Early-Start Versus Late-Start Icodextrin for Children Receiving Chronic Peritoneal Dialysis

Findings from the International Pediatric Peritoneal Dialysis Network

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Key Points

- Early icodextrin use preserved residual kidney function and improved BP versus glucose dialysate in pediatric peritoneal dialysis patients.
- Starting icodextrin within 1 year of commencing peritoneal dialysis reduced the risk of technique failure or death nearly five-fold versus later start.
- Children younger than 5 years on icodextrin had similar ultrafiltration and BP control with superior kidney function preservation versus older children.

Abstract

Background Experience with icodextrin use in children on long-term peritoneal dialysis (PD) is limited. We describe international icodextrin prescription practices and their effect on clinical outcomes: ultrafiltration, BP control, residual kidney function (RKF), technique and patient survival.

Methods We included patients younger than 21 years enrolled in the International Pediatric Peritoneal Dialysis Network between 2007 and 2024, on automated PD with a daytime dwell. Outcome analysis was restricted to patients with 6 months or greater follow-up. We used propensity score matching to balance baseline differences between icodextrin and glucose groups. Long-term outcomes and survival were analyzed by longitudinal linear mixed-effects models and Cox proportional hazards models, respectively, adjusting for key covariates. Sensitivity analyses addressed the effect of missing data.

Results Icodextrin was prescribed in 724 of 3573 (20.3%) patients, varying widely across world regions. Only "early-start" icodextrin (within 1 year of PD start) was associated with a significant decline in diastolic BP standard deviation score ($\beta=-1.31$, $P < 0.001$) and a slower decline in RKF ($\beta=0.11$, $P = 0.002$) compared with glucose use alone. "Late-starters" (starting icodextrin after ≥1 year on PD) compared with "early-starters" had more uncontrolled hypertension (38% versus 20%; $P < 0.001$), a higher antihypertensive agent requirement (68% versus 55%; $P = 0.03$) and an higher dialytic glucose exposure from baseline (5.4 versus 4.8 gm/kg per day; $P = 0.05$). Icodextrin use, both early and late, was independently associated with a positive linear increase in ultrafiltration sustained during follow-up compared with glucose use ($\beta=0.27$ and $\beta=0.33$, respectively; both $P < 0.01$). Peritonitis rates and dialysate leaks were similar between icodextrin and glucose groups. "Late-starters" had significantly increased risk of technique failure/death compared with "early-starters" (hazard ratio, 5.16; 95% confidence intervals, 1.57 to 17.0; $P = 0.007$).

Conclusion Icodextrin use improves ultrafiltration, but only early compared with delayed initiation conferred a five-fold higher likelihood of technique survival, better BP control, and preservation of RKF.

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Introduction

The importance of fluid and sodium removal to achieve euvolemia in patients on peritoneal dialysis (PD) is well recognized. Inadequate peritoneal ultrafiltration increases the risk of overhydration and hypertension, with the associated risks of cardiovascular disease. Loss of ultrafiltration capacity is an important cause of PD technique failure.[1,2] The incidence of ultrafiltration failure increases with dialysis vintage and is associated with changes in peritoneal membrane function, causing rapid absorption of glucose and loss of the osmotic gradient between dialysis fluid and peritoneal vessels.[3,4] In this case, maintaining sufficient ultrafiltration necessitates the use of hypertonic glucose solutions, which in turn cause injury to the mesothelial cells, enhance vascular permeability, and induce inflammation and peritoneal membrane fibrosis.[5–8]

Icodextrin, a type of glucose polymer obtained from starch, has been used as a substitute for glucose as an osmotic agent for PD in extended dwell exchanges since the 1990s. Randomized trials and meta-analyses in adults have consistently shown that icodextrin use is associated with reduced uncontrolled fluid overload and increased peritoneal ultrafiltration without systemic adverse events and without compromising residual kidney function (RKF).[9] The pediatric experience with icodextrin is limited to few observational studies only, demonstrating improved ultrafiltration, particularly in older children.[10]

We aimed to examine global icodextrin prescription patterns and determine whether early administration of icodextrin (1 year or less after starting PD) was associated with higher peritoneal ultrafiltration, better BP control, RKF preservation, and improved patient and technique survival when compared with late (more than 1 year after starting PD) icodextrin initiation or using only glucose-based dialysis solution.

Methods

The study included patients from the International Pediatric Peritoneal Dialysis Network (IPPN) registry (www.pedpd.org). The registry design, objectives, complete list of data variables collected, and details of the registry protocol, ethical agreement, and informed consent procedure have been published[11] and included in Supplemental Methods. The analyses have been performed on deidentified data extracted from the registry.

Data Extraction

Patients younger than 21 years at enrollment into the IPPN between April 2007 and January 2024 and treated with automated PD with a daytime dwell were included. Children receiving continuous ambulatory PD were excluded from the study as they are likely to be older and have substantial RKF, thus confounding the analysis. Demographic data, PD modality, dialysis prescription and solutions, residual urine volume, ultrafiltration, office BP, routine blood results, medications, and reasons for PD discontinuation, if applicable, were extracted from the database. Data on ultrafiltration and urine output were recorded as averages over 6-month intervals. The average PD fluid glucose concentration and dwell times/volumes over each interval observation time were used to calculate glucose exposure based on average glucose concentration of dialysate, total fluid turnover, and patient dry weight. Peritoneal equilibration test results and PD clearance studies were analyzed within 3 months of each update, whenever available. To address regional differences, we categorized the cohort into the following predefined regions: Asia (including Oceania, South-Asia, North and North-East Asia), East and Central Europe, Western Europe, Latin America, North America, and the Middle East.[12]

Study Cohorts

Four cohorts of patients were analyzed, as presented in Figure 1 and Supplementa1 Table 1 for the following purposes: (*1*) examining global prescription practices across all included patients; (*2*) identifying factors associated with conversion to icodextrin for daytime fill in incident dialysis patients, i.e., those with first registry visit within 90 days of starting PD); (*3*) comparing outcomes based on the timing of icodextrin start. We defined "early-start" as starting icodextrin within 1 year of initiating PD and "late-start" as beginning icodextrin more than 1 year after PD initiation; and (4) comparing icodextrin users (separately for "early-start" and "late-start") with a propensity score matched cohort of patients who never used icodextrin (glucose users). Clinical outcomes in (*2*), (*3*), and (*4*) were analyzed in patients with a follow-up period of at least 6 months. We selected a 1-year threshold to distinguish early from late icodextrin initiation, as significant peritoneal membrane changes are generally not observed before the first year of therapy. This time frame is also more relevant to pediatric patients, who have shorter dialysis vintage due to reduced waiting time for transplantation.

Exposure, Outcomes and Covariates

The primary exposure was icodextrin use; outcomes and covariates for study cohorts (*1*)–(*4*) are presented in Supplemental Table 1. The key outcomes examined were: (*1*) Changes in fluid status, including longitudinal changes in 24-hour ultrafiltration adjusted for body surface area (BSA), RKF (urine output adjusted to BSA, analyzed in patients with initial urine output >100 ml/m^2 per day; using this cutoff to define anuria), and BP SD scores (SDS; adjusted for age, sex, and height according to the National High BP Education Program Fourth Report).[12] Hypertension was defined as either systolic or diastolic BP greater than two SDS or as uncontrolled hypertension in patients receiving antihypertensive medications. (*2*) The composite outcome of permanent transfer to hemodialysis and non-infectious dialysis related deaths. (*3*) Peritonitis rate, as defined by the International Society for PD.[13]

Statistical Analysis

Detailed statistical analyses are presented in Supplemental Methods and Supplemental Table 1. Propensity scores, representing patients' estimated probabilities of receiving icodextrin versus glucose-based solutions, were derived from multivariable logistic regression models including covariates at the first recorded visit (age, sex, geographic

