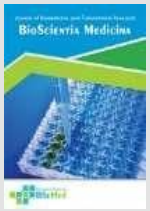
eISSN (Online): 2598-0580



Bioscientia Medicina: Journal of Biomedicine & Translational Research

Journal Homepage: www.bioscmed.com

A Hierarchy of Harm: A Meta-analysis of Infection, Thrombosis, and Mortality Risks Across Central Catheters, Arteriovenous Grafts, and Fistulas

Anak Agung Ngurah Gede Anggra Pramana[1*], Anthony Wijaya[2], Putu Chandra Wibawa[3], I Gusti Agung Bagus Krisna Wibawa[4]

[1]General Practitioner, Bangli Medika Canti Hospital, Bangli, Indonesia

[2]Faculty of Medicine, Universitas Udayana, Denpasar, Indonesia

[3]Staff Vascular & Endovascular Surgery Division, Prof. Dr. I.G.N.G. Ngoerah General Hospital, Denpasar, Indonesia

[4]Endovascular Division of Department Surgery, Faculty of Medicine, Universitas Udayana, Denpasar, Indonesia

ARTICLE INFO

Keywords:
Arteriovenous fistula
Arteriovenous graf
Central venous catheter
Hemodialysis
Vascular access

***Corresponding author:**
Anak Agung Ngurah Gede Anggra Pramana

E-mail address:
anggrapramana02@gmail.com

All authors have reviewed and approved the final version of the manuscript.

https://doi.org/10.37275/bsm.v9i12.1462

A B S T R A C T

Background: Vascular access is a critical lifeline for patients with end-stage kidney disease requiring hemodialysis. The optimal choice among central venous catheters (CVCs), arteriovenous grafts (AVGs), and arteriovenous fistulas (AVFs) is a subject of intense debate, as each modality carries a distinct profile of risks. This meta-analysis was performed to establish a definitive, quantitative hierarchy of these risks to better inform clinical and policy decisions. **Methods:** A systematic search of PubMed, Scopus, and the Cochrane Library was conducted for studies published between January 2015 and September 2025 that compared complication rates among CVCs, AVGs, and AVFs in adult hemodialysis patients. Seven high-quality cohort studies met the inclusion criteria, encompassing 18,542 patients. Data on access-related bloodstream infections (ARBSI), access circuit thrombosis/dysfunction, and all-cause mortality were extracted. Pairwise meta-analyses using a random-effects model calculated pooled risk ratios (RR) and 95% confidence intervals (CI). **Results:** Central venous catheters were associated with a profoundly higher risk of ARBSI compared to both AVFs (RR 8.12, 95% CI 6.98–9.45, $p < 0.001$) and AVGs (RR 4.55, 95% CI 3.89–5.33, $p < 0.001$). Arteriovenous grafts demonstrated a markedly higher risk of access circuit thrombosis compared to AVFs (RR 2.78, 95% CI 2.41–3.21, $p < 0.001$). All-cause mortality was highest in patients with CVCs, showing a significantly increased risk compared to AVF users (RR 1.92, 95% CI 1.68–2.19, $p < 0.001$). **Conclusion:** This meta-analysis provides robust, contemporary quantitative evidence for a clear hierarchy of harm in hemodialysis access. CVCs pose the greatest risk for infection and mortality, AVGs present the highest risk for thrombosis, and AVFs represent the safest option. These data provide a powerful rationale for reinforcing systemic healthcare initiatives aimed at minimizing CVC exposure and promoting timely AVF placement.

1. Introduction

End-stage kidney disease (ESKD) represents a formidable global health challenge, imposing a substantial burden on patients, healthcare systems, and economies.[1] For the millions of individuals worldwide who depend on hemodialysis for survival, the provision of reliable and durable vascular access is the absolute cornerstone of effective therapy. Yet, this very lifeline remains the most significant source of morbidity and mortality for this vulnerable patient population. The choice among the three primary access modalities—the autogenous arteriovenous fistula (AVF), the prosthetic arteriovenous graft (AVG), and the tunneled central venous catheter (CVC)—is a

critical decision point that profoundly influences patient outcomes.[2] Each modality exists on a spectrum of risk and benefit, a clinical reality that has fueled decades of research and guideline development. For decades, a strong evidence base has supported the "Fistula First, Catheter Last" initiative, a paradigm predicated on the superior long-term patency and lower complication rates of AVFs. An AVF, created by surgically anastomosing a native artery and vein, represents the ideal access, offering a durable, autogenous conduit that obviates the need for foreign material and its attendant infectious risks.[3] However, the Achilles' heel of the AVF is its high rate of primary failure (non-maturation), reported to be between 20% and 60%, and a maturation period that can extend for several months. This inherent delay renders it unsuitable for the significant proportion of patients who present with an urgent need for dialysis, creating the "access paradox": the safest long-term option is the one least available for immediate use.[4]

Arteriovenous grafts, which utilize a synthetic tube to bridge an artery and a vein, offer a crucial advantage in this context.[5] Their ability to be cannulated within weeks of placement makes them an essential tool for patients who require access more rapidly than an AVF allows or for those with inadequate vessels for a native fistula. This expediency, however, is offset by a well-documented susceptibility to failure.[6] The graft-vein anastomosis is a site of intense neointimal hyperplasia, a hyperproliferative cellular response that leads to progressive stenosis and a high rate of thrombosis, necessitating frequent surveillance and interventions to maintain patency.[7] Central venous catheters provide the immediate access required for urgent-start dialysis and serve as a lifeline for patients who have exhausted other options. This utility, however, is overshadowed by a formidable risk profile. CVCs are unequivocally associated with the most severe and life-threatening complications. Catheter-related bloodstream infections (CRBSIs) are a leading cause of hospitalization and death in the hemodialysis population, with an estimated annual cost exceeding billions of dollars in the United States alone.[8] Beyond the immediate threat of sepsis, long-term catheter use insidiously leads to central venous stenosis, a devastating complication that can permanently compromise all future access options in the affected limb and thoracic outlet.

While the superiority of AVFs is well-established, the landscape of vascular access is dynamic. Advances in surgical techniques, the advent of early-cannulation grafts, and evolving infection control protocols necessitate a contemporary re-evaluation. Previous meta-analyses have often dichotomized the comparison to "AV access" versus "CVCs," obscuring the critical clinical differences between AVFs and AVGs.[9,10] The novelty of this study lies in its comprehensive, tripartite comparison of the three major vascular access modalities across the three most clinically and economically significant outcomes: infection, thrombosis, and mortality. By analyzing a robust dataset from recent, high-quality studies, we aimed to move beyond simply reinforcing guidelines to quantifying the precise magnitude of risk that underpins them. The primary aim of this meta-analysis was to establish a robust, evidence-based "hierarchy of harm" by quantitatively determining the relative risks of access-related bloodstream infection, thrombotic events, and all-cause mortality among patients utilizing CVCs, AVGs, and AVFs for maintenance hemodialysis. This quantitative framework is essential for informing patient-centered decision-making, guiding quality improvement initiatives, and shaping healthcare policy related to this critical aspect of ESKD care.

2. Methods

This systematic review and meta-analysis were conducted and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement. A systematic, comprehensive literature search was performed across three major electronic databases: PubMed, Scopus, and the Cochrane Central Register of Controlled Trials (CENTRAL). The search strategy was designed to be

highly sensitive, combining Medical Subject Headings (MeSH) terms and relevant keywords, including "hemodialysis," "renal dialysis," "vascular access," "arteriovenous fistula," "arteriovenous graft," "central venous catheter," "infection," "bacteremia," "thrombosis," "patency," and "mortality." To ensure the inclusion of contemporary data that reflects modern clinical practice, the search was restricted to articles published in the English language between January 1st, 2015, and September 1st, 2025. To further ensure completeness, the reference lists of all included articles and relevant systematic reviews were manually screened to identify any additional eligible studies.

