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# A tRial Evaluating Mid Cut-Off Value Membrane Clearance of Albumin and Light Chains in HemoDialysis Patients: A Safety Device Study

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**Keywords**
Albumin · Dialysis membrane · Dialyzer · Efficacy · Free light chains · Mid cut-off · Safety · Hemodialysis

**Abstract**
***Background:*** A new class of dialysis membrane, the mid cut-off (MCO) dialyzer, has been developed to improve the clearance of uremic toxins in hemodialysis (HD). The a tRial Evaluating Mid cut-Off Value membrane clearance of Albumin and Light chains in HemoDialysis patients (REMOVAL-HD) study aimed to determine if regular use of MCO dialyzer was safe and specifically did not result in a significant loss of albumin. ***Methods:*** This investigator initiated, crossover, longitudinal, device study was conducted across 9 centers in Australia and New Zealand ($n = 89$). Participants had a 4-week wash-in with high-flux HD, followed by 24-week intervention with MCO HD and a subsequent 4-week wash-out with high-flux HD. The primary outcome was change in serum albumin between weeks 4 and 28. Secondary outcomes included trends in serum albumin, changes in kappa- and lambda-free light chains (FLC), 6-min walk test (6MWT), malnutrition inflammation score (MIS), restless legs score and quality of life. ***Results:*** Participants had a mean age of 66 ± 14 years, 62% were men, 45% were anuric, and 51% had diabetes. There was no reduction in serum albumin following treatment with MCO HD (mean reduction –0.7 g/L, 95% CI –1.5 to 0.1). A sustained, unexplained reduction in serum



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albumin (>25%) was not observed in any participant. A reduction in FLC was observed 2 weeks into MCO HD (lambda-FLC: Δ −9.1 mg/L, 95% CI −14.4 to −3.7; kappa-FLC: Δ −5.7 mg/L, 95% CI −9.8 to −1.6) and was sustained for the rest of the study intervention. Both FLC increased after the cessation of MCO use. There was no improvement in restless legs symptoms, quality of life, 6MWT or MIS scores. ***Conclusions:*** Regular HD using the MCO dialyzer did not result in a significant fall in serum albumin. There were no effects on quality of life, functional status or nutrition. ***Trial Registration:*** Australian New Zealand Clinical Trials Registry Number (ANZCTRN) 12616000804482. 

## Introduction

Patients with end-stage kidney disease (ESKD) are often burdened with a myriad of complications including cardiovascular disease, infection and malnutrition resulting in high rates of hospitalization, reduced quality of life, and increased risk of death [1–3]. Retention of uremic toxins especially middle molecules that are not well cleared by current dialysis therapies may contribute to the disease burden in the ESKD cohort.

The clearance of middle-molecules has continued to improve with the evolution of dialysis technology over the last 20 years. The early low flux dialyzers provided limited removal of these molecules. With the advent of high-flux dialyzers and hemodiafiltration (HDF), the efficiency of middle molecule clearance by chronic hemodialysis (HD) has continually increased; however, the clearance of almost a third of the larger middle molecules (>25 kDa) is yet to be optimized [4]. Pore sizes of dialysis membranes are crucial in determining the clearance of larger middle molecules. However, membranes with larger pore sizes, such as the high cut-off dialyzer (HCO), were associated with substantial albumin loss requiring supplementation with an albumin solution following dialysis treatment. This resulted in the view that HCO membranes were unsafe and impractical for maintenance HD.

Advancement in manufacturing technology has led to the development of a new class of dialysis membrane called the mid cut-off (MCO) dialyzer [5]. This membrane has a pore size between those of a standard high flux and an HCO membrane with narrowly distributed pores to enhance membrane permeability and selectivity.

The safety and efficacy data for the MCO dialyzer in a clinical setting are limited. Small, short-term studies over 2–3 weeks found albumin loss can be greater than high-flux HD but variable when compared to online-HDF [6, 7]. These studies also demonstrated effective removal of middle molecules up to a molecular weight of 45 kDa. The longer-term outcomes with respect to change in serum albumin, tolerability and effectiveness of this novel dialyzer are yet to be established.

Thus, the primary aim of the a tRial Evaluating Mid cut-Off Value membrane clearance of Albumin and Light chains in HemoDialysis patients (REMOVAL-HD) study was to determine the safety of HD using a MCO dialyzer (Theranova; Baxter Healthcare, Sydney, Australia) with regard to its effect on change in serum albumin over 6 months in a prevalent HD cohort. This study also assessed the impact of MCO HD on the change in serum levels of larger middle-molecules as well as functional status, nutritional status and quality of life.