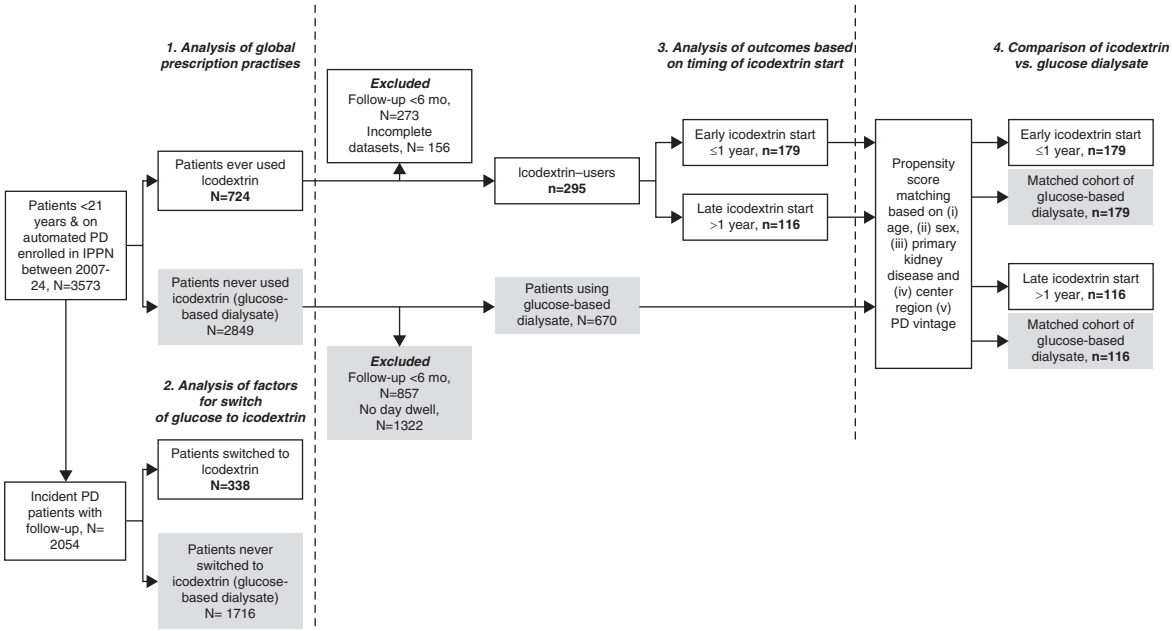

Figure 1. Flow of patients in the study. Figure shows four different subcohorts used for analysis of key outcomes[1–4] that are also listed in Supplemental Table 1. IPPN, International Pediatric Peritoneal Dialysis Network; PD, peritoneal dialysis.

region, primary kidney disease, and PD vintage). Propensity score matching using a one-to-one nearest-neighbor match without replacement was performed; postmatching balance was ensured for RKF and use of biocompatible fluids. Matching was performed separately for those with icodextrin "early-start" and "late-start" (Supplemental Figure 1 and Supplemental Tables 2 and 3). A longitudinal linear mixed-effects model with random patient-level intercepts was applied to analyze the effect of type of dialysate use (icodextrin versus glucose) and timing of icodextrin start (early versus late) on ultrafiltration adjusted for BSA, urine output adjusted for BSA, and diastolic BP SDS including the explanatory covariates in the models, as listed in Supplemental Table 1. Multivariable Cox proportional hazard ratios were estimated for factors associated with the conversion of glucose daytime dwell to icodextrin and to assess the impact of (*1*) icodextrin "early" versus "late-start," (*2*) icodextrin (early or late) versus glucose use on the composite outcome of permanent transfer to hemodialysis and noninfectious dialysis-related death (covariates listed in Supplemental Table 1). To minimize immortal time bias, follow-up for (*1*) early versus late initiation was calculated from the date of icodextrin initiation and for (*2*) early initiation versus glucose from the date of PD initiation. For late initiation versus glucose, only patients alive and still on PD at 1 year were included, and this landmark was used as the starting point for follow-up. Kaplan-Meier estimates were used to generate survival functions, and log-rank tests for equality of survival functions were used for analyzing the composite outcome. RKF data were missing for 16.8% of patients, while all other variables had complete data. To address this, we performed a sensitivity analysis by restricting propensity score matching to patients with available RKF data (Supplemental Figure 1). For the regression models, we used complete case analysis, which involved pairwise deletion to handle missing data. No imputation methods were used in this study. P value, from two-tailed tests, < 0.05 was considered statistically significant. Analyses were conducted using R Software 4.3.2 (R Core Team 2021).

Results

Incident (N=2054) and prevalent (N=1519) pediatric maintenance PD patients were enrolled in the IPPN registry from 126 pediatric dialysis centers in 43 countries. "Icodextrin users" (N=724) received icodextrin for at least 4 weeks during their time on PD and comprised 20.3% of patients, while 2849 (79.7%) patients never received icodextrin and constituted the "glucose users" group (Figure 1).

Patterns of Icodextrin Prescription

At first observation, icodextrin versus glucose users were older, more likely to be females with glomerular disease, previously transplanted, with longer dialysis vintage, lower RKF, more commonly on biocompatible solutions, and having higher fluid turnover (Table 1). Icodextrin use was associated with higher dialytic creatinine clearance and high membrane transport characteristics, in a subgroup of patients who had undergone a peritoneal equilibration test (n=870) and had urinary and dialytic clearance data (n=1491; Table 1). The use of icodextrin varied across regions: highest in the Middle-East (49%) and Western Europe (31%) and lowest in Latin America (5%) (Figure 2, A and B).

Factors Associated with Conversion to Icodextrin for Daytime Fill in Incident PD Patients

Factors determining conversion to icodextrin for daytime fill were analyzed in a subgroup of 338 incident dialysis patients who had their first registry entry within 90 days of

Table 1. Demographics of the pediatric peritoneal dialysis cohort

At First Observation on Icodextrin or Glucose	Icodextrin Users *N*=724	Glucose Users *N*=2849
Patient characteristics		
Age at initiation of KRT, yr	9.4 (3.5–13.5)	7.1 (1.6–12.3)
Age at initiation of PD, yr	10.0 (3.9–13.8)	7.7 (1.8–12.8)
Age, yr	11.5 (5.6–15.4)	8.3 (2.5–13.3)
0–4	168 (23)	1043 (37)
5–9	218 (30)	884 (31)
10–14	135 (19)	453 (16)
15–20	203 (28)	469 (17)
Regional variation		
Asia	126 (17)	797 (28)
Middle-East	63 (9)	66 (2)
East and Central Europe	108 (15)	428 (15)
Western Europe	313 (43)	691 (24)
North America	88 (12)	386 (14)
Latin America	26 (4)	481 (17)
Men/women (%)	366/358 (51/49)	1632/1217 (57/43)
Primary kidney disease		
CAKUT and ciliopathies	294 (41)	1291 (45)
Glomerulopathies	271 (37)	849 (30)
Metabolic diseases	13 (2)	53 (2)
Post-AKI CKD	33 (5)	152 (5)
Other	60 (9)	257 (9)
Unknown	53 (7)	247 (9)
Height SDS	-1.78 (-2.89–-0.77)	-1.84 (-2.97–-0.80)
BMI SDS	-0.03 (-0.92–0.78)	-0.07 (-1.04–0.83)
Hypertension/uncontrolled hypertension	258 (36)	938 (33)
Residual kidney function, ml/m^2 BSA/d[a]	115 (0–489)	462 (0–1064)
Anuria[a]	278 (49)	861 (34)
Treatment at inclusion		
PD vintage, yr	0.90 (0.42–2.21)	0.24 (0.07–0.72)
Previous transplant	66 (9)	174 (6)
Previous dialysis	195 (27)	854 (30)
Previous PD	147 (20)	620 (22)
Biocompatible PD fluid	371 (51)	1050 (37)
Glucose exposure, g/kg per d	4.8 (3.3–6.9)	4.0 (2.7–5.9)
Total PD fluid turnover, l/m^2 BSA per d	7.4 (5.6–9.6)	6.3 (4.5–8.1)
Ultrafiltration volume, ml/m^2 BSA per d	576 (366–887)	389 (190–645)
Medications		
≥ 2 antihypertensive drugs	287 (50)	899 (37)
RAAS inhibitors	110 (19)	493 (21)
Diuretics	544 (75)	1965 (69)
Additional calcium supplements	253 (35)	608 (21)
Non–calcium-based phosphate binder	99 (14)	940 (33)
Bicarbonate	287 (50)	899 (37)
Peritoneal equilibration test and clearance		
Weekly creatinine clearance, l/1.73 m^2 per wk[b]		
Urinary	3 (0–33)	23 (0–60)
Dialytic	41 (31–54)	29 (19–40)
Total	54 (39–76)	53 (35–84)
Peritoneal equilibration test[c]		
Low transporter	18 (20)	281 (36)
Low-average transporter	20 (23)	274 (35)
High-average transporter	21 (24)	159 (20)
High transporter	30 (34)	67 (9)

