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The Double-Icodextrin Dose Randomized Controlled Trial of a Double Icodextrin Dose for Older Patients on Incremental Continuous Ambulatory Peritoneal Dialysis

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Introduction: Icodextrin enhances ultrafiltration (UF) in patients on peritoneal dialysis (PD) but is restricted to 1 bag/d, according to regulatory authorities. The Double-Icodextrin Dose (DIDo) study is a prospective randomized trial investigating the superiority and safety of using 2 bags/d versus 1 bag/d of icodextrin to extend incremental (3 bags/d) continuous ambulatory PD (CAPD) duration in older incident patients.

Methods: After a 2-month "run-in" period, the patients were randomized to 2 icodextrin ("double dose") + 1 glucose or 1 icodextrin ("single dose") + 2 glucose dialysates daily. The primary end point was a composite of excessive use of hypertonic dialysates, transfer to another dialysis modality (automated PD [APD], nonincremental CAPD, or hemodialysis) or death at month 9. Secondary end points included mortality, daily UF, technique survival, rates of peritonitis and hospitalizations, and safety at month 18.

Results: Forty-one patients were randomized to double dose and 42 to single-dose icodextrin. Baseline characteristics were well-balanced between groups. At month 9, the proportion of patients who discontinued 3 exchanges/d was similar between those receiving the double and the single icodextrin dose (16 [39%] vs. 21 [50%]; HR: 0.69; 95% confidence interval: 0.35–1.33). The results were similar at month 18. Patients in the double dose icodextrin had higher net UF and less hypertonic dialysates use. Rates of peritonitis, hospitalizations, residual urine output decline and serious adverse events (SAEs) were similar between both groups.

Conclusion: In older patients on incremental CAPD, the double icodextrin dose did not reduce the primary outcome incidence compared with the single icodextrin dose. Significantly enhanced UF was observed in the double icodextrin dose group and no safety issue was identified.

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The incidence of kidney failure is steadily increasing worldwide, particularly among older people, which represents a major health care burden and necessitates tailored therapeutic strategies.[1,2]

CAPD is a widely used dialysis modality for treating older patients with kidney failure.[3-5] Incremental CAPD is particularly relevant for patients starting this therapy. It is a personalized approach that involves stepwise and individualized adjustments in the dialysis prescription (frequency and/or dose) over time, to accommodate individual patient's needs, health status, lifestyle, and tolerance while minimizing potential complications and burden of the technique. In addition, it might preserve residual kidney function for longer, a key factor of survival on dialysis.[6-8]

In the context of CAPD, 3 PD exchanges/d may reduce the treatment burden but increase the risk of low UF during the longer dwells. Because older patients may be more susceptible to fluid overload, tailored strategies for fluid management are required.[5,7] APD is one of those strategies but is not always feasible in elderly patients with cognitive dysfunction.

Icodextrin, a high molecular-weight glucose polymer, induces colloid osmosis, resulting in sustained UF and enhanced removal of excess fluid during longer dwell times,[9-11] thereby improving patients' outcome.[12] The addition of icodextrin to glucose-based CAPD regimens not only addresses fluid overload concerns but also enhances the efficiency of dialysis[13] and reduces the glucose load,[13] the primary cause of peritoneal membrane degradation.[14-16] Icodextrin has been shown to mitigate the deleterious effect of a common genetic variant in *AQP1* upon exposure to conventional glucose-based solutions.[17] Based on manufacturer and health authorities recommendations, a once-daily administration of icodextrin is usually prescribed. Some benefits of an off-label use of 2 icodextrin bags daily in terms of increased UF have been suggested.[18-20]

The DIDo study is a prospective international open-label randomized controlled trial aimed to investigate the efficiency and safety of using 2 versus 1 icodextrin bag/d, in older incident patients on incremental CAPD.

METHODS

Trial Design

The DIDo study (NCT01944852) is an open-label, randomized, multicenter study with 2 parallel groups. The study investigated the potential superiority and safety of using 2, as compared with 1, icodextrin bags/d, in a cohort of older (aged $>$ 60 yrs) incident patients on CAPD using incremental PD (3 bags/d), with the aim of prolonging the period of time for which incremental PD can be used. Another goal of the study was to question whether a paradigm shift in the CAPD prescription, allowing less glucose exposure from PD onset onward by using more icodextrin, would be a safe and efficient approach.

Patients were treated at 22 centers in 3 European countries, where clinicians have experience with icodextrin use. The study was divided into 2 periods, namely a "run-in period" of 2 months to test the PD technique efficacy, the tolerance of icodextrin and to achieve euvolemia, and a "treatment period" of 18 months (Supplementary Figure S1). Patients were randomized only after successfully completing the run-in phase.

The study was sponsored by Cliniques universitaires Saint-Luc, Brussels, Belgium. Baxter Healthcare, the manufacturer of icodextrin, provided a research Extramural Grant to support the study but had no role in the trial design or in the collection, analysis or interpretation of the data, or writing of the report. Additional grants were received from the French Society of Nephrology, the Saint-Luc Foundation, Brussels, Belgium and the Ligue des Insuffisants Rénaux, Brussels, Belgium. The study adhered to the principles of the Declaration of Helsinki and followed the regulatory procedures of the participating countries. The trial was monitored by a contract research organization, Keyrus Biopharma, Paris, France, according to standard operating procedures.

The design and initiation of the trial was led by a steering committee composed of academic and nonacademic investigators. This steering committee held the final responsibility for ensuring the accuracy, completeness, and interpretation of the data; the preparation of the manuscript; and the decision to submit it for publication.

Patients

Adult patients aged $\geq$ 60 years were eligible for inclusion if they had received a diagnosis of kidney failure requiring dialysis (estimated glomerular filtration rate $<$ 20 ml/min per 1.73 m^2 as calculated with the Modification of Diet in Renal Disease formula), if they could opt for incremental CAPD as the mode of kidney replacement therapy, and in whom at least 1.5 L dialysate could be safely instilled in their peritoneal cavity. Written informed consent was provided by the patients and data collection was performed in compliance with the requirements of the General Data Protection Regulation Directive and local Ethics Committees.

