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Baseline Characteristics and Representativeness of Participants in the BEST-Fluids Trial: A Randomized Trial of Balanced Crystalloid Solution Versus Saline in Deceased Donor Kidney Transplantation

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Background. Delayed graft function (DGF) is a major complication of deceased donor kidney transplantation. Saline (0.9% sodium chloride) is a commonly used intravenous fluid in transplantation but may increase the risk of DGF because of its high chloride content. Better Evidence for Selecting Transplant Fluids (BEST-Fluids), a pragmatic, registry-based, double-blind, randomized trial, sought to determine whether using a balanced low-chloride crystalloid solution (Plasma-Lyte 148) instead of saline would reduce DGF. We sought to evaluate the generalizability of the trial cohort by reporting the baseline characteristics and representativeness of the trial participants in detail. **Methods.** We compared the characteristics of BEST-Fluids participants with those of a contemporary cohort of deceased donor kidney transplant recipients in Australia and New Zealand using data from the Australia and New Zealand Dialysis and Transplant Registry. To explore potential international differences, we compared trial participants with a cohort of transplant recipients in the United States using data from the Scientific Registry of Transplant Recipients. **Results.** During the trial recruitment period, 2373 deceased donor kidney transplants were performed in Australia and New Zealand; 2178 were eligible, and 808 were enrolled in BEST-Fluids. Overall, trial participants and nonparticipants were similar at baseline. Trial participants had more coronary artery disease (standardized difference [d] = 0.09; $P = 0.03$), longer dialysis duration (d = 0.18, $P < 0.001$), and fewer hypertensive (d = –0.11, $P = 0.03$) and circulatory death (d = –0.14, $P < 0.01$) donors than nonparticipants. Most key characteristics were similar between trial participants and US recipients, with moderate differences ($|d| \geq 0.2$; all $P < 0.001$) in kidney failure cause, diabetes, dialysis duration, ischemic time, and several donor risk predictors, likely reflecting underlying population differences. **Conclusions.** BEST-Fluids participants had more comorbidities and received slightly fewer high-risk deceased donor kidneys but were otherwise representative of Australian and New Zealand transplant recipients and were generally similar to US recipients. The trial results should be broadly applicable to deceased donor kidney transplantation practice worldwide.

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INTRODUCTION

Delayed graft function (DGF) is a frequent complication of deceased donor kidney transplantation[1,2] associated with inferior outcomes and higher costs.[3-5] DGF occurs when ischemia-reperfusion injury sustained during transplantation results in poor kidney function and the need for dialysis treatment during the first week after transplantation.[6,7] Intravenous (IV) fluids administered during and after transplantation are critical for maintaining intravascular volume and kidney perfusion and play an important role in minimizing the risk of DGF.[8] Saline (0.9% sodium chloride) is the most commonly used IV fluid.[9,10] However, the supraphysiological chloride concentration in saline may increase the risk of DGF by promoting the development of hyperchloremic metabolic acidosis and acute kidney injury.[11-13] Balanced crystalloids with a lower chloride concentration avoid this acidosis and may improve kidney function.[14-16] Whether using a balanced crystalloid instead of saline is safe and improves kidney function after deceased donor kidney transplantation is unknown.[15]

The Better Evidence for Selecting Transplant Fluids (BEST-Fluids) trial was a pragmatic randomized controlled trial (RCT) to test the hypothesis that, compared with 0.9% saline, IV fluid therapy with a balanced low-chloride crystalloid solution, Plasma-Lyte 148, would reduce DGF incidence in deceased donor kidney transplant recipients.[10] BEST-Fluids incorporated broad eligibility criteria and closely aligned interventions and

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The analyses of these data are the responsibility of the authors alone and do not necessarily reflect the views or policies of the Department of Health and Human Services, nor does the mention of trade names, commercial products, or organizations imply endorsement by the US Government. The data reported herein were supplied by the Hennepin Healthcare Research Institute as a contractor for the SRTR. The interpretation and reporting of these data are the responsibility of the authors and in no way should they be seen as an official policy or interpretation by the SRTR or the US Government.

The data reported here were supplied by the Australia and New Zealand Dialysis and Transplant Registry (ANZDATA). The interpretation and reporting of these data are the responsibility of the authors and should not be viewed as an official policy or interpretation of the Australia and New Zealand Dialysis and Transplant Registry.

Clinical Trial Registration: Australia New Zealand Clinical Trials Registry ACTRN12617000358347; prospectively registered March 8, 2017. Registered on ClinicalTrials.gov; NCT03829488.

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follow-up procedures with standard transplant practice to maximize the applicability of trial findings to a broad range of transplant recipients. The primary outcome of DGF was defined as receiving dialysis in the first 7 d after transplantation.

A pragmatic registry-based RCT design was chosen to maximize internal validity and minimize bias while ensuring that external validity was optimized and could be directly assessed. Data on all kidney transplant recipients in Australia and New Zealand are routinely reported to the Australia and New Zealand Dialysis and Transplant (ANZDATA) Registry for clinical quality purposes. In BEST-Fluids, trial enrollment, randomization, and most data collection were embedded within the ANZDATA Registry.[10] Participant characteristics, the primary outcome, and many key secondary outcomes used in the trial were already collected routinely in the registry for all kidney transplant recipients. Thus, to fully inform the interpretation of the findings of BEST-Fluids once they become available, we sought to use registry data to compare the characteristics of trial participants with those of the population who would have met the trial eligibility criteria but were not enrolled in the study.

This article reports the baseline demographic, clinical, donor, and transplant characteristics, including those associated with the risk of DGF, for participants in the BEST-Fluids trial. The primary aim was to determine whether the trial participants were representative of deceased donor kidney transplant recipients in Australia and New Zealand during the recruitment period. To explore potential international generalizability, we also compared the trial participants with a contemporary US transplant cohort.

MATERIALS AND METHODS

Study Design

BEST-Fluids trial participants were compared with (1) all other patients who received deceased donor kidney transplants in Australia and New Zealand during the trial period and met the eligibility criteria but were not enrolled in the trial and (2) a contemporary cohort of deceased donor kidney-only transplant recipients in the United States.