## Materials and Methods

*Study Design and Oversight*

A comprehensive description of REMOVAL-HD study design has been published elsewhere [8]. REMOVAL-HD was an investigator-initiated, open-label, non-randomized, device study conducted in 9 in-center HD units in Australia and New Zealand. Recruitment commenced in January 2017 and the last participant follow-up occurred in April 2018. The study was coordinated and supported by the Australasian Kidney Trials Network (AKTN). A trial steering committee consisting of clinicians and statisticians were solely responsible for the trial design, conduct, data analysis, and manuscript preparation. The trial steering committee was also responsible for the scientific integrity of the trial by overseeing the monitoring of albumin levels, serious adverse events (SAE) and operational data. The study protocol was reviewed and critiqued by the AKTN Scientific Committee. Ethical approval was obtained from Institutional Ethics Committees for participating sites (Melbourne Health HREC [reference number: HREC/16/MH/228] for Australian sites and Northern B Health and Disability Ethics Committee [reference number: 16/NTB/126] for NZ sites) and local governance approval gained for each site. Informed signed consent was obtained from all participants. This study is registered with the Australian and New Zealand Clinical Trials Registry (ANZCTRN 12616000804482).

*Participants*

Eligible participants were >18 years of age, had been on chronic in-center HD for at least 12 weeks, had a functioning arteriovenous fistula or graft and were either oliguric or anuric. Participants with urine output >500 mL were excluded to minimize confounding by significant residual kidney function. The main exclusion criteria were based on conditions or medications that would impact serum albumin and confound the outcome of the study, including receiving active treatment for significant chronic infection or inflammatory conditions (autoimmune disease, inflammatory arthritis, and malignancy), dialysis catheter in-situ,

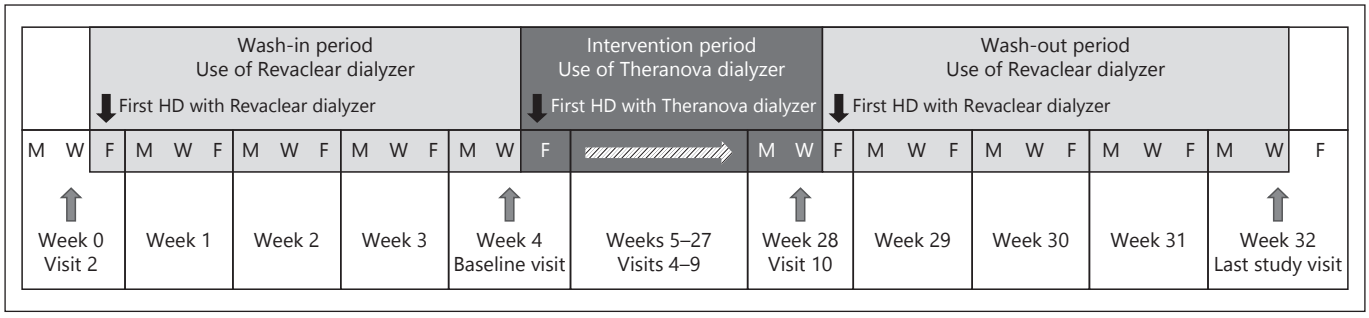


**Fig. 1.** REMOVAL-HD study schema. HD, hemodialysis.

receiving immunosuppression medication, low serum albumin (<30 g/L within 4 weeks of screening), and use of nutritional or dietary supplements to increase or reduce protein intake (including protein powder or weight loss supplements) that were unable to be ceased. Participants were also excluded if it was unlikely they would continue on maintenance HD at the study site throughout the study period for reasons including planned modality transfers such as scheduled kidney transplantation from an identified living donor, planned conversion to peritoneal dialysis or anticipated transfer to another dialysis unit, or an anticipated life expectancy of <12 months. Participants were also excluded if they required HDF treatment according to their treating physician, were pregnant or breast feeding, or were unable to complete study assessments.

*Study Procedures*

All visits occurred during participants' mid-week HD session (Fig. 1). Enrolled participants received a 4-week HD wash-in period (week 0–4) using a high-flux dialyzer (Revaclear R400; Baxter Healthcare, Sydney, Australia). This was followed by 24 weeks of the treatment phase HD (week 4–28) with the investigational device, the MCO dialyzer (Theranova 400; Baxter Healthcare, Sydney, Australia). Participants then received a 4-week HD wash-out period (week 28–32) using the Revaclear high-flux dialyzer again. Centers were advised to maintain the duration (3.0–5.5 h/session) and frequency of dialysis (3× week), target blood flow (>300 mL/min) and dialysate flow rate (500 mL/min) throughout the study period. All other aspects of care including anti-coagulation prescription were according to usual local practice. Duration of dialysis and any changes to blood flow and dialysate flow rates were collected at every study visit.

*Outcome Measures*

The principal focus of this study was participant safety. The primary outcome was change in centrally measured pre-dialysis serum albumin between baseline (week 4) and 6 months (week 28) during the treatment phase of HD with the MCO dialyzer. Other safety outcomes included change in serum albumin across all study visits during the treatment phase monitoring of any large reductions (>25%) in serum albumin level at every visit. In addition, SAEs were recorded regardless of whether they were related to the study intervention using standard criteria for clinical trials; in particular, details of deaths and number and duration of all-cause hospitalizations were collected.

