

The Next Evolution of HemoDialysis eXpanded: From a Delphi Questionnaire-Based Approach to the Real Life of Italian Dialysis Units

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Keywords

Hemodialysis expanded · Delphi · Hemodiafiltration · Hemodialysis · End-stage kidney disease

Abstract

Introduction: Impact assessment of new technologies in chronic hemodialysis (HD) is challenging due to HD patient frailty, the complexity of HD clinical trials and practice variability among countries. Among the most recent HD innovations, medium cut-off (MCO) dialyzers present an optimized membrane geometry that provides enhanced clearances for middle and large molecular weight uremic toxins (UT). These toxins are poorly cleared by available HD techniques and largely contribute to patient morbidity and mortality. The aim of this paper is to assess the available clinical evidence about MCO membranes and to identify the next steps needed to generate conclusive data on their use in HD. **Methods:** With this purpose, we first reviewed and compared the current HD technologies aimed to improve the clearance of middle and large UT; subsequently, we used a Delphi questionnaire to identify and discuss the consensus about MCO

efficacy within a large sample of the Italian Nephrology community. **Results and Conclusions:** Our investigation gathered a significant degree of consensus on the beneficial role of MCO membrane and expanded HD. Finally, we used our results to propose future trial designs and clinical investigations aimed to improve evidence quality about the use of these membranes in the present clinical scenario of dialysis units.

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Introduction

According to the 2018 US Renal Data System report, hemodialysis (HD) is associated with 166 deaths per 1,000 patient-year and 5-year survival as low as 42% [1]; this corresponds to an adjusted mortality rate more than 4-fold higher than what observed in the general population after match for age [1, 2]. European registry data provide a similar pic-

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ture, with an adjusted 5-year survival rate of 46% [3] Most of this excessive death burden is due to cardiovascular causes, which account for >50% of total fatal events [1, 4]. Additionally, dialysis is associated with high level of disability, poor social performance, and low quality of life [5].

These discouraging epidemiological data are largely nonattributable to the “classical” cardiovascular risk factors (e.g., hypertension, dyslipidemia, diabetes, smoking, diet, etc.) and compelling data demonstrated how end-stage kidney disease (ESKD) itself induces accelerated vascular aging through the accumulation of uremic toxins (UT). In particular, the so-called middle and large molecules (molecular weight between 0.5 and 15 kDa vs. 15–60 kDa, respectively) [6, 7] are poorly cleared by standard dialysis techniques and inexorably accumulate in tissues of ESKD patients, thus causing inflammation and accelerated tissue senescence [7]. Middle/large UT accumulation has also a causative role in the immune dysfunction observed in HD patients [8] and contributes to the incidence of infections and cancer, the second and third cause of death in this frail population [3, 9].

Over the last years, 2 main approaches have been used to increase the clearance of medium and large UT: (1) combination of diffusion with convection (online hemodiafiltration [OL-HDF]) and (2) design of new membranes with molecular cut-off similar to the human glomerulus (60 kDa) also named high retention onset or medium cut-off (MCO) dialyzers in order to distinguish them from the membranes able to filter large plasma proteins (high cut-off). Different studies are available on OL-HDF, but the opinions within the nephrological community about its efficacy in improving patient outcomes remain discordant [10]. On the other hand, few MCO studies are available to date, mostly focused on safety and feasibility. Overall, deciphering the impact of putative advancements in HD is particularly challenging because of the sizable differences in dialysis practice among countries [10] and the high comorbidity burden of HD patients [11, 12].

The aim of this paper is to discuss MCO membranes as new horizon in chronic HD and to contribute to the design of future clinical trials aimed to assess MCO impact on long-term clinical outcomes. With this purpose, we first discussed the available data about MCO in comparison to standard HD and to OL-HDF. Subsequently, we investigated within the Italian Nephrology community the perceived role of MCO membranes in ESKD patients using the Delphi approach, an unbiased method to detect consensus. Finally, we identified the key endpoints to be addressed in a randomized clinical trial aimed to evaluate the role of MCO membranes.

Solute Clearances and Outcomes in Online Hemodiafiltration

HD biophysics is based on simple diffusion, which is the best-known approach to achieve clearance of small soluble molecules, but it is largely ineffective for middle molecule removal. For instance, with the so-called high-flux dialyzers, urea clearance is often close to the dialysis plasma flow (200–300 mL/min), while β_2 -microglobulin clearance is <20 mL/min [13]. This corresponds to a weekly urea clearance reaching 10–15% of normal kidney function versus <0.5% for β_2 -microglobulin clearance. Thus, middle and large molecules inexorably accumulate in ESKD patients. On the other hand, purely convective techniques (hemofiltration[HF]) achieve the opposite performance with poorer clearances of small solutes and worse clinical outcomes than HD [14]. In OL-HDF, an ultra-pure dialysis solution is used for both HD and HF, thus combining the potential advantages of both techniques. The idea of a survival benefit in OL-HDF patients came at first from large retrospective studies [15, 16]. Afterward, two clinical trials (the Turkish trial and CONTRAST trial) failed to prove efficacy [17, 18]; a primary analysis of these RCTs showed that the incidence of all-cause mortality was not affected by treatment modality (HD or HDF). However, a post hoc analysis revealed that patients receiving higher convective treatment (>17.4 L/session in the Turkish Trial and 22 L/session in the CONTRAST Study) had a significant survival benefit. Subsequently, the ESHOL Study, in which HDF treatment was conducted with a minimum of 18 L/session of convection volume, was the first to show a significant reduction in all-cause mortality (30%), a nonsignificant reduction in cardiovascular mortality (33%), and a significant reduction in infection-related mortality (55%) by OL-HDF [19]. A subsequent meta-analysis combined the 3 studies together with a 4th cohort from French centers: OL-HDF patients experienced a 14% reduction in overall mortality and 23% decline in cardiovascular deaths [20]. Besides the hard clinical endpoints, almost all studies have proved that OL-HDF decreased serum β_2 -microglobulin [18, 19, 21] and subsequent investigations found improved bone mineral metabolism, enhanced erythropoiesis, reduced inflammation and better patient-reported outcomes, even when more frail population were studied [8, 14, 19, 22–25]. In the last years, France implemented OL-HDF registry data: the 2016 report included 28,000 patients, of which 5,500 were treated by OL-HDF; the registry reported a significant increase in survival for OL-HDF patients, mainly related to reduced cardiovascular events (16% of

