Icodextrin Versus Glucose Solutions for the Once-Daily Long Dwell in Peritoneal Dialysis: An Enriched Systematic Review and Meta-analysis of Randomized Controlled Trials

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Rationale & Objective: The efficacy and safety of icodextrin versus glucose-only peritoneal dialysis (PD) regimens is unclear. The aim of this study was to compare once-daily long-dwell icodextrin versus glucose among patients with kidney failure undergoing PD.

Study Design: Systematic review of randomized controlled trials (RCTs), enriched with unpublished data from investigator-initiated and industry-sponsored studies.

Setting & Study Populations: Individuals with kidney failure receiving regular PD treatment enrolled in clinical trials of dialysate composition.

Selection Criteria for Studies: Medline, Embase, CENTRAL, Ichushi Web, 10 Chinese databases, clinical trials registries, conference proceedings, and citation lists from inception to November 2018. Further data were obtained from principal investigators and industry clinical study reports.

Data Extraction: 2 independent reviewers selected studies and extracted data using a prespecified extraction instrument.

Analytic Approach: Qualitative synthesis of demographics, measurement scales, and outcomes. Quantitative synthesis with Mantel-Haenszel risk ratios (RRs), Peto odds ratios (ORs), or (standardized) mean differences (MDs). Risk of bias of included studies at the outcome level was assessed using the Cochrane risk-of-bias tool for RCTs.

Results: 19 RCTs that enrolled 1,693 participants were meta-analyzed. Ultrafiltration was improved with icodextrin (medium-term MD, 208.92 [95% CI, 99.69-318.14] mL/24 h; high certainty of evidence), reflected also by fewer episodes of fluid overload (RR, 0.43 [95% CI, 0.24-0.78]; high certainty). Icodextrin-containing PD probably decreased mortality risk compared to glucose-only PD (Peto OR, 0.49 [95% CI, 0.24-1.00]; moderate certainty). Despite evidence of lower peritoneal glucose absorption with icodextrin-containing PD (medium-term MD, −40.84 [95% CI, −48.09 to −33.59] g/ long dwell; high certainty), this did not directly translate to changes in fasting plasma glucose (−0.50 [95% CI, −1.19 to 0.18] mmol/L; low certainty) and hemoglobin A_{1c} levels (−0.14% [95% CI, −0.34% to 0.05%]; high certainty). Safety outcomes and residual kidney function were similar in both groups; health-related quality-of-life and pain scores were inconclusive.

Limitations: Trial quality was variable. The follow-up period was heterogeneous, with a paucity of assessments over the long term. Mortality results are based on just 32 events and were not corroborated using time-to-event analysis of individual patient data.

Conclusions: Icodextrin for once-daily long-dwell PD has clinical benefit for some patients, including those not meeting ultrafiltration targets and at risk for fluid overload. Future research into patient-centered outcomes and cost-effectiveness associated with icodextrin is needed.

The prevalence of kidney replacement therapy is expected to increase steeply.[1] Approximately 15% of dialysis patients globally use peritoneal dialysis (PD), and this proportion is increasing.[2] PD is probably associated

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with the same survival as hemodialysis (HD)[3-6] but presents certain lifestyle benefits (eg, patient satisfaction,[7-10] employment,[11-15] treatment flexibility,[16] and some aspects of health-related quality of life [HRQoL][17-21]). PD is not clinically appropriate for everyone,[22,23] and many patients require transfer to HD within their lifetime.[24-26]

The dialysate itself is an acknowledged Achilles heel of PD. Glucose is not an ideal osmotic agent because it is easily absorbed, thereby attenuating the osmotic gradient driving ultrafiltration (UF). This absorption can lead to hyperinsulinemia, hyperlipidemia, and weight gain.[27-29] Furthermore, glucose and its degradation products (GDPs) contribute to peritoneal fibrosis and vasculopathy and increased membrane permeability.[30-33] The resulting lower clearance of uremic toxins and volume overload probably contribute to the increased cardiovascular death in this population.[34-36]

Alternative osmotic agents have been a long-standing consideration.[37-39] Icodextrin is a soluble glucose

polymer that was first registered for sale in 1997, and is used widely (Fig S1). Three systematic reviews of randomized controlled trials (RCTs) have compared icodextrin-containing to glucose-only PD regimens.[40-42] However, their estimates of important outcomes such as mortality risk and hospitalization, as well as systemic metabolism and peritoneal function, have wide confidence intervals (CIs). This uncertainty may have arisen because of nonincluded evidence, such as unpublished data from published studies, studies published in non-English languages, and studies that have undergone regulatory as opposed to academic peer review.

The aim of this systematic review was to compare once-daily long-dwell icodextrin versus glucose in RCTs of patients with kidney failure undergoing PD. Primary outcomes were patient survival, PD technique survival, HRQoL, and UF volume. Secondary outcomes related to safety, kidney function, and laboratory parameters. A further aim was to incorporate evidence not previously meta-analyzed, with a view to a more comprehensive and transparent review. Key sources for obtaining additional data were manufacturers' clinical study reports (CSRs). These contain more complete clinical trial information,[43] and their inclusion in systematic reviews has been shown to reduce reporting biases,[44] particularly of harms outcomes.[45] Following calls for the release[46,47] and greater use of regulatory documents in systematic reviews,[48] this is the first case of industry volunteering these data for meta-analysis, as far as we are aware.

Methods

Study Reporting and Registration

This systematic review and meta-analysis is reported according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines.[49] The protocol was registered with PROSPERO (CRD42018096951)[50] and published prospectively.[51]

Eligibility Criteria and Outcomes

The population was adults and children with kidney failure receiving any type of PD. The intervention was long-dwell icodextrin used as a single osmotic agent, and the comparison was long-dwell glucose (any concentration) used as a single osmotic agent. Primary outcomes were patient survival (number of deaths during treatment), PD technique survival (number of conversions to HD), HRQoL (36-Item Short Form Health Survey [SF-36] generic questionnaire physical and mental component summaries; disease-specific modules' overall score), and peritoneal UF (net long-dwell UF in mL, total 24-hour UF in mL). Secondary outcomes were safety (serious and total adverse events [AEs] and AEs leading to withdrawal, hospitalizations, peritonitis, and uncontrolled fluid overload); kidney function (residual urine volume in mL/d; any other measure including weekly renal Kt/V_{urea} or residual glomerular filtration rate); drained body weight (in kg);

peritoneal creatinine and urea clearances (any measure); peritoneal glucose exposure (in g/24 h) and absorption (in g/long dwell); glycated hemoglobin {HbA_{1c}; %} level; plasma/serum concentrations of glucose, sodium, total cholesterol, and triglycerides (each in mmol/L); and inflow pain (number of events). Eligible study designs were (quasi-)RCTs (published and unpublished). There were no language or date restrictions.

Literature Search

The following databases were systematically searched from inception to November 2018: Medline (via PubMed), Embase, CENTRAL, Ichushi Web, and Chinese databases (China National Knowledge Infrastructure,[52] Chongqing,[53] Wanfang Data,[54] HK government library,[55] Hyread,[56] Ericdata,[57] National Digital Library of Theses and Dissertations in Taiwan,[4] Taiwan Journal Papers Index System,[5] TAO Taiwan Academic Online,[6] and Ariti Library[7]). Clinical trials registries were searched to identify ongoing and recently completed studies (ClinicalTrials.gov, International Clinical Trials Registry Platform, EU Clinical Trials Register, Japan registries network, and China's Clinical Trial Registry; Table S1). The search strategy was developed in collaboration with an experienced librarian and checked according to the Peer Review of Electronic Search Strategies guideline.[58] Table S2 provides details for all searches.

Between June and September 2018, all available conference proceedings of the American Society of Nephrology and International Society for Peritoneal Dialysis were screened. The reference lists of all included primary studies and relevant systematic reviews were manually cross-checked for additional studies. The relevant manufacturers (Baxter Healthcare[9] and Terumo[10]) were contacted to identify further studies and provide CSRs. In addition, principal investigators and other experts were contacted for additional references or data.

Study Selection

Two reviewers independently screened the titles and abstracts retrieved through Medline, Embase, and CENTRAL and assessed full texts of all potentially relevant articles against predefined selection criteria. Titles and abstracts identified in Ichushi-Web and Chinese databases were screened by 1 reviewer. Subsequently, abstracts and full texts of potentially relevant articles were assessed by 2 further reviewers. Disagreements were resolved through consensus or by consulting a third reviewer. Corresponding authors of eligible articles were contacted for clarification when necessary. Clinical trials registries were searched by 1 reviewer, and potentially relevant trials then were assessed by a further reviewer. Reasons for full-text exclusion were recorded (Table S3).

