinical monitors validated a randomly selected 12% of the data and all primary and secondary outcomes. Patients were followed until ICU discharge or death.

OUTCOMES

The primary outcome was the incidence of major catheter-related complications from the time of catheter insertion to 48 hours after catheter removal; major complications were defined as the composite of catheter-related bloodstream infection (*Medical Dictionary for Regulatory Activities* [MedDRA], version 17, code 10064687, grade 3 or higher) and symptomatic deep-vein thrombosis (MedDRA, version 17, code 10062169, grade 3 or higher), whichever occurred first (see the definitions in Table S2 in the Supplementary Appendix). Key secondary outcomes included the time to catheter-tip colonization and time to total deep-vein thrombosis after catheter removal.

A diagnosis of catheter-related bloodstream infection required catheter-tip colonization with the same phenotypic microorganism isolated from a peripheral blood culture.[16] For a diagnosis of catheter-related bloodstream infection with a potential skin contaminant, two separate peripheral-blood cultures had to grow the same microorganism that colonized the catheter tip. Colonization of the catheter tip was defined as 1000 or more colony-forming units per milliliter.[18] An adjudication committee that was unaware of the study-group assignments reviewed all suspected cases of catheter-related bloodstream infection.

If a patient had signs or symptoms of catheter-related deep-vein thrombosis, compression ultrasonography was used to confirm the diagnosis. The ultrasonography-confirmed diagnosis served as the deep-vein thrombosis component of the primary outcome.

The secondary safety outcome was the rate of major mechanical complications (grade 3 or higher) during insertion of the central venous catheter and follow-up. Mechanical complications were defined in accordance with the modified National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0 (definitions are provided in Table S2 in the Supplementary Appendix), with the modification that pneumothorax requiring chest-tube insertion was classified as grade 3 instead of grade 2.

STATISTICAL ANALYSIS

Our sample-size estimation is described in the Supplementary Appendix. We estimated that a total sample of 3333 catheters was required, given our initial assumptions about the incidence of catheter-related complications.

The statistical unit of analysis was the catheter. Analyses followed the intention-to-treat principle. A per-protocol sensitivity analysis excluded catheters that were not inserted in the allocated site and side of the body because of failure to gain vascular access. For cases in which catheter-tip culture data and blood-culture data were missing, follow-up was censored at catheter removal or at ICU discharge with the catheter, whichever occurred first. Complete case and multiple-imputation sensitivity analyses were also performed (described in the Supplementary Appendix).

The incidence of the primary outcome was compared among the three insertion sites in the three-choice comparison with the use of the overall log-rank test. Pairwise comparisons were conducted (combining insertion-site groups from among the catheters that were randomized in the three-choice scheme with the relevant groups from