The exclusion criteria were a contraindication for CAPD according to local practice, a life expectancy $<$ 6 months, the need for an amino-acid dialysate prescription; treatment with any investigational product within 30 days, or a history of drug or alcohol abuse within 3 months prior to the signature of the consent form. Additional exclusion criteria during the "run-in period" were allergy to icodextrin (cloudy dialysate

with a predominance of mononuclear cells at cytology examination or skin rash), the occurrence of severe symptomatic hypotension and/or excessive UF in the investigator's opinion, and the impossibility to achieve an adequate PD regimen within the run-in period (catheter dysfunction, peritoneal leaks, inadequate compliance, and psychosocial reasons).

Peritoneal Parameters

Peritoneal transport was assessed using a standardized 3.86% glucose-based peritoneal equilibration test (PET).[21] Peritoneal solute transfer rate was defined as the ratio of the creatinine level in dialysate to the creatinine level in plasma at 4 hours, and by the dissipation ratio of glucose from the peritoneal cavity at 4 hours as compared with the glucose concentration at the onset of the test. Sodium sieving was defined as the ratio of the sodium level in dialysate at the beginning of the dwell and the level at 1 hour in plasma, with a correction for sodium diffusion. Daily net UF; urine output; and CAPD adequacy, that is, total creatinine clearance and total Kt/V urea (in which "K" represents the urea clearance, "t" represents the treatment time, and "V" represents the urea distribution volume) were also recorded. All blood samples were collected 120 minutes after start of PET.

Randomization, Study Products, Procedures, and Follow-Up With Patients

Patients who met the inclusion criteria and did not present any of the exclusion criteria at the end of the "run-in period" were randomly assigned in a 1:1 ratio to receive either 3 CAPD exchanges daily using a double icodextrin dose (2 icodextrin + 1 glucose-based bags/d) or using a single icodextrin dose (1 icodextrin + 2 glucose-based bags/d). The randomization list was prepared at Keyrus Biopharma by centralized block randomization stratified by center.

Study products included icodextrin and glucose-based dialysates. Icodextrin 7.5% PD solution, a colloid osmotic agent, is a starch-derived, water-soluble glucose polymer licensed as "Extraneal" and produced by Baxter International, Inc. Extraneal is currently indicated for a single daily exchange for the long dwell (8–16 hours) during CAPD or APD for the management of kidney failure. It is also indicated to improve (compared with 3.86% glucose) long-dwell UF and clearance of creatinine and urea nitrogen in patients with high-average or greater transport characteristics, as defined using the PET. Regarding glucose-based dialysates, patients and treating nephrologists were free to use different concentrations of the glucose dialysate as required (1.36%, 2.27%, and 3.86%); however, to reduce variability, they should use either Dianeal PD4, Physioneal 35, or Physioneal 40 glucose solutions (with a bicarbonate/lactate buffer), all of which are produced by Baxter International, Inc. The glucose concentrations of all glucose-administered bags were recorded by patients in a daily diary. The dwell time for icodextrin was recommended to be between 8 and 16 hours and therefore used for the 'long dwell' as follows (Supplementary Figure S2):

- Patients in group "double icodextrin dose" were prescribed 2 icodextrin dwells of 10 hours + 1 glucose dwell of 4 hours,
- Patients in group "single icodextrin dose" were prescribed 1 icodextrin dwell of 16 hours + 2 glucose dwells of 4 hours.

The length of the icodextrin dwell regimen could be adapted at the discretion of the center. All national regulatory authorities from the 3 participating countries allowed the off-label use of 2 icodextrin bags/d for the duration of the study provided that a specific label regarding the study was put on the bags. The delivery of all dialysates to the patient was ensured by the patients' association, pharmacy, or company, similar to the usual delivery process for all patients on PD within the investigator centers.

All participating centers had broad experience with CAPD. Thus, delivery of good quality CAPD could be expected, and all data could be collected as part of routine clinical practice.

Outcomes

The primary hypothesis of the study was that the treatment with double icodextrin dose is superior to the reference standard of care treatment with single icodextrin dose in terms of the proportion of patients remaining on a 3 exchanges/d regimen at month 9 while avoiding excessive use of hypertonic dialysate solutions. The primary end point was therefore defined as a composite of excessive use of hypertonic glucose dialysate (> 15%, 3.86% or > 30% 2.27 % over a 4-week period), transfer of the patient to another dialysis modality (hemodialysis for > 1 month, APD, CAPD with > 3 exchanges/d) for any reason, or death of the patient. Secondary end points were overall mortality, PD technique survival, peritonitis occurrence, hospitalizations for any cause, UF capacity, and daily diuresis during PD therapy at month 18.

Safety was assessed in both arms of the study by the following events: SAEs, serum sodium concentration, and symptoms relevant to a low serum sodium concentration, hypotension (attributed to an excessive UF), and incidence of skin rash and/or sterile peritonitis with an excess of mononuclear cells, all potentially related to icodextrin prescription.

Statistical Analysis

Sample Size Considerations

This was a superiority trial that assumed that the rate of the primary outcome would be 30% in the double icodextrin dose regimen and 60% in the single icodextrin dose regimen with a statistical power of 80% and a type I error $\alpha = 5\%$ (2-sided) which led to a sample size estimation of 43 valid cases per treatment group. Allowing for a 10% rate of nonevaluable patients, the total number of patients to be randomized was estimated to be 96 patients (48 patients per group). Allowing for a 40% rate failure during the run-in period, the total number of patients to be included was evaluated at 160.

General Statistical Considerations

The statistical package SAS version 9.1 (SAS, Cary, NC) was used to produce the statistical analyses, summary tables and figures. In general terms, the results were displayed in the overall population and by intervention group. Quantitative variables were described by the number of observed values, mean, SD, median, lower quartile, upper quartile, minimum and maximum and qualitative variables by the absolute numbers and the percentages.

Comparison between the 2 arms was based on the intention to treat principle. A chi-square test was used (or a Fisher exact test if the conditions for a chi-square test were not satisfied) for qualitative data whereas a Student or Wilcoxon test (if the distribution of observations did not follow a Gaussian distribution) was used for quantitative variables.

Kaplan Meier survival curves were drawn to represent the occurrence of the primary outcome in the 2 groups, a log rank test was performed to compare the survival distribution.