Secondary outcomes included change in pre-dialysis serum level of middle molecules (lambda-free light chains [FLC], kappa-FLC and β2-microglobulin), change in inflammatory markers (high sensitivity C-reactive protein [hsCRP]) and coagulation profile (international normalized ratio/activated partial thromboplastin time [APTT]). Other secondary outcomes included quality of life (Edmonton Symptom Assessment System Revised) [9], restless leg syndrome symptoms (Restless Legs Syndrome Rating Scale) [10] erythropoietin resistance index in participants taking erythropoietin or darbepoetin (IU/kg/week/gHb; darbepoetin dose was converted to an erythropoietin-equivalent value using a dose conversion factor of 200:1) [11], functional status (6-min walk test) [12] and nutritional status (Malnutrition Inflammation Score) [13]. The various surveys were conducted by study coordinators.

Parameters that were measured in a central laboratory included serum albumin, lambda- and kappa-FLC, β2-microglobulin and hsCRP. Serum albumin, lambda-, and kappa-FLC were evaluated at every study visit and the remaining assessments were performed at baseline (week 4), midway through the study (week 16) and at completion of the intervention period (week 28). Samples were taken pre-dialysis on mid-week HD session and were stored at –80 °C until tested in a central laboratory.

*Statistical Analyses*

The study was powered to identify a change of 5% in serum albumin concentrations from a median baseline level of 35 g/L (SD of 5 g/L). A reduction >5% in serum albumin was associated with near doubling of mortality risk in HD patients [14]. To detect this change with 80% power at the 5% significance level, a sample size of 72 was needed. Allowing for a 15% loss to follow-up, a minimum of 85 participants was required to achieve the required sample size. The 95% CI for the mean difference in central serum albumin between 6 months and baseline was used to determine whether the change in albumin levels due to MCO HD fell within safe limits. Missing week 28 albumin data were replaced by the last observation under MCO dialyzer for the calculation of mean differences. Change in serum albumin levels across multiple time points and other continuous secondary outcomes were analyzed using linear mixed-effects regression models. Categorical secondary outcomes were analyzed using McNemar's test for comparisons between 6 months and baseline and generalized estimating equations for trends across the intervention period. All hypothesis tests were assessed at 5% level of significance. Statistical analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA).

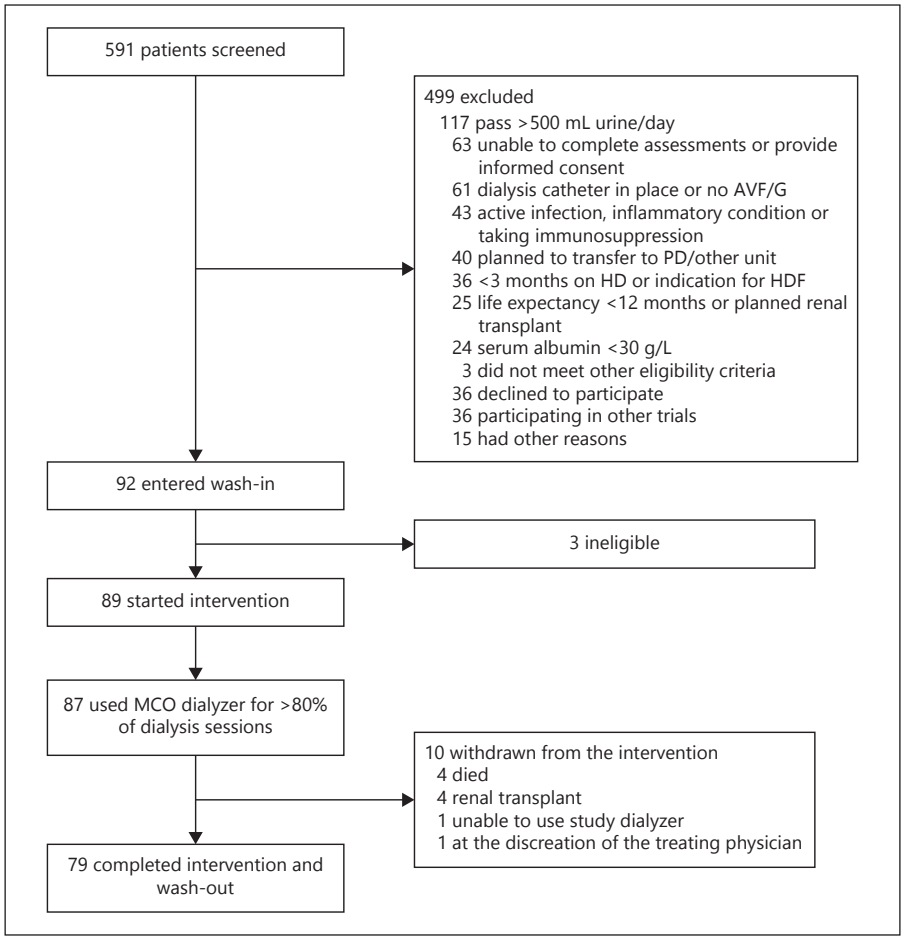


**Fig. 2.** Consort diagram for the REMOVAL-HD study. AVF, arteriovenous fistula; AVG, arteriovenous graft; HD, hemodialysis; HDF, hemodiafiltration; MCO, mid cut-off.

