Strategy to Expand High-Volume Hemodiafiltration Worldwide

Stefano Stuard, MD, PhD
Michael S. Anger, MD, FACP, FASN

There is increased scientific evidence that hemodiafiltration (HDF) positively affects clinical outcomes for dialysis patients. However, healthcare policy and reimbursement rates are among the challenges that limit the broader adoption of HDF in many countries. Overcoming these barriers requires that health policy experts look beyond the initial higher cost of HDF to factor in the long-term benefits for both healthcare systems and people on hemodialysis.

Online hemodiafiltration (HDF) is a technologically advanced dialysis modality that utilizes a specifically designed high-flux dialyzer and a dedicated hemodialysis machine.

Online HDF efficiently removes small-molecular-weight uremic solutes mainly through diffusive transport. Simultaneously, medium-sized molecules, such as beta 2-microglobulin, are preferentially removed through convective clearance, which depends on several factors, including blood flow, ultrafiltration (UF) rate, and dialyzer membrane characteristics (pore size and permeability). To maximize the removal of middle-sized toxins through convection, UF exceeds the desired fluid loss, and replacement (substitution, Qsub) fluid is administered to achieve the target fluid balance (Figure 1).

The term "online" refers to the fact that the dialysis machine generates the Qsub fluid from ultrapure dialysate in real time. This eliminates the need for pre-prepared substitution fluid bags.

High-volume HDF is designed to enhance the advantages of online HDF by increasing the Qsub fluid production and consequently boosting the convective clearance, thus enhancing the overall effectiveness of the treatment.

Technical Aspects of HDF

HDF dates to the late 1960s when Henderson published the first article on the use of UF and fluid replacement as a method of blood cleansing,[1] and it has undergone continuous improvement since then.[2] Since the late 1970s, due to the need for large volumes of substitution solution, the fresh sterile and non-pyrogenic (ultrapure) fluid has been made from dialysate and reinfused as substitution fluid (online HDF).[3] The substitution fluid (Qsub) is obtained by the cold sterilization of dialysate, achieved via a two-step ultrafiltration process using sterilizing ultrafilters.

Online HDF treatment modalities can be categorized based on the point of Qsub administration within the extracorporeal circuit into four distinct types.[4,5] The Qsub is introduced before the blood enters the dialyzer in pre-dilution HDF. In post-dilution HDF, the Qsub is infused after the dialyzer into the venous drip chamber (Figure 2). Less commonly utilized, mixed-dilution and mid-dilution HDF infuse the Qsub at distinct points within the extracorporeal circuit. In mixed-dilution HDF, the fluid is added both before and after the dialyzer, whereas in mid-dilution HDF, it is introduced into the midpoint of the circuit.

FIGURE 1 | DIFFUSION AND CONVECTION PROCESS

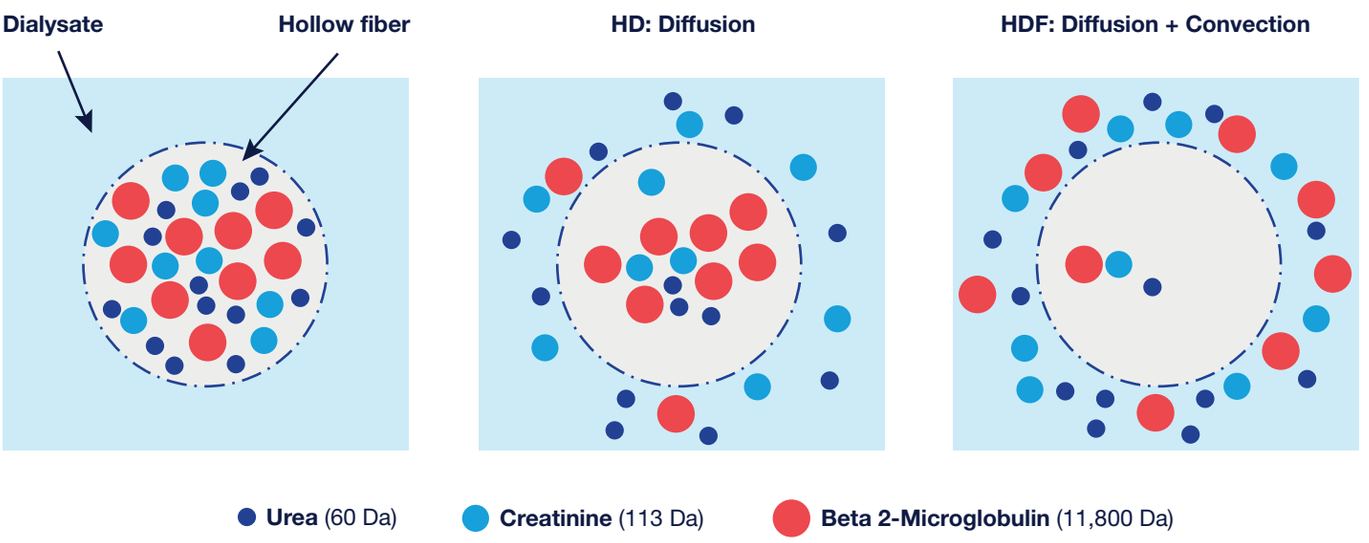
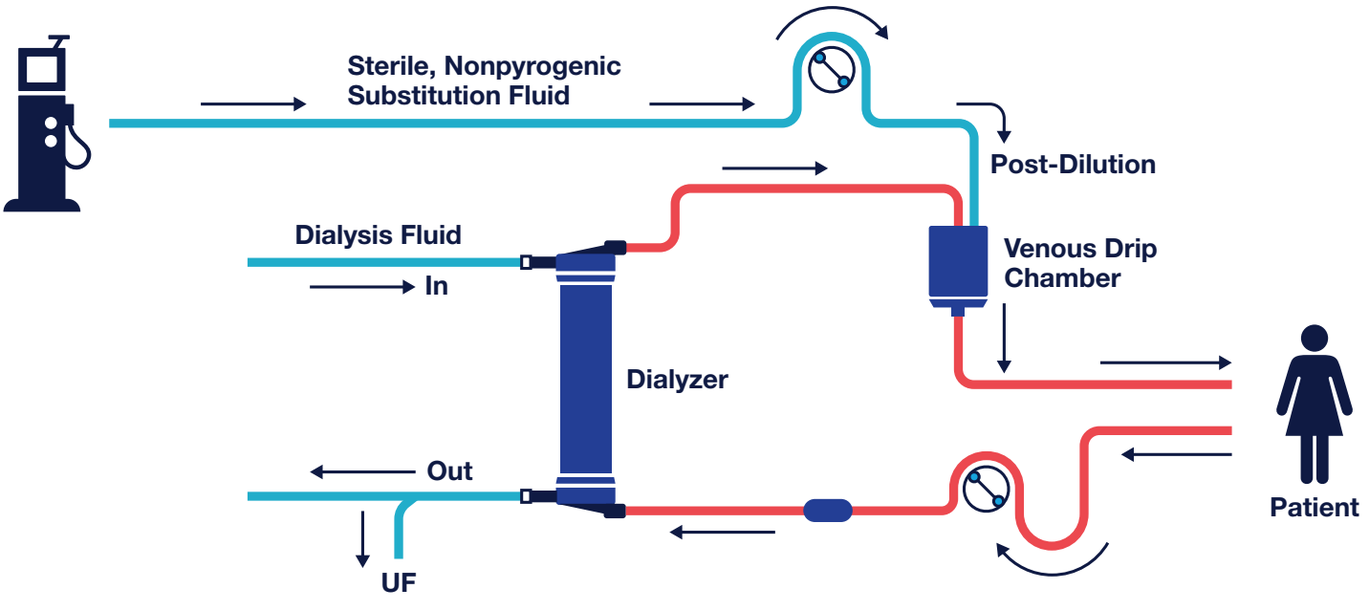