Values are median (interquartile range) or No. (%)
BMI, body mass index; BSA, body surface area; CAKUT, congenital anomalies of kidney and urinary tract; PD, peritoneal dialysis; PET, peritoneal equilibration test; SDS, SD score; RAAS, renin-angiotensin-aldosterone system.
[a]Information on urine output available 571 and 2854 patients in icodextrin and glucose groups, respectively
[b]Information on weekly creatinine clearance available in 176 and 1315 patients in icodextrin and glucose groups, respectively.
[c]Information on PET test results available in 89 and 781 patients in icodextrin and glucose groups, respectively

starting PD and who received icodextrin after a median 6.5 (interquartile range [IQR] 1.8 to 13.1) months from PD start (Figure 3). After adjustment, the probability of converting from glucose to icodextrin was higher with older age, uncontrolled hypertension, lower residual urine output, and high membrane transport characteristics ($P < 0.05$ for all, Table 2). Patients who were switched to icodextrin had higher glucose exposure corresponding to higher ultrafiltration volume and lower serum albumin levels ($P < 0.05$ for all, Table 2).

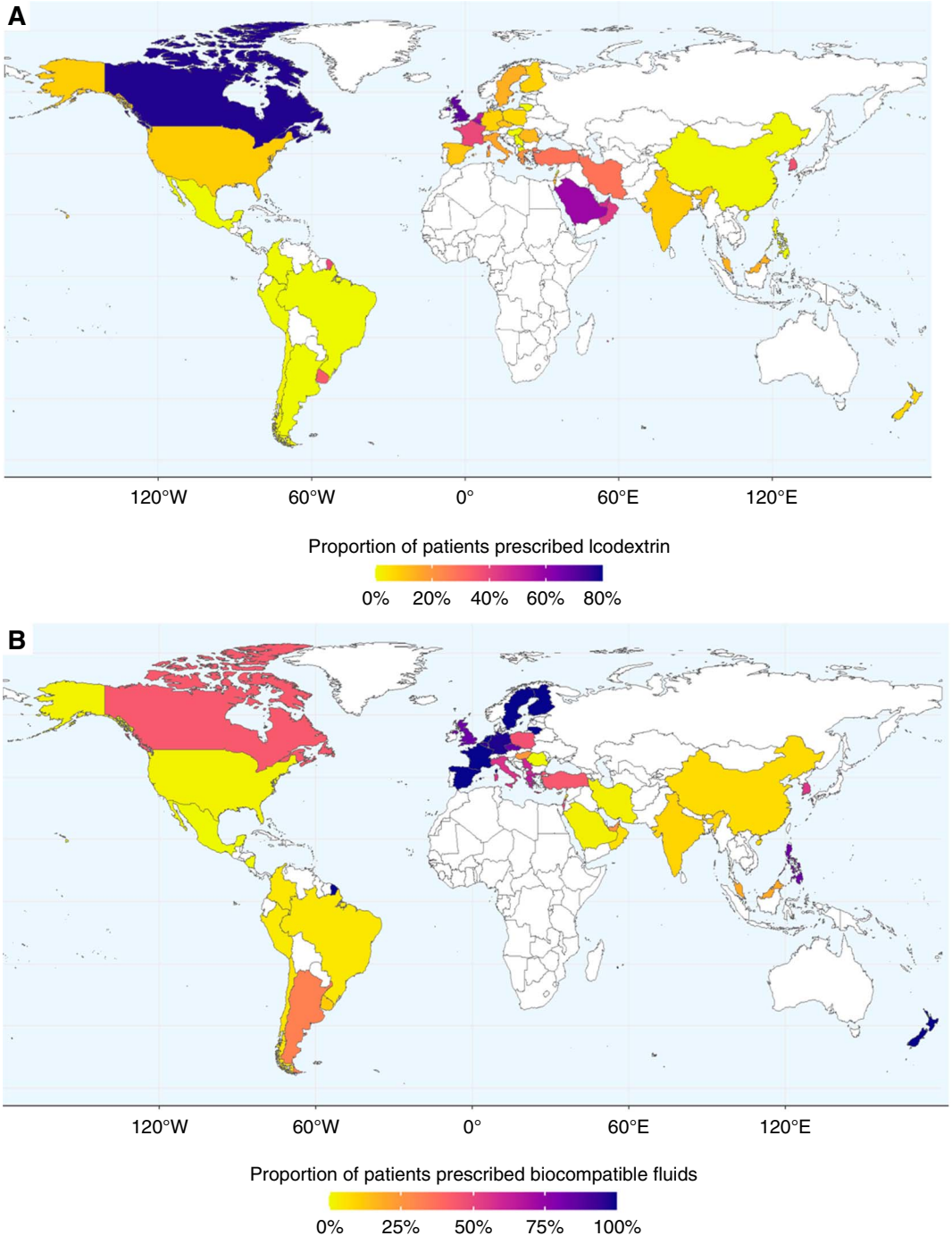

Figure 2. Proportion of patients prescribed icodextrin and biocompatible fluids in countries participating in the IPPN.

"Early" Versus "Late-Start" Icodextrin Use

Patient Characteristics

The baseline characteristics of 295 icodextrin users followed more than 6 months were largely representative of the overall cohort of 724 icodextrin users (Supplemental Table 4). These were divided into "early-start" (within 1 year of initiating PD, n=179; 61%) and "late-start" (>1 year, n=116; 39%) groups. The median PD vintage before the first icodextrin prescription was 0.15 (IQR 0.09 to 0.52) years in the "early-start" compared with 2.32 (1.40 to 3.47) years in the "late-start" group (Table 3). At the time of initiating icodextrin, the two groups were similar in age, sex, ethnicity, primary kidney disease, history of dialysis or transplant, and icodextrin dwell volume. The prevalence of hypertension/uncontrolled hypertension, requirement for antihypertensive medications, and total glucose exposure were similar between groups (P = 0.65, P = 0.20 and P = 0.52, respectively). "Late-starters" had lower height-SDS, lower serum albumin levels, higher iPTH, higher phosphate binder use, lower diuretic use, lower biocompatible fluid use (all $P < 0.001$), and higher ultrafiltration (P = 0.007) compared with "early-starters" (Table 3).

