Impact of Medium Cut-Off Dialyzers on Patient-Reported Outcomes: COREXH Registry

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Keywords

Hemodialysis · Medium cut-off membrane · Health-related quality of life · Restless legs syndrome · Dialysis symptoms

Abstract

Introduction: A new generation of hemodialysis (HD) membranes called medium cut-off (MCO) membranes possesses enhanced capacities for middle molecule clearance, which have been associated with adverse outcomes in this population. These improvements could potentially positively impact patient-reported outcomes (PROs). **Objective:** The objective of this study was to evaluate the impact of MCO membranes on PROs in a cohort of HD patients in Colombia. **Methods:** This was a prospective, multicenter, observational cohort study of 992 patients from 12 renal clinics in Colombia who were switched from high-flux HD to MCO therapy and observed for 12 months. Changes in Kidney Disease Quality of Life 36-Item Short Form Survey (KDQoL-SF36) domains, Dialysis Symptom Index (DSI), and restless legs syndrome (RLS) 12 months after switching to MCO membranes were compared with time on high-flux membranes. Repeated measures of ANOVA were used to evaluate changes in KDQoL-SF36 scores; severity scoring was used to assess DSI

changes over time; Cochran's Q test was used to evaluate changes in frequency of diagnostic criteria of RLS. **Results:** During 12 months of follow-up, 3 of 5 KDQoL-SF36 domains improved compared with baseline: symptoms ($p < 0.0001$), effects of kidney disease ($p < 0.0001$), and burden of kidney disease ($p < 0.001$). The proportion of patients diagnosed with RLS significantly decreased from 22.1% at baseline to 10% at 12 months ($p < 0.0001$). No significant differences in the number of symptoms (DSI, $p = 0.1$) were observed, although their severity decreased ($p = 0.009$). **Conclusions:** In conventional HD patients, the expanded clearance of large middle molecules with MCO-HD membranes was associated with higher health-related quality of life scores and a decrease in the prevalence of RLS.

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Introduction

Patient-reported measures (PRMs), including patient-reported outcomes (PROs), cover “any report coming from patients about a health condition and its treatment without interpretation of the patient's response by

a clinician or anyone else” and play a critical role in medical care as a source of information about clinical experiences and outcomes for patients [1]. The Standardized Outcomes in Nephrology (SONG) initiative prioritized the key research questions most relevant to stakeholders, strongly suggesting that patients’ main needs are focused on living well with chronic kidney disease (CKD) [2, 3].

Health-related quality of life (HRQoL) is a PRO that considers the subjective point of view of the patient and supports the evaluation of outcomes and healthcare quality [4]. Clinicians have long recognized the importance of measuring how people are feeling and the extent to which they are able to function in daily activities [5]. Patients on dialysis suffer from poor HRQoL, both from the myriad symptoms of end-stage renal disease (ESRD) and from the physical and mental burdens placed on them by their specific treatments [6].

The physical and mental HRQoL of dialysis patients (as measured by the 36-Item Short Form Survey [SF-36]) is worse than that observed for patients with chronic angina, diabetes mellitus, chronic lung disease, or hypertension [7]. In addition, dialysis patients also experience significantly higher rates of malnutrition, inflammation, hospitalization, and mortality compared with the healthy population [8, 9]. Preserving HRQoL may have important implications; Kalantar-Zadeh and colleagues showed that each 10-unit decrease in SF-36 score was associated with a 2.07-fold increase in the relative risk of death compared with the previous 12 months [9]. In addition, Liebman and colleagues [10] published comparable data showing that a mental component score decrease of ≥ 5 was associated with an increase in the risk of mortality. Over half of patients receiving chronic dialysis are expected to suffer from the effects of a range of symptoms, including fatigue, pain, pruritus, muscle cramps, difficulty with sleep, sexual dysfunction, and nausea, with the severity of symptoms adversely affecting patients’ quality of life (QoL) in terms of physical and psychosocial functioning [11, 12].