mortality reduction and 23% reduction in major vascular events) [26].

Nonetheless, the work group for HD adequacy in 2015 did not recommend HDF in the NKF-KDOQI guidelines [27]. As a matter of fact, all the mentioned studies had serious limitations and were at high risk for major sources of bias. For instance, in the control HD group of the CONTRAST Trial, low-flux membranes were used, while the HD patient group in the other studies was treated with high-flux or both membranes. Then, the rates of patients dropping out from these clinical trials were very high: 20.4% in the Turkish Trial, 33.4% in the CONTRAST trial, and 39% in ESHOL study. Forty-one percent of the dropouts in the Turkish Trial left the study for reasons other than death, including 11% of the patients allocated to HDF, who withdrew due to vascular access problems. These trials were at high risk of incomplete follow-up, dropouts were censored as nonfatal events and not followed up for primary outcome. Finally, convection strategies were highly heterogeneous, and most studies did not randomize the participants to specific targeted convection volumes related to body weight. The only reasonable option to improve evidence quality is to design trials with larger cohorts: the ongoing CONVINCENCE study aims to recruit 1,800 patients across 9 European nations and will hopefully provide definitive evidence [28].

Medium Cut-Off Membrane or HemoDialysis eXpanded: The State of the Art

Expanded HD (HDx) is a technique that combines diffusive and convective clearance, similarly to what described for HDF. This approach relies on new dialyzers with larger pore diameter and reduced fiber internal section [29]. MCO membrane pores are considerably wider than classical HF ones and have been specifically designed to increase the clearance of molecules larger than β 2-microglobulin (11 kDa), while retaining albumin (65 kDa). Indeed, the molecule typically used to investigate MCO-related kinetics is λ free light chain (λ FLC – 45 kDa). Beside membrane design, the reduction of fiber internal diameter increases the blood compartment resistance and promotes dialyzer internal filtration and back filtration. These phenomena induce a convection comparable to the classical HF and have proven efficacy for clearance of middle and large molecules without the need of substitution fluids [30].

A recent kinetic study indicated that internal filtration can be estimated as 31.6 mL/min for Q_b of 300 mL/min and 53.1 mL/min for Q_b of 400 mL/min (between 8 L and 12.7 L per a 4 h session) [31]. Compared to HDF, the exchanged

convective volume is nonadjustable. However, HDx presents the following advantages over HDF: is applicable also to patients with suboptimal vascular accesses, does not require specific software, and is achieved without increasing trans-membrane pressure, thus providing minimal stress to the filter. When compared to both high-flux HD and OL-HDF, HDx demonstrated similar clearances of solutes of 10–20,000 Da and improved removal of larger molecules [32]. Different authors have hypothesized that this improved UT clearance might reduce the inflammatory state of chronic HD patients. In a randomized clinical trial, MCO membranes were compared to regular high-flux HD; within 4 weeks, HDx patients showed decreased levels of IL-6 and TNF-alpha mRNA in peripheral blood mononuclear cells [33]. Belmouaz et al. [34] carried out a cross-over randomized study enrolling 40 chronic HD patients: study duration was 3 months, and the aim was to assess the efficiency of MCO dialyzer in UT removal in comparison to high-flux HD. The authors observed a significant reduction of both middle and large UT with MCO dialyzers; the improved clearance was observed for β 2 microglobulin, myoglobin (17 kDa), kappa free light chains (κ FLC – 22 kDa), prolactin (22 kDa), FGF-23 (32 kDa), and λ FLC. Two concerns raised about HDx are the loss of albumin and the back filtration of endotoxins. Recently, Weiner and colleagues [35] conducted a randomized clinical trial on 172 patients on maintenance HD. Patients that were randomized 1:1 to MCO or high-flux HD [35]. MCO was more efficient than HD in the removal of λ FLC (respectively, 33 vs. 17% reduction rate over 24 weeks) and noninferior in maintaining albumin levels (pre-HD serum albumin was 4 vs. 4.1 g/dL). Consistently with what was previously reported, the authors observed a significantly improved clearance for complement factor D, κ FLC, TNF α , and β 2-microglobulin, but not IL-6. Of note, the study included different ethnicity and patients had diabetes and vascular morbidity rates comparable to what observed in the general US HD population. Adverse events were similar between groups ($p = 0.87$) leading to 2 dropouts in the intervention and 3 in the control group, 3 patients died in each group, overall dropout rate was 24% and equally distributed in the 2 arms. In a recent prospective study, 22 patients underwent 9 dialysis sessions with routine dialysis parameters; one session was with an MCO dialyzer in HD and the other 8 with different dialyzers in OL-HDF. No differences in dialysate albumin loss or in the clearance of small and middle molecular range molecules were observed between the MCO versus OL-HDF [36]. Furthermore, Schepers et al. [37] investigated in vitro the back-filtration of endotoxins and identified no increased values with MCO dialyzers when compared to

