Medium Cut-Off Versus High-Flux Hemodialysis Membranes and Clinical Outcomes: A Cohort Study Using Inverse Probability Treatment Weighting

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BACKGROUND

Despite advances in the field of chronic hemodialysis (HD) and improvements in morbidity and mortality, outcomes for chronic HD patients are far from optimal. Improved clearance of uremic toxins may reduce their adverse effects on biological systems and lead to improved outcomes. Recent data suggest that increased removal of large middle molecules may improve clinical outcomes through impact on inflammation and atherosclerosis. Advances in bioengineering have allowed development of a novel medium cut-off membrane (**Theranova** 400/500, Vantive) that improves clearance of large middle-molecules 25 kDa and above.

OBJECTIVE

Determine whether there are differences in clinical outcomes when chronic HD patients are treated with **MCO** membranes compared to high-flux (HF) membranes.

METHODOLOGY

This was a retrospective, observational, multicenter, cohort study of patients undergoing HD (defined as received HD for 90 days) in Colombia. Patients were included from Vantive Renal Care Services network of renal between September 1, 2017 to November 30, 2017, with follow up to November 30, 2019. Enrollment occurred immediately for patients in the **MCO** membrane cohort once switched to this new membrane type. Inclusion criteria included: age >18 years; receiving expanded hemodialysis using an **MCO** membrane (**Theranova** dialyzer, Vantive, Deerfield, IL, USA) or conventional HD using HF membrane for a minimum of 4 hours 3 times per week. Patients in both cohorts were included from the same dialysis clinics and membrane allocation was not done by predetermined methods but rather by decisions by each individual clinician. Standard dialyzers available in renal clinics were used. Exclusion criteria were life expectancy of less than six months, active infection, metastatic disease, or a Charlson comorbidity index greater than eight.

Patients were divided into two cohorts according to the membrane used at the time of enrollment: 1) **MCO** membrane group or 2) HF group. Once a patient had been included in one of the two cohorts, the clinical teams were instructed not to change the membrane type unless determined by a medical decision or patient request.

OUTCOMES AND ANALYSIS

Primary outcome: hospitalization rate from any cause and hospitalization days per patient-year.

Secondary outcomes: non-fatal cardiovascular events (any hospitalization event for causes predefined in the International Classification of Diseases 10 as cardiovascular); time to death survival analysis from any cause; changes in serum albumin levels during follow-up.

Inverse Probability of Treatment Weighting (IPTW) using a propensity score was used to control differences between groups. The propensity score for each subject was calculated from a logistic regression model that included clinical and demographic variables as predictors of the exposure status such as age, sex, race, dialysis duration, CKD cause, hypertension history, diabetes history, cardiovascular disease history, Charlson comorbidity index, Karnofsky scale, urine output ml/day, BMI, serum albumin, hemoglobin, parathormone intact, phosphorous, potassium, Kt/V single pool, and normalized protein catabolic rate and the research site location. The IPTW for each individual subject was then calculated and the balance between exposed and unexposed groups in the weighted sample was evaluated based on descriptive methods (standardized differences, with a target value of < 0.1, and variance ratios) and inferential methods (over identification test for covariate balance), and the effect of the exposure on each outcome was estimated using robust standard errors. For the outcome hospitalization rate and days, negative binomial regression models were used for violation of the over dispersion assumption and Akaike and Bayesian Information criteria were used to compare the models; the association was estimated with Incidence Rate Ratio (IRR). Survival time was estimated in the full sample, and the weighed population according to membrane use; the log-rank test was used to compare the equality of the survival functions in the full sample; for comparison in the weighed population, we used Cox regression. To confirm the direction of the effect, negative binomial regression models in full sample were performed.

RESULTS

Patients

A total of 1098 patients were enrolled (564 in the **MCO** membrane group and 534 in the HF group); and 711 completed the total follow-up time (391 in the **MCO** membrane group and 320 in the HF). Mean age was 60.3 ±14.9 years in the **MCO** membrane group, and 60.8 ±15.0 years in the HF group, and 65.2% were male in the HF group and 59.6% in the HF group. The proportion of patients with diabetes mellitus was similar in the two groups, 43.6% for **MCO** membrane vs. 40.1% for HF, p = 0.23. Baseline albumin levels were 4.0 g/dl for **MCO** membrane vs. 4.0 g/dl for HF. After weighting using IPW, no statistically significant difference between groups in baseline characteristics was observed.