Interactions between the treatment group and the patients' age, sex, diabetes status, cardiovascular disease, body mass index, daily urine output, sodium serving at 1 hour of the PET, and daily fluid removal for the outcome variables were tested using a Cox model.

Mixed models with a random intercept by subject were used to assess the changes over time of the residual kidney function and the sodium level between the 2 study groups and the study group $\times$ time interaction effects.

The tests were 2-tailed and the type I error α was considered at 5% (2-sided) for all the tests and the confidence intervals presented.

Safety Analysis

The safety analysis population included all patients who received at least 1 dose of dialysate. All safety variables were summarized and compared between groups at each time point. SAEs, including cardiovascular and infectious events, and their characteristics (intensity, outcome, relation to treatment) were described for the safety population.

Interim Analysis

An interim statistical analysis of the safety variables was performed by Keyrus Biopharma when 50 randomized patients had reached visit 5 (i.e., month 9). Given the absence of any detected issues, the study was continued.

RESULTS

Patients

From July 2013 to September 2018, a total of 83 patients underwent randomization, with 41 patients assigned to receive double and 42 single icodextrin dose/d, respectively (Figure 1). The target number of patients was not reached because of longer-than-expected recruitment times and financial constraints, which led to an early termination of the recruitment period.

The characteristics of the patients, including demographic features, comorbidities, usual laboratory and CAPD-related values, and medications were well-balanced at baseline (Table 1). The median follow-up was 363 (interquartile range: 99–541) days.

Primary End Point

At 9 months from study start, the proportion of patients for which the prescription of a double icodextrin and a single icodextrin dose was stopped did not significantly differ between the 2 groups (16 [39%] vs. 21 [50%] respectively, hazard ratio: 0.69 ; 95% confidence interval: 0.35–1.33]) (Table 2, Figure 2). Of the patients, 61% and 50% were still on the 3-bags/d regimen at month 9 in the double and single icodextrin dose groups, respectively (non significant [NS]) (Table 2).

There was no difference between the 2 arms regarding each component of the primary end point: excessive use of hypertonic dialysate, death, and technical failure (Table 2, Supplementary Figures S3–S5, and Supplementary Table S1). There was a nonsignificant trend for an excessive use of hypertonic dialysates as a cause of study withdrawal in the single icodextrin dose group ($P = 0.07$, Supplementary Figure S3).

There was no significant interaction between the treatment group and age, the presence of diabetes or the presence of cardiovascular disease, body mass index, sodium sieving at 1 hour of the PET, and daily urine output (Figure 3).

Secondary End Points

At 18 months, the proportion of patients for which the prescription of a double icodextrin and a single icodextrin dose was stopped did not differ significantly

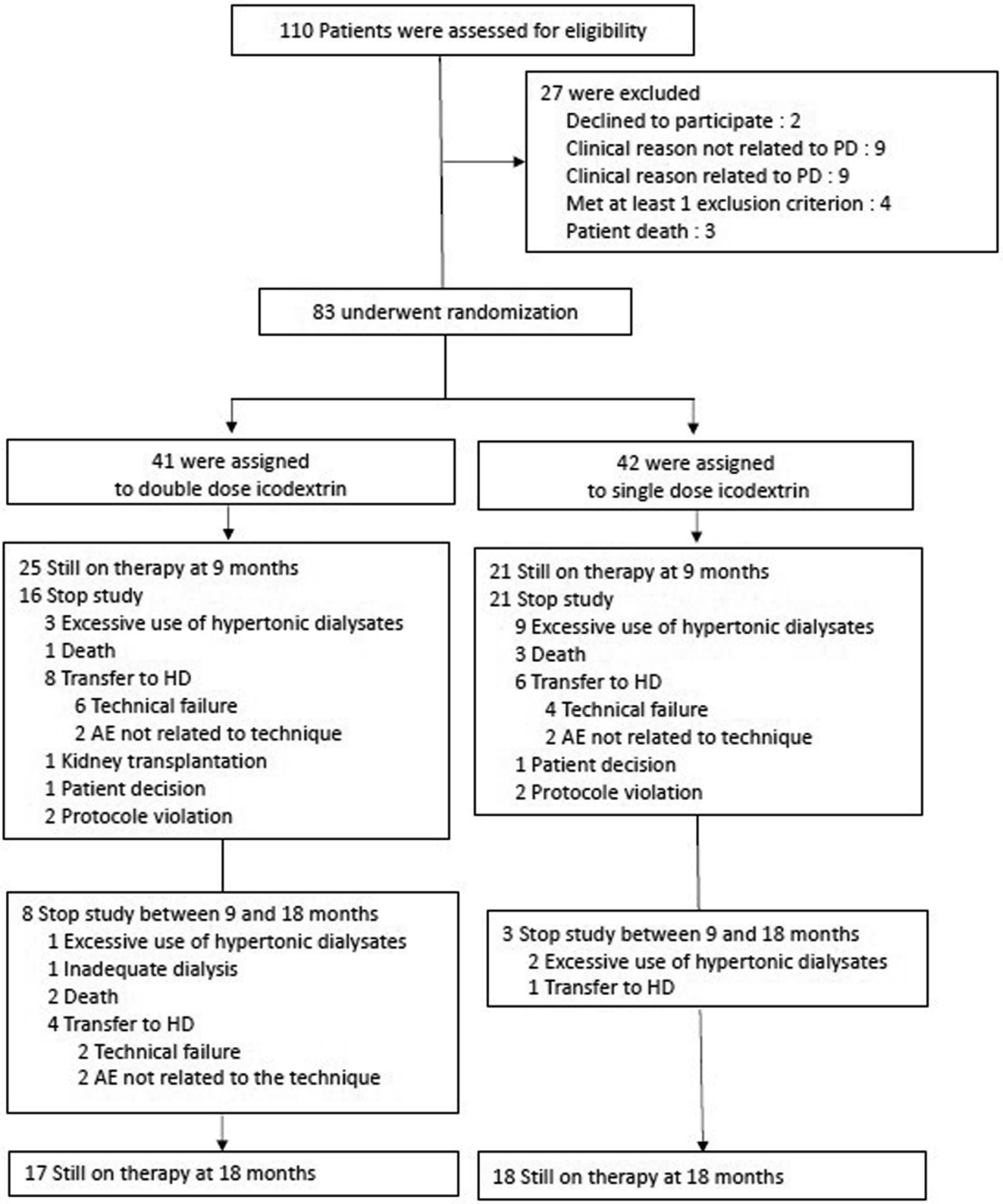


Figure 1. Patient enrollment. From July 2013 through September 2018, a total of 83 patients were randomized to receive either 2 or 1 icodextrin bag(s) daily. The median follow-up was 31 months (interquartile range: 17–43).