Data Extraction

Two reviewers independently extracted data using a standardized data extraction sheet. A predefined data set was collected for each trial, consisting of study characteristics

(country, number of centers, study duration, patient population, selection criteria, intervention and control group treatments, number of patients randomly assigned and analyzed, and funding source), patients' baseline characteristics (age, sex, body mass index, cause of kidney failure, peritoneal membrane transport characteristics by peritoneal equilibration testing, and residual glomerular filtration rate), and outcomes data for any time point reported. If a study generated multiple publications or unpublished reports, data were extracted from the most comprehensive and the others were used to complete this information. All authors were contacted for further data and clarification of discrepancies.

Assessment of Risk of Bias and Certainty of Evidence

Two reviewers independently assessed risk of bias of included studies at outcome level using the Cochrane risk-of-bias tool for RCTs.[59] The overall risk of bias for any study was considered high if any of the domains were judged to be at high risk of bias.

The reviewers independently assessed the certainty of evidence using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system, considering risk of bias, inconsistency, indirectness, imprecision, and other considerations (strength of the association and dose-response effects).[60-71] As is recommended by GRADE and the Cochrane Collaboration, assessment of the certainty of evidence was as high, moderate, low, or very low according to whether the results provided a very good, good, some, or unreliable indication of the likely effect, respectively. Standardized wording was used to report the estimated effects, based on the certainty of evidence in conjunction with the importance of the effect, also according to Cochrane Collaboration recommendations.[72]

Any disagreements were resolved through consensus or by consultation with a third reviewer.

Data Analysis/Statistics

For meta-analysis, trial results were grouped into short- (up to 6 weeks), medium- (3-6 months), and long-term treatment duration (1-2 years). No study had a duration between 6 weeks and 3 months or between 6 and 12 months. For studies reporting outcomes at multiple points in time, results were used for all available subgroups, each with the longest possible duration. Values reported as mg/dL were converted to mmol/L using molar weights. Mean and standard deviation (SD) values were estimated from median and interquartile range values using the method of Wan et al[73] and from 95% CIs using the methods recommended in the Cochrane Handbook.[74] In case no measure of variability was reported, SDs were imputed using the mean SD of all other studies in the same subgroup.[75,76] Intention-to-treat analyses were used when reported. When continuous data were available for only a fraction of the total population, an available-case analysis was

performed when possible to avoid inflating the precision of the effect estimate.[77] Data were meta-analyzed using RevMan, version 5.3 (Nordic Cochrane Centre, Cochrane Collaboration). Fixed-effect models were used for outcomes in the absence of heterogeneity ($I^2 = 0$), with sensitivity analyses using random-effects models. Otherwise, random-effects models were used. Dichotomous outcomes were analyzed using Mantel-Haenszel risk ratios (RRs) or, when event rates were low, Peto odds ratios (ORs). Continuous outcomes were pooled using the inverse-variance mean difference (MD) or the standardized MD. Absolute measures (risk difference or MD) were computed using GRADEpro GDT.[18,58] Point estimates were reported along with 95% CIs. Heterogeneity between trials was quantified using I^2 statistics.[78] For each outcome with 10 or more contributing studies, possible publication bias was evaluated by visual inspection of funnel plots for asymmetry (Fig S2) and by Egger test using Meta-Essentials, version 1.4.[79] For Egger test, the null hypothesis was that the funnel plot is symmetrical (measured by the intercept from regression of standard normal deviates against precision), with the alternative indicating the presence of funnel plot asymmetry. Data were entered by 1 reviewer and checked for accuracy and completeness by a second reviewer.

Forest plots for all outcomes that were meta-analyzed and further information on planned subgroup analyses (performed when data were available) and differences between protocol and review are provided in Figures S3-S7.[80]

Results

Search Results

The search of literature databases identified 895 articles. Additional records were obtained from trial registries (Table S2), Baxter Healthcare, and trial authors. Queries to Terumo did not provide any additional RCTs, nor did the manual search of conference abstracts. Thirty-nine documents (23 publications,[54,81-102] 10 CSRs,[103-112] and 6 data tables) related to 20 RCTs met inclusion criteria (Fig 1). Seventeen full-text articles were excluded (Table S3).

Trial and Patient Characteristics

Table 1 presents clinical characteristics of included trials. All were RCTs, 3 with crossover design.[81,98,102] Eligible patients were incident and prevalent adults receiving continuous ambulatory PD or automated PD, including diabetic,[93,99] nondiabetic,[81,86,88] or mixed patient collectives. Three studies[85,87,93] were limited to high/high-average transporters. The differential effects with these subpopulations were explored by subgroup analyses (Figs S4-S7).

Most trials explicitly excluded patients with acute peritonitis, but one focused specifically on such patients.[84] One study included solely patients with hypertension related to volume overload.[85] Baseline patient characteristics are detailed in Table S4.

Risk-of-Bias Assessment for Included Trials

The risk of bias of included studies is shown in Figure 2 (details in Table S5). Two studies were judged to be of high risk of bias overall[81,98] because of potential selective reporting, one of which was also of high risk of attrition bias.[98] For the remaining 18 RCTs, the overall risk of bias was low/unclear.

Grading of Recommendations

Table S6 provides the GRADE assessment by individual domains.[60] The certainty of evidence was high or moderate for 43 outcomes and low or very low for 12 outcomes. Table 2 shows GRADE assessment and summary of findings for selected outcomes.

Publication Bias

Visual inspection of the funnel plots showed no evidence of publication bias. Egger test did not reach statistical significance for 12 of 13 outcomes (Fig S2).

Patient Survival

Patient survival was reported by 19 RCTs (1,685 patients). Icodextrin-containing PD probably decreased mortality risk compared to glucose-only PD (Peto OR, 0.49 [95% CI, 0.24-1.00]; Figures 3 and S3A; for causes of death see Tables S7 and S8),[113] with moderate heterogeneity ($I^2 = 41\%$). The direction of this effect was consistent in the mid- and long-term subgroups, reflecting a cumulative dose effect. Only a single death occurred in all short-term

studies (641 participants). Heterogeneity may be: (1) clinical, with variable morbidity of populations (see Table S4), and (2) statistical, associated with the low event rate of 1.9%. Subgroup analyses for incident versus prevalent patients and diabetic versus nondiabetic patients (Figs S4A and S5A) showed the same trend.

The absolute control-group risk of death was 25 per 1,000 treated patients. In the icodextrin group, the risk difference was 13 fewer deaths per 1,000 (0-19 fewer). Our confidence in this result is moderate because despite low event rates, heterogeneity, and wide CIs, a positive effect emerges with long-term treatment and overall.

PD Technique Survival

PD technique survival was not defined consistently throughout studies, so we analyzed the number of conversions to HD. Pooled event rates for 18 contributing RCTs (1,401 participants) were low (2.6%). There was no difference between icodextrin and glucose overall (Peto OR, 0.77 [95% CI, 0.39-1.50]; moderate certainty) or for any subgroups (<6 weeks, 1.06 [95% CI, 0.07-17.03]; 3-6 months, 0.59 [95% CI, 0.23, 1.54]; 1-2 years, 0.98 [95% CI, 0.36-2.68]; incident patients [Fig S4B], 1.29 [95% CI, 0.28-6.03], prevalent patients, 0.81 [95% CI, 0.35-1.84]; diabetic patients [Fig S5B], 1.97 [95% CI, 0.50-7.69]; or nondiabetic patients [Fig S5B], 0.98 [95% CI, 0.27-3.60]). The absolute control-group rate of conversion to HD was 29 per 1,000 patients. The overall certainty of the evidence
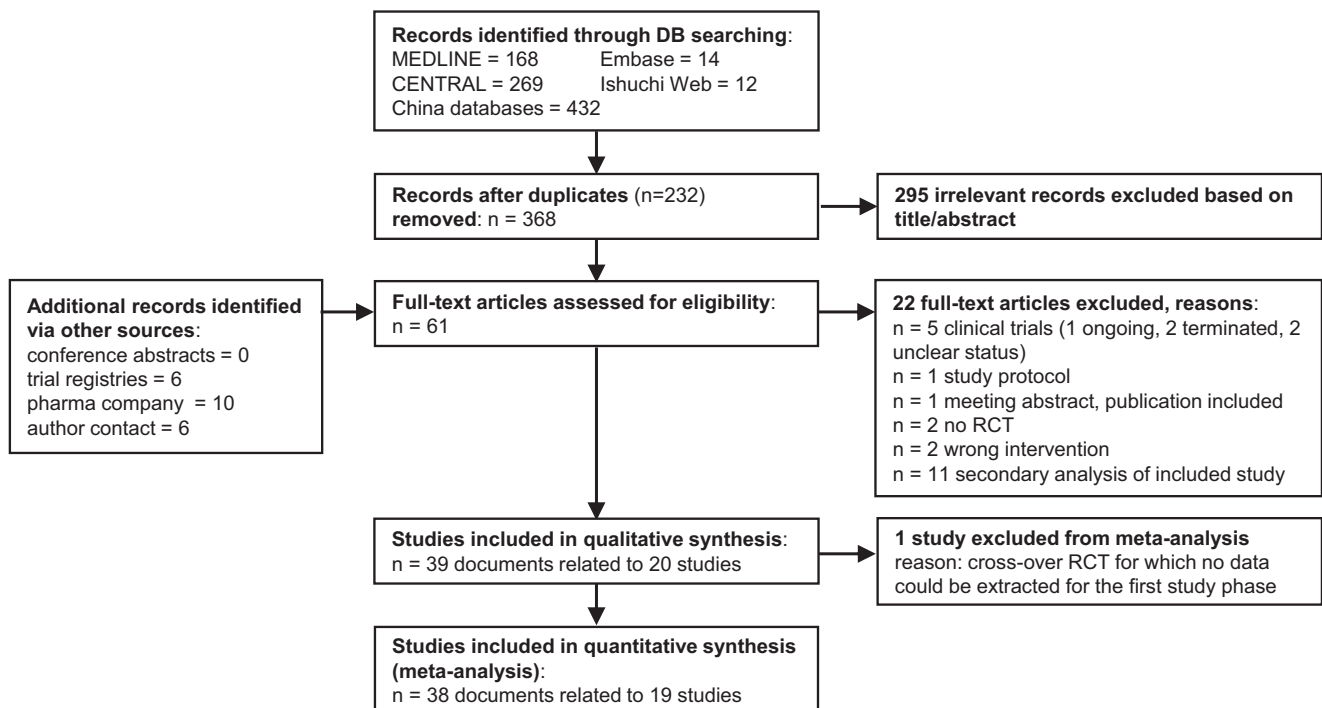
Figure 1. Flow diagram shows the systematic literature search and selection of articles. Abbreviation: RCT, randomized controlled trial.

