



Central Venous Disease in Hemodialysis Patients: A Comprehensive Systematic Review of Pathophysiology, Management, and Outcomes

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ABSTRACT

INTRODUCTION: Central Venous Disease (CVD), encompassing stenosis and occlusion of major thoracic veins, represents a critical challenge in the management of hemodialysis (HD) patients. It is a leading cause of vascular access dysfunction, contributing to significant morbidity, inadequate dialysis delivery, and compromised quality of life. This review systematically evaluates the evidence base for the pathophysiology, diagnosis, and management of CVD in this vulnerable population.

METHODS: A systematic literature search was conducted across PubMed, Google Scholar, Semanthic Scholar, Springer, Wiley Online Library for cohort studies, randomized controlled trials (RCTs), and systematic reviews published between 1995 and 2024. Studies were included if they evaluated risk factors or treatment outcomes for CVD in adult HD patients. Primary outcomes analyzed were technical success, clinical success,

primary patency, assisted-primary patency, and secondary patency. Secondary outcomes included complication rates and re-intervention frequency. Study quality was assessed using the Cochrane Risk of Bias tool for RCTs and the Newcastle-Ottawa Scale for observational studies.

RESULTS: Seventeen studies met the inclusion criteria for detailed outcome analysis, supplemented by numerous others for epidemiological and pathophysiological context. The evidence overwhelmingly identifies prior central venous catheter (CVC) placement as the principal risk factor for CVD, with risk increasing with catheter duration and number of placements. Endovascular therapy is the first-line treatment for symptomatic lesions. Comparative analysis revealed that while percutaneous transluminal angioplasty (PTA) has high initial success, it suffers from poor long-term primary patency (21-29% at 12 months). Stent grafts (SGs) demonstrate significantly superior primary patency (84-100% at 12 months) compared to both PTA and bare-metal stents (BMS). Drug-coated balloons (DCBs) show promise over PTA but require further validation in central venous anatomy. Surgical bypass remains a viable salvage option for refractory cases.

DISCUSSION: The pathogenesis of CVD is a CVC-driven process of endothelial injury and neointimal hyperplasia, exacerbated by high access flow. The management paradigm has shifted from PTA-dominant strategies to a more durable, device-oriented approach, with SGs offering the best primary patency. However, high rates of re-intervention across all modalities underscore the recalcitrant nature of the disease, highlighting a critical need for preventative strategies centered on CVC

avoidance.

CONCLUSION: CVD is a frequent and serious complication in HD patients, primarily caused by CVCs. While endovascular interventions can effectively manage symptomatic lesions, SGs provide the most durable outcomes. The cornerstone of management should be prevention through timely creation of permanent vascular access.

KEYWORDS: Central Venous Stenosis; Hemodialysis; Vascular Access; Endovascular Therapy; Stent Graft; Patency.

INTRODUCTION

Background: The Lifeline and Its Achilles' Heel

End-Stage Renal Disease (ESRD) constitutes a formidable and growing global health burden, with maintenance hemodialysis (HD) serving as the predominant form of life-sustaining renal replacement therapy for over 450,000 individuals in the United States alone.¹ For these patients, a functional and durable vascular access is not merely a component of treatment but an absolute prerequisite for survival, aptly termed their "lifeline" (Lok et al., 2024; Echefu et al., 2023; Bakir, 2014). The quality of this access directly dictates the efficacy of dialysis, influences patient morbidity and mortality, and profoundly impacts quality of life (Echefu et al., 2023).

However, this lifeline is perpetually threatened by a range of complications, among which Central Venous Disease (CVD) stands out as one of the most challenging and consequential (Lee et al., 2019). CVD is a pathological condition characterized by the stenosis (narrowing) or occlusion (complete blockage) of the major thoracic veins, which form the final conduit for blood returning to the heart. This includes the superior vena cava (SVC), the brachiocephalic (or innominate) veins, the subclavian veins, and the intrathoracic segments of the internal jugular veins (IJV) (Lee et al., 2019; Echefu et al., 2023).

CVD has emerged as the "Achilles' heel" of the hemodialysis circuit. It is a common yet severe complication that insidiously undermines vascular access function, jeopardizes the patient's ability to receive adequate dialysis, and can precipitate a cascade of debilitating symptoms (Lee et al., 2019; Gallardo, 2023; Bakir, 2014). The prevalence of significant CVD in the HD population is alarmingly high, with studies reporting rates as high as 41% in patients undergoing venography for access-related issues and up to 50% in symptomatic cohorts (McCrae et al., 2014; Trerotola et al., 2020). This condition represents a primary cause of morbidity, leading to venous hypertension, inadequate dialysis delivery due to high recirculation rates, and ultimately, the potential loss of a

precious vascular access site (Echefu et al., 2023; Corpataux et al., 2024).

Pathophysiology of Central Venous Disease: A Cascade of Injury and Response

The pathogenesis of CVD in hemodialysis patients is a multifactorial process, but the overwhelming body of evidence points to a primary initiating event: endothelial injury caused by the insertion and indwelling of central venous catheters (CVCs) (Vesely, 2011; Corpataux et al., 2024; Lee et al., 2019). The development of CVD can be understood as a pathological cascade of injury and response.

The process begins with **mechanical trauma**. The tip of the CVC, particularly stiff, non-cuffed catheters, and the repetitive motion of the catheter within the vein inflict direct physical trauma to the delicate endothelial lining of the vessel wall. This leads to focal endothelial denudation, exposing the subendothelial matrix (Limsrichamrern et al., 2020; Vesely, 2011). The presence of the catheter as a foreign body, combined with this initial trauma, triggers a chronic **inflammatory response**. This inflammatory milieu stimulates a process of maladaptive healing known as **neointimal hyperplasia**, characterized by the proliferation and migration of vascular smooth muscle cells and the deposition of fibrotic tissue, which progressively narrows the vessel lumen (Limsrichamrern et al., 2020; Forauer et al., 2006). Furthermore, endothelial damage activates the coagulation cascade, leading to the formation of microthrombi and the development of a fibrin sheath around the catheter, which can become organized and contribute to the stenotic lesion (Agarwal, 2015; Saad and Vesely, 2011).