between groups (24 [59%] vs. 24 [57%], respectively; hazard ratio: 0.92, 95% confidence interval: 0.52–1.63) (Table 2, Supplementary Table S1, and Supplementary Figures S6–S9). Of the patients, 41% and 43% remained on the 3-bags regimen/d at month 18 in the double and single icodextrin dose groups, respectively (NS). There was a nonsignificant trend for an excessive use of hypertonic dialysates as a cause of study

Table 1. Characteristics of the patients at baseline[a]

Characteristics	Double dose icodextrin ($n = 41$)	Single dose icodextrin ($n = 42$)
Age, yr	76.1 ± 7.9	75.2 ± 8.0
Female sex, *n* (%)	7 (17)	13 (31)
Weight, kg	78.3 ± 12.0	77.0 ± 15.7
Body mass index, kg/m^2	27.6 ± 3.9	27.6 ± 4.7
Cardiovascular disease, *n* (%)	28 (68)	23 (55)
Diabetes mellitus, *n* (%)	20 (48.8)	18 (42.8)
Blood pressure, mm Hg		
Systolic	134.2 ± 19.7	132.2 ± 20.3
Diastolic	74.8 ± 12.5	75.5 ± 10.4
Heart rate, beats/min	74.5 ± 13.2	72.8 ± 11.3
Laboratory values		
Hemoglobin, g/dl	11.3 ± 1.5	11.4 ± 1.1
Serum creatinine, mg/dl	5.4 ± 1.5	5.1 ± 1.7
Serum urea, mg/dl	123.8 ± 38.0	117.5 ± 38.6
eGFR (ml/min per 1.73 m^2)[b]	13.7 ± 4.9	13.7 ± 5.1
Plasma sodium (mmol/l)	135.6 ± 4.5	135.9 ± 4.1
Serum albumin (g/l)	33.7 ± 5.1	34.6 ± 4.7
Median C-reactive protein (IQR), mg/l	9 (1–27)	14 (1–253)
Peritoneal dialysis parameters		
Average volume per exchange (ml)	1878 ± 296	1816 ± (299)
Peritoneal equilibration test		
D/P creatinine	0.80 ± 0.1	0.78 ± 0.1
D/P sodium	0.92 ± 0.1	0.90 ± 0.2
D/D0 glucose	0.22 ± 0.1	0.23 ± 0.1
Ultrafiltration (ml/d)	470.7 ± 532.5	477.9 ± 489
Residual kidney function		
Urine volume (ml/d)	1289 ± 622	1187 ± 508
Total creatinine clearance (ml/min)	8.4 ± 3.9	10.1 ± 3.5
Total Kt/V urea	2.0 ± 0.8	2.1 ± 0.7
Medications at baseline		
Patients with ≥1 antihypertensive agents, *n* (%)	33 (80)	36 (86)
Nb of antihypertensive agents, mean (SEM)	2.3 (1.2)	2.1 (1.2)
ACE inhibitors or ARBs, *n* (%)	24 (59%)	26 (62%)
Beta blockers	24 (58%)	24 (57%)
Calcium-channel blockers	21 (51%)	20 (47%)
Patients with loop diuretics, *n* (%)	36 (88%)	42 (100%)
Furosemide		
n (%)	26 (63%)	31 (74%)
Dose, average (mg/d)	399.1 (334.9)	285.2 (273.2)
Bumetanide		
n (%)	10 (24%)	11 (26%)
Dose, average (mg/d)	4.6 (1.1)	6.0 (3.0)
Statins	31 (76%)	23 (55%)
Steroids, *n* (%)	4 (10%)	3 (7%)
Aspirin	21 (51%)	24 (57%)
Vitamin D and analogs	33 (80%)	31 (74%)
Proton pump inhibitors	26 (63%)	24 (57%)

ACE, angiotensin-converting enzyme; ARB, angiotensin 2 receptor blocker; D/D0 glucose, dissipation ratio of the glucose from the peritoneal cavity at 4 hours as compared with the glucose concentration at the onset of the test; D/P creatinine, ratio of the creatinine level in dialysate to the creatinine level in plasma at 4 hours; D/P sodium, ratio of the sodium level in dialysate at the beginning of the dwell and the level at 1 hour in plasma; eGFR, estimated glomerular filtration rate; IQR, interquartile range; MDRD, Modification of Diet in Renal Disease.
[a]Plus-minus values are means ± SD. Body-mass index is the weight in kilograms divided by the square of the height in meters.
[b]As calculated with the MDRD formula.
To convert the values for creatinine to micromoles per liter, multiply by 88.4.

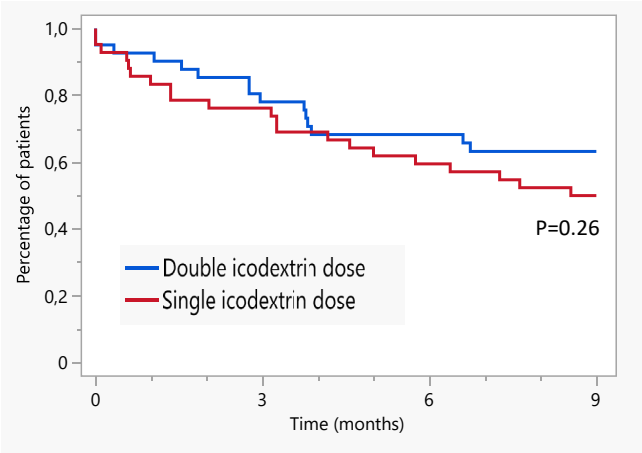
Table 2. Primary and secondary end points, incidence of peritonitis and hospitalization