The impact of contemporary renal replacement therapies on a patient’s perceived HRQoL is critical to treatment success. While hemodialysis (HD) therapy removes small solutes, the removal of larger molecules >25 kDa (often termed large middle molecules) is limited. Hemodiafiltration (HDF) therapy can remove middle molecules more effectively than HD [13, 14]. However, the effect of an improved uremic environment resulting from the clearance of middle molecules remains unclear based on randomized studies [15, 16].

Advances in membrane technology have led to the development of novel medium cut-off (MCO) membranes that have enhanced selectivity and increased permeability to conventional and large middle molecules [17]. This results in a steep sieving curve in which the molecular weight retention onset and molecular weight cut-off are very close to each other while remaining lower than that of albumin, mimicking the filtration profile of the native kidney [18]. The application of these membranes in clinical dialysis is known as expanded hemodialysis (HDx) therapy [17, 19, 20] due to the enhanced clearance of large middle molecules, which are associated with cardiovascular disease, immune modulation, and protein-energy wasting [21]. Initial studies have demonstrated that the MCO membrane removes toxins at least as effectively as a hemofilter used in HDF mode [22]. The goal is that this enhanced removal will improve PROs and QoL for dialysis patients. Our objective was to determine the impact of the MCO membrane on outcomes, including HRQoL, presence and severity of symptoms, as well as diagnostic criteria of restless legs syndrome (RLS), in a large multicentric cohort of patients in the Expanded Hemodialysis Registry Protocol in Colombia (COREXH, ISRCTN45211359, <https://doi.org/10.1186/ISRCTN45211359>).

Materials and Methods

Study Design and Patients

The COREXH registry is a prospective, multicenter, observational cohort study of patients undergoing dialysis with the MCO membrane in Colombia between September 1, 2017, and November 30, 2017. Patients with CKD who had been undergoing HD therapy for more than 90 days at a Renal Therapy Services network clinic that met Association for the Advancement of Medical Instrumentation water quality standards were invited to participate. Patients were at least 18 years of age and received HD therapy for a minimum of 4 h thrice weekly using the MCO dialyzer (Theranova[®]; Baxter, Deerfield, IL, USA). Patients with a life expectancy of <6 months or an active infection diagnosed within the previous 4 weeks were not invited to participate. Patients were prospectively followed for 12 months from enrollment. We obtained information on the baseline state of health of the patients before the prescription of therapy with the MCO dialyzer.

As this was an observational study, where the procedure of HD was not changed in any respect, the study was considered to be without risk. All patients provided written informed consent, and the study was conducted in accordance with the principles of the Helsinki Declaration and Good Clinical Practices. The clinical research ethics committee of Renal Therapy Services reviewed and approved the protocol (original study protocol dated July 31, 2017, version 1.0).

Fig. 1. Patient flow for the COREXH registry. A total of 1,000 patients signed informed consent at 12 centers. From these, 8 patients did not meet participation criteria, leaving 992 patients eligible for baseline analysis. A total of 638 patients were eligible for 12-month follow-up assessment, with 354 lost to follow-up for the reasons provided. PD, peritoneal dialysis.

Assessments

Baseline (before switching to therapy with the MCO dialyzer) demographic and disease characteristics – including age; sex; cause of CKD; past medical history of hypertension, diabetes mellitus, and acute cardiovascular events; comorbidity index; Karnofsky performance status; and date of initiating chronic renal replacement therapy – were collected from patient electronic medical records. HD treatment parameters, including session duration, number of sessions per week, blood flow, dialysate flow, and type of vascular access, were recorded. Baseline values of KDQoL-SF36, Dialysis Symptom Index (DSI), and diagnostic criteria for RLS were captured from patient electronic medical records, and these measures were repeated at 6 and 12 months of follow-up. KDQoL-36 and DSI values were self-reported responses to surveys offered in hard copy format to the patient at the clinic with the process supported by a social worker at each site. For KDQoL-36, we used a version adapted cross-culturally into Colombian Spanish [23]. The nonresponse rate was 2.2%; the PRO measurements were made according to convenience, either before or after the midweek dialysis session. Patients diagnosed with RLS had to meet the 4 essential criteria proposed by the International Restless Legs Syndrome Study Group (IRLSSG) published in 2003 [24]. The treating nephrologist evaluated the presence of these criteria throughout the observation period.

