FRESENIUS MEDICAL CARE

Post-Dilution High-Volume Hemodiafiltration:

The next-generation of kidney replacement therapy

A practical guide for physicians

Stefano Stuard
Franklin W. Maddux

This handbook provides physicians and clinicians with a comprehensive review of components needed to implement post-dilution high-volume hemodiafiltration.

This educational material is intended to provide pertinent data to assist healthcare professionals in forming their own conclusions and making decisions. It is not intended to replace the judgment or experience of the attending physician or other medical professional. The post-dilution high-volume hemodiafiltration treatment prescription is the sole responsibility of the attending physician and/or nurse.

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Reviewed in June 2025

Acknowledgments and Dedication

This book has many fathers and mothers. Together, they represent countless decades of clinical experience in the use of hemodiafiltration (HDF) for treating patients with end-stage kidney disease. United by a shared commitment to advancing care, the contributors aim to offer physicians and, more broadly, the entire clinical team, a practical, evidence-based guide to post-dilution high-volume hemodiafiltration (HVHDF).

I would like to express my heartfelt gratitude to all the authors for their invaluable insights, inspiring contributions, and collegial collaboration throughout the creation of this work.

My sincere thanks also go to my colleagues at Fresenius Medical Care—in the Global Medical Office, Care Delivery, and Care Enablement—whose thoughtful feedback, expert guidance, and unwavering support significantly enhanced the scientific quality of this book. I am especially grateful for their patience and the many constructive, professional, and insightful suggestions they generously shared during the intense finalization period.

I also wish to acknowledge and thank the pioneers at Fresenius Medical Care who had the vision to recognize that hemodiafiltration has the potential to transform dialysis care, by improving both clinical outcomes and quality of life for tens of thousands of patients around the world.

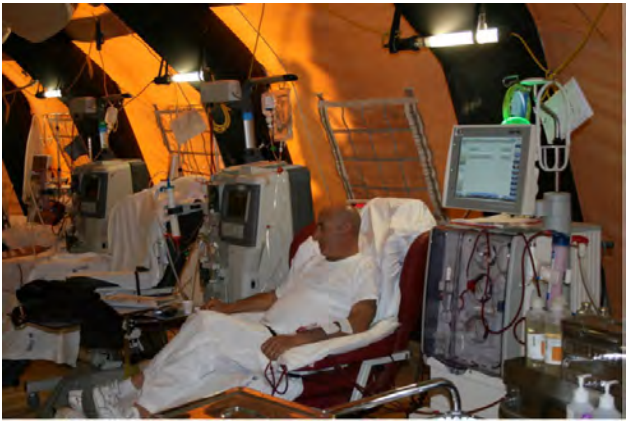
A special note of appreciation goes to Ms. Jeannine Sohayda, whose cheerful dedication and tireless support were instrumental in organizing the final manuscript. Her efficiency, attention to detail, and positive spirit were deeply appreciated.

Dedication

I dedicate this book to Mr. Benito Lucantonio*, who, in 2009, after the earthquake that devastated my city of L'Aquila (Italy) and destroyed the city public hospital, taught me an unforgettable lesson about resilience, dignity, and the true meaning of healing.

In the midst of chaos, as we established a temporary dialysis center inside a tent, he came to me with a simple but powerful request: to continue his hemodiafiltration therapy, even under those emergency conditions. He spoke with quiet conviction, telling me how much better he felt since starting HDF. His insistence was not a complaint—it was an expression of trust in a therapy that had restored his strength.

There, in that tent, as he received his treatment with gratitude and composure, I came to understand—not only clinically, but deeply and personally—the real value of hemodiafiltration. From that moment on, I knew this therapy was not only scientifically sound but also profoundly human.



To Mr. Lucantonio, with gratitude. You inspired this journey.

Stefano Stuard

* Mr. Lucantonio is currently living with a stable and well-functioning kidney transplant.

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Foreword

Dear Physician Colleagues,

We are proud to mark a pivotal moment in the evolution of kidney replacement therapy: the emergence of high-volume hemodiafiltration (HVHDF) as a new standard of care for patients with end-stage kidney disease (ESKD).

At Fresenius Medical Care, we have long believed in the transformative potential of HVHDF. Through decades of innovation and clinical leadership, we have introduced this therapy in more than 90 countries, delivering measurable improvements in patient outcomes. In Europe, HVHDF is now the routine treatment for the majority of our hemodialysis population—a testament to the dedication and collaboration of our clinicians, engineers, and global partners.

Today, we are honored to bring this life-enhancing therapy to people who need dialysis in the United States. In 2024, the U.S. Food and Drug Administration granted 510(k) clearance for our 5008X hemodialysis system. By early 2025, the first HVHDF treatments were successfully delivered in a U.S. Fresenius Kidney Care center. This milestone represents more than technological progress—it marks a clinical breakthrough that offers renewed hope and elevates the standard of kidney replacement therapy.

Yet, innovation alone is not enough. To ensure widespread adoption, we must also invest in education, operational readiness, and policy alignment. That is why we are committed to training clinicians, supporting real-world research, and working closely with stakeholders to integrate HVHDF into practice in a sustainable and equitable way.

This handbook reflects our commitment to knowledge-sharing and to empowering kidney care professionals with the tools and insights needed to deliver the highest quality care.

Thank you for your continued partnership and leadership in advancing dialysis treatment. Together, we are shaping the future of kidney care—one defined by innovation, collaboration, and an unwavering focus on what matters most: better outcomes for people who need dialysis.

Warm regards,

Helen Giza
Chief Executive Officer
Fresenius Medical Care

Preface

High-Volume Hemodiafiltration: A Scientific Foundation for the Future of Dialysis

By Bernard Canaud, MD, PhD*

Emeritus Professor of Medicine, Montpellier University, Montpellier, France

Emeritus Medical Officer, Global Medical Office, Fresenius Medical Care, Bad Homburg, Germany

Despite five decades of innovation, conventional hemodialysis (HD) has reached a therapeutic ceiling in its ability to improve survival and quality of life for patients with end-stage kidney disease (ESKD). Mortality remains unacceptably high, with cardiovascular disease accounting for more than 50% of deaths. While conventional HD removes small solutes such as urea through diffusive transport effectively, it fails to eliminate middle- and large-molecular-weight uremic toxins adequately. These solutes, implicated in chronic inflammation, cardiovascular dysfunction, malnutrition, mineral bone disorders, and immune dysregulation, remain largely uncovered by conventional dialysis, contributing to poor long-term outcomes.

These persistent unmet medical needs, recognized since the 1980s, form the scientific rationale for hemodiafiltration (HDF), and more specifically for post-dilution high-volume HDF (HVHDF). This advanced modality combines diffusive and convective clearance

* Prof. Bernard Canaud is internationally recognized as a leading authority on HDF with more than four decades of scientific research and clinical experience involving patients treated outside the United States. Although he does not practice medicine in the U.S., his perspectives on HDF are grounded in a robust body of evidence derived from randomized controlled trials, meta-analyses, and real-world studies, as well as his globally acknowledged clinical expertise. Importantly, the current scientific evidence supporting the efficacy and safety of HDF has been generated entirely in patient populations treated outside the United States. These data reflect real-world clinical practice across Europe, the Asia-Pacific region, Latin America, and other regions where HDF has been widely adopted for over two decades.

to achieve superior removal of a broader range of uremic toxins, including β2-microglobulin, pro-inflammatory cytokines and protein-bound solutes. HVHDF offers multiple clinical benefits: improved cardiovascular stability, reduced systemic inflammation, better nutritional status, enhanced patient well-being, and lower incidence of dialysis-related complications. Collectively, these benefits contribute to reducing the burden of kidney replacement therapy (KRT) at the patient, societal, and healthcare system levels.

For patients eligible for kidney transplantation, HVHDF provides a cardio-protective bridge, potentially improving post-transplant outcomes. For those not suitable for transplantation, it offers a more physiologically tolerable and outcome-oriented dialysis option that alleviates treatment burden.

Multiple randomized controlled trials (RCTs), including the landmark CONVINCE study, as well as large-scale registry analyses and individual patient data meta-analyses (IPD-MA), have consistently shown that HVHDF with convective volumes exceeding 23 liters/session is associated with reduced all-cause and cardiovascular mortality. These findings also demonstrate a dose-response relationship, reinforcing the concept that “more is better” when it comes to convective volume delivery.

Technological advances, notably with the Fresenius Medical Care 5008X platform and FX CorAL dialyzers, have facilitated broader adoption of HVHDF. Integrated systems with real-time feedback controls such as AutoSubplus, dynamically adjusts ultrafiltration to maintain an optimal filtration fraction up to 35%, thereby enhancing consistent and efficient convective solute clearance. Simultaneously, the use of substitution fluid, generated online and sterilized through redundant ultrafilters, ensures both microbiological safety and treatment sterility. This access to an unlimited supply of sterile fluid reduces staff workload by simplifying machine handling during priming, rinsing, or administering intravenous boluses, and eliminates the need for additional saline bags. Moreover, it contributes to improved biocompatibility of the extracorporeal treatment. In addition, the AutoFlow function, which automatically aligns dialysate flow with blood flow, reducing flow ratio to 1.2, further enhances treatment efficiency while substantially lowering water and electrolyte consumption. This synergy of performance, precision, and sustainability positions HVHDF as the

most environmentally responsible and clinically effective modality currently available in KRT.

From an economic perspective, HVHDF aligns closely with the principles of value-based care by optimizing clinical outcomes while reducing overall healthcare resource utilization. It enhances patient-reported outcomes, tends to reduce hospitalization rates, and supports long-term sustainability through more efficient use of water, energy, and dialysis supplies. As such, HVHDF represents not only a significant clinical advancement but also a strategic solution addressing both public health priorities and environmental stewardship in KRT.

In summary, HVHDF should be regarded as the next-generation standard in KRT. It addresses key limitations of conventional HD within routine treatment timeframes and delivers superior clearance across a wider spectrum of uremic toxins. By improving survival, enhancing quality of life, and supporting sustainable practices, HVHDF emerges as the most evidence-based and future-oriented dialysis modality. As detailed in this book, Fresenius Medical Care deserves recognition for its pioneering role in the development and global implementation of this innovative therapy, offering patients with ESKD both an optimal bridge to kidney transplantation and a more integrated, outcome-driven continuum of kidney care.

Chapter 1

Fresenius Medical Care & Hemodiafiltration

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Fresenius Medical Care & Hemodiafiltration

1.1 | A brief history

Fresenius Medical Care (FME) has led the global development, implementation, and adoption of online high-volume hemodiafiltration (HVHDF).

Through significant investments in research and development, strategic collaborations, and a strong commitment to leadership in innovation, FME has established itself as a trailblazer in advancing hemodiafiltration (HDF) technology and delivering its transformative benefits to patients with end-stage kidney disease (ESKD).

Visionary company leaders, including **Gerd Krick, Ben Lipps, Emanuele Gatti, Rice Powell, Katarzyna Mazur-Hofsaess, Craig Cordola, and Helen Giza**, have consistently championed innovation and excellence. Their dedication has solidified Fresenius Medical Care's position as a global leader in HVHDF, ensuring that this advanced therapy continues to improve patient outcomes globally and set new benchmarks in kidney replacement treatment.

In Germany in the mid-1970s, Fresenius AG (whose dialysis division would become FME in 1996) focused its efforts on two major initiatives: the development of equipment for hemofiltration (HF) and the creation of a new-generation hemodialysis (HD) system, which ultimately led to the introduction of the A2008 (1).

While the HD project, being more complex, took precedence, HF development remained limited to manually controlled setups combining existing components.

In 1976, contacts with the research team of Leber and Wizemann, based at the University Hospital in Giessen, Germany, introduced Fresenius AG to their pioneering work on HDF (2).

FME recognized the potential of integrating their advanced A2008 HD system with Sartorius's Haemoprocessor. This collaboration led to the creation of the first commercially available HDF system in Europe, the ABG-1 (1). This system utilized the A2008's closed hydraulic circuit, which proved ideal for extending its capabilities

to HDF, a feature still benefiting FME machines today. The ABG-1 featured modifications such as a substitution fluid heater and pump alongside Sartorius's automatic balancing device (Figure 1.1).

Figure 1.1. | Fresenius A2008C with the ABG-1 hemodiafiltration module, a joint development of Fresenius AG (Bad Homburg, Germany) and Sartorius AG (Gottingen, Germany). Source FME R&D archive.

The A2008C machine, equipped with its advanced volumetric fluid-balancing system, provided an ideal platform for integrating not only high-flux and HDF procedures but also the capability for online fluid preparation. Figure 1.2 presents a facsimile of a 1986 directive from Gerd Krick, mandating the acceleration and completion of the development and market introduction of an online HDF system (1).

A subsequent version, the ABG-II, was developed exclusively by Fresenius AG. The company's position was further strengthened by developing a polysulfone dialysis membrane. This new synthetic high-flux membrane set the benchmark for future synthetic membranes, offering high hydraulic permeability, superior biocompatibility, enhanced clearance of small and middle molecules, and a reduced risk of bacterial contamination.

The attenuation of bacterial contamination was a critical advancement, facilitating the development of a new generation of ultrafilters. These ultrafilters enabled the production of online substitution fluid directly from standard dialysate, thereby making online HDF feasible.

The dialysate ultrafilters, later marketed under the DIASAFE®*plus* brand, were progressively optimized for integration with FME dialysis machines. This system generated sterile substitution fluid directly from dialysate via a cold multi-stage ultrafiltration process, ensuring consistent quality and safety while eliminating the need for prepackaged sterile fluids.

Figure 1.2 | Written order and rationale by Fresenius AG Board Member Dr. G. Krick to boost and finish the development of the scientific, medical, and technical basis for a commercial online HDF system released in 1986 (1). Source: FME R&D archive Author translation: *'I believe there is agreement that online HDF in future will play an important role in the treatment of acute or chronic kidney patients; in this sense high-flux dialysis with highly permeable membranes is just a preliminary stage. For Fresenius as initiator of hemodiafiltration it is of outermost importance to belong to the pioneers of high-flux dialysis and on-line HDF again, especially because we have a much better position compared to nearly all competitors due to the new polysulfone membrane. We meanwhile agreed that – effective January 1st, 1986 and without any constraints – you will be responsible for the medical and scientific concept of an online HDF. This task includes (a) back filtration, (b) sterile and pyrogen filtration, (c) the question of IL- 1 generation, (d) the general improvement of dialysis by means of 'infusion.' The technical part of online HDF is addressed already in R&D Medical Devices by Dr. Polaschegg and his co-workers. Concepts to solve the technical problems already are available.... In case you face any problems during your work, including problems regarding cooperation with in-house employees, you are asked to inform me immediately..'* (1)

In 1987, Fresenius AG introduced its first approved and commercially available online HDF system in Europe (Figure 1.3), initially developed and approved by the German TÜV in its 1985 version.

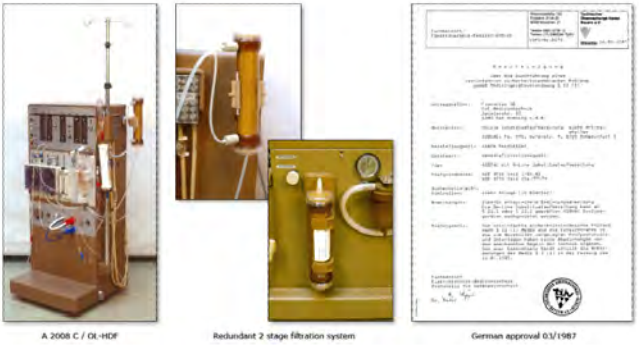


Figure 1.3. | First approved and commercially available Fresenius online HDF system for the HD machine A2008C(1987) and German approval. Source FME R&D archive.

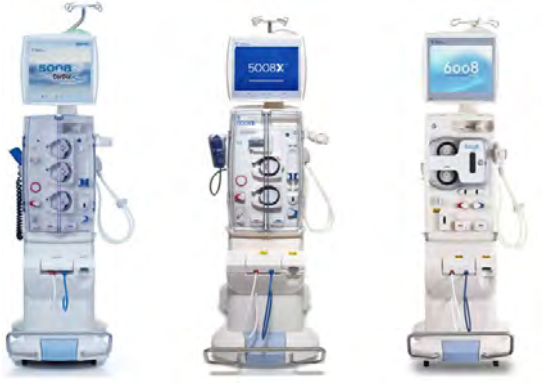
In 1998, the 4008H dialysis machine offered ONLINEplus™ technology as an optional feature outside the U.S. This technology enabled HVHDF by producing sterile substitution fluid directly from dialysate during treatment (Figure 1.4). The integration of this feature enhanced the machine's versatility, making it suitable for both conventional HD and online HDF while maintaining stringent standards for fluid sterility and treatment safety. This optional upgrade marked a significant step toward optimizing dialysis treatments for improved patient outcomes.

Figure 1.4. | Fresenius Medical Care 4008 H dialysis machine. Source: FME R&D archive.

Building upon this innovation, in 2005, following two decades of research and development, FME established online HDF as a standard feature in its 5008 dialysis machine outside the U.S. (Figure 1.5) (1, 3). This decision highlighted the growing appreciation of HDF's clinical superiority over conventional high-flux HD, supported by a growing body of real-world evidence (RWE) (4, 5).

Figure 1.5 | FME 5008 dialysis machine. Source: FME Care Enablement.

The evolution of dialysis technology led to the development of the 5008 and 6008 series machines (including the 5008X, the first Fresenius Medical Care device capable of performing online HDF in the U.S. market), which incorporate advanced features to enhance both treatment efficacy and operational efficiency. These innovations included automatic online fluid preparation, improved convective clearance, and optimized resource utilization, reducing costs compared to standalone HDF platforms. Furthermore, the 5008 and 6008 series machines were designed with an intuitive user interface, facilitating seamless operation and real-time monitoring. Their enhanced usability and accessibility improve treatment accuracy and workflow efficiency (Figure 1.6).



A B C

Figure 1.6 | Fresenius 5008S Cordiax (A), 5008X (B), and 6008 (C) dialysis machines. Source: FME archive.

Additionally, in 2005, HDF was established as standard therapy in FME Europe, the Middle East, and Africa (EMEA) NephroCare clinics (6).

FME has continued to advance technologies such as HDF by integrating clinical excellence with cutting-edge technical innovation. In his former role as EMEA Chief Medical Officer, **Bernard Canaud** played a pivotal role in redefining the standards of care for patients with ESKD. His work was instrumental in developing an early and robust evidence base demonstrating HDF as a superior KRT, significantly improving both intermediate and long-term patient

outcomes compared to conventional high-flux HD in patients in EMEA (7-30).

FME medical leadership, including key figures such as **Frank Maddux**, Global Chief Medical Officer, and **Stefano Stuard**, Global Clinical Officer for HDF, has been instrumental in establishing and upholding the highest medical standards for HDF treatments.

In 2014, post-dilution HVHDF was formally recognized as the gold standard in FME EMEA NephroCare clinics. This milestone was accompanied by the implementation of an HDF-specific key performance indicator (KPI), which set a target convective clearance volume for EMEA NephroCare clinics. The KPI mandated substitution volumes of ≥ 21 liters per session enabled HVHDF to be delivered at an optimal convective volume of ≥ 23 liters per session. By 2023, more than 62% of all HD patients in FME EMEA clinics were receiving HDF, with over 26,000 patients undergoing post-dilution HVHDF. These patients achieved a mean convective volume of 27.4 ± 4.9 liters per session, underscoring FME's operational excellence and commitment to delivering superior renal care (29).

The FME Global Medical Office has conducted numerous retrospective studies in patients dialyzed in FME EMEA NephroCare clinics, supporting the superiority of HVHDF over conventional HD (7, 13, 23, 31-34), a finding repeatedly confirmed by randomized prospective controlled trials such as CONTRAST, Turkish, ESHOL, and CONVINCE (35-38). Several studies have demonstrated a dose-response relationship between substitution/convective volume and relative survival rate, with comparable results (30, 39-41). Specifically, a substitution/convective volume exceeding 21/23 L per session, respectively, has exhibited the most favorable effect on mortality outcomes (42-44).

Despite the widespread implementation of online HDF in Europe for several decades and its more recent adoption in Asia, its utilization in the United States has been minimal. This limited uptake can be attributed to several factors, including potential skepticism of the results of the randomized controlled trials (RCTs) prior to CONVINCE (38), the increased technical complexity of HDF compared to HD, particularly regarding water management systems, and structural differences in healthcare delivery and reimbursement models. It also required a dialysis machine capable of online fluid generation, which

was previously unavailable in the U.S. Furthermore, the successful integration of HDF requires the development of specialized training programs and operational frameworks, necessitating adaptations within the healthcare infrastructure and in medical education and professional training systems.

FME in EMEA has been instrumental in advancing HVHDF by contributing to patient-reported outcomes research and cost-effectiveness analyses, underscoring HVHDF's value in improving quality of life and reducing long-term healthcare costs. FME consistently focuses on enhancing the sustainability of HVHDF by optimizing water and resource utilization in dialysis treatments. Advances in machine technology and the enhanced HVHDF prescription have reduced total water consumption (29). Waste reduction, improved energy efficiency, and aligning HVHDF with "green dialysis" is also an important goal.

1.2 | Educational initiatives

In addition to its technical contributions and high operational quality standards, FME emphasized the importance of continuous medical education and training. Recognizing the complexities of HVHDF, the company championed educational programs to empower nephrologists, clinical staff, and healthcare teams with the knowledge and skills to deliver this advanced therapy safely and effectively, a key requirement for establishing confidence in the nephrologist's ability to prescribe and manage HVHDF therapy.

The following strategic steps for FME will focus on implementing and expanding HVHDF in countries where its adoption remains limited to a minority of ESKD patients due to regulatory restrictions, reimbursement challenges, and healthcare system constraints (45).

- Targeting workshops and training programs to effectively bridge knowledge gaps in HVHDF, improving prescriber confidence and thereby expanding adoption.
- Partnering with CME and CEU accrediting organizations to provide comprehensive continuing education on HVHDF best practices and related clinical outcomes for nurses and physicians.
- Conducting U.S.-based health economic outcome studies to assess the comparative costs and outcomes associated with HVHDF versus traditional methods may provide valuable insights

into its financial sustainability.

- Ensuring that HVHDF can meet the primary clinical and financial challenges, as well as the diverse expectations of various stakeholders.
- Supporting and nurturing robust cross-functional networks involving researchers, healthcare organizations, industry partners, government agencies, and nephrology professional societies—an essential step in driving standard-setting, evidence-based practice, and innovation in HVHDF therapies.
- Actively engaging with multinational consortiums dedicated to advancing kidney care, such as the CONVINCE Study Consortium, which unites dialysis divisions in academic hospitals, general facilities, and private renal care providers, amplifying the focus on HVHDF and fostering cross-border learning.
- Promoting active patient participation in decision-making in collaboration with patient associations ensures that patient preferences and values are considered when selecting dialysis modalities.

Addressing these barriers will ensure wider access to HVHDF and its well-documented clinical benefits, thereby elevating the standard of care for ESKD patients worldwide. FME, with its expertise in dialysis technologies and quality operational excellence, is positioned to lead the adoption of HVHDF in the U.S. through the strategic deployment of the 5008X dialysis machine and FX CorAL dialyzers — devices specifically designed to facilitate the implementation of this therapy. The primary focus of this expansion will be the United States, where the transition to HVHDF aligns with current clinical demands and value-based care objectives. The FME EMEA region, with its proven success in HVHDF adoption, will serve as a benchmark. Sharing this region's best practices and clinical outcomes will inform U.S. strategies and other global markets.

In February 2024, FME received U.S. Food & Drug Administration (FDA) 510(k) clearance for the 5008X hemodialysis system (46). Following FDA clearance, FME reached a significant milestone in KRT in the U.S. on January 24, 2025. The first HVHDF (convective volume > 23 Liters/session) was successfully performed at a Fresenius Kidney Care (FKC) clinic in Wellesley, MA. This landmark session demonstrated the clinical feasibility of implementing HVHDF in the

U.S. healthcare setting and achieved an impressive substitution volume of 25.5 liters over 215 minutes of HDF treatment (Figure 1.7).

Figure. 1.7 | First U.S. ESKD patient treated with HVHDF and 5008X hemodialysis system, achieving a substitution volume of 25.5 L per session. The HVHDF treatment was performed at the FKC clinic in Wellesley, Massachusetts, on January 24, 2025.

This milestone represents a critical therapeutic advancement in KRT in a generation to patients in the U.S., signifying a breakthrough for the nephrology community.

Chapter 2

From Conventional Hemodialysis to High-Volume Hemodiafiltration

Chapter 2

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2.1 | Introduction

The profile of patients transitioning from chronic kidney disease (CKD) to maintenance hemodialysis (HD) is shifting toward an older population with multiple comorbid conditions (notably diabetes mellitus and heart failure). Despite improvements in dialysis care, overall survival for ESKD patients on HD remains poor. Cardiovascular disease is the single largest cause of mortality in this population; according to the 2023 United States Renal Data System Annual Data Report, over half (52.2%) of deaths with a known cause were related to cardiovascular disease (47). This elevated risk is attributed not only to the high prevalence of pre-existing cardiovascular conditions but also to the additional cardiovascular stress imposed by both ESKD as a condition and the HD procedure itself, such as fluid overload with uncontrolled hypertension (48, 49), hemodynamic instability (50, 51), chronic inflammation (52, 53) and oxidative stress (54), anemia (55), hyperphosphatemia as well as mineral bone disorders (56, 57), and increased circulating β2-microglobulin (β2M) levels (58, 59) (Figure. 2.1).

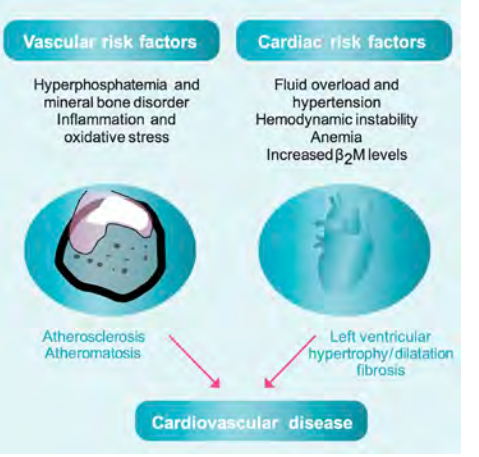


Figure 2.1. | Potential cardiovascular risk factors in dialysis patients.

These compounding factors create a “perfect storm” for the cardiovascular system, explaining why ESKD patients on dialysis face persistently elevated cardiovascular mortality rates despite managing traditional risk factors.

Dialysis modalities differ in the mechanisms by which uremic toxins are removed:

- **Conventional HD** primarily relies on diffusive clearance through osmotic gradients, concentration gradients generated across a semi-permeable membrane to eliminate small molecular-weight solutes.
- **Hemofiltration** removes solutes by convection through transmembrane pressure (TMP), which is especially effective in removing middle-molecular-weight (MMW) toxins. Convective clearance combines substitution volume infusion and removal (infusing sterile replacement (substitution) fluid ultrapure dialysate into the circulation at the same rate as it is removed through the dialysis filter, i.e., volume neutral) with ultrafiltration (net removal of fluid from the patient’s circulating blood volume).
- **Hemodiafiltration** combines diffusive and convective clearances, efficiently removing a broad molecular-weight spectrum of uremic toxins. Indeed, HDF efficiently removes small-molecular-weight uremic solutes (e.g., urea and creatinine) mainly through diffusive transport. Simultaneously, medium-sized uremic molecules (e.g., β2M) are preferentially removed through convective clearance (Figure 2.2).

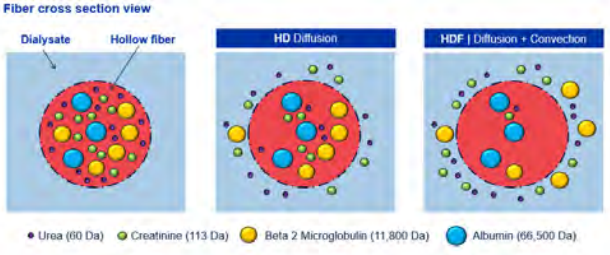


Figure 2.2 | Hemodiafiltration combines diffusion and convection clearances to improve solute removal.

- **High-volume HDF** achieved by delivering a high convective substitution volume each session maximizes uremic toxin removal. Notably, a large convection volume in HDF is associated with significantly lower mortality: achieving > 23 L of convective clearance per session has been linked to reduced overall and cardiovascular death rates compared to conventional high-flux dialysis (37, 38, 42, 44, 60).

This chapter will present the different dialysis modalities, focusing on the transport of different uremic toxins, with particular emphasis on HDF and its various modalities.

2.2 | Conventional Hemodialysis

Conventional (low- and high-flux) HD is an extracorporeal blood purification technique that leverages the physical and chemical properties of a semi-permeable membrane to achieve solute and fluid exchange between the blood and the dialysate compartments, driven by concentration gradients, pressure gradients, and osmotic forces.

The blood and dialysate flow in opposite directions (counter-current flow) to maximize concentration gradients and enhance diffusion. Conventional HD's goals are to remove uremic toxins as small solutes (e.g., urea, creatinine) and middle molecules (e.g., β2M), maintain electrolyte homeostasis, restore acid-base balance, and control fluid overload by removing excess plasma water to normalize the extracellular volume and blood pressure.

According to the permeability characteristics of the dialysis membrane, HD can be divided into low-flux and high-flux HD (if low-flux or high-flux hemodialyzers are utilized). These membranes allow selective passage of solutes, rejecting larger components such as proteins and blood cells while allowing small and middle molecules to pass through.

High-flux membranes permit considerably higher amounts of convection in addition to diffusion.

In conventional HD, uremic molecules are removed primarily through diffusive transport, driven by a concentration gradient between the blood (where uremic toxins are at a higher concentration) and the dialysate (where their concentration is lower) across the HD membrane (Figure 2.3).

Smaller molecules diffuse more rapidly than larger ones, as the diffusion rate is inversely related to molecular size. Consequently, HD is particularly effective at clearing smaller solutes, even when larger solutes are small enough to pass through the pores of the dialysis membrane.