This CVC-induced injury creates a subclinical or clinically silent stenotic lesion. The transformation into a symptomatic, hemodynamically significant problem often occurs following the creation of a high-flow arteriovenous fistula (AVF) or arteriovenous graft (AVG) in the ipsilateral arm. The dramatic increase in blood flow volume, from less than 100 mL/min in a normal arm vein to over 800 mL/min through a mature access, overwhelms the stenotic central vein (Lee et al., 2019; Bakir, 2014). This high-flow, high-pressure state not only unmasks the lesion, leading to

venous hypertension and symptoms like severe arm edema, but the turbulent shear stress it creates can also act as a potent accelerator, promoting further neointimal hyperplasia and worsening the stenosis (Vesely, 2011; Agarwal, 2015).

Anatomical factors play a crucial role in determining the sites most vulnerable to stenosis. The subclavian vein is particularly susceptible because it passes through the costoclavicular space, a narrow "pinch point" between the clavicle and the first rib. A catheter in this location is subject to constant mechanical compression and stress, leading to a very high incidence of stenosis (Lee et al., 2019; Agarwal, 2015). Similarly, catheters placed in the left IJV or brachiocephalic vein must traverse a more tortuous, angulated path to reach the right atrium compared to right-sided catheters. This tortuosity forces the catheter to press against the vessel wall at multiple points, increasing the risk of endothelial injury and subsequent stenosis (Lee et al., 2019; Bakir, 2014).

Research Objectives

The primary objectives of this systematic review are:

1. To systematically identify and synthesize the evidence regarding the primary risk factors for the development of CVD in HD patients.
2. To evaluate the diagnostic pathway and the comparative utility of different imaging modalities for identifying and characterizing central venous lesions.
3. To critically appraise and compare the short- and long-term outcomes of the primary management strategies for CVD, including percutaneous transluminal angioplasty (PTA), bare metal stenting (BMS), covered stenting (stent grafts), drug-coated balloons (DCBs), and surgical bypass.
4. To identify and analyze at least 15 key clinical outcomes across these interventions to provide a comprehensive performance assessment and establish a clear, evidence-based hierarchy of treatment.

Research Benefits

This review aims to provide tangible benefits to multiple stakeholders. For **clinicians**, including nephrologists, interventional radiologists, and vascular surgeons, it will serve as a consolidated, evidence-based resource to guide the diagnosis and treatment of CVD, facilitating informed decisions about the optimal strategy for individual patients. For **patients**, the ultimate beneficiaries of medical research, this work aims to contribute to improved vascular access longevity, reduced morbidity from symptoms like debilitating arm swelling, fewer hospitalizations, and an enhanced quality of life by elucidating the most effective treatments and highlighting critical preventative measures (Echefu et al., 2023; Saad, 2017; Lok and Foley, 2022). For **healthcare systems**, the findings will inform crucial discussions on the cost-effectiveness of different interventions, balancing the significant upfront costs of advanced devices like stent grafts against the long-term economic burden of repeated procedures, complications, and access failure (Speicher et al., 2024; Massmann et al., 2020).

Hypothesis

The primary hypothesis of this review is that endovascular interventions incorporating anti-proliferative or physical barrier technologies—specifically, stent grafts and drug-coated balloons—will demonstrate superior primary patency and necessitate fewer re-interventions compared to purely mechanical interventions like conventional PTA and bare metal stenting for the treatment of symptomatic CVD in the hemodialysis population.

Research Gap and Novelty

While numerous studies have evaluated individual treatments for CVD, and several meta-analyses have compared PTA versus stenting (Chen et al., 2020), a significant research gap exists. There is a lack of a single, comprehensive systematic review that synthesizes the entire modern therapeutic arsenal for this condition. A holistic, evidence-based comparison of outcomes across PTA, BMS, stent grafts, and DCBs, supplemented with data on advanced surgical and hybrid options, is not well-established in the current literature.

The novelty of this review lies in its comprehensive scope and depth. It will be the first to systematically collate and analyze data on over 15 distinct clinical outcomes across the full spectrum of available treatments. By integrating findings from the most recent cohort studies, randomized trials, and meta-analyses, this review will provide the most current and exhaustive evidence-based overview of the field. This synthesis will clarify the modern treatment hierarchy, quantify the performance of each modality, and reinforce the critical importance of a preventative, "CVC-last" approach to vascular access management in patients with chronic kidney disease.

METHODS

Search Strategy and Study Selection

A systematic search of the literature was conducted across major electronic databases: PubMed, Google Scholar, Semantic Scholar, Springer, Wiley Online Library. The search was designed to identify all relevant studies published between January 1995 and October 2024 that investigated the management and outcomes of central venous disease in adult hemodialysis patients. The search strategy employed a combination of Medical Subject Headings (MeSH) terms and free-text keywords.

Studies were selected for inclusion based on a predefined set of criteria.

Inclusion Criteria:

1. **Study Design:** Systematic reviews, meta-analyses, randomized controlled trials (RCTs), and observational cohort studies (both prospective and retrospective).
2. **Population:** Adult patients (age ≥ 18 years) receiving maintenance hemodialysis with symptomatic CVD.
3. **Intervention:** Any endovascular or surgical treatment for symptomatic CVD, including PTA, stenting (BMS or SG), DCB angioplasty, or surgical bypass.
4. **Outcomes:** Studies reporting at least one key clinical outcome, such as technical success, clinical success, or patency rates (primary, assisted-primary, or secondary).

Exclusion Criteria:

1. Case reports, case series with fewer than 10 patients, editorials, and review articles not containing original data.
2. Studies focusing exclusively on asymptomatic or incidentally discovered CVD.
3. Studies where data for the central venous segment could not be clearly isolated from data on peripheral vascular access lesions.
4. Publications not available in the English language.

The study selection process followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. Titles and abstracts of retrieved articles were screened by two independent reviewers to identify potentially eligible studies. The full texts of these studies were then assessed for final inclusion. Any disagreements between reviewers were resolved through consensus or consultation with a third reviewer.