End points	Double dose icodextrin ($n = 41$)	Single dose icodextrin ($n = 42$)
Primary outcome - no. (%)[a]	16 (39)	21 (50)
Excessive use of hypertonic bags	3	9
Inadequate dialysis	0	0
Death	1	3
Transfer to APD	0	0
Transfer to HD		
Technical failure	6	4
AE not related to the technique	2	2
Kidney transplantation	1	0
Still on therapy	25 (61)	21 (50)
Secondary outcome, *n* (%)[a]	24 (59)	24 (57)
Excessive use of hypertonic bags	4	11
Inadequate dialysis	1	0
Death	3	3
Transfer to APD	0	0
Transfer to HD[b]		
Technical failure	8	5
AE not related to the technique	4	2
Kidney transplantation	1	0
Still on therapy	17 (41)	18 (43)
Peritonitis, *n* (%)		
No. of patients with ≥ 1 peritonitis	5 (12)	10 (24)
No of peritonitis	7	15
Incidence rate[c]	56.50	33.22
Hospitalization, *n*		
No./patient[d]	1.41 (1.0)	1.48 (1.0)
No. of patients with > 1 hospitalization	28 (68)	27 (64)
Length of hospitalization (d)[d]	9.71 (6.0)	16.30 (7.0)
Length of hospitalization by patient[e] (d)[d]	21.36 (13.0)	36.81 (10.0)
Incidence rate[f]	7.96	7.33

AE, adverse event; APD, automated peritoneal dialysis; HD, hemodialysis.
[a]Other causes included consent withdrawal (1 patient in each group) and protocol violation (2 patients in each group).
[b]Number of patients.
[c]Expressed as the number of episode of peritonitis per patient-month.
[d]Mean (SEM).
[e]Among patients with at least 1 hospitalization.
[f]Expressed as the number of hospitalization per patient-month.

withdrawal at month 18 in the single icodextrin dose group ($P = 0.06$, Supplementary Figure S7). No patient was transferred to APD during the 18-month follow-up, whereas 1 patient from the double icodextrin dose group had to be switched to a 4 exchanges/d regimen between 9 and 18 months of follow-up because of inadequate dialysis.

Although the 2 groups had similar daily net UF at the onset of test (470.71 [532.45] vs. 477.91 [489.35] ml, NS), patients in the double icodextrin dose group showed higher daily net UF at various time points than those in the single icodextrin dose group (1000.4 [415.29] vs. 590.25 [587.15] [$P < 0.01$], 989.36 [503.95]



No. at risk				
Double icodextrin dose	41	32	27	25
Single icodextrin dose	42	32	25	21

Figure 2. Primary end point. Figure shows Kaplan-Meier curves for cumulative incidence of the primary outcome occurrence (excessive use of hypertonic glucose dialysate, transfer of the patient to another dialysis method for any reason, or death of the patient), as calculated in patients randomized to either 2 or 1 icodextrin bag/d.

vs. 699 [573.92] [NS], and 946.18 [515.24] vs. 578.81 [609.22] ml [NS] at 6, 9, and 18 months after study onset, respectively) (Figure 4). Urine output evolution throughout the study was similar in both groups and remained > 1 L at 9 and 18 months (Supplementary Table S2).

Peritonitis incidence and hospitalization rates were similar between the 2 groups (Table 2). At the onset of test, the mean serum sodium concentrations were not different between the 2 groups, with close means and SDs (135.88 [4.06] vs. 135.63 [4.47] mmol/l]). Patients in the double icodextrin dose group subsequently tended to have slightly lower serum sodium concentrations (particularly at month 9) than those in the single icodextrin dose group (Figure 5).

In terms of safety, 53 SAEs occurred in 31 patients in the double icodextrin dose and 52 in 30 patients in the single icodextrin dose arm. In 3 patients in each arm, SAEs led to patient death, whereas PD-technique–related SAEs resulted in technique withdrawal in 8 and 4 patients in the double-icodextrin and single-icodextrin dose groups, respectively (Table 3). None

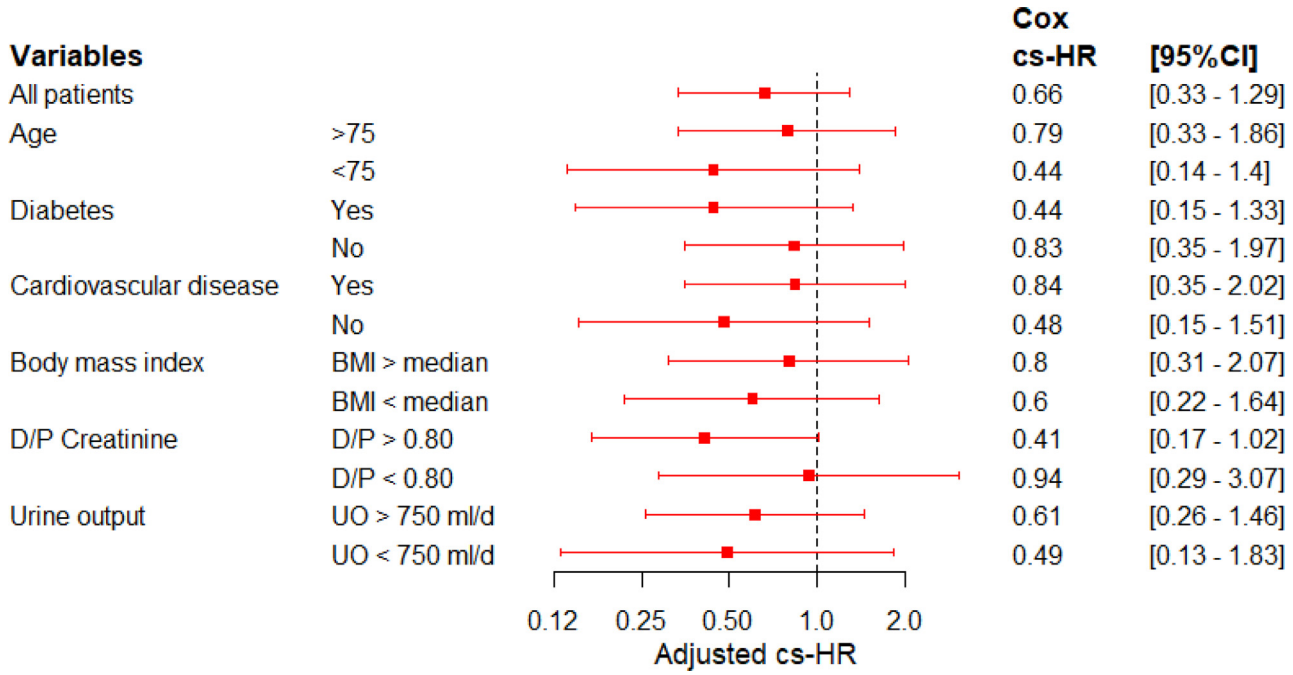


Figure 3. Subgroup analysis. Figure shows a forest plot with hazard ratios for primary outcome occurrence: an HR value > 1 indicates a higher risk in the double dose group whereas a value < 1 indicates a lower risk in the double icodextrin dose group, compared with the single icodextrin dose group.