FIGURE 2 | POST-DILUTION ONLINE HEMODIAFILTRATION: THE SUBSTITUTION FLUID IS INFUSED IN THE VENOUS DRIP CHAMBER



In Asia, pre-dilution HDF is preferred due to the lower blood flow rate (Qb) requested. Conversely, post-dilution online HDF is the dominant modality in Europe, accounting for roughly 90% of convective dialysis procedures. Post-dilution online HDF allows for a more favorable balance between elevated low-middle molecule solute clearance removal rates and reduced use of substitution volume compared to other online HDF techniques. The high UF rate increases the risk of membrane fouling with increased transmembrane pressure (TMP), shortened membrane lifespan, and reduced clearances. These factors limit the filtration fraction (UF rate/plasma flow rate x 100%) to around 25%–30% of the Qb.[6] Various automated feedback control systems have been introduced to adjust the infusion rate of Qsub based on Qb and dialyzer TMP. These systems aim to streamline the execution of online HDF while optimizing the intradialytic Qsub.

To mitigate the increased TMP caused by the protein fouling, Qsub is automatically reduced to keep the treatment stable, significantly reducing the number of alarms during dialysis.[7] Among the others, Fresenius Medical Care's (FME) AutoSub plus automatically adapts Qsub according to the Qb, blood viscosity, TMP, and attenuation of pressure pulses. Membrane characteristics are fundamental to minimizing protein fouling. One of the most important is a hydrophilic modification of the synthetic membrane surface to reduce protein adsorption and lead to performance stability during treatments.[8,9,10,11,12]

Clinical Benefits

In recent reviews, the advantages of online HDF compared to high-flux hemodialysis (HF-HD) were summarized.[13,14] Online HDF has demonstrated a direct effect in decreasing the incidence of intradialytic hypotensive episodes, better hemodynamic stability unrelated to improved sodium balance,[15,16,17] and a positive impact on cardiac remodeling.[18,19,20,21] Patients undergoing HDF have exhibited reductions in chronic inflammatory states[21,22] and oxidative stress[22,23] alongside enhancements in endothelial function and cardiovascular stiffness,[24,25,26] progression of atherosclerosis,[27] sympathetic tone activity,[28] and arrhythmogenicity.[29] HDF contributes to improving anemia management,[30,31,32] nutritional status,[32,33] physical activity,[34] enhancement of quality of life,[33,35,36,37] and protection of residual kidney function.[38]