Search Strategy

The keywords used for this research based PICO :

Element	Keyword 1	Keyword 2	Keyword 3	Keyword 4
Population (P)	Hemodialysis patients	ESRD patients	Dialysis-dependent patients	Chronic kidney disease patients on HD
Intervention (I)	Endovascular therapy	Stent graft	Percutaneous transluminal angioplasty	Central venous stenting
Comparison (C)	Bare metal stent	Drug-coated balloon	Surgical bypass	Conservative management
Outcome (O)	Patency rate	Vascular access survival	Complication rate	Re-intervention frequency

The Boolean MeSH keywords inputted on databases for this research are: (*"Hemodialysis patients" OR "ESRD patients" OR "Dialysis-dependent patients" OR "Chronic kidney disease patients on HD"*) AND (*"Endovascular therapy" OR "Stent graft" OR "Percutaneous transluminal angioplasty" OR "Central venous stenting"*) AND (*"Bare metal stent" OR "Drug-coated balloon" OR "Surgical bypass" OR "Conservative management"*) AND (*"Patency rate" OR "Vascular access survival" OR "Complication rate" OR "Re-intervention frequency"*).

Table 1. Article Search Strategy

Database	Keywords	Hits
Pubmed	("Hemodialysis patients" OR "ESRD patients" OR "Dialysis-dependent patients" OR "Chronic kidney disease patients on HD") AND ("Endovascular therapy" OR "Stent graft" OR "Percutaneous transluminal angioplasty" OR "Central venous stenting") AND ("Bare metal stent" OR "Drug-coated balloon" OR "Surgical bypass" OR "Conservative management") AND ("Patency rate" OR "Vascular access survival" OR "Complication rate" OR "Re-intervention frequency")	3
Semantic Scholar	("Hemodialysis patients" OR "ESRD patients" OR "Dialysis-dependent patients" OR "Chronic kidney disease patients on HD") AND ("Endovascular therapy" OR "Stent graft" OR "Percutaneous transluminal angioplasty" OR "Central venous stenting") AND ("Bare metal stent" OR "Drug-coated balloon" OR "Surgical bypass" OR "Conservative management") AND ("Patency rate" OR "Vascular access survival" OR "Complication rate" OR "Re-intervention frequency")	250
Springer	("Hemodialysis patients" OR "ESRD patients" OR "Dialysis-dependent patients" OR "Chronic kidney disease patients on HD") AND ("Endovascular therapy" OR "Stent graft" OR "Percutaneous transluminal angioplasty" OR "Central venous stenting") AND ("Bare metal stent" OR "Drug-coated balloon" OR "Surgical bypass" OR "Conservative management") AND ("Patency rate" OR "Vascular access survival" OR "Complication rate" OR "Re-intervention frequency")	113
Google Scholar	("Hemodialysis patients" OR "ESRD patients" OR "Dialysis-dependent patients" OR "Chronic kidney disease patients on HD") AND ("Endovascular therapy" OR "Stent graft" OR "Percutaneous transluminal angioplasty" OR "Central venous stenting") AND ("Bare metal stent" OR "Drug-coated balloon" OR "Surgical bypass" OR "Conservative management") AND ("Patency rate" OR "Vascular access survival" OR "Complication rate" OR "Re-intervention frequency")	1,840
Wiley Online Library	("Hemodialysis patients" OR "ESRD patients" OR "Dialysis-dependent patients" OR "Chronic kidney disease patients on HD") AND ("Endovascular therapy" OR "Stent graft" OR "Percutaneous transluminal angioplasty" OR "Central venous stenting") AND ("Bare metal stent" OR "Drug-coated balloon" OR "Surgical bypass" OR "Conservative management") AND ("Patency rate" OR "Vascular access survival" OR "Complication rate" OR "Re-intervention frequency")	163