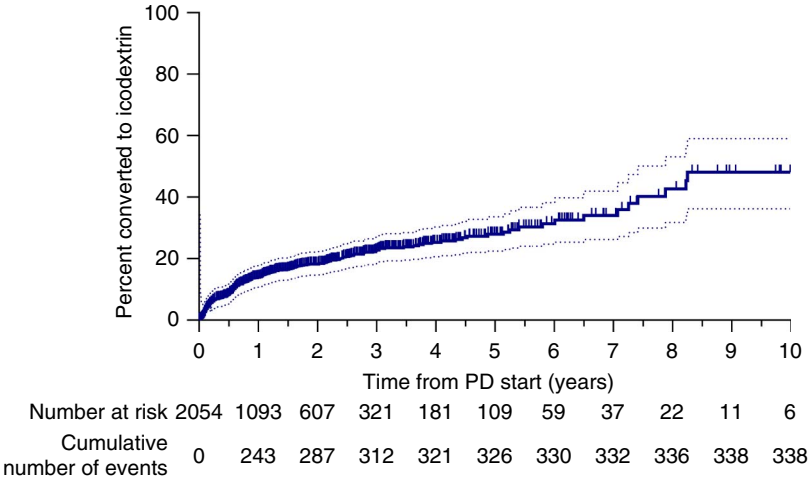

Figure 3. Kaplan-Meier curve showing the proportion (95% CI) of 2054 incident PD patients converted from glucose to icodextrin daytime dwell over 10-year cumulative time on dialysis. Median survival was not reached; tick marks represent censored data. CI, confidence interval. Figure 3 can be viewed in color online at www.cjasn.org.

Effect on BP Control and RKF Preservation

The median duration of follow-up was 1.5 (IQR, 0.9–2.3) years in the "early-start" and 1.4 (0.9–2.2) years in the late-start group ($P = 0.36$). At the last follow-up visit, "late-starters" versus "early-starters" had significantly higher rates of hypertension (38% versus 20%; $P < 0.001$) and greater need for antihypertensive medications (68% versus 55%; $P = 0.03$). In multivariable

Table 2. Factors associated with converting from glucose to icodextrin daytime dwell in incident peritoneal dialysis patients

Characteristic	Model 1: Including ultrafiltration n=1610[a]		Model 2: Including glucose exposure n=1610[a]		Model 3: Peritoneal membrane transport n=607[a]	
	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P
Age, yr	1.10 (1.06 to 1.13)	<0.001	1.09 (1.06 to 1.13)	<0.001	1.02 (0.94 to 1.11)	0.63
Male sex	0.76 (0.54 to 1.07)	0.11	0.74 (0.53 to 1.04)	0.08	0.86 (0.36 to 2.04)	0.73
Region						
Western Europe	Reference		Reference		Reference	
Asia	0.17 (0.10 to 0.29)	<0.001	0.21 (0.12 to 0.35)	<0.001	0.11 (0.03 to 0.41)	<0.001
Middle-East	1.27 (0.56 to 2.86)	0.56	1.29 (0.58 to 2.90)	0.53	2.70 (0.29 to 25.1)	0.38
East and Central Europe	0.82 (0.53 to 1.26)	0.37	0.88 (0.57 to 1.35)	0.55	1.28 (0.43 to 3.80)	0.65
North America	0.62 (0.33 to 1.18)	0.15	0.73 (0.39 to 1.40)	0.35	NE	
Latin America	0.32 (0.17 to 0.61)	<0.001	0.34 (0.18 to 0.65)	0.001	NE	
Glomerular etiology	0.96 (0.66 to 1.38)	0.81	1.09 (0.75 to 1.57)	0.65	1.04 (0.41 to 2.69)	0.93
Previous dialysis	0.64 (0.43 to 0.97)	0.04	0.72 (0.48 to 1.09)	0.12		
Uncontrolled hypertension	1.55 (1.09 to 2.21)	0.01	1.56 (1.10 to 2.21)	0.01		
Ultrafiltration volume, L/m^2 per d	1.55 (1.39 to 1.72)	<0.001				
Residual kidney function, ml/m^2 per d	0.60 (0.41 to 0.88)	0.008				
Albumin, g/L	0.96 (0.93 to 0.99)	0.006	0.96 (0.93 to 0.98)	0.003		
Glucose exposure, g/kg per d			1.08 (1.01 to 1.15)	0.02		
Peritoneal equilibration test						
Low transporter					Reference	
Low-average transporter					0.69 (0.19 to 2.49)	0.57
High-average transporter					1.64 (0.48 to 5.59)	0.43
High transporter					5.06 (1.45 to 17.7)	0.01

Hazard ratio and 95% confidence intervals are obtained in proportional hazards models. All models adjusted for patients' visit age, sex, geographic region, and etiology of disease (glomerular versus nonglomerular disease). Covariates in models 1 and 2 include previous dialysis, previous transplant, peritoneal dialysis vintage, serum albumin, biocompatible fluid use, hypertension and additionally time-varying ultrafiltration, and residual kidney function in model (*1*) and glucose exposure in model (*2*). Model 3 only includes peritoneal membrane transport characteristics as covariates.
CI, confidence interval; HR, hazard ratio; NE not estimable; the model could not generate a stable estimate because of sparse data or complete separation between exposure and outcome.
[a]Analyzed in patients with at least one follow-up visit.

Table 3. Parameters at icodextrin initiation in "early-start" and "late-start" groups

Characteristics at First Icodextrin Use	Early-Start, n=179	Late-Start, n=116	P
PD vintage	0.15 (0.09–0.52)	2.32 (1.40–3.47)	<0.001
Age, yr	10.9 (4.4–14.9)	11.6 (5.6–14.7)	0.27
Male/female	78/101 (43.6/56.4)	55/61 (47.4/52.6)	0.52
Caucasian ethnicity	94 (53)	56 (48)	0.48
Region			
Asia	17 (10)	24 (21)	0.006
Middle-East	5 (3)	16 (14)	<0.001
East and Central Europe	22 (12)	26 (22)	0.02
Western Europe	116 (65)	32 (28)	<0.001
North America	17 (10)	9 (8)	0.61
Latin America	2 (1)	9 (8)	0.008
Primary kidney disease			
CAKUT and ciliopathies	64 (36)	50 (43)	0.21
Glomerulopathies	71 (40)	40 (35)	0.37
Metabolic diseases	5 (3)	1 (1)	0.41
Post-AKI CKD	7 (4)	7 (6)	0.40
Other	18 (10)	11 (10)	0.87
Unknown	14 (8)	7 (6)	0.56
Height SDS	-1.48 (-2.35–-0.41)	-2.58 (-3.63–-1.53)	<0.001
Body mass index SDS	-0.32 (-1.24–0.63)	0.15 (-0.84–0.90)	0.004
Systolic BP SDS	1.27 (0.44–2.11)	1.30 (0.33–2.23)	0.73
Diastolic BP SDS	0.11 (-3.39–1.77)	1.15 (0.22–2.10)	<0.001
Hypertension/uncontrolled hypertension	68 (38)	41 (35)	0.65
Residual kidney function, ml/m^2 per d	215 (0–549)	70 (0–476)	0.06
Anuria	54 (40)	52 (52.5)	0.06
Biochemistry			
Hemoglobin, g/dl	11.3 (10.3–12.5)	10.7 (9.5–12.1)	0.02
Albumin, g/l	37 (32–41)	34 (31–37)	<0.001
Calcium, mmol/l	2.56 (2.43–2.66)	2.53 (2.40–2.65)	0.29
Phosphorus, mmol/l	1.65 (1.39–2.01)	1.71 (1.36–2.08)	0.66
Intact parathyroid hormone, pmol/l	95 (28–268)	221 (76–628)	<0.001
Bicarbonate, mEq/l	26.0 (24.0–29.0)	25.0 (23.0–28.0)	0.04
Treatment			
Previous dialysis	42.0 (24)	32.0 (28)	0.42
Previous PD	23 (13)	23 (20)	0.11
Previous transplant	19 (11)	11 (10)	0.75
Biocompatible PD fluid	134 (75)	53 (46)	<0.001
Glucose exposure, g/kg per d	5.2 (3.3–7.3)	4.9 (3.3–6.7)	0.52
Total PD fluid turnover, l/m^2 BSA per d	8.5 (5.9–10.1)	7.1 (5.5–9.3)	0.08
Icodextrin fill volume, ml/m^2 BSA	602 (495–740)	559 (460–810)	0.78
Ultrafiltration volume, ml/m^2 BSA per d	546 (373–758)	644 (422–1035)	0.007
Medications			
Antihypertensive drugs	55 (31)	44 (38)	0.20
RAAS inhibitors	48 (39)	54 (55)	0.02
Diuretics	42 (34)	14 (14)	<0.001
Additional calcium supplements	149 (83)	88 (76)	0.12
Non–calcium-based phosphate binder	33 (18)	46 (40)	<0.001
Bicarbonate	20 (11)	15 (13)	0.65

Values are median (interquartile range) or No. (%).
BSA, body surface area; CAKUT, congenital anomalies of kidney and urinary tract; PD, peritoneal dialysis; RAAS, renin-angiotensin-aldosterone system; SDS, SD score.

linear mixed-effects models fitted to repeated visit data during PD treatment, "late-starters" versus "early-starters" showed higher diastolic BP SDS (β=1.17, $P < 0.001$), a steeper decline in RKF (β=−0.05, $P = 0.008$), and higher ultrafiltration per BSA (β=0.20, $P = 0.04$) when adjusted for age (time-varying), sex, region, and disease etiology (Table 4). Although there was an increase in glucose exposure from baseline in "late-starters" (median 5.4 versus 4.8 g/kg per day; $P = 0.05$), the slope of dialytic glucose exposure over time in "early-start" and "late-start" groups was similar (β=0.43, $P = 0.19$; Supplemental Table 5).