Statistical Analysis

A statistical description was prepared for all the variables, including calculations of the central tendency measures and dispersion for quantitative variables, and absolute frequencies and percentages for qualitative variables. Scores corresponding to each of the 5 domains of KDQoL-36 were summarized as means and stan-

dard deviations (SDs). For the DSI, 2 scoring systems were considered: an overall scoring system, which was the total of all symptoms existing at the time of the evaluation, and a severity scoring system, in which each item was given a score between 1 and 5. Both scoring systems were summarized using means, medians, SDs, and interquartile ranges (IQRs). For RLS, the percentage of positive cases was calculated.

Changes in KDQoL-SF36 domains and results of DSI severity scoring over time were assessed using repeated measures ANOVA; a “one within” design was considered. To deal with lack of sphericity, *p* values were adjusted using Box’s conservative epsilon. For overall scoring of the DSI, the changeover repeated measures were evaluated using a nonparametrical approach (Friedman test). Cochran’s Q test was used to statistically evaluate if the percentage of patients having RLS changed over time as this test considers dependence between dichotomic values evaluated in repeated measures. Statistical analyses were performed using STATA 14® statistics software (StataCorp LLC, TA, USA). Considering the large sample size of the study, we selected a conservative *p* value of 0.01 for hypothesis testing.

Results

Patient Demographics

Of 1,000 patients who consented to participate, 992 from 12 clinics were included in the baseline analysis, with 638 remaining for the 12-month follow-up (Fig. 1). Most of the patients were male (62%), with a mean age at

Fig. 2. Longitudinal changes in patients meeting RLS diagnosis over 12 months of follow-up. Proportion of patients meeting the RLS diagnostic criteria at baseline as well as 6 and 12 months of follow-up after switching to the medium cut-off membrane. RLS, restless legs syndrome.

enrollment of 60.5 years (SD 15.1 years). A total of 917 patients (92.4%) had a history of hypertension, with 436 (43.9%) and 364 (36.7%) patients having a history of diabetes or cardiovascular disease, respectively. At the time of enrollment, included patients had been receiving high-flux HD for a median of 3.7 years (IQR 6.2) (Table 1). Dialysis and laboratory parameters are presented in Table 2.

Kidney Disease Quality of Life 36-Item Short Form Survey

Longitudinal Kidney Disease Quality of Life 36-Item Short Form Survey (KDQoL-36) scores for each of the 5 domains are shown in Table 3. Following 12 months of therapy with the MCO membrane, mean scores significantly increased from baseline for symptoms/problems (baseline: 78.6 [SD 15.8], 12 months: 81.5 [14.9]; $p < 0.0001$), effects of kidney disease (baseline: 69.7 [22.3], 12 months: 75.1 [21.0]; $p < 0.0001$), and burden of kidney disease (baseline: 46.2 [27.5], 12 months: 50.2 [32.2]; $p < 0.0001$). Scores for the mental and physical domains remained stable and did not change significantly from baseline. We did not observe any relevant differences in KDQoL-36 domains when analyzed by participating center (see online suppl. Table 1, available at www.karger.com/doi/10.1159/000508803).

Table 1. Patient demographics and characteristics at baseline

Baseline characteristics	N = 992	
Age, mean (SD), years	60.5	(15.1)
Sex, n (%)		
Male	619	(62.4)
Female	373	(37.6)
Medical history, n (%)		
Hypertension	917	(92.4)
Diabetes	436	(43.9)
Cardiovascular disease	364	(36.7)
Comorbidity index, n (%)		
0 to 3	802	(80.9)
4 to 6	170	(17.1)
≥ 7	20	(2)
Karnofsky PS score, ^a median (IQR)	80.0	(70, 90)
Dialysis vintage, median (IQR), years	3.7	(1.6, 7.8)

IQR, interquartile range; PS, performance status; SD, standard deviation. ^a Data available for 914 patients.