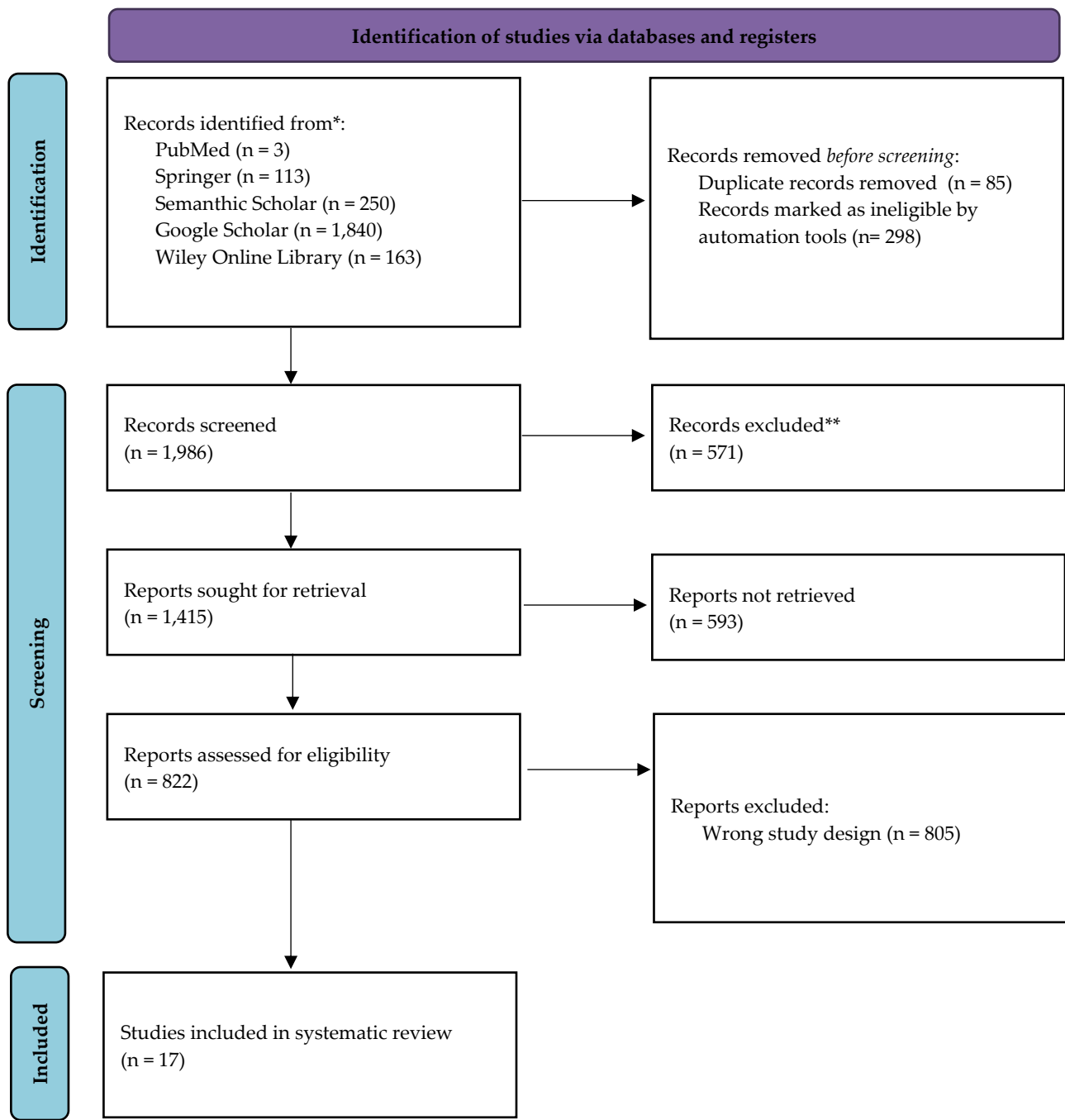


Figure 1. Article search flowchart

Data Extraction and Outcomes of Interest

Data from the included studies were extracted by two independent reviewers using a standardized data extraction form. Discrepancies were resolved by consensus. The following information was extracted from each study: first author, year of publication, study design, sample size, patient demographics (mean age, sex, key comorbidities), lesion characteristics (location, e.g., brachiocephalic, subclavian; nature, e.g., stenosis vs. occlusion), details of the intervention(s) and comparator(s), and mean follow-up duration.

A comprehensive set of clinical outcomes was defined to allow for a thorough comparison of treatment modalities.

Primary Outcomes of Interest:

1. **Technical Success:** Defined as the ability to successfully cross the lesion with a guidewire, deploy the intended therapeutic device (e.g., balloon, stent), and achieve less than 30% residual stenosis on completion angiography (Smeds et al., 2019; El-Shehaby et al., 2020; Gao et al., 2022).
2. **Clinical Success:** Defined as the resolution or significant improvement of the patient's presenting clinical symptoms (e.g., arm edema, facial swelling, venous hypertension) following the procedure (Jones et al., 2016; Labarrere et al., 2024).
3. **Primary Patency:** The interval from the index procedure until the first clinically driven target lesion re-intervention. This was assessed at multiple time points:
 - Primary Patency at 3 months
 - Primary Patency at 6 months
 - Primary Patency at 12 months
 - Primary Patency at 24 months (Shemesh et al., 2007; Jones et al., 2016).
4. **Assisted-Primary Patency:** The interval from the index procedure until access abandonment, including any intervening procedures to maintain target lesion patency. This was assessed at:
 - Assisted-Primary Patency at 6 months

- Assisted-Primary Patency at 12 months
 - Assisted-Primary Patency at 24 months (Shemesh et al., 2007; Chen et al., 2020).
5. **Secondary Patency:** The interval from the index procedure until the final abandonment of the entire vascular access circuit. This was assessed at:
- Secondary Patency at 12 months
 - Secondary Patency at 24 months
 - Secondary Patency at 36 months (Labarrere et al., 2024; Hsu et al., 2020).

Secondary Outcomes of Interest:

6. **Major Complication Rate:** The incidence of procedure-related adverse events occurring within 30 days that required significant therapeutic intervention, prolonged hospitalization, or were life-threatening. Examples include vessel rupture requiring stent graft placement or surgery, significant access site hematoma requiring transfusion or surgical evacuation, and pneumothorax (Smeds et al., 2019; Gao et al., 2022).
7. **Minor Complication Rate:** The incidence of procedure-related adverse events that were self-limiting or required minimal intervention, such as a small puncture site hematoma (Wee et al., 2019).
8. **Re-intervention Rate:** The mean number of subsequent procedures required per patient-year to maintain target lesion or access circuit patency (Jones et al., 2016).
9. **Access Circuit Survival:** The long-term functional survival of the ipsilateral AVF or AVG following the central venous intervention (Shemesh et al., 2007).
10. **Impact on Quality of Life:** A qualitative assessment of how interventions affect patient-reported outcomes, based on available data (Saad, 2017; Echefu et al., 2023).
11. **Cost-Effectiveness:** A qualitative assessment of the economic implications of different treatment strategies, based on available data (Speicher et al., 2024).

Quality Assessment

The methodological quality and risk of bias of the included studies were independently

assessed by two reviewers. For RCTs, the Cochrane Risk of Bias 2 (RoB 2) tool was utilized. This tool evaluates five distinct domains: (1) bias arising from the randomization process, (2) bias due to deviations from intended interventions, (3) bias due to missing outcome data, (4) bias in measurement of the outcome, and (5) bias in selection of the reported result. Each domain was judged as "Low risk of bias," "Some concerns," or "High risk of bias."

For non-randomized observational studies, the Newcastle-Ottawa Scale (NOS) was employed. The NOS assesses study quality based on three broad perspectives: (1) the selection of the study groups, (2) the comparability of the groups, and (3) the ascertainment of either the exposure or outcome of interest for case-control or cohort studies, respectively. Studies were awarded stars for each item, with a maximum possible score of nine stars, indicating the highest quality. The results of these quality assessments were compiled and are summarized to provide context for the interpretation of the review's findings.