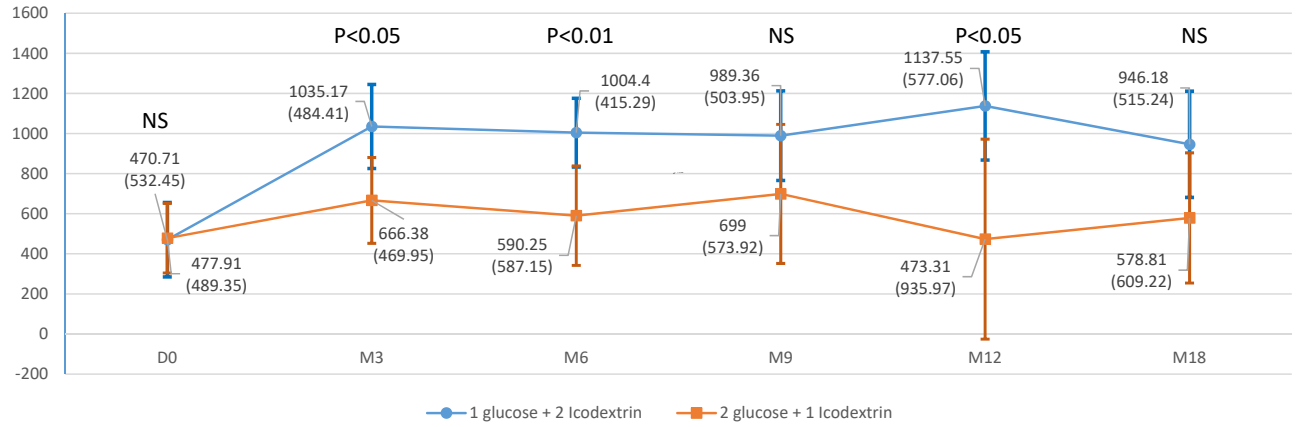


Figure 4. Description of the daily peritoneal fluid (ml) removal (ultrafiltration). Figure indicates the amount of daily peritoneal fluid (ml) removal (ultrafiltration) over time (mean [SD], 95% CI), ITT analysis in the 2 groups of patients treated with 1 or 2 icodextrin bags/d. CI, confidence interval; ITT, intention-to-treat.

of these SAEs were considered to be related to the study intervention by the treating physician.

DISCUSSION

In this open-label, randomized, prospective, multicenter study with 2 parallel groups, we did not detect a benefit from a double (2 bags/d) icodextrin dose in older patients on an incremental regimen with 3 bags/d CAPD to stay longer on this regimen compared with those on a single icodextrin bag/d. The absence of an effect of the double icodextrin dose on the study's primary end point was consistent independently of the causes for reaching the primary end point and across all prespecified subgroups. Of the patients, 61% and 50% remained on the 3 bags/d regimen at month 9 in the double and single icodextrin dose groups respectively, whereas this percentage was still 41% and 43% at month 18. An excessive use of hypertonic dialysates as a cause of study withdrawal was more prominent in the single icodextrin dose group. Increased daily net UF was observed in the double icodextrin dose group during the entire treatment period without affecting residual diuresis. Safety analysis appeared to be similar in both groups and no detrimental effect of the double icodextrin dose was observed.

The baseline characteristics showed that patients in the trial were representative of older patients beginning CAPD with a high risk for fluid retention; technique failure; transition to hemodialysis; and/or death because of their age, comorbid conditions, and medical history.[22] Significant rates of death, technical failure, and hospitalization were indeed observed in both groups. We designed the trial as a superiority trial, powered to detect a 30% higher risk of reaching the primary outcome in the single icodextrin dose group, which we considered a clinically relevant effect. Although the neutral result found in this trial does not rule out a beneficial effect of the double icodextrin dose (such as increased UF and reduced glucose load), the results were consistent in all prespecified subgroups and for the secondary end points. The excellent clinical care provided to both groups, evidenced by remarkably low peritonitis rates in comparison with recent data, overall patients' retention > 40% in an

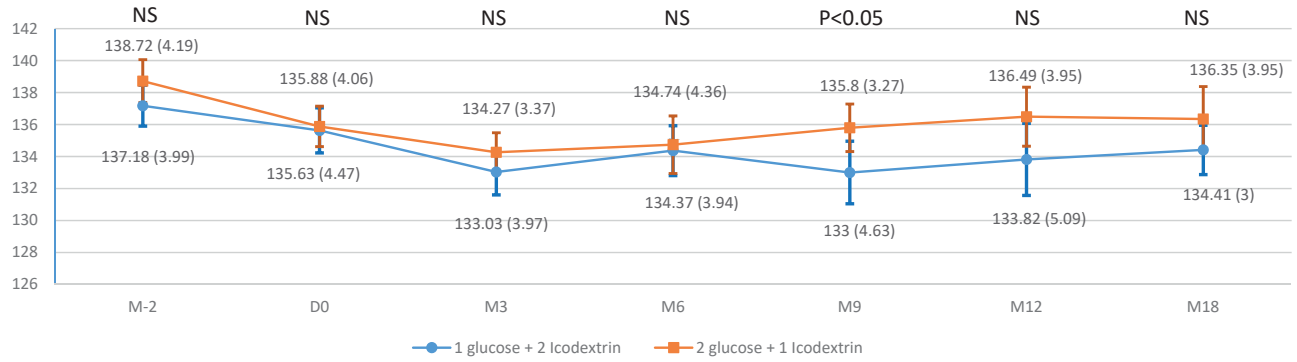


Figure 5. Evolution of serum sodium concentration (mmol/l) over time (Mean [SD], 95% CI). Serum sodium concentration (mmol/l) evolution over time (mean [SD], 95% CI), ITT analysis in the 2 groups of patients treated with 1 or 2 icodextrin bags/d. CI, confidence interval; ITT, intention-to-treat.