Details of the BEST-Fluids study design and protocol have been published previously.[10] Briefly, BEST-Fluids was an investigator-initiated, pragmatic, registry-based, multicenter, double-blind RCT that enrolled participants at hospitals in Australia (12 sites) and New Zealand (4 sites), representing 13 out of 17 adult transplant hospitals and 3 out of 8 children's hospitals. The trial was prospectively registered (Australia New Zealand Clinical Trials Registry ACTRN12617000358347). A total of 808 participants who received a kidney transplant between January 31, 2018, and August 10, 2020, were recruited.

Study Population

Participants were eligible for the BEST-Fluids trial if they had kidney failure, were admitted to a participating hospital for a deceased donor kidney transplant, and provided written informed consent. Participants were excluded if they (1) were receiving a multiorgan transplant (a kidney combined with another organ transplant), (2) were a child that weighed <20 kg or were considered by their physician too small for a blinded fluid study, or (3) had known hypersensitivity to the trial fluid preparations or packaging. Participants who were enrolled and randomized but had their kidney transplant surgery canceled were excluded from the analysis.

The comparison cohort included all deceased donor kidney-only recipients in Australia and New Zealand transplanted during the trial recruitment period (January 31, 2018, until August 10, 2020) who met the eligibility criteria but were not enrolled in the BEST-Fluids trial. Transplant recipients were excluded from the comparison cohort if they had enrolled in BEST-Fluids, received a multiorgan transplant, or were a child that weighed <20 kg at transplant. The US comparison cohort included all recipients of a deceased donor kidney-only transplant aged at least 18 y from January 1, 2018, to December 31, 2020, excluding recipients of dual or pediatric en bloc kidneys.

Data Sources

The ANZDATA Registry provided baseline demographic, clinical, and transplant characteristic data for trial participants and the comparison cohort from Australia and New Zealand. The Australia and New Zealand Organ Donor Registry, administered and managed by the ANZDATA Registry, provided data on donor characteristics linked to each transplant recipient's record. Data from the US Scientific Registry of Transplant Recipients (SRTR) were also used for this analysis; the SRTR data system includes data on all donors, wait-listed candidates, and transplant recipients in the United States, submitted by the members of the Organ Procurement and Transplantation Network.[17] The Health Resources and Services Administration, US Department of Health and Human Services, provides oversight to the activities of the Organ Procurement and Transplantation Network and SRTR contractors.

Data Variables

For transplant recipients in Australia and New Zealand, the collected demographics included age, gender, and ethnicity. Clinical characteristics (collected at the time of transplantation) included participant height, weight, body mass index (BMI), smoking status, cause of kidney failure, comorbidities (coronary artery disease, chronic lung disease, peripheral vascular disease, cerebrovascular disease, diabetes, and malignancy), and dialysis treatment history before transplantation. Transplant characteristics included the year of transplantation, graft number, peak panel reactive antibody (PRA), number of HLA mismatches, total ischemic time, and initial immunosuppression at the time of transplantation.

Donor characteristics collected included demographics (age, gender), donor type (brain or circulatory death), cause of death, cardiopulmonary resuscitation, comorbidities (treated hypertension, diabetes, smoking), preterminal kidney function (creatinine), preretrieval biopsy, the number of kidneys transplanted, and expanded criteria donor status.[18] The kidney donor risk index (KDRI) scores for each donor were calculated using the Australian modification of this score.[19,20] We also collected data on the treatment of donor kidneys with hypothermic machine perfusion before transplantation for trial participants from ANZDATA and directly as aggregate (not patient-level) data from the only hospital that used this technology during the trial period (Princess Alexandra Hospital, Brisbane).

To determine the differences in the location and type of kidney replacement therapy (KRT) between trial participants and nonparticipants before transplantation, we also collected data on transplant country and region, transplant center status of the hospital providing KRT, patient geographic location (metropolitan, regional, or remote for Australian participants), and the location of dialysis treatment received (home, satellite, in-center hemodialysis, or peritoneal dialysis).

For US recipients, data variables equivalent to those described above were used, where these were available in the SRTR dataset and were comparable to those available in ANZDATA.

There were very few (1% or less) missing data for most variables provided by ANZDATA, whereas data obtained from the SRTR for the US cohort had significant missing data for some variables. A complete case analysis approach was used for the comparative analyses.

Statistical Analysis

Continuous variables were expressed as means and SD or medians with interquartile ranges. Categorical variables were expressed as frequencies with percentages. Differences between the groups were quantified using standardized differences (d), where values of 0.2, 0.5, and 0.8 represented small, medium, and large differences, respectively.[21,22] Between-group hypothesis tests were conducted using independent sample *t*-tests, Wilcoxon rank-sum tests, or chi-squared tests. Linear, binomial, or multinomial logistic regression models with robust standard errors were used to compare donor characteristics for the Australian and New Zealand cohorts to account for clustering due to paired donors, that is, where 2 recipients received kidneys from the same donor. Donor characteristics were compared with those of the US cohort by using aggregate data from unique donors. *P* values of <0.05 were considered statistically significant. Statistical analyses were performed using Stata, version 17, and SAS, version 9.4.

Ethical Considerations

All the BEST-Fluids trial participants provided written informed consent. The BEST-Fluids trial received ethical approval from the Northern A Health and Disability Ethics Committee (approval number 17/NTA/62) for New Zealand and the Sydney Local Health District Human Research Ethics Committee, Royal Prince Alfred Hospital (approval numbers X17-0201 and HREC/17/RPAH/308), for Australia.

This study was deemed of negligible risk and exempted from ethics review by the University of Queensland Research Ethics and Integrity Committee (project numbers 2021/HE000022, approved February 1, 2021 [ANZDATA], and 2021/HE002522, approved November 24, 2021 [US SRTR]). The ANZDATA Registry provided deidentified participant-level data for this comparative study. All analyses of the SRTR dataset to produce the summary data were performed in Vancouver, Canada.