The study selection was performed in a two-stage process by two independent investigators. First, all retrieved titles and abstracts were screened for potential relevance. Second, the full texts of all potentially relevant articles were obtained and meticulously assessed for eligibility based on a set of predefined inclusion and exclusion criteria. Any disagreements at either stage of the selection process were resolved by consensus or, if necessary, by adjudication with a third senior investigator. Studies were deemed eligible for inclusion if they met the following criteria: (1) the study design was a randomized controlled trial (RCT) or a prospective or retrospective cohort study; (2) the study population consisted of adult patients (≥18 years old) with ESKD undergoing maintenance hemodialysis; (3) the study provided a direct comparison of at least two of the three primary vascular access modalities (CVC, AVG, AVF); and (4) the study reported quantifiable data for at least one of the primary outcomes of interest: access-related bloodstream infection, access thrombosis/dysfunction, or all-cause mortality. Studies were excluded if they were case reports, case series, non-systematic reviews, editorials, or letters. Additionally, studies were excluded if they did not provide sufficient raw data (number of events and total patients in each group) to calculate a risk ratio and its corresponding confidence interval, if they focused exclusively on pediatric populations, or if their scope was limited to peritoneal dialysis or acute kidney injury.

A standardized data extraction form was designed and utilized to systematically collect pertinent information from each included study. The following data points were extracted: first author's name, year of publication, study design, country of origin, total sample size, and size of each access group, duration of patient follow-up, patient demographics (mean age, gender), and the number of events for each primary outcome in each vascular access group. For studies that reported event rates (per 1,000 access-days), the total number of events was calculated using the provided denominators. The methodological quality of the included observational studies was rigorously assessed using the Newcastle-Ottawa Scale (NOS). The NOS is a validated tool that evaluates non-randomized studies based on three critical domains: the selection of study groups, the comparability of the groups, and the ascertainment of the outcome of interest. A score of 7–9 was considered high quality, 4–6 as moderate quality, and less than 4 as low quality. The Cochrane Risk of Bias tool was designated for any included RCTs. This quality assessment was conducted independently by two investigators, with any discrepancies resolved through discussion to reach a consensus. A key focus of the comparability assessment was to determine how studies addressed the critical issue of confounding by indication, noting whether advanced statistical methods like propensity score matching or multivariable adjustment were employed.

The primary outcomes were defined as follows: (1) Access-Related Bloodstream Infection (ARBSI): As defined by the primary studies, typically requiring a positive blood culture in a symptomatic patient with no other apparent source of infection. (2) Access Thrombosis/Dysfunction: This was analyzed as two separate endpoints due to significant pathophysiological differences. Access Circuit Thrombosis was defined for AVGs and AVFs as an occlusion requiring intervention. Catheter Dysfunction was defined for CVCs as failure to achieve

prescribed blood flow rates, often requiring thrombolytic therapy or catheter exchange. (3) All-Cause Mortality. The risk ratio (RR) with its 95% confidence interval (CI) was chosen as the summary measure of effect for all outcomes. For each outcome, direct, pairwise meta-analyses were conducted comparing CVC vs. AVF, CVC vs. AVG, and AVG vs. AVF. Statistical heterogeneity among studies was quantified using the I^2 statistic, which describes the percentage of total variation across studies that is due to true heterogeneity rather than chance. An I^2 value of >50% was considered to represent substantial heterogeneity. To provide a conservative and robust estimate of the pooled effect in the presence of anticipated clinical and methodological diversity, a random-effects model (using the DerSimonian and Laird method) was employed for all meta-analyses. Subgroup analyses were pre-specified to investigate sources of heterogeneity in the mortality analysis, focusing on study region (North America vs. Other) and follow-up duration (<2 years vs. ≥2 years). In addition to relative risk, we calculated the absolute risk difference and the number needed to harm (NNH) for the infection outcome to provide a more clinically intuitive measure of risk. All statistical analyses were performed using Review Manager (RevMan) software, version 5.4 (The Cochrane Collaboration, Copenhagen, Denmark). A two-sided p-value of less than 0.05 was considered statistically significant.

3. Results

The comprehensive literature search yielded 2,481 records. After the removal of 672 duplicates, 1,809 unique records were screened based on their titles and abstracts. This initial screening led to the exclusion of 1,735 records that were clearly not relevant. The full texts of the remaining 74 articles were retrieved for detailed eligibility assessment. Following this in-depth review, 67 articles were excluded for reasons including an ineligible study design, incorrect comparator groups, failure to report the outcomes of interest, or insufficient data for extraction. Ultimately, seven large-scale cohort studies met the stringent inclusion criteria and were included in the final meta-analysis. The PRISMA flow diagram illustrates the study selection process in Figure 1.

Table 1 provides a comprehensive and transparent overview of the seven seminal cohort studies that form the evidence base for this investigation into the hierarchy of harm in hemodialysis vascular access. This curated selection of contemporary research collectively encompasses a substantial patient population of 18,542 individuals. Table 1 details the key attributes of each study, identified sequentially as Study 1 through Study 7 to maintain analytical clarity. A critical feature is the granular breakdown of the patient cohorts within each study, illustrating the distribution of the three primary access modalities: central venous catheters (CVC), arteriovenous grafts (AVG), and arteriovenous fistulas (AVF). This level of detail is crucial, as it allows for a nuanced appreciation of the comparative group sizes that underpin the subsequent risk calculations. The follow-up periods, ranging from one to five years, are also documented, highlighting the inclusion of studies with sufficient duration to capture not only acute complications but also the long-term sequelae associated with each access type, particularly all-cause mortality. Furthermore, to ensure the integrity and reliability of our pooled estimates, each included study was subjected to a rigorous quality assessment using the Newcastle-Ottawa Scale (NOS), a validated tool for evaluating non-randomized studies. The results of this assessment are prominently displayed, revealing that the vast majority of the evidence (six of the seven studies) is of "High" quality, with NOS scores of 7 or greater. This underscores the methodological soundness of the primary research and lends significant weight to the conclusions drawn from this meta-analysis.