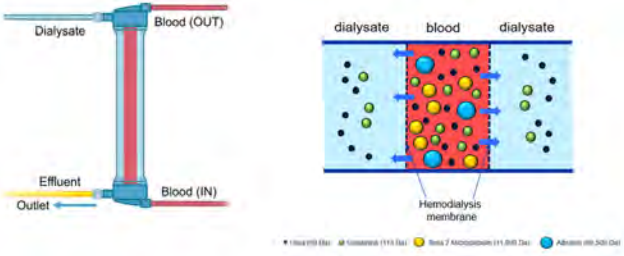


Figure 2.3 | Diffusive transport of uremic molecules in hemodialysis across a dialysis membrane during high-flux hemodialysis.

Fick's first law governs the rate of diffusion of solutes (Jd, amount of solute transferred per unit time) from the patient's blood to dialysate across the HD membrane.

$$J_d = D \times A \times T \times (dc / dx)$$

D: Diffusivity coefficient of the solute (molecular weight, solubility, electric charge, ...)

A: Surface area of the membrane

T: Temperature

dc: Concentration gradient dialysate/blood

dx: Membrane thickness (porosity, pore characteristics, hydrophilicity,...)

2.3 | Hemofiltration (Diafiltration)

In 1967, Henderson et al. introduced the concept of "diafiltration" as a method for removing toxins from blood through a pure convective therapy (61). This approach involved ultrafiltration volumes that exceeded the desired fluid removal, necessitating the infusion of replacement (substitution) fluid to achieve fluid balance and control hydration status and hemodynamic stability. Over time, the term "diafiltration" caused some confusion and was subsequently replaced by the term "hemofiltration" in 1976, as proposed by Burton.

Reliable clinical data on long-term maintenance HF emerged in the early 1970s, with significant contributions from German researchers such as Quellhorst et al. (1, 62). At the time, the widespread recognition of the efficacy of low-flux membranes to clear small molecular weight toxins but not MMW toxins sparked interest in identifying specific “middle molecules” left relatively untouched by conventional low-flux membranes, molecules that might explain the ongoing vicissitudes and complications experienced by patients receiving chronic low-flux HD.

This “middle molecule” hypothesis initially drove a research and development program focused on HF. Even if a particular (or particular class of) offending middle molecule proved elusive, a therapy which nonetheless removed middle molecules “**en masse**” had obvious therapeutic appeal. However, its clinical application in the late 1970s and 1980s was primarily justified by its stabilizing effect on blood pressure during and between dialysis sessions (17). Patients with cardiovascular comorbidities who regularly experienced hemodynamic instability and discomfort during conventional HD became the initial candidates for HF. HF is a KRT that relies on convective transport to achieve solute clearance.

Unlike traditional HD, predominantly based on diffusion, HF necessitates a highly permeable dialysis membrane capable of facilitating extensive ultrafiltration and solute removal.

To generate sufficient convection, ultrafiltration must be performed at a rate far exceeding the fluid volume required to achieve the patient’s dry weight. Consequently, a substitution fluid is administered to compensate for the ultrafiltered volume, adjusted for the intended weight loss. Convection increases the clearance of middle molecules over that provided by diffusion alone. It is a process where a positive hydrostatic pressure is applied to a fluid, causing it to flow across a semi-permeable membrane.

Solutes are carried with the fluid by "**solvent drag,**" meaning the fluid pulls the solutes through the membrane, enabling their removal (Figure 2.4), provided the solutes can pass through the membrane pores. Unlike conventional dialysis, HF does not require a dialysis fluid in the classical sense, as the convective transport mechanism drives solute removal (Figure 2.4).

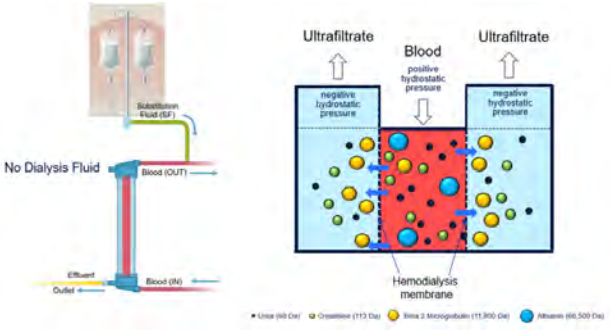


Figure 2.4 | Post-dilution hemofiltration treatment with sterile bags.

The transport dynamics of HF differ substantially from those of HD. Diffusive transport, which dominates in conventional HD, is highly efficient for the clearance of small solutes but becomes increasingly inefficient as molecular weight increases. Specifically, while diffusion effectively removes solutes with molecular weights below 1,000 Daltons (Da), clearance rates decline significantly for larger molecules, such that a 1,000 Da solute is removed at approximately half the rate of a 60 Da solute, like urea. In contrast, convection-based clearance in HF remains effective for larger solutes, making it the preferred mechanism for removing molecules exceeding 2,000–3,000 Da in molecular weight.

The efficiency of convective solute removal is inherently linked to the properties of the dialysis membrane, particularly its sieving characteristics. The mean pore size determines **Sieving Coefficient** (SC) at the innermost separating region of the membrane, which defines the selective retention or clearance of molecules. The SC for a given molecule and membrane is calculated based on the solute concentration in the fluid after filtration relative to the difference in solute concentration in the fluid (plasma) entering and exiting the dialyzer (SC = 2 CF / CPi + CP0). Solutes that can traverse the membrane's pores are carried along with the ultrafiltered fluid, making the membrane's SC a critical determinant of solute clearance. Ideally, the in vivo sieving profile of membranes employed in KRT should closely approximate the physiological sieving curve of the glomerular basement membrane. This ensures optimal removal of both small and larger molecular weight solutes, thereby enhancing the overall efficacy of the treatment.

The clearance achieved in HF is determined by the **Ultrafiltration Rate** (UFR); UFR is defined as the removal of plasma water and dissolved solutes across the membrane using a pressure gradient, typically controlled by the dialysis machine [UFR = Ultrafiltration coefficient of the membrane multiplied by TMP difference (blood-side pressure minus dialysate-side pressure)].

The membrane's hydraulic permeability dictates the UFR. To ensure efficient fluid and solute removal, HF requires the use of high-flux membranes with a minimum **Ultrafiltration Coefficient** (Kuf) of 20 mL/h/mmHg/m^2. The rate of convection of solute transport (Jd, amount of solute transferred per unit time) from the patient's blood to dialysate across the HD membrane is calculated by multiplying the UFR, the concentrate of solute (Cs), and the solute sieving coefficient (SC):

$$J_d = UFR \times Cs \times SC$$

UFR: Ultrafiltration rate (volume of plasma water removed per unit time)

Cs: Concentration of the solute in plasma water

SC: Sieving coefficient (fraction of solute passing through the membrane with water)

The magnitude of convective transport, excluding adsorption effects, mainly depends on the UFR, which is influenced by the hydraulic permeability of the membrane's support region. Convection, therefore, represents the extent to which solutes, determined by their sieving properties at the membrane's separating region, are transported along with the removed fluid, a process governed by the hydraulic permeability of the membrane wall.

In HF, middle molecules of uremic toxins are removed by maximizing convective transport through extensive UFR beyond the volume required to achieve the patient's dry weight.

Large substitution fluid volumes are necessary to fully leverage the convective mechanism for physiologically significant blood purification. This is achieved by operating at an optimal UFR relative to the blood flow rates feasible for individual patients, enabling high convective clearances for larger molecular-weight uremic toxins. Typical UFRs in HF are around 25-30% **of the blood flow rate** and are influenced by the patient's blood composition and degree of hydration.

From the outset, HF faced significant financial and clinical challenges. The high cost of large volumes of sterile intravenous replacement fluids in pre-packaged bags was not scalable due to manufacturing expense. At the same time, HF alone (in the absence of concomitant dialysate use, as in HD) proved less efficient than HD in clearing low molecular-weight solutes, such as urea and creatinine (Figure 2.5).

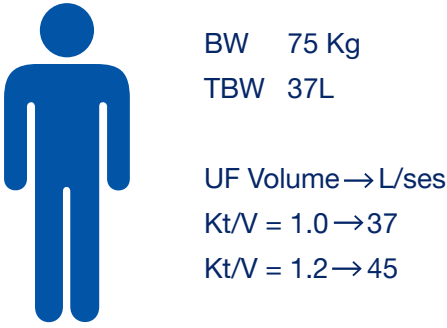


Figure 2.5 | Hemofiltration Kt/V performances and sterile solution consumptions in a patient with body weight (BW) of 75 Kg and 37 L of total body water (TBW).

To counteract the HF-related elevation in systemic urea concentration, longer dialysis times or greater volumes of substitution fluid were required—mainly when administered in pre-dilution mode (i.e., infused into the bloodline prior to passing through the dialysis filter) compared to post-dilution (i.e., infused into the bloodline after passing through the dialysis filter) to enhance convective flux. While improving solute removal, this approach further compounded the financial constraints associated with long-term HF maintenance.

To increase the efficiency of HF in the lower molecular weight range, HF was combined with HD, performed simultaneously, which led to the modality termed hemo**diafiltration**.

2.4 | Hemodiafiltration

HDF is an advanced dialysis modality that seamlessly integrates the principles of HD and HF within a single treatment session, enhancing both diffusive and convective solute clearance while maintaining patient safety.

HDF was initially performed using bags of sterile substitution fluid in combination with ultrapure dialysate provided by the HD machine. Modern technology utilizes a high-flux hemodialyzer paired with a specially designed dialysis machine that produces sterile substitution fluid in real-time, ensuring safe and efficient therapy delivery and eliminating the need for bags (Figure 2.6). Considering the identified HF limitations outlined above, "online" HDF addresses the challenge of administering very high substitution fluid volumes through online sterile fluid production by the machine, administered directly into the bloodline. In principle, the infusion of online-generated sterile substitution fluid into the closed-loop bloodlines may be pre-dilution or post-dilution. However, most current HDF platforms exploit post-dilution online fluid substitution.

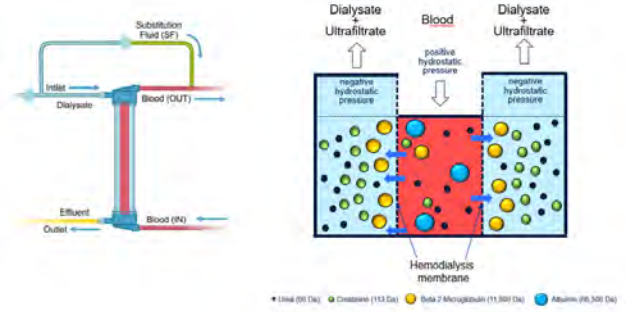


Figure 2.6 | In online post-dilution HDF, the solutes are carried with the fluid by solvent drag in addition to the diffusive transport.

Online HDF combines the diffusive and convective solute removal in a single therapy by ultrafiltering 25-35% of the blood volume processed (Filtration Fraction) using a high-flux hemodialyzer and maintaining fluid balance by infusing online sterile, non-pyrogenic substitution fluid directly into the patient's blood. Diffusion and enhanced convection enable the removal of both small- and middle-molecular-weight compounds along the UFR solvent drag effect through increased TMP.

Total ultrafiltration exceeds the desired fluid loss to maximize the removal of middle-sized toxins by convection. **Therefore, replacement (substitution) fluid must be infused into the extracorporeal circuit at an equal amount minus the desired fluid volume removal to achieve dry weight.**

The larger the volume of fluid removed by ultrafiltration (and subsequently replaced), the higher the efficiency of HDF.

Although both transport processes occur simultaneously, it is easier to conceptualize the sequence by assuming that diffusion occurs first, followed by the convective removal of the remaining solutes in the blood. For solutes that are effectively cleared by diffusion, such as urea, very little remains available for convective transport. Conversely, solutes not well cleared by diffusion, such as β2M, remain in higher concentrations and are more readily removed by convection. Therefore, combining diffusive and convective transport always results in greater total clearance than using either process alone under the same operational conditions (63, 64) (Figure 2.7).

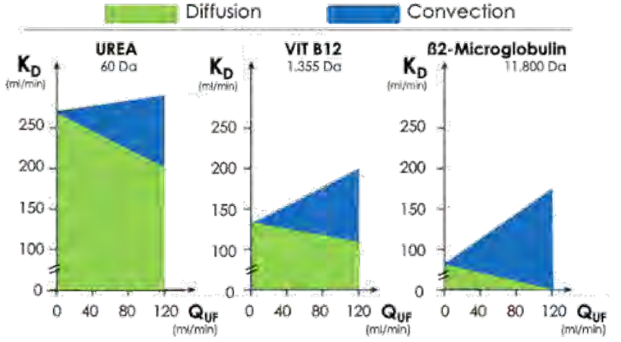


Figure 2.7 | The clearance in HDF of urea, vitamin B12 and β2-microglobulin at increasing ultrafiltration and convective transport (blood flow rate, 300 ml/min; diffusion green, convection blue. Modified from Ledebo (63).

2.5 | Online Hemodiafiltration Modalities

Online HDF treatment modalities can be categorized based upon the point of substitution fluid administration within the extracorporeal circuit into four distinct types: post-dilution HDF, pre-dilution HDF, mixed-dilution HDF and mid-dilution HDF (4, 5). Compared to post-dilution HDF, the dilution factor for pre-dilution HDF is 2, 1.5 for mixed-dilution HDF and mid-dilution HDF. Thus, in pre-, mixed-, and mid-dilution HDF, higher substitution volumes are needed than in post-dilution HDF.

2.5a Post-dilution HDF. Post-dilution HDF is the most commonly used mode of online HDF due to its superior ability to achieve high convective clearances and effective removal of soluble uremic toxins, particularly at normal or elevated blood flow rates.

The substitution fluid is infused downstream of the dialyzer into the venous drip chamber of the extracorporeal circuit (Figure 2.8).

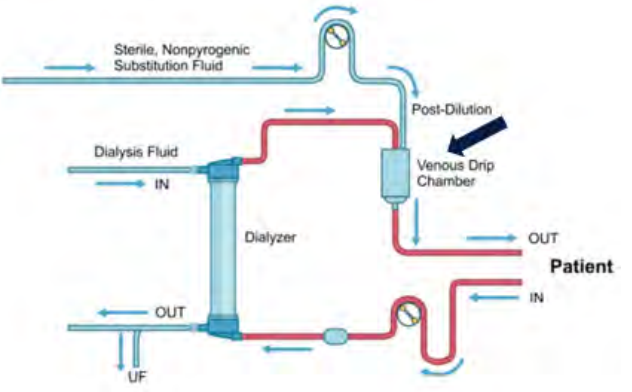


Figure 2.8 | Post-dilution hemodiafiltration.

The high UFR characteristic of post-dilution HDF increases serum protein concentrations as plasma water is removed, leading to a rise in blood viscosity and oncotic pressure. While this facilitates efficient solute removal, it also exposes the membrane to increased hemoconcentration and hyperviscosity.

Consequently, during post-dilution HDF, proteins, such as albumin and globulin, are deposited on the dialysis membrane surface, causing fouling that affects solute removal over time and biocompatibility. This phenomenon necessitates the careful management of filtration parameters.

A key limitation of post-dilution HDF is the restriction on the filtration fraction (FF), which is typically maintained at up to 30% of the blood flow rate. Exceeding this threshold risks hemoconcentration and further increases the likelihood of clot formation and membrane fouling, thereby reducing the efficiency of the treatment.

Despite these challenges, **post-dilution HDF remains the preferred modality in clinical practice due to its ability to maximize convective solute clearance while maintaining overall treatment efficacy at higher blood flow rates and reducing the overall water consumption.**

Proper optimization of ultrafiltration and substitution parameters is critical to achieving the best therapeutic outcomes in this mode. Therefore, in post-dilution HDF, the degree of convective transport is a critical determinant of overall treatment efficacy.

Several large-scale randomized clinical trials and meta-analyses demonstrated a survival advantage in patients undergoing post-dilution HDF, with convective volumes exceeding 23 liters (HVHDF) (37, 38, 42, 44). Achieving a convective volume of 23 L or more during HDF is a critical factor influencing clinical outcomes. From a clinical standpoint, a delivered convection volume of 23 liters per session, widely recognized as a surrogate marker of the convective dialysis dose, has emerged as a critical threshold associated with improved patient outcomes in HVHDF (37, 38, 42, 44). HVHDF enhances solute clearance, reduces inflammation, and improves survival rates and quality of life, making it a key target in high-efficiency HDF protocols.

2.5b Pre-dilution HDF. The substitution fluid is infused upstream of the dialyzer into the arterial side of the extracorporeal circuit (Figure 2.9). The pre-dilution mode reduces solute concentrations in the blood entering the dialyzer, leading to lower diffusive and convective clearance rates than the post-dilution mode. Despite the reduced solute clearance efficiency, pre-dilution HDF offers several advantages. Decreasing hematocrit and oncotic pressure preserves the TMP gradient along the membrane capillaries. This reduces the risk of clot formation and shear stress, potentially minimizing the formation of a "secondary membrane."

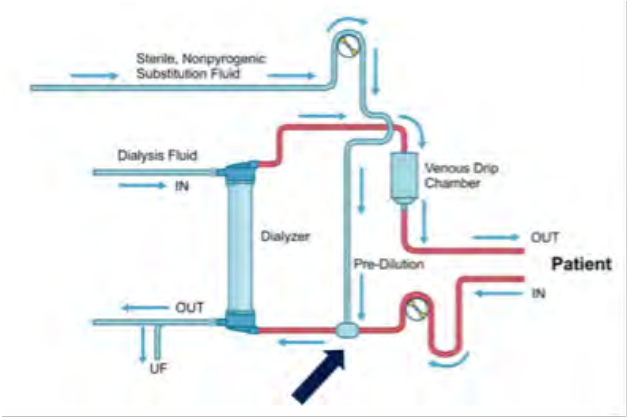


Figure 2.9 | Pre-dilution hemodiafiltration.

Achieving equivalent solute clearances in pre-dilution HDF requires a substitution volume approximately twice as large as that used in post-dilution HDF due to the dilution of solutes entering the hemodialyzer. In Asia-Pacific countries, pre-dilution HDF is widely used, representing 80 to 90% of HDF-treated patients in Japan, where lower blood flow rates are traditionally applied, favoring its use.

2.5c Mixed-dilution HDF. The substitution fluid is infused simultaneously at different rates into the extracorporeal circuit, with approximately 80% delivered upstream (pre-dilution) and 20% downstream (post-dilution) of the dialyzer (Figure 2.10).

Implementing mixed-dilution HDF requires specialized equipment. Specific blood tubing is needed to facilitate the dual infusion of substitution fluid, and a non-standard dialysis machine equipped with an additional pump is necessary to regulate the separate flows for pre- and post-dilution infusion.

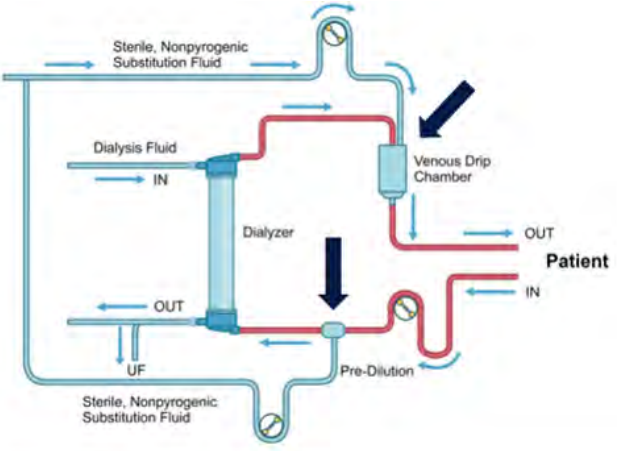


Figure 2.10 | Mixed-dilution hemodiafiltration.

This added complexity limits its widespread adoption. Mixed-dilution HDF represents a sophisticated modality that seeks to balance the strengths of pre- and post-dilution techniques. Optimizing fluid infusion distribution provides effective solute removal while reducing some of the operational challenges associated with other HDF modalities.

2.4d Mid-dilution HDF: Mid-dilution HDF is a non-conventional modality that employs a specially designed dialyzer with a unique inlet port for substitution fluid, enabling a combination of pre-dilution and post-dilution modes within the same treatment session (Figure 2.11). This approach leverages the advantages of both dilution strategies while addressing some of their respective limitations.

The dialyzer used in mid-dilution HDF features two distinct high-flux fiber bundles housed within the same unit: an outer annular region and an inner core region. These two compartments are separated by a specially designed header cap, which facilitates the sequential flow of blood and substitution fluid through the dialyzer.

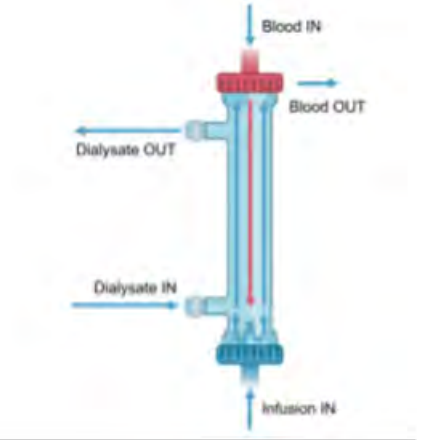
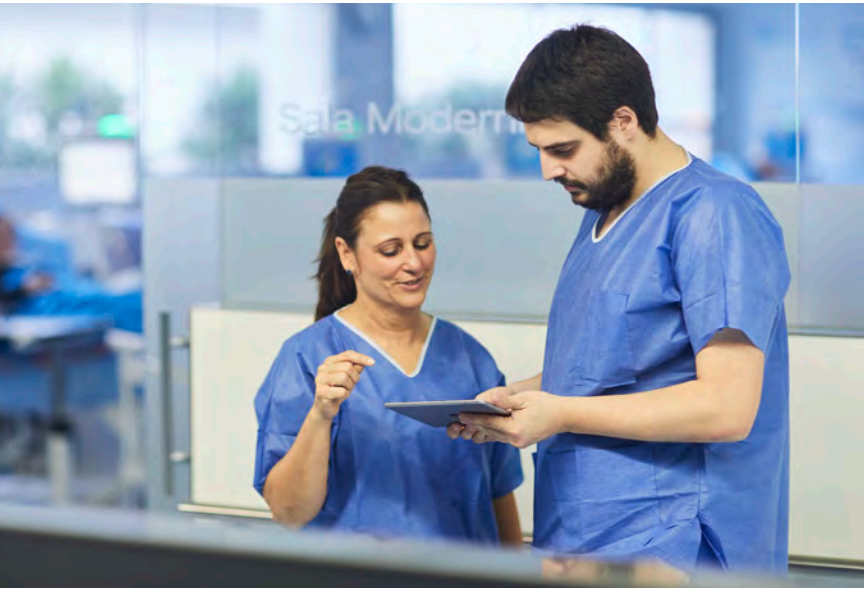


Figure 2.11 | Mid-dilution hemodiafiltration.

Mid-dilution HDF represents an innovative approach to combining the benefits of pre- and post-dilution modalities. However, the complexity of this setup and the requirement for specific dialyzer designs limit its accessibility and widespread application in routine clinical practice.

Chapter 3
Filtration Fraction



Filtration Fraction

The Filtration Fraction (FF) represents the fraction of plasma water filtered out of the blood across the dialysis membrane during treatment.

FF is the ratio between the convective volume and the plasma water flow rate:

$$FF(\%) = Q_{UF}/Q_{plasma} \quad [Q_{plasma} = Qb \times (1\text{-}Hct) \times (1\text{-}TP_{plasma})]$$

Q_{UF} = Convective volume (fluid removal and substitution fluid) in mL/min

Q_{plasma} = Plasma water flow rate, calculated from blood flow rate (Qb), hematocrit (Hct), and plasma protein concentration (TP_{plasma})

Higher blood flow rates increase the plasma water flow, reducing the relative FF for a given UFR.

In post-dilution HDF, the efficiency and safety of convective clearance are strongly influenced by the rheological properties of blood. Elevated hematocrit, albumin concentration, plasma fibrinogen, and lipid levels are known to increase blood and plasma viscosity. This increased viscosity reduces the mobility and flow of plasma water through the dialyzer membrane, thereby elevating the FF.

Higher vascular refilling capacity enhances total ultrafiltration.

A simplified version of the FF calculation exclusively divides the liters of convective volume/session (substitution fluid + net ultrafiltration) by the liters of blood volume processed during the session:

FF (%) = Convective Volume (L) / Blood Volume Processed (L)

Operating at the highest possible FF achieves the maximum substitution volume per treatment.

The recommended FF in HDF is typically 25–30%, depending on the mode of HDF (e.g., pre-dilution or post-dilution). A FF beyond 35% in

post-dilution HDF can lead to hemoconcentration, increasing the risk of clot formation, membrane fouling, reduced efficiency, and loss of dialyzer surface area. Continuous monitoring is mandatory to enable prompt automated intervention when necessary.

If the FF is fixed at the beginning of an HDF treatment and remains constant throughout the treatment, then the ultrafiltration in the form of net volume removal will increase the FF, leading to membrane fouling, risk of clotting, and loss of dialyzer surface area (28).

A salient challenge in designing an HDF platform is the ability to dynamically prescribe substitution fluid volume to maintain a FF compatible with efficient membrane performance while maximizing convective volume clearance.

A significant milestone in HDF was the development of a dialyzer stress test performed during dialysis. This TMP-based analysis assesses membrane stress caused by ultrafiltration and enables continuous adjustment of the infusion rate. In addition to the above-described TMP analysis, FME designed a biofeedback mechanism (AutoSub *plus*) that additionally analyzes information about the pressure modulations that are generated by the peristaltic blood pump. These pressure modulations propagate through the capillaries of the dialyzer and are assessed downstream. The incremental attenuation of the pressure amplitude reflects an increase in the membrane stress (28).

Those two advanced control mechanisms analyze dialyzer pressure measurements, facilitating an appropriate response and individualizing and maximizing the substitution infusion rate in real time. Furthermore, these innovations have substantially reduced the complexity of online HDF while enhancing intradialytic infusion efficiency in routine clinical practice (11, 28).

Chapter 4

Hemodiafiltration and Solute Clearances

Chapter 4

Hemodiafiltration and Solute Clearances

In 2003, the European Uremic Toxins (EUTox) working group introduced a uremic toxin classification based on the physicochemical properties influencing their clearance during conventional HD (65). The uremic solutes are broadly categorized into three major classes (66, 67):

Small water-soluble compounds (WSCs; <500 Da): These include compounds like urea, creatinine, uric acid, guanidino compounds efficiently removed by conventional HD due to their ease of diffusion driven by concentration gradients across the dialysis membrane. Conventional HD effectively removes them through diffusion, which serves as the primary transport mechanism.

Middle molecular weight substances (MMW, 0.5–40 kDa): Examples are β2M (11.8 kDa) and parathyroid hormone (9.5 kDa). MMWs are less effectively cleared by low-flux membranes and require HF with high-flux membranes for efficient removal from the patient's blood. The removal of MMW solutes relies on convection, where solute transport occurs via solvent drag caused by the TMP gradient.

Protein-Bound Uremic Toxins (PBUTs): This category includes molecules with low molecular weights, such as indoxyl sulfate and p-cresyl sulfate, which are characterized by their strong affinity for plasma proteins, particularly albumin, with binding rates exceeding 80%. Despite their low molecular weight, these PBUTs present a significant challenge for removal, as only the free (i.e., unbound) fraction can pass through the dialysis membrane (68).

By combining the mechanisms of HD and HF, HDF harnesses the enhanced clearance of larger solutes provided by HF while maintaining the high clearance of smaller solutes achieved through HD. This integration allows HDF to offer superior solute removal across a broader range of molecules than any other dialysis modality except for kidney transplantations (Figure 4.1).

HVHDF is particularly effective at removing middle molecules—solutes with molecular weights typically between 500 and 60,000 Da—that are inadequately cleared by conventional HD. Removing these molecules

improves patients' clinical profiles, addressing systemic inflammation, cardiovascular risks, dialysis-related amyloidosis, and other long-term complications associated with CKD, as outlined in Chapter 6. HVHDF is critical in ensuring these solutes are efficiently cleared.

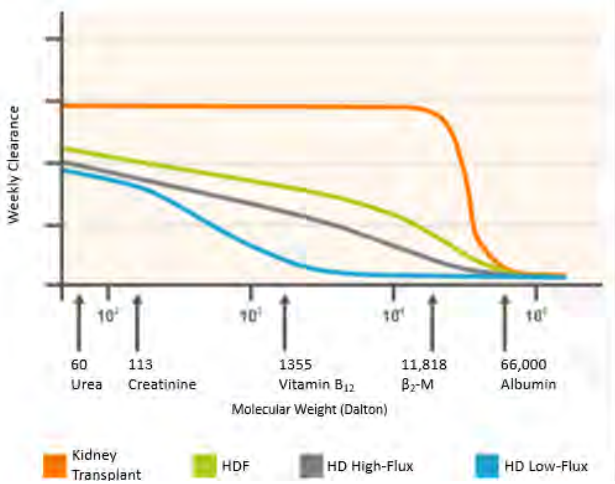


Figure 4.1 | Schematic weekly clearance of urea, creatinine, vitamin B12, and *β*2-microglobulin with different kidney replacement therapies.

Urea (60 Da): Urea clearance is significantly enhanced with HVHDF compared to conventional HD, depending on the volume of substitution fluid utilized (30, 69-73). For instance, the European Dialysis Outcomes and Practice Patterns Study (DOPPS) demonstrated that patients undergoing thrice-weekly HVHDF with substitution fluid volumes between 15.0 and 24.9 liters per session achieved higher Kt/V urea levels compared to patients receiving conventional HD (30). These findings highlight the potential of high-efficiency HDF to optimize small-molecule removal through adequate convective volume delivery, providing an effective alternative to conventional dialysis methods.

It is crucial to emphasize that the enhanced urea removal and the consequently higher Kt/V observed in patients treated with HVHDF, compared to those receiving high-flux HD, should never be used as a rationale for reducing dialysis treatment time.