"Early-Start" and "Late-Start" Icodextrin Cohorts Versus Matched Glucose User Cohorts

The comparison of early and late-start icodextrin groups with matched glucose group at first registry visit is presented in Supplemental Table 3. Both "early-start" and "late-start" groups showed higher ultrafiltration compared with their respective glucose user matched cohorts (β=0.25, P=0.009 and β=0.35, P=0.004, respectively; Figure 4, A and B, and Table 5). Patients with higher ultrafiltration volumes showed a lower RKF (β=−0.27, $P < 0.001$ and β=−0.33, $P < 0.001$, for "early-start" and "late-start" respectively; Table 5), which was associated

Table 4. Factors associated with ultrafiltration, BP control, and preservation of residual kidney function in icodextrin users at follow-up

Parameters	β	95% CI	P
(1) Association with ultrafiltration adjusted for BSA			
(Intercept)	0.21	−0.22 to 0.63	0.34
Time on icodextrin, yr	0.01	−0.06 to 0.08	0.75
Late versus early icodextrin start	0.20	0.01 to 0.38	0.04
Residual urine output, L/m^2/d	−0.24	−0.31 to −0.06	0.004
Albumin, g/L	0.01	−0.002 to 0.02	0.16
Day fill volume, L/m^2	0.40	0.20 to 0.60	<0.001
Interaction of time on icodextrin and late versus early icodextrin start	−0.07	−0.17 to 0.02	0.14
(2) Association with diastolic BP SDS			
(Intercept)	−1.46	−2.04 to −0.89	<0.001
Time on icodextrin, yr	−0.20	−0.31 to −0.08	0.001
Late versus early icodextrin start	1.17	0.68 to 1.68	<0.001
Interaction of time on icodextrin and late versus early icodextrin start	−0.02	−0.19 to 0.15	0.82
(3) Association with residual kidney function			
(Intercept)	2.5	2.4 to 2.7	<0.001
Baseline urine output, per 100 ml[a]	0.27	0.22 to 0.33	<0.001
Time on icodextrin, yr	−0.02	−0.06 to 0.01	0.15
Late versus early icodextrin start[b]	−0.09	−0.18 to −0.01	0.03
Previous dialysis	−0.08	−0.17 to 0.00	0.05
Diuretics	−0.06	−0.11 to 0.004	0.07
RAAS inhibitors	−0.06	−0.11 to 0.00	0.06
Interaction of time on icodextrin and late versus early icodextrin start	−0.05	−0.09 to −0.01	0.008

Models adjusted for age, sex geographic region, and etiology of disease (glomerular versus nonglomerular disease). Analyses were limited to patients with complete data (N=241) covariates included in model include (*1*) residual kidney function, albumin, day fill volume per body surface area, previous peritoneal dialysis; model (*2*) residual kidney function and ultrafiltration; and model (*3*) use of diuretics and renin-angiotensin-aldosterone system inhibitors, previous dialysis, baseline urine output.
A β coefficient from the linear mixed models represents the average change in the continuous outcome variable over the entire course of follow-up associated with a one-unit increase in a continuous explanatory covariate (or a change in level compared with the reference group for a categorical explanatory covariate), while holding all other covariates in the model constant and accounting for repeated measurements within individuals. Specifically, the β coefficient for the interaction term time on icodextrin (years).
CI, confidence interval; BSA, body surface area; PD, peritoneal dialysis; RAAS, renin-angiotensin-aldosterone system; SDS, SD score.
[a]Patients with urine output >100 ml/m^2/d at baseline included for analysis; urine output is log transformed to satisfy normality.
[b]Late versus early icodextrin start' represents the difference in the slope of outcome change over time between late-starters and early-starters (the reference group).

with a trend toward a higher daytime fill volume. "Early-start", but not "late-start" icodextrin, versus glucose dialysate use predicted lower diastolic BP SDS (β=−1.31, P < 0.001; Table 5). The rate of decline in RKF with time on PD was attenuated in early icodextrin users compared with their matched cohort of glucose users (β=0.11, P = 0.002, Figure 4C and Table 5). By contrast, the "late-start" icodextrin users had a steeper decline in RKF compared with their matched cohort of glucose users (β=−0.05, P = 0.04, Figure 4D and Table 5).

Technique and Patient Survival

In multivariable Cox regression models, late icodextrin start was independently associated with a significantly higher risk for the composite outcome of hemodialysis transfer or death compared with "early-start" (HR, 5.16; 95% confidence intervals [CIs] 1.57 to 17.0; P = 0.007), when adjusted for age, sex, geographic region, and etiology of CKD (Table 6). The technique and patient survival was 96% in the "early-start" group and 86% in the "late-start" group after 2.5 years of follow-up (log-rank P = 0.02; Figure 5). The reasons for technique failure in both the groups were ultrafiltration failure (n=2 and n=4, respectively) and peritonitis (n=6 and n=7, respectively).

There was no significant difference in the composite end point in the "early-start" icodextrin group compared with the matched glucose group (log-rank P = 0.96). However, difference in risk of technique failure/death in late icodextrin group compared with the matched glucose group was notable but not statistically significant (HR, 0.43; 95% CI, 0.17 to 1.08; P = 0.07) (Figure 6, A and B).

Sensitivity Analysis in Patients with RKF Data

Propensity score matching in patients with RKF data confirmed primary findings: both early-start and late-start icodextrin groups had higher ultrafiltration versus matched glucose users and early-start predicted slower RKF decline (Supplemental Table 6). Late icodextrin start was associated with higher risk of hemodialysis transfer or death versus early-start (HR, 3.98; 95% CI, 1.20 to 13.2; P = 0.02; Supplemental Table 7). No difference was seen between early-start and matched glucose users (log-rank P = 0.96). The lower risk in late-start versus glucose users was not statistically significant (HR, 0.55; 95% CI, 0.20 to 1.49; P = 0.08).