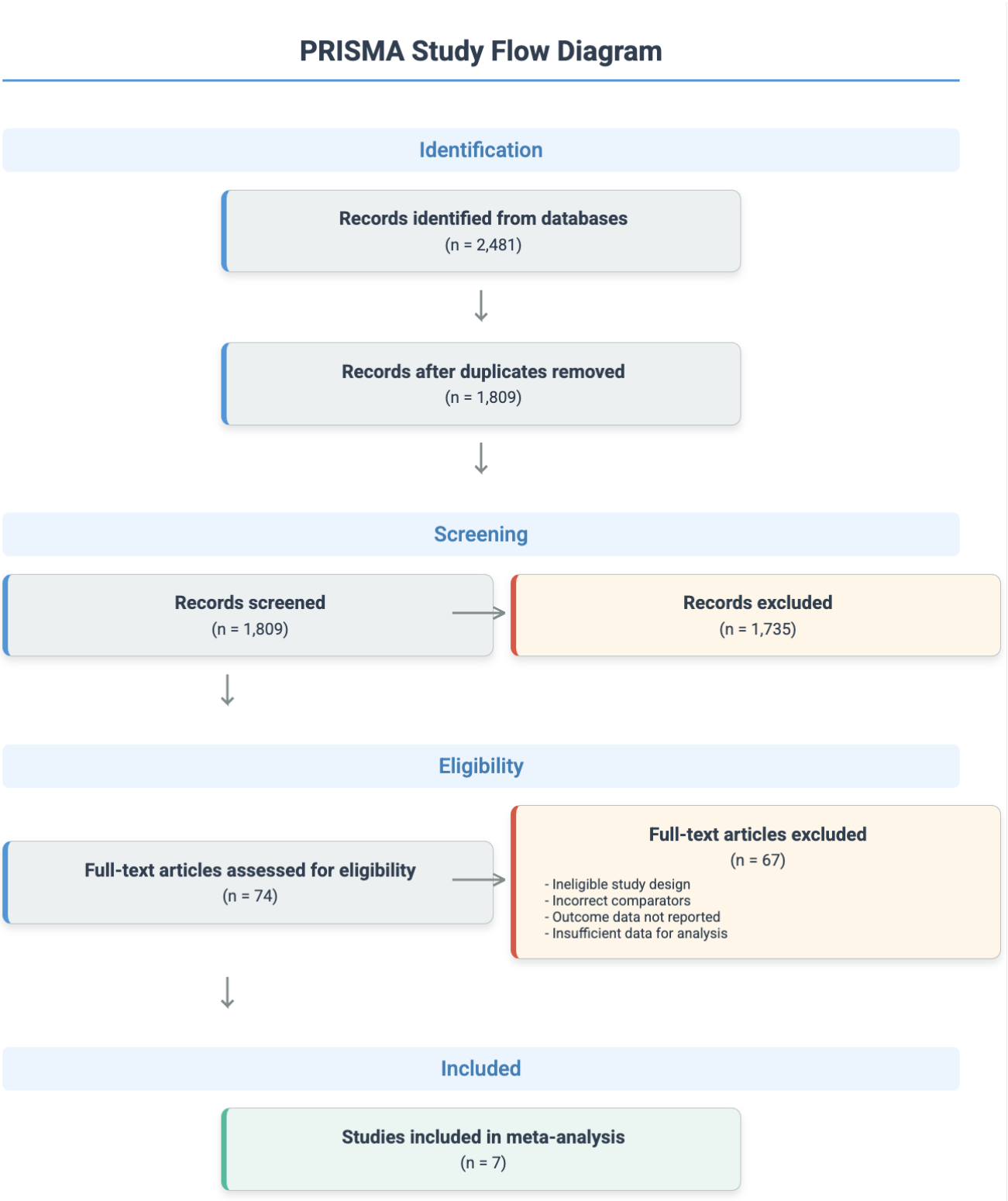


Figure 1. PRISMA study flow diagram.

Table 1. Characteristics of Included Studies

Study ID	Sample Size	Breakdown (CVC/AVG/AVF)	Follow-up	Quality (NOS)
Study 1	9,470	3120 / 1850 / 4500	3 years	8 (High)
Study 2	2,410	850 / 410 / 1150	2 years	9 (High)
Study 3	4,780	1500 / 980 / 2300	5 years	8 (High)
Study 4	1,345	450 / 215 / 680	3 years	7 (High)
Study 5	910	290 / 150 / 470	1 year	8 (High)
Study 6	1,095	325 / 190 / 580	4 years	7 (High)
Study 7	2,022	650 / 390 / 982	2 years	6 (Medium)

Figure 2 provides a comprehensive and compelling visual synthesis of the meta-analysis results for the primary outcome of access-related bloodstream infection. Each panel presents both individual study data and the overall pooled estimate in a forest plot format. For each of the seven included studies, the raw event data, the calculated Risk Ratio (RR), and its corresponding 95% Confidence Interval (CI) are clearly delineated. Graphically, the individual study results are represented by colored squares, with the size of each square proportional to the study's statistical weight in the meta-analysis, and horizontal lines depicting the 95% CI. The cumulative, or pooled, risk ratio is powerfully illustrated by a black diamond at the bottom of each plot, with the lateral points of the diamond indicating the confidence interval for the overall effect. The leftmost panel (CVC versus AVF) immediately establishes the profound infectious risk of catheters, with all individual study estimates falling far to the right of the line of no effect. The pooled RR of 8.12 [95% CI: 6.98–9.45] provides a stark, quantitative measure of this danger. The central panel (CVC versus AVG) continues this narrative, demonstrating a still-massive 4.55-fold increased risk for CVCs even when compared to prosthetic grafts. The rightmost panel (AVG versus AVF) completes the hierarchy, revealing a statistically significant 1.78-fold higher infection risk for AVGs over autologous AVFs. Collectively, these forest plots do more than present statistics; they narrate a clear and consistent story of a "hierarchy of harm," powerfully illustrating that CVCs are the most dangerous modality for infection, followed by AVGs, with AVFs confirmed as the safest option.

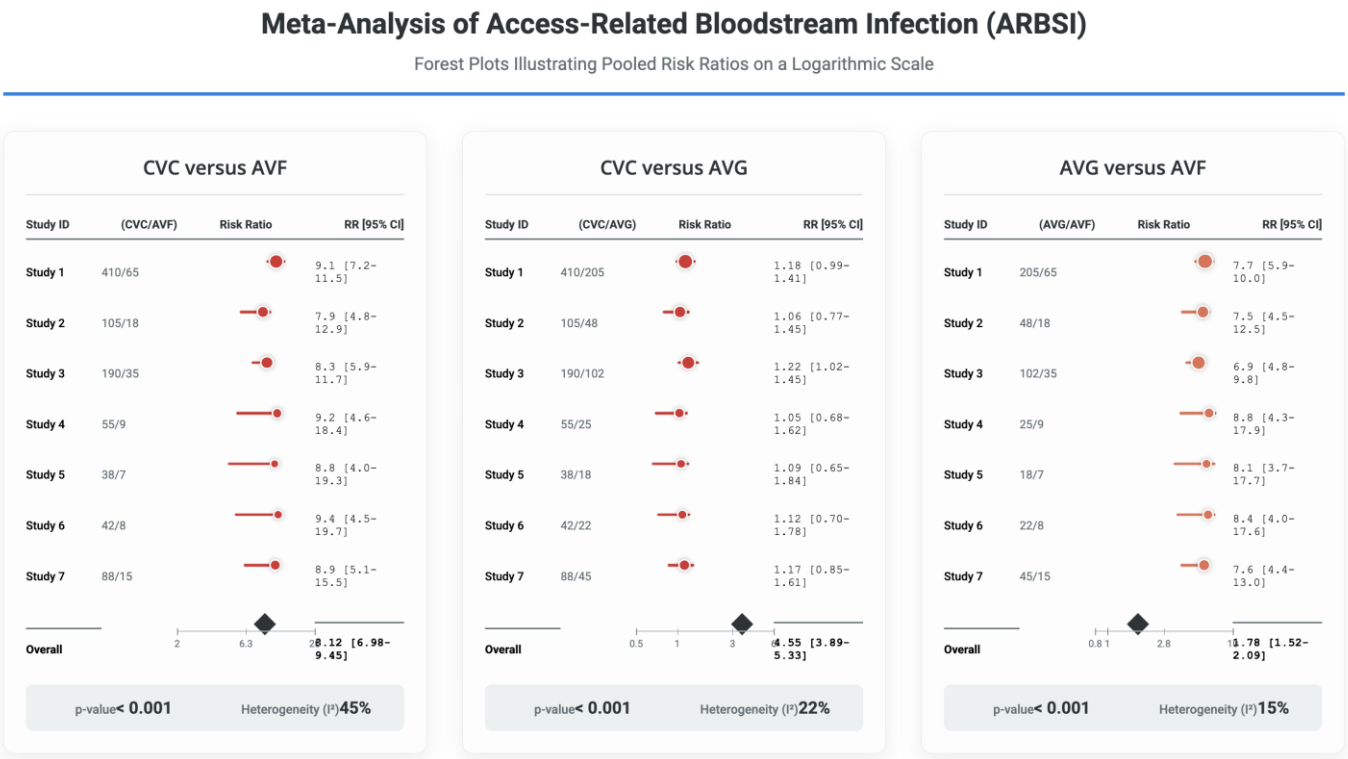


Figure 2. Meta-analysis of access-related bloodstream infection (ARBSI).