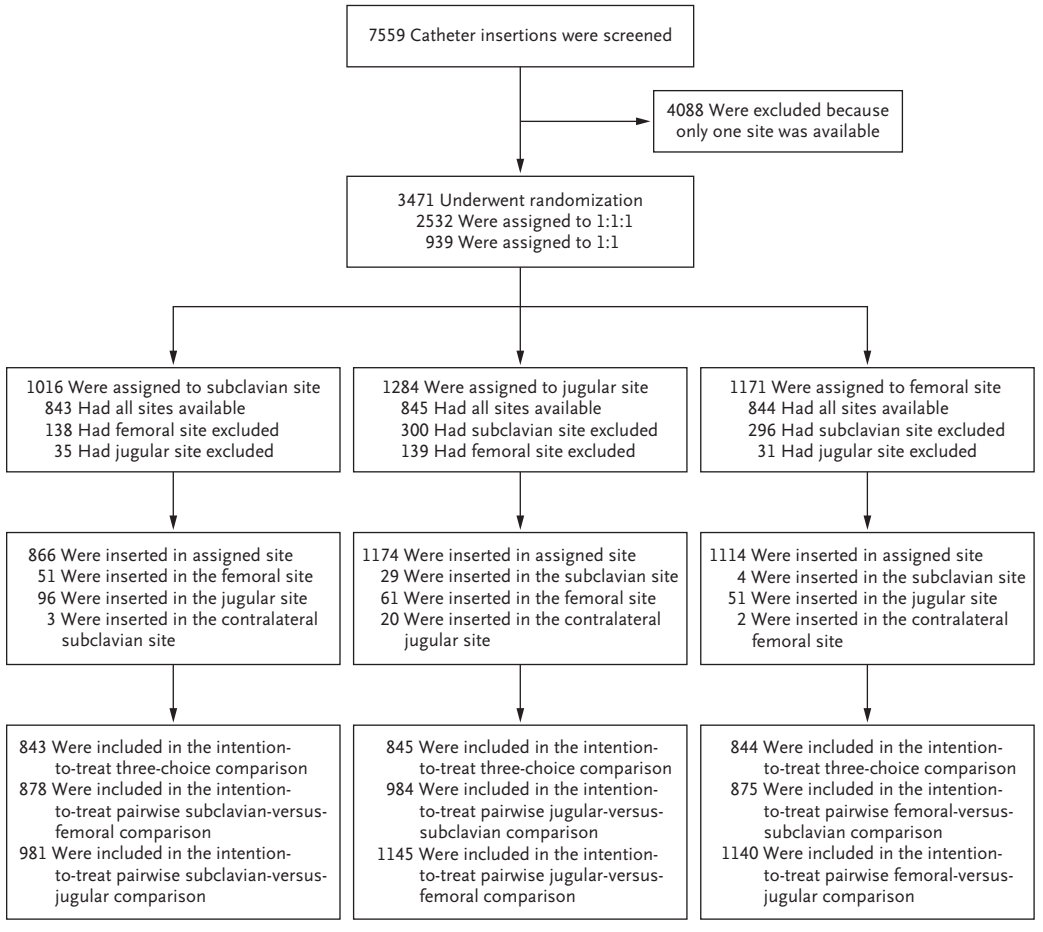


Figure 1. Screening and Randomization of Catheter Insertions.

Pairwise comparisons combine insertion-site groups from among the catheters that were randomized in the three-choice scheme with the relevant groups from the relevant two-choice scheme. For example, the subclavian insertion-site group that was included in the subclavian-versus-femoral pairwise comparison included 878 catheters: the 843 catheters assigned in the three-choice scheme (i.e., with all three sites available) plus the 35 catheters in patients for whom the jugular site was excluded.

the relevant two-choice scheme [Fig. 1]) with the use of a Cox model that included catheter site, stratification variables, and design variables (inclusion in the three-choice or the relevant two-choice scheme).[13] A robust sandwich covariance estimate was used to account for a possible clustering effect of multiple catheters per patient. A subsample sensitivity analysis that included one randomly selected catheter per patient was performed. The proportionality assumption was confirmed visually and tested by including the site as a time-dependent covariate in the Cox model.

The intention-to-treat secondary safety outcome was analyzed by means of a random-intercept logistic regression. Planned subgroup analyses of the primary outcome were conducted by testing the interaction term between each pairwise comparison and the use of alcoholic chlorhexidine for cutaneous antisepsis,[19-21] antibiotic treatment,[14] anticoagulation, body-mass index (the weight in kilograms divided by the square of the height in meters) greater than 28,[9] and selective site exclusion.[13] Similarly, subgroup analyses for the secondary safety outcome were conducted according to whether ultrasonography was used to guide insertion.[22]

We used SAS software, version 9.4 (SAS institute), for the statistical analyses. The Holm–Bonferroni method[23] was used to account for multiple testing of the primary outcome in the two superiority pairwise comparisons. Therefore, a P value of less than 0.025 was considered to indicate statistical significance for the lower P value,