RESULTS

Over the 31-mo recruitment period, 1350 potential participants were screened for enrollment, 856 were randomized, and 808 received a deceased donor kidney transplant and continued in the trial (Figure 1). Forty-eight participants did not receive transplants and were therefore excluded from the trial. Participants were recruited from 13 adult and 3 children's hospitals in Australia and New Zealand. During the same period, 2178 patients eligible for the trial received deceased donor kidney transplants at 25 hospitals (17 adult and 8 children's hospitals) in Australia and New Zealand (Figure 2). Accordingly, the ANZDATA comparison cohort

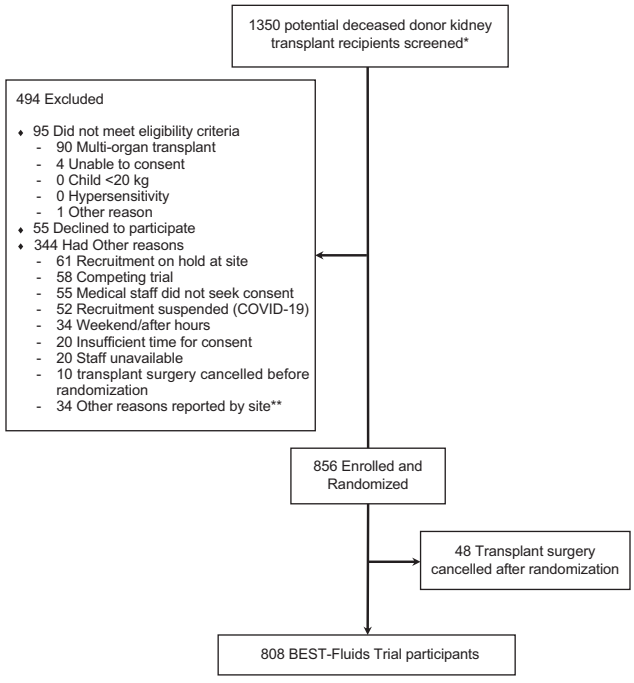

FIGURE 1. Screening and enrollment of participants in the BEST-Fluids trial. *Participants were considered screened for the trial if they were admitted for a potential transplant at a participating hospital after recruitment had been initiated at that site. **Other reasons for exclusion reported by sites included no translator (7), medical reasons (5), an overseas patient (5), developmental delay/intellectual disability (4), physician decision (4), patient anxiety (3), transplanted at a participating hospital for another nonparticipating hospital during COVID-19 (2), followed for safety reasons only (because of being given study fluids but not enrolled or randomized) (1), interstate logistics (1), a nonadherent patient (1), and transplant at another hospital (1). BEST-Fluids, Better Evidence for Selecting Transplant Fluids.

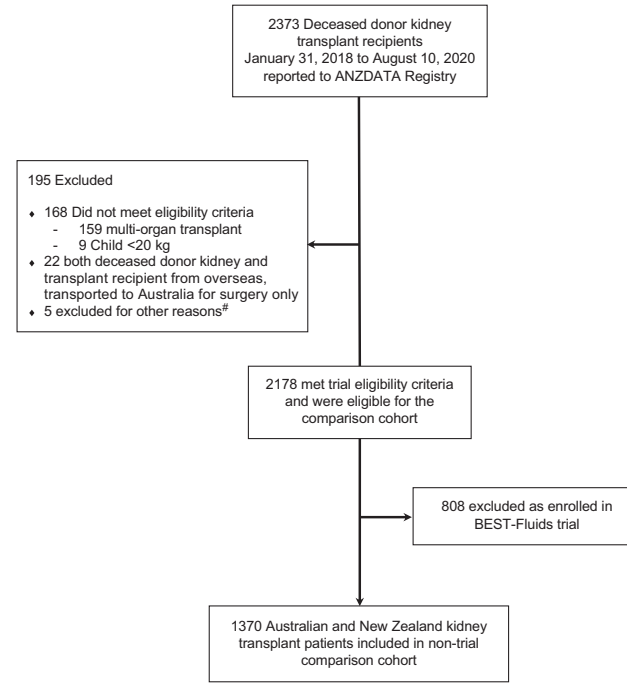

FIGURE 2. Selection and inclusion of participants in the ANZDATA Registry comparison cohort. #Other reasons for exclusion were as follows: participants were enrolled and randomized in BEST-Fluids, did not receive kidney transplant at the time, and were transplanted later but not reenrolled in the trial (3); participants were enrolled, randomized, and transplanted but withdrawn because of invalid or missing consent (2). ANZDATA, Australia and New Zealand Dialysis and Transplant Registry. ANZDATA, Australia and New Zealand Dialysis and Transplant; BEST-Fluids, Better Evidence for Selecting Transplant Fluids.

included 1370 (2178 less 808) transplant recipients who did not participate in the trial.

Characteristics of Trial Participants Compared With Other Australian and New Zealand Transplant Recipients

The baseline demographic, clinical, and transplant characteristics of the recipients are shown in Table 1. BEST-Fluids participants were similar to the ANZDATA cohort of non-trial participants in terms of age, gender, BMI, smoking status, cause of kidney failure, comorbidities (diabetes, chronic lung disease, peripheral vascular disease, and cerebrovascular disease), history of cancer, graft number, dialysis modality, number of HLA mismatches, peak PRA >0%, machine perfusion, and number of transplanted kidneys (|d| < 0.12; $P > 0.05$ for all comparisons). Comparing trial participants and other transplant recipients, there were differences in the number of children (0.5% versus 2.6%; d = –0.17, $P = 0.001$), and

TABLE 1.