Dialysis duration remains an independent risk factor for mortality, irrespective of the efficiency of solute clearance (74-76). While HVHDF provides superior clearance of uremic toxins compared to conventional HD, optimizing patient outcomes requires a holistic approach beyond Kt/V values. Shortening treatment time may counteract the benefits of HDF by compromising hemodynamic stability, fluid balance, and overall metabolic control (77, 78). Thus, implementing HVHDF should enhance both clearance and treatment adequacy rather than being used as a justification for shortening dialysis duration.

In addition, Canaud et al. highlighted that, by optimizing HDF prescriptions by incorporating automated ultrafiltration and substitution control, HVHDF can deliver a higher dialysis dose for small- and middle-molecule uremic compounds without increasing dialysis fluid consumption. This can be achieved by maintaining a high blood flow rate (i.e., >350 ml/min) and reducing the dialysate flow/blood ratio to 1.2 rather than 1.4, 1.5, or higher (29). Additionally, at equal dialysis doses, dialysis fluid consumption is significantly reduced, showing that HVHDF offers greater efficiency and environmental sustainability compared with high-flux HD (29).

Phosphate (95 Da): Phosphate removal during HDF is increased by 15–20%, enabling a reduction in the required doses of oral phosphate binders compared to conventional HD (56, 79-84). However, the impact on predialysis phosphatemia is modest, with reductions typically less than 15%. This limited effect is attributed to several factors, including increased dietary protein and phosphorus intake in patients transitioning to HDF due to improved appetite (37, 83, 85, 86). Additionally, phosphorus exhibits distinct removal kinetics compared to urea, as its clearance reaches a plateau phase beyond which further reductions in serum phosphate levels do not occur (86-88). A rebound in plasma phosphorus levels is also observed following the end of the dialysis session, a phenomenon seen in both HD and HDF (89).

***β*2-microglobulin** (~11,800 Da): In patients with ESKD, serum β2M accumulates and precipitates, forming fibrillary structures and amyloid deposits in bones, periarticular tissues, vessel walls, and internal organs, especially the heart. Elevated levels of β2M have been strongly associated with dialysis-related complications, such as amyloidosis, which can contribute to joint pain and carpal

tunnel syndrome, and with adverse cardiovascular and infectious outcomes. HDF demonstrates superior efficacy in removing β2M, when compared to conventional HD (59, 90-92) with a significant reduction in its circulating concentrations over a mid-term period (59, 93, 94). By lowering β2M concentrations, HDF addresses a key biomarker of uremic toxin accumulation and mitigates associated inflammatory and structural complications.

HDF is the most efficient KRT method to remove β2M and middle molecules, twice as much compared with high-flux HD. Ward et al. showed that, by highly efficient HDF operative conditions, the β2M clearance obtained was 73 ml / min, which means that the β2M mass removed during the 4-hour session was close to 200 mg per session (600 mg per week) (95). Considering that the clearance of β2M exhibits a linear relationship with convective volume, it can be anticipated that HVHDF offers the most effective means of removing β2M (96). This approach may be recommended for patients with β2M levels ≥ 27 mg/L to reduce the risk of mortality (59). It is also recommended for those with symptomatic manifestations of amyloidosis that significantly affect their quality of life, and cases such as arthropathy, bone cysts with pathologic fractures, carpal tunnel syndrome, systemic involvement, and symptomatic autonomic dysfunction (97).

A comprehensive meta-analysis of the effectiveness of high-flux HD and convective dialysis modalities, including HDF and HF, in removing β2M, was published in 2018 (59). Given the discrepancies in the literature regarding β2M clearance and the clinical benefits of different dialysis modalities, the authors of this meta-analysis sought to evaluate the determinants of effective β2M removal based on a systematic review of published studies. The analysis included 69 studies spanning from 2001 to 2017, incorporating data from 1,879 patients and 6,771 clearance measurements. Using a random effects meta-analysis and meta-regression model, the authors examined dialysis-related parameters such as membrane composition, modality, blood and dialysate flow rates, and substitution fluid rates (59). They found that while conventional high-flux HD achieved an average β2M clearance of 48.75 mL/min, convective therapies significantly outperformed this, with an average clearance of 87.06 mL/min. HDF, in particular, provided enhanced clearance, underscoring its potential superiority in removing MMW toxins. Notably, membrane material emerged as a key determinant of β2M clearance. High-flux

dialyzers composed of polyarylethersulfone exhibited superior β2M clearance in high-flux HD, whereas polysulfone (PS) membranes were associated with better performance in convective therapies such as HDF. The study also highlighted the role of blood flow and substitution fluid rates in optimizing β2M removal. Higher substitution fluid rates in post-dilution HDF resulted in superior clearance, while dialysate flow rates were not found to be a significant factor in enhancing β2M removal.

One intriguing finding was the substantial contribution of adsorption to β2M clearance, particularly when comparing blood-side versus dialysate-side measurements. Adjusted dialysate-side β2M clearances were significantly lower than whole blood clearances, suggesting that membrane adsorption plays a crucial role in trapping β2M beyond diffusive and convective mechanisms. The study found no clear secular trend indicating improved β2M clearance over time, indicating that, notwithstanding improved dialysis efficiency, limitations persist in removing β2M effectively (59).

Pre-dialysis serum *β*2M concentrations may not differ between HDF and high-flux HD (60). The primary limitation in β2M removal during post-dilution HDF is not due to the clearance capacity of the hemodiafilter itself but to the resistance within the patient's body to mass transfer. This resistance arises from the interaction between the patient's physiology and the dialysis system, which restricts the mobilization of β2M from tissue stores into the bloodstream for removal (98). During dialysis, a concentration gradient develops between well-perfused areas, where β2M is readily available for clearance, and deeper, poorly perfused compartments, where its movement is restricted. This phenomenon, known as the compartmentalization effect, results in an apparent sequestration of β2M within the body, limiting the efficiency of its removal even in HVHDF (98). Following dialysis, the β2M that remained in remote compartments begins to redistribute into circulation, causing a post-dialysis rebound in serum levels. The extent of this rebound reflects the imbalance created during the session and underscores the challenge of eliminating β2M (98).

Parathyroid Hormone Fragments (~9,000 Da), and **Fibroblast Growth Factor 23** (~32,000 Da) are implicated in CKD bone metabolism alterations. Elevated levels of these molecules contribute to CKD-related mineral and bone disorders (CKD-MBD), leading

to complications such as renal osteodystrophy and vascular calcification. By effectively reducing their plasma concentrations, HVHDF may play a role in mitigating the progression of CKD-MBD and its associated complications and may attenuate the need for calcimimetics (86, 99-103).

Leptin (~16,000 Da) is elevated in CKD and contributes to metabolic dysregulation, appetite suppression, and inflammation. It is implicated in ESKD patient malnutrition and anorexia (104, 105). A study by Kim et al. reported that HVHDF significantly reduces serum leptin levels compared to conventional low-flux HD, resulting in reduced circulating concentrations in HDF-treated patients (105, 106).

Inflammation is believed to contribute to the development and progression of other common complications in ESKD patients, including atherosclerosis, protein-energy wasting, and heart-related conditions. By lowering circulating levels of **inflammatory markers**, HDF may help mitigate the systemic inflammation commonly seen in CKD in adults and children (67, 79, 100, 107-113).

- **Pro-inflammatory Cytokines** (e.g., Interleukin-6 ~26,000 Da, Tumor Necrosis Factor-alpha ~17,000 Da) contribute to systemic inflammation and cardiovascular morbidity.
- **Complement Activation Products** (e.g., C3a, C5a ~8,000–15,000 Da, Adpsin ~24,000 Da) linked to inflammation and immune system dysregulation.
- **Angiogenin** (~14,000 Da) is elevated in CKD and is associated with vascular remodeling and inflammation.
- **Alpha-1-acid glycoprotein** (41,000-43,000 Da), also known as orosomucoid, is an acute-phase plasma protein mainly produced by the liver. It is part of the body's response to inflammation, infection, or trauma. Higher levels of alpha-1 acid glycoprotein predict future lower albumin levels in HD patients (114); HDF reduces its plasma concentration (115).

Advanced Glycation End Products (AGEs, >10,000 Da) are associated with oxidative stress, vascular damage, and cardiovascular complications. Their plasma values are reduced in diabetic and non-diabetic ESKD patients treated by HVHDF (79, 116).

HVHDF effectively removes **various MMW substances**, which may help mitigate comorbidities commonly associated with adverse

clinical outcomes in patients with ESKD. By targeting these uremic toxins, HVHDF offers a therapeutic advantage in improving the clinical profile and overall prognosis for ESKD patients.

- **Homocysteine** (135 Da): Approximately 20–30% of homocysteine in the blood is bound to albumin, thereby reducing its free fraction. Elevated levels of homocysteine are frequently observed in ESKD patients. Hyper-homocysteinemia contributes to endothelial dysfunction, oxidative stress, and thrombogenesis, increasing the risk of atherosclerosis and cardiovascular events (117). Badiou et al. observed a significantly higher removal of homocysteine with HDF compared with standard HD (118).
- **Insulin** (~5,800 Da, monomeric form, bound forms are higher) accumulates due to reduced renal clearance, contributing to disturbances in glucose metabolism. HDF might preserve insulin sensitivity in non-diabetic patients on kidney replacement therapies or improve insulin resistance in diabetic patients (119).
- **Free Hemoglobin Fragments** (~17,000 Da) increase during intravascular hemolysis. These fragments are often associated with complications if not rapidly cleared, including oxidative damage, vascular dysfunction, inflammation, cytotoxicity, and kidney injury (120).
- **Myoglobin** (~17,000 Da) is released in case of muscle injury or rhabdomyolysis-related drugs, toxins, infections, muscle ischemia, electrolyte and metabolic disorders, genetic disorders, and temperature-induced states such as neuroleptic malignant syndrome (NMS) and malignant hyperthermia (115, 121-123).
- **Retinol-Binding Protein 4** (~21,000 Da) accumulates in CKD and may contribute to insulin resistance and metabolic disturbances (124, 125).
- **Growth Hormone** (~22,000 Da) is elevated in CKD and is associated with insulin resistance and metabolic disorders (126).
- **Free Kappa and Lambda Immunoglobulin Light Chains** (~22,000 Da) at high levels can indicate multiple myeloma or other plasma cell dyscrasias. FLCs contribute to chronic inflammation, potentially increasing the risk of bacterial infection and vascular calcification (115, 127).
- **Transforming Growth Factor Beta** (~ 25,000 Da) promotes fibrosis and vascular calcification in CKD (128).

- **Hepcidin** (~25,000 Da) is a key regulator of iron metabolism, and elevated levels contribute to anemia and iron dysregulation. 3-Carboxy-4-methyl-5-propyl-2-furanpropionic acid, a protein-bound erythropoietic inhibitor, can be reduced in HDF, mainly when using protein-leaking high-flux membranes (129, 130).
- **Alpha-1 Microglobulin** (~26,000 Da) is a marker of tubular injury, accumulates in CKD and contributes to oxidative stress (131).
- ***β*-trace Protein** (23,000-29,000 Da), also known as prostaglandin D synthase or lipocalin-type prostaglandin D synthase, is a small glycoprotein with multiple biological roles. It functions as an enzyme catalyzing the conversion of prostaglandin H2 to prostaglandin D2. It is a biomarker of glomerular filtration function as well as a potential predictor of adverse cardiovascular outcomes (132). HDF reduces its plasma concentration (115).

Protein-Bound Toxins: Conventional HD primarily targets small, water-soluble solutes through diffusion, whereas HDF, due to its convective transport, facilitates superior clearance of protein-bound and larger uremic toxins. Ronco et al. showed a more significant reduction in both free and PBUTs in post-dilution online HDF compared to pre-dilution HDF (133). Toxins such as indoxyl sulfate and p-cresyl sulfate, implicated in cardiovascular morbidity and progression of CKD, are more effectively reduced with HDF. Evidence suggests modest improvements in the removal of protein-bound solutes like p-cresyl sulfate and indoxyl sulfate (134). 3-Carboxy-4-methyl-5-propyl-2-furanpropionic acid, a protein-bound erythropoietic inhibitor, can be reduced in HDF, mainly when using protein-leaking high-flux membranes (129, 130).

Chapter 5

Dialysate and Substitution Fluid Quality in Hemodiafiltration

Chapter 5

Dialysate and Substitution Fluid Quality in Hemodiafiltration

In online HDF therapy, the dialysis machine simultaneously generates both dialysate and substitution fluid on demand. Although these are distinct fluids, they share the same electrolyte composition.

Dialysate is ultrapure and flows countercurrent to the blood within the conventional dialysate compartment of the hemodialyzer. Substitution fluid is sterile and non-pyrogenic, and it is infused directly into the extracorporeal blood circuit to compensate for fluid removal.

HDF achieves enhanced clearance by removing large plasma water volumes via ultrafiltration, which must be replenished isovolumetrically with sterile substitution fluid. The introduction of ultrapure dialysate and substitution fluids, produced through cold sterilization, has been a pivotal advancement, enabling the routine delivery of HVHDF with optimal safety and efficacy.

Online HDF involves the generation of dialysate and substitution fluid through multiple purification processes, including reverse osmosis and sterilizing ultrafilters. These purification steps ensure that the fluids are sterile and non-pyrogenic. Figure 5.1 illustrates the method for generating ultrapure dialysis and sterile substitution fluids, essential for maintaining fluid balance during online HDF. Patients are directly infused with sterile substitution solutions, making stringent water treatment and a comprehensive quality control process critical for providing non-pyrogenic fluids of consistent and optimal quality.

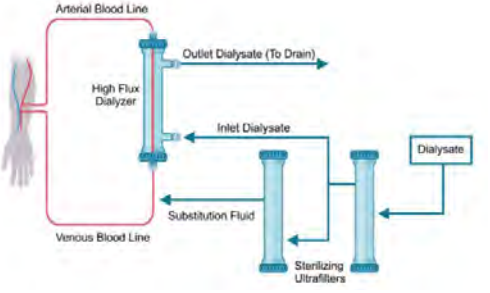


Figure 5.1 | Procedure for generating ultrapure dialysate and sterile substitution fluids.

In the U.S., the standards for ultrapure dialysis water are established by the Association for the Advancement of Medical Instrumentation (AAMI). They are incorporated into the regulatory framework by the Centers for Medicare & Medicaid Services (CMS). CMS has incorporated by reference the American National Standards Institute (ANSI)/AAMI RD52:2004 (135, 136) within its federal regulations, the current minimum regulatory requirement with which U.S. dialysis providers must comply (Table 5.1).

In some cases, dialysis providers may contract a third party to survey their facilities on behalf of CMS. The National Dialysis Accreditation Commission (NDAC) has incorporated the more stringent ANSI/AAMI/ISO 23500-2019 recommendations into its accreditation standards, with a particular focus on water and dialysate quality in dialysis facilities (137).

The **ANSI/AAMI/ISO 23500-2019** replaced the ANSI/AAMI 2014 version and comprises a comprehensive set of international standards developed collaboratively by AAMI, ANSI, and the International Organization for Standardization (ISO) (138). These standards provide guidance on the preparation and quality management of fluids used in HD and related therapies. Part 5 of this series, titled "Quality of Dialysis Fluid for Hemodialysis and Related Therapies," specifies the minimum chemical and microbiological quality requirements for dialysis fluids (139). It encompasses dialysis fluids used for HD and HDF, including substitution fluids for HDF and HF. This part ensures that the dialysis fluids meet stringent quality standards to safeguard patient health during treatment.

The sterile substitution fluid preparation begins with tap water, which undergoes rigorous pre-treatment through filters to eliminate microparticles, as well as organic and inorganic impurities. The filtered water is then processed through a reverse osmosis system, ensuring that the water meets the recommended chemical and microbiological quality standards for dialysis. The treated water is subsequently mixed with high-quality acid and bicarbonate concentrates within a hygienically designed and well-maintained flow path to produce standard dialysis fluid.

Standard dialysis fluid must comply with stringent microbiological quality recommendations, requiring a bacterial count of <100 CFU/mL bacterial count and an <0.50 EU/mL endotoxin level.

The DIASAFE®*plus* retains circulating bacteria, bacterial cell walls, and endotoxins, ultrafiltering the dialysis fluid and thus enabling the preparation of ultrapure dialysis fluid and sterile, non-pyrogenic substitution fluid. To achieve ultrapure quality, the standard dialysis fluid is further ultrafiltered using an ultrapure filter, resulting in ultrapure dialysate with bacterial counts <0.1 CFU/mL and endotoxin levels <0.03 EU/mL. This **ultrapure dialysate** serves as the foundation for performing both high-flux HD and HDF.

For online HDF, the ultrapure dialysate is converted into a sterile substitution fluid by passing it through a second sterile, quality-controlled ultrafilter positioned within the fluid pathway of the dialysis machine.

This final conversion ensures the substitution fluid meets the highest sterility assurance level (SAL) of 6 magnitudes, reducing viable bacterial contamination by 1,000,000. While sterility cannot be precisely quantified due to practical testing limitations, the substitution fluid must be free from viable bacteria and have an endotoxin level of <0.03 EU/mL, making it non-pyrogenic and suitable for infusion into patients (Table 5.1).

Test	AAMI RD52:2004 (CMS Adoption)	ISO/ANSI/AAMI 23500-5; 2019
	Limit	Limit
Dialysate Water		
Total microbial count (CFU/ml)	<200	<100
Endotoxin concentration (EU/ml)	<2	<0.5
Ultrapure Fluid		
Total microbial count (CFU/ml)	<0.1	<0.1
Endotoxin concentration (EU/ml)	<0.03	<0.03
Sterile substitution fluid		
Total microbial count (CFU/ml)		Sterile
Endotoxin concentration (EU/ml)		<0.03

Table 5.1 | Different colony forming units (CFU) and endotoxin concentrations in dialysate water, ultrapure dialysate, and sterile substitution fluid according to the AAMI RD52, and ISO/ANSI/AAMI 23500-5; 2019.

This rigorous process ensures the safety and efficacy of the fluids used in online HDF, thereby reducing the risk of pyrogenic reactions and chronic inflammation in dialysis patients. It also minimizes exposure to microbiological and endotoxin contaminants, which can contribute to cardiovascular and systemic complications.

In the 5008 dialysis machines, the cold sterilization of the online-produced substitution fluid is achieved via a two-stage ultrafiltration of the dialysate water using sterilizing ultrafilters (DIASAFE*plus*$_{US}$, Figure 5.2) (1, 140). With their large surface areas (2.2 m^2), the filters have a high adsorption capacity to eliminate endotoxins that may be present in dialysis fluids (Figure 5.2) (1). The endotoxins are retained onto polysulfone predominantly through hydrophobic-hydrophobic interaction, that is, the hydrophobic part of the endotoxins (the fatty acid chain of the lipid A molecule) binds with the hydrophobic domains of the polysulfone polymer (140, 141). The filters can be repeatedly disinfected and used for up to 100 treatments or up to 12 weeks (1, 140).

Figure 5.2 | Fresenius 5008X and DIASAFE*plus*$_{US}$ Dialyzers.

The ONLINE*plus* system prevents residual endotoxins and microorganisms from entering the substitution fluid. The dialysis machine uses an automated integrity test, a leakage test performed before each dialysis treatment to ensure the integrity and safety of the DIASAFE*plus*$_{US}$ ultrafilters (1).

This test is a crucial quality control step, particularly in online HDF, where the ultrafilters are responsible for producing sterile and non-pyrogenic substitution fluid from ultrapure dialysate (Figure 5.3).

Figure 5.3 | ONLINE*plus* system

Chapter 6

Clinical Evidence Supporting the Benefits of Hemodiafiltration

Chapter 6

Clinical Evidence Supporting the Benefits of Hemodiafiltration

HDF has gained increasing recognition as a superior KRT compared to conventional HD, primarily due to its enhanced efficacy in solute removal and improved clinical outcomes.

In recent reviews, the advantages of HDF to conventional HD were summarized (Table 6.1) (27, 28, 86, 142, 143). This section reviews the clinical evidence supporting the benefits of HDF, focusing on its impact on short-, middle-, and long-term outcomes, as well as morbidity and mortality, which serve as definitive clinical endpoints.

Summary of HDF / HVHDF Benefits
Short-Term Intermediate Outcomes
• Enhanced toxin clearance • Improved hemodynamic stability • Reduced sudden death risks • Reduced inflammation and oxidative stress • Better anemia management • Residual kidney function protection • Reduced incidence of intradialytic cramps • Reduction in skin hyperpigmentation
Middle-Term Intermediate Outcomes
• Reduced risk of amyloidosis and joint pain • Improved nutritional status • Reduced infection risk and hospitalization • Cardiovascular benefits • Improved neurological symptoms • Improved quality of life
Long-Term and Hard Outcomes
• Lower all-cause and cardiovascular mortality • Dose-response relationship

Table 6.1 | HDF and high-volume HDF effects on intermediate and final clinical outcomes.

6.1 | Short-Term Intermediate Outcomes

HDF demonstrates several short-term physiological and biochemical benefits:

6.1.1 - Enhanced toxin clearance

HDF, and mainly post-dilution HVHDF, effectively removes a broader spectrum of uremic toxins compared to conventional HD, particularly middle- and large-molecular weight solutes that are poorly cleared by diffusion alone. Through its combined diffusion and convection mechanism, HVHDF has comparable/superior clearance of small molecules (e.g., urea, creatinine). HDF surpasses HD in eliminating middle molecules, such as β2M, and large-molecular-weight uremic toxins, and enhances the clearance of PBUTs, contributing to improved patient outcomes. Please refer to **Chapter 4 | Hemodiafiltration and Solute Clearances** for more information.

6.1.2 - Improved hemodynamic stability

Efforts to enhance outcomes for ESKD patients increasingly focus on minimizing hemodynamic instability both during (intradialytic) and around (peridialytic) the dialysis procedure. **Intradialytic hypotension (IDH) can no longer be regarded as a benign condition.** Clinical and subclinical IDH is associated with myocardial stunning and hypoperfusion of critical organs, including the brain, gut, and kidneys. Its chronic manifestations have been linked to a range of adverse outcomes, including symptomatic distress, inadequate dialysis efficacy, increased risk of vascular access thrombosis, accelerated decline in residual kidney function, cardiovascular instability, and heightened mortality (77). These complications primarily result from repeated episodes of organ hypoperfusion, leading to cumulative organ damage and long-term physiological deterioration (144-146).

During HD, fluid removal occurs primarily from the intravascular compartment. **When the UFR exceeds the plasma refilling rate from both extracellular and intracellular compartments, a reduction in circulating blood volume occurs.** This effect is further amplified by cardiopulmonary redistribution of blood flow during dialysis and by dilating capacitance vessels due to dialysis-induced thermal stress, which increases the volume of unstressed blood and consequently reduces venous return.

In contrast to healthy individuals, who can tolerate a plasma volume decline of up to 15%—and in some cases even 25%—without significant clinical manifestations, patients with ESKD are susceptible to IDH even with a much smaller reduction in blood volume (147). This heightened vulnerability suggests an impairment in the normal compensatory mechanisms that regulate hypovolemia in this patient population.

The development of IDH is influenced by multiple factors, including interdialytic fluid accumulation, cardiovascular disease, antihypertensive therapy, and the physiological demands imposed by HD. IDH episodes arise when one or more compensatory mechanisms fail to respond to hypovolemia adequately. A rapid decline in plasma osmolality during the early phase of dialysis, mainly due to urea removal, can promote the intracellular shift of extracellular water, reducing plasma refilling (147). **The failure of the sympathetic nervous system to activate appropriately can impair acute hemodynamic responses to hypovolemia, further exacerbating IDH** (148, 149). Inadequate venoconstriction and insufficient arteriolar resistance adjustments further contribute to hemodynamic instability (148, 149). Additionally, cardiac compensation may be compromised due to reduced ventricular preload, diminished myocardial contractility, inadequate heart rate responses, and decreased cardiac output, all impairing circulatory homeostasis during dialysis (150).

The European Dialysis (EuDial) Working Group of the European Renal Association agreed that HDF does not reduce the frequency of IDH episodes compared to high-flux HD (60). However, EuDial also acknowledged that previous RCTs lacked a standardized definition of IDH, did not report dialysate temperatures (60) and provided limited documentation on antihypertensive therapy prescriptions and UFRs.

These methodological weaknesses have been addressed by evaluating data included in EuCliD (European Clinical Dialysis Database), a standardized electronic medical record system used in FME NephroCare clinics outside the United States (151, 152). Zoccali et al. conducted a study designed to emulate a RCT, analyzing 4,072 incident HD patients from FME EMEA NephroCare clinics who initiated antihypertensive drug treatment between January 2016 and December 2019 (153). While the study was not intended to demonstrate the direct impact of HDF on IDH risk, its findings

revealed that HDF, compared to standard HD, acted as an effect modifier (attenuator) of IDH risk, suggesting a potential protective role of HDF in improving hemodynamic stability (153).

The Italian Convective Study was a multicenter, randomized controlled trial involving 146 HD patients, assigned to HD (n=70), HF (n=36), and HDF (n=40) (154). The primary aim was to evaluate the effects of convective therapies (pre-dilution HF and HDF) on intradialytic symptomatic hypotension (ISH) and vascular stability, in comparison to standard HD. The results demonstrated a significant reduction in ISH with HDF (–50.9%, $p<0.001$) and a more modest decrease with HF (–18.4%, $p=0.011$), whereas patients on HD experienced a slight increase. Notably, pre-dialysis systolic blood pressure rose significantly in the HDF group, further suggesting improved hemodynamic stability (142, 143, 154).

Multiple studies have suggested that HDF is associated with a lower incidence of symptomatic IDH than HD. Additionally, HDF has demonstrated a direct effect in reducing the incidence of IDH episodes, independent of sodium balance improvements (154-156). These findings have been confirmed in multiple RCTs (37, 157, 158).

Given the multifactorial nature of IDH, **HDF appears to influence several of the underlying mechanisms of IDH, both directly and indirectly** (159, 160):

- One notable mechanism involves sodium retention influenced by the Gibbs–Donnan effect (159, 161). During online HDF sessions, sodium retention, driven by large convective volumes and its binding to albumin, increases blood osmolarity and facilitates fluid refilling from the interstitial compartment, contributing to hemodynamic stability (162). Since HVHDF requires the infusion of large substitution fluid volumes, a positive intradialytic sodium balance was postulated as a potential contributor to increased interdialytic fluid accumulation. However, despite concerns about potential hydro-saline overload, clinical trials have not observed persistent natremia (157). Chazot et al. have demonstrated this by a multicenter cross-sectional cohort study showing that post-dilution HVHDF is not associated with risk of fluid volume imbalance (163). Furthermore, better hemodynamic stability is not directly linked to improved sodium balance in HDF compared to high-flux HD (28, 164).

- It has been proposed that the infusion of an isotonic bicarbonate-buffered substitution solution may directly affect the endothelium, enhancing vascular refilling. Additionally, this process could influence the sodium balance within endothelial cells, thereby modulating vascular tone responses (27, 165, 166).
- Another possible factor is the cooling of blood during HDF sessions due to greater energy loss in the extracorporeal system (156, 167). This results in a lower core temperature and a negative heat balance, which may help reduce the frequency of IDH. However, in this respect, it must be noted that in isothermic treatments, the impact of HDF on IDH was no different from that during conventional HD (168) suggesting that multiple factors contribute to the hemodynamic benefits of HDF.
- Inflammatory responses triggered by exposure to the extracorporeal circuit, with complement activation and cytokine production, have traditionally been associated with IDH (169). Although advancements in membrane compatibility and the use of ultrapure water have reduced these effects, HDF appears to lower inflammatory markers further compared to conventional HD (170-172). However, a link between reduced inflammation and improved hemodynamic tolerance remains to be established.
- Additional mechanisms, including improved anemia management (173-175), improvement in nutritional status (175, 176), physical activity (177), enhancement of quality of life (176, 178-180), and protection of residual kidney function (181) may indirectly support hemodynamic stability in HDF patients. The combination of these factors highlights the multifaceted nature of HDF's benefits in managing IDH and improving overall patient outcomes during dialysis.
- Enhanced Volume Control: Convective clearance facilitates effective ultrafiltration, minimizing fluid overload while improving cardiovascular tolerance (86, 182, 183).

6.1.3 - Reduced sudden death risk

The EuDial Working Group of the European Renal Association agreed that, due to the low number of events in individual studies, differences in adjudication, age disparities, lack of data on pre-existing CVD, and the potential impact of electrolyte imbalances, no definitive conclusion can be drawn about the effects of HDF versus high-flux HD on sudden

cardiac death (SCD) (60). While no previous study on HDF has directly demonstrated a correlation between electrolyte imbalance and SCD, pre-dialysis serum potassium, calcium, and bicarbonate concentrations, as well as rapid electrolyte shifts, are possible causes of SCD. Dialysate electrolyte compositions varied among RCTs: potassium ranged from 1.5 to 3.0 mmol/L, calcium from 1.25 to 1.5 mmol/L, and bicarbonate from 25 to 37 mmol/L. In the FME EMEA NephroCare Clinics, strict medical control is applied regarding dialysate electrolyte prescriptions and blood electrolyte management in all ESKD patients undergoing extracorporeal therapies. Experience in determining whether HDF could reduce SCD more than high-flux HD was not analyzed. However, Vernooij et al. showed a statistically significant survival benefit for cardiac and cardiovascular deaths in those patients treated by HDF independently of the convection volume delivered (44). When convection volumes >23 L/session were achieved, the hazard ratio in the adjusted analysis was 0.62 (95% CI 0.40–0.97) (44).

6.1.4 - Reduced inflammation and oxidative stress

During each HD session, the patient's circulating blood exits the physiological protection provided by the endothelial cells lining the vascular system and comes into direct contact with the extracorporeal circuit. This exposure triggers a cascade of physical and chemical stimuli, leading to inflammatory and oxidative stress responses. The process begins with the venipuncture of the arteriovenous fistula and is perpetuated by the continuous interaction between the blood and the synthetic membrane of the extracorporeal HD circuit. These interactions have significant implications for both coagulation pathways and the immune system, contributing to systemic inflammatory responses and oxidative damage (184, 185).