Table 1. Characteristics of the Patients at Baseline.*

Characteristic	Three-Choice Comparison			Pairwise Comparison†		Pairwise Comparison†		Pairwise Comparison†	
	Jugular (N=845)	Femoral (N=844)	Subclavian (N=843)	Femoral (N=875)	Subclavian (N=878)	Jugular (N=984)	Subclavian (N=981)	Femoral (N=1140)	Jugular (N=1145)
Age	63.0±16.3	63.5±15.3	62.9±15.9	63.3±15.5	62.8±15.8	63.0±16.1	62.5±15.8	63.0±15.1	63.1±16.1
Male — no. (%)	531 (62.8)	545 (64.6)	543 (64.4)	572 (65.4)	570 (64.9)	621 (63.1)	635 (64.7)	748 (65.6)	721 (63.0)
SAPS II‡	57.1±19.4	56.1±18.9	55.1±20.2	56.1±18.9	55.2±20.1	56.9±19.6	54.8±20.2	57.3±19.7	57.7±20.3
Body-mass index	26.1±5.7	25.8±5.5	25.9±5.3	25.9±5.5	25.9±5.3	26.2±5.8	26.4±5.8	25.9±5.5	26.1±5.7
Diabetes mellitus — no. (%)	173 (20.5)	175 (20.7)	151 (17.9)	182 (20.8)	161 (18.3)	214 (21.7)	188 (19.2)	238 (20.9)	236 (20.6)
Cancer — no. (%)	76 (9.0)	96 (11.4)	74 (8.8)	97 (11.1)	77 (8.8)	82 (8.3)	83 (8.5)	140 (12.3)	120 (10.5)
AIDS — no. (%)	12 (1.4)	8 (0.9)	13 (1.5)	8 (0.9)	15 (1.7)	12 (1.2)	13 (1.3)	12 (1.1)	15 (1.3)
Neutrophil count <500/mm^3 — no. (%)	15 (1.8)	11 (1.3)	6 (0.7)	11 (1.3)	6 (0.7)	16 (1.6)	6 (0.6)	26 (2.3)	36 (3.1)
Tracheotomy — no. (%)	14 (1.7)	17 (2.0)	19 (2.3)	23 (2.6)	25 (2.8)	18 (1.8)	23 (2.3)	22 (1.9)	22 (1.9)
Antibiotic therapy — no. (%)	457 (54.1)	472 (55.9)	466 (55.3)	489 (55.9)	487 (55.5)	545 (55.4)	555 (56.6)	656 (57.5)	647 (56.5)
Anticoagulation therapy — no. (%)	257 (30.4)	259 (30.7)	249 (29.5)	272 (31.1)	259 (29.5)	308 (31.3)	311 (31.7)	368 (32.3)	365 (31.9)
Parenteral nutrition — no. (%)	49 (5.8)	61 (7.2)	47 (5.6)	68 (7.8)	56 (6.4)	67 (6.8)	72 (7.3)	70 (6.1)	62 (5.4)

* Plus–minus values are means ±SD. Numbers in the table are numbers of catheters; therefore, some patients are included more than once. The lack of independence between observations was taken into account in the generalized-estimating-equation models for the comparisons between groups, and none of the variables differed significantly between groups in these models.
† These comparisons combine insertion-site groups from among the catheters that were randomized in the three-choice scheme with the relevant groups from the relevant two-choice scheme.
‡ SAPS II denotes Simplified Acute Physiology Score II (values range from 0 to 163 points, with higher scores indicating a higher risk of death).

and a P value of less than 0.05 was considered to indicate significance for the higher P value.

RESULTS

BASELINE AND PROCEDURAL CHARACTERISTICS AND FOLLOW-UP

A total of 3027 patients were included in the study. A total of 3471 catheters (1284 jugular, 1171 femoral, and 1016 subclavian) were included, of which 2532 (72.9%) were randomly assigned in the three-choice scheme (845 jugular, 844 femoral, and 843 subclavian) (Fig. 1). The reasons for excluding one of the three sites are provided in the Table S3 in the Supplementary Appendix. Catheters were inserted in the randomly assigned site and side in 3154 cases (90.9%) overall, including 866 cases (85.2%) assigned to the subclavian site, 1174 cases (91.4%) assigned to the jugular site, and 1114 cases (95.1%) assigned to the femoral site (Fig. 1).

The characteristics of the patients at baseline according to the site of catheter insertion were well balanced between the groups within the three-choice comparison and the three pairwise comparisons (Table 1). Catheter-related and procedural characteristics are shown in Table 2. The use of anatomical landmarks was more frequent in the subclavian and femoral groups than in the jugular group. Catheterization was performed more quickly in the femoral group than in either of the other two groups. Alcohol-based products were the predominant cutaneous antiseptics used for cleaning the catheter insertion site; the frequency of the use of chlorhexidine-containing products was similar among the different insertion sites.