Restless Legs Syndrome Diagnostic Criteria

The proportion of patients meeting RLS diagnostic criteria significantly decreased over the follow-up period (Fig. 2), with 216/977 (22.1%), 102/818 (12.5%), and 66/661 (10.0%) of patients meeting the criteria at baseline and 6 and 12 months, respectively ($p < 0.0001$). A post hoc comparison showed statistically significant differences between each pair of repeated observations (baseline vs. 6 months: $p < 0.0001$; baseline vs. 12 months: $p < 0.0001$; 6 vs. 12 months: $p = 0.003$).

Dialysis Symptom Index

No significant differences in the mean number of symptoms were reported at baseline compared with 6 or 12 months of follow-up, being 10.3, 10.3, and 10.0, respectively ($p = 0.1$). However, mean severity scores significantly decreased from 30.7 (SD 22.3) at baseline to 29.9 (32) at 6 months and 28.5 (21.7) at 12 months of follow-up ($p = 0.009$) (Table 4). All 30 DSI items were reported at a lower frequency at 6 and 12 months compared with baseline, with marginally significant reductions in shortness of breath, dizziness/lightheadedness, and difficulty falling asleep observed. Four items consistently had the highest scores over time (dry skin, feeling tired, trouble falling asleep, and trouble staying asleep), and 4 items consistently had low scores over time (chest pain, diarrhea, swelling in legs, and vomiting) (Table 5).

Table 2. Dialysis and laboratory parameters at baseline and 12 months of follow-up

	Baseline, <i>n</i> = 992	12 months, <i>n</i> = 638
<i>Dialysis parameters</i>		
Vascular access, % (<i>n</i>)		
AV fistula	83.06 (824)	83.54 (533)
Catheter	14.52 (144)	13.95 (89)
Graft	2.42 (24)	2.51 (16)
Treatments/week, % (<i>n</i>)		
3	99.19 (984)	99.06 (632)
4	0.71 (7)	0.94 (6)
5	0.10 (1)	–
Duration of a dialysis session, mean (SD), h	4.01 (0.11)	4.01 (0.11)
Dialysate flow, mean (SD), mL/min	486.99 (52.21)	481.50 (54.56)
Blood flow, mean (SD), mL/min	352.05 (51.31)	355.43 (49.97)
Dialyzer type, % (<i>n</i>)		
Dicea 110 G (1.1 m ²)	0.20 (2)	–
Xenium XPH-210 (2.1 m ²)	0.40 (4)	–
Polyflux 140H (1.4 m ²)	2.22 (22)	–
Revaclear 300 (1.6 m ²)	78.02 (774)	–
Revaclear 400 (1.8 m ²)	19.15 (190)	–
Theranova 400 (1.7 m ²)	–	91.22 (582)
Theranova 500 (2.0 m ²)	–	8.78 (56)
<i>Clinical laboratory parameters</i>		
Albumin, mean (SD), g/dL	4.04 (0.33)	3.98 (0.34)
Hemoglobin, mean (SD), g/dL	11.89 (1.72)	11.87 (1.66)
Phosphorous, mean (SD), mg/dL	4.60 (1.38)	4.54 (1.32)
PTHi, median (IQR), pg/mL	327.80 (165.30, 625.30)	309.50 (173.00, 562.00)
hsCRP, mean (SD), mg/L	1.11 (2.83)	2.36 (15.68)
spKt/V _{urea} , mean (SD)	1.62 (0.34)	1.71 (0.36)

AV, arteriovenous; hsCRP, high-sensitivity C-reactive protein; IQR, interquartile range; PTHi, parathyroid hormone; SD, standard deviation; spKt/V_{urea}, standardized Kt/V_{urea}.