HDF has been shown to mitigate systemic inflammation directly (171, 172) and oxidative stress (171, 172) compared to standard HD. This improvement is attributed to the use of ultrapure dialysis fluid, improved hemodynamic stability, enhanced anemia management, and the superior removal of medium- and large-molecular-weight substances, including inflammatory mediators. Although direct evidence from large-scale clinical trials remains limited, HVHDF is considered the "least inflammatory" KRT. The observed reduction in chronic inflammation likely contributes to the improved long-term survival outcomes associated with HDF.

By addressing key drivers of inflammation and oxidative stress, HDF offers a promising approach to enhancing cardiovascular health and patient outcomes in dialysis.

HDF significantly reduces systemic inflammatory and oxidative stress markers such as: high sensitivity C-reactive Protein (hsCRP) and Interleukin-6 (IL-6), Tumor Necrosis Factor-alpha, Complement Activation Product, Soluble CD40 ligand, Advanced Glycation End (AGEs) products, oxidized low density lipoprotein, pentraxin, and others. This has been attributed to the removal of middle molecules implicated in systemic inflammation and oxidative stress (67, 79, 100, 107-111, 116, 170-172). Convective transport in HDF reduces cytokine levels and inflammatory markers while downregulating proinflammatory monocyte subsets such as $CD14^+$ and $CD16^+$ (186). A reduction in systemic inflammation has been particularly notable in diabetic patients, potentially due to the downregulation of dendritic cell maturation and better control of the sympathetic nervous system (187). In a prospective pediatric study, Ağbaş et al. demonstrated that, after just three months of HDF therapy, total antioxidant capacity (TAC) increased significantly in children, both with and without residual renal function (171).

A study based on the randomized controlled CONvective TRAnsport STudy (CONTRAST) investigated the long-term effects of online HDF compared to low-flux HD on systemic inflammation, measured by hsCRP and IL-6, in patients with ESKD (170). The study followed 405 patients for up to three years, analyzing serial measurements of CRP and IL-6. A broader cohort of 714 patients was assessed for longitudinal changes in serum albumin levels. The results showed that patients undergoing HD exhibited a progressive increase in CRP and IL-6 levels over time, whereas levels remained stable in those treated with HDF. After adjustments for baseline variables, the annual rate of increase in CRP was found to be 20% higher in HD patients, while IL-6 rose by an additional 16% per year relative to those on HDF. The inflammatory advantage of HDF was most pronounced in anuric patients, suggesting that the absence of residual kidney function may amplify the benefits of convective clearance on systemic inflammation. The study provides robust evidence supporting the hypothesis that HDF mitigates systemic inflammation, particularly for CRP and IL-6, without adversely impacting nutritional status as reflected in albumin levels. These findings support the broader adoption of HDF

as a preferred dialysis modality for reducing inflammation-related complications in patients undergoing maintenance dialysis (143, 170).

6.1.5 - Better anemia management

HDF has shown significant potential benefits in optimizing anemia management in patients with ESKD (143). By effectively removing larger uremic molecules, reducing systemic inflammation and oxidative stress, improving the iron metabolism, and enhancing phosphate balance, HDF offers a multifaceted approach to improving treatment outcomes and reducing dependence on pharmacological interventions more efficiently than conventional HD (70, 188-193).

The mechanisms by which HDF influences anemia management are highlighted below.

- Enhanced removal of uremic toxins: HDF effectively removes larger uremic molecules that inhibit erythroid progenitor cells (194-196). For example, HDF with endogenous reinfusion (HFR) has demonstrated a reduction in the suppression of burst-forming unit-erythroid (BFU-E) proliferation (197) which plays a key role in red blood cell production.
- Reduction in systemic inflammation and erythropoiesis-stimulating agent (ESA) responsiveness: HDF, by lowering the systemic inflammation level, improves the ESA responsiveness (198). Indeed, HDF increases the clearances of inflammatory cytokines that suppress and affect precursor cells at different stages of erythropoiesis (52, 199). A reduction in systemic inflammation lowers hepcidin, leading to higher iron levels available for erythropoiesis.
- Improvement in Iron Metabolism and Utilization: Patients undergoing HDF have been found to require lower doses of ESAs, suggesting improved iron utilization and erythropoiesis efficiency (20). Elevated hepcidin levels in CKD patients contribute to functional iron deficiency, complicating anemia management. HDF has been shown to lower circulating hepcidin levels, thereby increasing iron availability for erythropoiesis and supporting a more sustained hematological response (200) minimizing the need for excessive iron supplementation. The REDERT study and a propensity-matched study of 3373 incident patients reported lower erythropoietin resistance index (ERI) and reduced hepcidin with HDF (173, 174). Together, these mechanisms indicate a more

favorable iron metabolism profile with HDF, potentially reducing the need for excessive iron supplementation.

- HDF improves phosphate removal more effectively than conventional HD, contributing to better parathyroid hormone (PTH) regulation. Given the interplay between phosphate homeostasis, PTH, and erythropoiesis, improved phosphate removal may contribute to more stable hemoglobin levels and reduced ESA requirements in HDF-treated patients (201, 202).
- Clinical studies have shown that HDF can prolong the lifespan of red blood cells compared to standard HD, resulting in more stable hemoglobin levels. One study reported a significant increase in red blood cell survival following a single HDF session (203).

The cumulative evidence suggests that HDF offers several advantages in the management of anemia compared to conventional HD. Patients in HDF therapy require lower doses of ESAs, suggesting improved iron utilization and erythropoiesis efficiency. The combined use of HDF with long-acting intravenous ESAs seems to benefit anemia management by reducing ERI (27). However, large-scale RCTs are needed to conclusively determine the magnitude of HDF's benefit for anemia in ESKD. The overall impact of HDF on anemia management appears to be particularly relevant for patients with inflammation-related ESA resistance, where the reduction in inflammation and improved iron metabolism may play a crucial role in optimizing treatment outcomes (143).

To illustrate the benefits of HVHDF on anemia management, we analyzed data from FME EMEA NephroCare clinics collected in June 2024, covering 16 European countries. To minimize potential bias and ensure a more accurate assessment, we excluded all patients with central venous catheters (CVCs), thereby preventing the inadvertent inclusion of individuals with undetected inflammation or infection associated with CVCs and enhancing the validity of our findings. The study included all patients aged 18 years or older with a body weight between 40 and 120 kg, a dialysis vintage of at least three months a blood flow rate exceeding 330 mL/min with arteriovenous fistula (AVF) or arteriovenous graft (AVG), and who had completed at least 12 out of 13 treatments in June 2024 (Table 6.2).

	HFD	HVHDF	HVHDF vs. HFD
Patients (n)	5,082	13,460	62.2%
Female (%)	37.1	36.2	-2.6%
Age (years)	65	64	-2.1%
Charlson Comorbidity Index (n)	3.9	4.1	3.9%
Dry Body Weight (Kg)	75.1	75.5	0.6%
Time On Dialysis (months)	71	83	14.1%
Weekly Treatment Time (min/week)	726	729	0.4%
Blood Flow (mL/min)	364	369	1.2%
Dialysate Flow (mL/min)	483	443	-9.0%
OCM single pool Kt/V	1.60	1.74	8.0%
Substitution Volume / session (L)		24.3	
Convective Volume / Session (L)		26.7	
C-Reactive Protein (mg/L)	10.33	8.64	-19.6%
Ferritin (ng/mL)	634	586	-8.2%
Pts with IV Iron therapy (%)	53	52	-1.2%
Monthly IV Iron dose (mg/month)	422	424	0.5%
Hb current month (g/dL)	11.2	11.2	0.4%
Pts with IV ESA therapy (%)	74.7	69.6	-7.2%
Monthly IV ESA dose (IU/month)	19,019	17,582	-8.2%
Albumin (g/dL)	4.1	4.0	-1.9%

Table 6.2 | Patients treated in FME EMEA NephroCare clinics by High-Volume Hemodiafiltration (HVHDF) and high-flux HD (HFD). Selection criteria adopted: Aged >18 years or older, body weight 40-120 kg, dialysis vintage >3 months, blood flow rate >330 mL/min with arteriovenous fistula or graft.

We gathered information from 18,542 prevalent patients, 5,082 in high-flux HD and 13,460 in post-dilution HVHDF. All patients received iron sucrose, with a target ferritin range of 450–650 ng/mL and a target hemoglobin range of 10–12 g/dL. The proportion of patients requiring ESAs was 7.2% lower in the HVHDF group, with an 8.2% reduction in average ESA dose compared to patients on high-flux HD. The findings of this real-world study suggest that HVHDF may enhance anemia management by improving the clearance of inflammatory mediators that inhibit erythropoiesis. However, further

analysis is required to confirm this effect while rigorously controlling for potential confounding variables.

6.1.6 - Residual kidney function protection

HDF indirectly contributes to better preservation of residual kidney function over time versus conventional HD (181, 204). Ultrapure dialysate and biocompatible dialysis membranes have been suggested as effective measures to preserve residual kidney function, potentially matching the outcomes seen with peritoneal dialysis. HDF, with its superior hemodynamic stability and ability to mitigate micro-inflammatory conditions, is theoretically poised to offer advantages in maintaining residual urine output over prolonged treatment durations. However, despite these theoretical benefits, robust evidence from large-scale observational studies or RCTs remains lacking to substantiate this hypothesis. Further research is warranted to elucidate the potential of HVHDF in this context.

6.1.7 - Reduced incidence of intradialytic cramps

Muscle cramps are a distressing complication of HD, affecting a significant percentage (33-86%) of ESKD patients, and 5-20% of dialysis sessions are accompanied by muscle cramps (205-207). These painful contractions, often occurring toward the end of a dialysis session, can lead to early termination of treatment, contributing to under-dialysis and negatively impacting patients' quality of life (208).

The exact mechanism underlying intradialytic muscle cramping remains unclear but is likely multifactorial. Potential causes include hemodynamic instability, electrolyte imbalances, and metabolic disturbances. Cramps are more frequent in patients experiencing IDH, those with high UFRs, or those whose target weight is not accurately set. Factors such as hypo-osmolality, tissue hypoxia, electrolyte disturbances, vitamin deficiencies, and elevated serum leptin levels have also been implicated (209-212). Additionally, plasma intact parathyroid hormone (IPTH) levels above recommended targets may increase the risk of cramping (213).

Despite numerous proposed interventions, no single treatment has proven universally effective. Preventive strategies focus on minimizing hemodynamic instability, particularly by optimizing target weight, UFRs, and dialysate composition. Higher dialysate sodium and individualized magnesium, calcium, and potassium levels may

help reduce cramping, though they come with trade-offs, such as increased thirst and interdialytic weight gain. Stretching exercises targeting affected muscle groups have been recommended as a first-line intervention. Other potential treatments include carnitine, vitamin E, and vitamin C supplementation, though evidence remains inconsistent (214).

HDF has been suggested as a potential way to reduce cramps. Some studies demonstrated a beneficial effect of HDF on health-related quality of life (HRQoL) in association with fewer episodes of intradialytic cramps (96). Karkar et al. found that post-dilution HDF significantly reduces the incidence of intradialytic cramps (178). Similarly, Morena et al. found a significantly lower incidence of sessions with muscle cramps ($p=0.03$) in elderly patients undergoing HDF (157). Children receiving HDF also had fewer incidences of cramps compared to those treated with HD (215).

However, direct evidence supporting the superiority of HDF in preventing cramps remains limited.

6.1.8 - Reduced skin hyperpigmentation

Online HDF has been associated with a significant decrease in skin hyperpigmentation among patients with ESKD, likely due to its superior clearance of β2-microglobulin and other pigmentary middle-molecular-weight toxins (e.g., melanin). Lin et al. reported improved skin pigmentation in ESKD patients with increased and more frequent HDF, though without objective colorimetric assessment (216). Moon et al. subsequently demonstrated that HDF significantly reduced skin pigmentation compared to low-flux HD, identifying HDF as an independent predictor of decreased melanin index in the forehead region (217). Shibata et al. confirmed that HD patients exhibited darker skin than healthy controls, and those on online HDF experienced notable skin lightening, coinciding with a reduction in β2M levels (218).

These findings suggest that MMW accumulation contributes to uremic skin changes and that HDF offers a dermatological benefit beyond traditional uremia management.

6.2 | Middle-term intermediate outcomes

Over months to years, HDF demonstrates sustained benefits that translate to improved patient well-being and fewer complications:

6.2.1 - Reduced risk of amyloidosis and joint pain

Multiple studies confirm that HDF effectively lowers β2M (59, 90-94), reducing the risk of dialysis-related amyloidosis (DRA), including carpal tunnel syndrome and related complications (142, 219).

DRA plays a contributory role in the widespread cardiovascular disease observed in patients with ESKD (59, 220, 221). The clearance of β2M exhibits a direct linear correlation with convective volume, making HVHDF the most effective modality for β2M removal (91, 222). This approach is particularly recommended for patients with β2M concentrations exceeding 27 mg/L, as this threshold has been associated with a reduced risk of mortality (86).

HVHDF is also indicated for individuals experiencing symptomatic DRA, particularly those presenting with severe manifestations such as arthropathy, bone cysts with pathological fractures, carpal tunnel syndrome, systemic involvement, and symptomatic autonomic dysfunction (86). Patients who transition from HD to HVHDF have experienced an increased range of motion in the extremities and reduced joint pain (86, 223).

6.2.2 - Improved nutritional status

HDF has been associated with improved appetite, increased dietary protein intake, and the preservation of lean body mass (142, 175, 224). High convective volume may improve nutritional status and help prevent protein-energy wasting in ESKD patients (175).

Many clinical studies have demonstrated that, indirectly, HDF improves nutritional status (175, 176). Malnutrition-Inflammation Complex Syndrome (MICS), a common condition among dialysis patients, significantly contributes to increased hospitalization and mortality rates (225). This syndrome involves anorexia and protein-energy wasting, driven by the accumulation of middle molecules and elevated levels of pro-inflammatory markers like leptin, IL-6, TNF-α, and IL-1β (226). These factors are closely associated with decreased albumin and pre-albumin levels, reduced muscle mass,

and diminished physical endurance, which collectively exacerbate the nutritional and functional decline of ESKD patients.

Leptin, a molecule frequently elevated in dialysis patients, plays a pivotal role in appetite suppression, metabolic dysregulation, and inflammation (104, 105). HVHDF has demonstrated greater effectiveness in removing leptin compared to conventional HD, potentially improving appetite regulation and nutritional status (105, 106).

Clinical evidence indicates that patients treated with HDF maintain lean tissue and body cell mass more effectively and achieve higher protein intake than those on high-flux HD. The superior convective clearances offered by HDF, particularly beneficial in inflammatory cachexia, are associated with improved dry weight, somatic protein status, and the mitigation of catabolic processes. By addressing the complex interactions of inflammation (227), malnutrition, and metabolic dysregulation, HDF shows promise in enhancing the clinical outcomes and quality of life for ESKD patients.

HDF may cause slight increases in the loss of amino acids, water-soluble vitamins, and trace elements; appropriate oral supplementation can help maintain nutritional balance (142, 228, 229).

6.2.3 - Reduced infection risk

HVHDF emerges as a promising therapy to mitigate infection risks and improve clinical outcomes for ESKD patients through enhanced removal of middle molecules and improved hemodynamic stability. ESKD patients are at significantly increased risk of infectious complications, which are the leading cause of hospitalizations and the second leading cause of death after cardiovascular conditions (230, 231). This elevated risk is closely linked to the immune dysfunction associated with CKD (232).

Uremia leads to innate and adaptive immune system impairment, including dysfunction of neutrophils and monocytes (233), depletion of dendritic cells, naïve and central memory T cells, and B cells (234). The uremic environment contributes to immune system dysfunction by accumulating medium and large uremic toxins. For instance, free light chains of immunoglobulins, retinol-binding protein-4 (RBP-4), fibroblast growth factor-23 (FGF-23), and alpha-1 acid glycoprotein reduce leukocyte activity through various mechanisms (226). Similarly,

degranulation-inhibiting protein (DIP) and granulocyte-inhibitory protein (GIP) impair glucose uptake and polymorphonuclear leukocyte chemotaxis, while complement factor D decreases immunocomplex clearance and inhibits granulocyte degranulation (227).

HD patients face additional risks due to their vascular access. Patients with CVCs are at higher risk (235-237). The shared environment of dialysis centers, where exposure to pathogens is heightened as well as poor hygiene, hypoalbuminemia, comorbidities, and underlying chronic infections further exacerbate the risk of infections (237-239). Notably, older age and diabetes also significantly increase susceptibility (237-240).

Although conventional HD therapies aim to mitigate some of these risks, they have shown limited success in reducing infection rates.

The EuDial Working Group of the European Renal Association agreed on the following consensus key points (60):

- HDF is associated with a similar risk of all-cause and infection-related hospitalizations as high-flux HD (60).
- HDF may be associated with a lower risk of infection-related mortality compared to high-flux HD (60).

The EuDial Working Group also reported in their consensus statement that, although the mechanisms are unclear, HDF may have a beneficial effect on immune function. HDF may enhance immune system function by facilitating the clearance of inflammatory cytokines and improving leukocyte function (143).

Several cytokines and inflammatory mediators, which are MMW substances, are removed by HDF. Furthermore, greater hemodynamic stability in HDF may reduce intestinal ischemia and bacterial translocation (60). Indeed, HVHDF has been associated with improved immune system outcomes. It effectively removes a broad spectrum of uremic toxins, including GIP, which has been implicated in immune suppression (241). Recent findings further emphasize the immune benefits of HDF. Sustained seroprotection and increased lymphocyte proliferation were observed in response to influenza A vaccination in chronic kidney patients undergoing HDF compared to HD (86, 242). HDF patients vaccinated against SARS-CoV-2 develop higher antibody levels and exhibit a more sustained immune response than those on HD (86, 243, 244).

The ESHOL clinical trial demonstrated a 55% reduction in infectious mortality for patients treated with HVHDF compared to those receiving high-flux HD (37, 86). Additionally, there was a 22% reduction in hospitalization rates for infections in the HDF group (37, 86). These benefits may result from improved clearance of immunosuppressive toxins and enhanced hemodynamic stability, which reduces episodes of intestinal ischemia and bacterial translocation (86, 245).

The CONVINCE study also highlighted HDF's potential to reduce infection-related mortality, including deaths from COVID-19. Patients treated with HVHDF had a lower risk of infection-related deaths compared to those on conventional HD (0.69; 95% CI, 0.49 to 0.96) (38).

In a **meta-analysis of five randomized controlled trials** (n=4,153), Vernooij et al. compared 2,083 patients treated with HDF to 2,070 patients receiving HD. **When the analysis was restricted to those achieving convection volumes greater than 23 liters, the adjusted hazard ratio for infection-related mortality (including and excluding COVID-19) was 0.51 (95% CI, 0.28–0.93) compared to the HD (44).**

An unpublished FME study, based on EMEA NephroCare EuCliD data (Zhang et al.) shows that, across the entire patient cohort evaluated, rates of hospital admissions and hospital days were numerically lower in the HDF group compared to the HD group (0.82 vs. 1.02 admissions per person-year and 7.71 vs. 8.31 days per person-year, respectively). Furthermore, patients in the HDF group had a 17% reduction in the risk of hospital admissions (adjusted hazard ratio [HR], 0.83; 95% confidence interval [CI], 0.81–0.85) and a 9% reduction in the risk of hospital days (adjusted incidence rate ratio [IRR], 0.91; 95% CI, 0.87–0.94). Treatment with HDF was associated with lower incidence rates of hospital admissions and hospital days due to cardiovascular disease (CVD), all infections, infections excluding COVID-19, and fluid-related events compared to treatment with HD. Patients treated with HVHDF experienced the lowest rates of hospital admissions (IRR: 0.77; 95% CI, 0.75–0.79) and hospital days (IRR: 0.82; 95% CI, 0.79–0.86) compared to those treated with HD.

6.2.4 - Cardiovascular benefits

Evidence indicates that HDF reduces cardiovascular risks and cardiovascular mortality for dialysis patients (27). Over many years, the cumulative impact of chronic inflammation, oxidative stress, and uremic toxin accumulation accelerates vascular aging, leading to arterial stiffness, calcification, and endothelial dysfunction (27). HDF treatments significantly enhance various health factors, delivering notable cardiovascular benefits. While the intricate interplay of these effects renders their contributions challenging to isolate, their collective impact significantly improves cardiovascular outcomes. It reduces cardiovascular mortality in ESKD patients treated by HDF. In a recent review article, Canaud et al. classified the **beneficial effects of HDF into two categories (27): direct and indirect effects, with both influencing cardiovascular outcomes:**

- **Direct effects:** HDF has demonstrated a direct effect in decreasing the incidence of intradialytic hypotensive episodes, better hemodynamic stability, unrelated to improved Na^+ balance (154-156), and a positive impact on cardiac remodeling (164, 170, 246, 247). Patients undergoing HDF have exhibited superior reductions in chronic inflammatory states (170, 171) and oxidative stress (171, 172), alongside enhancements in endothelial function and cardiovascular stiffness (248-250), progression of atherosclerosis (215), sympathetic tone activity (251) and arrhythmogenicity (252). PBUTs indoxyl sulfate and p-cresyl sulfate are strongly associated with endothelial dysfunction, inflammation, vascular calcification, and increased cardiovascular and all-cause mortality. It has been demonstrated that HVHDF enhances the clearance of indoxyl sulfate and p-cresyl sulfate (134, 253, 254). Post-hoc analysis of the HDFit trial over six months showed a monthly reduction of indoxyl sulfate in pre-dialysis plasma and a significant reduction in p-cresyl sulfate among patients with HVHDF (convection volume >27.5 L) compared to high-flux HD (253). This enhanced middle-molecule clearance leads to reductions in systemic inflammation and improved endothelial health, which are central to HDF's cardiovascular benefits (253).
- **Indirect effects:** Indirectly, HDF contributes to anemia correction (173-175), improvement in nutritional status (175, 176), physical activity (177), enhancement of quality of life (176, 178-180) and protection of residual kidney function (181).

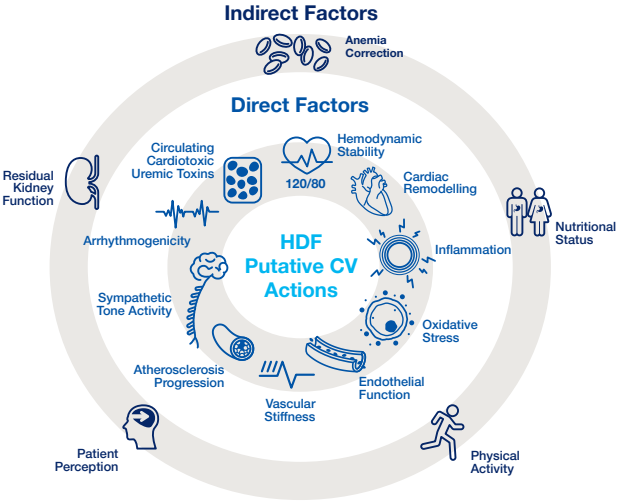


Figure 6.1 | Putative factors and mechanisms in cardiovascular protection in patients treated by HVHDF. Modified Canaud et al. (27).

6.2.5 - Neurological benefits

Neurological benefits include improvement of peripheral neuropathy and preservation of cognitive function.

6.2.5a - Peripheral polyneuropathy

Clinically, patients present with symptoms such as insomnia, irritability, restless legs syndrome (RLS), and pruritus. Peripheral polyneuropathy is the most prevalent long-term manifestation, characterized by a distal, symmetrical sensorimotor polyneuropathy that primarily affects the lower extremities. The condition arises due to the accumulation of uremic toxins (e.g., indoxyl sulfate, p-cresyl sulfate, and β2M), which damage peripheral nerves, and oxidative stress, contributing to demyelination and axonal degeneration. Risk factors include long dialysis vintage, inadequate dialysis dose, diabetic neuropathy, and advanced age. Sensory deficits, paresthesia, diminished tendon reflexes, muscle atrophy, and weakness are the most common symptoms (255-258).

Preliminary studies suggest that HDF may have a preventive or decelerating effect on the progression of peripheral neuropathy. Observations indicate that nerve excitability remains closer to normal in patients undergoing HDF, likely due to the efficient removal of medium-weight uremic molecules (259). Additionally, transitioning patients from conventional HD to HDF has been associated with significant reductions in uremic pruritus (178, 260, 261).

HVHDF may effectively manage RLS in dialysis patients, likely through enhanced removal of middle molecules and oxidized proteins implicated in neuroinflammation. Sakurai et al. described two cases where patients with recurrent RLS experienced significant symptom relief following HVHDF (262). Symptom resolution was consistently linked to an α1-microglobulin (α1-MG) removal rate ≥40%. Notably, RLS symptoms reappeared when patients switched back to conventional hemodialysis or when the α1-MG removal efficiency declined (262). These findings suggest that α1-MG removal may serve as a therapeutic target marker and that HVHDF offers a promising non-pharmacologic strategy for controlling RLS in ESKD patients.

However, while these symptomatic improvements and potential quality of life benefits are reported, uremia-related neurological damage leading to sensorimotor polyneuropathy has not shown significant treatability (263). This underscores the complexity of uremic neuropathy and suggests that while HDF may offer certain symptomatic benefits, it does not significantly alter the underlying progression of neuropathic damage.

6.2.5b - Cognitive function

Patients undergoing HD exhibit consistently poorer performance across multiple cognitive domains compared to the general population. These domains include global cognition, attention and orientation, concept formation and reasoning, construction and motor skills, executive functioning, language, and memory (264).

Cognitive impairments are common but underdiagnosed findings in HD patients (265). The prevalence of cognitive impairments among patients with ESKD, as assessed through neuropsychological tests, ranges from 16% to 38%, depending on the sample and the criteria used to define impairment (266). Poor cognitive function in the dialysis population is not limited to older adults but occurs across

the entire age spectrum (267). Indeed, moderate to severe chronic cognitive impairment was found in 70% of patients receiving HD aged >55 years (268).

The pathogenesis of cognitive impairment in HD patients is multifactorial, involving several contributing factors that can be divided into three interconnected groups (264) (Table 6.3):

Category	Risk Factors
Traditional Risk Factors	Advanced age, low education, physical inactivity, depression, poor sleep, atherosclerosis, hyponatremia
ESKD-Related Risk Factors	Malnutrition-Inflammation-Atherosclerosis (MIA) syndrome, inflammation, oxidative stress, vascular calcification, mineral disorders, low vitamin D, anemia, fluid overload, arterial stiffness
Hemodialysis-Related Risk Factors	Dialysis vintage, uremic toxin accumulation, cerebral hypeperfusion, altered cerebral blood saturation, aluminum toxicity

Table 6.3 | Risk factors for cognitive impairment in hemodialysis patients.

a. **Traditional risk factors:** advanced age, low level of education, physical inactivity, depression and poor sleep quality (264), atherosclerosis (269), and hyponatremia (270);

b. **ESKD-related risk factors:** Malnutrition-Inflammation-Atherosclerosis syndrome (264), inflammation and oxidative stress (271), vascular calcification/mineral bone disorders/low vitamin D (272, 273), anemia (273), fluid overload, and arterial stiffness (264);

c. **Hemodialysis-related risk factors:** Dialysis vintage (264), uremic toxins accumulation (274), cerebral hypoperfusion (275-277), changes in regional cerebral blood saturation (278), aluminum toxicity (279). One of the primary mechanisms is intradialytic hemodynamic instability, which can lead to reduced cerebral perfusion, resulting in recurrent ischemic events and subsequent brain damage. This process increases the risk of vertebrobasilar infarcts (280) and white matter disease (281), both of which are associated with cognitive decline.

Improving cognitive function in ESKD patients remains an unresolved challenge. However, by addressing multiple risk factors associated with cognitive decline, HVHDF presents a promising strategy for

preserving cognitive function and enhancing the long-term quality of life in this population. Recent evidence from Rose et al. has demonstrated that, compared to high-flux dialysis, HVHDF patients experienced a slower decline in cognitive function (p=0.049) (282). In 2025 the EuDial Working Group agreed that HDF may better preserve cognitive function than high-flux HD (60).

The following section, "Improved quality of life (QoL)," elaborates on this subject in greater detail.

6.2.6 - Improved quality of life (QoL)

The assessment of physical and psychosocial dimensions of perceived health, commonly referred to as health-related quality of life (HRQoL) and its influence on clinical decision-making, is increasingly recognized as a critical component in assessing dialysis effectiveness and future clinical studies should expand their focus beyond traditional outcomes to include quality of life and patient-reported outcome measures. These aspects provide a comprehensive evaluation of patient well-being, encompassing both physiological functionality and the broader psychological and social impacts of CKD and its treatment (283-285).

Understanding the mechanisms underlying patient-reported outcomes requires a different perspective than that applied to conventional clinical endpoints. While improved solute removal and physiological enhancements may contribute to symptom reduction and a better overall health perception, the precise biological and physiological pathways that influence HRQoL warrant further investigation.

While some investigations suggest no significant differences in HRQoL scores between patients receiving HD and those undergoing HDF, other studies have reported improvements in daily life (252, 286, 287). The HDFit trial observed a slight increase in physical activity, as reflected in higher step counts among patients treated with HDF (177), though no significant impact on sleep duration was detected (288). One of the primary challenges in analyzing these findings lies in the limitations of existing studies, including small sample sizes and short follow-up periods. Additionally, commonly used generic HRQoL assessment tools, such as the SF-36 and EQ-5D, may fail to adequately capture dialysis-specific patient perceptions.

The CONVINCE study addressed these limitations by employing a more comprehensive evaluation approach aligned with the Standardized Outcomes in Nephrology (SONG) initiative (282). It utilized the Patient-Reported Outcomes Measurement Information System (PROMIS®), an advanced electronic registry system that dynamically adapts questions based on extensive data repositories. In the CONVINCE study, the primary analysis demonstrated that HVHDF was associated with a survival benefit over HD (38). The secondary analysis by Rose et al. examined HRQoL across eight key domains, including physical function, cognitive function, fatigue, sleep disturbance, anxiety, depression, pain interference, and social participation. HRQoL assessments were conducted at baseline and three-month intervals throughout the study. While both groups exhibited a gradual decline in HRQoL over time, the rate of deterioration was significantly slower in the HVHDF group (282). The most pronounced difference was observed in cognitive function, where HD patients experienced a steeper decline than those undergoing HVHDF. Additional benefits were noted in physical function, pain interference, and social participation, suggesting that HVHDF may mitigate the decline in overall well-being experienced by patients on HD (282).