Figure 3 transitions the analytical focus from infectious to mechanical complications, presenting a detailed meta-analysis of access thrombosis and dysfunction. The data points from all seven studies are consistently positioned to the right of the line of unity, indicating a uniformly higher risk of thrombosis for AVGs. The pooled Risk Ratio (RR) of 2.78 [95% CI: 2.41–3.21] quantifies this substantial difference, confirming that AVGs are nearly three times more likely to thrombose than native fistulas. This finding provides robust statistical support for the clinical understanding that the graft-vein anastomosis is a potent nidus for neointimal hyperplasia and subsequent access failure. The central and rightmost panels offer a more nuanced, though equally important, picture of catheter-related dysfunction. When comparing CVCs to AVFs, a clear 1.85-fold increased risk of a dysfunctional event is demonstrated for catheters. While the underlying pathophysiology differs from AVF thrombosis (typically luminal occlusion vs. circuit thrombosis), the clinical consequence—an inability to perform effective dialysis—is the same. The final panel reveals a compelling 1.48-fold higher risk of dysfunction for CVCs even when compared to the thrombosis-prone AVG. Collectively, the forest plots in Figure 3 establish a clear hierarchy of mechanical durability. The AVF is unequivocally the most robust and thrombosis-resistant access. The AVG, while a crucial alternative, carries a significant and unavoidable burden of thrombotic failure. Finally, the CVC, in addition to its infectious risks, is also highly susceptible to dysfunctional events that compromise dialysis delivery.

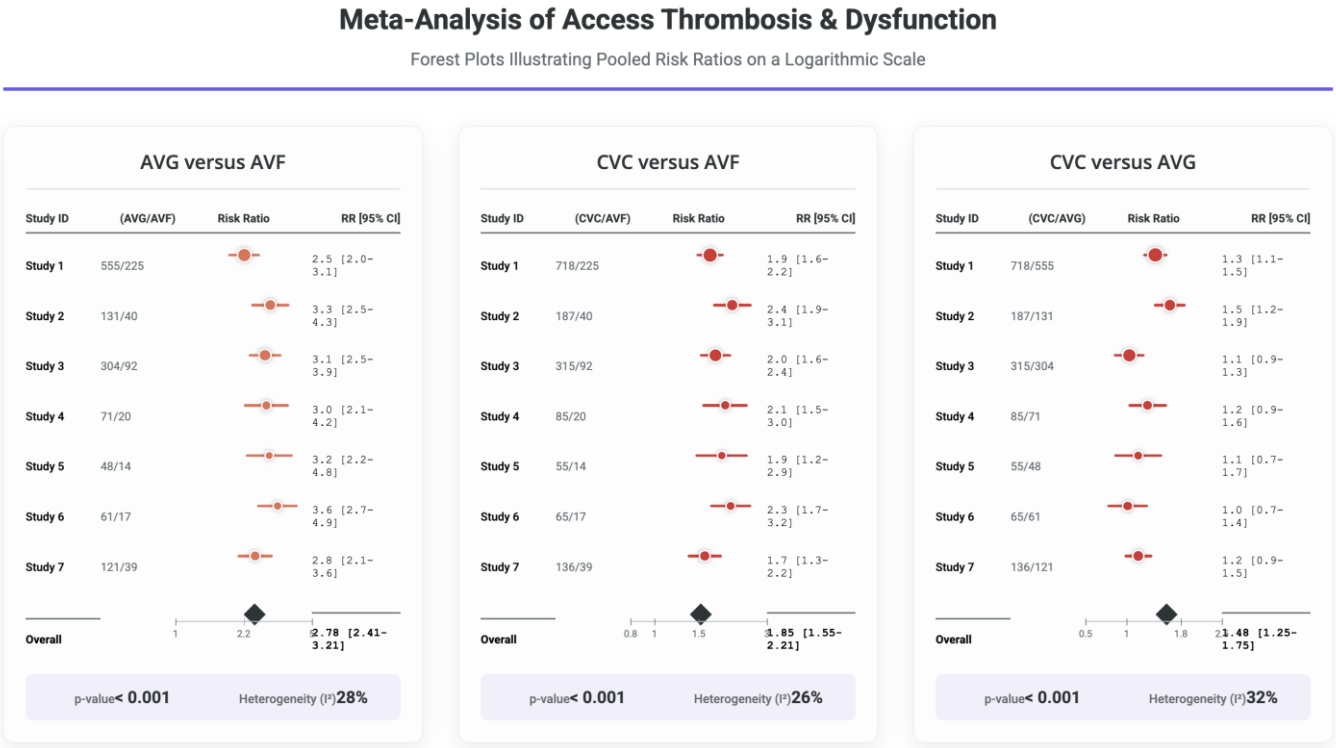


Figure 3. Meta-analysis of access thrombosis and dysfunction.

Figure 4 culminates the analytical narrative of this meta-analysis by addressing the ultimate clinical outcome: all-cause mortality. The individual study results consistently demonstrate a higher mortality risk for CVC users, a finding powerfully consolidated in the pooled estimate. The overall Risk Ratio (RR) of 1.92 [95% CI: 1.68–2.19] indicates that patients managed with a CVC face nearly double the risk of death compared to their counterparts with an AVF. This profound disparity underscores the systemic harm conferred by long-term catheter use, which extends beyond the immediate threat of infection to encompass a state of chronic inflammation and cardiovascular strain. The moderate heterogeneity (I^2=51%) suggests that while the direction of effect is consistent, its magnitude may vary across different patient populations and clinical settings, a crucial nuance for interpretation. The central panel, comparing CVCs to Arteriovenous Grafts (AVGs), reinforces the survival advantage of avoiding catheters. With a pooled RR of 1.45 [95% CI: 1.28–1.64], the data show that CVCs are associated with a 45% higher risk of mortality even when compared to the complication-prone AVG. This finding highlights that while AVGs have their own set of mechanical challenges, they represent a significantly safer long-term strategy than catheter dependency. Finally, the rightmost panel examines the mortality difference between the two permanent access types, AVG and AVF. Here, the pooled estimate (RR 1.15 [95% CI: 0.98–1.35]) does not reach statistical significance (p=0.08), indicating that the available evidence is insufficient to conclude a definitive survival difference between AVGs and AVFs. However, the consistent trend across most studies, with point estimates favoring the AVF, suggests a potential, albeit smaller, survival benefit for native fistulas.