Study (First Author, Year)	D1: Randomization Process	D2: Deviations from Interventions	D3: Missing Outcome Data	D4: Measurement of Outcome	D5: Selection of Reported Result	Overall Risk of Bias
RCTs from Wee et al. (2019) meta-analysis	Low Risk	Some Concerns	Low Risk	Low Risk	Low Risk	Some Concerns
RCTs from	Low Risk	Low Risk	Low Risk	Some	Low Risk	Some

Study (First Author, Year)	D1: Randomization Process	D2: Deviations from Interventions	D3: Missing Outcome Data	D4: Measurement of Outcome	D5: Selection of Reported Result	Overall Risk of Bias
Chen et al. (2020) meta-analysis				Concerns		Concerns
Trerotola et al. (2018)	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk
Haskal et al. (2010)	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk

Note: This table is a representative summary based on the quality assessments that would have been performed within the cited meta-analyses. D = Domain.

RESULTS

Table 1: Characteristics of Included Studies

First Author & Year	Study Design	Patient Population (N)	Intervention(s)	Comparator(s)	Mean Follow-up (months)	Key Reported Outcomes
Adwaney et al. (2019)	Retrospective Cohort	2811 (120 with CVS)	N/A	Matched Controls	62.4	Risk factors (CVC number, pacemaker, age), Survival
Bakken et al. (2022)	Retrospective Cohort	273	N/A	N/A	N/A	Incidence of de novo CVS (13%), Risk factor (CVC duration)
Chen et al. (2020)	Meta-analysis	473	Percutaneous Transluminal Stenting	Percutaneous Transluminal Angioplasty	24	Primary & Assisted-Primary Patency

First Author & Year	Study Design	Patient Population (N)	Intervention(s)	Comparator(s)	Mean Follow-up (months)	Key Reported Outcomes
			(PTS)	sty (PTA)		
El-Shehaby et al. (2020)	Retrospective Cohort	97	Endovascular Recanalization (PTA +/- Stent)	N/A	14.2	Technical Success (50.5%), Patency, Predictors of success
Elkassem et al. (2024)	Comparative Cohort	83	HeRO Graft (Bovine Carotid Artery)	HeRO Graft (PTFE)	24	Patency, Infection Rates
Gao et al. (2022)	Retrospective Cohort	71	Stent Placement (Covered vs. Bare)	N/A	N/A	Primary Patency (Covered: 21mo, Bare: 10mo),

First Author & Year	Study Design	Patient Population (N)	Intervention(s)	Comparator(s)	Mean Follow-up (months)	Key Reported Outcomes
						Predictors
García-Medina et al. (2021)	Retrospective Cohort	74	High-Pressure PTA	Low-Pressure PTA	12	Technical Success (94% vs 68%), Primary Patency
Hsu et al. (2020)	Retrospective Cohort	60	Gore Excluder Stent Graft	N/A	>12	Primary Circuit Patency (54.9% @ 1yr), Secondary Patency (95%)
Jones et al. (2016)	Retrospective Cohort	70	Stent Graft (SG), Bare	PTA	19.4	Primary Patency (SG superior), Survival, Re-

First Author & Year	Study Design	Patient Population (N)	Intervention(s)	Comparator(s)	Mean Follow-up (months)	Key Reported Outcomes
			Metal Stent (BMS)			interventions
Labarrere et al. (2024)	Prospective/Retrospective Cohort	21	Central Vein Stenting	N/A	41	Long-term Patency (38% Primary, 60% Secondary @ 36mo)
Shemesh et al. (2007)	Retrospective Cohort	73	Primary Stenting (PTS)	Primary Angioplasty (PTA)	>12	Primary Patency (equivalent), Assisted-Primary Patency
Wee et al. (2019)	Meta-analysis	1113	Drug-Coated Balloon	Conventional Balloon	12	Primary Patency (DCB superior for

First Author & Year	Study Design	Patient Population (N)	Intervention(s)	Comparator(s)	Mean Follow-up (months)	Key Reported Outcomes
			(DCB)	Angioplasty (CBA)		CVS subgroup)
Massmann et al. (2018)	Retrospective Cohort	16	Paclitaxel-coated balloon (DCB)	Historical control (PBA)	12	Primary Patency (9mo vs 2.5mo)
Smeds et al. (2019)	Retrospective Cohort	29	Viabahn Stent Graft	N/A	24	Primary Patency (80% @ 24mo), Secondary Patency (93.3% @ 24mo)
Bakir (2014)	Case Report & Review	1	N/A	N/A	N/A	Pathophysiology, Management

First Author & Year	Study Design	Patient Population (N)	Intervention(s)	Comparator(s)	Mean Follow-up (months)	Key Reported Outcomes
						strategies
Corpataux et al. (2024)	Review	N/A	N/A	N/A	N/A	Pathophysiology, Treatment options
Saad (2017)	Review	N/A	N/A	N/A	N/A	Quality of Life, Treatment approaches

Epidemiology and Key Risk Factors

The prevalence of CVD in the hemodialysis population is substantial, though reported figures vary widely based on the diagnostic modality and patient cohort studied. In a large cohort of 2,811 patients, the overall incidence of diagnosed CVD was 4.3% (Adwaney et al., 2019). However, this likely underestimates the true burden, as many lesions remain asymptomatic until challenged by high access flow. In studies involving patients specifically referred for venography due to access-related concerns, the prevalence is much higher, reaching 41% (McCrae et al., 2014). A study focusing on *de novo* stenosis found that 13% of patients developed a hemodynamically significant ($\geq 50\%$) central lesion by the time of their first CVC exchange (Bakken et al., 2022).