Four large randomized controlled trials (RCTs) have demonstrated the superiority of online HDF over HF-HD with respect to clinical outcomes, particularly in reducing the mortality of individuals with end-stage kidney disease (ESKD).[39,40,41,42] Peters et al. conducted an individual patient data meta-analysis of the four RCTs and found that online HDF was associated with a 14% reduction in all-cause mortality and a 23% reduction in cardiovascular mortality compared to HF-HD.[43] Many retrospective data analysis studies have yielded comparable results, showing a dose-response relationship between substitution/convective volume and survival rate.[44,45,46,47,48,49,50,51,52] Specifically, a substitution/convective volume exceeding 21/23 L per session has been associated with the most favorable effect on lowering mortality.[44,45,46,47,48] In the CONVINCE study, a multinational interventional randomized controlled trial funded by the European Union's Horizon 2020 Research and Innovation Program, 1,360 individuals with ESKD were recruited from 61 dialysis centers from public and private sectors in 8 countries.[53] The post-dilution high dose (volume) HDF (HVHDF), defined as convection volumes ≥ 23 L (range ±1 L) per session, reduced the risk of all-cause mortality by 23% compared to HF-

HD.[53] A recent systematic review and meta-analysis of five RCTs showed that online HDF significantly reduced the risk of cardiovascular-related deaths by 25% and all-cause mortality by nearly 20% compared with the HD group; additionally, HDF effectively reduced the risk of infection-related mortality by 31%.[39, 40, 41, 53, 54, 55]

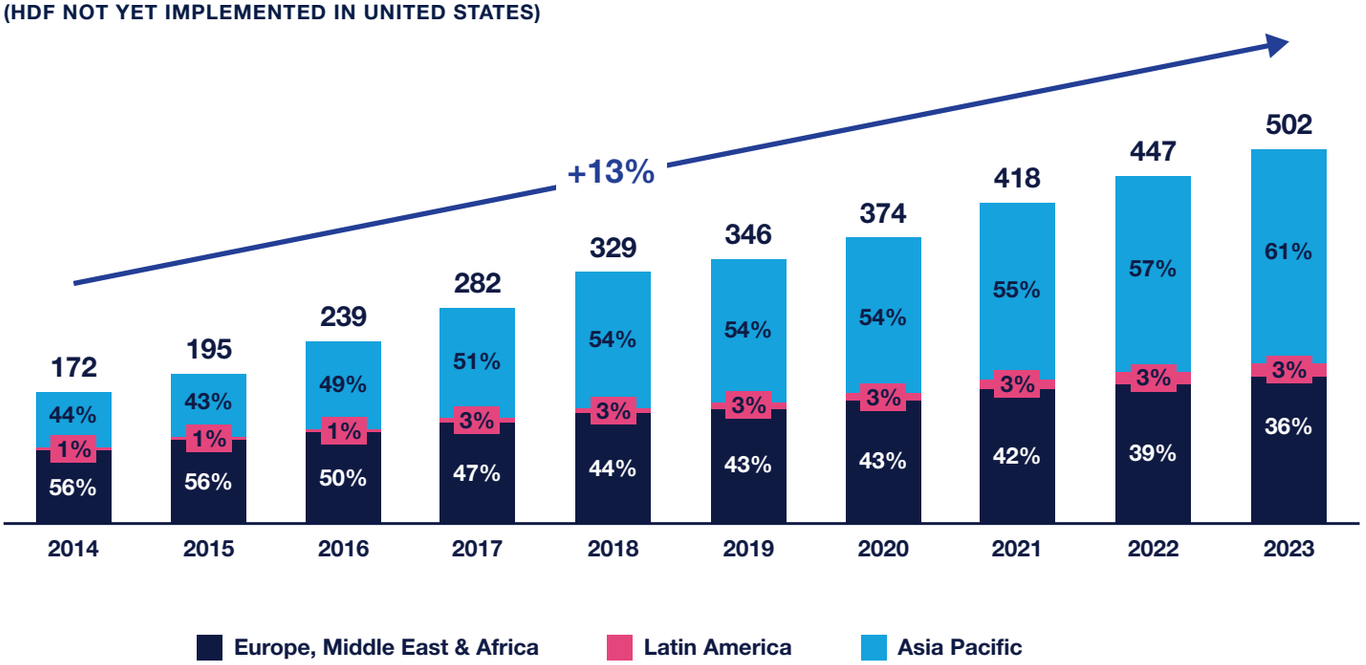
Challenges to Adoption

Despite the evidence that post-dilution HVHDF improves clinical outcomes and quality of life, its worldwide adoption remains limited. From 2014 to 2023, the number of HDF patients worldwide grew by an average of 13% per year (Figure 3).[58] Expanding HVHDF more globally requires addressing the barriers to adoption. Canaud et al. postulated that HVHDF acceptance might be affected by regulatory and technical issues, clinical evidence of benefit, and healthcare policies, including reimbursement rates.[57] All countries worldwide have approved online HDF's clinical use, and regulatory and technical aspects have become more accessible to address.[57] Despite the increased scientific evidence demonstrating the positive impact of HVHDF on clinical outcomes, healthcare policy and reimbursement rates remain the most significant challenges limiting the broader adoption of HVHDF in many countries. Japan has encouraged the use of HDF by approving its payment under national health insurance and setting higher reimbursement rates in 2012.[57] The number of patients treated by HDF has been rising since 2012 to reach 191,492 by the end of 2022, which accounted for 55.1% of all dialysis patients.[58] In 2022, approximately 31% of people with ESKD receiving hemodialysis in Europe were treated by online HDF,[56] though there is high variability between European countries. Some European countries have recognized the potential of HDF to improve patient outcomes while keeping healthcare costs stable, leading them to implement policies aimed at increasing its uptake. In 2018, the National Institute for Health and Care Excellence in the U.K. recognized the superiority of HDF in their guidelines.[59] Some countries have incentivized the uptake of HDF by offering higher reimbursement rates (e.g., Czech Republic). Others have introduced restrictions, either by specific indications (e.g., Poland), by setting a threshold limit (e.g., Italy), or by making HDF payment coverage dependent upon individual payer's/health insurance policies (e.g., Slovenia). In some European countries, HDF is allowed but reimbursed at the same rate as HF-HD.