Table 1. Clinical Characteristics of Included Studies

Study	Design, Duration, Funding	Setting; N	Patient Population	Key Exclusion Criteria	Intervention	Control
Bredie[81] (2001)	Crossover RCT, 6 + 6 wk, public + Baxter	1 center in NL; 22	Prevalent CAPD	Peritonitis, DM	Noct 1× ico + day 2-3× ≥1.36% glu (Dianeal)	Noct 1× ≥1.36% glu + day 2-3× ≥1.36% glu (Dianeal)
Chang[82] (2016)	Open-label RCT, 12 mo, Baxter	8 centers in KR; 49 ico, 51 glu	Incident + prevalent CAPD; urine ≥ 750 mL/d	<12-mo life expectancy; prior ico, APD, HD; volume overload	Noct 1× ico + day 2× 1.36% glu (Physioneal)	1× ≥2.27% + 2× 1.36% glu per 24 h (Physioneal)
Chen[83] (2018)	Open-label RCT, 2 y, Baxter	1 center in TW; 21 ico, 22 glu	Adults; incident APD	<12-mo life expectancy, serious disease	Day 1× ico + noct ≥1.36% glu (Dianeal) via auto cycles	Day 1-2× ≥1.36% glu + noct ≥1.36% glu via auto cycles (Dianeal)
Chow[84] (2014)	Open-label RCT, 4 mo, public	1 center in HK; 23 ico, 33 glu	Adults; prevalent CAPD; peritonitis	Prior ico, clinically unstable	Noct 1× ico + day 2-3× ≥1.36% glu (Dianeal)	3-4× ≥1.36% glu per 24 h (Dianeal)
Davies [85,103] (2003)	Double-blind RCT, 6 mo, Baxter	Multiple centers in DE, SE, UK; 28 ico, 22 glu	Adults; prevalent CAPD/APD; PD: ≥2.27% glu avg over day; urine > 750 mL/d; H/HA; fluid overload	<12-mo life expectancy, peritonitis, prior ico, other PD soln	Noct 1× ico (CAPD) or day 1× ico (APD) + BL PD Rx (fixed) for rest of 24 h (Dianeal)	Noct 1× 2.27% glu (CAPD) or day 1× 2.27% glu (APD) + BL PD Rx (fixed) for rest of 24 h (Dianeal)
de Moraes[86] (2015)	Open-label RCT, 3 mo, Baxter	7 centers in BR; 33 ico, 27 glu	Adults; prevalent APD; H/HA/LA	Peritonitis; DM; <12-mo life expectancy; HIV, cancer	Day 1× ico + noct ≥1.36% glu (Dianeal) via auto cycles	Day 1× 2.27% glu + noct ≥1.36% glu via auto cycles (Dianeal)
Finkelstein[87,104] (2005)	Double-blind RCT, 2 wk, Baxter	US, AU; 47 ico, 45 glu	Adults; prevalent APD; H/HA	Peritonitis	Day 1× ico + BL PD Rx (fixed) for rest of 24 h (Dianeal)	Day 1× 3.86% glu + BL PD Rx (fixed) for rest of 24 h (Dianeal)
Konings[88] (2003)	Open-label RCT, 4 mo, Baxter	6 centers in NL, DE; 22 ico, 18 glu	Prevalent CAPD/APD	Peritonitis, type 1 DM, cancer, CHF/CAD ≥ NYHA III	Noct 1× ico (CAPD) or day 1× ico (APD) + BL PD Rx (fixed) for rest of 24 h (Dianeal)	Noct 1× 1.36% glu (CAPD) or day 1× 1.36% glu (APD) + BL PD Rx (fixed) for rest of 24 h (Dianeal)
Lin[89,105] (2009)	Double-blind RCT, 4 wk, public	7 centers in CN; 98 ico, 103 glu	Adults; prevalent CAPD; PD: 2.27% glu long-dwell, any transporters	Infection; hepatitis, cancer, cardiac diseases	Noct 1× ico + day 2-3× 1.36%-2.27% glu (Dianeal)	Noct 2.27% glu + day 2-3× 1.36%-2.27% glu (Dianeal)
Mistry[90,91,106] (1994)	Open-label RCT, 6 mo, M. L. Labs[a]	11 centers in UK; 106 ico, 103 glu	Adults; prevalent CAPD; ≤1× 3.86% glu	Peritonitis	Noct 1× ico + day 2-3× ≥1.36% glu (Dianeal)	Noct 1× ≥1.36% glu + day 2-3× ≥1.36% glu (Dianeal)
Ota[92,107] (2003)	Double-blind RCT, 4 wk, Baxter	16 centers in JP; 28 ico, 29 glu	Adults; prevalent CAPD	Peritonitis; infection, hepatitis, cancer	Noct 1× ico + day 3-4× 1.36%-2.27% glu (Dianeal)	Noct 1× 1.36%-2.27% glu + day 3-4× 1.36%-2.27% glu (Dianeal)
Paniagua[93] (2009)	Open-label RCT, 12 mo, public + Baxter	4 centers in MX; 30 ico, 29 glu	Adults; prevalent CAPD; DM; H/HA	Peritonitis, hepatitis, HIV, cancer	Noct 1× ico + day 3× ≥1.36% glu (Dianeal)	Noct 1× ≥2.27% glu + day 3× ≥1.36% glu (Dianeal)
Plum[94,108] (2002)	Open-label RCT, 12 wk, Baxter	8 centers in EU; 20 ico, 19 glu	Prevalent APD; PD: 2.27% glu long-dwell	Dry period infection, peritonitis, hepatitis, HIV, cancer	Day 1× ico + noct ≥1.36% glu (Dianeal) via auto cycles	Day 1× 2.27% glu + noct ≥1.36% glu via auto cycles (Dianeal)
Posthuma[95-97,109] (2000)	Open-label RCT, 1 y, public + M. L. Labs[a]	1 center in NL; 19 ico, 19 glu	Adults; incident + prevalent APD	Peritonitis, <24-mo life expectancy	Day 1× ico + noct ≥1.36% glu (Dianeal) via auto cycles	Day 1× ≥1.36% glu + noct ≥1.36% glu via auto cycles (Dianeal)
Rodríguez-Carmona[98] (2007)	Crossover RCT, 10+10 d, Baxter	1 center in ES; 21	Prevalent APD	NR	Day 1× ico + noct ≥1.36% glu & 1.1% amino acid soln (Dianeal, Nutrineal) via auto cycles	Day 1× ≥1.36% glu + noct ≥1.36% glu & 1.1% amino acid soln via auto cycles (Dianeal, Nutrineal)

(Continued)