Baseline characteristics of BEST-Fluids trial participants compared with other Australian and New Zealand deceased donor kidney transplant recipients in the ANZDATA Registry

Characteristic	Total (N = 2178)	ANZDATA (N = 1370)	BEST-Fluids (N = 808)	Standardized difference (d) (BEST-Fluids—ANZDATA)	*P*
Age (y)					
Mean (SD)	52.0 (14.1)	51.8 (14.4)	52.5 (13.5)	0.05	0.27
Gender					0.52
Male	1361 (62.5%)	849 (62.0%)	512 (63.4%)	0.03	
Female	817 (37.5%)	521 (38.0%)	296 (36.6%)	–0.03	
Children <16	39 (1.8%)	35 (2.6%)	4 (0.5%)	–0.17	0.001
Ethnicity					<0.001
Asian	245 (11.9%)	168 (13.3%)	77 (9.7%)	–0.1	
Arab	54 (2.6%)	34 (2.7%)	20 (2.5%)	–0.005	
Australian Aboriginal or Torres Strait Islander	122 (5.9%)	74 (5.9%)	48 (6.0%)	–0.007	
White/European	1232 (59.9%)	761 (60.3%)	471 (59.2%)	–0.02	
Indian Subcontinent	93 (4.5%)	58 (4.6%)	35 (4.4%)	–0.001	
New Zealand Māori	64 (3.1%)	18 (1.4%)	46 (5.8%)	0.24	
Pacific peoples	115 (5.6%)	53 (4.2%)	62 (7.8%)	0.16	
Other	132 (6.4%)	95 (7.5%)	37 (4.6%)	–0.12	
Not recorded/missing	121	109	12		
Weight presurgery (kg)					
Mean (SD)	79.2 (18.8)	77.9 (18.9)	81.4 (18.4)	0.19	<0.001
Body mass index (kg/m^2)					
Mean (SD)	28.1 (13.2)	27.8 (13.4)	28.8 (12.9)	0.08	0.09
Smoking status					0.11
Never	1224 (57.6%)	789 (59.3%)	435 (54.8%)	–0.09	
Former	698 (32.8%)	423 (31.8%)	275 (34.6%)	0.06	
Current	203 (9.6%)	119 (8.9%)	84 (10.6%)	0.06	
Missing	53	39	14		
Cause of kidney failure					0.07
Diabetic nephropathy	454 (22.1%)	286 (22.4%)	168 (21.6%)	–0.02	
Hypertension	162 (7.9%)	90 (7.1%)	72 (9.3%)	0.08	
Glomerulonephritis	794 (38.7%)	489 (38.4%)	305 (39.2%)	0.02	
Reflux nephropathy	111 (5.4%)	66 (5.2%)	45 (5.8%)	0.03	
Polycystic kidney disease	256 (12.5%)	153 (12.0%)	103 (13.2%)	0.04	
Other	276 (13.4%)	191 (15.0%)	85 (10.9%)	–0.12	
Missing	125	95	30		
Coronary artery disease	462 (21.3%)	270 (19.9%)	192 (23.8%)	0.09	0.03
Chronic lung disease	221 (10.2%)	130 (9.6%)	91 (11.3%)	0.05	0.21
Peripheral vascular disease	258 (11.9%)	169 (12.5%)	89 (11.0%)	–0.04	0.32
Cerebrovascular disease	129 (6.0%)	82 (6.0%)	47 (5.8%)	–0.01	0.83
Diabetes					0.78
None	1525 (70.3%)	1525 (70.3%)	1525 (70.3%)	0.01	
Type 1	65 (3.0%)	41 (3.0%)	24 (3.0%)	–0.002	
Type 2	580 (26.7%)	371 (27.2%)	209 (25.9%)	–0.03	
History of any malignancy	282 (12.9%)	170 (12.4%)	112 (13.9%)	0.04	0.33
History of nonskin malignancy	184 (8.4%)	115 (8.4%)	69 (8.5%)	0.01	0.91
Year of transplant					<0.001
2018	865 (39.7%)	581 (42.4%)	284 (35.1%)	–0.15	
2019	923 (42.4%)	518 (37.8%)	405 (50.1%)	0.25	

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TABLE 1. (CONTINUED)

Baseline characteristics of BEST-Fluids trial participants compared with other Australian and New Zealand deceased donor kidney transplant recipients in the ANZDATA Registry

Characteristic	Total (N = 2178)	ANZDATA (N = 1370)	BEST-Fluids (N = 808)	Standardized difference (d) (BEST-Fluids—ANZDATA)	*P*
2020	390 (17.9%)	271 (19.8%)	119 (14.7%)	–0.13	
Graft number					0.16
1	1930 (88.6%)	1219 (89.0%)	711 (88.0%)	–0.03	
2	207 (9.5%)	121 (8.8%)	86 (10.6%)	0.06	
3+	41 (1.9%)	30 (2.2%)	11 (1.4%)	–0.06	
Dialysis modality before transplant					0.18
Hemodialysis	1439 (66.1%)	889 (64.9%)	550 (68.1%)	0.07	
Peritoneal dialysis	702 (32.2%)	460 (33.6%)	242 (30.0%)	–0.08	
None (preemptive transplant)	37 (1.7%)	21 (1.5%)	16 (2.0%)	0.03	
Dialysis duration (mo)					
Mean (SD)	37.3 (32.5)	35.1 (29.5)	41.0 (36.8)	0.18	<0.001
Median (IQR)	29 (15–49)	28 (14–47)	31 (17–52)		0.003
Peak panel reactive antibody (%)					
Mean (SD)	18 (33)	17 (32)	20 (34)	0.09	0.03
Median (IQR)	0 (0–22)	0 (0–10)	0 (0–30)		0.02
0%	1465 (67.3%)	946 (69.1%)	519 (64.4%)	–0.10	0.07
1%–98%	644 (29.6%)	382 (27.9%)	262 (32.5%)	0.10	
≥99%	67 (3.1%)	42 (3.1%)	25 (3.1%)	0.00	
Missing	2	0	2		
Number of HLA mismatches					0.48
0	70 (3.2%)	42 (3.1%)	28 (3.5%)	0.02	
1–2	613 (28.2%)	394 (28.8%)	219 (27.2%)	–0.04	
3–4	652 (30.0%)	396 (28.9%)	256 (31.8%)	0.06	
5–6	841 (38.6%)	538 (39.3%)	303 (37.6%)	–0.03	
Total ischemic time (h)					
Mean (SD)	10.7 (4.8)	10.5 (4.8)	11.0 (4.8)	0.01	0.02
Median (IQR)	10 (7–13)	10 (7–13)	10 (7–13)		0.01
Missing	65	63	2		
Number of kidneys transplanted into recipient					0.34
1	2125 (97.6%)	1340 (97.8%)	785 (97.2%)	–0.04	
2	53 (2.4%)	30 (2.2%)	23 (2.8%)	0.04	
Machine perfusion of kidney[a]	45 (2.1%)	25 (1.8%)	20 (2.5%)	0.19	0.30
Any induction immunosuppression (Y/N)	2068 (94.9%)	1270 (92.7%)	798 (98.8%)	0.30	<0.001
Induction immunosuppression reported[b]					
Basiliximab	1851 (85.0%)	1132 (82.6%)	719 (89.0%)	0.18	<0.001
T-cell depletion	234 (10.7%)	138 (10.1%)	96 (11.9%)	0.06	0.19
B-cell depletion	2 (0.1%)	2 (0.1%)	0	–0.05	0.28
Immunoglobulin	42 (1.9%)	30 (2.2%)	12 (1.5%)	–0.05	0.25
Eculizumab	2 (0.1%)	1 (0.1%)	1 (0.1%)	0.02	0.71
Maintenance immunosuppression reported[c]					
Glucocorticoid	2103 (96.6%)	1303 (95.1%)	800 (99.0%)	0.23	<0.001
Cyclosporin	155 (7.1%)	37 (2.7%)	118 (14.6%)	0.43	<0.001
Tacrolimus	1940 (89.1%)	1260 (92.0%)	680 (84.2%)	–0.24	<0.001
Mycophenolic acid derivative	2094 (96.1%)	1303 (95.1%)	791 (97.9%)	0.15	0.001
mTOR inhibitor	16 (0.7%)	6 (0.4%)	10 (1.2%)	0.09	0.03
Azathioprine	4 (0.2%)	3 (0.2%)	1 (0.1%)	–0.02	0.62
Other	1 (0.0%)	1 (0.1%)	0	–0.04	0.44