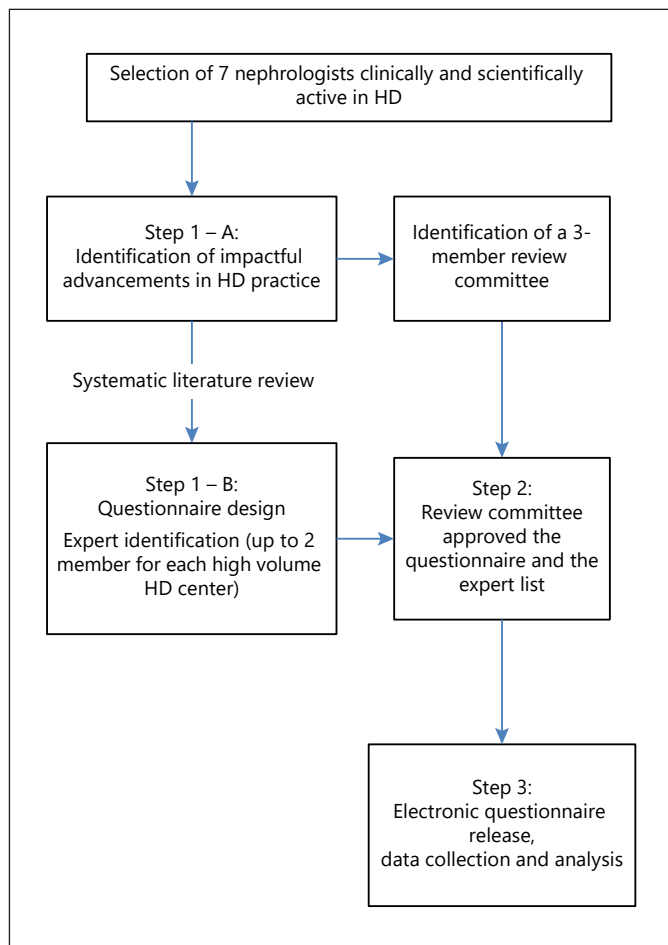


Fig. 1. Graphic description of the Delphi method with the different study phases.

high-flux membranes. This finding was confirmed in a subsequent investigation that included a broader spectrum of bacterial toxins [38]. Thus, in contrast with OL-HDF, HDx could be potentially used without ultra-pure water systems. To summarize the state of the art of HDx, MCO membranes have shown a safe profile in terms of albumin loss in the dialysate and of endotoxin back filtration and provide an enhanced clearance of middle and large UT in comparison to high-flux HD and OL-HDF together with a potential anti-inflammatory activity.

Delphi Questionnaire Approach to Identify Consensus among Italian Nephrologists

As a second step, we decided to identify the current consensus on MCO dialyzers among the Italian Nephrology community, in areas where OL-HDF has been wide-

ly used over the last years. Although consensus-based investigations might be biased, agreement assessment is important in trial design and could predict the acceptance of a new therapeutic approach within the healthcare community.

We designed a 3-step process in accordance to the Delphi method standards [39] (Fig. 1). The Delphi method consists of sequential questionnaires. After the experts answer each round of questionnaires, the inquiring panel collects all the answers and delivers a summary report to the experts. Then, the experts review either agree or disagree with the other experts' answers and are given the opportunity to provide updated opinions based on what they understand from the summary report.

Methods

At first, a board of seven experts was selected by using bibliographic and clinical parameters: they had to have worked in dialysis units for at least 10 years and to have contributed to the medical literature devoted to HD advancements (at least 5 publications in the last 5 years). During the first meeting, the board identified a first set of topics. Subsequently, the members performed a systematic literature analysis and, in a second meeting, elaborated and approved the questionnaire. Concomitantly, the same board identified 59 high volume HD centers across the country; each center selected up to two local experts to answer the questionnaire for a total of 71 nephrologists. For the identification of the local experts, the Board members agreed on the following characteristics: (1) physician with experience of HD and with direct contact with patients (no Department/Unit director) for >5 years; (2) no more than 2 clinicians from the same hospital/unit. In the second step, a panel of three independent experts, identified by the Board members, reviewed, and approved both the questionnaire and the nephrologist list. Finally, the questionnaire was electronically released, and the answers were collected over a 2-month period. The whole process is depicted in Figure 1.

For each selected topic, the board elaborated up to 6 statements and the 71 experts were asked to grade from 1 to 5 their level of agreement (1: complete disagreement, 2: disagreement, 3: agreement, 4: strong agreement, 5: complete agreement). We defined consensus as agreement or disagreement rate $\geq 66\%$ (a commonly used threshold [40]). Since this study did not analyze patients' data but was related to personal opinions and knowledge of the scientific literature, local Ethic Committee approval was not required.

Statement 1

According to your clinical experience and literature data, medium cut-off (MCO) dialysis or Expanded Hemodialysis (HDx):

Agreement level	1	2	3	4	5	TOT
1.1 Associates with reduced mortality, mainly from cardiovascular causes	0	14	12	14	1	41
	34%		66%			100%
1.2 Associates with a reduction in the systemic inflammation and, consequently, an improvement of dialysis-related anemia	0	6	15	16	4	41
	15%		85%			100%
1.3 Provides a better clearance for middle/high molecular weight uremic toxins	0	0	13	21	7	41
	0%		100%			100%
1.4 Associates with improved treatment hemodynamic, independently from the cause of kidney disease	2	9	17	12	1	41
	27%		73%			100%

Fig. 2. Expert panel agreement about the 1st statement. Agreement level was defined as: (1) complete disagreement, (2) disagreement, (3) agreement, (4) strong agreement, and (5) complete agreement. Consensus was defined as agreement or disagreement $\geq 66\%$. Green, positive consensus; yellow, borderline positive consensus; red, absence of consensus or negative consensus.