Table 3. Safety—serious adverse events (SAEs) of interest

Serious adverse events	Double dose icodextrin (n = 41)	Single dose icodextrin (n = 42)
Number of SAEs	53	52
Patients with ≥ 1 SAE	31	30
SAE resulting in death	3	3
Cardiovascular event	11	11
Cardiac event	5	7
Lower limb ischemia	5 (1[a])	1
Mesenteric ischemia	1	-
Stroke	-	3
Infection		
Pulmonary	4 (1[a])	5
Septicemia	-	4 (1[a])
Influenza	1	-
Clostridium infection	1	-
Neoplasia	-	3 (2[a])
PD-technique–related SAEs		
Peritonitis (n; [b])	7 (5; 1[b])	15 (10; 2[b])
Exit-site/Tunnel infection (n; [b])	3 (3; 3[b])	-
Leakage (n; [b])	7 (7; 4[b])	3 (3; 2[b])

PD, peritoneal dialysis.
[a]number of events resulting in patient's death (1 additional case of death because of therapy cessation in the double-dose icodextrin arm).
[b]Number of events resulting in PD technique withdrawal.

incremental CAPD regimen at month 18 and surprisingly good outcomes among the patients on a single icodextrin dose, could account for the absence of differences in outcomes between the 2 groups. The high success rate in the single icodextrin dose group probably reduced the effect size used for sample size calculation, which has increased the risk of the study to be underpowered. In addition, it is likely that the recruitment of only half the sample size target contributed to the study being underpowered. In addition, it would have been of interest to detect whether the incidence of the *AQP1* deleterious genotype was the same in both groups.[17]

In older patients on CAPD, incremental dialysis is an individualized adjustment in the dialysis prescription (frequency and/or dose) over time according to clinical and dialysis parameters, including actual residual kidney function. Recent retrospective data from Ontario where incremental PD was prescribed in 175 subjects with kidney failure indicates that it is a safe approach to initiate dialysis and that it offers satisfactory outcomes, provided there is close monitoring of the patients, comprehensive evaluation of their clinical responses, and prompt adjustment of the prescription.[23] The data from the DIDo study, showing that almost half of the patients in each group were still on a 3 bags/d regimen at month 18 indicates that incremental PD was a valid approach to accommodate individual patients' needs and health status in our population, an observation that supports the recent International Society for Peritoneal Dialysis guidelines on that topic.[24]

The primary focus of the DIDo study was to evaluate the efficacy and safety of prescribing a double icodextrin dose. Our trial enrolled only patients scheduled to start CAPD with icodextrin, a regimen appropriate for a population characterized by fast peritoneal small solute transport status, increased fluid retention, and a higher propensity for developing cardiovascular complications and death.[25,26] Recent data from international Peritoneal Dialysis Outcomes and Practice Patterns Study (Australia/New Zealand, Canada, Japan, the UK, and the US) showed that icodextrin was prescribed in an average of 35% of the patients, > 43% of them in all countries, except in the US, where it was only in 17% of the patients and also associated with a far greater use of hypertonic glucose solutions.[14] Given that glucose is regarded as the primary cause for peritoneal membrane degradation,[16,21,27] minimizing the use of hypertonic dialysates should be encouraged. In this context, achieving a daily average net UF of 1000 ml in the double icodextrin dose group, which is more than double that achieved with a single icodextrin dose, is notable and has the potential not only to improve fluid status and quality of life of patients but also to preserve their peritoneal membrane integrity. The higher number of patients requiring an excess of hypertonic bags in the single icodextrin dose group in the present study supports this concept. Still, it is important to remind patients that increased UF does not necessarily protect them from overhydration because the ultimate fluid status also depends on salt and fluid intake, which are data always difficult to be quantified in clinical studies. Finally, our finding aligns with preliminary observational data[18–20] suggesting the benefits of the double icodextrin dose for increasing net UF.

The added benefit of using 2 icodextrin dialysates per day also lies in its colloid properties as follows: icodextrin can remain for > 10 hours in the peritoneal cavity while still providing sustained UF, allowing patients a greater flexibility in the schedule of their PD exchanges while on incremental therapy with 3 exchanges/d.[10]

In daily clinical practice, nephrologists may hesitate to prescribe icodextrin because of potential side-effects, such as sterile macrophagic peritonitis[28] or exfoliative dermatitis.[29] However, none of these effects were observed in either group in the present study, with a median follow-up of 363 days. Another concern regarding icodextrin is related to the accumulation of its metabolites, such as maltose, maltotriose, and other oligomers. These metabolites are absorbed through the lymphatics and remain in the extracellular fluid compartment, raising measured plasma osmolality and osmolal gap, and resulting in hyponatremia due to a water shift from

the intra- to the extra-cellular compartments.[11,17,18] Hyponatremia was more pronounced in patients receiving a double icodextrin dose than in those receiving a single icodextrin dose per day. However, sodium concentration remained within acceptable limits and did not result in clinical symptoms or in the need for protocol discontinuation in any patient. In addition, the double icodextrin dose did not detrimentally affect residual urine output compared with the single dose, although this observation must be interpreted with caution given the challenges associated with urine collection in patients on dialysis and with the notion that reduced UF in patients on PD, as it is in the single icodextrin dose group, is often linked to increased urine volumes. Finally, incidence of peritonitis, hospitalizations and SAEs, though not negligible in such a high-risk population, did not significantly differ between both groups. Therefore, the absence of harmful effects from using the double icodextrin dose supports its application in older patients on CAPD in whom there is a need to enhance UF while avoiding hypertonic glucose dialysates.