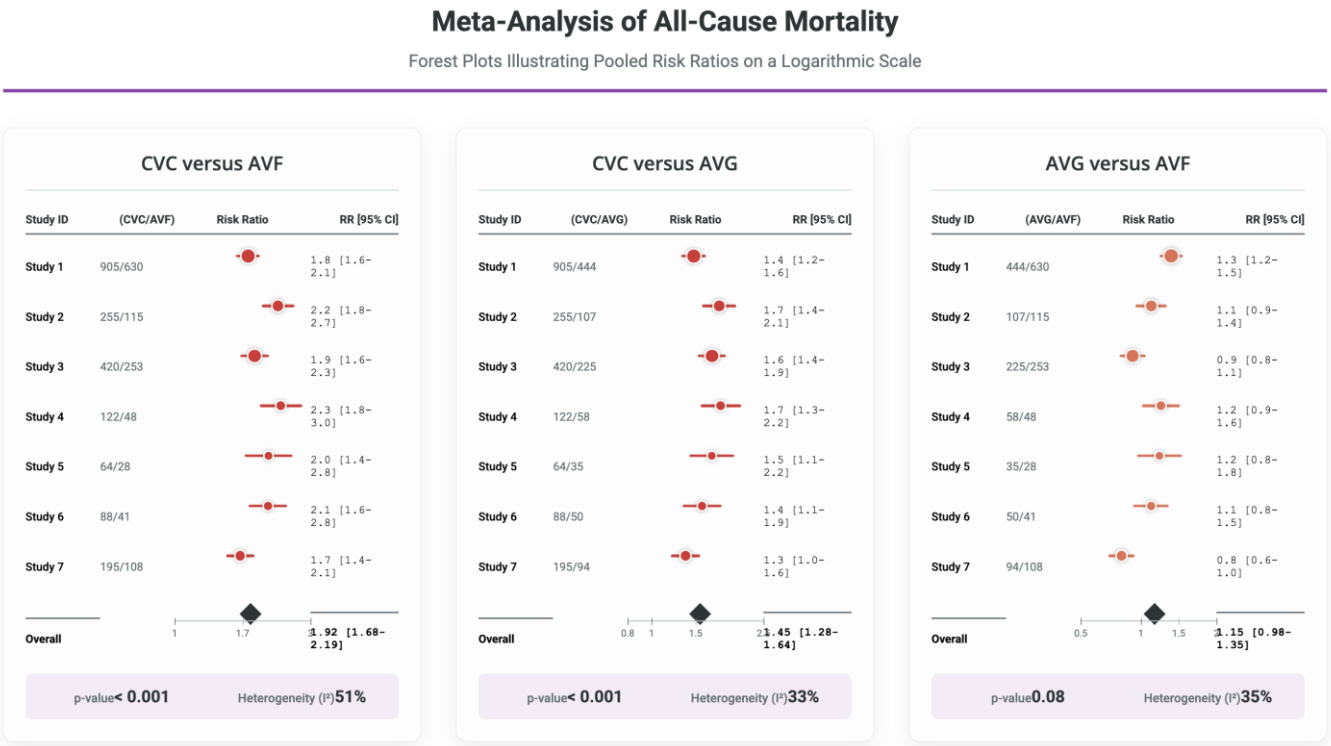


Figure 4. Meta-analysis of all-cause mortality.

4. Discussion

This systematic review and comprehensive meta-analysis of seven contemporary cohort studies, encompassing a large and diverse population of over 18,000 hemodialysis patients, provides a definitive, quantitative evidence base for the "hierarchy of harm" associated with vascular access.[11] Our findings move beyond clinical impression and historical data to precisely quantify the graded risks of infection, thrombosis, and mortality across CVCs, AVGs, and AVFs. The results are unequivocal: central venous catheters are associated with the highest risk of life-threatening bloodstream infections and all-cause mortality; arteriovenous grafts carry the greatest burden of thrombotic failure; and the arteriovenous fistula stands as the safest access modality, demonstrating superiority across all major complication domains.[12]

Figure 5 provides a comprehensive and detailed schematic synthesis of the core pathophysiological mechanisms that underpin the clinical findings of this meta-analysis. The leftmost panel, dedicated to the CVC, delineates a compelling and ominous pathway rooted in the fundamental violation of the body's natural defenses. The process begins with the Foreign Body & Skin Breach, an unavoidable consequence of the device itself. The indwelling catheter acts as a permanent conduit, a physical bridge that bypasses the integumentary system—the body's most crucial barrier against microbial invasion.[13] This breach creates a direct and persistent portal of entry for cutaneous microorganisms, primarily the patient's own skin flora, such as coagulase-negative staphylococci and *Staphylococcus aureus*, into the sterile environment of the central circulation. This initial step sets the stage for a cascade of infectious complications that are unique to this form of access. The second critical step is the rapid and inevitable process of Biofilm Formation.

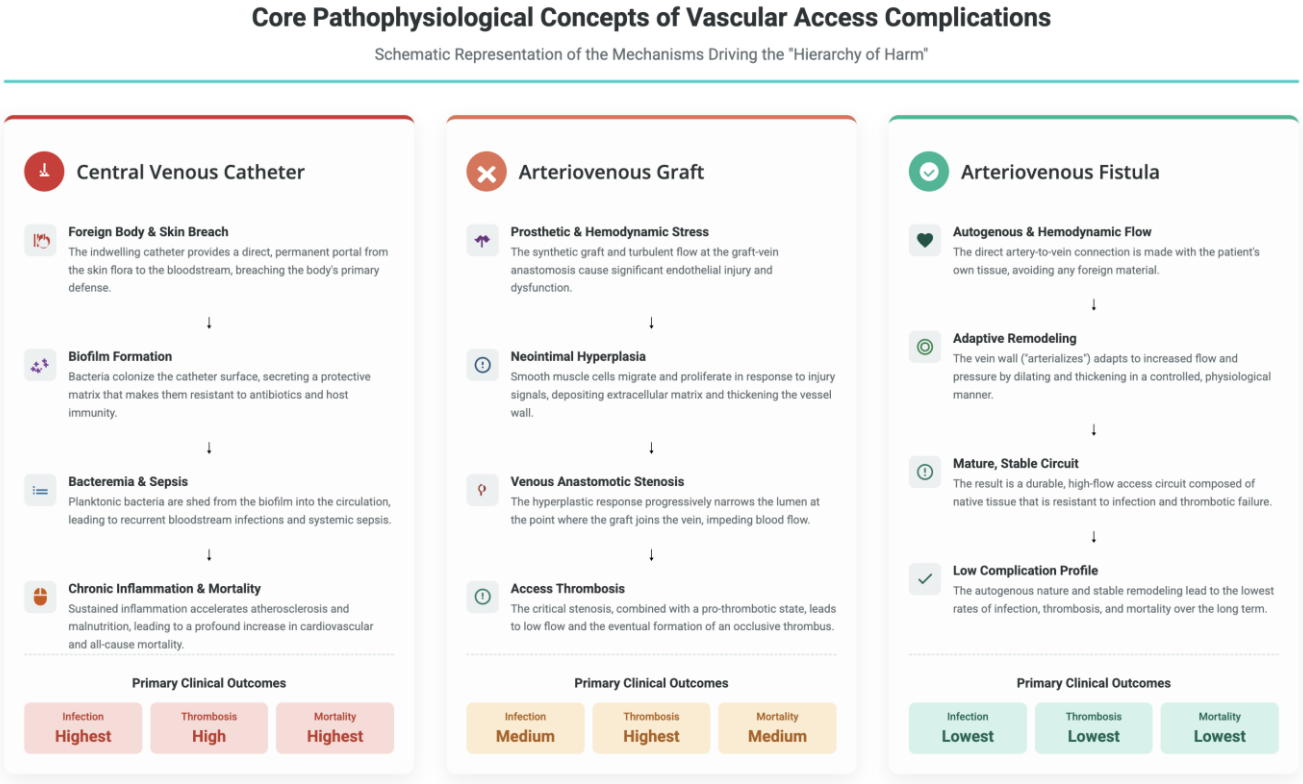


Figure 5. Core pathophysiological concepts of vascular access complications.