Item 1: MCO Dialyzers

This first item was designed to evaluate the opinion of Italian Nephrologists on HDx in comparison to clinical practice and literature data regarding high-flux HD and OL-HDF (Fig. 2). First, the expert panel was asked whether HDx might improve patient survival by reducing cardiovascular morbidity and mortality (Item 1.1) and reached a positive consensus on this issue (66% of agreement). Additionally, 85% of experts agreed that HDx may reduce patients' inflammation and improve anemia (Item 1.2); all of them acknowledged the increased clearance of the middle/large molecules (Item 1.3), and the 73% endorsed the improved intradialytic hemodynamics (Item 1.4).

Item 2 and 3: Biofeedback Systems and Use of Citrate as Dialysis Buffer

A well-designed clinical trial must minimize the number of confounders. The ESHOL study demonstrated how a large number of centers are needed to enroll a sufficient number of patients and guarantee study reproducibility. As such, due to the abovementioned differences in HD practice, is of primary relevance the identification of other potentially impactful advancements in HD that must be either avoided or better considered during the design of a clinical trial aimed to evaluate MCO performance (Fig. 3). With this purpose, the expert panel identified the

use of biofeedback systems and of citrate as dialysis solution buffer as two of the most relevant variables: also, for these items, consensus was investigated based on literature findings following the Delphi approach.

Biofeedback systems combine online monitoring of hematocrit and/or serum sodium with a software-adjusted trans-membrane pressure: these devices aim to calibrate the ultrafiltration on patient volemia, thus preventing excessive hemoconcentration and hypotension in subjects with neurovascular dysfunction. Also in this case, a large consensus was obtained for each statement: the panel acknowledged an improved intra-dialytic hemodynamic with a positive impact on patient cardiovascular morbidity (Items 2.1 and 2.2). Over 80% of the experts believed that ESKD patients with neurovascular dysfunction are more likely to achieve the prescribed treatment dose if monitored with biofeedback systems, thus also improving their inflammatory status (Items 2.4 and 2.5). Finally, the whole panel endorsed an improved quality of life, while 80% believed that the prevention of excessive hemoconcentration and hypotension might reduce vascular access thrombosis.

Most of dialysis solutions have acetate as buffer, mainly because of its low propensity to precipitate with calcium and other cations. In recent years, citrate anion has emerged as alternative with a putative double gain: an intrinsic anti-inflammatory effect and the prevention of ac-

Statement 2

According to your clinical experience and literature data, hemodialysis biofeedback systems aimed to control patient serum sodium and volemia in hypotension-prone patients:

Agreement level	1	2	3	4	5	Total
3.1 Associates with a reduction of dialytic hypotensive episodes with a consequent mortality reduction, mainly from cardiovascular causes	0	3	8	21	9	41
	7%		93%			100%
3.2 Associates with improved treatment hemodynamic, independently from the cause of kidney disease	0	0	11	19	11	41
	0%		100%			100%
3.3 Improves uremic toxin removal as consequence of the achievement of treatment target	3	3	17	16	2	41
	15%		85%			100%
3.4 Reduces systemic inflammation as consequence of the achievement of treatment target	2	6	15	16	2	41
	20%		80%			100%
3.5 Improves patient well-being (Quality of Life – QoL)	0	0	13	23	5	41
	0%		100%			100%
3.6 Decreases the risk of vascular access thrombosis	3	5	20	9	4	41
	20%		80%			100%

Statement3

According to your clinical experience and literature data, the use of citrate as dialysis buffer:

Agreement level	1	2	3	4	5	Total
4.1 Associates to heparin dose reduction and/or reduced line clotting	0	7	11	15	8	41
	17%		83%			100%
4.2 Reduces systemic inflammation and vascular calcification	0	4	24	10	3	41
	10%		90%			100%
4.3 Provides a better clearance for middle/high molecular weight uremic toxins	2	10	21	7	1	41
	29%		71%			100%
4.4 Associates with improved treatment hemodynamic, independently from the cause of kidney disease	3	9	20	7	2	41
	29%		71%			100%
4.5 Associates with an improved acid-base balance during and between dialysis treatments	1	4	26	8	2	41
	12%		88%			100%

Fig. 3. Expert panel agreement about the 2nd and 3rd statements. Agreement level was defined as: (1) complete disagreement, (2) disagreement, (3) agreement, (4) strong agreement, and (5) complete agreement. Consensus was defined as agreement or disagreement $\geq 66\%$. Green, positive consensus; yellow, borderline positive consensus; red, absence of consensus or negative consensus.

etate induced vasodilation [41, 42]. When asked about citrate use as dialysis solution buffer, 83% of panel agreed about the reduction of heparin need and of circuit clotting, 90% acknowledged the improvement of patient inflammatory status, 71% agreed about the improved removal of middle/large molecules and about an overall improvement of intradialytic hemodynamics; finally, 88% believed that citrate use improves intra- and interdialytic acid-base status without significant variation of Ca/P balance.