[a]Ethnicity was categorized as reported in the ANZDATA Registry; this may be either self-reported or clinician-reported.
[b]Princess Alexandra Hospital, Brisbane only; no other centers in Australia or New Zealand used machine perfusion during the trial period.
[c]For both induction and maintenance immunosuppression, the proportions are out of the total number in each group reported at baseline.
ANZDATA, Australia and New Zealand Dialysis and Transplant Registry; BEST-Fluids, Better Evidence for Selecting Transplant Fluids; IQR, interquartile range; mTOR, mammalian target of rapamycin.

ethnicity ($P < 0.001$), with more New Zealand Māori (5.8% versus 1.4%; d = 0.24) and Pacific Islanders (7.8% versus 4.2%; d = 0.16) and fewer Asians (9.7% versus 13.3%; d = –0.10). Compared with other transplant recipients, the trial participants had higher preoperative weights (mean ± SD, 81.4 ± 18.4 versus 77.9 ± 18.9 kg; d = 0.19, $P < 0.001$), slightly more coronary artery disease (24% versus 20%; d = 0.09, $P = 0.03$), and a slightly longer dialysis duration (median [interquartile range] 31 [17–52] mo versus 28 [14–47] mo; d = 0.18, $P < 0.001$). There were also differences in the proportion

TABLE 2.

Location and characteristics of KRT provided to BEST-Fluids trial participants compared with other Australian and New Zealand deceased donor kidney transplant recipients in the ANZDATA Registry

Characteristic	Total (N = 2178)	ANZDATA (N = 1370)	BEST-Fluids (N = 808)	Standardized difference (BEST-Fluids—ANZDATA)	*P*
Transplant country					<0.001
Australia	1920 (88.2%)	1301 (95.0%)	619 (76.6%)	−0.54	
New Zealand	258 (11.8%)	69 (5.0%)	189 (23.4%)	0.54	
Transplant state (AU)					<0.001
New South Wales	555 (28.9%)	409 (31.4%)	146 (23.6%)	−0.18	
South Australia	158 (8.2%)	95 (7.3%)	63 (10.2%)	0.10	
Queensland	381 (19.8%)	122 (9.4%)	259 (41.8%)	0.80	
Victoria	627 (32.7%)	500 (38.4%)	127 (20.5%)	−0.40	
Western Australia	199 (10.4%)	175 (13.5%)	24 (3.9%)	−0.35	
Center providing KRT before transplant					<0.001
Non-transplanting hospital	1013 (46.5%)	524 (38.2%)	489 (60.5%)	0.46	
Transplanting hospital	1165 (53.5%)	846 (61.8%)	319 (39.5%)	−0.46	
Location of patient domicile at transplant[a]					0.01
Major city	1370 (72.1%)	951 (74.1%)	419 (68.0%)	−0.13	
Regional	472 (24.9%)	292 (22.8%)	180 (29.2%)	0.15	
Remote	57 (3.0%)	40 (3.1%)	17 (2.8%)	−0.02	
Not recorded/missing	279	87	192		
Location of dialysis treatment at transplant					0.66
Home	1058 (48.6%)	672 (49.1%)	386 (47.8%)	−0.03	
In-center	1083 (49.7%)	677 (49.4%)	406 (50.2%)	0.02	
Not on dialysis	37 (1.7%)	21 (1.5%)	16 (2.0%)	0.03	

[a]These data were derived from postcodes and were only available for Australian patients; all New Zealand patients were recorded as having missing data.
ANZDATA, Australia and New Zealand Dialysis and Transplant Registry; AU, Australia; BEST-Fluids, Better Evidence for Selecting Transplant Fluids; KRT, kidney replacement therapy.

of trial participants who received any induction immunosuppression (99% versus 93%; d = 0.30, $P < 0.001$), basiliximab (89% versus 83%; d = 0.18, $P < 0.001$), maintenance glucocorticoids (99% versus 95%; d = 0.23, $P < 0.001$), and cyclosporin (15% versus 3%; d = 0.43, $P < 0.001$). Trial participants were more likely to have been transplanted in 2019 than nonparticipants (d = 0.25, $P < 0.001$).