The median duration of catheter use was 5 days for each of the three insertion sites (Table 2). No patients were lost to follow-up. Catheter-tip cultures and peripheral-blood cultures were missing in 101 cases (2.9%). Data on asymptomatic deep-vein thrombosis were missing in 2049 cases (59.0%).

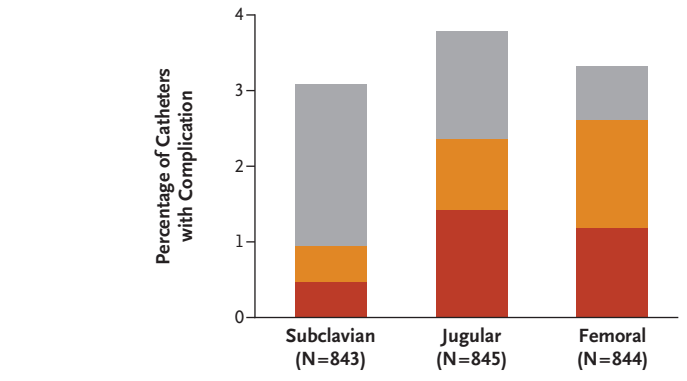
CATHETER-RELATED INFECTION AND SYMPTOMATIC DEEP-VEIN THROMBOSIS

In the three-choice comparison, there were 50 nonduplicate primary outcome events (i.e., events that did not occur in the same catheter), and their incidence differed according to the randomly assigned site of catheter insertion, with 8 events in the subclavian group, 20 events in the jugular group, and 22 events in the femoral group (1.5, 3.6, and 4.6 per 1000 catheter-days, respectively;

Table 2. Catheter-Related and Procedural Characteristics.*

Characteristic	Three-Choice Comparison			Pairwise Comparison†		Pairwise Comparison†		Pairwise Comparison†	
	Jugular (N=845)	Femoral (N=844)	Subclavian (N=843)	Femoral (N=875)	Subclavian (N=878)	Jugular (N=984)	Subclavian (N=981)	Femoral (N=1140)	Jugular (N=1145)
Skin antisepsis and catheter care — no. (%)‡									
Alcoholic chlorhexidine	366 (43.3)	363 (43.0)	380 (45.1)	372 (42.5)	391 (44.5)	439 (44.6)	435 (44.3)	468 (41.1)	477 (41.7)
Alcoholic povidone–iodine	364 (43.1)	361 (42.8)	355 (42.1)	383 (43.8)	374 (42.6)	426 (43.3)	421 (42.9)	500 (43.9)	498 (43.5)
Aqueous povidone–iodine	83 (9.8)	86 (10.2)	82 (9.7)	86 (9.8)	87 (9.9)	86 (8.7)	95 (9.7)	134 (11.8)	131 (11.4)
Other or unknown	32 (3.8)	34 (4.0)	26 (3.1)	34 (3.9)	26 (3.0)	33 (3.4)	30 (3.1)	38 (3.3)	39 (3.4)
Use of anatomical landmarks to guide insertion — no. (%)§	276 (32.7)¶	623 (73.8)¶	723 (85.8)¶	648 (74.1)¶	758 (86.3)¶	314 (31.9)¶	847 (86.3)¶	825 (72.4)¶	360 (31.4)¶
Time for insertion — min	12.6±9.1¶	11.6±9.0¶	12.8±9.2¶	11.6±9.0¶	12.8±9.3¶	12.8±9.5	12.8±9.2	11.7±9.0¶	12.7±9.5¶
Insertion failure — no. (%)	65 (7.7)¶	45 (5.3)¶	124 (14.7)¶	45 (5.1)¶	126 (14.3)¶	75 (7.6)¶	148 (15.1)¶	57 (5.0)¶	100 (8.7)¶
Duration of catheterization — days									
Mean	6.5±5.6	5.9±4.8	6.4±5.3	5.9±4.8¶	6.5±5.4¶	6.7±5.8	6.8±5.7	5.8±4.8¶	6.5±5.4¶
Median (range)	5 (3–9)	5 (2–8)	5 (3–9)	5 (3–9)	5 (2–8)	5 (3–9)	5 (3–9)	5 (2–8)	5 (3–9)
Reason for catheter removal — no. (%)									
No longer required	497 (58.8)	492 (58.3)	485 (57.5)	505 (57.7)	500 (56.9)	570 (57.9)	547 (55.8)	624 (54.7)	641 (56.0)
Death	181 (21.4)	137 (16.2)	151 (17.9)	142 (16.2)	159 (18.1)	211 (21.4)	175 (17.8)	223 (19.6)	259 (22.6)
Suspected catheter infection	89 (10.5)	112 (13.2)	109 (12.9)	119 (13.6)	118 (13.4)	111 (11.3)	143 (14.6)	157 (13.8)	135 (11.8)
Systematic‖	18 (2.1)	22 (2.6)	20 (2.4)	22 (2.5)	21 (2.4)	19 (1.9)	25 (2.5)	27 (2.4)	26 (2.3)
Other or unknown	60 (7.1)	81 (9.6)	78 (9.3)	87 (9.9)	80 (9.1)	73 (7.4)	91 (9.3)	109 (9.6)	84 (7.3)