Peritonitis and Leaks Associated Access Revision Rates

Peritonitis rates were similar in the "early-start" and "late-start" groups (0.27 versus 0.26 episodes/person-year; P = 0.68) comparable with the respective matched glucose users (0.26 and 0.23 episodes/patient-year; P = 0.75 and P = 0.99]. Access revision rates due to

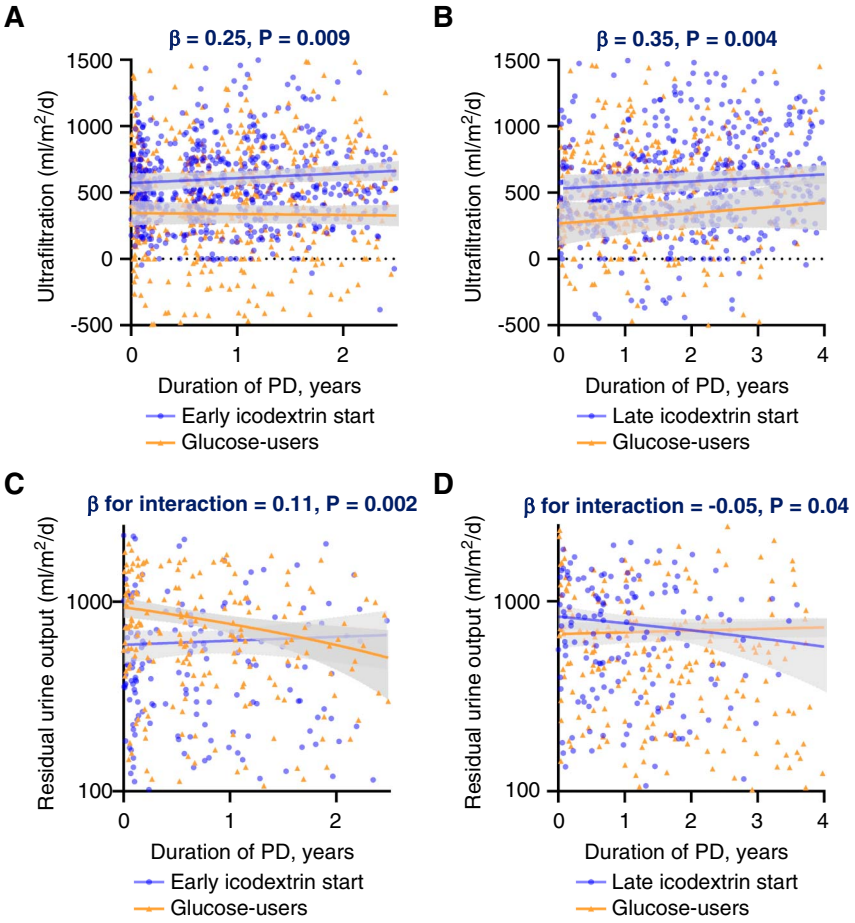

Figure 4. Ultrafiltration and residual urine output trajectories in early and late Icodextrin users vs glucose-matched controls. Slope of ultrafiltration adjusted for BSA over cumulative time on PD in patients with (A) early and (B) late icodextrin start compared with respective matched glucose users. Slope of RKF over cumulative time on PD in patients with (C) early and (D) late icodextrin start compared with respective matched glucose users. Solid lines show the predicted mean trajectory, and gray areas represent 95% CI. BSA, body surface area; RKF, residual kidney function.

dialysate leaks were reported in 30 patients—two among those using icodextrin and 28 in patients receiving glucose-based solutions (0.008 versus 0.02 episodes per 1000 patient-years, respectively; $P = 0.02$).

Subgroup Analysis: Comparison of Icodextrin Use in Younger (<5 Years) and Older (5 Years and Older) Children

Ultrafiltration (adjusted to BSA) was comparable in children younger than 5 years (n=76 with median age 2.5 year; 25.8% of the cohort) and 5 years and older (n=219, median age 13.2 year) at icodextrin start (Supplemental Table 8). Icodextrin fill volume was 510 (351–653) ml/m^2 in younger children compared with 625 (502–782) ml/m^2 in those 5 years and older ($P < 0.001$). Younger patients on icodextrin were more likely to have uncontrolled hypertension, but the two groups were otherwise comparable for sex, primary kidney disease, geographic region, and history of dialysis (Supplemental Table 8). Multivariable linear mixed-effects models, adjusted for sex, region, and disease etiology, showed comparable slopes of ultrafiltration (adjusted to BSA) and diastolic BP SDS in the two groups (Supplemental Table 9). Patients on icodextrin younger than 5 years showed better preservation of RKF over time on PD compared with those older than 5 years receiving icodextrin (β=0.09, $P < 0.001$; Supplemental Table 9).

Discussion

We examined the effect of icodextrin use on ultrafiltration, BP, RKF and the risks of mortality, technique failure, and peritonitis in a large international, prospective cohort of children undergoing maintenance PD. Prescription patterns varied by region, with early use favored in Western Europe. Icodextrin used within 1 year of initiating PD was associated with a five-fold lower risk of technique failure and mortality than delayed use. Early icodextrin use was also associated with improved BP and better preservation of RKF compared with glucose-only solutions.

We observed significant variability in icodextrin prescription practices even within countries from similar geographic regions. Analyses were adjusted for biocompatible fluid use since their prescription correspond to that of icodextrin in some areas of the world. However, differences in icodextrin use, particularly in Western Europe, suggest that regional protocols and availability play a larger role than economic factors. International adult PD registries show that differences in center-level protocols,

Table 5. Ultrafiltration, BP control, and preservation of RKF at follow-up analyzed in (A) "early-start" and (B) "late-start" icodextrin groups compared with matched glucose users in each group

Parameters	(A) Early Icodextrin Start and Matched Glucose Users N=179+179			(B) Late Icodextrin Start and Matched Glucose Users N=116+116		
	β	95% CI	P	β	95% CI	P
(1) Association with ultrafiltration adjusted for BSA, L/m² per d						
(Intercept)	0.05	−0.34 to 0.73	<0.001	0.20	−0.15 to 0.46	0.32
PD duration, yr	−0.04	−0.15 to 0.06	0.41	0.03	−0.05 to 0.11	0.45
Residual urine output, L/m² per d	−0.27	−0.39 to −0.14	<0.001	−0.33	−0.47 to −0.18	<0.001
Day fill volume, L/m²				0.23	−0.04 to 0.46	0.06
Icodextrin versus glucose dialysate	0.25	0.07 to 0.44	0.009	0.35	0.11 to 0.58	0.004
PD duration[a] icodextrin dialysate	0.07	−0.08 to 0.22	0.39	−0.02	−0.09 to 0.08	0.96
(2) Association with diastolic BP SDS						
(Intercept)	0.19	−0.27 to 0.67	0.41	0.64	0.12 to 1.17	0.01
PD duration, yr	−0.15	−0.29 to 0.01	0.04	−0.10	−0.21 to 0.004	0.06
Residual urine output, L/m² per d				−0.24	−0.46 to −0.04	0.02
Icodextrin versus glucose dialysate	−1.31	−1.73 to −0.89	<0.001	0.18	−0.22 to 0.58	0.38
PD duration[a] icodextrin dialysate	−0.10	−0.30 to 0.11	0.34	0.00	−0.12 to 0.11	0.93
(3) Association with residual kidney function, ml/m² per d						
(Intercept)	2.5	2.4 to 2.6	<0.001	2.7	2.6 to 2.9	<0.001
Baseline urine output, per 100 ml[b]	0.04	0.03 to 0.04	<0.001	0.03	0.02 to 0.03	<0.001
PD duration, yr	−0.11	−0.16 to −0.07	<0.001	−0.02	−0.06 to 0.02	0.36
Icodextrin versus glucose dialysate	−0.12	−0.20 to −0.05	0.001	−0.01	−0.09 to 0.11	0.86
Previous dialysis	−0.08	−0.17 to 0.01	0.08	−0.09	−0.18 to −0.00	0.05
Diuretics				−0.06	−0.12 to −0.00	0.07
RAAS inhibitors	−0.05	−0.11 to 0.00	0.07	−0.06	−0.12 to −0.00	0.04
Interaction of PD duration and icodextrin versus glucose dialysate	0.11	0.04 to 0.17	0.002	−0.05	−0.09 to 0.−0.002	0.04