Clinical Outcomes

In the weighted sample, **MCO** membrane was associated with fewer all-cause hospitalization events rate per patient-year, IR = 0.93 [95% CI 0.82–1.03] versus 1.13 [95% CI 0.96–1.30] for HF, corresponding to a significant IRR **MCO** membrane/HF of 0.82 [95% CI 0.68-0.99]; p = 0.04.

There was no significant difference in hospital days; p = 0.73. Across both groups, cardiovascular events were the most frequent cause of hospitalization (28.5% **MCO** membrane vs 31.1% HF).

The non-fatal cardiovascular event rate per patient-year was lower in the **MCO** membrane group, IR = 0.18 [95% CI 0.14-0.22] versus IR = 0.28 [95% CI 0.19-0.36] for HF, corresponding to a significant IRR **MCO** membrane/HF of 0.66 [95% CI 0.46-0.96]; p = 0.03.

There was no significant difference in survival between **MCO** membrane vs HF dialyzers, HR = 0.88 [95% CI 0.64 to 1.23]; p = 0.48.

Table 1 shows clinical outcomes, and Figures 1 and 2 show survival curves.

Table 1. Clinical outcomes in full simple and weighted samples.

Clinical Outcomes	Crude Estimate (95% CI)	*P* value	Adjusted Estimate With IPTW (95% CI)	*P* value
Hospitalization events[a]				
HF membrane	1.07 (0.99-1.14)	—	1.13 (0.96-1.30)	—
MCO membrane	0.79 (0.73-0.84)	—	0.93 (0.82-1.03)	—
IRR	0.74 (0.67-0.82)	<0.01	0.82 (0.68-0.99)	0.04
Hospital days[a]				
HF membrane	10.18 (9.96-10.4)	—	13.21 (10.47-15.95)	—
MCO membrane	6.45 (6.29-6.62)	—	12.47 (9.36-15.59)	—
IRR	0.63 (0.61-0.66)	<0.01	0.94 (0.68-1.30)	0.73
Nonfatal cardiovascular events[a]				
HF membrane	0.25 (0.21-0.28)	—	0.28 (0.19-0.36)	—
MCO membrane	0.16 (0.13-0.18)	—	0.18 (0.14-0.22)	—
IRR	0.64 (0.52-0.80)	<0.01	0.66 (0.46-0.96)	0.03
Time to death[b]				
HR **MCO**/HF membrane	0.66 (0.50-0.89)	0.01	0.88 (0.64-1.23)	0.48

Note: The IRR was defined as **MCO** membrane/HF.
Abbreviations: CI, confidence interval; HR, hazard ratio; IPTW, inverse probability of treated weighting; IRR, incidence rate ratio.
aNegative binomial regression and expressed as hospital days per patient-years.
bCox proportional regression.

FIGURES 1 and 2. Survival curves according to the type of dialyzer membrane. Figure 1 compares the survival functions in the full sample (crude), finding a statistically significant difference in favor of the **MCO** membrane and Figure 2 compares the survival functions in weighted samples, where no difference is observed statistically significant.