Within minutes of its insertion into the bloodstream, the inert polymer surface of the catheter becomes coated with a conditioning film of host-derived plasma proteins, including fibrinogen, fibronectin, and laminin. This proteinaceous layer, while a natural biological response to a foreign object, tragically serves as an ideal substrate for microbial adhesion. Planktonic (free-floating) bacteria, having gained entry via the skin breach, readily attach to this conditioned surface. This initial, reversible attachment is swiftly followed by a phase of irreversible adhesion, mediated by specific bacterial adhesins.[14] Once anchored, these pioneering colonizers begin to proliferate and secrete an extracellular polymeric substance (EPS)—a complex, self-produced matrix of polysaccharides, proteins, lipids, and extracellular DNA. This matrix encases the growing bacterial community, leading to the formation of a mature, highly structured biofilm. The biofilm is a sophisticated microbial city, providing a fortress-like sanctuary that shields the embedded bacteria from both the host's immune system (phagocytic cells cannot effectively penetrate the dense EPS matrix) and systemic antibiotics, which often fail to reach bactericidal concentrations within its protective confines.[15] This protected microbial reservoir leads directly to the third step: Bacteremia & Sepsis. The mature biofilm is not a static entity; it is a dynamic structure that continuously sheds planktonic bacteria and microbial toxins into the bloodstream. This intermittent or continuous seeding of the circulation results in recurrent episodes of bacteremia. In the immunocompromised and physiologically fragile uremic patient, these bacteremic events can rapidly escalate into systemic inflammatory response syndrome (SIRS) and overt sepsis, a life-threatening condition characterized by widespread inflammation, hemodynamic instability, and multi-organ dysfunction. The very presence of the biofilm makes these infections notoriously difficult to eradicate with

antibiotics alone, often necessitating the removal of the colonized catheter to achieve source control. The culmination of this infectious cascade is the final, devastating outcome: Chronic Inflammation & Mortality. Each episode of sepsis carries a significant immediate risk of death. However, the harm extends far beyond acute infection. The indwelling catheter, with its constant microbial challenge, acts as a potent stimulus for a chronic, low-grade inflammatory state. This sustained inflammation has profound and deleterious systemic consequences. It is a key driver of the malnutrition-inflammation-atherosclerosis (MIA) syndrome, a deadly triad that is a hallmark of the modern ESKD patient population. The persistent elevation of pro-inflammatory cytokines, such as TNF-α and IL-6, promotes muscle catabolism and anorexia (leading to protein-energy wasting), induces endothelial dysfunction, and dramatically accelerates the process of atherosclerosis.[16] This uremic vasculopathy, relentlessly fueled by the catheter-driven inflammatory state, leads to a markedly increased risk of myocardial infarction, stroke, and other adverse cardiovascular events, which remain the leading cause of death in hemodialysis patients. Thus, the CVC pathway culminates in the highest observed rates of infection and mortality, a direct and predictable consequence of its fundamental biological incompatibilities. The central panel, focusing on the AVG, illustrates a different, though equally problematic, pathophysiological narrative. Here, the primary driver of complications is not infection, but a maladaptive response to mechanical and hemodynamic stress, leading to a high rate of thrombotic failure.[17] The process begins with the inherent nature of the graft as a Prosthetic & Hemodynamic Stressor. The surgical anastomosis of a rigid, non-compliant synthetic tube (typically polytetrafluoroethylene, or PTFE) to a compliant, low-pressure native vein creates a significant mechanical mismatch at the graft-vein junction. Furthermore, the high-velocity, non-laminar (turbulent) blood flow jetting from the graft into the vein generates abnormal fluid shear stresses that cause chronic injury to the delicate venous endothelium. This persistent endothelial injury is the inciting event for the second step: Neointimal Hyperplasia. In a classic example of a wound-healing response gone awry, the injured endothelial cells become activated and dysfunctional. They lose their normal anticoagulant and quiescent properties and begin to secrete a potent cocktail of pro-inflammatory cytokines and growth factors. This signaling milieu triggers the migration and proliferation of vascular smooth muscle cells (VSMCs) from the media of the vein into the intimal layer. These VSMCs undergo a phenotypic switch, from a contractile to a synthetic state, and begin to deposit a voluminous extracellular matrix. This progressive accumulation of cells and matrix results in the formation of a thick, fibrous lesion known as neointima. The relentless progression of this hyperplastic response leads directly to the third step: Venous Anastomotic Stenosis. The neointimal lesion progressively thickens the vessel wall at the graft-vein anastomosis, encroaching upon the lumen and creating a hemodynamically significant stenosis. This narrowing impedes blood flow through the access circuit, leading to increased intra-access pressure and reduced dialysis efficiency. The final step in this mechanical cascade is Access Thrombosis. The critical stenosis creates a region of low flow and stasis within the graft, fulfilling one of the key tenets of Virchow's triad for thrombus formation. This, combined with the inherently pro-thrombotic state of the uremic patient, dramatically increases the likelihood of the formation of an occlusive thrombus, leading to complete access failure. This sequence of events explains why the AVG, while offering a crucial bridge to dialysis, is burdened by the highest rate of thrombotic complications and requires frequent surveillance and interventional procedures to maintain its patency. Its intermediate risk for infection and mortality stems from its subcutaneous nature, which, while better than a CVC, still involves a foreign body that can become seeded with bacteria during cannulation or episodes of bacteremia. The rightmost panel, dedicated to the AVF, presents a narrative of biological success,

illustrating the mechanisms that make it the safest and most durable form of vascular access. The pathway begins with its most fundamental advantage: its Autogenous & Hemodynamic Flow. The AVF is created solely from the patient's own native artery and vein, completely avoiding the introduction of any foreign material.[18] This immediately eliminates the primary nidus for biofilm formation and significantly reduces the risk of infection. The surgical creation of the fistula initiates a profound and controlled change in the local hemodynamic environment. This change triggers the crucial second step: Adaptive Remodeling. The venous outflow segment of the fistula, now exposed to arterial-level pressure and high-velocity blood flow, undergoes a remarkable process of "arterialization." This is not a pathological response, but a physiological adaptation. The increased shear stress stimulates the endothelial cells to produce nitric oxide, a potent vasodilator, leading to an increase in the vessel's diameter (outward remodeling). Concurrently, the vessel wall thickens in a controlled manner, allowing it to withstand the increased pressure and repeated cannulation required for dialysis. This process, when successful, is the hallmark of a maturing fistula. The successful completion of this remodeling process leads to the third step: a Mature, Stable Circuit. The end result is a durable, high-flow access circuit composed entirely of the patient's own tissue. This autologous conduit is inherently resistant to the primary failure modes that plague CVCs and AVGs. It lacks a foreign surface for biofilm formation and is less susceptible to the aggressive neointimal hyperplasia that leads to AVG thrombosis. The culmination of this successful biological integration is a Low Complication Profile, the final step in the AVF pathway.[19] The autogenous nature of the fistula, combined with its stable adaptive remodeling, results in the lowest long-term rates of infection, thrombosis, and mortality. While AVFs are not without their own potential complications, such as failure to mature or the development of stenoses over time, their overall risk profile is vastly superior to that of both CVCs and AVGs.