Since 2004, HVHDF has been adopted as standard therapy in FME Europe, Middle East, and Africa (EMEA) NephroCare clinics. In January 2014, FME EMEA implemented an infusion volume greater than 21 L per session as a new quality key performance indicator (KPI) for patients receiving treatment with post-dilution online HDF. Over a decade, over half of all people with ESKD treated in FME EMEA clinics have been treated according to this target. As of 2023, more than 26,000 prevalent patients (dialysis vintage in FME clinics > 90 days, receiving 12–13 treatments/month) were treated using post-dilution online HDF with a mean convective volume of 26.4±4.9 L.

In contrast, there is some suggestion that using mid-medium cut-off dialyzers may be non-inferior to HVHDF in reducing all-cause mortality. The MOTheR study trial is an open-label multicenter prospective trial designed to evaluate the efficacy and safety of using a mid-medium cut-off dialyzer compared to HVHDF in dialysis patients in Spain for up to 36 months.[60] Preliminary data suggest it may be non-inferior in reducing all-cause mortality. Other potential benefits associated with HVHDF have not yet been reported for the MOTheR trial.[58]

FIGURE 3 | ONLINE-HDF PATIENT GROWTH (THOUSANDS) BY REGION AND GLOBAL AVERAGE ANNUAL INCREASE (HDF NOT YET IMPLEMENTED IN UNITED STATES)



Strategies for Adoption

To further expand HVHDF adoption worldwide, several strategies could be implemented:

1. Bridging the knowledge gap

2. Addressing sustainability concerns

3. Emphasizing long-term cost savings/value proposition

4. Fostering cross-functional collaboration for HVHDF advancement

5. Implementing patient empowerment

1. Through targeted workshops and training programs, knowledge gaps in HVHDF can be bridged effectively, significantly enhancing comprehension. Managing HVHDF programs, experiences, success stories, and lessons learned can be disseminated through identified reference centers, inspiring broader adoption. Standardization of HVHDF procedures, including implementing specific KPIs (e.g., treatment time ≥ 240 minutes, convective volume ≥ 23 L), minimizes variability, ensures adherence to best practices, and fosters efficient workflow. Additionally, integrated systems equipped with dedicated machines, dialyzers, and automated feedback controls for infusion rate adjustments can improve operational efficiency and help mitigate the learning curve for healthcare personnel.

2. Conducting health economic outcome studies assessing the comparative costs and outcomes associated with HVHDF versus traditional methods may provide valuable insights into its financial sustainability. Shroff and the EUDIAL Working Group highlighted concerns regarding the sustainability and environmental impact of HVHDF due to the larger infusion volume required compared to conventional high-flux HD, and they speculated that the associated cost outweighs the benefits.[61] On the contrary, Canaud et al. demonstrated that optimally prescribed post-dilution online HDF emerges as the most environmentally friendly choice.[62] This approach not only excels in enhancing solute clearance across all molecular weights but also offers the potential to significantly reduce water and dialysate consumption by allowing lower dialysate flow rates without compromising clearances.[62]

3. Online HDF is capable of meeting the main clinical and financial challenges as well as the diverse expectations of various stakeholders (patients, physicians, industry healthcare providers, and funders).[63] While evidence suggests favorable patient outcomes with HVHDF, questions regarding its cost-effectiveness compared to high-flux HD persist. While the upfront investment in HVHDF infrastructure may initially seem restrictive, focusing on its long-term returns, such as reduced hospitalizations, increased survival, decreased medication requirements, and improved quality of life, legitimizes the initial expenditure.

4. Robust cross-functional networks involving researchers, healthcare organizations, industry partners, government agencies, and nephrology societies are essential for driving standard-setting, evidence-based practice, and innovation in HVHDF. This type of collaboration is essential to demonstrate this therapy's long-term savings and value proposition, including reduced hospitalizations and co-morbid events. Active engagement in multinational consortiums dedicated to advancing renal care, such as the CONVINCE study—which unites dialysis divisions in academic hospitals, general facilities, and private renal care providers—amplifies the focus on HVHDF and fosters cross-border learning. These alliances can potentially promote the dissemination of best practices across diverse contexts, accelerate knowledge generation, and support broader worldwide implementation of HVHDF, focusing on resource optimization, safety, efficacy, and environmental sustainability.

5. Promoting active patient participation in the decision-making process, in collaboration with patient associations, ensures that patient preferences and values are considered when selecting dialysis modalities. Providing accessible educational materials, including relevant information about potential benefits and drawbacks, can facilitate informed decision-making and encourage greater patient acceptance and active participation in HVHDF programs.

Conclusion

Achieving widespread adoption of HVHDF necessitates a multifaceted and collaborative strategy that addresses current challenges effectively. The proposed interventions should be implemented through a multistakeholder approach. By fostering the expansion of HVHDF, the overarching goal of enhancing patient care and clinical outcomes on a global scale while ensuring its sustainable delivery can be achieved.

While the upfront investment in HVHDF infrastructure may initially seem restrictive, focusing on its long-term returns, such as reduced hospitalizations, increased survival, decreased medication requirements, and improved quality of life, legitimizes the initial expenditure.