## Results

*Demographic Characteristics*

The study screened 591 participants of whom 92 were enrolled and entered wash-in; 89 started the MCO HD intervention and provided analyzable data and 87 were sufficiently compliant with the intervention (at least 80% use of MCO dialyzer) to be included in the main analysis of the primary outcome (Fig. 2). Baseline characteristics at study entry are shown in Table 1. Participants had a mean age of 66 ± 14 years, 62% were men, 45% were anuric and 51% were diabetic. The mean pre-dialysis serum albumin at entry was 35.8 ± 3.9 g/L. The mean pre-dialysis concentration values at baseline of β2-microglobulin, kappa- and lambda-FLC were 21.0 ± 5.5, 154.8 ± 56.7, and 206.9 ± 74.6 mg/L respectively.

There was no difference in duration of dialysis across the different treatment periods ($p = 0.1$). There were also no changes to blood flow and dialysate flow rates from baseline readings.

*Serum Albumin*

The average reduction in serum albumin from baseline to 6 months (week 28) was –0.7 g/L (95% CI –1.5 to 0.1; baseline serum albumin of 35.8 ± 3.9 g/L to 6 months serum albumin of 35.1 ± 4.0 g/L, $p = 0.1$) for the 87 treatment compliant participants and similarly was –0.7 g/L (95% CI –1.5 to 0.1, $p = 0.08$) for all 89 participants. There was no significant linear change in serum albumin across study visits (Fig. 3). A sustained, unexplained reduction in serum albumin of >25% for 2 consecutive visits was not observed in any participant.

Additional analysis was undertaken to evaluate the impact of hsCRP levels on the serum albumin. Participants were divided into 2 groups of high (hsCRP >4.3 mg/L) and low (hsCRP ≤4.3 mg/L) hsCRP based on median baseline hsCRP value of 4.3 mg/L. The mean serum albumin level during intervention period with MCO dialyzer was higher in the low hsCRP group compared to the high hsCRP group (low hsCRP group; mean serum albumin = 36.4 ± 3.3 g/L versus high hsCRP group; mean serum al-

**Table 1.** Participant characteristics prior to intervention with MCO dialyzer

| Characteristics ($n$ = 89) | |
|---|---|
| Age, years | 66.5±14.5 |
| Gender | |
| Female | 34 (38 |
| Male | 55 (62) |
| Ethnicity | |
| Caucasoid | 66 (74) |
| Aboriginal or Torres Strait Islander | 1 (1) |
| Maori | 8 (9) |
| Pacific Islander | 4 (4.5) |
| Asian | 6 (7) |
| Other | 4 (4.5) |
| Body mass index, kg/m$^2$ | 28.8±5.8 |
| Primary cause of renal disease | |
| Diabetic nephropathy | 33 (37) |
| Hypertension/vascular | 13 (15) |
| Glomerulonephritis | 10 (11) |
| Reflux nephropathy | 3 (3) |
| Polycystic kidney disease | 6 (7) |
| Other | 19 (21) |
| Unknown | 5 (6) |
| Transplant prior to dialysis | 6 (7) |
| Type of access | |
| AVF | 82 (92) |
| AVG | 7 (8) |
| Urine output | |
| Anuric | 40 (45) |
| Oliguric (<500 mL/day) | 49 (55) |
| Urine volume, mL/24 h | 200 (130–300) |
| Systolic blood pressure, mm Hg | 145.7±20.8 |
| Diastolic blood pressure, mm Hg | 71.6±12.9 |
| Diabetes mellitus | 45 (51) |
| Ischemic heart disease | 21 (24) |
| Smoking (former and current) | 46 (52) |
| ESAS-R score | 1.1 (0.5–2.0) |
| Serum albumin, g/L | 35.8±3.9 |
| Lambda-FLC, mg/L* | 206.9±74.6 |
| Kappa-FLC, mg/L** | 154.8±56.7 |
| β2-microglobulin, mg/L | 21.0±5.5 |
| hsCRP, mg/L | 7.7±8.7 |
| Hemoglobin, g/L | 113.0±12 |
| Transferrin, g/L | 1.95±0.4 |

Results are reported as $n$ (%) for categorical variables, mean ± SD, or median (IQR) as appropriate. Blood pressure measurements were taken pre-dialysis.

* A patient with extreme lambda value of 4,100 mg/L was excluded.

** A patient with extreme kappa value of 2,300 mg/L was excluded.

MCO, mid cut-off; AVF, arteriovenous fistula; AVG, arteriovenous graft; ESAS-R, Edmonton Symptom Assessment System Revised; FLC, free light chains; hsCRP, high sensitivity C-reactive protein.

bumin = 34.5 ± 3.9 g/L, $p$ = 0.001). However, there was no significant interaction between hsCRP groups and study visits ($p$ = 0.5).