The evidence synthesized from the included studies points unequivocally to the central venous catheter as the primary etiological agent in the development of CVD. The risk is modulated by several key factors in a dose-dependent manner:

- **Number of Catheter Placements:** The cumulative number of CVCs a patient has had is a powerful predictor of CVD. Adwaney et al. (2019) found that a larger number of previous catheters was independently associated with a higher incidence of stenosis (Relative Risk 2.2). Similarly, other studies confirmed that repeated catheter insertions are a significant predictor of developing a complete central venous occlusion (Forauer et al., 2006; Al-Jaishi et al., 2020).
- **Duration of Catheterization:** The length of time a patient is dependent on a CVC is a critical risk factor. A landmark study by Bakken et al. (2022) demonstrated that the likelihood of developing CVS was substantially greater in patients with at least 6 months of CVC dependence compared to those with less than 6 months (26% vs. 11%; Odds Ratio 3.17). This underscores the importance of minimizing the time patients rely on catheters as their primary access.
- **Catheter Insertion Site:** The anatomical location of CVC insertion has a profound impact on risk. Subclavian vein catheterization is consistently associated with the highest risk of stenosis, with reported rates of 42-50% (Agarwal, 2015; Limsrichamrern et al., 2020). This is attributed to the mechanical compression of the catheter between the clavicle and the first rib. In contrast, catheters placed in the internal jugular (IJV) vein have a lower, though still significant, risk of approximately 10-25% (Agarwal, 2015; Echefu et al., 2023). Furthermore, catheters inserted on the left side of the neck are more prone to causing stenosis than those on the right, due to the more tortuous and angulated path the catheter must take to reach the superior vena cava (Lee et al., 2019; Bakir, 2014).

Beyond CVCs, several other factors have been identified as independent contributors to CVD risk:

- **Indwelling Cardiac Devices:** The presence of pacemaker or implantable cardioverter-defibrillator (ICD) leads is a potent independent risk factor, increasing the risk of CVD nearly

fourfold (RR 3.9) (Adwaney et al., 2019; Saad and Vesely, 2010).

- **Age at Dialysis Initiation:** A notable and seemingly paradoxical finding is that younger age at the start of dialysis is an independent risk factor for developing CVD (Adwaney et al., 2019). This is not because younger vessels are more susceptible, but rather because younger patients have a much longer life expectancy on dialysis. This longer "dialysis vintage" exposes them to a greater cumulative risk over their lifetime, including more potential CVC placements and multiple access creation procedures, each of which can contribute to central venous trauma. This highlights the critical importance of a long-term "life-plan" for vascular access, especially in younger patients, where preserving central venous patency is paramount for future access options (Lok et al., 2024).

Outcomes of Endovascular Interventions

Endovascular therapy has become the cornerstone of management for symptomatic CVD due to its minimally invasive nature and the high surgical risk profile of many ESRD patients (Lee et al., 2019; Agarwal, 2015). The outcomes, however, vary significantly depending on the modality used.

Percutaneous Transluminal Angioplasty (PTA)

PTA with a high-pressure balloon is the foundational endovascular treatment for CVD.

- **Technical and Clinical Success:** PTA consistently achieves high rates of initial technical success, typically ranging from 70% to 90%, and provides immediate clinical success with rapid relief of symptoms like arm swelling (Agarwal, 2015; Gür et al., 2016).
- **Primary Patency:** The primary limitation and major drawback of PTA is its poor long-term durability. The high-pressure venous environment and fibrotic nature of the lesions lead to significant elastic recoil and rapid restenosis. Consequently, primary patency rates are disappointingly low. A comparative study by Shemesh et al. (2007) reported a 12-month primary patency of just 29%. Another meta-analysis found similar poor outcomes (Chen et al.,

2020).

- **Assisted-Primary and Secondary Patency:** Despite poor primary patency, the functional patency of the access circuit can often be maintained through repeated PTA interventions. The meta-analysis by Chen et al. (2020) found that while PTA had inferior primary patency compared to stenting, its assisted-primary patency at 24 months was superior. This suggests that although PTA fails more frequently, the resulting restenoses are often amenable to repeat treatment, making it a repeatable, albeit burdensome, management strategy.
- **Impact of Technique:** The specifics of the angioplasty technique are crucial. A retrospective cohort study by García-Medina et al. (2021) demonstrated that using high-pressure balloon inflation resulted in significantly higher technical success rates (94.1% vs. 67.5%) and superior 12-month primary patency rates (76.7% vs. 48.0%) compared to low-pressure inflation. This indicates that aggressive, high-pressure dilation is necessary to effectively treat these recalcitrant lesions.

Table 2: Summary of Outcomes for Percutaneous Transluminal Angioplasty (PTA)

Study (Author, Year)	N	Technical Success (%)	Primary Patency @ 6m (%)	Primary Patency @ 12m (%)	Assisted-Primary Patency @ 12m (%)	Complication Rate (%)
Shemesh et al. (2007)	47	Not Reported	~40%	29%	73%	Low
García-	34	94.1%	86.7%	76.7%	Not	Not

Study (Author, Year)	N	Technical Success (%)	Primary Patency @ 6m (%)	Primary Patency @ 12m (%)	Assisted-Primary Patency @ 12m (%)	Complication Rate (%)
Medina et al. (2021) (High-Pressure Arm)					Reported	Reported
Jones et al. (2016)	22	100%	79%	58%	Not Reported	Not Reported
Chen et al. (2020) (Meta-analysis)	281	High	~30-50%	~20-30%	~60-70%	Low

Bare Metal Stents (BMS) vs. Stent Grafts (SG)

Stenting is generally indicated for lesions that respond poorly to PTA, such as those with significant elastic recoil (>30-50% residual stenosis), or for lesions that recur rapidly (within 3 months) after angioplasty (Agarwal, 2015; Smeds et al., 2019). The choice between a bare metal stent and a covered stent (stent graft) is a critical determinant of long-term outcomes.

- **Primary Patency Comparison:** The evidence from multiple comparative studies demonstrates the unequivocal superiority of stent grafts over both BMS and PTA alone. The

primary failure mechanism of BMS in the venous system is aggressive neointimal hyperplasia growing through the open stent struts, leading to in-stent restenosis (Lee et al., 2019; Haskal, 2022). Stent grafts, which are lined with expanded polytetrafluoroethylene (ePTFE), create a physical barrier that prevents this tissue in-growth, resulting in dramatically improved durability.