Models adjusted for age, sex, geographic region, and etiology of disease (glomerular versus nonglomerular disease).
Covariates included: model (*1*) residual kidney function, albumin, day fill volume per BSA, previous PD; model (*2*) residual kidney function, ultrafiltration; and model (*3*) use of diuretics and RAAS inhibitors, previous dialysis, baseline urine output.
A β coefficient from the linear mixed models represents the average change in the continuous outcome variable over the entire course of follow-up associated with a one-unit increase in a continuous explanatory covariate (or a change in level compared with the reference group for a categorical explanatory covariate), while holding all other covariates in the model constant and accounting for repeated measurements within individuals. Specifically, the β coefficient for the interaction term PD duration.
BSA, body surface area; PD, peritoneal dialysis; RAAS, renin-angiotensin-aldosterone system; SDS, SD score.
[a]Icodextrin dialysate represents the difference in the slope of outcome change over time on PD between icodextrin users and glucose users (the reference group).
[b]Patients with urine output >100 ml/m² per day at baseline included for analysis; urine output is log transformed to satisfy normality.

including that for routine peritoneal membrane function testing, may account for about 25% of this variability.[14,15] In this study, icodextrin use was associated with high membrane transport status, consistent with recommendations for long dwells in high transporters.[16,17] However, membrane transport testing in a subset showed that approximately 40% of icodextrin users were low or low-average transporters, suggesting center practices, not transport status, primarily guided use. Use in low transporters is justified by randomized controlled trials (RCTs) showing improved ultrafiltration and BP control across all transport types.[18,19] In our study, conversion to icodextrin from glucose-based dialysis solutions was associated with low RKF, hypertension, low serum albumin, and high glucose exposure, factors indicating that fluid overload was already established and prompted the use of icodextrin to enhance ultrafiltration. Differences in icodextrin prescribing across pediatric centers may stem from limited data on its effect on technique survival and mortality; adult trials may suffer from low power and short follow-up to study these outcomes adequately.[9,20]

Our study shows that an "early-start" of icodextrin confers patient and technique survival advantages compared with delayed icodextrin use. These findings align with adult registry data showing lower mortality and technique failure rates in early icodextrin users (within 180 days of PD start) compared with propensity matched glucose users[21] and a 12% reduction in technique failure within the first year.[22] Furthermore, we have shown that icodextrin was more often prescribed to patients with surrogate markers of overhydration and ultrafiltration failure risk. The improved outcomes in this group suggest icodextrin may offset survival disadvantages in high-risk patients— a hypothesis supported by national cohort studies,[21,23–25] and adjusting for modality, membrane transport type, and RKF,[23] but not by the PD Outcomes and Practice Patterns Study, where icodextrin was used reactively in sicker patients.[14] Thus, the results of our study, together with the above data in adults, support the real-world advantage associated with icodextrin, especially when used early. In our study, late-starters exhibited lower serum albumin, higher parathyroid hormone levels,

Table 6. Factors associated with composite outcome of technique failure and death in icodextrin users

Characteristic	Model 1		Model 2	
	HR (95% CI)	*P*	HR (95% CI)	*P*
Timing of icodextrin start				
Early-start	Reference		Reference	
Late-start	5.16 (1.57 to 17.0)	0.007	3.76 (1.14 to 12.4)	0.03
Age, yr	0.95 (0.87 to 1.05)	0.34	0.99 (0.90 to 1.09)	0.87
Male sex	0.59 (0.20 to 1.71)	0.33	0.65 (0.20 to 2.10)	0.47
Glomerular etiology	0.80 (0.24 to 2.71)	0.72	0.53 (0.14 to 1.98)	0.35
Region				
Western Europe	—		—	
Asia	0.17 (0.02 to 1.49)	0.11	0.14 (0.02 to 1.33)	0.09
Eastern Europe	1.35 (0.40 to 4.57)	0.63	0.53 (0.13 to 2.13)	0.37
North America	0.43 (0.04 to 4.46)	0.48		
Albumin, g/l	0.85 (0.77 to 0.94)	0.001	0.85 (0.76 to 0.95)	0.006
Previous dialysis	3.81 (1.13 to 12.9)	0.03		
Residual urine output, per 100 ml/m^2 per d			0.76 (0.52 to 1.11)	0.15

Hazard ratio and 95% confidence intervals are obtained in proportional hazards models. All models adjusted for patients' visit age, sex, geographic region, and etiology of disease (glomerular versus nonglomerular disease). Covariates in both models include previous dialysis, previous transplant, PD vintage, serum albumin, biocompatible fluid use, hypertension and additionally glucose exposure in model 1 (n=295), and time-varying ultrafiltration and residual kidney function in model 2 (n=241)
Unadjusted event rates for early-start and late-start groups are 0.03 per 10-person years (8 events in 2681 person-years) and 0.05 per 10-person years (11 events in 2118 person-years), respectively. Covariates were eliminated through backward elimination based on akaike information criterion (AIC) in model 2.

and increased use of phosphate binders, suggesting more advanced CKD that may have contributed to their higher mortality and technique failure. Alternatively, the late-starters may have delayed conversion until complications necessitating a switch to icodextrin. Therefore, we propose that starting icodextrin early and preemptively before the development of overt volume overload or complications of CKD is beneficial in the long-term rather than using icodextrin as a salvage therapy,[26] especially in patients at high-risk for membrane failure.

Our study confirms that peritoneal ultrafiltration is significantly augmented with icodextrin compared with

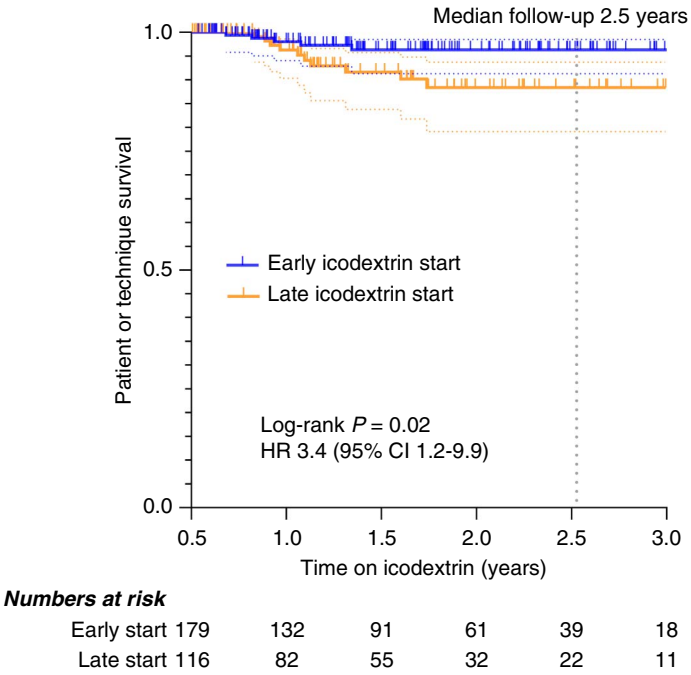

Figure 5. Kaplan-Meier estimates of composite end point of technique and patient survival in 179 patients with early icodextrin start and 116 with late icodextrin start. The median cumulative time on icodextrin was 2.5 years (dashed line). The risk of technique failure or noninfectious dialysis related death was 3.6% in early-start versus 13.5% in the late-start group at 2.5 year of icodextrin use (log-rank P = 0.02).