*Secondary Outcomes*

Middle Molecules

A reduction in FLC was observed 2 weeks into MCO HD (lambda-FLC: Δ –9.1 mg/L, 95% CI –14.4 to –3.7, $p$ = 0.001; kappa-FLC: Δ –5.7 mg/L, 95% CI –9.8 to –1.6, $p$ = 0.007; Table 2), which plateaued and remained unchanged throughout the intervention period (Fig. 4a, b). However, levels of both FLC significantly increased following cessation of HD with the MCO dialyzer during the wash-out high-flux HD phase (lambda-FLC: Δ 7.9 mg/L, 95% CI 0.8 to 14.9, $p$ = 0.03; kappa-FLC: Δ 8.2 mg/L, 95% CI 1.3 to 15.1, $p$ = 0.02; Table 2). There was no significant change in β2-microglobulin for the duration of treatment with MCO dialyzer (Table 3).

Patient Reported Measures and Functional Assessment

Only 6% of patients fulfilled the criteria for restless legs syndrome at baseline; symptoms did not change throughout the study period. Similarly, symptom burden and quality of life assessed using Edmonton Symptom Assessment System Revised yielded a low median score of 1.1 (0.5–2.0) at baseline and no significant change following the use of the MCO dialyzer. Functional and nutritional status of the participants was also unchanged in this study (Table 3).

Other Measures

Measures of coagulation, erythropoietin resistance index and hsCRP did not change during the intervention period (Table 3).

Adverse Events

There were no reported SAEs related to the MCO dialyzer for the entire duration of the study. There were no participants who required albumin infusion during the study. All-cause mortality, all-cause hospitalization and infection-related hospitalization were stable throughout study period and, importantly, did not demonstrate a probable relationship with use of MCO dialyzers (Table 4).

## Discussion

The REMOVAL-HD trial primarily found regular use of the MCO dialyzer in chronic HD patients was safe and did not result in a significant fall in serum albumin. In

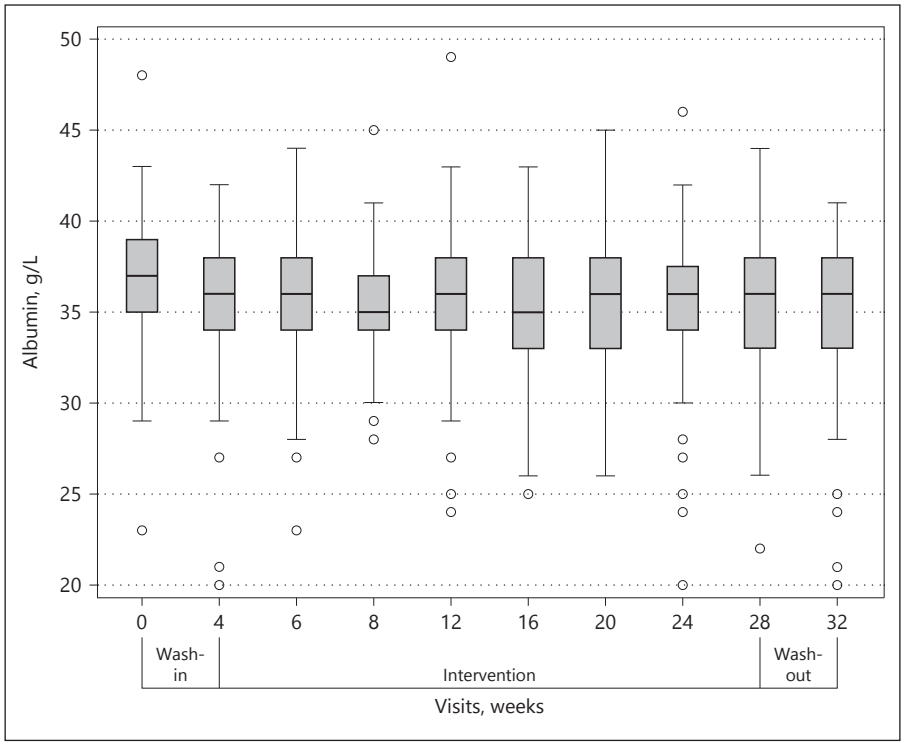


**Fig. 3.** Trend in centrally measured serum albumin throughout entire study period.

**Table 2.** Change in lambda- and kappa-FLC following initial exposure (week 4–6) and cessation of MCO dialyzer (week 28–32) respectively

| | Average change from week 4–6 (95% CI) | *p* value | Average change from week 28–32 (95% CI) | *p* value |
|---|---|---|---|---|
| Lambda-FLC, mg/L | –9.1 (–14.4 to –3.7) | 0.001 | 7.9 (0.8 to 14.9) | 0.03 |
| Kappa-FLC, mg/L | –5.7 (–9.8 to –1.6) | 0.007 | 8.2 (1.3 to 15.1) | 0.02 |

FLC, free light chains; MCO, mid cut-off.

addition, the study demonstrated a change in the pre-dialysis level of middle molecules compared to high-flux HD with a fall in the serum level of FLC being apparent by 2 weeks of the 24-week MCO HD period and a rebound in the concentrations of both kappa- and lambda-FLC evident after reverting back to standard high-flux HD. There were no immediate or medium-term effects observed with respect to symptom burden, functional status or nutrition.