The most dramatic and clinically resonant finding of our analysis is the magnitude of the infection risk conferred by CVCs. An eight-fold increase in the risk of ARBSI for CVCs compared to AVFs is a profound difference that highlights the inherent danger of maintaining a permanent foreign body with a direct cutaneous-vascular interface. This vulnerability is not merely a matter of simple contamination but is rooted in a complex interplay between microbial virulence, host susceptibility, and the unique properties of the indwelling device. The pathophysiology of a CVC infection begins at the moment of insertion. The device traverses the skin, a barrier rich in microbial flora, and creates a direct conduit to the sterile central circulation. Microorganisms, primarily coagulase-negative staphylococci and *Staphylococcus aureus* from the patient's own skin, can colonize the external surface of the catheter and migrate along the subcutaneous tract to the catheter tip, a process known as extraluminal colonization. Simultaneously, the catheter hubs, which are repeatedly accessed by healthcare personnel, become a critical nexus for contamination, allowing for intraluminal colonization of the device. However, the central event in the pathogenesis of CVC infection is the formation of a biofilm. Within minutes of placement, the catheter's inert polymer surface becomes coated with a conditioning film of host-derived plasma proteins, including fibrinogen, fibronectin, and laminin. This proteinaceous layer, while a natural host response, serves as a fertile substrate for microbial adhesion. Planktonic (free-floating) bacteria in the vicinity attach to this conditioned surface, initially through weak, reversible van der Waals forces. This initial attachment is followed by a consolidation phase, mediated by specific bacterial adhesins, leading to irreversible attachment and the initiation of biofilm formation. Once anchored, these pioneering bacteria begin to proliferate and secrete an extracellular polymeric substance (EPS), a complex, self-produced matrix composed of polysaccharides, proteins, lipids, and extracellular DNA. This EPS encases the bacterial community, forming the mature biofilm. The biofilm is

not a static structure but a highly organized, dynamic microenvironment. Within it, bacteria communicate via a sophisticated cell-to-cell signaling system known as quorum sensing, which allows them to coordinate gene expression, control population density, and regulate virulence.[20] The biofilm architecture, with its water channels and heterogeneous micro-colonies, protects the embedded bacteria from both the host's immune system (phagocytes cannot penetrate the dense matrix) and systemic antibiotics, which often fail to reach bactericidal concentrations within the biofilm. This explains the recalcitrant nature of CVC infections and the high rates of relapse even after prolonged antibiotic therapy. The only definitive cure is often the removal of the colonized device. In stark contrast, the AVF, being composed entirely of autologous tissue, presents no foreign surface for biofilm formation. While cannulation site infections can occur, they are typically localized to the skin and subcutaneous tissue and rarely lead to sustained bacteremia. The AVG occupies an intermediate position in this hierarchy. As a prosthetic device, it is susceptible to infection, particularly if a hematoma develops around the graft or if the cannulation technique is poor. However, because the graft is entirely subcutaneous, it lacks the direct skin-to-bloodstream interface of a CVC, significantly reducing the risk of microbial entry and subsequent biofilm-related bacteremia.

In the domain of access patency, our results confirm that the AVG is the most fragile of the permanent access options. The nearly three-fold higher risk of thrombosis for AVGs compared to AVFs is a direct consequence of the maladaptive biological response to a prosthetic conduit placed in a high-flow arterialized circuit. The primary site of failure is the graft-vein anastomosis, a region that becomes a crucible of adverse hemodynamics and dysregulated cellular proliferation. The underlying pathology is neointimal hyperplasia, a process akin to a hyper-exuberant wound healing response. The surgical anastomosis of a rigid, non-compliant prosthetic graft to a compliant native vein creates a significant mechanical mismatch. This, combined with the high-velocity, non-laminar (turbulent) blood flow jetting from the graft into the vein, generates abnormal fluid shear stresses on the venous endothelium. This hemodynamic insult is the initiating event. The venous endothelial cells, which are not accustomed to arterial-level shear stress, become activated and dysfunctional. They lose their normal anticoagulant and anti-proliferative properties and begin to express adhesion molecules, pro-inflammatory cytokines, and potent growth factors. This endothelial injury triggers a cascade of events. Circulating platelets adhere to the site of injury, become activated, and release their granular contents, including platelet-derived growth factor (PDGF) and transforming growth factor-beta (TGF-β). These are powerful mitogens and chemoattractants for vascular smooth muscle cells (VSMCs), the primary cellular protagonists of neointimal hyperplasia. Recruited inflammatory cells, particularly macrophages, also infiltrate the area and release their own array of cytokines and growth factors. Under the influence of this potent signaling milieu, VSMCs in the media of the vein undergo a phenotypic switch. They de-differentiate from a quiescent, contractile state to a highly active, synthetic state. They migrate from the media, through the internal elastic lamina, and into the intima, where they proliferate vigorously. These synthetic VSMCs then deposit a voluminous extracellular matrix, rich in collagen and proteoglycans. This progressive accumulation of cells and matrix thickens the vessel wall, encroaches upon the lumen, and forms a hemodynamically significant stenosis. Eventually, this stenosis restricts blood flow to a critical level, predisposing the graft to low-flow thrombosis and complete occlusion. In contrast, the creation of an AVF initiates a process of adaptive remodeling, or "arterialization." The vein, exposed to arterial pressure and flow, gradually dilates and its wall thickens. When this process is successful (outward remodeling), it results in a durable, autologous conduit capable of withstanding repeated cannulation and supporting high dialysis blood flows. While stenoses can still

develop in AVFs, they are typically less aggressive and occur over a longer time course than the rampant neointimal hyperplasia seen in AVGs. The distinct mechanism of CVC failure, primarily due to the formation of a pericatheter fibrin sheath and luminal thrombosis, is a process driven by the activation of the coagulation cascade on a foreign surface, rather than the complex cellular proliferation that dooms the AVG.

The ultimate measure of harm is patient survival, and our analysis demonstrates a clear and significant mortality disadvantage for CVC users. The near-doubling of the all-cause mortality risk for patients with a CVC compared to those with an AVF is a sobering statistic that reflects the systemic consequences of this access choice. This excess mortality is not solely attributable to fatal septic episodes, but rather to a multifactorial process of cumulative injury. Sepsis from ARBSI is, of course, a major contributor. Each episode of bloodstream infection carries a substantial risk of hemodynamic collapse, multi-organ failure, and death. However, the harm extends far beyond acute infection. The indwelling CVC, with its propensity for subclinical microbial colonization and intermittent bacteremia, acts as a potent stimulus for a chronic inflammatory state. In the uremic patient, who is already burdened by inflammation, the CVC adds fuel to the fire. This chronic inflammation is a key driver of the malnutrition-inflammation-atherosclerosis (MIA) syndrome, a deadly triad that characterizes the modern ESKD patient. The systemic release of pro-inflammatory cytokines, such as tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6), has devastating downstream effects. These cytokines promote muscle catabolism and anorexia, leading to protein-energy wasting. They directly contribute to endothelial dysfunction, impairing vasodilation and promoting a pro-thrombotic vascular phenotype. Critically, chronic inflammation accelerates the process of atherosclerosis. It promotes the oxidation of low-density lipoproteins, the recruitment of macrophages into the vessel wall (foam cell formation), and the destabilization of atherosclerotic plaques. This uremic vasculopathy, exacerbated by the CVC-driven inflammatory state, leads to a dramatically increased risk of myocardial infarction, stroke, and other adverse cardiovascular events, which remain the leading cause of death in the hemodialysis population. It is imperative to acknowledge the role of confounding by indication in this observational data. Patients who receive CVCs are often sicker, more frail, and have more comorbidities at baseline, all of which independently increase their mortality risk. While the included studies employed statistical adjustments to mitigate this bias, residual confounding may persist. Nonetheless, the consistency and large magnitude of the effect across multiple large, well-conducted studies, combined with the strong biological plausibility of the multiple intersecting pathways of harm, provide a compelling case that the CVC itself is a significant, independent contributor to the observed excess mortality.