From Delphi Approach to the Real Life in Dialysis Units: Design of Future Clinical Trials with MCO

Despite the compelling need for coordinated and systematic interventions, the dialysis prospect is incredibly fragmented, possibly because of the low evidence available on the different options [27, 43], the high rate of failure of clinical trials in ESKD [44, 45], and the different health policies that various countries implemented to approach such an expensive and long-term procedure [10]. In this clinical setting, it becomes crucial to identify any possible technological or pharmacological improvement that could impact on patients' morbidity and mortality.

MCO dialyzers enhance the clearance of middle and large UT and might improve HD patient outcomes. Based on previously published data, expected patient mortality in HD clinical trial is 30% at 3 years, being lower than registry data due to inclusion criteria [19]. Moreover, a dropout rate of at least 20% is expected in HD trials, mainly due to change of residence and kidney transplantation. Finally, we argue that a 20–25% difference in patient mortality at 3 years could be observed when comparing MCO to standard high-flux HD. This projection is extrapolated by HDF data and lays between ESHOL results (–33% in mortality risk) and registry data where patients were unselected (–15%). Considering these findings altogether, a numerosity of 1,500 patients should be required in a 2-arm study with 3 years follow-up. However, as HDF is nowadays considered a standard of care in multiple countries and is the only other technique that includes diffusion and convection, a third arm should be considered, thus increasing study size to 2,250 patients. A RCT of these proportions would be highly expensive and would require >5 years in trial design, development, and publication. Thus, alternative approaches are warranted to improve the available evidence and justify such a large resource deployment. A cross-over design would allow to pair patient data. This approach limits sampling/ran-

domization biases and requires fewer patients. However, if any of the analyzed treatment has a “carry-over” effect it might affect the other treatment outcome. Let's hypothesize a cross-over study comparing 2 treatments with carry-over effects (a more effective Treatment A and a less effective Treatment B): in group transitioning from A to B this latter would falsely appear as more effective while in the opposite group treatment A would falsely appear as less effective. The net results would be an apparent reduction in treatment difference. A washout interval may reduce this bias but would entail longer trial duration and higher costs.

The use of surrogate endpoints in dialysis is still limited but might be a reasonable option for the design of preliminary studies or RCT interim analysis. Multiple variables that have been associated with cardiovascular performance in HD patients have more rapid variation and could early detect a possible trial success or failure. Among them, the most validated are the changes in echography assessment of left ventricle mass [46] or doppler estimation of arterial stiffness via pulse wave velocity [47]. A more recent technique (dynamic contrast-enhanced CT imaging) can be used to acquire high-resolution cardiac images and provide an accurate estimation of cardiac perfusion [48]. Moreover, regional and national study registry might improve and standardize the long-term follow-up of chronic HD patients reporting adverse events and causes of death using MCO. Up to now, most of the studies on MCO were based on the assessment of safety (in particular albumin loss in dialysate) and performances (reduction ratio/clearances of middle/large UT); next studies should be aimed to evaluate clinical effectiveness and long-term patient outcomes.

Finally, it is important to balance trial randomization and/or data analysis for potential confounders. Citrate dialysis and biofeedback techniques improve dialysis tolerance and reduce patient inflammation thus potentially affecting patients' outcomes. Multiple factors coexist in causing hypotension, one of the most frequent complications in HD: heart failure prevalence in ESKD is about 36%, up to 80% of patients suffer from either uremic or diabetic dysautonomia and arterial compliance is often impaired by both atherosclerosis and vascular calcifications [41, 45, 49, 50]. Such neurovascular dysfunctions worsen patient prognosis and affect dialysis tolerance as well as quality of life: in particular, intradialytic hypotension often requires fluid resuscitation and treatment interruption, thus preventing patients from reaching the target treatment dose. Santoro et al. [51] performed a crossover trial in hypotension-prone HD patients and ob-

served that biofeedback HD improved treatment tolerance. A subsequent investigation extended the finding to patients with minor intradialytic symptoms; the authors observed a 70% drop in hypotensive episodes and a 30% reduction in cramps, nausea, abdominal pain, and headache [52]. In 2013, a meta-analysis pooled 2 randomized controlled trials and 6 crossover studies; median patient number was 27 and quality of evidence was rated as low. The authors concluded that biofeedback systems significantly reduce intradialytic hypotension, but larger trials are needed to assess the impact on other clinical outcomes [53].

Acetate is the most used dialysis solution buffer due to its chemical properties: however, acetate is a vasoactive and pro-inflammatory molecule that can trigger endothelial injury and lipid synthesis [42]. In recent years, citrate has been used in different dialytic settings. In acute kidney injury requiring renal replacement therapy citrate is used as regional anticoagulant agent, as the citrate down-regulates the coagulation cascade by chelating calcium; while in chronic HD, citrate can be used at low concentration (0.8–1 mM) as solution buffer instead of acetate [54, 55]. This trivalent anion has anti-inflammatory and antioxidant properties, increases intracellular glutathione production, reduces complement activation, and promotes mitochondrial oxidative metabolism [41]. In a recent investigation, 45 patients were treated sequentially with acetate and citrate buffered dialysis for 9 months [41]; during citrate treatment, the authors observed increased dialysis efficacy (estimated by eKt/V) and a significant reduction in several inflammatory markers, including fibrinogen, CRP, IL-6, and the adipokine chemerin [56]. Kossmann et al. [57] observed an improved eKt/V in 142 HD patients treated for 6 months with citrate dialysis. In January 2020, French registry data about citrate dialysis have been published; survival analysis of 700 patients showed a trend toward a benefit in citrate dialysis that did not reach statistical significance ($p = 0.06$) and remained not significant in the multivariate analysis [58]. Of note, citrate patients had a significantly lower erythropoietin resistance index despite having lower albumin levels and being more often treated with ACE-inhibitors (a drug class associated with erythropoietin resistance). Only future randomized clinical trials could determine whether biofeedback and citrate dialysis are effective in improving patients' outcomes; however, given the preliminary evidence, we encourage to consider the use of these techniques as potential confounders in a possible HD trial.

