chronic kidney disease

We still go for the jugular: implications of the 3SITES central venous catheter study for nephrology

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The 3SITES study randomly assigned a nontunneled central venous catheter site in over 3000 adults treated in intensive care units. The subclavian site was associated with a lower rate of short-term complications, including catheter-related bloodstream infection and deep venous thrombosis, compared to the femoral or internal jugular site. Nephrologists should be aware of this study and should continue to advocate for alternatives to subclavian vein catheter placement in patients with chronic kidney disease who are expected to require arteriovenous access for dialysis in the future.

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Patients with acute kidney injury and chronic kidney disease frequently require nontunneled central venous catheterization for the treatment of acute illness, and temporary catheters continue to be widely used for emergent inpatient hemodialysis initiation. Minimizing catheter complications and preserving veins for hemodialysis vascular access are important goals in the care of these patients.

The 3SITES study randomly assigned a nontunneled central venous catheter site in over 3,000 adults treated in 10 intensive care units in France.[1] Central vein suitability for catheter insertion was determined clinically. Randomization was 1:1:1 for subclavian, internal jugular, or femoral site when sites all were available ($n = 2532$), while allocation was paired when only 2 sites were deemed usable ($n = 939$). All study sites followed the French Haute checklist and US Centers for Disease Control and Prevention guidelines for preventing intravascular catheter-related infections.[2] The primary composite outcome combined catheter-related bloodstream infection and symptomatic deep venous thrombosis confirmed by ultrasound. Median catheter duration was 5 days. In the 3-arm randomization, subclavian catheters were associated with significantly fewer primary composite events than internal jugular or femoral catheters (incidence rates of 1.5, 3.6, and 4.6 per 1000 catheter days, respectively, $P = 002$). Pneumothorax treated with chest-tube insertion was more common with subclavian catheters (14 or 1.5% vs. 4 or 0.4% for internal jugular catheters), but this difference was not statistically significant. Results were similar in the paired allocation, with a lower risk of the primary composite outcome for subclavian catheters and no statistically significant difference between the internal jugular and femoral sites. Important limitations of the study include crossover between the randomized site and actual catheter insertion site, nonrandom utilization of ultrasound-guided catheter insertion, limited proportion of participants with ultrasound assessment of asymptomatic deep venous thrombosis, and no use of daily chlorhexidine bathing or impregnated dressings. Although there were no exclusions for kidney disease, catheters were not inserted for renal replacement therapy, and baseline estimated glomerular filtration rate was <60 ml/min per 1.73 m^2 in only 9% of subjects ($n = 277$). The risk of complications by anatomic site was similar in these participants, suggesting that the results are generalizable to patients with chronic kidney disease (J.-J. Parienti, personal communication, 2015).

Although the 3SITES study did not include central venous catheters intended for renal replacement therapy, rates of the primary composite outcome were similar to catheter-related

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Table 1 | Suggestions for venous access in patients with chronic kidney disease[a]

(**A**) Identify chronic kidney disease (CKD) patients who may need vascular access for hemodialysis treatment in the future
1. Estimated glomerular filtration rate (eGFR) <45 ml/min per 1.73 m^2 (CKD stage 3b or higher)[b]
2. Dialysis (hemodialysis or peritoneal dialysis)
3. Functioning kidney transplant

(**B**) Venous access in patients with the above conditions
1. The dorsal veins of the hand are preferred for phlebotomy and peripheral venous access
2. If the dorsal veins of the hand are not feasible, use the dominant arm for phlebotomy
3. The internal jugular veins are the preferred site for central venous access, using the right before the left in general
4. The external jugular veins are an acceptable alternative for venous access
5. The subclavian veins should not be used for central venous access unless there are no other options
6. Placement of a peripherally inserted central catheter should be avoided. Use the single-lumen internal jugular catheter instead, using the right before the left when feasible

(**C**) Develop and implement a policy and procedure for venous access for the health system
1. Engage a multidisciplinary team including administrators, nephrologists, interventionalists, nursing, phlebotomy, and other relevant services
2. Adapt above to local practice and resources

[a]Adapted from the Kidney Disease Outcomes Quality Initiative vascular access clinical practice guidelines, American Society of Diagnostic and Interventional Nephrology position paper, and Fistula First Catheter Last Initiative.
[b]The target population for implementation of these guidelines is based on the level of eGFRs, with variability across the clinical guidelines; we have adopted an intermediate eGFR <45 ml/min per 1.73 m^2 for these recommendations.