Dr. Stefano Stuard
Senior Vice President, Global Clinical Officer
Hemodiafiltration
Global Medical Office

Dr. Stefano Stuard joined Fresenius Medical Care in 2010 as a Medical Director in FME's NephroCare business in the Europe, Middle East, and Africa (EMEA) region. Dr. Stuard's career includes more than 14 years in clinical governance roles with Fresenius Medical Care's EMEA and Latin America regions. In his most recent role, he supported NephroCare medical leadership in his role as Chief Clinical Officer for the EMEA countries. Dr. Stuard has long been a champion of online hemodiafiltration as a kidney replacement therapy, overseeing its steady growth in NephroCare clinics. By June 2024, more than 61 percent of patients in our European Union clinics were treated by High-Volume Hemodiafiltration.

In his current role, Dr. Stuard will focus on educating nephrologists in FME's Care Delivery business segment and will support many of the aspects of our development of a comprehensive plan to make HDF therapy a standard of care. Dr. Stuard previously served as vice president and head of the EMEA Center of Excellence for Clinical and Therapeutic Governance and 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.

Dr. Michael Anger
Senior Vice President
Medical Officer, In Center Dialysis
Medical Officer, Quality & Regulatory
Global Medical Office

Dr. Anger's 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.

References

1. L.W.B. Henderson, A. Besarab, A. Michaels, and L.W. Bluemle, Jr., "Blood Purification by Ultrafiltration and Fluid Replacement (Diafiltration)," *Transactions of the American Society for Artificial Internal Organs* 13, no. 1 (April 1967): 216–26.
2. T. Roy, "Historical Milestones of a Long Pathway" in *On-Line Hemodiafiltration: The Journey and the Vision*, ed. G. Krick and C. Ronco, Contributions to Nephrology (Basel: S.Karger AG, 2011), 1–14.
3. L.W. Henderson, M.L. Sanfelippo, and E. Beans, "'On line' Preparation of Sterile Pyrogen-Free Electrolyte Solution," *Transactions of the American Society for Artificial Internal Organs* 24, no. 1 (April 1978): 465–67.
4. B. Canaud, R. Lévesque, D. Krieter, S. Desmeules, L. Chalabi, H. Moragués, et al., "On-line Hemodiafiltration as Routine Treatment of End-Stage Renal Failure: Why Pre- or Mixed Dilution Mode Is Necessary in On-line Hemodiafiltration Today?" *Blood Purification* 22, no. 2 (2004): 40–48.
5. B. Canaud, "Online hemodiafiltration. Technical options and best clinical practices" in *Hemodiafiltration*, ed. C. Ronco, B. Canaud, and P. Aljama, Contributions to Nephrology (Basel: S.Karger AG, 2007), 110–22.
6. L. Pstras, C. Ronco, and J. Tattersall, "Basic physics of hemodiafiltration," *Seminars in Dialysis* 35, no. 5 (2022): 390–404.
7. F. Maduell, M. Arias, J. Garro, M. Vera, M. Fontsere, X. Barros, et al., [Guidelines for automated manual infusion: a practical way of prescribing postdilution on-line hemodiafiltration]. *Nefrologia* 30, no. 3 (2010): 349–53.
8. A.M. Zawada, T. Lang, B. Ottillinger, F. Kircelli, M. Stauss-Grabo, and J.P. Kennedy, "Impact of Hydrophilic Modification of Synthetic Dialysis Membranes on Hemocompatibility and Performance," *Membranes* 12, no. 10 (2022): 932.
9. A.M. Zawada, P. Melchior, C. Schall, A. Erlenkotter, T. Lang, T. Keller, et al., "Time-Resolving Characterization of Molecular Weight Retention Changes among Three Synthetic High-Flux Dialyzers," *Artificial Organs* 46, no. 7 (2022): 1318–27.
10. P. Melchior, A. Erlenkotter, A.M. Zawada, D. Delinski, C. Schall, M. Stauss-Grabo, et al., "Complement Activation by Dialysis Membranes and its Association with Secondary Membrane Formation and Surface Charge," *Artificial Organs* 45, no. 7 (2021): 770–78.