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Statement of Ethics

Given the nature of the study, an ethics statement is not applicable. All the Nephrologists who participated to the survey provided written informed consent.

Conflict of Interest Statement

C.R. is part of the editorial board of the Journal; all the other authors declare that they have no conflict of interest.

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Author Contributions

S.D. collected the data, performed data analysis, and wrote the manuscript; V.C. and M.M. conceived the manuscript; V.C., M.M., M.D., G.D., P.F., A.L., and C.R. contributed to project design, literature search, and interpretation. All authors reviewed and approved the manuscript.

Data Availability Statement

All data generated or analyzed during this study are included in this article. Further enquiries can be directed to the corresponding author.

References

- 1 USRDS [Internet]. [cited 2019 Dec 7]. Available from: <https://www.usrds.org/2018/view/Default.aspx>.
- 2 Cozzolino M, Mangano M, Stucchi A, Ciceri P, Conte F, Galassi A. Cardiovascular disease in dialysis patients. *Nephrol Dial Transplant*. 2018 Oct;33(Suppl 3):iii28–34.
- 3 ERA-EDTA registry annual report 2017. 152.
- 4 Kramer A, Pippias M, Noordzij M, Stel VS, Afentakis N, Ambühl PM, et al. The European Renal Association – European Dialysis and Transplant Association (ERA-EDTA) registry annual report 2015: a summary. *Clin Kidney J*. 2018 Feb;11(1):108–22.