bacteremia rates previously reported for tunneled hemodialysis catheters (2.5–5.5 per 1000 catheter days) and approximately 2-fold lower than those reported for nontunneled hemodialysis catheters (3.8–12.8 per 1000 catheter days).[3,4] The longer duration of exposure with hemodialysis catheters carries higher cumulative risk of bacteremia and other complications, including thrombosis (intramural, mural, and right atrial), fibrin sheaths, and central venous stenosis or occlusion. Central venous stenosis is a major barrier to arteriovenous access creation for hemodialysis, and is associated with the number of catheter insertions, duration of catheter exposure, and use of the subclavian site. Catheter contact with the vessel wall is postulated to cause endothelial damage and turbulent flow, which may initiate release of prothrombotic cytokines, leading to thrombosis, fibrosis, and stenosis.[5] The catheter site with the least vessel wall contact is the right internal jugular.

The 3SITES study did not include a number of interventions that have been shown to reduce dialysis catheter complications. In several randomized trials, use of antibiotic lock solutions significantly reduced the rates of catheter-related bacteremia for both nontunneled and tunneled hemodialysis catheters.[3,4] The US Centers for Disease Control and Prevention has recommended 9 interventions to prevent bloodstream infections in hemodialysis, including hand hygiene, scrubbing of the catheter hub, and use of chlorhexidine skin antisepsis with each hemodialysis treatment. This practical approach resulted in 30% to 50% reductions in bacteremia compared to usual care in quality improvement studies.[6] The most common form of skin antisepsis in the 3SITES study was alcohol-based, with similar rates of chlorhexidine use across central venous sites.[1]

Nephrology practitioners should be aware of the 3SITES study, particularly in settings where non-nephrologists insert dialysis or other catheters for kidney disease patients. Catheter site selection should be incorporated into a comprehensive approach to preserve veins for future arteriovenous access in patients with chronic kidney disease who are expected to require dialysis (Table 1). Clinical practice guidelines and position papers have recommended vein preservation for patients with estimated glomerular filtration rates either ≤30 ml/min per 1.73 m^2 (Kidney Disease Outcomes Quality Initiative),[7] ≤45 ml/min per 1.73 m^2 (Fistula First Catheter Last Initiative),[8] or ≤60 ml/min per 1.73 m^2 (American Society of Diagnostic and Interventional Nephrology),[9] based in part on local resources and practices. Further investigation will inform the optimal timing and methods to preserve veins and limit catheter complications; in the meantime, the lower risk of acute complications with subclavian catheters must be weighed against the higher risk of central venous stenosis in patients with chronic kidney disease who are expected to require dialysis in the future.

DISCLOSURE

All the authors declared no competing interests.

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cardiovascular disease

Sodium–glucose cotransporter 2 inhibition and cardiovascular risk reduction in patients with type 2 diabetes: the emerging role of natriuresis

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Inhibition of sodium–glucose cotransporter 2 causes both glycosuria and natriuresis, leading to reductions in hyperglycemia, body weight, blood pressure, and proteinuria. The recently published EMPA-REG OUTCOME study demonstrated significant cardiovascular and mortality benefits of sodium–glucose cotransporter 2 inhibition with empagliflozin in patients with type 2 diabetes and established cardiovascular disease, and may suggest a broader role for sodium–glucose cotransporter 2 inhibition in patients with heart failure.

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Sodium–glucose cotransporter 2 inhibition (SGLT2i) induces glycosuria by blocking proximal tubular glucose reabsorption, thereby reducing hemoglobin A1c (HbA1c) and weight in patients with type 2 diabetes. Beyond these glycosuria-mediated effects, SGLT2i blocks proximal tubular sodium reabsorption, increasing distal sodium delivery to the macula densa, thereby increasing tubuloglomerular feedback, which leads to afferent arteriolar vasoconstriction, reduced intraglomerular pressure, and decreased hyperfiltration in animals and humans.[1] These renal functional effects with SGLT2i are likely responsible for a 30% to 40% reduction in proteinuria, an effect that is largely independent of reductions in blood pressure, weight, or HbA1c.[2]

In addition to influencing renal function, HbA1c, and weight, SGLT2i exerts salutary effects on cardiovascular risk factors (Figure 1), including a reduction in systolic (~4–6 mm Hg) and diastolic blood pressure (~2 mm Hg), arterial stiffness, and plasma uric acid levels, with neutral overall effects on lipids.[3–6] The antihypertensive effect