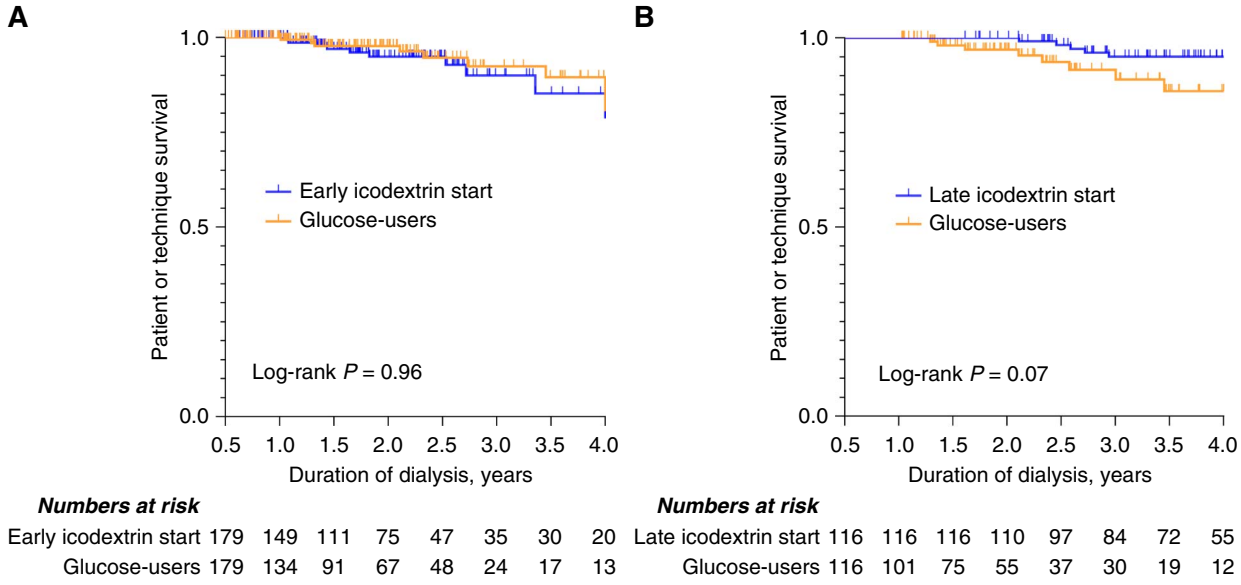

Figure 6. Technique and patient survival by timing of icodextrin start vs. glucose matched cohort. Kaplan-Meier estimates of composite end point of technique and patient survival in patients with early icodextrin start (A) and late icodextrin start (B) compared with respective matched glucose users.

glucose solutions, consistent with adult meta-analyses.[9,20,27,28] This is clinically relevant, as the multicenter initiative for patient outcomes in dialysis-peritoneal dialysis study of over 700 adults found that volume overload, measured by bioimpedance, to be an independent predictor of mortality and hemodialysis need.[29] Our study demonstrates that icodextrin provides a sustained ultrafiltration advantage over glucose-based dialysate, supporting better volume control throughout follow-up—especially in early users. This benefit may translate into significant patient and technique survival gains in adequately powered future studies. Early icodextrin use also led to better BP control, aligning with adult RCTs showing improved hypertension management and reduced need for antihypertensives.[30–33]

We have shown that early initiation of icodextrin was associated with superior preservation of RKF, likely driven by more consistent volume control and sustained urine output throughout the day, despite higher baseline glucose exposure in these patients. Our observation of a slower decline in residual function among icodextrin users aligns with findings from a recent enriched systematic review of 19 RCTs (N=1693), which included five trials providing high-certainty evidence that icodextrin preserves RKF even with reduced extracellular volume.[20] A positive association between icodextrin use and lower urine volumes, reported in a previous IPPN study, might have suggested more rapid loss of RKF in icodextrin compared with glucose-based dialysis. However, it is most likely that patients with failing RKF were selectively treated with icodextrin.[34] By contrast, our propensity matched analysis—accounting for demographics, disease etiology, baseline urine output, and biocompatible fluid use—allows a more valid assessment of the influence of icodextrin on RKF.

It has been suggested that icodextrin may behave differently in young children: a study of 8 children (median age 2.8 years) found half showed icodextrin reabsorption even with reduced dwell times, mostly in high transporters.[35] Approximately 25% of patients who received icodextrin in our study were younger than 5 years and, contrary to the literature, showed comparable ultrafiltration (adjusted to BSA) and BP control compared with older children, indicating its efficacy in younger children. Older studies linked ultrafiltration with age and height,[35,36] but fill volume also plays a key role, with a fill volume of $>$ 550 ml/m^2 BSA being associated with a higher ultrafiltrate.[10] Our average icodextrin fill volume was 559 ml/m^2 BSA, possibly explaining the better outcomes in our young cohort. Despite benefits, factors such as the increased risk of hernia and leaks in young children, or concerns about body perception in adolescents with large daytime dwell volumes, should be considered when prescribing icodextrin. These concerns, based on previous reports, were not assessed systematically in the present analysis. In our analysis, which focused on dialysate leaks requiring access revisions, the incidence was lower in the icodextrin group, although the low event rate limits the clinical significance of this finding.

Although this largest study performed on icodextrin use in children provides real-world prescription practices in an international cohort and is generalizable to pediatric chronic PD patients on automated PD with a daytime dwell, some limitations of our work must be acknowledged. The observational nature of the study precludes causal inference. Limitations of registry data include averaged values of glucose exposure, ultrafiltration, and urine output. Although propensity score matching was used to mitigate indication bias, unmeasured factors such as membrane transport status, center-specific prescribing practices, and clinician decision making could not be accounted for, and residual confounding may persist. A sensitivity analysis restricted to patients with complete data on RKF yielded consistent results, supporting the robustness of our findings. The small event rate of technique failure/deaths may not provide sufficient power in survival analyses. Our study lacked objective measurements of volume

status by bioimpedance spectroscopy or echocardiographic parameters, levels of serum sodium, and assessment of dietary salt and fluid intake. The number of patients receiving different types of biocompatible fluids (Physioneal, Balance, and BicaVera) was too low and variably distributed across groups to allow for subgroup analysis. Owing to the exploratory nature of the study no formal sample size estimation was performed. Caution with icodextrin use is required due to risks of hyperosmolar hyponatremia and risk of long-term peritoneal membrane damage from acidic pH that were not analyzed in this study.

In summary, we show that icodextrin was independently associated with a higher sustained ultrafiltration compared with glucose-based dialysis. "Early-start" of icodextrin within a year of PD initiation conferred over a five-fold greater technique and patient survival compared with delayed start as well as better BP control and preservation of RKF. Therefore, we strongly advocate for a proactive approach to icodextrin use earlier in the PD course to improve patient outcomes.

Disclosures

Disclosure forms, as provided by each author, are available with the online version of the article at http://links.lww.com/CJN/C416.

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Declarative Statements

This study includes clinical experimentation and received Institutional Review Board or Ethics Committee approval. All patients provided written informed consent. This study includes clinical experimentation and complies with the Declaration of Helsinki.

Data Availability Statement

Original data generated for the study are or will be made available in a public access repository upon publication. Data Type: Observational Data. Repository Name: Other. The data (completely deidentified IPPN registry data) supporting the findings of this study are openly available in repository Mendeley Data at 10.17632/gnnw45mdtm.1.

Supplemental Material

This article contains the following supplemental material online at http://links.lww.com/CJN/C417.

Supplemental Table 1. Four analytical cohorts with their corresponding exposure, outcomes, and covariates.

Supplemental Table 2. Multivariable logistic regression models predicting icodextrin use versus glucose-only use analyzed separately for (*1*) early and (*2*) late icodextrin users, before and after propensity score matching. Matching was performed based on age, sex, geographical region, primary kidney disease, and dialysis vintage at icodextrin initiation.

Supplemental Table 3. Characteristics of icodextrin users (early-start and late-start) compared with matched glucose users.

Supplemental Table 4. Clinical and biochemical characteristics at the time of initiation of icodextrin 9.

Supplemental Table 5. Factors associated with glucose exposure in icodextrin users at follow-up.

Supplemental Table 6. Sensitivity analysis: ultrafiltration and BP control at follow-up in patients with urine output data. Sensitivity analysis in (A) "early-start" and (B) "late-start" icodextrin groups compared with matched glucose users in each group.

Supplemental Table 7. Sensitivity analysis: Factors associated with composite outcome of technique failure and death in icodextrin users restricted to patient with available data on RKF.

Supplemental Table 8. Clinical and biochemical features at the time of initiation of icodextrin in patients <5 and ≥5 years.

Supplemental Table 9. Ultrafiltration, BP control, and preservation of RKF at follow-up in patients <5 and ≥5 years on icodextrin.

Supplemental Figure 1. Love plot showing standardized mean differences for covariates between glucose users and early (A and B) or late (C and D) icodextrin groups, before (red) and after (blue) propensity score matching. The sensitivity analysis (B and D) was restricted to patients with available data on RKF.

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