- 5 Dąbrowska-Bender M, Dykowska G, Żuk W, Milewska M, Staniszewska A. The impact on quality of life of dialysis patients with renal insufficiency. *Patient Prefer Adherence*. 2018 Apr;12:577–83.
- 6 Vanholder R, Smet RD, Glorieux G, Argilés A, Baummeister U, Brunet P, et al. Review on uremic toxins: classification, concentration, and interindividual variability. *Kidney Int*. 2003 May;63(5):1934–43.
- 7 Wolley MJ, Hutchison CA. Large uremic toxins: an unsolved problem in end-stage kidney disease. *Nephrol Dial Transplant*. 2018 Oct;33(Suppl 3):iii6–11.
- 8 Cavallari C, Dellepiane S, Fonsato V, Medica D, Marengo M, Migliori M, et al. Online hemodiafiltration inhibits inflammation-related endothelial dysfunction and vascular calcification of uremic patients modulating miR-223 expression in plasma extracellular vesicles. *J Immunol*. 2019 Apr;202(8):2372–83.
- 9 Wolley M, Jardine M, Hutchison CA. Exploring the clinical relevance of providing increased removal of large middle molecules. *Clin J Am Soc Nephrol*. 2018 May;13(5):805–14.
- 10 Ward RA, Vienken J, Silverstein DM, Ash S, Canaud B. Regulatory considerations for hemodiafiltration in the United States. *Clin J Am Soc Nephrol*. 2018 Sep;13(9):1444–9.
- 11 De Vriese AS. Should statins be banned from dialysis? *J Am Soc Nephrol*. 2017 Jun;28(6):1675–6.
- 12 Liu G, Long M, Hu X, Hu CH, Liao XX, Du ZM, et al. Effectiveness and safety of warfarin in dialysis patients with atrial fibrillation. *Medicine*. 2015 Dec;94(50):e2233.
- 13 Cheung AK, Rocco MV, Yan G, Leyppoldt JK, Levin NW, Greene T, et al. Serum β -2 microglobulin levels predict mortality in dialysis patients: results of the HEMO study. *J Am Soc Nephrol*. 2006 Jan;17(2):546–55.
- 14 Locatelli F, Altieri P, Andrulli S, Bolasco P, Sau G, Pedrini LA, et al. Hemofiltration and hemodiafiltration reduce intradialytic hypotension in ESRD. *J Am Soc Nephrol*. 2010 Oct;21(10):1798–807.
- 15 Panichi V, Rizza GM, Paoletti S, Bigazzi R, Aloisi M, Barsotti G, et al. Chronic inflammation and mortality in haemodialysis: effect of different renal replacement therapies. Results from the RISCAVID study. *Nephrol Dial Transplant*. 2008 Jul;23(7):2337–43.
- 16 Vilar E, Fry AC, Wellsted D, Tattersall JE, Greenwood RN, Farrington K. Long-term outcomes in online hemodiafiltration and high-flux hemodialysis: a comparative analysis. *Clin J Am Soc Nephrol*. 2009 Dec;4(12):1944–53.
- 17 Ok E, Ascig T, Toz H, Ok ES, Kircelli F, Yilmaz M, et al. Mortality and cardiovascular events in online haemodiafiltration (OL-HDF) compared with high-flux dialysis: results from the Turkish OL-HDF study. *Nephrol Dial Transplant*. 2013 Jan;28(1):192–202.
- 18 Grooteman MPC, van den Dorpel MA, Bots ML, Penne EL, van der Weerd NC, Mazairac AHA, et al. Effect of online hemodiafiltration on all-cause mortality and cardiovascular outcomes. *J Am Soc Nephrol*. 2012 Jun;23(6):1087–96.
- 19 Maduell F, Moreso F, Pons M, Ramos R, Mora-Macià J, Carreras J, et al. High-efficiency postdilution online hemodiafiltration reduces all-cause mortality in hemodialysis patients. *J Am Soc Nephrol*. 2013 Feb;24(3):487–97.
- 20 Peters SAE, Bots ML, Canaud B, Davenport A, Grooteman MPC, Kircelli F, et al. Haemodiafiltration and mortality in end-stage kidney disease patients: a pooled individual participant data analysis from four randomized controlled trials. *Nephrol Dial Transplant*. 2016;31(6):978–84.
- 21 Schiff H. Online hemodiafiltration and mortality risk in end-stage renal disease patients: a critical appraisal of current evidence. *Kidney Res Clin Pract*. 2019 Jun;38(2):159–68.
- 22 den Hoedt CH, Bots ML, Grooteman MPC, van der Weerd NC, Mazairac AHA, Penne EL, et al. Online hemodiafiltration reduces systemic inflammation compared to low-flux hemodialysis. *Kidney Int*. 2014 Aug;86(2):423–32.
- 23 Morena M, Jaussent A, Chalabi L, Leray-Moragues H, Chenine L, Debure A, et al. Treatment tolerance and patient-reported outcomes favor online hemodiafiltration compared to high-flux hemodialysis in the elderly. *Kidney Int*. 2017;91(6):1495–509.
- 24 Panichi V, Scatena A, Rosati A, Giusti R, Ferro G, Malagnino E, et al. High-volume online haemodiafiltration improves erythropoiesis-stimulating agent (ESA) resistance in comparison with low-flux bicarbonate dialysis: results of the REDERT study. *Nephrol Dial Transplant*. 2015 Apr;30(4):682–9.
- 25 Rama I, Llaudó I, Fontova P, Cerezo G, Soto C, Javierre C, et al. Online haemodiafiltration improves inflammatory state in dialysis patients: a longitudinal study. *PLoS One*. 2016 Oct;11(10):e0164969.
- 26 Mercadal L, Franck JE, Metzger M, Urena Torres P, de Cornelissen F, Edet S, et al. Hemodiafiltration versus hemodialysis and survival in patients with ESRD: the French renal epidemiology and information network (REIN) registry. *Am J Kidney Dis*. 2016 Aug;68(2):247–55.
- 27 Daugirdas JT, Depner TA, Inrig J, Mehrotra R, Rocco MV, Suri RS, et al. KDOQI clinical practice guideline for hemodialysis adequacy: 2015 update. *Am J Kidney Dis*. 2015 Nov;66(5):884–930.
- 28 Blankestijn PJ, Fischer KI, Barth C, Cromm K, Canaud B, Davenport A, et al. Benefits and harms of high-dose haemodiafiltration versus high-flux haemodialysis: the comparison of high-dose haemodiafiltration with high-flux haemodialysis (CONVINCE) trial protocol. *BMJ Open*. 2020 Feb;10(2):e033228.
- 29 Ronco C, Marchionna N, Brendolan A, Neri M, Lorenzin A, Martínez Rueda AJ. Expanded haemodialysis: from operational mechanism to clinical results. *Nephrol Dial Transplant*. 2018 Oct;33(Suppl_3):iii41–7.
- 30 Ronco C, Brendolan A, Lupi A, Metry G, Levin NW. Effects of a reduced inner diameter of hollow fibers in hemodialyzers. *Kidney Int*. 2000 Aug;58(2):809–17.
- 31 Lorenzin A, Neri M, Lupi A, Todesco M, Santimaria M, Alghisi A, et al. Quantification of internal filtration in hollow fiber hemodialyzers with medium cut-off membrane. *Blood Purif*. 2018;46(3):196–204.
- 32 Kirsch AH, Lyko R, Nilsson L-G, Beck W, Amdahl M, Lechner P, et al. Performance of hemodialysis with novel medium cut-off dialyzers. *Nephrol Dial Transplant*. 2017 Jan 1;32(1):165–72.
- 33 Zickler D, Schindler R, Willy K, Martus P, Pawlak M, Storr M, et al. Medium cut-off (MCO) membranes reduce inflammation in chronic dialysis patients: a randomized controlled clinical trial. *PLoS One*. 2017 Jan;12(1):e0169024.
- 34 Belmouaz M, Bauwens M, Hauet T, Bossard V, Jamet P, Joly F, et al. Comparison of the removal of uraemic toxins with medium cut-off and high-flux dialyzers: a randomized clinical trial. *Nephrol Dial Transplant*. 2020 Feb 1;35(2):328–35.
- 35 Weiner DE, Falzon L, Skoufos L, Bernardo A, Beck W, Xiao M, et al. Efficacy and safety of expanded hemodialysis with the theranova 400 dialyzer: a randomized controlled trial. *Clin J Am Soc Nephrol*. 2020 Sep;15(9):1310–9.
- 36 Maduell F, Rodas L, Broseta JJ, Gomez M, Xipell M, Guillen E, et al. Medium cut-off dialyzer versus eight hemodiafiltration dialyzers: comparison using a global removal score. *Blood Purif*. 2019;48(2):167–74.
- 37 Schepers E, Glorieux G, Eloit S, Hulko M, Boschetti-de-Fierro A, Beck W, et al. Assessment of the association between increasing membrane pore size and endotoxin permeability using a novel experimental dialysis simulation set-up. *BMC Nephrol*. 2018 Jan;19:1.
- 38 Hulko M, Dietrich V, Koch I, Gekele A, Gebert M, Beck W, et al. Pyrogen retention: comparison of the novel medium cut-off (MCO) membrane with other dialyser membranes. *Sci Rep*. 2019 May;9(1):6791.
- 39 McMillan SS, King M, Tully MP. How to use the nominal group and Delphi techniques. *Int J Clin Pharm*. 2016 Jun;38(3):655–62.
- 40 Chao X, Dong Y, Kou G, Peng Y. How to determine the consensus threshold in group decision making: a method based on efficiency benchmark using benefit and cost insight. *Ann Oper Res*. 2021 Feb. Epub ahead of print.
- 41 Dellepiane S, Medica D, Guarena C, Musso T, Quercia AD, Leonardi G, et al. Citrate anion improves chronic dialysis efficacy, reduces systemic inflammation and prevents Chemerin-mediated microvascular injury. *Sci Rep*. 2019 Jul;9(1):10622.
- 42 Noris M, Todeschini M, Casiraghi F, Roccatello D, Martina G, Minetti L, et al. Effect of acetate, bicarbonate dialysis, and acetate-free biofiltration on nitric oxide synthesis: implications for dialysis hypotension. *Am J Kidney Dis*. 1998 Jul;32(1):115–24.