The MCO dialyzer is a new generation of HD membrane larger pore sizes and a tighter distribution of the pores when compared to standard high-flux HD membranes [4]. This novel membrane, in theory, is hypothesized to improve clinical outcomes and symptom burden by providing a better clearance of uremic toxins, especially larger middle molecules. However, increasing pore sizes of dialysis membranes can be associated with a significant loss of albumin and resultant fall in serum albumin, as demonstrated with the HCO dialyzer. Hutchison et al. [15] found the use of the HCO dialyzer in the chronic HD setting resulted in 6 g of albumin loss per dialysis session. Therefore, any new treatment that can potentially result in a significant loss of albumin, such as with the MCO dialyzer, must be rigorously evaluated in immediate and long-term clinical practice.

A few small, short-term studies demonstrated the varying ranges of albumin loss that were generally tolerated following the use of the MCO dialyzer. Using an earlier prototype of the MCO dialyzer, Zickler et al. [16] found an almost a 2 g/L reduction in serum albumin con-

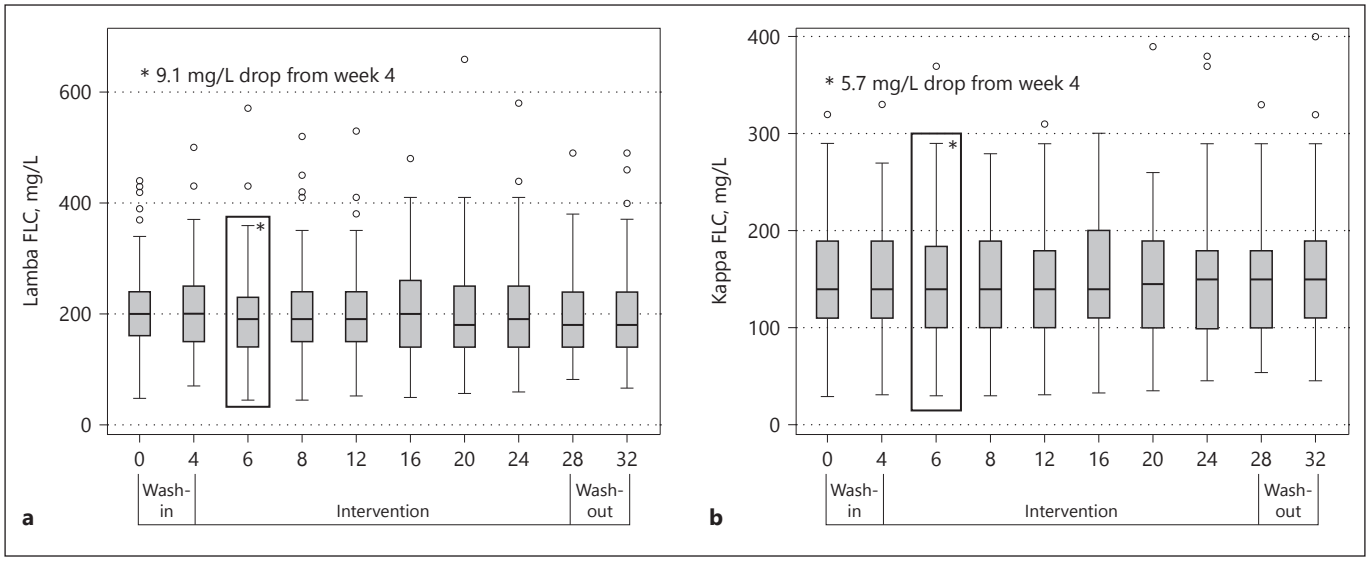


**Fig. 4.** Trend in lambda- (**a**) and kappa- (**b**) FLC throughout the entire study period. FLC, free light chains.

**Table 3.** Change in other laboratory measures, functional status, nutritional status and symptom burden following commencement of MCO dialyzer

| | Week 4 ($n$ = 89) | Week 16 ($n$ = 84) | Week 28 ($n$ = 79) | Change at week 16 (95% CI)* | Change at week 28 (95% CI)* |
|---|---|---|---|---|---|
| Lab measures | | | | | |
| INR | 1.3±0.7 | 1.3±0.7 | 1.3±0.6 | 0.02 (–0.08 to 0.12) | 0.04 (–0.05 to 0.12) |
| APTT, s | 30.6±5.7 | 31.8±9.5 | 31.5±8.6 | –0.92 (–2.76 to 0.93) | –0.41 (–1.98 to 1.17) |
| β2-microglobulin, mg/L | 20.9±5.5 | 21.3±6.4 | 20.2±5.0 | –0.34 (–1.38 to 0.7) | 0.73 (–0.17 to 1.64) |
| hsCRP, mg/L | 7.7±8.7 | 10.3±17.8 | 8.8±13.5 | –2.35 (–6.15 to 1.45) | –0.96 (–3.92 to 2.00) |
| Other secondary outcome measures | | | | | |
| MIS | 5.9±3.2 | 6.3±3.5 | 6.5±3.8 | 0.37 (–0.12 to 0.86) | 0.49 (–0.09 to 1.08) |
| ESAS-R | 1.1 (0.5–2.0) | 1.1 (0.4–2.2) | 1.2 (0.5–2.4) | 0.01 (–0.29 to 0.30) | 0.16 (–0.20 to 0.53) |
| ERI* | 0.8±0.6 | 0.9±0.6 | 0.9±0.6 | 0.07 (–0.02 to 0.15) | –0.05 (–0.09 to 0.2) |
| 6MWT, m# | 323.3±150.8 | 324.0±138 | 330.3±140.3 | 3.26 (–14.56 to 21.08) | 7.91 (–37.09 to 52.9) |