Table 1 (Cont'd). Clinical Characteristics of Included Studies

Study	Design, Duration, Funding	Setting; N	Patient Population	Key Exclusion Criteria	Intervention	Control
Takatori[99] (2011)	Open-label RCT, 2 y, public	23 centers in JP; 21 ico, 20 glu	Adults; incident CAPD/APD; DM; urine ≥ 400 mL/d	Cancer, prior PD	Noct 1× ico + day ≤3× 1.36%-2.27% glu (Dianeal)	≤4× 1.36%-2.27% glu per 24 h (Dianeal)
Wolfson A[100,110] (2002)	Double-blind RCT, 4 wk, Baxter	36 centers in US, CA; 90 ico, 85 glu	Adults; prevalent CAPD/APD; PD: 2.27% glu long-dwell	Peritonitis, liver disease	Noct 1× ico (CAPD) or day 1× ico (APD), PD Rx for rest of 24 h unclear	Noct 1× 2.27% glu (CAPD) or day 1× 2.27% glu (APD), PD Rx for rest of 24 h unclear
Wolfson B[54,100,111] (2002)	Double-blind RCT, 12 mo, Baxter	42 centers in US, CA; 175 ico, 112 glu	Adults; prevalent CAPD/APD; PD: 2.27% glu long-dwell	Peritonitis, liver disease	Noct 1× ico (CAPD) or day 1× ico (APD), PD Rx for rest of 24 h unclear	Noct 1× 2.27% glu (CAPD) or day 1× 2.27% glu (APD), PD Rx for rest of 24 h unclear
Yoon[101] (2014)	RCT, 1 y, public	8 centers in KR; 41 ico, 39 glu	Incident CAPD	Cancer, liver cirrhosis, bedridden/tube-fed	Noct 1× ico + day 2× ≥1.36% glu (Physioneal)	3× ≥1.36% glu per 24 h (Physioneal)
Yu[102,112] (2002)	Crossover RCT, 4 + 4 wk, Baxter	1 center in TW; 44 ico, 44 glu	Adults; prevalent CAPD; PD: 2.27% glu long-dwell	Peritonitis, infection, cancer, HIV, liver disease	Noct 1× ico + day 3× ≥1.36% glu (Dianeal)	Noct 1× 2.27% glu + day 3× ≥1.36% glu (Dianeal)

Abbreviations: APD, automated peritoneal dialysis; AU, Australia; auto, automated; avg, average; BL, baseline; BR, Brazil; CA, Canada; CAD, coronary artery disease; CAPD, continuous ambulatory peritoneal dialysis; CHF, congestive heart failure; CN, China; day, daytime; DE, Germany; DM, diabetes mellitus; ES, Spain; EU, Europe; glu, glucose; H/HA/LA/L, high/high-average/low-average/low transporters; HD, hemodialysis; HIV, human immunodeficiency virus; HK, Hong Kong; ico, icodextrin; JP, Japan; KR, South Korea; MX, Mexico; NL, Netherlands; noct, nocturnal; NR, not reported; NYHA, New York Heart Association; PD, peritoneal dialysis; RCT, randomized controlled trial; Rx, prescription; SE, Sweden; soln, solution; TW, Taiwan; UK, United Kingdom; US, United States.
[a]M. L. Laboratories, the previous ico manufacturer.

was assessed to be moderate. The number of patients who received a kidney transplant was balanced between groups (Table S9).

Of note, not included in this analysis is that a large but unquantifiable proportion of patients in the glucose group of long-term studies underwent an increase in glucose concentration or icodextrin to obtain increased UF. This is an explicit finding in almost all of the long-term studies in the glucose groups, confounding the comparison with the icodextrin groups.[82,83,93,97,99,101] This favors technique survival in the glucose group by ameliorating UF failure and potentially masks benefit from icodextrin.

Quality of Life

HRQoL results were obtained from 2 RCTs with 12 months' duration, 1 with published[54] and 1 with unpublished[93] data. Results for the SF-36 generic questionnaire (MD for Physical Component Summary score, 0.95 [95% CI, −2.96 to 4.86]; MD for Mental Component Summary score, 0.33 [95% CI, −7.41 to 8.06]) and the overall score of disease-specific modules (MD, 0.60 [95% CI, −4.93 to 6.13]; Fig S3C) were inconclusive. No subgroup analyses were performed due to the small number of contributing studies.

Exclusion of the open-label study considered at high risk of bias for this outcome[93] did not change this conclusion. The certainty of the available evidence for all HRQoL outcomes is low or very low, mainly due to lack of blinding and the low number of contributing RCTs.

Peritoneal UF

UF (any measure) was more effective in the icodextrin than glucose group for up to 6 months, but no difference between groups was seen in the long-term (Fig 4A).

Sensitivity analysis excluding studies using neutral-pH low-GDP glucose dialysate in the control group[82,101] did not change the direction or magnitude of this effect (Fig S3D). The weighted mean net long-dwell UF in the glucose group was 261 (short term), 215 (medium term), and 465 mL (long term). It was higher for icodextrin versus glucose by 230 to 290 mL for any treatment duration (Fig S3E). A similar effect was also demonstrable for UF expressed as mL per day (Fig S3F). The overall certainty of evidence is high for up to 6 months' treatment duration but was downgraded for the long-term subgroup because of unexplained heterogeneity.

In the subgroup analysis for transport category, the superiority of icodextrin versus glucose was large in both high/high-average and low-average transporters, whereas there was no difference in low transporters (Figs 4B and S6B). UF was improved with icodextrin compared with any strength of glucose PD solution (Fig S7C). Incident and prevalent patients (Fig S4C), as well as diabetic and nondiabetic patients (Fig S5C), benefited from icodextrin in terms of UF.
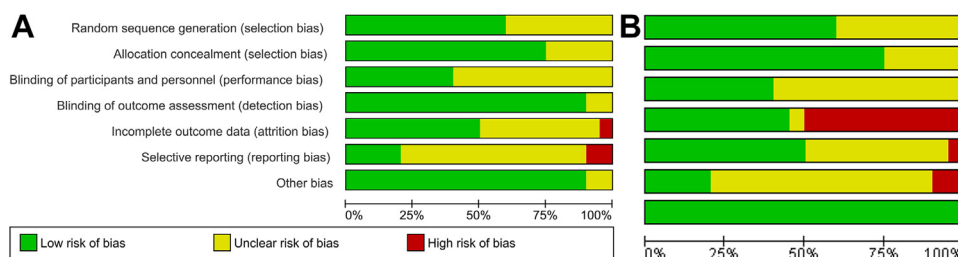
Figure 2. Review authors' judgments about each risk-of-bias item for (A) objective and (B) subjective outcomes for all 20 included studies.[139]

Adverse Events

Safety outcome results were similar for icodextrin and glucose, including the number of serious AEs (RR, 0.91 [95% CI, 0.76-1.10]; Fig S3G), total AEs (RR, 1.04 [95% CI, 0.94-1.16]; Fig S3H); AEs leading to withdrawal (RR, 0.87 [95% CI, 0.65-1.17]; Fig S3I), hospitalizations (RR, 0.81 [95% CI, 0.64-1.04]; Fig S3J), and peritonitis (RR, 1.08 [95% CI, 0.88-1.32]; Fig S3K). The certainty of the evidence is moderate to high for these safety outcomes.