* Plus–minus values are means ±SD.
† These comparisons combine insertion-site groups from among the catheters that were randomized in the three-choice scheme with the relevant groups from the relevant two-choice scheme.
‡ Alcoholic chlorhexidine included 2% chlorhexidine with 70% isopropyl alcohol used in a one-step procedure, 0.5% chlorhexidine with 70% ethanol and 0.25% chlorhexidine, 0.025% benzalkonium chloride with 4% benzyl alcohol, both used in a four-step procedure. Alcoholic povidone–iodine included 5% povidone–iodine with 70% ethanol used in a four-step procedure. Aqueous povidone-iodine included 10% povidone–iodine used in a four-step procedure.
§ Other catheters were inserted with the use of ultrasonography.
¶ Results between groups were significant at $P<0.05$, as assessed with the use of generalized-estimating-equation models for each group comparison.
‖ Systematic refers to catheter removal after a certain period to prevent catheter complications.



	Subclavian (N=843)	Jugular (N=845)	Femoral (N=844)
Mechanical (grade ≥3)	18 (2.1%)	12 (1.4%)	6 (0.7%)
Symptomatic deep-vein thrombosis	4 (0.5%)	8 (0.9%)	12 (1.4%)
Bloodstream infection	4 (0.5%)	12 (1.4%)	10 (1.2%)

Figure 2. Complications in the Three-Choice Comparison, According to Insertion-Site Group.

The primary end point (the composite of symptomatic deep-vein thrombosis and bloodstream infection) differed significantly among the insertion-site groups (P=0.02 by the log-rank test), as did the principal safety secondary end point (mechanical complications) (P=0.047 by the chi-square test).

P=0.02) (Fig. 2). Corresponding Kaplan–Meier curves showed a constant increase in risk for each insertion-site group (Fig. S1 and S2 in the Supplementary Appendix). In pairwise comparisons for the primary outcome in groups from the three-choice and two-choice schemes combined (Table 3), the risk of the primary outcome was significantly higher in the femoral group than in the subclavian group (hazard ratio, 3.5; 95% confidence interval [CI], 1.5 to 7.8; P=0.003) and in the jugular group than in the subclavian group (hazard ratio, 2.1; 95% CI, 1.0 to 4.3; P=0.04), whereas the risk in the femoral group was similar to that in the jugular group (hazard ratio, 1.3; 95% CI, 0.8 to 2.1; P=0.30).

In a sensitivity analysis that included one randomly selected catheter per patient, the results were consistent with those in the primary analysis (Table S4 in the Supplementary Appendix). Differences between the subclavian group and the other two groups were larger in the per-protocol sensitivity analysis (Table S5 in the Supplementary Appendix), because half of the catheter-related bloodstream infections in the subclavian group occurred in catheters that were, in fact, inserted elsewhere. The results of complete-case and multiple-imputation sensitivity analyses were consistent with those in the primary analysis (Table S6 in the Supplementary Appendix).