- 43 Herrington WG, Staplin N, Haynes R. Kidney disease trials for the 21st century: innovations in design and conduct. *Nat Rev Nephrol*. 2020 Mar [cited 2019 Dec 18];16(3):173–85.
- 44 Tsai C, Marcus LQ, Patel P, Battistella M. Warfarin use in hemodialysis patients with atrial fibrillation: a systematic review of stroke and bleeding outcomes. *Can J Kidney Health Dis*. 2017 Oct;4:2054358117735532.
- 45 Palmer SC, Craig JC, Navaneethan SD, Tonelli M, Pellegrini F, Strippoli GF. Benefits and harms of statin therapy for persons with chronic kidney disease: a systematic review and meta-analysis. *Ann Intern Med*. 2012 Aug;157(4):263–75.
- 46 Mishra RK, Dubin RF. The effects of frequent hemodialysis on left ventricular mass, volumes, and geometry. *Clin J Am Soc Nephrol*. 2013 Dec;8(12):2025–7.
- 47 Townsend RR, Anderson AH, Chirinos JA, Feldman HI, Grunwald JE, Nessel L, et al. Association of pulse wave velocity with chronic kidney disease progression and mortality. *Hypertension*. 2018 Jun;71(6):1101–7.
- 48 Hur L, McIntyre CW. Current and novel imaging techniques to evaluate myocardial dysfunction during hemodialysis. *Curr Opin Nephrol Hypertens*. 2020 Nov;29(6):555–63.
- 49 Carreira MAMQ, Nogueira AB, Pena FM, Kiyuchi MG, Rodrigues RC, Rodrigues RR, et al. Detection of autonomic dysfunction in hemodialysis patients using the exercise treadmill test: the role of the chronotropic index, heart rate recovery, and R-R variability. *PLoS One*. 2015 Jun;10(6):e0128123.
- 50 Sipahi I, Fang JC. Treating heart failure on dialysis: finally getting some evidence. *J Am Coll Cardiol*. 2010 Nov;56(21):1709–11.
- 51 Santoro A, Mancini E, Basile C, Amoroso L, Di Giulio S, Usberti M, et al. Blood volume controlled hemodialysis in hypotension-prone patients: a randomized, multicenter controlled trial. *Kidney Int*. 2002 Sep;62(3):1034–45.
- 52 Wolkotte C, Hassell DR, Moret K, Gerlag PG, van den Wall Bake AW, van der Sande FM, et al. Blood volume control by biofeedback and dialysis-induced symptomatology. A short-term clinical study. *Nephron*. 2002;92(3):605–9.
- 53 Nesrallah GE, Suri RS, Guyatt G, Mustafa RA, Walter SD, Lindsay RM, et al. Biofeedback dialysis for hypotension and hypervolemia: a systematic review and meta-analysis. *Nephrol Dial Transplant*. 2013 Jan;28(1):182–91.
- 54 Gattas DJ, Rajbhandari D, Bradford C, Buhr H, Lo S, Bellomo R. A randomized controlled trial of regional citrate versus regional heparin anticoagulation for continuous renal replacement therapy in critically ill adults. *Crit Care Med*. 2015 Aug;43(8):1622–9.
- 55 Ahmad S, Callan R, Cole J, Blagg C. Increased dialyzer reuse with citrate dialysate. *Hemodial Int*. 2005 Jul;9(3):264–7.
- 56 Pizzarelli F, Cantaluppi V, Panichi V, Toccafondi A, Ferro G, Farruggio S, et al. Citrate high volume on-line hemodiafiltration modulates serum Interleukin-6 and Klotho levels: the multicenter randomized controlled study “Hephaestus”. *J Nephrol*. 2021 Oct;34(5):1701–10.
- 57 Kossmann RJ, Gonzales A, Callan R, Ahmad S. Increased efficiency of hemodialysis with citrate dialysate: a prospective controlled study. *Clin J Am Soc Nephrol*. 2009 Sep;4(9):1459–64.
- 58 Potier J, Dolley-Hitze T, Hamel D, Landru I, Cardineau E, Queffeuilou G, et al. Long-term effects of citric acid-based bicarbonate haemodialysis on patient outcomes: a survival propensity score-matched study in Western France. *Nephrol Dial Transplant*. 2020 Jul 1; 35(7):1228–36.