11. G. Ehlerding, W. Ries, M. Kempkes-Koch, E. Ziegler, A. Erlenkotter, A.M. Zawada, et al., "Randomized Comparison of Three High-Flux Dialyzers During High-Volume Online Hemodiafiltration—the comPERFORM Study," *Clinical Kidney Journal* 15, no. 4 (2022): 672–80.
12. G. Ehlerding, A. Erlenkotter, A. Gauly, B. Griesshaber, J. Kennedy, L. Rauber, et al., "Performance and Hemocompatibility of a Novel Polysulfone Dialyzer: A Randomized Controlled Trial," *Kidney360* 21, no. 6 (2021): 937–47.
13. B. Canaud, P.J. Blankestijn, M.P.C. Grooteman, and A. Davenport, "Why and How High Volume Hemodiafiltration May Reduce Cardiovascular Mortality in Stage 5 Chronic Kidney Disease Dialysis Patients? A Comprehensive Literature Review on Mechanisms Involved," *Seminars in Dialysis* 35, no. 2 (2022): 117–28.
14. T. Lang, A.M. Zawada, L. Theis, J. Braun, B. Ottillinger, P. Kopperschmidt, et al., "Hemodiafiltration: Technical and Medical Insights," *Bioengineering* 10, no. 2 (2023): 145.
15. F. Locatelli, P. Altieri, S. Andrulli, P. Bolasco, G. Sau, L.A. Pedrini, et al., "Hemofiltration and Hemodiafiltration reduce intradialytic hypotension in ESRD," *Journal of the American Society of Nephrology* 21, no. 10 (2010): 1798–1807.
16. J. Donauer, C. Schweiger, B. Rumberger, B. Krumme, and J. Bohler, "Reduction of Hypotensive Side Effects During Online-Haemodiafiltration and Low Temperature Haemodialysis," *Nephrology Dialysis Transplantation* 18, no. 8 (2003): 1616–22.
17. F.M.V. Sande, J.P. Kooman, C.J. Konings, and K.M.L. Leunissen, "Thermal Effects and Blood Pressure Response During Postdilution Hemodiafiltration and Hemodialysis: The Effect of Amount of Replacement Fluid and Dialysate Temperature," *Journal of the American Society of Nephrology* 12, no. 9 (2001): 1916–20.
18. A. Rodriguez, M. Morena, A.S. Bargnoux, L. Chenine, H. Leray-Moragues, J.P. Cristol, et al., "Quantitative Assessment of Sodium Mass Removal Using Ionic Dialysance and Sodium Gradient as a Proxy Tool: Comparison of High-Flux Hemodialysis versus Online Hemodiafiltration," *Artificial Organs* 45, no. 8 (2021): E280–E92.
19. A. Czifra, A. Pall, J. Kulcsar, K. Barta, A. Kertesz, G. Paragh, et al., "Hemodialysis and Hemodiafiltration Differently Modulate Left Ventricular Diastolic Function," *BMC Nephrology* 14 (2013): 76.
20. V. La Milia, C. Ravasi, F. Carfagna, E. Alberghini, I. Baragetti, L. Buzzi, et al., "Sodium Removal and Plasma Tonicity Balance Are Not Different in Hemodialysis and Hemodiafiltration Using High-Flux Membranes," *Journal of Nephrology* 32, no. 3 (2019): 461–69.
21. C.H. den Hoedt, M.L. Bots, M.P. Grooteman, N.C. van der Weerd, A.H. Mazairac, E.L. Penne, et al, "Online Hemodiafiltration Reduces Systemic Inflammation Compared to Low-Flux Hemodialysis," *Kidney International* 86, no. 2 (2014): 423–32.
22. A. Agbas, N. Canpolat, S. Caliskan, A. Yilmaz, H. Ekmekci, M. Mayes, et al., "Hemodiafiltration Is Associated with Reduced Inflammation, Oxidative Stress and Improved Endothelial Risk Profile Compared to High-Flux Hemodialysis in Children," *PLoS One* 13, no. 6 (2018): e0198320.
23. V. Filiopoulos, D. Hadjiyannakos, P. Metaxaki, V. Sideris, L. Takouli, A. Anogiati, et al., "Inflammation and Oxidative Stress in Patients on Hemodiafiltration," *American Journal of Nephrology* 28, no. 6 (2008): 949–57.
24. I.M. Mostovaya, P.J. Blankestijn, M.L. Bots, A. Covic, A. Davenport, M.P. Grooteman, et al., "Clinical Evidence on Hemodiafiltration: A Systematic Review and a Meta-Analysis," *Seminars in Dialysis* 27, no. 2 (2014): 119–27.
25. T. Ohtake, M. Oka, K. Ishioka, K. Honda, Y. Mochida, K. Maesato, et al., "Cardiovascular Protective Effects of On-line Hemodiafiltration: Comparison with Conventional Hemodialysis," *Therapeutic Apheresis and Dialysis* 16, no. 2 (2012): 181–88.