The results for the secondary outcomes of catheter-tip colonization and total deep-vein thrombosis also favored the subclavian group (Table 3). Kaplan–Meier curves of these data are shown in Figures S3 and S4 in the Supplementary Appendix, respectively. The causative pathogens identified in each case of catheter-related bloodstream infection and catheter-tip colonization are shown in Table S7 in the Supplementary Appendix. Among the 171 blood samples drawn for culture to determine the differential time to positivity in patients discharged from the ICU with their central venous catheter in place, the one catheter-related bloodstream infection identified with the use of this method was subsequently confirmed in a catheter-tip culture.

MECHANICAL COMPLICATIONS

The frequency of major mechanical complications in the three-choice comparison (Fig. 2) differed according to insertion-site group (P=0.047), with 18 events in the subclavian group, 12 events in the jugular group, and 6 events in the femoral group. Pneumothorax accounted for 13 events in the subclavian group and 4 events in the jugular group. In the pairwise comparisons (Table 3), there were significantly fewer mechanical complications in the femoral group than in the subclavian group (odds ratio, 0.3; 95% CI, 0.1 to 0.8; P=0.03), but there were no significant differences in the other pairwise comparisons.

SUBGROUP ANALYSES

None of the preplanned subgroup analyses showed a significant interaction for the primary outcome (Table S9 in the Supplementary Appendix). With regard to major mechanical complications, there was a significant interaction between the use of ultrasonography and the comparison between the femoral group and the jugular group (P=0.007), as well as a nonsignificant trend for an interaction between the use of ultrasonography and the comparison between the femoral group and the subclavian group (P=0.07); the differences between the groups in these two comparisons were larger when ultrasonography was not used to guide catheter insertion (Table S9 in the Supplementary Appendix).

DISCUSSION

In this randomized, controlled trial, catheterization of the subclavian vein was associated

Table 3. Intention-to-Treat Pairwise Comparisons for the Trial Outcomes.

Outcome	Femoral versus Subclavian				Jugular versus Subclavian				Femoral versus Jugular			
	Femoral	Subclavian	Hazard Ratio (95% CI)*	P Value	Jugular	Subclavian	Hazard Ratio (95% CI)*	P Value	Femoral	Jugular	Hazard Ratio (95% CI)*	P Value
	number				*number*				*number*			
Catheters	875	878	—	—	984	981	—	—	1140	1145	—	—
Catheter-days	5198	5739	—	—	6573	6651	—	—	6658	7427	—	—
Primary composite outcome†	25	8	3.5 (1.5–7.8)	0.003	23	11	2.1 (1.0–4.3)	0.04	33	30	1.3 (0.8–2.1)	0.30
Bloodstream infection	11	4	3.4 (1.0–11.1)	0.048	13	6	2.3 (0.8–6.2)	0.11	15	21	0.9 (0.5–1.8)	0.81
Symptomatic deep-vein thrombosis	15	5	3.4 (1.2–9.3)	0.02	10	6	1.8 (0.6–4.9)	0.29	20	9	2.4 (1.1–5.4)	0.04
Secondary outcome												
Catheter-tip colonization	107	39	3.4 (2.4–5.0)	<0.001	104	42	2.5 (1.7–3.5)	<0.001	145	121	1.6 (1.2–2.0)	0.003
Deep-vein thrombosis‡	46	19	3.0 (1.7–5.3)	<0.001	69	20	3.1 (1.9–5.0)	<0.001	62	78	0.9 (0.7–1.3)	0.68
Major mechanical complications	6	18	0.3 (0.1–0.8)§	0.03	12	22	0.5 (0.3–1.1)§	0.09	7	13	0.5 (0.2–1.4)§	0.19
Arterial injury	4	1	—	—	2	2	—	—	4	2	—	—
Hematoma	0	1	—	—	4	1	—	—	0	4	—	—
Pneumothorax	NA	13	—	—	4	14	—	—	NA	4	—	—
Miscellaneous¶	2	3	—	—	2	5	—	—	3	3	—	—

* Values in this column are hazard ratios unless otherwise indicated. All hazard ratios were adjusted for stratification variables (intensive care unit and antibiotic use) and design variables (three-choice vs. two-choice scheme). The confidence intervals for hazard ratios are robust confidence intervals taking into account multiple catheters per patient. NA denotes not applicable.