Uncontrolled Fluid Overload

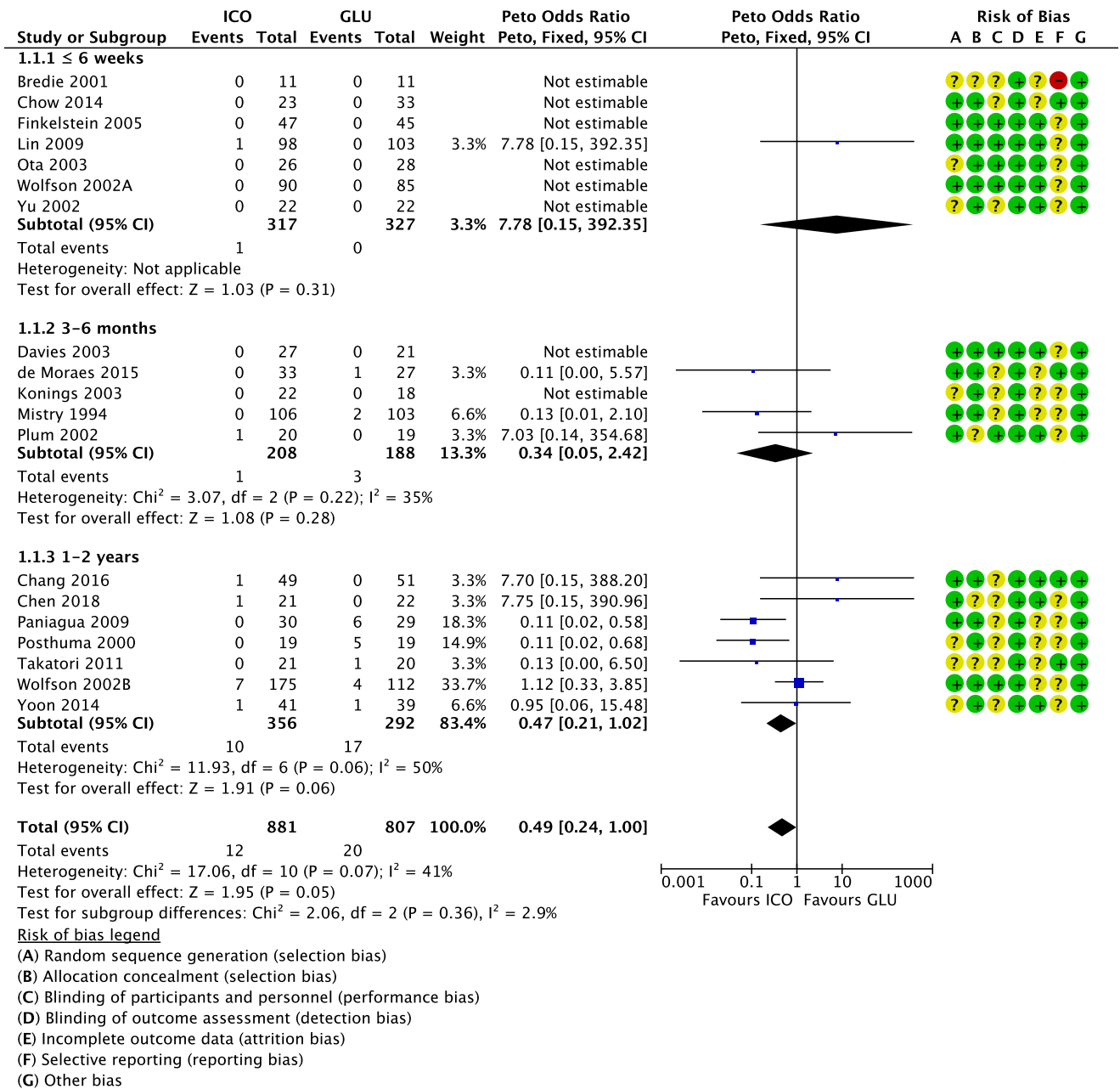Definitions of this outcome varied. The quoted definitions are "withdrew prior to study completion due to uncontrolled fluid overload"[82]; "shift to [icodextrin] use in [glucose] group, the reason is reduced UF capacity with [glucose] solution" (Dr Chen); "UF failure leading to withdrawal"[86]; "uncontrolled fluid overload"[90]; "uncontrolled fluid overload" (Dr Paniagua); "causes for withdrawal: water removal failure" (Dr Takatori); and "admitted to the hospital due to a reduced UF."[112]

Icodextrin reduced the risk for uncontrolled fluid overload overall and for the long-term subgroup (Figs 5 and S3L). The control group rate of uncontrolled fluid overload was 95 per 1,000 patients. Icodextrin led to a risk difference of 54 fewer per 1,000 (23-72 fewer). Our confidence in the evidence is high.

Table 2. Summary of Findings and Certainty of Evidence for Selected Outcomes GRADE)

| Outcome | No. of Pts (Studies) | Event Rates or No. of Pts | | Relative Effect (95% CI) | Anticipated Absolute Effects | | Overall Certainty of Evidence |
		Glucose	Icodextrin		Effect With Glucose	Difference With Icodextrin (95% CI)	
Primary Outcomes							
Mortality	1,685 (19 RCTs)	20/805 (2.5%)	12/880 (1.4%)	OR, 0.49 (0.24-1.00)	Risk was 25 per 1,000	RD, 13 fewer per 1,000 (19 fewer to 0 fewer)	⊕⊕⊕○ Moderate
PD technique failure	1,401 (18 RCTs)	20/695 (2.9%)	17/706 (2.4%)	OR, 0.77 (0.39-1.50)	Risk was 29 per 1,000	RD, 6 fewer per 1,000 (17 fewer to 14 more)	⊕⊕⊕○ Moderate
QoL[a]	116 (2 RCTs)	48	68	–	Weighted mean was 76.8	MD, 0.6 higher (4.93 lower to 6.13 higher)	⊕⊕○○ Low
Net peritoneal ultrafiltration							
≤6 wk	694 (6 RCTs)	358	337	–	Weighted mean was 261 mL	MD, 282.49 higher (238.31 higher to 326.67 higher)	⊕⊕⊕⊕ High
3-6 mo	362 (6 RCTs)	181	182	–	Weighted mean was 215 mL	MD, 286.45 higher (75.36 higher to 497.55 higher)	⊕⊕⊕⊕ High
1-2 y	104 (3 RCTs)	48	56	–	Weighted mean was 465 mL	MD, 237.38 higher (213.1 lower to 687.87 higher)	⊕⊕○○ Low
Secondary Outcomes							
SAE	1,303 (11 RCTs)	124/613 (20.2%)	142/690 (20.6%)	RR, 0.91 (0.76-1.10)	Risk was 202 per 1,000	RD, 18 fewer per 1,000 (49 fewer to 20 more)	⊕⊕⊕⊕ High
Pts with peritonitis	1,348 (15 RCTs)	117/631 (18.5%)	152/717 (21.2%)	RR, 1.08 (0.88-1.32)	Risk was 185 per 1,000	RD, 15 more per 1,000 (22 fewer to 59 more)	⊕⊕⊕⊕ High
Uncontr fluid overload	602 (8 RCTs)	28/295 (9.5%)	11/307 (3.6%)	RR, 0.43 (0.24-0.76)	Risk was 95 per 1,000	RD, 54 fewer per 1,000 (72 fewer to 23 fewer)	⊕⊕⊕⊕ High

Note: Only absolute values considered.
Abbreviations: CI, confidence interval; GRADE, Grading of Recommendations Assessment, Development and Evaluation; KDQOL, Kidney-Disease Specific Quality of Life; MD, mean difference; OR, odds ratio; PD, peritoneal dialysis; pt, patient; QoL, quality of life; RCT, randomized controlled trial; RD, risk difference; RR, risk ratio; SAE, serious adverse event; uncontr, uncontrolled.
[a]KDQOL disease-specific module.

Study or Subgroup	ICO Events	Total	GLU Events	Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
1.1.1 ≤ 6 weeks						
Bredie 2001	0	11	0	11		Not estimable
Chow 2014	0	23	0	33		Not estimable
Finkelstein 2005	0	47	0	45		Not estimable
Lin 2009	1	98	0	103	3.3%	7.78 [0.15, 392.35]
Ota 2003	0	26	0	28		Not estimable
Wolfson 2002A	0	90	0	85		Not estimable
Yu 2002	0	22	0	22		Not estimable
Subtotal (95% CI)		317		327	3.3%	7.78 [0.15, 392.35]
Total events	1		0			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.03 (P = 0.31)

Study or Subgroup	ICO Events	Total	GLU Events	Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
1.1.2 3–6 months						
Davies 2003	0	27	0	21		Not estimable
de Moraes 2015	0	33	1	27	3.3%	0.11 [0.00, 5.57]
Konings 2003	0	22	0	18		Not estimable
Mistry 1994	0	106	2	103	6.6%	0.13 [0.01, 2.10]
Plum 2002	1	20	0	19	3.3%	7.03 [0.14, 354.68]
Subtotal (95% CI)		208		188	13.3%	0.34 [0.05, 2.42]
Total events	1		3			

Heterogeneity: Chi² = 3.07, df = 2 (P = 0.22); I² = 35%
Test for overall effect: Z = 1.08 (P = 0.28)

Study or Subgroup	ICO Events	Total	GLU Events	Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
1.1.3 1–2 years						
Chang 2016	1	49	0	51	3.3%	7.70 [0.15, 388.20]
Chen 2018	1	21	0	22	3.3%	7.75 [0.15, 390.96]
Paniagua 2009	0	30	6	29	18.3%	0.11 [0.02, 0.58]
Posthuma 2000	0	19	5	19	14.9%	0.11 [0.02, 0.68]
Takatori 2011	0	21	1	20	3.3%	0.13 [0.00, 6.50]
Wolfson 2002B	7	175	4	112	33.7%	1.12 [0.33, 3.85]
Yoon 2014	1	41	1	39	6.6%	0.95 [0.06, 15.48]
Subtotal (95% CI)		356		292	83.4%	0.47 [0.21, 1.02]
Total events	10		17			

Heterogeneity: Chi² = 11.93, df = 6 (P = 0.06); I² = 50%
Test for overall effect: Z = 1.91 (P = 0.06)

	ICO Events	Total	GLU Events	Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Total (95% CI)		881		807	100.0%	0.49 [0.24, 1.00]
Total events	12		20			

Heterogeneity: Chi² = 17.06, df = 10 (P = 0.07); I² = 41%
Test for overall effect: Z = 1.95 (P = 0.05)
Test for subgroup differences: Chi² = 2.06, df = 2 (P = 0.36), I² = 2.9%