Table 3. Changes in KDQoL-36 score over 12 months of follow-up

KDQoL-36 domain	Statistic	Baseline, <i>n</i> = 971	6 months, <i>n</i> = 808	12 months, <i>n</i> = 642	<i>p</i> value ^a
Symptoms/problems	Mean	78.6	81.0	81.5	<0.0001
	SD	15.8	15.4	14.9	
Effects of kidney disease	Mean	69.7	72.8	75.1	<0.0001
	SD	22.3	22.0	21.0	
Burden of kidney disease	Mean	46.2	48.9	50.2	<0.001
	SD	27.5	29.9	32.3	
SF-12 physical	Mean	41.1	41.0	41.7	0.3
	SD	11.1	11.2	10.5	
SF-mental	Mean	51.1	51.9	52.3	0.02
	SD	11.6	11.3	11.1	

KDQoL-36, Kidney Disease Quality of Life 36-Item Short Form Survey; SD, standard deviation; SF, short form. ^a For hypothesis testing, type-I error significance was set at *p* = 0.01.

Table 4. Changes in DSI over 12 months of follow-up

DSI domain	Statistic	Baseline, <i>n</i> = 977	6 months, <i>n</i> = 813	12 months, <i>n</i> = 642	<i>p</i> value
Number of symptoms	Mean	10.3	10.3	10.0	0.1 ^a
	SD	6.6	6.7	6.6	
	Median	9	9	9	NA
	IQR	10	10	9	
Symptom severity score	Mean	30.7	29.9	28.5	0.009 ^b
	SD	22.3	32.0	21.7	
	Median	26	26	23	NA
	IQR	32	30	31	

DSI, Dialysis Symptom Index; IQR, interquartile range; NA, not applicable; SD, standard deviation. ^a By Friedman's test. ^b By ANOVA.

Discussion/Conclusion

Chronic HD aims to improve survival while maintaining or minimizing any negative impact on patient QoL. High-flux membranes are unable to effectively remove large middle molecules or those molecules that have a molecular diameter larger than the pore size, which may contribute to poor nutritional and inflammation status and reduced QoL [25]. The MCO membrane enables expanded removal of large middle molecules compared with high-flux HD, including myoglobin, β 2-microglobulin, macroglobulin, homocysteine, as well as λ - and κ -free light chains [22]. This property could translate into myriad benefits for patients receiving dialysis [22, 26].

Table 5. Changes in frequency of DSI over 12 months of follow-up

Item, <i>n</i> (%)	Baseline, <i>n</i> = 989	6 months, <i>n</i> = 850	12 months, <i>n</i> = 600	<i>p</i> value ^a
Constipation	278 (28.11)	241 (28.32)	157 (26.17)	0.1
Nausea	229 (23.15)	186 (21.86)	129 (21.46)	0.4
Vomiting	108 (10.92)	82 (9.65)	55 (9.15)	0.4
Diarrhea	170 (17.19)	154 (18.12)	88 (14.64)	0.08
Decreased appetite	277 (28.01)	253 (29.73)	175 (29.12)	0.2
Muscle cramps	477 (48.23)	384 (45.18)	253 (42.1)	0.07
Swelling in the legs	200 (20.22)	155 (18.21)	110 (18.33)	0.7
Shortness of breath	214 (21.64)	207 (24.32)	124 (20.63)	0.02 ^b
Dizziness/lightheadedness	268 (27.1)	207 (24.32)	127 (21.13)	0.01 ^b
Restless legs or difficulty keeping legs still	260 (26.29)	223 (26.24)	164 (27.33)	0.9
Numbness/tingling in the feet	372 (37.61)	298 (35.02)	219 (36.44)	0.3
Feeling tired/lack of energy	529 (53.49)	460 (54.05)	330 (54.91)	0.9
Cough	325 (32.89)	306 (36)	200 (33.28)	0.2
Dry mouth	406 (41.05)	362 (42.54)	254 (42.26)	0.7
Bone or joint pain	426 (43.07)	364 (42.77)	256 (42.6)	0.5
Chest pain	196 (19.82)	168 (19.74)	101 (16.81)	0.08
Headache	379 (38.32)	319 (37.49)	225 (37.44)	0.4
Muscle pain	365 (36.94)	284 (33.37)	222 (36.94)	0.3
Difficulty concentrating	299 (30.23)	275 (32.31)	184 (30.62)	0.4
Dry skin	540 (54.6)	448 (52.64)	352 (58.57)	0.2
Scratchy/itching	441 (44.59)	386 (45.36)	253 (42.1)	0.1
Feeling worried	434 (43.88)	376 (44.18)	252 (42)	0.05
Feeling nervous	259 (26.19)	240 (28.2)	158 (26.33)	0.2
Difficulty falling asleep	489 (49.44)	397 (46.71)	270 (45)	0.02 ^b
Problems maintaining sleep	458 (46.31)	382 (44.94)	261 (43.5)	0.2
Feeling irritable	300 (30.33)	267 (31.41)	184 (30.67)	0.8
Feeling sad	405 (40.99)	343 (40.31)	249 (41.5)	0.3
Feeling anxious	290 (29.35)	243 (28.59)	159 (26.5)	0.09
Decreased interest in sex	413 (41.84)	342 (40.33)	255 (43.52)	0.8
Difficulty becoming sexually aroused	383 (38.8)	340 (40.14)	255 (43.52)	0.02 ^b