Recently the EuDial Working Group agreed that HDF may better preserve self-reported physical symptoms, cognitive function, and HRQoL than high-flux HD. Furthermore, they found that improved physical activity levels may be achieved in patients receiving HDF than in those undergoing high-flux HD (60).

6.3 | Long-term and hard outcomes

6.3.1 - Lower all-cause and cardiovascular mortality

While the short- and medium-term HDF benefits outlined above are particularly relevant from the patient's perspective, the cumulative advantages of HDF contribute to long-term outcomes compared to conventional HD.

RCTs, meta-analyses, and RWE studies have been undertaken to evaluate the effect of HDF/HVHDF on all-cause mortality relative to conventional HD. Current clinical evidence indicates that HDF, when delivered with high convection volumes (>23 L/session), is associated with improved patient survival compared to high flux HD.

In 2025, the EuDial published a consensus statement assessing the efficacy of HDF versus high-flux HD in both adult and pediatric populations (60).

This document, grounded in systematic meta-analyses of RCTs and expert interpretation, evaluated key clinical domains, including all-cause and cardiovascular mortality, cardiovascular events, health-related quality of life, and surrogate biochemical markers. The 22 consensus points aimed to support clinical decision-making without establishing a definitive standard of care. From these points, the working group reached the following conclusions regarding all-cause and cardiovascular mortality.

- High convection volume is associated with reduced overall and CV mortality in patients receiving HDF compared to those on high-flux HD. The effect size depends on both the convection volume delivered (target greater than 23 L/session) and the patient's overall health (60).
- Achieving a high convection volume requires optimal vascular access, and this is usually more likely to be reached in patients dialyzed through an AVF rather than a CVC or graft (60).
- All-cause mortality appears to be lower in patients treated by HDF than in those treated by high-flux HD. However, this effect cannot be generalized to the entire dialysis population, as its size depends on both the patient's overall health (not simply on age, diabetes, or pre-existing cardiovascular disease) and the delivered convection volume (target greater than 23L/session) (60).

Numerous RCTs have been conducted over the years to assess the impact of HDF on all-cause mortality compared to standard HD. The following are the most clinically relevant randomized controlled trials (RCTs). Six large European RCTs (Italian Convective Study, CONTRAST, Turkish, ESHOL, FRENCHIE, and CONVINCE) have compared HDF with conventional HD in terms of clinical outcomes of ESKD patients (35-38, 154, 157) (Table 6.4).

Study	Country	Sample Size (HD/HDF)	Mean Sub / Conv Vol. (L/session)	Primary Outcome	Key Findings
Italian Convective Study (154)	Italy	70/40	Sub 30-40 (pre-dilution)	ISH	ISH ↓ 50.9% with HDF
CONTRAST (35)	Dutch Canada	356/358	Sub 19.8	All-cause mortality	No difference overall, but benefit with high-volume HDF
Turkish Study (36)	Turkey	391/391	17.2/19.5	All-cause mortality + CV events	No difference overall, better survival in high-efficiency HDF
ESHOL (37)	Spain	450/456	21.8/23.9	All-cause mortality	30% lower all-cause mortality in HDF
FRENCHIE (157)	France	191/190	20/21	Intradialytic tolerance	Better tolerance; no difference in mortality
CONVINCE (38)	Multinational	677/683	23/25.5	All-cause mortality	HDF ↓ all-cause mortality by 23% (HR 0.77)

Table 6.4 | Six large European RCTs. Sub=substitution; Conv= convection; CV=cardiovascular; ISH=intradialytic symptomatic hypotension.

The **CONTRAST and Turkish studies** have not provided clear evidence of whether post-dilution HDF is superior or not to conventional HD (35, 36). However, secondary analyses of both trials demonstrated a survival benefit when higher convection volumes were achieved (35, 36): In the CONTRAST study, patients with a convection volume greater than 21.9 L/session had a significantly lower mortality rate (HR=0.62; 95% CI, 0.41–0.83) (35). Similarly, in the Turkish study, patients with a substitution volume exceeding 17.4 L/session had a significantly lower mortality risk (HR=0.71; 95% CI, 0.07–0.71; p=0.01) (36).

In 2013, the **ESHOL trial**, a multicenter, open-label, RCT, showed that high-efficiency post-dilution HDF reduces all-cause mortality compared with conventional HD (37). 906 chronic ESKD patients were

assigned either to continue HD (n=450) or to switch to high-efficiency post-dilution HDF (n=456) (37). HDF patients had a 30% lower risk of all-cause mortality (HR, 0.70; 95% CI, 0.53–0.92; P=0.01), and 33% lower risk of cardiovascular mortality (HR, 0.67; 95% CI, 0.44–1.02; P=0.06) (37). Post hoc analysis showed mortality risk reductions of 40% (HR=0.60; 95 % CI, 0.39–0.90) and 45% (HR=0.55; 95 % CI, 0.34–0.84) in patients receiving convection volumes between 23–25 L/session and >25 L/session, respectively (37).

In 2017, the **FRENCHIE** clinical trial found no significant difference in mortality in its secondary analyses when comparing conventional HD with post-dilution HDF. However, the convective volumes achieved in this study were lower than those reported in the ESHOL trial, which may have influenced the findings (157).

In the **CONVINCE study**, a multinational interventional RCT funded by the European Union's Horizon 2020 Research and Innovation Program, 1,360 ESKD patients from 61 dialysis centers in eight countries across the public and private sectors (Spain, Romania, Germany, Portugal, France, Hungary, the Netherlands, and the United Kingdom) were recruited (38). The trial investigated the impact of HVHDF on survival rates and HRQoL, considering economic implications from both a short-term (two-year) and a long-term (lifetime) perspective (38). Participants were randomized into two groups: 683 patients received high-flux HD with a Kt/V>1.4, while 677 prevalent patients underwent post-dilution HVHDF, achieving a minimum convection volume of ≥23 L per session (38). With a median follow-up of 30 months, the study demonstrated a 23% reduction in all-cause mortality among patients receiving HVHDF (HR=0.77; 95% CI, 0.65–0.93). This survival benefit was attributed to the administration of post-dilution, high-dose HDF, defined as a convection volume of ≥23 L (±1 L) per session (38). Additionally, the CONVINCE trial revealed that HVHDF provided a positive effect on patients' quality of life relative to HD, particularly on cognitive function (282).

"High-Volume Hemodiafiltration vs. High-Flux Hemodialysis Registry Trial (H4RT)" is an ongoing RCT exploring the clinical benefits of HVHDF over HD (42). This UK-based registry trial aims to provide further insights into the comparative effectiveness of high-volume HDF, defined as targeting a substitution volume of more than 23 L per session in post-dilution mode, compared to high-flux HD (42), with results anticipated by 2026.

Before 2016, several **meta-analyses** assessed convective dialysis techniques, but they did not focus exclusively on HDF (142). Instead, they broadly compared diffusion-based versus convection-based therapies such as hemofiltration (diafiltration), acetate-free biofiltration (AFB), and paired filtration dialysis (PFD), and provided only a limited evaluation of the impact of convective volume (44). In 2016, the **European pooling project** combined, in an individual patient data meta-analysis, four RCTs (CONTRAST, Turkish, ESHOL and FRENCHIE studies) (N=2793 patients) that compared HDF (N=1400, post-dilution HDF mode) to conventional HD (N=1393) on clinical outcomes (44). After a median follow-up of 2.5 years, the largest survival benefit was for patients with the highest convective volume (>23 L per 1,73 m^2 body surface area per session) with a 22% reduction in all-cause mortality (HR=0.78; 95% CI, 0.62–0.98), and a reduction of 31% in cardiovascular mortality (HR=0.69; 95% CI, 0.47–1.00) after an adjustment for age, gender, albumin, creatinine, history of CV diseases, and history of diabetes (44).

In an **individual patient pooled data-analysis**, Vernooij et al. combined the five European RCTs (CONTRAST, Turkish, ESHOL, FRENCHIE, and CONVINCE studies, 4,153 patients) (35-38, 40) and compared HDF (N=2,083, post-dilution mode) to standard HD (N=2,070) on clinical outcomes (44). The primary outcome was all-cause mortality, with secondary analyses examining cardiovascular mortality, infection-related deaths, sudden death, and transplantation rates. This analysis found that, after a median follow-up period of 30 months, 23.3% of patients in the HDF group had died, compared to 27.0% in the HD group (HR=0.84; 95% CI, 0.74–0.95). The most significant survival benefit is in older patients (≥65 years), patients without diabetes, patients without cardiovascular disease, and patients on dialysis for ≥30 months. No clear survival benefit was observed in younger patients (<65 years), patients with diabetes, and patients with low albumin (<4 g/dL, malnourished). Cardiovascular mortality was also lower in the HDF group, with 8.1% of patients dying from cardiovascular causes compared to 9.8% in the HD group (HR=0.78; 95% CI, 0.64–0.96) (44). Notably, the study found no significant differences in treatment effects across patient subgroups, meaning the benefits of HDF applied broadly regardless of factors such as age, diabetes status, or history of cardiovascular disease (44).

Cardiovascular mortality was also lower in the HDF group, with 8.1% of patients dying from cardiovascular causes compared to 9.8% in the HD group (HR=0.78; 95% CI, 0.64–0.96) (44). Notably, the study found no significant differences in treatment effects across patient subgroups, meaning the benefits of HDF applied broadly regardless of factors such as age, diabetes status, or history of cardiovascular disease (44).

While RCTs remain the gold standard for establishing causal efficacy, their applicability to routine clinical practice is often constrained by methodological features such as narrow inclusion criteria, tightly controlled protocols, and intensive follow-up procedures. These design characteristics, although necessary to ensure internal validity, may limit external validity and reduce the generalizability of findings to the heterogeneous and clinically complex ESKD population (289-295). As highlighted by Canaud et al., RWEs, derived from observational cohorts, registries, and clinical databases, offer valuable insights into treatment effectiveness, safety, and applicability across broader and more representative patient populations, reflecting the diversity of real-world patient populations and practice settings (142, 143).

Several RWE studies have reported comparable results related to the reduction of all-cause mortality, showing a dose-response relationship between substitution/convective volume and relative survival rate (7, 13, 23, 30, 31, 39, 41, 296-298). Specifically, a substitution/convective volume exceeding 21/23 L per session, respectively, has exhibited the most favorable effect on mortality outcomes (13, 23, 31, 34, 296, 297).

In 2006, **DOPPS** demonstrated a significantly longer survival in patients treated with HDF using a substitution volume greater than 15 L (30).

Data from the **French National Registry** reported a significant association between HDF and improved survival, with a HR of 0.84 for all-cause mortality and 0.73 for cardiovascular mortality (40).

The **Australia and New Zealand Dialysis and Transplant Registry** (ANZDATA) similarly reported reduced all-cause mortality in patients treated with HDF, with HRs of 0.79 in the Australian cohort and 0.88 in New Zealand.

Additionally, cardiovascular mortality was significantly lower in the Australian HDF population (HR 0.78) (41). **The Japanese Society for Dialysis Therapy (JSDT) registry** supports these results, indicating that predilution HDF was associated with a reduction in all-cause mortality (HR 0.83), particularly when high-volume convective doses were employed (39).

In **Latin America**, propensity score-matched cohort studies conducted in Brazil and Colombia demonstrated substantial mortality reductions in HDF-treated patients, with HRs for all-cause mortality of 0.71 and 0.45, respectively (299, 300).

Recently, two observational studies evaluated the real-world effectiveness of HDF and HVHDF compared to high-flux HD in a large, unselected patient population treated at FME NephroCare clinics across Europe, Asia, Africa, and Latin America (32, 301). The analyses were based on data extracted from **EuCliD**. In the first study, Strogoff-de-Matos et al. assessed mortality risk among Brazilian patients with kidney failure, comparing outcomes between those treated with HDF and those receiving high-flux HD (301). The cohort included 8,391 end-stage kidney disease (ESKD) patients treated at 29 dialysis facilities in Brazil between January 1, 2022, and December 31, 2023: 6,787 received only high-flux HD, while 2,836 received HDF. In a time-updated analysis, patients treated with HDF had a significantly lower adjusted risk of all-cause mortality compared to those on HD (HR 0.73) (301). HDF was also associated with reduced cardiovascular mortality but not with lower infection-related mortality. The mortality benefit was consistent across subgroups and more pronounced in patients under 65 years (HR 0.56) compared to those aged 65 or older (HR 0.82) (301). In the second study, Zhang et al. assessed the effectiveness of HVHDF compared to high-flux HD in a large, unselected patient population across FME NephroCare clinics in 23 different countries (Bosnia and Herzegovina, Croatia, Czech Republic, Estonia, Finland, France, Hungary, Italy, Kazakhstan, Kyrgyzstan, Netherlands, Poland, Portugal, Romania, Russia, Serbia, Slovakia, Slovenia, South Africa, Spain, Sweden, Turkey, and Ukraine) (32). The analysis, from 2019 to 2022, was based on 85,117 adults and aimed to complement findings from the CONVINCE study. HDF was associated with a 22% reduction in all-cause mortality compared to HD, and the benefits were consistent across different patient subgroups, regardless

of age, dialysis vintage, diabetes, or cardiovascular disease. The risk reduction increased to 30% for those receiving HVHDF (≥23 L convection volume per session) (32). Additionally, HDF demonstrated a 31% lower risk of cardiovascular death compared to HD (32). The study also analyzed the impact of COVID-19 and confirmed that the benefits of HDF persisted independent of infection status (32). Sensitivity analyses validated the robustness of these findings, showing similar results when adjusting for country-level variations, patient demographics, and dialysis parameters (32).

6.3.2 - Dose-response relationship

One of the most important findings of the individual patient data meta-analysis by Vernooij et al. was the strong dose-response relationship between convection volume and mortality risk. The higher the convection volume achieved during HDF, the lower the risk of death. The group of HDF patients was divided into three tertiles based on the delivered convective volume: low volume (<19 L), middle volume (19–23 L), and high volume (>23 L) per session. Patients receiving a convection volume of at least 23 L per session experienced the most significant outcome benefits. A delivered convection volume >23 L in post-dilution HDF was associated with a risk reduction of 37% for all-cause mortality (HR=0.63; 95% CI, 0.50–0.79) and a decrease of 42% for cardiovascular deaths (HR=0.58; 95% CI, 0.40–0.85), after adjustment for age, sex, creatinine, history of cardiovascular disease, and history of diabetes (44) (Table 6.5).

	Standard haemodialysis n=2070	Haemodiafiltration convection volume, L per session		
		<19 (n=370)	19–23 (n=641)	>23 (n=959)
All-cause mortality				
Unadjusted	Reference	0.92 (0.74–1.15)	0.93 (0.78–1.11)	0.70 (0.59–0.83)
Adjusted*	Reference	0.85 (0.67–1.08)	1.06 (0.87–1.29)	0.63 (0.50–0.79)
Cardiovascular mortality				
Unadjusted	Reference	0.98 (0.68–1.41)	0.76 (0.56–1.04)	0.74 (0.55–0.98)
Adjusted*	Reference	0.99 (0.68–1.44)	0.84 (0.60–1.16)	0.58 (0.40–0.85)
Cardiac cardiovascular death				
Unadjusted	Reference	0.71 (0.39–1.28)	0.58 (0.37–0.92)	0.74 (0.52–1.06)
Adjusted*	Reference	0.75 (0.41–1.37)	0.65 (0.40–1.04)	0.62 (0.40–0.97)
Infection-related mortality, including COVID-19				
Unadjusted	Reference	1.14 (0.70–1.85)	0.95 (0.63–1.44)	0.57 (0.39–0.82)
Adjusted*	Reference	1.02 (0.59–1.77)	1.22 (0.73–2.03)	0.51 (0.28–0.93)
Infection-related mortality, excluding COVID-19				
Unadjusted	Reference	1.21 (0.74–1.99)	1.04 (0.68–1.61)	0.51 (0.34–0.78)
Adjusted*	Reference	1.02 (0.59–1.77)	1.22 (0.73–2.03)	0.51 (0.28–0.93)

*Adjusted for age, sex, creatinine, history of cardiovascular disease, and history of diabetes.

Table 6.5 | All-cause and cause-specific mortality by convection volume (with standard HD as a reference). From Vernooij et al, Lancet. 2024 Oct 25:S0140-6736(24)01859-2.

By showing significant reductions in all-cause and cardiovascular mortality and demonstrating a clear dose-response relationship, the study provides a robust foundation for expanding the use of HVHDF in clinical practice across a wide range of patient and treatment characteristics (Figure 6.2).

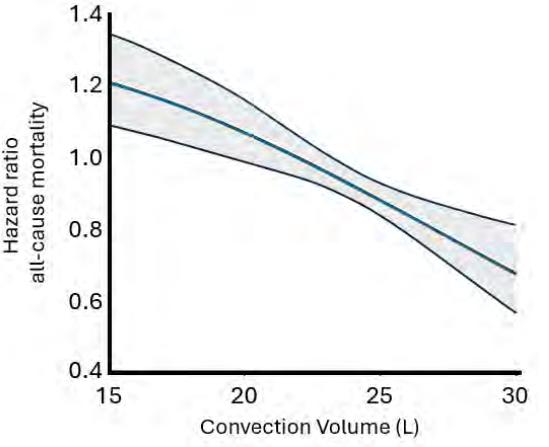


Figure 6.2 | Dose–response curve of the relation between convection volume plotted against hazard ratios of all-cause mortality, based on data from patients treated with HDF. The gray area represents the 95% CI. Adapted from Vernooij et al., 2024. (44)

Chapter 7

High-Volume Hemodiafiltration: Health Economics and Sustainability

Chapter 7

High-Volume Hemodiafiltration: Health Economics and Sustainability

Although evidence indicates that HVHDF improves patient outcomes, concerns remain regarding its cost-effectiveness and environmental sustainability compared to HD.

Although the initial investment in HVHDF infrastructure may seem significant, it is important to consider the long-term benefits, such as improved quality of care, increased survival, and more efficient resource utilization, which can help to offset these potential upfront costs gradually.

HVHDF addresses critical clinical and financial challenges, meeting the expectations of multiple stakeholders, including patients, physicians, healthcare providers, and funders (5).

Health economic outcome studies comparing HVHDF and traditional HD could provide valuable insights into its sustainability.

Schouten et al. have executed a comprehensive cost-utility evaluation of HVHDF compared to high-flux HD ESKD patients (302). The trial examined the impact of HDF on survival rates and HRQoL, taking into account economic implications from both short-term (two-year) and long-term (lifetime) perspectives. The financial assessment was based on data from the CONVINCE trial and existing literature. The study considered both direct healthcare costs, such as dialysis sessions and hospitalizations, and indirect costs, including productivity losses and informal caregiving.

Given the established superiority of HVHDF in reducing mortality, the investigators sought to determine whether these clinical benefits justify the increased costs associated with its implementation.

Conducted across 61 centers in eight European countries, the trial randomized 1,360 adult patients undergoing HD for at least three months. Patients were allocated either to high-dose HDF or to continue receiving conventional high-flux HD. The study followed them for at least two years, gathering data on healthcare costs, quality-adjusted life years (QALYs), and broader economic implications.

The main results of the trial demonstrated a substantial survival advantage for patients treated with HDF, with a 23% lower risk of all-cause mortality compared to those treated with HD. The cost-utility analysis employed a Markov cohort model to assess outcomes over both a two-year and lifetime horizon, revealing that HDF led to an incremental cost per QALY of €31,898–€37,344 over two years and €27,068–€36,751 over a lifetime. These variations reflect differences in dialysis staff costs across different scenarios.

While HDF was associated with greater overall costs due to increased life expectancy and the corresponding need for additional dialysis sessions, sensitivity analyses indicated that at a willingness-to-pay threshold of €50,000 per QALY, the probability of its cost-effectiveness surpassed 90%. When intervention costs in additional life years were excluded, which lowered the economic burden of longer survival, **the incremental cost-effectiveness ratio decreased significantly to €13,231 per QALY**.

A key driver of cost differences was the expense of dialysis disposables, as well as increased water and electricity consumption in HDF. However, these costs were partially offset by reduced medication use and potential improvements in patient HRQoL. Hospitalization costs were slightly higher in the HDF group, though the study acknowledged that more detailed analyses are needed to explore the causes of these admissions. This analysis highlighted variations in cost structures across countries, and the authors recommended that healthcare organizations tailor findings to local economic conditions. The results emphasize the need to integrate clinical effectiveness with economic viability in treatment decisions, particularly in resource-intensive areas like dialysis care. Ultimately, the CONVINCE trial presents a compelling case for HDF as a cost-effective therapy for ESKD.

While requiring greater initial resource allocation, its demonstrated survival benefits, coupled with favorable cost-per-QALY ratios, suggest that high-dose HDF represents a valuable investment in patient care (302).

Shroff and the EuDial Working Group have raised concerns about the sustainability and environmental impact of HVHDF, given its larger infusion volume requirements compared to conventional high-flux HD, speculating that the associated costs may outweigh the benefits (303). Conversely, Canaud et al., analyzing real-world data from over 26,000 patients treated in FME EMEA clinics, along with simulation

modeling, demonstrated that **optimally prescribed post-dilution online HDF is more environmentally friendly compared to high-flux HD** (29). By reducing the dialysate flow rate to 430 mL/min (reflecting a Qd : Qb ratio 1.2, instead of 1.4 or 1.5) and integrating automated ultrafiltration and substitution control, post-dilution HVHDF achieves a higher dialysis dose for both small- and middle-molecule uremic toxins while reducing the dialysis fluid consumption compared to standard HD (29). These findings highlight the potential of HVHDF as a more sustainable and resource-efficient dialysis modality while maintaining superior treatment efficacy (29). HVHDF enhances solute clearance across all molecular weights and significantly reduces water and dialysate consumption by enabling lower dialysate flow rates without compromising clearance efficiency (29).

Post-dilution HVHDF uses ultrapure dialysate more efficiently than traditional HD or other HDF modalities (29). It increases the clearance of middle molecules, improves quality of life, and reduces hospital admissions and lengths of stay (304). These reductions in hospitalizations lead to cost savings for healthcare systems. Enhanced removal of uremic toxins also decreases the need for supportive medications, such as phosphate binders and erythropoiesis-stimulating agents. Furthermore, HVHDF minimizes saline usage for system priming and rinsing, reducing plastic waste and associated costs. Replacing disposable components with recyclable or reusable alternatives can further mitigate plastic waste.

Dialysis machines capable of online sterile fluid generation can minimize reliance on saline and substitution fluid packaging, lowering the energy consumption and CO_2 emissions associated with their production and transportation. Improved patient quality of life and social impact can also increase patient productivity.

Optimally prescribed post-dilution online HVHDF emerges as a sustainable and effective therapy, balancing clinical excellence with environmental responsibility (305, 306).

HDF addresses the ecological challenges of traditional dialysis by reducing water and saline usage, minimizing plastic waste, and decreasing the carbon footprint.

With improved patient outcomes and long-term cost savings, HVHDF represents a forward-looking approach to KRT, benefiting patients, healthcare systems, and the environment.

Chapter 8

Practical Implementation and Prescription Post-Dilution High-Volume Hemodiafiltration

Chapter 8

Practical Implementation and Prescription Post-Dilution High-Volume Hemodiafiltration

RCTs, meta-analyses, RWE studies, and recommendations from the EuDial Working Group of the European Renal Association consistently demonstrate that, within conventional thrice-weekly HD schedules, post-dilution HVHDF significantly improves the survival rate, independent of patient subgroups defined by individual characteristics, when the delivered convection volume exceeds 23 L per session (37, 38, 42, 44, 60). According to the EuDial consensus agreement, the extent of this benefit is also influenced by the patient's overall health status (60).

Currently, there are no known or documented contraindications for HDF. Therefore, in principle, all dialysis patients would benefit from a 12-week trial of HVHDF.

DOPPS from 2014 found that nephrologists from Europe indicated that the following patient characteristics are strong indications for treatment with HDF (307): Dialysis-related amyloidosis, polyneuropathy, hemodynamic instability, longer life expectancy, prior dialysis treatment for 10 years, heart failure, prior dialysis treatment for 5 years, worsening nutritional status, coronary artery disease, diabetes, large patient size, and/or being elderly. There are few eligibility considerations for HVHDF, and most patients with ESKD would be considered suitable. Patients who may not be considered for treatment with post-dilution HVHDF include those with consistently low and unstable blood flow rates, heart conditions who can only dialyze with low blood flow, and high blood viscosity who are at risk for fiber clogging (e.g., polycythemia, high blood concentration of fibrinogen and lipids) (28, 308).

Several factors can affect success in reaching the planned targets of substitution fluid volume in post-dilution HDF (309). The first is patient characteristics, such as vascular access type and vascular access flow. The second set of factors are associated with the dialysis prescription, including the type of dialyzer, the selected needles, the level of blood flow rate (within the limits allowed by the vascular access), and the duration of the dialysis session. The management of the treatment is important as well, since the integrity of the dialyzer

is also ensured by a correct anticoagulation regimen. The third set of factors are machine features controlling aspects of the HDF (Figure 8.1).

This chapter shows how to optimize the treatment prescription to perform HVHDF. Moreover, the process of switching patients from HD to HVHDF and the procedure for initiating HDF in incident stable (i.e., not crashing) patients who are not yet on dialysis will be defined.

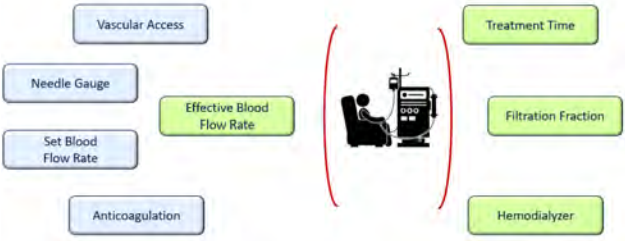


Figure 8.1 | Factors impacting the substitution fluid volume generation in post-dilution hemodiafiltration. In green are the factors associated with the dialysis prescription, and in light blue the factors influencing the effective blood flow rate.

The following items will be discussed in detail:

8.1. Vascular access

8.2. Treatment prescription

- 8.2.A Blood flow
- 8.2.A1 Needle size, catheter lumen
- 8.2.A2 Extracorporeal pressure regimen
- 8.2.A3 How to achieve high substitution volume
- 8.2.A4 Workflow: How to achieve the highest blood flow rate
- 8.2.B Dialysis treatment time
- 8.2.C Prescription of anticoagulants
- 8.2.D Prescription of dialysate flow rate
- 8.2.E Prescription of dialysate and substitution fluid electrolytes
- 8.2.E1 Prescription of dialysate and substitution fluids bicarbonate
- 8.2.E2 Prescription of dialysate and substitution fluids potassium

8.2.E3 Prescription of dialysate and substitution fluids sodium

8.2.E4 Prescription of dialysate and substitution fluids calcium and magnesium

8.2.F Prescription of dialysate and substitution fluids glucose

8.2.G Prescription of hemodialyzer

8.3. Dialysis procedures in stable incident patients starting HDF

8.4. Switching stable and regularly dialyzed patients from high-flux HD to HVHDF

8.1 | Vascular access

A well-functioning vascular access is essential for the successful delivery of dialysis, regardless of the treatment modality. Vascular access dysfunction is a major cause of morbidity, requiring interventional procedures or hospitalization (310).

HVHDF can be performed using any type of vascular access, including AVFs, AVGs, or permanent CVCs. AVF and AVG with an access flow of >600 mL/min can be considered sufficient to allow adequate blood flow (Qb).

Qb should not exceed 80% of the vascular access flow. Good vascular access is a prerequisite for performing post-dilution HVHDF, provided that adequately sized needles (15 G or larger) are used. CVCs typically provide lower and more variable blood flow rates, which may impact treatment efficiency.

Regular vascular access blood flow monitoring can predict the need for interventions before unusability and significantly reduce the number of thrombosis events (311).

8.2 | Treatment prescription

8.2.A - Blood flow

Qb is a fundamental determinant of dialysis adequacy in both high-flux HD and HDF treatment. **The achieved blood flow is the most crucial predictor of convective volume achievement, as it facilitates ultrafiltration flow rate while limiting the filtration fraction to less than 30%** (96, 308, 309, 312, 313). Most studies rely on prescribed Qb (pQb) rather than effective Qb (eQb), which may introduce inaccuracies in assessing dialysis efficacy. The eQb—the actual blood flow reaching the dialyzer—can be substantially lower than the pQb

due to factors such as low arterial bloodline pressure, resistance in AVF, AVG, or CVC, vascular access recirculation, cardiopulmonary recirculation, needle size, long catheter lumens (which may increase blood viscosity), and anticoagulation (314). The degree of discrepancy between pQb and eQb varies among individuals, making eQb a more accurate parameter for evaluating the relationship between Qb and clinical outcomes. In pre-dilution HDF, the substitution fluid dilutes the blood, effectively reducing the volume of undiluted blood reaching the dialyzer. In post-dilution HDF, there is no reduction in eQb because substitution fluid is added after the dialyzer. The eQb is effectively used for solute clearance, making post-dilution more efficient than pre-dilution in removing uremic toxins. The Qb exhibits a positive correlation with shear rate, which plays a crucial role in mitigating the formation of the secondary protein layer. Higher Qb reduces membrane fouling by enhancing shear forces, thereby preserving dialyzer membrane permeability and sustaining its sieving capacity over time. A vascular access with blood flow rates of 350–400 mL/min will be most successful in achieving the high convective volume associated with improved outcomes without the need to increase the dialysis treatment time (96, 315). To achieve full perfusion of all capillary fibers and optimize shear rate, a Qb of at least 200 mL/min per 1.0 m^2 of dialyzer surface area is required (308, 309). This flow rate ensures an adequate shear stress per fiber, effectively minimizing membrane fouling and maintaining dialyzer efficiency in currently available capillary dialyzers (309).