Our trial has several limitations. First, it was an open-label trial because blinding was deemed impractical. Therapeutic decisions, such as for instance. the adaptation of the diuretic dose, may have been influenced by the treatment arm assigned to each patient. Second, a center effect and the expertise of clinicians in the field of PD may have influenced the management of the various complications observed during the study. Nevertheless, the excellent outcomes observed in the single icodextrin dose group argues against all these possibilities. Third, the prolonged time required for patient recruitment, because of inherent protocol complexities, makes it difficult to exclude the possibility that a learning curve in patient management could have affected the study results. Finally, the results should be interpreted with caution, considering the small number of patients, the relatively short follow-up, and the important residual kidney function at the onset of the study.

In this prospective, international, randomized, open-label, parallel-group trial in older patients with PD, a double icodextrin dose initiated at PD start did not result in a lower cumulative incidence of the composite primary end point of excessive use of hypertonic glucose dialysate, transfer of the patient to another dialysis method for any reason, or death of the patient; compared with patients receiving a single daily icodextrin dose. Patients receiving the double icodextrin dose experienced significantly improved UF volumes, with an excellent safety profile throughout the study.

APPENDIX

List of the members of the DIDo Study Group

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DISCLOSURE

EG reports support for the present study from Baxter Healthcare; grants for other studies from Baxter Healthcare; consulting fees from Fresenius Medical Care and NxStage; honoraria for lectures or presentations from Baxter Healthcare, Fresenius Medical Care, NxStage, Dirinco, AstraZeneca, Bayer, and Astellas; and travel support from AstraZeneca. CB reports honoraria for lectures and presentations from Baxter Healthcare, Vantive, and Fresenius Medical Care; and travel grant from MSD. KF reports grants from Baxter Healthcare and honoraria for lectures and presentations from Baxter Healthcare and Fresenius Medical Care. BB reports speaker's fees from Baxter Healthcare. MJ reports grants from AstraZeneca; consulting fees from Astellas,

AstraZeneca, Bayer, Boehringer Ingelheim, Cardiorenal, CSL Vifor, GSK, Stada Eurogenerics, and Vertex; honoraria for lectures or presentations from Astellas, AstraZeneca, Bayer, Boehringer Ingelheim, and Menarini; payment for expert testimony from Stada Eurogenerics; and travel grants from AstraZeneca and Boehringer Ingelheim. MJ is cochair of Kidney Disease Improving Global Outcome (KDIGO, the global guidelines in nephrology). MW reports grants from Baxter Healthcare, consulting fees from Triomed, honoraria for lectures or presentations from Baxter Healthcare and Fresenius Medical Care, and travel grant from Medici. JN reports grants from Novartis and Baxter Kidney care Advisory Board 2024. All the other authors declared no competing interests.

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study, including individual patient data and a data dictionary that defines each field in the data set, will be made available as deidentified participant data to researchers who propose to use the data for individual patient data meta-analysis. Data will be shared following approval of the proposal by the corresponding author and completion of a signed data-access agreement.

AUTHOR CONTRIBUTIONS

The DIDo trial was designed by EG (Department of Nephrology, cliniques universitaires Saint-Luc, Université catholique de Louvain, Brussels, Belgium), TL (Department of Nephrology, Centre Universitaire des Maladies Rénales, UNICAEN, CHU de Caen Normandie, Normandie Université, Caen, France), DA (Department of Nephrology, Hôpital de Vichy, Vichy, France), and BB (Department of Nephrology, Dialysis, and Renal Transplantation, University Hospitals Leuven, Belgium). All the writing committee members contributed to the design of the study. For French and UK health authorities contact, FV (Department of Nephrology, Centre Hospitalier Universitaire Bichat, Paris, France) and MW (Sheffield Kidney Institute, Sheffield Teaching Hospitals NHS Foundation Trust, Sheffield, UK) joined the DIDo committee. Data collection was performed by the CRO, Keyrus BioPharma. Statistical analyses were performed by Keyrus BioPharma and verified by TL, CB (both at Department of Nephrology, Centre Universitaire des Maladies Rénales, UNICAEN, CHU de Caen Normandie, Normandie Université, Caen, France), and AB (Statistical Methodology and Computing Service technological platform, UCLouvain, Louvain-la-Neuve, Belgium). EG wrote the initial version of the report, and all the authors contributed to revising it. All the authors approved the manuscript before submission.

SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Figure S1. Study design.

Figure S2. Schematic description of the daily dialysate prescription according to treatment groups.

Figure S3. Figure shows Kaplan-Meier curves for cumulative incidence of the use of excessive predefined ($>$ 15% 3.86% or $>$ 30% 2.27% over a 4-week period) hypertonic dialysates at month 9 in patients randomized to either 2 or 1 icodextrin bag/d.

Figure S4. Figure shows Kaplan-Meier curves for cumulative incidence of death at month 9 in patients randomized to either 2 or 1 icodextrin bag/d.

Figure S5. Figure shows Kaplan-Meier curves for cumulative incidence of transfer to hemodialysis (combining technical failure and occurrence of an adverse event unrelated to the technique) at month 9 in patients randomized to either 2 or 1 icodextrin bag/d.

Figure S6. Figure shows Kaplan-Meier curves for cumulative incidence of the secondary outcome occurrence (excessive use of hypertonic glucose dialysate, transfer of the patient to another dialysis method for any reason, or death of the patient) at month 18 in patients randomized to either 2 or 1 icodextrin bag/d.

Figure S7. Figure shows Kaplan-Meier curves for cumulative incidence of the use of excessive predefined ($>$ 15% 3.86% or $>$ 30% 2.27% over a 4-week period) hypertonic dialysates at month 18 in patients randomized to either 2 or 1 icodextrin bag/d.

Figure S8. Figure shows Kaplan-Meier curves for cumulative incidence of death at month 18 in patients randomized to either 2 or 1 icodextrin bag/d.

Figure S9. Figure shows Kaplan-Meier curves for cumulative incidence of transfer to hemodialysis (combining technical failure and occurrence of an adverse event unrelated to the technique) at month 18 in patients randomized to either 2 or 1 icodextrin bag/d.

Table S1. Specific secondary end points occurring within month 9 after start of run-in, and between month 9 and month 18.

Table S2. Urinary volume (ml)/d over time (mean [95% confidence interval]).

Study Protocol.

STROBE Checklist.

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