The primary strength of this meta-analysis is its large, cumulative sample size and the inclusion of contemporary studies, which provide a current and statistically robust estimate of access-related risks. The tripartite, pairwise comparison offers a more granular and clinically relevant analysis than previous studies that simply compared CVCs to all AV access combined. However, the inherent limitations of a meta-analysis of observational studies must be acknowledged. Despite the high quality of the included cohort studies and their use of statistical adjustments, the potential for residual confounding by indication can never be entirely eliminated. There was also moderate statistical heterogeneity in some of the analyses, particularly for mortality, which likely reflects underlying differences in patient populations, healthcare practices, and outcome definitions across the various studies and healthcare systems.

5. Conclusion

This comprehensive meta-analysis provides definitive, quantitative evidence to establish a clear and clinically significant hierarchy of harm for hemodialysis vascular access. Central venous

catheters are unequivocally the most dangerous modality, associated with the highest rates of life-threatening bloodstream infection and all-cause mortality. Arteriovenous grafts, while a vital alternative to CVCs, are the most prone to thrombotic failure driven by an aggressive neointimal hyperplastic response. The arteriovenous fistula remains, by a significant margin, the safest and most durable access option, with the lowest risk across all major complication categories. These findings powerfully reinforce the guiding principles of the "Fistula First, Catheter Last" initiative and should galvanize efforts at the patient, provider, and system levels to prioritize timely AVF creation and minimize patient exposure to the substantial and preventable harms of long-term central venous catheter use. The field must continue to pursue innovations, such as bioengineered grafts and novel anti-stenotic therapies, that may one day alter this established hierarchy and further improve the safety of this life-sustaining therapy.

6. References

1. Morisi N, Montani M, Ehode EN, Virzì GM, Perrone S, Malaguti V, et al. Evaluating short-term outcomes of tunneled and non-tunneled central venous catheters in hemodialysis. J Clin Med. 2024; 13(13): 3664.
2. Di Pinto D, Adragna M, Mamani J, Mendoza L, Maita G, Rodríguez S, et al. Bacteremia associated with non-tunneled central venous catheters in children undergoing chronic hemodialysis. Arch Argent Pediatr. 2024; 122(4): e202310259.
3. Sun J, Fan H, Cui T. Management of tunneled-cuffed catheters in hemodialysis patients with hypotension and recurrent central venous thrombosis: a single-center retrospective cohort study. Sci Prog. 2025 Jan; 108(1): 368504251323761.
4. Gharaibeh KA, Abdelhafez MO, Guedze KEB, Siddiqi H, Hamadah AM, Verceles AC. Impact of initial jugular vein insertion site selection for central venous catheter placement on hemodialysis catheter complications. J Crit Care. 2025; 87(155011): 155011.
5. Saiki K, Fujita T, Toyama Y, Yokoyama T, Yamanaka M. Successful hemodialysis catheter placement into a stenosed femoral vein using balloon dilation for central venous access. Radiol Case Rep. 2025; 20(8): 4051–5.
6. Burgess JS, Beaver JD, London M, Rohan V, Orland P, Yevzlin A, et al. Prospective multicenter study of a novel endovascular venous anastomotic procedure and device for implantation of an arteriovenous graft for hemodialysis. J Vasc Access. 2024; 25(4): 1244–51.
7. Elshafei AM, Elwakeel HA, Abdelzaher DG, Emad Eldin M, Mohamed FK. The influence of graft diameter on the patency rates of axillaryaxillary arteriovenous grafts in hemodialysis patients. Egypt J Surg. 2024; 43(3): 610–5.
8. Wang R, Wang S, Xue X, Yue X, Wang X, Wang P, et al. Multiple single cannulation technique improves the outcomes of arteriovenous graft in hemodialysis patients: a retrospective study. Sichuan Da Xue Xue Bao Yi Xue Ban. 2024; 55(4): 1001–6.
9. Samuel M, Nagy MM, Abdelghany MM, Hussein MM. Outcome of upper limb arteriovenous prosthetic graft versus lower limb arteriovenous access for hemodialysis in patients with exhausted vascular accesses. Minia J Med Res. 2024.
10. Lin HY-H, Shien T, Xu J-W, Kuo Y-J, Chen P-L, Niu S-W, et al. The application of blood flow sound contrastive learning to predict arteriovenous graft stenosis of patients with hemodialysis. PLoS One. 2024; 19(8): e0308385.
11. Li XJ, Zheng GF, Zhao X, Sun H, Fu QN. Factors influencing primary patency time of percutaneous transluminal balloon angioplasty for hemodialysis arteriovenous grafts. Zhonghua Yi Xue Za Zhi. 2024;

104(32): 3037–41.
12. Wan H, Liu H, Lin ZQ, Huang XY, Huang SC, Liu YF, et al. Efficacy and safety of early cannulation arteriovenous grafts for hemodialysis. Zhonghua Yi Xue Za Zhi. 2024; 104(32): 3059–62.
13. Yen C-C, Tu H-P, Lin T-C, Li K-Y, Chen S-C. Routine clinic surveillance on arteriovenous graft patency in hemodialysis patients with previous access complications. Int J Med Sci. 2025; 22(5): 1064–71.
14. Hongsakul K, Srihasarn S, Janjindamai P, Akkakrisee S, Bannangkoon K, Rookkapan S, et al. The optimal time of percutaneous pharmacomechanical thrombolysis for the treatment of thrombosed hemodialysis arteriovenous graft. Semin Dial. 2025; 38(2): 132–8.
15. Jeong J, Choi SY, Kim YJ, Lee EJ. A comparison of arteriovenous grafts and fistulas in lower extremity hemodialysis procedures. J Vasc Surg. 2025; 82(1): 240–7.
16. Liang H-L, Chen MC-Y, Su I-L, Chiang C-L, Chen C-L. In-valve stent graft placement to reduce edge stenosis for recoil venous anastomotic stenosis in arteriovenous graft hemodialysis patients. J Vasc Access. 2025; 11297298251364334.
17. Li Y, He Y, Falzon I, Fairbourn B, Tingey S, Imrey PB, et al. Dynamic remodeling of human arteriovenous fistula wall obtained from magnetic resonance imaging during the first 6 months after creation. Kidney Int Rep. 2022; 7(8): 1905–9.
18. Anderson EM, Huber TS, Neal D, Berceli SA, Shah SK, Stone DH, et al. The impact of reintervention on arteriovenous fistula maturation and functional patency in the Hemodialysis Fistula Maturation study. Kidney Med. 2025; 7(8): 101036.
19. Talebi R, Talebi R, Chen J, Yang A, Patil S, DiMuzio PJ, et al. Prior central venous catheter placement and age are associated with earlier intervention after permanent hemodialysis access creation. Hemodial Int. 2025; 29(1): 17–23.
20. Raimann JG, Chu F-I, Kalloo S, Zhang H, Maddux F, Wang Y, et al. Delayed conversion from central venous catheter to non-catheter hemodialysis access associates with an increased risk of death: a retrospective cohort study based on data from a large dialysis provider. Hemodial Int. 2020; 24(3): 299–308.