Results are reported as $n$ (%) for categorical variables, mean ± SD, or median (IQR) as appropriate.

* Number of patients for ERI at week 4 = 59, week 16 = 58, week 28 = 57; # number of patients for 6MWT at week 4 = 61, week 16 = 49 and week 28 = 42.

MCO, mid cut-off; INR, international normalized ratio; APTT, activated partial thromboplastin time; hsCRP, high sensitivity C-reactive protein; MIS, malnutrition inflammation score; ESAS-R, Edmonton Symptom Assessment System Revised; ERI, erythropoietin resistance index; 6MWT, 6-min walk test.

centration compared to no reduction in serum albumin with high-flux HD in a 4 weeks crossover study of 48 patients. Kirsch et al. [6] showed the median albumin loss with the newer MCO dialyzers were 2.9–3.2 g per dialysis session compared to an average of 0.2–0.4 g losses with high-flux HD and HDF treatments, respectively, following 4 dialysis sessions in 39 patients. In contrast, Garcia-Prieto et al. [7] instead found albumin loss was significantly lower with the MCO dialyzer when compared to online-HDF (0.3 vs. 3.1 g per dialysis session respectively) in a 3-week cross-over study of 18 patients. On the contrary, a tolerable loss of serum albumin with MCO dialyzer may enhance the removal of protein bound uremic toxins such as indoxyl-sulphate and p-cresol sulphate [17]. However, this potential benefit needs to be carefully evaluated in clinical studies.

**Table 4.** SAEs* by category during wash-in, intervention and wash-out periods

| Category | Events during wash-in, % | Events during intervention period, % | | | Events during wash-out, % |
|---|---|---|---|---|---|
| | week 0–4 | week 6 | week 12 | week 28 | week 28–32 |
| Infection | 3 | 1 | 1 | 0 | 3 |
| Renal | 0 | 1 | 2 | 3 | 4 |
| Cardiovascular | 1 | 1 | 1 | 1 | 0 |
| Hematology | 0 | 0 | 0 | 1 | 0 |
| Neurological | 0 | 0 | 0 | 0 | 0 |
| Psychological | 0 | 0 | 0 | 0 | 0 |
| Gastrointestinal | 1 | 1 | 0 | 1 | 1 |
| Cancer/neoplasm | 0 | 0 | 0 | 2 | 0 |
| Others | 1 | 1 | 3 | 1 | 4 |

* No SAEs, deaths or hospitalizations were considered probably related to the MCO dialyzer.
SAE, serious adverse event; MCO, mid cut-off.

The current REMOVAL-HD study provides a detailed evaluation of the impact of the MCO dialyzer on serum albumin concentration in a clinical setting with chronic HD patients over a period of 6 months. The study showed serum albumin levels were stable over 6 months and the overall albumin concentration decline was minimal at 0.7 g/L. In addition, an immediate decline in serum albumin following commencement of the MCO dialyzer was not seen and the treatment was well tolerated without any reported adverse event related to this membrane. These findings provide good evidence that albumin loss will not be a limitation to HD with the MCO dialyzer.

The present REMOVAL-HD study also assessed the change in pre-dialysis serum levels of 3 middle molecules of varying sizes, β2-microglobulin (11.8 kDa), kappa-FLC (22.5 kDa) and lambda-FLC (45 kDa). Standard high-flux HD and HDF therapies provide excellent clearances of β2-microglobulin. A recent meta-analysis of 69 studies found the average clearance of this middle molecule was 48.8 and 87.1 mL/min for high-flux HD and convective therapies (including HDF), respectively [18]. The reduction rate of β2-microglobulin was related to membrane composition, blood flow rates and substitution volume [18]. Thus, it is not surprising that the present study and other published studies [16, 19] did not find a change in the levels of β2-microglobulin following conversion to the MCO HD from standard dialysis treatments.

Short-term studies of 2–12 weeks duration have shown greater removal of larger middle molecules (>22.5 kDa) following the use of the MCO dialyzer. Zickler et al. [16] reported that the MCO dialyzer effectively reduced inflammatory cytokines, including tumor necrosis factor-α and interleukin-6 levels, and kappa- and lambda-FLC, compared to high-flux HD following 12 weeks of treatment. Kirsch et al. [6] found the reduction ratio of several middle molecules, including FLC, was superior to both high-flux HD and HDF following 4 dialysis sessions. However, other short-term studies found the removal of middle molecules including prolactin, myoglobin and α1-glycoprotein using MCO dialyzer was superior to high-flux HD but equivalent to HDF treatment [7, 20].