26. E. Charitaki and A. Davenport, "Does Hemodiafiltration Reduce Vascular Stiffness Measured by Aortic Pulse Wave Velocity Compared with High-Flux Hemodialysis?" *Hemodialysis International* 18, no. 2 (2014): 391–95.
27. R. Shroff, C. Smith, B. Ranchin, A.K. Bayazit, C.J. Stefanidis, V. Askiti, et al., "Effects of Hemodiafiltration versus Conventional Hemodialysis in Children with ESKD: The HDF, Heart and Height Study," *Journal of the American Society of Nephrology* 30, no. 4 (2019): 678–91.
28. J.W. Chang, W.S. Yang, J.W. Seo, J.S. Lee, S.K. Lee, and S.K. Park, "Continuous Venovenous Hemodiafiltration versus Hemodialysis as Renal Replacement Therapy in Patients with Acute Renal Failure in the Intensive Care Unit," *Scandinavian Journal of Urology* 38, no. 5 (2004): 417–21.
29. I. Nistor, S.C. Palmer, J.C. Craig, V. Saglimbene, M. Vecchio, A. Covic, et al., "Convective versus Diffusive Dialysis Therapies for Chronic Kidney Failure: An Updated Systematic Review of Randomized Controlled Trials," *American Journal of Kidney Diseases* 63, no. 6 (2014): 954–67.
30. D. Marcelli, I. Bayh, J.I. Merello, P. Ponce, A. Heaton, F. Kircelli, et al., "Dynamics of the Erythropoiesis Stimulating Agent Resistance Index in Incident Hemodiafiltration and High-Flux Hemodialysis Patients," *Kidney International* 90, no. 1 (2016): 192–202.
31. V. Panichi, A. Scatena, A. Rosati, R. Giusti, G. Ferro, E. Malagnino, et al., "High-Volume Online Haemodiafiltration Improves Erythropoiesis-Stimulating Agent (ESA) Resistance in Comparison with Low-Flux Bicarbonate Dialysis: Results of the REDERT Study," *Nephrology Dialysis Transplantation* 30, no. 4 (2015): 682–89.
32. P. Molina, B. Vizcaino, M.D. Molina, S. Beltran, M. Gonzalez-Moya, A. Mora, et al., "The Effect of High-Volume Online Haemodiafiltration on Nutritional Status and Body Composition: The ProtEin Stores prEservaTion (PESET) Study," *Nephrology Dialysis Transplantation* 33, no. 7 (2018): 1223–35.
33. M. Aichi, T. Kuragano, T. Iwasaki, S. Ookawa, M. Masumoto, K. Mizusaki, et al., "Hemodiafiltration Improves Low Levels of Health-Related Quality Of Life (Qol) and Nutritional Conditions of Hemodialysis Patients," *ASAIO Journal* 68, no. 2 (2022): 297–302.
34. R. Pecoits-Filho, J. Larkin, C.E. Poli-de-Figueiredo, A.L. Cuvello-Neto, A.B.L. Barra, P.B. Goncalves, et al, "Effect of Hemodiafiltration on Measured Physical Activity: Primary Results of the HDFIT Randomized Controlled Trial," *Nephrology Dialysis Transplantation* 36, no. 6 (2021): 1057–70.
35. A. Karkar, M. Abdelrahman, and F. Locatelli, "A Randomized Trial on Health-Related Patient Satisfaction Level with High-Efficiency Online Hemodiafiltration versus High-Flux Dialysis," *Blood Purification* 40. no. 1 (2015): 84–91.
36. A. Hazim, L. Adarmouch, A. Eloury, J. Aasfara, M. Asly, and I. Slassi, "Hemodialysis-Related Headache: Still a Challenge in 2020? Effect of Conventional versus Online Hemodiafiltration from a Study in Casablanca, Morocco," *Artificial Organs* 45, no. 6 (2021): 602–7.
37. K. Kantartzi, S. Panagoutsos, E. Mourvati, A. Roumeliotis, K. Leivaditis, V. Devetzis, et al., "Can Dialysis Modality Influence Quality of Life in Chronic Hemodialysis Patients? Low-Flux Hemodialysis versus High-Flux Hemodiafiltration: A Cross-Over Study," *Renal Failure* 35, no. 2 (2013): 216–21.
38. E. Vilar, A.C. Fry, D. Wellsted, J.E. Tattersall, R.N. Greenwood, and K. Farrington, "Long-Term Outcomes in Online Hemodiafiltration and High-Flux Hemodialysis: A Comparative Analysis," *Clinical Journal of the American Society of Nephrology* 4, no. 12 (2009): 1944–53.
39. F. Maduell, F. Moreso, M. Pons, R. Ramos, J. Mora-Macia, J. Carreras, et al., "High-Efficiency Postdilution Online Hemodiafiltration Reduces All-Cause Mortality in Hemodialysis Patients," *Journal of the American Society of Nephrology* 24, no. 3 (2013): 487–97.