The location and characteristics of KRT received before transplantation are shown in Table 2. Compared with the ANZDATA cohort, a higher proportion of trial participants were transplanted in New Zealand (23% versus 5%; d = 0.54, $P < 0.001$) and the Australian state of Queensland (42% versus 9%, d = 0.81, $P < 0.001$). Furthermore, more trial participants were cared for at a nontransplanting hospital before transplantation (61% versus 38%; d = 0.46, $P < 0.001$) or were from regional areas (29% versus 22%, d = 0.15, $P < 0.01$). The proportions of patients receiving home-based dialysis and those not yet on dialysis before transplantation did not differ.

The characteristics of the deceased donors for these recipients are presented in Table 3. The groups did not differ in donor age, cause of death, receipt of cardiopulmonary resuscitation, weight, BMI, diabetes, smoking status, admission, terminal creatinine, or expanded criteria donor status ($|d| < 0.1$, $P > 0.05$, for all comparisons). The trial participant group had slightly fewer male donors (56% versus 62%, d = −0.11, $P = 0.03$), fewer donors after circulatory determination of death (25% versus 31%, d = −0.14, $P = 0.008$), and fewer donors with treated hypertension (22% versus 27%, d = −0.11, $P = 0.03$) than the other transplant recipients. The mean KDRI was slightly lower for trial participants than for other transplant recipients (1.33 versus 1.39; d = −0.14, $P = 0.007$). However, there were similar proportions of both groups that received higher- and lower-risk KDRI tertile kidneys. More trial participants had kidneys that had been biopsied before transplantation (16% versus 12%; d = 0.13, $P = 0.01$).

Comparison of Trial Participants With US Transplant Recipients 2018 to 2020

Tables S1 and S2 (SDC, http://links.lww.com/TXD/A469) show the baseline recipient and donor characteristics of the 808 BEST-Fluids participants (585 deceased donors) and 46 050 US transplant recipients (26 864 deceased donors), respectively. Age (52 ± 13 versus 54 ± 13 y, d = −0.15, $P < 0.001$), proportion of White ethnicity (59% versus 57%, d = 0.05, $P < 0.001$), BMI (29 ± 13 versus 28 ± 13 kg/m^2, d = 0.08, $P < 0.001$), and peak PRA (20 ± 34% versus 26 ± 37%, d = −0.16, $P < 0.001$) showed small but significant differences. A lower proportion of trial participants had diabetic nephropathy, hypertension, or "other" as the primary cause of kidney failure (22% versus 30%, d = −0.23; 9% versus 23%, d = −0.61; and 11% versus 21%, d = −0.42, respectively, $P < 0.001$). BEST-Fluids participants were more likely to have glomerulonephritis or polycystic kidney disease as the primary cause of kidney failure (39% versus 16%, d = 0.67; and 13% versus 8%, d = 0.30, respectively; $P < 0.001$). Compared with recipients in the United States, BEST-Fluids participants had less type 2 diabetes (26% versus 35%, d = −0.24, $P < 0.001$), shorter total dialysis duration (41 ± 37 versus 55 ± 40 mo, d = −0.35, $P < 0.001$), shorter total ischemic time (11 ± 5 versus 18 ± 9 h, d = −0.78, $P < 0.001$), fewer HLA mismatches (Table S1, SDC, http://links.lww.com/TXD/A469, $P < 0.001$), and less commonly received T-cell depleting induction immunosuppression (12% versus 76%, d = −1.73, $P < 0.001$). Both groups predominantly used calcineurin inhibitor-based triple immunosuppression after transplantation, but there were some differences, notably, a higher proportion of glucocorticoids and cyclosporin in Australia and New Zealand (99% versus 72%, d

TABLE 3.

Characteristics of deceased donors for BEST-Fluids trial participants compared with donors for other Australian and New Zealand kidney transplant recipients in the ANZDATA Registry

Characteristic	Total (N = 2178)	ANZDATA (N = 1370)	BEST-Fluids (N = 808)	Standardized difference (BEST-Fluids—ANZDATA)	*P*
Age (y)					
Mean (SD)	46.6 (16.6)	47.0 (16.5)	46.0 (16.5)	−0.06	0.22
Gender					0.03
Male	1301 (59.7%)	847 (61.8%)	454 (56.2%)	−0.11	
Female	877 (40.3%)	523 (38.2%)	354 (43.8%)	0.11	
Donor type					0.008
Donor after circulatory death	628 (28.8%)	427 (31.2%)	201 (24.9%)	−0.14	
Donor after brain death	1550 (71.2%)	943 (68.8%)	607 (75.1%)	0.14	
Cause of donor death					0.70
Cerebral hypoxia/ischemia	829 (38.1%)	514 (37.5%)	315 (39.0%)	0.03	
Cerebral infarct	120 (5.5%)	85 (6.2%)	35 (4.3%)	−0.08	
Intracranial hemorrhage	752 (34.5%)	473 (34.5%)	279 (34.5%)	0.0001	
Traumatic brain injury	377 (17.3%)	235 (17.2%)	142 (17.6%)	0.01	
Other neurological condition	45 (2.1%)	27 (2.0%)	18 (2.2%)	0.02	
Non-neurological condition	55 (2.5%)	36 (2.6%)	19 (2.4%)	−0.02	
Donor received CPR	1053 (48.4%)	651 (47.5%)	402 (49.9%)	0.05	0.36
Weight (kg)					
Mean (SD)	81.9 (22.8)	81.9 (22.9)	81.9 (22.6)	0.0001	1.00
Body mass index (kg/m^2)					
Mean (SD)	27.7 (6.7)	27.7 (6.7)	27.7 (6.6)	0.01	0.90
Diabetes	162 (7.4%)	111 (8.1%)	51 (6.3%)	−0.07	0.19
Treated hypertension	534 (24.7%)	360 (26.5%)	174 (21.7%)	−0.11	0.03
Smoking status					0.69
Never	806 (37.1%)	517 (37.8%)	289 (35.9%)	−0.04	
Former	457 (21.0%)	281 (20.6%)	176 (21.8%)	0.03	
Current	909 (41.9%)	568 (41.6%)	341 (42.3%)	0.01	
Admission serum creatinine (μmol/L)					0.71
Mean (SD)	90.2 (46.1)	90.5 (50.2)	89.7 (38.3)	−0.02	
Median (IQR)	81 (63–105)	80 (62–105)	83 (64–105)		
Terminal serum creatinine (μmol/L)					0.33
Mean (SD)	94.7 (90.3)	96.3 (89.9)	91.8 (91.1)	−0.05	
Median (IQR)	69 (56–94)	69 (56–97)	68.5 (56–91)		
Preretrieval biopsy performed	296 (13.6%)	164 (12.0%)	132 (16.3%)	0.13	0.01
Expanded criteria donor	658 (30.2%)	430 (31.4%)	228 (28.2%)	−0.07	0.18
Kidney donor risk index (KDRI)					
Mean (SD)	1.37 (0.46)	1.39 (0.46)	1.33 (0.44)	−0.14	0.007
KDRI tertile[a]					0.06
First	721 (33.3%)	444 (32.6%)	277 (34.5%)	0.04	
Second	721 (33.3%)	434 (31.9%)	287 (35.7%)	0.08	
Third	721 (33.3%)	482 (35.4%)	239 (29.8%)	−0.12	