FIGURE 1

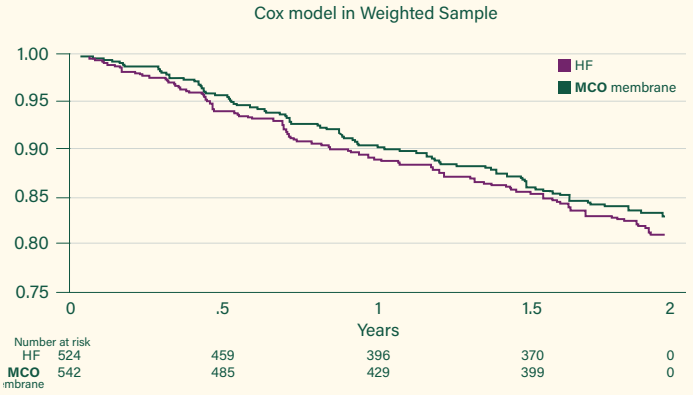
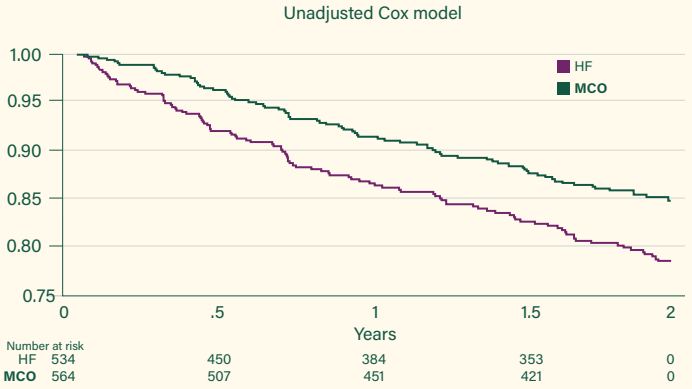


FIGURE 2

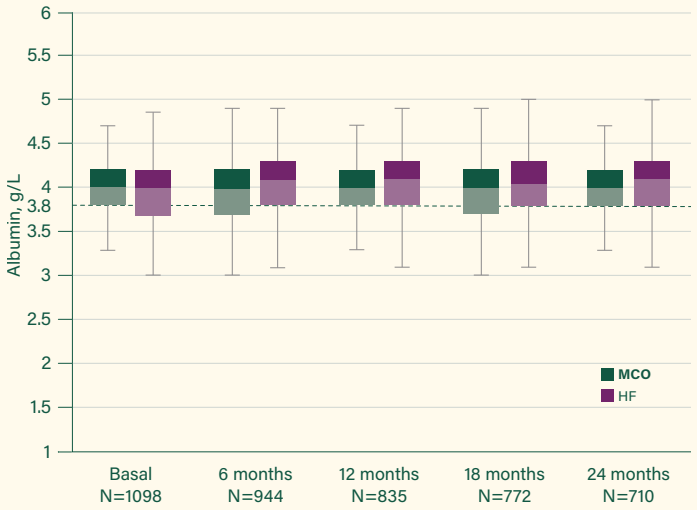


Laboratory Results

There were no differences between the two groups in albumin, phosphate, potassium, or parathyroid hormone evaluated with the split-plot ANOVA test at baseline or at 6, 12, 18, and 24 months of follow-up. Values for hemoglobin and single-pool Kt/V were higher in the **MCO** membrane group at baseline, which continued during follow-up (p < 0.01).

Serum albumin levels remained stable during the 24-month period, see Figure 3.

FIGURE 3. Serum albumin levels



DISCUSSION AND CONCLUSIONS

This cohort study showed that patients treated with **MCO** membranes had lower rates of hospitalization and cardiovascular events compared with patients treated with HF membranes. These data support the hypothesis that increased clearance of pro-inflammatory middle-molecules could reduce the occurrence of chronic inflammation, atherosclerosis, structural heart disease and immunodeficiency, thereby reducing the frequency of hospitalization events, particularly for cardiovascular causes.

No difference was found in all-cause mortality or cardiovascular mortality, which could be explained by the short period of follow-up of two years.

There were no differences in serum albumin levels between groups over 2 years of follow-up, demonstrating that stable serum albumin levels are maintained with **MCO** membranes.

Strengths and Limitations

This study's strength lies in the large number of patients included, standardized data collection with robust quality controls and statistical analysis methods used to deal with the confounding inherent in this type of observational study.

The main weakness of the study is its observational nature. Despite the robust statistical analysis there remains the possibility that unmeasured variables may still generate residual imbalance, skewing the results.

CONCLUSION

This large cohort study demonstrated that there is a lower incidence of hospitalization events and non-fatal cardiovascular events in chronic HD patients dialyzed with **MCO** membranes compared to those treated with HF membranes. These results should be corroborated with randomized controlled trials. These results should be corroborated with randomized controlled trials.

HDx therapy with the MCO membrane is associated with fewer hospitalization events and non-fatal cardiovascular events, and no change in serum albumin compared with HF HD over 2 years follow-up.