8.2.A1 - Needle size, catheter lumen

The internal lumen diameter of fistula needles is a critical determinant of vascular access resistance, as governed by the Hagen-Poiseuille law, where resistance to blood flow is inversely proportional to the fourth power of the lumen radius (309). **For prevalent patients, at least 15 G needles are usually recommended** for both the arterial and the venous cannulation sites. A smaller needle should only be used in exceptional cases, e.g., if the vascular access flow rate is below 400 mL/min, the vessel is too small to be cannulated with a 15 G needle, the fistula is not yet mature, or if shortly after fistula revision a hematoma is present and bleeding time is prolonged. By switching to a bigger needle (e.g., from 17 G to 15 G) at constant arterial pressure (P_{ART}, e.g. -200 mmHg), the blood flow increases (Figure 8.2). CVC must have an inner lumen diameter of ≥2 mm to ensure adequate flow dynamics and minimize resistance (12, 316).

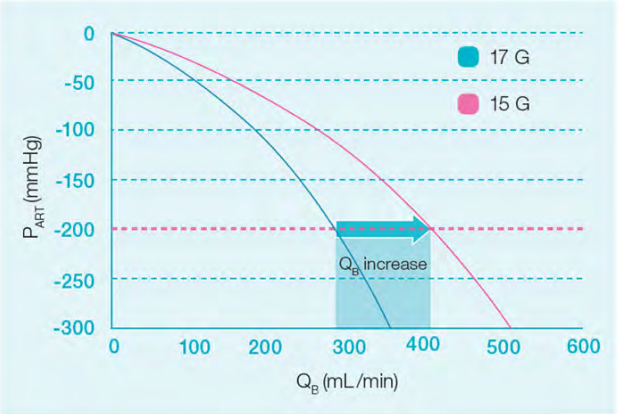


Figure 8.2 | Selection of needle size. Unpublished FME data.

8.2.A2 - Extracorporeal pressure regimen

A typical arterial pressure (P_{ART}) value in AVF or AVG is around -200 mmHg, usually resulting in venous pressures around +230 mmHg. To individually maximize Qb for dialysis, increase the Qb until the patientindividual limit for arterial or venous pressure is reached. The P_{ART} is measured at the arterial line before the blood pump.

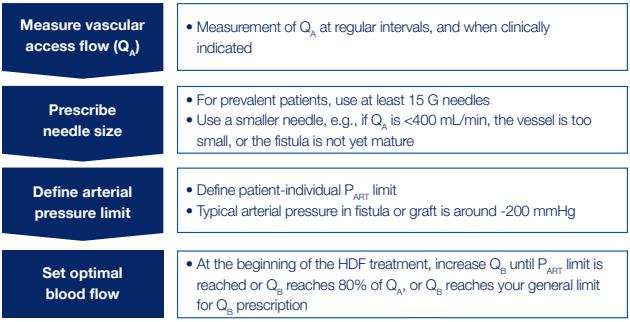
It is suggested to increase the Qb until one of the following conditions is fulfilled, whichever is fulfilled first:

- The targeted P_{ART} is reached.
- Qb reaches 80% of the vascular access flow.
- Qb reaches the general limit for Qb prescription in the clinic.

8.2.A3 - How to achieve high substitution volume

In patients with vascular access limitations, achieving high substitution volumes via increasing blood flow rate (Qb) may not always be feasible. In such cases, an automated regulation system, such as AutoSub *plus* (FME), becomes particularly valuable. This system optimizes substitution volume delivery, enabling higher convective clearances even when Qb cannot be increased. By implementing AutoSub *plus*, more patients could achieve a target substitution volume of ≥ 21 L per treatment, thereby enhancing the efficacy of HVHDF therapy (28).

8.2.A4 - Workflow: How to achieve the highest blood flow rate



8.2.B - Dialysis treatment time

Dialysis treatment time, quantified as the product of individual session length and weekly frequency, is a pivotal and autonomous determinant of blood purification efficacy. Substitution volume and processed blood volume **increase** with dialysis time.

Prolonged treatment durations have been empirically validated to confer multiple clinical advantages, notably enhancing the clearance of solutes characterized by low intrinsic mass transfer coefficients, mitigating osmotic fluctuations, reducing the requisite UFR, and augmenting the convective dose administered (309). These benefits are equally pertinent to HDF (309, 317-319). Consequently, individualized optimization of treatment parameters is imperative for both high-flux HD and HDF modalities. Personalized treatment adjustments are essential for maximizing the benefits of both HD and HDF.

Increasing the treatment time or the Qb proportionally increases the substitution volume, potentially enhancing the convective clearance of middle- and large-molecular-weight solutes (Figure 8.3).

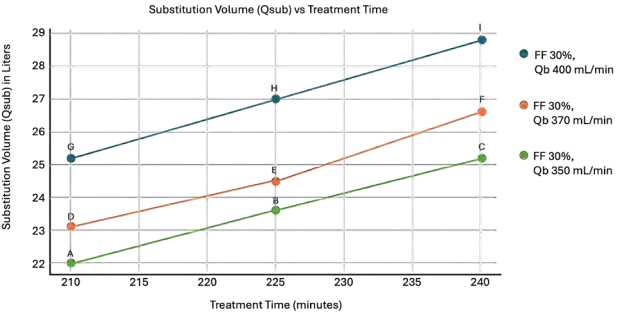


Figure 8.3 | Examples for the calculation of the substitution volume considering a Filtration Fraction (FF) 30% and a Blood Flow Rate (Qb) of 350 ml/min: Treatment time (TrT) 210 min: Substitution volume (QSub) = 22.0 L; TrT 225 min: Qsub = 23.6 L; TrT 240 min: Qsub = 25.2 L. FF 30% and a Qb of 370 ml/min: TrT 210 min: QSub = 23.1 L; TrT 225 min: QSub = 24.5 L; TrT 240 min: QSub = 26.6 L. FF 30% and a Qb of 400 ml/min: TrT 210 min: QSub = 25.2 L; TrT 225 min: QSub = 27.0 L; TrT 240 min: QSub = 28.8 L

These calculations demonstrate that increasing the treatment time or the Qb proportionally elevates the substitution volume, potentially enhancing the convective clearance of middle- and large-molecular-weight solutes.

8.2.C - Prescription of anticoagulants

During HD, the coagulation system is activated, necessitating the use of anticoagulation to prevent clot formation within the extracorporeal circuit (ECC). Preventing clotting within the extracorporeal circuit is fundamental to optimizing HDF efficacy and ensuring patient safety.

In routine practice, one of the following anticoagulants is usually prescribed to prevent the coagulation of the blood:

- Unfractionated heparin (UFH) (MW 4000 – 40000 Da)
- Low-molecular-weight heparin (LMWH) (MW 4000 – 8000 Da)

UFHs carry a higher negative charge than LMWH (320). Given that most dialyzer membranes are also negatively charged, the electrostatic repulsion between UFH and the membrane likely reduces UFH adsorption during HDF.

This suggests that UFH removal during HDF may be less than anticipated based solely on its molecular size. As a result, UFH dose during this type of treatment may be lower than anticipated. Despite this, the specific conditions within the dialyzer during HDF, such as increased convective transport and higher FFs, can elevate the risk of clot formation within the extracorporeal circuit (320). No specific modifications are necessary compared to its use in high-flux HD, as both the loading dose and maintenance infusion remain unchanged. UFH dosing in both HDF and HD is typically individualized, guided by activated partial thromboplastin time (aPTT) measurements and visual inspection for clot formation in the air trap chamber. These monitoring practices are consistent across both modalities, ensuring appropriate anticoagulation tailored to each patient's needs (320).

LMWHs are categorized as middle-molecular-weight compounds. As such, they are susceptible to enhanced removal through convection, the principal mechanism of solute clearance in HDF. The CONTRAST study reported approximately 10% higher LMWH dose in HDF patients compared to HD patients (321). However, studies have shown that the clearance of LMWHs like enoxaparin and dalteparin remains relatively low during both HD and HDF. This is likely due to their negative charge, which reduces adsorption onto the similarly charged dialyzer membranes (320, 322, 323). Therefore, membrane characteristics, particularly electrical charge, play a significant role in LMWH removal during dialysis. The LMWH's infusion as a single bolus at treatment initiation requires careful consideration of the injection site to maintain optimal antithrombotic activity. Empirical evidence has demonstrated that immediate injection of LMWH into the arterial bloodline results in a 20% to 30% loss of the active compound, leading to diminished anticoagulant efficacy. Consequently, higher doses may be required to achieve equivalent anticoagulant effects (324). To mitigate this loss and preserve LMWH's full anticoagulant potential, the preferred method of administration is direct injection into the venous needle or venous bloodline (309). If arterial line administration is necessary, delaying the injection can significantly enhance the bioavailability and efficacy of LMWH (309). Implementing these evidence-based strategies ensures adequate anticoagulation during HDF, reducing the risk of clotting-related complications, and maintaining circuit patency. Please note that most LMWHs are licensed for arterial bloodline administration. Nevertheless, the consumption of LMWHs is usually lower when administered to the venous side of the bloodline.

For dalteparin, a starting dose of 60 IU/kg has been found adequate in HDF patients (320, 325). Given the increased coagulation activation in HDF, future monitoring may benefit from assessing thrombin-antithrombin (TAT) complex levels in addition to anti-factor Xa activity to better evaluate anticoagulation efficacy (320).

Patients receiving oral anticoagulant therapy (e.g., warfarin) represent special cases. However, in patients already receiving coumarin therapy, the heparin (UFH/LMWH) starting dose for extracorporeal therapy may be reduced to 50% of the standard dose to mitigate the cumulative anticoagulant effect and reduce the risk of bleeding, as supported by clinical guidance (320, 326).

8.2.D - Prescription of dialysate flow rate

It is recommended to adopt the following Qd:Qb ratio prescription (29):
Qd:Qb = 1.2:All patients.

IF:	THEN:
spKt/V is >1.8	Qd:Qb 1.0
spKt/V is <1.4	Qd:Qb 1.3
spKt/V remains <1.4	Increase Qd:Qb 0.1 to a maximum Qd/Qb of 1.5
spKt/V remains <1.4 after the above adjustments	Increase the dialyzer surface area
spKt/V remains <1.4 after the above adjustments	Increase the treatment time

HDF combines diffusion and convection to enhance solute clearance and improve patient outcomes. While Qb and substitution volume are often the primary focus in optimizing HDF, dialysate flow rate (Qd) plays a critical role in increasing treatment efficacy. Qd is the rate at which dialysate is delivered to the dialyzer and serves as the driving force for diffusive clearance, primarily removing small molecular weight uremic toxins, such as urea and creatinine. However, in HDF, combining high-volume ultrafiltration (convective transport) with diffusive clearance requires careful balancing of Qd to optimize both mechanisms. Determining the ideal Qd for HDF involves balancing dialysis efficiency with cost-effectiveness and machine capabilities. Typical Qd values in HDF settings range between 500 and 800 mL/min, depending on the HDF modality. **In post-dilution HDF, substitution fluid is infused after the dialyzer, maximizing**

convective clearance. Since diffusion remains unaffected, Qd can be maintained at 500–600 mL/min.

Mesic et al. investigated the impact of automated adjustment of dialysate flow rates based on blood flow in optimizing dialysate consumption while maintaining or improving dialysis dose (327). Conducted as a randomized crossover trial across multiple dialysis centers, the research compared conventional HD with HDF, applying an automated Qd:Qb ratio of 1.2. This led to 8.5% lower dialysate consumption while still achieving a 3.5% increase in dialysis dose (Kt/V) (327). More recently, Canaud et al. evaluated dialysis fluid consumption and efficiency in post-dilution HVHDF compared to high-flux HD, aiming to optimize resource use while maintaining or improving dialysis efficacy (29). Conventional high-flux HD typically sets the Qd:Qb ratio between 1.4 and 1.5, leading to substantial dialysate consumption, averaging around 125 liters per session (29). When HVHDF is optimized with a reduced Qd:Qb of 1.2, HVHDF achieves the same or better solute clearance while reducing total dialysis fluid consumption to approximately 99 liters per session, representing a 26% reduction compared to traditional HDF (29) (Figure 8.4).

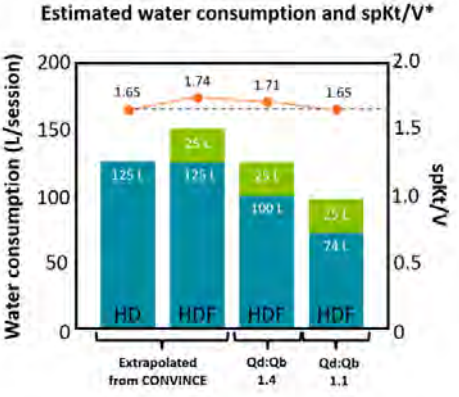


Figure 8.4 | Graphic adapted from Canaud et al. (29). *Estimates are based on presumed prescription during the CONVINCE trial (Qd:Qb 1.4) and observed Qb and substitution volumes (assuming no net UF). The dialysate volume consumption/session is shown in dark green, and the convective volume/ session in light green.

The impact of these optimizations is evident in both water savings and treatment effectiveness. Despite reducing dialysate volume, optimized HDF maintains urea clearance comparable to HD, with a Kt/V ranging from 1.65 to 1.71 (29) (Figure 8.4). Moreover, β2M removal was enhanced due to convective transport, making HVHDF a superior modality for eliminating small and larger uremic toxins and a more sustainable alternative to high-flux HD (29).

8.2.E - Prescription of dialysate and substitution fluid electrolytes

Independent of the treatment modality, dialysate and substitution fluid electrolytes such as potassium (K^+), sodium (Na^+), calcium (Ca^{2+}), magnesium (Mg^{2+}), and bicarbonate (HCO_3^-) should be prescribed in a reasonable range based on clinical basis, tolerance, and outcomes, and must be monitored regularly.

The electrolyte concentrations in the dialysate and substitution fluid are identical, making it impossible to have two different concentrations.

The electrolyte levels in the dialysate and substitution fluid used for HVHDF may need to be adjusted compared to those used in conventional HD to prevent electrolyte imbalances. Indeed, in HVHDF, the initial electrolyte shift is greater than in conventional HD treatments. In conventional dialysis, electrolytes back-diffuse from the dialysate into the patient's blood within the dialyzer.

However, in post-dilution HDF, electrolytes are directly infused with the substitution fluid into the patient's blood via the venous drip chamber. One key consideration is the bicarbonate concentration, which may need to be reduced to avoid overcorrection of the metabolic acidosis commonly observed in ESKD patients (308, 328).

The bicarbonate exchange also influences the serum potassium concentration. A rapid increase in serum bicarbonate is associated with a faster decline in serum potassium because increasing the blood's pH causes the movement of K^+ into the intracellular space.

Sodium balance is another critical factor that requires careful modulation in post-dilution HVHDF. The sodium concentration in the dialysis fluid (and substitution fluid) should be adjusted to a level lower than that of the patient's plasma water.

These findings underscore the importance of tailoring dialysis fluid composition to optimize electrolyte homeostasis in HVHDF while

mitigating potential complications related to bicarbonate and sodium handling.

Electrolyte serum concentration: The electrolyte serum concentration at the end of dialysis depends mainly on the concentration of respective electrolytes in the dialysis fluid and not on the dialysis modality (329).

Electrolyte shift: In high-flux HD and HVHDF, the initial electrolyte shift is greater than in low-efficiency HD treatments, i.e., in treatments with low blood flow rate.

8.2.E1 - Prescription of dialysate and substitution fluid bicarbonate

For patients initiating hemodialysis therapy, a gradual correction of chronic uremic acidosis is recommended. This approach prioritizes cardiovascular stability during the early treatment phase, while minimizing the risk of complications associated with rapid alkalization, such as post-dialysis alkalosis, particularly in the context of both HD and online HDF (77). In prevalent patients, the dialysate bicarbonate concentration may be progressively increased to 30–32 mEq/L, with adjustments based on pre- and post-dialysis bicarbonate levels and the patient's overall metabolic status (77). Montagud-Marrahi et al., in a prospective cohort study of patients on stable chronic HDF, analyzed the impact of reducing dialysate bicarbonate concentration from 35 to 32 mEq/L on plasma bicarbonate levels (328). A 3 mEq/L reduction in dialysate bicarbonate significantly and safely decreased both pre- and post-dialysis total carbon dioxide (TCO_2) levels, thereby preventing overcorrection of acidosis and contributing to improved control of secondary hyperparathyroidism (328).

Independent of the treatment modality, dialysis fluid bicarbonate should be prescribed based on regularly monitoring the predialysis serum bicarbonate level.

There is no exclusive (or single) international guideline for metabolic acidosis correction in maintenance ESKD patients, and recommendations in national guidelines vary by country.

a. National Kidney Foundation/Kidney Disease Outcomes Quality Initiative (NKF/KDOQI) Guidelines 2000 and 2003 state that serum HCO_3^- should be monitored regularly at monthly intervals, and correction of metabolic acidemia by maintaining serum

bicarbonate ≥22 mmol/L should be a goal in the management of individuals undergoing maintenance dialysis (330, 331).

b. European Renal Best Practice Guideline (EBPG) on Nutrition for metabolic acidosis states that mid-week pre-dialysis serum HCO_3^- levels should be maintained at 20–22 mmol/l (332).

c. United Kingdom Renal Association recommends an optimal pre-dialysis serum bicarbonate in the range 18.0-26.0 mmol/L, remembering to consider measurement errors (e.g., due to exposure to air) when interpreting level [1C] (333).

d. Caring for Australians with Renal Impairment (CARI) Guidelines state that optimal pre-dialysis HCO_3^- levels should be ≥22 mmol/L (334).

e. DOPPS stated in 2013 that HCO_3^- levels >23 mmol/L are not associated with increased mortality (335), in contrast to a previous analysis in 2004 that defined as optimal a pre-dialysis HCO_3^- in the range 19-22 mEq/L (336).

Excessively high bicarbonate concentrations in the dialysate, and in the substitution fluid in the case of HDF, can cause metabolic alkalosis. Conversely, insufficient bicarbonate levels may lead to metabolic acidosis. At the start of HD, the bicarbonate shift is more pronounced in HVHDF compared to low-efficiency HD treatments. This larger bicarbonate shift leads to a more rapid correction of acidosis. Serum bicarbonate levels are influenced by the back-diffusion of bicarbonate across the dialyzer membrane and by the infusion of substitution fluid. One key consideration is the bicarbonate concentration, which may need to be reduced to avoid overcorrection of the metabolic acidosis commonly observed in HD patients (308, 328).

Patients undergoing high-flux HD and HDF with elevated dialysate bicarbonate concentrations are at an increased risk of adverse effects due to rapid correction of acidosis and the potential development of an alkalotic state. These risks include hypokalemia, caused by potassium clearance via dialysis and its intracellular shift due to rising pH, hypocalcemia, hypomagnesemia, prolonged QT interval on the electrocardiogram, vasodilation, hypotension, suppression of minute ventilation, cerebral ischemia, and accelerated vascular calcification (337-345). Tentori et al. demonstrated a positive association between higher dialysate bicarbonate concentrations and increased mortality, cardiovascular hospitalizations, and IDH

(335). Another study found that reducing the dialysate HCO_3^- concentration decreased IDH (346).

During treatment, the principle of diffusion regulates serum bicarbonate levels, preventing them from exceeding the dialysis fluid's bicarbonate concentration, as set by the machine's "bicarbonate" setting. To achieve the desired serum bicarbonate concentration, physicians should individually adjust the dialysate or replacement fluid levels using the dialysis machine, whether in HD or HDF.

Dialysis fluid and substitution fluid typically contain a combination of bicarbonate and acetate/citrate. The type and concentration of acetate/citrate are determined by the acid concentrate used, which varies between formulations. In both HD and HDF, bicarbonate and acetate/citrate diffuse across the dialyzer membrane into the blood. In HDF, these components also reach the blood via the substitution fluid. Once in the patient's blood, acetate/citrate is metabolized into bicarbonate, contributing to the overall circulating bicarbonate concentration. Sánchez-Canel et al. investigated the acid-base status of patients undergoing HDF with bicarbonate dialysate containing 3 mEq/L of acetate or Acetate-Free Biofiltration (AFB) (347). The study found that acetate concentrations remained stable during and after AFB. In contrast, acetate concentrations increased by approximately 0.05 mmol/L during HDF at the midpoint of treatment, remained unchanged post-HDF, and returned to baseline levels after the session. Bicarbonate concentrations were comparable between HDF and AFB, though AFB demonstrated slightly greater bicarbonate replenishment. These findings align with the results of Smith et al., indicating that only a minimal amount of dialysate acetate is transferred to the patient during HDF. This small acetate load does not significantly impact blood bicarbonate concentrations or the bicarbonate administered during treatment (348).

8.2.E2 - Prescription of dialysate and substitution fluids potassium

For prevalent patients, the dialysate potassium concentration may be adjusted to a range of 2-3 mEq/L, based on pre- and post-dialysis plasma potassium levels (77).

After a prolonged interdialytic interval, serum K^+ levels should ideally range between ≥4.0 and ≤6.0 mEq/L (333). Potassium plays a critical role in maintaining the resting cell membrane potential, neuromuscular excitability, and the rhythmicity of cardiac pacemaker activity (349). HD and HDF treatments induce a rapid decline in serum K^+ concentration, most notably during the first 60 minutes of therapy. Subsequently, plasma K^+ levels stabilize, reaching a steady state during the final hour of dialysis (211, 350-352).

A lower dialysate potassium concentration facilitates greater potassium removal from the bloodstream, resulting in reduced post-dialysis serum potassium levels (353). Additionally, the bicarbonate exchange also affects the serum K^+ concentration. A rapid increase in serum bicarbonate is associated with a faster decline in serum K^+ because increasing the blood's pH causes the movement of K^+ into the intracellular space.

This abrupt reduction in plasma K^+ alters the intracellular-to-extracellular potassium concentration gradient, transmembrane potential, and cardiac cell repolarization. These changes predispose patients to IDH by reducing cardiac output and increasing the risk of arrhythmias, prolonged QT interval on the electrocardiogram, and ectopic ventricular beats (354, 355).

Hypokalemia during dialysis sessions has been associated with brief episodes of paroxysmal atrial fibrillation, particularly during the last two hours of treatment (356, 357). Dialysate K^+ levels <2 mEq/L have been linked to an elevated incidence of cardiac events (358-360).

To mitigate the risk of intradialytic hypokalemia, strict dietary potassium control may reduce the necessity for low dialysate K^+ levels (361).

8.2.E3 - Prescription of dialysate and substitution fluids sodium

Studies evaluating total sodium mass have consistently ruled out the presence of a positive sodium balance in patients undergoing

HDF (246, 362). During HDF, where significant convective volumes are removed, albumin—acting as a non-removable anion—becomes increasingly concentrated on the blood side of the dialysis membrane. This concentration gradient promotes sodium retention, which binds to albumin to maintain electrical equilibrium as dictated by the Gibbs–Donnan effect (159, 161).

The Gibbs-Donnan effect results in a lower Na^+ concentration in the ultrafiltrate compared to the plasma water from which it is derived, leading to an increase in plasma water Na^+ concentration along the dialyzer length. In conventional HD, this Na^+ accumulation is mitigated by concurrent diffusive Na+ transfer into the dialysis fluid. However, in post-dilution HDF, where UFRs are significantly higher, diffusive Na^+ loss may be insufficient to offset the Gibbs-Donnan driven increase in plasma Na^+ concentration. This results in a higher Na^+ burden for the patient, with the magnitude of the effect being directly proportional to the convection rate (308, 363).

The retention of Na^+ in this context results in elevated osmolarity within the blood compartment, thereby enhancing fluid refilling from the interstitial compartment (162). This mechanism may contribute to the improved hemodynamic stability observed during HDF. Furthermore, the enhanced hemodynamic tolerance might also be attributed to an increase in pre-dialysis systolic blood pressure, as reported in several studies (92, 154). While this potential benefit could theoretically lead to hydrosaline overload, clinical trials have not demonstrated a sustained increase in natremia (37), nor have they identified markers indicative of fluid overload in patients treated with HVHDF.

A recent study investigating sodium removal in post-dilution HDF versus high-flux HD found no significant difference in Na^+ balance when a dialysis fluid sodium concentration of 1 mmol/L lower than the pre-dialysis plasma Na^+ concentration (138 and 139 mmol/L, respectively) was used (246, 308).

8.2.E4 - Prescription of dialysate and substitution fluids calcium and magnesium

The online HDF parameters have a negligible effect on ionized calcium and magnesium (364). Independent of the treatment modality, dialysis fluid Ca^{++} should be prescribed based on regularly monitoring the predialysis serum calcium level.

Both HD and HDF require careful dialysate Ca^{++} adjustment to optimize calcium balance, support cardiovascular stability, and minimize long-term complications such as vascular calcification and bone disorders. Maintaining an optimal Ca^{++} balance in ESKD patients is a complex process influenced by several factors, including plasma calcium levels, PTH, the use of phosphate binders and vitamin D analogs, and IDH risk and cardiac arrhythmias. These factors act in concert and require careful consideration for optimal outcomes. Therefore, dialysate Ca^{++} prescription should be carefully individualized (365).

The KDOQI guidelines recommend a corrected total serum Ca^{++} goal range of 8.4–10.2 mg/dL (2.1–2.54 mmol/L) (366). The correction of acidosis and the development of post-dialysis alkalosis can lead to hypocalcemia, particularly when low dialysate Ca^{++} concentrations are used. Hypocalcemia is associated with pro-arrhythmogenic effects that may induce IDH (367-369).

In patients undergoing HD and HDF, intradialytic reductions in plasma Ca^{++} levels have been inversely correlated with prolonged QTc interval on the electrocardiogram, suggesting that larger reductions in plasma calcium are associated with more significant increases in QTc at the end of the dialysis session (367-369). The KDIGO 2017 guidelines recommend a dialysate Ca^{++} range of 1.25–1.5 mmol/L (370, 371). However, dialysate Ca^{++} levels within this range have distinct physiological effects:

- Dialysate Ca^{++} 1.25 mmol/L: Accelerates bone turnover and increases hemodynamic instability, leading to a higher incidence of arrhythmias and sudden cardiac arrest (206, 372), likely due to QT interval prolongation (373).
- Dialysate Ca^{++} 1.5 mmol/L: Improves cardiac muscle contractility and enhances hemodynamic stability during dialysis (374).
- Dialysate Ca^{++} 1.75 mmol/L: Stimulates sympathetic activity,

enhancing myocardial contractility, reducing intradialytic blood pressure declines, and improving intradialytic hemodynamic stability (375, 376). However, long-term use is associated with accelerated vascular calcification, bone and mineral imbalance, and the development of adynamic bone disease (365, 370, 371, 377, 378).

Leenders et al. conducted a systematic review and meta-analysis demonstrating that higher circulating magnesium (Mg) levels are inversely associated with all-cause and cardiovascular mortality in patients with chronic kidney disease (379). These findings suggest that increasing serum magnesium may help reduce cardiovascular risk in this population (379). In HD patients, modification of this risk factor may be readily achieved by increasing dialysate Mg concentration (379).

In HD patients, the use of dialysate Mg concentrations of 0.75 to 1.0 mEq/L has been associated with improved hemodynamic stability, reduced IDH, and enhanced cardiovascular safety. Kyriazis et al. identified a dialysis solution containing 0.25 mmol/L Mg and 1.25 mmol/L Ca^{++} as a major cause of IDH due to an impairment of myocardial contractility, and showed that increasing dialysate Mg level to 0.75 mmol/L could prevent IDH frequently seen with the use of 1.25 mmol/L dialysate Ca (380).

8.2.F - Prescription of dialysate and substitution fluids glucose

Both hypoglycemia and hyperglycemia should be avoided to ensure hemodynamic stability during HD, emphasizing the importance of tight glycemic control and regular blood glucose monitoring. While glucose-free dialysate has been proposed to prevent hypertriglyceridemia and minimize the potential risk of bacterial proliferation in the dialysate (211), its use poses a significant risk of hypoglycemia, particularly in diabetic patients receiving insulin therapy (381).

To mitigate these risks, a dialysate glucose concentration of 5.55 mmol/L (1 g/L) is recommended as an optimal balance to maintain glucose homeostasis during HD.

For HD and HDF treatments, dialysis fluid containing glucose is recommended. Ideally, the dialysis treatment does not alter the blood glucose level. In the Turkish (36) and the Catalonian HVHDF (37)

studies, 5.55 mmol/L (1 g/L) of dialysis fluid glucose were prescribed with satisfactory results.

Independent of the treatment modality, potassium removal may be higher with glucose-free dialysis fluid because glucose can induce insulin production, which promotes K^+ entry into cells. Subsequently, less K^+ is available for removal during dialysis. Caloric loss with glucose-free dialysis fluid may be increased. Maintaining stable blood glucose levels is essential in patients with ESKD to reduce the risk of IDH.

8.2.G - Prescription of the hemodialyzer

Modern dialysis membranes must meet a comprehensive set of criteria to ensure safety, efficacy, and biocompatibility in dialysis treatments. This is particularly relevant for HVHDF due to its substantially increased transmembrane filtration. The following are the key criteria that collectively define the ideal dialysis membrane for HVHDF (383):

1. Performance: An effective dialysis membrane must exhibit high removal rates for both fluid and a broad spectrum of uremic toxins, including small solutes (e.g., urea) and middle- to large-molecular-weight toxins (e.g., β2M). This ensures optimal dialysis adequacy and the reduction of systemic complications related to uremic toxin accumulation. However, the membrane must avoid inadvertent loss of essential proteins, mainly albumin (~66 kDa), which can occur in highly porous or overly “open” membranes, to prevent its loss that may lead to the development of malnutrition (384). Balancing permeability for solute removal with selectivity for albumin retention is critical for both efficacy and patient safety. Dialyzer performance is not a constant value but decreases over treatment time, especially during the first 30 minutes of dialysis (385-388). This reduction in performance is mainly caused by the contact and adsorption of plasma proteins to the membrane, leading to the buildup of a protein layer on the inner membrane surface, which provides additional resistance for uremic toxin removal. This may necessitate more pressure on the membrane to achieve the same membrane ultrafiltration as at the start of the treatment (28).