KDRI tertile here refers to the distributions of the individual KDRI scores in the combined Australian and New Zealand cohorts (n = 2178).
ANZDATA, Australia and New Zealand Dialysis and Transplant Registry; BEST-Fluids, Better Evidence for Selecting Transplant Fluids; CPR, cardiopulmonary resuscitation; IQR, interquartile range; KDRI, kidney donor risk index.

= 2.01; and 15% versus 0.6%, d = 1.86, respectively, $P < 0.001$). Deceased donor kidneys in Australia and New Zealand were much less likely to be machine-perfused before transplantation (3% versus 30%, d = −1.48, $P < 0.001$).

The 585 donors for the 808 BEST-Fluids participants were significantly older than the 26 864 US donors during the study period (46 ± 17 versus 39 ± 16 y, d = 0.44, $P < 0.001$). Furthermore, BEST-Fluids donors were more likely to have died of cerebral anoxia (38% versus 11%, d = 0.88) but less likely to have died after a cerebrovascular event (40% versus 56%, d = −0.36) or head trauma (18% versus 27%, d = −0.29) (all $P < 0.001$) and were more likely to be smokers (42% versus 17%, d = 0.70, $P < 0.001$) and expanded criteria donors (29% versus 15%, d = 0.46, $P < 0.001$). However, BEST-Fluids donors had lower admission and terminal serum creatinine concentrations (0.99 ± 0.42 versus 1.79 ± 1.44 mg/dL, d = −0.56; and 1.03 ± 1.02 versus 1.33 ± 1.28 mg/dL, d = −0.24, respectively, both $P < 0.001$), less diabetes (7% versus 9%, d = −0.14, $P = 0.01$), and less hypertension (22% versus 29%, d = −0.20, $P < 0.001$) than US deceased donors. No significant differences were observed between the groups in terms of gender or donor type (donation after brain death versus donation after circulatory death [DCD]).

DISCUSSION

To maximize the applicability of trial findings to clinical transplantation, BEST-Fluids was a pragmatic RCT closely

aligned with clinical practice, with broad eligibility criteria. We sought to recruit a trial population representative of the general population of patients with kidney failure who received deceased donor kidney transplants. We found that a significant majority of all deceased donor kidney transplant recipients in Australia and New Zealand during the trial enrollment period (2178 of 2373; 92%) met the trial eligibility criteria, confirming that these were broad and pragmatic. During active recruitment at the participating sites, 1350 were screened for participation, and a high proportion (63%) of these were enrolled in the trial. Of those who were not enrolled, only 95 (7%) were ineligible, 55 (4%) declined to participate, and the remainder (344; 25%) were not enrolled because of factors largely unrelated to the trial design. Indeed, BEST-Fluids participants made up a substantial proportion (808 of 2178; 37%) of all eligible deceased donor kidney transplants performed during the trial period in Australia and New Zealand. Compared with nonparticipants, trial participants had no clinically meaningful differences in baseline characteristics, including those relevant to the risk of the primary trial outcome of DGF; thus, significant selection bias was absent.

Minor differences in characteristics between trial participants and nonparticipants were identified. First, the trial participants were ethnically and geographically different from the other recipients, reflecting differences in trial participation, recruitment rates, and durations at different hospitals. For example, recruitment rates were higher in New Zealand and the Australian state of Queensland than in other Australian states, reflecting the fact that the participating transplant hospitals in New Zealand and Queensland began recruitment early in the trial and maintained high recruitment throughout, whereas other hospitals joined later or did not participate in the study. In addition, the proportion of New Zealand Māori and Pacific Islanders enrolled was higher, and the proportion of Asian ethnicity was lower. Trial participants were less likely to be under the care of a transplanting hospital before transplantation, likely because of differences in the organization of transplant and dialysis services in different jurisdictions. Nevertheless, trial participants were recruited from metropolitan and regional areas and a range of hospitals (both small and large centers) across Australia and New Zealand, including Aboriginal and Torres Strait Islander Australians and New Zealand Māori, 2 groups that experience a high burden of kidney failure and poor access to transplantation compared with other population groups.[23-25]

Second, the clinical characteristics differed slightly between the groups, although these are unlikely to affect the generalizability of the trial. The trial participants had a slightly higher burden of comorbid conditions at baseline (coronary artery disease, body weight, and longer dialysis duration). Conversely, the trial cohort received slightly fewer kidneys from donors with hypertension and at higher risk of DGF (ie, DCD). More trial participants also received induction immunosuppression, glucocorticoids, or cyclosporin. These small differences (all values of $d < 0.20$, except for induction immunosuppression [0.30], glucocorticoids [0.23], and cyclosporin [0.34]) likely reflected the variability between higher and lower recruiting jurisdictions and participating and nonparticipating hospitals in transplant waiting times, organ donation rates, donor acceptance practices, and immunosuppression use,[26,27] rather than systematic differences between those recruited at a given site and those who were not. The observed differences in cyclosporin use were due to 1 high-enrolling hospital (Auckland City Hospital) that used cyclosporin in standard risk recipients and would not be expected to affect DGF incidence.[28] However, the slightly lower proportion of DCD kidneys (absolute difference 6%, $d = -0.14$) received by the trial participants might be expected to slightly reduce the risk of DGF.