Of the 2 FLC isotypes, the higher molecular weight of lambda-FLC (45 kDa) provides the greatest discriminatory value for comparing the increased removal of middle molecules offered by MCO dialyzer compared to conventional high-flux membranes. In the present study, the reduction of the lambda- and kappa-FLC was seen following 2 weeks of treatment with the MCO dialyzer but did not decline any further. Whether this is related to redistribution of the FLC into the intravascular compartment resulting in a new measured steady state in these patients requires further evaluation. However, there was a significant rebound in the concentration of both FLC to the baseline levels following cessation of MCO dialyzer, supporting the hypothesis that this dialyzer can result in sustained reduction in large middle molecules. The ability to provide sustained removal large middle molecules such lambda FLC suggests that MCO HD is a promising therapy to enhance the removal of other large middle molecules such as soluble tumor necrosis factor receptor-1, fibroblast growth factor-23, advanced glycosylated end products that are not cleared by current conventional HD therapies but are strongly implicated in chronic inflam-

mation and accelerated cardiovascular disease in patients with ESKD [4]. However, removal of these middle molecules is merely indicative of surrogate markers of potential clinical benefits of MCO dialyzer in ESKD patients and needs to be robustly evaluated in randomized controlled trials with patient-centered outcomes. In addition, long-term efficacy of MCO HD in comparison to HDF treatment will also need to be examined in future clinical trials.

The current study did not find any effect on functional, nutritional or quality of life outcomes with the use of the MCO dialyzer over a 6-month period. This study was not sufficiently powered to detect changes in symptom burden. In addition, the baseline results indicate that these participants had a relative low symptom burden. The average modified ESAS symptom score for unselected HD patients was previously reported as 7.5 ± 2.5 [21], almost 7 times higher than the baseline score in the present study. Similarly, restless legs syndrome was only 6% in this study cohort compared to the frequency of 13–65% reported in other study populations [22]. In addition, recruitment of "less inflamed" cohort and the relatively short duration of follow-up may also have contributed to the absence of effect on clinical outcomes. These factors should be considered for the design of future clinical studies. Larger randomised controlled trials are required to evaluate if MCO dialyzer has an important impact on patient-reported outcome measures.

The strengths of the study include adequate power to detect a clinically important change in serum albumin and the study designed to represent routine clinical practice, limiting study burden on participants and clinical staff. However, the study has limitations, the major one being the single-arm design. In addition, post-dialysis serum and dialysate concentrations of albumin and middle molecules were not performed and may have provided more in-depth evidence especially regarding the efficacy of this membrane. Participant-level information on the type of dialysate including citrate-based dialysis buffer that may have an impact on middle molecules removal was not collected during the study period. By design, this study excluded major factors that may impact serum albumin measurements and confound the primary outcome in order to assess the independent effect of MCO dialyser on serum albumin. As a result, this study recruited participants who were less likely to be malnourished or inflamed and had a low symptom burden, thus limiting generalizability to the broad dialysis population. In addition, the subgroup analyses for inflamed patients are limited by power and the low hsCRP.

## Conclusion

REMOVAL-HD demonstrated that regular use of MCO dialyzer for 6 months in chronic HD patients was safe and did not result in a significant fall in serum albumin. This study's results support the hypothesis that albumin loss will not be a limitation of the future application of the MCO dialyzer in chronic HD. Future randomized controlled trials are required to assess the efficacy of the MCO dialyzer for clinical and long-term outcomes.

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## Statement of Ethics

Ethical approval was obtained from Institutional Ethics Committees for each participating site. The study was performed in accordance with the 2013 Fortaleza, Brazil 7th Revision of the Declaration of Helsinki, the National Health and Medical Research Council Statement on Ethical Conduct of Human Research (2015), Joint National Health and Medical Research Council/AVCC Statement and Guidelines on Research Practice (1997), applicable ICH guidelines, ISO 14155:2011 and Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95) annotated with Therapeutic Goods Administration comments. Informed signed consent was obtained from all participants. This study is registered with Australian and New Zealand Clinical Trials Registry (ANZCTRN 12616000804482).


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## Author Contributions

C.A.H. is the principal investigator and was actively involved in the conception and design of the study. R.K., C.A.H., C.M.H., M.J.J., D.W.J., and E.M.P. were involved in study design and conduct. P.-A.P.-B. is the trial coordinator and L.A.V. is the data manager. E.M.P. and DD are the trial statisticians. R.K. and C.A.H. drafted the manuscript. C.A.H., R.K., C.M.H., M.J.J., M.A.R., Y.J.C., M.G.W., A.H., P.E.M., C.L.N., S.S., and N.D.T. were responsible for recruitment, data collection and management. All authors also reviewed and edited the manuscript and approved the final version. The protocol was reviewed and critiqued by AKTN Scientific Committee.

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