DSI, Dialysis Symptom Index. ^a Cochran's Q test for proportions at moments in time. ^b Considered to be marginally significant.

Improving the HRQoL and PROs for dialysis patients is a therapeutic goal, with studies demonstrating the impact of HRQoL on patient outcomes [27]. Poor mental health is an independent risk factor for mortality [28], and decreases in the 2 main QoL domains – mental and physical health – correlate with reduced PROs and survival [29, 30]. Finally, QoL correlates with nutrition, potentially predicting longevity [31]. Rambod and colleagues [31] reported that the Malnutrition-Inflammation Score (MIS) correlated with levels of middle molecules, including interleukin-6 and C-reactive protein, with a higher MIS being associated with lower SF-36 scores and ultimately mortality in patients receiving HD over 5 years. These results match ours, supporting the hypothesis that expanded clearance of large middle molecules improves measures of QoL over 12 months.

Using KDQoL-36, the Dialysis Outcomes and Practice Patterns Study demonstrated that the adjusted mortality risk increased by 25% with each 10-point reduction in the physical component summary, 13% with each 10-point reduction in the mental component summary, and 11% with each 10-point reduction in the kidney disease component summary [32]. Similarly, the CONTRAST study demonstrated that decreases in physical function, emotional health, and social functioning were significantly associated with mortality over 2 years [33] and were independent of age [33]. It is encouraging that we observed a positive impact of the expanded removal of large middle molecules on QoL measures in adult patients.

To our knowledge, this is the first study that measures HRQoL and the frequency and severity of symptoms, as well as the presence of diagnostic criteria for RLS, in patients receiving MCO membrane-based HD. Significant improvements were observed in 3 of the 5 HRQoL domains measured by KDQoL-36 – symptoms/problems, effects of kidney disease, and burden of kidney disease – and were most pronounced in the kidney disease effects domain. The effect size is modest but consistent across the full 12-month follow-up period, suggesting that the expanded clearance of large middle molecules provided by the MCO membrane may be associated with improvements in patient QoL. Regarding the size of this effect, the difference in QoL found was between 3 and 5 points per domain, which is slightly higher than that found between different types of dialysis therapy in the USA [34]; furthermore, and contrary to the expected outcomes for patients receiving chronic dialysis, QoL trended towards improvement over the course of the follow-up.