2. TMP is one of the major determinants of the achieved convective volume. The ideal HDF membrane should exhibit a steep decline in sieving coefficients, ensuring optimal selectivity for solute removal and stable ultrafiltration coefficient during the entire dialysis treatment, avoiding TMP-related problems (decrease in substitution volume delivered). Specifically, the membrane should have sieving coefficients close to 1 for middle-sized molecules, enabling their efficient clearance while maintaining sieving coefficients close to 0 for larger molecules such as albumin. This selectivity is encapsulated in the delicate balance between the molecular weight retention onset (MWRO) and the molecular weight cut-off (MWCO), which collectively define the membrane's permeability slope. Achieving this balance is critical for optimizing the membrane's performance and ensuring effective toxin removal and albumin retention. In summary, the main performance characteristics of a dialyzer for HVHDF are the following:
    - Minimized protein fouling/adsorption.
    - Performance stability during the treatment.
    - Ultrafiltration coefficient: ≥50 mL/h/mmHg.
    - Sieving coefficient β2M: >0.6.
    - Sieving coefficient albumin: <0.001.
    - Low internal blood flow resistance to optimize the filtration fraction (i.e., fiber diameter >180 µm, length <30 cm).
    - Surface: ≥ 1.6 ± 0.2 m^2. The dialyzer surface area should be adapted to HDF performance and the delivered extracorporeal Qb (77, 309).
3. Biocompatibility: The membrane must limit the activation of immune and inflammatory pathways triggered by interactions between blood and artificial surfaces within the extracorporeal circuit. Biocompatibility reduces the risk of adverse effects such as complement activation, platelet aggregation, and oxidative stress. This is achieved by designing membrane surfaces with specific chemical and physical properties to minimize these unavoidable interactions.
4. Cytotoxicity: A key safety requirement is preventing substances from leaching into the patient's bloodstream from the dialysis membrane or other extracorporeal circuit components. Leached

substances can interact with tissues, causing unwanted cellular reactions, toxicity, or inflammation. Therefore, dialysis membranes must be manufactured with materials that are chemically stable, inert, and free from cytotoxic additives.

5. Sterilization: To ensure patient safety, dialysis membranes must undergo rigorous sterilization to eliminate microbial contaminants. However, these procedures must not alter the membrane's structural or functional characteristics, as any degradation could compromise performance or biocompatibility. Advanced sterilization methods, such as steam sterilization or gamma irradiation, are commonly used to meet these stringent requirements.
6. Endotoxin retention: Dialysis fluids can potentially be contaminated with bacterial endotoxins, which, if not adequately retained, may cause persistent low-grade inflammation and associated cardiovascular and systemic complications in dialysis patients. Modern dialysis membranes are engineered with high endotoxin retention capabilities to serve as an additional protective barrier, ensuring that dialysis fluids meet ultrapure standards.

8.3 | Dialysis procedures in stable incident patients starting HDF

Dialysis treatment for adult patients with ESKD may be initiated with HDF support (77, 309). In such cases, it is recommended to implement HDF stepwise while monitoring patient response and tolerance. Recently, Stuard et al. documented the HD procedures adopted in FME EMEA NephroCare clinics for initiating HD and HDF therapy in stable incident patients (77).

FME EMEA NephroCare has developed HD strategies and procedures to optimize the management and seamless transition of stable incident patients with ESKD. For these patients, a stepwise approach is recommended: progressively increasing the substitution volume, starting with 5 L in the second week of dialysis, then adding 5 L per week to reach a substitution volume ≥21 L/session by the fifth week of dialysis (Table 8.1 adapted from Stuard et al.) (77).

HD procedures in stable incident patients

Time	1st Week	2nd Week	3rd Week	4th Week	5th Week
Frequency (n)	≥2	≥3	≥3	≥3	≥3
Treatment Time (min)	120 - 180	≤180	≤240	≤240	≥240
Dialyzer area surface (m^2)	≤1.4	≤1.4	≤1.4	≤1.4	1.6 ± 0.2*
Blood Flow (ml/min)	≤150	≤200	≤250	≤300	≥340
Dialysate flow (ml/min); Autoflow	300; 1.5	300; 1.5	400; 1.2	400; 1.2	≥500; ≥1.2†
spKt/V	No Targets				≥1.4
Post-Dilution Qsub (L)	0	≤5	≤10	≤15	≥21
Ultrafiltration rate (ml/h/Kg)	≤10.0				
Dialysate Bicarbonates (mEq/L)	≤28 **	≤29 **	≤30 **	≤31 **	≤32 **
Dialysate Sodium (mEq/L)	140 - 143	140 - 142	140 - 141	139 - 140	138 - 140
Dialysate Potassium (mEq/L)	3 **	3 **	2-3 **	2-3 **	2-3 **
Dialysate Calcium (mmol/L)	1.50 - 1.75 **				
Dialysate Glucose (mg/dl)	100				
Dialysate Temperature (°C)	36.5 (<36.0 in case of IDH)				
Food during dialysis	Avoid				
Blood pressure monitoring	Pre-, Post-, and every 30 minutes. It is more frequent in the case of IDH				
AHTs	Tapering the AHTs while decreasing the body weight				
Diuretics	Only in interdialytic days in overloaded patients with RRF				
Blood tests***	Before 1st HD	Weekly	Weekly	Weekly	Monthly

Table 8.1 | Qsub: Substitution Volume. AHTs: antihypertensive drugs. IDH: Intradialytic hypotension. RRF: residual kidney function. *Increase the dialyzer surface area according to patient characteristics. **Adjust the dialysate electrolyte prescription according to the patient's blood test results. ***Hemoglobin, urea, calcium, bicarbonate, potassium, and sodium. †Increase in case spKt/V <1.4.

8.4 | Switching stable and regularly dialyzed patients from high-flux HD to HVHDF

Switching a stable prevalent patient from high-flux HD to post-dilution HVHDF can enhance the removal of middle molecules and potentially improve clinical outcomes, provided that high convective volumes (≥ 23 L/session) are achieved.

At FME Fresenius Kidney Care centers in the United States, a dedicated and structured algorithm has been developed, approved, and implemented to guide the transition of adult, stable ESKD patients, defined as those receiving high-flux HD for more than 30 days, from high-flux HD to HVHDF.

More broadly, it is recommended that the first HDF session be scheduled mid-week (e.g., Wednesday or Thursday). For prevalent patients, the probing period is shorter compared to stable incident patients starting HDF. In such cases, initiating HDF involves only a few key steps, making the transition process both streamlined and clinically feasible (309):

1. **Needle Gauge:** 15 G
2. **Anticoagulation:** Unfractionated heparin: no dose adjustment. Low molecular weight heparin (LMWH): (a) if administered via the venous line, no dose adjustment is needed; (b) if administered via the arterial line, a dose increase of 20–30% is recommended. Delayed administration via the arterial line may significantly enhance the bioavailability and efficacy of LMWH.
3. **Dialyzer:** A high-flux dialyzer is required, with an ultrafiltration coefficient of ≥50 mL/h/mmHg and a surface area of ≥1.6±0.2 m^2 (77, 309). The membrane should have a high sieving coefficient for middle molecules (e.g., B2M sieving coefficient ≥ 0.6) and an albumin sieving coefficient of <0.001. The membrane should be designed to minimize protein adsorption on its surface, reducing the risk of secondary membrane fouling during treatment.
4. **Blood Flow Rate (Qb):** Qb is a critical determinant of convection volume, and it represents the most important limiting factor in post-dilution HVHDF. Experts recommend targeting blood flows between 340–450 mL/min for post-dilution HVHDF to achieve high convective volumes (9, 12, 20, 77, 309). If Qb may not reach this range, a high convection volume can be obtained by increasing the treatment time, adjusting the filtration fraction

using an auto-substitution mode (390, 393-396) (e.g., FME AutoSub Plus: refer to Chapter 12.2).

5. **Substitution fluid rate (Qsub):** Prescribe Qsub on manual mode (309). Start with a 50 ml/min in post-dilution mode, increasing by 25 mL/min per week to reach 100–125 mL/min (309). Once parameters stabilize, consider switching to automated Qsub-controlled mode (309).
6. **Dialysate Flow (Qd):** It is suggested to maintain an AutoFlow Qd/Qb Ratio of 1.2 to ensure balanced dialysis performance (77).
7. **Dialysate electrolytes:** The dialysate electrolyte composition should be tailored based on clinical response and individual patient tolerance (309).
8. **HVHDF and Kt/V >1.4 not reached:** If a convection volume ≥23 L is not reached, increase treatment time and/or dialyzer surface area (309). If single pool Kt/V<1.4, consider increasing autoflow above 1.2, if further increases in Qb are not feasible, and large dialyzer surface areas are already in use (77). If HDF is used and the Kt/V exceeds 2.0, decrease the autoflow to ≤1.0 (77).

Chapter 9

Strategy to prioritize patient selection for the implementation of HVHDF

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Strategy to prioritize patient selection for the implementation of HVHDF

To date, there are no known or documented contraindications for HDF. Therefore, in principle, all dialysis patients could benefit from the advantages of HVHDF. To implement HVHDF effectively in a clinic where all patients are currently receiving high-flux HD, the following prioritization rules are recommended:

9.1 | Eligibility Criteria

Before considering the switch from high-flux dialysis to post-dilution HVHDF, it is suggested to evaluate if patients meet the following baseline requirements:

- Blood flow rate ≥330 ml/min. A well-functioning AVF is preferred. Patients with CVCs or AVGs may be considered if they can achieve Qb >330 ml/min.
- Treatment time ≥210 minutes/session.
- Anticoagulants: Preventing clotting within the extracorporeal circuit is mandatory to optimize HDF efficacy and ensure patient safety.
- Normal blood viscosity: Patients with high blood viscosity (e.g., polycythemia, high blood concentration of fibrinogen and lipids) are at higher risk of fiber clogging.

9.2 | Prioritization Based on Clinical Benefit

Once eligibility is confirmed, prioritize patients based on the potential benefits of HVHDF:

A) High Priority

1. Patients capable of achieving high convection volumes ≥ 23 L/session.
2. Patients on active kidney transplantation list.
3. Patients with hemodynamic instability.
4. Patients with heart failure, coronary artery disease.

5. Patients with high ultrafiltration needs requiring substantial fluid removal.
6. Patients with large body size.

B) Moderate Priority

1. Patients with residual kidney function. Those maintaining urine output >1000 mL/24 hours may experience improved toxin clearance with HVHDF.
2. Patients with elevated serum phosphorus levels.
3. Patients with dialysis-related amyloidosis.
4. Patients with worsening nutritional status.
5. Patients with polyneuropathy.
6. Patients with itching.

C) Lower Priority

1. Patients with limited vascular access. Individuals with CVCs or AVGs that cannot achieve high Qbs may not realize the full benefits of HVHDF.
2. Patients with shorter session durations. Those unable to undergo 4-hour sessions may not achieve the necessary convection volumes for optimal HVHDF efficacy.
3. Patients who are not compliant with the dialysis procedure and accompanying prescriptions, mainly the frequency and duration of dialysis treatment, should have lower priority.
4. Patients with life expectancy of less than 3 months.
5. Patients intolerant of heparin or anticoagulants.

9.3 | Implementation Considerations

- Gradual transition: Begin with high-priority patients, monitoring their response closely before expanding to other groups.
- Monitor convection volumes: To maximize HVHDF benefits, aim for a target convection volume of > 23 liters per session.
- Patient education: Inform patients about the potential advantages and any risks associated with HVHDF to ensure informed decision-making.

- Resource assessment: Ensure the availability of necessary equipment and trained staff to support HVHDF therapy.
- By adhering to these criteria, clinics can effectively identify and prioritize patients who are most likely to benefit from transitioning to HVHDF, thereby optimizing clinical outcomes and resource utilization.

Chapter 10
Medication and Hemodiafiltration

Chapter 10

Medication and Hemodiafiltration

10.1 | Introduction

By combining diffusive and convective solute transport, HDF enhances the clearance of a broad spectrum of uremic toxins. Kidney failure and dialysis techniques can alter the pharmacokinetics of numerous drugs significantly. Dosing modifications may be needed, based on either the administered dose or alterations to the dosing interval. These changes are not limited to drugs primarily eliminated via renal excretion; medications predominantly metabolized by the liver may also require dose adaptation if their metabolites are water-soluble, active (or toxic), and exhibit low protein binding.

Importantly, HDF's enhanced solute removal capacity relative to HD raises the possibility of increased drug clearance, which must be accounted for to avoid subtherapeutic exposures.

It is important to note that evidence regarding the necessity of further dose adjustment, specifically for HDF, remains limited.

This chapter aims to elucidate the determinants of drug clearance in patients undergoing intermittent HD and HDF. **Despite its growing use, clinical pharmacokinetic studies in the HDF population remain scarce, likely due to the relatively recent integration of online HDF into standard dialysis practice.**

This paucity of data is especially critical for drugs with narrow therapeutic indices, where precise dosing is essential to avoid toxicity or therapeutic failure.

Not all drugs are removed equally by HD in patients with ESKD. Conventional HD removes primarily small, water-soluble, and unbound drugs through diffusion. HDF adds a convective clearance component that enhances the removal of larger solutes, particularly those in the middle-molecular-weight range. The interplay of three main factors influences the extent of drug clearance during HD or HDF: drug-related characteristics, elimination pathways, and dialysis treatment parameters.

10.2 | Drug-related characteristics

Several pharmacokinetic properties determine the efficiency with which HD and HDF remove a drug. The most relevant physicochemical characteristics include molecular weight (MW), protein binding, volume of distribution (Vd), and route of elimination.

1. **Molecular weight (MW)**: Small molecules diffuse and filter more readily than larger ones; therefore, size is a primary determinant of dialysis clearance. Low MW drugs (e.g., <400 Da) are usually dialyzed efficiently, whereas conventional HD removes large molecules (several thousand Da or more) less efficiently. HDF and high-flux membranes extend the upper size limit for removal (clearance relatively unaffected up to ~30–40 kDa due to convection). High-flux HD or HDF can clear some drugs in the 400–15,000 Da range via convection. For instance, the antibiotic vancomycin (MW 1,449.3 Da) is not removed by low-flux HD, is only partially cleared by high-flux HD, and demonstrates increased clearance with HDF (397). In contrast, very large molecules, such as monoclonal antibodies, exceed membrane pore sizes and are not dialyzable (397).
2. **Protein binding (PB)**: Only the free (unbound) fraction of a drug in plasma is available for filtration or convection. Drugs with high PB (e.g., >90%) exhibit limited dialytic clearance, as only a small proportion of the total plasma concentration is accessible for removal. For instance, warfarin (~99% albumin-bound) is not removed by HD or HDF in meaningful volumes. Similarly, ceftriaxone, a highly protein-bound antibiotic (85–95%), exhibits low volume clearance by HDF. In contrast, drugs with low PB, such as gentamicin (<10%), have a high free plasma concentration and are dialyzed readily. A PB threshold ~80% is generally considered to reduce dialyzability significantly (397). While HDF may enhance solute removal through convection, it does not overcome the limitations posed by PB. Protein-drug complexes are too large to pass through dialysis membranes. Although limited adsorption of some protein-bound drugs may occur with specific membranes, this process is unpredictable and usually clinically insignificant.
3. **Volume of distribution (Vd)**: TThe Vd reflects the extent to which a drug is distributed into tissues relative to the plasma. Drugs with a large Vd (>1 L/kg)—typically due to high lipid

solubility and low plasma PB—distribute extensively into extravascular compartments and are poorly accessible to dialysis. Dialysis acts on the intravascular space. Thus, for drugs with large Vd, only a small proportion is present in plasma at any given time. Even if the plasma concentration is reduced by dialysis, the total body clearance remains limited due to slow redistribution from tissues. A classic example is digoxin, which has a very large Vd (~7 L/kg) and is poorly removed by dialysis despite its low MW. Similarly, lipophilic β-blockers such as propranolol and carvedilol, with Vd values ranging from 2 to 5 L/kg or more, exhibit minimal clearance; carvedilol's dialytic clearance is near zero. Conversely, drugs with low Vd—indicating confinement to plasma and extracellular fluid—are more readily dialyzed. Lithium exemplifies this: with a low Vd (~0.7 L/kg) and no PB, it remains within the extracellular space and is highly dialyzable (397). In general, hydrophilic drugs (often low Vd) are efficiently cleared by dialysis if their MW and PB allow for it. Highly lipophilic agents, such as benzodiazepines or tricyclic antidepressants (with very large Vd), are largely tissue-bound and thus not removed by dialysis effectively. Figure 10.1 summarizes the evaluation of drug characteristics to assess the potential increment of drug clearance by HDF (397).

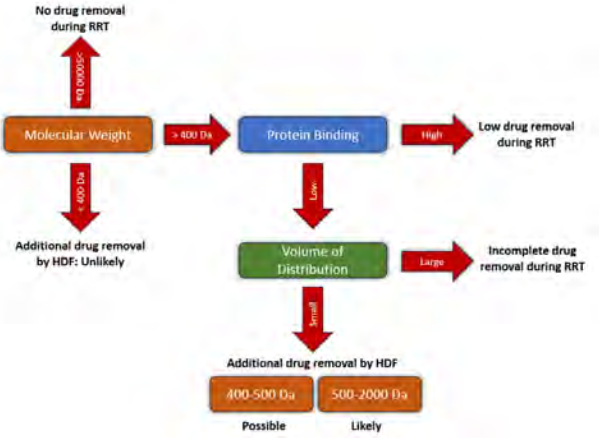

Figure 10.1 | Hemodiafiltration and drug pharmacokinetic properties.

4. **Route of elimination**: The elimination of a drug from the systemic circulation occurs through both renal and non-renal pathways. The relevance of dialysis in drug removal largely depends on the predominant route of elimination. For medications that undergo significant non-renal clearance—primarily through hepatic metabolism—dialysis contributes minimally to overall elimination. For instance, warfarin is almost entirely metabolized by the liver and excreted mostly unchanged in the urine; it does not accumulate in kidney failure and is not dialyzable. Similarly, many benzodiazepines and opioids are primarily metabolized hepatically; dialysis demonstrates minimal effect on their parent compounds. Nevertheless, some of their active metabolites, such as morphine-6-glucuronide or 1-hydroxymidazolam, are excreted renally and may accumulate in patients with impaired kidney function. This has the potential to lead to prolonged sedation or toxicity. In contrast, drugs that are eliminated predominantly via the kidneys will accumulate in renal failure and may be removed by dialysis effectively. Kidney clearance encompasses glomerular filtration, active tubular secretion, and reabsorption. Impairment of renal clearance may involve not only a reduction in glomerular filtration but also decreased active secretion or reabsorption, as observed with specific agents such as piperacillin or flucloxacillin. In general, the greater the contribution of renal clearance to a drug's total elimination, the more significant the role of KRT becomes in its removal. It is also important to recognize that kidney failure can alter other pharmacokinetic processes, including drug absorption, distribution, and metabolism. Drug absorption may be reduced due to uremic neuropathy, intestinal edema, or interactions with concomitant medications. These alterations further complicate pharmacologic management in patients undergoing dialysis.

10.3 | Patient characteristics

Critical illness can significantly alter drug pharmacokinetics and enhance variability in clearance.

Conditions such as sepsis, volume expansion, and capillary leak syndrome promote fluid shifts from the intravascular to the interstitial space, resulting in increased Vd. Concurrent hypoalbuminemia reduces PB, thereby increasing the free (unbound) fraction of drugs. This shift may increase the dialyzability of normally protein-bound drugs more amenable to removal by dialysis.

Furthermore, oxidative metabolic pathways may be either upregulated or impaired in critically ill patients, influencing the metabolism of certain drugs. Other metabolic processes, such as acetylation, may also be affected, leading to altered drug clearance dynamics.

The presence of residual kidney function plays an important role, particularly for drugs that undergo active tubular secretion (e.g., piperacillin, oseltamivir) or tubular reabsorption (e.g., lithium, levetiracetam). Even minimal residual kidney function can contribute significantly to total drug clearance and must be considered when individualizing dosing regimens. For example, a patient with residual diuresis may continue to eliminate certain drugs between HDF sessions, potentially requiring a different dosing strategy than an anuric patient with no remaining kidney function.

10.4 | Mechanisms of drug clearance in HD vs. HDF

Several factors influence drug clearance during dialysis, including treatment duration, frequency, and intensity. HD primarily facilitates solute removal through **diffusion** across a semi-permeable membrane, where blood and dialysate flow on opposite sides, allowing solutes to move along concentration gradients. Small molecules diffuse readily, while larger solutes exhibit slower diffusion kinetics (397). Low-flux HD removes low-molecular-weight compounds efficiently; however, its effectiveness declines as molecular size increases. High-flux HD employs membranes with larger pore sizes and incorporates a degree of convective transport, thereby enhancing the clearance of middle molecules—those up to a few thousand Da in molecular weight (397).

In HD, solute removal also occurs via **ultrafiltration** (fluid removal under hydrostatic pressure), which contributes to solute clearance by solvent drag. HDF combines diffusion and high-volume **convection**. In HDF, a high-flux dialysis filter, a controlled ultrafiltration rate, and sterile replacement fluid infusion are used. This yields a high convective clearance in addition to diffusive clearance (397). Convection can remove larger solutes that diffuse poorly, efficiently: as large volumes of plasma water are filtered, solutes up to ~30–40 kDa can be "dragged" through the membrane, provided they fit through the pores (397). Consequently, HDF is particularly effective at removing larger molecules that are poorly cleared by diffusion alone. It is important to note that both HD and HDF primarily act on the intravascular compartment; drugs distributed in extravascular tissues may subsequently redistribute into the plasma between sessions. In general, the combined use of diffusive and convective mechanisms in HDF yields superior overall solute and drug clearance compared to HD, particularly for compounds with higher molecular weights or limited diffusivity (397).

Several **prescription-dependent parameters** modulate drug clearance in both HD and HDF. Higher blood and dialysate flow rates sustain steep concentration gradients, thereby enhancing diffusion.

Key dialyzer characteristics—such as surface area, ultrafiltration coefficient, and membrane composition—also impact solute removal. Membranes with larger surface areas or increased porosity promote greater clearance. Adsorptive properties of the membrane

may further contribute to drug removal, particularly for protein-bound compounds.

In HDF, convective volume is a critical determinant of solute clearance: higher ultrafiltration volumes, provided that appropriate fluid replacement is administered, substantially enhance the elimination of middle and larger molecules (397).

Regardless of modality, only the free (unbound) fraction of a drug in plasma is available for removal, and solute movement continues until a dynamic equilibrium is achieved between blood and dialysate compartments.

Post-dialysis, plasma drug concentrations may increase again due to redistribution from peripheral tissues. In clinical practice, dialysis-related drug clearance is expressed either as a clearance rate (mL/min) or as a percentage removed per session. This dialysis-associated clearance is additive to any residual renal clearance the patient retains. A detailed understanding of the interaction between diffusive and convective mechanisms is essential for predicting the dialytic behavior of specific drugs.

The main characteristics of drug clearance during HDF are described in Table 10.1.

Drug characteristics	**Molecular weight**
	Protein binding
	Volume of distribution
	Route of elimination
Patient characteristics	**Disease state (e.g., sepsis)**
	Hypo-albuminemia
	Residual kidney function
	Body size
Dialysis characteristics	**Convection volume**
	Dialyzer specifications (KUF, membrane surface area, membrane composition)
	Blood and dialysate flow rate
	Treatment time
	Treatment frequency

Table 10.1 | Determinants of drug clearance during HDF.

10.5 | Anti-infective agents during HDF

Anti-infective agents, including antibacterial, antifungal (antimycotic), and antiviral compounds, display a broad spectrum of pharmacokinetic and physicochemical properties that influence their behavior during dialysis. Although data on drug clearance during conventional HD are available for many of these agents, specific evidence regarding their removal by online HDF remains limited. To optimize anti-infective therapy in patients undergoing HDF, it is essential to select dosing regimens that consider both the drug's pharmacokinetic profile and the enhanced solute removal capabilities of HDF, particularly its convective clearance. Therapeutic drug monitoring (TDM) serves as an important strategy for individualized dosing in this context. By measuring drug concentrations in biological fluids, TDM facilitates personalized dose adjustments based on each patient's pharmacokinetic response, thereby enhancing therapeutic efficacy and reducing the risk of toxicity.

Aminoglycosides (tobramycin, gentamicin, amikacin, streptomycin, netilmicin): Aminoglycosides are small, hydrophilic antibiotics (e.g., gentamicin MW ~478 Da) with negligible PB and a low Vd (~0.25 L/kg). They are almost entirely eliminated renally. Consequently, in ESKD these drugs have prolonged half-lives, but they are also highly dialyzable. Intermittent HD can remove a large fraction of an aminoglycoside dose. HDF and high-flux dialyzers increase this clearance further. As a result, dosing for gentamicin in HD patients usually involves giving a dose after dialysis or using higher doses less frequently, as well as monitoring levels. HDF does not dramatically change aminoglycoside removal compared to high-flux HD, because even purely diffusive HD already clears them efficiently (their small size makes diffusion dominant). The key concern is to avoid accumulation and toxicity by accounting for the significant dialysis clearance. In practice, TDM is often employed for aminoglycosides in HD patients. A summary of aminoglycosides characteristics is listed in Table 10.2.

Aminoglycosides	MW (Da)	PB (%)	Vd (L/kg)	HDF Removal	Clinical Considerations
Gentamicin	478	0-30	0.23-0.30	Possibly	Full dose pre-dialysis + TDM
Tobramycin	467.5	<5	0.22–0.33	Possibly	Full dose pre-dialysis + TDM
Amikacin	585.6	<20	0.22–0.29	Likely	Full dose pre-dialysis + TDM
Streptomycin	581.6	34-35	0.26	Likely	Full dose pre-dialysis + TDM
Netilmicin	475.6	<5	0.16–0.3	Possibly	Full dose pre-dialysis + TDM

Table 10.2 | Aminoglycosides removal; MW = molecular weight; PB = protein binding; Vd = Volume of distribution. Based on data from Jager et al. (397).

Glycopeptides (vancomycin, teicoplanin): Vancomycin is a glycopeptide hydrophilic antibiotic with a middle MW (~1,449 Da) and moderate PB (~30–50%). Its Vd is about 0.6–1.0 L/kg—primarily in extracellular fluid—and >80% of it is excreted by the kidneys (397). Vancomycin was thought to be poorly dialyzable with low-flux membranes. HDF allows even more efficient removal of vancomycin (and similar-sized antibiotics) than diffusion alone. Therefore, when a patient is switched from standard HD to HDF, vancomycin dosing may need to be intensified to avoid underdosing. This means that HD patients on vancomycin often require supplemental dosing after each dialysis treatment to maintain therapeutic levels. A common strategy is to administer vancomycin during dialysis or post-dialysis on HD days, with doses adjusted based on pre-dialysis trough levels. ESKD patients usually need 1 g once or twice weekly. In patients receiving HDF treatment, higher doses are required; possible doses are 1 g initially, followed by 500 mg at every dialysis session for 3 sessions (398). A summary of glycopeptides characteristics is listed in Table 10.3.

Glycopeptides	MW (Da)	PB (%)	Vd (L/kg)	HDF Removal	Clinical Considerations
Teicoplanin	1875–1891	90–95	0.94–1.4	Likely	Post-dialysis, as high-flux HD + TDM
Vancomycin	1449	10–60	0.47–1.1	Likely	Post-dialysis, as high-flux HD + TDM

Table 10.3 | Glycopeptides removal; MW = molecular weight; PB = protein binding; Vd = Volume of distribution. Based on data from Jager et al. (397).

Penicillins: Amoxicillin, clavulanic acid, and benzylpenicillin are hydrophilic compounds, have a relatively low MW (<500 Da), with low Vd, and a range of PB characteristics, from 15% to above 80%. High-flux HD removes them with an unlikely additional effect of convection (397). Flucloxacillin has a PB of 95% and is not dialyzed (398). Piperacillin (±Tazobactam) has a relatively high MW of 517.6 Da and low PB. The addition of convection to diffusion increases its clearance (400), and the dose is as in GFR <20 mL/min. A summary of penicillins characteristics is listed in Table 10.4.

Penicillins	MW (Da)	PB (%)	Vd (L/kg)	HDF Removal	Clinical Considerations
Amoxicillin	365.4	15–25	0.3	Unlikely	Post-dialysis, as high-flux HD (+TDM)
Clavulanic acid	199.2	25	0.3	Unlikely	Post-dialysis, as high-flux HD (+TDM)
Benzylpenicillin	334.4	60–85	0.3–0.42	Unlikely	Post-dialysis, as high-flux HD (+TDM)
Flucloxacillin	453.9	95	0.13	Unlikely	Post-dialysis, as high-flux HD (+TDM)
Piperacillin	517.6	20–30	0.18–3	Likely	Post-dialysis, as eGFR 10–20 mL/min (+TDM)
Tazobactam	300.3	0.18–0.33	20–30	Unlikely	Post-dialysis, as high-flux HD (+TDM)

Table 10.4 | Penicillins removal; MW = molecular weight; PB = protein binding; Vd = Volume of distribution. Based on data from Jager et al. (397).

C**ephalosporins:** Ceftazidime (MW 546.6 Da), cefuroxime (MW 424.4 Da), and cefotaxime (MW 455.5 Da) have a low Vd and lower PB (<50%). They are cleared efficiently by dialysis, and increased drug removal during HDF is anticipated, so dosing frequency must be adjusted, or supplemental doses given (397). Due to their high PB, 85–95% and 80%, respectively, extracorporeal clearance by HDF is less likely for ceftriaxone and cefazolin (343). TDM should be employed for cephalosporins in HD patients. A summary of cephalosporins characteristics is listed in Table 10.5.

Cephalosporins	MW (Da)	PB (%)	Vd (L/kg)	HDF Removal	Clinical Considerations
Ceftazidime	546.6	5–24	0.18–0.4	Likely	Post-dialysis, as eGFR 10–20 mL/min (+TDM)
Cefuroxime	424.4	33–50	0.13–0.18	Possibly	Post-dialysis, as high-flux HD (+TDM)
Cefotaxime	455.5	40	0.15–0.55	Possibly	Post-dialysis, as high-flux HD (+TDM)
Ceftriaxone	554.6	85–95	0.12–0.18	Possibly	Post-dialysis, as high-flux HD (+TDM)
Cefazolin	454.5	80	0.13–0.22	Possibly	Post-dialysis, as high-flux HD (+TDM)

Table 10.5 | Cephalosporins removal; MW = molecular weight; PB = protein binding; Vd = Volume of distribution. Based on data from Jager et al. (397).