Forest plot x-axis: 0.001   0.1   1   10   1000 — Favours ICO   Favours GLU

Risk of Bias columns: A B C D E F G

Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
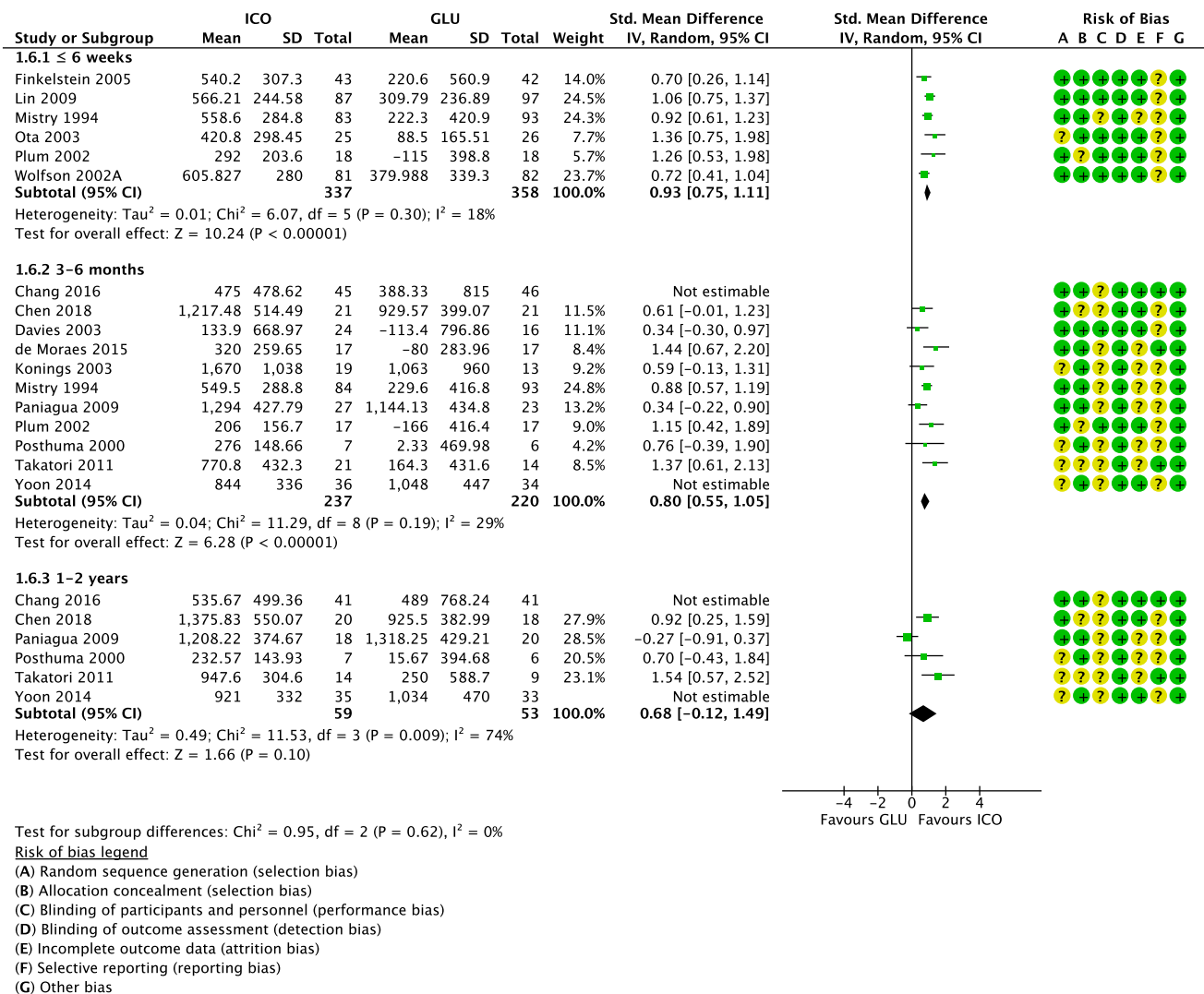(F) Selective reporting (reporting bias)
(G) Other bias

Figure 3. Mortality events; short term after 6 or more weeks, medium term after 3 to 6 months, and long term after 1 to 2 years. Risk of bias legend: (A) Random sequence generation (selection bias), (B) allocation concealment (selection bias), (C) blinding of participants and personnel (performance bias), (D) blinding of outcome assessment (detection bias), (E) incomplete outcome data (attrition bias), (F) selective reporting (reporting bias), and (G) other bias. Abbreviations: CI, confidence interval; GLU, glucose; ICO, icodextrin.

Glucose Exposure

Peritoneal membrane glucose exposure was defined as total amount of glucose infused over 24 hours. Patients in the icodextrin group were exposed to ~45 g less daily glucose than those in the glucose group (Fig S3M), with no observable differences by treatment duration.

Daily glucose absorption was defined as the difference between the total amount of glucose administered over 24 hours minus the amount remaining in drained effluent. In the icodextrin group, patients absorbed ~42 g less daily glucose than in the glucose group (Fig S3N), again with no differences by treatment duration.

Study or Subgroup	ICO Mean	ICO SD	ICO Total	GLU Mean	GLU SD	GLU Total	Weight	Std. Mean Difference IV, Random, 95% CI
1.6.1 ≤ 6 weeks								
Finkelstein 2005	540.2	307.3	43	220.6	560.9	42	14.0%	0.70 [0.26, 1.14]
Lin 2009	566.21	244.58	87	309.79	236.89	97	24.5%	1.06 [0.75, 1.37]
Mistry 1994	558.6	284.8	83	222.3	420.9	93	24.3%	0.92 [0.61, 1.23]
Ota 2003	420.8	298.45	25	88.5	165.51	26	7.7%	1.36 [0.75, 1.98]
Plum 2002	292	203.6	18	−115	398.8	18	5.7%	1.26 [0.53, 1.98]
Wolfson 2002A	605.827	280	81	379.988	339.3	82	23.7%	0.72 [0.41, 1.04]
Subtotal (95% CI)			337			358	100.0%	0.93 [0.75, 1.11]
Heterogeneity: Tau² = 0.01; Chi² = 6.07, df = 5 (P = 0.30); I² = 18%								
Test for overall effect: Z = 10.24 (P < 0.00001)								
1.6.2 3–6 months								
Chang 2016	475	478.62	45	388.33	815	46		Not estimable
Chen 2018	1,217.48	514.49	21	929.57	399.07	21	11.5%	0.61 [−0.01, 1.23]
Davies 2003	133.9	668.97	24	−113.4	796.86	16	11.1%	0.34 [−0.30, 0.97]
de Moraes 2015	320	259.65	17	−80	283.96	17	8.4%	1.44 [0.67, 2.20]
Konings 2003	1,670	1,038	19	1,063	960	13	9.2%	0.59 [−0.13, 1.31]
Mistry 1994	549.5	288.8	84	229.6	416.8	93	24.8%	0.88 [0.57, 1.19]
Paniagua 2009	1,294	427.79	27	1,144.13	434.8	23	13.2%	0.34 [−0.22, 0.90]
Plum 2002	206	156.7	17	−166	416.4	17	9.0%	1.15 [0.42, 1.89]
Posthuma 2000	276	148.66	7	2.33	469.98	6	4.2%	0.76 [−0.39, 1.90]
Takatori 2011	770.8	432.3	21	164.3	431.6	14	8.5%	1.37 [0.61, 2.13]
Yoon 2014	844	336	36	1,048	447	34		Not estimable
Subtotal (95% CI)			237			220	100.0%	0.80 [0.55, 1.05]
Heterogeneity: Tau² = 0.04; Chi² = 11.29, df = 8 (P = 0.19); I² = 29%								
Test for overall effect: Z = 6.28 (P < 0.00001)								
1.6.3 1–2 years								
Chang 2016	535.67	499.36	41	489	768.24	41		Not estimable
Chen 2018	1,375.83	550.07	20	925.5	382.99	18	27.9%	0.92 [0.25, 1.59]
Paniagua 2009	1,208.22	374.67	18	1,318.25	429.21	20	28.5%	−0.27 [−0.91, 0.37]
Posthuma 2000	232.57	143.93	7	15.67	394.68	6	20.5%	0.70 [−0.43, 1.84]
Takatori 2011	947.6	304.6	14	250	588.7	9	23.1%	1.54 [0.57, 2.52]
Yoon 2014	921	332	35	1,034	470	33		Not estimable
Subtotal (95% CI)			59			53	100.0%	0.68 [−0.12, 1.49]
Heterogeneity: Tau² = 0.49; Chi² = 11.53, df = 3 (P = 0.009); I² = 74%								
Test for overall effect: Z = 1.66 (P = 0.10)								

Test for subgroup differences: Chi² = 0.95, df = 2 (P = 0.62), I² = 0%

Favours GLU Favours ICO
−4 −2 0 2 4

Risk of Bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Figure 4. Ultrafiltration (any measure); (A) by duration of treatment; (B) by transport category including high/high-average (H/HA), low-average (LA), and low (L) transporters. Risk of bias legend: (A) random sequence generation (selection bias), (B) allocation concealment (selection bias), (C) blinding of participants and personnel (performance bias), (D) blinding of outcome assessment (detection bias), (E) incomplete outcome data (attrition bias), (F) selective reporting (reporting bias), and (G) other bias. Abbreviations: CI, confidence interval; GLU, glucose; ICO, icodextrin.