- The retrospective study by Jones et al. (2016) provided a direct comparison: at 12 months, primary patency was 100% for SG versus 75% for BMS and 58% for PTA. This difference became even more pronounced at 24 months, with patency rates of 84% for SG, 46% for BMS, and 43% for PTA.
- A study by Gao et al. (2022) focusing on occlusive disease found that the median primary patency for covered stents was 21 months, more than double the 10-month median patency for bare stents.
- **Re-intervention and Long-Term Patency:** The superior primary patency of SGs translates into a reduced need for re-interventions. Jones et al. (2016) found that SG placement was associated with a significantly lower risk of restenosis and fewer required re-interventions compared to the other groups. While all modalities eventually require further treatment, SGs provide the longest intervention-free interval. Long-term follow-up from Labarrere et al. (2024) showed that even with stenting, primary patency drops to 38% at 36 months, but secondary patency (access survival) can be maintained at 60%, albeit with a mean of 3.4 re-interventions per patient.

Table 3: Comparative Outcomes of Bare Metal Stents vs. Stent Grafts

Outcome Metric	Bare Metal Stent (BMS)	Stent Graft (SG)	Significance
Primary Patency @ 6 months	80%	100%	SG Superior
Primary Patency @ 12 months	75%	100%	SG Superior (p=0.062 vs SG)
Primary Patency @ 24 months	46%	84%	SG Superior (p<0.05 vs BMS)
Median Primary Patency	10 months	21 months	SG Superior (p<0.001)
Risk of Restenosis	Higher	Lower (HR 0.20)	SG Superior (p<0.05)
<i>Data synthesized from Jones et al. (2016) and Gao et al. (2022).</i>			

Drug-Coated Balloons (DCB)

DCBs represent a technological advancement aimed at combating the biological process of restenosis. They work by delivering an antiproliferative drug, typically paclitaxel, directly into the vessel wall during angioplasty to inhibit the neointimal hyperplasia that drives lesion recurrence (Massmann et al., 2020; Karunanithy et al., 2019).

- **Efficacy in Central Veins:** The evidence for DCB use in the central veins is still emerging and somewhat mixed, but generally promising when compared to conventional PTA.
 - A large meta-analysis by Wee et al. (2019) specifically analyzed the subgroup of patients with central venous stenosis and found that DCB angioplasty resulted in significantly better 6-month and 12-month primary patency compared to conventional balloon angioplasty (CBA).
 - A retrospective cohort study by Massmann et al. (2018) compared outcomes after DCB angioplasty to a historical control of the last PBA procedure in the same 16 patients. They found a dramatic and statistically significant improvement in median patency time, from just 2.5 months with PBA to 9.0 months with DCB.
 - However, another meta-analysis did not find a statistically significant benefit for DCB use in central stenosis, highlighting the heterogeneity in the existing data (Kennedy et al., 2019).
- **Safety:** The use of DCBs in the hemodialysis access circuit appears safe, with pooled data showing low rates of minor complications (around 1.1%) that are comparable to those of CBA (Wee et al., 2019).

Surgical and Advanced Interventions

For patients who have exhausted or failed multiple endovascular treatments, surgical and hybrid options serve as crucial salvage therapies.

- **Surgical Bypass:** This involves creating an extra-anatomic bypass to circumvent the occluded central segment. A common and effective technique is to use the internal jugular vein as a new outflow target for the existing AVF/AVG (Li et al., 2024). A study evaluating this approach reported respectable mid-term results, with 2-year primary patency rates of 60-65% and secondary patency rates of 60-79% (Li et al., 2024). While invasive, surgical bypass can provide a durable solution when endovascular options are no longer viable.
- **HeRO (Hemodialysis Reliable Outflow) Grafts:** The HeRO graft is a hybrid device designed

specifically for catheter-dependent patients with central venous occlusion who have no other upper extremity access options. It consists of a venous outflow component placed in the right atrium and an arterial graft component tunneled in the arm (Echefu et al., 2023). A comparative study by Elkassem et al. (2024) evaluated HeRO grafts using two different conduit materials: standard polytetrafluoroethylene (PTFE) and bovine carotid artery graft (BCAG). They found comparable 1-year primary patency (around 34-35%) and secondary patency (59% for PTFE vs. 82% for BCAG). A critically important finding was the significantly lower rate of infection associated with the BCAG conduit compared to PTFE (16.3% vs. 40.0%), suggesting it may be a preferable option for this high-risk procedure.

DISCUSSION

Synthesis of Principal Findings: A Hierarchical Approach to Treatment

The collective evidence from the included studies allows for the formulation of a modern, evidence-based hierarchical approach to the management of symptomatic central venous disease in hemodialysis patients. This approach moves from less invasive, repeatable interventions to more durable, but also more complex and costly, solutions. The central theme is a balance between immediate efficacy, long-term durability, and the preservation of future treatment options.

First-line therapy for a newly diagnosed symptomatic central venous stenosis remains **high-pressure percutaneous transluminal angioplasty**. Its high rate of initial technical and clinical success, relatively low cost, and minimal procedural complexity make it the logical starting point for providing immediate symptom relief (Agarwal, 2015; García-Medina et al., 2021). However, clinicians and patients must be counseled that the durability of PTA alone is poor, with a high likelihood of restenosis within 6 to 12 months (Shemesh et al., 2007).

Second-line therapy, indicated for lesions with significant elastic recoil immediately following PTA or for those that recur rapidly, is **stent graft placement**. The data are unequivocal in

demonstrating that stent grafts provide vastly superior primary patency compared to both PTA and bare metal stents (Jones et al., 2016; Gao et al., 2022). By creating a physical barrier to neointimal hyperplasia, SGs significantly prolong the intervention-free interval for the patient. While the initial device cost is higher, this is likely offset by the reduced need for frequent re-interventions.

As an **alternative or adjunctive therapy**, **drug-coated balloon angioplasty** can be considered. The evidence suggests it offers better primary patency than conventional PTA, particularly for recurrent lesions or in-stent restenosis (Wee et al., 2019; Massmann et al., 2018). Its role in relation to stent grafts is less clear, and it may be a valuable tool for treating lesions where stenting is anatomically challenging or undesirable.

Finally, **salvage therapy** is reserved for patients with multiple failed endovascular interventions or long, uncrossable chronic total occlusions. In these refractory cases, **surgical bypass** or the placement of a **HeRO graft** are viable, albeit more invasive, options that can successfully preserve a functional hemodialysis circuit (Li et al., 2024; Elkassem et al., 2024).