Carbapenems: Imipenem, cilastatin, and meropenem have a relatively low MW (<500 Da), low Vd, and low PB characteristics, ranging from 2% to 40%. High-flux HD removes them with an unlikely additional effect of convection (397). Tamme et al. have shown that, in patients with sepsis treated with HDF, a substantial amount of doripenem was eliminated (397, 401). Ertapenem PB is 85-95%, and its removal by convection is unlikely. TDM should be employed for carbapenems in HD patients (397). A summary of carbapenems characteristics is listed in Table 10.6.

Carbapenems	MW (Da)	PB (%)	Vd (L/kg)	HDF Removal	Clinical Considerations
Imipenem	317.4	13–21	0.17–0.3	Unlikely	Post-dialysis, as high-flux HD (+TDM)
Cilastin	380.4	40	0.22	Unlikely	Post-dialysis, as high-flux HD (+TDM)
Meropenem	383.5	2	0.35	Unlikely	Post-dialysis, as high-flux HD (+TDM)
Doripenem	420.5	8	0.24	Possibly	Post-dialysis, as high-flux HD (+TDM)
Ertapenem	475.5	85–95	0.1	Unlikely	Post-dialysis, as high-flux HD (+TDM)

Table 10.6 | Carbapenems removal; MW = molecular weight; PB = protein binding; Vd = Volume of distribution. Based on data from Jager et al. (397).

Sulfonamides and trimethoprim: Trimethoprim, sulfamethoxazole, and sulfadiazine have a relatively low MW (<300 Da), moderate PB, and a low Vd. HD clears these compounds, and no additional clearance by HDF is expected (397).

Macrolides: These lipophilic agents have a large Vd, moderate to high degree of PB, and low to moderate renal clearance. Therefore, neither HD nor HDF is expected to remove macrolides efficiently from the plasma (397).

Quinolones: Ciprofloxacin, levofloxacin, moxifloxacin, norfloxacin, and ofloxacin are lipophilic agents, with large Vd and a relatively low MW. Consequently, they exhibit minimal removal by high-flux HD and HDF (397).

Other antibiotics: Colistin and the inactive prodrug colistin methanesulfonate (CMS) have a small Vd and moderate PB. Due to the high MW of CMS, additional clearance from HDF is likely (397). Normal loading dose in critically ill patients, the non-HDF days: 2.25 million units/day in 2 divided doses; HDF days: 3 million units/day after dialysis (399). Metronidazole is a lipophilic compound with a moderate Vd, MW 171.2 Da, and PB ~20%. No additional HDF removal compared with HD is anticipated (397). Linezolid is a hydrophilic compound with low MW (337.3 Da), small Vd, and moderate PB. No additional removal by HDF compared with HD is anticipated (397). Daptomycin is a hydrophilic compound, with a very high MW (1620.7 Da) and high PB. When using HDF, some extra clearance should be anticipated. TDM assays are not widely used.

Antimycotics: Amphotericin B (MW is ~924 Da, PB >95%), lipophilic with a high Vd. It is essentially not dialyzable by HD or HDF. Itraconazole, voriconazole, and posaconazole are lipophilic compounds with high PB. The HDF removal is unlikely. Fluconazole (MW 306 Da, PB ~10%) is highly water-soluble and is cleared readily by HD. The additional effect of convection is unlikely (397).

Antivirals: Additional effect of convection is unlikely for the following drugs: tenofovir, cidofovir, efavirenz, nevirapine, etravirine, rilpivirine, saquinavir, ritonavir, indinavir, nelfinavir, amprenavir, lopinavir, fosamprenavir, tipranavir, simeprevir, boceprevir, elvitegravir, dolutegravir, aciclovir, ganciclovir, foscarnet, atazanavir, darunavir, and oseltamivir (320). The additional removal by convection is possibly for adefovir dipivoxil, raltegravir, and telaprevir (320).

A summary of antiviral characteristics is listed in Table 10.7.

Antivirals	MW (Da)	PB (%)	Vd (L/kg)	HDF Removal	Clinical Considerations
Adefovir dipivoxil	501.5	<4	0.4	Possibly	Dialyzed. Dose as in GFR<10 mL/min. 10 mg / 72 h
Raltegravir	444.4	83	no data	Possibly	Dialyzed. Dose as in normal renal function
Telaprevir	679.8	59–76	252	Possibly	Possibly dialyzed. Dose as in normal renal function

Table 10.7 | Antivirals removal; MW = molecular weight; PB = protein binding; Vd = Volume of distribution. Based on data from Ashley et al. (399).

10.6 | Vitamins

Current evidence does not support the need to modify vitamin supplementation in patients treated with HDF compared to those receiving conventional HD.

Water-soluble vitamins, particularly vitamin C (ascorbic acid, MW 176 Da) and vitamin B6 (pyridoxine, MW 169 Da), are removed efficiently during dialysis, primarily through diffusion due to their small molecular size and lack of PB (402). However, clinical studies have shown that serum concentrations of these vitamins are not significantly lower in HDF-treated patients compared to those on HD, likely due to dietary intake and standard supplementation practices. Vitamin B12 (cobalamin, MW 1346 Da) presents a different profile. Although it is a water-soluble vitamin, it is highly protein-bound, which limits its dialytic clearance. Differences in its removal between HD and HDF have been reported (404), but the clinical significance of these variations remains uncertain, and no specific dosing adjustments are currently recommended. For other B-complex vitamins such as vitamin B1 (thiamine, MW 265 Da), B2 (riboflavin, MW 376 Da), and B9 (folate, MW 441 Da), the dialytic removal is generally low. This is primarily due to their larger distribution volumes and, in some cases, moderate PB, which reduces their availability in plasma for filtration or diffusion.

In summary, although the dialytic clearance of certain vitamins differs among individual compounds and dialysis modalities, routine vitamin supplementation practices are generally adequate for both.

10.7 | Anticoagulants

Coumarin derivatives, such as warfarin, are metabolized by the liver, have a high degree of plasma PB, primarily to albumin. As a result of their pharmacokinetic properties—namely, hepatic elimination and limited free plasma fraction—coumarins are not removed appreciably during HDF. Consequently, their anticoagulant effect remains unaffected by the convective and diffusive processes inherent to HDF. In patients receiving long-term oral anticoagulation with coumarins, regular monitoring of the international normalized ratio (INR) is essential to ensure therapeutic efficacy and to minimize the risk of bleeding or thrombotic complications. Coumarins are not suitable agents for anticoagulation of the extracorporeal circuit during dialysis procedures. However, in patients already receiving coumarin therapy, it is recommended to initiate extracorporeal anticoagulation with a reduced heparin dose—typically 50% of the standard starting dose—to mitigate the cumulative anticoagulant effect and reduce the risk of bleeding, as supported by clinical guidance (326).

Unfractionated Heparins: See Chapter 8.2.C.

Low-Molecular-Weight Heparins: See Chapter 8.2.C.

Indirect Factor Xa Inhibitors: For patients with heparin-induced thrombocytopenia (HIT), fondaparinux (MW 1728 Da) can be considered as an alternative. It is excreted to 64–77% by the kidney as an unchanged compound (399). The clearance of fondaparinux is higher during high-flux HD as compared to low-flux HD (405). Mahieu et al. evaluated the feasibility, effectiveness, tolerability, and pharmacokinetics of fondaparinux anticoagulation in HDF (406). Their recommendation is to adjust the dosage of fondaparinux to body weight and to initiate therapy at a dose of 0.03 mg/kg to prevent accumulation, and dose titration can be achieved by targeting post-dialysis anti-Xa activity (406). Fondaparinux may be used safely and provides adequate anticoagulation for HDF in patients with HIT (406).

Direct Thrombin and Direct Factor Xa Inhibitors: Dabigatran (MW 627 Da) is a potent, competitive, reversible direct thrombin inhibitor and is the main active principle in plasma. Mainly excreted in the urine (85%) and 6% via the feces (399), HD removes approximately 50–60% of dabigatran over 4 hours with a 700 mL/min dialysate flow rate and a blood flow rate of 200 mL/min or 350–390 mL/min, respectively (399). The risk of accumulation and the unpredictable

effect of dialysis rule out dabigatran for use in HD patients. There are currently no published clinical data on the use of bivalirudin or argatroban during HDF. Both agents, direct thrombin inhibitors, may be employed for extracorporeal circuit (ECC) anticoagulation in patients with HIT, with dosing guided by activated partial thromboplastin time (aPTT) or activated clotting time (ACT) (320). No significant differences in pharmacokinetics or anticoagulant efficacy are expected between HD and HDF for these agents (320). Direct oral anticoagulants (DOACs), also referred to as non-vitamin K antagonist oral anticoagulants (NOACs) historically, include agents such as dabigatran, rivaroxaban, apixaban, and edoxaban. These medications are generally contraindicated in patients with severe renal impairment or ESKD, due to their partial or predominant renal clearance and limited clinical data in dialysis populations (407). Their removal by either HD or HDF is inefficient due to extensive PB and a large Vd, which can lead to a rebound phenomenon after dialysis (320).

10.8 | Antiepileptic drugs (AEDs)

Patients with ESKD may require AEDs for seizure control or other indications such as neuropathic pain. In the context of HDF, it is essential to understand the pharmacokinetics and dialyzability of AEDs to prevent subtherapeutic exposure, accumulation, or toxicity.

Key suggestions:

- Post-dialysis supplementation: Needed for highly dialyzable AEDs like levetiracetam, gabapentin, and pregabalin to prevent trough-level drops and seizure recurrence.
- Avoid relying on total drug levels in hypoalbuminemic patients (e.g., with phenytoin or valproic acid). Measure or estimate free levels for dosing accuracy.
- TDM is suggested when available, especially for drugs with a narrow therapeutic index or when transitioning between dialysis modalities (e.g., from HD to HDF).

A summary of antiepileptic characteristics is listed in Table 10.8.

Drug	MW (Da)	PB (%)	Vd (L/kg)	HDF Removal	Clinical Considerations
Levetiracetam	~170	<10	0.5–0.7	Likely	Dialyzed. 750 mg loading dose then 500–1000 mg once daily
Gabapentin	~171	0%	0.6–0.8	Likely	Dialyzed. Loading dose of 300–400 mg in pts who have never received gabapentin. Maintenance dose of 200–300 mg after each HD session and increase according to tolerability.
Pregabalin	~159	<1	0.4–0.6	Likely	Dialyzed. Dose as in GFR <15 mL/min. Initial dose 25 mg daily and titrate according to tolerability and response.
Topiramate	~339	~15–20	0.6–0.8	Likely	Dialyzed. Dose as in GFR=10–20 mL/min. Initially 50% of normal dose and increase according to response.
Lamotrigine	~256	~55%	~1.4	Possibly	Unknown dialyzability. Dose as in GFR<10 mL/min. Monitor for loss of efficacy after HDF.

Drug	MW (Da)	PB (%)	Vd (L/kg)	HDF Removal	Clinical Considerations
Phenobarbital	~232	~50%	~0.6–1.2	Possibly	Some clearance during HDF. Dose as in GFR<10 mL/min. Reduce dose by 25–50% and avoid very large single doses. Consider monitoring levels.
Phenytoin	~252	~90	0.6	Possibly	Only ~10% is free. Not significantly removed. Dose as in normal renal function. Dose based on free phenytoin levels in hypoalbuminemia.
Valproic Acid	~144	>90	0.15–0.2	Unlikely	Highly PB. Not dialyzable. Dose unaffected by HDF. Monitor free drug in hypoalbuminemia.
Carbamazepine	~236	~75–85	0.8–2.0	Unlikely	Lipophilic and PB. Dialysis not clinically significant. Dose as in normal renal function.
Clonazepam	~315	~85%	~3.0	Unlikely	Unknown dialyzability. Dose as in GFR<10 mL/min. Start at low dose and increase according to response.

Table 10.8 | Antiepileptic removal; MW = molecular weight; PB = protein binding; Vd = Volume of distribution. Based on data from Ashley et al. (399)

Valproic acid (VPA) is not removed easily by extracorporeal therapies (ECTRs) because it is highly protein-bound at therapeutic levels (408). However, in acute overdose, PB becomes saturated, increasing the free drug fraction and enhancing extracorporeal clearance (408). The Extracorporeal Treatments in Poisoning (EXTRIP) workgroup recommends ECTR in valproic acid toxicity under the following circumstances (408). In case of acute VPA intoxication, ECTR is recommended if VPA concentrations exceed 1,300 mg/L or if cerebral edema or shock attributable to VPA toxicity are present. ECTR is suggested in patients with VPA concentrations >900 mg/L, coma, or respiratory depression requiring mechanical ventilation, hyperammonemia, or pH <7.10. Among available modalities, HDF has been proposed as an effective and safe option for VPA removal in acute intoxication (409).

10.9 | Other Medications

Table 10.9 lists selected medications commonly used in dialysis patients, along with their key pharmacokinetic properties and dialyzability in HDF and high-flux HD. These drugs span various categories, including cardiovascular and others.

Drug	MW (Da)	PB (%)	Vd (L/kg)	HDF Removal	Clinical Considerations
Acetylcysteine	163	50	0.33-0.47	Likely	Dose as in normal renal function.
Allopurinol	136.1	<5	1.6	Likely	Dose as in GFR<10 mL/ min: 100 mg daily or 100 mg on alternate days
Ascorbic acid	176.1	25	N/A	Likely	Dose as in normal renal function.
Aspirin	180.2	80–90	0.1–0.2	Likely	Dose as in normal renal function
Atenolol	266	3	1.1	Likely	Dose after dialysis to maintain BP control.
Baclofen	213	30	0.7	Likely	Dialyzable; use reduced dose; 5 mg once a day and titrate according to response.
Enalapril	492	50-60	0.17	Likely	Dose after dialysis; dose as in GFR=10–20 mL/min: start with 2.5 mg per day and increase according to response.
Folic acid	441.4	70	N/A	Likely	Dose as normal renal function
Hydroxyurea	76	75-80	0.5	Likely	Dose after dialysis; 20% of normal dose and titrate to response.
Isosorbide	236.1	<1	2–4	Likely	Dose as in normal renal function
Lisinopril	441	0	0.44-0.51	Likely	Dose post-HDF to maintain BP control. Dose as in GFR<10 mL/min: initial dose 2.5 mg daily and titrate according to response.
Lithium	74	0	0.5-0.9	Likely	Dose after dialysis; avoid if possible or reduce dose to 25–50% and monitor concentration carefully.
Melatonin	232.3	60	65–88	Likely	Dose as in GFR<10 mL/min

Drug	MW (Da)	PB (%)	Vd (L/kg)	HDF Removal	Clinical Considerations
Metoprolol tartrate	684.8	10–12	5.6	Likely	Dose as in GFR<10 mL/min. start with small doses and titrate in accordance with response.
Midodrine HCl	290.7	Negligible	N/A	Likely	Initial dose, 2.5 mg if <70 kg, 5 mg if >70 kg. For HD pts, start at a low dose and increase to a maximum of 30 mg; a second dose can be given midway through dialysis (maximum dose 10 mg).
Morphine	285	20–35	3-5	Likely	The active metabolites are removed significantly. Dose as in GFR<10 mL/min; use small doses (25% of dose), and extended dosing intervals. Titrate according to response.
Oxycodone HCl	351.8	45	1.2–6.31	Likely	Dose as in GFR<10 mL/min. Start with small doses e.g 50% of dose.
Ranitidine	314	15	1.4	Likely	Dose as in GFR<10 mL/min. Oral: 50–100% of normal dose. IV: 50 mg 12 hourly
Sitagliptin	523.3	38	198	Likely	Dose as in GFR<30 mL/min: 25 mg once daily.
Theophylline	180	40–60	0.5	Likely	Removed in toxicity; monitor levels if chronic use. Dose as in normal renal function.
Tramadol HCL	299.8	20	45721	Likely	Dose as in GFR < 10 mL/min. 50 mg every 8 hours initially and titrate dose as tolerated.

Table 10.9 | MW = molecular weight; PB = protein binding; Vd = Volume of distribution; N/A= not available. Based on data from Ashley et al. (399).

Table 10.10 lists selected medications commonly used in dialysis patients, along with their key pharmacokinetic properties and their dialyzability in HDF and high-flux HD, categorized as “unlikely.”

Drug	MW (Da)	PB (%)	Vd (L/kg)	HDF Removal	Clinical Considerations
Amlodipine besylate	567.1	>95	20	Unlikely	Dose as in normal renal function
Calcitriol	416.6	99.9	No data	Unlikely	Not dialyzed. Dose as in normal renal function
Cetirizine HCl	461.8	93	0.45	Unlikely	Dose as in GFR<10 mL/min
Cinacalcet HCl	393.9	93–97	1000	Unlikely	Dose as normal renal function
Escitalopram oxalate	414.4	<80	12–26	Unlikely	Dose as in GFR<10 mL/min
Ezetimibe	409.4	99.7	N/A	Unlikely	Dose as normal renal function
Famotidine	337.4	15–20	1.1–1.4	Unlikely	Dose as in GFR<10 mL/min
Ferrous sulfate	278	N/A	N/A	Unlikely	Dose as normal renal function
Furosemide	533.6	99.5	396	Unlikely	Dose as normal renal function
Glipizide	445.5	98–99	0.13–0.16	Unlikely	Dose as in GFR<10 mL/min
Hydralazine HCl	196.6	87	0.5–0.9	Unlikely	Dose as in GFR=10–20 mL/min.
Hydroxyzine HCl	447.8	N/A	19.5	Unlikely	Dose as in GFR=10–20 mL/min
Lanthanum carbonate	457.8	>99.7	Not abs.	Unlikely	Dose as in normal renal function
Levothyroxine sodium	798.9	99.97	8.7–9.7	Unlikely	Dose as in normal renal function
Loratadine	382.9	97–99	N/A	Unlikely	Dose as in normal renal function
Losartan potassium	461	>98	0.4	Unlikely	Dose as in GFR<10 mL/min
Patiromer calcium sorbitex	344.5	N/A	N/A	Unlikely	Dose as normal renal function
Polyethylene glycol	3350	Not abs.	Not abs.	Unlikely	Dose as in normal renal function
Prednisolone	360.4	70–95	1.3–1.7	Unlikely	Dose as in normal renal function
Sevelamer carbonate	Large	N/A	N/A	Unlikely	Dose as in normal renal function

Drug	MW (Da)	PB (%)	Vd (L/kg)	HDF Removal	Clinical Considerations
Sucroferric oxyhydroxide	866.5	N/A	Not abs.	Unlikely	Dose as in normal renal function.
Torasemide	348.4	>99	0.09–0.33	Unlikely	Dose as in normal renal function

Table 10.10 | MW = molecular weight; PB = protein binding; Vd = Volume of distribution. N/A= not available; Not abs. = Not absorbed. Based on data fromAshley et al. (399).

Table 10.11 lists selected medications commonly used in dialysis patients, along with their key pharmacokinetic properties and their dialyzability in HDF and high-flux HD, categorized as “unknown and possibly.”

Drug	MW (Da)	PB (%)	Vd (L/kg)	HDF Removal	Clinical Considerations
Amiodarone HCl	681.8	96	60	Unknown	Dose as in normal renal function.
Atorvastatin calcium	1209.4	>98	381	Unknown	Dose as in normal renal function.
Bisoprolol	767	30	3.5	Possibly	Partially cleared; adjust dose post-HDF if needed.
Bumetanide	364.4	95	0.2–0.5	Unknown	Dose as in normal renal function
Calcium acetate	158.2	N/A	N/A	Unknown	Dose as in normal renal function
Calcium carbonate	100.1	40	N/A	Unknown	Dose as in normal renal function.
Carvedilol	406.5	>98	2	Unknown	Dose as in normal renal function.
Cholecalciferol (vit. D3)	384.6	50-80	N/A	Possibly	Dose as in GFR<10 mL/min
Clonidine HCl	266.6	30–40	3–6	Unknown	Dose as normal renal function
Doxazosin mesylate	547.6	98	1–1.7	Unknown	Dose as normal renal function
Labetalol HCl	364.9	50	5.6	Unknown	Dose as in normal renal function
Lidocaine HCl	288.8	66	1.3	Unknown	Dose as normal renal function
Loperamide HCl	513.5	80	N/A	Unknown	Dose as in GFR<10 mL/min
Mirtazapine	265.4	85	107	Unknown	Dose as in GFR<10 mL/min
Nifedipine	346.3	92-98	1.4	Unknown	Dose as in GFR<10 mL/min
Omeprazole	345.4	95	0.3	Unknown	Dose as normal renal function
Ondansetron HCl	293.4	70–76	2	Unknown	Dose as normal renal function
Pantoprazole sodium	383.4	98	0,15	Unknown	Dose as in normal renal function
Rosuvastatin	1001	90	134	Unknown	Dose as in GFR<10 mL/min
Sertraline HCl	342.7	>98	25	Unknown	Dose as in normal renal function

Drug	MW (Da)	PB (%)	Vd (L/kg)	HDF Removal	Clinical Considerations
Spironolactone	416.6	90	N/A	Unknown	Dose as in GFR<10 mL/min
Tamsulosin HCl	445	99	0.2	Unknown	Dose as in GFR<10 mL/min
Tizanidine	290	30	2.4	Possibly	Partially removed; dose as in GFR<25 mL/min; initial dose 2 mg once daily and slowly increase by 2 mg increments. Increase the daily dose before increasing the frequency of administration.
Trazodone HCl	408.3	89–95	1–2	Unknown	Dose as in GFR<10 mL/min: 50 mg every 8 hours initially and titrate dose as tolerated.
Valsartan	435.5	94–97	17	Unknown	Dose as in GFR=10–20 mL/min
Venlafaxine	277	27	7.5	Possibly	Partially removed; active metabolite may accumulate. Dose as in GFR<10 mL/min: reduce total dose by 50%.

Table 10.11 | MMW = molecular weight; PB = protein binding; Vd = Volume of distribution. N/A= not available; Not abs. = Not absorbed. Based on data from Ashley et al. (399).

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Dr. Stuard supports NephroCare medical leadership in his role as Chief Clinical Officer for the Europe, Middle East, and Africa (EMEA) regions. He previously served as vice president and head of the EMEA Center of Excellence for Clinical and Therapeutic Governance and continues as the operational medical counsel for the company's clinical services business in EMEA. Dr. Stuard's distinguished career includes more than 13 years in clinical governance roles with Fresenius Medical Care's EMEA and Latin America regions. He has also served as a director/consultant for nephrology and dialysis departments in Italian public and private hospitals. He has published over 220 scientific publications in peer-reviewed journals.

Dr. Stuard received his PhD in nephrology from the University of Bologna (Italy). He received his Doctor of Medicine and surgery as well as a post-graduate specialization in nephrology, magna cum laude, from the University of Chieti (Italy). He received an award from the European Society of Artificial Organs for his contribution in the field of artificial organs. Dr. Stuard is also a member of European Renal Association Kidney Relief in Disasters Task Force.

Michael S. Anger, MD, FACP, FASN
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Dr. Anger is the Medical Officer for In-Center Dialysis and the Medical Officer for Quality & Regulatory. His medical training and internal medicine residency were completed at Hahnemann University, and his adult and pediatric nephrology fellowships took place at the University of Colorado School of Medicine. He is a clinical professor of medicine at the University of Colorado School of Medicine, Fellow

of the American College of Physicians, Fellow of the American Society of Nephrology, and member of the honor medical society Alpha Omega Alpha. Prior to joining the Global Medical Office at Fresenius Medical Care, Dr. Anger had been the Chief Medical Officer of American Renal Associates as well as president and senior partner of Western Nephrology in Denver, Colorado, where he also led the research and interventional nephrology divisions.

Dinesh K. Chatoth, MD
Chief Clinical Officer
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Dr. Chatoth is the Chief Clinical Officer of Fresenius Kidney Care and serves as Chair of the Pharmaceutical & Therapeutics Committee. He is the former president and Chief Executive Officer of Georgia Nephrology, a 16-member physician practice in Atlanta, Georgia. Dr. Chatoth has also served in different leadership roles at the Gwinnett Health System in Georgia, including serving as the Chair of the Department of Medicine. He is also the former Co-Chair of the East Division Medical Advisory Board for Fresenius Medical Care. He has worked with the KDOQI workgroup for Peritoneal Dialysis and currently serves as a member of the PDOPPS U.S. Advisory Workgroup. He has a keen interest in promoting home dialysis as a modality of choice for patients requiring renal replacement therapy and oversees home therapy initiatives for the Global Medical Office.

Rainer Himmele, MD, MSHM
Senior Vice President, Global Medical Information & Education
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Dr. Himmele obtained his clinical training at the University Children's Hospital, Division of Pediatric Nephrology, in Heidelberg and received his medical education from the Universities of Heidelberg, Vienna, New York, and Zurich. He completed a research doctorate in Molecular Genome Analysis at the German Cancer Research Center

and holds a Master of Science degree in Healthcare Management from the University of Heidelberg and Mannheim Business School.

Dr. Himmele has 25 years of nephrology experience in the U.S. and Europe and is passionate about providing concise medical information, clinical best practice education, and the development of innovative healthcare products that result in meaningful improvements in patient care.

Benjamin E. Hippen, MD, FASN, FAST
Global Head of Clinical Affairs,
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Chief Medical Officer, Care Delivery

Dr. Hippen oversees the global clinical care delivery programs for Fresenius Medical Care, ensuring we deliver exceptional care and support to all patients under our care. Dr. Hippen specializes in ethical, organizational, and public policy issues in nephrology and transplantation. His contributions have advanced patient care initiatives and influenced broader clinical leadership, integrating transplantation into the dialogue among practicing nephrologists and within our Care Delivery framework.

Dr. Hippen received an undergraduate degree from Rice University and completed his medical school and internal medicine residency training at the Baylor College of Medicine. Thereafter, he completed a general nephrology and transplant nephrology fellowship at the University of Alabama in Birmingham. After completing his nephrology and transplant training, Dr. Hippen joined Metrolina Nephrology Associates, P.A. in Charlotte, North Carolina, a 40-nephrologist private practice, where he served as the medical director of two in-center hemodialysis facilities and, for several years, served as the medical director of a home therapies facility. During his time in Charlotte, he became a Clinical Professor of Medicine at the UNC Chapel Hill School of Medicine. Prior to joining Fresenius Medical Care in September 2021, Dr. Hippen served terms on the Ethics Committee and Membership and Professional Standards Committees of the Organ Procurement and Transplantation Network, served on the Board of Directors and was the chair of the Medical Advisory Board of ESRD Network 6, and served on the

founding physician practice board of InterWell Health. Consonant with his ongoing research interests in ethical, organizational, and public policy issues in nephrology and transplantation, Dr. Hippen is the author of more than 70 peer-reviewed articles, essays, reviews, and book chapters.

Robert J. Kossmann, MD, FACP, FASN
Executive Vice President, Global Head of Medical Affairs, Chief Medical Officer, Care Enablement

Dr. Kossmann served as executive vice president and chief medical officer for Fresenius Medical Care (FME) North America from 2019 to 2021 and chief medical officer for FME's Renal Therapies Group, the company's medical equipment and renal pharmaceuticals division, from 2014 to 2019.

Dr. Kossmann has held a variety of leadership roles where he has provided guidance to the nephrology field, including as former president of the Renal Physicians Association (RPA); a founding member of RPA's Nephrology Coverage Advocacy Program (now Policy Advocacy Leadership program); a nephrology advisor to the American Medical Association's Relative Value Scale Update Committee; and founder of the New Mexico Renal Disease Collaborative Group.

A practicing nephrologist for two decades, Dr. Kossmann trained in nephrology at the University of Washington in Seattle and holds his bachelor's and Doctor of Medicine degrees from Case Western Reserve University in Cleveland, Ohio.

Len A. Usvyat, PhD
Senior Vice President
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Len A. Usvyat supports advanced analytics and data-driven functions within FME to advance the Global Medical Office agenda and support the Care Delivery and Care Enablement organizations.

These functions include real-world evidence generation activities as well as applied data science efforts across various parts of the enterprise. Usvyat's team supports these functions through data analytics and data engineering, research, and publications, as well as project management and administrative efforts. The team integrates advanced analytics into the clinical care of people with kidney disease, supports generation of clinical evidence to meet regulatory requirements and post-market surveillance of the FME products portfolio, uses real-world data to examine the clinical and cost effectiveness of FME products, and generates insights that can be used in improving care of people with kidney disease worldwide.

Usvyat chairs FME's Predictive Analytics Steering Committee, co-leads Global Advanced Analytics Alignment days, serves on the Steering Committee for the Apollo database, and works closely with the global MONitoring Dialysis Outcomes (MONDO) initiative, an international consortium of dialysis providers.

Usvyat has published more than 100 manuscripts in peer-reviewed journals. He holds a master's degree from the University of Pennsylvania and a doctorate from the University of Maastricht in the Netherlands.

Franklin W. Maddux, MD, FACP
Global Chief Medical Officer,
Member of the Management Board

Franklin W. Maddux oversees the delivery of high-quality, value-based care for the world's most expansive kidney care organization. His distinguished career encompasses more than three decades of experience as a physician, expert nephrologist, technology entrepreneur, and healthcare executive.

Dr. Maddux joined FME's North America region in 2009 after the company acquired Health IT Services Group, a leading electronic health record (EHR) software company, which he founded. He developed one of the first laboratory electronic data interchange programs for the U.S. dialysis industry and later created one of the first web-based EHR solutions, now marketed under Acumen Physician Solutions.

He previously served as chief medical officer and senior vice president for Specialty Care Services Group and is the former president of Virginia's Danville Urologic Clinic, where he was a practicing nephrologist for nearly two decades. His writings have appeared in leading medical journals, and his pioneering healthcare information technology innovations are part of the permanent collection of the National Museum of American History at the Smithsonian Institution.

An alumnus of Vanderbilt University, Dr. Maddux earned his medical degree from the School of Medicine at the University of North Carolina at Chapel Hill, where he holds a faculty appointment as clinical associate professor.

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