Approximately 2.5 to 15% of the healthy population is estimated to meet the International Diagnostic Criteria for RLS. For patients with ESRD, ~20 to 25% of patients show overt (moderate-to-severe) RLS, while 62% present milder forms [35, 36]. While the pathogenic mechanisms for uremic RLS are unknown, the most widely accepted hypothesis for idiopathic RLS is a dysfunction of the dopaminergic system and reduced iron stores in specific regions in the brain [37]. A removal rate of 35% of α 1-microglobulin (α 1-MG; a heme scavenger) is associated with an improvement in RLS symptoms [38]; it is not clear if elevated α 1-MG levels are toxic per se and, for now, should be used as a biomarker [38]. It is noteworthy that patients can completely recover from uremic RLS symptoms 1–21 days after a successful kidney transplant [39]. In addition, for patients who again become dependent on dialysis, RLS symptoms return 10–60 days after reinitiating HD, supporting the role of uremic toxicity in the pathogenesis of RLS [39]. This is likely to be due to the levels of middle molecules that were not well removed during dialysis either prior to transplant or after rejection. Importantly, we show a significant (54.86%) decrease in the proportion of patients meeting the diagnostic criteria for RLS at 12 months compared with baseline. Combined with the difficulties in correlating uremic toxin removal with RLS occurrence as well as the consistent, yet limited, data indicating HD has minimal impact on RLS [40], our results suggest that the expanded clearance of large middle molecules with the MCO membrane (comparable with the natural kidney) may alleviate the development and impact of RLS. In addition, we observed a modest reduction in the severity of dialysis symptoms (mean DSI) after switching to the MCO membrane. This observation may contribute to our understanding of the importance of middle molecule removal on common dialysis symptoms including anorexia, fatigue, or pruritus. Of note is the decrease in the proportion of patients with difficulties falling asleep, as well as in the presence of dizziness/lightheadedness, as this was likely related to improvements in RLS and sleep pattern, which has been previously linked to the clearance of middle molecules in the literature [25, 41].

Our study has several strengths supporting the validity of our results. We observed patients prospectively for 12 months, enabling the longitudinal measurement of outcomes, including QoL and PROs, and comparison with historical baseline values, allowing us to directly assess the impact of switching to the MCO membrane. Our data were obtained from a large cohort of patients ($N =$

992) from multiple clinics, with every attempt made to maintain the quality of care. Thus, we can be confident that our observations provide a robust measure of current treatment practices and their impacts. Our study does have limitations. Being a registry, there is no randomization or blinding to the intervention, creating potential for biases in the observed and the observer; in addition, there was no comparator group, and this may decrease to some extent the level of causality that can be attributed to the different practices. However, the substantial number of patients and the longitudinal follow-up period, in our view, make this a nonnegligible body of evidence.

After switching to the MCO membrane, the population in this study presented not only a statistically significant improvement in their HRQoL (measured with KDQoL-36) in 3 of the 5 domains (symptoms/problems, effects of kidney disease, and burden of kidney disease) but also a significant decrease in the prevalence of RLS. If validated in other studies, these findings may support the routine use of MCO membranes in HD patients, enhancing the standards of care.

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Statement of Ethics

All patients provided written informed consent, and the study was conducted in accordance with the principles of the Helsinki Declaration and Good Clinical Practices. The clinical research

ethics committee of Renal Therapy Services reviewed and approved the protocol (original study protocol dated July 31, 2017, version 1.0).

Conflict of Interest Statement

Drs. Alarcon and Bunch and Mr. Sanabria are full-time employees of Renal Therapy Services-Latin America, Bogotá, Colombia. Drs. Ardila and Zuñiga and Ms. Vesga are full-time employees of Renal Therapy Services-Colombia, Bogotá, Colombia. Dr. Rivera is a full-time employee of Baxter Healthcare Corporation, Chicago, IL, USA, and has a patent for Membran zur Behandlung des Rest Leg Syndrome pending. Mr. Sánchez has received an honorarium for consultancy from Renal Therapy Services-Colombia.

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Author Contributions

J.C.A., A.B., F.A., and E.Z.: original research project conception and design, data acquisition, and data interpretation. J.V. and M.S.: original research project conception and design, data acquisition, statistical analysis, and data interpretation. A.R.: original research project conception and design and data interpretation. R.S.: original research project conception and design, statistical analysis, and data interpretation. All authors have been involved in the drafting of the manuscript or revising it critically for important intellectual content and provided final approval of the version to be published. All authors verify that they have met all the journal's requirements for authorship. All authors agree to be accountable for all aspects of the work, ensuring the accuracy and integrity of the publication. All authors approved the final manuscript draft submitted for publication. The authors received no financial compensation for the development of the manuscript.

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