† Some catheters had two events.

‡ The numbers of ultrasonographic evaluations in the three pairwise comparisons were 744 (398 in the femoral group and 346 in the subclavian group), 786 (399 in the jugular group and 387 in the subclavian group), and 955 (497 in the femoral group and 458 in the jugular group).

§ The value for major mechanical complications is an odds ratio computed by random-intercept logistic regression, rather than a hazard ratio.

¶ The specific miscellaneous mechanical complications for each pairwise comparison are listed in Table S8 in the Supplementary Appendix.

with a reduced risk of the combined outcome of catheter-related bloodstream infection and symptomatic deep-vein thrombosis. This was true in a comparison with femoral-vein catheterization, as others have suggested,[8] but also in a comparison with jugular-vein catheterization. These findings are consistent with the Centers for Disease Control and Prevention guideline for preventing intravascular catheter-related infections, in which the recommendation is to "use a subclavian site, rather than a jugular or a femoral site, in adult patients."[16] However, subclavian-vein catheterization was associated with an increased risk of mechanical complications.

The low incidence of catheter-related bloodstream infection in the ICUs in our study is consistent with data from other ICUs.[24] Moreover, the differences in the incidences of catheter-related bloodstream infection and symptomatic deep-vein thrombosis according to insertion site are consistent with the differences found in catheter-tip colonization and total deep-vein thrombosis. Of note, the incidence of total deep-vein thrombosis should be interpreted with caution, because more than half of the inserted catheters had missing data for this secondary outcome, entirely because of missing data for asymptomatic patients.

There are probably several factors contributing to our findings. The subcutaneous course of the subclavian catheter before entry into the vein is generally longer than for the other two types. The subclavian insertion site has the lowest bacterial bioburden[25,26] and is relatively protected against dressing disruption.[27] Finally, subclavian catheters are associated with less thrombosis.[7,8]

The overall risk of mechanical, infectious, and thrombotic complications of grade 3 or higher was similar among the three insertion sites (Fig. 2), which suggests that an ideal site for central venous catheter insertion does not exist when all types of complications are considered to be of equal concern. However, the expected duration of catheterization is important, because the cumulative risk of infectious and thrombotic complications increases with increasing catheter exposure, whereas the risk of mechanical complications does not. Furthermore, the mechanical complications associated with subclavian catheter insertion can be limited by ultrasonographic guidance[28,29] and physician experience with the procedure.[30] Pneumothorax, which accounted for most of the difference in mechanical complications among insertion sites in our study, can be diagnosed promptly and treated immediately. This may not be the case for catheter-related bloodstream infection or deep-vein thrombosis. Decisions regarding the choice of insertion site should therefore be considered on a case-by-case basis.

A number of limitations of this trial should be considered. The use of ultrasonographic guidance during catheter insertion was not randomized. This may have influenced the risk of mechanical and infectious complications found in this study, although the reduction in catheter infection risk associated with the use of ultrasonography that was found in one randomized study[22] was not confirmed in a subsequent large observational study.[31] Daily chlorhexidine bathing[32,33] and chlorhexidine-impregnated dressings[34] were not used. Whether these measures influence the difference in infectious risk between insertion sites is unknown. Last, we did not study the use of peripherally inserted central venous catheters. Peripherally inserted central venous catheters have been associated with a risk of infection similar to that associated with central venous catheters among patients in the ICU and with a higher risk of thrombosis.[35,36]

In conclusion, in the 3SITES study, we found that catheterization of the subclavian vein was associated with a lower risk of the composite outcome of catheter-related bloodstream infection and symptomatic deep-vein thrombosis than that associated with catheterization of either the jugular vein or femoral vein. However, subclavian-vein catheterization was associated with a higher risk of mechanical complications, primarily pneumothorax.

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APPENDIX

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