We observed several differences between the BEST-Fluids trial participants and the US cohort of transplant recipients. Population characteristics and transplant practices differ between countries and have been documented previously.[29] Given the size of the US dataset, small differences in characteristics (that may not be clinically meaningful) between the groups were associated with a high degree of statistical significance. Hence, it is important to consider standardized differences in these comparisons. In the United States, there was a higher proportion of patients with diabetes (either as a cause of kidney failure or as a comorbidity), greater use of T-cell–depleting induction immunosuppression, longer total ischemic times, and greater use of machine perfusion. T-cell depletion use varies within and between countries,[30-32] and although it has been postulated to be associated with a lower risk of DGF,[33] this has not been confirmed in randomized trials.[34-36] The longer the ischemic time, the higher the expected risk of DGF,[6] whereas increased use of machine perfusion would be expected to lower the risk of DGF.[37] Meanwhile, deceased donors in Australia and New Zealand were older and more likely to be expanded criteria donors, albeit with lower terminal serum creatinine values. It is beyond the scope of this study to explain these differences. However, the main question remains whether they are associated with a significantly different risk of DGF in these 2 populations. In a multicenter prospective study of DGF in a US cohort with similar characteristics to the SRTR cohort described here, the incidence of DGF was 38%.[1] This is similar to the postulated DGF incidence of 36% used for the sample size calculations in BEST-Fluids, which was confirmed by a blinded review of the event rate for the first 113 trial participants,[10] and to the DGF incidence reported in other settings.[38,39] Thus, BEST-Fluids results should be generalizable to the US deceased donor kidney transplant population and other populations with similar DGF risk.

BEST-Fluids was the first large multicenter kidney transplant trial to prospectively assess participant representativeness by using a registry-based design. The importance of representativeness when considering the applicability of trial results is increasingly recognized,[40] and we argue that the need to comprehensively evaluate the external validity of trials[41] makes a strong case for the routine separate publication of the types of analyses reported here to fully inform clinicians. However, most currently published trial reports are limited to reporting data on the number of patients screened, which provides limited information about the underlying population who might have been eligible for the trial. Although registries have been used to retrospectively determine the representativeness of trial participants in nephrology[42] and are increasingly being used in other medical disciplines,[43] they have not been used in transplantation trials despite their widespread use and availability.[29]

The major strengths of this study were the completeness and reliability of the data used for comparisons and the very

low amount of missing data for the Australian and New Zealand patients. Trial enrollment and key data collection for BEST-Fluids were embedded into ANZDATA, a population-based clinical quality registry that collects and reports demographics, comorbidity, and outcome data on all kidney transplants in Australia and New Zealand.[44] By adopting this approach, we could use the same data collection approaches and definitions to directly assess the representativeness of the trial participants compared with other transplant recipients during the trial period. Although this analysis was performed retrospectively, the implementation plan was prespecified,[10] and all data were collected prospectively.

This study has some limitations. ANZDATA does not collect all factors that might have been relevant to representativeness, such as socioeconomic status, distance from the transplanting hospital, primary language spoken, or severity of comorbidities. Similarly, we did not have information on laboratory data (other than donor creatinine) or other recipient factors that may have affected DGF risk (eg, preoperative fluid status, dialysis requirement, or plasma exchange). The comparison with the US cohort was limited to summary data, and data on several important characteristics (including comorbidities, dialysis modality, and smoking) were either unavailable or unreliable because of very high levels of missing data.[45] Several variables included in the US cohort comparison also had notable missing data, particularly machine perfusion (21% missing) and cause of donor death (25%), which might have affected the results for these and other (eg, proportions of expanded criteria donors) comparisons. In addition, although there have been previous comparisons of data from the US SRTR and ANZDATA,[29] the validity of such comparisons has not been rigorously audited. Finally, although these comparisons were intended to explore generalizability, we acknowledge that it is difficult to draw firm conclusions until full trial results including subgroup analyses are available.

The highest priority for a RCT is to generate unbiased results with high internal validity to draw causal inferences about the tested intervention. This often comes at the expense of external validity, and it is well recognized that trial populations, as identified by Kennedy-Martin et al, are often "highly selected and have a lower risk profile than real-world populations, with the frequent exclusion of elderly patients and patients with comorbidities."[41] Pragmatic trial designs allow for the evaluation of the effectiveness of interventions because they are used in routine clinical care.[46,47] We have shown that, by combining this with the use of a population-based disease registry for trial data collection and follow-up,[29] representativeness assessments can be incorporated into routine trial reporting to readily determine the applicability of trial findings, thereby facilitating rapid implementation.[48]

In conclusion, participants in the BEST-Fluids trial broadly represented the Australian and New Zealand kidney transplant recipient population. Importantly, the trial included representative proportions of Aboriginal and Torres Strait Islander Australians, New Zealand Māori, and Pacific peoples, groups who are disproportionately affected by kidney failure in these 2 countries. The trial participants had a slightly higher comorbidity burden and received fewer high-risk donor kidneys. These small differences were likely due to the different recruitment rates in the 2 countries and at different hospitals and reflect variability in approaches to care in these settings rather than systematic differences between recruited and nonrecruited participants. In addition, the trial participants were generally similar to US transplant recipients, with most differences being small or because of known underlying population differences. The results of the BEST-Fluids trial should be applicable to most deceased donor kidney transplant recipients.

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