There was no clear difference in fasting plasma glucose levels (Fig S3O) between groups. No difference in HbA$_{1c}$ levels was observed (Fig S3P).

Other Outcomes

There was no difference in kidney function (eg, medium-term residual urine volume MD, 43.02 [95% CI, −94.73 to 180.77] mL; high certainty; Fig S3Q-R), drained body weight (eg, medium-term MD, −0.34 [95% CI, −2.54 to 1.86] kg; high certainty; Fig S3S), or inflow pain (eg, medium-term RR, 1.05 [95% CI, 0.51-2.17]; very low certainty; Fig S3T) between treatment arms. Icodextrin improved short-term peritoneal small-molecule clearance and decreased serum lipid levels, but these effects were not sustained (Fig S3U-X). Serum sodium concentration was lower in icodextrin-treated patients (Fig S3Y).

Discussion

In this systematic review, we show that icodextrin resulted in increased UF, fewer episodes of fluid overload, reduced daily glucose absorption, and probably decreased mortality risk. The findings concerning mortality risk are consistent with observational data.[114-122] The review highlights differential benefit in high/high-average transport patients, a subgroup with particularly high mortality risk.[34-36] This finding is again consistent with observational data.[123-125] In this review, there is a potential effect modification by whether the control group received neutral-pH low-GDP glucose dialysate. Directionally, the omission of the 2 studies[82,101] that used these fluids did not change our estimates. Of note, the mortality effect is driven by studies with the most events (ie, those with longer follow-up),
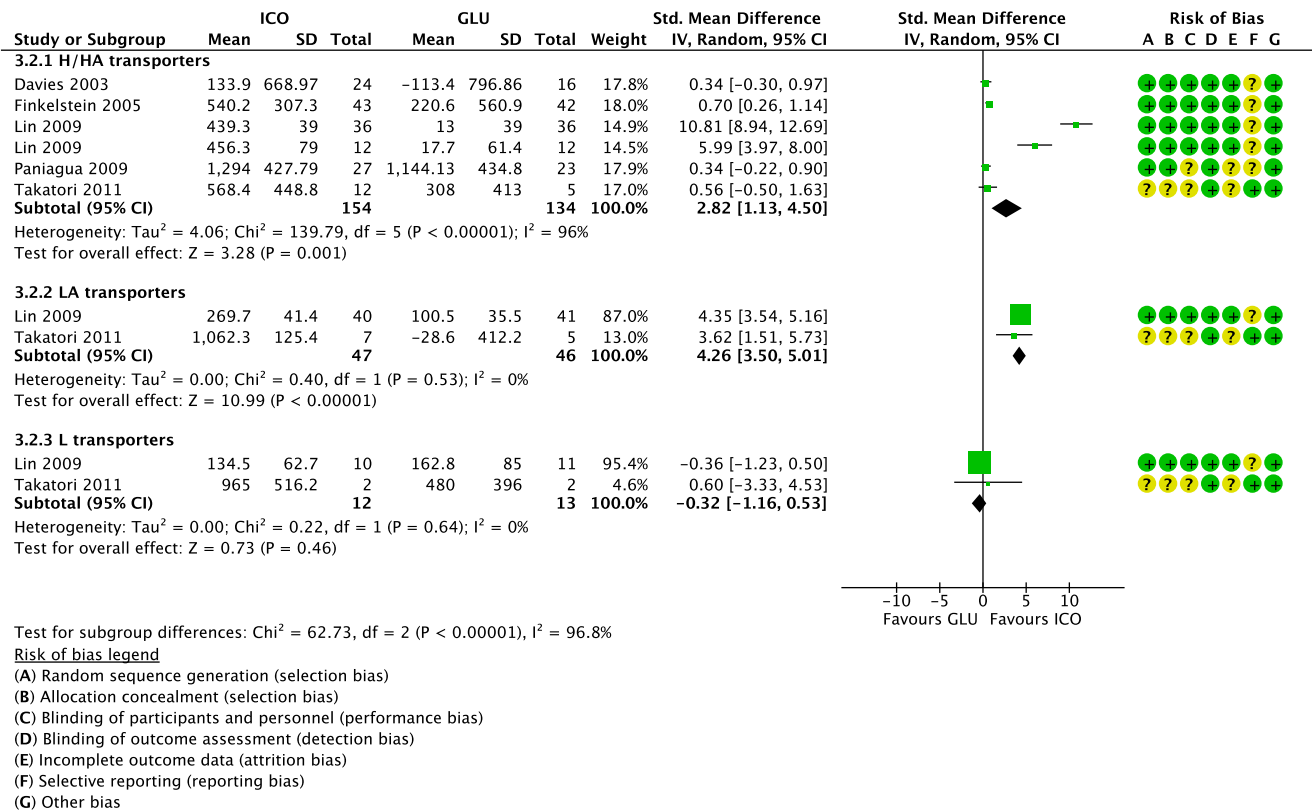
Figure 4. (*Con'd*).

with higher-risk cohorts (eg, Paniagua et al,[93] in which patients all had diabetes and moreover were high or high-average transporters) or from older eras when mortality rates were higher (eg, Posthuma et al,[95-97] in which patients were recruited from 1994-1997). Unlike the studies of East Asian populations[82,83,92] and those with relatively healthy cohorts,[85,90] the former studies have generally higher-risk participants, who are both more sensitive to intervention and contributing the majority of events to the analysis.

UF was increased in the icodextrin group, but the benefit was attenuated in long-term studies. This may be due to the mentioned confounding from higher glucose concentrations or icodextrin use in the glucose groups in these trials.[82,83,93,97,99,101] There was no benefit to icodextrin in terms of PD technique failure. However, this outcome is confounded by co-interventions or contamination between groups, as described in the Results section. In addition, the selection of patients for all clinical trials (including those in this meta-analysis) results in participants who are more likely to be treatment adherent and hence less likely to "fail" on PD. Unsurprisingly, our findings contrast with those of observational studies, which generally show improved technique survival with icodextrin.[114-117,120,121,126] There were short-term benefits with icodextrin in terms of small-solute clearance and serum cholesterol levels. Importantly, none of these identified benefits were accrued at the cost of greater AEs, loss of residual kidney function, or peritonitis. Data for

patient-centered outcomes were scarce and evidence was uncertain; available data suggested no difference in HRQoL or inflow pain between groups.