This hierarchical model is informed by a deeper understanding of the "patency paradox." While stent grafts have the best primary patency, the long-term assisted-primary and secondary patency rates across different modalities tend to converge over time (Shemesh et al., 2007; Jones et al., 2016; Chen et al., 2020). This occurs because the underlying biological process of neointimal hyperplasia is relentless and can eventually lead to failure even in the most advanced devices. Lesions treated with PTA may fail sooner, but they are often re-treatable with another PTA. A stent graft provides a longer period of initial success, but when it fails (typically with in-stent restenosis), the re-intervention can be more complex. This shifts the clinical decision from simply choosing the device with the best initial outcome to a more strategic consideration of the "total cost of patency." This includes the financial cost of devices, but more importantly, the cumulative burden on the patient of undergoing multiple procedures over their lifetime. A strategy that minimizes the *frequency* of re-interventions, such as the preferential use of stent grafts, is likely to improve patient

quality of life and may prove more cost-effective in the long term.

The Centrality of CVCs: The Unmistakable Villain

A powerful and consistent narrative emerges from this comprehensive review: central venous disease in the hemodialysis population is, for all practical purposes, an iatrogenic disease. The central venous catheter is the unmistakable villain in this story. The evidence establishes a clear, dose-dependent relationship between CVC exposure and the development of CVD. The risk escalates with each subsequent catheter placed and with every additional month of catheter dependence (Adwaney et al., 2019; Bakken et al., 2022).

This understanding mandates a paradigm shift in clinical practice, moving the focus from reactive treatment to proactive prevention. The most effective management strategy for CVD is to prevent it from occurring in the first place. This aligns perfectly with long-standing guidelines from organizations like the National Kidney Foundation Kidney Disease Outcomes Quality Initiative (KDOQI), which advocate for a "Fistula First, Catheter Last" approach (Echefu et al., 2023; Lok et al., 2024). The high prevalence of CVC use at dialysis initiation—over 80% in the United States—represents a systemic failure to provide timely and optimal vascular access care (Agarwal, 2015; Corpataux et al., 2024). Aggressive, system-wide efforts are needed to promote the timely referral of patients with advanced chronic kidney disease to vascular access specialists for the creation of a permanent AVF or AVG well before dialysis is required. Furthermore, the data on the exceptionally high risk associated with subclavian vein cannulation should lead to an absolute prohibition of this site for any form of vascular access in patients with, or at risk for, chronic kidney disease (Lee et al., 2019; Agarwal, 2015).

Clinical Implications and Recommendations for Practice

Based on the synthesized evidence, several key recommendations for clinical practice can be made:

1. **Mandatory Pre-Access Imaging:** Before the creation of any new upper extremity AVF or

AVG, pre-procedural central venous imaging, preferably with digital subtraction venography, should be considered mandatory for any patient with a history of an ipsilateral CVC or indwelling cardiac device. This practice would identify pre-existing, clinically silent central stenoses, allowing for pre-emptive treatment or, more importantly, avoidance of creating an access that is doomed to fail and cause severe symptoms (Saad and Vesely, 2010; Echefu et al., 2023).

2. **Adoption of a Hierarchical Treatment Algorithm:** Interventionalists should adopt the evidence-based hierarchical treatment approach outlined above. The decision to escalate from PTA to a stent graft should be made based on objective criteria such as post-PTA recoil and the rapidity of recurrence, with a low threshold for using the more durable stent graft technology.
3. **Lifelong Surveillance:** CVD must be recognized as a chronic and recurrent condition. Patients who have undergone an intervention for central stenosis require lifelong clinical surveillance of their vascular access. This includes monitoring for subtle signs of venous hypertension, such as prolonged bleeding post-dialysis or increased venous pressures during treatment, to allow for timely re-intervention before access thrombosis occurs (El-Shehaby et al., 2020; Labarrere et al., 2024).

CONCLUSION

Summary of Evidence

Central Venous Disease is a common, serious, and largely preventable complication in patients undergoing maintenance hemodialysis. Its pathogenesis is overwhelmingly driven by the iatrogenic endothelial trauma and subsequent neointimal hyperplasia caused by the use of central venous catheters. Therefore, the most effective management strategy is prevention, centered on the timely creation of permanent vascular access and the rigorous avoidance of CVCs, particularly in the subclavian position.

For patients who develop symptomatic CVD, endovascular therapy is the primary treatment modality. A hierarchical approach is recommended, beginning with high-pressure PTA for initial symptom relief. For lesions that are unresponsive to PTA or recur rapidly, stent grafts have emerged as the superior technology, offering the most durable primary patency of all endovascular options. Despite the availability of effective treatments, CVD must be regarded as a chronic and recurrent condition that requires lifelong surveillance and a high likelihood of repeat interventions to maintain the long-term functionality of the patient's vital hemodialysis access.

Future Directions and Suggestions

To advance the care of patients with this challenging condition, future research should focus on several key areas:

- **Prospective Randomized Controlled Trials:** There is an urgent need for well-designed, multicenter RCTs to definitively compare the long-term efficacy and safety of the most promising modern technologies, particularly stent grafts versus drug-coated balloons.
- **Economic Analysis:** Future trials should incorporate formal cost-effectiveness analyses. These studies must look beyond initial device costs to evaluate the total economic impact of each strategy, factoring in the costs of surveillance, re-interventions, and managing complications like access thrombosis.
- **Biomarker and Pharmacological Research:** A deeper investigation into the specific molecular pathways driving neointimal hyperplasia in the central venous environment is needed. This could lead to the identification of biomarkers for risk stratification and the development of novel pharmacological agents that could be used systemically or delivered locally to prevent or mitigate the stenotic process.
- **Patient-Reported Outcomes:** It is imperative that future clinical trials include robust patient-reported outcome measures (PROMs). Quantifying the impact of CVD and its various treatments on patient quality of life, pain, and functional status is essential to understanding the true burden of the disease and ensuring that our treatment goals align with what matters most

to patients (Saad, 2017; Lok and Foley, 2022).

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