40. E. Ok, G. Asci, H. Toz, E.S. Ok, F. Kircelli, M. Yilmaz, et al., “Mortality and Cardiovascular Events in Online Haemodiafiltration (OL-HDF) Compared with High-Flux Dialysis: Results from the Turkish OL-HDF Study,” *Nephrology Dialysis Transplantation* 28, no. 1 (2013): 192–202.
41. M.P. Grooteman, M.A. van den Dorpel, M.L. Bots, E.L. Penne, N.C. van der Weerd, A.H. Mazairac, et al., “Effect of Online Hemodiafiltration on All-Cause Mortality and Cardiovascular Outcomes,” *Journal of the American Society of Nephrology* 23, no. 6 (2012): 1087–96.
42. L. Mercadal, J.E. Franck, M. Metzger, P. Urena Torres, F. de Cornelissen, S. Edet, et al., “Hemodiafiltration versus Hemodialysis and Survival in Patients With ESRD: The French Renal Epidemiology and Information Network (REIN) Registry,” *American Journal of Kidney Diseases* 68, no. 2 (2016): 247–55.
43. S.A. Peters, M.L. Bots, B. Canaud, A. Davenport, M.P. Grooteman, F. Kircelli, F. Locatelli, F. Maduell, M. Morena, M.J. Nubé, et al., “Haemodiafiltration and Mortality in End-Stage Kidney Disease Patients: A Pooled Individual Participant Data Analysis from Four Randomized Controlled Trials,” *Nephrology Dialysis Transplantation* 31, no. 6 (June 2016): 978–84.
44. L. Neri, K. Gurevich, Y. Zarya, S. Plavinskii, F. Bellocchio, S. Stuard, et al., “Practice Patterns and Outcomes of Online Hemodiafiltration: A Real-World Evidence Study in a Russian Dialysis Network,” *Blood Purification* 50, no. 3 (2021): 309–18.
45. G. Imamović, R. Hrvačević, S. Kapun, D. Marcelli, I. Bayh, A. Grassmann, et al., “Survival of Incident Patients on High-Volume Online Hemodiafiltration Compared to Low-Volume Online Hemodiafiltration and High-Flux Hemodialysis,” *International Urology and Nephrology* 46, no. 4 (2014): 1191–200.
46. B. Canaud, C. Barbieri, D. Marcelli, F. Bellocchio, S. Bowry, F. Mari, et al., “Optimal Convection Volume for Improving Patient Outcomes in an International Incident Dialysis Cohort Treated with Online Hemodiafiltration,” *Kidney International* 88, no. 5 (2015): 1108–16.
47. B. Canaud, I. Bayh, D. Marcelli, P. Ponce, J.I. Merello, K. Gurevich, et al., “Improved Survival of Incident Patients with High-Volume Haemodiafiltration: A Propensity-Matched Cohort Study with Inverse Probability of Censoring Weighting,” *Nephron* 129, no. 3 (2015): 179–88.
48. F. Maduell, J. Varas, R. Ramos, A. Martin-Malo, R. Pérez-Garcia, I. Berdud, et al., “Hemodiafiltration Reduces All-Cause and Cardiovascular Mortality in Incident Hemodialysis Patients: A Propensity-Matched Cohort Study,” *American Journal of Nephrology* 46, no. 4 (2017): 288–97.
49. B. Canaud, J.L. Bragg-Gresham, M.R. Marshall, S. Desmeules, B.W. Gillespie, T. Depner, et al., “Mortality Risk for Patients Receiving Hemodiafiltration versus Hemodialysis: European Results from the DOPPS,” *Kidney International* 69, no. 11 (2006): 2087–93.
50. E.J. See, J. Hedley, J.W.M. Agar, C.M. Hawley, D.W. Johnson, P.J. Kelly, et al., “Patient Survival on Haemodiafiltration and Haemodialysis: A Cohort Study Using the Australia and New Zealand Dialysis and Transplant Registry,” *Nephrology Dialysis Transplantation* 34, no. 2 (2019): 326–38.
51. K. Kikuchi, T. Hamano, A. Wada, S. Nakai, and I. Masakane, “Predilution Online Hemodiafiltration Is Associated With Improved Survival Compared with Hemodialysis,” *Kidney International* 95, no. 4 (2019): 929–38.
52. L. Mercadal, J.E. Franck, M. Metzger, P. Urena Torres, F. de Cornelissen, S. Edet, et al., “Filtration versus Hemodialysis and Survival in Patients with ESRD: The French Renal Epidemiology and Information Network (REIN) Registry,” *American Journal of Kidney Diseases* 68, no. 2 (2016): 247–55.
53. P.J. Blankestijn, R.W.M. Vernooij, C. Hockham, G.F.M. Strippoli, B. Canaud, J. Hegbrant, et al., “Effect of Hemodiafiltration or Hemodialysis on Mortality in Kidney Failure,” *New England Journal of Medicine* 389, no. 8 (2023): 700–709.
54. M. Morena, A. Jaussent, L. Chalabi, H. Leray-Moragues, L. Chenine, A. Debure, et al., “Treatment Tolerance and Patient-Reported Outcomes Favor Online Hemodiafiltration Compared to High-Flux Hemodialysis in the Elderly,” *Kidney International* 91, no. 6 (2017): 1495–1509.
55. M.G.M. Guimarães, F.P.M. Tapioca, N.R. Dos Santos, F.P.D.C. Tourinho Ferreira, L.C. Santana Passos, and P.N. Rocha, “Hemodiafiltration versus Hemodialysis in End-Stage Kidney Disease: A Systematic Review and Meta-Analysis,” *Kidney Medicine* 18, no 6 (2024): 1–6.
56. Fresenius Medical Care, *Market & Competitor Survey, Internal data of Fresenius Medical Care AG*, last update year: 2022.
57. B. Canaud, K. Köhler, J.M. Sichart, and S. Möller, “Global Prevalent Use, Trends and Practices in Haemodiafiltration,” *Nephrology Dialysis Transplantation* 35, no. 3 (2020): 398–407.
58. Japanese Society for Dialysis Therapy Renal Data Registry, *2022 Annual Dialysis Data Report, JSDT Renal Data Registry* (2024), https://docs.jsdt.or.jp/overview/file/2022/pdf/introduction.pdf.
59. National Institute for Health and Care Excellence (NICE), *NICE guideline (NG107): Renal Replacement Therapy and Conservative Management* (London: NICE; c2018), http://www.nice.org.uk/guidance/ng107.
60. P. de Sequera, R. Perez-Garcia, A. Vega, S. Martinez-Vaquera, J.G. Acosta, K. Perez Del Valle, et al., “Trial Design of the MOTheR HDx Study: A Multicenter, Open-Label, Prospective, Randomized Study to Explore the Morbidity and Mortality in Patients Dialyzed with the Theranova HDx in Comparison with Online Hemodiafiltration,” *Clinical Kidney Journal* 16, no. 11 (2023): 2254–61.
61. R. Shroff, C. Basile, F. van der Sande, and S. Mitra, “EuDial Working Group of the European Renal A. Haemodiafiltration for All: Are We CONVINCEd?” *Nephrology Dialysis Transplantation* 38, no. 12 (2023): 2663–5.
62. C. Bernard, A. Gagel, A. Peters, A. Maierhofer, and S. Stuard, “Does Online High-Volume Hemodiafiltration Offer Greater Efficiency and Sustainability Compared to High-Flux Hemodialysis? A Detailed Simulation Analysis Anchored in Real-World Data,” *Clinical Kidney Journal* (2024): sfae147.
63. E. Gatti and C. Ronco, “Seeking an Optimal Renal Replacement Therapy for the Chronic Kidney Disease Epidemic: The Case for On-Line Hemodiafiltration,” *Contribution to Nephrology* 175 (2011): 170–85.