Several findings relate broadly to carbohydrate metabolism. First, increased serum oligosaccharide levels are well known to occur with icodextrin but, as we show, do not lead to an overall excess of AEs. These icodextrin metabolites are responsible for the decrease in serum sodium levels that we identified, which is mainly dilutional in nature; that is, a pseudohyponatremia. Second, the reduction in daily glucose absorption with icodextrin-containing PD regimens might be expected to reduce blood glucose levels.[86,127] However, our analysis showed no difference in HbA$_{1c}$ and fasting plasma glucose levels between groups. Given results of the IMPENDIA-EDEN trial,[128,129] a single exchange of icodextrin per day instead of glucose may be clinically insufficient as a glucose-sparing PD regimen. Alternatively, the effect may be too small to be demonstrable in our data set, which includes many nondiabetic patients (a "sub–meta-analysis" of the effect of icodextrin-containing PD regimens on glycemic control exclusively in diabetic patients is underway). Third, icodextrin might be expected to ameliorate the progressive damage to peritoneal membrane structure and function that occurs over time on PD. Icodextrin reduces daily exposure of the peritoneum to glucose and contains lower levels of GDPs compared with conventional glucose solutions[130-132] with probably
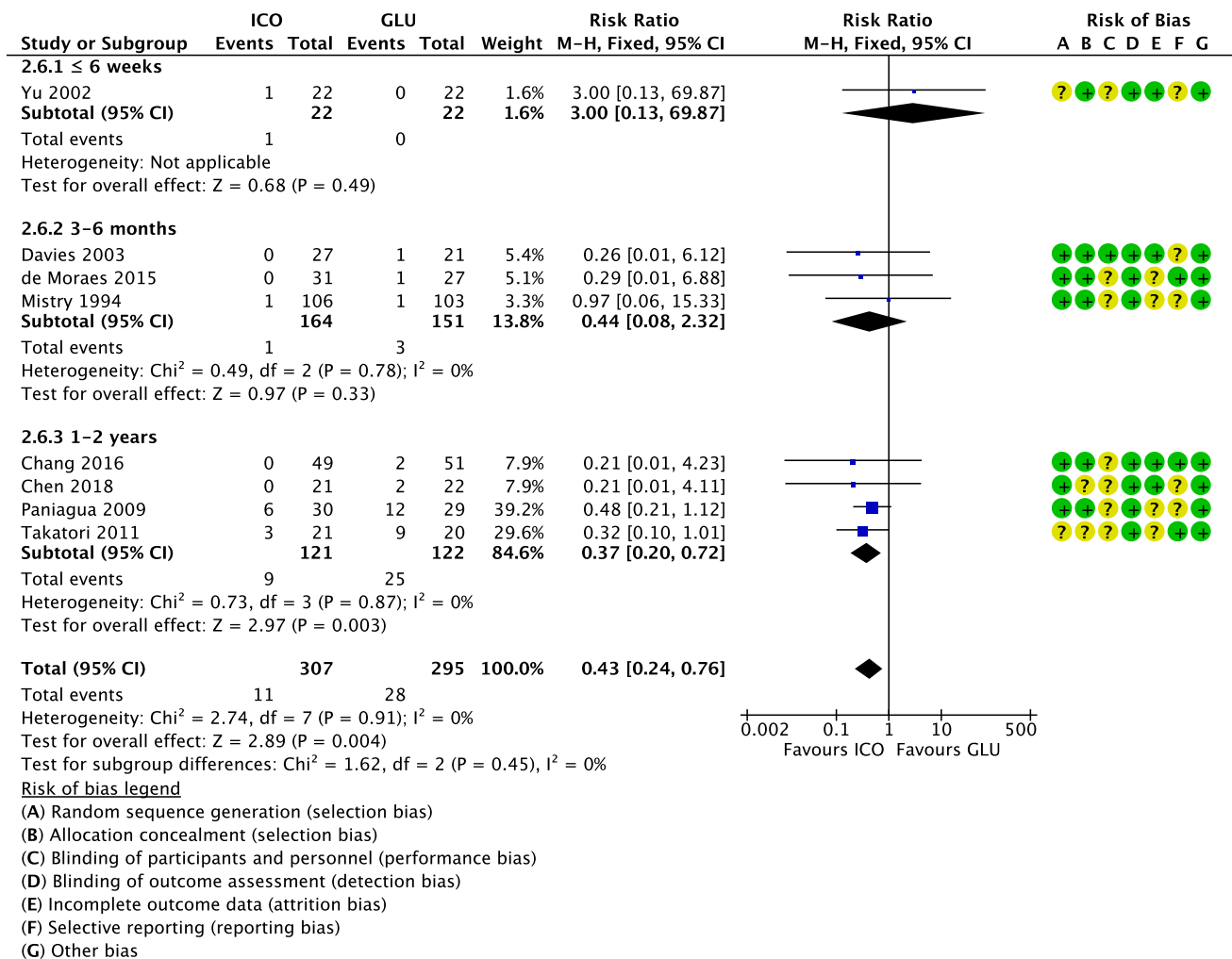
Figure 5. Uncontrolled fluid overload. Results with random-effects modeling are: risk ratio (RR; ≤6 weeks, 3.00 [0.13-69.87]; 3-6 months, 0.45 [0.08-2.58];1-2 years, 0.39 [0.21-0.75];total, 0.43 [0.24-0.78]. Risk-of-bias legend: (A) random sequence generation (selection bias), (B) allocation concealment (selection bias), (C) blinding of participants and personnel (performance bias), (D) blinding of outcome assessment (detection bias), (E) incomplete outcome data (attrition bias), (F) selective reporting (reporting bias), and (G) other bias. Abbreviations: CI, confidence interval; GLU, glucose; ICO, icodextrin; SD, standard deviation; Std, standardized.

greater peritoneal biocompatibility.[89,133] Despite this, we showed no sustained difference in peritoneal small-solute clearance between icodextrin-containing and glucose-only PD regimens. Again, it may be that a single exchange of icodextrin per day instead of glucose is clinically insufficient as a PD regimen with enhanced biocompatibility. Alternatively, peritoneal clearance may be too insensitive as a marker of peritoneal membrane structure; there is evidence that the peritoneal solute transport rate is better.[134]

Trial quality varied among included RCTs (Table S5). The patients analyzed here may not be representative of the true patient population due to our reliance on published RCTs, with restrictive selection criteria in some instances. Only 2 trials reported and analyzed the outcome of diabetic patients independently, resulting in inconclusive subgroup analyses. There were not as many trial results as desirable for the assessments over the long term. The

results should be interpreted with understanding of the inherent limitations of included studies.

We did not corroborate our results of mortality analysis using time-to-event methods on individual patient data, which is a future priority. In addition, we did not assess potentially important mechanistic outcomes, including blood pressure,[82,88,89,100] antihypertensive medication burden,[82,85,87,90,93,97] and extracellular fluid volume.[82,85,88,89,93,100,102] The analyses are not adjusted for multiple comparisons, as per standard operating procedures for meta-analysis.[135]

The 3 previous meta-analyses of icodextrin versus glucose did not always identify the same benefits as ours. The differences arise from the enriched data used in the current study (Table 3). To quote Jefferson et al, "Systematic reviews that use only published data perpetuate such [reporting] bias and possibly compound the issue through the credibility afforded by the systematic

Table 3. Comparison of Previous Systematic Reviews With the Present Study (Exemplary Outcomes)

	Htay et al[40]	He et al[41]	Qi et al[42]	Present Study
Patients included				
Studies	13	9	9	20
Patients randomly assigned	1,322	578	1,190	1,714
Patient survival				
Studies	6		4	19
Patients evaluable	816		735	1,685
PD technique failure				
Studies	4			18
Patients evaluable	350			1,401
UF, any measure				
Studies	4		2	15
Patients evaluable	102		131	1,120
Peritoneal CL$_{cr}$				
Studies	3	4	5	10
Patients evaluable	237	326	528	922
Peritoneal CL$_{urea}$				
Studies		4	4	10
Patients evaluable		326	508	908
Serum glucose				
Studies		4		5
Patients evaluable		266		388
Serum triglycerides				
Studies		3		7
Patients evaluable		241		560

Abbreviations: CL$_{cr}$, creatinine clearance; CL$_{urea}$, urea clearance; PD, peritoneal dialysis; UF, ultrafiltration.

review."[48](p 210) In the current study, the principal investigators of included studies often provided abstracted or raw data and were included as authors of this study to stand fully accountable for the results obtained. Additionally, we have included CSRs of industry-sponsored trials containing extensive source data,[136] all subjected to rigorous regulatory review.[58] Thus, we were able to assess a markedly greater number of outcomes than previous reviews.[137]

There is an urgent need to improve PD outcomes and reduce associated costs.[138] Icodextrin provides a possible opportunity of increased survival, with a decrease in important complications such as fluid overload. Icodextrin appears in many clinical practice guidelines, although with variable indications (Table S10). This variability is probably responsible for markedly different icodextrin uptake between health jurisdictions (Fig S1). Based on our updated results, there is likely to be benefit from increased access to and earlier use of icodextrin for patients in many parts of the world. A revision of relevant best practice recommendations is warranted, guided by experts after due deliberation of evidence and context.

It is unlikely that there will be any further large-scale RCTs comparing icodextrin and glucose. Future efforts should focus on health economics and patient-centered outcomes. Further insights into cost-effectiveness/-utility

and treatment preferences for icodextrin-based PD solutions would be welcome.

In conclusion, our systematic review demonstrates substantial clinical benefits for icodextrin based on high-level evidence and suggests an attributable benefit in the global PD population from greater and perhaps earlier access to icodextrin for appropriate patients.

Supplementary Material

Supplementary File (PDF)

Item S1: Supplementary methods.

Figure S1: Prevalent PD patients on icodextrin, by country.

Figure S2: Funnel plots for all outcomes with ≥10 included studies.

Figure S3: Forest plots for all outcomes that were meta-analyzed, and for all sensitivity analyses.

Figure S4: Forest plots for subgroup analysis for incident vs prevalent patients.

Figure S5: Forest plots for subgroup analysis for diabetic vs nondiabetic patients.

Figure S6: Forest plots for subgroup analysis for transport types.

Figure S7: Forest plots for subgroup analysis for glucose concentration.

Table S1: Potentially relevant studies identified in clinical trials registries that are not already included in the review.

Table S2: Search strategies in databases and clinical trials registries.

Table S3: List of excluded studies.

Table S4: Baseline characteristics of included patients.

Table S5: Risk-of-bias assessment at study level.

Table S6: Certainty assessment (GRADE).

Table S7: Causes of death reported within studies.

Table S8: Causes of death in the US dialysis population.

Table S9: Patients who received a kidney transplant.

Table S10: Global guidelines around icodextrin use.

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